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DNA vaccines against Zika virus speed into clinical trials

Less than 6 months after Zika infection was declared a public health emergency, the first clinical trials of DNA vaccines against the virus are beginning.

Chris Morrison

By the end of 2016 at least two vaccines against Zika will have completed Phase I safety trials, marking the first significant clinical progress towards preventing transmission of the virus. Farthest along the development pathway are two competing DNA vaccines from the biotech company Inovio and the US National Institute of Allergy and Infectious Diseases (NIAID), showcasing the technology's potential advantages over traditional vaccine approaches.

Zika emerged as a threat in 2015, and in February 2016 the World Health Organization deemed it a public health emergency, highlighting a link between Zika infection and the devastating birth defect microcephaly. Despite the previous obscurity of the disease and funding shortfalls, industry and academia have been able to move extremely quickly to generate clinic-ready vaccine candidates. This is in part because Zika is closely related to other flaviviruses such as West Nile or Dengue for which vaccines already exist, and it illustrates industry's willingness to leap into a space where public health concerns and commercial opportunity overlap.

It also reflects some of the advantages that DNA vaccines could offer over commonly used vaccine platforms. DNA vaccines act by delivering the genetic code of a viral antigen into the nuclei of host cells, relying on the cellular machinery to then produce the antigen so that it can generate an immune response. As a result, these vaccines can be rationally designed based on genetic analysis of viral DNA. And because DNA vaccines consist primarily of strings of DNA, adds Inovio CEO Joseph Kim, "you can engineer them and manipulate them much easier compared to live attenuated viruses." They are also relatively simple to manufacture and purify, and their thermostability means they can be transported without the hassle of cold-chain storage.

Although DNA vaccine technologies have been in development since the 1990s, no DNA vaccines have yet made it to market for human use owing to efficacy issues. Success against Zika could now pave the way for renewed interest. "I think the DNA vaccine platform is going to be a competitive platform not only for Zika but for any future vaccines," says Anthony Fauci, the longtime director of the NIAID.

Delivery dilemmas

Inovio's vaccines are created by piecing together the most important or conserved sequences for multiple variations of chosen antigens to form a so-called consensus sequence, which the company says means that the vaccine can offer protection against multiple strains of a virus. For its Zika candidate vaccine GLS-5700, it has focused on the DNA that encodes the Zika pre-membrane and envelope (prM-Env) protein that forms the virus's outer protective envelope, an approach that has worked well in vaccines against related flaviviruses. Although too much consensus "becomes gibberish," says Kim, Inovio has spent 15 years optimizing an algorithm to find the right consensus balance for its DNA vaccines. The company boasts a broad portfolio of 15 DNA vaccines against a variety of infectious diseases and cancers, and has partnered with the likes of Roche and MedImmune. But none of its vaccines has yet been proved effective in a pivotal trial. (Its most advanced candidate, a vaccine against HPV to treat cervical dysplasia, completed Phase II in July 2014 and is expected to enter Phase III trials later this year, says Kim.)

In July, 40 healthy volunteers began receiving GLS-5700 in three intradermal doses, spaced one month apart.

Previous generations of DNA vaccines for diseases such as HIV and various cancers from companies like Merck & Co., Wyeth and Vical have worked well in mice but clinical studies "failed miserably," says Kim. They were safe but did not generate any specific immunity in patients, and those companies mostly went on to pursue alternative vaccine platforms (Vical and partner Astellas are testing a Phase III cytomegalovirus DNA vaccine in organ transplant recipients). Injecting DNA plasmids into the muscle or into or under the skin was not enough, says Kim; the vaccine was destroyed before it could enter the cell, much less the cell nucleus where the vaccine can access the cellular machinery necessary for it to begin to provoke an immune response. As is the case with other oligonucleotide-based therapies like RNA interference or gene therapy, delivery was the greatest hurdle for DNA vaccines.

Inovio has pursued multiple delivery technologies and has settled on electroporation: millisecond-long bursts of electricity that open up the cellular membrane to let DNA plasmids pass through. "Any DNA vaccine that does not use electroporation will not work in the clinic," Kim contends.

Others argue that the electroporation approach is not required, and will be too difficult to scale in any case. NIAID is using a needleless pressure-based delivery system developed by the company PharmaJet. Its DNA vaccine candidate uses the full-length prM-Env as an antigen (*Nature*, published online 28 June 2016) and will likely enter into an 80-subject Phase I trial in August. Should the trial go as planned, NIAID plans to move into a Phase IIb trial in early 2017.

The biotech start-up Pharos Biologicals also hopes to have a DNA vaccine for Zika in Phase I trial by the end of 2016. It is using a nanoparticle delivery system that traffics the vaccine straight to the lymphatic system for better uptake by antigen-presenting cells, says Chief Science Officer J. Thomas August.

Pick your platform

Industry and academia have also tapped other vaccine platforms for alternative candidates. The NIAID and collaborators at the Walter Reed Army Institute of Research, in Silver Spring, Maryland, USA, have entered an agreement with Sanofi Pasteur to develop a more traditional vaccine, a purified inactivated virus vaccine candidate. Fauci says that project should enter Phase I trials towards the end of 2016. The NIAID is also working with the Brazilian non-profit Butantan Institute, in São Paulo, on a live attenuated Zika vaccine based on chimeric vaccine technology successfully used to create a vaccine against the related Dengue virus.

The NIAID also announced in July that it will collaborate with GlaxoSmithKline (GSK) to develop a Zika vaccine built with a self-amplifying mRNA vaccine platform, a technology GSK acquired as part of its US$7 billion acquisition of Novartis's vaccine business in 2014. This genetic vaccine could offer advantages over its DNA vaccine competition. Whereas DNA vaccines need to get into the nucleus of the cell, mRNA vaccines only need to get into the cytoplasm, says Ripley Ballou, Vice-President Vaccines at GSK. "The hurdle for doing that is much lower," he contends, and can be achieved with use of a nanoparticle.

GSK's mRNA vaccines use the RNA of an alphavirus as a starting point and swap out the virus's protein coat for a viral antigen sequence of interest. Inside the cell, the vaccines behave like viruses, replicating, becoming double-stranded, pumping out antigen and triggering immune responses. As a new technology, it will face additional regulatory scrutiny, Ballou admits. "I would love to see it in the clinic by the beginning of 2017, but we have to have those conversations" with regulators, he cautions.

"I don't want to be overconfident but most of us who are involved with this feel reasonably certain that we will get a good vaccine for Zika," says Fauci. "The critical issue is to do it as quickly, safely and efficiently as possible so that if the outbreak continues or spreads to other regions of the world we'll have a vaccine that was proved in a good clinical trial to be safe and effective."