EDITORS' pick

Inovio

A Pennsylvania company hopes to turn synthetic DNA vaccines into rapid response agents against flu epidemics and cancer.

Inovio Pharmaceuticals, a startup based in Blue Bell, Pennsylvania, claims to have made the first DNA-based cancer vaccine to generate potent and durable T-cell responses in a human cancer. Last October, the company published phase 1 trial results obtained with their therapeutic vaccine VGX-3100 designed to prevent cervical dysplasias caused by human papilloma virus (*Sci. Transl. Med.* **4**, 155, 2012). A month earlier, an interim analysis of Inovio's universal DNA-based H1N1 vaccine, designed with the help of an algorithm that identifies consensus sequences, successfully induced protective immune responses to nine key influenza viruses, including the 1918 pandemic strain.

The DNA vaccine field has been waiting for compelling human data since the technology came to the fore in the early 1990s. At a Cold Spring Harbor meeting in 1992, various key players, including Inovio co-founder David Weiner from the University of Pennsylvania in Philadelphia and researchers from Merck of Whitehouse Station, New Jersey, got together to share data about the exciting new technology of injecting DNA into mice to elicit immune responses. In 2000, Weiner and a former student, J. Joseph Kim, who had also worked at Merck, founded the synthetic vaccine company VGX Pharmaceuticals, hoping to finally fix the inadequacies of a technology that had failed to convince in primates. Nine years later, after VGX merged with its competitor Inovio Biomedical, Kim was president and CEO of a new company—Inovio Pharmaceuticals.

Inovio has raised \$60 million to date. Much of this funding originally came from the University of Pennsylvania, where the company was founded, Merck, the Bill and Melinda Gates Foundation and the US National Institutes of Health, which awarded Inovio \$23.5 million over five years in 2008. More recently, Inovio has also raised private funding.

Ultimately, Inovio has taken two approaches to optimizing DNA vaccine

technology. First, the company has improved DNA constructs to drive maximal expression, including humanizing the codon sequences, improving the leader sequences for better solubility of the expressed antigens and optimizing the RNA structure for stability. Second, Kim says, a key realization was that natural peptide sequences might not always be the best immunizing antigen. Instead, Inovio's researchers make entirely synthetic sequences encoding peptides that are more cross-reactive than any one individual natural strain or tumor type.

Instead of trying to second-guess which short peptides might be antigenic, Inovio uses DNA encoding full-length proteins and allows the body to process them into optimal antigen fragments. A computer algorithm is used to select the best synthetic DNA by aligning all known sequences of the antigen of interest and then employing manual identification of the most immunologically dominant and conserved residues based on a priori knowledge; according to Kim, the final choices require a lot of human input. For targeting variable viruses like influenza, Inovio can craft a cocktail of synthetic molecules designed to be broadly reactive against many strains at once. In contrast, a traditional seasonal vaccine can, at most, incorporate four different strains and these need to be predicted in advance. Kim says they are very close to covering every major strain of influenza ever reported. And Inovio, currently with a 60-person-strong staff, is not stopping with influenza—it also has pipeline vaccines for malaria, HIV, hepatitis C, cancer and many others, with some as advanced as phase 2. So far, with over 400 patients in about 900 procedures, their DNA vaccines have been well-tolerated with a good safety profile.

Another hurdle was how to get DNA into tissues more efficiently. After trying many delivery modalities, the company settled on *in vivo* electroporation and has acquired a considerable portfolio of intellectual property on the approach. Kim says Inovio is

J. Joseph Kim, President and CEO of Inovio.

currently partnering with a larger company to optimize low-cost, battery-powered DNA delivery devices.

According to Ted Ross, of the University of Pittsburgh, the beauty of synthetic genes is their delivery versatility. Although Inovio is currently heavily invested in electroporation, he says, DNA vaccines should be amenable to delivery by any convenient platform (in case Inovio wanted to sublicense sequences to companies with other delivery methods). One question Ross has about Inovio's SynCon algorithm is whether their consensus sequences are representative; Inovio's algorithm queries publicly available antigen sequences so it might be subject to sampling bias if small flu outbreaks lead to large numbers of individual sequence deposits in the database. Kim counters that their consensus sequence choices do confer broad reactivity. Whatever the case, Ralph Baric at the University of North Carolina, Chapel Hill School of Public Health, Chapel Hill, North Carolina, remains upbeat about Inovio's approach; he thinks that rational synthetic sequence design can maximize performance and vastly accelerate vaccine production, and could prove especially helpful during an outbreak. A lot now rides on how Inovio's synthetic vaccines progress in ongoing human efficacy trials.

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