Alzheimer's Disease Metabolomics Consortium (ADMC)

NIH National Institute on Aging

ACCELERATING MEDICINES PARTNERSHIP (AMP)

NIH: West Coast Metabolomics Center

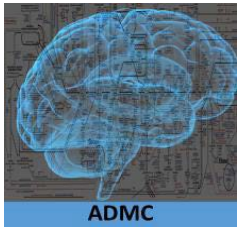
FNIH Foundation for the National Institutes of Health

RUSH UNIVERSITY

Duke University School of Medicine

EMORY UNIVERSITY

Targeted Metabolomics of Circulating and Central Lipid Mediators: Searching for Peripheral Biomarkers of Central Effects



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Sage BIONETWORKS

Oct 25, 2018

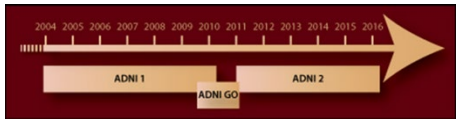
USDA

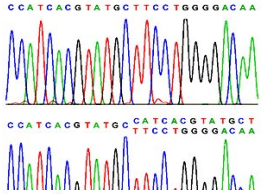
COLUMBIA UNIVERSITY

UCDAVIS UNIVERSITY OF CALIFORNIA

ADMC Mapping Metabolic Failures Across Trajectory of Disease

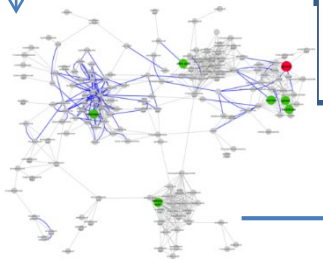
Connecting central and peripheral changes

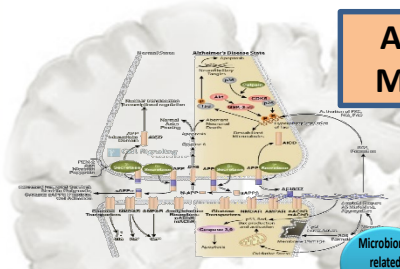




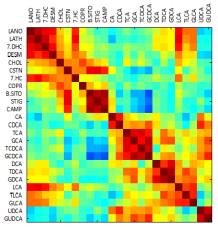
Genomics and transcriptomics

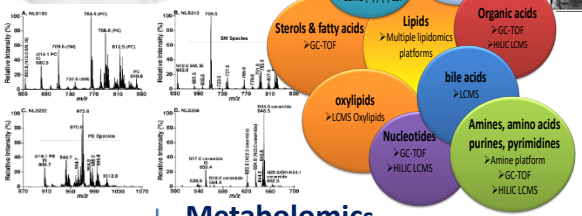
Metabolome-Genome links
Enzymes/genes implicated



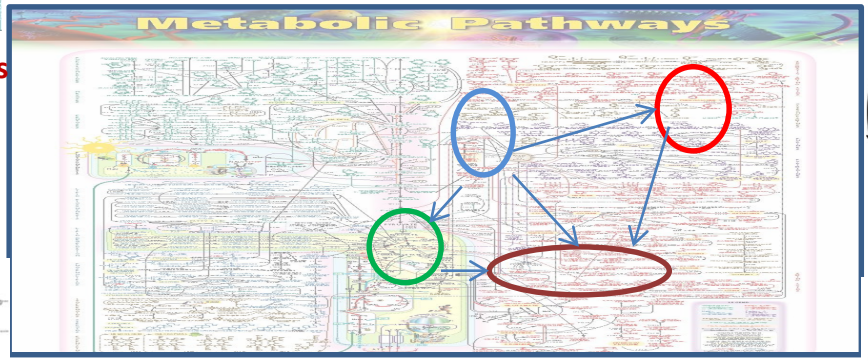


AD CSF Markers

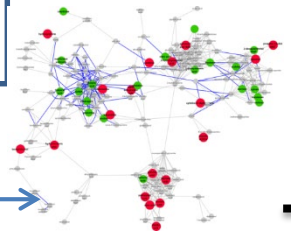




Metabolomics

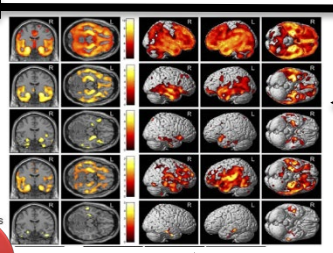


Changes in biochemical pathways and network as disease progresses - New targets for drug design and biomarkers

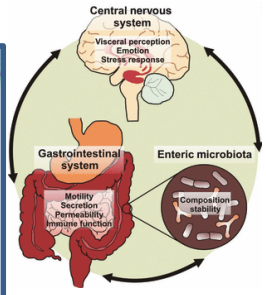


AD Progression

Imaging



(Gut Brain Axis, Liver Brain Axis, environment, diet)



Connect peripheral and central biochemical changes

ADNI I Baseline Datasets and Longitudinal Profiling

Targeted and Non Targeted Metabolomics Lipidomics Platforms

P180
Amines, acylcarnitines, PC, SM (180)

Bile Acid
Cholesterol and gut microbiome metabolism (20)

Purine (10)

PE plasmalogen (10)

PC, LPC NESI (30)

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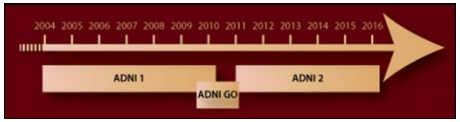
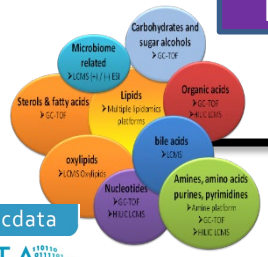


Non Targeted Metabolomics (300)

Non Targeted lipidomics Davis and Baker 400-500 lipids

Targeted "mediator lipidomics"

Highly informative compounds (40)



SCIENTIFIC DATA

OPEN Data Descriptor: Targeted metabolomics and medication classification data from participants in the ADNI1 cohort

www.nature.com/scientificdata

SCIENTIFIC DATA

OPEN Data Descriptor: Generation and quality control of lipidomics data for the alzheimer's disease neuroimaging initiative cohort

Bile Acids Submitted

Neurotransmitters Catecholamine (6)

Methylation

Nightingale
NMR Small molecules and Lipoproteins (220)

Analysis ongoing

Broad biochemical coverage, high level of standardization
Implementation of a standardized processing and QC pipeline for metabolomics data

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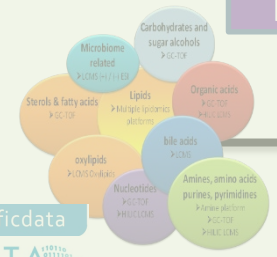

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Todays Focus

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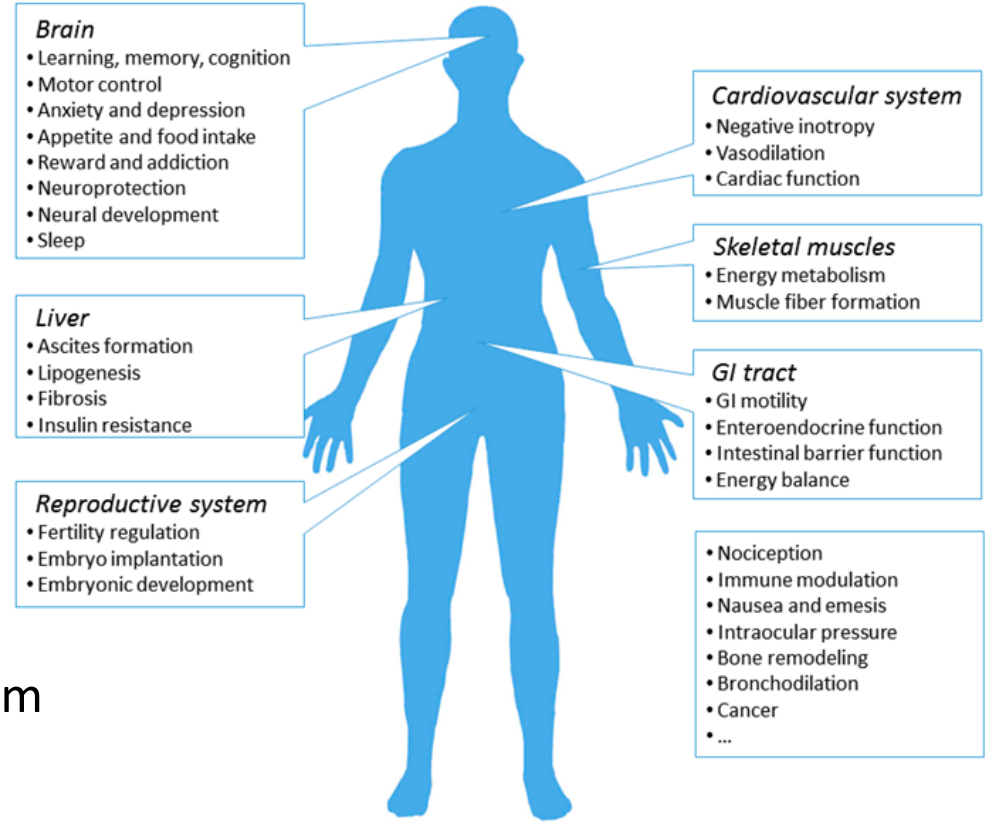
ADMC Lipid Mediator Profiling

We are primarily profiling two lipid mediator cascades encompassing 5 major branches from 5 precursor fatty acids, with ancillary coverage of bile acid and glucocorticoid metabolism.

- Oxylipins and Endocannabinoids

- These mediators influence:
  - Neural function
  - Vascular function
  - Inflammation
  - Cell growth and repair
  - Energy balance and metabolism
  - And more…



Oxylipins and Alzheimer's Disease

Oxylipins encompass mediators of inflammation and vascular function and markers of oxidative stress

- Aβ-accumulation toxicity counteract by COX inhibitors (PMID: 27190010)
- Aβ pathology associated with CYP2C19 SNIPs (PMID: 29473050)
- AD increases:
  - 12/15-LOX expression (PMID: 15111312)
  - plasma and postmortem brain auto-oxidation markers (PMID: 15717023)
  - rodent brains COX, CYP, and 5-LOX metabolites (PMID: 18931664)

Endocannabinoids are neuroprotective

- AD reduces:
  - Postmortem brain arachidonoylethanolamide (AEA), which correlates with Aβ42 increases and cognitive decline (PMID: 24256258)

Targeted Mediator LC-MS/MS Assays

Protein precipitation

Filtration

UPLC

MS/MS

96 well high-throughput extraction

ESI(-)-UPLC-MS/MS with internal standards for 111 mediators, 5 PUFAs, and 4 NSAIDs in 16min.

ESI(+)-UPLC-MS/MS with internal standards for 23 bile acids and 9 steroids in 16min.

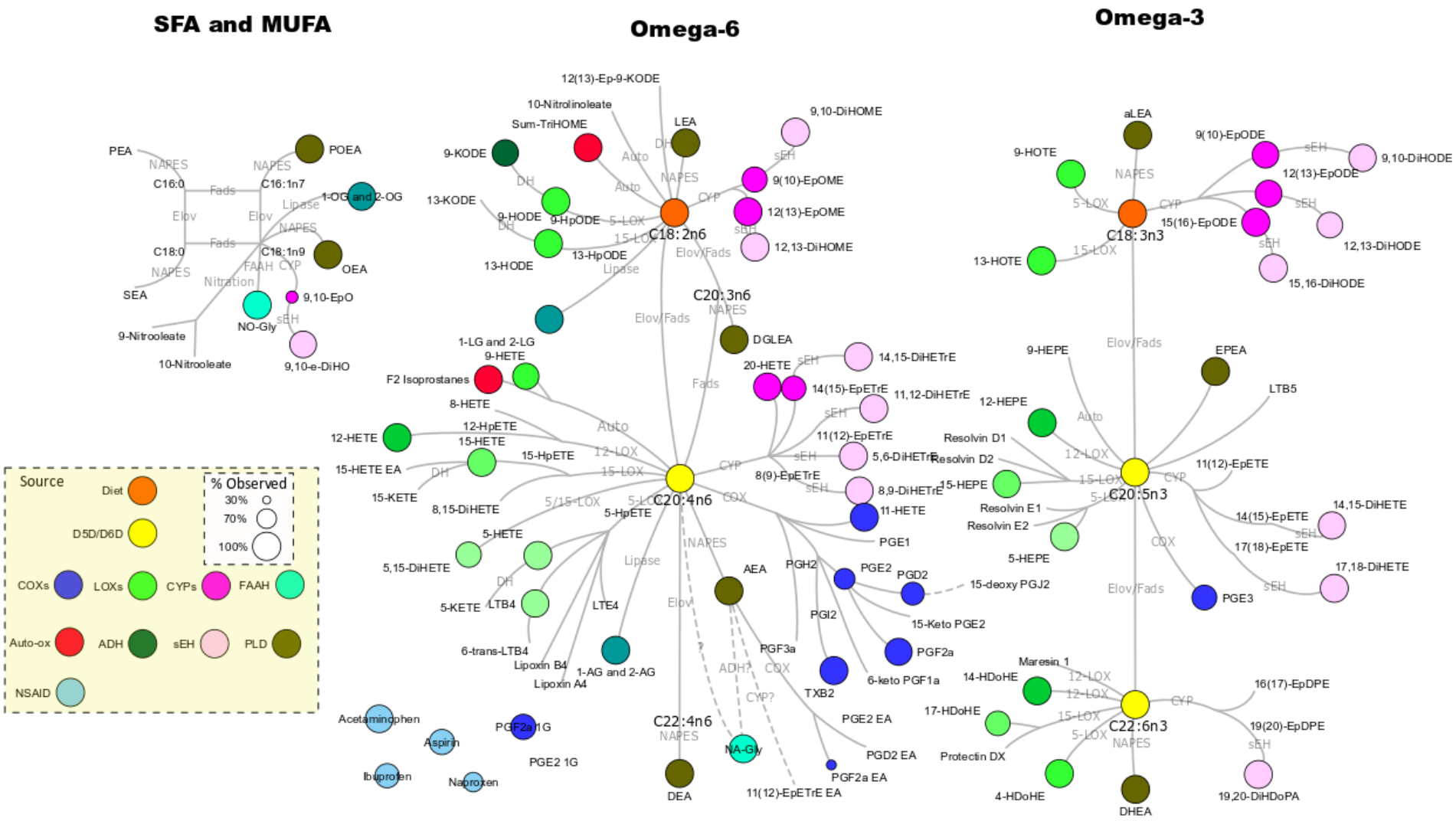
145 analytes quantified

		>LOD in >70% of Samples		
Analytes	Total n	Serum* (10 µL)	Plasma (10 µL)	CSF (100 µL)
Oxylipins	83	46	42	10
Endocannabinoids	21	17	17	3
NSAIDs	4	4	3	3
PUFAs	5	5	5	3
Bile Acids	23	17	16	11
Steroids	9	7	7	6

*Clotting influences some compounds 12-LOX and Thromboxane profiles in serum.

Serum Oxylipin and Endocannabinoid Coverage

Results from 230 serum samples from subjects with a range of cognitive impairment (no AD)



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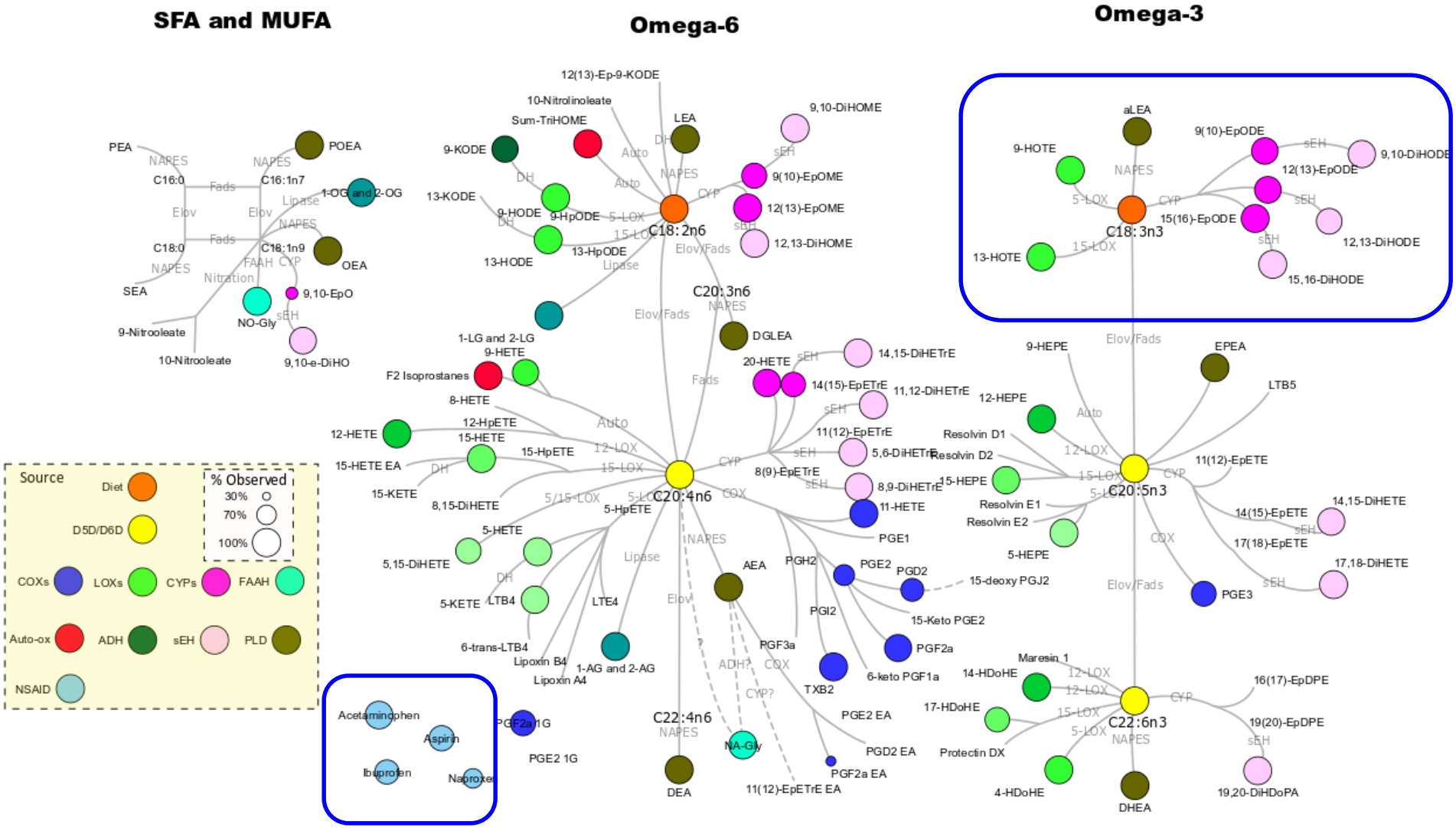
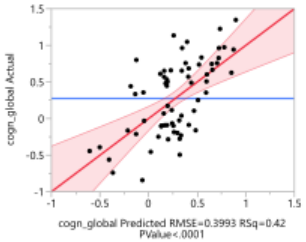


Fasted serum can predict global cognitive function

- In a cohort with normal to mild cognitive impairment:
- Predictors are CYP and LOX metabolites of alpha-linolenic acid (18:3n3), ibuprofen and age

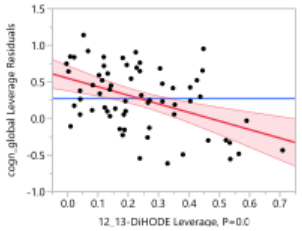
Whole model

Actual by predicted plot

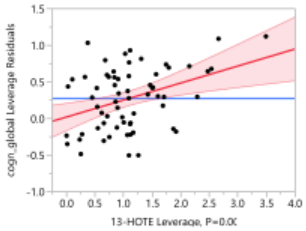


Leverage plots

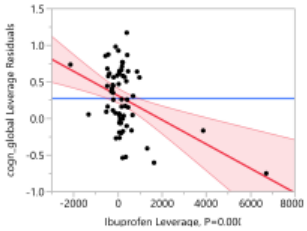
12,13-DiHODE



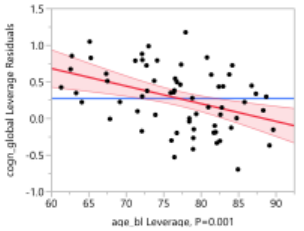
13-HOTE



Ibuprofen



Age



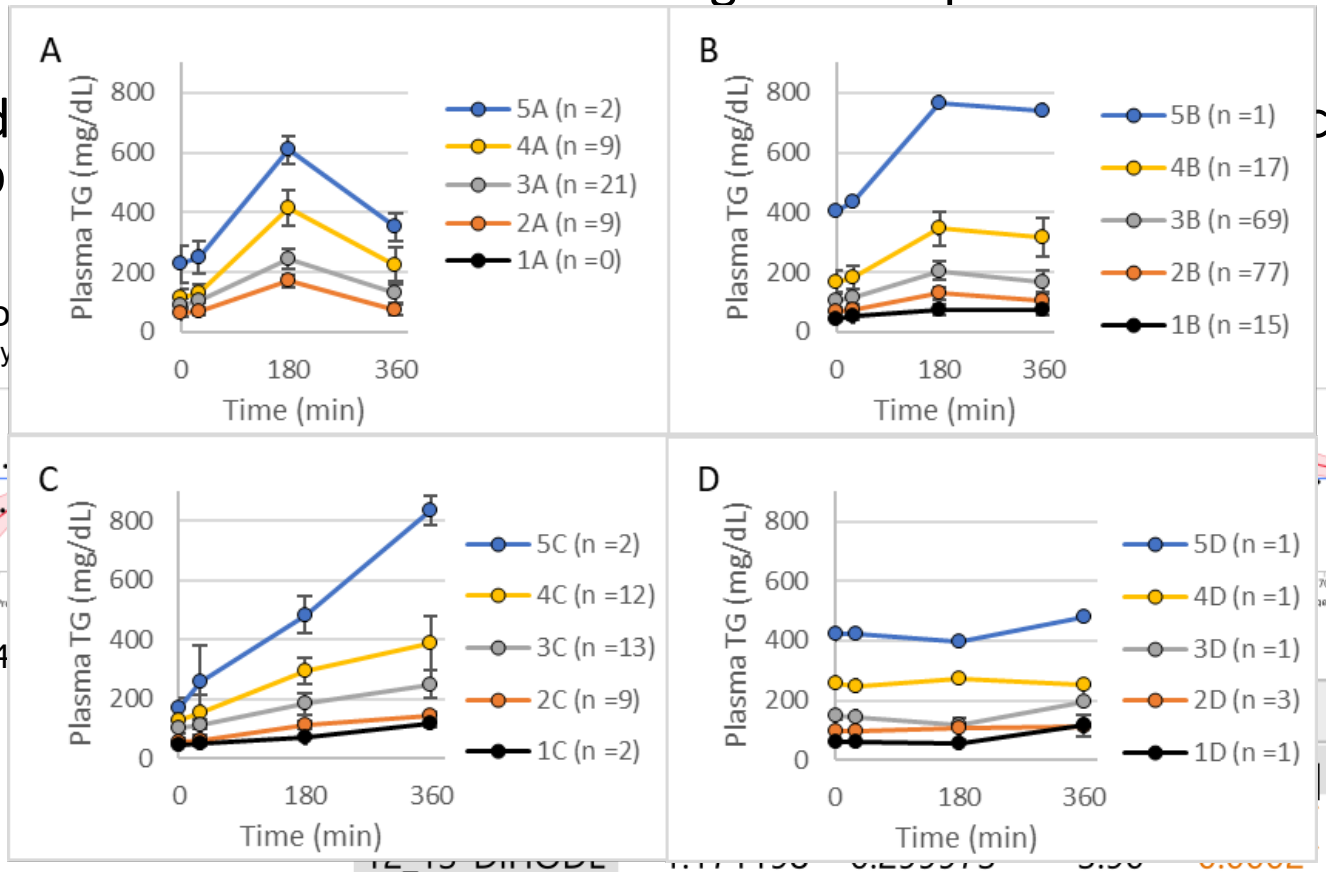
R2 = 0.42; P <0.0001

Parameter Estimates

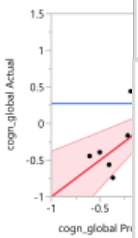
Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	2.1861752	0.548699	3.98	0.0002*
12_13-DiHODE	-1.171198	0.299973	-3.90	0.0002*
13-HOTE	0.2326082	0.072895	3.19	0.0023*
Ibuprofen	-0.000166	4.62e-5	-3.59	0.0007*
age_bl	-0.024039	0.006928	-3.47	0.0010*

Fasted serum can predict global cognitive function

- In a cohort with normal to mild cognitive impairment:
- Pred … cid (18:3n3), ibup …

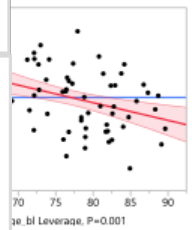


Who…
Actual by…



R2 = 0.4…

Age



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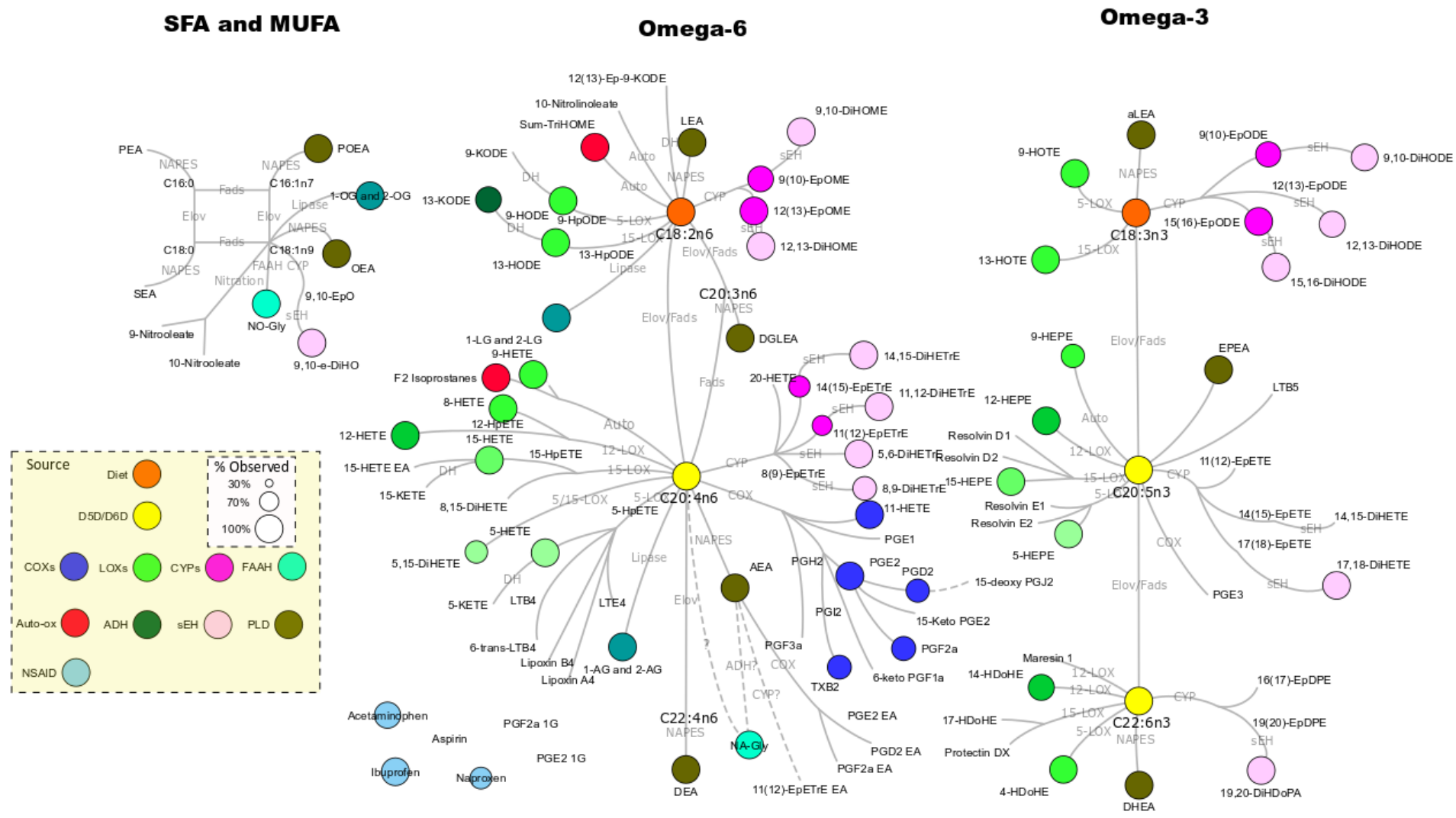
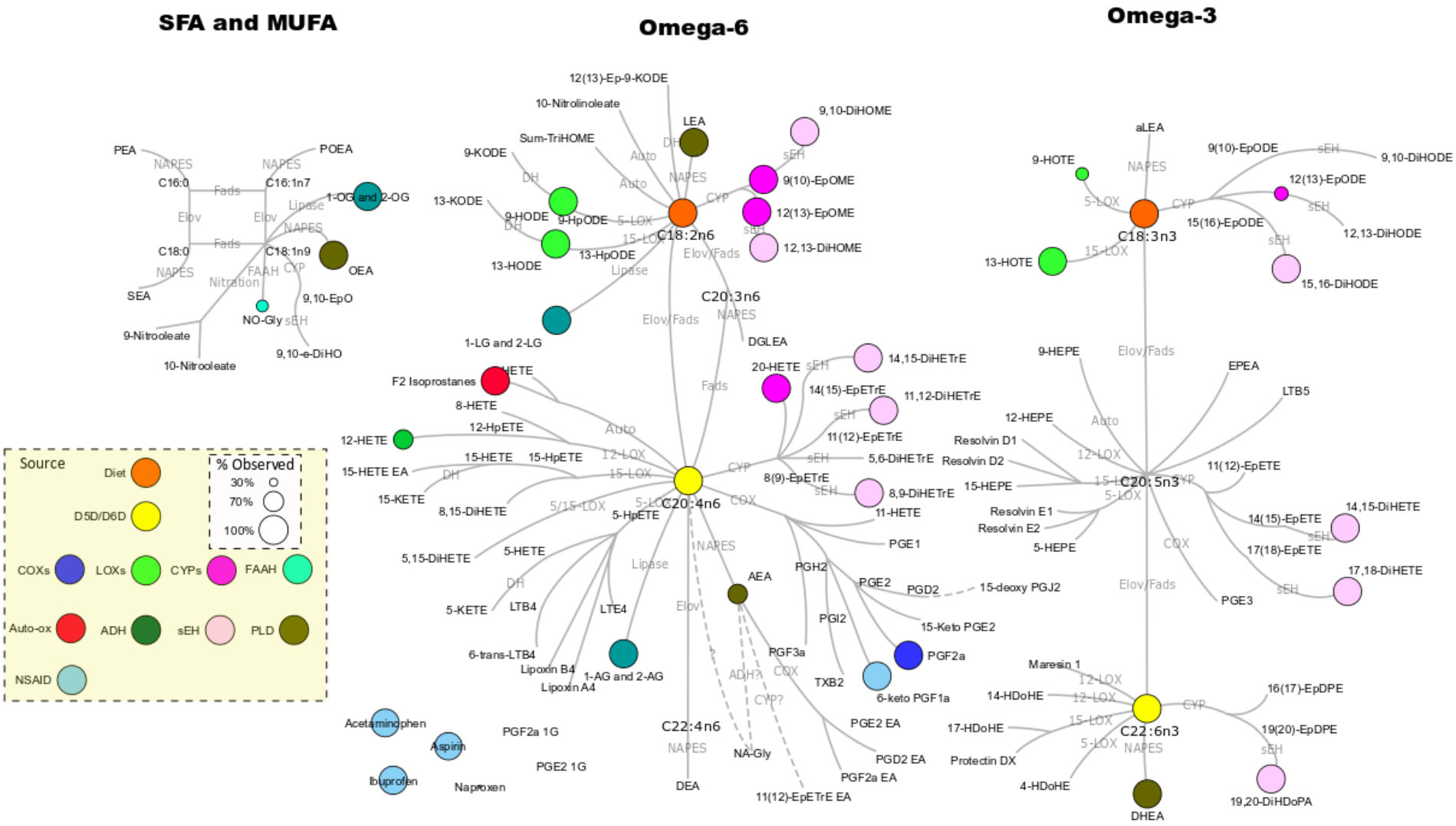
AD & Control Plasma Oxylipin and Endocannabinoid Coverage

Results from 300 plasma samples from Control and AD subjects

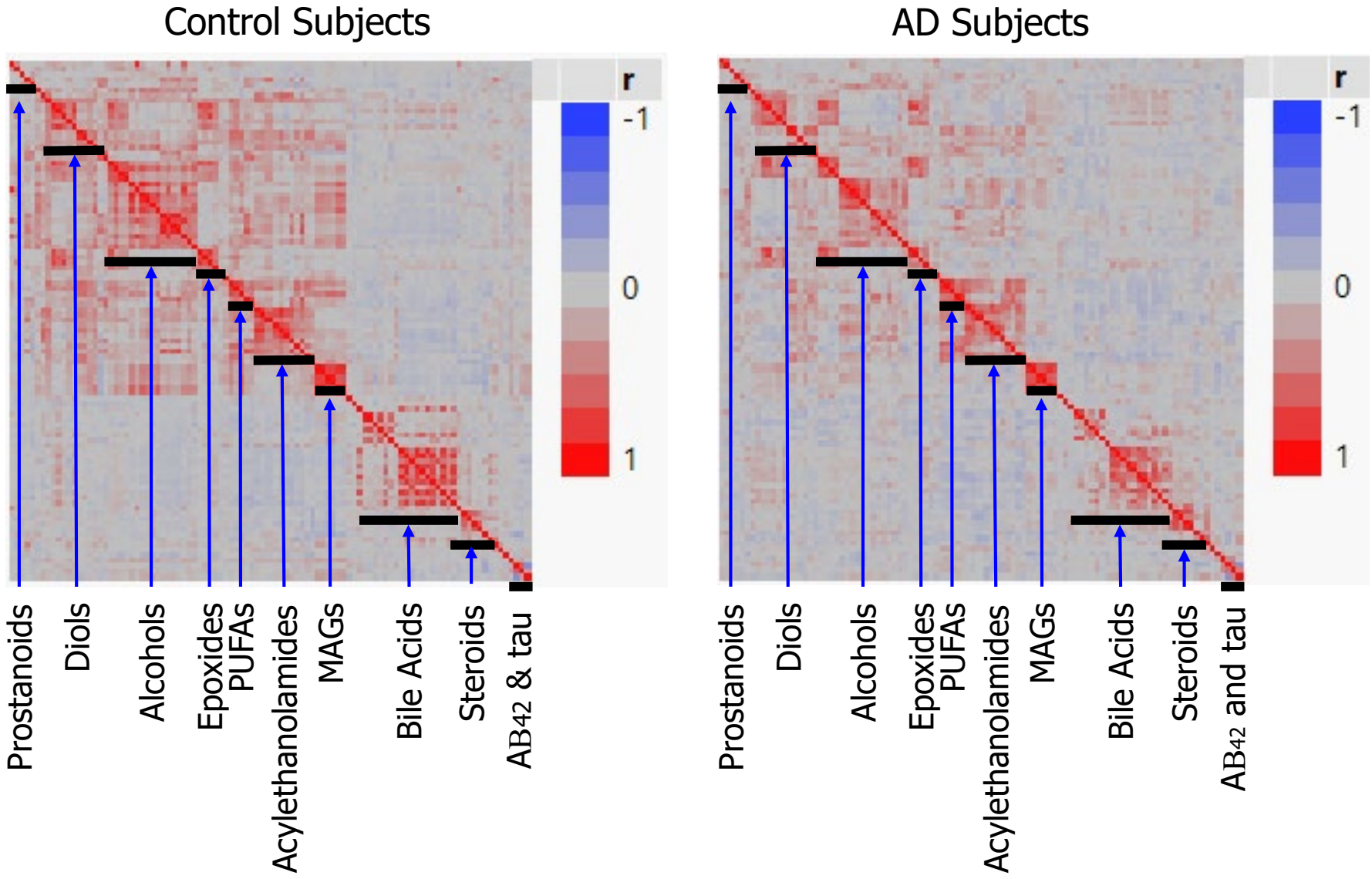


AD & Control CSF Oxylipin and Endocannabinoid Coverage

Results from 300 plasma matched CSF samples from Control and AD subjects

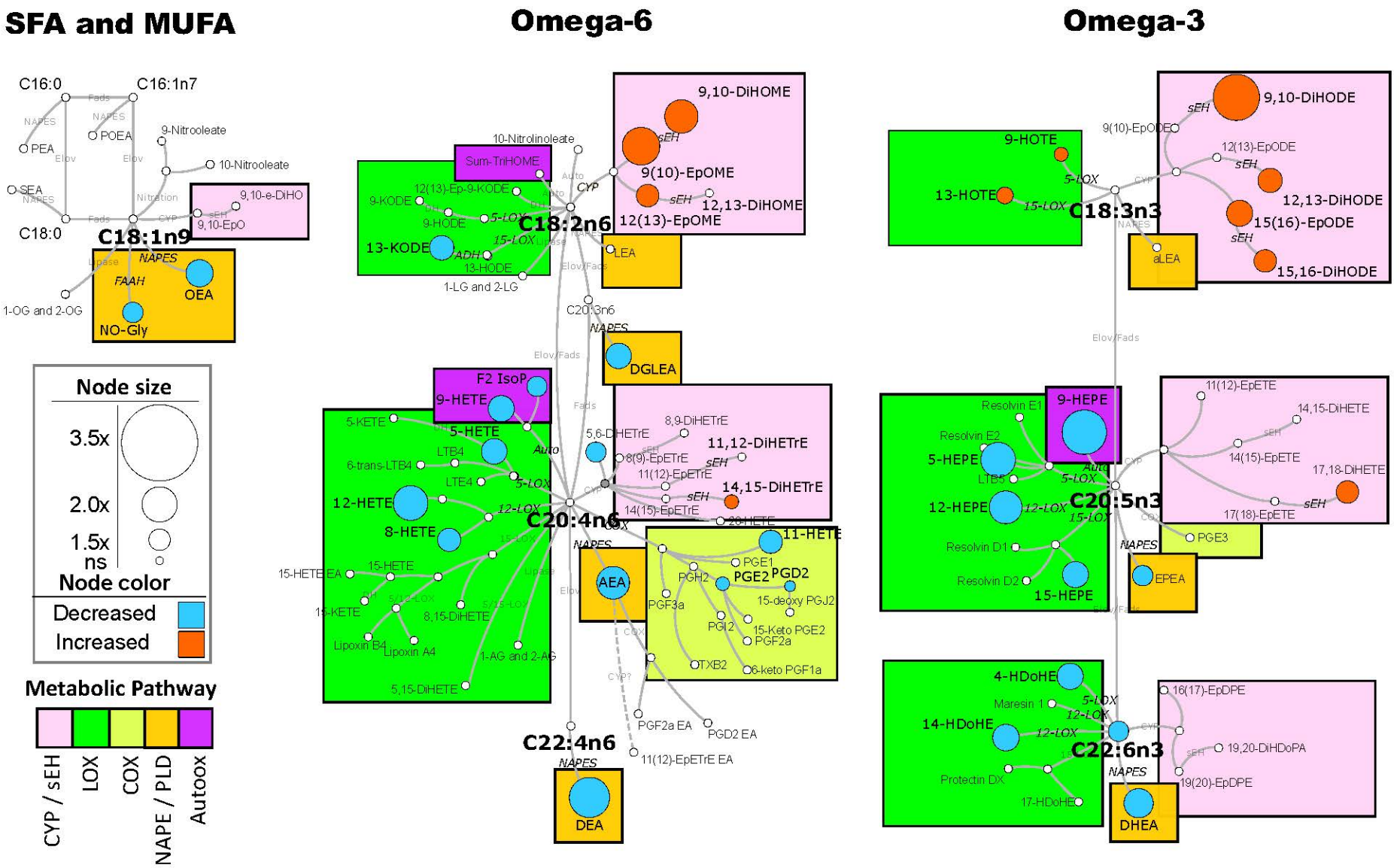


AD Changes Plasma Mediator Correlation Structure



AD-Dependent Plasma Oxylipin and Endocannabinoid Changes

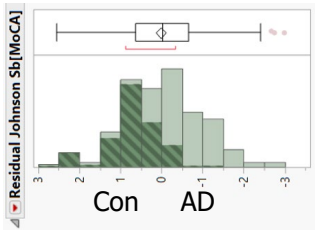
Results from 300 plasma samples from Control and AD subjects



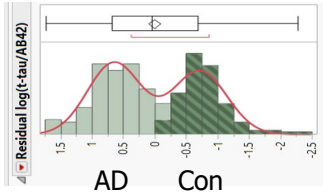
Metabolite networks relate to different AD markers

Stepwise linear regressions to build simple predictors of AD markers:

- **Montreal Cognitive Assessment (MoCA) scores**
  - Low Acylethanolamides 15-LOX and COX products, with high secondary bile acid conjugates



- **Log(tau/AB42)**
  - Low Acylethanolamides and CYP and sEH products



AD Changes Plasma Mediator Correlation Structure

- Metabolite markers of clinically relevant factors offer novel insights to interpret the mechanisms associated with identified AD markers.

- Mediator profiling is likely showing pathophysiological responses, and may not have disease specificity (Biomarkers of Response).

	Sens-(1-Spec)	True +	True -	False +	False -
All Variables (n=4)	**0.9369**	**142**	**130**	**3**	**6**
Log(tau/AB42)	0.8708	140	123	10	8
MoCA	**0.8017**	**132**	**121**	**12**	**16**
All Mediators Only (n =14)	0.7791	131	118	14	17
MoCA predictors (n =9)	**0.6747**	**121**	**114**	**19**	**27**
Tau/AB predictors (n =8)	0.6581	123	110	23	25

Summary

- Circulating lipid mediators from both fasting serum and plasma can predict cognitive function, suggesting a links between peripheral metabolism and cognitive function.

- Results support a general reduction in peripheral endocannabinoid tone, and lipoxygenase metabolism and an activation of CYP-dependent oxylipin metabolism in AD.

- Mass spec based profiling of lipid metabolism can provide robust and informative measures for AD research from low sample volumes of archived samples.

Alzheimer's Disease Metabolomics Consortium Team Members

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SAGE Networks
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Jan Krumsiek and Team

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Ameer Taha

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Alexandra Kueider-Paisley
P. Murali Doraiswamy (AD clinician)
Colette Blach (Database)
Arthur Moseley (Duke Proteomics and Metabolomics Core PI)
Will Thompson, (Duke Proteomics and Metabolomics Core, Metabolomics Leader)
Siamak Mahmoudiandehkordi (Statistics)
Rebecca Baillie (Lipid metabolism)
Kathleen Welsh-Bohmer
Brenda Plassman

Why expolore lipid mediators?

- Increasing evidence suggests Alzheimer's has early metabolic perturbations and high diabetes co-morbidity.

- Alterations in cholesterol/lipid metabolism are observed in AD, and genetic variants in these pathways alter AD risk.

- Inflammatory changes in lipid signaling have been broadly implicated in neuro-degenerative disorders.

- Advances in LC-MS/MS targeted lipid mediator metabolomics allow broad coverage of these and other interacting metabolic cascades from precious samples.

Plasma and Serum profiles in the Emory and RUSH cohorts