

Human Vaccines & Immunotherapeutics: News

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Sanofi Pasteur shows efficacy of its dengue vaccine in phase 3

The world's first, large-scale Dengue Vaccine efficacy study successfully achieved its primary clinical endpoint Sanofi Pasteur recently announced that the first of two pivotal phase 3 efficacy studies with its dengue vaccine candidate has achieved its primary clinical endpoint. The efficacy study showed a significant reduction of 56% of dengue disease cases and a good safety profile for the vaccine.

Dengue is a threat to nearly half of the world's population and is a pressing public health priority in many countries in Asia and Latin America where epidemics occur. According to the World Health Organization (WHO), up to 100 million people are infected annually with dengue, 500,000 of whom develop dengue hemorrhagic fever (DHF), the severe form of the disease. Dengue infection tends to be underreported because it is often misdiagnosed due to a large spectrum

of clinical symptoms from mild non-specific illness to life-threatening complications and due to the limitations of the surveillance systems. There is no specific treatment for dengue.

Sanofi Pasteur has been working on a dengue vaccine for >20 y. Their vaccine candidate is the first such vaccine in advanced development, and has been tested in >40,000 volunteers. The current randomized observer-blinded placebo-controlled multicenter Phase 3 trial included 10,275 children aged 2–14 y from dengue-endemic areas of Indonesia, Malaysia, Philippines, Thailand and Vietnam. Subjects were randomized to receive either three injections of vaccine or placebo (2 to 1 ratio) on a 0–6–12 mo schedule. The primary endpoint was the number of symptomatic virologically-confirmed dengue cases caused by any serotype. Initial results confirmed the good safety profile of the vaccine and showed

a 56% reduction of dengue disease cases in the vaccinated group. Long-term follow-up of the study participants is planned.

"This achievement is the result of more than 20 years of work in the field of dengue, collaborating with investigators, volunteers, authorities, scientific experts and international organizations," said Dr Olivier Charmeil, President and CEO of Sanofi Pasteur. "Developing a dengue vaccine for the benefit of children and their parents is at the heart of our mission. Our goal is to make dengue the next vaccine-preventable disease and to support the WHO's ambition to reduce dengue mortality by 50% and morbidity by 25% by 2020."

The findings of this first large-scale efficacy study will be further complemented by results from the second phase 3 study, which is ongoing in Latin America and should be completed in 3Q14.

New glioblastoma vaccine: Safe and immunogenic in phase 1

The German biopharmaceutical company immatics biotechnologies has successfully completed a phase 1 trial of its brain cancer vaccine IMA950. Based on the positive safety and immunogenicity data, immatics and its collaborators Cancer Research UK and Cancer Research Technology have entered a license agreement in which immatics will continue to develop its cancer vaccine IMA950 for glioblastoma, the most common and lethal adult brain tumor.

The vaccine IMA950 consists of 11 HLA-restricted tumor-associated peptides (TUMAPs). The TUMAPs, identified by immatics using its proprietary drug discovery platform XPRESIDENT are known to be overexpressed on the surface of glioblastoma tumors. They trigger the patient's immune system to recognize and kill tumor cells while leaving healthy cells unharmed.

This Phase 1 multicenter study, conducted at seven sites across the UK, included 45 patients with newly diagnosed glioblastoma. They were treated with IMA950 in addition to

standard of care (surgery and concomitant or adjuvant chemotherapy with temozolomide). IMA950 met the agreed primary endpoints of safety and immunogenicity. In particular, 90% of patients responded to the vaccine, in comparison to the pre-defined goal of 60%.

According to the chief investigator of the Phase 1 study, Professor Roy Rampling, brain tumors are a particularly difficult type of cancer to treat with conventional methods, but they have recently been accepted as a possible target for immunotherapy. He said: "In our study, we investigated whether patients newly diagnosed with the most common and aggressive type of malignant brain tumour called glioblastoma could mount an appropriate immune response when given IMA950 and if the vaccine was safe. IMA950 was very simple to administer and was very well tolerated. Importantly, we were very pleased to see that nearly all patients mounted an immune response that could be detected in the blood, which is the first step in establishing clinical activity before determining patient benefit in

subsequent studies."

IMA950 is developed under the Clinical Development Partnerships (CDP) joint initiative of Cancer Research UK's Drug Development Office (DDO) and Cancer Research Technology (CRT). Under the CDP scheme, companies retain rights to their drugs while allowing Cancer Research UK's DDO to undertake early clinical development work to assess the treatment's benefit to cancer patients. IMA950 is the first of nine products developed under the CDP initiative to complete a clinical trial and be taken forward by the company.

Dr. Paul Higham, CEO of immatics, said: "I am delighted that we are in a position to take the development of IMA950 forward for the treatment of patients with glioblastoma. This is our third cancer vaccine to have shown promising results. There is clearly a high need for new therapies for glioblastoma, which is a very hard-to-treat cancer, with very poor survival rates. The DDO has been an excellent partner and we are very grateful for the work

FDA approves sublingual hay fever immunotherapeutic

The US Food and Drug Administration (FDA) has recently approved a novel treatment for hay fever. The sublingual tablet Ragwitek, developed by Merck and Co, is recommended for adults aged 18–65 y.

People with ragweed allergy suffer from stuffy noses with sneezing, itching and congestion, as well as itchy and watery eyes. These symptoms often affect the quality of sleep and impair daily activities. Moreover, these problems often precede the development of asthma. Current treatments include various nasal sprays as well as injectable immunotherapeutic products.

The new tablet Ragwitek, made of ragweed pollen, is the first sublingual hay fever

treatment. Patients place it under their tongue once a day to stimulate immunity against the ragweed allergen. While the first dose is taken in a health care professional's office to monitor for any adverse reactions, Ragwitek may be taken at home after that. Treatment is typically started three months prior to the start of ragweed pollen season (September in the US) and continued throughout the season.

“The approval of Ragwitek offers millions of adults living with ragweed pollen allergies in the United States an alternative to allergy shots to help manage their disease,” said Dr. Karen Midthun, director of the FDA's Center for Biologics Evaluation and Research.

Critics say that people who are allergic to

ragweed are often also allergic to other plants, so taking Ragwitek may not completely resolve hay fever symptoms. However, it may be a first step in making this kind of allergy treatment a possibility. Taking a pill against ragweed allergy would be much simpler than a series of injections, which has been the standard treatment until now.

If a person also is allergic to other plants, it would mean taking a separate pill for each. This may become possible in the near future—both Merck and Stallergenes have recently received FDA approval for their pills (Grastek and Oralair) for treatment of grass pollen allergies.

Combining the cancer vaccine DPX-Survivac with immune modulators

The company Immunovaccine presented positive preclinical and clinical data on their DepoVax-based vaccines, and in particular on their brain cancer candidate vaccine DPX-Survivac, at the recent Annual Meeting of the American Association for Cancer Research (AACR).

DepoVax is a patented formulation that provides controlled and prolonged exposure of antigens plus adjuvant to the immune system, resulting in a strong, specific and sustained immune response with the capability for single-dose effectiveness. The DepoVax platform is highly flexible, allowing it to work with a broad range of target antigens in various therapeutic applications. Immunovaccine's lead candidate DPX-Survivac consists of survivin-based peptide antigens formulated in the DepoVax adjuvanting platform. Survivin is a promising tumor-associated antigen, broadly overexpressed in solid tumors and blood cancers including ovarian, breast, colon and lung cancers, among others.

The first study presented by Immunovaccine at this year's AACR showed that the immunomodulating agent metronomic cyclophosphamide (mCPA) enhances the immunogenicity of DepoVax-based vaccines in preclinical cancer models consistent with previously reported phase 1 data showing a similar enhancement of DPX-Survivac in patients. In the animals, combination therapy was able to eliminate advanced tumors that could not be treated with vaccine or mCPA alone. The addition of an anti-PD-1 checkpoint inhibitor to the DepoVax vaccine/mCPA combination resulted in further enhanced anti-tumor activity, which allowed the treatment of more advanced tumors.

“These study results represent strong support for Immunovaccine's belief that combination immunotherapies will be essential to treat cancer,” said Dr. Marc Mansour, Chief Operating Officer of Immunovaccine. “Combining a vaccine with immune modulators like cyclophosphamide may be most

effective in patients with no evidence of disease and with a high rate of recurrence, while combining vaccine-based therapies with synergistic checkpoint inhibitors may be particularly useful for patients with more aggressive disease.”

A second study detailed immune responses from Immunovaccine's Phase 1 study of DPX-Survivac in ovarian cancer patients. The vaccine induced durable target T-cell responses, which were more robust when DPX-Survivac was combined with cyclophosphamide as an immune modulator. These results, together with the preclinical data, provide strong support for the potential of combining DPX-Survivac with complementary immune modulators and immunotherapies.

Immunovaccine expects to initiate a Phase 2 trial of DPX-Survivac in ovarian cancer patients in Canada, as well as a Phase 1/2 trial of the vaccine in brain cancer patients in Italy later this year.

Two Meningococcal B vaccines receive FDA ‘Breakthrough Therapy’ designation

Two recent decisions by the FDA should pave the way for finally introducing meningococcal B (MenB) vaccines in the US. The FDA designated both Novartis' Bexsero and Pfizer's

rLP2086 as a Breakthrough Therapy, which entitles candidates for serious or life-threatening conditions to an expedited development and review process.

Novartis already has an approved vaccine against MenB disease on the market. Bexsero, which consists of three MenB surface proteins and outer membrane vesicles, is available in

Europe, Canada and Australia and can be used from two months of age. In the US, the vaccine only recently received Breakthrough Therapy designation, and Novartis plans to file for licensure as early as 2Q14. Although not licensed in the US, Bexsero was given to students and staff at Princeton University and University of California Santa Barbara in early 2014 following MenB outbreaks on their campuses. Under an Investigational New Drug (IND) designation, Novartis provided nearly 30,000 doses of the vaccine to halt the spread of infection. "The recent outbreaks on US university campuses have shown that meningitis B is unpredictable and can strike at any time with devastating consequences," said Dr. Andrin Oswald, Division Head, Novartis Vaccines. "A US license for Bexsero is the only sustainable solution to ensure timely responses to future outbreaks and to provide access to parents and physicians across the country. We will continue to work with the FDA to bring Bexsero to

the US as soon as possible."

Pfizer received Breakthrough Therapy designation for its vaccine candidate, bivalent rLP2086, currently under investigation for the prevention of invasive MenB disease in persons 10–25 y of age. The vaccine targets the LP2086 bacterial surface protein. Pfizer's clinical development program includes Phase 2 and 3 trials evaluating > 20,000 subjects, about 14,000 of whom will receive the investigational vaccine. Pfizer plans to file for licensure of the bivalent rLP2086 vaccine as soon as mid-2014. "Pfizer is developing this meningococcal B vaccine candidate to help protect adolescents and young adults against a difficult to diagnose and often deadly disease," said Dr. Emilio Emini, Senior Vice President of Vaccine Research and Development for Pfizer. "We are encouraged by the FDA's recognition of the need to prevent meningococcal B disease, and the Breakthrough Therapy designation highlights the urgent need for prevention

of meningococcal B disease."

N. meningitidis serogroup B is the leading cause of bacterial meningitis and septicemia in the developed world. Invasive meningococcal disease is a rare but rapidly progressing and aggressive disease, that can kill or cause serious life-long disability, including brain damage, hearing loss, and amputations. Initial symptoms of the disease are often nonspecific and flu-like, making it difficult even for health care professionals to diagnose the disease in its early stages. Vaccination is thus the best defense against the disease, which leaves little time for intervention.

Of the five meningococcal serogroups (A, B, C, W-135 and Y) that have been responsible for the majority of meningococcal disease, serogroup B is the only one for which no broadly-protective vaccine is currently approved in the US.

MERS vaccine is technically feasible, but is it commercially feasible?

According to a new report in the journal *Vaccines*,¹ an investigational vaccine candidate against the recently emerged Middle East Respiratory Syndrome Coronavirus (MERS-CoV) blocked infection in preclinical studies. A second vaccine candidate against Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), developed on a similar platform, also inhibited virus infection in animals.

In the past, vaccine strategies for emerging pathogens have been limited due to the sudden nature in which the virus first appears and delayed by the protracted traditional vaccine development process. In the current study, researchers from the University of Maryland School of Medicine (UMSM) and the company Novavax have used a novel method to rapidly develop vaccines against previously unknown viruses, such as MERS-CoV and SARS-CoV. The vaccine candidates are based on the major surface spike (S) protein, a SARS-CoV and MERS-CoV surface protein responsible for attaching the virus to cells, formulated using Novavax' proprietary recombinant nanoparticle vaccine technology. Both experimental vaccines induced neutralizing antibodies, or immune responses, that prevent virus from infecting cells. This peer-reviewed manuscript describes a novel method to rapidly develop vaccines against previously unknown viruses,

such as MERS-CoV, which appear suddenly and cause severe illnesses in humans.

"The emergence of SARS-CoV and MERS-CoV demonstrates how coronaviruses can spill over from animals into humans at any time, causing lethal disease," said Dr Matthew Frieman from UMSM and corresponding author on the publication. "Despite efforts to create a vaccine against SARS-CoV, no vaccine candidate has, to date, been successfully licensed for use. We have demonstrated that this novel method rapidly creates SARS-CoV and MERS-CoV vaccines that induce neutralizing antibodies in mice."

"Our protein nanoparticle vaccine technology is proving to have the potential to respond rapidly to emerging viruses such as MERS-CoV and certain potential pandemic influenza strains, addressing what are clearly urgent public health needs," said Gale Smith PhD, Vice President of Vaccine Development at Novavax. "Novavax will continue to evaluate this technology to produce highly immunogenic nanoparticles for coronavirus, influenza, and other human disease pathogens with the potential for pandemic and sustained human to human transmission."

MERS-CoV was first identified in 2012 and is one of a family of viruses with the potential to rapidly spread from a benign infection of

animals to cause severe disease in humans. According to the World Health Organization (WHO), MERS-CoV thus far has resulted in 107 deaths out of 345 infections, the majority of which are characterized by severe illness and hospitalizations. MERS-CoV is more deadly than the related SARS-CoV, but does not seem to spread as quickly in humans.

After MERS cases recently increased in Saudi Arabia, officials invited five international vaccine makers to visit and discuss the development of an affordable vaccine. But while the know-how to create a vaccine against MERS-CoV may exist, the question remains whether it makes sense both financially and from a public health standpoint.

Virology experts suggest that instead of spending millions on immunization to halt the infection's spread, it would be better to trace its source, thought to potentially be among camels. Even if such a vaccine was developed, there is the question of whom to vaccinate. In the past two years, MERS-CoV infected around 350 people across the Middle East, Europe, Asia and North Africa. But many of the cases are concentrated: of 91 cases reported in Saudi Arabia in April this year, 73 cases occurred in Jeddah, many of them in health care workers.

Dr Bart Haagmans from the Netherlands'Erasmus Medical Centre believes

that developing a vaccine against MERS may not be a high priority for drugmakers given the syndrome's thusfar limited scope. He told *Reuters*: "I question whether there would really be any interest from vaccine companies to

develop a human vaccine at this stage. That is what we know already from many other viral infections where there are only a very limited number of people affected. It is common sense and general knowledge, I would say."

Reference

1. Coleman CM, et al. Vaccine 2014; 32:3169-74; PMID:24736006; <http://dx.doi.org/10.1016/j.vaccine.2014.04.016>

Stemline's synthetic multi-peptide cancer vaccine enters Phase 2

The FDA recently accepted Stemline Therapeutics' Investigational New Drug (IND) application for SL-701, a therapeutic vaccine candidate against brain cancer. FDA acceptance enables the company to advance SL-701 into a Phase 2 trial of adults with glioblastoma multiforme (GBM) in first recurrence.

The vaccine candidate SL-701 is comprised of multiple synthetic peptides engineered for increased immunoreactivity against targets overexpressed on the cancer stem cells (CSCs) and tumor bulk of gliomas, the most common type of brain cancer. The subcutaneously-administered cancer therapy is based on a vaccine developed at University of Pittsburgh that demonstrated single agent clinical efficacy, including complete responses (CRs) and partial responses (PRs) in Phase 1/2 trials

conducted by the university in adults and children with high-grade gliomas, including GBM.

The upcoming Phase 2 trial, sponsored by Stemline Therapeutics, will include 80–100 patients in multiple centers. The study will be designed to evaluate SL-701 in adults with GBM that has recurred following initial treatment with surgery, radiation, and chemotherapy. Co-primary endpoints will be overall response rate and survival.

Dr. Eric Rowinsky, Stemline's Chief Medical Officer, commented: "We are very excited to be opening our first of two expected INDs this year. If the data generated by our SL-701 study are in-line with the results of earlier studies, we intend to work with the regulatory authorities towards registration and commercialization. In addition to SL-701, our other clinical

program, SL-401, a targeted therapy directed to the interleukin-3 receptor which is over-expressed on CSCs and tumor bulk of a wide range of hematologic malignancies, is also on track for IND filing and initiation of studies this year."

David Reardon, MD, Clinical Director, Center of Neuro-oncology at the Dana-Farber Cancer Institute, and primary investigator of the upcoming study, commented,

GBM and other high-grade gliomas are particularly aggressive cancers that arise from glial tissue and account for approximately 14,000 new cases of brain cancer diagnosed in the US each year. Treatment options are limited and prognosis continues to remain poor.

Evolution of whooping cough bacterium may reduce vaccine effectiveness

According to a new study, the *Bordetella pertussis* bacterium that causes whooping cough has changed—most likely in response to the vaccine used to prevent the disease. The bacterium no longer produces a key surface antigen called pertactin, which is a component of some current pertussis vaccines. The change in surface protein composition could result in reduced vaccine effectiveness.

A current acellular pertussis vaccine – composed of pertussis toxin, filamentous haemagglutinin and pertactin – was introduced in Australia in 1997, replacing the previous whole-cell vaccine.

A team of Australian researchers analyzed strains of *B. pertussis* from across Australia and found that many strains no longer produce pertactin. 320 bacteria samples from patients with whooping cough were obtained

during 2008–12 from five states (NSW, Victoria, Queensland, South Australia and Western Australia). The proportion of pertactin-free bacteria rose from 5% of cases tested in 2008 to 78% in 2012. The study was recently published in the journal *Emerging Infectious Diseases*.²

"It's like a game of hide and seek. It is harder for the antibodies made by the body's immune system in response to vaccination to search and destroy the whooping cough bacteria which lack pertactin," said the senior author of the study, Dr. Ruiting Lan. "This could mean that these pertactin-free strains have gained a selective advantage over bacterial strains with the pertactin protein."

Pertactin-free pertussis strains have been detected not only in Australia but also in countries such as France and the US. According to

Dr Lan, the fact that they have arisen independently in different countries suggests that the change may have happened in response to the vaccine. He said: "More studies are needed to better understand the effects of vaccination on the evolution of the organism."

There is no evidence that the pertactin-free strains are more harmful than other strains, and it is not yet clear whether they reduce the effectiveness of the vaccine in the short or long-term.

Reference

2. Lam C, et al. Emerg Infect Dis 2014; 20:626-33; PMID:24655754; <http://dx.doi.org/10.3201/eid2004.131478>