Molecular Effects of Peripheral Surgery on the Aging Human Brain

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Disclosures:

- Private Legal Consulting Work
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Surgery: A Common Major Stressor for the Aging Brain

6.2 million major inpatient surgeries/year among Americans age ≥65 (Becher RD et al, *Annals of Surgery*, 2024)

≥ 20 million Americans age ≥65 undergo inpatient & outpatient surgery/year (Elixhauser A et al, *Arch Surg* 2010)

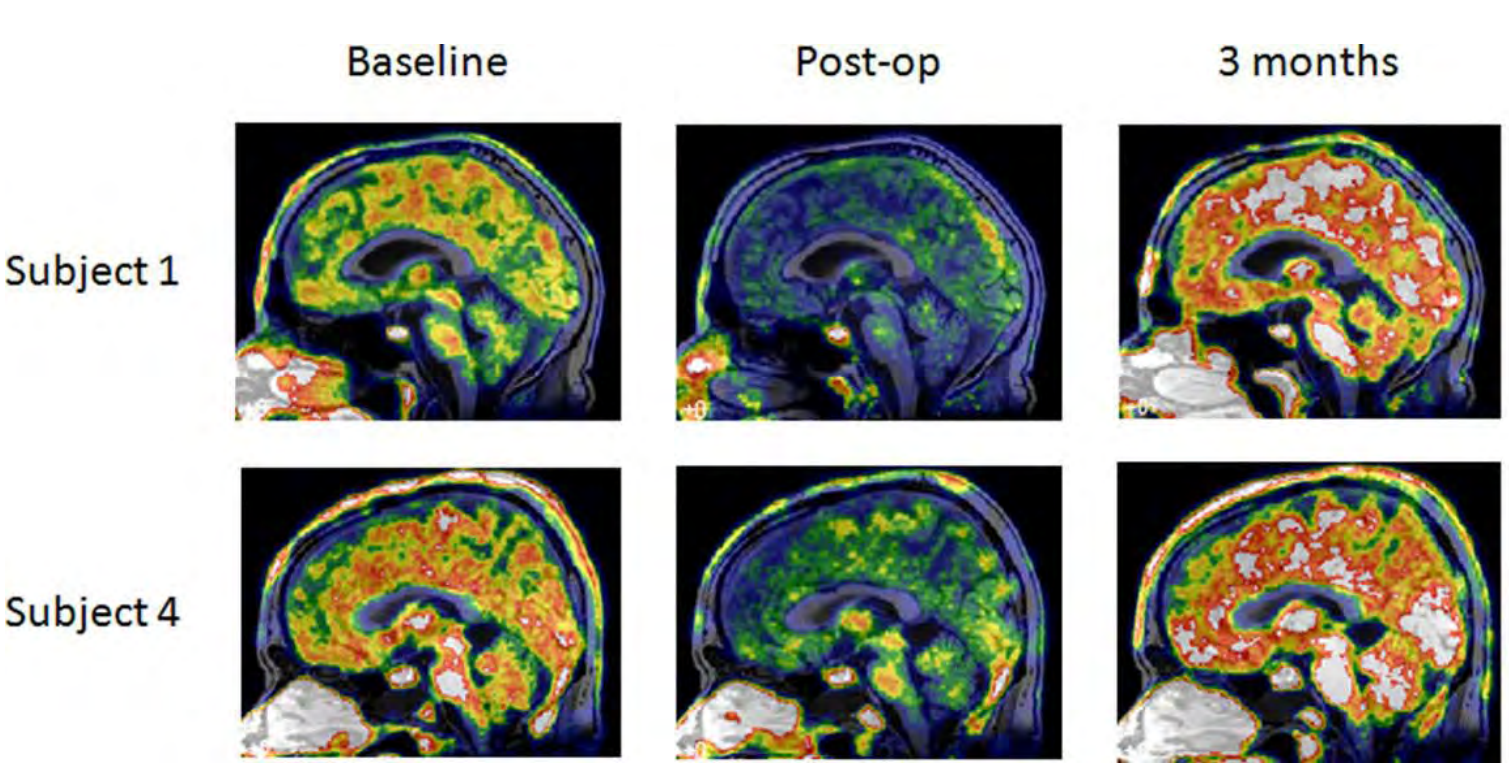
-1 year mortality rate after major inpatient surgery among Americans age ≥65 is 13.4% (Gill TM et al, JAMA Surg, 2022)

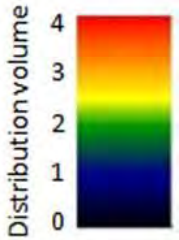
The Most Common Postoperative Complications Among Older Americans Affect the Brain

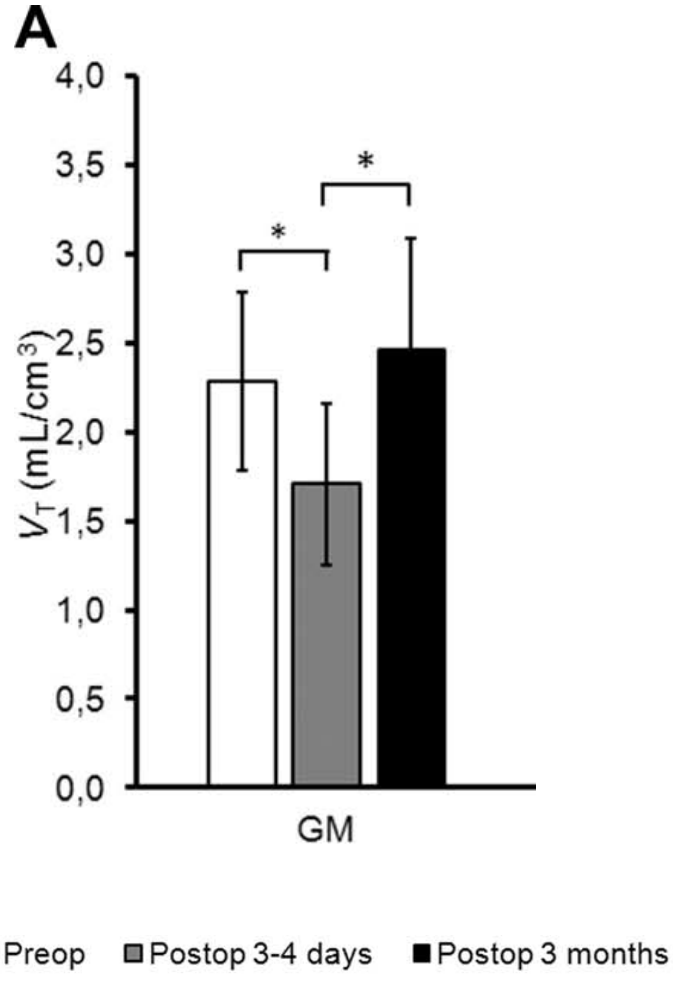
Complication	Rate	Total
Stroke w/in 30 days	0.3%	~21,000
Delirium w/in 30 days	3.6%	216,000
Cognitive Decline (3 months)	>10%	>600,000

References: Glance LG, *JAMA Surg 2022*; Lander HL, *JAMA Netw Open*, 2025; Moller JT, *Lancet*, 1998; Berger M, *Anesthes Clinics,* 2015

What are the effects of Peripheral Surgery on the Aging Human Brain?







-Forsberg A et al, *Annals of Neurology*, 2017

What is ApoE?

-main cholesterol transport protein in the brain, produced by astrocytes, carries cholesterol to neurons

-has 3 allelic variants, ε2, ε3, ε4

-ApoEε4 has an allele frequency of 14%

-ApoEε4 homozygotes have a 10-30x fold increase in Alzheimer's disease risk

-ApoEε4 is the most common genetic risk factor for late onset Alzheimer's disease

What is CN-105?

-A five amino acid peptide from the receptor binding region of the APOEe4 protein, which blocks the interaction between APOEe4 and its receptor (LRP)

Dr Danny Laskowitz,
Duke Neurology

What is CN-105's pharmacology, safety?

-Plasma half life =3 hours, crosses blood-brain barrier

-Excellent safety record in phase I study at DCRU

-Guptill JT et al, *J Clin Pharmacol*, 2017

-Currently in a Phase II multi-center study for Sub-Arachnoid Hemorhage (SAH)

Why study ApoE in surgical patients?

-Leading hypothesis for why ApoEε4 →Alzheimer's is *via increased neuro-inflammation*

-Neuroinflammation and other pathology takes decades to develop in Alzheimer's disease

-Yet, neuroinflammation occurs within 24 hrs after non-cardiac, non-neurologic surgery in older adults

-Berger M et al, *Front Immunology*, 2017
-Tang J et al, *Anesthesiology*, 2011
-Buvanendran et al, *Anesthesiology*, 2006

MARBLE- Modulating ApoE signalling to Reduce Brain inflammation, deLirium and postopErative cognitive dysfunction

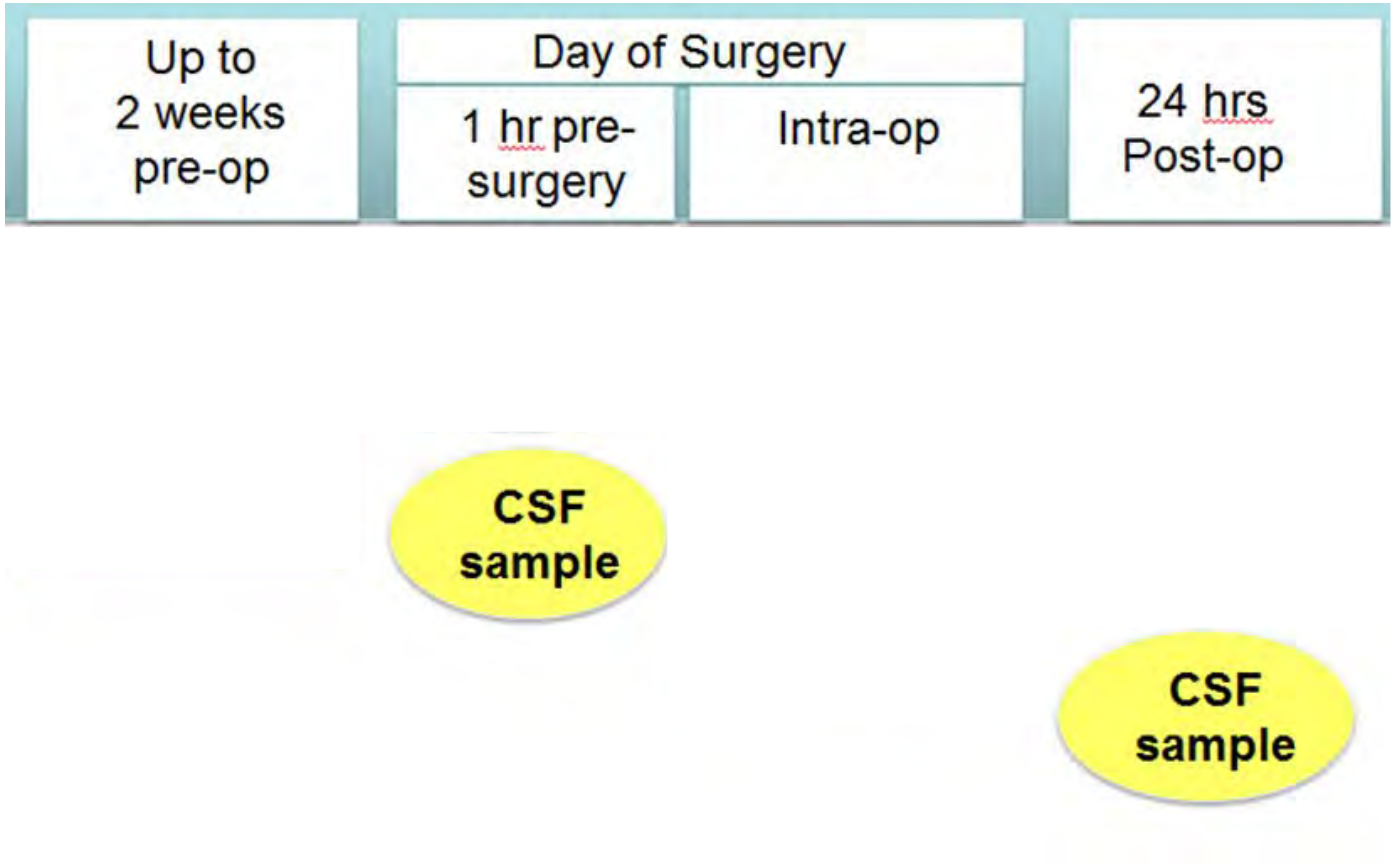
Inclusion Criteria

1. Age > or = 60
2. English Speaking
3. Surgery Scheduled for >2 hrs
4. Planned overnight hospital admission

Exclusion Criteria

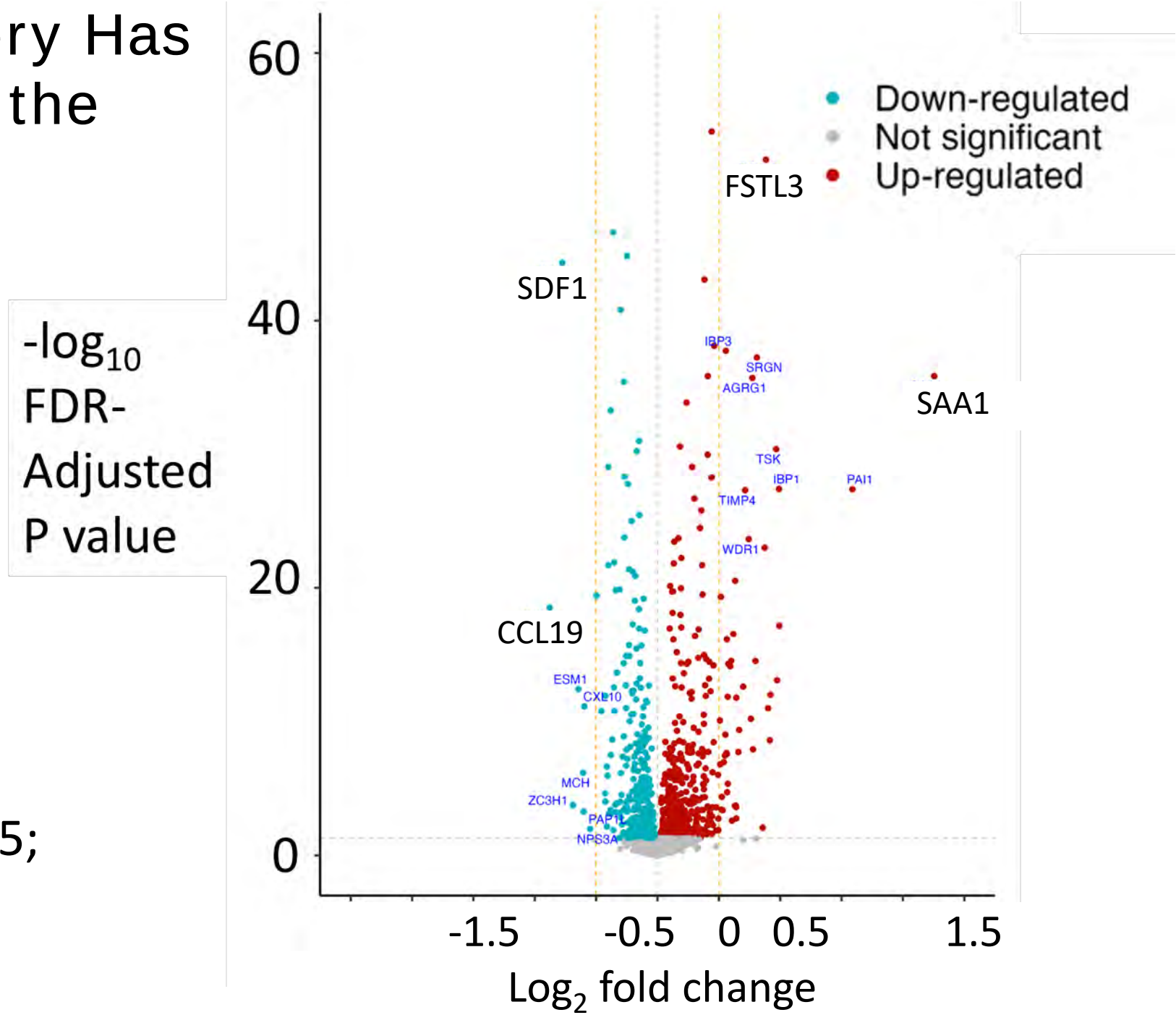
1. Prison Inmates
2. Planned Chemotherapy prior to 6 wk postop visit
3. Unable to undergo Lumbar Punctures
4. Major Head Trauma between preop, 6 wk postop visits

MARBLE Study Patient Flow Diagram



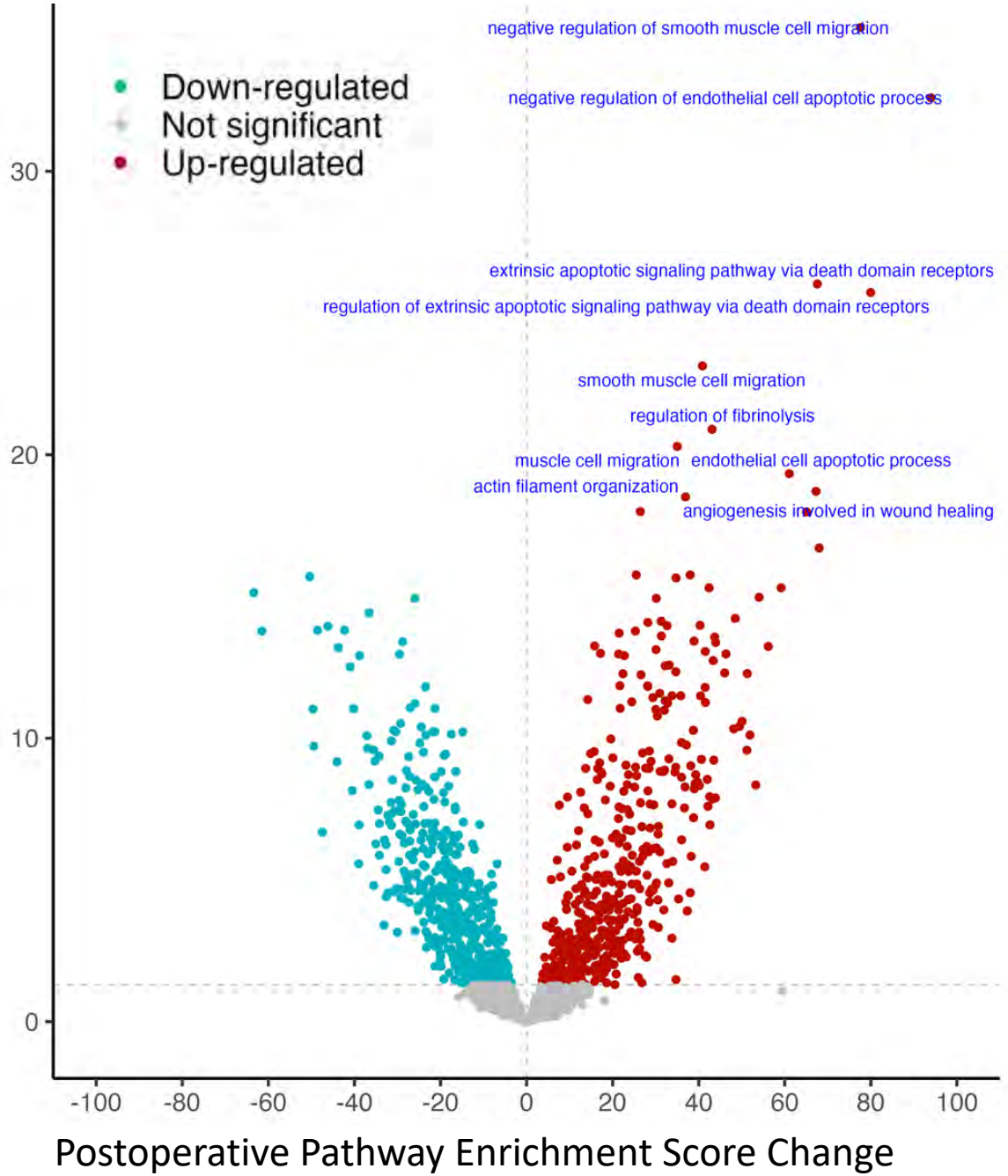
Baseline Patient Characteristics	Value
Age	68.9 (5.0)
Sex- male/female	65.0% / 35.0%
Education (years)	16.3 (3.4)
Race-Caucasian/White	118 (86.1%)
Black/African American	10 (7.3%)
Asian	2 (1.5%)
American Indian/Alaskan Native/Other/Unknown	7 (5.1%)
ApoE-e4 carrier	38 (27.7%
BMI	29.7 (5.0)
Surgery Type- Thoracic	9 (6.6%)
General	20 (14.6%)
Urologic/Gynecologic	44 (32.1%)
Orthopedics	52 (38.0%)
ENT	7 (5.1%)
Plastic	5 (3.6%)

Major Peripheral Surgery Has Widespread Effects on the Human CSF Proteome:



-Zou H et al, *MEDRXIV,* 2025; *Communications Medicine (Under Review*)

Effects of Major Peripheral Surgery on Human CSF Protein Pathways:



$-\log_{10}$ FDR-Adjusted P value

-Zou H et al, *MEDRXIV,* 2025; *Communications Medicine (Under Review*)

CSF Protein Pathways Significantly Altered from before to 24 hours after Surgery

Up-regulated pathways	**Beta**	**Std.Err**	**Adj.P**
negative regulation of smooth muscle cell migration	77.574	4.183	8.53E-36
negative regulation of endothelial cell apoptotic process	93.981	5.417	2.56E-33
extrinsic apoptotic signaling pathway via death domain receptors	67.583	4.641	9.49E-27
extrinsic apoptotic signaling pathway regulation via death domain receptors	79.959	5.556	1.89E-26
smooth muscle cell migration	40.878	3.068	7.28E-24
Down-regulated pathways	**Beta**	**Std.Err**	**Adj.P**
regulation of non-canonical NF kB signal transduction	-50.390	4.940	1.98E-16
negative regulation of leukocyte apoptotic process	-63.415	6.381	7.28E-16
sulfur compound metabolic process	-25.949	2.638	1.16E-15
proteoglycan metabolic process	-36.575	3.801	3.77E-15
leukocyte apoptotic process	-46.150	4.912	1.13E-14

Conclusions

1) Peripheral Surgery leads to Widespread and Large Changes in the CSF Proteome 24 hours Later, with alterations in over half of all CSF protein pathways.

2) Significant Changes in Endothelial cell, Smooth Muscle cell, and Leukocyte Biology in the human CNS 24 hours after peripheral surgery.

3) Could dysregulation of these typical postoperative CSF pathway changes underlie postoperative CNS complications (ie stroke, delirium, cognitive dysfunction, etc)?

4) Could drugs that target these pathways improve postoperative brain recovery (ie resilience against CNS complications) among older adults?

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-NIA R01-AG073598

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-Duke/UNC ADRC

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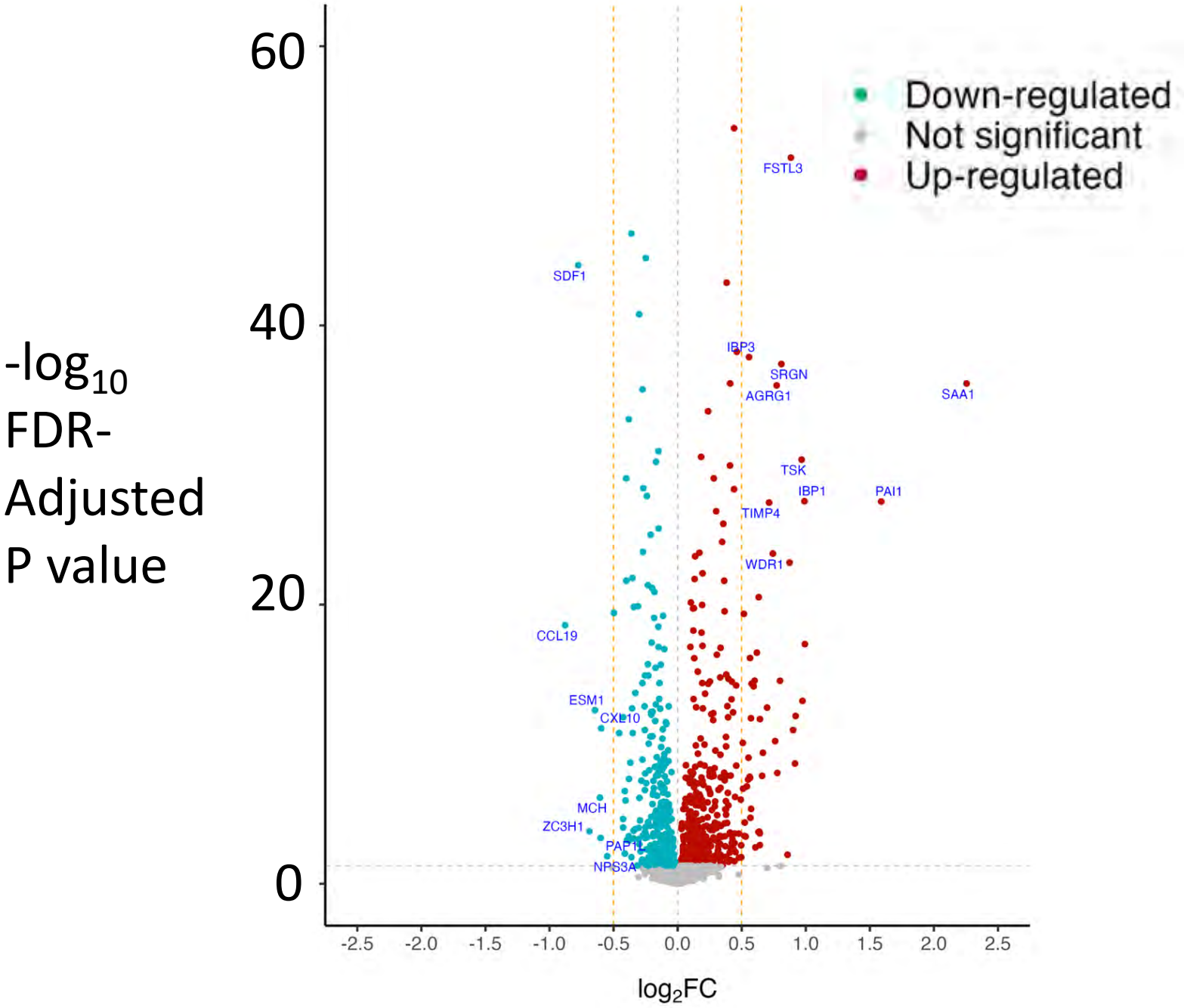
-Mary Cooter, Morgan Rosser (statisticians)

-**Surgery Collaborators**

-Patients

Thanks To:


-log10 FDR-Adjusted P value
60
40
20
0
Down-regulated
Not significant
Up-regulated
FSTL3
SDF1
IBP3
SRGN
AGRG1
SAA1
TSK
IBP1
PAI1
TIMP4
WDR1
CCL19
ESM1
CXL10
MCH
ZC3H1
PAP1
NPS3A
-2.5
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
log2FC