NHLBI’s Strategic Plan Promotes Advances in Research Approaches

Research
- Informatics
- Systems analysis

Better Understanding

NHLBI
- Feedback

Improved Public Health
- Knowledge networks
- Education

Tools Infrastructure Technologies Teams Resources Workforce
Planning Principals

Our Approach
Work in partnership in an ever evolving environment.

- International Organizations
- Researchers
- Professional Societies
- Voluntary Health Organizations
- Federal-State-Local Agencies
- Corporations
- Foundations
- Community Organizations
- Patient Advocacy Groups
NHLBI Strategic Plan Objectives

- Develop a scientific blueprint for the next decade.
  - A living, working plan from an inclusive and participatory process.
  - Identify strategic priorities where NHLBI:
    - Initiates – does not happen unless the Institute takes a lead
    - Catalyzes – Institute facilitates the outcome
    - Supports – investigator-initiated research
• **Goal 1**
  Improve understanding of the molecular and physiologic basis of health and disease. Use that understanding to develop improved approaches to disease prevention, diagnosis and treatment. *Form → Function*

• **Goal 2**
  To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases. *Function → Cause*

• **Goal 3**
  Generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery. *Cause → Cures*
NHLBI Strategic Plan Leads Toward Personalized / Pre-emptive Medicine

Prevent Disease

Personalize Care

Cure Disease

Strategic Plan
Need to Transform Medical Research in the 21st Century

<table>
<thead>
<tr>
<th>20th Century</th>
<th>21st Century</th>
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<tbody>
<tr>
<td>• Treat disease when symptoms appear and normal function is lost</td>
<td>• Intervene before symptoms appear and preserve normal function for as long as possible</td>
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<tr>
<td>• Did not understand the molecular and cellular events that lead to disease</td>
<td>• Understanding preclinical molecular events and ability to detect patients at risk</td>
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<tr>
<td>• Expensive in financial and disability costs</td>
<td>• Orders of magnitude more effective</td>
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The Future Paradigm: Transform Medicine from Curative to Preemptive

Predictive ↔ Personalized ↔ Preemptive

Participatory
Path to Earlier Diagnosis, Better Prognosis, and Personalized Management

Barrier: Lack of well-defined pre-clinical lung phenotype
Asthma-specific SNP chip, co-developed with Affymetrix, will be validated by screening 5,000 Asthma samples.

Gene Expression Profiling reveals unique patterns which will
- Expedite Diagnosis
- Predict Response to Treatment
- Determine Likelihood of Exacerbation

\[ \text{Molecular Phenotype} \]
Young children with recurrent wheeze are a treatment dilemma

- Just 1/3 have persistent asthma after age 6
- Would daily therapy be appropriate for these children?
- How can you identify and avoid unnecessary treatments for the remaining 2/3?

API identifies phenotypic characteristics of those at highest risk

**Asthma Predictive Index (API)**

Identifies high risk children ages 2 & 3:

- > 4 wheezing episodes in the past year (at least one must be MD diagnosed)

**PLUS**

- One major criteria
  - Parent with asthma
  - Atopic dermatitis
  - Aero-allergen sensitivity

**OR**

- Two minor criteria
  - Food sensitivity
  - Peripheral eosinophilia (≥4%)
  - Wheezing not related to infection
Prevention and Personalized Medicine for ARDS

- Will earlier alterations in ventilation prevent ARDS? Gajic and colleagues
- Can ventilation settings be personalized? Marini and others
Molecular Prognosis/Diagnosis for ARDS?

Biomarkers

Genomics

Mannose Binding Lectin-2 Genotype

Crit Care Med 35: 48, 2007 Gong et al
Phenotypic Predictors for Disease Diagnosis

- **SubPopulations and Intermediate Outcome Measures In COPD Study (SPIROMICS)**
- A planned, multicenter observational study to:
  - Phenotype 3000 patients with COPD
  - Classify subpopulations by molecular & clinical characteristics
  - Validate intermediate outcome measures
NHLBI Strategic Plan Goals

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DLD Clinical Research Networks
Excel in Translational Research

NIH NHLBI ARDS Clinical Trials Network

COPD CRN
COPD Clinical Research Network

CARE
IPFnet
SARP

National Heart Lung and Blood Institute
Variations in Drug Response

All patients:
- Same diagnosis,
- Same drug

Different Responses
- No Benefit
  - + Toxicity
- + Benefit
  - + Toxicity
- + Benefit
  - No Toxicity
- No Benefit
  - No Toxicity
Targeted Drug Strategies to Prevent Disease Progression

Antibody: Anti-IL-13

Chemokine receptors: CCR3

Kinase inhibitors: p38 MAP

Enzyme inhibitors: PDE-4 inhibitors

Personalized Medicine: Asthma as a Prototype

- Identification of b-adrenergic receptor polymorphisms
- Demonstration that different haplotype combinations affect agonist response and adverse effects in some patients
- Prospective studies which evaluate treatment response at the genetic level
- Therapeutic regimen based on individual genotype and phenotype
Genetic Predictors of Response

The Effect of Polymorphisms of the $\beta_2$-Adrenergic Receptor on the Response to Regular Use of Albuterol in Asthma

Elliot Israel, Jeffrey M. Drazen, Stephen B. Liggett, Homer A. Boushey, Reuben M. Cherniack, Vernon M. Chinchilli, David M. Cooper, John V. Fahy, James E. Fish, Jean-C. Fogg, Monica Kraft, Sushil, Stein and Bright, Carita, Merck, University Thor.

Lancet 2004;364:1505-12

Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial


Am J Respir Crit Care Med 2006;173:519-26

$\beta$-Adrenergic Receptor Polymorphisms and Response to Salmeterol

Realizing the Promise of Pharmacogenomics: Opportunities and Challenges

Draft Report of the Secretary’s Advisory Committee on Genetics, Health, and Society

Available for Public Comment: March 23 - June 1, 2007

http://www4.od.nih.gov/oba/SACGHS/public_comments.htm
Strategies to Prevent Asthma

Potential Preventive Strategies

- Diet: probiotics
- Pharmacologics: leukotriene modifiers
- Immunomodulators: CpG oligodeoxynucleotides
- Protective exposures: dirt!

Genetics

Birth

Rural environment
Early exposure to older sibs/children

Many infections
No Allergies

Genetics

Allergic sensitization
Widespread use of antibiotics
Western lifestyle
Urban environment

Few infections
Allergies/Asthma

Allergies/Asthma

No Allergies

Many infections

Birth
Training of New Clinical Investigators
NHLBI Strategic Plan Goals

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# Participatory Research

## National Asthma Education and Prevention Program

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<th>Guidelines Development and Utilization</th>
<th>Partnership Activities</th>
<th>Community Targeted Activities</th>
<th>FLGA Collaborations</th>
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<td>Asthma Coalitions Contracts</td>
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<td>MDI Transition Initiative</td>
<td>World Asthma Day</td>
<td>JOSH Special Issue School Lessons Learned</td>
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<td>HEDIS</td>
<td>Physician Asthma Care Program</td>
<td>Reducing Asthma Disparities Workshop</td>
<td>Public Housing Initiative HUD/NHLBI</td>
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<td>Asthma 2003 Conference</td>
<td>Screening for Asthma in Children Project</td>
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<tr>
<td>Pt. Education Booklet</td>
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Participatory Research (continued)

- Integrate campaign into organizational activities
- Provide distribution vehicle
- Set up Web link
- Offer spokespeople
The Strategic Plan and Innovative Lung Research
Promote NIH Goals for Transformation of Medicine

Predictive

- Predictive Index
- Biomarkers
- Pharmacogenetics
- SPIROMICS

Predictive

- ARDS
- Asthma
- COPD

Participatory

- NAEPP
- PEAK
- Early Origins
- Awareness Campaigns

Personalized

- Targeted Drugs
- Ventilation

Preemptive
NIH Core Strategic Vision

- Transform medicine and health from a Curative to a Preemptive paradigm
- Support basic research to identify the earliest molecular stages of disease in complex biological systems
- Accelerate translation of findings from the bench to the bedside to the community
- Provide the evidence and knowledge base to allow for a rational transformation of our healthcare system
Future Directions

Basic Discovery  Clinical  Communication

Genomics  Proteomics
Stem Cell Research  Tissuegenesis  Cell Imaging  Translational
The Future Paradigm: Preempt Disease

- **Preclinical**
  - Molecular preemption

- **Tolerable**
  - Cost savings

- **Intolerable**
  - Symptom management
  - Curative treatment

- **Disease Burden**
- **Cost**
- **Time**
Statewide Program

Statewide Asthma Training for Minnesota School Personnel
Janet Keysser, Patricia L. Splett, Susan Ross, Erica Fishman

- MN Dept of Health Strategic Plan on Asthma builds on NAEPP Guidelines and CDC State Initiatives
- Healthy Learner’s Asthma Initiative creates asthma friendly school policies and education programs
Discovery: COPD Research Is Rapidly Advancing

Challenge is to integrate data from

- Clinical studies
- Biomarker analyses
- Histopathology
- Genomics / Genetics
- Animal models


Goal One: Form to Function

**Goal 1**: To improve understanding of the molecular and physiological basis of health and disease and use that understanding to develop improved approaches to disease diagnosis, treatment, and prevention.

**Challenge 1.1**
To delineate mechanisms that relate molecular events to health and disease.

1.1.a Develop a detailed understanding of the molecular, cellular, and physiological mechanisms that maintain health from embryonic development to the end of the human lifespan.

1.1.b Identify intracellular targets of key signaling and transcriptional pathways in normal and pathologic states.

1.1.c Determine key genetic variants that are associated with specific diseases and delineate the molecular mechanisms that account for susceptibility or resistance to disease.

1.1.d Define molecular, cellular, and organ-specific responses to environmental challenges, and the mechanisms by which heritable and non-genetic factors interact in disease initiation and progression and in therapeutic response.

1.1.e Determine the role of systemic pathological processes, such as inflammation, immunity, and infection, in the development and evolution of disease.
Goal One: Form to Function (continued)

**Challenge 1.2**

To discover biomarkers that differentiate clinically relevant disease subtypes and that identify new molecular targets for application to prevention, diagnosis – including imaging, and therapy.

- **1.2.a** Identify molecular signatures that allow complex disease phenotypes to be stratified into clinically relevant categories.

- **1.2.b** Develop in vivo molecular imaging methods and probes for investigating the biology of disease processes.
Goal Two: Function to Causes

**Goal 2:** To improve understanding of the clinical mechanisms of disease and thereby enable better prevention, diagnosis and treatment.

**Challenge 2.1**
To accelerate translation of basic research findings into clinical studies and trials and to promote the translation of clinical research findings back to the laboratory.

- **2.1.a** Integrate advances in regenerative biology to develop clinically feasible applications.
- **2.1.b** Apply discoveries in nanotechnology to the development of new diagnostic and therapeutic strategies.
- **2.1.c** Integrate, analyze, and share extant and emerging genotypic and phenotypic data.

**Challenge 2.2**
To enable early and accurate risk stratification and diagnosis of cardiovascular, lung, and blood disorders.

- **2.2.a** Exploit noninvasive imaging methods to detect and quantify subclinical disease.
- **2.2.b** Apply new discoveries in biomarkers to improve risk assessment, diagnosis, prognosis, and prediction of response to therapy.
Goal Two: Function to Causes (continued)

**Challenge 2.3**
To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases.

- **2.3.a** Improve the understanding of the interactions between genetic and environmental factors that influence disease development and progression and response to therapy.
- **2.3.b** Identify and evaluate interventions to promote health and treat disease in genetically defined patient subgroups by altering developmental or environmental exposures including drugs, diet and exercise, sleep duration and quality, and infectious agents and allergens.

**Challenge 2.4**
To enhance the evidence available to guide the practice of medicine, and improve public health.
Goal Three: Causes to Cures

Goal 3: To generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.

Challenge 3.1
To complement bench discoveries and clinical trial results with focused behavioral and social science research.

3.1.a Develop and evaluate new approaches to implement proven preventive and lifestyle interventions.

3.1.b Develop and evaluate policy, environmental, and other approaches for use in community settings to encourage and support lifestyle changes.

3.1.c Develop and evaluate interventions to improve patient, provider, and health system behavior and performance in order to enhance quality of care and health outcomes.
**Challenge 3.2**
To identify cost-effective approaches for prevention, diagnosis, and treatment.

3.2.a Evaluate the risks, benefits, and costs of diagnostic tests and treatments in representative populations and settings.

3.2.b Develop research designs, outcome measures, and analytical methods to assess prevention and treatment programs in community and health-care settings across populations and lifespan.

**Challenge 3.3**
To promote the development and implementation of evidence-based guidelines in partnership with individuals, professional and patient communities, and health care systems and to communicate research advances effectively to the public.

3.3.a Establish evidence-based guidelines for prevention, diagnosis, and treatment and identify gaps in knowledge.

3.3.b Develop personalized and community- and health care system-oriented approaches to increase the use of evidence-based guidelines by individuals, communities, health care providers, public institutions, and, especially, by populations that experience a disproportionate disease burden.

3.3.c Communicate research advances effectively to the public.
Preventing Early Asthma in Kids

Randomized Trial in Children with Recurrent Wheeze and Positive API

**Results:**
- Symptoms returned when daily therapy was withdrawn
- Daily inhaled corticosteroids significantly reduced symptom days and need for oral steroids
- Daily therapy did not prevent progression of disease

**Conclusions:**
- The API is a valuable clinical tool for selecting young wheezers who will benefit from daily therapy
- Research to discover treatments to prevent disease is needed