Research Strategy: Andrea Pfeifer

Disentangling neurodegenerative diseases

Alzheimer's disease is a complex condition for which we have yet to find a truly effective treatment. Notwithstanding the US approval of Aduhelm in June, there is still a lot to be learned about this disease and other neurodegenerative disorders. In an article published in *MedNous* in 2020, I explained how we at AC Immune are applying our knowledge and learnings from many years of research to explore a range of approaches that include antibodies, vaccines, small molecules, and diagnostics. We believe that this combination of approaches has the potential to diagnose, prevent, treat and possibly even cure these devastating diseases.

In this article, I update our strategy and explain how our recent acquisition of assets from the Austrian company Affiris AG advances our work across several diseases. Announced in July, the deal involves the purchase of Affiris' portfolio of therapeutics targeting alpha-synuclein (alpha-syn), notably Affiris' PD01 programme, a clinically validated active vaccine candidate for the treatment of Parkinson's disease. Parkinson's disease, the second most common neurodegenerative disease after Alzheimer's, affects over six million people worldwide. Our new asset, which is Phase 2 ready, will become the cornerstone of our approach for addressing Parkinson's, together with our alpha-syn positron emission tomography (PET) tracer to help with early diagnosis.

Therapeutic vaccination, aimed at clearing misfolded and aggregated proteins, represents one of several promising strategies that we have adopted to disrupt the debilitating path of neurodegenerative diseases. With PD01, we have added a third vaccine candidate to our pipeline and accelerated our Parkinson's disease programme. The other two are an anti-amyloid-beta vaccine and an anti-tau vaccine which are in clinical development (please see Table 1). The three vaccine candidates address misfolded-protein targets associated with both Alzheimer's and Parkinson's diseases. Through the continued development of our active vaccination programme, we hope to translate what has been done in infectious disease to neurodegeneration.

Precision medicine approach

Table 1 illustrates that diagnosis using PET tracers is an integral part of our strategy. Our precision medical approach begins with early disease detection using PET and state-of-the art tracer techniques that detect aggregated proteins. Using these technologies, it is possible to detect proteinopathies 10 to 20 years before the onset of clinical symptoms. For example, neurologists and psychiatrists currently diagnose Alzheimer's disease using a series of cognitive function tests. However, cognitive deficits are not quantifiable in patients until long after the pathogenesis begins. Using tracer techniques it is possible to identify people at risk based on the presence of misfolded proteins. This provides an opportunity to intervene much closer to the time of disease onset. Simply put, this is the best strategy for preserving a patient's quality of life since, once neurons are damaged and depleted, they cannot be replaced.

Though the precise cause of Parkinson's and Alzheimer's diseases remains elusive, the accumulation of misfolded versions of the alpha-syn and tau proteins seemingly contribute to the pathogenesis of these diseases. More specifically, the abnormal deposition of misfolded proteins leads to protein aggregation, eventually contributing to the formation of neurofibrillary tangles. Additionally, research published in *Reviews in the Neurosciences* in 2019 demonstrated that even before these tangles are formed, the misfolded proteins prove toxic to nerve cells. Misfolded tau contributes to the formation of amyloid plaques that are characteristic of Alzheimer's and in Parkinson's, altered conformations of alpha-syn feature prominently in Lewy bodies. Lewy bodies are a hallmark of the neuromotor disorder, and a form of dementia known as Lewy-body dementia. In turn, toxic conformational changes to each of these proteins serve as vaccination targets for two of the vaccines in our pipeline.

The third vaccine, PD01, generates a target-specific antibody response against pathological oligomeric alpha-syn to inhibit spreading as well as downstream neurodegeneration. This positions it ideally for prevention and early treatment and an ideal complement to our existing therapeutic small molecule and antibody candidates which also target pathologically misfolded alpha-syn at potentially different stages of the disease. These candidates have been derived from our small molecule platform Morphomer and our platform for generating conformation specific antibodies, SupraAntigen.

At the time of acquisition, Affiris had already demonstrated the safety of PD01. Normally, the alpha-syn protein regulates the trafficking of synaptic vesicles across the synaptic junction and subsequent neurotransmitter release, therefore, in its appropriately folded form, the protein is vital to a healthy functioning nervous system. To avoid targeting any healthy alpha-syn protein, PD01 sensitises the human immune system to detect a pathological, oligomeric form of alpha-syn. Affiris's use of an oligomeric form of alpha-syn – a protein comprised of repeating units of alpha-syn structures – stems from finding the repeating version of the protein in the tangled Lewy bodies associated with Parkinson's disease.

PD01 has successfully completed a randomised Phase 1 trial in 21 patients, the results of which were published in *The Lancet Neurology* in 2020. In this study, the anti-alpha-syn vaccine was safe and well tolerated over several years, resulting in a strong and boostable antibody response. Evidence of target engagement was also observed with a 50% reduction in pathological oligomeric alpha-syn in the CSF of patients treated with PD01. Importantly, the trial also showed a correlation between changes in pathological oligomeric alpha-syn and changes in Unified Parkinson's

Disease Rating Scale Score, which is indicative of a signal of clinical efficacy. These results suggest PD01 could be an industry-leading anti-alpha-syn vaccine.

PD01 provides an ideal complement to AC Immune's existing alpha-syn development pipeline because it helps to complete the spectrum of potential diagnostic and treatment modalities addressing this well characterised target. AC Immune's portfolio now includes a vaccine (PD01), a therapeutic anti-alpha-syn antibody, a small molecule aggregation inhibitor (Morphomer alpha-syn), and a first-in-class diagnostic imaging agent that detects a misfolded version of the alpha-syn protein.

AC Immune has two vaccines for Alzheimer's disease in Phase 2 targeting phospho-tau and amyloid-beta and reported highly encouraging readouts earlier this year. In collaboration with our partner Janssen Pharmaceuticals Inc, we have expanded a Phase 1b/2a trial for the phospho-tau vaccine candidate, ACI-35.030. Phospho tau is one of two identifiable, misfolded proteins that comprise amyloid plaques found in advanced Alzheimer's patients. The amyloid-beta targeting vaccine, ACI-24, is currently undergoing investigation in an open-label Phase 2 extension trial for Alzheimer's patients.

Thus, our extensive expertise in neurodegenerative diseases and vaccine development means that we are able to rapidly initiate a Phase 2 trial for PD01. After optimising the formulation of PD01, which is known as ACI-7104, we plan to conduct an adaptive, biomarker-based, Phase 2 trial in patients with idiopathic Parkinson's disease.

The Phase 2 study will include untreated patients and patients treated with Monoamine Oxidase Type-B (MAO-B) inhibitors. Physicians commonly prescribe MAO-inhibitors because the treatment may provide a modest improvement of the motor symptoms associated with the disease. All study participants will have demonstrated stable disease for greater than three months.

The design of the trial consists of two stages, with a seamless transition between the two. The first stage will evaluate a participant's initial dose-response to ACI-7104. These assays will focus on immunogenicity against alpha-syn and pathological alpha-syn species. Progression of motor and non-motor symptoms of Parkinson's disease will be monitored, together with digital imaging and fluid biomarkers.

Other therapeutic approaches

Other therapeutic approaches in the AC Immune pipeline include antibody therapeutics that target misfolded proteins. These include semorinemab (anti-tau), crenezumab (anti-amyloid-beta) and an anti-alpha-syn antibody therapy in preclinical development. Our pipeline also includes small molecule inhibitors. In 2018, we partnered with Eli Lilly and Company to advance the development of Morphomer tau aggregation inhibitors, including ACI-3024, a proprietary small molecule developed by our internal research team. This has completed a Phase 1 trial and is being further evaluated for efficacy in models of rare tauopathies. These are a group of rare neurodegenerative diseases pathologically defined by the presence of tau protein aggregates in the brain.

Key pathological, misfolded neurodegenerative proteins associated with amyloid-beta, tau, alpha-syn and TDP-43 all feature in the AC Immune pipeline because they are all toxic to individual neural cells and promote the formation of neurofibrillary tangles. Additionally, each of the severely debilitating neurodegenerative pathologies associated with the misfolding of these proteins does not exist in isolation; rather the path to pathogenesis demonstrates significant overlap.

Consequently, AC Immune leverages many years of invaluable cross-disciplinary knowledge and experience between different strategic treatment approaches, and diagnostic technologies to support one of the most comprehensive pipelines in the field of neurodegenerative diseases, strengthened by the acquisition of PD01.

Through the development of this pipeline and adopting a personalised approach to treatment, we endeavour to move the treatment of neurodegenerative disorders into the early stages of disease. The prevention of neurodegeneration is the eventual therapeutic goal. Just as Covid-19 mobilised nations to fight a virus, we hope that the prevalence of neurodegenerative disorders will bring people together to move the research and treatment options forward.

Table 1. AC Immune pipeline

Target	Product candidate	Indication	Development
Tau	**ACI-35.030** (*anti-p Tau vaccine*)	AD[1] treatment	Phase 1b/2a
	Semorinemab (*anti-Tau antibody*)	AD treatment (*mild-to-moderate*)[2]	Phase 2
	Morphomer Tau aggregation inhibitor	Rare Tauopathies (ACI-3024)	Preclinical
		AD treatment	Preclinical
	Tau-PET[3] tracer	AD diagnostic	Phase 2
		PSP[4] diagnostic	Phase 1
Abeta	**Crenezumab** (*anti-Abeta antibody*)	AD prevention[5]	Phase 2
	ACI-24 (*anti-Abeta vaccine*)	AD treatment (*Down syndrome*[6])	Phase 1b
		AD treatment	Phase 2
a-syn[7]	**ACI-7104** (*anti-a-syn vaccine*)	PD[8], a-synucleinopathies	Phase 1
	A-syn-PET tracer	PD, a-synucleinopathies	First-in-Human

(1) Alzheimer's disease; (2) Open label extension study is ongoing; (3) Positron emission tomography; (4) Progressive supranuclear palsy; (5) Prevention trial API-ADAD in Colombia; (6) Down syndrome-related Alzheimer's disease; (7) alpha-synuclein; (8) Parkinson's disease

For further information please see https://ir.acimmune.com/events-and-presentations/investor-presentation

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