INTERVIEW

OPENCORONA: lessons learned from a pandemic vaccine consortium

Early in the COVID-19 pandemic, the EU-funded OPENCORONA project brought together academics, manufacturers, and technology providers in the quest to develop a vaccine. Now, the resulting DNA vaccine is in clinical trials and its developers believe that the ability to induce broad T cell immunity will make it a valuable addition to the current vaccine lineup. **Charlotte Barker,** Editor, *Vaccine Insights*, speaks to two of the consortium leaders, **Matti Sällberg,** Professor, Karolinska Institutet, and **Eva-Karin Gidlund,** Head of Alliance & Business Development, NorthX Biologics to find out more.

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Q What is the OPENCORONA project?

MS: The OPENCORONA project started in the early days of the pandemic. When we realized in January 2020 that COVID-19 was likely to become a pandemic, my lab

at Karolinska Institutet started looking at vaccine design. We knew from the start it would be a DNA vaccine because we had a lot of resources already in place for this platform. When the EU put out a call for vaccine development proposals, we were able to form a consortium of seven partner organizations that had the capacity to take a vaccine all the way from the research discovery phase into the clinic. Now, 2 years and 10 months on, the first subject in the Phase I clinical trial has been vaccinated.

EKG: It's a Horizon 2020 Pan-European project with a budget of €3 million and we are proud to have brought a vaccine to clinical trial in under 3 years on that comparatively low budget. Other vaccines made it onto the market quicker, but because we took a different approach to the design of our vaccine, we believe it has some important advantages over existing vaccines and will be valuable as a booster.

Q Who are the partners in the consortium?

MS: The consortium consists of:

- Karolinska Institutet: responsible for project coordination, vaccine design, early testing, and selection in animal models;
- Folkhälsomyndigheten (Public Health Agency of Sweden): provided access to BSL-4 and BSL-3 animal facilities and mouse and ferret models for challenge studies;
- Justus Liebig University Giessen: carried out testing to ensure the vaccine candidates did not over-activate the immune system and cause cytokine storms;
- IGEA SPA: designed and developed a CE-marked delivery device for *in vivo* electroporation of DNA vaccines;
- North X Biologics: produced HQ plasmid to be used in toxicological studies and GMP plasmid for the phase 1 clinical study;
- Adlego (now Scantox): performed toxicological testing according to GLP;
- Karolinska University Hospital: currently running the phase 1 clinical trial.

Q How did you approach the initial vaccine design?

MS: We are used to working with viruses like hepatitis C, which are extremely genetically variable, so our approach is to include as much as possible of the virus, including conserved elements. For COVID-19, we did not want to focus only on spike (S) protein epitopes because while the S protein can induce neutralizing antibodies it also has a high mutation rate, and it is the T cell responses that protect us from severe disease and death in the long run.

Most COVID vaccines used the 2003 SARS outbreak as a blueprint, taking the S protein, modifying it with the known stabilization mutations, and producing it as an RNA, DNA,

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– **Matti Sällberg**

protein, or adenoviral vector. We decided from the beginning to go a different way, even if it took longer.

We included the receptor binding domain (RBD) of the S protein, which binds to ACE-2 receptors. The RBD is genetically variable, so we included RBDs from three different variants—Wuhan, Alpha, and Beta. Fortuitously, the Beta variant shares many mutations with the Omicron variants that later swept the globe.

We combined these with the membrane (M) protein and the nucleocapsid (N) protein. Both have a very high homology between the current circulating strains in humans and those present in bats and other animals. We wanted to protect against different types of SARS-CoV.

We believe this combination of antigens makes our vaccine well-suited to use as a booster dose, as it adds new responses to complement the responses induced by the Spike-based vaccines.

Q What was different about working on a pandemic vaccine versus previous projects you've been involved with?

EKG: For me, the way we adapted the project as a result of the constantly emerging new data that appeared during the pandemic was totally new. For example, once people began receiving COVID-19 vaccines, we re-designed the clinical trial to allow for the fact that most people would have been vaccinated by the time we finished recruiting.

MS: That is true. There were two major changes in direction. After 9 months, different variants of the virus started showing up, and we realized we had to redesign to include some of these variants in the vaccine. Unfortunately for North X, that meant redoing the HQ batch production! Of course, that caused a delay, but I think it's made the final vaccine more timely, offering protection against a wider range of variants.

As Eva said, we also changed the clinical trial design from being a first-line vaccine to a booster vaccine.

Q What steps did you take to allow you to move as quickly as possible?

EKG: Those who have experienced writing an EU funding application will know that it typically takes months. Matti called us about this proposal and said, 'Can you have it ready by next week?' One of the things that sped up the project and made it possible was that lengthy decision-making was put aside. In a pandemic, everybody has to be on their toes and take decisions fast, even when we don't have all the facts. The call for proposals from the EU was only open for a few weeks and the review process was dramatically streamlined.

MS: One of the most essential things was that we already had the contacts we needed. We had partnerships in place for manufacturing and delivery technology. And we worked together very effectively, with each member of the consortium actively preparing for their step, so there was no time lost.

EKG: The fact that Matti's group had data from previous DNA vaccines they had worked on also helped and made it much easier to take decisions.

MS: We already knew that DNA vaccines work in humans, and how to design, test, and deliver them. As it turned out, RNA vaccines were the frontrunners, but in January 2020, RNA vaccines had never been used outside small clinical trials. If you had said in 2019 that we would be making RNA vaccines for a pandemic, no one would have believed you.

Q What stage is the project at now?

MS: We recently initiated a randomized, double-blind, placebo-controlled, dose-escalation phase I clinical trial in healthy adult volunteers who have previously received three RNA vaccine doses, and we will follow them for 3 months to track neutralizing antibodies and T cell responses. We are also having them take a rapid antigen test every week during the trial to get an idea of reinfection rates.

We see our vaccine as a complement to existing vaccines. Preclinical studies showed strong and broad T cell activation with our vaccine so we believe it might particularly benefit those with an inability to produce antibodies or an altered immune system, like dialysis patients.

Q What are the key factors for a successful consortium?

EKG: Collaborating in the middle of a pandemic is not easy, but our consortium of seven partners has worked very well together throughout. Indeed, I have never experienced such a successful consortium, despite not being able to meet in person for many months.

When Matti mapped out this consortium, he was careful to include different areas of expertise, with limited crossover. Of course, we communicate and collaborate, but each entity has a distinct role.

Our grant coordinator and project manager worked hard to keep track of all seven partners and make sure that we all delivered on time. Planning became especially important because many resources became scarce during the pandemic. Items that may have been delivered within 4 weeks pre-pandemic are now taking 3 or even 12 months. Planning is everything.

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– **Eva-Karin Gidlun**

Openness and straightforward communication are also key. You need to be able to say early on when you will not be able to deliver your timelines and ask for help when you need it.

MS: For a scientist, a big challenge is knowing when to stop experimenting. Every day you come up with a better idea, a different way of doing things, but you cannot keep doing that in clinical development. When you find a candidate, you need to say 'stop' or "go."

That is hard for a scientist to live with because the same day you commit to a candidate drug, you may come up with a better idea. You must realize that this 'better idea' will take another 2 years to reach the same point. It's tough to adapt to that way of thinking but it was essential for everyone to understand that we have a defined goal—to do a clinical trial. My experience of large consortia is that projects are too often talked to death or changed to death! With a small group, this risk is minimized.

Q What lessons have you learned from this project and from the pandemic more generally?

MS: One of my big lessons from the pandemic is to never be surprised that you're surprised. Again and again, the pandemic has shown us that we still have a lot to learn. One must be humbled by the learning process!

EKG: For me, it emphasized that cash is king. The vaccines that made it into the clinic within a year had many more zeros in their funding allocation than ours! If you can, ask for more money than you think you need. We learned so much during this project, and this pandemic, that we all have things we would like to explore further.

MS: Yes, with double the money, things certainly would have moved faster!

EKG: Another lesson to take from the project is that consortia like this are a good opportunity for a private company to engage with early-phase research. I would encourage companies like ours to be bolder in collaborating and building ongoing relationships with academics.

MS: It is good for academia too. By taking part in clinical development, academics understand much more clearly how a product is made.

EKG: All of us have had the opportunity to learn from different sectors and fields, and follow the vaccine from idea to development, manufacturing, release, and now clinical trials. It's been a real journey!

BIOGRAPHIES

MATTI SÄLLBERG got his DDS and PhD from Karolinska Institutet in 1992, a post doc from Scripps Research Institute, and was appointed professor in biomedical analysis at Karolinska Institutet in 2000. He was co-founder of SVF Vaccines AB in 2015. His major research interests are viral immunology, immunotherapies, and vaccines

EVA-KARIN GIDLUND is the Head of Alliance and Business Development at NorthX Biologics (NorthX). Eva-karin has a PhD in Medicine from the Karolinska Institutet in Stockholm. Her main focus as a scientist for the last decade have been genetic and epigenetic changes and modifications in healthy humans and in patients. She is a former TEDxSpeaker, Bünsow Business speaker, author and international presenter that has competed in the Science Grand Prix . In 2019 after a postdoc, she became Collaborations Development Manager for a large CDMO within the Cell- and Gene Therapy filed. In 2021 she was appointed the Head of Alliance and Innovation at NorthX. In October 2021, the Swedish government recognised NorthX as a national and international innovation hub and now a new era and shift from a CDMO towards an innovation centre is emerging. Her main goal is to bridge the gap between innovation, academia, SMEs and the pharma industry to supply innovative medicines to patients and to help early phase innovative companies to reach success.

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AUTHORSHIP & CONFLICT OF INTEREST

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