

Human Vaccines: News

Successful Phase I study for novel *Staphylococcus aureus* vaccine

Recently, the biopharmaceutical company Inhibitex, Inc. (Alpharetta, GA) announced promising Phase I data of a novel three-antigen *S. aureus* investigational vaccine.

S. aureus is a leading cause of hospital-acquired infections in the US. The emergence of hard-to-treat methicillin-resistant *S. aureus* (MRSA), in both the hospital and the community setting, and the additional costs to treat these infections provide a rationale for the development of a vaccine to prevent *S. aureus* infections.

The candidate vaccine SA3 Ag is based on Inhibitex's proprietary MSCRAMM technology

platform. This technology is based on a family of surface proteins found on pathogenic bacteria that enable them to attach to tissue and initiate an infection. SA3 Ag is comprised of *S. aureus* capsular polysaccharide serotypes 5 and 8 conjugated to CRM₁₉₇ and the recombinant surface-expressed MSCRAMM protein, clumping factor A. Pfizer has worldwide exclusive rights to the company's MSCRAMM protein platform for the development of staphylococcal vaccines.

Pfizer presented data of the double-blind randomized placebo controlled Phase I at this

year's ECCMID/ICC in Milan (Italy). The study included 408 healthy volunteers and showed that the candidate vaccine elicited a positive antibody response to each of the three components.

"We are very encouraged with the initial safety and immunogenicity profile of SA3Ag in this Phase 1 trial," stated Dr. Joseph Patti, Senior Vice President and Chief Scientific Officer of Inhibitex, Inc. "We are pleased with the clinical progress of the staph vaccine program by our partner Pfizer and look forward to its continued development."

Influenza vaccination during pregnancy protects babies

According to a new study, babies born to women who receive the influenza vaccine while pregnant are almost 50% less likely to be hospitalized for the flu than babies born to mothers who are not vaccinated during pregnancy.

A study published in the *American Journal of Obstetrics & Gynecology*¹ set out to determine the impact of maternal vaccination on influenza hospitalizations in infants. The researchers analyzed data collected by a vaccine surveillance network in three US counties over the course of seven flu seasons between 2002 and 2009. The data included information about 1,510 babies who had been hospitalized

with fever, respiratory symptoms or both within the first six months of life and who had undergone laboratory testing for influenza infection. The study showed that infants born to mothers who received the influenza vaccine during pregnancy were 45–48% less likely to be hospitalized with laboratory-confirmed influenza.

This is the first population-based, laboratory-confirmed study to demonstrate a benefit for infants of influenza-vaccinated mothers.

Pregnant women are generally recommended to get vaccinated against influenza because they are known to experience increased morbidity and mortality during

pregnancy and in the immediate postpartum period if they get the flu.

"We also know that mothers pass antibodies through the placenta to the baby. This study showed us that receiving the influenza vaccine during pregnancy not only protects the mother, but also protects the baby in the early months of life," explained lead researcher, Dr. Katherine Poehling, from Wake Forest Baptist Medical Center (Winston-Salem, NC).

Reference

1. Poehling KA, et al. *Am J Obstet Gynecol* 2011; 204:S141-8 .

Sinovac advances vaccine against human enterovirus 71

Recently, Sinovac Biotech Ltd., a leading provider of biopharmaceutical products in China, announced the commencement of the Phase II clinical trial for its proprietary inactivated EV71 vaccine against hand, foot and mouth disease (HFMD) following the announcement of positive results from their Phase I trial.

Enterovirus 71 (EV71) causes HFMD among children under ten years old. While HFMD is a common and usually mild childhood disease, it is sometimes associated with complications such as viral or aseptic meningitis or encephalitis. There have been a number of outbreaks of HFMD caused by EV71 in

the Asia-Pacific region since 1997 including in China, Malaysia, Singapore, Australia and Taiwan. There is no treatment or vaccine available for enterovirus infections.

Sinovac's randomized, double-blind, placebo-controlled phase I study was initiated in the Guangxi Province at the end of 2010 and included 168 volunteers in three different groups: adults, young children and infants. The EV71 vaccine was well-tolerated without major safety issues in each of the three target groups, and preliminary data showed that it could induce an effective immune response.

Dr. Weidong Yin, Chairman and CEO of Sinovac, remarked: "We were pleased to achieve this significant milestone in the development of our proprietary novel EV71 vaccine. HFMD represents a significant unmet medical need given the global lack of an identifiable treatment or vaccine against this disease that results in pediatric fatalities. We completed the Phase I clinical trial for all three population groups and reported positive safety and tolerance profiles, as well as good immune responses induced by the vaccine candidates. We are on track to commence the Phase II trial in one or two months."

The purpose of the Phase II clinical trial is to determine the dosage level through evaluating the immunogenicity and safety of Sinovac's EV71 vaccine candidate, and to provide the

reference data for an eventual Phase III clinical trial. The phase II clinical trial is designed as a single-center, randomized, double-blinded, placebo-controlled study with 540 healthy

volunteers from 3 to 35 months old separated into three age groups. It is anticipated to take 6 months to complete the phase II clinical trial.

HIV weakness revealed

Researchers at Ragon Institute of Massachusetts General Hospital, MIT and Harvard University have identified sections of an HIV protein where mutations would actually undermine the virus's ability to survive and reproduce. Targeting these newly identified viral protein sequences could lead to the development of more effective HIV vaccine candidates.

Although global HIV infection rates have decreased over the past decade, there are still more than 33 million people living with AIDS, mostly in developing countries with limited access to antiretroviral drugs that can control the infection. The only real solution would be the development of an effective vaccine, which has proven difficult so far, in part because HIV mutates so rapidly.

It is believed that an effective HIV vaccine will have to include both an antibody and a T-cell component. Designers of the T-cell arm of a vaccine have tried to target single amino acids that seem unable to evolve to a different form, with the goal of inducing mutations that weaken the virus's fitness. This strategy has had limited success, because mutations elsewhere in the viral protein can help restore the loss of fitness.

A new study published online in the journal *Proceedings of the National Academy of*

*Sciences*¹ looked not just at single mutations but tried to determine whether there are groups of amino acids within viral proteins that evolve together in a coordinated way. The research team analyzed available HIV protein sequences obtained from infected patients using a mathematical approach, including a method called random matrix theory. Initially developed to study high-energy physics, this approach has also been applied in other fields such as economics and biology. Focusing on the HIV structural protein gag, the authors identified five co-evolving groups of amino acids within the protein. They looked at each pair of sites within the groups, calculating whether a double mutation was beneficial or detrimental to the virus's survival. They also analyzed triplets and larger groups. The group that showed the highest proportion of detrimental mutation was termed sector 3. Structural analysis revealed that amino acids in sector 3 are located at interfaces between proteins that form the viral capsid surrounding the virus's genetic material.

"If you make multiple mutations to these amino acids, it is difficult for the virus to assemble the capsid", explained senior author Dr. Arup Chakraborty from MIT (Boston, MA).

When the findings were also tested against human clinical data, the researchers discovered that T cells in patients who control HIV without medication do in fact disproportionately target sector 3 amino acids at multiple points. In accordance, HIV strains with multiple mutations in this sector were rarely found, indicating that those strains are less likely to survive.

The researchers suggest designs for test vaccines based on the vulnerabilities they found in the gag protein, and are now looking for vulnerable targets in other HIV proteins.

According to Dr. Rafi Ahmed, Professor of Immunology at the Emory University Vaccine Center (Atlanta, GA), the paper offers an exciting new approach to designing HIV vaccines. "It breaks new ground in terms of vaccine design and potential insights into why elite controllers are more effective at controlling HIV infection, and it provides additional protein regions to examine," Dr. Ahmed said.

Reference

1. Dahirel V, et al. Proc Natl Acad Sci USA 2011; 108:11530-5.

BiondVax's universal flu vaccine successful in Phase II

TBiondVax Pharmaceuticals Ltd. (Ness Ziona, Israel) recently announced that its universal influenza vaccine has successfully met primary and secondary endpoints of the first Phase II trial. The universal influenza vaccine Multimeric-001 is designed to provide multi-season and multi-strain protection against all human influenza virus strains, including both seasonal as well as pandemic influenza strains such as Swine or Avian flu. BiondVax's innovative technology utilizes a unique proprietary combination of conserved epitopes from influenza virus proteins to activate the immune system for a cross-protecting and long-lasting effect.

Two hundred healthy volunteers participated in the randomized, double-blind, placebo-controlled Phase II study, conducted at two clinical centers in Israel. The Multimeric-001 universal influenza vaccine was found to be safe and well tolerated, thus meeting the primary endpoint of the study. The vaccine also induced robust humoral and cell-mediated immune responses, representing secondary study endpoints. Subjects who received two doses of the Multimeric-001 vaccine in an adjuvanted 500 µg formulation showed a statistically significant increase in the level of IgG antibodies against the Multimeric-001 vaccine. It was also found that the vaccine caused a statistically significant elevation in the secretion of

Interferon- γ , a known anti-viral agent. In addition, the Multimeric-001 vaccine, when used in conjunction with a commercially available seasonal influenza vaccine (trivalent inactivated vaccine, or TIV), enhanced the performance of the TIV relative to TIV alone by increasing the rates of Hemagglutination Inhibition (HI) seroconversion to influenza strains both included and not-included in the TIV itself. These results suggest that the vaccine has the potential—when administered prior to future seasonal or pandemic influenza outbreaks—to raise the general level of preparedness in the population, by improving protection and broadening cross-strain coverage offered by the strain dependent influenza vaccines.

Dr. Ron Babecoff, BiondVax's CEO, said: "We are very excited with these positive Phase IIa results. We have confirmed, in what is to our knowledge the first Phase II study of a universal influenza vaccine ever conducted in the world, that the Multimeric-001 vaccine is not

only safe and immunogenic on its own, but it also has the potential to enhance the performance of traditional strain-dependant flu vaccines. We are more convinced than ever that this product will provide real benefit to people all over the world, bringing the ultimate goal

of a universal influenza vaccine closer than ever before."

BiondVax now prepares to commence a Phase II trial in 110 participants aged 65 and over in the fourth quarter of 2011.

Vaccine against renal cell carcinoma enters Phase III

The German biopharmaceutical company Immatics Biotechnologies GmbH recently announced the initiation of a pivotal Phase III trial of IMA901, the company's lead cancer vaccine for the treatment of renal cell carcinoma (RCC).

IMA901 is comprised of ten different tumor-associated peptides (TUMAPs) found to be highly over-expressed in the majority of RCC patients. This peptide-based vaccine offers a stable, off-the-shelf formulation as well as robust and easily scalable manufacturing.

The Phase III clinical trial, called the IMPRINT study, is designed to demonstrate the overall survival benefit of IMA901 in combination with the standard first-line therapy sunitinib (Sutent by Pfizer) in RCC patients. The global

multicenter, randomized, controlled study will include approximately 330 patients with metastatic and/or locally advanced RCC who are candidates for receiving standard first-line therapy. The primary endpoint of the study is overall survival in patients receiving IMA901 in combination with sunitinib versus sunitinib alone. Overall survival will also be tested in patients who are positive for a prospectively defined biomarker signature, which was identified as being predictive for improved clinical outcome in IMA901-vaccinated patients in the previous Phase II study. Further secondary endpoints include progression-free survival, safety and tolerability, and cellular immunomonitoring to assess the T-cell response to the peptides contained in IMA901.

Carsten Reinhardt, CMO of Immatics, said: "The start of this Phase III trial with IMA901 is a key milestone in Immatics' clinical development. The protocol for this trial builds on the encouraging insights gained from the Phase II study and feedback from key opinion leaders as well as successful meetings with regulatory agencies both in Europe and the US. We look forward to confirming the positive overall survival data seen in the phase II study as advanced renal cell cancer still has a very high unmet medical need."

Besides IMA901, Immatics' pipeline also includes IMA910, in Phase II for colorectal cancer, and IMA950, which is being developed for glioma.

Promising antigen for new TB vaccine: EspC

A recent study has identified a protein secreted by tuberculosis (TB) bacteria that could be a promising new vaccine candidate as well as a useful diagnostic tool for TB.

TB is caused by *Mycobacterium tuberculosis* (MTB), which infects the lungs and spreads through the air as a result of coughing. Each year, there are nine million new cases of TB, with 4700 people dying every day worldwide. The only available TB vaccine BCG is derived from *M. bovis*, which infects cattle and is closely related to MTB and offers only partial protection.

In the new study published in *Proceedings of the National Academy of Sciences*,¹ Professor Ajit Lalvani and colleagues examined immune responses to the protein EspC in 45 people with active TB, 27 people with latent TB infection, and 27 uninfected BCG-vaccinated

controls. EspC triggered a stronger immune response in people infected with the TB bacterium than any other known molecule. Only 2 out of 27 BCG-vaccinated controls responded to the antigen, demonstrating the specificity of the response. Further experiments revealed that this is because the TB vaccine lacks genes that are needed to secrete EspC. As a result, the BCG vaccine does not induce an immune response to this protein, and deploying it as a new TB vaccine will likely provide additive immunity over and above that provided by BCG. EspC could also be useful as a diagnostic tool, since an immune response to it is seen in TB-infected subjects, but not in non-infected subjects previously vaccinated with BCG. The currently used tuberculin skin prick test (Mantoux test) does not allow this distinction.

Dr. Ajit Lalvani from Imperial College London (UK) stated: "We've shown that EspC, which is secreted by the bacterium, provokes a very strong immune response, and is also highly specific to MTB. This makes it an extremely promising candidate for a new TB vaccine that could stimulate broader and stronger immunity than BCG. Surprisingly, our results also show that this molecule could underpin next-generation diagnostic blood tests that can rapidly detect latent TB infection."

Reference

1. Millington KA, et al. Proc Natl Acad Sci USA 2011; 108:5730-5.

Vaxart's first oral vaccine starts clinical trials

The San Francisco (CA) based biotechnology company Vaxart Inc. has recently begun dosing volunteers in a Phase I clinical trial of its oral avian influenza (H5N1) vaccine candidate. This is the first clinical study evaluating a vaccine that uses the company's novel oral-delivery platform technology based on adenovirus vectors.

"This first trial in humans is important, because if safety is demonstrated with one vaccine, we can expect that later vaccines using the same Vaxart technology will also be safe," said Vaxart founder and CSO Dr. Sean Tucker.

Besides the currently tested H5N1 candidate vaccine, the company has a pipeline of additional vaccines in development, all based

on its oral-delivery technology. Central to the company's approach is the incorporation of a unique adjuvant in the viral vector that delivers the vaccine antigen. Vaxart's adjuvant works by binding to Toll-Like Receptor 3 to stimulate a potent immune response when the vaccine is taken orally.

Interestingly, all Vaxart vaccines use the same vector or delivery vehicle, meaning that the company's novel approach has overcome the main obstacle to vector-based vaccination: anti-vector immune responses. People who have been naturally exposed to adenovirus, or have been vaccinated using an adenoviral vector, will develop antibodies to the vector itself. These anti-vector antibodies reduce the effectiveness of later vaccines using the same

vector. Vaxart's pre-clinical data confirm that serum anti-vector neutralizing responses are not mirrored in the intestinal environment, allowing oral delivery to circumvent pre-existing immunity. In animals, the company demonstrated robust immune responses against multiple targets following a series of oral vaccines, despite using the same delivery vehicle.

Vaxart also announced the issuance of US patent no. 7,879,602, which provides broad protection for the company's oral-delivery technology. "This patent greatly increases the value of our portfolio because it covers all methods we know of for oral vaccination with a re-usable platform technology," said Vaxart's CEO Dr. Michael Finney.

©2011 Landes Bioscience.
Do not distribute.