Advancing Discovery Science for Public Health Impact

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Council of Councils Meeting
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Turning Discovery Science Into Public Health Impact:
Knowledge of Risk Factors to Prevent Heart Disease

**Risk Factors**
- High blood pressure
- Smoking
- High blood cholesterol
- Overweight/Obesity
- Physical inactivity
- Diabetes
- Family history
- Age

**Observational Studies**

**Basic Research**
- Framingham Risk Factors
- Intramural Research Program: Frederickson, Stadtmans
- Clinical Research: Tangier's Disease (HDL Cholesterol)
- Brown and Goldstein: Nobel Prize (LDL Cholesterol)

**Public Health Implementation Science**
- Value of Lifestyle Interventions
- Roy Vagelos: Statins
- NHLBI Trial: Lowering Cholesterol Cuts CHD Risk

**Clinical Research**

**Collaboration/Role of Industry**

**Intramural Research Program**

National Heart, Lung, and Blood Institute
Inheriting a Legacy of Excellence & Stewardship: The Public Health Impact of NHLBI Investments

Heart disease death rate for 1958: 56 per 10,000 people

10 deaths per 10,000 people

Heart Disease down 68%

Cancer down 10%
(down 20% since 1990 peak)

19 18
2010 cancer death rate: 17 per 10,000
Compared with 1958, a reduction of 2

Stroke down 79%

2010 stroke death rate: 4 per 10,000
Compared with 1958, a reduction of 14

2010 death rate: 18 per 10,000
Compared with 1958, this is a reduction of 38 deaths per 10,000

2010 cancer death rate: 17 per 10,000
Compared with 1958, a reduction of 2

2010 stroke death rate: 4 per 10,000
Compared with 1958, a reduction of 14

Adapted from: New York Times, January 4, 2014
Data: Centers for Disease Control and Prevention; National Vital Statistics System
Guided from Observation to Intervention: Extending the Legacy in Hypertension to Management and Control

A Randomized Trial of Intensive vs. Standard BP Control

SPRINT-MIND
Memory and Cognition in Decreased Hypertension

After 3 yrs of intervention and 5 yrs follow-up, intensive treatment reduced:
• Incidence of mild cognitive impairment (MCI)
• Combined incidence of MCI or probable dementia
• Progression of cerebral white matter lesions

Intensive management of SBP to target <120 mmHg reduced complications of high BP by 25% and death by 27% as compared to SBP target <140 mm Hg.

Building Upon a Legacy of Excellence: Improving Lung Outcomes with Discovery Science

- Building a lung atlas at the single cell level (e.g., LungMAP)
- Identifying phenotypes, biomarkers (i.e., deep learning of COPDGene CT images to subphenotype disease)
- Conducting adaptive trials and precision interventions for asthma (e.g., PrecISE)
- Observational Studies
- Identifying risk factors associated with lung disease & resilience (COPD in non-smokers)
- Conducting systematic evidence reviews and health education (e.g., COPD National Action Plan)
- Developing novel therapeutics targeted to risk profiles or sub-phenotypes
Turning the Curve in Pulmonary Disease
Innovating for Challenges Ahead

- Infant RDS
- ARDS
- Cystic Fibrosis
- Early COPD
- Late COPD
- COPD/OSA Overlap
Navigating the Present and Charting Our Future…

- **Accountable Stewardship**
  - Enduring Principles
  - Fiscal Update
    - Investing in Investigator-Initiated Science
    - Investing in People Not Projects
  - Strategic Vision: Addressing Research Priorities

- **Advancing Discovery for Public Health Impact**
  - Curing Sickle Cell Disease
  - Legacy of Excellence in Cardiovascular Research
  - Social and Behavioral Determinants of Heart Disease

- **Seizing Unprecedented Opportunities**
  - Precision Medicine and Prevention
  - Data Science
NHLBI Enduring Principles

- Value investigator-initiated fundamental discovery science.
- Maintain a balanced, cross-disciplinary portfolio (basic, translational, clinical, population science).
- Train a diverse new generation of leaders in science.
- Support implementation science that empowers patients and enables partners to improve the health of the nation.
- Innovate an evidence-based elimination of health inequities in the U.S. and around the world.
Aligning Institute-Solicited Science with the Strategic Vision Goals & Objectives

Objective 1: Normal Biology
Objective 2: Pathobiology, Onset, & Progression of HLBS diseases
Objective 3: Population Differences
Objective 4: Precision Medicine

Objective 5: Novel Diagnostics & Therapeutics
Objective 6: Clinical & Implementation Research
Objective 7: Data Science
Objective 8: Workforce & Resources
Prioritized Investments in Investigator-Initiated Science: Bending the Curve

<table>
<thead>
<tr>
<th>Grant Program</th>
<th>FY17 Paylines</th>
<th>FY17 # Awards (Success Rate)</th>
<th>FY18 Paylines</th>
<th>FY18 # Awards (Success Rate)</th>
<th>FY19 Paylines</th>
</tr>
</thead>
<tbody>
<tr>
<td>R01</td>
<td>15%ile</td>
<td>708 (23.3%)</td>
<td>15%ile</td>
<td>711 (24.2%)</td>
<td>16%ile</td>
</tr>
<tr>
<td>ESI</td>
<td>25%ile</td>
<td>145 (30.3%)</td>
<td>25%ile</td>
<td>156 (32.7%)</td>
<td>26%ile</td>
</tr>
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FY2018 budget increase enabled NHLBI to make more awards for investigator-initiated science.

Fulfilling the Mission: Goal for ESI R01 Success Rates Greater or Equal to General Pool

NIH National Heart, Lung, and Blood Institute
Nurturing a Diverse Next Generation of Leaders: Multi-level Strategies to Expand Opportunities

Current Activities

**Diversity**
- BUILD/Mentoring Networks
- R25/PRIDE
- Diversity K Awards
- Diversity Supplements

**Career Development**
- ESI Bridge (R56) Awards
- Loan Repayment Program
- Mentored Clinician-Scientist (K08)
- K Awards: FY18 Success 36%
- ESI R01s: FY18 Success 33%

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**Focused Initiatives**
- K-R03 awards
- R35 for Emerging Investigators
- R01 Physician-Scientist Award for ESIs
- Stimulating Access to Research in Residency (StARR) (R38) & StARR Transition Scholar (StARRTS) (K38)
- Career Pathway to Independence in Blood Science Award for Physician Scientists (K99/R00)
Investing in People and Not Projects: NHLBI’s Approach to the R35 Program

NHLBI R35 Program

88 R35s awarded in FY17- FY19

Outstanding and Emerging Investigator Awards
To promote scientific productivity and innovation by providing stable and flexible funding
7 years of support at $600,000/per year
NHLBI Supports Trans-NIH and Trans-HHS Priorities

HEAL Initiative: Sleep and Circadian-Dependent Mechanisms Contributing to Opiate Use Disorder (OUD) and Response to Medication Assisted Treatment (MAT)

RFA-HL-19-028 (R01- Clinical Trial Not Allowed)
RFA-HL-19-029 (U01 – Clinical Trial Optional)

THE INCLUDE PROJECT

Multiple systems involved in DS require a trans-NIH approach

NHLBI-supported DS Research

Mechanisms for Cell Signaling in the Control of Cardiomyogenesis
Genomic Analysis of Congenital Heart Defects and Acute Lymphoblastic Leukemia in Children with Down Syndrome
Data Fusion: A Sustainable, Scalable, Open Source Registry Advancing PVD Research

For full list of HEAL Funding Opportunities, visit https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative
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Moving from Vision to Implementation: Highlights of NHLBI Strategic Priorities

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Building on the Strategic Input from the Council of Councils

Novel Therapeutics: Sickle Cell Disease
Cardiovascular Disparities
Leveraging Data Science: Omics & Imaging
Building Upon a Legacy of Excellence: Improving Sickle Cell Disease Outcomes with Discovery Science

“Sickle Cell Anemia” Term Coined

Hemoglobin Cause for SCD Defined

Transfusion Therapy and Silent Infarct
Hydroxyurea improves HbF production

“Sickle Cell Trait Protects Against Malaria & HbF with more favorable course

Excellence in Hemoglobinopathies

Comprehensive SCD Implementation Science Strategy to Improve Health Outcomes in the US and Globally

Opportunity for Implementation Science strategies to improve treatment initiation and adherence

Basic Research
- Pathobiology
- Genotype/Genomics
- Cell Biology

T1: Laboratory Proof of Principle
T2: Pre-Clinical to Early Human Trials
T3: Pivotal Clinical Trials
T4: Implementation Research


Hydroxyurea use among children w/ SCD (7693 children in Medicaid)

HU use was low across all years & states
- 78% received no HU in a year
- 18% received > 300 days of HU in a year

Is the Time Ripe for a Cure of the First ‘Molecular’ Disorder? New Technologies Toward Curative Strategies

Gene therapy options to address SCD

Addition of:
- β-Globin
- Anti-sickling β-Globin
- γ-Globin
- β/γ Hybrids

Correction of A-T mutation by:
- CRISPR-Cas9
- ZFNs
- TALENs

HbF induction through:
- Chemical inducers
- Targeting regulatory genes
- Enhancer disruption
- Forced chromatin looping
- HPFH mutation

- Patient attained normal blood cell counts.
- Engrafted stem cells were capable of long-term repopulation.

Total of 18 patients:
- Stable Hemoglobin production
- Decreased vaso-occlusive events

Leveraging Collaborative Partnerships on the Path to SCD Cures

Identify and support the most promising genetic therapies for scalable cures.

Areas of Focus
- Patient Engagement
- Therapeutics Development
- Date Repository
- Clinical & Econ Impact Analysis
- Clinical Platforms & Networks

Highlights from “60 Minutes”
Could Gene Therapy Cure Sickle Cell Anemia?

March 2019
Moving from Vision to Implementation: Highlights of NHLBI Strategic Priorities

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- Novel Therapeutics: Sickle Cell Disease
- Cardiovascular Disparities
- Leveraging Data Science: Omics & Imaging
Heart Disease Mortality: An Evolving Story
CVD Mortality Reveals Place Matters in Health Inequities

Overall, heart disease death rates down over 70% since 1950. However, progress has slowed.

U.S. County-Level Mortality From CVD (both sexes, 2014)

NCHS Data Brief No. 254. August 2016
Roth, et al. JAMA, May 16, 2017
Translating Discovery Science into Public Health Impact: From ‘Nucleotides-to-Neighborhoods’

**Bench Research**
- Discovery Science
  - Animal Studies
- Preclinical

**Bedside**
- 1st Human Studies
- Controlled Observations
- Phase I/II Trials

**Patients**
- Phase III Trials
- Guideline Development

**Practices**
- Phase IV Trials
- Comparative Effectiveness Research

**Real World**
- Implementation and Dissemination Science

**Biomedical Model**
- Discovery Science T1
- Translation to Humans T2
- Translation to Patients T3
- Translation to Clinical Practices T4
- Translation to Real World Settings

**Biomedical and Socioecological Model**
- Modified/adapted from M Khoury et al Genet Med 2007 and Harvard Catalyst CTSA
Health Disparities: A Complex Multi-Level Challenge

Social Environment/‘Exposome’
- Racism
- Inactivity
- Diet
- Psychosocial Stress
- Sleep Disturbance
- Social Deprivation
- Neighborhood Features

The Bio-Social Interface

Biological Interface Systems
- Microbiome
- Immune System
- Epigenome

Transcriptome / Proteome

Genomic Variation
- Population History

Inflammation
- Oxidative Stress

Vascular Dysfunction

Vascular Disease
What does it mean locally? Social Determinants of Heart Disease: Interplay of Social and Biological Systems

Washington, DC Segregation

Anthocyanin and miRNA-10b

Racial Segregation
Socioeconomic Status

Food Desert
Unhealthy Diet

Biosocial Interface
Microbiome

Immune System Activation

Vascular Disease

New York Times: Mapping Segregation; 7/8/15
Addressing Persistent Disparities in Hypertension
“Place Matters” in Health Equity

In black participants of the CARDIA study, reductions in systolic blood pressure over 25 years were associated with decreases in racial segregation of participant’s place of residence.

Systems Biology Framework for Developing Tailored Therapies: Harnessing New Technologies to Improve Health Outcomes

Leveraging New Technologies for HLBS Disorders

Data Science and AI
Identify behavioral contributors and molecular mechanisms of disease

Precision Medicine
Tailor treatments across populations
TOPMed: A Diverse Genome-Phenome Resource Enabling Data Science with Public Health Impact

An expansive data resource for integrated exploration of multi-omics data with molecular, behavioral, imaging, environmental, and clinical data in heart, lung, blood, and sleep disorders.

Phenotype Diversity represents 145K WGS samples from Phase 1-4 X01s.
Envisioning a Communal, Global Discovery Platform for Multi-Disciplinary Open Science

Registries with clinical data and biological samples (i.e. All of Us, GTEX)

Datasets & Biospecimen from over 100 Clinical & Epi studies (LungMap)

Longitudinal Phenotypic data from diverse populations (Personal Sensor Data)

Individual participant data from practice-changing clinical trials

Genomics and Phenomics data from diverse HLBS cohort/clinical studies
Building a Communal Trans-NIH Platform for Multi-Disciplinary Open Science

Accelerating Data to Knowledge and Knowledge to Discovery

- Make data accessible to medical, scientific community
- Ensure data interoperability with other data sets
- Drive discovery
- Enhance tools and treatments available for clinicians
- Revolutionize prevention and treatment of disease
Realizing the Promise of Precision Medicine: Harnessing Data Science to Improve Health Outcomes

Resource platforms enabling discovery of molecular pathways, subphenotypes, & treatment targets

Leveraging AI & deep learning of neural networks from CT in COPDGene to characterize disease severity and predict acute exacerbations and mortality

Public Health Impact
- Identifying COPD prior to symptom onset
- Linking structural, functional and biological changes
- Identifying high-risk subgroups in large populations

What if… We Employed Polygenic Risk Scores to Refine Risk and Optimize Therapy for Chronic Conditions?

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

“The polygenic score identified 20-fold more people at comparable or greater risk than were found by familial hypercholesterolemia mutations in previous studies.”

A Paradigm for Translating Discovery to Public Health Impact for Heart, Lung, Blood and Sleep Research

**Identify Disease Risk**
- Track early risk, identify disease categories

**Expand Diagnostic Capabilities**
- Novel use of artificial intelligence & machine learning

**Perform Deep Phenotyping**
- Patient-centric data mining through discovery science (e.g., TOPMed and Data STAGE)

**Conduct Clinical Research**
- Biomarkers & therapeutic targets identified through Omics

**Develop Tailored Treatments**
- Improve disease management and health outcomes

**Transform Health Outcomes**
- Improve health and quality of life
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NIH
National Institutes of Health