Lars Nieba – CEO, Engimmune

We have prioritized understanding the market potential and the patient populations we are targeting. In particular, our work in precision oncology and especially precision immunology has resonated well with the market

05.11.2024

Tags: Switzerland, Europe, Engimmune, CAR-T, Biotech

Lars Nieba PhD, CEO of Engimmune, shares insights into the company's innovative approach to T-cell therapies and its strategic direction as it prepares for its Series A funding round. Nieba discusses the promising therapeutic areas Engimmune is targeting—particularly liver cancer and immunology—and the company's unique technology that harnesses soluble T-cell receptors. He also touches on the challenges for Swiss and European biotechs to keep up with their US counterparts.

You joined the company less than two years ago. Can you tell us more about your background and what brought you to EngImmune?

I studied biochemistry in Freiburg and then moved to Munich and Zurich to work with a professor named Andreas Plückthun, who is the co-founder of Morphosys—a German biotech company. It was during this time that I first became connected to the biotech industry, which led me to choose a career in this field instead of pursuing academia. I then was involved in building a company called Cytos Biotechnology in Switzerland, which was a fascinating experience. At that time, the venture capital landscape was not as developed as it is today, and I wanted to gain a better understanding of the financial aspects of the industry. To do that, I completed my executive MBA at the University of St. Gallen here in Switzerland.

After that, I joined Roche, where I spent about 15 years in various positions, gaining experience in both business development and technical development, as well as clinical supply and clinical operations. This provided me with a broad overview of the industry. I then went on to work at Bayer in Switzerland, focusing on their biologics portfolio, where I led the development of a prefilled syringe for one of their major products.

Eventually, I wanted to return to biotech and became the CEO and CTO of a company in Oslo called Nordic Nanovector that was involved in the radiotherapeutics space. Unfortunately, the clinical results did not meet our expectations, and the venture did not succeed. I then had the opportunity to join Engimmune during a crucial growth phase, where I could help develop strategies to move the company forward.

Can you provide a brief overview of Engimmune's history and its core mission?

Engimmune began as a spin-off from ETH Zurich, founded by Rodrigo Vazquez-Lombardi and Sai Reddy, a professor at ETH. Rodrigo had been a postdoc in Sai's lab, and together, they focused on the potential TCRs and how powerful they could be, particularly in cellular therapies. TCRs offer a significant advantage because, in essence, the body has TCRs for almost every peptide, whether it is related to cancer or autoimmune diseases like type 1 diabetes. The key challenge is identifying and activating the right TCRs to fight these conditions. We have made considerable progress in this area.

Lombardi and Reddy worked on engineering what we call TCR-T cells. However, the main challenges with cellular therapies is that they are difficult to develop and extremely expensive, especially when dealing with autologous cells, which require a very complex manufacturing process. From the start, they aimed to find ways to improve this process.

When I joined the team, we focused on protein-based T-cell engagers. This would help solve several issues since it allows for off-the-shelf usage, adds versatility in molecule design, and makes manufacturing much easier. However, the challenge with soluble TCRs is the need for strong binding. TCRs naturally bind quite weakly, at a micromolar level, which is not strong enough for a soluble version. Since TCRs are monovalent, with only one binding site, and the MHC molecules they target are sparsely distributed on cell surfaces, we had to enhance their binding strength dramatically—by a factor of one million, down to picomolar levels. Achieving this level of improvement is not easy, and we also had to ensure that enhancing the binding did not result in cross-reactivity to healthy tissues.

This is where EngImmune's innovation, rooted in the work from Lombardi and Reddy's lab, came into play, we combine protein engineering with AI to develop next-generation therapies. Importantly, we generate our own data in the lab, which we feed into machine learning algorithms. This helps us ask, "What would a better binder look like?" The results from AI often outperform what we can achieve in the lab, and through iterative cycles, we learn which residues to modify for improved binding. Today, we have achieved picomolar binding without any cross-reactivity.

Additionally, TCRs are naturally large and somewhat unstable molecules. By identifying stabilizing mutations, we have been able to enhance their stability, which has allowed us to fully establish our platform and technologies. Now, we are well-positioned to focus on the development of more promising therapies in the future.

What therapeutic areas is Engimmune focused on and could you share more details about the pipeline you are developing?

We have chosen to focus on two main therapeutic areas. The first is liver cancer, which is the fourth leading cause of cancer-related deaths worldwide and has a high unmet need. Liver cancer is considered a "cold" cancer, meaning it does not respond as well to immunotherapy. Our approach is to overcome so-called T-cell exhaustion, a state where T cells, after being exposed to chemotherapy or other treatments, become ineffective at attacking cancer cells. We are working on strategies to re-engage these T cells so they can be better activated and kill cancer cells, and we are seeing promising progress.

The second area we are focusing on is immunology, particularly skin diseases. What is exciting here is that TCRs can also play a role beyond oncology. We are applying a similar concept, but instead of killing cells, we aim to suppress inflammation, which is crucial in autoimmune and inflammatory diseases.

In terms of our pipeline, ENGI-002 is our lead candidate for lung cancer, while ENGI-003 is being developed for liver cancer. The lung cancer therapy is particularly promising because it is only expressed in cancerous tissue, making it highly targeted. However, our liver cancer candidate is perhaps the most innovative as it addresses T-cell exhaustion, which is a significant barrier in treating this type of cancer.

What is even more groundbreaking is how we are now exploring TCRs in immunology. Traditionally, TCRs have been used in oncology, but we saw potential in using them to target immune-related

diseases. By making the TCRs soluble, we are able to create more flexible T-cell engagers. In oncology, we use this technology to kill cancer cells, while in immunology, we aim to suppress unwanted immune responses. This versatility is one of the key strengths of our platform, and it is allowing us to expand into new disease areas. We believe this is a real breakthrough for our technology.

How does your approach to T-cell therapies differ from existing solutions, particularly in addressing the unmet needs of patients?

In oncology, one of the key limitations with traditional antibody-based therapies is that they can only target antigens on the surface of cells, which represents just about 10 percent of the human proteome. In contrast, TCRs are designed to recognize peptide-MHC complexes, where the peptides are processed internally within the cell and then presented on the cell surface. This gives us access to intracellular antigens, which account for 90 percent of the human proteome, opening up a whole new range of targets that were previously inaccessible. This is one of the major advantages of our approach.

Another important aspect is that peptide-MHC complexes are not highly expressed on the surface of cells, typically with only 50 to 100 copies present, compared to antibody targets, which can have thousands of copies. At first glance, this lower expression might seem like a disadvantage. However, in the case of cold tumors, which are difficult to infiltrate because they have fewer blood vessels, this actually becomes an advantage. With fewer binding sites, our T-cell engagers are more likely to penetrate deeper into the tumor and remain there longer. This increases the likelihood of attracting T-cells to the site, which can then effectively kill the tumor cells.

In the field of immunology today, while there are effective drugs available, many treatments are still systemic, similar to where oncology was 20 years ago. Early oncology treatments like chemotherapy were broad and often toxic, and the same holds true for some of the first biologics in immunology, which can cause systemic side effects. What we aim to do with our TCR-based therapies is bring a level of precision that drastically reduces side effects while targeting specific pathways. This is why we are not just focused on precision oncology but also pioneering precision immunology, a very new and exciting field.

Funding is critical for any biotech company. Could you provide insight into your current funding stage and the strategies you envision to further advance Engimmune's pipeline?

We are fortunate to have two strong investors backing us: Novo Holdings from Denmark and Pureos Bioventures, based here in Switzerland. Novo is a significant player globally and helps us open doors internationally, while Pureos has been instrumental in establishing connections within the Swiss ecosystem. The combination of these two investors provides a well-rounded support network, both globally and locally.

We completed our seed round about two years ago, and we are now preparing for our Series A funding round, where we will be reaching out to global investors. Having compelling science is essential, no doubt, but you also need to present products that clearly demonstrate their potential. While the science is the foundation, it is the viability and promise of the products that ultimately attract investors and secure funding.

When selecting targets for development, we always keep market potential in mind. If there is no significant market opportunity, even the most compelling science may struggle to gain investor confidence. It is crucial to focus on areas with a high unmet need, evaluate the competitive landscape, and determine whether our technology can achieve the necessary outcomes. This approach not only strengthens our pitch to investors but also ensures we are developing therapies that align with what pharma companies are looking for. It is about balancing groundbreaking science with market viability to ensure long-term success.

Although you have not officially launched Series A funding, you have been engaging with investors and stakeholders. How has Engimmune been received by VCs and other investors in today's cautious financial environment?

The key word here is technology. There is certainly a lot of innovation out there, and scientifically, it is essential to clearly explain how your technology stands apart from others. However, it is not just about having a unique approach—you also need to demonstrate whether the final outcomes are truly different when addressing the same patient populations.

Over the past two to three years, there has been a decline in risk capital, which has forced us to sharpen our focus. It is no longer enough to have just compelling science. One key piece of feedback we have received is the importance of thinking carefully about what truly differentiates

us in the market. Thanks to our investors, we have prioritized understanding the market potential and the patient populations we are targeting so we can present a clear and complete story to investors. In particular, our work in precision oncology and especially precision immunology has resonated well with the market. Given this, I am optimistic about our ability to successfully move forward with our Series A funding.

Beyond funding, what additional value or support are these investors contributing to Engimmune's development?

First of all, both investors are represented on our board, which ensures they are directly involved in shaping the company's direction. What is particularly valuable is that both of our board members, along with others from these investment groups, bring significant hands-on experience in drug development. For example, our board member from Novo Seeds, Jørgen Søberg Petersen, has a background at Merck, and Dominik Escher, from Pureos, founded ESBATech which was eventually aquired by Novartis. Their deep industry experience has been incredibly helpful.

Beyond their direct involvement, they also open doors for us in several important ways. They connect us not only to other potential investors but, more crucially, to experts in fields that are critical to our development, whether that be clinical input or business strategy. This kind of access helps us gain valuable insights early in the process. While we are responsible for executing the work, having that network available is a huge asset, and both investors are deeply engaged in ensuring we follow the right strategy for the company's growth.

What are the advantages and challenges of being a biotech company based in Switzerland? How does the Swiss environment support or hinder growth in this sector?

Switzerland has a long history in the pharmaceutical industry, which is a significant advantage. With two of the world's largest companies based in Basel, alongside others in places like Lac Léman, Zug, and Zurich, we have a tremendous concentration of expertise. Additionally, Switzerland is home to top-tier universities like ETH Zurich, EPFL, the University of Zurich, and the Universities of Basel and Bern, which provides access to an incredible talent pool. The presence of leading hospitals nearby also adds to this advantage, making it easier to attract skilled professionals and develop collaborations.

Switzerland has also invested heavily in infrastructure, which supports the growth of smaller biotech companies. For example, facilities like the one we are currently provide valuable resources for startups. However, there are areas where Switzerland—and Europe as a whole—can improve. While we excel scientifically, often leading the US in research publications, we lag in translating that science into commercial products. The US dominates in patent generation and venture funding, and that is where Europe, including Switzerland, needs to step up.

One challenge is that within Europe, we sometimes compete with each other, rather than thinking collectively about building global hubs for biotech and other industries. This fragmentation prevents us from reaching the critical mass needed for long-term success. Switzerland has made strides, and we see strong hubs like Paris, Copenhagen—thanks to the Novo Foundation—and the UK's Cambridge-Oxford-London triangle. Still, there is room to think more broadly about collaboration across Europe.

Another challenge is the relative lack of venture capital willing to take higher risks. European VCs and their backers tend to be more risk-averse compared to their US counterparts, which affects how innovation progresses. While we are more efficient in generating outcomes per investment, we need to find ways to make this more successful on a larger scale. Developing a more risk-tolerant environment would help us better compete with the US in the biotech sector.

Engimmune already has a notably large team for a preclinical-stage company. Could you explain the rationale behind this and your approach to handling development in-house?

Right now, we are a team of around 20 people, and the focus has been primarily on discovery. We have made significant progress in advancing the science, and to achieve that, we needed a lot of hands-on work. That is why we built up a strong platform early on, which is now fully operational and enables us to quickly develop new molecules.

I believe it was the right decision to invest in creating a robust discovery engine. It required taking some calculated risks and bold steps, especially in terms of thinking about what we wanted to achieve. We have successfully reached the stage of producing soluble TCRs, which came with its own challenges. But this approach allows us to generate valuable data rapidly. And in this industry, data is the currency that allows you to move forward, whether it is securing additional funding or advancing development.

Looking ahead, what do you see as the next major inflection point for Engimmune?

The next major inflection point for EngImmune is definitely our Series A financing. This is crucial from both a financial and scientific development perspective. Furthermore, in the next six months, we plan to achieve lead selection of our two pre-clinical candidates, ENGI-002 and ENGI-003. These selections will provide us with very important data sets that will guide our progress and growth.

I believe Engimmune is not only a great innovative company but also represents a promising new modality in the market. There are a few molecules currently available that have demonstrated the potential to make a significant impact on patients' lives. Our ultimate goal is to save lives, and it is essential to explore new modalities that can truly help patients. This focus will drive our vision for the company's future.

See more interviews