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
September 24-25  2007
Public Health Applications of Human Biomonitoring
Advances in biomarker development have improved our ability to detect early changes at the molecular and cellular level.
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

Evo
ing Tech
ologies?
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-Change Research Paradigm

National Center for Computational Toxicology

NERL Cincinnati

NERL RTP

Genomics Core

S. Edwards

NHEERL

Region 5

Johns Hopkins
Michigan State University
Mercy College
UNC at Chapel Hill

Rutgers University
Harvard U.

Westat
Labcorp
RTI
EA
South West Research Institute

Henry Ford Health System

ECD HSD ETD
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

SOURCE

INTERNAL DOSE

INTEGRATED DOSE

EARLY RESPONSES

HEALTH OUTCOME
MICA

Questionnaire
Diet
Time activity

Fingernails
urine
blood
Odor test

Lung function
NO ex

Vacuum dust and
Passive monitoring

BMI
Blood Pressure
O2 Saturation
Cell differentials
Blood Chemistry
Cytokines
Creatinine
cotinine
Medications

Asthma

Lung function

NO ex

Vacuum dust and
Passive monitoring

Blood Chemistry
Cytokines
Creatinine
cotinine
Medications

Asthma
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

MICA RODENT Phase 1

Childhood asthma Phase 2
MICA Nested Within Detroit Children’s Health Study

Questionnaire

Lung Function

Biomarkers

MICA

MICA AIR
National Exposure and Research Laboratory

Detroit Exposure Aerosol Research Study “DEARS”
MICA

- 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

Obesity

Cardiovascular Risk

Asthma
Asthma studies by race

MICA  85% African American
Study Design

Particulate matter (PM) (concentrated to 200-600µg/m³)

Detroit-area Urban Air

Ambient Levels of PM and air toxics

Rodents: Blood and Lung Tissue

Gene Expression Profiles

Inflammatory Markers

Asthmatic and nonasthmatic Children n=200

Susceptibility Factors: Genetic Variation-RNA, DNA

Ambient Levels

Internal Dose

Effective Dose

Early Biological Effect

Pre-Clinical Effects

Clinical Disease

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

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

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Rodent Study

Detroit AIR

Concentrated Air Particles Exposures
MSU Mobile Air Research Laboratory (AirCARE 1)
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:** Metals (Lead, Mercury), Metabolites of Polycyclic Aromatic Hydrocarbons, Cotinine, and Creatinine

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

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

- Detroit-area Urban Air
- Ambient Levels of PM and air toxics
- Gene Expression Profiles
- Inflammatory Markers
- Asthmatic and nonasthmatic Children n=200

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

**Particulate matter (PM) (concentrated to 200-600µg/m³)**

**Rodents: Blood and Lung Tissue**

**Susceptibility Factors: Genetic Variation-RNA, DNA**
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
CINCGENATI CHILDRENS HOSPITAL

NORMAL

Stable Asthmatics

UnStable Asthmatics

NASAL EPITHELIAL CELLS
HEAT MAP MICA

Elaine Hubal
David Reif
National Center for Computational Toxicology

Biomarkers Exposure/Clinical indicators
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
Integration of Diverse Set of exposure, effects and susceptibility

Gene expression arrays

genes, pathways, and networks

bioinformatic

computational

statistical analysis.
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