DIABETES RESEARCH CENTERS

2014 NIDDK Diabetes Research Center Directors' Annual Meeting

September 10, 2014

Bethesda North Marriott Hotel and Conference Center

Bethesda, MD

National Institute of Diabetes and Digestive and Kidney Diseases

DIABETES RESEARCH CENTERS

2014 Meeting of the Diabetes Centers' Directors

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    a. Presentation (J. Hyde)
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    f. Joslin Diabetes Center
    g. University of Alabama at Birmingham
    h. UCSD/UCLA
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    j. University of Chicago
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    o. Washington University in St. Louis
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Agenda
2014 Diabetes Center Directors' Meeting
Wednesday, September 10, 2014

Bethesda North Marriott Hotel & Conference Center
5701 Marinelli Road
North Bethesda, MD 20852

7:30 – 8:00 am	Registration
8:00 – 8:10 am	Welcome and opening remarks (Dr. Greg Germino)
8:10 – 9:00 am	The view from NIDDK: • Updates (J. Hyde) • Perspectives & Opportunities (J. Fradkin)
9:00 – 9:15 am	Report from the Diabetes Centers Executive Committee (J. Schaffer)
9:15 – 9:35 am	NIDDK Summer Medical Student Program: report (A. Powers)
9:35 - 10:00 am	Accelerating Medicine Partnerships Program (P. Smith)
10:00 – 10:15 am	4D Nucleome and Human Islet Research Network (HIRN) (O. Blondel)
10:15 – 10:30 am	Break
10:30 – 11:00 am	Follow-up to NIDDK Centers Report; M.D. Basic Researchers (G. Germino)
11:00 – 11:30 am	Mutant Mouse Regional Resource Centers, DK Net and Integrated Islet Distribution Program (K. Abraham)
11:30 – 11:45 am	General Discussion
11:45 – 1:00 pm	Lunch (on your own)
1:00 – 1:30 pm	Best practices & issues related to DRC applications (e.g. incorporating university-wide cores into DRCs) (J. Schaffer; J. Hyde)
1:30 – 1:45 pm	U.S.-Mexico Research Training Collaboration with NIH/NIDDK (R. Sherwin)
1:45 – 2:00 pm	Engaging Computational Scientists in Diabetes Research: follow-up from National Advisory Council discussion (J. Schaffer)
2:00 – 2:15 pm	Break
2:15 – 2:30 pm	Diabetes Research Centers: up-coming RFAs (J. Hyde)
2:30 – 2:45 pm	Submitting Complex Electronic Applications & Progress Reports (J. Hyde)
2:45 – 3:00 pm	Diabetes Research Centers website: updates/changes (J. Hyde)
3:00 – 3:15 pm	Wrap-up, final comments & adjourn

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DIABETES RESEARCH CENTERS

UPCOMING NIH/NIDDK MEETINGS & WORKSHOPS

Host-Microbiota Interactions: Sept. 8-9, 2014
How Host Physiology and Disease Pathophysiology Are Affected by the Gut Microbiota
Natcher Building, NIH Campus, Bethesda, MD
Meeting Website

Small Blood Vessels: Big Health Problems Sept. 18-19, 2014
Sponsored by the Trans-NIH Small Vessel Biology Working Group
(NINDS, NHLBI, NEI, ODP and ORWH)
John Edward Porter Neuroscience Research Center, NIH Campus, Bethesda, MD
Meeting Website

Cardiovascular Disease and Type 1 Diabetes October 8-9, 2014
Lister Hill Auditorium, NIH Campus, Bethesda, MD
Meeting Website

2014 Mid-Atlantic Diabetes Research Symposium October 10, 2014
Lister Hill Auditorium, NIH Campus, Bethesda, MD
Meeting Website

Translation of Disease Genetics to High-Throughput Drug Screening: October 28-29, 2014
Humanized Drosophila, Zebrafish, and *c. elegans* Models of
Genetically Complex Diseases
Natcher Building, NIH Campus, Bethesda, MD

Minimal Standards for Human Brown Fat Detection Using FDG-PET November 4, 2014
TBA

NIDDK New PI Workshop December 2-3, 2014
Natcher Building, NIH Campus, Bethesda, MD
Meeting Website

NIDDK K Awardees' Workshop April 16-17, 2015
Lister Hill Auditorium, Bethesda, MD

DIABETES RESEARCH CENTERS

Current Funding Opportunity Announcements

RFA-DK-14-017: Type 1 Diabetes Complications IMPACT Award (DP3)

RFA-DK-14-021: Consortium on Beta-Cell Death and Survival (HIRN-CBDS) (UC4)

RFA-DK-14-025: Identification of Novel Targets and Pathways Mediating Weight Loss, Diabetes Resolution and Related Metabolic Disease after Bariatric Surgery in Humans (R01)

PAR-14-323: Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity Development (R01)

PAR-13-366: Pragmatic Research in Healthcare Settings to Improve Diabetes Prevention and Care (R18)

PAR-13-367: Planning Grants for Pragmatic Research in Healthcare Settings to Improve Diabetes Prevention and Care (R34)

RFA-DK-14-005: NIDDK Clinician Scientist Mentoring Award to Promote Workforce Diversity (K05)

RFA-DK-14-024: Advanced Clinical Trials to test Artificial Pancreas Device Systems in Type 1 Diabetes (UC4)

RFA-DK-14-022: Improving Diabetes Management in Young Children with Type 1 Diabetes (DP3)

PAR-14-262: Long-Term Outcomes of Bariatric Surgery Using Large Datasets (R01)

RFA-DK-14-006: U.S.-India Bilateral Collaborative Research Partnerships (CRP) on Diabetes Research (R21)

PAR-14-006: Seeding Collaborations for Translational Research to Discover and Develop New Therapies for Diseases and Conditions within NIDDK's Mission (Revisions) (R01)

RFA-DK-14-014: Diabetes Impact Award-Closed Loop Technologies: Clinical, Physiological and Behavioral Approaches to Improve Type 1 Diabetes Outcomes (DP3)

RFA-DK-14-015: Diabetes Impact Award-Closed Loop Technologies: Development and Integration of Novel Components for an Automated Artificial Pancreas System (DP3)

PAR-11-157: NIDDK Multi-Center Clinical Study Cooperative Agreement (U01)

PAR-13-305: Collaborative Interdisciplinary Team Science in NIDDK Research Areas (R24)

PAR-14-301: NIDDK Central Repositories Non-renewable Sample Access (X01)

PAR-13-352: Translational Research to Improve Obesity and Diabetes Outcomes (R01)

PAR-12-265: Ancillary Studies to Major Ongoing Clinical Research Studies to Advance Areas of Scientific Interest within the Mission of the NIDDK (R01)

PAR-14-257: Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies (DP3)

PAR-14-258: Research Using Subjects From Selected Type 1 Diabetes Clinical Studies (Living Biobank) (DP3)

PAR-13-074: Small Grants for New Investigators to Promote Diversity in Health-Related Research (R03)

PAR-14-073: Shared Instrumentation Grant Program (S10)

PAR-13-114: Improvement of Animal Models for Stem Cell-Based Regenerative Medicine (R01)

PAR-13-228: Biomarkers for Diabetes, Digestive, Kidney and Urologic Diseases Using Biosamples from the NIDDK Repository (R01)

PAR-13-231: Phenotyping Embryonic Lethal Knockout Mice (R01)

NIH Big Data to Knowledge (BD2K) Enhancing Training:

RFA-HG-14-007: Mentored Career Development Award in Biomedical Big Data Science for Clinicians and Doctorally Prepared Scientists (K01)

RFA-HG-14-005: Revisions to Add Biomedical Big Data Training to Active Institutional Training Grants (T32)

Opening Remarks

Diabetes Research Centers Directors' Meeting

Gregory G. Germino, M.D.
Deputy Director

National Institute of Diabetes and Digestive and Kidney Diseases

September 10, 2014

National Institute of Diabetes and Digestive and Kidney Diseases

FY 2014 Budget & Paylines

NIH

	FY 2013	FY 2014	Change
Total Program…….	$29.15B	$30.15B	$1.0B

NIDDK

Total Program…….	$1.835B	$1.881B	$46.1M

Paylines

Nominal…….	11th	13th
ESI……..	16th	18th

National Institute of Diabetes and Digestive and Kidney Diseases

President's Budget Request
FY 2015

NIH

	FY 2014	FY 2015	Change
Total Program…….	**$30.15B**	**$30.36B**	**$210M**

NIDDK

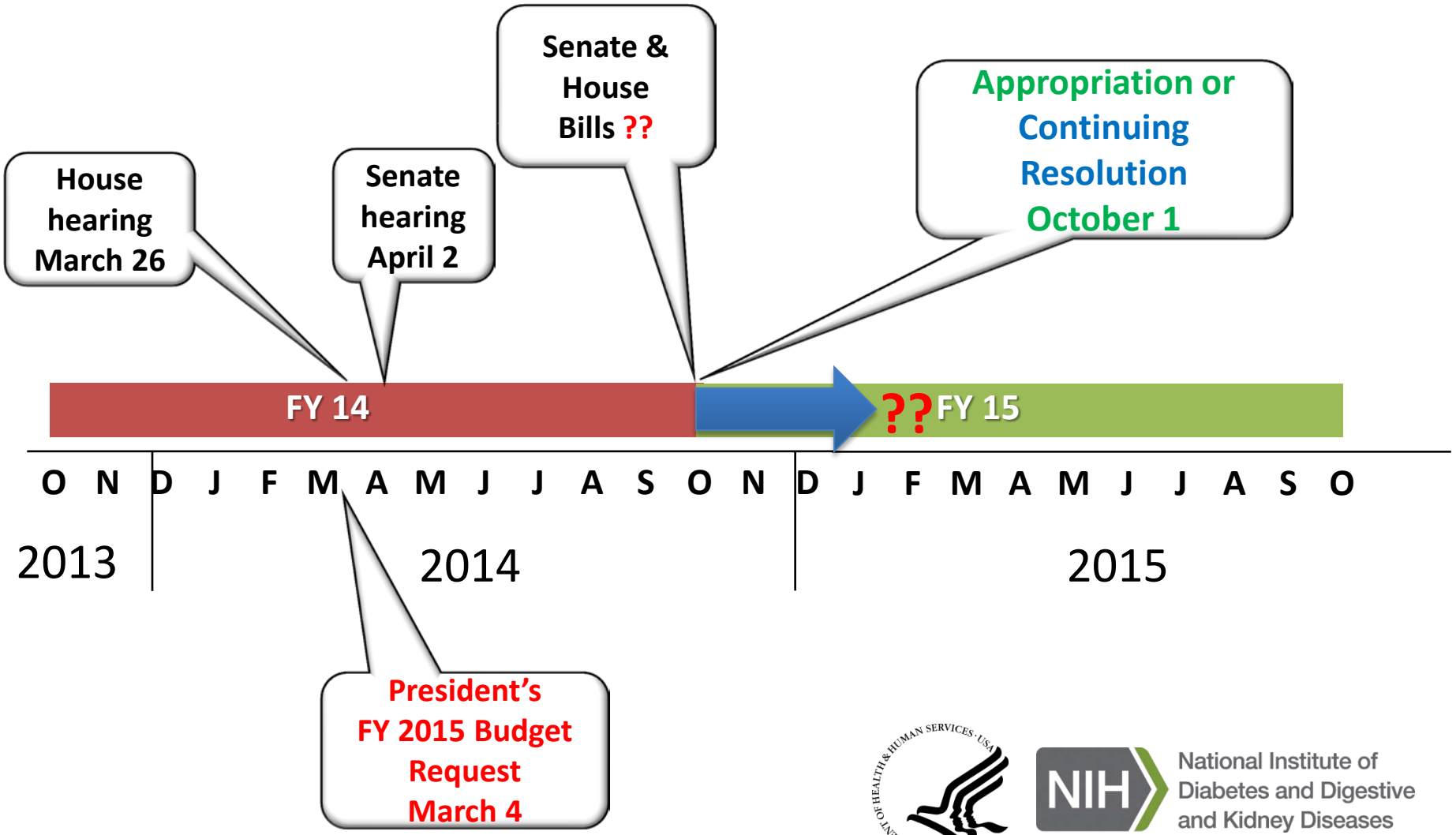
Total Program…….	**$1.881B**	**$1.893B**	**$12M**

http://officeofbudget.od.nih.gov/pdfs/FY15/FY2015_Overview.pdf

http://www.niddk.nih.gov/about-niddk/budget-legislative-information/Documents/NIDDK%20to%20IC%203%204%202014%20FINAL.PDF.pdf

National Institute of Diabetes and Digestive and Kidney Diseases

2015 Budget Events



National Institute of Diabetes and Digestive and Kidney Diseases

Stimulating Peripheral Activity to Relieve Conditions

Electroceuticals/Bioelectronic Medicines: A Novel Therapy?

NATURE | COMMENT

Drug discovery: A jump-start for electroceuticals

Kristoffer Famm, Brian Litt, Kevin J. Tracey, Edward S. Boyden & Moncef Slaoui

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MAGAZINE 15 COMMENTS

Can the Nervous System Be Hacked?

By MICHAEL BEHAR MAY 23, 2014

a research roadmap

Karen Birmingham, Viviana Gradinaru, Polina Anikeeva, Warren M. Grill, Victor Pikov, Bryan McLaughlin, Pankaj Pasricha, Douglas Weber, Kip Ludwig and Kristoffer Famm

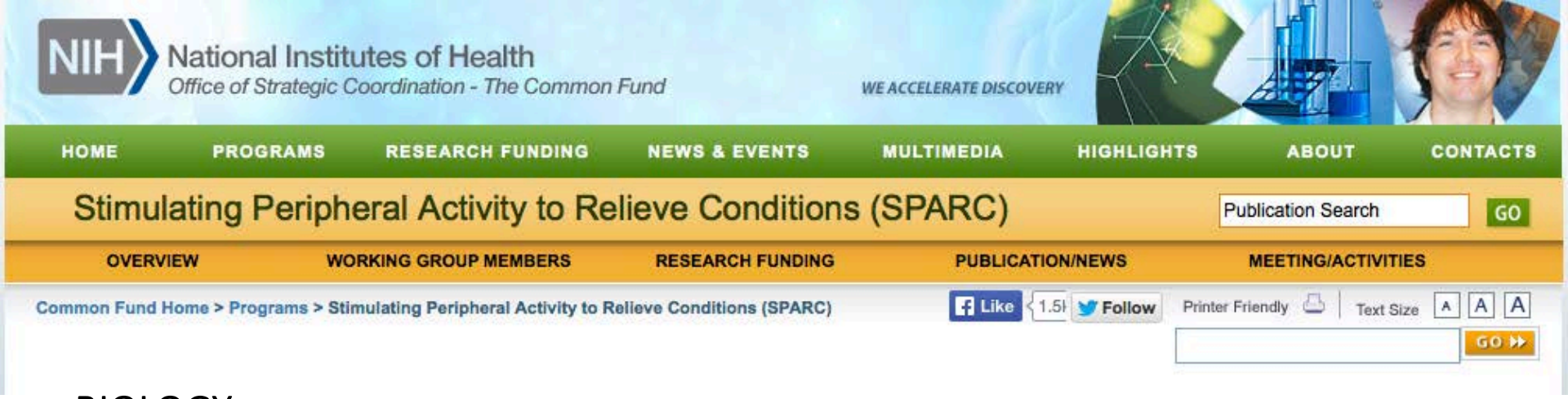
Realizing the vision of a new class of medicines based on modulating the electrical signalling patterns of the peripheral nervous system needs a firm research foundation.

Stimulating Peripheral Activity to Relieve Conditions

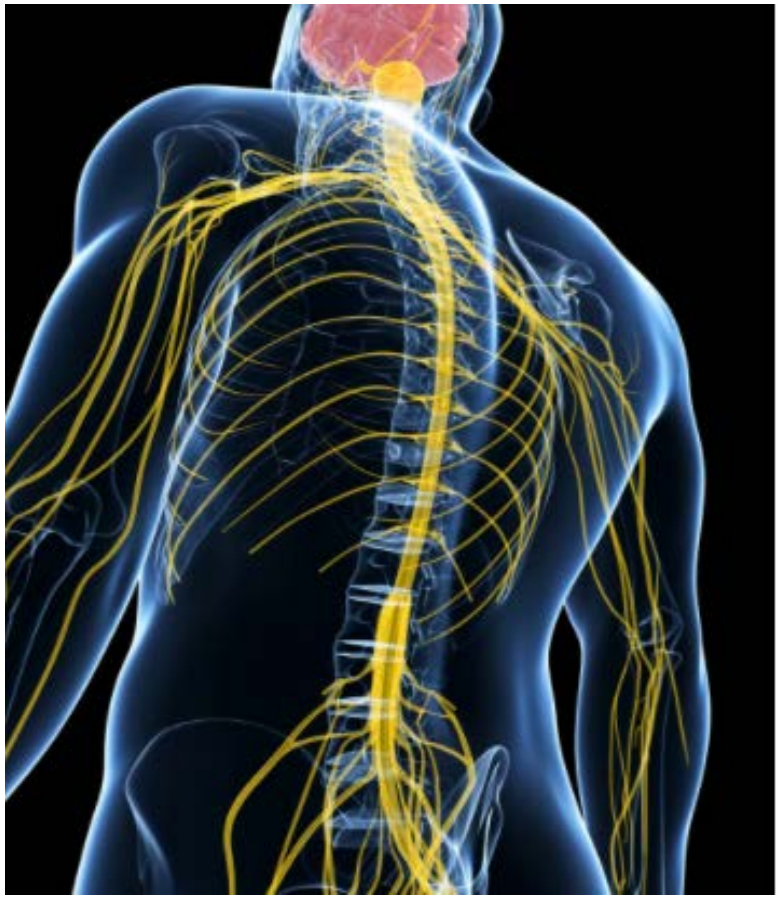
Program Goals:

- To apply recent advances and emerging technologies to develop detailed, integrated functional anatomical circuit maps, and then
- To use these maps with new and emerging electrode designs to improve existing neuromodulation therapies or to pursue new indications

National Institute of Diabetes and Digestive and Kidney Diseases



- BIOLOGY
  - Develop detailed, integrated functional and anatomical neural circuit maps in 5 organ systems
- NEXT GENERATION TOOLS
  - Develop and pilot novel electrode designs, stimulation protocols, and minimally invasive procedures to improve existing RX and promote new ones
- CLINICAL DEMONSTRATIONS FOR SMALL MARKET INDICATIONS
- DATA COORDINATION



http://commonfund.nih.gov/sparc/

Breakdown of SPARC Budget - $248 M over 6.5 years

	FY15	FY16	FY17	FY18	FY19	FY20	FY21
Initiative 1 – Biology							
Stage 1	3.5						
Stage 2		20	20	20			
Stage 3					25	25	25
Initiative 2 – Next Generation Technology							
Stage 1	2.5						
Stage 2		5	5	5			
Stage 3		8	8	8	8	8	8
Initiative 3 – Small Market Indications		5.25	5.25	5.25	5.25	5.25	5.25
Initiative 4 – Data Coordination Center		1.25	2.25	2.25	2.25	2.25	2.25
Total	**6**	**39.5**	**40.5**	**40.5**	**40.5**	**40.5**	**40.5**

National Institute of Diabetes and Digestive and Kidney Diseases

Upcoming NIH Policy Change

NIH to balance sex in cell and animal studies

- NIH will begin phasing in policies over the course of the FY15 requiring grantees to address inclusion of both sexes in preclinical research.
- NIH will issue Guide notices that will explain what new information should be included in applications and progress reports to address sex differences and the timing of these new requirements.
- NIH will be developing guidelines for reviewers as they consider the information about the sex of animals in their evaluation of applications.

National Institute of Diabetes and Digestive and Kidney Diseases

New Public Face of NIDDK

www.niddk.nih.gov

NIH National Institute of Diabetes and Digestive and Kidney Diseases

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Open grant, contract, and cooperative agreement listings with closing dates and contacts

Funded Grants & Grant History
Application success rates, funding priorities, and trends

Funding Process
Tips for applicants; human subjects research information; grant review and management resources; and commonly used funding mechanisms, including diversity and small business programs

Research Programs & Contacts
Research program and staff contacts for researchers seeking funding

Research Training & Career Development
Grant programs for students, postdocs, and faculty

Research at NIDDK
Labs, faculty, and research opportunities located on NIDDK campuses in Maryland and Arizona

Research Resources
Protocols, repositories, mouse models, plasmids, and more

Technology Advancement & Transfer
Material transfer agreements, technology licensing, and public/private collaborations

Meetings & Events
Past and upcoming scientific meetings sponsored or hosted by NIDDK

...otect their kidneys

...n forces to speed ...al is to...

...increasingly linked to liver

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conduct basic, translational and clinical research across a broad spectrum of research topics and serious, chronic diseases and conditions related to the institute's mission. In addition, the NIDDK supports research training for students and scientists at various stages of their careers and a range of education and outreach programs to bring science-based information to patients and their families, health care professionals and the public.

...DK DIRECTOR
...Rodgers, M.D., M.A.C.P.

- Meet the Director
- Mission & Vision
- NIDDK Director's Update
- NIDDK Annual Report 2014

LOOKING FOR AN INTERNSHIP AT NIDDK?

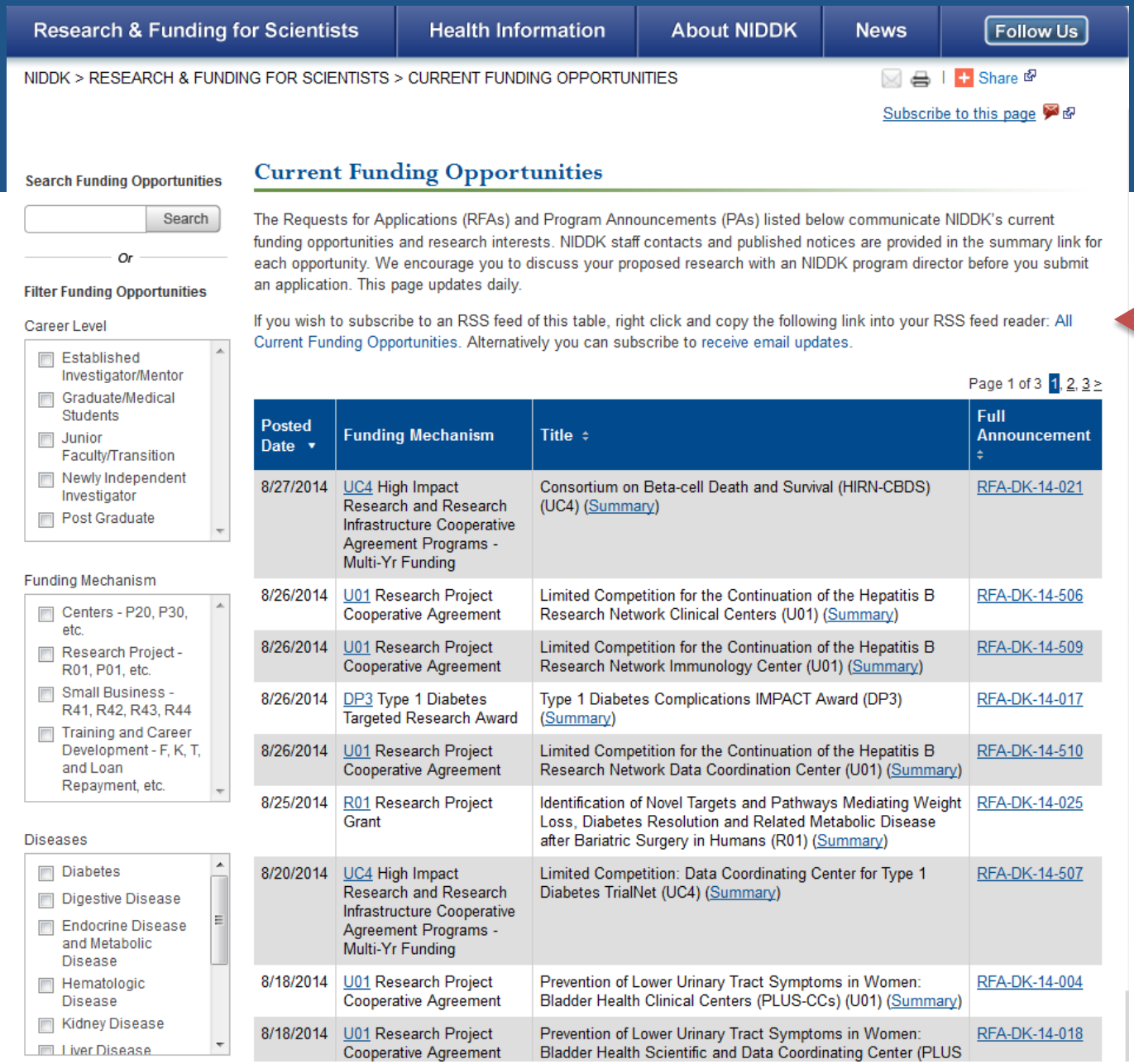
Work side-by-side with leading NIH scientists

TOP TEN TIPS FOR FUNDING SEEKERS

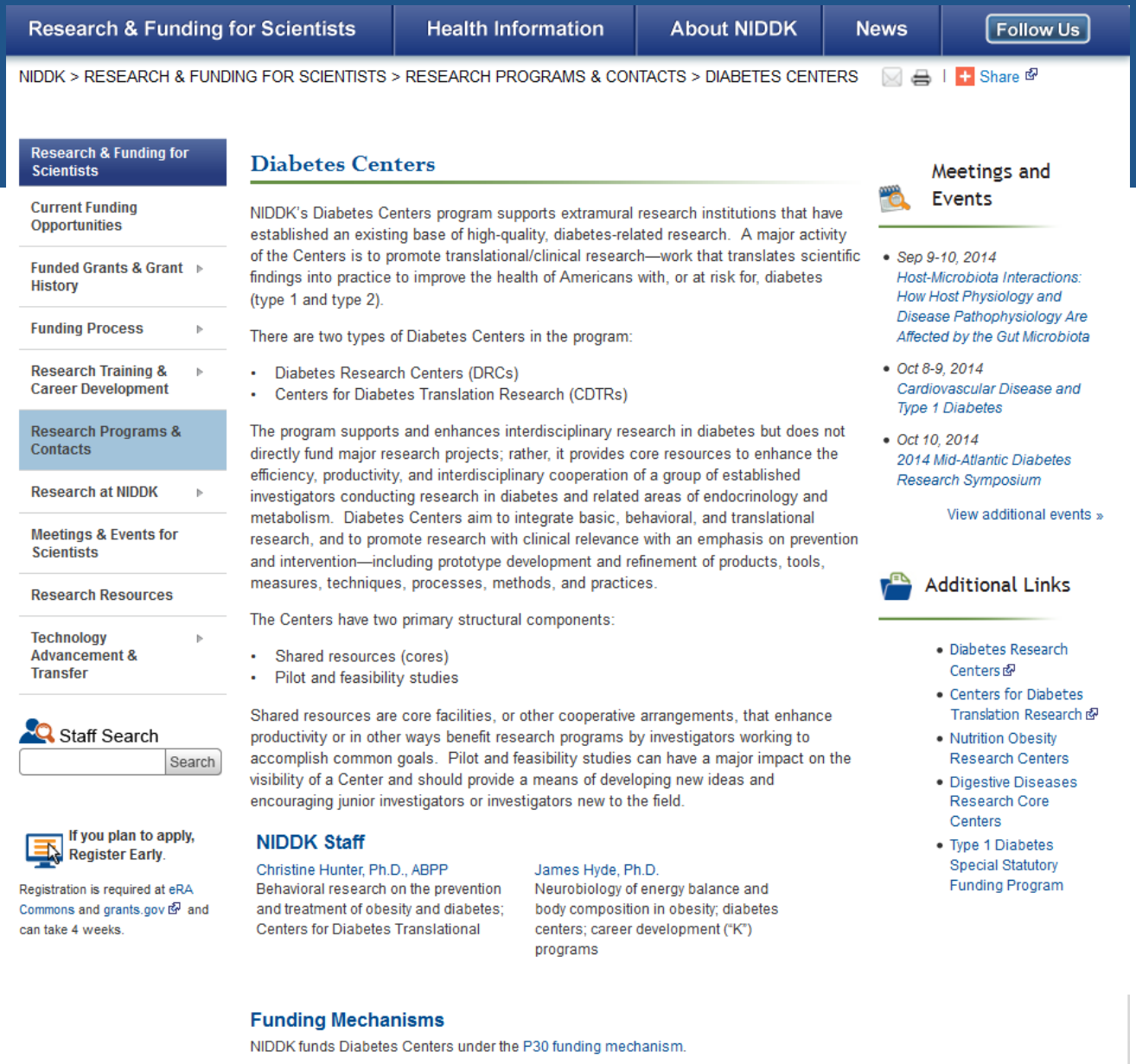
Where to register and what to do before you apply for a funding opportunity

FAST TRACK SBIR/STTR FUNDING

Learn how SBIR & STTR applications can fast track Phase I and Phase II funding



http://www.niddk.nih.gov/research-funding/current-opportunities/Pages/FO.aspx



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Research Programs & Contacts
Research at NIDDK
Meetings & Events for Scientists
Research Resources
Technology Advancement & Transfer

Staff Search
Search

If you plan to apply, Register Early.
Registration is required at eRA Commons and grants.gov and can take 4 weeks.

Diabetes Centers

NIDDK's Diabetes Centers program supports extramural research institutions that have established an existing base of high-quality, diabetes-related research. A major activity of the Centers is to promote translational/clinical research—work that translates scientific findings into practice to improve the health of Americans with, or at risk for, diabetes (type 1 and type 2).

There are two types of Diabetes Centers in the program:

- Diabetes Research Centers (DRCs)
- Centers for Diabetes Translation Research (CDTRs)

The program supports and enhances interdisciplinary research in diabetes but does not directly fund major research projects; rather, it provides core resources to enhance the efficiency, productivity, and interdisciplinary cooperation of a group of established investigators conducting research in diabetes and related areas of endocrinology and metabolism. Diabetes Centers aim to integrate basic, behavioral, and translational research, and to promote research with clinical relevance with an emphasis on prevention and intervention—including prototype development and refinement of products, tools, measures, techniques, processes, methods, and practices.

The Centers have two primary structural components:

- Shared resources (cores)
- Pilot and feasibility studies

Shared resources are core facilities, or other cooperative arrangements, that enhance productivity or in other ways benefit research programs by investigators working to accomplish common goals. Pilot and feasibility studies can have a major impact on the visibility of a Center and should provide a means of developing new ideas and encouraging junior investigators or investigators new to the field.

NIDDK Staff

Christine Hunter, Ph.D., ABPP
Behavioral research on the prevention and treatment of obesity and diabetes; Centers for Diabetes Translational

James Hyde, Ph.D.
Neurobiology of energy balance and body composition in obesity; diabetes centers; career development ("K") programs

Funding Mechanisms

NIDDK funds Diabetes Centers under the P30 funding mechanism.

Meetings and Events

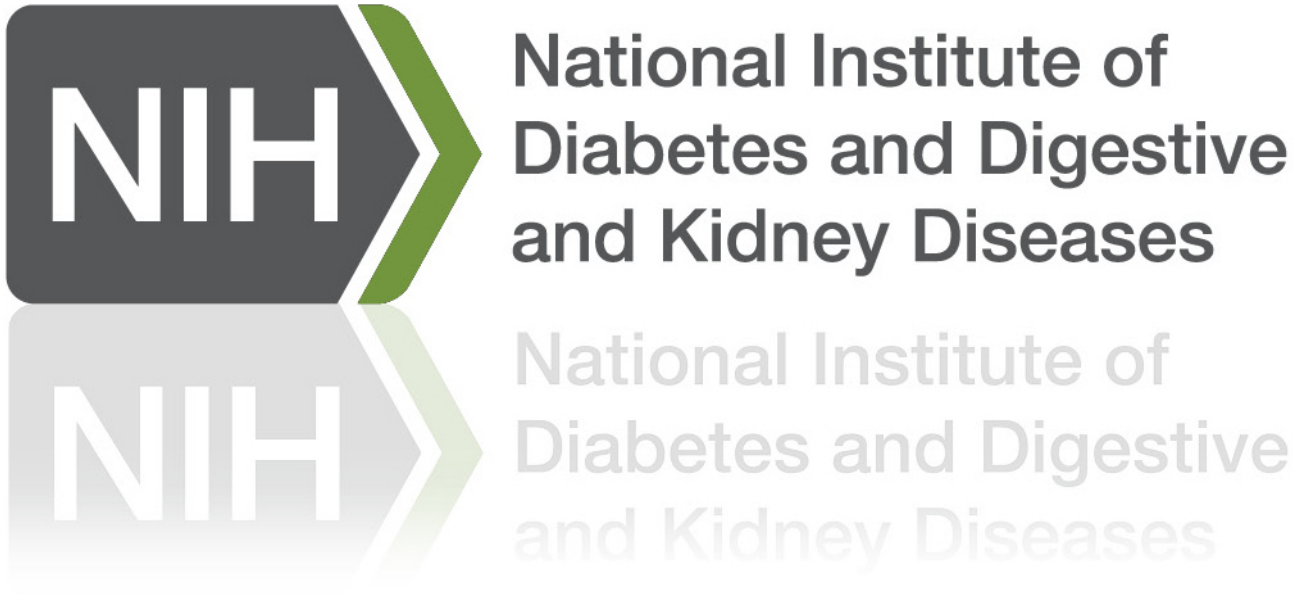
- *Sep 9-10, 2014* *Host-Microbiota Interactions: How Host Physiology and Disease Pathophysiology Are Affected by the Gut Microbiota*
- *Oct 8-9, 2014* *Cardiovascular Disease and Type 1 Diabetes*
- *Oct 10, 2014* *2014 Mid-Atlantic Diabetes Research Symposium*

View additional events »

Additional Links

- Diabetes Research Centers
- Centers for Diabetes Translation Research
- Nutrition Obesity Research Centers
- Digestive Diseases Research Core Centers
- Type 1 Diabetes Special Statutory Funding Program

http://www.niddk.nih.gov/research-funding/research-programs/Pages/diabetes-centers.aspx


NIH
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Diabetes and Digestive
and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

2014 Diabetes Center Directors' Meeting

Bethesda, MD

National Institute of Diabetes and Digestive and Kidney Diseases

2013-14 Diabetes Centers Executive Committee

- **Jean Schaffer, Washington University, Chair**
- Mimmo Accili, Columbia University
- Larry Chan, Baylor College of Medicine
- Martin Myers, University of Michigan
- Jerry Olefsky, University of California, San Diego
- Jerry Palmer, U Washington (Council liaison)
- Jeff Pessin, Albert Einstein College of Medicine

National Institute of Diabetes and Digestive and Kidney Diseases

2014 Diabetes Center Directors' Meeting

- Meeting Book: http://diabetescenters.org/niddk-directors-meeting
  - Agenda
  - Up-coming meetings of interest
  - Current Funding Opportunities (notification of additional opportunities will be sent via e-mail when published in NIH Guide)
  - Featured Publications from Centers (2013-2014)
  - Template for annual progress reports
    - Paper and RPPR
  - Additional materials for presentations at the meeting

2014 Diabetes Center Directors' Meeting

- Brief Overview of Agenda:
  - 8:00 – 10:15: presentations
  - 10:15 – 10:30: break
  - 10:30 – noon: presentations
  - Noon – 1:00: Lunch (on your own; map in book)
  - 1:00 – 2:00: presentations
  - 2:00-2:15: break
  - 2:15-3:00 presentations
  - Transportation: if needed, see John at the registration desk to arrange for cab to airport

National Institute of
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and Kidney Diseases

Perspectives and Opportunities

Directors' Meeting
Diabetes Research Centers

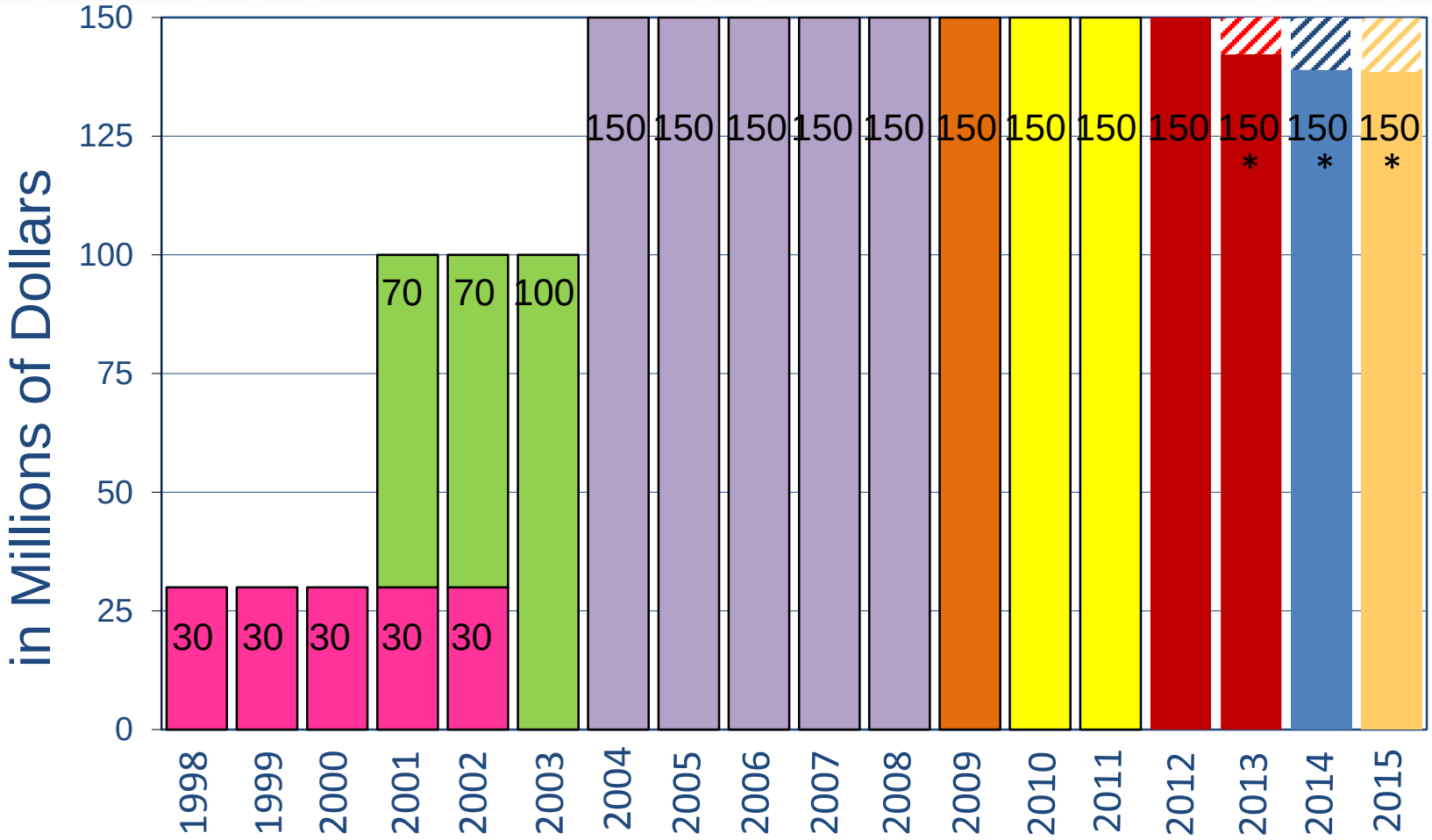
Judith Fradkin, M.D.

Director, Division of Diabetes, Endocrinology,

and Metabolic Diseases, NIDDK

September 10, 2014

Laws Provide $2.19 Billion over 18 years*



P.L. 105-33
P.L. 106-554
P.L. 107-360
P.L. 110-173
P.L. 110-275
P.L. 111-309
P.L. 112-240
P.L. 113-93

* Due to the Budget Control Act of 2011, which sequestered funds for mandatory programs, actual funding levels were reduced to $142.35 million in FY13 and $139.2 million in FY14; FY15 estimated funding is $139.05 million. Total funding (FY98-15) is estimated to be $2.1606 billion.

Planning Meeting for Research Supported by the SDP
April *8-9, 2015*

- Coordinated by the statutory Diabetes Mellitus Interagency Coordinating Committee (DMICC)

- Panel of external scientific and lay experts will consider proposals and suggest opportunities for:

  - New research initiatives to be supported in FY16 and/or FY17 (should SDP be continued)

  - Continuations/expansions of ongoing programs

National Institute of Diabetes and Digestive and Kidney Diseases

Planning Meeting for Research Supported by the SDP
Panel Members

- *Autoimmunity*: Dr. Jeff Bluestone, Dr. Peter Gregersen, Dr. Jane Salmon
- *Transplantation*: Dr. Ronald Gill, Dr. Stanislaw Stepowski
- *Clinical*: Dr. Robert Sherwin, Dr. John Buse, Dr. Betty Diamond
- *Behavior*: Dr. Georgeanna Klingensmith, Dr. Timothy Wysocki
- *Biostatistics*: Dr. Mark Espeland
- Epidemiology: Dr. Elizabeth Selvin
- *Beta cell biology*: Dr. Mike German, Dr. Maike Sander
- *Genetics*: Dr. Rudy Leibel
- *Complications*: Dr. Matthew Breyer, Dr. Robert Eckel, Dr. Nigel Calcutt, Dr. Thomas Gardner
- *Artificial pancreas*: Dr. Irl Hirsch, Dr. Richard Bergenstal
- *Patient perspective*: Ellen Leake

Note – Panel members have expertise in multiple areas.

NIH National Institute of Diabetes and Digestive and Kidney Diseases

Human Islet Research Network

HIRN

What is HIRN?

A network of small research consortia, each focused on a specific biological challenge.

HIRN's mission

To support collaborative translational research to understand how human beta cells are lost in T1D, and find innovative strategies to protect and/or to replace functional beta cell mass.

Consortium on **T**argeting **A**nd **R**egeneration

Consortium on **H**uman **I**slet **B**iomimetics

Coordinating **C**enter — HIRN CC

Administrative **H**ub — NIH NIDDK

Bioinformatics **C**enter — HIRN BC

Consortium for **M**odeling **A**utoimmune **I**nteractions

Consortium on **B**eta Cell **D**eath and **S**urvival

FY15 T1D FOAs Expansions

- Consortium on Beta-cell Death and Survival (HIRN-CBDS) (UC4) (March 3, 2015)
- TrialNet
  - Biomarkers and Mechanisms
  - Type 1 Diabetes TrialNet Clinical Centers (U01) (December 3, 2014)
- Research Using Subjects From Selected Type 1 Diabetes Clinical Studies (Living Biobank) (DP3) (Nov 20, 2014)
- TEDDY multi-'omics

National Institute of Diabetes and Digestive and Kidney Diseases

FY15 T1D FOAs
Artificial Pancreas

- Diabetes Impact Award-Closed Loop Technologies: Development and Integration of Novel Components for an Automated Artificial Pancreas System (DP3) (Nov 24, 2014)
- Advanced Clinical Trials to test Artificial Pancreas Device Systems in Type 1 Diabetes (UC4) (April 15, 2015)
- SBIR/STTR

National Institute of Diabetes and Digestive and Kidney Diseases

FY15 T1D FOAs

- Type 1 Diabetes Complications IMPACT Award (DP3) (March 19, 2015)
- Improving Diabetes Management in Young Children with Type 1 Diabetes (DP3) (March 18, 2015)

National Institute of Diabetes and Digestive and Kidney Diseases

FY15 FOAs
Regular NIDDK Appropriation

- Identification of Novel Targets and Pathways Mediating Weight Loss, Diabetes Resolution and Related Metabolic Disease after Bariatric Surgery in Humans (R01) (March 16, 2015)
- NIDDK Clinician Scientist Mentoring Award to Promote Workforce Diversity (K05) (Nov 24, 2014)

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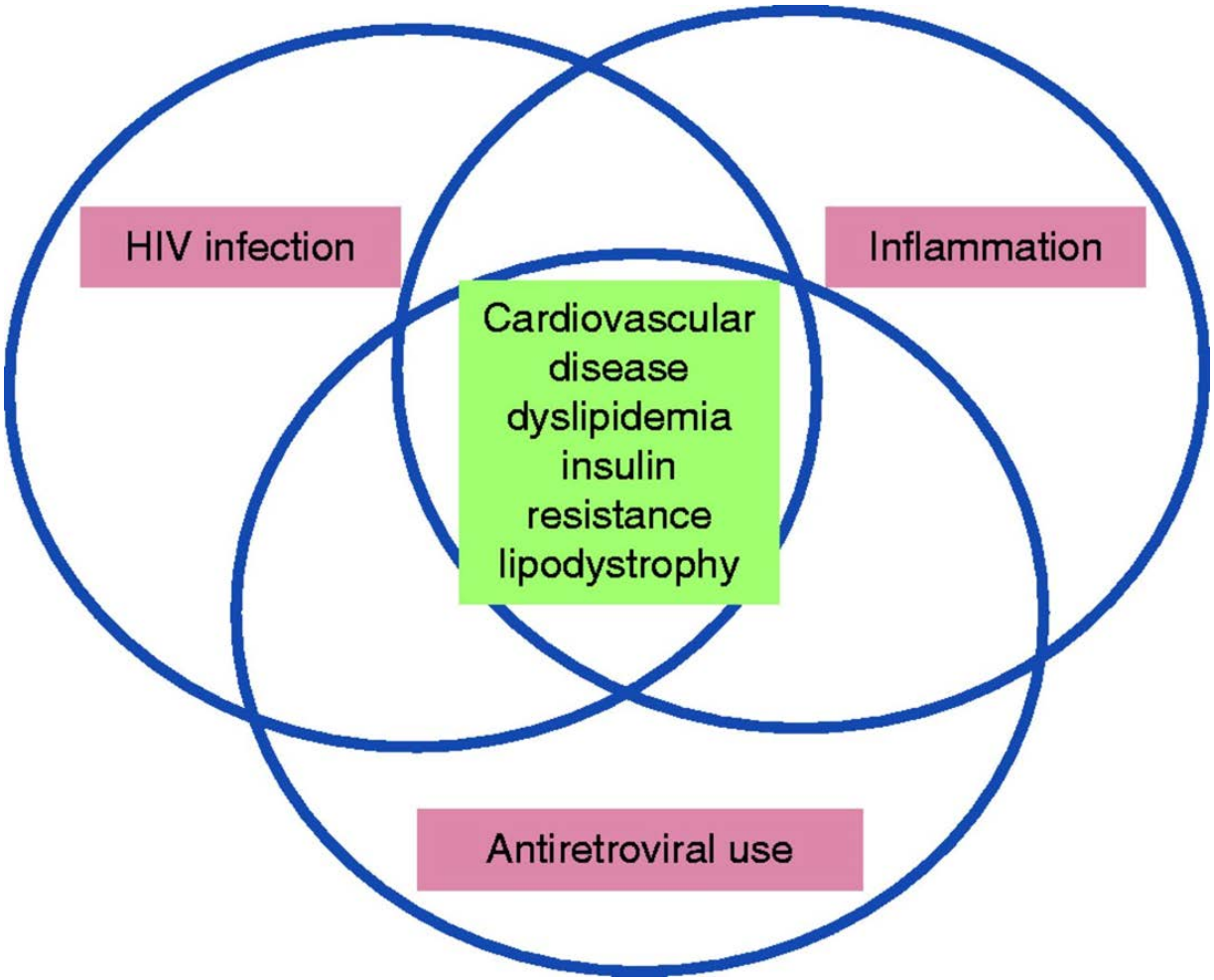
Likely FOA: Overlapping contribution of ART use, HIV infection, and inflammation to metabolic disease



- The etiology of metabolic/endocrine complications in HIV-infected individuals despite viremic control is most likely related to the interplay of host, viral, and ART factors

Srinivasa S and Grinspoon SK. Eur J Endocrinol 2014;170:R185-R202

National Institute of Diabetes and Digestive and Kidney Diseases

Priority Areas

- Disparities (large variation in diabetes incidence and outcomes by geography, education, SES, race/ethnicity)
- Diabetes and ageing (cognition, frailty, sarcopenia)
- Impact of Sleep and Circadian Disruption on Energy Balance and Diabetes
- Bariatric surgery
- Intrauterine environment

National Institute of Diabetes and Digestive and Kidney Diseases

U.S. India Collaborative Diabetes Research

- June 2012 Joint Statement
- February 2013 Scientific Workshop
- May 2014 RFA-DK-14-006 (R21)
- September 2015 awards

National Institute of Diabetes and Digestive and Kidney Diseases

Research to Practice Translation Current R34/ R18 Program

- Supports research to close the gap between research and actual real world dissemination and implementation
  - Retain effectiveness
  - Potential for scalability and sustainable outside of tightly controlled research settings and populations
- Much of the current portfolio focuses on community based settings and delivery outside of the healthcare setting
- Example of success:
  - 2011: Congressional legislation established the CDC-led National Diabetes Prevention Program
  - Largely based on research we funded to test the DPP lifestyle intervention delivered in the YMCA

National Institute of Diabetes and Digestive and Kidney Diseases

Research to Practice Translation Opportunities and Future Directions

- Identify gaps in the translation portfolio:
  - What research is needed to change healthcare practice more rapidly?
  - How can we support research to meaningfully inform diabetes related clinical decision making and health policy?
  - Is it coming in to traditional FOAs?
  - Does it requires unique scientific expertise and methods expertise in review/SEP?
- Conclusion: need more research with a focus on healthcare delivery
  - Capitalize on time of dramatic change in healthcare and existing healthcare infrastructure

National Institute of Diabetes and Digestive and Kidney Diseases

New Programmatic Directions

- Continued Focus:
  - High risk populations/ reducing health disparities
  - Generalizability and scalability to “real world” context and practice
  - Potential for sustainability outside of research period
  - Cost relative to health benefit

- Shift in Focus: Healthcare Delivery
  - Pragmatic Trials in Healthcare
  - Evaluation of Natural Experiments in Healthcare

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Pragmatic Research in Healthcare PAR 13-366 (R18) and PAR 13-367 (R34)

- Solicit pragmatic research designs--evaluate the effectiveness of interventions or therapies in research that maximizes the applicability of the trial's results to routine care conditions
  - Test novel, practical, and cost efficient healthcare based strategies to improve health outcomes

- Research must:
  - Be integrated into existing healthcare settings
  - Leverage existing resources within these practices
    - Minimal intervention staff/infrastructure expenditures

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Evaluation of Natural Experiments in Healthcare PAR-13-365 (R18)

- Escalating rates of diabetes and healthcare costs occurs against a time of dynamic change for healthcare in the U.S.
- Intent of changes: improve health outcomes and reduce costs
- Limited evidence about how well these changes in healthcare work to improve diabetes or of their benefit relative to costs
- Research Goals:
  - Support rigorous evaluation of “natural experiments” in healthcare
  - Identify what works for whom in actual clinical practice with diverse populations, and/or patients with multiple co-morbidities
  - Provide data to more rapidly inform clinicians, healthcare systems, employer/purchasers, and policy makers

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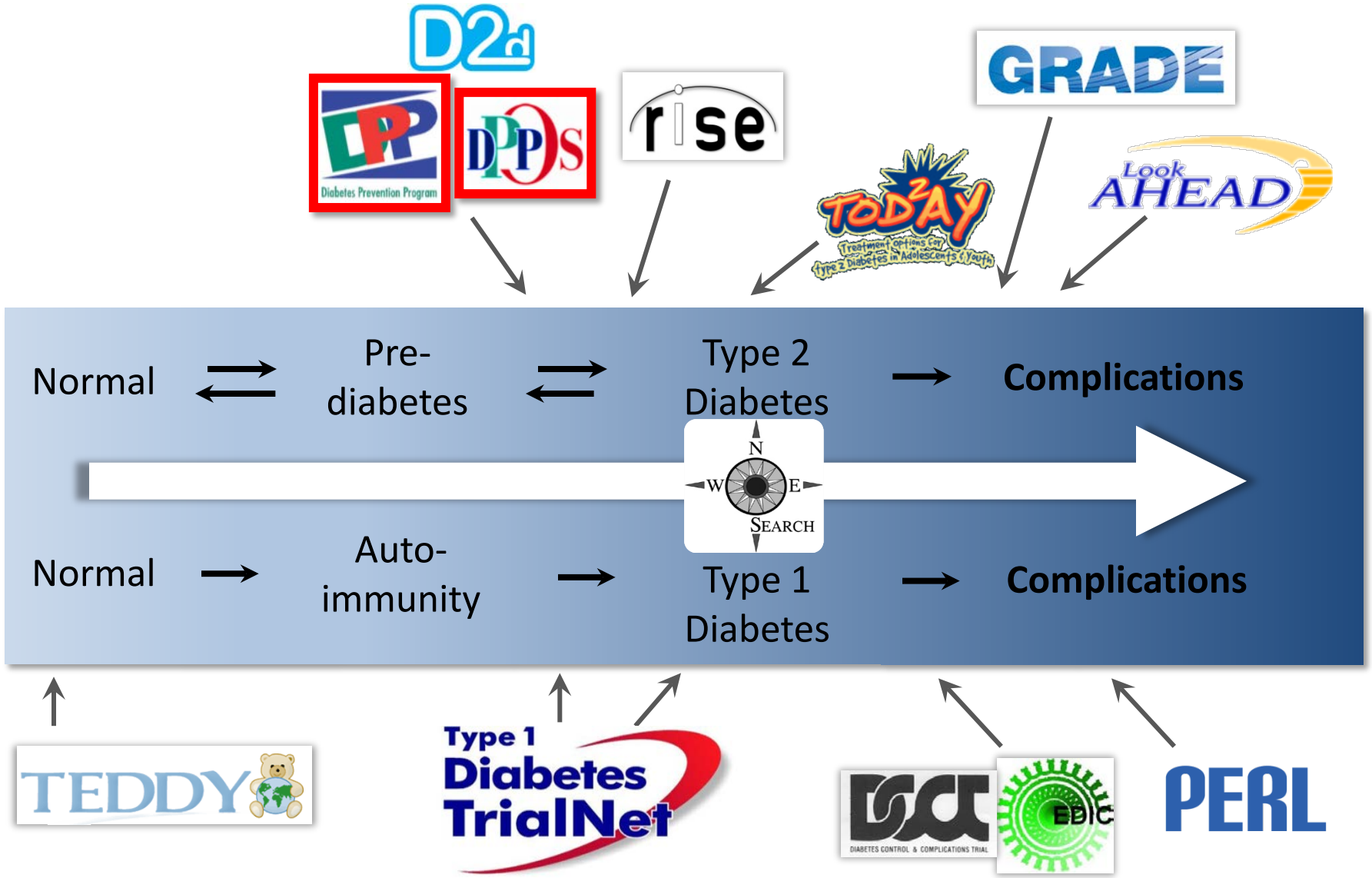
NIDDK Clinical Studies: Diabetes



New Networks Facillitating Research

NIH HCS Research Collaboratory

Clinics throughout the United States

PATIENT CARE

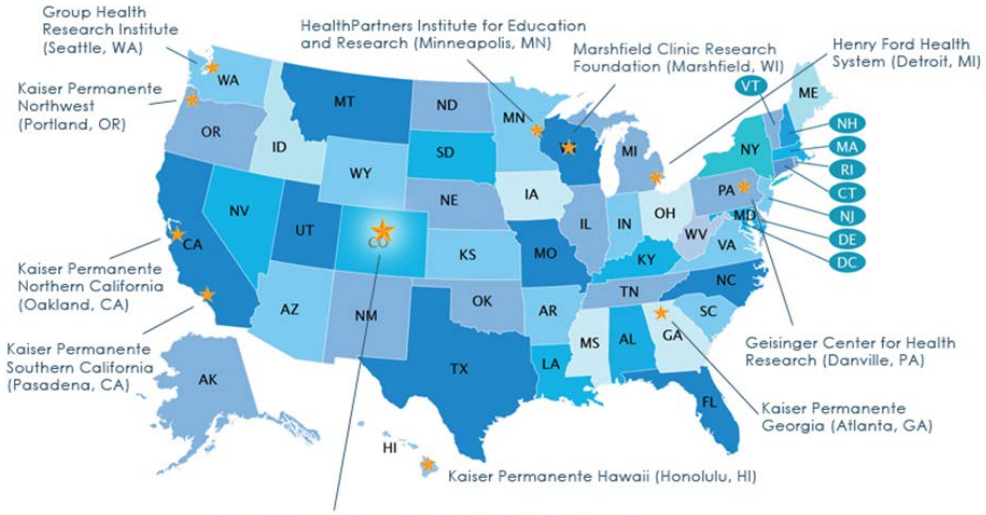
HEALTH CARE DELIVERY ORGANIZATIONS

RESEARCH

Leverage and expand capabilities to enable:

- Pragmatic Trials
- New Technologies

SUPREME-DM



What will PCORnet do for research?

pcornet

The National Patient-Centered Clinical Research Network

NIDDK Central Repositories
Resource Created in 2003

- **Database repository:**
  - Maintain archival datasets,
  - Respond to queries about data, stored samples
- **Biosample repository:**
  - Processing and archival storage of biological specimens
- **Genetics repository:**
  - Create immortalized cell lines, DNA extraction

NIDDK Central Repositories' Holdings

- **Samples and data stored from >50 major multi-site clinical studies in diabetes, digestive, kidney, liver, and urologic diseases**
- **Samples and data stored from 15 multi-site DEM clinical studies in diabetes**

Total Number of Samples:

NIDDK	DEM
8,324,372	4,707,979

National Institute of Diabetes and Digestive and Kidney Diseases

Oversight of Repository Samples

- **NIDDK has custodianship of all samples and data transferred to the Repositories and no IP protections are attached**
- **The Steering Committee of each study or study group has control of the samples and data during a "proprietary period"**

Requesting Usage of Repository Samples and Evaluation Process

- **Samples and data requested through web**
- **Data access and DNA (renewable)**

  Reviewed by NIDDK staff
- **Requests for biosamples (not renewable)**

  PAR-11-306: NIDDK Central Repositories Non-renewable Sample Access **(X01)**

  Reviewed by external panel for scientific merit

National Institute of Diabetes and Digestive and Kidney Diseases

Funding Opportunities Announcements for Clinical Consortia Resources

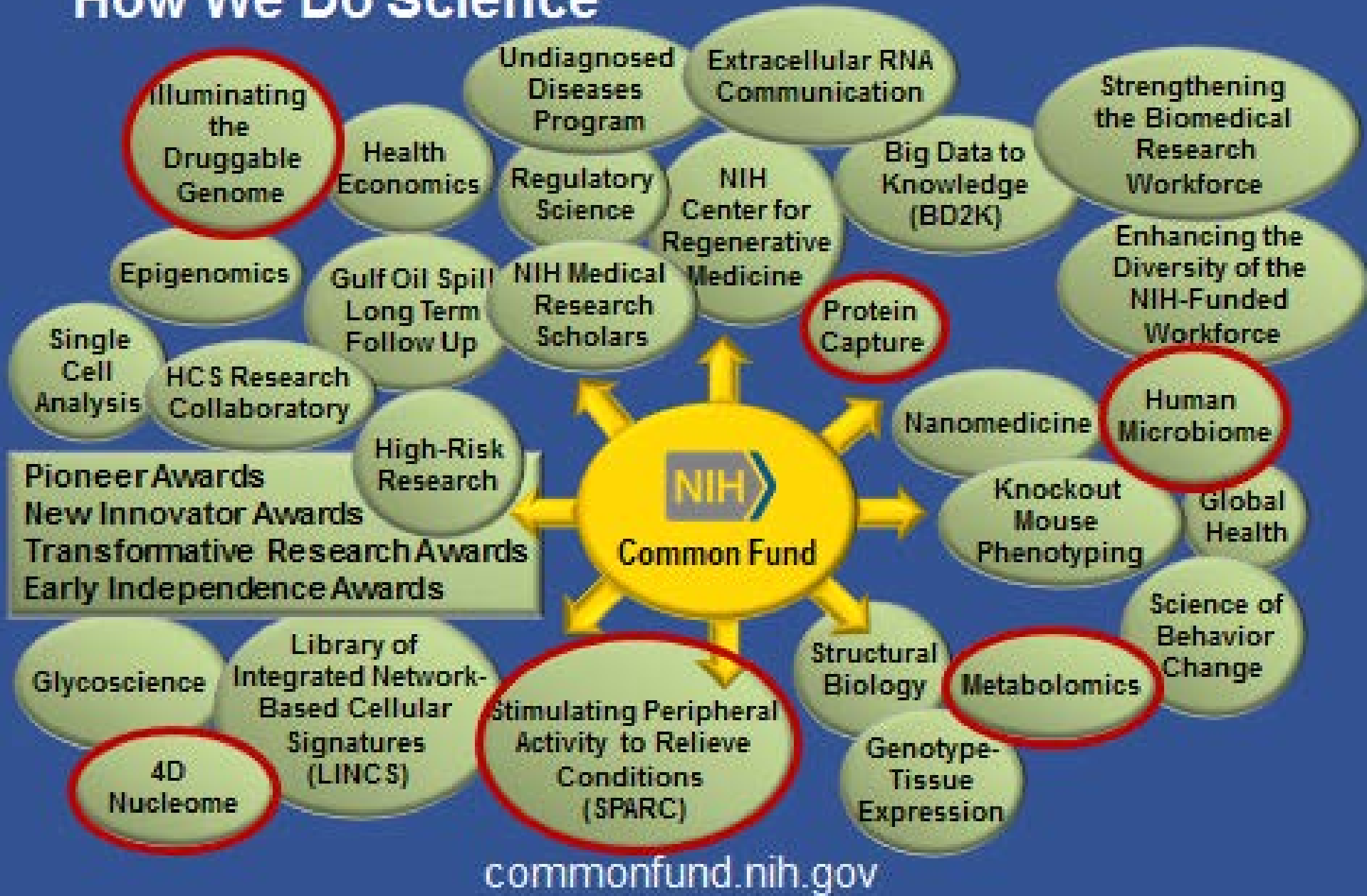
NIDDK

- **PAR-12-265**: Ancillary Studies to Major Ongoing Clinical Research Studies to Advance Areas of Scientific Interest within the Mission of the NIDDK **(R01)**
- **PAR-13-228**: Biomarkers for Diabetes, Digestive, Kidney and Urologic Diseases Using Biosamples from the NIDDK Repository **(R01)**

T1D

- **PAR-14-064** Research Using Subjects from Selected Type 1 Diabetes Clinical Studies **(DP3)**
- **PAR-14-065**: Research Using Biosamples from Selected Type 1 Diabetes Clinical Studies **(DP3)**

Common Fund Programs Aim To Transform How We Do Science



commonfund.nih.gov

The Human Microbiome Project


INSIGHT FEATURE NATURE|Vol 449|18 October 2007|

nature

The Human Microbiome Project

Peter J. Turnbaugh, Ruth E. Ley, Micah Hamady, Claire M. Fraser-Liggett, Rob Knight & Jeffrey I. Gordon


ARTICLE 14 JUNE 2012 | VOL 486

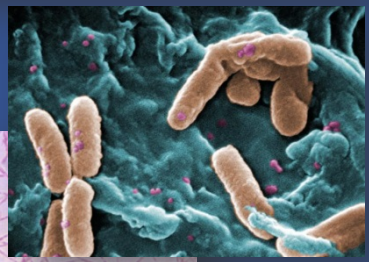
A framework for human microbiome research

The Human Microbiome Project Consortium*


ARTICLE 14 JUNE 2012 | VOL 486

Structure, function and diversity of the healthy human microbiome

The Human Microbiome Project Consortium*



Co-Chaired by Directors:
NIAID, NIDDK, NHGRI, NIDCR

Presidential Early Career Award for Scientists and Engineers (PECASE) Recipient

Dr. Shingo Kajimura
of the University of California, San Francisco

National Institute of Diabetes and Digestive and Kidney Diseases

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and Kidney Diseases

DIABETES RESEARCH CENTERS

Diabetes Centers EXECUTIVE COMMITTEE

2014 Roster

Jean Schaffer, Washington University in St. Louis (Chair)

Mimmo Accili, Columbia University

Larry Chan, Baylor College of Medicine

Martin Myers, University of Michigan

Jerry Olefsky, University of California, San Diego

Jeff Pessin, Albert Einstein College of Medicine

Jerry Palmer, University of Washington
NIDDK Advisory Council liaison

DIABETES CENTERS EXECUTIVE COMMITTEE REPORT 2013-2014

During 2013-2014 the Diabetes Center Executive Committee included the following Center directors:

Center Director	Program	Lines of communication
Jeff Pessin	Einstein	BADERC, Joslin
Martin Meyers	Michigan	Chicago, Vanderbilt
Jerry Olefsky	UCSD/UCLA	Colorado, UCSF
Jerry Palmer	U Washington	DK National Advisory Council
Jean Schaffer (chair)	Washington U	UAB, Penn
Mimmo Accili	Columbia	Yale, DK National Advisory Council
Larry Chan	Baylor	JHU/UMD

Conference calls were held approximately every other month and covered the following topics:

Review of the last Director's Meeting in May 2013: Overall the meeting was considered a success.

Planning 2014 Annual meeting: The agenda for the annual meeting was discussed. One topic suggested that we will discuss today is the sometimes different interpretations of RFAs and guidelines between applicants and reviewers and how to communicate best practices for the centers model.

Reporting DRC research publications: We have transitioned from individual center-generated publication lists to MyNCBI-generated publication lists on non-competing and competing applications. The only publications that will on the MyNCBI-generated list are those that cite the DRC grant number and link through MyNCBI. While this process should facilitate generation of reports to NIH, several considerations are worth noting:

1. Associated non-compliant publications will delay awards.
2. Publications that used center resources, but fail to cite the grant, can be affiliated post-hoc, but otherwise remain non-reported.
3. Some publications that contain acknowledgment of the DRC center may not automatically link through MyNCBI.
4. Centers will need to maintain information regarding specific core utilization because it is not possible to link to this in MyNCBI.

RPPR format for progress reports: Effective10/17/14, the RPPR format will be required for annual progress reports.

Executive Committee Membership: The Committee's goal is to improve communication between Center leadership and program staff at NIDDK. We welcome participation and suggestions of topics for discussion. Center Directors interested in serving should contact Jim Hyde. Mimo Accili, Larry Chan, and Jean Schaffer will rotate off, and George King and Tim Garvey will join the committee. Martin Myers will chair the committee.

DIABETES RESEARCH CENTERS

The Medical Student Research Program in Diabetes is sponsored by the National Institutes of Health through the NIDDK and allows medical students to conduct research under the direction of an established scientist in the areas of diabetes, hormone action, physiology, islet cell biology or obesity at an institution with one of the NIDDK-funded Research Centers during the summer between the first and second year or second and third year of medical school.

The goal of the Program is to encourage medical students to consider research in diabetes and its complications as a career and to educate students about diabetes. Program Consultants assist students in selecting an appropriate research project and preceptor. **Prior research experience is not required**. In addition to working on his/her own research project, each student views web-cast seminars addressing clinical and research aspects of diabetes mellitus and its complications.

Students spend 2-3 months working on their research project at a Diabetes Center and receive a weekly stipend. Commencement dates and conclusion for the program are reasonably flexible; however, all students will present their results at a research symposium in Nashville, TN (travel funds provided).

You must be a U.S. citizen or a permanent resident to participate in this program.

Questions regarding the Program should be directed to:

NIDDK Medical Student Research Program in Diabetes
E-mail: niddk.diabetes.student.research@vanderbilt.edu

The NIDDK Medical Student Research Program in Diabetes is funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Medical Schools of Students Participating in the 2014 NIDDK Medical Student Research Symposium

Boston University
Brown University
Case Western Reserve University
Columbia University
Dartmouth University
Eastern Virginia Medical School
Florida Atlantic University
George Washington University
Georgetown University
Indiana University
Jefferson Medical College
Loma Linda University
Loyola University - Chicago
Marshall University
Medical College of Georgia
Medical University of South Carolina
Meharry Medical College
Mercer University
Michigan State University
Midwestern University - Glendale
National University of Ireland - Galway
New York Medical College
Northeast Ohio Medical University
Pennsylvania State University
Ponce School of Medicine
Rosalind Franklin University
Rush Medical College
Rutgers NJ Medical School - Newark
Rutgers Robt Wood Johnson - Piscataway
Saint Louis University
San Juan Bautista School of Medicine
Stony Brook Medicine
Texas A&M Health Science Center
Texas Tech University
Thomas Jefferson Medical College
Tufts University
Tulane University
University Alabama - Birmingham
University Missouri - Kansas City
University of Arkansas
University of California - Los Angeles
University of Central Florida
University of Connecticut
University of Hawai'i
University of Illinois - Champaign-Urbana
University of Illinois - Chicago
University of Iowa
University of Kansas
University of Kentucky
University of Louisville
University of Maryland
University of Miami
University of Michigan
University of Missouri - Columbia
University of Nebraska
University of Nevada
University of North Carolina
University of North Dakota
University of Oklahoma
University of Pennsylvania
University of Puerto Rico
University of Rochester
University of Southern California
University of Tennessee
University of Toledo
University of Vermont
University of Washington
Washington University
Wayne State University

Application and Program Statistics
NIDDK Medical Student Symmer Research Program
Summer 2013 and 2014

Applications:

Year 2014 - 551 applications from 137 medicalschools for 87 positions
Year 2013 - 568 applications from 138 medical schools for 88 positions
Year 2012 - 395 applications from 114 medical schools for 78 positions
Year 2011 - 486 applications from 111 medical schools for 76 positions
Year 2010 - 431 applications from 104 medical schools for 68 positions
Year 2009 - 197 applications from 82 medical schools for 56 positions

2013 Program				2014 Program		
Center	# participants	# participants from medical schools associated with a DERC/DRTC	# applicants listing Center as #1, 2, 3 choice	# participants	# participants from medical schools associated with a DERC/DRTC	# applicants listing Center as #1 or 2 choice
AECOM	2	2	115			
Baylor	2	1	73			
Boston Area	5	0	69	7*	0	79
Columbia	7	0	185	7*	1	148
JHopkins/Univ MD	8*	0	124	8*	0	95
Joslin	6	1	94	9*	0	86
UAB	6	5	43	6	4	15
UCLA/UCSD	8*	0	158	5*	0	153
UCSF	4	2	135	4	1	94
Univ Chicago	4	0	130	4	0	102
Univ Michigan	9*	2	74	9*	3	44
Univ Pennsylvania	6	1	111	4	2	86
Univ Washington	6	0	68	7*	1	48
Vanderbilt - NIDDK	6	0	100	6	0	81
Washington Univ	4	1	54	6*	1	27
Yale	4	0	66	5*	1	44
Sub-total	87**			87		
Vanderbilt - T35 grant	32			32		
TOTAL	119			119		

*indicates students added with support from the Diabetic Complications Consortium (DCC)
**indicates student withdrew too late to be replaced

Student Participant Demographics 2014		US Medical School Enrollment 2013**		US Census 2010	
Race		Race		Race	
African American	6 (5%)	African American	5743 (7%)	African American	38.9 million (13%)
American Indian	2 (<1%)	American Indian	651 (<1%)	American Indian	2.9 million (0.9%)
Asian	41 (35%)	Asian	18530 (22%)	Asian	14.7 million (5%)
Caucasian	46 (39%)	Caucasian	48109 (58%)	Caucasian	173.1 million (56%)
Hispanic	18 (15%)	Hispanic	7581 (9%)	Hispanic	50.5 million (16%)
Native Hawaiian or Pacific Islander	0	Native Hawaiian or Pacific Islander	219 (<1%)	Native Hawaiian or Pacific Islander	0.5 million (0.2%)
Other/No answer	6 (5%)	Other/No answer	4078 (5%)	Other/two races	28.1 million (9%)
Gender		Gender		Gender	
Female	78 (66%)	Female	38948 (46.6%)	Female	156,964,000 (50.8%)
Male	41 (34%)	Male	44524 (53.4%)	Male	151,781,000 (49.2%)

**The category totals may not add to the total enrollees since a person could designate multiple categories.
Source: AAMC

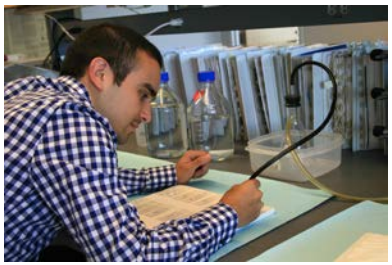
Residency of NIDDK Medical Student Participants

Specialty	2010 Participants (100% response rate)	2011 Participants (76% response rate)	National Average (2014 data)*
Internal Medicine	26%	25%	25%
Pediatrics	13%	23%	10%
Anesthesiology	3%	7%	4%
Dermatology	3%	2%	<1%
Emergency Medicne	8%	9%	7%
Family Medicine	4%	5%	12%
Neurology	2%	2%	2%
Ob/Gyn	6%	0%	5%
Ophthalmology	7%	2%	**
Otolaryngology	7%	2%	1%
Pathology	4%	0%	2%
Peds/Psych/Child Psych	2%	0%	<1%
Physical Medicine and Rehabilitation	0%	4%	<1%
Psychiatry	2%	4%	5%
Radiation Oncology	3%	2%	<1%
Radiology	5%	7%	1%
Surgery (General)	5%	4%	5%
Urology	0%	2%	1%

* 2014 NRMP data; some subspecialties (e.g., surgical) not included

** Information not available; Ophthalmology residency applicants must complete PGY-1 prerequisite training.

NIDDK Medical Student Research Program in Diabetes



- Sixth summer (2009-2014)
- 4-8 students/Diabetes Center
- Funding
  - Supplement to T32s at Diabetes Centers
  - Diabetic Complications Consortium

DIABETES RESEARCH CENTERS

NIDDK Medical Student Research Program - Summer 2014

November

- Recruit/advertise
  - Deans of all US Medical schools
  - First-year class presidents of all US Medical schools
  - AAMC email (~1500 individuals)
  - National Hispanic Medical Association
  - Association of Native American Medical Students
  - Electronic/Web site

March-April

- Students apply and select 2 Diabetes Research Centers
- Each Center reviews and lists students
- "Matching" of students/centers

DIABETES RESEARCH CENTERS

Some Stats – See Handout

	2009	2010	2011	2012	2013	2014
# applicants	197	431	486	395	568	551
# medical schools	82	104	111	114	138	137
# participants	83	92	101	102	114	119^
# medical schools	40	49	49	58	65	69^

^ Includes students supported by Diabetes Complications Consortium and students in Vanderbilt T35 program

Demographics

Student Participant Demographics 2014		US Medical School Enrollment 2013**		US Census 2010	
Race		Race		Race	
African American	6 (5%)	African American	5743 (7%)	African American	38.9 million (13%)
American Indian	2 (<1%)	American Indian	651 (<1%)	American Indian	2.9 million (0.9%)
Asian	41 (35%)	Asian	18530 (22%)	Asian	14.7 million (5%)
Caucasian	46 (39%)	Caucasian	48109 (58%)	Caucasian	173.1 million (56%)
Hispanic	18 (15%)	Hispanic	7581 (9%)	Hispanic	50.5 million (16%)
Native Hawaiian or Pacific Islander	0	Native Hawaiian or Pacific Islander	219 (<1%)	Native Hawaiian or Pacific Islander	0.5 million (0.2%)
Other/No answer	6 (5%)	Other/No answer	4078 (5%)	Other/two races	28.1 million (9%)
Gender		Gender		Gender	
Female	78 (66%)	Female	38948 (46.6%)	Female	156,964,000 (50.8%)
Male	41 (34%)	Male	44524 (53.4%)	Male	151,781,000 (49.2%)

Additional Students Supported by the Diabetic Complications Consortium (DCC)

	2013	2014
# Additional Students	10	19
Centers Accepting Students	3	10/14

NIDDK Medical Student Research Program - Summer 2014

May - June - July

- 8-12 weeks of research
- Webcasts

August

- Research symposium
- Poster presentations (some moderated)

DIABETES RESEARCH CENTERS

Summer Program in Obesity, Diabetes and Nutrition Related Research Training - T35 at Maryland

NIDDK Medical Student Research Symposium

- Visiting Professors
  - Andrea Cherrington, M.D. (UAB)
  - Richard Kibbey, M.D., Ph.D. (Yale)
- Career pathways/advice
  - Residency Program Directors

DIABETES RESEARCH CENTERS

Program Oversight

- Advisory Committee
  - Art Castle (NIDDK)
  - James Hyde (NIDDK)
  - Steven Kahn (University of Washington)
  - Louis Philipson (University of Chicago)
  - Mike Rickels (Penn)
  - Fred Wondisford / Sally Radovick (Johns Hopkins)

Evaluation, Challenges, Items for Discussion

- Students and centers mostly satisfied
  - Student interactions at some Centers
- NIDDK says… (Art Castle, Jim Hyde)
- Number of students applying to some Diabetes Centers
- How to select the most meritorious students

of Applicants/Research Center

2013 Program				2014 Program		
Center	# participants	# participants from medical schools associated with a DERC/DRTC	# applicants listing Center as #1, 2, 3 choice	# participants	# participants from medical schools associated with a DERC/DRTC	# applicants listing Center as #1 or 2 choice
AECOM	2	2	115			
Baylor	2	1	73			
Boston Area	5	0	69	7*	0	79
Columbia	7	0	185	7*	1	148
JHopkins/Univ MD	8*	0	124	8*	0	95
Joslin	6	1	94	9*	0	86
UAB	6	5	43	6	4	15
UCLA/UCSD	8*	0	158	5*	0	153
UCSF	4	2	135	4	1	94
Univ Chicago	4	0	130	4	0	102
Univ Michigan	9*	2	74	9*	3	44
Univ Pennsylvania	6	1	111	4	2	86
Univ Washington	6	0	68	7*	1	48
Vanderbilt - NIDDK	6	0	100	6	0	81
Washington Univ	4	1	54	6*	1	27
Yale	4	0	66	5*	1	44
Sub-total	87**			87		
Vanderbilt - T35 grant	32			32		
TOTAL	119			119		

DIABETES RESEARCH CENTERS

Evaluation, Challenges, Items for Discussion

- Students and centers mostly satisfied
  - Student interactions at some Centers
- NIDDK says… (Art Castle, Jim Hyde)
- Number of students applying to some Diabetes Centers
- How to select the most meritorious students
- Visiting professors - #
- Follow up
  - 1/3 do more research or present research

Residency Choice of Participants

Specialty	2010 Participants (100% response rate)	2011 Participants (76% response rate)	National Average (2014 data)*
Internal Medicine	26%	25%	25%
Pediatrics	13%	23%	10%
Anesthesiology	3%	7%	4%
Dermatology	3%	2%	<1%
Emergency Medicne	8%	9%	7%
Family Medicine	4%	5%	12%
Neurology	2%	2%	2%
Ob/Gyn	6%	0%	5%
Ophthalmology	7%	2%	**
Otolaryngology	7%	2%	1%
Pathology	4%	0%	2%
Peds/Psych/Child Psych	2%	0%	<1%
Physical Medicine and Rehabilitation	0%	4%	<1%
Psychiatry	2%	4%	5%
Radiation Oncology	3%	2%	<1%
Radiology	5%	7%	1%
Surgery (General)	5%	4%	5%
Urology	0%	2%	1%

National Institute of Diabetes and Digestive and Kidney Diseases

T2D GENETICS ACCELERATING MEDICINES PARTNERSHIP

NIDDK Diabetes Centers Meeting

September 10, 2014

Accelerating Medicines Partnership (AMP) Problem Statement

A significant cause of late stage drug development failures, whose incidence has increased 165% since the early 1990s*, is poor understanding of targets

Problem

Insufficient understanding of targets/pathways involved in diseases → R&D investment against the wrong targets

No single group can change this efficiently and quickly

- Scale beyond abilities of even large academic labs
- Benefits too diffuse for any one pharma co. to pursue
- Necessary skills span these groups

Solution

Systematic characterization of complex, heterogeneous diseases, combining clinical & molecular information to:

- Facilitate rational selection of targets
- Identify patients and specific subpopulations for trials and customized prophylaxis, diagnosis and treatment decisions

Work collaboratively across government, academia and industry to harness collective capabilities, scale & resources

*Source: Pammoli et. al, "The productivity crisis in pharmaceutical R&D" Nature Reviews Drug Discovery June 2011

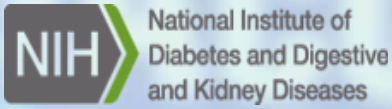
FNIH
Foundation for the National Institutes of Health

Proposed Partnerships & Strategies

Technical Group	Research plan topics	Estimated timeline & cost/year	Description
Schizophrenia & related disorders	Prodrome	5 yrs, $8 M	Conduct longitudinal study in at-risk cohorts to identify phenotypic/genetic markers that predict conversion to psychosis & provide a regulatory approval path
	Deep sequencing (allelic series)	3 yrs, $3 M	Validate potential gene targets through deep sequencing to identify highly penetrant rare alleles
Alzheimer's Disease	Embed exploratory biomarkers in clinical trials	5 yrs, $10 M	Embed (ie, incentivize the use of) exploratory biomarkers in upcoming clinical trials to develop biomarkers of disease progression and surrogate endpoints
	Systems biology on human tissue	3 yrs, $2 M	Conduct systems biology in human brain samples to identify genetic nodes and networks linked to AD to support target identification and validation
Type II Diabetes	Knowledge portal	5 yrs, $4 M	Create a knowledge portal containing comprehensive T2DM data sets to enable elucidation of relationships between genetic variation and risk of T2D and its complications & target identification
	Deep genetics	5 yrs, $4 M	Generate human genetic data for high priority targets of interest to inform potential drug efficacy and safety and elucidate disease mechanisms
	Call-back studies (deep phenotyping)	5 yrs, $2 M	Conduct deep hypothesis-driven phenotyping on patients with novel T2DM LoF/GoF variants to identify and validate potential targets
RA, Lupus & related disorders	Disease deconstruction	5, yrs $11 M	Conduct extensive profiling of specific immune modules in informative cohorts to create a pathway/network map of RA & Lupus to identify targets; targets then validated via RNAi - Informative cohorts undergo similar profiling, with differences in # of timepoints and tissues samples analyzed accounting for differences in cost
	Early RA	$1 M	
	Established RA	$4 M	
	Lupus Nephritis	$3 M	
	Skin Lupus	$3 M	

FUNDING PARTNERS T2D AMP

- **NIH**



- **PHARMA**

- **NON-PROFITS**

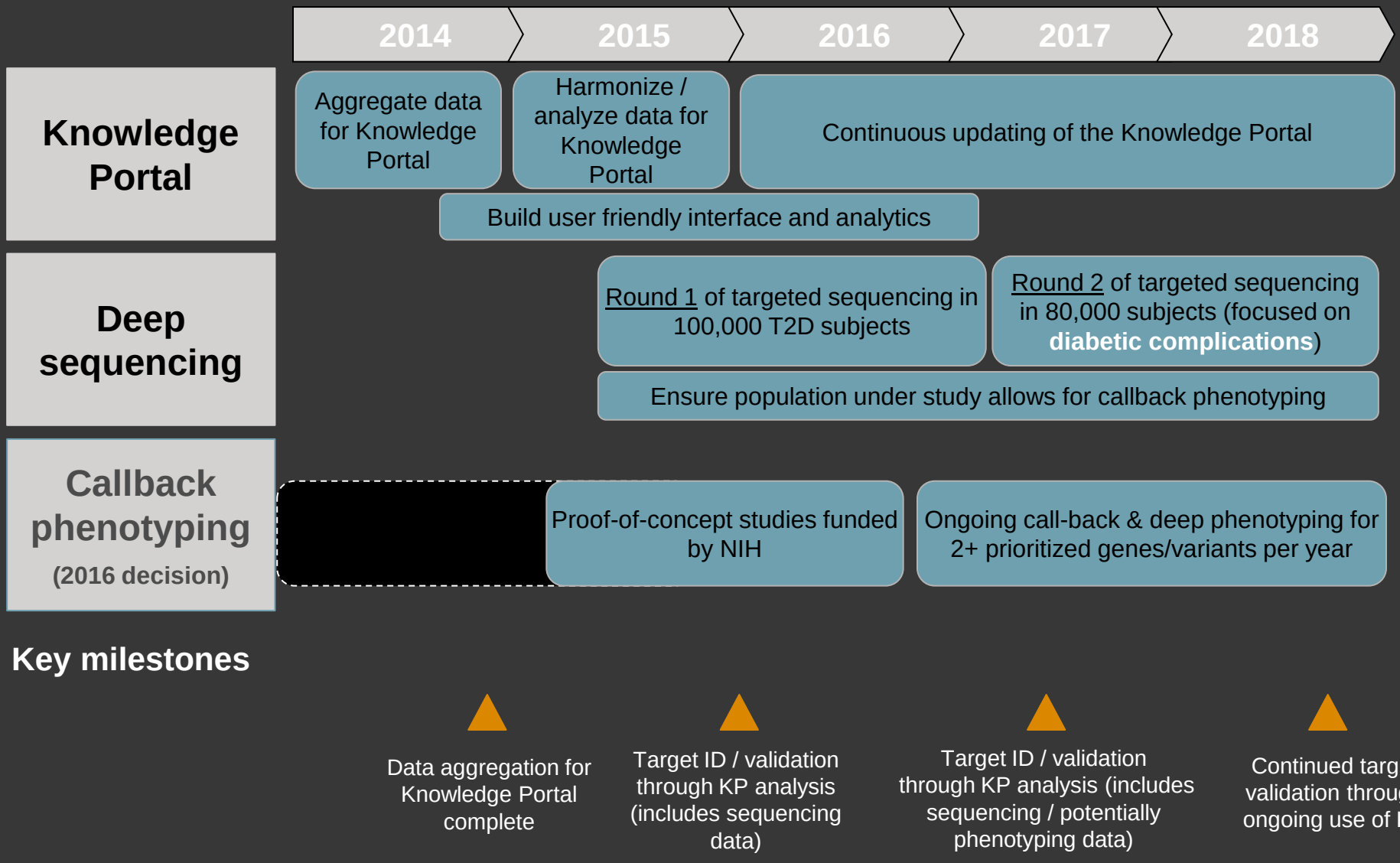
GOALS

- **Follow Footprints of Disease Risk in our Genes to Identify New Pathways for Therapeutic Development**
- **Increase the Number of Investigators Who Can Contribute to Target Discovery and Validation**
- **Leverage All Available Resources to Strengthen Evidence for Novel Targets (Epigenetics, Expression QTLs,…)**
- **Support Clinical Studies on Individuals with Genotypes of Particular Interest for Target Validation**

STRATEGY

- **Build Knowledge Portal to make genetic data and analytical tools available to the broad scientific community**
- **Expand available Genetic and Phenotype data with broad representation across ethnic/racial groups**
- **Validate targets with in depth physiological studies in individuals with defined variants**

AMP T2D TIMELINE




Drug Development
Non-Profit
Lupus
disease
cures
Molecules
science
Accelerating
collaboration
treatments
Alzheimer's
health
Targets
Public
Patients
Medicines
clinical trials
Private
Partnership
Rheumatoid Arthritis
Type 2 Diabetes
research

The 4D Nucleome Common Fund Program

4DN Co-Chairs: Dinah S. Singer, NCI
Phil Smith, NIDDK

4DN Coordinators: Judy Mietz, NCI
Olivier Blondel, NIDDK

National Institutes of Health
Office of Strategic Coordination - The Common Fund

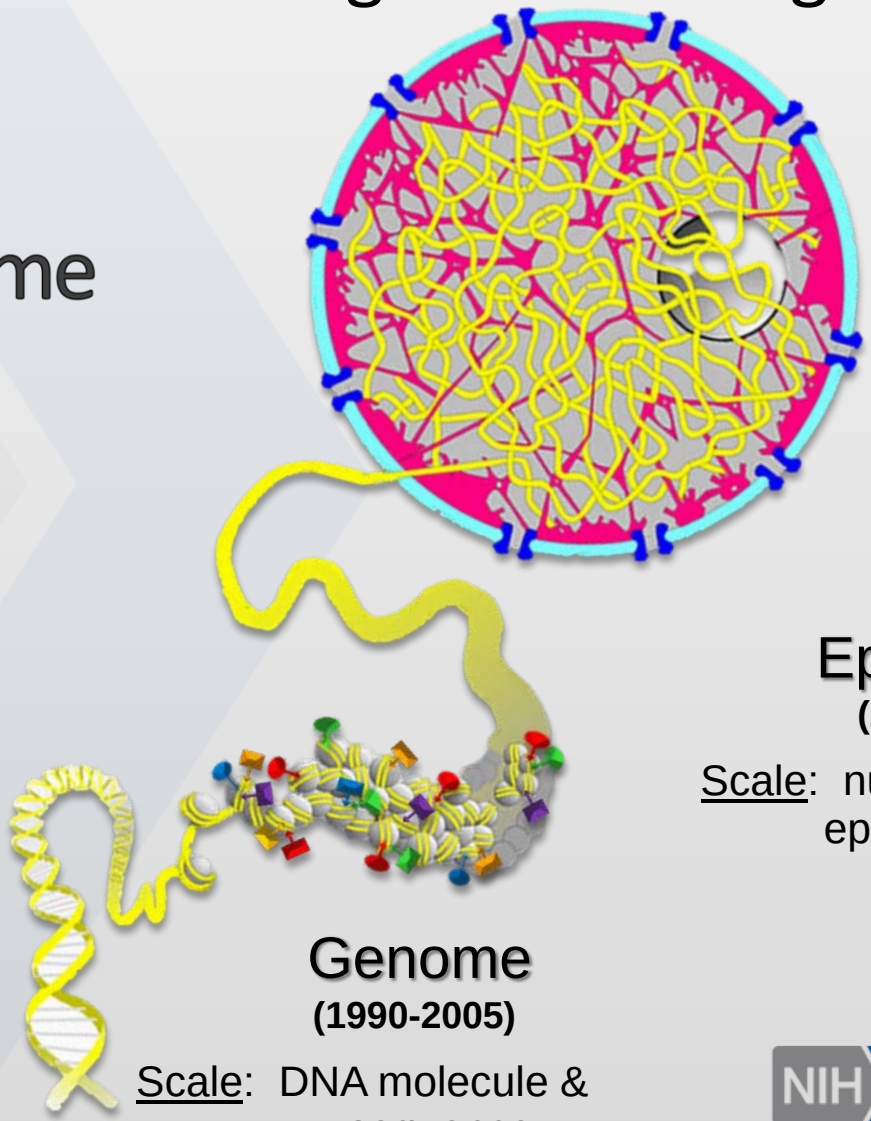
Finishing the Job:
Understanding Genome Organization

4D Nucleome

ENCODE

ROADMAP epigenomics PROJECT

Human Genome Project



3D Nucleome
(2015-2022?)

Scale: cell nucleus & chromatin domains

Epigenome
(2005-2015)

Scale: nucleosome & epigenetic marks

Genome
(1990-2005)

Scale: DNA molecule & sequence

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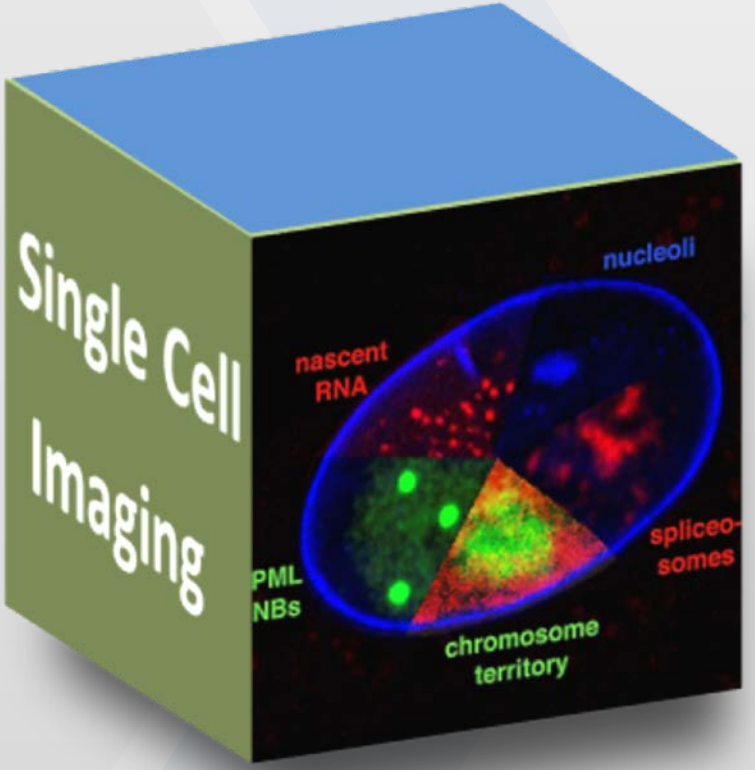
Mounting Evidence:
The Third Dimension Matters



- The spatial distribution of the genome is not random;
- Chromatin is organized in chromosomal neighborhoods associated with nuclear structures of unknown function;
- This organization is dynamic in time and space.

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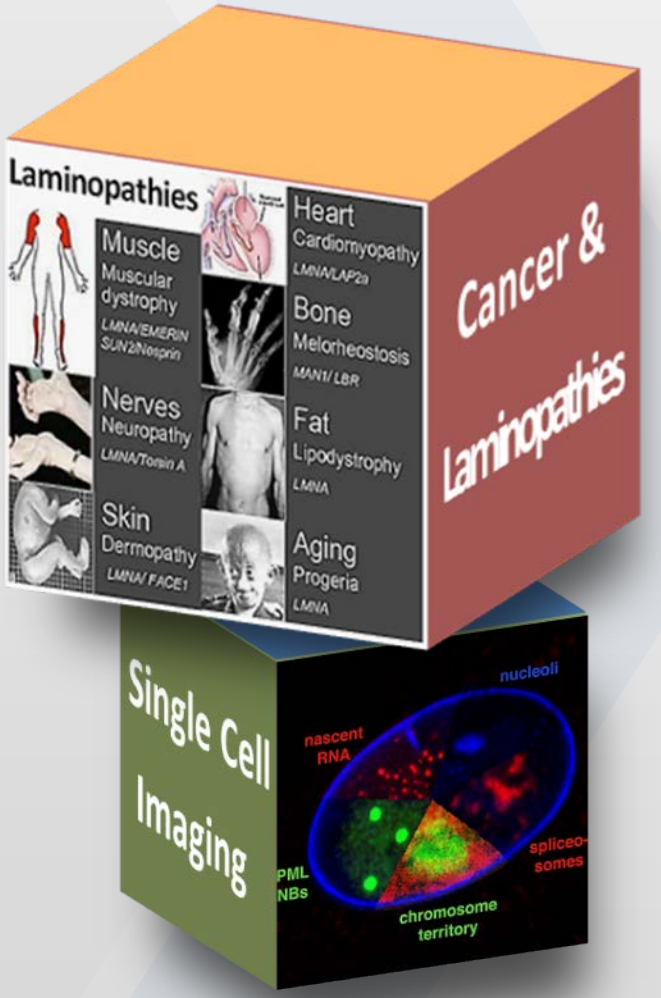
4D Nucleome

Mounting Evidence:
The Third Dimension Matters



- Alterations of genome organization are associated with laminopathies, cancer and premature aging syndromes;

- Features are often cell- or tissue-specific, and include:
  - loss of genome integrity;
  - global changes in epigenetic marks;
  - widespread modifications of gene expression programs.

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Mounting Evidence:
The Third Dimension Matters

- 93% of disease-associated genetic variants reside in non-coding regulatory sequences with unknown targets;

- Mapping physical interactions between regulatory variants and promoters would help identify disease-associated target genes;

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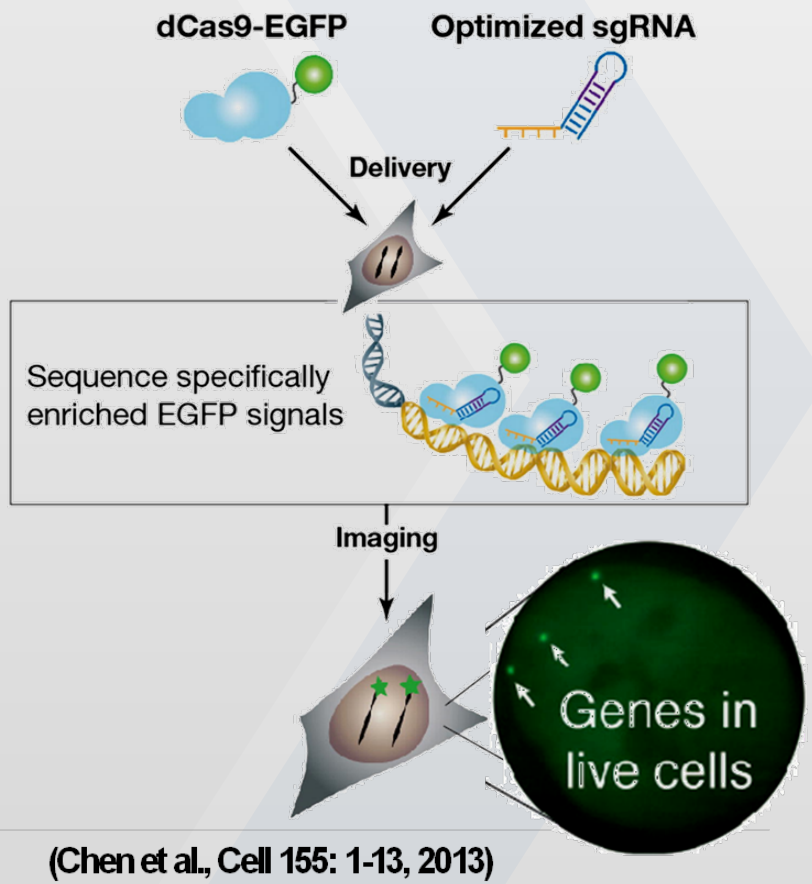
4D Nucleome

Mounting Evidence:
The Third Dimension Matters

- Chromosome Conformation Capture (3C) allows mapping of long-range looping interactions between genes and regulatory elements.

- First-generation maps suggest that the genome is organized in physically defined Transcription Associated Domains (TADs) and “transcription factories”.

A CRISPR Picture Of The Nuclear Genome



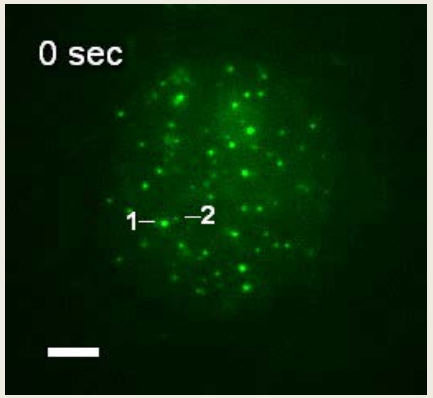
(Chen et al., Cell 155: 1-13, 2013)

The gene-editing CRISPR/Cas system can be used to:

- modify gene regions & regulatory elements in cells to test the organizational models inferred from the mapping of chromatin interactions;
- directly image genetic elements and follow them dynamically in live cells.

Imaging telomere dynamics:

(Lei Qi Lab, UCSF)



The 3rd Dimension Matters In Diabetes And Obesity As Well…

LETTER

doi:10.1038/nature13138

Obesity-associated variants within *FTO* form long-range functional connections with *IRX3*

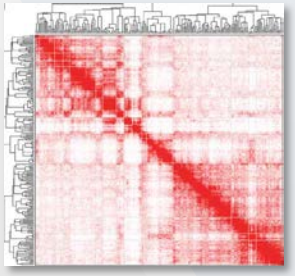
Scott Smemo[1]*, Juan J. Tena[2]*, Kyoung-Han Kim[3]*, Eric R. Gamazon[4], Noboru J. Sakabe[1], Carlos Gómez-Marín[2], Ivy Aneas[1], Flavia L. Credidio[1], Débora R. Sobreira[1], Nora F. Wasserman[1], Ju Hee Lee[3], Vijitha Puviindran[3], Davis Tam[3], Michael Shen[1], Joe Eun Son[5], Niki Alizadeh Vakili[3], Hoon-Ki Sung[5], Silvia Naranjo[2], Rafael D. Acemel[2], Miguel Manzanares[6], Andras Nagy[5], Nancy J. Cox[1,4], Chi-Chung Hui[3], Jose Luis Gomez-Skarmeta[2] & Marcelo A. Nóbrega[1]

nature genetics

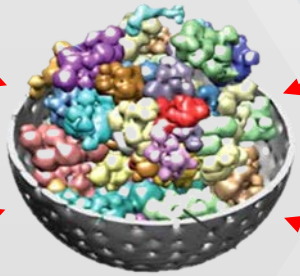
Pancreatic islet enhancer clusters enriched in type 2 diabetes risk-associated variants

Lorenzo Pasquali[1,2,14], Kyle J Gaulton[3–5,14], Santiago A Rodríguez-Seguí[1,13,14], Loris Mularoni[1,2], Irene Miguel-Escalada[6], İldem Akerman[1,2], Juan J Tena[7], Ignasi Morán[8], Carlos Gómez-Marín[7], Martijn van de Bunt[3–5], Joan Ponsa-Cobas[8], Natalia Castro[1,2], Takao Nammo[1,13], Inês Cebola[8], Javier García-Hurtado[1,2], Miguel Angel Maestro[1,2], François Pattou[9], Lorenzo Piemonti[10], Thierry Berney[11], Anna L Gloyn[4,5], Philippe Ravassard[12], José Luis Gómez-Skarmeta[7], Ferenc Müller[6], Mark I McCarthy[3–5] & Jorge Ferrer[1,2,8]

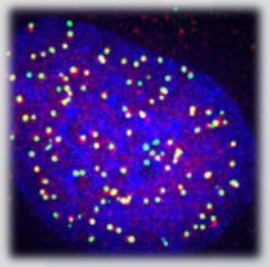
Deliverables of the 4DN Program



Global interactions between gene loci and regulatory elements.

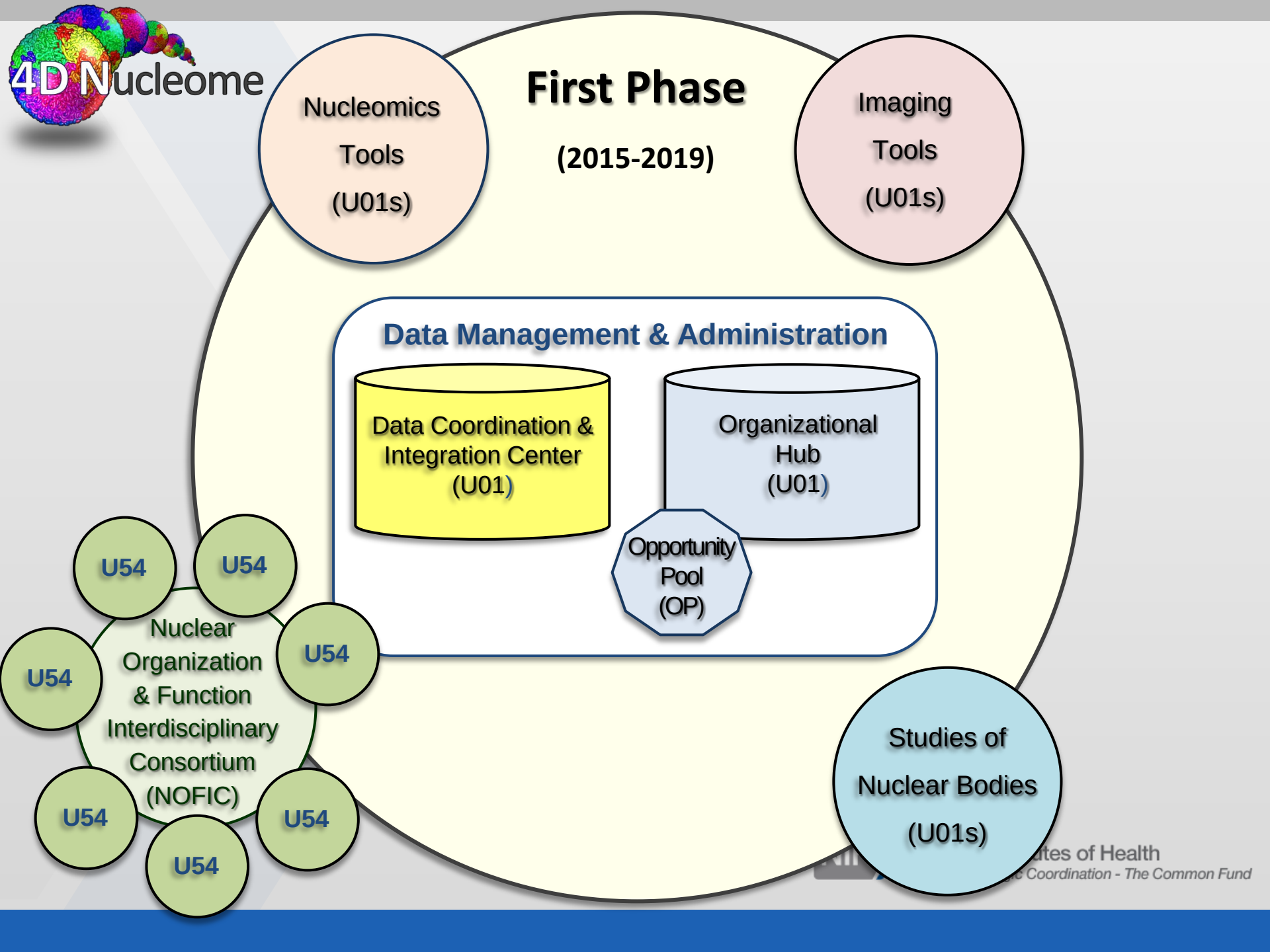


Predictive modeling of structure/function relationships.



Imaging dynamics of nuclear interactions in single cells.

- **Next generation tools** to explore the relationship between genome organization and function;
- **Reference maps** of the 3D organization of the genome in a variety of human cells/tissues and cell states;
- **Predictive models** of genome structure/function relationships;
- **Model validation** through controlled disruption of nuclear architecture and single-cell imaging.
- **Development of community standards** and metrics.


4D Nucleome
First Phase
(2015-2019)
Nucleomics Tools (U01s)
Imaging Tools (U01s)
Data Management & Administration
Data Coordination & Integration Center (U01)
Organizational Hub (U01)
Opportunity Pool (OP)
U54
U54
U54
U54
U54
U54
U54
Nuclear Organization & Function Interdisciplinary Consortium (NOFIC)
Studies of Nuclear Bodies (U01s)
tes of Health
Coordination - The Common Fund

4D Nucleome

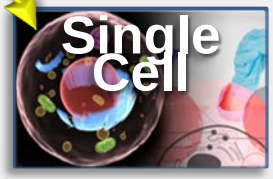
Second Phase

(2020-2023)

Validation of Structure/Function Relationships (U01s)

Nuclear Dynamics in Organs & Tissues (U01s)

Co-Funding?



NIH BD2K

ENCODE

Data Management & Administration

Data Coordination & Integration Center (U01)

Organizational Hub (U01)

Opportunity Pool (OP)

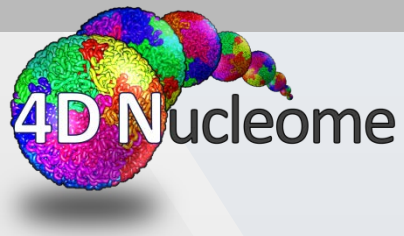
Co-funding with participating ICs

NIH

U54 U54 U54 U54 U54 U54 U54

Nuclear Organization & Function Interdisciplinary Consortium (NOFIC)

Role of 4DN in Development & Disease (R01s)



Questions?

Human Islet Research Network

HIRN Program Team:

Sheryl Sato; Kristin Abraham
Corinne Silva; Guillermo Arreaza-Rubin;
Olivier Blondel.

DEPARTMENT OF HEALTH & HUMAN SERVICES-USA

NIH National Institute of Diabetes and Digestive and Kidney Diseases

Human Islet Research Network

A Solution To The Uncertainty Of SDP Funding

- The Special Diabetes Program (SDP) is a Congressional Appropriation to support research on the prevention, treatment and cure of T1D.
- SDP-supported projects include research consortia (BCBC), large clinical studies (TrialNet, TEDDY) and many stand-alone initiatives.
- SDP appropriations are passed one fiscal year at a time, making multi-year support and long-term planning difficult.
- NIDDK is now allowed to use SDP funds from a given fiscal year to issue multi-year awards such as DP3s or UC4s.
- HIRN provides a funding platform for repeated and cumulative research investments in response to successive SDP appropriations.

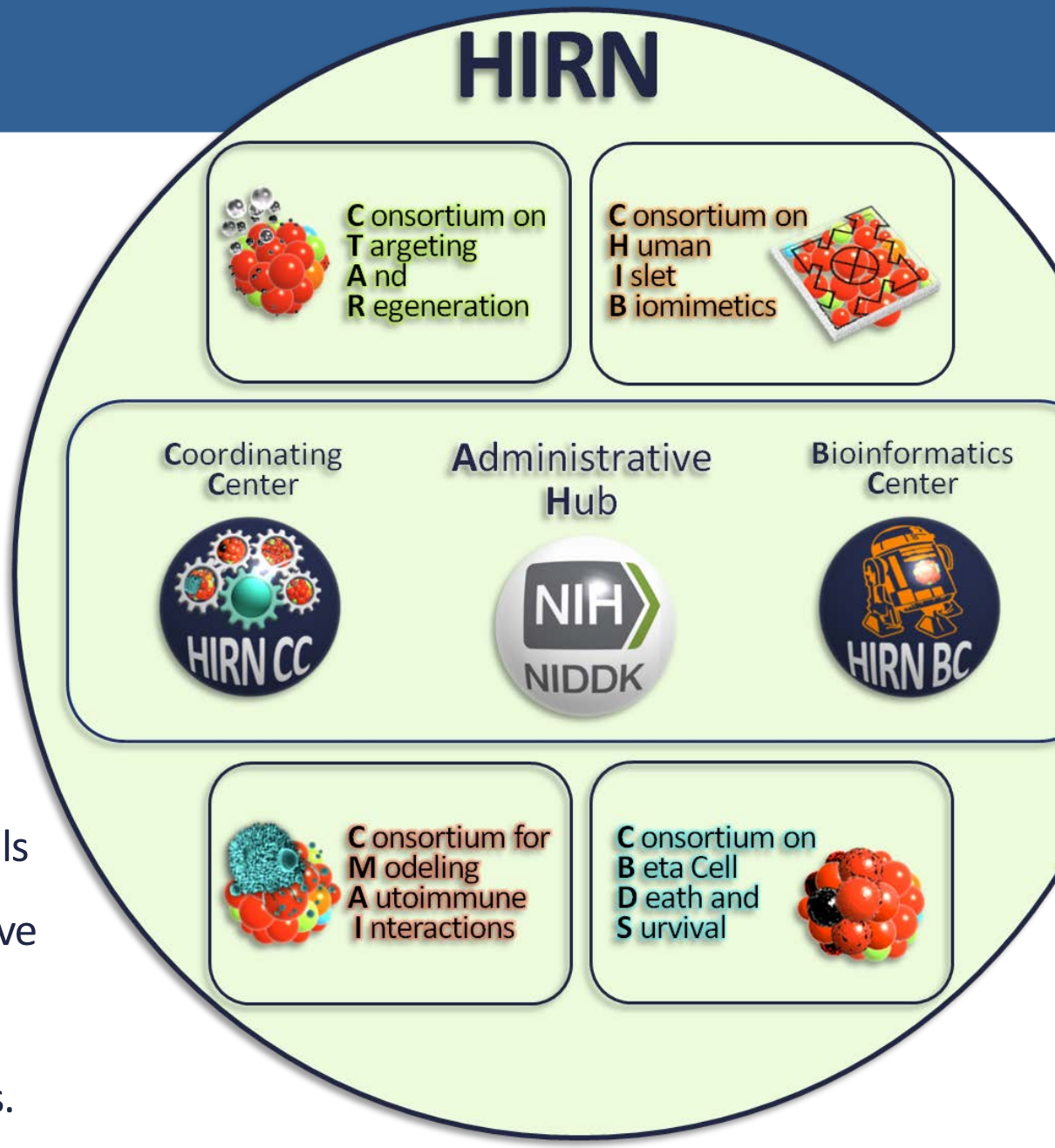
Human Islet Research Network

What is HIRN?

A network of small research consortia, each focused on a specific biological challenge.

HIRN's mission

To support collaborative translational research to understand how human beta cells are lost in T1D, and find innovative strategies to protect and/or to replace functional beta cell mass.

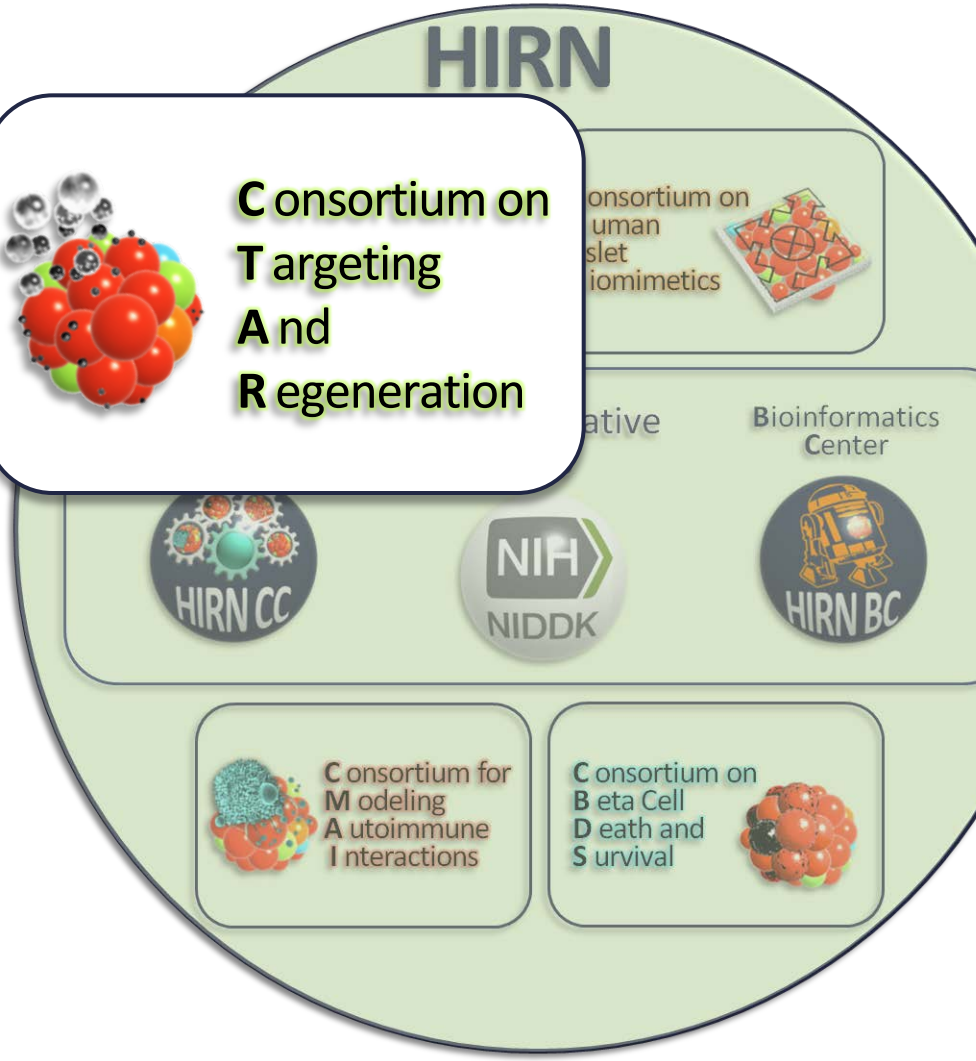


Consortium on Targeting And Regeneration

CTAR's mission

To increase functional human beta cell mass *in vivo* through controlled manipulation of beta cell replication or islet plasticity, reprogramming of adult cells into beta-like cells, or protection of beta cells from autoimmune destruction.

FY14 Investment: $14M/5yrs

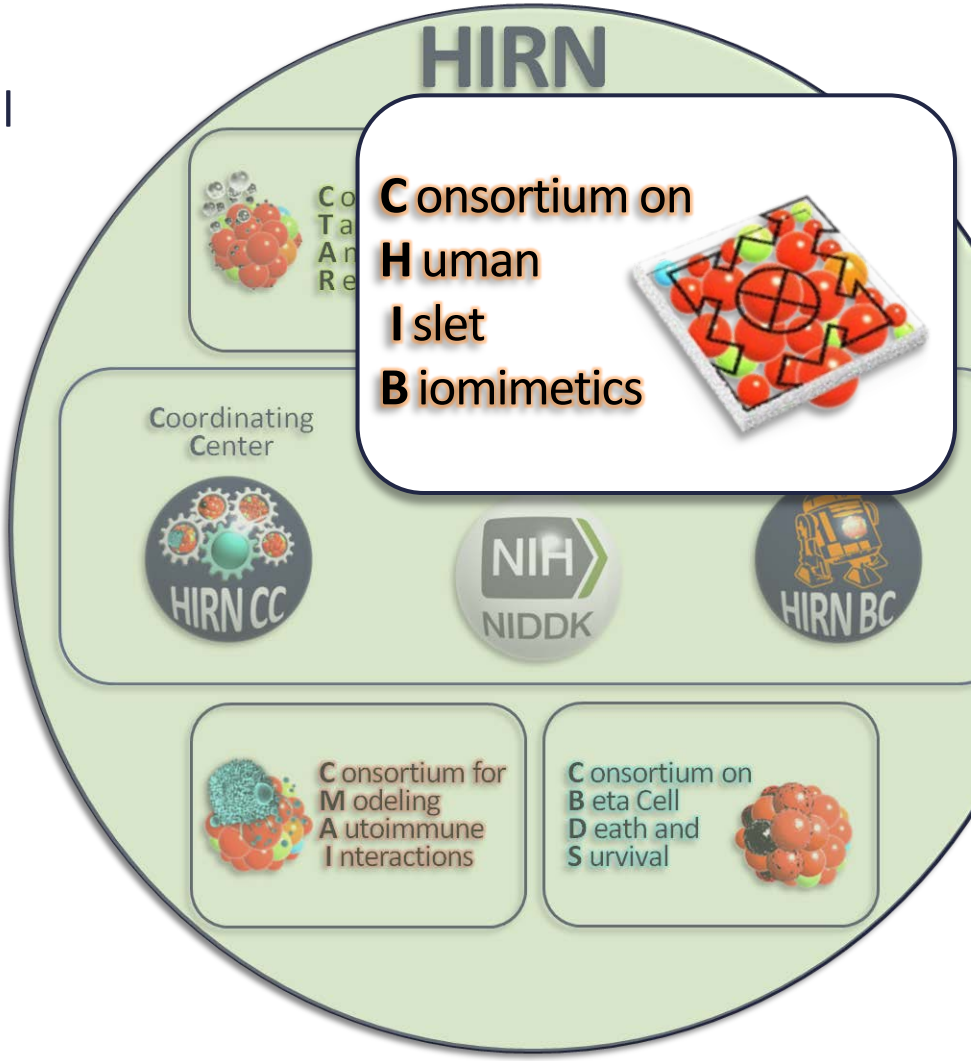


Consortium on Human Islet Biomimetics

CHIB's mission

To develop human islet microphysiological systems (biomimetics) that will allow the long-term in vitro survival of mature, functional human islet-like structures for discovery, disease modeling and drug screening.

FY14 Investment: $21M/5yrs



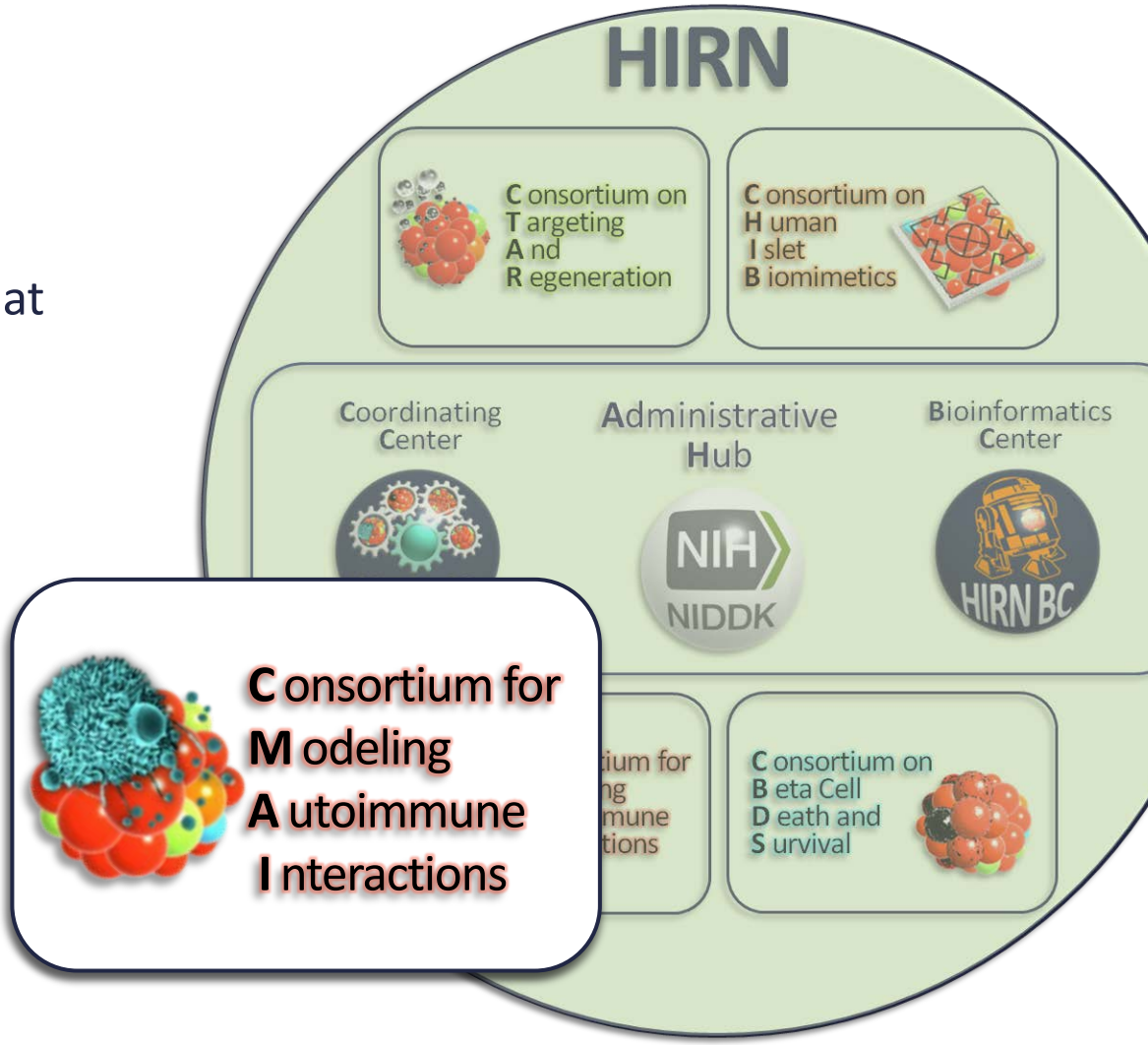
Human Islet Research Network

Consortium for Modeling Autoimmune Interactions

CMAI's mission

To develop robust in vitro and in vivo systems that can model the sequence of molecular events that occur as human beta cell dysfunction and autoimmune destruction commence in T1D.

FY14 Investment: $13M/5yrs

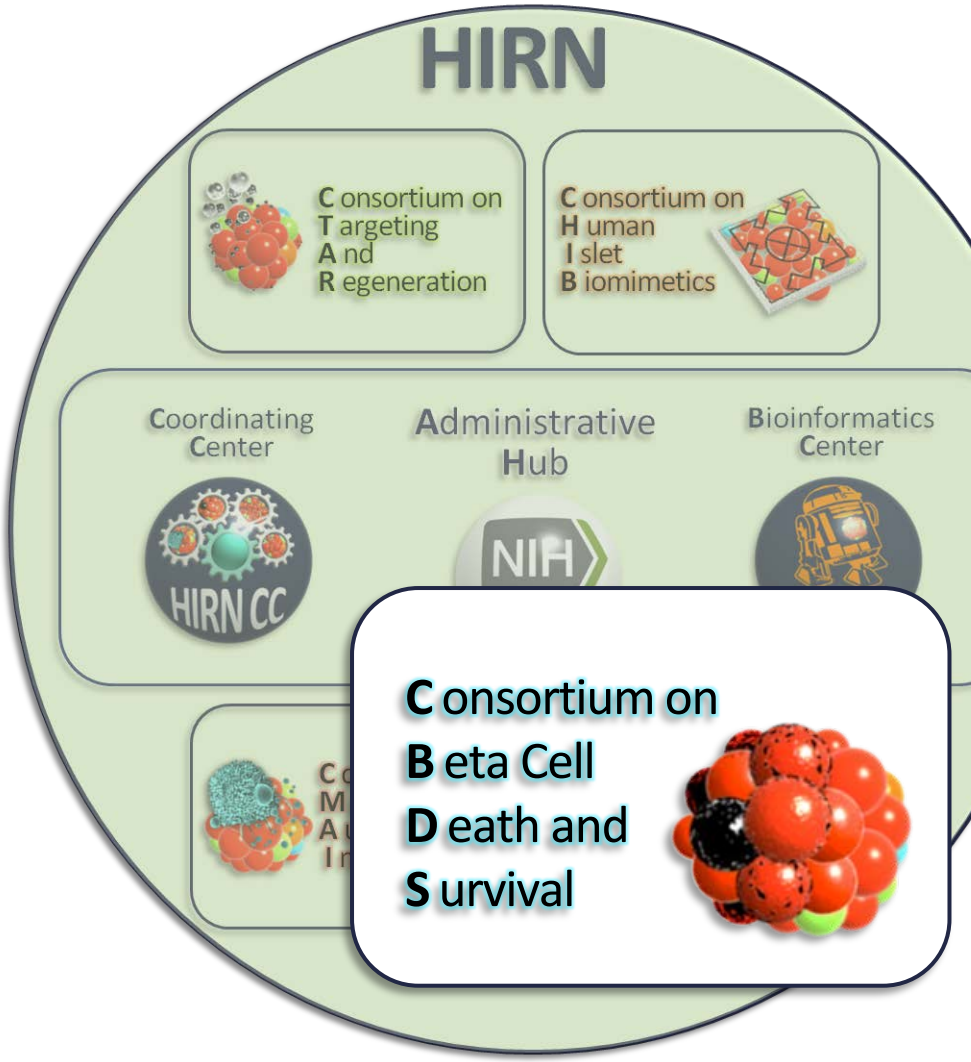


Consortium on Beta Cell Death and Survival

CBDS's mission

To interrogate human blood and tissues to study beta cell disappearance in early T1D, to discover highly specific biomarkers of beta cell injury in asymptomatic T1D, and to protect the residual beta cell mass as early as possible in the disease process.

FY14 Investment: $12M/3yrs



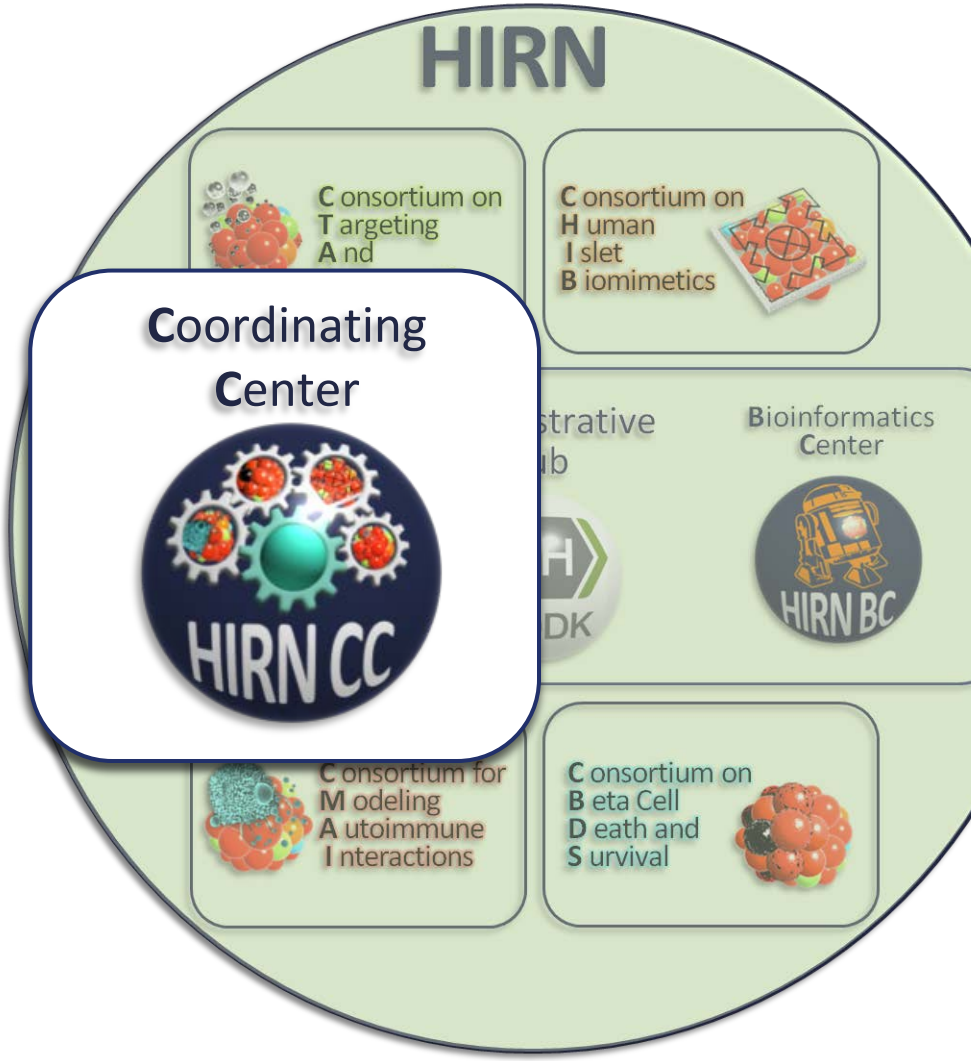
Human Islet Research Network

HIRN
Coordinating Center

HIRN-CC's mission

- Organize interactions
- Facilitate collaborations
- Oversee opportunity pool programs
- Enable the timely sharing of data and reagents

Investment: $1M/yr for 5 years

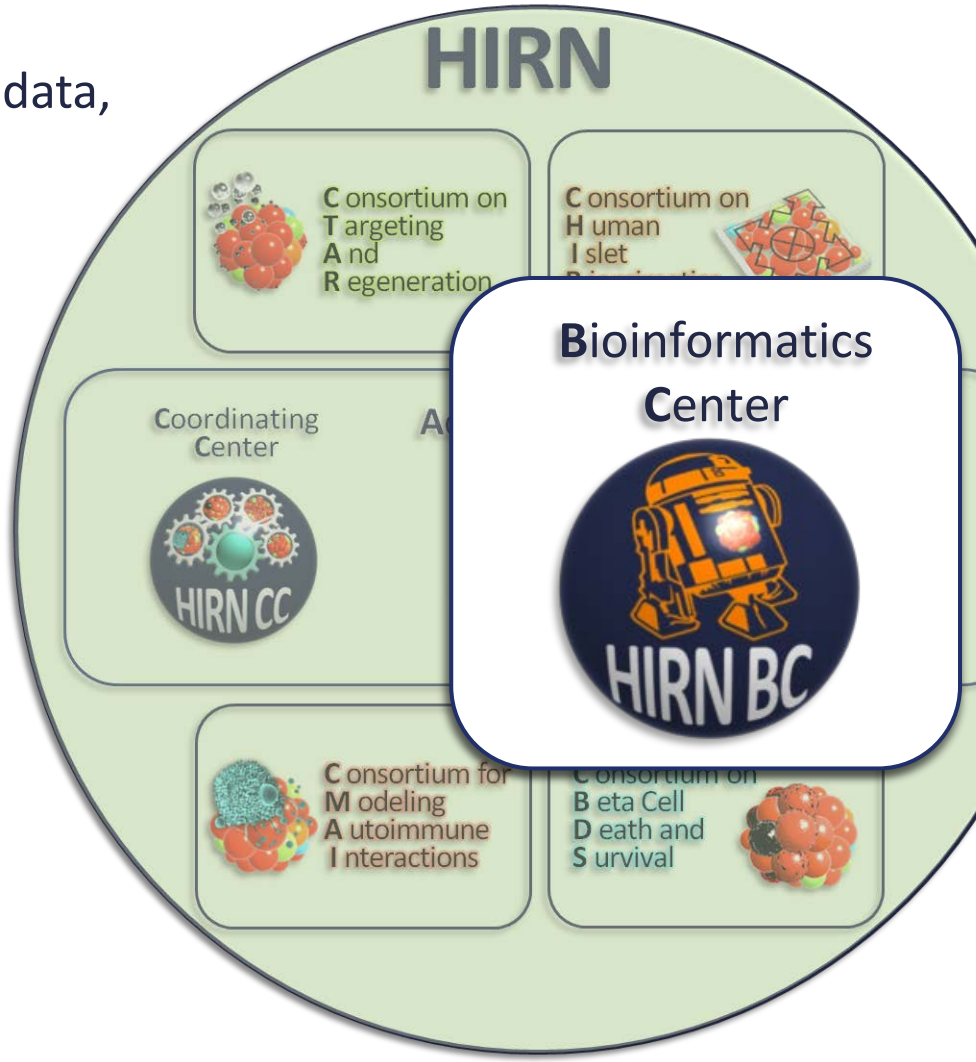


HIRN
Bioinformatics Center

HIRN-BC's mission

- Archive and curate HIRN data and metadata, and provide user-friendly access
- Develop tools and ontologies for data annotation and to facilitate analyses across data types
- Assist HIRN investigators with data deposition and analysis
- Link HIRN's datasets to relevant outside data repositories

Investment: $0.5M/yr for 5 years



Geographical Representation And Future Initiatives

FY15:

New CBDS initiative on technologies for transcriptomics, proteomics and/or metabolomics analysis of archived human pancreata with single cell resolution.

P&F Program for new investigators outside of HIRN;

FY16 & FY17:

Planning Phase - Development of new HIRN initiative concepts.

Human
Islet
Research
Network

Questions?

Follow-Up to NIDDK Centers Report/ MD Basic Researchers

Diabetes Research Centers Directors' Meeting

Gregory G. Germino, M.D.
Deputy Director

National Institute of Diabetes and Digestive and Kidney Diseases

September 10, 2014

National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK Centers Review

- Process
  - Review began in 2/10 and concluded in 9/12 with release of final report
  - Included discussions with NIDDK's Advisory Council, site visits, and comment periods

- Key Findings
  - Enhancing synergy and center value
  - Strengthening the P&F program
  - Core support and access
  - Core business models
  - Potential value of more small centers
  - Center membership

National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK Centers Review—
2 Years Later

- Established Working Groups of NIDDK Centers Program Directors
  - Harmonized NIDDK Centers RFAs
    - ❖ Standard required tables
    - ❖ Uniform language on core functions, administrative core functions
    - ❖ Consistent review criteria
  - Developed best practices documents
    - ❖ Categories for membership, cores, P&F programs
    - ❖ Plan to post on Web by end of calendar year

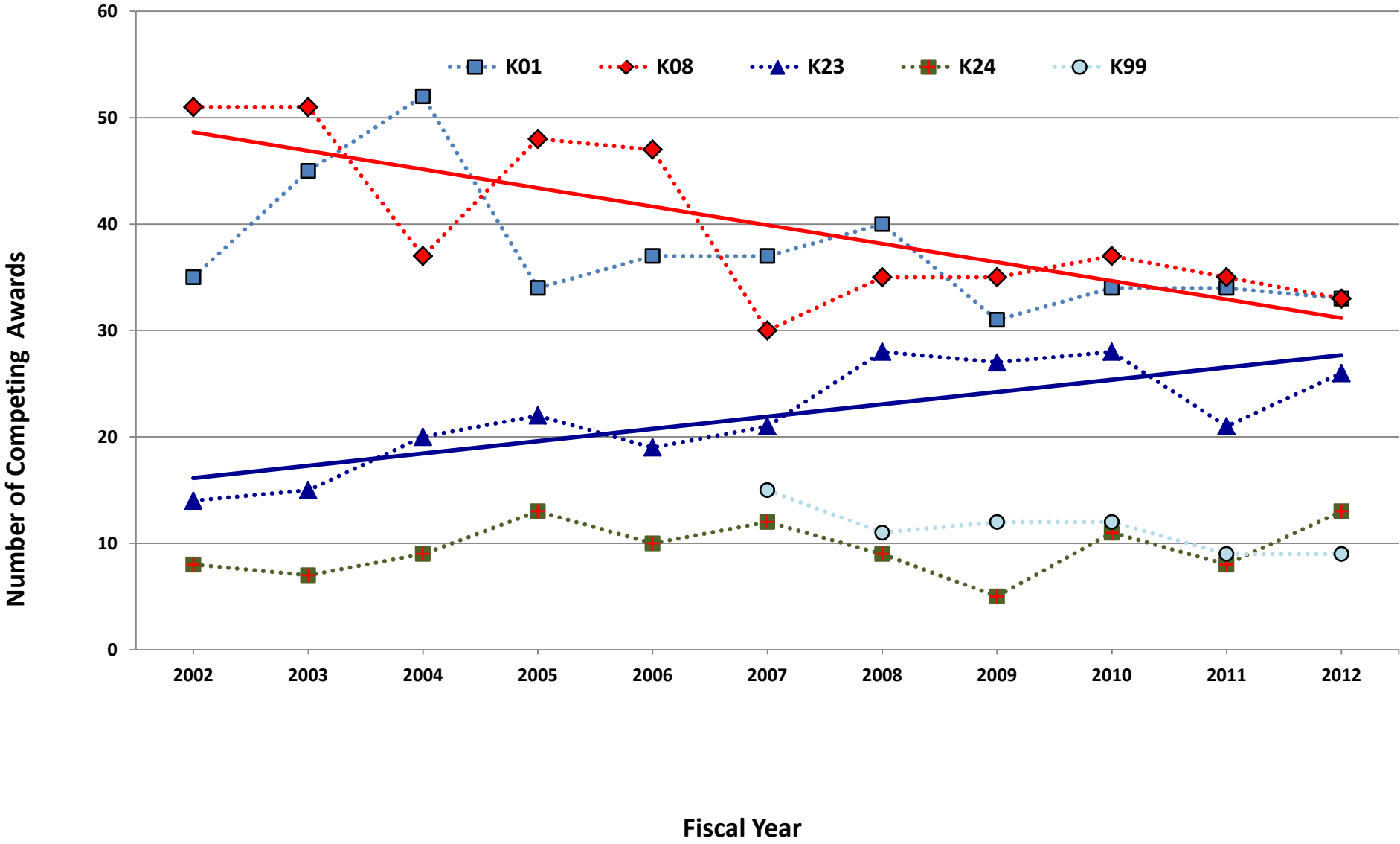
National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK Centers Review—
2 Years Later

- Maximizing regional value of Centers
  - P&F Programs expanded
  - Efforts to open cores to outside users
  - Utilizing nearby expertise: creation of cores at outside institutions

National Institute of Diabetes and Digestive and Kidney Diseases

Observation: Number of Competing K08 Awards Has Steadily Declined



Given

- Unique role of MD scientists
- Long-standing concerns about their status
- Observed decline in K08 awards

We collected add'l data…

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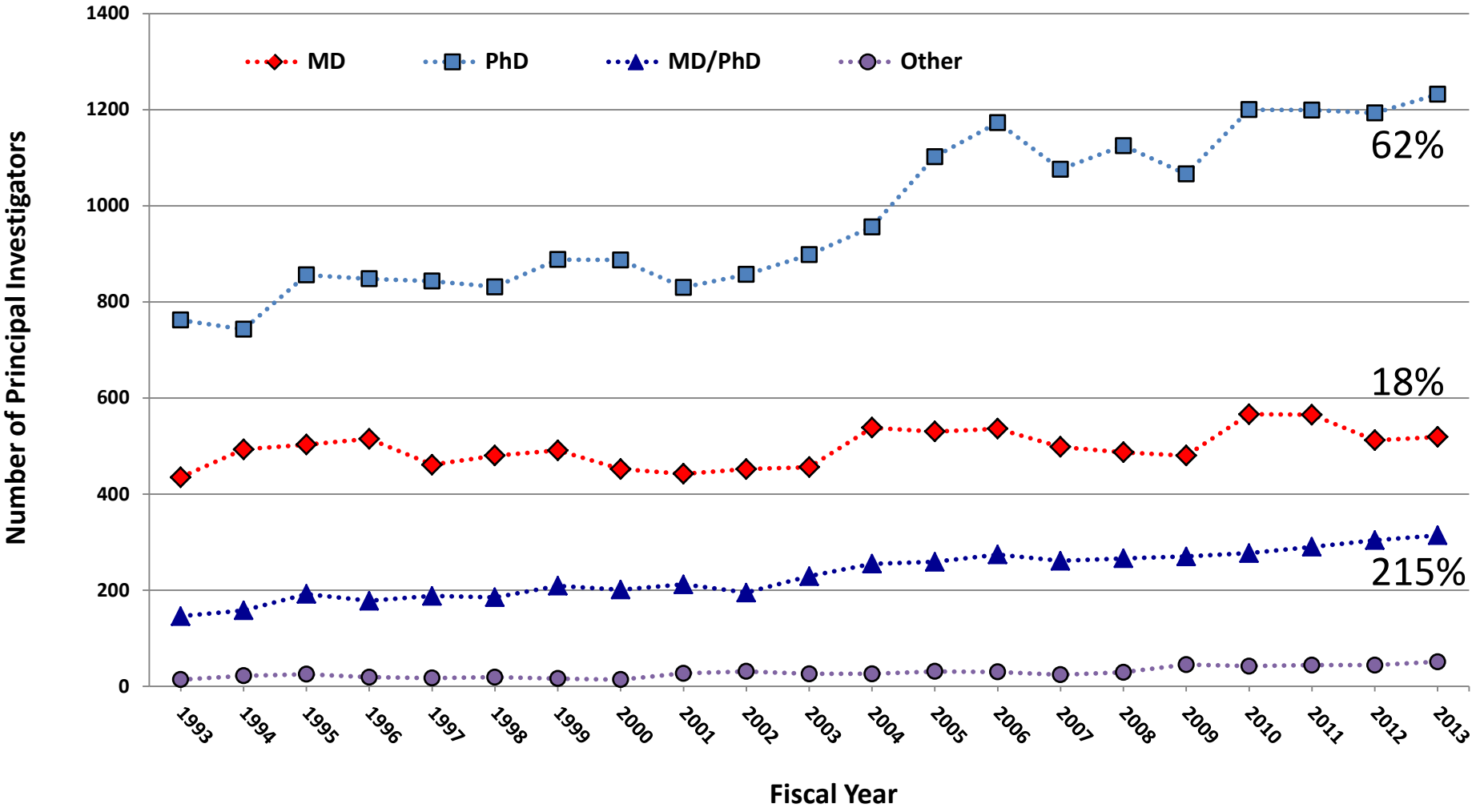
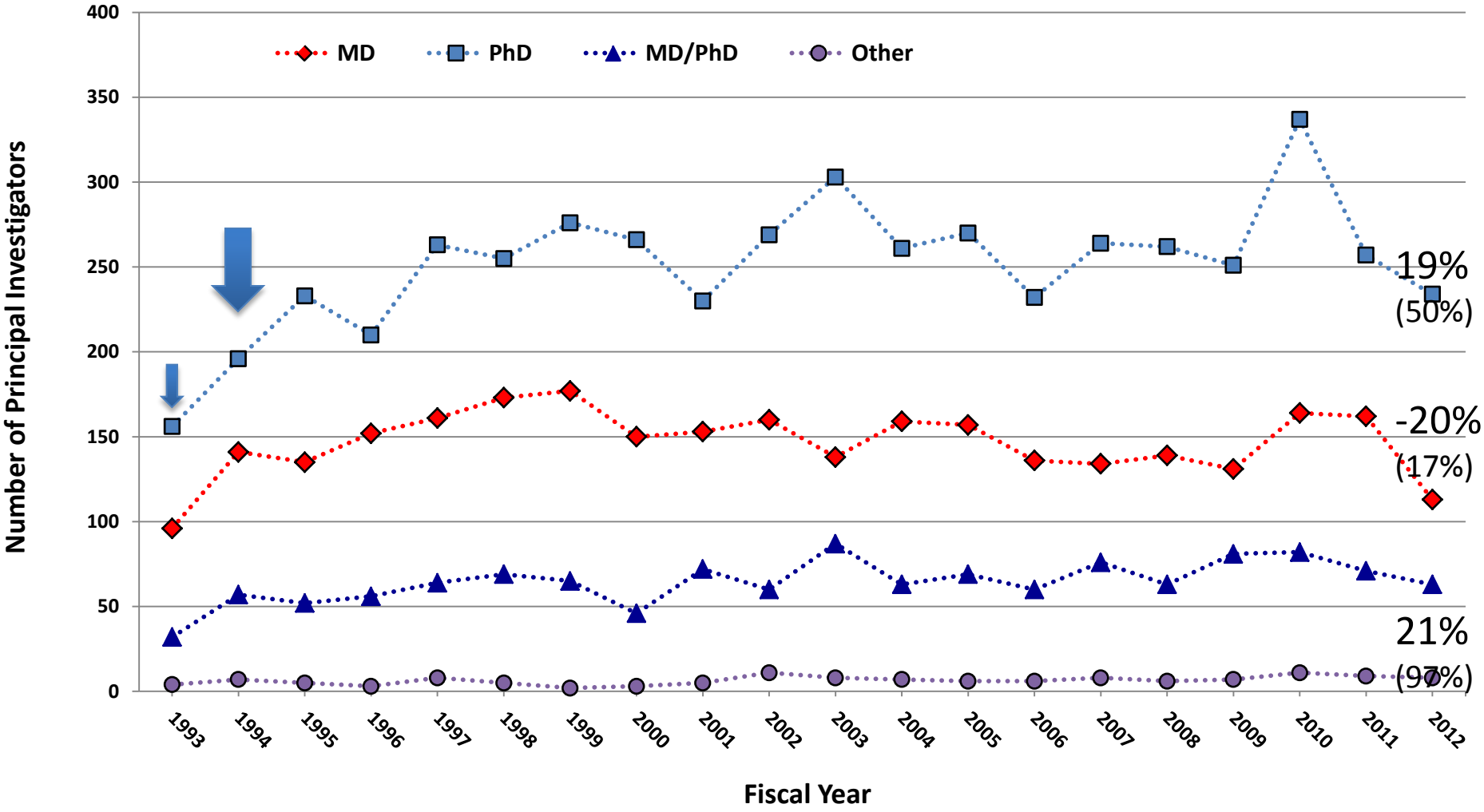
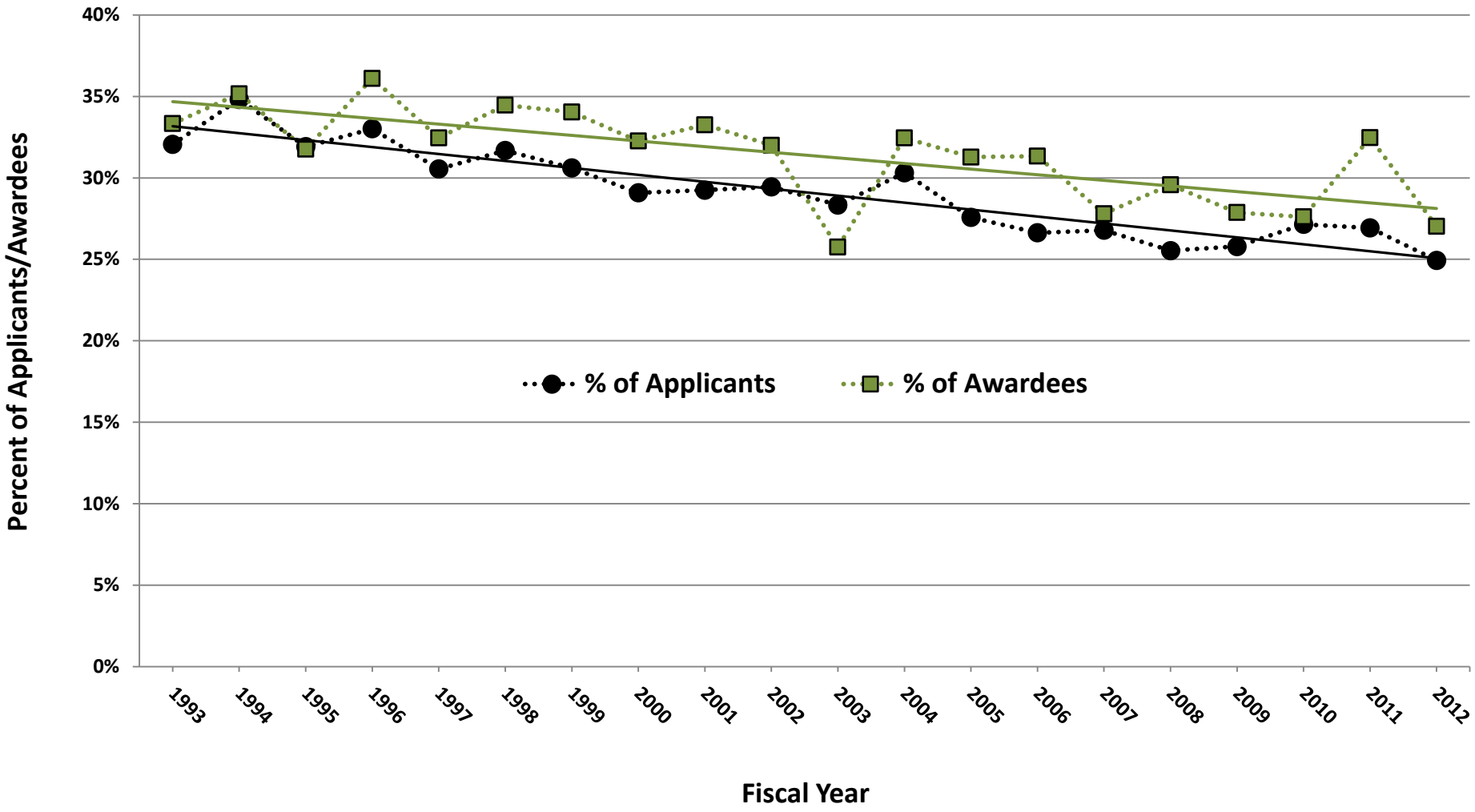
No. Unique PIs Submitting R01 (or equiv.) Applications



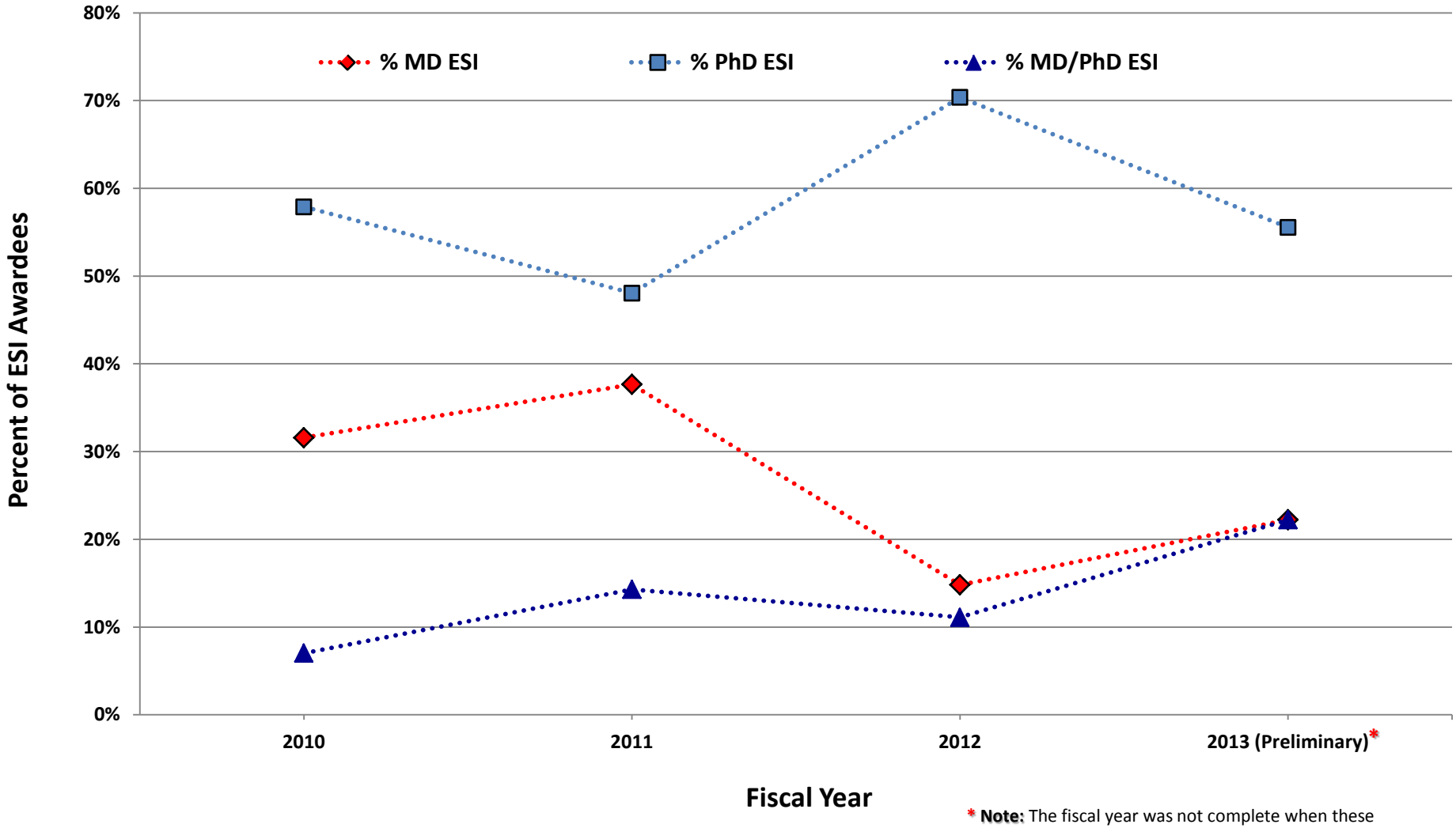
No. PIs Supported by ≥1 NIDDK R01 Award (or equiv.)



Unique MD R01 Applicants/R01 Awardees (NIDDK)

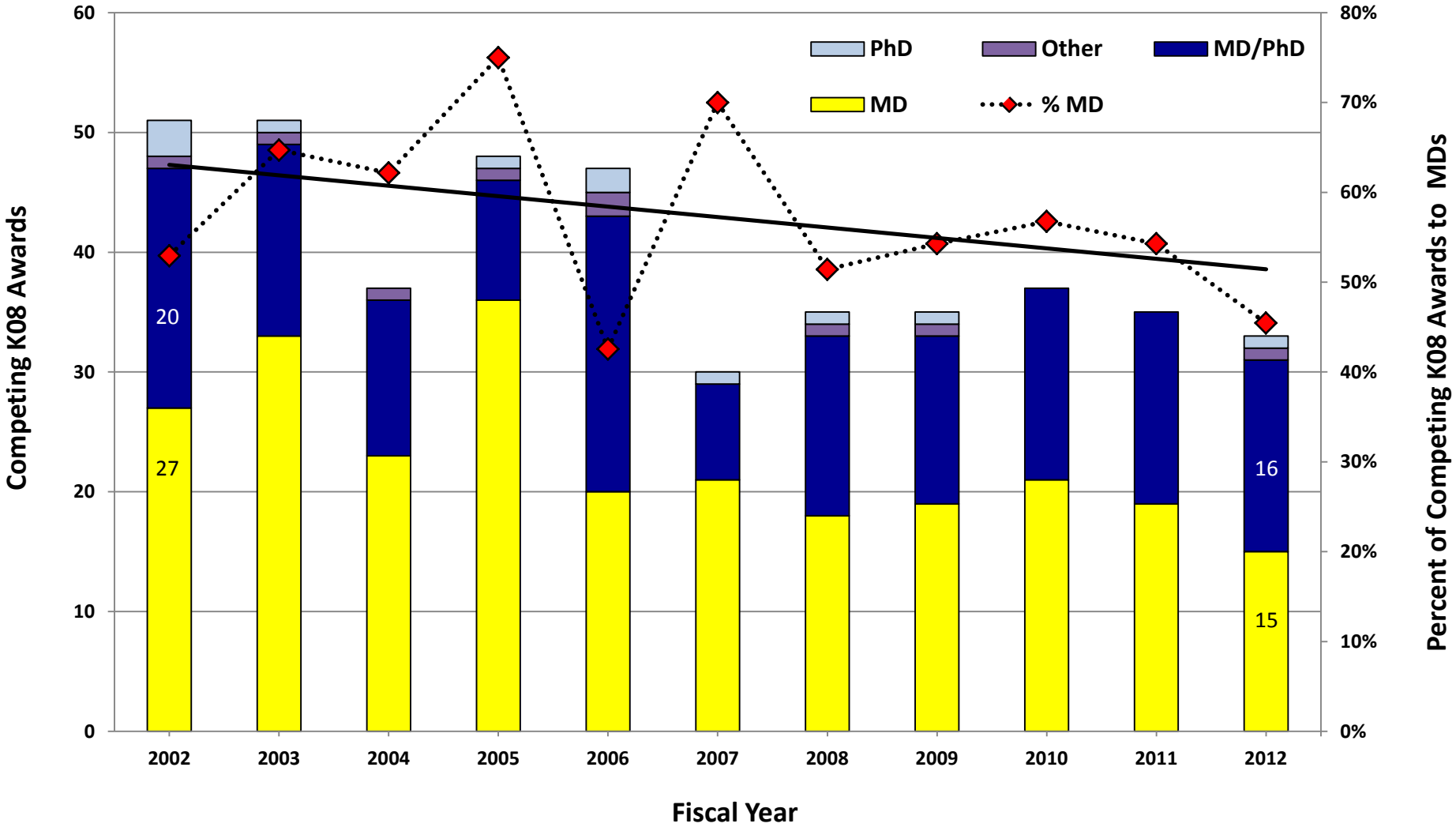


NIDDK ESI Awardees by Degree



* **Note:** The fiscal year was not complete when these preliminary FY 2013 data were drawn. It is likely that these percentages will change somewhat when final.

NIDDK K08 Awards



The most recent data are even more distressing…

Applications

FY	MD	MD\PHD	Other	PHD	Grand Total
2004	71	27	3	2	103
2005	72	25	1	3	101
2006	60	39	4	2	105
2007	48	17		4	69
2008	43	31	2	2	78
2009	47	30	3	3	83
2010	51	25	2	1	79
2011	46	27	3		76
2012	38	33	1	2	74
2013	35	21			56

Awards

FY	MD	MD\PHD	Other	PHD	Grand Total
2004	23	13	1		37
2005	36	10	1	1	48
2006	20	23	2	2	47
2007	21	8		1	30
2008	18	15	1	1	35
2009	19	14	1	1	35
2010	21	16			37
2011	19	16			35
2012	15	16	1	1	33

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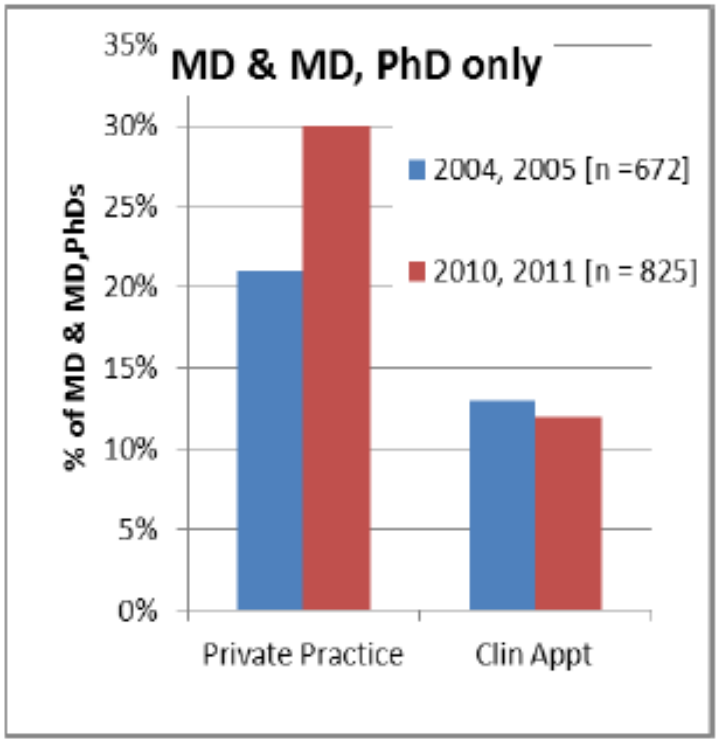
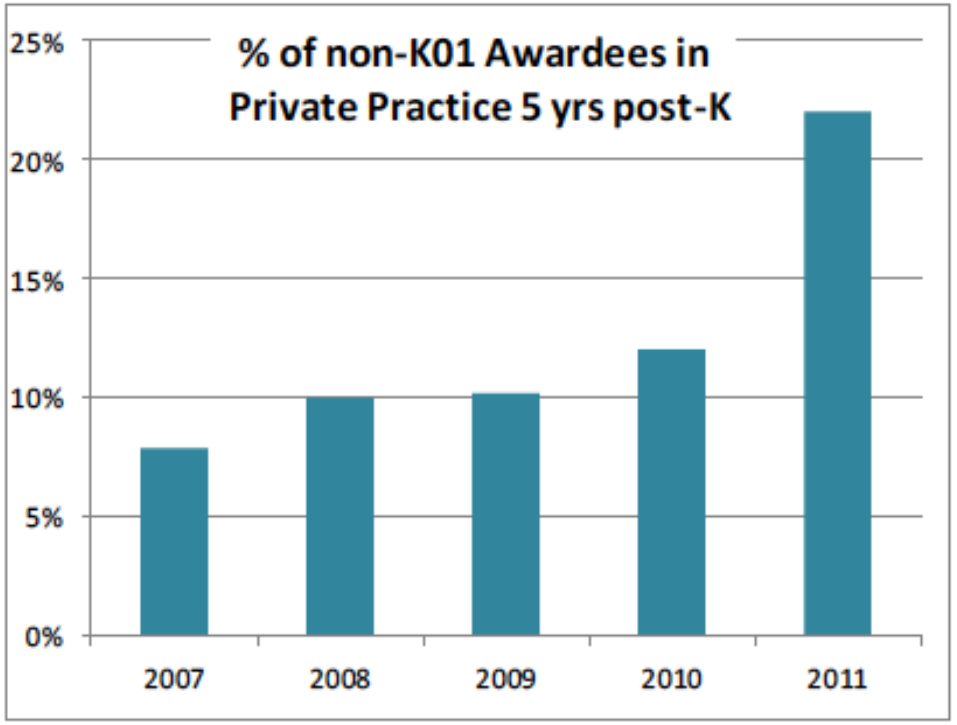
The pipeline is increasingly leaky…

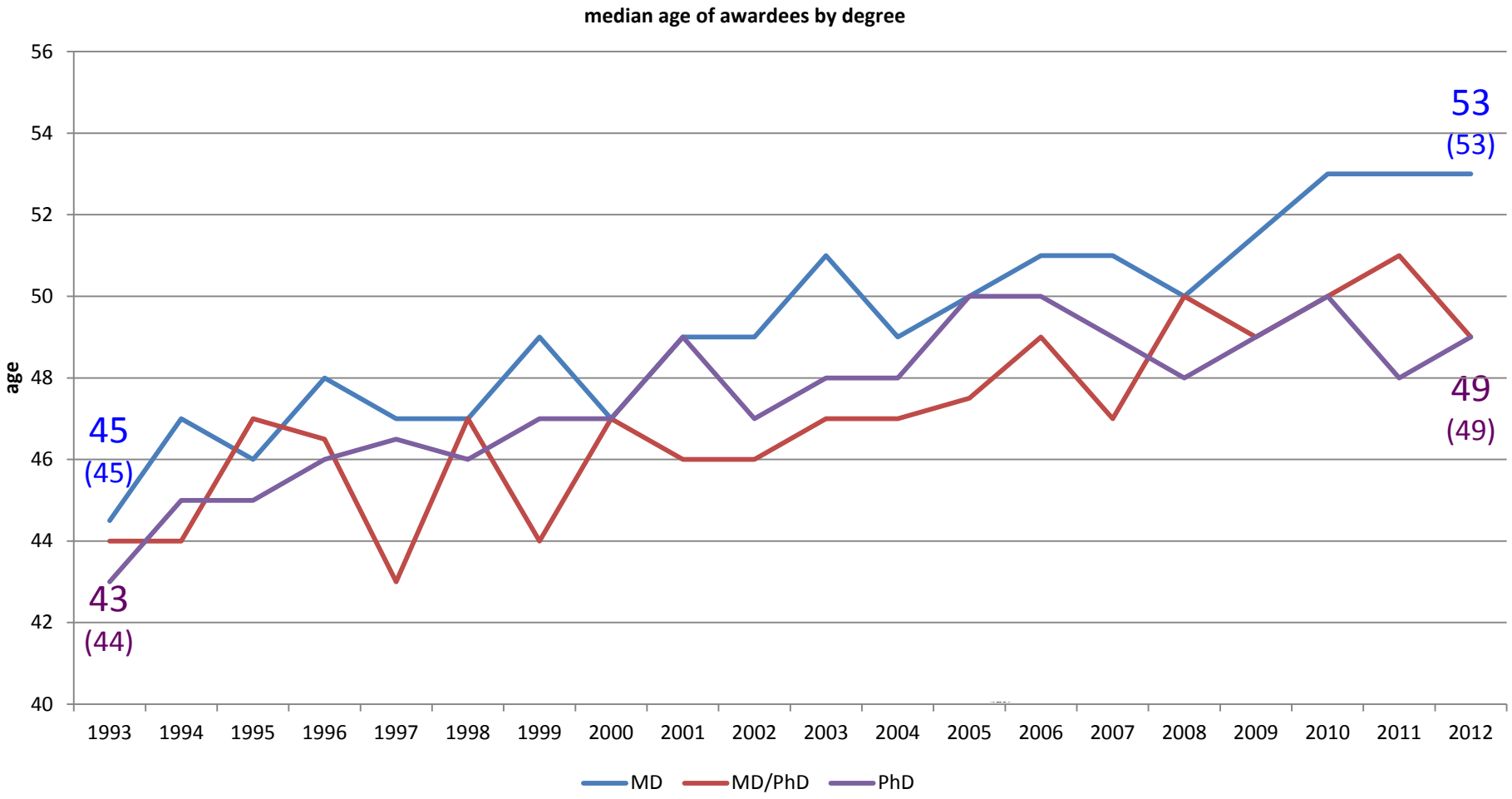
T32 trainees:



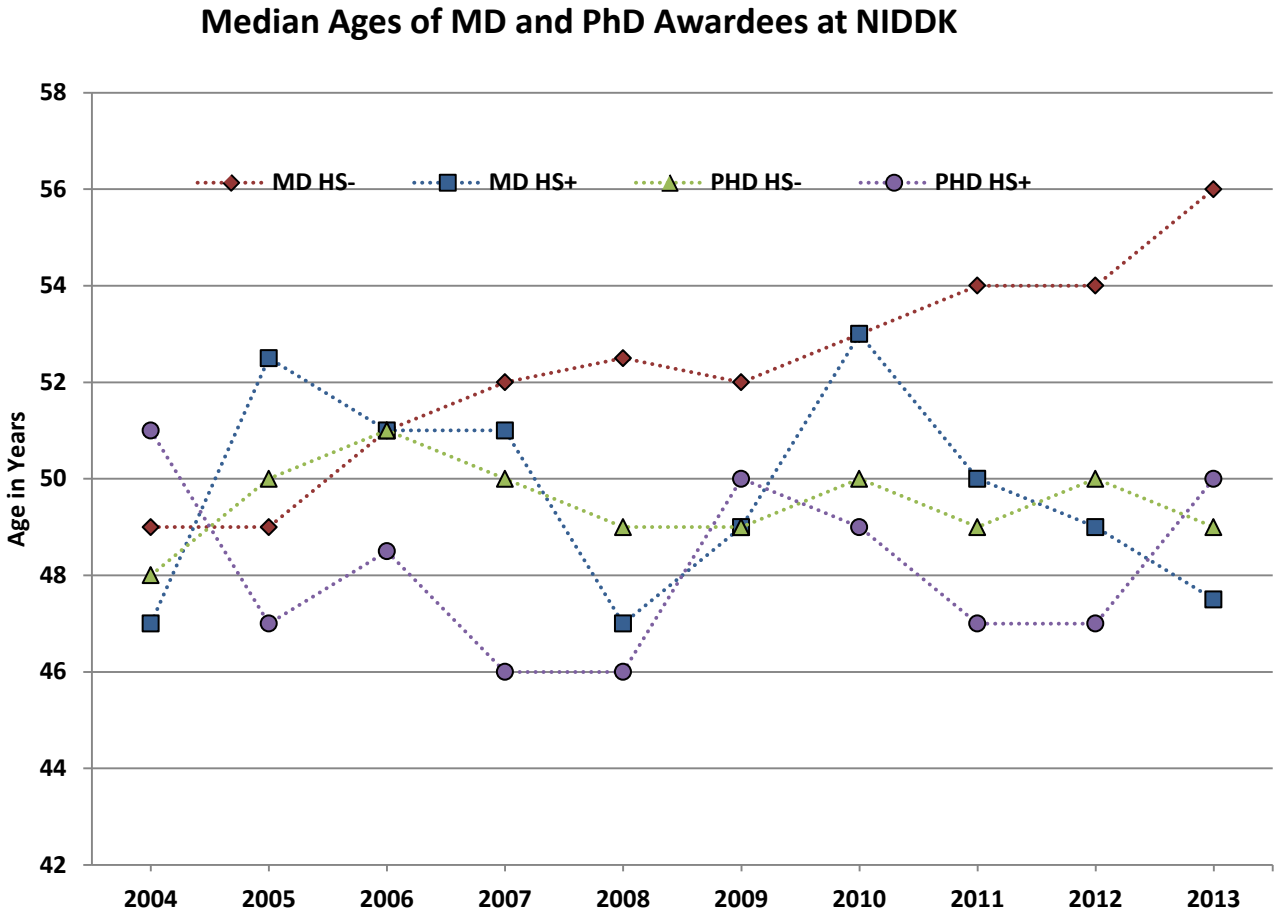
K-awardees



And the median age of MD investigators is rising more rapidly…



Increase in MD HS- award median age is primary factor



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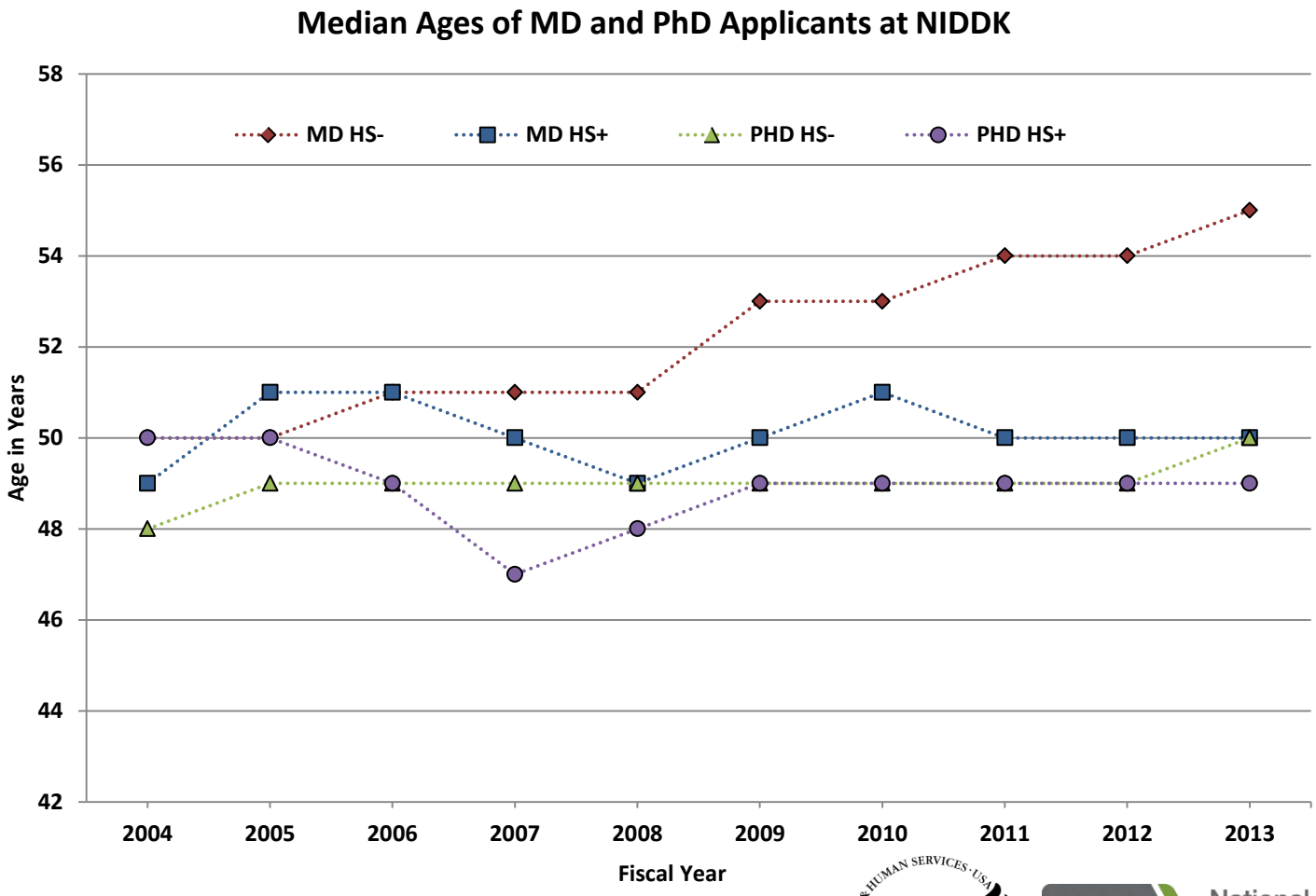
Rates of application and award are similar



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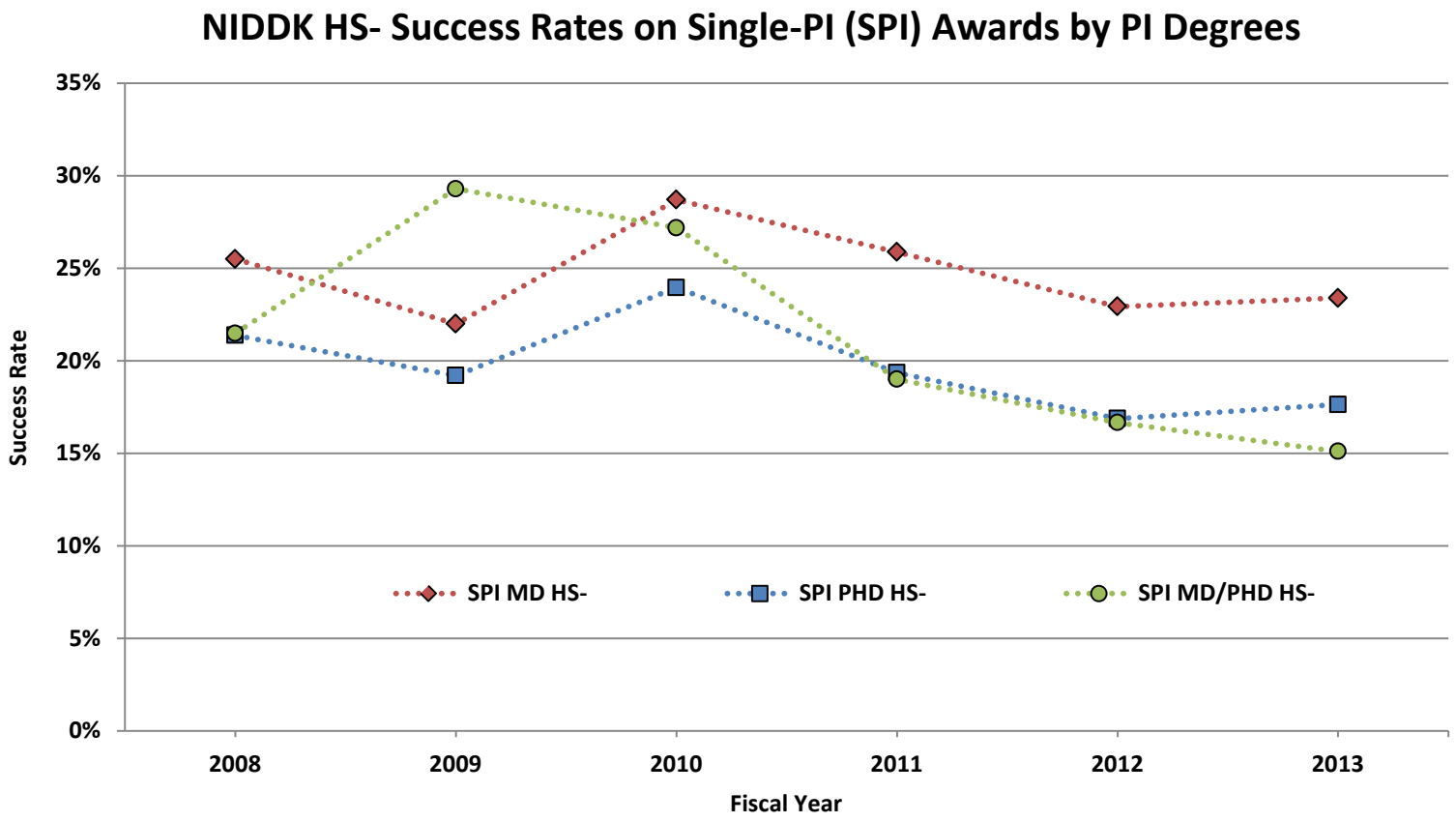
MD HS- scientists are among our most successful investigators



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Conclusions

- **The proportion of PIs that are MDs within NIDDK portfolio is declining**
  - Far fewer entering basic science research track
    - 63% decline in no. of K08 since 2002
    - Increase in K23 partially compensates
  - More MDs dropping out early
    - Increased proportion in private practice 5y post-K and T32.
  - Fewer ESI awards to MDs
  - Net result: median age of MD PIs is rising faster than PhDs
    - Driven mostly by MD HS- investigators
    - True loss of MD basic likely masked by increase in clinical MD

Reasons?

- High cost of education
- Changing medical education
- Changing nature of medical centers, clinical practice and medical reimbursement
- Changing expectations regarding work-life balance
- Increase in no. of MDs who are caregivers
- Perception of high risk/high failure rate

Entrepreneur model not working well!

National Institute of Diabetes and Digestive and Kidney Diseases

RFA-DK-14-005

NIDDK Clinician Scientist Mentoring Award to Promote Workforce Diversity (K05)

Goal: To provide support to mid-career health-professional doctorates or equivalent for protected time to devote effort to basic, epidemiological or outcomes research and to act as research mentors to early-stage investigators from diverse backgrounds underrepresented in biomedical and behavioral research

Application Due Date: November 24, 2014

More information: http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-14-005.html

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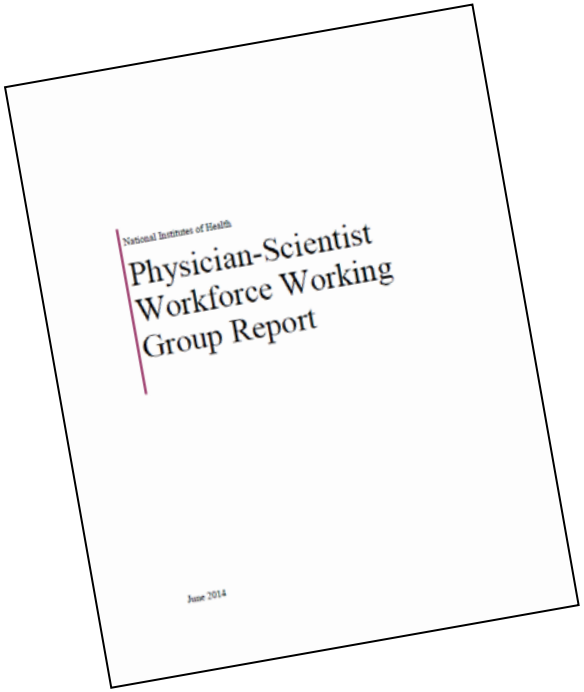
This is an NIH concern



In June 2014, a working group of the Advisory Council to the Director presented their findings on the physician-scientist workforce

http://acd.od.nih.gov/psw.htm

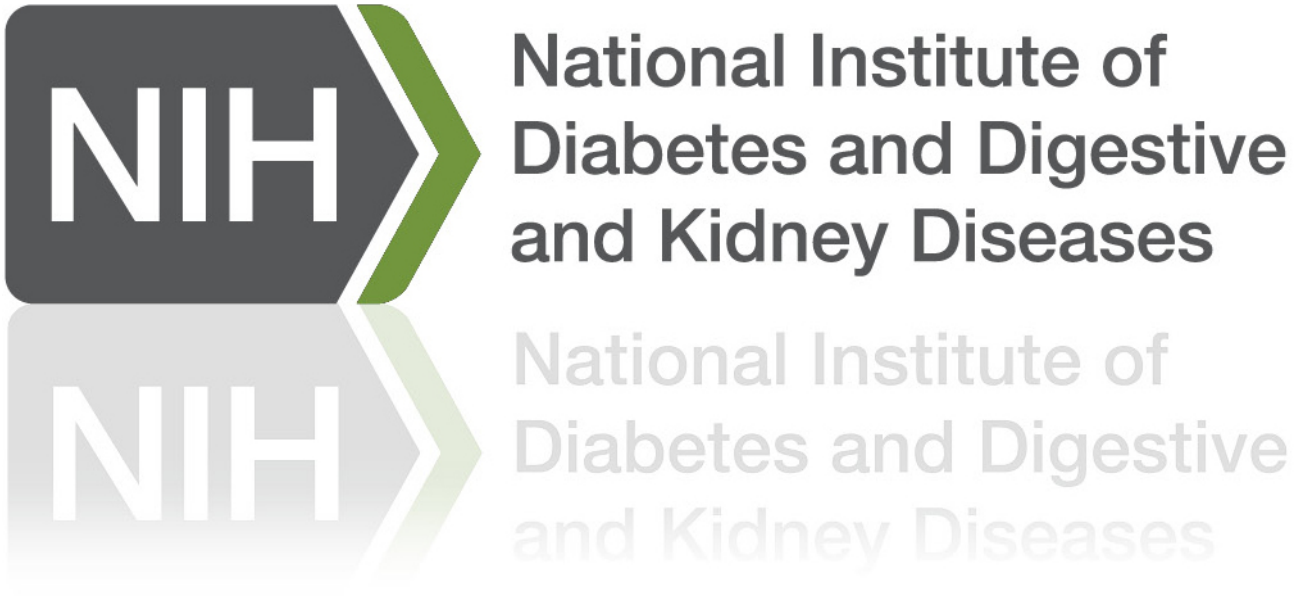
National Institute of Diabetes and Digestive and Kidney Diseases

Recommendations of the Working Group

- Sustain strong support for MD/PhD programs
- Establish physician-scientist-specific K99/R00-equivalent granting mechanism
- Expand loan repayment programs and increase $ amounts of loan forgiven
- Support pilot grant programs to test existing & novel approaches to improve and/or shorten research training
- Intensify efforts to increase diversity in the physician-scientist workforce

National Institute of Diabetes and Digestive and Kidney Diseases

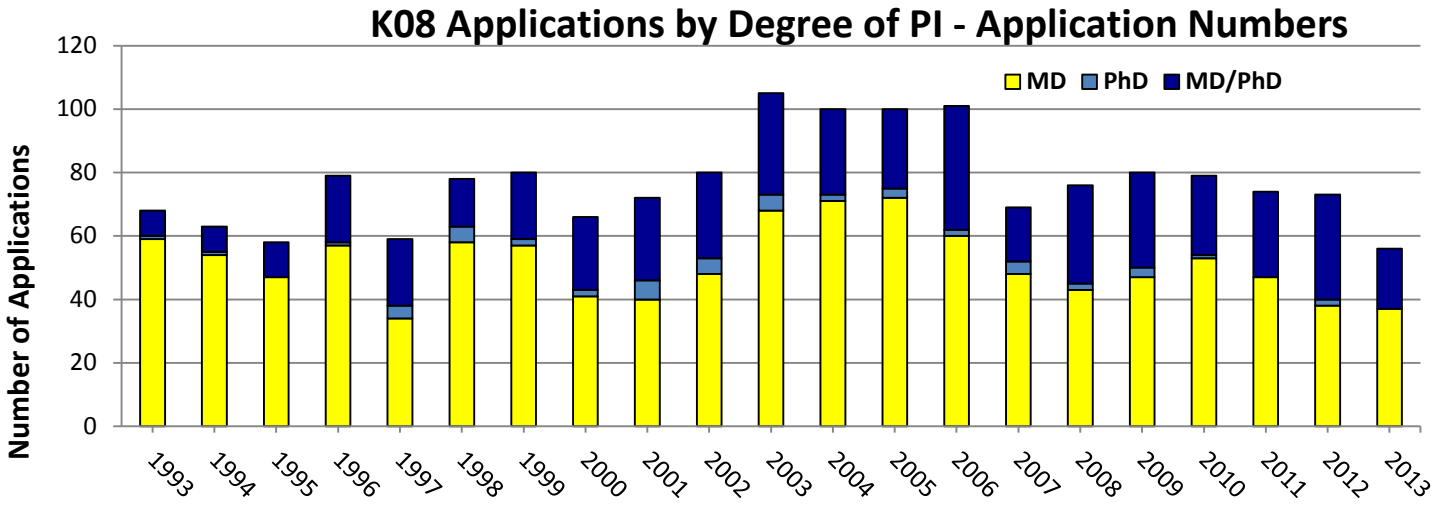
Questions and Discussion

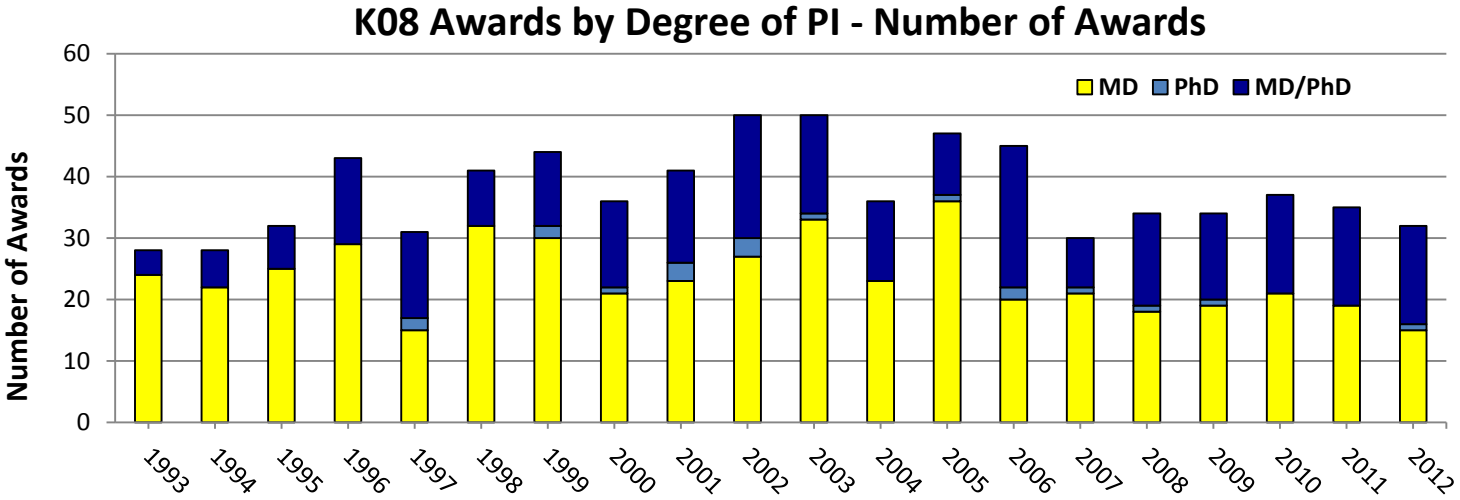


Additional Data

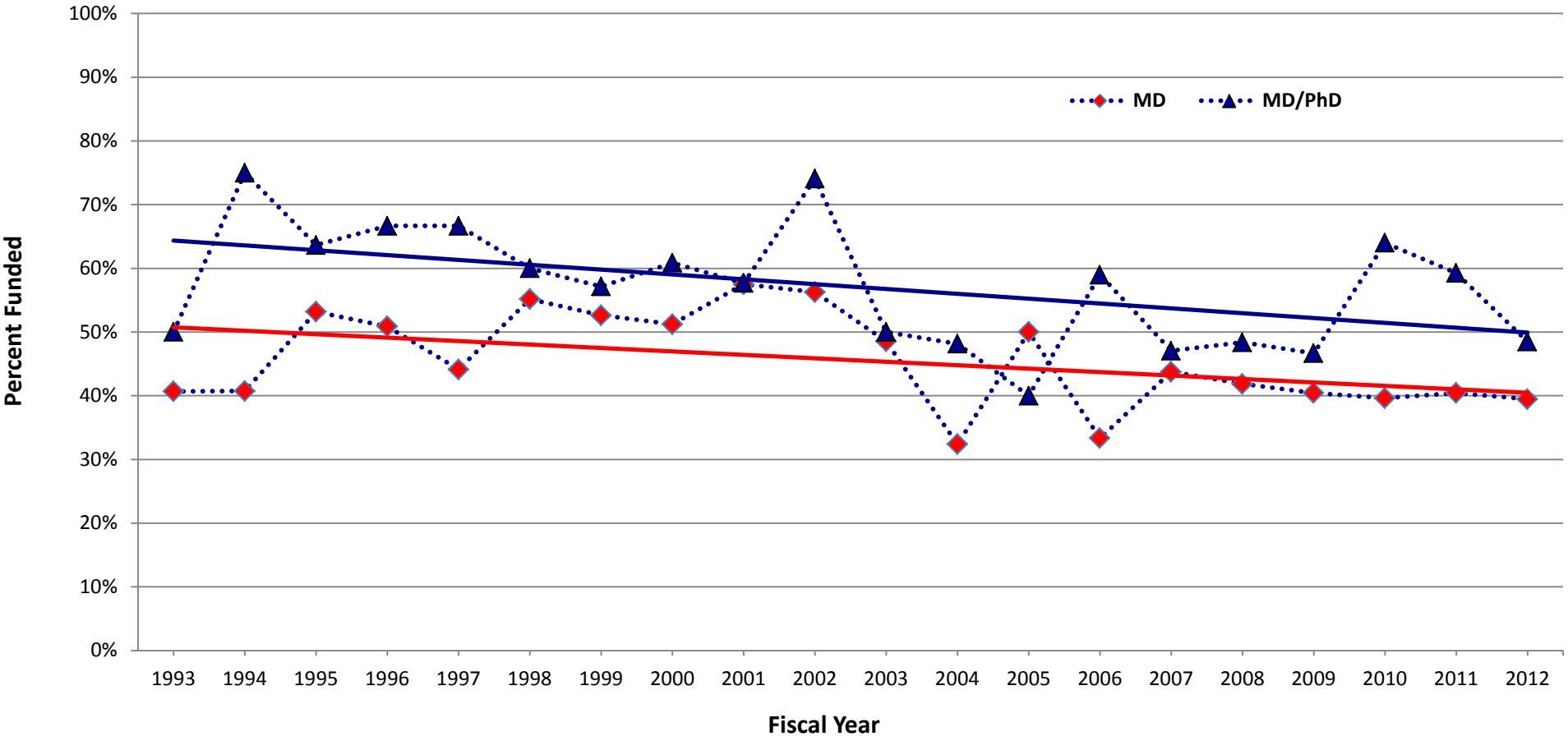
- From AAMC '03-'12:
  - MD-PhD: from 418 to 599 matriculants (+43%)
  - Medical School graduates: from 15,531 to 17,341 (+12%)
- K01 vs K08 success rates

FY	K01 apps	K01 awards	success rate (%)		K08 apps	K08 awards	success rate (%)
2003	90	46	51.1		91	54	59.3
2004	122	51	41.8		97	38	39.2
2005	103	34	33		86	48	55.8
2006	97	38	39.2		86	47	54.7
2007	106	38	35.8		58	31	53.4
2008	75	40	53.3		74	35	47.3
2009	70	31	44.3		71	35	49.3
2010	96	33	34.4		74	37	50
2011	104	35	33.7		70	35	50
2012	104	33	31.7		66	33	50


K08 Applications by Degree of PI - Application Numbers
Number of Applications
120
100
80
60
40
20
0
MD
PhD
MD/PhD
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013


K08 Awards by Degree of PI - Number of Awards
Number of Awards
60
50
40
30
20
10
0
MD
PhD
MD/PhD
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012

Success Rates of MD and MD/PhD K08 Applicants



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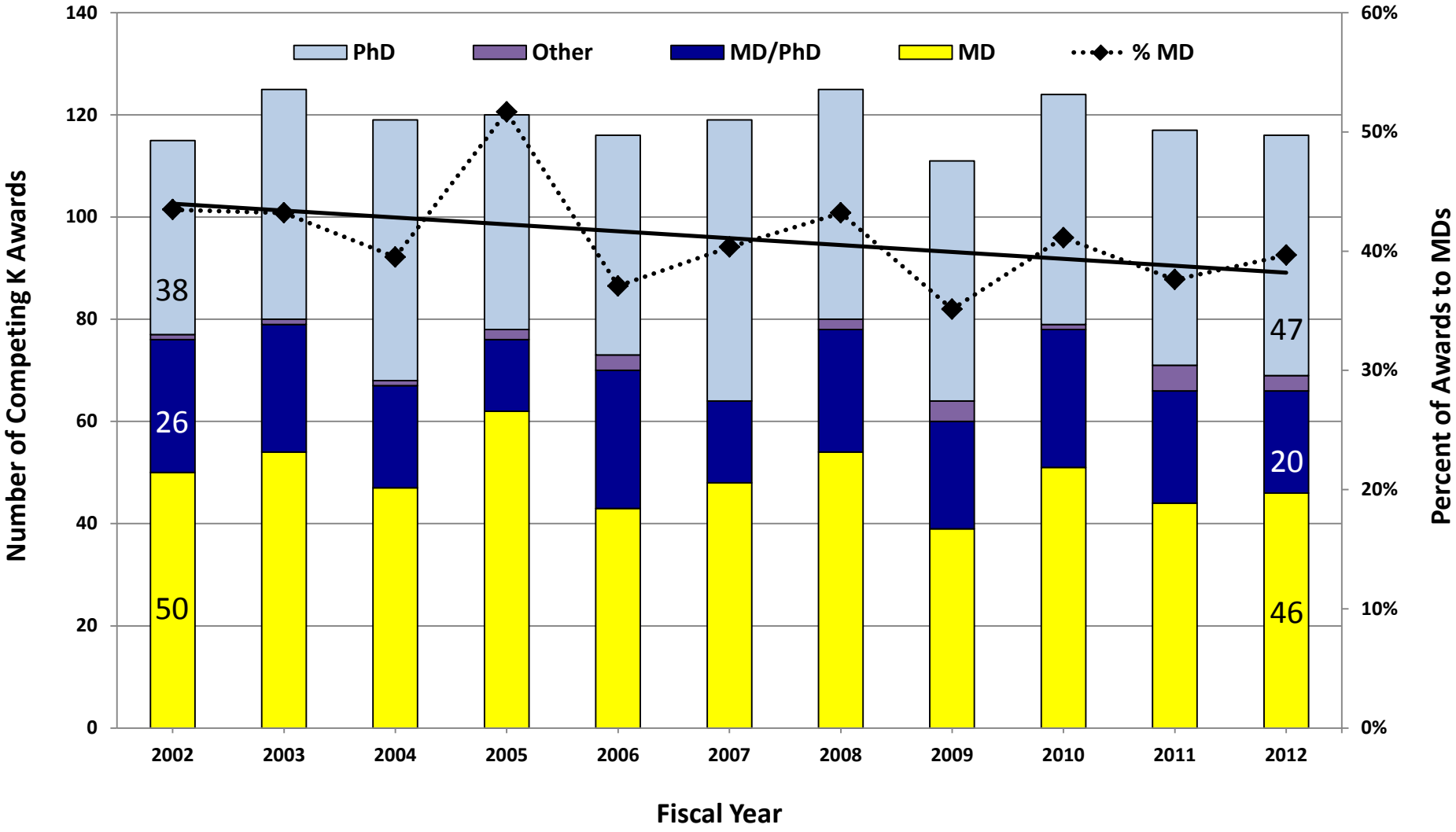
Number of Select NIDDK K Awards by Degree



3Topics Today:

1. Mutant Mouse Regional Resource Centers (MMRRC)
2. NIDDK Information Network (DKnet)
3. Integrated Islet Distribution Program (IIDP)

Topics Today:

1. Mutant Mouse Regional Resource Centers (MMRRC)
2. NIDDK Information Network (DKnet)
3. Integrated Islet Distribution Program (IIDP)

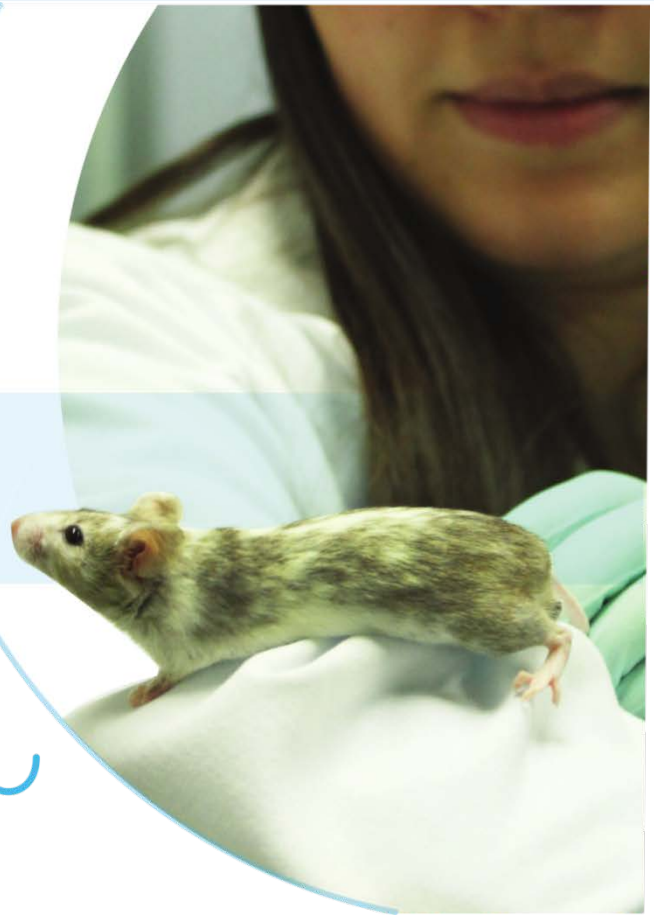
National Institute of Diabetes and Digestive and Kidney Diseases

MMRRC

Mutant Mouse Regional Resource Centers

supported by the National Intitute of Health

a repository for the archiving and distribution of mutant mouse models, ES cell lines, germplasm, and mice



Find or donate your mouse model today

mmrrc.org *established 1999*

Sponsored by: DPCPSI DIVISION OF PROGRAM COORDINATION, PLANNING, AND STRATEGIC INITIATIVES

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH National Institutes of Health *Turning Discovery Into Health*

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

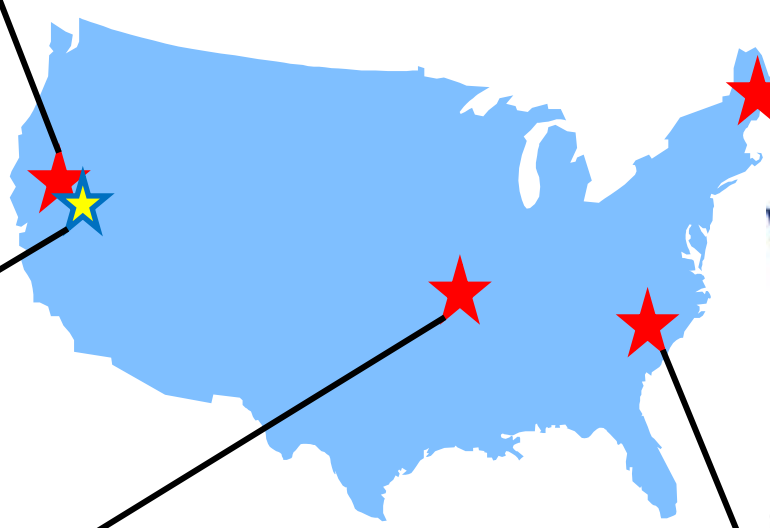
NIH National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

MMRRC @ UCDavis
Mutant Mouse Regional Resource Centers supported by NIH

MMRRC
Mutant Mouse Regional Resource Centers
supported by the National Intitute of Health

ICSC
UCDAVIS
UNIVERSITY OF CALIFORNIA
(Informatics, Coordination & Service Center



The Jackson Laboratory
Leading the search for tomorrow's cures

MMRRC University of Missouri Mutant Mouse Regional Resource Center

MMRRC at UNC
Mutant Mouse Regional Resource Centers supported by NIH

DEPARTMENT OF HEALTH & HUMAN SERVICES-USA

NIH National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

MMRRC
Mutant Mouse Regional Resource Centers
supported by the National Intitute of Health

Value-added Research Resources:

- **More than 30,000 mutant alleles in mice, germplasm, ES cells**
- Expertise in mouse genetics, husbandry, cryopreservation
- Gut microbiome analysis (UC-Davis, UMO-Columbia)
- CRISPR/Cas9 genome editing
- Broad-based phenotyping capabilities
- Collaborative Cross (UNC)
- MegaMUGA low-cost high density genotyping platform
- Bioinformatics Services

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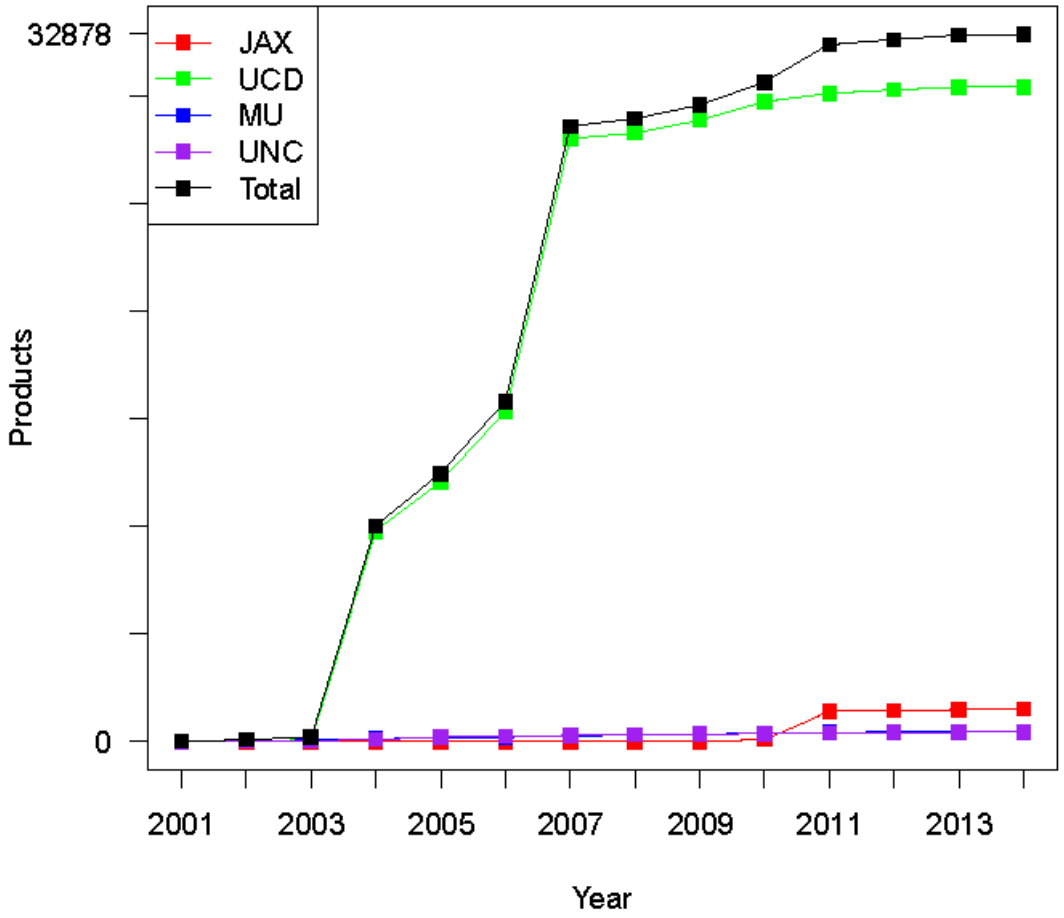
MMRRC Metrics

MMRRC
Mutant Mouse Regional Resource Centers
supported by the National Intitute of Health

Cumulative Holdings

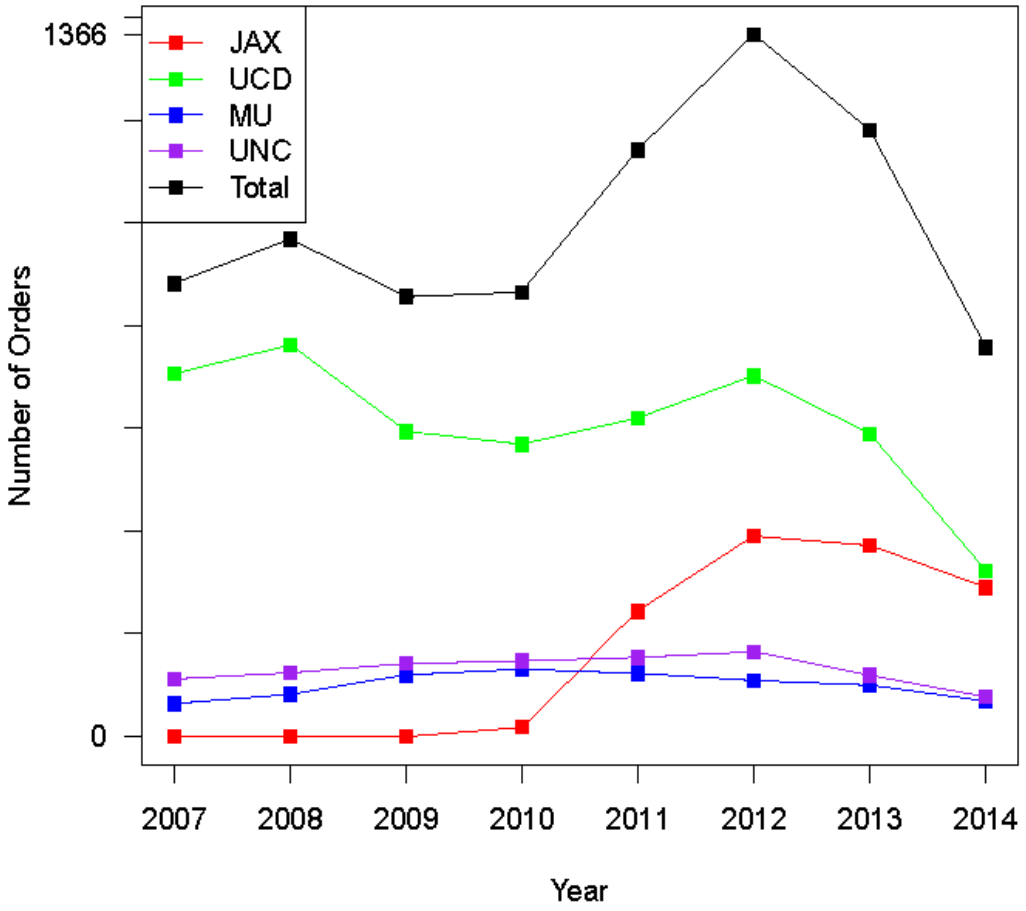


National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

MMRRC Metrics

Orders



(first 6 months)

MMRRC
Mutant Mouse Regional Resource Centers
supported by the National Intitute of Health

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

Donating mutant mouse lines to the MMRRC:

MMRRC
Mutant Mouse Regional Resource Centers
supported by the National Intitute of Health

NIH-funded

- Type 1– Individual investigator-initiated deposition
- Type 2– NIH-designated deposition
- Type 3– Contract/agreement-based deposition

Donor-funded

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National Institute of Diabetes and Digestive and Kidney Diseases

MMRRC
Mutant Mouse Regional Resource Centers
supported by the National Intitute of Health

Focus on Reproducibility:

- Critical QC assessment of incoming strains
- Thorough strain description
- Genetic identity of strains confirmed
- Background genetic screening
- Strains maintained under biosecurity SOP's, health monitoring
- Detailed descriptions of MMRRC facilities, husbandry
- Scientific and professional veterinary oversight

www.mmrrc.org

National Institute of Diabetes and Digestive and Kidney Diseases

Topics Today:

1. Mutant Mouse Regional Resource Centers (MMRRC)
2. NIDDK Information Network (DKnet)
3. Integrated Islet Distribution Program (IIDP)

The NIDDK Information Network

Why a DKnet(work) & why now?

- Technological advances are driving the production of many large datasets in different forms/formats
- New data mining tools are being used to extract novel information and to stimulate formation of new hypotheses
- NIDDK projects have contributed to this "avalanche" of data:
  - DGAP, Stem cell GAP, BCBC, AMDCC, MMPC, and NURSA + GUDMap, GWAS, T1DGC and numerous clinical studies
- The challenge is **how to best communicate & leverage existing data/resources:**
  - to inform our understanding of disease mechanisms
  - to stimulate new lines of investigation
  - to enhance b to b translation

National Institute of Diabetes and Digestive and Kidney Diseases

Piloting the concept: dkCOIN

NIDDK Consortium Interactivity Network

What are NIDDK's consortial data & resources? Where are they?

dkCOIN goal: to demonstrate feasibility of producing a "unified storefront" that presents aggregated data and resources from 5 DK supported basic science consortia: BCBC, MMPC, DiaComp, NURSA, T1Dbase

- Allow for easy searches for data/resources
- Seamless integration across platforms
- Proof of principle of an informatics network concept
- Scalable to include additional resources

National Institute of Diabetes and Digestive and Kidney Diseases

dkCOIN's success led to establishment of DKnet

(RFA-DK-11-030; U24 awarded December 2012)

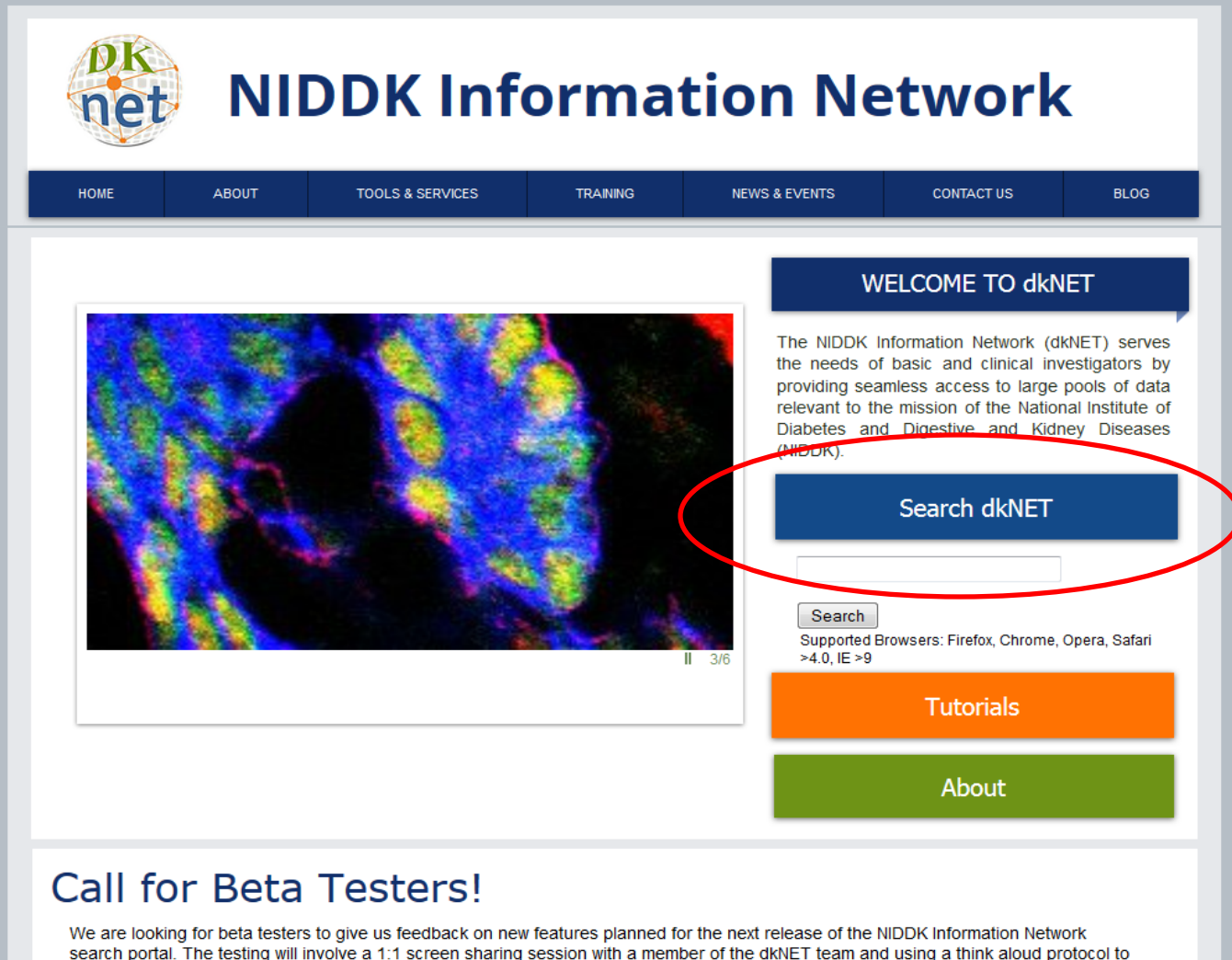
www.dknet.org

DKnet team: (UCSD)

- *Maryann Martone PI*
- *Jeff Grethe*
- *Trish Whetzel*

DK program staff

- *Art Castle*
- *Ron Margolis*
- *(Kristin Abraham)*



COMMUNITY HOME DKNET WEBSITE LOGIN HELP

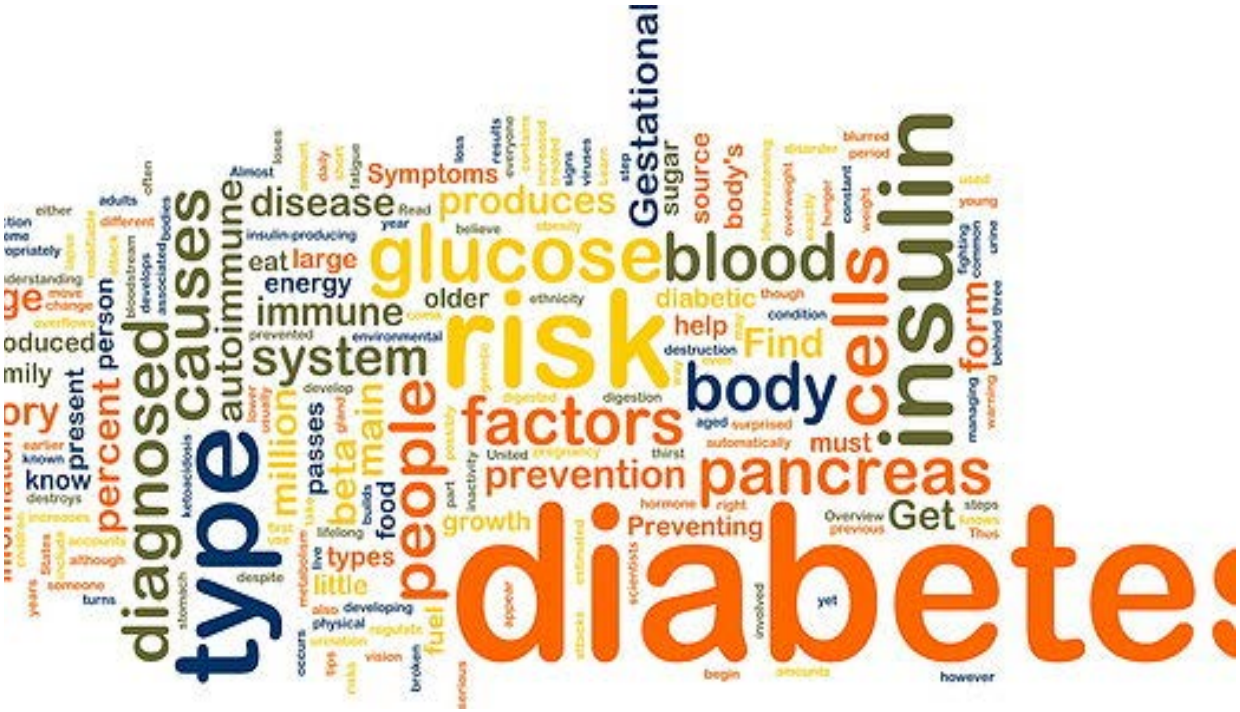
COMMUNITY RESOURCES MORE RESOURCES LITERATURE

NIDDK Information Network

dkNET provides a catalog of resources important to research on kidney, urologic, hematologic, digestive, metabolic and endocrine diseases, diabetes and nutrition.

JOIN THE COMMUNITY ▶

Data being captured by DKnet reflects the research areas of our investigators



SUBCATEGORIES

- Antibodies 2,247,301
- Vectors 30,378
- Embryonic stem cell 39
- PCR Primer 54

SOURCES

- AntibodyRegistry: ABs 2,247,115
- BCBC: Resources 159
- Nuclear Receptor Signaling Atlas: Antibody 61
- AddGene: Plasmids 30,241
- BCBC: Adenovirus 137
- Nuclear Receptor Signaling Atlas: NURSA 59

Showing 1 to 23 out of 2,277,772 Results from the search: *

Antibody Registry
RAB27A Antibody
The Novus Biologicals RAB27A Antibody Catalog number NBP1-46413 (Immunohistochemistry, Western Blot human) is described by the AntibodyRegistry.

Beta Cell Biology Consortium
Monoclonal Human E-cadherin raised in Mouse
The Beta Cell Biology Consortium provides Monoclonal Human E-cadherin raised in Mouse mice with the gene CDH1 modified.

BL438
A polyclonal antibody raised in Rabbit against SRC-3 that can be used for Immunoprecipitation, Western Blot.

addgene
pDEST51-LRRK2-Y1699C plasmid
The H. sapiens (human) pDEST51-LRRK2-Y1699C with the genetic insert LRRK2 (AURA17, DARDARIN, PARK8, RIPK7, ROCO2) plasmid
vector backbone: pEF-DEST51
vector type: Mammalian Expression ; Destination Vector
provided by Addgene (reference id PMID:18397888).

Beta Cell Biology Consortium
OE.Rabbit.GM.CMV
Adenovirus expressing GM (GM) driven by the CMV promoter.

Embryonic Stem Cell Line : ER-alpha
Embryonic Stem Cell Line : ER-alpha interacts with gene(s): ESR1
According to: Nuclear Receptor Signaling Atlas 20382891

Beta Cell Biology Consortium
Pdx1^{CFP}
The Beta Cell Biology Consortium provides Pdx1^{CFP} mice with the gene Pdx1 modified.

Rxra_40
Rxra_40 interacts with gene(s): Rxra
According to: Nuclear Receptor Signaling Atlas

SUBCATEGORIES

- Antibodies 86
- Vectors 0
- Embryonic stem cell 0
- PCR Primer

SOURCES

- AntibodyRegistry: ABs 81
- BCBC: Resources 5
- Nuclear Receptor Signaling Atlas: Antibody 0
- AddGene: Plasmids 0
- BCBC: Adenovirus 0
- Nuclear Receptor Signaling Atlas: NURSA 0

Showing 1 to 4 out of 86 Results from the search: **antibody** **nkx6.1** and also Included Terms X

Antibody Registry

anti NKX6-1 (C-term) antibody

The Acris Antibodies GmbH anti NKX6-1 (C-term) antibody Catalog number AP52893PU-N (manufacturer recommendations: Igg E, WB; ELISA; Western Blot human; mouse; hu, ms) is describe AntibodyRegistry.

Beta Cell Biology Consortium

Monoclonal Rat Nkx6.1 raised in Mouse

The Beta Cell Biology Consortium provides Monoclonal Rat Nkx6.1 raised in Mouse mice with the gene Nkx6-1 modified.

Antibody Registry

Goat Anti-NKX6.1 Polyclonal Antibody, Unconjugated

The R&D Systems Goat Anti-NKX6.1 Polyclonal Antibody, Unconjugated Catalog number AF5857 (manufacturer recommendations: Immunohistochemistry; Western Blot; Immunohistochemistry human; mouse) is described by the AntibodyRegistry.

Beta Cell Biology Consortium

Monoclonal Rat Nkx6.1 raised in Mouse

The Beta Cell Biology Consortium provides Monoclonal Rat Nkx6.1 raised in Mouse mice with the gene Nkx6-1 modified.

dkNET is supported by The National Institute of Diabetes and Digestive and Kidney Diseases under grant U24DK097771

NIDDK Information Network

dkNET provides a catalog of resources important to research on kidney, urologic, hematologic, digestive, metabolic and endocrine diseases, diabetes and nutrition.

Antibody Registry

Showing 1 - 1 results out of 1 with the query: * with filters: Antibody%20ID:AB_11147598 X

Antibody ID	Antibody Name	Antibody Target	Vendor	Cat Num	Clonality	Clone ID	Host Organism	Comments	Proper Citation	Reference
AB_11147598	anti NKX6-1 (C-term) antibody	anti NKX6-1 (C-term)	Acris Antibodies GmbH Go To Vendor	AP52893PU-N	unknown		rabbit	manufacturer recommendations: Igg E, WB; ELISA; Western Blot human; mouse; hu, ms	(Acris Antibodies GmbH Cat# AP52893PU-N, RRID:AB_11147598)	

NIDDK Information Network

SUBCATEGORIES

- Antibodies 86
- Vectors 0
- Embryonic stem cell 0
- PCR Primer 0

SOURCES

- AntibodyRegistry: ABs 81
- BCBC: Resources 5
- Nuclear Receptor Signaling Atlas: Antibody 0
- AddGene: Plasmids 0
- BCBC: Adenovirus 0
- Nuclear Receptor Signaling Atlas: NURSA 0

Showing 1 to 4 out of 86 Results from the search: **antibody** **nkx6.1** and also Included Terms X

Antibody Registry

anti NKX6-1 (C-term) antibody

The Acris Antibodies GmbH anti NKX6-1 (C-term) antibody Catalog number AP52893PU-N (manufacturer recommendations: Igg E, WB; ELISA; Western Blot human; mouse; hu, ms) is describe AntibodyRegistry.

Beta Cell Biology Consortium

Monoclonal Rat Nkx6.1 raised in Mouse

The Beta Cell Biology Consortium provides Monoclonal Rat Nkx6.1 raised in Mouse mice with the gene Nkx6-1 modified.

Antibody Registry

Goat Anti-NKX6.1 Polyclonal Antibody, Unconjugated

The R&D Systems Goat Anti-NKX6.1 Polyclonal Antibody, Unconjugated Catalog number AF5857 (manufacturer recommendations: Immunohistochemistry; Western Blot; Immunohistochemistry human; mouse) is described by the AntibodyRegistry.

Beta Cell Biology Consortium

Monoclonal Rat Nkx6.1 raised in Mouse

The Beta Cell Biology Consortium provides Monoclonal Rat Nkx6.1 raised in Mouse mice with the gene Nkx6-1 modified.

1 2 3 4 5 6 Next

dkNET is supported by The National Institute of Diabetes and Digestive and Kidney Diseases under grant U24DK097771

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Monoclonal Rat Nkx6.1 raised in Mouse - Antibody RES309

Antibody Information

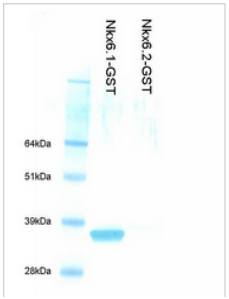
Antibody ID:	AB2023
Antigen:	Nkx6.1 (NCBI Gene ID: 65193)
Type:	Monoclonal
Isotype:	IgG1
Immunogen Source:	Fusion Protein
Raised In:	Mouse
Peptide:	GST-Nkx6.1(aa299-365)
Source of Antigen:	Rat
Cross Reacts With:	Mouse,Rat
Affinity Purified:	Affinity Purified
Purity Details:	*Not provided*
Positive Control:	Adult mouse pancreas
Notes:	*Not provided*

Applications and Uses

Application	Concentration	Storage Buffer	Protocols and Description
WB	0.5 ug/ml	PBS, 0.05% Sodium Azide	Description: *Not provided* Protocols: *Not provided*
IHC-AlFr	1:1000	PBS, 0.05% Sodium Azide	Description: *Not provided* Protocols: 1. TSA staining protocol

Associated Images

Image 1



Description:
Western blot with mAb F55A12. Lane 1. SeeBlue Plus2 pre-staind Standard. Lane 2. GST-Nkx6.1(aa299-365). Lane 3. GST-Nkx6.2(aa208-277)

Reference:
Not provided

Access Status

This resource is publicly viewable.

Request this Resource

Request from a repository

Primary contributor: Antibody Core (Retired)
Co-contributed by:
- Antibody Core (USA)

Resource Tags

AbCore, antibody, DSHB, Monoclonal, Nkx6.1, Rat

Login to edit tags

Read more about tags

Resource History & Actions

Approved on
Last modified on Sep 27, 2004

Login to edit or request an edit

Related resources

BCBC

No matching resources

Other Consortia

No matching resources

Data courtesy of dkCOIN. Only public resources are displayed.

SUBCATEGORIES

- Opportunities 28,128
- Funded Grants 175,802

SOURCES

- Grants.gov: Opportunity 28,128
- Integrated: Grants 175,802

Showing 1 to 20 out of 203,930 Results from the search: *

River Conservation Tools and Learning Network Development
The National Park Service Contacts: June Zastrow, 303-987-6718 June_Zastrow@nps.gov E-mail address: June_Zastrow@nps.gov has announced that they will fund River Conservation Tools and Learning Network Development project (see P14AS00287), with a closing date of Thu Sep 04 00:00:00 PDT 2014.

ROLE OF MUC1 IN THE GENESIS OF ALLERGIC ASTHMA
A R21 grant awarded to KIM, KWANG CHUL by the NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES 2009, funded from 06/05/2009 to 05/31/2010. Project number: 1R21AI073988-01A1.

SNPLMA Riparian Restoration Muddy River
The Bureau of Land Management Contacts: Gretchen Eykelbosh, Grants and Agreements Specialist, 775-861-6740 geykelbosh@blm.gov E-mail address: geykelbosh@blm.gov has announced that they will fund SNPLMA Riparian Restoration Muddy River project (see L14AS00243), with a closing date of Tue Aug 05 00:00:00 PDT 2014.

Characterization of Mutagenesis, Mutational Spectra and Mechanisms of Toxicity
A P01 grant awarded to WOGAN, GERALD N by the NATIONAL CANCER INSTITUTE 2009, funded from 04/01/2009 to 12/31/2009. Project number: 2P01CA026731-30.

Living Coast Discovery Center Student Scientist Series
The Fish and Wildlife Service Contacts: Deetta Gibbons, 760-930-0168 deetta_gibbons@fws.gov E-mail address: deetta_gibbons@fws.gov has announced that they will fund Living Coast Discovery Center Student Scientist Series project (see F14AS00407), with a closing date of Fri Aug 29 00:00:00 PDT 2014.

FBT-PET Study of Aging Skeletal Muscle
A R21 grant awarded to DELBONO, OSVALDO by the NATIONAL INSTITUTE ON AGING 2009, funded from 02/01/2009 to 01/31/2010. Project number: 1R21AG033385-01.

Idaho 2016 Challenge Cost Share Program
The Bureau of Land Management Contacts: Christine Shaver, Grants Management Officer, 208-373-3817 cshaver@blm.gov E-mail address: cshaver@blm.gov has announced that they will fund Idaho 2016 Challenge Cost Share Program project (see L14AS00325), with a closing date of Fri Dec 12 00:00:00 PST 2014.

Molecular and cellular mechanisms of vascular patterning by PlexinD1 signaling
A R01 grant awarded to TORRES-VAZQUEZ, JESUS by the NATIONAL HEART, LUNG, AND BLOOD INSTITUTE 2009, funded from 12/01/2008 to 11/30/2009. Project number: 1R01HL092263-01A1.

OAH

SUBCATEGORIES

- Opportunities 1,478
- Funded Grants 37,555

SOURCES

- Grants.gov: Opportunity 1,478
- Integrated: Grants 37,555

Showing 1 to 20 out of 39,033 Results from the search: **diabetes** and **aging** and also Included Terms X

GRANTS.GOV

[Surveillance, Natural History, Quality of Care and Outcomes of Diabetes Mellitus with Onset in Childhood and Adolescence (U-18)]
The Centers for Disease Control and Prevention Contacts: CDC PGOTIM Phone 770-488-2700 E-mail address: pgotims@cdc.gov has announced that they will fund Surveillance, Natural History, Quality of Care and Outcomes of Diabetes Mellitus with Onset in Childhood and Adolescence (U-18) project (see RFA-DP10-001), with a closing date of Fri Apr 30 00:00:00 PDT 2010.

INTEGRATED THROUGH SciCrunch

[Epidemiology of Type 2 Diabetes Mellitus in Adults]
A ZIA grant awarded to KNOWLER, WILLIAM by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES . Project number: 1ZIADK069000-46.

GRANTS.GOV

[Regional and International Differences in Health and Longevity at Older Ages (R01)]
The National Institutes of Health Contacts: NIH OER Webmaster FBOWebmaster@OD.NIH.GOV E-mail address: FBOWebmaster@OD.NIH.GOV has announced that they will fund Regional and International Differences in Health and Longevity at Older Ages (R01) project (see RFA-AG-11-004), with a closing date of Thu Oct 14 00:00:00 PDT 2010.

INTEGRATED THROUGH SciCrunch

[Lactation and Incidence of Diabetes Mellitus in CARDIA Women]
A R01 grant awarded to GUNDERSON, ERICA PAULINE by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2013, funded from 09/17/2013 to 05/31/2014. Project number: 3R01DK090047-03S1.

GRANTS.GOV

[Regional and International Differences in Health and Longevity at Older Ages (R21)]
The National Institutes of Health Contacts: NIH OER Webmaster FBOWebmaster@OD.NIH.GOV E-mail address: FBOWebmaster@OD.NIH.GOV has announced that they will fund Regional and International Differences in Health and Longevity at Older Ages (R21) project (see PA-13-124), with a closing date of Wed Sep 07 00:00:00 PDT 2016.

INTEGRATED THROUGH SciCrunch

[Lactation and Incidence of Diabetes Mellitus in CARDIA Women]
A R01 grant awarded to GUNDERSON, ERICA PAULINE by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2011, funded from 07/12/2011 to 05/31/2012. Project number: 1R01DK090047-01A1.

GRANTS.GOV

[Regional and International Differences in Health and Longevity at Older Ages (R03)]
The National Institutes of Health Contacts: NIH OER Webmaster FBOWebmaster@OD.NIH.GOV E-mail address: FBOWebmaster@OD.NIH.GOV has announced that they will fund Regional and International Differences in Health and Longevity at Older Ages (R03) project (see PA-13-123), with a closing date of Wed Sep 07 00:00:00 PDT 2016.

INTEGRATED THROUGH SciCrunch

[A Novel Therapy for Restricted Induction of Tolerance to Treat Diabetes Mellitus]
A R43 grant awarded to MURTHY, KANNEGANTI by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2013, funded from 02/19/2013 to 01/31/2015. Project number: 1R43DK094622-01A1.

NIDDK Information Network

SUBCATEGORIES

- Opportunities 0
- Funded Grants 139

SOURCES

- Grants.gov: Opportunity 0
- Integrated: Grants 139

Showing 1 to 10 out of 139 Results from the search: **funding drosophila model diabetes** and also Included Terms X

SciCrunch

[Tunable Insulin Resistance in a Drosophila Model of Diabetes](#)
A R43 grant awarded to GRACHEVA, ELENA M by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2010, funded from 09/01/2010 to 06/30/2012. Project number: 1R43DK089853-01.

SciCrunch

[Using Drosophila to Screen p38 Inhibitors Targeted to the Liver as Novel Diabetes](#)
A R43 grant awarded to GRACHEVA, ELENA M by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2009, funded from 09/10/2009 to 08/31/2011. Project number: 1R43DK084803-01.

SciCrunch

[A Drosophila Model for Genetic Studies of Metabolism](#)
A RC1 grant awarded to THUMMEL, CARL S. by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2009, funded from 09/19/2009 to 08/31/2010. Project number: 1RC1DK086426-01.

SciCrunch

[Systemic regulation of energy homeostasis using a Drosophila Leptin model](#)
A K99 grant awarded to RAJAN, AKHILA by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2014, funded from 08/01/2014 to 07/31/2015. Project number: 1K99DK101605-01A1.

SciCrunch

[A Drosophila Model to Study Genetic Interaction Between the Circadian Clock and M](#)
A F32 grant awarded to SEAY, DANIEL JASON by the NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES 2010, funded from 06/01/2010 to 05/31/2011. Project number: 1F32GM093572-01.

SciCrunch

[Drosophila Model for Genetics of Obesity](#)
A R01 grant awarded to ZINN, KAI G by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2010, funded from 11/19/2009 to 08/31/2010. Project number: 3R01DK070154-04S1.

SciCrunch

[Genetic Regulation of Drosophila Hematopoiesis](#)
A R01 grant awarded to FOSSETT, NANCY G by the NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES 2011, funded from 09/15/2011 to 08/31/2012. Project number: 2R01DK072229-06A1.

SciCrunch

[Genetic analysis of damage-induced intestinal stem cell division in Drosophila](#)

NIDDK Information Network

SOURCES

Nuclear Receptor Signaling Atlas: NURSA 11
MMPC: MMPC 108
Diabetic Complications Consortium: Diabetes Data 63
GUDMAP: Protocols 64
BCBC: Protocol 55

Showing 1 to 20 out of 301 Results from the search: *

DamIP: A novel method to identify DNA binding sites in vivo
DamIP: A novel method to identify DNA binding sites in vivo interacts with gene(s):
According to: Nuclear Receptor Signaling Atlas

UC Davis - LDL Protocol
The National Mouse Metabolic Phenotyping Centers provides mice with the genotype UC Davis - LDL Protocol () with the gene modified.

Echocardiography: Mouse
The Diabetic Complications Consortium provides Echocardiography: Mouse mice with the gene modified.

Preparing OCT blocks of kidney tissue
Preparing OCT blocks of kidney tissue protocol developed by the .

FACS of Human Islet Cell Types
Cell sorting protocol for FACS of Human Islet Cell Types

Mutual information identifies sequence positions conserved within the nuclear receptor superfamily: approach reveals functionally imp
regions for DNA binding specificity
Mutual information identifies sequence positions conserved within the nuclear receptor superfamily: approach reveals functionally important regions for DNA binding specificit
According to: Nuclear Receptor Signaling Atlas

Evaluation of Mitochondrial Function
The National Mouse Metabolic Phenotyping Centers provides mice with the genotype Evaluation of Mitochondrial Function () with the gene modified.

Determination of Podocyte Number and Density in Rodent Glomeruli
The Diabetic Complications Consortium provides Determination of Podocyte Number and Density in Rodent Glomeruli mice with the gene modified.

NIDDK Information Network

SOURCES

Nuclear Receptor Signaling Atlas: NURSA 11
MMPC: MMPC 108
Diabetic Complications Consortium: Diabetes Data 63
GUDMAP: Protocols 64
BCBC: Protocol 55

Showing 1 to 20 out of 301 Results from the search: *

DamID: A novel method to identify DNA binding sites in vivo
DamID: A novel method to identify DNA binding sites in vivo interacts with gene(s):
According to: Nuclear Receptor Signaling Atlas

UC Davis - LDL Protocol
The National Mouse Metabolic Phenotyping Centers provides mice with the genotype UC Davis - LDL Protocol () with the gene modified.

Echocardiography: Mouse
The Diabetic Complications Consortium provides Echocardiography: Mouse mice with the gene modified.

Preparing OCT blocks of kidney tissue
Preparing OCT blocks of kidney tissue protocol developed by the .

FACS of Human Islet Cell Types
Cell sorting protocol for FACS of Human Islet Cell Types

Mutual information identifies sequence positions conserved within the nuclear receptor superfamily: approach reveals functionally imp
regions for DNA binding specificity
Mutual information identifies sequence positions conserved within the nuclear receptor superfamily: approach reveals functionally important regions for DNA binding specificit
According to: Nuclear Receptor Signaling Atlas

Evaluation of Mitochondrial Function
The National Mouse Metabolic Phenotyping Centers provides mice with the genotype Evaluation of Mitochondrial Function () with the gene modified.

Determination of Podocyte Number and Density in Rodent Glomeruli
The Diabetic Complications Consortium provides Determination of Podocyte Number and Density in Rodent Glomeruli mice with the gene modified.

NIDDK Information Network

SOURCES

- Nuclear Receptor Signaling Atlas: NURSA 0
- MMPC: MMPC 1
- Diabetic Complications Consortium: Diabetes Data 1
- GUDMAP: Protocols 0
- BCBC: Protocol 0

Showing 1 to 2 out of 2 Results from the search: **nephropathy**

[Validation of Mouse Models of Diabetic Nephropathy]

The National Mouse Metabolic Phenotyping Centers provides mice with the genotype Validation of Mouse Models of Diabetic Nephropathy () with the gene modif

[Validation of Mouse Models of Diabetic Nephropathy]

The Diabetic Complications Consortium provides Validation of Mouse Models of Diabetic Nephropathy mice with the gene modified.

1

SUBCATEGORIES

- Functional Genomics Study 104
- Image 145,255
- Real Time PCR 182
- Co-Immunoprecipitation 249
- Expression 3,862

SOURCES

- BCBC: Resources 104
- Diabetic Complications Consortium: Diabetes Data 245
- GUDMAP: Image 145,010
- Nuclear Receptor Signaling Atlas: NURSA 431
- GUDMAP: Expression 3,862

Showing 1 to 20 out of 149,652 Results from the search: *

Gene expression analysis of control versus VHLH KO islets
The Beta Cell Biology Consortium provides Gene expression analysis of control versus VHLH KO islets mice with the gene 4930583H14Rik, Adm, Ak4, Aldoc, Astn1, Ccdc109b, Egln3, Fam
Pdk1, Pfkfb3, Pfkp, Plod2, Prelid2 modified. PMID:19056893

Normal glomeruli
The Diabetic Complications Consortium provides Normal glomeruli mice with the gene Nos3 modified.

GUDMAP-Little
ISH (In Situ Hybridisation) data for gene microfibrillar associated protein 5 from the testis at TS 21

RXRalpha : Macrophage activation expression patterns of nuclear receptors
RXRalpha : Macrophage activation expression patterns of nuclear receptors interacts with gene(s): Rxra
According to: Nuclear Receptor Signaling Atlas 16051664

RTA
RTA interacts with gene(s): HSPD1, KIAA1967, RBFOX2, SHMT1
According to: Nuclear Receptor Signaling Atlas 21620140

GUDMAP-Little
ISH (In Situ Hybridisation) data shows that expression of gene versican is present in the ureter at TS 20

Brown preadipocyte IRS knockout profiling 1
The Beta Cell Biology Consortium provides Brown preadipocyte IRS knockout profiling 1 mice with the gene modified. PMID:15895078

FVB-FXRnull non-diabetic female control liver showing ceroid-like pigment accumulation
The Diabetic Complications Consortium provides FVB-FXRnull non-diabetic female control liver showing ceroid-like pigment accumulation mice with the gene Nr1h4 modified.

GUDMAP-Little

Expression Database > Gene Strips

Result of *Gene* query for *microfibrillar associated protein 5*

Column Selection | Default Order | Display 20

1 Row: Page 1 of 1

	Gene	Synonyms	Disease	Theiler Stage	Expression Profile	Expression Images	Microarray expression profile	RNA-SEQ
	Mfap5	MAGP-2	OMIM(0)	TS17-28				View on UCSC Browser

Items in My Genes: 0

Add | Replace

Get intersection with

Get difference with

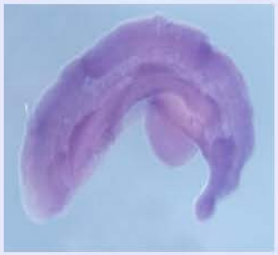
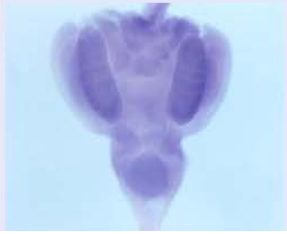
Expression Database
Tissue Summaries
Analysis
Downloads
Data Source
Collections

Expression Database

Gene: Mfap5

Column Selection

12 Row: Page 1 of 2

TS17	TS20	TS21
GUDMAP:7533 TS17 	GUDMAP:7534 TS20 	GUDMAP:9968 TS21 
GUDMAP:7533 TS17 	GUDMAP:7534 TS20 	GUDMAP:9968 TS21 
GUDMAP:9967 TS17 	GUDMAP:7535 TS20 	GUDMAP:9968 TS21 

SUBCATEGORIES

Mouse 344

Rat N/A

SOURCES

Diabetic Complications Consortium: Diabetes Data 139

BCBC: Resources 86

MMPC: MMPC 95

Integrated: Animals 0

T1DBase: Resource 21

Nuclear Receptor Signaling Atlas: NURSA 3

Showing 1 to 43 out of 344 Results from the search: *

FVB-Ins2^{Akita}

The Diabetic Complications Consortium provides FVB-Ins2^{Akita} mice with the gene Ins2 modified.

Gt(ROSA)26Sor$^{tm1(GCK*)Ydor}$

The Beta Cell Biology Consortium provides Gt(ROSA)26Sor$^{tm1(GCK*)Ydor}$ mice with the gene Gck, Gt(ROSA)26Sor modified.

C57BL/6J-Tg(Hk2)

The National Mouse Metabolic Phenotyping Centers provides mice with the genotype C57BL/6J-Tg(Hk2) () with the gene Hk2 modified.

NOD.B6-Idd3$^{C57BL/6J}$ Idd10$^{C57BL/6J}$ Idd18$^{C57BL/6J}$/1538MrkTacJ

The T1Dbase provides NOD.B6-Idd3$^{C57BL/6J}$ Idd10$^{C57BL/6J}$ Idd18$^{C57BL/6J}$/1538MrkTacJ Mouse Congenic strains with the gene 1700013F07Rik, 1700027A23Rik, 1700061I17Rik, 170009... 1810062G17Rik, 2010016I18Rik, 4833424O15Rik, 4921515J06Rik, 4930429B21Rik, 4930432M17Rik, 4930443G12Rik, 4930556A17Rik, 4930564D02Rik, 4932438A13Rik, 4933421E11... 6530418L21Rik, A630076J17Rik, A730020M07Rik, Abca4, Abcd3, Acad9, Actl6a, Adad1, Adora3, Agl, Ahcyl1, Al504432, Aknad1, Alg14, Alx3, ...[more]

PR KO mouse

PR KO mouse interacts with gene(s): Pgr

According to: Nuclear Receptor Signaling Atlas 15845616

DBA/2J-Ins2^{Akita}

The Diabetic Complications Consortium provides DBA/2J-Ins2^{Akita} mice with the gene Ins2 modified.

Insm1$^{tm1.1Mgn}$

The Beta Cell Biology Consortium provides Insm1$^{tm1.1Mgn}$ mice with the gene Insm1 modified.

C57BL/6J-Hfabp$^{-/-}$

The National Mouse Metabolic Phenotyping Centers provides mice with the genotype C57BL/6J-Hfabp$^{-/-}$ () with the gene Fabp3 modified.

NIDDK Information Network

SUBCATEGORIES

Mouse 39

Rat N/A

SOURCES

Diabetic Complications Consortium: Diabetes Data 14

BCBC: Resources 2

MMPC: MMPC 17

Integrated: Animals 0

T1DBase: Resource 6

Nuclear Receptor Signaling Atlas: NURSA 0

Showing 1 to 28 out of 39 Results from the search: **C57BL/6J** and also Included Terms X

C57BL/6J

The Diabetic Complications Consortium provides C57BL/6J mice with the gene modified.

Gck^{tm3Mgn}

The Beta Cell Biology Consortium provides Gck^{tm3Mgn} mice with the gene Gck modified.

C57BL/6J

The National Mouse Metabolic Phenotyping Centers provides mice with the genotype C57BL/6J (C57BL/6J is the most widely used inbred strain and the first to have its genome sequenc is refractory to many tumors, it is a permissive background for maximal expression of most mutations. C57BL/6J mice are resistant to audiogenic seizures, have a relatively low bone de related hearing loss. They are also susceptible to diet-induced obesity, type 2 di ...[more]

NOD.B6-Idd3$^{C57BL/6J}$ Idd10$^{C57BL/6J}$ Idd18$^{C57BL/6J}$/1538MrkTacJ

The T1Dbase provides NOD.B6-Idd3$^{C57BL/6J}$ Idd10$^{C57BL/6J}$ Idd18$^{C57BL/6J}$/1538MrkTacJ Mouse Congenic strains with the gene 1700013F07Rik, 1700027A23Rik, 1700061I17Rik, 1700 1810062G17Rik, 2010016I18Rik, 4833424O15Rik, 4921515J06Rik, 4930429B21Rik, 4930432M17Rik, 4930443G12Rik, 4930556A17Rik, 4930564D02Rik, 4932438A13Rik, 4933421E 6530418L21Rik, A630076J17Rik, A730020M07Rik, Abca4, Abcd3, Acad9, Actl6a, Adad1, Adora3, Agl, Ahcyl1, Al504432, Aknad1, Alg14, Alx3, ...[more]

(C57BL/6J X DBA/2J)F2

The Diabetic Complications Consortium provides (C57BL/6J X DBA/2J)F2 mice with the gene modified.

Gck^{tm2Mgn}

The Beta Cell Biology Consortium provides Gck^{tm2Mgn} mice with the gene Gck modified.

C57BL/6J Nrf2

The National Mouse Metabolic Phenotyping Centers provides mice with the genotype C57BL/6J Nrf2 () with the gene modified.

NOD.B6(PL)-Idd3$^{C57BL/6}$/MrkTacJ

The T1Dbase provides NOD.B6(PL)-Idd3$^{C57BL/6}$/MrkTacJ Mouse Congenic strains with the gene 4932438A13Rik, Adad1, Bbs12, Bbs7, Ccna2, Cetn4, Exosc9, Fqf2, Gm12540, Il2

SUBCATEGORIES

- Mouse 23
- Rat N/A

SOURCES

- Diabetic Complications Consortium: Diabetes Data 2
- BCBC: Resources 0
- MMPC: MMPC 0
- Integrated: Animals 0
- T1DBase: Resource 21
- Nuclear Receptor Signaling Atlas: NURSA 0

Showing 1 to 12 out of 23 Results from the search: **NOD** and also Included Terms X

SWR/J

The Diabetic Complications Consortium provides SWR/J mice with the gene modified.

NOD.B6-Idd3$^{C57BL/6J}$ Idd10$^{C57BL/6J}$ Idd18$^{C57BL/6J}$/1538MrkTacJ

The T1Dbase provides NOD.B6-Idd3$^{C57BL/6J}$ Idd10$^{C57BL/6J}$ Idd18$^{C57BL/6J}$/1538MrkTacJ Mouse Congenic strains with the gene 1700013F07Rik, 1700027A23Rik, 1700061I17Rik, 1700095B22Rik, 1810062G17Rik, 2010016I18Rik, 4833424O15Rik, 4921515J06Rik, 4930429B21Rik, 4930432M17Rik, 4930443G12Rik, 4930556A17Rik, 4930564D02Rik, 4932438A13Rik, 4933421E11Rik, 5330417 6530418L21Rik, A630076J17Rik, A730020M07Rik, Abca4, Abcd3, Acad9, Actl6a, Adad1, Adora3, Agl, Ahcyl1, Al504432, Aknad1, Alg14, Alx3, ...[more]

NON/LtJ

The Diabetic Complications Consortium provides NON/LtJ mice with the gene modified.

NODTac.129S6-Idd3^{129}

The T1Dbase provides NODTac.129S6-Idd3^{129} Mouse Congenic strains with the gene 1700017G19Rik, 1700018B24Rik, 1700034I23Rik, 1810062G17Rik, 3110057O12Rik, 4930429B21Rik, 4930556 4932438A13Rik, Acad9, Actl6a, Adad1, Ankrd50, Anxa5, Arpm1, Atp11b, Bbs12, Bbs7, Ccdc144b, Ccdc39, Ccna2, Cetn4, Cldn11, D3Ertd254e, D3Ertd751e, Dcun1d1, Dnajc19, Eqfem1, Exosc9, Fat4, Fo Gm10731, Gm12540, Gm12565, Gm15118, Gm2011, Gm2050, Gm2100, Gm2107, Gm2124, Gm2136, Gm2212, Gm2881, Gm2900, Gm ...[more]

NOD.B10Sn-H2^{b}/J

The T1Dbase provides NOD.B10Sn-H2^{b}/J Mouse Congenic strains with the gene 0610007P22Rik, 0610011F06Rik, 1110021J02Rik, 1110038B12Rik, 1700001C19Rik, 1700008K24Rik, 1700022N22R 1700067P10Rik, 1700097N02Rik, 1700122O11Rik, 1810013A23Rik, 2300002M23Rik, 2310039H08Rik, 2310061I04Rik, 2410017I17Rik, 2410137M14Rik, 2900010M23Rik, 3110082D06Rik, 4921501 4930511I11Rik, 4930526A20Rik, 4930528F23Rik, 4930539E08Rik, 4930564C03Rik, 9130008F23Rik, 9830107B12Rik, A330017A19Rik, A530064D06Ri ...[more]

NOD.B10-Idd9.2^{B10}Idd9.3^{B10}

The T1Dbase provides NOD.B10-Idd9.2^{B10}Idd9.3^{B10} Mouse Congenic strains with the gene 1700012P22Rik, 1700029I01Rik, 2510039O18Rik, 2610109H07Rik, 2610305D13Rik, 6330411D24Rik, 9430007A20Rik, Aadacl3, Aqtrap, Angptl7, Anp32b-ps1, Apitd1, BC080695, C87977, Camta1, Car6, Casz1, Clcn6, Clstn1, Cort, Ctnnbip1, D530049N12Rik, Dffa, Dhrs3, Efhd2, Eno1, Errfi1, Exosc10, Fb Fbxo44, Fbxo6, Fhad1, Fv1, Gm13023, Gm13034, Gm13035, Gm13040, Gm13043, Gm13050, Gm13051, Gm13057, Gm13072, Gm13078, Gm1 ...[more]

NOD.B10-Idd9.1$^{C57BL/10SnJ}$/1565MrkTacJ

The T1Dbase provides NOD.B10-Idd9.1$^{C57BL/10SnJ}$/1565MrkTacJ Mouse Congenic strains with the gene 1110065P20Rik, 1700003M07Rik, 1700029G01Rik, 1700057H15Rik, 1700125D06Rik, 1810019J16Rik, 3100002H09Rik, 4930429E23Rik, 4930465A12Rik, 4930546G22Rik, 5730409E04Rik, 9530002B09Rik, 9930104L06Rik, A3galt2, Adc, Adprhl2, Ahdc1, Aim1l, Ak2, Akirin1, Arid1a, Atpif AU040320, Bai2, BC003266, BC013712, Bmp8a, Bmp8b, Bsdc1, C77080, Cap1, Catsper4, Ccdc21, Ccdc28b, Cd164l2, Cd52, Cdca8, Cited4, CK137 ...[more]

COMMUNITY RESOURCES | MORE RESOURCES | LITERA

NOD

NIDDK Information Network

CATEGORIES ▶ Materials | Funding | Protocol | Data | Organisms | Mouse

SUBCATEGORIES

- Mouse
- Rat

SOURCES

- Diabetic Complications Consortium: Diabetes Data
- BCBC: Resources
- MMPC: MMPC
- Integrated: Animals
- T1DBase: Resource
- Nuclear Receptor Signaling Atlas: NURSA

Please visit the site and provide input: www.dknet.org

Site will be rapidly evolving over the next year as more/new activities are added, eg:

HIRN Human Islet Research Network

ISCC Intestinal Stem Cell Consortium

National Institute of Diabetes and Digestive and Kidney Diseases

Topics Today:

1. Mutant Mouse Regional Resource Centers (MMRRC)
2. NIDDK Information Network (DKnet)
3. Integrated Islet Distribution Program (IIDP)

IIDP
Integrated Islet Distribution Program

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

IIDP Isolation Centers & CC

IIDP Integrated Islet Distribution Program

DEPARTMENT OF HEALTH

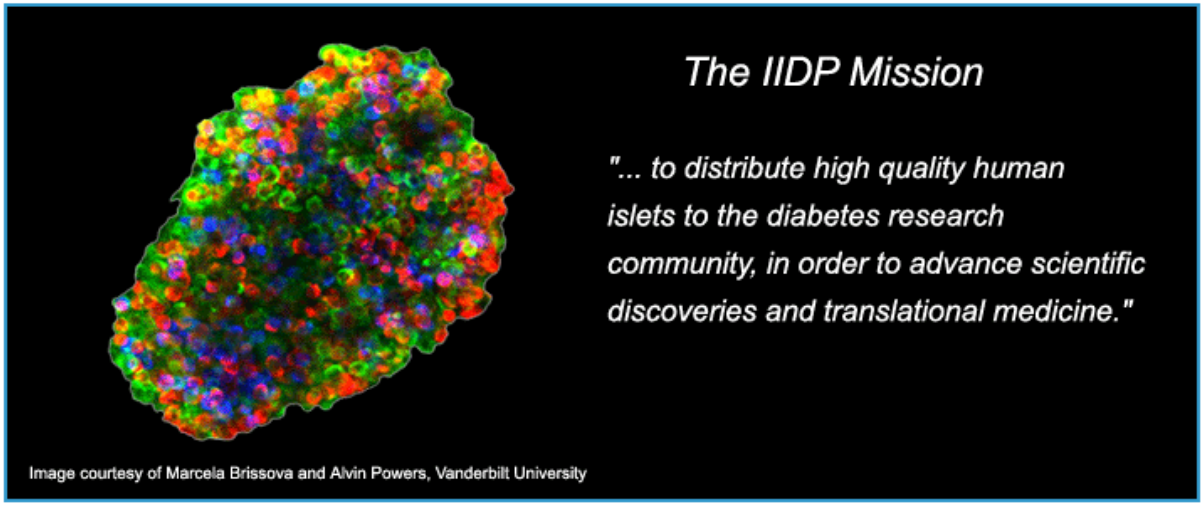
NIH Diabetes and Digestive and Kidney Diseases

https://iidp.coh.org

IIDP
Integrated Islet Distribution Program

Coordinated by City of Hope
Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

- Overview
- Organizational Structure
- IIDP Applications
- IIDP Pilot Program
- IIDP Publications
- Newsletters
- Workshops-Counting Manual



PROGRAM UPDATE!
IIDP Cost Reconstruction Announcement

Overview

Overview of the Program

The Integrated Islet Distribution Program (IIDP) funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and with support from the Juvenile Diabetes Research Foundation International (JDRFI), replaced the NCRR and JDRFI funded National Islet Cell Resource Consortium which ended July 31, 2009. The IIDP is now supported by NIDDK and continues to provide islet availability for fundamental research. The IIDP acknowledges and appreciates previous

For Investigators

Information for Investigators

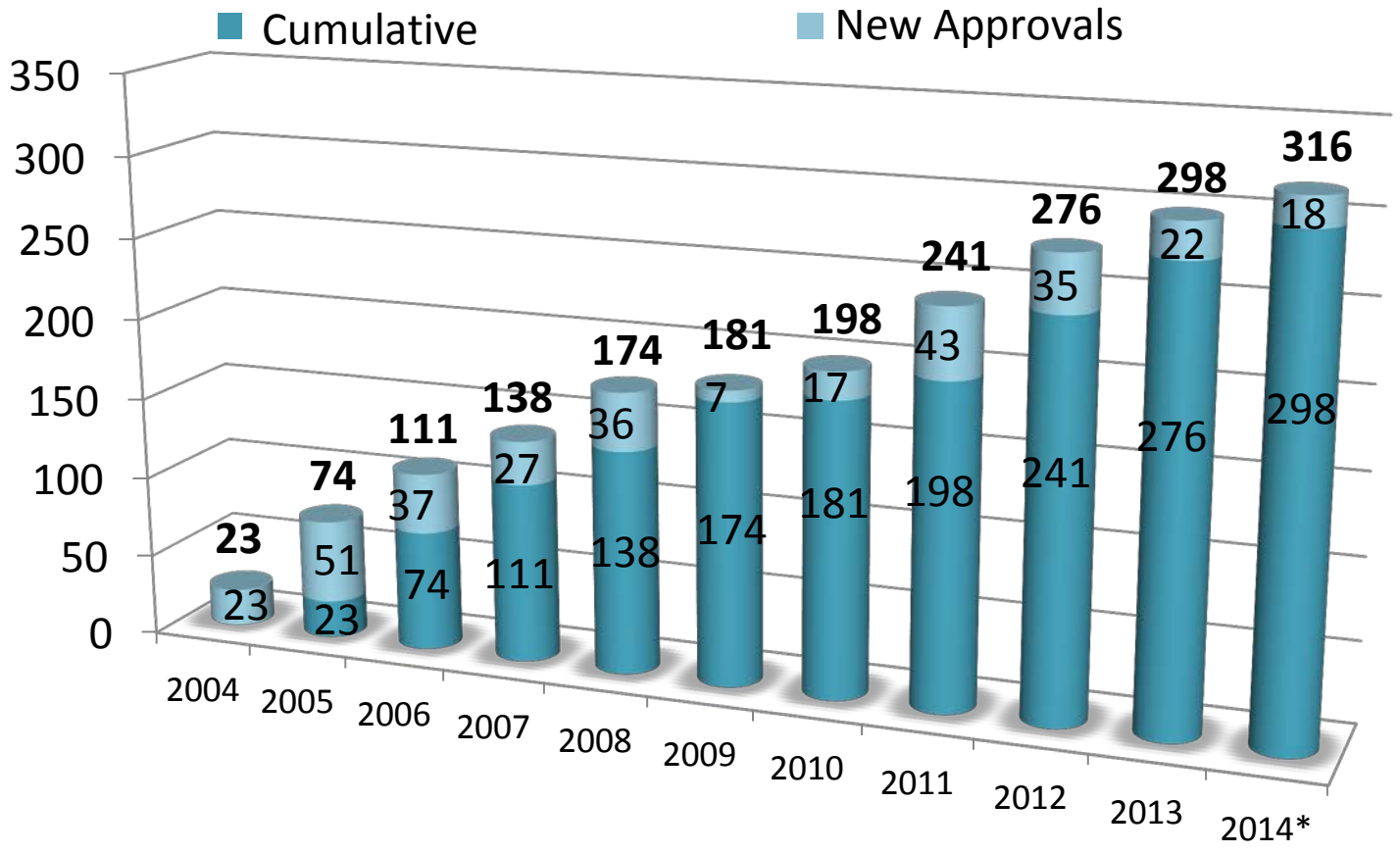
All investigators requesting islets must complete and submit an application to the IIDP Coordinating Center. In addition to the completed application form, applicants must also submit a concise but thorough and informative description of the specific objectives, methods associated with the use of islets, rationale for the number of islets requested and statistical methodologies to be employed. Click here for grant related verbiage.

For Centers

Organization

The IIDP organization consists of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Project Officer, an External Evaluation Committee, and the Coordinating Center at City of Hope. The IIDP integrates an interactive group of academic laboratories including IIDP centers and the Clinical Islet Transplant centers. The IIDP Coordinating Center is responsible for broadcasting the availability of of human islets to investigators nationwide.

IIDP supported studies are increasing



*2014 data through 8/27/14

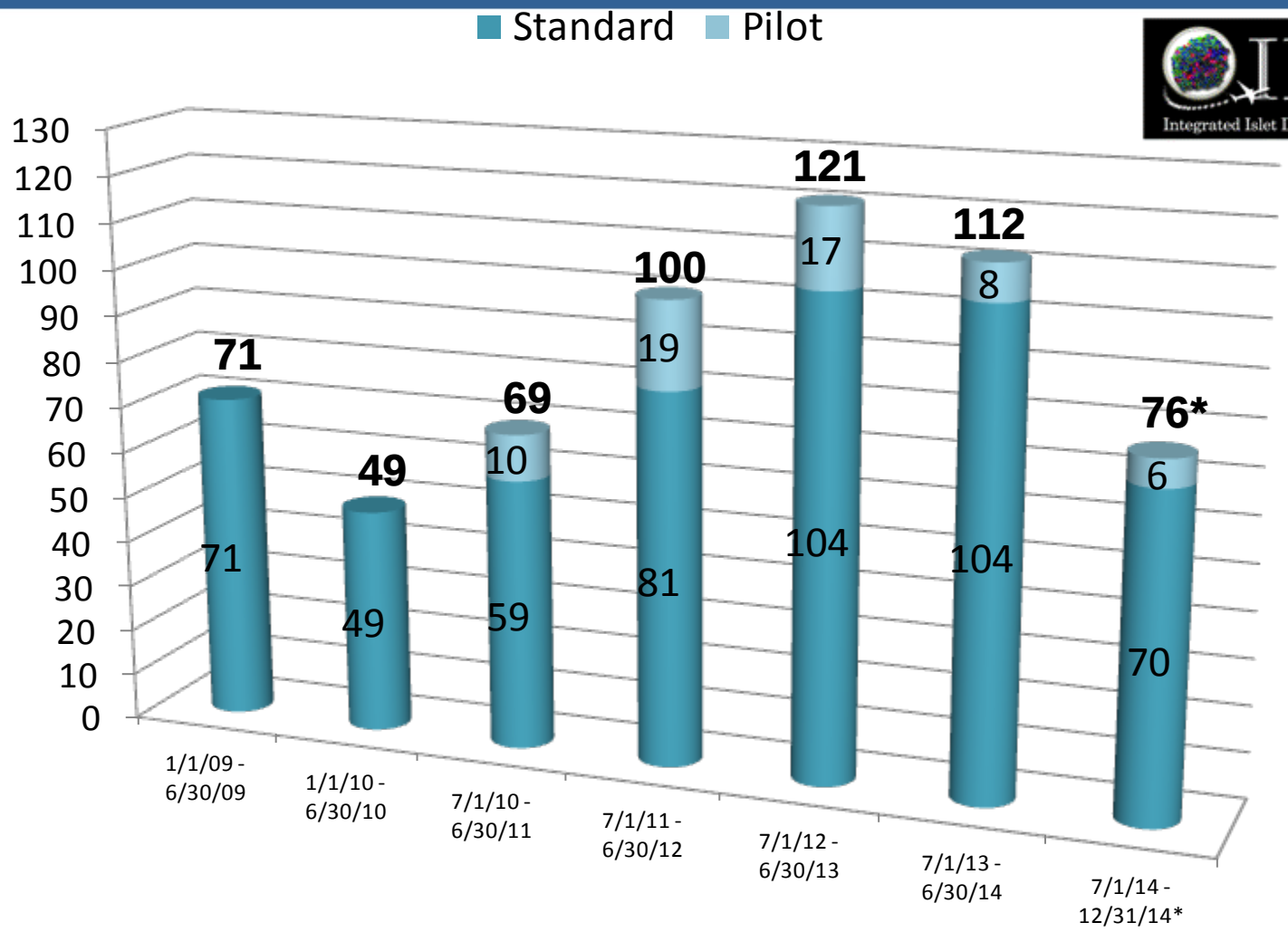
Diabetes Research Projects Supported by ICR/IIDP

Sub-Area of Research	Number of Studies (n=316)*
**Approved from Feb. 12, 2004 – August 27, 2014*	**Prevention and Treatment**
Preservation of Beta-Cell Mass/Function	33
Autoimmunity	17
Clinical Interventions	27
Generation of Beta-Cells from Stem Cells	16
Beta-Cell Growth/Differentiation	37
Other	14
≥2 Prevention and Treatment Sub-Areas	19
	Pathophysiology
Genetics	7
Insulin	1
Metabolism	1
Glucose Homeostasis	6
Endocrine Pancreas	5
Cell Signaling/Regulation	13
Other	8
≥ 2 Pathophysiology Sub-Areas	7
	Both Major Areas or Not Reported
> 2 any Sub-Areas	100
Not Reported	5

Islet Distributions are increasing each year

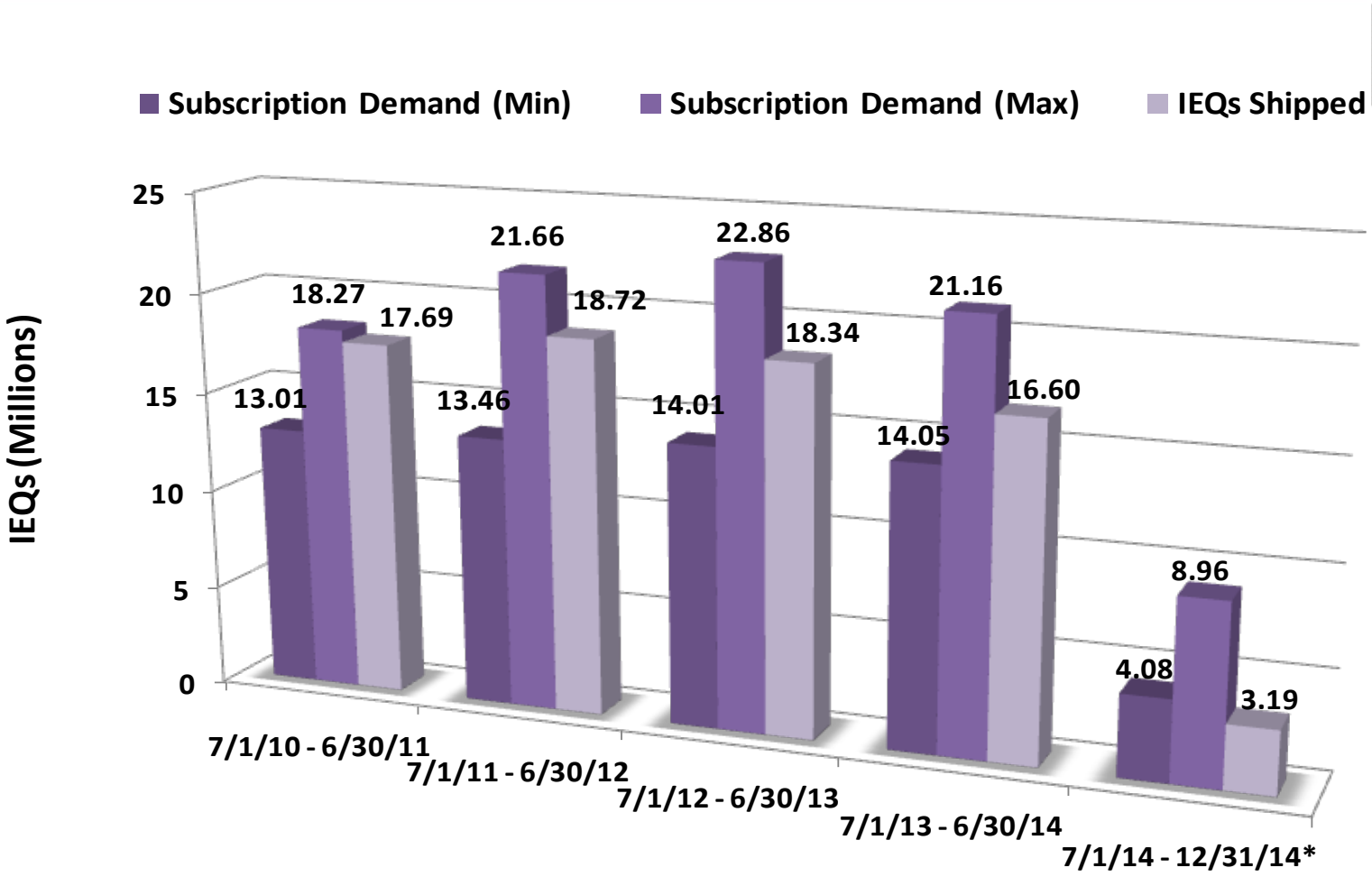
*Data through 8/27/14

~100-120 researchers access IIDP resources each year



*NOTE: Data through 8/27/2014

Subscription Demand vs. Islet Distributions



*Data through 8/27/14

NOTE: Includes Pilot Program Distributions

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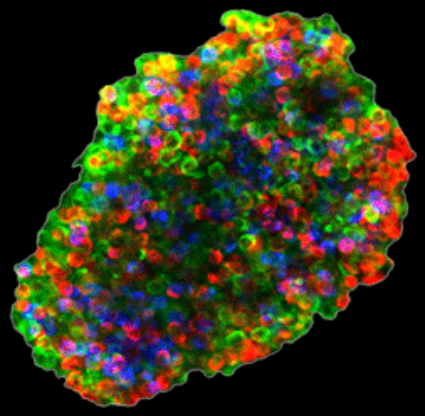

Image courtesy of Marcela Brissova and Alvin Powers, Vanderbilt University

The IIDP Mission

"... to distribute high quality human islets to the diabetes research community, in order to advance scientific discoveries and translational medicine."

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IIDP
Integrated Islet Distribution Program

Date: July 24, 2014

NOTICE TO IIDP COMMUNITY: Upcoming changes to IIDP cost-sharing price structure

Dear Subscriber:

We are writing this communication to inform you of future changes in the cost-sharing price structure that you will encounter in receiving human islets.

As you are aware, the Integrated Islet Distribution Program (IIDP) has been heavily subsidized by NIDDK/NIH with a special Congressional Appropriation for Type 1 Diabetes serving as the principal funding source. Importantly, these funds have enabled notable strides in human islet discovery research and expanded research efforts in this important field. Commensurate with these endeavors, the demand for these valuable tissues has increased and we believe this trend will continue into the foreseeable future.

In an effort to ensure our ability to provide high quality human islets for research, NIH has asked IIDP to move toward a modified financial support model that is designed to provide the program with a higher level of funding predictability and self-amortization. Towards this end, **starting in January 2015, IIDP will be increasing the cost sharing component provided by investigators for access to IIDP resources from the current $0.03/islet equivalent (ieq) subscription rate to $0.12/ieq.** This new rate is designed to approach the actual costs charged to IIDP by the islet isolation centers. As a result, all new or competing research applications, including NIH applications submitted for the October/November 2014 cycle and beyond, should include the new IIDP rate of $0.12/ieq as a specific budget line item.

We are aware that for many current subscribers this price increase may stress budgets that were negotiated prior to the increase. Therefore, the following accommodations will be provided for active research awards. Any applications that are currently under consideration at NIH that include the cost of islets from IIDP will be administratively adjusted at the time of award to accommodate the new $0.12 rate. Ongoing NIH grants that were originally funded at the lower rate will be considered for supplemental NIH funds on a case by case basis. Requests for supplemental funding to support increased costs of islets must be well justified and submitted to NIDDK for administrative review (application details coming soon). Investigators using IIDP resources to support non-NIH funded projects, including JDRF and ADA awardees and PIs supported by other funding agencies, should contact their respective funding organizations to explore options.

IIDP
Integrated Islet Distribution Program

https://iidp.coh.org

Coordinated by City of Hope
Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Home | Overview | Centers | Investigators | Publications | Login | City of Hope

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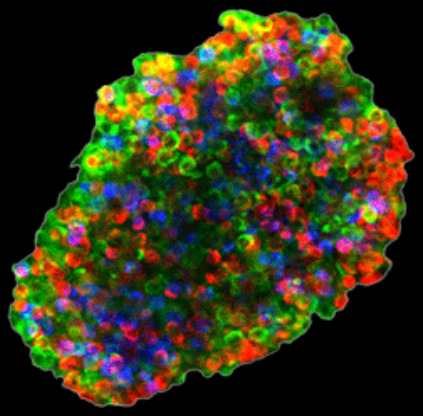

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PROGRAM UPDATE!
IIDP Cost Reconstruction Announcement

New cost structure starts with January 2015 subscriptions!! (from .03 to .12/ieq)

Transition Plan:

1. Pending NIH awards will have budgets adjusted prior to award
2. Current NIH awards will be supplemented (FOA coming soon)
3. Current JDRF awards will be supplemented (FOA coming soon)
4. New applications should incorporate new cost structure in request

National Institute of
Diabetes and Digestive
and Kidney Diseases

BEST PRACTICES AND DIABETES CENTERS APPLICATIONS

A recommendation was made from the Diabetes Centers Executive Committee to discuss issues related to interpretation of the DRC program guidelines/RFA and best practices for our respective center applications. Specific areas for focus are those aspects in which the NIDDK program has provided applicant centers latitude to respond with the most effective and compelling center proposals for their particular institutions, yet review panels may interpret the program goals or guidelines differently. These issues arise in spite of considerable effort by NIDDK Program and Review Staff to educate review panels with respect to the DRC Program. Discussion of these issues has the potential to inform the presentation of these issues in our own applications, the crafting of future RFAs, and our own consideration of these issues as participants in review panels (in which Center Directors are often asked to participate and lead discussion). The following topics were suggested:

1. One common approach is to use DRC resources to support DRC member use of an established institutional Core. Given limited DRC resources and the high cost of establishing/supporting technology intensive cores, this can be a particularly effective way to leverage institutional support for NIDDK science. How do we best communicate in applications and in the RFA that this core model can be responsive to NIDDK's RFA?

2. Given the relatedness of approaches in DRC and NORC programs, what are the best practices regarding cores that are jointly sponsored by these P30 programs?

3. An important characteristic for successful DRCs is the ability to evolve to meet the changing needs of diabetes researchers. New (often small) cores can be appropriate, yet they can be judged harshly by the standards of fully established, mature cores. How do we stress the desirability of nimbleness and timeliness and the need to evaluate different kinds of cores (established, new) by different criteria?

4. What are the best models for incorporating investigators outside the primary DRC institution into Center activities including core use and participation in Pilot & Feasibility Programs? Should these investigators be incorporated into the formal Research Base?

5. Publications are linked to specific cores and the Pilot & Feasibility Programs in renewal applications. What about diabetes-related publications by Center members that are not linked to cores and Pilot program, yet have clearly benefited from the broader DRC environment?

Workshop
Technology-based Strategies for the Management of Diabetes Mellitus and its Complications
Mexico City, March 3-4, 2014

The 2 day workshop addressed the problem of the increasing burden of diabetes and obesity and its complications in Mexico and the US with a focus on areas where collaborative research between Mexican and US groups could be most fruitful.

Attendees included: US NIH leaders, Mexico NIH Leaders, Scientists from US and Mexico, and Senior Govt. Officials from Mexico

The Problem Facing Mexico in the Next Decade

Mexico is facing a Diabetes ‘Disaster' as the Prevalence of Obesity and Diabetes Has Increased Past the High Rates in the US.

Some highlights of the Meeting Discussions:

1. Improved screening, community outreach, and care delivery approaches in high risk diabetes areas in both the US and Mexico.

2. New devices/tests to follow and treat complications, e.g. (a) inexpensive retinoscopes with links to telemedicine; (b) biomarkers for progression of renal disease; or (c) procedures to speed healing and/or early detection of foot ulcers.

3. Joint basic medical research co-funded projects.

4. Post–doctoral training.

4. Health Policy: Mexico has recently imposed a sugar or soda tax (10%) on soft drinks and an 8% tax on junk foods in an attempt to address their obesity epidemic. They recognize major initiatives are required or their health care costs will explode.

Potential Mechanisms for Collaboration between the US and Mexico

Program announcement for research projects related to diabetes, diabetes complications or obesity involving collaboration between US and Mexican scientists with Mexico paying costs of research in Mexico.

NIH-M-NIH funding for joint clinical projects comparing interventions to improve prevention and health outcomes on both sides of US Mexico border (e.g. diabetes screening, prevention or telemedicine effort).

Potential joint US and Mexico studies of natural experiments or health care policies in Mexico, e.g. studies testing the application of the sugar tax.

Opportunities for Mexican new investigators to obtain research training in the U.S. if Mexico pays their stipends. NIDDK will provide funds annually to support costs of the research they perform as administrative supplements to centers, clinical consortia or other grants.

Provide technical assistance in developing SBIR-like programs in Mexico.

ENGAGING COMPUTATIONAL SCIENTISTS IN DIABETES RESEARCH
Follow up from NIDDK National Advisory Council Discussion 09/03/14

INTRODUCTION
We are witnessing evolution of scientific approaches that involve large computational problems and big data sets. Leveraging these computational approaches has potential to transform the biology that is focus of NIDDK's mission. Study of biological problems of interest to NIDDK has potential to spark evolution of computational approaches. Effective incorporation of computational approaches into NIDDK-focused science requires expertise in NIDDK-focused biology AND distinct expertise in computational approaches.

Current Approaches at NIH include:

1. Data Science Approaches through NIH Central that support eCommons, Career Development and Training Awards (T32 NHGRI, K01 NHGRI), curriculum awards, Centers of Excellence in Data Sciences (networked consortium of core centers that apply established pipelines, project-focused basic instruction, some custom services). These could address but are not restricted to NIDDK-focused science.
2. Existing NIDDK-sponsored training mechanisms could be used for engaging computational scientists in NIDDK-related areas (F31, F32, K01, K25, T32).

Issues:
Wet labs in NIDDK-focused science would ideally go beyond generation of samples to be handed off for core analysis and instead gain experience and deeper understanding of the methodological approaches and their uses. This has potential to improve the science and facilitate ability of next generation of scientists to leverage big data. But faculty and trainees with strong biology background may have insufficient training in mathematical, statistical, or programming approaches to effectively mine large data sets in customized way..

For computational biologists most interested in discovery of mathematical and computational underpinnings of analysis algorithms that can facilitate design and evaluation of new approaches, simple scripting to reformat files and extract data from databases may not have appeal. Academically, core services can be considered unrewarding or unrewarded. How does the field help computational scientists identify important new questions that can benefit from design and evaluation of new algorithms, when these scientists often lack training in NIDDK-related areas of biology to inform those investigations?

Co-mentored F/K series trainee and their program could serve to integrate the biological and computational approaches, mentors in different fields will have motivation for mentoring in own area of work for which funding exists. Trainees with background in computational sciences and programming may lack biological background relevant to NIDDK science.

FOR DISCUSSION--Ways in which Diabetes Research Centers might be leveraged:

1. Summer program modeled after the NIDDK Summer Medical Student Program to attract computationally focused undergraduates or medical students to NIDDK-related science

2. Supplemental funding through existing DRC P&F Programs to add new computationally-focused approaches and collaborations

DIABETES RESEARCH CENTERS

2014 Institutional Diabetes Center Websites

Albert Einstein College of Medicine: http://www.einstein.yu.edu/centers/diabetes-research/

Baltimore Area (JHU/UMD): http://www.hopkinsmedicine.org/drtc/index.html

Baylor College of Medicine: http://www.bcm.edu/diabetescenter/

Boston Area: http://www.baderc.org/

Columbia University: http://derc.cumc.columbia.edu/

Joslin Diabetes Center: http://www.joslin.org/diabetes-research/DRC-core-labs.html

University of Alabama at Birmingham: http://www.uab.edu/shp/drc/

UCSD/UCLA: http://drc.ucsd.edu/index.shtml

UCSF: http://diabetes.ucsf.edu/DERC

University of Chicago: http://drtc.bsd.uchicago.edu/

University of Michigan: http://www.med.umich.edu/mdrtc/

University of Pennsylvania: http://www.med.upenn.edu/idom/derc/

University of Washington: http://depts.washington.edu/diabetes/

Vanderbilt University: http://www.mc.vanderbilt.edu/diabetes/drtc/

Washington University in St. Louis: http://diabetesresearchcenter.dom.wustl.edu/index.htm

Yale University: http://derc.yale.edu/index.aspx

NIDDK DIABETES CENTERS
NON-COMPETING RENEWALS
(TYPE 5 PROGRESS REPORT)
INSTRUCTIONS
2014-2015

I. FORM PAGES

- Face page
- Cumulative Budget for Center (PHS 2590 Form Page 2)
- Budget and Justification for each Core (submit PHS 2590 Form Page 2 for each Core)
- List of **NEW key personnel** followed by their biographical sketches
- **Other support for all key personnel ONLY** (i.e. only for personnel listed as "KEY" in the Notice of Grant Award, or their recent replacements); please verify that "other support" information is current and that effort does not exceed 12 calendar months for any individual.
- **Budget note (2014):** increases due to inflation are NOT allowed [see: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-064.html]; for example, budget requests in progress reports that include salary increases (i.e. above FY2014 level of support) will be administratively reduced, and therefore the total amount of funds awarded will be decreased in the non-competing Notice of Award.

CENTER PROCESS MEASURES *(#sII-V)*

II. RESEARCH BASE (1-2 pages MAX for narrative text, exclusive of any Tables)

(Table) A. List Current Center Investigators – **list only changes** in membership since last year's report

- New members (name, dept, area of interest)
- Members lost (due to transfer, inactivity or other)

(Table) B. Enumeration & list of

- Publications directly traceable to center activities during the past year

Using My Bibliography provide a My NCBI generated PDF list of publications (see http://www.nlm.nih.gov/pubs/techbull/nd12/nd12_myncbi_pdf.html for instructions). My Bibliography will display the correct text format, and if available, include the appropriate reference number (PMID, PMCID, or NIHMSID), and compliance status. If a publication is not compliant with the public access policy NIH staff will contact the PD/PI and business official to inform them that the award will be delayed until a reply to the email is received with evidence of compliance or a satisfactory explanation (e.g., the sole author has passed away before they were able to process the manuscript for posting to PubMed Central). Generally, it takes weeks to bring publications into compliance; therefore, PD/PIs are advised to do so as soon as possible to ensure their award is renewed in a timely manner.

- Major changes in research grant support (new and/or ending from prior year)

(Text) C. New collaborative activities

- List & briefly describe any new Center programs, projects, or collaborations that would not have been possible without Center resources (including new collaborations with other DK Center Programs, e.g. NORCs, CDTRs)
- List collaborative publications, if applicable (include PMCID#)

III. ADMINISTRATION + ENRICHMENT CORES (1-2 pages MAX for narrative text, exclusive of any Tables)

(Text or Table) A. Activities raising awareness and interest in diabetes research and clinical care at center institutions, locally, regionally, and nationally:

- Center website developments
- Diabetes Research Center-sponsored seminars & symposia (only those sponsored by or supported with Diabetes Center funds)
- Regional and national presentations (list all that were sponsored by or supported with Diabetes Center funds; i.e. presentations of research that was supported by Diabetes Center funds)
- Collaborations with other Diabetes Research Centers, institutions and centers

(Text or Table) B. Activities enhancing diabetes education and training opportunities for patients, students, scientists and clinicians:

- Enumerated changes in related Ts, F & K awards
- Joint activities (training, symposia, etc.; may be incorporated in IIIA, if desired)

IV. BIOMEDICAL & TRANSLATIONAL RESEARCH CORE REPORTS
(1-2 pages MAX for narrative text per core, exclusive of any Tables)

For each core:

(Table or Text) A. Significant changes from previous year

- New personnel
- New services or changes in existing services

(Table or Text) B. Usage metrics (tabulated)

- Number of users - broken down by members vs nonmembers, including the distribution of core activity for each
- Number of assays/services over the past year (**see attached format Table from most recent RFA as an example for each core)**
- Number of publications citing center support that used the core

(Text) C. Significant accomplishments

- R&D to improve core services; briefly describe new, innovative services that are being developed
- Surveys to evaluate core services
- 2-3 papers highlighting scientific advances supported by the core (PMCID# plus brief description)

V. PILOT & FEASIBILITY PROGRAM (1-3 pages MAX for any narrative text, exclusive of any Tables)

Note: For those Centers with an expanded P&F Program (with additional funds through one of the recent RFAs), please submit separate P&F reports (i.e. two separate reports for your institutional P&F program and the expanded P&F program)

(Table) A. Solicitation

- Number of new (or continuing) P&F applications reviewed (may also include number of letters of intent received, if applicable)
- Types of applications reviewed
  - new invest, established investigator new to field, innovative partnership
  - basic, clinical, phase I translation, prevention & control
  - diabetes, endo, obesity, autoimmunity, transplantation
  - inter or trans-disciplinary
- Review process (only if altered from previous years)

(Table or Text) B. New Awards

- Number of new (or continuing) P&F awards
- Types of awards
  - new investigator, established investigator new to field, innovative partnership
  - basic, clinical, phase I translation, prevention & control
  - diabetes, endo, obesity, autoimmunity, transplantation
  - inter or trans-disciplinary
  - joint funding (with other centers or programs)
- P&F Award titles, PI names, brief descriptions (the supported P&F project descriptions should be 2-3 sentences at a minimum; the best P&F project descriptions are usually written by the P&F awardees)
- **see attached format Table from most recent RFA as an example**

(Table or Text) C. Awards funded in previous year(s)

- Titles, PIs, brief description (repeated from prior year report)
- Progress – brief description (short paragraph)
- Presentations, manuscripts, publications (include PMCID#)
- New funding

CENTER IMPACT MEASURES *(#VI)*

VI. MAJOR RESEARCH ACCOMPLISHMENTS (1-2 pages MAX for narrative text)

A. Select **up to three significant findings** and provide PMCID# for supporting center citations that typify activity at your center and that highlight recent research accomplishments.

B. Describe progress along a translational continuum in your center for a selected topic area/project. This can be a retrospective analysis, or an example of a current project or area that is actively progressing along the translational continuum.

VII. PROGRESS MADE WITH ANY SUPPLEMENTAL FUNDS

If your Diabetes Center received supplemental funds in the past 1-3 years, please be sure to include an update on progress made with these funds. Examples include:

- NIDDK funds for equipment (list equipment purchased, if not reported previously)
- NIDDK funds for a diversity supplement (report research progress and include budget request if supplement was approved for second year of support)
- NIDDK funds for "R24 seeding projects" (report research progress)

VIII. CHECKLIST, HUMAN SUBJECTS, VERTEBRATE ANIMALS, & OTHER REQUIRED FORM PAGES

Specific Examples:

- Inclusion Enrollment Report Format Page (submit this form page for each P&F awardee using human research subjects during the past 1-2 years)
- Targeted/Planned Enrollment Format Page (submit this form page for each new P&F awardee who plans to study human research subjects, but whose study is just beginning and enrollment hasn't started yet)
- IRB and/or IACUC approval information for all P&F studies involving human research subjects and/or vertebrate animals (a listing, with approval dates, PI names, project title, etc., is acceptable)
- For Center cores using human research subjects and/or vertebrate animals, provide a list of approvals that are specific to the core (i.e. NOT the approvals of all investigators using a core during the past year), if any
- Note: If your Center grant is currently approved for research involving human research subjects and/or vertebrate animals, we will need at least one current copy of the appropriate approval information in order to keep this designation active.
- All Personnel Report
- **External Advisory Report: If your Center has a report from an External Advisory meeting during the past year, please include a copy in your annual progress report.**
- **The Difference Between PMID and PMCID when reporting publications to NIH**

USE OF CORE FACILITIES
during last 12-month budget period

For each Core provide information on the use of the Core's services for the last 12-month period of support.

To avoid unwieldy tables, group services whenever possible, i.e all 'assays', all 'animals', all 'consultations' and provide more details in the core description.

CORE: Biochemistry

DETERMINATIONS/SERVICES RENDERED

A. Insulin, Ghrelin, CCK, leptin measurements
B. RNA, DNA isolations
C. Serum, cell, tissue storage
D. Consultation

User	Funded Project	Period of Performance	A	B	C	D	Actual use and comments
Adams	R01DK 099999	03/1/2009 – 07/30/2012		X		X	B. 5 per month for months D. 20 hours over the course of 12 months
Knight	P/F project	07/01/2010-06/30/2011	X			X	A. 100 samples per month for 3 months D. 10 hours

List Center Members first, alphabetically, followed by users who are not Center Members, also alphabetically.

PILOT PROJECT OUTCOME TABLE

Provide information on the most recent 5 or, if possible, 10 yr period. By adding to this Table each year in the progress report, you should have less work for the renewal application.

P/F #	PI (Dept)	Dates/Amount of P/F project	Title of Project	A	P	Applications Funded/Pending	Project Period	Still in Diabetes Research?
01	John Doe (Physiology)	07/01/10 - 06/30/11 $10,000	Role of NPY in the Regulation of Energy Balance	1		NIH R01 - pending	01/01/12 – 12/31/16	Yes
02	Mary Hathaway (Medicine/Endo)	07/01/10 – 06/30/12	Role of GI Hormones in Insulin Resistance	2	1	R21DK088888	09/01/12 – 8/31/14	Yes
03								
etc								

A = Abstracts

P = Publications

* Under "Applications Funded/Pending", list the grant received most proximate in time to the P/F award, i.e. for investigators who received funding 5-10 years ago, this may not be current funding.

NIDDK DIABETES CENTERS
NON-COMPETING RENEWALS
(TYPE 5 PROGRESS REPORT)
RPPR FORMAT GUIDELINES
2014-2015

NIH Research Performance Progress Report (RPPR) Instruction Guide:
http://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf

Center grants (P-mechanisms) will use the Multi-Component RPPR structure.

Section 7.6 contains supplemental instructions for Multi-Project RPPRs (e.g. P30/P60) and Single-Project RPPRs with Complicated Structure [Pilot Only]

The RPPR will include an Overall Component PLUS several Individual Components.

Individual Components for Center grants include: Administrative Core, Biomedical Research Cores, P&F Program(s), and Enrichment Program

7.6.1 Overall Component (complete sections A-H)

Section A: Cover Page

Section B: Accomplishments:

B.1 What are the major goals of the project?

Emphasize the synergy, collaboration and integration of major activities of the project. Report the major goals specific to an individual component under that component/core.

B.2 What was accomplished under these goals?

For this reporting period describe for the overall award: 1) major activities; 2) significant results, including major findings, developments, or conclusions (both positive and negative), and 3) key outcomes or other achievements. Include a discussion of stated goals not met. Report the accomplishments of individual projects and cores under that component.

• Select up to three significant findings and supporting center citations that typify activity at your center and that highlight recent research accomplishments.

• Describe progress along a translational continuum in your center for a selected topic area/project. This can be a retrospective analysis, or an example of a current project or area that is actively progressing along the translational continuum.

• New Collaborative activities: List & briefly describe any new Center programs, projects, or collaborations that would not have been possible without Center resources. List collaborative publications, if applicable.

• Describe activities raising awareness and interest in diabetes research and clinical care at center institutions, locally, regionally, and nationally:

• Regional and national presentations (list all that were sponsored by or supported with Diabetes Center funds; i.e. presentations of research that was supported by Diabetes Center funds)

• Diabetes Research Center-sponsored seminars & symposia (only those sponsored by or supported with Diabetes Center funds)

• Describe activities enhancing diabetes education and training opportunities for patients, students, scientists and clinicians:

• Enumerated changes in related Ts, F & K awards

• Joint activities (training, symposia, etc.; may be incorporated as part of Enrichment Program section, if desired)

B.3 Is there one or more Revision/Supplement associated with this award or a project under this award for which reporting is required?

If the Revision/Supplement is associated with a specific project or core, identify the component.

If your Diabetes Center received supplemental funds in the past 1-3 years, please be sure to include an update on progress made with these funds. Examples include:

• NIDDK funds for equipment (list equipment purchased, if not reported previously)

• NIDDK funds for a diversity supplement (report research progress and include budget request if supplement was approved for second year of support)

B.5 How have the results been disseminated to communities of interest?

If there are individual projects/cores designed to disseminate information or conduct outreach activities, report those activities under that component.

B.6 What do you plan to do during the next reporting period to accomplish the goals?
Report goals and objectives of individual projects or cores under that component.

Section C: Products

C.1 Publications. (see pages 55-57 of RPPR instructions)

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from the award?

C.2 Website(s) or other internet site(s). Provide details on any new Center website developments.

C.3 Technologies or techniques.

C.4 Inventions, patent applications and/or licenses.

C.5 Other products and resources.

C.5 a Other products
Identify any other significant products that were developed under the overall project. Report other products and resources resulting from an individual project or core under that component.

C.5.b Resource sharing
Report resource sharing for an individual project or core under that component.

D.1 Participants

Specify the component(s) on which the individual worked in the appropriate text box. This personnel information is for the entire project.

Personnel/participant information is NOT entered within each individual component/core; all senior/key personnel should be included in the Overall Component section.

D.2 Personnel Updates

Personnel questions (D.2.a.-e.) are applicable to entire project. For D.2.b, new senior/key personnel, identify the component(s) on which the individuals worked or will work. For D.2.e, new other significant contributors identify the component(s) on which the individual worked or will work.

Upload biosketches for all new senior/key personnel in Section D.2.b

Upload current 'other support' information for all senior/key personnel in Section D.2.c

'Other support' information is only needed for key personnel (listed in the Notice of Award), or their recent replacements. Please verify that the 'other support' information is current and the effort does not exceed 12 person/calendar months for any individual.

List any new Center members who are not senior/key personnel as other significant contributors in section D.2.e.

E.1 Not Applicable.
E.3 Not Applicable.
F.1 Not Applicable.

F.3 Significant changes to Human Subjects, Vertebrate Animals, Biohazards, and/or Select Agents.
If there are changes in any of the following areas check the appropriate box and provide a d3escription of the changes. If applicable, report the change under the relevant component.

Section G – Special Reporting Requirements

G.1 Upload PDF file of Consolidated Publication List

G.2 Not Applicable.

G.3 Not Applicable.

G4.b Inclusion enrollment data. ***Include inclusion enrollment data for any P&F projects involving human research subjects***

G.4.c ClinicalTrials.gov
Associate the number with the relevant project or core, if applicable.

G.12 F&A Costs [Applicable to SNAP awards only.]

H. Budget (not needed for Overall Component; required for each Individual Component)

For multi-project RPPRs complete the budget for each component and for each subaward; see Section 7.6.1. **A summary budget will be system-generated based on the budgets completed for the components and will be included in the final .pdf submitted to the Agency.** The composite budget summaries will reflect the direct costs for the grantee. Although the direct and indirect costs for subawards are direct costs to the grantee institutions, these costs will be listed as a separate line item, called "consortium" and will include all consortium costs. The total consortium costs for the summary budget are automatically calculated by the system and reflect the sum of the consortium costs (budget line item F.5 of the project budget) for the project budgets with the grantee institution DUNS and the total direct and indirect costs (budget line item I.) for project budgets with a DUNS different from that of the grantee institution.

Administrative Core Component (complete sections A-H)

B.1.a Have the major goals changed since the initial competing award or previous report?
B.2 What was accomplished under these goals?
B.3 Competitive Revisions/Administrative Supplements. For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?
B.4 What opportunities for training and professional development has the project provided?
B.5 How have results been disseminated to communities of interest?
B.6 What do you plan to do for the next reporting period to accomplish the goals?

C.1 Publications. Not applicable to Administrative Core
C.2 Website(s) or other internet site(s).
C.3 Technologies or techniques.
C.4 Inventions, patent applications and/or licenses.
C.5 Other products and resources.
C.5 .a Other products

Section D – Participants (should be reported in Overall Component)

Section F – Changes

Section G – Special Reporting Requirements

Upload PDF file for any additional information you would like to report (e.g. External Advisory Committee Report, etc.)

H.1 Budget Form [Multi-Project RPPRs only]

When a grantee institution is the lead on the Component, follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component, sections A-K. The budget justification should be uploaded as item K, and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).

When a collaborating institution is the lead on the Component, the information from the collaborating institution should be used to complete the project budget, following the instructions

Biomedical Research Core Components (complete sections A-H)

B.1.a Have the major goals changed since the initial competing award or previous report?
B.2 What was accomplished under these goals?

Including significant accomplishments

- R&D to improve core services; briefly describe new, innovative services that are being developed
- Surveys to evaluate core services
- Provide narrative or brief description for 2-3 papers highlighting scientific advances supported by the core (this should be provided for each core)
- Number of users - broken down by members vs nonmembers, including the distribution of core activity for each

B.3 Competitive Revisions/Administrative Supplements. For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?
B.4 What opportunities for training and professional development has the project provided?
B.5 How have results been disseminated to communities of interest?
B.6 What do you plan to do for the next reporting period to accomplish the goals?

C.1 Publications.
C.2 Website(s) or other internet site(s).
C.3 Technologies or techniques.
C.4 Inventions, patent applications and/or licenses.
C.5 Other products and resources.
C.5 .a Other products

Section D – Participants (should be reported in Overall Component)

Section F – Changes

Provide details for any new core personnel. Describe new services or changes in existing services.

Section G – Special Reporting Requirements

G.1 Upload PDF file of 'Use of Core Facilities' (upload separately for each core; see attached sample at end of document)

H.1 Budget Form [Multi-Project RPPRs only]
When a grantee institution is the lead on the Component, follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component, sections A-K. The budget justification should be uploaded as item K, and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).
When a collaborating institution is the lead on the Component, the information from the collaborating institution should be used to complete the project budget, following the instructions

P&F Program Components (complete sections A-H) Please use the 'project' (not 'core') component for the P&F program, if possible

B.1.a Have the major goals changed since the initial competing award or previous report?

B.2 What was accomplished under these goals?

Solicitation

- Number of new (or continuing) P&F applications reviewed (may also include number of letters of intent received, if applicable)
- Types of applications reviewed
    - new invest, established investigator new to field, innovative partnership
    - basic, clinical, phase I translation, prevention & control
    - diabetes, endo, obesity, autoimmunity, transplantation
    - inter or trans-disciplinary
- Review process (only if altered from previous years)

New Awards

- Number of new (or continuing) P&F awards
- Types of awards
    - new investigator, established investigator new to field, innovative partnership
    - basic, clinical, phase I translation, prevention & control
    - diabetes, endo, obesity, autoimmunity, transplantation
    - inter or trans-disciplinary
    - joint funding (with other centers or programs)
- P&F Award titles, PI names, brief descriptions (the supported P&F project descriptions should be 2-3 sentences at a minimum; the best P&F project descriptions are usually written by the P&F awardees)

- **see attached format Table from most recent RFA as an example**

Awards funded in previous year(s)

- Titles, PIs, brief description (repeated from prior year report)
- Progress – brief description (short paragraph)
- Presentations, manuscripts, publications, new funding

B.3 Competitive Revisions/Administrative Supplements. For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?
B.4 What opportunities for training and professional development has the project provided?
B.5 How have results been disseminated to communities of interest?
B.6 What do you plan to do for the next reporting period to accomplish the goals?

C.1 Publications from P&F awardees should be included in the overall component (part of your MyNCBI report).

C.2 Website(s) or other internet site(s).
C.3 Technologies or techniques.
C.4 Inventions, patent applications and/or licenses.
C.5 Other products and resources.
C.5 .a Other products

Section D – Participants (should be reported in Overall Component)

Section F – Changes

Section G – Special Reporting Requirements

G.1 Upload PDF file of 'Pilot Project Outcome Table' see attached sample at end of document

H.1 Budget Form [Multi-Project RPPRs only]
When a grantee institution is the lead on the Component, follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component, sections A-K. The budget justification should be uploaded as item K, and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).
When a collaborating institution is the lead on the Component, the information from the collaborating institution should be used to complete the project budget, following the instructions

Enrichment Program Component (complete sections A-H)

B.1.a Have the major goals changed since the initial competing award or previous report?

B.2 What was accomplished under these goals?

• Diabetes Research Center-sponsored seminars & symposia (only those sponsored by or supported with Diabetes Center funds)

B.3 Competitive Revisions/Administrative Supplements. For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?
B.4 What opportunities for training and professional development has the project provided?
B.5 How have results been disseminated to communities of interest?
B.6 What do you plan to do for the next reporting period to accomplish the goals?

C.1 Publications. Not applicable
C.2 Website(s) or other internet site(s).
C.3 Technologies or techniques.
C.4 Inventions, patent applications and/or licenses.
C.5 Other products and resources.
C.5 .a Other products

Section D – Participants (should be reported in Overall Component)

Section F – Changes

Section G – Special Reporting Requirements

G.1 Upload PDF file for any additional information you would like to report

H.1 Budget Form [Multi-Project RPPRs only]
When a grantee institution is the lead on the Component, follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component, sections A-K. The budget justification should be uploaded as item K, and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).
When a collaborating institution is the lead on the Component, the information from the collaborating institution should be used to complete the project budget, following the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component, sections A-K.

For multi-projects RPPRs the grantee must complete the DUNS and Organization Name fields, as the DUNS number will not automatically populate to the DUNS number.

USE OF CORE FACILITIES
during last 12-month budget period

For each Core provide information on the use of the Core's services for the last 12-month period of support.

To avoid unwieldy tables, group services whenever possible, i.e all 'assays', all 'animals', all 'consultations' and provide more details in the core description.

CORE: Biochemistry

DETERMINATIONS/SERVICES RENDERED

A. Insulin, Ghrelin, CCK, leptin measurements
B. RNA, DNA isolations
C. Serum, cell, tissue storage
D. Consultation

User	Funded Project	Period of Performance	A	B	C	D	Actual use and comments
Adams	R01DK 099999	03/1/2009 – 07/30/2012		X		X	B. 5 per month for months D. 20 hours over the course of 12 months
Knight	P/F project	07/01/2010-06/30/2011	X			X	A. 100 samples per month for 3 months D. 10 hours

List Center Members first, alphabetically, followed by users who are not Center Members, also alphabetically.

PILOT PROJECT OUTCOME TABLE

Provide information on the most recent 5 or, if possible, 10 yr period. By adding to this Table each year in the progress report, you should have less work for the renewal application.

P/F #	PI (Dept)	Dates/Amount of P/F project	Title of Project	A	P	Applications Funded/Pending	Project Period	Still in Diabetes Research?
01	John Doe (Physiology)	07/01/10 - 06/30/11 $10,000	Role of NPY in the Regulation of Energy Balance	1		NIH R01 - pending	01/01/12 – 12/31/16	Yes
02	Mary Hathaway (Medicine/Endo)	07/01/10 – 06/30/12	Role of GI Hormones in Insulin Resistance	2	1	R21DK088888	09/01/12 – 8/31/14	Yes
03								
etc								

A = Abstracts

P = Publications

* Under "Applications Funded/Pending", list the grant received most proximate in time to the P/F award, i.e. for investigators who received funding 5-10 years ago, this may not be current funding.

NIH and Other PHS Agency Research Performance Progress Report (RPPR) Instruction Guide

Document Version 8.0.0

July 18, 2014

Forms Approved Through 08/31/2015
OMB No. 0925-0002

CONTACT US

Document Comments:
We value your feedback on this document. Please email your comments to eRACommunications@mail.nih.gov.

For policy-related questions:
Please email grantspolicy@od.nih.gov.

Troubleshooting support:

New Help Desk Ticketing System!

Log-in with your eRA Commons username and password to access the eRA Help Desk web ticketing system to submit a help desk ticket online, view status of your prior tickets, and update your tickets.

- Access the eRA Help Desk web ticketing system **with your eRA Commons user name and password**.
- *Having trouble logging in?*
  Click here to submit an online request if you are **not able to log in** or **do not have an eRA Commons account**.
- **NIH Staff/Agency Partner Staff**, click here to access the eRA Help Desk web ticketing system.

For information, see the flyer on the new Help Desk Ticketing System (PDF - 212 KB).

Or to contact the eRA Help Desk directly:
Web: http://grants.nih.gov/support (Preferred method of contact)
Toll-free: 1-866-504-9552
Phone: 301-402-7469
Email: s2ssupport@mail.nih.gov (for System-to-System support)

Hours: Mon-Fri, 7:00 a.m. to 8:00 p.m. Eastern Time, except for Federal Holidays

DISCLAIMER STATEMENT

No data shown in illustrations represents any real account, project, or individual. Any resemblance to actual accounts, projects, or individuals is purely coincidental.

DOCUMENT HISTORY

Date	Commons System Version	Document Version	Description of Change	Author
4/25/2012	3.3.3.1	1.0.0	Develop initial draft of document	eRA Documentation Team
6/8/2012	3.3.3.1	2.0.0	Updated for June 2012	eRA Documentation Team
10/15/2012	3.5.1.4	3.0.0	Updated for October 2012	eRA Documentation Team
4/19/2013	3.7.0.2	4.0.0	Updated for April 2013 ER	eRA Communications
7/19/2013	3.8.0.7	5.00	Updated for July 2013 ER	eRA Communications
11/7/2013	3.10.0.4	6.0.0	Added complex RPPRs; budget forms	eRA Communications
1/31/2014	3.11.0.5	7.0.0	Updated for AHRQ and multi-year funded awards	eRA Communications
4/25/2014	3.12.0.7	7.1.0	Corrected text and screen prints	eRA Communications
7/18/2014	3.14.0.10	8.0.0	Updated PA PRAM feature; inclusion forms	eRA Communications

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 Purpose

The purpose of this document is to provide those preparing the Research Performance Progress Report (RPPR) with an explanation of the RPPR module in the eRA Commons and the information required in the report. This document also provides the steps for accessing and completing the report in eRA Commons, as well as navigating, validating, routing, and submitting the RPPR to the awarding agency.

1.1 NIH

Progress reports for NIH Streamlined Noncompeting Award Process (SNAP) and Fellowship Awards must be submitted using the eRA RPPR Commons Module. Progress reports submitted in another format for SNAP and Fellowships will not be processed by the NIH and will require resubmission in the RPPR format. Refer to the notice NOT-OD-13-035 for more information.

Currently, non-SNAP type 5 progress reports, including multi-project and training, may be submitted either electronically using the RPPR or in paper using the PHS 2590 but not both. Refer to NOT-OD-13-013 and NOT-OD-14-079. As detailed in NOT-OD-14-092, NIH will require the RPPR for all Type 5 non-SNAP progress reports submitted on or after October 17, 2014.

Progress reports for NIH multi-year funded (MYF) awards (project period and budget period are the same and are longer than one year) must be submitted using the eRA RPPR Commons Module. http://grants.nih.gov/grants/policy/myf.htm. Refer to NOT-OD-14-026.

For SBIR/STTR Fast-Track Phase II applications (SBIR/STTR Fast-Track Phase I final progress reports), follow the instructions in the Non-Competing Continuation Progress Report PHS 2590 (http://grants.nih.gov/grants/funding/2590/2590.htm).

NIH continues development of the RPPR for the final progress report and for administrative extensions (Type 4s; e.g., SBIR/STTR Fast-Track Phase II applications). NIH will continue to update the community as progress is made.

1.2 Agency for Healthcare Research and Quality (AHRQ)

The Agency for Healthcare Research and Quality (AHRQ) will require its Fellowship grantees to use the eRA commons RPPR module in 2014 (see NOT HS-14-003), and will transition most other AHRQ awards to the RPPR later in 2014. The RPPR includes numerous references to the NIH Grants Policy Statement, 8.1.2 requirement that significant changes in objectives and scope require prior approval of the agency; for AHRQ awardees the analogous requirement is in the HHS Grants Policy Statement under Prior-Approval Requirements.

2 Background and Paperwork Burden

The NIH Research Performance Progress Report (RPPR) implements the uniform reporting format for interim research progress reporting developed under the auspices of the National Science and Technology Council, through the Committee on Science and the Research Business Models Subcommittee, and established by the Office of Management and Budget for use by agencies that support research and research-related activities.

For NIH and the Agency for Healthcare Research and Quality (AHRQ), the RPPR has replaced the Ruth L. Kirschstein National Research Service Award Individual Fellowship Progress Report for Continuation Support (PHS 416-9) and it will ultimately replace the Public Health Service (PHS) Non-competing Continuation Progress Report (PHS 2590). Other PHS agencies that will eventually utilize the NIH RPPR are the Food and Drug Administration, and Centers for Disease Control and Prevention. Non-NIH agencies may have requirements that differ from those for NIH grantees; refer to the Notice of Award (NoA) or contact the Grants Management Specialist named in the NoA.

Progress reports are required to continue support of a PHS grant for each budget year within a competitive segment. The NIH RPPR is not used for submitting a Final Progress Report; instructions for submitting a Final Progress Report are at http://grants.nih.gov/grants/funding/finalprogressreport.pdf.

PHS estimates that it will take approximately 15 hours to complete this progress report. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. If you have comments regarding the burden estimate or other aspect of the collection of information, including suggestions for reducing the burden, send comments to: NIH, Project Clearance Office, 6705 Rockledge Drive MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0002). Do not send progress reports to this address.

3 RPPR Due Dates

Grantees can determine which progress reports are due through the website located at: http://era.nih.gov/commons/quick_queries/index.cfm#progress, and should periodically check the site, which is updated on or around the 30th of each month. Progress report due dates are also available in the eRA Commons Status system. In addition, automatic e-mail notifications are sent to the PD/PI prior to due date.

3.1 NIH

- SNAP: If an award is issued under the SNAP (Streamlined Noncompeting Award Process) provisions, the progress report is due the 15th of the month preceding the month in which the budget period ends (e.g., if the budget period ends 11/30, the due date is 10/15). If the 15th falls on a weekend or Federal holiday, the due date is automatically extended to the next business day. Grantees should consult the NoA to determine when SNAP procedures apply.
- Non-SNAP: If an award is not issued under the SNAP provisions, the progress report is due the first of the month preceding the month in which the budget period ends (e.g., if the budget period ends 11/30, the due date is 10/1).
- Fellowships: For Fellowships the progress report is due two months before the beginning date of the next budget period. Occasionally the Notice of Award (NoA) will indicate a different due date which will supersede these dates.
- MYF: Progress Reports for MYF awards are due annually on or before the anniversary of the budget/project period start date of the award. The reporting period for a MYF progress report is the calendar year preceding the anniversary date of the award.

3.2 Agency for Healthcare Research and Quality (AHRQ)

For AHRQ grantees, if the start date for the pending noncompeting continuation (type 5) is 10/1 through 4/1, the progress report due date is two months prior to the budget period start date. For example, the due date will be 12/1 for a grant with a budget start date of 2/1. If the start date for the pending type 5 is 4/2 through 9/30, the progress report due date is four months prior to the budget period start date. For example, the due date will be 5/1 for a grant with a budget start date of 9/1. For T32 awards, the progress report is due three months prior to the budget start date.

4 Data Entry, PDF Attachments, and Style

4.1 Data or Text Box, and PDF Size Limits

Most text entry boxes have an 8,000 character limit (~3 pages); this limit is standardized across federal agencies implementing the RPPR and entry of more than 8,000 characters is prevented by the system. In an effort to reduce grantee burden and encourage concise responses NIH has stated the recommended length of the response for some questions and, for agency-specific questions has limited the length of the response with text boxes with a limit of less than 8,000 characters. AHRQ grantees should follow NIH recommended lengths for text entries.

Warning: Text exceeding 8,000 characters is cut to 8,000 when using the *cut and paste* feature.

PDF file uploads (attachments) do not have page limits, but may not be more than 6 megabytes (6MB). PDF attachments are utilized when there may be a need for a grantee to provide considerable detail (e.g., change in human subject protocols that requires a new or revised Protection of Human Subjects section as described in Part II of the competing application instructions). Even when developing PDF responses, grantees are encouraged to be concise and avoid unnecessary detail.

4.2 PDF Attachments

Grantees should generate text attachments using any word processing software and then convert those files to PDF before attaching the files to the appropriate section in the progress report. The PDF format is used to preserve document formatting. All PDF attachments must be submitted as individual files. Although some software packages allow bundling of multiple PDFs into a single file, eRA systems cannot support “Bundling” or “Portfolio” features at this time. Use of these features may result in delays in agency acceptance of the progress report. Paginated PDF files are also discouraged since they can interfere with system pagination of the entire RPPR document upon submission to the agency. File names will be used and displayed in the assembled PDF submitted to the agency.

Save all files with descriptive file names of 50 characters or less and be sure to only use standard characters in file names: A through Z, a through z, 0 through 9, and underscore (_). Do not use any special characters (example: &, -, *, %, /, and #) or spacing in the file name, and for word separation use an underscore (e.g., My_Attached_File.pdf).

Use an Arial, Helvetica, Palatino Linotype, or Georgia typeface, a black font color, and a font size of 11 points or larger. (A Symbol font may be used to insert Greek letters or special characters; the font size requirement still applies.) Type density, including characters and spaces, must be no more than 15 characters per inch. Type may be no more than six lines per inch.

Use standard paper size (8 ½" x 11). Use at least one-half inch margins (top, bottom, left, and right) for all pages. No information should appear in the margins, including the PI’s name and page numbers.

4.3 Style

Use English and avoid jargon. Abbreviations and language that may not be known to the broader scientific community should be avoided unless clearly defined. Internet Web site addresses (URLs) should not be used unless provided under C.2.

5 Navigation

The RPPR is completed using the eRA Commons system. The report in Commons consists of separate screens for each of the sections listed below:

A. Cover Page

B. Accomplishments

C. Products

D. Participants

E. Impact

F. Changes

G. Special Reporting Requirements

H. Budget

Users may work on various sections in any order, however, it is important to click the **Save** button in the navigation bar before leaving a screen in order to retain data entered on that screen. Upon submission to the awarding agency, the system will generate a PDF of the progress report, which may be viewed from the *RPPR Menu* screen using the **View** button.

Once submitted, the final RPPR, in PDF format, is accessible in Commons via the *Status Information* screen. Refer to the section titled *Viewing the Final RPPR in Commons* for detailed steps.

Note that a link to a site outside the RPPR (e.g., U.S. Select Agency Registry in F.3.d, ClinicalTrials.gov in G.4.c, or the NIH human embryonic stem cell Registry in G.6) opens a site in a new browser window. You must close that window to return to the RPPR. Do not close the browser or use the browser's back button.

Figure 1: RPPR Navigation Links from Cover Page

5.1 Initiate the RPPR

Only the PD/PI or the PD/PI delegate may initiate an RPPR. When there are multiple PIs (MPI), only the Contact PI or the PD/PI delegate of the Contact PI may initiate the report. To initiate, the user can choose from one of two ways to access the RPPR functionality:

1. Access RPPR from **Status**:
    a. Select the **Status** tab from the Commons menu options.
    b. Select the **List of Applications/Grants** link from the *Status* screen or from the menu options.

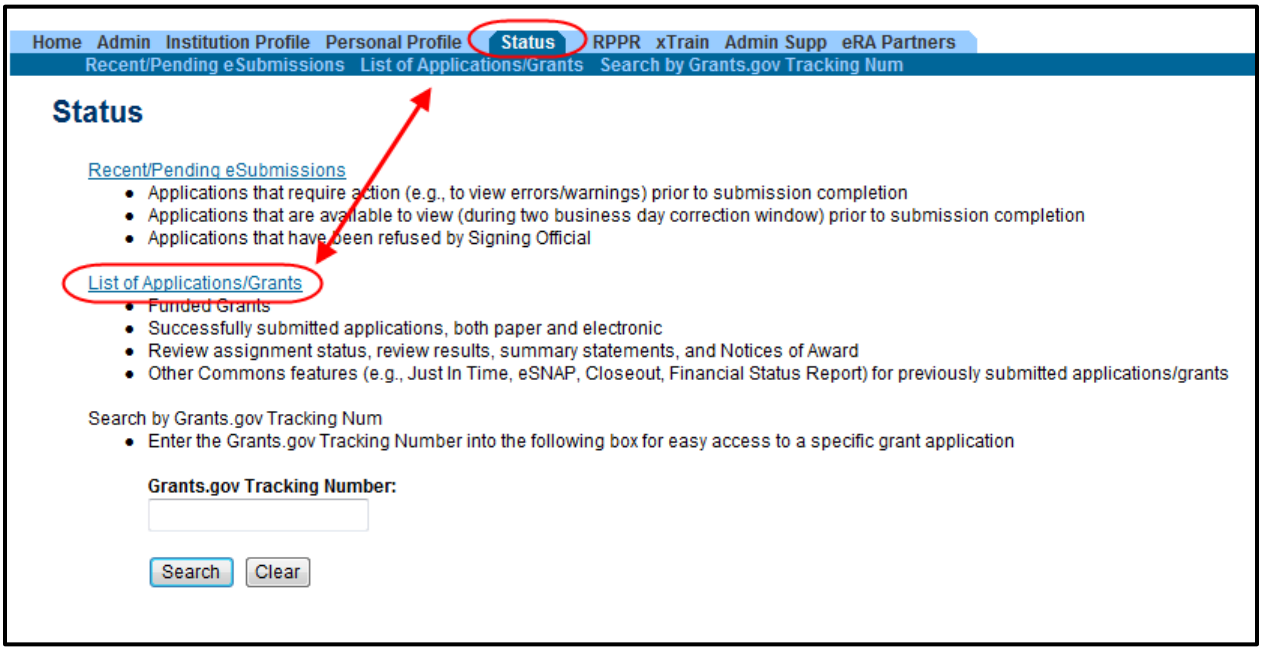
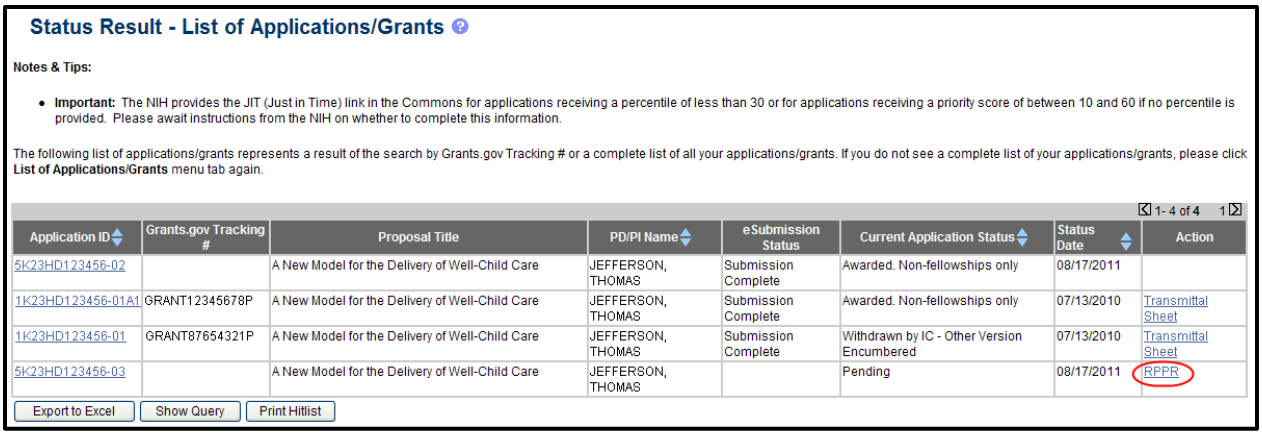


Figure 2: Status Screen and List of Applications/Grants Links

    c. From the *Status Result – List of Applications/Grants* screen, locate the grant and select the **RPPR** link from the **Action** column for the specific grant. The **RPPR** link for the current reporting period is available once the Notice of Award for the prior year has been issued. This link remains available until the RPPR for the current reporting year has been submitted.

    For multi-year funded awards, the link will display as **RPPR Year <X>**, the <X> representing the reporting year. The link for a multi-year funded award is available two months prior to the RPPR due date for the current reporting period and remains available until the RPPR is submitted.

NOTE: While **RPPR Year <X>** links for multiple years may appear at the same time in *Status*, you are prevented from initiating a reporting year's progress report until the progress report(s) of the previous year(s) has been submitted.



Status Result - List of Applications/Grants

Notes & Tips:

- **Important:** The NIH provides the JIT (Just in Time) link in the Commons for applications receiving a percentile of less than 30 or for applications receiving a priority score of between 10 and 60 if no percentile is provided. Please await instructions from the NIH on whether to complete this information.

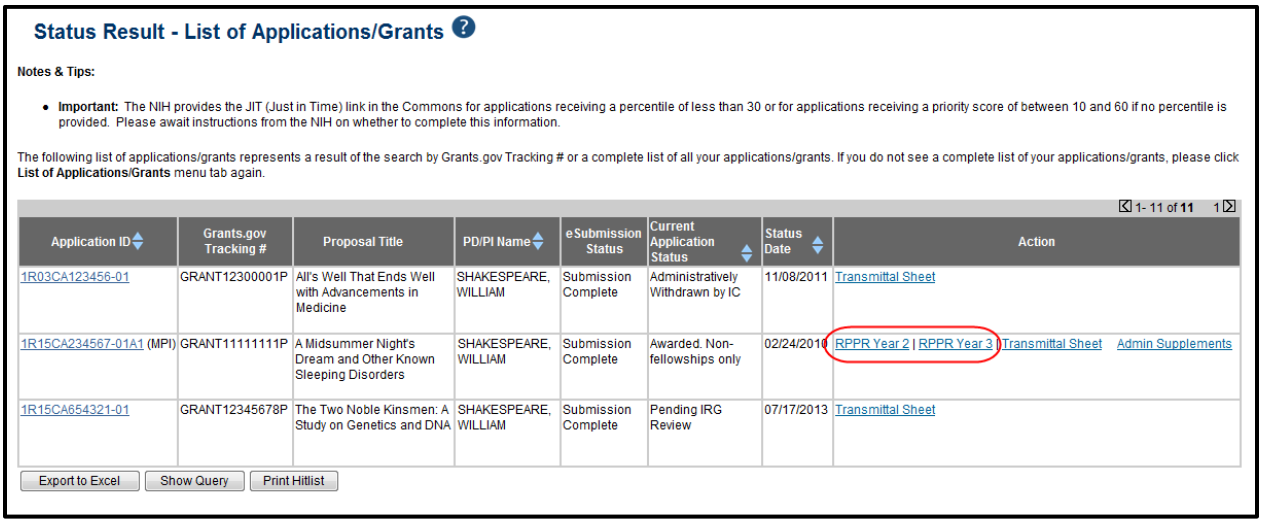
The following list of applications/grants represents a result of the search by Grants.gov Tracking # or a complete list of all your applications/grants. If you do not see a complete list of your applications/grants, please click **List of Applications/Grants** menu tab again.

1- 4 of 4 1

Application ID	Grants.gov Tracking #	Proposal Title	PD/PI Name	eSubmission Status	Current Application Status	Status Date	Action
5K23HD123456-02		A New Model for the Delivery of Well-Child Care	JEFFERSON, THOMAS	Submission Complete	Awarded. Non-fellowships only	08/17/2011	
1K23HD123456-01A1	GRANT12345678P	A New Model for the Delivery of Well-Child Care	JEFFERSON, THOMAS	Submission Complete	Awarded. Non-fellowships only	07/13/2010	Transmittal Sheet
1K23HD123456-01	GRANT87654321P	A New Model for the Delivery of Well-Child Care	JEFFERSON, THOMAS	Submission Complete	Withdrawn by IC - Other Version Encumbered	07/13/2010	Transmittal Sheet
5K23HD123456-03		A New Model for the Delivery of Well-Child Care	JEFFERSON, THOMAS		Pending	08/17/2011	RPPR

Export to Excel | Show Query | Print Hitlist

Figure 3: RPPR Link on Status Result – List of Applications/Grants



Status Result - List of Applications/Grants

Notes & Tips:

- **Important:** The NIH provides the JIT (Just in Time) link in the Commons for applications receiving a percentile of less than 30 or for applications receiving a priority score of between 10 and 60 if no percentile is provided. Please await instructions from the NIH on whether to complete this information.

The following list of applications/grants represents a result of the search by Grants.gov Tracking # or a complete list of all your applications/grants. If you do not see a complete list of your applications/grants, please click **List of Applications/Grants** menu tab again.

1- 11 of **11** 1

Application ID	Grants.gov Tracking #	Proposal Title	PD/PI Name	eSubmission Status	Current Application Status	Status Date	Action
1R03CA123456-01	GRANT12300001P	All's Well That Ends Well with Advancements in Medicine	SHAKESPEARE, WILLIAM	Submission Complete	Administratively Withdrawn by IC	11/08/2011	Transmittal Sheet
1R15CA234567-01A1 (MPI)	GRANT11111111P	A Midsummer Night's Dream and Other Known Sleeping Disorders	SHAKESPEARE, WILLIAM	Submission Complete	Awarded. Non-fellowships only	02/24/2010	RPPR Year 2 | RPPR Year 3 | Transmittal Sheet Admin Supplements
1R15CA654321-01	GRANT12345678P	The Two Noble Kinsmen: A Study on Genetics and DNA	SHAKESPEARE, WILLIAM	Submission Complete	Pending IRG Review	07/17/2013	Transmittal Sheet

Export to Excel | Show Query | Print Hitlist

Figure 4: Multi-Year Award RPPR Link

–OR–

1. Access RPPR from **RPPR** tab:

    a. Select the **RPPR** tab from the Commons menu options.

The *Manage RPPR* screen displays. *Manage RPPR* is used to view the progress reports to which the user has access and allows the user to select a progress report in order to perform various actions. PD/PIs or users delegated PD/PI updating authority uses the *Manage RPPR* screen to view their own progress reports. SOs and AOs use the screen to search for grants from their institutions and/or for grants routed to them for review.

    b. Select the specific grant by clicking the hyperlink in the **Grant Number** column on the *Manage RPPR* screen.

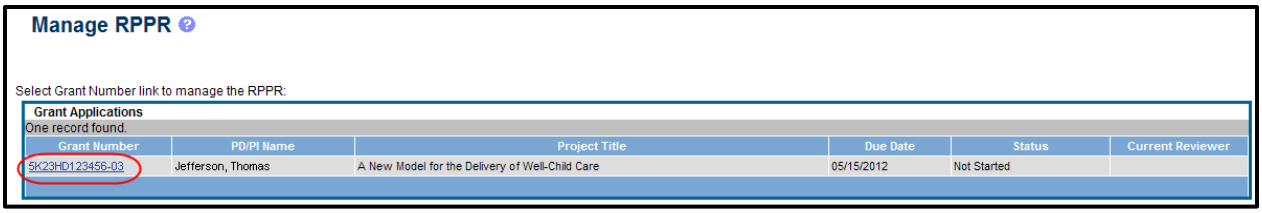


Figure 5: Manage RPPR List of Grant Applications

If an RPPR exists already, Commons displays the report for editing.

The *RPPR Menu* screen displays. The options for the uninitiated report are **Initiate** and **Cancel**. Once an RPPR is in progress, the buttons for other options are enabled. These options are discussed later, following the steps for initiation.

NOTE: For multi-year funded awards, the following message displays when attempting to initiate an RPPR if the previous year's report has not been submitted:

The Multi-Year RPPR for the previous year must be submitted prior to initiating this Multi-Year RPPR.

In this case, the option to initiate is disabled.

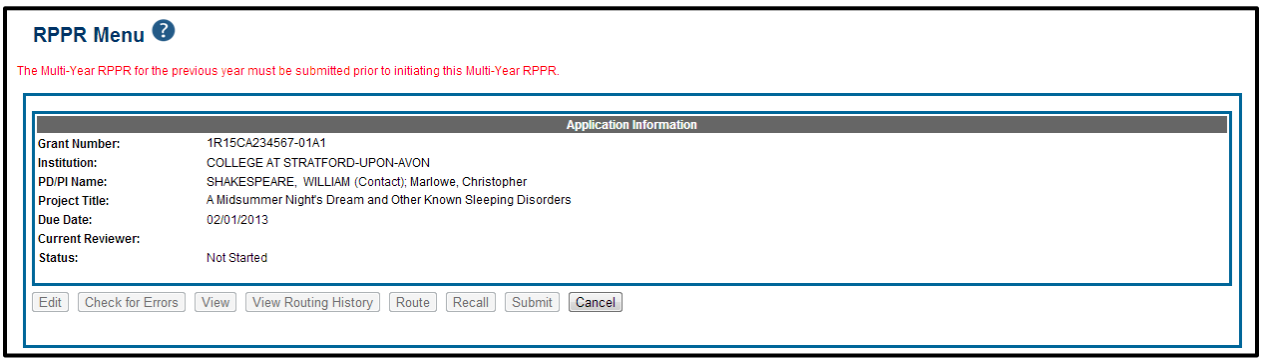


Figure 6: Multi-Year RPPR Error Message

The *RPPR Menu* screen includes the following fields:

Grant Number

This is the complete number of the grant

Grantee Institution

This field contains the name of the applicant's institution

PD/PI Name

The PD/PI of the grant award for which the progress report is being prepared. In the case of MPIs, a list of PD/PI names displays with the Contact PD/PI indicated by the word *Contact*.

Project Title

The project title of the grant

Due Date

NIH

The due date of the progress report for awards issued under the SNAP (Streamlined Noncompeting Award Process) provisions is the 15th of the month preceding the month in which the budget period ends (e.g., if the budget period ends 11/30, the due date is 10/15). If the award is not issued under SNAP provisions, the progress report is due the first of the month preceding the month in which the budget period ends (e.g., if the budget period ends 11/30, the due date is 10/1). If the due date falls on a weekend or federal holiday, the due date is automatically extended to the next business day. Progress reports for Fellowships are due two months before the beginning date of the next budget period. Occasionally the Notice of Award (NoA) will indicate a different due date which will supersede these dates. Grantees should consult the NoA to determine when SNAP procedures apply.

AHRQ

For AHRQ grantees, if the start date for the pending noncompeting continuation (type 5) is 10/1 through 4/1, the progress report due date is two months prior to the budget period start date. For example, the due date will be 12/1 for a grant with a budget start date of 2/1. If the start date for the pending type 5 is 4/2 through 9/30, the progress report due date is four months prior to the budget period start date. For example, the due date will be 5/1 for a grant with a budget start date of 9/1. For T32 awards, the progress report is due three months prior to the budget start date.

Current Reviewer

The name of the current reviewer or organization (e.g., PD/PI name, NIH). This value is blank before the RPPR is initiated.

Status

The current state of the progress report. Possible values are as follows: *Not Started, PD/PI Work in Progress, Reviewer Work in Progress,* and *Submitted to Agency*.

Buttons

The displayed and enabled buttons vary depending on the status of the RPPR and/or the limitations of the current user's role. The possible available actions include the following:

- **Initiate**: Begins the RPPR process. Available for grants with a status of *Not Started*. Access is granted to PD/PIs and PD/PI delegates. An RPPR can be initiated even if required information in the *Personal Profile* and *Institution Profile* sections is missing. If any of this information is incorrect or missing, a prompt will appear to correct/complete the information after initiating the report. Processing may continue on the RPPR without making the corrections; however, the RPPR will not pass validations for submission to the agency until the errors are corrected.
- **Edit**: Opens the RPPR for edits. Available for progress reports with a status of *Work in Progress (WIP)*. Access is granted to PD/PIs or PD/PI delegates when the PD/PI is the current reviewer, AOs when the AO is the current reviewer, and SOs when the SO is the current reviewer. The **Edit** button allows the user to view and edit RPPR information.
- **View**: Opens the RPPR report in PDF format, as it will be seen by the agency. Available for progress reports with a status of *Work in Progress (WIP)* or *Submitted to Agency*.

Access is granted to PD/PIs, PD/PI delegates, and reviewers. Until the RPPR is submitted to agency, the PDF report shows a status of *Draft* and a blank submission date.

- **Check for Errors**: Checks the RPPR for any errors or warnings. Available for progress reports with a status of *Work in Progress (WIP)*. Access is granted to any user with access to the grant. The RPPR can be validated at any time while in the status of *WIP* and can be validated multiple times.
- **View Routing History**: Opens a page that displays a routing history table. Available for progress reports with a status of *Work in Progress (WIP)* or *Submitted to Agency*. Access is granted to PD/PIs, PD/PI delegates, and reviewers.
- **Route**: Routes the RPPR to the next reviewer for further review or corrections. Available for progress reports with a status of *Work in Progress (WIP)*. Access is granted to the current reviewer. A PD/PI delegate cannot route an RPPR to the next reviewer.
- **Recall**: Recalls RPPRs that have been forwarded to another reviewer and resets the user as the current reviewer. Available for reports with a status of *Work in Progress (WIP)*. Access is granted to the last reviewer (who recalls the report from the current reviewer). Signing Officials and PD/PIs can recall an RPPR even if they are not the last reviewer whenever it has a status of *Reviewer Work in Progress*. This is useful in situations when a RPPR has been routed to the wrong person or to someone who is unavailable.
- **Submit**: Submits the RPPR to the Agency. Available for reports with a status of *Work in Progress (WIP)*. Access is granted to the SO when the SO is the current reviewer and to the PD/PI when the PD/PI has been delegated *Progress Report* authority.

NOTE: A PD/PI with *Progress Report* authority cannot submit a non-SNAP or F RPPR.

- **Cancel**: Closes the *RPPR Menu* screen and returns the user to the previous screen.

2. Select the **Initiate** button to begin the RPPR.

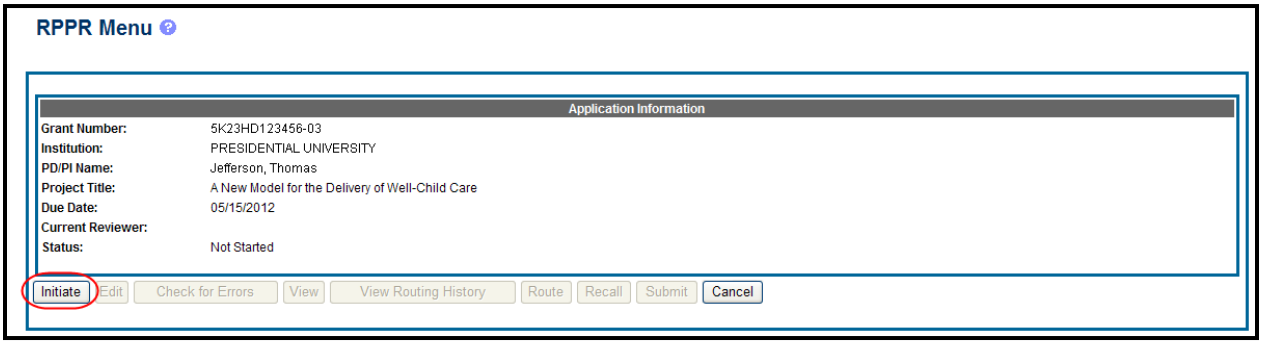


Figure 7: RPPR Menu for Initiating the Report

Once initiated, Commons creates the report in a *PD/PI Work in Progress* status and sets the current reviewer. A message displays as follows:

The RPPR has been successfully initiated.

NOTE: If at any time initiation fails due to business rules validations, error or warning messages display on the screen.

Once initiated, the editing process can begin. The RPPR is accessed for editing via the *RPPR Menu* screen. The editing feature for single-project RPPRs is different from those of multi-project RPPRs. The steps for accessing each type of RPPR are outlined in the sections that follow. Refer to *Accessing a Single-Project RPPR for Editing* or *Accessing a Multi-Project and Single-Project with Complicated Structure RPPR for Editing* as appropriate.

5.2 Edit the RPPR

Once an RPPR is initiated, its status becomes *PD/PI Work in Progr*ess and it becomes available for editing. The PD/PI or delegate uses the **Edit** option for viewing and completing the report. Additionally, this option is available to the SO or AO when that user is the current reviewer of the report.

NOTE: For RPPRs with multiple PD/PIs (MPI awards), only the Contact PD/PI has access to the **Edit** feature unless the Contact PD/PI has granted progress report authority to other PD/PIs. Without this authority, MPIs can only view the RPPR PDF and its routing history.

There are two means of accessing the progress report for editing. These are similar methods used for initiating the report and are as follows:

Access RPPR from **Status**:

a. Select the **Status** tab from the Commons menu options.

b. Select the **List of Applications/Grants** link from the *Status* screen.

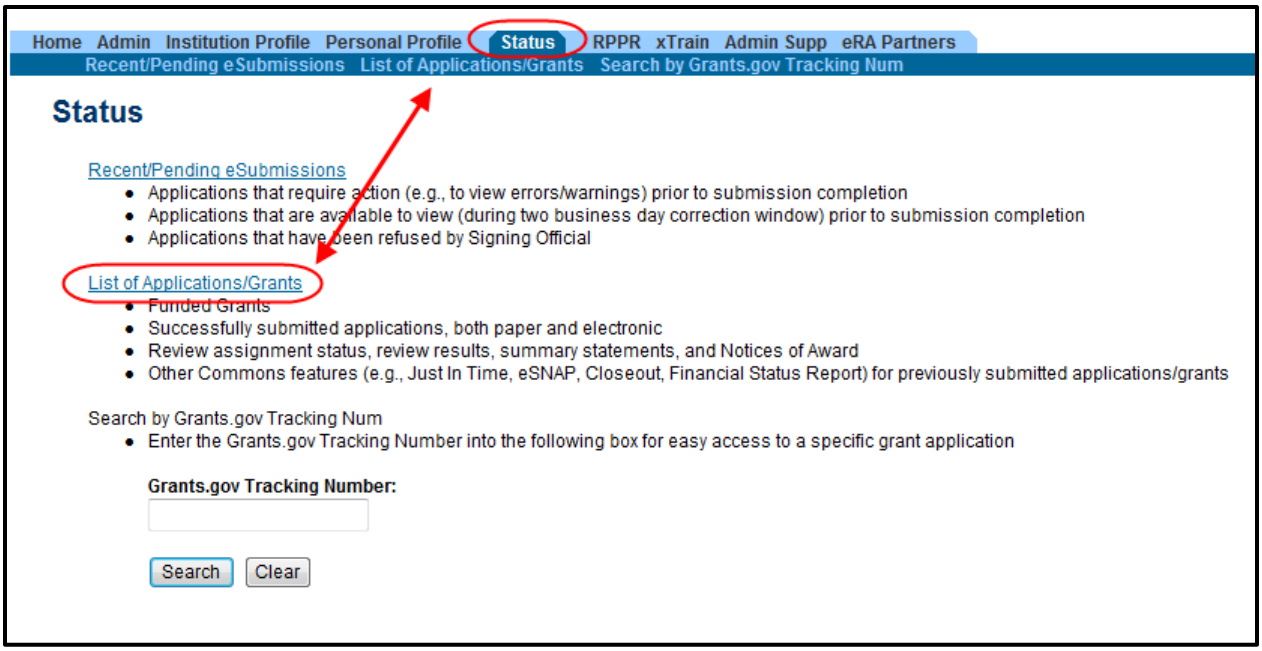


Figure 8: Status Screen and List of Applications/Grants Links

c. From the *Status Result – List of Applications/Grants* screen, locate the grant and select the **RPPR** link from the **Action** column for the specific grant. For multi-year funded awards, the link will display as **RPPR Year <X>**, the <X> representing the reporting year.

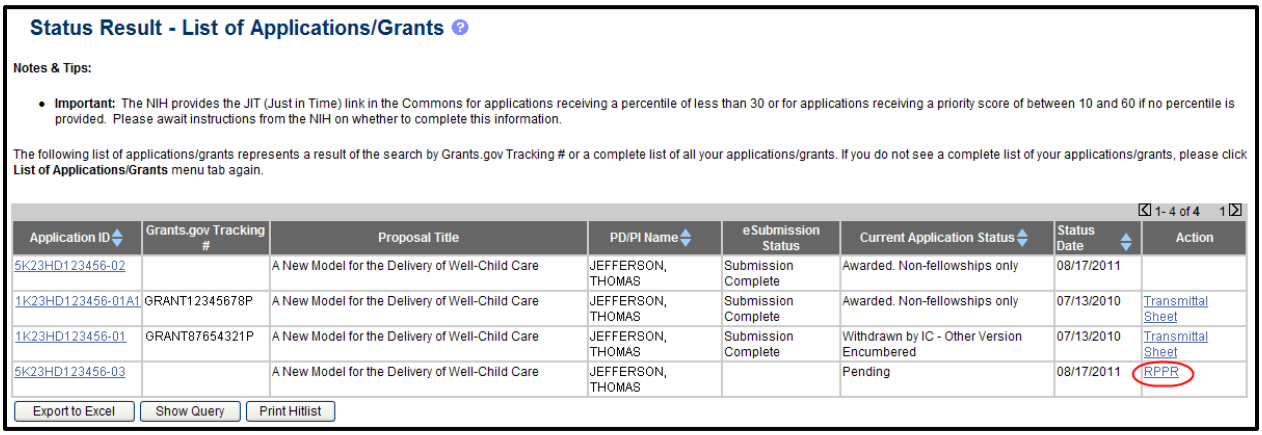


Figure 9: RPPR Link on Status Result – List of Applications/Grants

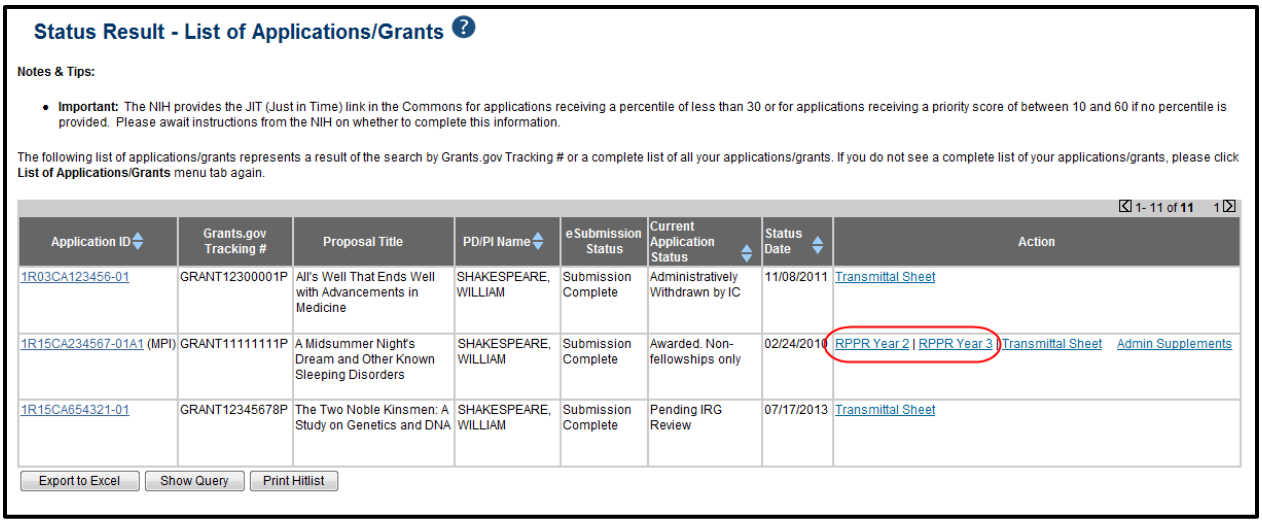


Figure 10: Multi-Year Funded Award RPPR Link

–OR–

Access RPPR from **RPPR** tab:

a. Select the **RPPR** tab from the Commons menu options.

b. Select the specific grant by clicking the hyperlink in the **Grant Number** column on the *Manage RPPR* screen. SOs/AOs must perform a query first.

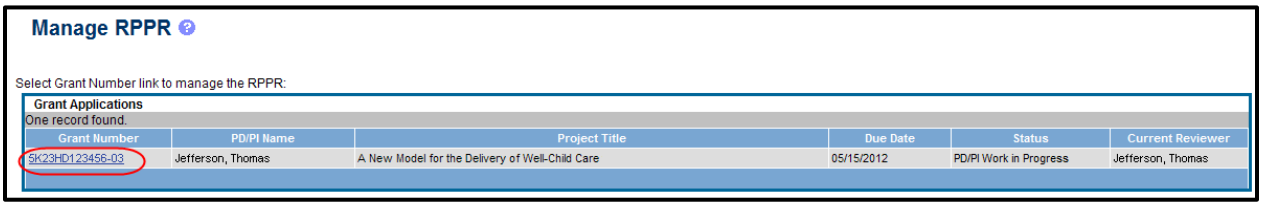


Figure 11: Manage RPPR List of Grant Applications

The appropriate *RPPR Menu* screen – either for single-project or multi-project RPPRs – displays with editing options.

5.2.1 Accessing a Single-Project RPPR for Editing

For single-project awards, the *RPPR Menu* screen displays with buttons for the following available options:

Edit

Check for Errors

View

View Routing History

Route

Cancel

NOTE: Once an RPPR has been routed for review, the **Recall** and **Submit** buttons are enabled. These functions are covered in subsequent chapters.

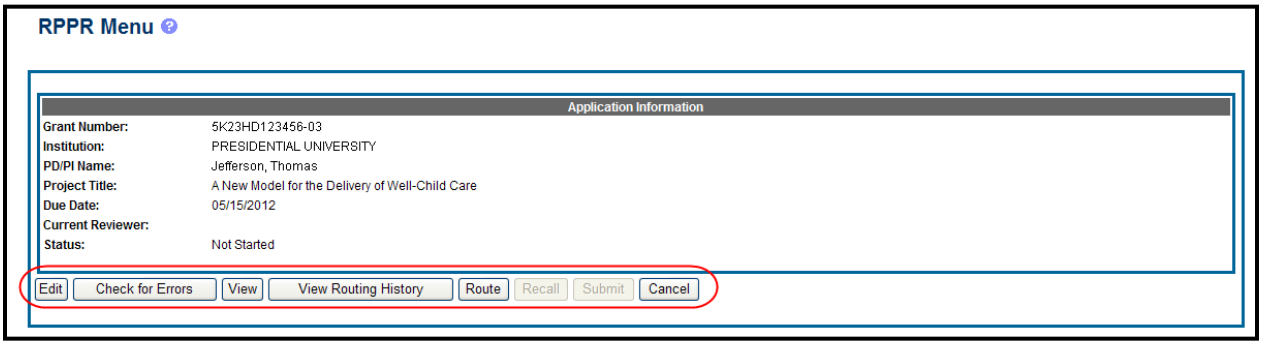


Figure 12: RPPR Menu Buttons

Select the **Edit** button to open the RPPR for editing.

Refer to the section of this document titled *Editing the RPPR Forms* for more information on editing the forms.

5.2.2 Accessing a Multi-Project and Single-Project with Complicated Structure RPPR for Editing

A *multi-project RPPR* is a progress report submitted for a funded program (activity code) which has multiple, interrelated components sharing a common focus or objective.

A *component* (for the purposes of applications and progress reports) is a distinct, reviewable part of the multi-project application or progress report for which there is a business need to gather detailed information identified in the funding opportunity announcement (FOA).

Components typically include general information (component organization, project periods, project title, etc.), performance sites, personnel, and budget. The FOA defines the construction and naming convention for the application; the funded application defines the construction and naming convention for the progress report.

For multi-project awards, the *RPPR Menu* screen displays with buttons for the following available options found within the **Application Information** section of the screen:

View

View Routing History

Route

Cancel

NOTE: Once an RPPR has been routed for review, the **Recall** and **Submit** buttons are enabled. These functions are covered in subsequent chapters.

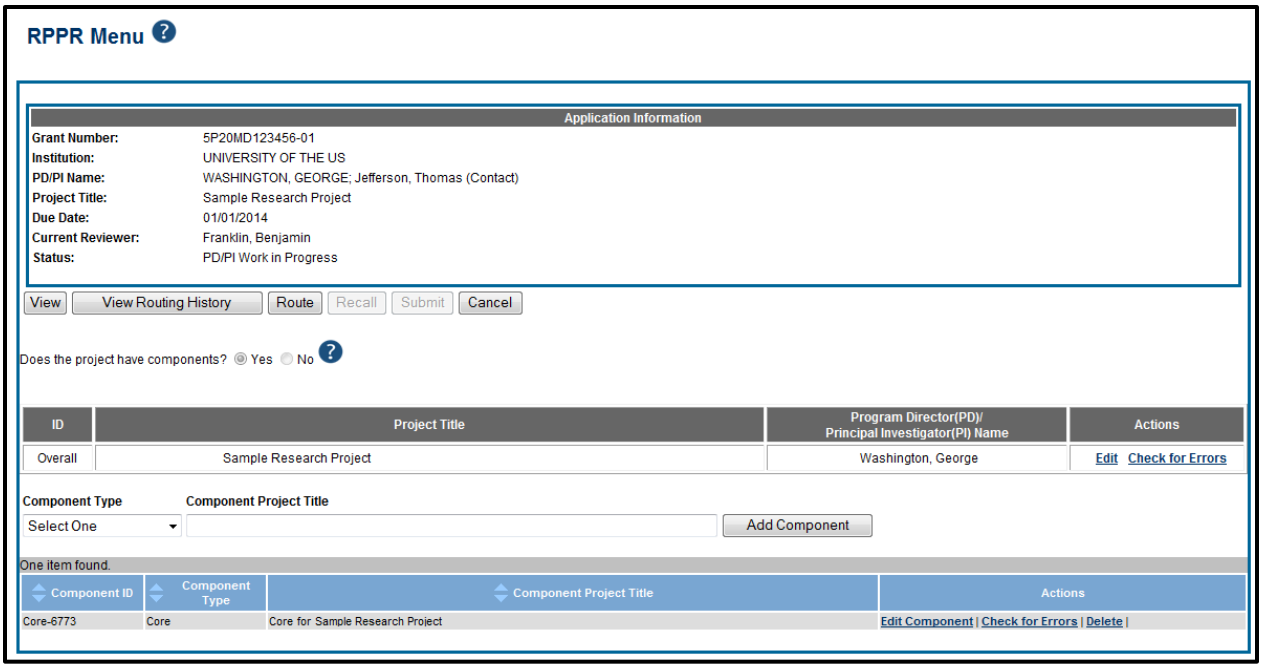


Figure 13: RPPR Menu Options for Multi-Project RPPRs

Overall

Below the **Application Information** is a table showing the Overall **ID**, **Project Title**, **Program Director/Principal Investigator (PD/PI) Name**, and an **Actions** column with links.

The *RPPR Menu* for a multi-project RPPR without components does not include the component table. Additionally, the **No** radio button on the **Does the project have components?** field is selected.

Refer to the figure below for an example of a single-project with complicated structure RPPR.

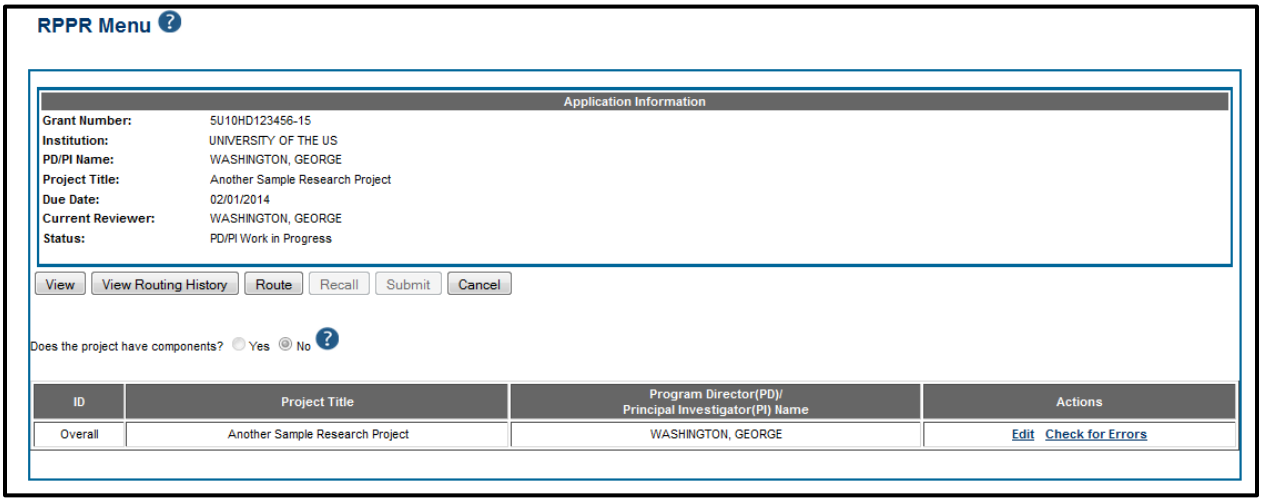


Figure 14: RPPR Menu for Single-Project with Complicated Structure

To edit the RPPR for the Overall, select the **Edit** link from the **Actions** column.

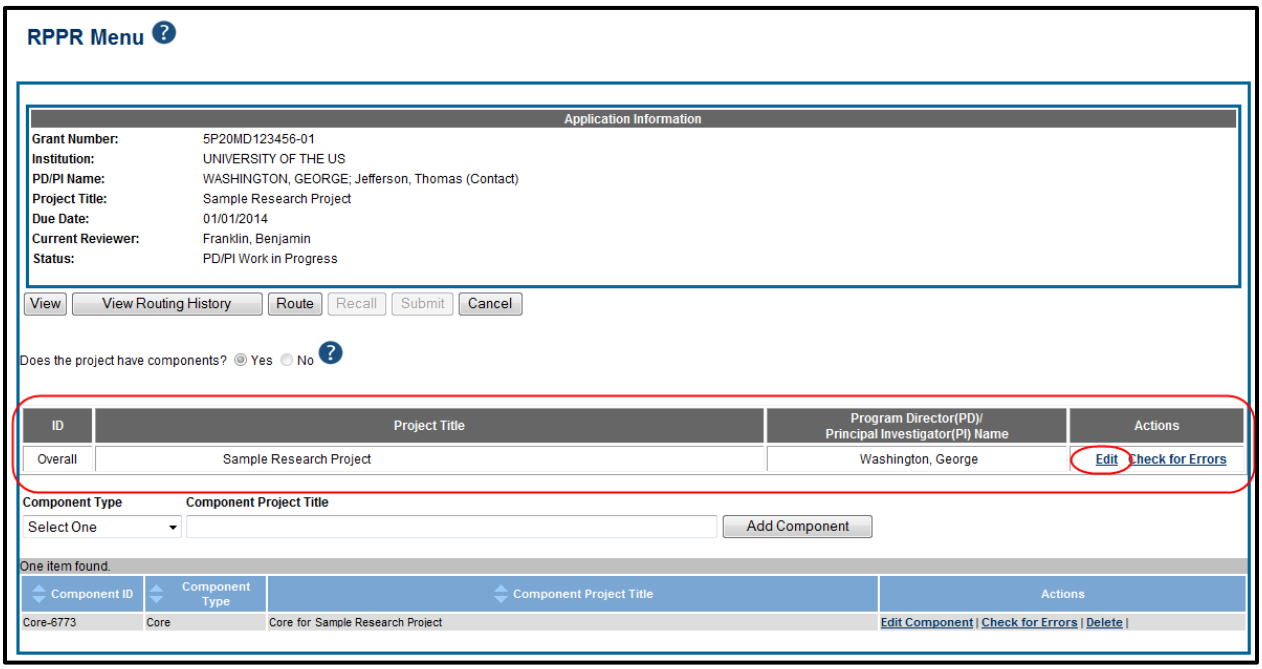


Figure 15: Edit Link for Overall

Individual Components

If individual components exist in the RPPRs, you can add them to the RPPR (and/or edit them) by selecting the **Yes** radio button next to the question **Does the project have components?** Selecting **Yes** displays the **Add Component** feature.

NOTE: Any individual components previously added will already be displayed in a table beneath this feature. In this scenario, the **Does this project have components?** option is disabled. This includes components which were part of a previously submitted progress report for the grant.

To add an individual component:

1. Select the correct option from the **Component Type** drop-down list.
2. Enter the **Component Project Title**.
3. Select the **Add Component** button.

Added individual components display in a table beneath the Overall, showing the **Component ID**, **Component Type**, **Component Project Title**, and available links in the **Actions** column.

4. Select the **Edit Component** link in the **Actions** column for the component to edit its RPPR.

Refer to the section of this document titled *Editing the RPPR Forms* for more information on editing the RPPR forms.

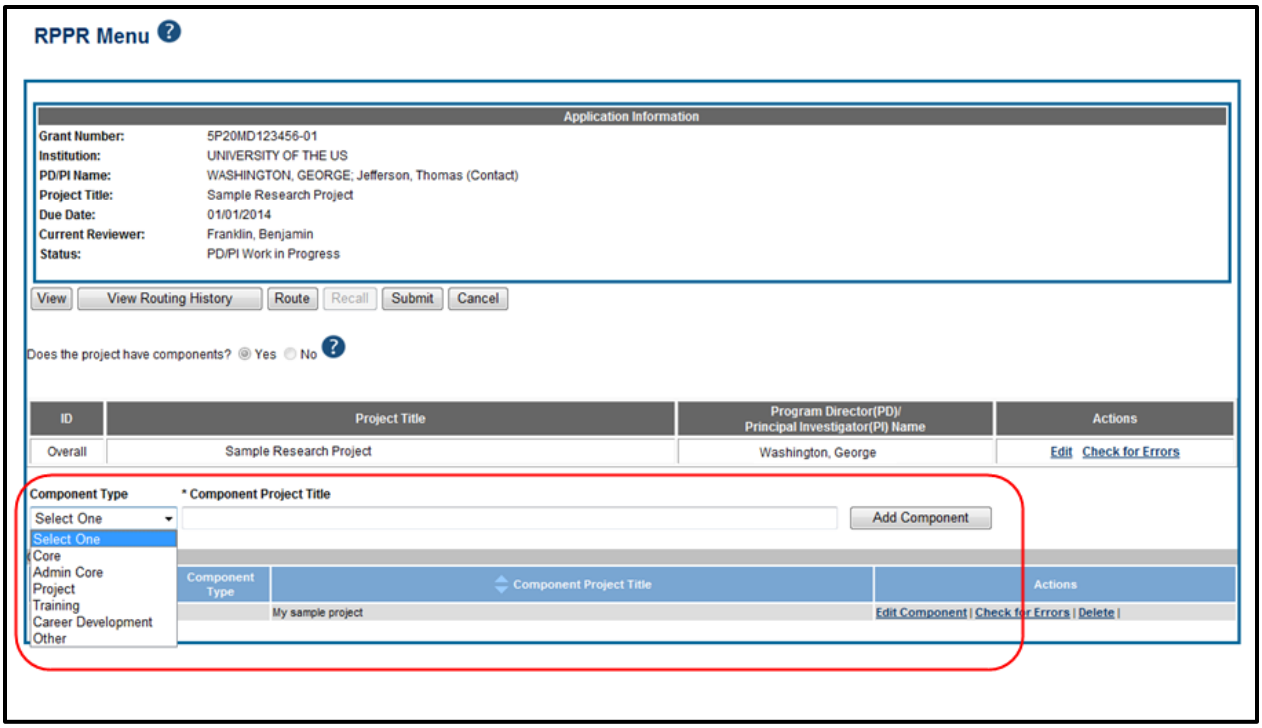


Figure 16: Adding and Editing Individual Components

Individual components can be removed from the RPPR by selecting the corresponding **Delete** link from the **Actions** column of the specific component, followed by the **OK** button on the confirmation pop-up message. *The delete option is not available for Overall.*

IMPORTANT: If you choose to delete a component, all data related to this component – including all budget data – will be lost. ***This data cannot be recovered once it has been deleted.***

5.2.3 Editing the RPPR Forms

After selecting the appropriate editing option, the RPPR section *A. Cover Page* displays. The *Cover Page* includes information about the grant, PD/PI, signing and administrative officials, organization, and project/reporting/budget periods. Some of this information may be auto-populated. For more information on the *Cover Page*, refer to the section of this document titled *Section A – Cover Page* located in the *Instructions for RPPR Sections A–H*.

1. Update the information as necessary and select the **Save** button.

The *Cover Page* includes tabs at the top and links at the bottom of the page for navigating to the other sections (e.g., **Accomplishments, Participants**), which may be completed in any order. Before navigating to and from any of these sections, it is always necessary to select the **Save** button to save all changes on the current page. Navigating away from any page on the RPPR without selecting **Save** results in the loss of any information entered prior to the last save.

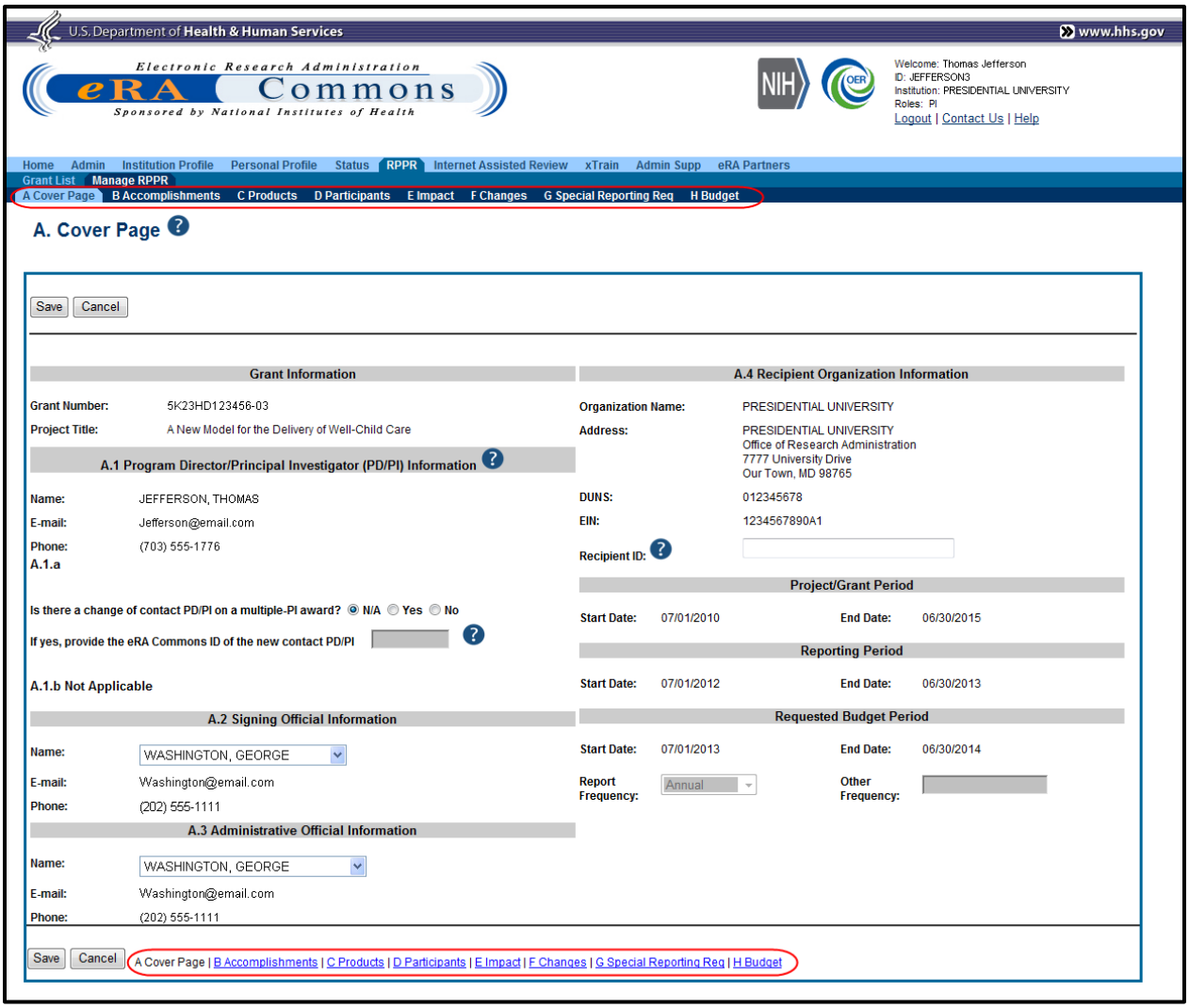


Figure 17: RPPR Cover Page and Section Navigation Links

2. Sections can be completed in any order. To navigate and populate the other sections of the RPPR, select the appropriate link from the top or bottom of the page.

The same navigational links appear on each section of the RPPR. For information on the specific fields in each section refer to Chapter 6 *Instructions for RPPR Sections A–H*.

3. Complete the appropriate fields of the report.

Details for completing each section are discussed later in this document. Many of the fields on these pages, however, behave in a similar manner and are discussed below.

Add/New

To use the Add/New feature, enter or select data into the appropriate fields. Select the **Add/New** button to add the data to a table.

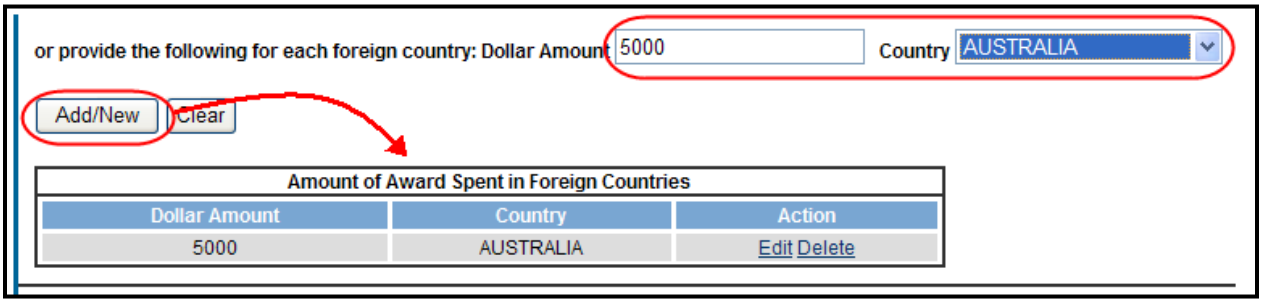


Figure 18: Add/New Feature

Items can be edited or deleted from the table using the **Action** links.

Text Box

All text boxes on the RPPR have character limits. The number of characters available is reflected beneath each text box as characters are entered.

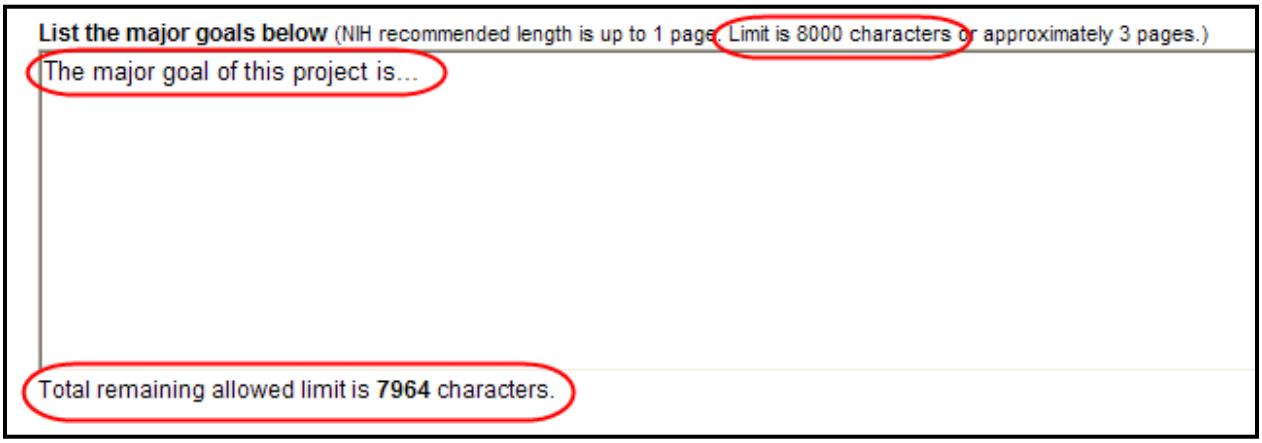


Figure 19: Total Remaining Characters

Changing Saved Responses

While in WIP status, answers may be changed. A warning message displays as follows:

The entered/uploaded response will be deleted. Do you wish to continue?

The user editing the information can choose to **Continue** or **Cancel** the action. Choosing **Continue** deletes the previous response, removes any attachments, and disables the relevant fields associated with the question. Choosing **Cancel** cancels the change.

4. Select the **Save** button before navigating to the next page.
5. To return to the *RPPR Menu,* select the **Cancel** button.

When an RPPR is ready for review and submission, it is routed to the next reviewer. Refer to the section of this document titled *Route the RPPR* for steps on routing to the next reviewer.

5.2.4 Editing the RPPR Budget Forms

Budget Form (H.1)

To add a budget, choose an option from the drop-down list and select the **Add Budget** button. The added budget type appears in the first table. Use the **Edit** link in the **Action** column to open the form for editing. Select the **Save** button before exiting the form. Most awards now use the SF424 R&R budget form. However, training awards may use the SF424 and/or the PHS 398 training budget. Please contact the Grants Management Specialist assigned to your grant if you have questions on the appropriate form to use.

Budget types include:

- SF 424 Research & Related Budget form
- PHS 398 Training Budget

NOTE: Budget types can be deleted by selecting the **Delete** link from the **Action** column for the specific budget type.

Subaward Budget Form (H.2)

To add a subaward budget, choose an option from the drop-down list and select the **Add Subaward** button. The added budget type appears in the second table. Use the **Edit** link in the **Action** column to open the form for editing. Select the **Save** button before exiting the form.

Subaward budget types include:

- SF 424 Research & Related Subaward Budget form
- PHS 398 Subaward Training Budget

The grantee may select up to 30 subaward budgets.

NOTE: Subaward budget types can be deleted by selecting the **Delete** link from the **Action** column for the specific subaward.

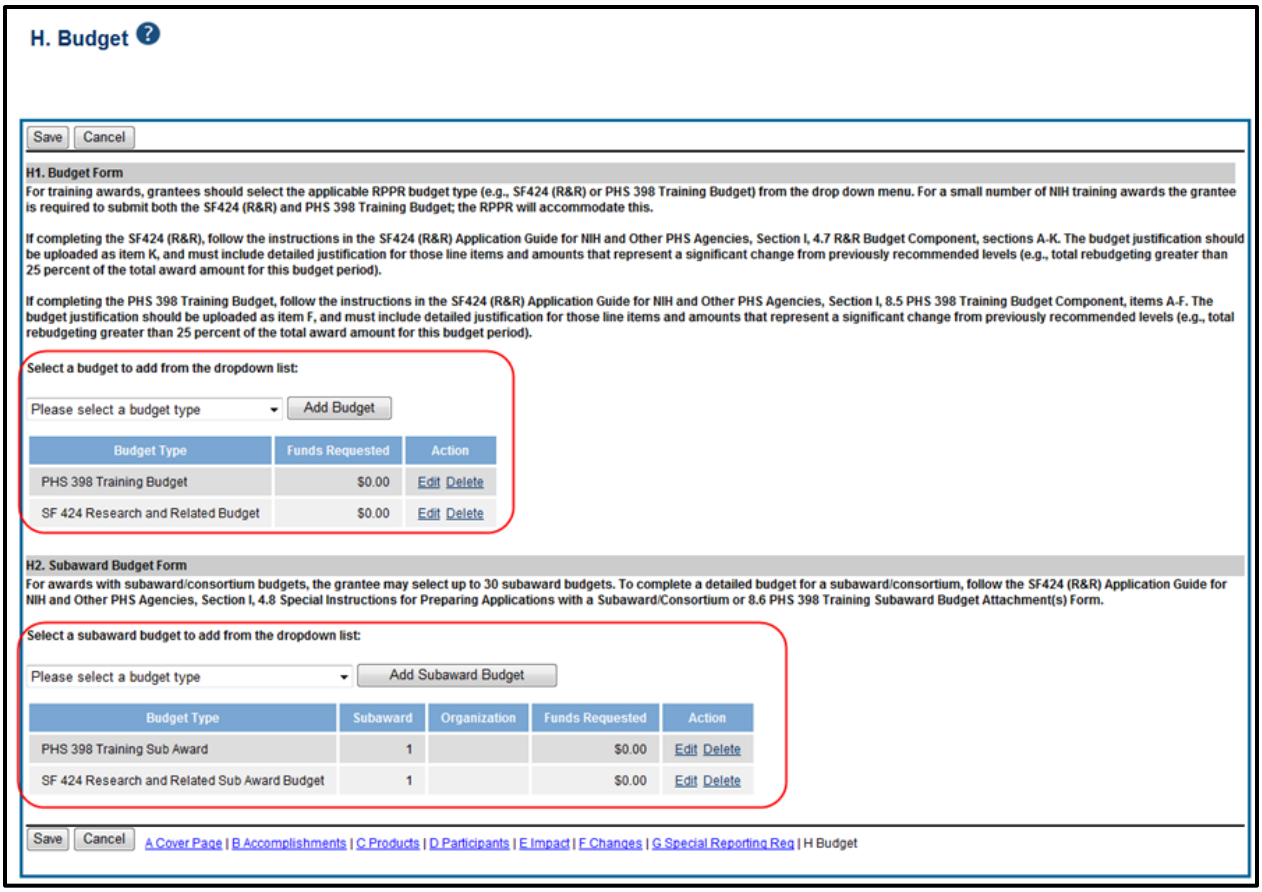


Figure 20: RPPR H. Budget - Questions H.1 Budget Form & H.2 Subaward Budget Form

NOTE: Remember to save the information before exiting the form by selecting one of the **Save** buttons located at the top and bottom of the form.

For single-project RPPRs, the DUNS number will automatically populate the DUNS number of the grantee organization on the budget form.

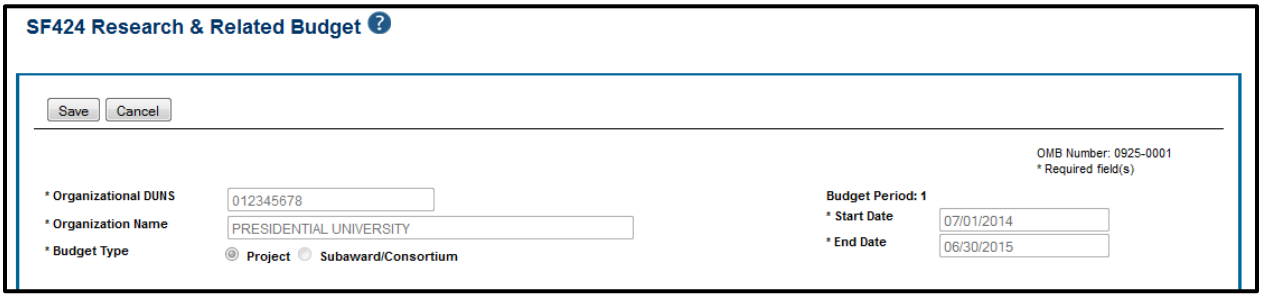


Figure 21: Organizational DUNS on SF 424 Research & Related Budget

For multi-component RPPRs the grantee must enter the DUNS and Organization Name fields, as the DUNS number will not automatically populate the DUNS number.

To add the DUNS number:

Enter the DUNS number into the **Organizational DUNS** field or select the magnifying glass icon to search for and select the DUNS number.

The **Organizational DUNS** field updates with the information and the **Enter Name of Organization** field updates to reflect the new DUNS.

To add the organization name:

Enter the organization name into the **Organization Name** field or select the magnifying glass icon to search for and select the new organization name.

The **Organization Name** field updates with the information and the **Organizational DUNS** field updates to reflect the new organization.

NOTE: If subaward budgets are completed, the system will not calculate the budget line item F.5 for the main budget (see figure below). Total consortium costs for the main budget **MUST** be computed and entered manually into budget line item F.5.

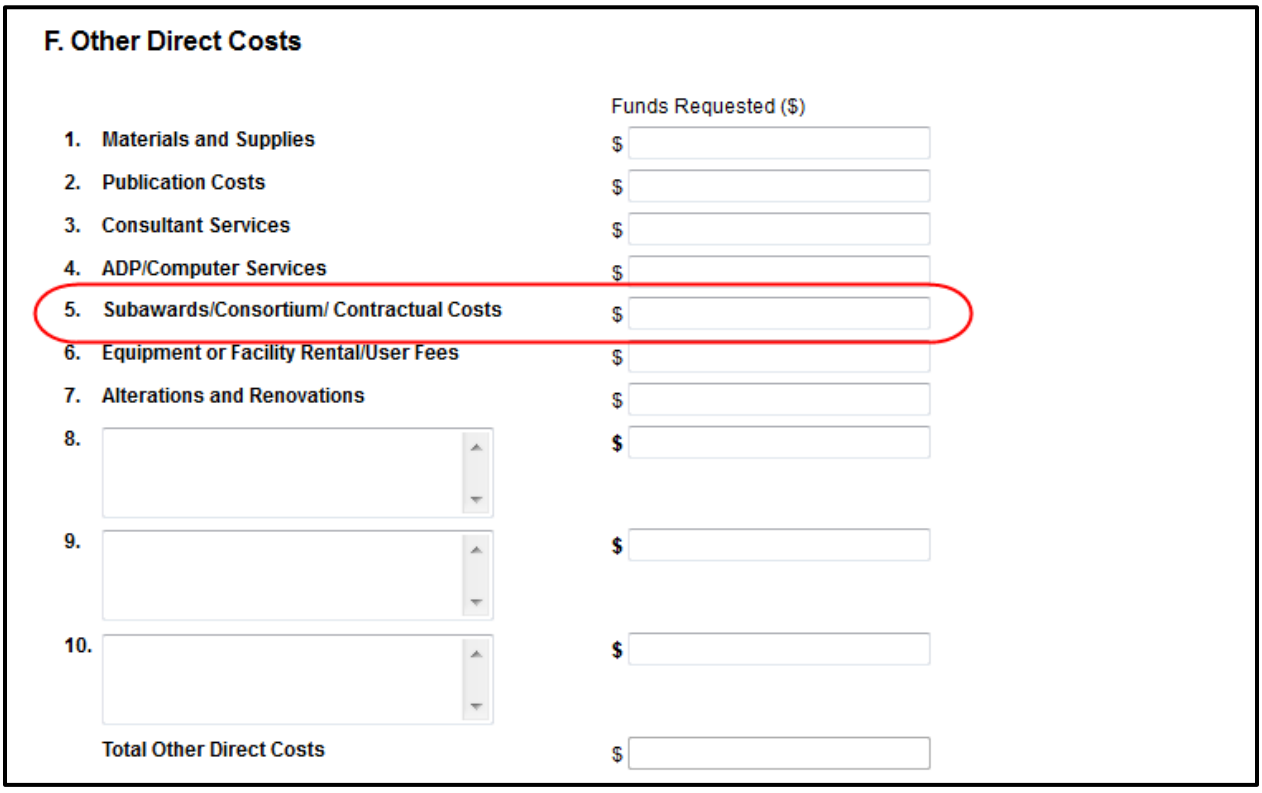


Figure 22: SF 424 R&R Budget Form - Question F.5

5.3 Check RPPR for Errors and Warnings

At any time before an RPPR is submitted to agency, an error check can be performed to verify that the report passes the business rules and system validations in place. Any user who has access to the RPPR may perform the error check.

5.3.1 Checking for Errors on Single-Project RPPRs

To perform an error check on the RPPR for single-project RPPRs, select the **Check for Errors** button from the *RPPR Menu* screen.

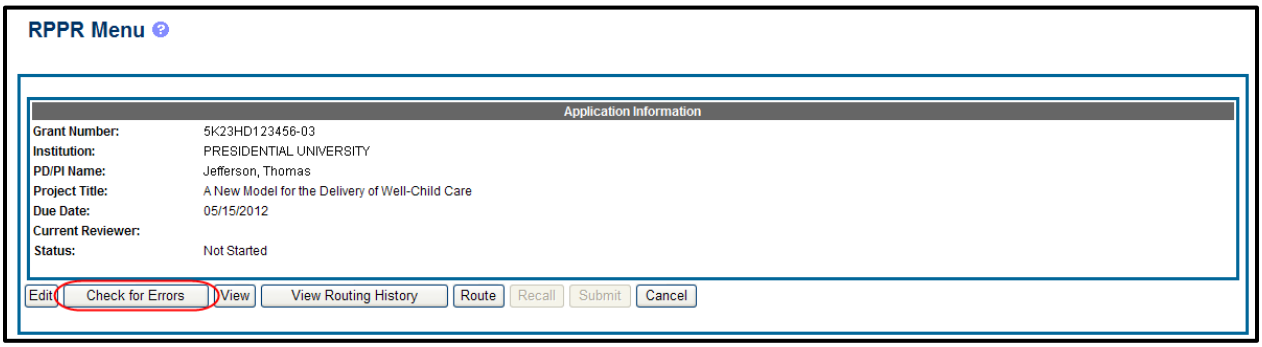


Figure 23: Check for Errors Button on RPPR Menu for a Single-Project RPPR

If errors or a warning exist, the appropriate error or warning message displays for each failed occurrence. **All errors must be corrected prior to submission**; the system will prevent submission of an RPPR containing errors. However, the system will not prevent submission of an RPPR when a warning message is displayed.

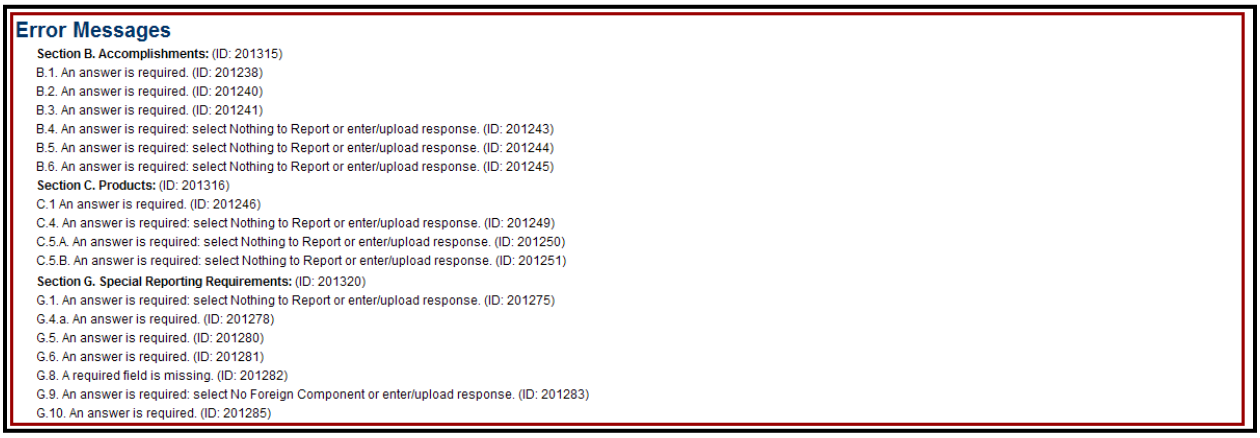


Figure 24: RPPR Error Messages (Examples)

If all validations pass, a message displays indicating: *No errors found on validation.*

5.3.2 Checking for Errors on a Multi-Project RPPR

To perform an error check on the Overall or individual component of a multi-project RPPR, select the **Check for Errors** link from the **Actions** column of the *RPPR Menu* screen for the Overall or individual component being validated.

NOTE: Refer to section *5.3.2 Accessing a Multi-Project and Single-Project with Complicated Structure RPPR for Editing* for information on adding individual components to the RPPR.

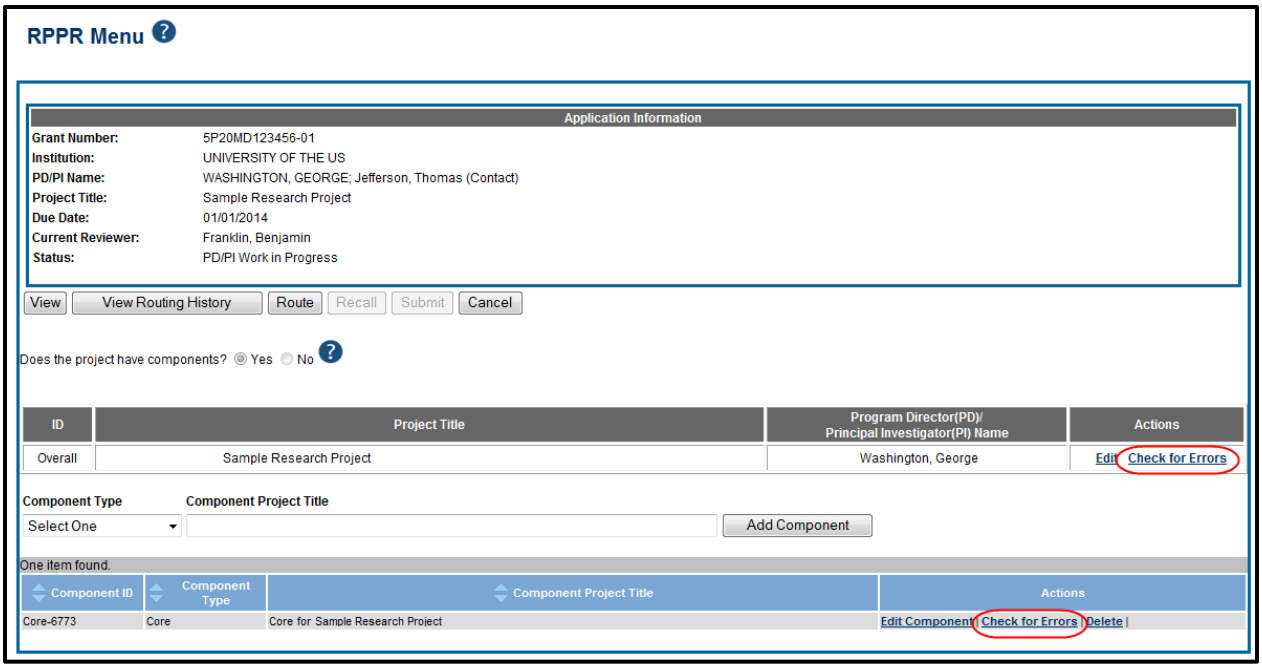


Figure 25: Check for Errors Links for Multi-Project RPPRs

If errors or a warning exist for the chosen component, the appropriate error or warning message displays for each failed occurrence. Select the **Check for Errors** button of the other components to perform a check against them.

All errors must be corrected prior to submission; the system will prevent submission of an RPPR containing errors. However, the system will not prevent submission of an RPPR when a warning message is displayed.

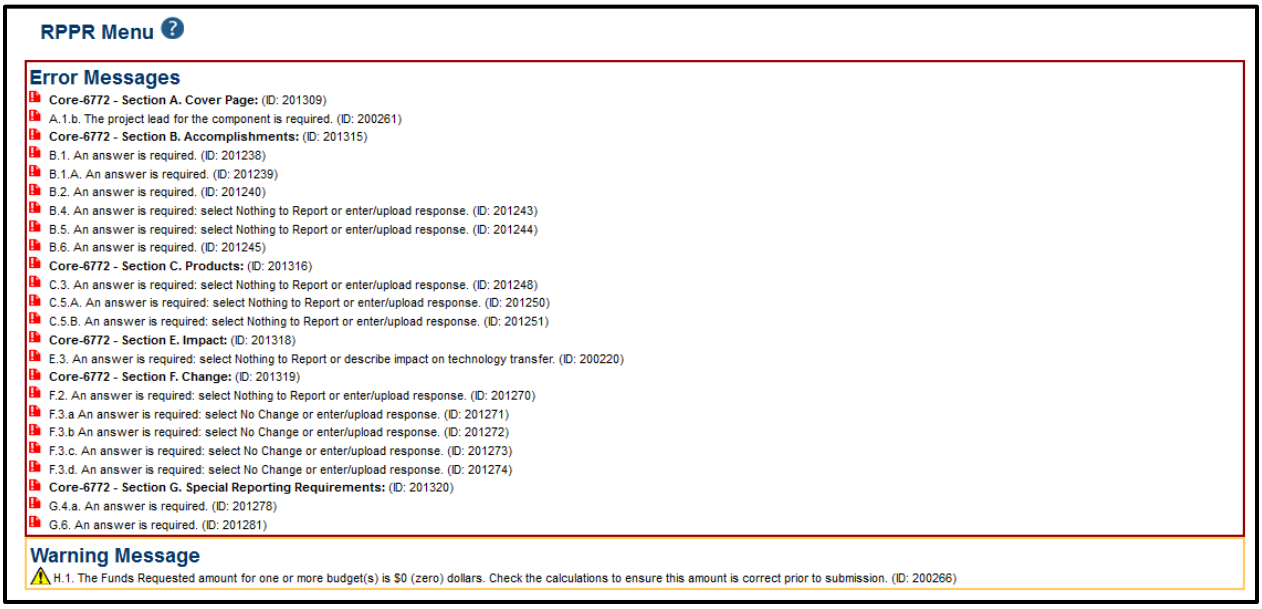


Figure 26: Errors and Warnings for One Component of a Multi-Project RPPR

If all validations pass, a message displays indicating: *No errors found on validation.*

5.4 Route the RPPR

Progress reports in *Work in Progress (WIP)* status can be routed to others for review or corrections by the current reviewer of the report. The routing feature is found on the *RPPR Menu* screen.

NOTE: A PD/PI delegate cannot route an RPPR to the next reviewer.

To route an RPPR to the next reviewer:

1. Select the **Route** button from the *RPPR Menu* screen.

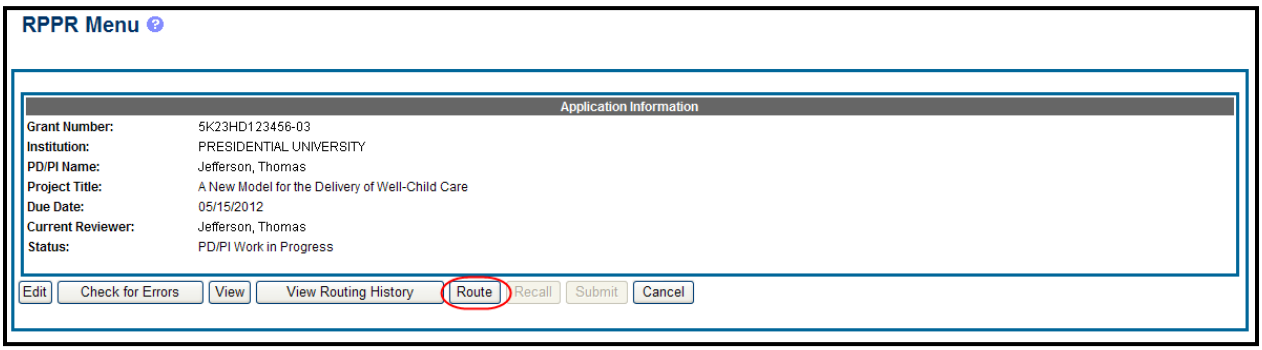


Figure 27: RPPR Menu – Route Button

NOTE: The figure above shows the *RPPR Menu* for a single-project RPPR, however, multi-project RPPRs have a similar **Route** button on their own *RPPR Menu* screen.

The *Route RPPR to Next Reviewer* screen displays. From this screen, the next reviewer can be chosen from a list of reviewers, and comments can be added.

2. Select a reviewer from the **Next Reviewer** drop-down list.
3. *Optional*: Enter comments in the **Comments** text box to provide information to the next reviewer.
4. Select the **Submit** button.

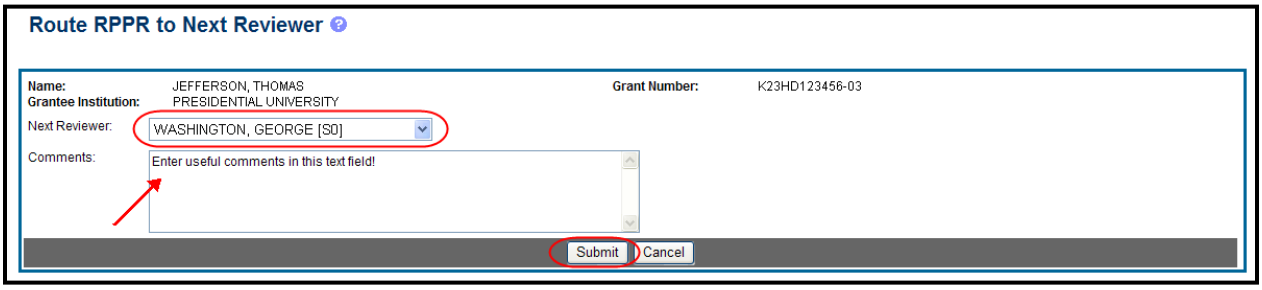


Figure 28: Route RPPR to Next Reviewer

5. *When routed by the PD/PI only*: The PD/PI Assurance statement displays. Select the **I Agree** button to continue.

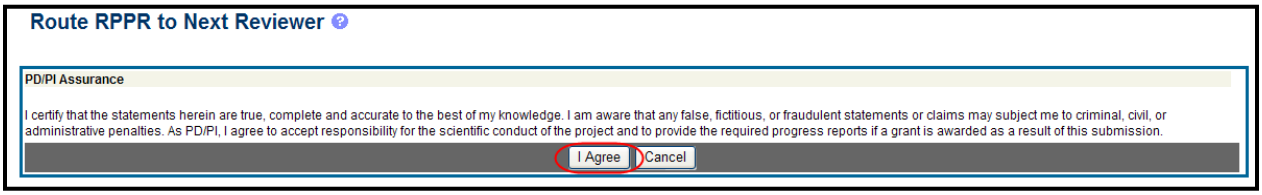


Figure 29: PD/PI Assurance Statement

The *RPPR Menu* displays once again. If the routing is successful, the message on the screen reads as follows:

The RPPR was successfully routed to [Selected Reviewer User ID], [Selected Reviewer Name].

The person who routed the RPPR can no longer edit the report (**Edit** button becomes disabled). The editing feature is now available only to the new reviewer. The RPPR status is updated to *Reviewer Work in Progress*.

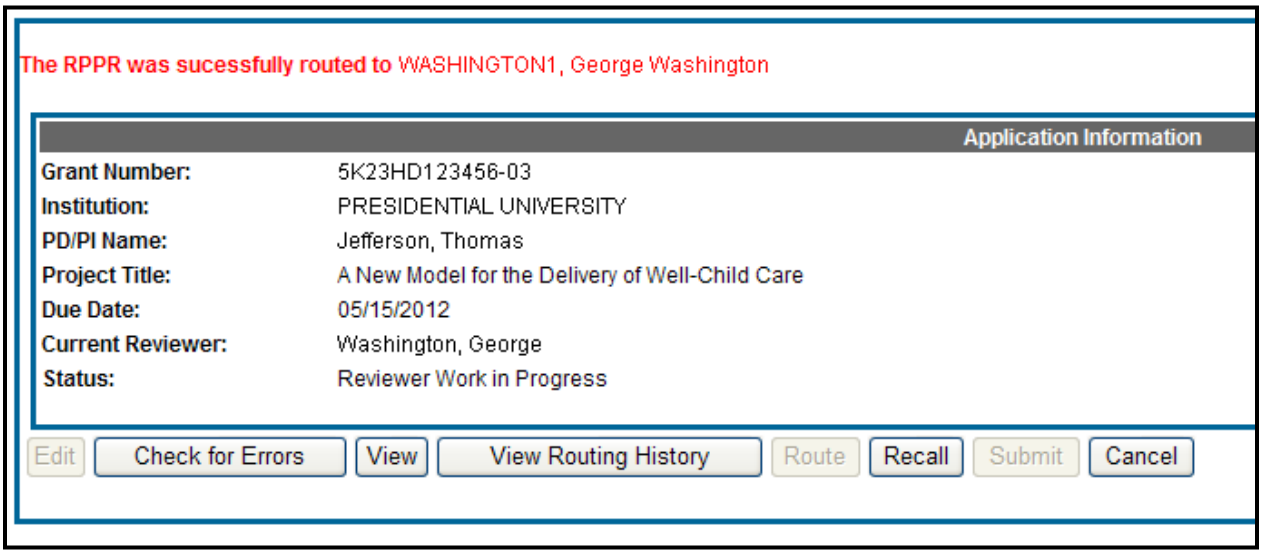


Figure 30: RPPR Successfully Routed

5.5 Recall the RPPR

RPPRs that have been routed to a reviewer can be recalled by the person who performed the routing action. This is useful in situations when the report was routed to the wrong person or the reviewer is unavailable. The last reviewer of the report is able to recall it; however, Signing Officials at the Institution and the Contact PD/PI who are not the last reviewer can also recall the report when it is in a status of *Reviewer Work in Progress*.

NOTE: A PD/PI delegate does not have the ability to recall the RPPR.

To recall an RPPR, select the **Recall** button from the *RPPR Menu* screen.

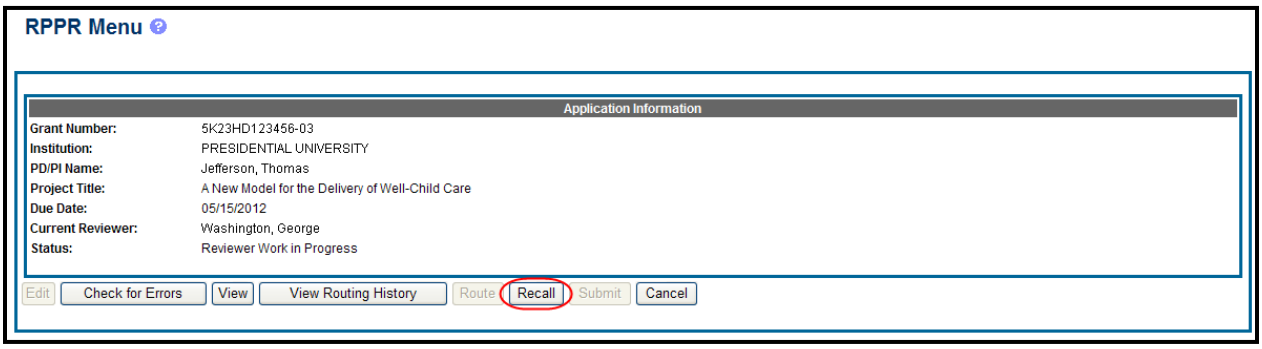


Figure 31: RPPR Menu – Recall Button

A message displays on the screen indicating: *The RPPR has been successfully recalled. You have been set as the Current RPPR Reviewer.*

The status of the RPPR is updated to *PD/PI Work in Progress* or *Reviewer Work in Progress*, the reviewer from whom the RPPR is recalled receives an email informing him of the action, and the RPPR routing audit history is updated to reflect the action.

Additionally, the **Edit** and **Route** buttons are enabled, providing the new reviewer with the ability to continue editing the RPPR or to route it to another reviewer.

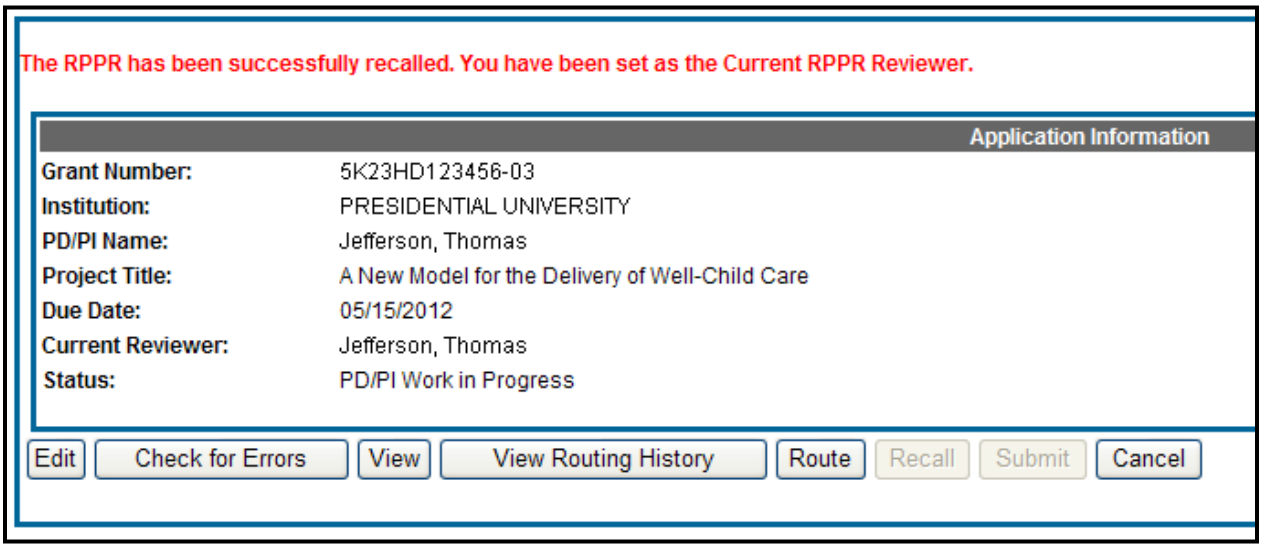


Figure 32: RPPR Successfully Recalled

5.6 Submit the RPPR to Agency

Grantees are **strongly** encouraged to view the RPPR prior to submission to ensure that the correct information and attachments are provided (see 5.7 *View the RPPR*).

Completed and validated RPPRs in a status of *Work in Progress* can be submitted to the Agency for acceptance. This act is performed by the Signing Official (SO) when the SO is the current

reviewer of the report. For SNAP awards only, PD/PIs may also submit the report if they have been delegated submit authority by the SO.

NOTE: A PD/PI with *Progress Report* authority cannot submit a non-SNAP or F RPPR.

To submit the RPPR to agency:

1. Select the **Submit** button from the *RPPR Menu* screen.

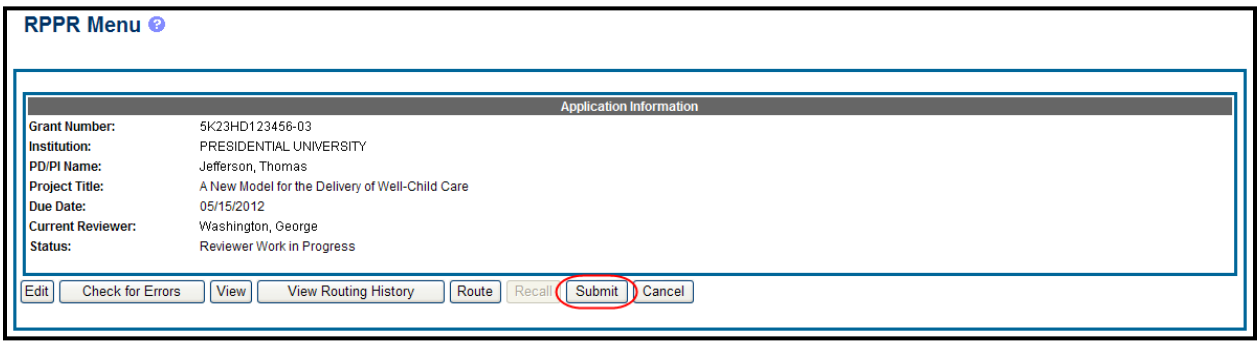


Figure 33: Submit Button on RPPR Menu

The *Submit RPPR* screen displays a certification statement as follows:

In submitting this RPPR, the SO (or PD/PI with delegated authority), certifies to the best of his/her knowledge that the grantee organization is in compliance with the terms and conditions specified in the Notice of Award and Grants Policy Statement, and verifies the accuracy and validity of all administrative, fiscal, and scientific information in the progress report. The SO (or PD/PI with delegated authority) further certifies that the grantee organization will be accountable for the appropriate use of any funds awarded and for the performance of the grant-supported project or activities resulting from the progress report. Deliberate withholding, falsification, or misrepresentation of information could result in administrative actions such as withdrawal of a progress report, suspension and/or termination of an award, debarment of individuals, as well as possible criminal penalties. The grantee institution may be liable for the reimbursement of funds associated with any inappropriate or fraudulent conduct of the project activity.

2. Select the **I Agree** button to sign off on the certification.

The RPPR is validated for systemic and business rules. If there are any validation failures, they are indicated by error messages on the *RPPR Menu* screen. Errors must be corrected in order to submit the RPPR.

If warnings exist, they are displayed on the *RPPR Menu* screen. Although the RPPR can be submitted with warnings present, the warning messages should be reviewed to determine if an issue should be addressed.

3. *If Warnings Exist*: To address issues associated with warnings, select the **Cancel** button, correct the issue, and resubmit the RPPR again. To continue with submission despite the warnings, select the **OK** button.

If all validations pass, the *RPPR Menu* screen displays the following message: *The RPPR has been successfully submitted to PHS.*

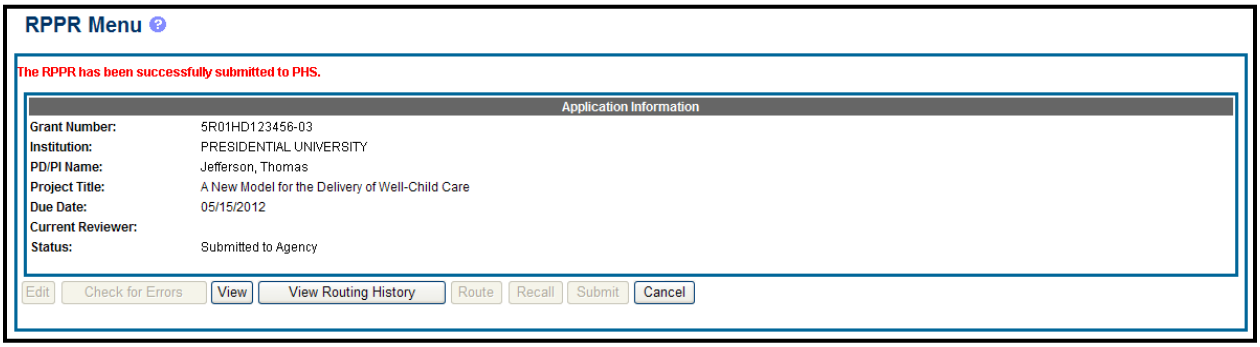


Figure 34: Successful Submission Message

The current reviewer is updated to the awarding agency, the RPPR status is updated to *Submitted to Agency*, and the RPPR Submission date is recorded. The routing history is updated to reflect the submission to Agency.

Any citations associated with the RPPR in C.1. Publications are officially associated with the award in MyNCBI.

If inclusion enrollment data are reported in the RPPR, this information will be attached in PDF format and subsequently updated into the eRA inclusion data system for NIH staff review and acceptance. The data then becomes the data of record for the particular grant year.

When an RPPR is submitted to Agency, email notification is sent to the PD/PI (Contact PI) on the grant and the SO and AO assigned to the RPPR.

5.6.1 Submission Errors and Warnings for Multi-Project RPPRs

Upon submission, multi-project RPPRs are validated for systemic and business rules just as are single-project RPPRs. However, for multi-projects, the errors and warnings are displayed differently. When errors and/or warnings are found on multi-project RPPRs, the *RPPR Menu* screen displays the Overall messages followed by the messages of the other components.

All errors must be corrected in order to submit the RPPR.

If warnings exist, they are displayed on the *RPPR Menu* screen under the errors. Although the RPPR can be submitted with warnings present, the warning messages should be reviewed to determine if an issue should be addressed.

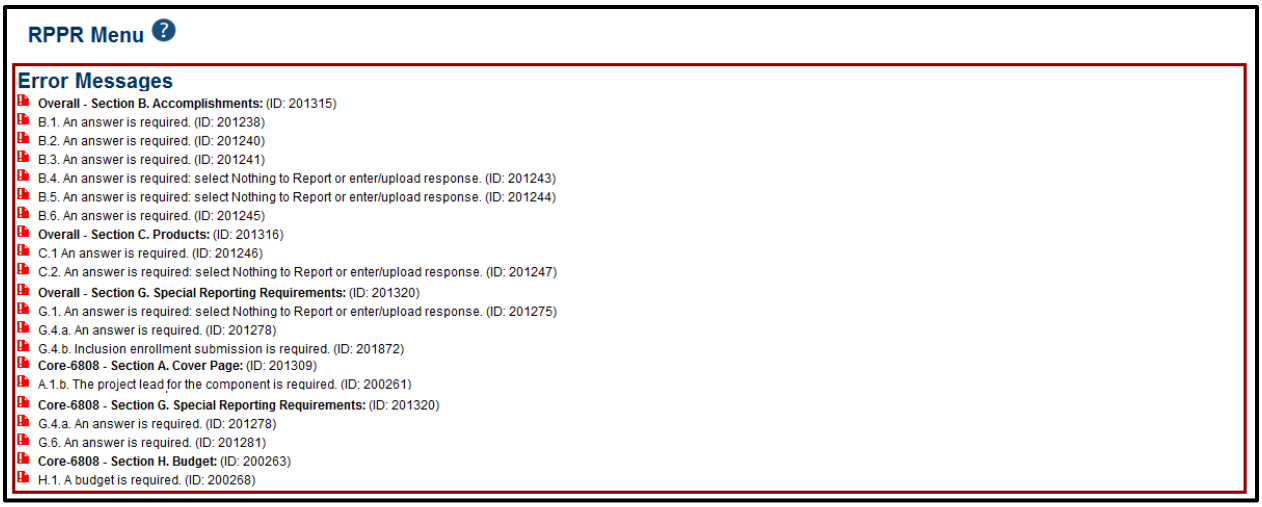


Figure 35: Sample of Multi-Project RPPR Error Messages

5.7 View the RPPR

As indicated in 5.6, grantees are **strongly** encouraged to view the RPPR prior to submission to ensure that the correct information and attachments are provided (see 5.6 *Submit the RPPR to Agency*).

PD/PIs, PD/PI delegates, and reviewers can view a PDF version of an RPPR in *Work in Progress (WIP)* or *Submitted to Agency* status to see how it will be seen by the Agency. Until the RPPR is submitted to agency, the PDF report shows a status of *Draft* and a blank submission date.

To view the RPPR form, select the **View** button from the *RPPR Menu* screen.

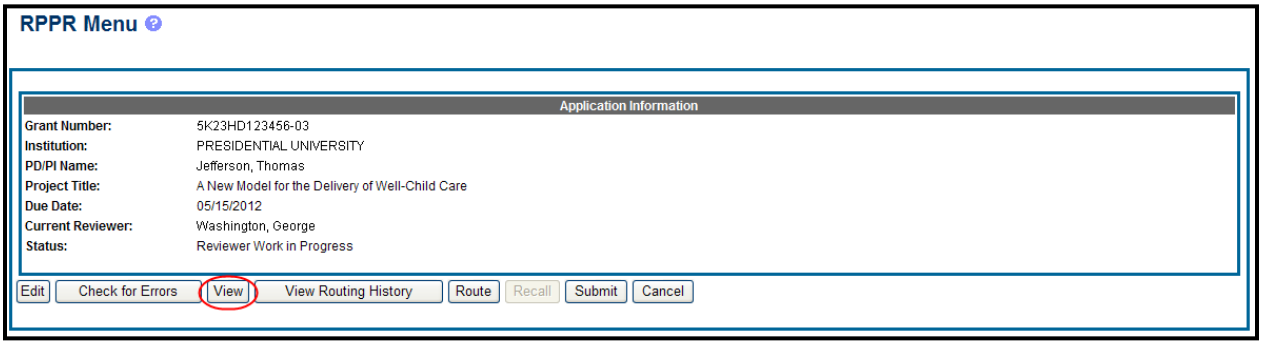


Figure 36: RPPR Menu – View Button

5.8 View Routing History

From initiation to submission to Agency, the routing of an RPPR is captured for auditing purposes. PD/PIs, PD/PI delegates, and reviewers can view the routing history for *Work in Progress* or *Submitted to Agency* RPPRs at any time, even when they are not the current reviewer.

To view the routing history:

1. Select the **View Routing History** button from the *RPPR Menu* screen.

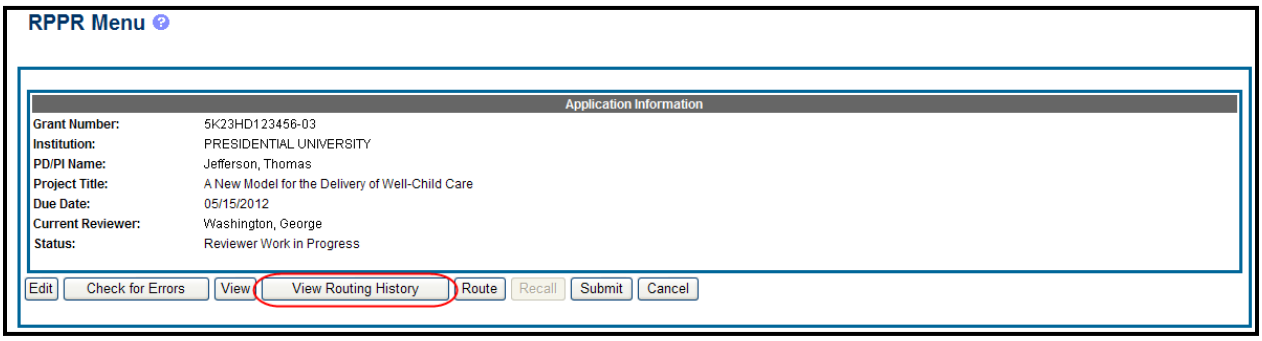


Figure 37: RPPR Menu – View Routing History Button

The *Routing History* screen displays showing the **Reviewer Name**, **Action**, **Notification Sent** (date and time), **Date of Action**, **Next Reviewer Name**, and **Comments** (when available).

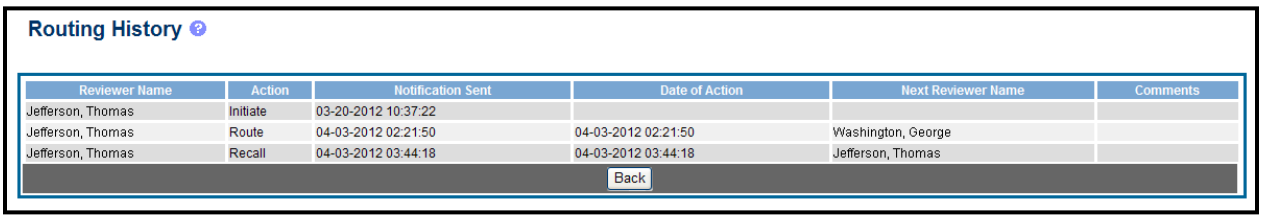


Figure 38: RPPR Routing History

2. To close the screen, select the **Back** button.

5.9 Viewing the Final RPPR in Commons

The final RPPR, in PDF format, is accessible in Commons within the *Status Information* screen. To view the final RPPR, perform the following steps:

1. From Commons, select the **Status** menu option.
2. Select the link for **List of Applications/Grants**.

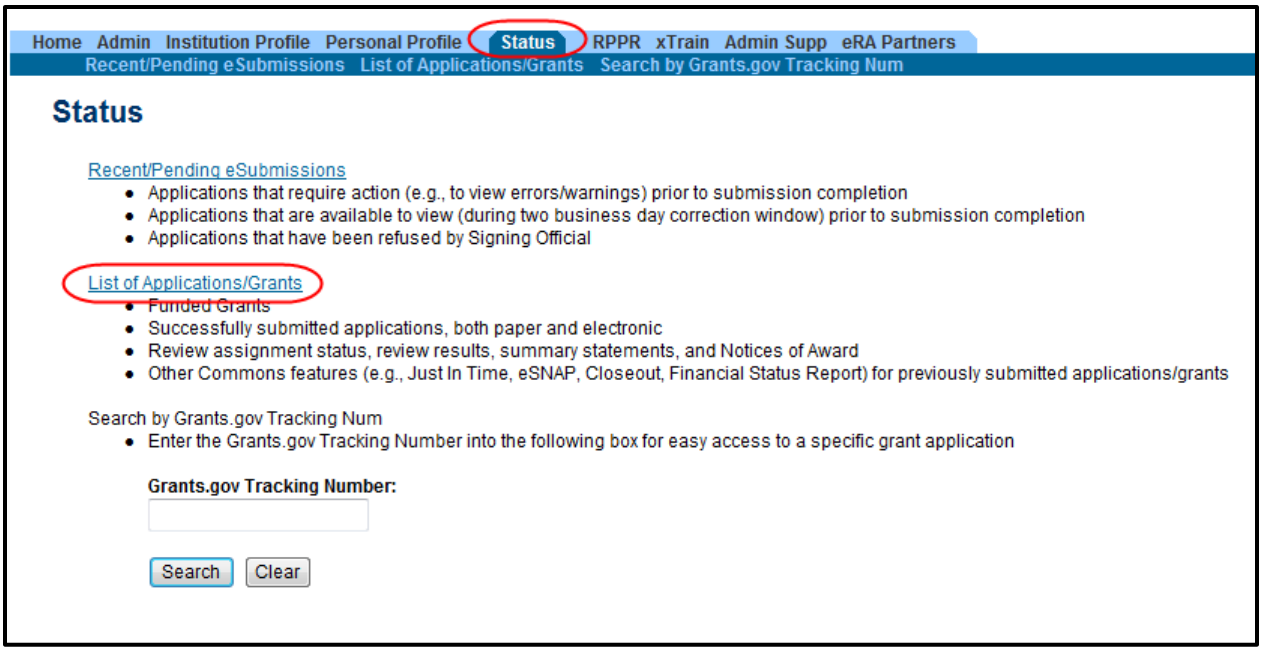


Figure 39: Status Menu Option

3. From the *Status Result – List of Applications/Grants* screen, select the hyperlink for the specific Application ID.

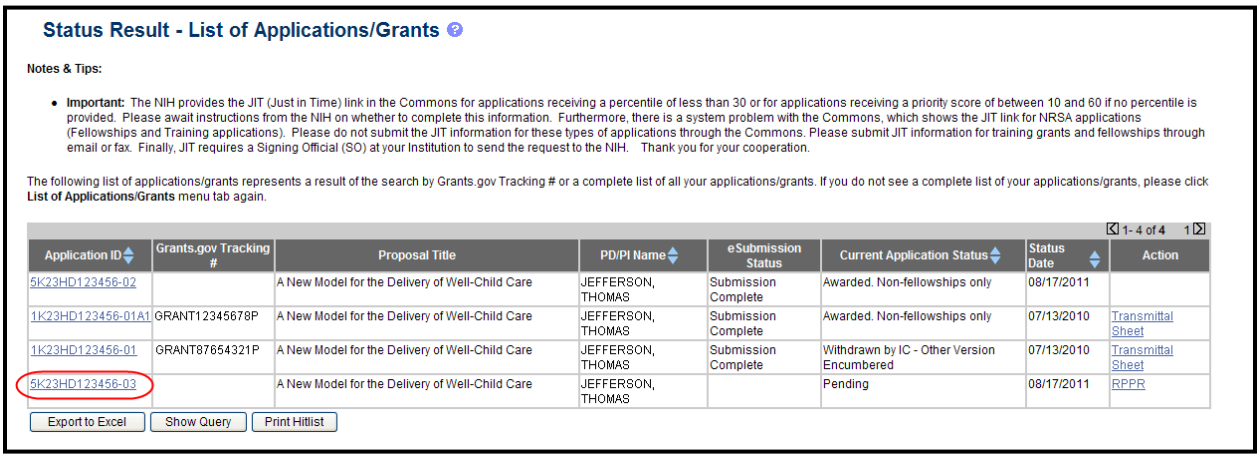


Figure 40: Application ID hyperlink

The *Status Information* screen displays with the **Other Relevant Documents** section in the top right corner.

4. The progress reports for incrementally-funded and multi-year funded awards are displayed differently in **Other Relevant Documents**.

    a. *For an incrementally-funded RPPR:* Select the **e-Application** link from the **Other Relevant Documents** section of the *Status Information* screen.

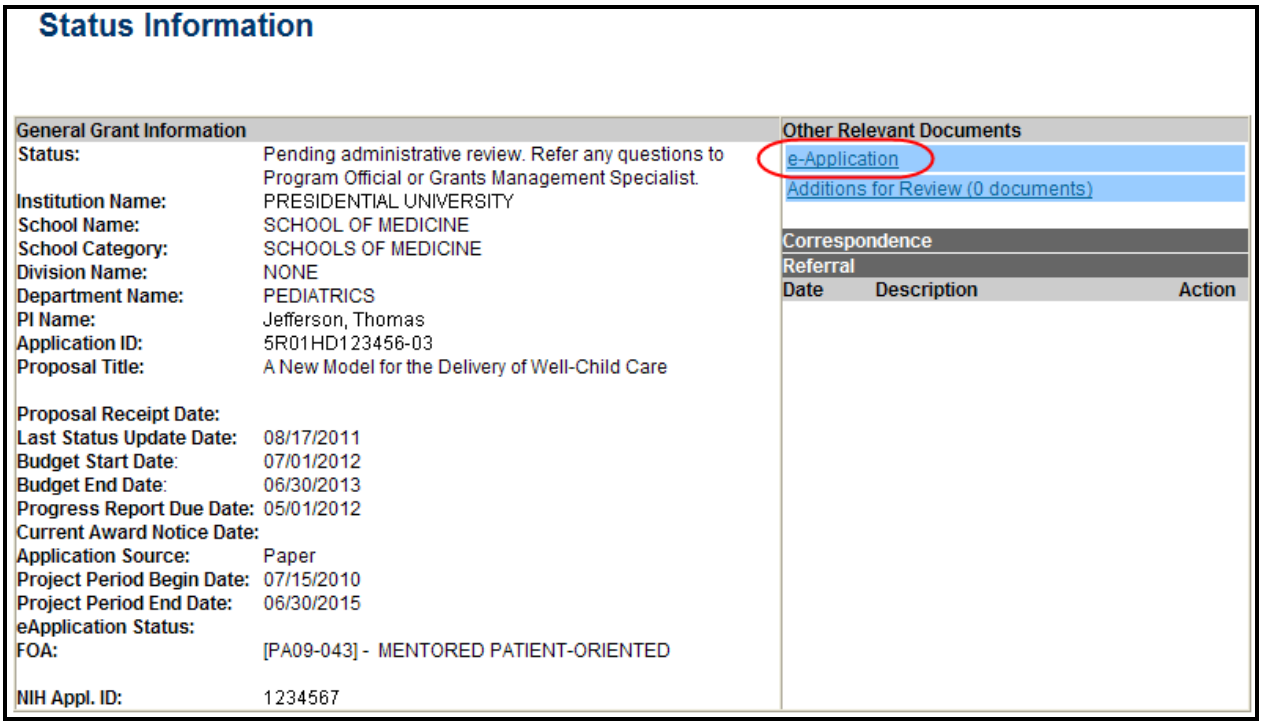


Figure 41: Status Information Screen – e-Application Link

b. For multi-year funded awards: Select the appropriate year's link in the **Research Performance Progress Report** section. Links will appear as follows: **RPPR Year <X> <MM/DD/YYYY>**

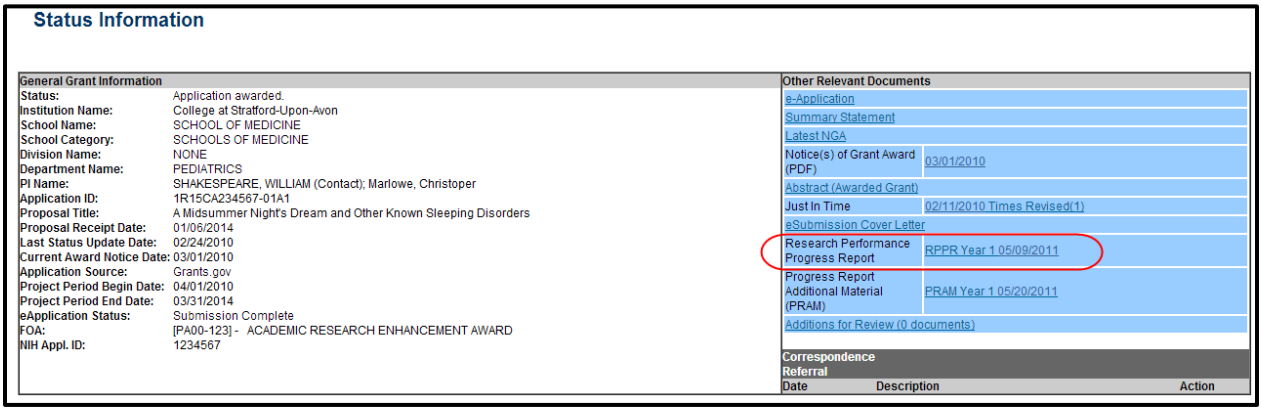


Figure 42: Status Information Screen for Multi-Year RPPR

The PDF version of the RPPR opens in a separate window.

NOTE: The submitted RPPR can also be accessed from the *RPPR Menu* screen. The **View** button opens the PDF version of the RPPR.

5.10 Public Access Progress Report Additional Materials (PRAM)

The Public Access Progress Report Additional Materials (PRAM) feature provides a means for the grantee to enter, review, and submit information in response to the automated notification sent when an NIH grantee organization submits an RPPR with non-compliant publications. The system sends the automated email to the PD/PI requesting verification that all publications are in compliance with the NIH Public Access Policy. The SO and AO assigned to the RPPR on the cover page (see 6.1 *Section A – Cover Page*) will receive a copy (cc:) of the email. While an email response to the GMS and PO is acceptable at this time, the grantee is encouraged to respond using the Public Access PRAM feature in eRA Commons. AHRQ does not use the PRAM feature for public access compliance notifications.

Using the PRAM feature, grantees can upload and submit a My NCBI PDF report demonstrating that previously non-compliant papers reported on the RPPR are now compliant. Compliant papers have a status of *Complete*, *N/A* (not applicable), *PMC Journal in Process*, or *In process at NIHMS*. Please see http://publicaccess.nih.gov/include-pmcid-citations.htm for additional information. If unable to provide the verification of compliance, grantees can upload and submit justification for why specific publications cannot be brought into compliance.

As with the RPPR, a PD/PI (or Contact PI in the case of multiple PIs) can enter the Public Access PRAM, but can only submit it if the PD/PI is delegated with *Submit Progress Report* authority. Otherwise, only the SO can submit the PRAM to Agency.

The following sections cover the steps for initiating and submitting Public Access PRAM.

5.10.1 Initiate Public Access PRAM

The PD/PI (Contact PI) or PD/PI Delegate can initiate Public Access PRAM by following the steps below:

1. Access the eRA *Commons Status Result – List of Applications/Grants* screen.
2. Select the **Public Access PRAM** link from the **Action** column of the appropriate grant.

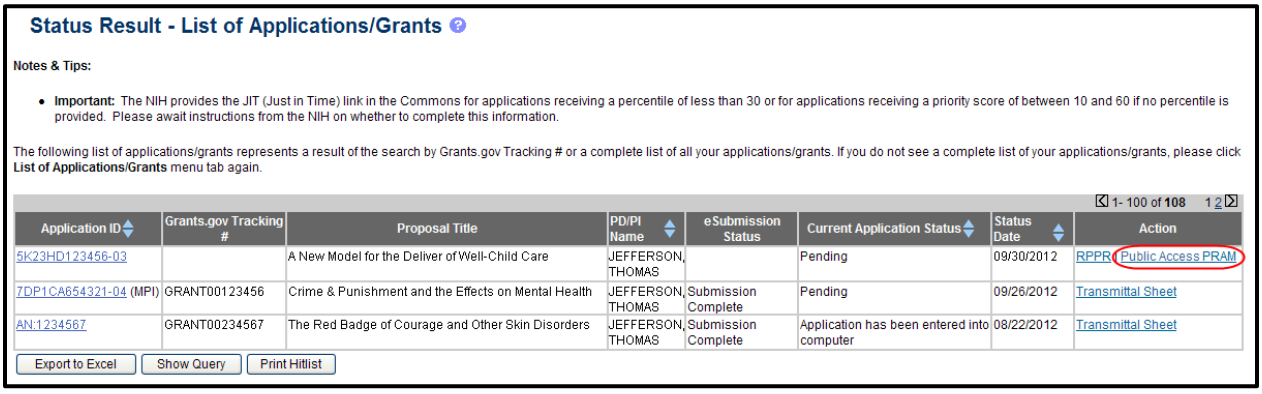


Figure 43: Public Access PRAM Link

The *Progress Report Additional Materials (PRAM)* screen displays. **Grant Information** including Grant Number, PD/PI Name, Project Title, Institution, Status, and Current Reviewer displays at the top of the screen. The **Public Access Compliance** section at the bottom contains

guidance for responding to the automated email requesting evidence of compliance with a field and buttons for uploading and maintaining attachments.

3. Use the **Add Attachment** button to browse and select the My NCBI PDF or another PDF document providing justification. Note that selecting the **Cancel** button closes the screen instead.
4. Select the **Route** button at the bottom of the screen.

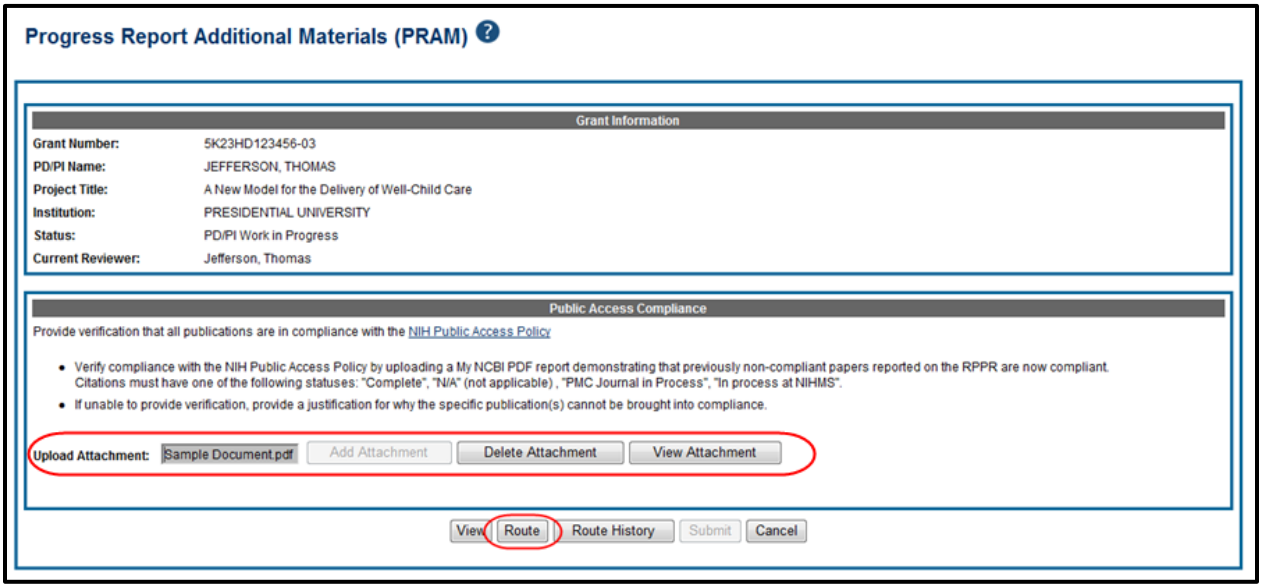


Figure 44: Routing the Public Access PRAM

NOTE: The options for **Delete Attachment** and **View Attachment** display once an attachment has been uploaded.

5. *Optional:* Select the **View Attachment** button to view the document. Select the **Delete Attachment** button to remove the document.

When the **Route** button is selected, the *Route PRAM to Next Reviewer* screen displays. A list of all available reviewers exists in the drop-down for **Next Reviewer**.

6. Select an SO from the **Next Reviewer** drop-down list.
7. Enter text into the **Comments** field as necessary. This is not a mandatory field.
8. Select the **Submit** button to continue.

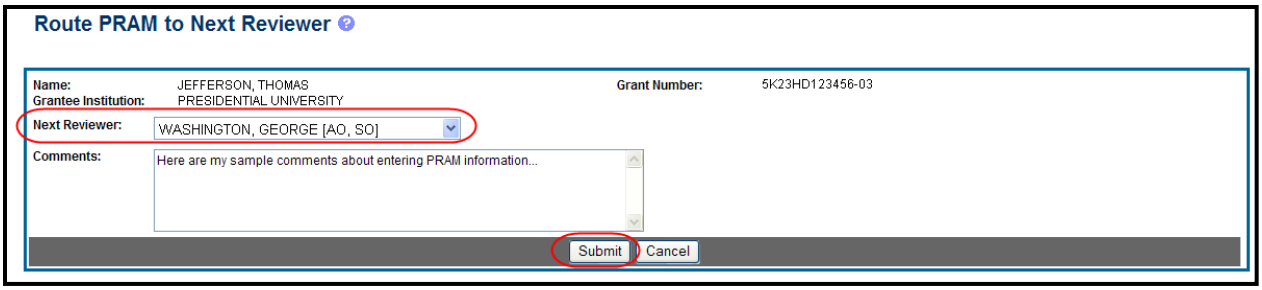


Figure 45: Route Public Access PRAM to Next Reviewer

The *Route PRAM to Next Reviewer* screen displays the PD/PI Assurance statement.

9. Read the assurance statement and select the **Submit** button to agree to the content and continue routing the PRAM to the next reviewer.

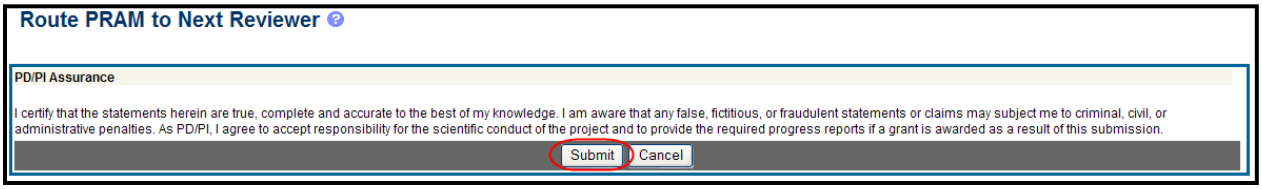


Figure 46: Public Access PRAM PD/PI Assurance Statement

The *Progress Report Additional Materials (PRAM)* screen displays with a message indicating that the PRAM was successfully routed to the selected reviewer. Additionally, the status is updated and shown as *Reviewer Work in Progress*. At this point, the PD/PI can only view the PRAM and may not edit it. To be able to allow the PD/PI to edit the PRAM, the SO needs to route the PRAM back to the PD/PI using steps similar to those above.

At the time of routing, an email is sent to the PD/PI and the selected SO (or other Next Reviewer) to notify them of the event.

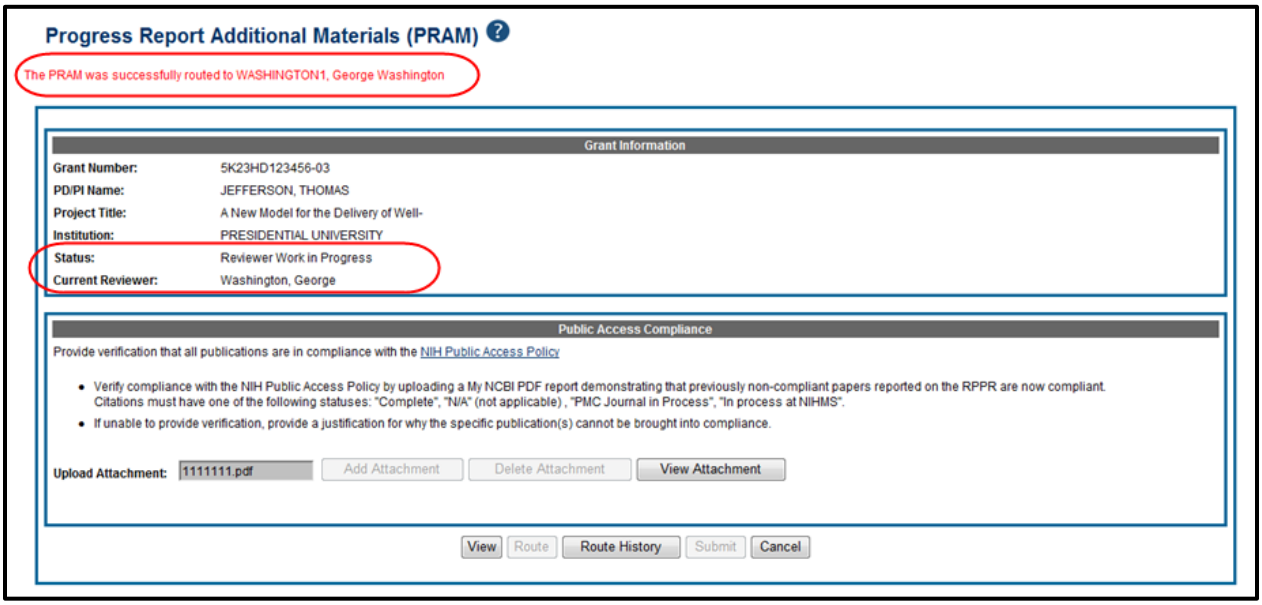


Figure 47: Successfully Routed Public Access PRAM

5.10.2 Submit Public Access PRAM

When the Public Access PRAM is in *Reviewer Work in Progress* status, the Signing Official (SO) can submit it to the Agency. PD/PIs may also submit the information if they have been delegated *Submit Progress Report* authority by the SO.

To submit the Public Access PRAM:

1. Access the **Status** screen on eRA Commons.
2. Enter the appropriate query parameters to locate the grant and select the **Search** button.

The *Status Result – General Search* screen displays with the matching information.

3. From the **Action** column, select the link for **PRAM**.

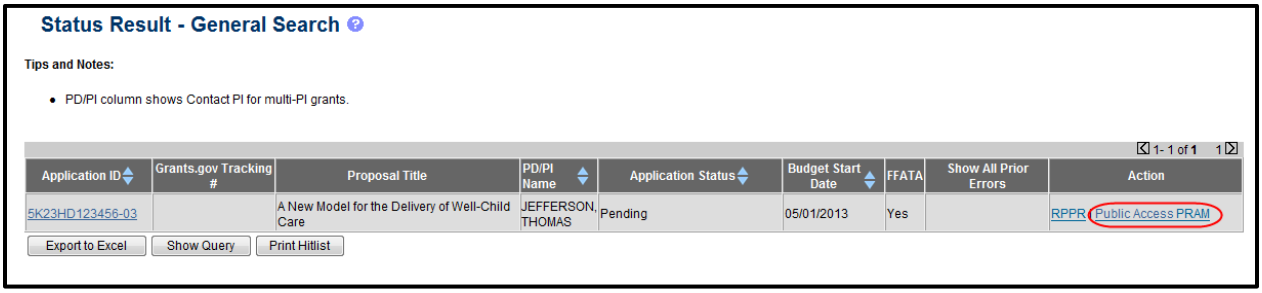


Figure 48: Public Access PRAM Link for SO

The *Progress Report Additional Materials (PRAM)* screen displays. The screen displays **Grant Information** on top and the PD/PI comments in the text box at the bottom of the screen. In addition to submitting the PRAM, from this screen, the SO also may **View** the PRAM as a PDF, **Route** it to another reviewer (or back to the PD/PI), and view the **Route History**. Select any of

the appropriate buttons to perform these actions. Follow the steps below to continue submitting the PRAM.

4. Select the **Submit** button.

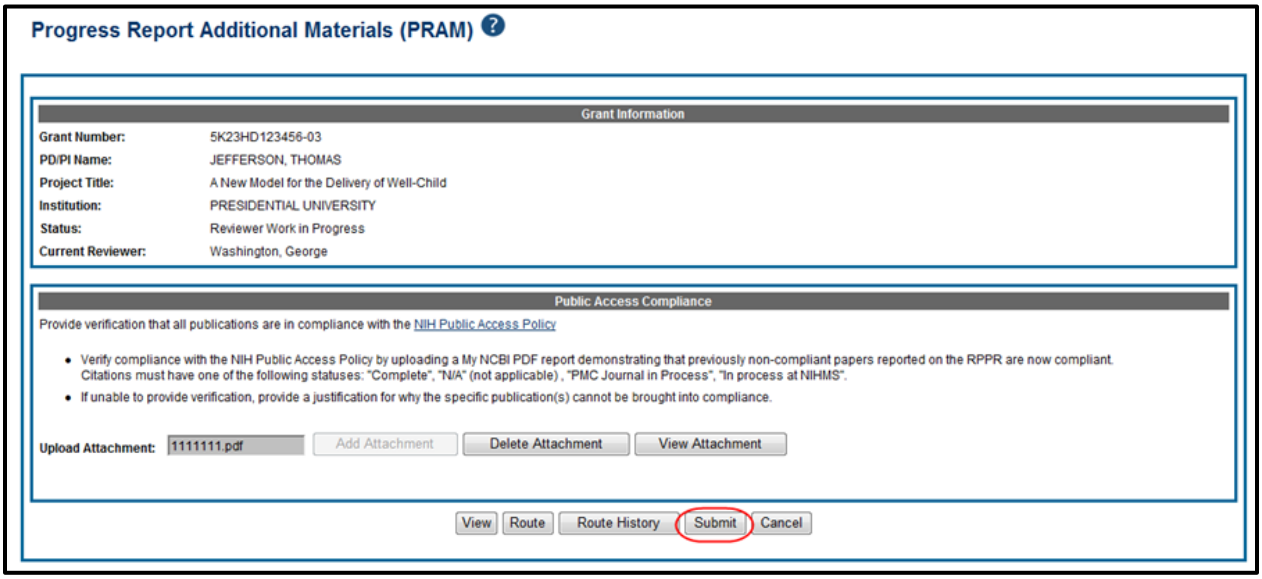


Figure 49: Submitting Public Access PRAM

The *Submit PRAM to Agency* screen displays. By continuing from this screen, the SO certifies that the submitting organization is in compliance with the terms and conditions specified in the Notice of Award and Grants Policy Statement. The SO also verifies that the information provided in the PRAM is valid and accurate.

5. Read certification agreement. Select the **I Agree** button to continue submitting the information. (Selecting the **Cancel** button closes the screen and returns the *Progress Report Additional Materials* screen without submitting the material.)

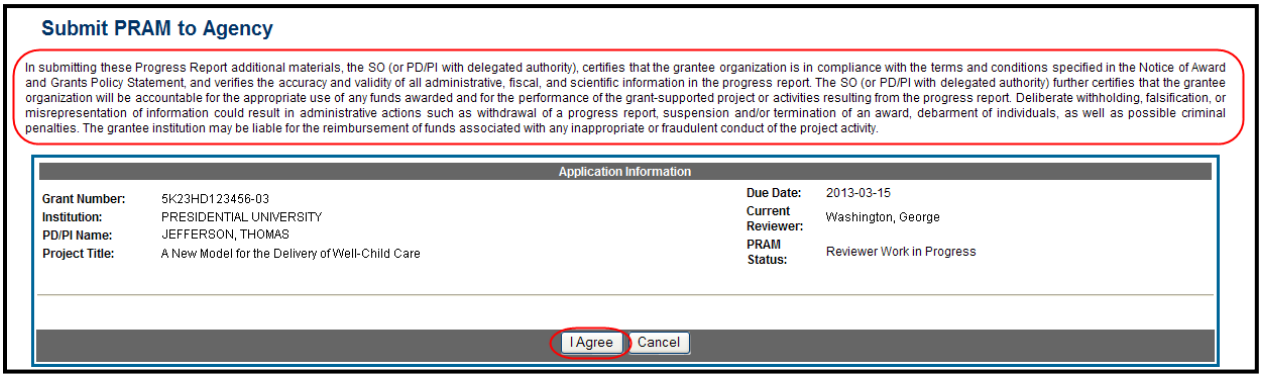


Figure 50: SO Certification of Public Access PRAM

The *Progress Report Additional Materials (PRAM)* screen displays with a message indicating that the PRAM was successfully submitted. The current reviewer is updated to the awarding

agency, the PRAM status is updated to *Submitted to Agency*, and the PRAM submission date is recorded. The routing history is updated to reflect the submission to Agency.

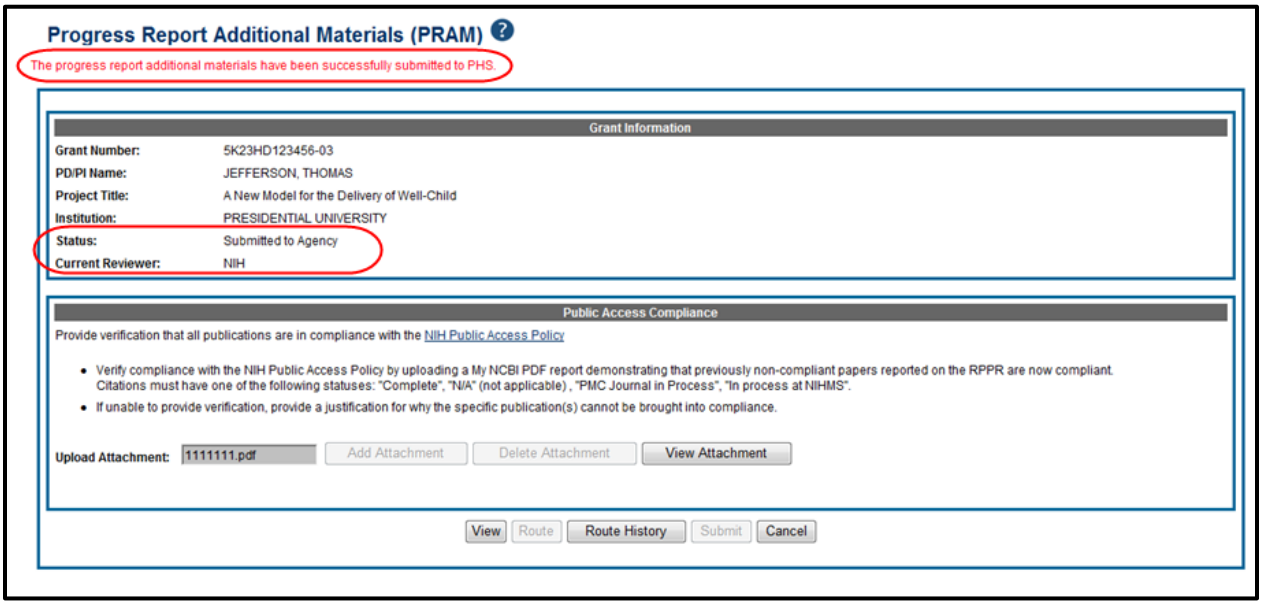


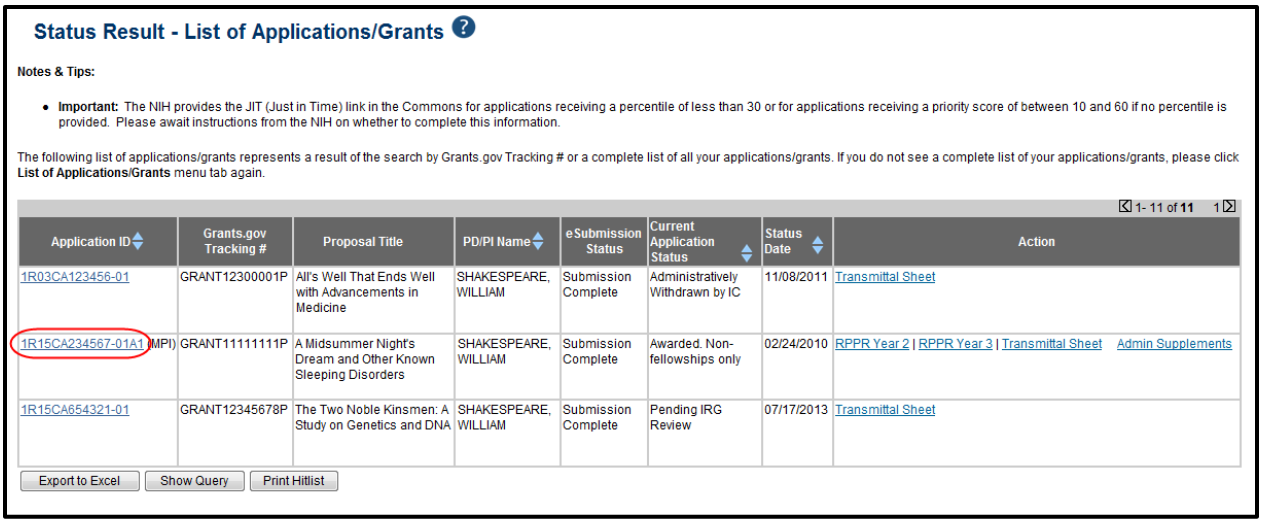
Figure 51: Public Access PRAM Submitted to Agency

When PRAM is submitted to Agency, an email notification is sent to the PD/PI (Contact PI) on the grant, the submitting SO, the SO assigned to the RPPR, and AO assigned to the RPPR and the **Public Access PRAM** link will no longer be available.

NOTE: To view the submitted PRAM, select the **View** button on the *Progress Report Additional Materials (PRAM)* screen. This option opens the PRAM PDF in a separate window. The Public Access PRAM will appear as the final page of the PDF document. See below for display of IC Requested PRAM.

5.10.3 View Public Access PRAM for Multi-Year Funded Awards

After submitting Public Access PRAM for multi-year funded awards, users with access to the grant information may view the PRAM via the *Status Information* screen. *Status Information* is accessed by selecting the **Application ID** hyperlink from the *Status Result – General Search* (SOs) and *Status Result – List of Applications/Grants* (PIs) screens.



Status Result - List of Applications/Grants

Notes & Tips:

- **Important:** The NIH provides the JIT (Just in Time) link in the Commons for applications receiving a percentile of less than 30 or for applications receiving a priority score of between 10 and 60 if no percentile is provided. Please await instructions from the NIH on whether to complete this information.

The following list of applications/grants represents a result of the search by Grants.gov Tracking # or a complete list of all your applications/grants. If you do not see a complete list of your applications/grants, please click **List of Applications/Grants** menu tab again.

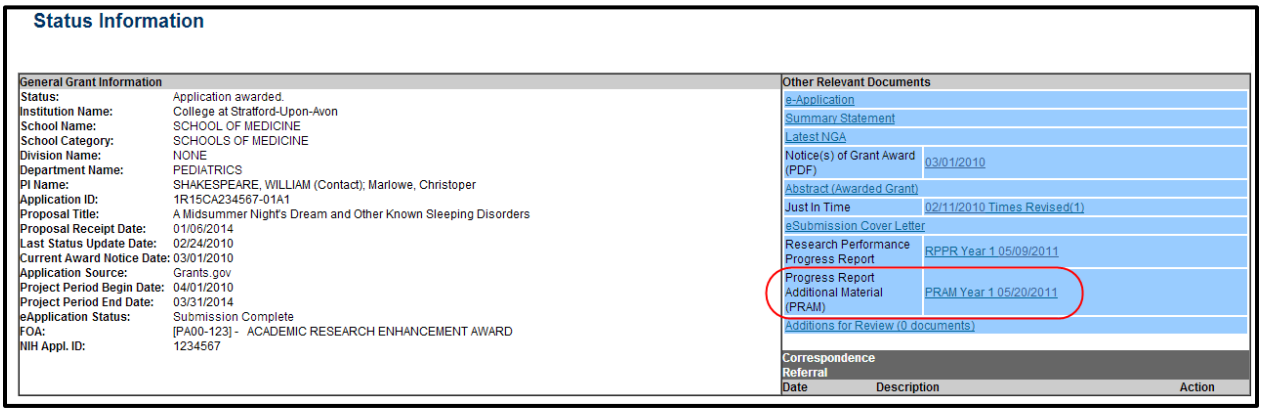
1- 11 of **11** 1

Application ID	Grants.gov Tracking #	Proposal Title	PD/PI Name	eSubmission Status	Current Application Status	Status Date	Action
1R03CA123456-01	GRANT12300001P	All's Well That Ends Well with Advancements in Medicine	SHAKESPEARE, WILLIAM	Submission Complete	Administratively Withdrawn by IC	11/08/2011	Transmittal Sheet
1R15CA234567-01A1 (MPI)	GRANT11111111P	A Midsummer Night's Dream and Other Known Sleeping Disorders	SHAKESPEARE, WILLIAM	Submission Complete	Awarded. Non-fellowships only	02/24/2010	RPPR Year 2 | RPPR Year 3 | Transmittal Sheet Admin Supplements
1R15CA654321-01	GRANT12345678P	The Two Noble Kinsmen: A Study on Genetics and DNA	SHAKESPEARE, WILLIAM	Submission Complete	Pending IRG Review	07/17/2013	Transmittal Sheet

Export to Excel | Show Query | Print Hitlist

Figure 52: Status Results Showing Hyperlink for Application ID

From the *Status Information* screen, select the hyperlink in the area marked **Progress Report Additional Material (PRAM)** in the **Other Relevant Documents** section. The PRAM links for multi-year funded awards display as **PRAM Year <X> <date submitted**>.



Status Information

General Grant Information

Status:	Application awarded.
Institution Name:	College at Stratford-Upon-Avon
School Name:	SCHOOL OF MEDICINE
School Category:	SCHOOLS OF MEDICINE
Division Name:	NONE
Department Name:	PEDIATRICS
PI Name:	SHAKESPEARE, WILLIAM (Contact); Marlowe, Christoper
Application ID:	1R15CA234567-01A1
Proposal Title:	A Midsummer Night's Dream and Other Known Sleeping Disorders
Proposal Receipt Date:	01/06/2014
Last Status Update Date:	02/24/2010
Current Award Notice Date:	03/01/2010
Application Source:	Grants.gov
Project Period Begin Date:	04/01/2010
Project Period End Date:	03/31/2014
eApplication Status:	Submission Complete
FOA:	[PA00-123] - ACADEMIC RESEARCH ENHANCEMENT AWARD
NIH Appl. ID:	1234567

Other Relevant Documents

e-Application	
Summary Statement	
Latest NGA	
Notice(s) of Grant Award (PDF)	03/01/2010
Abstract (Awarded Grant)	
Just In Time	02/11/2010 Times Revised(1)
eSubmission Cover Letter	
Research Performance Progress Report	RPPR Year 1 05/09/2011
Progress Report Additional Material (PRAM)	PRAM Year 1 05/20/2011
Additions for Review (0 documents)	

Correspondence

Referral

Date Description Action

Figure 53: MYF Award PRAM Link in Status Information

5.11 IC (Agency) Requested Progress Report Additional Materials (PRAM)

The IC (Agency) Requested Progress Report Additional Materials (PRAM) feature provides a means for the grantee to enter, review, route, and submit information in response to specific request(s) by the Grants Management Specialist at the IC (or AHRQ, if applicable) for additional information following the submission of an RPPR.

As with the RPPR, a PD/PI (or Contact PI in the case of multiple PIs) can enter the PRAM, but can only submit it if the PD/PI is delegated with *Submit Progress Report* authority. Otherwise, only the SO can submit the PRAM to Agency.

The following sections cover the steps for initiating and submitting IC Requested PRAM.

NOTE: IC requested PRAM is not available for multi-year funded awards at this time.

5.11.1 Initiate IC Requested PRAM

The PD/PI (Contact PI) or PD/PI Delegate can initiate IC Requested PRAM by following the steps below:

1. Access the eRA *Commons Status Result – List of Applications/Grants* screen.
2. Select the **IC Requested PRAM** link from the **Action** column of the appropriate grant.

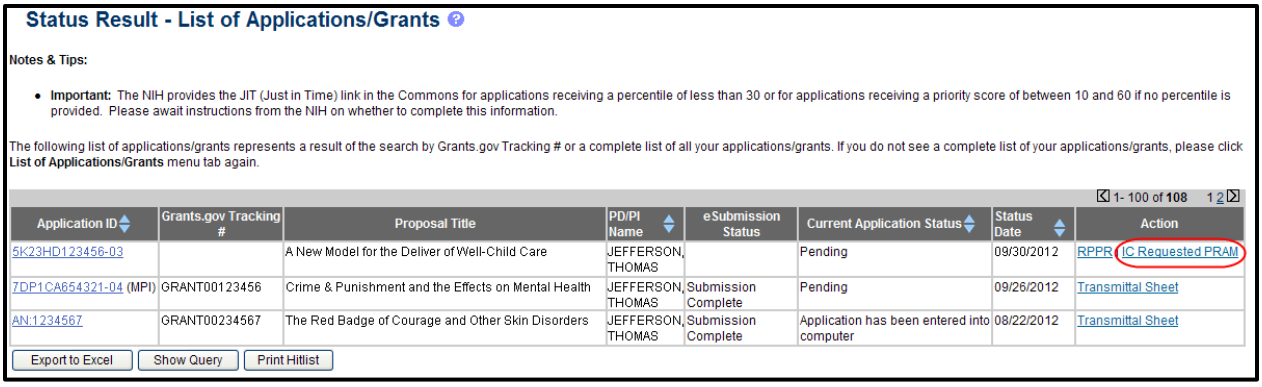


Figure 54: IC Requested PRAM Link

The *Progress Report Additional Materials (PRAM)* screen displays. **Grant Information**, including Grant Number, PD/PI Name, Project Title, Institution, Status, and Current Reviewer, displays at the top of the screen. The **Additional Materials Requested by IC** section at the bottom provides a means for adding the requested materials. Up to 100 attachments can be submitted, but all attachments must be in the form of PDF files.

3. Select the **Add Attachment** button in the **Additional Materials Requested by IC** section of the screen.

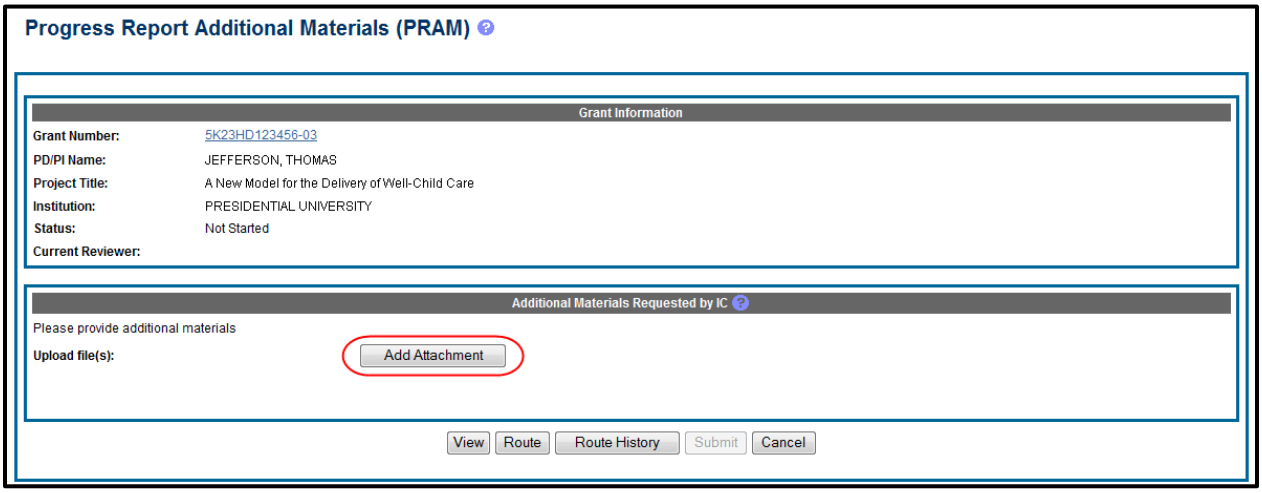


Figure 55: Add Attachment Button for IC Requested PRAM

4. Use the *Upload Attachment* pop-up **Browse** and **Upload** buttons to search for and attach the appropriate file. Repeat for all necessary attachments.

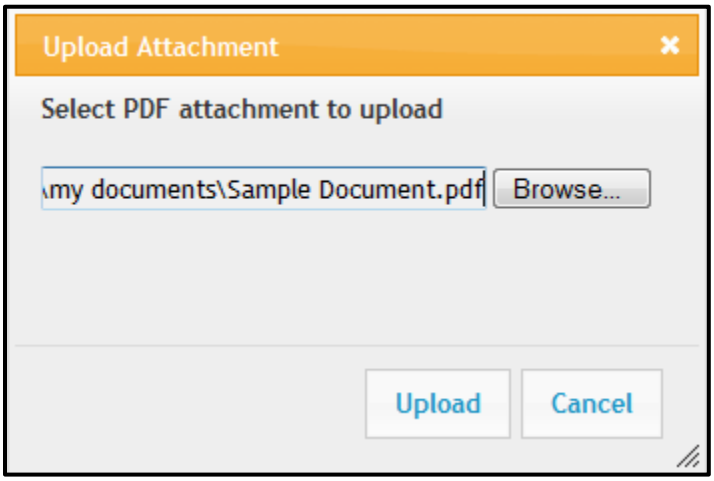


Figure 56: Upload Attachment Pop-up

The **Additional Materials Requested by IC** section updates to show a table of all attachments. The table displays the **Document Name** and **Action** links of **View** and **Delete** for each attachment.

5. *Optional*: Select the document's **View** link in the **Action** column to view the attachment.
6. *Optional*: Select the document's **Delete** link in the **Action** column to remove the attachment.

NOTE: The options for **View** and **Route History** may be selected at this time. Selecting the option for **Cancel** closes the screen without saving or routing the PRAM information.

7. Select the **Route** button to send the PRAM for review.

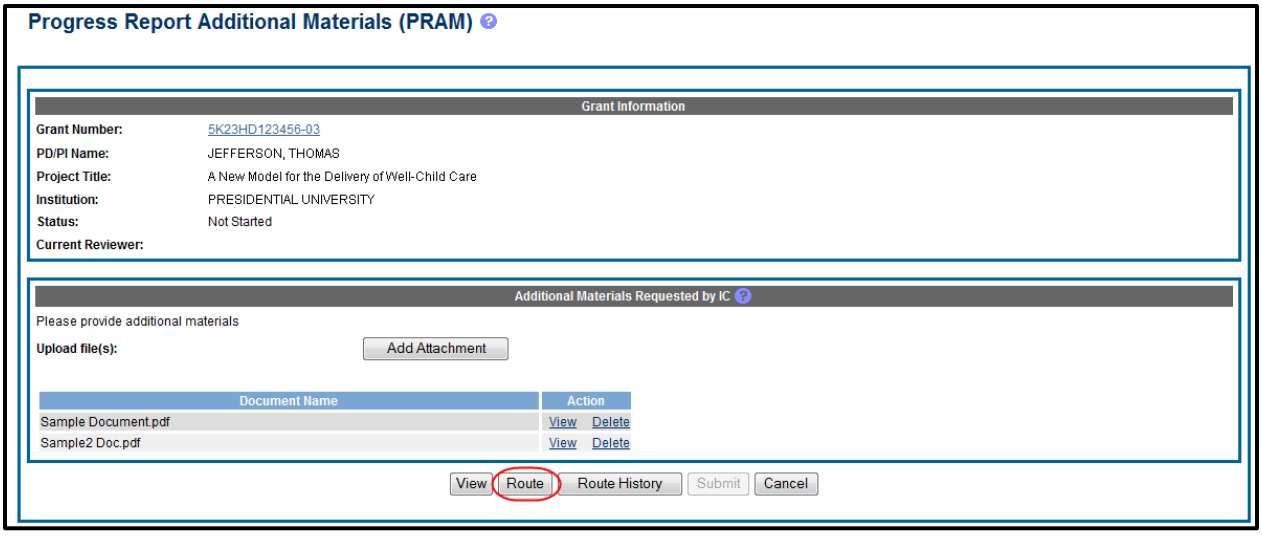


Figure 57: Routing the IC Requested PRAM

When the **Route** button is selected, the *Route PRAM to Next Reviewer* screen displays. A list of all available reviewers exists in the drop-down for **Next Reviewer**.

8. Select a name from the **Next Reviewer** drop-down list.
9. Enter text into the **Comments** field as necessary. This is not a mandatory field.
10. Select the **Submit** button to continue.

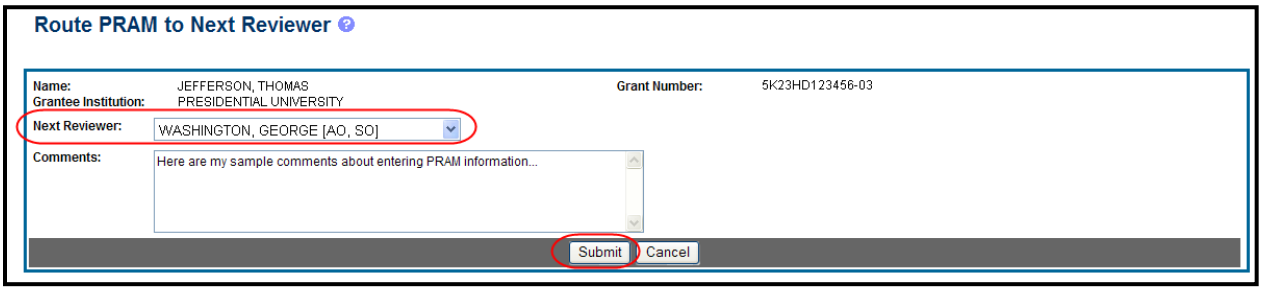


Figure 58: Route IC Requested PRAM to Next Reviewer

The *Route PRAM to Next Reviewer* screen displays the PD/PI Assurance statement.

11. Read the assurance statement and select the **Submit** button to agree to the content and continue routing the PRAM to the next reviewer.

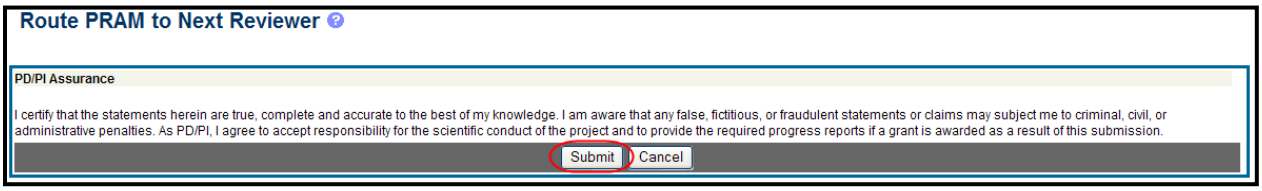


Figure 59: IC Requested PRAM PD/PI Assurance Statement

The *Progress Report Additional Materials (PRAM)* screen displays with a message indicating that the PRAM was successfully routed to the selected reviewer. Additionally, the status is updated and shown as *Reviewer Work in Progress*. At this point, the PD/PI can only view the PRAM, the attachments, and the Route History; the PD/PI may not edit the PRAM. To be able to allow the PD/PI to edit the PRAM, the SO needs to route the PRAM back to the PD/PI using routing steps similar to those above.

At the time of routing, an email is sent to the PD/PI and the selected SO (or other Next Reviewer) to notify them of the event.

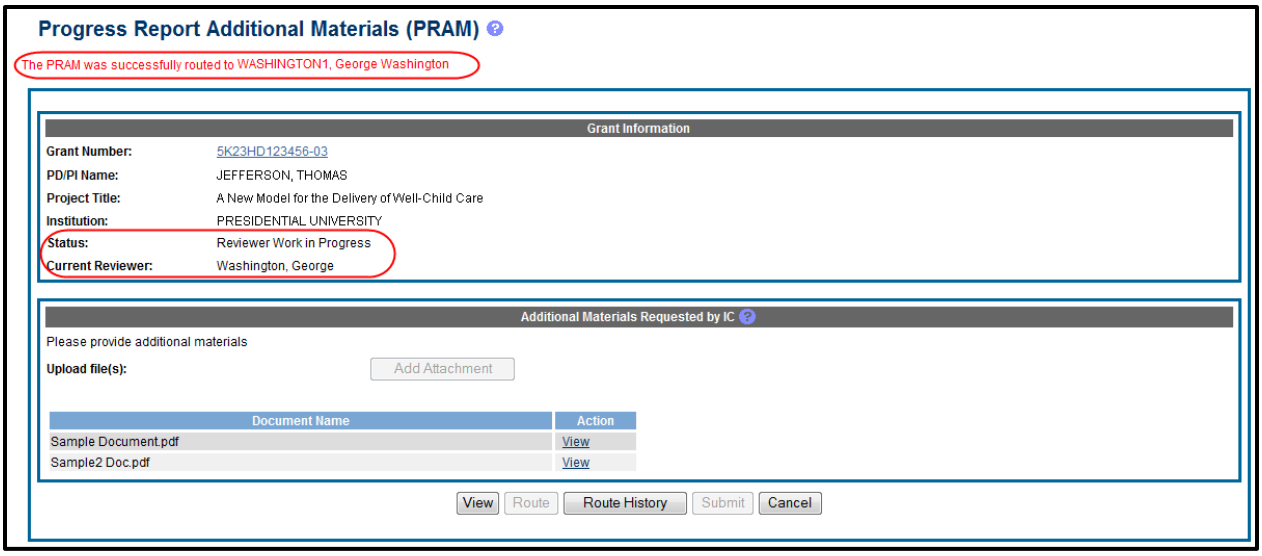


Figure 60: Successfully Routed IC Requested PRAM

5.11.2 Submit IC Requested PRAM

When the IC Requested Progress Report Additional Materials (PRAM) is in *Reviewer Work in Progress* status, the Signing Official (SO) can submit it to the Agency. PD/PIs may also submit the information if they have been delegated *Submit Progress Report* authority by the SO.

To submit the PRAM:

1. Access the **Status** screen on eRA Commons.
2. Enter the appropriate query parameters to locate the grant and select the **Search** button.

The *Status Result – General Search* screen displays with the matching information.

3. From the **Action** column, select the link for **IC Requested PRAM**.

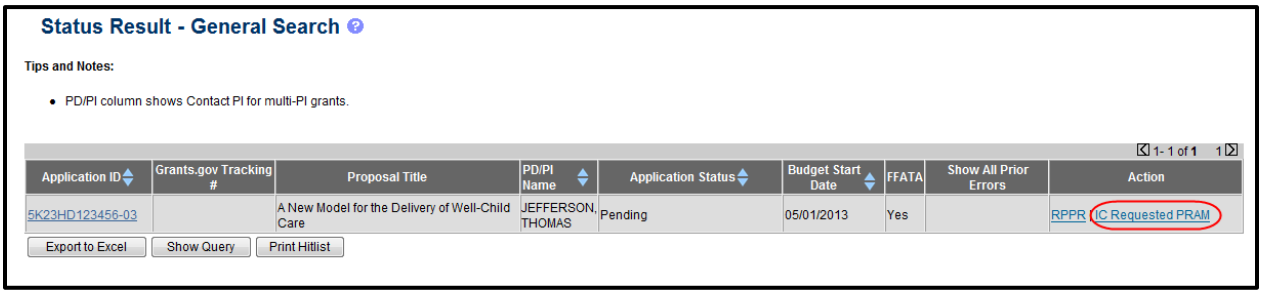


Figure 61: IC Requested PRAM Link for SO

The *Progress Report Additional Materials (PRAM)* screen displays. The screen displays **Grant Information** on top and the files attached by the PD/PI in the **Additional Materials Requested by IC** portion at the bottom. The attached files may be viewed or removed and additional PDF files may be added if necessary.

4. *Optional*: Select the document's **View** link in the **Action** column to view the attachment.

5. *Optional*: Select the document's **Delete** link in the **Action** column to remove the attachment.
6. *Optional*: Select the **Add Attachment** button to attach additional files. Up to 100 PDF files may be attached.

Before submitting, the SO also may **View** the PRAM as a PDF, **Route** it to another reviewer (or back to the PD/PI), and view the **Route History**. Select any of the appropriate buttons to perform these actions. Follow the steps below to continue submitting the PRAM.

7. Select the **Submit** button.

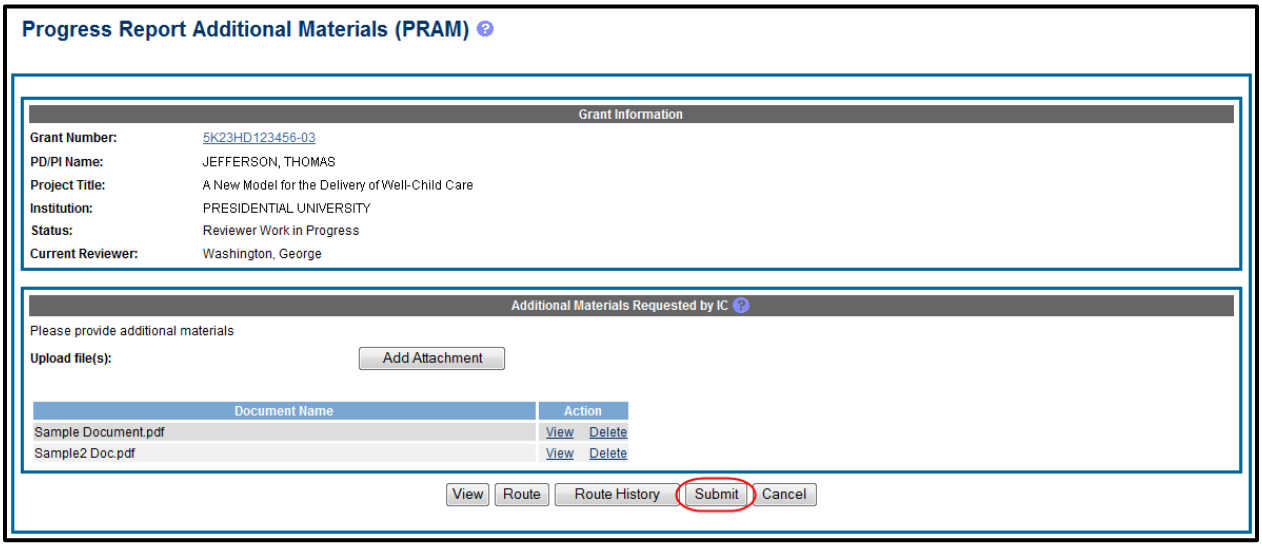


Figure 62: Submitting IC Requested PRAM

The *Submit PRAM to Agency* screen displays. By continuing from this screen, the SO certifies that the submitting organization is in compliance with the terms and conditions specified in the Notice of Award and Grants Policy Statement. The SO also verifies that the information provided in the PRAM is valid and accurate.

8. Read certification agreement. Select the **I Agree** button to continue submitting the information. (Selecting the **Cancel** button closes the screen and returns the *Progress Report Additional Materials* screen without submitting the material.)

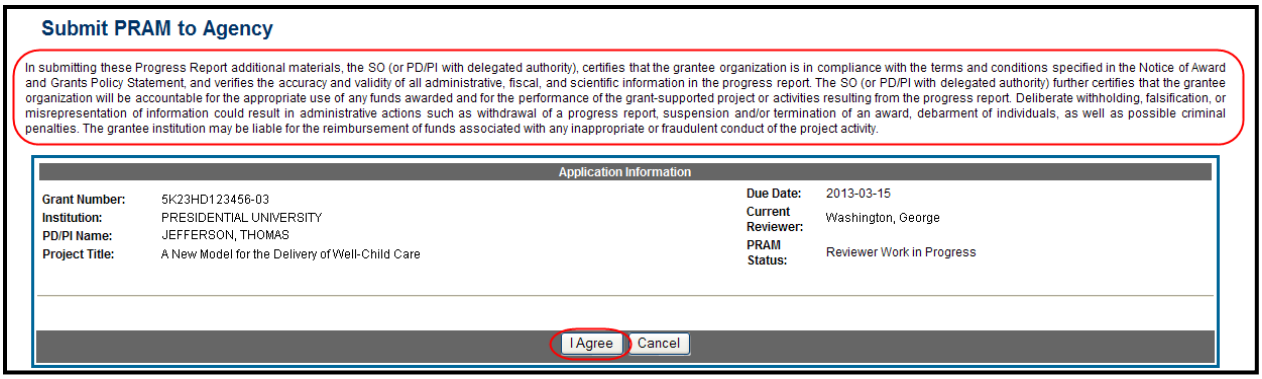


Figure 63: SO Certification of PRAM

The *Progress Report Additional Materials (PRAM)* screen displays with a message indicating that the PRAM was successfully submitted. The current reviewer is updated to NIH, the PRAM status is updated to *Submitted to Agency*, and the PRAM submission date is recorded. The routing history is updated to reflect the submission to Agency.

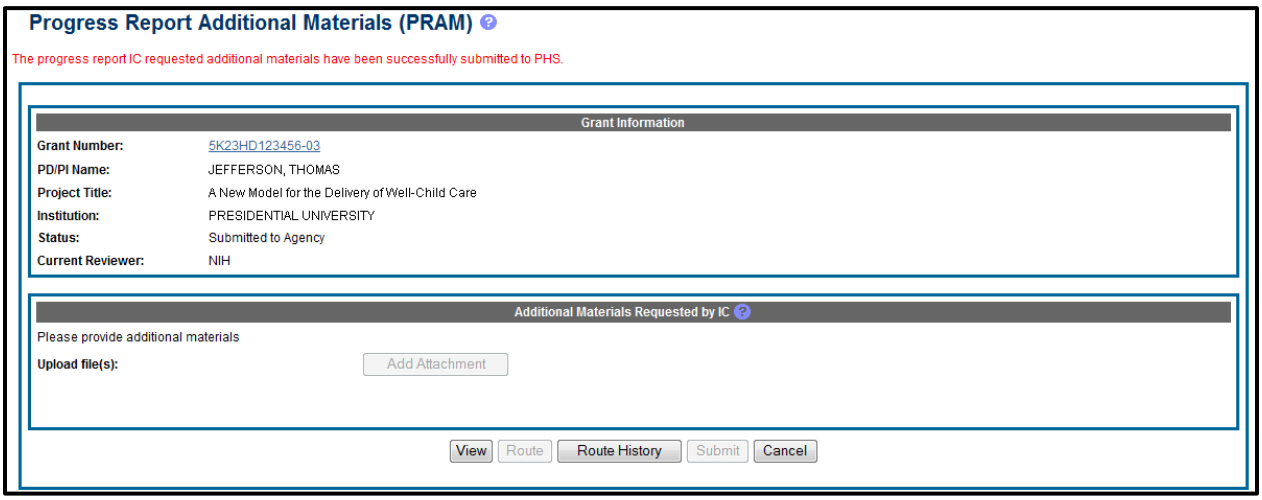


Figure 64: IC Requested PRAM Submitted to Agency

When PRAM is submitted to Agency, an email notification is sent to the PD/PI (Contact PI) on the grant, the submitting SO, the SO assigned to the RPPR, and AO assigned to the RPPR.

Once the IC Requested PRAM is submitted, the **View** button remains on the PRAM screen to provide a preview of the latest PRAM submission; however, the ability to view or delete the individual attachments is removed. The ability to upload and submit additional attachments remains until the grant is awarded. Follow the steps provided in the *Initiate IC Requested PRAM* section to add additional attachments (starting with Step 3).

NOTE: If multiple PRAM submissions were completed, selecting the **View** button only provides a preview of the latest PRAM submission. To view all submissions as one document, access the *Status Information* screen for the grant and select the PRAM link. For more information, refer to the *View IC Requested PRAM from Status Information* section of this document.

5.11.3 View IC Requested PRAM from Status Information

After submitting IC Requested PRAM, Commons users with access to the grant information may view the PRAM via the *Status Information* screen. The *Status Information* is accessed by selecting the **Grant Number** hyperlink from the *Progress Report Additional Materials (PRAM)* screen or by selecting the **Application ID** hyperlink from *Status Result – General Search* (SOs) and *Status Result – List of Applications/Grants* (PIs) screens.

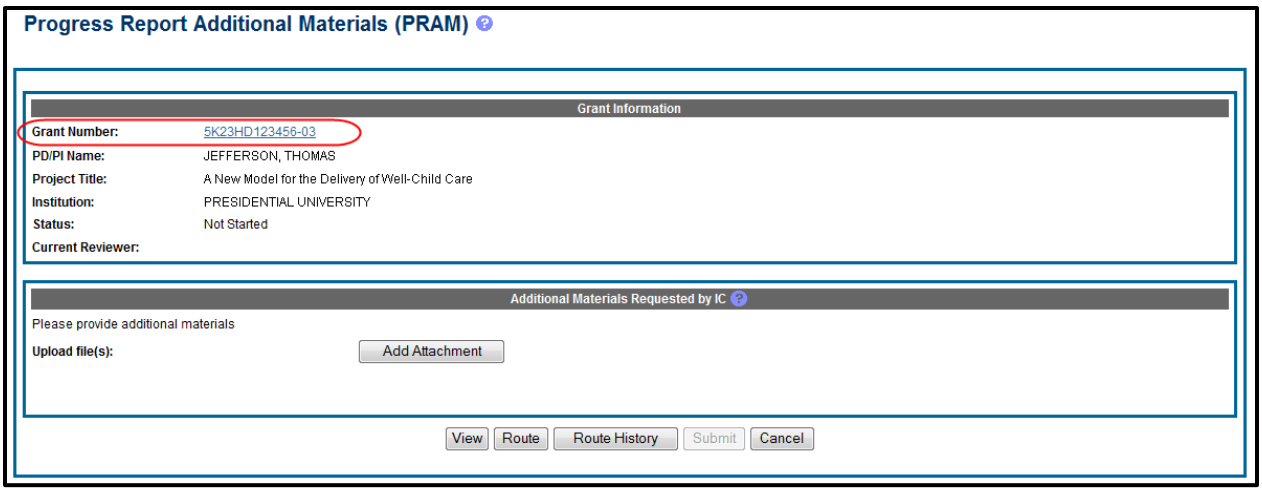


Figure 65: Grant Number Hyperlink on PRAM Screen

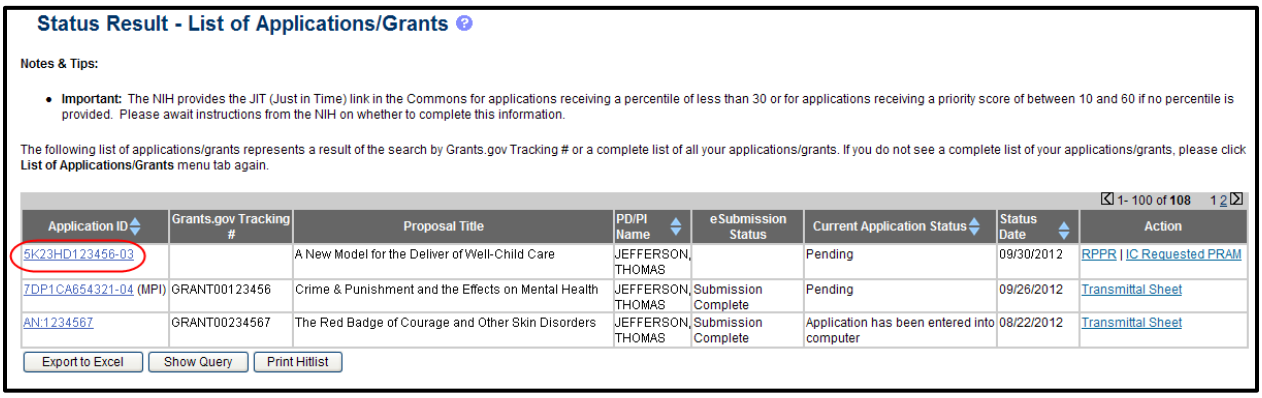


Figure 66: Application ID Hyperlink on Status Result for PIs

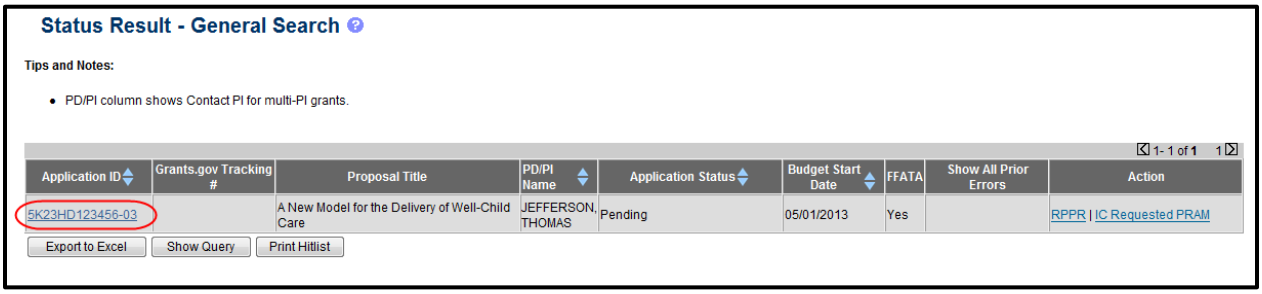


Figure 67: Application ID Hyperlink on Status Result for SOs

From the *Status Information* screen, select the hyperlink in the area marked **Progress Report Additional Material (PRAM)** in the **Other Relevant Documents** section.

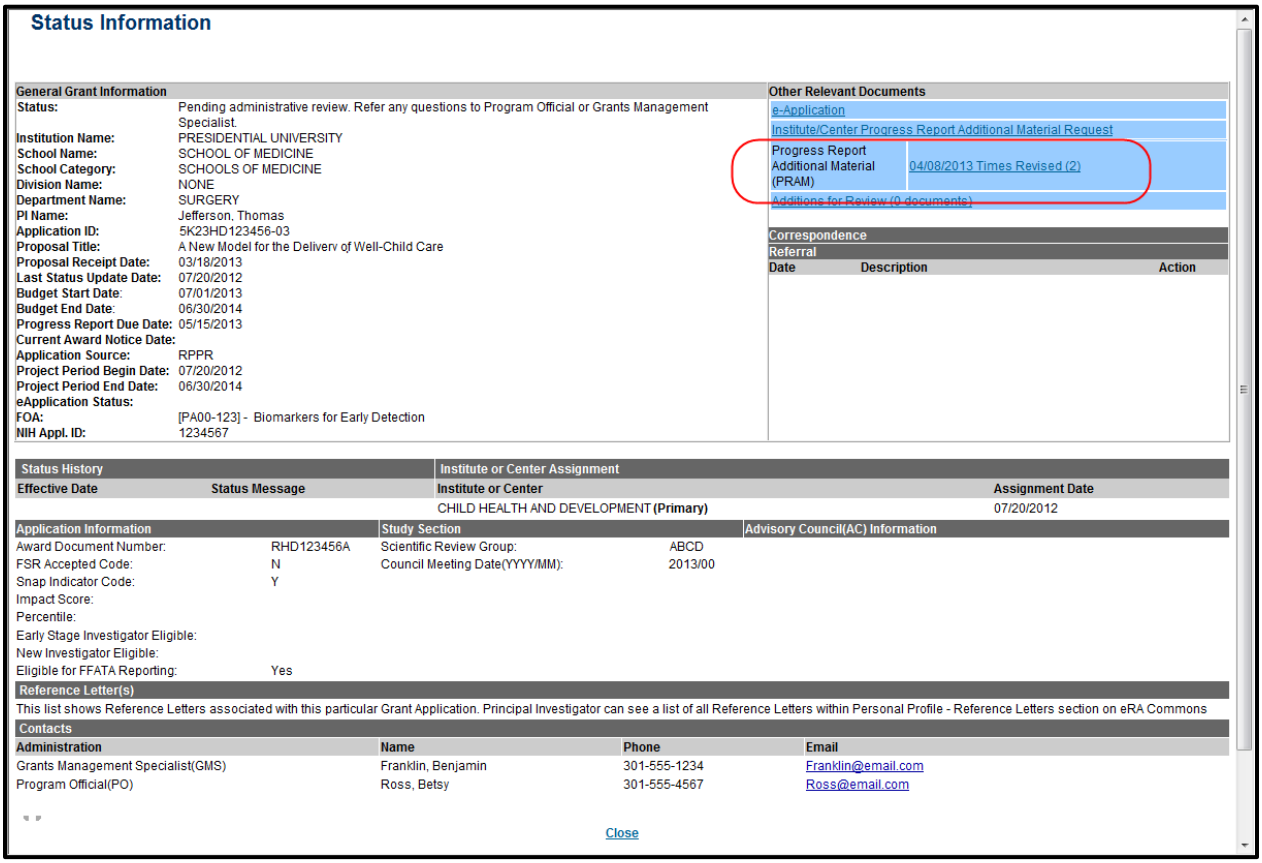


Figure 68: Status Information with PRAM Link

The Progress Report Additional Materials file opens as a PDF document. The file is formatted to provide an information header section for each PRAM submission followed by the attached documents provided during that submission. If multiple submissions of IC Requested PRAM were completed, the additional materials are separated in the document with the most recent submission displayed first followed by earlier submissions in reverse chronological order. Information in the document can be navigated using the provided bookmarks on the left.

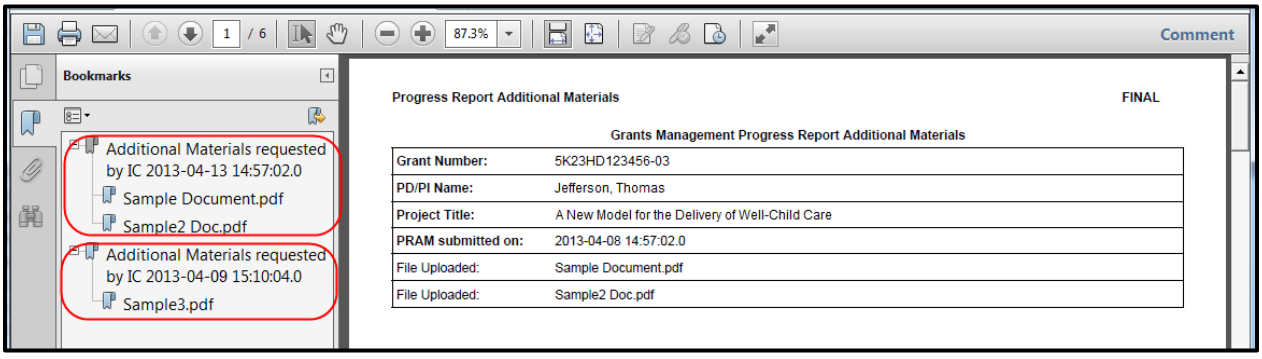


Figure 69: PDF of Multiple Submitted PRAM

6 Instructions for RPPR Sections A–H

The instructions in chapter 6 apply to the following awards: D71, DP1, DP5, G08, G11, G13, P40, R00, R01, R03, R18, R21, R33, R34, R36, R37, R56, RC1, RC2, RL1, S21, S22, SC1, SC2, SC3, U1B, UC2, UH1, UH2, and UH3; and also to the following multi-year funded awards, including: C06, DP2, DP3, DP4, R15, R55, RC3, RC4, RF1, UA5, UC4, UC6, UF1. Many of these instructions apply to other awards but there may be exceptions (items that are not applicable, replace, or are in addition) for awards not listed above. Refer to the table in chapter 7 *Supplemental Instruction for Specific Grant Award Types* and follow the appropriate instruction for the applicable activity code of other awards. Activity codes listed in 7.6 Multi-Project Awards and Single-Project Awards with Complicated Structure that are issued under the Streamlined Non-competing Award Process (SNAP) will complete the RPPR as described in this section. The electronic RPPR display is dynamic and shows the appropriate questions and instructions based on the activity code and SNAP status of the award.

Agency-specific reporting requirements and instructions are denoted by the DHHS logo displayed to the left of the requirement or instruction, as illustrated here.

Not Applicable next to a particular item indicates that item does not apply to the particular kind of award, and the item should be ignored.

References to *competing application instructions* means either the SF424 (R&R) Application Guides (http://grants.nih.gov/grants/funding/424/index.htm) or the PHS 398 Grant Application (http://grants.nih.gov/grants/funding/phs398/phs398.html).

The RPPR may not be used for prior approval requests, with the exception of requesting prior approval for a reduction in the level of effort of the PD/PI or other senior/key personnel named in the Notice of Award under D.2 of the RPPR. All other prior approval requests must be submitted directly to the Grants Management Officer of the awarding component in accord with the Grants Policy Statement, 8.1.2.

6.1 Section A – Cover Page

The RPPR section A. Cover Page includes information about the award, PD/PI, organization, and project/reporting/budget periods. Much of this information is pre-populated from data in eRA systems, but certain fields are editable.

The addresses, emails and phone numbers are pre-populated from the Commons Profile. To update contact information as displayed, go to the Commons Profile and save the changes there.

To select a Signing Official and Administrative Official, choose a name from the associated drop-down box. The SO and AO may be the same individual. The SO need not be the SO that submits the RPPR.

If there is a change to the Contact PD/PI (Multiple-PD/PI awards only), select the **Yes** radio button and enter the Commons ID of the new Contact PD/PI in the associated field. The change in Contact PD/PI does not take effect until the agency accepts the report and issues an NoA. The Contact PD/PI must have a PD/PI role in the eRA Commons and must be associated with the

grantee institution. The RPPR is not an appropriate vehicle for a prior approval request to change, add, or delete PD/PIs.

The **Recipient ID** field allows the grantee to record an internal tracking number or identifier for its own use. It is not a mandatory field and the awarding agency will disregard the information.

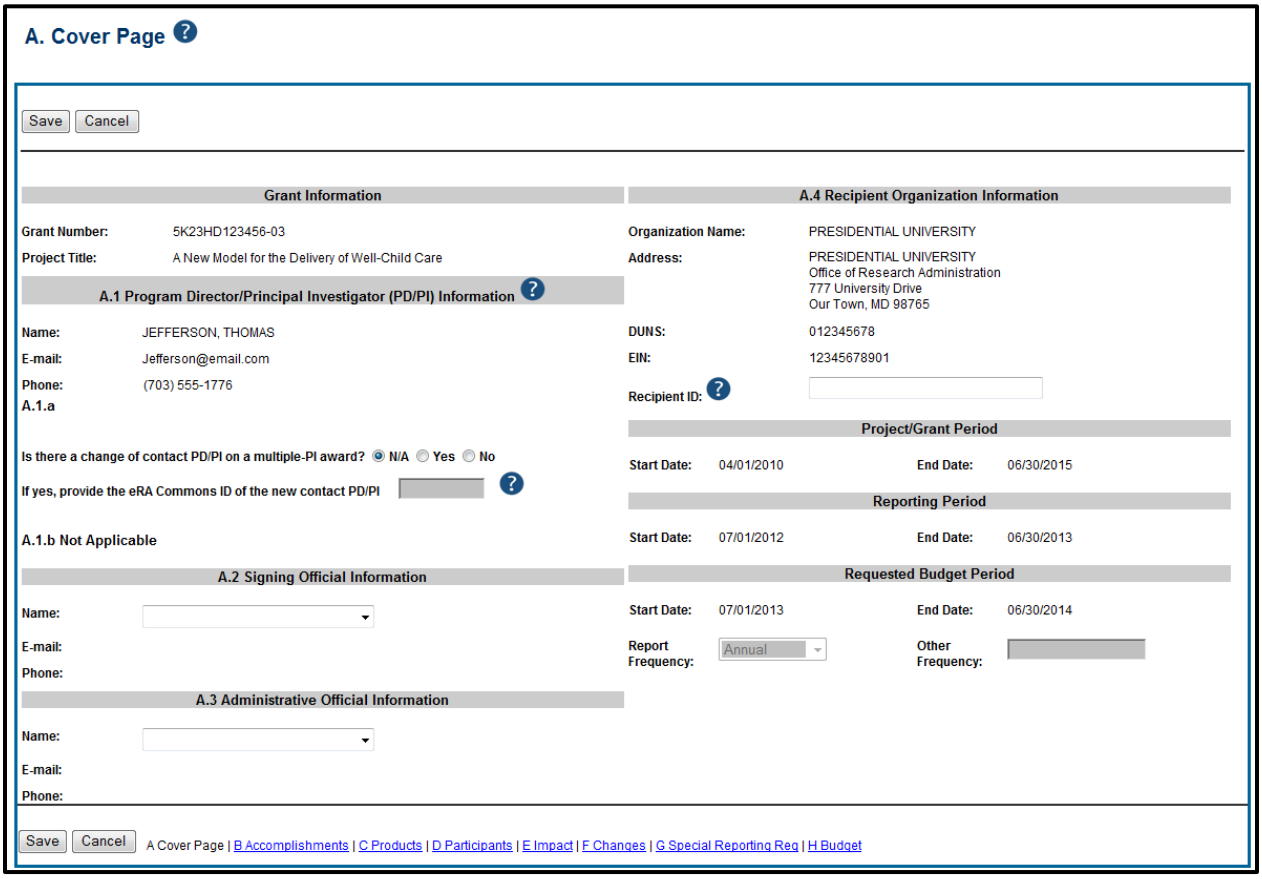


Figure 70: RPPR Section A. Cover Page

6.2 Section B – Accomplishments

The RPPR section B. Accomplishments allows the agency to assess whether satisfactory progress has been made during the reporting period.

PD/PIs are reminded that the grantee is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. See agency-specific instructions for submission of these requests.

B.1 What are the major goals of the project?

List the major goals of the project as stated in the approved application or as approved by the agency. If the application lists milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion. Generally, the goals will not change from one reporting period to the next. However, if the awarding agency approved changes to the goals during the reporting period, list the revised goals

and objectives. Also explain any significant changes in approach or methods from the agency approved application or plan.

Goals are equivalent to *specific aims*. Significant changes in objectives and scope require prior approval of the agency (e.g., NIH Grants Policy Statement, 8.1.2).

The specific aims must be provided in the initial RPPR (i.e., first non-competing type 5 submission). In subsequent RPPRs this section will pre-populate with the aims/goals previously entered, and may be amended by answering **Yes** to question B.1.a.

B.1.a Have the major goals changed since the initial competing award or previous report?

Select **Yes** if the major goals/specific aims have changed since the initial competing award or previous report, and provide a revised description of major goals/specific aims. Remember that written prior approval from the awarding agency grants official is required for significant changes in the project or its direction. The RPPR is not an appropriate vehicle to request such a change.

The first year that an RPPR is submitted any revised goals should be entered into the text box for B.1. In subsequent years, if the user selects **Yes** the text box under B.1.a for entering revised major goals will be provided.

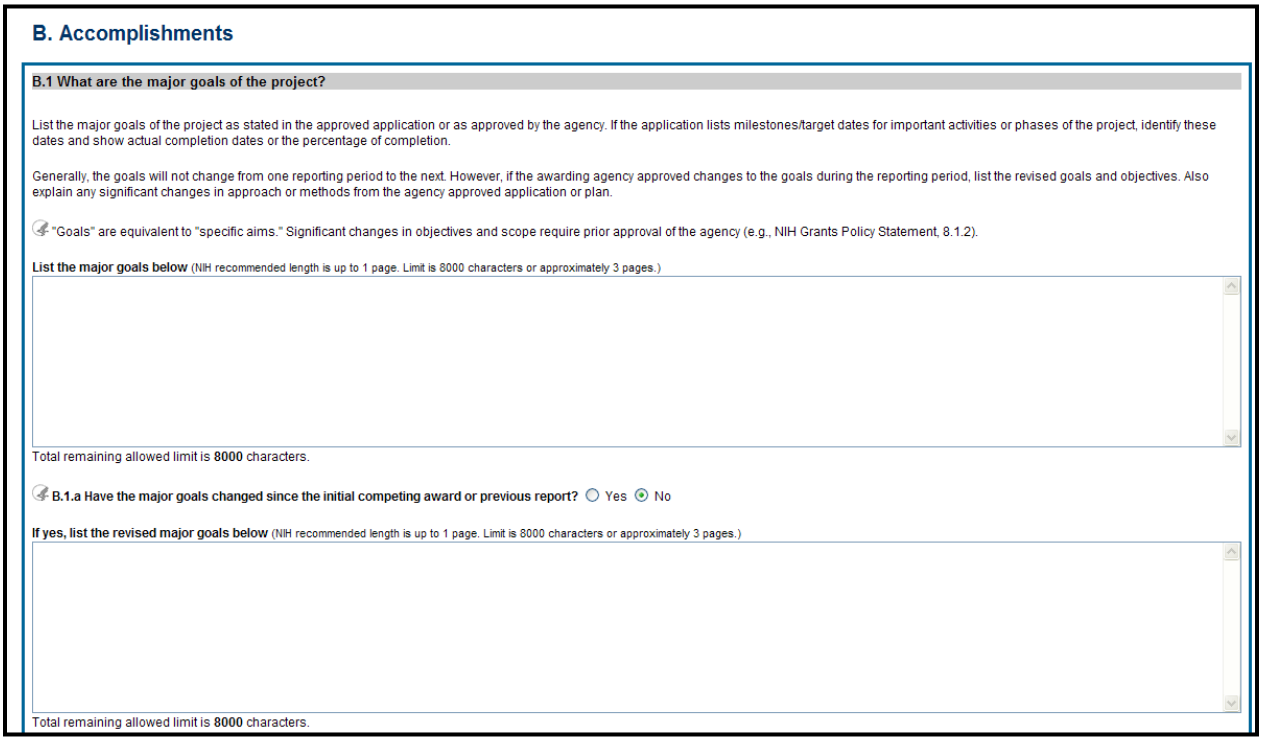


Figure 71: RPPR Section B. Accomplishments – Question B1

B.2 What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results, including major findings, developments, or conclusions (both positive and negative); and 4) key outcomes or other achievements. Include a discussion of stated goals not met. As the project progresses, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Goals are equivalent to *specific aims*. In the response, emphasize the significance of the findings to the scientific field. For most NIH awards the response should not exceed 2 pages.

B.3 Competitive Revisions/Administrative Supplements.

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

If yes, identify the Revision(s)/Supplements(s) by grant number (e.g., 3R01CA098765-01S1) or title and describe the specific aims and accomplishments for each Revision/Supplement funded during this reporting period. Include any supplements to promote diversity or re-entry, or other similar supplements to support addition of an individual or a discrete project.

The NoA will indicate any reporting requirements. Be advised that the NoA incorporates requirements of the FOA that may also include reporting requirements.

Select the **Add/New** button to add the data to the table.

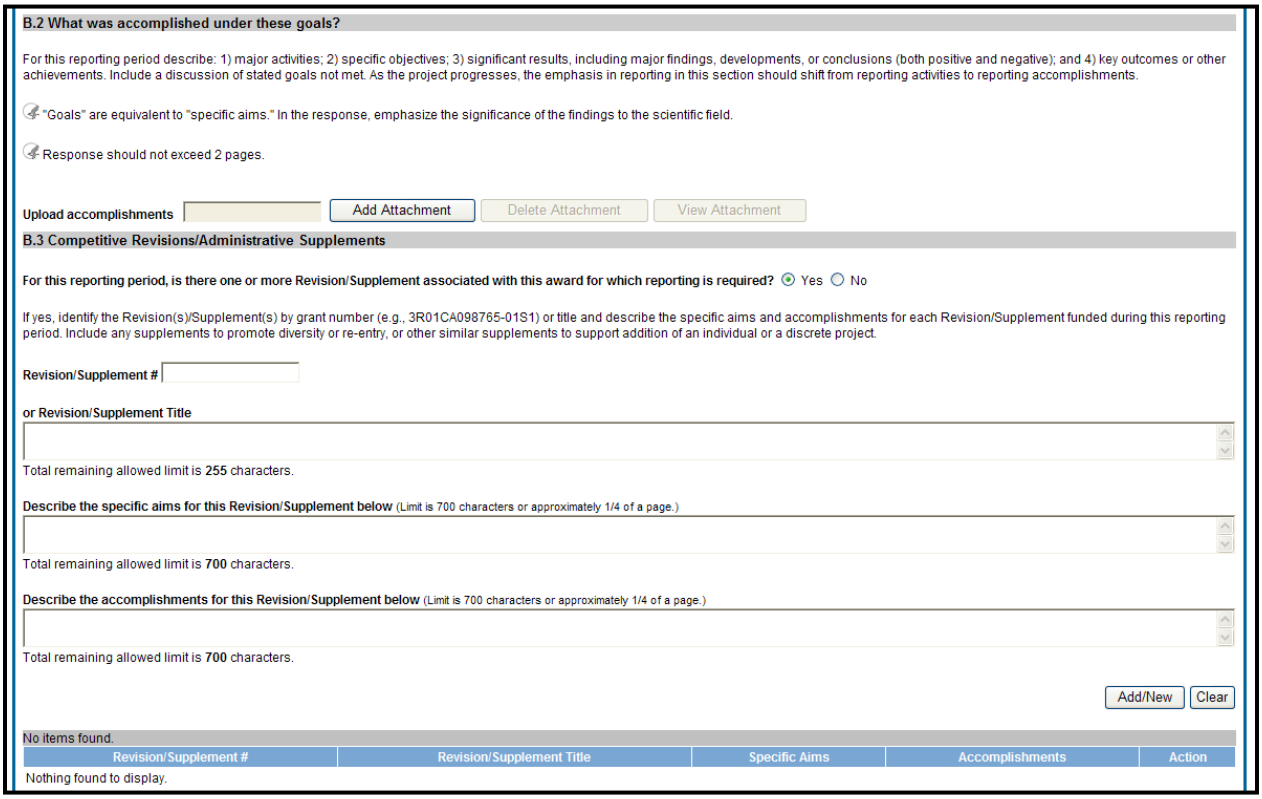


Figure 72: RPPR Section B. Accomplishments – Questions B2 & B3

B.4 What opportunities for training and professional development has the project provided?

If the research is not intended to provide training and professional development opportunities or there is nothing significant to report during the reporting period, select **Nothing to Report**.

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. *Training* activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. *Professional development* activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

For all projects reporting graduate students and/or postdoctoral participants in Section D., describe whether your institution has established Individual Development Plans (IDPs) for those participants. Do not include the actual IDP, instead include information to describe how IDPs are used, if they are used, to help manage the training for those individuals. This information is not requested for AHRQ grantees.

For T, F, K, R25, R13, D43 and other awards or award components designed to provide training and professional development opportunities, a response is required. Do not reiterate what is reported under Accomplishments. Limit the response to this reporting period.

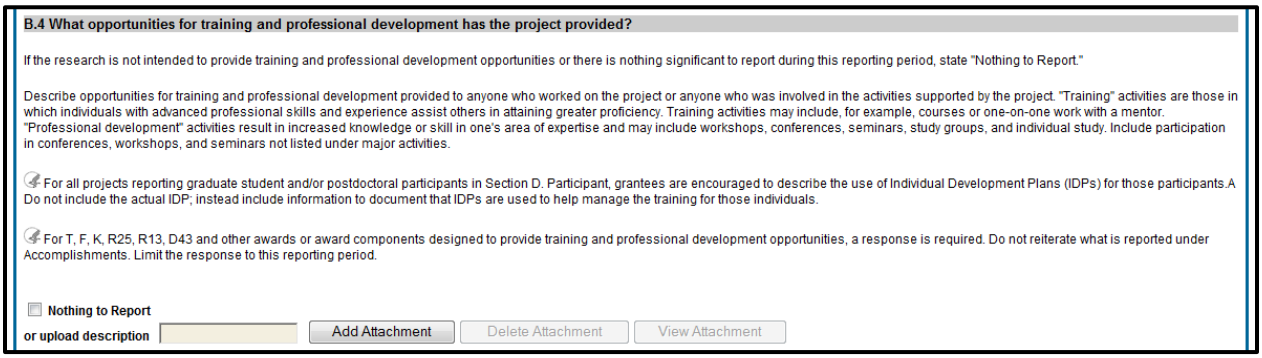


Figure 73: RPPR Section B. Accomplishments – Question B4

B.5 How have results been disseminated to communities of interest?

Describe how the results have been disseminated to communities of interest. Include any outreach activities that have been undertaken to reach members of communities who are not usually aware of these research activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Reporting the routine dissemination of information (e.g., websites, press releases) is not required. For awards not designed to disseminate information to the public or conduct similar outreach activities, a response is not required and the grantee should select **Nothing to Report**. A detailed response is only required for awards or award components that are designed to disseminate information to the public or conduct similar outreach activities. Note that scientific publications and the sharing of research resources will be reported under *Products*.

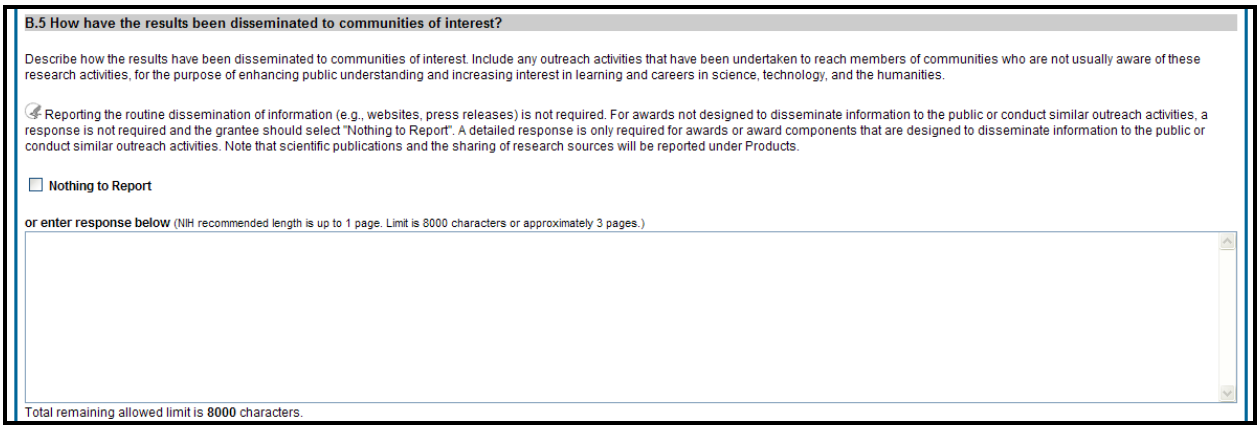


Figure 74: RPPR Section B. Accomplishments – Question B5

B.6 What do you plan to do for the next reporting period to accomplish the goals?

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Remember that significant changes in objectives and scope require prior approval of the agency (e.g., NIH Grants Policy Statement, 8.1.2.).

Include any important modifications to the original plans. Provide a scientific justification for any changes involving research with human subjects or vertebrate animals. A detailed description of such changes must be provided under Section F. Changes.

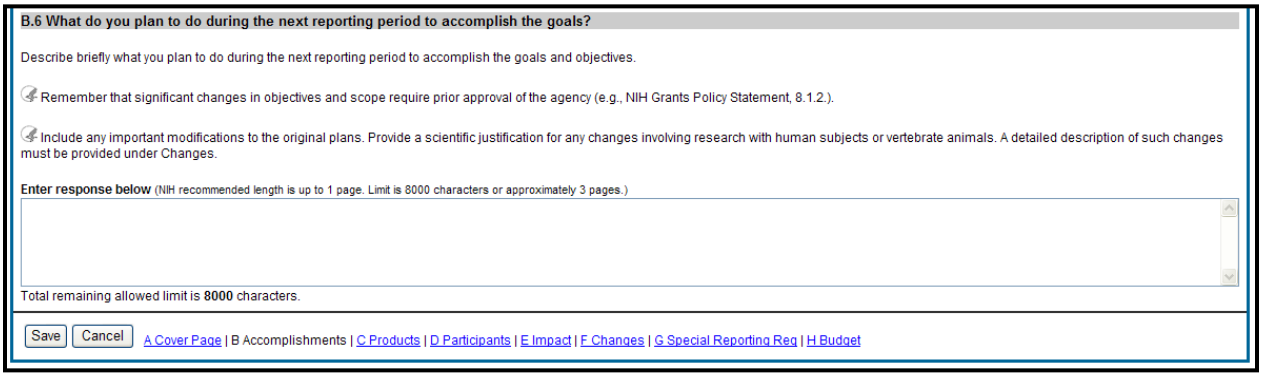


Figure 75: RPPR Section B. Accomplishments – Question B6

6.3 Section C – Products

The RPPR section C. Products allows agencies to assess and report both publications and other products to Congress, communities of interest, and the public.

C.1 Publications.

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from the award?

PD/PIs are required to report all publications that arise from their NIH award in this section. Publications listed in other parts of the RPPR will not be tracked as award products. If there are publications to report select **Yes** and ensure that the **Associate with this RPPR** box is checked as appropriate. If there are no publications to report select **No**. The tables draw information from the PD/PI's My NCBI account. PD/PIs can log in to their My NCBI account via the **My NCBI** link at the top of C.1. PD/PIs that do not have a My NCBI account can create one by simply logging in to My NCBI with their eRA Commons credentials, which will automatically create a My NCBI account. Any changes they make to their My Bibliography collection will be reflected in the RPPR once the screen is refreshed (i.e., by clicking the **Save** button). For more information on My NCBI, see:

Get Started with My NCBI: Access My NCBI, Register, and Sign In
Edit Your My Bibliography Settings (Add a Delegate)

The first table, **All Publications Associated with this Project in My NCBI**, lists all publications that are in the PD/PI's My Bibliography collection, are associated with this award, and have not been reported in previous electronic progress reports for this award.

The first column **Associate with this RPPR** is automatically checked. Leaving the box checked upon submission associates the publication with this progress report, results in the publication being displayed in RePORT, and makes the award-publication association in My NCBI permanent and the association will be reported in PubMed. Unchecking the box disassociates the publication with this progress report and, upon submission of the RPPR to NIH, removes the award-publication association in My NCBI.

The second column, **NIH Public Access Compliance**, indicates the current compliance status with the NIH Public Access Policy. This information is from My NCBI. Publications that fall under the Public Access Policy and are non-compliant still must be reported. Generally, it takes weeks to bring publications into compliance; PD/PIs are advised to do so as soon as possible to ensure their award is renewed in a timely manner. For more information, see Manage Compliance with the NIH Public Access Policy in My NCBI and the NIH Public Access website. The compliance status for AHRQ grantees will be indicated as NA (not applicable) until such time as AHRQ implements a public access policy.

Note that the publication data in these tables is dynamic until the progress report is submitted to the agency. Any change to the data occurring in PubMed, PubMed Central, the PD/PI's My Bibliography account, or in the compliance status of a publication will refresh upon saving the C.1 Products section, or opening the RPPR in another session. When the progress report is submitted to the agency, the publication data is frozen in the progress report.

The second table, **Publications not associated with this project in MyNCBI**, lists all other publications that are in the PD/PI's My Bibliography collection but do not have an association with this award. Checking **Associate with this RPPR** box will associate a publication with the award both in the progress report and in My NCBI. Refreshing this screen (i.e., clicking the **Save** button) will also move the newly associated publications from this table to the first table. Similarly, publications disassociated in the first table will appear in this table when the screen is refreshed.

The final table, **Publications previously reported for this project**, lists publications reported in a previous electronic progress report for this award. Grantees are responsible for ensuring that

these publications comply with the Public Access policy even if they were provisionally compliant (listed as *in Progress*) when previously reported.

The report may be submitted with noncompliant publications; however the system will generate an automated email to the PD/PI (with cc to the AO and SO) requesting that the grantee provide evidence of compliance or an explanation (e.g., the sole author has passed away before s/he was able to process the manuscript for posting to PubMed Central) by a specified due date two weeks prior to the next budget start date. The grantee must respond either via an email to the GMS and PO, or may respond via the Progress Report Additional Materials (**PRAM**) link found on the eRA Commons Status page. The **PRAM** link provides a text box in which the grantee may respond through the eRA Commons. The grantee will be able to view the PRAM in the grant folder. See Section 5.10 *Public Access Progress Report Additional Materials (PRAM)* for more information.

Publications listed in other parts of a progress report are not captured electronically. They will not be included in this table, and may not be listed as resulting from this award in RePORT.

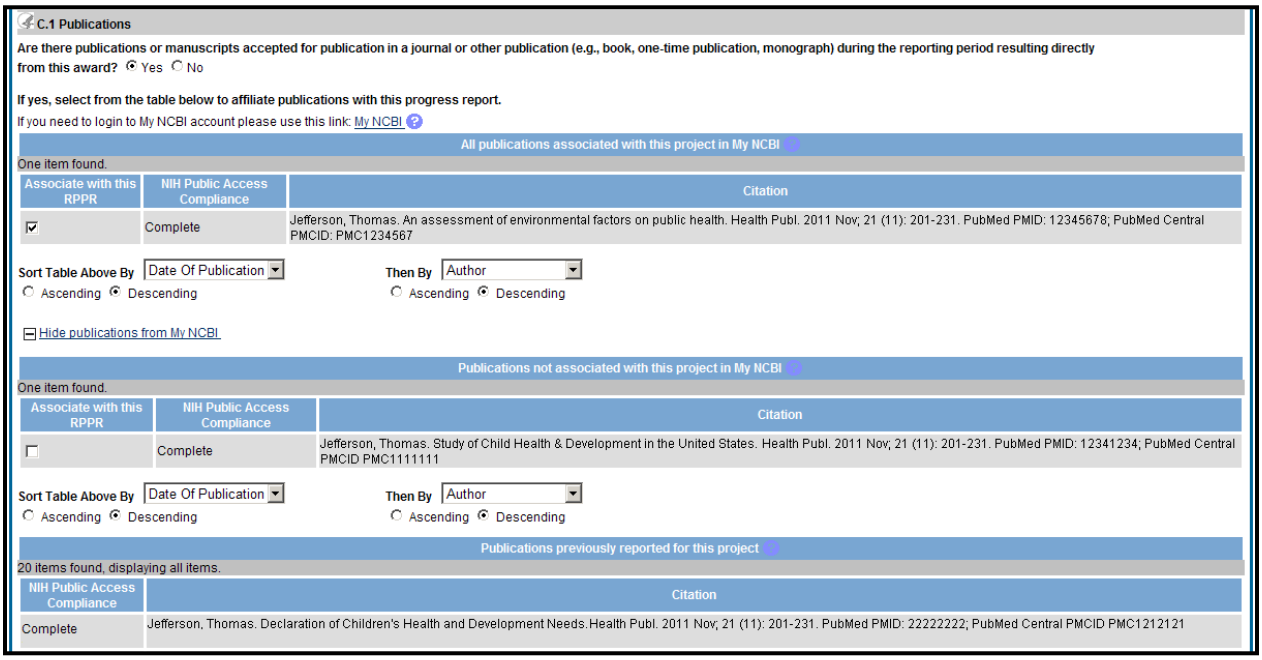


Figure 76: RPPR Section C. Products – Question C1

C.2 Website(s) or other internet site(s).

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above.

For awards not designed to create or maintain one or more websites, select **Nothing to Report**. A description is only required for awards designed to create or maintain one or more websites. Limit the response to this reporting period.

C.3 Technologies or techniques.

Identify technologies or techniques that have resulted from the research activities. Describe the technologies or techniques and how they are being shared.

Limit the response to this reporting period.

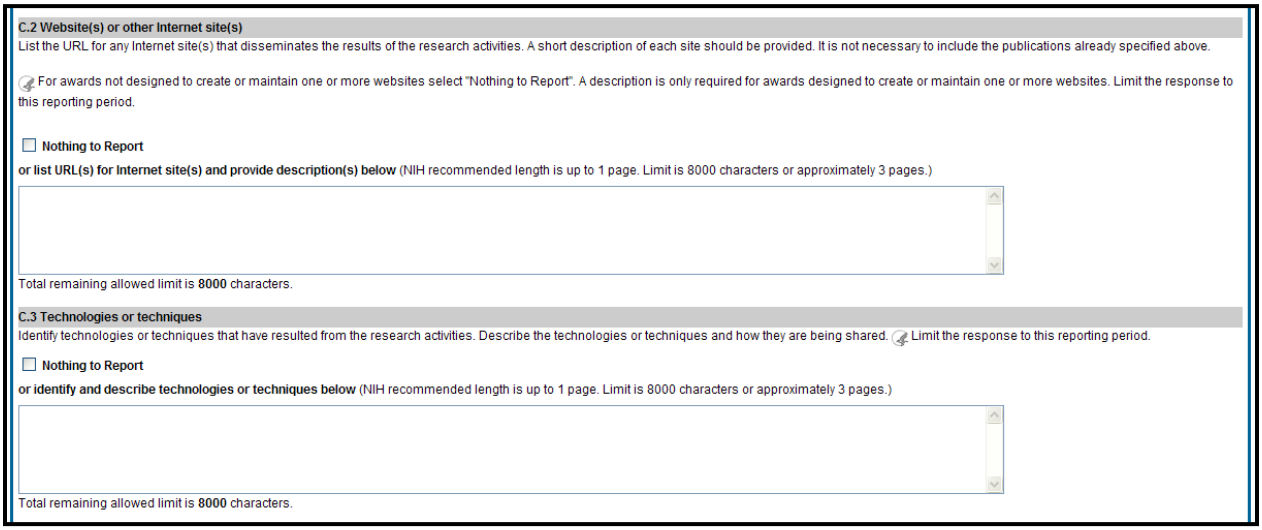


Figure 77: RPPR Section C. Products – Questions C2 & C3

C.4 Inventions, patent applications and/or licenses.

Have inventions, patent applications and/or licenses resulted from the award during this reporting period?

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

Reporting of inventions through iEdison is strongly encouraged.

C.5 Other products and resources.

C.5.a Other products

Identify any other significant products that were developed under this project.

Describe the product and how it is available to be shared with the research community. Do not repeat information provided above. Limit the response to this reporting period.

Examples of other products are: audio or video products; data and research material (e.g., cell lines, DNA probes, animal models); databases; educational aids or curricula; instruments or equipment; models; protocols; and software or netware.

C.5.b Resource Sharing

PD/PIs and grantee organizations are expected to make the results and accomplishments

of their activities available to the research community and to the public at large. For additional information on NIH Sharing Policies and Related Guidance on NIH-Funded Research Resources see http://grants.nih.gov/grants/sharing.htm.

If the initial research plan addressed, or the terms of award require, a formal plan for sharing final research data, model organisms, Genome Wide Association Studies data, or other such project-specific data, describe the progress in implementing that plan. For sharing model organisms, include information on the number of requests received and number of requests fulfilled during this reporting period. If the sharing plan is fully implemented, provide a final statement on data sharing.

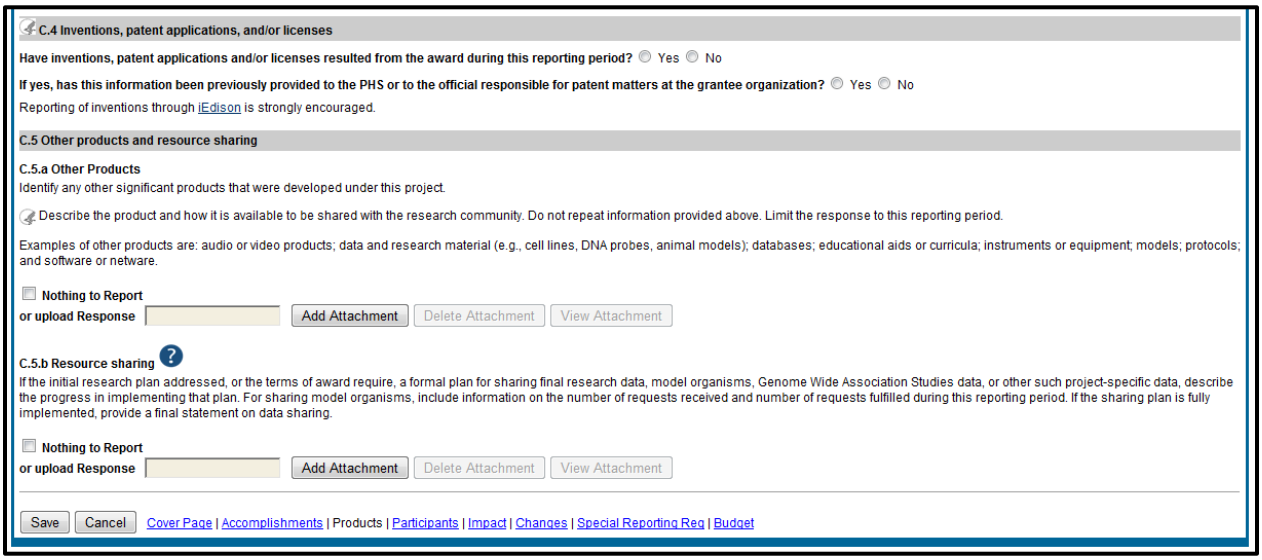


Figure 78: RPPR Section C. Products – Questions C4 & C5

6.4 Section D – Participants

The RPPR Section D. allows the agency to know who has worked on the project to gauge and report performance in promoting partnerships and collaborations.

D.1 What individuals have worked on the project?

Provide or update the information for: (1) program director(s)/principal investigator(s) (PDs/PIs); and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours or 8.3% of annualized effort).

Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person has worked on the project for any significant length of time. For example, if an undergraduate student graduates, enters graduate school, and continues to work on the project, show that person as a graduate student.

NIH Instructions:

- An individual's Commons user ID may be used to partially populate his or her information
- A Commons ID is required for all individuals with a postdoctoral role and/or supported by a Reentry or Diversity Supplement. The Commons ID is strongly encouraged, but currently optional, for all other project personnel. AHRQ only requires a Commons ID for individuals in a postdoctoral role.
- Individuals with a postdoctoral-like role should be identified as *Postdoctoral (scholar, fellow, or other postdoctoral position)*
- Do not include Other Significant Contributors who are not committing any specified measurable effort to this project
- Do not report personnel for whom a PHS 2271 Appointment form has been submitted through xTrain
- Required fields are marked with an *

eRA Commons User ID: Entering the User ID allows selection of "Populate from Profile" which will partially populate the individual's information. Those with an Administrator role in the eRA Commons may search for user IDs by following the instructions at:

http://era.nih.gov/commons/commons-help/1001.htm

Senior/key personnel are defined as the PD/PI and other individuals who contribute to the scientific development or execution of a project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Typically these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level may be considered senior/key personnel if their involvement meets this definition. Consultants and those with a postdoctoral role also may be considered senior/key personnel if they meet this definition.

Last 4 digits of SS# and Month/Year of birth: The provision of the partial Social Security number and month/year of birth are voluntary, and the information is used only for program management purposes.

Project Role: PD/PI names and information from their Commons Profile(s) will be prepopulated. To update the PD/PI information as displayed, go to the Commons Profile and save the changes there. For all other personnel, select from a dropdown menu of the following options:

- **Co-Investigator**
- **Faculty**
- **Postdoctoral (scholar, fellow or other postdoctoral position)**
- **Technician**
- **Staff Scientist (doctoral level)**
- **Statistician**

- **Graduate Student (research assistant)**
- **Non-Student Research Assistant**
- **Undergraduate Student**
- **High School Student**
- **Consultant**
- **Other (specify)**

Supplement Support: If personnel are supported by a Reentry or Diversity Supplement indicate type of supplement in this field.

Person Months: The metric for expressing the effort (amount of time) devoted to a specific project. The effort is based on the type of appointment of the individual with the organization; e.g., calendar year, academic year, and/or summer term; and the organization's definition of such. For instance, some institutions define the academic year as a 9-month appointment while others define it as a 10-month appointment.

Include (1) the PD/PI regardless of effort devoted to the project and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation.

Round to the nearest whole person month that the individual worked on the project. For example, if the individual worked 2.25 person months, indicate 2 person months. If the individual worked 4.7 person months, indicate 5 person months. If the PD/PI worked 0.5 to 1 person month, round up to 1 person month. If the PD/PI worked 0.1 to 0.4 person month, round down to 0 (zero).

To calculate person months, multiply the percentage of effort associated with the project by the number of months of the appointment. For example:

- 25% of a 9 month academic year appointment equals 2.25 (academic year) person months (.25 x 9 = 2.25). Round down to 2.
- 90% of a 12 month calendar appointment equals 10.8 (calendar year) person months (.90 x 12 = 10.8). Round up to 11.
- 35% of a 3 month summer term appointment equals 1.05 (summer) person months (.35 x 3= 1.05). Round down to 1.
- If the regular pay schedule of an institution is a 9 month academic year and the PD/PI will devote 9 academic months at 30% time/effort and 3 months summer term at 30% time/effort , then 3 academic months (.30% x 9 = 2.7, round up to 3), and 1 summer month (.30 x 3 = .9, round up to 1) should be reported

Person months reported on the RPPR are intentionally rounded to the nearest whole number to provide for generalized reporting consistent across federal agencies that support research activities. Although it is possible to report 0 (zero) person month for the PD/PI on the RPPR if the PD/PI worked .1 to .4 person month, a PD/PI must have measurable effort. Change in Level of Effort for the PD/PI(s) and other senior key/personnel designated in the NoA is reported under D.2.a below.

Is the individual's primary affiliation with a foreign organization?

Check **No** if the individual's primary affiliation is with a foreign organization but the individual is working on this award solely while in the U.S.

If **Yes**, provide the name of the organization and country.

Select the **Add/New** button to add the data to the table.

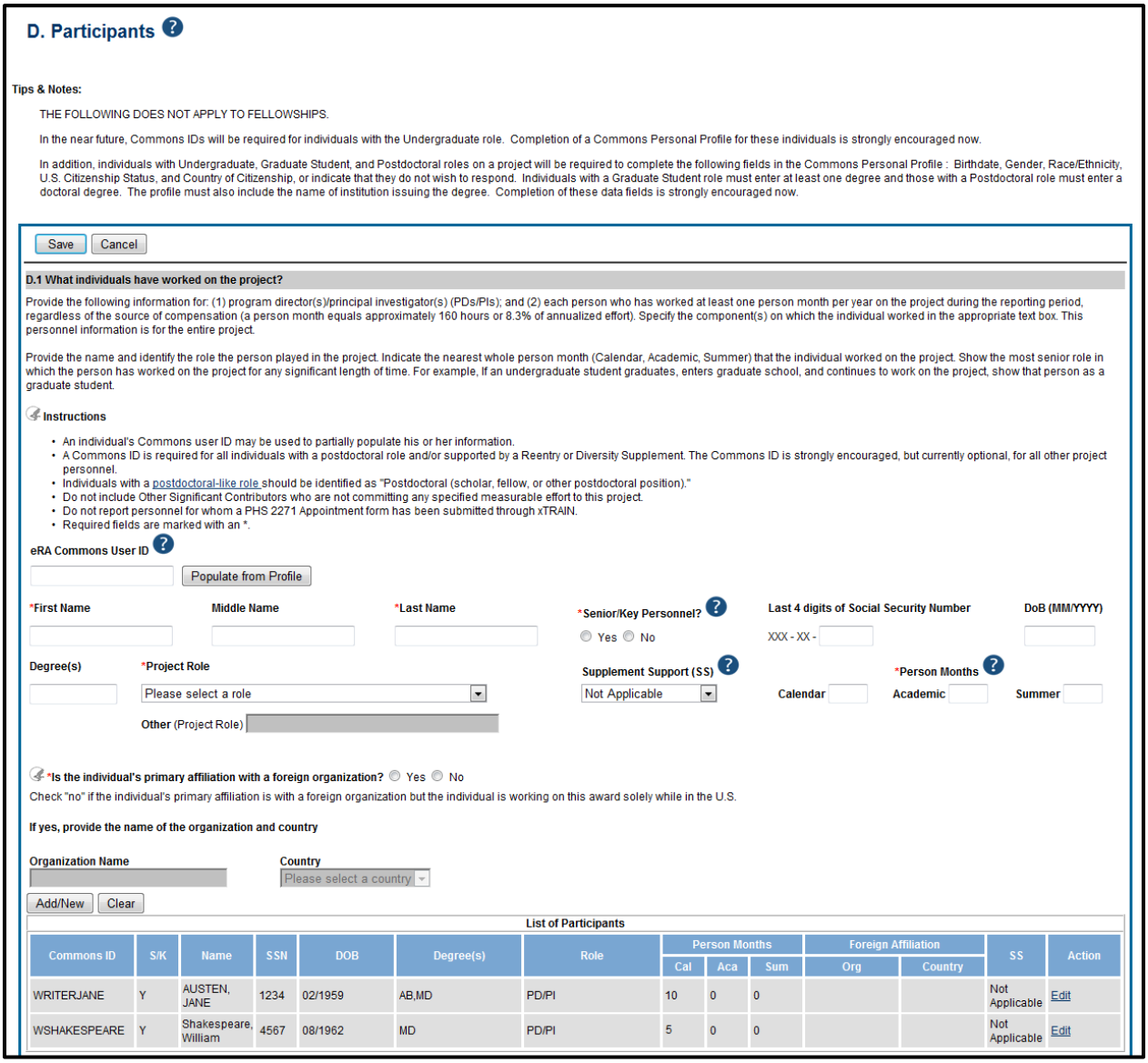


Figure 79: RPPR Section D. Participants – Question D1

D.2 Personnel Updates.

D.2.a Level of effort.

Will there be, in the next budget period, either (1) a reduction of 25% or more in the level of effort from what was approved by the agency for the PD/PI(s) or other senior/key personnel designated in the Notice of Award, or (2) a reduction in level of effort below the minimum amount of effort required by the Notice of Award?

Reductions are cumulative, i.e., the 25% threshold may be reached by two or more successive reductions that total 25% or more. Once agency approval has been given for a significant change in the level of effort, then all subsequent reductions are measured against the approved adjusted level. Selecting **Yes** constitutes a prior approval request to the agency and the issuance of a subsequent year of funding constitutes agency approval of the request.

D.2.b New senior/key personnel.

Are there, or will there be, new senior/key personnel?

Senior/key personnel are those identified by the grantee institution as individuals who contribute in a substantive measurable way to the scientific development or execution of the project, whether or not salaries are requested. Typically these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level may be considered senior/key personnel if the involvement meets this definition. Consultants may be considered senior/key personnel if they meet this definition.

If yes, upload biosketches and other support for all new senior/key personnel.

Follow the biosketch instructions in the competing application guide and provide active other support for all new senior/key personnel. Combine all biosketches and other support into a single PDF.

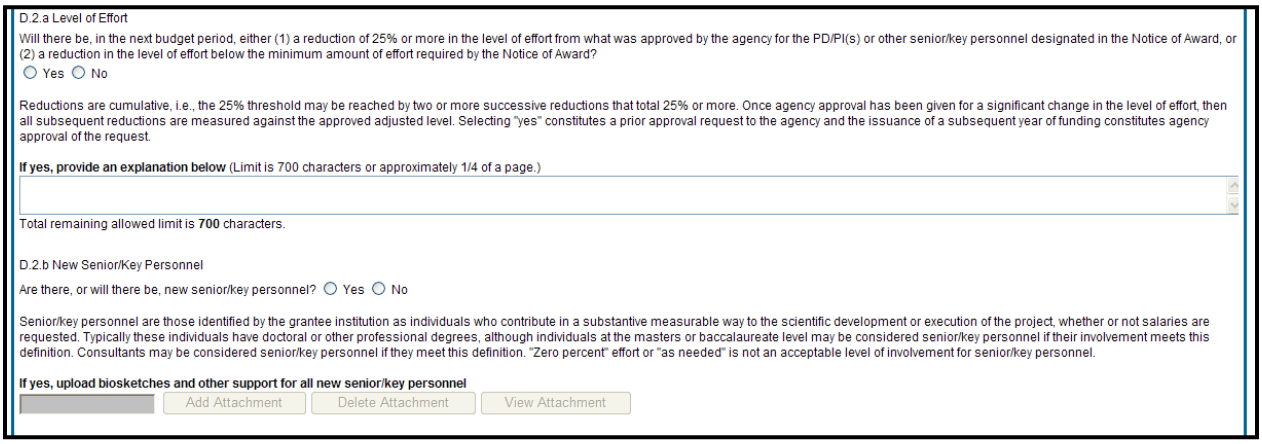


Figure 80: RPPR Section D. Participants – Questions D2a & D2b

D.2.c Changes in other support.

Has there been a change in the active other support of senior/key personnel since the last reporting period?

If yes, upload active other support for senior/key personnel whose support has changed and indicate what the change has been. List the award for which the progress report is being submitted and include the effort that will be devoted in the next reporting period.

Select **Yes** only if active support has changed for the PD/PI(s) or senior/key personnel.

If a previously active grant has terminated and/or if a previously pending grant is now active, submit complete Other Support information using the suggested format and instructions found at http://grants.nih.gov/grants/funding/2590/Non-competing_othersupport.docx. Annotate this information so it is clear what has changed from the previous submission.

Submission of other support information is not necessary if support is pending or for changes in the level of effort for active support reported previously.

Other support information should be submitted only for the PD/PI and for those individuals considered by the grantee to be key to the project for whom there has been a change in other support. Senior/key personnel are defined as individuals who contribute in a substantive measurable way to the scientific development or execution of the project, whether or not a salary is requested. Do not include other support information for Other Significant Contributors; e.g., those that may contribute to the scientific development or execution of the project, but are not committing any specified measurable effort to the project.

D.2.d New other significant contributors.

Are there, or will there be, new other significant contributors?

Other significant contributors are individuals who have committed to contribute to the scientific development or execution of the project, but are not committing any specified measurable effort (i.e., person months) to the project.

If yes, upload biosketches for all new other significant contributors.

D.2.e Will there a change in the MPI Leadership Plan for the next budget period?

Change in status of PD/PI requires prior approval of the agency (e.g., NIH Grants Policy Statement, 8.1.2.6). In accord with the NIH GPS, 9.5, revision of the Leadership Plan during the project period may be accomplished through a joint decision of the PD/PIs and reported in the RPPR. Prior approval of a change in the MPI Leadership Plan is not required.

If yes, upload a revised MPI Leadership Plan that includes a description of the change(s).

All multiple PD/PI awards have a Leadership Plan that describes the roles and areas of responsibility of the named PD/PIs, the process for making decisions concerning scientific directions, allocation of resources, disputes that may arise, and other information related to the management of the proposed team science project. If there has been any change in the governance and/or organizational structure of the Leadership Plan, provide a description, including communication plans and procedures for resolving conflicts, and any changes to the administrative, technical, and scientific responsibilities of the PD/PIs. If the progress report includes a change in the Contact PD/PI (*Cover Page, A.1*) address this change and the impact, if any, the change has on the administrative, technical, and scientific responsibilities of the PD/PIs. A request to change from a multiple PD/PI model to a single PD/PI model, or a change in the

number or makeup of the PD/PIs on a multiple PD/PI award, requires the prior approval of the GMO. The progress report is not the appropriate vehicle to request such a change.

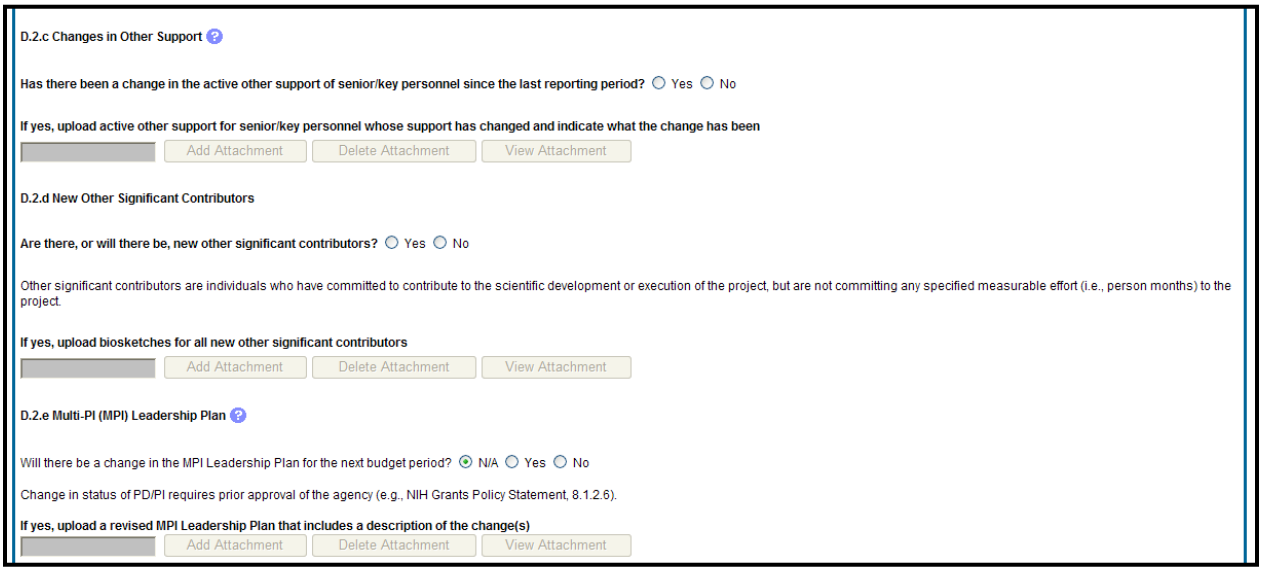


Figure 81: RPPR Section D. Participants – Questions D2c – D2e

6.5 Section E – Impact

The RPPR Section E Impact will be used to describe ways in which the work, findings, and specific products of the project have had an impact during this reporting period.

E.1 Not Applicable for most awards. See chapter 7 Supplemental Instructions.

E.2 What is the impact on physical, institutional, or information resources that form infrastructure?

Describe ways, if any, in which the project made an impact, or is likely to make an impact, on physical, institutional, and information resources that form infrastructure, including:

- physical resources (such as facilities, laboratories, or instruments);
- institutional resources (such as establishment or sustenance of societies or organizations); or
- information resources, electronic means for accessing such resources or for scientific communication, or the like.

If the award or award component(s) is not intended to support physical, institutional, or information resources that form infrastructure, select **Nothing to Report**.

E.3 Not Applicable for most awards. See chapter 7 Supplemental Instructions.

E. 4 What dollar amount of the award's budget is being spent in foreign country(ies)?

For domestic awardees provide the dollar amount obligated to first-tier subawards to foreign entities for this reporting period. For foreign awardees provide the dollar amount of the award, excluding all first-tier subawards to U.S. entities, for this reporting period. Dollars

provided should reflect total costs.

If more than one foreign country identify the distribution between the foreign countries.

Report only cumulative first-tier subawards dollars by country. Do not report foreign travel, purchases, etc., unless part of a first-tier subaward to a foreign country.

Select the **Add/New** button to add the data to the table.

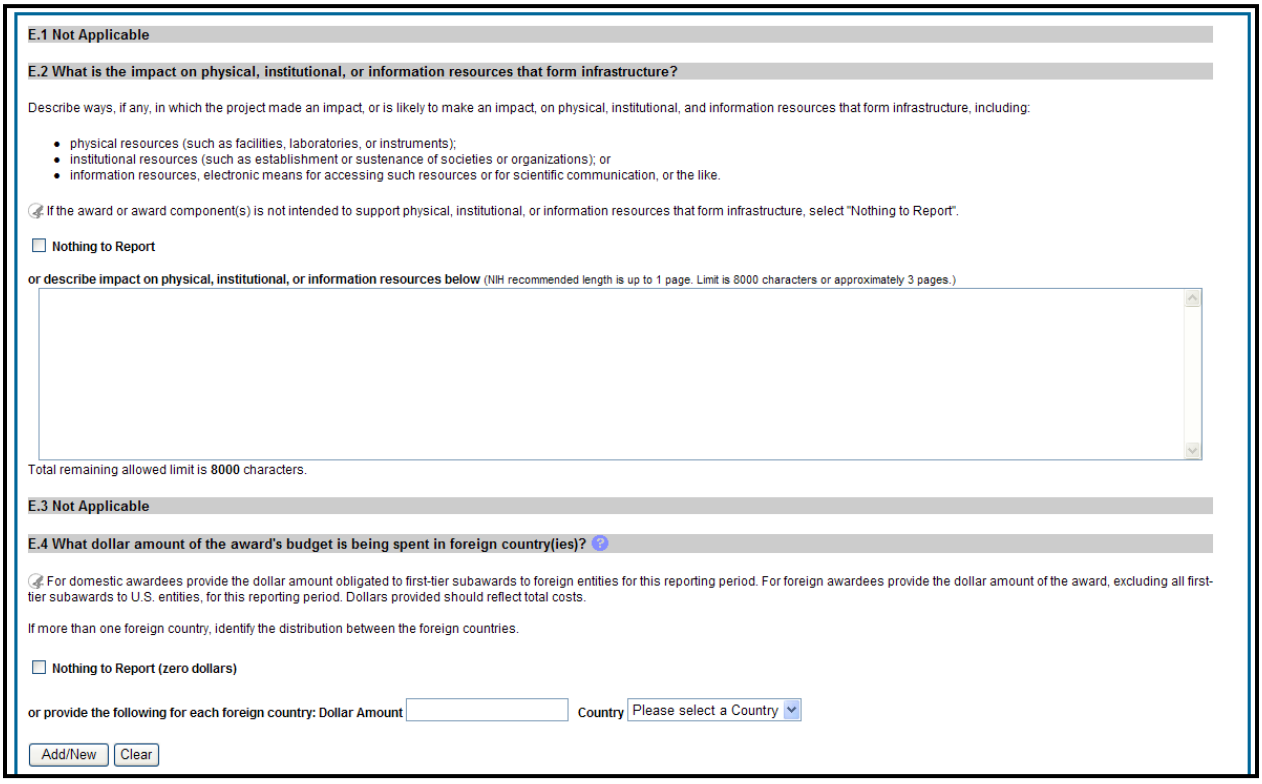


Figure 82: RPPR Section E. Impact – Questions E1 through E4

6.6 Section F – Changes

The RPPR Section F addresses Changes. Grantees are reminded that significant changes in objectives and scope require prior approval of the agency.

F.1 Not Applicable to most awards. See chapter 7 Supplemental Instructions.

F.2 Actual or anticipated challenges or delays and actions or plans to resolve them.

Describe challenges or delays encountered during the reporting period and actions or plans to resolve them.

Describe only significant challenges that may impede the research (e.g., accrual of patients, hiring of personnel, need for resources or research tools) and emphasize their resolution.

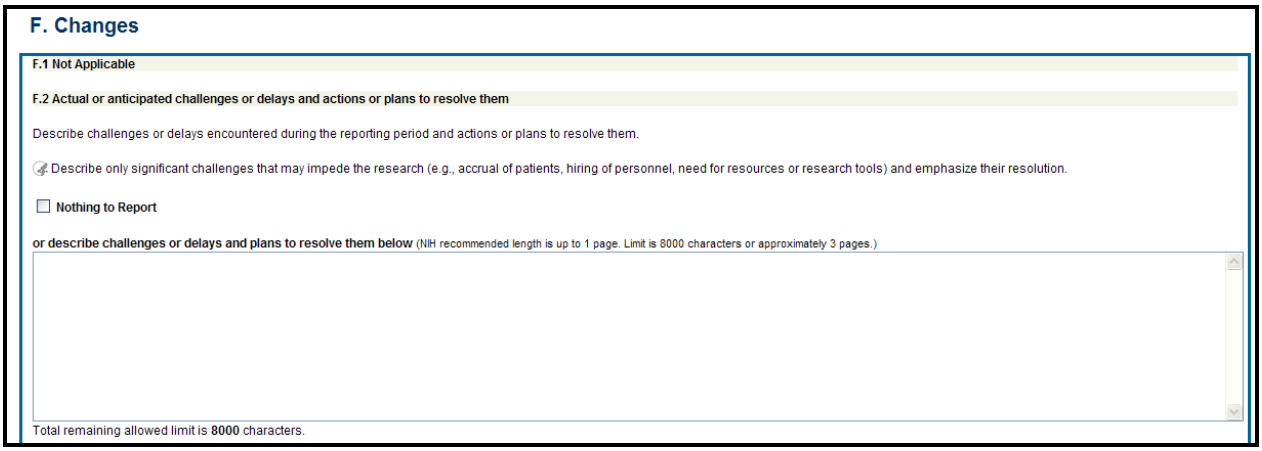


Figure 83: RPPR Section F. Changes – Questions F1 & F2

F.3 Significant changes to human subjects, vertebrate animals, biohazards, and/or select agents.

Describe significant deviations, unexpected outcomes, or changes in approved protocols for human subjects, vertebrate animals, biohazards and/or select agents during this reporting period.

Remember that significant changes in objectives and scope require prior approval of the agency (e.g., NIH Grants Policy Statement, 8.1.2.). If there are changes in any of the following areas, check the appropriate box and provide a description of the changes.

F.3.a Human Subjects

If human subject studies are or will be different from the previous submission, include a description and explanation of how the studies differ and provide new or revised Protection of Human Subjects Section and Inclusion of Women, Minorities, and Children sections as described in the competing application instructions. Additional or modified Planned Enrollment Reports may also be necessary and uploaded in Section G.4.b of the RPPR.

F.3.b Vertebrate Animals

If there are or will be significant changes to the uses of vertebrate animals from the previous submission, provide a description of the changes. Examples of changes considered to be significant include, but are not limited to, changing animal species, changing from noninvasive to invasive procedures, new project/performance site(s) where animals will be used, etc. If studies involving live vertebrate animals are planned and were not part of the originally proposed research design, provide a new or revised Vertebrate Animal Section as described in the competing application instructions.

F.3.c Biohazards

If the use of biohazards is or will be different from that in the previous submission, provide a description and explanation of the difference(s).

F.3 d Select Agents

If the possession, use, or transfer of Select Agents is or will be different from that proposed in the previous submission, including any change in the select agent research location and/or the required level of biocontainment, provide a description and explanation of the differences. If the

use of Select Agents was proposed in the previous submission but has not been approved by regulatory authorities, provide an explanation. If studies involving Select Agents are planned and were not part of the originally proposed research design, provide a description of the proposed use, possession, transfer, and research location as described in the competing application instructions.

U.S. Select Agent Registry information:
http://www.selectagents.gov/Select%20Agents%20and%20Toxins.html

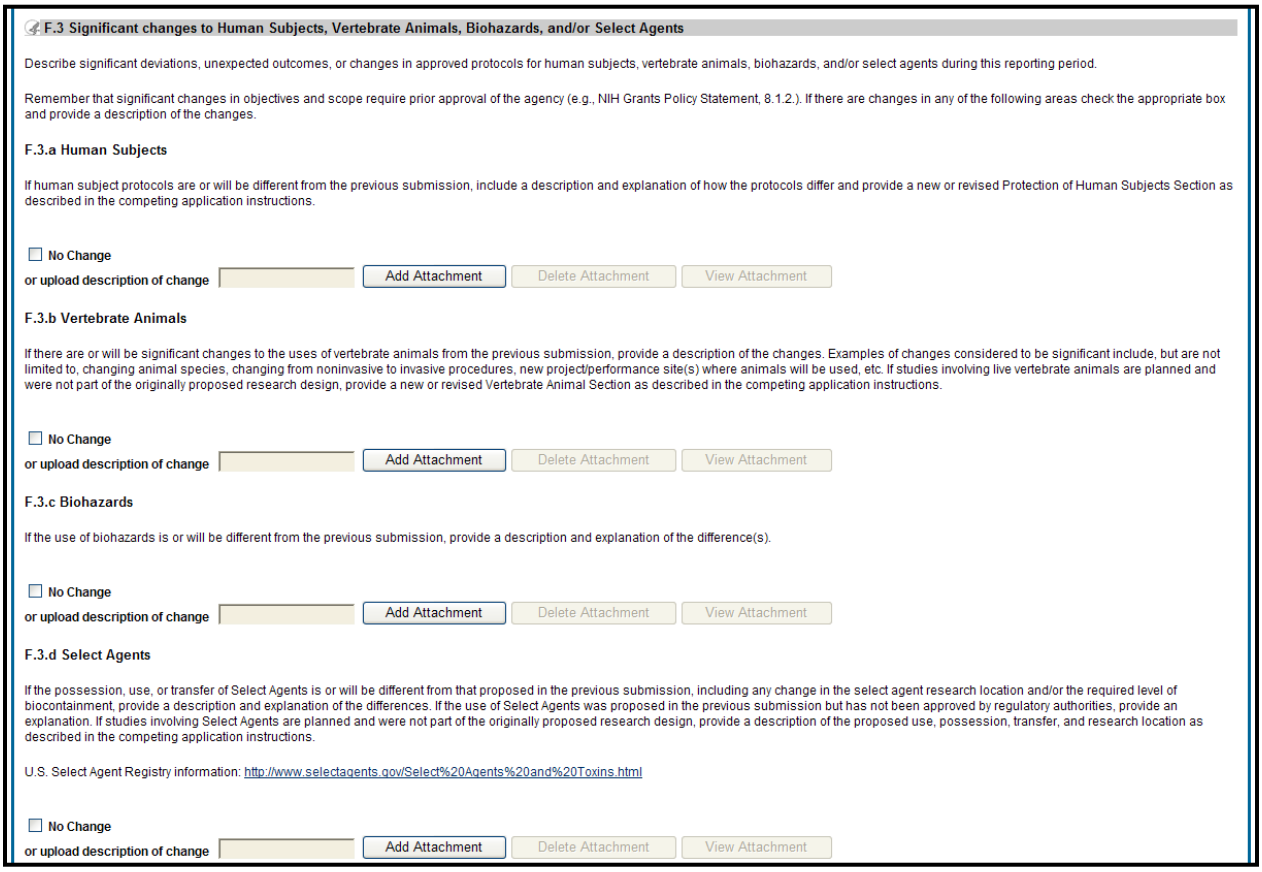


Figure 84: RPPR Section F. Changes – Question F3

6.7 Section G – Special Reporting Requirements

The RPPR Section G Special Reporting Requirements address agency-specific award terms and conditions, as well as any award specific reporting requirements.

G.1 Special Notice of Award and Funding Opportunity Announcement Reporting Requirements

Address any special reporting requirements specified in the award terms and conditions in the Notice of Award (NoA) or Funding Opportunity Announcement (FOA).

***G.2 Not* Applicable to most awards. See chapter 7 *Supplemental Instructions*.**

***G.3 Not* Applicable to most awards. See chapter 7 *Supplemental Instructions*.**

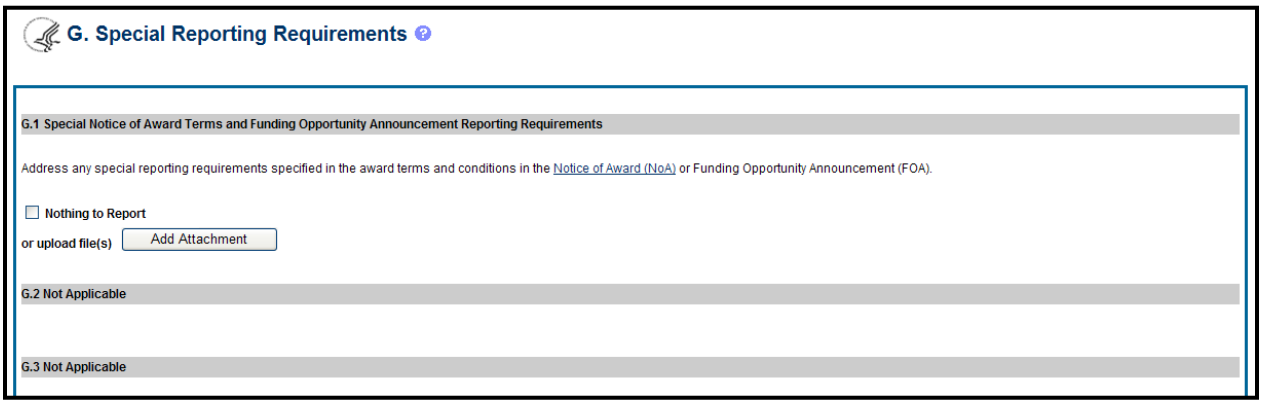


Figure 85: RPPR Section G. Special Reporting Requirements – Questions G1 through G3

G.4. Human Subjects

G.4.a Does the project involve human subjects?

If activities involving human subjects are planned at any time during the next budget period at the grantee organization or at any other project/performance site or collaborating institution, select **Yes**. Select **Yes** even if the project is exempt from the Regulations for the Protection of Human Subjects. Select **No** if activities involving human subjects are not planned at any time during the next budget period.

Policy on research involving human subjects, including definitions, can be found in the NIH Grants Policy Statement or in the competing application instructions.

Is the research exempt from federal regulations? Not applicable unless the answer to G.4.a. is **Yes**. If **all** of the proposed human subjects research meet the criteria for one or more of the exemptions from the requirements in the DHHS regulations (45 CFR 46.101(b)), **Yes** should be selected, and the appropriate exemption number(s) checked. The six categories of research exempt from the DHHS human subject regulations appear in Part III of the competing application instructions, under Definitions, Human Subjects.

If in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services, or the NIH Office of Extramural Research, Office of Extramural Programs at OEPMailbox@mail.nih.gov.

Note that if the proposed research involves only the use of human data or biological specimens, first determine whether the research involves human subjects. The exemptions do not apply if the research does not involve human subjects. For help determining whether research that involves the use of human data or biological specimens is human subjects research, refer to the NIH Research Involving Human Subjects website.

Does this project involve a clinical trial? Not applicable unless the answer to G.4.a. is **Yes**. The NIH defines a clinical trial as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or

devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

Phase I clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

If yes, is this an NIH defined Phase III Clinical Trial?

An NIH-defined *Phase III clinical trial* is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

G4.b Inclusion enrollment data.

Unless otherwise notified by NIH staff**,** reporting the cumulative enrollment of subjects and the distribution by sex/gender, race, and ethnicity is required for NIH-defined clinical research, as defined in the competing application instructions. If there are details or concerns related to inclusion enrollment progress, or if the cumulative enrollment data does not reflect the planned enrollment by sex/gender, race, and/or ethnicity, the reasons for this should be addressed in Section F.3.a of the RPPR.

Update the inclusion enrollment form(s) with the total cumulative enrollment data collected to-date. You can access the inclusion enrollment report form in Section G.4.b. (or immediately below). This form should be saved in PDF format and uploaded in G.4.b.

For RPPRs with budget period start dates BEFORE October 1, 2014, use the Inclusion Enrollment Report format.

If you are preparing this progress report for a start date ON or AFTER October 1, 2014, use the Cumulative Inclusion Enrollment Report format.

You may have more than one inclusion enrollment report form. These forms will be uploaded as PDF in Section G.4.b of the RPPR.

If new clinical studies have started and planned enrollment was not previously provided, submit Planned Enrollment Report(s) as well as the appropriate cumulative enrollment report form on cumulative enrollment to date. See Figure 87 below.

AHRQ grantees only: If inclusion enrollment reporting is required, download and complete the Cumulative Inclusion Enrollment Report, and upload it in Section G.4.b. If inclusion enrollment reporting is not required, select "Nothing to Report."

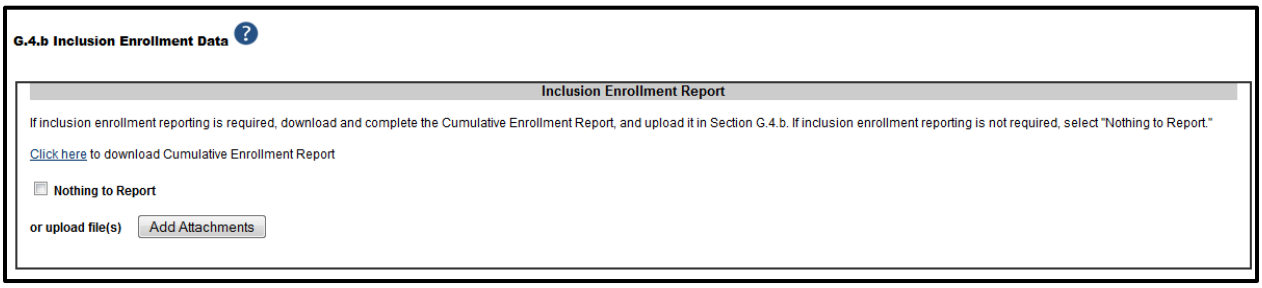


Figure 86: Question G.4.b for AHRQ Grantees Only

Guidance for Collecting and Reporting Inclusion Data: Below are instructions for how to collect and report data on the basis of sex/gender, race, and ethnicity with additional guidance for handling subpopulations, non-U.S. populations, changes to planned enrollment data, and NIH-defined Phase III clinical trials.

For questions about the NIH policies for inclusion, please refer to: http://grants.nih.gov/grants/funding/women_min/women_min.htm or contact the program officer.

Standards for Collecting Data from Study Participants: The Office of Management and Budget (OMB) Directive No. 15 defines minimum standards for maintaining, collecting and presenting data on ethnicity and race for all Federal (including NIH) reporting purposes. The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. The standards were revised in 1997 and now include two ethnic categories: Hispanic or Latino, and Not Hispanic or Latino. There are five racial categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White. Reports of data on ethnicity and race should use these categories. The definitions below apply for the ethnic and racial categories.

Ethnic Categories:

> **Hispanic or Latino:** A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino".

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America and maintains tribal affiliation or community.

Asian: A person having origins in any if the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

Reporting Data on Race and Ethnicity: NIH is required to use the above standards and definitions for race and ethnicity to allow comparisons to other federal databases, especially the census and national health databases. Federal agencies shall not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

When collecting data on ethnicity and race, as well as sex/gender, use the categories listed to obtain the data from individuals on the basis of self-identification. Participants should be asked to identify their ethnicity and their race. The OMB recommends collecting this information using two separate questions, with ethnicity information collected first followed by race, with the option to select more than one racial designation (http://www.whitehouse.gov/omb/fedreg_directive_15). **The NIH inclusion enrollment format is not designed for use as a data collection instrument**. Collect the data using instruments prepared for the study, and use that information to complete the NIH inclusion enrollment form(s). Study participants who self-identify with more than one of the racial categories should be reported in the aggregate in the "More Than One Race" category.

Collecting and Reporting Data on Subpopulations: Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self-identify with more than one ethnicity or race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study. The collection of greater detail is encouraged, e.g., on ethnic/racial subpopulations; however, any collection that uses more detail needs to be organized in such a way that the additional categories can be aggregated into the OMB categories for reporting data on ethnicity, race, and more than one race. Investigators who have data on subpopulations are encouraged to provide that information in the Comments field of the inclusion enrollment forms and/or in the text of their progress report.

Collecting and Reporting Data on Non-U.S. Populations: If conducting NIH-defined clinical research outside of the United States, design culturally appropriate data collection instruments that allow participants to self-identify their ethnic and/or racial affiliation in a way that is meaningful in the cultural and scientific contexts of the study. However, investigators will need to use the OMB-defined categories for reporting sex/gender, race and ethnicity to NIH (see definitions for each ethnic and racial category above), which will allow for completion of the inclusion enrollment form(s). Since OMB categories reference world-based geographic origin, this should facilitate completion of the form(s). **Enrollment of participants at non-U.S. sites should be reported to NIH on a separate inclusion enrollment form from that for reporting participants at U.S. sites, even if they are part of the same study**. For additional guidance and FAQs related to this topic, please refer to: http://grants.nih.gov/grants/funding/women_min/women_min.htm or contact the program officer.

Changes to Planned Enrollment: If there are changes from the planned enrollment originally approved for funding, contact the program officer to discuss updating/revising the planned enrollment, address the change in Section F.3.a of the RPPR, and provide the updated Planned Enrollment Report(s).

Reporting Data on NIH-defined Phase III Clinical Trials: If conducting an NIH-defined Phase III Clinical Trial, report on the cumulative enrollment (as described above) and indicate if any data analysis has begun for the trial. If analysis has begun or data have been published, report any progress made in evaluating potential differences on the basis on sex/gender, racial, and/or ethnicity.

G.4.c ClinicalTrials.gov.

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

If yes, provide the ClinicalTrials.gov identifier, NCT number (e.g., NCT00654321) for those trials.

See What NIH Grantees Need to Know About FADAA , and FAQ When must an applicable clinical trial be registered? If the grant number was entered into ClinicalTrials.gov, the ClinicalTrials.gov identifier (NCT number) may be readily identified by using the ClinicalTrials.gov Advanced Search and entering the grant number in the *Study IDs* field.

Select the **Add/New** button to add the data to the table.

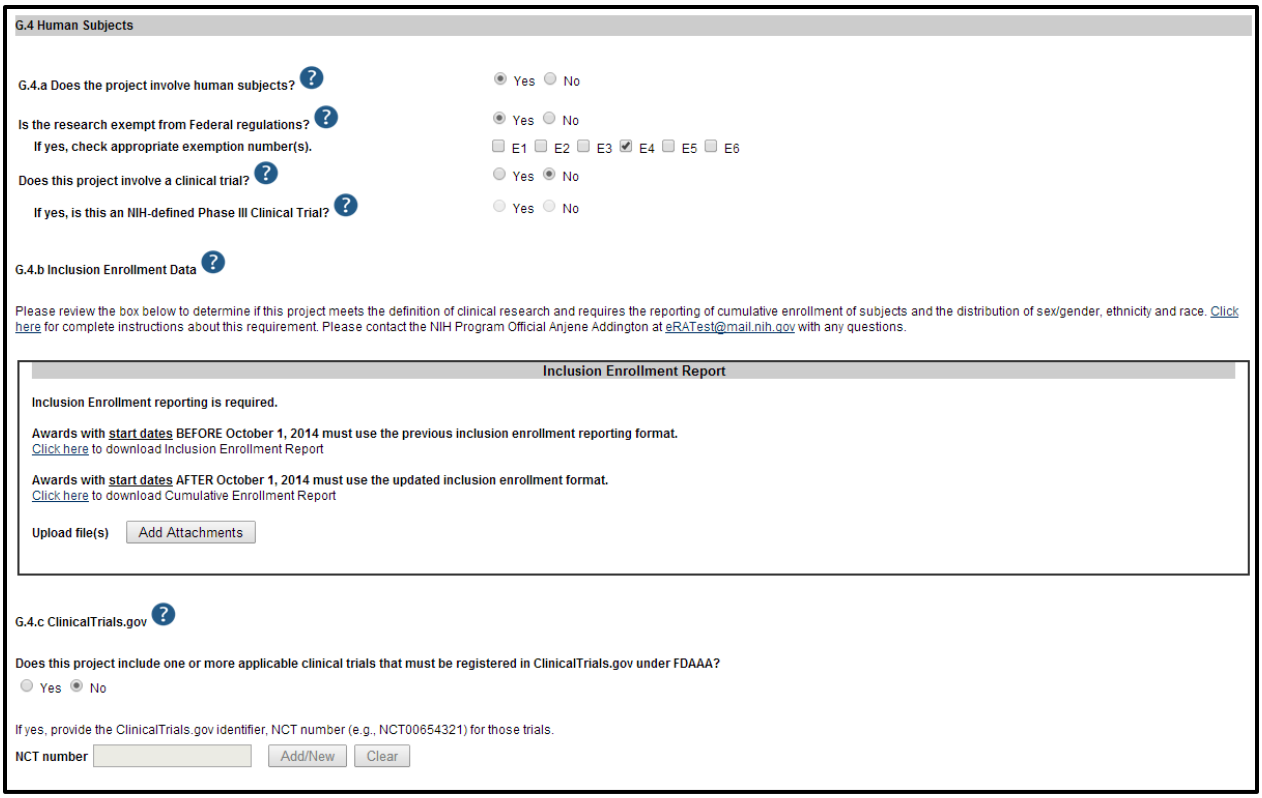


Figure 87: RPPR Section G. Special Reporting Requirements – Question G4

G.5 Human Subjects Education Requirement.

Are there personnel on this project who are or will be newly involved in the design or conduct of human subjects research?

If yes, provide the following:

- names of individuals,
- title of the human subjects education program completed by each individual, and
- a one-sentence description of the program.

G.6 Human Embryonic Stem Cell(s).

Does this project involve human embryonic stem cells?

Only hESC lines listed as approved in the NIH Registry may be used in NIH funded research.

If yes, identify the hESC Registration number(s) from the NIH Registry.

Select the **Add/New** button to add the data to the table.

If there is a change in the use of hESCs provide an explanation.

G.7 Vertebrate Animals

Does this project involve vertebrate animals?

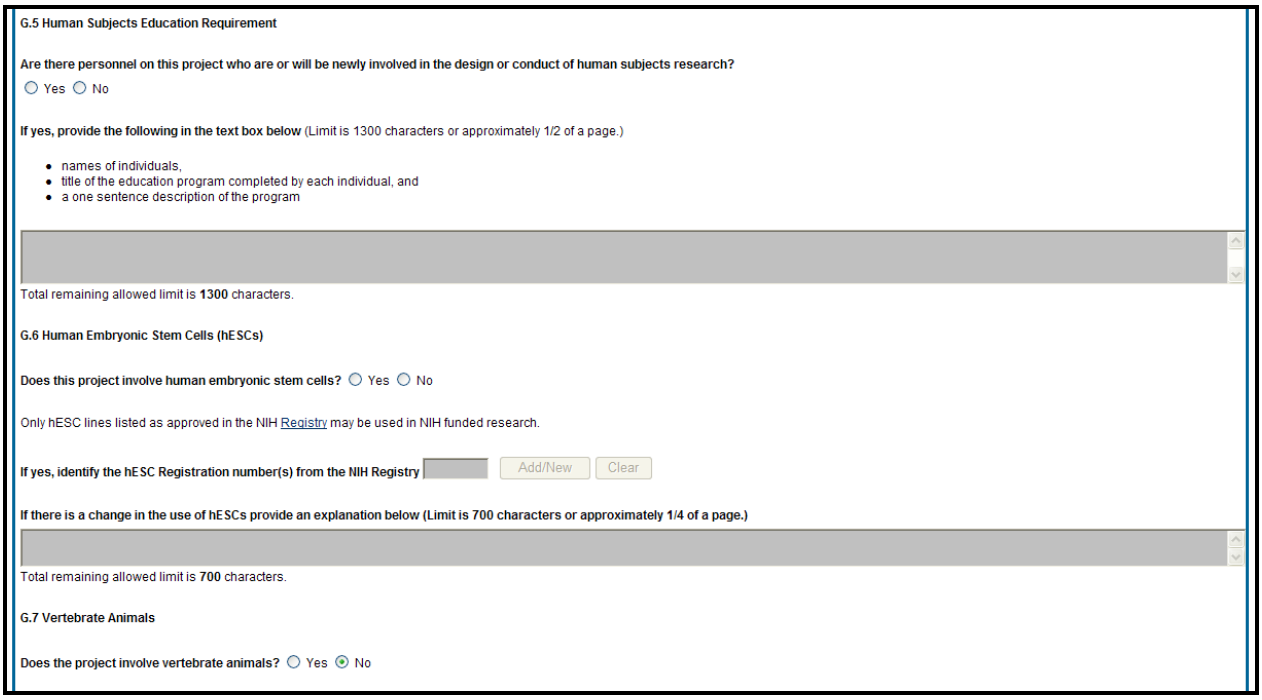


Figure 88: RPPR Section G. Special Reporting Requirements – Questions G5 through G7

G.8 Project/Performance Sites.

If there are changes to the project/performance site(s) displayed, edit as appropriate.

One of the sites indicated must be the identified as the Primary Performance Site. If including a new Project/Performance Site where either human subjects or vertebrate animals will be involved, address the change under F.3.a or F.3.b. If a Project/Performance Site is engaged in research involving human subjects, the grantee organization is responsible for ensuring that the Project/Performance Site operates under an appropriate Federal Wide Assurance for the protection of human subjects and complies with 45 CFR Part 46 and other NIH human subject related policies described in Part II of the competing application instructions and the *NIH Grants Policy Statement*.

For research involving live vertebrate animals, the grantee organization must ensure that all Project/Performance Sites hold OLAW-approved Assurances. If the grantee organization does not have an animal program or facilities and the animal work will be conducted at an institution with an Assurance, the grantee must obtain an Assurance from OLAW prior to the involvement of vertebrate animals.

Select the **Add/New** button to add the data to the table.

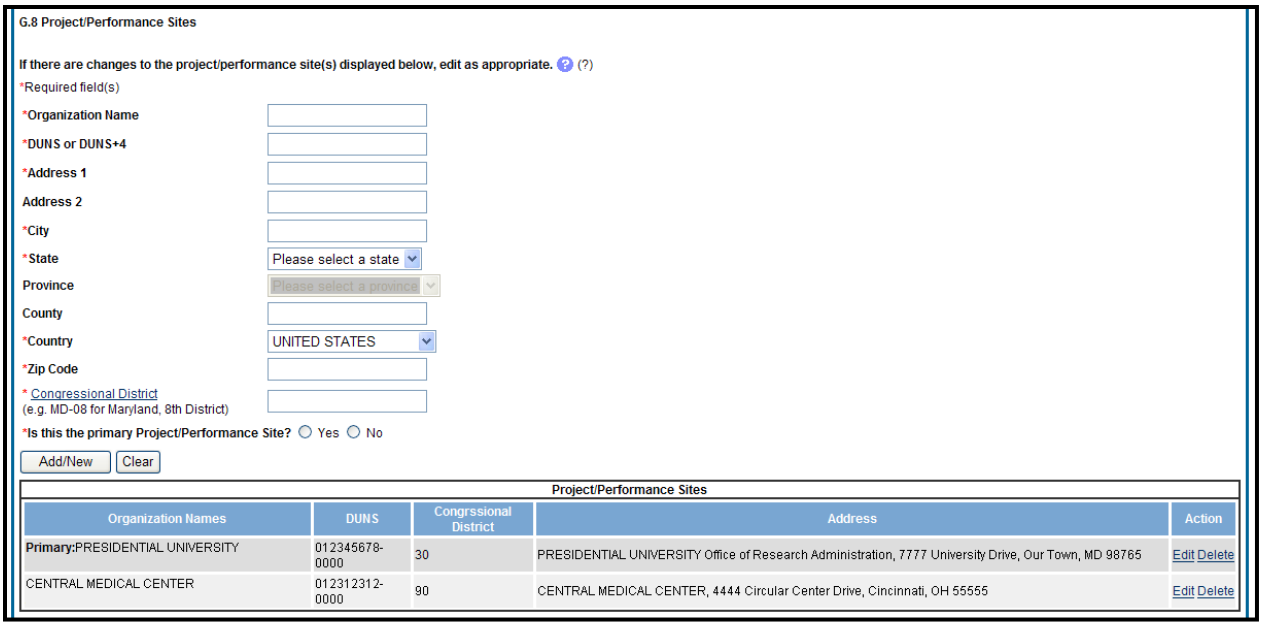


Figure 89: RPPR Section G. Special Reporting Requirements – Question G8

G.9 Foreign component.

Provide the organization name, country, and description of each foreign component.

Foreign component is defined as significant scientific activity that was performed outside of the United States, either by the grantee or by a researcher employed by a foreign organization, whether or not grant funds were expended. The following grant-related activities are significant and must be reported:

- involvement of human subjects or research with live vertebrate animals;
- extensive foreign travel by grantee project staff to collect data, or conduct surveys or sampling activities; or
- any grantee activity that may have an impact on U.S. foreign policy.

Examples of other grant-related activities that *may* be significant are:

- collaborations with investigators at a foreign site anticipated to result in co-authorship;
- use of facilities or instrumentation at a foreign site; or
- receipt of financial support or resources from a foreign entity.

Foreign travel for consultation does not meet the definition of foreign component.

Select the **Add/New** button to add the data to the table.

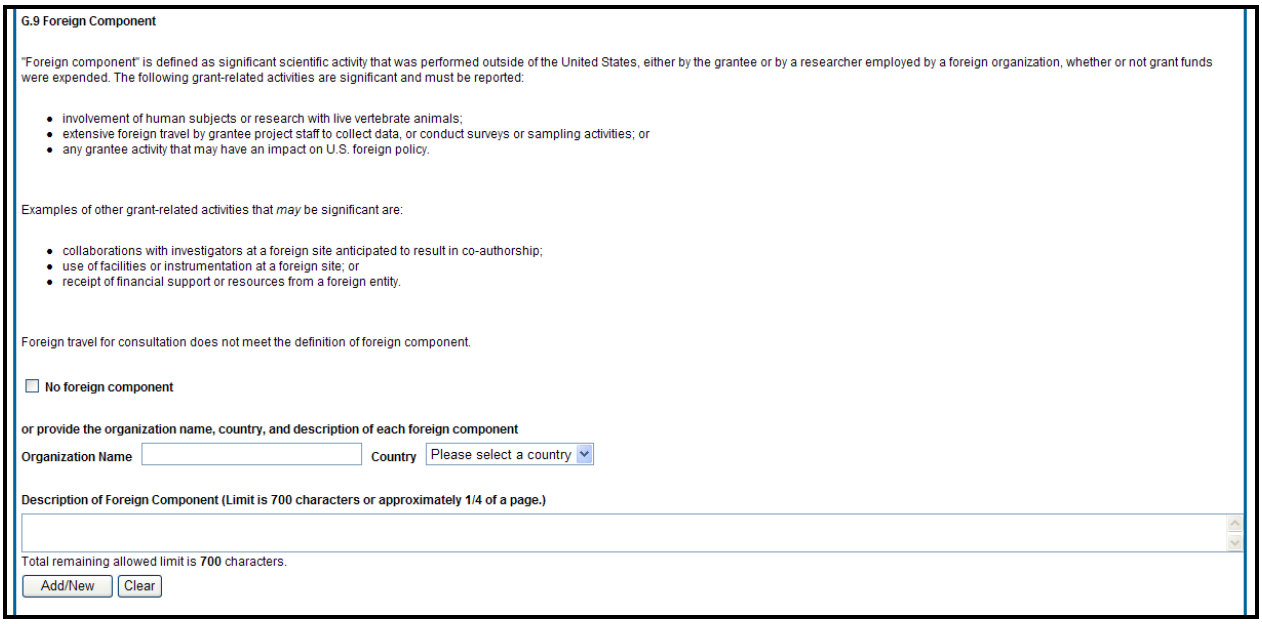


Figure 90: RPPR Section G. Special Reporting Requirements – Question G9

G.10 Estimated unobligated balance.

G.10.a Is it anticipated that an estimated unobligated balance (including prior year carryover) will be greater than 25% of the current year's total approved budget?

The *total approved budget* equals the current fiscal year award authorization plus any approved carryover of funds from a prior year(s). The numerator equals the total amount available for carryover and the denominator equals the current year's total approved budget.

If yes, provide the estimated unobligated balance.

G.10.b Provide an explanation for unobligated balance.

G.10.c If authorized to carryover the balance, provide a general description of how it is anticipated that the funds will be spent. To determine carryover authorization, see the Notice of Award.

Grantees not authorized to carryover unobligated balances automatically must submit a prior approval request to the awarding IC. See instructions in NIH Grants Policy Statement Section 8.1.2.4 Carryover of Unobligated Balances.

G.11 Program Income.

Is program income anticipated during the next budget period?

If yes, provide the amount and source(s).

Program Income is defined as gross income earned by the grantee organization, a consortium participant, or a contractor under the grant that is directly generated by the grant-supported project or activity or earned as a result of the award. Program income includes, but is not limited to, income from fees for services performed; charges for the use or rental of real property, equipment or supplies acquired under the grant; the sale of commodities or items fabricated under an award; charges for research resources; registration fees for grant-supported conferences,

and license fees and royalties on patents and copyrights. Program income from license fees and royalties from copyrighted material, patents, and inventions is exempt from reporting requirements unless otherwise specified in the terms and conditions of award.

Select the **Add/New** button to add the data to the table.

G.12 F&A Costs [applicable to SNAP awards only]

Is there a change in performance sites that will affect F&A costs?

If yes, provide an explanation.

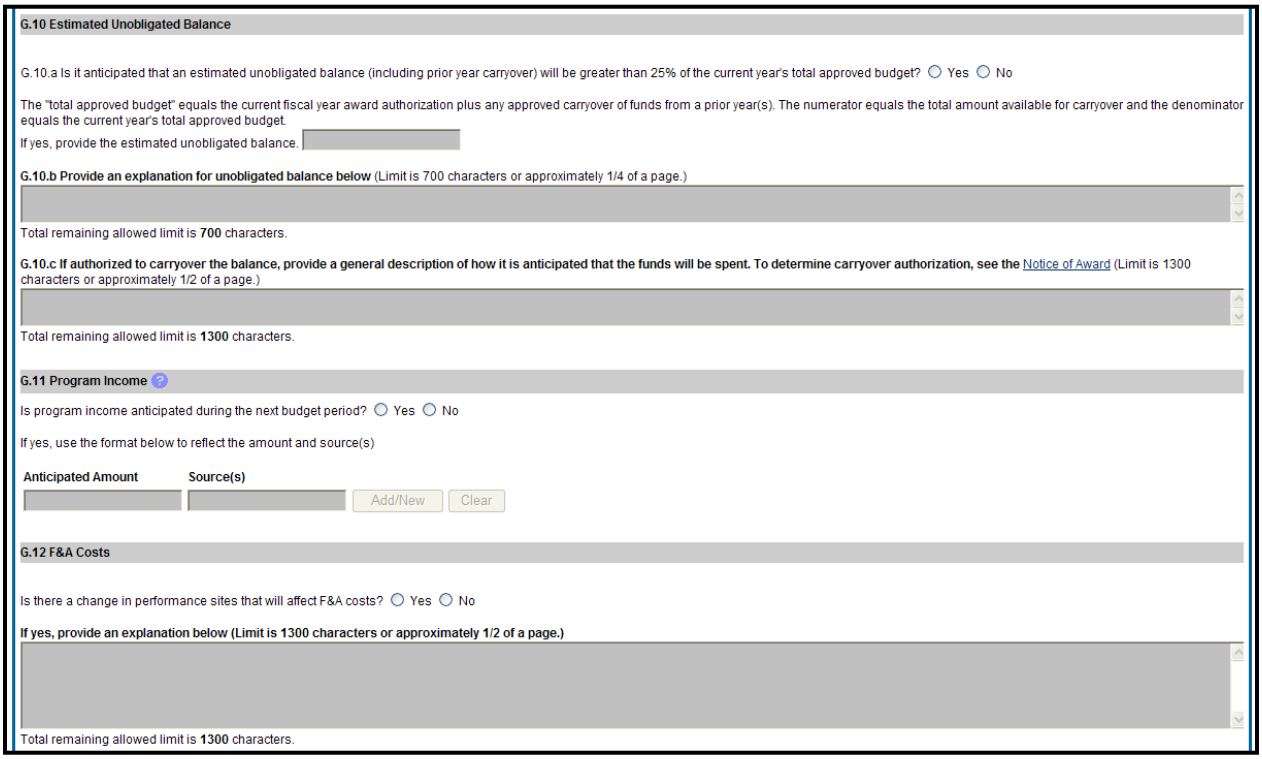


Figure 91: RPPR Section G. Special Reporting Requirements – Questions G10 through G12

6.8 Section H – Budget [Applicable to non-SNAP awards only]

H.1 Budget Form

To complete the detailed budget for this award select the SF424 Research and Related Budget from the drop down menu and follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Form, to complete the R&R budget, sections A-K, and the R&R Cumulative Budget, for the remainder of the project period. The budget justification should be uploaded as item K and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).

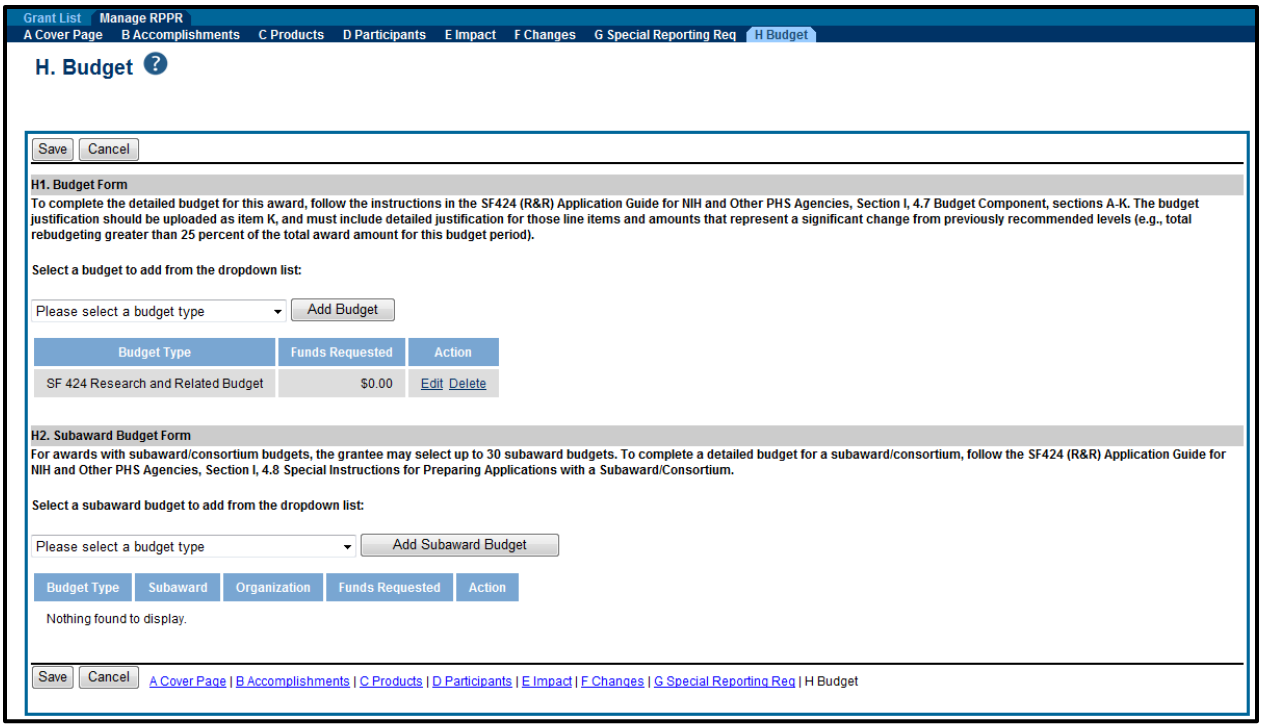


Figure 92: Section H.Budget of RPPR for a Non-SNAP Award

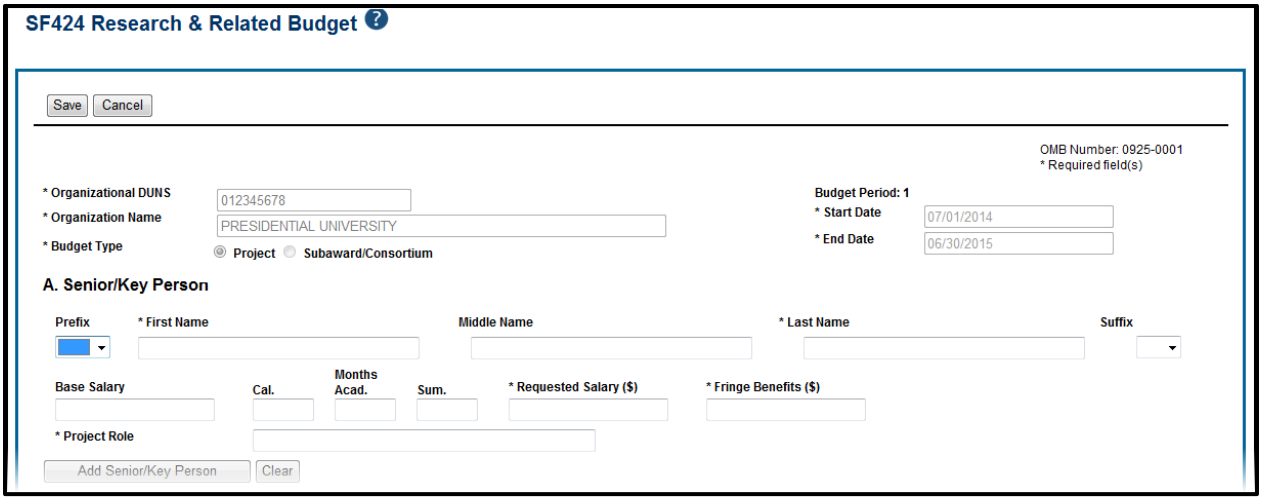


Figure 93: SF 424 Research & Related Budget Form Opened for Editing

NOTE: If subaward budgets are completed, the system will not calculate the budget line item F.5 for the main budget (see figure below). Total consortium costs for the main budget **MUST** be computed and entered manually into budget line item F.5.

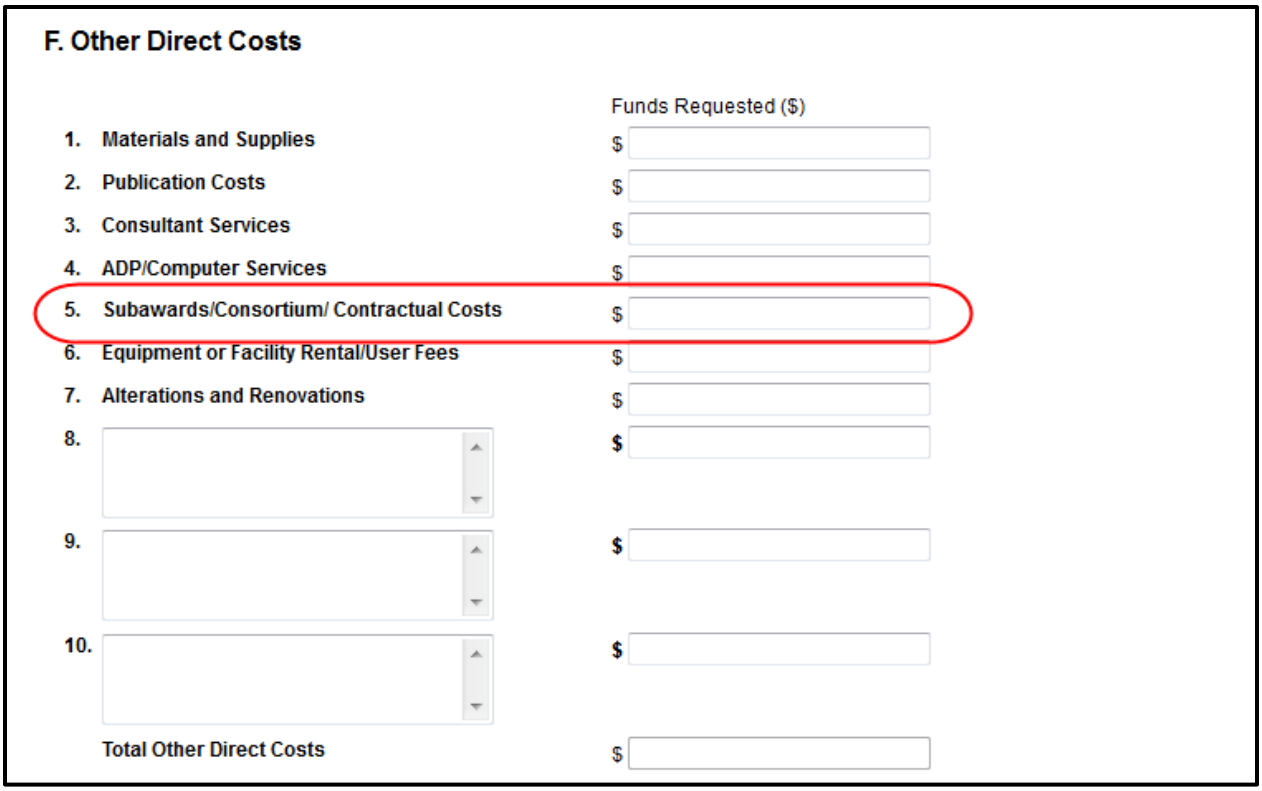


Figure 94: SF 424 R&R Budget Form - Question F.5

H.2 Subaward Budget Form

For awards with subaward/consortium budgets, select the SF424 Research and Related Budget Subaward Budget from the drop down menu and follow the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.8 Special Instructions for Preparing Applications with a Subaward/Consortium.

7 Supplemental Instructions for Specific Grant RPPR Types

The *RPPR Instructions* in chapter 6, Sections A–H, apply to the following awards: D71, DP1, DP5, G08, G11, G13, P40, R00, R01, R03, R18, R21, R33, R34, R36, R37, R56, RC1, RC2, RL1, S21, S22, SC1, SC2, SC3, U1B, UC2, UH1, UH2, UH3, **and** awards listed in Section 7.6 if they issued under SNAP. For all other awards, see Table 1 below and applicable supplemental instructions for specific grant award types that either replace or are in addition to the *Instructions for RPPR Sections A–H*.

Table 1: Applicable Supplemental Instructions

Applicable Supplemental Instructions	Award Activity Codes
7.1 Individual Career Development (K) Awards	K01, K02, K05, K06, K07, K08, K18, K22, K23, K24, K25, K26, K99, KL1
7.2 Fellowship Awards	F05, F30, F31, F32, F33
7.3 SBIR/STTR Awards	R41, R42, R43, R44, U43, U44, UT1, UT2
7.4 Training Awards	K12, KL2, R90, RL9, T15, T32, T34, T35, T37, T90, TL1
7.5 Educational Awards	D43, DP7, K30, R13, R25, RL5, T14, T36, U13, U2R
7.6 Multi-Project Awards and Single-Project Awards with Complicated Structure	G12, R34, M01, P01, P20, P2C, P30, P41, P42, P50, P51, P60, PL1, PM1, PN1, PN2, R24, R28, RM1, S06, S11, U01, U10, U19, U24, U2C, U34, U41, U42, U45, U54, U56, UC7, UL1, UM1, UM2

7.1 Individual Career Development (K) RPPRs

For Career Development Awards (i.e., K01, K02, K05, K06, K07, K08, K18, K22, K23, K24, K25, K26, K99, and KL1) follow the *Instructions for RPPR Sections A–H* in chapter 6, with the exceptions noted below:

B.4 What opportunities for training and professional development has the project provided?

Describe activities such as teaching, clinical care, professional consultation, service on advisory groups, and administrative activities. Indicate percent of time spent in each of these activities and the relationship to the awardee's research career development. For awards that include a requirement to mentor others (e.g., K05 and K24), indicate the percent of time devoted to mentoring activities, individuals mentored during the reporting period, the frequency and kinds

of mentoring, financial and other support provided to mentees, and the productivity of the mentoring relationship.

B. 6. What do you plan to do for the next reporting period to accomplish the goals?

Provide a timeline for the activities planned for the next year, including plans to apply for subsequent grant support. Recipients of transition awards (e.g., K22, K99) should report on progress in identifying an independent research position. Additionally, awardees charged with mentoring others (e.g., K05, K24) should provide information describing planned mentoring activities and proposed mentees (e.g., backgrounds, interests, professional levels, etc.) sufficient to evaluate the quality of the mentoring.

C.2. Not Applicable.

C.3. Not Applicable.

D.2.e Not Applicable.

E.1 Not Applicable.

E.2 Not Applicable.

E.3 Not Applicable.

F.1 Not Applicable.

G.2 Responsible Conduct of Research

Describe the responsible conduct of research instruction received (or instruction given as a course director, discussion leader, etc., in the case of senior fellows or senior career awardees) by formal and/or informal means, during this reporting period. If instruction or participation as a course director/discussion leader occurred in a prior budget period, note the dates of occurrence. Any activities undertaken to individualize instruction appropriate to career stage should be discussed. Address the five components: Format, Subject Matter, Faculty Participation, Duration, and Frequency. Additional detailed guidance on this requirement is found in the competing application instructions.

G.3 Mentor's Report

For mentored K awards, provide a letter signed by the mentor, in PDF format, assessing the awardee's progress and performance during this reporting period, both in research and in terms of development into an independent investigator in the area of the award. Include information on the availability of support for the candidate's research project during the next budget segment. For applicable career transition awards (e.g., K22, K99), the mentor should describe the awardee's efforts to transition into a permanent research position and the sponsor's contributions to that process. If required to submit letters from more than one mentor, letters should be assembled in one PDF file. For non-mentored K awards, select "Not Applicable."

G.11 Not Applicable.

G.12 Not Applicable.

H. Budget. [Applicable to non-SNAP awards only.]

H.1 Budget Form

Follow the instructions for SF 424 (R&R) for K awards in SF424 Part I, Section 7.4.6. Base the awardee's salary and fringe benefits request on a full-time, 12-month appointment following the guidelines in the appropriate career award instructions. Support for other personnel and amounts in other budget categories may be requested in accordance with applicable CDA guidelines.

NOTE: If subaward budgets are completed, the system will not calculate the budget line item F.5 for the main budget (see figure below). Total consortium costs for the main budget **MUST** be computed and entered manually into budget line item F.5.

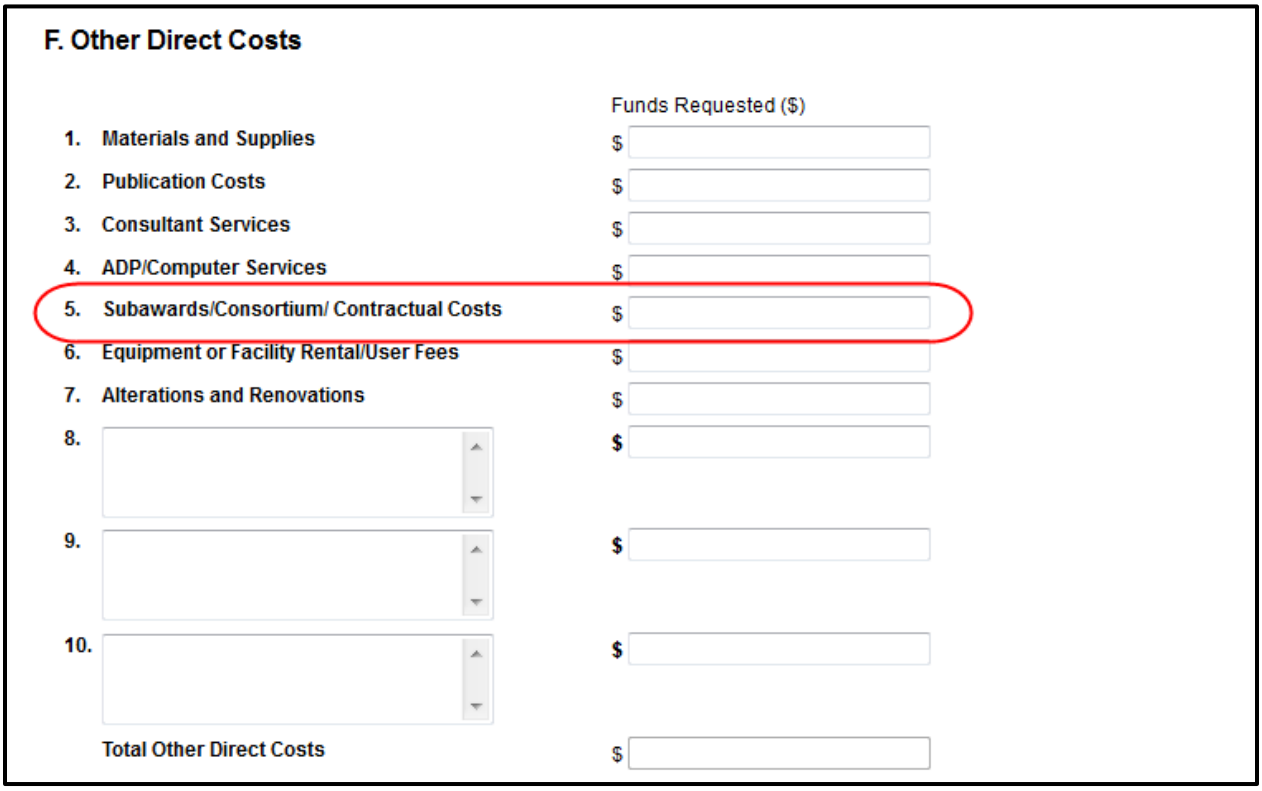


Figure 95: SF 424 R&R Budget Form - Question F.5

H.2 Subaward Budget Form

For awards with subaward/consortium budgets, the grantee may select up to 30 subaward budgets. To complete a detailed budget for a subaward/consortium, follow the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.8 Special Instructions for Preparing Applications with a Subaward/Consortium.

7.2 Fellowship RPPRs

For Fellowship Awards (i.e., F05, F30, F31, F32, and F33), follow the *Instructions for RPPR Sections A–H* in chapter 6, with the exceptions noted below:

B.6 What do you plan to do during the next reporting period to accomplish the goals?

Include any course work and any important modifications to the original plans. Provide a scientific justification for any changes involving research with human subjects or vertebrate animals. A detailed description of such changes must be provided under Changes.

C.2 Not Applicable.

C.3 Not Applicable.

C.4 Not Applicable.

D.1 Not Applicable.

D.2.a Not Applicable

D.2.b Not Applicable.

D.2.e Not Applicable.

E.1 Not Applicable.

E.2 Not Applicable.

E.3 Not Applicable.

F.1 Not Applicable.

G.2 Responsible Conduct of Research

Describe the responsible conduct of research instruction received (or instruction given as a course director, discussion leader, etc., in the case of senior fellows or senior career awardees) by formal and/or informal means, during this reporting period. If instruction or participation as a course director/discussion leader occurred in a prior budget period, note the dates of occurrence. Any activities undertaken to individualize instruction appropriate to career stage should be discussed. Address the five components: Format, Subject Matter, Faculty Participation, Duration, and Frequency. Additional detailed guidance on this requirement is found in the competing application instructions.

G.3 Sponsor Comments

Provide a letter signed by the sponsor, in PDF format, assessing the quality of the research training (including academic work) and research progress made by the Fellow during this reporting period.

G. 10 Not Applicable.

G.11 Not Applicable.

G.12 Not Applicable.

H. Not Applicable.

7.3 SBIR/STTR RPPRs

For SBIR/STTR Awards (i.e., R41, R42, R43, R44, U43, U44, UT1, and UT2), follow the *Instructions for RPPR Sections A–H* in chapter 6, with the exceptions noted below:

B.2 What was accomplished under these goals?

Goals is equivalent to *specific aims and/or milestones*.

B.3 Competitive Revisions/Administrative Supplements

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

If yes, identify the Revision(s) by grant number (e.g., 3R01CA098765-01S1) or title and describe the specific aims and/or milestones for each Revision. Include any supplements to promote or enhance diversity and re-entry, or other similar supplements to support addition of an individual or a discrete project.

B.6 What do you plan to do during the next reporting period to accomplish the goals?

For FastTrack and Phase II progress reports include a one-page abstract describing the research plan for Phase II and, as necessary, an updated commercialization plan.

C.5.a Other products

For SBIR/STTR awards commercial technologies will be addressed under Impact.

E.1 Not Applicable.

E.3 What is the impact on technology transfer?

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- transfer of results to entities in government or industry;
- instances where the research has led to the initiation of a start-up company; or
- adoption of new practices.

E.3.a Commercialization Activities.

Report on the status of commercialization activities resulting from the award:

- ☐ Nothing to report or select one or more of the following:
- ☐ Sales = $_____
- ☐ Licensing revenue = $_____
- ☐ 3rd Party investment since award start (Non-federal) = $_____
- ☐ Sale of company
- ☐ Sale of technology rights
- ☐ Company merger related to product
- ☐ Joint venture agreement
- ☐ Marketing/Distribution agreement(s)
- ☐ Manufacturing agreement(s)
- ☐ R&D agreements

- ☐ Customer alliance(s)
- ☐ Other _____ [60 character limit]

E.3.b FDA Interactions.

Report on interactions with the Food and Drug Administration during the reporting period related to the technology that is the subject of the award:

- ☐ Not applicable to this technology or select one or more of the following:
- ☐ Discussion with FDA not initiated
- ☐ Discussion with the FDA initiated
    - o Approval in Progress
        - ▪ Applied for approval
        - ▪ Review ongoing
        - ▪ In human clinical trials
        - ▪ Other_____
    - o Approval Granted: Type _____
    - o Not approved

F.1 Not Applicable.

G.2 Not Applicable.

G.3 Not Applicable.

G.12 F & A Costs. [Applicable to SNAP awards only.]

H. Budget [Applicable to non-SNAP awards only.]

H.1 Budget Form

To complete the detailed budget for this award, follow the instructions in the SF424 (R&R) SBIR/STTR Application Guide for NIH and Other PHS Agencies, Section I, 4.6 Budget Component, sections A-K. The budget justification should be uploaded as item K, and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).

NOTE: If subaward budgets are completed, the system will not calculate the budget line item F.5 for the main budget (see figure below). Total consortium costs for the main budget **MUST** be computed and entered manually into budget line item F.5.

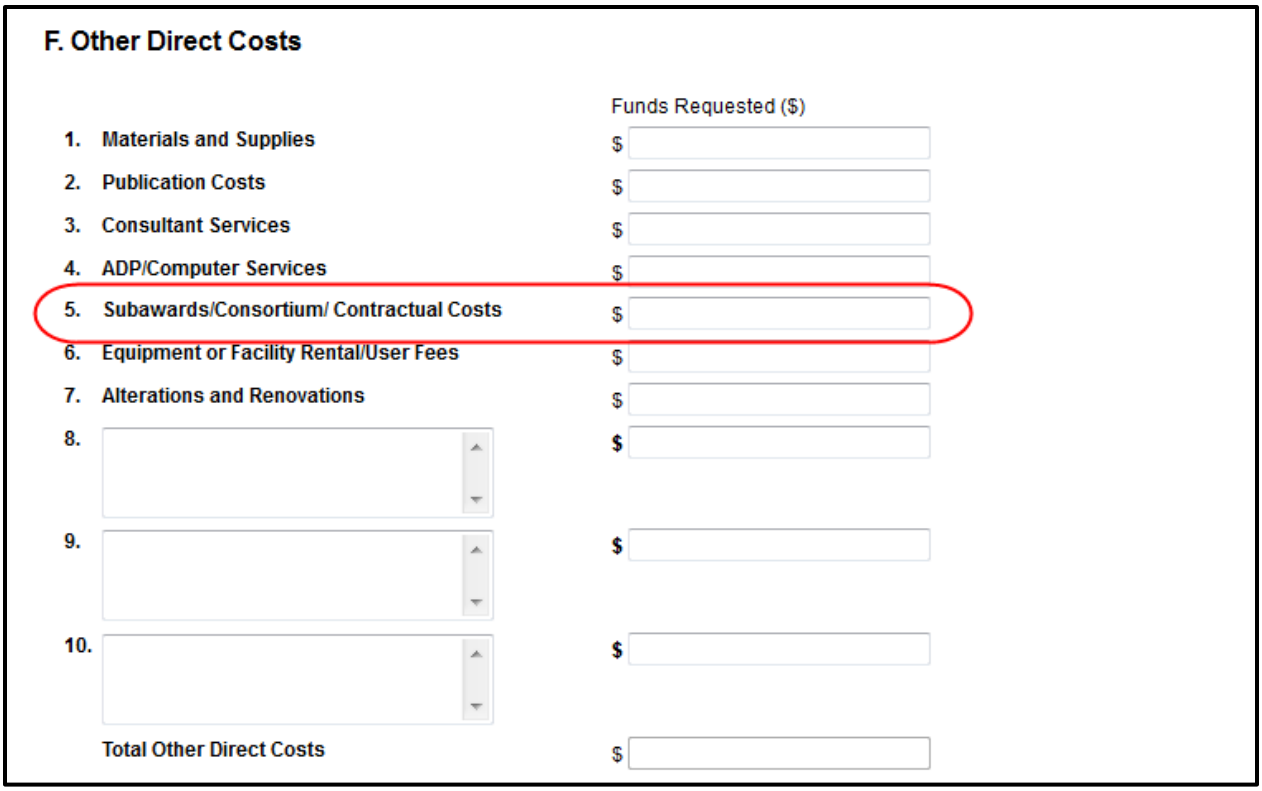


Figure 96: SF 424 R&R Budget Form - Question F.5

H.2 Subaward Budget Form

For awards with subaward/consortium budgets, the grantee may select up to 30 subaward budgets. To complete a detailed budget for a subaward/consortium, follow the SF424 (R&R) SBIR/STTR Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component.

7.4 Training RPPRs

For Training Awards (i.e., K12, KL2, R90, RL9, T15, T32, T34, T35, T37, T90, and TL1) and multi-year funded training awards (i.e., KM1) follow the *Instructions for RPPR Sections A–H* in chapter 6, with the exceptions noted below:

B.1. What are the major goals of the project?

Provide a description of the training objectives and goals. List the major goals of the project as stated in the approved application or as approved by the agency. If the application lists milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

B.2 What was accomplished under these goals?

Since the last report or application, describe implementation of training and other specific programmatic objectives, and the recruitment and retention of trainees from diverse groups.

B.4 What opportunities for training and professional development has the project provided?

For all awards provide a PDF that includes the following items: (1) completed Trainee Diversity Report format page to report on the diversity of the trainees supported by the award during the reporting period (generally not applicable for FIC awards); (2) a paragraph for each trainee/scholar supported by the award in the reporting period that identifies mentor, research project, and course work of each trainee/scholar. Include conference presentations, honors, fellowships, workshops and related activities. This description should be sufficient to allow evaluation of the trainees' progress towards the goals of the training grant.

For T awards, include updated data on trainees supported by the training grant in Table 12A and/or 12B, from the competing application instructions as applicable, to reflect trainees supported by the grant in the reporting period.

For D43, TU2, T15, T32, T37, T90, U2R, U90, and TL1 awards, include program statistics for doctoral training in Table 12A.

The Trainee Diversity Report format page is available at: http://grants.nih.gov/grants/funding/2590/2590.htm.

B.6 What do you plan to do during the next reporting period to accomplish the goals?

Include plans for any modification based on the findings of your internal evaluations.

C.1 Publications

It will be necessary for the Program Director to add trainee publications to his/her MyBib. They may be placed in the section entitled **Other Publications**.

C.2 Not Applicable.

C.3 Not Applicable.

C.4 Not Applicable.

C.5.b Not Applicable.

D.1 What individuals have worked on the project?

Provide or update the following information only for K12 and KL2 progress reports: (1) program director(s)/principal investigators(s) (PDs/PIs); and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours or 8.3% of annualized effort). Do not report personnel for whom a PHS 2271 Appointment form has been submitted through xTRAIN. If not reporting on a K12 or KL2 award, disregard this section.

D.2.b New senior/key personnel.

Are there new training faculty?

If yes, provide biosketches and other support for all new training faculty.

E.1 Not Applicable.

E.2 Not Applicable.

E.3 Not Applicable.

F. 1 Changes in approach and reasons for change

Describe changes in the program for the next budget period, including changes in training faculty. Include, as appropriate, the role of external advisory committees, significant new training content, procedures or experiences, and indicate how these aid in strengthening and realizing the objectives and goals of the program.

F.2 Not Applicable.

F.3 Significant changes to Human Subjects, Vertebrate Animals, Biohazards, and/or Select Agents

Complete this section only if the use or care of human subjects, vertebrate animals, biohazards and/or select agents is not reported under another NIH award.

G.2 Responsible Conduct of Research

Describe the nature of the responsible conduct of research instruction and the extent of trainee (or scholar, in the case of the Institutional Career Development Programs) and faculty participation. Include a description of any enhancements and/or modifications to the five instructional components (Format, Subject Matter, Faculty Participation, Duration, and Frequency) from the plan described in the competing application. Faculty members who were contributors to formal instruction in responsible conduct of research during the last budget period must be named. Additional detailed guidance on this requirement is found in the competing application instructions.

G.3 Not Applicable

G.6 Human Embryonic Stem Cells (hESCs)

Complete this section only if the use of hESCs is not reported under another NIH award.

G.11 Not Applicable.

G.12 Not Applicable.

H. Budget

For training awards, grantees should select the applicable RPPR budget type (e.g., SF424 (R&R) or PHS 398 Training Budget) from the drop down menu. For a small number of NIH training programs the grantee is required to submit both the SF424 (R&R) and PHS 398 Training Budget; the RPPR will accommodate this.

H.1 Budget Form

If completing the SF424 (R&R), follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 R&R Budget Component, sections A-K. The budget justification should be uploaded as item K, and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).

If completing the PHS 398 Training Budget, follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 8.5 PHS 398 Training Budget Component, items A-F. The budget justification should be uploaded as item F, and must include detailed justification for those line items and amounts that represent a significant change from

previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).

NOTE: If subaward budgets are completed, the system will not calculate the budget line item F.5 for the main budget (see figure below). Total consortium costs for the main budget **MUST** be computed and entered manually into budget line item F.5.

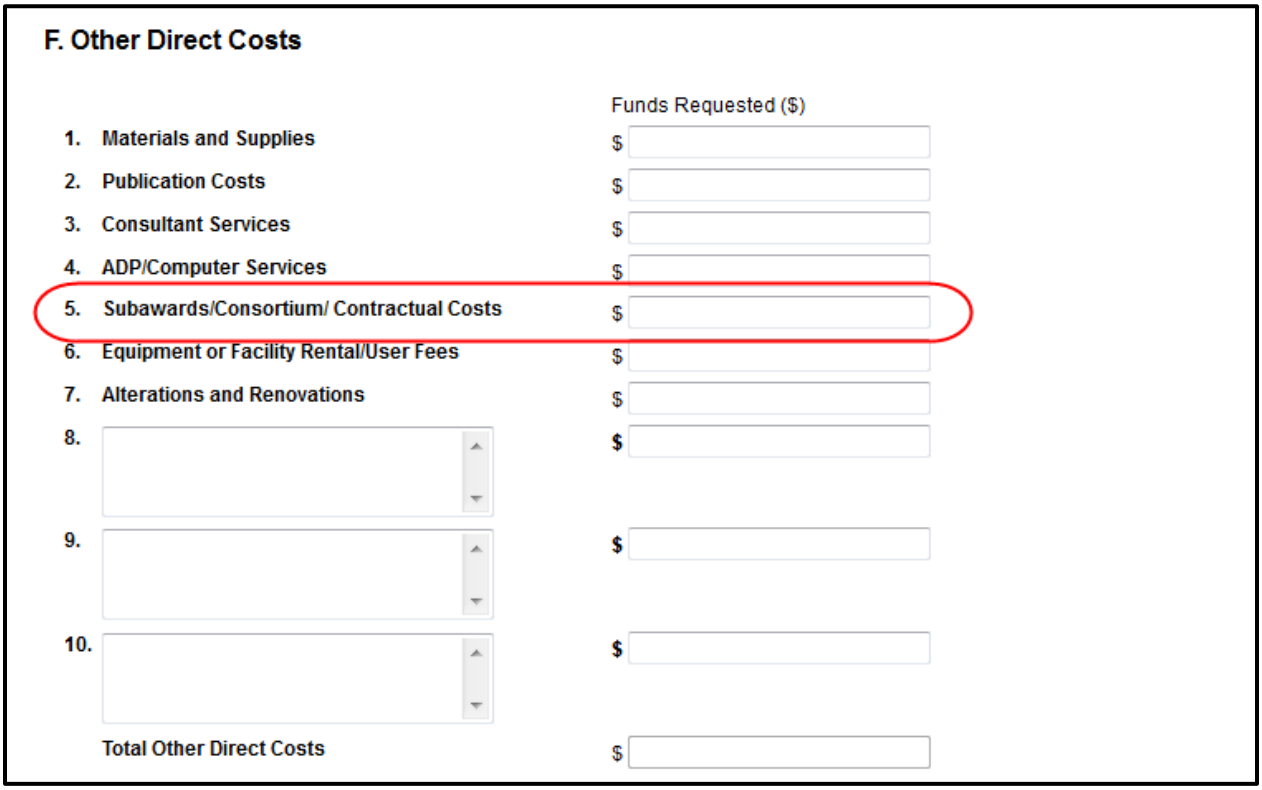


Figure 97: SF 424 R&R Budget Form - Question F.5

H.2 Subaward Budget Form

For awards with subaward/consortium budgets, the grantee may select up to 30 subaward budgets. To complete a detailed budget for a subaward/consortium, follow the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.8 Special Instructions for Preparing Applications with a Subaward/Consortium or 8.6 PHS 398 Training Subaward Budget Attachment(s) Form.

7.5 Education RPPRs

For Education Awards (i.e., D43, DP7, K30, R13, R25, RL5, T14, T36, U13, and U2R), follow the *Instructions for RPPR Sections A–H* in chapter 6, with the exceptions noted below:

B.4 What opportunities for training and professional development has the project provided?

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project.

Training activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. *Professional development* activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities. Grantees with NIH institutional training grant awards with the following specified activity codes are required to provide program statistics for doctoral training in Table 12A: D43, TU2, T15, T32, T37, T90, U2R, U90, and U54/TL1.

For T, F, K, R25, R13, D43 and other awards or award components designed to provide training and professional development opportunities, a response is required. Do not reiterate what is reported under Accomplishments. Limit the response to this reporting period.

C.3. Not Applicable.

C.4 Not Applicable.

C.5.b Not Applicable.

E.1 What is the impact on the development of human resources?

Describe how the project made an impact or is likely to make an impact on human resource development in science, engineering, and technology. For example, how has the project: 1) provided opportunities for research and teaching in the relevant fields; 2) improved the performance, skills, or attitudes of members of underrepresented groups that will improve their access to or retention in research, teaching, or other related professions; 3) developed and disseminated new educational materials or provided scholarships; or 4) provided exposure to science and technology for practitioners, teachers, young people, or other members of the public?

E.2 Not Applicable.

E.3 Not Applicable

F.1 Changes in approach and reasons for change

Describe changes for the next budget period. Include, as appropriate, the role of external advisory committees, significant new content, procedures or experiences, and indicate how these aid in strengthening and realizing the objectives and goals of the award.

G.2 Responsible Conduct of Research

If required in the FOA for this award, describe the nature of the responsible conduct of research instruction and the extent of participant and faculty involvement. Include a description of any enhancements and/or modifications to the five instructional components (Format, Subject Matter, Faculty Participation, Duration, and Frequency) from the plan described in the competing application. Faculty members who were contributors to formal instruction in responsible conduct of research during the last budget period must be named. Additional detailed guidance on this requirement is found in the competing application instructions.

G.3 Not Applicable.

G.12 F&A Costs [Applicable to SNAP awards only.]

7.6 Multi-Project RPPRs and Single-Project RPPRs with Complicated Structure

For the purposes of the RPPR, the following activity codes are always categorized as multi-project awards or single-project awards with complicated structures: G12, M01, P01, P20, P2C. P30, P41, P42, P50, P51, P60, PL1, PM1, PN1, PN2, R24, R28, RM1, S06, S11, U01, U10, U19, U24, U2C, U34, U41, U42, U45, U54, U56, UC7, UL1, UM1, and UM2. These activity codes awards may or may not include multiple components (projects, cores), but they all could potentially include multiple components. For multi-project awards, the grantee will follow the instructions for the overall portion of the RPPR below and for *each* component of the RPPR the grantee will follow the instructions under component instructions in section 7.6.2.

The *Instructions for RPPR Sections A–H* in chapter 6, are applicable to these activity codes (even if the award does not include multiple components) with the following exceptions.

7.6.1 Overall

B.1 What are the major goals of the project?

Emphasize the synergy, collaboration and integration of major activities of the project. Report the major goals specific to an individual component under that component.

B.2 What was accomplished under these goals?

For this reporting period describe for the overall award: 1) major activities; 2) significant results, including major findings, developments, or conclusions (both positive and negative), and 3) key outcomes or other achievements. Include a discussion of stated goals not met. Report the accomplishments of individual projects and cores under that component.

B.3 Is there one or more Revision associated with this award or a project under this award for which reporting is required?

If the Revision is associated with a specific project or core, identify the component.

B.5 How have the results been disseminated to communities of interest?

If there are individual projects/cores designed to disseminate information or conduct outreach activities, report those activities under that component.

B.6 What do you plan to do during the next reporting period to accomplish the goals?

Report goals and objectives of individual projects or cores under that component.

C.5 a Other products

Identify any other significant products that were developed under the overall project. Report other products and resources resulting from an individual project or core under that component.

C.5.b Resource sharing

Report resource sharing for an individual project or core under that component.

D.1 Participants

In addition to the instructions in *Section 6.4*, specify the component(s) on which the individual worked in the appropriate text box. This personnel information is for the entire project.

NOTE: If an individual is associated with multiple components, some components may be hidden to reduce the size table. Where applicable, use the **show more** link to display all of an individual's components in the row. Use the **show less** link to collapse the information.

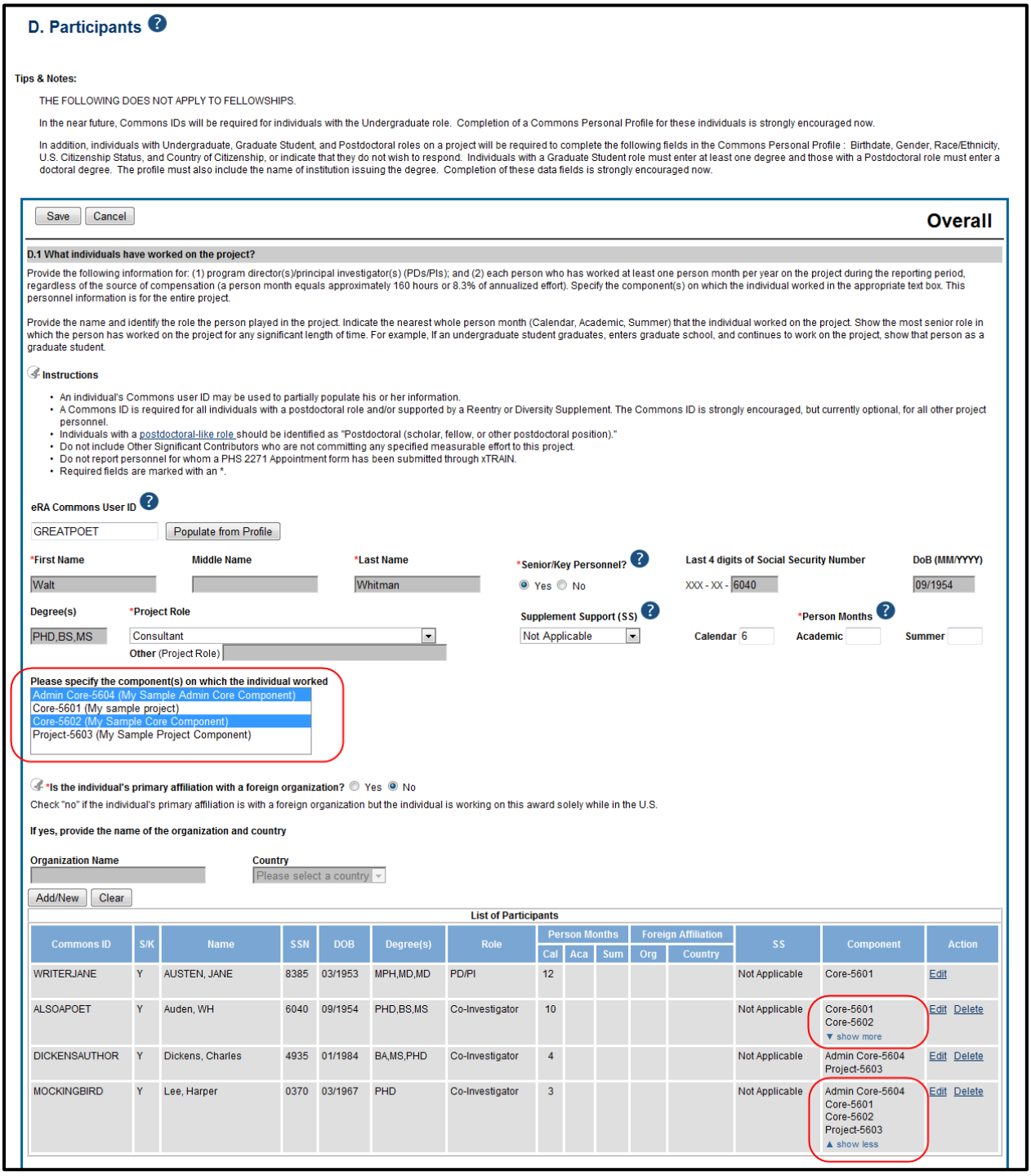


Figure 98: D.1 Specifying the Components for an Added Individual

D.2 Personnel Updates

Personnel questions (D.2.a.-e.) are applicable to entire project. For D.2.b, new senior/key personnel, identify the component(s) on which the individuals worked or will work. For D.2.e, new other significant contributors, identify the component(s) on which the individual worked or will work.

E.1 Not Applicable.

E.3 Not Applicable.

F.1 Not Applicable.

F.3 Significant changes to Human Subjects, Vertebrate Animals, Biohazards, and/or Select Agents.

If there are changes in any of the following areas check the appropriate box and provide a d3escription of the changes. If applicable, report the change under the relevant component.

G.2 Not Applicable.

G.3 Not Applicable.

G.4.c ClinicalTrials.gov

Associate the number with the relevant project or core, if applicable.

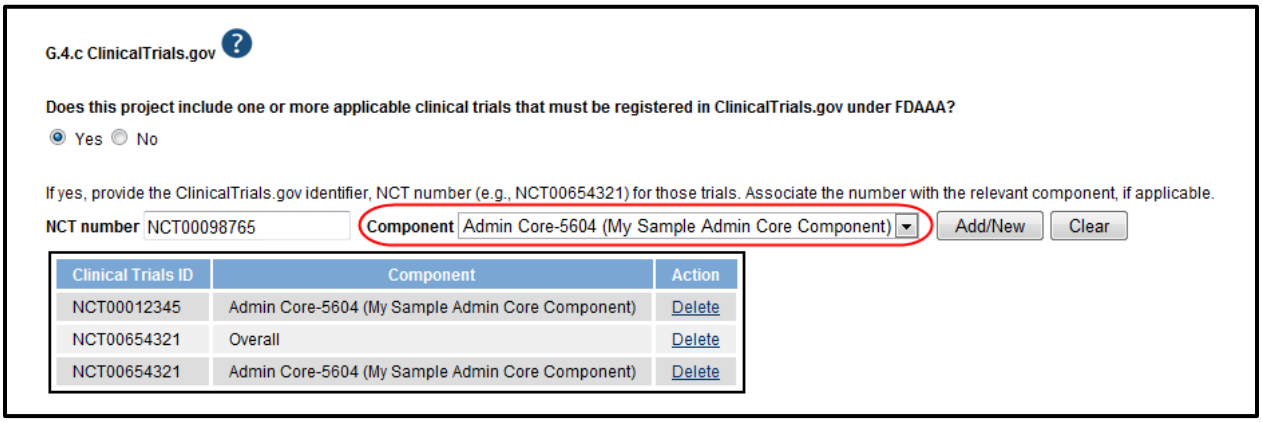


Figure 99: Associating a Component with the NCT Number

G.12 F&A Costs [Applicable to SNAP awards only.]

H. Budget

For multi-project RPPRs complete the budget for each component and for each subaward; see Section 7.6.1. A summary budget will be system-generated based on the budgets completed for the components and will be included in the final .pdf submitted to the Agency. The composite budget summaries will reflect the direct costs for the grantee. Although the direct and indirect costs for subawards are direct costs to the grantee institutions, these costs will be listed as a separate line item, called "consortium" and will include all consortium costs. The total consortium costs for the summary budget are automatically calculated by the system and reflect the sum of the consortium costs (budget line item F.5 of the project budget) for the project budgets with the grantee institution DUNS and the total direct and indirect costs (budget line item I.) for project budgets with a DUNS different from that of the grantee institution.

H.1 Budget Form [Single-Project RPPRs with Complicated Structure only]

For Single-Project RPPRs with Complicated Structure , follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component, sections A-K. The budget justification should be uploaded as item K, and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).

NOTE: If subaward budgets are completed, the system will not calculate the budget line item F.5 for the main budget (see figure below). Total consortium costs for the main budget **MUST** be computed and entered manually into budget line item F.5.

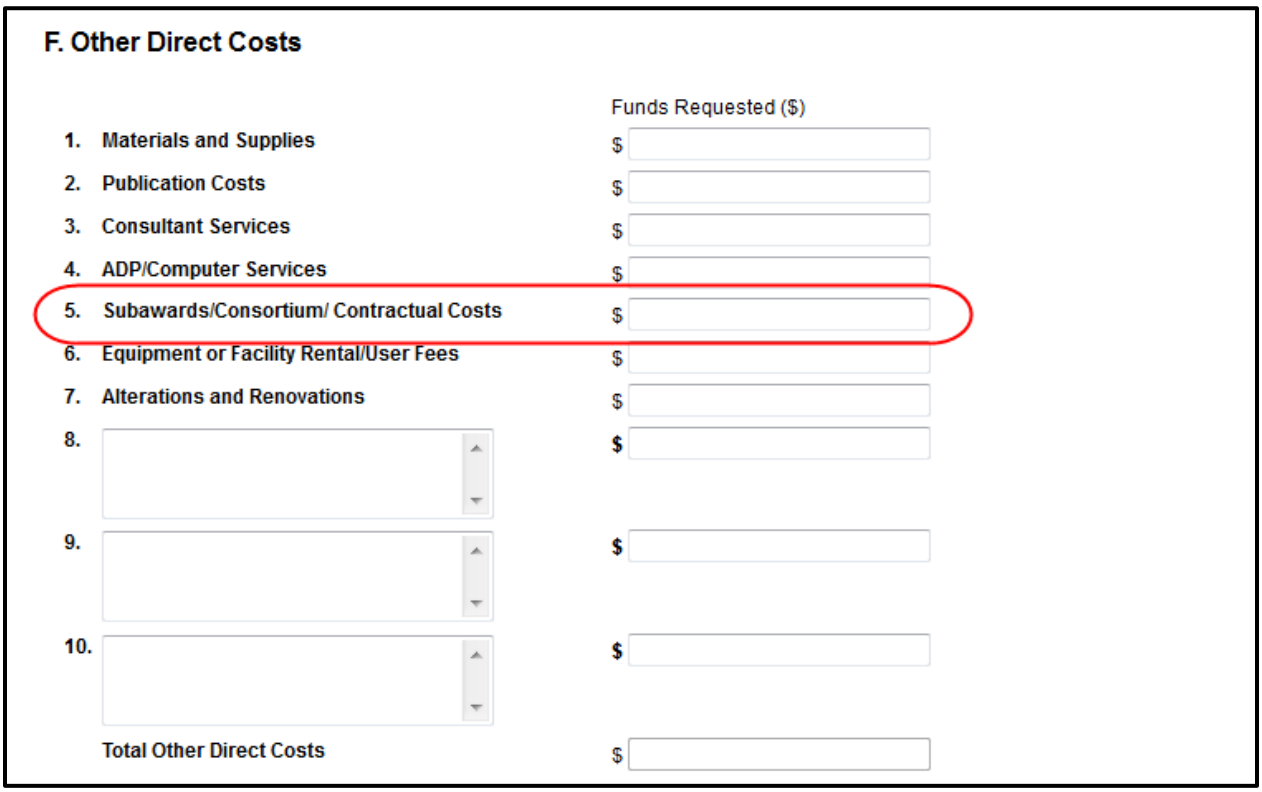


Figure 100: SF 424 R&R Budget Form - Question F.5

H.2 Subaward Budget Form [Single-Project RPPRs with Complicated Structure only]

For awards with subaward/consortium budgets, the grantee may select up to 30 subaward budgets. To complete a detailed budget for a subaward/consortium, follow the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.8 Special Instructions for Preparing Applications with a Subaward/Consortium.

7.6.2 Component Instructions

For *each* component, click the **Add Component** button, and complete the instructions. The *Instructions for RPPR Sections A–H* in chapter 6 are applicable to each individual component with the following exceptions:

A. Provide the title or identifying number of the component.

A.1 Provide the name, email, phone number and address of the PI of the component.

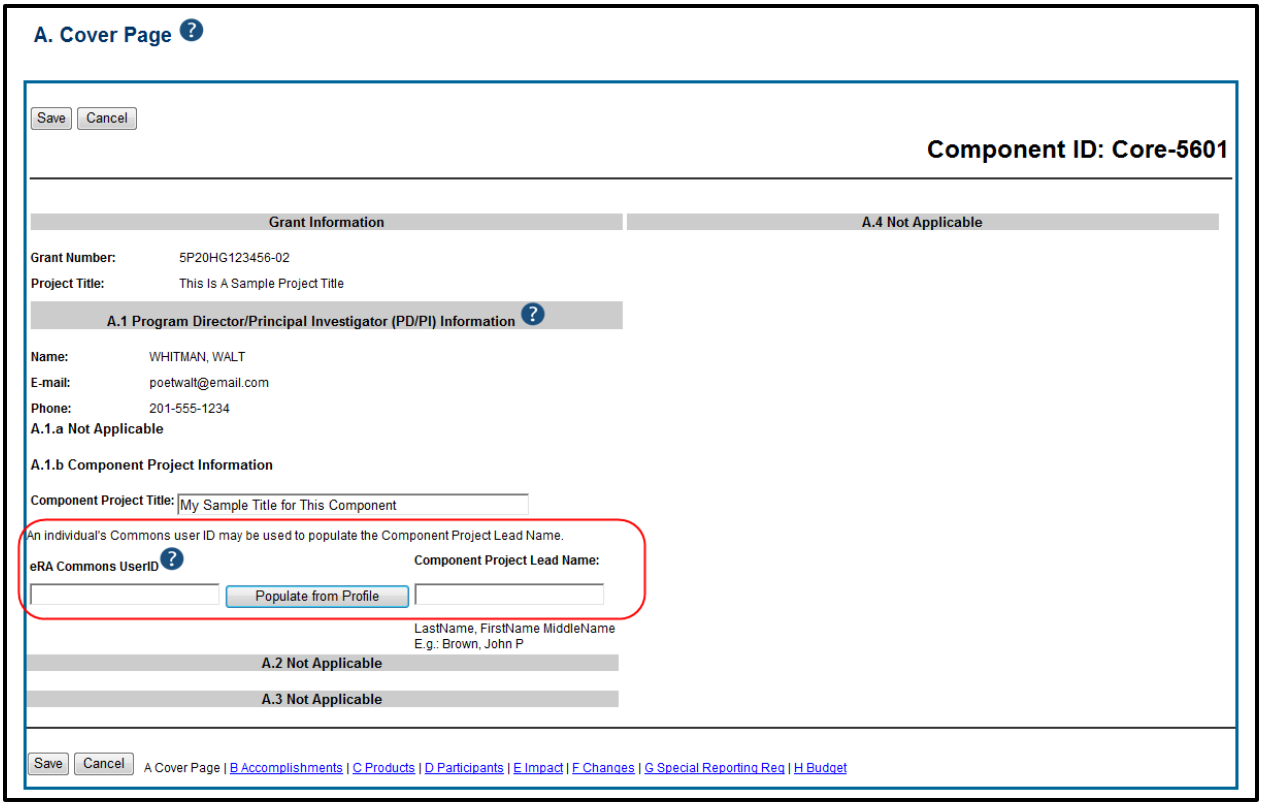


Figure 101: Sample of Section A. Cover Page for a Component

B. 3 Not Applicable.

B.5 How have the results been disseminated to communities of interest?

Reporting the routine dissemination of information (e.g., websites, press releases) is not required. If the Component is not designed to disseminate information to the public or conduct similar outreach activities, select **Nothing to Report**. If the Component is designed to disseminate information or conduct outreach activities, report those activities here. Note that scientific publications and the sharing of research resources will be reported under *Products*.

C.1 Not Applicable.

C.2 Not Applicable.

C.4 Not Applicable.

D. Not Applicable.

E.1 Not Applicable.

E.2 Not Applicable.

E.3 What is the impact on technology transfer?

Describe ways in which the component made an impact, or is likely to make an impact, on commercial technology or public use, including:

- transfer of results to entities in government or industry;
- instances where the research has led to the initiation of a start-up company; or
- adoption of new practices.

E.4 Not Applicable.

F.1 Not Applicable.

G.1 Not Applicable.

G.2 Not Applicable.

G.3 Not Applicable.

G.4.c Not Applicable.

G.5 Not Applicable.

G.7 Not Applicable.

G.8 Not Applicable.

G.9 Not Applicable.

G.10 Not Applicable.

G.11 Not Applicable.

G.12 Not Applicable.

H. Budget

H.1 Budget Form [Multi-Project RPPRs only]

When a grantee institution is the lead on the Component, follow the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component, sections A-K. The budget justification should be uploaded as item K, and must include detailed justification for those line items and amounts that represent a significant change from previously recommended levels (e.g., total rebudgeting greater than 25 percent of the total award amount for this budget period).

When a collaborating institution is the lead on the Component, the information from the collaborating institution should be used to complete the project budget, following the instructions in the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.7 Budget Component, sections A-K.

For multi-projects RPPRs the grantee must complete the DUNS and Organization Name fields, as the DUNS number will not automatically populate to the DUNS number.

NOTE: If subaward budgets are completed, the system will not calculate the budget line item F.5 for the main budget (see figure below). Total consortium costs for the main budget **MUST** be computed and entered manually into budget line item F.5.

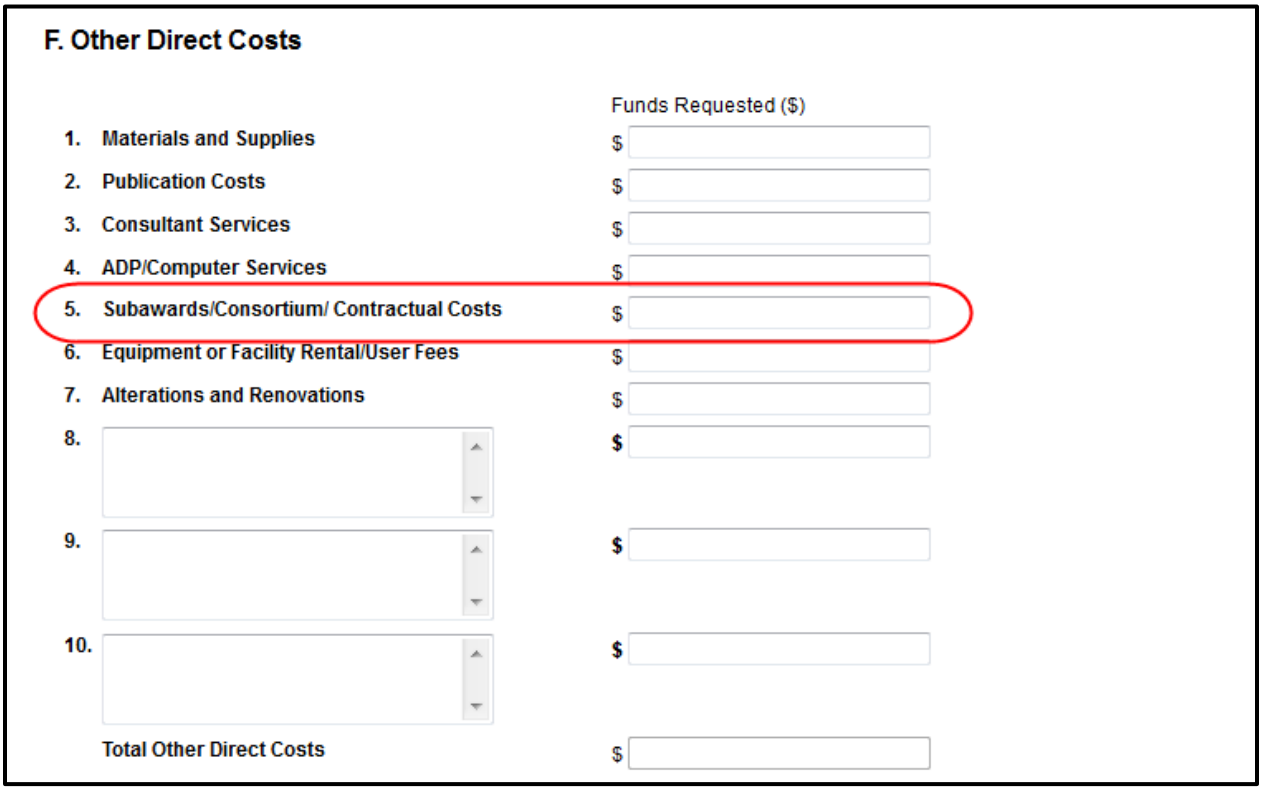


Figure 102: SF 424 R&R Budget Form - Question F.5

H.2 Subaward Budget Form [Multi-Project RPPRs only]

If the component has subaward/consortium budgets, follow the SF424 (R&R) Application Guide for NIH and Other PHS Agencies, Section I, 4.8 Special Instructions for Preparing Applications with a Subaward/Consortium. Describe manual entry of subawards

8 Assurances/Certifications

The list of Assurances, and Certifications, and other Policies that apply to progress reports submitted to NIH and other PHS agencies are explained in Part III: Policies, Assurances, Definitions, and Other Information. Applicants and grantees must comply with a number of additional public policy requirements. Refer to the NIH Grants Policy Statement (http://grants.nih.gov/grants/policy/policy.htm), or the HHS Grants Policy Statement (http://www.hhs.gov/asfr/ogapa/grantinformation/hhsgps107.pdf), as applicable, for additional information.

The policies, assurances and certifications listed in Part III may or may not be applicable to the project, program, or type of applicant organization. If unable to certify compliance, provide an explanation and upload it in G.1 Special Notice of Award and Funding Opportunity Announcement Reporting Requirements.

Submission of the RPPR to the agency includes the following certification:

In submitting this RPPR, the SO (or PD/PI with delegated authority), certifies that the grantee organization is in compliance with the terms and conditions specified in the Notice of Award and Grants Policy Statement, and verifies the accuracy and validity of all administrative, fiscal, and scientific information in the progress report. The SO (or PD/PI with delegated authority) further certifies that the grantee organization will be accountable for the appropriate use of any funds awarded and for the performance of the grant-supported project or activities resulting from the progress report. Deliberate withholding, falsification, or misrepresentation of information could result in administrative actions such as withdrawal of a progress report, suspension and/or termination of an award, debarment of individuals, as well as possible criminal penalties. The grantee institution may be liable for the reimbursement of funds associated with any inappropriate or fraudulent conduct of the project activity.

9 Government Use of Information Under the Privacy Act

Privacy Act Statement. The NIH maintains application and grant records as part of a system of records as defined by the Privacy Act: NIH 09-25-0036, *Extramural Awards and Chartered Advisory Committees (IMPAC 2), Contract Information (DCIS),* and *Cooperative Agreement Information, HHS/NIH*: http://oma.od.nih.gov/ms/privacy/pa-files/0036.htm.

National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK Diabetes Research Centers

Up-Coming RFAs

National Institute of Diabetes and Digestive and Kidney Diseases

Fiscal Year 2017

- **RFA**: Published in NIH Guide- Fall 2015 (electronic applications; ASSIST)
- Application deadline: Early Summer 2016
- Initial Review: Fall 2016
- Earliest Funding: April 2017 (FY2017)
- Renewal Applications:
  - Joslin Diabetes Center
  - University of Pennsylvania
  - Vanderbilt University

National Institute of Diabetes and Digestive and Kidney Diseases

Fiscal Year 2018

- **RFA**: Application deadline: 1st quarter 2017
- Renewal Applications:
  - Columbia University
  - Johns Hopkins University & University of Maryland
  - University of Alabama at Birmingham
  - University of California, San Diego & UCLA
  - University of Chicago
  - University of Michigan
  - University of Washington
  - Washington University in St. Louis
  - Yale University

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute of
Diabetes and Digestive
and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

Submitting Electronic NIH Grant Applications: Annual Progress Reports

National Institute of Diabetes and Digestive and Kidney Diseases

Submitting Electronic Diabetes Research Center (P30) Progress Reports

Starting October 17, 2014, Research Performance Progress Report (RPPR) format is required for P30 grants

NIH RPPR User Guide

- RPPR instructions updated July 18, 2014

http://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf

- Supplemental instructions: 7.6 Multi-Project Awards and Single-Project Awards with Complicated Structure

Terminology

Multi-Project RPPR:

- A progress report submitted for a funded program (activity code) which has multiple, interrelated components that share a common focus or objective.

A "**component**" (for the purposes of applications and progress reports) is a distinct, reviewable part of a multi-project application or progress report for which there is a business need to gather detailed information identified in the funding opportunity announcement (FOA).

- Components typically include general information (component organization, project period, project title, etc.), performance sites, personnel, and budget.

- The FOA defines the construction and naming convention for the application; the funded application defines the construction and naming convention for the progress report.

Multi-Project RPPRs

- Multi-Project RPPRs
  - The RPPR will include all activity codes that have been coded to have multiple components.
  - Multi-project (e.g., P01, P30)
    - Projects with more than one component
- RPPR structure
  - RPPR questions at overall project level
  - RPPR questions at the component level
    - Questions not applicable to component
      - E.g., Publications, Websites, Inventions, Participants, Inclusion/Enrollment, Unobligated Balance

Public Access Policy

- NIH will delay processing Type 5s that are not compliant with the public access policy.
- Bringing papers into compliance:
  - Use My NCBI's My Bibliography
  - Process may take several weeks
- PD/PIs must collaborate with project leads and supported authors to ensure all papers are in My Bibliography and thus linked to the RPPR.
- For additional resources: see http://publicaccess.nih.gov/index.htm

Public Access Policy (cont'd)

- Compliance indicated in RPPR Section C.1 or the PHS 2590 PDF report generated by My NCBI
- Notifications of Public Access non-compliance
  - Automatically sent to grantees for RPPRs
  - Manually sent to grantees for PHS 2590s
- Awardees must provide evidence of compliance with the public access policy to receive an award
- Additional resources available at http://publicaccess.nih.gov/
- Direct questions to PublicAccess@NIH.gov.

RPPR Resources

- RPPR Webpage: http://grants.nih.gov/grants/rppr/
  - RPPR Instruction Guide, archived training materials (including webinars), FAQs (http://grants.nih.gov/grants/rppr/faqs.htm)
- eRA Help Desk: http://era.nih.gov/help/index.cfm#era

RPPR (FY2015)

- Jim has developed an RPPR ‘template’ for P30 grants as a starting point, and he will send this to all Diabetes Research Center PIs.
    - Please share with appropriate administrative assistants
- This template will be updated as questions arise, and as the RPPR instructions are updated.

National Institute of
Diabetes and Digestive
and Kidney Diseases

National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK Diabetes Research Centers Website Update

National Institute of Diabetes and Digestive and Kidney Diseases

What's New

- Upcoming Symposia & Meetings
- Bionic pancreas outperforms insulin pump in adults, youth
- CDC: More than 29 million Americans have diabetes; 1 in 4 doesn't know
- NIDDK Research Update: Inflammation in the Brain Links Obesity and Aging
- Spring 2014 NIDDK Director's Update
- NIDDK Recent Advances & Emerging Opportunities 2014

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Funding Opportunities

- Consortium on Beta-cell

Diabetes Research Centers

IN THE SPOTLIGHT

Nancy J. Cox, Ph.D.

Academic Interests:Dr. Cox is a human geneticist studying common disorders with complex patterns of transmission, including type 1 and type 2 diabetes, polycystic ovary syndrome, inherited thyroid defects, asthma, autism, attention d.. MORE

University of Chicago

THE UNIVERSITY OF CHICAGO

The University of Chicago Diabetes Research and Training Center (DRTC) provides resources for the support and coordination of the research and training activities in diabetes and related metabolic and endocrine disorders of a large and growing number of ind... MORE

Diabetes Centers Overview

The NIDDK-supported Diabetes Research Centers (DRCs), formerly known as Diabetes Endocrinology Research Centers (DERCs) and Diabetes Research and Training Centers (DRTCs), are part of an integrated program of diabetes and related endocrinology and metabolism research. Centers provide increased, cost effective collaboration among multidisciplinary

Centers In The News

- WUSTL: Dr. Colin Nichols elected to Royal Society
- COLUMBIA: Limited Recovery of b-Cell Function After Gastric Bypass Despite Clinical Diabetes Remission
- BADERC: Diabetes in Latin America: Unskinny genes
- YALE: James Rothman shares 2013 Nobel Prize in Physiology or Medicine
- VANDERBILT: Study sheds new light on type 2 diabetes development
- BADERC: David M. Altshuler, MD, PhD, receives ENDO 2014 Roy O. Greep Award

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Featured Publications

DIABETES RESEARCH CENTERS

What's New

- Upcoming Symposia & Meetings
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Featured Publications

CENTERS for
DIABETES TRANSLATION RESEARCH

New CDTR Website!

HOME CENTERS SERVICES PUBLICATIONS RESOURCES

Centers for Diabetes Translation Research Overview

The NIDDK-supported Centers for Diabetes Translation Research (CDTR) are part of an integrated program whose cores support and enhance diabetes type II translation research (e.g. bedside to practice and the community, dissemination and implementation science). The purpose of the CDTRs is to enhance the efficiency, productivity, effectiveness and multidisciplinary nature of diabetes translation research. Centers are intended to improve the quality and multidisciplinary nature of research of diabetes translational research through shared access to specialized technical expertise.

Vanderbilt
Center for Diabetes Translation Research

The CDTRs serve as a key component of the NIDDK-supported research program to translate efficacious research findings into practice and the community to improve the health of Americans with, or at risk for, diabetes. CDTRs will enhance scientific progress and improve the uptake of research by providing support and expertise for rigorous translation research aimed at prevention and improved treatment of diabetes (type 1, type 2 and gestational) and related conditions. To meet these goals, CDTRs will provide core services and consultation locally, regionally, and nationally in areas relevant to the NIDDK translation research agenda. To learn more about the NIDDK type II translation research priorities in diabetes, please see the *Clinical Research to Practice: Translational Research* chapter in *Advances and Emerging Opportunities in Diabetes Research: A Strategic Planning Report of the Diabetes Mellitus Interagency Coordinating Committee (DMICC)*.

Tom Elasy
Director

The objectives of the Centers are to bring together investigators from relevant disciplines in a manner that will enhance and extend the effectiveness of their research. CDTRs will provide core services and consultation locally, regionally, and nationally in areas relevant to the NIDDK translation research agenda.

NIH National Institute of Diabetes and Digestive and Kidney Diseases

What's New

- Upcoming Symposia & Meetings
- NIH Director's Blog: "Brown Fat, White Fat, Good Fat, Bad Fat"
- NIH launches study of long-term effects of blood glucose during pregnancy
- For National Diabetes Month, NIH urges actions to reach health goals
- "Biggest Loser" study finds modest diet and exercise can sustain weight loss
- Family problem-solving sessions help teens better manage diabetes

more

Funding Opportunities

- Phenotyping Embryonic Lethal Knockout Mice (R01)
- Biomarkers for Diabetes, Digestive, Kidney and Urologic Diseases Using Biosamples from the NIDDK Repository (R01)
- Improvement of Animal Models for Stem Cell-Based Regenerative Medicine (R01)
- High-End Instrumentation Grant Program (S10)

Pilot And Feasibility

P&F program

The Diabetes Center Pilot and Feasibility (P&F) program provides seed support for new and innovative research projects directed at basic biomedical, clinical and translational research questions relevant to diabetes and its complications.

The P&F program is designed to support:

- new investigators
- established investigators new to diabetes research
- established diabetes investigators pursuing high impact/high risk projects or projects that are a significant departure from their usual work

Individual Center P&F programs may also be structured to provide support for establishing interdisciplinary collaborations and to help forge new partnerships between basic scientists and clinical researchers.

For more information about Pilot and Feasibility opportunities in the NIDDK Diabetes Center program, please visit the following individual center P&F websites:

Diabetes Research Centers Pilot and Feasibility	
Albert Einstein College of Medicine	University of Alabama at Birmingham
Baylor College of Medicine	University of Chicago
Boston Area DRC	University of Michigan
Columbia University	University of Pennsylvania
Johns Hopkins/University of Maryland	University of Washington
Joslin Diabetes Center	Vanderbilt University
UCSD/UCLA	Washington University
UCSF	Yale University

P&F database

The P&F database provides access to researchers' institutions, departments, and interests. It is a secure web page requiring users to **login** before viewing or searching the database.

Once you are logged in, please visit the **P&F database**.

Diabetes Center P&F Program - commonalities and diversities of practices

- Diabetes Centers P&F Grant Programs

Centers In The News

- Frederick L. Brancati, M.D., M.H.S., 1959-2013
- UCHICAGO: Dr. Graeme Bell awarded 2012 Manpei Suzuki International Prize
- John C. Hutton, PhD: 1948-2012
- George S. Eisenbarth, MD, PhD: 1947-2012
- EINSTEIN: Preventing Diabetes and Its Complications Offers Public Health Challenge
- COLUMBIA: New Brain Target for Appetite Control Identified

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Featured Publications

- Weight Change, Psychological Well-Being, and Vitality in Adults Participating in a Cognitive-Behavioral Weight Loss Program.
- The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS.
- Cross-sectional associations between measures of sleep and markers of glucose

What's New

- Upcoming Symposia & Meetings
- Bionic pancreas outperforms insulin pump in adults, youth
- CDC: More than 29 million Americans have diabetes; 1 in 4 doesn't know
- NIDDK Research Update: Inflammation in the Brain Links Obesity and Aging
- Spring 2014 NIDDK Director's Update
- NIDDK Recent Advances & Emerging Opportunities 2014

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Funding Opportunities

- Consortium on Beta-cell Death and Survival (HIRN-CBDS) (UC4)
- Type 1 Diabetes Complications IMPACT Awards (DP3)
- Identification of Novel Targets and Pathways Mediating Weight Loss, Diabetes Resolution and Related Metabolic Disease after Bariatric Surgery in Humans (R01)
- Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity

Pilot & Feasibility

P&F Program | P&F Reviewer Database

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Study In the Spotlight

Washington University
Xiong Su, Ph.D.
xsu@wustl.edu

2011 P&F Awardee
Adipocyte-derived Exosomes: Regulation and Metabolic Functions

For more information about Pilot and Feasibility opportunities in the NIDDK Diabetes Center program, please visit the following individual center P&F websites:

Diabetes Research Centers Pilot and Feasibility	
Albert Einstein College of Medicine	University of Alabama at Birmingham
Baylor College of Medicine	University of Chicago
Boston Area	University of Michigan
Columbia University	University of Pennsylvania
Johns Hopkins/University of Maryland	University of Washington
Joslin Diabetes Center	Vanderbilt University
UCSD/UCLA	Washington University

Centers In The News

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- BADERC: David M. Altshuler, MD, PhD, receives ENDO 2014 Roy O. Greep Award

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Featured Publications

- Risk perception and self-management in urban, diverse adults with type 2 diabetes: the improving diabetes outcomes study.
- Allosteric Inhibition of the IRE1α RNase Preserves Cell Viability and Function during Endoplasmic Reticulum Stress.
- Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch.

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Pilot & Feasibility

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- Ablation of PRDM16 and beige adipose causes metabolic dysfunction and a subcutaneous to visceral fat switch.

Pilot and Feasibility Reviewers

P&F Program | P&F Reviewer Database

The Center field allows you to select pandf reviewers for a specific Center, click on Apply to submit.

Center

<Any> Apply

Reviewer	Degrees	Institution	Department	Position	Interests	Interest Group	Email	Telephone	State
Al-Awqati, Qais		Columbia University	Medicine-Nephrology	Professor	Kidney complications	Complications	qa1@columbia.edu		New York
Al-Noori, Salwa	Ph.D.	University of Washington	Behavioral Sciences Psychiatry	Acting Instructor	brain, hypoglycemia	Diabetes (Type 1 and Type 2), Neuroscience	saan@u.washington.edu	(206) 277-4520	Washington
Albers, John	Ph.D.	University of Washington	Medicine	Research Professor	atherosclerosis, Lipoproteins	Complications, Lipids/Lipid Metabolism	jja@u.washington.edu	(206) 685-3330	Washington
Albu, Jeanine		St. Luke's-Roosevelt Hospital Center		Associate Professor	body composition, Obesity	Obesity/Body Composition	jba1@columbia.edu		New York
Alegre, Maria-Luisa	M.D. Ph.D.	University of Chicago	Medicine	Associate Professor	autoimmunity, Tolerance, transplantation	Immunology/Inflammation/ Transplantation	malegre@medicine.bsd.uchicago.e	(773) 834-4317	Illinois

Showing all 1421 rows Show: All Auto 25 50 100

XLS

Website Updates

- Website Project: P&F awardees' database
  - Web-based data input
  - May be downloaded by each Center
  - Beta-test site: http://diabetescenters.org/niddktest/pandf_outcomes
  - University of Michigan is assisting with beta testing

Pilot Project Outcomes

[Edit] [Export] [Clone]

We are providing the following pre-formatted table to assist in preparing your application.

1. Provide information on the most recent 5 or, if possible, 10-year period. Complete and organize by Year Funded.
2. P&F Type Key:
   N= New Investigator; NTD= Established Investigator, New to Diabetes research; E = Established Investigator; with new, innovative research idea
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Center	P&F #	PI	Department	Award Period	Amount of P&F Award (direct costs)	Pilot Project Title	P&F Type	A	P	Application
Albert Einstein College of Medicine	1	Smith, Elizabeth	Biochemistry	07/01/2012 - 06/30/2013	$50,000	Role of serotonin receptors in T1D autoimmunity	E	1	0	Applicat Applicat
Albert Einstein College of Medicine	2	Doe, Jane	Surgery	05/01/2013 - 04/30/2014	$75,000	AECOM Pilot Project 2	N	1	1	Grant 1 Grant 2
University of Michigan	1	Doe, John	Physiology	06/30/2009 - 06/29/2010	$45,000	Role of leptin receptors in the arcuate nucleus	N	1	1	NIH/NI ADA 12 NIH/NH
University of Michigan	2	Wilson, Mary	Endocrinology	07/01/2010 - 06/30/2012	$100,000	Regulation of Beta Cell Mass in T2D	NTD	2	2	R21DK0

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Center	P&F #	PI	Department	Award Period	Amount of P&F Award (direct costs)	Pilot Project Title	P&F Type	A	P	Application
Albert Einstein College of Medicine	1			13	$50,000	Role of serotonin receptors in T1D autoimmunity	E	1	0	Applicat Applicat
Albert Einstein College of Medicine	2			14	$75,000	AECOM Pilot Project 2	N	1	1	Grant 1 Grant 2
University of Michigan	1	Doe, John	Physiology	06/30/2009 - 06/29/2010	$45,000	Role of leptin receptors in the arcuate nucleus	N	1	1	NIH/NI ADA 12 NIH/NH
University of Michigan	2	Wilson, Mary	Endocrinology	07/01/2010 - 06/30/2012	$100,000	Regulation of Beta Cell Mass in T2D	NTD	2	2	R21DK(

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Center	P&F #	PI	Department	Award Period	Amount of P&F Award (direct costs)	Pilot Project Title	P&F Type	A	P	Applications/ Grants	Pending/ Funded	Project Period	Still in Diabetes
Albert Einstein College of Medicine	1	Smith, Elizabeth	Biochemistry	07/01/2012 - 06/30/2013	$50,000	Role of serotonin receptors in T1D autoimmunity	E	1	0	Application 1 Application 2	Pending Pending	04/01/2013 - 03/31/2014 05/01/2013 - 06/30/2014	Yes
Albert Einstein College of Medicine	2	Doe, Jane	Surgery	05/01/2013 - 04/30/2014	$75,000	AECOM Pilot Project 2	N	1	1	Grant 1 Grant 2	Pending Pending	05/01/2013 - 04/30/2014 05/01/2013 - 04/30/2014	Yes
University of Michigan	1	Doe, John	Physiology	06/30/2009 - 06/29/2010	$45,000	Role of leptin receptors in the arcuate nucleus	N	1	1	NIH/NIDDK R01 ADA 12345 NIH/NHLBI R21	Pending Pending Pending	12/01/2013 - 11/30/2018 09/01/2013 - 08/31/2015 09/01/2013 - 08/31/2015	Yes
University of Michigan	2	Wilson, Mary	Endocrinology	07/01/2010 - 06/30/2012	$100,000	Regulation of Beta Cell Mass in T2D	NTD	2	2	R21DK012345	Funded	07/01/2012 - 06/30/2013	Yes
University of Michigan	3	Smith, John	Medicine	07/01/2012 - 06/30/2014	$30,000	Michigan Pilot Project 3	NTD	0	0	NIH 1	Pending	10/01/1010 - 09/30/0015	Yes

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National Institute of
Diabetes and Digestive
and Kidney Diseases

Xiaoping Zhao,[1,2,3] Xiaoli,[1,2] Haihong Zong,[1] Arian Abdulla,[1,2] Ellen S.T. Yang,[1] Qun Wang,[4] Jun-Yuan Ji,[4] Jeffrey E. Pessin,[1,5] Bhaskar C. Das,[6] and Fajun Yang[1,2]

Inhibition of SREBP Transcriptional Activity by a Boron-Containing Compound Improves Lipid Homeostasis in Diet-Induced Obesity

Diabetes 2014;63:2464–2473 | DOI: 10.2337/db13-0835

PHARMACOLOGY AND THERAPEUTICS

Dysregulation of lipid homeostasis is intimately associated with obesity, type 2 diabetes, and cardiovascular diseases. Sterol regulatory-element binding proteins (SREBPs) are the master regulators of lipid biosynthesis. Previous studies have shown that the conserved transcriptional cofactor Mediator complex is critically required for the SREBP transcriptional activity, and recruitment of the Mediator complex to the SREBP transactivation domains (TADs) is through the MED15-KIX domain. Recently, we have synthesized several boron-containing small molecules. Among these novel compounds, BF175 can specifically block the binding of MED15-KIX to SREBP1a-TAD in vitro, resulting in an inhibition of the SREBP transcriptional activity and a decrease of SREBP target gene expression in cultured hepatocytes. Furthermore, BF175 can improve lipid homeostasis in the mouse model of diet-induced obesity. Compared with the control, BF175 treatment decreased the expression of SREBP target genes in mouse livers and decreased hepatic and blood levels of lipids. These results suggest that blocking the interaction between SREBP-TADs and the Mediator complex by small molecules may represent a novel approach for treating diseases with aberrant lipid homeostasis.

The current prevalence of obesity substantially increased the incidence of several comorbidities, including type 2 diabetes, cardiovascular diseases, and some types of cancer (1,2). Strikingly, ~70% of diabetic patients are also diagnosed with nonalcoholic fatty liver disease (NAFLD) (3), which is often associated with hepatic insulin resistance (4). The most common feature of NAFLD is excessive fat accumulation in hepatocytes. Although fatty acids from diets and adipose tissue lipolysis support re-esterification in the liver to drive triglyceride synthesis, up to 30% of hepatic fatty acids are from de novo lipogenesis in NAFLD, but <5% in normal individuals (5,6). In addition, increased hepatic de novo lipogenesis may lead to dyslipidemia and atherosclerosis, the primary risk factors for heart disease.

Among the known lipogenic regulators, sterol regulatory-element binding protein (SREBP) transcription factors are master regulators of lipid homeostasis (7–9). Through activating the expression of rate-limiting lipogenic and cholesterogenic genes, such as fatty acid synthase (*FAS*) and HMG-CoA reductase (*HMGCR*), SREBPs promote the biosynthesis of fatty acids, triglycerides, and cholesterol (7–9). Therefore, suppressing the SREBP pathway may efficiently inhibit lipid biosynthesis. The three mammalian

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X.Z. and X. contributed equally to this study.

nature COMMUNICATIONS

ARTICLE

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Autophagy proteins regulate ERK phosphorylation

Nuria Martinez-Lopez[1,2], Diana Athonvarangkul[1,2], Priti Mishall[3], Srabani Sahu[1,2] & Rajat Singh[1,2,4,5]

Autophagy is a conserved pathway that maintains cellular quality control. Extracellular signal-regulated kinase (ERK) controls various aspects of cell physiology including proliferation. Multiple signalling cascades, including ERK, have been shown to regulate autophagy, however whether autophagy proteins (ATG) regulate cell signalling is unknown. Here we show that growth factor exposure increases the interaction of ERK cascade components with ATG proteins in the cytosol and nucleus. ERK and its upstream kinase MEK localize to the extra-luminal face of autophagosomes. ERK2 interacts with ATG proteins via its substrate-binding domains. Deleting *Atg7* or *Atg5* or blocking LC3 lipidation or ATG5–ATG12 conjugation decreases ERK phosphorylation. Conversely, increasing LC3-II availability by silencing the cysteine protease ATG4B or acute trehalose exposure increases ERK phosphorylation. Decreased ERK phosphorylation in $Atg5^{-/-}$ cells does not occur from overactive phosphatases. Our findings thus reveal an unconventional function of ATG proteins as cellular scaffolds in the regulation of ERK phosphorylation.

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Original article

MOLECULAR METABOLISM

Control of obesity and glucose intolerance via building neural stem cells in the hypothalamus*

Juxue Li [1,2,3], Yizhe Tang [1,2,3], Sudarshana Purkayastha [1,2,3], Jingqi Yan [1,2,3], Dongsheng Cai [1,2,3,*]

ABSTRACT

Neural stem cells (NSCs) were recently revealed to exist in the hypothalamus of adult mice. Here, following our observation showing that a partial loss of hypothalamic NSCs caused weight gain and glucose intolerance, we studied if NSCs-based cell therapy could be developed to control these disorders. While hypothalamus-implanted NSCs failed to survive in mice with obesity, NF-κB inhibition induced survival and neurogenesis of these cells, leading to effects in counteracting obesity and glucose intolerance. To generate an alternative cell source, we revealed that iPS-derived NSCs were converted into htNSCs by neuropeptide treatment. Of note, obesity condition potentiated the transfer of carotid artery-injected NSCs into the hypothalamus. These iPS-derived cells when engineered with NF-κB inhibition were also effective in reducing obesity and glucose intolerance, and neurogenesis towards POMCergic and GABAergic lineages was accountable. In conclusion, building NSCs in the hypothalamus represents a strategy for controlling obesity and glucose disorders.

Keywords Neural stem cells; iPS; Hypothalamus; NF-κB; Neuropeptide; Obesity; Glucose tolerance

1. INTRODUCTION

Feeding, body weight and glucose balance are regulated by the mediobasal hypothalamus (MBH) in the central nervous system (CNS), and this regulation is mediated importantly by melanocortin signals from the arcuate nucleus (ARC), in particular anorexigenic proopiomelanocortin (POMC) neurons and orexigenic agouti-related peptide (AGRP) neurons [1–6]. These two neuronal types are sensitively and dynamically affected by systemic hormones such as leptin and insulin which fluctuate according to feeding and fat mass conditions, and this process is physiologically critical for maintaining body weight homeostasis [1–7]. However, when chronically challenged under high-fat diet (HFD) condition, these neurons reduce the responsiveness to leptin and insulin, and these changes contribute to the mechanism of HFD-induced obesity and type-2 diabetes (T2D) [1–7]. In addition to these signaling changes, research during recent years has begun to show that hypothalamic neural organization and neuronal numbers are altered under chronic HFD feeding [8–10]. For example, it was revealed that prolonged HFD feeding leads to a fractional loss (~10%) in POMC neurons in the hypothalamus [10–12]. Intriguingly, *Pomc* gene expression is known to be divergently regulated [13,14], and was shown to be present in neural precursors which give rise to various neuronal types [15]. In relation to this background, we have been interested in understanding if impaired hypothalamic neurogenesis might play a role in the development of HFD-induced obesity. In agreement with this idea, several evidences were recently documented to indicate that the hypothalamus of adult rodents has neurogenesis [16–21]. We showed that the MBH contain adult hypothalamic NSCs (htNSCs), and these cells appear to be involved in the hypothalamic control of metabolic physiology [11]. Herein, we extended to study if htNSCs could be developed to treat obesity and related glucose disorders, and if so, what technological approaches could be introduced to promote the practical employment of this technique.

2. RESULTS

2.1. Partial loss of htNSCs leads to weight gain and glucose intolerance

We recently showed that dietary obesity is associated with impaired survival and neurogenesis of htNSCs [11]. In this context, we studied if htNSCs could be developed to treat or prevent against obesity and related metabolic disorders. We first tested if a loss of endogenous htNSCs in mice could be sufficient to lead to these metabolic disorders. To do so, we generated a mouse model with adult-onset ablation of dividing Sox2-positive htNSCs in the MBH. Briefly, adult C57BL/6 mice received MBH injection of lentiviruses expressing Sox2 promoter-driven Herpes simplex virus type-1 thymidine kinase (Hsv1-TK), a kinase that works to convert a nontoxic nucleoside analog, ganciclovir (GCV), into the toxic product which acts as a chain terminator during DNA replication and therefore kills dividing Sox2-positive cells [22–25]. Injection of matched control lentiviruses was performed in control mice for comparison. All these mice were then chronically treated with GCV to

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Article

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Baseline Characteristics and Latino Versus Non-Latino Contrasts Among *Bronx A1C* Study Participants

Elizabeth A. Walker[1], Lynn D. Silver[2], Shadi Chamany[2], Clyde B. Schechter[1], Jeffrey S. Gonzalez[1], Jeidy Carrasco[2], Danielle Powell[2], Diana Berger[2], and Charles E. Basch[3]

Abstract

We describe baseline demographic and psychosocial characteristics of low-income, diverse diabetes adults enrolled in a telephonic intervention trial. Environment for the study was New York City (NYC) A1C Registry program. Baseline data were analyzed from 941 participants randomized to either telephonic/print or print-only intervention to improve glycemic control. Summary statistics for key variables were calculated; we highlight baseline contrasts between Latino and non-Latino participants. There were high proportions of Latino (67.7%) and non-Latino Black (28.0%) participants from South Bronx. Mean age was 56.3 years, almost 70.0% were foreign born, and 55.8% preferred Spanish language. Mean A1C was 9.2% and mean body mass index (BMI) 32.1 kg/m^2. There were significant contrasts between Latino and non-Latino participants for behavioral and psychosocial variables. This telephonic intervention study succeeded in randomizing a

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International Journal of Obesity (2014) **38**, 60–68

www.nature.com/ijo

PEDIATRIC ORIGINAL ARTICLE

US pediatric population-level associations of DXA-measured percentage of body fat with four BMI metrics with cutoffs

M Heo[1], J Wylie-Rosett[1], A Pietrobelli[2,3], GC Kabat[1], TE Rohan[1] and MS Faith[4]

OBJECTIVE: Four body mass index (BMI) metrics—BMI, BMI z-score, BMI percentile and BMI%—are commonly used as proxy measures for children's adiposity. We sought to determine a BMI metric that is most strongly associated with measured percentage of body fat (%BF) in the US pediatric population stratified by sex, age and race/ethnicity, and to determine cutoffs that maximize the association for each BMI metric.

SUBJECTS, DESIGN AND METHODS: %BF was measured by dual-energy X-ray absorptiometry among $N = 6120$ US boys and girls aged 8.0–17.9 years old from the National Health and Nutrition Examination Survey 1999–2004. We fit piecewise linear regression models with cutoffs to %BF data using each BMI metric as the predictor stratified by sex, race/ethnicity and age. The slopes were modeled differently before and after the cutoffs which were determined on the basis of grid searches.

RESULTS: BMI z-score was in general most strongly associated with %BF for both boys and girls. The associations of the four BMI metrics were lowest for boys aged 12–13.9 years and girls aged 16–17.9 years, and strongest for Mexican-American boys and for non-Hispanic Black girls. Overall, the associations were stronger for girls than for boys. In boys, BMI had the lowest association with %BF ($R^2 = 0.39$) for all ages combined. The fold changes in slopes before and after cutoffs were greatest in general for BMI percentiles regardless of age, sex and race/ethnicity. BMI z-score cutoffs were 0.4 for both boys and girls for all ages combined. Except for BMI, the slopes after the cutoffs were in general greater than those before.

CONCLUSIONS: All BMI metrics were strongly associated with %BF when stratified by age and race/ethnicity except that BMI was the least associated with %BF in boys for all ages combined. Overall, BMI z-score was superior for evaluation of %BF, and its cutoff of 0.4 can also serve as a threshold for careful monitoring of weight status.

International Journal of Obesity (2014) **38,** 60–68; doi:10.1038/ijo.2013.134

Keywords: pediatric obesity; percentage of body fat; BMI metrics; growth

INTRODUCTION

Excessive body fat is a serious public health concern not only for the adult population but also for the pediatric population.[1] Pediatric obesity is associated with a number of comorbidities including type II diabetes,[2] hyperlipidemia,[3] hypertension[4], and thus elevated risk of cardiovascular diseases.[5,6] Furthermore, pediatric obesity, and its associated comorbidity, can be carried into adulthood.[7,8] Therefore, the assessment of excess body fat during childhood is critically important. To this end, advanced techniques such as dual-energy X-ray absorptiometry (DXA) are utilized in pediatric samples to more accurately measure body fat.[9–11] However, body mass index (BMI; $kg\,m^{-2}$), weight in kilograms (kg) divided by the square of height in meters (m), is a widely used anthropometric proxy measure of adiposity because it is much easier to measure, and thus more practical in clinical or research settings. For example, the American Academy of Pediatrics emphasizes BMI screening and use in routine clinical practice[12] as well as in schools.[13] In children, however, in order to take growth into account, pediatric adiposity is more often measured by the following age-sex-adjusted measures derived from BMI: BMI z-score, BMI percentile and BMI%.[14] BMI% is defined as $100 \times \log_e$(BMI/age-sex-adjusted median BMI), and thus it is a relative age-sex-adjusted BMI. Herein, these four measures are referred to as BMI metrics following the terminology used by Field *et al.*[15] The BMI metrics include BMI itself.

Pediatric obesity is defined based on the age-sex-adjusted BMI percentile which is derived from the Centers for Disease Control and Prevention 2000 growth charts,[16] whereas adult obesity is defined based on BMI.[17] For example, pediatric overweight and obesity are defined as $85 \leqslant$ BMI percentile < 95 and BMI percentile $\geqslant 95$, respectively, in the US. However, a study has shown that of the BMI metrics, BMI percentile is least associated with DXA-measured percentage of body fat (%BF) among the BMI metrics in children aged 5–18.7 years.[15] On the other hand, Pietrobelli *et al.*[18] validated the use of BMI for the prediction of DXA-measured %BF in a relatively small sample of Italian children aged 5–19 years old. Mei *et al.*[19] further supported the validity of BMI stratified by age in predicting underweight and overweight in children aged 2–19 years old using skinfold thickness data from the third National Health and Nutrition Examination Survey (NHANES III; conducted during 1988–1994) data in addition to DXA-measured %BF data from three independent studies. Furthermore, a study of a small sample of Italian prekindergarten children aged 29–68 months suggested that BMI and BMI% are more relevant for representing changes in adiposity over 9 months[20] than the other metrics. Nonetheless, Freedman and Sherry [21] argued that although BMI is

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Risk Perception and Self-Management in Urban, Diverse Adults with Type 2 Diabetes: The Improving Diabetes Outcomes Study

Erica Shreck · Jeffrey S. Gonzalez · Hillel W. Cohen · Elizabeth A. Walker

Published online: 6 February 2013

Abstract *Purpose and Background* The relationship between risk perceptions and diabetes self-care remains ambiguous. This study aimed to assess baseline, 1-year follow-up, and change score relationships among perceived risk, diabetes self-care, and glycemic control for adult individuals participating in a behavioral intervention that improved glycemic control relative to the active control.
Method One-year randomized trial compared a behavioral telephonic intervention with a print only intervention. Participants (N=526) are members of a union/employer sponsored health benefit plan, with $HbA_{1c} \geq 7.5$ %, prescribed at least one oral diabetes medication. Participants rated perceived risk of diabetes and its complications and diabetes self-care at baseline and 1 year. Data were collected in a large urban area in the USA.
Results There were no relationships between risk perceptions and glycemic control during the study. Baseline perceived risk predicted follow-up self-care. Additionally, participants assigned to the intervention group showed significant changes in dietary and exercise adherence at high levels of risk knowledge and low levels of optimistic bias.
Conclusion Perceived risk relates to dietary, exercise, and medication adherence in diabetes. The perceived risk construct might foster a more coherent conceptualization of the relationship between one's diabetes, possible complications, and diabetes self-care behaviors.

Keywords Risk perception · Diabetes · Self-care · Glycemic control

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Introduction

Risk perception plays a role in many theories of health behavior, including the Health Belief Model, Protection Motivation Theory, and the Subjective Expected Utility theory [1–3]. It is often defined as perceived probability, likelihood, or susceptibility to harm. The construct has been explored in relation to behavior, such that risk perceptions can affect one's engagement in protective or harmful behaviors, just as protective and harmful behaviors can reciprocally influence one's risk perception [4]. Some studies in the area of chronic illness have shown positive relationships between perceived risk and adherence to protective health behaviors [5], while other studies report negative or no associations between the two [6–9]. Consequently, inconsistent results support defining the nature of the relationship between risk perceptions of chronic disease and health behaviors more clearly, especially in the complex area of diabetes self-management.

Diabetes is a chronic disease that is characterized either by an absolute insulin deficiency (type 1 diabetes) or by insulin resistance/abnormal secretion (type 2 diabetes) [10]. The WHO (2011) estimates that 346 million people worldwide

Cell Metabolism
Article

Glutamate Mediates the Function of Melanocortin Receptor 4 on Sim1 Neurons in Body Weight Regulation

Yuanzhong Xu,[1] Zhaofei Wu,[1] Hao Sun,[1] Yaming Zhu,[1] Eun Ran Kim,[1] Bradford B. Lowell,[2] Benjamin R. Arenkiel,[3] Yong Xu,[4] and Qingchun Tong[1,5,6,*]

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SUMMARY

The melanocortin receptor 4 (MC4R) is a well-established mediator of body weight homeostasis. However, the neurotransmitter(s) that mediate MC4R function remain largely unknown; as a result, little is known about the second-order neurons of the MC4R neural pathway. Single-minded 1 (*Sim1*)-expressing brain regions, which include the paraventricular nucleus of hypothalamus (PVH), represent key brain sites that mediate melanocortin action. We conditionally restored MC4R expression in Sim1 neurons in the background of *Mc4r*-null mice. The restoration dramatically reduced obesity in *Mc4r*-null mice. The anti-obesity effect was completely reversed by selective disruption of glutamate release from those same Sim1 neurons. The reversal was caused by lower energy expenditure and hyperphagia. Corroboratively, selective disruption of glutamate release from adult PVH neurons led to rapid obesity development via reduced energy expenditure and hyperphagia. Thus, this study establishes glutamate as the primary neurotransmitter that mediates MC4Rs on Sim1 neurons in body weight regulation.

INTRODUCTION

The obesity epidemic has imposed a major social and economic burden on our society. As such, this epidemic demands a clear understanding of its mechanistic cause. Over the past decades, a large body of evidence has established the importance of the melanocortin pathway in body weight regulation. Inactivation of the melanocortin 4 receptor (*Mc4r*) gene produces massive obesity in both rodents and humans (Farooqi and O'Rahilly, 2005; Huszar et al., 1997), suggestive of underlying common neural pathways that regulate body weight between these two species. MC4R-expressing neurons, which mediate the effects of α-melanocyte-stimulating hormone (α-MSH) released from proopiomelanocortin neurons and agouti-related protein (AgRP) released from AgRP neurons, have been directly linked to feeding behavior and energy expenditure (Cone, 2005; Elmquist et al., 2005). However, although there is a well-established role for MC4Rs in obesity development, the neurotransmitter(s) that mediate the function of MC4Rs remain unclear, and as a result, little is known about the second-order neurons that mediate the function of MC4R-expressing neurons.

The paraventricular nucleus of hypothalamus (PVH) is known to control body weight and express abundant MC4Rs and has been identified as a major brain site of melanocortin action (Balthasar et al., 2005). Interestingly, hypomorphism of single-minded 1 (*Sim1*), a transcription factor required for PVH development, produces obesity, and genetic deletion of *Sim1* selectively in the PVH leads to obesity (Michaud et al., 2001; Tolson et al., 2010). Notably, while MC4Rs are broadly expressed in the brain, selective MC4R restoration in Sim1 neurons (PVH and parts of the amygdala) greatly rescues the obesity in *Mc4r*-null mice (Balthasar et al., 2005; Kishi et al., 2003; Liu et al., 2003), suggesting a major role for MC4R function in Sim1 neurons toward body weight regulation. Consistent with the cell-type-selective function of MC4Rs in Sim1 neurons, MC4R restoration in other brain areas, such as hindbrain and spinal cord, showed little effect on obesity in *Mc4r*-null mice (Rossi et al., 2011; Sohn et al., 2013). Thus, despite broad expression of *Mc4r* in the brain, Sim1 neurons are one key site that mediates MC4R action on body weight regulation. Therefore, identification of the neurotransmitter(s) and signaling mechanisms that mediate MC4R function in Sim1 neurons is critical to delineate the MC4R neural pathway in body weight regulation.

The PVH contains diverse groups of neurons that use peptides, glutamate, GABA, or dopamine as neurotransmitters

Review

CellPress

Emerging roles of hematopoietic cells in the pathobiology of diabetic complications

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Diabetic complications encompass macrovascular events, mainly the result of accelerated atherosclerosis, and microvascular events that strike the eye (retinopathy), kidney (nephropathy), and nervous system (neuropathy). The traditional view is that hyperglycemia-induced dysregulated biochemical pathways cause injury and death of cells intrinsic to the organs affected. There is emerging evidence that diabetes compromises the function of the bone marrow (BM), producing a stem cell niche-dependent defect in hematopoietic stem cell mobilization. Furthermore, dysfunctional BM-derived hematopoietic cells contribute to diabetic complications. Thus, BM cells are not only a victim but also an accomplice in diabetes and diabetic complications. Understanding the underlying molecular mechanisms may lead to the development of new therapies to prevent and/or treat diabetic complications by specifically targeting these perpetrators.

Hyperglycemia induced organ dysfunctions

The discovery of insulin about 90 years ago, together with other advances in medical therapy, have markedly improved the quality of life and life expectancy of people with type 1 and type 2 diabetes. Nowadays, diabetic patients rarely die of the acute complications of ketoacidosis. With a much longer lifespan, however, the majority of people with diabetes will develop chronic diabetic complications, the cause of much morbidity and mortality.

Hyperglycemia is the ultimate cause of diabetic complications. Hyperglycemia induces several biochemical processes with important pathogenic implications, such as rendering cells more vulnerable to oxidative stress, increasing production of advanced glycation end-products (AGEs) that alter the function of intracellular proteins and extracellular matrix, increasing protein kinase C activity that causes blood flow abnormalities, vascular permeability, and microvascular matrix protein accumulation, and inducing post-translation modification of transcription factors that results in altered gene expression [1–3]. Cells in various tissues and organs, such as endothelial cells, pericytes (capillary support cells), and Müller cells in the retina, endothelial cells, mesangial cells, and podocytes in the kidney glomerulus, and neurons and Schwann cells, as well as endothelial cells of the vasa nervorum in the peripheral nerves, are susceptible to hyperglycemia-induced damage.

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Glossary

CC chemokine ligand 2 (CCL2): also known as MCP1, is expressed by most nucleated cells in response to proinflammatory cytokines or stimulation of innate immune receptors. CCL2 binds to its receptor CCR2 (CCR2 also binds to CCL7 or MCP3) expressed by monocytes, HSCs and a subset of natural killer cells, and mediates recruitment of these cells to inflammatory foci.
CXC chemokine ligand 12 (CXCL12): also known as SDF1-α, is expressed by stromal cells including nestin$^+$ MSCs in part under the control of the sympathetic nervous system. CXCL12 binds to its receptor CXCR4, also known as CD184, expressed on hematopoietic cells. The CXCL12/CXCR4 complex is involved in regulating and retaining HSPCs in the BM.
Endothelial progenitor cells (EPCs): commonly defined as mononuclear cells positive for both immature cell and endothelial markers such as CD34 and VEGFR-2 and/or CD133 in humans. They exist in the peripheral blood and the BM, and enhance vascular repair through re-endothelialization and neovascularization. EPCs are decreased in various vascular disorders. They also have received attention for their potential utility in cell therapy.
Hematopoietic stem cells (HSCs): a group of self-renewing cells capable of producing daughter cells that proliferate and mature to provide all adult blood cells in erythroid, myeloid, and lymphoid lineages.
Hematopoietic stem and progenitor cells (HSPCs): a term used to describe both hematopoietic stem cells (HSC) and progenitor cells (HPC). HSCs differentiate and become multipotent progenitor cells. Multipotent progenitor cells further differentiate into more committed oligopotent progenitor cells that eventually mature to individual lineages of hematopoietic cells. HPCs have little to no self-renewal capacity. HSPC is frequently used when distinction between HSC and HPC is unclear or unnecessary.
Leukostasis: an acute syndrome characterized by abnormal intravascular leukocyte aggregation and clumping. Inflammatory hematopoietic cells adhere to capillary endothelial cells, occluding blood flow and damaging endothelial cells.
LSK cells: a lineage-negative (Lin)$^-$stem cell antigen 1 (SCA1)$^+$KIT$^+$ (LSK) population that is used to isolate HSCs in mice. The subset of LSK cells is heterogeneous in terms of self-renewal potential and contains long-term reconstituting HSCs (LT-HSCs) as well as short-term reconstituting HSCs (ST-HSCs). LT-HSCs maintain potential for self-renewal and multi-lineage differentiation throughout life and are the *bona fide* stem cells of hematopoiesis, whereas ST-HSCs, which derive from LT-HSCs, are multipotent but limited in self-renewal potential. ST-HSCs subsequently produce multi- and oligopotent progenitors. Lineage means a collection of cell surface markers for all terminally differentiated populations.
Stem cell niche: the physical, molecular, and cellular microenvironment that regulates stem cell function in harmony with stem cell autonomous mechanisms, maintaining the balance between quiescence, self-renewal, differentiation, and mobilization of stem cells.

Cell Metabolism
Article

The REGγ Proteasome Regulates Hepatic Lipid Metabolism through Inhibition of Autophagy

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SUMMARY

The ubiquitin-proteasome and autophagy-lysosome systems are major proteolytic pathways, whereas function of the Ub-independent proteasome pathway is yet to be clarified. Here, we investigated roles of the Ub-independent REGγ-proteasome proteolytic system in regulating metabolism. We demonstrate that mice deficient for the proteasome activator REGγ exhibit dramatic autophagy induction and are protected against high-fat diet (HFD)-induced liver steatosis through autophagy. Molecularly, prevention of steatosis in the absence of REGγ entails elevated SirT1, a deacetylase regulating autophagy and metabolism. REGγ physically binds to SirT1, promotes its Ub-independent degradation, and inhibits its activity to deacetylate autophagy-related proteins, thereby inhibiting autophagy under normal conditions. Moreover, REGγ and SirT1 dissociate from each other through a phosphorylation-dependent mechanism under energy-deprived conditions, unleashing SirT1 to stimulate autophagy. These observations provide a function of the REGγ proteasome in autophagy and hepatosteatosis, underscoring mechanistically a crosstalk between the proteasome and autophagy degradation system in the regulation of lipid homeostasis.

INTRODUCTION

Macroautophagy (hereafter referred to as autophagy) is a conserved degradative process that is essential for cellular homeostasis and quality control and mediates degradation of damaged or excess proteins and organelles in lysosomes (Mizushima, 2007). Its dysregulation is involved in many physiological disorders and human diseases (Mizushima, 2007). Recent studies reveal that autophagy is required for breakdown of lipid droplets, and inhibition of autophagy leads to steatosis and fatty liver in mice (Czaja, 2010; Singh et al., 2009). Autophagy also regulates adipocyte differentiation and fat storage (Zhang et al., 2009). These findings present autophagy as a therapeutic target that could potentially be manipulated to treat diseases accompanied by excess lipid accumulation (Singh and Cuervo, 2012). Nevertheless, regulatory factors linking autophagy and lipid metabolisms urgently await discovery.

SirT1 (yeast Sir2) is a protein deacetylase that acts as a master metabolic sensor of NAD+ and has been reported to modulate lifespan and cellular metabolism (Guarente, 2000). SirT1 reduces fat accumulation in white adipose (Picard et al., 2004) and promotes browning of white adipose (Qiang et al., 2012). SirT1 overexpression reduces high-fat diet (HFD)-induced steatosis and improves insulin sensitivity (Pfluger et al., 2008), whereas loss of SirT1 leads to liver steatosis and inflammation (Purushotham et al., 2009). In addition, SirT1 provides a cell survival advantage in response to stress by deacetylating a number of substrates, such as p53 (Luo et al., 2001) and FOXOs (Brunet et al., 2004). SirT1 can be regulated by FOXO3a, p53, and HIC1 at the level of transcription (Chen et al., 2005; Nemoto et al., 2004) and is regulated by DBC1 through protein-protein interaction (Zhao et al., 2008). SirT1 expression is augmented following fasting (Nemoto et al., 2004). We previously reported that DNA damaging agents also induce SirT1 expression (Wang et al., 2006). Importantly, overexpression of SirT1 stimulates autophagy, and SirT1 knockout (KO) MEF cells cannot fully activate autophagy under starved conditions (Lee et al., 2008). However, molecular factors and mechanisms that control SirT1 autophagic function are largely unexplored.

BRIEF REPORT

Abatacept in B7-1–Positive Proteinuric Kidney Disease

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SUMMARY

Abatacept (cytotoxic T-lymphocyte–associated antigen 4–immunoglobulin fusion protein [CTLA-4–Ig]) is a costimulatory inhibitor that targets B7-1 (CD80). The present report describes five patients who had focal segmental glomerulosclerosis (FSGS) (four with recurrent FSGS after transplantation and one with primary FSGS) and proteinuria with B7-1 immunostaining of podocytes in kidney-biopsy specimens. Abatacept induced partial or complete remissions of proteinuria in these patients, suggesting that B7-1 may be a useful biomarker for the treatment of some glomerulopathies. Our data indicate that abatacept may stabilize β1-integrin activation in podocytes and reduce proteinuria in patients with B7-1–positive glomerular disease.

From the Department of Medicine, Massachusetts General Hospital and Harvard Medical School (C.-C.Y., A.W., S.H., D.B., M.A.A., A.G., P.M.), Department of Pathology, Brigham and Women's Hospital and Harvard Medical School (A.W.), and Division of Nephrology, Children's Hospital Boston (P.F.) — all in Boston; the Graduate Institute of Medicine, College of Medicine (C.-C.Y.), and Department of Internal Medicine (J.-M.C., H.-C.C.), Kaohsiung Medical University, Kaohsiung, Taiwan; the Division of Nephrology and Hypertension (A.F., D.M., M.H.F., C.F., V.G.) and Lilian Jean Kaplan Division of Kidney–Pancreas Transplantation, Miami Transplant Institute, Department of Surgery (J.S., L.C., G.C., G.W.B.), University of Miami Miller School of Medicine, Miami; the Division of Nephrology, Mount Sinai School of Medicine, New York (K.N.C.); and Pediatric Nephrology, Children's Hospital, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (J.O.). Address reprint requests to Dr. Mundel at the Division of Nephrology, Massachusetts General Hospital, 149 13th St., Charlestown, MA 02129, or at mundel.peter@mgh.harvard.edu.

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THE RENAL GLOMERULI ARE HIGHLY SPECIALIZED STRUCTURES THAT ensure selective ultrafiltration of plasma, by which most proteins are retained in the blood.[1] The glomerular filtration barrier consists of the glomerular capillary endothelium, the glomerular basement membrane, and specialized cells, the podocytes, that serve as a final barrier to urinary loss of plasma proteins.[1] Disrupted podocyte function damages the kidney filtration mechanism, resulting in proteinuria and, in some circumstances, the nephrotic syndrome.[1] Proteinuria is common to a heterogeneous group of kidney diseases, including minimal-change disease, FSGS, membranous nephropathy, and diabetic nephropathy, all of which affect millions of persons worldwide and often result in end-stage renal disease (ESRD).[1] In particular, primary FSGS as well as recurrent FSGS after kidney transplantation remain largely untreatable, leading to ESRD and, after transplantation, to allograft loss.[2]

Abatacept (CTLA-4–Ig) is an inhibitor of the T-cell costimulatory molecule B7-1 (CD80).[3] B7-1 is induced in podocytes in various animal models of proteinuria.[4] Podocyte B7-1 expression is not evident in normal human kidney podocytes but is found in patients with certain glomerular diseases. Because we observed B7-1 immunostaining in 13 of 21 randomly selected biopsy specimens of native kidneys from patients with proteinuric kidney disease, including primary FSGS, we deduced that B7-1 had been induced during the disease. We also observed B7-1 staining in every biopsy specimen from patients with recurrent FSGS that we examined. We treated five patients with abatacept[3]; nephrotic-range proteinuria resolved in

Cell

Ablation of PRDM16 and Beige Adipose Causes Metabolic Dysfunction and a Subcutaneous to Visceral Fat Switch

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SUMMARY

A clear relationship exists between visceral obesity and type 2 diabetes, whereas subcutaneous obesity is comparatively benign. Here, we show that adipocyte-specific deletion of the coregulatory protein PRDM16 caused minimal effects on classical brown fat but markedly inhibited beige adipocyte function in subcutaneous fat following cold exposure or β3-agonist treatment. These animals developed obesity on a high-fat diet, with severe insulin resistance and hepatic steatosis. They also showed altered fat distribution with markedly increased subcutaneous adiposity. Subcutaneous adipose tissue in mutant mice acquired many key properties of visceral fat, including decreased thermogenic and increased inflammatory gene expression and increased macrophage accumulation. Transplantation of subcutaneous fat into mice with diet-induced obesity showed a loss of metabolic benefit when tissues were derived from PRDM16 mutant animals. These findings indicate that PRDM16 and beige adipocytes are required for the "browning" of white fat and the healthful effects of subcutaneous adipose tissue.

INTRODUCTION

Obesity has become a global epidemic, contributing to increases in the prevalence of type 2 diabetes, hypertension, cardiovascular disease, and certain cancers. Generally, two broad categories of obesity are recognized: visceral (VISC) and subcutaneous (SubQ). The location where fat is deposited appears to have a great influence on the likelihood of an individual developing many of the sequelae of obesity (Gesta et al., 2007). Importantly, VISC adiposity is strongly associated with increased mortality, even in individuals with a normal body mass index (Pischon et al., 2008). SubQ adiposity, however, appears to be comparatively benign (Manolopoulos et al., 2010). The association between regional fat deposition and adverse health complications was first noted with pioneering clinical descriptions in the 1950s (Vague, 1956). It has also been recognized for centuries that men have a greater propensity for deposition of VISC fat, while premenopausal women have a greater tendency to accumulate fat in SubQ stores, though substantial variation exists in both sexes (Vague, 1947).

The relationship between site of adipose tissue accumulation and metabolic disease has been shown in several animal models. Transgenic mice overexpressing 11-β HSD-1 in adipose tissue develop VISC obesity along with insulin resistance, diabetes, and hyperlipidemia (Masuzaki et al., 2001). Conversely, transgenic mice overexpressing adiponectin or mitoNEET in adipose tissue develop remarkable SubQ obesity, but remain metabolically healthy (Kim et al., 2007; Kusminski et al., 2012). The functional importance of these adipose depots has been directly demonstrated in studies showing metabolic benefit by transplantation of SubQ fat or surgical removal of VISC fat (Gabriely et al., 2002; Tran et al., 2008).

These divergent metabolic effects of different adipose depots have raised interest in the unique properties of VISC and SubQ fat. VISC fat is notable for having a substantial degree of inflammation when obesity is present. Originally recognized as the secretion of TNFα and other inflammatory cytokines from fat tissue of obese animals (Hotamisligil et al., 1993), it is now known that there is a broad increase in a variety of immune cells

LETTER

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An excitatory paraventricular nucleus to AgRP neuron circuit that drives hunger

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Hunger is a hard-wired motivational state essential for survival. Agouti-related peptide (AgRP)-expressing neurons in the arcuate nucleus (ARC) at the base of the hypothalamus are crucial to the control of hunger. They are activated by caloric deficiency and, when naturally or artificially stimulated, they potently induce intense hunger and subsequent food intake[1–5]. Consistent with their obligatory role in regulating appetite, genetic ablation or chemogenetic inhibition of AgRP neurons decreases feeding[3,6,7]. Excitatory input to AgRP neurons is important in caloric-deficiency-induced activation, and is notable for its remarkable degree of caloric-state-dependent synaptic plasticity[8–10]. Despite the important role of excitatory input, its source(s) has been unknown. Here, through the use of Cre-recombinase-enabled, cell-specific neuron mapping techniques in mice, we have discovered strong excitatory drive that, unexpectedly, emanates from the hypothalamic paraventricular nucleus, specifically from subsets of neurons expressing thyrotropin-releasing hormone (TRH) and pituitary adenylate cyclase-activating polypeptide (PACAP, also known as ADCYAP1). Chemogenetic stimulation of these afferent neurons in sated mice markedly activates AgRP neurons and induces intense feeding. Conversely, acute inhibition in mice with caloric-deficiency-induced hunger decreases feeding. Discovery of these afferent neurons capable of triggering hunger advances understanding of how this intense motivational state is regulated.

To identify monosynaptic inputs to AgRP neurons, we used a modified rabies virus SADΔG–EGFP (EnvA)[11] in combination with Cre-dependent helper adeno-associated viruses (AAVs) expressing TVA (receptor for the avian sarcoma leucosis virus glycoprotein EnvA; AAV8-FLEX-TVA–mCherry) and RG (rabies envelope glycoprotein; AAV8-FLEX–RG). When used with *Agrp-IRES-Cre* mice, TVA and RG, respectively, allow for rabies infection of AgRP neurons and subsequent retrograde transynaptic spread[11,12] (Fig. 1a). AAV targeting of the helper viruses was specific to AgRP neurons (Supplementary Fig. 1). Three weeks post-AAV transduction, we injected SADΔG–EGFP (EnvA) into the same area and examined brains 7 days later for $EGFP^+$ signal. We detected the highest number of $EGFP^+$ cells in the ARC (38%), probably representing the initially infected AgRP neurons, and possibly local afferents (Fig. 1b; Supplementary Fig. 2). We next evaluated distant upstream anatomical areas for $EGFP^+$ neurons and found that the vast majority were located in two hypothalamic nuclei, the dorsal medial hypothalamus (DMH, 26%) which contains both glutamatergic and GABAergic neurons[13] and the paraventricular hypothalamus (PVH, 18%) consisting primarily of glutamatergic neurons[13] (Fig. 1b; Supplementary Fig. 2). Finally, we also observed a smaller number of $EGFP^+$ cells in other hypothalamic sites (Supplementary Fig. 2).

We next used channelrhodopsin (ChR2)-assisted circuit mapping (CRACM)[14,15] to both confirm and determine valence of functional monosynaptic connectivity between afferents and AgRP neurons. CRACM involves *in vivo* targeted expression of ChR2, a photoexcitable cation channel, in presumptive presynaptic upstream neurons (and their terminals), followed by *ex vivo* electrophysiologic assessment in acute brain slices of light-evoked postsynaptic currents in candidate downstream neurons. To investigate excitatory input to AgRP neurons, we stereotaxically injected Cre-dependent AAV expressing ChR2–mCherry (AAV8-DIO-ChR2–mCherry) (Supplementary Fig. 3a) into brain sites of *Vglut2-IRES-Cre; Npy-hrGFP* mice[13]. VGLUT2 (also known as SLC17A6) is the glutamate synaptic vesicle transporter expressed in the hypothalamus, hence *Vglut2-IRES-Cre* mice target relevant excitatory neurons[13]. As AgRP neurons co-express neuropeptide Y (NPY), *Npy-hrGFP* mice allow visualization of AgRP neurons[16,17]. Consistent with the rabies tracing, we detected light-evoked excitatory post-synaptic currents (EPSCs) in all $VGLUT2^{DMH}\rightarrow AgRP^{ARC}$ neurons tested (latency between onset of light and EPSC = 4.7 ± 0.2 ms; Fig. 1c; Supplementary Fig. 3f). These were blocked by CNQX (6-cyano-7-nitroquinoxaline-2,3-dione), an AMPA receptor antagonist, confirming their glutamatergic nature. Next, we examined monosynaptic connections between $VGLUT2^{PVH}\rightarrow AgRP^{ARC}$ neurons and again, consistent with the rabies mapping, we observed light-evoked EPSCs in all AgRP neurons tested (latency = 4.9 ± 0.4 ms; Fig. 1d; Supplementary Fig. 3g). These also were blocked by CNQX.

In addition, we selectively expressed ChR2 in the ventral medial hypothalamus (VMH) and lateral hypothalamus (LH), two sites with few $EGFP^+$ cells, and also the ARC, which could provide local afferents, and investigated possible connectivity to AgRP neurons. In agreement with the negative rabies data, no light-evoked EPSCs were detected in 36 out of 37 $VGLUT2^{VMH}\rightarrow AgRP^{ARC}$ neurons tested (Supplementary Fig. 3b, h) or in any $VGLUT2^{LH}\rightarrow AgRP^{ARC}$ neurons tested (Supplementary Fig. 3c, i). Likewise, we failed to detect light-evoked EPSCs in any $VGLUT2^{ARC}\rightarrow AgRP^{ARC}$ neurons tested (Supplementary Fig. 3d, j). However, and as previously noted[18], glutamatergic VMH neurons were monosynaptically connected to nearby pro-opiomelanocortin (POMC) neurons ($VGLUT2^{VMH}\rightarrow POMC^{ARC}$), as we observed light-evoked EPSCs in all POMC neurons tested (latency = 4.4 ± 0.2 ms; Supplementary Fig. 3e).

The CRACM studies suggest marked differences in the strength of $VGLUT2^{PVH}\rightarrow AgRP^{ARC}$ versus $VGLUT2^{DMH}\rightarrow AgRP^{ARC}$ inputs. First, the amplitude of light-evoked EPSCs generated from $VGLUT2^{PVH}$ inputs were approximately threefold greater (Fig. 1e). Second, the effectiveness of light pulses in evoking EPSCs differed, with DMH inputs showing a much higher failure rate (~32%; Fig. 1f; Supplementary Fig. 4) compared

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LETTER

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Human oocytes reprogram adult somatic nuclei of a type 1 diabetic to diploid pluripotent stem cells

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The transfer of somatic cell nuclei into oocytes can give rise to pluripotent stem cells that are consistently equivalent to embryonic stem cells[1–3], holding promise for autologous cell replacement therapy[4,5]. Although methods to induce pluripotent stem cells from somatic cells by transcription factors[6] are widely used in basic research, numerous differences between induced pluripotent stem cells and embryonic stem cells have been reported[7–11], potentially affecting their clinical use. Because of the therapeutic potential of diploid embryonic stem-cell lines derived from adult cells of diseased human subjects, we have systematically investigated the parameters affecting efficiency of blastocyst development and stem-cell derivation. Here we show that improvements to the oocyte activation protocol, including the use of both kinase and translation inhibitors, and cell culture in the presence of histone deacetylase inhibitors, promote development to the blastocyst stage. Developmental efficiency varied between oocyte donors, and was inversely related to the number of days of hormonal stimulation required for oocyte maturation, whereas the daily dose of gonadotropin or the total number of metaphase II oocytes retrieved did not affect developmental outcome. Because the use of concentrated Sendai virus for cell fusion induced an increase in intracellular calcium concentration, causing premature oocyte activation, we used diluted Sendai virus in calcium-free medium. Using this modified nuclear transfer protocol, we derived diploid pluripotent stem-cell lines from somatic cells of a newborn and, for the first time, an adult, a female with type 1 diabetes.

We have previously reported the derivation of pluripotent stem cells containing a reprogrammed genome derived from an adult somatic cell, and a haploid oocyte genome[12]. Development to the blastocyst stage only occurred in the presence of the oocyte genome; diploid nuclear transfer cells arrested development at the cleavage stages, failing to express embryonic genes. To improve developmental potential and transcriptional reprogramming in diploid nuclear transfer oocytes, we tested the effect of histone deacetylation (HDAC) inhibitors, as well as changes to the artificial activation protocol on developmental potential. These modifications were based on the report that HDAC inhibitors improved development after somatic cell nuclear transfer in mouse oocytes[13], and on our observation that parthenogenetic development was more efficient when oocytes were activated with the translation inhibitor puromycin[14] than when activated with the kinase inhibitor 6-dimethylaminopurine (6-DMAP)[12] (Extended Data Fig. 1). To minimize the effect of potential variation in oocyte quality, for each condition we used oocytes from at least four donors (Fig. 1a). We first tested the use of puromycin for oocyte activation in somatic cell nuclear transfer without removing the oocyte genome, resulting in efficient development to the blastocyst stage (Fig. 1a). However, development of diploid nuclear transfer oocytes still arrested at cleavage stages (Fig. 1a). Only when we applied the HDAC inhibitor scriptaid during the first embryonic interphase, did we observe development to the morula and blastocyst stages at a low frequency (Fig. 1a). Further improvement in developmental potential was observed when both puromycin and 6-DMAP were combined during oocyte activation, resulting in development to expanded blastocysts (Fig. 1a, b and Extended Data Fig. 2a, b). Puromycin promotes oocyte activation by inhibiting translation of cyclin B[15,16], whereas 6-DMAP inhibits the activity of meiotic kinases; their combined use may result in a more complete or more rapid inactivation of meiotic kinases. These results show that an improved activation protocol and the use of an HDAC inhibitor enabled development of nuclear transfer cells to the blastocyst stage in the absence of the oocyte genome.

Because development beyond the cleavage stage requires gene expression[17], development to the morula and blastocyst stages indicates transcriptional activity of the transferred somatic cell genome. Whereas previous nuclear transfer protocols did not result in expression of a green fluorescent protein (GFP) transgene contained in the somatic cell genome[12], 58% (14 of 24) of the nuclear transfer cells treated with HDAC inhibitor were GFP positive (Fig. 1b), and had a global gene expression profile similar to *in vitro* fertilized (IVF) embryos (Fig. 1c), demonstrating that transcriptional reprogramming was extensive. Of the 7 nuclear transfer blastocysts obtained using optimized protocols, 3 formed an outgrowth (Extended Data Fig. 2c), but none gave rise to an embryonic stem (ES) cell line.

More recently, it has become possible to derive diploid pluripotent stem-cell lines from fetal fibroblasts[18]. The derivation of cell lines from an 8-month-old subject with Leigh syndrome was also stated, although no karyotype or evidence of pluripotency was provided. While the use of the HDAC inhibitor to obtain blastocyst development is consistent with our data and a previous report[19], the authors also attributed successful derivation to the use of caffeine during oocyte enucleation to promote nuclear envelope breakdown and condensation of somatic chromatin, the use of a hormone stimulation protocol yielding a small number of high-quality oocytes, and to the use of an electrical pulse for oocyte activation. As it remained unclear whether diploid nuclear transfer ES cells could reliably be derived from postnatal somatic cells, we determined the requirements for blastocyst development and ES cell derivation using adult somatic cells of a type 1 diabetic female (age 32 years, age of onset 10 years) and human foreskin fibroblasts of a male newborn for nuclear transfer.

We first determined whether oocyte enucleation interfered with the condensation of transferred somatic chromatin, a process correlating with developmental potential[20]. When we transferred somatic cell genomes at G1 or G0 stages of the cell cycle into enucleated oocytes, 17 out of 23 (74%) assembled a spindle within 1–4 h after transfer as determined by microtubule birefringence[21] or immunostaining (Fig. 2a). Somatic chromosomes were condensed and phosphorylated on serine 28 of histone H3, but not aligned on a metaphase plate, because unreplicated

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Cell Metabolism
Article

Activation of Calcium/Calmodulin-Dependent Protein Kinase II in Obesity Mediates Suppression of Hepatic Insulin Signaling

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SUMMARY

A hallmark of obesity is selective suppression of hepatic insulin signaling ("insulin resistance"), but critical gaps remain in our understanding of the molecular mechanisms. We now report a major role for hepatic CaMKII, a calcium-responsive kinase that is activated in obesity. Genetic targeting of hepatic CaMKII, its downstream mediator p38, or the p38 substrate and stabilizer MK2 enhances insulin-induced p-Akt in palmitate-treated hepatocytes and obese mouse liver, leading to metabolic improvement. The mechanism of improvement begins with induction of ATF6 and the ATF6 target p58^{IPK}, a chaperone that suppresses the PERK—p-eIF2α—ATF4 branch of the UPR. The result is a decrease in the ATF4 target TRB3, an inhibitor of insulin-induced p-Akt, leading to enhanced activation of Akt and its downstream metabolic mediators. These findings increase our understanding of the molecular mechanisms linking obesity to selective insulin resistance and suggest new therapeutic targets for type 2 diabetes and metabolic syndrome.

INTRODUCTION

Obesity is the leading cause of insulin resistance, metabolic syndrome, and type 2 diabetes (T2D), but therapeutic options are limited due to critical gaps in our knowledge of molecular mechanisms linking obesity with the metabolic disturbances of insulin resistance and T2D (Samuel and Shulman, 2012). A key factor in T2D is an inappropriate increase in hepatic glucose production (HGP), which results from selective hepatic insulin resistance together with impaired suppression of glucagon signaling (Lin and Accili, 2011). In addition to elevated HGP, selective insulin resistance contributes to other critical maladies associated with T2D, including cardiovascular disease, the leading cause of death in these patients (Bornfeldt and Tabas, 2011; Leavens and Birnbaum, 2011).

We recently elucidated a pathway through which glucagon stimulates HGP in fasting and in obesity, and in obesity this pathway contributes to hyperglycemia (Ozcan et al., 2012; Wang et al., 2012). The pathway is triggered downstream of the glucagon receptor by PKA-mediated activation of the endoplasmic reticulum (ER) calcium release channel, inositol 1,4,5-triphosphate receptor (IP3R). Channel opening, which is also promoted by a glucagon receptor-phospholipase C pathway that generates IP3, results in release of calcium from ER stores, which then activates the cytoplasmic calcium-sensitive kinase, calcium/calmodulin dependent-protein kinase II (CaMKII). CaMKII then activates the MAPK p38α, which phosphorylates FoxO1 in a manner that promotes FoxO1 nuclear translocation. Nuclear FoxO1 induces target genes that are rate limiting for glycogenolysis and gluconeogenesis, notably *G6pc* and *Pck1*. This CaMKII-FoxO1 pathway is complemented by the activation of the calcium-sensitive phosphatase calcineurin, which promotes CRTC2-mediated induction of the FoxO1 transcriptional partner, PGC1α (Wang et al., 2012). Moreover, recent studies have shown that calcium transport back into the ER, mediated by sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA), is dysfunctional in obesity (Fu et al., 2011; Park et al., 2010), which could contribute to both the amplitude and the duration of the pathological calcium response. Collectively, these data point to the importance of intracellular calcium metabolism and CaMKII in enhanced HGP in obesity. However, a critical remaining question in this area was whether CaMKII plays a role in the other major pathological process in obesity and T2D, namely selective insulin resistance.

Defective insulin signaling is a major feature of selective hepatic insulin resistance in obesity (Brown and Goldstein, 2008; Könner and Brüning, 2012). In normal physiology, insulin stimulates insulin autophosphorylation of the insulin receptor (IR), which promotes to Tyr-phosphorylation of insulin receptor substrates 1 and 2 (IRS-1/2). Through a series of downstream processes involving lipid mediators and protein kinases, p-IRS-1/2 leads to Ser/Thr-phosphorylation and activation of

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Obesity Activates a Program of Lysosomal-Dependent Lipid Metabolism in Adipose Tissue Macrophages Independently of Classic Activation

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SUMMARY

Obesity activates a complex systemic immune response that includes the recruitment of macrophages and other immune cells to key metabolic tissues. Current models postulate that obesity and excess lipids classically activate macrophages, polarizing them toward an M1 (inflammatory) state. Little is known about noninflammatory functions of adipose tissue macrophages (ATMs). Here, we show that the expansion of adipose tissue (AT) across models of obesity induces a program of lysosome biogenesis in ATMs and is associated with lipid catabolism but not a classic inflammatory phenotype. This program is induced by factors produced by AT and is tightly coupled to lipid accumulation by ATMs. Inhibition of ATM lysosome function impairs lipid metabolism and increases lipid content in ATMs and reduces whole AT lipolysis. These data argue that ATMs contribute quantitatively to the development of obesity-induced inflammation but also serve an important role in lipid trafficking independent of their inflammatory phenotype.

INTRODUCTION

Changes in metabolic state, including obesity, fasting, thermogenic challenges, weight loss, and caloric restriction, broadly activate the immune system (Feuerer et al., 2009; Kosteli et al., 2010; Nguyen et al., 2011; Obstfeld et al., 2010; Talukdar et al., 2012; Weisberg et al., 2003; Winer et al., 2011; Wu et al., 2011; Wu et al., 2007; Xu et al., 2003). In adipose tissue (AT), obesity leads to the accumulation of macrophages to the extent that, in the most obese individuals, as many as half of all cells in a fat depot are macrophages (Weisberg et al., 2003). Efforts to understand the role that AT macrophages (ATMs) play in metabolism have focused largely on characterizing the inflammatory phenotypes and functions of ATMs (Chawla et al., 2011). Indeed, several studies have suggested that, in addition to the quantitative increase in ATMs, obesity elicits a qualitative inflammatory switch in ATM phenotypes (Lumeng et al., 2007a, b).

These studies have described that, in lean animals, alternatively activated M2-like macrophages predominate, but, with the onset of obesity, there is recruitment and accumulation of classically activated macrophages that form multinucleated giant cells and express CD11c and markers of M1 polarization (Lumeng et al., 2007a, b). Most of these studies have focused on the expression of a few genes; e.g., *Tnf*, *Il6*, *Arg1*, or *Nos2*, or surface antigens (e.g., CD206) to categorize ATMs as M1 or M2 (Lumeng et al., 2007a, b). However, these findings are at odds with whole-tissue expression and other analysis of ATM populations. For example, in whole AT, the expression of *Arg1* and CD206+ cells increases in obese individuals despite the fact that they are markers of M2 polarized cells (Bourlier et al., 2008; Shaul et al., 2010). Nonetheless, the observation that the treatment of non-ATMs, including bone-marrow-derived, peritoneal, and immortalized macrophage-like cells, with saturated fatty acids or conditioned medium of adipocyte cell lines induces an increase, albeit a modest increase in comparison to lipopolysaccharide (Lichtenstein et al., 2010; Shi et al., 2006; Suganami et al., 2007), in M1 gene expression has lead to a model in which excess lipids released from adipocytes during the development of obesity drives M1 polarization (Osborn and Olefsky, 2012).

Although macrophages share common immune and reparative roles and stereotypical inflammatory responses to many stimuli, they also possess distinct tissue-specific developmental programs, phenotypes, and functions that are regulated by their cellular context (Pollard, 2009). In AT, macrophages develop and differentiate in a lipid-rich environment, but the developmental program and tissue-specific functions of ATMs, including those related to lipid metabolism, have been largely unexplored. In contrast, the well-studied functions of osteoclasts (multinucleated bone macrophages) demonstrate that macrophages can play critical roles in local tissue-specific metabolic functions (Edwards and Mundy, 2011). We hypothesized that developmental signals produced by AT similarly drive the differentiation of ATMs and functions that are adapted to a lipid-rich environment.

Defining the tissue-specific functions of ATMs and how those functions are altered by obesity offers the possibility of identifying pathways that are fundamental to normal and pathologic function of AT. In an attempt to identify cellular functions of ATMs that are regulated by adiposity, we profiled AT and purified ATMs, finding that a program of lysosome biogenesis is activated by obesity. Surprisingly, we did not find that this program

ORIGINAL ARTICLE

Null Mutation in Hormone-Sensitive Lipase Gene and Risk of Type 2 Diabetes

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ABSTRACT

BACKGROUND

Lipolysis regulates energy homeostasis through the hydrolysis of intracellular triglycerides and the release of fatty acids for use as energy substrates or lipid mediators in cellular processes. Genes encoding proteins that regulate energy homeostasis through lipolysis are thus likely to play an important role in determining susceptibility to metabolic disorders.

METHODS

We sequenced 12 lipolytic-pathway genes in Old Order Amish participants whose fasting serum triglyceride levels were at the extremes of the distribution and identified a novel 19-bp frameshift deletion in exon 9 of *LIPE*, encoding hormone-sensitive lipase (HSL), a key enzyme for lipolysis. We genotyped the deletion in DNA from 2738 Amish participants and performed association analyses to determine the effects of the deletion on metabolic traits. We also obtained biopsy specimens of abdominal subcutaneous adipose tissue from 2 study participants who were homozygous for the deletion (DD genotype), 10 who were heterozygous (ID genotype), and 7 who were noncarriers (II genotype) for assessment of adipose histologic characteristics, lipolysis, enzyme activity, cytokine release, and messenger RNA (mRNA) and protein levels.

RESULTS

Carriers of the mutation had dyslipidemia, hepatic steatosis, systemic insulin resistance, and diabetes. In adipose tissue from study participants with the DD genotype, the mutation resulted in the absence of HSL protein, small adipocytes, impaired lipolysis, insulin resistance, and inflammation. Transcription factors responsive to peroxisome-proliferator–activated receptor γ (PPAR-γ) and downstream target genes were down-regulated in adipose tissue from participants with the DD genotype, altering the regulation of pathways influencing adipogenesis, insulin sensitivity, and lipid metabolism.

CONCLUSIONS

These findings indicate the physiological significance of HSL in adipocyte function and the regulation of systemic lipid and glucose homeostasis and underscore the severe metabolic consequences of impaired lipolysis. (Funded by the National Institutes of Health and others).

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Article

Glucagon Regulates Hepatic Kisspeptin to Impair Insulin Secretion

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SUMMARY

Early in the pathogenesis of type 2 diabetes mellitus (T2DM), dysregulated glucagon secretion from pancreatic α cells occurs prior to impaired glucose-stimulated insulin secretion (GSIS) from β cells. However, whether hyperglucagonemia is causally linked to β cell dysfunction remains unclear. Here we show that glucagon stimulates via cAMP-PKA-CREB signaling hepatic production of the neuropeptide kisspeptin1, which acts on β cells to suppress GSIS. Synthetic kisspeptin suppresses GSIS in vivo in mice and from isolated islets in a kisspeptin1 receptor-dependent manner. Kisspeptin1 is increased in livers and in serum from humans with T2DM and from mouse models of diabetes mellitus. Importantly, liver *Kiss1* knockdown in hyperglucagonemic, glucose-intolerant, high-fat-diet fed, and *Lepr*$^{db/db}$ mice augments GSIS and improves glucose tolerance. These observations indicate a hormonal circuit between the liver and the endocrine pancreas in glycemia regulation and suggest in T2DM a sequential link between hyperglucagonemia via hepatic kisspeptin1 to impaired insulin secretion.

INTRODUCTION

Glucagon and insulin are secreted by pancreatic α and β cells, respectively, to precisely control blood glucose homeostasis. An early hallmark of type 2 diabetes mellitus (T2DM) is dysregulated glucagon secretion by pancreatic α cells. Nondiabetic humans exhibit postprandial suppression of blood glucagon, while individuals with T2DM lack this suppression and may even exhibit increased glucagon levels. In addition, studies in subsets of patients with T2DM suggest that elevated glucagon secretion occurs antecedent to β cell dysfunction (see D'Alessio [2011] and references therein).

Upon binding to its receptor Gcgr, glucagon activates cellular adenosine-3′-5′-cyclic monophosphate (cAMP)-protein kinase A (PKA) signaling to stimulate hepatic glucose production (HGP) and cause hyperglycemia (Chen et al., 2005). While hyperglycemia stimulates insulin secretion from β cells, transgenic upregulation of PKA activity in hepatocytes in mice results, as expected, in increased HGP and hyperglycemia but paradoxically in impaired GSIS (Niswender et al., 2005). Consistent with the idea that glucagon may be causally linked to β cell dysfunction are findings made during exogenous glucose infusion in rats, where insulin secretion only fails after blood glucagon levels rise and recovers upon glucagon inactivation by neutralizing antiserum (Jamison et al., 2011).

Based on these considerations for hyperglucagonemia and β cell dysfunction in T2DM, we reasoned that independent of HGP and hyperglycemia, glucagon signaling in the liver initiates a process that impacts on GSIS. We tested this hypothesis by comparing a mouse model of liver-specific PKA disinhibition (L-ΔPrkar1a mice, see below) with a model of hyperglycemia resulting from intravenous glucose infusion (D-glucose mice) combined with array-based gene expression analysis for secreted hepatic peptides, and we identified *Kiss1*, which encodes the neuropeptide kisspeptin1 to be upregulated in livers of L-ΔPrkar1a—but not in D-glucose—mice and to be directly stimulated by glucagon action via Gcgr on hepatocytes.

Kisspeptin1 has been described to be synthesized in the central nervous system and to regulate hypothalamic gonadotropin releasing hormone (GnRH) neurons and is processed to multiple biologically active, N-terminally truncated fragments, including kisspeptin 54 (K54), K14, K13, and K10, of which the latter exerts

Cell

A Zebrafish Embryo Culture System Defines Factors that Promote Vertebrate Myogenesis across Species

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SUMMARY

Ex vivo expansion of satellite cells and directed differentiation of pluripotent cells to mature skeletal muscle have proved difficult challenges for regenerative biology. Using a zebrafish embryo culture system with reporters of early and late skeletal muscle differentiation, we examined the influence of 2,400 chemicals on myogenesis and identified six that expanded muscle progenitors, including three GSK3β inhibitors, two calpain inhibitors, and one adenylyl cyclase activator, forskolin. Forskolin also enhanced proliferation of mouse satellite cells in culture and maintained their ability to engraft muscle in vivo. A combination of bFGF, forskolin, and the GSK3β inhibitor BIO induced skeletal muscle differentiation in human induced pluripotent stem cells (iPSCs) and produced engraftable myogenic progenitors that contributed to muscle repair in vivo. In summary, these studies reveal functionally conserved pathways regulating myogenesis across species and identify chemical compounds that expand mouse satellite cells and differentiate human iPSCs into engraftable muscle.

INTRODUCTION

Skeletal muscle is a highly specialized tissue composed of nondividing, multinucleated muscle fibers that contract to generate force. Skeletal muscle is formed during embryogenesis in a region of the embryo known as the myotome. In addition to generating differentiated muscle fibers, embryonic progenitor cells also give rise to specialized muscle-forming stem cells, known as satellite cells (Gros et al., 2005; Seale et al., 2000). Injury-induced satellite cell proliferation both replenishes the satellite cell pool and produces differentiated myoblasts, which fuse with existing myofibers and one another to regenerate muscle tissue.

Satellite cells are defined anatomically by their localization beneath the basal lamina of muscle fibers (Mauro, 1961) and molecularly by their expression of the paired-box transcription factor Pax7 (Seale et al., 2000). Transplantation-based studies in animal models have demonstrated the utility of engrafted satellite cells for regenerating diseased muscle (Cerletti et al., 2008; Fukada et al., 2004; Kuang et al., 2007; Montarras et al., 2005; Sacco et al., 2008; Sherwood et al., 2004; Tanaka et al., 2009), and analyses of mouse and human muscles indicate that their loss during aging contributes to age-associated muscle weakness (Brack et al., 2005; Cerletti et al., 2012; Chakkalakal et al., 2012; Shefer et al., 2010). Thus, muscle satellite cells are promising targets for cell therapies, but the realization of this promise has been hindered by the paucity of satellite cells that can be isolated or expanded from adult muscle tissue.

In contrast to satellite cells, embryonic stem cells (ESCs) and, more recently, induced pluripotent stem cells (iPSCs), can expand indefinitely in culture. Although some success has been achieved in directing the myogenic differentiation of ESCs/IPSCs through genetic manipulation, selective culture, and cell sorting approaches (Awaya et al., 2012; Barberi et al., 2007; Darabi et al., 2008; Mizuno et al., 2010; Zheng et al., 2006), the generation of well-differentiated muscle cells from human or murine pluripotent cells has proved challenging. In this study, we took a cross-systems approach to identify conserved molecular pathways that regulate muscle specification and

Original Investigation

Association Between a Genetic Variant Related to Glutamic Acid Metabolism and Coronary Heart Disease in Individuals With Type 2 Diabetes

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IMPORTANCE Diabetes is associated with an elevated risk of coronary heart disease (CHD). Previous studies have suggested that the genetic factors predisposing to excess cardiovascular risk may be different in diabetic and nondiabetic individuals.

OBJECTIVE To identify genetic determinants of CHD that are specific to patients with diabetes.

DESIGN, SETTING, AND PARTICIPANTS We studied 5 independent sets of CHD cases and CHD-negative controls from the Nurses' Health Study (enrolled in 1976 and followed up through 2008), Health Professionals Follow-up Study (enrolled in 1986 and followed up through 2008), Joslin Heart Study (enrolled in 2001-2008), Gargano Heart Study (enrolled in 2001-2008), and Catanzaro Study (enrolled in 2004-2010). Included were a total of 1517 CHD cases and 2671 CHD-negative controls, all with type 2 diabetes. Results in diabetic patients were compared with those in 737 nondiabetic CHD cases and 1637 nondiabetic CHD-negative controls from the Nurses' Health Study and Health Professionals Follow-up Study cohorts. Exposures included 2 543 016 common genetic variants occurring throughout the genome.

MAIN OUTCOMES AND MEASURES Coronary heart disease—defined as fatal or nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, or angiographic evidence of significant stenosis of the coronary arteries.

RESULTS A variant on chromosome 1q25 (rs10911021) was consistently associated with CHD risk among diabetic participants, with risk allele frequencies of 0.733 in cases vs 0.679 in controls (odds ratio, 1.36 [95% CI, 1.22-1.51]; $P = 2 \times 10^{-8}$). No association between this variant and CHD was detected among nondiabetic participants, with risk allele frequencies of 0.697 in cases vs 0.696 in controls (odds ratio, 0.99 [95% CI, 0.87-1.13]; $P = .89$), consistent with a significant gene × diabetes interaction on CHD risk ($P = 2 \times 10^{-4}$). Compared with protective allele homozygotes, rs10911021 risk allele homozygotes were characterized by a 32% decrease in the expression of the neighboring glutamate-ammonia ligase (*GLUL*) gene in human endothelial cells ($P = .0048$). A decreased ratio between plasma levels of γ-glutamyl cycle intermediates pyroglutamic and glutamic acid was also shown in risk allele homozygotes ($P = .029$).

CONCLUSION AND RELEVANCE A single-nucleotide polymorphism (rs10911021) was identified that was significantly associated with CHD among persons with diabetes but not in those without diabetes and was functionally related to glutamic acid metabolism, suggesting a mechanistic link.

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Annals of Internal Medicine | ORIGINAL RESEARCH

Salicylate (Salsalate) in Patients With Type 2 Diabetes

A Randomized Trial

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Background: Short-duration studies show that salsalate improves glycemia in type 2 diabetes mellitus (T2DM).

Objective: To assess 1-year efficacy and safety of salsalate in T2DM.

Design: Placebo-controlled, parallel trial; computerized randomization and centralized allocation, with patients, providers, and researchers blinded to assignment. (ClinicalTrials.gov: NCT00799643)

Setting: 3 private practices and 18 academic centers in the United States.

Patients: Persons aged 18 to 75 years with fasting glucose levels of 12.5 mmol/L or less (≤225 mg/dL) and hemoglobin A_{1c} (HbA_{1c}) levels of 7.0% to 9.5% who were treated for diabetes.

Intervention: 286 participants were randomly assigned (between January 2009 and July 2011) to 48 weeks of placebo ($n = 140$) or salsalate, 3.5 g/d ($n = 146$), in addition to current therapies, and 283 participants were analyzed (placebo, $n = 137$; salsalate, $n = 146$).

Measurements: Change in hemoglobin A_{1c} level (primary outcome) and safety and efficacy measures.

Results: The mean HbA_{1c} level over 48 weeks was 0.37% lower in the salsalate group than in the placebo group (95% CI, −0.53% to −0.21%; $P < 0.001$). Glycemia improved despite more reductions in concomitant diabetes medications in salsalate recipients than in placebo recipients. Lower circulating leukocyte, neutrophil, and lymphocyte counts show the anti-inflammatory effects of salsalate. Adiponectin and hematocrit levels increased more and fasting glucose, uric acid, and triglyceride levels decreased with salsalate, but weight and low-density lipoprotein cholesterol levels also increased. Urinary albumin levels increased but reversed on discontinuation; estimated glomerular filtration rates were unchanged.

Limitation: Trial duration and number of patients studied were insufficient to determine long-term risk–benefit of salsalate in T2DM.

Conclusion: Salsalate improves glycemia in patients with T2DM and decreases inflammatory mediators. Continued evaluation of mixed cardiorenal signals is warranted.

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For author affiliations, see end of text.

* For a list of contributors for the Targeting Inflammation Using Salsalate in Type 2 Diabetes Study, see **Appendix 1** (available at www.annals.org).

Salicylate is one of the oldest drugs in clinical practice, with documented use of relevant plant extracts for treating pain and inflammation dating back at least 3500 years (1). Nevertheless, its medicinal properties and mechanisms of action remain incompletely understood. Chemically pure forms were introduced during the 19th century (2, 3), but by the century's end, salicylate had been acetylated by chemists to yield aspirin, which became the most used—and most marketed—drug in history (1, 4). The mechanism of aspirin is well-established; the acetyl group covalently modifies a serine at the active site of the cyclooxygenase (COX) enzymes (5), making it the prototypic nonsteroidal anti-inflammatory drug (NSAID). Salicylate lacks an acetyl group and, thus, must have a different mechanism of action. Neither salicylate nor prodrugs, including salsalate or trilisate, which are marketed for pain, have been tested for efficacy and safety under what regulatory agencies now consider to be current standard practice in clinical trials.

Interest in salicylate was renewed after suggestions that it lowers blood glucose in type 2 diabetes mellitus (T2DM) (6). Results from proof-of-principle studies using salsalate in patients with T2DM demonstrated reduced blood glucose, triglyceride, free fatty acid, and C-reactive protein concentrations; improved glucose utilization during euglycemic hyperinsulinemic clamp (defined as the glucose infusion rate required to maintain euglycemia at steady state during insulin infusion); and increased circulating insulin and adiponectin levels (7). The National Institutes of Health–sponsored TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) trials determine whether this generic and inexpensive drug is safe, tolerated, and efficacious in diabetes. Stage 1, a dose-ranging study, was reported (8); stage 2 of TINSAL-T2D is a larger study to assess the magnitude and durability of glycemic efficacy over 1 year, tolerability, and an array of safety variables relevant to patients with diabetes.

METHODS

Design Overview

Stage 2 of TINSAL-T2D was a single-blind, placebo lead-in, randomized (1:1), placebo-controlled, parallel clinical trial to assess whether salsalate is superior to placebo in

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LETTERS

Thioredoxin-interacting protein regulates insulin transcription through microRNA-204

Guanlan Xu, Junqin Chen, Gu Jing & Anath Shalev

Beta-cell dysfunction and impaired insulin production are hallmarks of diabetes[1], but despite the growing diabetes epidemic, the molecular mechanisms underlying this disease have remained unclear. We identified thioredoxin-interacting protein (TXNIP), a cellular redox regulator, as a crucial factor in beta-cell biology and show that beta-cell TXNIP is upregulated in diabetes, whereas TXNIP deficiency protects against diabetes by preventing beta-cell apoptosis[2,3]. Here we show that TXNIP and diabetes induce beta-cell expression of a specific microRNA, miR-204, which in turn blocks insulin production by directly targeting and downregulating *MAFA*, a known insulin transcription factor. In particular, we first discovered the regulation of miR-204 by TXNIP by microarray analysis, followed by validation studies in INS-1 beta cells, islets of Txnip-deficient mice, diabetic mouse models and primary human islets. We then further found that TXNIP induces miR-204 by inhibiting the activity of signal transducer and activator of transcription 3 (STAT3), a transcription factor that is involved in miR-204 regulation[4,5]. We also identified *MAFA* as a target that is downregulated by miR-204. Taken together, our results demonstrate that TXNIP controls microRNA expression and insulin production and that miR-204 is involved in beta-cell function. The newly identified TXNIP–miR-204–MAFA–insulin pathway may contribute to diabetes progression and provides new insight into TXNIP function and microRNA biology in health and disease.

Production and release of adequate amounts of insulin by pancreatic beta cells is a prerequisite for maintaining normal glucose homeostasis. Indeed, beta-cell dysfunction and impaired insulin production are key factors in the pathogenesis of diabetes[1], but despite the growing worldwide diabetes epidemic, the molecular mechanisms involved in this disease process have only begun to be discovered. Recently we identified TXNIP, a cellular redox regulator[6], as a crucial factor in beta-cell biology. In particular, we previously showed that beta-cell TXNIP was upregulated in diabetes, whereas TXNIP deficiency protected against type 1 and type 2 diabetes by preventing beta-cell apoptosis and increasing whole-pancreas beta-cell mass[2,3,7–11]. Furthermore, we revealed the pathways by which TXNIP induces apoptosis[2,10] and discovered that TXNIP shuttles within the beta cell and translocates from the nucleus into the mitochondria, where it initiates the mitochondrial apoptotic cascade[10]. The discovery that under normal conditions TXNIP is localized primarily in the nucleus combined with our previous gene expression profiling studies demonstrating that ~95% of all altered genes are downregulated by TXNIP[9] raised the possibility that TXNIP might be involved in the control (particularly the inhibition) of beta-cell gene expression, which prompted us to study the potential effects of TXNIP on microRNA expression.

MicroRNAs (small 20- to 24-nt noncoding RNAs) recognize and bind target mRNAs through imperfect base pairing, which leads to mRNA degradation or translational inhibition of the target mRNA and downregulation of target gene expression[12–14]. MicroRNAs are rapidly emerging as important regulators of gene expression in health and disease and were also recently discovered to have various roles in diabetes and beta-cell biology[15–21].

Comparison of our TXNIP-overexpressing INS-1 beta-cell line (INS-TXNIP) and a control INS-1 beta-cell line expressing LacZ (INS-LacZ) using miRCURY LNA microRNA Arrays (Exiqon) and an absolute difference threshold of 0.7 in LogMedianRatio (1.6-fold change) revealed five microRNAs (miR-139-5p, miR-193, miR-204, miR-200c and miR-141) that were upregulated in response to TXNIP overexpression (**Supplementary Table 1**). After confirming these findings by quantitative real-time PCR, we investigated the role of these microRNAs by systematically knocking them down using specific inhibitor oligonucleotides and assessing the effects on insulin production, a key aspect of beta-cell function. However, only knockdown of miR-204 had a significant ($P < 0.05$) effect and led to an increase in insulin expression. Moreover, only overexpression of miR-204, but not any of the other microRNAs, resulted in a marked decrease in insulin mRNA expression (**Supplementary Fig. 1a**).

Notably, miR-204 (which is fully conserved between human, rat and mouse) (**Supplementary Fig. 1b**) has not been implicated in beta-cell biology but is highly expressed in insulinomas[22]. Consistent with this observation, miR-204 was readily detectable in INS-1 cells, but in agreement with the results from the other microRNAs, its expression was even higher in primary human islets, whereas its expression in mouse islets was lower than in INS-1 cells (**Supplementary Fig. 1c**). Of note, human pancreatic islets are also one of the major sites of miR-204 expression according to the microRNA.org website,

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Dysfunctional mitochondrial bioenergetics and oxidative stress in Akita$^{+/Ins2}$-derived β-cells

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Mitchell T, Johnson MS, Ouyang X, Chacko BK, Mitra K, Lei X, Gai Y, Moore DR, Barnes S, Zhang J, Koizumi A, Ramanadham S, Darley-Usmar VM. Dysfunctional mitochondrial bioenergetics and oxidative stress in Akita$^{+/Ins2}$-derived β-cells. *Am J Physiol Endocrinol Metab* 305: E585–E599, 2013. First published July 2, 2013; doi:10.1152/ajpendo.00093.2013.—Insulin release from pancreatic β-cells plays a critical role in blood glucose homeostasis, and β-cell dysfunction leads to the development of diabetes mellitus. In cases of monogenic type 1 diabetes mellitus (T1DM) that involve mutations in the insulin gene, we hypothesized that misfolding of insulin could result in endoplasmic reticulum (ER) stress, oxidant production, and mitochondrial damage. To address this, we used the Akita$^{+/Ins2}$ T1DM model in which misfolding of the insulin 2 gene leads to ER stress-mediated β-cell death and thapsigargin to induce ER stress in two different β-cell lines and in intact mouse islets. Using transformed pancreatic β-cell lines generated from wild-type Ins2$^{+/+}$ (WT) and Akita$^{+/Ins2}$ mice, we evaluated cellular bioenergetics, oxidative stress, mitochondrial protein levels, and autophagic flux to determine whether changes in these processes contribute to β-cell dysfunction. In addition, we induced ER stress pharmacologically using thapsigargin in WT β-cells, INS-1 cells, and intact mouse islets to examine the effects of ER stress on mitochondrial function. Our data reveal that Akita$^{+/Ins2}$-derived β-cells have increased mitochondrial dysfunction, oxidant production, mtDNA damage, and alterations in mitochondrial protein levels that are not corrected by autophagy. Together, these findings suggest that deterioration in mitochondrial function due to an oxidative environment and ER stress contributes to β-cell dysfunction and could contribute to T1DM in which mutations in insulin occur.

diabetes mellitus; β-cell; mitochondrial respiration; endoplasmic reticulum stress; mitochondrial quality control

INSULIN RELEASE from pancreatic β-cells is largely dependent on mitochondrial and endoplasmic reticulum (ER) function and plays a critical role in maintaining blood glucose homeostasis. The synthesis of insulin in β-cells is an energy-requiring process, with as much as 50% of the total protein of these cells committed to generation of this single protein when stimulated (51). Insulin requires posttranslational processing before it is secreted, and it has been shown that mutations that lead to misfolding may cause neonatal diabetes (11, 51). Once considered rare, monogenic mutations in insulin are becoming recognized as causes of neonatal diabetes mellitus. They can also be causative factors for type 1b diabetes or maturity-onset diabetes of the young and in some cases early onset type 2 diabetes mellitus (T2DM) (27, 50). Mutations in the insulin gene lead to defective processing and accumulation of proinsulin in the ER, inducing ER stress. In addition, the consequent dysregulation of blood glucose homeostasis can initiate serious diabetic complications such as cardiovascular disease, neuropathy, and nephropathy (8). Thus, prevention or treatment of β-cell injury and diabetes mellitus onset/progression continues to be a challenge, particularly for the group of patients with mutations in the insulin gene.

It has been established that there is a potential link between the ER and the mitochondria, and this has been suggested to contribute to β-cell dysfunction in both type 1 diabetes mellitus (T1DM) and T2DM pathogenesis (3, 16, 43, 52, 58). One proposed sequence of events is that ER stress leads to disruption of Ca^{2+} flow to the mitochondria, causing mitochondrial dysfunction and triggering a series of cyclic events, such as oxidative stress, that culminates in induction of cell death (30). To counter the cell death processes and development of T1DM, prosurvival mechanisms such as autophagy can be initiated in β-cells (6). Autophagy is a multistep process that targets damaged proteins and organelles for degradation and efficiently regulates organelle turnover within the cell (57). The targeting of phagophores to dysfunctional mitochondria is dependent on mitochondrial quality and ubiquitinated proteins (17, 25). A decrease in mitochondrial quality can be identified by increased mitochondrial ROS production, mitochondrial fission, decreased membrane potential, mtDNA damage, and suppressed bioenergetic function (20). How mitochondrial morphology plays an important role in β-cell dysfunction is still unclear (52). In addition, how autophagy responds to metabolic stress and impacts bioenergetic function and cellular redox status is not well understood (26, 28, 47). This is important to understand since lack of degradation of damaged mitochondria can induce oxidative stress and cell death (20, 38).

As a means to identify mechanisms that contribute to T1DM and associated complications, several experimental models have been developed (4, 34, 49, 59). In particular, there are two animal models representative of the syndromes mentioned above known as the Munich *Ins2*^{C95S} mutant mouse (19) and the Akita$^{Ins2+/-}$ mouse (60). The Akita mouse model contains

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PLOS ONE

Improved Metabolic Health Alters Host Metabolism in Parallel with Changes in Systemic Xeno-Metabolites of Gut Origin

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Abstract

Novel plasma metabolite patterns reflective of improved metabolic health (insulin sensitivity, fitness, reduced body weight) were identified before and after a 14–17 wk weight loss and exercise intervention in sedentary, obese insulin-resistant women. To control for potential confounding effects of diet- or microbiome-derived molecules on the systemic metabolome, sampling was during a tightly-controlled feeding test week paradigm. Pairwise and multivariate analysis revealed intervention- and insulin-sensitivity associated: (1) Changes in plasma xeno-metabolites (''non-self'' metabolites of dietary or gut microbial origin) following an oral glucose tolerance test (e.g. higher post-OGTT propane-1,2,3-tricarboxylate [tricarballylic acid]) or in the overnight-fasted state (e.g., lower γ-tocopherol); (2) Increased indices of saturated very long chain fatty acid elongation capacity; (3) Increased post-OGTT α-ketoglutaric acid (α-KG), fasting α-KG inversely correlated with Matsuda index, and altered patterns of malate, pyruvate and glutamine hypothesized to stem from improved mitochondrial efficiency and more robust oxidation of glucose. The results support a working model in which improved metabolic health modifies host metabolism in parallel with altering systemic exposure to xeno-metabolites. This highlights that interpretations regarding the origins of peripheral blood or urinary ''signatures'' of insulin resistance and metabolic health must consider the potentially important contribution of gut-derived metabolites toward the host's metabolome.

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Introduction

Pre-diabetes and type 2 diabetes mellitus (T2DM) are defined by elevated blood glucose following an overnight fast or at 2 hr following an oral glucose tolerance test (OGTT) [1]; however, a clinically-significant increase in blood sugar is a late event in disease progression and is not an optimal prognostic. Identifying more sensitive T2DM risk markers or those that track deteriorating insulin sensitivity would have potential value as clinical diagnostics and would help elucidate the underlying pathophysiology. Advancements in metabolomics technologies to interrogate hundreds of metabolites in human blood or urine hold promise in this regard. Recent metabolomics studies have highlighted that human insulin resistance, T2DM, and T2DM risk involve significant perturbations in lipid and amino acid metabolism in addition to glucose, as reflected in altered phosphatidylcholine derivatives, positive associations with blood branched-chain amino acids (BCAAs), 2-hydroxybutyrate (2-HB), long- and medium-chain acylcarnitines, and negative associations with blood glycine and linoleoyl-glycerophosphocholine (L-GPC)[2–16].

Measurement of blood metabolites in the overnight-fasted state, while valuable, may not unmask subtle phenotypes associated with insulin resistance or pre-diabetes that manifest when the body's metabolic machinery is challenged. Since insulin resistance involves impairment of normal glucose and insulin homeostasis, metabolomics analyses following an OGTT are an attractive means to identify biochemical pathways associated with individual variability in insulin action and blood sugar control. To our knowledge, only five studies have reported post-OGTT blood metabolite profiling in humans [17–21]. These reports highlighted

Original Article
CLINICAL TRIALS: BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

The Progression of Cardiometabolic Disease: Validation of a New Cardiometabolic Disease Staging System Applicable to Obesity

Fangjian Guo[1], Douglas R. Moellering[1] and W. Timothy Garvey[1,2]

Objective: To validate a Cardiometabolic Disease Staging (CMDS) system for assigning risk level for diabetes, and all-cause and cardiovascular disease (CVD) mortality.

Design and Methods: Two large national cohorts, CARDIA and NHANES III, were used to validate CMDS. CMDS: Stage 0: metabolically healthy; Stage 1: one or two metabolic syndrome risk factors [other than impaired fasting glucose (IFG)]; Stage 2: IFG or impaired glucose tolerance (IGT) or metabolic syndrome (without IFG); Stage 3: two of three (IFG, IGT, and/or metabolic syndrome); and Stage 4: type 2 diabetes mellitus/CVD.

Results: In the CARDIA study, compared with Stage 0 metabolically healthy subjects, adjusted risk for diabetes exponentially increased from Stage 1 [hazard ratio (HR) 2.83, 95% confidence interval (CI): 1.76-4.55], to Stage 2 (HR 8.06, 95% CI 4.91-13.2), to Stage 3 (HR 23.5, 95% CI 13.7-40.1) (*P* for trend <0.001). In NHANES III, both cumulative incidence and multivariable adjusted HRs markedly increased for both all-cause and CVD mortality with advancement of the risk stage from Stages 0 to 4. Adjustment for body mass index (BMI) minimally affected the risks for diabetes and all-cause/CVD mortality using CMDS.

Conclusion: CMDS can discriminate a wide range of risk for diabetes, CVD mortality, and all-cause mortality independent of BMI, and should be studied as a risk assessment tool to guide interventions that prevent and treat cardiometabolic disease.

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Introduction

The spectrum of cardiometabolic disease begins with insulin resistance, a trait that is expressed early in life, and then progresses to the clinically identifiable high-risk states of metabolic syndrome and prediabetes, and then to type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). The consequences of cardiometabolic disease are severe. T2DM, which is epidemic in the United States (1) and worldwide (2), is associated with elevated risk for morbidity and mortality (3) and high social costs (1), and CVD remains the leading cause of death in Western societies. To stem the increasing prevalence of T2DM and to reduce CVD risks, it will be necessary to identify high-risk individuals early in the progression of cardiometabolic disease and intervene with effective strategies for disease prevention.

Obesity can exacerbate insulin resistance and impel cardiometabolic disease progression. However, the relationship between generalized obesity, as measured by the body mass index (BMI, kg/m^2), and cardiometabolic disease is complex. For example, insulin resistance exists largely independent of BMI (4), and BMI is a poor predictor of CVD compared with measures of fat distribution such as waist/hip ratio (5). Also, up to 30% of obese individuals (i.e., BMI $\geq$ 30)

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The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the National Center for Health Statistics, or the Centers for Disease Control and Prevention, or the National Heart, Lung, and Blood Institute.

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Author Contributions: Dr. Garvey and Dr. Guo conceived the study and analyzed data. Dr. Moellering reviewed and edited the manuscript. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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Racial/ethnic disparities in association between dietary quality and incident diabetes in postmenopausal women in the United States: the Women's Health Initiative 1993–2005

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Objective. To examine the association of dietary quality and risk of incident diabetes overall and by race/ethnicity among postmenopausal women enrolled in the Women's Health Initiative (WHI).

Research methods and procedures. The WHI recruited 161,808 postmenopausal women between 1993 and 1998, and followed them until 2005. Incident diabetes was determined annually over an average of 7.6 years from enrollment. At baseline, all participants completed a Food Frequency Questionnaire (FFQ). Dietary quality was assessed by the Alternate Healthy Eating Index (AHEI), calculated from the baseline FFQ responses.

Results. There were 10,307 incident cases of self-reported treated diabetes over 1,172,761 person-years of follow-up. Most participants did not meet the AHEI dietary goals; that is, only 0.1% of women met or exceeded the recommended consumption of vegetables, and few (17.3%) met or exceeded the recommended level for total fiber. After adjusting for potential confounders, women in the highest quintile of the AHEI score were 24% less likely to develop diabetes relative to women in the lowest quintile of AHEI [hazard ratio (HR) = 0.76 (95% CI: 0.70–0.82)]. This association was observed in Whites [HR = 0.74 (95% CI: 0.68–0.82)] and Hispanics [HR = 0.68 (95% CI: 0.46–0.99)], but not in Blacks [HR = 0.85 (95% CI: 0.69–1.05)] or Asians [HR = 0.88 (95% CI: 0.57–1.38)].

Conclusion. These findings support a protective role of healthful eating choices in reducing the risk of developing diabetes, after adjusting for other lifestyle factors, in White and Hispanic postmenopausal women. Future studies are needed to investigate the relationship between dietary quality and risk of diabetes among Blacks and Asians in relationship to other lifestyle factors.

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Epigenome-Wide Association Study of Fasting Measures of Glucose, Insulin, and HOMA-IR in the Genetics of Lipid Lowering Drugs and Diet Network Study

Known genetic susceptibility loci for type 2 diabetes (T2D) explain only a small proportion of heritable T2D risk. We hypothesize that DNA methylation patterns may contribute to variation in diabetes-related risk factors, and this epigenetic variation across the genome can contribute to the missing heritability in T2D and related metabolic traits. We conducted an epigenome-wide association study for fasting glucose, insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) among 837 nondiabetic participants in the Genetics of Lipid Lowering Drugs and Diet Network study, divided into discovery (N = 544) and replication (N = 293) stages. Cytosine guanine dinucleotide (CpG) methylation at ~470,000 CpG sites was assayed in CD4$^+$ T cells using the Illumina Infinium HumanMethylation 450 Beadchip. We fit a mixed model with the methylation status of each CpG as the dependent variable, adjusting for age, sex, study site, and T-cell purity as fixed-effects and family structure as a random-effect. A Bonferroni corrected P value of 1.1×10^{-7} was considered significant in the discovery stage. Significant associations were tested in the replication stage using identical models. Methylation of a CpG site in *ABCG1* on chromosome 21 was significantly associated with insulin ($P = 1.83 \times 10^{-7}$) and HOMA-IR ($P = 1.60 \times 10^{-9}$). Another site in the same gene was significant for HOMA-IR and of borderline significance for insulin ($P = 1.29 \times 10^{-7}$ and $P = 3.36 \times 10^{-6}$, respectively). Associations with the top two signals replicated for insulin and HOMA-IR ($P = 5.75 \times 10^{-3}$ and $P = 3.35 \times 10^{-2}$, respectively). Our findings suggest that methylation of a CpG site within *ABCG1* is associated with fasting insulin and merits further evaluation as a novel disease risk marker.

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Candidate gene and genome-wide association studies (GWAS) have identified a number of sequence variants that explain some of the interindividual variation in the susceptibility for type 2 diabetes (T2D) (1,2). However, a large component of heritable T2D risk remains poorly understood, with less than half of total genetic variation explained by known single nucleotide polymorphisms (SNPs), a problem known as missing heritability (3–6).

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Cell Metabolism
Article

LXRs Regulate ER Stress and Inflammation through Dynamic Modulation of Membrane Phospholipid Composition

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SUMMARY

The fatty acyl composition of phospholipids determines the biophysical character of membranes and impacts the function of membrane proteins. Here, we define a nuclear receptor pathway for the dynamic modulation of membrane composition in response to changes in cellular lipid metabolism. Ligand activation of liver X receptors (LXRs) preferentially drives the incorporation of polyunsaturated fatty acids into phospholipids through induction of the remodeling enzyme Lpcat3. Promotion of Lpcat3 activity ameliorates endoplasmic reticulum (ER) stress induced by saturated free fatty acids in vitro or by hepatic lipid accumulation in vivo. Conversely, Lpcat3 knockdown in liver exacerbates ER stress and inflammation. Mechanistically, Lpcat3 modulates inflammation both by regulating inflammatory kinase activation through changes in membrane composition and by affecting substrate availability for inflammatory mediator production. These results outline an endogenous mechanism for the preservation of membrane homeostasis during lipid stress and identify Lpcat3 as an important mediator of LXR effects on metabolism.

INTRODUCTION

Phospholipids (PLs) are important components of biological membranes and precursors of numerous signaling molecules. PL membranes compartmentalize living cells, form intracellular organelles, and provide platforms for a wide variety of physiological processes, such as vesicle trafficking, signal transduction, molecular transport, and biosynthesis. PLs also act as substrates for the generation of diverse bioactive molecules involved in signal transduction, including eicosanoids, lysophosphatidic acid (LPA), and diacylglycerol (Holzer et al., 2011; Spector and Yorek, 1985).

The fatty acyl composition of PLs determines the biophysical characteristics of membranes, including fluidity and the assembly of specific membrane subdomains (Holzer et al., 2011; Spector and Yorek, 1985). Therefore, changes in fatty acyl composition can affect the properties of proteins associated with membranes and influence the biological processes that occur on them. Modification of the fatty acyl composition of membranes influences a range of cell processes, most importantly the activity of membrane-bound enzymes and transporters and the localization of acylated proteins in membrane subdomains (Cornelius, 2001; Fu et al., 2011; Holzer et al., 2011). For example, membrane fatty acyl composition affects the activity of the Na^+/K^+-adenosine triphosphatase (ATPase) and the sarcoplasmic-endoplasmic reticulum calcium ATPase-2b (*SERCA2b*) (Cornelius, 2001; Li et al., 2004). It is also known that incorporation of saturated fatty acids into plasma membrane recruits c-Src kinase to lipid raft domains and increases its activity (Holzer et al., 2011).

In mammalian cells, PLs are initially synthesized by the de novo pathway and subsequently undergo remodeling through fatty acyl deacylation and reacylation, a pathway referred to as the Lands cycle (Lands, 1958). As a result, saturated fatty acids are preferably linked at the *sn-1* position and unsaturated fatty acids at the *sn-2* position. This diversity and asymmetric distribution is established largely by the remodeling process, as the de novo PL synthesis process has little fatty acyl-coenzyme A (CoA) substrate specificity. In the liver, a major enzyme that catalyzes the formation of phosphatidylcholine (PC) from saturated lysophosphatidylcholines (LysoPCS) and unsaturated fatty acyl-CoAs is lysophosphatidylcholine acyltransferase 3 (Lpcat3) (Hishikawa et al., 2008; Li et al., 2012; Zhao et al., 2008). Lpcat3 preferentially synthesizes PC containing unsaturated fatty acids, particularly arachidonic acid (20:4) and linoleic acid (18:2), at the *sn-2* position.

To date, most studies of the effects of PL fatty acyl composition on biological systems have utilized in vitro biochemical

ARTICLE

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Effect of natural genetic variation on enhancer selection and function

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The mechanisms by which genetic variation affects transcription regulation and phenotypes at the nucleotide level are incompletely understood. Here we use natural genetic variation as an *in vivo* mutagenesis screen to assess the genome-wide effects of sequence variation on lineage-determining and signal-specific transcription factor binding, epigenomics and transcriptional outcomes in primary macrophages from different mouse strains. We find substantial genetic evidence to support the concept that lineage-determining transcription factors define epigenetic and transcriptomic states by selecting enhancer-like regions in the genome in a collaborative fashion and facilitating binding of signal-dependent factors. This hierarchical model of transcription factor function suggests that limited sets of genomic data for lineage-determining transcription factors and informative histone modifications can be used for the prioritization of disease-associated regulatory variants.

Inter-individual genetic variation is a major cause of diversity in phenotypes and disease susceptibility. Although sequence variants in gene promoters and protein-coding regions provide obvious prioritization of disease-causing variants, most (88%) genome-wide association study (GWAS) loci are in non-coding DNA, suggesting regulatory functions[1]. Prioritization of functional intergenic variants remains challenging, owing in part to an incomplete understanding of how regulation is achieved at the nucleotide level in different cell types and environmental contexts[2–11]. Recent studies have described important roles for lineage-determining transcription factors (LDTFs), also referred to as pioneer factors or master regulators, in selecting cell-type-specific enhancers[12–15], but the sequence determinants that guide their binding are poorly understood. Previous findings in macrophages and B cells suggest a hierarchical model of regulatory function[6], in which a relatively small set of LDTFs collaboratively compete with nucleosomes to bind DNA in a cell-type-specific manner (Fig. 1A, a and b). The binding of these factors is proposed to 'prime' DNA by initiating deposition of histone modifications that are associated with *cis*-active regulatory regions (Fig. 1A, b and c) and enable concurrent or subsequent binding of signal-dependent transcription factors that direct regulated gene expression[6,13,15,16] (Fig. 1A, c–e). In principle, this model provides a straightforward framework that allows non-coding variants to be classified with respect to their ability to directly perturb LDTF binding and their potential to exert indirect effects on binding of other LDTFs and signal-dependent transcription factors. To test the validity of this model and its ability to explain effects of genetic variation on transcription factor binding and function, we exploited the naturally occurring genetic variation between the inbred C57BL/6J and BALB/cJ mouse strains (~4 million single nucleotide polymorphisms (SNPs) and ~750 k indels[17]) as an '*in vivo* mutagenesis screen'.

Direct effects of genetic variation

First, we quantified genome-wide binding patterns of macrophage LDTFs PU.1 and C/EBPα from both mouse strains using chromatin immunoprecipitation followed by massively parallel sequencing (ChIP-Seq). These experiments identified a combined 82,154 PU.1 and 54,874 C/EBPα peaks, with less than 1% of sites exhibiting highly significant strain-specific binding (PU.1, $n = 496$; C/EBPα, $n = 263$; fourfold tag count ratio, false discovery rate (FDR) $< 1 \times 10^{-14}$, >90% located >3 kilobases (kb) from gene promoters) (Fig. 1B, C and Extended Data Fig. 1a). Strain-specific binding was defined using biological ChIP-Seq replicates, which yielded <0.2% empirical false positives (Extended Data Fig. 1b–g). Differential binding of PU.1 and C/EBPα was significantly correlated with differential expression of the nearest gene as measured by RNA-Seq (Fig. 1D). There were no apparent differences in genomic context for strain-similar and strain-specific binding at inter- or intragenic sites (>3 kb to promoters) as defined by CpG content, distance from nearest gene or repetitive element, or conservation score (Extended Data Fig. 2a). Instead, strain-specific binding was highly correlated with polymorphism frequency. We observed fivefold enrichment of polymorphisms at strain-specific versus strain-similar PU.1- and C/EBPα-bound regions (Fig. 1E and Extended Data Fig. 2b), with the greatest variant density at the peak centres (Extended Data Fig. 2c, d).

To investigate the direct effects of sequence variants on transcription factor binding, we identified the most enriched position weight matrices (PWMs) in genomic regions marked by histone H3 lysine 4 di-methylation (H3K4me2) or bound by PU.1 or C/EBPα (Extended Data Fig. 3a and Supplementary Table 1). This analysis consistently identified consensus and degenerate motifs for the LDTFs PU.1, C/EBP and AP-1 as the most highly enriched PWMs. Notably, the frequency of mutations in these motifs increased with strain-specific binding of PU.1 and C/EBPα (Extended Data Fig. 2e, f). Excluding strain-specific loci without *cis*-variation (~11%), 41% of strain-specific PU.1 binding directly associated with strain-specific mutations in PU.1 motifs in the other strain. For C/EBPα, 44% of strain-specific binding associated with strain-specific C/EBPα motifs (Fig. 1F).

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Cell

Increased Adipocyte O_2 Consumption Triggers HIF-1α, Causing Inflammation and Insulin Resistance in Obesity

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SUMMARY

Adipose tissue hypoxia and inflammation have been causally implicated in obesity-induced insulin resistance. Here, we report that, early in the course of high-fat diet (HFD) feeding and obesity, adipocyte respiration becomes uncoupled, leading to increased oxygen consumption and a state of relative adipocyte hypoxia. These events are sufficient to trigger HIF-1α induction, setting off the chronic adipose tissue inflammatory response characteristic of obesity. At the molecular level, these events involve saturated fatty acid stimulation of the adenine nucleotide translocase 2 (ANT2), an inner mitochondrial membrane protein, which leads to the uncoupled respiratory state. Genetic or pharmacologic inhibition of either ANT2 or HIF-1α can prevent or reverse these pathophysiologic events, restoring a state of insulin sensitivity and glucose tolerance. These results reveal the sequential series of events in obesity-induced inflammation and insulin resistance.

INTRODUCTION

Obesity is characterized by low-grade chronic inflammation in adipose tissue, liver, and skeletal muscle (Glass and Olefsky, 2012; Shu et al., 2012). This inflammatory state progresses during the course of obesity and can lead to systemic insulin resistance, hyperinsulinemia, and glucose intolerance (Lee et al., 2011b). In obesity, adipocyte hypertrophy—combined with compromised adipose tissue vascularization—restricts oxygen availability, leading to areas of adipose tissue hypoxia (Pasarica et al., 2009), and recent evidence suggests that this can cause adipose tissue dysfunction in obesity (Hosogai et al., 2007). The hypoxia response is largely mediated by hypoxia-inducible factors (HIFs). HIFs are heterodimeric basic helix-loop-helix transcription factors composed of two dimeric subunits: an oxygen-sensitive α subunit and a ubiquitously and constitutively expressed β subunit, HIF-1β (ARNT) (Keith et al., 2012). There are two major α subunits, HIF-1α and HIF-2α, which are differentially regulated by oxygen tension and metabolic signals (Keith et al., 2012). Under normal conditions, α subunits are hydroxylated by prolyl hydroxylases (PHDs), which allows the ubiquitin ligase Von Hippel-Lindau tumor suppressor (VHL) to ubiquitinate HIF-1α, which is then targeted for proteolytic degradation via the proteasomal pathway. The hydroxylation step is inhibited under hypoxic conditions, leading to stabilization and increased expression of HIF-1α. HIF-1α and HIF-2α regulate different subsets of genes, although they can share common targets such as *VEGF* and *GLUT1* (Keith et al., 2012). In arginine homeostasis, HIF-1α induces *iNOS* expression and increases nitric oxide (NO) production from arginine, whereas HIF-2α stimulates *arginase* expression, and suppresses NO production (Branco-Price et al., 2012; Melillo et al., 1996; Takeda et al., 2010). Therefore, identification of differential roles of adipocyte HIF-1α and HIF-2α is essential to understand the molecular mechanisms of the metabolic consequences of adipose tissue hypoxia in obesity.

Recently, it has been reported that adipocyte-specific HIF-1α-overexpressing mice develop insulin resistance with increased adipose tissue inflammation due to induction of the fibrotic program (Halberg et al., 2009). Deletion of either *HIF-1β* or *HIF-1α* in adipocytes protects mice from high-fat diet (HFD)-induced insulin resistance (Jiang et al., 2011; Krishnan et al., 2012; Lee et al., 2011a). Deletion of HIF-1β results in the loss of transcriptional activity of both HIF-α factors and other factors that bind HIF-1β, such as the Aryl hydrocarbon receptor (AhR)

Cell

Eosinophils and Type 2 Cytokine Signaling in Macrophages Orchestrate Development of Functional Beige Fat

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SUMMARY

Beige fat, which expresses the thermogenic protein UCP1, provides a defense against cold and obesity. Although a cold environment is the physiologic stimulus for inducing beige fat in mice and humans, the events that lead from the sensing of cold to the development of beige fat remain poorly understood. Here, we identify the efferent beige fat thermogenic circuit, consisting of eosinophils, type 2 cytokines interleukin (IL)-4/13, and alternatively activated macrophages. Genetic loss of eosinophils or IL-4/13 signaling impairs cold-induced biogenesis of beige fat. Mechanistically, macrophages recruited to cold-stressed subcutaneous white adipose tissue (scWAT) undergo alternative activation to induce tyrosine hydroxylase expression and catecholamine production, factors required for browning of scWAT. Conversely, administration of IL-4 to thermoneutral mice increases beige fat mass and thermogenic capacity to ameliorate pre-established obesity. Together, our findings have uncovered the efferent circuit controlling biogenesis of beige fat and provide support for its targeting to treat obesity.

INTRODUCTION

Obesity, which affects 1.4 billion adults globally, represents the greatest current threat to human health (Finucane et al., 2011). Chronic imbalance between energy intake and energy expenditure causes obesity for which there is no effective therapy (Harms and Seale, 2013; Lowell and Spiegelman, 2000). Thus, a major challenge for biomedical sciences is to identify targetable pathways that can decrease energy intake or increase energy expenditure. One of the most promising targets for treatment of human obesity is brown adipose tissue (BAT) (Enerbäck, 2010; Harms and Seale, 2013), but adult humans lack this thermogenic interscapular organ (Lidell et al., 2013). However, recent studies have demonstrated that adult humans harbor a separate depot of brown adipocytes that are cold inducible and interspersed among white adipocytes in the supraclavicular, para-aortic, and suprarenal regions (Cypess et al., 2009; Saito et al., 2009; van Marken Lichtenbelt et al., 2009; Virtanen et al., 2009). Because these human brown adipocytes share some molecular, histologic, and functional characteristics with cold-inducible beige adipocytes found in the subcutaneous white adipose tissue (scWAT) of mice (Cypess et al., 2013; Liu et al., 2013; Sharp et al., 2012; Wu et al., 2012, 2013), there is great clinical interest in the therapeutic targeting of beige fat for the treatment of obesity (Enerbäck, 2010; Harms and Seale, 2013). However, our lack of understanding of how cold triggers the development of functional beige fat is a major barrier for its therapeutic translation.

Uncoupling protein-1 (UCP1), which dissipates the mitochondrial electrochemical gradient to stimulate cellular respiration, mediates the thermogenic activity of both brown and beige adipocytes (Cannon and Nedergaard, 2010, 2011; Feldmann et al., 2009). Despite this similarity in thermogenesis, multiple lines of evidence indicate that brown and beige adipocytes have unique expression profiles that likely contribute to their tissue-specific functions (Harms and Seale, 2013). First, unlike interscapular brown adipocytes that arise from $Myf5^{+}/Pax7^{+}$ myogenic precursors (Lepper and Fan, 2010; Seale et al., 2008; Timmons et al., 2007), beige adipocytes residing in the scWAT of mice do not have a history of $Myf5^{+}$ expression (Seale et al., 2011). Second, brown adipocytes constitutively express Ucp1 after differentiation, whereas beige adipocytes specifically increase expression of Ucp1 in response to environmental cold, and agonists of the β-adrenergic receptor or peroxisome proliferator-activated receptor-γ (Ppar-γ) (Liu et al., 2013; Ohno et al., 2012; Wu et al., 2012). Third, a number of genes, such as Klhl13, Ear2, Tbx1, Tmem26, and CD137, are preferentially expressed in beige adipocyte precursors (Liu et al., 2013; Sharp et al., 2012; Wu et al., 2012). Together, these findings suggest that beige and brown adipocytes are likely to have complementary functions in the maintenance of energy balance and thermogenesis;

Cell

Allosteric Inhibition of the IRE1α RNase Preserves Cell Viability and Function during Endoplasmic Reticulum Stress

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SUMMARY

Depending on endoplasmic reticulum (ER) stress levels, the ER transmembrane multidomain protein IRE1α promotes either adaptation or apoptosis. Unfolded ER proteins cause IRE1α lumenal domain homo-oligomerization, inducing *trans* autophosphorylation that further drives homo-oligomerization of its cytosolic kinase/endoribonuclease (RNase) domains to activate mRNA splicing of adaptive XBP1 transcription factor. However, under high/chronic ER stress, IRE1α surpasses an oligomerization threshold that expands RNase substrate repertoire to many ER-localized mRNAs, leading to apoptosis. To modulate these effects, we developed ATP-competitive IRE1α *K*inase-*I*nhibiting *R*Nase *A*ttenuators—KIRAs—that allosterically inhibit IRE1α's RNase by breaking oligomers. One optimized KIRA, KIRA6, inhibits IRE1α in vivo and promotes cell survival under ER stress. Intravitreally, KIRA6 preserves photoreceptor functional viability in rat models of ER stress-induced retinal degeneration. Systemically, KIRA6 preserves pancreatic β cells, increases insulin, and reduces hyperglycemia in Akita diabetic mice. Thus, IRE1α powerfully controls cell fate but can itself be controlled with small molecules to reduce cell degeneration.

INTRODUCTION

Secreted and transmembrane proteins fold and assemble in the endoplasmic reticulum (ER) through reactions catalyzed by ER-resident activities. When these reactions are saturated or corrupted, cells experience "ER stress," and unfolded protein accumulation in the ER triggers intracellular signaling pathways termed the unfolded protein response (UPR). The UPR induces transcription of genes encoding ER chaperones, oxidoreductases, and ER-associated degradation (ERAD) components (Travers et al., 2000), while inhibiting translation (Harding et al., 2000). These outputs are adaptive because they enhance ER protein-folding capacity, reduce secretory protein load, and promote degradation of ER unfolded proteins.

However, if ER stress remains irremediably high and adaptive outputs are overwhelmed, alternative "terminal UPR" signals trigger apoptosis. Although cell death under high ER stress may protect organisms from exposure to improperly folded secretory proteins, many human degenerative diseases, such as diabetes mellitus and retinopathies, may be caused by excessive ER stress-induced cell death (Shore et al., 2011). Mechanistic understanding of critical terminal UPR signaling events may lead to effective therapies for such conditions.

Unfolded ER proteins activate three ER transmembrane sensors—PERK, ATF6, and IRE1α—by changing their oligomerization state in the ER membrane (Kohno, 2007). IRE1α, the most ancient of these components, senses unfolded proteins either directly or indirectly through an ER lumenal domain that

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Glucose Sensor *O*-GlcNAcylation Coordinates with Phosphorylation to Regulate Circadian Clock

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SUMMARY

Posttranslational modifications play central roles in myriad biological pathways including circadian regulation. We employed a circadian proteomic approach to demonstrate that circadian timing of phosphorylation is a critical factor in regulating complex GSK3β-dependent pathways and identified *O*-GlcNAc transferase (OGT) as a substrate of GSK3β. Interestingly, OGT activity is regulated by GSK3β; hence, OGT and GSK3β exhibit reciprocal regulation. Modulating *O*-GlcNAcylation levels alter circadian period length in both mice and *Drosophila*; conversely, protein *O*-GlcNAcylation is circadianly regulated. Central clock proteins, Clock and Period, are reversibly modified by *O*-GlcNAcylation to regulate their transcriptional activities. In addition, *O*-GlcNAcylation of a region in PER2 known to regulate human sleep phase (S662–S674) competes with phosphorylation of this region, and this interplay is at least partly mediated by glucose levels. Together, these results indicate that *O*-GlcNAcylation serves as a metabolic sensor for clock regulation and works coordinately with phosphorylation to fine-tune circadian clock.

INTRODUCTION

Circadian rhythms in physiology and behavior are present in a variety of organisms from plants and bacteria to humans. These rhythms are controlled by endogenous molecular clocks even in the absence of external cues (e.g., light). The fact that circadian clocks are evolutionarily conserved supports the view that precise rhythms are essential for organisms to survive. Perturbations of circadian rhythms and sleep have been associated with many human ailments such as metabolic syndrome, cardiovascular disease, depression, epilepsy, and cancer (Bass and Takahashi, 2010; Climent et al., 2010; Duez and Staels, 2010; Wulff et al., 2010).

Glycogen synthase kinase 3β (GSK3β) is an important signaling mediator that has central functions in diverse physiological pathways including transcription, cell-cycle regulation, metabolism, development, neuronal function, and oncogenesis, among others (Rayasam et al., 2009). These diverse functions of GSK3β can be attributed to the large number of substrates it can phosphorylate. GSK3β is a constitutively active serine/threonine kinase with a preference for primed substrates and is inactivated in response to multiple stimuli by phosphorylation at S9 (Cohen and Frame, 2001). GSK3β is also a crucial circadian clock regulator (Iitaka et al., 2005; Martinek et al., 2001). Lithium (a GSK3β inhibitor) treatment lengthens the circadian period and delays the phase of rhythmic clock gene expression (Abe et al., 2000; Iitaka et al., 2005), although a recent report showed that inhibition of GSK3β activity by small molecule inhibitors or siRNAs shortens the circadian period (Hirota et al., 2008). In order to further understand the effects of GSK3β activity on various biological pathways in general and circadian regulation in particular, we employed a proteomic approach to elucidate the complexity of the GSK3β circadian phosphoproteome. Interestingly, we identified *O*-GlcNAc transferase (OGT) from the chemical-genetic proteomic screen as a substrate of GSK3β. GSK3β was previously shown to be *O*-GlcNAcylated by OGT in vitro (Lubas and Hanover, 2000). Since our data suggest that OGT and GSK3β regulate each other and GSK3β is a critical molecular clock component, we investigated the possibility of *O*-GlcNAcylation as a regulatory posttranslational modification in circadian regulation.

O-linked N-acetylglucosamine (*O*-GlcNAc) glycosylation has emerged as one of the most common protein posttranslational modifications with the second most abundant high-energy compound, UDP-GlcNAc, as the direct donor. Two enzymes regulate *O*-GlcNAcylation: the OGT attaches UDP-GlcNAc to the serine and threonine residues of proteins through a beta-glycosidic *O*-linkage, while *O*-GlcNAcase (OGA) hydrolyzes *O*-GlcNAc from proteins (Hart et al., 2011). OGT and OGA are highly regulated to prevent unnecessary *O*-GlcNAc cycling (Sekine et al., 2010). Here we report that *O*-GlcNAcylation and circadian clock are reciprocally regulated and that *O*-GlcNAcylation modulates CLOCK-dependent transcriptional activity by post-translationally regulating components of the molecular clock.

Cost-Effectiveness of MODY Genetic Testing: Translating Genomic Advances Into Practical Health Applications

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To evaluate the cost-effectiveness of a genetic testing policy for *HNF1A*-, *HNF4A*-, and *GCK*-MODY in a hypothetical cohort of type 2 diabetic patients 25–40 years old with a MODY prevalence of 2%.

RESEARCH DESIGN AND METHODS

We used a simulation model of type 2 diabetes complications based on UK Prospective Diabetes Study data, modified to account for the natural history of disease by genetic subtype to compare a policy of genetic testing at diabetes diagnosis versus a policy of no testing. Under the screening policy, successful sulfonylurea treatment of *HNF1A*-MODY and *HNF4A*-MODY was modeled to produce a glycosylated hemoglobin reduction of −1.5% compared with usual care. *GCK*-MODY received no therapy. Main outcome measures were costs and quality-adjusted life years (QALYs) based on lifetime risk of complications and treatments, expressed as the incremental cost-effectiveness ratio (ICER) (USD/QALY).

RESULTS

The testing policy yielded an average gain of 0.012 QALYs and resulted in an ICER of 205,000 USD. Sensitivity analysis showed that if the MODY prevalence was 6%, the ICER would be ∼50,000 USD. If MODY prevalence was >30%, the testing policy was cost saving. Reducing genetic testing costs to 700 USD also resulted in an ICER of ∼50,000 USD.

CONCLUSIONS

Our simulated model suggests that a policy of testing for MODY in selected populations is cost-effective for the U.S. based on contemporary ICER thresholds. Higher prevalence of MODY in the tested population or decreased testing costs would enhance cost-effectiveness. Our results make a compelling argument for routine coverage of genetic testing in patients with high clinical suspicion of MODY.

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Genetic Complexity in a *Drosophila* Model of Diabetes-Associated Misfolded Human Proinsulin

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ABSTRACT *Drosophila melanogaster* has been widely used as a model of human Mendelian disease, but its value in modeling complex disease has received little attention. Fly models of complex disease would enable high-resolution mapping of disease-modifying loci and the identification of novel targets for therapeutic intervention. Here, we describe a fly model of permanent neonatal diabetes mellitus and explore the complexity of this model. The approach involves the transgenic expression of a misfolded mutant of human preproinsulin, hINS^{C96Y}, which is a cause of permanent neonatal diabetes. When expressed in fly imaginal discs, hINS^{C96Y} causes a reduction of adult structures, including the eye, wing, and notum. Eye imaginal discs exhibit defects in both the structure and the arrangement of ommatidia. In the wing, expression of hINS^{C96Y} leads to ectopic expression of veins and mechano-sensory organs, indicating disruption of wild-type signaling processes regulating cell fates. These readily measurable "disease" phenotypes are sensitive to temperature, gene dose, and sex. Mutant (but not wild-type) proinsulin expression in the eye imaginal disc induces IRE1-mediated XBP1 alternative splicing, a signal for endoplasmic reticulum stress response activation, and produces global change in gene expression. Mutant hINS transgene tester strains, when crossed to stocks from the *Drosophila* Genetic Reference Panel, produce F_1 adults with a continuous range of disease phenotypes and large broad-sense heritability. Surprisingly, the severity of mutant hINS-induced disease in the eye is not correlated with that in the notum in these crosses, nor with eye reduction phenotypes caused by the expression of two dominant eye mutants acting in two different eye development pathways, *Drop* (*Dr*) or *Lobe* (*L*), when crossed into the same genetic backgrounds. The tissue specificity of genetic variability for mutant hINS-induced disease has, therefore, its own distinct signature. The genetic dominance of disease-specific phenotypic variability in our model of misfolded human proinsulin makes this approach amenable to genome-wide association study in a simple F_1 screen of natural variation.

MODEL organisms are widely employed in mechanistic studies of human Mendelian disease (Bedell *et al.* 1997a,b; Chintapalli *et al.* 2007; Lieschke and Currie 2007; Ocorr *et al.* 2007; Passador-Gurgel *et al.* 2007; Schlegel and Stainier 2007; Lessing and Bonini 2009). They are likewise an important resource for investigating the genetic underpinnings of continuously varying quantitative traits (Palsson and Gibson 2004; Telonis-Scott *et al.* 2005; Wang *et al.* 2005, 2006; Dworkin and Gibson 2006; Bergland *et al.* 2008; Gibson and Reed 2008; Ayroles *et al.* 2009; Dworkin *et al.* 2009; Goering *et al.* 2009; Mackay *et al.* 2009, 2010, 2011). Numerous models of human disease have been established in the fly (reviewed in Pandey and Nichols 2011), including transgenic models of diseases ranging from neurodegeneration/retinal degeneration (Bilen and Bonini 2005; Ryoo *et al.* 2007; Lessing and Bonini 2009; Yu and Bonini 2011) to cancer (Rudrapatna *et al.* 2012). Success with genetic screens to identify suppressors and enhancers of disease when mutants are overexpressed in a developing tissue, such as the eye-antennal imaginal disc, suggested to us that it might be possible to generate a fly model of misfolded insulin-associated diabetes.

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Effect of Genetic Variation in a *Drosophila* Model of Diabetes-Associated Misfolded Human Proinsulin

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ABSTRACT The identification and validation of gene–gene interactions is a major challenge in human studies. Here, we explore an approach for studying epistasis in humans using a *Drosophila melanogaster* model of neonatal diabetes mellitus. Expression of the mutant preproinsulin (hINS^{C96Y}) in the eye imaginal disc mimics the human disease: it activates conserved stress-response pathways and leads to cell death (reduction in eye area). Dominant-acting variants in wild-derived inbred lines from the Drosophila Genetics Reference Panel produce a continuous, highly heritable distribution of eye-degeneration phenotypes in a hINS^{C96Y} background. A genome-wide association study (GWAS) in 154 sequenced lines identified a sharp peak on chromosome 3L, which mapped to a 400-bp linkage block within an intron of the gene *sulfateless* (*sfl*). RNAi knockdown of *sfl* enhanced the eye-degeneration phenotype in a mutant-hINS-dependent manner. RNAi against two additional genes in the heparan sulfate (HS) biosynthetic pathway (*ttv* and *botv*), in which *sfl* acts, also modified the eye phenotype in a hINS^{C96Y}-dependent manner, strongly suggesting a novel link between HS-modified proteins and cellular responses to misfolded proteins. Finally, we evaluated allele-specific expression difference between the two major *sfl*-intronic haplotypes in heterozygtes. The results showed significant heterogeneity in marker-associated gene expression, thereby leaving the causal mutation(s) and its mechanism unidentified. In conclusion, the ability to create a model of human genetic disease, map a QTL by GWAS to a specific gene, and validate its contribution to disease with available genetic resources and the potential to experimentally link the variant to a molecular mechanism demonstrate the many advantages *Drosophila* holds in determining the genetic underpinnings of human disease.

LIMITATIONS imposed by human subject research can be overcome by investigating models of human disease in experimental organisms. *Drosophila* can provide genetic insights relevant to human biology and disease, owing to the conservation of fundamental cellular and developmental processes. We constructed a fly model of protein-misfolding disease, by creating a transgene of a diabetes-causing, human mutant preproinsulin (hINS^{C96Y}) that could be expressed in the eye imaginal discs and other tissues (Park *et al.* 2013). This misfolded proinsulin protein causes the loss of insulin-secreting pancreatic beta cells and diabetes in humans and mice (Støy *et al.* 2007). When misexpressed in the *Drosophila* eye imaginal disc, it disrupts eye development, resulting in a reduced eye area in adult flies (Park *et al.* 2013).

In the accompanying article (Park *et al.* 2013), we crossed the transgenic line bearing the mutant preproinsulin and an eye-specific Gal4 driver (GMR >> hINS^{C96Y}) with a subset of the lines from the Drosophila Genetics Reference Panel (DGRP). The F1 lines displayed a wide, nearly continuous, range of heritable eye-degeneration phenotypes, suggesting a polygenic basis for this genetic background variation (Park *et al.* 2013). To investigate the genetic basis of this background variation, here we performed a genome-wide association study in a larger set of 154 DGRP lines.

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PLOS ONE

Sweet Taste Receptor Deficient Mice Have Decreased Adiposity and Increased Bone Mass

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Abstract

Functional expression of sweet taste receptors (T1R2 and T1R3) has been reported in numerous metabolic tissues, including the gut, pancreas, and, more recently, in adipose tissue. It has been suggested that sweet taste receptors in these non-gustatory tissues may play a role in systemic energy balance and metabolism. Smaller adipose depots have been reported in T1R3 knockout mice on a high carbohydrate diet, and sweet taste receptors have been reported to regulate adipogenesis *in vitro*. To assess the potential contribution of sweet taste receptors to adipose tissue biology, we investigated the adipose tissue phenotypes of T1R2 and T1R3 knockout mice. Here we provide data to demonstrate that when fed an obesogenic diet, both T1R2 and T1R3 knockout mice have reduced adiposity and smaller adipocytes. Although a mild glucose intolerance was observed with T1R3 deficiency, other metabolic variables analyzed were similar between genotypes. In addition, food intake, respiratory quotient, oxygen consumption, and physical activity were unchanged in T1R2 knockout mice. Although T1R2 deficiency did not affect adipocyte number in peripheral adipose depots, the number of bone marrow adipocytes is significantly reduced in these knockout animals. Finally, we present data demonstrating that T1R2 and T1R3 knockout mice have increased cortical bone mass and trabecular remodeling. This report identifies novel functions for sweet taste receptors in the regulation of adipose and bone biology, and suggests that in these contexts, T1R2 and T1R3 are either dependent on each other for activity or have common independent effects *in vivo*.

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Introduction

Sweet taste perception by the tongue is mediated by the G protein-coupled receptors T1R2 and T1R3 [1,2]. These receptors are reported to function as obligate heterodimers to provide input on the caloric and macronutrient content of ingested food. However, sweet taste receptors have been identified in an increasing number of extra-gustatory tissues [3–7], often regulating metabolic processes [8–13]. In pancreatic β-cells, sweet taste receptors act to augment glucose-induced insulin secretion in response to artificial sweeteners [11] and fructose [13]. In addition, mice lacking gustducin, a mediator of taste receptor signaling, have reduced glucagon-like peptide-1 (GLP-1) and insulin secretion on account of the loss of sweet taste receptor activity in GLP-1-secreting enteroendocrine cells of the gut [12]. However, sweetener-stimulated GLP-1 secretion appears to be dependent on T1R3, but not T1R2 expression [14], suggesting that these receptors may also function independently of each other in some contexts, perhaps as homodimers.

In addition to effects on insulin and incretin secretion [10,13], sweet taste receptors may also have metabolic roles in adipose tissue. Masubuchi *et al* reported that T1R2 and T1R3 are expressed in 3T3-L1 cells, and that T1R3 is induced during differentiation and mediates inhibition of adipogenesis by artificial sweeteners [15]. Our group also observed that T1R2 and T1R3 are expressed throughout adipogenesis; however, in our hands, saccharin and acesulfame potassium enhance adipogenesis and suppress adipocyte lipolysis through a mechanism independent of both T1R2 and T1R3 [16]. An additional study has shown that T1R3 knockout (KO) animals are resistant to sucrose-induced obesity and have smaller fat depots on a high-sucrose diet [17],

Leptin Acts Independently of Food Intake to Modulate Gut Microbial Composition in Male Mice

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Shifts in the composition of gut bacterial populations can alter host metabolism and may contribute to the pathogenesis of metabolic disorders, including obesity. Mice deficient in leptin action are obese with altered microbiota and increased susceptibility to certain intestinal pathogens. Because antimicrobial peptides (AMPs) secreted by Paneth cells represent a major mechanism by which the host influences the gut microbiome, we examined the mRNA expression of gut AMPs, several of which were decreased in leptin receptor (LepR)-deficient *db/db* mice, suggesting a potential role for AMP modulation of microbiota composition. To address the extent to which the alterations in gut microbiota and AMP mRNA expression in *db/db* mice result from increased food intake vs other defects in leptin action, we examined the effects of pair feeding and gut epithelial LepRb ablation on AMP mRNA expression and microbiota composition. We found that the phylum-level changes in fecal microbial content and AMP gene expression persist in pair-fed *db/db* mice, suggesting that these differences do not stem from hyperphagia alone. In addition, despite recent evidence to support a role for intestinal epithelial LepRb signaling in pathogen susceptibility, ablation of LepRb from the intestinal epithelium fails to alter body weight, composition of the microbiota, or AMP expression, suggesting a role for LepRb elsewhere for this regulation. Indeed, gut LepRb cells are not epithelial but rather constitute a previously uncharacterized population of perivascular cells within the intestinal submucosa. Overall, our data reveal a role for LepRb signaling extrinsic to the intestinal epithelium and independent of food intake in the control of the gut microbiome. **(*Endocrinology* 155: 748–757, 2014)**

The mechanisms by which the intestinal epithelium interacts with the indigenous gut microbiota to maintain a healthy equilibrium capable of tolerating commensal bacteria while swiftly responding to pathogens are not well understood (1). Dynamic interactions between gut microbes and the host modulate gut cellular proliferation, including the production of secretory cells and gut-associated immune cells (1). Dysregulation of the host-microbiome interaction may contribute to the pathogenesis of systemic metabolic disorders such as obesity (2, 3), metabolic syndrome (4), and cardiovascular disease (5). Shifts in fecal microbial populations correlate with obesity in both mice and humans, suggesting that certain bacterial constituents may modulate the susceptibility or response to weight gain (2, 6). One of the mechanisms by which gut bacteria may influence the host is through fermentation of otherwise indigestible dietary nutrients, rendering them available for host absorption, or through the generation of metabolites that modulate host biology (2, 7). Indeed, the absence of microbes in germ-free animals decreases caloric uptake from the diet and prevents diet-induced obesity. Reintroduction of gut microbes into germ-free mice in-

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Abbreviations: AMP, antimicrobial peptide; DAPI, 4,6-diamidino-2-phenylindole; FCS, fetal calf serum; HBSS, Hanks' balanced salt solution; LepR, leptin receptor; SMA, smooth muscle actin; TBST, Tris-buffered saline/Tween 20.

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Otopetrin 1 Protects Mice From Obesity-Associated Metabolic Dysfunction Through Attenuating Adipose Tissue Inflammation

Chronic low-grade inflammation is emerging as a pathogenic link between obesity and metabolic disease. Persistent immune activation in white adipose tissue (WAT) impairs insulin sensitivity and systemic metabolism, in part, through the actions of proinflammatory cytokines. Whether obesity engages an adaptive mechanism to counteract chronic inflammation in adipose tissues has not been elucidated. Here we identified otopetrin 1 (Otop1) as a component of a counterinflammatory pathway that is induced in WAT during obesity. Otop1 expression is markedly increased in obese mouse WAT and is stimulated by tumor necrosis factor-α in cultured adipocytes. Otop1 mutant mice respond to high-fat diet with pronounced insulin resistance and hepatic steatosis, accompanied by augmented adipose tissue inflammation. Otop1 attenuates interferon-γ (IFN-γ) signaling in adipocytes through selective downregulation of the transcription factor STAT1. Using a tagged vector, we found that Otop1 physically interacts with endogenous STAT1. Thus, Otop1 defines a unique target of cytokine signaling that attenuates obesity-induced adipose tissue inflammation and plays an adaptive role in maintaining metabolic homeostasis in obesity.

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Obesity poses significant risk to patient health owing to its associated metabolic disorders. White adipose tissue (WAT) stores the bulk of body fat and also plays an important role in endocrine metabolic signaling (1,2), whereas brown adipose tissue (BAT) defends against cold and obesity through uncoupled mitochondrial respiration (3,4). Obesity is associated with chronic low-grade inflammation in adipose tissues (5–9). The pathogenic role of the persistent activation of inflammatory signaling in metabolic disease has been demonstrated in numerous mouse models. An emerging view suggests that attenuating the proinflammatory response may provide significant metabolic benefits in obesity. While therapeutic development targeting inflammation remains in its early stage in humans, several candidates have shown promise, including salsalate, a prodrug of salicylate (10), and interleukin (IL)-1 receptor antagonists (11). In addition,

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PATHOPHYSIOLOGY

Cell

The Diabetes Susceptibility Gene *Clec16a* Regulates Mitophagy

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SUMMARY

Clec16a has been identified as a disease susceptibility gene for type 1 diabetes, multiple sclerosis, and adrenal dysfunction, but its function is unknown. Here we report that Clec16a is a membrane-associated endosomal protein that interacts with E3 ubiquitin ligase Nrdp1. Loss of Clec16a leads to an increase in the Nrdp1 target Parkin, a master regulator of mitophagy. Islets from mice with pancreas-specific deletion of Clec16a have abnormal mitochondria with reduced oxygen consumption and ATP concentration, both of which are required for normal β cell function. Indeed, pancreatic Clec16a is required for normal glucose-stimulated insulin release. Moreover, patients harboring a diabetogenic SNP in the Clec16a gene have reduced islet Clec16a expression and reduced insulin secretion. Thus, Clec16a controls β cell function and prevents diabetes by controlling mitophagy. This pathway could be targeted for prevention and control of diabetes and may extend to the pathogenesis of other Clec16a- and Parkin-associated diseases.

INTRODUCTION

Genome-wide association studies (GWASs) are a powerful approach to the identification of genes involved in common human diseases yet are limited by the identification of variants in the loci of genes with completely unknown functions. Further, many SNPs identified in GWAS are found in intergenic regions that affect the function of transcriptional enhancers located far from the disease-relevant gene. Thus, it is critical to directly examine the functional role of potential disease genes and to correlate gene variation in potential enhancers to expression of the putative associated gene. Molecular understanding of new disease loci may provide important insights into the pathogenesis of human diseases and reveal new therapeutic targets (Pociot et al., 2010).

C-type lectin domain family 16, member A (Clec16a; KIAA0350), a gene locus associated with type 1 diabetes mellitus (T1DM), multiple sclerosis, and adrenal dysfunction (Hakonarson et al., 2007; IMSGC, 2009; Skinningsrud et al., 2008; WTCCC, 2007), is a 24-exon gene that encodes a large protein (1,053 amino acids) with evolutionary conservation of the N terminus but no recognizable conserved motifs. Little is known of mammalian Clec16a function or of its role in disease pathogenesis.

Here we discover a key role for Clec16a in the regulation of mitophagy, a selective form of autophagy necessary for mitochondrial quality control (Ashrafi and Schwarz, 2013). Utilizing proteomics analyses, we determine that the E3 ubiquitin ligase Neuregulin receptor degradation protein 1 (Nrdp1 or RNF41) interacts with Clec16a and mediates Clec16a functions, through the Nrdp1 target Parkin, in multiple cell types. We find a key role for Clec16a in the maintenance of glucose homeostasis through its effect on the mitochondrial health of pancreatic β cells and, consequently, glucose-stimulated insulin secretion. Lastly, we demonstrate that a diabetogenic SNP in the CLEC16A locus correlates with islet CLEC16A expression, β cell function, and glycemic control in human subjects.

RESULTS

Identification of E3 Ubiquitin Ligase Nrdp1 as a Specific Partner of Clec16a

We hypothesized that Clec16a plays an important role in multiple tissues and that the identification of novel Clec16a-interacting partners might shed light on its function. To this end, we utilized

Brief report

Targeting the cell cycle inhibitor p57^{Kip2} promotes adult human β cell replication

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Children with focal hyperinsulinism of infancy display a dramatic, non-neoplastic clonal expansion of β cells that have undergone mitotic recombination, resulting in paternal disomy of part of chromosome 11. This disomic region contains imprinted genes, including the gene encoding the cell cycle inhibitor p57^{Kip2} (*CDKN1C*), which is silenced as a consequence of the recombination event. We hypothesized that targeting p57^{Kip2} could stimulate adult human β cell replication. Indeed, when we suppressed *CDKN1C* expression in human islets obtained from deceased adult organ donors and transplanted them into hyperglycemic, immunodeficient mice, β cell replication increased more than 3-fold. The newly replicated cells retained properties of mature β cells, including the expression of β cell markers such as insulin, PDX1, and NKX6.1. Importantly, these newly replicated cells demonstrated normal glucose-induced calcium influx, further indicating β cell functionality. These findings provide a molecular explanation for the massive β cell replication that occurs in children with focal hyperinsulinism. These data also provided evidence that β cells from older humans, in which baseline replication is negligible, can be coaxed to re-enter and complete the cell cycle while maintaining mature β cell properties. Thus, controlled manipulation of this pathway holds promise for the expansion of β cells in patients with type 2 diabetes.

Introduction

Hyperinsulinism of infancy is a clinical syndrome of pancreatic β cell dysfunction characterized by a failure to suppress insulin secretion in the presence of hypoglycemia (1). In most patients, the disease is caused by recessive mutations of the sulfonylurea receptor 1 (SUR1) gene *ABCC8* or the potassium channel (KIR6.2) gene *KCNJ11* (2, 3), encoding the two subunits of the β cell ATP-sensitive K^+ (K_{ATP}) channel, which controls insulin secretion. Histologically, hyperinsulinism presents as two major subtypes: diffuse and focal (4). The diffuse form involves all β cells (5), while in focal hyperinsulinism, adenomatous hyperplasia occurs within a limited region of the pancreas. This mass of β cells originates from clonal expansion of a single cell, in which a recessive mutation of either the *ABCC8* or *KCNJ11* gene is inherited on the paternal allele (Figure 1A). On that background, a somatic recombination of the p terminus of chromosome 11 occurs during fetal development, resulting in duplication of the paternal allele concomitant with loss of the maternal allele, leading to homozygosity for the mutated *ABCC8/KCNJ11* locus and uniparental disomy for all genes telomeric to *ABCC8/KCNJ11* (6, 7). The duplicated segment contains several maternally expressed imprinted genes including *CDKN1C*, which encodes the cyclin-dependent kinase inhibitor p57^{Kip2} (8). Therefore, in β cells descendant from this mutant precursor, p57^{Kip2} expression is extinguished (9).

p57^{Kip2} causes cell cycle arrest in terminally differentiated cells through inhibition of several G1 cyclin/CDK complexes, and its loss is related to multiple malignancies (10). Furthermore, loss of p57^{Kip2} in focal hyperinsulinism lesions correlates with increased proliferation (11). Therefore, we hypothesized that p57^{Kip2} has a major role in preventing β cell regeneration and that manipulation of its expression may enhance proliferation of adult human β cells.

Results and Discussion

Since p57^{Kip2} is expressed in β cells of humans but not in those of rodents, we used islets from deceased human organ donors for our study. To modulate p57^{Kip2} expression, we used shRNA-mediated gene suppression delivered by lentiviral particles, which can efficiently transduce nondividing cells and express the shRNA construct (12). First, we tested multiple shRNAs to specifically abolish *CDKN1C* mRNA expression in HEK293 cells (Figure 1B) and used the most efficient construct (p57c) to produce lentiviral particles. Transduction of human islets with p57^{Kip2} shRNA lentivirus caused over a 70% reduction in *CDKN1C* mRNA levels (Figure 1C) in infected cells, while it did not affect the mRNA levels of other cell cycle inhibitors such as p16, p21, and p27 (Supplemental Figure 1A; supplemental material available online with this article; doi:10.1172/JCI69519DS1). Cultured human islets transduced with lentiviral particles and cultured for 72 hours showed strong expression of turbo-GFP in about 25% of the cells (Figure 1D). According to flow cytometric analysis (Supplemental Figure 1B), an additional 20% of islet cells expressed lower levels of turbo-GFP.

Attempts at stimulating human β cell replication in cultured, lentivirally transduced human islets were unsuccessful (data not shown). Therefore, we chose to transplant transduced human islets under the kidney capsule of immunodeficient mice, which allows for islet revascularization and exposure to host factors. Immunodeficient mice were rendered diabetic using streptozotocin (STZ) to provide an additional mitogenic stimulus for the transplanted β cells (13). During the entire transplantation period (~20 days), replicating cells were labeled by the thymidine analog BrdU, which was supplied in the drinking water. Immunostaining of the grafts

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LETTER

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The nuclear receptor Rev-erbα controls circadian thermogenic plasticity

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Circadian oscillation of body temperature is a basic, evolutionarily conserved feature of mammalian biology[1]. In addition, homeostatic pathways allow organisms to protect their core temperatures in response to cold exposure[2]. However, the mechanism responsible for coordinating daily body temperature rhythm and adaptability to environmental challenges is unknown. Here we show that the nuclear receptor Rev-erbα (also known as Nr1d1), a powerful transcriptional repressor, links circadian and thermogenic networks through the regulation of brown adipose tissue (BAT) function. Mice exposed to cold fare considerably better at 05:00 (Zeitgeber time 22) when Rev-erbα is barely expressed than at 17:00 (Zeitgeber time 10) when Rev-erbα is abundant. Deletion of *Rev-erbα* markedly improves cold tolerance at 17:00, indicating that overcoming Rev-erbα-dependent repression is a fundamental feature of the thermogenic response to cold. Physiological induction of uncoupling protein 1 (Ucp1) by cold temperatures is preceded by rapid downregulation of *Rev-erbα* in BAT. Rev-erbα represses Ucp1 in a brown-adipose-cell-autonomous manner and BAT Ucp1 levels are high in *Rev-erbα*-null mice, even at thermoneutrality. Genetic loss of *Rev-erbα* also abolishes normal rhythms of body temperature and BAT activity. Thus, Rev-erbα acts as a thermogenic focal point required for establishing and maintaining body temperature rhythm in a manner that is adaptable to environmental demands.

The molecular clock is an autoregulatory network of core transcriptional machinery orchestrating behavioural and metabolic programming in the context of a 24-h light–dark cycle[1,3]. The importance of appropriate synchronization in organismal biology is underscored by the robust correlation between disruption of clock circuitry and development of disease states such as obesity, diabetes mellitus and cancer[4–6]. Tissue-specific clocks are entrained by environmental stimuli, blood-borne hormonal cues, and direct neuronal input from the suprachiasmatic nucleus located in the hypothalamus to ensure coordinated systemic resonance[1,7].

One of the defining metrics of circadian patterning is body temperature[8], which is highest in animals while awake and lowest while asleep[1]. A major site of mammalian thermogenesis is BAT, which is characterized by high glucose uptake, oxidative capacity and mitochondrial uncoupling[2]. Despite a substantial body of literature examining various regulatory aspects of BAT function and body temperature, little is known about the mechanisms controlling circadian thermogenic rhythms and, more importantly, how this patterning influences adaptability to environmental challenges. The circadian transcriptional repressor Rev-erbα has been previously linked to the regulation of glucose and lipid metabolism in tissues such as skeletal muscle, white adipose and liver[9–15], but its influence on BAT physiology remains unknown.

We investigated the function of Rev-erbα in controlling temperature rhythms and thermogenic plasticity through integration of circadian and environmental signals. All experiments were performed on C57BL/6 mice and, unless otherwise noted, at murine thermoneutrality (~29–30 °C) to avoid confounding background contributions from the 'browning' of white adipose depots or partial stimulation of BAT activity[16]. At thermoneutrality, the circadian oscillations of *Rev-erbα* gene expression (Fig. 1a) and protein levels (Extended Data Fig. 1a) in BAT were similar to other tissues[11,17], peaking in the light and being nearly absent in the dark. *Rev-erbα* ablation altered *Bmal1* (also known as *Arntl*) transcription but did not affect the rhythmicity of *Rev-erbβ* (also known as *Nr1d2*), *Cry1*, *Cry2*, *Per1*, *Per2*, *Per3* or *Clock* (Extended Data Fig. 1b), consistent with the mild circadian phenotype observed previously[17].

To evaluate the role of Rev-erbα in BAT, C57BL/6 wild-type and *Rev-erbα* knockout mice were subjected to an acute cold challenge from Zeitgeber time (ZT) 4–10 (11:00–17:00) when Rev-erbα levels peak in wild-type animals. In accordance with previous reports that thermoneutrally acclimated C57BL/6 mice fail to thrive during acute cold stresses[16,18,19], body temperatures of wild-type animals dropped markedly when shifted from 29 °C to 4 °C (Fig. 1b), and this inability to maintain body temperature was associated with failure to survive the cold exposure (Fig. 1c). By contrast, *Rev-erbα* knockout mice maintained body temperature and uniformly survived the ZT4–10 cold challenge.

Notably, these studies were all performed during the day, when Rev-erbα peaks in wild-type mice. As Rev-erbα is physiologically nearly absent at night, we next explored whether the circadian expression of *Rev-erbα* imposed a diurnal variation in cold tolerance. Previous studies of animals exposed to cold at either mid-morning or early afternoon reported modest differences in tolerance, but this effect was believed to be a result of altered vasodilation[20]. Notably, during the dark period, when Rev-erbα levels are at the nadir of their physiological rhythm, wild-type mice were fully able to protect their body temperature and were phenotypically indistinguishable from *Rev-erbα* knockout mice in both body temperature regulation (Fig. 1d) and survival (Fig. 1e) following cold challenge. These findings implicate Rev-erbα in establishing a circadian rhythm of cold tolerance through suppression of heat-producing pathways.

The increased cold tolerance of *Rev-erbα* knockout mice was associated with higher oxygen consumption rates compared to wild-type littermates (Fig. 1f). Food intake (Extended Data Fig. 2a), basal muscle activity and cold-induced shivering (Fig. 1g and Extended Data Fig. 2b) were unchanged between genotypes, indicating that the Rev-erbα-dependent differences in oxidative capacity were probably due to alterations in a BAT-driven, non-shivering thermogenic program. Indeed, BAT isolated from cold-challenged *Rev-erbα* knockout animals consumed more oxygen than BAT from wild-type mice (Fig. 1h). Moreover,

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Report

Testing the Role of Myeloid Cell Glucose Flux in Inflammation and Atherosclerosis

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SUMMARY

Inflammatory activation of myeloid cells is accompanied by increased glycolysis, which is required for the surge in cytokine production. Although in vitro studies suggest that increased macrophage glucose metabolism is sufficient for cytokine induction, the proinflammatory effects of increased myeloid cell glucose flux in vivo and the impact on atherosclerosis, a major complication of diabetes, are unknown. We therefore tested the hypothesis that increased glucose uptake in myeloid cells stimulates cytokine production and atherosclerosis. Overexpression of the glucose transporter GLUT1 in myeloid cells caused increased glycolysis and flux through the pentose phosphate pathway but did not induce cytokines. Moreover, myeloid-cell-specific overexpression of GLUT1 in LDL receptor-deficient mice was ineffective in promoting atherosclerosis. Thus, increased glucose flux is insufficient for inflammatory myeloid cell activation and atherogenesis. If glucose promotes atherosclerosis by increasing cellular glucose flux, myeloid cells do not appear to be the key targets.

INTRODUCTION

When a myeloid cell encounters inflammatory cues, such as the Gram-negative bacterial outer membrane component lipopolysaccharide (LPS) and cytokines governing innate and adaptive immunity, such as interferon-γ (IFN-γ), it undergoes inflammatory activation often referred to as classical (M1) activation. This process is associated with increased glucose flux through glycolysis and the pentose phosphate pathway (Vats et al., 2006; Krawczyk et al., 2010, Haschemi et al., 2012; O'Neill and Hardie, 2013) and reduced mitochondrial oxidation (Vats et al., 2006; O'Neill and Hardie, 2013). Increased glycolysis in myeloid cells is not only a consequence of inflammatory activation but is of critical importance for the ability of these cells to govern inflammatory processes (O'Neill and Hardie, 2013; Tannahill et al., 2013). The shift to glycolysis is due, at least in part, to upregulation of the glucose transporter GLUT1 and enzymes in the glycolytic pathway, including the 6-phosphofructose-2-kinase isoform PFKFB3, and downregulation of tricarboxylic acid (TCA)-cycle enzymes (Tannahill et al., 2013), and to increased production of nitric oxide, which inhibits oxidative phosphorylation (Everts et al., 2012). Furthermore, the enzyme carbohydrate kinase-like protein CARKL, which is dramatically downregulated by LPS in macrophages and regulates flux through the nonoxidative arm of the pentose phosphate pathway, has recently been shown to inhibit the classical activation of these cells (Haschemi et al., 2012). Together, these findings indicate that increased flux of glucose through glycolysis and the pentose phosphate pathway relative to mitochondrial oxidation is a key feature of inflammatory myeloid cells required for optimal inflammatory functions of these cells.

Increased glucose flux in myeloid cells might explain the increased inflammatory activity of these cells in diabetes and, by inference, might also explain complications of diabetes associated with increased myeloid cell activation. This is logical because diabetes is characterized by hyperglycemia and increased inflammatory activation of myeloid cells (Kanter et al., 2012; Nagareddy et al., 2013) as well as myelopoiesis (Nagareddy et al., 2013). A glucose-dependent increase in production of cytokines by macrophages in the artery wall in diabetic mice is associated with worsened atherosclerosis (Nagareddy et al., 2013), a major complication of diabetes leading to myocardial infarction and stroke (Bornfeldt and Tabas, 2011). Blocking diabetes-induced inflammatory activation of myeloid cells prevents diabetes-accelerated atherosclerosis

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The p75 Neurotrophin Receptor Is Required for the Major Loss of Sympathetic Nerves From Islets Under Autoimmune Attack

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Our goal was to determine the role of the p75 neurotrophin receptor (p75NTR) in the loss of islet sympathetic nerves that occurs during the autoimmune attack of the islet. The islets of transgenic (Tg) mice in which β-cells express a viral glycoprotein (GP) under the control of the insulin promotor (Ins2) were stained for neuropeptide Y before, during, and after virally induced autoimmune attack of the islet. Ins2-GP^{Tg} mice injected with lymphocytic choriomeningitis virus (LCMV) lost islet sympathetic nerves before diabetes development but coincident with the lymphocytic infiltration of the islet. The nerve loss wasmarked and islet-selective. Similar nerve loss, chemically induced, was sufficient to impair sympathetically mediated glucagon secretion. In contrast, LCMV-injected Ins2-GP^{Tg} mice lacking the p75NTR retained most of their islet sympathetic nerves, despite both lymphocytic infiltration and development of diabetes indistinguishable from that of p75NTR wild-type mice. We conclude that an nducible autoimmune attack of the islet causes a marked and islet-selective loss of sympathetic nerves that precedes islet collapse and hyperglycemia. The p75NTR mediates this nerve loss but plays no role in mediating the loss of islet β-cells or the subsequent diabetes. p75NTR-mediated nerve loss may contribute to the impaired glucose counterregulation seen in type 1 diabetes.

Two neuropathies associated with diabetes are well-recognized: diabetic autonomic neuropathy (1–3) and somatosensory neuropathy (4,5). Their multiple mechanisms have been linked to chronic hyperglycemia (6,7) in a unifying hypothesis (8). There is also less extensive evidence for acute damage to sensory (9) and sympathetic (10,11) innervation supplying the islet. This mechanism may involve insulin deficiency instead of hyperglycemia. Sympathetic defects may contribute to the impaired glucagon response to hypoglycemia seen early in type 1 diabetes (12), since activation of pancreatic sympathetic nerves stimulates glucagon secretion (13–15), and hypoglycemia activates these nerves (16,17).

Since the glucagon response to insulin-induced hypoglycemia depends both on relief from tonic inhibition by the islet β-cell (18) and active stimulation by the autonomic nervous system (19), defects in both have been proposed as causes of this impairment (18,19). One autonomic defect, which we named early sympathetic islet neuropathy (eSIN), is present in diabetic BB rats (20), NOD mice (21,22), and type 1 diabetic humans (23). This marked loss of islet sympathetic nerves is sufficient to impair the glucagon response to sympathetic activation (21,24). Since eSIN is not present in either chemically induced diabetes (20,21) or in type 2 human diabetes (23), it is likely triggered by the immune attack on the islet, a hypothesis that was strengthened by finding a strong correlation between invasive insulitis and the loss of islet sympathetic nerves in NOD mice (21).

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FGF19 action in the brain induces insulin-independent glucose lowering

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Insulin-independent glucose disposal (referred to as glucose effectiveness [GE]) is crucial for glucose homeostasis and, until recently, was thought to be invariable. However, GE is reduced in type 2 diabetes and markedly decreased in leptin-deficient *ob/ob* mice. Strategies aimed at increasing GE should therefore be capable of improving glucose tolerance in these animals. The gut-derived hormone FGF19 has previously been shown to exert potent antidiabetic effects in *ob/ob* mice. In *ob/ob* mice, we found that systemic FGF19 administration improved glucose tolerance through its action in the brain and that a single, low-dose i.c.v. injection of FGF19 dramatically improved glucose intolerance within 2 hours. Minimal model analysis of glucose and insulin data obtained during a frequently sampled i.v. glucose tolerance test showed that the antidiabetic effect of i.c.v. FGF19 was solely due to increased GE and not to changes of either insulin secretion or insulin sensitivity. The mechanism underlying this effect appears to involve increased metabolism of glucose to lactate. Together, these findings implicate the brain in the antidiabetic action of systemic FGF19 and establish the brain's capacity to rapidly, potently, and selectively increase insulin-independent glucose disposal.

Introduction

In addition to insulin secretion and insulin sensitivity (Si), insulin-independent mechanisms are critical to normal glucose homeostasis (1). Given that such mechanisms contribute at least as much to normal glucose tolerance as does insulin itself (1), it is surprising how little is known about them. This lack of research interest can be traced to the widespread perception of insulin-independent glucose disposal, which has been termed glucose effectiveness (GE; the ability of glucose to promote its own disposal, independently of insulin), as the fixed, obligate, and unregulated mechanism whereby insulin-insensitive tissues meet ongoing fuel needs. Yet glucose intolerance and type 2 diabetes (T2D) are characterized by decreases of GE as well as of insulin secretion and action (1). In leptin-deficient *ob/ob* mice, for example, GE was shown recently to be reduced by approximately 70%, based on minimal model analysis of data obtained from a frequently sampled i.v. glucose tolerance test (FSIGT) (2). Based on its importance to glucose homeostasis, we hypothesized that any intervention capable of normalizing glucose tolerance in these mice should do so, at least in part, by increasing GE.

FGF19 and its rodent homolog, FGF15, is one of three members of the family of hormonal FGFs. FGF19 is secreted by enterocytes located in the distal small intestine following activation of the nuclear bile acid receptor, FXR, by bile acid binding (3). In addition to its well-established role in the negative feedback control of hepatic bile acid synthesis (4, 5), FGF19 exerts potent antidiabetic effects in rodent models, including *ob/ob* mice (6). Similarly, transgenic overexpression of FGF19 improves glucose tolerance in diet-induced obese mice (6, 7), whereas FGF15-deficient mice display impaired glucose tolerance that is corrected by FGF19 administration (8).

Although initially thought to act primarily via FGFR4 receptors in the liver, the antidiabetic effects of FGF19 appear to involve a different FGF receptor subtype, because they are preserved in FGFR4-deficient mice (9). Instead, several findings implicate FGFR1 in this effect. First, systemic administration of a FGF19 variant that activates FGFR1 but not FGFR4 ameliorates diabetes in *ob/ob* mice, while this effect is absent for a FGF19 variant that activates FGFR4 but not FGFR1 (10). Second, the potent glucose-lowering effect of FGF19 is mimicked by monoclonal antibodies that selectively activate a specific FGFR1 isoform (FGFR1c) (11). Although activation of FGFR1 in peripheral tissues, such as brown and white adipose tissue, may contribute to glucose lowering, this receptor is also expressed in mediobasal hypothalamic areas involved in glucose homeostasis (12, 13), and administration of FGF19 directly into the brain improves glucose tolerance in both *ob/ob* mice (6) and diet-induced obese rats (14).

The current studies were undertaken to determine whether the antidiabetic effect of systemically administered FGF19 involves a central site of action and, if so, to determine the contribution(s) made by insulin-dependent and -independent mechanisms to this effect. We report that, in *ob/ob* mice, the glucose-lowering effect of systemic FGF19 is reduced by approximately 50% when its action in the brain is blocked by i.c.v. administration of an FGFR antagonist. Thus, the brain plays a key role in the antidiabetic effects of this hormone. To investigate how FGF19 action in the brain affects systemic glucose metabolism, we performed a FSIGT 2 hours after i.c.v. injection of either FGF19 or its vehicle in *ob/ob* mice as well as in vehicle-injected C57BL/6 controls. Glucose and insulin data from the FSIGT were analyzed using the minimal model method, which has been widely used in humans (1) and was recently validated in mice (including in *ob/ob* mice) (2), as a tool with which to measure insulin secretion, Si, and GE. Surprisingly, we found that the potent antidiabetic effect of i.c.v. FGF19 in *ob/ob* mice did not involve increases of either insulin secretion or Si. Instead, the

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Obesity Alters Adipose Tissue Macrophage Iron Content and Tissue Iron Distribution

Adipose tissue (AT) expansion is accompanied by the infiltration and accumulation of AT macrophages (ATMs), as well as a shift in ATM polarization. Several studies have implicated recruited M1 ATMs in the metabolic consequences of obesity; however, little is known regarding the role of alternatively activated resident M2 ATMs in AT homeostasis or how their function is altered in obesity. Herein, we report the discovery of a population of alternatively activated ATMs with elevated cellular iron content and an iron-recycling gene expression profile. These iron-rich ATMs are referred to as MFe^{hi}, and the remaining ATMs are referred to as MFe^{lo}. In lean mice, ~25% of the ATMs are MFe^{hi}; this percentage decreases in obesity owing to the recruitment of MFe^{lo} macrophages. Similar to MFe^{lo} cells, MFe^{hi} ATMs undergo an inflammatory shift in obesity. In vivo, obesity reduces the iron content of MFe^{hi} ATMs and the gene expression of iron importers as well as the iron exporter, ferroportin, suggesting an impaired ability to handle iron. In vitro, exposure of primary peritoneal macrophages to saturated fatty acids also alters iron metabolism gene expression. Finally, the impaired MFe^{hi} iron handling coincides with adipocyte iron overload in obese mice. In conclusion, in obesity, iron distribution is altered both at the cellular and tissue levels, with AT playing a predominant role in this change. An increased availability of fatty acids during obesity may contribute to the observed changes in MFe^{hi} ATM phenotype and their reduced capacity to handle iron.

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Obesity is marked by the preferential accumulation of inflammatory M1 adipose tissue (AT) macrophages (ATMs), which play an important role in the development of AT inflammation and insulin resistance (IR) (1). The onset of AT dysfunction has important implications systemically, as AT inflammation and dysregulated lipolysis both promote ectopic lipid deposition and the accompanying metabolic consequences (2). Not surprisingly, a vast majority of the current literature is focused on mechanisms contributing to the recruitment and M1 polarization of infiltrating ATMs. Unfortunately, there remains a paucity of information regarding the physiological role of resident M2 polarized ATMs, as well as the manner by which resident ATM function is compromised in obesity. This represents an important gap in our current understanding of AT physiology, as defining the contribution of resident ATMs to AT homeostasis is a crucial step toward identifying the mechanisms underlying AT dysfunction in obesity.

Recently, the area of AT iron metabolism has received increasing attention. Adipogenesis, which is associated with the upregulation of various genes involved in iron metabolism (3), is induced by heme-iron through

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Changes in B-Type Natriuretic Peptide and BMI Following Roux-en-Y Gastric Bypass Surgery

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Obesity and attendant complications including type 2 diabetes mellitus, hypertension (HTN), and heart disease are worldwide epidemics with incompletely understood associations. Mechanisms underlying the association of HTN and obesity include upregulation of the renin-angiotensin-aldosterone system, sympathetic nervous system, insulin resistance, and adipose tissue activity, but a paradoxically downregulated cardiac natriuretic peptide system, cardiovascular system, and altered renal function (1). Recent studies suggest that natriuretic peptide deficiency may provide a link between obesity-related HTN and insulin resistance (2). Weight loss through bariatric surgery has reduced or eliminated HTN in multiple randomized controlled trials, perhaps through decreased plasma volume, but other mechanisms including changes in the cardiac natriuretic peptide system and lipolysis remain obscure (3). Understanding natriuretic peptide concentration changes following Roux-en-Y gastric bypass (RYGB) surgery may help elucidate the mechanism and impact of paradoxically low concentrations in obesity. We characterized changes in B-type natriuretic peptide (BNP) and N-telopeptide pro-BNP (NT-proBNP) in obese subjects after RYGB surgery by measuring concentrations at baseline and 6, 12, and 24 months postoperatively to enhance our understanding of BNP's role in weight loss and hemodynamics in this population.

We studied 40 obese subjects with BMI $\geq$35 kg/m^2 and at least one comorbid condition who participated in a separate randomized, controlled clinical trial examining the effects of RYGB surgery combined with omentectomy. That study was published previously (4). We obtained previously collected plasma samples from subjects randomized to RYGB alone or RYGB with omentectomy at surgery. This longitudinal study comprised five study visits at which blood was collected in EDTA tubes, centrifuged immediately, and plasma was stored at −80°C until assays were performed. BNP and NT-proBNP were measured using commercially available peptide enzyme immunoassays (Penninsula Laboratories, San Carlos, CA; Biomedica Immunoassays, Vienna, Austria, respectively). Linear mixed-effects model analysis was used to evaluate the change in BNP and NT-proBNP over time. Covariates included age, systolic blood pressure, BMI, alanine aminotransferase, hematocrit, fat body mass, lean body mass, and homeostasis model assessment of

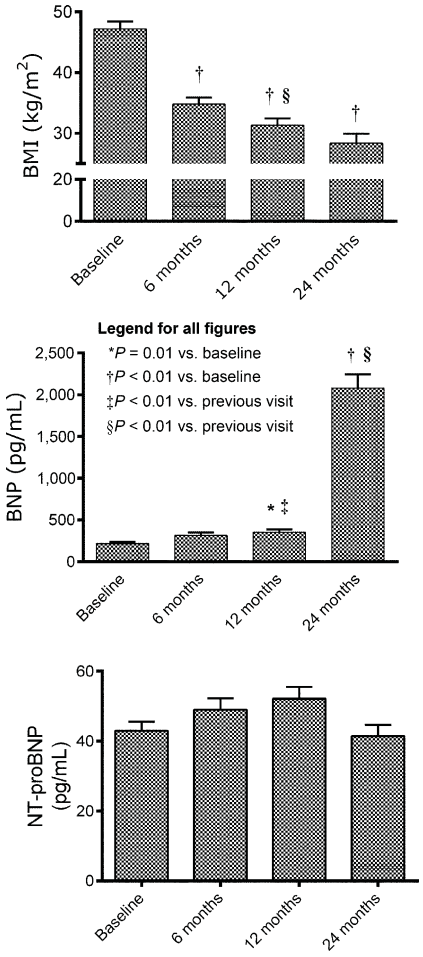

Figure 1—BMI, BNP, and NT-proBNP changes over 24 months of follow-up.

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Inactivation of specific β cell transcription factors in type 2 diabetes

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Type 2 diabetes (T2DM) commonly arises from islet β cell failure and insulin resistance. Here, we examined the sensitivity of key islet-enriched transcription factors to oxidative stress, a condition associated with β cell dysfunction in both type 1 diabetes (T1DM) and T2DM. Hydrogen peroxide treatment of β cell lines induced cytoplasmic translocation of MAFA and NKX6.1. In parallel, the ability of nuclear PDX1 to bind endogenous target gene promoters was also dramatically reduced, whereas the activity of other key β cell transcriptional regulators was unaffected. MAFA levels were reduced, followed by a reduction in NKX6.1 upon development of hyperglycemia in *db/db* mice, a T2DM model. Transgenic expression of the glutathione peroxidase-1 antioxidant enzyme (GPX1) in *db/db* islet β cells restored nuclear MAFA, nuclear NKX6.1, and β cell function in vivo. Notably, the selective decrease in MAFA, NKX6.1, and PDX1 expression was found in human T2DM islets. MAFB, a MAFA-related transcription factor expressed in human β cells, was also severely compromised. We propose that MAFA, MAFB, NKX6.1, and PDX1 activity provides a gauge of islet β cell function, with loss of MAFA (and/or MAFB) representing an early indicator of β cell inactivity and the subsequent deficit of more impactful NKX6.1 (and/or PDX1) resulting in overt dysfunction associated with T2DM.

Introduction

Oxidative stress appears to contribute to pancreatic islet β cell dysfunction in both type 1 (T1DM) and type 2 (T2DM) diabetes (1–6). As a consequence, understanding how oxidative stress impacts β cells is clearly of therapeutic relevance. Compelling evidence indicates that the accumulation of ROS, such as hydroxyl radical and hydrogen peroxide (H_2O_2) generated by increased glucose and/or lipid metabolism, causes cell inactivation and death (7). For example, the levels of oxidative stress markers are significantly higher in human T2DM islets (e.g., 3-nitrotyrosine and 8-hydroxy-2′-deoxyguanosine) (8, 9). Notably, islet β cells have unusually low antioxidant enzyme levels (e.g., glutathione peroxidase-1 [GPX1] and catalase), thus exposing their proteins, lipids, and/or DNA to oxidative modifications (10, 11). Importantly, antioxidant treatment can prevent the onset of diabetes in animal models of T1DM (6, 12) as well as improve β cell function in T2DM animal models (3–6, 12, 13) and human T2DM islets (8, 9, 14).

Maturity-onset diabetes of the young (MODY) typically results from mutations in islet-enriched transcription factors, with 6 of 9 MODY genes encoding transcription factors that are required in β cell development and/or function (15, 16). Furthermore, mutations in other distinct islet transcription factors decrease β cell function in vivo (e.g., MAFA, refs. 17, 18; NGN3, ref. 19; and PAX6, refs. 20, 21). Collectively, these observations indicate that islet β cell transcription factors could be primary targets of oxidative stress, with reduced (or induced) expression of their target genes resulting in cell dysfunction.

Experiments with β cell lines have demonstrated that 2 transcription factors, MAFA and PDX1, are inactivated under the oxidative stress conditions imposed by supraphysiological glucose levels (22). For example, the reduction in insulin-driven reporter activity and insulin mRNA levels coincided with a specific reduction in PDX1 and MAFA gel-shift binding activity, although the change in MAFA occurred earlier than in PDX1 and correlated more closely with the loss in insulin expression (23). Notably, mice only lacking MAFA in the pancreas (i.e., termed $Mafa^{\Delta Panc}$) (18) are glucose intolerant, but have normal fasting glucose levels, whereas loss of PDX1 from islet β cells causes overt hyperglycemia (24–27). These data suggest that β cell inactivity results from the stepwise loss of MAFA and then PDX1 under glucotoxic conditions (22, 23, 28). Interestingly, the N-acetyl-L-cysteine antioxidant improved both MAFA (referred to as RIPE3b1 activator) and PDX1 gel-shift–binding ability as well as β cell function in HIT-T15 β cells and in the ZDF T2DM rat model (3, 4). Moreover, transgenic β cell–specific *Gpx1* expression profoundly increased β cell function in the T2DM *db/db* mouse model, coinciding with the recovery of nuclear MAFA (5). The insulin secretion defects in human T2DM islets were also improved in vitro upon treatment with ROS scavengers (8, 9, 14).

In this study, islet-enriched transcription factor levels and activity in β cell lines were first screened for sensitivity to H_2O_2, an effector of oxidative stress. Our results demonstrated that MAFA, MAFB, PDX1, and NKX6.1 were selectively inactivated. We further observed that MAFA and NKX6.1, the latter being essential for islet β cell development and function (29–31), were sequentially and selectively lost upon induction of hyperglycemia in *db/db* mice. Nuclear NKX6.1 and MAFA were restored by transgenic *Gpx1* antioxidant enzyme production in *db/db* islet β cells. Importantly, MAFA, MAFB, PDX1, and NKX6.1 levels were also severely

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Pancreatic β Cell Dedifferentiation in Diabetes and Redifferentiation following Insulin Therapy

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SUMMARY

Diabetes is characterized by "glucotoxic" loss of pancreatic β cell function and insulin content, but underlying mechanisms remain unclear. A mouse model of insulin-secretory deficiency induced by β cell inexcitability (K_{ATP} gain of function) demonstrates development of diabetes and reiterates the features of human neonatal diabetes. In the diabetic state, β cells lose their mature identity and dedifferentiate to neurogenin3-positive and insulin-negative cells. Lineage-tracing experiments show that dedifferentiated cells can subsequently redifferentiate to mature neurogenin3-negative, insulin-positive β cells after lowering of blood glucose by insulin therapy. We demonstrate here that β cell dedifferentiation, rather than apoptosis, is the main mechanism of loss of insulin-positive cells, and redifferentiation accounts for restoration of insulin content and antidiabetic drug responsivity in these animals. These results may help explain gradual decrease in β cell mass in long-standing diabetes and recovery of β cell function and drug responsivity in type 2 diabetic patients following insulin therapy, and they suggest an approach to rescuing "exhausted" β cells in diabetes.

INTRODUCTION

Type 2 diabetes is characterized by β cell dysfunction, the mechanism of which is controversial (Ahlqvist et al., 2011; Butler et al., 2003; Hur et al., 2010; Nolan and Prentki, 2008; Prentki and Nolan, 2006; Puri and Hebrok, 2012; Robertson et al., 2004; Talchai et al., 2012b; Wajchenberg, 2007). When faced with persistent hyperglycemia, the normal pancreatic β cell first responds with compensatory increase in insulin secretion and β cell mass (Ahrén, 2005; Bernal-Mizrachi et al., 2000; Heit et al., 2006; Jhala et al., 2003). However, chronic hyperglycemia gradually also leads to a paradoxical "glucotoxic" loss of β cell mass and insulin content that has typically been attributed to enhanced β cell apoptosis (Butler et al., 2003; Lupi and Del Prato, 2008; Poitout and Robertson, 2008; Porat et al., 2011; Prentki and Nolan, 2006). Progressive deterioration in β cell function and marked reduction of β cell mass are classic findings in type 2 diabetic human islets, regardless of the therapy (Cnop et al., 2005; Del Prato et al., 2007; Sakuraba et al., 2002; UK Prospective Diabetes Study Group, 1998a, 1998b), and reduced glucose-stimulated insulin secretion (GSIS) as well as increased rates of β cell apoptosis and decreased β cell survival have been detected in islets from human diabetic pancreases (Butler et al., 2003; Tanaka et al., 2002; Weinberg et al., 2007). In general, however, the impairment of β cell function in diabetic islets may be much greater than could be explained by the observed increase in the rate of apoptosis (Butler et al., 2003), and β cell death may not be the main contributor to the marked loss of β cell mass.

An alternative mechanism for diabetic loss of insulin content has recently received attention (Talchai et al., 2012b). The transcription factor FoxO1 is a major determinant of cell fate in enteroendocrine cells. In islets that lack FoxO1 in β cells, Talchai et al. (2012b) demonstrated β cell dedifferentiation to endocrine progenitor-like cells during stress-induced hyperglycemia. In addition to processes impinging on β cell survival and, hence, on islet mass, β cell dedifferentiation can also be observed in vitro (Weinberg et al., 2007). Dedifferentiation in common forms of β cell failure has also been inferred from partial pancreatectomy studies (Jonas et al., 1999). Together, these studies raise the possibility that dedifferentiation and conversion into other endocrine cell types may be an underrecognized mechanism of β cell failure in multiple forms of diabetes and, moreover, that this process might conceivably be reversible.

Insulin secretory failure due to inexcitability is a major cause of monogenic neonatal diabetes (Flanagan et al., 2009; Gloyn et al., 2004) and a prominent contributor to human type 2 diabetes (Nielsen et al., 2003; Riedel et al., 2005; Villareal et al., 2009). Our studies reveal that a major mechanism of β cell loss in diabetes resulting from secretory failure due to inexcitability (Remedi et al., 2009) is also dedifferentiation. Even more striking, additional experiments show that intensive insulin therapy, by reversing the hyperglycemia, leads to redifferentiation to mature β cells. These results provide a potential explanation for gradual decrease in β cell mass in long-standing and poorly controlled human diabetes, as well as for recovery of β cell function and sulfonylurea responsivity, as can be observed in type 2 diabetic patients after intensive insulin therapy (Torella et al., 1991; Wajchenberg, 2007).

Insulin-Regulated Protein Palmitoylation Impacts Endothelial Cell Function

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Objective—Defects in insulin signaling are associated with abnormal endothelial cell function, which occurs commonly in cardiovascular disease. Targets of insulin signaling in endothelial cells are incompletely understood. Protein S-palmitoylation, the reversible modification of proteins by the lipid palmitate, is a post-translational process relevant to cell signaling, but little is known about the role of insulin in protein palmitoylation.

Approach and Results—To test the hypothesis that insulin alters protein palmitoylation in endothelial cells, we combined acyl-biotin exchange chemistry with stable isotope labeling by amino acids in cell culture to perform quantitative proteomic profiling of human endothelial cells. We identified ≈380 putative palmitoylated proteins, of which >200 were not known to be palmitoylated; ≈10% of the putative palmitoylated proteins were induced or suppressed by insulin. Of those potentially affected by insulin, <10 have been implicated in vascular function. For one, platelet-activating factor acetylhydrolase IB subunit gamma (PAFAH1b3; not previously known to be palmitoylated), we confirmed that insulin stimulated palmitoylation without affecting PAFAH1b3 protein abundance. Chemical inhibition of palmitoylation prevented insulin-induced angiogenesis in vitro; knockdown of PAFAH1b3 had the same effect. PAFAH1b3 knockdown also disrupted cell migration. Mutagenesis of cysteines at residues 56 and 206 prevented palmitoylation of PAFAH1b3, abolished its capacity to stimulate cell migration, and inhibited its association with detergent-resistant membranes, which are implicated in cell signaling. Insulin promoted the association of wild-type PAFAH1b3 with detergent-resistant membranes.

Conclusions—These findings provide proof of principle for using proteomics to identify novel insulin-inducible palmitoylation targets relevant to endothelial function. **(*Arterioscler Thromb Vasc Biol*. 2014;34:346-354.)**

Key Words: endothelial cells ■ insulin ■ lipoylation

Insulin resistance, usually reflecting decreased insulin-dependent glucose transport in peripheral tissues and decreased insulin-dependent suppression of endogenous glucose production, can occur independent of hyperglycemia if compensatory insulin secretion is sufficiently robust. However, sustained insulin resistance can have pleiotropic effects that are associated with cardiovascular complications.[1] Optimal management to minimize the risk of these complications is unresolved.[2–5] Insulin is an important mediator of endothelial function,[6] and inactivation of the endothelial cell insulin receptor in mice increases atherosclerosis independent of traditional risk factors.[7] However, the molecular mediators of insulin signaling in endothelial cells remain poorly understood. Identifying novel endothelial cell targets of insulin treatment could provide insight into the relationship between metabolism and inflammation that occurs in the setting of insulin resistance.

Lipids are involved in insulin signaling and impact endothelial cell function. Lipid molecules can integrate information to alter homeostasis through well-characterized mechanisms including the activation of nuclear receptors[8] and the complex network of lipid-modifying enzymes.[9] Less is known about how lipids affect cellular homeostasis through protein modifications, such as prenylation, myristoylation, and palmitoylation.[10] Unlike other lipidation reactions, protein S-palmitoylation is reversible and post-translational, making it inherently suitable (serving as an on/off switch based on the presence or absence of palmitate) for regulating function. G-proteins, scaffold proteins, kinases, vesicle proteins, and others use palmitoylation to modulate growth, differentiation, embryonic development, and cell–cell interactions.[11,12] Our recent observations point to an unexpected role for de novo lipogenesis in S-palmitoylation of endothelial nitric oxide synthase (eNOS) in blood vessels[13] and mucin 2 in the intestine.[14] Both of these palmitoylation events may be relevant to metabolic disorders because de novo lipogenesis is regulated by insulin.

Palmitoylated proteins have been identified in yeast, neurons, and certain membrane fractions.[15–17] Little is known about palmitoylation targets influenced by insulin. We tested the hypothesis that insulin alters the dynamics of protein

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Xenin-25 delays gastric emptying and reduces postprandial glucose levels in humans with and without Type 2 diabetes

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Chowdhury S, Reeds DN, Crimmins DL, Patterson BW, Laciny E, Wang S, Tran HD, Griest TA, Rometo DA, Dunai J, Wallendorf MJ, Ladenson JH, Polonsky KS, Wice BM. Xenin-25 delays gastric emptying and reduces postprandial glucose levels in humans with and without Type 2 diabetes. *Am J Physiol Gastrointest Liver Physiol* 306: G301–G309, 2014. First published December 19, 2013; doi:10.1152/ajpgi.00383.2013.—Xenin-25 (Xen) is a neurotensin-related peptide secreted by a subset of glucose-dependent insulinotropic polypeptide (GIP)-producing enteroendocrine cells. In animals, Xen regulates gastrointestinal function and glucose homeostasis, typically by initiating neural relays. However, little is known about Xen action in humans. This study determines whether exogenously administered Xen modulates gastric emptying and/or insulin secretion rates (ISRs) following meal ingestion. Fasted subjects with normal (NGT) or impaired (IGT) glucose tolerance and Type 2 diabetes mellitus (T2DM; $n = 10–14$ per group) ingested a liquid mixed meal plus acetaminophen (ACM; to assess gastric emptying) at *time zero*. On separate occasions, a primed-constant intravenous infusion of vehicle or Xen at 4 (Lo-Xen) or 12 (Hi-Xen) pmol·kg^{-1}·min^{-1} was administered from zero until 300 min. Some subjects with NGT received 30- and 90-min Hi-Xen infusions. Plasma ACM, glucose, insulin, C-peptide, glucagon, Xen, GIP, and glucagon-like peptide-1 (GLP-1) levels were measured and ISRs calculated. Areas under the curves were compared for treatment effects. Infusion with Hi-Xen, but not Lo-Xen, similarly delayed gastric emptying and reduced postprandial glucose levels in all groups. Infusions for 90 or 300 min, but not 30 min, were equally effective. Hi-Xen reduced plasma GLP-1, but not GIP, levels without altering the insulin secretory response to glucose. Intense staining for Xen receptors was detected on PGP9.5-positive nerve fibers in the longitudinal muscle of the human stomach. Thus Xen reduces gastric emptying in humans with and without T2DM, probably via a neural relay. Moreover, endogenous GLP-1 may not be a major enhancer of insulin secretion in healthy humans under physiological conditions.

xenin; GIP; GLP-1; glucagon; incretin; gastric emptying; insulin secretion

THE ENTEROENDOCRINE (EE) system is composed of numerous subtypes of singly dispersed EE cells scattered throughout the gastrointestinal epithelium (6, 51). Peptides released from EE cells regulate gastrointestinal function (6, 51) and glucose homeostasis (5, 14, 33). Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are hormones that are produced predominantly by intestinal L cells in the distal intestine and K cells in the proximal small intestine, respectively. Both are released into the circulation immediately after meal ingestion in response to nutrients present in the lumen of the gut, but not to those in the blood. Both peptides amplify glucose-stimulated insulin secretion and have been coined "incretins" (5, 14, 33).

Xenin-25 (Xen) is a 25-amino acid neurotensin-related peptide produced by a subset of GIP-producing cells (4, 15). Genetic and pharmacological data indicate that effects of Xen are mediated by neurotensin receptor-1 [NTSR1 (19, 24, 35, 57)]. In animals, Xen delays gastric emptying (25), reduces food intake (2, 10, 27), increases gut motility (17), augments gall bladder contractions (23), and enhances secretion from the exocrine pancreas (16). Many of these Xen effects are known to be mediated by neurons (9, 10, 23, 25, 27). In vivo mouse studies from our (54) and another (30) laboratory demonstrated that Xen increases the effects of GIP on insulin release. We further showed that Xen does not act directly on beta cells (54). Rather, Xen initiates a cholinergic relay in the periphery without activating regions of the brain associated with afferent or efferent signaling. Thus effects of Xen on insulin release may be independent of the central nervous system. Consistent with this hypothesis, effects of Xen on gall bladder contractions are inhibited by atropine, but not vagotomy (23).

As in our mouse studies, we recently showed that administration of Xen to humans during intravenous graded glucose infusions increased the effects of exogenously administered GIP on insulin secretion rates (ISRs) in humans with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT), but not in those with Type 2 diabetes mellitus [T2DM (53)]. Infusion of Xen alone had no effect in any group. With meal ingestion, GIP and other gut-derived factors are released into the circulation, suggesting that exogenously administered Xen may have different effects in conjunction with orally vs. intravenously administered nutrients. The purpose of the present study was to determine whether exogenously administered Xen modulates gastric emptying and glucose, insulin, C-peptide, glucagon, Xen, GIP, and GLP-1 levels as well as ISRs in response to meal ingestion.

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Leptin reverses diabetes by suppression of the hypothalamic-pituitary-adrenal axis

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Leptin treatment reverses hyperglycemia in animal models of poorly controlled type 1 diabetes (T1D)[1–6], spurring great interest in the possibility of treating patients with this hormone. The antidiabetic effect of leptin has been postulated to occur through suppression of glucagon production, suppression of glucagon responsiveness or both; however, there does not appear to be a direct effect of leptin on the pancreatic alpha cell[7]. Thus, the mechanisms responsible for the antidiabetic effect of leptin remain poorly understood. We quantified liver-specific rates of hepatic gluconeogenesis and substrate oxidation in conjunction with rates of whole-body acetate, glycerol and fatty acid turnover in three rat models of poorly controlled diabetes, including a model of diabetic ketoacidosis[8]. We show that the higher rates of hepatic gluconeogenesis in all these models could be attributed to hypoleptinemia-induced activity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in higher rates of adipocyte lipolysis, hepatic conversion of glycerol to glucose through a substrate push mechanism and conversion of pyruvate to glucose through greater hepatic acetyl-CoA allosteric activation of pyruvate carboxylase flux. Notably, these effects could be dissociated from changes in plasma insulin and glucagon concentrations and hepatic gluconeogenic protein expression. All the altered systemic and hepatic metabolic fluxes could be mimicked by infusing rats with Intralipid or corticosterone and were corrected by leptin replacement. These data demonstrate a critical role for lipolysis and substrate delivery to the liver, secondary to hypoleptinemia and HPA axis activity, in promoting higher hepatic gluconeogenesis and hyperglycemia in poorly controlled diabetes.

To understand the mechanisms driving hyperglycemia in T1D, we induced T1D in otherwise normal rats using streptozotocin. Rats with T1D had severe fasting hyperglycemia and ketoacidosis associated with approximately 90% lower plasma insulin and leptin concentrations and 90% higher plasma glucagon concentrations compared to control nondiabetic rats (**Fig. 1a–d** and **Supplementary Table 1**). These changes occurred without any differences in the relative contributions of hepatic gluconeogenesis (91 ± 4% compared to 91 ± 2% (mean ± s.e.m.) in control rats and those with T1D, respectively) and renal gluconeogenesis (9 ± 4% compared to 9 ± 2% in control rats and those with T1D, respectively) to rates of whole-body glucose production. Normalizing plasma leptin concentrations in the rats with T1D with a 6-h intra-arterial leptin infusion resulted in 240 mg dl^{-1} lower plasma glucose concentrations compared to rats infused with an equal volume of saline associated with reversal of ketoacidosis without any differences in plasma insulin, glucagon, adiponectin or fibroblast growth factor 21 (FGF-21) concentrations or in the phosphorylation of the glucagon target cyclic AMP response element-binding protein (CREB) (**Fig. 1a–d** and **Supplementary Fig. 1a–c**). Notably, normalization of plasma glucagon concentrations in these rats did not occur until 24 h after leptin treatment, which was 18 h after the normalization of plasma glucose. Leptin treatment in rats with T1D was associated with 60% lower hepatic gluconeogenesis rates through reductions in the conversion of both pyruvate and glycerol to glucose (**Fig. 1e**). In contrast, although total tricarboxylic acid (TCA) cycle flux (V_{TCA}) did not change, fatty acid oxidation was greater in the livers of rats with T1D compared to control nondiabetic rats, and this perturbation was reversed with leptin treatment (**Supplementary Fig. 1d**). The lower contribution of glycerol to hepatic gluconeogenesis with leptin treatment was strongly associated with lower rates of whole-body lipolysis in treated compared to untreated rats with T1D, as reflected by 60% lower rates of whole-body glycerol and palmitic acid turnover and plasma glycerol and non-esterified fatty acid (NEFA) concentrations in the treated rats (**Fig. 1f,g** and **Supplementary Fig. 1e,f**). The higher rates of whole-body lipolysis in leptin-deficient rats with T1D were also associated with threefold higher acetate turnover, 250% higher plasma acetate concentrations and 80% higher liver acetyl-CoA concentrations, all of which were reversed with leptin treatment (**Fig. 1h,i** and **Supplementary Fig. 1g**).

As acetyl-CoA is a potent allosteric activator of pyruvate carboxylase activity[9–12] and an inhibitor of pyruvate dehydrogenase (PDH) activity[13], the observed alterations in hepatic acetyl-CoA concentrations in the untreated and leptin-treated rats with T1D probably

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Development and function of human innate immune cells in a humanized mouse model

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Mice repopulated with human hematopoietic cells are a powerful tool for the study of human hematopoiesis and immune function *in vivo*. However, existing humanized mouse models cannot support development of human innate immune cells, including myeloid cells and natural killer (NK) cells. Here we describe two mouse strains called MITRG and MISTRG, in which human versions of four genes encoding cytokines important for innate immune cell development are knocked into their respective mouse loci. The human cytokines support the development and function of monocytes, macrophages and NK cells derived from human fetal liver or adult CD34$^+$ progenitor cells injected into the mice. Human macrophages infiltrated a human tumor xenograft in MITRG and MISTRG mice in a manner resembling that observed in tumors obtained from human patients. This humanized mouse model may be used to model the human immune system in scenarios of health and pathology, and may enable evaluation of therapeutic candidates in an *in vivo* setting relevant to human physiology.

Small-animal models such as mice are frequently used for *in vivo* studies of mammalian, especially human, immune responses. However, fundamental differences in immune function exist between species[1,2] and frequently, knowledge gained from mouse studies cannot be translated to humans.

One promising approach for studying human immune function *in vivo* is to use immunodeficient mice transplanted with human hematopoietic stem and progenitor cells[2,3]. However, the development and function of several human immune cell types, such as monocytes, macrophages and NK cells, is largely defective in currently available models of humanized mice[2]. More specifically, human monocytes and macrophages are present at low frequency[4,5], and although a report showed that these cells are functional[4], another report identified functional impairments and an immature phenotype of human monocytes[6]. The maturation, function and homeostasis of human NK cells are also defective in existing humanized mice[7,8]. These limitations highlight a need to develop humanized mice that model a more complete and functional human innate immune system.

The defects in human innate immune cell development in existing humanized mice are most likely due to limited reactivity of mouse cytokines with corresponding human cytokine receptors[9]. Several strategies to attempt to circumvent this issue by delivering human cytokines to the mouse host have been described[10,11]; some rely on administered exogenous cytokines[7] or cytokine-encoding plasmids[5,12], whereas others use introduced transgenes encoding human cytokines[13–15]. However, high systemic concentrations of cytokines can result in artifactual effects such as the mobilization and exhaustion of hematopoietic stem cells[13] or supraphysiological cell frequencies.

The approach of knocking in human cytokine genes to replace their mouse counterparts has the advantage of ensuring appropriate tissue-, cell- and context-specific expression of the human cytokine[10]. Furthermore, in the scenario of homozygous human cytokine knock-in mice, if the human cytokine is not fully reactive with the corresponding mouse cytokine receptor, mouse cell populations dependent on signaling from that cytokine may exhibit numerical or functional defects; these defects confer an additional competitive advantage on transplanted human cells[10]. This knock-in gene replacement strategy has been used to 'humanize' several cytokine-encoding genes. For example, humanization of the gene encoding thrombopoietin (*Thpo*, also known as *Tpo*) had resulted in enhanced maintenance of functional human hematopoietic stem cells capable of multilineage differentiation, of sustaining long-term high engraftment in the bone marrow (BM) and of serial transplantation[16]; humanization of the genes encoding interleukin 3 (*Il3*) and granulocyte-macrophage colony-stimulating factor 2 (GM-CSF; *Csf2*) had lead to the development of functional human alveolar macrophages[17]; and humanization of the *Csf1* gene, which encodes M-CSF, had resulted in increased numbers of human monocytes or macrophages in multiple tissues[18]. Although each of these gene replacements improved the development and function of individual cell types (**Supplementary Table 1**),

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A Humanized Mouse Model of Autoimmune Insulitis

Many mechanisms of and treatments for type 1 diabetes studied in the NOD mouse model have not been replicated in human disease models. Thus, the field of diabetes research remains hindered by the lack of an in vivo system in which to study the development and onset of autoimmune diabetes. To this end, we characterized a system using human CD4$^+$ T cells pulsed with autoantigen-derived peptides. Six weeks after injection of as few as 0.5 × 10^6 antigen-pulsed cells into the NOD-*Scid Il2rg*$^{-/-}$ mouse expressing the human HLA-DR4 transgene, infiltration of mouse islets by human T cells was seen. Although islet infiltration occurred with both healthy and diabetic donor antigen-pulsed CD4$^+$ T cells, diabetic donor injections yielded significantly greater levels of insulitis. Additionally, significantly reduced insulin staining was observed in mice injected with CD4$^+$ T-cell lines from diabetic donors. Increased levels of demethylated β-cell–derived DNA in the bloodstream accompanied this loss of insulin staining. Together, these data show that injection of small numbers of autoantigen-reactive CD4$^+$ T cells can cause a targeted, destructive infiltration of pancreatic β-cells. This model may be valuable for understanding mechanisms of induction of human diabetes.

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The development of type 1 diabetes involves a combination of genetic and environmental factors governing susceptibility to and/or protection from disease (1). NOD mice, the most widely studied model of human type 1 diabetes, share a number of disease characteristics, including autoantigens, the chronicity of the autoimmunity, and major histocompatibility complex (MHC) homology, but significant differences between the two still remain (e.g., the time of progression from insulitis to clinical diabetes, the sex bias of disease incidence) (2). Because of these differences and others, many mechanisms and treatments that have been verified in NOD mice have failed to translate to successful treatments in humans (3,4). Therefore, developing model systems in which human cells involved in diabetes can be directly studied is imperative.

The antigens involved in type 1 diabetes have largely been identified through autoantibodies found in individuals at risk for and with the disease. They include preproinsulin (PPI), GAD65, and islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP) as well as other antigens recognized by polyclonal antibodies (islet cell antibodies) (5). T cells directed against these antigens are believed to cause β-cell destruction, but little direct evidence shows that this is the case. The technical problems in studying the functions of autoreactive T cells include difficulties in growing and maintaining autoantigen-reactive lines and the lack of a suitable model system in which they can be studied.

Previous studies have analyzed histopathology (6–8) and T-cell tetramer staining (9) of pancreata from cadaveric diabetic donors. In these studies, CD8$^+$ T cells

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MARRIOTT

Restaurants Around the Hotel

American		
Meritage, Hotel Lobby	$$, Casual, Breakfast, Dinner Daily, Lunch Mon-Fri	Ext. 6240
Chef Geoff, 12256 Rockville Pike	$$, Casual, Lunch M0n-Sat, Dinner Daily * 5 min. driving	Ph. 240-621-3090
Matchbox,1699 Rockville Pike	$$, Casual, Lunch, Dinner Daily * 7 min driving	Ph. 301-816-0369
Mosaic, 186 Halpine Rd (Congr. Plza)	$,Casual, Breakfast,Lunch, Dinner Daily * 7 min driving	Ph. 301-468-0682
Ruby Tuesday, 12266 Rockville Pike	$$, Casual, Lunch, Dinner Daily*5 to 10 min. driving	Ph. 301-230-1952
Seasons 52, 11414 Rockville Pike	SS, Casual, Lunch, Dinner Daily ** 7 min walking	Ph. 301-984-5252
Silver Diner 12276 Rockville Pike	$, Casual, Breakfast, Lunch, Dinner Daily*5 min. driving	Ph. 301-770-2828
TGI Friday, 12147 Rockville Pike	$$, Casual, Lunch , Dinner Daily * 5 min driving	Ph. 301-231-9048
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Amina Thai, 5065 Nicholson La, (Tha)	$$, Casual, Lunch & Dinner Daily 10 min walking	Ph. 301-770-9509
Far East, 5055 Nicholson La.(Chi)	$$, Casual, Lunch & Dinner Daily 10 min walking	Ph. 301-881-5552
Hinode, 134 Congressional Lane	$$, Casual, Lunch, Mon-Fri, Dinner, Daily* 8 min. driving	Ph. 301-816.2190
P.F Chang's, (White Flint) (Chi, Mong)	$$, Casual, Lunch, Dinner, Daily*10 min walking	Ph. 301-230-6933
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Tara Thai 12071 Rockville Pike (Tha, Phil)	$$, Casual, Lunch, Dinner Daily*5 min. driving	Ph. 301-231-9899
Tony Lin's, 12015 Rockville Pike (Chi)	$$, Casual, Lunch, Dinner, Daily*5 min. driving	Ph. 301-468-5858
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Mykonos Grill, 121 Congressional La. (Gk)	$$, Casual, Dinner, Tue-Sun * 8 min driving	Ph. 301-770-5999
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Amici Miei 1093 Seven Locks Rd	$$, Casual, Lunch Mon-Sat, Dinner Daily * 8 min driving	Ph. 301-545-0966
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The Potomac Grill, 1093 Rockville Pike	$$, Casual, Lunch, Dinner, Daily*6min driving	Ph. 301-738-8181

$-Inexpensive**$$-Moderate**$$$-Mid-Expensive**$$$$-Expensive

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