

# AC Immune's Quest To Make Alzheimer's Disease Preventable

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The number of people with dementia, a progressive neurologic disorder that causes the brain to shrink and brain cells to die, is predicted to more than triple to 152 million by 2050. The cost of caring for these patients is expected to double to \$2 trillion in the next eight years alone.

But what if it were possible to detect the biomarkers of Alzheimer's and other neurodegenerative diseases through a simple test before people developed symptoms and avoid their onset through drugs or a vaccine?

AC Immune, a Lausanne, Switzerland-based biotech company led by Andrea Pfeifer, aims to do just that. By pairing cutting-edge diagnostics with highly selective therapeutic agents, the company wants to shift the treatment paradigm of neurodegenerative disease towards earlier diagnosis and disease prevention.

"I feel like we are at a crossroads in neuroscience," says Pfeifer, who has a PhD in toxicology and cancer research. "We now have the tools that were lacking" to make precision medicine, an emerging practice that uses an individual's genetic and biomarker data to diagnose early – before symptoms set in – and guide prevention and treatment of

disease, a reality, she says. In the coming weeks the company expects to announce the results of a nine-year-long clinical trial that it hopes will prove that Alzheimer's disease is preventable.

Pfeifer, who will receive the Aenne Burda Award for Creative Leadership at the DLD conference in Munich on May 21, has devoted her entire career to improving human health. While working at the U.S.'s National Cancer Institute (NCI), Laboratory of Human Carcinogenesis, she developed the first human cell lines used as models for studying lung and liver cancer which today are licensed for applications ranging from medical research to drug testing; while heading food conglomerate Nestlé's global research she transformed the company's research direction from chemistry to precision nutrition based on biology and, for the past 19 years as CEO of AC Immune, she has overseen the development of multiple investigational vaccines, antibodies, small molecule drugs and diagnostic agents that could ultimately make the difference in how diseases such as Alzheimer's and Parkinson's are diagnosed, treated and potentially even cured.

AC Immune, which was named a World Economic Forum pioneer in 2009 and went public in 2016 on NASDAQ, currently has ten therapeutic and three diagnostic candidates in its pipeline. Six are currently in Phase 2 clinical trials. Along the way AC Immune has had to overcome major setbacks and learned some valuable lessons about innovating for impact that could be helpful to other companies.

## **Impacting Human Health**

Pfeifer began her scientific career focusing on cancer research and, in 1984 joined the U.S.'s National Cancer Institute as a postdoctoral fellow. Her work focused on trying to find the mutations that caused lung cancer. Frustrated by the long lead times in developing cancer treatments, she returned to Europe, joined Nestlé, and began focusing on how to improve people's health through food. She became head of Nestlé Global Research and brought her knowledge of molecular diagnostics to the food industry. Over the next 13 years she would transform the company's research direction from chemistry to precision nutrition based on biology. Pfeifer's team, for example, sequenced the genome of the bifidus bacterium, resulting in the first probiotic yogurt. "I was helping people live better and longer but it was not enough," says Pfeifer. "It was not the kind of hard-core science and contribution that I wanted."

Then she met the co-founders of her future company: Nobel laureate Jean-Marie Lehn, Claude Nicolau, Fred Van Leuven, and the late NIH scientist and Lasker Award winner, Roscoe Brady. The four scientists approached Pfeifer with a technology that had the capability to target plaques and tangles in the brain caused by misfolding protein. The researchers were mainly studying prions, proteins that can trigger neighboring proteins to misfold abnormally and spread in a virus-like manner throughout the brain. The scientists recognized the same mechanism of action in Alzheimer disease, Pfeifer saw a huge unmet need and an opportunity to improve millions of lives.

“If working on cancer was frustrating, targeting this area – Alzheimer’s – with new technology and new vision seemed very promising,” she says. In January 2003 she left Nestlé and returned to her roots in medical research to more closely examine how errors in the ways proteins fold contribute to hundreds of diseases, including Alzheimer’s and Parkinson’s .

AC Immune’s technology platform evolved to address two key problems. First, the human body does not make antibodies against misfolded proteins because, although pathogenic, misfolded proteins are not recognized as foreign invaders in the body and escape immune system detection. Secondly, the difference between a normal protein and a pathological protein is only related to a change in the way the protein structure is configured, making drug specificity for misfolded proteins difficult to achieve.

To address the first problem AC immune developed a drug discovery technology, dubbed SupraAntigen, to harness the immune system to make immunotherapies and vaccines capable of selectively targeting proteins in specific conformations, i.e. pathological misfolded proteins. The second problem is addressed with a related technology platform, called Morphomer, that can generate small molecules which similarly bind only to the targeted proteins when they are misfolded.

## **Lessons Learned**

In the 19 years she has led AC Immune Pfeifer says she has learned some valuable lessons. Among them: the importance of striking the right partnerships and how establishing the right culture can help a company bounce back from setbacks.

Not long after the company’s launch in 2003, Genentech, an American biotechnology corporation which became a subsidiary of Roche in 2009, approached AC Immune about collaborating on an antibody. “I almost said no,” says Pfeifer. “We were a very small company.” Nonetheless a deal was struck relatively quickly. Working with a professional partner turned out to be a game-changer, says Pfeifer. “Making antibodies is an art and turning them into products is even more of an art,” she says. “They were one of the first biotechnology companies and knew everything about antibodies, and, at that time, we knew almost nothing. If we had not struck that early partnership, I don’t think we would be the same company today.”

In the early days AC Immune did not have enough money to pay big salaries so its scientists tended to be right out of school. “Our employees were very young, and they got to learn from the best in the world,” she says.

The company soon signed a second deal with Genentech and later secured strategic partnerships with two of the world’s leading pharmaceutical companies, Eli Lilly and Company, and Janssen Pharmaceuticals, which is Johnson & Johnson’s therapeutics arm.

The early partnerships helped the company share the risk with its partners, accelerate the partnered products’ development, and allowed it to gain substantial funds to advance its proprietary programs, all while lining up more than \$3 billion in potential milestone

payments, Pfeifer says. This meant that it did not need to raise money from outside investors until it went public in 2016.

It has not, however, been all smooth sailing. In 2019 the company experienced a major setback when a phase three clinical trial failed. “I went into mourning for two days – not more – and then sat down and said ‘Ok, why did this happen?’ We did some very strong analysis and developed a hypothesis.” The company realized it needed biomarkers in order to study its therapeutic candidates in more homogenous populations and moved to solve both issues.

Due to careful planning, AC Immune had enough money in the bank to absorb the setback and did not have to lay off any staff, says Pfeifer. “I am always very cautious when it comes to money, because, if you don’t have it you lose the power to make decisions,” she says. In addition to funding what has kept the company going comes down to three things: having a clear five-year-strategy that is upgraded every year; being very selective in the people it hires, to ensure it produces top-level science; and instilling a company culture based on purpose and hope, she says.

Pfeifer, who helped pioneer the way for women in biotech, says she is particularly proud of the fact that 60% of AC Immune scientists are women, way above the industry average. “The women are all top in their field,” she adds.

“When you have a goal based on societal impact it is so easy to attract talent and align your team,” she says. “Even if things are hard there is always the hope in front of you that one day you will be able to say: ‘I contributed a medicine that is making a huge difference in people’s lives.’”

### **Potentially Game-Changing New Developments**

The road to finding a treatment for Alzheimer’s has been fraught with difficulties. The largest drug companies and government research organization have spent billions trying to find a cure with little to show for it. Last June the U.S. Food and Drug Administration approved aducanumab, sold under the brand name Aduhelm, in a controversial decision. It was the first new therapy for Alzheimer’s disease in nearly two decades, and some analysts predicted it would be a multi-billion-dollar seller. But inconclusive clinical trials and a vote against approval by the FDA’s expert panel have cast a shadow over the drug.

Meanwhile other drug companies have had disappointing results when testing their treatments in The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), an adaptive platform trial testing multiple drugs to slow or prevent the progression of Alzheimer’s disease in a genetic patient population.

Pfeifer sees these developments as proof that there is no silver bullet. Such a wide range of factors are involved in Alzheimer’s that she argues that precision medicine and combination therapy – much like in cancer – is probably going to be necessary to properly diagnose and treat neurodegenerative diseases.

To be able to prevent a disease, first you need to be able to identify the specific pathologies causing it. To that end AC Immune is actively pursuing positron-emission topography (PET) tracers against multiple targets, including tau and alpha-synuclein, which is also present in Parkinson's disease, and TDP-43, another hallmark protein pathology observed in Alzheimer's disease as well as other neurodegenerative diseases like amyotrophic lateral sclerosis (ALS).

The ultimate goal is for people at risk of a disease to be able to get tested regularly and be given preventative treatment before symptoms emerge.

In March of this year, AC Immune announced a major step forward for individuals living with multiple system atrophy (MSA) – a related disease that, like Parkinson's, is characterized by misfolding and clumping of alpha-synuclein in the brain. In its [press release](#), AC Immune said their PET tracer, which was developed with the support of the Michael J. Fox Foundation, can identify people with MSA from control volunteers, people with Parkinson's disease and people with Lewy body dementia. This has been impossible with current technologies and clinicians often struggle to properly diagnose MSA patients – which is important because treatment strategies for each of these diseases are different. If validated, AC Immune said its new tracer should be a powerful steppingstone toward a critical alpha-synuclein diagnostic tool in Parkinson's disease patients as well as for MSA.

“It is a major, major achievement,” says Pfeifer. “No one else wanted to spend the time and money to do this. We have been fighting for many years to develop diagnostic imaging so we can create better clinical trials and treat patients early before the disease kills their neurons.”

At the same time AC Immune is working on potential preventative treatments targeting all four key proteins involved in Alzheimer's disease. “We believe that ultimately it will be some combination of these that will provide the answer,” Pfeifer says.

A number of AC Immune products target the beta-amyloid protein. Genentech is testing whether one of them, called crenezumab, can prevent the onset of Alzheimer's in a high-risk population in the Aburrá Valley of Columbia who are genetically predisposed to develop Alzheimer's disease in their 40s, and often die in their 50s. If the treatment works, it would be the first to show how Alzheimer's might be prevented. Results are expected in the coming weeks.

Crenezumab is the first antibody tested in a setting where all patients from this large Columbian genetic cohort are asymptomatic at the start of the trial, says Pfeifer. Up until then it was not possible to test developed compounds on healthy people. AC Immune's compound was an exception, she says, because it has almost no side effects.

There are 252 people in the trial. All are carrying the mutation but had not yet begun to show signs of the disease at the onset of the trial. If after at least five years most are still healthy “it means we really have a chance to prevent Alzheimer's and give people hope,” says Pfeifer. “I am praying this study is positive. It will bring my dream a little closer.”

If a fully humanized monoclonal antibody like crenezumab proves effective in preventing Alzheimer's disease why work on vaccines? The cost of rolling out preventative drug treatments globally would be prohibitive, says Pfeifer. Vaccines could be developed for a fraction of the cost and administered yearly, as opposed to monthly antibody treatments, and unlike monoclonal antibodies, vaccines can be produced anywhere in the world. "If you really want to manage the disease globally then you need a vaccine," she says.

COVID has helped ease acceptance of vaccines, says Pfeifer. The pandemic "really showed global vaccination is beneficial and effective and it saved so many lives," she says. "I think it will help us a lot in making an Alzheimer's vaccine available."

### **Prevention Is Within Reach**

Pfeifer says she is convinced that prevention of Alzheimer's is within reach. "My days are very, very long and in my down moments I sometimes think there are easier ways to make a living," says Pfeifer. "But I am on this mission with my team and, even if it is sometimes hard, we have to complete it."

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