Congratulations

Linda Harootyan, GSA
Deputy Executive Director

Retiring to an advisory role

Marie Bernard, M.D., NIH
Deputy Director, NIA

Donald P. Kent Award
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.”
Biomedical Research’s Impact on U.S. Health

Accomplishments

- Cardiovascular disease death rates have fallen > 70% in the last 60 years
- Cancer death rates now falling ~1% per year; each 1% drop saves ~$500 billion
- HIV therapies enable people in their 20s to live a full life-span

U.S. Life Expectancy
Economic and social implications of aging societies

Sarah Harper

The challenge of global population aging has been brought into sharper focus by the financial crisis of 2008. In particular, growing national debt has drawn government attention to two apparently conflicting priorities: the need to sustain public spending on pensions and health care versus the need to reduce budget deficits. A number of countries are consequently reconsidering their pension and health care provisions, which account for up to 40% of all government spending in advanced economies. Yet population aging is a global phenomenon that will continue to affect all regions of the world. By 2050 there will be the same number of old as young in the world, with 2 billion people aged 60 or over and another 2 billion under age 15, each group accounting for 21% of the world’s population.

Fig. 3. Demographic deficit in OECD member nations. Observed and projected size of the incoming (20–24) and outgoing (60–64) working-age cohorts in OECD countries, 2000–2030. Source: OECD figures, Oxford Institute of Population Ageing, 2012.
Public Law 93-296
93rd Congress, S. 755
May 31, 1974

An Act

To amend the Public Health Service Act to provide for the establishment of a National Institute on Aging.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Section 1. This Act may be cited as the “Research on Aging Act of 1974”.

Sec. 2. The Congress finds and declares that—

(1) the study of the aging process, the one biological condition common to all, has not received research support commensurate with its effects on the lives of every individual;

1974: GSA Plays Major Role in NIA’s Development

By Robert Binstock, PhD

May 4, 1976
Vol. XXVIII, No. 9
NIH GeroScience Interest Group (GSIG): NIA – and Beyond!

- Trans-NIH organization of 20 Institutes to:
  - Raise awareness of the relevant role played by aging biology in the development of diseases and disabilities
  - Promote discussion and co-funding of initiatives
- Organized 2013 Geroscience Summit, leading to:
  - Publication of a set of opinion pieces
  - Planning of a future meeting
  - Drafting of a book on geroscience
  - Funding an R24 (resource grant)
- Today in *Cell*: published article, “Geroscience: Considering aging as a common driver of chronic diseases and a target for novel interventions”
Aging Research: Making Headlines

**THE LANCET**

Comment

Health in an ageing world—what do we know?

Richard Suzman, John R Beard, Ties Boerma,
Somnath Chatterji

Published online November 6, 2014

**THE LANCET**

Perspectives

Profile

Richard Suzman: helping the world to grow old more gracefully

Published online November 6, 2014
Aging Research—Where Do We Stand and Where Are We Going?

Leonard Guarente
Creative Minds: REST-ling with Alzheimer’s Disease
Posted on March 25, 2014 by Dr. Francis Collins

Caption: The REST protein (green) is dormant in young people but switches on in the nucleus of normal aging human neurons (top), apparently providing protection against diseases. In these neurons REST is lost in neuron nuclei, including abnormal neurons associated with early stages of Alzheimer’s disease.
Credit: Yankner Lab, Harvard Medical School

Creative Minds: Path to Longevity May Start With ... Bats and Mole Rats!
Posted on May 8, 2014 by Dr. Francis Collins

Caption: DNA studies are unraveling the secrets of these mammals (clockwise from top left): naked mole rat, bowhead whale, and Brandt’s currey.
Credit: Clockwise from top left: Smithsonian’s National Zoo, National Oceanic and Atmospheric Administration, Vadim Gladyshev, Genome Institute, NIH

Could Flavanols Reverse Age-Related Memory Decline?
Posted on November 4, 2014 by Dr. Francis Collins

Caption: Cocoa beans and cocoa powder, which are rich in antioxidant compounds called flavanols.
Credit: Mars Inc.

Secrets of a Supercentenarian’s Genome
Posted on April 29, 2014 by Dr. Francis Collins

Caption: Hendrikje van Andel-Schipper (2nd from the left) in her youth. She was born June 29, 1890, premature and so tiny that no one thought she would survive. However, she lived to be 115.
Credit: Ramon Schipper

Can Something in Young Blood Give a Boost to Old Brains?
Posted on May 13, 2014 by Dr. Francis Collins

Caption: Fountain of Youth
Credit: NIH
Major Opportunities for Biomedical Research

- Apply breakthrough knowledge and technologies to enhance understanding of biology and disease
- Translate basic science into better treatments
- Improve health care through science
- Reinvigorate the biomedical research community
Understanding the Brain …
Capturing the Imagination
**BRAIN: High Priority Research Areas**

- **Discovering diversity:** Identify and provide access to different brain cell types to determine roles in health and disease.
- **Maps at multiple scales:** Generate circuit diagrams that vary in resolution from synapses to the whole brain.
- **The brain in action:** Produce dynamic picture of the functioning brain by developing and applying improved methods for large-scale monitoring of neural activity.
- **Demonstrating causality:** Link brain activity to behavior with precise tools that change neural circuit dynamics.
BRAIN: High Priority Research Areas

- **Identifying fundamental principles**: Produce conceptual foundations for understanding biological basis of mental processes using new theoretical and data analysis tools.

- **Advancing human neuroscience**: Develop new technologies to understand the human brain and treat its disorders; create/support integrated human brain research networks.

- **From BRAIN Initiative to the brain**: Apply all of these new approaches to discover how dynamic patterns of neural activity are transformed into cognition, emotion, perception, and action in health and disease.
BRAIN Initiative
First Awards Announced, September 2014

- $46M to >100 researchers in 15 states; 3 nations
- 58 projects, including efforts to:
  - Develop innovative technologies to advance basic neuroscience
  - Create and optimize technologies for recording and modulating large groups of cells that act together in circuits
Setting the Stage for 21st Century Biomedicine
Cost of Sequencing a Human Genome
September 2001–July 2014

$100,000,000
$10,000,000
$1,000,000
$100,000
$10,000
$1,000

4,905
In response to 2012 Presidential Initiative to fight AD, NIH launched ADSP, a large-scale sequencing project to:

- Identify risk and protective gene variants
- Determine why some at-risk individuals do not develop AD
- Discover new pathways for disease prevention and treatment

Overseen by NIA and NHGRI

- Conducted in collaboration with two major consortia across the U.S.
- Open access to data for approved researchers
In response to the 2012 Presidential Initiative to fight Alzheimer's Disease (AD), the National Institutes of Health (NIH) launched the Alzheimer's Disease Sequencing Project (ADSP), a large-scale sequencing project to:

- Identify risk and protective gene variants
- Determine why some at-risk individuals do not develop AD
- Discover new pathways for disease prevention and treatment

Overseen by the National Institute on Aging (NIA) and the National Human Genome Research Institute (NHGRI), the project is conducted in collaboration with two major consortia across the United States. Open access to data is available for approved researchers.

Sequence data was released in Summer 2014:
- Whole genome sequencing data: 578 subjects from 111 families
- Whole exome sequencing data: ~11,000 subjects (5,000 cases; 5,000 controls; 1,000 additional from families affected by AD)

Grants were recently awarded to support data analysis.
The Cancer Genome Atlas

- Coordinated effort to accelerate understanding of cancer through genome analysis to improve diagnosis, treatment, and prevention

- Provides analysis of > 20 types of cancer, including
  - Leukemia
  - Breast
  - Colon
  - Bladder
  - Brain
  - Lung
  - Ovary
  - Thyroid

- All of which generates a tremendous quantity of data...
Myriad Data Types

- Genomic
- Other ‘Omic
- Imaging
- Phenotypic
- Exposure
- Clinical
Harnessing Data to Improve Health: BD2K (Big Data to Knowledge)

NIH’s 6-year initiative to:

- Facilitate use/sharing of large, complex biomedical data sets through new policies, resources, standards
- Develop new analytical methods and software
- Enhance training of data scientists, computer engineers, bioinformaticians, other researchers
- Establish Centers of Excellence to address biomedical analytics, computational biology, medical informatics
  
  Awards announced in October
Major Opportunities for Biomedical Research

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Disorders with Known Molecular Basis

Source: Online Mendelian Inheritance in Man, Morbid Anatomy of the Human Genome

~500 with therapy
National Center for Advancing Translational Sciences (NCATS)

Mission:
To catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions.

http://ncats.nih.gov/
NCATS Program: Human Tissue Chip for Drug Screening

- Goal: develop biochip to screen for safe, effective drugs
  - Liver, heart, lung, other cell types
  - Use to predict toxicity; efficacy
- NIH phase 1 awards (2012): to create individual chips
  - Twelve projects to develop 3-D cellular microsystems representing human organ systems
  - Seven projects to explore potential of stem cells to differentiate into multiple cell types
- Phase 2 awards (2014): cell incorporation; organ integration
  - Support 11 institutions, to collaborate over three years
Tissue Chips: 3D Perfused Model of Human Liver for Study of Metastatic Cancer

- Liver: a major site of metastasis – need model to study:
  - How local microenvironment in metastatic site affects tumor cell response to chemotherapy
  - How dormant tumor cell “wakes up”; becomes expanding metastasis
Tissue Chips: 3D Perfused Model of Human Liver for Study of Metastatic Cancer

High Resolution “3D Printing” of scaffolds

12-well microfluidic bioreactor plate (LiverChip)

Liver Sinusoid
Tissue Chips: 3D Perfused Model of Human Liver for Study of Metastatic Cancer

Liver Cells

12-well microfluidic bioreactor plate (LiverChip)

Triple Negative Breast Cancer Cells
Tissue Chips: 3D Perfused Model of Human Liver for Study of Metastatic Cancer

Demant breast cancer cells

Perfused liver tissue

“network biomarkers” of tumor-liver interactions

Multiplex measurements of cell-cell signaling molecules, systems biology analysis

Linda Griffith, Ph.D.; MIT
Drug Companies Join NIH in Study of Alzheimer's, Diabetes, Rheumatoid Arthritis, Lupus

Ten Drug Companies Form Pact With NIH to Find Paths to New Medicines

By MONICA LANGLEY and JONATHAN D. ROCKOFF
Feb. 3, 2014 11:00 a.m. ET

Ten rival drug companies partner with government

Rival drug companies plan to collaborate on research against key diseases.

In an unprecedented move designed to jump-start medical science, 10 rival drug companies that normally compete fiercely against each other will now cooperate not just with government researchers and nonprofits, but with each other.

NIH, drug companies team up to target diseases

The National Institutes of Health is partnering with researchers from 10 rival drug companies to generate new treatments to change the way the world fights disease.

NIH, 10 Drug Companies Partner to Study Four Diseases

Ramping up its efforts in drug discovery, the National Institutes of Health (NIH) today unveiled what it called an unprecedented $202 million, 5-year partnership with 10 drug companies aimed at finding new treatments for Alzheimer's disease, diabetes, rheumatoid arthritis, and lupus.

The partners will change the way the world fights disease.
AMP: Partnership Will Invest >$230M over Five Years on Pilot Projects

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<tr>
<th>Government</th>
<th>Industry</th>
<th>Non-Profit Organizations</th>
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<td>NIH</td>
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<td>Alzheimer’s Association</td>
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<td>FDA</td>
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<td>Alzheimer’s Drug Discovery Foundation</td>
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<td>Bristol-Myers Squibb</td>
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<td>USAgainstAlzheimer’s</td>
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AMP Pilot Project

Alzheimer’s Disease

- Incentivize use of exploratory biomarkers in clinical trials to develop biomarkers of disease progression and surrogate endpoints
- Work with FDA to ensure clinical path forward for biomarkers
- Conduct network analysis using human brain samples to identify genetic nodes and networks to support target validation
AMP Pilot Project
Type 2 Diabetes (T2DM)

- Create knowledge portal of comprehensive genotype/phenotype data on T2DM and diabetic complications
- Use informatics to identify predictors of risk, potential targets
- Conduct targeted sequencing/genotyping of high priority targets as defined by industry
- Conduct hypothesis-driven phenotyping with high priority LoF/GoF variants to validate potential targets
AMP Pilot Project
Autoimmune Disorders: Rheumatoid Arthritis (RA), Lupus

- Analyze tissue and blood samples from RA and lupus patients to pinpoint molecules and pathways involved at a single cell level
- Use modular, molecular analysis to identify differences and make comparisons at various stages of disease
- Make data available via knowledge portal
Major Opportunities for Biomedical Research

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Focus on Falls: NIH and PCORI*

- Falls: increasingly common, serious problem among elderly
  - In 2012, > 2.4 million over 65 treated in ER
  - And nearly 24,000 of them died – nearly double the number of deaths in 2002

* Patient Centered Outcomes Research Institute

New York Times Magazine, November 2, 2014
Falls: increasingly common, serious problem among elderly
- In 2012, > 2.4 million over 65 treated in ER
- And nearly 24,000 of them died – nearly double the number of deaths in 2002

NIH and PCORI launched 5-year, $30M study: “Randomized Trial of a Multifactorial Fall Injury Prevention Strategy”
- Will bring together researchers, stakeholders, and patients around U.S. to determine best prevention strategies
- Led by investigators from Brigham & Women’s/ Harvard, Yale, and UCLA

* Patient Centered Outcomes Research Institute
Fall Risk Prediction Using Wearable Wireless Sensors
Go4Life: For a Longer Health Span

- NIA’s interactive, customizable exercise and physical activity campaign

www.nia.nih.gov/Go4Life
Go4Life: For a Longer Health Span

- NIA’s interactive, customizable exercise and physical activity campaign
- Modeled on NIH’s successful Diabetes Prevention Program [DPP]
- Designed to encourage older adults to become more active

www.nia.nih.gov/Go4Life
Major Opportunities for Biomedical Research

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Supporting Innovative People and Ideas

- NIH Director’s Early Independence Awards
- New Innovator Award
- Transformative R01
- NIH Director’s Pioneer Award
Preparing a Diverse and Talented Biomedical Research Workforce

Interrelated approaches to encourage diversity:

- Appointment of Chief Officer for Scientific Workforce Diversity, Hannah Valantine, M.D.
- Ensuring Fairness in Peer Review
- Major new grants program announced last week:
  - Building Infrastructure Leading to Diversity (BUILD)
  - National Research Mentoring Network (NRMN)
  - Coordination and Evaluation Center (CEC)
An Example from My Own Lab
Hutchinson-Gilford Progeria Syndrome: Phenotype

- Loss of hair
- Diminished subcutaneous fat
- Growth retardation
- Skeletal abnormalities
- Cardiovascular disease
- Early death
A “Silent” Mutation Causes Progeria

Normal LMNA sequence

Mutation:
GGC => GGT (G608G)

Exon 10

Exon 11

12

3’UTR

Lamin A Processing

Normal Lamin A processing

FTase ↓

ZMPSTE24 ↓

Upstream cleavage (ZMPSTE24)

Mature lamin A (72 kDa)

Hutchinson-Gilford progeria syndrome

FTase ↓

ZMPSTE24 ↓

Upstream cleavage abolished

Progerin

Phenotypes in Interphase HGPS Cells

Could a Drug Block Production of the Toxic Protein?
Patient Fibroblasts: *In vitro* 72 Hour FTI Treatment

Children With Progeria Were Enrolled In a Clinical Trial of a Farnesyltransferase Inhibitor

Photographs Provided by The Progeria Research Foundation
Results of the Clinical Trial: Improvements With Lonafarnib Therapy

Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome

Is progerin expressed in normal individuals?
RT-PCR Demonstrates Abnormal Splice

N1-4: normal
H1-2: HGPS

Exon 11

Normal: lamin A

lamin A
progerin

Forward primer

Exon 1--10
Exon 11

12 3’UTR

Reverse primer

progerin
Human longevity and common variations in the *LMNA* gene: a meta-analysis

Karen N. Conneely,¹ Brian C. Capell,²* Michael R. Erdos,² Paola Sebastiani,³ Nadia Solovieff,³ Amy J. Swift,² Clinton T. Baldwin,⁴ Temuri Budagov,⁵ Nir Barzilai,⁵ Gil Atzmon,⁵ Annibale A. Puca,⁶ Thomas T. Perls,⁴ Bard J. Geesaman,⁷ Michael Boehnke⁸ and Francis S. Collins²

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**Stage 1:**
- NECS:
- French:
- SICS:
- Ashkenazi:

**Meta-analysis:**

![Odds ratio graph](image)
Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by the careful investigation of cases of rarer forms of disease.

~ William Harvey, Letter IX, to John Vlackveld, 24 Apr 1657