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Review

New Horizons in Alzheimer Research from Amyloid and Beyond

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Abstract

The Amyloid and Tau Hypothesis of Alzheimer's disease once thought to be the key have shown marginal results but are bolstered by the recent revival of the Aducanumab study and some positive data on some anti-Tau drugs. It still behoves us to look at other mechanisms which include whole blood transfusions, an Epigenetic approach, a-derivative of a Parkinson's drug a low dose of an anti-epileptic drug, an antibiotic against P Gingivitis and many new approaches not directly involving Amyloid and Tau. Other newer approaches were also presented at CTAD 2019.

Keywords

Alzheimer's; Alzheimer therapeutics amyloid; Tau; an epigenetic approach gingivitis antiepileptics; blood transfusions

1. Introduction

Alzheimer's disease (AD) has long been a challenging and confounding disease to treat with pharmaceutical approaches. Based on decades of research, there have been two well described biological correlates of Alzheimer's disease: the buildup of abnormal amyloid-beta protein aggregates in the brain and the development of hyperphosphorylated tau protein tangles. Amyloid-beta plaques had been the focus of much of the research on AD most recently.

The process by which amyloid-beta plaques develop has been well characterized as a two steps process. First, the amyloid precursor protein (APP) is cleaved by the beta-site amyloid precursor protein-cleaving enzyme (BACE1/β-secretase) producing the C99 protein fragment. C99 is then cleaved by γ-secretase, producing amyloid-beta oligomers which clump together to form amyloid plaques. These plaques are thought to interfere with synaptic signaling, causing AD [1].

With this process in mind, investigational products have been designed to target the development of these beta-amyloid plaques (See Table 1). The two most popular strategies to this end have been to interfere with the production of the amyloid oligomers by inhibiting one of the enzymes involved in their production, or to directly target the amyloid plaques, frequently using an antibody approach. Unfortunately, both these strategies, while frequently appearing promising in early trials, ultimately did not show efficacy and were not approved. There are several different types of products that have been created in the last several years in which the pharmaceutical companies have attempted to get to market. This article will present multiple strategies of these companies and some current ongoing studies.

Table 1 Key AD agents in development (amyloid-directed).

Compound	Company	MOA	Phase
Solanezumab (LY2062430)	Lilly	Passive Immunotherapy	3
Gantenerumab (RG1450)	Roche	Passive Immunotherapy	3
BAN2401	Eisai / Biogen	Passive Immunotherapy	3
Crenezumab (MABT5102A)	Roche(Genentech)	Passive Immunotherapy	3
ACI-24	AC Immue	Active Immunotherapy	2a
Dnanemab (LY3002813)	Lilly	Passive Immunotherapy (N3pG-Aβ)	2
Brain Shuttle Gantenerumab	Roche	Passive Immunotherapy	1
KHK-6640	Kyowa Hakko Kirin	Passive Immunotherapy	1

2. BACE1 Inhibitors

Several drugs had been in production that targeted the BACE1 enzyme. The BACE1 enzyme is found only in Alzheimer's patients and cleaves APP to form the C99 fragment. These drugs included MK-8931 (Merck), AZD3293 (AstraZeneca/Lilly), E2609 (Eisai/Biogen) and JNJ 5486911 (Janssen) (See Table 2). Phase 2 or 3 trials for all these drugs were all eventually discontinued either due to lack of efficacy or unfavorable risk/benefit profile.

Table 2 Key AD agents in development (Tau-directed II).

Compound	Company	MOA	Phase
E2814	Eisai	Anti-Tau MAb	1 (Healthy & Prodromal to Moderate AD)
TPI-287 (ARC-100)	Cortice	Microtubule Stabilizer	1 (PSP) & 1 (M2M AD)
BIIB080 (Ionis-MAPTRx)	Biogen/Ionis	Antisense Oligonucleotide (tagents Tau expression)	1 (Mild AD)
BIIB076 (NI-105)	Biogen/Neurimmune	Anti-Tau MAb	1 (Mild AD)
UCB0107	UCB	Anti-Tau MAb	1 (Healthy)
Lilly OGA Inhibitor	Lilly	O-GlcNAcase Inhibitor	1
ACI-3024	Lilly / AC Immune	Tau Morphomer (small molecule Tau aggregation inhibitor)	1 (Healthy)
AADvac2	AXON Neuroscience	Anti-Tau MAb	Preclinical
ST-501	Sangamo Therapeutics	Tau-Directed Zinc Finger Nuclease Transcription Factor	Preclinical
Ta-1505	Merck	Anti-Tau MAb (pSer413)	Preclinical

3. Monoclonal Antibodies

Another strategy for targeting beta-amyloid plaques is to target those proteins that have already begun to build up using monoclonal antibodies which will bind directly to the amyloid proteins. Several companies have come out an anti-beta-amyloid antibody that had been in phase 2 and 3 trials. These biologics include: bapineuzumab (Pfizer/Janssen), gantenerumab (Roche), crenezumab (Roche/Genentech), Solemunazemab (Lilly), and all of which failed to show efficacy in phase 3 trials for treating patients who were already experiencing cognitive decline. Still, some of these drugs are being investigated for efficacy in preventing AD in subjects who do not yet have symptoms of AD. One drug of particular interest is BAN2401, a monoclonal anti-Aβ antibody which is currently in a phase 3 trial examining patients with early symptomatic AD [2].

Recently, aducanumab, a monoclonal antibody from Biogen, which had formerly been declared a failure in phase 3 has gained new interest after new analysis was performed on a larger dataset, and Biogen chose to go forward with a regulatory filing of the drug. Biogen claims this reanalysis suggests that aducanumab was successful in combating cognitive decline associated with AD and serves as evidence in support of anti-Aβ antibody approaches [2]. Details regarding the content of this reanalysis are scheduled to be released in December 2019.

4. Aβ Targeting Prevention Studies

While many products targeting the amyloid pathway have had limited success in reversing or stopping the progression of AD, there has been recent interest in investigating some of these treatments for the prevention of AD in patients not currently affected by the characteristic

symptoms of AD. Both BAN2401 and Eisai E2609 (elenbecestat), previously mentioned in this article, have been selected for studies by the Alzheimer's Clinical Trials Consortium for preventing the development of AD. These trials will investigate both the effectiveness of the BACE1 inhibitor elenecestat alone, and the effectiveness of elenecestat followed by the anti-Aβ antibody BAN2401 in preventing the onset of AD (See Table 1). These trials are scheduled to begin in 2020.

Additionally, two additional studies launched by the Alzheimer's Prevention Initiative in partnership with pharmaceutical companies and research institutions focus on Alzheimer's prevention in populations without AD, but who possess genetic predisposition for the disease. The API Autosomal Dominant Alzheimer's Disease (ADAD) Colombia Trial investigates the use of Crunazemab for the prevention of AD in a Colombian population that suffers from dominant, genetically heritable mutation that causes early onset Alzheimer's. The API Generation Program aims to investigate the use of CAD106, an active amyloid-targeting vaccine by Novartis and CNP520, a BACE1 inhibitor by Novartis/Amgen, in preventing the development of AD in healthy populations genetically predisposed to AD.

5. Non-Aβ Approaches

Considering recent failures in amyloid-targeting approach to Alzheimer's treatment, approaches that seek to treat Alzheimer's disease through alternative pathways are increasingly attractive. Below are several drugs which are currently being evaluated for effectiveness against Alzheimer's disease, and do not target amyloid beta.

5.1 GV-971 (Green Valley Pharmaceutical)

In late 2018, Green Valley Pharmaceutical released positive results of the carbohydrate-based drug, GV-971 in a phase 3 trial [3]. Participants receiving the drug showed statistically significant improvement in cognition (tested by the ADAS-Cog 12 test) over participants receiving placebo. While GV-971 does aim at Aβ accumulation, it also effects other targets thought to be involved in the development of AD including neuroinflammation and gut microbiome dysbiosis. Efficacy in this phase 3 serves as evidence for the validity of such a multitarget approach [3]. This has also just been recently approved conditionally in China for the treatment of AD.

5.2 AADvac1 (Axon)

AADvac1 is a vaccine that aims to stimulate the immune system to target misfolded Tau protein tangles associated with AD [4]. A recent phase 2 study shows encouraging results, indicating a good safety profile and evidence of impact on multiple AD biomarkers including a significant impact on blood Neurofilament Light Chain (NfL) levels, a biomarker indicative of neuronal loss (See Table 3). On November 24th of 2019, Axon released positive phase 2 results, suggesting that the vaccine causes a decrease in neurodegeneration, improved cognitive endpoints, and produced favorable changes in several other biomarkers associated with the disease [5].

Table 3 Key AD gents in development (Tau directed I).

Compound	Company	MOA	Phase
LMTX	TauRx	Tau Aggregation Inhibitor	3
AADvac1	AXON Neuroscience	Active (Tau) Immunotherapy	2 (Mild AD)
Cosuranemab (BIIB092)	Biogen	Anti-Tau MAb	2 (Early AD)
ABBV-8E12	Abbvie / C2N	Anti-Tau MAb	2 (Early AD)
RO7105705	Genentech / AC Immune	"Effectorless" Anti-Tau MAb	2 (pAD to Moderate AD)
Zagotenemab (LY3303566)	Lilly	Anti-Tau MAb	2 (Early Symptomatic AD)

5.3 ABBV-8E12 (Abbvie)

ABBV-8E12 targets tau protein tangles with a humanized anti-tau antibody (West et al., n.d.). This treatment failed futility analysis in phase 2 for progressive supranuclear palsy but is still in an ongoing phase 2 trial for Alzheimer's disease (See Table 3) [6].

5.4 Oyz-2001 (Oryzon)

Oryzon takes an epigenetics approach, using a dual inhibitor of the LSD1 histone demethylase, the most common histone demethylase in the prefrontal cortex and MAO-B [7]. Studies have implicated this drug to the treatment of multiple Central Nervous System (CNS) disorders including ADHD, borderline personality disorder and Alzheimer's disease (See Table 4). Importantly, there is substantial data suggesting OYZ-2001 can ameliorate aggression and other personality changes associated with AD and other CNS diseases [7].

Table 4 Key AD agents in development (symptomatic).

Compound	Company	MOA	Phase
Suvn-502	SUVWN	5-HT6 Antagonist	2a
Brexpiprazoile (OPC-34712)*	Lundbeck/Otsuka	D2 Dopamine Partial Agonist	3
AVP-786*	Avanir/ Otsuka	Dextromethorphan / Quinidine	3
ORY-2001	Oryzon Genomics	LSD1 / MAO-B Inhibitor	2
AXS-05*	Axsome Therapeutics	Bupropion / Dextromethorphan	2 / 3
Primavanserin**	Acadia	5-HT2A Inverse Agonist	3

* In development for treatment of agitation symptoms of AD.

** In development for treatment of dementia-related psychosis.

5.5 COR388 (Cortexyme)

It is known that there is an association between gum disease bacteria and dementia. The bacteria P. gingivalis, associated with chronic periodontitis, has been found in brains of patients with AD. This bacterium secretes toxic proteases known as gingipains which are thought to have detrimental interactions with tau proteins [8]. COR388 is a bacterial virulence factor inhibitor which targets P. gingivalis. Pre-clinical studies have shown that chronic exposure of P. gingivalis can induce AD-like pathology in animal models, and these pathologies can be prevented by treatment with COR388. COR388 is currently being tested in a phase 2/3 study [8].

5.6 Troriluzole (Biohaven)

Overactive glutamate activity can cause excitotoxicity and neuronal death and is thought to be a factor in AD development [9]. Troriluzole is shown to reduce synaptic levels of glutamate by upregulating glutamate transporters in glial cells. Troriluzole has been well tolerated in phase 1 trials and is currently being studied in phase 2/3 trials [10].

5.7 AGB101 (Agenebio)

Patients with AD are known to present with higher rates of subclinical seizures, and it is thought that these seizures may play a role in AD pathology in patients with mild cognitive impairment [11]. With regards to this thought process, AGB101 is being investigated. It is a low dose formulation of the atypical anticonvulsant levetiracetam being researched as a treatment for mild cognitive impairment associated with early stage AD. In phase 2 trials, low dose levetiracetam has been shown to improve memory performance by reducing hippocampal overactivity [12].

5.8 Best Time to Treat

Prevention studies have been a struggle for many pharmaceutical companies to jump start as funding for these studies is low, but the need is quite high. If a patient could be treated with any of the above medications earlier on using the APOE biomarkers within trials prior to PET scans, this would be extremely beneficial. The prior knowledge of the participants would be identified as amyloid positive earlier and progression of the disease could be slowed quicker. This could allow the patients to be treated faster and could potentially help at risk patients with familial history.

According to many of the pharmaceutical companies across the global, the best time of day to treat is often left up to the principal investigators who are tracking the symptoms, adverse reactions to the possible medications, and the medical history is the participants who are completing these trials. However, most medication trials mentioned above are day medications according to the mechanism of actions.

5.9 Reasons for Failures

There have been many treatments in the past that have gotten into Phase 2 or Phase 3 studies but then have not derived the data that the pharmaceutical companies are seeking to show efficacy. Many endpoints were not met overall with “lackluster data” which then other companies seem to change their methods after. This is because a “futility analysis” was been seen within the

data showing the drugs to be improbable to slow cognitive deterioration. Merck's BACE1 study had this happen after reaching Phase 3 in their prodromal trial [13]. Once this failed, Amgen and Novartis changed their BACE trial strategies, yet Lilly reclaimed a BACE investigational product after purchasing assets from AstraZeneca [14].

6. Conclusion

Although Amyloid theories act as a cause but not marker of Alzheimer Disease is waning, it seems likely the Biogen will move forward with a submission to FDA and Eisai continues to pursue its BAN2401 monoclonal antibody. Tau is still a viable target and encouraging results were presented recently by Axon with their Anti-Tau Ag. Despite this, we must move forward with newer Non-Amyloid approaches of which several good examples were presented above (also see Figure 1). Although still early these newer approaches preliminary have shown very encouraging preliminary results.

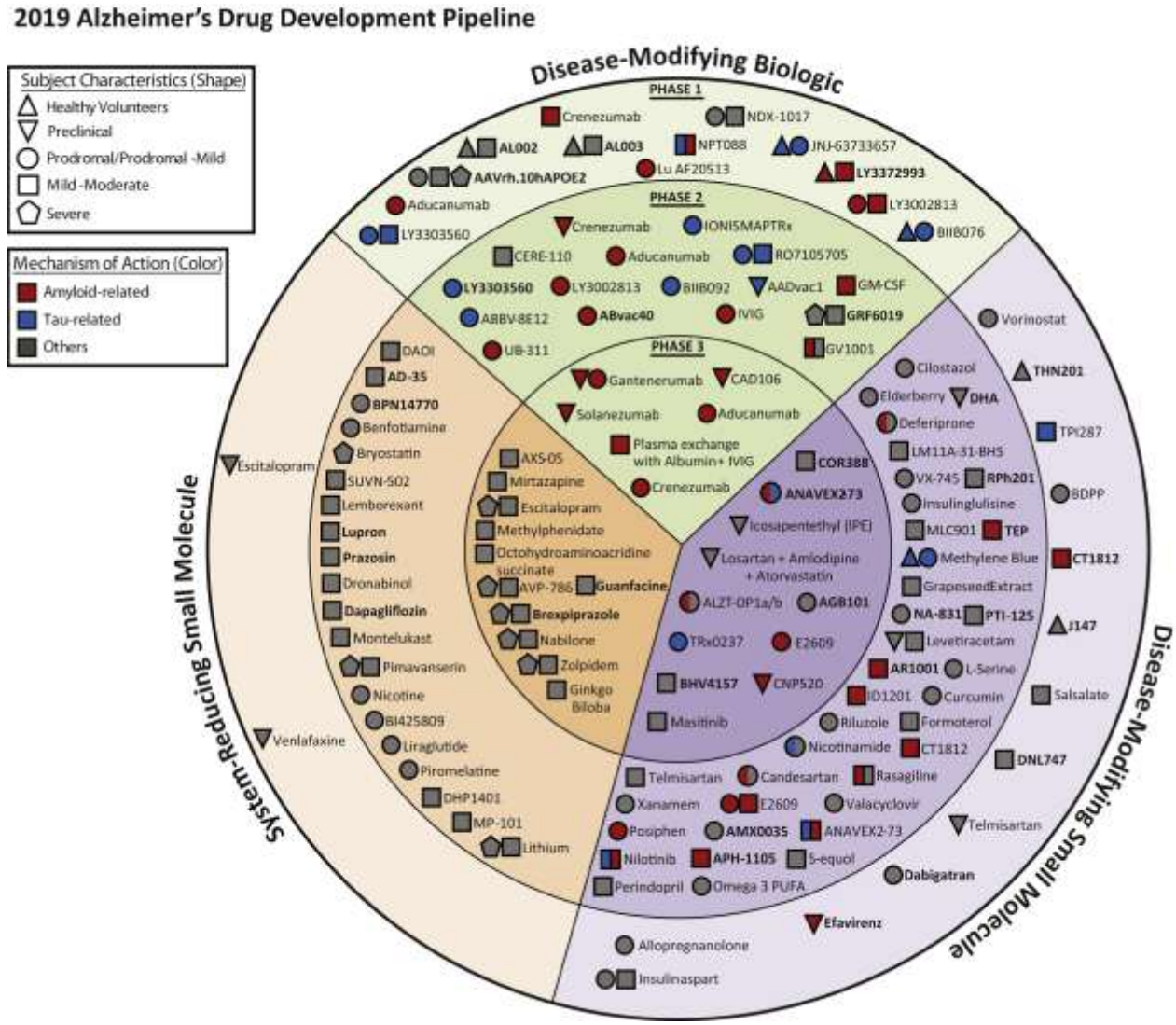

Figure 1 AD drug development pipeline [15].

Author Contributions

Dr Jeffrey T. Apter is the Founder and President of Global Medical Institutes and is the Lead Principal Investigator for Princeton Medical Institute. He has been a research collaborator in the Departments of Psychology and Molecular Biology at various educational institutions around the world. Dr. Apter has published over 30 articles in the areas of psychiatric and Alzheimer's research in conjunction with Princeton University. Dr. Apter is a founding member of the New Jersey Alzheimer Association Scientific Advisory Board and is nationally known as a thought leader in Alzheimer's Research. He is also a founding member of the American Association of Geriatric Psycho-endocrinology and the International Society of CNS Clinical Trials and Methodology (ISCTM).

Kaylee White, MA has worked within the field of psychology on many levels for the last 8 years. She has been currently been working with Dr. Apter for about 3 ½ years in pharmaceutical clinical research and has been the primary psychometrician/rater at corporate site in Princeton, NJ. She is currently seeking a Ph.D. at The Chicago School of Professional Psychology with a dissertation topic focused on caregiver burden of Alzheimer's patients and the difference related to culture between the United States and Argentina.

Competing Interests

The authors have declared that no competing interests exist.

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