

# Welcome to the 39<sup>th</sup> Meeting of the NIH Advisory Committee on Research on Women's Health



CELEBRATING A  
QUARTER CENTURY  
IN WOMEN'S HEALTH RESEARCH

NIH Campus, Porter Neuroscience Center  
April 10, 2015



## Turning Discovery into Health

- Basic Research on Human Health and Disease
- Translational Research and Clinical Studies
- Funding for Training and Biomedical Workforce Development

*Sex is a Biological Variable*  
*Study Both Sexes*



# We've Been Busy

- Methods and Techniques for Integrating the Biological Variable Sex into Preclinical Research (October 2014)
- NIH Interdisciplinary Women's Health Research Symposium (November 2014)



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• Countless meetings/presentations to NIH working groups, staff, NIH leadership



- NHLBI Roundtable (NYC February 2015)
- United Nations World Women's Health and Development Forum (February 2015)



# Enhancing Study of Male and Female Biology in Preclinical Research: *It Takes a Village*

- Scientific progress emerging in NIH-funded laboratories
  - Administrative Supplements
- Congressional interest and support
- Journal policies to improve reporting standards (including information about sex)
- NIH policy for considering sex as a biological variable in preclinical research
- Resources for the scientific community



# Enabling a Re-Search of a Scientific Question

“The ORWH administrative supplement had a huge impact on the direction of research in my lab ... my competitive renewal will focus on continuing studies begun with the supplement.”

-- Dr. Catherine Woolley



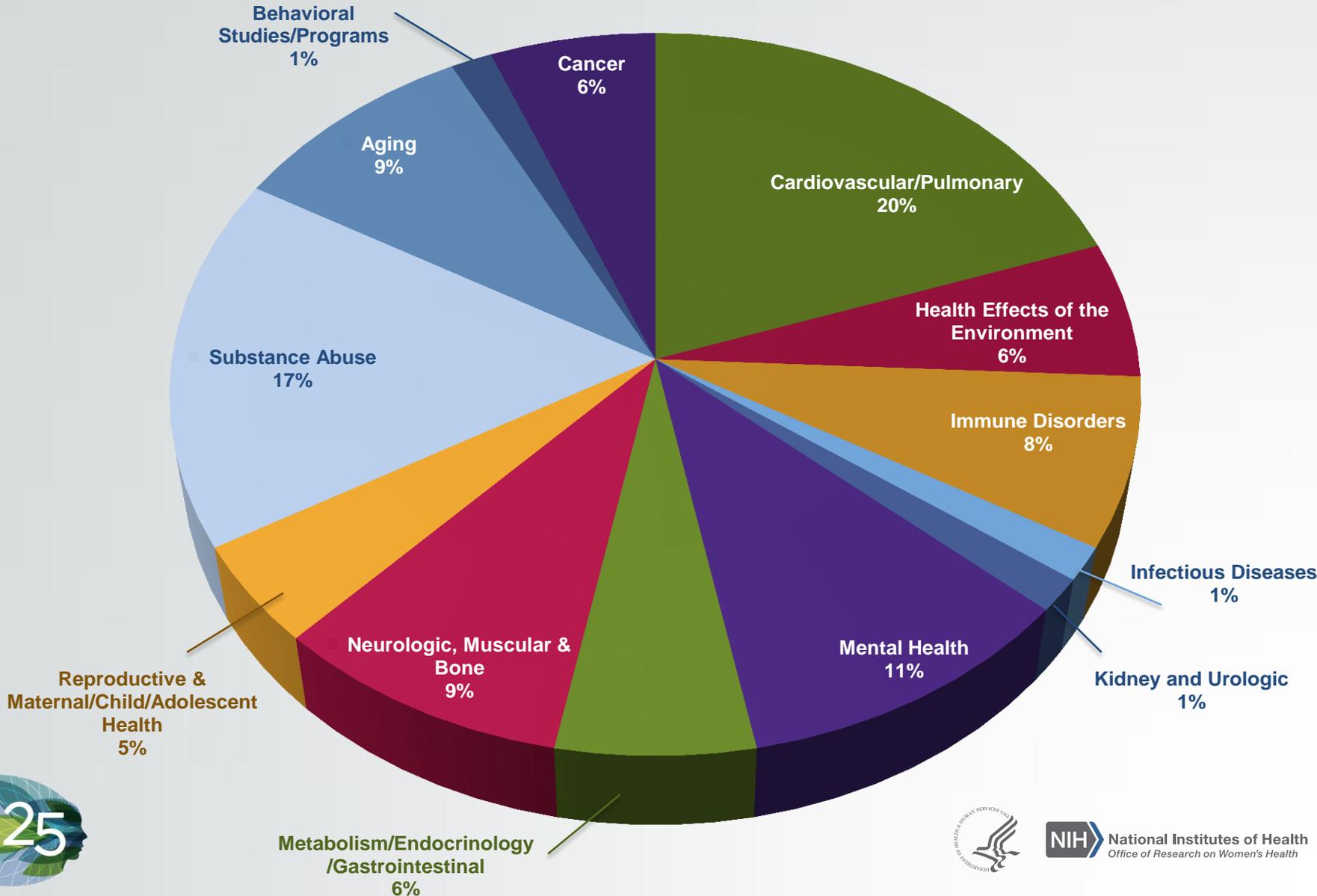
## Neuron

### **Estradiol Acutely Suppresses Inhibition in the Hippocampus through a Sex-Specific Endocannabinoid and mGluR-Dependent Mechanism**

Guang Zhe Huang<sup>1</sup> and Catherine S. Woolley<sup>1,\*</sup>

“... this is the first demonstration of a sex-specific mechanism of synaptic modulation in a non-reproductive region of the brain.” –C.L.

# FY 2014 Administrative Supplements Across Health Areas



# ORWH Administrative Supplements for Research on Sex/Gender Differences (FY 2013, FY 2014)

## Selected Topics (FY 2014)

- Molecular and Functional Mechanisms of Pediatric Heart Failure
- Translating Molecular Signal Pathways to Orthopaedic Trauma Care
- Systems Genetic Analysis of Methamphetamines
- Enhancing Neonatal Immunity to *Streptococcus* Pneumonia
- Role of Rapid IFN $\gamma$  Secretion by CD-Positive T cells in Clearance of Food-Borne Listeria
- Psychiatric Outcomes of Children at High and Low Risk for Depression
- Acute to Chronic Transition in Ergonomic Muscle Pain: Nociceptor Mechanisms
- The Role of Cell Death in Lupus Nephritis
- Sensory Plasticity in Migraine
- Vascular Injury and Recovery in Diabetic Ischemic Stroke

## Selected Approaches (FY 2013, FY 2014)

“... add a second group of animals of the opposite sex for comparative analyses”

“... leverage already existing samples/technologies to identify gender-specific differences in biomarkers”

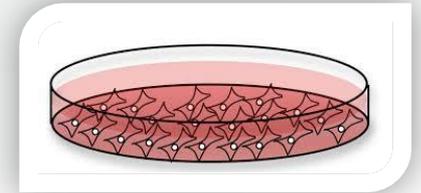
“... characterize the effects of sex in pharmacogenomics phenotypes”

“... test methodological issues for understanding sex differences”

“... test for differences in epigenetic marks in males and females”

# FY 2015 Administrative Supplements: Update

- Robust response: Applications received from 21 NIH Institutes and Centers
- Earliest funding: July 2015
- Different from last year: asked IC reviewers to identify not only alignment with strategic plan goal/objective 1-3 but also to identify the “sex-based” approach used:
  - Add the opposite sex
  - Increase sample size
  - Conduct new comparative analyses
  - Single-sex study (with justification)



Of special interest are studies to understand the influence of biological sex on cells, including primary cell cultures, in vitro cell cultures, explants and transformed cells

# 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.

**A** growing chorus of concern, from scientists and laypeople, contends

shorter term, however, the checks and balances that once ensured scientific fidelity

Crucial experimental design elements that are all too frequently ignored include blinding, randomization, replication, sample-size calculation and the effect of sex differences.

# Cromnibus: Reproducibility

The agreement expects NIH to:

- Stress experimental rigor and transparency
  - Develop incentives for scientists to undertake confirmation studies
  - Develop best practice guidelines for conduct of replicable research
  - Develop guidelines to encourage research transparency in the reporting of methods and findings
- Implement an NIH-wide policy and trans-NIH oversight to address replication concerns
  - Update in the 2016 budget request on the activities NIH has on-going toward this effort, the annual measure and amount of resources spent or estimated each year toward this effort



*H.R.83 -  
Consolidated and  
Further Continuing  
Appropriations Act,  
2015*

# Cromnibus: Sex as a Biological Variable



*H.R.83 -  
Consolidated and  
Further Continuing  
Appropriations Act,  
2015*

- The agreement recommends to NIH:
  - institute requirements that investigators utilize valid experimental design including consideration of sex as a biological variable in preclinical research on animals, cells, and human subjects, as scientifically appropriate
  - expand policy to require indication of sex in preclinical grant applications, progress reports and subsequent publications
  - for investigators studying both sexes, require analysis of preclinical data by sex, when scientifically appropriate
  - give priority to proposals that include adequate numbers of women and men, and a robust plan for analysis and distribution of findings

NIH is “directed to report on preclinical research [in their biennial report] in terms of the proportion of studies that incorporate sex as a biological variable and of those studies which analyze data by sex as part of grant review, award, and oversight processes” by Institute and Center across NIH

# New Journal Policies to Enhance Reproducibility

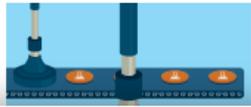
## Science

EDITORIAL

### Journals unite for reproducibility

**R**eproducibility, rigor, transparency, and independent verification are cornerstones of the scientific method. Of course, just because a result is reproducible does not necessarily make it right, and just because it is not reproducible does not necessarily make it wrong. A transparent and rigorous approach, however, can almost always shine a light on issues of reproducibility. This light ensures that science moves forward, through independent verifications as well as the course corrections that come from refutations and the objective examination of the resulting data.

It was with the goal of strengthening such approaches in the biomedical sciences that a group of editors representing over 30 major journals, representatives from funding agencies, and scientists at the June 2014 meeting in Washington, D.C., agreed on a common set of principles and guidelines in Reporting Preclinical Research (see [www.nih.gov/about/reporting-preclinical-research.htm](http://www.nih.gov/about/reporting-preclinical-research.htm)) that list proposed journal policies and author reporting requirements to promote transparency and reproducibility.



menters were blind to the conduct of the experiment, how the sample size was determined, and what criteria were used to include or exclude any data. Journals should recommend the deposition of data in public repositories where available and link data bidirectionally to the published paper. Journals should strongly encourage, as appropriate, that all materials used in the experiment be shared with those who wish to replicate the experiment. Once a journal publishes a paper, it assumes the obligation to consider publication of a refutation of that paper, subject to its usual standards of quality.

The more open-ended portion of the guidelines suggests that journals establish best practices for image-based data (such as screening for manipulation and storing full-resolution archival versions) and how



Marcia McNutt  
Editor-in-Chief  
Science Journals

The new guidelines suggest that journals include in their information for authors their policies for statistical analysis and how they review the statistical accuracy of work under consideration. Any imposed page limits should not discourage reproducibility. The guidelines encourage using a checklist to ensure the reporting of important experimental parameters, such as standards used, number and type of replicates, statistics, method of randomization, whether experi-

*“...scientific journals are standing together in their conviction that reproducibility and transparency are important...”*

The existence of these guidelines does not obviate the need for replication or independent verification of research results, but should make it easier to perform such replication.

Some of the journals at the meeting already had implemented all or most of these principles and guidelines. But the important point is that a large number of scientific journals are standing together in their conviction that reproducibility and transparency are important issues.† As partners to the research enterprise in the communication and dissemination of research results, journals want to do their part to raise the standards for the benefit of all scientists and the benefit of society. The hope is that that these guidelines will not be viewed as onerous, but as part of the quality control that justifies the public trust in science.

— Marcia McNutt

\*See [www.nature.com/news/1.16259](http://www.nature.com/news/1.16259). †A list of all journals and publishers signatory to the principles and guidelines is at [www.nih.gov/about/reporting-preclinical-research.htm](http://www.nih.gov/about/reporting-preclinical-research.htm).

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## nature

EDITORIALS

**CONSERVATION** Saving species is far from a walk in the park p.8

**WORLD VIEW** Psychology gears up to check its workings p.9



**BREAKFAST** Chimps plan days to ensure they nab tastiest figs p.11

### Journals unite for reproducibility

Consensus on reporting principles aims to improve quality control in biomedical research and encourage public trust in science.

**R**eproducibility, rigour, transparency and independent verification are cornerstones of the scientific method. Of course, just

the sample size was determined and what criteria were used to include or exclude any data. Journals should recommend deposition of data in

An example for animal experiments is reporting the source, species, strain, sex, age, husbandry, inbred and strain characteristics, or transgenic animals,

The leaders assembled at the American Association for the Advancement of Science's headquarters in June 2014 to discuss principles and guidelines for preclinical biomedical research. The gathering was convened by the US National Institutes of Health, *Nature* and *Science* (see *Science* 346, 679; 2014).

The discussion ranged from what journals were already doing to address reproducibility — and the effectiveness of those measures — to the magnitude of the problem and the cost of solutions. The attendees agreed on a common set of Principles and Guidelines in Reporting Preclinical Research (see [go.nature.com/ezj11p](http://go.nature.com/ezj11p)) that list proposed journal policies and author reporting requirements in order to promote transparency and reproducibility.

The guidelines recommend that journals include in their information for authors their policies for statistical analysis and how they review the statistical accuracy of work under consideration. Any imposed page limits should not discourage reproducibility. The guidelines encourage using a checklist to ensure reporting of important experimental parameters, such as standards used, number and type of replicates, statistics, method of randomization, whether experiments were blinded, how

ensure reporting of important experimental parameters.”

(for example, screening for manipulation, storing full-resolution archival versions) and for describing experiments in full. An example for animal experiments is to report the source, species, strain, sex, age, husbandry and inbred and strain characteristics for transgenic animals. For cell lines, one might report the source, authentication and mycoplasma contamination status. The existence of these guidelines does not obviate the need for replication or independent verification of research results, but should make it easier to perform such replication.

Some of the journals at the meeting had already had all or most of these principles and guidelines in place. But the point is that a large number of scientific journals are standing together in their conviction that reproducibility and transparency are important issues. As partners to the research enterprise in the communication and dissemination of research results, we want to do our part to raise the standards for the benefit of scientists and of society. The hope is that these guidelines will be viewed not as onerous, but as part of the quality control that justifies the public trust in science. ■



# Sex as a Biological Variable (SABV): NIH Policy Activities

- RFI released (September 2014)
- SABV policy to be released this fall (FY 2016 submissions for FY 2017 funding)
- Placement, criteria, and language of sex as a biological variable in grant applications
  - Collaborated with NIH Working Group on Rigor & Transparency
  - Fall 2014 – present: Met with NIH leadership (IC Directors, SDs, EPMC, EAWG)

## Other current efforts

- Developing resources for the scientific community
- Developing plans for evaluation of the policy
- Informing/developing study section training materials
  - Already hearing anecdotes of study sections talking about SABV in reviews

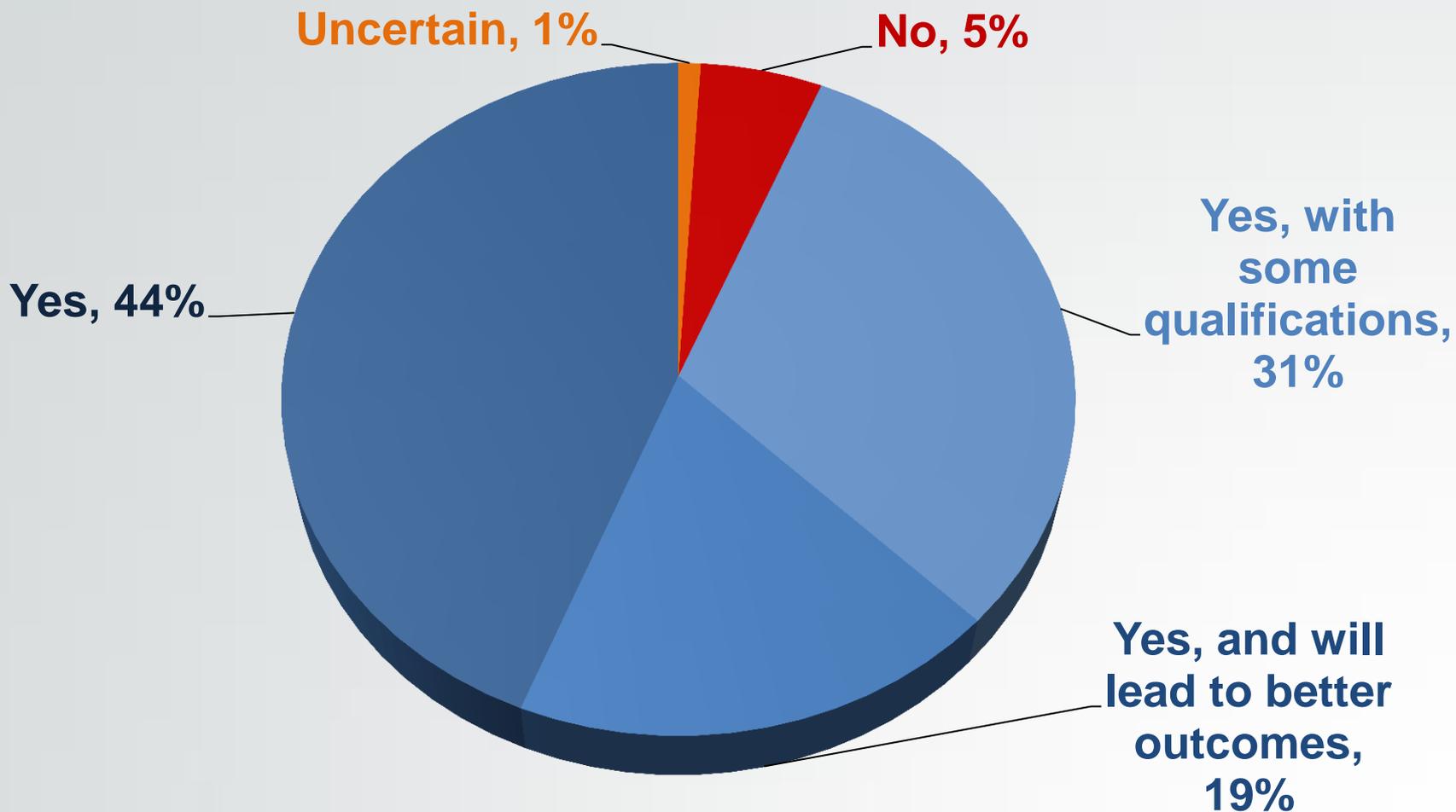


# Request for Information: Considering Sex as a Biological Variable (SABV)



- Does considering SABV affect the reproducibility, rigor, and/or generalizability of research findings?
- What are the areas of science or phases of research that might benefit from consideration of SABV?
- What are the main impediments of considering SABV?
- How can NIH facilitate considering SABV?
- Other comments?

# Most RFI Respondents Agreed that Considering Sex as a Biological Variable Affects Rigor, Transparency



# Public Perspectives on Policy Change

- Individual interpretation of the proposed NIH policy frames public feedback
  - Uncertainty + underlying assumption by some that a blanket policy is forthcoming that will require all NIH-funded researchers to include both sexes in their studies
- Major impediments include cost and constraints on methodological and experimental design
- Favor a flexible approach to policy implementation
- Encourage NIH to promote best practices and awareness of sex as a biological variable in research design and analysis



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# NIH Programs that Promote the Study of Both Sexes: NIA Interventions Testing Program

- Standardized preclinical evaluation of health-span prolonging interventions (“anti-aging” treatments)
- Test subjects = male and female genetically heterogeneous mice, bred as 4-way cross
- 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

## **17 $\alpha$ Estradiol:**

Extended lifespan in males but not females

## **Rapamycin:**

Extended lifespan in both sexes

## **NDGA, Aspirin:**

significant lifespan extension in males

Miller et al. An Aging Interventions Testing Program: study design and interim report. *Aging Cell*. 2007;6:565-75.

# NIH Programs that Promote the Study of Both Sexes: KOMP

**nature  
biotechnology**

A mouse knockout library for secreted and transmembrane proteins

Tracy Tang<sup>1</sup>, Li Li<sup>2</sup>, Jerry Tang<sup>2</sup>, Yun Li<sup>2</sup>, Wei Yu Lin<sup>3</sup>, Flavius Martin<sup>3</sup>, Deanna Grant<sup>1</sup>, Mark Solloway<sup>1</sup>, Leon Parker<sup>4</sup>, Weilan Ye<sup>4</sup>, William Forrest<sup>5</sup>, Nico Ghilardi<sup>1</sup>, Tamas Oravecz<sup>6</sup>, Kenneth A Platt<sup>6</sup>, Dennis S Rice<sup>6</sup>, Gwenn M Hansen<sup>6</sup>, Alejandro Abuin<sup>6</sup>, Derek E Eberhart<sup>6</sup>, Paul Godowski<sup>3</sup>, Kathleen H Holt<sup>6</sup>, Andrew Peterson<sup>1</sup>, Brian P Zambrowicz<sup>6</sup> & Frederic J de Sauvage<sup>1</sup>



- Rigor, generalizability, and utility
  - Broad phenotypic screen of 472 knock-out lines
    - Validated assays, relevant to therapeutic areas
    - All animals screened at the same age, same order of assays
    - “Eight homozygous mice (equally divided between males and females) per assay... as we were most interested in seeing effects shared by the sexes.”
      - Results reported for M/F aggregated, M alone, and F alone
- One of many approaches to account for sex as a biological variable



Tang T, et al. A mouse knockout library for secreted and transmembrane proteins. *Nat Biotechnol.* 2010;28:749-55.



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# NIH Resources to Promote the Study of Both Sexes: Cell Resources

## NIGMS Human Genetic Cell Repository



Cryogenic tanks filled with liquid nitrogen and millions of vials of frozen cells. Credit: Coriell Institute for Medical Research.

The NIGMS Human Genetic Cell Repository [🔗](#) is a collection of well-characterized, high-quality human cells for use in biomedical research. Established by NIGMS in 1972 and housed at the Coriell Institute for Medical Research in Camden, New Jersey, the repository contains more than 11,300 cell lines and 5,700 DNA samples derived from them. The specimens, which are equally divided between those from males and those from females, were acquired from individuals with inherited diseases, apparently healthy individuals and individuals of diverse geographic origins. Almost 900 diseases [🔗](#) and 40-plus population groups [🔗](#) are currently represented in the repository. It also includes a collection of induced pluripotent stem (iPS) cell lines that carry disease gene mutations or are normal control iPS cell lines.

The NIGMS cell repository Web site [🔗](#) includes a list of collections, ordering information, sample submission instructions and frequently asked questions.

# Learn More Online

## Methods and Techniques for Integrating the Biological Variable Sex into Preclinical Research

National Institutes of Health  
Porter Neuroscience Center

October 20, 2014

"Our goal is to transform how

NIH National Institutes of Health  
Office of Research on Women's Health



### The Science of Sex and Gender in Human Health: Online Course

- The Basic Science and the Biological Basis for Sex – and Gender-Related Differences
- Sex and Gender Differences in Health and Behavior
- New! The Influence of Sex & Gender on Disease Treatment

#### Module 3. The Influence of Sex and Gender on Disease Expression and Treatment

- Sexual Dimorphism in Metabolic Bone Density
- Cardiovascular Disease in Women: A Focus on Estrogen
- ... in ...
- ...

Exploring the Biological Contributions to Human Health  
Does Sex Matter?



INSTITUTE OF MEDICINE

## Reading Room: Journal Articles About Studying Both Sexes

- Recommendations concerning the new U.S. National Institutes of Health initiative to balance the sex of cells and animals in preclinical research <#>  
This article reports the deliberations of a September 2014 workshop at Georgetown University in which scientists with varying perspectives discussed NIH's policy to ensure that NIH-funded researchers consider sex in preclinical studies. (November 2014)
- NIH initiative to balance sex of animals in preclinical studies: generative questions to guide policy, implementation, and metrics <#>  
This review article, authored by the present, past, and future presidents of the Organization for the Study of Sex Differences, poses a series of questions to promote discussion and generate ideas about research, educational, and evaluation strategies to improve the sex balance in research. (November 2014)
- Does a Change in Health Research Funding Policy Related to the Integration of Sex and Gender Have an Impact? <#>  
This report analyzes the impact of a requirement, introduced in December 2010, that all Canadian Institutes of Health Research applicants indicate whether their research designs accounted for sex or gender. The report may inform policy interventions by health research funders. (June 2014)
- Female mice liberated for inclusion in neuroscience and biomedical research <#>  
This meta-analysis of 293 articles on behavioral, morphological, physiological, and molecular traits demonstrates that variability is not significantly greater in females than males for a range of endpoints, and it shows that variability is substantially greater in males than females for many traits. (March 2014)
- First steps for integrating sex and gender considerations into basic experimental biomedical research <#>  
This paper describes some of the specific challenges to the incorporation of sex and gender considerations in research involving cell cultures and laboratory animals, and it suggests a number of strategies that allow basic experimental researchers to feasibly and meaningfully



### News & Events

Photo Gallery

Resources

About ORWH

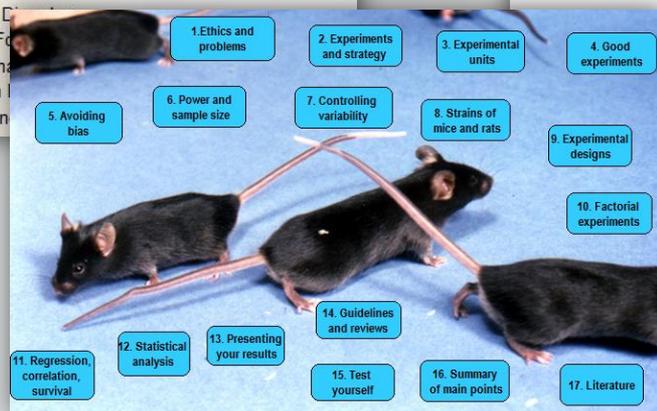
## Research & Training Resources

NIH's Office of Research on Women's Health (ORWH) is committed to providing information and tools to the scientific community to help incorporate consideration of the biologic variable of sex in preclinical research design, analysis, and reporting, which strengthens science.

- [Methods and Techniques for Integrating the Biological Variable Sex into Preclinical Research](#)
- [Specialized Centers of Research \(SCOR\) on Sex Differences program](#)
- [Online Education on Sex and Gender Differences](#)
- [Reading Room: Journal Articles About Studying Both Sexes](#)
- [Studying Sex to Strengthen Science: Questions & Answers](#)
- [Proposed Principles and Guidelines for Reporting Preclinical Research](#)
  - [Journals unite for reproducibility, Nature](#)
  - [Journals unite for reproducibility, Science](#)
- [Exploring the Biological Contributions to Human Health: Does Sex Matter? \(2001 IOM Report\)](#)
- [Sex-Specific Reporting of Scientific Research: A Workshop Summary](#)

### Additional Resources

- [Interactive Online Short Course](#) <#>  
This short course on experimental design was created for research scientists working with laboratory animals.
- [NHLBI Sex Bias in Cardiovascular Research Working Group Executive Summary, September 22, 2014](#)
- [NIH Office of Extramural Research](#)



[www.nih.gov/sexinscience](http://www.nih.gov/sexinscience)



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# The 4 Cs of Studying Sex to Strengthen Science



## Consider

Design studies that take sex into account, or explain why it isn't incorporated



## Collect

Tabulate sex-based data



## Characterize

Analyze sex-based data



## Communicate

Report and publish sex-based data

# Discussion

- Which approaches, techniques, and methods are ready for application to women's health research and the investigation of sex/gender in health and disease?
- How will we know as a scientific community that we have been successful?



Which approaches, techniques, and methods are ready for application to women's health research and investigation of sex/gender in health and disease?



How will we know as a scientific community that we have been successful?



# Thank you.

