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P42ES030990

MEMCARE (Metals and Metal Mixtures: Cognitive Aging, Remediation, and Exposure Sources)

To understand and mitigate the effects of exposure, particularly early life exposure, to metals and metal mixtures on late life cognitive health.

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Yale

McLean HOSPITAL

Harvard John A. Paulson School of Engineering and Applied Sciences

Arizona State University

Forsyth

DARTMOUTH

Boston Children's Hospital
Until every child is well

Center for Health, Work & Environment
colorado school of public health

Radiation and Public Health Project

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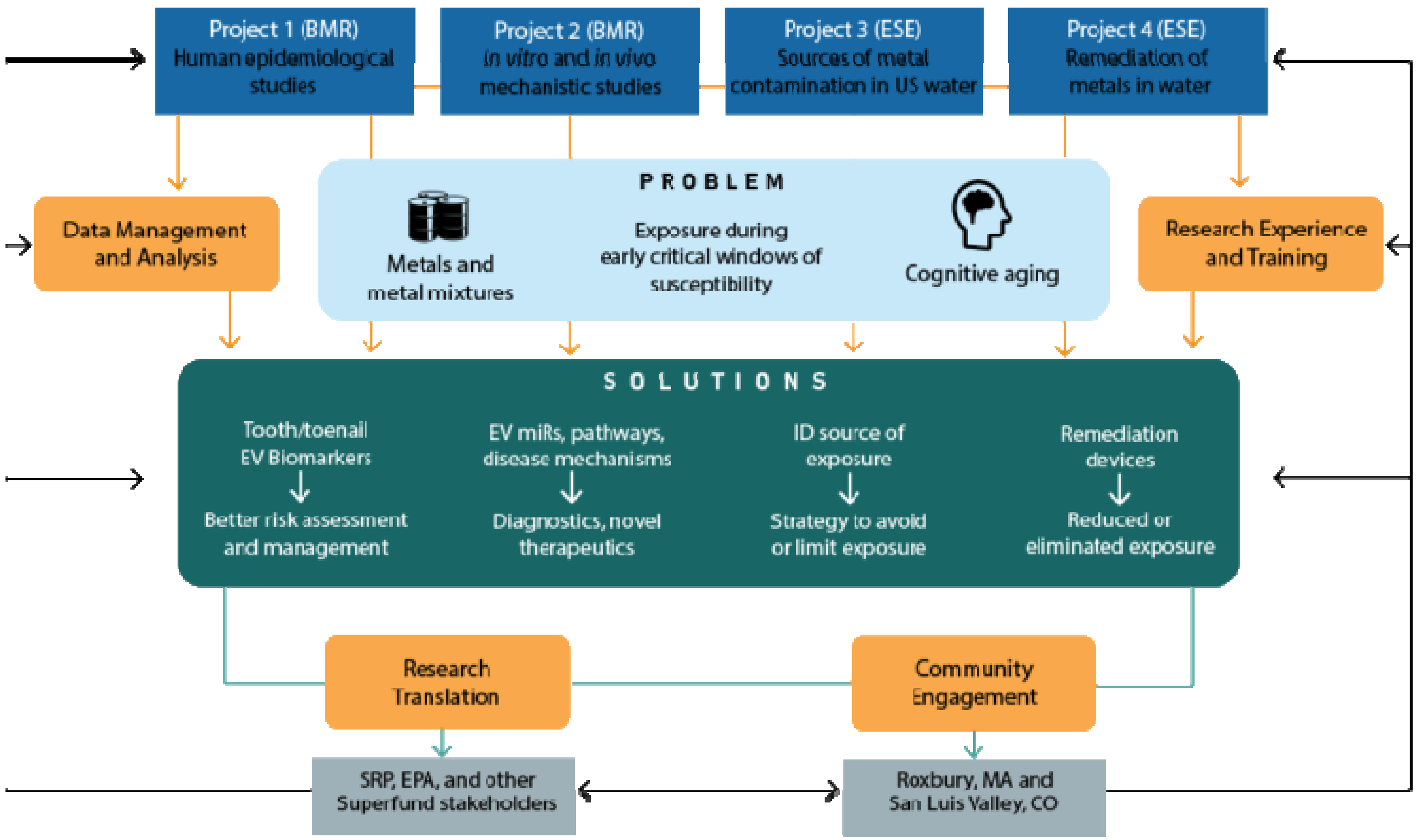

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Project 1: Early life metals exposures and late life cognitive function

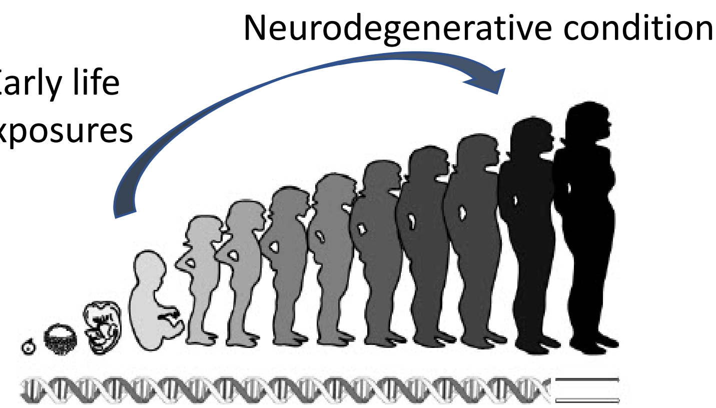
Co-Leaders: Marc Weisskopf and David Christiani
Harvard T.H. Chan School of Public Health

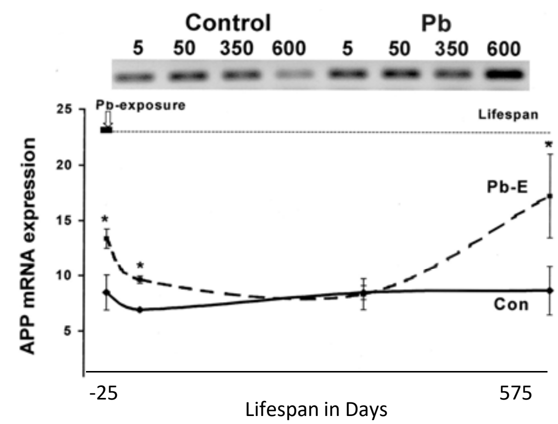
Current knowledge

- In utero/early life metals exposures associated with impaired neurodevelopment
- Later life metals exposure associated with worse cognitive function

Developmental Origins of Health and Disease (DOHAD)

- In utero/early neo-natal lead (Pb) exposure related to late life Alzheimer's like neuropathology in animal models
- No human data





Rat data

Basha et al., 2005

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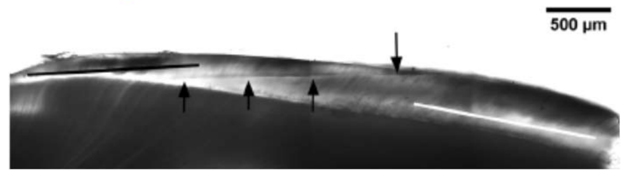
Project 1: Early life metals exposures and late life cognitive function



Part of a lower incisor of a SLBT participant

Enamel (lighter) on top; dentin (darker) below.

Black arrows: neonatal line visible as a darker line in the lighter enamel.

White bar (lower right): Prenatal region (roughly second trimester)

Black bar (top left): Postnatal region (roughly first few months post pregnancy)

Aims:

- Assess association of in utero/early life exposure to metals with worse cognitive function in later life
- Assess adult EV miRNA for associations with metals and cognition

Teeth as a biomarker of early life metals exposure

- Baby teeth develop both pre and postnatally with identifiable timing
- Laser ablation ICP-MS to measure metals

St. Louis Baby Teeth (SLBT) study

- Children born in the 1950s donated baby teeth
- ~70 years old now
- Re-contacting to assess cognitive function and other aspects of life and health

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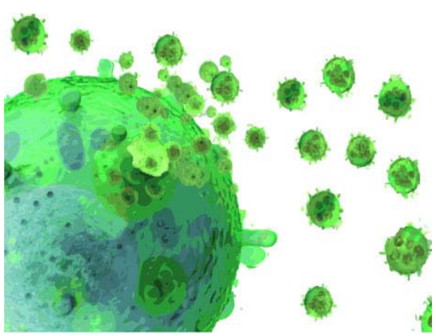
Project 2: Extracellular Vesicle (EV) miRNAs in cognitive function decline associated with early-life metal exposure

Co-Leaders: Quan Lu, Harvard T.H. Chan School of Public Health and
Takao Hensch, Boston Children's Hospital

Extracellular vesicles



- Cell communication
- Biomarkers

Our goal is to establish EV miRNAs not only as novel biomarkers for metal exposure-related cognitive function, but also as a likely mechanistic basis for metal-induced neurotoxicity and cognitive impairment.

We hypothesize that metal exposures in early life alter EV miRNAs in the brain and that these changes in EV miRNAs affect the function of neurons and neural stem cells to accelerate cognitive aging.

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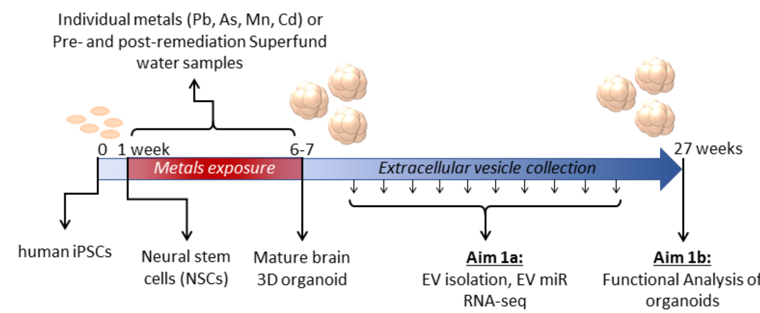
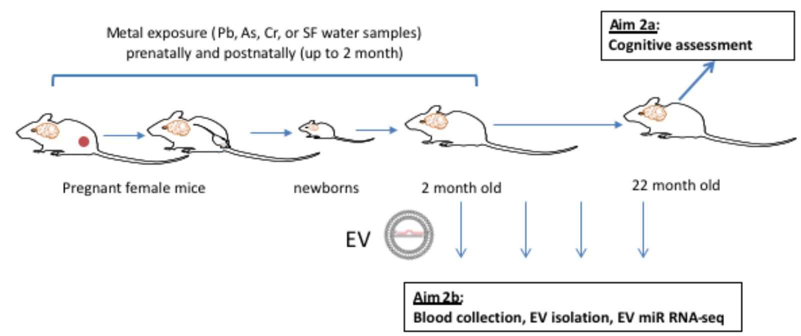
Specific Aims of Project 2

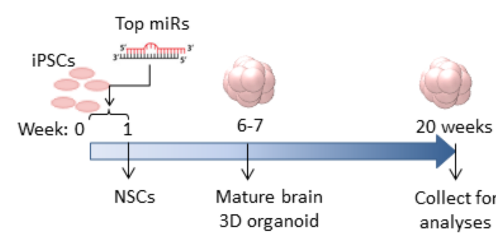
- to determine the effects of metal exposures on EV miRNAs and neural cell functions using 3D brain organoids



- to determine the effects of early-life metal exposures on cognitive function and EV miRNAs in late-life mice



- to determine the <u>functional</u> role of EV miRNAs in modulating functions of neural cells and cognitive function in mice and in brain organoids



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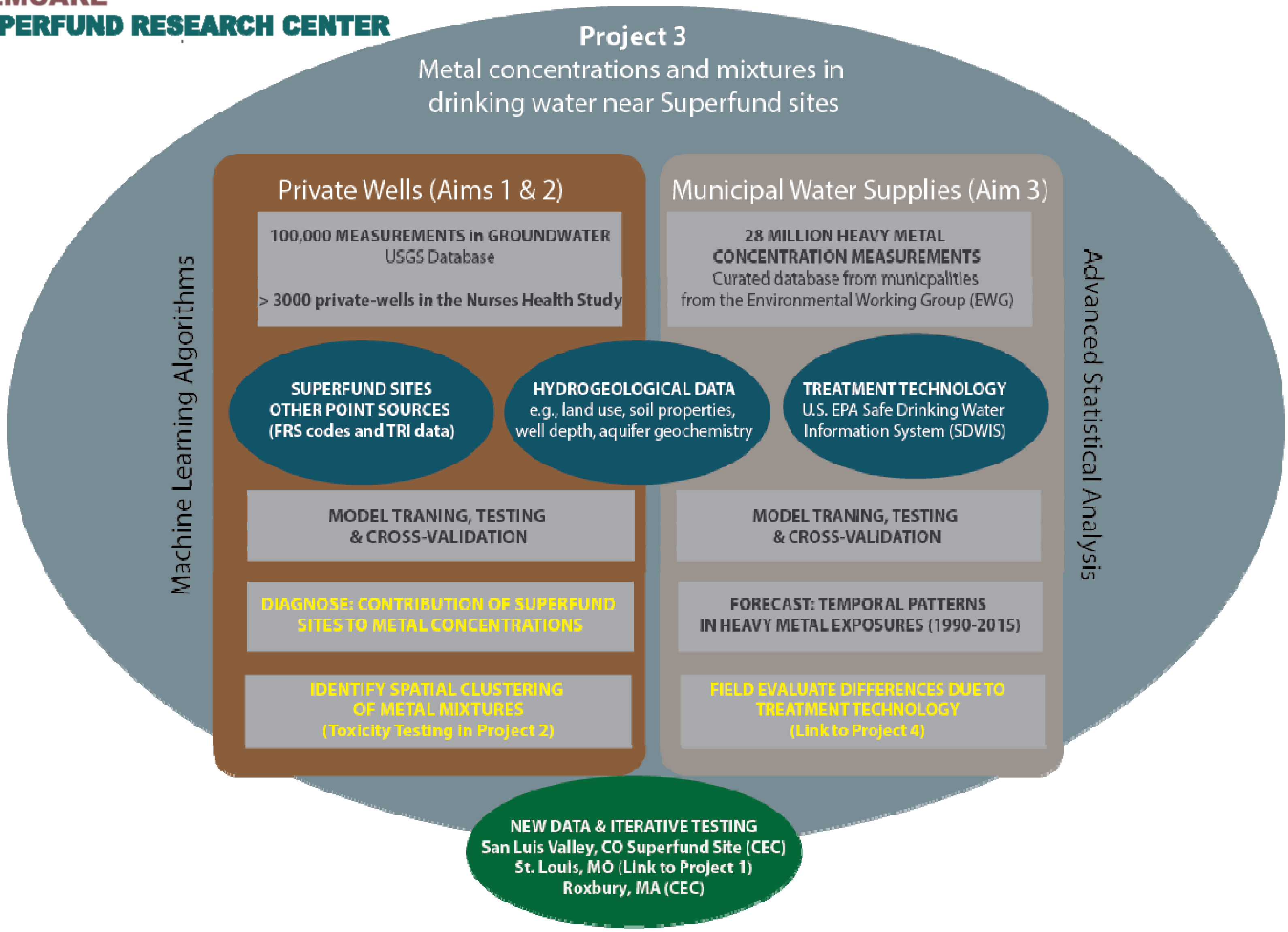

Co Leaders:
Elsie Sunderland
Francine Laden

HARVARD School of Engineering and Applied Sciences

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Biogeochemistry of Global Contaminants HARVARD

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Motivation

Contamination of drinking water is a significant public health concern

- Private wells serve 15% of US population and lack routine monitoring
- USGS in 2009 found 23% contaminated at a level of health concern

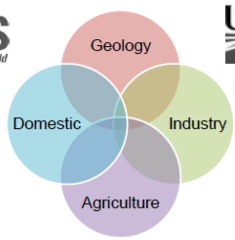
Direct measurements of water quality is:


Low coverage


Expensive


Delayed

Models with readily available data can help



USGS science for a changing world
USDA
PRISM GROUP
NWQMC
Ohio Environmental Protection Agency
dnr gis
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Research objectives

- Assemble a comprehensive dataset of measurement data for private wells, and predictor variables representing the sources, transport and fate of heavy metals in soils and groundwater
- Develop and test a random forest model to estimate groundwater exposure to arsenic, lead and cadmium in private wells
- Assess the predictive performance of the model at levels of exposure that are relevant for epidemiologic studies.

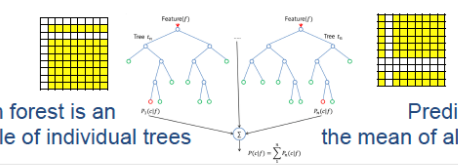
Data & Method

- National heavy metals occurrence data from the Water Quality Portal for well water quality collected during 1989-2017
- Candidate predictors are informed by ground water contamination processes

Population density (1990, 2000, 2010)
Soil organic carbon (2011)
Other soil geochemistry (2007-2010)
Hydrologic landscape: slope, sand%, relief, flat land% (2003)

EPA Toxic Release Inventory (1987-2015)
Climate variables: temperature, precipitation (1981-2010)
Well depth (1990-2017)
Groundwater recharge (2011)

- Random forest model was trained to predict As, Pb, Cd levels and the probability of exceeding 10 μg/L



Random forest is an ensemble of individual trees

Predicted value is the mean of all of the trees

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Results

72,976 wells measured for As
91,600 wells measured for Pb
99,055 wells measured for Cd (1989-2017)

Using a hybrid mechanistic-empirical approach, the model captured the variability in measurements of As, Pb, and Cd levels in ground water.

Table 1. Evaluation of cross-validated models for predicting concentrations and probability of exceeding 10 μg/L

	R^2_{cont}	MSE_{cont}	R^2_{dicho}	MSE_{dicho}
As	0.78	234.5	0.78	0.035
Pb	0.80	221.8	0.83	0.013
Cd	0.51	1498.0	0.74	0.024

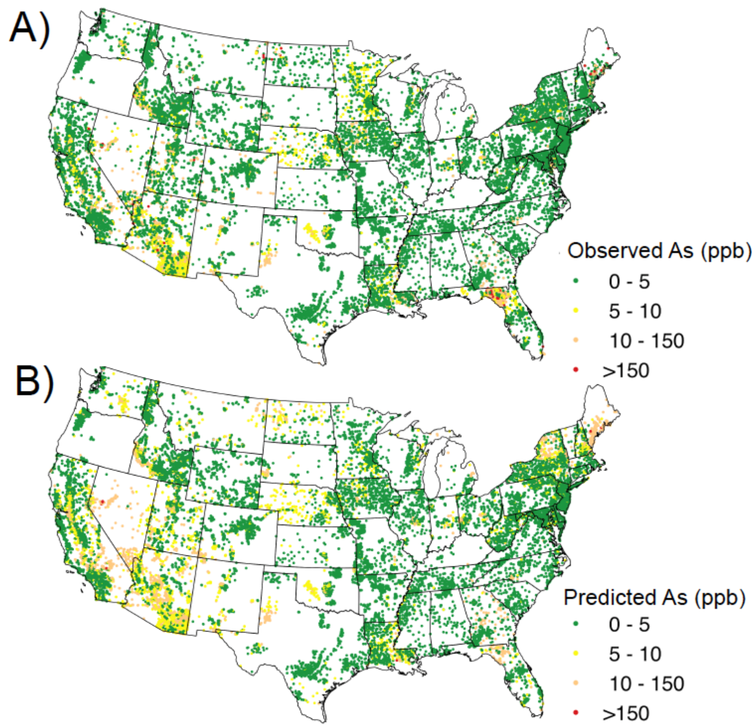

Figure 2. Spatial distribution of A) observed and B) predicted concentration of As in wells.

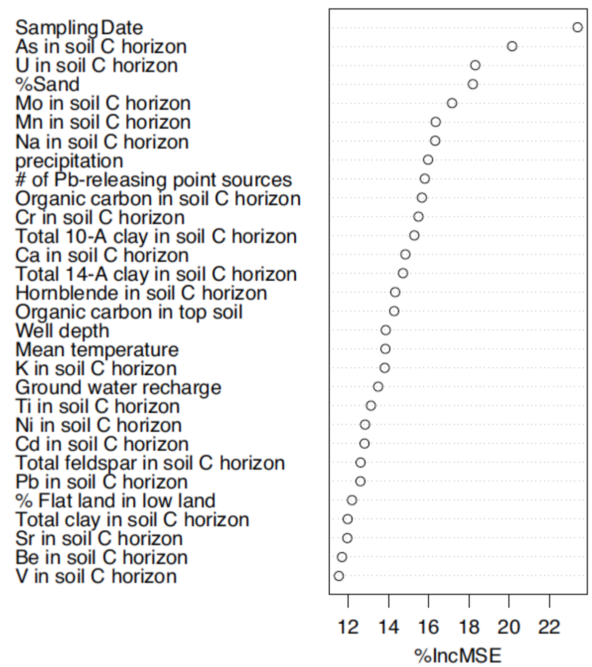

Figure 3. Top 30 variables predicting As levels in random forest model.

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Results (cont.)

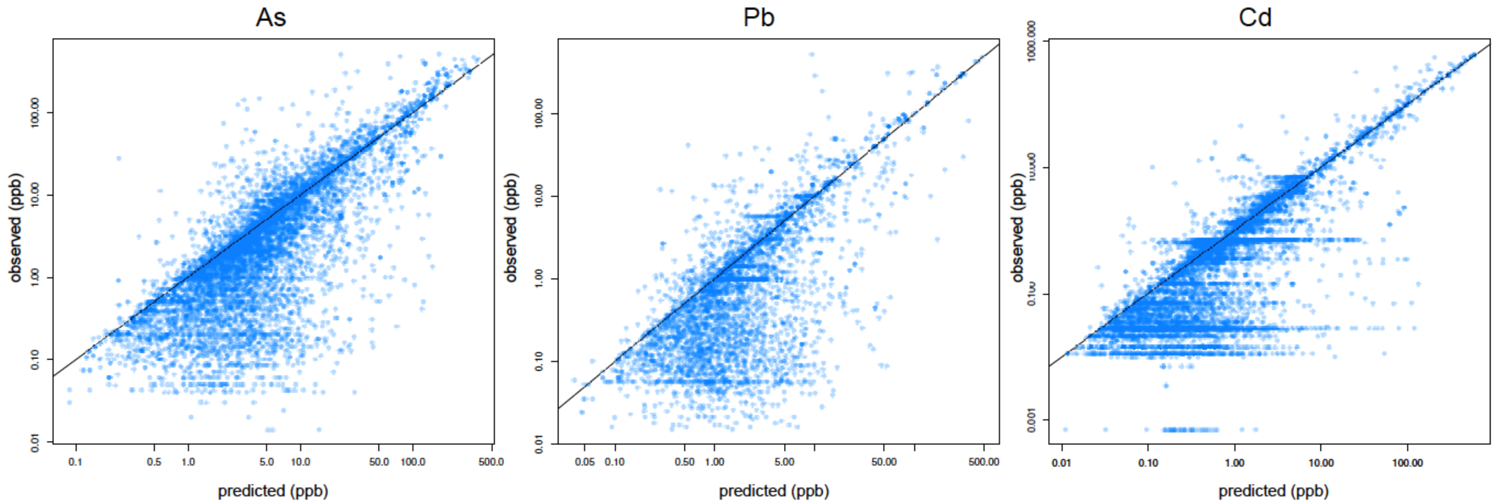

Figure 4. Observed vs predicted groundwater concentrations of As, Pb and Cd for private wells in the testing set across the continental US.

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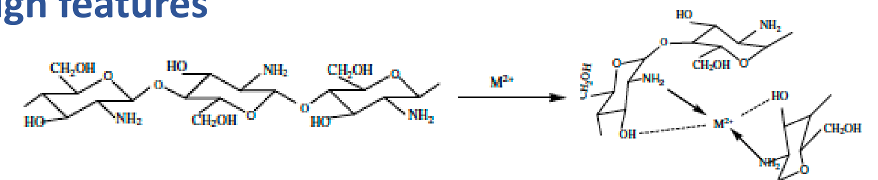
Project 4: Design and optimization of advanced selective sorbent materials for metal remediation of drinking water

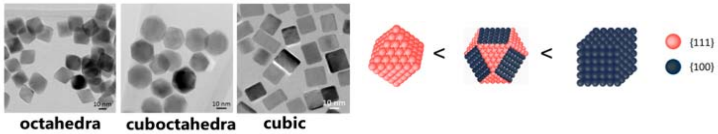
Julie Zimmerman, Yale University

Christopher Muhich and Paul Westerhoff, Arizona State University

The goal of this project is to **design and develop advanced selective adsorbent materials** informed by empirical observations on capacity and selectivity to evaluate functional performance; fine and near edge x-ray spectroscopy to elucidate mechanism; and novel computational approaches from the molecular to system scale to inform sorbent optimization.

Aim 1: Optimizing synthesis and systematic characterization of two sorbent platforms with novel bottom-up design features



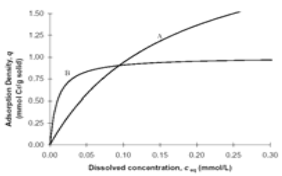


Platform 1: Transition metal crosslinked biopolymers (TMC)

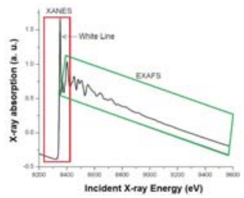
Platform 2: Crystal facet engineering of nano metal oxides (NMOs)

Aim 2: Design of optimized Platform 1 for selective removal of target metal oxoanions in competitive environments through small-scale packed bed water treatment systems

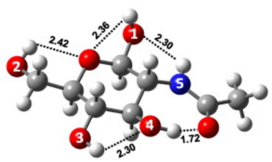
1. batch sorption experiments



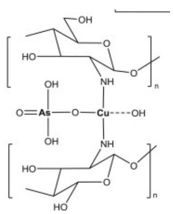
2. characterization of sorption mechanism



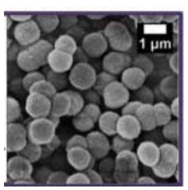
3. DFT models + machine learning



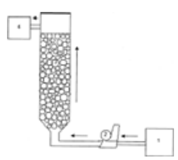
4. Surface complexation and mass transport modeling



5. *a priori* design of optimized **Platform 1** sorbents

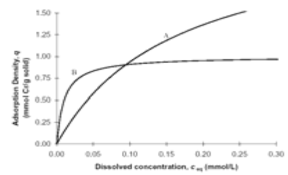


6. scale up and pilot testing in packed beds

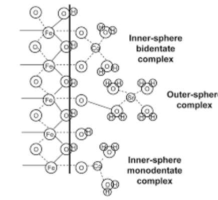


Aim 3: Design of optimized Platform 2 and incorporation in macroporous electrospun polymers for selective removal of target metals in competitive environments through small-scale fiber membrane-based water treatment systems

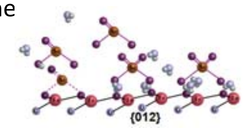
1. batch sorption experiments



2. characterization of sorption mechanism

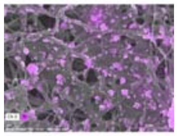


3. DFT models + machine learning

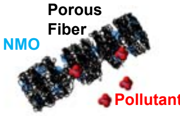


4. *a priori* design of optimized **Platform 2** sorbents

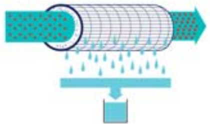
5. Incorporating optimizing **Platform 2** NMO into porous, electrospun fibers



6. optimization of NMO-fibers through mass transport modeling



7. scale up and pilot testing in NMO-fiber membrane



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Platform 1

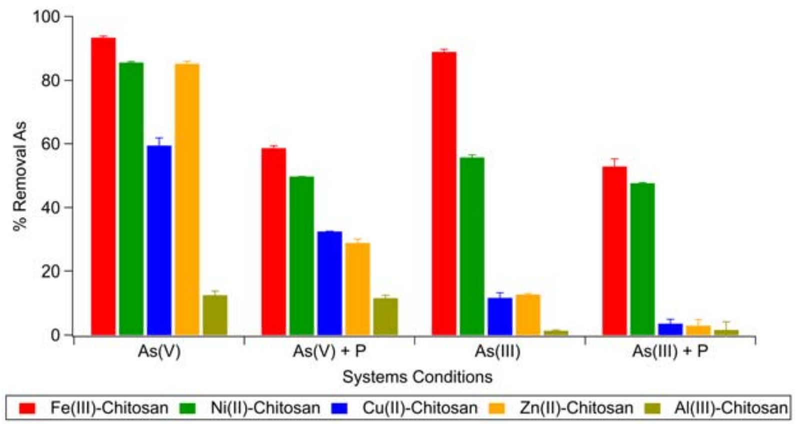

Figure 1. Comparison of arsenic removal performance by Fe(III)-chitosan, Ni(II)-chitosan, Cu(II)-chitosan, Zn(II)-chitosan, and Al(III)-chitosan in various systems conditions. Starting concentrations were 4 ppm As and 25 mM acetate buffer pH 6, and 16 ppm P when present.

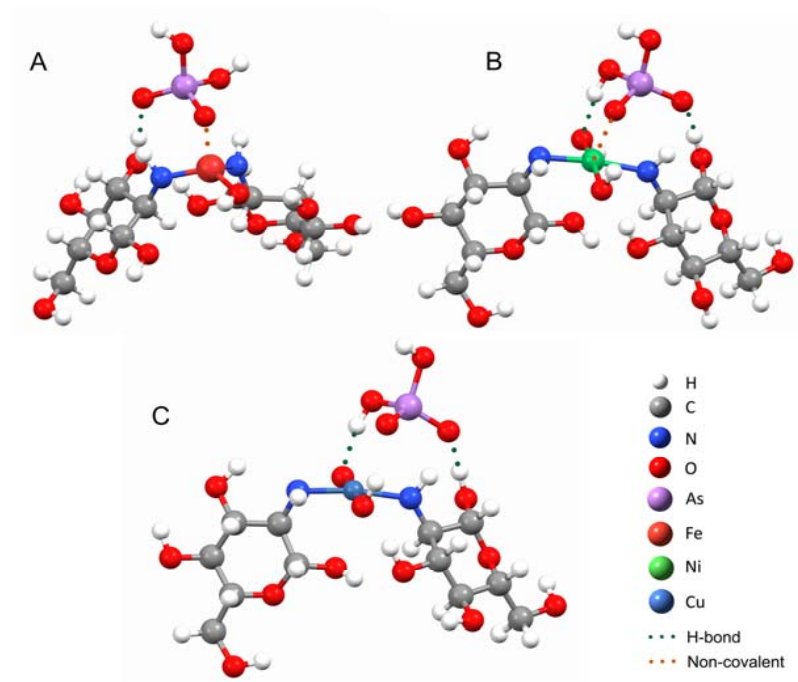

Figure 2. DFT optimized geometries of As(V) adsorption by Fe(III)-chitosan (Figure 4.6a), Ni(II)-chitosan (Figure 4.6b) and Cu(II)-chitosan (Figure 4.6C). Each element in the structure is represented with a different color with while for H, gray for C, blue for N, red for O, purple for As, light red for Fe, green for Ni, and light blue for Cu. Green dots depict hydrogen bonding interactions between As(V) and the metal-chitosan complex. Orange dots indicate inner-sphere non-covalent interactions between As(V) and the metal-chitosan complex.

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Platform 2

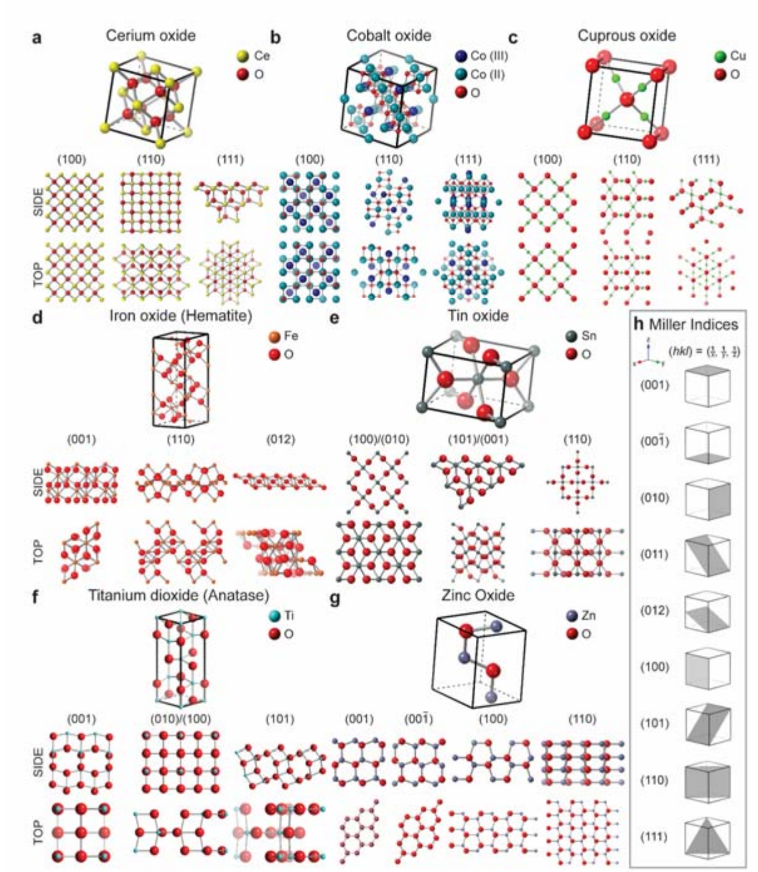

Figure 3. (Top) Atomic crystal structure with unit cell and respective facet surface structures (middle: side view; bottom: top view) of nanoscale metal oxides: (a) Cerium oxide , (b) Cobalt oxide, (c) Cuprous oxide, (d) Iron oxide (hematite), (e) Tin oxide, (f) Titanium dioxide (anatase), and (g) Zinc oxide. (h) Common low-index crystal planes or facets identified by Miller indices.

MEMCARE Cores

Administrative Core
Director: Quan Lu
Deputy Director: Julie Zimmerman
Research Translation Coordinator: Trina von Stackelberg
Administrative Coordinator: Julie Goodman

Research Experience and Training Coordination Core (RETCC)
Susan Korrick
Elsie Sunderland

Data Management and Analysis Core (DMAC)
Brent Coull
Xihong Lin

Community Engagement Core (CEC)
Kathy James
Tamarra James-Todd

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Data Management and Analysis Core (DMAC)

- **DMAC Leads:**
  - Brent Coull, bcoull@hsph.harvard.edu, 617-432-2376
  - Xihong Lin, xlin@hsph.harvard.edu, 617-432-2914
- **Aims:**
  - State-of-the-art data management
  - Ensure sound statistical principles for center design and analysis
  - Provide support in geographic information systems (GIS)
  - Conduct mission related research.
  - Disseminate methodological developments via articles, case studies, web-based software, and short courses.
  - Provide education and training for Center students and researchers
  - Ensure all projects use state-of-the-art approaches to statistical computing.

Data and DMAC Activities

- **Data:** ‘omics data; imaging data; neurological phenotypes; metal biomarker data; water metal concentrations; residential locations, rich point and areal spatial data; simulation output of molecular geometries, energies, and charges.
- **Data Sharing Strategies:**
  - Submission of ‘omics data to dbGAP.
  - Submission of data to NIH Data Commons when appropriate.
  - Use of an open science web portal (OSF) in conjunction with the Harvard Dataverse
  - Free and open-source software packages (DEGAUSS) that are based on containerization, meaning these executable programs contain all code and data when appropriate.
- **Also Using:**
  - Bioinformatics
  - Geographical Information Sciences (GIS) technologies
  - Computational modeling

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Community Engagement Core

Kathy James, University of Colorado
Tamara James-Todd, Harvard T.H. Chan School of Public Health

The Dimock Center (Roxbury, MA)

Harvard University

- Urban partner
- Contamination of neighborhood soil—air pollution
- *Possible* water contaminants due to older housing stock/pipes

San Luis Valley (Colorado)

University of Colorado-AMC

- Rural partner and mining community
- Long history of water contamination with metals
- Soil contamination with metals

Objective 1: Community Activities—Online Presence

- Social media– community partners, health clinics, public health centers
- Website advertising: community partners
- Local newspaper and radio
- Hard copy: community flyers
- Facebook, YouTube channel, and Twitter
- Set up bi-annual webinars for mass viewing and recorded
- Set up a community Vlog and Q&A location through YouTube and Facebook
- Online focus groups targeting pregnant women

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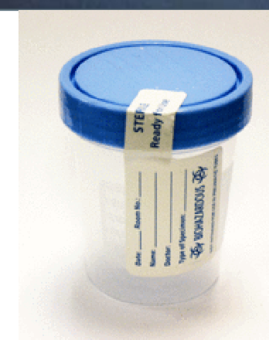
Objective 2: Participant Recruitment and Engagement in Citizen Science

- <u>Recruitment of Pregnant Women and Children</u>
  - Clinic nurse/midwife will recruit and provide study information
  - Study personnel will contact participants via email or phone
  - Online/telephone consent process (Cisco Jabber)

- <u>Data Collection (4 collection points across 1 year of follow up)</u>
  - Demographic and exposure survey completed online
  - Citizen Science
    - Water, urine, soil sample collection kit mailed to participant
    - Sample collection supplies and instructions (8th grade level with pictures)
  - Electronic gift cards to local grocery store with fresh fruit and veggies



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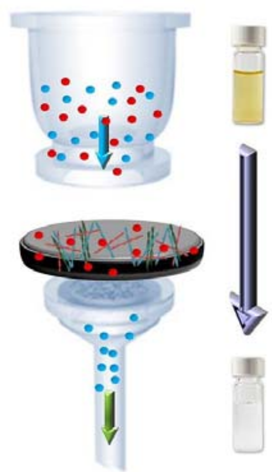
Objective 3: Evaluating interventions for mitigation

- Install water treatment system in qualified participant homes (metals levels > EPA maximum contaminant levels)
    - o Monitor water and urine levels after installation
- Improve environmental health literacy within the community related to metals, neurological outcomes, and reducing exposure to vulnerable populations



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THANKS to

Dr. Bill Suk, Dr. Danielle Carlin and many others at the Superfund Research Program (SRP) for guidance and advice

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