The USA: National Institutes of Health (NIH) as Driver for the Clinical Scientist and Medical Research

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Outline

• NIH Overview
• Current areas of NIH emphasis
• Challenges in translational research
• Role of National Center for Advancing Translational Sciences and the NIH Clinical Center
“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.”
The National Institutes of Health

Extramural only

No Funding Authority
Core Components of the NIH Mission

• **Extramural Research** - Supporting research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout United States and overseas

• **Intramural Research** – Conducting research in its own laboratories

• **Training** - Helping train research investigators

• **Communication** - Fostering communication of medical information
NIH Extramural & Intramural Funding
FY 2014: $30.15 Billion

Spending at NIH
Spending Outside NIH
NIH’s Commitment to Basic Research

- Basic Research
- Applied Research
NIH’s Impact on U.S. Health and Medicine

U.S. Life Expectancy

- Reduction in deaths from:
  - Heart disease
  - Stroke
  - HIV/AIDS

- Increased survival rates for:
  - Breast cancer
  - Cervical cancer
  - Colon cancer

NIH Accomplishments

- Life expectancy gains worth ~$3.2 trillion annually

- Cardiovascular disease death rates have fallen > 60% in the last half-century

- HIV therapies enable people in their 20s to live to age 70+

- Cancer rates now falling ~1% per year; each 1% drop saves ~$500 billion
Impact of NIH-Supported Research On U.S. Economy

• In 2011, NIH research supported 432,000 jobs at more than 2,500 institutions, small businesses nationwide

• In 2011, NIH funding generated $62 billion in new economic activity—double taxpayers’ investment

• NIH serves as foundation for entire U.S. medical innovation sector that:
  – Employs 1 million U.S. citizens
  – Generates $84 billion in wages, salaries
  – Exports $90 billion in goods, services

Source: An Economic Engine: NIH Research, Employment and the Future of the Medical Innovation Sector, United Medical Research, May 2011
Every Voice Counts

General Public
Scientists
Voluntary Organizations
Scientific Review Committees
U.S. President
Director's Council of Public Representatives (COPR)
Boards of Scientific Counselors
Public Members on Advisory Councils
NIH Staff
Congress
Scientist Council Members
Advisory Committee to the Director (ACD)
Ad Hoc Advisors
Physicians & Other Health Professionals
Professional Societies
Industry

Every Voice Counts
NIH Leading the Way...

- Genomics
- Cell Therapy/Regenerative Medicine
- Vaccine Development
- Human Microbiome
- BRAIN initiative
- Big Data Problem
Genetic Variants Associated with Disease Risk
Cost of Sequencing a Human Genome

September 2001 - October 2013

5,096
Disorders with Known Molecular Basis

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

<500 with therapy
Leading in Genome-Wide Association: 
Age-Related Macular Degeneration

Genome-wide association studies in Asians confirm the involvement of ATOH7 and TGFBR3, and further identify CARD10 as a novel locus influencing optic disc area.


Identification of a Candidate Gene for Astigmatism

Margarida C. Lopes, Pietro G. Hysi, Virginie J. M. Verhoeven, Stuart Macgregor, Alex W. Hewitt, Grant W. Montgomery, Phillippa Cumberland, Johannes R. Vingerling, Terri L. Young, Cornelia M. van Duijn, Ben Oostra, Andre G. Uitterlinden, Jugnoo S. Rabi, David A. Mackey, Caroline C. W. Klaver, Toby Andrew, and Christopher J. Hammond.

Genome-wide association study of primary open angle glaucoma risk and quantitative traits

Jane Gibson, Helen Griffiths, Gabriella De Salvo, Mick Cole, Aby Jacob, Alex MacLeod, Yit Yang, Geeta Menon, Angela Cree, Sarah Ennis, Andrew Lotery.

A genome-wide association study for corneal curvature identifies the platelet-derived growth factor receptor alpha gene as a quantitative trait locus for eye size in white Europeans

Jeremy A. Guggenheim, George McMahon, John P. Kemp, Sared Akhtar, Beatrice St Pourcain, Kate Northstone, Susan M. Ring, David M. Evans, George Davey Smith, Nicholas J. Timpson, Cathy Williams.
Autism Spectrum Disorders (ASD)

• 1 in 88 U.S. children affected
• NIH-funded study of ASD children and their families
  • Sequence genomes to identify genetic similarities
ASD: Genomic Discoveries

• Whole-exome sequencing of ~600 families (ASD child, unaffected parents)
• Boosted estimate of high-risk autism genes from ~200 to ~1000
• Strong evidence for 3 new autism genes: SCN2A, KATNAL2, CHD8
  – Accounts for very small % of ASD
  – But provides valuable clues to biological mechanisms of ASD
The Cancer Genome Atlas: Comparing “Fingerprints” of Cancer Types

Coordinated effort to accelerate understanding of cancer through genome analysis to improve ability to diagnose, treat, and prevent cancer

- Searching for shared genomic fingerprints
  - 12 cancer types
  - Tumor samples from 3,300 patients

- Found 127 significantly mutated genes shared by subsets of samples across cancer types

- Potential significance for ... 
  - “Precision medicine” – customizing treatment for individual patients
  - Therapeutic development – identifying key cellular pathways to find likely drug targets

http://directorsblog.nih.gov/
Developing Promise of Cell Therapy

iPSCs

• To study toxicology
• Generate tissues and cells for transplantation
• Understand how to prevent and treat birth defects
• Cell therapy
Vaccine Development

The Need for a Universal Flu Vaccine

• Up to 50,000 U.S. deaths associated with flu annually

• $87 billion in economic costs

• Protection currently involves getting a flu shot every year

• Universal vaccine: one shot provides lasting immunity to most strains

• Vaccine would also protect against an emerging flu pandemic
The Human Microbiome: Transforming Our Understanding of Health and Disease

A core gut microbiome in obese and lean twins

The Long-Term Stability of the Human Gut Microbiota

Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis
The Brain Initiative
“The Next Great American Project”

Learning the Language of the Brain
(NIH initial investment $40M)
BRAIN Initiative – NIH goals

- Generate a Census of Cell Types
- Create Structural Maps of the Brain
- Develop New Large-Scale Network Recording Capabilities
- Develop A Suite of Tools for Circuit Manipulation
- Link Neuronal Activity to Behavior
- Integrate Theory, Modeling, Statistics, and Computation with Experimentation
- Delineate Mechanisms Underlying Human Imaging Technologies
- Create Mechanisms to Enable Collection of Human Data
- Disseminate Knowledge and Training
The Big Data Problem
Myriad Data Types

Genomic

Other ‘Omics

Imaging

Phenotypic

Exposure

Clinical
NIH Is Tackling the “Big Data” Problem

- New leadership position: Associate Director for Data Science
- Scientific Data Council
- Big Data to Knowledge (BD2K)
  - Major trans-NIH initiative
  - Goal: by decade's end, enable a quantum leap in the ability of the biomedical research enterprise to maximize the value of the growing volume and complexity of biomedical data
Despite advances and promise, translational research has problems...

• Slow
• Expensive
To Speed Drug Development and reduce costs NIH is pursuing:

• Drug repurposing
• New approaches to toxicology
• Modifying organizational structure
Two Approaches to Develop New Therapeutics

1-2 years

>400,000 compounds, 10 yrs

3000 drugs

Target → Screen → Test chemicals on target → Lead Product → GMP → Preclinical → Clinical Trials → FDA approval

>400,000 compounds, 10 yrs

3000 drugs
Rescuing, Repurposing, Repositioning

NIH – INDUSTRY ROUNDTABLE
April 21-22, 2011

Exploring New Uses for Abandoned and Approved Therapeutics

The NC GC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics
Ruili Huang, * Noël Souttih, * Yuhong Wang, Adam Yaagab, Paul Shinn, Ajit JadHAV, Dac-Trung Nguyen, Christopher P. Austin

Small-molecule compounds approved for use as drugs may be “repurposed” for new indications and studied to determine the mechanisms of their beneficial and adverse effects. A comprehensive collection of all small-molecule drugs approved for human use would be invaluable for systematic repurposing across human diseases, particularly for rare and neglected diseases, for which the cost and time required for development of a new chemical entity are often prohibitive. Previous efforts to build such a comprehensive collection have been limited by the complexities, redundancies, and semantic inconsistencies of drug naming within and among regulatory agencies worldwide; a lack of clear conceptualization of what constitutes a drug; and a lack of access to physical samples. We report here the creation of a definitive, complete, and nonredundant list of all approved molecular entities as a freely available electronic resource and a physical collection of small molecules amenable to high-throughput screening.


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.

University in St. Louis, university researchers have access to a database of 500 Pfizer drugs and failed candidates that they test in animal models.

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 8,900 so-called 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 NCAI as “an integral

Drugs repurposing programmes get lift off
Asher Mullard
Toxicology
Tissue Chips for Drug Screening

• Goal
  – Develop chip to screen for safe, effective drugs
    • Liver, heart, lung, other cell types

• NIH, DARPA contribute ~$70M each over 5 years
  – FDA provides regulatory science guidance

• Awards announced in 2012

Lung chip
Wyss Institute

Blood-brain barrier chip
J. Wikswo, Vanderbilt
Accelerating Translation Within and Outside NIH
The National Center for Advancing Translational Sciences (NCATS)

Catalyzing Translational Innovation within and outside NIH

Christopher P. Austin, M.D.
DIRECTOR, NCATS
NCATS Programs and Initiatives

Clinical and Translational Science Activities
• Clinical and Translational Science Awards

Rare Diseases Research and Therapeutics
• Therapeutics for Rare and Neglected Diseases
• Office of Rare Diseases Research

Re-engineering Translational Sciences
• NIH Chemical Genomics Center
• Toxicology in the 21st Century
Clinical and Translational Science Awards

CTSAs:

• Academic homes for translational research
• Support a national consortium
• To improve clinical and translational research nationwide
• Accelerate the research translation process
• Provide innovative training for clinical and translation researchers
Clinical and Translational Science Awards (CTSA) Program Sites
CTSA Translational Challenges

- Data interoperability
- Clinical trial networks
- EHRs for research
- IRB federation
- Patient recruitment
- Clinical diagnostic criteria
- Clinical outcome criteria
- Biomarker qualification process
- Shortening time of clinical trials
- Methods to better measure impact on health
NIH Clinical Center

- World’s largest clinical research center
  - Founded 1953
- “There’s no other hospital like it”
- Recipient of Lasker~Bloomberg Public Service Award (2011)
Clinical Center Profile

- >480,000 patients since opening in 1953
- 240 beds; FY 2013 Budget $397.6M
- Hospital surrounded by research labs
- Every patient is on a research protocol
- Care is free
- Patient travel/housing provided as needed
- 2,800 CC employees + ~4,000 employees from 17 ICs that use hospital
- 1,255 credentialed physicians
- 1,530 active protocols
  - Interventional/Clinical Trials - 730 (47%)
  - Natural History - 715 (47%)
  - Screening - 66 (4%)
  - Training - 26 (2%)
Major Emphasis

- Study of the pathophysiology of disease
- First in human with new therapeutics
- Study of patients with rare diseases

18 – 25 million people in the United States have a rare disease!
Undiagnosed Diseases and NIH

- Undiagnosed Diseases Program (launched 2008)
  - Patients with longstanding medical conditions that have eluded diagnosis come to the NIH Clinical Center
  - Trans-NIH staff, led by Dr. William Gahl, has:
    - Evaluated ~3,000 medical records
    - Accepted ~700 cases
    - Determined a diagnosis in ~25%

HARD CASES: INVESTIGATING RARE & TOUGH DISEASES
Dr. William Gahl is one of the last, best hopes for people suffering from rare, debilitating, and undiagnosed medical conditions

FEB 25
CBSNews.com / CBS Evening News / CBS This Morning
60 MINUTES
NIH Clinical Center’s Specialized Services

- Biomechanics laboratory
- Metabolic chambers
- Imaging
- Cell therapy
- GMP facility for drug formulation
- High containment patient care unit
Training

- Curriculum in Clinical Research
- Sabbatical in Clinical Research Management
- “Summer Camp” for PhD Candidates
- Medical Research Scholars Program
- Clinical Research Training On-Line course

http://clinicalcenter.nih.gov/training/index.html
Training
NIH Curriculum in Clinical Research

Introduction to the Principles & Practice of Clinical Research
15,741 participants since course introduced in 1995

Principles of Clinical Pharmacology
9,654 participants since course began in 1998

Ethical and Regulatory Aspects of Human Subjects Research
5,503 participants since course began in 1999

http://clinicalcenter.nih.gov/training/index.html
Since 1995, Over 30,000 students world-wide have participated in the NIH Curriculum in Clinical Research.
Concluding Messages

• The opportunities (and needs) in translational science are huge and systematic, so require systematic solutions

• The scale of the opportunities/needs requires transformational change to deliver logarithmic improvements

• 21st century needs cannot be solved with 20th century structures

• NIH is transforming to meet these opportunities and needs for the benefit of patients
Thank you!