Research Strategy: Andrea Pfeifer

Hope rekindled for Alzheimer's disease treatment

More than 100 years have passed since the discovery of Alzheimer's disease. Yet today the world faces a health crisis: the number of people with dementia, which describes symptoms that impact memory, is predicted to more than triple to 152 million by 2050 and the cost of treatment is expected to double to $2 trillion by 2030. Moreover, there is no way yet to delay, prevent or cure Alzheimer's disease, the most common form of dementia. With age considered to be the greatest risk factor for Alzheimer's, and global populations getting progressively older, the need for diagnostics and treatments has become ever more critical.

But challenges are also opportunities. The recent announcement by Biogen Inc and Eisai Co Ltd of plans to seek US regulatory approval for aducanumab is one such opportunity. Although Phase 3 studies of the monoclonal antibody had been stopped for futility, a subsequent dataset showed that the drug may work at a high dose. The decision to proceed with registration followed discussions with the US Food and Drug Administration.

This is a huge boost to the field of neurodegenerative diseases, and exciting both for patients and researchers: it could mean that the concept that it is too late to intervene with anti-beta-amyloid therapies at the symptomatic stage of Alzheimer's disease may have to be revisited. But it's clear that the field is changing rapidly. On 10 February, Eli Lilly and Co and Roche announced that two Alzheimer's drugs did not meet their primary endpoint in the DIAN-TU study in a genetic patient population. However, the DIAN-TU study had only small sample sizes and the initial doses of both drugs might have been too low to show an effect. With such a complex set of factors known to contribute to the development of Alzheimer's disease, we have maintained at AC Immune that drugs targeting beta-amyloid must be considered alongside a range of approaches. This is why we continue to focus on antibodies, vaccines, small molecules and diagnostics – which we believe will ultimately make the difference in how we diagnose, treat and potentially even cure people suffering from these debilitating and life-changing diseases.

We are doing this by pioneering precision medicine in neurodegenerative diseases and targeting misfolding proteins, an approach which is applicable across multiple diseases. Proteins carry out many structural functions in the human body, but to perform these tasks they need to fold correctly into three-dimensional shapes. Errors in the way proteins fold contribute to hundreds of diseases including Parkinson's and Alzheimer's diseases.

Our two technology platforms address two key problems. First, the human body does not make antibodies against misfolded proteins because, although pathogenic, misfolded proteins are still recognised as 'self' and do not generate an immune response. Second, the difference between a normal protein and a pathological protein is only related to a conformational change in the protein structure, making drug specificity difficult to achieve.

To address the first problem, our co-scientific founders created technology that generates immunotherapies against conformation specific targets. These include vaccines for active immunisation such as an anti-amyloid beta vaccine and an anti-tau vaccine, both in early clinical development, as well as a passive immunisation approach based on antibodies. The second problem is addressed by a technology platform that can generate small molecules which have been shown to bind to misfolded proteins. These molecules are intended to break up neurotoxic aggregates and inhibit their aggregation and seeding. This platform has generated three therapeutic and two diagnostic development candidates.

What can we learn from other fields?

Many scientists have begun to support the idea that combination therapies are going to be required to successfully treat Alzheimer's disease, a strategy that was pioneered and is now common in the treatment of cancer and HIV. We think that this will be the case in Alzheimer's as well because it is a complex disease with many contributing and potentially causal factors. As such, it may be difficult for a drug with a mechanism of action focused on a single part of the disease process – such as beta-amyloid plaques – to have a meaningful impact, especially in symptomatic patients.

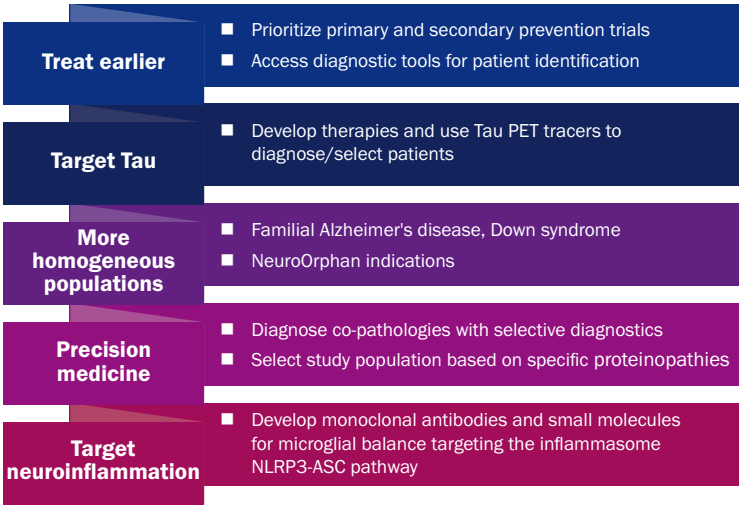
Even if one of the approaches shows significant benefit we are unlikely to find the silver bullet or cure, in the form of a therapy that targets one protein. It's more likely that multiple points of intervention are going to be required to completely reverse and cure the disease.

This means that precision medicine is probably going to be necessary to properly diagnose and treat neurodegenerative diseases, including Alzheimer's. It is for this reason that we are actively pursuing positron-emission tomography (PET) tracers against multiple relevant targets, including tau, alpha-synuclein and TDP-43, a major pathological protein in Alzheimer's disease and other diseases like amyotrophic lateral sclerosis

It is clear from the above that we at AC Immune believe it is imperative to look at all the possible approaches to treating Alzheimer's and other neurodegenerative diseases, because the prevalence of co-pathologies may indicate a need for different therapies at different stages, with combination therapies as the ultimate requirement. These could involve different interventions with disease modifiers at various stages of disease progression and may include anti-beta-amyloid and anti-tau immunotherapies or combinations of small and large molecules.

Tau is the next most advanced therapeutic strategy after beta-amyloid, so it makes sense that this approach is now coming into more focus. But there is a lot more behind the tau approach: beta-amyloid doesn't show a tight correlation with symptoms, but tau does, even at later stages of the disease. More specifically, tau pathology spreads with a characteristic spatiotemporal pattern throughout the brain, coinciding with both clinical symptoms and disease progression in Alzheimer's. Slowing the propagation of tau pathology may

A strategy for treating Alzheimer's disease



Source: AC Immune SA

therefore slow disease progression and reduce cognitive decline, and anti-tau therapies have shown promise in slowing the progression of tau pathology in animal models of tauopathy. So, there's a good possibility that tau may work in patients, even where beta-amyloid has little impact.

In short, tau may provide hope for effectively treating Alzheimer's patients who already have been diagnosed. Our partner Roche has recently initiated a Phase 2 trial with our anti-tau antibody, semorinemab, in moderate Alzheimer's patients and already had a separate Phase 2 trial running in mild Alzheimer's patients. We have also initiated a Phase 1 study of a small molecule tau inhibitor that will be studied in neurodegenerative diseases that are characterised by the presence of pathological tau aggregates under a collaboration with Eli Lilly and Company, and a Phase 1b/2a clinical trial to evaluate an anti-phospho-tau compound designed to reduce and prevent the spread and development of tau pathology. The goal is to treat early and moderate Alzheimer's.

Multiple approaches against Alzheimer's

As mentioned earlier, it is unlikely that any one approach will prove to be a magic bullet for Alzheimer's disease. Tau is a focus for our company but we have a number of other products which address other targets, and we believe that ultimately it will be some combination of these that will provide the answer.

A number of these products target beta-amyloid, notably crenezumab, which is being developed in partnership with Roche and had seemingly negative results in its two CREAD Phase 3 studies last year. In light of the aducanumab news, the Phase 3 crenezumab data now need to be reviewed and revisited. Our anti-amyloid beta vaccine, ACI-24, is in Phase 2 development in Alzheimer's following a successful Phase 1/2a study that showed promising safety, target engagement and trends of clinical efficacy. ACI-24 is also being developed for the treatment of Alzheimer's-like symptoms in people with Down syndrome, who are genetically predisposed to develop the disease earlier in life.

It is clear that Alzheimer's is a multi-target disease with a high level of other proteinopathies and co-pathologies. John Robinson from the group of John Trojanowski has recently published a study showing that Alzheimer's patients with a high degree of amyloid and tau pathologies show a high level of co-pathologies with up to 55% showing alpha-synuclein and up to 40% TDP-43. So alpha-synuclein and TDP-43 could play an important role in neurodegenerative diseases, including Alzheimer's, and are an important part of our research.

We have generated several antibodies with binding profiles to TDP-43 and we recently announced a research partnership with leading scientists at the University of Pennsylvania in the US focused on studying the pathological mechanisms of TDP-43 misfolding and aggregation. Our anti-alpha-synuclein antibody is in discovery in Parkinson's disease.

Pursuing precision medicine and combination therapy approaches, based on patients' specific proteinopathies, requires diagnostics to identify and track patients. Diagnostics have the potential to enable more precise patient characterisation and potentially more precise prediction of Alzheimer's, so they have a crucial role to play in our arsenal against the disease.

A fascinating study

I would like to sum up by bringing us back to where we started and the role of beta-amyloid in Alzheimer's disease, with an example of why so many people – not least myself – are so fascinated by and dedicated to fighting Alzheimer's and other neurodegenerative diseases.

The region of Antioquia in Colombia is home to the largest concentration in the world of people who carry a rare genetic mutation that makes them 100% certain to develop Alzheimer's disease. And as devastating as Alzheimer's is anywhere, this is a particularly cruel version – it strikes when people are in their mid-40s and leads to death about a decade later. It is a tragic situation and a substantial healthcare challenge in and of itself.

At the same time, it is also a perfect scientific laboratory and the centre of a multimillion-dollar US National Institutes of Health-backed study trying to find out for the first time whether Alzheimer's disease may be preventable, using AC Immune's crenezumab. The unique characteristics of the patient population make this a perfect example of our focus on testing in homogeneous populations. As such, it has the potential to help us overcome the issue of treating the disease too late, and whether it can even be prevented.

The first data from this landmark Alzheimer's Prevention Initiative trial are expected early in 2022. It could provide us with more information on the causes of Alzheimer's disease and how to prevent it than we have ever had before – and underline the importance of pursuing all possible approaches as we seek a solution to this public healthcare crisis.

This article was written by Prof Andrea Pfeifer, co-founder and CEO of AC Immune, a biotech company headquartered in Lausanne, Switzerland.