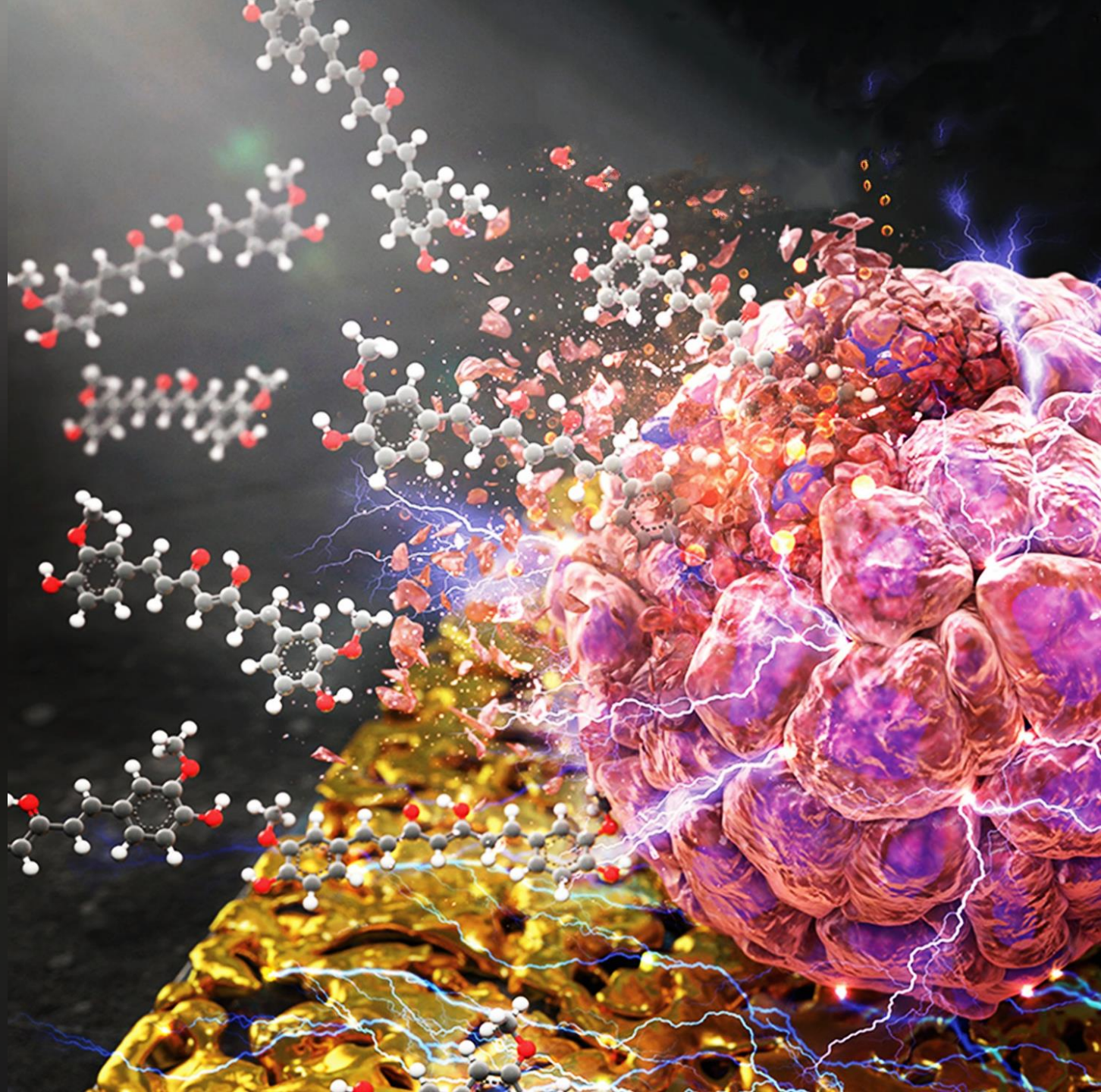
Keck School of Medicine of USC

ShARP
SUPERFUND PFAS ASSESSMENT, REMEDIATION & PREVENTION

Deciphering the molecular and cellular mechanisms underlying PFAS-associated MASLD



Ana Maretti-Garcia, MS, PhD

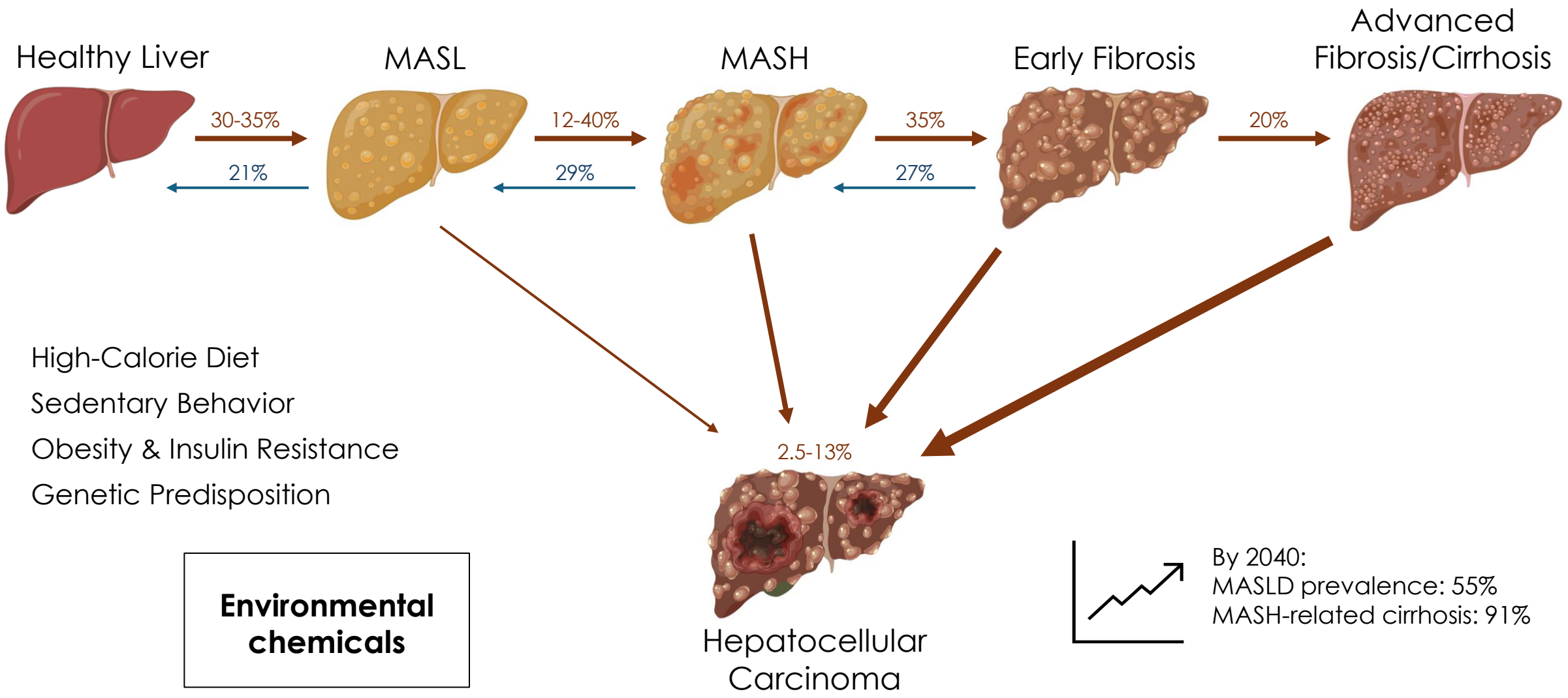
Assistant Professor, Department of Medicine, University of Southern California

Co-Investigator, ShARP Center

NIEHS SRP Risk e-Learning Webinar Series:
***From Cells to Solutions* – Session III**

January 21, 2026

Natural History of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)



What are PFAS?

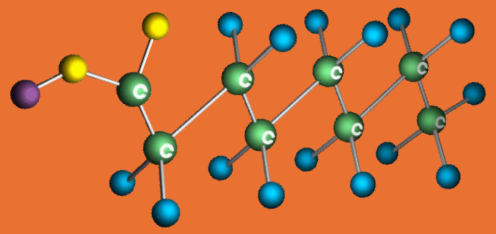
> 10,000 chemicals

Widely used in industrial applications

Resistant to degradation

Detected in the blood of almost everyone in the U.S

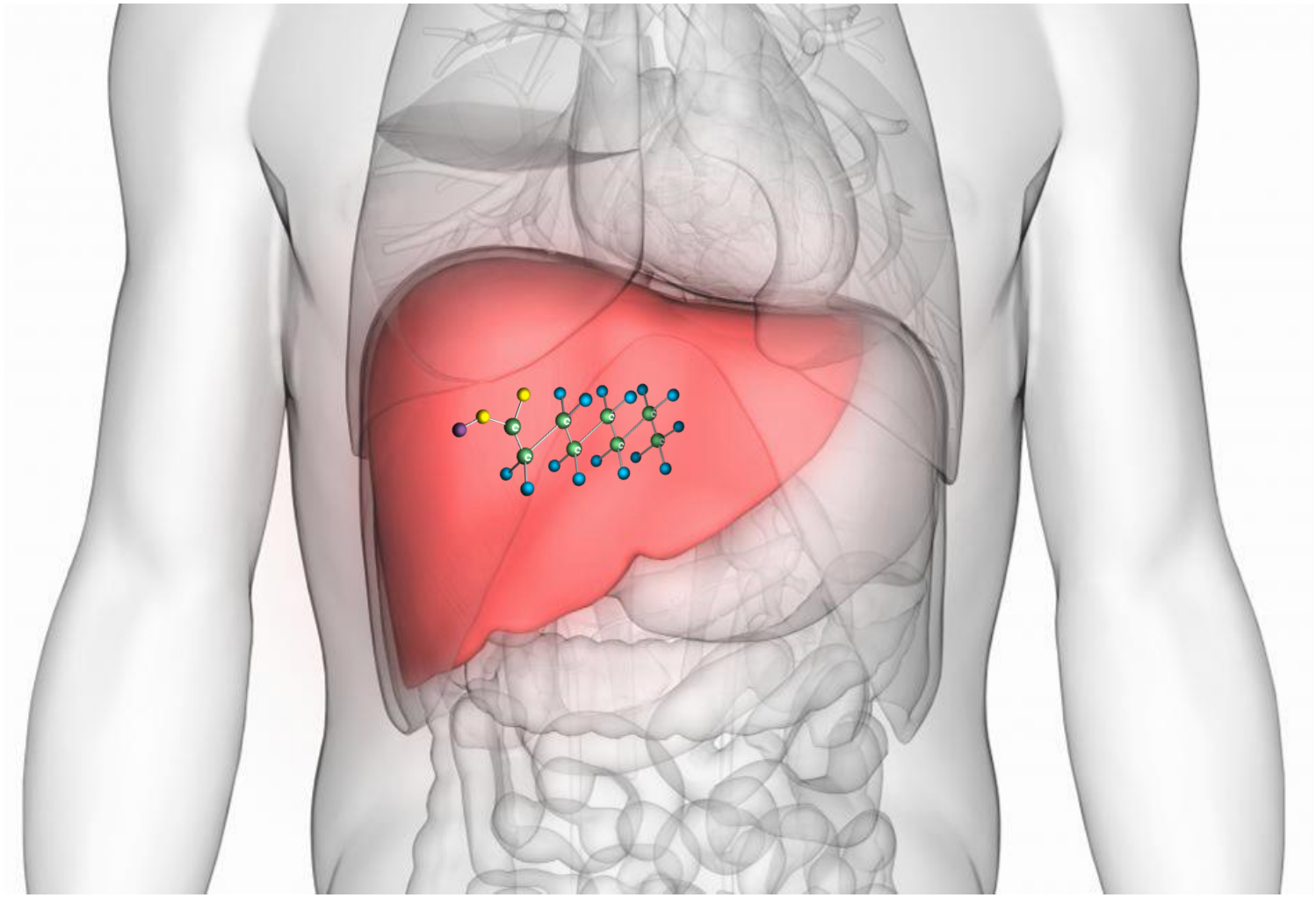
PFAS



Exposure Sources

- Contaminated water
- Nonstick cookware
- Food packaging
- Personal care products
- Textiles (Outdoor Gear & Waterproof Clothing)

Hepatic Effects of PFAS Exposure



What do we know?

Hepatic Injury

Lin et al., 2010 (PFOA)
Gleason et al., 2015 (PFOS)
Costello et al., 2022 (PFOA, PFOS, PFNA)

Metabolic Dysfunction

Fleisch et al., 2017 (PFOA, PFOS, PFNA, PFHxS, PFDeA)
Rosen et al., 2022 (PFNA, PFOS)

Dyslipidemia

Schlezinger et al., 2021 (PFOA)
Averina et al., 2021 (PFNA, PFDA)

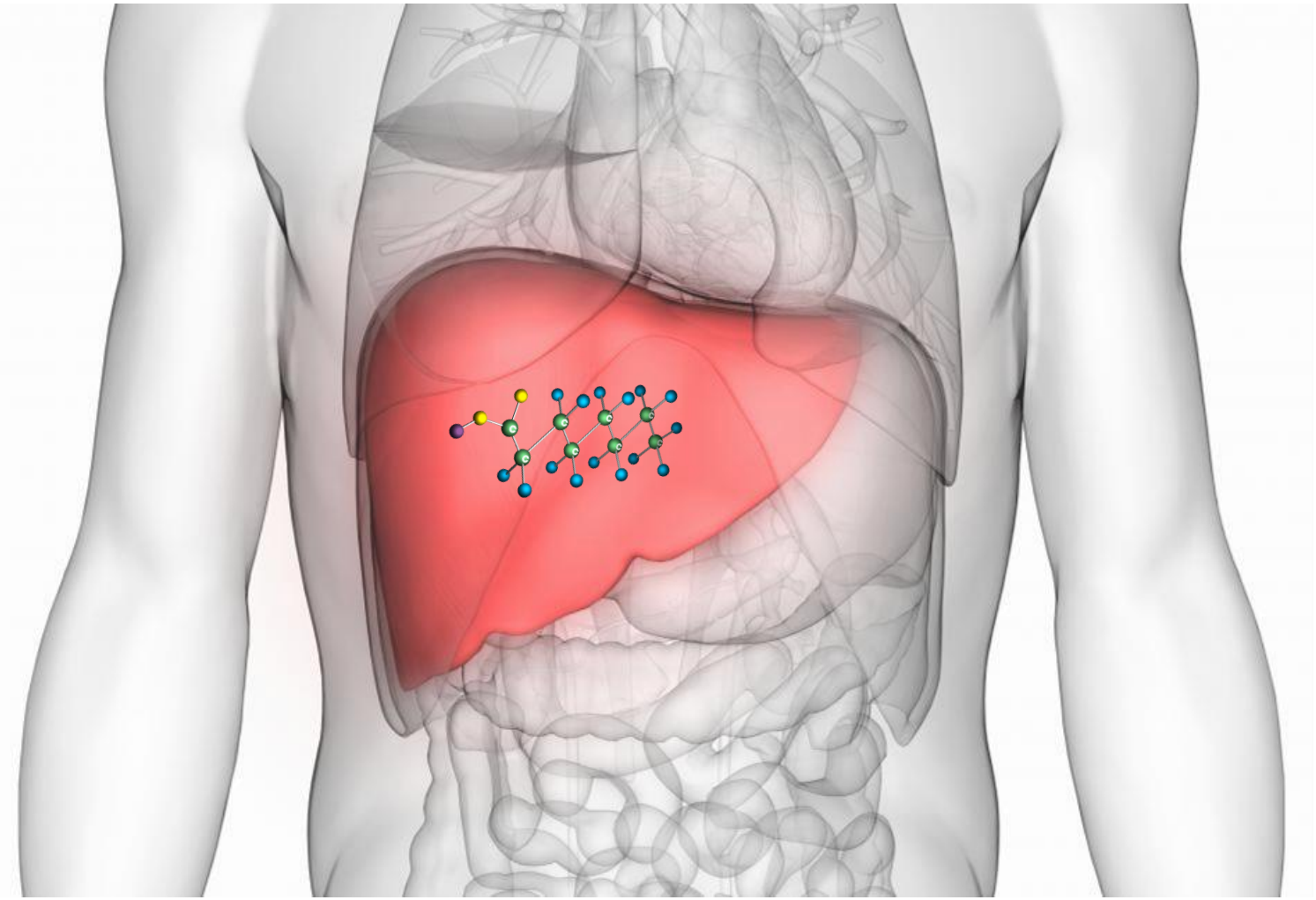
Steatosis and Inflammation

Jin et al., 2020 (PFOS, PFHxS)
Zhang et al., 2023 (PFHxS)
Wu et al., 2023 (PFOA, PFNA)

Cancer

Goodrich et al., 2022 (PFOS)

Hepatic Effects of PFAS Exposure



Current Knowledge Gaps and Limitations

Mechanisms are unknown

- Pathways and metabolism cascades
- Cell-specific impact
- Changes in cell-cell communication

Available experimental models

- Animal models do not recapitulate human disease
- Human studies require years of follow-up
- *2D in vitro* models only use single cell types in self-assembled monolayers

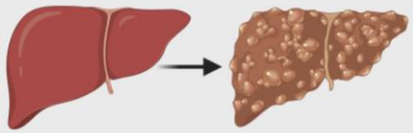
Data integration

- Current studies do not integrate *in vitro* or *in vivo* datasets with human data

ShARP

SUPERFUND PFAS ASSESSMENT, REMEDIATION & PREVENTION

Understanding the causal effects of PFAS in human liver disease



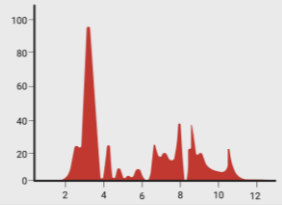
Discovering mechanisms of PFAS hepatotoxicity

Biomedical Research Projects

Project 1: Mechanisms of PFAS Hepatotoxicity

Project 2: PFAS-induced MASLD in Youth

Developing methods for comprehensive PFAS environmental assessment



Identifying sustainable PFAS interventions

Environmental Engineering Research Projects

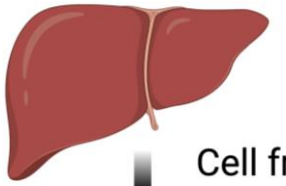
Project 3: Fate and Transport of PFAS

Project 4: PFAS Remediation and Treatment

In Vitro Study: Multi-donor 3D Human Liver Spheroids

insphero

Cell Sources



Cell from human postmortem liver

Production of 3D InSight™ Human Liver Microtissues

Hepatocytes
(5 male and 5 female donors)

Non-parenchymal cells
(1 donor)

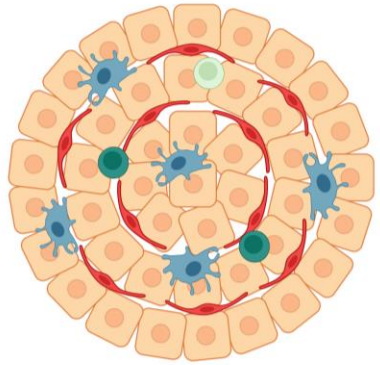
Kupffer Cells

Lymphocytes

Natural Killer Cells

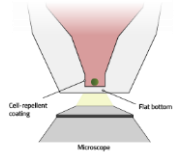
Endothelial Cells

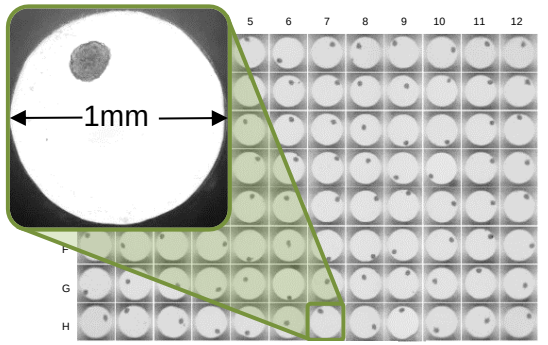
Cell aggregation



Quality Control

- Macroscopic observation (spheroid formation)
- Microtissue size
- Immunohistochemistry markers
- Cytokines
- Metabolites
- Liver enzymes





In Vitro Study: Previous PFAS toxicological studies

High-Throughput Transcriptomic Analysis of Human Primary Hepatocyte Spheroids Exposed to Per- and Polyfluoroalkyl Substances as a Platform for Relative Potency Characterization

Andrea Rowan-Carroll,* Anthony Reardon,* Karen Leingartner,* Remi Gagné,* Andrew Williams,* Matthew J. Meier,* Byron Kuo,* Julie Bourdon-Lacombe,† Ivy Moffat,† Richard Carrier,† Andy Nong,* Luigi Lorusso,‡ Stephen S. Ferguson,§ Ella Atlas,*,1 and Carole Yauk*,¶,1

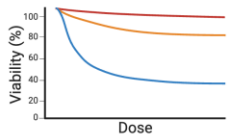
TOXICOLOGICAL SCIENCES, 181(2), 2021, 199–214

Potency Ranking of Per- and Polyfluoroalkyl Substances Using High-Throughput Transcriptomic Analysis of Human Liver Spheroids

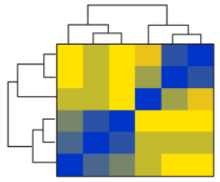
Anthony J.F. Reardon,* Andrea Rowan-Carroll,* Stephen S. Ferguson,† Karen Leingartner,* Remi Gagne,* Byron Kuo,* Andrew Williams,* Luigi Lorusso,‡ Julie A. Bourdon-Lacombe,§ Richard Carrier,§ Ivy Moffat,§ Carole L. Yauk,*,¶,1 and Ella Atlas*,‖,1

TOXICOLOGICAL SCIENCES, 184(1), 2021, 154–169

Cytotoxicity Assessment



LDH assay



TempO-Seq

Table 1. Number of Differentially Expressed Genes in the PFAS-Treated Spheroids Relative to Controls for Each Time Point and Concentration

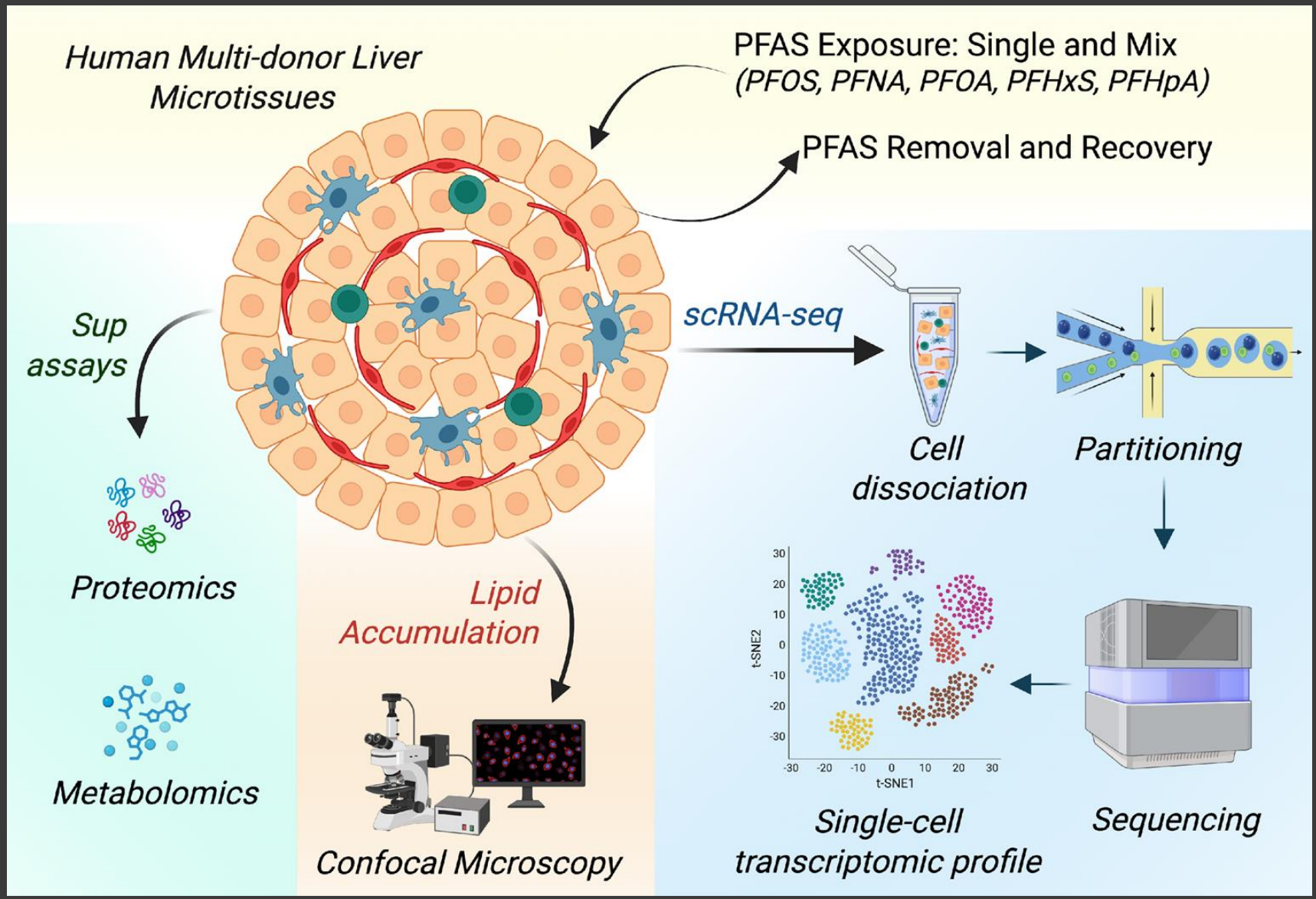
PFAS	Day	0.02 μM	0.1 μM	0.2 μM	1 μM	2 μM	10 μM	20 μM	50 μM	100 μM
PFOA	1	0	8	36	8	19	79	69	227	465
	4	22	30	35	41	14	42	100	184	782
	10	14	7	2	4	10	82	101	593	Cytotoxic
	14	4	0	8	9	6	76	96	Cytotoxic	Cytotoxic
PFBS	1	0	1	0	5	49	5	0	44	73
	4	0	5	20	20	0	0	8	0	59
	10	2	1	0	1	2	0	7	54	76
	14	0	0	6	0	1	2	0	2	52
PFOS	1	1	85	3	6	51	167	277	Cytotoxic	Cytotoxic
	4	6	12	30	48	62	251	313	Cytotoxic	Cytotoxic
	10	2	7	4	6	60	163	466	Cytotoxic	Cytotoxic
	14	1	0	3	1	6	249	398	Cytotoxic	Cytotoxic
PFDS	1	0	1	0	6	22	59	81	177	186
	4	0	17	15	7	20	340	247	171	273
	10	0	30	0	43	40	134	175	232	231
	14	1	3	1	18	100	182	147	211	340

In Vitro Study: PFAS impact in Liver Spheroids

Lucy Golden, PhD
PI -Project 1

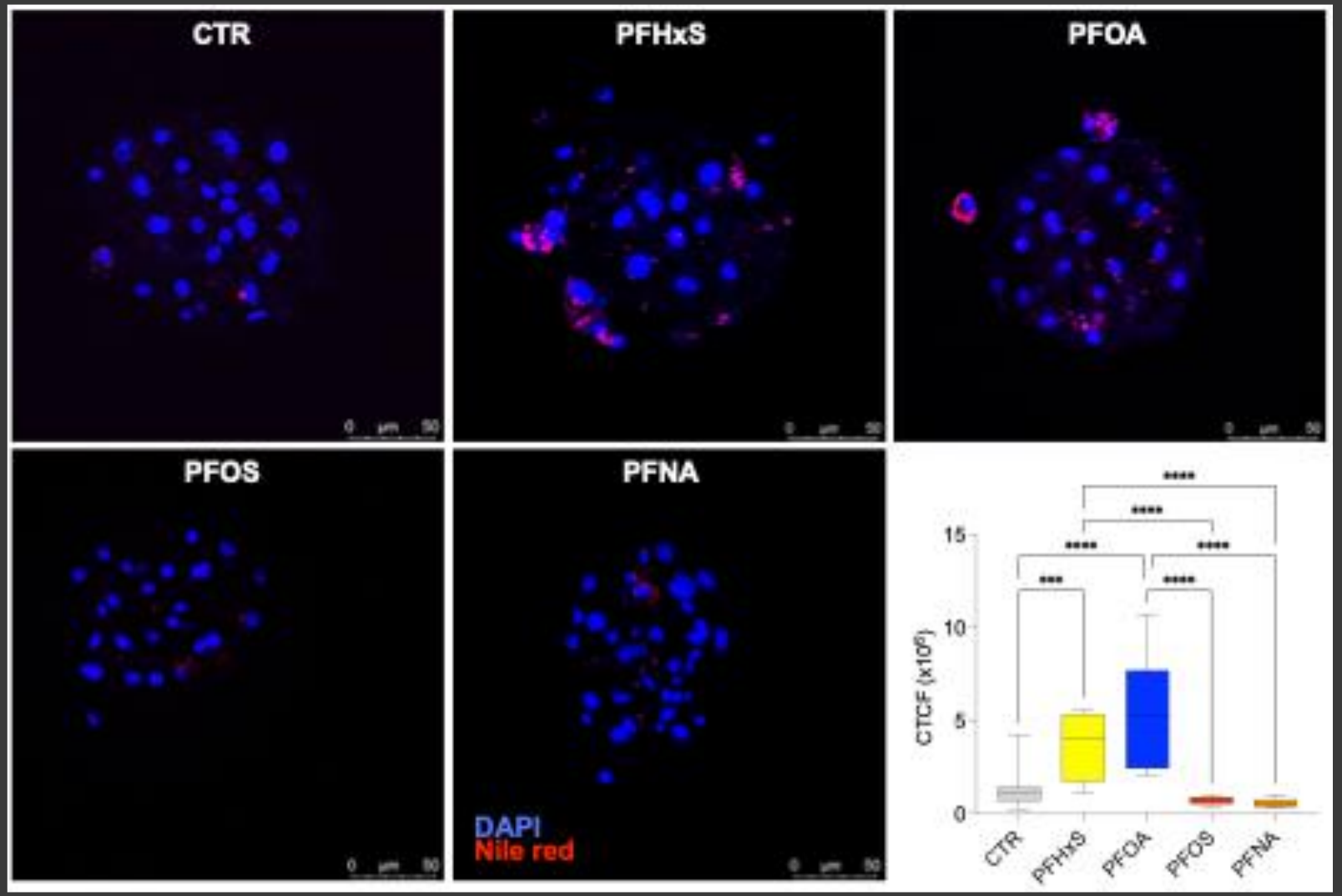
Ana Maretti-Mira, PhD
Co-I – Project 1

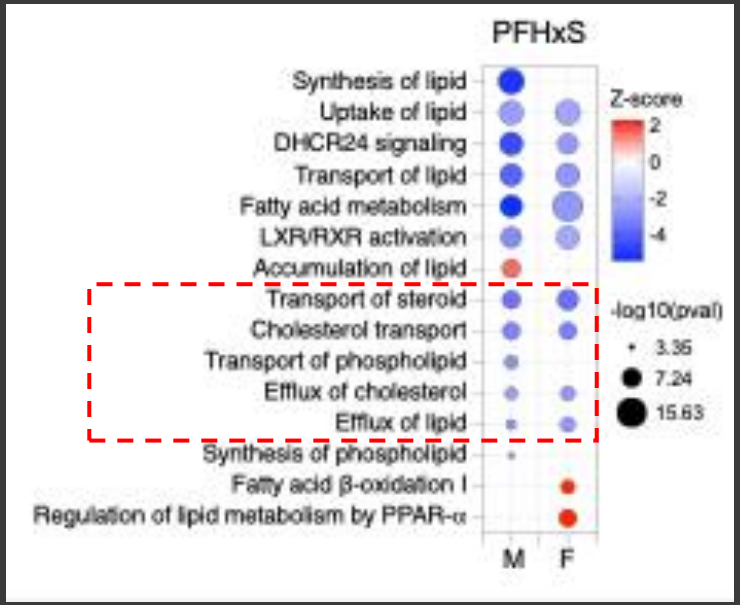
Matthew Salomon, PhD
Co-I – Project 1 and DMAC

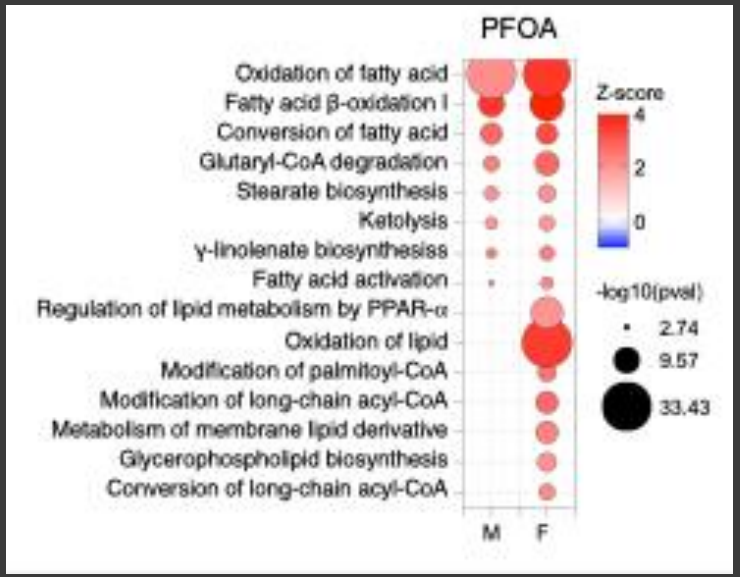


P42ES036506
P30ES007048

In Vitro Study: Mechanisms of PFAS disruption of lipid metabolism

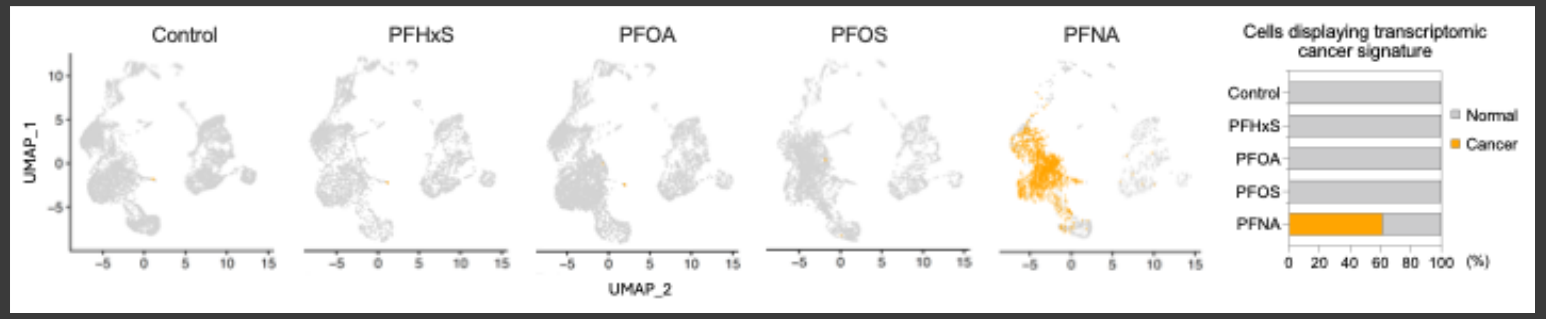






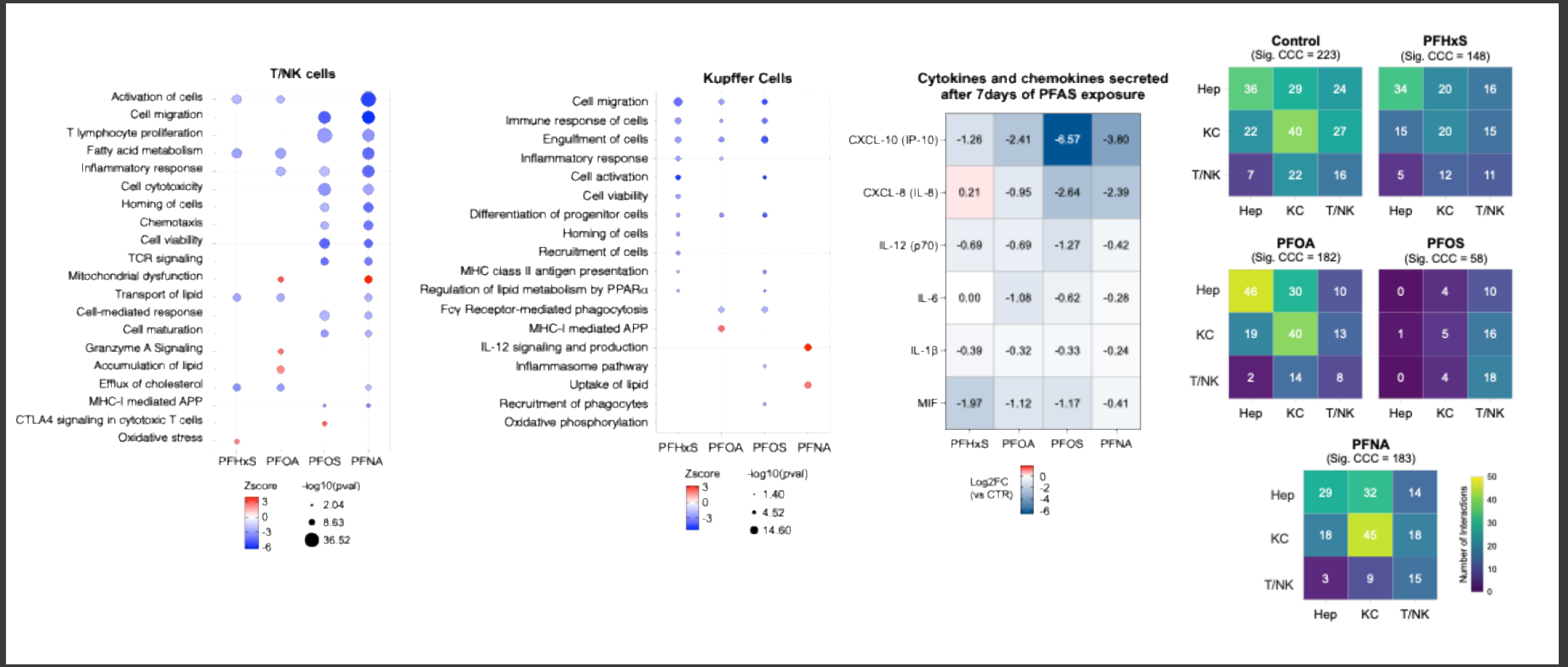
Golden-Mason & Salomon et al. Environment International 2025 (PMID: 40914107)

In Vitro Study: Pro-oncogenic mechanisms of PFAS



Golden-Mason & Salomon et al. Environment International 2025 (PMID: 40914107)

In Vitro Study: Immunosuppressive and Cell-Cell Communication Effects

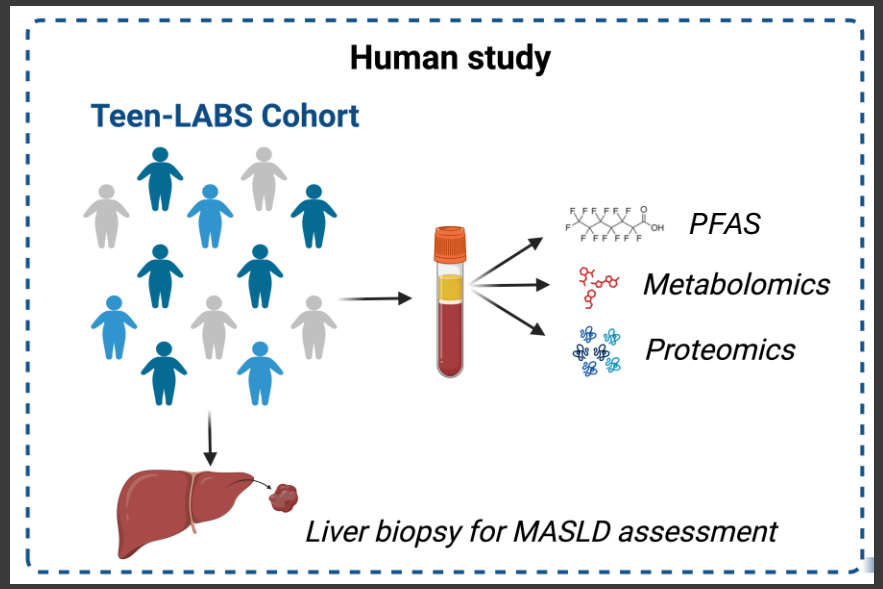


Golden-Mason & Salomon et al. Environment International 2025 (PMID: 40914107)

Translational Study: Mechanisms underlying PFHpA-associated MASLD

Lida Chatzi, MD, PhD
ShARP Director
PI – Project 2

Brittney Baumert, PhD
Postdoctoral Scholar
USC



Baumert & Maretti-Mira et al. Communications Medicine 2025 (PMID: 41162609)

Translational Study: Human Study

Teen-Longitudinal Assessment of Bariatric Surgery (LABS) cohort

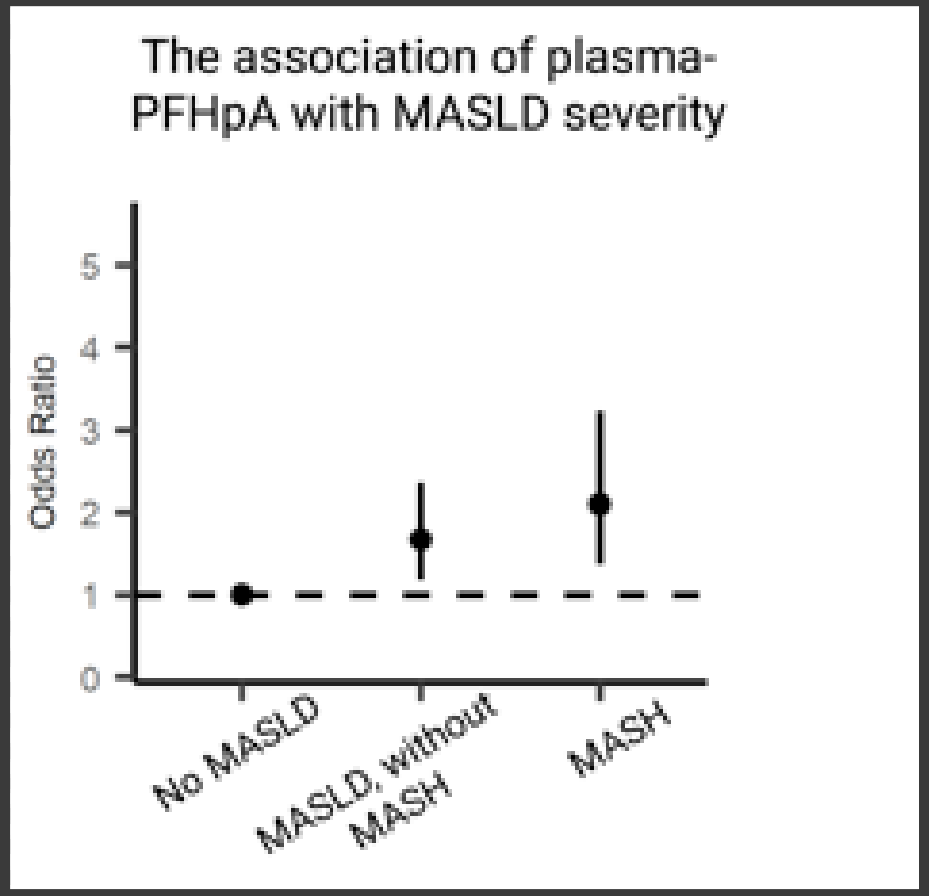
N=186

Age: 17.1 years

Sex: female (76.3%)

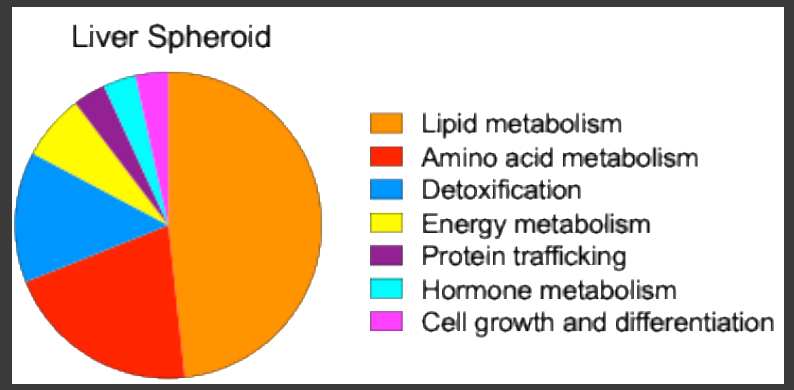
Race: white (72%)

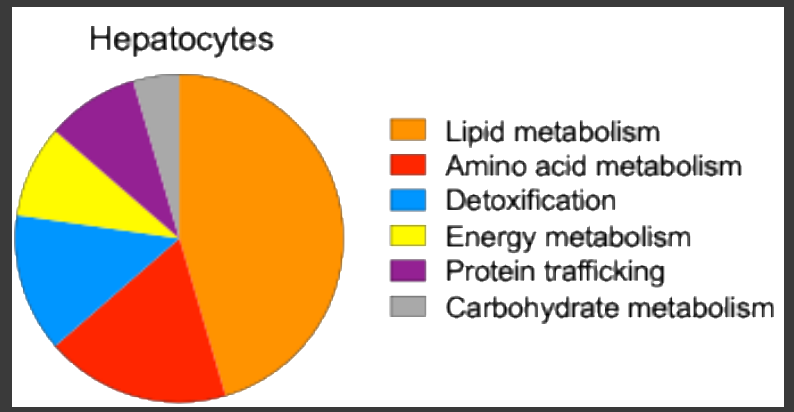
Parental income: ≤ $75k (77.4%)

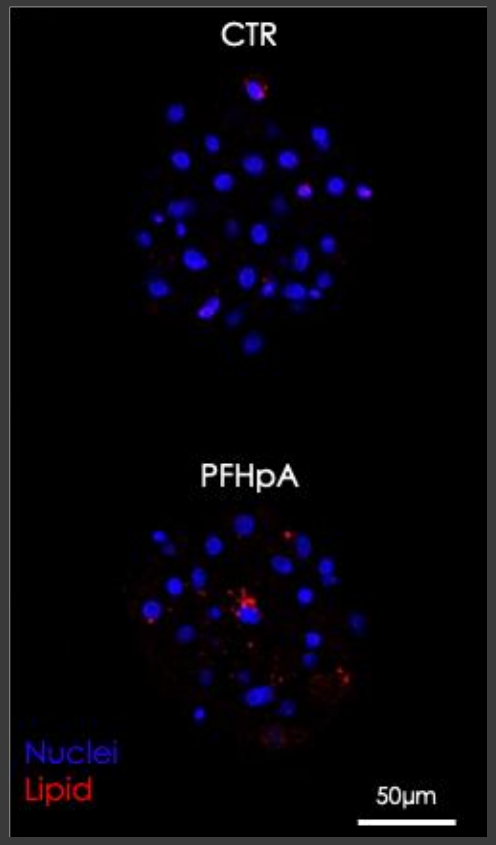


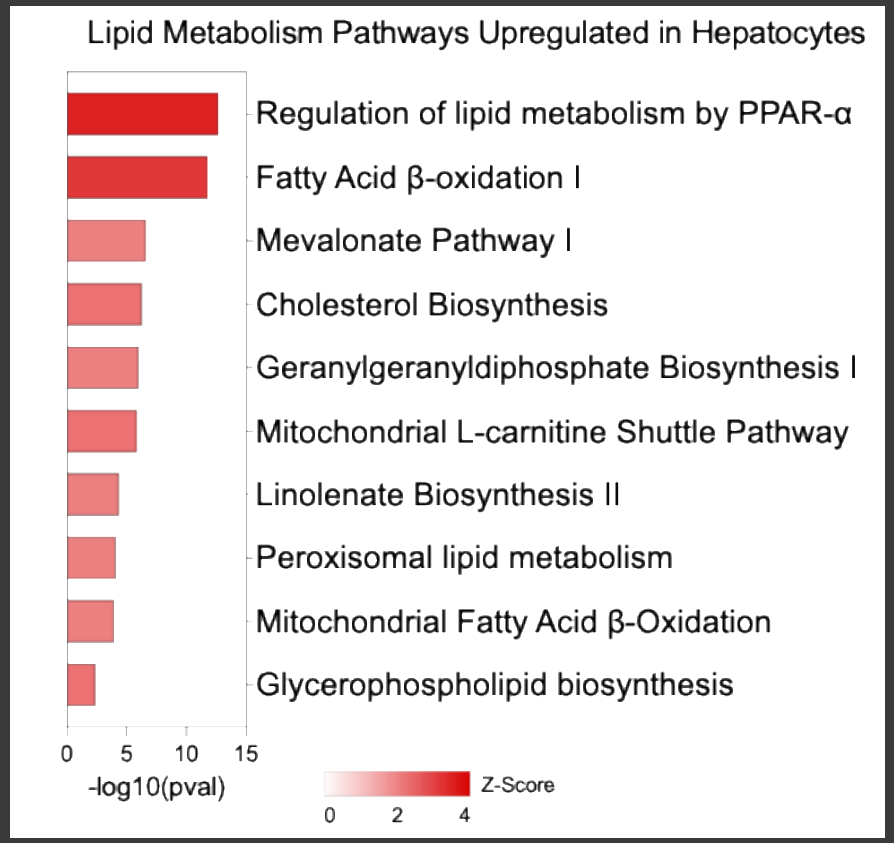
Baumert & Maretti-Mira et al. Communications Medicine 2025 (PMID: 41162609)

Translational Study: In Vitro Study



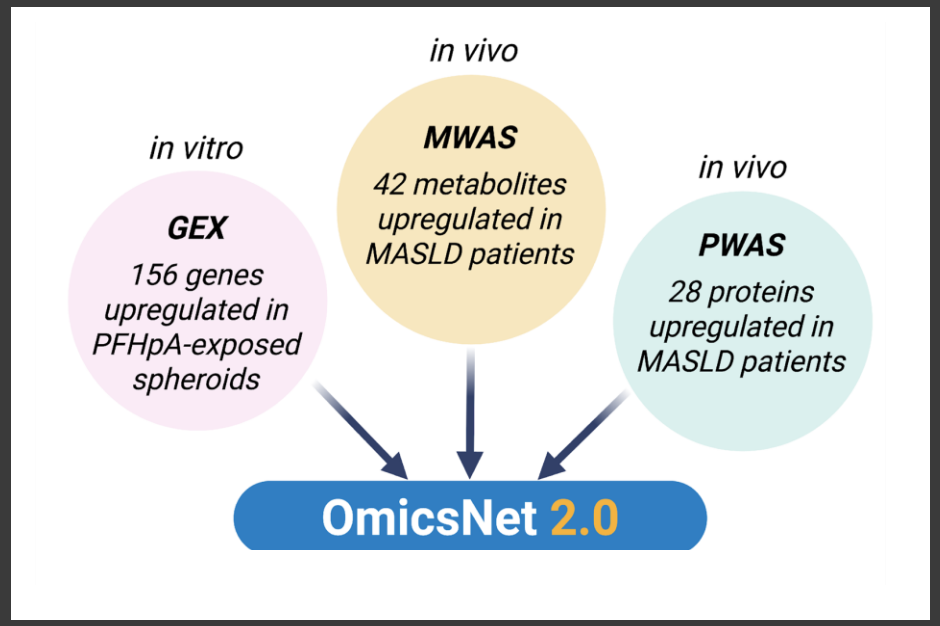


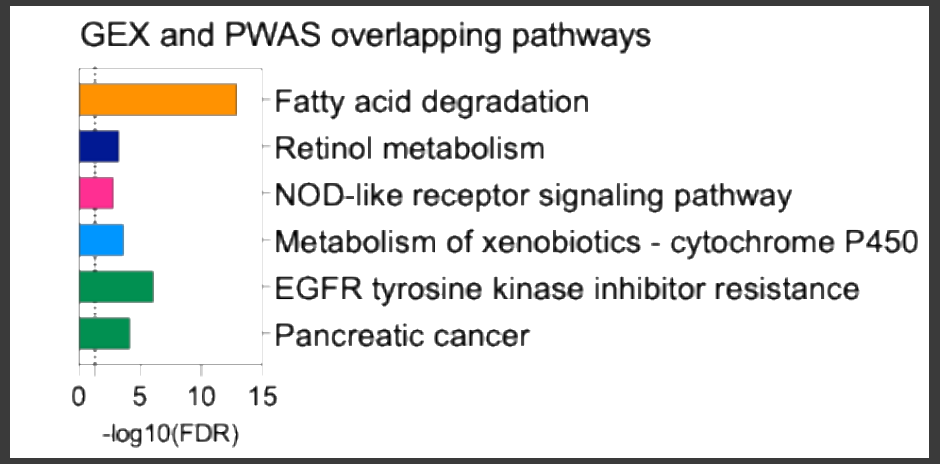


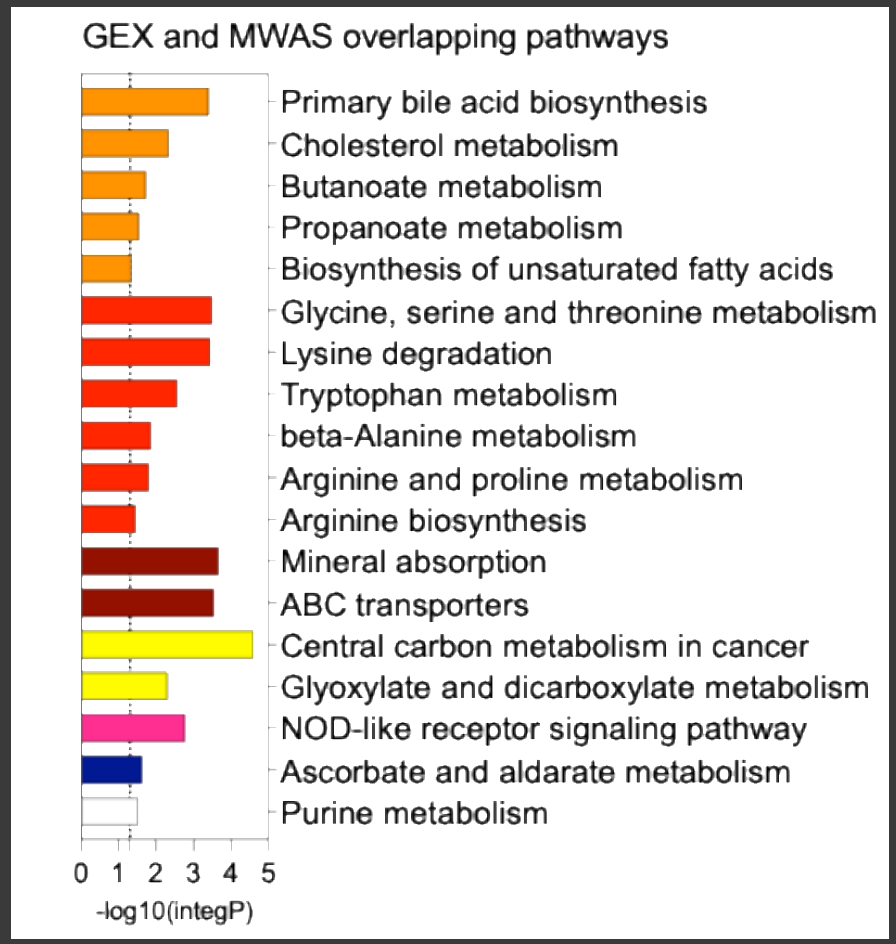


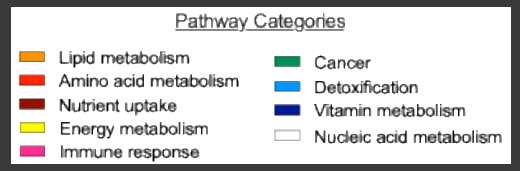
Baumert & Maretti-Mira et al. Communications Medicine 2025 (PMID: 41162609)

Translational Study: Integration of In Vitro and Human Datasets









19 metabolites
6 proteins

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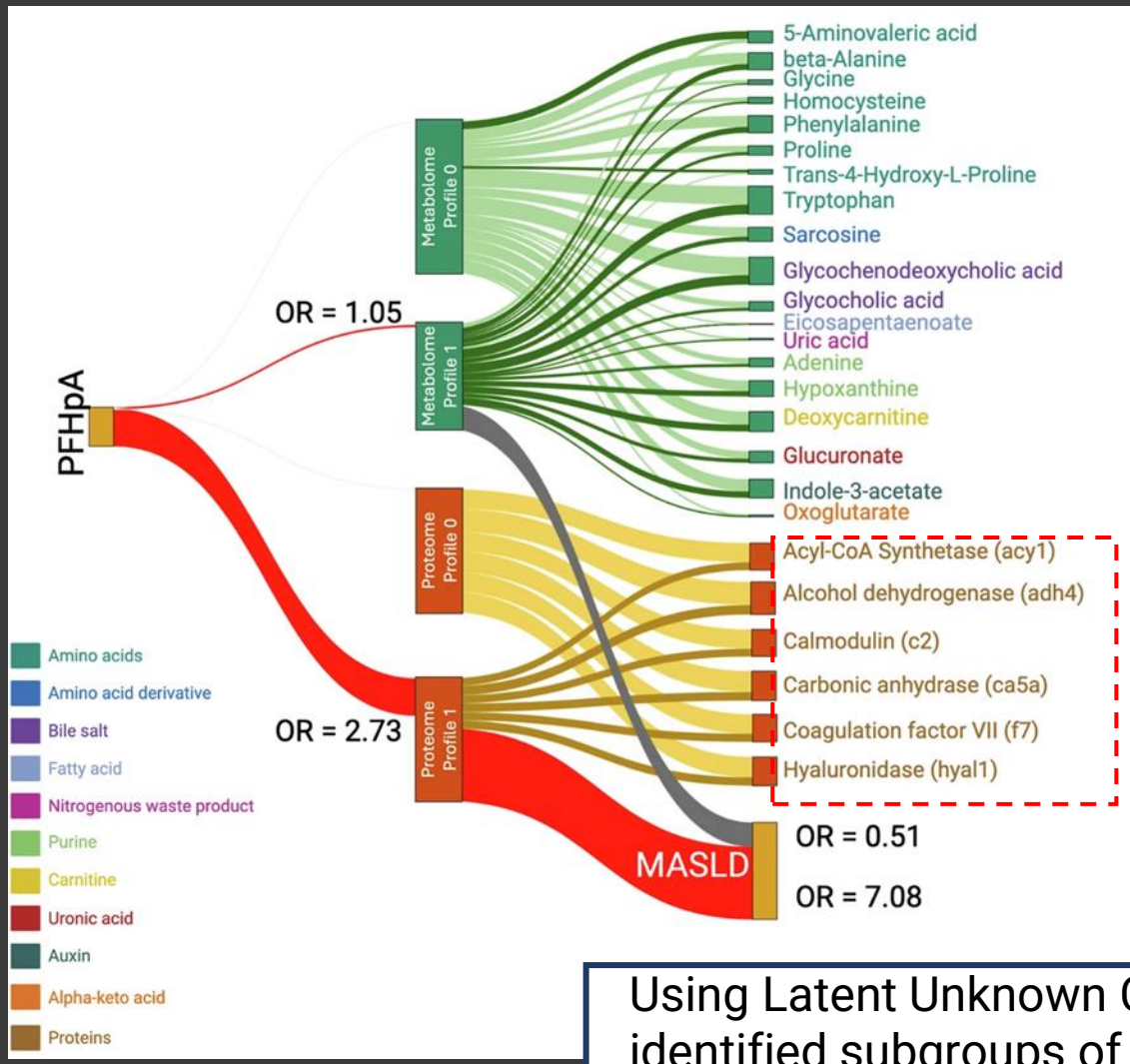
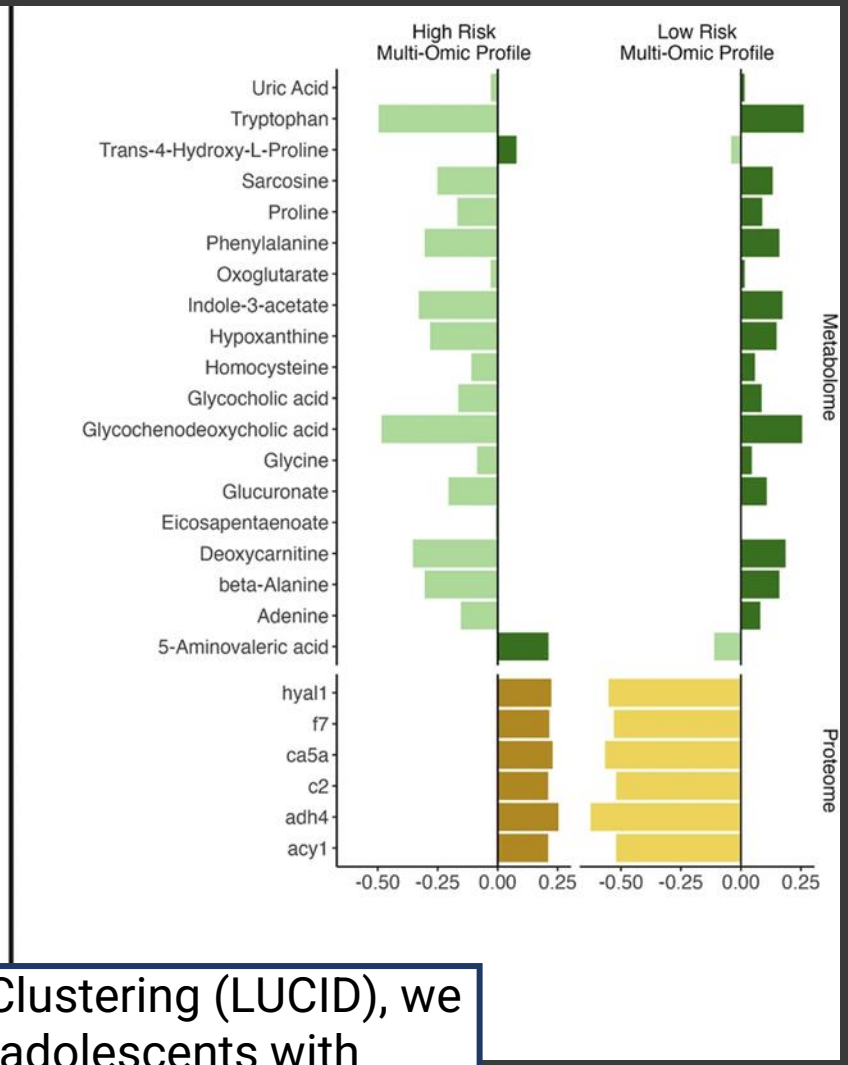
Translational Study: Extrapolation of In Vitro-Human Data Integration

David Conti, PhD
DMAC Lead





Using Latent Unknown Clustering (LUCID), we identified subgroups of adolescents with increased risk of MASLD

Baumert & Maretti-Mira et al. Communications Medicine 2025 (PMID: 41162609)

In Progress & Next Steps:

PFAS Mixture
equal amounts of
PFOA, PFOS, PFNA
PFHxS, PFHpA

Final Concentration
20µM

Exposure Time
Short: 1 week
Long: 2 weeks

Removal
PFAS mix: 1 week
Recovery: 1 week

PFAS Mixture
plasma ratios of
PFOS, PFOA, PFNA
PFHxS, PFHpA
(56:18:6:18:1)

Final Concentrations
20nM and 80nM

Exposure Time
1 week
3 weeks

Single PFAS
PFOS, PFOA, PFNA
PFHxS, PFHpA

Final Concentrations
20nM and 80nM

Exposure Time
1 week
3 weeks

Emerging PFAS
6:2FTSA, PFHpS,
TFA

Dose-response Concentrations
0.02-20µM

Exposure Time
1 week

Acknowledgements

University of Southern California
- Lucy Golden, PhD
- Matt Salomon, PhD
- Lida Chatzi, MD, PhD
- Brittney Baumert, PhD
- David Conti, PhD
- Rob McConnell, MD

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- Douglas Walker, PhD

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- Veronica Vierra, PhD
- Scott Bartell, PhD

InSphero Inc
- Sue Grepper
- Radina Kostadinova

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Questions?

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ShARP
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