Personalized Asthma Management: Addressing Environmental Impact

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Disclosure

Consultant for Boehringer Ingelheim, Genentech, Glaxo Smith Kline, Merck, Novartis, and Roche

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Learning Objectives

- Identify variability in treatment response for asthma
- Provide insight into the role of the environment on variable treatment response
- Indicate the role of the CEHC in identifying environmental impact on personalized medicine.
CLIC Study

Characterizing the Response to a Leukotriene Receptor Antagonist and an Inhaled Corticosteroid

Funded by NHLBI
CLIC Study Timeline

### Assessment/Characterization
- Consent
- Asthma Hx
- eNO
- PFTs
- BD response
- Biomarkers
- Genetics
- Diary and PFM

### Treatment Phase
- Week -1
  - Review diary
  - eNO
  - PFTs
- Week 0
  - Review diary
  - eNO
  - PFTs
- Week 4
  - Methacholine
- Week 8
  - Skin testing
- Week 12
- Week 16
Primary Outcome: Change in Pre-BD FEV\textsubscript{1}

## FEV$_1$ Response ≥ 7.5%: Odds Ratio

<table>
<thead>
<tr>
<th>Baseline Characteristic (Categorical)</th>
<th>FP</th>
<th>Mt</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ &lt; 90% predicted (pre-BD)</td>
<td>4.16**</td>
<td>1.78</td>
</tr>
<tr>
<td>FEV$_1$/FVC &lt; 0.80 (pre-BD)</td>
<td>4.26**</td>
<td>2.40*</td>
</tr>
<tr>
<td>Methacholine PC$_{20}$ ≤ 1 mg/ml</td>
<td>2.62*</td>
<td>1.17</td>
</tr>
<tr>
<td>eNO &gt; 25 ppb</td>
<td>2.75*</td>
<td>2.03</td>
</tr>
<tr>
<td>TEC &gt; 350 cells/mm$^3$</td>
<td>2.34*</td>
<td>1.62</td>
</tr>
<tr>
<td>Serum ECP &gt; 15 $\mu$g/L</td>
<td>2.78**</td>
<td>1.18</td>
</tr>
<tr>
<td>IgE &gt; 200 kU/L</td>
<td>2.86**</td>
<td>0.96</td>
</tr>
<tr>
<td>uLTE$_{4}$ &gt; 100 pg/mg</td>
<td>2.03</td>
<td>3.22*</td>
</tr>
<tr>
<td>Female</td>
<td>1.14</td>
<td>2.30</td>
</tr>
<tr>
<td>Minority</td>
<td>0.84</td>
<td>1.98</td>
</tr>
<tr>
<td>Age ≤ 10 years</td>
<td>0.64</td>
<td>2.50*</td>
</tr>
</tbody>
</table>

**p ≤ 0.01; *p ≤ 0.05

Ref. Szefler SJ and the CARE Network.

Factors Influencing Disease Onset, Severity and Effect of Therapeutic Intervention

- Genetics – Predisposition to disease
- Epigenetics – Indicator of gene-environment interaction
- Personalized medicine – selecting medications to reduce impact of gene-environment interaction on those predisposed to develop disease
Genetics, Epigenetics, and Personalized Medicine
15 million polymorphisms
1 base pair variant/200 base pairs
Uniqueness is defined every 1000 bp
Early Intervention for Asthma Prevention

Aberrant immune development & responses

1° Prevention
2° Prevention
Early Intervention

How Do we Move Forward?

Guiding principles

- *Family history* is a strong predictive feature.
- *NIH guidelines* have helped set standard of care but application is limited.
- *Clinical monitoring* is the most practical method but may underestimate disease activity.
- *Genetic testing* is still in discovery stage.
- *Biomarkers* require careful validation before general clinical application.
- *Electronic medical records* facilitate summary of natural history.
NIEHS/EPA Childhood Environmental Health Center Grant:
The Environmental Determinants of Airway Disease in Children

Microorganisms \[\rightarrow\] Innate Immunity \[\rightarrow\] Allergens

Environment Ozone Microbial Toxins \[\rightarrow\] Innate Immunity \[\rightarrow\] Genetics Candidate Genes Mouse Strains

Children, Mice, Immune Cells

Susceptibility to Infection \[\rightarrow\] Allergic Airway Disease

Airway Disease in Children
Denver Center Projects

Project 1: Higher levels of endotoxin exposure cause persistent, problematic asthma and that key environmental and genetic modifiers contribute to endotoxin susceptibility and pathological asthmatic responses in children.

Project 2: Ozone exposure in the early postnatal phase alters lung development and modifies the host immune response to early life viral infection and allergen exposure, thereby contributing to the development of reactive airway disease.

Project 3: Expression of toll-like receptors in the lung are influenced by environmental and genetic factors, and the dynamic expression of toll receptors has profound effects on lung host defense and consequently the development of lung infections and allergic airway disease.
Community Outreach and Translation Core

• Investigators, practitioners, and community stakeholders
• Community Advisory Board: multi-disciplinary, multi-regional, multi-sectoral, dedicated, engaged, and appropriately opinionated
• Community engagement and community based participatory research
• Goal is to improve the health of children at risk
Project 1: CAMP Questions

• Does home endotoxin exposure worsen asthma?
  – Obstruction
  – Inflammation
  – Twitchiness
  – Persistence
  – Severe attacks

• Does allergy + exposure amplify endotoxin’s toxicity?

• Do genetic variants in the endotoxin recognition receptor alter endotoxin’s effects on asthma?
CAMP Trial and Continuations

**Trial**
- Screening & Baseline Phase: 5 visits, 2 – 4 months
- Treatment Phase: 3 visits per year, 4 – 6 years
- Transition Phase: 2 visits, 4 months
- Randomize: Bud, Ned, Plbo
- Study Rx: Discontinued

**Continuations**
- Follow-up Phase: 1-4 visits per year, 12 years
- Enroll in CAMPcs, CAMPcs2, CAMPcs3
- Refer back to PCP for Rx per NAEPP guidelines

**Study Details**
- Dec 1993 – Sept 95: 1,041 children 5-12 years of age
- Mild to moderate persistent asthma
Rationale for Analysis of FEV$_1$ as Outcome: General Framework

FEV$_1$ (% normal level at age 20)

- Normal
- Early Decline
- Reduced Growth
- Rapid Decline

Age (yr)
Future Approaches to Asthma Management

• **Early intervention** to prevent and control asthma
• Anticipate and *prevent asthma exacerbations*
• Apply **biomarkers** to monitor disease activity
• Use **genetics/epigenetics** to identify risk category for disease onset/severity
• **Immunomodulators** to alter course of disease
Genetics, Epigenetics, and Personalized Medicine
Epigenetics: Control of Gene Expression

*right time, right place, right amount*

From ENCODE Consortium
Epigenetics and Airway Immunology

Innate Immune Instruction

Antigen + Environmental Signals
Dendritic cell

Adaptive Immunity

Th$_n$ → Th$_1$ → IFN-$\gamma$ → Cell-mediated immunity
→ Th$_{17}$ → IL-17/22 → Auto-immunity/Inflammation
→ Tr$_1$ → IL-10 → Immune regulation
→ Th$_2$ → IL-4/5/13 → Asthma/Atopy

Differentiation (Days)

Transcription (Hours)
Epigenetics and Airway Immunology

Innate Immune Instruction

Antigen + Environmental Signals

Dendritic cell

Adaptive Immunity

Thn

Th1

IFN-γ

Th17

IL-17/22

Tr1

IL-10

Th2

IL-4/5/13

STAT4, T-bet

RORγT

FoxP3

GATA3

Differentiation (Days)

Transcription (Hours)

Shin. J Immunology 2005; 175:7143

Auto-immunity/Inflammation


Fields. J Immunology 2002; 169:647

Asthma is Influenced by the Environment

Devereux. *Nature Reviews Immunology* 2006; 6:869
Etiology of Asthma

Environmental Asthma

Epigenome

Genetic Vulnerability

Epigenetics and Asthma

- non-Mendelian pattern of inheritance
- Influenced by the environment
- Affected by *in utero* exposures
- Alter/involve maturation of T cells
Susceptibility Genes in Asthma
[multiple genes – single disease]
Asthma is a Major Public Health Problem

- Affects millions of children and adults world-wide (over 30 million in the U.S.)
- More prevalent among children and minorities
- Cost of asthma continues to increase (> $10 billion annually in the U.S.)

Eder. *NEJM* 2006; 355:2226
NIAID Inner City Asthma Consortium

- Inner City Environment
- Immune Development
- Allergy and Asthma
- Microbiota (environmental and gut)
- Epigenome
Denver Public School Asthma Program

A collaboration of community partners creating school-based asthma programs
DPS Elementary Schools Asthma Disparities

Above 90% free/reduced lunch
>75-90% free/reduced lunch
Above 50% African American
Above 75% Hispanic
50-75% Hispanic
Above 10% asthma prevalence

Above 90% free/reduced lunch
>75-90% free/reduced lunch
Above 10% asthma prevalence

Denver Public Schools
Elementary School Boundaries
2007-08

Denver Public Schools
Department of Planning and Innovation
August 21, 2007
Hospitalizations for Asthma in Children: *Canada*

* 20 - 25% of all hospitalizations in Canada for childhood asthma exacerbations occur in September

Project 2

Environmental Determinants of Early Host Response to RSV and Allergen
Overall Objective

Define how reactive airway disease (asthma) develops in response to common triggers (RSV, Allergen), influenced by environmental factors (Ozone, Endotoxin) in early life.
Specific Aims

• Determine the effects of ozone on postnatal lung development, innate immunity (TLRs expression) and airway function.

• Define how ozone influences the early postnatal response to RSV and HDM allergen, and determines the development of asthma-like phenotype.

• Determine how endotoxin (bacterial air contaminant) influences the development of asthma by modifying the early response to RSV and HDM allergen, following postnatal ozone exposure.
Toll-like Receptors

- TLRs (pathogen recognition receptors)
The overall goal of this project is to understand how and why air pollution alters lung host defense.
Specific Aim 1

Determine the effect of *in vitro* exposures to ozone and/or PAMPs on the expression of TLRs in murine macrophages and DCs.

**Ozone**

**PAMPs**

**Ozone + PAMPs**

**TLR expression**

**TLR distribution**

**Cytokine production**

129/SvIm

A/J

BALB/c

C57/B6

DBA/2J
Specific Aim 2

Determine the effect of *in vivo* exposures to ozone and/or PAMPs on the expression of TLRs in mouse lungs.

**Aim 1 Data**

- 129/SvIm
- A/J
- BALB/c
- C57/B6
- DBA/2J

**Ozone**

- PAMPs
- Ozone + PAMPs

**TLR expression**

**TLR distribution**

**Lung inflammation**

**AHR**
Specific Aim 3

Determine the effect of *in vivo* exposures to ozone and/or PAMPs on susceptibility of mice to lung pathogens.

**Aim 2 Data**

129/SvIm
A/J
BALB/c
C57/B6
DBA/2J

**Ozone**

PAMPs

**Ozone + PAMPs**

**Lung pathogens**

- Morbidity
- Pathogen Clearance
- Lung inflammation
- AHR
Specific Aim 4

Determine the effect of \textit{in vivo} exposures to ozone and/or PAMPs on house dust mite (HDM) induced allergic airway disease in mice.

Aim 2 Data

129/SvIm
A/J
BALB/c
C57/B6
DBA/2J

Ozone
PAMPs
Ozone + PAMPs

HDM sensitization/challenge

Allergic Inflammation
AHR
Anticipated Significance and Impact

• Airway disease in children is a major *public health problem*

• *Air pollutants* exacerbate airway disease in children and enhance the susceptibility to infectious agents

• Children are more *vulnerable* to air pollution (lung development, immune development, and increased exposures)

• Innate immune receptors represent primary forms of *host defense* and are altered by air pollution

• Our *center* will address some of the basic precepts about asthma – *in utero* exposures, developmental biology, immune responsiveness, community impact, and outreach and education
Genetics, Epigenetics, and Personalized Medicine

- Identify those at risk
- Preclinical disease
- Define disease biologically
- Individualize prognosis
- Personalize treatment
Communication sources

• Websites:
  www.nationaljewish.org/cehc
  NIEHS/EPA CEHC web site
• Director: david.schwartz@ucdenver.edu
• Co-Director: szeflers@njhealth.org
• Community Outreach: cicuttol@njhealth.org