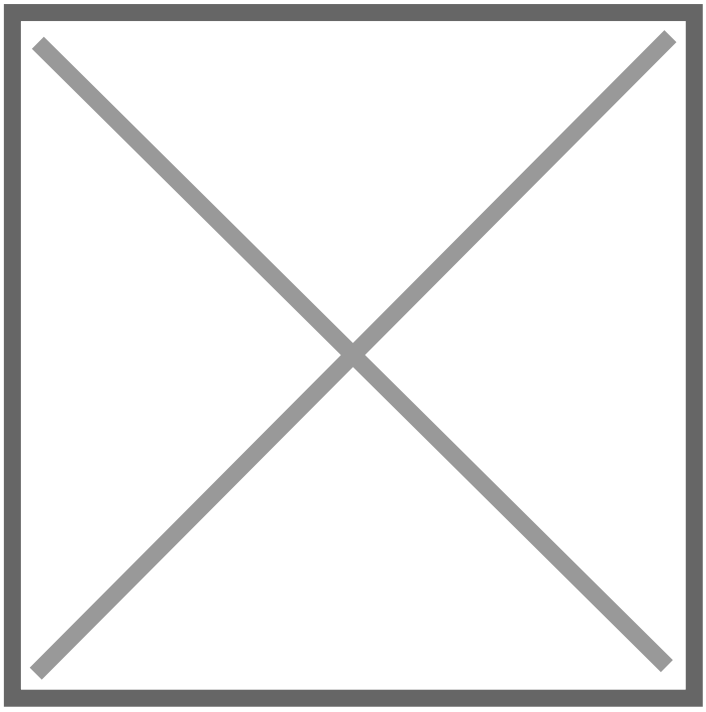
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Promising Alzheimer's Treatment

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Promising Alzheimer's Treatment

Despite the failure of a slew of drugs in the market and research projects reaching a dead end, industry pundits predict that the alzheimer's market is humungous and can change the dynamics of the industry by 2015

A hundred years ago, when a disease showing loss of neuron cells and the discovery of a sticky mass of plaque on nerves filled with tangled fibers was first reported, the number of patients afflicted with this so called rare disorder was just two. Today, the numbers can be mind-boggling and the situation a race against time. At an international conference on neurodegenerative diseases held in Berlin, it was reported that in the European Union alone around five million people suffered from dementia, of whom 60 - 70 percent were alzheimer's patients. In Germany alone approximately 1.2 million people suffer from alzheimer's disease. About 700,000 people in the UK have a form of dementia and more than half have alzheimer's disease. In less than 20 years nearly one million people will be living with dementia, by 2051 it is expected to reach 1.7 million. Around 4.5 million alzheimer's patients live in the United States.
For many decades since it was discovered, the disease still remains incurable. Scientists across world are trying to bring out a feasible and workable treatment for a disease described since time immemorial as incurable and degenerative. This apart, the industry had also seen large scale clinical trials kick started by big-wig names, halting or reaching a dead end due to 'insufficient knowledge about the disease'.
However, the silver lining in the cloud is that scientists and companies are still on the search for newer breakthroughs and therapeutic treatments and we will be seeing a slew pipeline drugs for alzheimer's in the coming years. A recent announcement by a group of scientists at Aberdeen University led by Professor Claude Wischik has raised antennas. The team published results of early trials of a new drug, suggesting it could be at least twice as effective as current medicines in slowing progression of the disease. Moreover, Wyeth and Elan announcing the commencement of the phase-III trials of the much awaited Bapineuzumab, has but raised hopes of the scientific community.

Breakthrough and evolution
One of the breakthroughs in alzheimer's took place way back in 1985 when scientists were able to identify the insoluble deposits in the brain as amyloid-beta plaques which was later zeroed in as the hallmark for alzheimer's disease. This was the base from which further research development commenced.
Turning back to history, it was Blocq and Marinesco who first described plaques in the grey matter in 1892. The connection of plaques and demential illness was discovered by alzheimer in 1906. Bielschowsky supposed in 1911 the amyloid-nature of the plaques. Statistical investigations were performed by J A N Corsellis and M Franke in the 1970s. In 1985 succeeded the biochemical identification of amyloid beta. But there are more unsolved questions of plaque formation and its importance. From then on research activities and therapeutic interventions have been formulated primarily to target these insoluble plaque deposits in the brain.

The hiccups

Despite the breakthrough discovery in 1985, even over the past one decade there have been no path breaking success stories in alzheimer's. Drugs to combat alzheimer's have been slow to arrive, with many failed efforts. The five medications approved since 1993 only treat the symptom of weak memory. Pfizer's Aricept and Novartis' Exelon prevent the breakdown of the neurotransmitter acetylcholine that's part of the mechanism of memory (as does Cognex, which Pfizer no longer actively markets). Johnson & Johnson's Razadyne works similarly, but also makes the so-called nicotinic receptors produce acetylcholine. Namenda, from Forest Labs (FRX), prevents another neurotransmitter called glutamate from overexciting memory receptors of nerve cells.

Even Bapineuzumab (whose phase-III clinical trials are being conducted by Wyeth and Elan Corp) had to go through a bumpy stretch. Bapineuzumab (AAB-001) is a humanized monoclonal antibody that received fast track designation from the US Food and Drug Administration (FDA) for treatment of mild to moderate alzheimer's disease. Fast track designation facilitates development and may expedite regulatory review of drugs that the FDA recognizes as potentially addressing an unmet medical need for serious or life-threatening conditions. In late 2001, some 300 alzheimer's patients, aged between 50 and 85, were injected with an experimental vaccine, code name AN1792, on the supposition they might develop antibodies to help clear their brains of the plaque. But after most patients had been given just two doses, 18 developed signs of encephalitis, a severe inflammation of the brain. In January 2002, the study was halted.

However four years later, patients who had developed the hoped-for antibodies after just a couple of doses of AN1792 were found to exhibit significantly slower cognitive decline than those who had not. Trials for Bapineuzumab were immediately commenced.

Flurizan was another product which had to face the brunt of failure. Myriad Genetics commenced its clinical trial of Flurizan, which was aimed at blocking enzymes that form the beta-amyloid clumps. However the company announced later that it would abandon development of Flurizan. Flurizan seemed to work in mice, but it failed to show a statistically-significant benefit during a 12-month long phase-II study involving 207 patients.

Technological upgradation

The recent development that has been the hot debate is the root cause of the disease. There are two schools of thought here. One camp believes that tau, the protein that is found in large amounts in an abnormal form in tangles, is the cause of neural cell death in alzheimer's disease while the second school of thought believes that beta-amyloid, the protein that makes up the core of alzheimer's plaques is the main culprit. The emergence of tau as a possible cause of alzheimer's disease reflects a recent shift in the mainstream scientific perception about the disease. For many years, beta-amyloid was thought to be the only real candidate for the cause of alzheimer's disease. There is a third school of thought which believes that perhaps inflammation could be the cause of the disease.

There have been some interesting studies and clinical trials conducted over the recent years. Way back in 2006, three studies were presented at an international conference which did raise antennas up—all the studies again proving that antibodies targeting amyloid beta(A- beta) could hold the key to a breakthrough alzheimer's therapy.

In the first study, a group from the Mayo Clinic, led by Joseph F Poduslo, and Thomas M Wengenack, developed IgG4.1, a domain-specific, monoclonal antibody against the fibrillar A-beta 42 immunoglobulin. Fragmenting this antibody and modifying it with the polyamine known as putrescine provides several advantages compared with the whole IgG, including increased permeability through the blood-brain barrier (BBB) and increased binding to the antigen.

The second study, supported by Eli Lilly and Company, tested a humanized monoclonal antibody to the A-beta peptide, directed at the central domain of A-beta, for safety and biomarker changes in humans. The 'amyloid-beta hypothesis' states that the amyloid-beta peptide has a primary causal role in alzheimer's. After administering a humanized monoclonal antibody to amyloid-beta intravenously, the antibody binds to the peptide, inactivating it. Administration of the antibody could increase the rate of clearance of amyloid-beta from the brain, thus addressing what is thought to be the major source of pathology in AD.

The third study, led by Norman Relkin and Marc Weksler from Weill Medical College of Cornell University in New York City, looked at Intravenous immunoglobulin (IVIg), a purified human polyclonal antibody preparation made from the plasma of thousands of carefully screened blood donors and containing antibodies to the A-beta peptide.

Market potential

Alzheimer's disease market in the seven major markets was worth $6.1 billion in the year 2005 and will increase to $7.8 billion by the year 2010. Another reliable report states that the global anti-alzheimer's market was valued at $5.6 billion in 2007, an increase of 21.3 percent over sales in 2006. The leading brands of cholinesterase inhibitors include Aricept, Exelon, and Reminyl. Several new therapies are expected to be in the market and the shares of various types of approaches are estimated for the future up to the year 2015. Over 130 different compounds are at various stages of development for the treatment of alzheimer's disease. There are non-pharmacological approaches such as vagal nerve stimulation and cerebrospinal fluid shunting, which are in clinical trials. Over 77 trials are still in progress.

According to Muralidharan Nair, partner, advisory services, Ernst & Young, "On a global level, alzheimer's is the one of the key areas of research for companies as other segments like cardiology have matured over the years. Now the investment for cardiology has been reduced and instead it has been shifted to areas like central nervous system (CNS) under which alzheimer's is a priority. Moreover in regions like the US and Europe there is a booming ageing population which makes the

market all the more lucrative for investment. In India too there is an active market but unfortunately there is lack of understanding about the disease coupled with medicines being expensive. Even in alzheimer's, only regenerative medicines play a crucial role."

"Alzheimer's is a very complex disease. There are various sub-categories of patients and the causes are different. Some are age-related some are caused by injuries, or sometimes it get triggered due to stroke, sometimes it maybe genetic as well. So there is a whole complexity," said Dr. Rajender Kamboj, president, NCE, Lupin Pharma Ltd.

"Everyday we are learning more about the disease that knowledge will help us to develop some important anti-alzheimer's drugs. In the 1990s we had very little knowledge about alzheimer's, today we know a lot more. So its progressive learning," said Ninad Deshpanday, president, NDDS, Lupin Pharma Ltd.

The way forward

While commenting on the future developments of alzheimer's treatment Sandhya Kamath, senior research analyst, healthcare,Technical Insights, Frost and Sullivan, said, "In terms of technology, advances in validation of the tangle theory or tau hypothesis promise to accelerate efforts toward deciphering other underlying aspects of alzheimer's disease (AD) pathogenesis. Power3 Medical has completed proof-of-concept and clinical validation studies with the NuroPro blood test that involves testing 59 proteins in the patient's serum to precisely detect alzheimer's. Sustained efforts are on to develop drugs that could either delay or stop the progression of the disease, as a result of which a lot of such disease modifying drugs are in preclinical or clinical development."

Despite the discontinuation of various projects, industry experts claim that the scientific community is still in the learning process of the causes of the disease. An apparent breakthrough in the treatment of alzheimer's was announced by scientists at UK-based Aberdeen University recently. The team led by Professor Claude Wischik published results of early trials of a new drug, suggesting it could be at least twice as effective as current medicines in slowing progression of the disease. The drug, called rember, slowed cognitive decline by 81 percent, Wischik said in a paper presented to the international conference on alzheimer's disease in Chicago. Rember is the first drug to act on the protein, tau that helps brain cells keep their structure and communicate with each other. Wischik's research suggested rember could reduce the tau tangles and slow the deterioration of the brain. People taking it for 50 weeks had a slower decline in blood flow to the parts of the brain that are important for memory than those taking a dummy pill.

Wischik is co-founder of TauRx Therapeutics, which is developing the alzheimer's treatment. Larger-scale trials are now needed to confirm the safety of this drug and establish how far it could benefit the thousands of people living with this devastating disease. Wischik's results were based on a phase-II study of 321 people with mild and moderate alzheimer's disease in the UK and Singapore. They were divided into four groups, three taking different doses of rember and a fourth group taking a placebo.

After 50 weeks those with both mild and moderate alzheimer's who were taking rember experienced an 81 percent reduction in mental decline compared with those on the placebo. The final 'phase-III' trial will hopefully be conducted next year. If that trial proves successful, the drug could be available by 2012.

One of the biggest problems and challenge with alzheimer's disease is that it currently cannot be diagnosed at the early stage of the disease. Researchers are currently studying ways to diagnose the disease before the first symptoms of the disease appear, which requires a highly invasive brain biopsy or a postmortem examination. Several studies are underway to find better methods to confirm an alzheimer's diagnosis in living people.

Nayantara Som