



# Cultivating a Culture of ‘Sex Matters’

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**Methods and Techniques for Integrating the Biological  
Variable “Sex” in Preclinical Research**

Office of Research on Women’s Health

October 20, 2014

# Session IV: Cultivating a culture of 'Sex Matters' across multiple disciplines

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- To determine where gender fits into the research realm

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### Role of the T cell in the genesis of angiotensin II–induced hypertension and vascular dysfunction

Tomasz J. Guzik, Nyssa E. Hoch, Kathryn A. Brown, Louise A. McCann, Ayaz Rahman, Sergey Dikalov, Jorg Goronzy, Cornelia Weyand, David G. Harrison

J. Exp. Med. 2007;204:2449–2460, October 1, 2007 (10.1084/jem.20070657).

Originally published at <http://jem.rupress.org> on Sep 17, 2007

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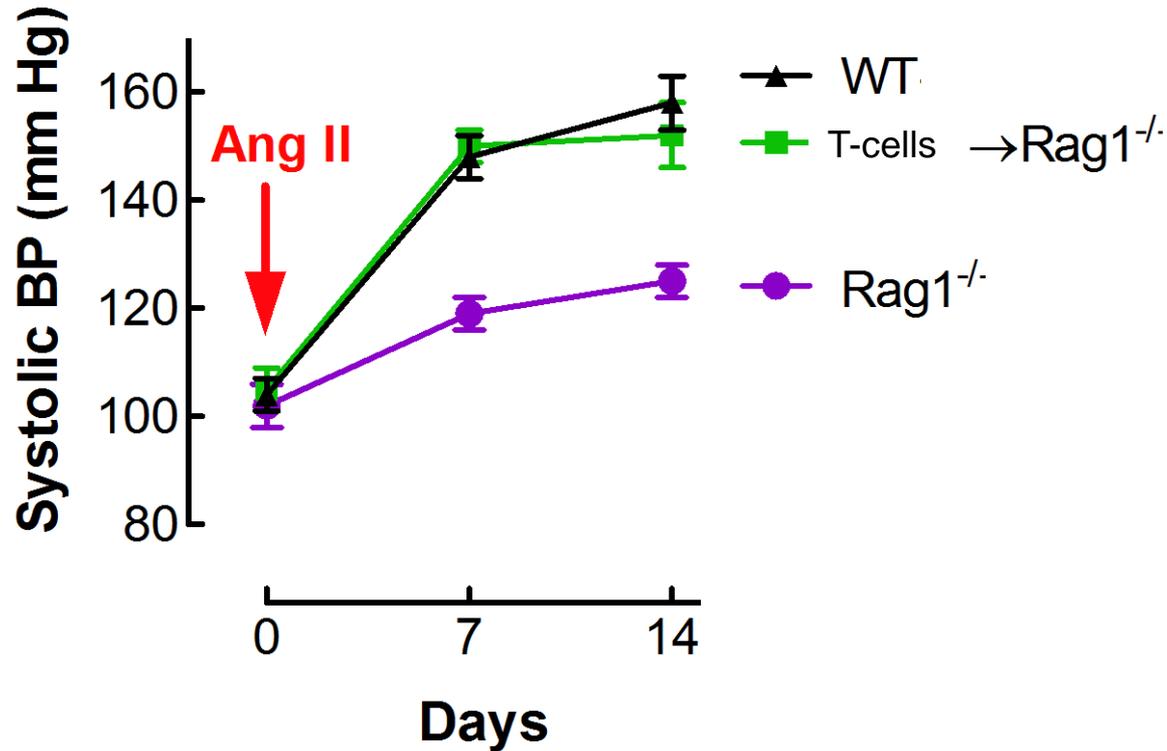
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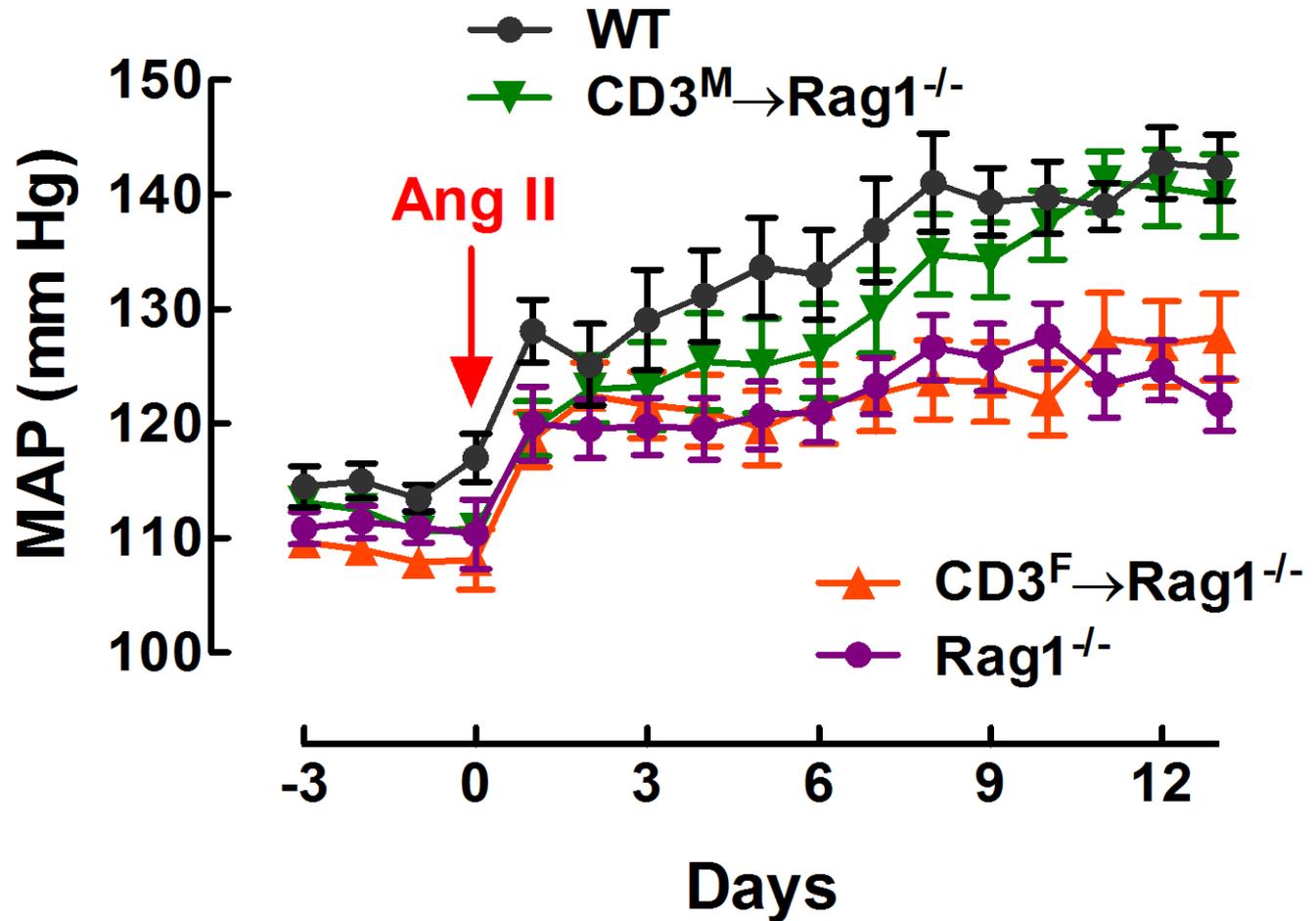
# Adoptive transfer of T cells restores the magnitude of angiotensin II-dependent hypertension in T cell deficient mice



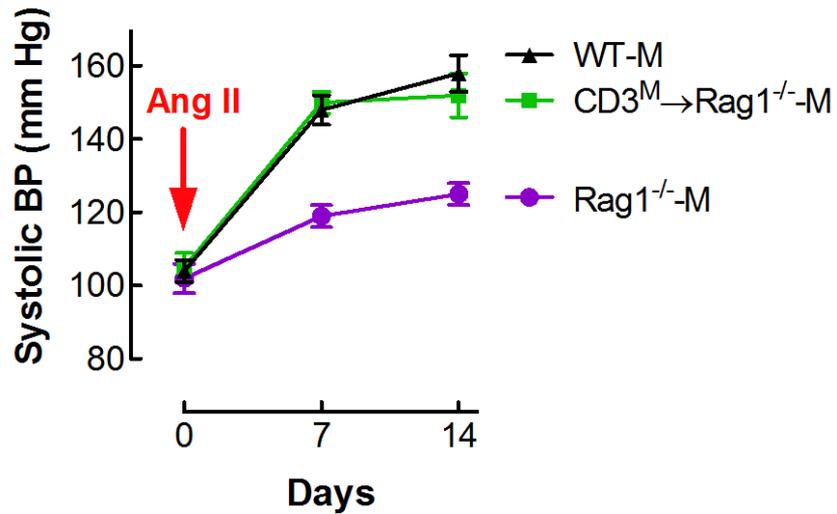
# Sex-specific T-cell modulation of hypertension



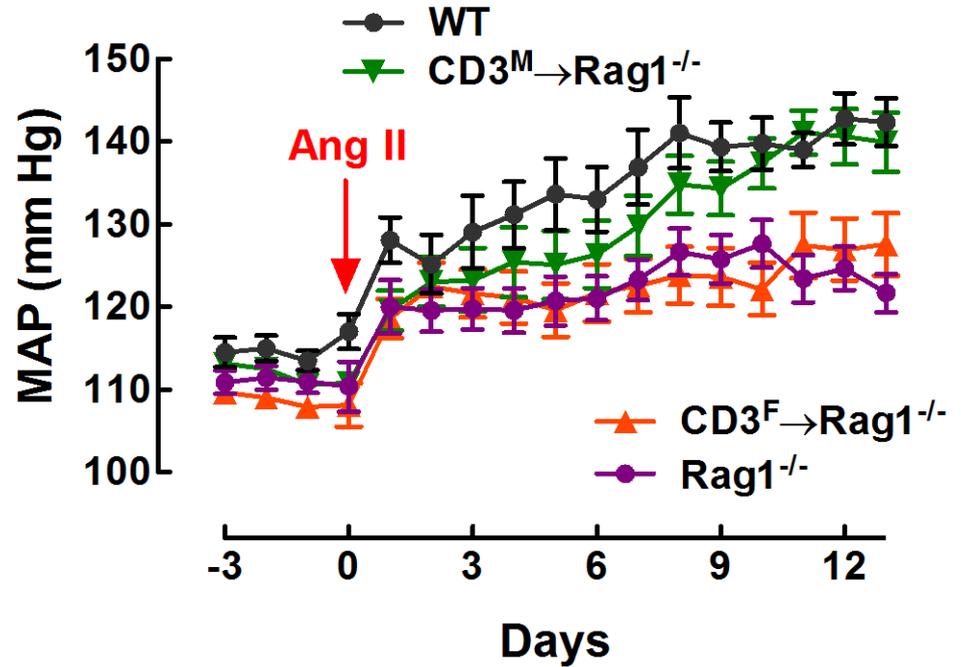
Hong Ji, MD



# Sex-specific T-cell modulation of hypertension



Guzik TJ et al. J Exp Med 2007

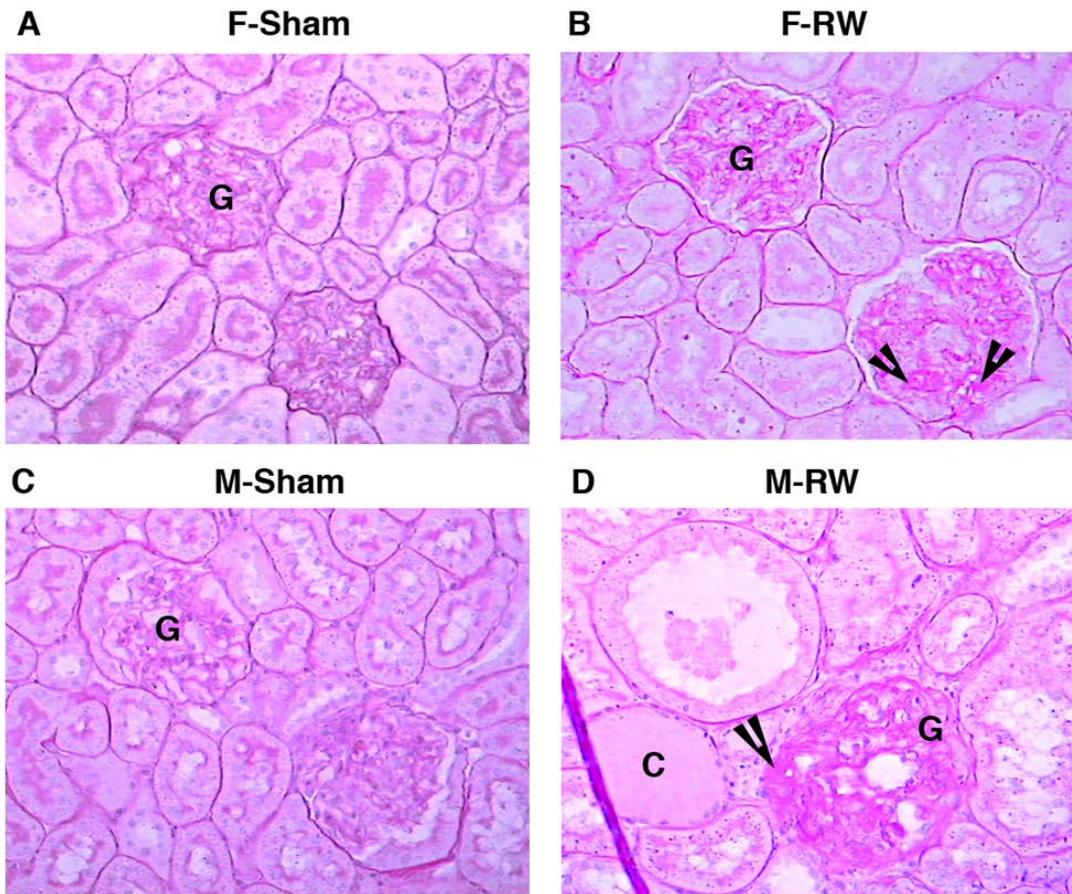


Ji et al. Hypertension, 2014

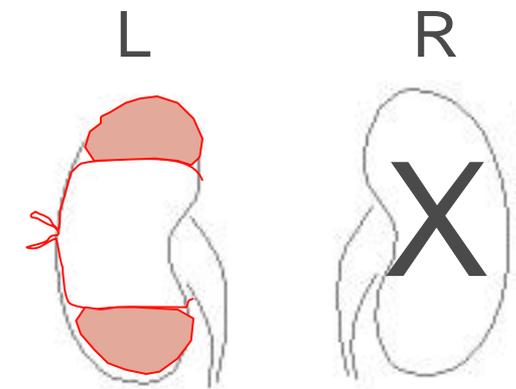


Hong Ji, MD

# Glomerular and tubular damage in renal wrap hypertension is greater in male than female rats



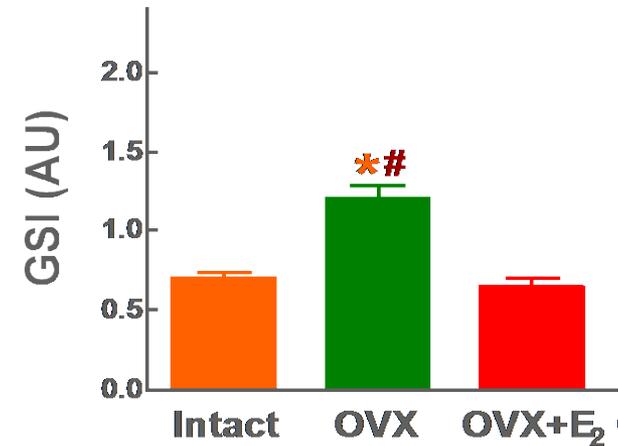
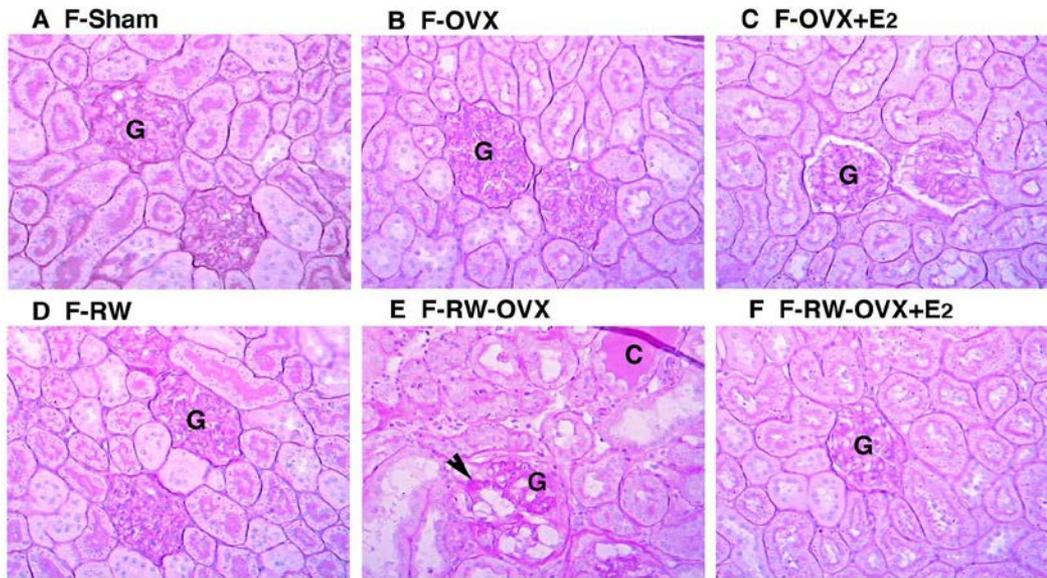
*Renal wrap (RW)*



Hong Ji, MD

*Ji et al, AJP: Heart, Circ Physiol 288: H43, 2005*

# 17 $\beta$ -Estradiol replacement prevents the aggravating effect of ovariectomy on glomerular and tubular damage in RW rats



*Ji et al, AJP: Renal Physiol 288: F513, 2005*



Carlo Pesce, PhD



Stefano Menini, PhD

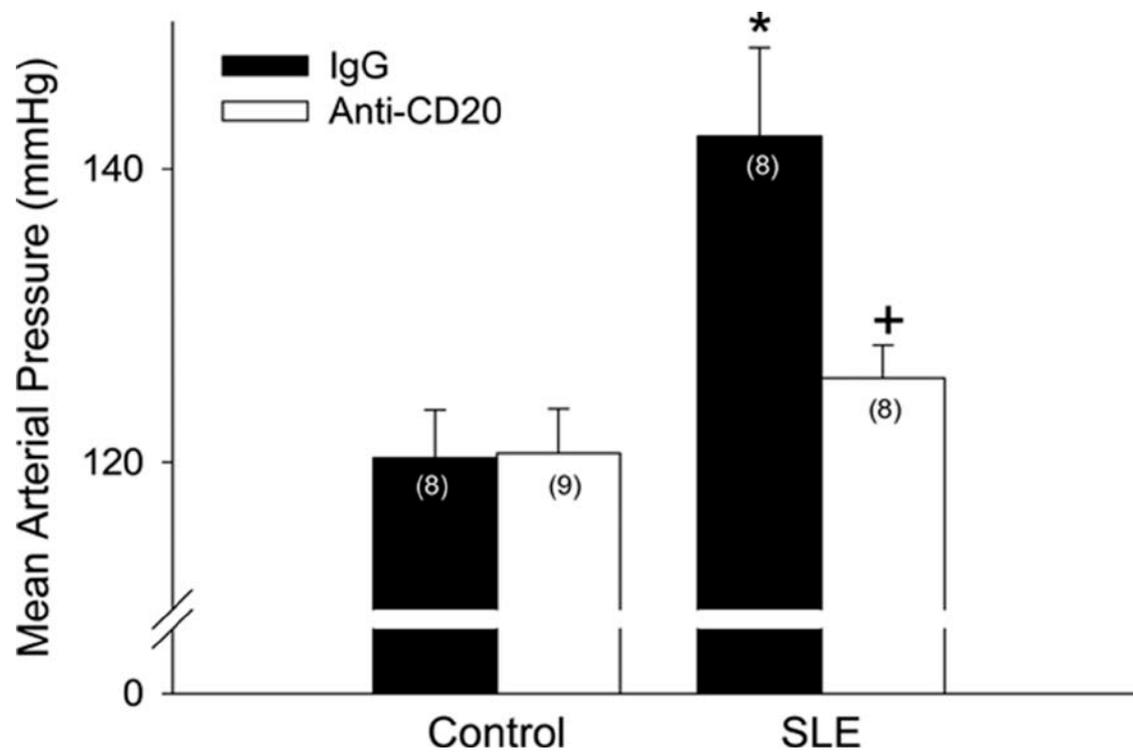


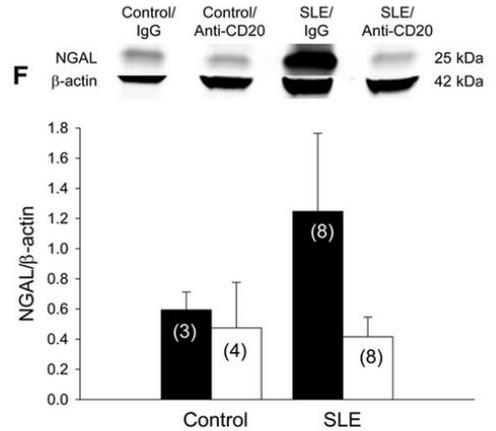
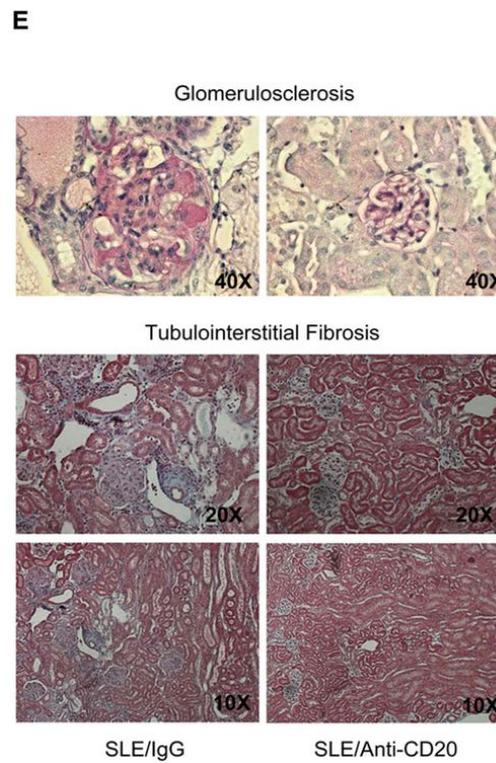
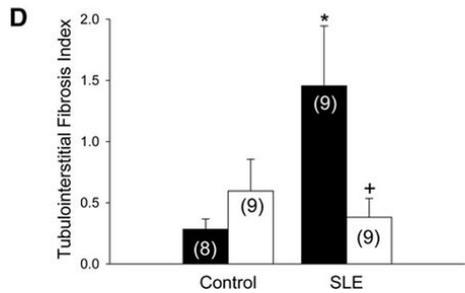
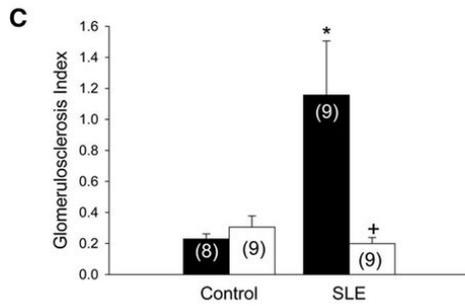
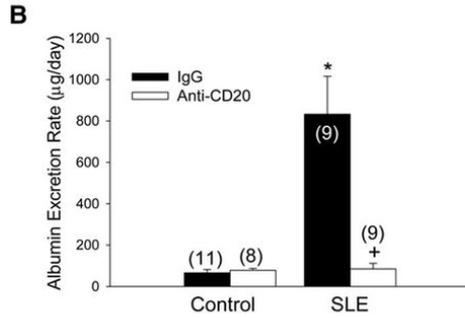
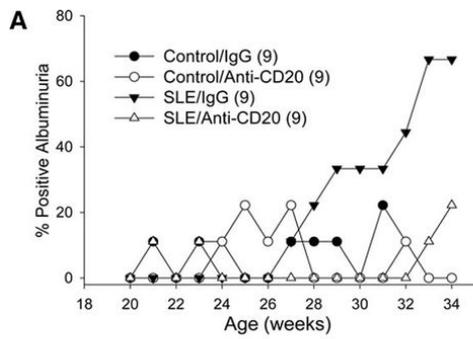
# NZBWF1 mouse

*Mouse model of systemic lupus erythematosus*



Mike Ryan





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- To determine where gender fits into the research realm
- **To determine if there is research space for single sex studies and if such studies will result in no harm (add'n examples)**
  - **Mechanisms of susceptibility vs resilience to disease**

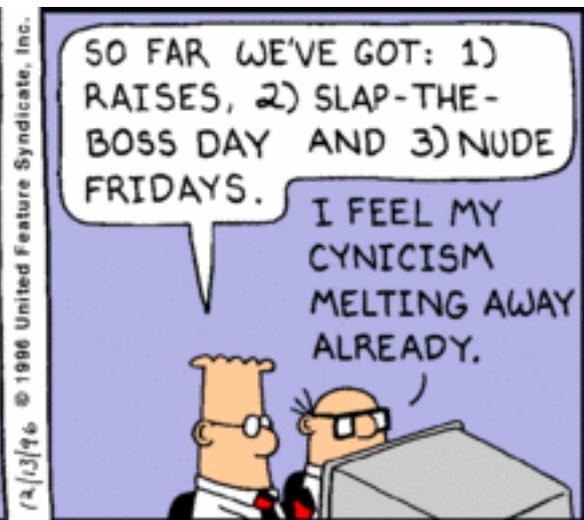
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- **How can we cultivate a culture of ‘Sex Matters’?**

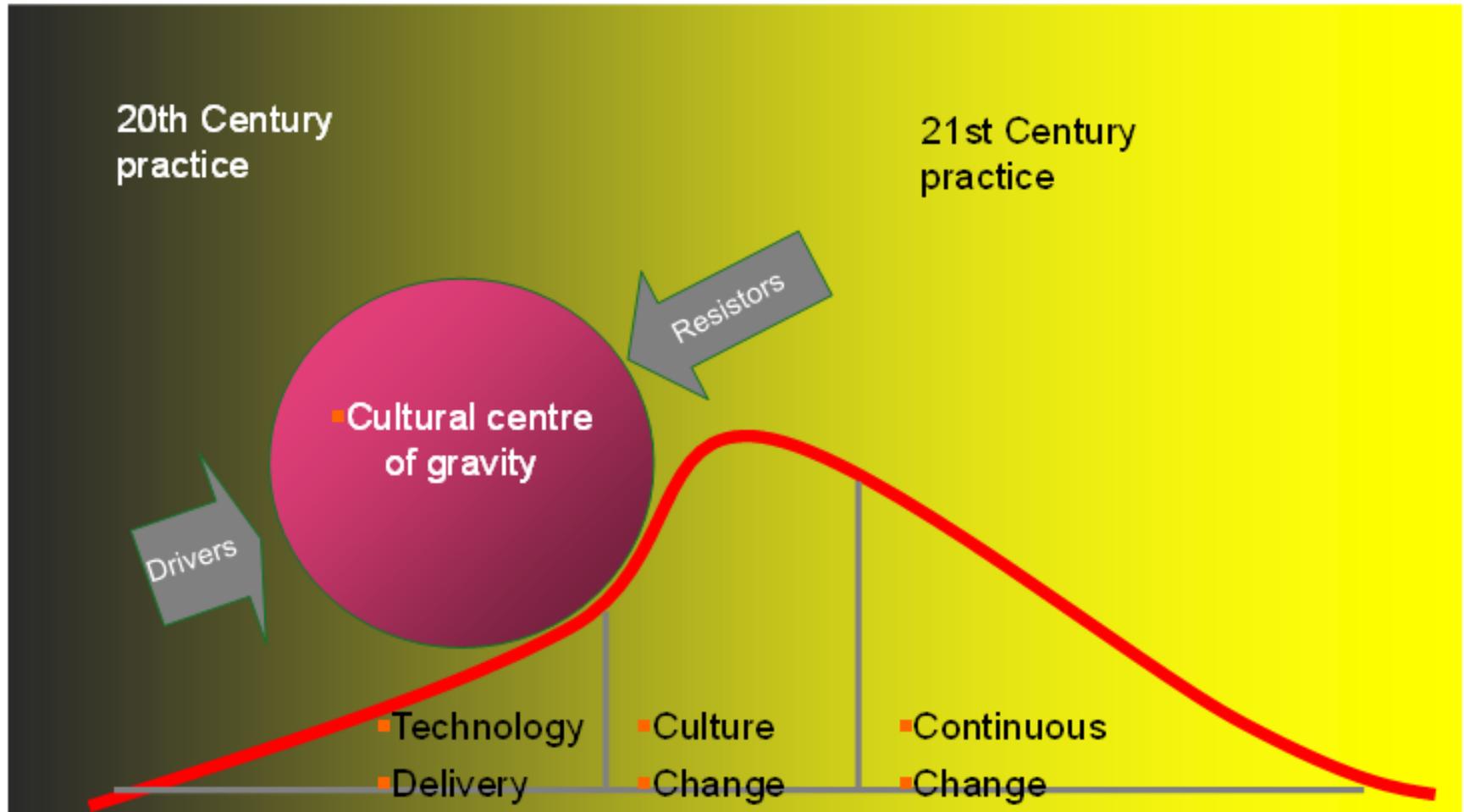




S. Adams E-mail: SCOTTADAMS@AOL.COM

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# The Uphill Challenge of Culture Change



# The 9 Steps to Organizational Culture Change

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## ***DEFINE: Begin with the end in mind***

- Step 1 – Evaluate your current culture and performance
- Step 2 – Clarify your initial vision
- Step 3 – Clarify values and expected behaviors

## ***ALIGN: Teamwork is working together toward a common vision***

- Step 4 – Clarify strategic priorities
- Step 5 – Engage your team in defining goals
- Step 6 – Clarify and track key measures

## ***MANAGE: A culture of discipline a principle of greatness***

- Step 7 – Maintain a management system for priorities and goals
- Step 8 – Manage communication habits and routines
- Step 9 – Build motivation throughout the process

# How Do We Measure Success?



# Short-term Metrics

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- Number of applications and grant awards proposing Single Sex Studies (**SSS**) in males (**SSS-M**) and those in females (**SSS-F**)
- Number of applications and grant awards proposing Dual Sex Studies (**DSS**)
- Ratio of DSS:SSS among applications and grant awards
- Of SSS, the average ratio of SSS-M: SSS-F among applications and grant awards
- Of DSS, the average ratio of male to female animals proposed per application (M:F/application) and that proposed per grant award (M:F/grant)

# Preparing the Vertebrate Animal Section (VAS)



## What is the VAS?

The VAS is the section of grant applications, contract proposals, and cooperative agreements where you describe the use of animals in your work. There are 5 points you must address.

## Which studies require a VAS?

You must provide a VAS if your work involves the use of live vertebrate animals, including generating custom antibodies and obtaining tissue from live vertebrate animals.

## What if there is more than one performance site?

You need to complete all 5 points of the VAS for each performance site.

## What information should be provided in the VAS?

### • POINT 1

**Description of animals and how they will be used**  
In detail, describe the proposed use of animals for the study. Identify the species, strains, ages, sex, and number of animals.

#### Have you included?

- ◇ Concise description of the proposed work using animals
- ◇ Procedures (e.g., injections, blood collection)
- ◇ Surgical procedures, including anesthetic regimes, monitoring, and recovery
- ◇ Species, strains, ages, sex
- ◇ Number of animals

### • POINT 2

#### Justifications for use of animals

Justify the use of animals, the choice of species, and the numbers of animals. Provide rationale for use of animals in short supply, that are costly, or in large numbers.

#### Have you justified?

- ◇ Use of animals and why alternatives cannot be used
- ◇ Choice of species
- ◇ Number of animals and how determined

### • POINT 3

#### Veterinary care

Provide information on the veterinary care of the animals.

#### Have you provided?

- ◇ Brief account of veterinary staff and their availability for routine and emergency care
- ◇ How often animals are observed or monitored
- ◇ Any additional monitoring or support that may be required (e.g., post-procedural, post-surgical care)
- ◇ Indicators for veterinary intervention to alleviate discomfort, distress, or pain (e.g., body scoring, weighing)

### • POINT 4

**Provisions to minimize discomfort, distress, pain, and injury**

Describe the procedures to minimize discomfort, distress, pain, and injury to that which is unavoidable in the conduct of scientifically sound research. Describe use of analgesics, anesthetics, tranquilizing drugs, and comfortable restraining devices/methods, where appropriate, to minimize discomfort, distress, pain, and injury.

#### Have you described?

- ◇ Circumstances when animals may experience discomfort, distress, pain or injury
- ◇ Procedures to alleviate discomfort, distress, pain or injury
- ◇ Use of tranquilizers, analgesics and anesthetics (identify drugs by name/class)
- ◇ Provisions for special care or housing
- ◇ Plans for post-surgical care, if applicable
- ◇ Humane experimental endpoints, if relevant
- ◇ Use of restraint devices/methods, if relevant

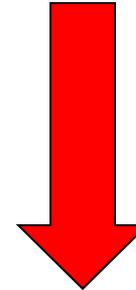
### • POINT 5

#### Euthanasia

Describe any method of euthanasia and the reason(s) for selecting it. State if the method(s) is consistent with the recommendations of the *AVMA Guidelines on Euthanasia* (PDF). If not, include a scientific justification for not following the recommendations.

#### Have you indicated?

- ◇ Method(s) of euthanasia and reason(s) for selection
- ◇ If the method(s) of euthanasia is consistent with the recommendations of the *AVMA Guidelines on Euthanasia*
- ◇ Scientific justification for the method(s) of euthanasia that is not consistent with the recommendations of the *AVMA Guidelines on Euthanasia*



### • POINT 1

## Description of animals and how they will be used

In detail, describe the proposed use of animals for the study.

Identify the species, strains, ages, sex, and number of animals.

### Have you included?

- ◇ Concise description of the proposed work using animals
- ◇ Procedures (e.g., injections, blood collection)
- ◇ Surgical procedures, including anesthetic regimes, monitoring, and recovery
- ◇ Species, strains, ages, sex
- ◇ Number of animals

For more information, download the worksheet at <http://grants.nih.gov/grants/olaw/VASchecklist.pdf>

OFFICE OF LABORATORY ANIMAL WELFARE  
OFFICE OF EXTRAMURAL RESEARCH  
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

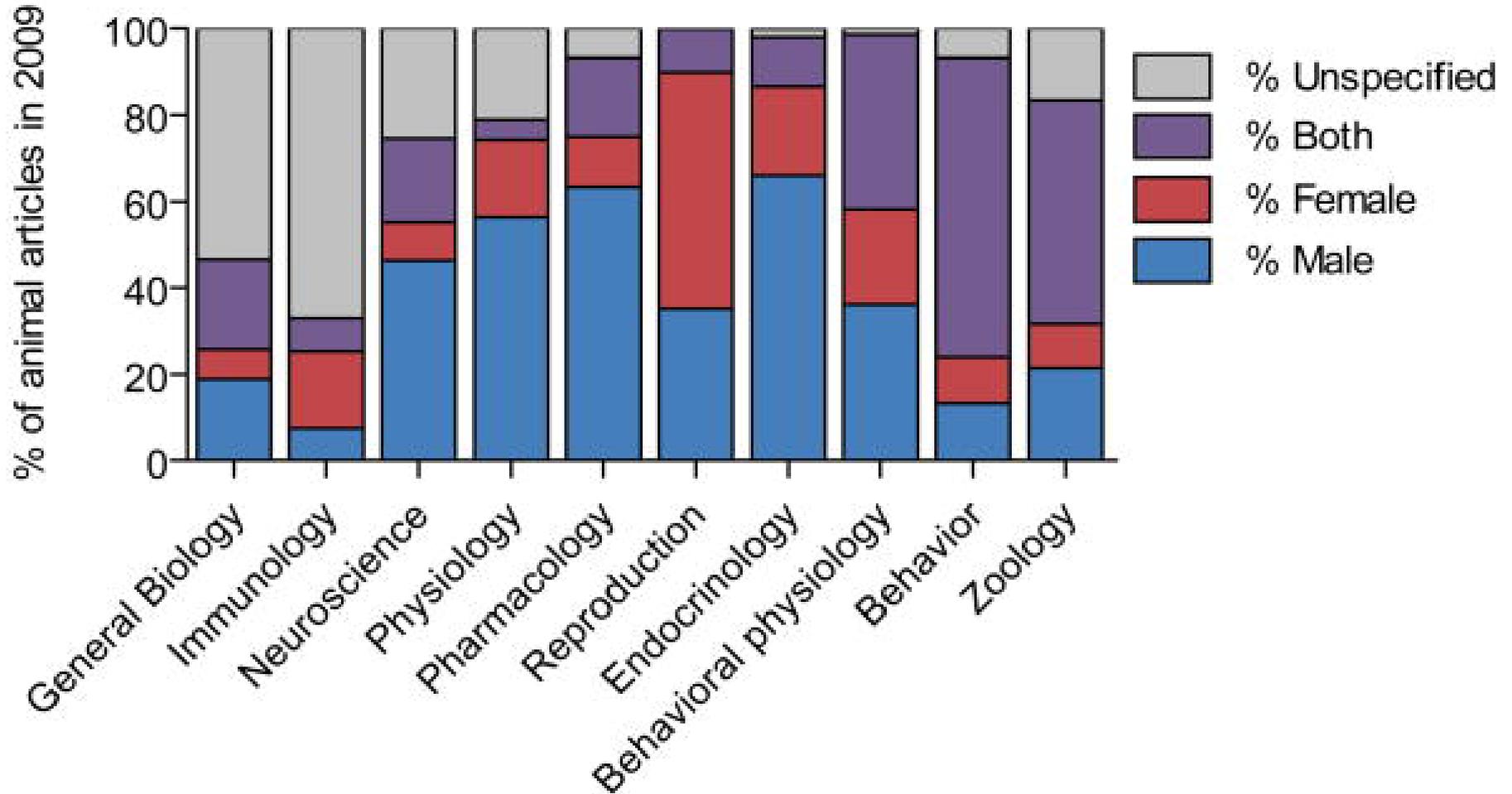
January 18, 2012

# Mid-term Metrics

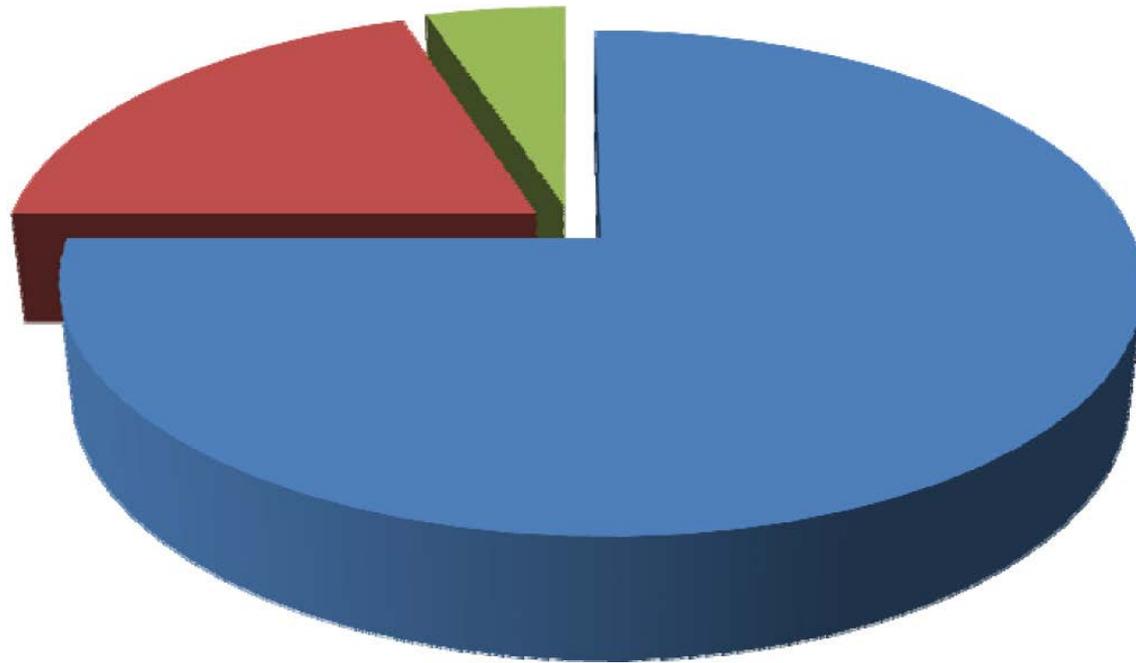
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- Number of published papers on a single sex study (**PPS**) citing NIH support conducted solely in male (**PPS-M**) or solely in female (**PPS-F**) animals
- Number of published papers citing NIH support using both sexes (**PPD**)
- Ratio of PPD:PPS citing NIH support
- Of PPS, the average ratio of PPS-M:PPS-F citing NIH support

# 2009 Survey on Nonhuman Mammals



Most folks do not know the sex of their cells



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## When and How to Comply

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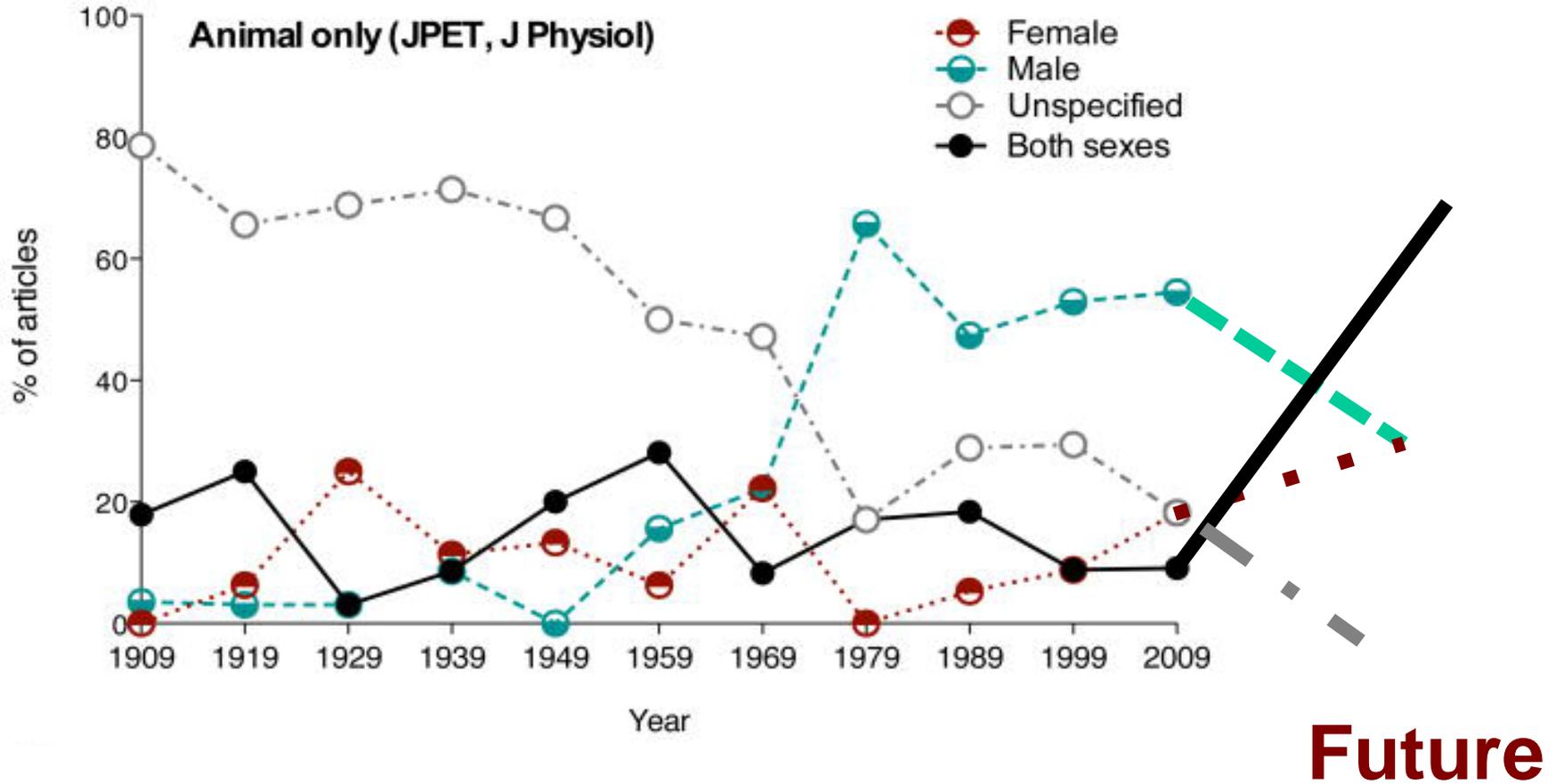
### Overview:

To advance science and improve human health, NIH makes the peer-reviewed articles it funds publicly available on [PubMed Central](http://www.ncbi.nlm.nih.gov/pmc/) (<http://www.ncbi.nlm.nih.gov/pmc/>). The NIH public access policy requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to PubMed Central immediately upon acceptance for publication. [\[more\]](http://publicaccess.nih.gov/policy.htm) (<http://publicaccess.nih.gov/policy.htm>)

Last Updated: Tuesday, March 18, 2014



# The sex of Animals in Preclinical Research Publications

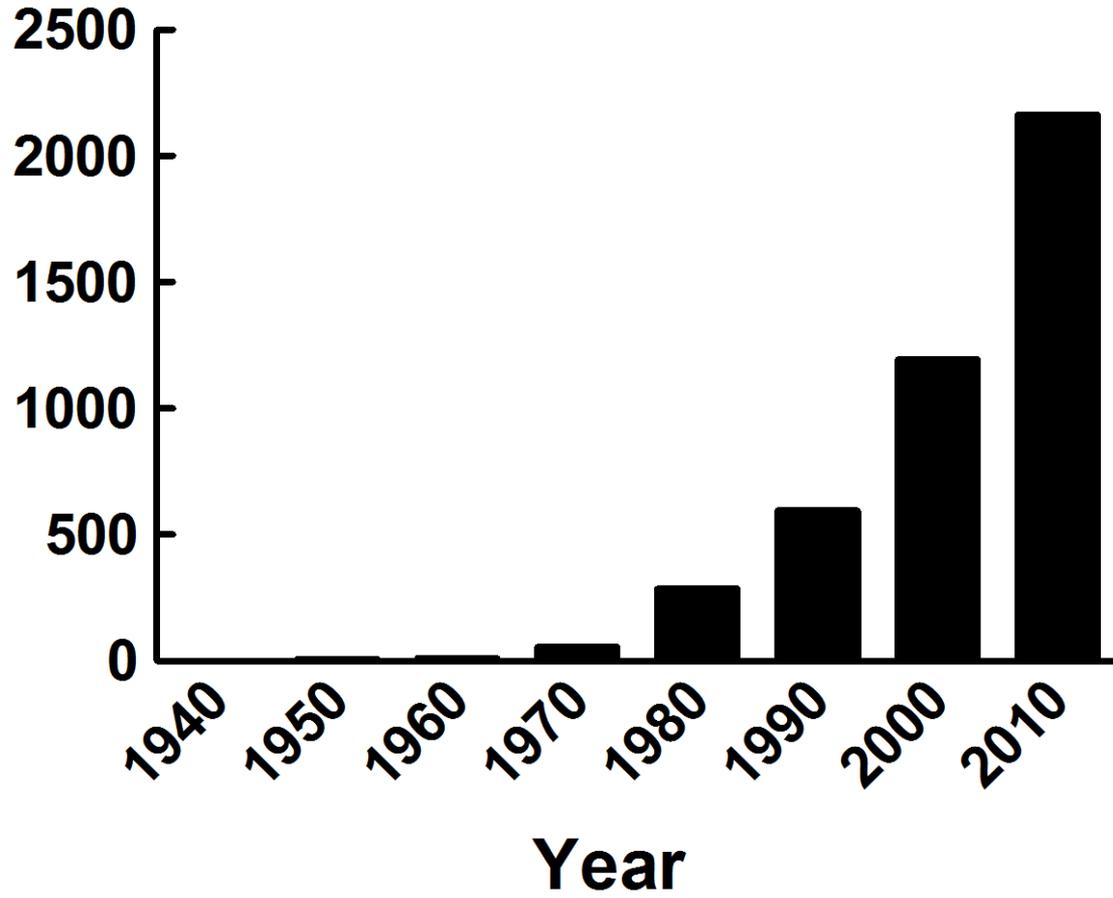


# Mid-term Metrics

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- Number of published papers on a single sex study (**PPS**) citing NIH support conducted solely in male (**PPS-M**) or solely in female (**PPS-F**) animals
- Number of published papers citing NIH support using both sexes (**PPD**)
- Ratio of PPD:PPS citing NIH support
- Of PPS, the average ratio of PPS-M:PPS-F citing NIH support
- Of PPD, the number and frequency of those PPD reporting a sex difference or the absence of a difference in a meaningfully powered comparison for a measured parameter either in the paper or on-line supplement

**Annual Number of Paper Published  
on Sex/Gender Differences**



# Long-term Metrics

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- Number of clinical studies and trials whose design explicitly addresses sex-specific hypotheses revealed by preclinical studies or proposes study and pooled analysis of males and females due to the lack of preclinical sex differences
- Number of established and newly developed drugs with sex-specific labeling by the FDA
- Number of consensus statements and clinical guidelines recommending sex-specific therapeutic strategies for treating disorders and diseases because of sex differences in efficacy and/or safety
- Reductions in sex-specific skewing of adverse event reporting

**Table 3. Prescription drugs withdrawn from the US market (1997–2000).**

Drug	Type of drug	Patient population	Primary health risk
<i>Prescription drugs with evidence of greater health risks in women</i>			
Pondimin®	Appetite suppressant	Women	Valvular heart disease
Redux®	Appetite suppressant	Women	Valvular heart disease
Rezulin®	Diabetic	Women	Liver failure
Lotronex®	Gastrointestinal	Women	Ischemic colitis
Seldane®	Antihistamine	Women and men	Torsades de Pointes
Posicor®	Cardiovascular	Women and men	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal®	Antihistamine	Women and men	Torsades de Pointes
Propulsid®	Gastrointestinal	Women and men	Torsades de Pointes
<i>Prescription drugs without evidence of greater health risks in women</i>			
Raxar®	Antibiotic	Women and men	Torsades de Pointes
Duract®	Analgesic and anesthetic	Women and men	Liver failure

# LET'S MAKE THE NEXT GENERATION TOBACCO-FREE

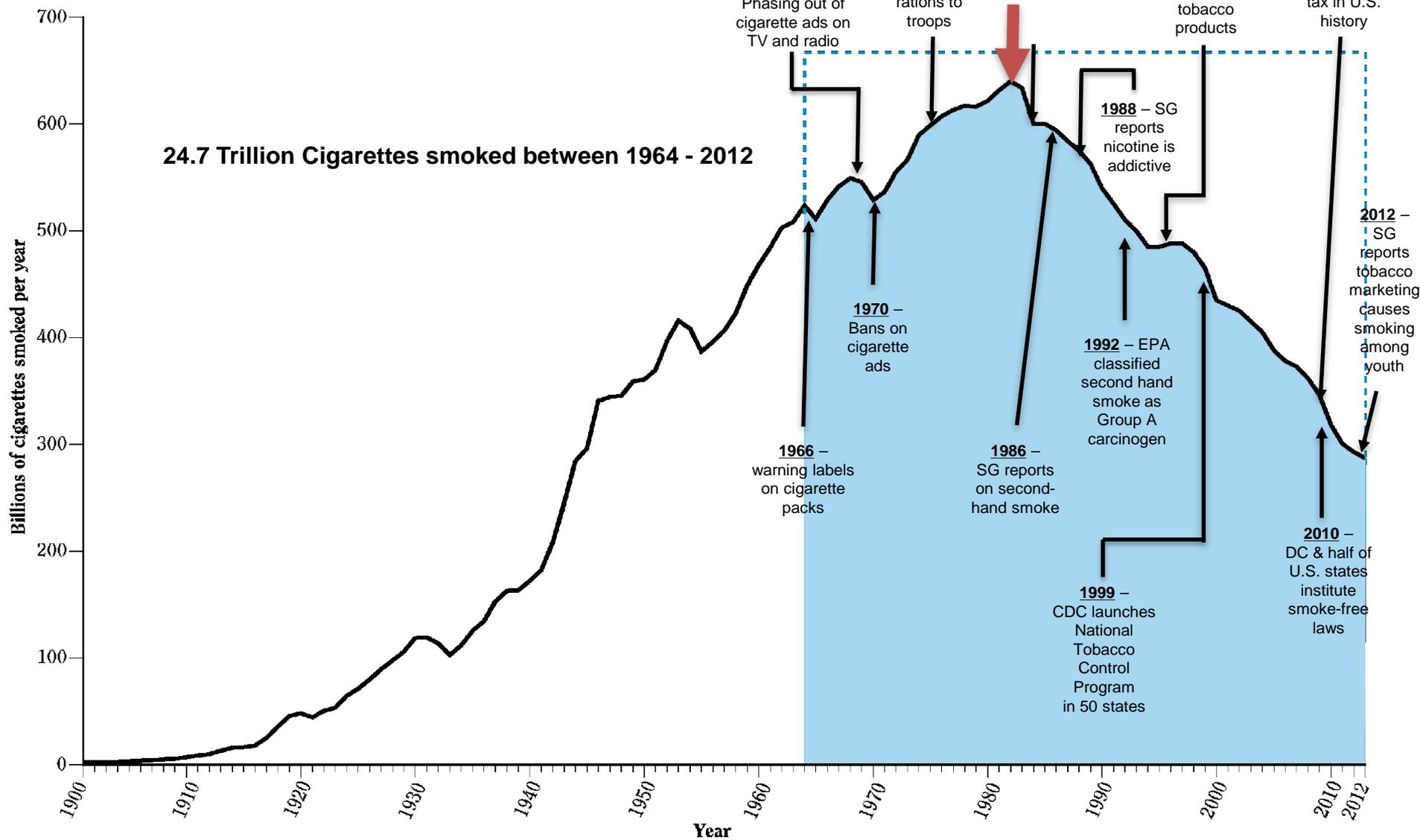
Your Guide to the 50th Anniversary Surgeon General's  
Report on Smoking and Health



U.S. Department of Health and Human Services



**Figure 2 Total cigarette consumption, United States, 1900–2012**



Source: Miller 1981; U.S. Department of Agriculture 1987, 1996, 2005, 2007a,b; Centers for Disease Control and Prevention 2012.

Note: Data shown are annual total consumption of cigarettes. This differs from Figure 2.1, which reports the annual adult (18 years of age and older) per capita consumption.

# SUCCESS

