#CHAIR2017

10TH ANNUAL CHAIR SUMMIT

neuroscience CME

Master Class for Neuroscience Professional Development

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Provided by CME Outfitters

Treatment Targets in Alzheimer's Disease

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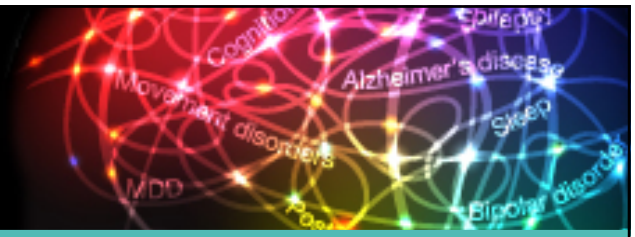
Disclosures

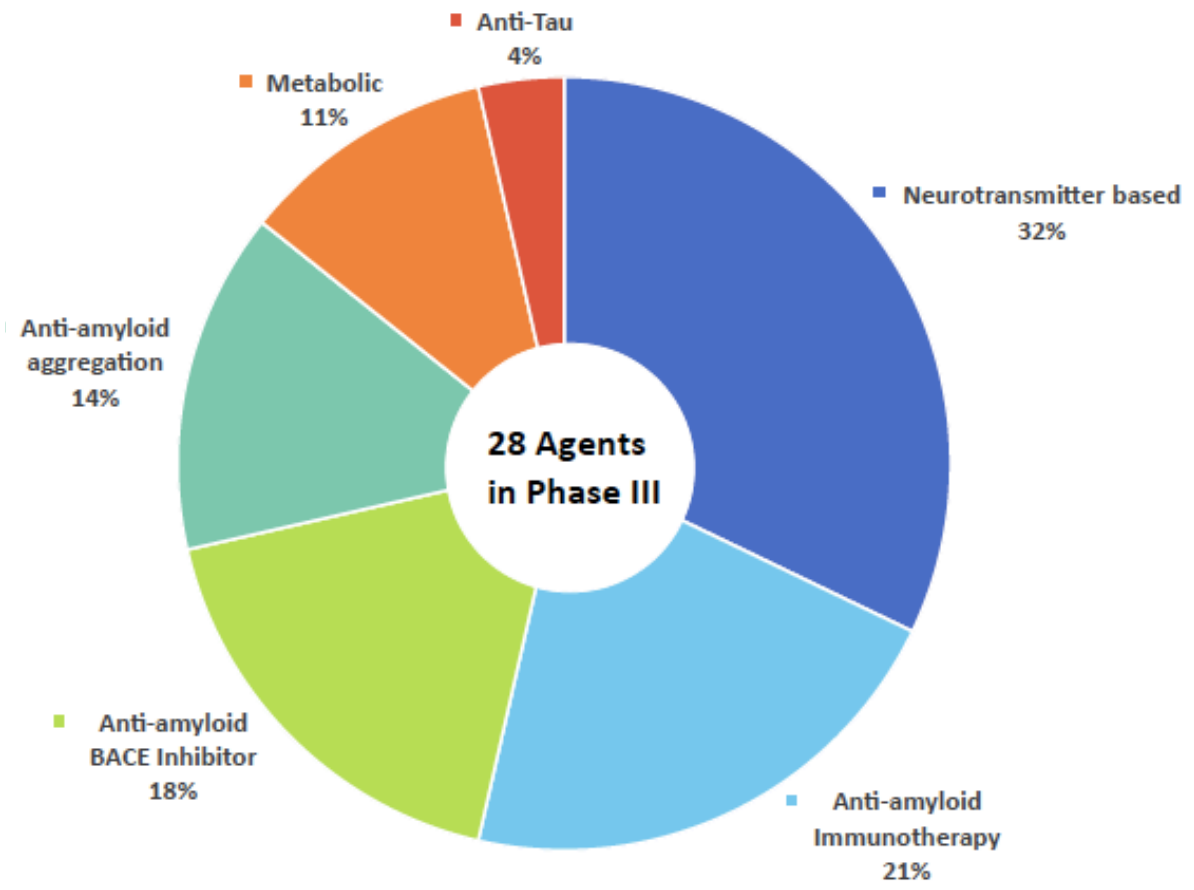


- ***Research/Grants:*** MECTA Corporation; Merck & Co. Inc.
- ***Consultant:*** Multiple Energy Technologies; Anthem Insurance

Learning Objective 1

Explore treatment targets in AD and agents in development that target these pathways.

Mechanisms of Action of Agents for AD in Phase 3 Development



Mechanisms of action of agents in phase III. Abbreviation: BACE, β-site amyloid precursor protein cleaving enzyme.

Cummings J, et al. *Alz Dement*. 2017;367-384.

Agents in Development for AD

Compound	Target	Type	MOA
Adacanumab	Aβ	Fully human IgG1mAb	Passive immunotherapy
Crenezumab	Aβ	Humanized mAb	Passive immunotherapy
Gantenerumab	Aβ	Humanized mAb	Passive immunotherapy
Solanezumab	Aβ	Humanized mAb	Passive immunotherapy
ALZT-OP1	Aβ	Small molecule	Anti-inflammatory
AZD3293	Aβ	Small molecule	BACE inhibitor
CNP520	Aβ	Small molecule	BACE inhibitor

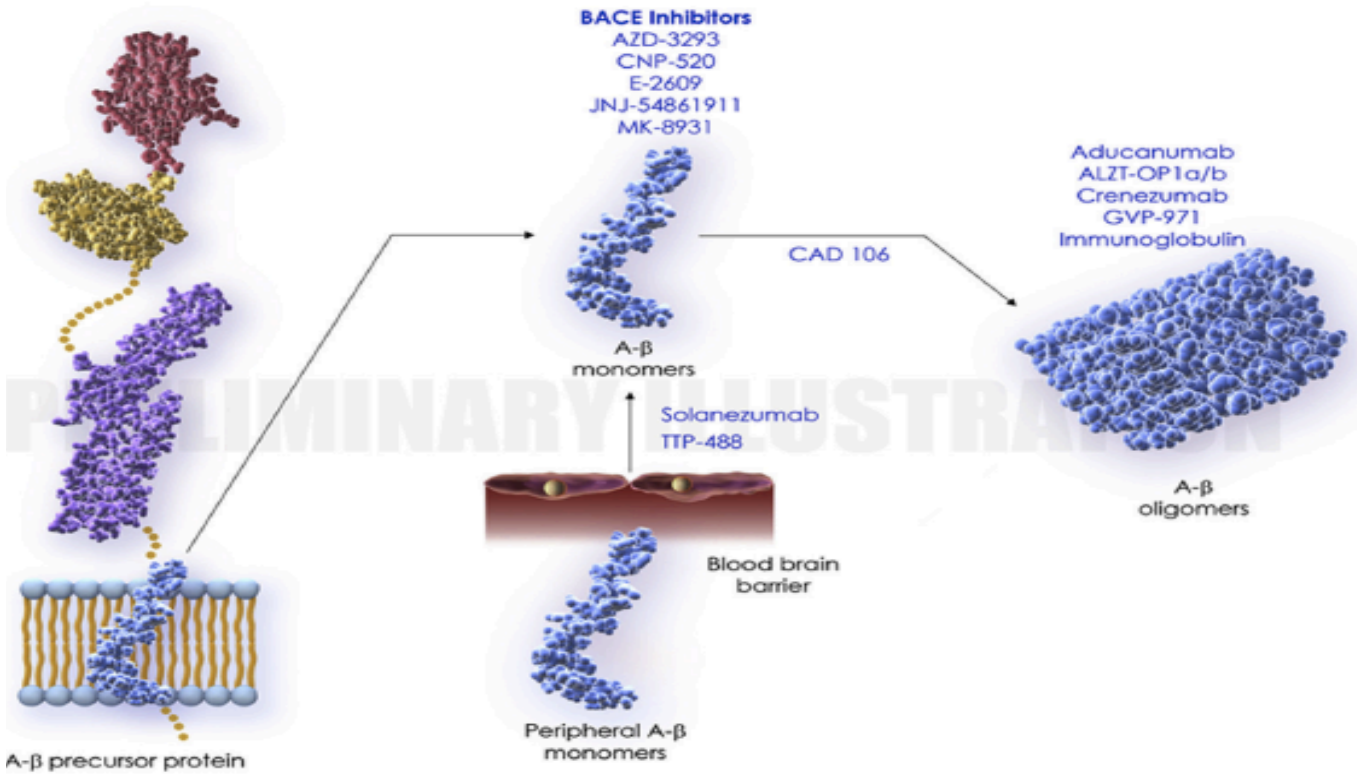
BACE = beta-site amyloid precursor protein cleaving enzyme/
Alzforum. http://www.alzforum.org/therapeutics.

Agents in Development for AD (cont'd)

Compound	Target	Type	MOA
Elenbecestat	Aβ	Small molecule	BACE inhibitor
Lananbecestat	Aβ	Small molecule	BACE inhibitor
Verubecestat	Aβ	Small molecule	BACE inhibitor
AGB101	Aβ	Small molecule	Anti-epileptic drug
Azeliragon	Aβ	Small molecule	RAGE inhibitor
RVT-101	Other	Small molecule	$5HT_6$ receptor antagonist
LMTM	Tau	Small molecule	Tau aggregation inhibitor

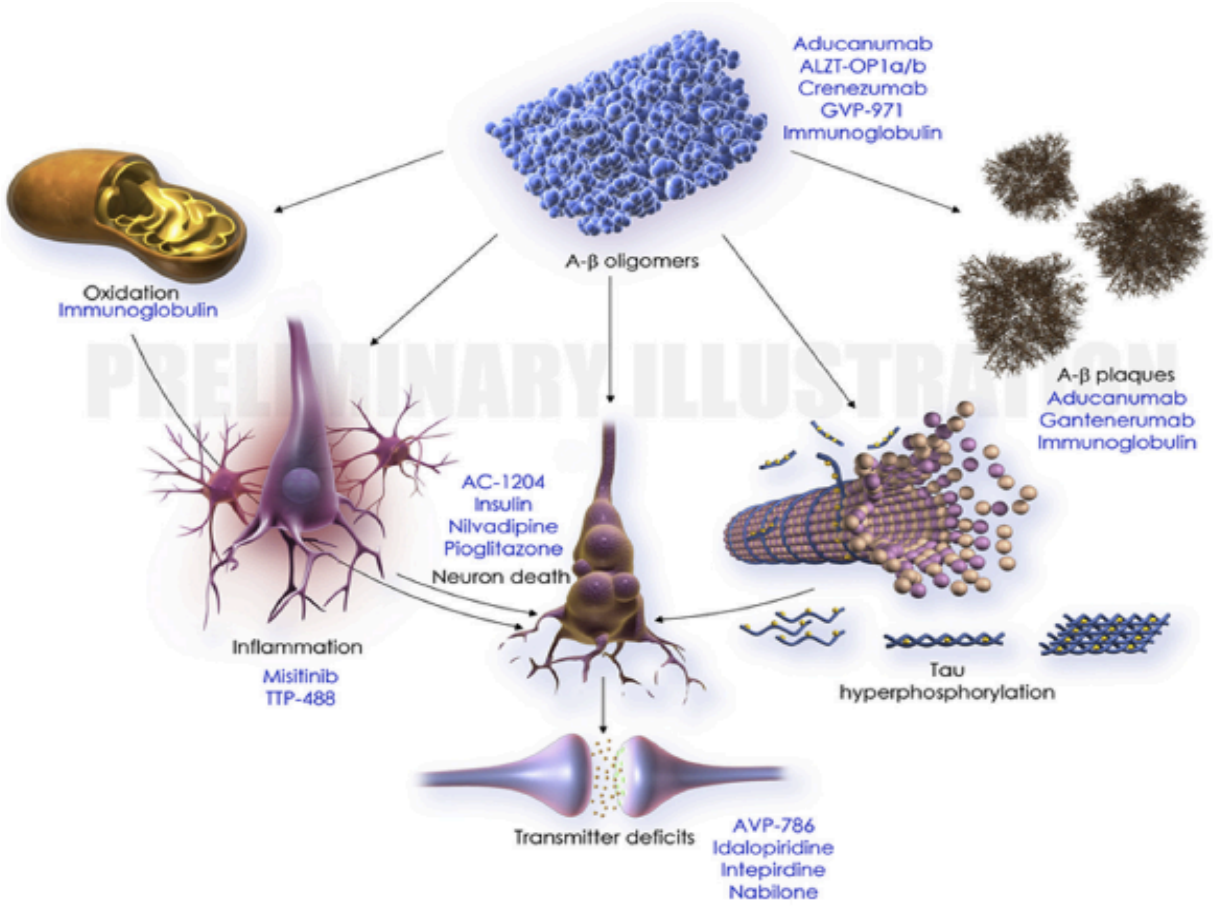
LMTM = Leuco-methylthioninium, RAGE = receptor for advanced glycation end products.
Alzforum. http://www.alzforum.org/therapeutics.

Proposed Biology of AD: Amyloid Cascade



Cummings J, et al. *Alz Dement*. 2017;367-384.

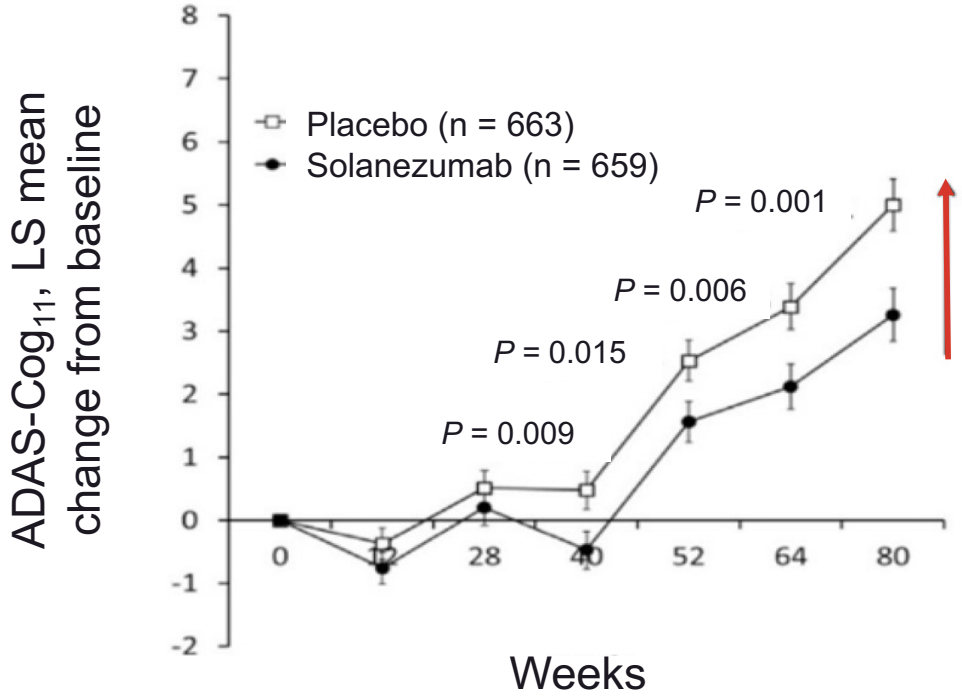
Proposed Biology of AD: Downstream Pathophysiology



Cummings J, et al. *Alz Dement*. 2017;367-384.

Combined EXPEDITION 1 and 2 Data for Solanezumab in Mild and Moderate AD

Pooled data from EXPEDITION 1 and 2 show less decline from baseline in ADAS-Cog scores



Modeled mean group difference (95% CI): 1.141 (0.35, 2.47)
P = 0.009

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognition.

Siemers E, et al. *Alzheimer's Dement*. 2016;12:110-120.

EXPEDITION 3

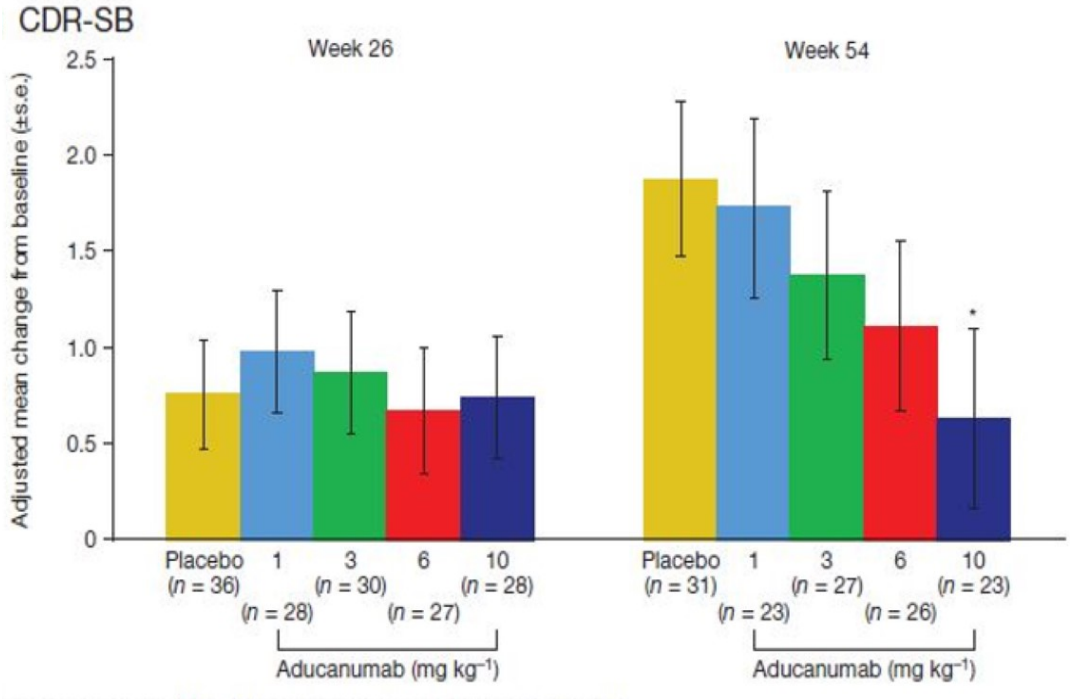
- Randomized, double-blind, placebo-controlled, phase 3, 80-week trial + open label extension
- 2129 patients with mild AD
  - Aged 55 to 90 years
  - Probable AD
  - Amyloid positive
  - MMSE score 20 to 26
- Intervention
  - Solanezumab 400 mg IV q4w **OR** Placebo
- Patients treated with solanezumab did not experience a statistically significant slowing in cognitive decline compared with patients treated with placebo (p = 0.095), as measured by the ADAS-cog14

MMSE = mini mental state exam.

Honig LS, et al. CTAD 2016.

PRIME CDB-SB Data for Aducanumab

- Change from baseline on the CDR-SB
  - Demonstrated dose-dependent slowing of clinical progression with aducanumab treatment at one year
  - Dose-response, $p < 0.05$, with the greatest slowing for 10 mg kg^{-1} ($p < 0.05$ versus placebo)



CDR-SB = clinical dementia rating scale-sum of boxes.

Sevigny J, et al. *Nature*. 2016;537:50-56.

PRIME Study Design and Results

- Randomized, double-blind, placebo-controlled, phase 1b trial
- Participants
  - 165 adults
  - Aged 50 to 90 years
  - Mild/prodromal AD
- Intervention, q4W for 1 year
  - Fixed dose of IV aducanumab
    - 1 mg/kg
    - 3 mg/kg
    - 6 mg/kg
    - 10 mg/kg
  - Placebo

- Results
  - Clinical assessments were exploratory as the study was not powered to detect clinical change
  - Aducanumab penetrates the brain and decreases Aβ in a time- and dose dependent manner
  - Aducanumab-treated patients with had decreased SUVR scores after 1 year of treatment experienced a stabilization of clinical decline on both CDR-SB and MMSE scores
  - Patients with a smaller or no decrease experienced clinical decline similar to patients receiving placebo

SUVR = standardized uptake value ratio.

Sevigny J, et al. *Nature*. 2016;537:50-56.

PRIME: 12-Month Interim Analysis of Titration Dosing

- Added 31 APOE-ε4 carriers
- Randomized to placebo or titrated aducanumab: 1mg/kg for 2 doses, 3 mg/kg for 4 doses, 6 mg/kg for 5 doses, and 10 mg/kg thereafter
- Week 52 average expected dose: 5.3 mg/kg

- Results
  - Significant decreases in brain Aβ with titrated aducanumab in mean PET SUVR ($p < .001$)
    - Aducanumab: -0.171
    - Placebo: 0.014
  - Similar results for titration-dose cohort and fixed-dose cohort in slowing of clinical decline (CDR-SB and MMSE)
  - ARIA incidence lower with titrated dosing vs higher fixed dosing of aducanumab in APOE-ε4

Viglietta V, et al. AAN 2017. Abstract S7.003.

LMTM in Mild AD

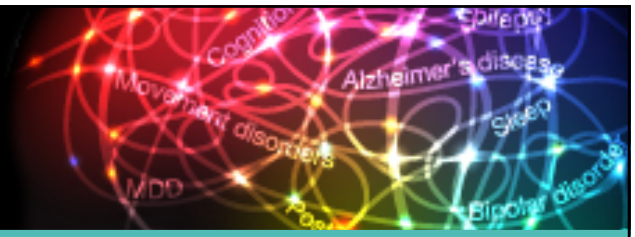
- Double-blind, placebo-controlled, phase 3, 15-month trial
- Patients (N = 891) with mild-to-moderate AD randomized to
  - LMTM: 75 mg or 125 mg BID
  - Control: LMTM, 4 mg BID
- Co-primary endpoints assessed at week 65 in ITT population
  - ADAS-COG
  - ADCS-ADL
- Results
  - Primary analysis was negative
  - No benefit of LMTM as add-on treatment for patients with mild-to-moderate AD was observed

Gauthier S, et al. *Lancet*. 2016;388:2873-2884.

Drugs Recently Granted Fast-Track Approval

- ALZ-801
  - Optimized prodrug of tramiprosate
  - Phase 3 program will focus initially on a genetically defined group of high-risk patients (APOE4/4 homozygote)
- CT1812
  - First in class, orally administered small molecule
  - Inhibits binding of beta amyloid (Aß) oligomers to neuronal receptors and facilitates clearance of Aß oligomers into the cerebrospinal fluid
  - Recently completed Phase 1b/2 in patients with mild-to-moderate AD

Call to Action



- Be aware of emerging agents for AD and their mechanisms of action
- Be up-to-date on evidence regarding patient populations and efficacy of agents in clinical trials

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.