Mechanistic Indicators of Childhood Asthma (MICA) - Integrating Environmental, Clinical and Susceptibility Markers to Improve the Impact of Human Air Pollution Studies.

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Human Studies Division
ORD NHEERL EPA
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Public Health Applications of Human Biomonitoring
Advances in biomarker development have improved our ability to detect early changes at the molecular and cellular level.
Clinical Disease

Exposure
Battery of endpoints capturing Net effect—over several mechanisms of action/ classes

- Comet assay
- P53
- FISH
- 1-OH pyrene
- Cholinesterase inhibition
- Cross-linking metals formaldehyde
- HPRT
- DNA adducts methods
- Mutagen sensitivity
- Oxidative damage
- Mutagenicity

Integrated measure of dose across classes of chemicals
Evolving Technologies

Environment
Health Scientists

Clinicians

Exposure
Clinical Disease

Questions:

- Environment
- Health Scientists
- Clinicians
Environmental Studies Benefit from Knowledge Gained from Clinical Disease Studies (and visa versa)

- What factors affect a person's risk for a number of health conditions.
- Early indicators/detection of disease
- Identify Genetic variants that increase susceptibility
- Determine whether the effect of genetic variants that increase risk is different in the presence of environmental exposures
Change in research paradigm

- Work across disciplines
- Give up data for the greater good
- Communicate
MICA

- A childhood asthma study and Parallel rodent study
- A NHEERL and NCCT Computational Toxicology study
- Combines and Integrates biomarkers of exposure effects and susceptibility in the context of clinical measurements and disease (asthma) outcome.
National Center for Computational Toxicology

Goals
Improve linkages in the source to outcome paradigm

• Provide predictive models for Hazard ID
• Improve Quantitative Risk assessment Dose, species, chemical class

7 New Starts --- MICA
RNA--- Blood Gene expression
DNA ----11 genes 55 SNP
Objective

Increase our understanding of asthma by assessing the complex gene/environmental relationships through the combined use of innovative methods to manage and analyze multifactorial data.
11 polymorphic genes
55 SNP
National Exposure and Research Laboratory

Detroit Exposure Aerosol Research Study “DEARS”
200 children (asthma and no asthma) 9-12 years of age

100 families participated in self monitoring (indoor outdoor) as part of MICA air

Vacuum Dust and medication list brought to clinic

Educational and “station walk through” presentation to provide context to the study

Consent assent and Questionnaire

Lung function, NO ex and odor testing

Blood, urine, fingernails collected

> 90 percent of subjects provided samples at each station.
MICA Childhood Study
Multiple Risk Factors

- Asthma
- Obesity
- Cardiovascular Risk

1
2
3
Asthma studies by race

MICA  85% African American
Study Design

**Biomarkers of Integrated Dose:**
Metals (Lead, Mercury),
Metabolites of Polycyclic Aromatic Hydrocarbons, Cotinine, and Creatinine

**Biomarkers of Early Effect:**
Autoantibodies, Mutagenicity Gene Expression
Inflammatory Markers

**Susceptibility Factors:** Genetic Variation-RNA, DNA

**Ambient Levels**
Internal Dose
Effective Dose
Early Biological Effect
Pre-Clinical Effects
Clinical Disease

**Detroit-area Urban Air**
Particulate matter (PM) (concentrated to 200-600µg/m³)

**Ambient Levels of PM and air toxics**

**Rodents: Blood and Lung Tissue**
Gene Expression Profiles
Inflammatory Markers

**Asthmatic and nonasthmatic Children n=200**

**Clinical-relevant Outcomes:**
Allergies, Asthma, Respiratory Symptoms, Lung Function
NOex VOC

**Environmental Levels**
Detroit-area Urban Air
Particulate matter (PM) (concentrated to 200-600µg/m³)

**Inhalation Exposure**
Ambient Levels of PM and air toxics
Rodent Study

Detroit AIR

Concentrated Air Particles Exposures
Air Particle Concentrator and Inhalation Exposure System for Laboratory Rodents

Animals are exposed to concentrated fine and ultrafine particles in specially designed shoebox cages
MICA (I)
Evaluate Utility of Rodent models for analyzing gene expression data in childhood asthma study

Brown Norway Rats

- Air/Saline
- Air/Ova
- CAPS/Saline
- CAPS/Ova
Study Design

Biomarkers of Integrated Dose:
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Metabolites of Polycyclic Aromatic Hydrocarbons,
Cotinine, and Creatinine

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Autoantibodies, Mutagenicity
Gene Expression
Inflammatory Markers

Clinically-relevant Outcomes:
Allergies, Asthma, Respiratory Symptoms,
Lung Function

NOex VOC

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Susceptibility Factors: Genetic Variation-RNA, DNA

Ambient Levels
Internal Dose
Effective Dose
Early Biological Effect
Pre-Clinical Effects
Clinical Disease

Clay

MICA

United States Environmental Protection Agency
Gene expression - RNA
Genotyping – DNA (11 genes 55 SNP)

- **AIR/DUST**
  - Indoor outdoor
  - PAH VOC No2 O3
  - Allergens Molds

- **INTERNAL DOSE**
  - Metals
  - Heavy Metals
  - PAH metabolites
  - ETS Pb Hg
  - Napthols Phenanthrols

- **INTEGRATED DOSE**
  - ROS Cholinesterase
  - Mutagenicity
  - 1 OH Pyrene
  - Antibodies to nervous system Cotinine proteins
  - Coagulation factors

- **Health Effect Asthma**
  - Lung function NOex
  - Antioxidants
  - Allergen skin testing
  - Plasma ROS Cytokines
  - Blood panel
  - Cell surface markers
### Passive monitoring: \( \text{NO}_2, \text{PAHs, VOC, (indoor and outdoors)} \)

<table>
<thead>
<tr>
<th>Vacuum dust</th>
<th>Metals, PAHs, aero-allergens, mold, endotoxin</th>
</tr>
</thead>
</table>

### Biomarkers--- Clinical and Environmental

<table>
<thead>
<tr>
<th>Urine</th>
<th>Cotinine, Creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>Metals: Mercury, Cadmium, Arsenic, Chromium, Manganese, Nickel</td>
</tr>
<tr>
<td>Urine</td>
<td>1- hydroxypyrene (1-OH pyrene) Napthols, Phenanthrols, Hydrocarbon Metabolites phthalates</td>
</tr>
<tr>
<td>Urine</td>
<td>Mutagenicity Assays</td>
</tr>
<tr>
<td>Serum</td>
<td>Autoantibodies for nervous system proteins, Blood Chemistry, Total IgE and specific antibodies to common aero-allergens (multiscreen inhalant and food antibody series)- *dust mite, Cockroach, Mouse, Rat Urine Protein,</td>
</tr>
<tr>
<td>Plasma</td>
<td>Reactive Oxygen Species, cytokines (IL4, 6 IL13), tumor necrosis factor-alpha, c-reactive protein, fibrinogen</td>
</tr>
<tr>
<td>Whole Blood</td>
<td>Hematology panel, lead and mercury, Gene expression (RNA), glycosolated hemoglobin</td>
</tr>
<tr>
<td>Nails</td>
<td>Mercury, Cadmium, Arsenic, Chromium, Manganese, Nickel</td>
</tr>
<tr>
<td>Serum</td>
<td>IgE-inducing proteins associated with fungal exposures</td>
</tr>
</tbody>
</table>
11 polymorphic genes
55 SNP
NOW WHAT ???
NASAL EPITHELIAL CELLS

J. ALLERGY CLIN IMMUNOL VOLUME 115, NUMBER 2

NORMAL
Stable Asthmatics
UnStable Asthmatics

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Biomarkers Exposure/Clinical indicators

Subjects

Elaine Hubal
David Reif
National Center for Computational Toxicology

HEAT MAP MICA
Biomarker Needs

- Exposure biomarkers in the context of clinical health indicators
- Mechanistic information test biological plausibility in rodents
- Validation of surrogate cells with target tissue responses

Archiving of biological and environmental samples and measurements as new technologies advance
Summary

• High-data content technologies, elucidating the genetic and environmental basis for toxicity and disease
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PHASE II MICA

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