Gli Anticorpi Monoclonali nella Malattia di Alzheimer

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Table 1 Overview of Alzheimer's disease clinical trials from clinicaltrials.gov

Year registered	Phase 1	Phase 2	Phase 3	Total
2002	0	2	3	5
2003	0	5	7	12
2004	1	9	4	14
2005	4	19	9	32
2006	5	14	6	25
2007	16	22	8	46
2008	25	27	9	61
2009	28	30	14	72
2010	16	24	11	51
2011	15	26	4	45
2012	14	28	8	50
Total	124	206	83	413

Table 2 Number of trials for agents with varying mechanisms of action

Year registered	Symptomatic for cognition	Symptomatic for behavior	Disease-modifying small molecule	Disease-modifying immunotherapy	Therapeutic device	Stem cells	Total
2002	1	3	0	1	0	0	5
2003	5	1	4	0	2	0	12
2004	5	2	6	0	1	0	14
2005	10	3	16	3	0	0	32
2006	12	1	8	4	0	0	25
2007	18	1	17	10	0	0	46
2008	23	1	18	15	4	0	61
2009	31	2	19	17	2	1	72
2010	11	2	23	13	2	0	51
2011	17	2	17	5	3	1	45
2012	18	4	17	8	2	1	50
Total	151	22	145	76	16	3	413
Percent	36.56	5.33	35.11	18.40	3.87	0.73	100

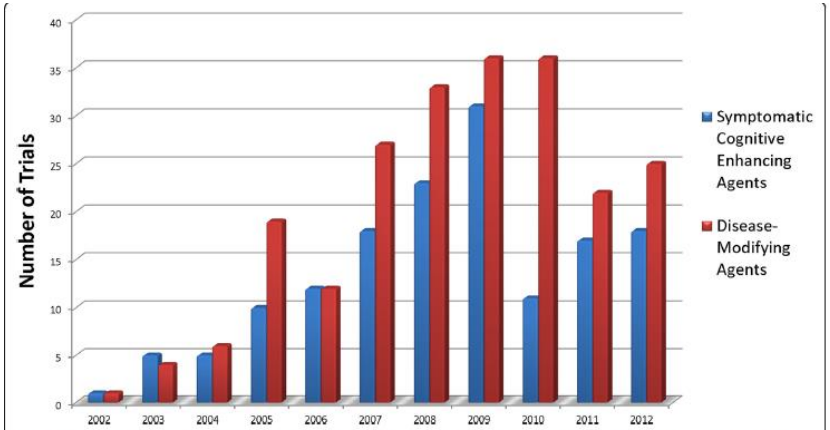

Figure 1 Comparison of number of trials of symptomatic cognitive-enhancing agents and of disease-modifying agents in the 2002 through 2012 period.

ClinicalTrials.gov

2224 studies found for: alzheimer's disease

538 studies found for: alzheimer's disease | Open Studies

121 studies found for: frontotemporal dementia

54 studies found for: frontotemporal dementia | Open Studies

83 studies found for: lewy body disease

39 studies found for: lewy body disease | Open Studies

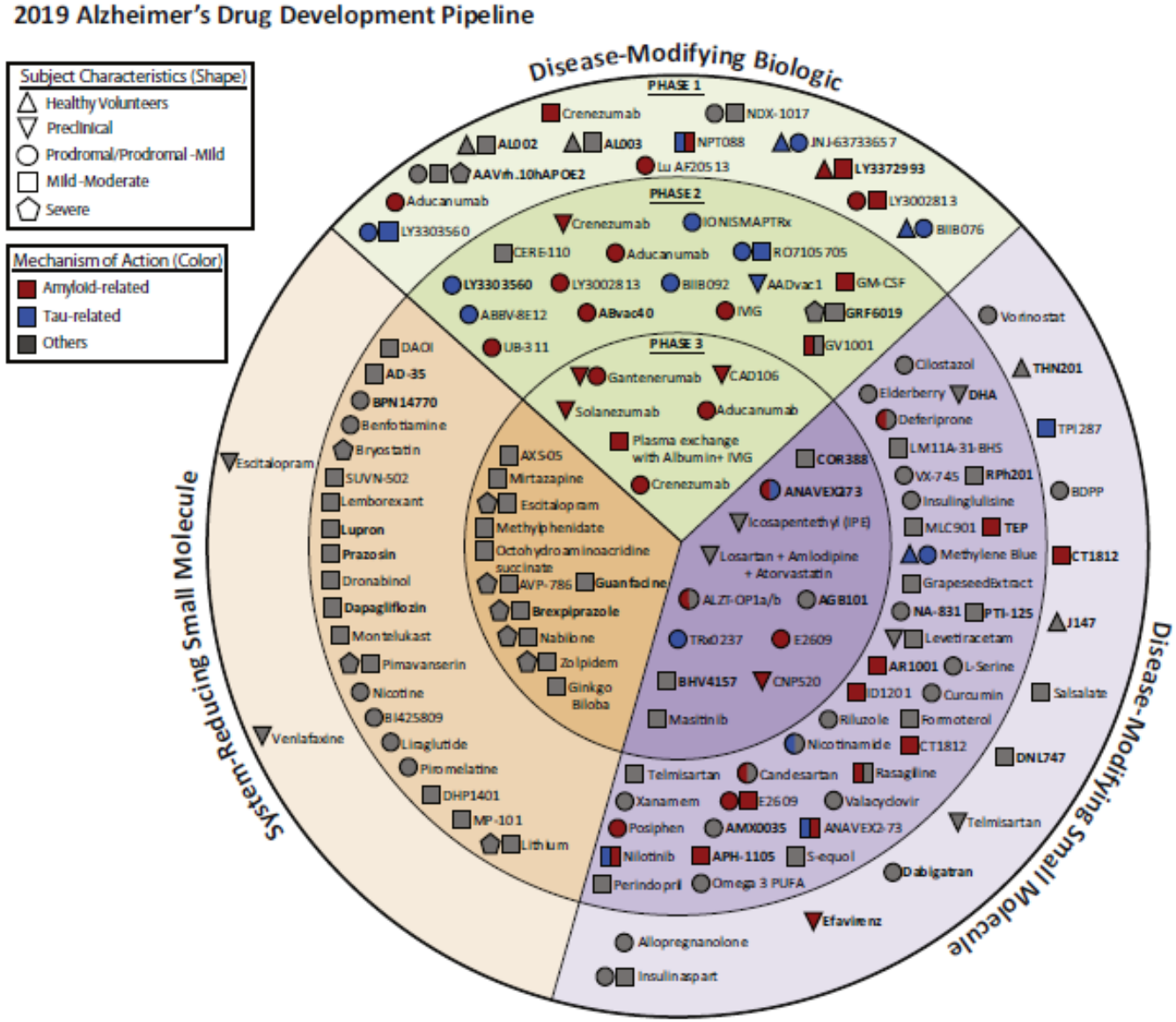

Fig. 1. All compounds in AD clinical trials as of February 12, 2019 (the inner ring shows phase 3 agents; the middle ring is comprised of phase 2 agents; the outer ring presents phase 1 compounds; agents in green areas are biologics; agents in purple areas are disease-modifying small molecules; agents in orange areas are symptomatic agents addressing cognitive enhancement or behavioral and neuropsychiatric symptoms; the shape of the icon shows the population of the trial; the icon color shows the class of target for the agent.). Bolded names represent agents new to that phase since 2018.

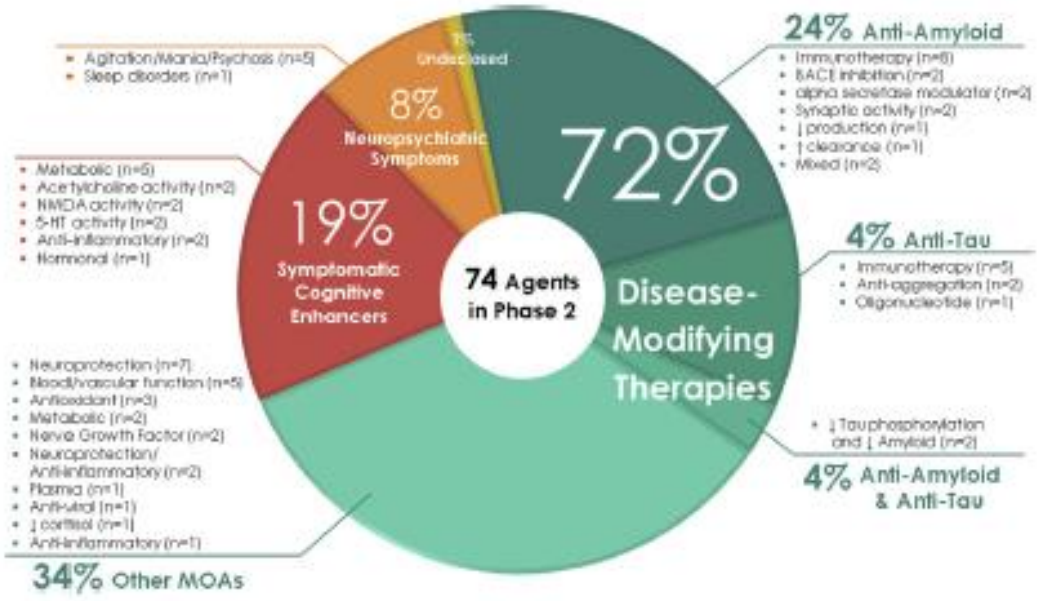

Fig. 3. Mechanisms of action of agents in phase 2.

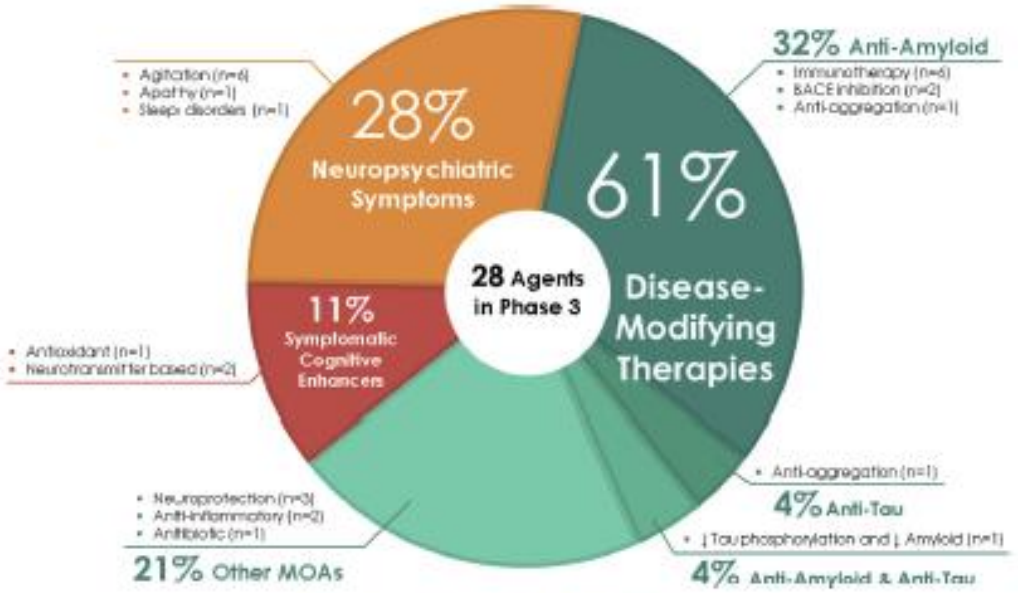

Fig. 2. Mechanisms of action of agents in phase 3.

Trial fallito: Eli Lilly ritira il farmaco anti-Alzheimer

Solanezumab, considerato tra i prodotti più promettenti contro la malattia, non ha superato i test clinici di fase 3.

Impatto negativo di 150 milioni di dollari

Malattia di Alzheimer, alt a due studi di fase III su anticorpo monoclonale di Roche

Il farmaco continua ad essere studiato in un trial che ha arruolato 300 partecipanti provenienti dalla Colombia che presentano una mutazione autosomica dominante del gene della presenilina-1 (PSEN1). Si tratta di una rara alterazione genetica che predispone allo sviluppo dei primi sintomi dell'Alzheimer intorno ai 45 anni e che porta alla demenza completa intorno ai 50 anni. Il trial avrà una durata di 5 anni.

Questo studio determinerà se il trattamento con crenezumab di persone che portano questa mutazione prima dell'insorgenza dei sintomi della malattia rallenterà o preverrà il declino delle capacità cognitive e funzionali. Questo studio è realizzato in collaborazione con il Banner Institute ed è finanziato dal National Institute on Aging

BAN2401 interrotto per futilità

Aprile 2019
Malattia di Alzheimer: interrotto lo sviluppo clinico del farmaco aducanumab

L'anticorpo monoclonale non si è dimostrato efficace nel rallentare il declino cognitivo e funzionale dei pazienti

The NEW ENGLAND JOURNAL of MEDICINE

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Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease

Lawrence S. Honig, M.D., Ph.D., Bruno Vellas, M.D., Michael Woodward, M.D., Mercè Boada, M.D., Ph.D., Roger Bullock, M.D., Michael Borrie, M.B., Ch.B., Klaus Hager, M.D., Niels Andreasen, M.D., Ph.D., Elio Scarpini, M.D., Hong Liu-Seifert, Ph.D., Michael Case, M.S., Robert A. Dean, M.D., Ph.D., Ann Hake, M.D., Karen Sundell, B.S., Vicki Poole Hoffmann, Pharm.D., Christopher Carlson, Ph.D., Rashna Khanna, M.D., Mark Mintun, M.D., Ronald DeMattos, Ph.D., Katherine J. Selzler, Ph.D., and Eric Siemers, M.D.

BACKGROUND

Alzheimer's disease is characterized by amyloid-beta (Aβ) plaques and neurofibrillary tangles. The humanized monoclonal antibody solanezumab was designed to increase the clearance from the brain of soluble Aβ, peptides that may lead to toxic effects in the synapses and precede the deposition of fibrillary amyloid.

METHODS

We conducted a double-blind, placebo-controlled, phase 3 trial involving patients with mild dementia due to Alzheimer's disease, defined as a Mini–Mental State Examination (MMSE) score of 20 to 26 (on a scale from 0 to 30, with higher scores indicating better cognition) and with amyloid deposition shown by means of florbetapir positron-emission tomography or Aβ1-42 measurements in cerebrospinal fluid. Patients were randomly assigned to receive solanezumab at a dose of 400 mg or placebo intravenously every 4 weeks for 76 weeks. The primary outcome was the change from baseline to week 80 in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; scores range from 0 to 90, with higher scores indicating greater cognitive impairment).

RESULTS

A total of 2129 patients were enrolled, of whom 1057 were assigned to receive solanezumab and 1072 to receive placebo. The mean change from baseline in the ADAS-cog14 score was 6.65 in the solanezumab group and 7.44 in the placebo group, with no significant between-group difference at week 80 (difference, −0.80; 95% confidence interval, −1.73 to 0.14; P=0.10). As a result of the failure to reach significance with regard to the primary outcome in the prespecified hierarchical analysis, the secondary outcomes were considered to be descriptive and are reported without significance testing. The change from baseline in the MMSE score was −3.17 in the solanezumab group and −3.66 in the placebo group. Adverse cerebral edema or effusion lesions that were observed on magnetic resonance imaging after randomization occurred in 1 patient in the solanezumab group and in 2 in the placebo group.

CONCLUSIONS

Solanezumab at a dose of 400 mg administered every 4 weeks in patients with mild Alzheimer's disease did not significantly affect cognitive decline. (Funded by Eli Lilly; EXPEDITION3 ClinicalTrials.gov number, NCT01900665.)

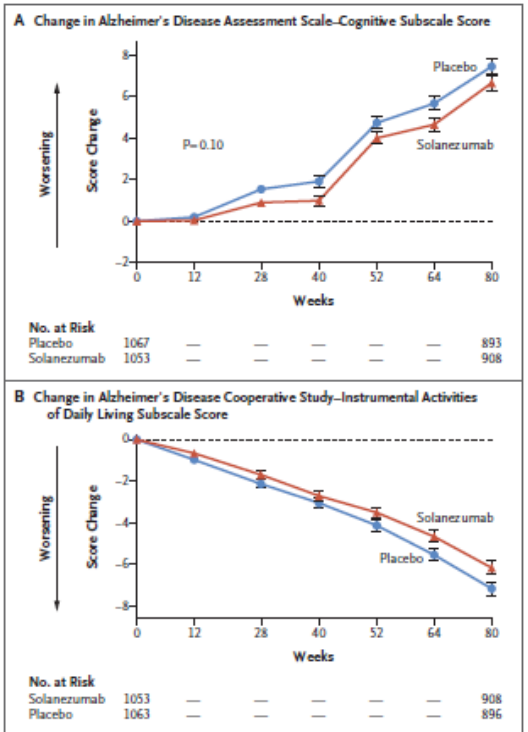


Figure 2. Primary Outcome and Secondary Functional Outcome.

Panel A shows the results for the primary outcome, the least-squares mean change from baseline (dashed line) in the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (on a scale from 0 to 90, with higher scores indicating greater cognitive impairment). Panel B shows the results regarding the secondary functional outcome of the least-squares mean change from baseline (dashed line) in the instrumental subscale of the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; this subscale assesses complex activities such as using public transportation, managing finances, or shopping (on a scale from 0 to 56, with lower scores indicating greater functional loss). In both graphs, I bars indicate the standard error.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=1072)	Solanezumab (N=1057)	P Value
Age — yr	73.3±8.0	72.7±7.8	0.07
Female sex — no. (%)	631 (58.9)	600 (56.8)	0.34
Race — no./total no. (%)†			0.76
White	894/986 (90.7)	878/970 (90.5)	
Black	19/986 (1.9)	14/970 (1.4)	
Asian	71/986 (7.2)	75/970 (7.7)	
Multiple or other	2/986 (0.2)	3/970 (0.3)	
APOE ε4 allele — no./total no. (%)	685/1033 (66.3)	712/1027 (69.3)	0.14
Education — yr	13.7±3.8	13.7±3.7	0.91
Duration since symptom onset — yr	4.3±2.6	4.2±2.5	0.41
Duration since diagnosis — yr	1.6±1.7	1.5±1.6	0.13
Acetylcholinesterase inhibitor or memantine use — no. (%)	856 (79.9)	822 (77.8)	0.24
ADAS-cog14 score‡	29.7±8.5	28.9±8.3	0.02
ADCS-iADL score§	45.4±8.1	45.6±7.9	0.44
MMSE score¶	22.6±2.9	22.8±2.8	0.12
FAQ score‖	10.6±7.1	10.3±6.8	0.36
CDR-SB score**	3.9±2.0	3.9±1.9	0.54

* Plus–minus values are means ±SD. APOE denotes apolipoprotein E.
† Race was reported by the patient.
‡ Scores on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14) range from 0 to 90, with higher scores indicating greater cognitive impairment.
§ The instrumental subscale of the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-iADL) is used to assess complex activities such as using public transportation, managing finances, or shopping; scores range from 0 to 56, with lower scores indicating greater functional loss.
¶ Scores on the Mini–Mental State Examination (MMSE) range from 0 to 30, with higher scores indicating better cognition.
‖ Scores on the Functional Activities Questionnaire (FAQ) range from 0 to 30, with higher scores indicating greater functional loss.
** Scores on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) range from 0 to 18, with higher scores indicating greater impairment.

Ma perchè sono falliti questi studi?

Cosa ci possono insegnare?

The “rights” of precision drug development for Alzheimer’s disease

Abstract

There is a high rate of failure in Alzheimer’s disease (AD) drug development with 99% of trials showing no drug-placebo difference. This low rate of success delays new treatments for patients and discourages investment in AD drug development. Studies across drug development programs in multiple disorders have identified important strategies for decreasing the risk and increasing the likelihood of success in drug development programs. These experiences provide guidance for the optimization of AD drug development. The “rights” of AD drug development include the right target, right drug, right biomarker, right participant, and right trial. The right target identifies the appropriate biologic process for an AD therapeutic intervention. The right drug must have well-understood pharmacokinetic and pharmacodynamic features, ability to penetrate the blood-brain barrier, efficacy demonstrated in animals, maximum tolerated dose established in phase I, and acceptable toxicity. The right biomarkers include participant selection biomarkers, target engagement biomarkers, biomarkers supportive of disease modification, and biomarkers for side effect monitoring. The right participant hinges on the identification of the phase of AD (preclinical, prodromal, dementia). Severity of disease and drug mechanism both have a role in defining the right participant. The right trial is a well-conducted trial with appropriate clinical and biomarker outcomes collected over an appropriate period of time, powered to detect a clinically meaningful drug-placebo difference, and anticipating variability introduced by globalization. We lack understanding of some critical aspects of disease biology and drug action that may affect the success of development programs even when the “rights” are adhered to. Attention to disciplined drug development will increase the likelihood of success, decrease the risks associated with AD drug development, enhance the ability to attract investment, and make it more likely that new therapies will become available to those with or vulnerable to the emergence of AD.

Keywords: Alzheimer’s disease, Drug development, Clinical trials, Biomarkers

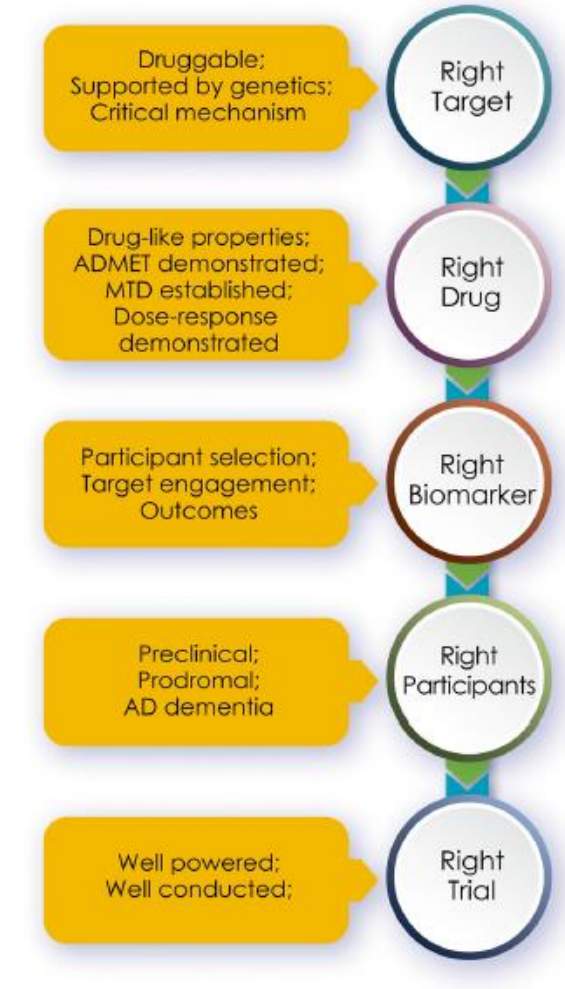
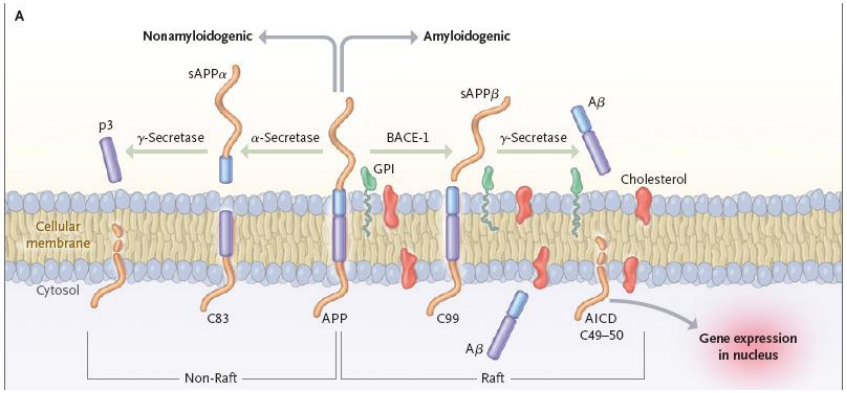
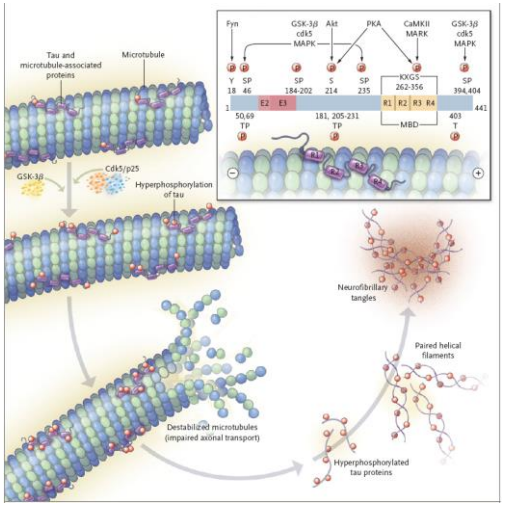


Fig. 1 The rights of AD drug development

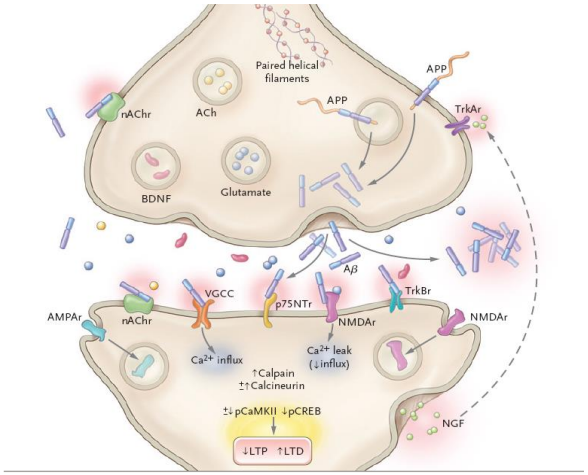
***The right target*: PATHOGENESIS OF ALZHEIMER'S DISEASE (AD)**



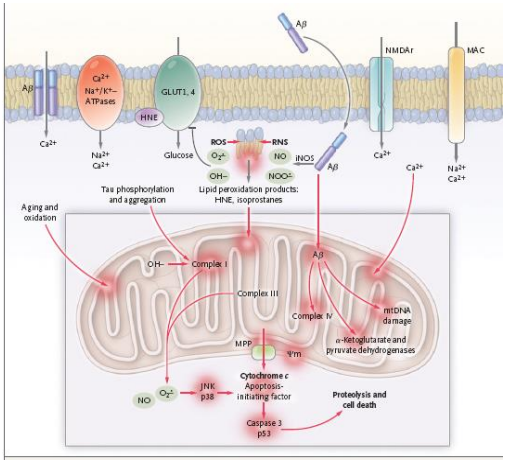
APP METABOLISM



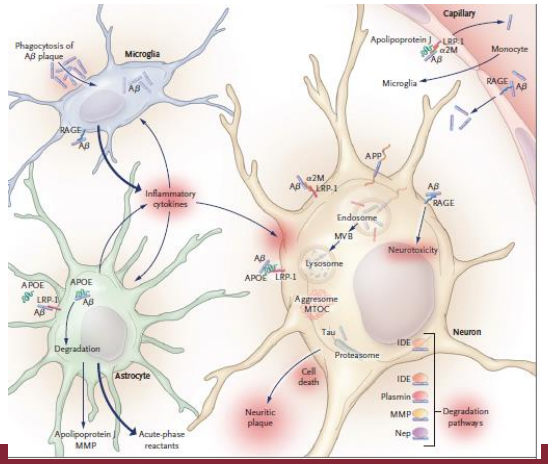
TAU HYPERPHOSPHORILATION



SYNAPSIS DYSFUNCTION



OXIDATIVE STRESS

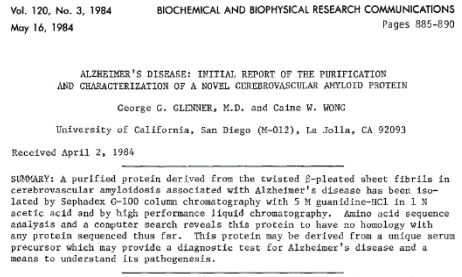


INFLAMMATION

Querfurth HW and LaFerla FM. Mechanism of disease-Alzheimer's Disease;N Engl J Med; 2010:362:329-44

La genetica ha indirizzato…..

1984



Vol. 120, No. 3, 1984 BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
May 16, 1984 Pages 885-890

ALZHEIMER'S DISEASE: INITIAL REPORT OF THE PURIFICATION AND CHARACTERIZATION OF A NOVEL CEREBROVASCULAR AMYLOID PROTEIN

George G. GLENNER, M.D. and Caine W. WONG

University of California, San Diego (M-012), La Jolla, CA 92093

Received April 2, 1984

SUMMARY: A purified protein derived from the twisted β-pleated sheet fibrils in cerebrovascular amyloidosis associated with Alzheimer's disease has been isolated by Sephadex G-100 column chromatography with 5 M guanidine-HCl in 1 N acetic acid and by high performance liquid chromatography. Amino acid sequence analysis and a computer search reveals this protein to have no homology with any protein sequenced thus far. This protein may be derived from a unique serum precursor which may provide a diagnostic test for Alzheimer's disease and a means to understand its pathogenesis.

1991 APP

Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease

Alison Goate*, Marie-Christine Chartier-Harlin*, Mike Mullan*, Jeremy Brown*, Fiona Crawford*, Liana Fidani*, Luis Giuffra†, Andrew Haynes‡, Nick Irving*, Louise James‡, Rebecca Mant||, Phillippa Newton*, Karen Rooke*, Penelope Roques*, Chris Talbot*, Margaret Pericak-Vance§, Allen Roses§, Robert Williamson*, Martin Rossor*, Mike Owen|| & John Hardy*¶

Presenilina 1 1995

Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease

R. Sherrington*, E. I. Rogaev*, Y. Liang*, E. A. Rogaeva*, G. Levesque*, M. Ikeda*, H. Chi*, C. Lin*, G. Li*, K. Holman*, T. Tsuda*, L. Mar†, J.-F. Foncin§, A. C. Bruni||, M. P. Montesi||, S. Sorbi¶, I. Rainero#, L. Pinessi#, L. Nee☆, I. Chumakov**, D. Pollen††, A. Brookes†, P. Sanseau¶¶, R. J. Polinsky‡‡, W. Wasco‡‡, H. A. R. Da Silva§§, J. L. Haines‡‡, M. A. Pericak-Vance§§, R. E. Tanzi‡‡, A. D. Roses§§, P. E. Fraser*, J. M. Rommens† & P. H. St George-Hyslop*¶||

1995
Presenilina 2

Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene

E. I. Rogaev*, R. Sherrington*, E. A. Rogaeva*, G. Levesque*, M. Ikeda*, Y. Liang*, H. Chi*, C. Lin*, K. Holman*, T. Tsuda*, L. Mar†, S. Sorbi‡, B. Nacmias‡, S. Placentini‡, L. Amaducci‡, I. Chumakov§, D. Cohen§, L. Lannfelt||, P. E. Fraser*, J. M. Rommens† & P. H. St George-Hyslop*¶

The amyloid hypothesis of Alzheimer's disease at 25 years

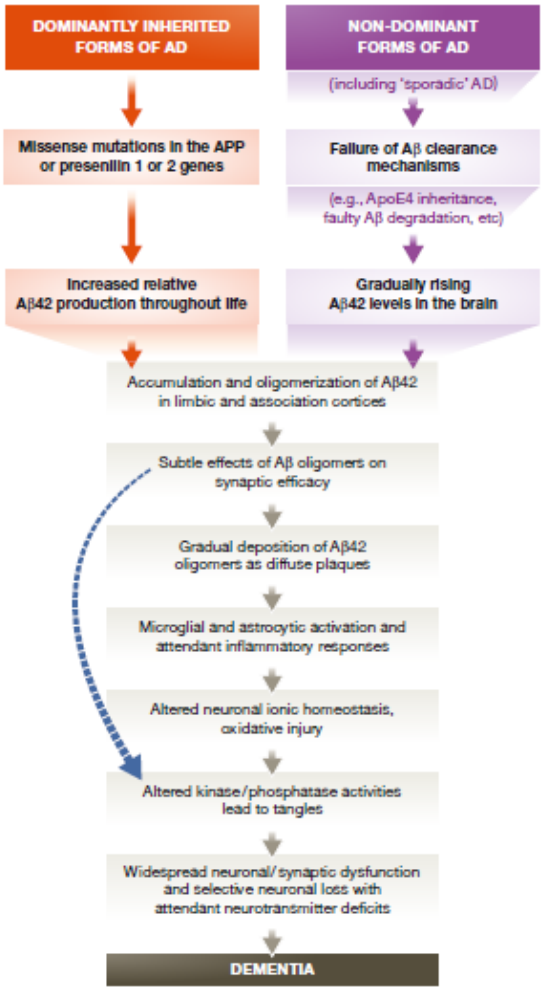


Figure 1. The sequence of major pathogenic events leading to AD proposed by the amyloid cascade hypothesis.
The curved blue arrow indicates that Aβ oligomers may directly injure the synapses and neurites of brain neurons, in addition to activating microglia and astrocytes.

Table 1. Findings that appear to undercut the amyloid hypothesis of AD and counterarguments that could explain these discrepancies.

Findings	Counterarguments
Amyloid plaque burden correlates much less well with degree of cognitive impairment than do neurofibrillary tangle counts	Aβ deposits appear to be a very early and widespread event that is distant to the clinical dementia and can lead to many downstream cellular and molecular changes (e.g., microgliosis, neuritic dystrophy, tangles, etc.) that are more proximate to and causative of neuronal dysfunction
Many humans show sometimes abundant Aβ deposits at death but were not noticeably demented	Some or many of these deposits are diffuse plaques (not rich in abnormal neurites and glia); the patients were often not tested rigorously before death; and Aβ oligomer levels per plaque are much lower than in AD brains (Esparza et al, 2013), suggesting that plaques can effectively sequester oligomers in a non-diffusible, less neurotoxic state, at least up to a point
Some human neuropathological studies suggest tangles may precede amyloid plaques	Such studies may not have searched systematically for diffuse plaques or soluble Aβ oligomers in the brain. Human genetics proves that Aβ-elevating APP mutations lead to downstream alteration and aggregation of wild-type tau, whereas tau mutations do not lead to Aβ deposition and amyloid-related dementia
A hypothesis that AD is fundamentally due to loss of presenilin function has been put forward	AD-causing presenilin mutations may indeed act through partial loss of function of this protease, but these heterozygous mutations do not produce clinically detectable loss of presenilin function (e.g., Notch phenotypes), and organismal development and function are normal until the carriers develop typical AD symptoms in mid-life, heralded by elevated Aβ42/43 to Aβ40 ratios. Moreover, 99.9% of all AD patients have wild-type presenilins
Numerous clinical trials of anti-amyloid agents have not met their pre-specified endpoints	Several of these agents had inadequate preclinical data, poor brain penetration, little human biomarker change, and/or low therapeutic indexes (e.g., tramiprosate; R-flurbiprofen; semagacestat). Most such failed trials enrolled many patients in the late-mild and moderate stages of AD, whereas other trials conducted in very mild or mild AD produced suggestive evidence of clinical benefit. AD trials done prior to obligatory amyloid-PET imaging turned out to have up to ~25% of subjects that were amyloid-negative (i.e., did not have AD)

Neuron 85, March 18, 2015

Immunotherapeutic Approaches for Alzheimer's Disease

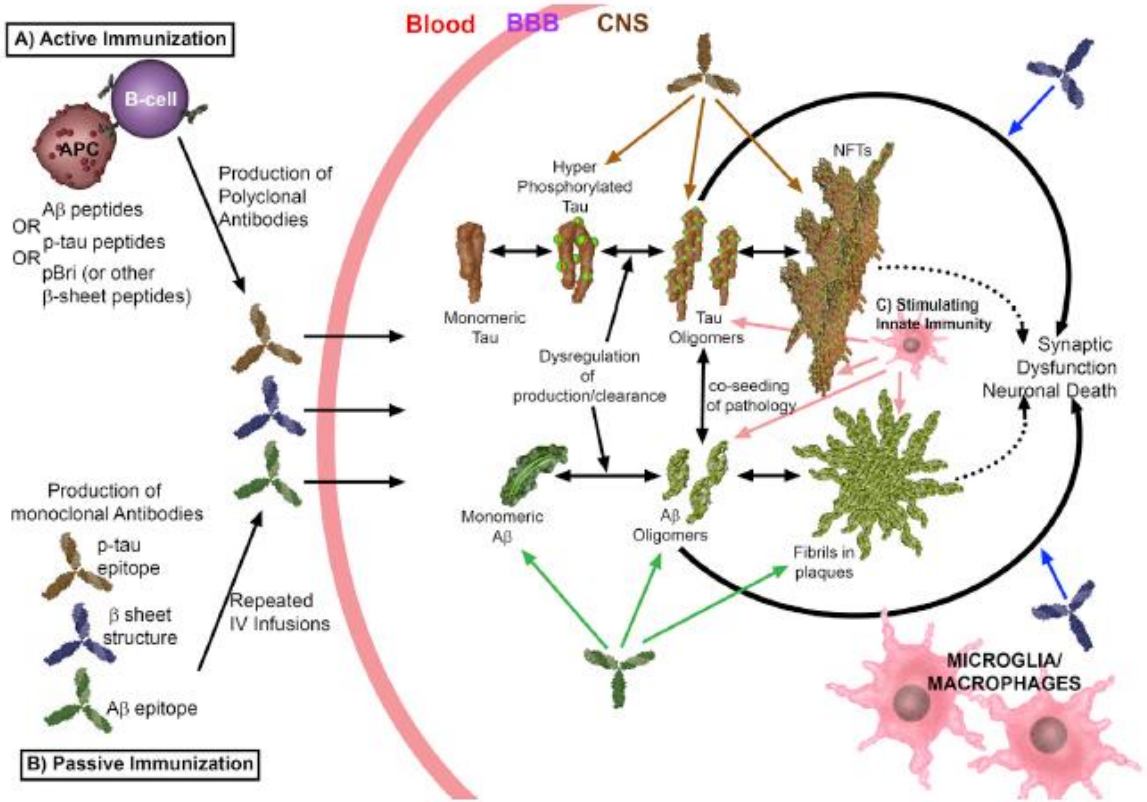


Figure 2. Different Immunotherapeutic Approaches to Ameliorate AD Pathology

(A) Active immunization can be performed using Aβ peptides, phosphorylated tau (ptau) peptides, or preparations such as pBri as an immunogen. These immunogens are presented to B cells by antigen-presenting cells (APC). Use of Aβ peptides or ptau peptides will give rise to the production by B cells of antibodies to Aβ or ptau epitopes, respectively. Use of pBri (or equivalent preparations of an immunogen that is a non-self peptide, in a stabilized, oligomeric β sheet conformation) will lead to the production of antibodies that recognize both Aβ and tau pathological conformers (but not normal monomeric sAβ or tau proteins).

(B) Passive immunization can be performed by the production of mAbs that bind to Aβ, ptau, or β sheet pathological conformations. These antibodies need to be infused systemically in concentrations sufficient for adequate BBB penetration (typically only ~0.1% of a systemically injected mAb will cross the BBB).

Once antibodies cross the BBB (using either active or passive immunization), they will act to enhance the clearance and degradation of their targets. Additional or alternative mechanisms may include disaggregation or neutralization of their target (i.e., blocking of toxicity). Antibodies to Aβ will recognize normal sAβ, oligomeric Aβ, and/or deposited fibrillar Aβ (with varying preference depending on the type[s] of antibodies to Aβ). Similarly, antibodies to ptau will recognize monomeric ptau species, oligomeric tau, and/or NFTs, with varying preference depending on the specific anti-ptau antibody(ies). Antibodies to β sheet will simultaneously act to ameliorate both Aβ and tau pathologies by specifically binding pathological conformers, without binding to normal sAβ or tau.

(C) Stimulation of innate immunity also can be used to ameliorate AD pathology by enhancing microglia/macrophage function via TLRs or related pathways. Microglia/macrophages are stimulated similarly by the immune complexes produced using active or passive immunization approaches.

Un po' di storia per capire il presente

Primo vaccino: AN1792

Sospeso per casi di meningoencefalite

Nei superstiti comparsa di risposta anticorpale

Table 2 *Active immunotherapies in Alzheimer's disease, in clinical Phase II, as of January 2013*

Company	Drug	Aβ epitope	Clinical stage
Alzheimer immunotherapy	ACC-001	N-terminal, Aβ1-6	Phase II
Novartis/Cytos	CAD106	N-terminal, Aβ1-6	Phase II
GSK/Affiris	AFFITOPE AD02	N-terminal, Aβ1-6	Phase II

- Pre-aggregated Abeta1-42 and QS21 as adjuvant
- Polysorbate 80 as an emulsioner, was added to increase solubility of Abeta1-42
- Shift from a Th2 humoral responces to a proinflammatory TH1 responce
- Postmortem examination: drammatic clearance of plaques in the brain parenchima

Journal of Internal Medicine, 2014, 275; 284–295

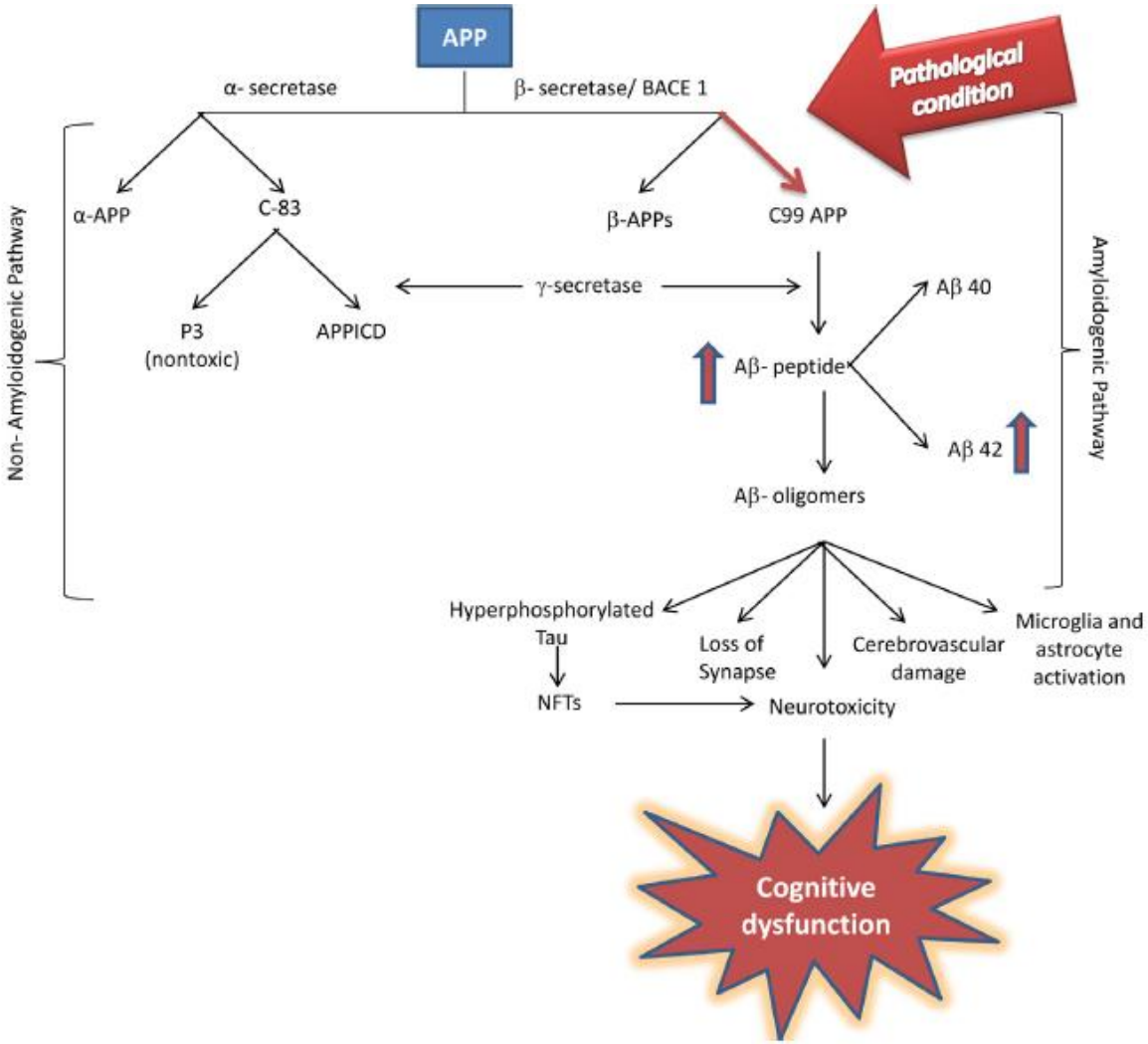


Fig. 1. Diagrammatic presentation of APP processing pathways.

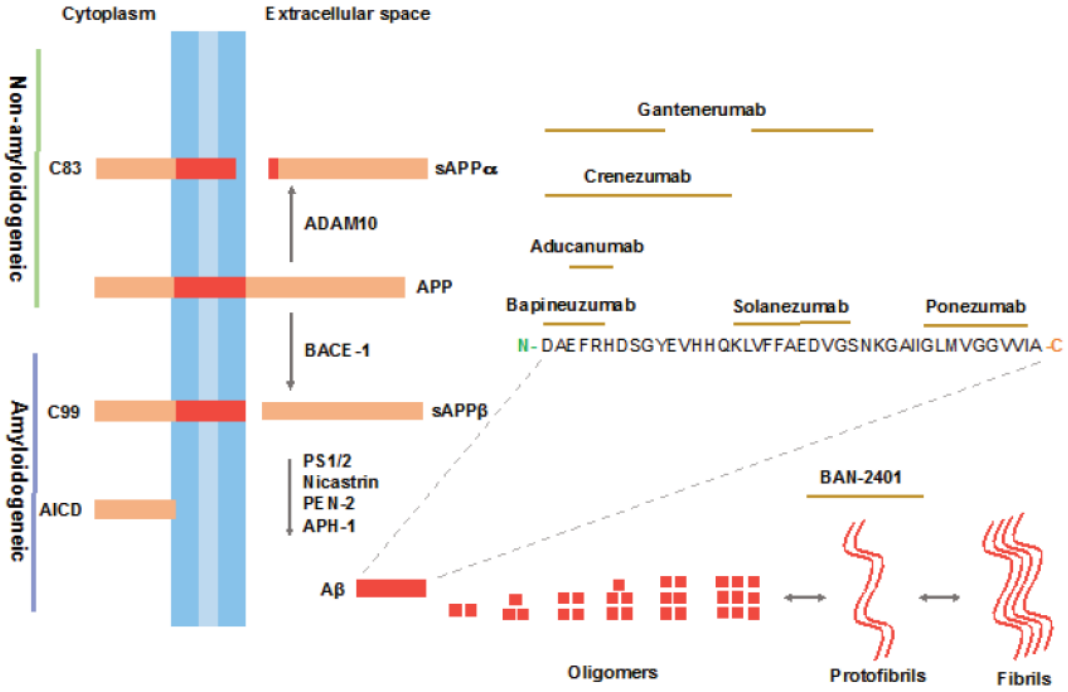


Figure 1. Processing of APP and Aβ mAb epitopes. In the Non-amyloidogenic pathway APP is first cleaved by α-secretase (ADAM-10) producing two fragments, sAPPα and C83, the late is cleaved by the γ-secretase complex generating the p3 and AICD peptides. The Amyloidogenic pathway involves the cleavage of APP by β-secretase (BACE1) producing the sAPPβ and C99 fragments; C99 is then processed by the γ-secretase complex producing Aβ and AICD peptides. The Figure shows the epitope region within the Aβ sequence for sequence-derived mAb.

Passive Immunotherapy						
mAb	Company of origen	Antigen or Epitope /IgG	Binding species	Clinical trial phase	AD Patient status	Result
Crenezumab	AC Immune/Genentech	Pyroglutamate- Aβ1-15(A)/hIgG4	Oligomers, fibrils and plaques	II	Mild	Decreased Aβ levels
Bapineuzumab	Janssen/Pfizer	NT Aβ1-5 (E)/hIgG1	Monomer, fibrils and amyloid plaques	III	Mild to moderate	Stabilized Aβ levels
Ponezumab	Janssen/Pfizer	CT Aβ40 (E)/hIgG2a	Aβ40>monomers, oligomers and fibrils	II	Mild to moderate	Decreased Aβ levels
Solanezumab	Eli Lilly	Aβ16-24 (E)/hIgG1	Monomers>oligomers and fibrils	III	Mild	Decreased Aβ levels
Gantenerumab	Roche	NT Aβ1-10 and central region Aβ18-27 (E)/human IgG1	Monomers, oligomers and fibrils	III	Prodromal to mild	Decreased Aβ levels
Aducanumab	Biogen	NT Aβ3-6 (E)/human IgG1	Oligomers and fibrils	Ib	Prodromal to mild	Decreased Aβ levels
BAN-2401	Biogen/Eisai/ BioArctic	Aβ42 AM protofibrils (A)/hIgG1	Protofibrils	I	Mild	NR

A: Antigen; E: Epitope; hIgG: Humanized IgG; NT: N-terminal region; CT: C-terminal region; AM: Arctic mutation; NR: Not reported

Source: http://www.clinicaltrials.gov

Monoclonal Antibodies Bind Different Epitopes and Conformations of Amyloid-β

					Conformations Recognized			
Antibody	Manufacturer	Origin	Subclass	Epitope	Monomer	Oligomer	Fibril	ARIA-E
Bapineuzumab	Pfizer Inc./Janssen Pharmaceuticals, Inc.	Humanized	IgG1	AA 1–5	Yes	Yes	Yes	High
Solanezumab	Eli Lilly and Company	Humanized	IgG1	AA 16–26	Yes	No	No	Low
Gantenerumab	Hoffman-La Roche	Human	IgG1	AA 3–12, 18–27	Weak	Yes	Yes	High (?)
Crenezumab	Genentech, Inc.	Humanized	IgG4	AA 13–24	Yes	Yes	Yes	Low
Ponezumab	Pfizer Inc.	Humanized	IgG2	AA 30–40	Yes	No	No	None
BAN2401	BioArctic Neuroscience, AB/Eisai Co., Ltd.	Humanized	IgG1	Protofibrils	—	—	—	—
Aducanumab	Biogen, Inc.	Human	IgG1	AA 3–6	No	Yes	Yes	High

Epitope, Conformations Recognized, and ARIA-E are explained further in the text. Dashes indicate absence of information.

AA, amino acid; ARIA-E, amyloid-related imaging abnormalities-edema; Ig, immunoglobulin.

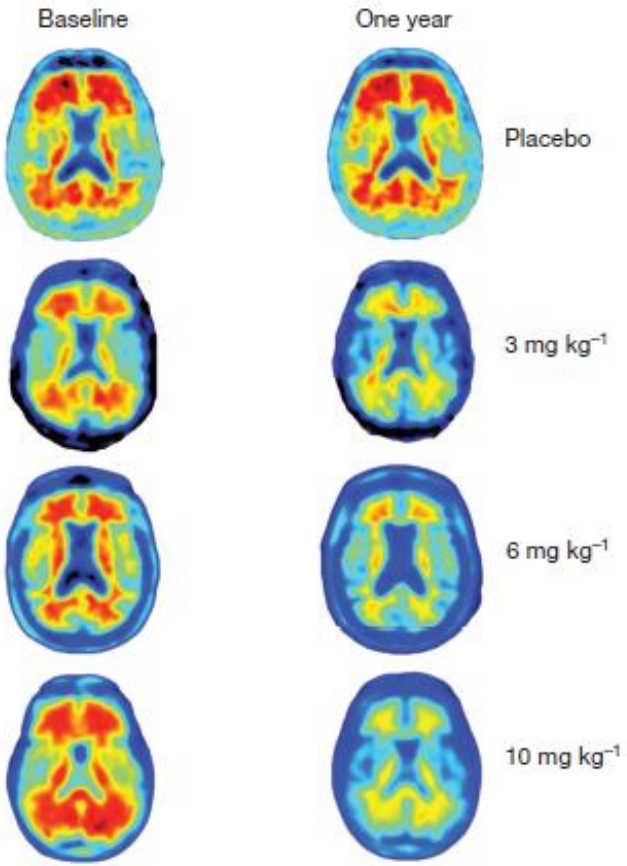
Biol Psychiatry. 2018 February 15; 83(4): 311–319. doi:10.1016/j.biopsych.2017.08.010.

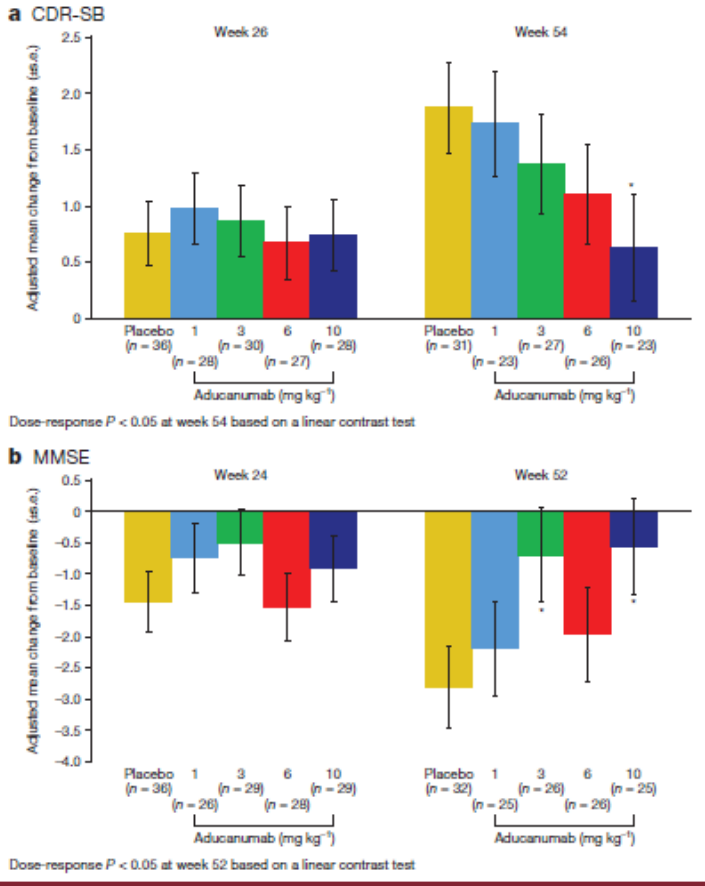
Drug	Publication	Phase	Sample	Participants	Age, Years	Dose	Duration, Weeks	Efficacy	ARIA-E	Biomarkers
Bapineuzumab	Salloway *et al*., 2009 (15)	2	234	Mild-moderate AD	50–85	0.15, 0.5, 1, 2 mg/kg IV every 3 months	78	Failed primary end points	17%, retrospective analysis	No effect on CSF Aβ42, tau, or p-tau
Bapineuzumab	Rinne *et al*., 2010 (19)	2	28	Mild-moderate AD	50–80	0.5, 1, 2 mg/kg IV every 3 months	78		Retrospective analysis combined with Salloway, 2009	↓Cortical ^{11}C-PiB compared with baseline and placebo
Bapineuzumab	Salloway *et al*., 2014 (21)	3	2204	Mild-moderate AD	50–88	0.5, 1, 2 mg/kg IV every 3 months	78	Failed primary end points	15.3% of *APOE* ε4 carriers, 4.2%, 9.4%, and 14.2% of three dose groups in noncarriers	↓Cortical ^{11}C-PiB and ↓CSF p-tau in *APOE* ε4+
Solanezumab	Farlow *et al*., 2012 (27)	2	52	Mild-moderate AD	>50	100, 400, 1600 mg/ month IV	52		No cases	↑Aβ40 and ↑Aβ42 in CSF
Solanezumab	Doody *et al*., 2014 (28)	3	2052	Mild-moderate AD	>55	400 mg IV every month	78	Failed primary end points; ↓decline in mild AD subgroup	0.9% solanezumab vs. 0.4% placebo	No effect on brain Aβ (PET); ↑Aβ40 and ↑Aβ42 in CSF
Solanezumab	Completed	3	2129	Mild AD, Aβ+	55–90	400 mg IV every month	78	Failed primary end point		No effect on brain Aβ or tau (PET)
Gantenerumab	Ostrowitzki *et al*., 2012 (34)	1	18	Mild-moderate AD	50–90	60, 200 mg IV every 4 weeks	24		2/6 participants on 200-mg dose	↓Cortical ^{11}C-PiB compared with baseline
Gantenerumab	Ongoing	2/3	799	Prodromal AD, Aβ+	50–85	105 or 225 mg SC every 4 weeks	104	Nonsignificant benefit in rapid progressors, post hoc		
Crenezumab	Cummings *et al*., in press (38)	2	431	Mild-moderate AD	50–80	300 mg SC every 2 weeks, 15 mg/kg IV every 4 weeks	68	Failed primary end points	1 case, *APOE* ε4 homozygote	↑CSF Aβ42
Crenezumab	Completed	2	91	Mild-moderate AD	50–80	300 mg SC every 2 weeks, 15 mg/kg IV every 4 weeks	68	Failed primary end points		No effect on brain Aβ (PET); ↑Aβ in CSF
Crenezumab	Ongoing	3		Mild-prodromal AD, Aβ+	50–85		100			
BAN2401	Ongoing	2		Mild-prodromal AD, Aβ+	50–90	2.5, 5, 10 mg/kg IV every 2 weeks, 5, 10 mg/kg IV every 4 weeks	78			
Ponezumab	Landen *et al*., 2013 (44)	1		Mild-moderate AD	>50	10 mg/kg IV	52	Failed primary end points	No cases	↓CSF Aβ42
Aducanumab	Sevigny *et al*., 2016 (50)	1	165	Mild-prodromal AD, Aβ+	50–90	1, 3, 6, 10 mg/kg IV every 4 weeks	54	Exploratory; ↓decline in CDR (10 mg/kg) and MMSE (3, 10 mg/kg)	3%, 6%, 37%, 41% of four dose groups	↓Cortical [^{18}F]-florbetapir
Aducanumab	Ongoing	3		Mild-prodromal AD, Aβ+	50–85		78			

AD, Alzheimer's disease; Aβ+, positive for amyloid-β biomarker (PET or CSF); *APOE* ε4+, positive for *APOE* ε4; ARIA-E, amyloid-related imaging abnormalities-edema; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; IV, intravenous; MMSE, Mini-Mental State Examination; PET, positron emission tomography; p-tau, phosphorylated tau; ^{11}C-PiB, [^{11}C]-Pittsburgh compound B; SC, subcutaneous.

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.





- Approccio anti-Proteina tau

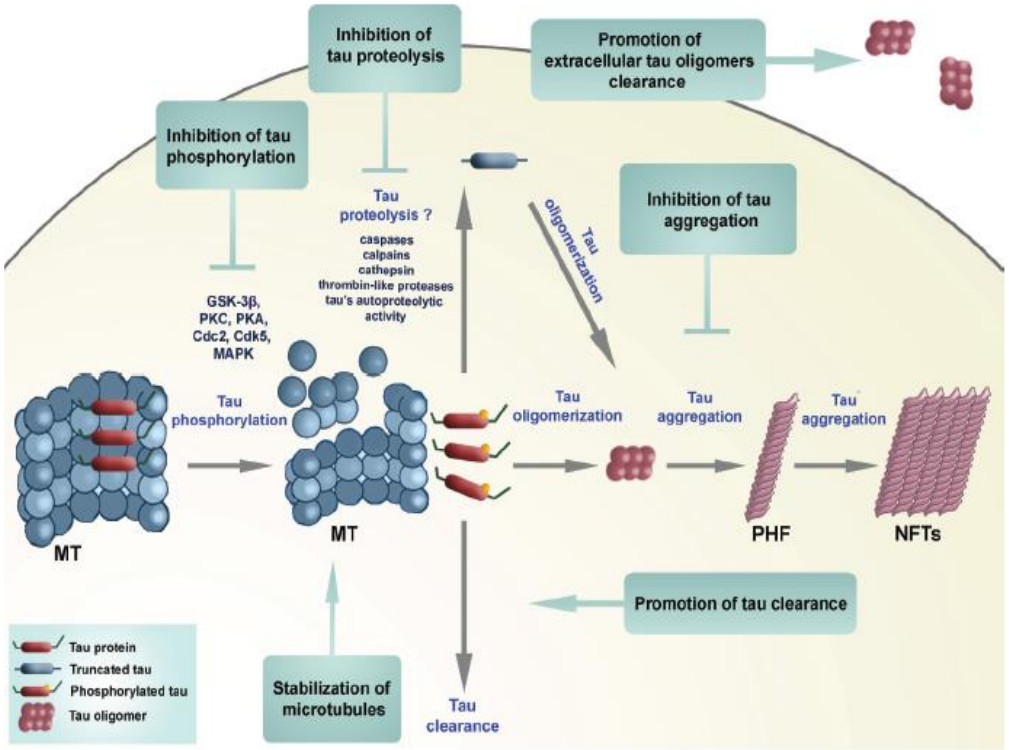


Figure 7. Diagram showing potential neuroprotective strategies to reduce tau aggregates. See text for details.

Biomolecules **2016**, *6*, 6; doi:10.3390/biom6010006

Immunotherapeutic Approaches for Alzheimer's Disease

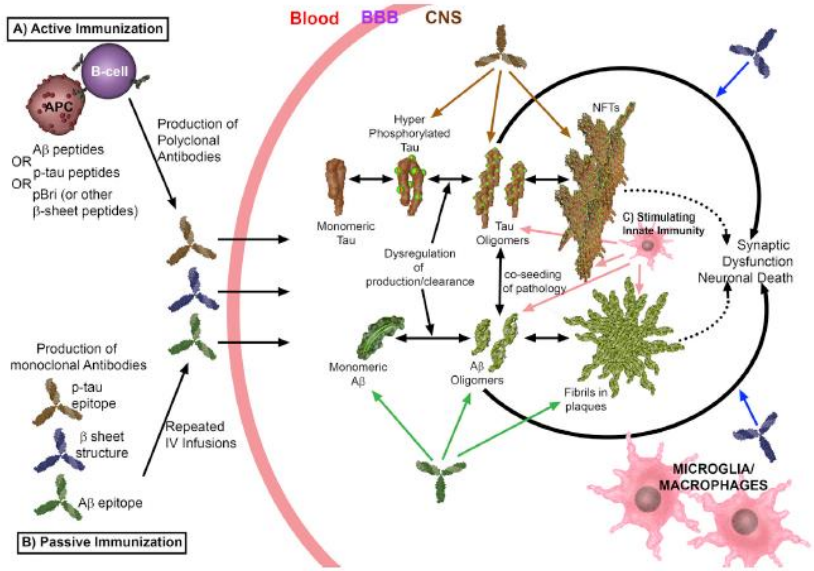


Figure 2. Different Immunotherapeutic Approaches to Ameliorate AD Pathology

(A) Active immunization can be performed using Aβ peptides, phosphorylated tau (ptau) peptides, or preparations such as pBri as an immunogen. These immunogens are presented to B cells by antigen-presenting cells (APC). Use of Aβ peptides or ptau peptides will give rise to the production by B cells of antibodies to Aβ or ptau epitopes, respectively. Use of pBri (or equivalent preparations of an immunogen that is a non-self peptide, in a stabilized, oligomeric β sheet conformation) will lead to the production of antibodies that recognize both Aβ and tau pathological conformers (but not normal monomeric sAβ or tau proteins).
(B) Passive immunization can be performed by the production of mAbs that bind to Aβ, ptau, or β sheet pathological conformations. These antibodies need to be infused systemically in concentrations sufficient for adequate BBB penetration (typically only ~0.1% of a systemically injected mAb will cross the BBB).
Once antibodies cross the BBB (using either active or passive immunization), they will act to enhance the clearance and degradation of their targets. Additional or alternative mechanisms may include disaggregation or neutralization of their target (i.e., blocking of toxicity). Antibodies to Aβ will recognize normal sAβ, oligomeric Aβ, and/or deposited fibrillar Aβ (with varying preference depending on the type[s] of antibodies to Aβ). Similarly, antibodies to ptau will recognize monomeric ptau species, oligomeric tau, and/or NFTs, with varying preference depending on the specific anti-ptau antibody(ies). Antibodies to β sheet will simultaneously act to ameliorate both Aβ and tau pathologies by specifically binding pathological conformers, without binding to normal sAβ or tau.
(C) Stimulation of innate immunity also can be used to ameliorate AD pathology by enhancing microglia/macrophage function via TLRs or related pathways. Microglia/macrophages are stimulated similarly by the immune complexes produced using active or passive immunization approaches.

•Nel 2007 primo tentativo di vaccinazione tau su topi trangenici
Risultati incoraggianti ma al momento uno studio di fase I
È stato dimostrato che gli Ab anti-tau passano la BEE e sono catturati da recettori Fc a bassa affinità interagendo con la tau a livello lisosomiale

AADVac1:peptide sintetico derivato dai residui di 294-305 di tau, che sono coinvolti nella Polimerizzazione della tau
ACI-35: integra i residui di 393-408 in liposomi
Risposta anticorpale verso la conformazione della proteina

Neuron 85, March 18, 2015

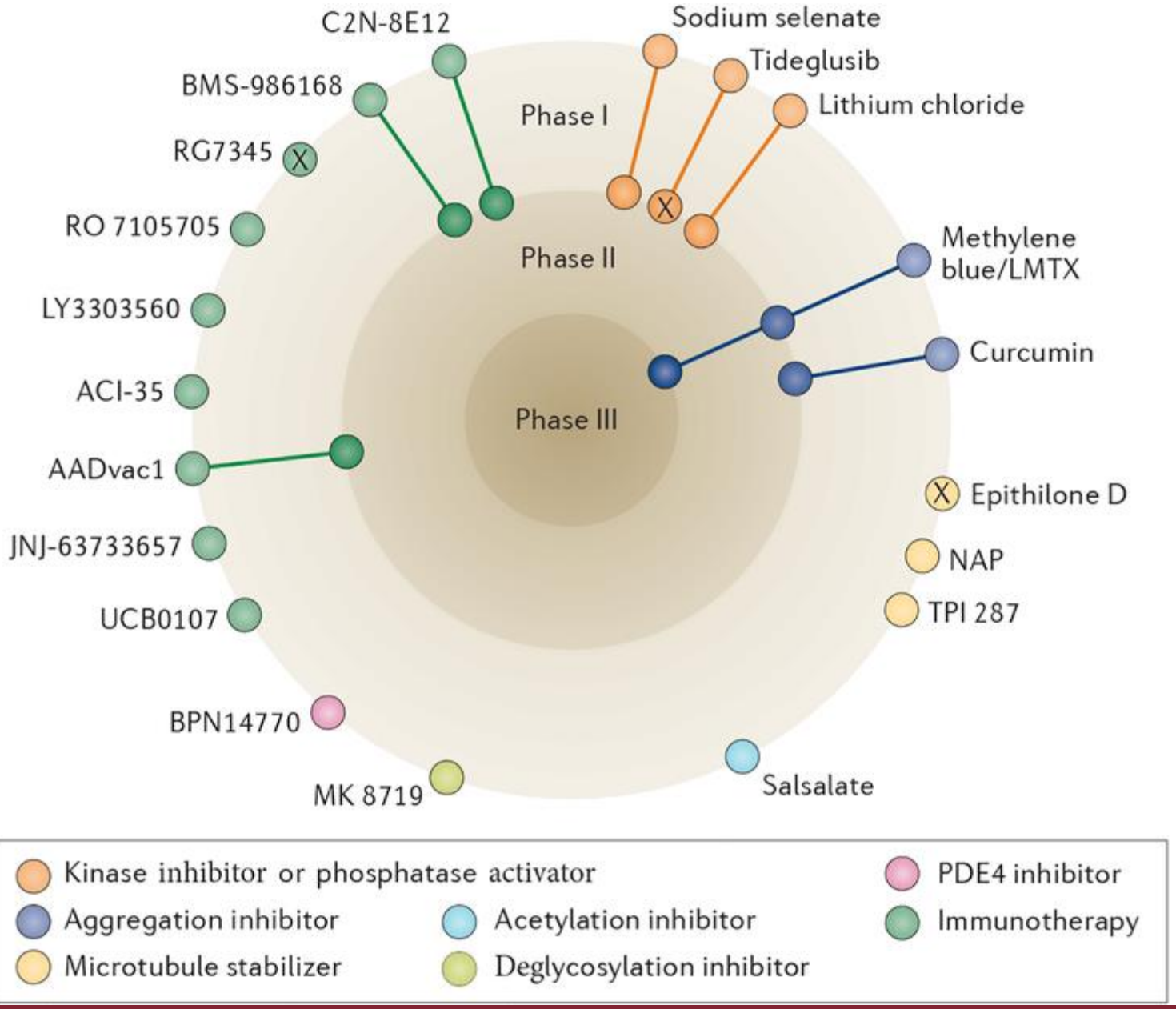
COMMENTARY

"Tau immunotherapy: Hopes and hindrances"

ABSTRACT

Alzheimer's disease (AD) is a progressive neurological disorder having two major pathological hallmarks: the extracellular senile plaques and intracellular neurofibrillary tangles composed of amyloid beta protein and hyperphosphorylated tau respectively. Removal of protein deposits from AD brains are the newer attempts for treating AD. The major developments in this direction have been the amyloid and tau based therapeutics. While senile plaque removal employing monoclonal antibodies (mAbs) restore brain function in mouse models of AD, tau has been recently introduced as the major neurodegenerative factor mediating neural cell death. So, several research groups have focused on tau therapy. So far, the outcome of tau immunotherapy has been promising and clearance of hyperphosphorylated tau has been shown to restore the brain function in animal models. But the point is which phosphorylated tau is the most critical form to be removed from the brain, especially because removal of physiologic tau can cause neurodegenerative consequence. Recently, we have shown that phosphorylated tau at Thr231 in the *cis* conformation is a very early driver of neurodegeneration and *cis* mAb treatment efficiently restores brain structure and function in TBI models. Because of efficient therapeutic effects in mice model of TBI and considering *cis* pT231-tau accumulation in AD brains, it could be a very good candidate for tau immunotherapy upon several tauopathy disorders including AD.

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 2, 277–284



Nat Rev Neurol. 2018 Jul; 14(7): 399–415

Tau-targeting therapies for Alzheimer disease

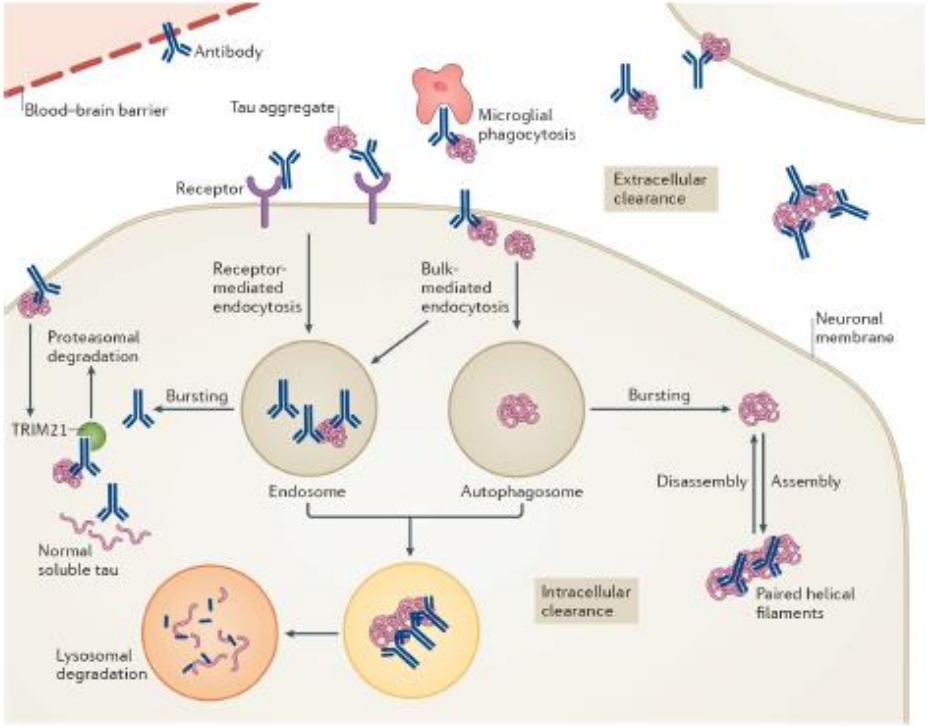


Figure 3 |. Proposed modes of action of anti-tau antibodies.
Antibodies can target tau both extracellularly and intracellularly. Pathological tau mostly resides within neurons but in certain individuals and/or tauopathies, it is also evident in other cell types, primarily glia (in particular, astrocytes and oligodendrocytes). A much smaller pool of tau aggregates is found extracellularly, in the form of small aggregates that are not easily detected or as remnants of neurofibrillary tangles following the death of the neuron. Some anti-tau antibodies are not readily taken up into neurons, presumably because of their unfavourable charge and, therefore, they work principally in the extracellular compartment. Within this compartment, antibodies might sequester tau aggregates, interfere with their assembly and promote microglial phagocytosis, with the overall effect of blocking the spread of tau pathology between neurons. Other antibodies are easily detected within neurons, in association with tau, and have been shown to work both intracellularly and extracellularly. Within the cells, these antibodies could bind to tau aggregates within the endosomal–lysosomal system and promote their disassembly, leading to enhanced access of lysosomal enzymes to degrade the aggregates; sequester tau assemblies in the cytosol and prevent their release from the neuron; or promote proteosomal degradation via E3 ubiquitin–protein ligase TRIM21 binding. The most efficacious antibodies are likely to target more than one pathway and/or pool of tau.

Nat Rev Neurol. Author manuscript; available in PMC 2019 July 01.

Clinical trials of tau-targeting immunotherapies for Alzheimer disease

Agent	Clinical trial identifier	Dates	Trial description	Trial status
Active immunotherapy				
AADvac1	NCT01850238	2013–2015	Phase I randomized, double-blind, placebo-controlled safety and tolerability study in mild to moderate AD (n =30)	Completed
	NCT02031198	2014–2016	Phase I unmasked 18-month follow-up for patients in previous study (n = 25)	Completed
	NCT02579252	2016–2019	Phase II randomized, double-blind, placebo-controlled, safety and efficacy study in mild AD (n = 185)	Recruiting
ACI-35	ISRCTN13033912	Started 2013	Phase I randomized, double-blind, placebo-controlled safety, tolerability and immunogenicity study in mild to moderate AD (n = 24)	Completed
Passive immunotherapy				
RG7345	NCT02281786	2015	Phase I randomized, double-blind single ascending dose safety study in healthy individuals (n = 48)	Completed
BMS-986168	NCT02294851	2014–2016	Phase I randomized double-blind, placebo-controlled safety and tolerability study in healthy individuals (n = 65)	Completed
	NCT02460094	2015–2017	Phase I randomized, double-blind, placebo-controlled, multiple ascending dose study in PSP (n=48)	Completed
	NCT02658916	2016–2019	Phase I extension study for participants in previous trial (n = 48)	Enrolling by invitation
	NCT03068468	2017–2020	Phase II randomized, double-blind, placebo-controlled, parallel-group efficacy study in PSP (n=396)	Active, not enrolling
C2N-8E12	NCT02494024	2015–2016	Phase I randomized, double-blind, placebo-controlled, single ascending dose safety and tolerability study in PSP (n = 32)	Active, not recruiting
	NCT02985879	2016–2019	Phase II randomized, double-blind, placebo-controlled, multiple-dose safety and efficacy study in PSP (n = 330)	Recruiting
	NCT02880956	2016–2020	Phase II randomized, double-blind, placebo-controlled efficacy and safety study in early AD (n = 400)	Recruiting
RO 7105705	NCT02820896	2016–2017	Phase I randomized, double-blind, placebo-controlled, single or multiple ascending dose safety and efficacy study in healthy individuals and patients with mild to moderate AD (n = 74)	Completed
LY3303560	NCT02754830	2016–2017	Phase I randomized, double-blind, placebo-controlled, single-dose escalation study to assess safety in healthy individuals and patients with mild to moderate AD (n = 90)	Active, not recruiting
	NCT03019536	2017–2020	Phase I randomized, parallel-assignment, multiple-dose escalation safety and efficacy study in mild cognitive impairment and mild to moderate AD (n = 132)	Recruiting
JNJ-63733657	NCT03375697	Started 2017	Phase I randomized safety and tolerability trial in healthy individuals and patients with prodromal or mild AD (n = 64)	Recruiting
UCB0107	NCT03464227	Started 2018	Phase I randomized safety and tolerability trial in healthy individuals (n = 52)	Recruiting

AD, Alzheimer disease; PSP, progressive supranuclear palsy.

Therapeutic Inhibition of the Complement System in Diseases of the Central Nervous System

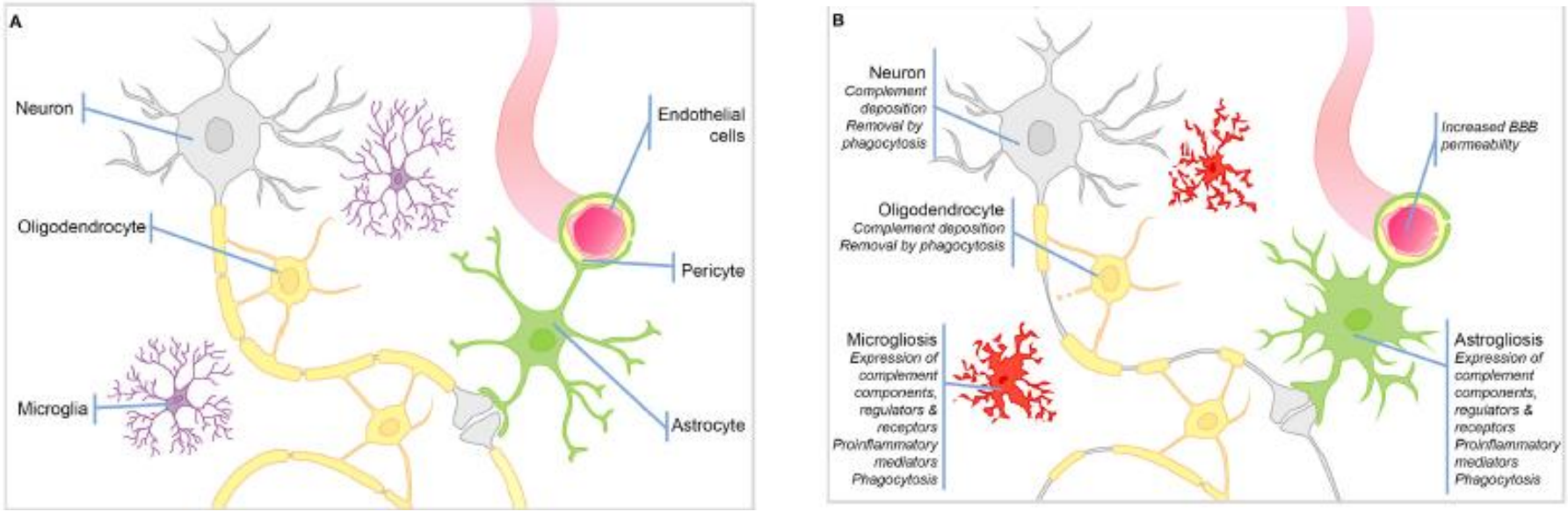


FIGURE 1 | Schematic representation of cell types in the brain and their responses to injury. **(A)** Schematic representation of the cell types in the healthy brain. **(B)** During CNS injury and disease the BBB is compromised. There is significant microgliosis and astrogliosis, characterized by glial cell proliferation, upregulation of complement components, regulators and receptors, proinflammatory mediators, and active phagocytosis. Complement protein expression/deposition are increased on neurons and oligodendrocytes tagging them for removal by phagocytosis and driving neurodegeneration and demyelination.

In fase di avvio uno studio su un Ab diretto contro Il recettore TREM2 (triggering receptor expressed on Myeloid Cell2) espresso dalla microglia

REVIEW
published: 04 March 2019
doi: 10.3389/fimmu.2019.00362

E nel futuro…….?

Amyloid-β and Tau
The Trigger and Bullet in Alzheimer Disease Pathogenesis

The defining features of Alzheimer disease (AD) include conspicuous changes in both brain histology and behavior. The AD brain is characterized microscopically by the combined presence of 2 classes of abnormal structures, extracellular amyloid plaques and intraneuronal neurofibrillary tangles, both of which comprise highly insoluble, densely packed filaments. The soluble building blocks of these structures are amyloid-β (Aβ) peptides for plaques and tau for tangles. Amyloid-β peptides are proteolytic fragments of the transmembrane amyloid precursor protein, whereas tau is a brain-specific, axon-enriched microtubule-associated protein. The behavioral symptoms of AD correlate with the accumulation of plaques and tangles, and they are a direct consequence of the damage and destruction of synapses that mediate memory and cognition. Synapse loss can be caused by the failure of live neurons to maintain functional axons and dendrites or by neuron death. During the past dozen years, a steadily accumulating body of evidence has indicated that soluble forms of Aβ and tau work together, independently of their accumulation into plaques and tangles, to drive healthy neurons into the diseased state and that hallmark toxic properties of Aβ require tau. For instance, acute neuron death, delayed neuron death following ectopic cell cycle reentry, and synaptic dysfunction are triggered by soluble, extracellular Aβ species and depend on soluble, cytoplasmic tau. Therefore, Aβ is upstream of tau in AD pathogenesis and triggers the conversion of tau from a normal to a toxic state, but there is also evidence that toxic tau enhances Aβ toxicity via a feedback loop. Because soluble toxic aggregates of both Aβ and tau can self-propagate and spread throughout the brain by prionlike mechanisms, successful therapeutic intervention for AD would benefit from detecting these species before plaques, tangles, and cognitive impairment become evident and from interfering with the destructive biochemical pathways that they initiate.

Table. Tau-Dependent Effects of Aβ

Study	System	Summary of Main Results
Götz et al,[5] 2001	Mouse	Tangle formation accelerated by injection of Aβ fibrils into the brain
Lewis et al,[6] 2001 and Hurtado et al,[7] 2010	Mouse	Mutant APP expression accelerates tangle formation by mutant tau
Roberson et al,[8] 2007	Mouse	Tau required for learning and memory deficits when plaques are present
Leroy et al,[9] 2012	Mouse	A feedback loop connects Aβ and tau pathologies
Ittner et al,[10] 2010	Mouse	Aβ causes tau-dependent excitotoxicity at NMDA receptors
Rapoport et al,[11] 2002	1° Neurons	Aβ fibrils are cytotoxic
King et al,[12] 2006	1° Neurons	AβOs cause tau-dependent MT loss
Nussbaum et al,[13] 2012	1° Neurons	Pyroglutamylated AβOs cause tau-dependent cytotoxicity
Seward et al,[14] 2013	1° Neurons	AβOs cause tau-dependent, ectopic cell cycle reentry
Shipton et al,[15] 2011	Brain slice	AβOs cause tau-dependent impairment of long-term potentiation
Vossel et al,[16] 2010	1° Neurons	AβOs cause tau-dependent inhibition of mitochondrial transport on MTs
Zempel et al,[17] 2013	1° Neurons	AβOs cause tau-dependent MT severing and synaptic damage in dendrites

JAMA Neurol. 2014;71(4):505-508. doi:10.1001/jamaneurol.2013.5847

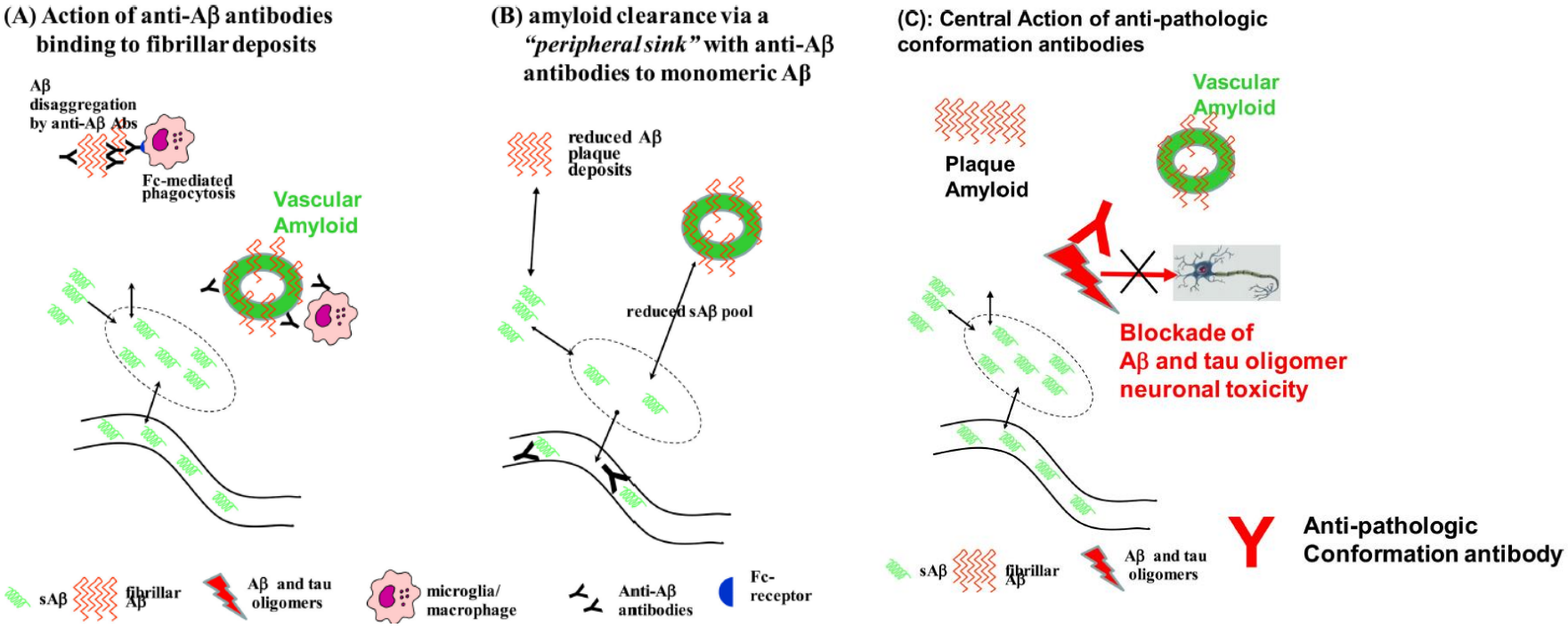


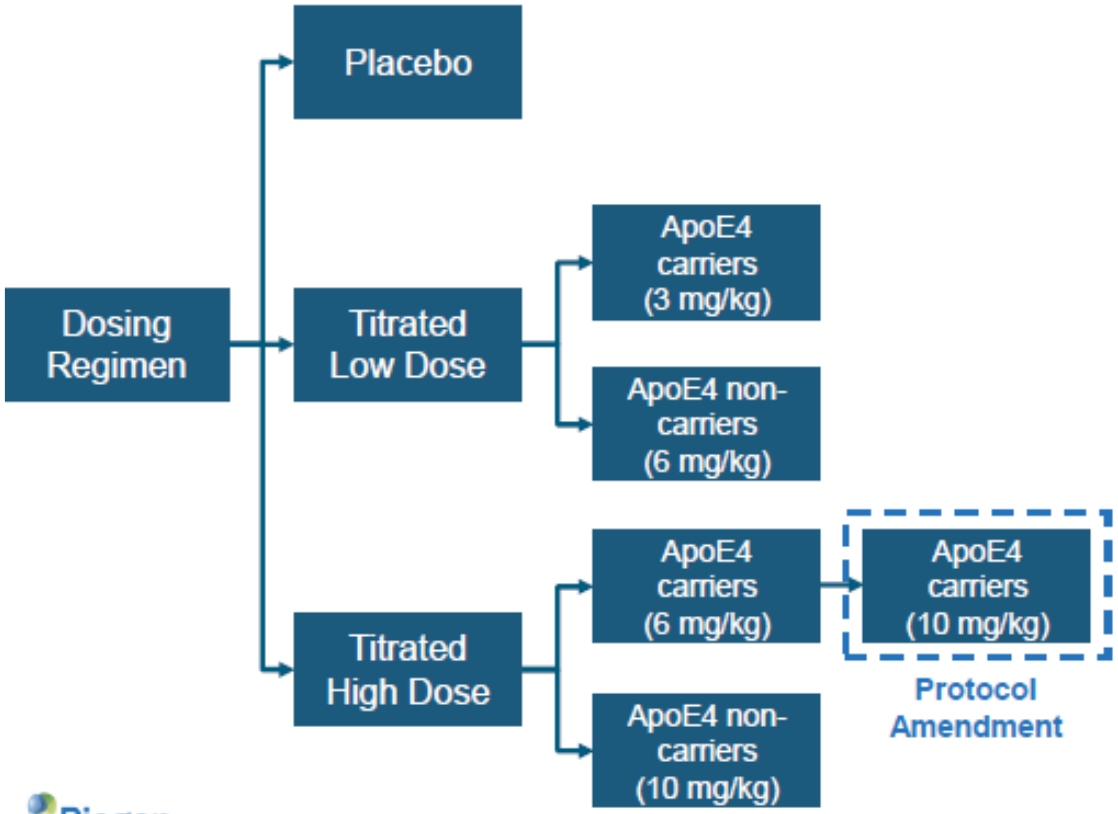
Figure 1. Different mechanisms by which immunotherapy can target AD related pathology
A) Active immunization using Aβ peptides as an immunogen or passive immunization with antibodies that binding to fibrillar Aβ deposits will led to opsonization of plaques and vascular amyloid and resulting macrophage/microglia clearance of deposits. However, this may also lead to excessive inflammation and ARIA, in association with vessel amyloid being cleared.

B) Antibodies to Aβ that specifically bind monomeric forms (such as solanezumab), can sequester and clear sAβ in the peripheral circulation, forming a "peripheral sink", whereby the brain Aβ peptide pool is reduced, gradually reducing deposited plaque and vessel amyloid. This method of AD pathology reduction, appears to be only potentially effective in very early stages of disease progress.
C) Active or passive immunization that specifically target oligomeric conformations of Aβ and/or tau have the advantage that these oligomeric species are thought to be the chief mediators of neurotoxicity. Such approaches have a much lower likelihood of inducing ARIA, as vessel amyloid is not directly targeted.

Expert Rev Vaccines. 2016 ; 15(3): 401–415.

quali speranze?

EMERGE and ENGAGE dosing regimens



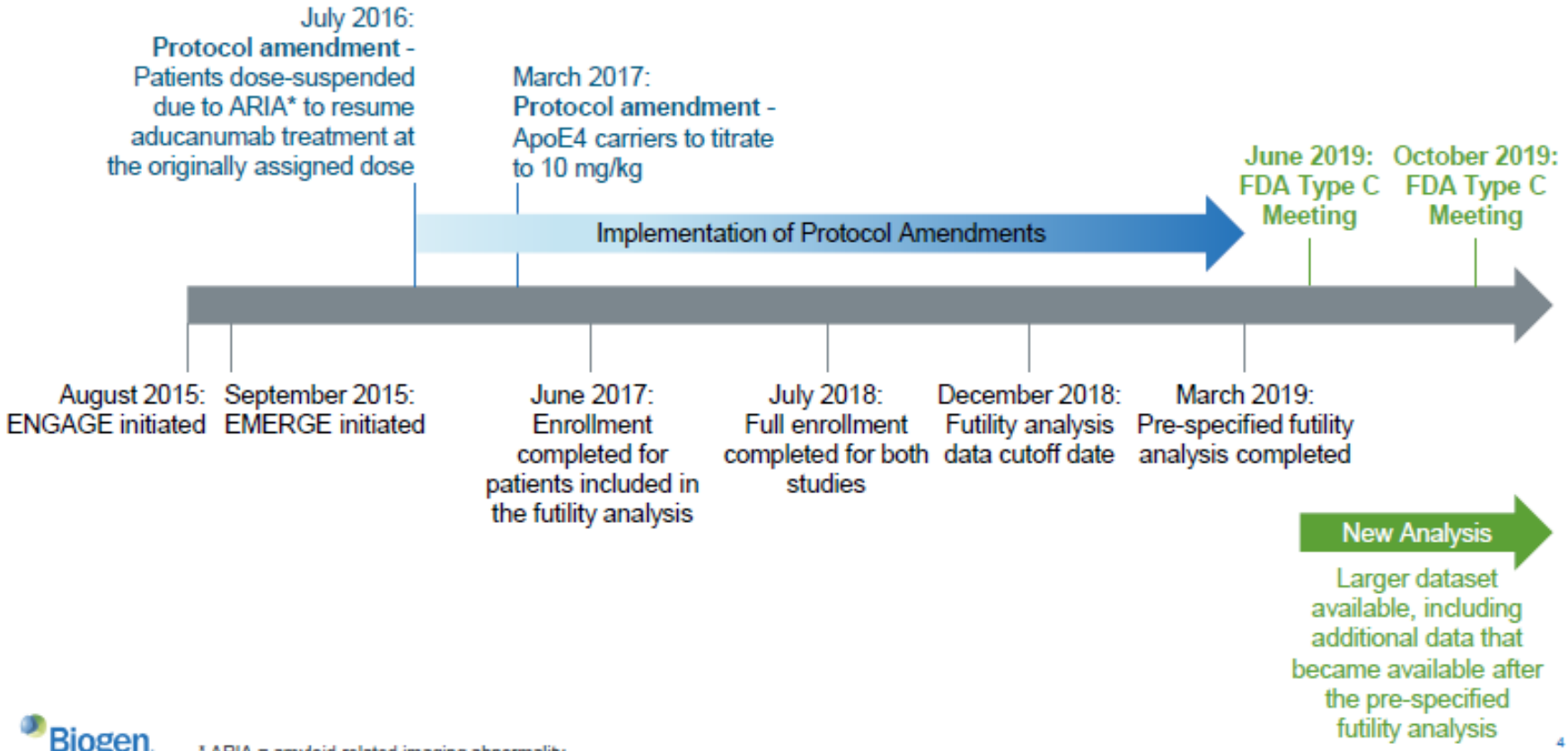
EMERGE/ENGAGE Overview

- Two identically designed Phase 3 studies
- Enrolled patients with mild cognitive impairment due to Alzheimer's disease (AD) and mild AD dementia
- All patients screened with PET* for elevated brain amyloid beta levels
- ~ 2/3 of patients were ApoE4 carriers in each study, well balanced across arms
- Primary endpoint: CDR-SB# at 18 months
- All treatment arms included titration

Biogen

* PET = positron emission tomography
# CDR-SB = Clinical Dementia Rating-Sum of Boxes

EMERGE and ENGAGE timeline



Biogen

* ARIA = amyloid-related imaging abnormality

Outline of available datasets

Dataset	Subject Population	EMERGE n (%)	ENGAGE n (%)
Futility	Opportunity to Complete (OTC)[a]	803 (49%)	945 (57%)
Larger Dataset	Opportunity to Complete (OTC)[b]	982 (60%)	1,084 (66%)
	Intent to Treat (ITT)[c]	1,638 (100%)	1,647 (100%)
	Amyloid beta PET sub-study	485 (30%)	582 (35%)

[a] Subjects who have had the opportunity to complete week 78 visit by December 26, 2018.
[b] Subjects who have had the opportunity to complete week 78 visit by March 20, 2019.
[c] All subjects' data (data after March 20, 2019, are censored for efficacy analyses).

Biogen

EMERGE (larger dataset)

	ITT Population		OTC Population	
	% Reduction vs. Placebo[a] p-value		% Reduction vs. Placebo[a] p-value	
	Low dose (N=543)	High dose (N=547)	Low dose (N=329)	High dose (N=340)
CDR-SB	**-14%** 0.117	**-23%** 0.010	**-16%** 0.134	**-23%** 0.031

[a]: difference in change from baseline vs. placebo at Week 78. Negative percentage means less decline in the treated arm.

N: numbers of randomized and dosed subjects that were included in the analysis. Placebo = 548 (ITT) and 313 (OTC).

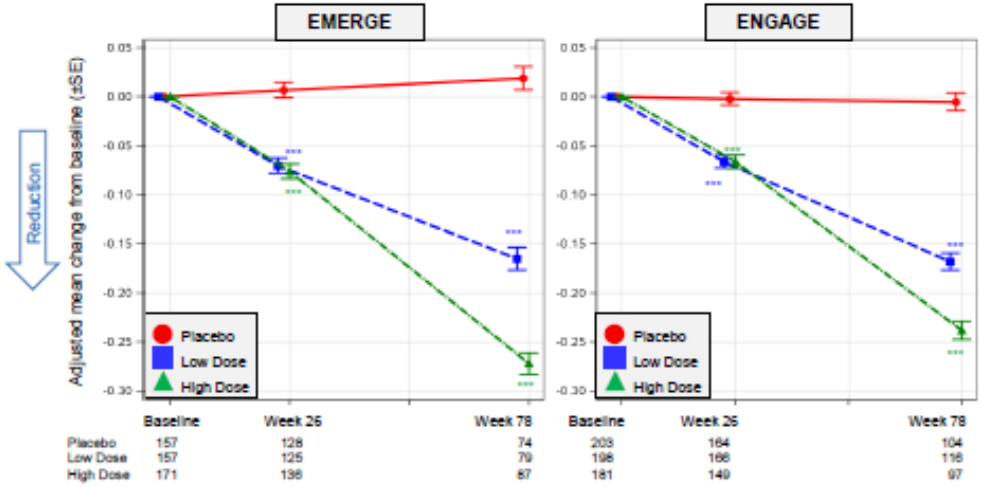
	ITT Population		OTC Population	
	% Reduction vs. Placebo[a] p-value		% Reduction vs. Placebo[a] p-value	
	Low dose (N=543)	High dose (N=547)	Low dose (N=329)	High dose (N=340)
MMSE	**3%** 0.690	**-15%** 0.062	**3%** 0.872	**-23%** 0.032
ADAS-Cog13	**-14%** 0.167	**-27%** 0.010	**-10%** 0.410	**-25%** 0.038
ADCS-ADL-MCI	**-16%** 0.156	**-40%** 0.001	**-20%** 0.117	**-46%** 0.0002

[a]: difference in change from baseline vs. placebo at Week 78. Negative percentage means less decline in the treated arm.

N: numbers of all randomized and dosed subjects that were included in the analysis. Placebo = 548 (ITT) and 313 (OTC).

MMSE = Mini-Mental State Examination; ADAS-Cog13 = AD Assessment Scale-Cognitive Subscale 13 Items;
ADCS-ADL-MCI = AD Cooperative Study-Activities of Daily Living Inventory Mild Cognitive Impairment Version

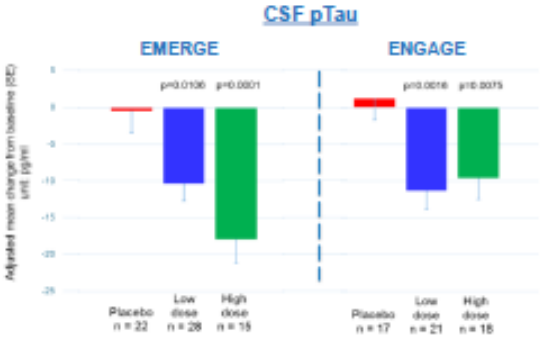
Amyloid PET SUVR: Longitudinal change from baseline

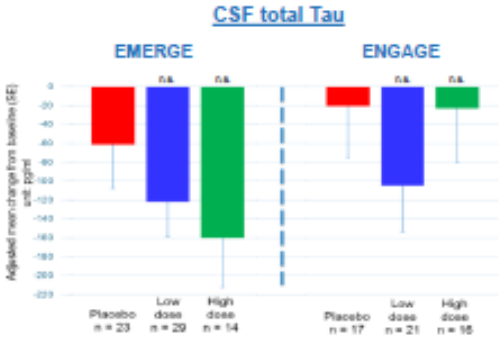


Biogen

Nominal p values: ***P<0.001 vs. placebo.

CSF biomarkers of tau pathology and neurodegeneration in AD are reduced in aducanumab-treated subjects





CSF pTau and CSF total Tau measured at 18 months (data analyzed using ANCOVA); n.s. = not significant

Biogen

The right partecipant

ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–7

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

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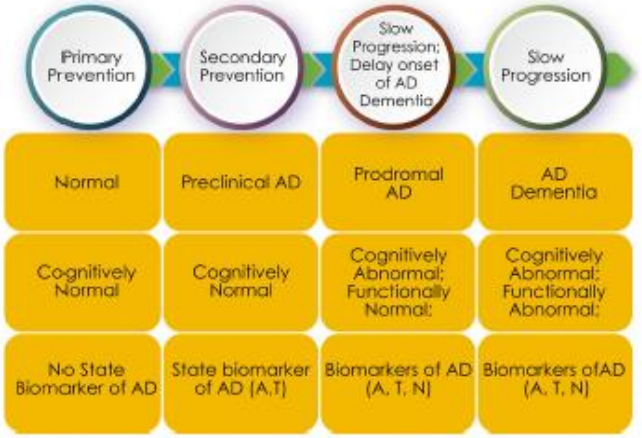
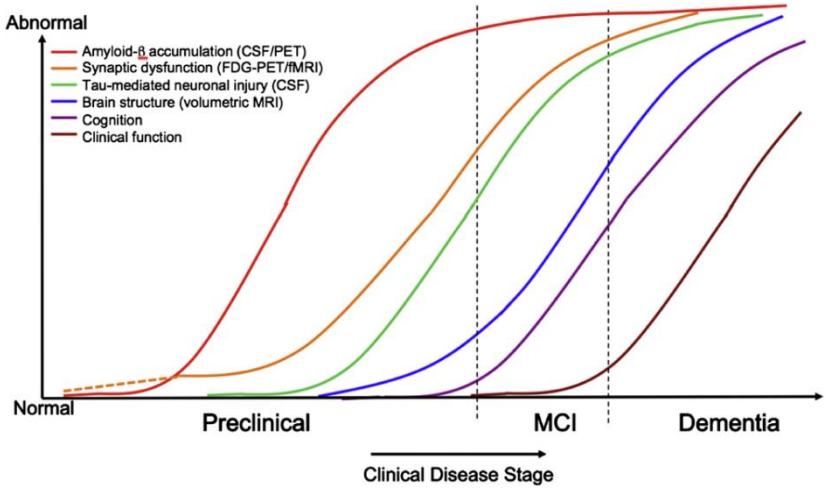
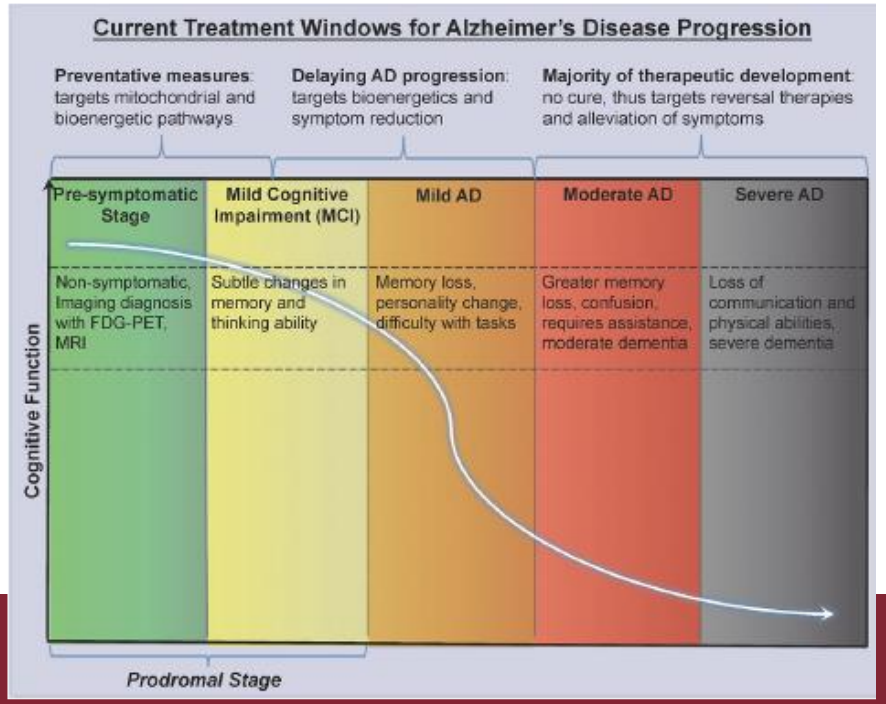


Fig. 2 Spectrum of AD and the corresponding cognitive and biomarker state of trial participants (A, amyloid abnormalities; T, tau abnormalities; N, neurodegeneration)





The right biomarker

Predittivo e prognostico

Table 1 Role of biomarkers in AD drug development

Role in trial	Examples of biomarker used
Identification of trial population	Presence of presenilin 1 (PS1), presenilin 2 (PS2), or amyloid precursor protein (APP) mutations; ApoE-4 plus TOMM40; trisomy 21
Confirmation of diagnosis; exclude non-AD diagnoses	Amyloid imaging; CSF AD signature
Prognosis and course projection	In MCI, ApoE-4 carriers progress more rapidly
Amyloid production and clearance (target engagement)	Stable isotope-labeled kinetics (SILK); BACE activity reduction with BACE inhibitor; CSF Aβ reduction by BACE inhibitor or gamma-secretase inhibitor
Impact of therapy on brain circuit and network function	fMRI; EEG
Impact of therapy on intermediate targets	Amyloid imaging; CSF amyloid; tau PET; CSF phospho-tau
Disease modification	MRI atrophy; CSF total tau; FDG PET; neurofilament light
Stratification for trial analysis	ApoE-4 genotype
Side effect monitoring	MRI surveillance for amyloid-related imaging abnormalities (ARIA); liver function tests; complete blood counts; electrocardiography

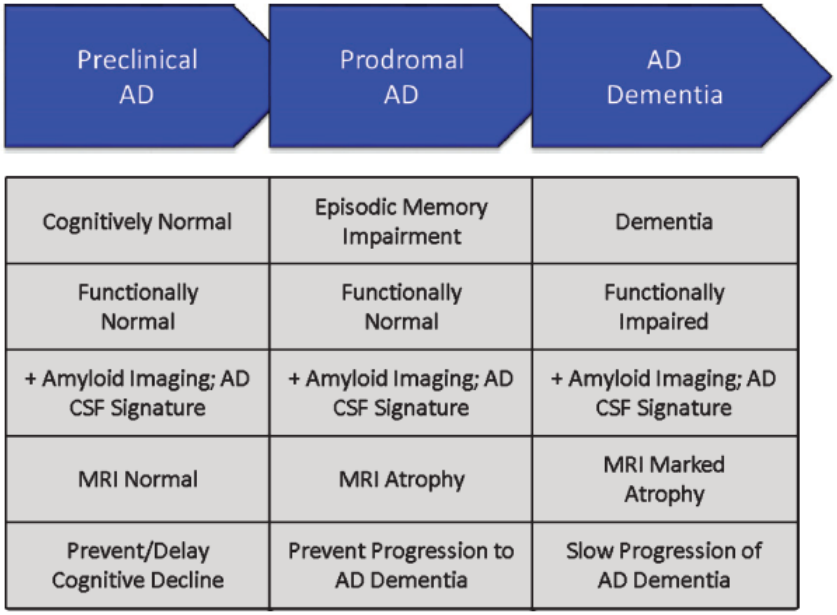


Fig. 6. Phases of Alzheimer's disease (AD) as defined by cognitive, functional, and biomarker observations. Trial goals for each phase are noted.

Table 2
Outcome tools used for the progressive phases of Alzheimer's disease [39, 40, 63–70]

Feature	Preclinical AD	Prodromal AD	AD Dementia
Cognition	Preclinical Alzheimer Cognitive Composite (PACC); Alzheimer Prevention Initiative Cognitive Composite (APCC) Test	Clinical Dementia Rating- Sum of Boxes (CDR-sb); AD Composite Score (ADCOMS); Integrated AD Rating Scale (iADRS)	Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog); Severe Impairment Battery (SIB); Neuropsychological Test Battery (NTB)
Function	None	Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS ADL) Scale, Mild Cognitive Impairment (MCI)	Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS ADL) Scale; Disability Assessment for Dementia (DAD)
Trial Outcome	Drug-placebo difference in biomarker considered reasonably likely to predict clinical benefit; Reduction in cognitive decline compared to placebo	Drug-placebo difference in a composite outcome plus biomarker outcomes supportive of disease modification (composite differences between drug and placebo should not be due exclusively to cognitive benefits of therapy)	Drug-placebo difference in dual cognitive and functional or global outcomes plus biomarker outcomes supportive of disease modification

The "rights" of precision drug development for Alzheimer's disease

Table 3 Five "rights" implemented across the spectrum of drug development

Right element	Target identification	Drug candidate optimization	Non-clinical assessment	Phase 1	Phase 2	Phase 3
Target	Druggable target identified in AD biology		PD effect supported	PD effect may be assessed with biomarkers	PD effect supported by biomarkers	PD effect supported by biomarkers and clinical outcomes
Drug		Chemical properties	ADME; toxicity; efficacy in animals	PK, ADME in healthy volunteers; MTD established; BBB penetration established	PK, PD in AD	PD in AD
Biomarker			Development of biomarkers useful in trials	Toxicity biomarkers	Patient selection; target engagement biomarkers	Patient selection; DM; toxicity; predictive biomarkers
Patient				Healthy volunteers; AD for immuuno-therapy trials	Prodromal AD, AD dementia	High-risk normal subjects; prodromal AD; AD dementia
Trial				Single ascending dose; multiple ascending dose	Drug-placebo difference at endpoint; adaptive designs	Drug-placebo difference at endpoint; adaptive designs; delay to milestone

AD Alzheimer's disease; *ADME* absorption, distribution, metabolism, excretion; *DM* disease modification; *PK* pharmacokinetics; *PD* pharmacodynamic

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