Council of Councils September 5, 2014

NIH Update

September 5th, 2014

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Topics

Budget Update

- Piloting Longer-Term, Stable Support
- Including Males and Females in Cell and Animal Research





Note: The 3.7 % Real Annual Growth is based on real compound annual growth between 1971 and 2000. Dollar values are adjusted to 2012 Dollars using the Biomedical Research and Development Price Index (BRDPI), http://officeofbudget.od.nih.gov/gbiPriceIndexes.html. Source: NIH Office of Extramural Research and Office of Budget source data (March 29, 2014)

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Enhancing Support for Extramural Research

- At a time of unprecedented budgetary constraints, what approaches can be offered that would enhance support for extramural research, without an increased cost?
- Can we build on the successful experience generated from the Pioneer Awards, and expand such programs in the ICs?
- What would be the important attributes of such approaches?
 - Enhanced flexibility for the investigator
 - Promotion of risk-taking
 - Longer duration of support
 - Solid level of support
 - Less focus on project details in the application

Enhancing Support for Extramural Research

- Could these approaches help eliminate the "perverse incentives," which contribute to a hypercompetitive atmosphere and may even lead to reproducibility problems?
- Are there existing programs that can be augmented or modified to enhance support of research?
 - Or, are there less effective approaches that can be phased out gradually?

Origins of the NIH Director's Pioneer Award Program

- Begun in 2004 as one of the first programs of the NIH Roadmap
- Initiated to address concerns that high risk, visionary research was not being supported due to the conservative nature of existing NIH funding mechanisms.
- Based on the premise that "Person Based" application and review processes would reward past creativity and encourage innovators to go in new directions
- Research to be conducted must represent a substantial departure from the work that the investigator (or anyone else) has done in the past: PIONEERING RESEARCH.
- Experiment in science management with a new mechanism

Do different award designs produce different outcomes/value?

- In 2004, few, if any analyses had been published.
 In the interim, evaluations have been conducted.
- Anecdotal evaluations
 - Lack quantification
 - Lack control groups

Examples of Evaluating Value

Incentives and Creativity: Evidence from the Academic Life Sciences Pierre Azoulay, Joshua S. Graff Zivin, and Gustavo Manso National Bureau of Economics Research (Revisions appeared in 2008, 2009, and January 2011)

Enhancing Philanthropy's Support of Biomedical Scientists: Proceedings of a Workshop on Evaluation George R. Reinhart, Editor National Research Council (2006)

Report of the International Review Committee on the Discovery Grants Program

National Sciences and Engineering Research Council of Canada (April 2008)

The Scientific Century: securing our future prosperity The Royal Society, London (March 2010)

Welcome Trust Strategic Plan 2010-2020 Extraordinary Opportunities

Evaluating How Award Design Affects Outcome

Incentives and Creativity: Evidence from the Academic Life Sciences Pierre Azoulay, Joshua S. Graff Zivin, and Gustavo Manso National Bureau of Economics Research (Revisions appeared in 2008, 2009, and January 2011)

Enhancing Philanthropy's Support of Biomedical Scientists: Proceedings of a Workshop on Evaluation SCIENCE & TECHNOLOGY POLICY INSTITUTE George R. Reinhart, Editor National Research Council (2006) An Outcome Evaluation of the

Report of the International Review Committee on the Discovery Grants Program Bhavya Lal National Sciences and Engineering Alyson G. Wilson Seth Jonas

Research Council of Canada (April 2008)

The Scientific Century: securing our future prosperity The Royal Society, London (March 2010) pproved for public release

Welcome Trust Strategic Plan 2010-2020 Extraordinary Opportunities

Elizabeth C. Lee Amy M. Richards Vanessa I. Peña

distribution is unlimited IDA Paper P-4899

National Institutes of Health (NIH)

Uniformly conclude that higher impact, more innovative science results when:

- Applications are shorter, with less prelim data
- Review is based more on person's track record
- Applicants get constructive feedback from review
- Grants provide more support
- Grants provide a longer duration of support
- PI's have flexibility to change direction

Other agencies have adopted this type of award

- Wellcome Trust
- Research Council of Canada
- Royal Society
- European Research Council

Longer-Term, Stable Support

Rock Talk

Helping connect you with the NIH perspective

Posted on July 17, 2014 by Sally Rockey and Francis Collins

Formula for Innovation: People + Ideas + Time

In these times of tight budgets and rapidly evolving science, we must consider new ways to invest biomedical research dollars to achieve maximum impact—to turn scientific discoveries into better health as swiftly as possible. We do this by thinking strategically about the areas of research that we support, as well as the process by which we fund that research.

Historically, most NIH-funded grants have been "project-based," which means that their applications have clearly delineated aims for what will be accomplished during a defined project period. These research project grants typically last three to five years and vary in award amount. For example, the average annual direct cost of the R01 grant—the gold standard of NIH funding—was around \$282,000 in FY 2013, with an average duration of about 4.3 years.

We often hear from investigators at all career stages



Research Project Grants

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Sustained Support - Flexibility

- Several NIH Institutes and Centers (IC) will be developing new funding opportunities to offer more sustained support to investigators' research programs.
- These longer term awards will not follow a onesize-fits-all approach; leaders of each NIH IC will decide if they wish to embark on these awards based on the balance of their portfolios and their strategic planning needs. In addition, each IC will decide the appropriate size and duration of their awards.

Pilots

- The National Cancer Institute's Outstanding Investigator Award, which will provide long-term support to investigators who have extraordinary records of cancer research productivity and who propose to conduct exceptional research. Applicants may request up to \$600,000 annually in direct costs, for up to seven years.
- The National Institute of General Medical Sciences (NIGMS) recently issued a request for information to obtain community feedback on their concept of the "Maximizing Investigators' Research Award." This award would support all NIGMS-funded research in an investigator's laboratory. Funding would range from \$150,000-\$750,000 in direct costs annually for five years (the current average for an NIGMS R01 is about four years).
- Experience and feedback from pilots and RFIs will inform NIH next steps.

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Every System is Exquisitely Tuned to Get the Results it Gets

- What is "default" biology?
 - In the lab: male cells and animals
 - In the clinic: 70-kg male
- But, female is not equal to non-male
 - Just like minorities are not "non-whites"



Image via Wikispaces.com

- Rigor and reproducibility
 - Every experiment is part of larger system, the quest to understand fundamental basic living systems
 - Approaches and results should be consistent and free of bias at the outset

nature

NIH plans to enhance reproducibility

Francis S. Collins and Lawrence A. Tabak discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

Instead, a complex array of other factors seems to have contributed to the lack of reproducibility. Factors include poor training of researchers in experimental design; increased emphasis on making provocative statements rather than presenting technical details; and publications that do not report basic elements of experimental design⁴. Crucial experimental design elements that are all too frequently ignored include blinding, randomization, replication, sample-size calculation and the effect of sex differences. And some scientists reputedly use a 'secret sauce' to make their experiments work and withhold details from publication or describe them only vaguely to retain a competitive edge5. What hope is there that other scientists will be able to build on such work to further biomedical progress?

The Average Human: Who Is S/He?

able 3.1 Estimated Atomic Composition of the Lean 70- Male Juman Body ^{749,751,752,817}					
Element	Sym	# of Atoms	Element	Sym	# of Atoms
Hydrogen	н	4.22 x 10 ²⁷	Cadmium	Cd	3 x 10 ²⁰
Oxygen	O	1.61 x 10 ²⁷	Boron	В	2 x 10 ²⁰
Carbon	C	8.03 x 10 ²⁶	Manganese	Mn	1 x 10 ²⁰
Nitrogen	N	3.9 x 10 ²⁵	Nickel	Ni	1 x 10 ²⁰
Calcium	Ca	1.6 x 10 ²⁵	Lithium	Li	1 x 10 ²⁰
Phosphorus	P	9.6 x 10 ²⁴	Barium	Ba	8 x 10 ¹⁹
Sulfur	S	2.6 x 10 ²⁴	Lod ine	1	5 x 10 ¹⁹
Sodium	Na	2.5 x 10 ²⁴	Tin	Sn	4 x 10 ¹⁹
Potassium	ĸ	2.2 x 10 ²⁴	Gold	Au	2 x 10 ¹⁹
Chlorine	CI	1.6 x 10 ²⁴	Zirconium	Zr	2 x 10 ¹⁹
Magnesium	Mg	4.7 x 10 ²³	Cobalt	Co	2 x 10 ¹⁹
Silicon	Si	3.9 x 10 ²³	Cesium	Cs	7 x 10 ¹⁸
Fluorine	F	8.3 x 10 ²²	Mercury	Hg	6 x 10 ¹⁸
Iron	Fe	4.5 x 10 ²²	Arsenic	As	6 x 10 ¹⁸
Zinc	Zn	2.1 x 10 ²²	Chromium	Cr	6 x 10 ¹⁸
Rubidium	Rb	2.2 x 10 ²¹	Molybdenum	Mo	3 x 10 ¹⁸
Strontium	Sr	2.2 x 10 ²¹	Selenium	Se	3 x 10 ¹⁸
Bromine	Br	2 x 10 ²¹	Beryllium	Be	3 x 10 ¹⁸
Aluminum	AI	1 x 10 ²¹	Vanadium	V	8 x 10 ¹⁷
Copper	Cu	7 x 10 ²⁰	Uranium	U	2 x 10 ¹¹
Lead	Pb	3 x 10 ²⁰	Radium	Ra	8 x 10 ¹⁰

DRUGS IN **R&**D 2012; 12 (3): 141-163

Pharmacokinetics, Safety, and Tolerability of GLPG0259, a Mitogen-Activated Protein Kinase–Activated Protein Kinase 5 (MAPKAPK5) Inhibitor, Given as Single and Multiple Doses to Healthy Male Subjects

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory and joint degenerative disease, which affects almost 1% of the adult population worldwide, with onset classically occurring between the ages of 30 and 50 years, and a higher prevalence in women. The disease is characterized by pain, stiffness, and restricted mobility ...

Why was this drug tested in males only?

Over-Reliance on Male Animal Models

Animal studies: Six fields relied on rodents in **80 percent** or more of animal studies (general biology, immunology, neuroscience, physiology, pharmacology, and endocrinology).



Source: Zucker I, Beery AK. Males still dominate animal studies. Nature. 2010; 465: 690.

Males Still Dominate Animal Studies



Zucker, Beery, Nature : 465, 690 : 2010

Why Research Sex/Gender Influences?



Many significant sex factors in diseases/organs are **related** to reproduction.

Many significant sex factors in diseases/organs are **unrelated** to reproduction.

Sex differences are not always differences: "sex factors."



What are we missing by not including sex and gender in investigations at all levels?

What harm are we doing by not including sex and gender in investigations at all levels?

Success Story: Interventions Testing Program at the National Institute on Aging

- Standardized program for preclinical evaluation of the efficacy of interventions aimed at prolonging health-span and/or life-span
- Provides NIA with mechanism to evaluate possible health dangers of purported, but untested, "anti-aging" treatments
- Test subjects = male and female genetically heterogeneous mice, bred as the four-way cross
- Design compares multiple experimental agents to two control groups
- Sufficient numbers of male and female mice tested: 80% chance of detecting an increase/decrease in lifespan of about 10 percent



National Institute on Aging

17αEstradiol: Extended lifespan in males but not females

Rapamycin: Extended lifespan in both sexes

NDGA, Aspirin: significant lifespan extension in males

NIH in 2014: Studying Sex to Strengthen Science





Problem Looking for female/male differences is like a blind spot in biomedical research, leaving gaps in our knowledge.

Solution

Sex is a fundamental biological variable that must be considered throughout the biomedical research continuum.



Action NIH is requiring a deliberate approach in considering sex in cells and animals to make sure men and women get the full benefit of medical research.



Outcome

When researchers consider sex as a fundamental biological variable, NIH continues to deliver rigorous science that drives medical advances.

NIH cannot do this alone and is working on multiple fronts with stakeholders in the public and private sectors.

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COMMENT



NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

NIH Takes Steps to Address Sex Differences in Preclinical Research

May 14, 2014

Over the past two decades, we have learned a great deal about how men and women respond differently to medications. This knowledge came after a concerted effort in the early '90s to increase the number of women in NIH-funded clinical research. Today, just over half of NIH-funded clinical research participants are women. Unfortunately, experimental design in cell and animal research has not always followed suit. An over-reliance on male animals, and neglect of attention to the sex of cells, can lead to neglect of key sex differences that should be guiding clinical studies, and ultimately, clinical practice. NIH is taking action to address this shortfall as outlined by Janine A. Clayton, M.D., Director of the NIH Office of Research on Women's Health, and me in the *Nature* Comment below.

Francis S. Collins, M.D., Ph.D. Director, National Institutes of Health

The New York Times

Labs Are Told to Start Including a Neglected Variable: Females



Slate MILLING MILLING

Why Are All the Lab Rats Boys? NIH Tells Drug Researchers to Stop Being Sexist Pigs.

NEWS & ANALYSIS

NATIONAL INSTITUTES OF HEALTH

Science

Needed: More Females in Animal and Cell Studies

Jennifer Couzin-Frankel



US government to require affirmative action for female lab mice NATURE NEWS BLOG

By Amanda Marcotte

NIH to require sex-reporting in preclinical studies

14 May 2014 [18:00 BST] Posted by Sara Reardon | Category: Biology & Biotechnology, Drug discovery Institutions, Policy, Publishing



The Research for All Act

(Original Signature of Member)



- H.R.
- To amend the Federal Food, Drug, and Cosmetic Act to provide for expedited review of drugs and biological products to provide safer or more effective treatment for males or females, to amend the Public Health Service Act to enhance the consideration of sex differences in basic and clinical research, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

Mr. COOPER introduced the following bill; which was referred to the Committee on _____

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to provide for expedited review of drugs and biological products to provide safer or more effective treatment for males or females, to amend the Public Health Service Act to enhance the consideration of sex differences in

- Provides for expedited review of drugs and biologics to provide safer and more effective treatment for males and females.
- Amends the Public Health Service Act to enhance the consideration of sex differences in basic and clinical research.
- Requires the NIH to issue guidelines to ensure the inclusion of both sexes and the analysis of sex differences.
- Requires that NIH track statistics on the use of male and female animals, cells, and tissues in basic research.
- Codifies NIH Special Centers of Research on Sex Differences.

Research

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NIH OFFICE OF RESEARCH ON WOMEN'S HEALTH (ORWH)

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Studying Sex to Strengthen Science (S4)

"Our goal is to transform how science is done."

 Janine A. Clayton, M.D. Associate Director for NIH Research on Women's Health

Learn More 🕨







History of Inclusion

Latest News

NIH Takes Steps to Address Sex Differences in Preclinical Research, NIH Director's Statement

Filling the Gaps: NIH to Enact New Policies to Address Sex Differences, ORWH Director's Blog

Rock Talk: More on Addressing Sex Differences in Preclinical Studies, OER Director's Blog

Highlights

Studying Sex to Strengthen Science: Questions & Answers

Nature Comment: NIH to balance sex in cell and animal studies

Media Contact

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Funding: ORWH In Partnership with NIH ICs



Specialized Centers of Research

11 funded centers, \$113.7 million investment from FY 2002 to 2013



Administrative Supplements

50 Supplements funded in FY13 for a total of \$5 million

Addressing Sex Differences in Research through the NIH Common Fund

As one component of an NIH-wide strategy to account for sex differences in pre-clinical research, the NIH Common Fund is providing supplemental funds to existing grants to bolster sex difference analyses.

Common Fund Supplements for Sex Difference Analysis: \$3.9M in FY14

Genotype-Tissue Expression (GTEx)

- Identifying transcripts and splice variants that are differentially expressed in males and females
- Sex differences in brain that are under epigenetic control
- H3Africa
 - Sex differences in cardiovascular and metabolic disease associated with aging
 - Interactions between sex and psychiatric conditions associated with neurological disorders

LINCS (Library of Network-based Cellular Signatures)

Cellular signatures of cardiotoxicity for males and females

Metabolomics

- Sex differences in circadian rhythm and sleep
- Sex-specific mediators of HDL function and statin effects in patients with cardiovascular disease

High-Risk High-Reward

- New Innovator: sex-gene interactions in autism
- Early Independence Award: sex differences in response to meningitis vaccination in Mali
 - The unexpected research findings that males and females respond differently to vaccinations exemplifies the need to *empirically* determine when sex differences matter

Questions

- How do we assess implementation of the new policy?
- How do we assess its impact over the long-term?









NIH. Turning Discovery Into Health







