VACCINEINSIGHTS

RNA VACCINES PART 1: EXPLORING FUTURE POTENTIAL

SPOTLIGHT

INTERVIEW

Understanding and improving immune responses to RNA vaccines

Charlotte Barker, Editor, *Vaccine Insights*, speaks to **Justin Richner,** Assistant Professor, University of Illinois at Chicago, about unleashing the potential of mRNA vaccines by increasing the durability of immune responses

JUSTIN RICHNER earned his doctoral degree in 2011 from the University of California at Berkeley under the mentorship of Dr Britt Glaunsinger. He performed his post-doctoral studies at Washington University in St Louis with Dr Michael Diamond studying viral immunology and vaccine development. Dr Richner started his independent lab in 2018 and is currently an Assistant Professor in the Microbiology and Immunology Department at the University of Illinois Chicago College of Medicine.

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Q How did you get involved in the field of immunology?

JR: The overarching field throughout my scientific research, even from the undergraduate level, has been host–pathogen interactions. I began studying a bacterial

pathogen that infected an Arabidopsis plant, *Pseudomonas syringae*. That piqued my interest to go to graduate school at the University of California Berkley to study host–pathogen interactions, where I became interested in viruses and how they were able to infect host organisms.

After my graduate work, I became interested in how the host responded to the virus. I completed a post-doc with Michael Diamond at Washington University in St Louis, where we studied the host response to flaviviruses. I first established a project studying West Nile virus, and when the Zika virus outbreak occurred in 2016, we shifted the focus of my research to understanding the immune response on both the host and pathogen side of this relatively unstudied virus. I became interested in understanding the host response to these flaviviruses and how to develop medical countermeasures to combat these viruses. This was how I got into both immunology and vaccinology.

At the time, we were working with Moderna, who had a new vaccine platform in development. The Zika pandemic enabled a scenario where we could use this new technology to combat this emerging pathogen. That is where our work on the mRNA vaccine platform began.

Q What are the positives and negatives of immune responses to mRNA vaccines?

JR: In terms of immunogenicity, an advantage of the mRNA platform is that we can generate robust humoral immune responses as well as CD4 and CD8 T cell responses. Now we have administered billions of doses of mRNA vaccines in humans, the high efficacy of the platform has been demonstrated. This efficacy has been seen in other diseases in smaller numbers, including in the Zika virus RNA vaccines in early-phase clinical trials.

On the other hand, we are seeing some levels of reactogenicity with the mRNA platform. These are minor adverse events, including classic immune responses such as malaise and low-grade fever, and seem to be slightly higher with RNA vaccines than with other platforms. There are also low levels of myocarditis in RNA vaccine recipients. That being said, these are very safe vaccines. The frequency of serious adverse events is very low, and we can work further on reducing the level of minor adverse events.

Another weakness we see is low immune durability with the SARS-CoV-2 mRNA vaccine. There have been many publications within this area showing antibody titers are declining. This is why regular booster doses are recommended.

Interestingly, if we look at data from Phase 1 human trials for the Zika RNA vaccines, we do not see the same reduced durability of the immune response. One big question in the field is whether we will see robust immune durability with RNA vaccines. Are the immune durability problems observed with the SARS-CoV-2 vaccines because of the specific biology of the virus, or will this occur globally across all RNA vaccines? The way that the spike antigen is presented in the SARS-CoV-2 vaccines will be different from other viral antigens. This will have an important influence on how we think about immune durability and understand the differences in how antigen presentation influences downstream adaptive immune responses. There is also a lot of work in the field on understanding the native immune pathways that are being induced by these vaccines.

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Q What do we know about the specific aspects of immunity in aged populations that pose a challenge for vaccine developers?

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JR: Aged individuals, in general, develop reduced immune responses to infectious diseases, as well as vaccines. This is well documented in influenza literature, where we see much lower vaccine efficacy in elderly populations versus younger healthy populations.

In general, age correlates with a higher increase in some markers of inflammation, including higher base levels of inflammatory cytokines. In the context of infectious disease or vaccination, younger people develop a robust rapid response that quickly goes up. The elderly seem to mount a much more limited response that does not reach the same magnitude as a younger response; we see a blunted and delayed adaptive immune response. There are multiple factors affecting this, including a lower frequency of naïve T cells, in addition to delayed activation of the T cell response.

Intriguingly with the SARS-CoV-2 mRNA vaccines, we did not see this age-dependent decline in immune responses. The elderly developed robust immune responses to the mRNA vaccine platform, which was a pleasant surprise. The magnitude of the antibody titers and the T cell response appeared to be equivalent in younger adults and the elderly after a two-dose vaccination schedule. It seems that the elderly can overcome this basal defect in their immune system, but it is still unclear why.

There has however been some evidence that immune durability is lower in older populations, meaning a more rapid decline of antibody titers than in younger populations. This is an area requiring further research to understand if it is unique to the SARS-CoV-2 antigen.

Q What questions remain to be answered about immune responses to RNA vaccines?

JR: One thing many people in the field are working on is understanding innate immune responses. Another advantage of RNA vaccines is that they do not require an additional adjuvant. RNA vaccines are considered self-adjuvating. The main component driving this self-adjuvant property is an ionizable lipid, which is a component of the lipid nanoparticle structure. There are several interesting studies showing these ionizable lipids are highly immunogenic and able to stimulate innate immune responses. The field is moving towards understanding the molecular pathways that are engaged by these ionizable lipids, and how these interface with the pattern recognition receptors to drive innate immune responses. The area is ripe for discovery.

Q What's next for your work and for the field as a whole?

JR: We are interested in developing novel flavivirus vaccines using this mRNA platform. We are currently working on an mRNA vaccine to combat both Dengue and Zika viruses. These viruses are co-circulating and are both transmitted by the same mosquito vectors.

For Dengue virus, there are replication-competent live attenuated vaccines; however, we know that some of the epitopes in these vaccines can drive antibody-dependent enhancement and lead to more severe disease in naive individuals. This was seen for the DENGVAXIA vaccine, which mimicked a primary Dengue infection and led to an antibody-dependent enhancement phenomenon. In our lab, we use the RNA platform to modulate the specific epitopes driving antibody-dependent enhancements to make a safer vaccine. We have previously taken the same approach to Zika virus vaccines. Importantly, this is not possible with a live-attenuated platform.

We are also working on understanding the innate immune properties of these vaccines and testing different lipid formulations to see if we can modulate innate immune responses to optimize vaccine immunogenicity and reactogenicity.

I still consider myself a virologist at heart, so I am most interested in understanding how we can inhibit viral infectious diseases. I am interested in how we can use this platform and the information we have about antigens to make vaccines, particularly against viruses that have failed to develop robust vaccine responses in previous attempts. A classic example is HIV; after decades of research, we still do not have a vaccine for HIV. There are other vaccines that fit the same mold, but we have not been able to generate good immune responses.

Influenza is a virus that is ripe for some new ideas in the vaccine field, due to the 9–12-month window we have to work in. If you could shorten this by several months, it could greatly increase the efficacy of the annual influenza vaccines. The mRNA platform could certainly help here.

Another benefit of the RNA platform is that we can rapidly generate new hypotheses and test them quickly in large numbers. As the field of vaccinology moves forward, it will be interesting to see how far RNA-based vaccines will overtake other platforms, and how far they will be limited by the durability of immune responses.

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AUTHORSHIP & CONFLICT OF INTEREST

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