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EVAXION

Using AI to create a vaccine revolution

Clinical stage company Evaxion Biotech is using artificial intelligence (AI) to simulate the immune system and create predictive models to identify novel targets for vaccines against bacterial and viral diseases and immunotherapies for cancer.

Infectious diseases, both viral and bacterial, cause around a quarter of deaths worldwide, and are responsible for many days lost to work and education. Vaccines are a crucial tool in prevention of infection, which was underlined by the success of vaccines in the COVID-19 pandemic. By reducing the need for antibiotics in bacterial infections, vaccines are also a crucial part of the fight against the rise in antimicrobial resistance (AMR).

"There has been an increased interest in infectious diseases and vaccines post COVID-19," said Pär Comstedt, VP of Infectious Disease Vaccine Development at Evaxion. "This will likely increase as AMR unfortunately worsens." Founded in 2008, the clinical stage biotech Evaxion's aim is to lead the exploration of AI to help to develop new and superior vaccines and immunotherapeutics for patients in need.

Building the company

The people behind Evaxion are Andreas Holm Mattsson, Chief AI and Culture Officer, and Niels Iversen Møller, the company's previous CBO. Mattson was working on his PhD at the Technical University of Denmark (DTU) when he created the initial technology.

"I built an early version of our AI bacterial infectious-diseases platform EDEN [Efficacy Discriminative Educated Network] and joined forces with Niels to find a way to partner with the biopharma industry to provide antigens as targets for pipeline development. I knew that the industry would eventually be open to AI technology, so we kept going without salary for a time—two guys living out of suitcases for seven years!" said Mattsson. "DTU is a pioneer in immunoinformatics, and this helped us to build a team."

Evaxion's research and growth depended on a patchwork of non-dilutive funding and grants, including from the Defense Advanced Research Projects Agency (DARPA), as well as collaborations with biopharma companies, which allowed the company to validate its technology. Other funding sources have included a loan from the European Investment Bank (EIB) to support AI vaccine research, and a grant from the National Institutes of Health (NIH) for the development of a lead gonorrhea vaccine candidate.

Evaxion closed an initial public offering (IPO) in February 2021, raising $30 million, and moved to purpose-built offices and laboratories at the DTU Science Park in Hørsholm near Copenhagen, Denmark. This brought the company's facilities all together on one site. A follow-on public offering raised $27.6 million in November 2021.

Using AI to create a discovery revolution

The company has three key validated AI platforms: EDEN, Rapidly Adaptive Viral Response (RAVEN) and Personalized Immuno Oncology using NeoEpitope Efficacy Ranking (PIONEER). These platforms enable the company to identify antigens with potential in vaccine product candidate and therapeutics faster and at a fraction of the cost of current approaches (Fig. 1).

"We can find targets more quickly than traditional approaches, and we can also find targets that cannot be found in other ways," said Comstedt. The technologies are based around a machine-learning group of AI models trained on Evaxion's unique dataset. The models analyze information about antigens that interact with the immune system.

"Evaxion is organized into projects rather than departments, making us more flexible, transparent and focused on innovation. We have regular forums where we discuss projects and share information leveraging our collective intelligence and cross-functionality," said Mattsson.

EDEN identifies B cell antigens that share features with known highly protective proteins and have potential to trigger a robust and protective immune response against almost any bacterial infectious disease. It has been validated preclinically in seven different bacterial pathogens.

The process begins with a bacterial proteome, and the EDEN platform creates a ranking list of novel protective proteins, with the top 20 or 30 selected for vaccine-antigen design and structural modelling. The protection and immunogenicity are then verified in animal models and functional assays. Results from preclinical trials are fed back to the bioinformatics team in an iterative manner, and the leads then return to preclinical trials. The antigens are optimized, fusion proteins are created and, after adjuvant and modality testing, they are made ready for chemistry, manufacturing, and controls (CMC). Finally, the best product candidate for development is defined.

"We begin with a bacterial genome, and we can have candidates in as little as 48 hours, compared with many years for companies using the reverse-vaccinology approach. This gives us and our partners a head start on the development process," said Comstedt. "We have been successful at creating leads in all the bacteria we have tested."

PIONEER is used to accurately and efficiently identify patient-specific neoantigens for personalized oncology immunotherapies. These tumor-specific epitopes are selected to trigger a strong T cell response, training the patient's immune system to target and kill tumor cells with limited or no impact on healthy cells.

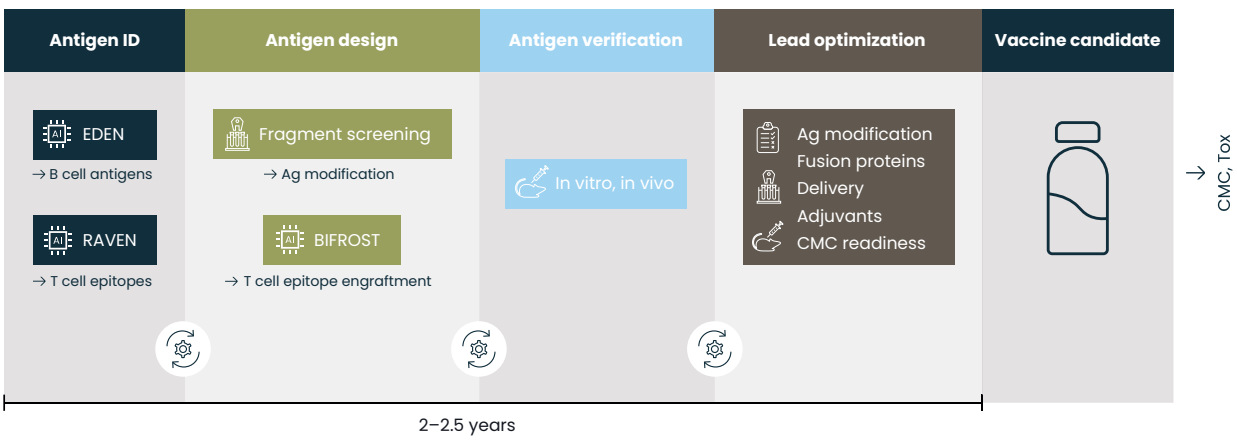

Fig. 1 | Evaxion's discovery of vaccine candidates against infectious diseases. Complementary Evaxion AI platforms and capabilities combine to enable design of next-generation vaccines with the capacity to evoke both cellular and humoral immunity against diverse pathogens. Ag, antigen; CMC, chemistry, manufacturing, and controls; EDEN, Efficacy Discriminative Educated Network; RAVEN, Rapidly Adaptive Viral Response; Tox, toxicology.

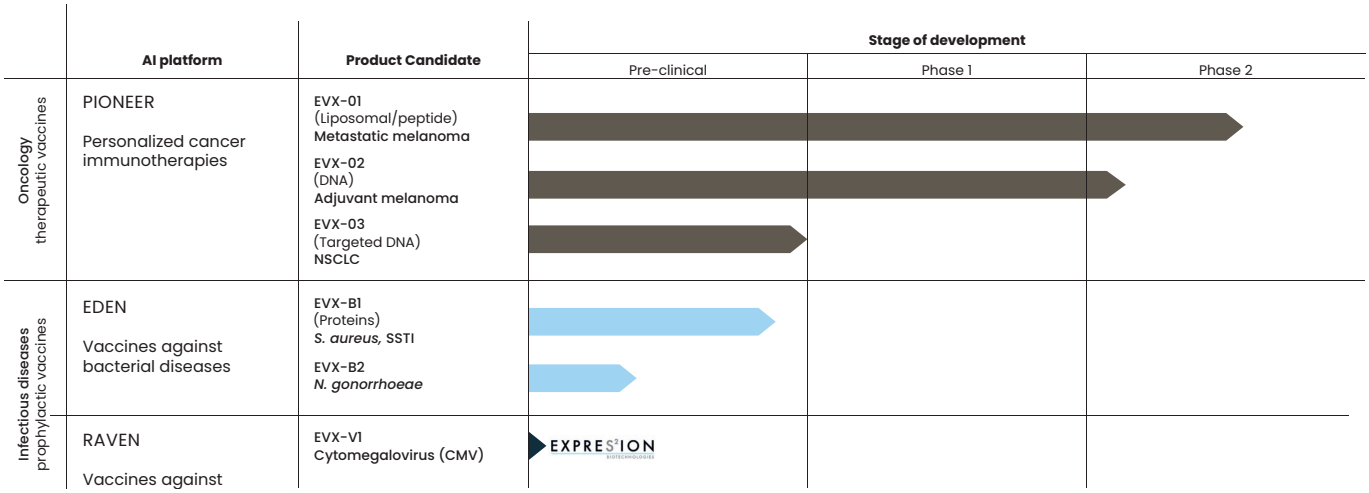

Fig. 2 | Evaxion's clinical development pipeline. Evaxion's unique AI platforms underlie the portfolio of differentiated vaccine programs. AI, artificial intelligence; NSCLC, non-small-cell lung cancer; SSTI, skin and soft tissue infections.

The role of the RAVEN platform is to identify vaccine candidates against any existing, emerging and mutating viruses. Vaccines created from leads identified by RAVEN target both T and B cells, with a robust and durable humoral and cellular response. This has potential to create a broader, more reliable and more future-variant-agnostic vaccine, including in viruses where it hasn't been possible to create vaccines until now. RAVEN antigens can be delivered as peptides, proteins, mRNA or DNA.

"RAVEN combines the technology and the learnings from EDEN and PIONEER," said Comstedt. "We find B cell antigens using EDEN, and then select T cell epitopes using modules in PIONEER. We then use Bayesian Inference for Fragments Of protein Structures (BIFROST) to graft them together without changing the protein structure."

Building an infectious-diseases pipeline

The lead candidate in the EDEN pipeline is EVX-B1, a multi-component prophylactic vaccine against *Staphylococcus aureus*. It targets several virulence factors as well as toxins and covers a variety of strains (Fig. 2). It has been validated through in silico analyses and preclinical studies, including lethal sepsis and skin-abscess models of infection. The vaccine is in development to prevent skin and soft-tissue infections (SSTIs) and has potential in other *S. aureus* infections.

EVX-B2, a multi-component prophylactic gonorrhea vaccine, is being developed in collaboration with the University of Massachusetts Chan Medical School (UMass Chan). "Development of a vaccine against *Neisseria gonorrhoeae* is critical, as rates of the infection are increasing worldwide, and the number of strains resistant to antibiotics is rapidly proliferating," said Sanjay Ram, professor of medicine at UMass Chan.

Gonorrhea can result in infertility, ectopic pregnancy, blindness in newborns, life-threatening sepsis infection, and increased risk of HIV transmission. According to the World Health Organization (WHO), cases of super-gonorrhea are emerging, with resistance to ceftriaxone, azithromycin, penicillin, sulfonamides, tetracycline, fluoroquinolones and macrolides.

"We need additional approaches, such as safe and effective vaccines in high-risk populations, alongside new antibiotics," said Ram. Evaxion used its EDEN platform to identify B cell antigens. The UMass Chan team, led by Sunita Gulati (professor of medicine) and Ram tested 26 candidates, with the final vaccine comprising a fusion of two proteins not previously described as vaccine antigens. EVX-B2 has high levels of immunogenicity. Anti-EVX-B2 antibodies showed significant bactericidal activity against most of 50 clinically relevant strains in vitro and immunization of mice with EVX-B2 attenuated vaginal colonization by a number of different *Neisseria gonorrhoeae* strains. Late-stage preclinical trials are under way. "This was a very productive and co-operative collaborative effort. Discussions were open and two-way," said Ram.

In December 2022, Evaxion signed a vaccine-discovery collaboration agreement with ExpreS^{2}ion Biotechnologies. Evaxion will use its RAVEN platform to identify antigen targets against cytomegalovirus (CMV) and design a vaccine, EVX-V1, with ExpreS^{2}ion manufacturing the antigen constructs. ExpreS^{2}ion will have an exclusive right to license the resulting CMV vaccine candidate.

Expanding into cancer

Evaxion also has a clinical stage cancer pipeline (Fig. 2). As Mattsson explained, Evaxion wanted to add another therapeutic area to de-risk its discovery and development pipeline, and increase the opportunities for raising money.

"We chose cancer because we would be able to get to proof of concept more quickly, and potentially get more investment. There are also a lot of cross-overs with infectious disease where we were pioneering in T cell antigen prediction," said Mattsson.

The personalized cancer therapeutic candidates are based on Evaxion's PIONEER technology. EVX-01, a liposomal/peptide immunotherapy, has moved into a phase 2 trial in combination with Merck & Co's PD-1 inhibitor pembrolizumab (Keytruda) for the treatment of checkpoint inhibitor-naïve patients with unresectable or metastatic melanoma. In a phase 1 trial, patients showed a high response rate compared with historical controls. In an ongoing collaboration, Merck & Co, known as MSD outside North America, will supply pembrolizumab.

EVX-02, a personalized DNA therapeutic vaccine in development for adjuvant melanoma, is in phase 1/2a clinical trials in resected disease. Interim data showed T cell responses in all patients, confirming a proof of mechanism for the DNA-delivery technology. The vaccine was well tolerated.

EVX-03, a targeted DNA therapeutic vaccine optimized with an antigen-presenting cell (APC)-targeting unit, has shown tumor reduction at low doses and a clear dose response in preclinical models. Clinical development will target non-small-cell lung cancer (NSCLC).

Evaxion and Pantherna Therapeutics recently announced the results of a collaborative preclinical study investigating delivery of tumor neoantigens identified by Evaxion's PIONEER platform, using Pantherna's lipid-nanoparticle mRNA platform, resulting in a strong immune response and complete inhibition of tumor growth.

The company's latest cancer AI platform is ObsERV, which will be used to identify patient-specific virus targets (endogenous retroviruses or ERVs), a new source of targets for personalized cancer vaccines that opens up a new treatment paradigm in cancer, acting on tumors that are normally unresponsive to immunotherapy.

"This truly underlines our ongoing, iterative improvement and the cross-pollination between our platforms for infectious disease and cancer," said Mattsson.

Evaxion's partnerships

Evaxion's aim is to develop its immunotherapeutics and vaccines to get proof-of-principle data, validate the technologies, and to seek partnerships. The company is currently seeking co-development or outlicensing partnerships for EVX-B1 and EVX-B2, along with new target collaborations.

"We are a piece in the ecosystem and are open to partner with vaccine developers on vaccine discovery and development programs across infectious disease and immuno-oncology," said Mattsson.

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