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
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
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

Markers of Exposure

- Exposure
- Internal Dose
- Bio Effective Dose
- Early Bio Effect
- Altered Struc/Func
- Clinical Cancer
- Progression

Markers of susceptibility/resistance

Exposure assessments
Questionnaires
Environmental measurements

Genetics-Genomics
Biomarkers
Transcriptomics
Proteomics
Metabolomics

After: Molecular Epidemiology, Schulte & Perera
Example of proteomics: Proteins are the functional units of an organism
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
Human Health/Disease

Environmental Exposures

- Benzene
- Polycyclic Aromatic Hydrocarbons (PAHs)
- Halogenated Compounds
- Metals/Metalloids

Age/Time

Individual Susceptibility
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 leads to:
- More Susceptible
- Less Susceptible

Resulting in:
- Disease
- No Disease
Gene A from Person 1

GCA AGA GAT  AAT TGT
  Ala  Arg  Asp  Asn  Cys

Gene A from Person 2

GCA AAA GAT  AAT TGT
  Ala  Lys  Asp  Asn  Cys

Protein Product

More Susceptible

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

- Toxicant
- Absorption
- Phase I (e.g. CYPs)
- Phase II (e.g. GSTs)
- Excretion

BUT

We don't know much of mechanisms of toxicity

Toxicity

What genes are important for susceptibility?
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?

- 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

Current Uses
- Cell biology
- Cancer
- Signal transduction

It's time for Toxicology!
Functional importance of almost every gene can be determined at the same time!

Gene 1 KO
Gene 2 KO
Gene 3 KO
Gene n KO

Grow yeast with
Toxicant

Collect and count flags

Grows well
Grows poorly
Grows okay

Indifferent
Susceptible
Resistant
Prioritized list of susceptibility genes in yeast to identify human candidate susceptibility genes

Susceptible
yGene 2 → hGene2
yGene n → hGene n

Resistant
yGene 3 → hGene 3
yGene n

Find human equivalents of yeast gene (if there is one)
Test prioritized human susceptibility genes in human cells

Toxicant → Human Cell → Measure toxicity

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

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)
Lung cancer mortality in men according to exposure in childhood
(SMR = standardized mortality ratio = observed/expected deaths)

Age at death
30 – 34

born after 1957
1989 1998

peak arsenic


SMR

rest Chile exposed

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 \textit{in utero} and/or in early childhood.

- Children with the highest gamma radiation exposure in Hiroshima and Nagasaki under age 10 did \textbf{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”

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

NaCl before and after laser irradiation

Nano-onions

PbSe

Cover Photo: C&E News
May 1, 2006
On-Chip Artificial Pore


Uses resistive pulse sensing to detect:
1. nm-sized colloids
2. single cells
3. single molecules
Applications

Particle Sizing

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

A Novel Immunoassay

- 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., H₂O₂)
  - Hydroxyl radical is unselective
Fe Nanoparticles as Reductants

Currently used for contaminant reduction

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