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VACCINE INSIGHTS

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EXPERT INSIGHT

PAT to the future: combining *in silico* tools and analytics for streamlining process development of aluminum-adjuvanted vaccines

Andrea Albano and Angelo Palmese

Aluminum-based adjuvants are used in multiple commercial vaccines. However, optimization of drug product formulation and fill and finish processes still present challenges. Aluminum-containing vaccines are generally formulated in stirred tank reactors, as they have been proven to be the best vessel to ensure homogeneity of the product in the solid–liquid system, thus promoting adsorption during formulation phases and increasing the surface area of aluminum particles available for interaction with antigens. The stability of aluminum-containing vaccine suspensions is an important factor that affects several product quality attributes. In addition, antigen adsorption on the surface of aluminum particles may lead to a modification of their colloidal stability, which requires thorough investigation through diverse experiments and off-line analytics for a robust product design. Hence, analytical approaches and technologies that are able to properly characterize the behavior of aluminum-containing vaccine suspensions in stirred tank reactors may represent a game changer for vaccine process design and optimization.

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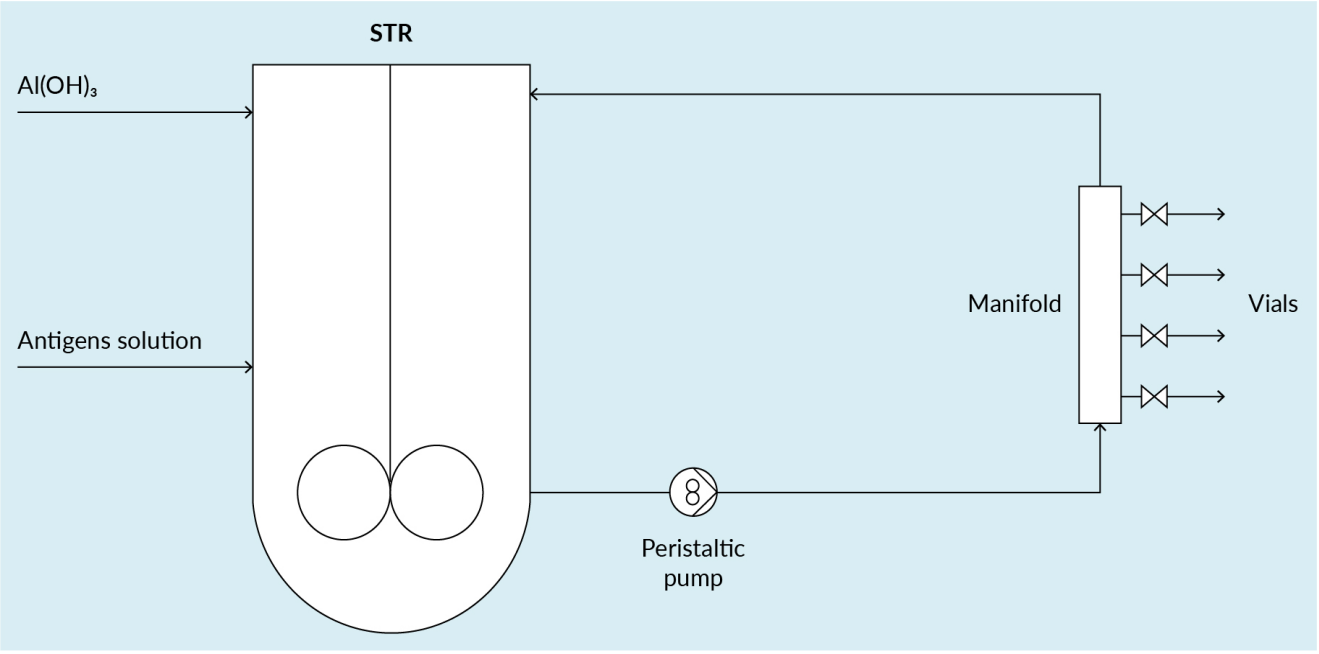
ALUMINUM ADJUVANTED VACCINES & PROCESS CHALLENGES

Aluminum-based adjuvants are widely used in development and commercial vaccines. The widespread use of aluminum-containing adjuvants is due to their excellent safety, which has been proven through the use of hundreds of millions of doses in humans over several decades [1]. Furthermore, they are readily available, inexpensive, and generally accepted by regulatory agencies. Besides their role as an adjuvant, antigens adsorbed to aluminum salts often present improved stability, enabling the preparation of liquid formulations, which typically have a long shelf life under refrigerated conditions [2,3]. Despite their wide and established use, the optimization of drug product formulation and fill and finish processes still present challenges and are often far from optimal. Quite often, large-scale process parameters are defined based on worst-case conditions and are not necessarily optimal, for example, in terms of product shear stress and energy consumption. Process analytical technologies (PAT) and computational fluid dynamics (CFD) can help to identify optimum process parameters and, if used properly, could be pivotal in the design of next-generation aluminum-based vaccine processes.

Aluminum-based vaccines are generally formulated in stirred tank reactors (STRs) as they have proven to be the best unit operation to ensure homogeneity of the product in the solid–liquid system, promoting adsorption during formulation phases, and increasing the surface area of aluminum particles available for interaction with antigens (Figure 1) [4]. STRs are also used for fill and finish activities. Post-formulation, the final drug product is left to sediment, resulting in a solid cake at the bottom of the vessel. This cake must be resuspended, and the resulting suspension must be demonstrated to be homogeneous before fill and finish activities can be commenced. During filling, the homogeneity of the final drug product is ensured via mechanical stirring, thus guaranteeing that each vial contains the target amount of aluminum-adjuvanted product [4].

FIGURE 1

Schematic representation of formulation in STR and filling processes for aluminum-adjuvanted vaccines.



The stability of aluminum-containing vaccine suspensions is an important factor that affects several product quality attributes, such as the degree of antigen adsorption, which, in turn, is linked to adjuvanticity and is a crucial element in the design of potent vaccines [5]. In addition, antigen adsorption on the surface of aluminum particles may lead to a modification of their colloidal stability (e.g., flocculation events or nonoptimal product characteristics and suspension behavior), which must be deeply investigated through diverse experiments and off-line analytics for a robust product design.

The determination of the sedimentation characteristics of aluminum-containing vaccines is pivotal to the determination of the hydrodynamic properties of their suspensions. Characteristics such as the sedimentation rate and sedimentation volume ratio are currently measured *ex situ*, and analytical methods frequently require transferring of the suspension from its original container to some specialized glassware for measurement (usually performed via visual monitoring or laser scattering analyzers and optical scanner analyzers). The sedimentation rate is determined based on the dynamics of the phase separation interface over time [6]. However, similar analytical approaches cannot be applied during the large-scale formulation of vaccines in STRs (i.e., its original container), and despite technological advances in the field of process analytics, real-time monitoring of homogeneity, sedimentation, and the re-suspension of aluminum-containing vaccine suspensions still pose challenges, since technologies to directly monitor suspension properties in STRs are lacking.

Therefore, process parameters for fill and finish activities are often set on experience and empirical approaches, rather than being optimized based on a deep understanding and detailed process characterization at a manufacturing scale.

The availability of analytical approaches and technologies able to deeply characterize the behavior of aluminum-based vaccine suspensions in STR may represent a game changer for vaccine process design and optimization, leading to a tremendous increase in process and product understanding that will ultimately translate into better processes, with obvious advantages for patients. Furthermore, fast and reliable methods for the development of more robust processes lead to a reduction of time to market and manufacturing costs, through a combination of process parameter optimization and reduction in deviations and scrappage.

According to the US FDA [7], PAT is a system for analyzing and controlling manufacturing through real-time measurements of critical quality and performance attributes of in-process materials and processes, to ensure final product quality. Besides advantages linked to manufacturing process control, the implementation of PAT provides deep process characterization, thus leading to improved robustness, risk reduction, and optimization of capacity, through the implementation of a QbD approach. Furthermore, the large amount of real-time data acquired through PAT will be instrumental for the future design of more reliable processes that can be adjusted in real-time, thus enabling the production of next-generation vaccines in line with the 'Industry 4.0' ambition [8]. Last but not least, PAT implementation also represents the fundamental first step toward the realization of real-time release testing strategies [8].

Examples of PAT for vaccine drug product processes in the public domain are mostly linked to the determination of aluminum content and antigen adsorption; there exist few examples of other types of applications. Near-infrared (NIR) spectroscopy has been used recently for the determination of aluminum content in aluminum-adjuvanted vaccines, but NIR measurements were demonstrated to be impacted by the sedimentation of product [9]. Nuclear magnetic resonance has been used for the quantification of aluminum phosphate (free and total phosphate; total aluminum) directly [10], within an adjuvanted product. Further characteristics of the aluminum particles (e.g., sedimentation behavior)

cannot be determined. More recently, Fourier transform infrared spectroscopy has been used for off-line and in-line monitoring of antigen adsorption to aluminum particles [11–13], and infrared spectroscopy has been applied in-line to monitor surfactant concentration during a tangential flow filtration step [14]. Even though both off-line (e.g., laser diffraction) and in-line (e.g., focused beam reflectance measurement) technologies have been used for the characterization of particles [15], none of the tools used were able to monitor and characterize the behavior of aluminum-vaccine suspensions in formulation tanks, at multiple scales (from laboratory small scale up to manufacturing scale), in real-time. It is the opinion of the authors that, considering the conventional portfolio of analytical methods, analytical tools able to address this need are not readily available. The applicability of new technologies that are not currently used for biopharma processes must therefore be explored, whilst also combining hard technologies with *in silico* tools for process characterization.

A promising *in silico* tool to study, characterize, and optimize process steps involving aluminum is CFD. CFD is a computational science developed to determine the motion of fluids with specific constraints (i.e., inside a STR with a given impeller stirred speed). CFD relies on models based on fundamental physics [16], which allow for the generation of scale- and equipment-independent correlation, which can be used to transfer processes across laboratories and manufacturing facilities. The recent improvement in computing power has helped CFD to become an essential asset for many industries [17–21], and it is also being used to model sedimentation processes.

When multi-phase systems, such as adjuvants, have to be modeled single-phase CFD models have been combined with more advanced modeling techniques such as Eulerian-Eulerian, interface tracking, and Eulerian-Lagrangian such as the CFD-discrete element method [22]. Not surprisingly, the more advanced applications of CFD for sedimentation phenomena were developed by ocean engineers to optimize sedimentation tanks [23–25] but mainly focused on hindered and compression settling in secondary sludge, a largely monodispersed solids, where bulk sedimentation velocity is effectively described by functions such as double Vesilind (Takacs, having success in modeling both cohesive and non-cohesive particle settling [26,27]. CFD-based models have also been used to optimize operational conditions for homogenizing solid concentration and to predict particle size [28,29].

CFD can be used for aluminum-adjuvanted vaccines to:

- Predict particle size and concentration distribution of aluminum at different operational conditions (e.g., stirred speed, aluminum concentration, working volume);
- Evaluate the superficial area of aluminum available to promote antigen adsorption;
- Predict sedimentation rates; and
- Quantify the shear undergone by the product during formulation and fill/finish.

Despite these capabilities, tools for validating CFD models are not readily available. To this end, the development of PAT for monitoring aluminum-adjuvanted vaccines in real-time represents a promising approach for experimentally confirming *in silico* predictions. Therefore, the combination of CFD and PAT could allow for the design of scaled-down systems that are representative of manufacturing conditions to study the effect of critical process parameters on the desired critical quality attributes. The combination could also allow for the optimization of manufacturing process parameters, towards the development of finding the perfect balance between homogenizing power and shear to avoid impact on product and develop sustainable processes in the mid-to-long term.

STRs used for vaccine drug product processes are stainless steel containers of various

sizes and volumes and are generally characterized by the presence of an inlet for the excipients, antigen, and adjuvants to enter and an outlet for moving the drug product towards the filling station, in addition to the housing for the impeller. They are generally not designed for hosting probes and in-line sensors, as the product quality control occurs in the final container. It is therefore difficult to employ classical probes-based PAT. A potential solution is non-invasive technologies that can be utilized to reconstruct time-evolving multidimensional process knowledge, which can be used to optimize the fill and finish process [30].

Such technologies could be developed and employed for a range of both qualitative and quantitative metrics, such as monitoring of mixing, flow characterization, phase holdup quantification, concentration monitoring, malfunction detection, process control, cleaning-in-place, monitoring separation and phase boundaries, and assessing homogeneity of solid particle suspensions. Also, these and other techniques should be designed to be able to monitor aluminum concentration in both pipes and the STR, improving process knowledge as well as supporting the validation of mechanistic models, such as CFD.

To the best of our knowledge, there is currently no information available in the public domain on such a technology employed in vaccine manufacturing. The realization of this technology therefore represents an opportunity, but also presents challenges that will need to be addressed.

TRANSLATION HIGHLIGHTS

The biopharmaceutical industry has started adapting to the digital transformation as a means towards production improvements and process control [31,32]. An essential element of the digital transformation of manufacturing processes (both at drug substance and drug product level) is the implementation of PAT, as an information input for process control and the creation of digital replicas of the manufacturing process (hybrid modeling and digital twins) [32,33]. The new digital tools will allow unprecedented levels of process control, allowing for improved and more robust manufacturing processes, and for improved product quality by coping with process variability. Increased process robustness and in-line process control will also result in shorter times to market by facilitating scale-up and transfer, ultimately leading to a clear competitive advantage [34].

So far, PAT has been successfully implemented as a process control element for numerous manufacturing processes of small-molecule pharmaceuticals [35,36]. However, the increased complexity of biopharmaceuticals (and their respective manufacturing processes) impose a challenges for finding suitable PAT methods [37].

As for vaccines, the complexity is even greater, but the availability of PAT for understanding and controlling manufacturing processes will result in enormous advantages, particularly for aluminum-containing suspensions.

The combination of *in silico* tools, such as CFD, with novel, non-invasive, and low-cost PAT, such as NIR and other spectroscopic tools, supported by the proper information/operational technology infrastructure, will allow the development of digital twins, which in turn will open the door to faster development of new vaccines, reducing the time to market and improving pandemic preparedness.

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INTERVIEW

Can new vaccine technology confront drug-resistant bacterial infections?

Drug-resistant microbial infections are a growing problem—could next-generation vaccines be part of the solution? **Casey Nevins,** Assistant Editor, *Vaccine Insights,* speaks with **Michael Super,** Director of ImmunoMaterials, Wyss Institute for Biologically Inspired Engineering, about ciVAXTM, a new broad-spectrum biomaterial vaccine platform targeting bacterial infections and septic shock.

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Q How did you become interested in working with vaccines?

MS: I grew up in South Africa and Namibia, where my father was a pediatrician. At that time, he was the only pediatrician in the whole of Namibia, a country bigger than France. This meant that he saw a lot of children in both rural and city settings. I was thinking of pursuing medicine, so I tagged along with him when he went to work and saw the prevalence of infectious diseases in Africa firsthand, which inspired me to work in this field.

Q What are you working on right now?

MS: I am working on a next-generation vaccine for malaria. There have been recent successful vaccines for malaria (RTS,S and R21) but multiple boosters are required to achieve durable efficacy. That would be impossible in some parts of Africa due to travel distances—you are lucky if you see a patient more than once given how far they have to travel to the clinic. We are interested in getting a longer duration of protection from a single injection.

I am also working on a vaccine technology to protect against skin infection with methicillin-resistant *Staphylococcus aureus* and septic shock from a lethal *Escherichia coli* challenge. There are currently no approved *S. aureus* vaccines, and we believe that our technology can make a real difference [1].

Q What prompted your research concerning septic shock? What questions were you trying to answer?

MS: At the time that I started this work, I was funded (with Professor Donald Ingber) by the US Defense Advanced Research Projects Agency (DARPA) to create a dialysis-like treatment for sepsis. The concept was to filter pathogens from the blood using beads containing mannose binding lectin (MBL) fused to the Fc portion of an immunoglobulin—FcMBL [2].

MBL, which is part of the lectin pathway of the complement system, has been a thread throughout my career. MBL binds to sugars on the surface of pathogens, which are different from those found on our own cells, to determine whether cells are friend or foe.

While I was conducting this research for US DARPA, a close colleague, Ed Doherty, was working on cancer vaccines with Professor David Mooney. Their vaccine, already in clinical trials, uses a scaffold made up of mesoporous silica rods to bind the antigens.

I looked at the work we were each doing and said, "Why don't we try and put these two together and see if we can come up with an infectious disease vaccine?" So, we captured the pathogen with the FcMBL beads that we had developed, and merged that with the Mooney Lab scaffold technology.

To our surprise, we achieved very robust immune responses with this method. However, this technology does not allow us to identify individual antigens. It captures and presents the whole organism and allows the immune system to pick up what is dangerous and present it, via dendritic cells, to the rest of the immune system.

Q Can you give us a more in-depth look into the ciVAXTM technology?

MS: Essentially, we took the mesoporous silica rods from the Mooney technology and attached three things onto them: granulocyte-macrophage colony-stimulating factor as a recruiting factor for the dendritic cells; cytosine–phosphate–guanosine as a stimulator to the immune system; and the FcMBL beads with the pre-captured antigen. This was injected

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subcutaneously in mouse, pig, and rabbit models. We did not need to boost the mice, even for challenge with multiple pathogens, however, we did boost the pigs, before challenging with *E. coli* in our septic shock model. All the vaccinated pigs survived this lethal challenge.

We also carried out experiments to test how broad the protection was. We vaccinated mice against a gram-negative bacterium, *Enterobacter cloacae*, and then challenged those mice with a different gram-negative bacterium *E. coli*, and achieved very good protection. In other words, we were able to capture antigens that were shared between *E. cloacae* and *E. coli*, and thus protect against a lethal *E. coli* challenge.

To a vaccinologist, these are exciting results, because normally it is hard to achieve good protection even between two strains of *E. coli* in the same animal. One could even envisage making a vaccine 'in the field' to protect the rest of the herd in an agricultural setting.

Q Can you use these vaccines to confront drug-resistant bacterial infections?

MS: In theory, yes. For example, when we compared methicillin-sensitive *Staphylococcus aureus* (MSSA) versus methicillin-resistant *Staphylococcus aureus* (MRSA), our FcMBL technology bound equally well or better to the MRSA pathogens and the vaccine protected against MRSA. FcMBL binds many of the bacterium we looked at and we are developing further lectins to try and fill the gaps. The technology has shown efficacy in mouse models of perioperative joint infections. We do not foresee any risk of drug resistance with these innate capture and presentation systems.

We envisage the vaccines being given alongside antibiotics and expect to see a synergistic effect. As the antibiotic kills the pathogen and releases materials containing pathogen-associated molecular patterns, it will further boost the efficacy of the vaccine.

Q Could this technology be used to combat human epidemics?

MS: I believe it could, but it will be tricky getting this through regulatory approval, since regulatory authorities focus on the safety, purity and consistency of the vaccine. In a case like this with a mixture of antigens made from the pathogen lysate, it will be hard to achieve purity and consistency. By using the power of mass spectrometry, we will be able to identify the antigens, but we would need to do detailed immunology to determine which antigens are most important in the lysate.

The lysate vaccine could have a place in an emergency, like a pandemic, where there is a rush to develop an effective vaccine. For other applications, e.g. epidemics, our strategy would be to identify the key antigens, and make mixtures of recombinant versions of these to present on the mesoporous silica or one of our other platforms. There is a lot of work to do in making the right niche for the immune system to pick up, transport and present the antigens to develop a strong immune response, but I strongly believe in this technology.

Q What do you see as the priorities in vaccine development?

MS: Since animals suffer from many of the same or very similar infections to humans, we should not be thinking of our animal models as just models. Moving forward, we should take a One Health approach, which concerns both animal and human health. We know that diseases like HIV and COVID-19 originated in an animal reservoir before jumping to humans, and I think it is incredibly important to shift research towards animal reservoirs to protect animals and humans.

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BIOGRAPHY

MICHAEL SUPER's work covers engineering of proteins and devices for diagnostics and therapeutic applications. In his PhD thesis and postdoctoral work, he discovered the clinical relevance of innate immune system opsonins, especially mannose-binding lectin (MBL). These proteins are first-line defense against pathogens and bind to the high density and pattern of bacterial cell wall carbohydrates as well as to many fungi, viruses, parasites, and toxins (more than 100 different pathogen species). In addition, Super identified the first mutations in MBL which cause the deficiency in MBL titer and complement activation function and which have been implicated in susceptibility to childhood infections and predispose adults to infections. In addition to his academic career, Super brings 17 years of biopharma experience.

In new research at the Wyss Institute, Super has re-engineered MBL as an Fc-fusion protein for high level expression, ease of purification, and optimal orientation of conjugation to surfaces (e.g., beads and filters). This novel protein has the same broad-spectrum pathogen binding as wild-type MBL, but has none of the side effects of wild-type MBL, (e.g., complement and coagulation activation). In this project, he has supplied FcMBL for conjugation to beads and pathogen capture for producing the vaccine.

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VACCINEINSIGHTS

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SPOTLIGHT

Navigating vaccine distribution: tools to increase vaccine equity

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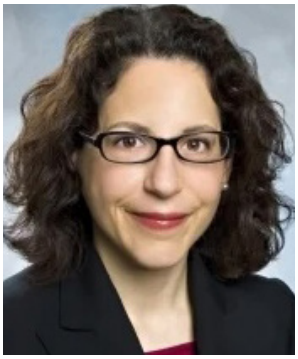

"With uncertain vaccine supply, decision makers needed localized updated data to plan efficient and equitable vaccine delivery."

VIEWPOINT

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Early in the COVID-19 pandemic, vaccine distribution in the US was irregular. Each public health jurisdiction had different regulations and procedures. In addition, many Americans live in vaccine deserts, without convenient access to vaccines. This article describes two tools created to increase vaccine equity throughout the country—the COVID-19 Vaccine Allocation Planner and the Vaccine Equity Planner.

In the US, there has been a longstanding call for investments in public health infrastructure, including national data tracking systems. The state-specific, complex nature of the existing immunization systems poses challenges.

The COVID-19 pandemic highlighted the urgency to modernize the architecture of immunization record-keeping. Not knowing the amount of vaccine supply that was administered and delivered to various populations made it difficult for the nation to efficiently allocate a scarce resource equitably. Compounding the lack of centralized record-keeping across the country, all 64 public health jurisdictions in the US had different levels of available technical resources to analyze and assess their own data.

To address this challenge, the COVID-19 Vaccine Allocation Planner emerged as a tool to help jurisdictions plan for the early stages of vaccine distribution. This tool allowed planners to understand how much vaccine they would need to send to different counties, according to equity guidelines written by the National Academy for Science, Engineering, and Medicine and the CDC's Advisory Committee on Immunization Practices. It quantified the number of people in each county that met various criteria for being prioritized so that states could distribute accordingly.

During the pandemic, the scarce supply of vaccines relied upon existing secure cold chain resources to protect them. They were delivered to locations that could accommodate them—not based on where risk was highest. So, while there were approximately 50,000 active vaccination sites, these sites were, for the most part, concentrated in high-population centers, leaving many Americans without close geographic access to vaccines.

With 15% of unvaccinated Americans naming travel considerations as a primary roadblock in obtaining a vaccination, this geographic barrier made reaching the goal of 70% country-wide vaccination rate very difficult [2].

To address the issue of vaccine deserts, public health leaders need clear and accurate data about where distance is a barrier and how it could be addressed.

Accordingly, the Vaccine Equity Planner (VEP) was built as part of a private–academic partnership. The open-access, online tool (available at www.vaccineplanner.org) [2] located active vaccination sites using databases from the government, retail pharmacies, and data aggregators. It then identified catchment areas around current sites that were 15 or 30 min by car, 30 min by public transport, or 15 or 30 min walking, using calculations provided by a team at Google. The areas not part of any site's catchment area were termed vaccine deserts [1]. The tool enabled planners to look at social vulnerability within vaccine deserts, according to the CDC's Social Vulnerability Index, to prioritize efforts and plan for equity. Planners could also identify potential sites for vaccination delivery within deserts, including health-related sites, schools, or places of worship. As the end of the national effort to vaccinate the population for free grew near, the tool added the option to see what percentage of people lack health insurance in each desert [1]. Data from the VEP allowed for targeted outreach and intervention, and, because it was updated frequently, provided a time series for officials to evaluate the effectiveness of their interventions in improving geographic access to the COVID-19 vaccine [2].

While the VEP was successful in enabling informed public health planning during the COVID-19 pandemic, to prepare for future pandemics, it will be important to create a tool that incorporates all barriers to vaccine access, not just geographic barriers. For example, level of vaccine confidence, historical injustice, language differences, and lack of paid time off work are all barriers to equitable vaccine administration. In addition, further work is required to recognize and rectify the correlated inequities that exist within vaccine deserts. Vaccine deserts not only depict disparities in

access to a vaccine but, in a broader context, they are also oftentimes primary care deserts. Tools like the VEP can be integrated into planning and monitoring to assess progress in accelerating equitable, efficient, and effective delivery.

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BIOGRAPHY

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In the midst of the pandemic, Weintraub expanded her portfolio to support public health decision makers to deliver COVID-19 vaccines. She advises public health departments, employers, the US Department of Health and Human Services, and Ministries of Health. Her work has been published in the *New England Journal of Medicine*, *Nature*, *Health Affairs*, and *Harvard Business Review* and cited by *The New York Times*, BBC, Netflix, and National Public Radio.

Weintraub was named a Young Global Leader by the World Economic Forum and is a Health Innovator Fellow of the Aspen Global Leadership Network. Weintraub graduated from Yale University, Stanford School of Medicine, and completed her medical training at Brigham and Women's Hospital.

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VACCINEINSIGHTS

TOOLS OF TOMORROW

SPOTLIGHT

INTERVIEW

Developing an mRNA–LNP vaccine to combat Lyme disease

Matthew Pine

Lyme disease is the most common vector-borne disease in the US, but there is currently no vaccine to treat the nearly half a million people infected every year. **Casey Nevins,** Assistant Editor, *Vaccine Insights,* speaks with **Matthew Pine,** RNA Therapeutics Scientist, InVitro Cell Research, about how a misconception led to the withdrawal of the only human vaccine to date, and prospects for a new vaccine leveraging mRNA technology.

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Q How did you get involved with vaccine science?

MP: I was introduced to vaccines during an internship at Merck where I worked on a project in collaboration with Moderna, developing a vaccine for respiratory syncytial virus (RSV) with the novel mRNA–lipid nanoparticle (LNP) platform. That was my first introduction to mRNA–LNP vaccines, and I continued working with them during my PhD at the University of Pennsylvania, developing a vaccine for Lyme disease.

Q Why are there no human vaccines for Lyme disease on the market today?

MP: Nearly half a million people in the US are diagnosed with Lyme disease every year, and if the infection goes undetected, it can have severe consequences. A preventative vaccine would be able to curtail what has become the most common vector-borne disease in the US.

A vaccine known as LYMErix™ was approved and commercialized in 1998 by GSK. However, LYMErix was taken off the market in 2002 after individuals who received the vaccine complained of arthritis. The theory that LYMErix was responsible for this response was disproven through several methods, the most notable of which was that placebo recipients and vaccine recipients both had the same frequency of arthritis. Unfortunately, a paper was published in the same year that the vaccine was commercialized suggesting that the chosen antigenic target, outer surface protein A (OspA), was potentially cross-reactive with human lymphocyte function-associated antigen-1 (hLFA-1). This cross-reactivity could potentially cause an arthritic autoimmune response through a molecular mimicry mechanism.

Even though GSK won the resulting lawsuit and proved that the vaccine was safe, once that negative narrative started, it became hard to make the vaccine commercially viable, so GSK took it off the market.

Q What lessons can be learned from the development and subsequent removal from the market of LYMErix?

MP: That we do not necessarily have to reinvent the wheel or let past failures dictate how we should move forward. In fact, most of the Lyme disease vaccines produced since LYMErix have still focused on OspA. For example, there is currently an OspA-based vaccine in phase 3 that is a collaboration between Valneva and Pfizer. In addition, there is a veterinary vaccine for dogs that contains OspA and a chimeric OspC.

In the US, there are numerous strains of *Borrelia burgdorferi*—the bacterial agent that causes Lyme disease. In all of those strains, OspA is very widely conserved. An OspA vaccine, therefore, has the potential to provide universal protection. This characteristic is essential because it is very common for Lyme patients to get one strain and then be reinfected with another strain.

OspA is also upregulated in the tick midgut, so when the tick feeds on a vaccinated individual, it takes in those OspA antibodies, which subsequently kill the bacteria in the tick midgut before it traverses to the tick saliva for transmission to humans.

Q Can you describe the immune response seen in mice after receiving the mRNA–LNP OspA vaccine you developed?

MP: First, we did a side-by-side comparison of the mRNA–LNP OspA vaccine to a recombinant OspA protein adjuvanted with alum, which is the same basic formulation as

LYMErix [1]. Throughout these experiments, the mRNA–LNP OspA vaccine showed a comparatively greater immunogenic effect.

Starting with the T cell response of the mRNA–LNP OspA vaccine, we observed robust $CD8^+$ and $CD4^+$ T cell responses that were antigen-specific to OspA. Diving deeper, we wanted to look at a subset of $CD4^+$ T cells—the T follicular helper (Tfh) cells—because they are really important in the germinal center (GC) response that generates high affinity antibodies. We found that the Tfh cell response was also very robust with mRNA–LNP immunization.

Tfh cells work in concert with GC B-cells, so we investigated the antigen-specific GC B-cells and saw, again, a significant increase in OspA-specific GC B-cells with the mRNA–LNP as compared to the recombinant protein. We also looked at the terminal outputs of the GC B-cell response, memory B-cells and long-lived plasma cells. We saw a robust antigen-specific memory B-cell and long-lived plasma cell response. Lastly, we looked at OspA-specific antibodies over a period of 6 months and observed a superior humoral response.

While our data shows that the immunogenicity is favorable, we needed to ensure that the vaccine functions against the bacteria. To prove this, we showed that mice had a higher degree of protection from infection with *B. burgdorferi* after receiving a single low dose of OspA mRNA–LNP, as compared with the recombinant protein or negative control [1].

Q What are the next steps in the development and potential commercialization of this vaccine?

MP: For this vaccine in particular, the next steps would be to move to larger animals, like non-human primates, and then to clinical trials. Moderna is currently developing two investigational mRNA Lyme disease vaccines (one for US bacterial strains and one for international strains) and employing what is likely a similar approach to ours, so it may not be necessary for us to continue to develop our vaccine.

Our vaccine was largely a proof of concept. As far as I know, our published research on the vaccine was the second paper showing that an mRNA–LNP vaccine can be developed against a bacterial target. The first paper was from a group in Israel that developed an mRNA–LNP vaccine against *Yersinia pestis* [2].

In terms of commercialization, there is still a sentiment in a subset of the Lyme disease community that OspA will forever be a no-go, but I truly believe it is the best antigenic target. For successful commercialization, researchers will have to continue debunking the myths around OspA and showing that it is a safe target. I am certainly rooting for Pfizer/Valneva and Moderna to create successful OspA-based Lyme vaccines in the next few years.

It is interesting that 25 years later, we are back at the same target as in 1998. Sometimes a good vaccine is just a good vaccine.

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BIOGRAPHY

MATTHEW PINE completed his BSc in Biology and Theology from Franciscan University of Steubenville in 2018, before gaining a PhD in Cell and Molecular Biology from the University of Pennsylvania in 2023. Co-mentored by Nobel Laureate Drew Weissman MD PhD and Norbert Pardi PhD, his graduate thesis work focused on developing an mRNA–LNP vaccine for Lyme disease. He now works as a scientist in RNA Therapeutics at InVitro Cell Research, LLC.

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