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

Jane E. Gallagher Ph.D.
Human Studies Division
ORD NHEERL EPA

September 24-25 2007

Public Health Applications of Human Biomonitoring

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Advances in biomarker development have improved our ability to detect early changes at the molecular and cellular level.

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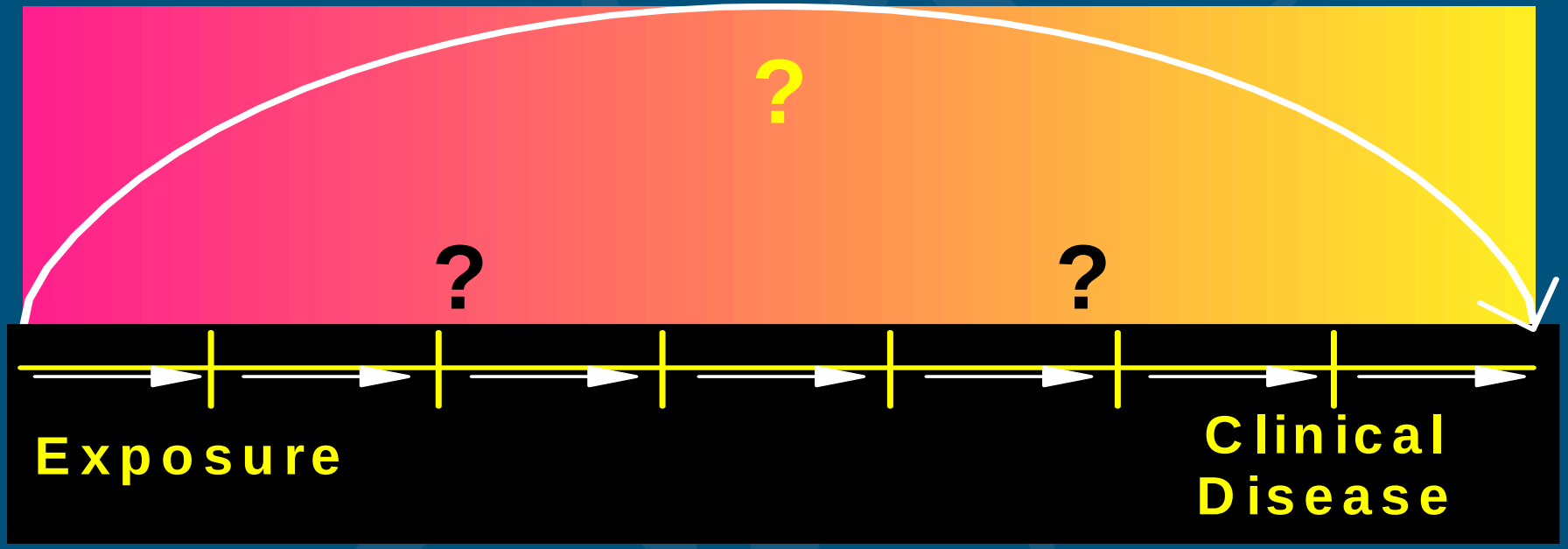

Battery of endpoints capturing Net effect–over several mechanisms of action/ classes

- 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

EvolvingTechnologies

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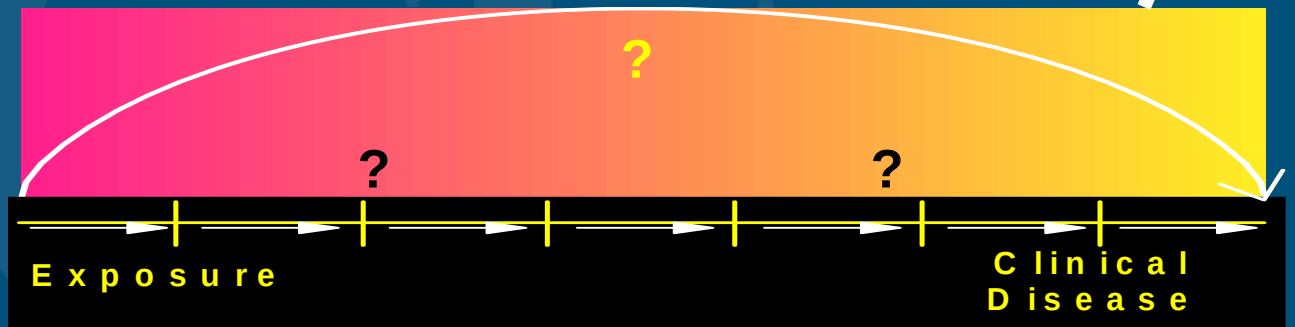
Environment Health Scientists

Clinicians



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Environmental Studies Benefit from Knowledge Gained from Clinical Disease Studies (and visa versa)

- What factors affect a persons 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

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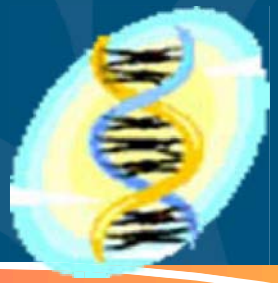
MICA



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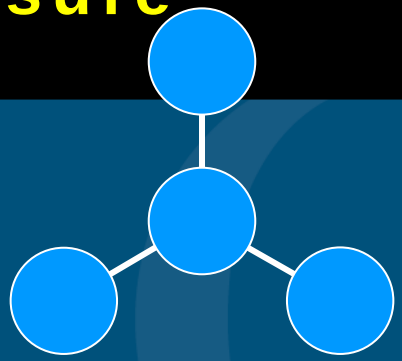
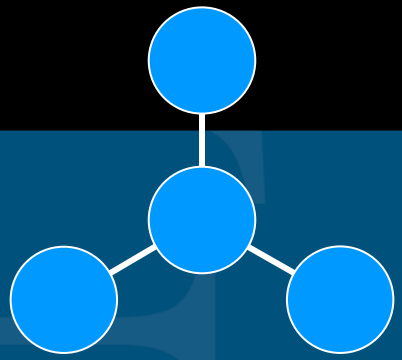
Exposure

Clinical Disease





Biological Fluids/cells

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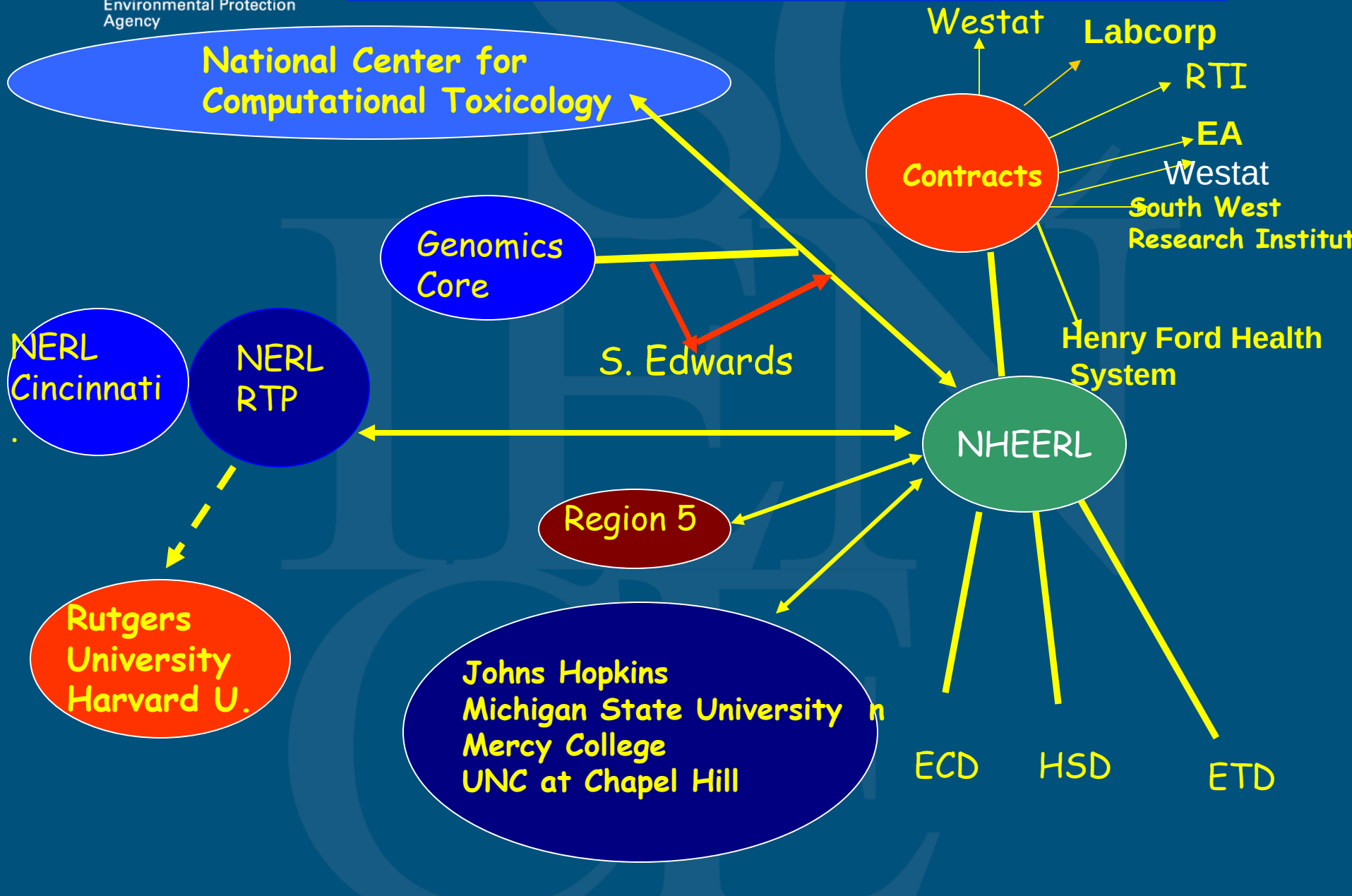
Change in research paradigm

- Work across disciplines
- Give up data for the greater good
- communicate

MICA-
Change Research Paradigm



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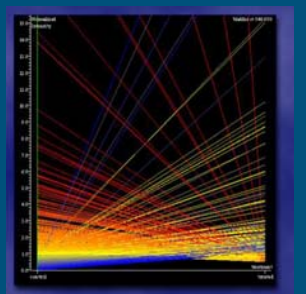
MICA

- 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.



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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

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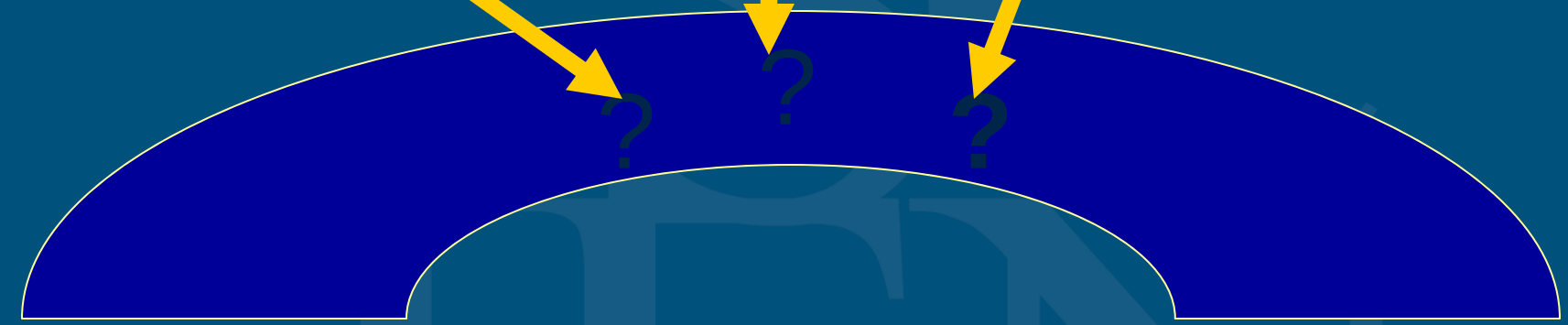
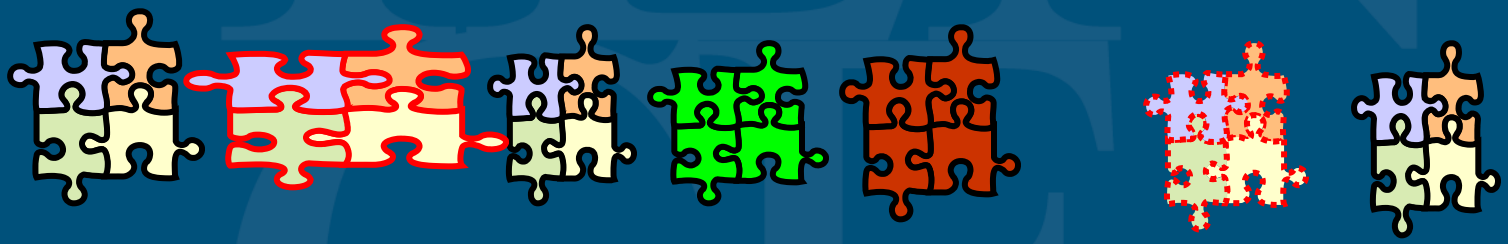
RNA--- Blood Gene expression
DNA ----11 genes 55 SNP



SOURCE

HEALTH OUTCOME



INTERNAL DOSE

INTEGRATED DOSE

EARLY RESPONSES

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MICA

Questionnaire
Diet
Time activity

Fingernails

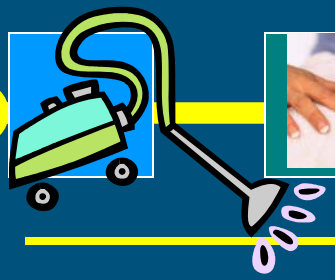
urine

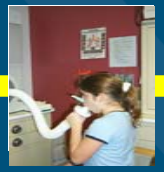
blood

Odor test

Lung function

NO ex





Asthma

Vacuum dust and

Passive monitoring

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

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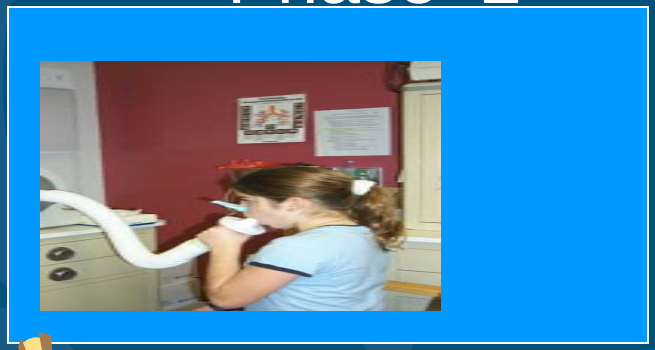
MICA

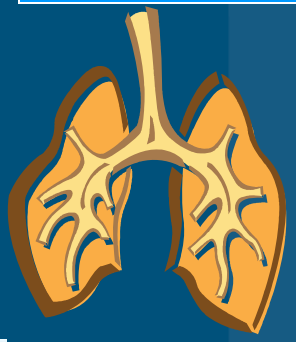
Objective

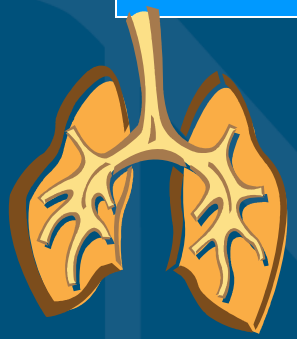
Increase our understanding of asthma by assessing the complex gene/environmental relationships through the combined use of innovative methods to manage and analyze multifactorial data

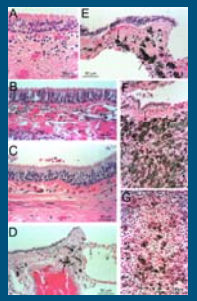
MICA RODENT Phase 1

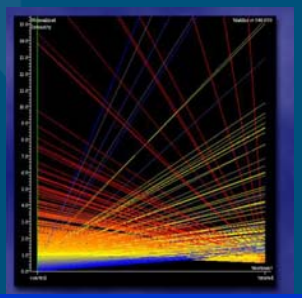
Childhood asthma Phase 2

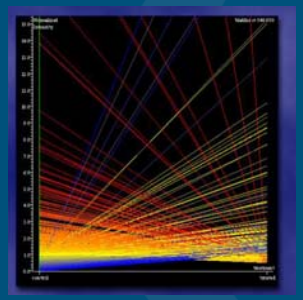






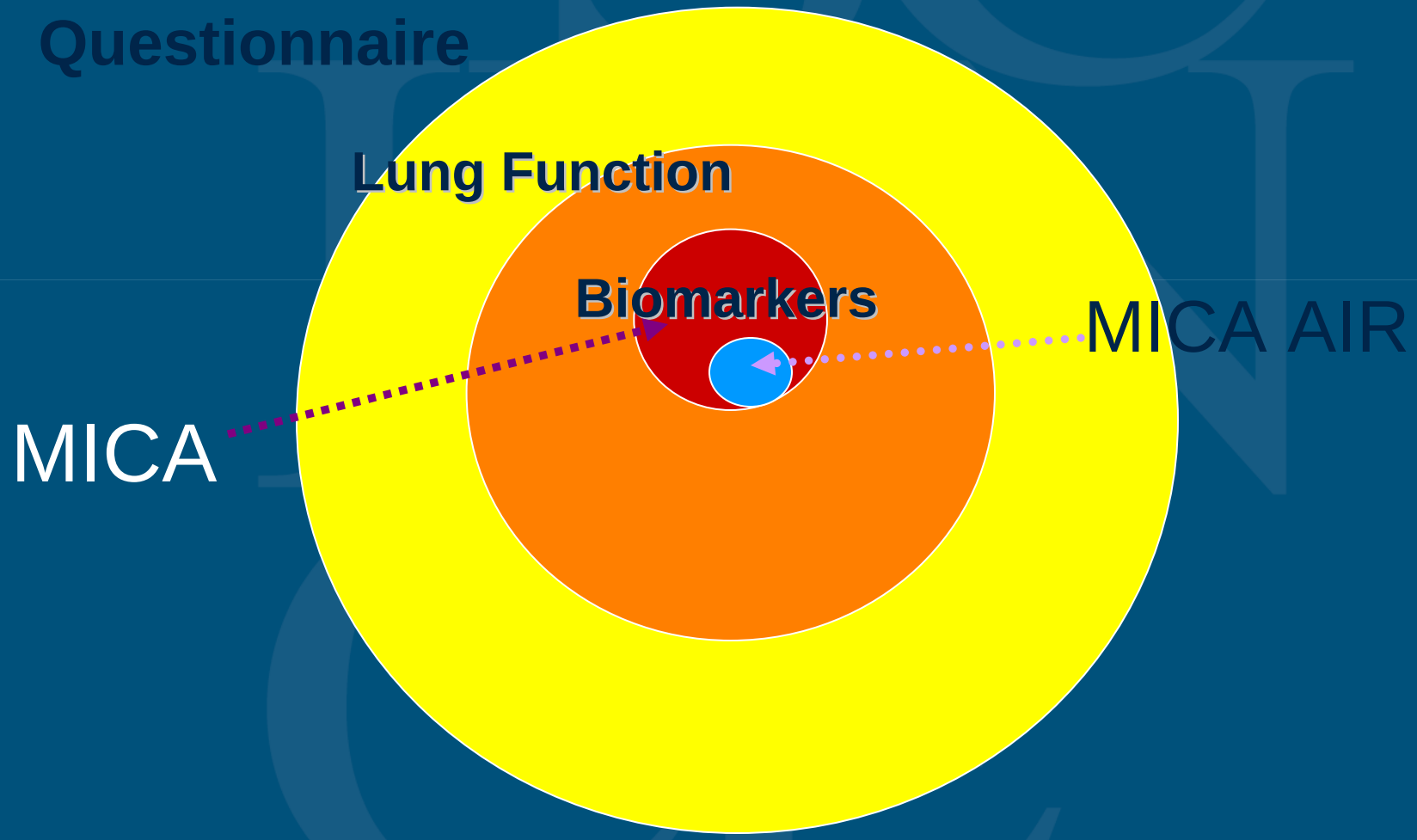






11 polymorphic genes
55 SNP

MICA Nested Within Detroit Children's Health Study



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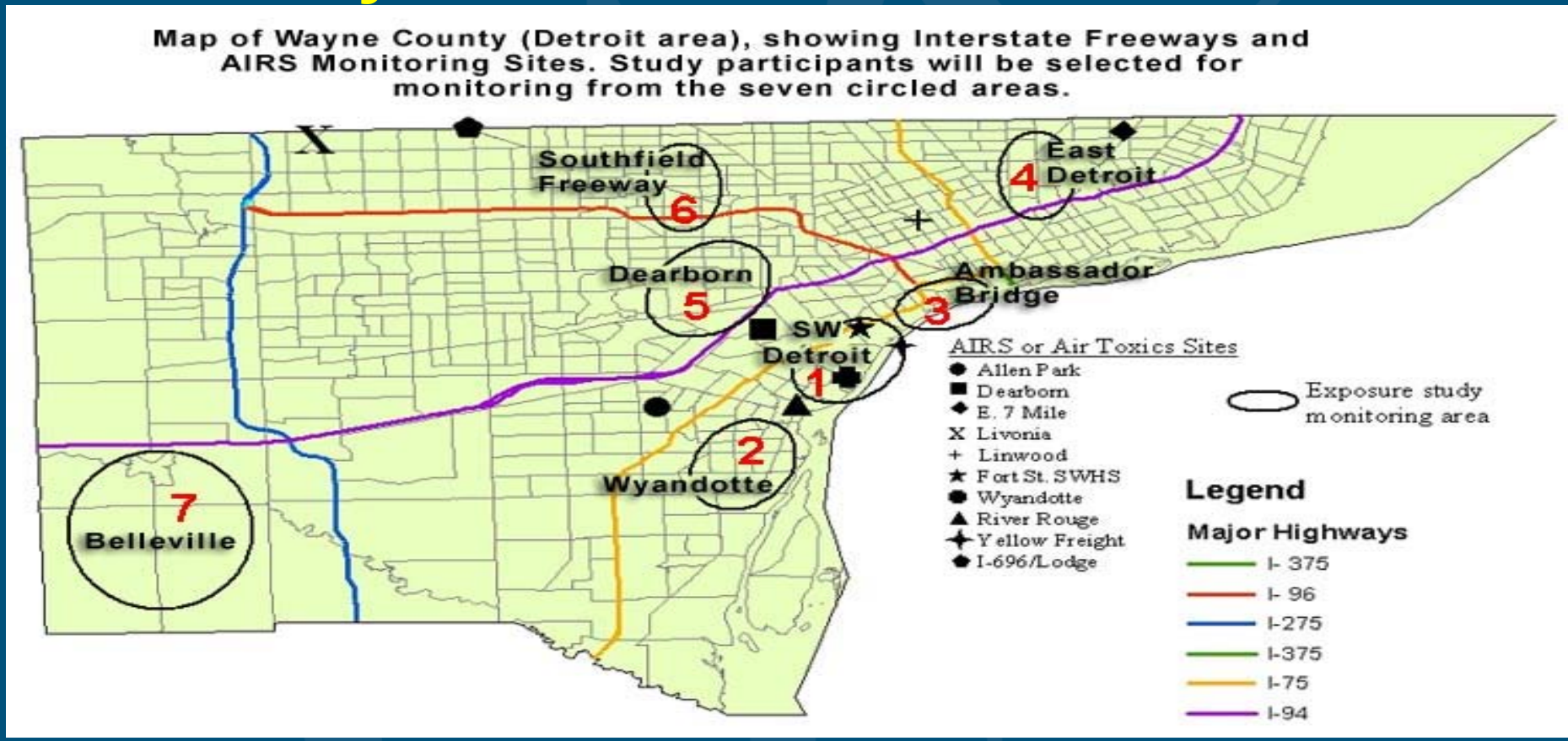
National Exposure and Research Laboratory

Detroit Exposure Aerosol Research Study "DEARS"



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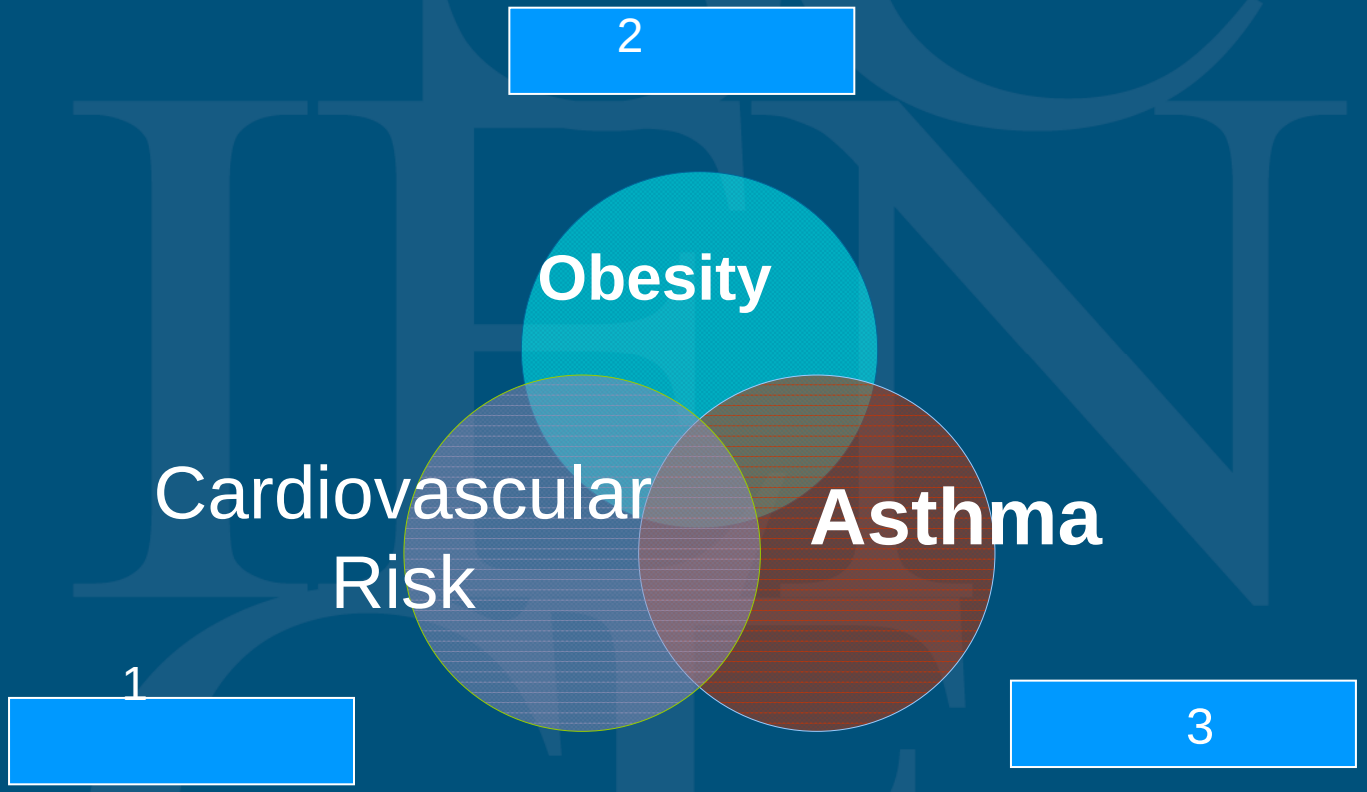
MICA

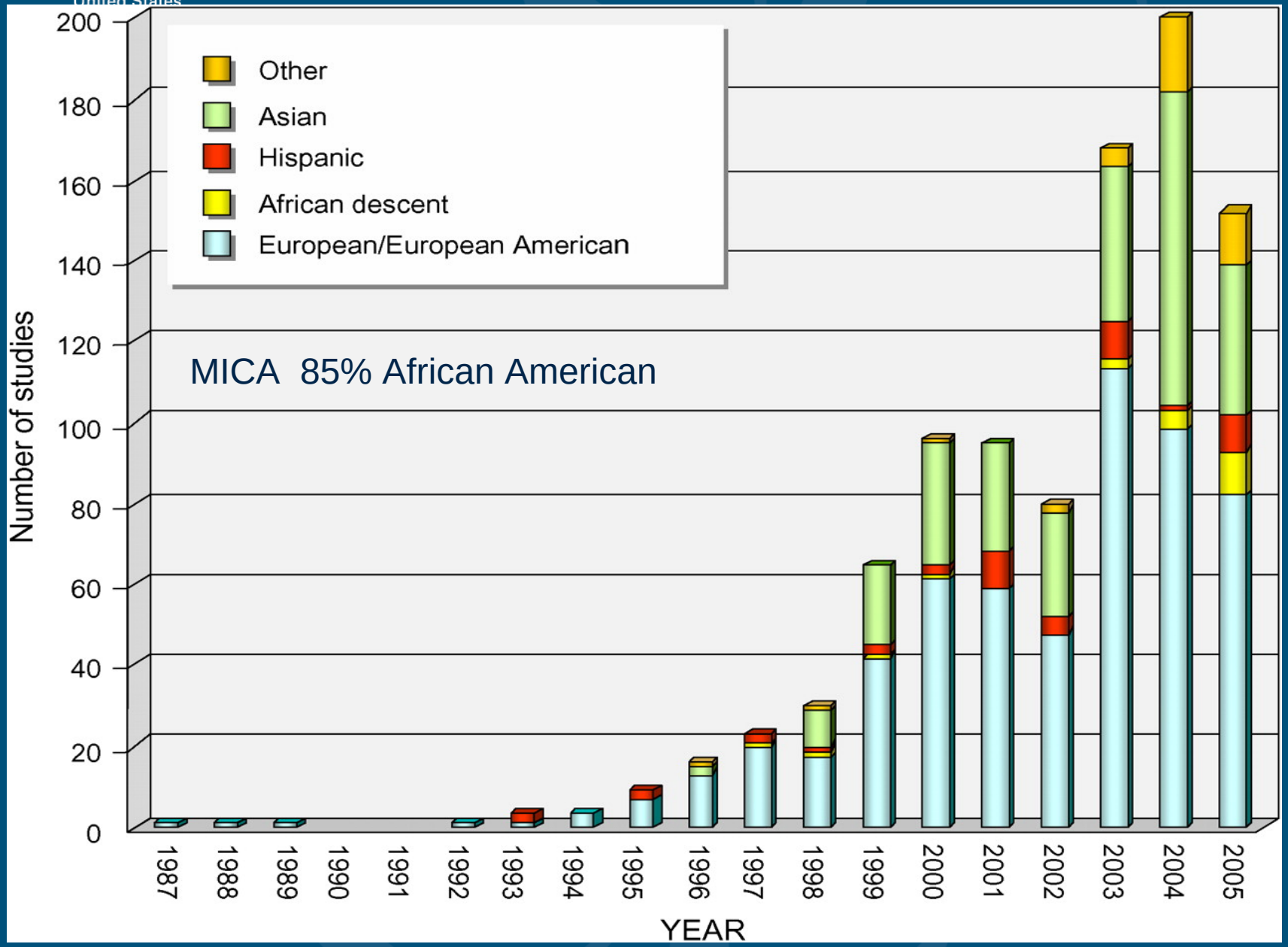
- 200 children (asthma and no asthma) 9-12 years of age
- 100 families participated in self monitoring (indoor outdoor) as part of MICA air
- Vacuum Dust and medication list brought to clinic
- Educational and “station walk through” presentation to provide context to the study
- Consent assent and Questionnaire
- 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



Asthma studies by race



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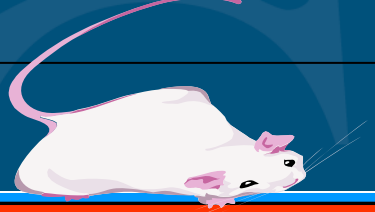
Study Design



Particulate matter (PM) (concentrated to 200-600µg/m^3)

Rodents: Blood and Lung Tissue

Detroit-area Urban Air

Gene Expression Profiles

Inflammatory Markers

Ambient Levels of PM and air toxics

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

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MSU Mobile Air Research Laboratory (*AirCARE 1*)

J Harkema

Air Particle Concentrator and Inhalation Exposure System for Laboratory Rodents

Animals are exposed to concentrated fine and ultrafine particles in specially designed shoebox cages

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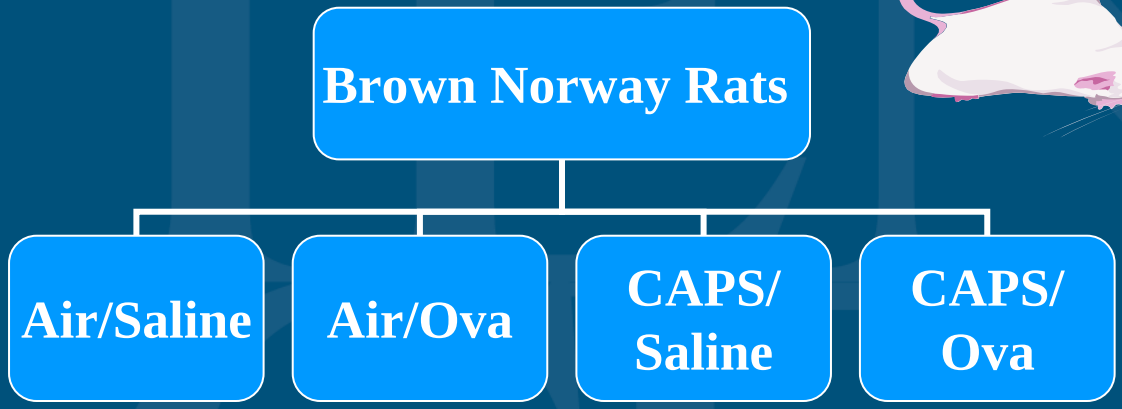
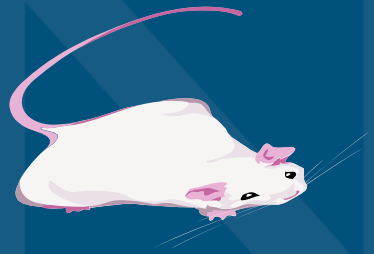
MICA (I)

Evaluate Utility of Rodent models for analyzing gene expression data in childhood asthma study





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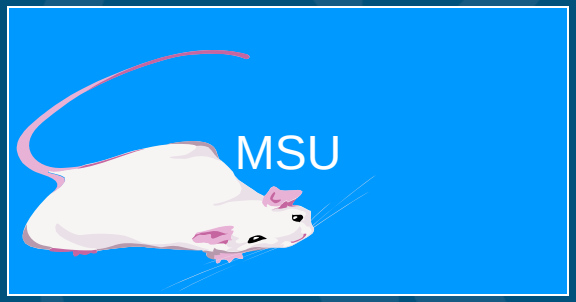

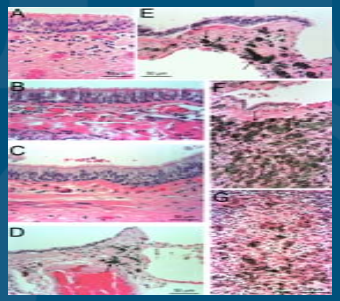

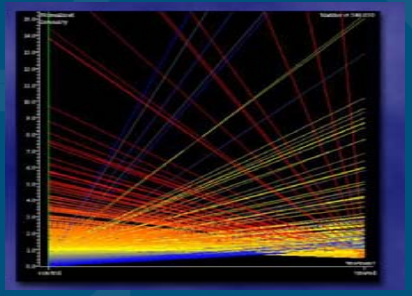

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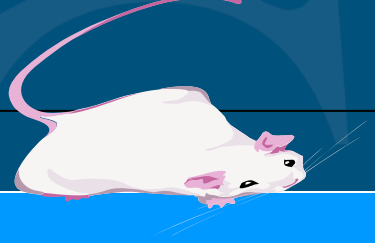
Study Design



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

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

Gene expression - RNA
Genotyping –DNA (11 genes 55 SNP)

Indoor outdoor

- PAH VOC No2
- O3
- Allergens
- Molds

Metals

- Heavy Metals
- PAH metabolites
- ETS
- Pb Hg
- Napthols
- Phenanthrols

ROS

- Cholinesterase
- Mutagenicity
- 1 OH Pyrene
- Antibodies to nervous system
- Cotinine
- proteins
- Coagulation factors

Lung function

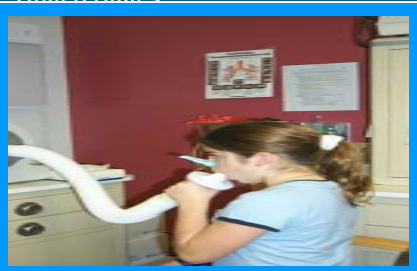
- NOex
- Antioxidants
- Allergen skin testing
- Plasma ROS
- Cytokines
- Blood panel
- Cell surface markers

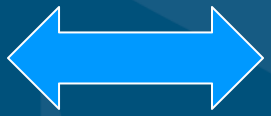
Passive monitoring: NO_2, PAHs VOC, (indoor and outdoors)

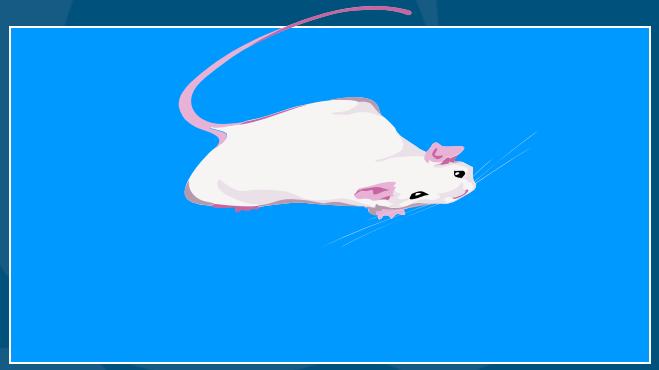
Vacuum dust	Metals, PAHs,aero-allergens mold, endotoxin)

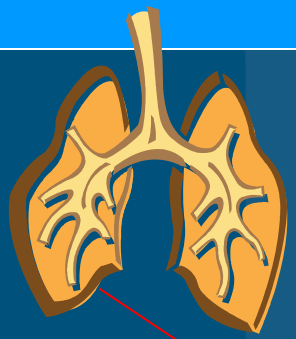
Biomarkers--- Clinical and Environmental

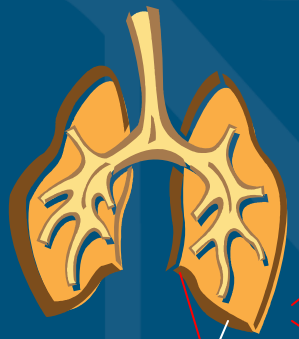
Urine	Cotinine Creatinine
Urine	Metals: Mercury, Cadmiun, Arsenic, Chromium, Manganese, Nickel
Urine	1- hydroxpyrene (1-OH pyrene) Napthols, Phenanthrols, Hydrocarbon Metabolites phthalates
Urine	Mutagenicity Assays
Serum	Autoantibodies for nervous system proteins, Blood Chemistry, Total IgE and specific antibodies to common aero-allergens (multiscreen inhalant and food antibody series)- *dust mite, Cockroach , Mouse, Rat Urine Protein,
Plasma	Reactive Oxygen Species, cytokines (IL4, 6 IL13), tumor necrosis factor-alpha, c-reactive protein, fibrinogen
Whole Blood	hematology panel, lead and mercury, Gene expression (RNA), glycosolated hemoglobin
Nails	Mercury, Cadmium, Arsenic, Chromium, Manganese, Nickel
Serum	IgE-inducing proteins associated with fungal exposures

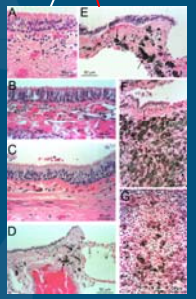


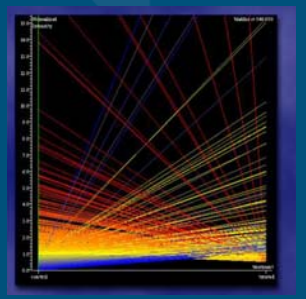


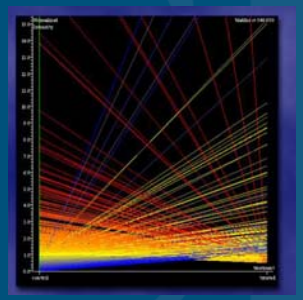












11 polymorphic genes
55 SNP

NOW WHAT ???

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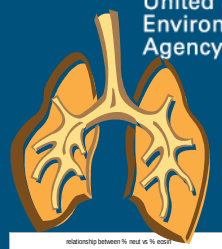

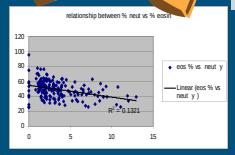

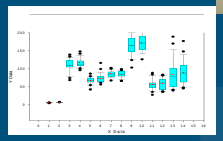

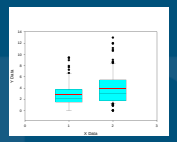

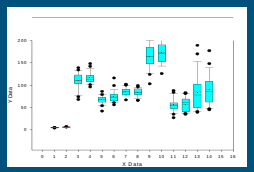

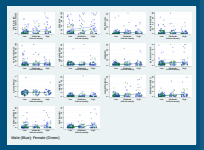

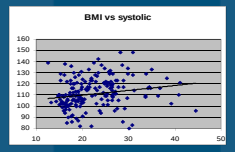

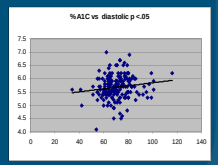

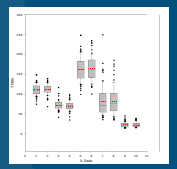

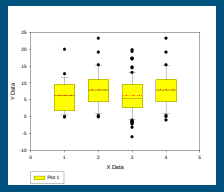

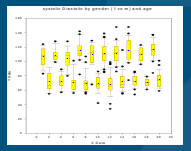

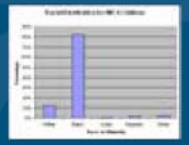

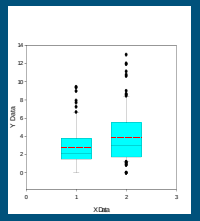

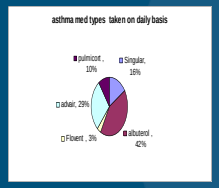

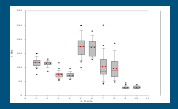

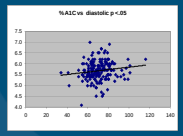

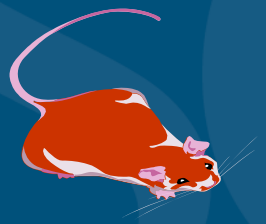

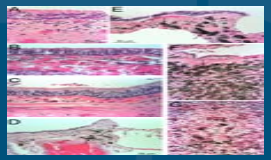

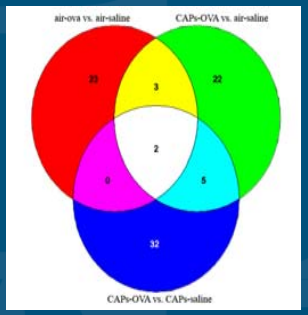

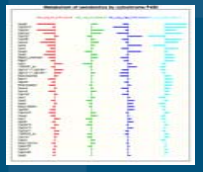

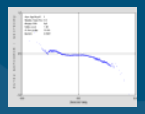

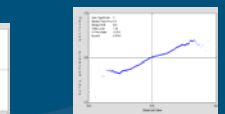

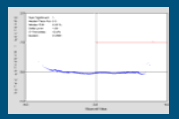

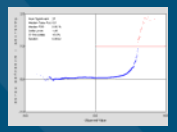

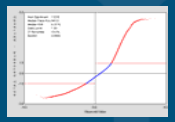

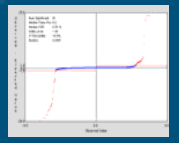

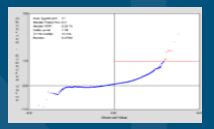

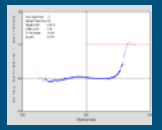

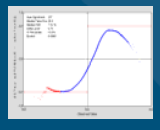

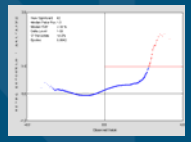

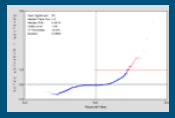

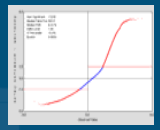

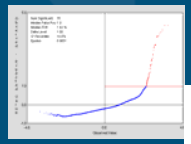

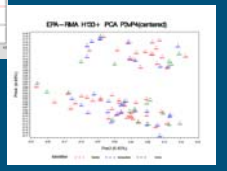

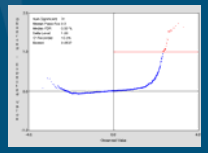

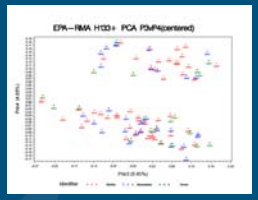

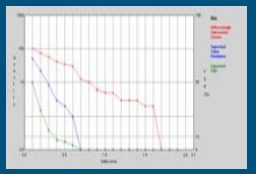

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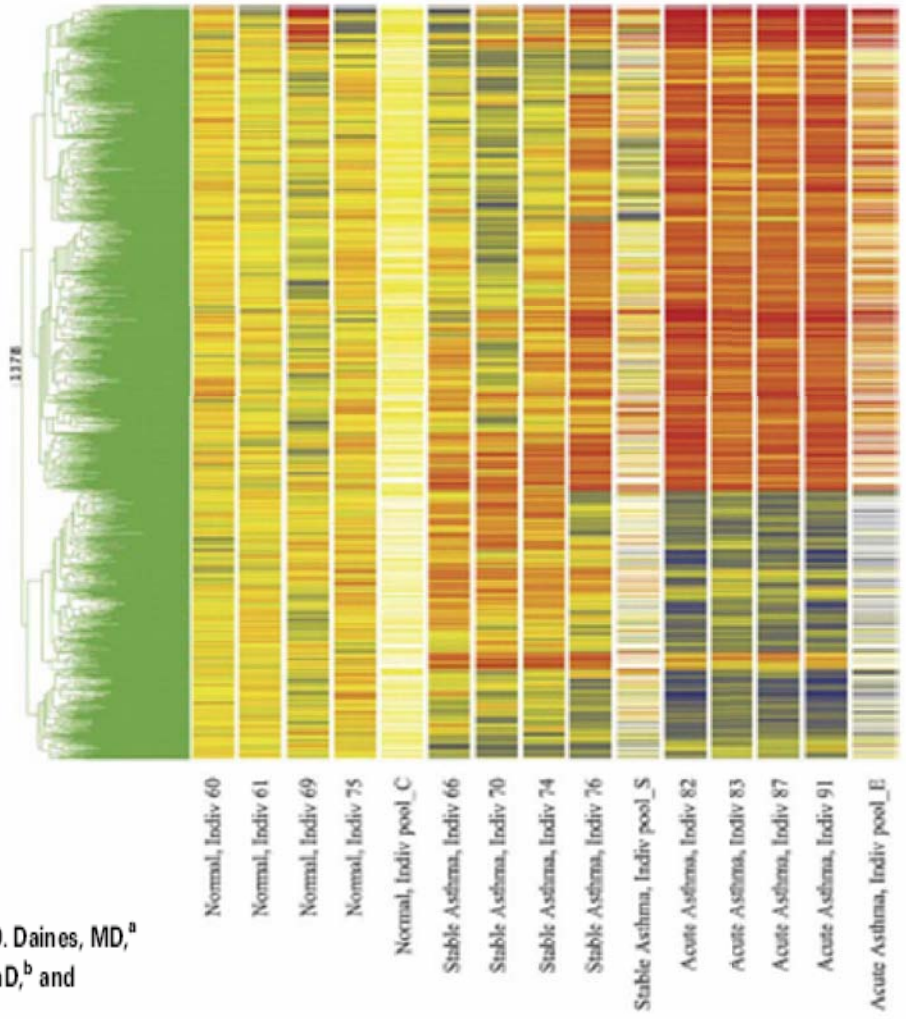
J ALLERGY CLIN IMMUNOL
VOLUME 115, NUMBER 2

NORMAL

Stable Asthmatics

UnStable Asthmatics

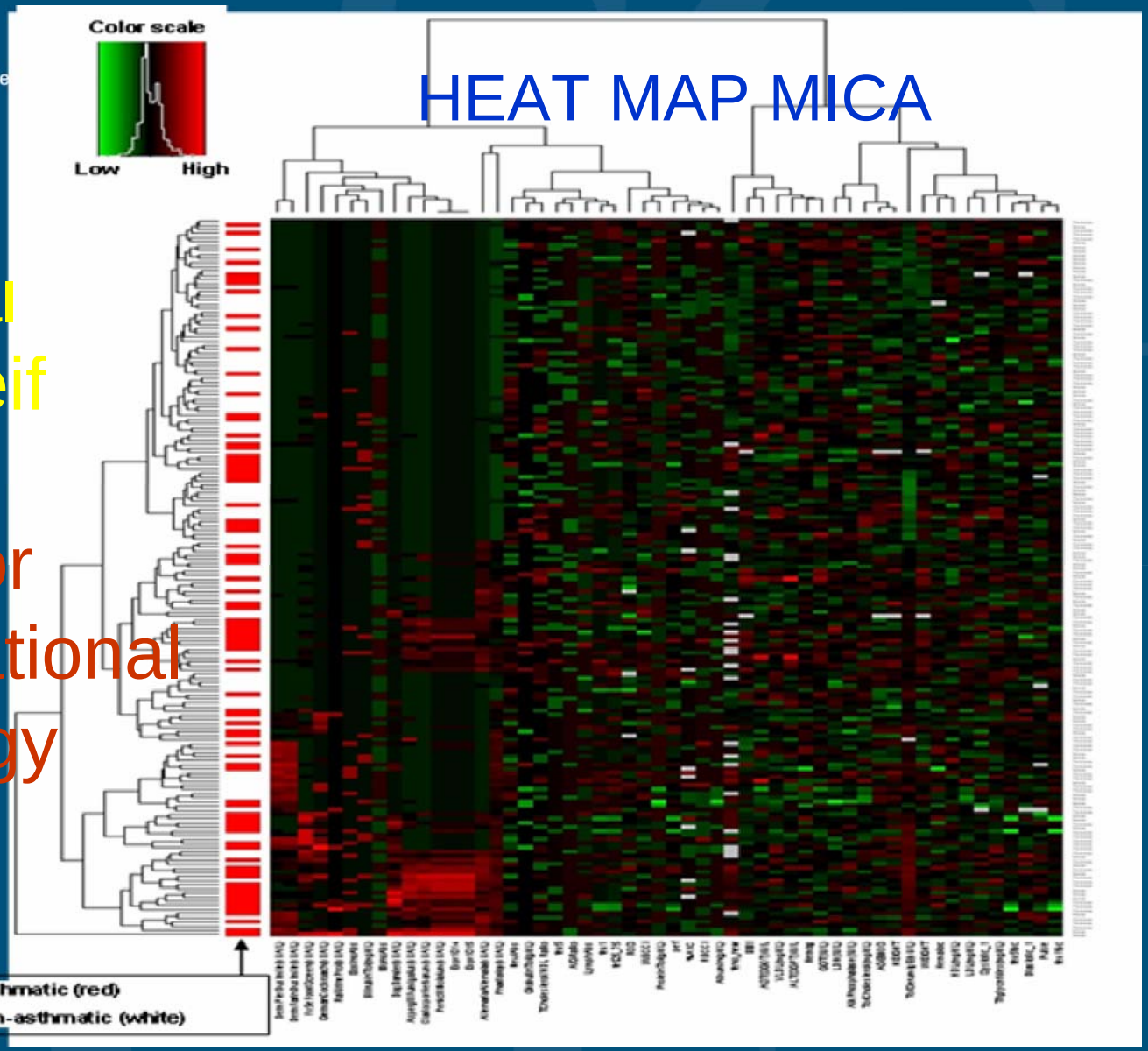
NASAL EPITHELIAL CELLS



Jesus R. Guajardo, MD, MHPE,[a] Kathleen W. Schleifer, PhD,[b] Michael O. Daines, MD,[a] Richard M. Ruddy, MD,[c] Bruce J. Aronow, PhD,[d] Marsha Wills-Karp, PhD,[b] and Gurjit K. Khurana Hershey, MD, PhD[a] *Cincinnati, Ohio*

EPA
United States
Environmental Prote
Agency

Elaine Hubal
David Reif
National
Center for
Computational
Toxicology



Subjects

Biomarkers Exposure/Clinical indicators

EPA United States Environmental Protection Agency

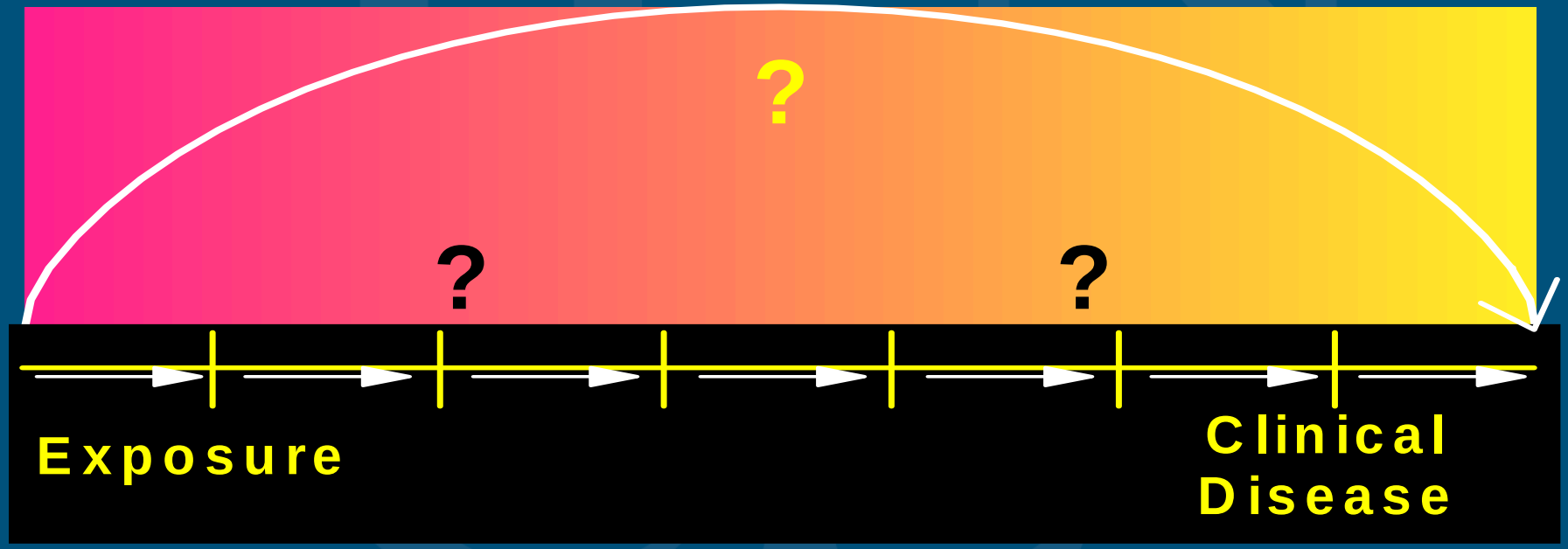
Biomarker Needs

- 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

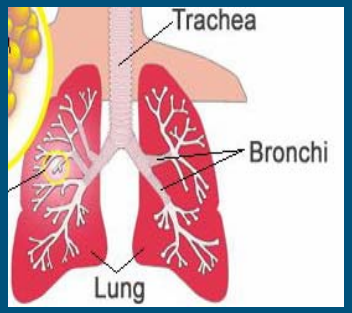
Summary

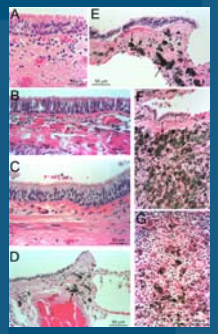
- High-data content technologies, elucidating the genetic and environmental basis for toxicity and disease



Integration of Diverse Set of exposure, effects and susceptibility

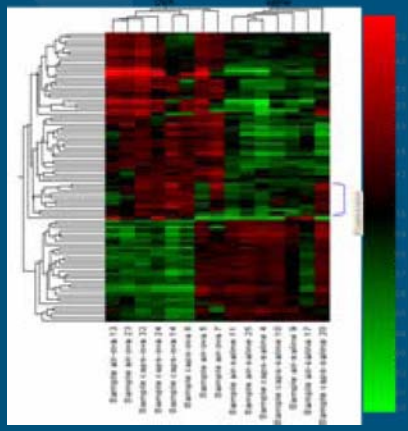
EPA United States Environmental Protection Agency





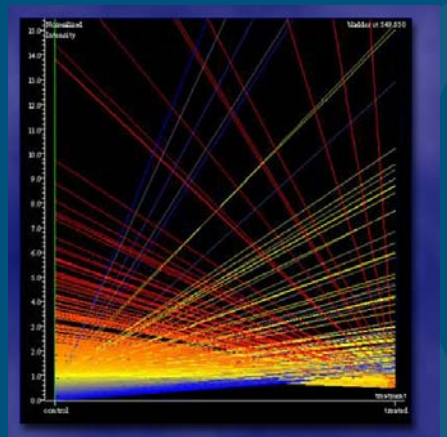
Gene expression arrays

bioinformatic



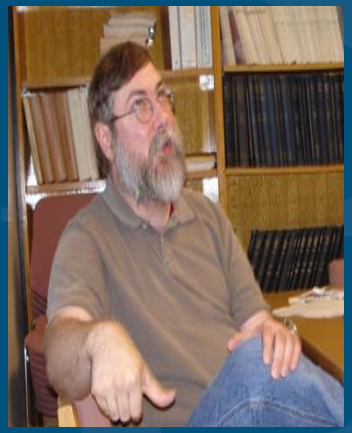
statistical analysis.

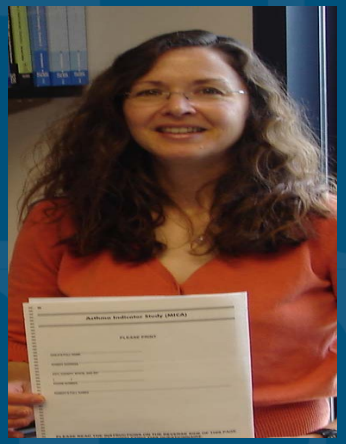
computational



genes, pathways, and networks

Acknowledgements





PHASE II MICA

National Health Exposure and Effects Laboratory

Stephen Edwards
Elaine Hubal
David Reif

National Center for Computational Toxicology

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Genomics core
Susan Hester
Chris Corton

NHEERL Office of the Director
Stephen Edwards

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David DeMarini

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George Bollweg
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