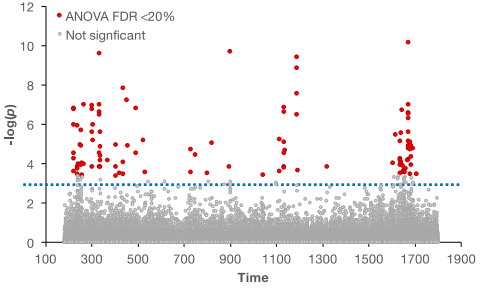
The exposome and health



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The exposome: a Wild idea

Editorial

Complementing the Genome with an ''Exposome'': The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

Christopher Paul Wild

Molecular Epidemiology Unit, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom

Defined the "*Exposome*" as all exposures from conception onwards, including those from lifestyle, diet and the environment.

A systematic, unbiased, and omic-scale examination of external factors contributing to disease or health status*

*avoid candidate gene search faults

The Nature of Nurture: Refining the Definition of the Exposome

Gary W. Miller[1] and Dean P. Jones

Rollins School of Public Health, School of Medicine, Emory University, Atlanta, Georgia 30322

The cumulative measure of environmental influences and corresponding biological responses throughout the lifespan

A strategy for exposomics

The exposome is vast. We need a suite of tools to capture the breadth of external factors that influence health: satellite imaging, wearable devices, sensors, sentinel animals, computational approaches, and analysis of biological samples.

The approach that we have taken is to use high-resolution mass spectrometry (HRMS) to extract as much data as possible out of human blood samples.

HRMS on plasma/serum provides an excellent initial scan of the exposome, capturing hundreds of exogenous chemicals/features, as well as the biological state of the individual. It can be conducted on biobanked samples, leveraging the large longitudinal studies supported by other mechanisms.

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could take

The approach that we ~~have taken~~ is to use high-resolution mass spectrometry (HRMS) to extract as much data as possible out of ~~human~~ blood samples.

Dog/Cat/Goldfish

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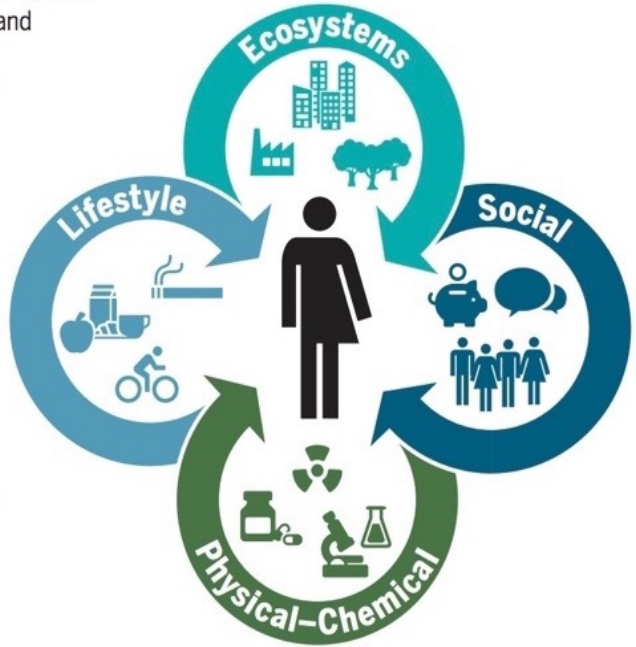
External factors → internal biological signals

Ecosystems
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

Lifestyle
Physical activity
Sleep behavior
Diet
Drug use
Smoking
Alcohol use

Social
Household income
Inequality
Social capital
Social networks
Cultural norms
Cultural capital
Psychological and mental stress



Physical–Chemical
Temperature/humidity
Electromagnetic fields
Ambient light
Odor and noise
Point, line sources, e.g. factories, ports
Outdoor and indoor air pollution
Agricultural activities, livestock
Pollen/mold/fungus
Pesticides
Fragrance products
Flame retardants (PBDEs)
Persistent organic pollutants
Plastic and plasticizers
Food contaminants
Soil contaminants
Drinking water contamination
Groundwater contamination
Surface water contamination
Occupational exposures

Vermeulen, Schymanski, Barabasi, Miller, Science, 2020

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Social
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- Inequality
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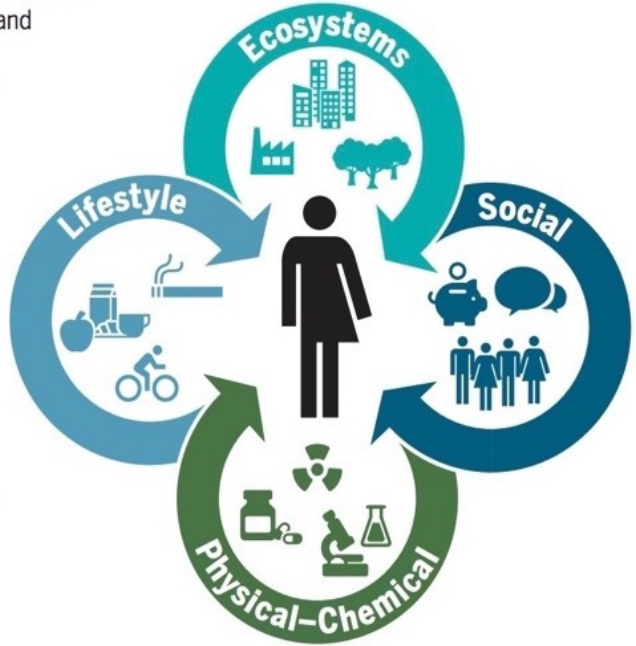
- Psychological and mental stress



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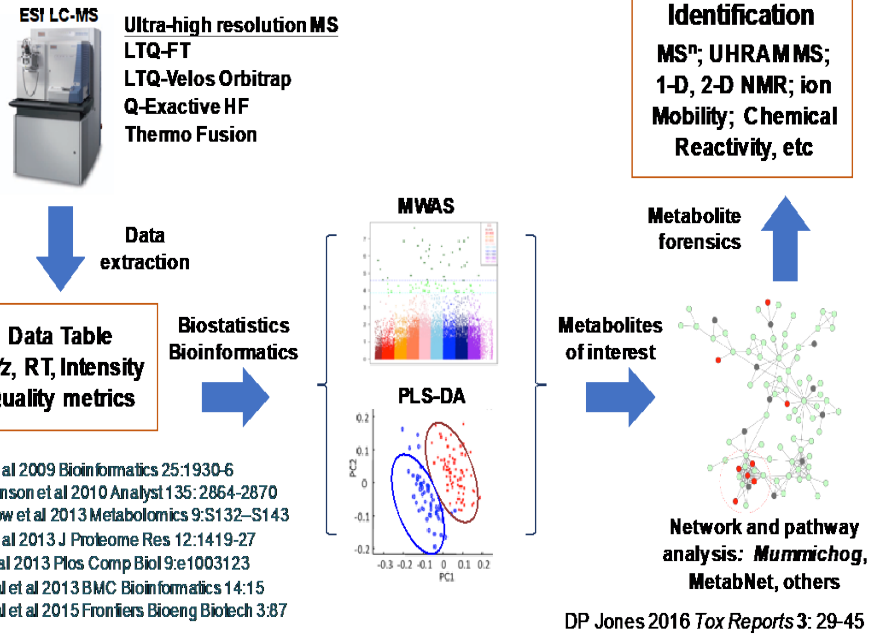
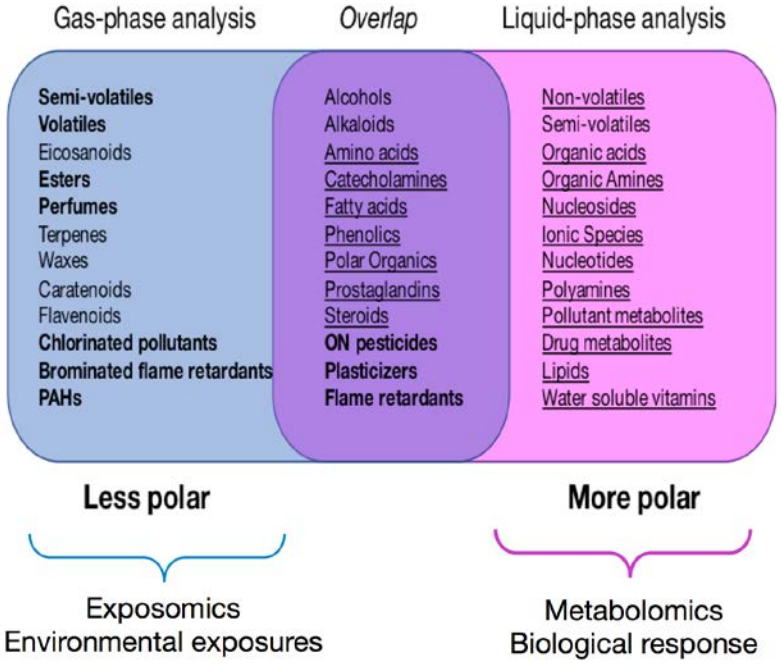
Vermeulen, Schymanski, Barabasi, Miller, Science, 2020

LC and GC based high resolution mass spectrometry to detect exogenous chemicals and endogenous metabolites



T Yu et al 2009 Bioinformatics 25:1930-6
JM Johnson et al 2010 Analyst 135: 2864-2870
Q Sotlow et al 2013 Metabolomics 9:S132–S143
T Yu et al 2013 J Proteome Res 12:1419-27
S Li et al 2013 Plos Comp Biol 9:e1003123
K Uppal et al 2013 BMC Bioinformatics 14:15
K Uppal et al 2015 Frontiers Bioeng Biotech 3:87

DP Jones 2016 *Tox Reports* 3: 29-45



Walker, Miller, Jones

Because authentic standards are rarely available for xenobiotics and their metabolites, identification relies heavily on accurate mass and RT matching with databases

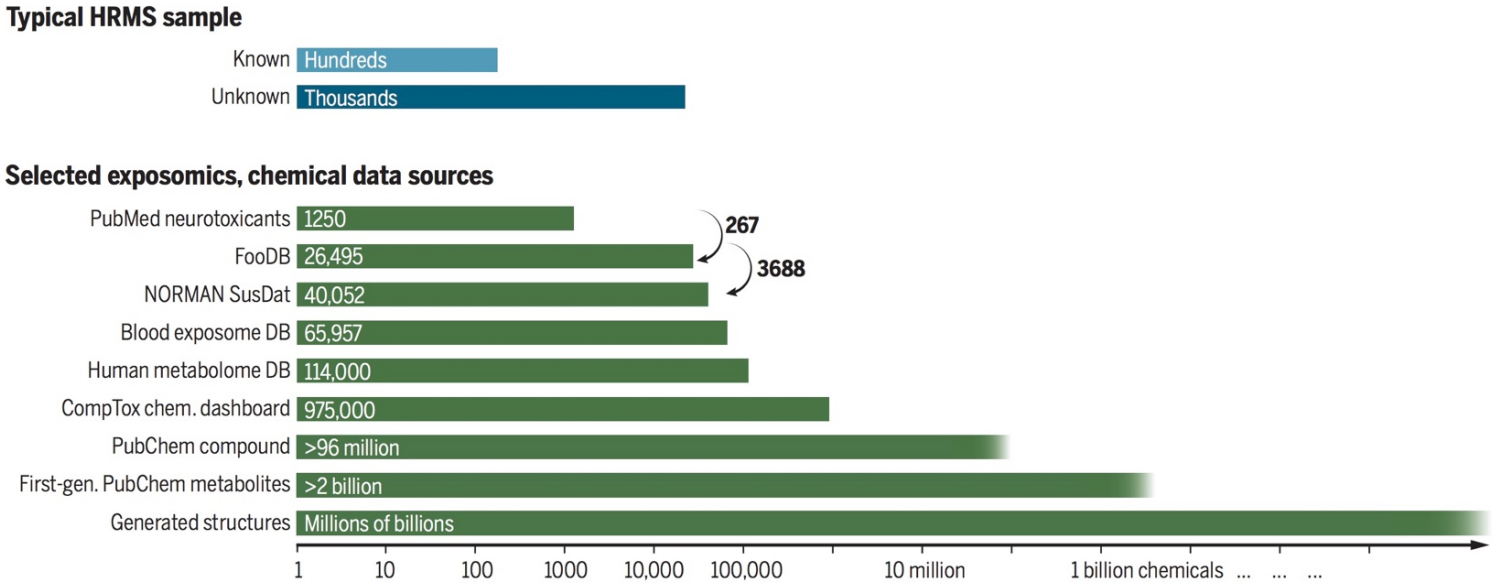
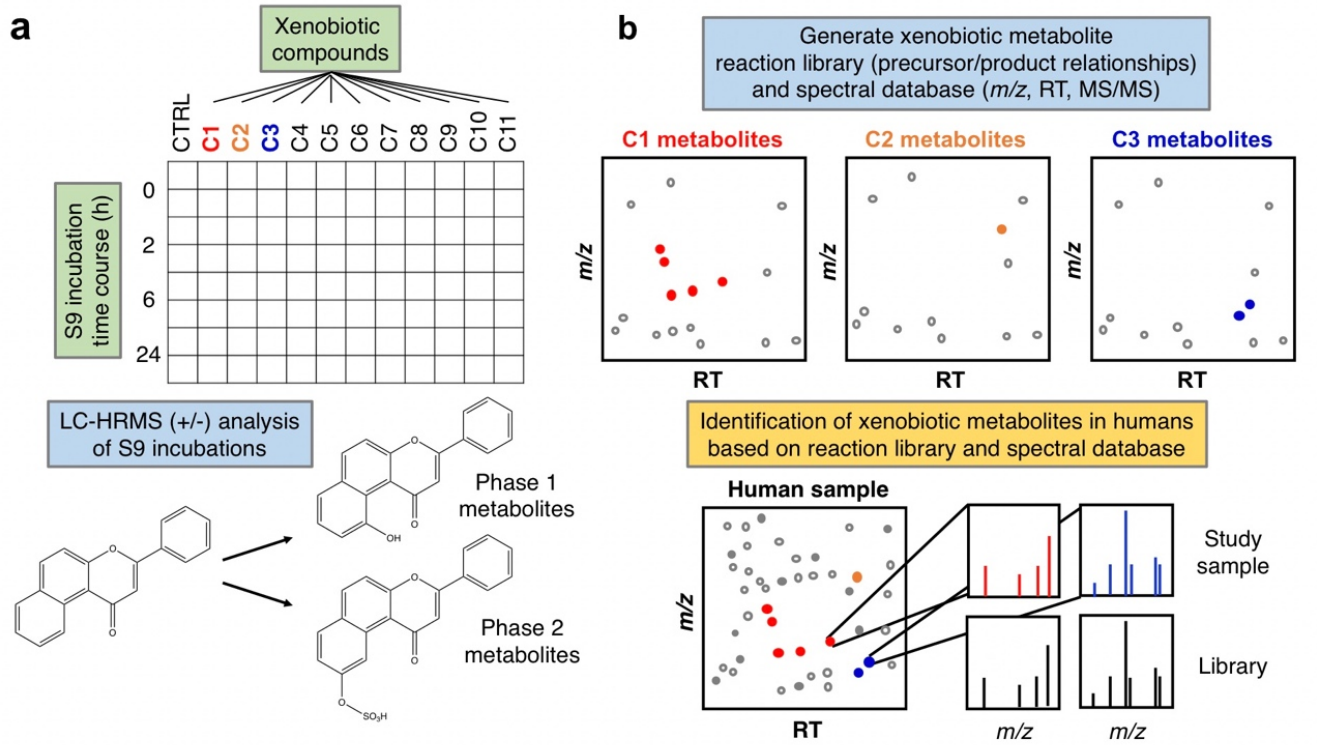


Fig. 2. Chemical complexity of HRMS and the exposome. Top: Known versus unknown features in a typical HRMS measurement [data from (*7*)]. Bottom: Selected data sources relevant to the chemical exposome (*10*–*14*, *19*). Arrows show the overlap of potential neurotoxicants in FooDB (http://foodb.ca/) and FooDB components in NORMAN SusDat (www.norman-network.com/nds/susdat/) (prioritized chemicals of environmental interest).

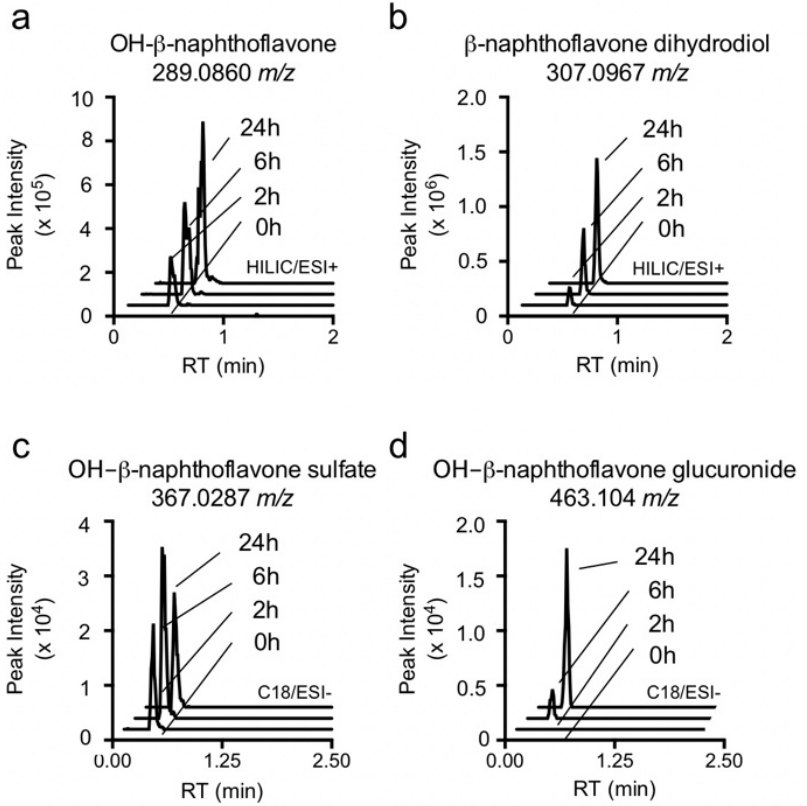
Science. 367: 392-396, 2020

Large-scale xenobiotic metabolite identification for exposomics



Liu et al., Nature Communications, 2021

Human liver S9 enzymes generate phase I and II xenobiotic metabolites in a time-dependent manner

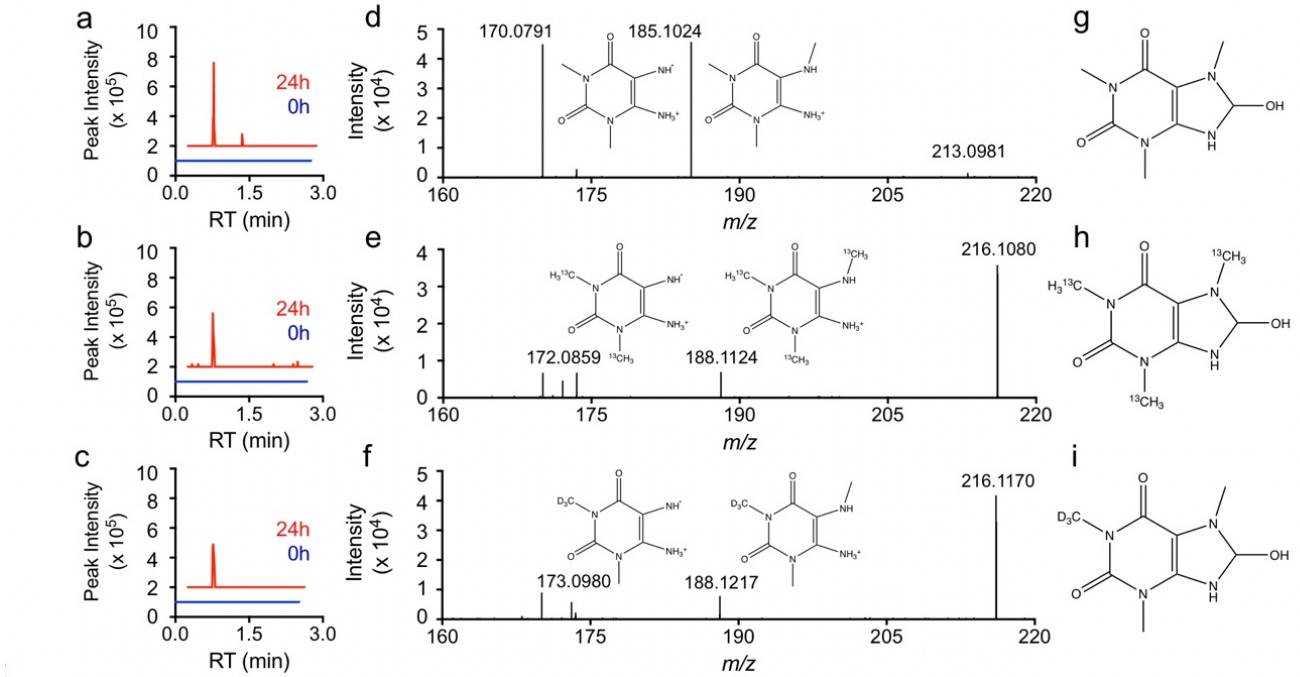


e

- + Abundance

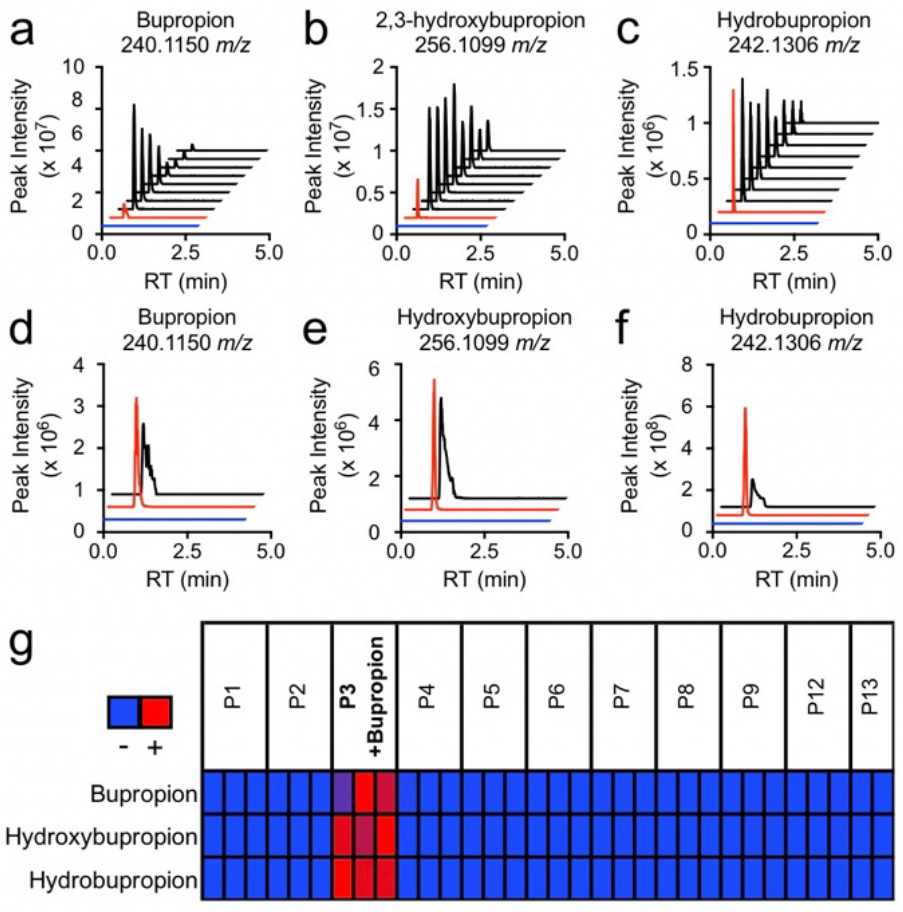
Precursor	Metabolite	0	2	6	24 h
APAP	APAP sulfate				
	OH-APAP sulfate				
	APAP-GSH				
	APAP glucuronide				
	APAP-cysteine				
	OH-APAP GSH				
β-NF	OH- β-NF				
	β-NF dihydrodiol				
	OH- β-NF glucuronide				
	OH- β-NF sulfate				
Caffeine	Paraxanthine				
Nicotine	Nornicotine				
	Nicotine glucuronide				
	Cotinine				
	OH-cotinine				
Chlorzoxazone	OH-CLZ				
	CLZ glucuronide				
	CLZ sulfate				
	OH-CLZ glucuronide				
	OH-CLZ sulfate				
Tolbutamide	OH-tolbutamide				
Bupropion	OH-bupropion				
	Hydrobupropion				
B[a]P	OH-B[a]P				
	OH-B[a]P glucuronide				
	OH-B[a]P sulfate				
Pazopanib	Demethyl pazopanib				
	OH-pazopanib				

Stable isotope-assisted unexpected metabolite identification



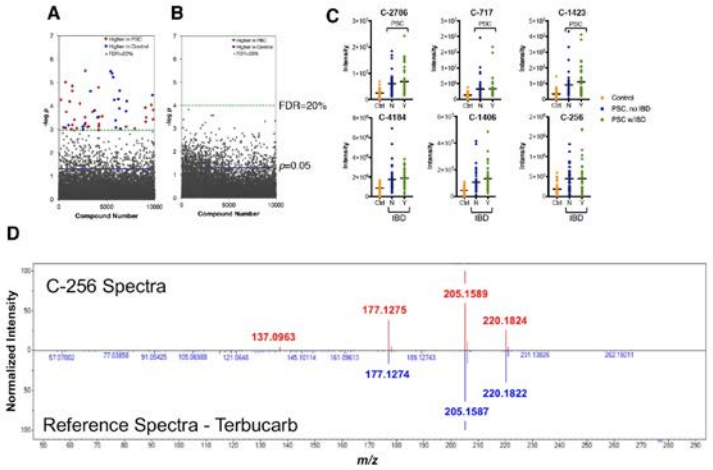
Liu et al., Nature Communications, 2021

Identification of documented xenobiotic exposure

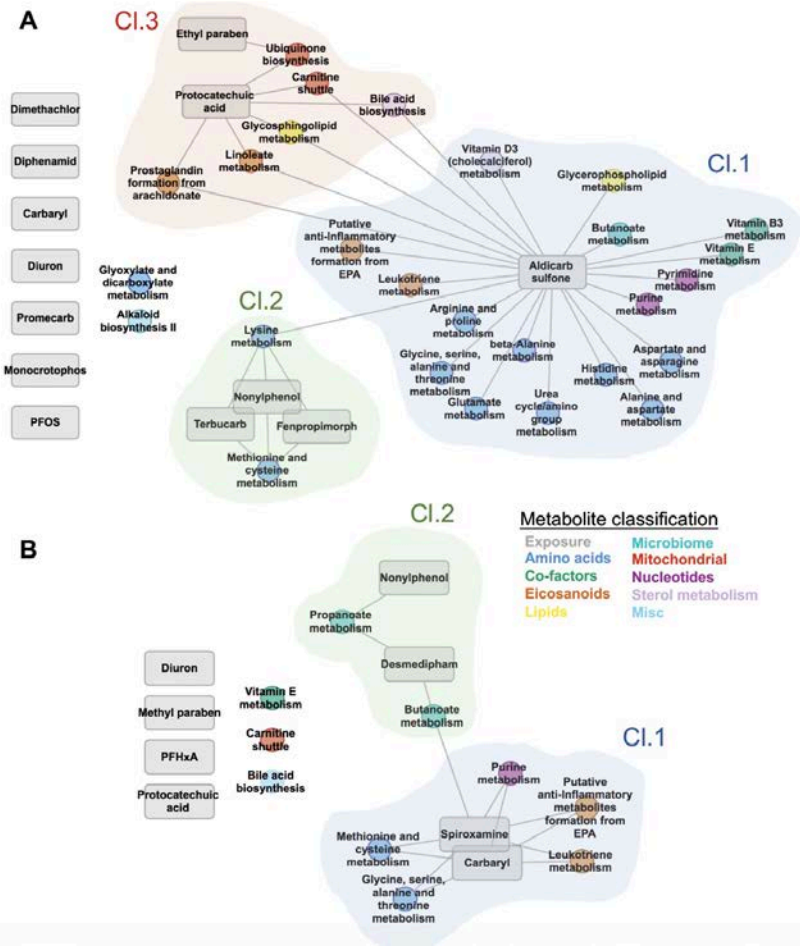


Liu et al., Nature Communications, 2021

Mayo Clinic, Emory, Columbia
Primary sclerosing cholangitis
EWAS x MWAS
*high incidence of liver cancer

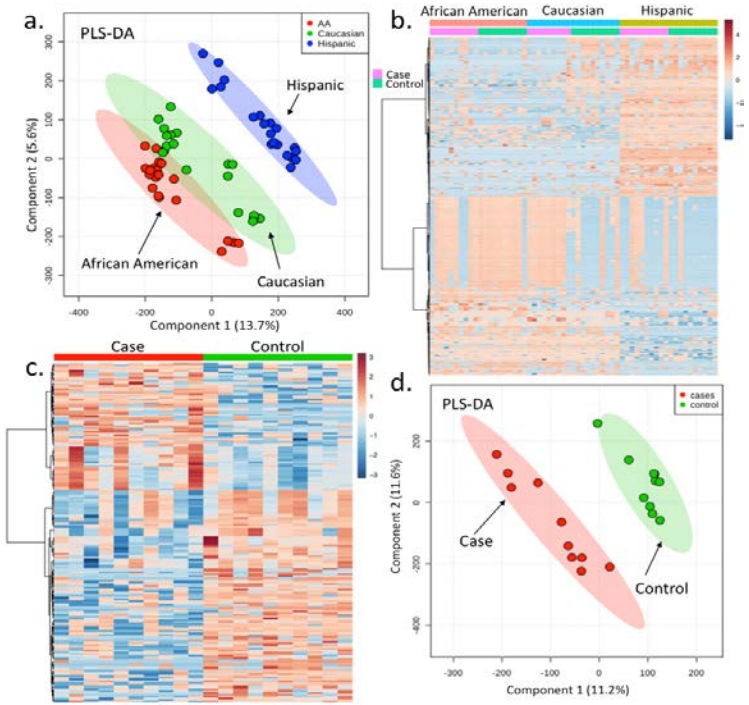


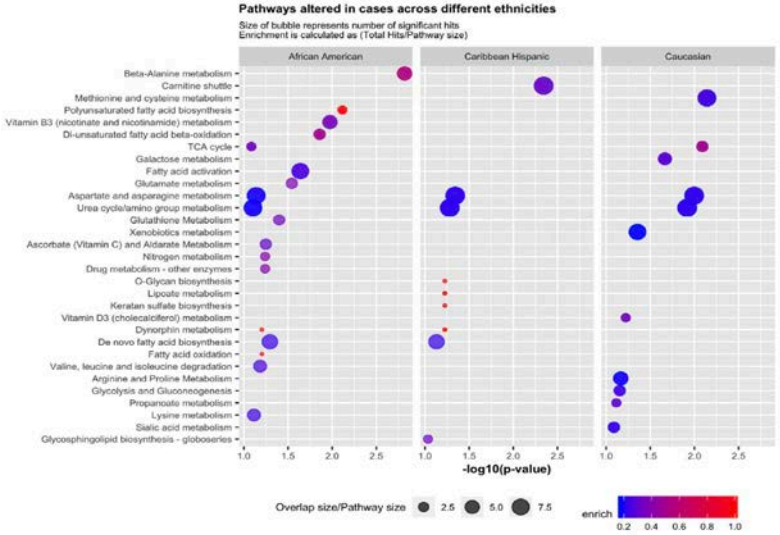
Exogenous chemicals vs. endogenous metabolites



Walker et al., Hepatology Communications, Nov, 2021

Alzheimer's disease and WHICAP





N=160

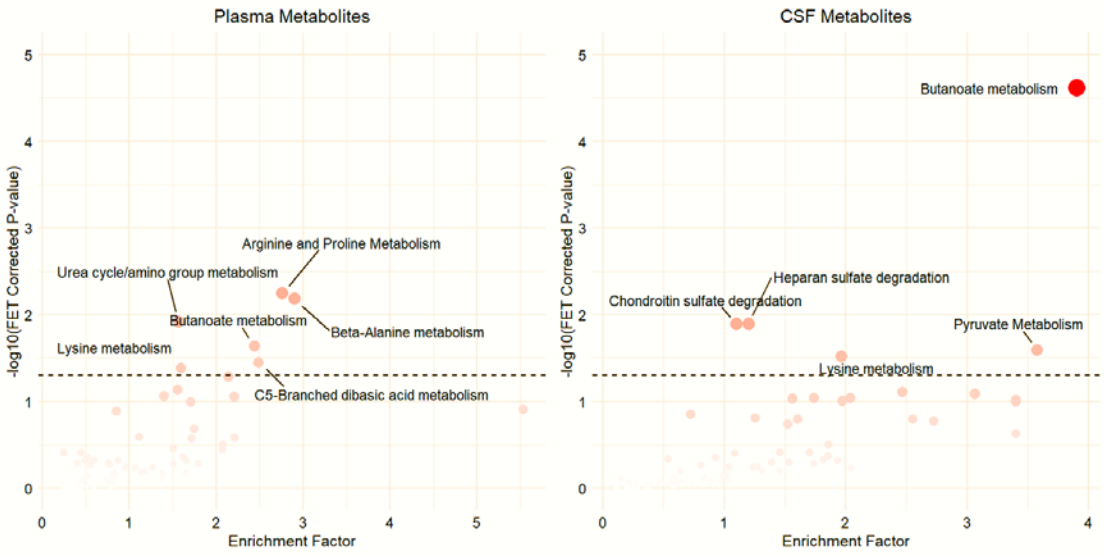
Vardarajan, Kalia, et al.
Alzheimer's Dementia, 2020
Richard Mayeux, PI

Table 2. Number of blood samples	SA1		SA 2a	All Aims
	Controls	Incident AD	Prevalent AD	Metabolomes
2 +	724	247	375	3,692
3 (or more) ++	760	529	260	4,647
Totals	1484	776	635	8,339

EFIGA Genetic epidemiology of Alzheimer's disease in Caribbean Hispanics

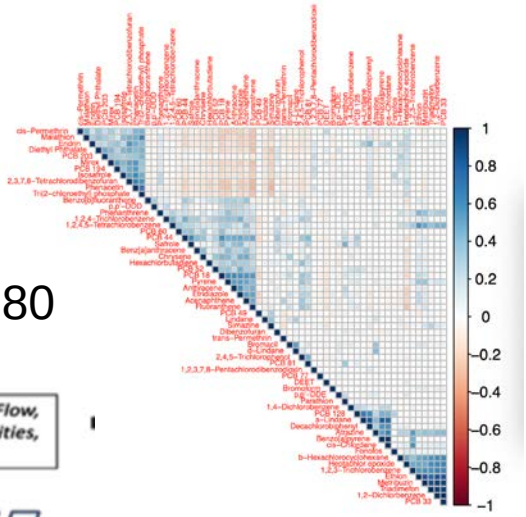
AD biomarkers: Nfl, AB40, AB42, total-Tau, pTau181, pTau 217
CSF and plasma
LC-HRMS is completed
data analysis in process
GC-HRMS pending

84 control, 33 AD (will increase 4x)



Based on observation that Caribbean Hispanics in Northern Manhattan have increased risk of AD, Richard Mayeux started EFIGA. Located in the Dominican Republic, EFIGA follows participants over time with cognitive testing, blood and CSF samples.

Exposomics of cognitive decline



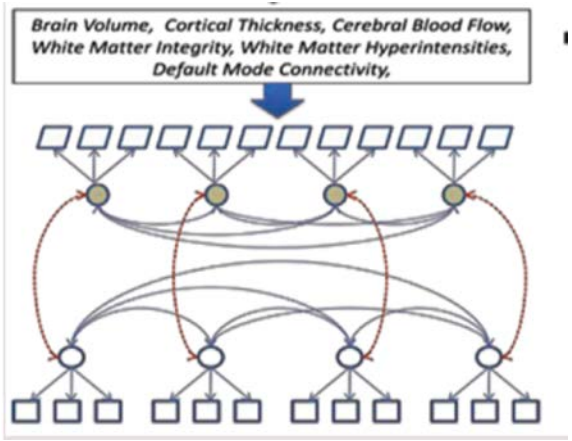
12 cognitive tasks that assess:

- episodic memory
- fluid reasoning ability
- perceptual speed
- vocabulary

fMRI imaging during tasks plasma collected at baseline and 5-yr follow up

IQ tests administered

Yaakov Stern, PI -20/group
Ages 20, 30, 40, 50, 60, 70, 80



LC-HRMS-untargeted (Kalia, Miller-Columbia)
GC-HRMS-targeted(80)/untargeted (Manz, Pennell-Brown)

Alzheimer's disease (93), Mild cognitive impairment (50), controls (59)
APOEgentoype, CSF (AB42, pTau)

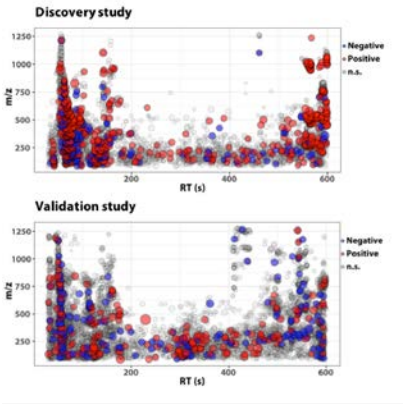


Table 4. Putative compound identification of plasma features from MWAS.

m/z	RT	Change in AD	Putative compound(s)	Predicted adduct	ID level[a]	Notes
129.0661	89	Higher	Glutamine (2 ppm)	-H_2O+H	1	--
231.1205	211	Higher	5S,6S-epoxy-15R-hydroxy-ETE (+Na, 0 ppm)	--	3	--
246.9550	127	Higher	Numerous database matches	-H_2O+H	--	Contains halogen (Cl and/or Br)
334.1410	86	Lower	Piperettine (1			--
349.1515	80	Lower	Piperine (1 ppm)	+ACN+Na	4	--
386.8946	61	Higher	1,1-Dichloro-2-(dihydroxy-4'-chlorophenyl)-2-(4'-chlorophenyl)ethylene (9 ppm)	+K	2	Contains halogen (Cl and/or Br)
662.0933	158	Higher	GDP-D-mannuronate (+ACN+H [M+1], 0 ppm); Chaetocin (-2H_2O+H [M+1], 8 ppm); Blighinone (+H [M+1], 9 ppm)	[M+1] isotope	4	--
663.4524	36	Higher	Lipid A-disaccharide-1-P (+2H, 2 ppm); Aluminium dodecanoate (+K, 2 ppm)	--	4	--

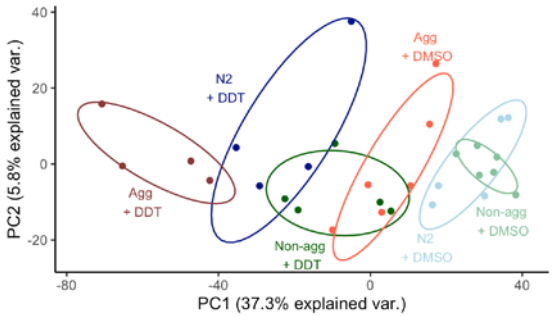
Hydroxyated metabolite of DDE

[a]ID level indicates annotation confidence: 1, *m/z* and retention time confirmed with MS^2, 2: Multiple/isotopes present; 3: *m/z* matched single adduct mass within 10 ppm mass error, 4: *m/z* matched adduct mass of multiple isobaric species, probable identifications listed.

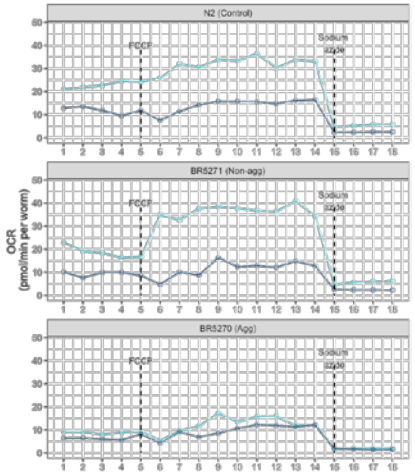
*Adduct of rivastigmine strongest feature associated with AD

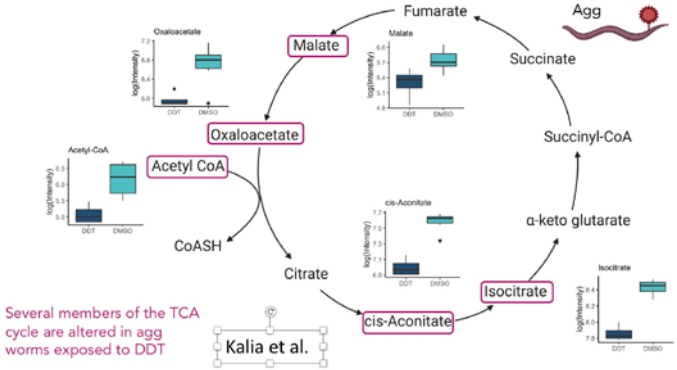
Niedzwiecki, Walker, Howell, Watts, Jones, Miller, Hu preliminary data

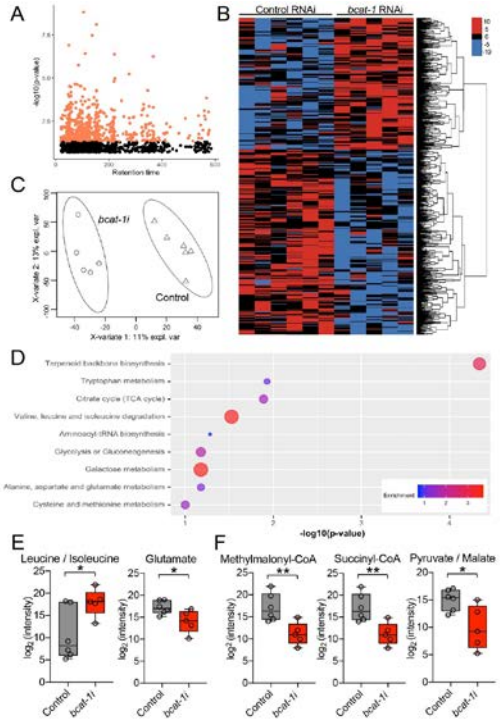
DDT, p-Tau, and metabolites in Alzheimer's



The metabolomic/ exposomic analysis works in *C. elegans*







Kalia et al., posted on bioRxiv

Mor et al., PNAS, 2020

Cross-species analysis

Worms and plasma

Annotation	*C. elegans*	Human plasma
Lipoamide	Lower (p = 0.027)	Negative (p = 0.035)
Diethylthiophosphoric acid	Lower (p = 0.044)	Negative (p = 0.015)
11, 12-dihydroxy eicosatrienoic acid	Higher (p = 0.029)	Positive (p = 0.01)
N-acetyl-lysine	Lower (p = 0.042)	Negative (p = 0.033)
Cystine	Lower (p = 0.01)	Negative (p = 0.032)

Worms and CSF

Annotation	*C. elegans*	Human CSF
Tyrosine	Lower (p = 0.046)	Negative (p = 0.039)
Carnitine	Lower (p = 0.0001)	Negative (p = 0.048)
Cystine	Lower (p = 0.011)	Negative (p = 0.031)
N,N-dimethylaniline-N-oxide	Lower (p = 0.00002)	Negative (p = 0.042)

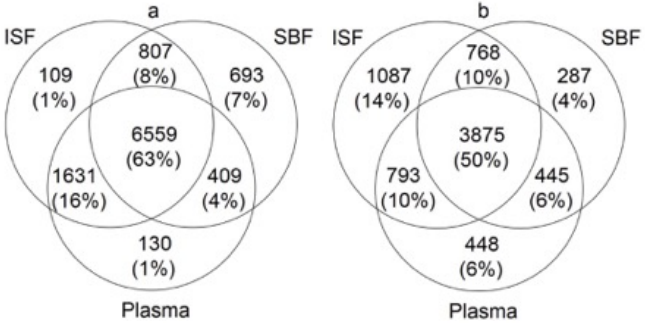
If we can perform this analysis between humans and *C. elegans*, an organism with only 959 cells in its entire body, the comparison from humans to dogs is undoubtedly feasible.

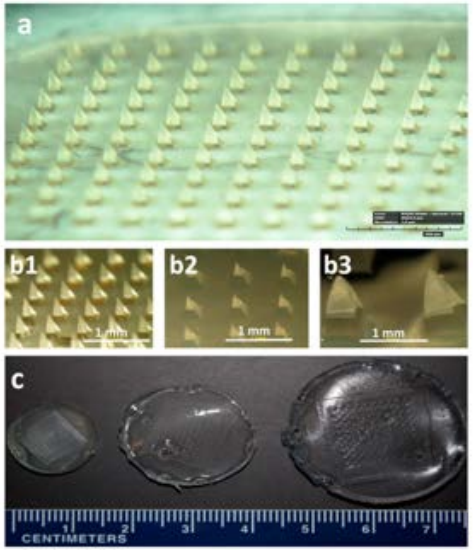
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

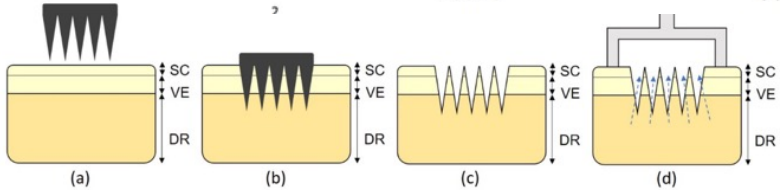
INTERSTITIAL FLUID

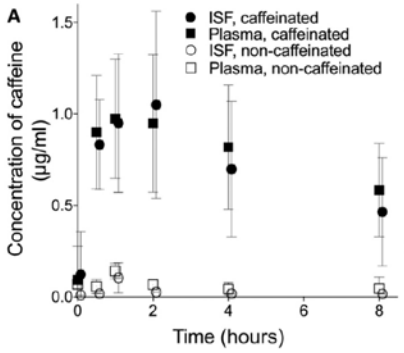
Sampling interstitial fluid from human skin using a microneedle patch

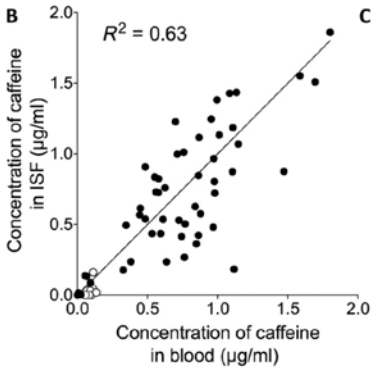
Pradnya P. Samant[1], Megan M. Niedzwiecki[2,3], Nicholas Raviele[1], Vilinh Tran[4], Juan Mena-Lapaix[1], Douglas I. Walker[2,3,4], Eric I. Felner[5], Dean P. Jones[4], Gary W. Miller[2,6], Mark R. Prausnitz[1]*









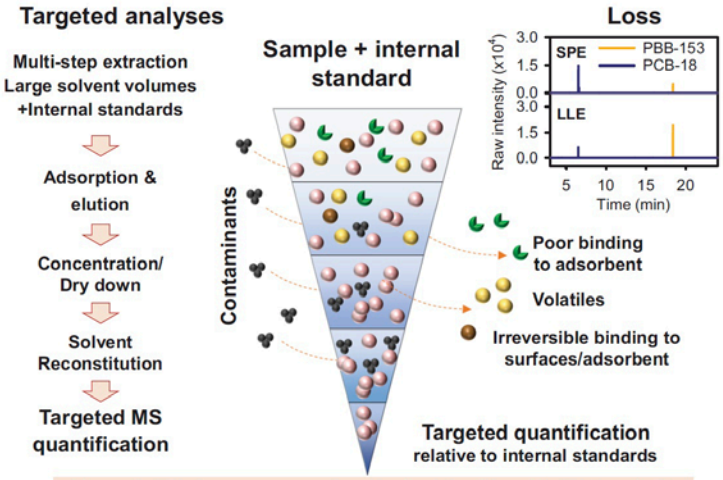


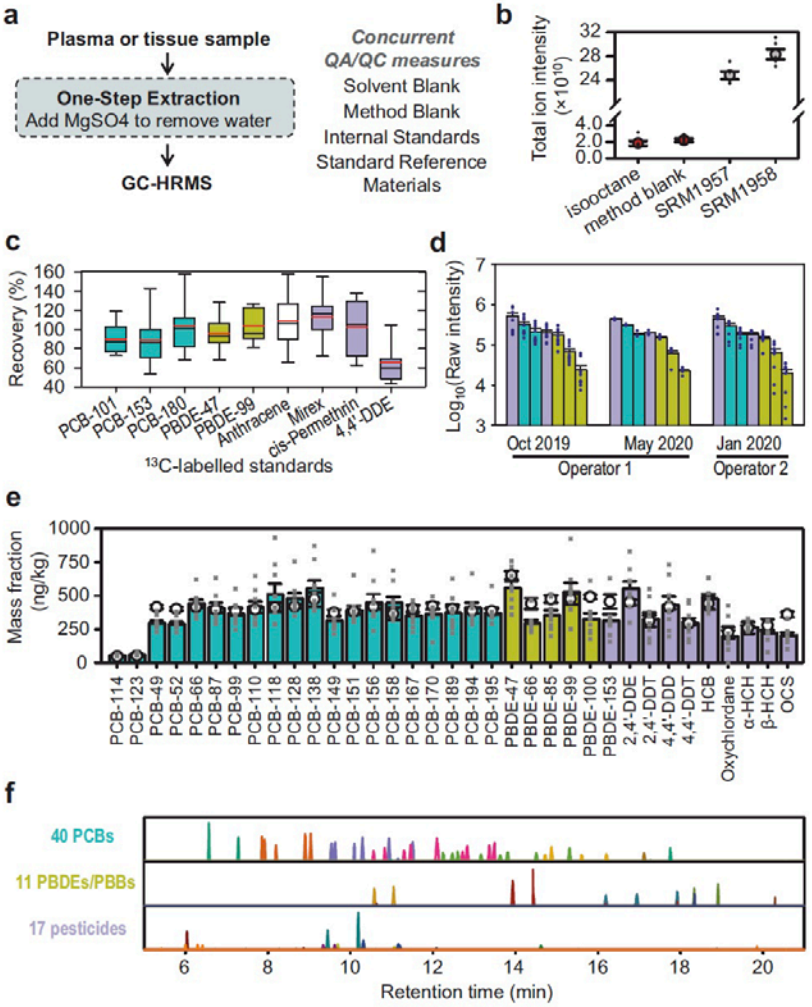
C

PK parameter	Plasma	ISF
C_{max} (µg/ml)	1.06 (0.31)	1.03 (0.42)
t_{max} (hours)	1 (0.61)	1 (0.61)
$AUC_{(0\text{-}8h)}$ (µg/ml·hour)	0.084 (0.031)	0.148 (0.116)
$t_{1/2}$ (hours)	9.4 (3.9)	7.5 (5.0)
CL (liter/hour)	4.1 (2.9)	4.7 (2.8)

Science Translational Medicine, 2020

A scalable workflow to characterize the human exposome-Hu et al., Nature Communications 2021





Express liquid extraction to LC-HRMS

Toward Capturing the Exposome: Exposure Biomarker Variability and Coexposure Patterns in the Shared Environment

Ming Kei Chung,[†] Kurunthachalam Kannan,[‡] Germaine M. Louis,[§] and Chirag J. Patel[*,†]

"Shared household explained 43% and 41% of the total variance for PFASs and blood metals, but less than 20% for the remaining 11 EDC classes."

"Our findings suggest that individual, rather than shared environment, could be a major factor influencing the covariation of the exposome."

*N.B. couples do not share their environments in the first 20-30 years of life. Need to pay attention to developmental windows/life stages.

Environ. Science & Technol., 2018

The exposome in companion animals

Exposomics is gaining acceptance within the U.S. biomedical research community. We must continue to innovate and demonstrate to be able to analyze biobanks like NIH All of Us, UK Biobank. NCI Cohort Consortium.

The approaches I have described have been used in a variety of animals: mice, rats, drosophila, zebrafish, *C. elegans*, and dogs.

There are essentially no technical limitations. HRMS-based exposomics and metabolomics can be performed on blood samples from any species. The question is what are we trying to learn? Are we trying to identify hundreds of environmental compounds in companion animals? Are we trying to discover links to disrupted global metabolism? Are we looking for specific contaminants?

The exposome in companion animals

I favor untargeted HRMS due to its relative lack of streetlamp bias, but that is merely my opinion. Targeted approaches have greater sensitivity and greater confidence in identification, but they require that you know what you are looking to measure. But then you must ask yourself:

The exposome in companion animals

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1) Do you know what you are looking for?

The exposome in companion animals

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1) Do you know what you are looking for?
2) Do you really know that you know what you are looking for?

Acknowledgements

- Miller Lab (Columbia)
- Jones Lab (Emory)
- Walker Lab (Mt. Sinai)
- Pennell Lab (Brown)
- Lazaridis Group (Mayo)
- Pollitt Lab (Yale)
- Irving CTSA Biomarkers Lab (Columbia)
- Mayeux team (Columbia)
- Stern team (Columbia)
- Schymanski team (Luxembourg)
- Klanova team (Czech Republic)
- Barouki team (France)
- Vermeulen team (Netherlands)
- NIEHS, NIA, NIDDK

COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

COLUMBIA | PRECISION MEDICINE

Precision medicine and the exposome
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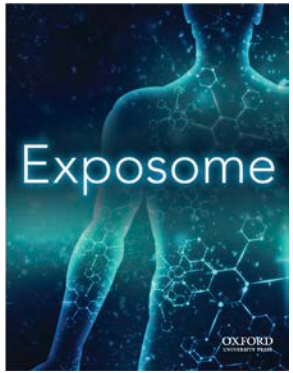

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Editorial

Exposome: a new field, a new journal

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I would like to suggest that there is need for an 'exposome' to match the genome…

Christopher Wild.[1]

Essentially, once one subtracts the genetic component from the phenotypic manifestations, one is left with E. We have incredible clinical, cellular, and molecular characterization of the pheno-