Extraordinary Opportunities for Biomedical Research

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

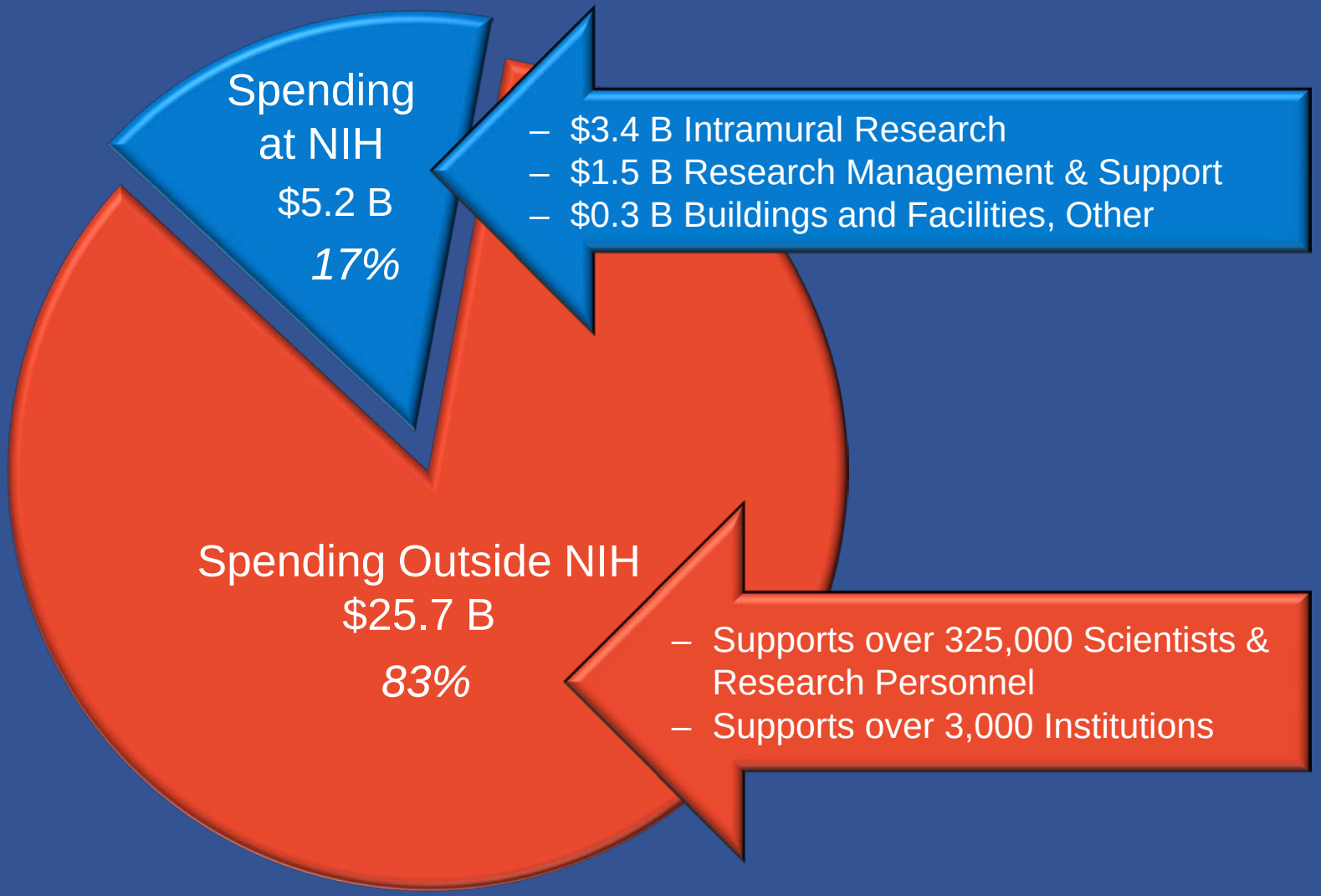
Council of Councils
February 1, 2012

NIH: Steward of Medical and Behavioral Research for the Nation

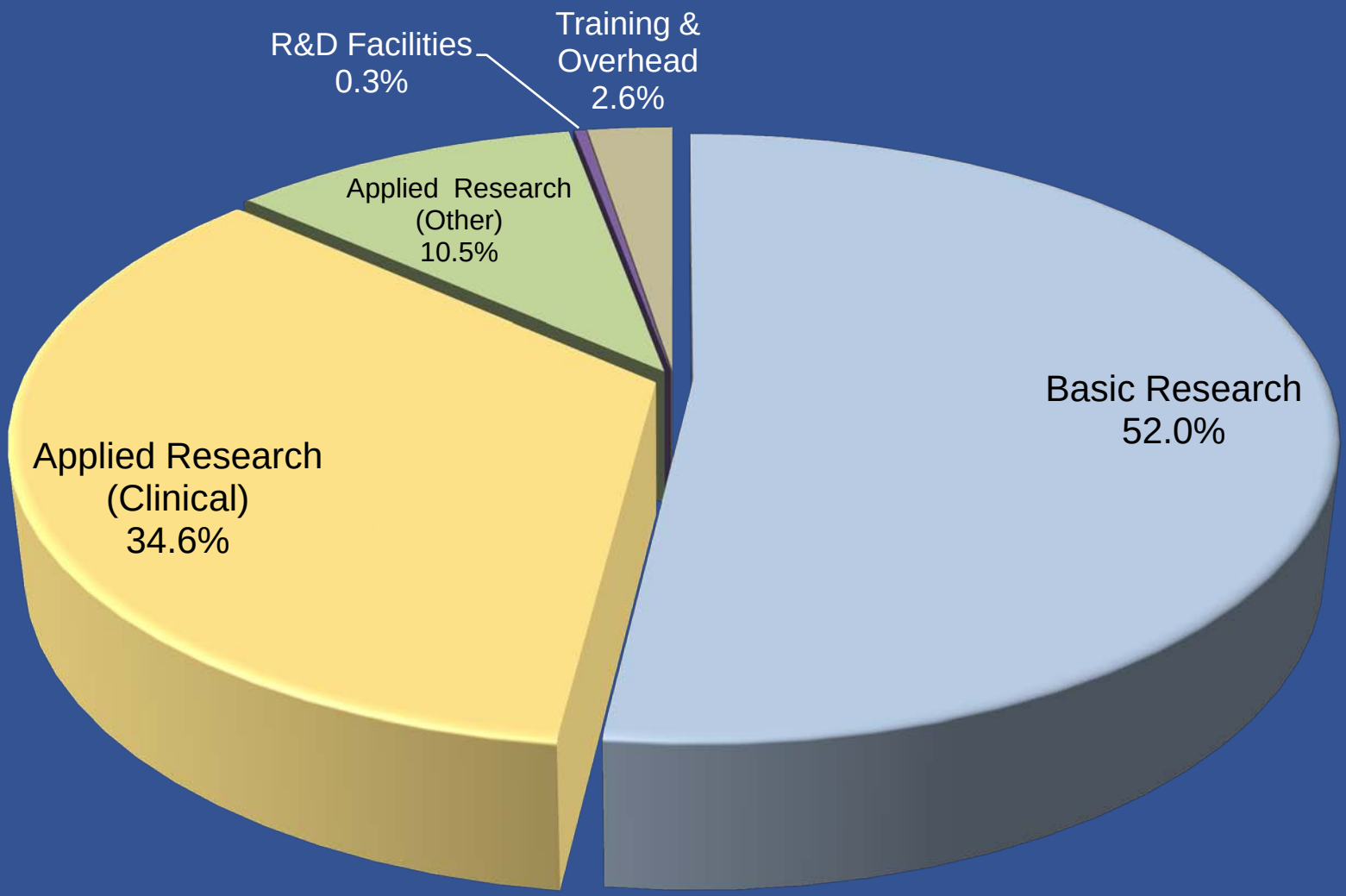
"Science in pursuit of fundamental knowledge about the nature and behavior of living systems… and the application of that knowledge to extend healthy life and reduce the burdens of illness and disability."

NIH Extramural & Intramural Funding

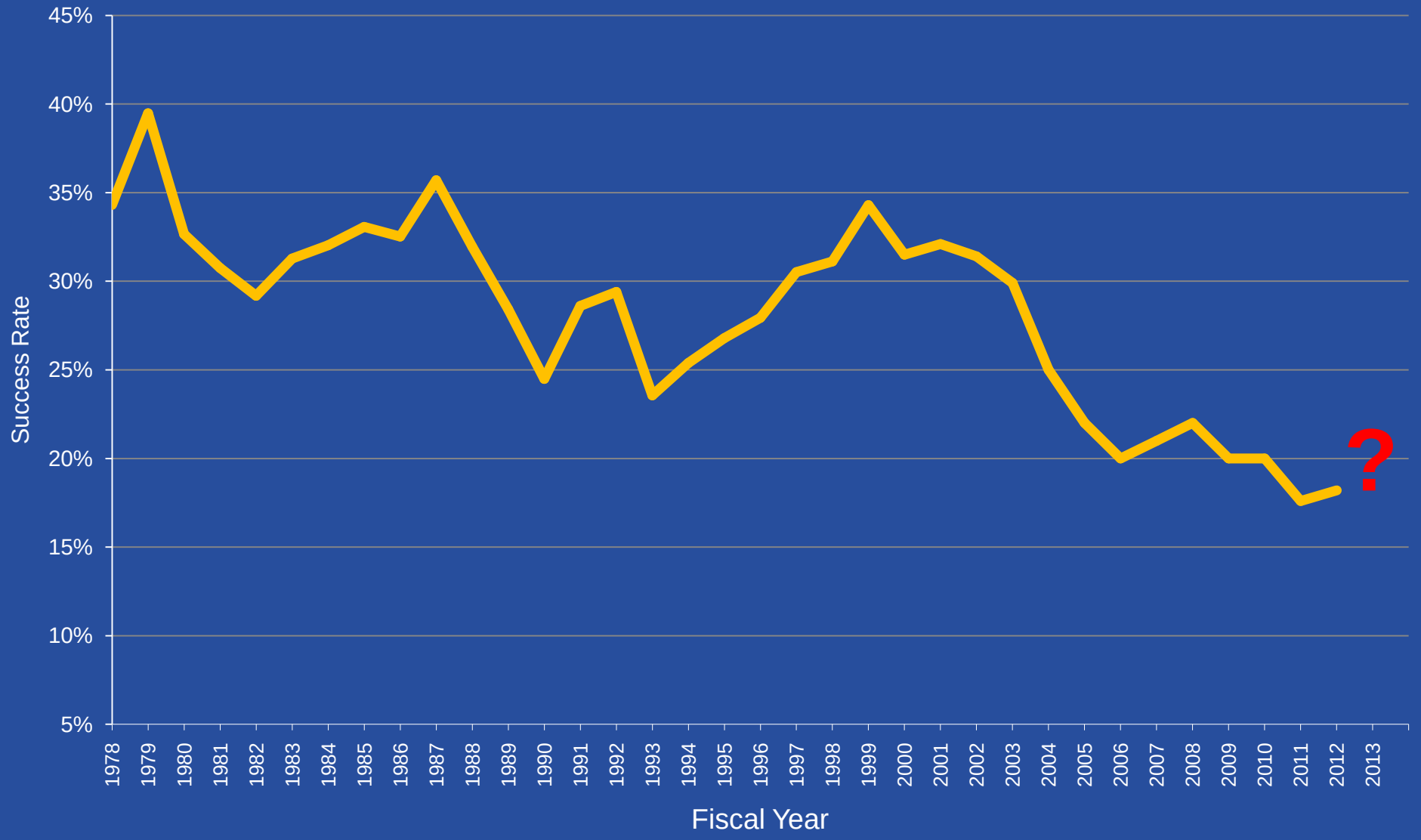
FY 2012 Enacted: $30.9 Billion



FY 2011 Percent Distribution of Basic and Clinical Research



Grant Success Rates
FY 1978-2013



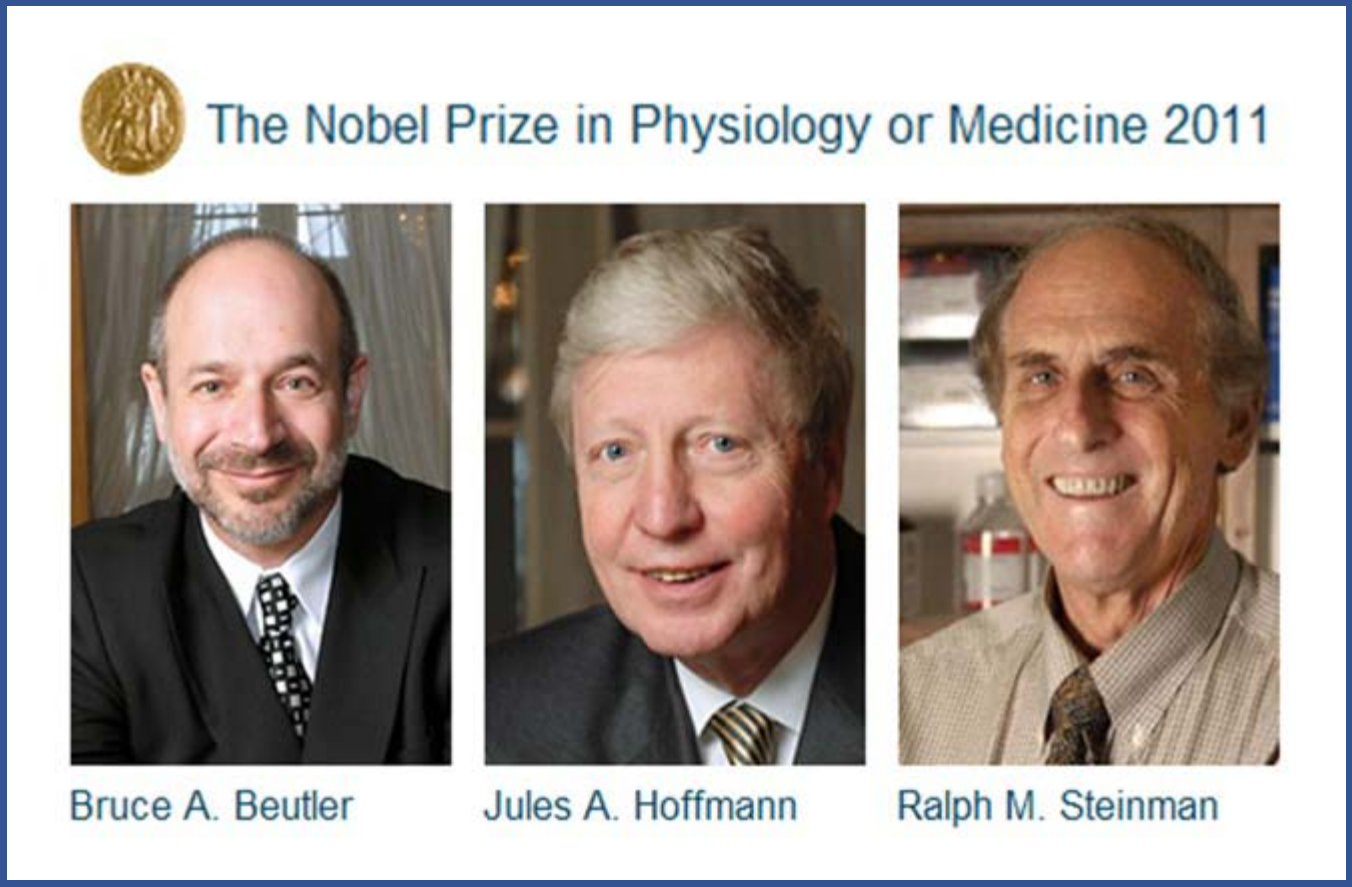
"But the bravest are surely those who have the clearest vision of what is before them, glory and danger alike, and yet notwithstanding go out to meet it."

– Thucydides

Extraordinary Opportunities

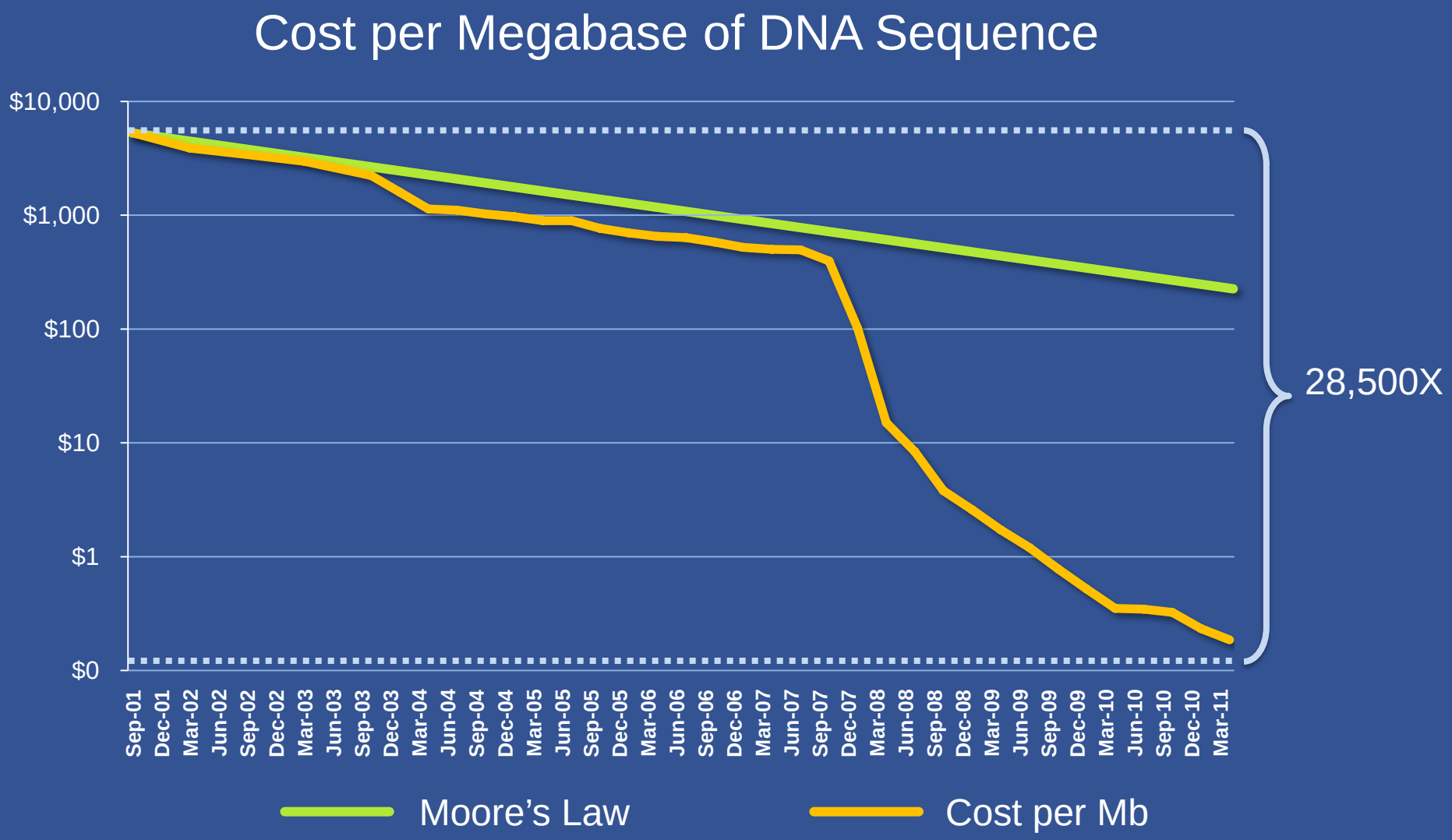
- Investing in Basic Research
- Accelerating Discovery Through Technology
- Advancing Translational Sciences
- Encouraging New Investigators and New Ideas

Investing in Basic Research



NIH-supported Nobel Prize Winners: 135

Sequencing Costs Drop Faster than Moore's Law



Extraordinary Opportunities

- Investing in Basic Research
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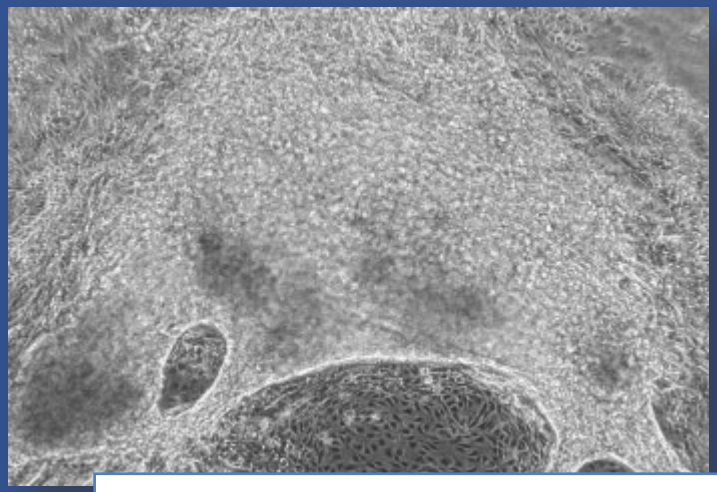
- Advancing Translational Sciences
- Encouraging New Investigators and New Ideas

Exciting Technologies
Human iPS Cells



Science

AAAS

Science **318**, 1917 (2007)

Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells

Junying Yu,[1,2]* Maxim A. Vodyanik,[2] Kim Smuga-Otto,[1,2] Jessica Antosiewicz-Bourget,[1,2] Jennifer L. Frane,[1] Shulan Tian,[3] Jeff Nie,[3] Gudrun A. Jonsdottir,[3] Victor Ruotti,[3] Ron Stewart,[3] Igor I. Slukvin,[2,4] James A. Thomson[1,2,5]*

Cell *131*, 861–872, November 30, 2007 ©2007 Elsevier Inc.

Cell

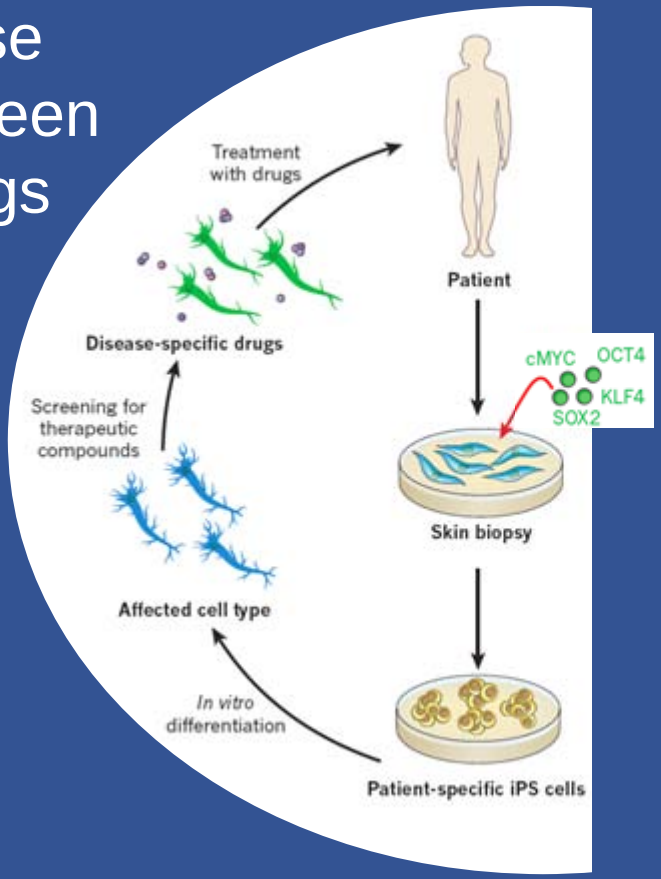
Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors

Kazutoshi Takahashi,[1] Koji Tanabe,[1] Mari Ohnuki,[1] Megumi Narita,[1,2] Tomoko Ichisaka,[1,2] Kiichiro Tomoda,[3] and Shinya Yamanaka[1,2,3,4,*]

[1]Department of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan
[2]CREST, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan
[3]Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA
[4]Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8507, Japan

Human iPS Cells, 5 Years Later: Promise for Research and Therapy

Model disease *in vitro* to screen potential drugs



Nature, Jan 19, 2012 vol 481

iPS Models of Disease

- > 45 diseases to date
  - Neurological
  - Hematological
  - Metabolic
  - Cardiovascular
  - Primary Immunodeficiency
  - Other

Table 2 | Diseases modelled with iPS cells

Disease	Molecular defect of donor cell	Cell type differentiated from iPS cells	Disease phenocopied in differentiated cells	Drug or functional tests
Neurological				
Amyotrophic lateral sclerosis (ALS)	Heterozygous Leu144Phe mutation in SOD1	Motor neurons and glial cells	ND	No
Spinal muscular atrophy (SMA)	Mutations in *SMN1*	Neurons and astrocytes, and mature motor neurons	Yes	Yes
Parkinson's disease	Multifactorial; mutations in *LRRK2* and/or *SNCA*	Dopaminergic neurons	No	Yes
Huntington's disease	72 CAG repeats in the huntingtin gene	None	NA	No
Down's syndrome	Trisomy 21	Teratoma with tissue from each of the three germ layers	Yes	No
Fragile X syndrome	CGG triplet repeat expansion resulting in the silencing of *FMR1*	None	NA	No
Familial dysautonomia	Mutation in *IKBKAP*	Central nervous-system lineage, peripheral neurons, haematopoietic cells, endothelial cells and endodermal cells	Yes	Yes
Rett's syndrome	Heterozygous mutation in *MECP2*	Neural progenitor cells	Yes	Yes
Mucopolysaccharidosis type IIIB (MPS IIIB)	Homozygous mutation in *NAGLU*	Neural stem cells and differentiated neurons	Partially	Yes
Schizophrenia	Complex trait	Neurons	Yes	Yes
X-linked adrenoleukodystrophy (X-ALD), childhood cerebral ALD (CCALD) and adrenomyeloneuropathy (AMN)	Mutation in *ABCD1*	Oligodendrocytes and neurons	Partially	Yes
Haematological				
ADA SCID	Mutation or deletion in *ADA*	None	ND	No
Fanconi's anaemia	*FAA* and *FAD2* corrected	Haematopoietic cells	No (corrected)	No
Schwachman–Bodian–Diamond syndrome	Multifactorial	None	NA	No
Sickle-cell anaemia	Homozygous HbS mutation	None	NA	No
β-Thalassaemia	Homozygous deletion in the β-globin gene	Haematopoietic cells	ND	No
Polycythaemia vera	Heterozygous Val617Phe mutation in *JAK2*	Haematopoietic progenitors (CD34$^+$CD35$^+$)	Partially	No
Primary myelofibrosis	Heterozygous mutation in *JAK2*	None	NA	No
Metabolic				
Lesch–Nyhan syndrome (carrier)	Heterozygous mutation in *HPRT1*	None	NA	No
Type 1 diabetes	Multifactorial; unknown	β-Cell-like cells (express somatostatin, glucagon and insulin; glucose-responsive)	ND	No
Gaucher's disease, type III	Mutation in *GBA*	None	NA	No
α1-Antitrypsin deficiency (A1ATD)	Homozygous mutation in the α1-antitrypsin gene	Hepatocyte-like cells (fetal)	Yes	No
Glycogen storage disease Ia (GSD1a)	Defect in glucose-6-phosphate gene	Hepatocyte-like cells (fetal)	Yes	No
Familial hypercholesterolaemia	Autosomal dominant mutation in *LDLR*	Hepatocyte-like cells (fetal)	Yes	No
Crigler–Najjar syndrome	Deletion in *UGT1A1*	Hepatocyte-like cells (fetal)	ND	No
Hereditary tyrosinaemia, type 1	Mutation in *FAH01*	Hepatocyte-like cells (fetal)	ND	No
Pompe disease	Knockout of *GAA*	Skeletal muscle cells	Yes	No
Progressive familial cholestasis	Multifactorial	Hepatocyte-like cells (fetal)	ND	No
Hurler syndrome (MPS IH)	Genetic defect in *IDUA*	Haematopoietic cells	No	No
Cardiovascular				
LEOPARD syndrome	Heterozygous mutation in *PTPN11*	Cardiomyocytes	Yes	No
Type 1 long QT syndrome	Dominant mutation in *KCNQ1*	Cardiomyocytes	Yes	No
Type 2 long QT syndrome	Missense mutation in *KCNH2*	Cardiomyocytes	Yes	Yes
Primary immunodeficiency				
SCID or leaky SCID	Mutation in *RAG1*	None	NA	No
Omenn syndrome (OS)	Mutation in *RAG1*	None	NA	No
Cartilage-hair hypoplasia (CHH)	Mutation in *RMRP*	None	NA	No
Herpes simplex encephalitis (HSE)	Mutation in *STAT1* or *TLR3*	Mature cell types of the central nervous system	No	No
Other category				
Duchenne muscular dystrophy	Deletion in the dystrophin gene	None	NA	No
Becker muscular dystrophy	Unidentified mutation in dystrophin	None	NA	No
Dyskeratosis congenita (DC)	Deletion in *DKC1*	None	NA	No
Cystic fibrosis	Homozygous deletion in *CFTR*	None	NA	No
Friedreich's ataxia (FRDA)	Trinucleotide GAA repeat expansion in *FXN*	Sensory and peripheral neurons, and cardiomyocytes	Partially	No
Retinitis pigmentosa	Heterogeneity in causative genes and mutations: mutations in *RP9*, *RP1*, *PRPH2* or *RHO*	Retinal progenitors, photoreceptor precursors, retinal-pigment epithelial cells and rod photoreceptor cells	Yes	Yes
Recessive dystrophic epidermolysis bullosa (RDEB)	Mutation in *COL7A1*	Haematopoietic cells, and epidermis-like keratinocytes that differentiate into cells of all three germ layers *in vivo*	Partially	Yes
Scleroderma	Unknown	None	NA	No
Osteogenesis imperfecta	Mutation in *COL1A2*	None	NA	No

An extended version of this table includes references and more information about drug and functional tests (Supplementary Table 1). *ABCD1*, ATP-binding cassette, sub-family D, member 1; *ADA*, adenine deaminase; *CFTR*, cystic fibrosis transmembrane conductance regulator; *COL1A2*, α2-chain of type I collagen; *COL7A1*, α1-chain of type VII collagen; *DKC1*, dyskerin; *FAA*, Fanconi's anaemia, complementation group A; *FAD2*, Fanconi's anaemia, complementation group D2; *FAHD1*, fumarylacetoacetate hydrolase; *FMR1*, fragile X mental retardation 1; *FXN*, frataxin; *GAA*, acid α-glucosidase; *GBA*, acid β-glucosidase; HbS, sickle haemoglobin; *HPRT1*, hypoxanthine phosphoribosyltransferase 1; *IDUA*, α-L-iduronidase; *JAK2*, Janus kinase 2; *KCNH2*, potassium voltage-gated channel, subfamily H (eag-related), member 2; *KCNQ1*, potassium voltage-gated channel, KQT-like subfamily, member 1; *LDLR*, low-density lipoprotein receptor; *LRRK2*, leucine-rich repeat kinase 2; *MECP2*, methyl CpG binding protein 2; NA, not applicable; *NAGLU*, α-N-acetylglucosaminidase; ND not determined; *PRPH2*, peripherin 2; *PTPN11*, protein tyrosine phosphatase, non-receptor type 11; *RAG1*, recombination activating gene 1; *RHO*, rhodopsin; *RMRP*, RNA component of mitochondrial-RNA-processing endoribonuclease; *RP*, retinitis pigmentosa; SCID, severe combined immunodeficiency; *SMN1*, survival of motor neuron 1; *SNCA*, α-synuclein; SOD1, superoxide dismutase 1; *STAT1*, signal transducer and activator of transcription 1; *TLR3*, Toll-like receptor 3; *UGT1A1*, UDP glucuronosyltransferase 1 family, polypeptide A1.

Nature, Jan 19, 2012 vol 481, 295-96

iPS Models of Disease: Long QT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 7, 2010 VOL. 363 NO. 15

Patient-Specific Induced Pluripotent Stem-Cell Models for Long-QT Syndrome

Alessandra Moretti, Ph.D., Milena Bellin, Ph.D., Andrea Welling, Ph.D., Christian Billy Jung, M.Sc., Jason T. Lam, Ph.D., Lorenz Bott-Flügel, M.D., Tatjana Dorn, Ph.D., Alexander Goedel, M.D., Christian Höhnke, M.D., Franz Hofmann, M.D., Melchior Seyfarth, M.D., Daniel Sinnecker, M.D., Albert Schömig, M.D., and Karl-Ludwig Laugwitz, M.D.

LETTER

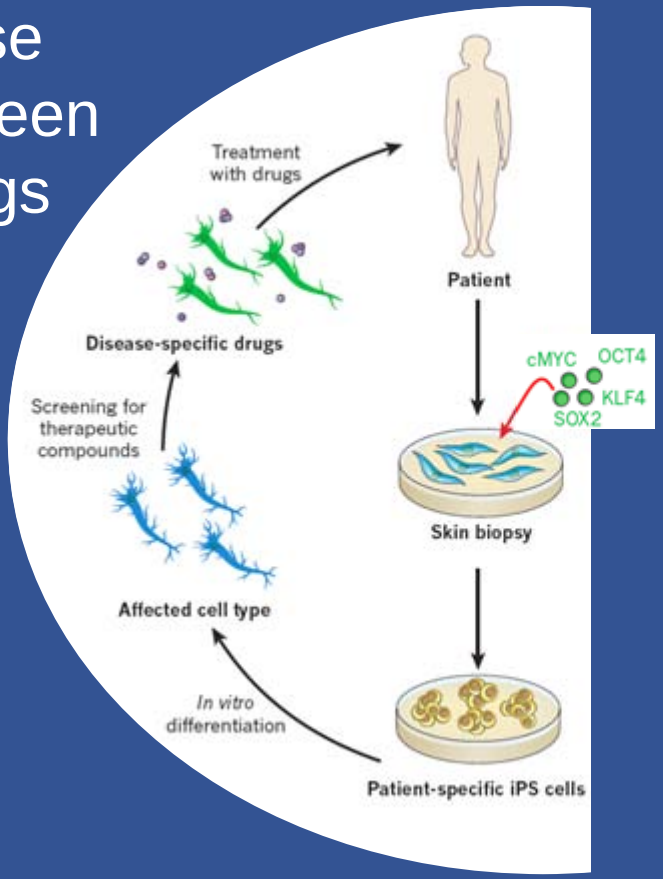
NATURE | VOL 471 | 10 MARCH 2011

Modelling the long QT syndrome with induced pluripotent stem cells

Ilanit Itzhaki[1]*, Leonid Maizels[1]*, Irit Huber[1]*, Limor Zwi-Dantsis[1], Oren Caspi[1], Aaron Winterstern[1], Oren Feldman[1], Amira Gepstein[1], Gil Arbel[1], Haim Hammerman[2], Monther Boulos[2] & Lior Gepstein[1,2]

Human iPS Cells, 5 Years Later: Promise for Research and Therapy

Model disease *in vitro* to screen potential drugs



Facilitate personalized cell therapy

Nature, Jan 19, 2012 vol 481

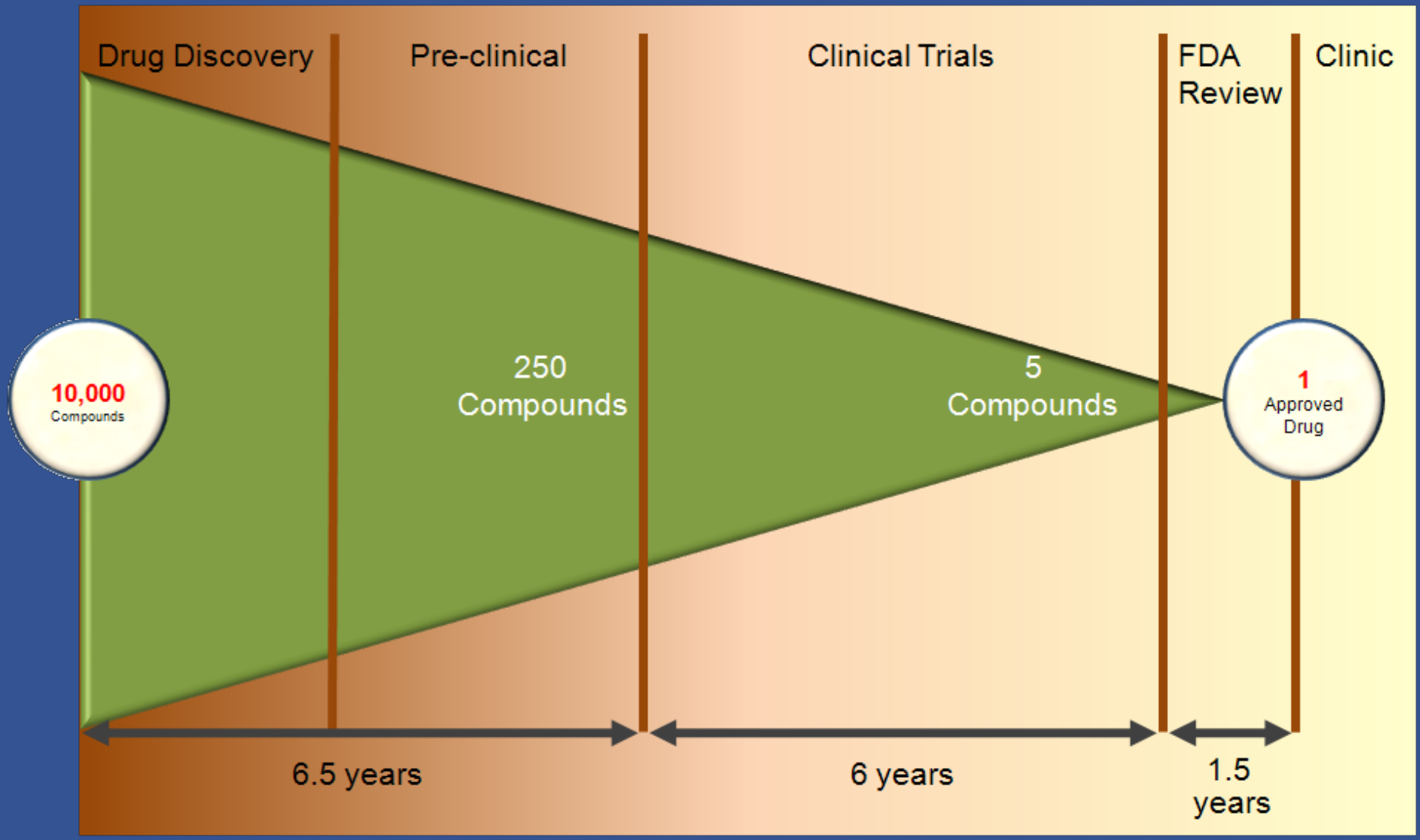
NIH Center for Regenerative Medicine (NIH-CRM)

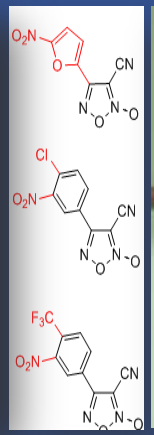
- Vast unmet need; therapies exist for ~200 of ~4000 conditions with defined molecular causes
- Tap into NIH Intramural's proven ability to assemble interdisciplinary teams, build community resources
- Desire to capitalize on NIH Clinical Center's strengths
  - Well-defined patient cohorts, many with life-threatening, rare, or neglected diseases
  - GMP facility for cellular therapies
  - Expertise in gene therapy/stem cell transplantation

Extraordinary Opportunities

- Investing in Basic Research
- Accelerating Discovery Through Technology
- Advancing Translational Sciences
- Encouraging New Investigators and New Ideas

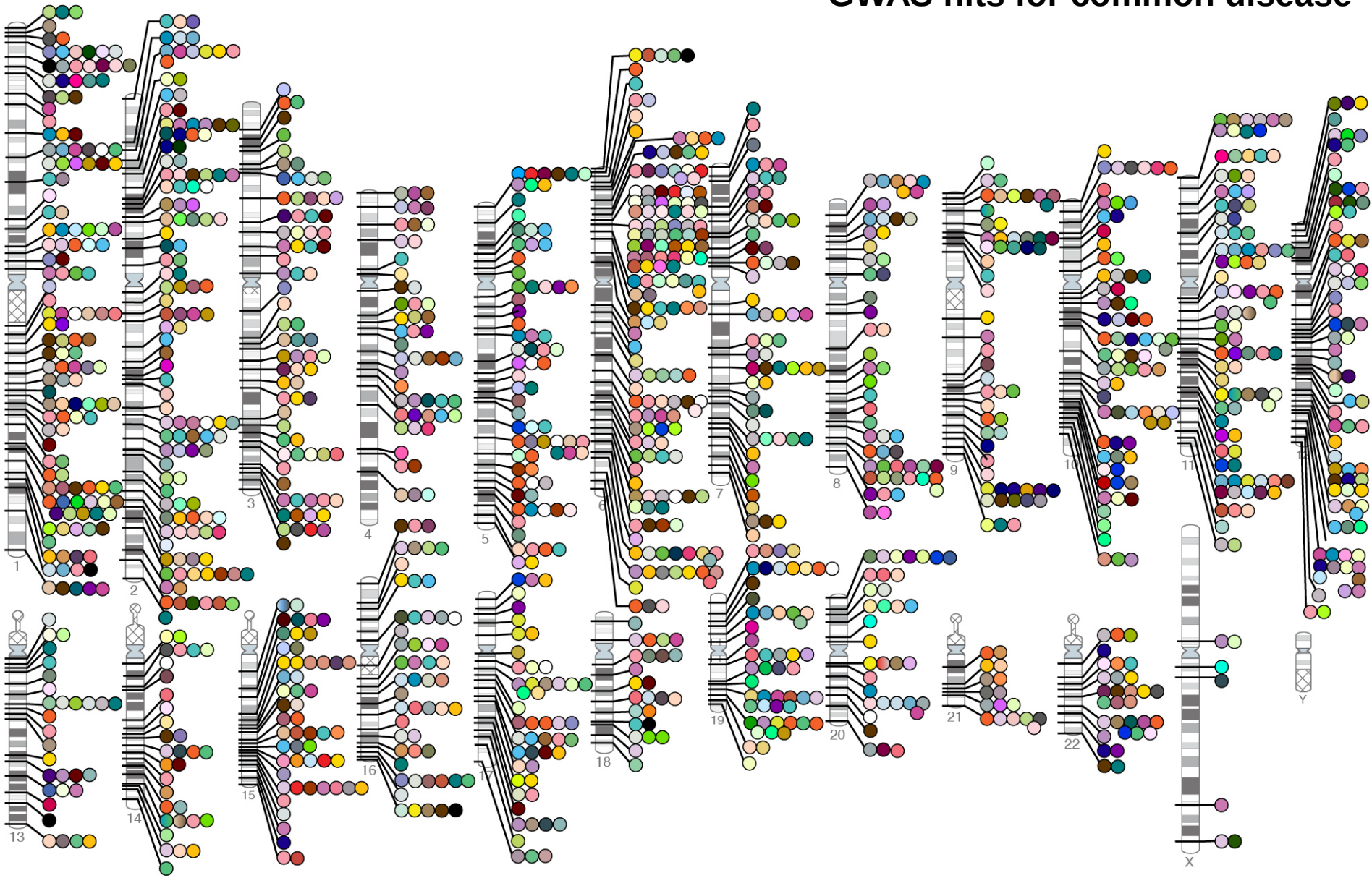
Advancing Translational Sciences



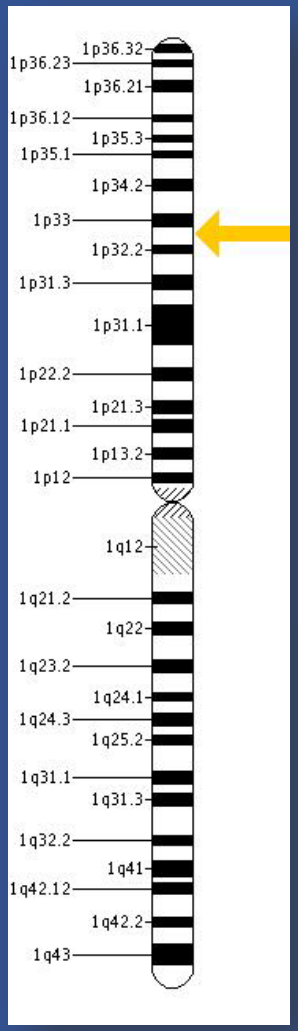


Disease | Target ID | Assay Dev. | HTS | Probe to Lead | Pre-Clinical | FDA IND | Ph. I | Ph. II | Ph. III | FDA Re-view | Clinic

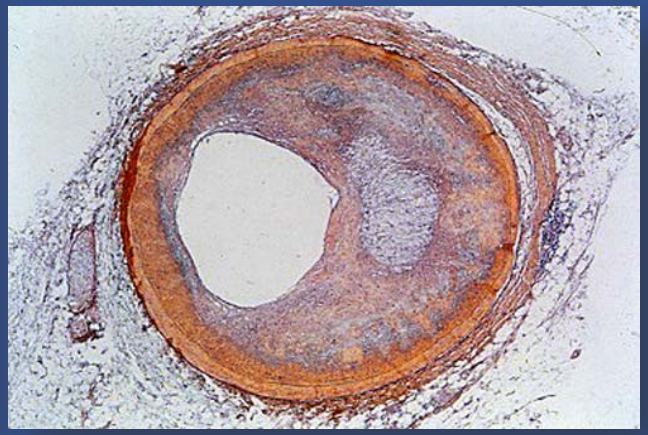
GWAS hits for common disease

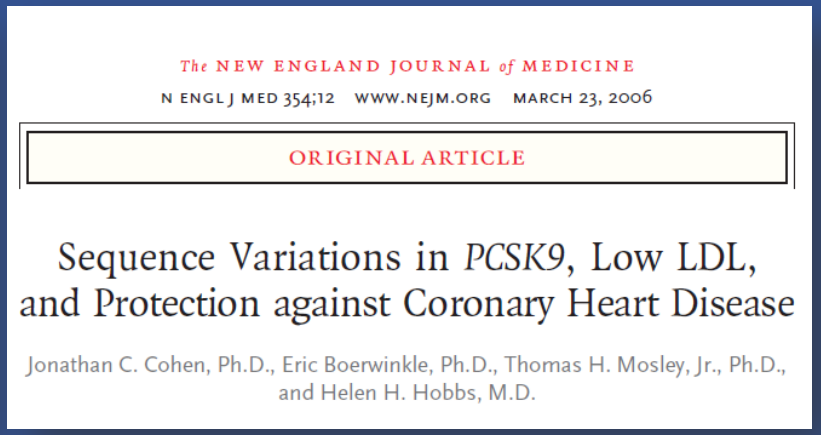


PCSK9 Inhibitors: The Next Statins?



- Certain mutations result in **reduced** PCSK9 protein, **lower** levels of LDL, and **decreased** risk of heart disease
- Possible new target for managing cholesterol
- Multiple PCSK9 inhibitors now in early phase clinical trials





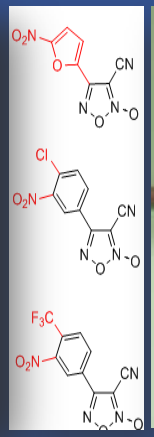
The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 354;12 WWW.NEJM.ORG MARCH 23, 2006

ORIGINAL ARTICLE

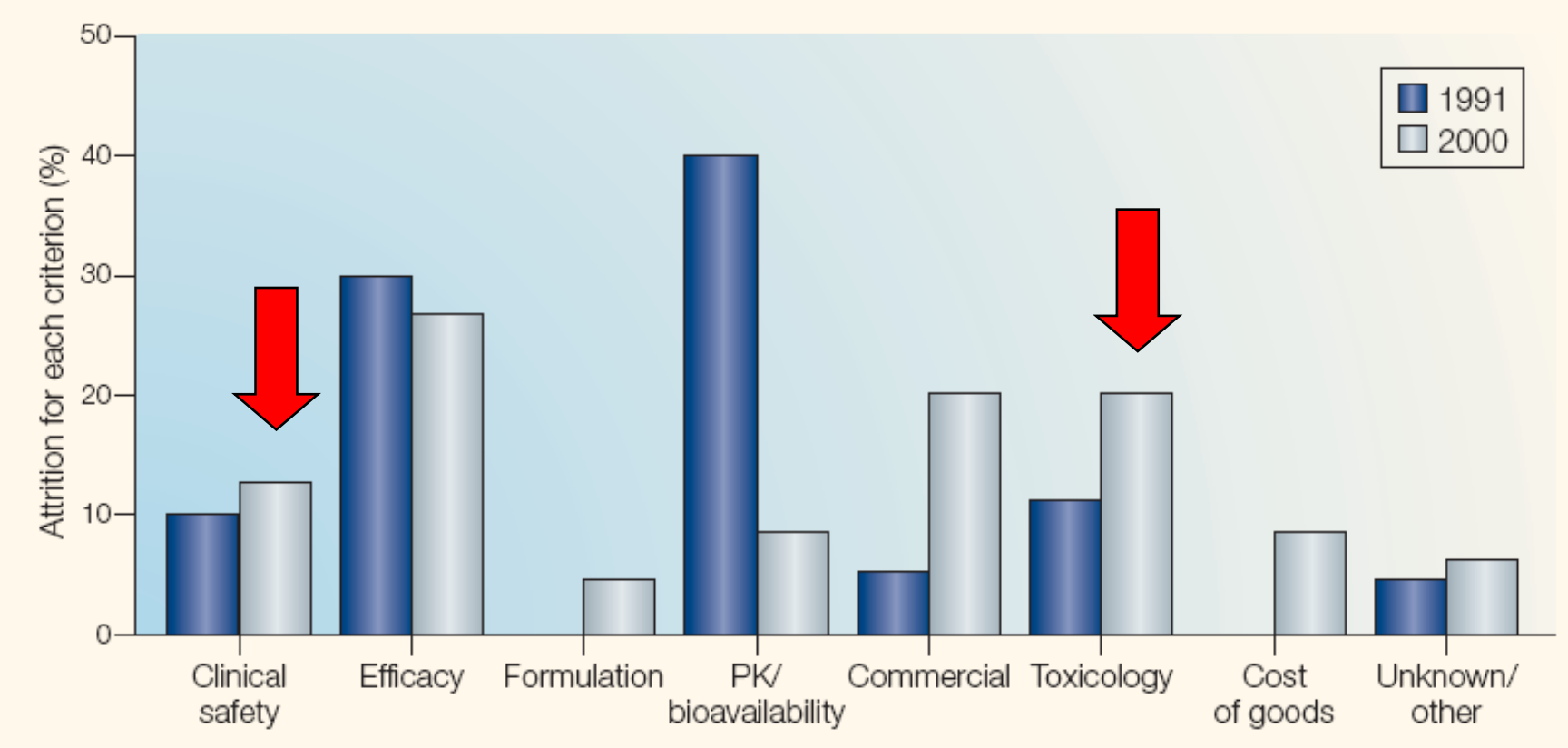
Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.



Disease | Target ID | Assay Dev. | HTS | Probe to Lead | Pre-Clinical | FDA IND | Ph. I | Ph. II | Ph. III | FDA Re-view | Clinic

Toxicity is the Most Common Reason for Drug Development Failure

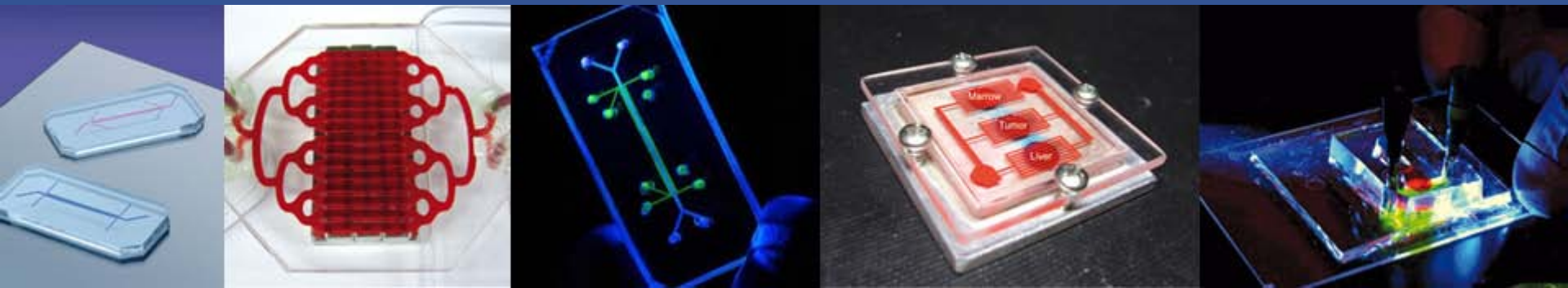


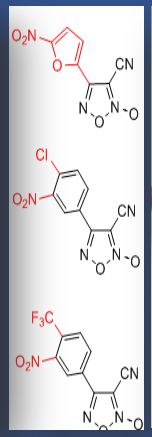
Preclinical (21%) + Clinical (12%) Tox = 33% of all failures

Kola and Landis, *Nature Reviews Drug Discovery* 3, 711-716, 2004

Better Ways to Predict Drug Safety
New NIH-DARPA-FDA Collaboration

- Part of President's "Lab to Market" initiatives
- Goal: develop chip to screen for safe, effective drugs
  - Liver, heart, lung, other cell types
  - Designed for multiple different readouts
- NIH, DARPA to commit ~$70 million each over 5 years
- FDA to offer guidance
- First Requests for Proposals *(due January 26, 2012)*
  - Seeking best ideas in engineering, biology, toxicology





Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. I	Ph. II	Ph. III	FDA Re-view	Clinic

Rescuing, Repurposing, Repositioning

BIOMEDICINE

24 June 2011 Vol. 332 no. 6037 p. 1492 **Science**

NIH's Secondhand Shop for Tried-and-Tested Drugs

Although the U.S. National Institutes of Health (NIH) has made waves with a proposed new center aimed at translational research, so far the main innovation has been to put scattered existing programs under the same roof. But this month NIH Director Francis Collins unveiled something fresh: an effort to persuade drug companies to open up their troves of abandoned drugs to academics, who would look for new uses.

But NIH officials think there's merit in a more systematic effort. One reason is efficiency, NIH Associate Director for Science Policy Amy Patterson explained to the NIH board this month. Although only 1 in 10,000 potential therapeutic compounds will become a drug, the majority fail in late trials because of lack of efficacy, not safety. That means toxicity often isn't a barrier, Patterson said. She cited an estimated success rate of 30% for repurposed drugs. And NIH says that

As for logistics, the agency has made a small start. In April, NIH's intramural Chemical Genomics Center unveiled a public database listing all 8000 or so approved drugs along with structural data (*Science Translational Medicine*, 27 April, http://scim.ag/chem-genome). Researchers can apply to have the center test their cell or molecular assays against the drugs to look for "hits," or possible biological activity.

For unapproved drugs, Patterson says, NIH envisions a system of databases that would allow researchers to "window-shop" by viewing public data. If they see a compound that interests them, they might access a company's proprietary data through service companies.

NIH hopes to complete the model master agreement within 6 to 8 months, Patterson says. The drug rescue and repurposing project will be led by a team at NCATS as "an integral

NIH DRUG REPURPOSING

Drug	Initial Indication	Subsequent Indication
AZT	Antineoplastic	HIV/AIDS
Ceftriaxone	Bacterial infection	Amyotrophic lateral sclerosis
Hydroxyurea	Cancers	Sickle cell anemia
Metformin	Type 2 diabetes	Breast cancer
Pioglitazone	Type 2 diabetes	Hepatic steatosis
Raloxifene	Osteoporosis	Breast cancer
Tamoxifen	Breast cancer	Bipolar disorder

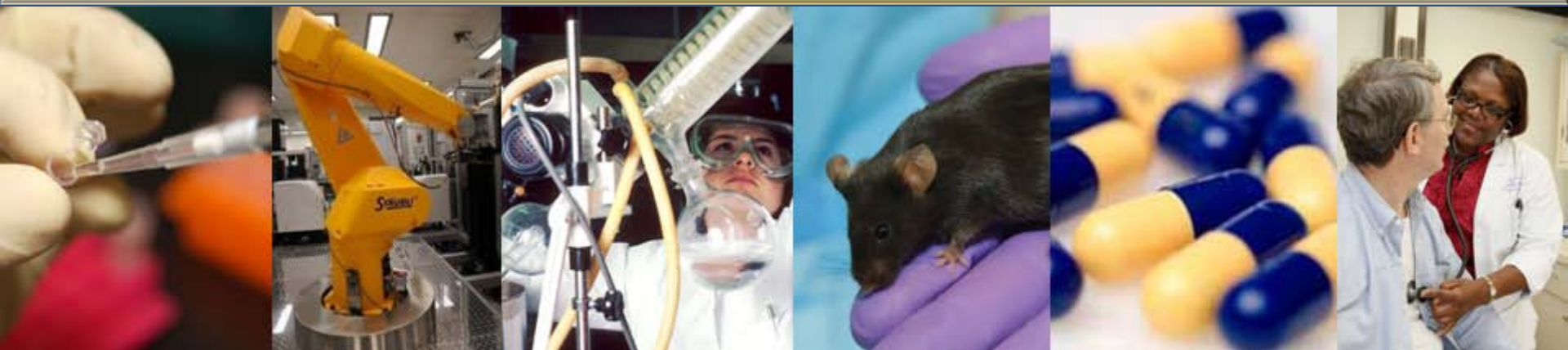
Double duty. NIH researchers have found new uses for several therapeutics.

National Center for Advancing Translational Sciences (NCATS)

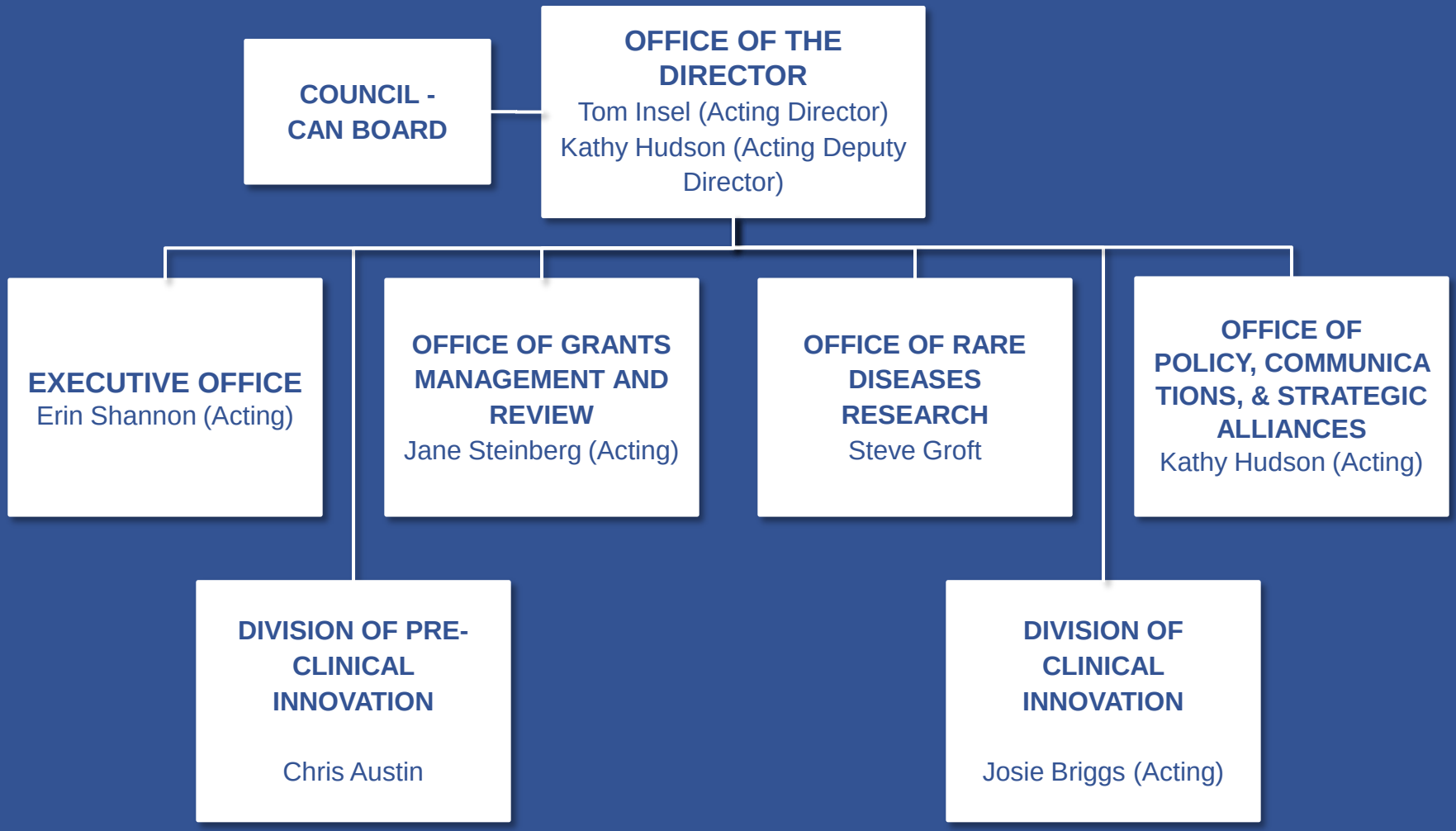
Mission:

To advance the discipline of translational science and catalyze the development, testing, and implementation of novel diagnostics and therapeutics across a wide range of human diseases and conditions.

http://ncats.nih.gov/



NCATS Organization



NCATS:

- Complements – does not compete with – the private sector
- Facilitates – does not duplicate – the translational research activities supported and conducted by the NIH Institutes and Centers
- Reinforces – does not reduce – NIH's commitment to basic science research

Extraordinary Opportunities

- Investing in Basic Research
- Accelerating Discovery Through Technology
- Advancing Translational Sciences
- Encouraging New Investigators and New Ideas

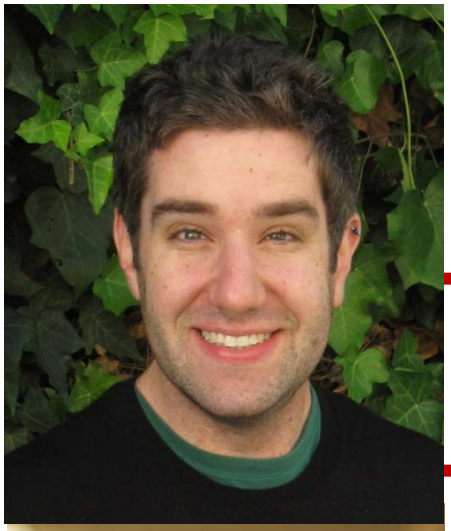
Opportunities for Tomorrow
NIH Investing in New, Transformative Ideas

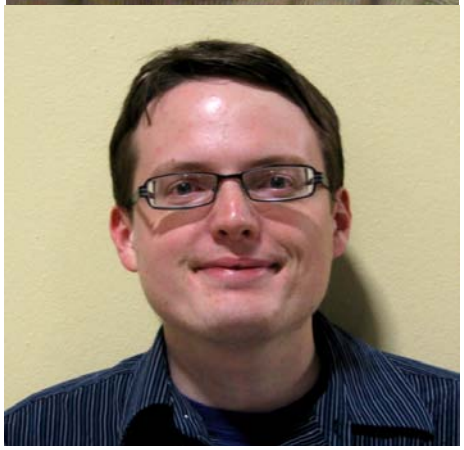
- NIH-Lasker Clinical Research Scholars
- Transformative R01
- NIH Director's Pioneer Award
- New Innovator Award
- NIH Director's Early Independence Awards

30 under 30
Science & Innovation

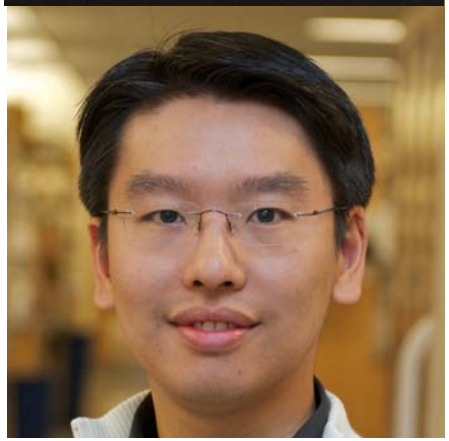
John Calarco
Harvard University

James S. Fraser
UC San Francisco





Jeffrey M. Kidd
Stanford University



Harris H. Wang
Harvard Medical School

Additional
2011 Awardees
Highlighted

ACD Working Group on the Future Biomedical Research Workforce

- **Shirley Tilghman, Ph.D.,** co-chair
  Princeton University
- **Sally Rockey, Ph.D.,** co-chair
  NIH
- **Sandra Degen, Ph.D.**
  University of Cincinnati
- **Laura Forese, M.D.**
  Weill Cornell Medical Center
- **Donna Ginther, Ph.D.**
  University of Kansas
- **Arthur Gutierrez-Hartmann, M.D.**
  University of Colorado Denver
- **Freeman Hrabowski, Ph.D.**
  Univ of Maryland, Baltimore County
- **James Jackson, Ph.D.**
  University of Michigan, Ann Arbor
- **Leemor Joshua-Tor, Ph.D.**
  Cold Spring Harbor Laboratory
- **Richard Lifton, M.D., Ph.D**.
  Yale School of Medicine
- **Garry Neil, M.D.**
  Johnson & Johnson
- **Naomi Rosenberg, Ph.D.**
  Tufts University
- **Bruce A. Weinberg, Ph.D.**
  The Ohio State University
- K**eith Yamamoto, Ph.D.**
  Univ of California, San Francisco

Opportunities for Tomorrow

Greater Diversity in Research Workforce

African Americans, Hispanics, and Native Americans:

- Represent 31% of U.S. college age population but only account for 14% of undergraduates in life sciences
- And even fewer in later stages

Greater Diversity in Research Workforce

NIH's Plan for Action:

POLICYFORUM

SOCIOLOGY

Weaving a Richer Tapestry in Biomedical Science

NIH leadership discusses the need for renewed efforts to increase diversity in the U.S. biomedical research workforce.

Lawrence A. Tabak* and Francis S. Collins*

As much as the U.S. scientific community may wish to view itself as a single garment of many diverse and colorful threads, a unifying consideration of actual data reminds us that our nation's biomedical research workforce remains nowhere near as rich as it could be. An analysis performed by a team of researchers primarily supported by the National Institutes of Health (NIH) and published in this issue of *Science*, reveals that from 2000 to 2006, black (*1*) grant applicants were significantly less likely to receive NIH research funding than were white applicants. The gap in success rates amounted to 10 percentage points, even after controlling for education, country of origin, training, employer characteristics, previous research awards, and publication record (*2*). Their analysis also showed a gap of 4.2 percentage points for Asians; however, the differences between Asian and white

of early career reviewers, including represented populations

view process for bias and develop

for grant applicants

vice on additional action steps

ACD Working Group on Diversity in the Biomedical Research Workforce

- **Reed Tuckson, M.D.,** co-chair
  UnitedHealth Group
- **John Ruffin, Ph.D.,** co-chair
  NIH
- **Lawrence Tabak, D.D.S., Ph.D.**
  NIH
- **Ann Bonham, Ph.D.**
  AAMC
- **Jordan Cohen, M.D.**
  AAMC
- **José Florez, M.D., Ph.D.**
  Harvard Medical School
- **Gary Gibbons, M.D.**
  Morehouse School of Medicine
- **Renee Jenkins, M.D.**
  Howard University
- **Tuajuanda Jordan, Ph.D.**
  Lewis and Clark College
- **Wayne Riley, M.D., M.P.H., M.B.A.**
  Meharry Medical College
- **Samuel Silverstein, M.D.**
  Columbia University Medical Center
- **Dana Yasu Takagi, Ph.D.**
  University of California, Santa Cruz
- **Maria Teresa Velez, Ph.D.**
  University of Arizona
- **M. Roy Wilson, M.D., M.S.**
  Charles R. Drew University
- **Keith Yamamoto, Ph.D.**
  University of California, San Francisco
- **Clyde Yancy, M.D.**
  Northwestern University

“If we’re going to create jobs now and in the future, we're going to have to out-build and out-educate and out-innovate every other country on Earth.”

President Obama
Signing of America Invents Act
Thomas Jefferson High School
September 16, 2011

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