Drug Repurposing for Use in the AD Population

considerations and limitations

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Disclosures

Advisor to:

- *Alopexx Enterprises, LLC*
- *CannScience*
- *Cognoptix, Inc.*
- *IntelGenx*
- *KalGene*
- *Neurodyn*
- *Treventis Corp.*

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Drug Repurposing-Repositioning

(an alternative opportunity)

What is it?

- ***Definition**: The use of established drugs in new therapeutic indications to create novel value and streamlined clinical development/treatments*
- ***Approach**: Repositioning of drugs that have been approved for other indications, or have failed for other indications in clinical trials*
- *Success examples in cancer, cardiovascular disease, incontinence, irritable bowel syndrome, obesity, erectile dysfunction, smoking cessation, psychosis, attention deficit disorder and baldness*
- *Some classes have potential in AD based on known mechanisms, epidemiological evidence or preliminary clinical trials.*
- *Uptake?*
  - *NIH- and MRC-supported drug repurposing programs with Pharma partnerships & agreements launched in US and UK in 2011-2012.*
  - *Support for repurposing contained within recommendations from the NIH Alzheimer's disease research summit – 2015.*
  - *Under consideration for developing ADCS strategies.*

The usual path to drug discovery-development
(gross generalizations)

- *Preclinical*
  - *Basic research leading to target identification*
  - *Assay development, screening*
  - *Target validation in preclinical models of disease*
  - *Lead molecule identification and optimization*
    - *Physical chemical properties, pharmacokinetics, pharmacodynamics*
    - *ADMET: Absorption, Distribution, Metabolism, Excretion, Toxicity*
  - *Formulations and bulk manufacturing*
  - *Safety, genotoxicity, multi-species toxicology, etc.*
- *Clinical*
  - *Phase 1 safety and exposure*
  - *Phase 2 target engagement, multiple dosing in patients, proof of concept*
  - *Pivotal phase 3 registration studies*

- *Timing and cost for neurological disease*
  - *2-5 years for preclinical phase, up to10 years for clinical phase*
  - *Up to $1B, perhaps more*
  - *Extremely low success rate*

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Shortcuts potentially afforded by drug repurposing for neurological disease

- *Eliminates need for most, and perhaps all preclinical R&D*
- *Established safety substantially reduces time and costs required to advance candidate treatment through clinical trials*
- *Clinical*
  - *Phase 1 safety and exposure studies may be substantially reduced or eliminated*
  - *Phase 2 target engagement, multiple dosing in patients, proof of concept still required, but dosing guidance and knowledge of brain penetration are often facilitated from previous studies*
  - *Pivotal phase 3 registration studies may also be shortened or more effectively designed based on the "facilitated" Phase 2 results*
- *Timing and cost for neurological disease*
  - *Strong potential for increased success rate, or faster path to discontinuation*
  - *Risks:benefits for patients are better defined*
  - *May streamline requlatory considerations*
  - *5-10 years for clinical phase still possible, but can save up to 10 years overall*
  - *Much less costly*

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Example #1: Levetiracetam (Keppra®)

Current indication: epilepsy

Overall rationale:

- *Strong preclinical mechanistic support in numerous basic science studies.*
- *Hippocampal overactivity ramps up during MCI due to AD.*
  - *Greater hippocampal activation in fMRI studies in age-dependent memory impairment, aMCI, presymptomatic ApoE4 carriers and presymptomatic familial AD.*
  - *Magnitude predicts subsequent cognitive decline/conversion to AD.*
  - *Correlates with extent of AD-specific brain atrophy in aMCI.*
- *Entorhinal cortex hypo-activity is present in MCI due to AD.*
  - *EC neurons are the first to degenerate in AD.*
- *Successful multi-dose phase 2 studies provided dosing optimization*
  - *At doses ~1/4 those typically used as anti-convulsant, "normalizes" hippocampal hyper-activity and EC hypo-activity, while enhancing memory task performance.*
- *Safety risks deemed acceptable at anti-seizure doses for epilepsy are further reduced at doses relevant to MCI, leading to streamlined regulatory path to clinical trial approval.*

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Levetiracetam: The HOPE4MCI Trial

Hippocampal Overactivity Prevention in the Elderly

- *A randomized double-blind trial of levetiracetam in MCI.*
- *Co-PIs: Drs. Michela Gallagher and Marilyn Albert*
- *Sponsor: AgeneBio*
- *Funding: Public-private partnership – AgeneBio, NIH, Johns Hopkins Univ.*
- *Study interventions: subjects randomized to once-daily extended-release formulation (AGB101) containing 220 mg levetiracetam vs. placebo*
- *Phase 3 registration study, sample size 830 subjects*
  - *Subjects: MCI due to AD with positive florbetapir amyloid-PET scan.*
  - *Treatment duration: 18 months*
  - *>200 sites in US, Canada & Europe*
  - *Planned launch 4Q2016*

HOPE4MCI

HOPE4MCI is a landmark public-private partnership supported by:

NIH National Institute on Aging

AGENEBIO™

JOHNS HOPKINS UNIVERSITY

The HOPE4MCI Trial

- *Primary efficacy outcome: Change in Clinical Dementia Rating – Sum of Boxes (CDR-SB) – FDA-endorsed primary endpoint to measure impact on reducing cognitive decline over 18 month study duration.*
- *Key secondary efficacy outcome: Neuronal injury as measured by change in entorhinal cortex atrophy by structural MRI.*
- *Additional secondary outcomes*
  - *CDR (global, memory box)*
  - *Neuropsychological tests*
  - *Other MRI measures*
  - *GDS (geriatric depression scale)*

www.HOPE4MCI.org
Clinicaltrial@agenebio.com

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Example #2: Telmisartan (Micardis®)

Current indication: hypertension

Overall rationale:

- *Longitudinal cohort studies have established links between mid-life hypertension and AD.*
- *Controlling hypertension, which is often concomitant with other vascular risk factors, vascular dysfunction and cerebrovascular pathologies, has been shown to slow cognitive decline.*
- *Recent studies place "white-matter hyperintensities" as a cerebrovascular pathology that corresponds in time with the onset of amyloid deposition in both familial and late-onset AD, suggesting that this "vasculopathy" may be an important therapeutic target.*
- *Mechanistic and epidemiologic evidence exists for a sub-class of anti-hypertensive agents as additionally neuroprotective: the angiotensin receptor blockers (ARBs; "sartans").*

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Sartans – Potential benefits over ACEIs

- *ACEIs (the most commonly prescribed anti-hypertensive drugs) and sartans both act on the renin-angiotensin system (RAS) and have demonstrated benefits through various mechanisms in delaying MCI conversion to AD.*
- *Key RAS receptors in the brain are AT1 (activation produces neurotoxic effects) and AT2, AT4 and Mas (neuroprotective).*
  - *Centrally-acting ACEIs decrease activity at all of these receptors through ACE inibition.*
  - *Sartans selectively block AT1, allowing activation of AT2, AT4 and MAS.*
- *ACEIs may increase cholinergic transmission by increasing ACh, but may be amyloidogenic since ACE cleaves Abeta.*
- *Sartans increase insulin degrading enzyme, which degrades Abeta.*
- *Telmisartan through activation of PPAR-gamma may support the blood-brain barrier, may influence brain glucose metabolism and have anti-inflammatory & anti-atherosclerotic effects.*

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The Sartan-AD Trial

- *"A randomized, open-label, proof of concept study of telmisartan vs. the ACEI perindopril in hypertensive mild-moderate AD patients"*
- *PI: Sandra Black, MD FRCP(C); Co-PI: Dr. Krista Lanctot*
- *Toronto Dementia Research Alliance, University of Toronto*
- *Sponsor: Sunnybrook Research Institute*
- *Funding: Alzheimer's Drug Discovery Foundation-Canada and Weston Brain Institute*
- *Study interventions: once-daily Perindopril 2-8 mg/day; Telmisartan 40-80 mg/day*
- *Phase 2a study, planned sample size 240, 11 sites throughout Canada, enrolment period 12-18 months, 3 year study overall.*

Toronto Dementia Research Alliance

UNIVERSITY OF TORONTO

Sunnybrook HEALTH SCIENCES CENTRE

www.tdra.ca

The Sartan-AD Trial

- *Primary objective: Determine the comparative efficacy and safety of perindopril vs. telmisartan in reducing brain atrophy as indexed by MRI assessment of brain ventricular enlargement in mild-moderate probable AD participants who have treated hypertension*
- *Hypotheses:*
  - *Primary outcome: Patients randomized to telmisartan will have a smaller increase in ventricular size (reduced brain volume loss) compared to those on perindopril at 12 months follow-up.*
  - *Safety outcome: Treatment with telmisartan will be as well tolerated as perindopril on blood pressure and other vital signs, electrolyte panel, and adverse events.*
- *Secondary objective: Determine comparative efficacies on cognitive and functional measures, and on other structural brain imaging measures*
- *Hypotheses:*
  - *Secondary outcomes: Patients randomized to telmisartan will have less decline in cognition and function and will show less loss in other selected brain structures*

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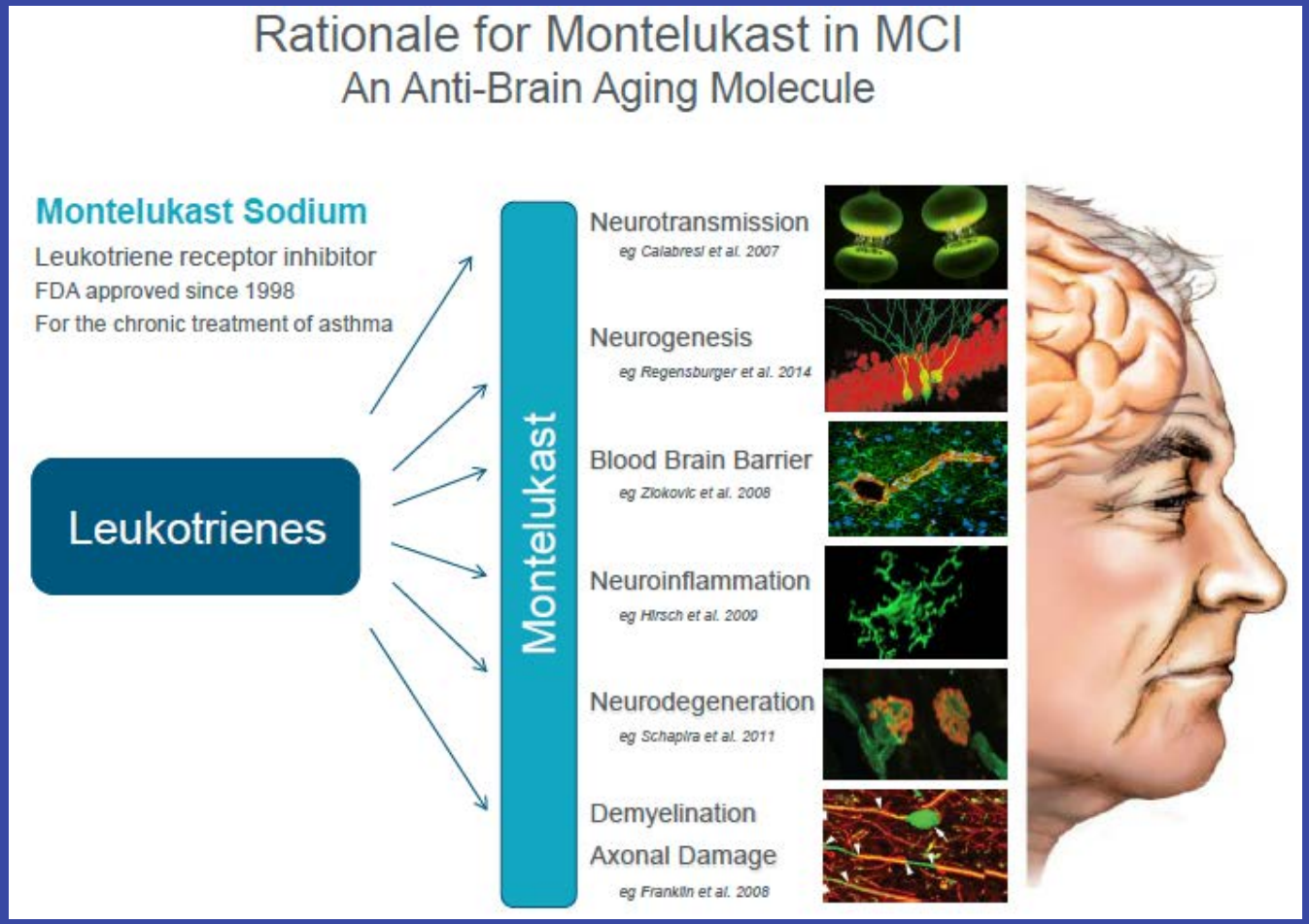
Example #3: Montelukast (Singulair®)
Current indication: asthma

- *Novel formulation – oral film*
- *Preclinical evidence based on several mechanisms*
  - *Impacts on leukotriene-mediated pathways that impact on neurotransmission, neurogenesis, blood-brain barrier integrity, neuroinflammation, neurodegeneration and axonal damage*
  - *Studies in preclinical animal models of Lewy Body Dementia and MCI provide evidence for improvements in learning and memory*
- *Known safety/efficacy in chronic treatment of asthma*
- *Phase 1 study tbd followed by phase 2 safety/efficacy studies in appropriate patient cohort*

IntelGenx Corp.
http://www.intelgenx.com

Montelukast Oral Film
For Improvement of Cognitive Function in MCI and AD

Montelukast - Rationale



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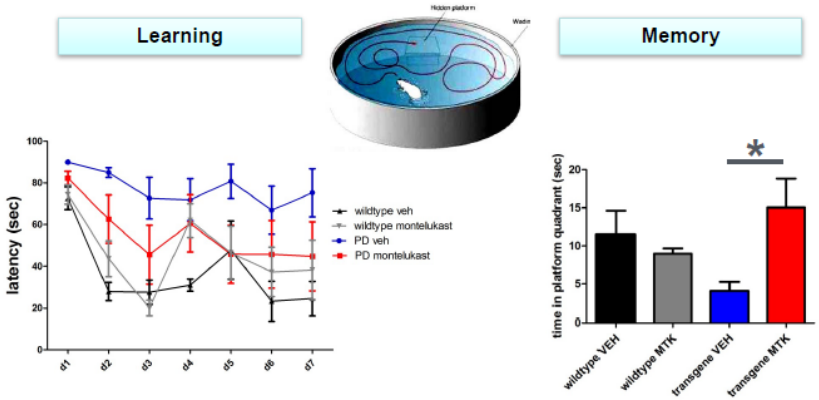
Montelukast – Preclinical model studies

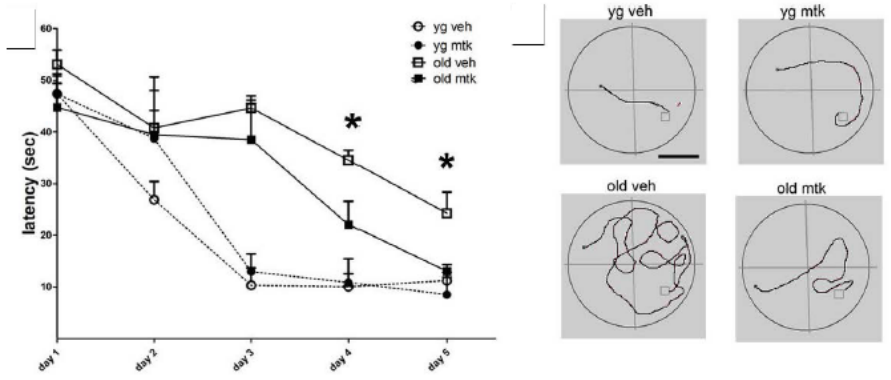
Montelukast Improves Cognition
In an Animal Model of Lewy Body Dementia

- **In the WM-Test**



Montelukast Improves Learning Capacity
In an Animal Model of MCI

- **In the WM-Test**



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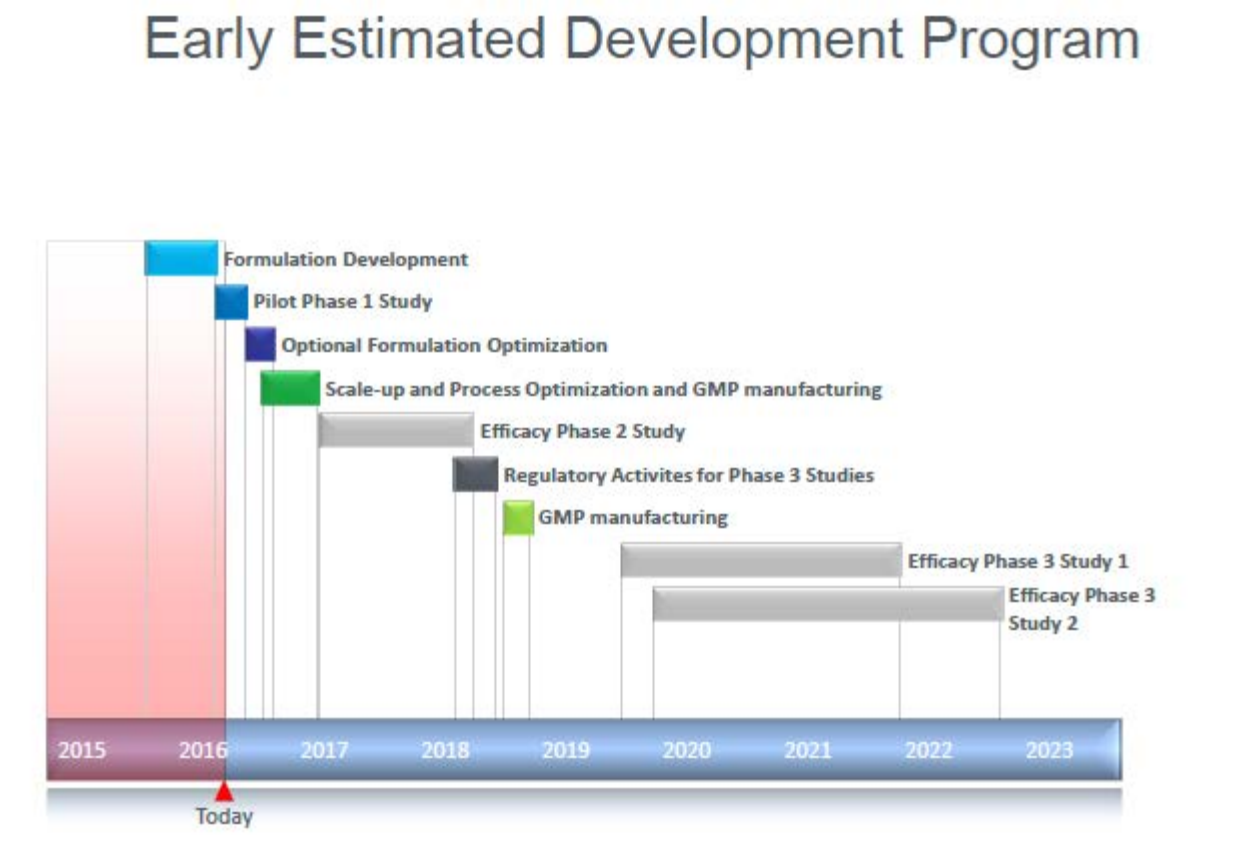
Montelukast – Projected clinical development path



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Other Potential Examples
(not comprehensive list)

Previous examples:

- *Anti-fungal Clioquinol for AD – Prana*
- *Anti-histamine Dimebon for AD – Medivation and Pfizer*
- *Various statins and NSAIDs*
- *Urinary analgesic/anti-infective/anti-spasmodic Methylene Blue – TauRx*
- *Retinoid receptor agonists (i.e. anti-cancer drug bexarotene)*

Examples under consideration/clinical investigation:

- *Calcium channel blockers (anti-hypertensives)*
- *Nasal insulin, metformin & glucagon-like peptide GLP1 analogues (anti-diabetics)*
- *Certain anti-cancer drugs*
  - *Example: Fyn kinase inhibitor Saracatinib (AZD0530) based on preclinical mechanistic, genetic risk factor and animal model studies, building on known pharmacokinetics in humans, known AE profile at (non-efficacious) anti-cancer doses. Status: phase 1b CONNECT trial now recruiting for multiple ascending dose study to assess safety/tolerability in AD patients.*
    - *NCATS/AstraZeneca – clinical sites Yale, Banner Health, ATRI, UBC*

Drug Repurposing-Repositioning
(Issues)

- *Risk-benefit ratio*
  - *All drugs have side-effects*
  - *Treatment of patients in pre-symptomatic disease phases = exposing healthy patients to drug risks.*
  - *Safety risks must be balanced against known mechanisms of action and dosing, particularly in the absence of a demonstrated clinical need.*

- *Challenges*
  - *Still requires determination of optimal dosing and administration*
  - *Still requires proof-of-concept in clinical trials, but may shorten clinical path*
  - *Economics. New funding models (i.e., cross-sector consortia) and intellectual property policies may be necessary.*
    - *Patent life*
    - *Payer support*
    - *Generics*

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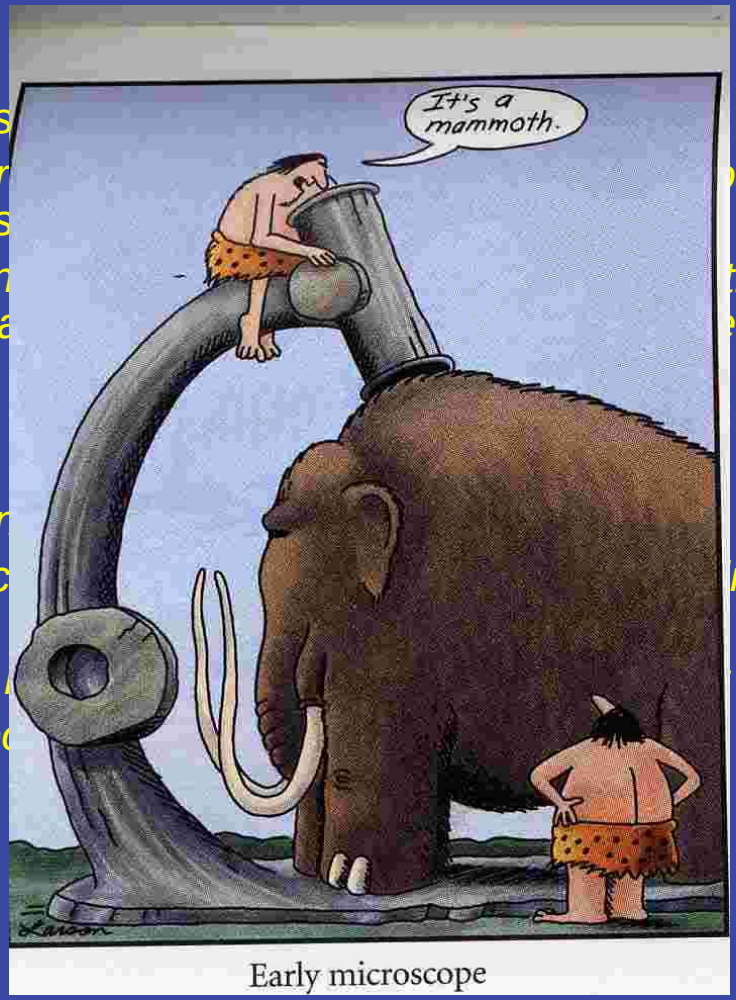

Early microscope

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Summary

- *Several promising agents have been identified for repurposing potential to treat AD.*
- *Mechanisms of action, dose and safety issues must be understood.*
- *Important to consider: what sub-populations of patients should be exposed to the selected agents, and what is the optimal stage of disease for administration?*
- *How will economic issues be mitigated in the event of success?*

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Backups

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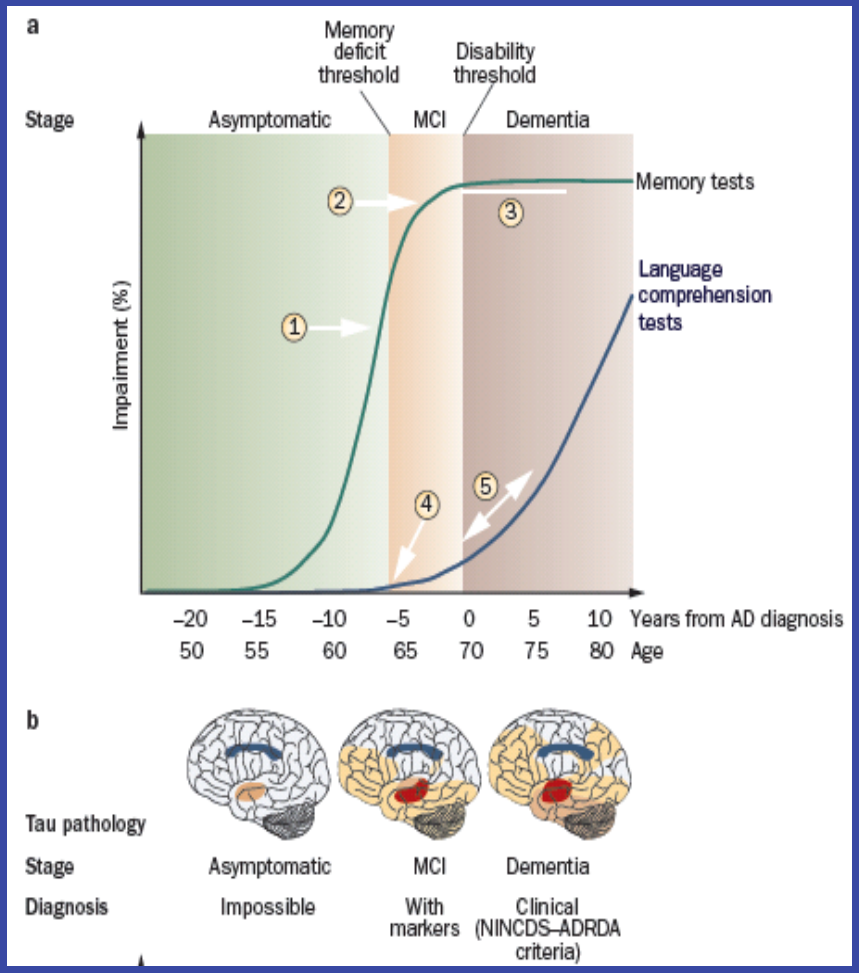
Natural progression of cognitive markers in AD



1. Memory test changes
2. Rapid maximal impairment useful for MCI diagnosis
3. Limited usefulness for tracking disease progression
4. Verbal comprehension changes start later, limited diagnostic use
5. More sensitive at dementia stage

The clinical use of structural MRI in Alzheimer disease

Giovanni B. Frisoni, Nick C. Fox, Clifford R. Jack Jr, Philip Scheltens and Paul M. Thompson

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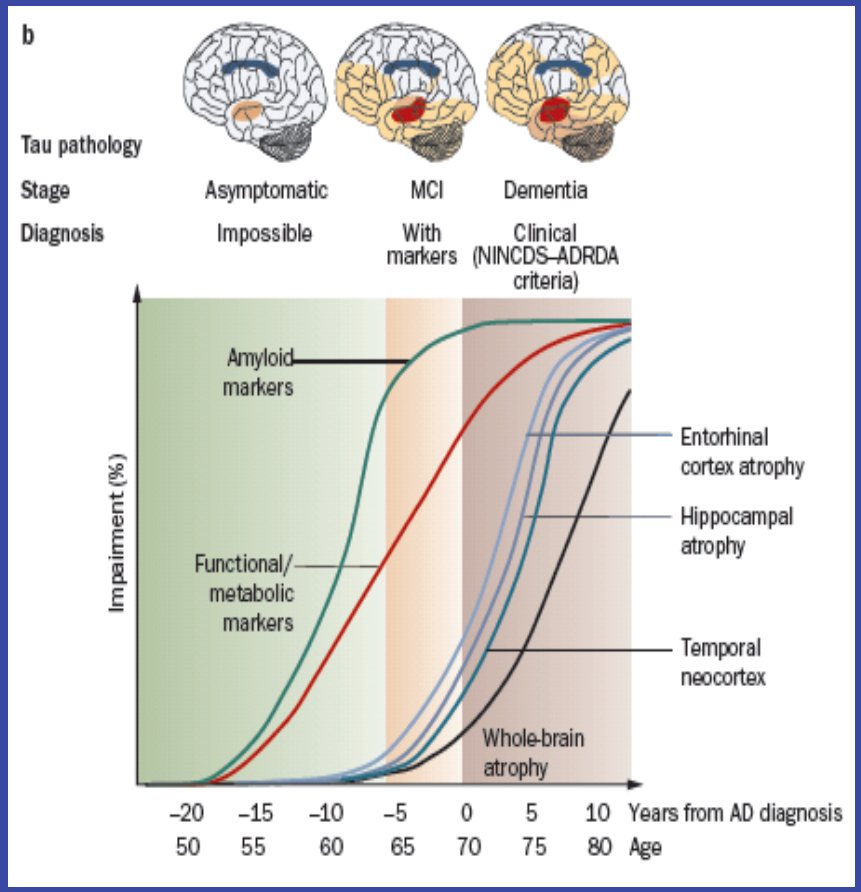
Natural progression of pathological markers



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- Amyloid markers (CSF, PET) detected early, but plateau by MCI
- Functional & metabolic markers (fMRI, ^{18}FDG-PET) abnormal by MCI and progress into dementia stages
- Structural changes (sMRI) follow temporal pattern of clinical disease, brain atrophy and tau pathology

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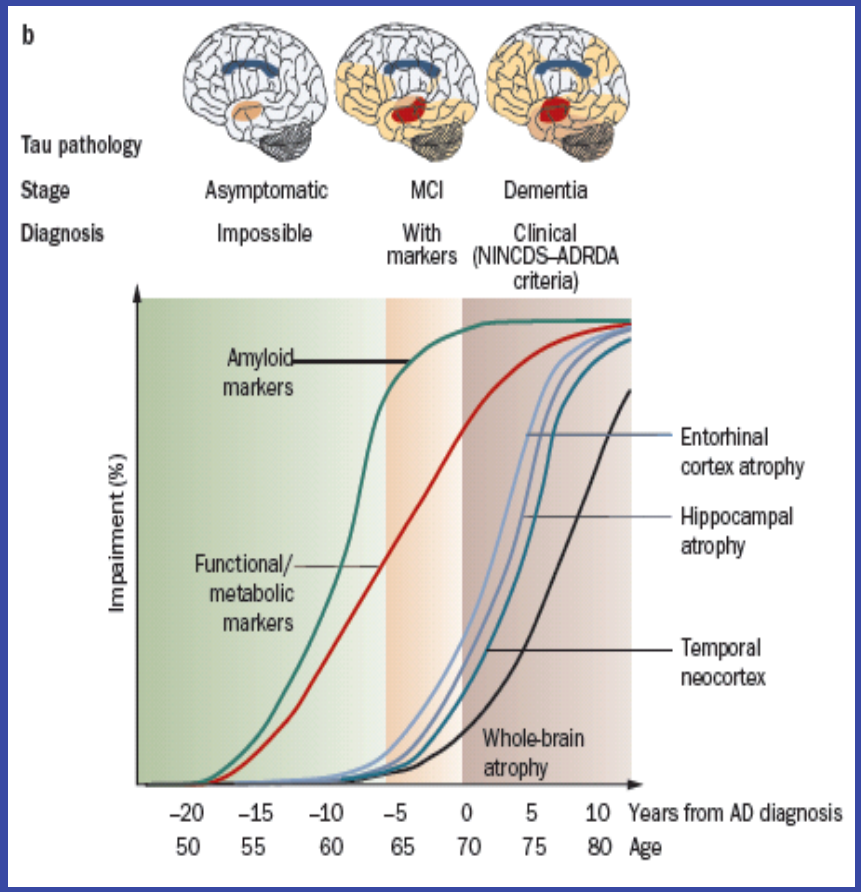
So what is this telling us?



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Anti-amyloid therapies will likely work only as preventatives.

Administration following onset of dementia is likely too late.

Key: identification of patients at risk in prodromal stages.

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