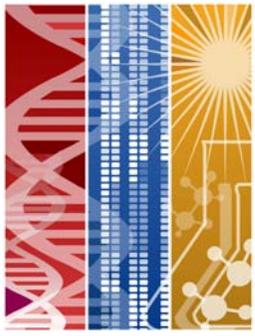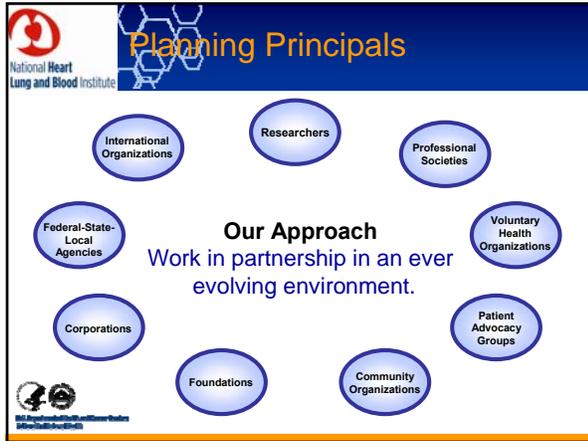## Slide 1

NHLBI Strategic Plan: Future Opportunities for Lung Research

Elizabeth G. Nabel, M.D.

Director, National Heart, Lung, and Blood Institute

University of Minnesota
April 30, 2007

Slide 2

NHLBI's Strategic Plan Promotes Advances in Research Approaches

Research → Tools, Infrastructure, Technologies, Teams, Resources, Workforce → NHLBI

Informatics, Systems analysis

Feedback

Better Understanding → Knowledge networks, Education → Improved Public Health

Slide 3

Planning Principals

International Organizations

Researchers

Professional Societies

Federal-State-Local Agencies

Voluntary Health Organizations

Our Approach
Work in partnership in an ever evolving environment.

Corporations

Patient Advocacy Groups

Foundations

Community Organizations

Slide 4

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*

Slide 5

NHLBI Strategic Plan Goals

Goal 1 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. *Form → Function*

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

Slide 6

NHLBI Strategic Plan Leads Toward Personalized / Pre-emptive Medicine

Prevent Disease

Personalize Care

Cure Disease

Strategic Plan

Slide 1: Need to Transform Medical Research in the 21st Century

20th Century	21st Century
Treat disease when symptoms appear and normal function is lost	Intervene before symptoms appear and preserve normal function for as long as possible
Did not understand the molecular and cellular events that lead to disease	Understanding preclinical molecular events and ability to detect patients at risk
Expensive in financial and disability costs	Orders of magnitude more effective

Slide 2: The Future Paradigm: Transform Medicine from Curative to Preemptive

Predictive ↔ Personalized ↔ Preemptive

Participatory

Slide 3: 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

Molecular Phenotype

Slide 4: Phenotypic Predictors for Prognosis and Choosing Therapies

- 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	OR	Two minor criteria
Parent with asthma		Food sensitivity
Atopic dermatitis		Peripheral eosinophilia (≥4%)
Aero-allergen sensitivity		Wheezing not related to infection

CARE

Slide 5: Prevention and Personalized Medicine for ARDS

The New England Journal of Medicine

Will earlier alterations in ventilation *prevent* ARDS?
Gajic and colleagues

Can ventilation settings be personalized?
Marini and others

Slide 6: Molecular Prognosis/Diagnosis for ARDS?

Mannose Binding Lectin-2 Genotype (ARDS, Septic Shock — 54AA, 54AB, 54BB)

Biomarkers

Genomics

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

ARDSnet
COPD CRN — COPD Clinical Research Network
NIH NHLBI ARDS Clinical Trials Network
ACRN
CARE
IPFnet
CAMP
SARP

Variations in Drug Response

Different Responses

All patients:
- Same diagnosis,
- Same drug

No Benefit + Toxicity

+ Benefit + Toxicity

+ Benefit No Toxicity

No Benefit No Toxicity

Targeted Drug Strategies to Prevent Disease Progression

Anti-IL-13
IL-13Rα2
CCR3
p38 MAP
PDE-4 inhibitors

Nat Rev Drug Discov. 2004 Oct;3(10):831-44.

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

Slide 1: Genetic Predictors of Response

Am J Respir Crit Care Med 2002;162:75-80

The Effect of Polymorphisms of the β₂-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,

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

β-Adrenergic Receptor Polymorphisms and Response to Salmeterol

Michael E. Wechsler, Erik Lehman, Stephen C. Lazarus, Robert F. Lemanske, Jr., Homer A. Boushey, Aaron Deykin, John V. Fahy, Christine A. Sorkness, Vernon M. Chinchilli, Timothy J. Craig, Emily DiMango, Monica Kraft, Frank Leone, Richard J. Martin, Stephen P. Peters, Stanley J. Szefler, Wenlei Liu, and Elliot Israel, for the National Heart, Lung, and Blood Institute's Asthma Clinical Research Network

Slide 2: Secretary's Advisory Committee

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

Slide 3: Strategies to Prevent Asthma

Potential Preventive Strategies

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

Birth

Genetics
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

Slide 4: Training of New Clinical Investigators

Slide 5: NHLBI Strategic Plan Goals

Goal 1 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. *Form → Function*

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Slide 6: Participatory Research

National Asthma Education and Prevention Program

Guidelines Development and Utilization	Partnership Activities	Community Targeted Activities	FLGA Collaborations
Update 2002	Guidelines Implementation Working Group	Asthma Coalitions Contracts	Congressional Report and Inventory
Update 2006	Asthma Managed Care Initiative: Respiratory Therapists	Coalition Outreach and Support	DHHS Action Against Asthma
Pregnancy Guidelines	Emergency Department Approaches to Care	School Based Initiative	Data Fact sheet
HP 2010 Progress Review	MDI Transition Initiative	World Asthma Day	JOSH Special Issue School Lessons Learned
HEDIS	Physician Asthma Care Program	Reducing Asthma Disparities Workshop	Public Housing Initiative HUD/NHLBI
RAND Policy Report	Physician Asthma Care Education Program	AHRQ State Leader Manual	Cross-Agency Collaborations (CDC/NIAID; CMS; HRSA/EPA)
Asthma 2003 Conference	Screening for Asthma in Children Project		
Pt. Education Booklet			

Participatory Research
- 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