



Pediatric Research Institute (PRI)

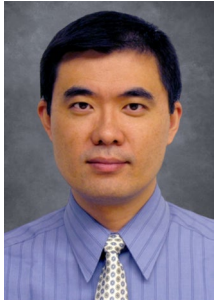
**Lu Cai, MD, PhD
Director**

September 12, 2022

Purposes

- Brief introduction of the PRI
- Can PRI's research impact the reputation of UofL, the Department and Norton Children's?
- What types collaborative opportunities can the PRI, provide the pediatric faculty?

Primary faculty



**Jun
Cai,**
MD,
PhD

- Neuron-glia communication in neurodevelopmental disorders, neonatal opioid withdrawal syndrome, traumatic injury, and neurodegenerative diseases
- Pediatric brain tumors
- Obesity-related brain pathogenesis
- Environmental metal neurotoxicity



**Lu
Cai**
MD,
PhD

- Mechanisms and innovative therapies to prevent **diabetic complications**
- Trace elemental nutrition
- Environmental impact on children's health
- Radiation biology



**Evelyne
Gozal,**
PhD

- Developmental consequences of intermittent hypoxia on CNS maturation and cell survival.
- Neurovascular Signaling in Autism Spectrum Disorders
- Endothelial dysfunction in systemic and neuro-inflammatory disease



**Yi
Tan,**
PhD

- The role of SDF-1/CXCR4/CXCR7 axes in diabetic complications.
- The role of FGFs (e.g.: FGF1, FGF5, FGF6, FGF14, FGF16, FGF21, etc.) in diabetic complications.
- Anti-oxidative mechanisms of metallothionein and Nrf2 in diabetic complications.



**John
Wise, Jr.**
PhD

- Neurotoxicology of heavy metals (hexavalent chromium, cadmium)
- Interaction of neurotoxicology and age
- Role(s) of heavy metals as gerontogens
- Environmental toxicology of heavy metals in wildlife populations
- Interactions between DNA damage responses and protein quality control pathways

Primary faculty



Jun Cai,
MD, PhD

Project 1 - Molecular targets for therapeutic intervention in rotational acceleration-deceleration neonatal brain injury (NIH NS098170, KSCHIRT, and NeuroCure Foundation/ongoing)

Collaborators: Drs. **Christopher Shields** (Norton Neuroscience Institute) and **Thomas Moriarty** (Norton Children's Neuroscience Institute)

Project 2 - Glial dyshomeostasis and therapeutic interventions in the demyelination diseases (e.g. MS)

Collaborators: Drs. **Christopher Shields** (Norton Neuroscience Institute) and **Greg Barnes** (Norton Children's Neuroscience Institute/UofL Autism Center)

Project 3 – Synergic effects of cadmium exposure and diet-induced obesity on brain impairments and autism-associated behaviors (NIH ES030283 - UofL CIEHS Pilot Grant/ongoing).

Collaborators: Drs. **Greg Barnes** (Norton Children's Neuroscience Institute/UofL Autism Center) and **Lu Cai** (PRI)

Project 4 – Sleep disordered breathing during pregnancy, white matter deficits, and neurodevelopmental disorders in offspring (NIH RR017702 - UofL COBRE Subproject).

Collaborators: Drs. **Greg Barnes** (Norton Children's Neuroscience Institute/UofL Autism Center) and **Evelyne Gozal** (PRI)

Project 5- Targeting Pediatric High-Grade Glioma with Combination Anti-Metabolic and Cellular Therapies (Kentucky PCRTF/ongoing)

Collaborators: Drs. **William T. Tse**, **Michael Huang**, **Ashok Raj** (Norton Children's Cancer Institute/UofL Pediatrics), and **Lu Cai** (PRI)

Project 6 - White matter deficits and myelin plasticity in neonatal opioid withdrawal syndrome

Collaborators: Dr. **Lori Ann Devlin-Phinney** (Norton Children's Hospital/UofL Pediatrics).

Primary faculty



Lu Cai

MD, PhD

Professor

Trace elemental nutrition
Environmental impact on
children's health

On-going

NIH/HLBI, 1R01HL125877 (Yi Tan, PI)

Role: Co-I

05/2017 – 02/2023 (NCE)

A novel mechanism of stromal cell derived factor 1 (SDF-1) protection of diabetic cardiomyopathy.

NIH/HLBI, R01HL160927 (Yi Tan, PI)

Role: Co-I

12/01/2021 – 11/30/2026

Fibroblast growth factor 1 prevents hyperlipidemia and atherosclerosis.

NIH R21 (John Wise Jr., PI)

Role: Co-I

09/16/2021 – 09/15/2023

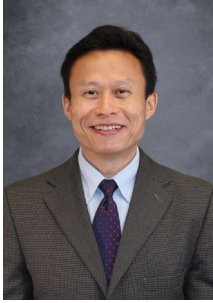
Cr(VI)-Induced DNA Damage Contributes to Brain Aging

NIH P30 ES030283 (Christopher States, PI)

Roles:

07/01/2020 – 06/30/2025

- 1) Leader for Multi-Organs Toxicology Research Interesting group;
- 2) Shared Resource Director of Environmental metals, at the Integrated Toxicomics & Environmental Measurement Facility Core (ITEMFC), UofL CIEHS.
- 3) Co-I (Jun Cai, PI for the 1-year pilot grant, 05/01/2021 – 10/31/2022), *“Disruption of β -catenin destruction complex and ASD-like behaviors in whole- life cadmium exposure and postnatal obesity”*



Yi Tan,
PhD

On-going

NIH/HLBI, **R01HL125877**

Role: PI

05/2017 – 02/2023 (NCE)

A novel mechanism of stromal cell derived factor 1 (SDF-1) protection of diabetic cardiomyopathy.

NIH/HLBI, **R01HL160927**

Role: PI

1

2/01/2021 – 11/30/2026

Fibroblast growth factor 1 prevents hyperlipidemia and atherosclerosis.

NIH/NIDDK, **R01DK131442**

04/01/2022 – 03/31/2027

Role: Co-I (Deng, PI)

The role of neutral ceramidase in intestinal fucosylation and liver steatosis and inflammation.

Pending

NIH R01, **R01DK132163**

(04/01/2023 – 03/31/2028)

Role: PI

Dual targeting CXCR4 and CXCR7 prevents diabetic kidney disease.

R0 Percentile: **31%**;

Resubmitted on July 15, 2022

NIH/HLBI, R01

Role: Co-I (Huang, PI)

09/2022-08/2027

Preventive and therapeutic effects of Nrf2 activators on pulmonary hypertension and right ventricular dysfunction via metallothioneins.

NIH/NIDDK, U01

Role: Co-I (Watson, PI)

12/2022-11/2027

Healthy You: Kentucky Healthy Glucose in Youth Project.

NIH/HLBI, R01

Role: Co-I (Cai, PI)

04/2023-03/2028

Ignored, but very important role of RV in T1D-induced DCM.

Primary faculty



John Wise, Jr.
PhD

- **Neurotoxicology of heavy metals (hexavalent chromium, cadmium)**
- Interaction of neurotoxicology and age
- Role(s) of heavy metals as gerontogens
- Environmental toxicology of heavy metals in wildlife populations
- Interactions between DNA damage responses and protein quality control pathways

Primary faculty

On-going

NIEHS/NIA, Role: PI 09/16/21-09/15/23
Cr(VI)-Induced DNA Damage Contributes to Brain Aging
The major goals of this grant are to assess the interaction of age and hexavalent chromium toxicology.

Pending/Submitted

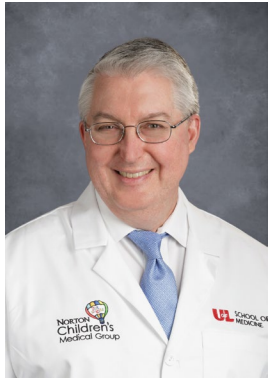
Cr(VI)-Induced DNA Damage Contributes to Brain Aging
NIEHS, Role: PI 12/01/2022 – 12/01/2027
To be reviewed 7/26/22
NIH ONES

To be submitted

NIH Katz R01: Heavy Metals and Genotoxicity Contribute to Severity of Autism Spectrum Disorder and Associated Co-Morbidities.
Role: Co-PI

Awards 2021 - 2022:

1. Term-track to Tenure-track
2. SOT MSS Bruce Fowler Young Investigator Award
3. Symposium Chair at ISTERH/ICTEM
4. 2022 EMGS New Investigator Travel Award
5. 2023 Symposium Chair at SOT
6. Invited Manuscript Submission to Frontiers in Aging Neuroscience



Greg Barnes, M.D., Ph.D.

- Genomics, Neuron-glia communication and neuro-inflammation in neuro-developmental disorders
- Diagnostic AI in Autism Spectrum Disorder
- Neurovascular Signaling in Autism Spectrum Disorders
- Environmental neurotoxicity in ASD



William T. Tse, MD

- Stem cell transplant and cellular therapy for pediatric cancers
- Translational collaboration with PRI faculty



Kupper Wintergerst, MD

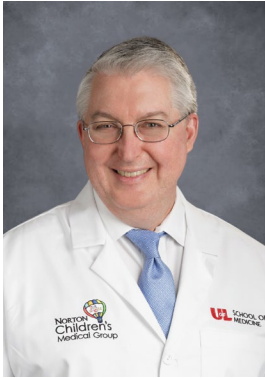
Professor of Pediatrics
 Chief, Division of Pediatric Endocrinology
 Director, TrialNet Diabetes Studies
 Co-Director, Children's Metabolic Bone Center



Sara Watson, MD

Associate Professor of Pediatrics
 Division of Pediatric Endocrinology

Secondary faculty



Greg Barnes, M.D., Ph.D.

- Genomics, Neuron-glia communication and neuro-inflammation in neuro-developmental disorders
- Diagnostic AI in Autism Spectrum Disorder
- Neurovascular Signaling in Autism Spectrum Disorders
- Environmental neurotoxicity in ASD

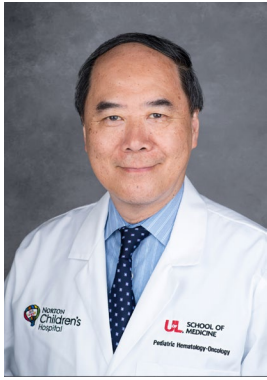
SUMMARY: Collaborating with **8** clinicians at the Norton Healthcare and 10 UL PhD faculty, **8** awarded grants (NIH, Kentucky State, HRSA, NSF, Foundation, Industry= \$8 million dollars) and **30** peer-reviewed review papers and **1** US Patent since 2016.

Scientific Positions: Executive Director, Autism Neuroscience group, Neurodevelopmental Core Director for 2 NIH grants: NIEHS ES030283 and UG1OD024954

PRI Laboratory Personnel: 1 Research Associate, 3 graduate students, 1 technician, and research-track resident(s)/clinical fellow(s)

Core Facilities:

- 1) Rodent surgical facility:
 - (i) stereotactic injection of drugs, cells, and viruses in CNS
 - (ii) rodent models of autism, epilepsy, and demyelination-remyelination
- 2) Whole rodent *in vivo* hypoxia/hyperoxia exposures or sleep deprivation: constant exposure or intermittent exposure
- 3) Rodent Neurophysiology recording set up for EEG and cell neurophysiology
- 4) Rodent neurobehaviors (w/Dr. Jun Cai) and nerve conduction:
 - (i) Neurocognition, anxiety-like behavior, depression, social interaction, and motor and sensory functions
 - (ii) Motor evoked potentials and somatosensory evoked potentials



William T. Tse, MD

Joanna Mroczkowska,
PhD

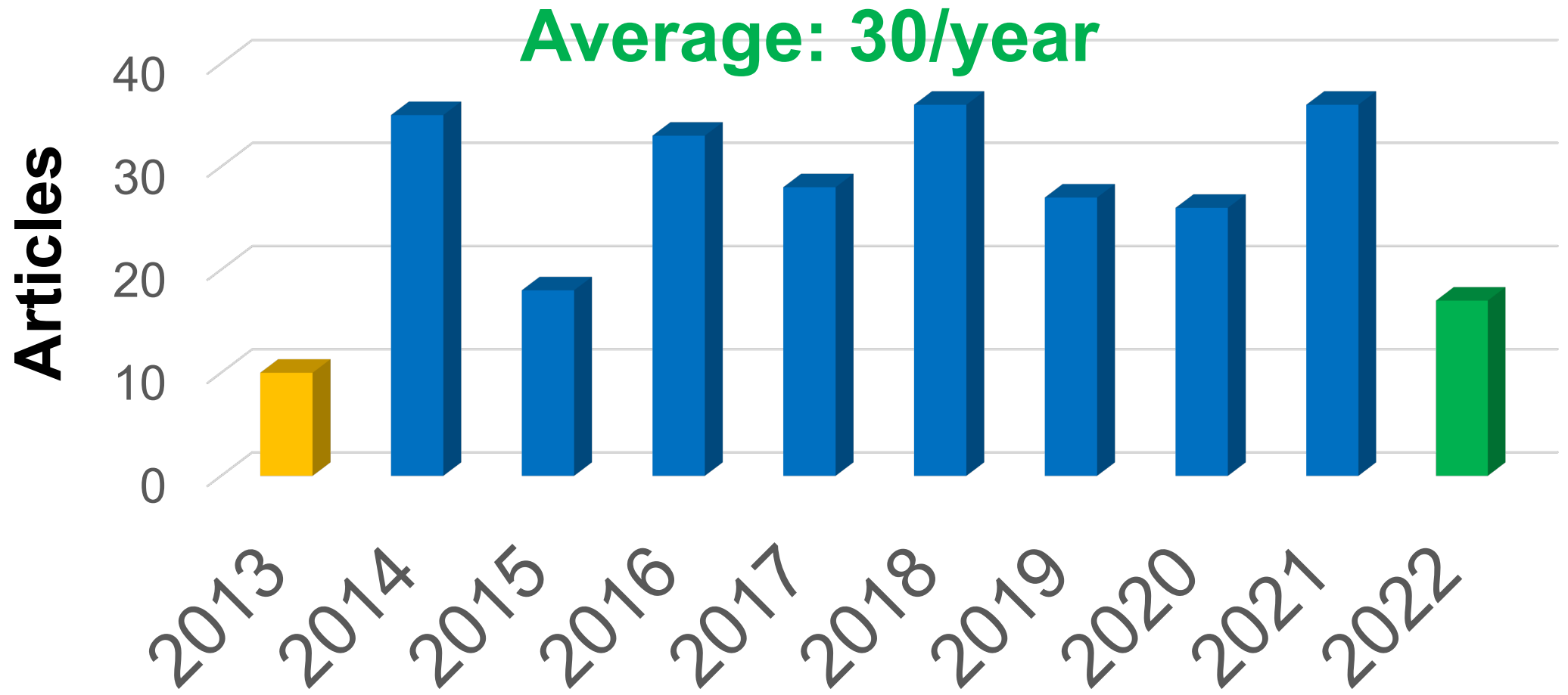
Baxter I, Rm: 219, PRI



Secondary faculty

- (1) Characterize the **phenotypic heterogeneity** of human **Chimeric Antigen Receptor T cells** (CAR-T cells) and identify the phenotype that associates with **enhanced anti-tumor functionality** and **long-term persistence**
- (2) Using the new technology of **multiplex immunofluorescence imaging**, characterize the **tumor immune microenvironment** (TIME) surrounding **pediatric solid tumors** and correlate the composition and distribution of tumor-infiltrating immune cells with **clinical outcomes**
- (3) By **genomic editing** techniques, develop **dual-specificity, universal-donor CAR-T cells** that replace the α and β chains of T cell receptors with CAR chains against two tumor markers and test the enhanced effectiveness of the cells in **eliminating pediatric solid tumors**

PRI Faculty Publications per year (past 10 years)



Did these research activities
contribute to UofL, Dept. of
Pediatrics and Norton Children's
Hospital's reputation ?

UNIVERSITY OF
LOUISVILLE.

Center for Integrative Environn

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Life Style Factors

Socioeconomic

Diet

Smoking

Alcohol, etc.

Exposure to Pollutants

Metals

VOCs

PCBs

POPs, etc.

Life Stage

Genetics

Gender

Multi-Organ Toxicology

Neurodevelopmental Toxicology

Cancer

Genome Transcriptome
UofL Genomics and
UofL DNA Facilities

Proteome
UofL Core and Clinical
Proteomics Labs

Environmental Metals
UofL Wise and
Cai Labs

Metabolome
UofL CREAM,
Center for Regulatory
and Environmental
Analytical
Metabolomics

Microbiome
UofL Functional
Microbiomics Core
Facility

Exposure Assessment
UofL Inhalation
Facility and *Diabetes
& Obesity Center*
Bioanalytical Core

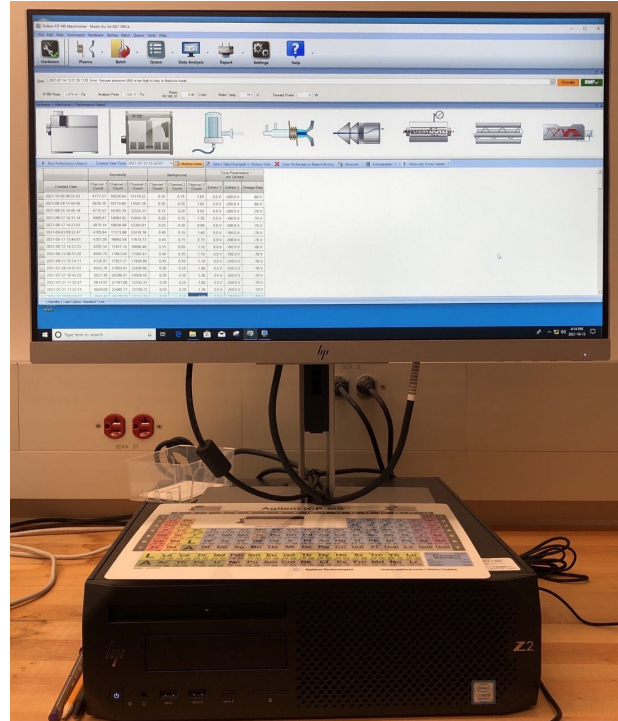
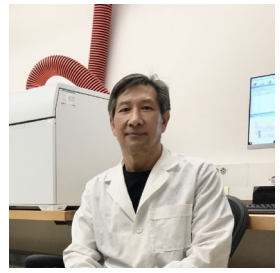
Omics & Exposure Facility Core (OEFC)

Figure 1. OEFC integration within the University of Louisville (UofL) shared resource facility environment

DEPARTMENT OF PEDIATRICS

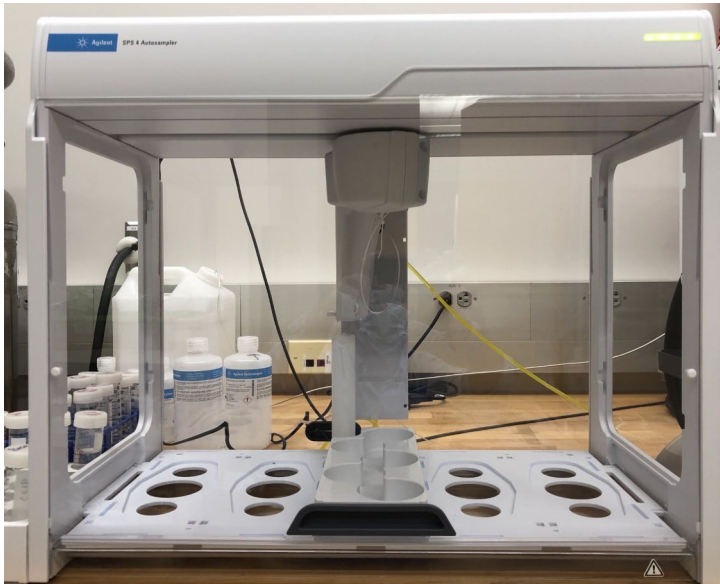
U of L SCHOOL OF
MEDICINE

ICP-MS, led by Drs. Lu Cai/Jason Xu



Work Station

Only one in
campus



Advantages for metal assay by ICP-MS:

- **Extremely high sensitivity:** detect low as to ppt level
- **Wide elemental coverage:** almost all elements except several gas, up to **30 metals assay one time**
- **Short acquisition time:** full mass acquisition in less than 5 minutes
- **Few interference:** gas background
- **Small sample amount:** less than 5 mg or 50 ul sample (tissues, fluids, cells, plants, soil... ..)
- **Simple sample preparation:** acid digestion, dilution and assay.

The Art of Translational Research - *collaboration*

Lu Cai, MD, PhD
Professor – Pediatrics,
Radiation Oncology,
Pharmacology & Toxicology
Director, Pediatric
Research Institute

Kupper Wintergerst, MD
Professor, Chief –
Pediatric Endocrinology
Director – Wendy Novak
Diabetes Center



Jun Cai, MD, PhD
Associate Professor –
Pediatrics,
Pharm & Toxicology
Pediatric Research Institute

Lori Devlin, DO, MHA, MS
Professor, Neonatal Medicine

1. **Norton Children's Neuroscience Institute:** Christopher Shields /Thomas Moriarty,
 - 1) *NIH NS098170/completed, KSCHIRT/completed, & NeuroCure Foundation/ongoing,*
 - 2) *NIH R01 application is scheduled for submission. 14 peer-reviewed papers.*
2. **Norton Children's Neuroscience Institute/UofL Autism Center:** **Greg Barnes**,
 - 1) *NIH ES030283 - UofL CIEHS Pilot Grant/ongoing,*
 - 2) *NIH R01 application is scheduled for submission.*
 - 3) *7 peer-reviewed papers.*
3. **Norton Children's Cancer Institute/UofL Pediatrics:** **Drs. William T. Tse**, Michael Huang, Ashok Raj
 - 1) *Project from Kentucky PCRTF/ongoing*
 - 2) *Under review*

Expertise in Diabetic Cardiomyopathies: Worldwide

Based on [2,631 eligible articles](#) published [since 2012](#)

Expertise for each place or person. Longer is better. For example, [Lu Cai](#) equates to the top-rated expert in [Diabetic Cardiomyopathies](#) in the world during the



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- [Jilin University](#)
- [INSERM France](#) [C](#)
- [Johns Hopkins University](#)
- [University of Louisville](#)
- [Ministry of Education China](#) [C](#)
- [St. Michael's Hospital](#)
- [University of Alberta](#)
- [Monash University](#)
- [People's Liberation Army](#) [C](#)

Expert

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- [Cai, Lu](#)
- [Ritchie, R](#)
- [Abel, E Dale](#)
- [Marwick, T H](#)
- [Packer, Milton](#)
- [Glatz, J F](#)
- [Zheng, Yang](#)
- [Delbridge, L M](#)
- [Xu, Zhe](#)
- [Rodrigues, Brian](#)
- [Diamant, M](#)
- [Tan, Yi](#)
- [Wende, Adam R](#)

Research support

NIH, R01, R21

**National Science Foundations
(NSF)**

Department of Defense

Foundations

- Am Diabetes Association
- Am Heart Association
- Juvenile Diabetes Res. Foundation
- Neuronal Research Societies

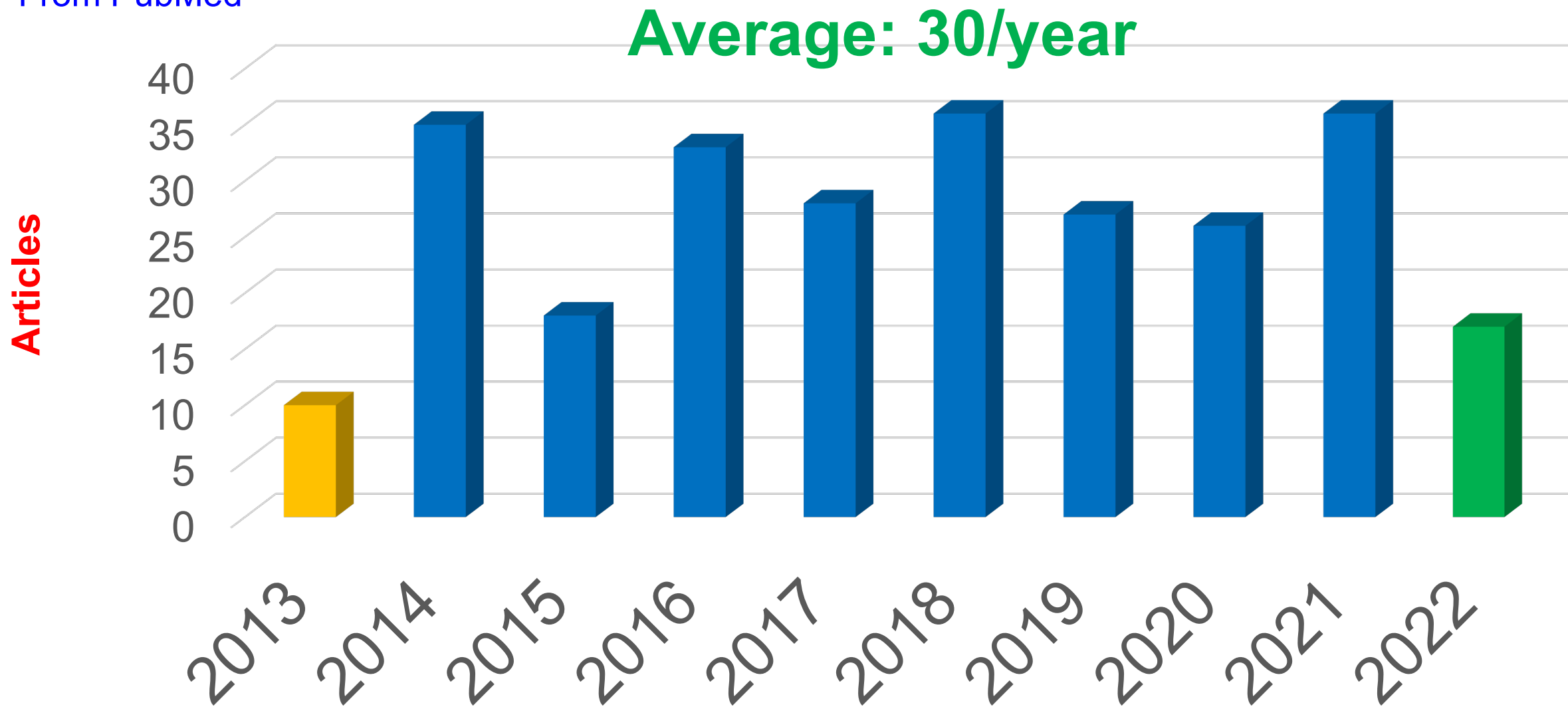
Kentucky State

Department/Norton Hospital

How do these PI's
excellent works
contribute to the
recognition and the
reputation of PRI, the
Pediatric Department
and Norton Hospital?

PRI faculty publications/year in the past 10 years

From PubMed



Examples of Collaboration Outcomes

1. Endocrinology: Drs. Kupper Wintergerst and Sara Watson

- Zn and metals in children with diabetes, NIH U01, *Healthy You: Kentucky Healthy Glucose in Youth Project*
- **US NEWS & World Report** ranking from Top 50 to #16!

2. Norton Children's Neuroscience Institute/UofL Autism Center: Dr. Greg Barnes:

- *NIH ES030283 - UofL CIEHS Pilot Grant/ongoing,*
- *NIH R01 application is scheduled for submission.*
- *7 peer-reviewed papers.*

3. Norton Children's Cancer Institute: Drs. William T. Tse and Ashok Raj

- One ongoing Project from Kentucky PCRTF/ongoing
- *Two PCRTF/submitting, projects by Jun Cai and Yi Tan*
- *Prenatal exposure to environmental metals may increase offspring leukemia (next) by Lu Cai*



Joint Appointment Faculty - Division of
Endocrinology



Lu Cai, MD, PhD

Professor of Pediatrics
Director, Pediatric Research Institute



Academic Phone Number: 502-852-2669 • Email Address: lu.cai@louisville.edu

Background

Dr. Cai received his MD in 1983 and Ph.D. in 1990 from Jilin University (formerly Norman Bethune University of Medical Sciences), China. He has had his postdoctoral training in the University of Western Ontario and McGill University (1993 – 1999), Canada.



Yi Tan, PhD

Associate Professor of Pediatrics
Carol B. McFerran Endowed Chair of Pediatric Diabetes Research



Academic Phone Number: 502-852-2654 • Email Address: yltan002@louisville.edu

Background

Dr. Tan received his PhD in Biomedical Engineering at Chongqing University, Chongqing, China in 2004. Then he became a Postdoc Fellow (2007), an Assistant Professor (2013), a tenured Associate Professor (2019), and an Endowed Chair (2020) in Departments of Pediatrics, Pharmacology and Toxicology, University of Louisville School of Medicine.

Expertise in Diabetic Cardiomyopathies: Lu Cai

Based on [42 eligible articles](#) published [since 2012](#)

[What is "eligible"?](#)

EXPERTISE LEVEL The expertise of Lu Cai ranks in the ...

- **Top 0.0079%**

AFFILIATION TIMELINE

Click  for institutional directory in table below. (Not always available.)

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Location			👤 Expert	2022	2021		2020		2019		2018		2017		2016		2015		2014		2013		2012	
Yearly article counts					0	3		2		4		3		5		5		2		9		4		1
📍	🏠	University of Louisville	🔍 📞 📁			3	0	2	0	4	0	3	0	5	0	4	0	2	0	8	1	1	0	
📍	🏠	Wenzhou Medical University	🔍 📁									2	0	1	0									
📍		Miscellaneous institutions in Wenzhou	🔍 📁									1	0											
📍	🏠	Jilin University	🔍 📁											2	0			1	0			3		1



Country

Includes continents

— Worldwide
— USA

Region

Includes US states, etc.

— US Eastern Zone
— US Central Zone
— Kentucky

City

Includes metro areas

— Louisville

Institution

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— University of Louisville
— Norton Children's Hospital

Expert

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— Cai, Lu
— Xu, Zhe
— Tan, Yi

Mechanisms
preclinical
Tan Y, Zhang
Nat Rev Cardiol
PMID: 32080

Impact factor

Nature: 69

Science: 63

Nat Rev Card: 49

102 citations

DEPARTMENT OF PEDIATRICS



82ND SCIENTIFIC SESSIONS

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Be sure to check this site for even more session coverage from the 82nd Scientific Sessions throughout the summer. The site will be updated weekly through August 2022.

June 5, 2022 | 6:45PM - 9:00PM CDT | Hilton New Orleans Riverside, Grand Ballroom A&B

 **A Modern Landscape of Non-Insulin Type 2 Diabetes Therapies**

W-0746 US DEL-909/04/2022 © Lilly USA, LLC 2022. All rights reserved.



Jean Frias, MD, FACE David Kruger, MD, MPH, BC-ADM John Anderson, MD

Cardiologists will provide 'map' for understanding, managing diabetic cardiomyopathy

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Cardiomyopathy is a familiar yet underappreciated complication of diabetes. Up to 35% of type 2 diabetes patients and about 14.5% of type 1 diabetes patients have some form of cardiac dysfunction, and the risk of cardiomyopathy rises as glycemic control fails.

"Diabetic cardiomyopathy is underappreciated in the clinic because it's so difficult to find pure diabetic cardiomyopathy not associated with other cardiovascular disease such as coronary artery disease, significant valvular disease, hypertension, or other cardiac diseases," said Yi Tan, PhD, Associate Professor of Pediatrics, Pharmacology and Toxicology, and the Carol B. McFerran Chair in Pediatric Diabetes Research at the University of Louisville Pediatric Research Institute.

Dr. Tan will review the latest research on the mechanisms that underlie the development of diabetic cardiomyopathy during the symposium [Diabetes with Cardiomyopathy—Does Anybody](#)



Yi Tan, PhD

Now cleared in the US

FreeStyle Libre 3 

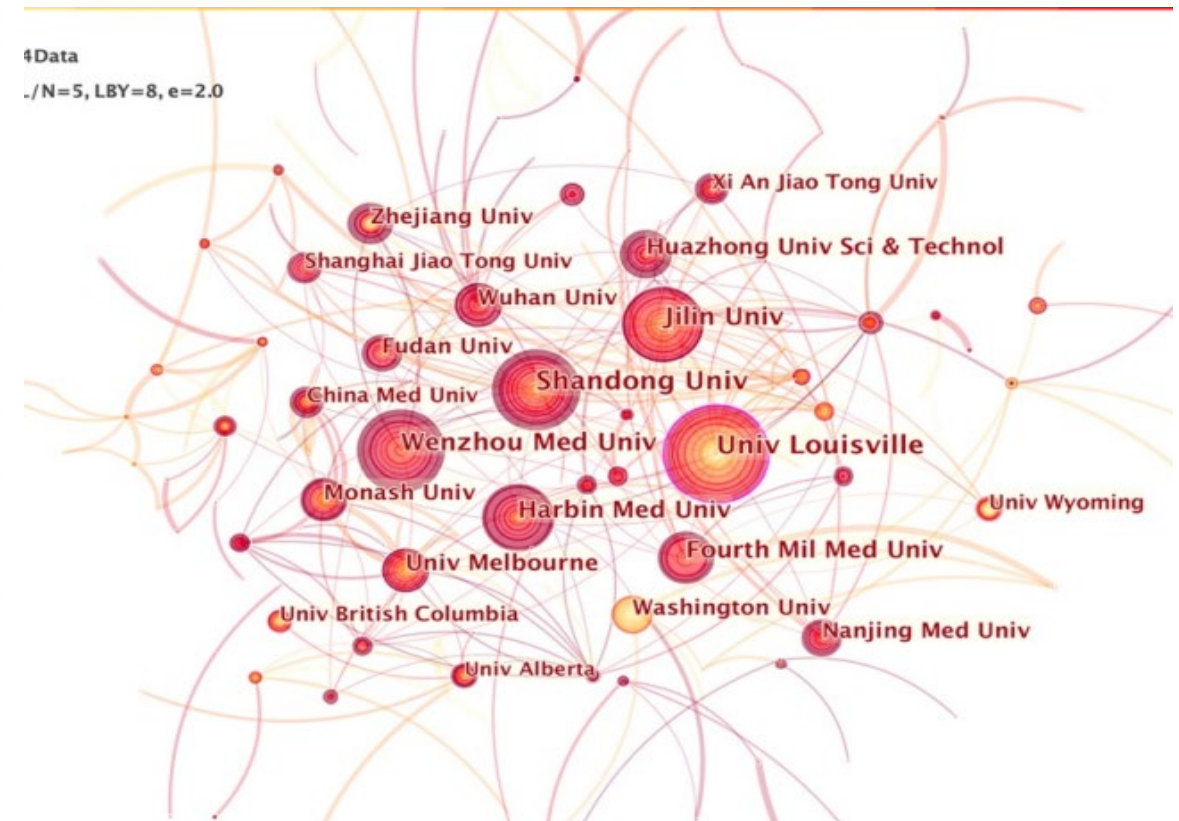
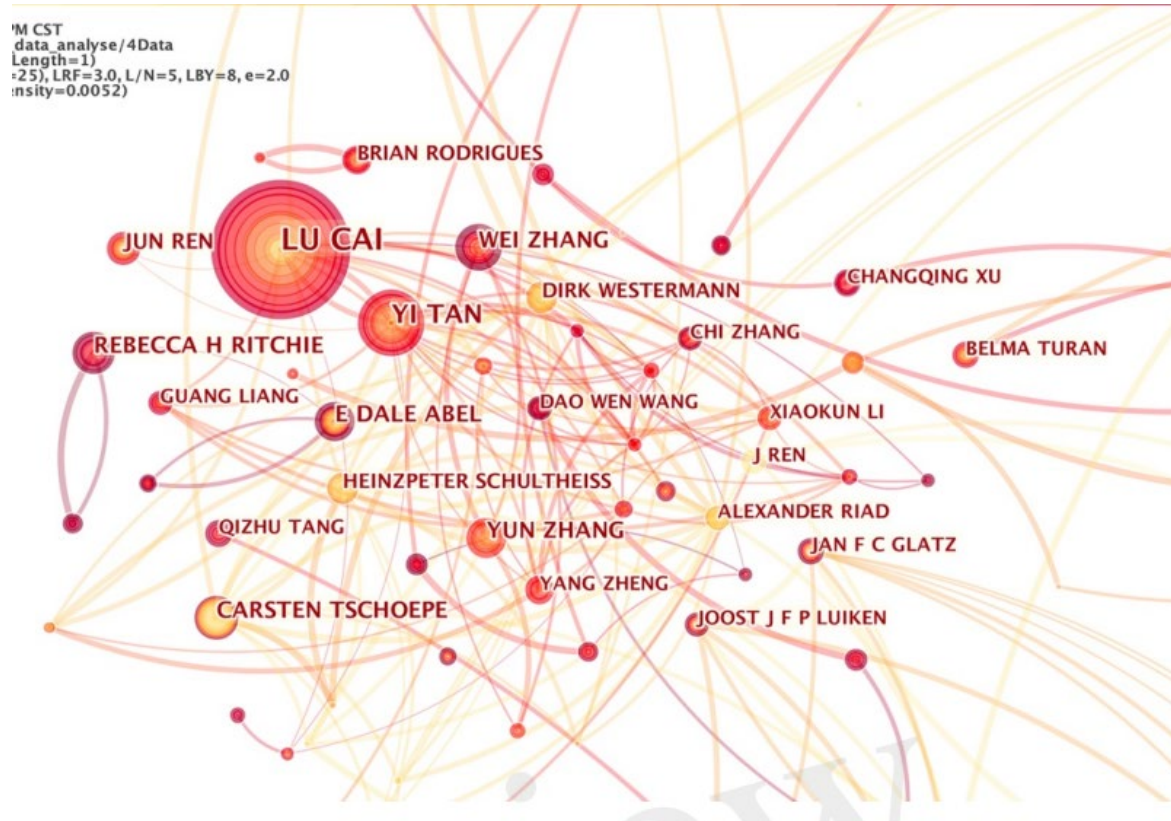
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LifeScan

The FreeStyle Libre 3 system is indicated for use in people with diabetes age 18 and older.
IMPORTANT SAFETY INFORMATION
Failure to use FreeStyle Libre 3 system as instructed in label may result in erroneous glucose low



A total of 4000 words, 7 figures, and 5 tables are included in this manuscript.

Knowledge Domain and Emerging Trends in Diabetic Cardiomyopathy: A Scientometric Review Based on CiteSpace Analysis



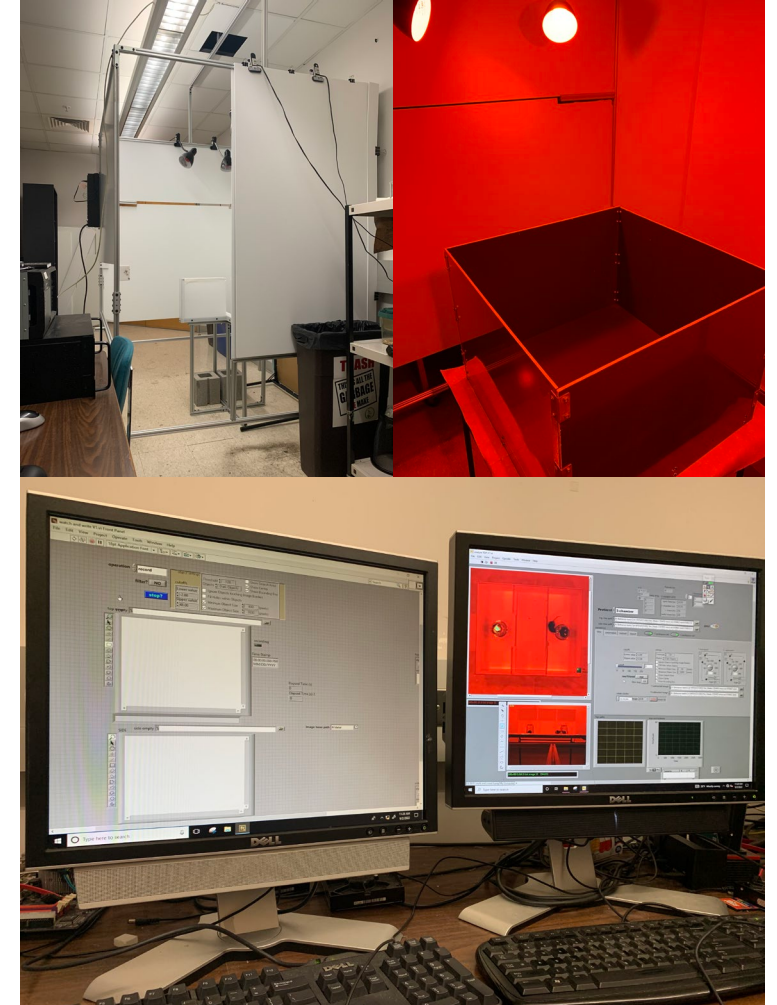
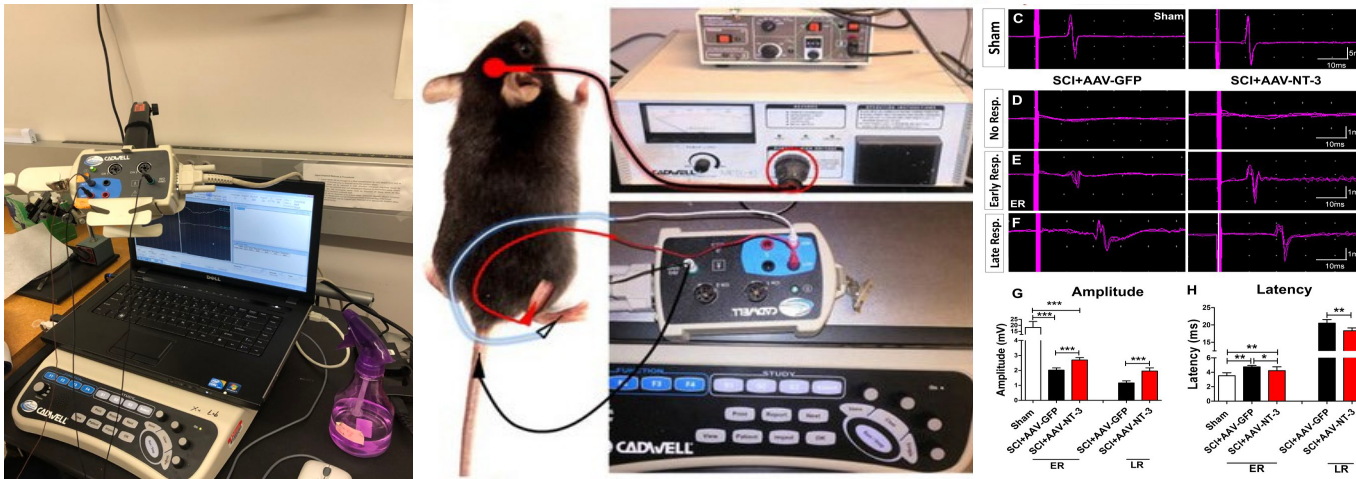
More translational collaboration with clinical groups

Are there any such opportunities?

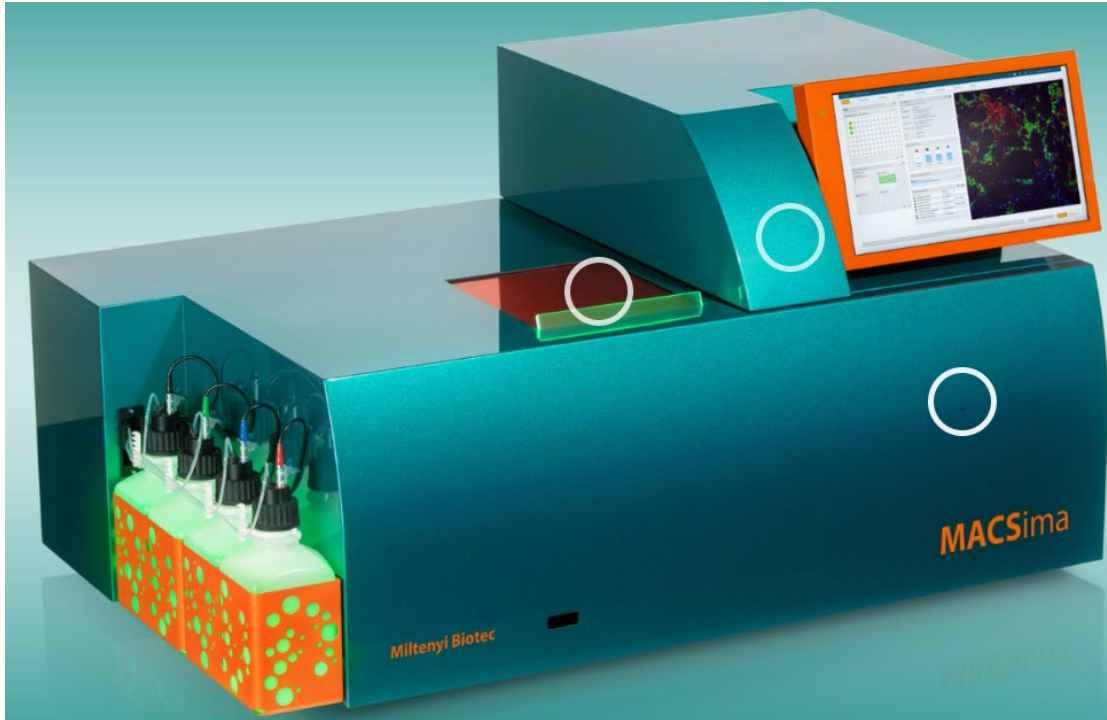
Core Facility, led by Dr. Barnes

Rodent neurobehaviors and nerve conduction:

- (i) neurocognition, anxiety-like behavior, depression, social interaction, and motor and sensory functions
- (ii) motor evoked potentials and somatosensory evoked potentials

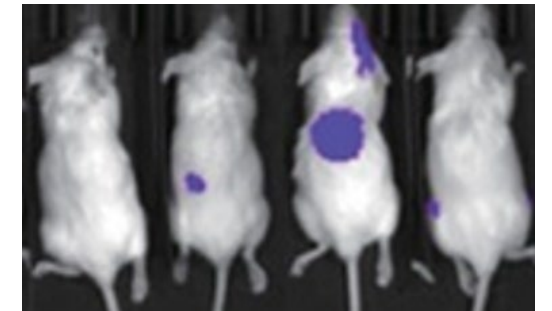


Multiplex Imaging Cores, led by Dr. Tse



The MACSima™ Imaging Platform

- Using a broad spectrum of recombinant ready-to-use antibodies
- Able to analyze hundreds of markers on a single sample
- **Multiple samples at a time,**
- **Various kinds of samples:** tissue slides, cell suspensions, cultured slides (dishes)



University of Louisville P30 grant , NIEHS

Center for Integrative Environmental Health Sciences

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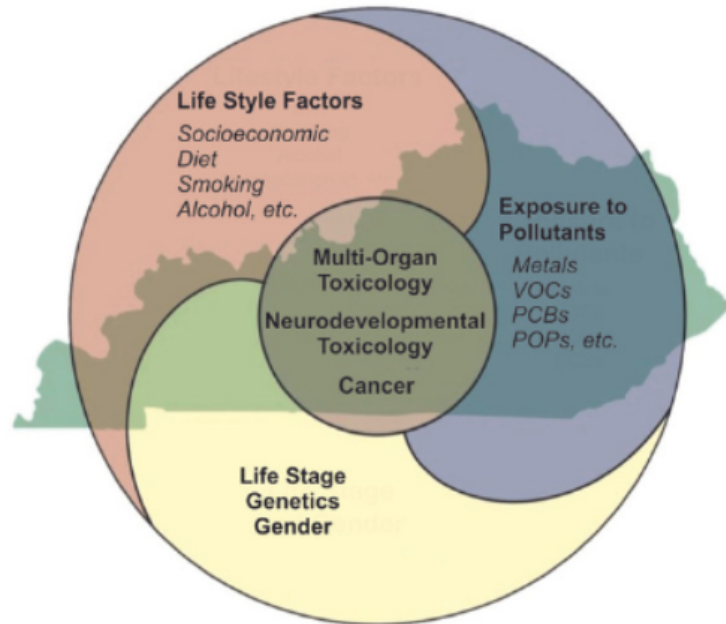
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**Congratulations
to the 2022
Pilot Project Awardees!**

2022 PPP Awards

Click on the photo to
view awardees.

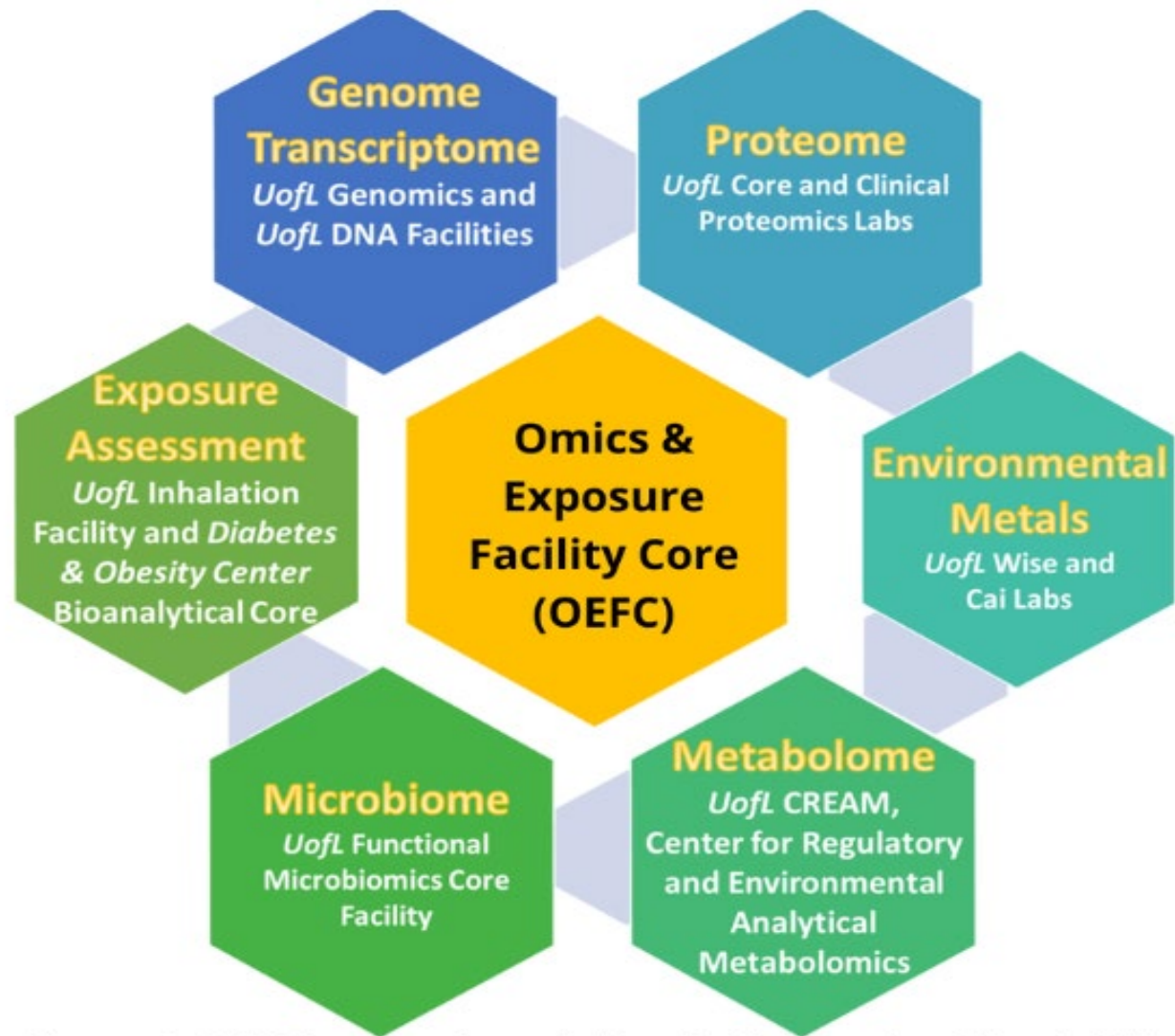


Figure 1. OEFC integration within the University of Louisville (UofL) shared resource facility environment

Examples the PRI faculty involved collaborations

Dr. Jiapeng Huang

- 1) \$1,500 award to measure metals for the serum and urine of patients with PAH and control (First year), collaborating with Lu Cai (CIEHS member)
- 2) \$5,000 for animal purchase to set up cadmium effect on the pathogenesis of PAH mouse model

Dr. Kupper Wintergerst

\$5,000 Awards to measure metal level levels in the serum of children with T1D & T2D, obtained from NIDDK, collaborating with Lu Cai (CIEHS member)

Dr. Jun Cai

Using animal model to measure brain metals and find some interesting clue, so request a pilot study (\$50,000) for defining whether metals exposure has impact leading to **autism-like diseases**, collaborating with **Dr. Greg Barnes** (CIEHS member) using neurobehavioral core

Collaborative opportunities??

YES!

***There are cores available and financial resources for you to
start collaborative work to
grow up the project!***

Thank you!!