Interdisciplinary research on environmental health issues in the Superfund Basic Research Program at Berkeley

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Preview

- Superfund Basic Research Program short history
- Key findings from previous years
- Current areas of research
- Research translation
- Discussion: areas of collaboration?

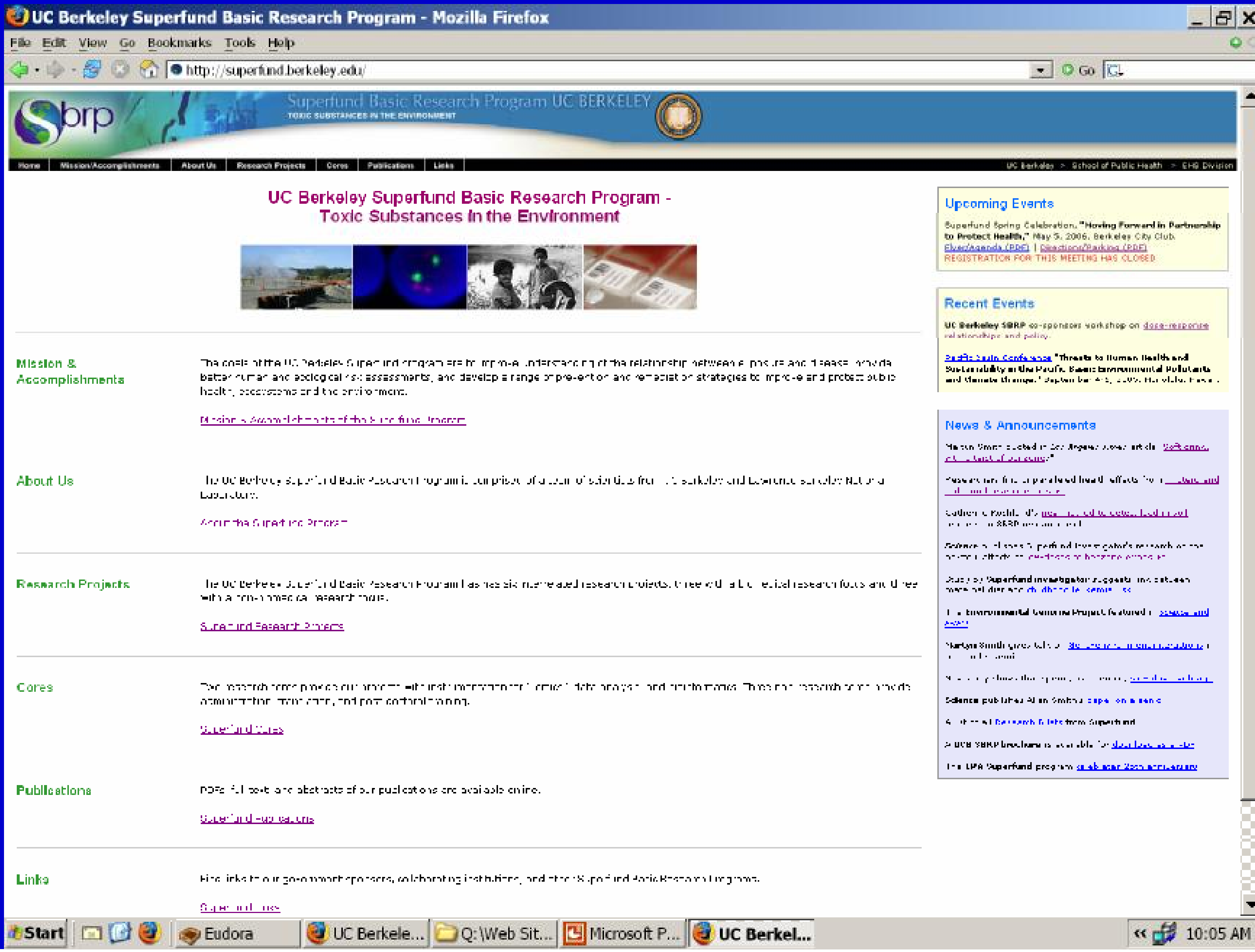
History of SBRP

- Run by National Institute of Environmental Health Sciences
- Began in 1987
- Multi-project grants
- 19 programs
  - including: Boston U, Brown, Columbia, Dartmouth, Duke, Harvard, Michigan State, Mount Sinai, NYU, Texas A&M, UC Davis, UCSD, UNC, UW, and others.

Key Accomplishments of the Berkeley Program

- Data on effects of low level exposures for risk assessments of arsenic and benzene
- First full-scale demonstration of steam injection for contaminant removal
- Demonstrated that most childhood leukemias begin before birth
- Successful use of stable isotopes to demonstrate the complete *in situ* biodegradation of chlorinated solvents by enhanced bioremediation
- Developed new method for measuring lead in soil

http://superfund.berkeley.edu



New Program

- Began May 2006
- Renewal process led to new areas of work and affiliation of new investigators
- First funding cycle to address research translation

Goals of the program

- enhance understanding of the relationship between exposure and disease;
- provide information to improve human and ecological risk assessments;
- develop a range of prevention and remediation strategies to improve and protect public health, ecosystems and the environment.

Theme: new technologies

- Nanotechnology and use of "omics" methods
- better detect Superfund chemicals in the environment;
- evaluate their effects on human health, especially the health of susceptible populations such as children;
- remediate their presence;
- reduce their toxicity.

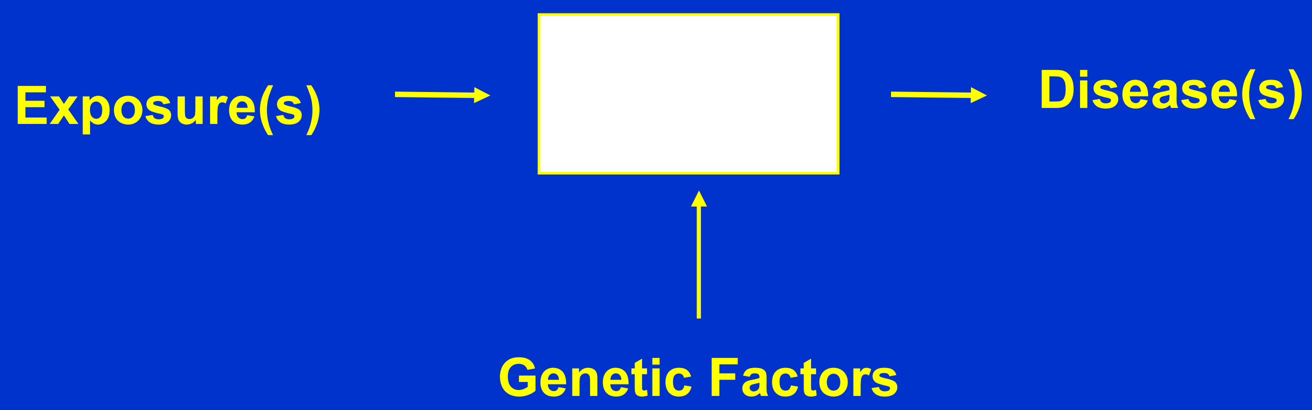
Project 1

Use new methods to develop biomarkers of chemical exposure and risk to understand causes of leukemia in children.

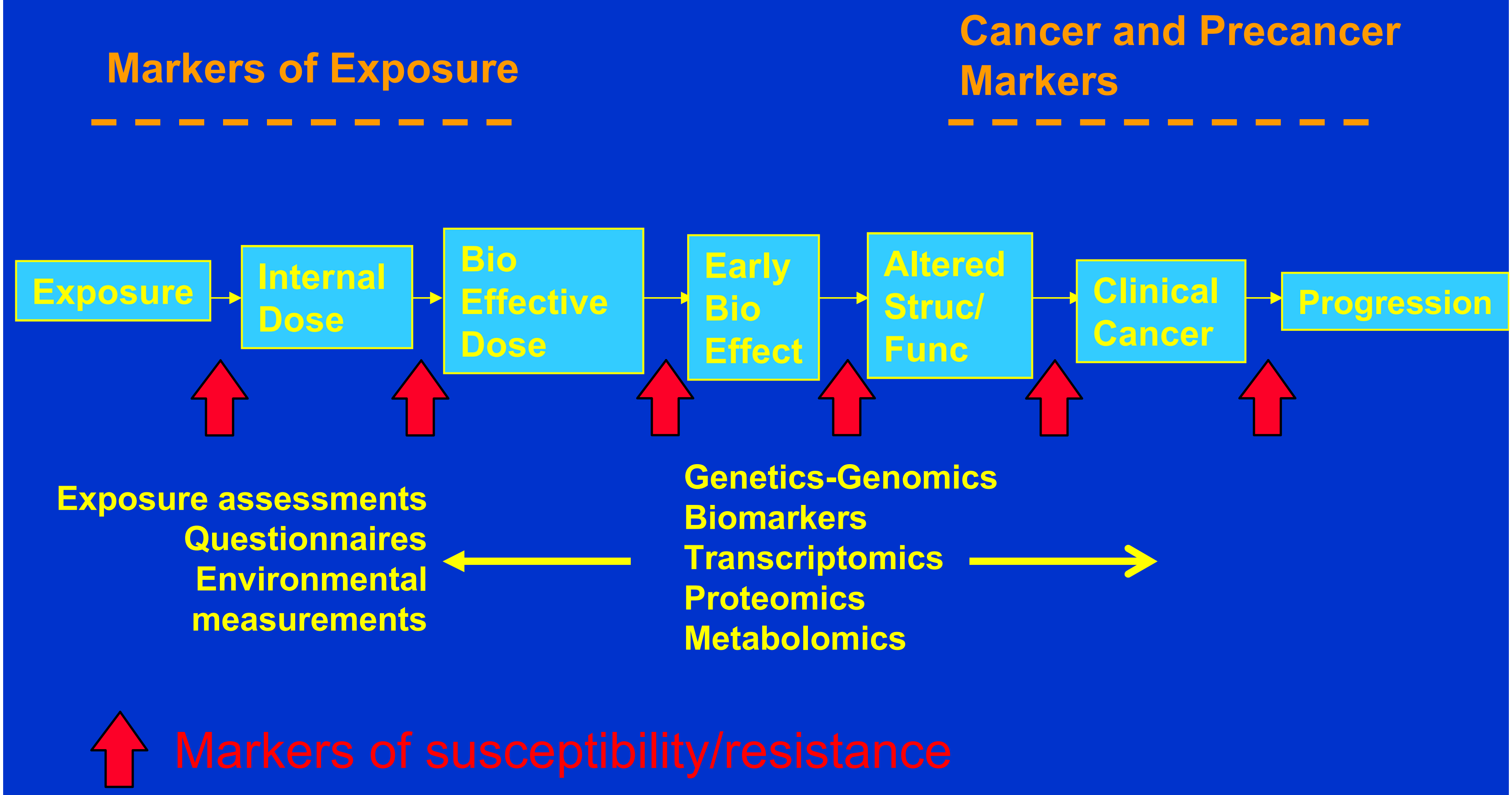
Leaders: Martyn Smith and Patricia Buffler

Molecular Epidemiology

Approach to incorporate molecular, cellular, and other biological measurements into epidemiologic research: an approach to expand the traditional black box.

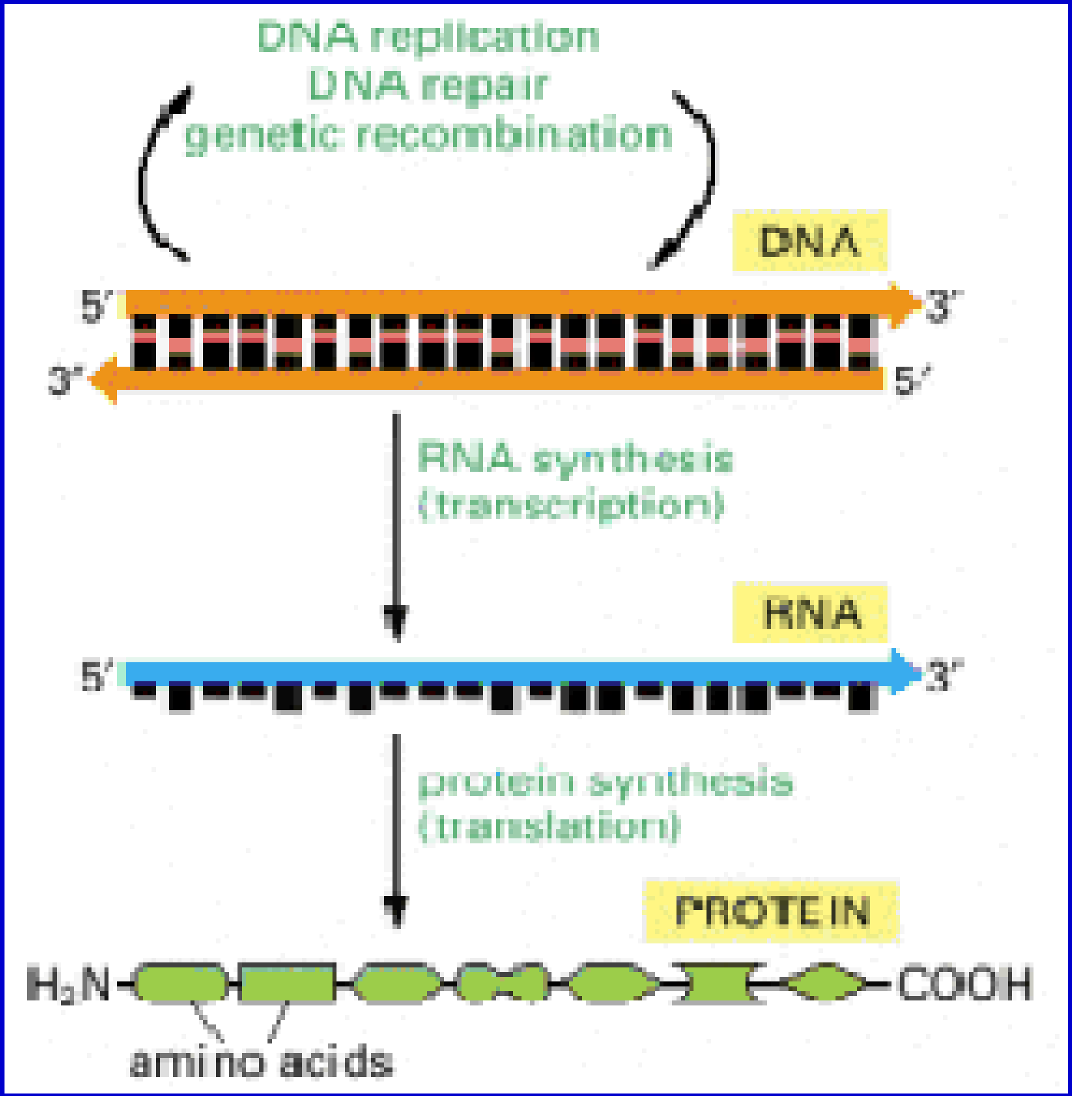


Molecular Epidemiology



After:Molecular Epidemiology, Schulte & Perera

Example of proteomics: Proteins are the functional units of an organism



Molecular Biology of the Cell 2002 Alberts *et al.*

The Northern California Childhood Leukemia Study (NCCLS)

- Population-based case-control study
- Started in 1995 – Enrollment to 2009
- Network of 9 pediatric oncology centers
- Inclusion of Hispanic population (47%)
- Multi-disciplinary team

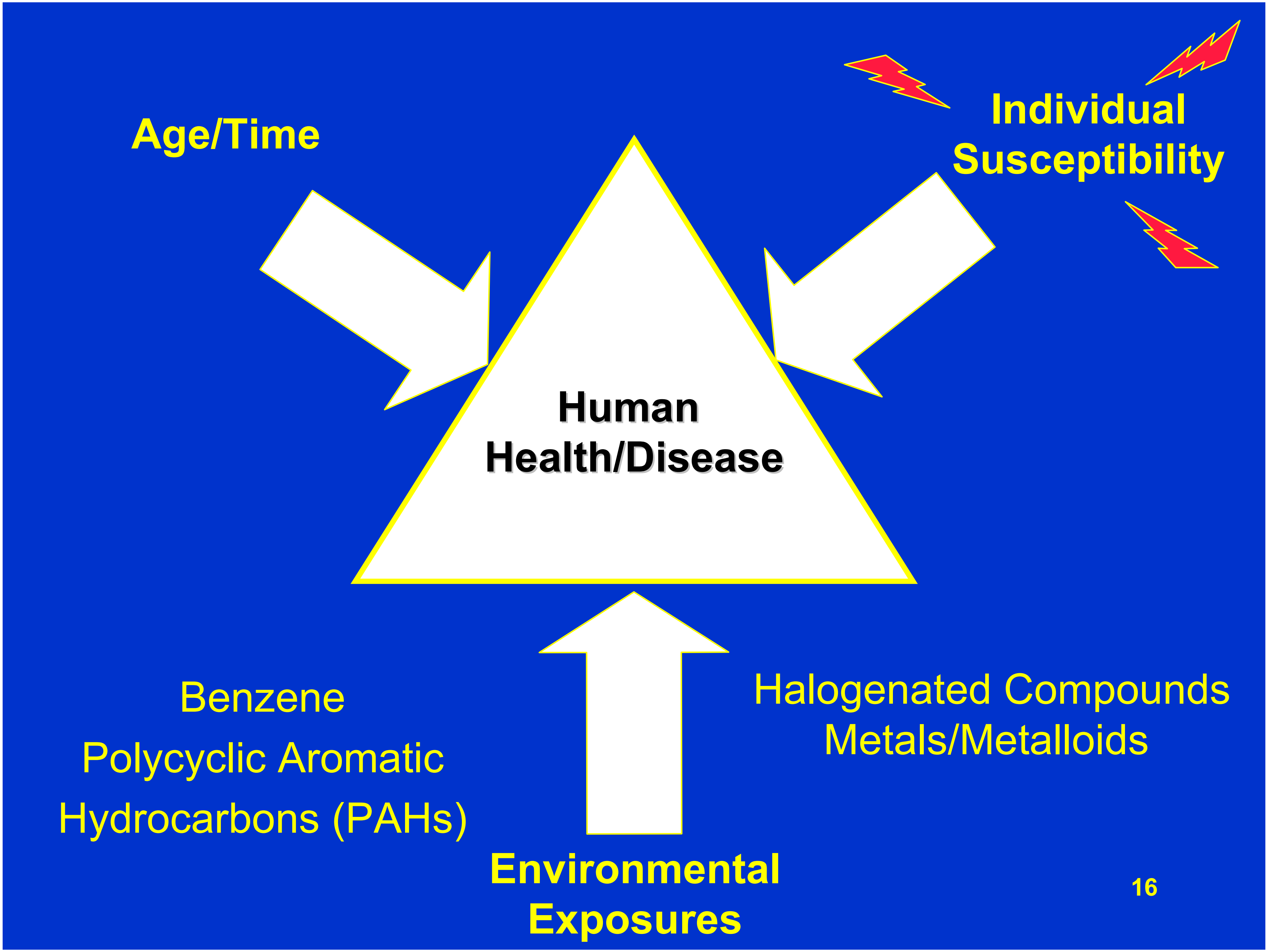
Project 1 Objectives

- **Characterize childhood leukemia subtypes by proteomics and gene expression profiling**
- **Measure blood protein adducts of benzene and naphthalene (a representative PAH) in serum from mothers of cases and controls.**
- **Measure blood protein adducts of benzene and naphthalene in the plasma of children with different forms of leukemia.**

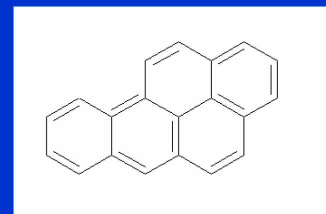
Project 2

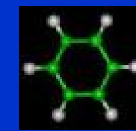
Use yeast and RNAi to identify targets of toxic chemicals and genes that contribute to susceptibility.

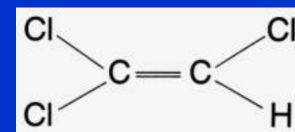
Leaders: Chris Vulpe and Luoping Zhang


Age/Time
Individual Susceptibility
Human Health/Disease
Benzene
Polycyclic Aromatic Hydrocarbons (PAHs)
Halogenated Compounds
Metals/Metalloids
Environmental Exposures
16

We are all different

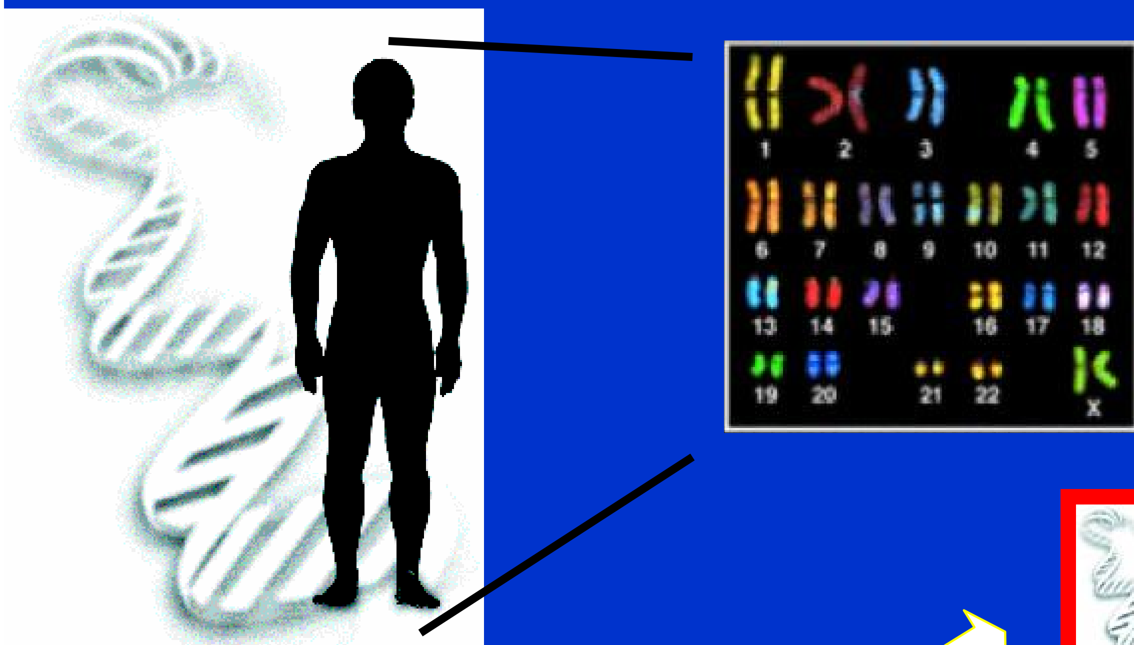






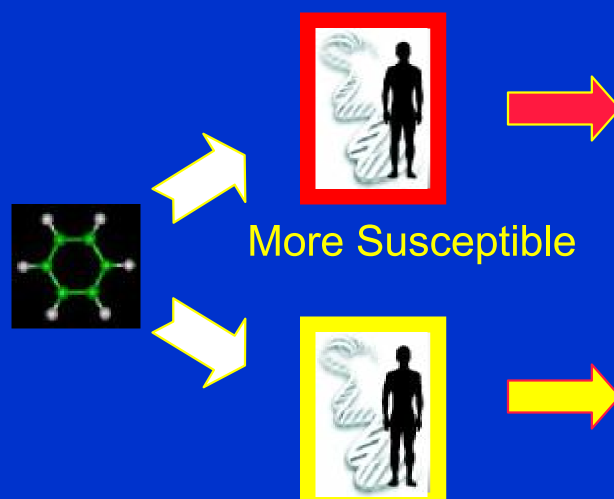
Human variability in susceptibility to environmental toxicants

Individual susceptibility can be modified by genetic variation



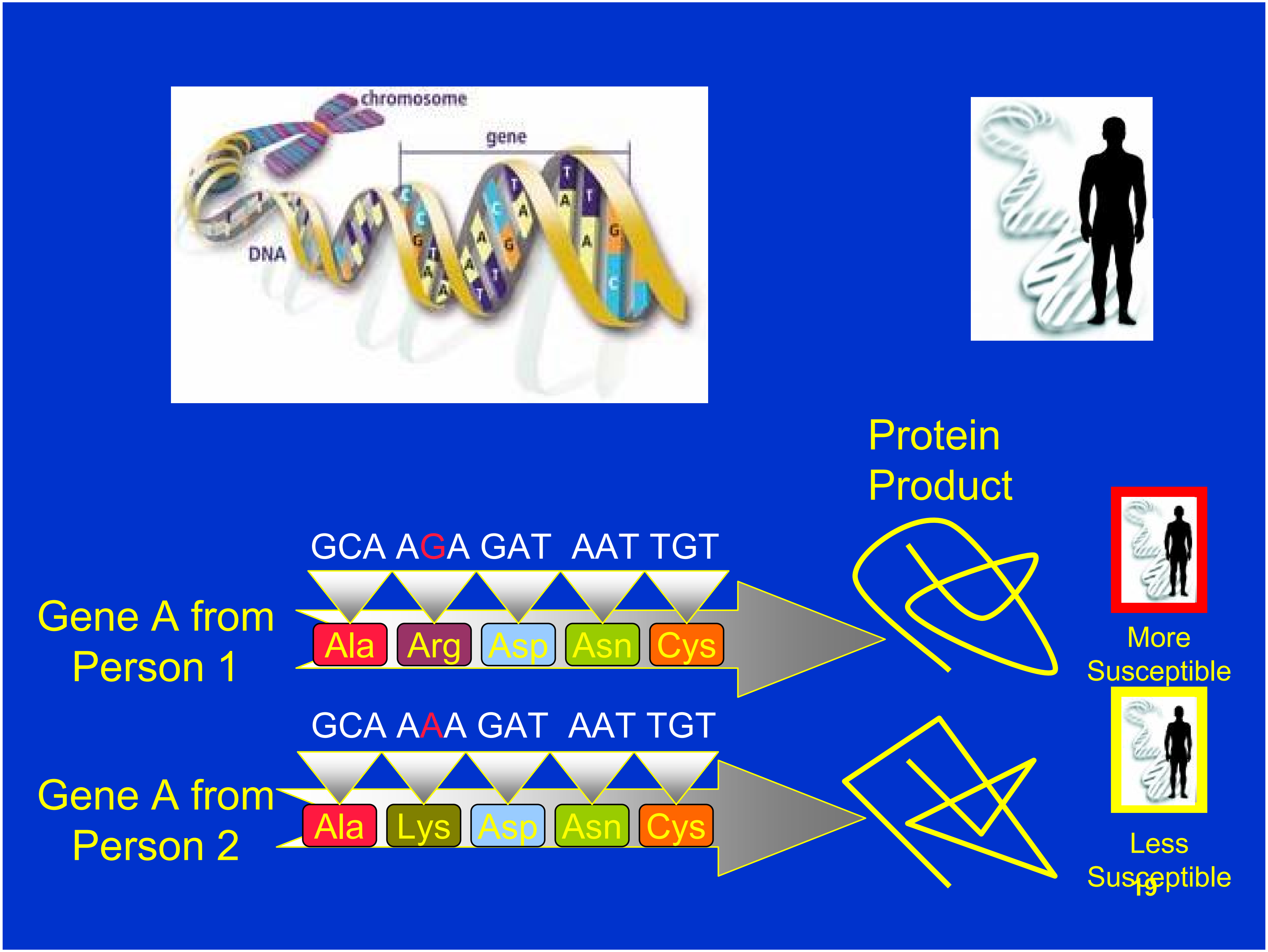
Variations contained in genes could make some people more susceptible than others

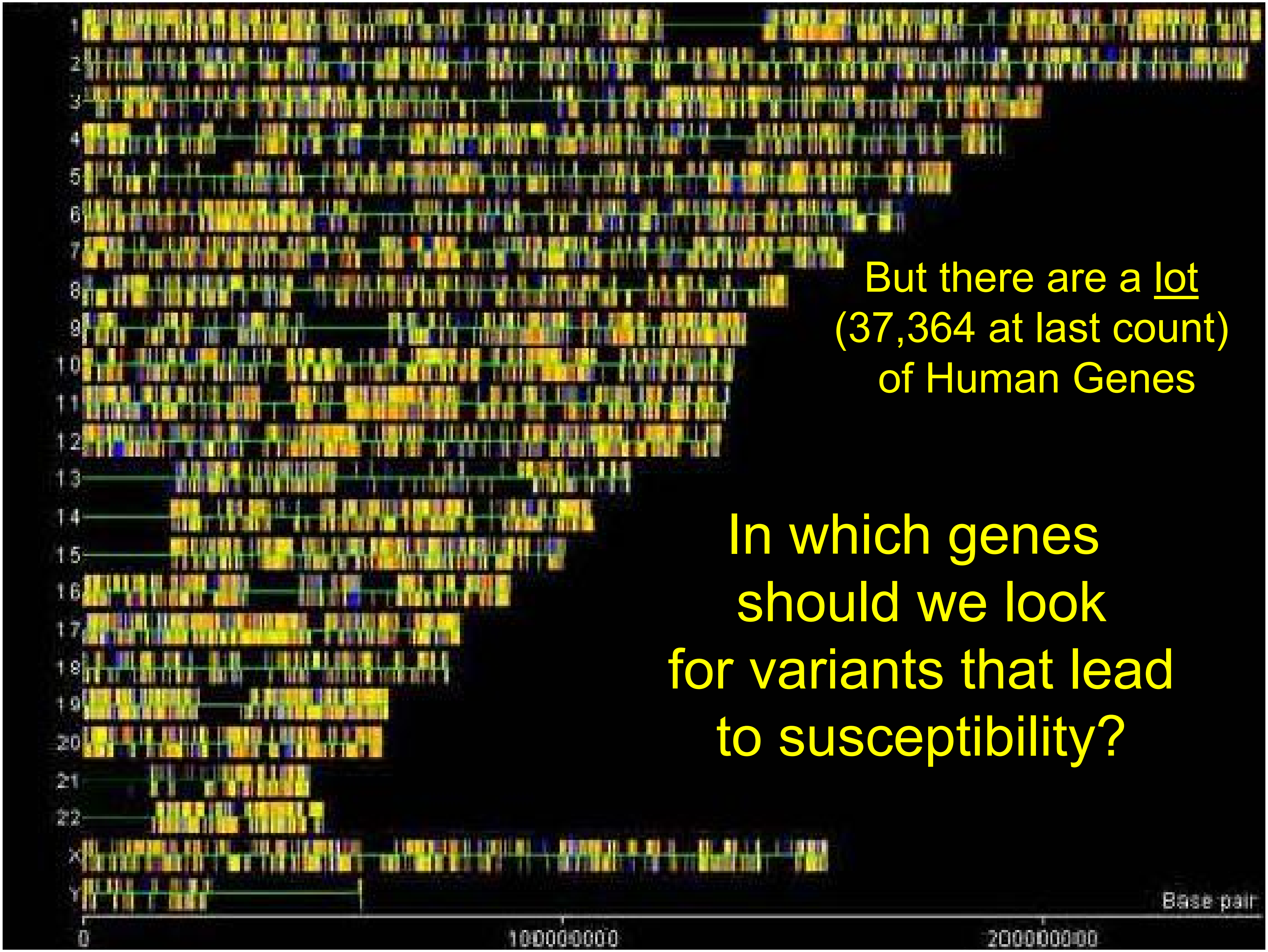
Toxicant exposure



More Susceptible → Disease

Less Susceptible → No Disease


chromosome
gene
DNA
Protein
Product
GCA AGA GAT AAT TGT
Gene A from
Person 1
Ala
Arg
Asp
Asn
Cys
More
Susceptible
GCA AAA GAT AAT TGT
Gene A from
Person 2
Ala
Lys
Asp
Asn
Cys
Less
Susceptible



But there are a lot
(37,364 at last count)
of Human Genes

In which genes should we look for variants that lead to susceptibility?

Which genes are important for susceptibility?

Use what we know of metabolism

BUT

We don't know much of mechanisms of toxicity

Toxicant

Absorption

Phase I (e.g. CYPs)

Phase II (e.g. GSTs)

Excretion

Toxicant

? ? ?

Toxicity

We (desperately) need new approaches to identify genes important for susceptibility to toxicants

Our approach: Use yeast to guide our choice of candidate genes

Why yeast?

<u>Current Uses</u>

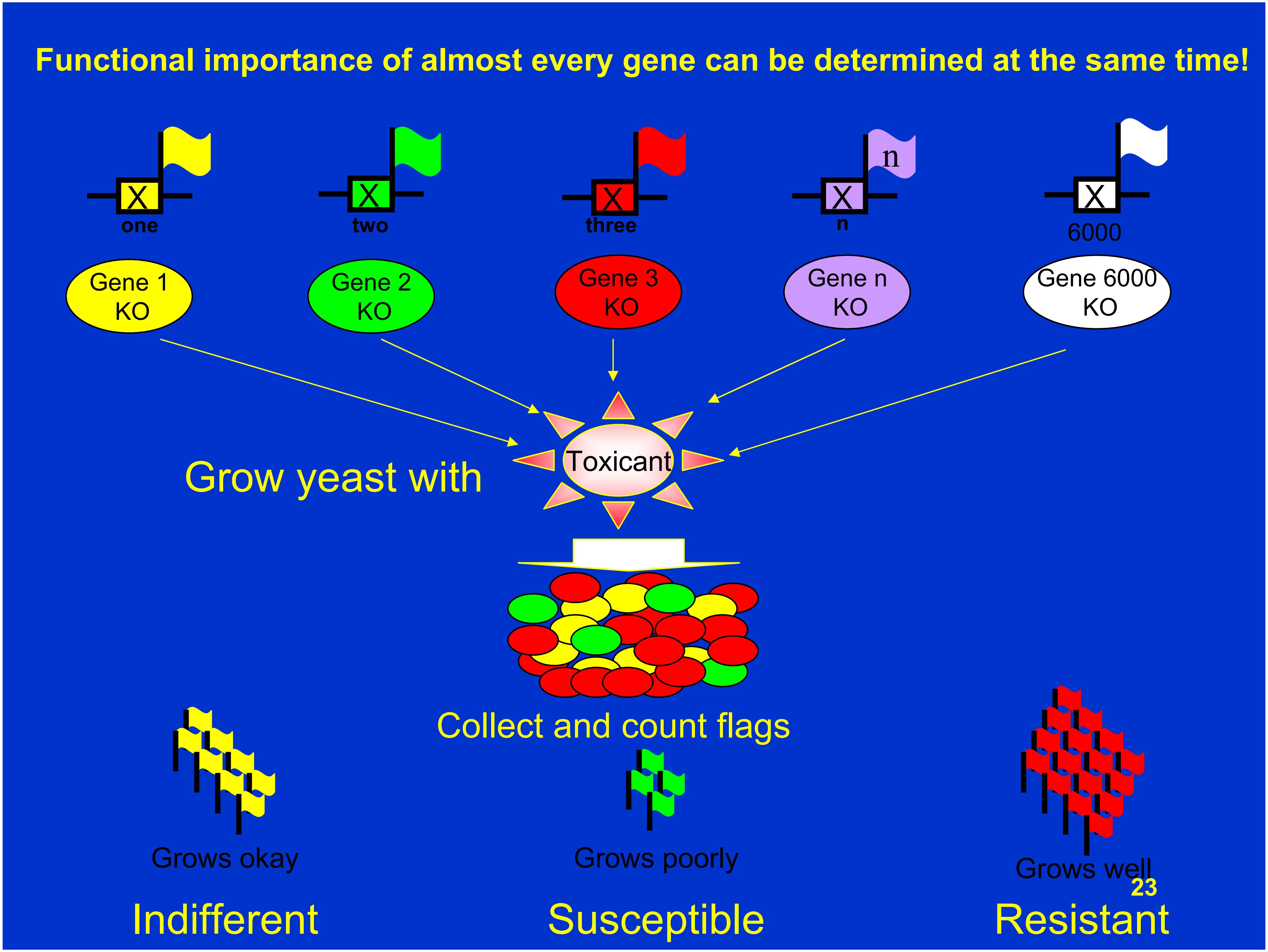
Cell biology
Cancer
Signal transduction

- **Conservation between human and yeast of fundamental genes and cellular pathways**

(~1/3 of yeast's ~6000 genes)

- **Hundreds of human disease genes also exist in yeast**
- **Yeast susceptible to toxicants**
- **Easy to use and abuse**

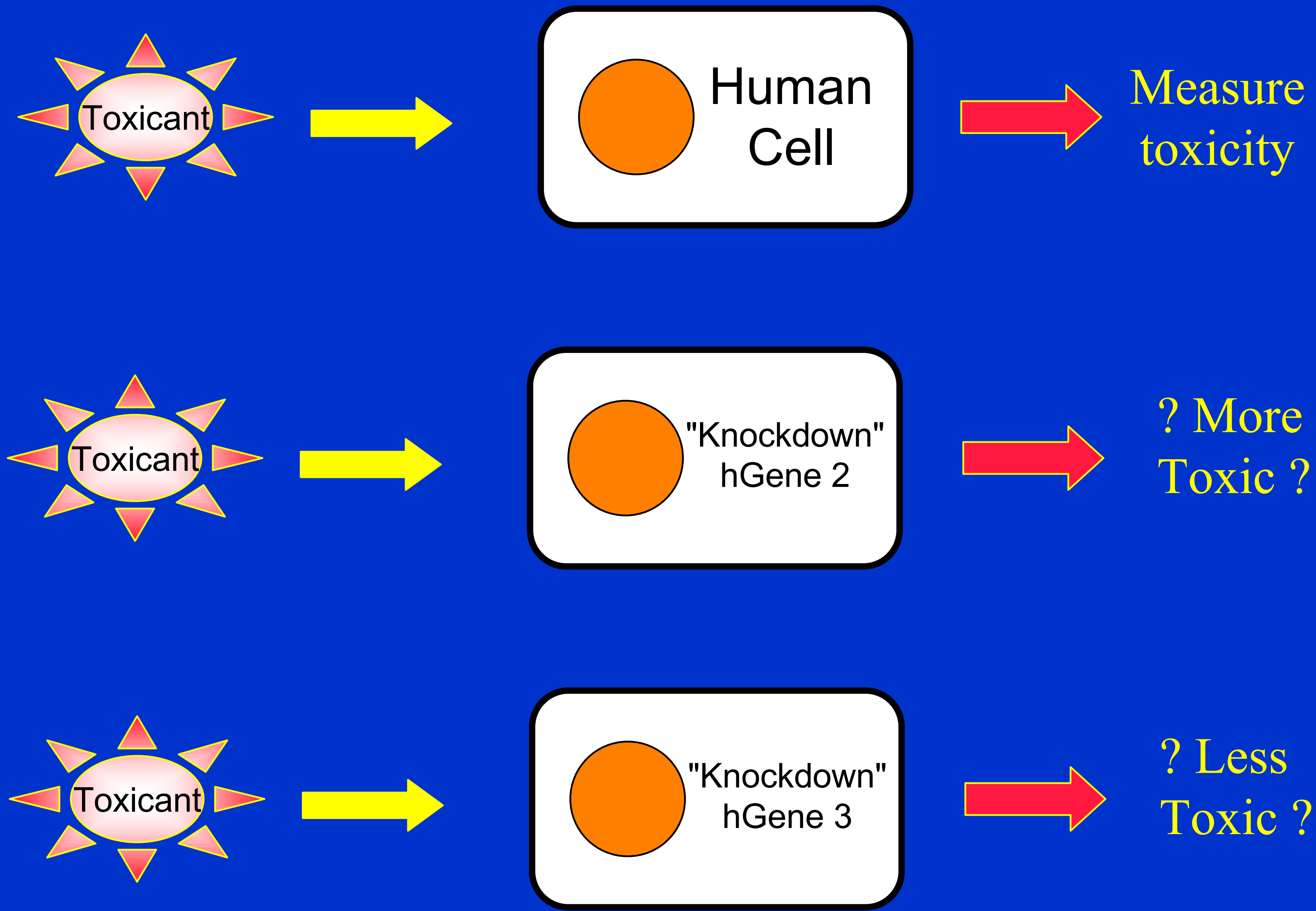
It's time
for
Toxicology!


Functional importance of almost every gene can be determined at the same time!
X
one
X
two
X
three
n
X
n
X
6000
Gene 1 KO
Gene 2 KO
Gene 3 KO
Gene n KO
Gene 6000 KO
Grow yeast with
Toxicant
Collect and count flags
Grows okay
Grows poorly
Grows well
Indifferent
Susceptible
Resistant

Prioritized list of susceptibility genes in yeast to identify human candidate susceptibility genes

Susceptible		Find human equivalents of yeast gene (if there is one)
yGene 2	→	hGene2
yGene n		
yGene n	→	hGene n
Resistant		
yGene 3	→	hGene 3
yGene n		

Test prioritized human susceptibility genes in human cells



Test validated human candidates in epidemiology/association studies

Project 3

Understanding pulmonary disease, mechanisms of toxicity and susceptibility to early life exposures to arsenic.

Leaders: Allan Smith and Martyn Smith

Key findings regarding common mechanisms for cancer and non-cancer effects and significance of early life exposures

The estimated cancer risk at the drinking water standard of 50 µg/L for arsenic is more than 100 times greater than that for any other drinking water contaminant

Smith AH, Lopipero PA, Bates MN, Steinmaus CM.
Arsenic epidemiology and drinking water standards.
Science 296: 2145-6, 2002

The lost and forgotten arsenic-exposed population

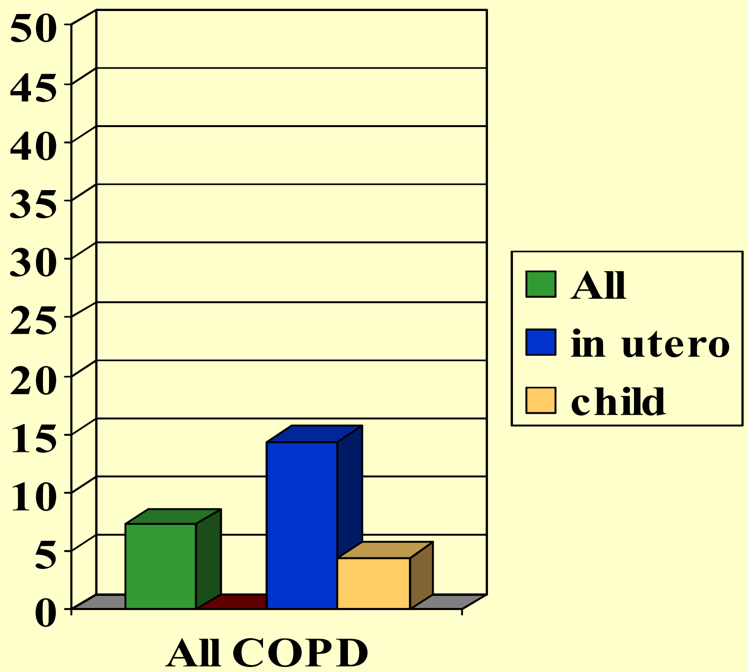
"the number of people consuming water from private wells with arsenic concentrations above 10 μg/L **could be over 2 million people**"

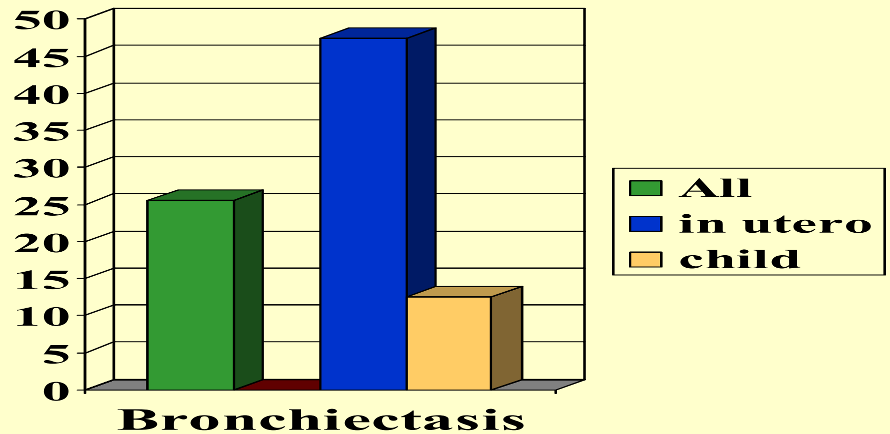
Where is this population?

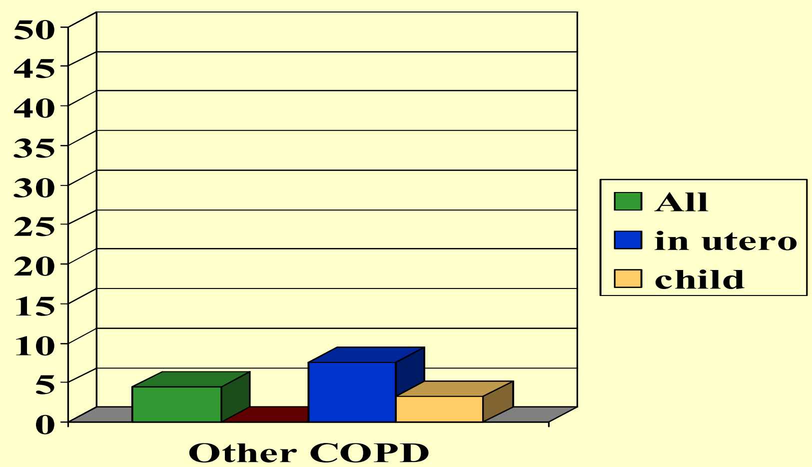
Right here in the USA

Steinmaus et al. In Press.

Mortality (SMRs) from Chronic Obstructive Pulmonary Disease, age 30-49, for those born in the very high exposure period (in utero exposure) or just before (child)



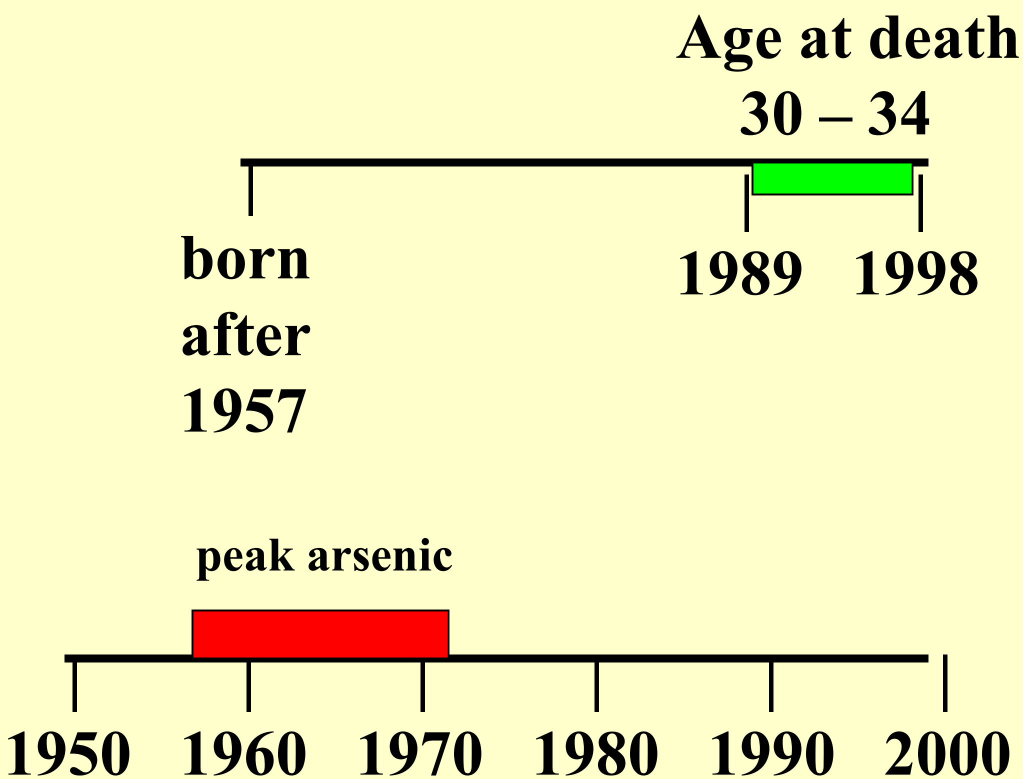


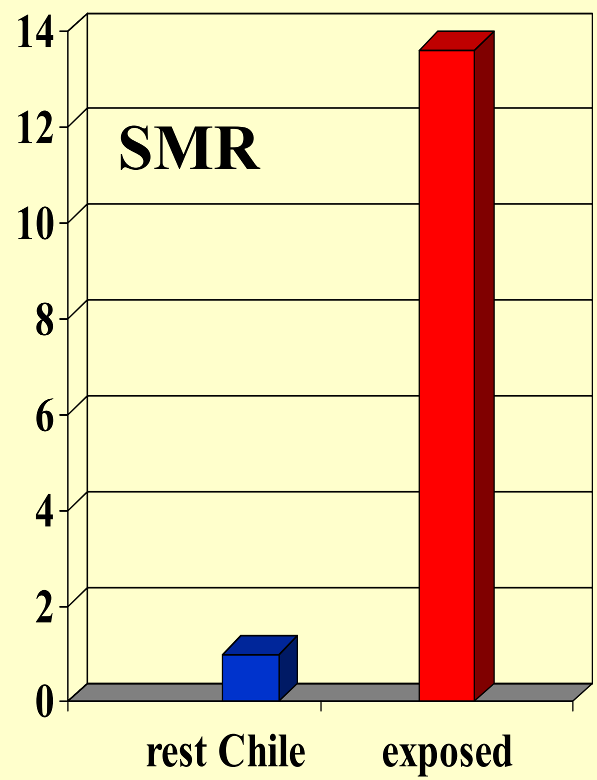


p<0.001 except other COPD p=0.004

Lung cancer mortality in men according to exposure in childhood

(SMR = standardized mortality ratio = observed/expected deaths)





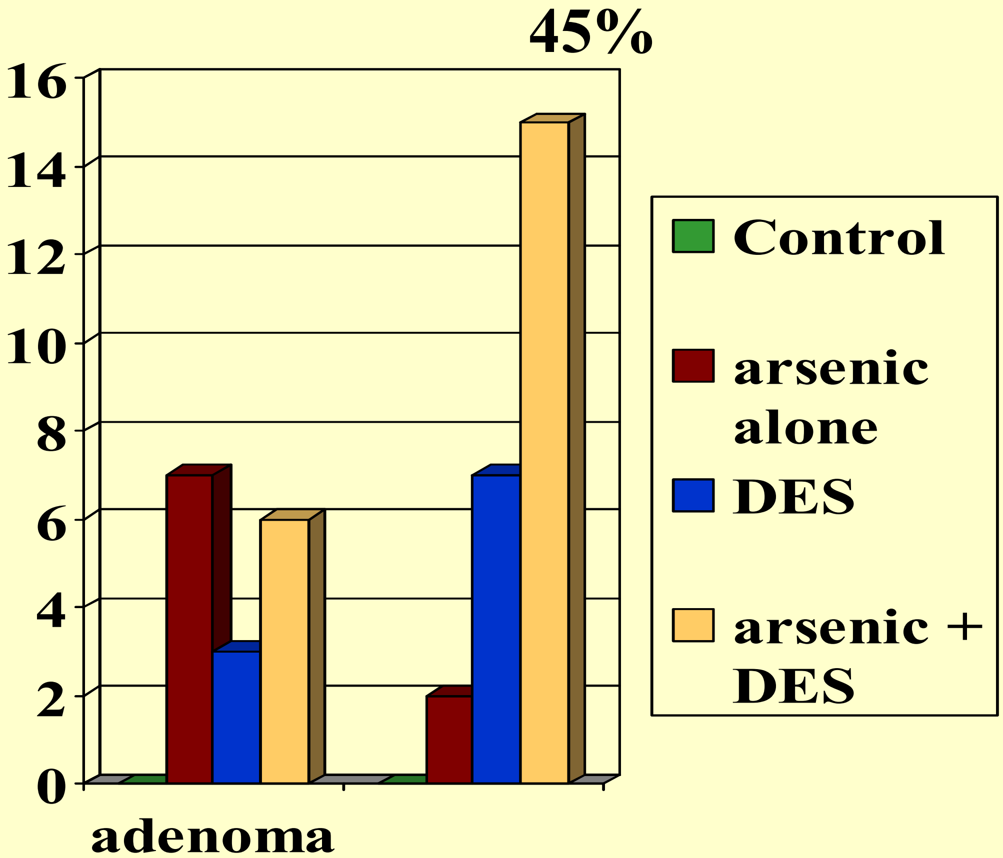
$p < 0.001$

The magnitude of the effects found on lung cancer and bronchiectasis mortality has no parallel with effects of other environmental exposures occurring *in utero* and/or in early childhood.

- Children with the highest gamma radiation exposure in Hiroshima and Nagasaki under age 10 did **not** experience increased lung cancer risks as adults.
- Those exposed in the age range of 10-19 years of age had lung cancer relative risk estimate of about **2.5** as young adults aged 30-39

In Press. Environmental Health Perspectives

Malignant Urogenital tumors from transplacental arsenic exposure plus postnatal DES



- Study involved CD1 mice
- "The present results clearly show that maternal exposure to inorganic arsenic is a complete transplacental carcinogen in the female offspring"

Waalkes MP et al. Cancer Research 66: 1337-45, 2006

Project 4

Application of 'omics' methods to optimize bioremediation by microbial reductive dehalogenation

Leaders: Lisa Alvarez-Cohen and Gary Andersen

Use "omics" methods to better target useful microbes for the remediation

Project 5

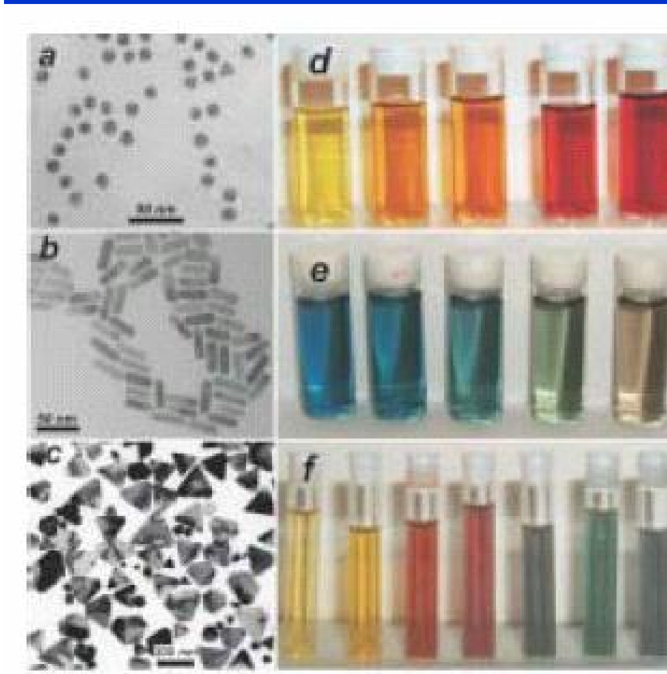
Nanotechnology-based environmental sensing

Leaders: Catherine Koshland and Donald Lucas

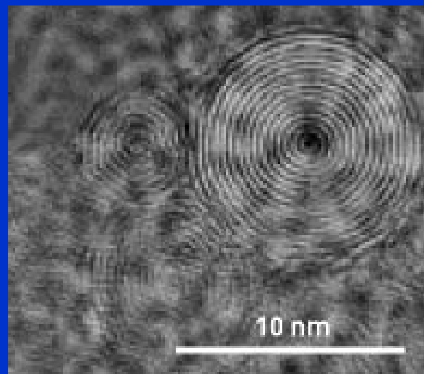
Why Nanotechnology?

- Nanomaterials exhibit different and sometimes unique properties when compared to gas phase or bulk materials
- Can we exploit these properties to detect and quantify species such as heavy metals and biomolecules used in remediation?

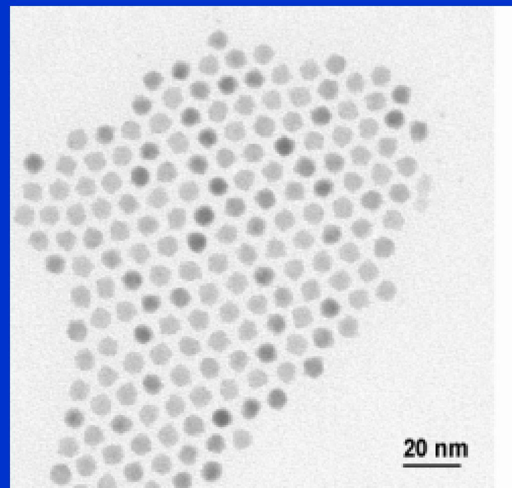
Nanoparticles are Everywhere!



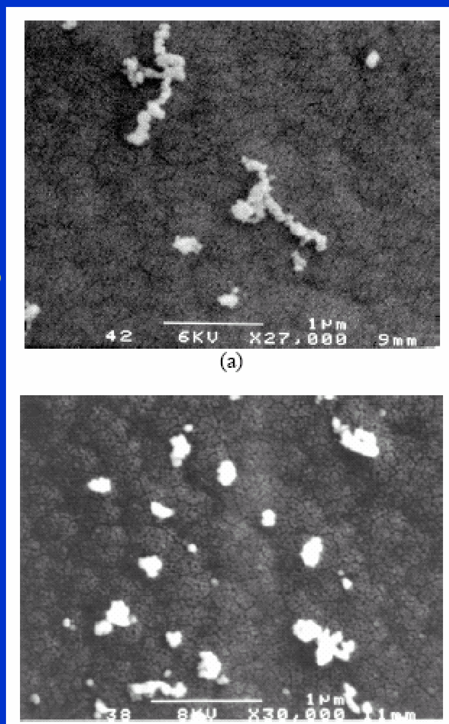
Au and Ag nanoparticles and nanorods



Nano-onions



PbSe

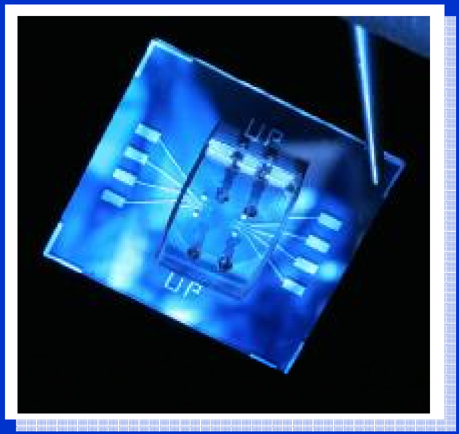


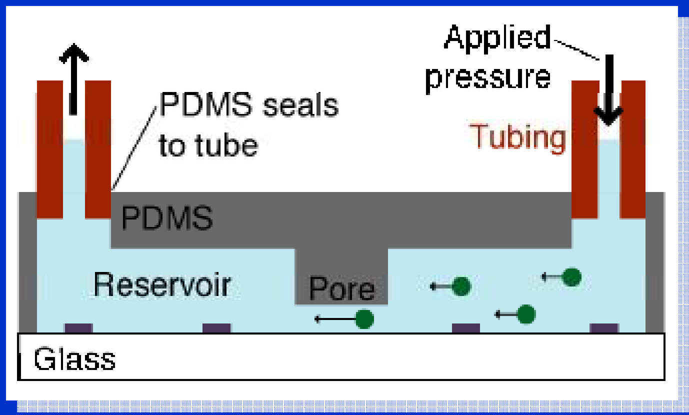
NaCl before and after laser irradiation

Cover Photo: C&E News May 1, 2006

On-Chip Artificial Pore

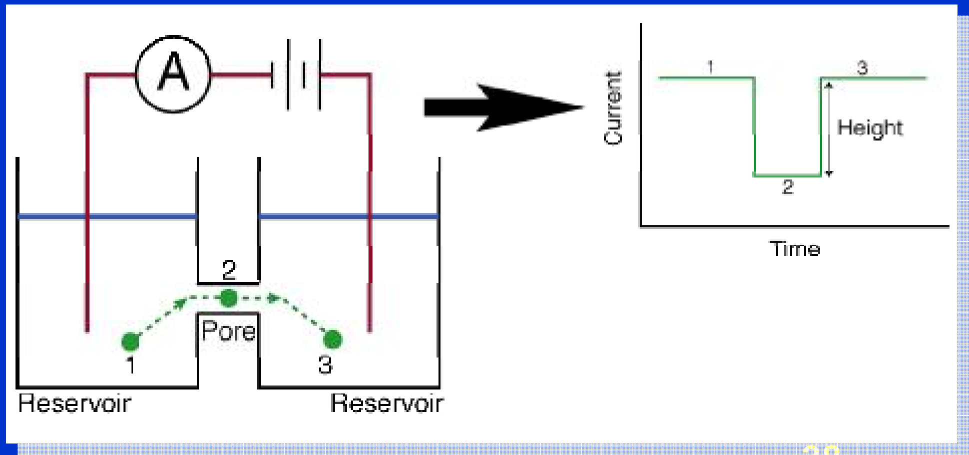
Saleh & Sohn, *Rev. Sci. Inst.* ( ) & *PNAS* ( )





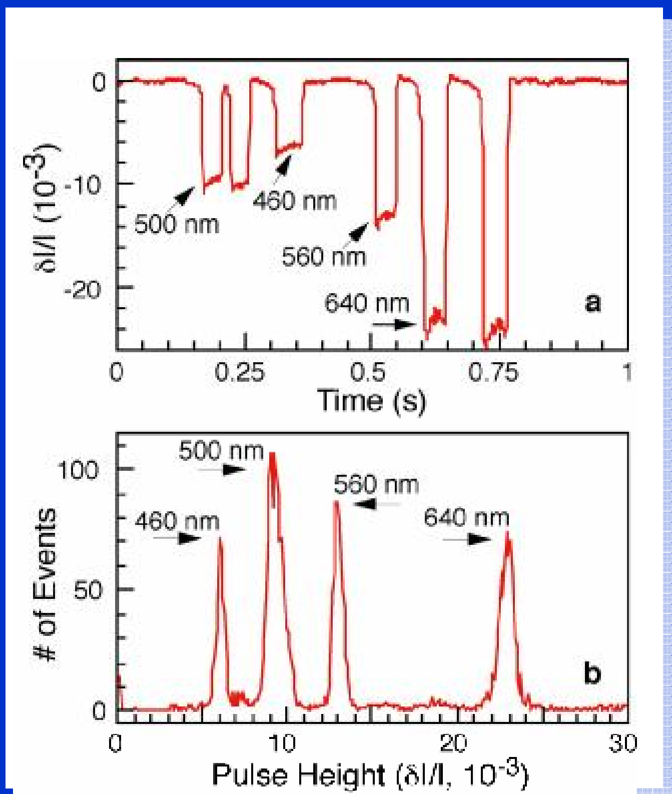
Uses resistive pulse sensing to detect:

1. nm-sized colloids
2. single cells
3. single molecules

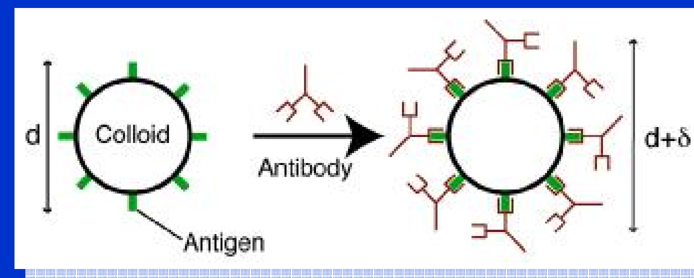


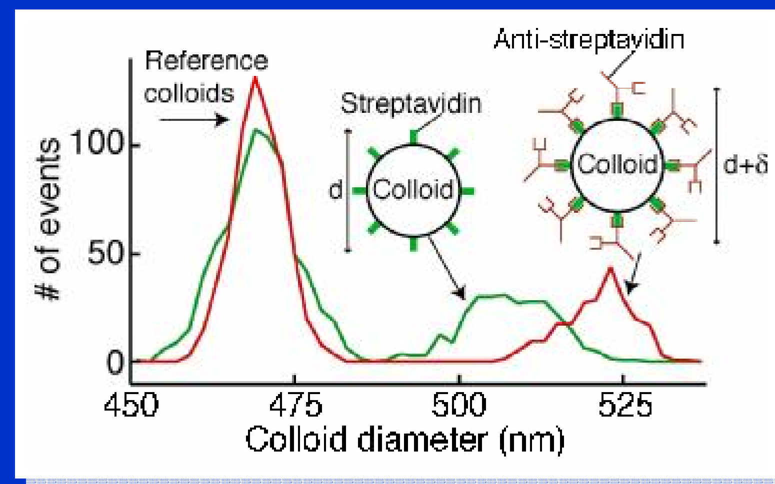
Applications

Particle Sizing



A Novel Immunoassay





- Pore length = 1um diam x 10 um long
- Device resolution corresponds to 2-4% variation of colloids

- Detects size change
- No labeling involved

Project 6

Site remediation by contaminant oxidation using nanoparticulate and granular zero-valent iron

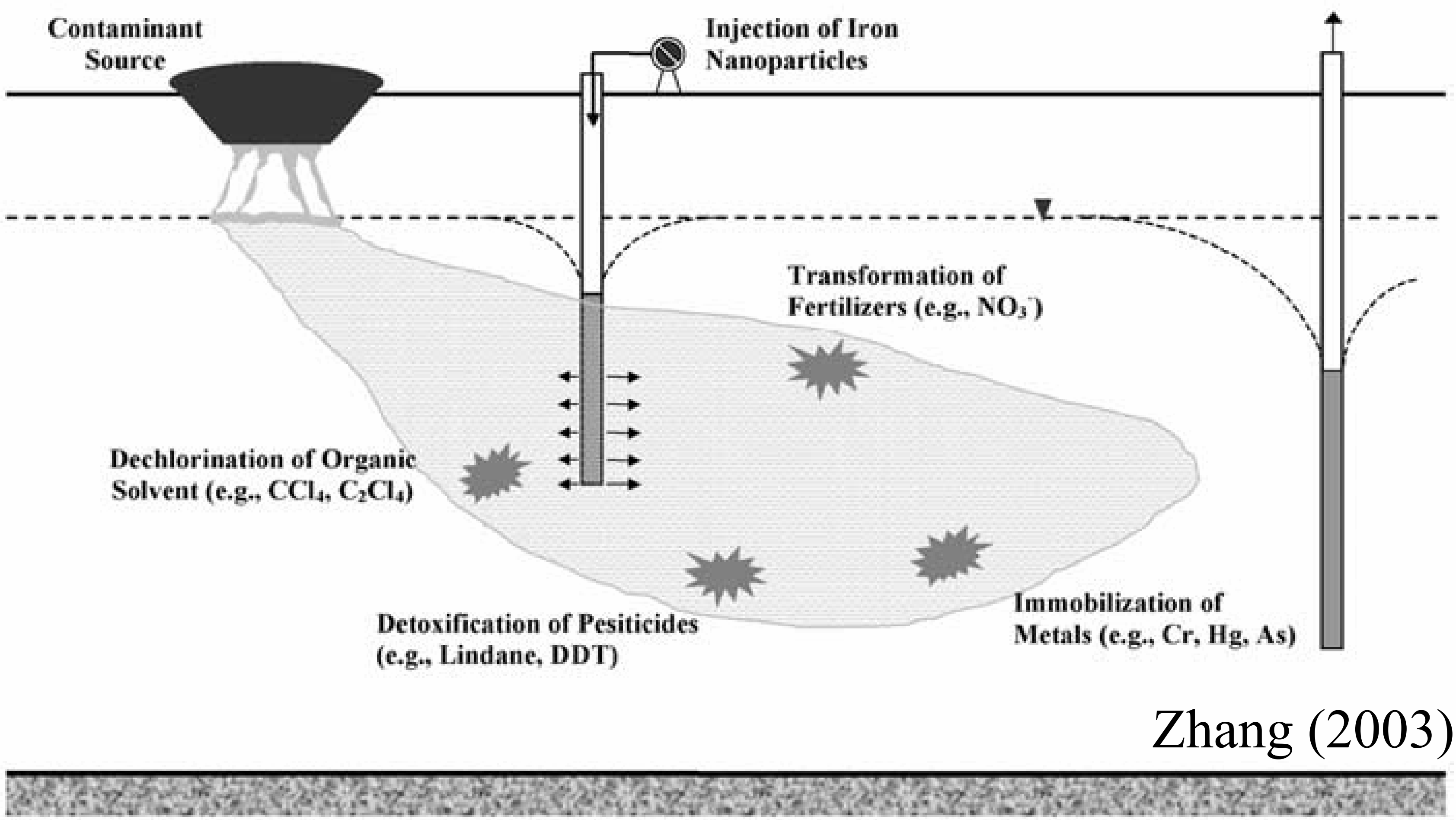
Leaders: David Sedlak and Fiona Doyle

Potential to use this technique for intractable cleanup problems

Oxidative Treatment Technologies

- Motivation
  - Recalcitrant polar contaminants (e.g., NDMA)
  - Hydrophobic contaminants (e.g., PCBs)
  - Passive treatment (e.g., As in groundwater)
- Limitations
  - Requires unstable reagents (e.g., H O)
  - Hydroxyl radical is unselective

Fe Nanoparticles as Reductants



Zhang (2003)

Oxidative Remediation with Iron

- Fe can convert O into a powerful oxidant
- Potential for selective oxidation on surface
- Potential applications
  - Passive treatment barriers
  - Soil and groundwater treatment
  - Drinking water treatment

Cores

A. Administration
   Leaders: Martyn Smith and Catherine Koshland

B. Research Translation
   Leaders: Amy Kyle and James Hunt

C. Toxicogenomics Laboratory
   Leaders: Christine Skibola and Chris Vulpe

D. Computational Biology
   Leaders: Mark van der Laan and Alan Hubbard

E. Training
   Leaders: Catherine Koshland and James Hunt

New directions at NIEHS

The new strategy emphasizes research focused on complex human disease, and calls for inter-disciplinary teams of scientists to investigate a broad spectrum of disease factors, including environmental agents, genetics, age, diet, and activity levels. Recent advances in technology make this emphasis on human health and new integrative approach possible."

Research translation in EH

- Research translation is part of some public health disciplines but not environmental health
  - Typically stops at generating the science
- Translation to date:
  - mostly about writing up results from specific studies in plain language that can be understood
  - Not synthesizing research results
  - Exceptions: clean air standards – done by agency
  - Some community based participatory research

Four approaches

1. Direct translation of immediate research findings
2. Communication between experts in technical disciplines and policy/stakeholder audiences on interpretation of science in policy contexts
3. Analyses of implications of key lines of research
4. Assess gaps between scientific knowledge and practice

Interpretation of results for policy

- Many issues involved in interpretation of results for policy
  - Constraints on agency analyses and actions
  - Factors considered relevant
- Limited understanding on both sides
  - Policy makers: understanding of research
  - Researchers: understanding policy context and why questions have to be answered
- Fruitful to engage both in joint discussion
  - What is relevant, how can it best be presented?
  - Information needed but not available

Analyses of lines of research

- Key lines of research for which we have competence
  - Not individual studies
- Practice and policy based on the body of literature and target audiences don't have time to do the synthesis
- Method are iterative involving consultation
  - "walkabout" to identify issues, elements of interest, and types of knowledge that are relevant
- Look from the policy side and then identify what knowledge is relevant

Gaps - research and practice

- Most complex
- Does practice reflect current knowledge?
  - Important because we think not
- Environmental health hasn't changed much in 20 years but knowledge has
- Methods need to be developed
- Need to apply scientific knowledge in "common sense" ways

Role of biomonitoring

- Biomonitoring data beginning to be more widely collected
  - NHANES by CDC
  - states, state consortia
  - Celebrity biomonitoring
  - Community biomonitoring
  - Other public interest or advocacy groups

What are we going to use it for?

- Justify legislation (PBDE ban in CA)
- Advocate for better controls (mercury)
- As part of environmental public health tracking
- Individual actions (stop eating fish)
- Promote consumer choices
- Nothing

Project

- Define the questions of interest
- Define the relevant knowledge base to answer them
  - Bring the expertise of our group and affiliates
  - Include knowledge in addition to academic researchers
- Develop analyses and case studies to apply knowledge to questions
- Two workshops for discussion and exploration

Discussion