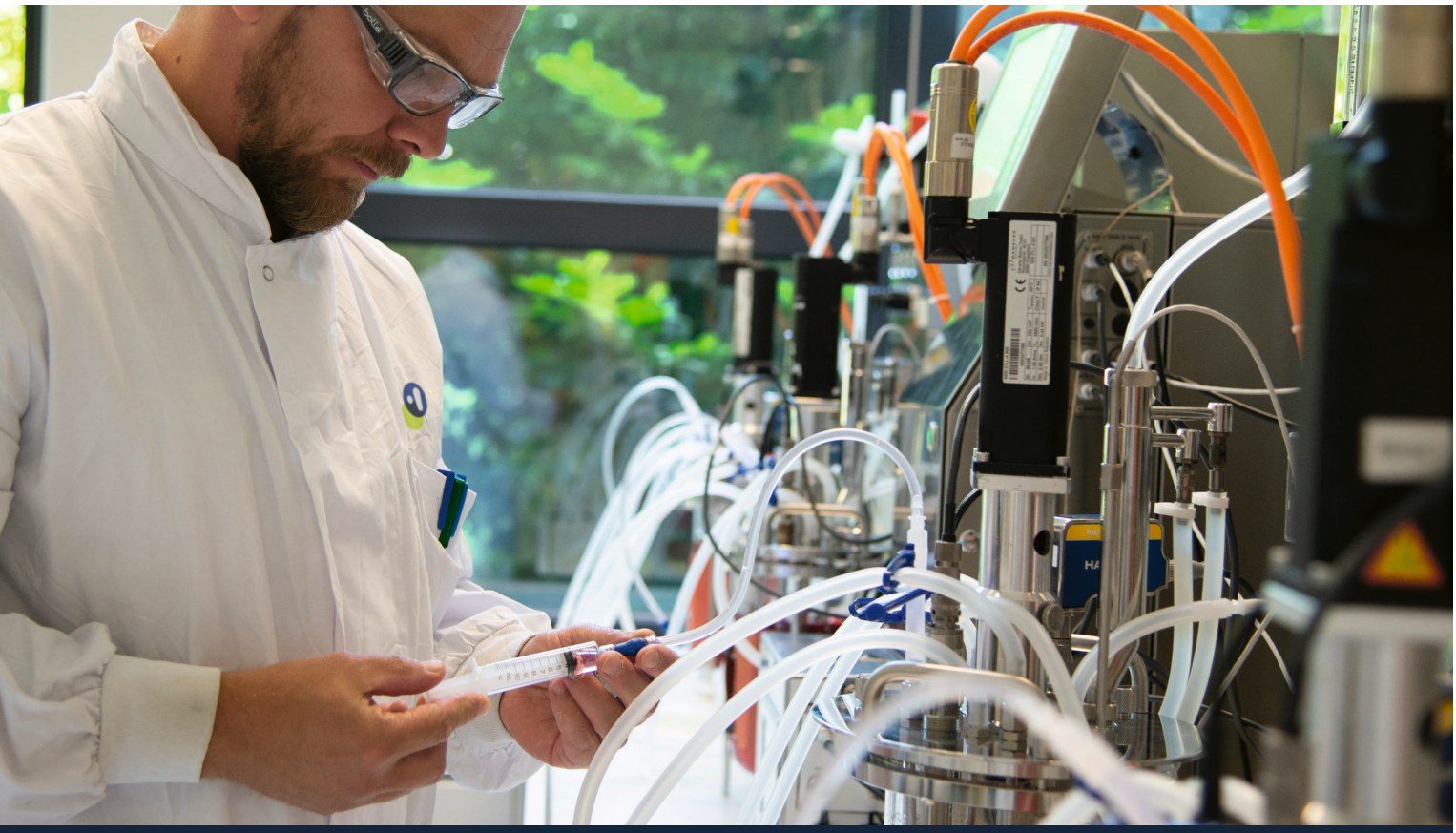
Insights into the OMV-Vacc, Intravacc's Outer Membrane Vesicle Platform for Vaccines.

Interview with **Dr. Dinja Oosterhoff**



OMV-Vacc at a glance

About

- The OMV-Vacc technology is based on the Outer Membrane Vesicles (OMVs) of gram-negative bacteria and is designed for the development of prophylactic vaccines.
- OMVs are spherical particles that are naturally released by gram-negative bacteria.
- Intravacc develops three types of OMV vaccines: homologous OMVs, heterologous OMVs, and click/mix OMVs.
- Corroborated by >80 scientific publications and covered by 9 patent families.

Application areas

- Bacterial, viral, and parasitic infection
- Antimicrobial resistance (AMR)
- Oncology

Interview with
Dr. Dinja Oosterhoff

Dr. Dinja Oosterhoff is the Vice President of Research & Development at Intravacc. She has a doctorate in medical oncology and currently oversees the company's vaccine technologies, aiming to expand their application space. We talked to her about OMV-Vacc, a vaccine platform based on Outer Membrane Vesicles (OMVs) that Intravacc has used to create novel vaccine candidates that stand out for the unique features of their composition or administration routes.

In your opinion, what are the most distinct advantages of Intravacc's OMV-Vacc platform?

One of the advantages of our OMV platform technology is that we've established the methods to express antigens from other bacteria in Neisseria meningitidis so that they end up in OMVs. We've also developed technology to link small peptides that are not immunogenic on their own to the OMVs and, in this way, transform them into an effective vaccine strategy. All the methods we use to tweak the vesicles and make them more efficient in eliciting immune responses distinguish us from other developers.

Another advantage are two specific genetic modifications of our OMVs. First, we have modified the LPS, or lipopolysaccharide, found

on the outer membrane of Gram-negative bacteria. LPS is generally reactogenic. It is recognized by the immune system and elicits an inflammatory response. The modification we introduced creates a detoxified version of LPS without impacting other OMV properties. Specifically, we deleted the LpxL1 gene involved in the synthesis of LPS, which leads to an underacylated lipid A that induces less potent cytokine production.

For the second genetic modification, we deleted the RmpM gene to weaken the link between the bacterium's peptidoglycan layer and the outer membrane. This results in higher blebbing rates that increase OMV yield. Importantly, both optimizations – detoxification and increased yield – are achieved without employing detergents to disrupt membranes and solubilize LPS. Thus, the composition, structure, and function of the OMVs remain intact.

How are antigens from a bacterium expressed in Intravacc's *N. meningitidis* OMVs?

OMVs can be derived directly from a Gram-negative bacterium if that is the target pathogen for a vaccine. These **homologous OMVs** offer broad protection against the target bacterium by incorporating and presenting natural antigens in their native conformation on the generated OMVs. We have done this for *Neisseria gonorrhoeae* and *Bordetella pertussis*. Our work optimizing the resulting vaccines against gonorrhea and pertussis, respectively, also included targeted mutations in the vesicles to ensure safety and guarantee high OMV production yield.

When the production of OMVs is not directly feasible, our OMV-Vacc platform offers the option of expressing antigens in our *N. meningitidis* backbone. These **heterologous OMVs** are behind, for example, our second gonorrhea vaccine, Avacc® 12. The bacterium *N. gonorrhoeae* is very similar to *N. meningitidis*, so we can replace *N. meningitidis* antigens with their *N. gonorrhoeae* counterparts. These are then expressed and presented in the OMVs with their natural configuration.

Another strategy to include antigens from other bacteria in the OMVs is to couple the antigen to a flexible linker system that attaches and presents antigenic proteins on *N. meningitidis* OMVs. A vector is created with the DNA sequence of the antigen fused to the sequence of the linker, and the fused product is cloned into *N. meningitidis*. Once expressed, the linker targets the antigen to the *N. meningitidis* membrane.

Intravacc's COVID-19 vaccine candidate leverages yet another strategy. Can you tell us about that?

In both the homologous and heterologous OMV strategies, the vaccine antigen is expressed by the bacterium generating the OMVs. However, antigen expression in bacteria isn't always wanted. In that case, we have two other strategies. For our **click OMVs**, we can conjugate antigenic peptides to the OMVs from the outside. That is, we adorn OMVs with immunogenic peptides.

In the case of our COVID-19 vaccine, the antigen we used was the large Spike protein. The vaccine consists of two components in a vial without any physical linkage, and the OMV functions as an adjuvant. We call this approach **mix OMV**. By mixing an antigen with the OMVs, the elicited immune response targets that antigen. In pre-clinical studies, the presence of the OMVs as adjuvants prompted a much stronger response against the Spike protein than when we administered the Spike protein alone. Our COVID-19 vaccine is in clinical trials, and we are excited to have data in the next couple of months.

You can see how this strategy can be a quick and easy development approach for new vaccine candidates. We can produce the OMVs in high quality and short timelines; that production process is in place. We can then work with a partner to optimize a formulation that mixes the OMVs with an antigen provided by the partner.

What are the criteria for using one OMV approach over another?

In practice, there are no steadfast rules. Our candidate OMV vaccines are examples of what can be done with OMV-Vacc rather than demonstrations of strict development routes. Each vaccine project has unique specifications. Not only are efficacy and safety paramount, but the target population, manufacturability, transportation, storage, shelf life, and administration route are also critical factors for the final product. The OMV-Vacc platform accommodates optimizing many of these parameters while offering a range of approaches to realize a vaccine. If you have a large antigen that is challenging to express in bacteria, the mix OMVs is a good approach. If you are working with a bacterial vaccine, our heterologous OMVs are attractive when the conformation of the antigen is essential to elicit a good immune response.

What has been particularly rewarding for me in working with the OMV-Vacc platform and the team behind it is that we have an extensive OMV toolkit that the team expertly adapts to meet the challenging asks of our partners and clients. And, if OMVs are not the best solution for a project's requirements, our experts can find the right solution with our other proprietary platforms.

Advantages of the OMV-Vacc platform

Proven safety: Non-infectious and with LPS detoxification, OMVs have a strong safety profile
Effective: OMVs intrinsically elicit a potent innate and adaptive immune response
Stability: OMVs maintain integrity, simplifying transport and long-term storage
High yield: Our platform has an optimized production efficiency
High purity: Our platform includes well-established and scalable purification steps
Versatility: Our platform allows combining OMVs with different antigen types
Flexible administration: OMV-based vaccines can be given intramuscularly and intranasally

Interested in exploring options with OMV-Vacc?
Contact our Business Development team: BD@intravacc.nl

Intravacc. Innovating vaccines

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