Welcome to the 39th Meeting of the NIH Advisory Committee on Research on Women’s Health

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)
- 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

“… 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

- Behavioral Studies/Programs: 1%
- Cancer: 6%
- Cardiovascular/Pulmonary: 20%
- Health Effects of the Environment: 6%
- Immune Disorders: 8%
- Infectious Diseases: 1%
- Kidney and Urologic: 1%
- Mental Health: 11%
- Neurologic, Muscular & Bone: 9%
- Metabolism/Endocrinology/Gastrointestinal: 6%
- Reproductive & Maternal/Child/Adolescent Health: 5%
- Substance Abuse: 17%
- Aging: 9%
### Selected Topics (FY 2014)

- Molecular and Functional Mechanisms of Pediatric Heart Failure
- Translating Molecular Signal Pathways to Orthopaedic Trauma Care
- Systems Genetic Analysis of Methamphetamine
- Enhancing Neonatal Immunity to *Streptococcus* Pneumonia
- Role of Rapid IFNγ 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 that the checks and balances that once ensured scientific fidelity are now too often absent. In the short term, however, the checks and balances that once ensured scientific fidelity are still in place, and there are crucial experimental design elements that are all too frequently ignored. These 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 ongoing toward this effort, the annual measure and amount of resources spent or estimated each year toward this effort
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

Journals unite for reproducibility

Reproducibility, 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 eke out a light on issues of reproducibility. This light ensures that science moves forward, through independent verifications as well as the control corrections that come from retractions 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 50 major medical journals, representatives from research universities, and representatives from medical institutions at the June meeting of the National Academy of Sciences and the Institute of Medicine united to develop new guidelines for reproducibility.

The new guidelines, which are published in the March 11 issue of *Science* (www.sciencemag.org/content/346/6205), are designed to improve the way that biomedical research is conducted. The guidelines include recommendations for improving the design, analysis, and reporting of research, and they are intended to help researchers and editors ensure that their work is reproducible.

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

- Uncertain, 1%
- No, 5%
- Yes, with some qualifications, 31%
- Yes, 44%
- Yes, and will lead to better outcomes, 19%
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

17αEstradiol:
Extended lifespan in males but not females

Rapamycin:
Extended lifespan in both sexes

NDGA, Aspirin:
Significant lifespan extension in males

NIH Programs that Promote the Study of Both Sexes: KOMP

- 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

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

NIGMS Human Genetic Cell Repository

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.
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?
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Thank you.