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ASIA EDITION

Multipronged Approach Against Alzheimer's Disease

September 1, 2023 | Analysis | By Ayesha Siddiqui

In July 2023, Eisai and Biogen received full traditional approval from the United States Food and Drug Administration (US FDA) for their Alzheimer's drug Leqembi (lecanemab-irmb). This drug is the first to target the disease's progression rather than merely addressing its symptoms. The approval has infused excitement and hope into the field of Alzheimer's drug development, known for frequent drug failures.

Alzheimer's Disease (AD) is an escalating global health crisis. In 2020, the World Health Organisation (WHO) noted over 50 million people had dementia worldwide; 60 per cent of them lived in low- to middle-income countries. The Asia Pacific region bears a hefty burden with dementia care costs at $185 billion, straining healthcare in populous economies, according to ADI (Alzheimer's Disease International). As we mark World Alzheimer's Day this year on September 21, let's take a stock of the advancements in the research and development in the Asia Pacific.

Alzheimer's, which leads to dementia in the elderly, is a neurodegenerative condition attributed to the accumulation of amyloid plaques and abnormal tau protein in the brain. Recent FDA approval of Eisai and Biogen treatment has sparked excitement and hope in the field after years of disappointments.

The field boasts a strong pipeline. As of January 1, 2023, globally there were 187 trials assessing 141 unique treatments for AD. Phase 3 included 36 agents in 55 trials; 87 agents were in 99 Phase 2 trials; and Phase 1 had 31 agents in 33 trials. Disease-modifying therapies were the most common drugs comprising 79 per cent of drugs in trials. Twenty-eight per cent of candidate therapies are repurposed agents (Source: Alzheimer's Association).

“Despite what seemed to be a lack of innovation in the field of neurodegenerative disease therapeutics in recent decades, we are seeing a shift in the industry over the last few years, with many exciting developments in medical research. The approval of Leqembi to treat early-stage AD, marked an important leap forward for the industry as the first AD drug to achieve statistically significant slowing in the rate of decline, although it did not halt or reverse cognitive decline. While these advancements are promising and highlight the possibility of progress for patients, families and caregivers, many questions remain unanswered about the clinical benefit of anti-amyloid therapies for AD. And with the continued increase in prevalence of degenerative brain disorders globally impacting more than 1 billion people worldwide,” said **Dr Arnon Rosenthal, Co-Founder, Chief Executive Officer, and Director of Alector, USA** Alector is exploring next-generation approaches to address this public health challenge.

In the Asia Pacific region, there has been a flurry of activity in both the diagnostics and therapeutics in AD, from blood tests for early detection to vaccines and other novel drugs. Let’s explore these advancements in detail.

Advancements in Alzheimer's disease

Diagnostics

Detecting and diagnosing Alzheimer's disease in its early stages is crucial for the effectiveness of potential treatments. Therefore, much of the research in AD is focused on refining early detection methods.

Alzheimer's is thought to result from the buildup of a nerve cell-degenerating protein, amyloid? (A?), in the brain. Currently, cerebrospinal fluid testing and PET imaging are used to detect A? accumulation.

“As PET testing is not easily accessible and expensive and CSF testing requires the need for lumbar puncture, researchers are working on the development of measuring these biomarkers in blood. Recent technological improvements resulted in the development of blood based biomarkers for neurodegenerative diseases", said a spokesperson from Fujirebio, Japan. The firm recently launched CLEIA assays in plasma or blood for the following markers: amyloid beta 1-42, amyloid beta 1-40, pTau181, NF-Light, pan-ApoE, ApoE4 and pTau217.

In 2022, Japan approved one of the world’s first blood test kits to detect signs of Alzheimer’s disease.The blood test kit, codeveloped with Eisai assists in identifying A? accumulation in the brain, by measuring A? levels in the blood using the company's automated immunoassay system. In the same year, Japan's Hokkaido University and Toppan developed a sensitive biosensing technique to detect A? levels. Using Digital ICA technology, this approach quantified amyloid ?-binding exosomes in small blood samples from the mouse model.

In addition, researchers from the US and Japan, made progress toward developing a simple behavioural test to measure an individual’s risk of developing Alzheimer’s before any symptoms arise.

“We developed and tried various complex cognitive tasks (mostly to have top-down executive control against bottom-up natural sensory-motor tendency), and obtain partially positive results (ie. the high-risk group showed substantially different performances relative to the age-matched control). Our paradigm may be further combined with the brain-heart measures to increase our diagnostic sensitivity,” said **Prof. Shinsuke Shimojo, Gertrude Baltimore Professor of Experimental Psychology. Prof. Shimojo is an affiliated faculty member with the Tianqiao and Chrissy Chen Institute for Neuroscience at Caltech, USA**.

In 2023, Cognitact Limited, a deep tech startup founded at HKUST (Hong Kong University of Science and Technology), introduced PlasmarkADTM in Hong Kong. This groundbreaking blood test service identifies early-stage Alzheimer's by examining 21 blood protein biomarkers using advanced proteomic technology and their exclusive machine learning algorithms.

Researchers in New Zealand are part of the international endeavour to halt AD through early detection which will allow early intervention in the disease process.

“To advance this goal we have established Dementia Prevention Research Clinics (DPRC). Our clinics underpin an ongoing, longitudinal study to understand the impact of AD and mate wareware (dementia) in Aotearoa-New Zealand from individual, cultural, and biological perspectives. Our investigations focus on development of novel interventions and identification of biomarkers of disease risk and progression. Our evaluations cover clinical, neuropsychological, neuroimaging, lifestyle

evaluations and APOE genotyping. Already, in collaboration with the Australian Imaging Biomarker and Lifestyle study we have identified a novel pattern of microRNA found in blood plasma which reflects AD progression. This is significant because microRNA controls a wide range of neuronal functions, which are dysregulated in AD. As microRNA are highly stable in plasma and can be measured by routine technologies, they may represent robust, stable, and easily accessible biomarkers capable of reflecting amyloid pathology, as well as multiple other aspects of AD as it progresses. Alongside this we are exploring both pharmacological and nonpharmacological interventions in AD, with a particular focus on a potentially therapeutic peptide derived from the amyloid precursor protein. Key next steps will ensure that the voices of MÃ?Â•ori, our first nations people, are represented in this work, in particular by building Kaupapa MÃ?Â•ori Methodologies which will enhance MÃ?Â•ori access to the DPRC," explained **Dr Joanna Williams, Associate Professor, Department of Anatomy, University of Otago, New Zealand.**

Therapeutics

Alzheimer's drug development primarily focuses on reducing amyloid beta plaque accumulation, although progress has been made in understanding the brain's immune system and genetic regulation. New targets include inhibiting tau aggregation, reducing inflammation etc.

South Korea is leading the research in the AD space. The Korean government is also bullish on advancing the field. The government finalised its fourth basic plan for promoting brain research revealing a goal of creating 10 specialised companies with a corporate value of 1 trillion won ($769.2 million) in the brain industry by 2027 and securing two domestic drugs for major brain diseases such as autism and dementia.

A couple of South Korean firms have already entered late stage trials. Chief among them is AriBio. Its lead candidate AR1001, a small molecule with polypharmacological features, shows promise for AD treatment. A phase 3 programme is underway for early AD patients. In April 2023, AriBio was chosen by the Ministry of Health and Welfare for the Electronic Drug Technology Development Project, aiming to use 'vibroacoustic stimulation' and gamma wave synchronisation for AD treatment.

In 2020, Neuraly, Inc., a subsidiary of D&D Pharmatech, received FDA approval for the phase 2B trial to assess NLY01's safety and efficacy for Alzheimer's. Over 500 participants with mild cognitive impairment will join the randomised, double-blinded, placebo-controlled trial across 100 sites in the US, Canada, and Europe. Trial results are anticipated by late 2023.

Another firm GemVax & KAEL Co.is focusing on GV1001. Originally developed as a cancer vaccine, GV1001 is a 16-amino-acid peptide comprising a sequence from the human enzyme telomerase reverse transcriptase (TERT). In non-cancer cells, GV1001 has antiinflammatory and antioxidant activity. That drug moved into phase 2 testing in 2022 in the US and Europe.

Among the initial trial projects include University of Ulsan College of Medicine,Spinout ADEL, which has developed an anti-tau antibody for AD. The firm began a phase 1 trial in 2022. Inhibition of tau aggregation is the most common pathway targeted after amyloid reduction. One of the front runners in this space is Singapore's TauRx Pharmaceuticals, whose lead candidate HMTM has completed various phase 3 trials and will be seeking the regulatory approval. In April 2023, Japan's largest drug maker Takeda licensed the Tau based preclinical programme from Canadian biotech Treventis.

Korean research institutes and universities have played a crucial role in unravelling Alzheimer's molecular mechanisms. They are now investigating novel strategies and enhancing existing treatments.

In 2022, Korea Advanced Institute of Science & Technology (KAIST) researchers developed a fusion protein drug, anti-Abeta-Gas6, to reduce Alzheimer's treatment side effects via a novel mechanism. Unlike traditional therapies, it lowered beta-amyloid accumulation without causing inflammation or neurotoxicity. This breakthrough could extend to other neurodegenerative and autoimmune diseases. In the same year, researchers at Gwangju Institute of Science and Technology (GIST) unveiled a method called 'ultrasound-based gamma entrainment' to combat Alzheimer's. By synchronising brain waves with external oscillations, they effectively reduced ?-amyloid plaques and tau protein accumulations in mouse models of AD, using ultrasound pulses at 40 Hz.

Some scientists have turned their attention to developing vaccines for the dreaded disease. In July 2023, researchers at Juntendo University Graduate School of Medicine in Tokyo, Japan developed an experimental vaccine that showed promise in mice.

"As the focus starts to shift towards prevention, we believe that other means of addressing neurodegeneration - vaccines targeting Abeta, Tau, a-syn and other targets of interest - will ultimately play a more central role. Because of their multiple advantages they could be administered before symptoms appear and could provide long-term protection against Alzheimer's

disease," said **Dr Andrea Pfeifer, CEO, AC Immune, Switzerland**. AC Immune is advancing vaccines against all three of the aforementioned targets in mid-stage clinical testing.

Another hot area where Asia is at forefront is around neurometabolism. Although ketogenic diet has been a treatment for centuries, research on keto neurotherapeutics for AD is a nascent stage with Singapore based Cerecin being the world leader.

"Because optimal brain performance can be described as a Yin and the Yang the balance between its structure (cell lipids) and its energy (cell metabolism). Treatment in AD may have partly failed because chronically inadequate glucose supply to some areas of the brain on the order of 10 per cent is present in people at risk of AD long before cognitive decline begins. However, brain ketone uptake is still normal even in moderately advanced AD. Hence, treatments that ignore the brain energy (glucose) deficit in AD would be predicted to produce fail or not clinically efficacy. Treatments that attempt to rescue brain fuel availability via ketones would be predicted to have a better chance of succeeding. Ketone bodies concentrations were directly correlated to the neurocognitive batteries including general cognition using the ADAS-Cog (The Alzheimer's Disease Assessment Scale–Cognitive Subscale) as required by FDA and shown by Cerecin's CER001 ketone agent. The phase 2 study showed -3.4 ADASCog up to 3 months. CER001 tricaprilin now preparing for a replication phase 3 towards global registration (FDA as well as APAC)," explained **Dr Marc Cantillon, Chief Medical Officer, Cerecin, Singapore**.

Approved drugs

During the last two decades Alzheimer's patients have been receiving drugs affecting their symptoms. No treatments were available that could slow down or prevent the disease. Despite many failures of drug developments, recently there has been a promising breakthrough with the approval of two disease modifying therapies. Both of them are immune therapies targetting the formation of the so-called amyloid plaques, one of the hallmarks of the disease.

In 2021, aducanumab (Aduhelm, Biogen) received accelerated approval and in 2023 lecanemab (Leqembi, Eisai) received full approval from the FDA.

"This a significant step forward in the search for a treatment that can modify the Alzheimer's disease process. It's important to remember that while the drugs have been shown to slow the rate of decline, this is not the same as restoring memory to a previous level, but nonetheless it is encouraging news," said **Dr Bill Brooks, Senior Research Fellow (Honorary) at NeuRA, Australia**. NeuRA is an independent, not-for-profit, medical research institute dedicated to improving the lives of people living with brain and nervous system disorders.

Echoing similar sentiments, Fujirebio spokesperson said, "However these therapies will not be able to cure the disease and need to be initiated early in the disease process to be fully effective. As AD is a multifactorial disease including many different pathways, the scientific field is considering a need for combinational treatment."

In 2019, Chinese regulators granted conditional approval to Green Valley Pharmaceuticals's Oligomannate, an Alzheimer's drug that is derived from seaweed.

Drugs awaiting approval

All eyes are now on Eli Lilly's donanemab. At the recent AAIC 2023 conference in Amsterdam, Eli Lilly presented promising data from their phase 3 trial with donanemab and approval of this third anti-amyloid drug is expected soon.

TauRx Pharmaceuticals leads with a potential Tau protein-targeting drug, showing promise in phase 3 trials. Anavex Life Sciences is developing blarcamesine, an M1 muscarinic and sigma-1 receptor agonist, for early Alzheimer's, with a phase 3 trial ending July 2024. AXON Neuroscience's AADvac 1 vaccine targets tau protein in phase 2 for mild Alzheimer's.

Cognition Therapeutics' ELAYTA (CT 1812) is a sigma-2 receptor antagonist in phase 2. Alkahest and Grifols' GRF 6019, a plasma-based therapy to boost cognition, is currently in phase 2 assessment.

Asia is at the forefront of Alzheimer's drug development, actively contributing to the development of novel therapies and early detection methods. The region's efforts are offering promising solutions to reduce the growing burden of Alzheimer's. As the research matures, Alzheimer's may become a distant memory.

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