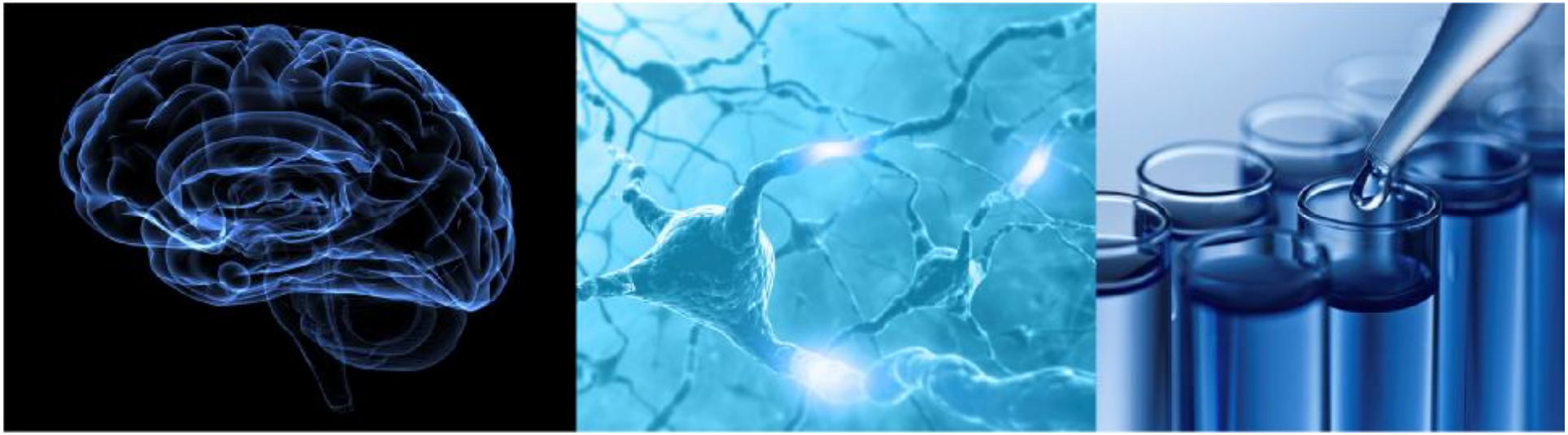
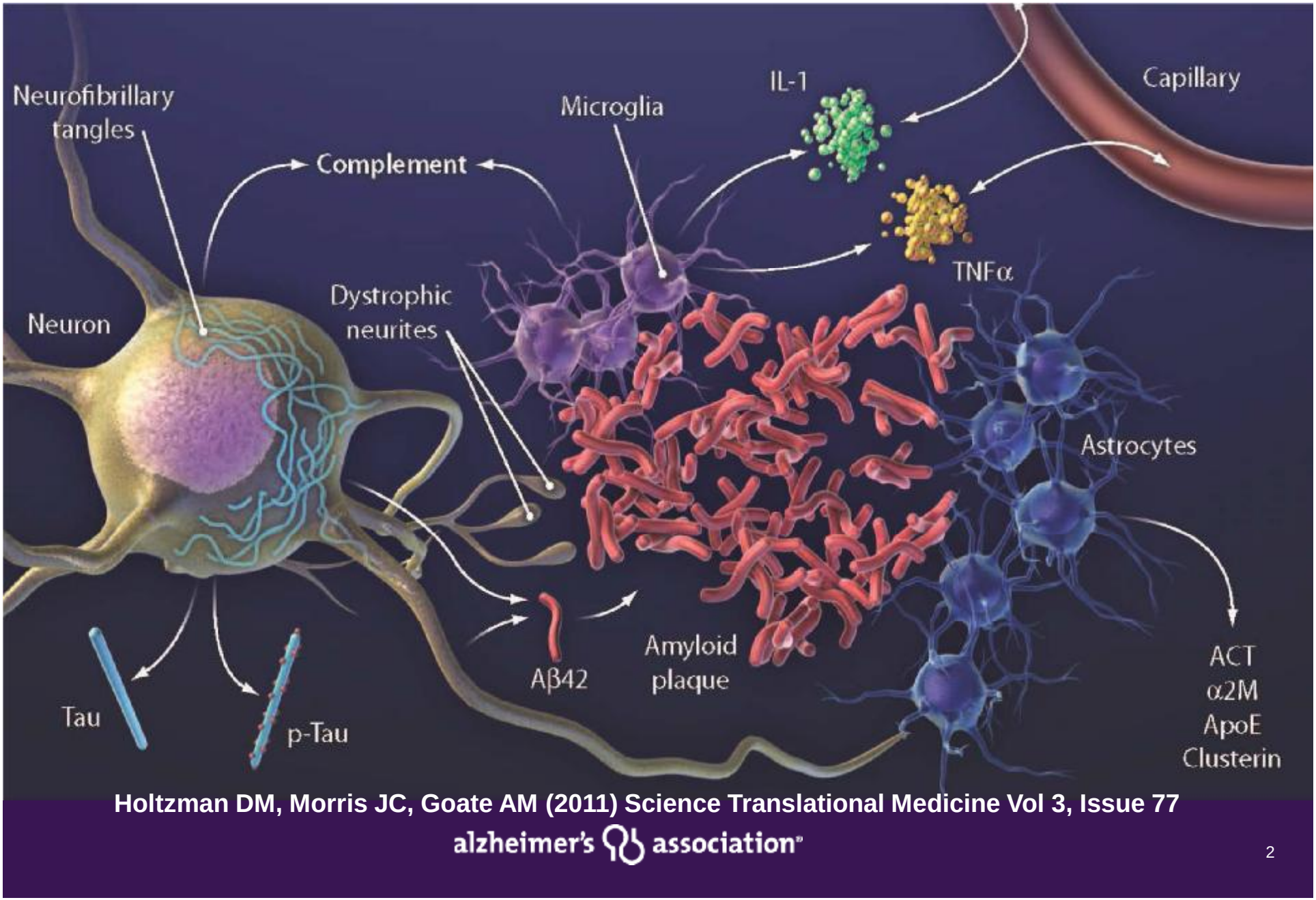


Drug/Drug and Drug/Biologic Combinations for Alzheimer's Disease

James Hendrix, PhD
Director of Global Science Initiatives
Alzheimer's Association

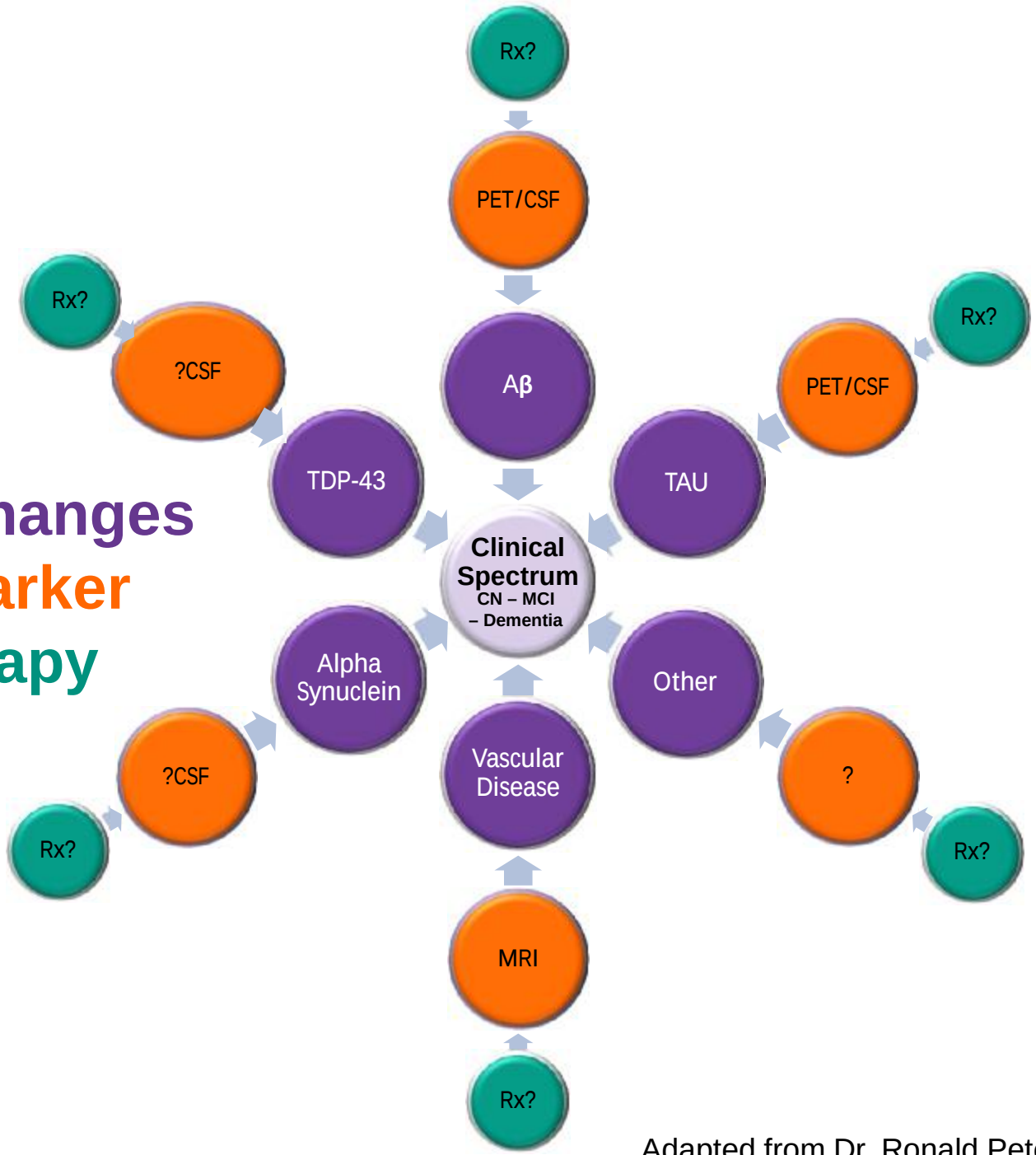
Model of Alzheimer's Pathology



Holtzman DM, Morris JC, Goate AM (2011) Science Translational Medicine Vol 3, Issue 77

alzheimer's association

Brain Changes
Biomarker
Therapy



Adapted from Dr. Ronald Petersen, Mayo Clinic

Current Alzheimer's Therapies

Cholinesterase Inhibitors

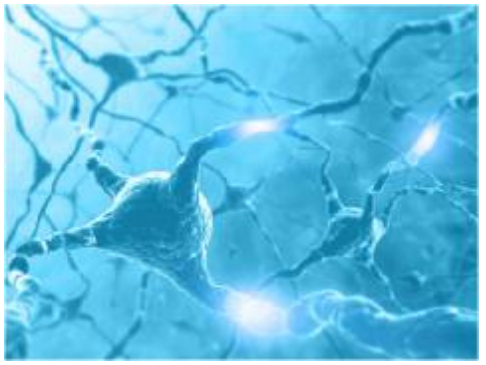
- tacrine (Cognex)
- donepezil (Aricept)
- rivastigmine (Exelon)
- galantamine (Razadyne)

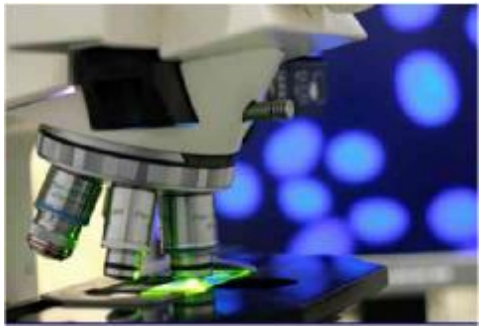
Glutamate Moderators

- memantine (Namenda)

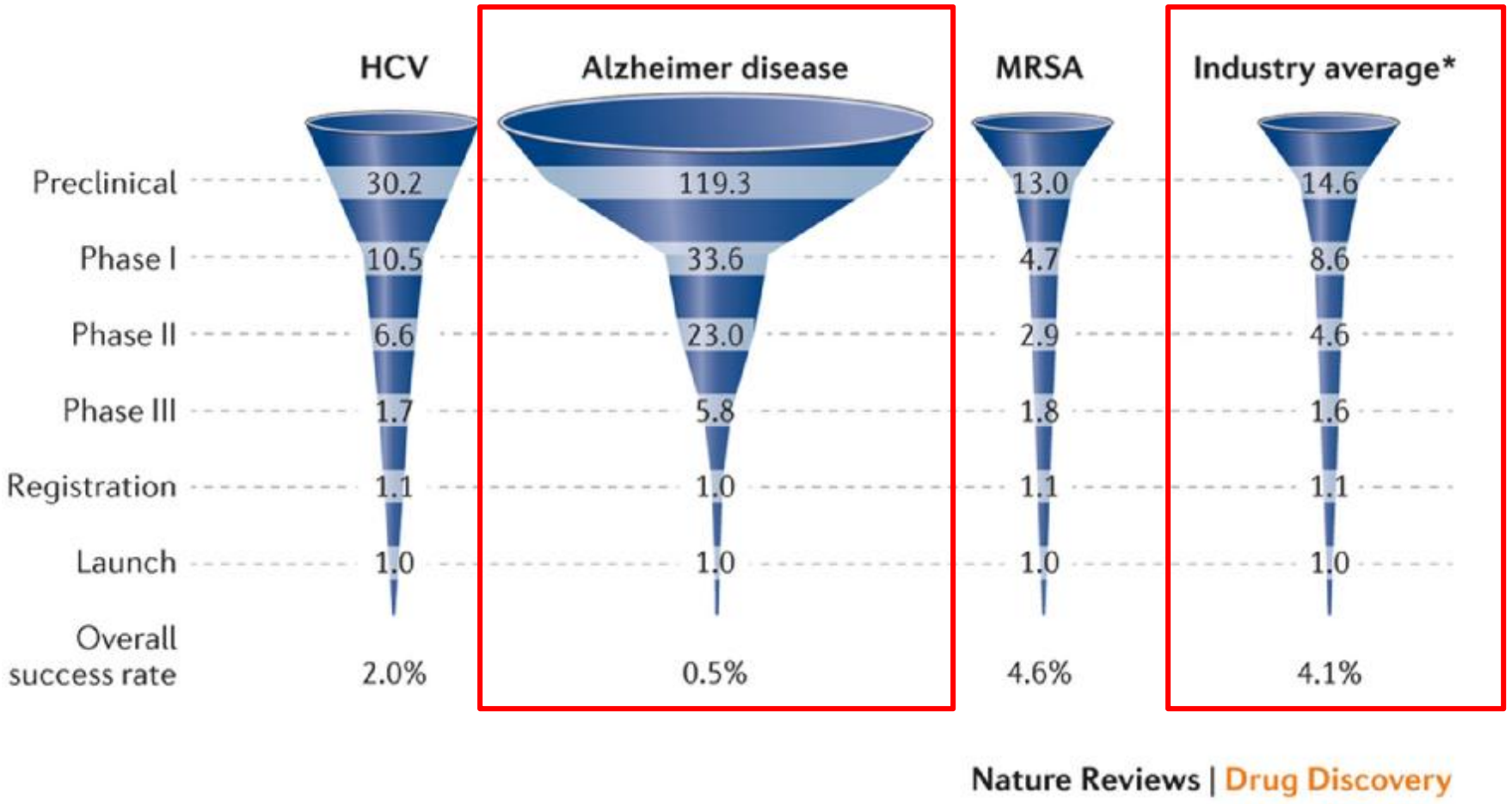
Combination

- donepezil + memantine (Namzaric)





Current Pipeline for Clinical Studies in Alzheimer's Disease



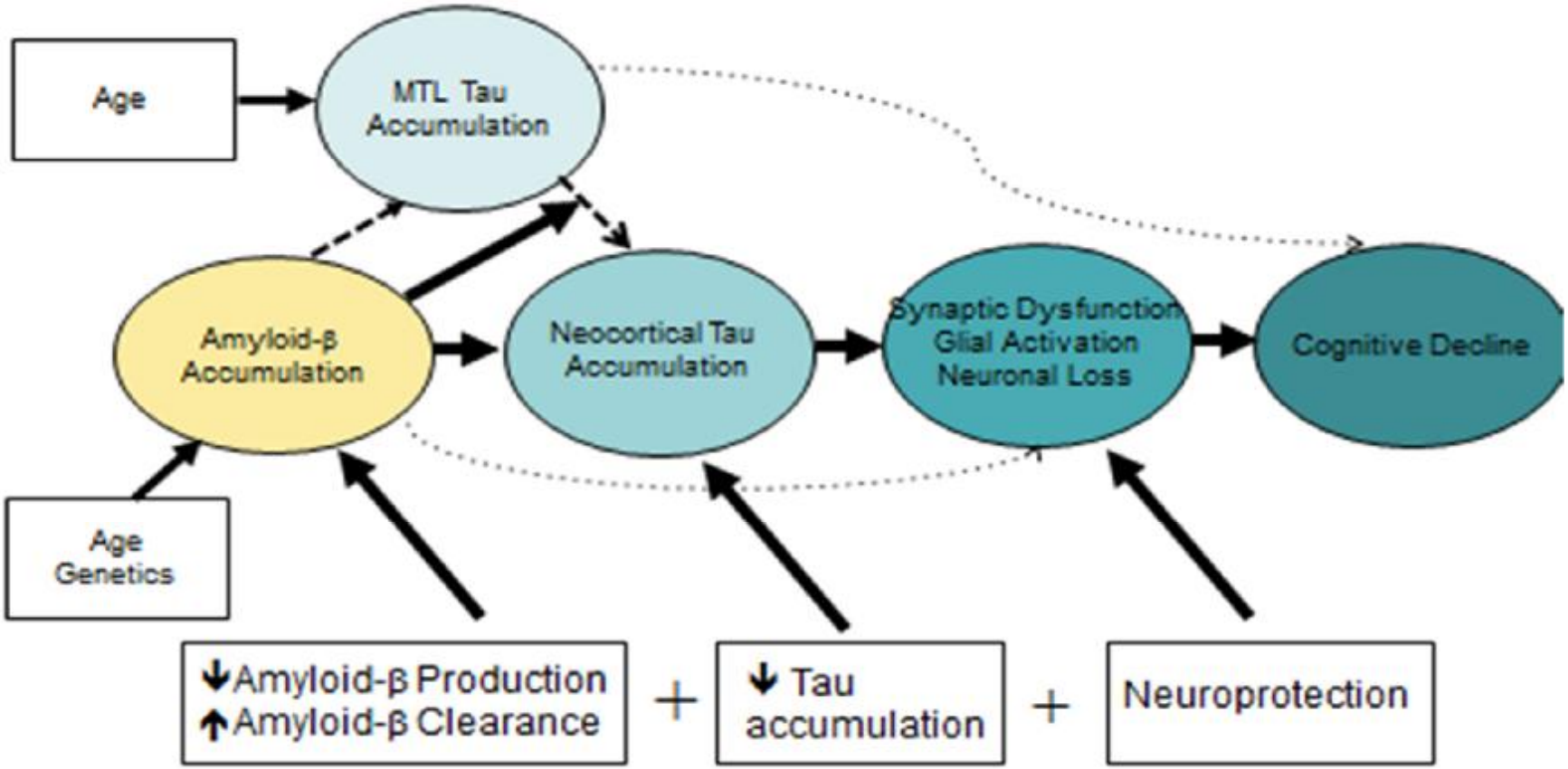
Potential Combination Symptomatic Treatments in Development

- RVT-101 (Axovant) – Phase III
  - 5HT6 Antagonist for treatment of cognition in Mild to Moderate AD when added to donepezil
- Idalopirdine (Lundbeck / Otsuka) – Phase III
  - 5HT6 Antagonist for treatment of cognition in Mild to Moderate AD when added to donepezil
- AVP-923: Dextromethorphan/Quinidine (Avanir) – Phase III
  - For treatment of agitation in AD
  - Approved for PBA in MS and ALS

Selected candidates in Phase 2 & 3 for AD

Candidate	Company	Mechanism
Aducanumab	Biogen	Humanized mAβ to the protofibrillar form of β-amyloid, an intermediate in the formation of amyloid plaques.
Albumin and Immunoglobulin	Grifols Biologicals	Naturally occurring antibodies with anti-inflammatory and immunomodulating properties.
AZD3293	Eli Lilly and AstraZeneca	Beta Secretase Cleaving Enzyme (BACE) Inhibitor
CAD106	Novartis	Aβ Immunotherapy. An active vaccination that aims to elicit a strong antibody response while avoiding inflammatory T cell activation.
E2609	Eisai / Biogen	BACE Inhibitor
Gantenerumab	Hoffmann-La Roche	Fully human monoclonal antibody that preferentially binds to aggregated Aβ.
Intranasal Insulin	Alzheimer's Disease Cooperative Study	Insulin resistance, reduced cerebrospinal fluid insulin levels, and reduced brain insulin signals have been found in AD patients, suggesting that a therapy aimed at correcting these deficiencies may be beneficial.
JNJ-54861911	Janssen	BACE Inhibitor
MK-8931	Merck	BACE Inhibitor
Nilvadipine	Archer Pharmaceuticals	Calcium channel blocker, approved for the treatment of hypertension and chronic major cerebral artery occlusion. May reduce Aβ accumulation and the counter-act cerebrovascular effects of Aβ.
Pioglitazone	Takeda	PPAR-γ receptor agonist, approved for Type II diabetes.
Sodium Oligo-mannurarate (GV-971)	Shanghai Greenvalley Pharmaceutical Co.	Inhibits beta-amyloid aggregation and cell division (Previously used for cancer)
Solanezumab	Eli Lilly	Humanized monoclonal antibody against beta-amyloid
TRx-0237	TauRx	Tau aggregation inhibitor

Combination treatment for Alzheimer's disease



Adapted from Sperling, Mormino, Johnson *Neuron* 2014

Potential Scenarios for Combinations of Disease Modifying Agents in AD

Scenario	Compounds	Examples
1	2 compounds 1 neuropathologic target 2 MOAs	Compound targeting production of Aβ (e.g., BACE inhibitor) plus immunotherapy to increase Aβ clearance (e.g., anti-amyloid monoclonal antibody against aggregated Aβ)
2	2 compounds 2 neuropathologic targets	Anti- Aβ plus Anti-Tau
3	2 compounds 2 MOAs	Anti- Aβ or Anti-Tau plus neuroprotective agent (e.g., anti-inflammatory or synaptic enhancer)

Hendrix, Bateman, Brashear, Duggan, Carrillo, et. al. Alzheimer's & Dementia 2016, 12 (5), 623–630.

Potential Challenges

- PK, PD, Safety (Drug-Drug Interactions)
- Dose finding
- Dosing regiments / Routes of administration
- Regulatory
- Business Issues

Non-Clinical Safety & PK Studies Required Prior to IND for a Dual Combination

Development Stage of Candidates	Safety / Tox	PK
2 Late Stage (Ph 3 or later) candidates	Minimal: Confirm no unwanted drug-drug interactions Unless suspected tox issue with combination (i.e. similar target organ toxicity)	Compare combination with monotherapy PK to confirm similar behavior
1 Late Stage + 1 Early Stage Candidate	Same as above	Same as above
2 Early Stage Candidates	Full Tox on combination*	Full PK on combination*

*Full evaluation is required only of the combination, not of each of the components individually if the drugs are not intended to be marketed individually.
(Hendrix, et. al. Alzheimer's & Dementia 2016, 12 (5), 623–630.)

2X2 Factorial Design of Anti-amyloid (A) and Anti-Tau (T) Combination Therapy vs. A or T Monotherapy

		Randomization of T	
		Anti-tau Drug (T)	Placebo (not T)
Randomization of A	**Anti-amyloid Drug (A)**	A and T	A, not T
	Placebo (not A)	T, not A	Not A, Not T

Tomaszewski, Gauthier, Wimo, Rosa-Neto J. Prevention of Alzheimer's Disease 2015, http://dx.doi.org/10.14283/jpad.2015.85.

Other Recommendations

- Use of transgenic animal models and human neural cell culture models to test combinations.
- Use of biomakers for enrolling participants and for measuring target engagement
- The development of a theragnostic biomarker for AD
- Adaptive trials that use interim results
- Obtain guidance from regulators on Proof of Concept study design
- Develop collaborative / consortia model to test candidates from different companies in combination

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