La Terapia della AD

Breaking news or old news ?

Brescia, 9 ottobre 2015

Orazio ZANETTI

Società Italiana di Gerontologia e Geriatria- Associazione Italiana di Psicogeriatria

U.O. Alzheimer - Centro per la Memoria

IRCCS, Centro S.Giovanni di Dio - Fatebenefratelli,

Brescia

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

SPERANZE E REALTA' PER LA CURA DELL'ALZHEIMER

Brescia, 11 novembre 2016

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IL PUNTO SULLA SPERIMENTAZIONE DEI FARMACI PER L'ALZHEIMER

Brescia, 7 LUGLIO 2017

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SOMMARIO

- **Il punto (il mondo reale)**
- **Aspetti etici e conclusioni**

Global leaders have set a deadline of 2025 for finding an effective way to treat or prevent AD.

In the United States in late 2010/early 2011, the National Alzheimer's Project Act (NAPA) was passed and signed into law. It required the creation of a national strategic plan to address the rapidly escalating AD crisis and the coordination of AD efforts across the federal government. The overarching research goal of the project is to "prevent or effectively treat Alzheimer's disease by 2025".

In December 2014, the G8 stated that dementia should be made a global priority with the aim of a cure or approved disease-modifying therapy (DMT) available by 2025.

2025 !

IL MONDO REALE
(The real world)

Gli informatori che ho incontrato negli ultimi dodici (24 ? o più ?) mesi

Citicolina (*“e le mitiche fiale da 1000 mg”*)

Omotaurina

Antiossidanti per il Cervello

XXX è un integratore alimentare particolarmente indicato quando è necessario proteggere il tessuto cerebrale dagli insulti dello stress ossidativo. XXX contiene

Carnosina, estratto di Ginkgo Biloba, vitamine del gruppo B (B1, B2, B3, B6, B9, B12), Selenio e L-cisteina,

coenzima Q10, vitamina E e β-carotene, vitamina C e flavonoidi.

glicerofosforil-etanolamina monoidrata

XXX «forte» contiene

Integratore alimentare a base di vitamina C ed E

INTEGRATORI ALIMENTARI - NUTRACEUTICI

COSTI AMPIAMENTE SUPERIORI AL DONEPEZIL

ED ALLA MEMANTINA

IL PUNTO SULLA SPERIMENTAZIONE DEI FARMACI PER L'ALZHEIMER

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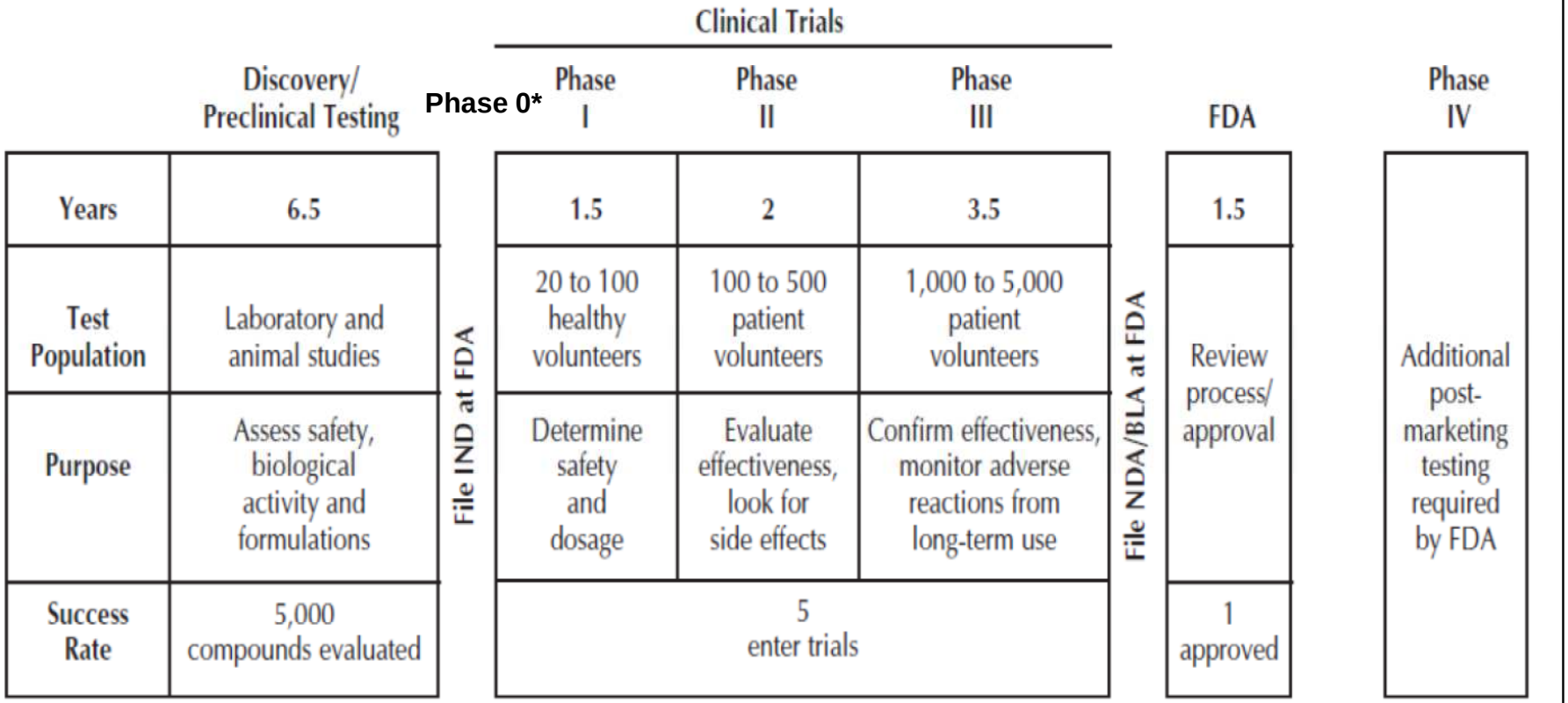
THE DRUG DISCOVERY, DEVELOPMENT AND APPROVAL PROCESS



Sette anni

*microdosi, piccoli gruppi

ITINERARIO DI 15 ANNI

Cummings et al. Alzheimer's Research & Therapy (2016) 8:39
DOI 10.1186/s13195-016-0207-9

Alzheimer's
Research & Therapy

REVIEW Open Access

Drug development in Alzheimer's disease: the path to 2025

Jeffrey Cummings[1*], Paul S. Aisen[2], Bruno DuBois[3], Lutz Frölich[4], Clifford R. Jack Jr[5], Roy W. Jones[6], John C. Morris[7], Joel Raskin[9], Sherie A. Dowsett[8] and Philip Scheltens[10]

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ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2017) 1-18

Alzheimer's & Dementia

Review Article

Alzheimer's disease drug development pipeline: 2017

Jeffrey Cummings[a,*], Garam Lee[a], Travis Mortsdorf[b], Aaron Ritter[a], Kate Zhong[c]

[a]Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA
[b]Touro University Nevada, Henderson, NV, USA
[c]Global Alzheimer Platform, Washington, D.C., USA

Alzheimer's disease: clinical trials and drug development

Francesca Mangialasche, Alina Solomon, Bengt Winblad, Patrizia Mecocci, Miia Kivipelto

Alzheimer's disease is the most common cause of dementia in elderly people. Research into Alzheimer's disease therapy has been at least partly successful in terms of developing symptomatic treatments, but has also had several failures in terms of developing disease-modifying therapies. These successes and failures have led to debate about the potential deficiencies in our understanding of the pathogenesis of Alzheimer's disease and potential pitfalls in diagnosis, choice of therapeutic targets, development of drug candidates, and design of clinical trials. Many clinical and experimental studies are ongoing, but we need to acknowledge that a single cure for Alzheimer's disease is unlikely to be found and that the approach to drug development for this disorder needs to be reconsidered. Preclinical research is constantly providing us with new information on pieces of the complex Alzheimer's disease puzzle, and an analysis of this information might reveal patterns of pharmacological interactions instead of single potential drug targets. Several promising randomised controlled trials are ongoing, and the increased collaboration between pharmaceutical companies, basic researchers, and clinical researchers has the potential to bring us closer to developing an optimum pharmaceutical approach for the treatment of Alzheimer's disease.

Lancet Neurol 2010; 9: 702–16

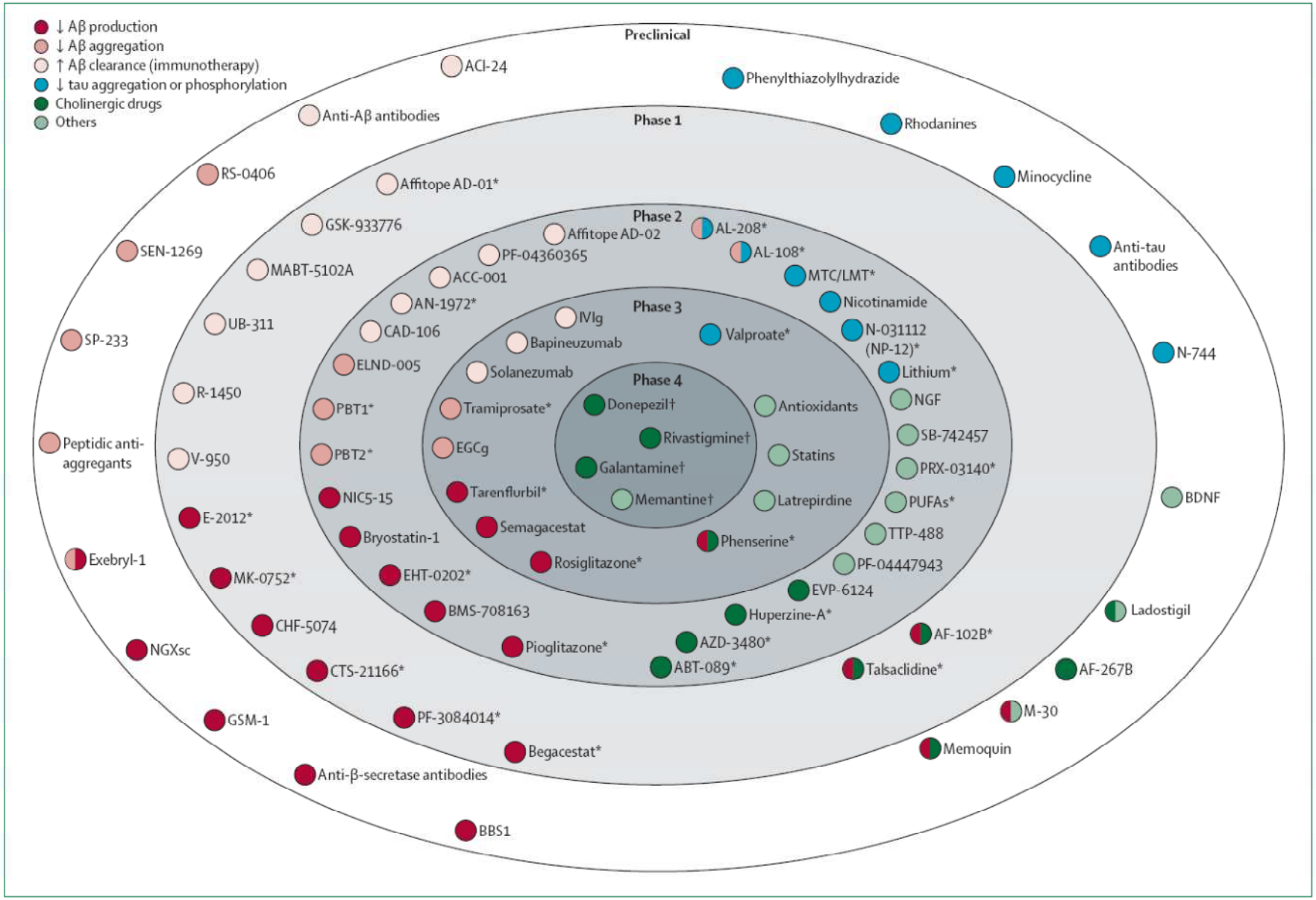

Figure: **Drug development in Alzheimer's disease**

Drugs being investigated for Alzheimer's disease therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from studies in vitro and animal models). Aβ=amyloid β. BBS1=anti-β-site antibodies. BDNF=brain-derived neurotrophic factor. EGCg=epigallocatechin-3-gallate. IVIg=intravenous immunoglobulin. LMT=leuco-methylthioninium. MTC=methylthioninium chloride. NGF=nerve growth factor. NGXsc=NGX series compounds. PUFAs=polyunsaturated fatty acids. GSM=γ-secretase modulator. RCT=randomised controlled trial. *RCTs in Alzheimer's disease not ongoing. †Drugs approved for the treatment of Alzheimer's disease.

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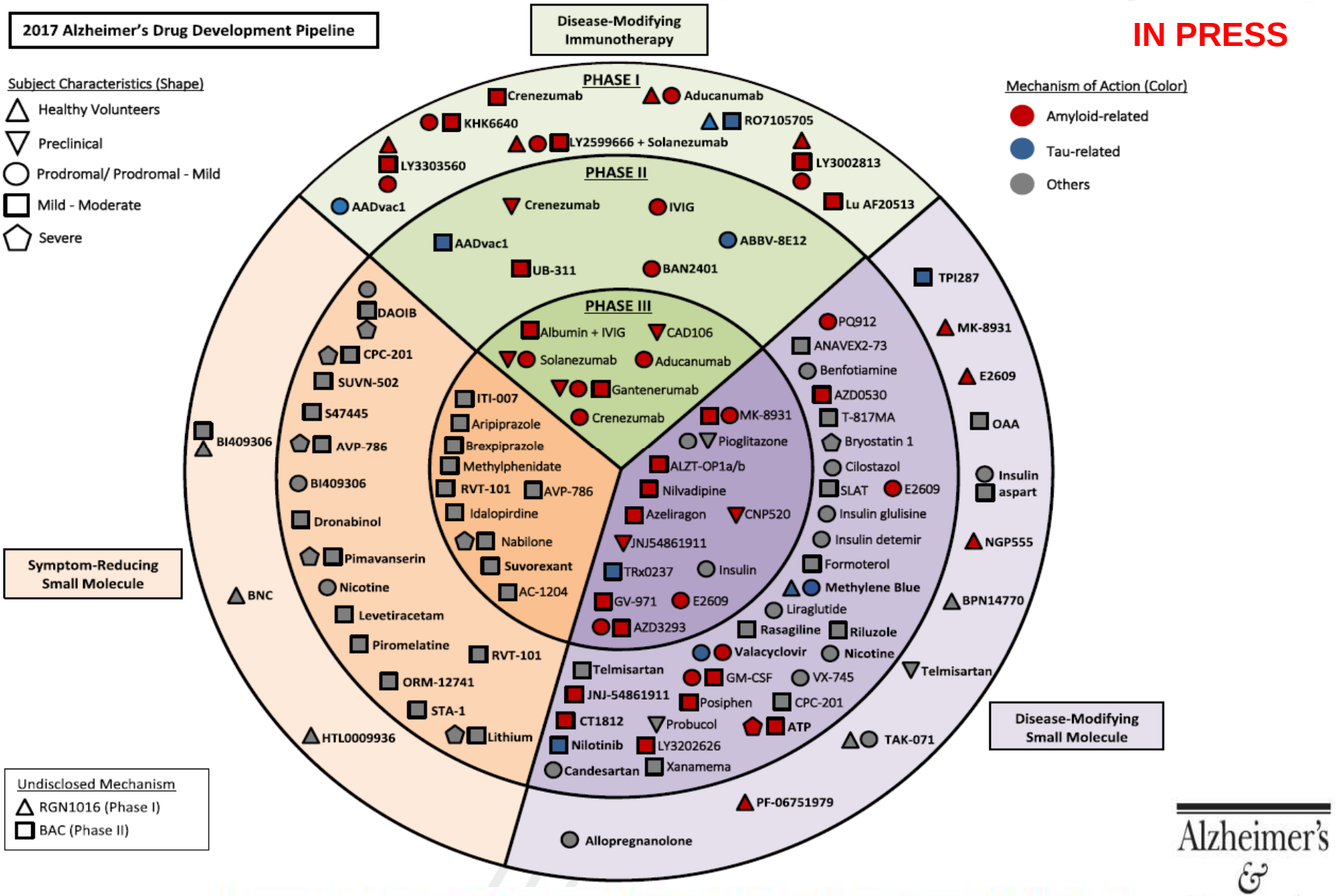


Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2017) 1-18

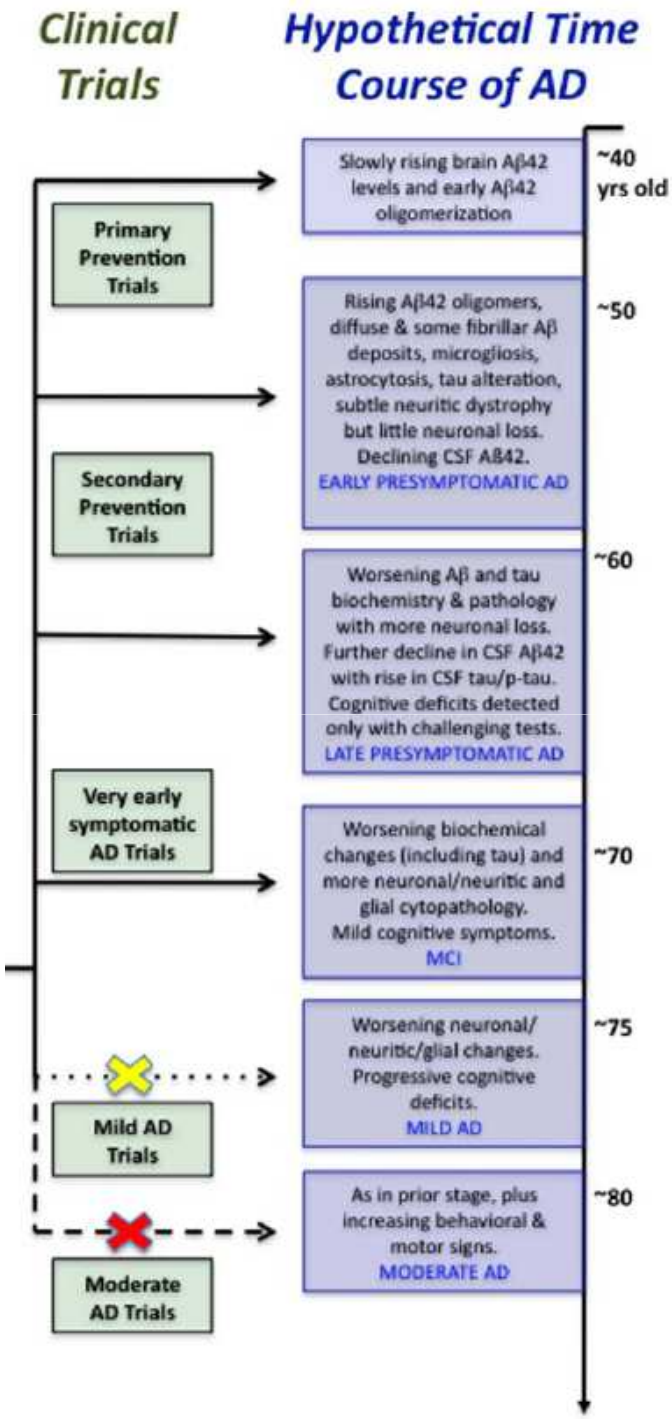
Alzheimer's & Dementia

ANNALS SPECIAL EDITION: THERAPEUTIC PROSPECTS

The Therapeutics of Alzheimer's Disease: Where We Stand and Where We Are Heading

Dennis J. Selkoe, MD

ANN NEUROL 2013;74:328–336



Selkoe DJ, 2013

Ushering in the study and treatment of preclinical Alzheimer disease

Jessica B. Langbaum, Adam S. Fleisher, Kewei Chen, Napatkamon Ayutyanont, Francisco Lopera, Yakeel T. Quiroz, Richard J. Caselli, Pierre N. Tariot and Eric M. Reiman

Langbaum, J. B. *et al. Nat. Rev. Neurol.* 9, 371–381 (2013); published online 11 June 2013; corrected online 16 July 2013; doi:10.1038/nrneurol.2013.107

Key points

- The pathogenic cascade of Alzheimer disease (AD) is thought to begin at least one to two decades prior to cognitive impairment
- Disappointing results of several AD drugs in late-stage trials have suggested the need for early therapeutic intervention, calling for development of biomarkers and sensitive cognitive measures of preclinical disease
- The best established measurements for detection and tracking of preclinical and clinical AD include MRI, fluorodeoxyglucose PET, amyloid PET, and cerebrospinal fluid measures of amyloid-β_{42}, total tau, and phospho-tau
- Studies of individuals with inherited AD can provide insights into cognitive and biomarker changes that precede clinical manifestation of AD, and are suitable candidates for ongoing monitoring and early-intervention strategies
- We are entering an era of AD prevention research, with a number of preclinical AD treatment trials in the planning stages or under way for several at-risk, cognitively unimpaired populations

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[c]*Global Alzheimer Platform, Washington, D.C., USA*

New therapies are urgently needed to treat affected patients and to prevent, defer, slow the decline, or improve the symptoms of AD.

It has been estimated that the overall frequency of the disease would be decreased by nearly 50% if the onset of the disease could be delayed by 5 years.

Symptomatic treatments are drugs aimed at control of neuropsychiatric symptoms and typically work through neurotransmitter mechanisms;

Disease-modifying therapies or treatments (DMTs) are agents that prevent, delay, or slow progression and target the underlying pathophysiologic mechanisms of AD.

We examined clinicaltrials.gov as of January 5, 2017.We captured all trials of all agents in phases I, II, and III.

We divided the symptomatic agents into those that are putative cognitive enhancing agents or those that address neuropsychiatric and behavioral symptoms.

DMTs were divided into those that target amyloid-related mechanisms,
those that have tau-related MOAs, and those with "other" mechanisms such as neuroprotection, anti-inflammatory MOAs, growth factors, or metabolic effects.

Stem cell therapies were included in the "other" category.

Jeffrey Cummings[a,*], Garam Lee[a], Travis Mortsdorf[b], Aaron Ritter[a], Kate Zhong[c]

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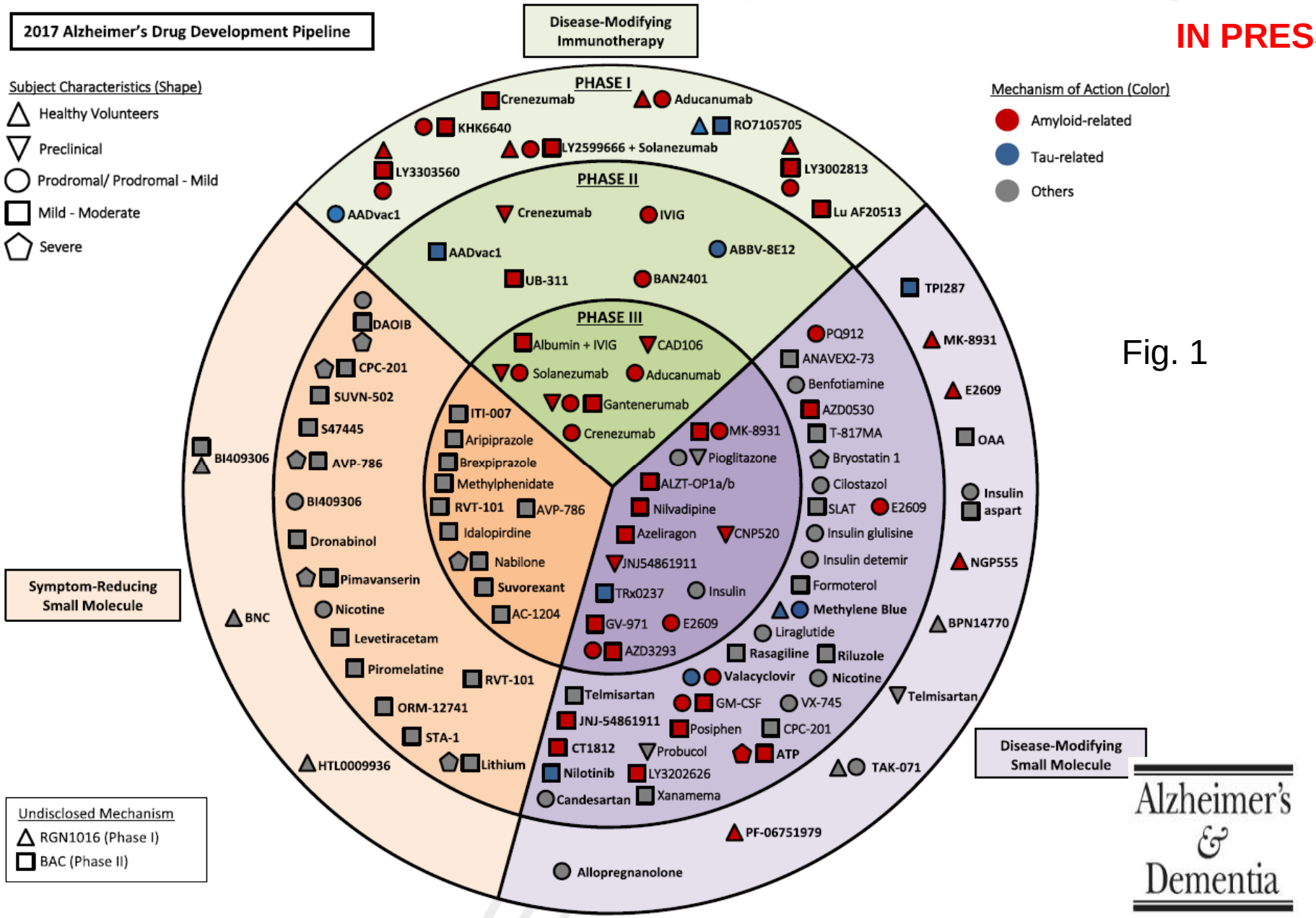

Fig. 1

Alzheimer's & Dementia

Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2017) 1-18

In all, there are 105 agents in the pipeline as shown on clinicaltrials.gov, of which

25 agents in 29 trials in phase I,
52 agents in 68 trials in phase II,
and 28 agents in 42 trials in phase III.

Across all stages, 70% are DMTs, 14% are symptomatic cognitive enhancers, 13% are symptomatic agents addressing neuropsychiatric and behavioral changes, and 2% have undisclosed MOAs.

Fig. 1

Of all trials, 65.5% are sponsored by the biopharma industry,

16.6%by AcademicMedical Centers,

3.6% by Academic Medical Center-NIHcollaborations, and 10.8%by the collaborations between consortiums/philanthropic organizations and one or more of the following: biopharma, NIH, and Academic Medical Centers. One trial is sponsored by NIH, one trial by biopharma-NIH collaboration, and one trial by a biopharma-NIH-Academic Medical Center collaboration.

Of the 24 agents whose MOA was revealed in phase I in 2017,
12 were directed at amyloid-related targets including eight immunotherapies,
three had taurelated MOAs,
and nine had other mechanisms including four symptomatic cognitive enhancers.
Overall, there were 20 DMTs and four symptomatic agents in phase I.
The MOA was not revealed for one agent.
Phase I trials were on average 755 days in duration (recruitment and treatment period) and involved 68 patients in each trial.

Phase II trials advance the agents from phase I to trial populations of patients with AD.
The goal of these trials is to establish preliminary efficacy based on a biomarker outcome, a clinical measure, or a combination of clinical and biomarker outcomes.
Phase IIa trials concentrate on efficacy, and phase IIb trials further refine dosing decisions about the number of doses to be advanced to phase III.
Of the 68 trials in phase II of the AD pipeline, 21 included patients with prodromal or prodromal and mild AD, 26 were trials for mild-moderate AD, one included patients with prodromal or mildmoderate AD, and one trial was for mild-moderate or severe AD.
Of the symptomatic trials, 10 were for mild-moderate AD and six were for mild-moderate or severe AD. On average, phase II trials were 1140 days in duration (recruitment plus exposure period) and involved 151 patients in each trial.

Cummings et al 2017

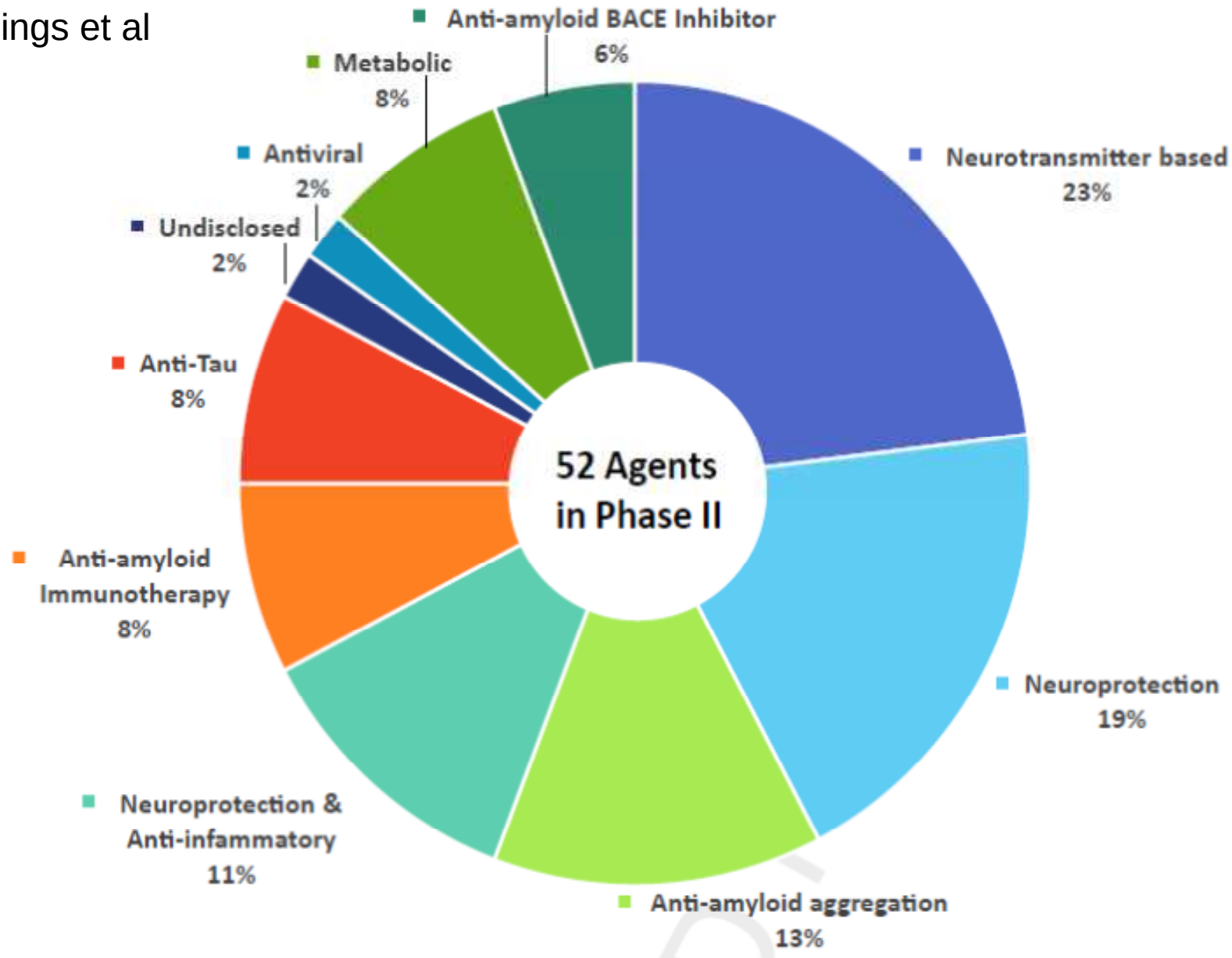

Fig. 2. Mechanisms of action of agents in phase II. Abbreviation: BACE, β-site amyloid precursor protein cleaving enzyme.

Phases II and III trials are often called “learn” and “confirm” trials, respectively, with phase III intended to confirm effects observed in phase II in larger populations treated for longer periods of time. In addition to providing crucial efficacy data, phase III trials also provide exposure data on larger numbers of patient-days essential to establishing the safety and tolerability of the candidate therapy.

Of the 28 agents in the 42 trials, there were 18 DMTs, three cognitive enhancing agents, and seven drugs for behavioral symptoms. Among the DMTs, 15 addressed amyloid targets, one involved a tau-related target, and two had a metabolic MOA. The DMTs include six immunotherapies (all addressing amyloid).

Of the drugs with amyloid targets, there were five BACE inhibitors, six immunotherapies, and four anti-aggregation agents.

Phase III

Phases II and III trials are often called “learn” and “confirm” trials, respectively, with phase III intended to confirm effects observed in phase II in larger populations treated for longer periods of time. In addition to providing crucial efficacy data, phase III trials also provide exposure data on larger numbers of patient-days essential to establishing the safety and tolerability of the candidate therapy.

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Cummings et al 2017

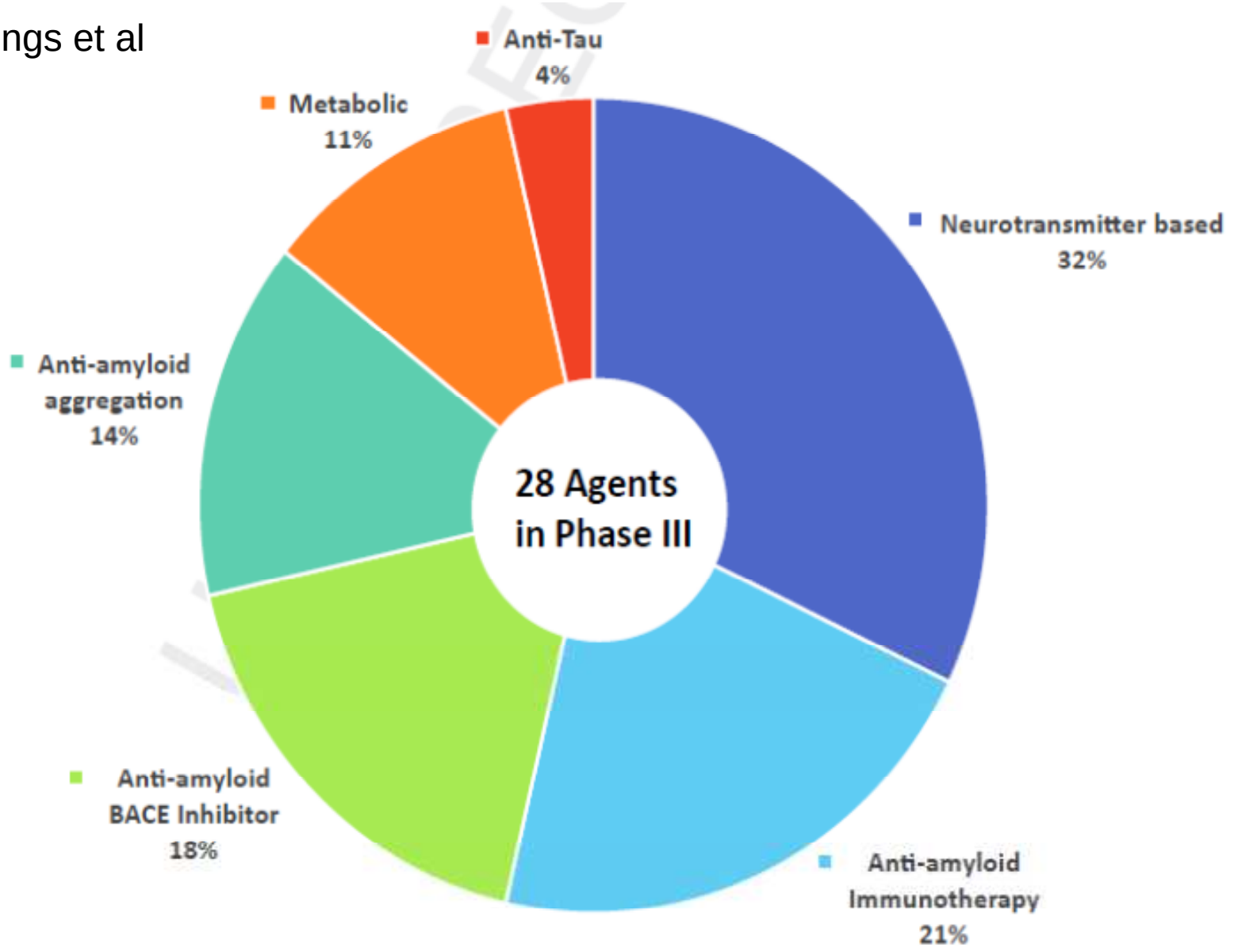
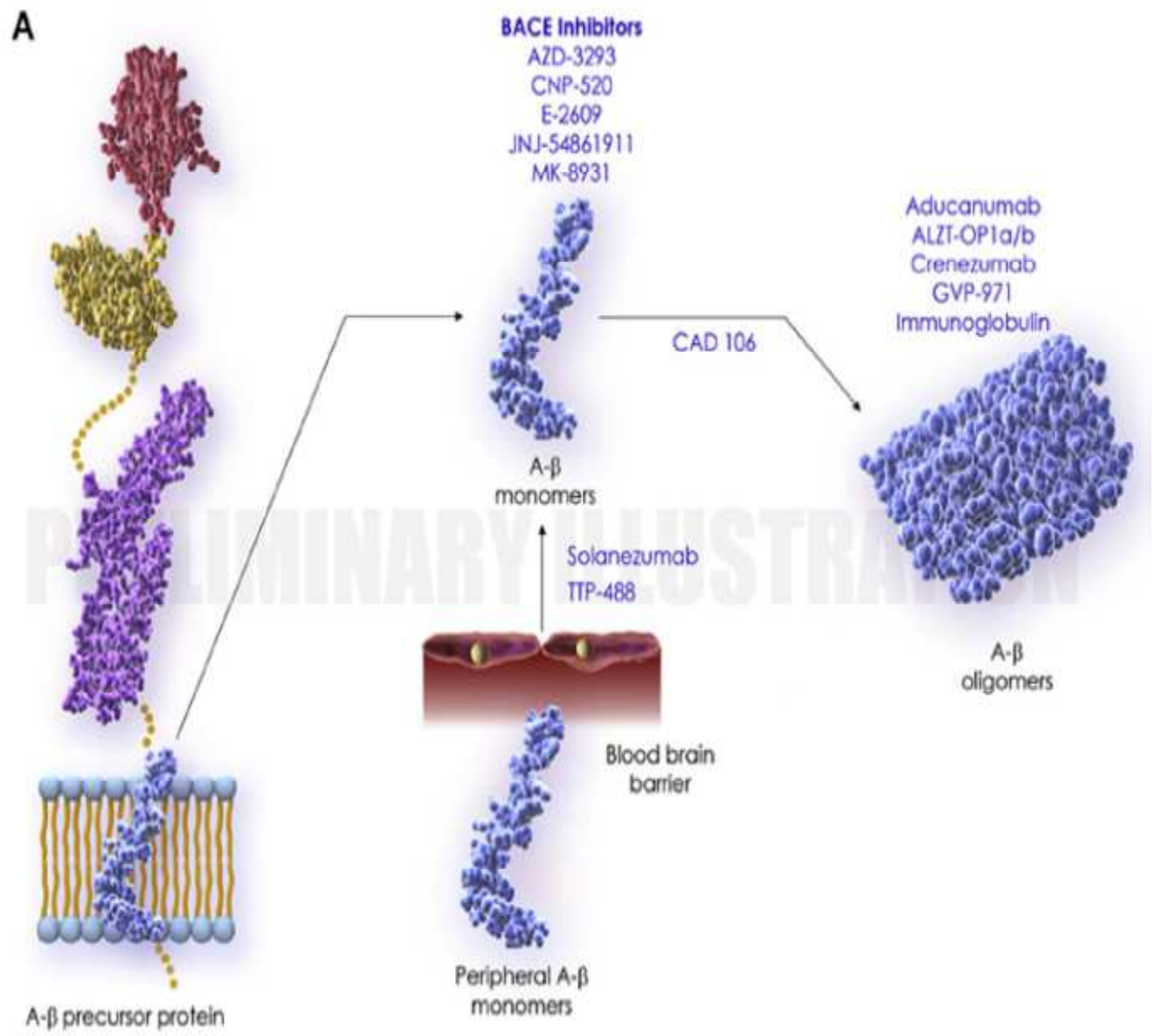


Fig. 3. Mechanisms of action of agents in phase III. Abbreviation: BACE, β-site amyloid precursor protein cleaving enzyme.


A
BACE Inhibitors
AZD-3293
CNP-520
E-2609
JNJ-54861911
MK-8931
Aducanumab
ALZT-OP1a/b
Crenezumab
GVP-971
Immunoglobulin
CAD 106
A-β
monomers
A-β
oligomers
Solanezumab
TTP-488
Blood brain
barrier
Peripheral A-β
monomers
A-β precursor protein

B

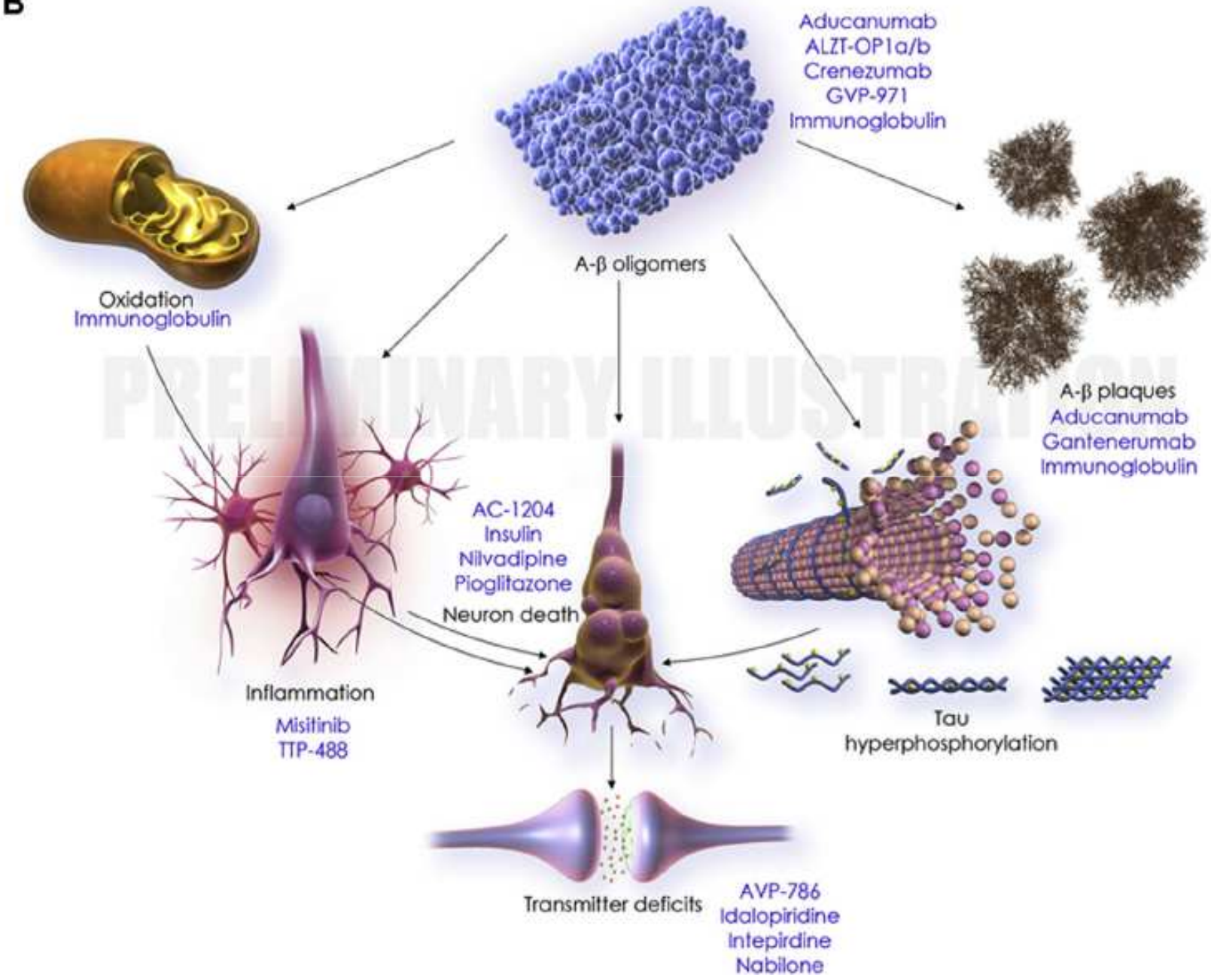

Aducanumab
ALZT-OP1a/b
Crenezumab
GVP-971
Immunoglobulin
A-β oligomers
Oxidation
Immunoglobulin
A-β plaques
Aducanumab
Gantenerumab
Immunoglobulin
AC-1204
Insulin
Nilvadipine
Pioglitazone
Neuron death
Inflammation
Misitinib
TTP-488
Tau
hyperphosphorylation
Transmitter deficits
AVP-786
Idalopiridine
Intepirdine
Nabilone

Table 4
Number of participants needed for AD clinical trials

	Phase I	Phase II	Phase III	Total
Healthy volunteers	864	120	0	984
Preclinical AD	66	323	7850	8239
Prodromal/prodromal-mild AD	597	3877	17,535	22,009
Mild-moderate AD	626	4528	17,099	22,253
Severe AD	0	568	20	588
Total	2153	9416	42,504	54,073

Abbreviation: AD, Alzheimer's disease.

Table 5
Biomarkers as outcome measures in phase II and phase III trials for agents in the Alzheimer's disease drug development pipeline (clinicaltrials.gov; 1/5/2017)

	N of trials (%)	
Biomarker	Phase III	Phase II
CSF amyloid	12 (28.6)	17 (25.0)
CSF tau	13 (31.0)	16 (23.5)
FDG-PET	5 (11.9)	10 (14.7)
vMRI	9 (21.4)	6 (8.8)
Plasma amyloid	4 (9.5)	5 (7.4)
Plasma tau	0	1 (1.5)
Amyloid PET	13 (31.0)	6 (8.8)
Tau PET	1 (2.4)	0

Table 2
Agents currently in phase II of Alzheimer's disease drug development (as of 1/5/2017)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
AADvac1	Anti-tau	Monoclonal antibody	NCT02579252	Recruiting	Axon Neuroscience	Dec-15	Feb-19
ABBV-8E12	Anti-tau	Monoclonal antibody	NCT02880956	Recruiting	AbbVie	Oct-16	Mar-21
ATP	Anti-amyloid	Inhibits amyloid misfolding and toxicity	NCT02279511	Active, not recruiting	Fundació Clínic per la Recerca Biomèdica, Spain	Nov-14	Nov-16
AD-SVF cells	Regenerative	AD-SVF cell infusion	NCT02912169*	Recruiting	Ageless Regenerative Institute	Nov-15	Dec-17
ANAVEX 2-73	Neuroprotective	Sigma-1 receptor agonist	NCT02244541	Active, not recruiting	Anavex Life Sciences	Dec-14	Oct-16
			NCT02756858	Recruiting, extension		Mar-16	Nov-18
Atomoxetine	Anti-amyloid	Adrenergic uptake inhibitor, SNRI	NCT01522404	Active, not recruiting	Emory University, NIA	Mar-12	Dec-17
AVP-786	Neurotransmitter based	Mixed transmitter effect	NCT02534038	Recruiting	Avanir	Oct-15	Mar-18
AZD0530 (saracatinib)	Anti-amyloid	Kinase inhibitor	NCT02167256	Active, not recruiting	Yale University, ATRI, AstraZeneca	Dec-14	Dec-17
BAC	Undisclosed	Undisclosed mechanism	NCT02886494	Not yet recruiting	Charsire Biotechnology	Nov-16	Nov-19
			NCT02467413	Not yet recruiting	Charsire Biotechnology, A2 Healthcare Taiwan Corporation	Mar-16	Dec-17
BAN2401	Anti-amyloid	Monoclonal antibody	NCT01767311	Recruiting	Eisai	Dec-12	Jul-18
Benfotiamine	Metabolic	Antioxidant	NCT02292238	Recruiting	Burke Medical Research Institute, Columbia University, NIA, ADDF	Nov-14	Nov-19
BI409306	Neuroprotective	Phosphodiesterase 9A inhibitor	NCT02240693	Recruiting	Boehringer Ingelheim	Jan-15	Oct-17
			NCT02337907	Recruiting	Boehringer Ingelheim	Jan-15	Oct-17
Bryostatin 1	Neuroprotective	Protein kinase C modulator	NCT02431468	Active, not recruiting	Neurotrope Bioscience	Jul-15	May-17
Candesartan	Neuroprotective, anti-inflammatory	Angiotensin receptor blocker	NCT02646982	Recruiting	Emory University	Jun-16	Sep-21
CB-AC-02 (Placenta derived-MSCs)	Regenerative	Stem cell therapy	NCT02899091*	Not yet recruiting	CHA Biotech Co.	Sep-16	Jun-18
Cilostazol	Neuroprotective	Phosphodiesterase 3 antagonist	NCT02491268	Recruiting	National Cerebral and Cardiovascular Center, Japan	Jul-15	Jul-18
CPC-201	Neuroprotective	Cholinesterase inhibitor + peripheral cholinergic antagonist	NCT02549196	Recruiting	Chase Pharmaceuticals	Oct-15	Dec-16
			NCT02434666	Active, not recruiting, Extension	Chase Pharmaceuticals	Jan-15	Dec-16
			NCT02860065	Not yet recruiting	Chase Pharmaceuticals	Sep-16	Jun-17
Crenezumab	Anti-amyloid	Monoclonal antibody	NCT01998841	Recruiting	Genentech, NIA, Banner Alzheimer's Institute	Dec-13	Sep-20
CT1812	Anti-amyloid	Sigma-2 receptor modulator	NCT02907567*	Recruiting	Cognition Therapeutics	Sep-16	May-17
DAOIB	Neurotransmitter based	NMDA enhancer	NCT02103673	Recruiting	Chang Gung Memorial Hospital, Taiwan	Feb-14	Sep-17
			NCT02239003	Recruiting	Chang Gung Memorial Hospital, Taiwan	Jan-12	Dec-17
Dronabinol	Neurotransmitter based	CB1 and CB2 endocannabinoid receptor partial agonist	NCT02792257	Not yet recruiting	Mclean Hospital, Johns Hopkins University	Aug-16	Dec-20
E2609	Anti-amyloid	BACE inhibitor	NCT02322021	Recruiting	Eisai, Biogen	Nov-14	Jan-18

(*Continued*)

Table 2
Agents currently in phase II of Alzheimer's disease drug development (as of 1/5/2017) (*Continued*)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
Formoterol	Neuroprotective, anti-inflammatory	β-2 adrenergic receptor agonist	NCT02500784	Recruiting	Palo Alto Veterans Institute for Research, Mylan, Alzheimer's Association	Jan-15	Jul-16
hUCB-MSCs	Regenerative	Stem cell therapy	NCT02054208*	Recruiting	Medipost	Feb-14	Feb-18
			NCT01547689*	Active, not recruiting	Affiliated Hospital to Academy of Military Medical Sciences, China	Mar-12	Dec-16
			NCT02513706	Not yet recruiting	South China Research Center	May-16	Oct-19
			NCT02672306*	Not yet recruiting	South China Research Center	May-16	Oct-19
			NCT02833792	Recruiting	Stemedica Cell Technologies	Jun-16	Jun-18
Insulin detemir (intranasal)	Metabolic	Increases insulin signaling in the brain	NCT01595646	Active, not recruiting	Wake Forest School of Medicine, Alzheimer's Association	Nov-11	Mar-17
Insulin glulisine	Metabolic	Increases insulin signaling in the brain	NCT02503501	Recruiting	HealthPartners Institute	Aug-15	Sep-17
JNJ-54861911	Anti-amyloid	BACE inhibitor	NCT02406027	Active, not recruiting, Extension	Janssen	Jul-15	Oct-22
Levetiracetam	Neurotransmitter based	Anticonvulsant	NCT02002819	Recruiting	University of California, San Francisco	Jun-14	Dec-17
Liraglutide	Metabolic	Glucagon-like peptide 1 receptor agonist	NCT01843075	Recruiting	Imperial College London	Jan-14	Mar-19
Lithium	Neurotransmitter based	Ion channel modulator	NCT02129348	Recruiting	New York State Psychiatric Institute, NIA	Jun-14	Apr-19
LY3202626	Anti-amyloid	BACE Inhibitor	NCT02791191	Recruiting	Eli Lilly	Jun-16	Aug-18
Methylene blue	Anti-tau	Tau inhibitor; neuronal stimulant	NCT02380573	Recruiting	Texas Alzheimer's Research and Care Consortium	Jul-15	Jul-18
NewGam 10% IVIG	Anti-amyloid	Polyclonal antibody	NCT01300728	Active, not recruiting	Sutter Health	Jan-11	Nov-17
Nicotine	Neurotransmitter based	Nicotinic acetylcholine receptor agonist	NCT02720445	Not yet recruiting	University of Southern California, NIA, ATRI, Vanderbilt University	Dec-16	Dec-19
Nilotinib	Anti-tau	Tyrosine kinase inhibitor	NCT02947893	Not yet recruiting	Georgetown University	Nov-16	Mar-18
ORM-12741	Neurotransmitter based	Alpha-2c adrenergic receptor antagonist	NCT02471196	Recruiting	Orion Corporation, Janssen	Jun-15	Jul-17
Pimavanserin	Neurotransmitter based	5-HT2A inverse agonist	NCT02035553	Active, not recruiting	Acadia	Nov-13	Nov-16
			NCT02992132	Recruiting	Acadia	Nov-16	Jun-19
Piromelatine	Neurotransmitter based	Melatonin receptor agonist; 5-HT 1A and 1D receptor agonist	NCT02615002	Recruiting	Neurim Pharmaceuticals	Nov-15	Mar-18
Posiphen	Anti-amyloid	Selective inhibitor of APP production	NCT02925650*	Not yet recruiting	QR Pharma, ADCS	Dec-16	Dec-18
PQ912	Anti-amyloid, anti-inflammatory	Glutaminyl-peptide cyclotransferase inhibitor	NCT02389413	Recruiting	Probiodrug AG, Julius Clinical, VU University Medical Center, Amsterdam	Mar-15	Mar-17

Table 2
Agents currently in phase II of Alzheimer's disease drug development (as of 1/5/2017) (*Continued*)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
Probucol	Neuroprotective, anti-inflammatory	Anti-hyperlipidemic	NCT02707458*	Not yet recruiting	Douglas Mental Health University Institute, Weston Brain Institute, McGill University	Apr-16	May-18
Rasagiline	Neuroprotective	Monoamine oxidase B inhibitor	NCT02359552	Recruiting	The Cleveland Clinic	Feb-15	May-17
Riluzole	Neuroprotective	Glutamate receptor antagonist; glutamate release inhibitor	NCT01703117	Recruiting	Rockefeller University	Apr-13	Nov-18
RVT-101	Neurotransmitter based	5-HT6 antagonist	NCT02910102	Recruiting	Axovant Sciences	Oct-16	Sep-17
S47445	Neurotransmitter based	AMPA receptor agonist; nerve growth factor stimulant	NCT02626572	Active, not recruiting	Servier	Feb-15	Dec-17
Sargramostim (GM-CSF)	Anti-amyloid	Granulocyte colony stimulator; amyloid removal	NCT01409915	Recruiting	University of Colorado, Denver, The Dana Foundation	Mar-11	Jan-17
			NCT02667496	Recruiting	Sanofi, NIA	Nov-16	Apr-18
Simvastatin + L-Arginine + Tetrahydrobiopterin (SLAT)	Neuroprotective	HMG-CoA reductase inhibitor and antioxidant	NCT01439555	Recruiting	University of Massachusetts, Worcester	Nov-11	Dec-16
STA-1	Neuroprotective, anti-inflammatory	Antioxidant properties of echinascoside	NCT01255046	Not yet recruiting	Sinphar Pharmaceuticals	Dec-15	Dec-18
SUVN-502	Neurotransmitter based	5-HT6 antagonist	NCT02580305	Recruiting	Suven Life Sciences	Sep-15	Jun-17
T-817 MA	Neuroprotective	Neurotrophic agent	NCT02079909	Active, not recruiting	Toyama Chemical, ADCS	Mar-14	Mar-17
Telmisartan	Neuroprotective, anti-inflammatory	Angiotensin II receptor blocker, PPAR-gamma agonist	NCT02085265	Recruiting	Sunnybrook Health Sciences Centre, ADDF	Mar-14	Aug-18
UB-311	Anti-amyloid	Monoclonal antibody	NCT02551809	Recruiting	United Neuroscience	Oct-15	Dec-17
Valacyclovir	Anti-amyloid, Anti-tau	Antiviral agent	NCT02997982	Recruiting	Umea University	Dec-16	Dec-17
VX-745	Neuroprotective, anti-inflammatory	P38 mitogen-activated protein kinase inhibitor	NCT02423200	Active, not recruiting	EIP Pharma	Apr-15	Nov-16
			NCT02423122	Active, not recruiting	EIP Pharma	Apr-15	Sep-16
Xanamema	Neuroprotective	Blocks 11-HSD1 enzyme activity, decreasing cortisol in brain	NCT02727699	Not yet recruiting	Actinogen Medical, ICON Clinical Research	Jun-16	Aug-18

Table 6
BACE inhibitors in clinical trials for AD

BACE inhibitors currently in phase II or III of development					
Agent (sponsor)	Clinicaltrials.gov identifier (trial name)	Phase	Population	Start date	Estimated end date
CNP520 (Novartis)	NCT02565511 (GENERATION)	II/III	Asymptomatic (homozygote APOE4)	11/2015	08/2023
E2609 (Eisai)	NCT02322021	II	MCI to moderate AD	11/2014	01/2018
	NCT02956486 (MISSION-AD1)	III	MCI to mild AD	10/2016	06/2020
JNJ54861911 (Janssen)	NCT02406027	II	MCI to mild AD	07/2015	10/2022
	NCT02569398	II/III	Preclinical (amyloid positive)	11/2015	05/2023
LY3202626 (Lilly)	NCT02791191 (NAVIGATE-AD)	II	Mild AD	06/2016	08/2018
LY3314814 (Lilly)	NCT02245737 (AMARANTH)	II/III	MCI to mild AD	9/2014	8/2019
	NCT02783573 (DAYBREAK ALZ)	III	Mild AD	7/2016	08/2021
Verubecestat (Merck)	NCT01739348 (EPOCH)	II/III	Mild to moderate AD	11/2012	06/2017

Abbreviations: AD, Alzheimer's disease; BACE, β-site amyloid precursor protein cleaving enzyme; MCI, mild cognitive impairment.

Table 7
Immunotherapies in clinical trials for AD (clinicaltrials.gov accessed 1/5/2017)

Agent	Sponsor	Target	Trial phase	Population
AADvac1	Axon Neuroscience	Anti-tau mAb	1	AD
AADvac1	Axon Neuroscience	Anti-tau mAb	2	Mild-moderate AD
ABBV-8E12	AbbVie	Anti-tau mAb	2	Early AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Healthy volunteers
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Prodromal-mild AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Mild-moderate AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	3	Early AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	3	Early AD
Albumin and immunoglobulin	Grifols	Polyclonal antibody targeting multiple forms of Aβ	3	Mild-moderate AD
BAN2401	Eisai	mAb targeting N terminal protofibrils	2	Early AD
CAD106	Novartis, NIA	$Aβ_{1–6}$, active vaccine	2	AD, at risk
Crenezumab	Genentech	mAb targeting soluble oligomer and fibrillar Aβ	1	Mild-moderate AD
Crenezumab	Genentech, NIA, Academic	mAb targeting soluble oligomer and fibrillar Aβ	2	ADAD
Crenezumab	Genentech	mAb targeting soluble oligomer and fibrillar Aβ	3	Prodromal-mild AD
Gantenerumab	Roche	mAb targeting aggregated Aβ	3	Mild AD
Gantenerumab	Roche	mAb targeting aggregated Aβ	3	Prodromal AD
Gantenerumab	Roche, Lilly, Alzheimer's Association	mAb targeting aggregated Aβ	2/3	AD, at risk
Solanezumab	Lilly, Roche, Alzheimer's Association	mAb targeting monomeric Aβ	2/3	AD, at risk
KH6640	Kyowa Hakko Kirin	mAb targeting aggregated Aβ	1	AD
Lu AF20513	Lundbeck		1	Mild AD
NewGam 10% IVIG	Sutter Health	Polyclonal antibody targeting multiple forms of Aβ	2	Amnestic MCI
LY2599666 & solanezumab	Lilly	Combination of BACE inhibitor and MAb targeting monomeric Aβ	1	MCI due to AD
LY3303560	Lilly		1	MCI due to AD-mild AD
LY30032813	Lilly		1	MCI due to AD
LY30032813	Lilly		1	Mild-moderate AD
RO7105705	Genentech	Anti-tau mAb	1	Mild-moderate AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Prodromal AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Preclinical AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Mild AD
UB-311	United Neuroscience	mAb targeting N terminal $Aβ_{1–14}$	2	Mild AD

Abbreviations: AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer's disease; mAb, monoclonal antibody; MCI, mild cognitive impairment; IVIG, intravenous immunoglobulin; NIA, National Institute on Aging.

Cummings et al. Alzheimer's Research & Therapy (2016) 8:39
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Alzheimer's
Research & Therapy

REVIEW Open Access

Drug development in Alzheimer's disease: the path to 2025

Jeffrey Cummings[1*], Paul S. Aisen[2], Bruno DuBois[3], Lutz Frölich[4], Clifford R. Jack Jr[5], Roy W. Jones[6], John C. Morris[7], Joel Raskin[9], Sherie A. Dowsett[8] and Philip Scheltens[10]

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ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2017) 1-18

Alzheimer's & Dementia

Review Article

Alzheimer's disease drug development pipeline: 2017

Jeffrey Cummings[a,*], Garam Lee[a], Travis Mortsdorf[b], Aaron Ritter[a], Kate Zhong[c]

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2. Interpretation: Our data show that there are 105 drugs in development for treatment of AD. There are more drugs in phase II (52) than in phase III (28) or phase I (25). The small number of phase I compounds suggests that there is insufficient drug discovery activity to supply new agents for testing in clinical trials.

President Obama articulated a goal of cure or meaningful treatment for AD by the year 2025 [5,29]. A recent analysis of AD drug development showed that it takes on average 13 years for a candidate treatment to move from laboratory to FDA review and 10 years for an agent to navigate the clinical development period from start of phase I to end of FDA review [30]. This means that under current circumstances, an agent must now be in phase II to possibly be approved by 2025 [5]. Although there are promising agents in the pipeline that could achieve this goal, it is clear that given the high rate of failure of AD drug development [31], the aim of having a repertoire of agents that could respond comprehensively and individually to a patient's clinical circumstances within the 2025 timeframe is in jeopardy.

SOMMARIO

- Il punto
- **Aspetti etici e conclusioni**

OPINION

Preclinical Alzheimer disease—the challenges ahead

Reisa A. Sperling, Jason Karlawish and Keith A. Johnson

Abstract | There is growing recognition that the pathophysiological process of Alzheimer disease (AD) begins many years prior to clinically obvious symptoms, and the concept of a presymptomatic or preclinical stage of AD is becoming more widely accepted. Advances in biomarker studies have enabled detection of AD pathology *in vivo* in clinically normal older individuals. The predictive value of these biomarkers at the individual patient level, however, remains to be elucidated. The ultimate goal of identifying individuals in the preclinical stages of AD is to facilitate early intervention to delay and perhaps even prevent emergence of the clinical syndrome. A number of challenges remain to be overcome before this concept can be validated and translated into clinical practice.

Sperling, R. A. *et al. Nat. Rev. Neurol.* **9**, 54–58 (2013); published online 27 November 2012; doi:10.1038/nrneurol.2012.241

- Ethical and practical concerns about disclosure of biomarker status in asymptomatic or very early symptomatic individuals need to be addressed. Solutions may vary by country. For example, in Australia, the current policy is nondisclosure of amyloid PET status, but as more is learned about the meaning of a positive amyloid scan, individuals may wish to be informed of their test results.

Alzheimer's Prevention Initiative: A Plan to Accelerate the Evaluation of Presymptomatic Treatments; Eric M. Reiman, MD, JessicaB.S. Langbaum, PhD, Adam S. Fleisher, MD,Richard J. Caselli, MD, Kewei Chen, PhD, Napatkamon Ayutyanont, PhD, Yakeel T.Quiroz, MA, Kenneth S. Kosik, MD, Francisco Lopera, MD, and **Pierre N. Tariot, MD**

Lancet Neurol 2013; 12: 207–16

Personal View

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

1) **Amyloid deposition**

2) **Neurodegeneration - synaptic dysfunction**

3) **Neuronal loss – brain atrophy**

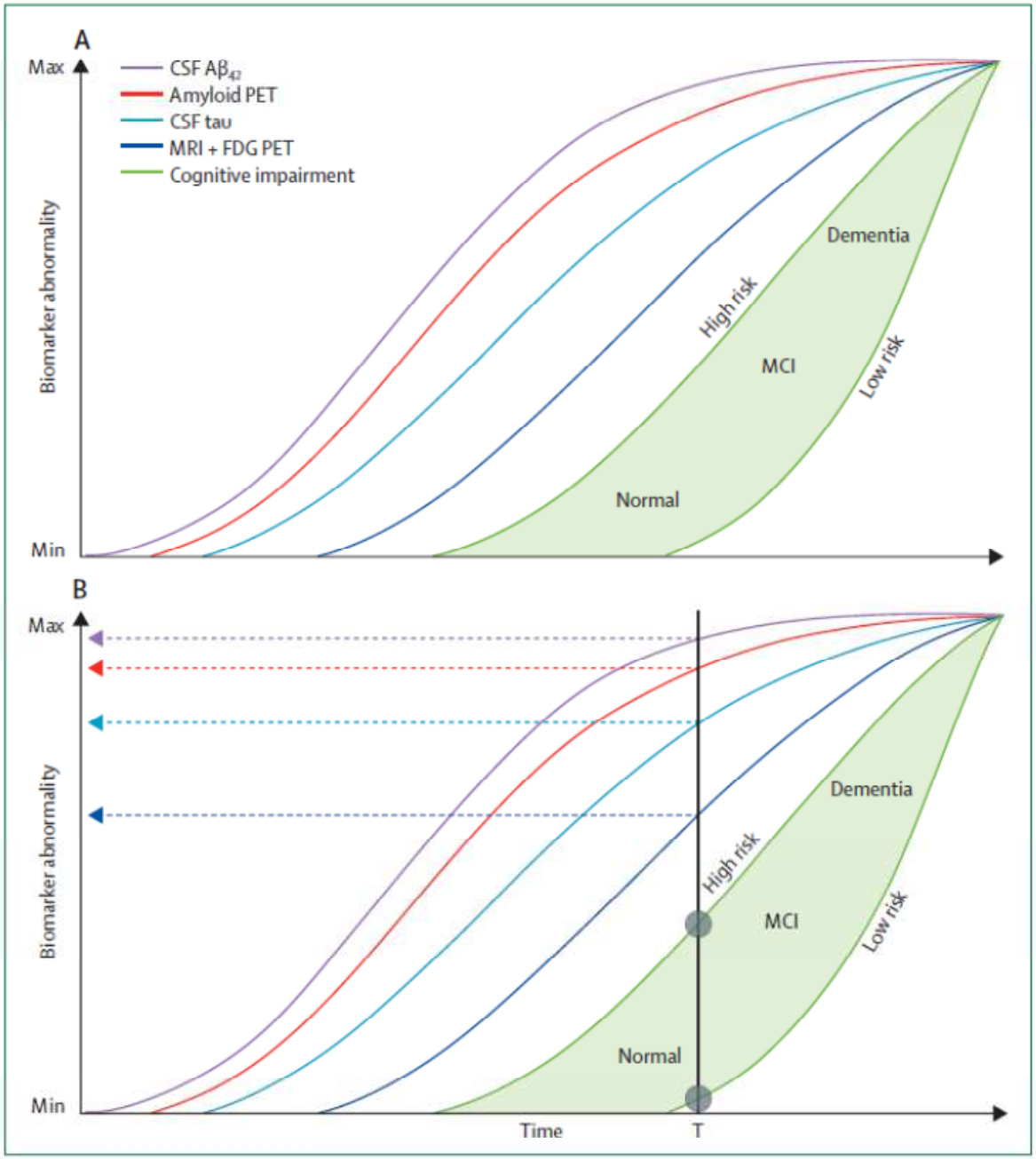

Figure 5: Revised model of dynamic biomarkers of the Alzheimer's disease pathological cascade

Lancet Neurol 2013; 12: 207–16

Lancet Neurol 2013; 12: 207–16

Personal View

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Not all patients with MCI have AD pathology and progress to dementia.

MCI negative to amyloidosis and/or neurodegeneration should not progress to dementia.

Not all patients with AD pathology progress to dementia. → **[aspetti etici]**

Uncertain progress on the fuzzy boundaries od AD

Whitehouse P.J., George D.R.

JAD, 2011;26:1-5

“The myth of Alzheimer’s”

What you aren’t being told about today’s most dreaded diagnosis (2008)

“Proprio mentre le parti superstiti del suo io diventavano sempre più piccole e frammentarie, io mi ostinavo a vederlo nella sua interezza. Continuavo ad amare, in maniera specifica e personale, l’uomo che sbadigliava in quel letto”

J. Franzen: Il Cervello di mio padre. In: Come stare soli. Einaudi, 2011.