Biomedical Research Opportunities: A View from NIH

University of Georgia
September 21, 2018

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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.
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NIH Funding for FY 2017:
• UGA: 140 awards, >$53.9 M
• GA: 1,237 awards, >$537.4 M
NIH Extramural & Intramural Funding

FY 2018 Budget: $37 Billion

Spending at NIH

Spending Outside NIH
Continued Support of NIH

- Essential aspects of supporting the NIH mission and advancing our human health include:
  - Strategic research investments
  - Enhanced stewardship
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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
  - Pregnancy & preterm birth
  - Inflammatory bowel disease
  - Prediabetes

www.hmpdacc.org
Intestinal microbiota influence cancer patient responses to immunotherapy


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
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  - Addressing Harassment in the Research Workplace
  - Next Generation of Researchers
- Advancing Science to Improve Public Health
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.

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

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

### How Well Are We Doing? Randomization...

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<thead>
<tr>
<th>Animal model</th>
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Courtesy of Dr. Michael Lauer, OER
## Sample Size Calculation ...

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<td>Mouse</td>
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</tr>
</tbody>
</table>


Courtesy of Dr. Michael Lauer, OER
"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."

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

But, Rigor and Reproducibility are Everyone’s Responsibility

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

Reproducibility of research: Issues and proposed remedies

David B. Allison*, Richard M. Shiffrin*, and Victoria Stodden

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 Hipps, Patrick B. Ryan, David Magidson, and Marc A. Suchard (4). This work leverages new large medical claims data to iden-
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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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“The scientific workforce has aged rapidly in recent years relative to the workforce as a whole... Decline in retirement ...”
What Young Scientists Are Saying

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

*SUFFERING IN SCIENCE*

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

*Nature* 2016;538:446-9
NIH-Supported Workforce Analyses Also Show This
Hard to Break In, Hard to Stay In

Dropout of First-Time R01-Funded NIH Investigators

- 1996-2000
- 2006-2010

Years Since First R01 Award

NIH Office of Extramural Research
A Bit More So for Women

Survival, %

Number at risk

Year from first RPG

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<th>Women</th>
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<td>982</td>
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<tr>
<td>25</td>
<td>339</td>
<td>110</td>
</tr>
</tbody>
</table>

Gender

- Men
- Women

Hechtman LA et al PNAS 2018
www.pnas.org/cgi/doi/10.1073/pnas.1800615115
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
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  - Helping End Addiction Long-Term (HEAL) Initiative
The Crisis: National Overdose Death Rates

1999

2016

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

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

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
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...

NIH HEAL INITIATIVE

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

Funding

NIH HEAL INITIATIVE

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.

www.nih.gov/heal-initiative
NIH...

Turning Discovery Into Health