Interviews

Two individuals at the forefront of innovation in medicine are Andrea Pfeifer, who is leading the way in active immunotherapy for Alzheimer's disease, and David Resühr, the brain behind several 3D-printed inventions that are transforming medical practice. They discuss their extensive clinical and research careers, and highlight advances in the field of medicine that will transform healthcare as we know it.

Featuring: Andrea Pfeifer & David Resühr

Andrea Pfeifer

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Q1 You began your career with a PhD in Toxicology Cancer Research and later pursued post-doctoral work in Molecular Carcinogenesis, before joining the food and beverage company Nestlé as Head of the Research Centre. How did you transition from a purely scientific background into the business world?

I am a dedicated scientist, and this journey began early on. When I was 6 years old, I told my parents I wanted to become a scientist, not fully knowing what I was talking about, but nothing changed my determination to actually execute this. And so, I started my career in cancer research, motivated by a family connection and a desire to find a cure for certain cancers, especially the ones still missing a cure.

I became involved in looking at precision medicine in cancer when I joined the National Cancer Institute (NCI). It was a pivotal time when people found out that not all cancers are the same, but that each cancer is different and has a different cause. Identifying the molecular basis of a cancer allows for the use of precision medicine. I remember the HER2 team, which developed the first breast cancer therapy for women using this new principle of targeting specific mutations in these cancers. In the Phase II study, women with a particular mutation were selected for the study, and the results were highly positive. This was the beginning of modern molecular-based carcinogenic cancer research, teaching me that you really have to get to the root cause of the disease and recognise that each person requires a different approach with precision medicine.

This experience influenced the development of our company, AC Immune. When clinical trials in Alzheimer's disease came back negative, I realised that we had to take the same approach as in cancer, look into the patients, and see what the underlying causes are. However, in Alzheimer's disease, the focus shifts from DNA to proteins, and identifying these is key. This is why, at AC

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Immune, there is always a parallel development of diagnostics and therapies around the same target.

The impact of my cancer research had a significant impact on the company, and on the field for that matter. My transition to Nestlé came from an interesting opportunity, which was to establish Life Sciences in Nestlé. Nestlé had basically no presence in this area, and I was able to run bioscience, plant science, and microbiology. I could really bring life sciences into the food industry, which I thought was a very interesting aspect. My time at Nestlé was wonderful, I learned so much, but I was really missing the hardcore science. I felt that my scientific experience, combined with my managerial and leadership skills, could probably do something good in the startup scene, a scene where there basically wasn't a single woman in Switzerland at the time.

When approached by the scientific founders of AC Immune, I was fascinated by the technology. I thought, 'This is something I should be doing.' We started from zero, no business plan, no product, no money, and brought it to where we are today, one of the leaders in neuroscience. It was quite a journey. It was very difficult in neuroscience, unlike with cancer where you can measure the mutated DNA, and you know exactly what possible drug you are looking for. Whereas, in neuroscience, there was no way to look into the brain, we couldn't actually do precision medicine. We were pioneers in developing tracers for tau, alpha synuclein, and TDP-43, enabling us to look into the brain of living patients for the first time. Now, we can perform precision medicine in neuroscience. Alzheimer's disease involves four key proteins: amyloid beta, which forms plaques; tau, which aggregates as tangles and TDP-43, also found in amyotrophic lateral sclerosis (ALS); and alpha-synuclein, the Lewy body present in Parkinson's disease. Each patient has different amounts of these proteins. So, if you want to treat beyond the 30% benefit that we see today, you have to treat the patient according to the underlying pathology. It's simple but complicated at the same time, and it was difficult to do at the start, because we just didn't have the tools.

Q2 As the head of Nestlé Global Research, you applied your expertise in molecular diagnostics to the food industry. Can you tell us about the process and significance of your team sequencing the genome of *Bifidobacterium*, which contributed to the creation of the first probiotic yoghurt?

We launched one of the first products involving the microbiome, which we called probiotics at the time. By the way, if you ask me what the future of the company will be, it's definitely in the microbiome, because my heart is still with it. It has a huge impact, even on brain diseases. There are now copious amounts of clinical data coming out that show that you can inhibit inflammation, prevent osteoporosis, enhance iron uptake, and normalise all gastrointestinal functions. I actually take probiotics now myself, and I can assure you it works, I feel so much better!

What is particularly new is the direct link between the microbiome and the brain. By eliminating bad bacteria in the intestine that produce proteins that go into the brain, you can inhibit conditions like Parkinson's disease, as shown in several ongoing clinical studies. What people always forget, and this is a very important aspect of Alzheimer's disease, is that there is a big lifestyle component. For example, the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is an important study demonstrating that proper lifestyle choices like exercise, eating properly, and maintaining a healthy weight, can reduce the risk of dementia by 40%. And if you combine this with the microbiome, I think you will have much bigger effects.

While we hope a vaccine to prevent Alzheimer's disease will be available soon, there are other preventative measures people can take. I want to just encourage everyone reading this article, that yes, medication is being developed, yes, diagnostics are becoming available, but there are things that you can already do today.

Q3 In 2003, you co-founded AC Immune, a biopharmaceutical company focused on advancing research in Alzheimer's disease. What inspired you to concentrate on neurodegenerative diseases, and what are the primary goals that AC Immune aims to achieve?

I can sum it up in one sentence: our goal is to prevent Alzheimer's disease worldwide. This is partly a dream, but it's also a matter of determination, because, as you know, we are working on vaccines. Today, thanks to improved diagnostics, in the clinical research setting, we can identify people at risk of Alzheimer's disease up to 20 years before symptoms occur. This provides an opportunity to make lifestyle changes and, potentially, also get a vaccine. If this vaccine, or what we call active immunotherapy, can actually prevent these proteins from aggregating in the brain, accumulating, and killing the neurons, then we can truly speak about prevention. In neurology, prevention is even more important because, unlike other tissues, neurons cannot be replaced once they're damaged by plaques or tangles. The brain doesn't regenerate in this way, so once the neurons are lost, they're gone for good. This is why it's essential to intervene at the preclinical stage, presymptomatic stage. To identify the people at risk and give them active immunotherapy.

Our ultimate goal is to have an active immunotherapy available by 2030 to eliminate this disease from the world.

Q4 As the CEO of AC Immune, how has the company evolved under your leadership, and what are the most significant contributions it has made to Alzheimer's disease research and treatment?

I think there are two components: one is how the company evolved, and the other is how the field evolved. One of the major changes since we started the company is that diagnostics have become available. In particular, over the last 2 years, blood biomarkers are no longer just a dream. You can actually get your blood tested for risk factors, like you do for cholesterol. The idea of having an active immunotherapy, eventually, like you take statins, is becoming a reality. Our company has made

major contributions to the imaging field by making these biomarkers available. We now understand that early treatment is crucial because you cannot reverse damage to dead neurons. Currently, we treat conditions much too late. Today, we understand that inhibiting plaque formation is one way to at least delay the disease, but we have to go one step further. Our goal should be prevention so that we can keep the brain intact.

In a way, our company evolved alongside the field, and we've made major contributions to diagnostics and active immunotherapy. We were pioneers in many respects, despite having faced setbacks. One thing I'm particularly proud of is that, despite the challenges, including the difficult situation that the biotech industry is in right now, we have shown constant growth and have never laid off any employees. We are a very conservative company. So, despite being in a very challenging field and facing setbacks, both within the field and for AC Immune, we have continued to develop and advance the science. When it comes to active immunotherapy, we are leaders today.

The Alzheimer's Prevention Initiative (API) study was the first prevention study in the world at the time. We didn't have biomarkers back then, so the only way to conduct a prevention study was to use a genetic population. This was done with a Colombian population, and unfortunately, the study was slightly underpowered, but it showed positive trends across all biomarkers. We started this study in 2013, and it wasn't until 2019 that imaging agents became available, showing just how far ahead we are. Last year, we announced the first prevention study in Alzheimer's disease with an anti-tau vaccine. This represents the second phase, where we can identify people who have the pathology but not yet the disease. We're working with presymptomatic individuals, which is called secondary prevention. Unlike our first study, this is not based on genetics.

So, we conducted the first API study and are now doing the first prevention study with active immunotherapy. Another study we have undertaken is a Phase II study of an active immunotherapy against amyloid plaques.

Additionally, we have an ongoing study on anti-alpha-synuclein targeting against Parkinson's disease. It's an active Parkinson's immunotherapy. All of this runs in parallel with our diagnostic tools, such as imaging agents, which will enable us to identify patients, monitor clinical responses, and more. We also have a preclinical pipeline, but I think the three active immunotherapies, combined with our clinical imaging agents, are our most significant contributions to the field.

Q5 How do you envision the field, and AC Immune, evolving?

Based on where we are today, I really believe that precision medicine has become a reality. This means that you'll soon be able to visit a normal doctor and have your amyloid beta or phospho-tau levels measured, and potentially gain access to preventive therapy. I expect this to become a reality in the next 5–10 years. I've also mentioned that Alzheimer's disease is a disease of at least four different targets, so I think that combination therapy is essential.

One aspect that is certainly adding to the whole story is inflammation. We know that inflammation plays a role in all different neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Therefore, I think managing inflammation will likely be a major factor in combination therapy. Lastly, nutrition, including the impact of the microbiome, could also make an impact alongside these therapies.

Q6 You are a member of the CEO Initiative (CEOi) on Alzheimer's disease. Could you share the key findings from the recently published paper, 'The global CEO initiative on Alzheimer's disease performance recommendations for blood-based biomarker tests'?

The CEO Initiative stems from my long-time collaboration with George Vradenburg, who is a major figure in the USA and in Alzheimer's disease research. After his mother-in-law died of Alzheimer's disease, he and his wife decided to take action, leading to the creation of UsAgainstAlzheimer's. I chose to represent the European side of this effort, helping to establish a global initiative that brings together major leaders. It's not just CEOs of companies, but regulatory leaders, the FDA, the FDA commissioner, the European Medicines Agency (EMA), and medical commissioners. The idea is to bring them all together, but in a relaxed situation where we really can discuss the issues, such as how we can advance the field, or why existing treatments aren't sufficient. Many governments and European communities are represented, making it a platform to discuss what needs to happen globally in our field.

The initiative started in Berlin, but I felt Lausanne was an ideal location, and now everyone is happy to gather in Lausanne once a year. This year marks Lausanne 11. One significant topic has been blood biomarkers, where our group of experts worked together to define what these biomarkers need to fulfil in order to be accepted as a primary or secondary diagnostic. For instance, they defined that, as a primary diagnostic, a biomarker should have 90% sensitivity and 85% specificity, among other criteria. This serves as a guideline for developing new biomarkers and also as a foundation for advising the FDA and EMA on how to use such biomarkers in practice.

This year, we'll have the opportunity to speak with the head of the EMA, who will be attending Lausanne 11. This offers a chance to potentially influence changes in Europe, especially regarding drugs that have been approved but are not yet fully meeting our expectations. It's a first step, and we need to make sure that they become available for people.

Q7 Looking ahead, how do you envision the landscape of Alzheimer's disease biomarker tests evolving?

We conduct a lot of validation tests for these biomarkers. In particular, for phospho-tau 217, the sensitivity and specificity are both above 90%, depending on the specific test. I think that, soon, people will be able to go to a doctor and get one of these blood tests done and we canm identify those at risk. At Lausanne 11, we will also be discussing the use of active immunotherapy and what needs to be done to make it globally available. This is a subject we must address now because it's a lengthy process to engage with governments and secure all the necessary manufacturing and distribution support.

The goal is to have therapies that can be administered before symptoms begin, as long as they are safe and effective. This is really the direction the field is moving toward, with a strong focus on prevention. We call it 'precision prevention', because while we aim for prevention, we want to do so using a precise, biomarker-based approach.

Q8 You have received numerous accolades, including the BioAlps Prize 2013, being named one of the top 10 women in biotech by Fierce Biotech, and one of the 300 most influential personalities in Switzerland. What advice do you have for young women hoping to start a career in biotechnology and medicine?

I consider this an achievement of AC Immune, that we are one of the few Swiss companies that has women on every level. I mean, some of the top scientists are women including both the CSO and the CMO. When we started the company, we had no money, we had nobody. We developed all of these very talented women in AC Immune, and today they are some of the world leaders in Alzheimer's disease research, running plenary sessions of 4,000 people. I'm very proud of it. And something I'm equally concerned about is how we can enhance the participation of young women. How can we stimulate and motivate young women to do this hard job?

When I received the Swiss Economic Forum Prize in 2021, I dedicated the prize to young women, to try and encourage them to take this as an example and go for it. I think this part is

very important, to show that it can be done, and that we're doing it with a lot of success. But it's not enough, a lot more needs to be done. In many meetings, I'm still in the only female CEO, it still happens to me. I never really wanted to have this sort of role, I never did in Nestlé, but you automatically get it whether you want it or not. Actually, to some of my young leaders here, I said to be aware that this is pretty hard work. So, I think giving a real example and encouraging them, and providing them with an environment, allows this to happen. When I'm asked, what should we do? I answer that they should believe in themselves. They should believe that they can do it, that they can do an equally good job, maybe even a better job, and that we need them. We need their contribution. We need their experience, but also their social contribution, their sensitivity in business, and we need their input. It's a pleasure for me to see how it can happen. But are we there? Not at all.

Q9 You have over 200 papers and abstracts published in leading scientific journals. Other than Alzheimer's disease, do you have plans to focus on other areas of medicine in the future?

The microbiome is a big one. It's very high on my list. Another one is to use precision medicine. Precision medicine, of course, applies to many areas of medicine. So, that's certainly one of the aspects I will always keep in mind. Developing women for business is another aspect, it's not a scientific paper, but it's a personal objective. Regarding ALS you will certainly see some activities from AC Immune, because of our imaging agent. Until very recently, diagnosing ALS could take up to 2 years. Having an imaging agent that can identify the relevant protein, which is, in this case, TDP-43 in the brain, is super important.

Last, but not least, there is a certain cross-reactivity of inflammation that is a part of all neurodegenerative diseases. Inflammation is also a significant factor in obesity, so some of the pathways and therapies that work for neurodegenerative diseases might also work in obesity. We are currently investigating one of these compounds. While I would hate for AC Immune to be overly credited for obesity, it is a possibility.

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