M2OVE-AD projects updates: Renin-Angiotensin-Endothelial Pathway in AD

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All our research volunteers

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RUSH

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Over-arching Aims

- **Investigate the contributions of *vascular dysfunction related to the endothelium* in the systemic and cerebral circulations to AD,**
- **Identify underlying molecular/cellular regulators**
- **Identify potential vascular and endothelial therapeutic targets**

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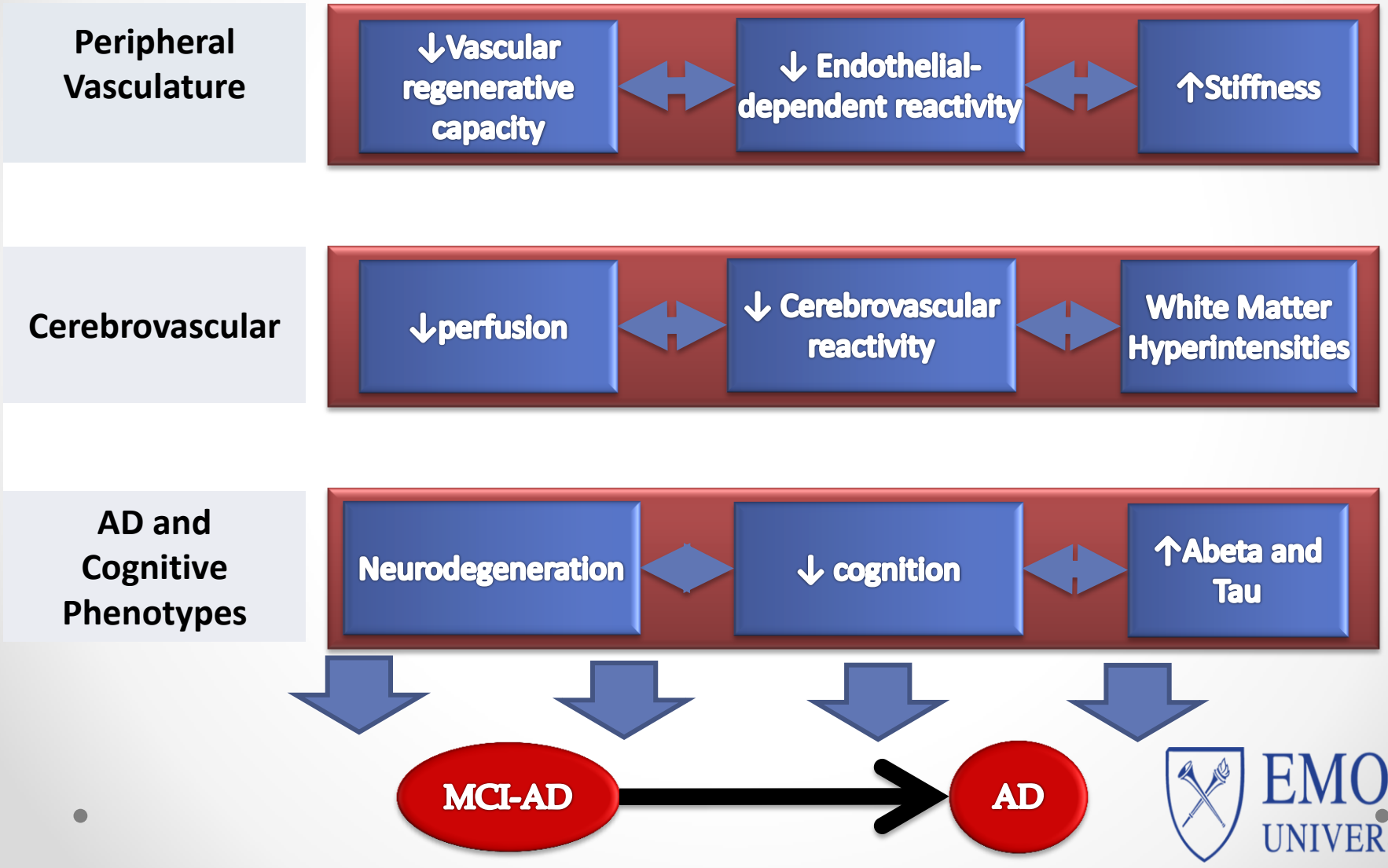
Peripheral and Central Vascular contributors



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M2OVE-AD 3 projects

- ***Project 1***: Longitudinal study of 250 individuals deeply phenotyped and followed for at least 2 years.
- ***Project 2***: 3 cohorts of TgF344 and WT rats(N=120) randomized into placebo or angiotensin receptor blocker (candesartan).
- ***Project 3***: Multi-"omic" Integrative analysis on biospecimen in Project 1and 2 with additional analysis of 400 brains from the ROS/MAP for developing.

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Project 1: M2OVE-AD cohort

N=253 (132 @ Y1)	Normal controls (n=150)	MCI (n=103)	P-value
Age	63±1.3	66±1.7	0.16
% women	69%	56%	0.25
% AA	45%	52%	0.04
BMI	25.5±0.9	28.9±1.9	0.08
Education	15.9±0.4	16.0 ± 0.6	0.86
MOCA	27±0.3	20±0.7	<0.0001
CDR (median)	0	0.5	0.001
Logical Memory	14±0.5	7±0.5	<0.0001
AD CSF signature*	24%	64%	0.0001
% HTN	40%	60%	0.20
% DM	13%	7%	0.54

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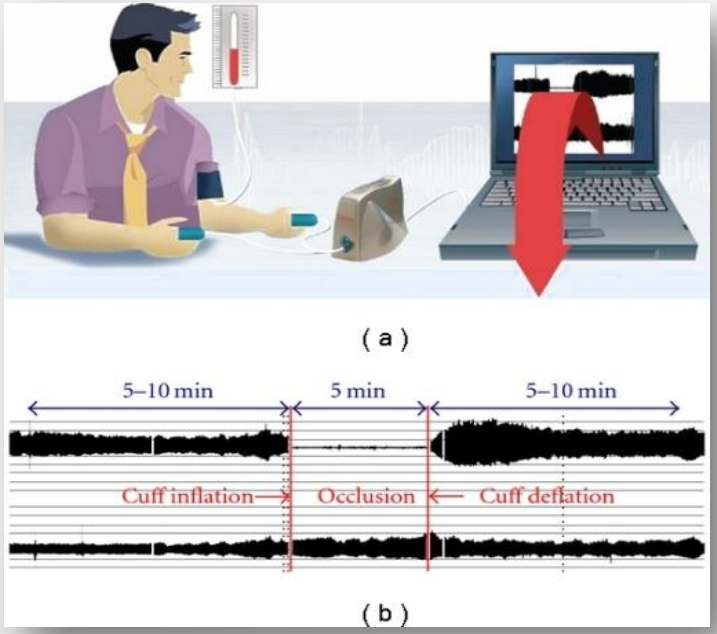
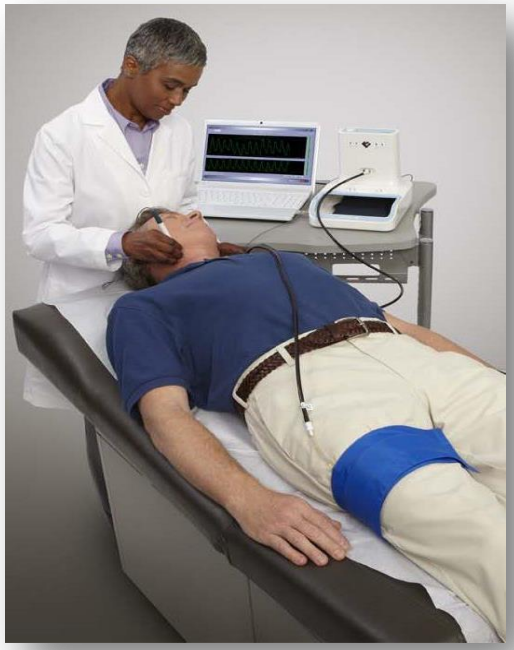
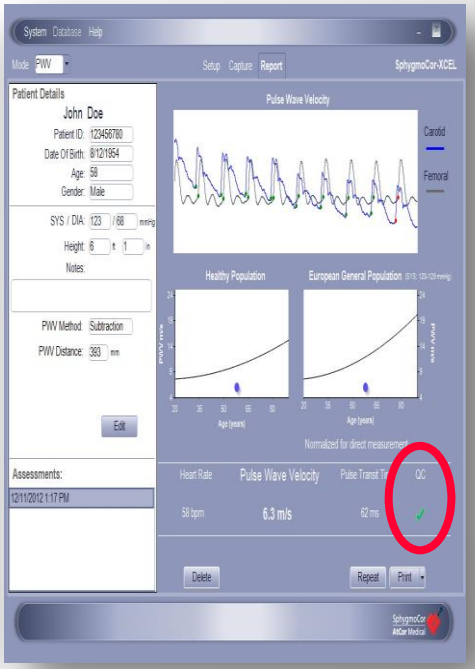
Peripheral Vascular function

Peripheral: digital pulse amplitude tonometry



Peripheral: Pulse Wave Velocity /IMT





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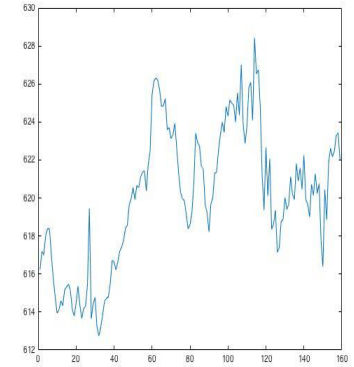
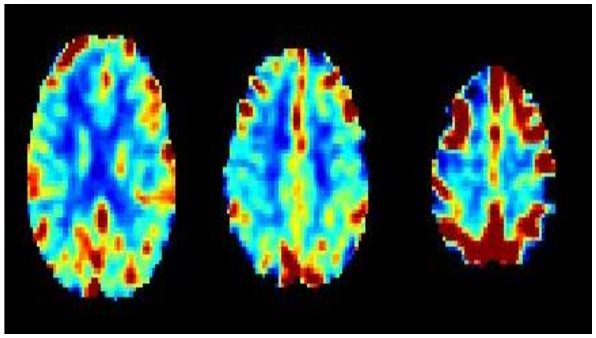
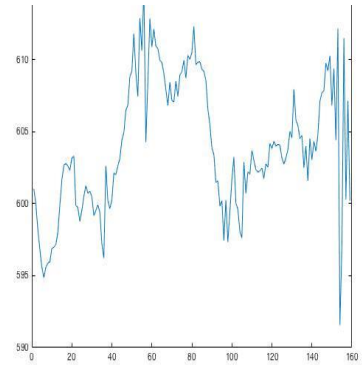
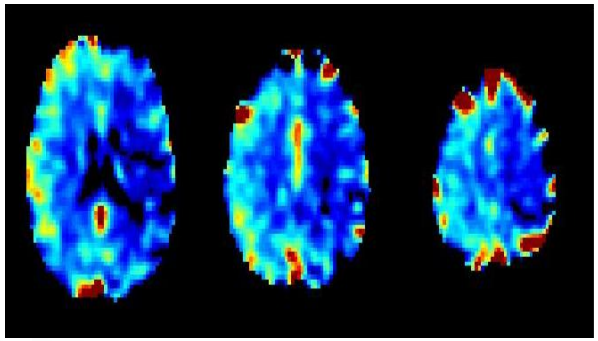
Central Vascular Measures

Central: BOLD sequence with CO2 challenge + beat-to-beat HR, BP, etCO2

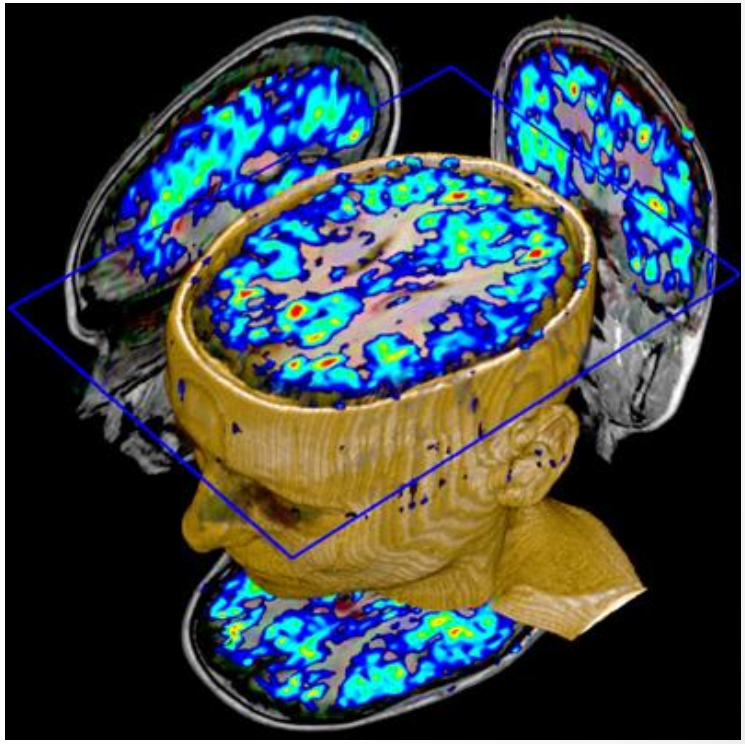








ASL- CBF



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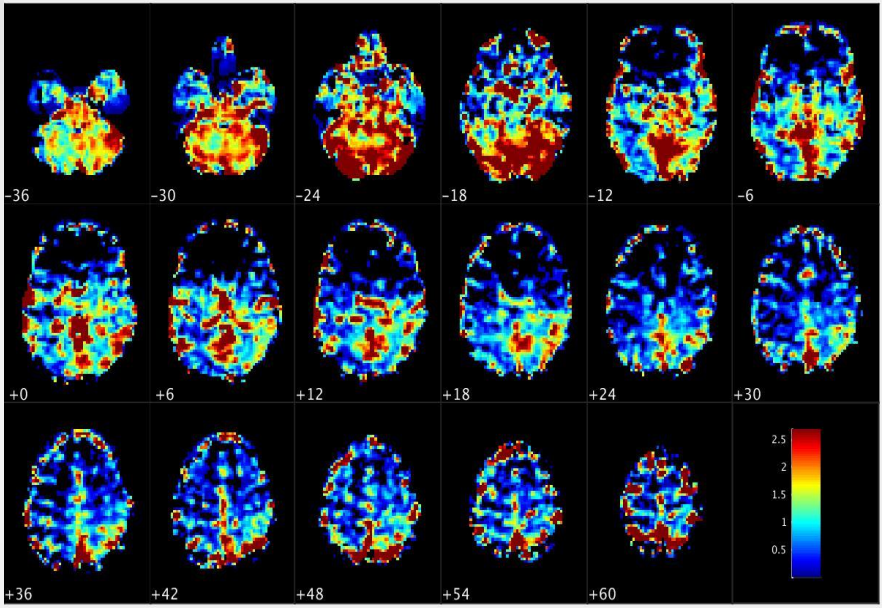
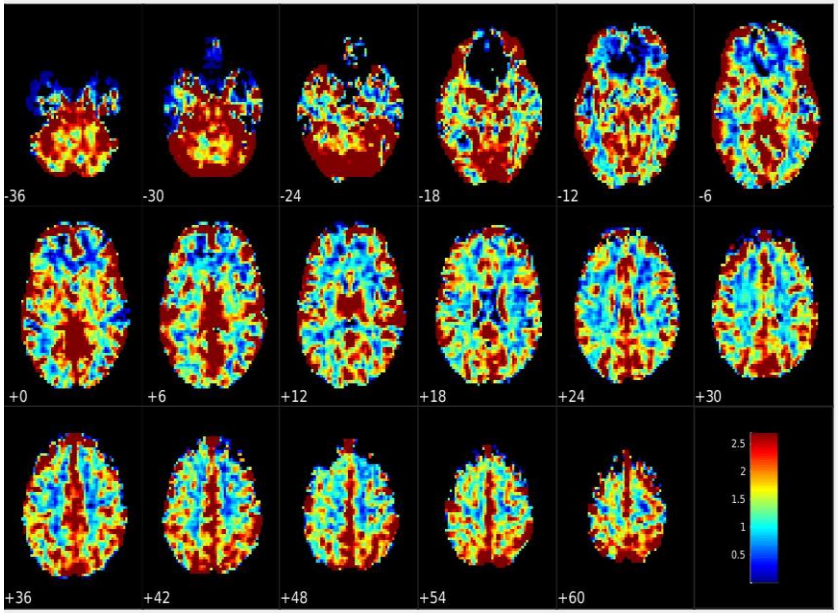
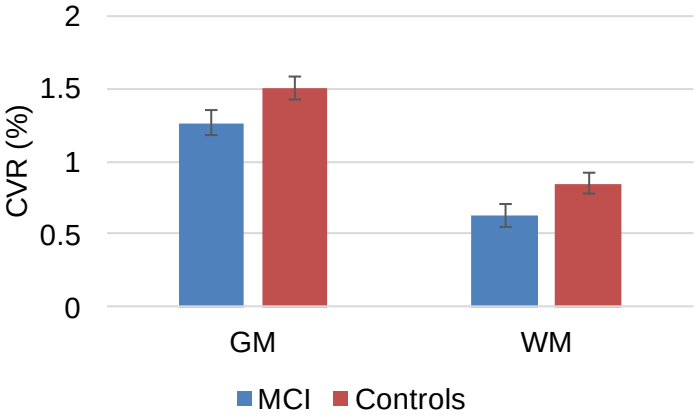
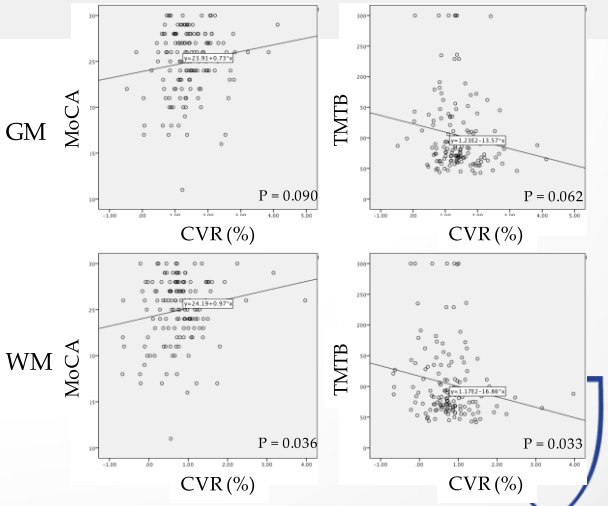
Cerebrovascular reactivity to CO2









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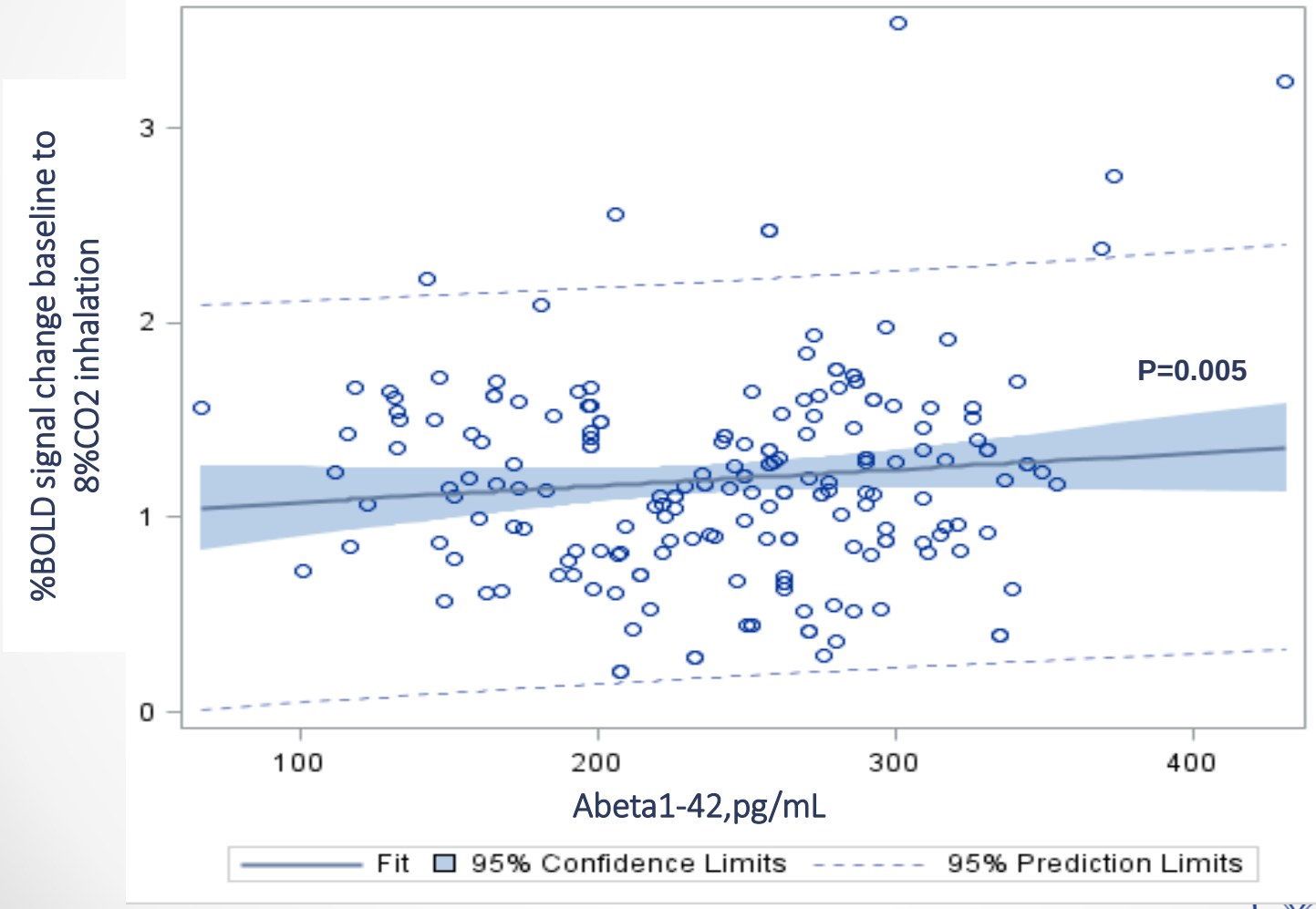
CSF ABeta$_{1-42}$ and poor cerebrovascular reactivity (CO_2-BOLD MRI)



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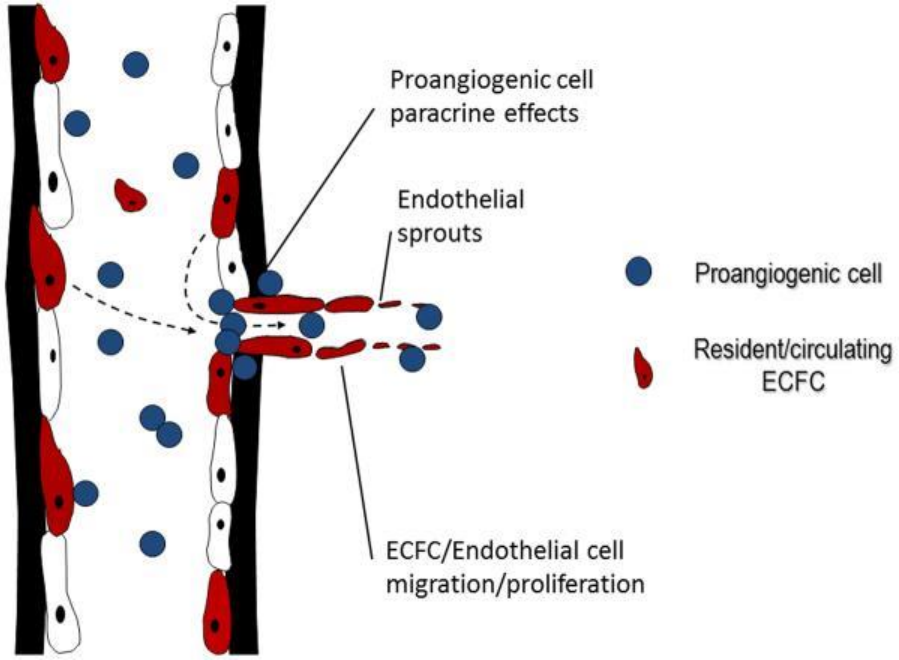
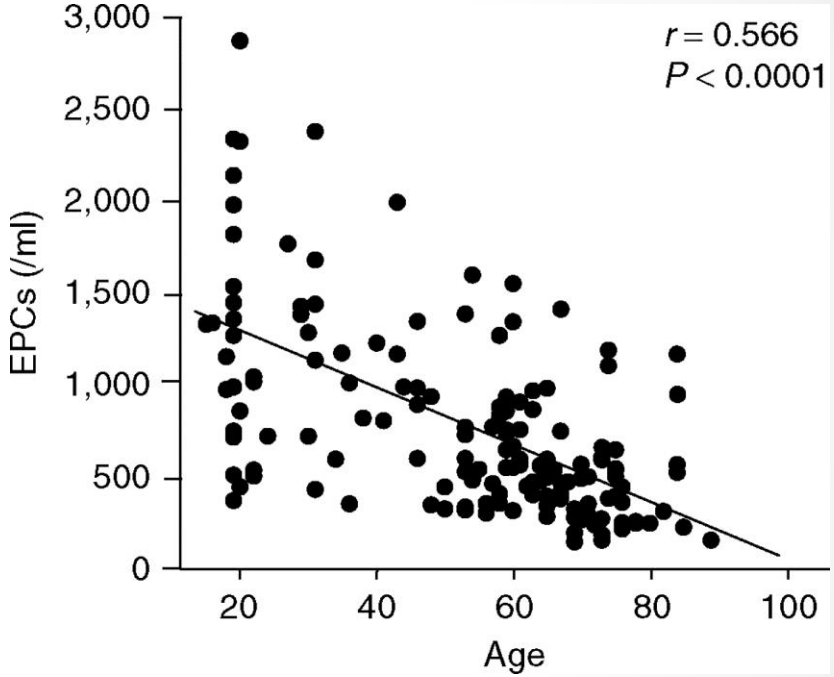
Bone-marrow derived Progenitor cells

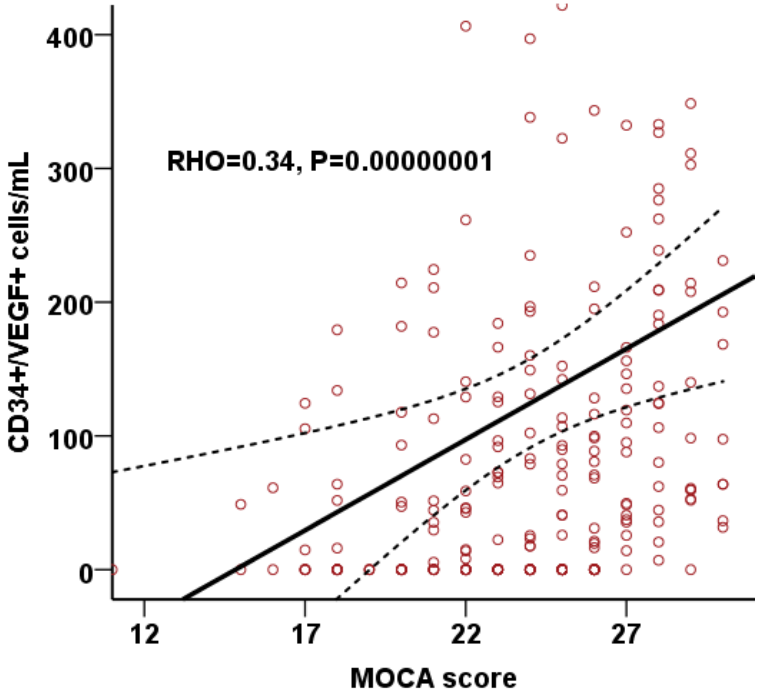


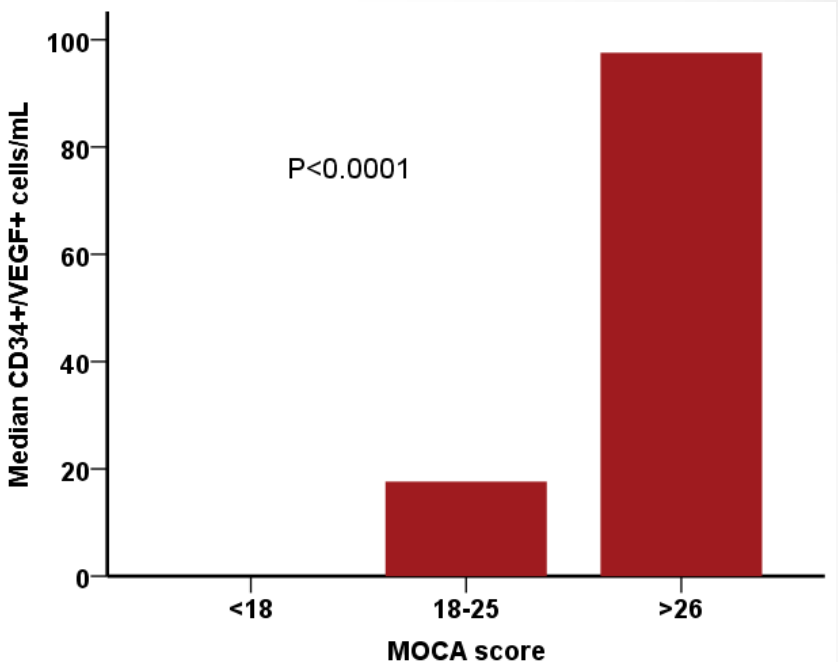
Bone marrow-derived proangiogenic cells are recruited to sites of tissue ischemia or damaged endothelium and secrete paracrine molecules to recruit circulating and tissue resident ECFC to participate in new blood vessel formation



Takashi Umemura et al. Am J Hypertens 2008;21:1203-1209

CD34+/VEGF+ PC severely depressed in MCI and correlate with MOCA score





	Normals	MCI	P-Value
CD34+	2555 (1573-3978)	1911 (1261-3159)	0.022
CD34+/CD133+	1974 (1157-2996)	1503 (966-2483)	0.016
CD34+/CXCR4+	1424 (821-2335)	1163 (694-1962)	0.098
CD34+/VEGF+	110 (45-208)	0 (0-73)	<0.0001

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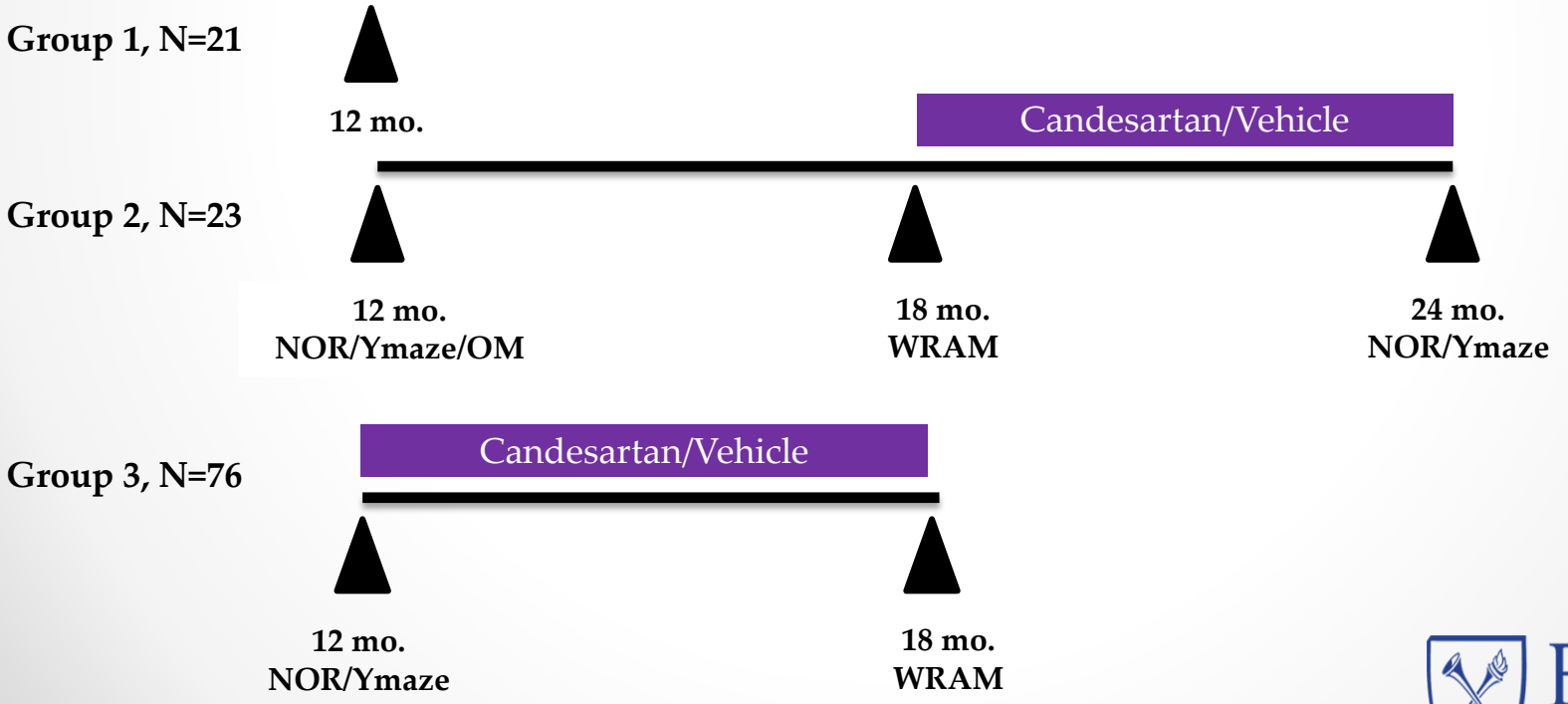
Project 2: 3 cohorts of TgF344-AD rats

- TgF344 are Fischer 344 background + two human: 'Swedish' mutant human APP (APP_{SW}) and Δ exon 9 mutant human presenilin-1 (*PS1ΔE9*)



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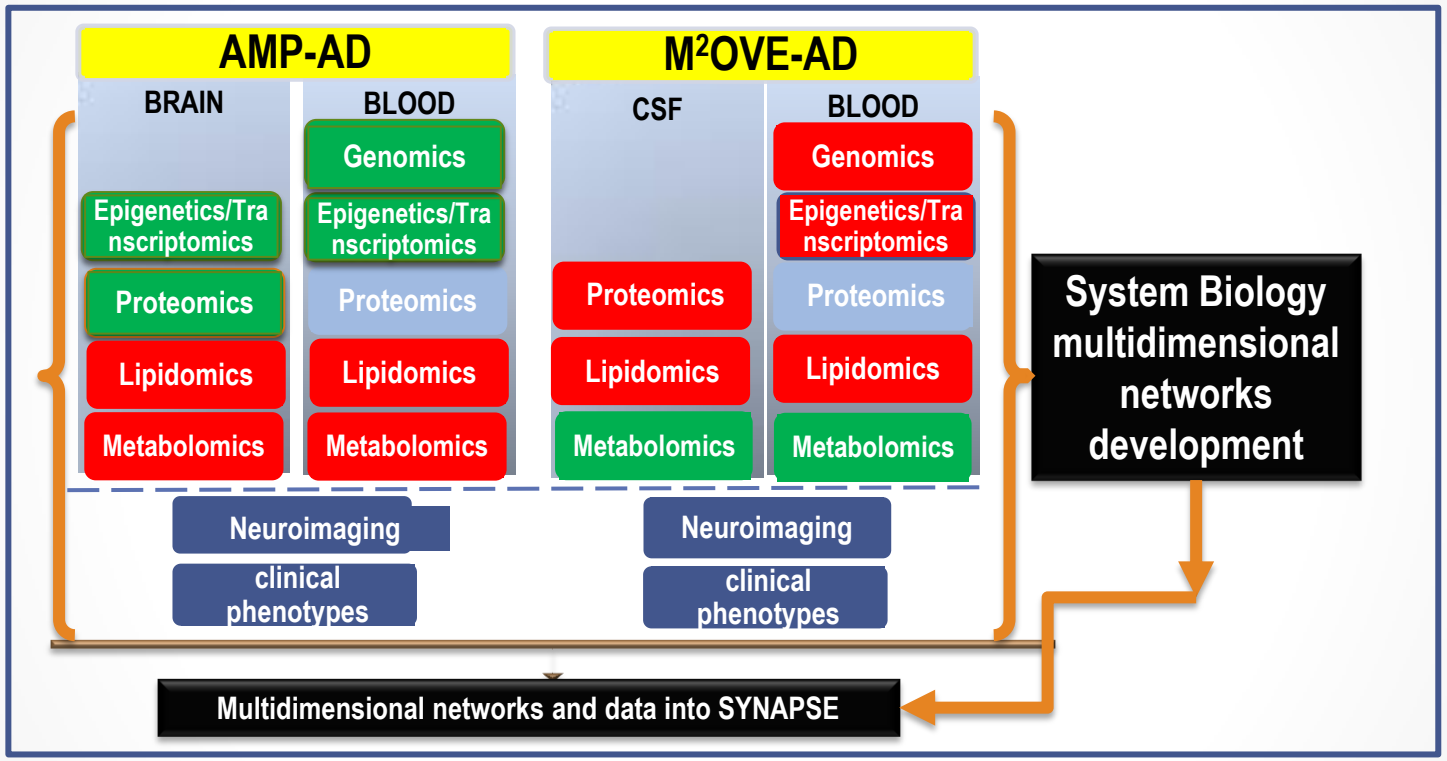
Project 3: Towards Building the multidimensional biomarkers



Study elements in AMP-AD (ROS/MAP) and M²OVE-AD. The 2 projects already include comparable molecular profiles and trait data (shown in blue), include individuals along the continuum of AD (pre-clinical, prodromal and dementia) and have brain tissue and biofluids.

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THANK YOU!