Implementing biomarker frameworks for Alzheimer's and vascular disease trials to reduce cognitive decline in T2DM

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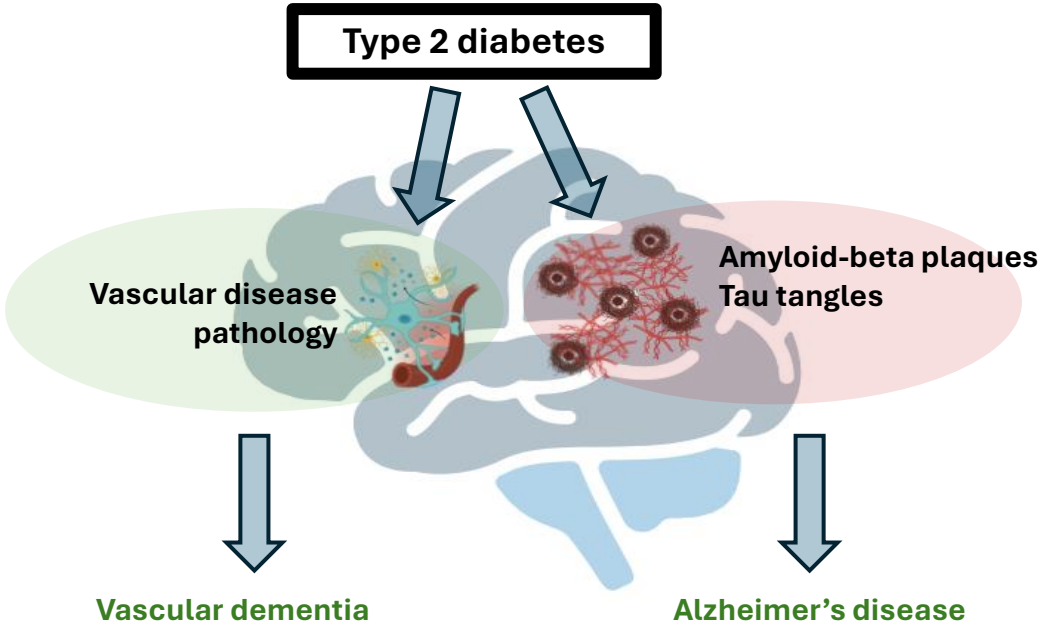
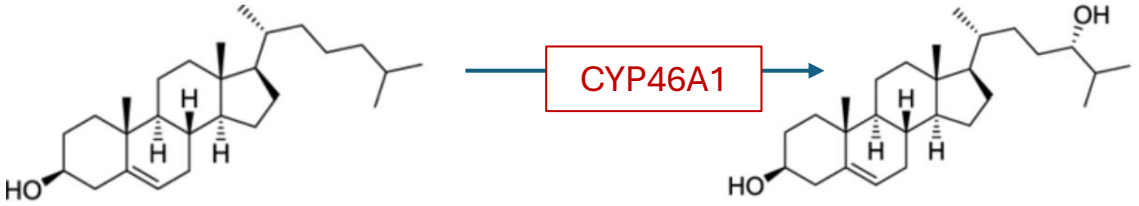
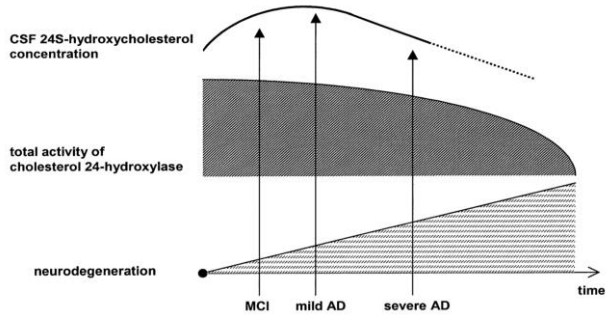
Patients with T2DM have AD risk, and are in need of tx



Targeting a new pathway: Brain cholesterol metabolism



Cholesterol **24S-hydroxycholesterol**



NEED TO OPTIMIZE CLINICAL TRIALS TO REDUCE SOURCE OF HETEROGENEITY

Trial checklist:

- ❑ Target patient group
- ❑ Trial design with ideal time points for embedded outcomes
- ❑ Cognitive outcome (efficacy)
- ❑ Biomarker outcomes (target engagement)

Implemented Frameworks:

FDA-BEST: -context of use of biomarkers

ATNIVS -validated AD biomarkers

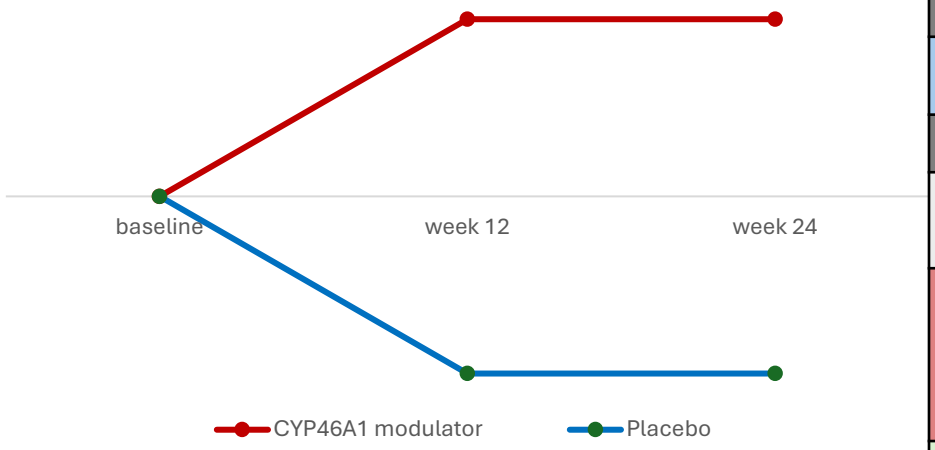
STRIVE-2 -validated vascular imaging markers

PROPOSED TRIAL DESIGN:
Optimizing both clinical efficacy and biological efficacy

Phase 2 study
Intervention: CYP46A1 modulator vs placebo over 24 wks
Target population: T2DM with VCI-ND

Trial checklist:
- ✓ Target patient group
- ✓ Trial design with ideal time points for embedded outcomes
- ✓ Cognitive outcome (efficacy)
- ✓ Biomarker outcomes (target engagement)

Primary outcome:
Efficacy: Cognition (NINDS-CSN) – demonstrated associations with VCI-ND
Secondary outcome:
Biological efficacy: AD, vascular, inflammation



		Baseline	Week 12	Week 24
Clinical outcome				
Outcome	**Cognition**	✓	✓	✓
Biomarkers of interest				
Biomarker of efficacy	**24S-hydroxycholesterol**	✓	✓	✓
ATNIVS	**Amyloid, Tau, Neurodegeneration, Inflammation, Vascular, Synuclein**	✓	✓	✓
STRIVE-2	**Vascular neuroimaging (eg: White matter hyperintensities)**	✓	✓	✓