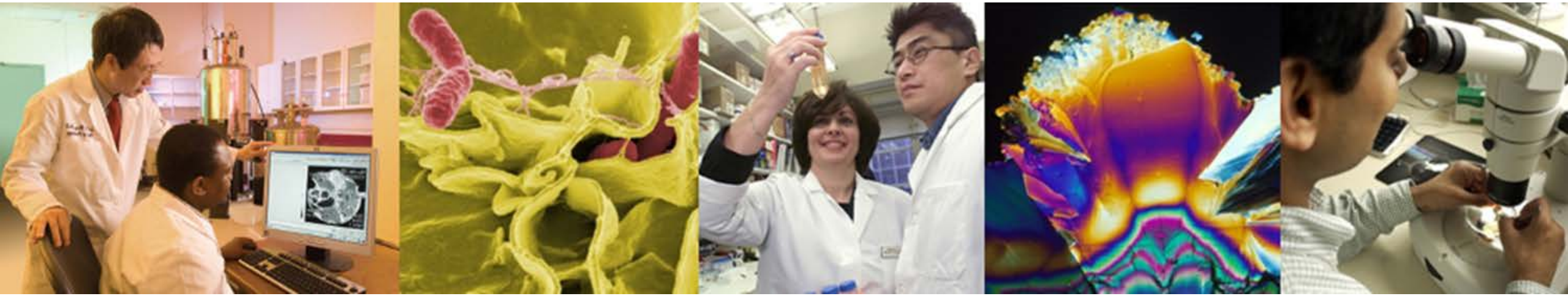
Biomedical Research Opportunities: A View from NIH

University of Georgia
September 21, 2018



Lawrence A. Tabak, DDS, PhD
Principal Deputy Director, NIH
Department of Health and Human Services

Topics for Today

- Introduction
- Unraveling Life's Mysteries through Basic Research
- Supporting Research Essentials
- Advancing Science to Improve Public Health

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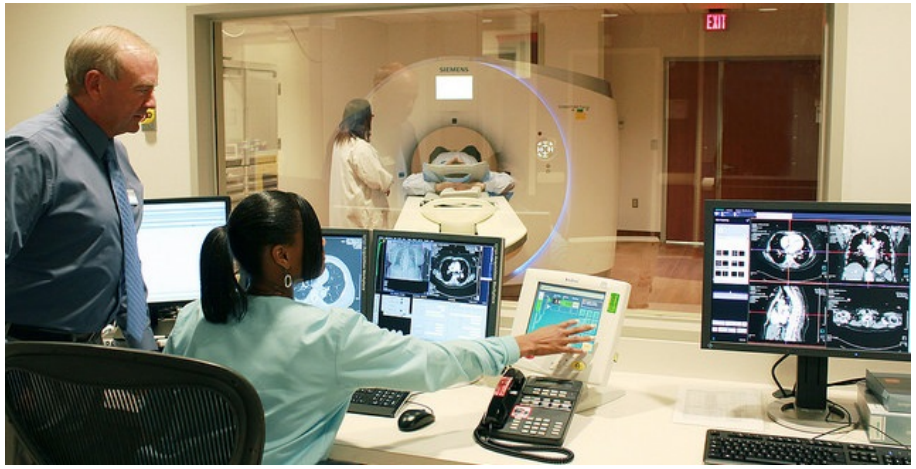
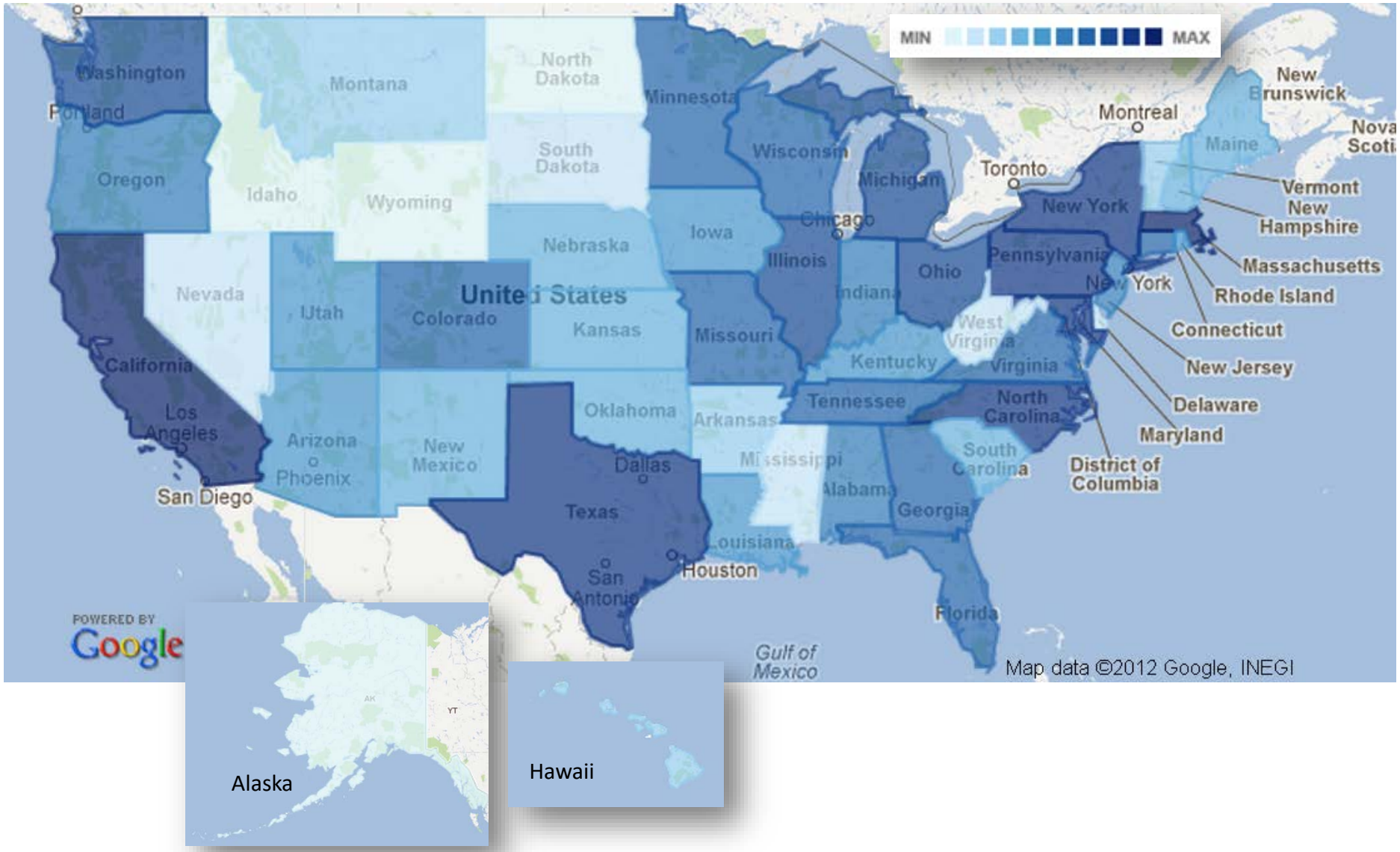
NIH: Steward of Medical and Behavioral Research for the United States

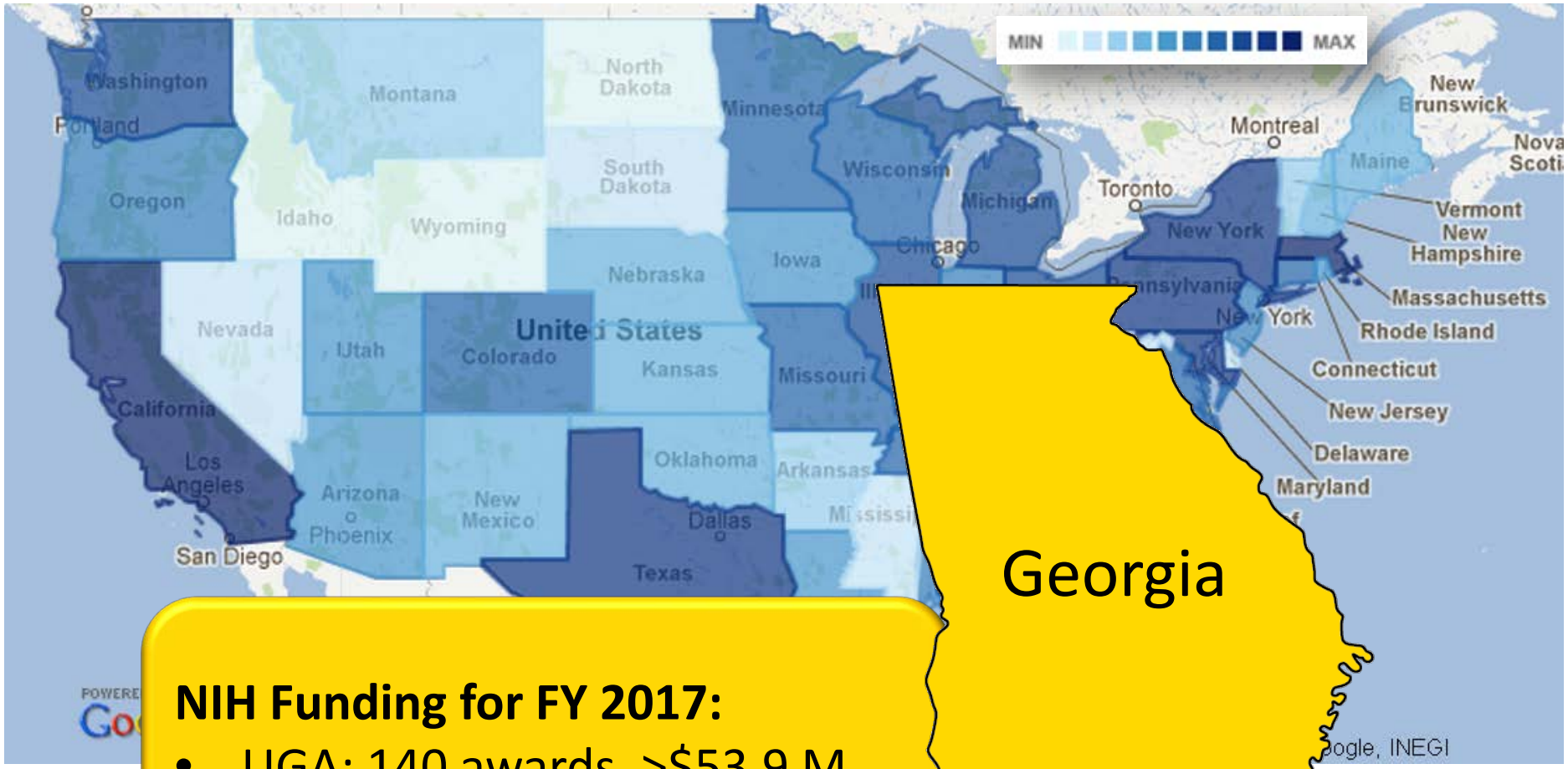
"Science in pursuit of **fundamental** knowledge about the nature and behavior of living systems… and the **application of that knowledge** to extend healthy life and reduce illness and disability."



NIH Funds Scientists Across U.S.



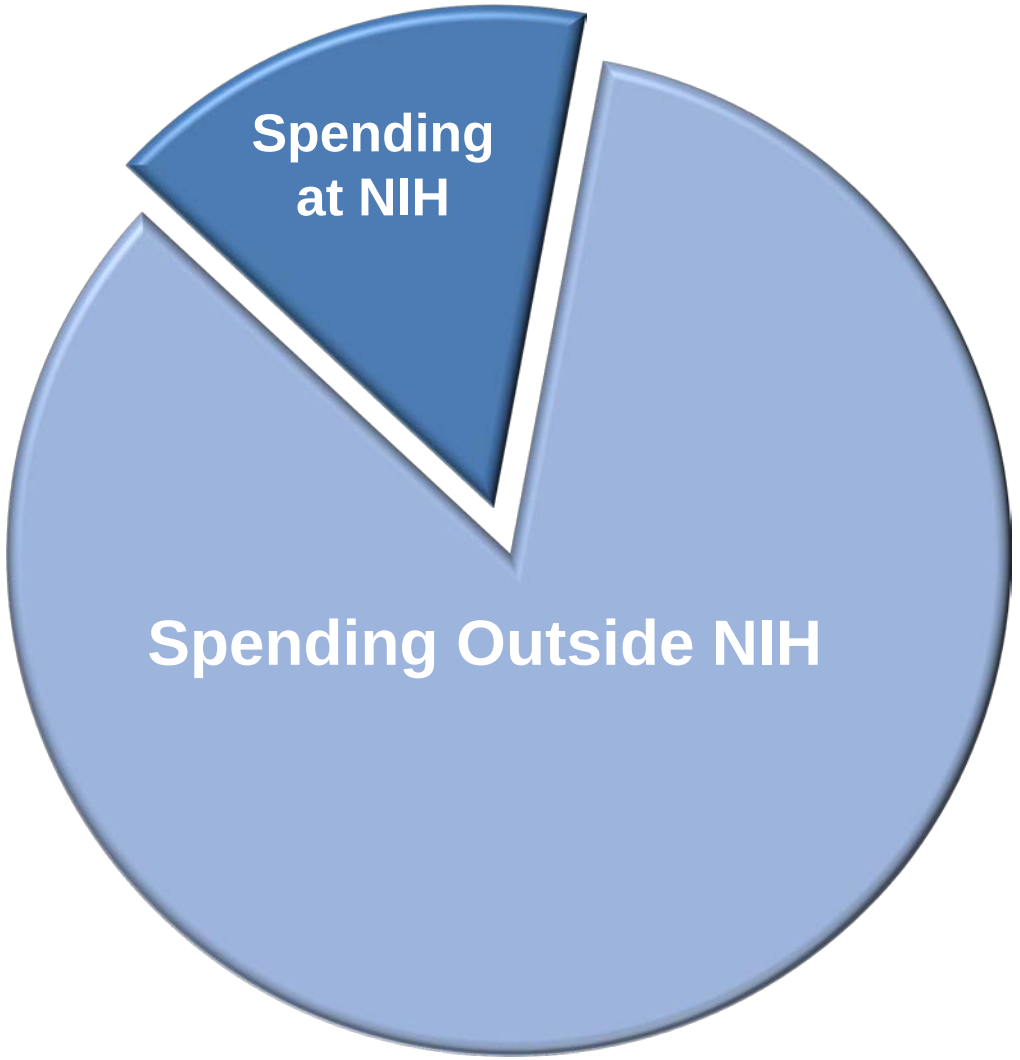
NIH Funds Scientists Across U.S.



Complex Carbohydrate Research Center at UGA

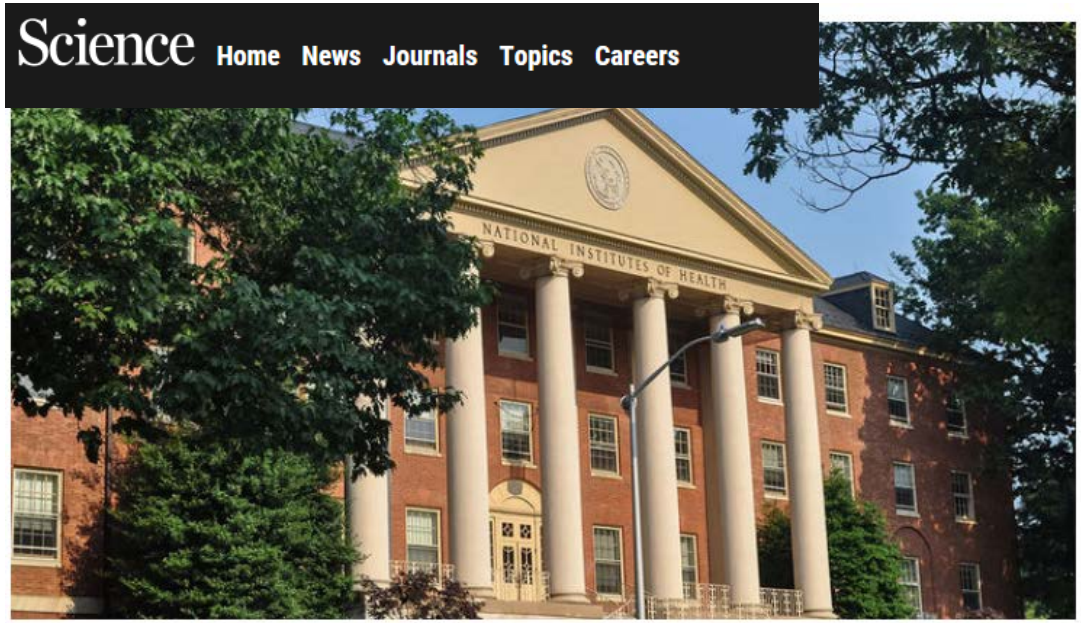
NIH Extramural & Intramural Funding

FY 2018 Budget: $37 Billion



Continued Support of NIH

Science Home News Journals Topics Careers



LYDIA POLIMENI/NATIONAL INSTITUTES OF HEALTH

NIH gets $2 billion boost in final 2019 spending bill

By Jocelyn Kaiser | Sep. 14, 2018 , 9:55 AM

Congress has approved a $2 billion raise, to $39.1 billion, for the National Institutes of Health (NIH) in a 2019 spending bill **approved by House of Representatives and Senate negotiators last night**.

As expected, the 5% boost matches **the Senate's proposed spending level** and surpasses **a $1.25 billion increase in a draft bill** passed by the House. President Donald Trump's **administration had requested $34.8 billion** for the fiscal year that begins 1 October. This is the fourth year in a row that NIH has received a substantial increase, after more than a decade of flat budgets.

- Essential aspects of supporting the NIH mission and advancing our human health include:
  - Strategic research investments
  - Enhanced stewardship

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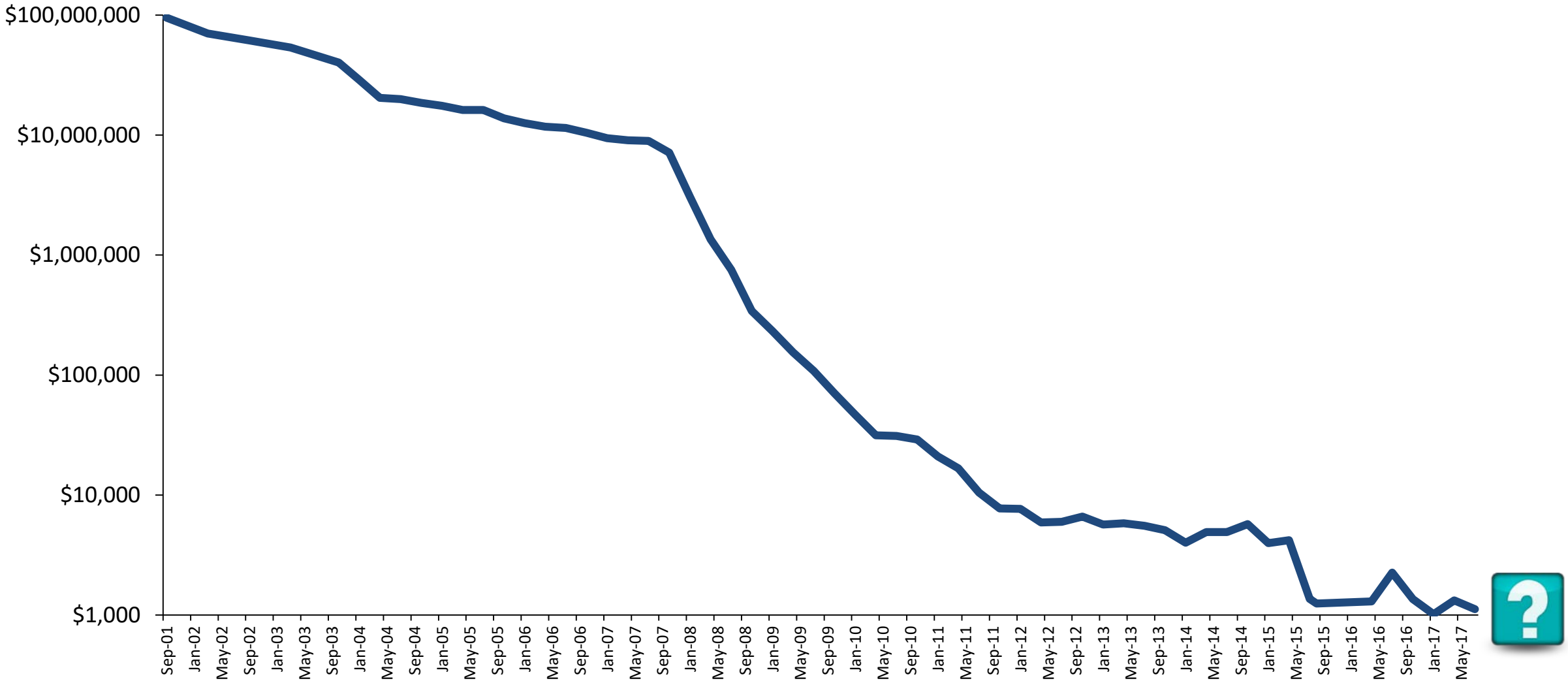
ENCODE
International HapMap Project
SINGLE CELL ANALYSIS PROGRAM
Follow that cell
db GaP
GENOTYPES and PHENOTYPES
H3Africa
Human Heredity and Health in Africa
4D Nucleome
Illuminating the Druggable Genome
THE CANCER GENOME ATLAS
Human Epigenome Atlas
METABOLOMICS
GAIN
GENETIC ASSOCIATION INFORMATION NETWORK
HMP
1000 Genomes
A Deep Catalog of Human Genetic Variation
Rethinking Clinical Trials™
A Living Textbook of Pragmatic Clinical Trials
BARD
GTR: GENETIC TESTING REGISTRY

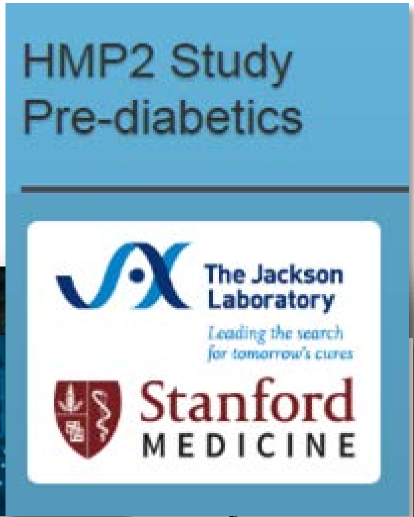
Cost of Sequencing a Human Genome

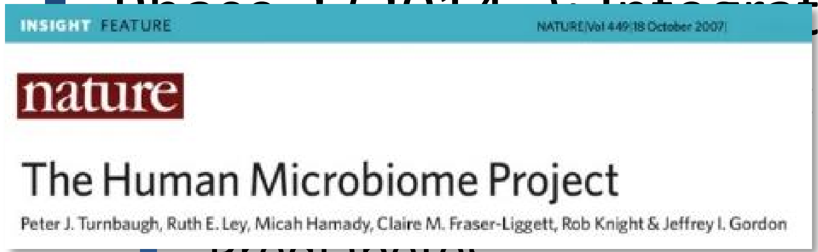
September 2001–July 2017

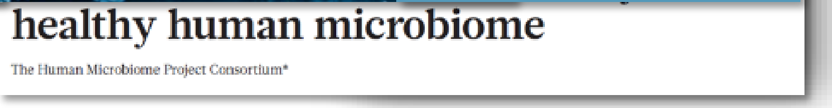


Uncovering Life's Foundations: The Human Microbiome Project

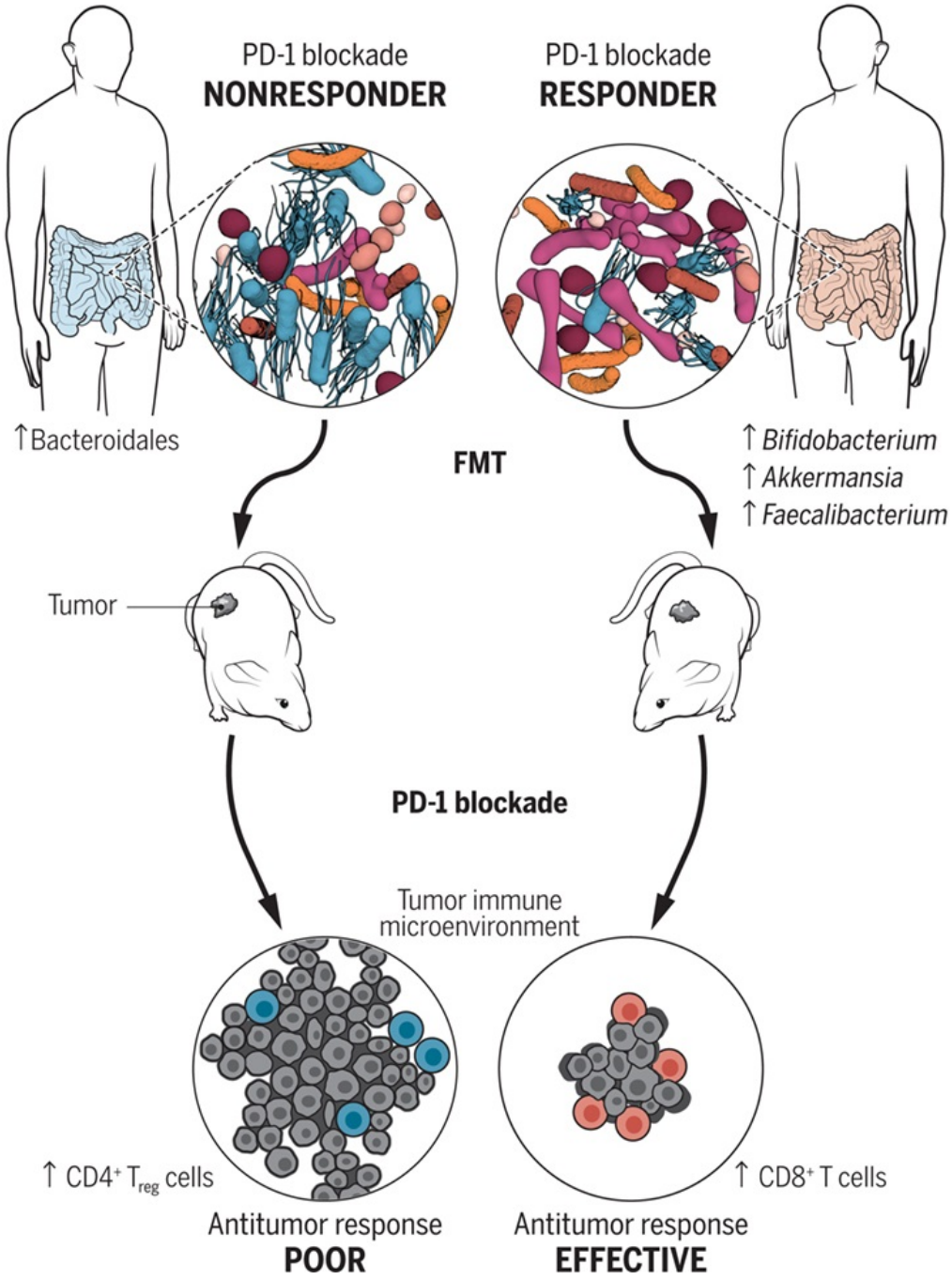
- Mission: generate resources for
  - Comprehensive characterization of microbiome
  - Analysis of role in health, disease
- Phase 1 (2008-2013)
  - Characterized microbial communities from 300 individuals across several body sites
  - Generated >14.23 terabytes of publicly-available information
- Phase 2 (2014-): Integrative Human Microbiome Project
  - h
  - Prediabetes







Intestinal microbiota influence cancer patient responses to immunotherapy



Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors.
Routy et al., Science. 2018 Jan 5; 359 (6371):91-97.

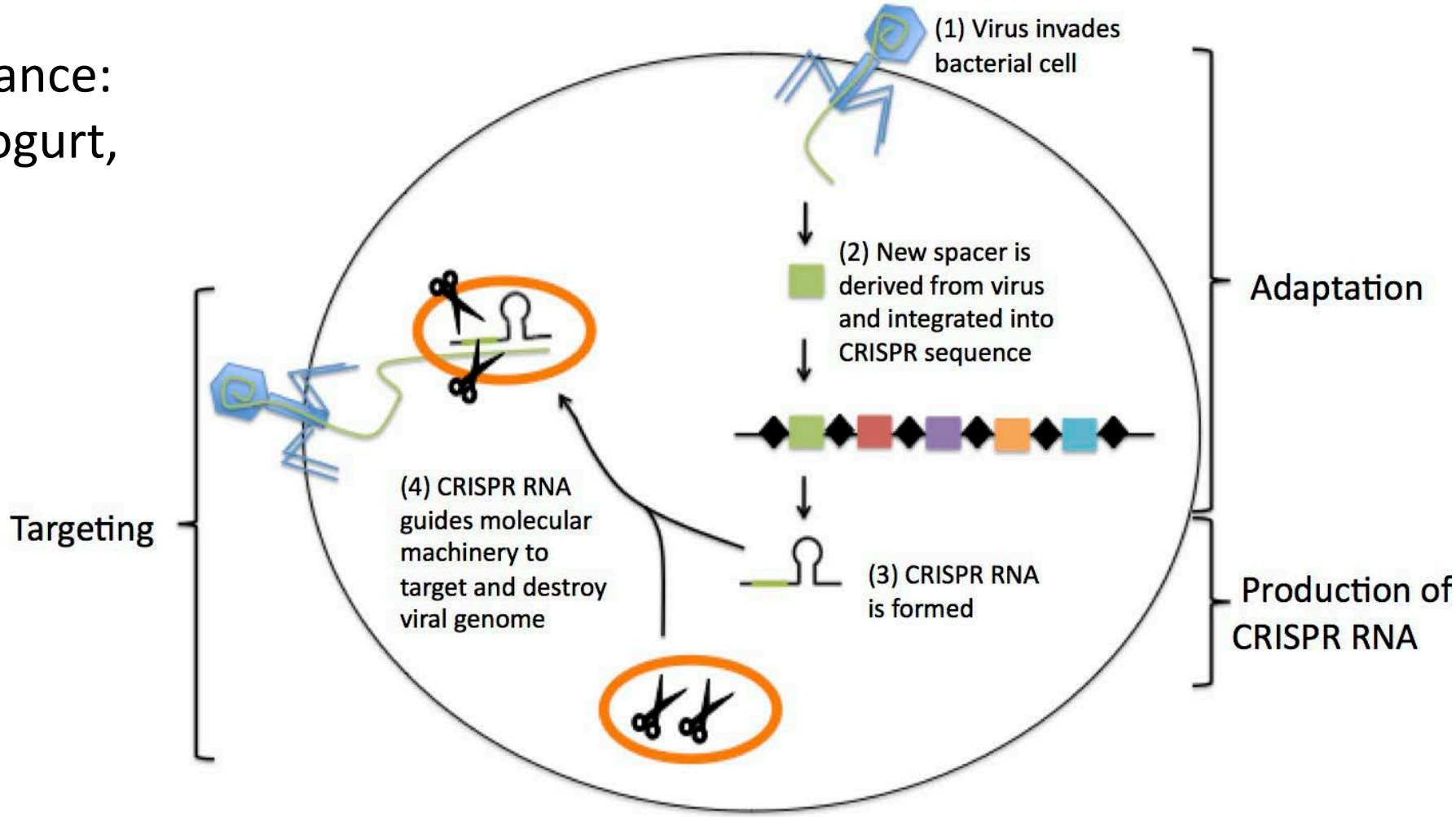
Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients.
Gopalakrishnan et al., Science. 2018 Jan 5; 359 (6371):97-103.

The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients.
Matson et al., Science. 2018 Jan 5;359(6371):104-108.

http://www.sciencemag.org/news/2015/11/gut-microbes-give-anticancer-treatments-boost

CRISPR-Cas9: An Ancient Defense Mechanism

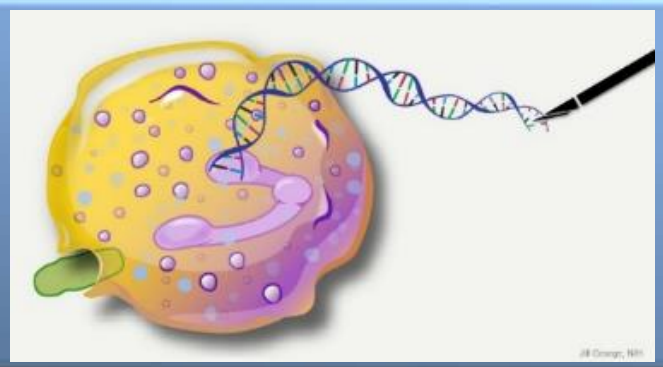
- Basic science advance: from studies of yogurt, bacteria viruses

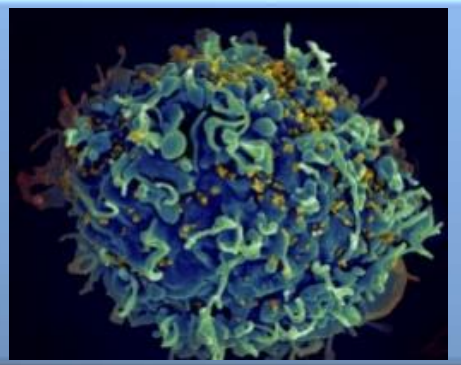
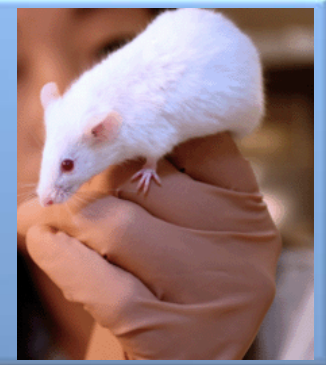


Adapted from Barrangou and Marraffini, Mol Cell (2014), and Harvard's Science in the News blog

CRISPR-Cas9 and Gene Editing

- Achieves targeted manipulation of genomes with enzyme (cas9) + guide RNA
  - Used to create knockouts and rapidly search for sequences (e.g., detect Zika in blood sample)
  - Activate and repress transcription using deactivated Cas9
- Has revolutionized basic molecular biology
- Producing mouse models has been greatly accelerated
- Newer technologies can correct point mutations – therapeutic use in humans?



CRISPR-Cas9: Toward 1st Cure for Molecular Disease?

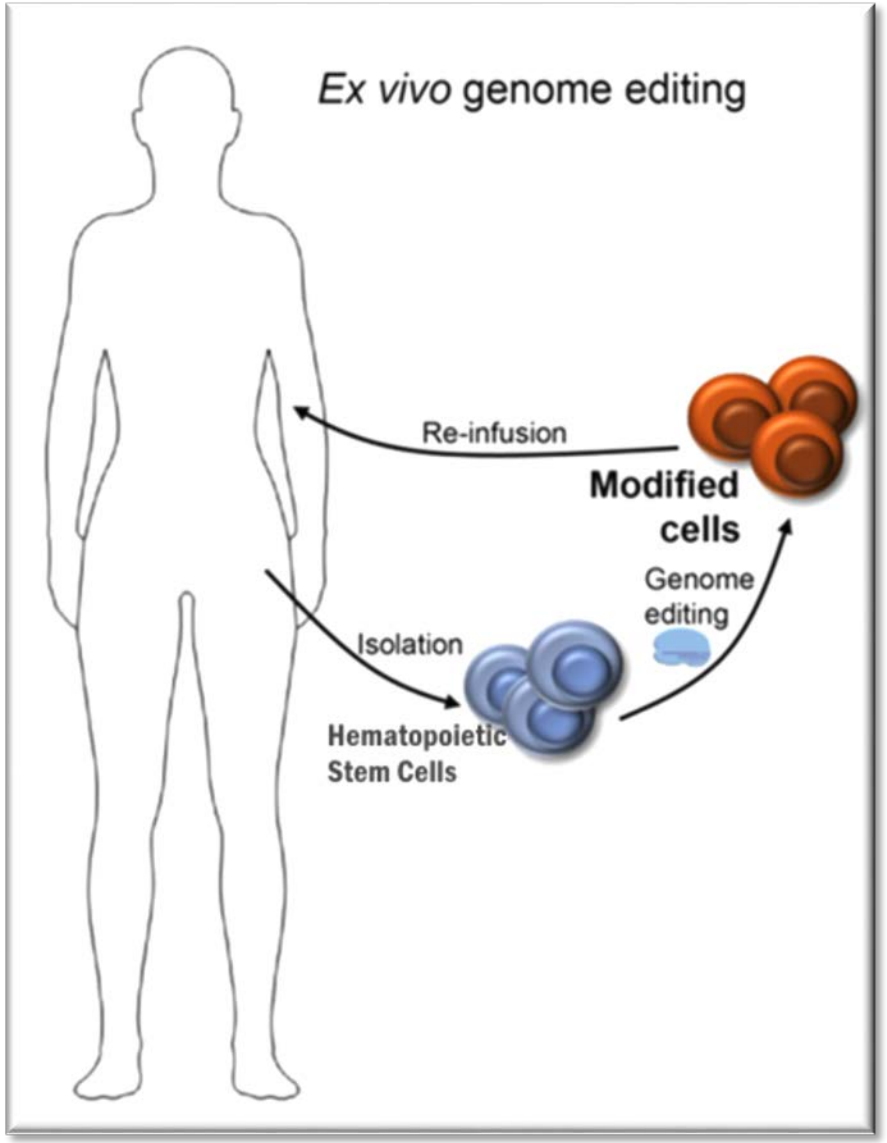
Sickle Cell Disease (SCD)

- **1910:** Disease described
- **1949:** Inheritance shown to be recessive
- **1957:** Genetic basis determined
- **1980:** Hemoglobin genes cloned
- **1998:** Hydroxyurea, first approved SCD drug
- **Today:** Bone marrow transplants, but few patients have match

CRISPR-Cas9: Toward 1st Cure for Molecular Disease?

Sickle Cell Disease (SCD)

- **Next decade:** Autologous bone marrow transplant with *ex vivo* somatic cell gene editing?
- In-human trials anticipated for 2018/2019
  - Stanford Center for Curative and Definitive Medicine: edit mutation that causes sickle cell
  - CRISPR Therapeutics: edit cells to produce fetal hemoglobin



New NIH Program:
Somatic Cell Genome Editing

Program will:

- Speed development of safe, effective editing tools for human patients
- Make tools widely available to researchers
- Reduce time, cost to develop new therapies

https://commonfund.nih.gov/editing

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

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  - Addressing Harassment in the Research Workplace
  - Next Generation of Researchers
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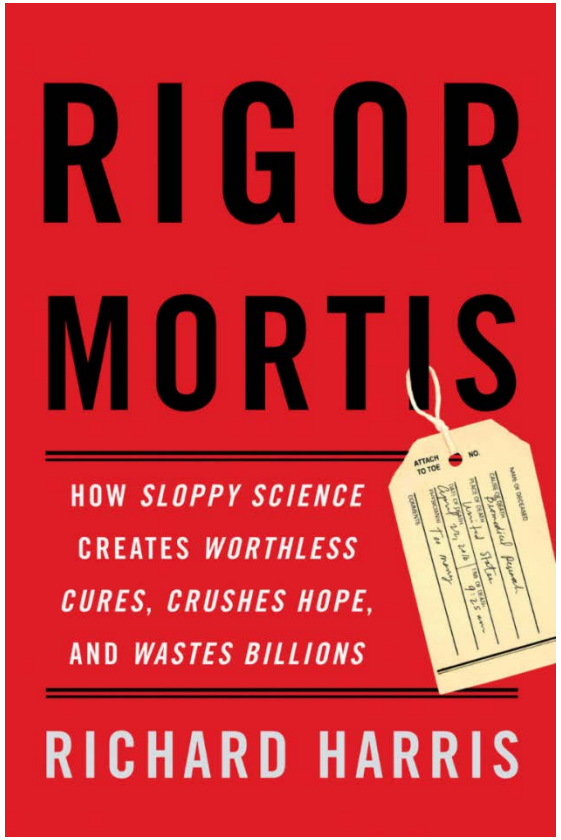
Rigor and Reproducibility in the News

Unreliable research

Trouble at the lab

Scientists like to think of science as self-correcting. To an alarming degree, it is not

"I SEE a train wreck looming," warned Daniel Kahneman, an eminent psychologist, in an open letter last year. The premonition concerned



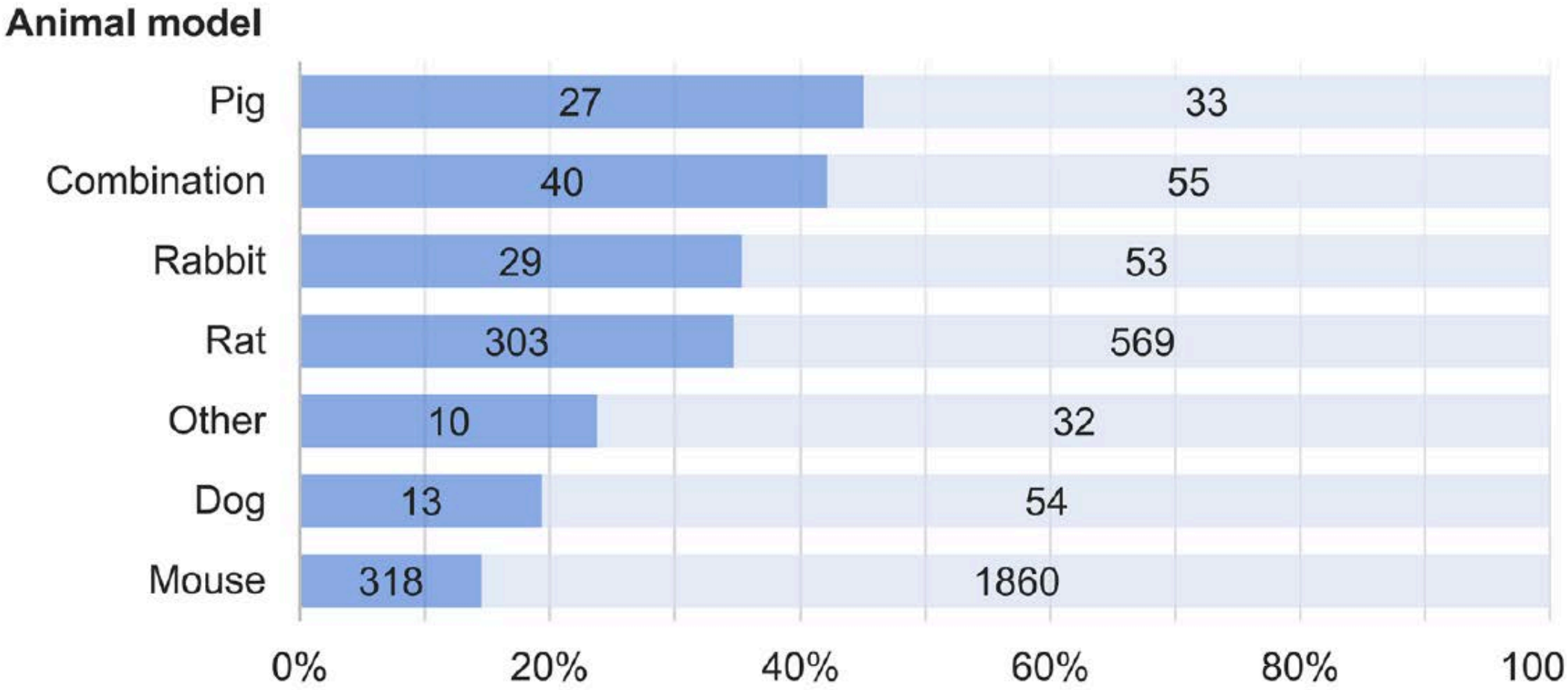
Problems:

- Animal models
- Cell lines
- Antibodies
- Poor study design
- Broken culture

http://www.economist.com/news/briefing/21588057-scientists-think-science-self-correcting-alarming-degree-it-not-trouble

Courtesy of Dr. Michael Lauer, OER

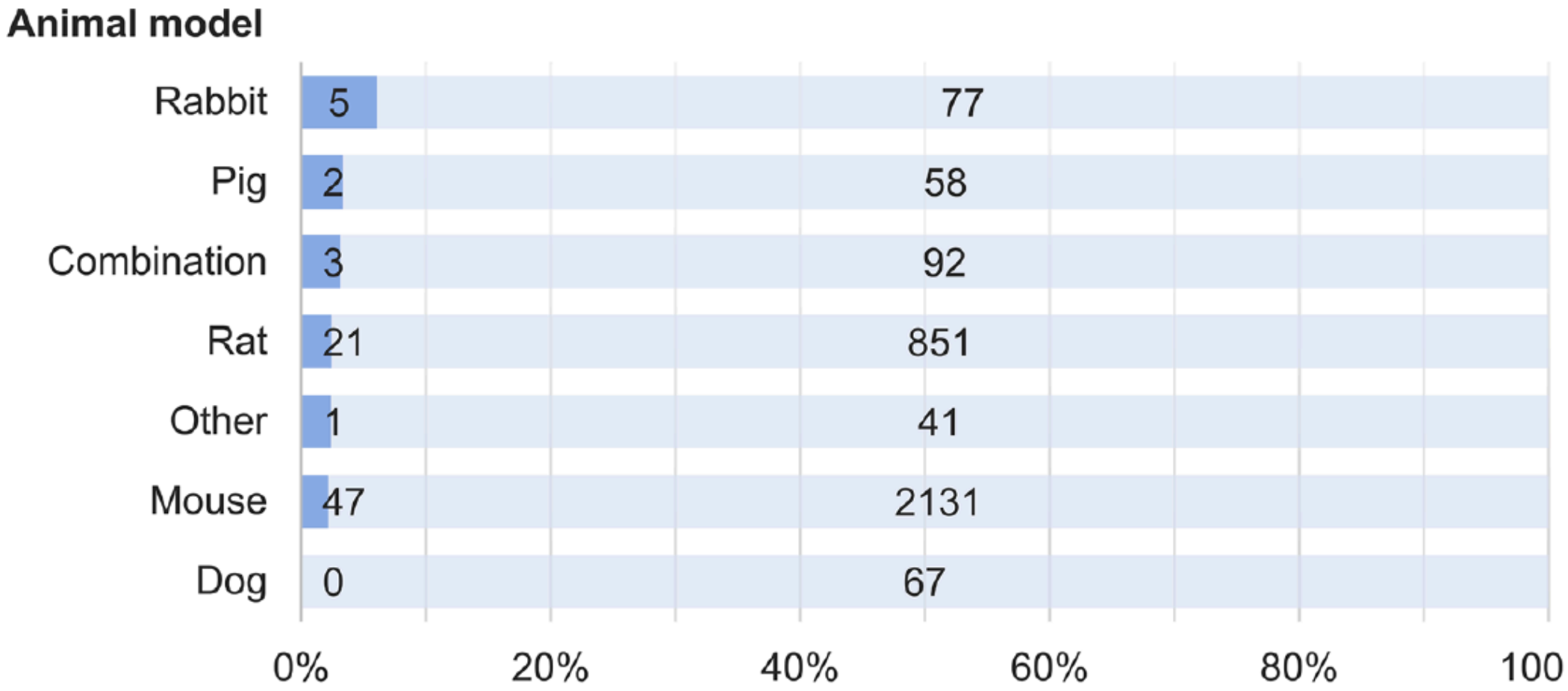
How Well Are We Doing? Randomization…



Ramirez FD, et al. Circulation Research. 2017;120:1916-26

Courtesy of Dr. Michael Lauer, OER

Sample Size Calculation …



Ramirez FD, et al. Circulation Research. 2017;120:1916-26

Courtesy of Dr. Michael Lauer, OER

ANALYSIS

"Power Failure"

Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[6] and Marcus R. Munafò[1]

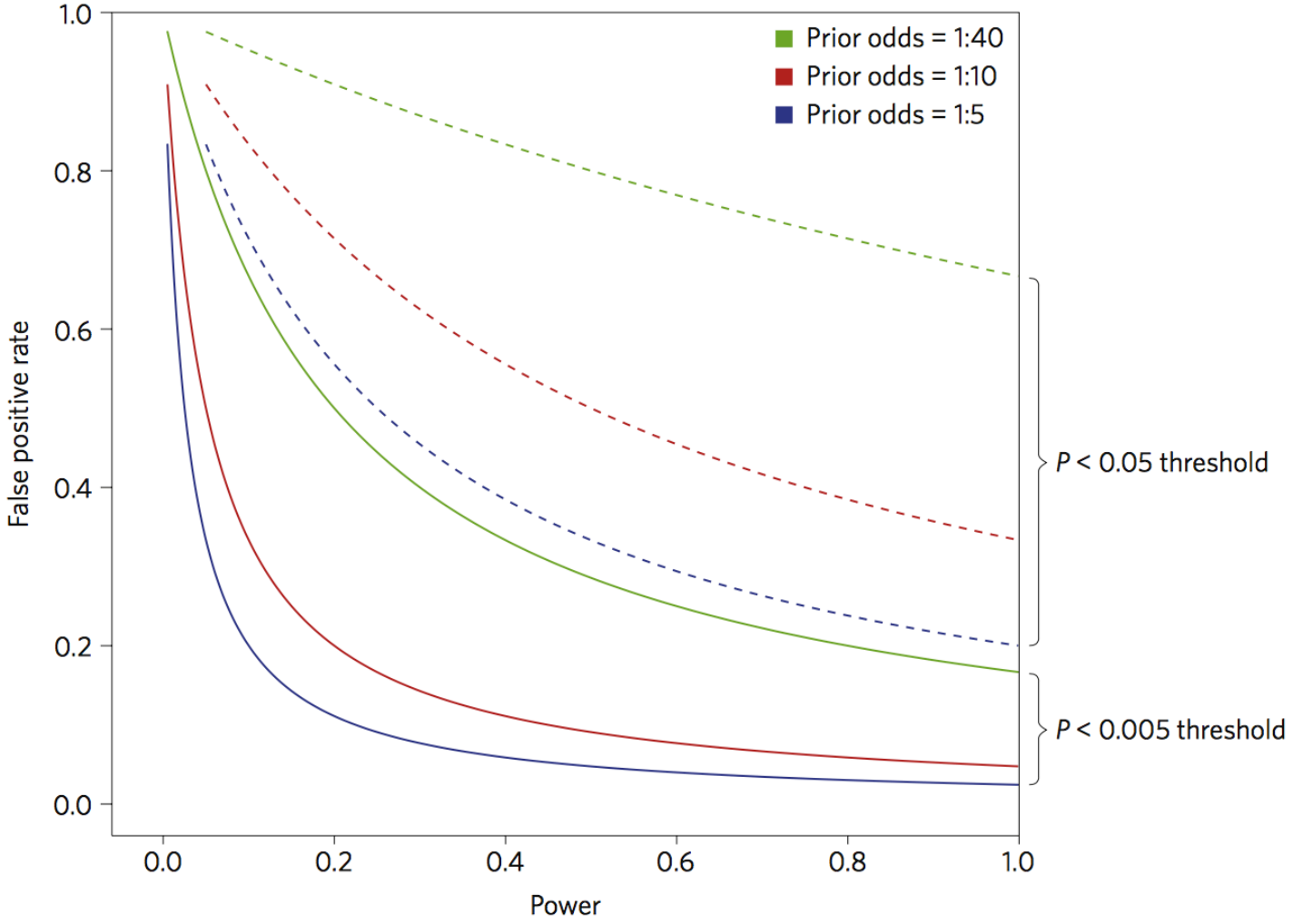
	Total animals used	Required *N* per study		Typical *N* per study	
		80% power	95% power	Mean	Median
Water maze	420	134	220	22	20
Radial maze	514	68	112	24	20

"What is particularly striking is the inefficiency of a continued reliance on small sample sizes. … Low power has an ethical dimension – unreliable research is inefficient and wasterful. This applies to both human and animal research."

Button KS et al. Nature Reviews Neuroscience. 2013;14:365-76

Courtesy of Dr. Michael Lauer, OER

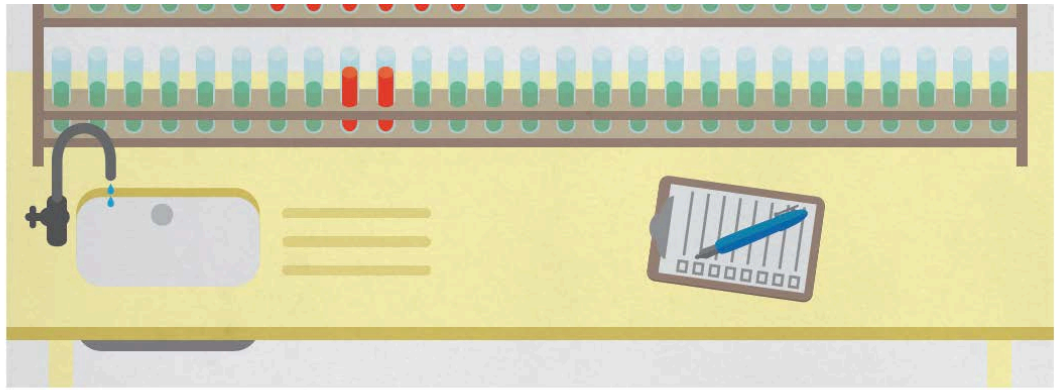
Is it Time to Redefine Statistical "Significance"?



"A much larger pool of scientists **are now asking a much larger number of questions**, possibly with much **lower prior odds** of success … Reducing the *P* value threshold for claims of new discoveries to 0.005 is an actionable step that will immediately improve reproducibility."

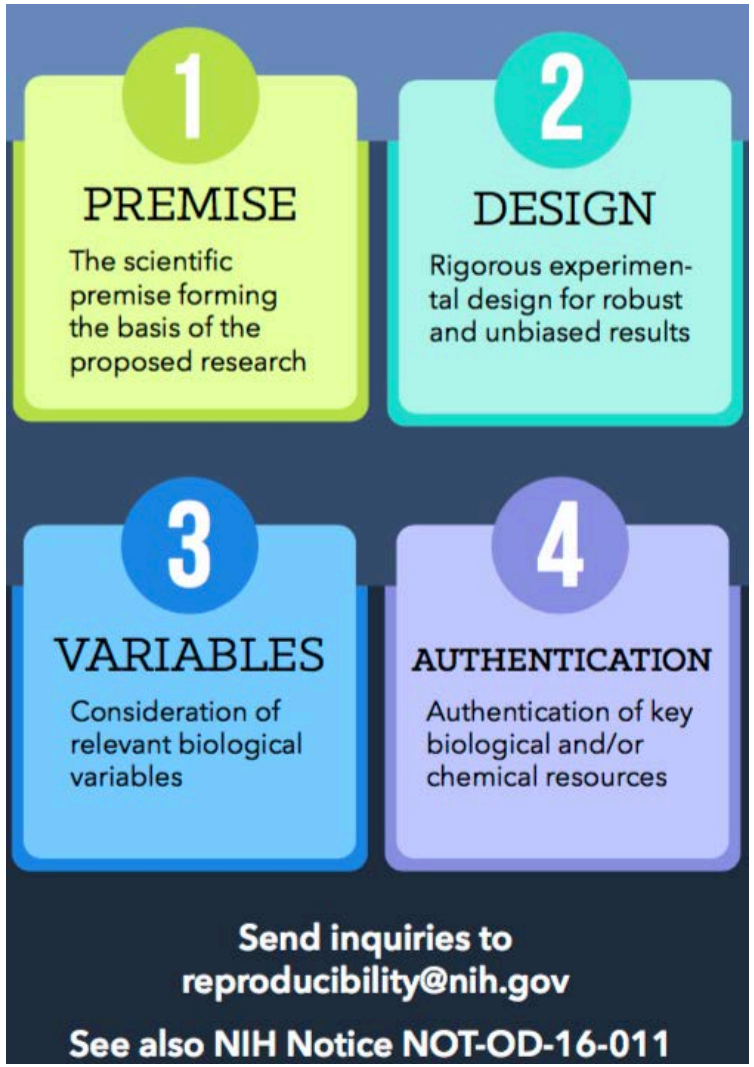
Nature Human Behavior 2017: https://www.nature.com/articles/s41562-017-0189-z.pdf

Key Components in NIH Applications



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.



https://grants.nih.gov/reproducibility/index.htm

Nature. 2014;505:612-13

But, Rigor and Reproducibility are Everyone's Responsibility

GBSI Global Biological Standards Institute™ ABOUT GBSI OUR W

Antibody Validation: Standards, Policies, and Practices

September 25, 2016 - September 27, 2016

Asilomar Conference Grounds

Enhancing Research Reproducibility:

Recommendations from the Federation of American Societies for Experimental Biology

EDITORIAL

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 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

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

Marcia McNutt
Editor-in-Chief
Science *Journals*

The FASEB Journal • Life Sciences Forum

Studying both sexes: a guiding principle for biomedicine

Janine Austin Clayton
Office of Research on Women's Health, National Institutes of Health, Bethesda, Maryland, USA

COLLOQUIUM INTRODUCTION

PNAS

Reproducibility of research: Issues and proposed remedies

David B. Allison[a], Richard M. Shiffrin[b,1], and Victoria Stodden[c]

Reproducibility has been one of the major tools science has used to help establish the validity and importance of scientific findings since *Philosophical Transactions of*

data," by Martijn J. Schuemie, George Hripcsak, Patrick B. Ryan, David Madigan, and Marc A. Suchard (4). This work leverages new large medical claims data to iden-

PNAS

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication

Marcia K. McNutt[a,1], Monica Bradford[b], Jeffrey M. Drazen[c], Brooks Hanson[d], Bob Howard[e],

Science 2014;346:1452-3; https://www.gbsi.org/event/asilomar/

FASEBJ. 2016;30:519-24 ; PNAS March 2018

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  - Rigor and Reproducibility
  - **Addressing Harassment in the Research Workplace**
  - Next Generation of Researchers
- Advancing Science to Improve Public Health

A Call for Action …

WORLD VIEW *A personal take on events*

Sexual harassment must not be kept under wraps

A female scientist who was harassed by a senior male colleague feels let down by the system that is supposed to protect her.

End harassment

Sexual harassment is a stain on science — and we must all take a stand against it.

"Science simply cannot afford to lose some of its best talent to boorishness."

http://www.nature.com/polopoly_fs/1.19196!/menu/main/topColumns/topLeftColumn/pdf/529257a.pdf
http://www.nature.com/polopoly_fs/1.13991!/menu/main/topColumns/topLeftColumn/pdf/502409b.pdf

National Academies Report

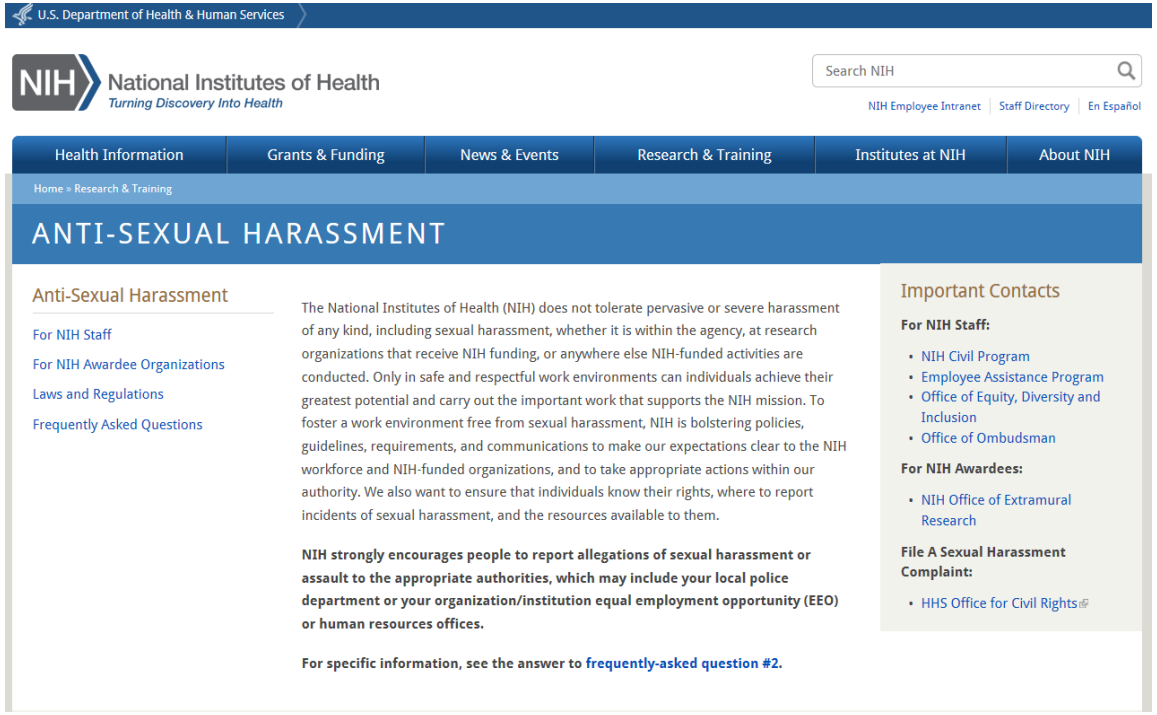
- Study co-funded by NIH

- The report describes three forms of sexual harassment:
  1) Unwanted sexual attention (verbal or physical sexual advances)
  2) Sexual coercion (when favorable treatment is conditioned on sexual activity)
  3) Gender harassment (sexist hostility, crude behavior)

..the cumulative effect of sexual harassment is a significant and costly loss of talent in academic science, engineering, and medicine, which has consequences for advancing the nation's economic and social well-being and its overall public health.

http://sites.nationalacademies.org/shstudy/index.htm

Supporting the workforce: anti-harassment initiatives



- Making resources available to the community, and sending a strong statement that sexual harassment and gender discrimination is unacceptable
- Establishing intramural program policies as an example
- Exploring other ways we could address the issue
- A culture change is needed, and universities – as the employers of NIH-funded scientists – must also take action

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Aging of the US Science Workforce

PNAS

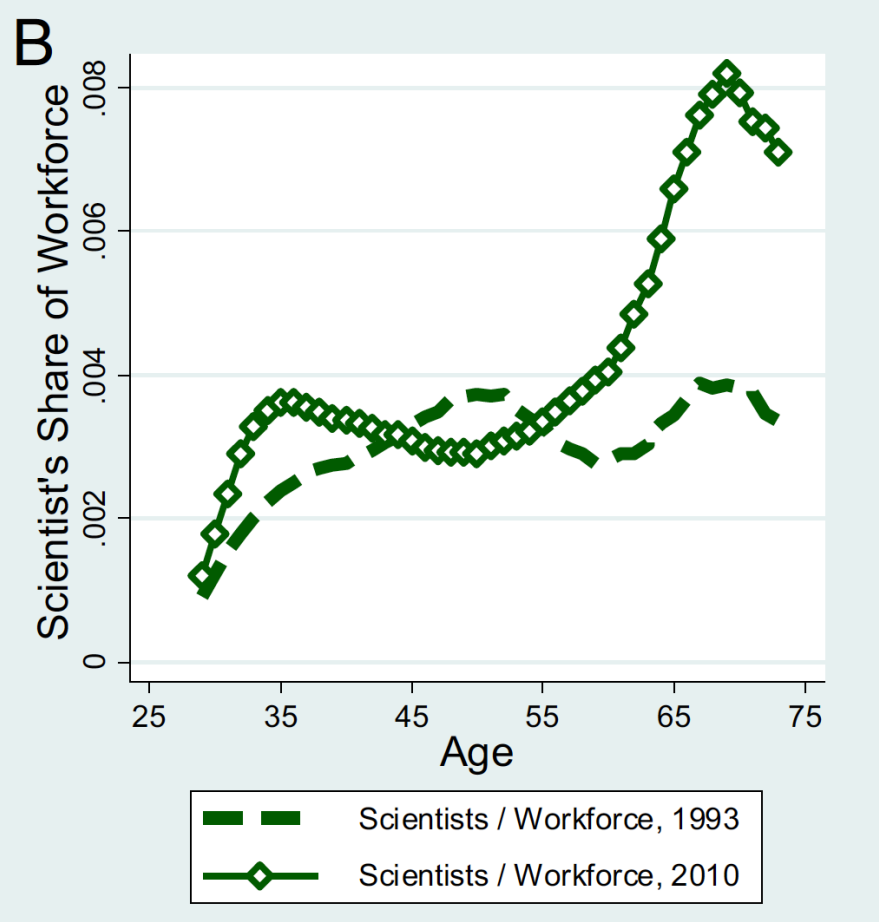
CrossMark

Why the US science and engineering workforce is aging rapidly

David M. Blau[a,b,1] and Bruce A. Weinberg[a,b,c]

[a]Department of Economics, Ohio State University, Columbus, OH 43210; [b]Institute of Labor Economics (IZA), 53113 Bonn, Germany; and [c]National Bureau of Economic Research, Cambridge, MA 02138

"The scientific workforce has aged rapidly in recent years relative to the workforce as a whole…
Decline in retirement … "



www.pnas.org/cgi/doi/10.1073/pnas.1611748114

What Young Scientists Are Saying

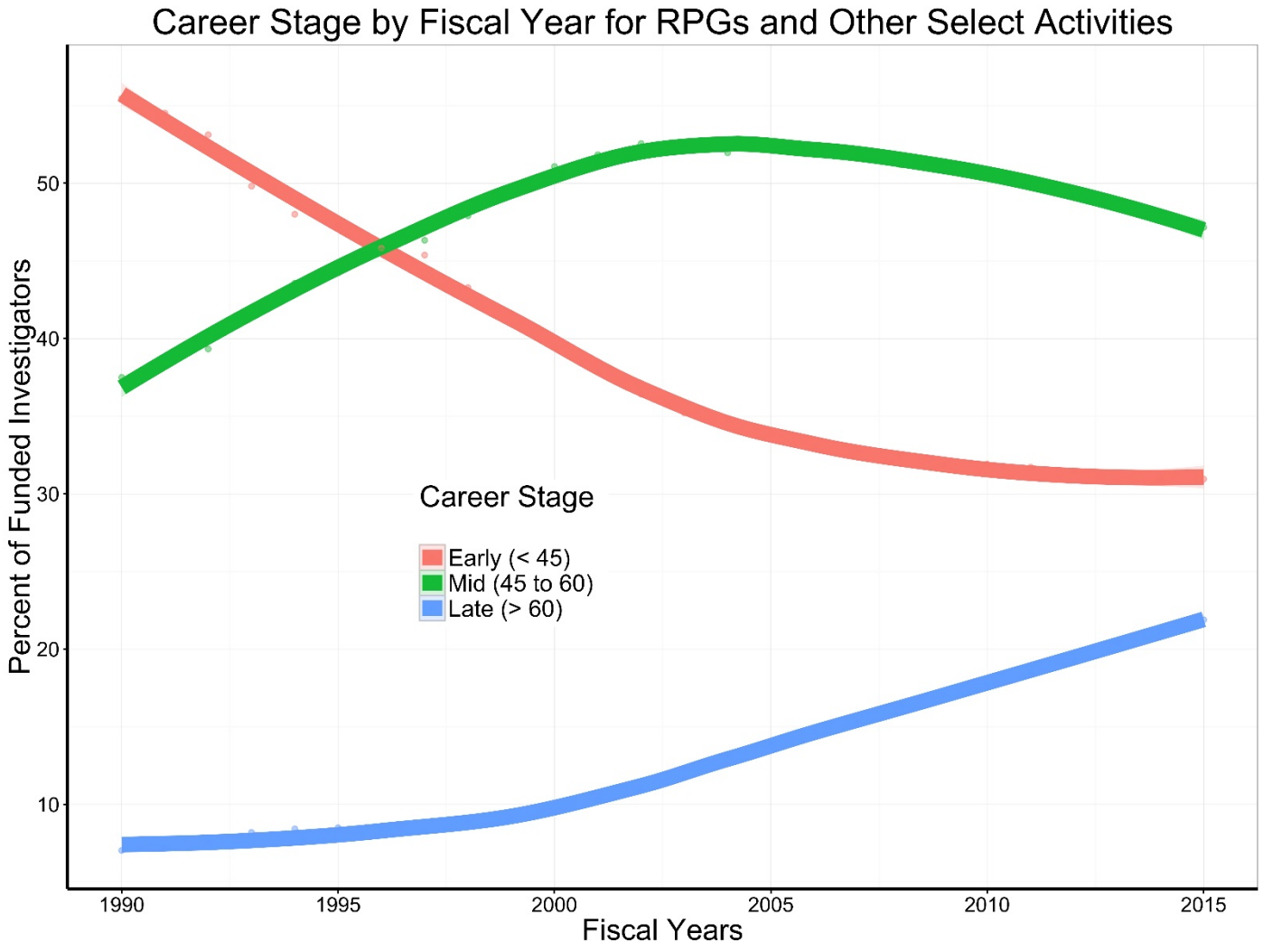
SUFFERING IN SCIENCE

We asked young scientists to tell us their concerns. This is what they said.

- Desperate pursuit of grants
- No time for science
- Extreme competition … to cut corners
- Dependence on senior scientists
- Administrative overload ... No help
- Long hours

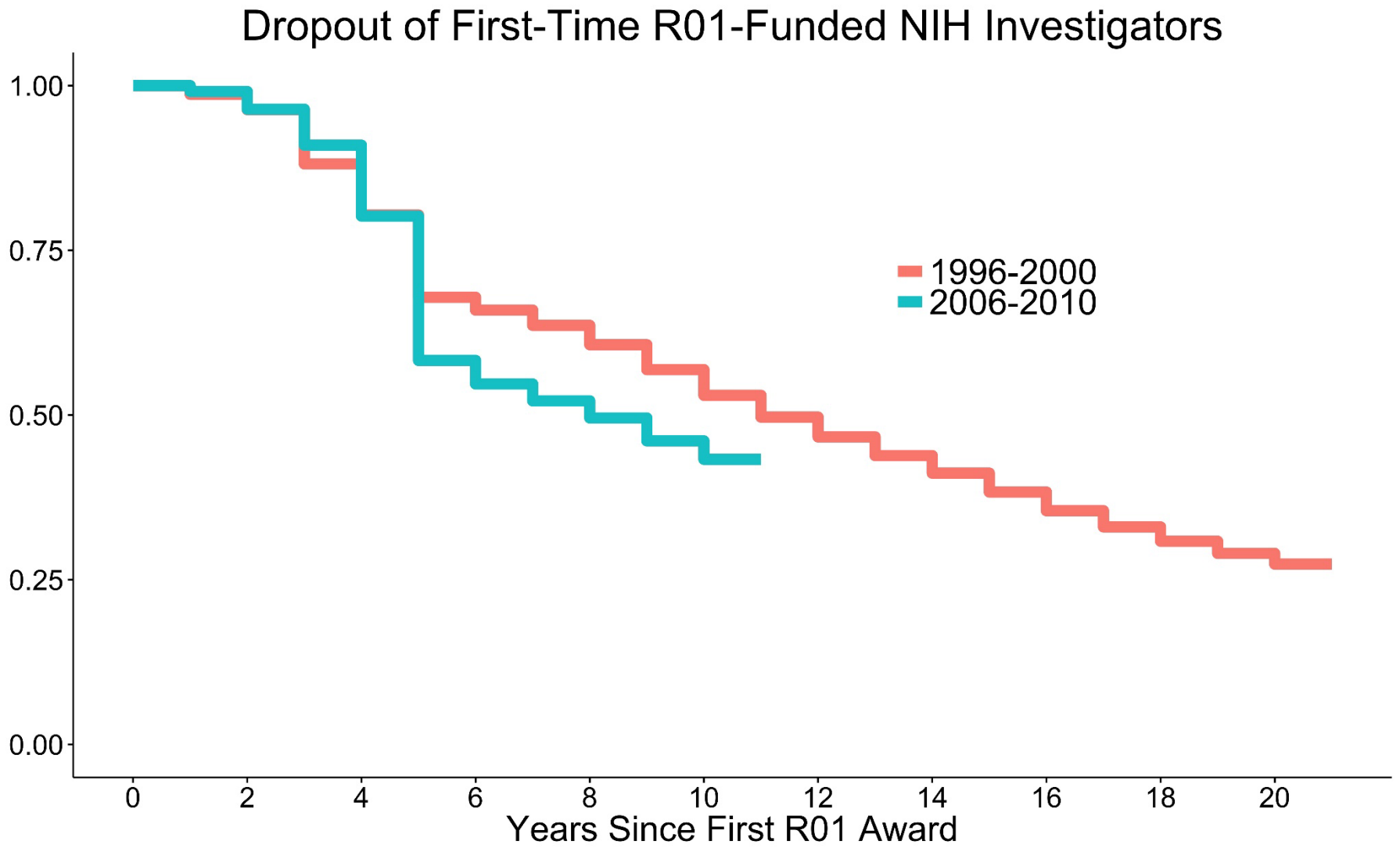
Nature 2016;538:446-9

NIH-Supported Workforce Analyses Also Show This

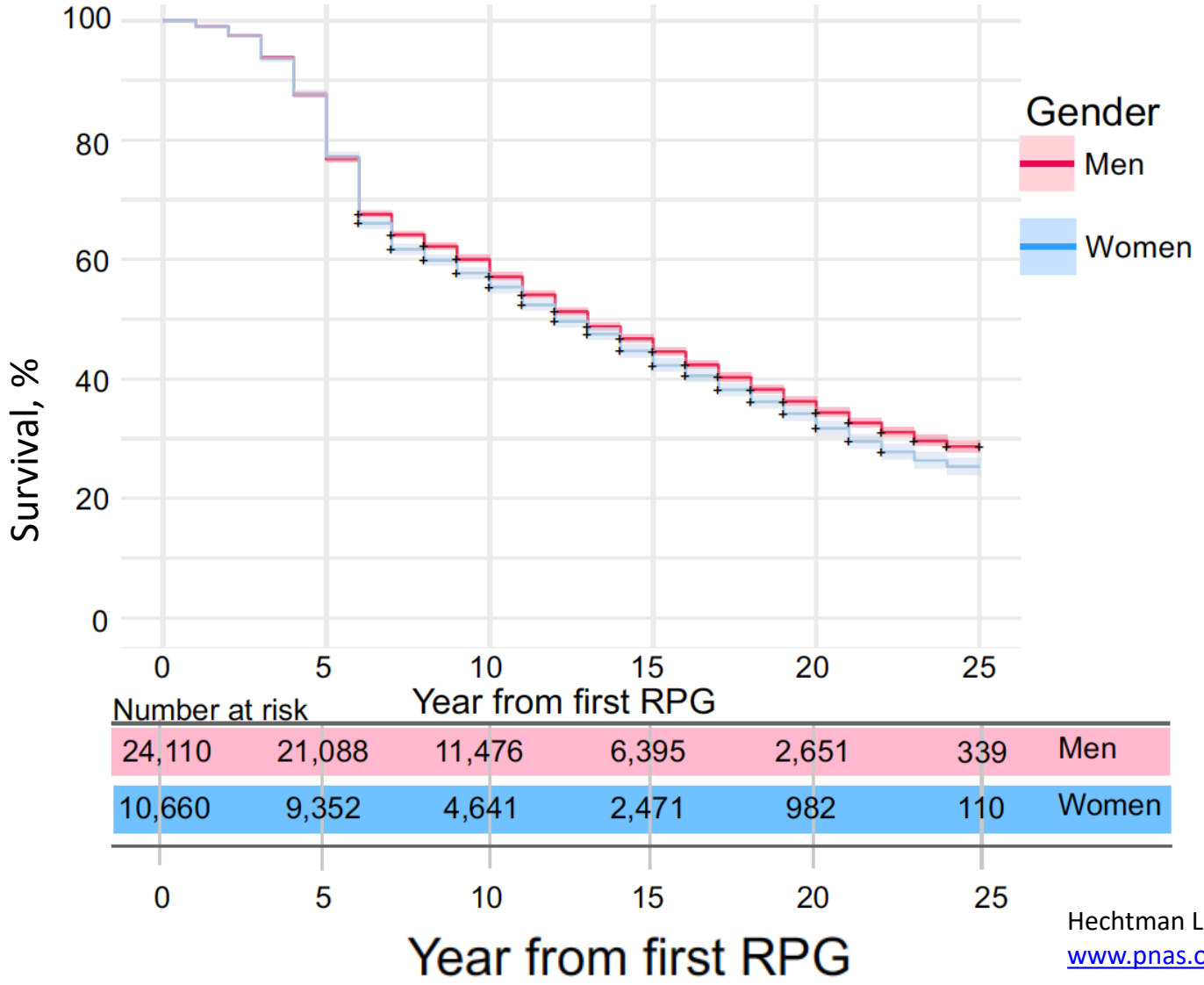


NIH Office of Extramural Research

Hard to Break In, Hard to Stay In



A Bit More So for Women



NIH/NIGMS

Hechtman LA et al PNAS 2018
www.pnas.org/cgi/doi/10.1073/pnas.1800615115

CONGRESS.GOV | Legislation

H.R.34 - 21st Century Cures Act

114th Congress (2015-2016) | Get alerts

Directs NIH Director to promote policies that will promote **earlier independence and increased funding** for new investigators

404M.Next generation of researchers (a)Next Generation of Researchers Initiative - *There shall be established within the Office of the Director of the National Institutes of Health, the* ***Next Generation of Researchers Initiative*** *(referred to in this section as the "Initiative"), through which the Director shall* ***coordinate all policies and programs*** *within the National Institutes of Health* ***that are focused on promoting and providing opportunities for new researchers and earlier research independence****.*

ACD Next Generation Researchers Initiative Working Group (NGRI WG)

- The NIH Director established a working group of the ACD, the NGRI WG, to refine and implement the initiative

- The NGRI WG membership is diverse and includes investigators at all levels – from graduate student to professor - working in different types of institutions, and engaged in a broad range of disciplines

Major Themes Discussed

- There is an urgent need to protect junior investigators for the future of the research workforce
- There is an equally urgent need to stabilize the career trajectories of successful and productive mid-career investigators
- Diversity must be enhanced and actively pursued
- Introduction of the “investigator at risk” category
  - Motivated by analyses showing that previous “early established investigator” definitions did not produce the desired effects
  - Emphasizes the stabilization of the workforce
  - Preempts the need to narrowly target the source of funds

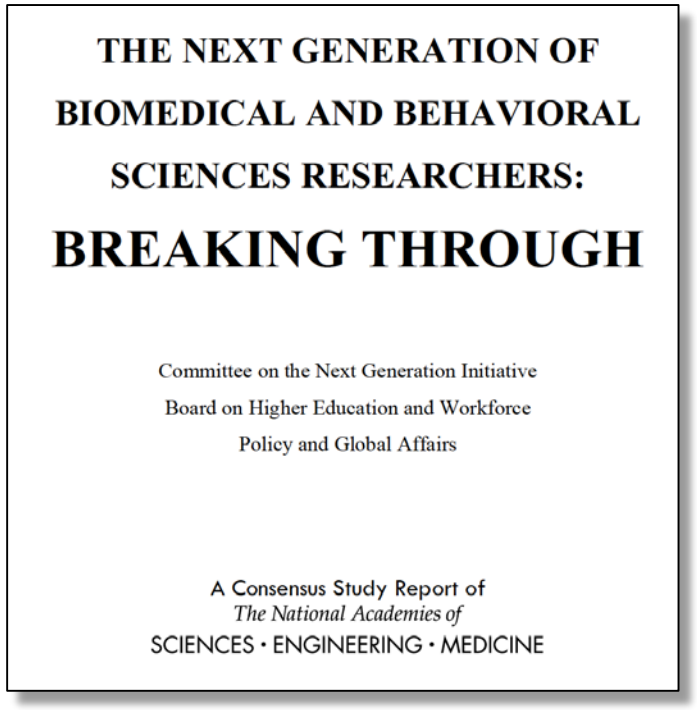
Draft recommendations presented in June include

- Shift the focus to supporting highly meritorious, “at risk”, investigators
- Stratification of peer review to ensure that applicants in similar career stages (e.g., ESIs) are evaluated together, in the same way
- Training, fellowship, and career awards as an effective space for integrating the importance of enhancing diversity as part of application review process
- Potential for changing biosketch instruction:
  - Asking applicants to address recent contributions to science, in existing biosketch format

NASEM NGRI Report

- Several recommendations under NIH purview along the same lines as WG thinking

- ACD NGRI WG discussing NASEM recommendations under NIH's purview



NGRI Working Group's next steps

- NIH's interim plans
  - Hope to fund ~1100 early-stage investigators across NIH in 2018
  - Drawing attention to meritorious at-risk investigators
- Further development of recommendations
- Final report at the December 2018 ACD meeting

A Team Effort

"The NASEM report presents its assessment and recommendations within a multi-actor systems context:

> *'Many stakeholders tend to hold the federal government responsible for this system, placing blame for failures at the feet of NIH, the principal funder of biomedical research. Doing so, however, obscures the important role that other organizations, particularly universities, must play in developing and implementing solutions.'*

We welcome the chance to work with other stakeholders to find those solutions."

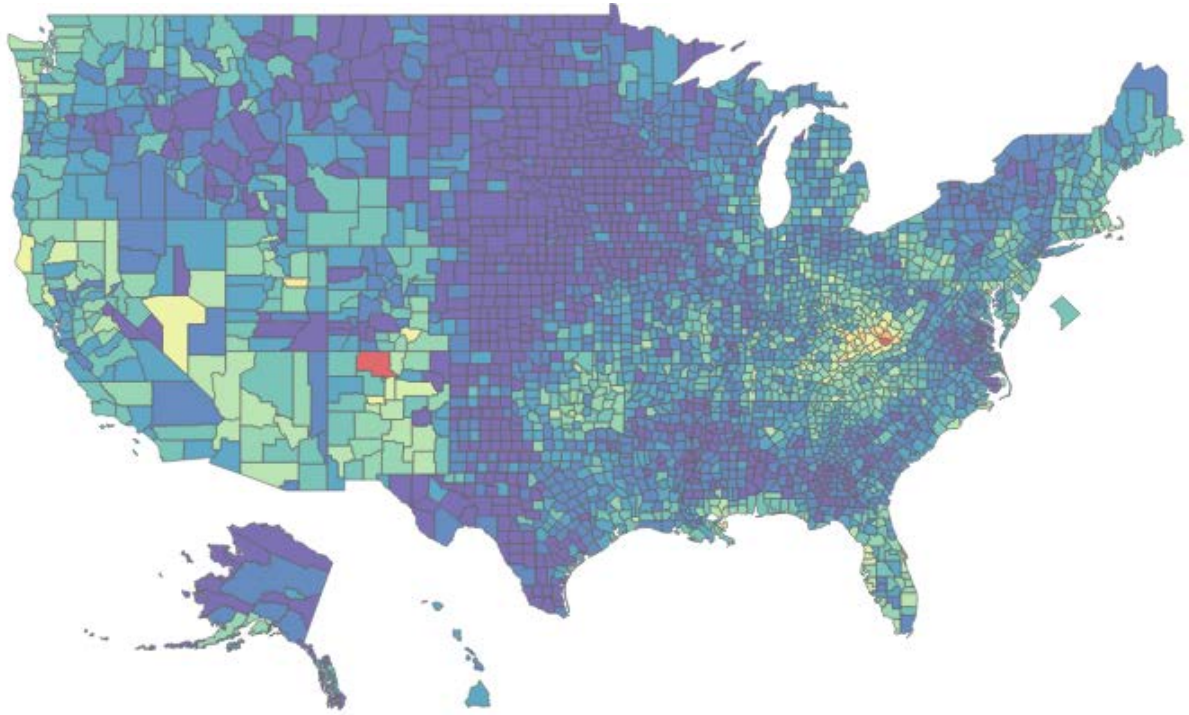
- Dr. Michael Lauer, Deputy Director for Extramural Research, NIH & NIH Director Dr. Francis Collins
  "**The Issue that Keeps Us Awake at Night"**
  https://nexus.od.nih.gov/all/2018/05/04/the-issue-that-keeps-us-awake-at-night

Topics for Today

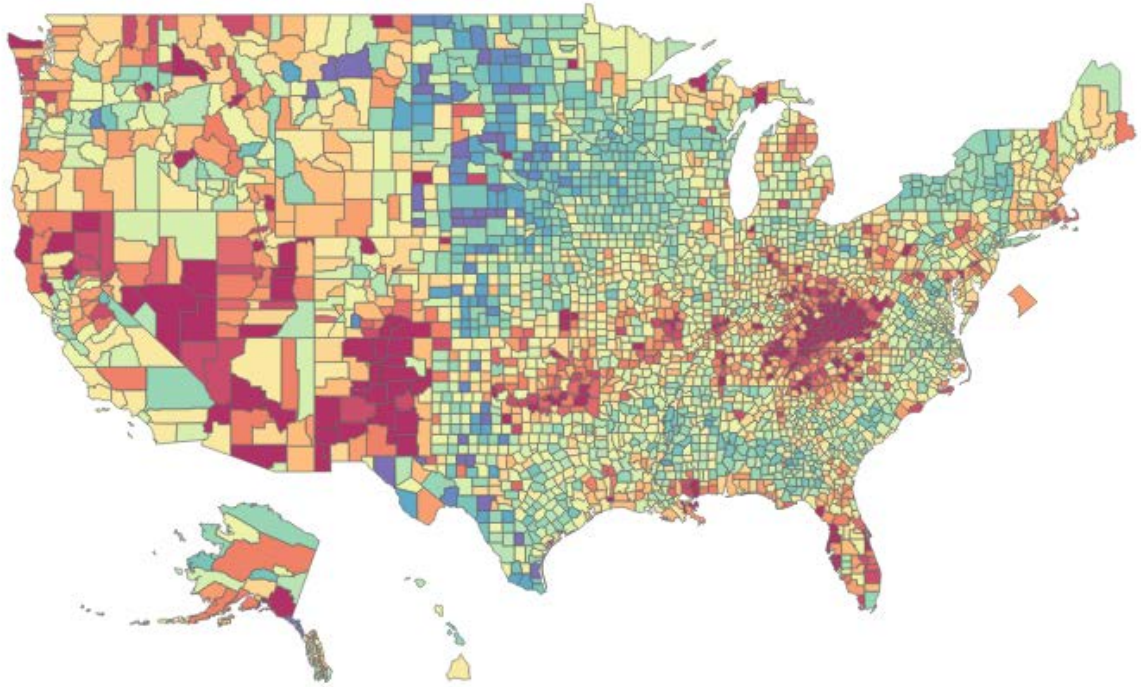
- Introduction
- Unraveling Life's Mysteries through Basic Research
- Supporting Research Essentials
- **Advancing Science to Improve Public Health**
  - **Helping End Addition Long-Term (HEAL) Initiative**

The Crisis: National Overdose Death Rates

1999



2016



Legend for estimated age-adjusted death rate (per 100,000 population)

<2	8-9.9	16-17.9	24-25.9
2-3.9	10-11.9	18-19.9	26-27.9
4-5.9	12-13.9	20-21.9	28-29.9
6-7.9	14-15.9	22-23.9	30+

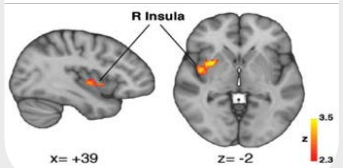
Source: https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm

NIH Responds to the Crisis With Research

Pain Management
Safe, more effective strategies

Non-Pharmacological Treatments (e.g., TMS)

Biomarkers for Pain



Vaccines or Antibodies Against Opioids or Pain Producing Chemicals

Non-Opioid Analgesics

Respiratory Stimulation Devices

Opioid Addiction Treatment
New and innovative medications and technologies

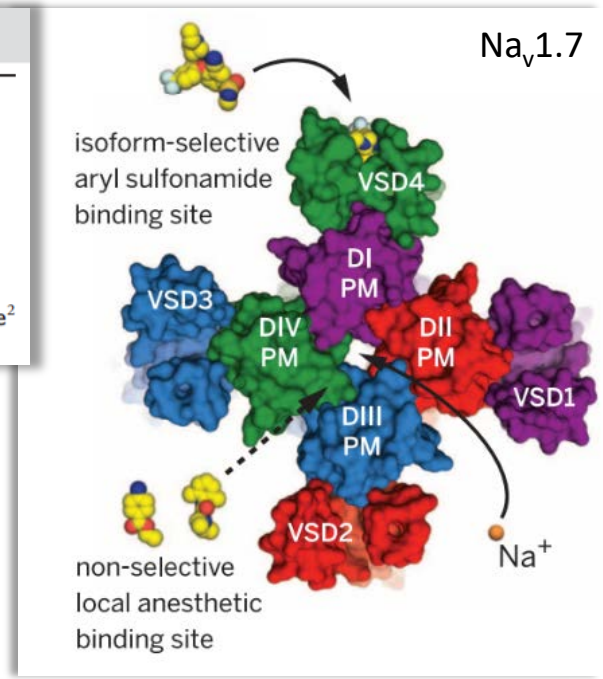
Overdose Reversal
Interventions to reduce mortality and link to treatment

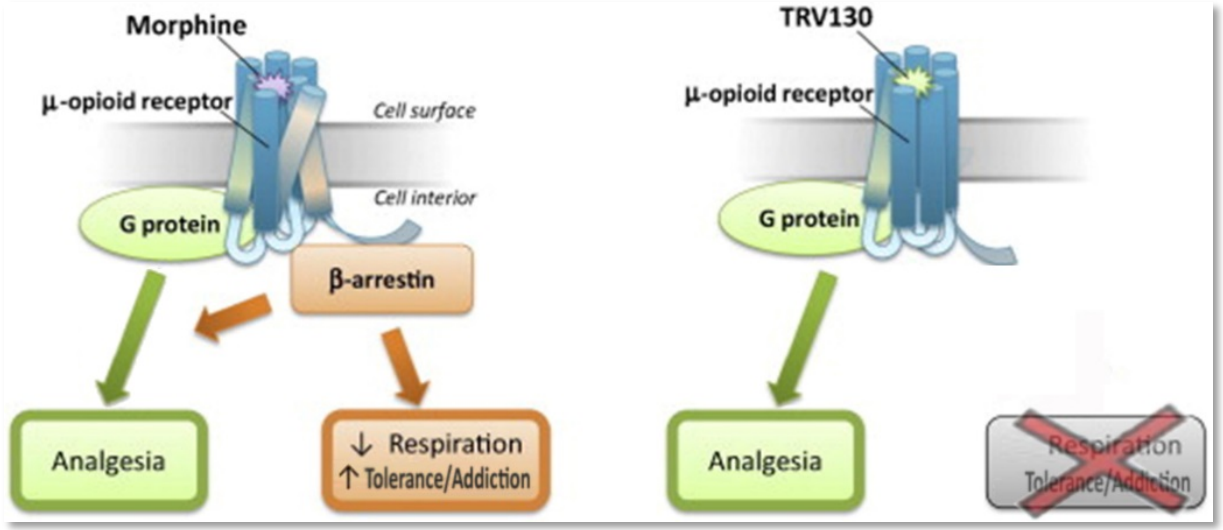
Some Successful NIH-Supported Innovations

NATURE|Vol 444|14 December 2006

An *SCN9A* channelopathy causes congenital inability to experience pain

James J. Cox[1]*, Frank Reimann[2]*, Adeline K. Nicholas[1], Gemma Thornton[1], Emma Roberts[3], Kelly Springell[3], Gulshan Karbani[4], Hussain Jafri[5], Jovaria Mannan[6], Yasmin Raashid[7], Lihadh Al-Gazali[8], Henan Hamamy[9], Enza Maria Valente[10], Shaun Gorman[11], Richard Williams[12], Duncan P. McHale[12], John N. Wood[13], Fiona M. Gribble[2] & C. Geoffrey Woods[1]





NIH Helping to End Addiction Long-term (HEAL) Initiative

- Funding of $500M/year provides opportunity to:
  - Improve prevention and treatment strategies, both in clinic and real world settings, for opioid misuse and addiction
  - Enhance pain management by furthering understanding of neurobiology of pain, developing non-addictive treatments, and building a Clinical Trial Network for pain
  - Develop shared platforms through public and private partners
- Coordinating with the Surgeon General, our sister HHS agencies, local government officials

NIH HEAL Initiative: Selected Priorities for 2018

Opioid Use Disorder

- Improve therapeutic approaches to addiction and overdose
- Carry out real world implementation research to optimize interventions
- Evaluate treatments, consequences of Neonatal Opioid Withdrawal Syndrome (NOWS)

Pain Management

- Understand neurobiology of chronic pain
- Develop new non-addictive treatments for pain
- Build Clinical Trial Network for chronic pain

Additional Research Priorities Coming in FY19

- Precision MAT and other treatments for addiction
- Non-pharmacological treatments
- Precision prevention for OUD
- Integrated models of pain management
- Linkages between pain, addiction, mental health and addiction



Follow HEAL and Find Funding Opportunities on our Website…

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Turning Discovery Into Health

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NIH HEAL INITIATIVE

HEAL Initiative

- Addiction Treatments
- Pain Management
- Public-Private Partnership
- Research Plan
- Funding
- Events
- News and Announcements
- Resources

Funding

NIH research program to explore the transition from acute to chronic pain

NIH outlines research plan to address the opioid epidemic

About the NIH HEAL Initiative

In April 2018, NIH launched the HEAL (Helping to End Addiction Long-term) Initiative, an aggressive, trans-agency effort to speed scientific solutions to stem the national opioid public health crisis. This Initiative will build on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction,

Email Updates

Sign up to receive email updates about the HEAL Initiative.

Sign up for updates

www.nih.gov/heal-initiative




NIH...

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Turning Discovery Into Health