Baylor-Rice Superfund Research Program

POLYCYCLIC AROMATIC HYDROCARBONS: ULTRASENSITIVE DETECTION, EARLY LIFE EXPOSURES-CLINICAL OUTCOMES (PRETERM BIRTHS, CHRONIC LUNG DISEASE, AND NEUROCOGNITIVE DEFICITS), PREVENTION AND REMEDIATION

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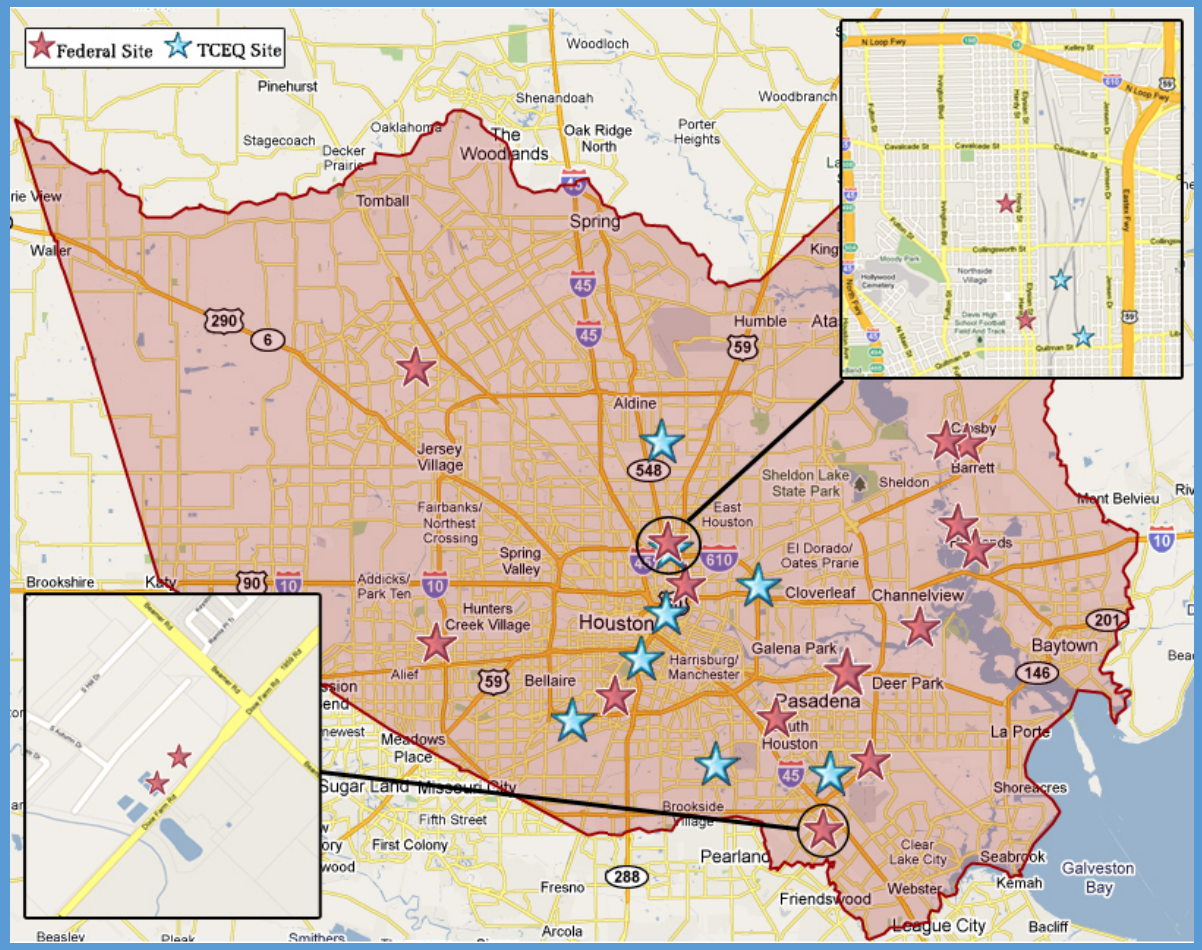
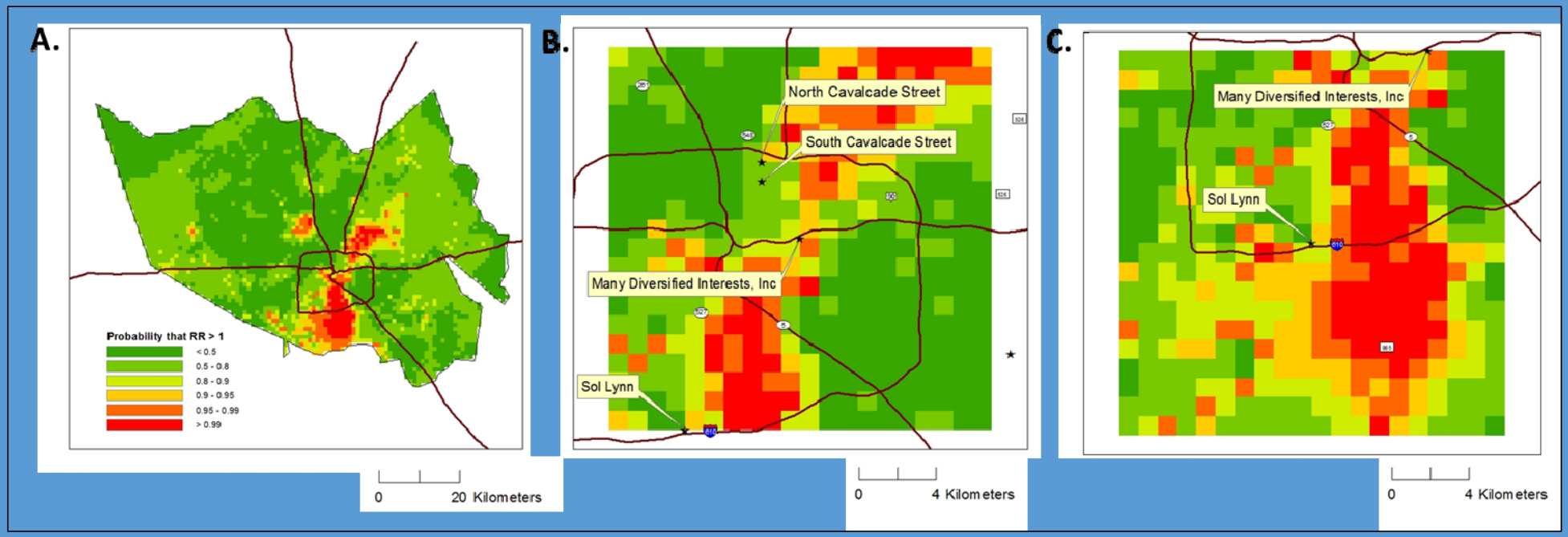

Federal Site
TCEQ Site
Woodloch
Pinehurst
Shenandoah
Woodbranch
Stagecoach
Oaklahoma
Decker Prairie
The Woodlands
Oak Ridge North
Porter Heights
Tomball
Spring
Waller
290
6
45
59
Humble
Aldine
548
Jersey Village
Sheldon Lake State Park
Sheldon
Barrett
Fairbanks/ Northest Crossing
East Houston
Spring Valley
610
El Dorado/ Oates Prairie
Brookshire
Katy
90
10
Addicks/ Park Ten
Hunters Creek Village
Cloverleaf
Channelview
Houston
Galena Park
Harrisburg/ Manchester
Baytown
201
146
Alief
Bellaire
Deer Park
Pasadena
Meadows Place
La Porte
Sugar Land
Missouri City
Shoreacres
Brookside Village
Fifth Street
First Colony
Pearland
Clear Lake City
Seabrook
Kemah
Galveston Bay
Fresno
288
Friendswood
Webster
League City
Bacliff
Arcola

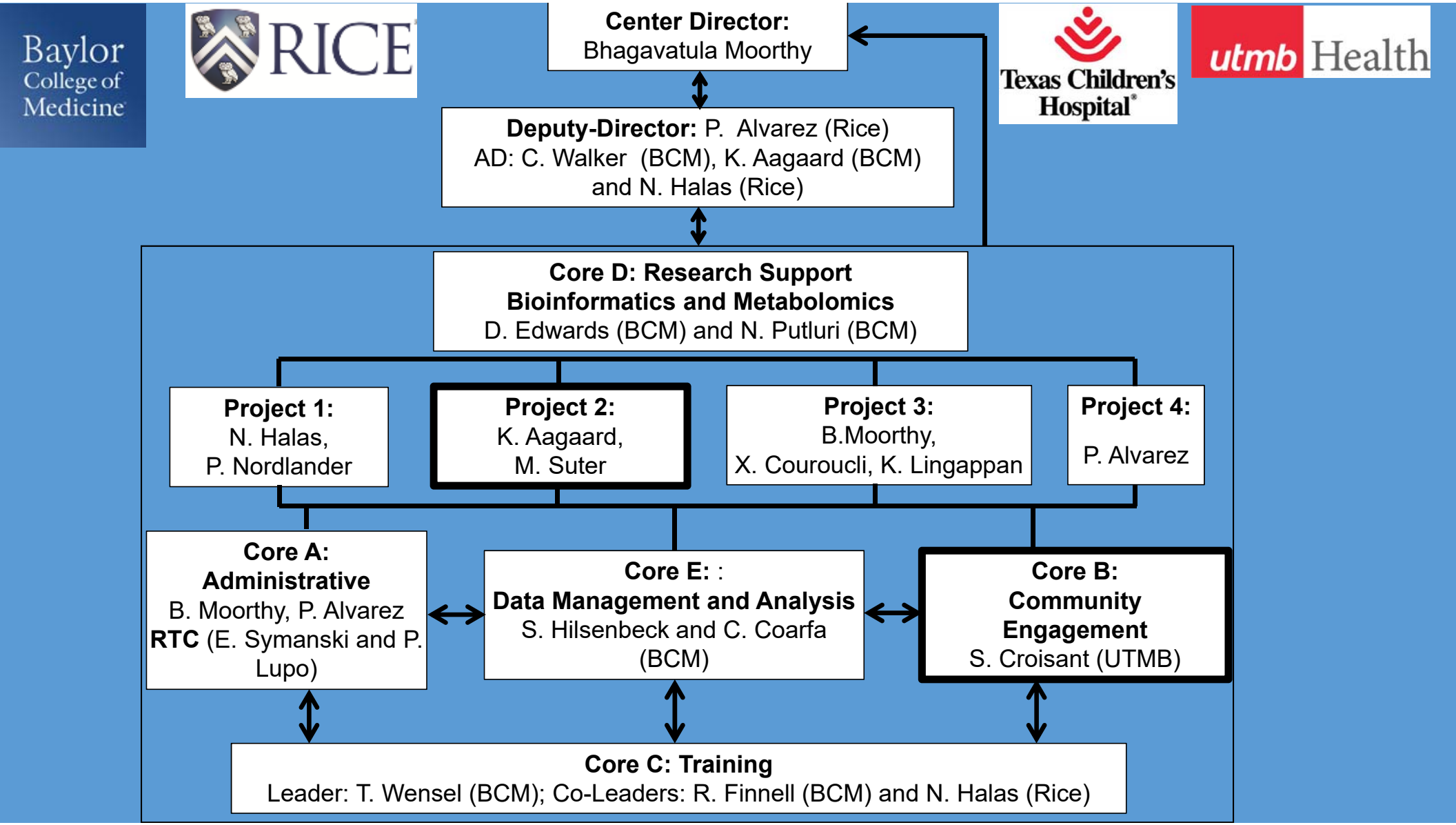
Geostatistical analysis reveals high risk of VLBW and preterm births around Superfund sites



Thompson et al, Environ Health, 2014

Over-Arching Hypothesis of the Center

Maternal exposure to polycylic aromatic hydrocarbons (PAHs), which are present in Superfund sites, increases the risks for preterm births (PTBs), and incrementally augments the major morbidities associated with PTBs such as bronchopulmonary dysplasia (BPD) (chronic lung disease) in premature infants.


Baylor College of Medicine
RICE
Texas Children's Hospital
utmb Health
Center Director:
Bhagavatula Moorthy
Deputy-Director: P. Alvarez (Rice)
AD: C. Walker (BCM), K. Aagaard (BCM)
and N. Halas (Rice)
Core D: Research Support
Bioinformatics and Metabolomics
D. Edwards (BCM) and N. Putluri (BCM)
Project 1:
N. Halas,
P. Nordlander
Project 2:
K. Aagaard,
M. Suter
Project 3:
B.Moorthy,
X. Courouclis, K. Lingappan
Project 4:
P. Alvarez
Core A:
Administrative
B. Moorthy, P. Alvarez
RTC (E. Symanski and P. Lupo)
Core E: :
Data Management and Analysis
S. Hilsenbeck and C. Coarfa
(BCM)
Core B:
Community
Engagement
S. Croisant (UTMB)
Core C: Training
Leader: T. Wensel (BCM); Co-Leaders: R. Finnell (BCM) and N. Halas (Rice)

Overall Center: Specific Aims

1. **Develop ultrasensitive detection and identification strategies for primary and secondary PAH- and *PAC*-based compounds in air, water, and soil based on optically active engineered nanomaterials (project 1).**

2. Determine molecular mechanisms by which early life exposure to PAH mixtures or other chemicals increases the risks for PTBs, which in turn leads to BPD in preterm infants (projects 2 and 3).

3. Develop novel remediation technologies to treat soils and sediments from superfund sites (e.g., Patrick Bayou in Houston, TX, *San Jacinto Waste Pitts, etc*.) or from soils contaminated with PAHs in a manner that completely removes the health risks while adding value to the impacted media (project 4).

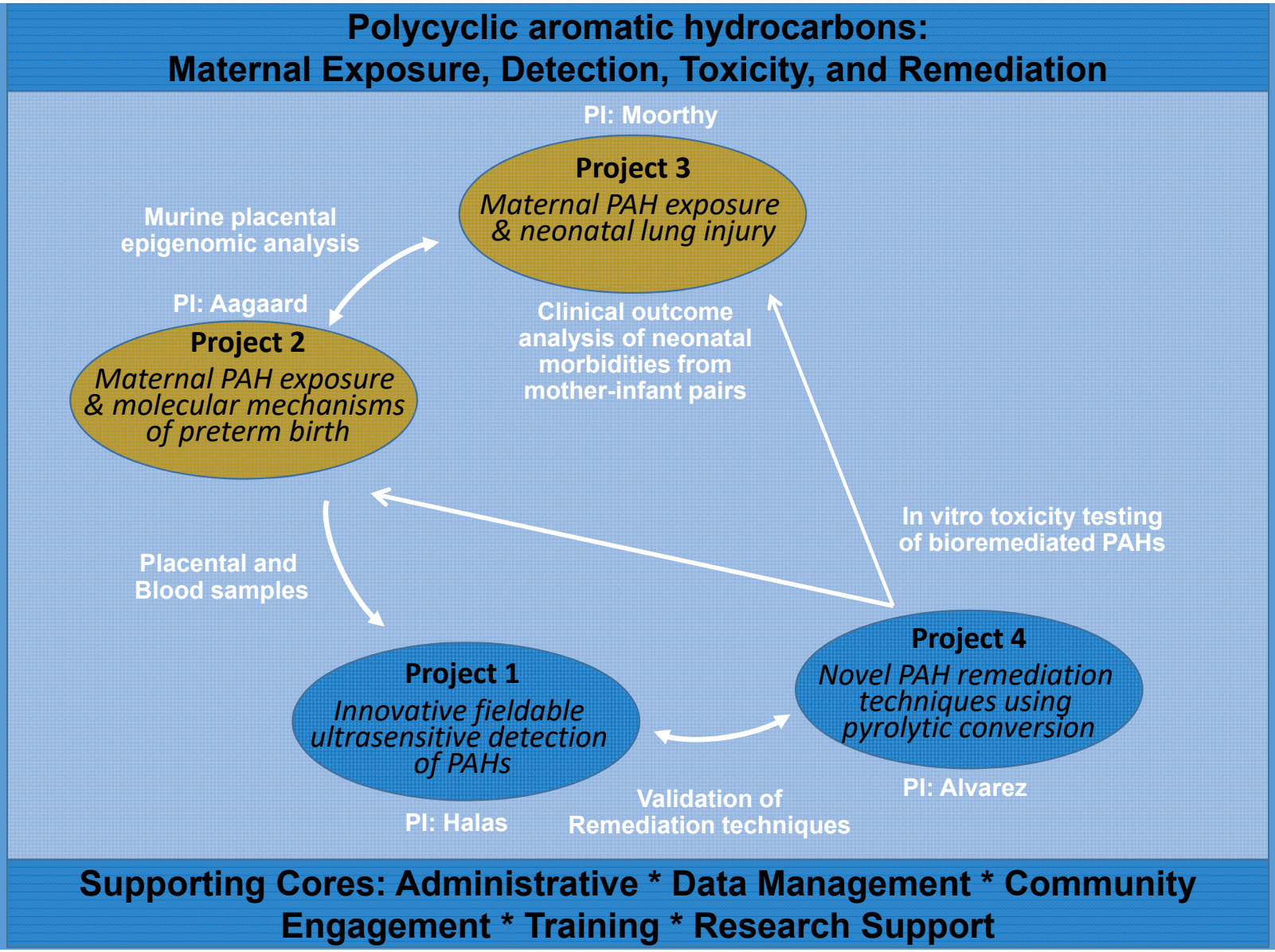
4. Develop novel strategies to prevent and reduce the public health burden associated with PAHs and other hazardous chemicals present in superfund sites [Community Engagement Core (CEC) (Core B)].

Overall Center: Specific Aims

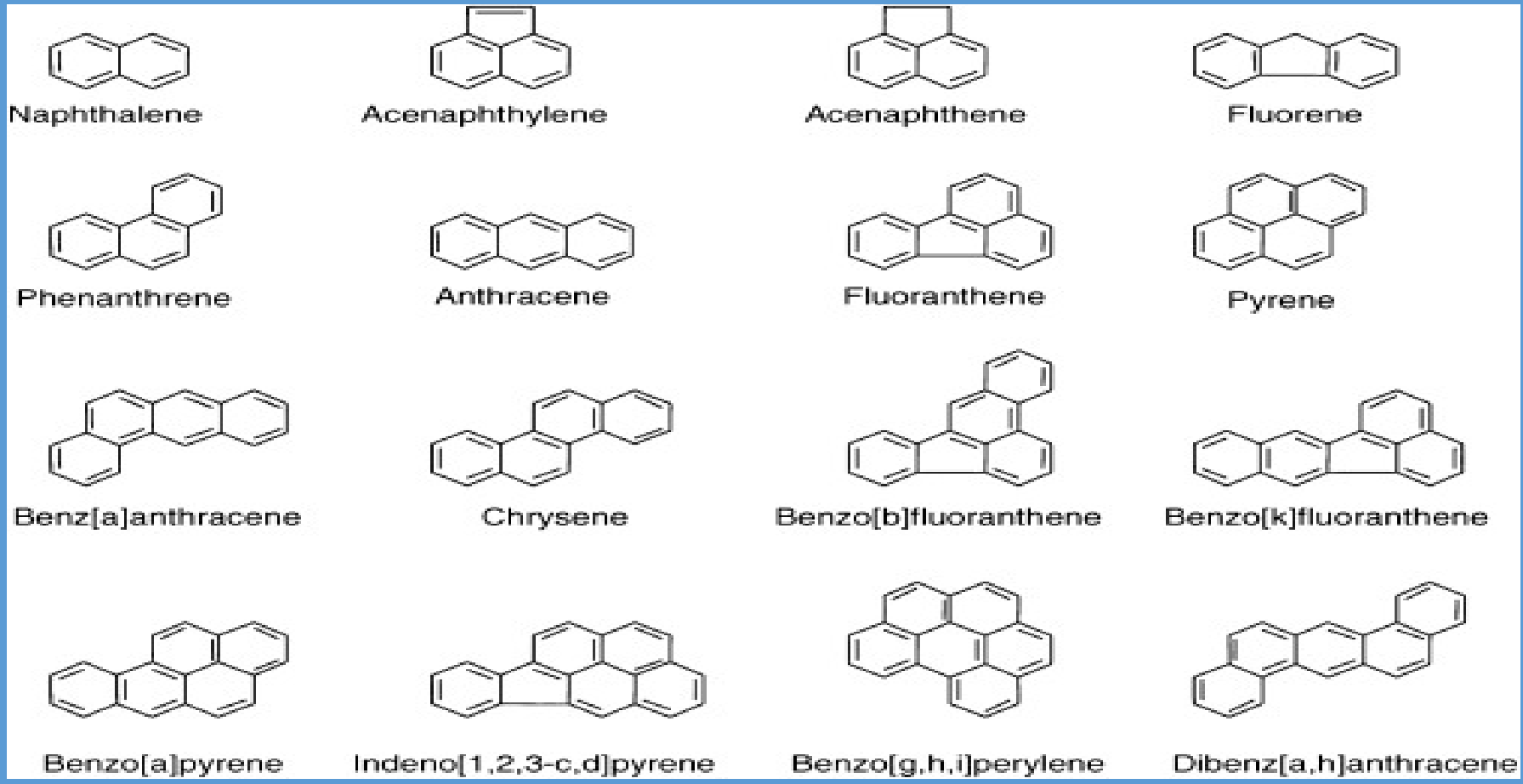
5. Develop partnerships with primary stakeholders (i.e. EPA, ATSDR, Texas EPA), communicate with NIEHS, foster collaborations among investigators within the SRP, with other SRP centers and develop technology transfer [Administrative and Research Translational Core (ARTC) (Core A)].

6. Train students and postdoctoral fellows in a cross-disciplinary manner, so next generation scientists, engineers, and physicians will make fundamental contributions to Environmental Health [Research Experience and Training Coordination Core (RETCC) (Core C)].

7. To support the management and integration of assets across all the projects and cores of the center [data management and Analysis core (DMAC) (Core D).


Polycyclic aromatic hydrocarbons:
Maternal Exposure, Detection, Toxicity, and Remediation
PI: Moorthy
Project 3
Maternal PAH exposure & neonatal lung injury
Murine placental epigenomic analysis
PI: Aagaard
Project 2
Maternal PAH exposure & molecular mechanisms of preterm birth
Clinical outcome analysis of neonatal morbidities from mother-infant pairs
In vitro toxicity testing of bioremediated PAHs
Placental and Blood samples
Project 1
Innovative fieldable ultrasensitive detection of PAHs
PI: Halas
Validation of Remediation techniques
Project 4
Novel PAH remediation techniques using pyrolytic conversion
PI: Alvarez
Supporting Cores: Administrative * Data Management * Community Engagement * Training * Research Support

Polycyclic Aromatic Hydrocarbons



Project 2: Investigating the role of PAH exposures associated with superfund site proximity in preterm birth etiology through placental transcriptomics and epigenomics

PI; Kjersti Aagaard and Co-leader Melissa Suter, Baylor College of Medicine, Houston, TX

Specific Aims:

Aim 1 Measure PAHs in placenta from existing term and preterm birth population-based and enriched cohorts (Superfund and non-Superfund areas): PAHs as biomarkers of exposure in relation to preterm birth

Aim 2*:* Use our established whole transcriptome and epigenomic pipelines to measure variation in gene expression and DNA methylation in the placenta, and integrate the data with PAH levels

Aim 3*:* Employ Geographic Information Systems (GIS) and wearable environmental exposure monitoring devices to determine the contribution of PAH exposure to preterm birth, as measured by distance from remediated and active Superfund sites

PROJECT 2

Research Experience and Training Coordination Core
- Train students and post-doctoral fellows in a cross-disciplinary manner

Administrative and Research Translation Core
- Communication with stakeholders, information disemination

Data Management and Analysis Core
- Data management, storage and analysis

Community Engagement Core
- Bidirectional communication
- Primary and secondary prevention

Research Support Core
- Omics Studies


Environmental sources of PAH

Vicinity to superfund sites

Food Chain Bioaccumulation

Maternal Exposure leading to Preterm Birth

Interaction with other projects

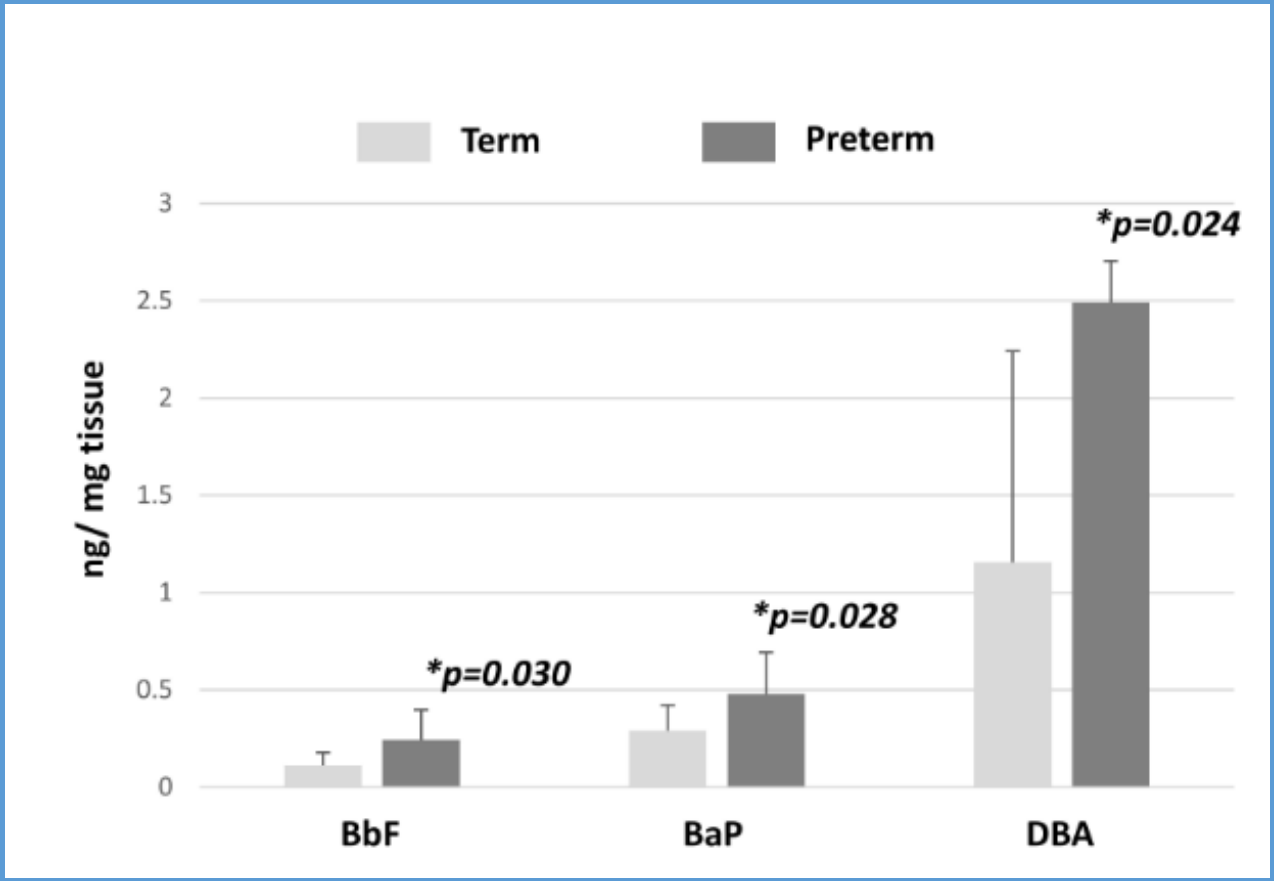
- X Project 1: SERS-based methods of PAH detection in biological samples
- X Project 3: Assessment of prematurity associated morbidities (BPD) and correlation with maternal PAH exposure
- X Project 4: Evaluate toxicity of parent and remediated PAHs on cytotrophoblasts

PAH detection and identification of biomarkers of PAH exposure associated with preterm birth

Measure variation in DNA methylation, and parallel gene expression in the placenta, and integrate the data with PAH levels.

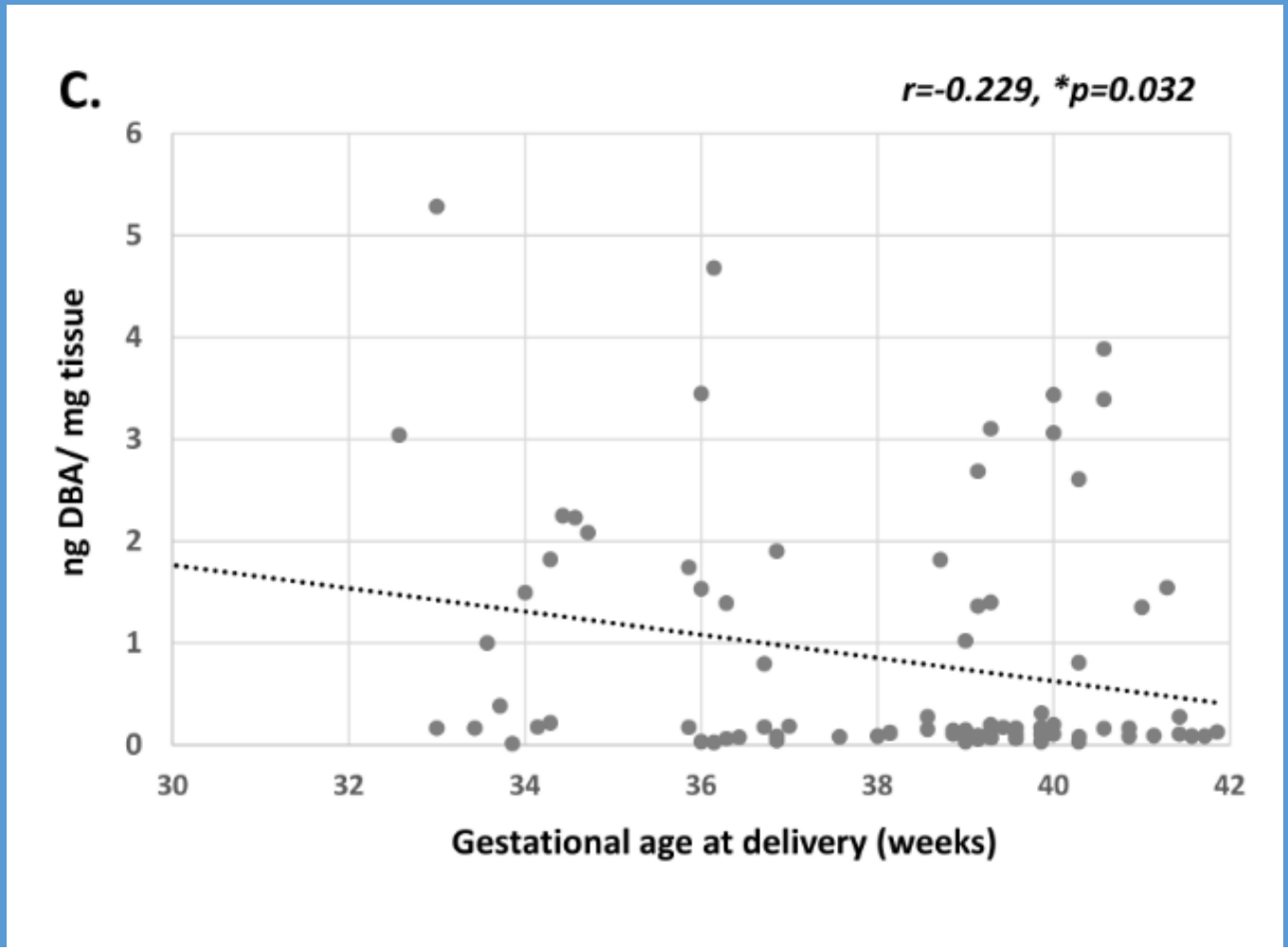

Targeted Epidemiology (Exposure monitoring wristband: will measure 62 PAHs as well as 1500 other chemicals) and Geostatistical modeling

Placental PAHs are higher in preterm deliveries in Superfund subjects



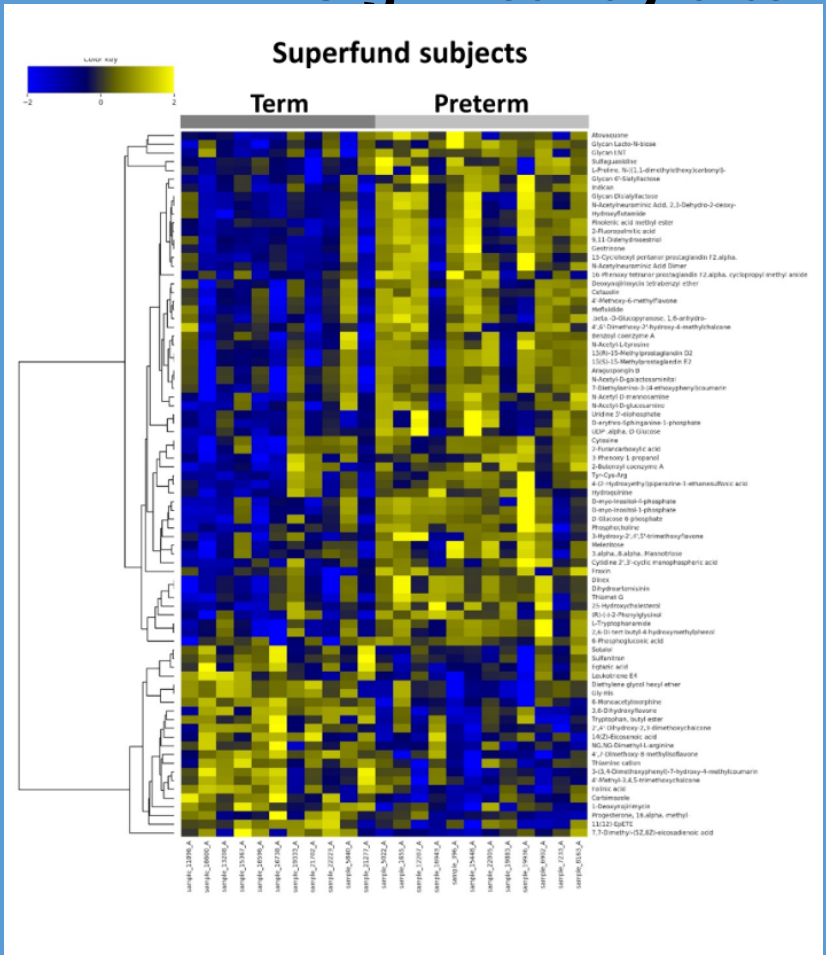
Suter et. al. BBRC, 2019

DBA levels are inversely correlated with Gestational Age



Suter et. al. BBRC, 2019

Unbiased metabolomics revealed 81 out of 570 metabolites significantly altered between term and preterm



Term vs. preterm (Superfund subjects)	
Pathway	p-value
Amino sugar and nucleotide sugar metabolism	0.019693
Pyrimidine metabolism	0.033969
Pentose phosphate pathway	0.055632

Suter et. al. BBRC, 2019

Project 3: Role of cytochrome P450 (CYP)1A/1B1 enzymes in the potentiation of neonatal lung injury in newborn mice exposed prenatally to PAHs, and increased risk of premature infants to chronic lung disease

PI, Moorthy, B, Co-leaders: Krithika Lingappan, Xanthi Couroucli

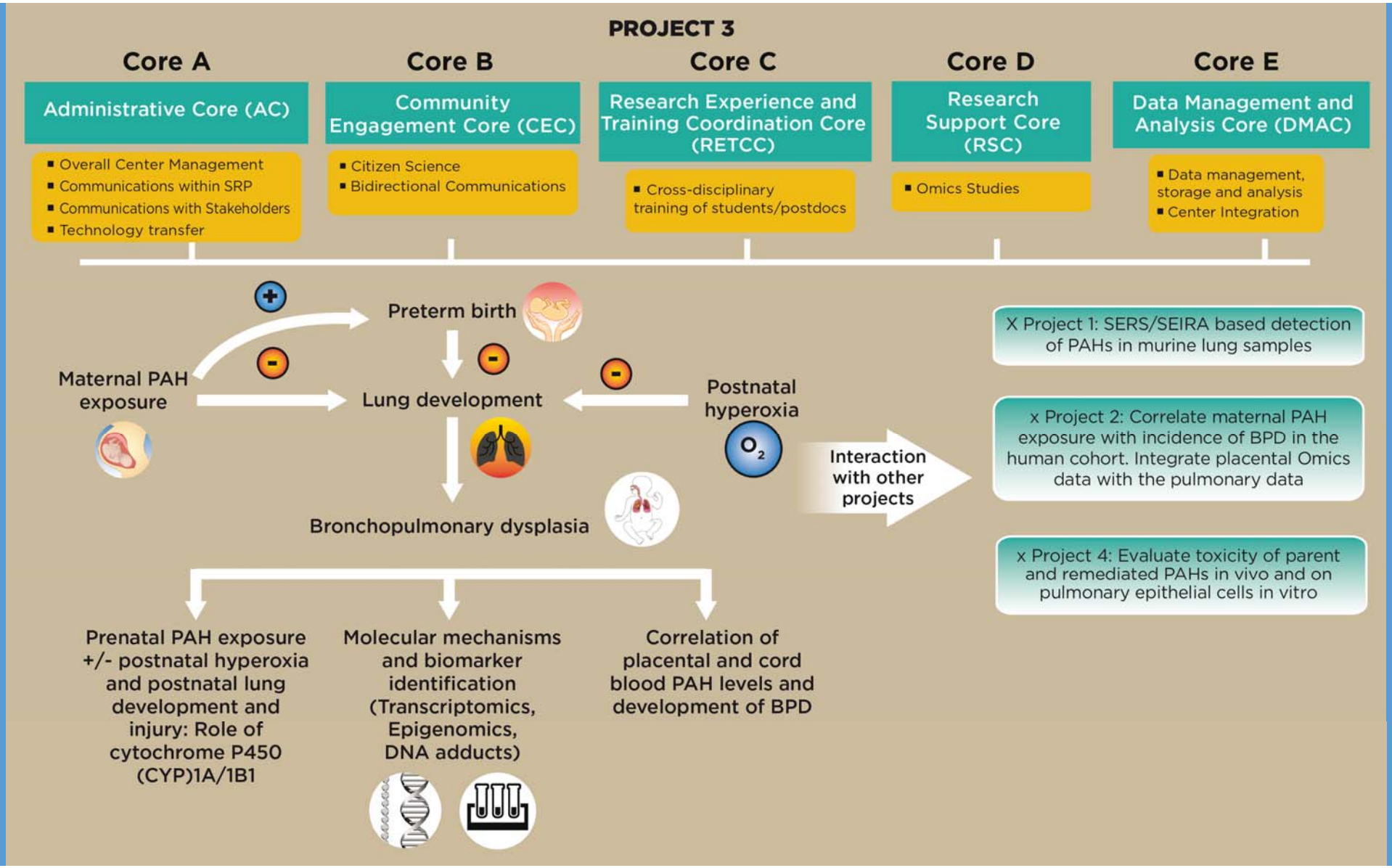
Specific Aims

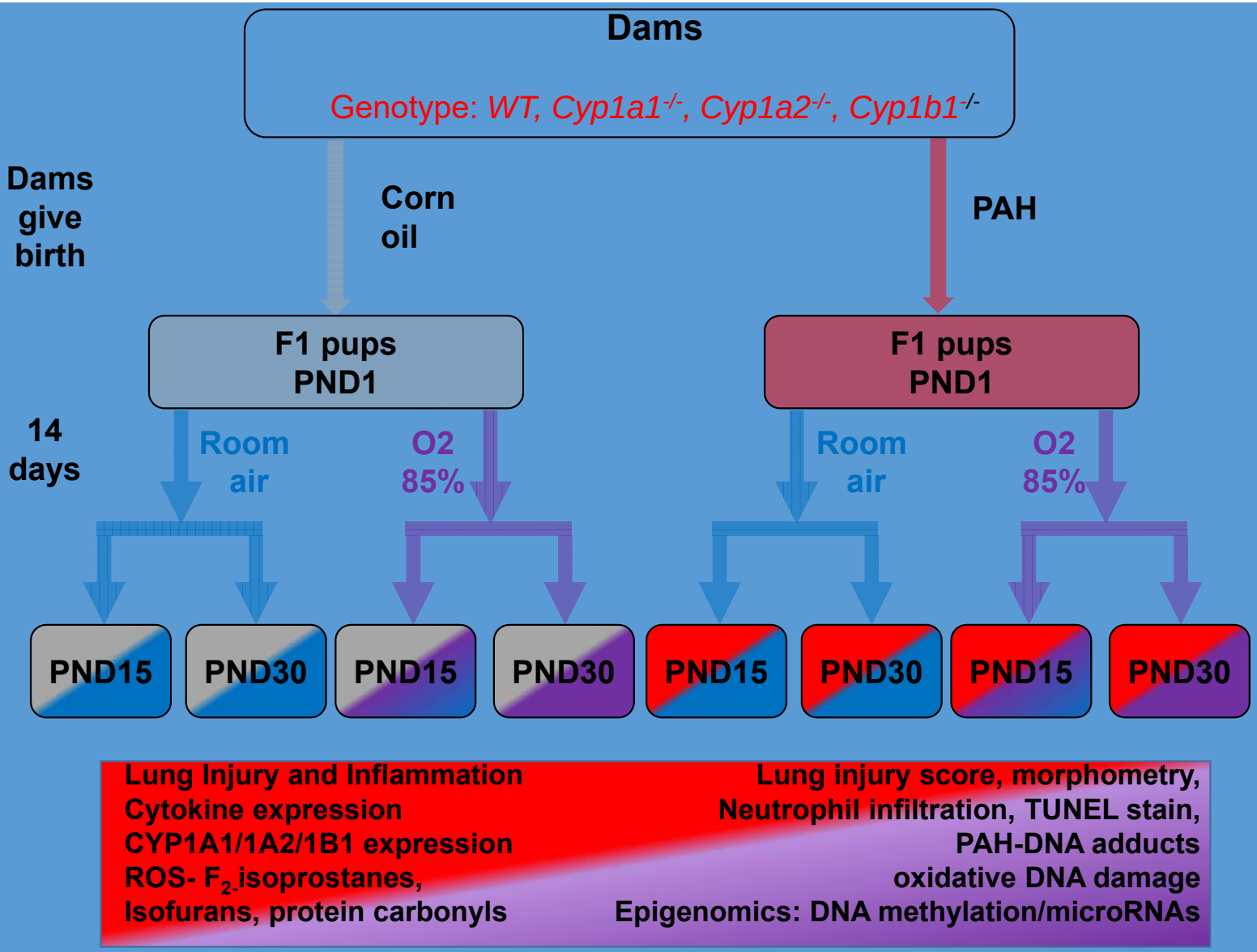
Aim 1. To test the hypothesis that prenatal exposure of wild type (WT) (C57BL/6J) mice or mice lacking *Cyp1a1, 1a2, 1b2* genes to the PAHs (BP + BbF + DBA) will result in differential potentiation of lung injury following postnatal hyperoxia

Aim 2: To determine the mechanisms by which prenatal PAHs will alter the susceptibility of neonatal mice to hyperoxia

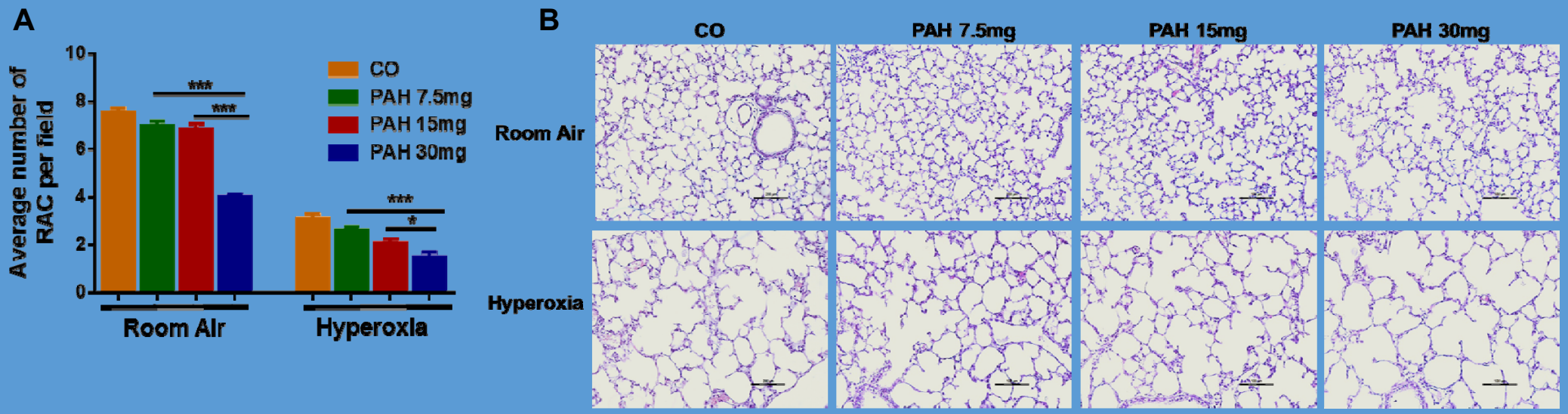
Aim 3: To test the hypothesis that mothers exposed to PAHs (that are present in superfund sites) are at a greater risk for preterm delivery, and that these infants will show increased susceptibility to develop BPD than those with lesser or no exposure

Aim 4: To determine the toxicity of remediated PAHs in (i) human pulmonary cells (e.g., BEAS-2B or A549 cells) *in vitro* and (ii) *in vivo* using mouse models

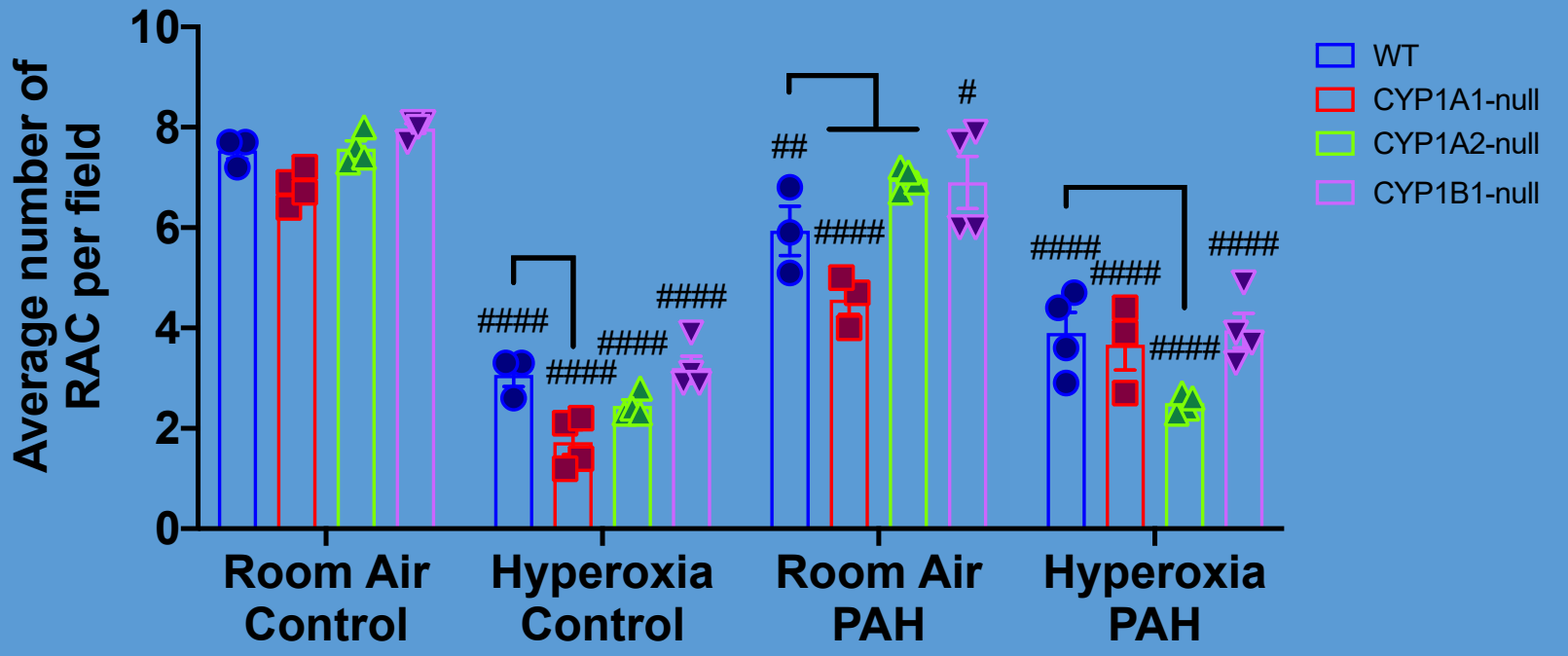

PROJECT 3
Core A
Administrative Core (AC)
Overall Center Management
Communications within SRP
Communications with Stakeholders
Technology transfer
Core B
Community Engagement Core (CEC)
Citizen Science
Bidirectional Communications
Core C
Research Experience and Training Coordination Core (RETCC)
Cross-disciplinary training of students/postdocs
Core D
Research Support Core (RSC)
Omics Studies
Core E
Data Management and Analysis Core (DMAC)
Data management, storage and analysis
Center Integration
Preterm birth
Maternal PAH exposure
Lung development
Postnatal hyperoxia
O2
Bronchopulmonary dysplasia
Interaction with other projects
X Project 1: SERS/SEIRA based detection of PAHs in murine lung samples
x Project 2: Correlate maternal PAH exposure with incidence of BPD in the human cohort. Integrate placental Omics data with the pulmonary data
x Project 4: Evaluate toxicity of parent and remediated PAHs in vivo and on pulmonary epithelial cells in vitro
Prenatal PAH exposure +/- postnatal hyperoxia and postnatal lung development and injury: Role of cytochrome P450 (CYP)1A/1B1
Molecular mechanisms and biomarker identification (Transcriptomics, Epigenomics, DNA adducts)
Correlation of placental and cord blood PAH levels and development of BPD


Dams
Genotype: WT, Cyp1a1-/-, Cyp1a2-/-, Cyp1b1-/-
Dams give birth
Corn oil
PAH
F1 pups PND1
F1 pups PND1
14 days
Room air
O2 85%
Room air
O2 85%
PND15
PND30
PND15
PND30
PND15
PND30
PND15
PND30
Lung Injury and Inflammation
Cytokine expression
CYP1A1/1A2/1B1 expression
ROS- F2-isoprostanes,
Isofurans, protein carbonyls
Lung injury score, morphometry,
Neutrophil infiltration, TUNEL stain,
PAH-DNA adducts
oxidative DNA damage
Epigenomics: DNA methylation/microRNAs

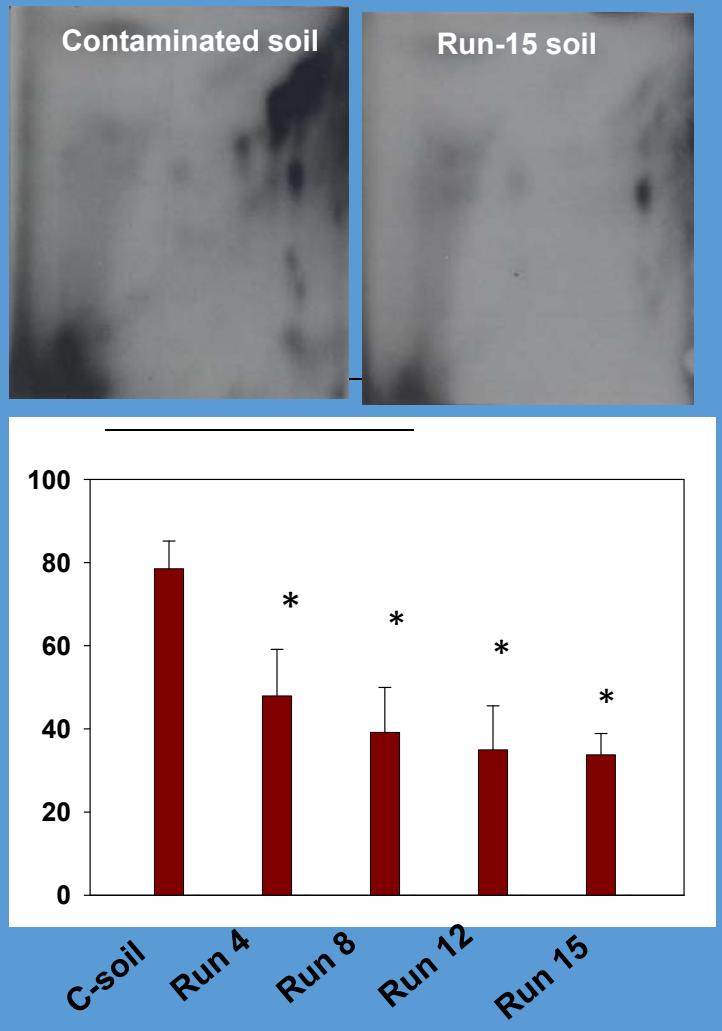
Effect of maternal PAH exposure on hyperoxic lung injury in neonatal mice-Dose Response



Effect of maternal PAH exposure on hyperoxic lung injury in WT, *Cyp1a1*-null, *Cyp1a2*-null, *Cyp1b1*-null mice



Levels of pulmonary DNA adducts from mice treated with extracts from contaminated and remediated soils



Core C: Research Experience and Training Coordination Core (RETCC)

PI, Theodore Wensel and Co-PI, Rick Finnell, Baylor College of Medicine

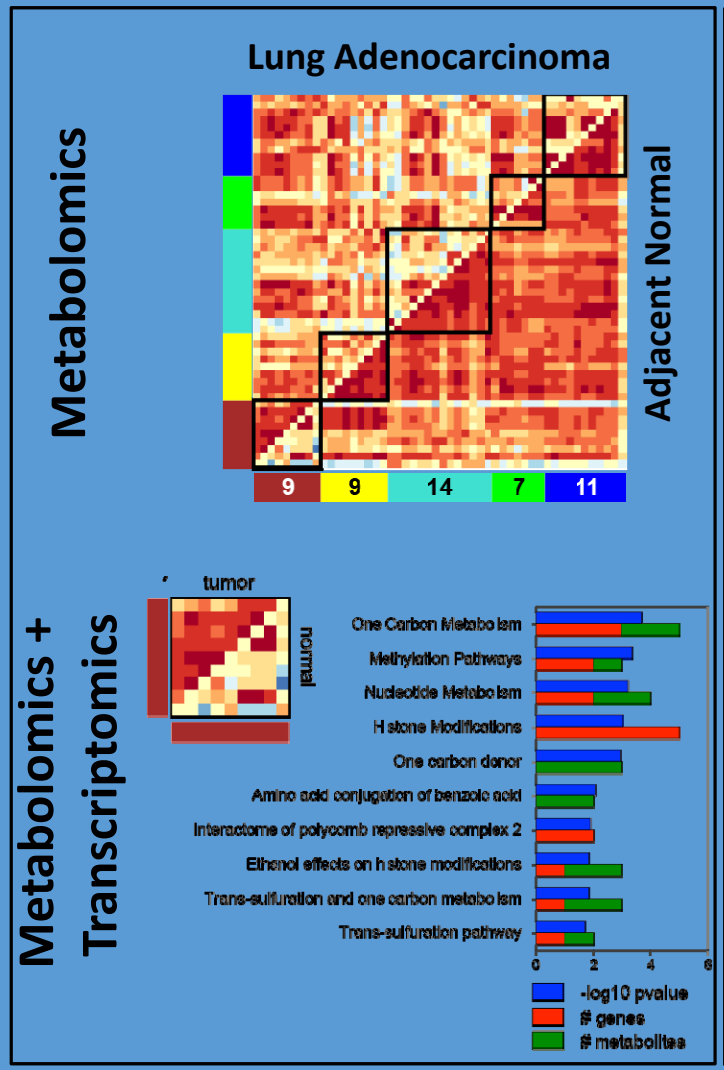
Specific Aims:

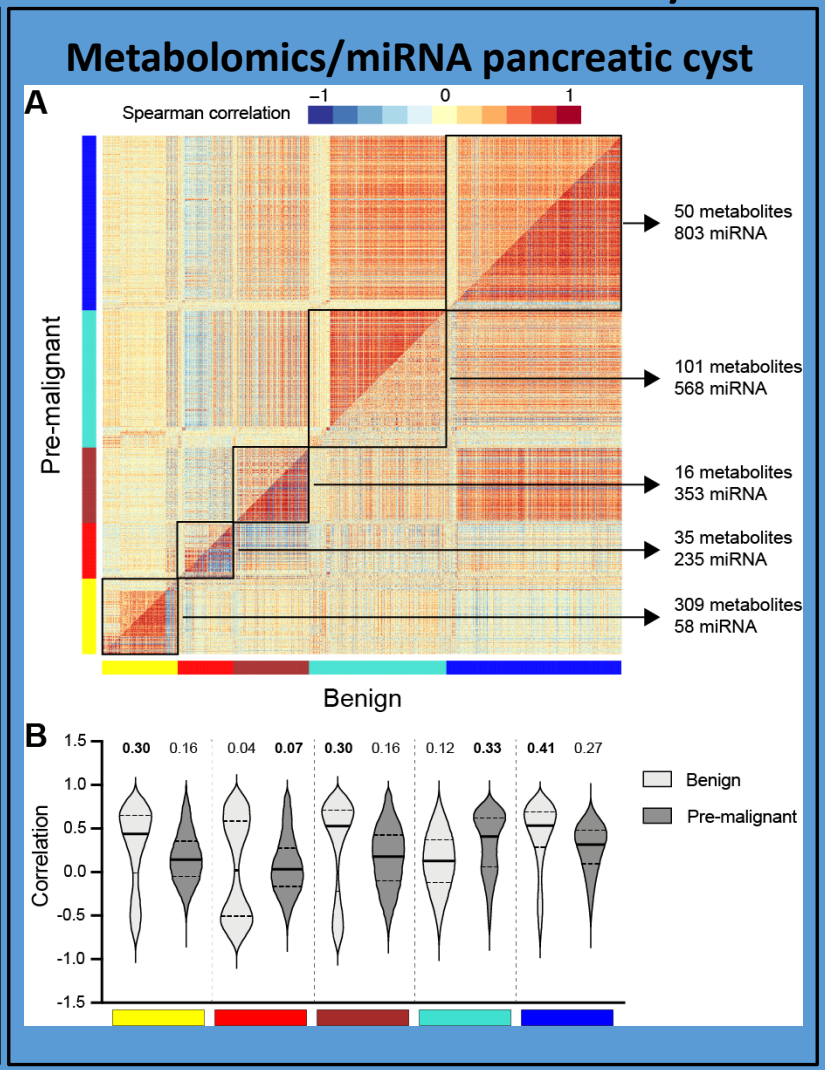
Aim 1: Promote Interdisciplinary Approaches to Training
The RETCC will have the benefit of relying on strong research programs at both Baylor College of Medicine (BCM), with the Graduate School of Biomedical Sciences, and Rice University's top engineering programs, including bioengineering and environmental engineering.

Aim 2: Coordinate Training Opportunities Outside the Laboratory with the Community Engagement, Administrative, and Data Management Cores. The RETCC will work with the other cores in the SRP to provide training outside of the laboratory environment.

Aim 3: Promote Career Development Opportunities and Communicate Trainee Progress. The RETCC will also coordinate career development opportunities within the SRP, again leveraging other resources available within the Texas Medical Center.

Network based multi-omics analysis





Complex networks

- **Transcriptomics**
- **Proteomics**
- **Metabolomics**
- **Mouse phenotype data**
- **Engineering projects data**

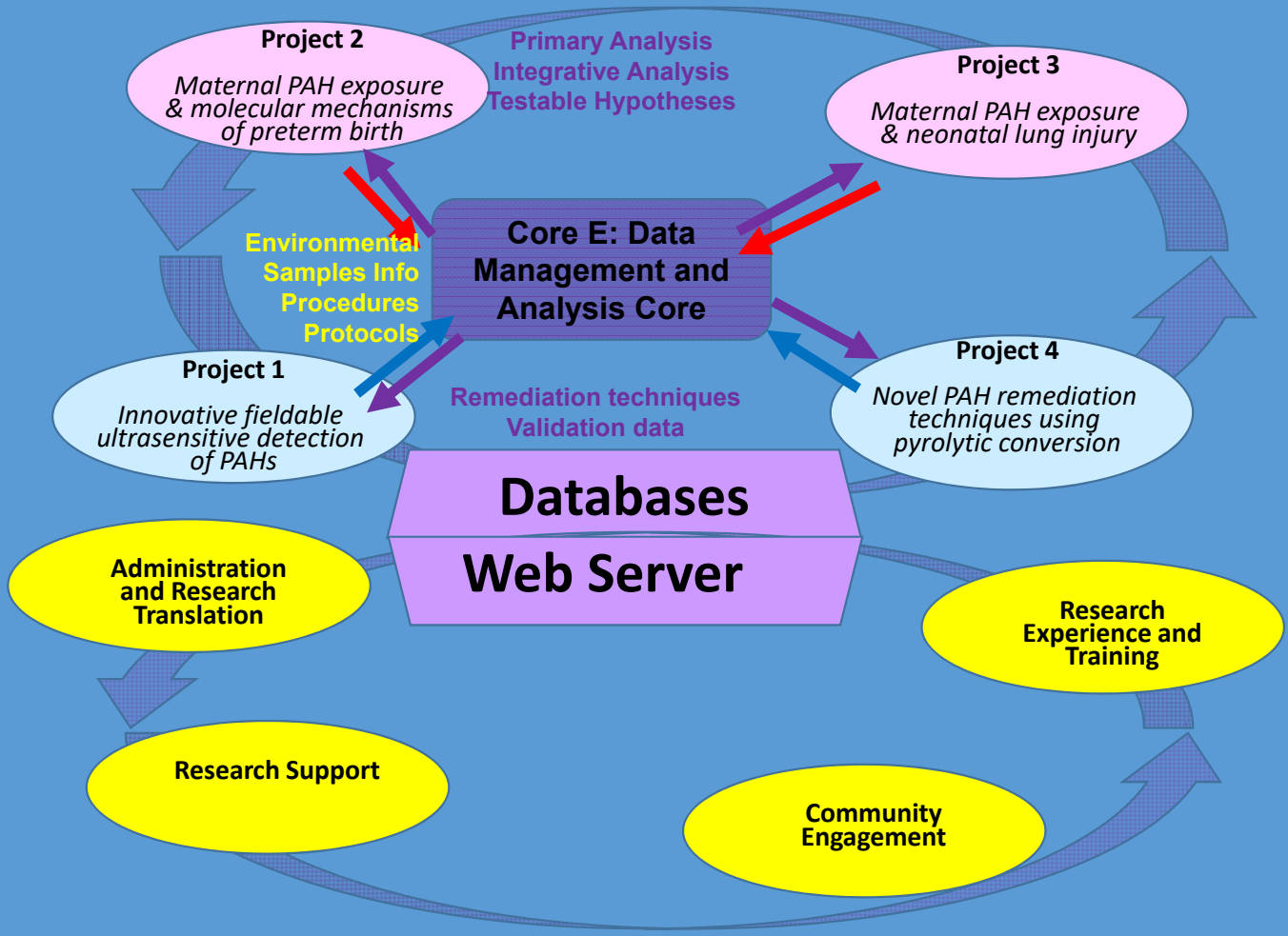
Multivariate modeling
Machine learning

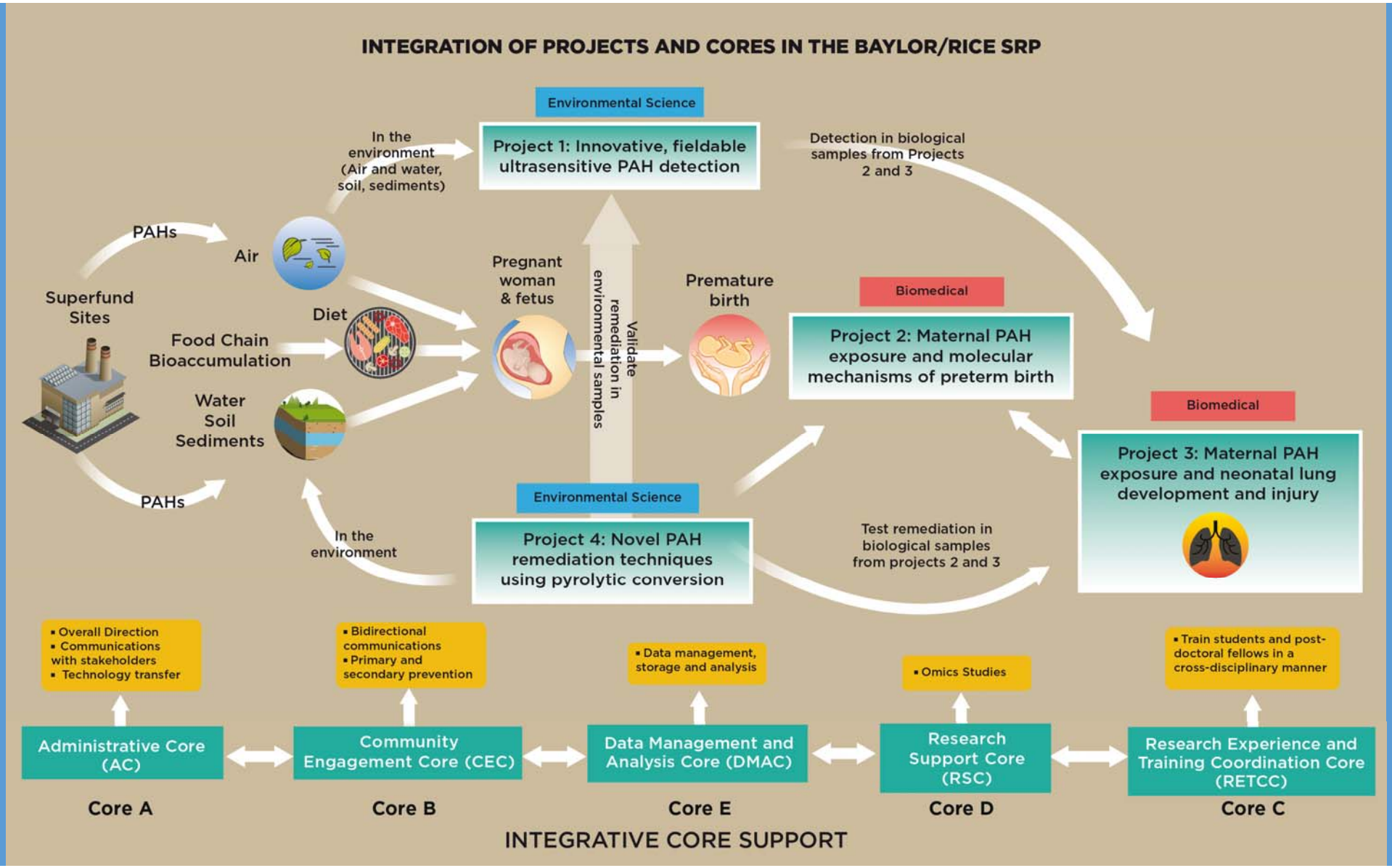
Data Management and Analysis Core

Specific Aims

1. **Implement a robust & comprehensive Data Management Plan**
2. **Provide expert analysis and consultation in the specialized areas of statistics and bioinformatics for all Projects**
3. **Conduct mission-related methods research in data management and data analysis**
4. **Assist with statistical and bioinformatics education**

Diagram of SRP Data Management Plan




INTEGRATION OF PROJECTS AND CORES IN THE BAYLOR/RICE SRP
Environmental Science
Project 1: Innovative, fieldable ultrasensitive PAH detection
In the environment (Air and water, soil, sediments)
Detection in biological samples from Projects 2 and 3
PAHs
Air
Superfund Sites
Diet
Food Chain Bioaccumulation
Water
Soil
Sediments
PAHs
Pregnant woman & fetus
Validate remediation in environmental samples
Premature birth
Biomedical
Project 2: Maternal PAH exposure and molecular mechanisms of preterm birth
Biomedical
Project 3: Maternal PAH exposure and neonatal lung development and injury
Environmental Science
Project 4: Novel PAH remediation techniques using pyrolytic conversion
In the environment
Test remediation in biological samples from projects 2 and 3
▪ Overall Direction
▪ Communications with stakeholders
▪ Technology transfer
▪ Bidirectional communications
▪ Primary and secondary prevention
▪ Data management, storage and analysis
▪ Omics Studies
▪ Train students and post-doctoral fellows in a cross-disciplinary manner
Administrative Core (AC)
Community Engagement Core (CEC)
Data Management and Analysis Core (DMAC)
Research Support Core (RSC)
Research Experience and Training Coordination Core (RETCC)
Core A
Core B
Core E
Core D
Core C
INTEGRATIVE CORE SUPPORT

Acknowledgements

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- **Baylor College of Medicine**
- **Texas Children's Hospital**

- **Key personnel and trainees**
- **Emily Pedraza**