Aging: From Cells to Societies – The NIH View

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

GSA 2014 Annual Scientific Meeting
November 6, 2014

Congratulations

Linda Harootyan, GSA
Deputy Executive Director

Retiring to an advisory role

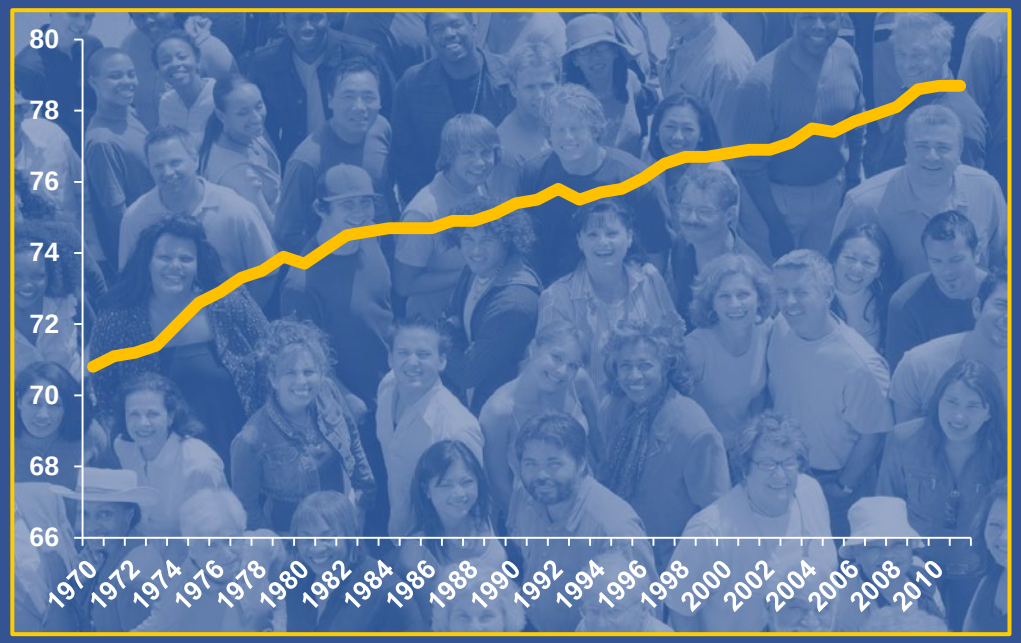
Marie Bernard, M.D., NIH
Deputy Director, NIA

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



U.S. Life Expectancy

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

31 OCTOBER 2014 • VOL 346 ISSUE 6209

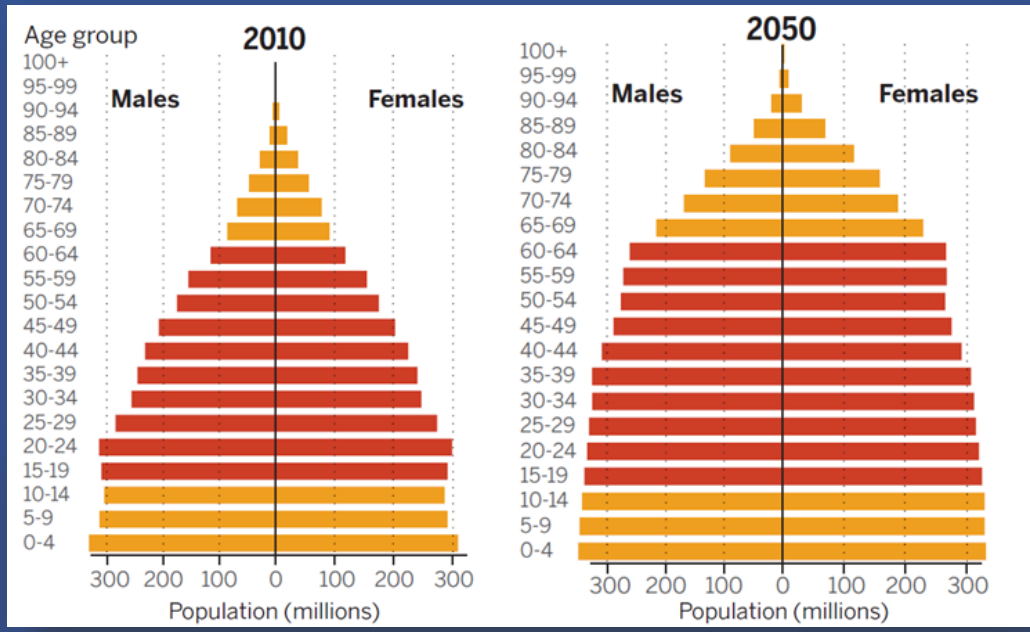
Science
AAAS

REVIEW

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.



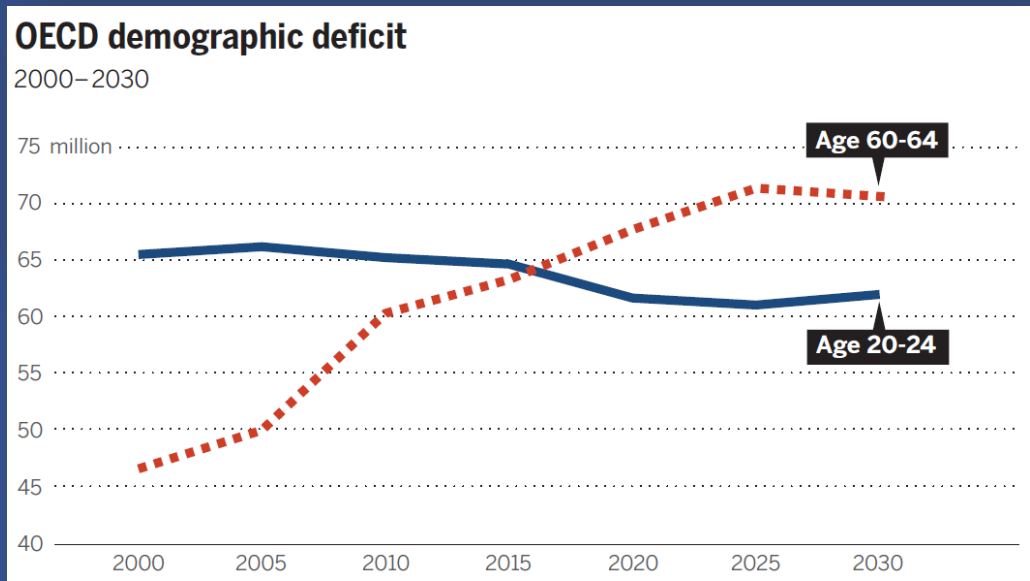


Fig. 3. Demographic deficit in OECD member nations. Observed and projected size of the incoming (20–24) and outgoing (60–64) working-age cohorts in OECD countries, 2000–2030. Source: OECD figures, Oxford Institute of Population Ageing, 2012.

NIH's National Institute on Aging: Celebrating 40 Years – with GSA's Help!

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;

March 2010 • gerontology news • 7

GSA65 GETTING BETTER WITH AGE
Celebrating 65 years | 1945–2010

key moment in history

A new special feature celebrating 65 years of GSA milestones

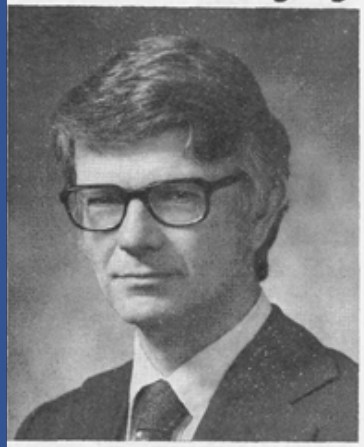
1974: GSA Plays Major Role in NIA's Development

By Robert Binstock, PhD

the NIH Record

May 4, 1976
Vol. XXVIII, No. 9

Dr. Robert Butler 1st Director, Nat'l Institute on Aging

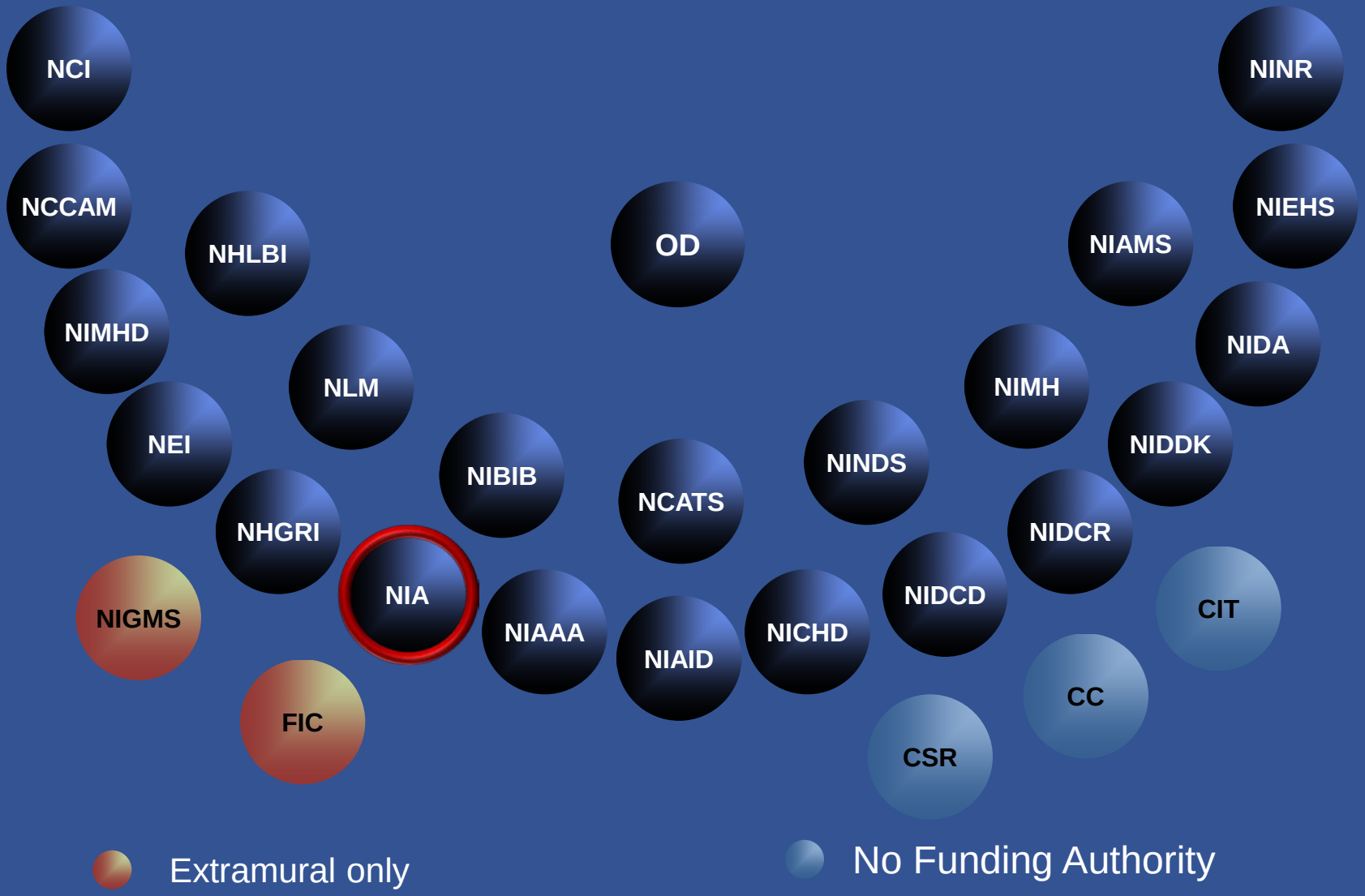


Dr. Butler, who was named one of the "Washingtonians of the Year" by "The Washingtonian" magazine, has actively participated in community and public affairs.

Dr. Robert N. Butler has been appointed the first Director of the National Institute on Aging. He will assume his new post on May 1.

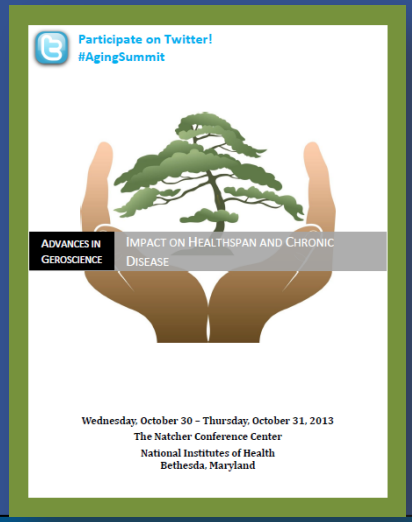
Previously, Dr. Butler was in private practice in Washington, D.C., as a psychiatrist and psychoanalyst.

The National Institutes of Health



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

Published online November 6, 2014

Profile

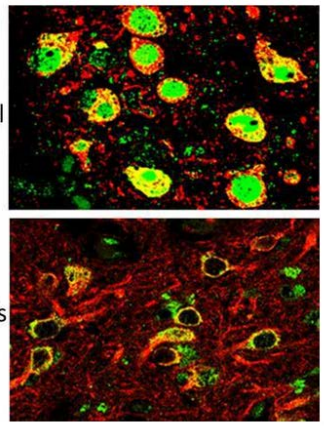
Richard Suzman: helping the world to grow old more gracefully

Aging Research: Making Headlines

NIH DIRECTOR'S BLOG

Creative Minds: REST-ling with Alzheimer's Disease

Posted on March 25, 2014 by Dr. Francis Collins



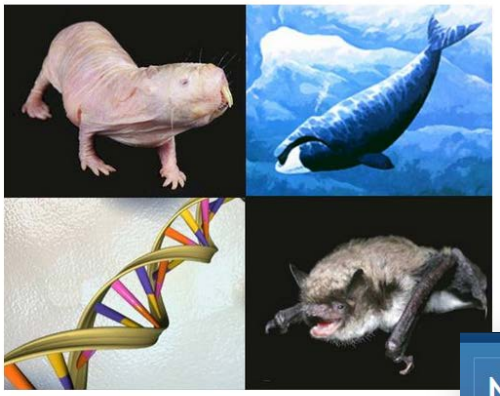
Caption: *The REST protein (green) is dormant in young people but switches on in the nucleus of normal aging human neurons (top), apparently providing protection ag including abnormal proteins assoc diseases. REST is lost in neuron nu early stages of Alzheimer's disease red.*

Credit: *Yankner Lab, Harvard Med*

NIH DIRECTOR'S BLOG

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 l*

Credit: *Clockwise from top left: Smithsonian's National Zoo; National Oceanic and Atmospheric Administration; Vadim Gladyshev; National Hu Genome Genome Research Institute, NIH*

NIH DIRECTOR'S BLOG

Could Flavanols Reverse Age-Related Memory Decline?

Posted on November 4, 2014 by Dr. Francis Collins

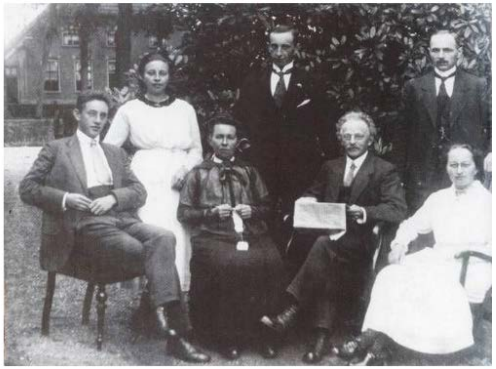
Caption: *Cocoa beans and cocoa powder, which are rich in antioxidant compounds called flavanols.*

Credit: *Mars Inc.*

NIH DIRECTOR

Secrets of a Supercentenarian's Genome

Posted on April 29, 2014 by Dr. Francis Collins



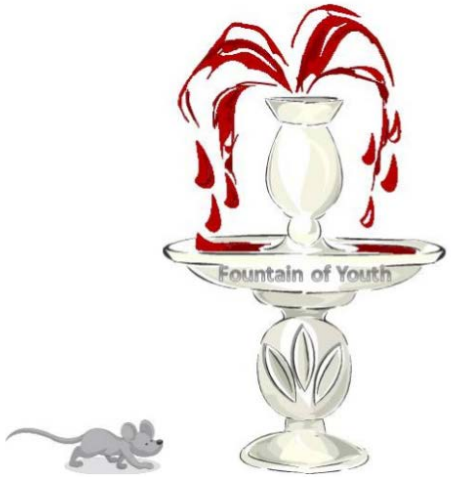
Caption: *Hendrikje van Andel-Schipper (2nd from the left) in her youth. She was born June 29, 1890, premature and so tiny that no one thought she would survive. However, she lived to be 115.*

Credit: *Ramon Schipper*

NIH D

Can Something in Young Blood Give a Boost to Old Brains?

Posted on May 13, 2014 by Dr. Francis Collins



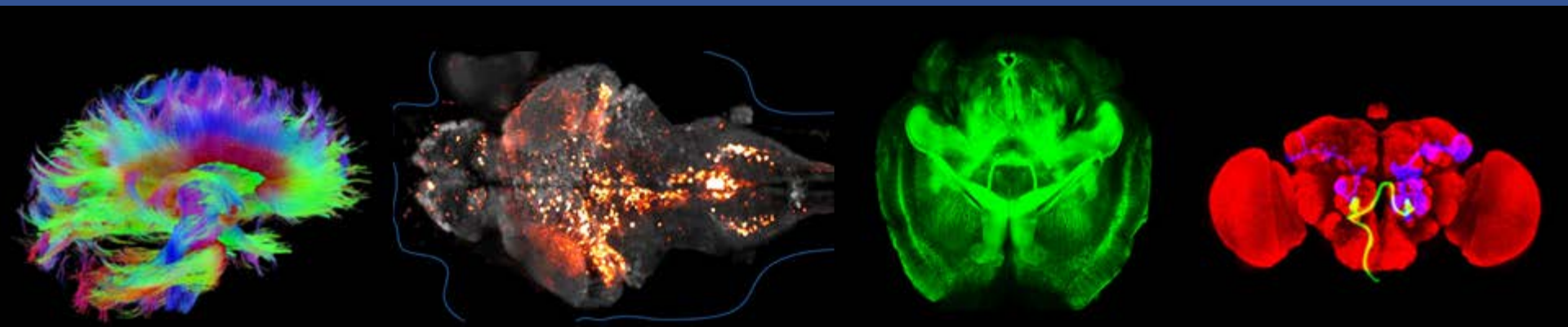
Major Opportunities for Biomedical Research

- 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

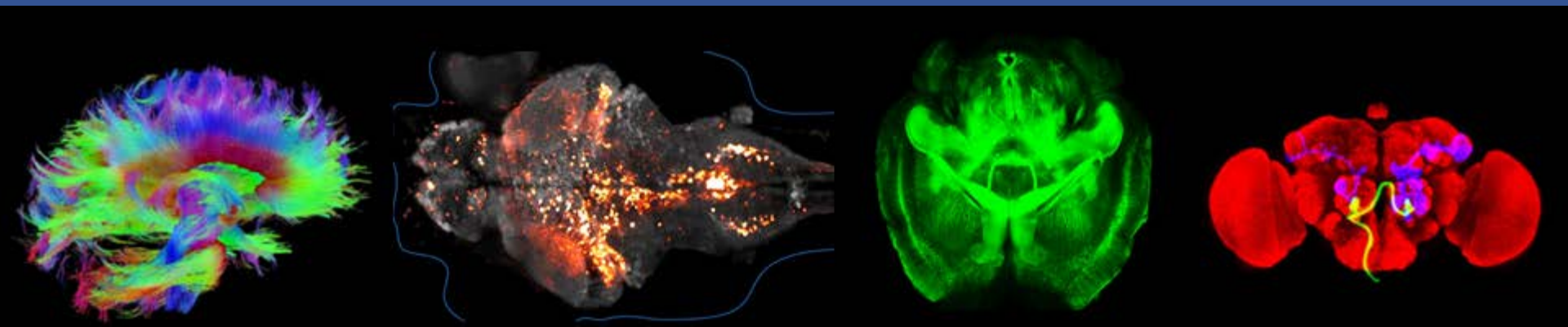
BRAIN: High Priority Research Areas

- 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

NBC NEWS

Next 'Moon Shot': U.S. Sc
Target Human Brain for E

BY MAGGIE FOX

magine using light to record someone's thoughts, or u

livescience

Brain Tech Projects Get $46 Million in Funding

By Bahar Gholipour, Staff Writer | September 30, 2014 01:31pm ET

REUTERS EDITION: U.S.

Obama's BRAIN initiative awards $46 million in grants

BY JULIE STEENHUYSEN

CHICAGO | Tue Sep 30, 2014 1:59pm EDT

U.S. President Barack Obama announces his administration's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative at the White House in Washington, April 2, 2013.

Bio·IT World

Next-Gen Technology • Big Data • Personalized Medicine

First NIH Grant Awards in BRAIN Initiative

September 30, 2014 | This morning, the NIH announced the recipients of its first round of grants tied to the nationwide BRAIN Initiative, totaling $46 million in funding for research meant

GEN

Genetic Engineering & Biotechnology News

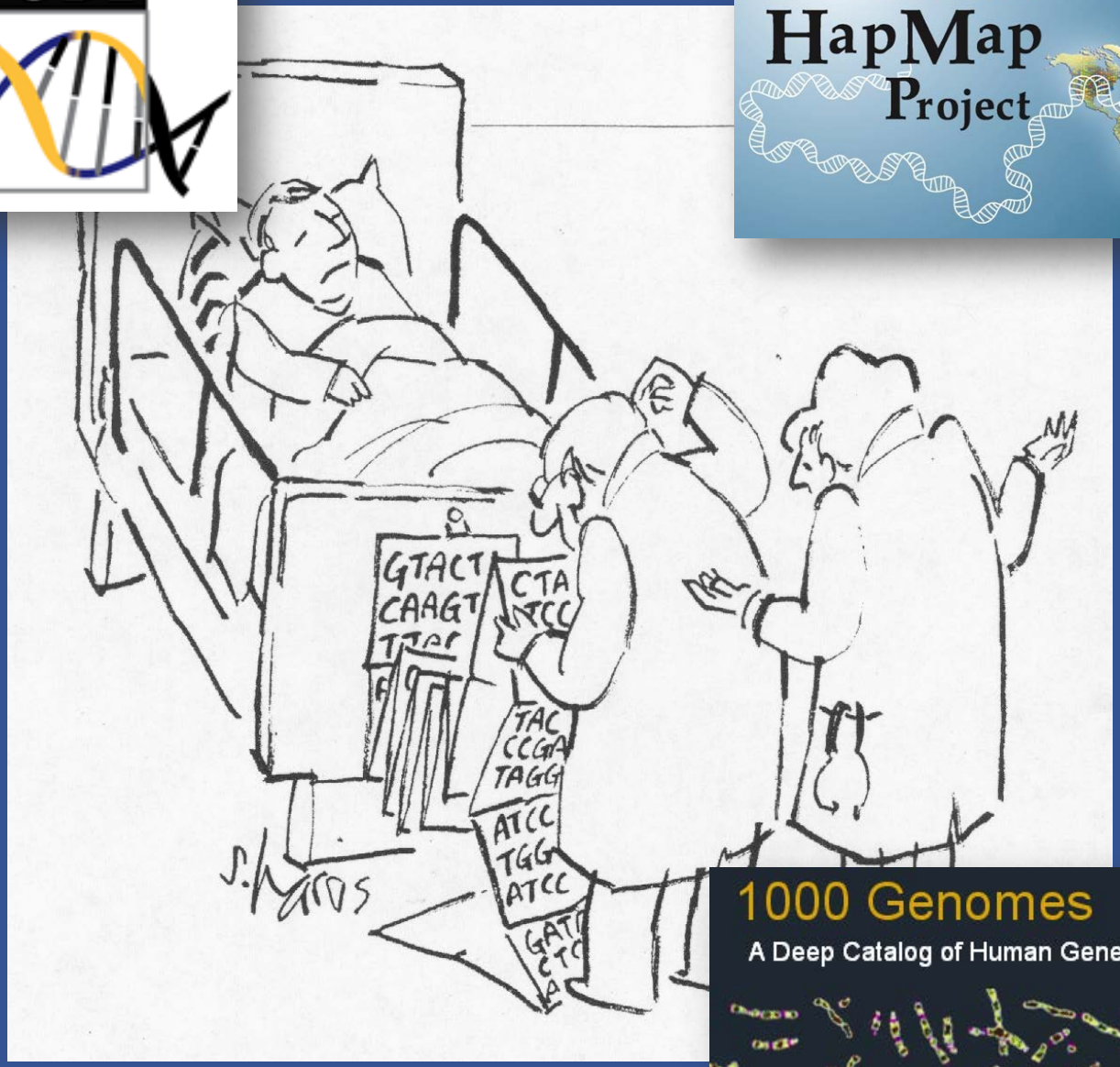
GEN News Highlights

Sep 30, 2014

BRAIN Initiative Scores Initial $46M from NIH

Setting the Stage for 21st Century Biomedicine

ENCODE



International HapMap Project

1000 Genomes

A Deep Catalog of Human Genetic Variation

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

S-01 M-02 J-03 S-03 M-04 J-05 S-05 M-06 J-07 S-07 M-08 J-09 S-09 M-10 J-11 S-11 M-12 J-13 S-13

www.niagads.org

The Alzheimer's Disease Sequencing Project (ADSP)

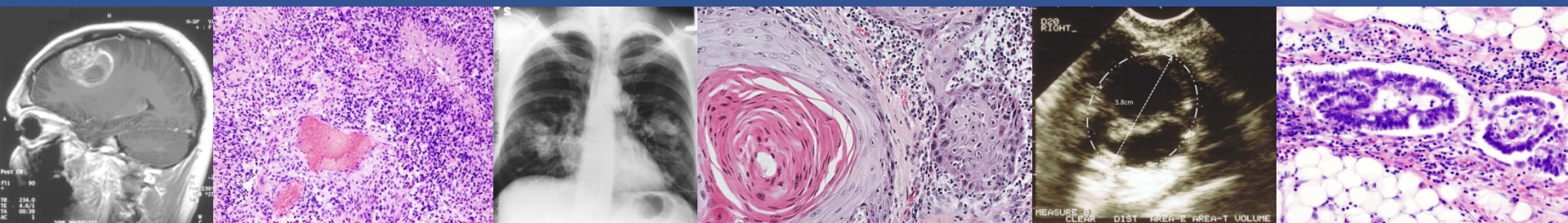
- In response to 2012 Presidential Initiative to fight AD, NIH launched ADSP, a large-scale sequencing project to:
  - Identify risk and protective gene variants
  - Determine why some at-risk individuals do not develop AD
  - Discover new pathways for disease prevention and treatment
- Overseen by NIA and NHGRI
  - Conducted in collaboration with two major consortia across the U.S.
  - Open access to data for approved researchers

www.niagads.org

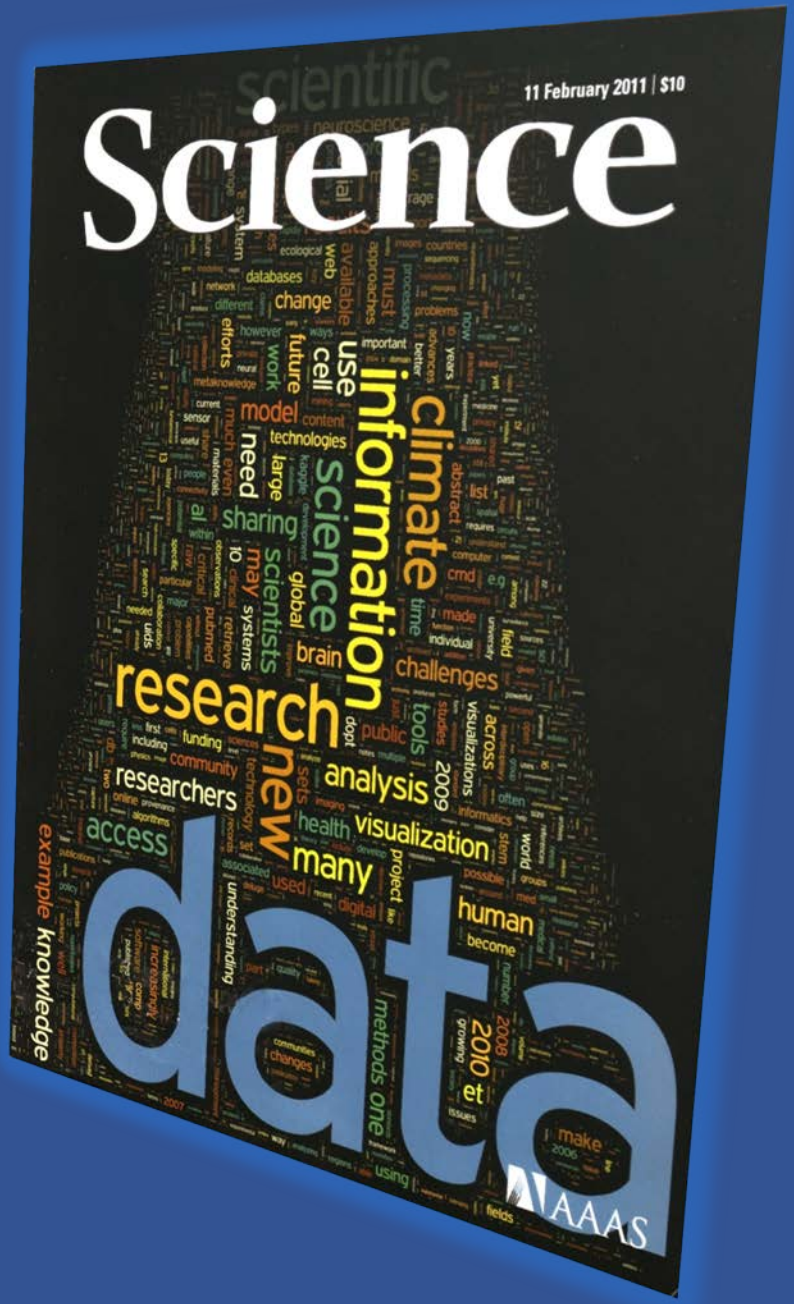
- Sequence data released, Summer 2014:
  - *Whole genome sequencing data:* 578 subjects from 111 families
  - *Whole exome sequencing data:* ~11,000 subjects (5,000 cases; 5,000 controls; 1,000 additional from families affected by AD)
- Grants recently awarded to support data analysis

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 …




4 September 2008 | www.nature.com/nature | $10
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
nature
THE BITER BIT
Viral infections for viruses
TROPICAL CYCLONES
The strong get stronger
BLACK HOLE PHYSICS
A new window on the Galactic Centre
BIG DATA
NATUREJOBS
Minnesota musings
SCIENCE IN THE PETABYTE ERA


11 February 2011 | $10
Science
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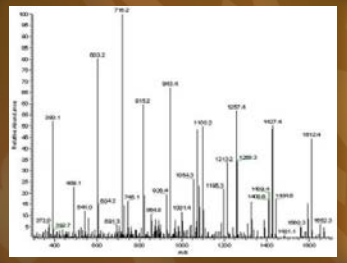
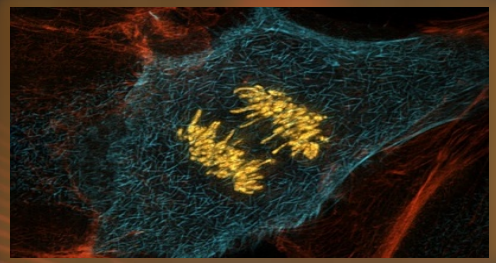
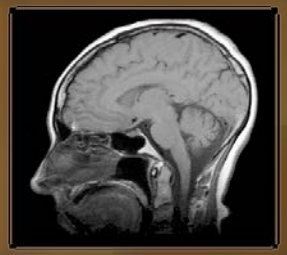
Myriad Data Types


Genomic




Other ‘Omic

Imaging


Phenotypic


Exposure


Clinical

Harnessing Data to Improve Health: BD2K (Big Data to Knowledge)

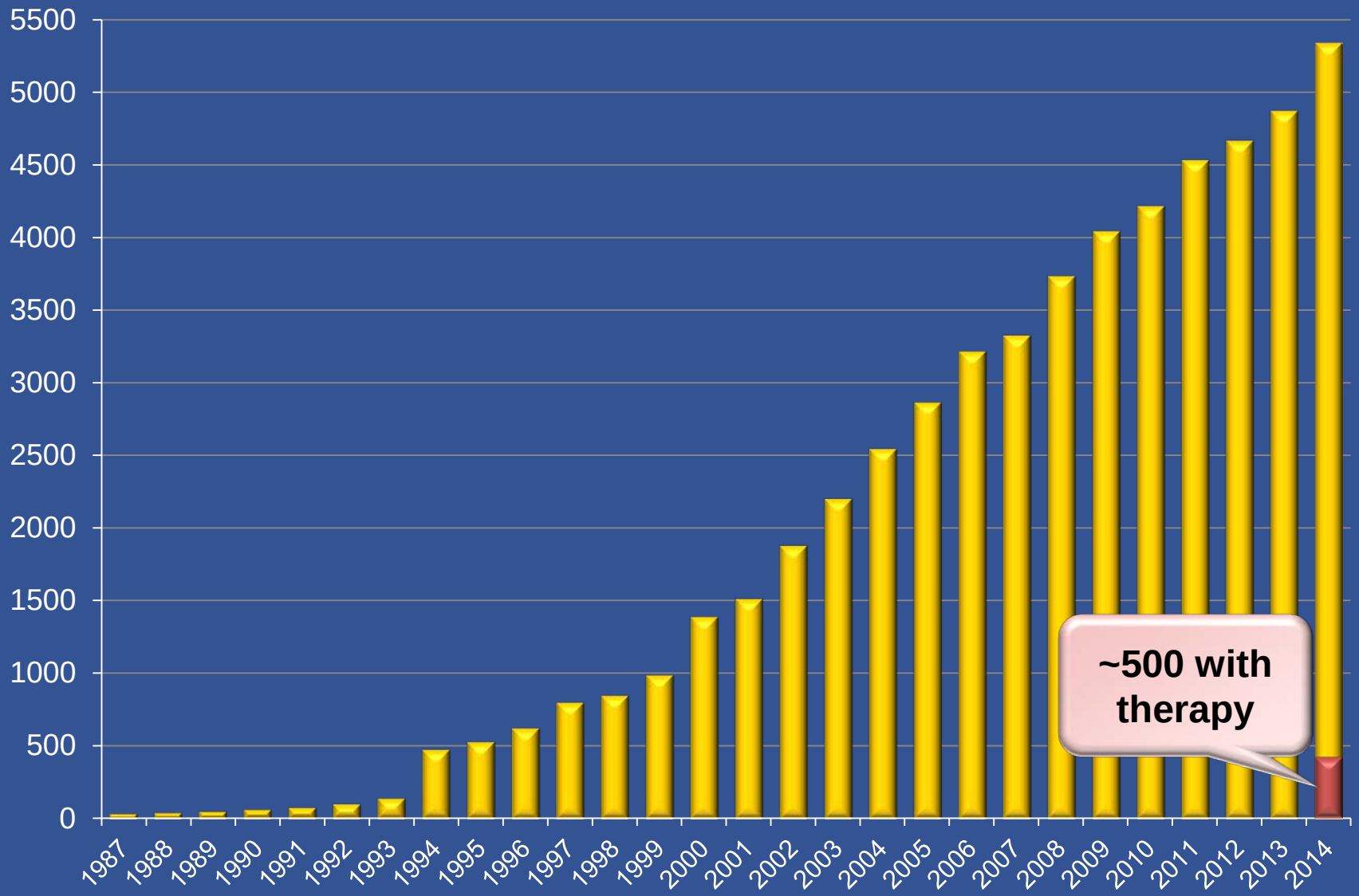
NIH's 6-year initiative to:

- 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

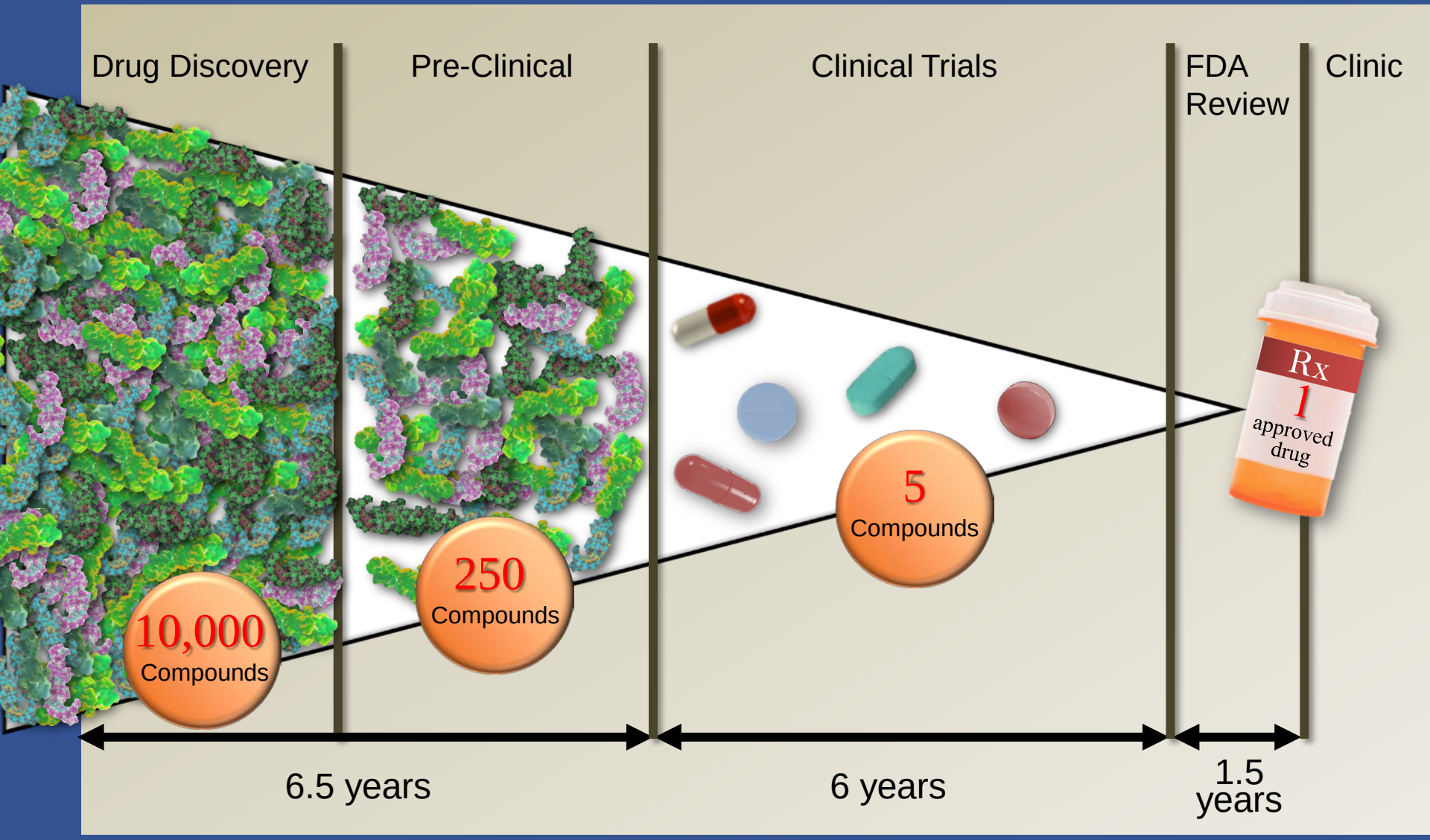
- Apply breakthrough knowledge and technologies to enhance understanding of biology and disease
- Translate basic science into better treatments
- Improve health care through science
- Reinvigorate the biomedical research community

Disorders with Known Molecular Basis



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

Therapeutic Development Pipeline



National Center for Advancing Translational Sciences (NCATS)

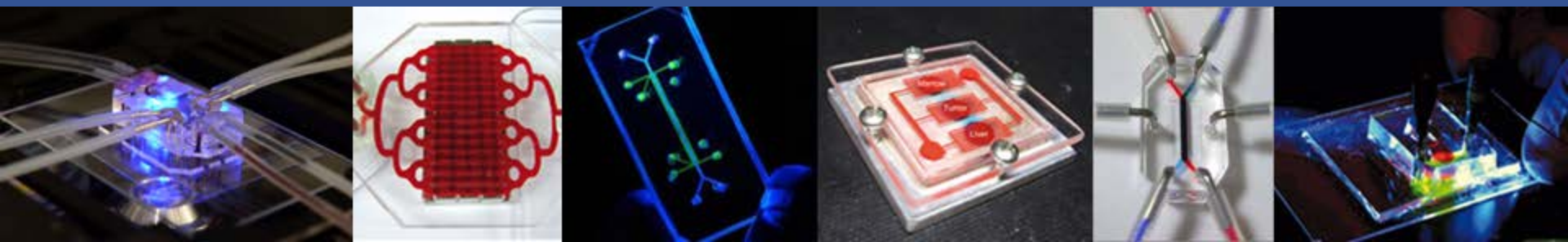
Mission:

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

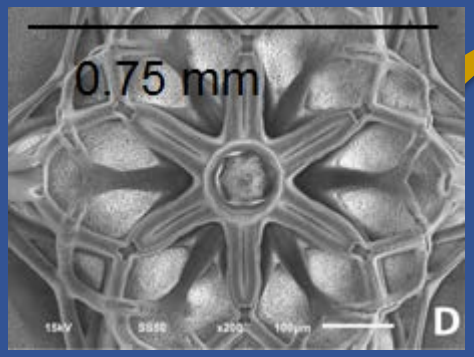


Tissue Chips: 3D Perfused Model of Human Liver for Study of Metastatic Cancer

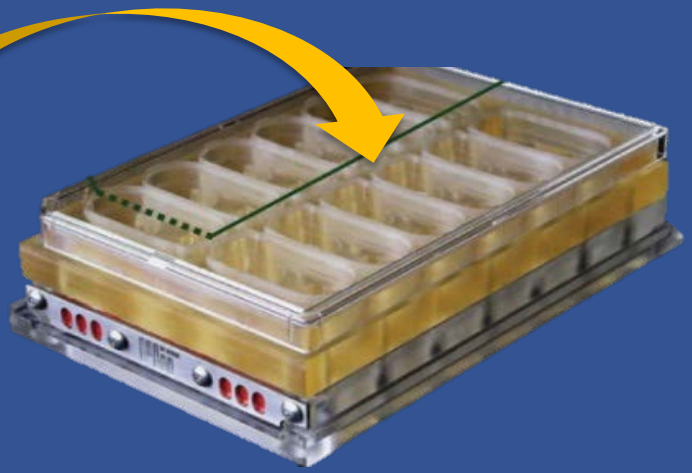
- Liver: a major site of metastasis – need model to study:
  - How local microenvironment in metastatic site affects tumor cell response to chemotherapy
  - How dormant tumor cell “wakes up”; becomes expanding metastasis

Linda Griffith, Ph.D.; MIT

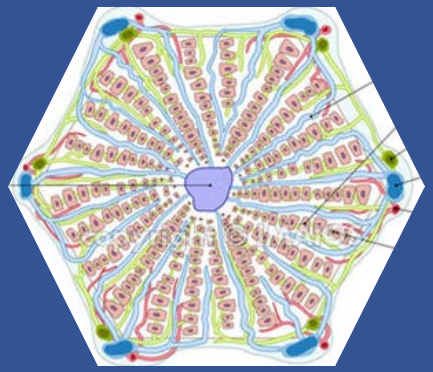
Tissue Chips: 3D Perfused Model of Human Liver for Study of Metastatic Cancer



High Resolution “3D Printing” of scaffolds



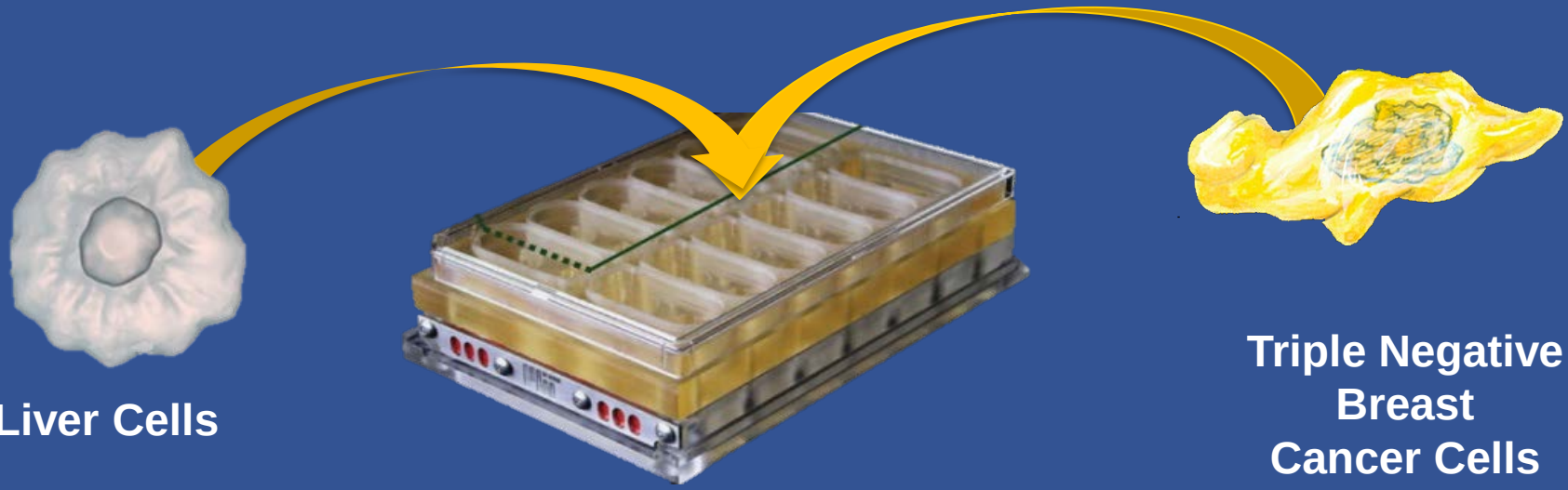
12-well microfluidic bioreactor plate (LiverChip)



Liver Sinusoid

Linda Griffith, Ph.D.; MIT

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



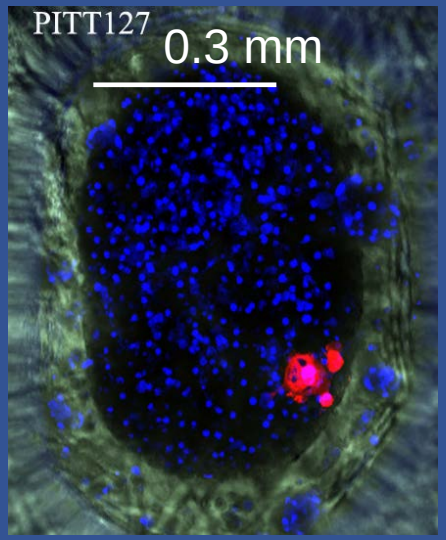
Liver Cells

12-well microfluidic bioreactor plate (LiverChip)

Triple Negative Breast Cancer Cells

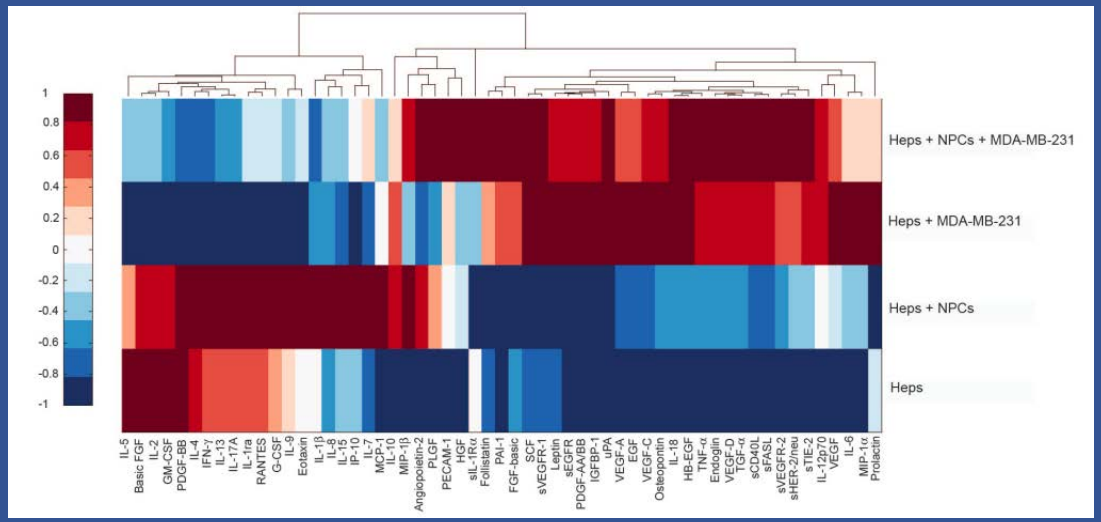
Linda Griffith, Ph.D.; MIT

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



Dormant 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

Accelerating Medicines Partnership (AMP)

www.nih.gov/amp

THE WALL STREET JOURNAL. | U.S.

U.S. NEWS

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 p.m. ET

The White House
Office of the Press Secretary

E-Mail | Tweet | Share | +

For Immediate Release — February 04, 2014

Statement by the President on the Accelerating Medicines Partnership

Today, my Administration is taking action to accelerate the development of life-saving drugs and to help identify new treatments and cures for diseases like Alzheimer's and diabetes. This new public-private partnership – the Accelerating Medicines Partnership – combines the considerable resources of America's government with the innovation of our private sector companies in an effort to find new answers to today's domestic and global public health challenges.

The Washington Post | PostTV | Politics | Opinions | Local | Sports | National

Health & Science

NIH announces novel venture with drug companies to fight major diseases

By Ariana Eunjung Cha, Published: February 4

USA TODAY
A GANNETT COMPANY

NEWS | SPORTS | LIFE | MONEY | TECH | TRAVEL | OPINION

Ten rival drug companies partne with government

Liz Szabo, USA TODAY 6:01 p.m. EST February 4, 2014

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

(Photo: Jack Gruber, USA TODAY)

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

CNN Health

February 4th, 2014
02:41 PM ET

NIH, drug companies team up to target diseases

The National Institutes of Health is partnering with researchers from 10 rival drug companies a
treatments fo

The partnersl
change the w

ScienceInsider
Breaking news and analysis from the world of science policy

NIH, 10 Drug Companies Partner to Study Four Diseases

By: Jocelyn Kaiser Tuesday, February 4, 2014 - 3:45pm | 4 Comments

Ramping up its efforts in drug discovery, the National Institutes of Health (NIH) today unveiled what it called an unprecedented $230 million, 5-year partnership with 10 drug companies aimed at finding new treatments for Alzheimer's disease, diabetes, rheumatoid arthritis, and lupus.

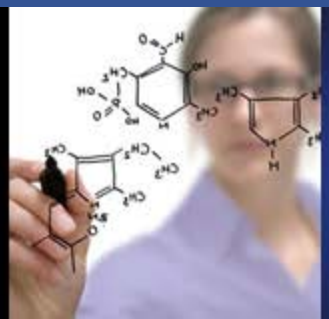
In a room at the Washington, D.C., National Press Club packed with representatives from industry, patient groups, and federal officials, NIH Director Francis Collins described the Accelerating Medicines Partnership (AMP). The goal is to cut down on the more than 95% failure rate for drug candidates. As a result, it now takes some 10 years and more than $1 billion to develop a

Accelerating Medicines Partnership/Camazine Scott

AMP: Partnership Will Invest >$230M over Five Years on Pilot Projects

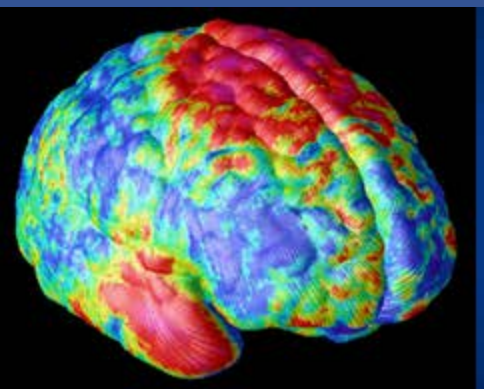
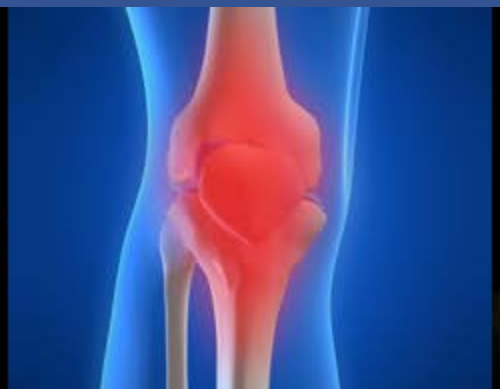
Government	Industry	Non-Profit Organizations
NIH FDA	AbbVie Biogen Idec Bristol-Myers Squibb GlaxoSmithKline Johnson & Johnson Lilly Merck Pfizer Sanofi Takeda	Alzheimer's Association Alzheimer's Drug Discovery Foundation American Diabetes Association Arthritis Foundation Foundation for the NIH Geoffrey Beene Foundation Juvenile Diabetes Research Foundation Lupus Foundation of America Lupus Research Institute / Alliance for Lupus Research PhRMA Rheumatology Research Foundation USAgainstAlzheimer's






AMP Pilot Project
Alzheimer's Disease

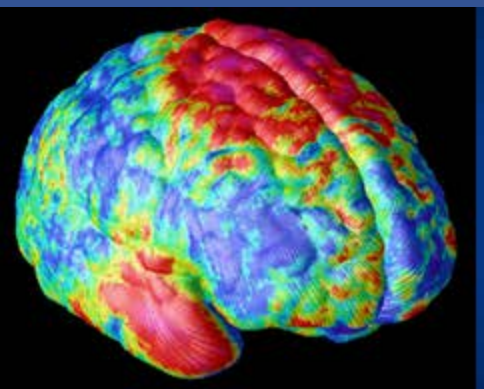
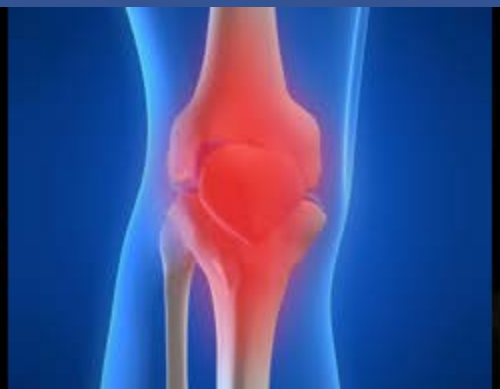
- Incentivize use of exploratory biomarkers in clinical trials to develop biomarkers of disease progression and surrogate endpoints
- Work with FDA to ensure clinical path forward for biomarkers
- Conduct network analysis using human brain samples to identify genetic nodes and networks to support target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

AMP Pilot Project

Type 2 Diabetes (T2DM)

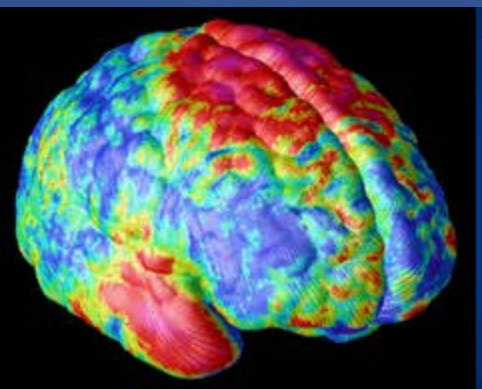
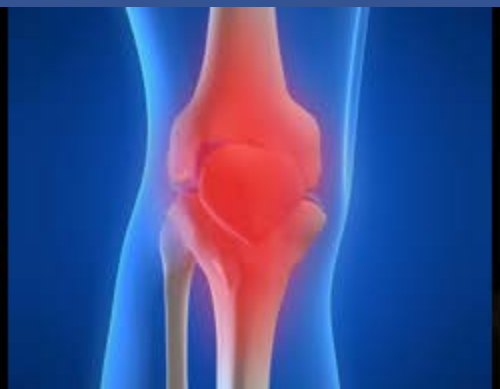
- Create knowledge portal of comprehensive genotype/ phenotype data on T2DM and diabetic complications
- Use informatics to identify predictors of risk, potential targets
- Conduct targeted sequencing/genotyping of high priority targets as defined by industry
- Conduct hypothesis-driven phenotyping with 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

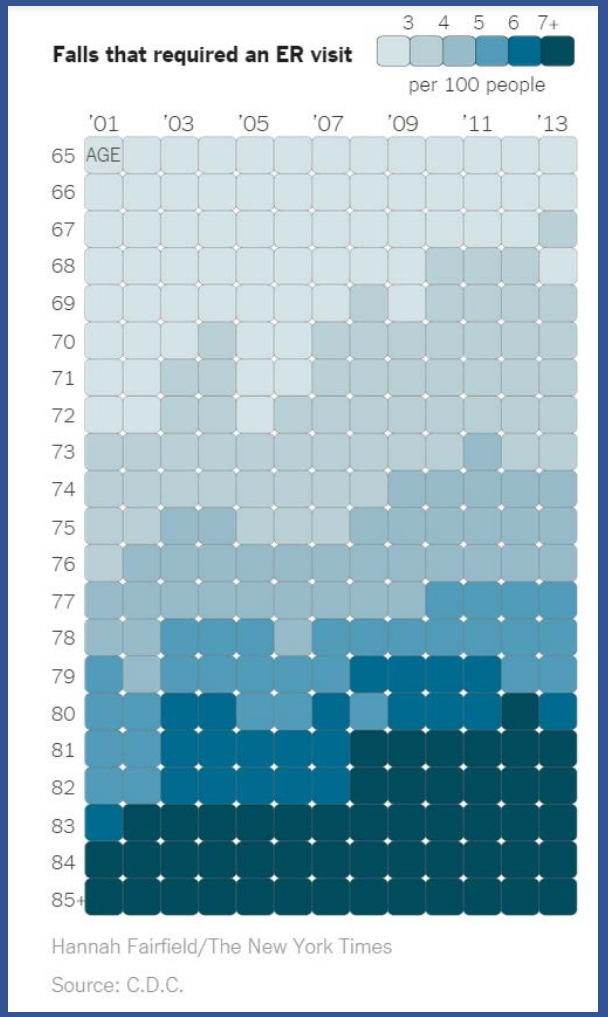



Major Opportunities for Biomedical Research

- 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

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

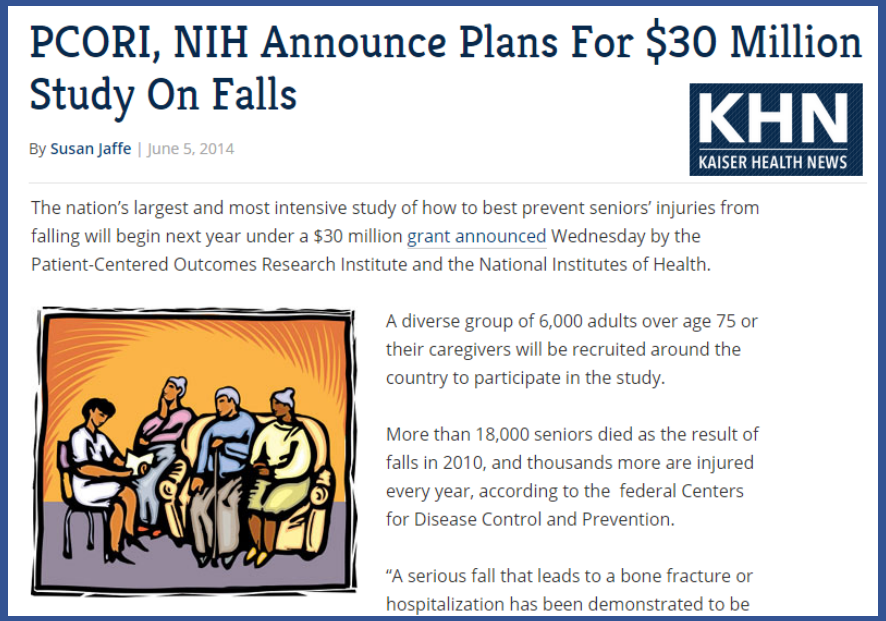


New York Times Magazine, November 2, 2014

* Patient Centered Outcomes Research Institute

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
- 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



PCORI, NIH Announce Plans For $30 Million Study On Falls

KHN KAISER HEALTH NEWS

By Susan Jaffe | June 5, 2014

The nation’s largest and most intensive study of how to best prevent seniors’ injuries from falling will begin next year under a $30 million grant announced Wednesday by the Patient-Centered Outcomes Research Institute and the National Institutes of Health.

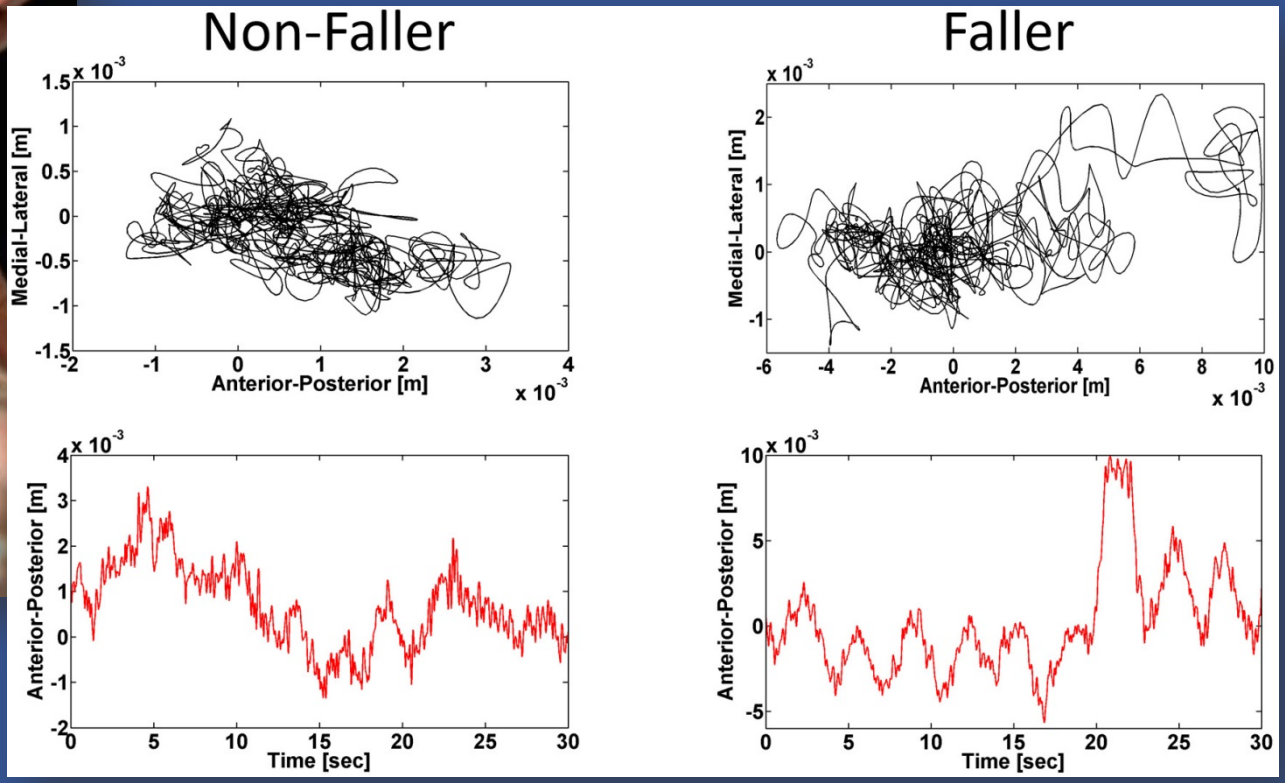
A diverse group of 6,000 adults over age 75 or their caregivers will be recruited around the country to participate in the study.

More than 18,000 seniors died as the result of falls in 2010, and thousands more are injured every year, according to the federal Centers for Disease Control and Prevention.

“A serious fall that leads to a bone fracture or hospitalization has been demonstrated to be

* Patient Centered Outcomes Research Institute

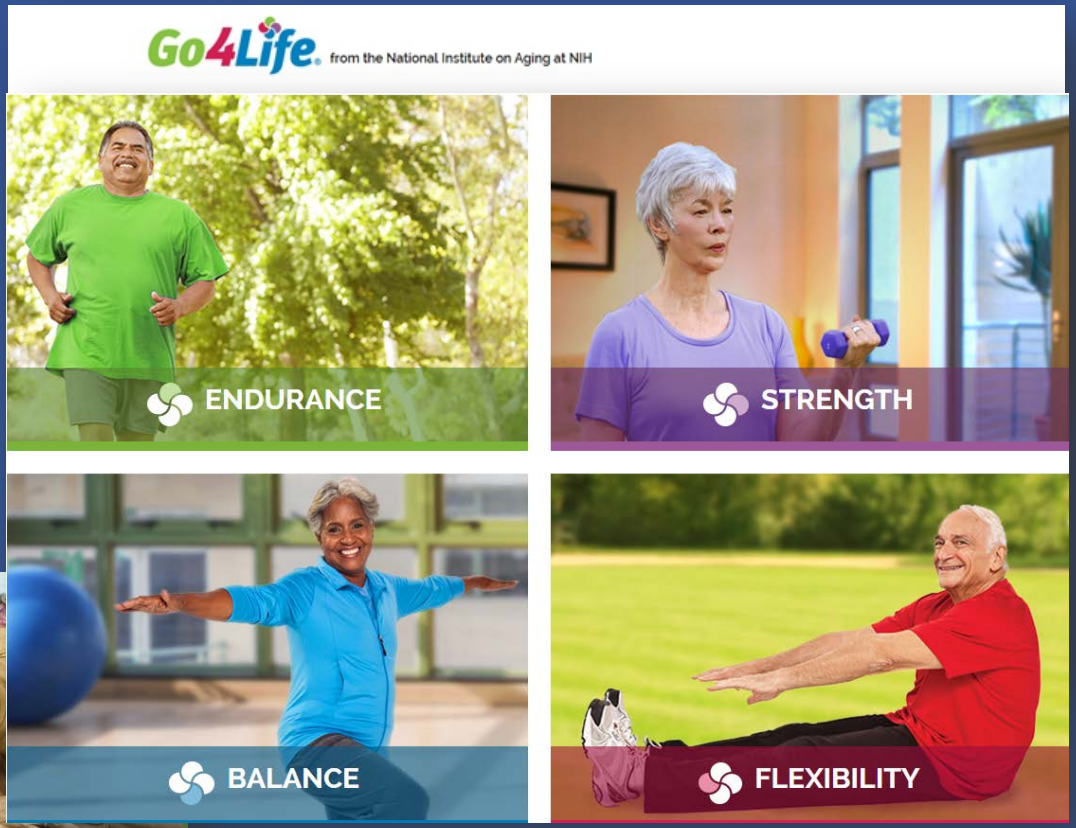
Fall Risk Prediction Using Wearable Wireless Sensors

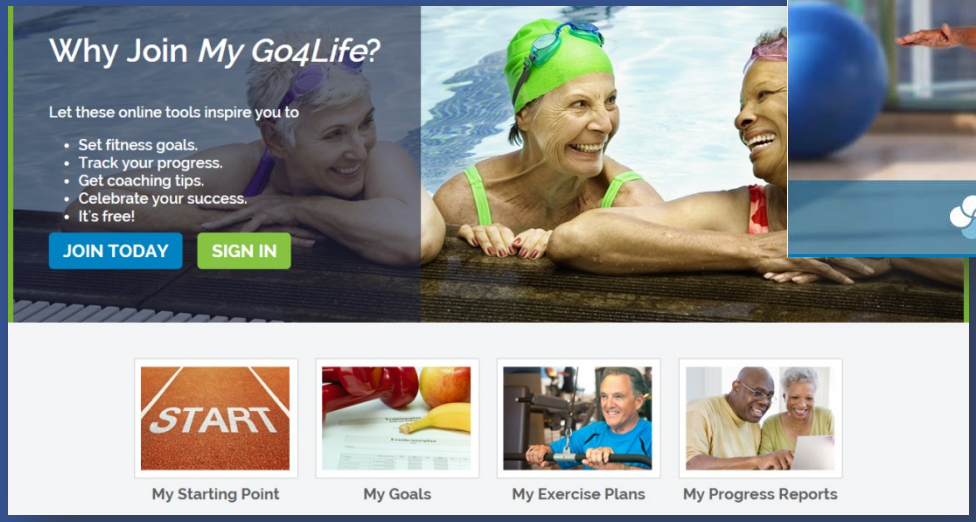


28 May 2014, SPIE Newsroom. DOI: 10.1117/2.1201405.005437

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

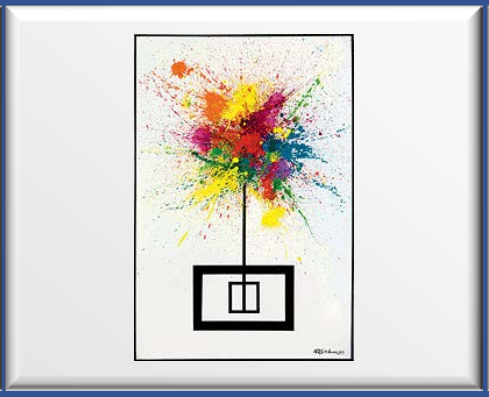
- NIA's interactive, customizable exercise and physical activity campaign
- Modeled on NIH's successful Diabetes Prevention Program [DPP]
- Designed to encourage older adults to become more active

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

Supporting Innovative People and Ideas

- NIH Director's Early Independence Awards
- New Innovator Award
- Transformative R01
- NIH Director's Pioneer Award



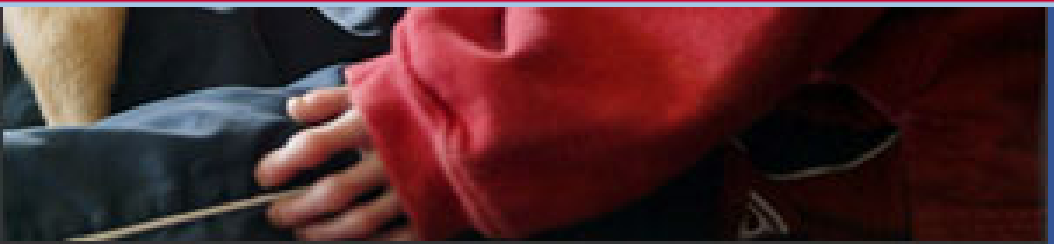
Preparing a Diverse and Talented Biomedical Research Workforce

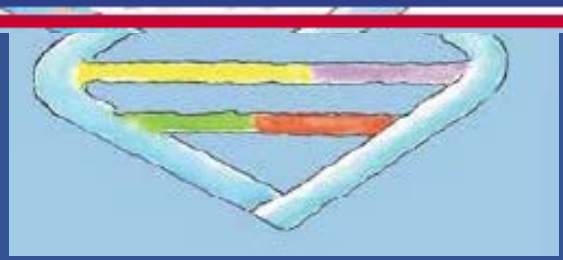
Interrelated approaches to encourage diversity:

- 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

Making Connections: From Cells to Societies

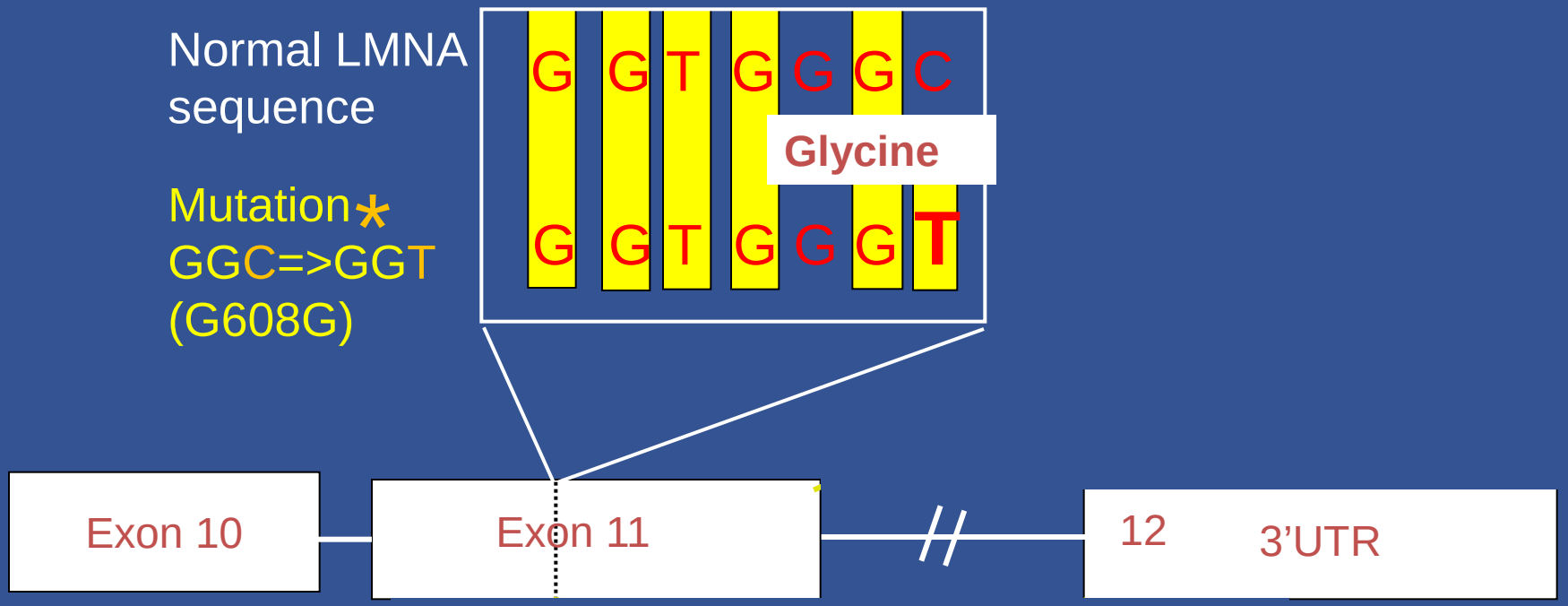




Hutchinson-Gilford Progeria Syndrome: Phenotype

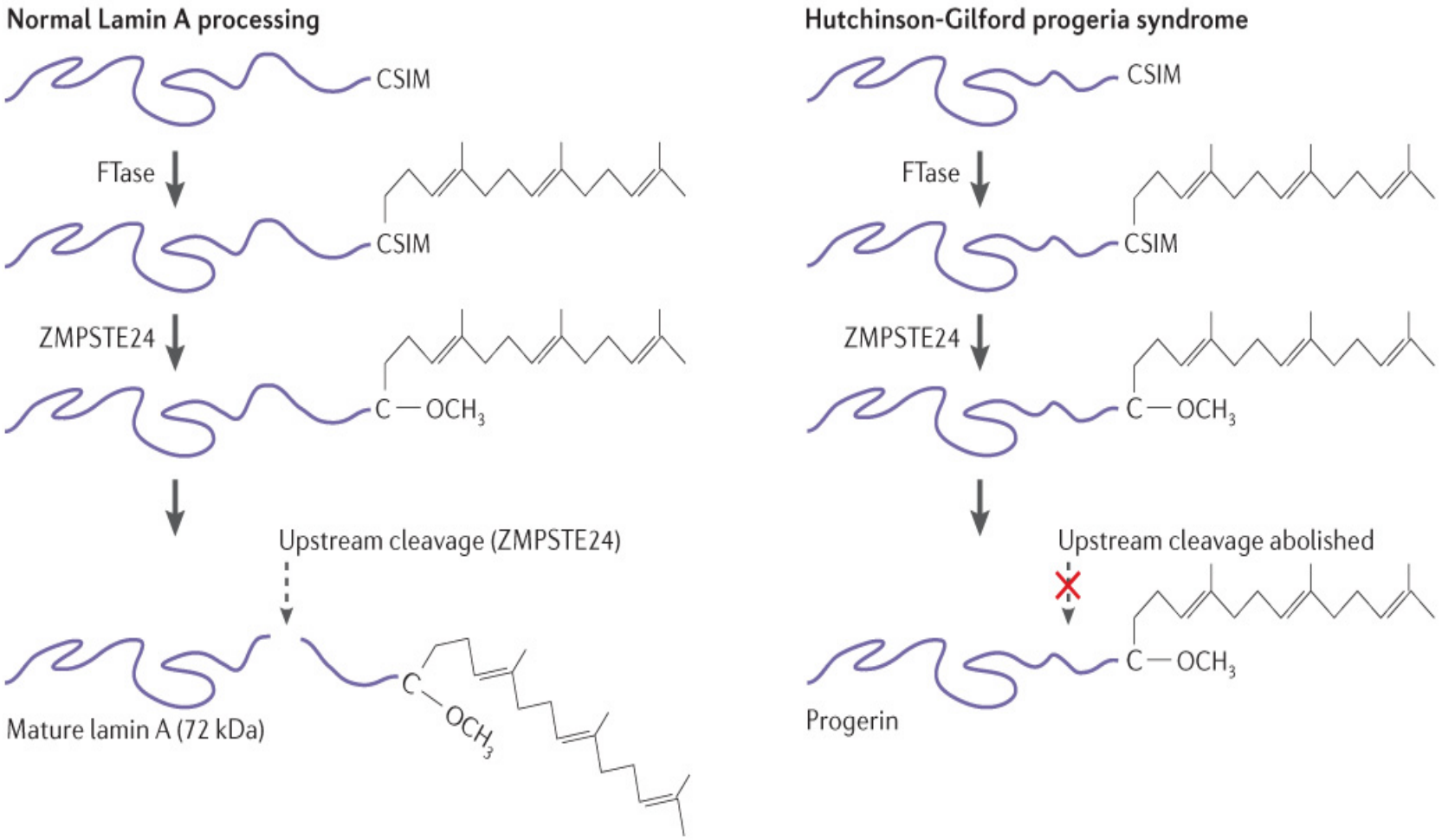
- Loss of hair
- Diminished subcutaneous fat
- Growth retardation
- Skeletal abnormalities
- Cardiovascular disease
- Early death

A “Silent” Mutation Causes Progeria



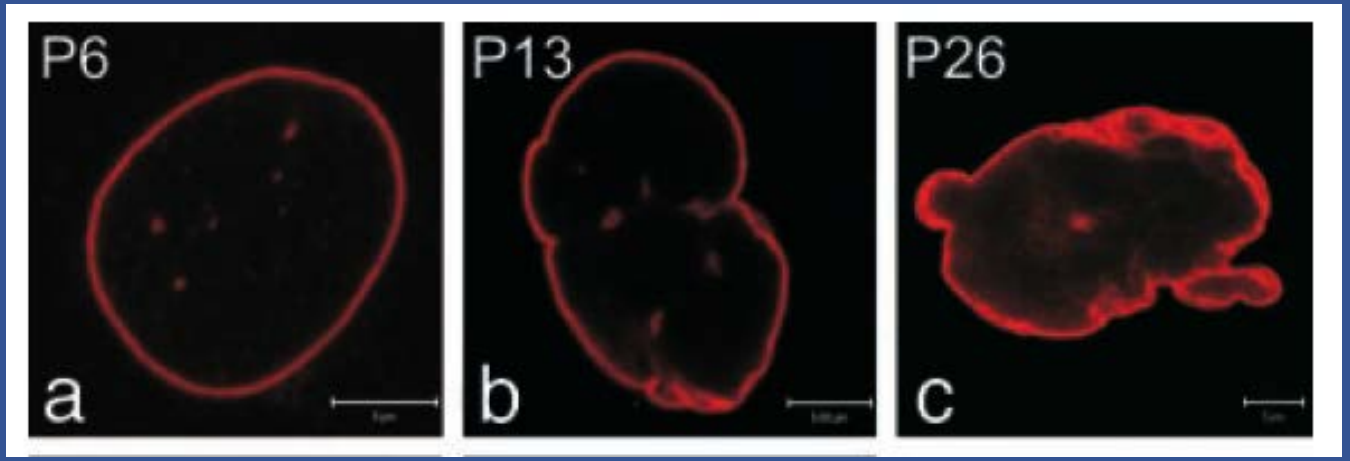
Eriksson, M. *et al*., *Nature* (2003)

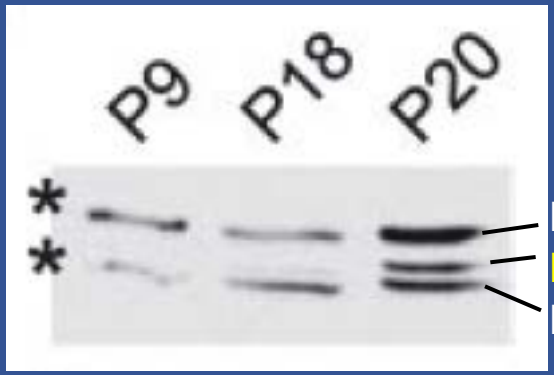
Lamin A Processing



Capell B.C. & Collins F.S., *Nat. Rev. Genet.* (2006)

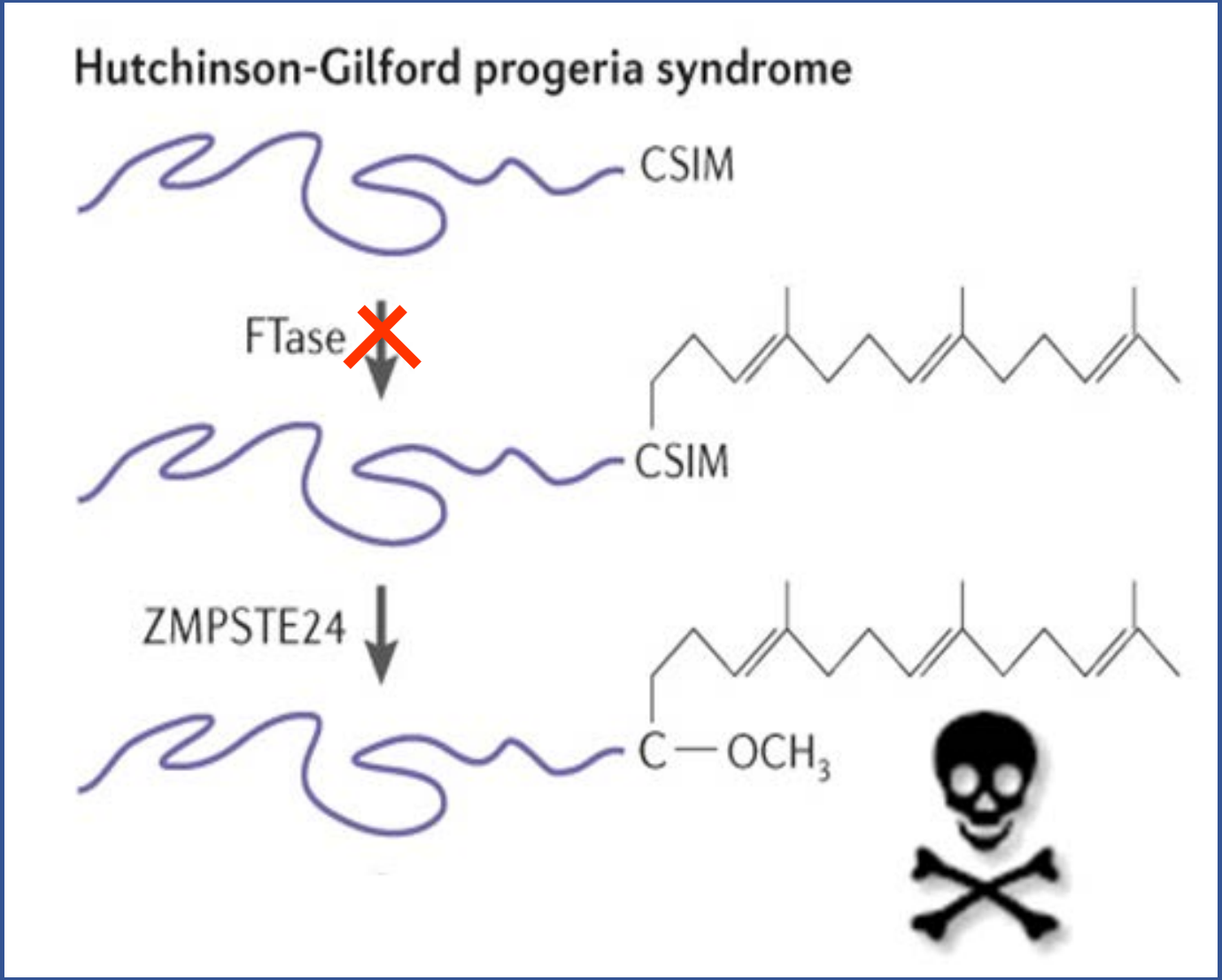
Phenotypes in Interphase HGPS Cells



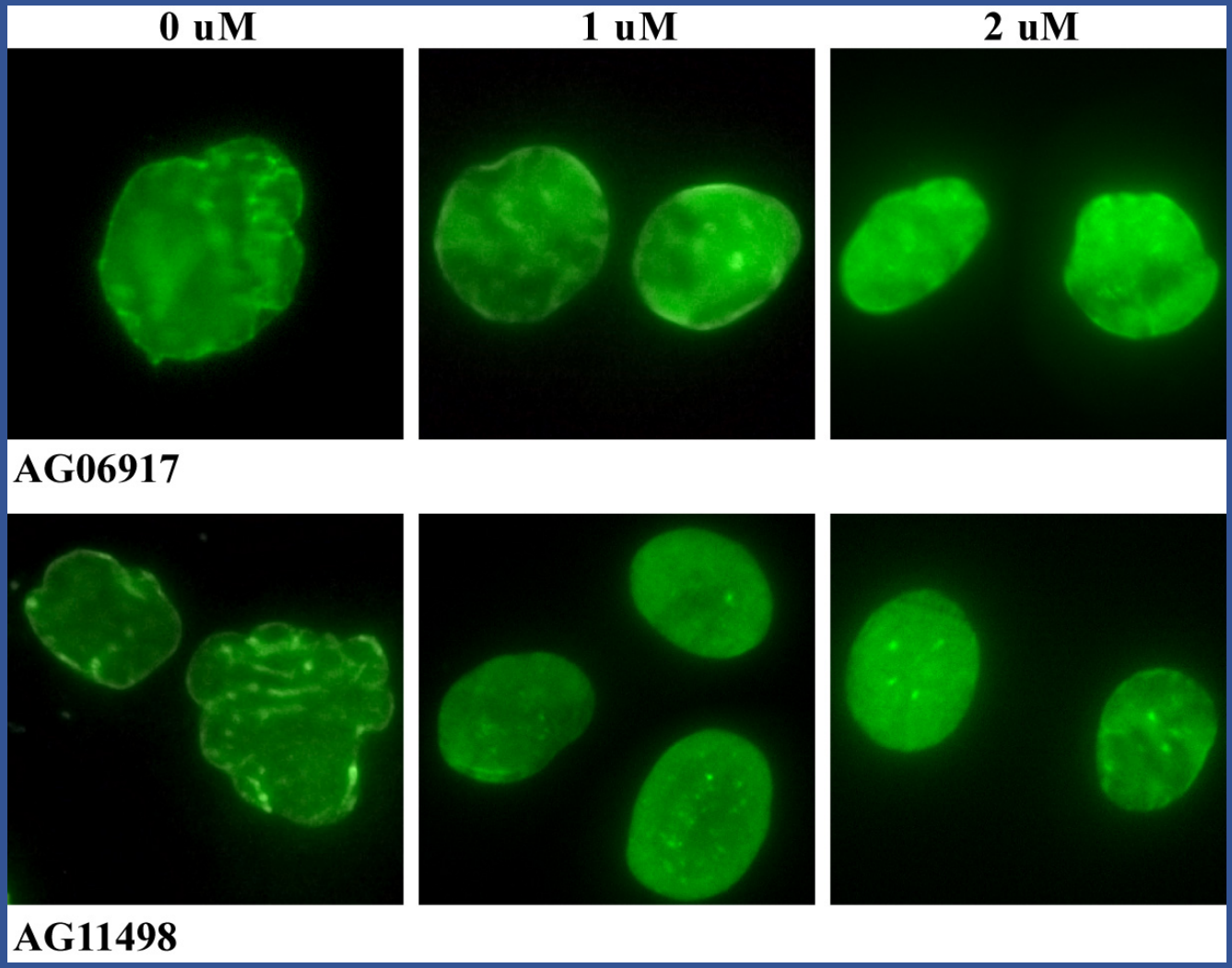


Goldman, R.D. *et al*., *Proc. Natl. Acad. Sci. USA* (2004)

Could a Drug Block Production of the Toxic Protein?



Patient Fibroblasts: *In vitro* 72 Hour FTI Treatment



Capell, B.C. *et al*., *Proc. Natl. Acad. Sci. USA* (2005)

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

Photographs Provided by The Progeria Research Foundation

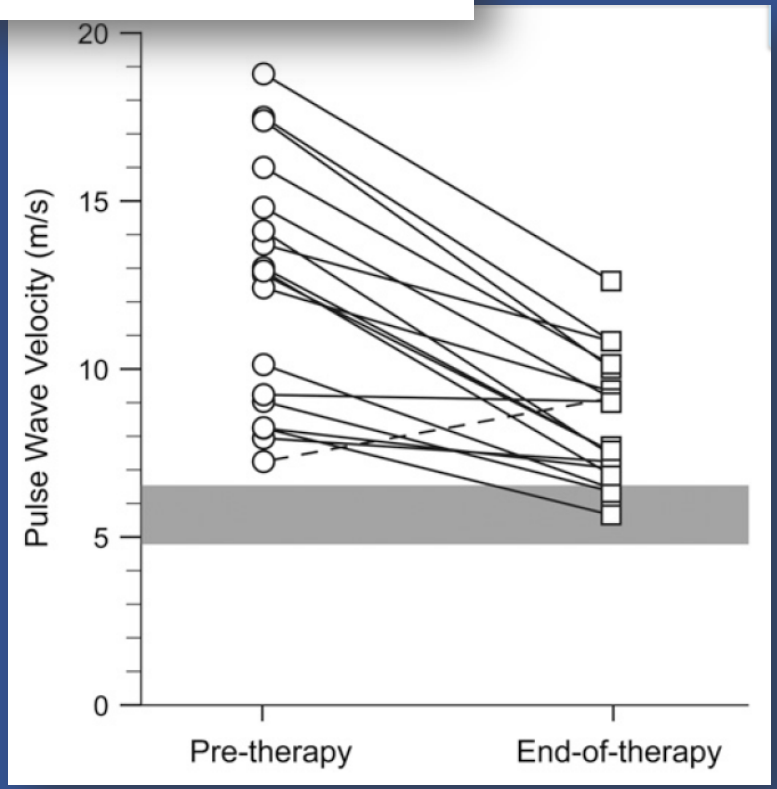
Results of the Clinical Trial: Improvements With Lonafarnib Therapy

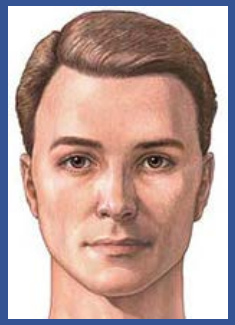
PNAS

October 9, 2012 | vol. 109 | no. 41

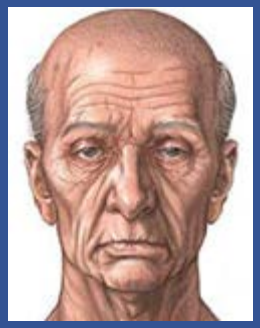
Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson–Gilford progeria syndrome

Leslie B. Gordon[a,b,c,1,2], Monica E. Kleinman[a,b,1], David T. Miller[d,e,f,1], Donna S. Neuberg[g,h], Anita Giobbie-Hurder[g], Marie Gerhard-Herman[i], Leslie B. Smoot[j], Catherine M. Gordon[c,k,l], Robert Cleveland[m], Brian D. Snyder[n,o], Brian Fligor[p], W. Robert Bishop[q], Paul Statkevich[q], Amy Regen[r], Andrew Sonis[r], Susan Riley[s], Christine Ploski[s], Annette Correia[s], Nicolle Quinn[t,u], Nicole J. Ullrich[v], Ara Nazarian[o], Marilyn G. Liang[d,w], Susanna Y. Huh[d,u], Armin Schwartzman[g,h], and Mark W. Kieran[x,y,2]



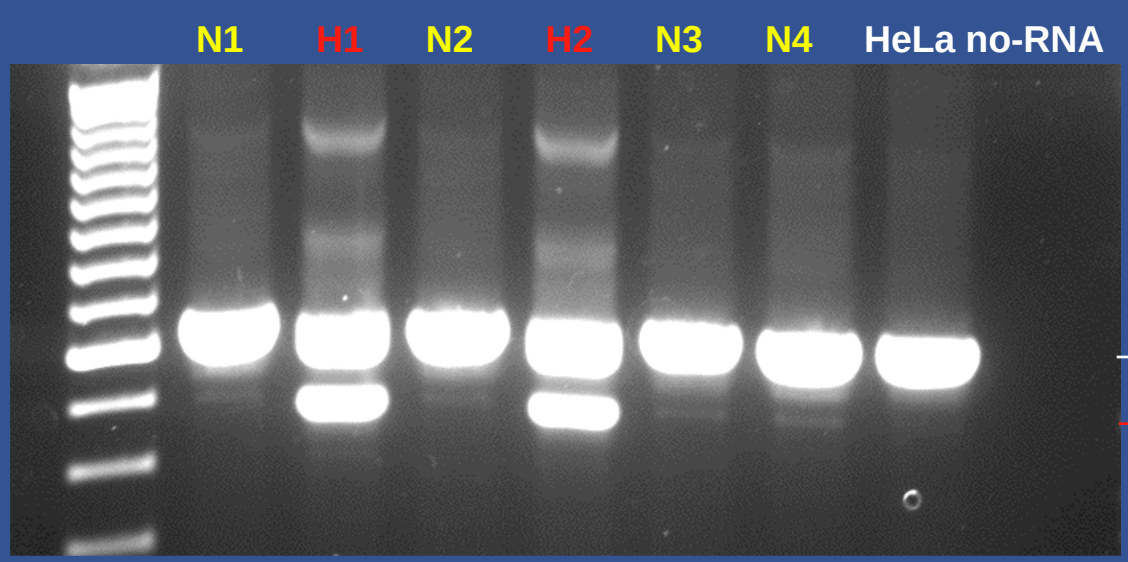


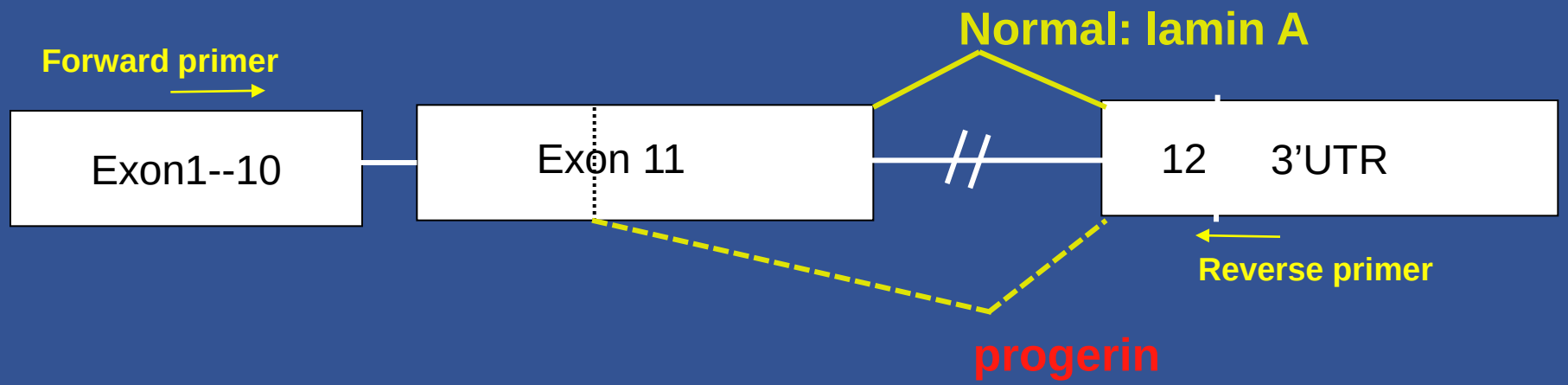
Normal aging



Is progerin expressed in normal individuals?

RT-PCR Demonstrates Abnormal Splice

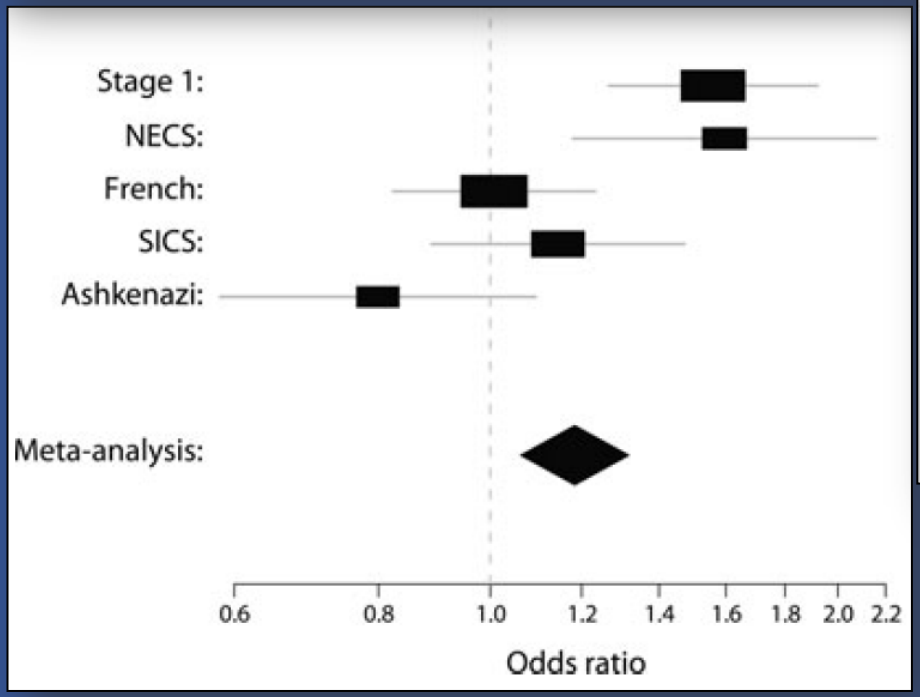


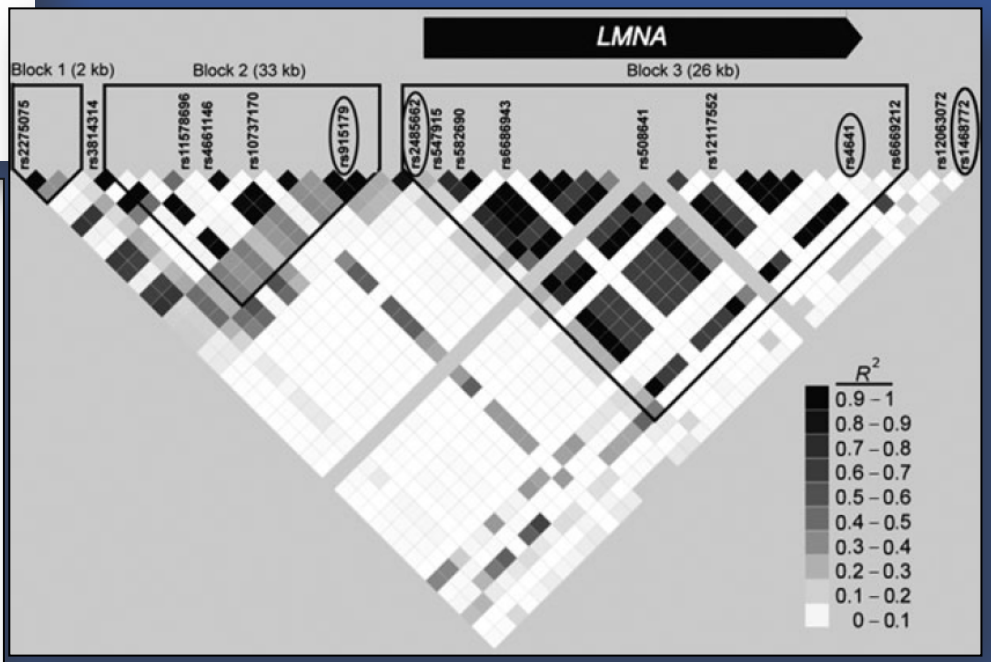


Aging Cell (2012) **11,** pp475–481

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 Boehnke[8] and Francis S. Collins[2]





Rare Diseases: Window on Nature?

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*

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