

THERAPEUTIC VACCINES FOR ALZHEIMER'S

Are We Close Enough?



Thematic Report By

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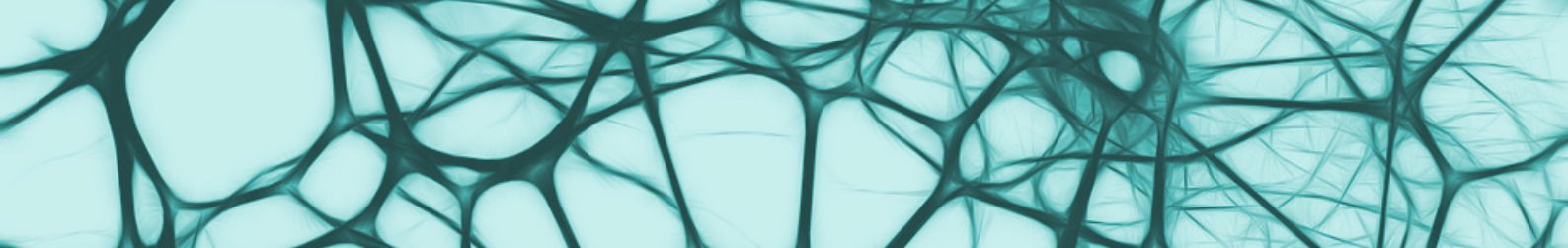
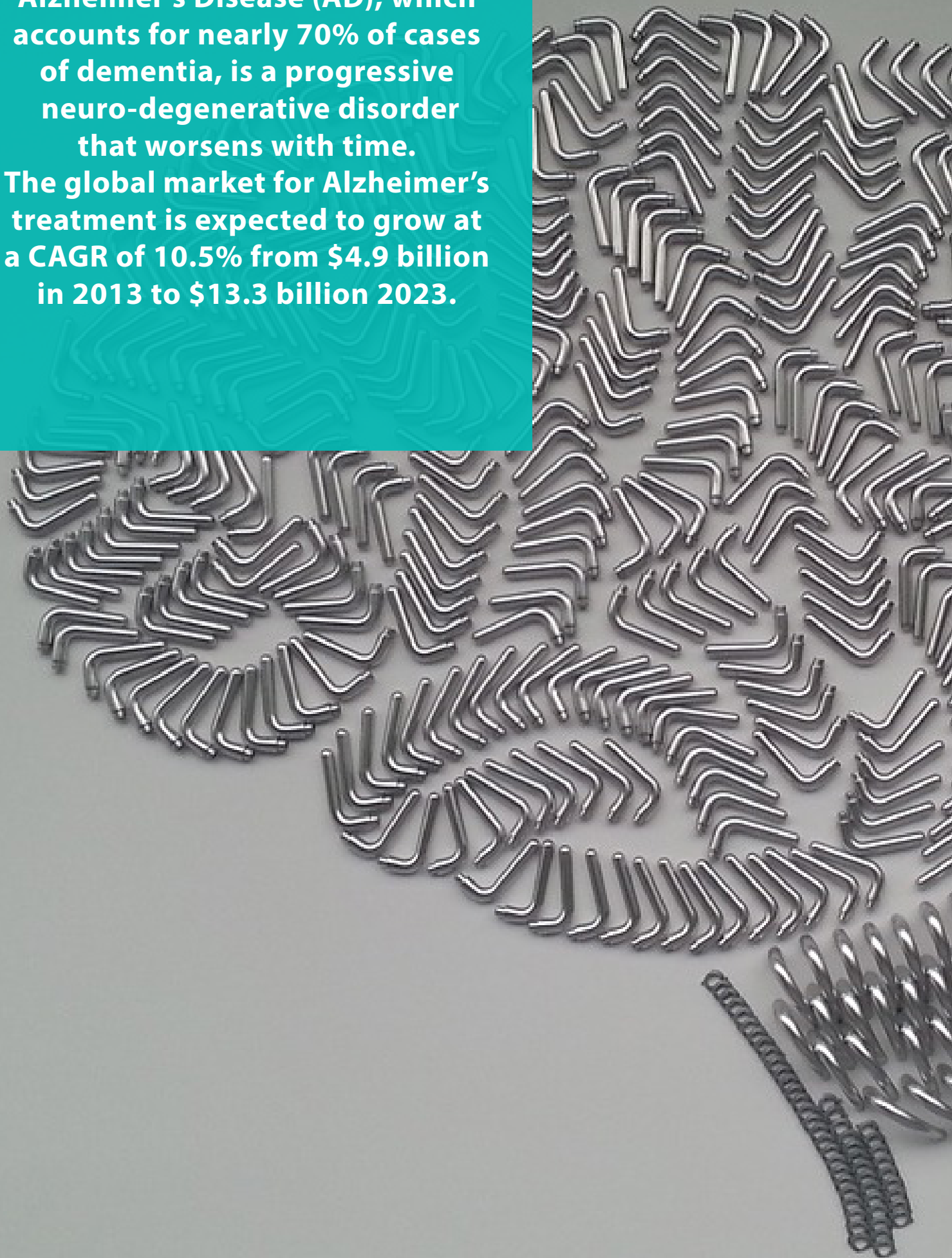
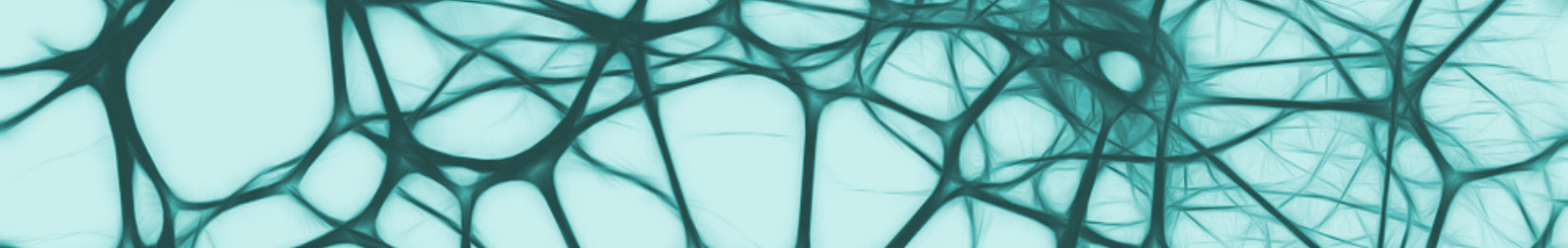


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Alzheimer's Disease (AD), which accounts for nearly 70% of cases of dementia, is a progressive neuro-degenerative disorder that worsens with time. The global market for Alzheimer's treatment is expected to grow at a CAGR of 10.5% from \$4.9 billion in 2013 to \$13.3 billion 2023.





AD Therapy Market Drivers

Prevalence of Disease and Increasing Geriatric Population

The number of dementia cases increases two-fold every twenty years, and there's a substantial prevalence among geriatric patients on account of greater life expectancy due to better healthcare access. This aging demographic may fuel the AD drug market.

Statistics suggest that prevalence of the disease would be steeper among low or middle-income countries, accounting for nearly 63% of such cases by 2030. This would drive the development of cost-effective therapies in the future.

Advancement in Diagnostic Capabilities

Currently, AD diagnosis is based on the use of symptoms as indicators.

Diagnosing AD is a challenging task as it requires evidence of alterations in the brain. With the significant research strides made in the development of diagnostic kits using biomarkers, we would be able to accurately predict AD cases in the near future, which would in turn, drive the drug market — especially for treatments that target early-stage AD.

Amyvid, a positron emission tomography imaging agent, is among the first agents developed that successfully identifies beta-amyloid plaques in living brain tissue.

Development of Next-generation Therapeutics

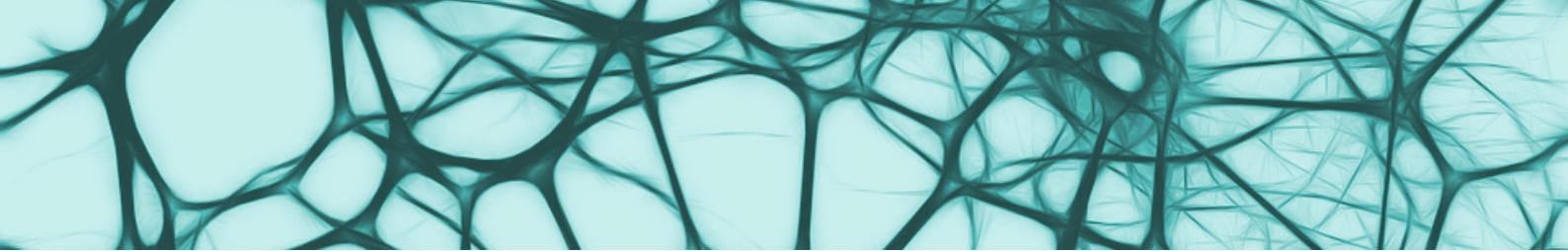
Currently available therapeutic options include cholinesterase inhibitors such as Razadyne® (galantamine), Exelon® (rivastigmine), Aricept® (donepezil) for the treatment of mild-to-moderate AD. They also include N-methyl D-aspartate (NMDA) antagonist such as Namenda® (memantine) for moderate to severe AD.

These drugs only provide symptomatic relief however, with no definitive means for prevention or cure.

According to a report by Alzheimer's Association, any treatment to delay the onset of the disease by 5 years that receives approval by 2025 can potentially reduce the number of cases by 42%. This could also reduce the cost of treatment by \$367 billion (by 2050) in the Americas.

Nearly 60 investigational drugs are undergoing FDA trials - treatments meant to cure, reverse, or prevent AD. The successful outcome of any of these clinical trials would turn out to be cash cows for pharmaceutical and biotechnology companies.





Targets for Drug Development in AD

Alzheimer's is primarily caused due to the deposition of two proteins: amyloid-beta (which is a major component of plaques) and hyper-phosphorylated tau. These proteins lead to inflammation, excess secretion of stimulatory neurotransmitters, mitochondrial dysfunction, and free radical damage.

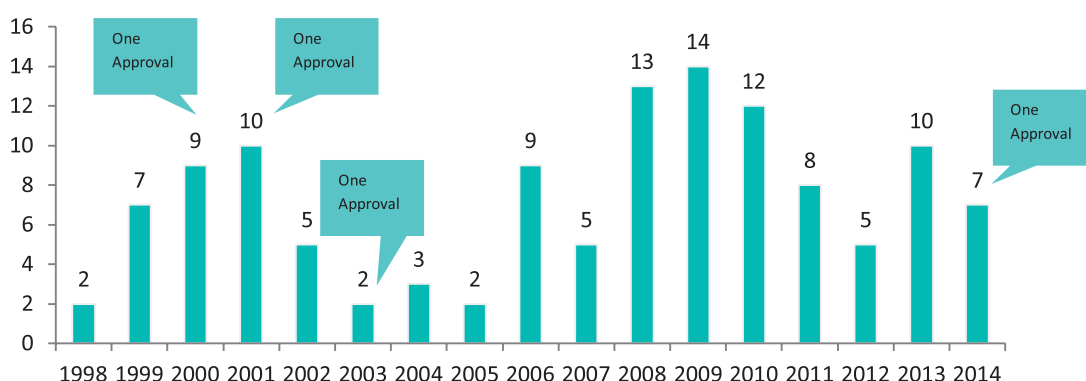
Targets	Strategies
Amyloid	• Decrease amyloid-beta production • Eliminate amyloid-beta production • Enhance immunity (Active immunity with vaccines & Passive immunity with antibodies) • Block amyloid-beta signalling • Inhibit amyloid-beta aggregation
Tau	• Prevent aggregation • Immunity enhancement with vaccines • Inhibit phosphorylation
Others	• Insulin sensitization • Stimulating nerve growth factors • Anti-ageing

AD Therapy Market Challenges — Developing Safe Next-generation Therapeutics

Although private companies and government organizations have pledged substantial capital in a bid to develop several promising AD therapies, most wash out during clinical trials.

Research suggests that from 1998-2014, 123 molecules have failed during their human trials at various phases, while only 4 drugs have been approved by the FDA — 1:30 ratio of successful therapy.

Drugs Under Clinical Trials



Source: www.phrma.org

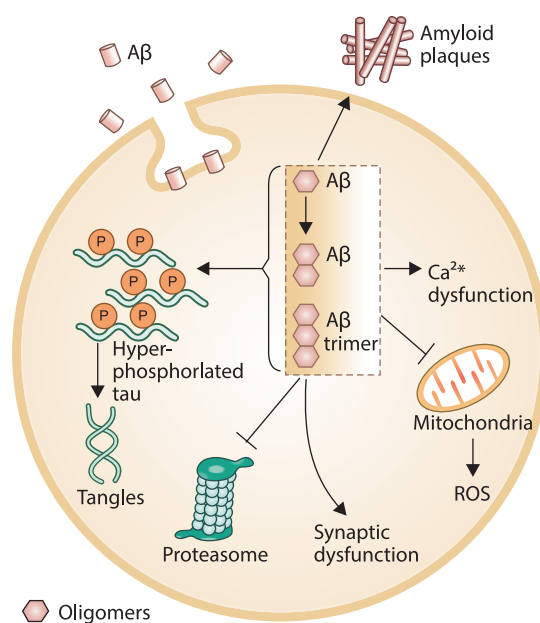
Despite significant research into understanding the molecular biology and pathology of Alzheimer's disease, a breakthrough treatment still remains elusive.

This gap is partly attributed to researchers' inability to categorize molecular characteristics into causes, effects, or signs of progression, owing to which the selection of plausible targets becomes difficult. This suggests that treatment or prevention of AD will require a multi-faceted approach rather than a single treatment.

AD Vaccines — An Overview

Molecular Biology of AD

Alzheimer's is a result of amyloid-beta ($A\beta$) aggregation giving rise to toxic species such as dimers, oligomers, and fibrils that bring about synapse loss. A few studies also suggest that $A\beta$ potentiates tau pathology, which then mediates toxicity. Hyperphosphorylated tau disrupts proteasome and mitochondria function, which then triggers calcium and synaptic dysfunction.



Source: *Nature Reviews, Neuroscience*

Therapeutic Vaccines for AD

The mechanism of active immunization by means of vaccines engages both T cells and B cells to promote the production of antibodies.

The concept of vaccines for AD was introduced by Dale Schenk and his colleagues in 1999, when they studied the disease-modifying effect of a vaccine comprised of $A\beta$ and adjuvant QS21 in APP transgenic mice. It was observed that the vaccine prevented plaque formation and attenuated behavioral deficits.

However, AN-1792 ($A\beta$ and adjuvant QS21) failed in the clinical trials as it resulted in cases of meningoencephalitis in 6% of the recipients, a condition caused by damaging the Th1 inflammatory response elicited by $A\beta$'s T-cell epitopes.

Given the potential for active immunization using $A\beta$ and tau, many companies are investing in the development of a second generation of vaccines that mitigate the risk of cellular autoimmunity by using $A\beta$ antigen shorter than 8 amino acids.

Technology and Commercial Ecosystem

Several advantages of active immunization — like the generation of stronger immune response in comparison to passive immunization — have proved lucrative to pharmaceutical companies and research organizations, who are working toward developing high-potential-low-toxicity vaccines.

Most research is a collaborative effort between companies or/and universities, mainly backed by government funding.

The US government has proposed to increase Alzheimer research funding by a whopping 60%, allocating \$936 million in its 2016 federal budget. This is bound to boost drug and molecular discoveries in AD.

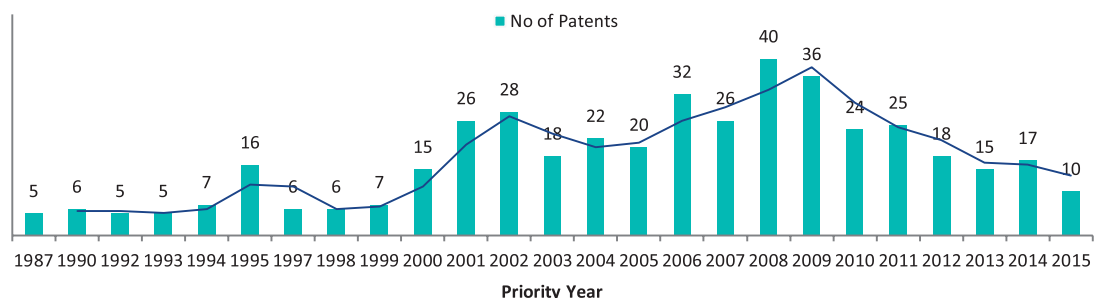
Patent Ecosystem

Patent Filing Velocity

Alzheimer's has drawn significant research interest from all directions: drug discovery, diagnostics, and molecular biology.

However, patent filing pertaining to AD vaccines has been limited to just about 400 patent families, with a declining trend post 2008.

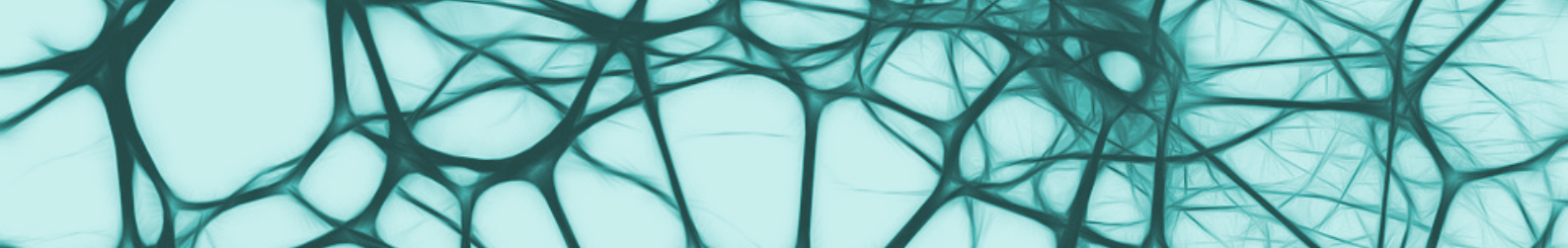
The initial upswing in patent filing was driven by the need to find a viable therapeutic alternative that could halt, cure, or prevent AD. Failure during clinical trials for a few vaccines hasn't much deterred patent research activity either.



Source: Aranca Research

Note: Low patent filing in the year 2014 onwards may be due to unpublished applications

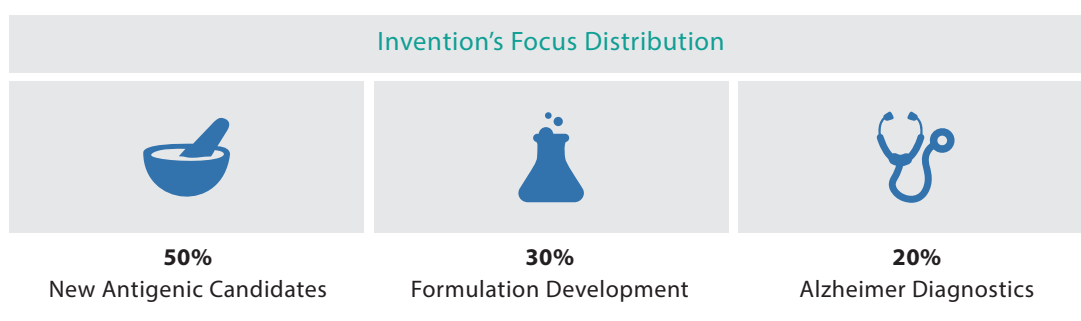




The A β -based vaccine has been the prime focus of patent filers, while tau-based vaccines still remain in their nascent stage.

The majority of the patents address problems of toxicity, specificity, peptide targeting, and enhancement of immune response. This is accomplished by delivering one or more means (such as peptides) using varied delivery systems, as well as through the construction of specific (and less toxic) antigenic candidates.

Patented Technologies Snapshot



Source: Thomson Innovation, Aranca Analysis

Formulation Development and Delivery Systems

Patented technologies to augment immune reactions include delivering the bound peptide to virus-like particles (bacteriophage) and adjuvants such as aluminum salt or MF59.

The presence of bacteriophages helps in the activation of memory Th cells, reducing the side-effects that were prevalent in AN-1792.

Another patented approach involves delivering both A β peptide and hyperphosphorylated tau along with on-bidesmosidic triterpene glycoside to stimulate Th2 immunity rather than Th1 immune response.

New Antigenic Candidates

In order to reduce toxicity and improve specificity, research is directed toward bringing about structural changes in the A β peptide and developing vaccines with tau proteins.

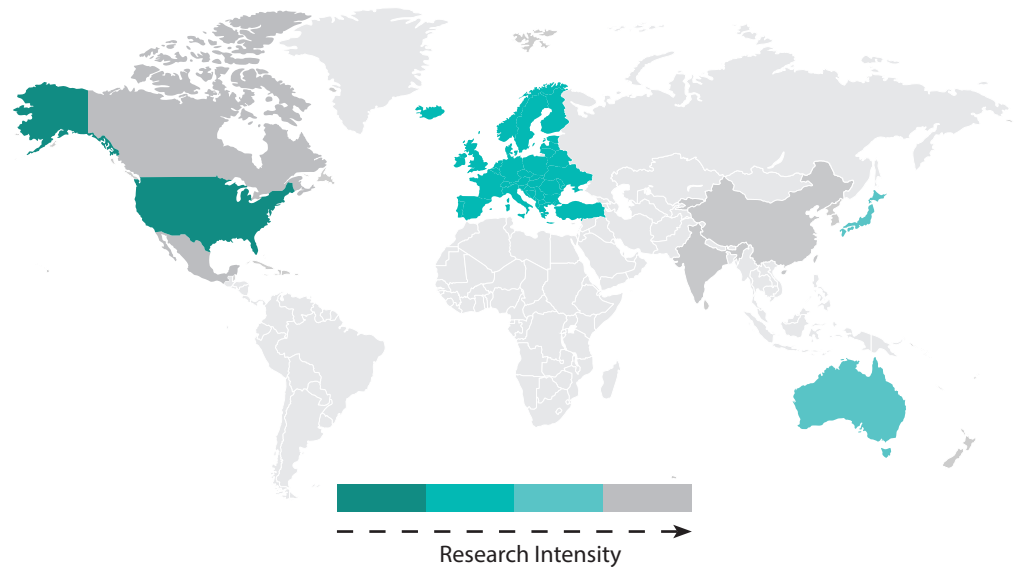
One such technology involves the addition of cysteine or its analog at the C-terminus of A β peptide. Administration of amyloid beta-derived diffusible ligands (ADDLs) assembled into soluble, globular, non-fibrillar, oligomeric structures, activates the formation of antibodies that target A β peptide aggregates.

Another patented vaccine technology involves the administration of γ -secretase activating protein (gSAP) or its fragments. This is done to modulate A β production through a mechanism involving its interactions with both γ -secretase and amyloid precursor protein C-terminal fragment. The gSAP peptide decreases A β without affecting NOTCH metabolism.

Research is well underway into technologies involving the delivery of a sendai-virus or plasmid vector that contains a sequence to encode mutant τ -protein (with mutation at P301L, P301S or P301T) to AD patients in order to elicit the generation of antibodies against hyperphosphorylated tau.



Top Research Contributors and Top Geographies



Researcher	Research Contribution
Abbott	3%
United Biomedical	3%
Univ. California	2%
Coley Pharm	2%
Univ. Jefferson	1.5%

Researcher	Research Contribution
Merck	10%
AC Immune	7.6%
Glaxo Group	6.67%
Novartis	5%
Affiris AG	3.5%
Cytos Biotechnology	2%
Axon Neurosciences	1%

Source: Aranca Research

The United States, which accounts for nearly 40% of AD therapeutics market share as of now, is at the top in terms of innovator geography (filing with USA as a Priority Country). Research in the US is mainly driven by aging demographics, favourable healthcare schemes, and research funded by health institutes like the NIH.

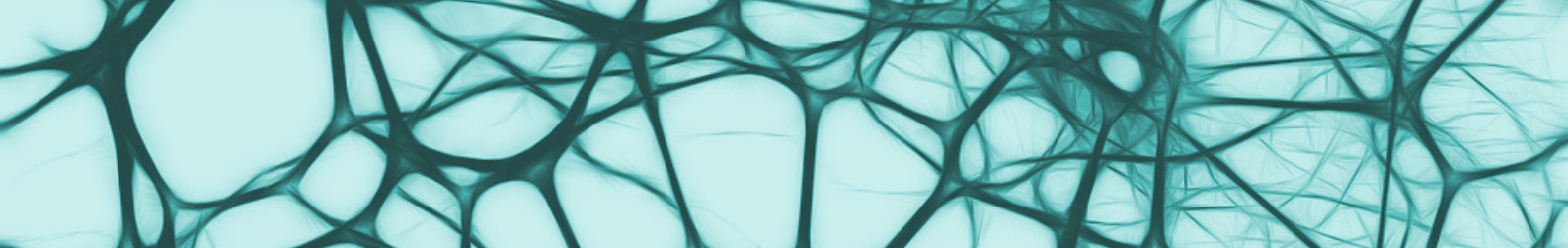
US-based companies such as Abbott and United Medical are actively researching the AD domain. Research in the US is also supported by contributions from universities such as the University of California and Jefferson University, either in collaboration with industry partners (University of California collaborated with Prothena Biosciences Ltd., Elan Pharm, Janssen, Neuralab Ltd., and Neotope Biosciences Ltd. to develop new antigenic candidates) or as standalone ventures.

Europe has also witnessed significant filing as it houses several research forerunners such as Merck, AC Immune, Glaxo Group, and Novartis.

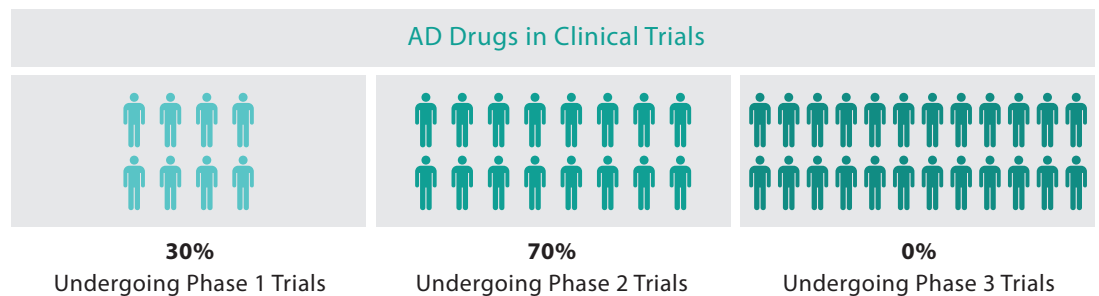
Japan, India, and Australia are also amping their research activity, owing primarily to an aging demographic that's likely to make them big markets in the future.

Major companies focus on pumping new antigenic candidates into their pipelines, with a few already having entered their clinical trials phase. Amongst the new candidates, there's a major focus on modifying amyloid protein for improved specificity and reduced toxicity. A successful clinical trial of any of these candidates would replace a significant number of current symptomatic therapies, transforming the AD drug market from symptom-based treatment to disease-modifying therapy.





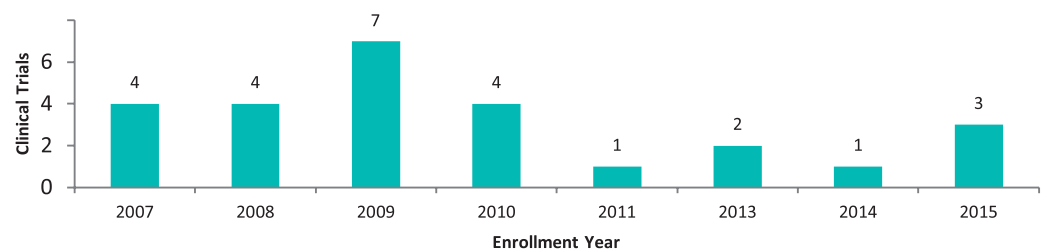
Therapies Under Development



Source: Thomson Innovation, Aranca Analysis

Vaccines for Alzheimer's constitute only 4% of the total clinical trials for AD at the US FDA, of which 70% represented phase 2 studies, and 30% represented phase 1 studies. These studies are conducted to establish the safety, efficacy, and tolerability of the candidates in mild and/or moderate AD cases. More than 70% of the studies begin during 2007-2010, of which 70% are in phase 2 trials.

Potentially viable vaccine therapy for AD could very well be a reality by 2017 if any of these candidates prove successful.



Source: Aranca Research

Two of these phase 2 studies — namely Affiris' AFFITOPE® AD02, and Pfizer and Janssen's ACC-001 — have reached the end of their development cycle due to unsatisfactory results.

AD02 is a synthetic peptide of six amino acids that mimics the N-terminus of A β . This immunogen lacks the most common T cell epitope, while it consisted of first 11–15 amino acids of A β (B-cell epitope). The company hypothesized that such an antigenic structure may allow the production of anti-A β antibodies while reducing inflammatory TH1 response. The outcome of the AD02 study showed that a placebo fared better than the candidate itself. The treatment with placebo — which consisted of an immunomodulator without any A β -based antigen — showed less hippocampal shrinkage in patients. Affiris is now exploring the clinical development of the placebo formulation for AD patient under the drug AD04.

On the other hand, although ACC-001 showed antibody generation in patients with fewer side effects, it did not show significant improvement in reducing the disease's progression.

Research and Collaboration in Developing Therapies for AD

Sponsors / Collaborators	Candidate	Technology
Pfizer Janssen Elan	ACC-001; ACC-001 + QS-21 (Adjuvant)	ACC-001 consists of A β fragment made up from 1-7 amino acids with an N-terminal end which is thought to avoid T-cell mediated response. The peptide is linked to a carrier made of inactivated diphtheria toxin. THE CANDIDATE HAS BEEN DISCONTINUED
Novartis	CAD106	Multiple copies of A β 1-6 peptide derived from the N-terminal B cell epitope of A β . Peptide is linked to Q β virus-like particle. THE CLINICAL TRIAL STUDY IS TO BE STARTED (Recruitment Ongoing)
Affiris GlaxoSmithKline	AFFITOPE AD02	Synthetic peptide of six amino acids mimicking the N-terminus of A β , THE CANDIDATE HAS BEEN DISCONTINUED
Affiris GlaxoSmithKline	AFFITOPE AD01	Targets A β . THE CANDIDATE HAS BEEN DISCONTINUED
Affiris GlaxoSmithKline	AFFITOPE AD03	Pyroglutamate modified A β . THE CLINICAL TRIAL STUDY IS ONGOING
Axon Neuroscience	AADvac1	Synthetic peptide derived from amino acids 294 to 305 of the tau sequence - KDNKHPGGGS, coupled to keyhole limpet hemocyanin. Adjuvant: Aluminium Hydroxide. THE CLINICAL TRIAL STUDY IS ONGOING
United Neuroscience United Biomedical, Inc. Taipei Veterans General Hospital Taiwan National Taiwan University Hospital	UB-311	UBiTh helper T cell technology and a particular site-specific epitope of A β . Equimolar mixture of 2 synthetic peptides coupled through an oligonucleotide spacer to the N-terminal A β 1-14. THE CLINICAL TRIAL STUDY IS ONGOING
Meso Scale Diagnostics	V950	A β amino-terminal peptides conjugated to ISCO-MATRIX®. THE CLINICAL TRIAL STUDY IS ONGOING
AC Immune	ACI-24	An array of truncated A β 1-15 sequences, sandwiched between palmitoylated lysines at either end. THE CLINICAL TRIAL STUDY IS ONGOING
AC Immune Janssen	ACI-35	16 copies of a synthetic tau fragment phosphorylated at residues S396 and S404 THE CLINICAL TRIAL STUDY IS ONGOING

Source: US FDA Clinical Trials Data and Aranca Research



Future Prospects

The development of AD vaccines has faced setbacks owing to failures in a few late-phase clinical trials. This is thought to be attributed to the misdiagnosis of populations with mild or moderate AD.

While some theories suggest that failed clinical trials may be due to the low dose of biologics given during trial phases on account of safety concerns, others postulate that A β could be the wrong target to begin with, as the density of A β plaque isn't always directly related to the severity of dementia.

The identification of correct target(s) for AD treatment, optimal population design, as well as testing safe and efficacious dosage during clinical trials is necessary to build a successful vaccine candidate. Current research would lean towards developing vaccines that possess new peptide candidates such as tau proteins and protofibrils – an intermediate species formed during the aggregation of monomeric A β to insoluble fibrils. Research into accurate diagnosis with the aid of biomarkers in order to avoid misdiagnosis is also gaining momentum.

Despite several efforts to develop a successful vaccine product, the technology would face competition from passive immunization — a relatively safer alternative — and newer technologies like beta-site amyloid precursor protein cleaving enzyme (BACE) inhibitors. BACE inhibitors are thought to fight the root cause of AD – the formation of A β plaque. They work by blocking the enzyme that's involved in the production of amyloid proteins. This class of drugs has received research attention from big players including Novartis, Amgen, Eli Lilly, Merck, Boehringer Ingelheim, and Eisai, among others.

With the advent of CRISPR, viable AD treatments could be well within reach.

AD can be treated by targeting the Amyloid precursor protein gene with CRISPR. A study conducted in April 2016 demonstrated that CRISPR was able to convert mutations associated with AD in 58% of target cells without causing unintended changes. Another study reported a conversion rate of 75%, which is certainly a very high rate of success. Altering 75% of target cells would, at the very least, allow treatments to minimize AD symptoms if complete treatment/reversal remains elusive.

The pharmaceutical industry is exploring all available options to develop a successful therapy for AD.

It's just a matter of time before we come up with the most viable techniques and technologies.

WE CAN HELP

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