

Alzheimer's Disease:

THE CURRENT STATE OF CLINICAL TRIALS

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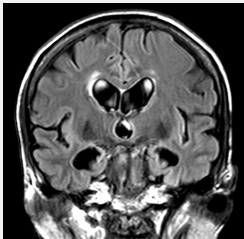
OUTLINE

BACKGROUND OF AD

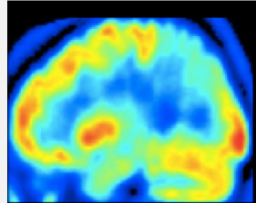
BACKGROUND OF CLINICAL TRIALS IN AD

CURRENT TRIALS IN AD

WHAT IS ALZHEIMER'S DISEASE?



MEMORY LOSS



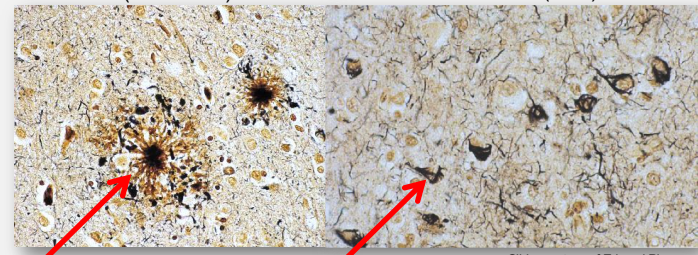
WORD-FINDING
DIFFICULTY
POOR NAVIGATION

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PATHOLOGY OF ALZHEIMER'S DISEASE



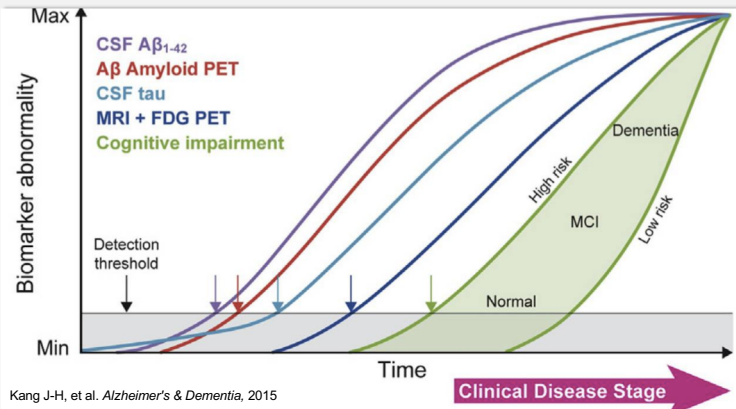
NEURITIC (AMYLOID) PLAQUE NEUROFIBRILLARY (TAU) TANGLES



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Slide courtesy of Edward Plowey

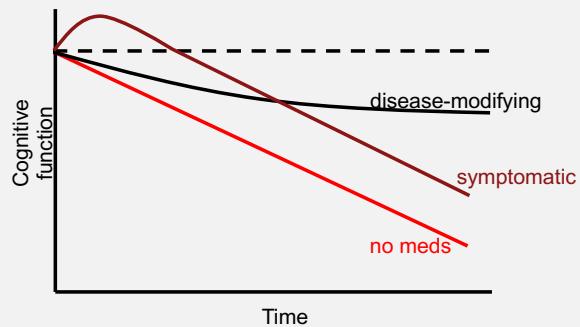
BIOMARKERS DEVELOP AT DIFFERENT TIMES



CHOLINESTERASE INHIBITORS: MAIN TREATMENT

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THERE ARE NO DISEASE MODIFYING DRUGS

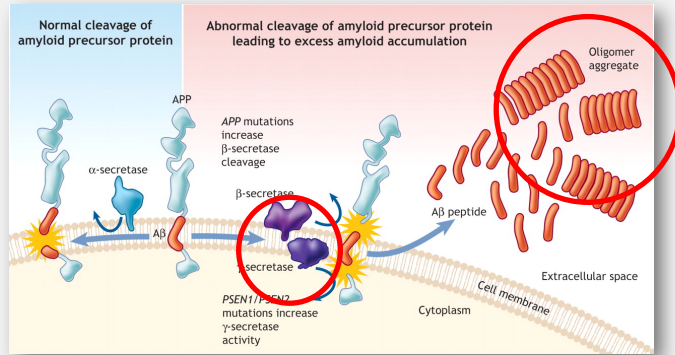


BACE INHIBITORS HAVE FAILED

	VERUBACESTAT (MERCK)	LANABECESTAT (Lilly/AZ)	ATABECESTAT (JNJ)	LY3202626 (Lilly)	ELENBECESTAT (Eisai)	CNP520 (Novartis)
Phase	III	III	III	II	III	III
Population	Mild AD, MCI	Mild AD, MCI	Normal	Mild AD	MCI/Mild AD	Normal
Outcome	Mild AD: no difference MCI: worse	Trend worse	Halted safety	Halted futility	Halted	Cognitive worsening

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MOST LARGE TRIALS HAVE TARGETED AMYLOID



Patterson et al., CMAJ, 2008

ANTI-AMYLOID ANTIBODIES

	Bapineuzumab	Solanezumab	Crenezumab	Gantenerumab	Aducanumab	BAN2401
Company	Pfizer/J&J	Eli Lilly	Roche/Genentech	Roche/Genentech	Biogen	Eisai/Biogen
Origin	Humanized	Humanized	Humanized	Human	Human	Humanized
Target	All forms of A β	Soluble A β	All forms of A β	Fibrillar & oligomeric forms of A β	Fibrillar & oligomeric forms of A β	A β protofibrils
Outcome	Failed	Failed	Failed	ONGOING!	Failed?	STARTING!

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Biogen Loses \$18B in Value as It Kills Aducanumab Alzheimer's Program

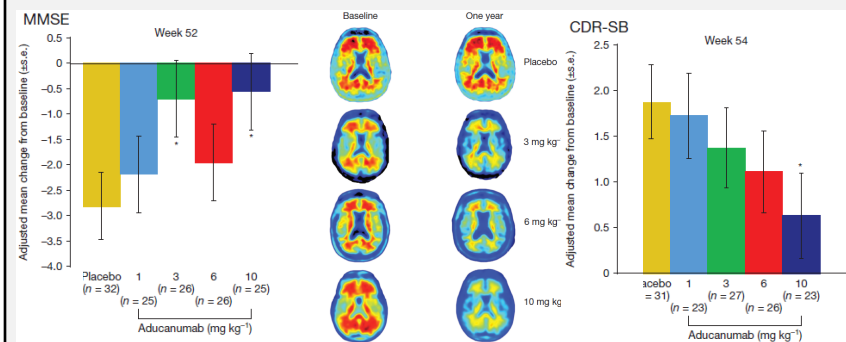
BIOTECH

In shocking reversal, Biogen to submit

The New York Times

*That New Alzheimer's Drug?
Don't Get Your Hopes Up Yet*

LESS PROGRESSION



Sevigny, et al. Nature 2016

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CURRENT TRIALS:

ONGOING

PREVENTION

- GENERATIONS 1, 2

MCI/ MILD AD

- Tango
- Tauriel

MODERATE AD

- Lauriet

ADVANCED AD

- PEACE AD

UPCOMING

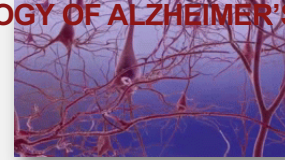
- BAN2401
- GAIN

COMPLETED

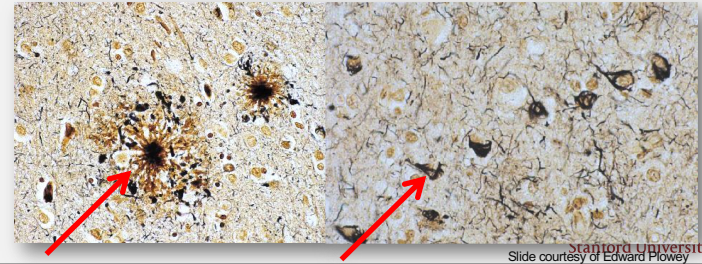
- APECS
- PLASMA
- BLAZE
- MISSION AD
- PRIME?
- EMERGE?
- CREAD

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PATHOLOGY OF ALZHEIMER'S DISEASE



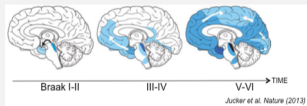
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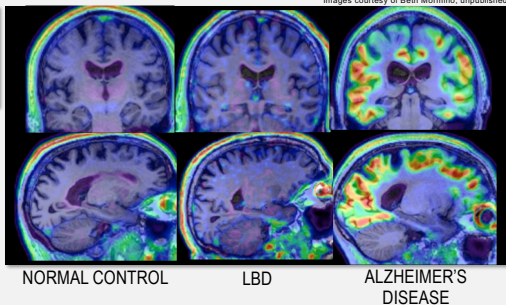
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Side courtesy of Edward Plowey

TAU IS A TARGET IN AD



Images courtesy of Beth Mormino, unpublished

COMPARED TO A β , TAU HAS A TIGHTER RELATIONSHIP TO SYMPTOMS AND PROGRESSION...



NORMAL CONTROL

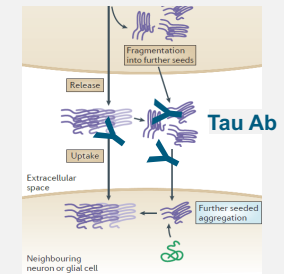
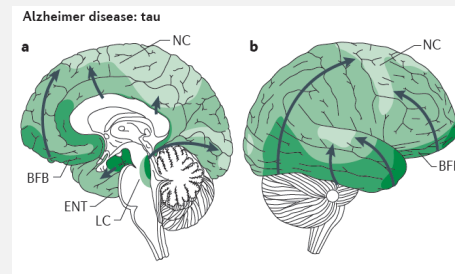
LBD

ALZHEIMER'S DISEASE

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TAU ANTIBODIES REDUCES TAU SPREADING



Brettschneider et al. 2015 Nat Rev Neurosci

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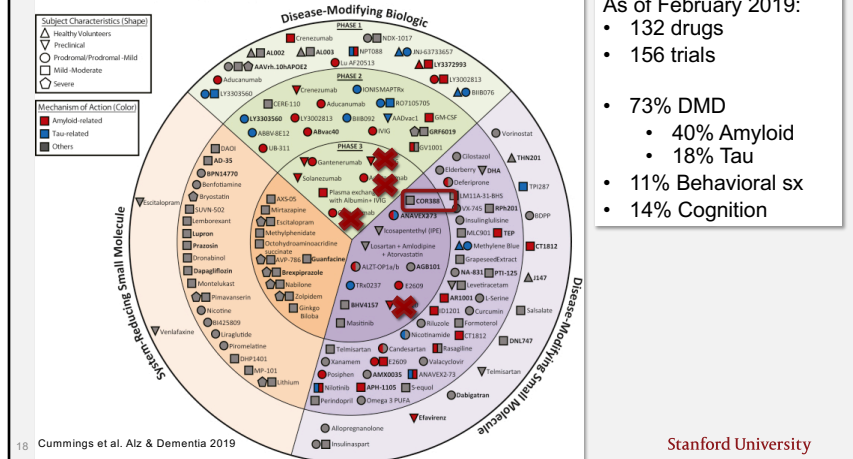
PHASE 2 TAU TRIALS

DRUG	SPONSOR	CLASS	POPULATION
AADvac1	Axon Neuroscience	Active immunotherapy	Mild AD
ABBV-8E12	Abbvie	Passive immunotherapy	MCI, AD (failed psp)
ANAVEX 2-73 OLE	Anavex Life Sciences	Sigma-1 receptor & musc agonist	Mild- mod AD
AZD0530	Astra-Zeneca	Src/abl kinase inhibitor	Mild AD
BIIB092 (TANGO)	Biogen	Immunotherapy	MCI, mild AD, PSP
IONIS MAPT Rx	Ionis/ Biogen	MAPT RNA inhibitor; antisense oligonucleotide	Mild AD
Methylene Blue	Texas AD Research	Tau protein aggregation inhibitor	Healthy, MCI, mild AD
Nicotinamide (Vit B3)	UCI	Histone deacetylase inhibitor	MCI, AD
Nilotinib	Georgetown	Tyrosine kinase inhibitor	AD
RO7105705 (TAURIEL, Lauriet)	Roche/Genentech	Immunotherapy	MCI/AD, Mod AD
LY3303560	Lilly	Immunotherapy	memory >6 months

CUMMINGS ET AL. J PREV ALZ Dis 2019; HTTP://DX.DOI.ORG/10.14283/JPAD.2019.14

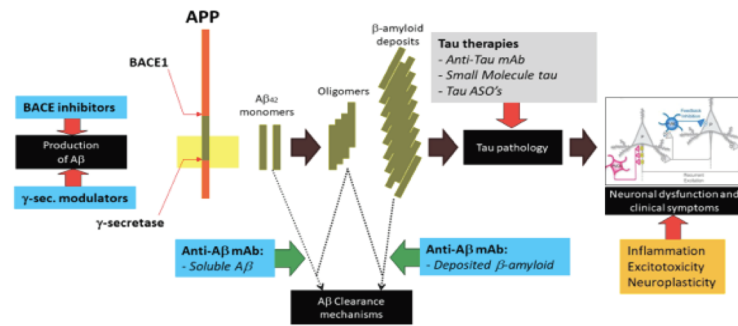
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2019 Alzheimer's Drug Development Pipeline



Opportunities for A β / β -amyloid Combination Therapies

Based on therapeutics currently in clinical development



- Targeting **soluble A β** by different mechanisms: BACE1 + GSM, BACE1 + anti-soluble A β mAb
- Targeting **soluble and insoluble A β** : BACE1/GSM + anti-A β mAb (plaque-specific)
- Targeting **A β / β -amyloid and second pathology** in combination: eg A β and tau

Gauthier et al. JPAD 2019

