

Human Vaccines: News

Sanofi Pasteur's dengue vaccine enters phase III trials

Last month, Sanofi Pasteur announced that its dengue vaccine is in the final stage of clinical development. The world's most clinically advanced dengue vaccine candidate entered its first Phase III clinical study in Australia, which is part of a global phase III clinical study program aimed at advancing the development of a novel vaccine for the prevention of dengue disease in children and adults.

There is no vaccine or treatment available for dengue fever, a mosquito-borne disease caused by four dengue virus serotypes. The disease is a threat to nearly three billion people and a public health priority in many countries of Latin America and Asia where epidemics occur. The Pediatric Dengue Vaccine Initiative (PDVI)

provides continuous up-to-date information about dengue fever outbreaks at www.denguewatch.org.

The study in Australia is the first to use dengue vaccine produced with industrial scale processes, and is aimed at demonstrating that production of the vaccine at industrial scale will meet consistency criteria required for market authorization by regulatory authorities.

"To address the global health challenge represented by dengue fever, we are conducting an unprecedented dengue vaccine research and development program as well as a scale up of vaccine production," said Dr. Wayne Pisano, President and CEO of Sanofi Pasteur. "We are now entering the final laps of a long run that

Sanofi Pasteur started almost 20 years ago. If successful, we are committed to introducing the vaccine in countries where dengue is of highest public health priority."

Sanofi Pasteur's candidate dengue vaccine, which targets all four virus serotypes, has previously been evaluated in clinical Phase I and II studies in adults and children in the US, Asia and Latin America. Overall, the vaccine has been well tolerated, and a balanced immune response against all four serotypes has been observed after three doses. Clinical studies in adults and children are ongoing in Mexico, Colombia, Honduras, Puerto Rico, Peru, the Philippines, Vietnam, Singapore, Australia and Thailand.

Negative news coverage erodes public support for mandatory HPV vaccine

Laws mandating the human papillomavirus (HPV) vaccine have caused debate among parents, politicians and medical experts. News coverage about such requirements tends to amplify this controversy, possibly leading to negative attitudes among the public about the value of the HPV vaccine or other vaccines.

Those are the findings of a recent study published in the November issue of the journal *Health Affairs* (2010, 29:2041-6). Researchers at the University of Michigan (Ann Arbor, MI) administered an Internet-based survey to a randomly-selected sample of participants, representative of the US population. Participants were assigned to two groups who then were exposed to two

different hypothetical news briefs about legislative action related to the HPV vaccine. One presented the HPV vaccine as enjoying widespread support and the other positioned the vaccine as controversial. The study found that awareness of controversy resulted in diminished public support for legally mandating the HPV vaccine.

The study is the first of its kind to examine directly the tie between controversy about a piece of health policy portrayed in the news media and public support for the policy. Based on this study and previous research, researchers suggest that prolonged exposure to controversy has the potential to erode public support for the policy.

"This research raises important questions about how the news media's tendency to report on controversy shapes public opinion about health policy," said Dr. Sarah Gollust, who led the study.

While support for HPV vaccine legislation waned in the shadow of controversy, support for other vaccines remained unchanged, which is an encouraging finding, according to Dr. Amanda Dempsey, co-author of the study. Some public health experts have worried that publicized controversy over the HPV vaccine could lead to public concerns about other childhood vaccines, an important issue because of recent outbreaks of vaccine-preventable diseases like whooping cough and measles in the US.

GlobeImmune's therapeutic HCV vaccine increases sustained virologic response

The biopharmaceutical company GlobeImmune (Louisville, CO) recently announced data from a phase IIb study of their therapeutic Hepatitis C virus (HCV) vaccine, showing that their investigational product substantially improved sustained virologic response (SVR) in patients.

GlobeImmune's investigational product GI-5005 for the potential treatment of chronic HCV infection is one of the company's

proprietary Tarmogen products. Tarmogens (targeted molecular immunogens) are whole, heat-killed recombinant *S. cerevisiae* yeast cells that have been engineered to express one or more disease-related proteins. GI-5005 contains conserved HCV proteins and is designed to generate an HCV-specific T-cell response. The product is being developed in combination with the current standard of care (SOC) —pegylated interferon and ribavirin.

GI-5005 was tested in combination with SOC in a Phase IIb trial in 140 subjects chronically infected with genotype 1 HCV. Prior non-responders receiving GI-5005 plus SOC had an SVR rate of 17% compared to an SVR rate of only 5% in patients receiving SOC alone. The suppression of HCV to undetectable levels for an extended period of time (SVR), and not necessarily the elimination of the virus from the liver, is the goal of hepatitis C treatment. Thus, the

data suggest that GI-5005 may have the potential to be the first successful therapeutic vaccine for patients chronically infected with HCV.

"Only 4-7 % of patients with genotype 1 HCV who were null, poor or partial responders to their first course of pegylated interferon-based therapy would be expected to achieve a sustained virologic response with a second course of treatment," said Dr. Paul Pockros from Scripps Clinic (La Jolla, CA). "In this study, GI-5005 conferred a three-fold improvement in SVR, an important treatment effect in this challenging patient population."

Additional immunological data from the Phase IIb study showed that GI-5005 improved

HCV-specific T-cell responses 10-fold over SOC alone in subjects with the *IL28B* T/T genotype (~20% of chronically infected patients), the subgroup most likely to fail treatment with SOC alone. The improved HCV-specific T cell immunity in *IL28B* T/T patients receiving GI-5005 plus SOC correlates with previously reported data that demonstrated a 60% improvement in SVR in chronically infected HCV patients with the *IL28B* T/T genotype when GI-5005 was added to standard of care (SOC) versus SOC alone (60% vs. 0% SVR).

"These data suggest that the fundamental deficit in patients carrying the T allele of the *IL28B* gene is a deficit in adaptive cellular

immunity, the mechanism that GI-5005 was designed to address," said Dr. David Apelian, Chief Medical Officer at Globelimmune. "We are confident that GI-5005 will become a cornerstone of HCV therapy, particularly for difficult to treat populations, such as *IL28B* T/T patients."

Globelimmune now plans to expand its recent Phase IIb study by enrolling 40 additional subjects with the *L28B* T/T genotype to further explore the potential treatment effect of GI-5005 in this patient population.

New consortium designs human trials of mosaic HIV vaccine

Designing and implementing the first human trial of a mosaic HIV vaccine candidate is the declared goal of a newly formed consortium, which includes many of the world's leading researchers and organizations devoted to HIV vaccine development. With this novel strategy, experts attempt to counter one of the most daunting challenges in HIV vaccine design, namely the virus' extensive genetic diversity.

While traditional HIV vaccines are designed to stimulate the body's immune system to recognize naturally occurring stretches of specific amino acids in the virus's proteins, mosaic vaccines are composed of many sets of synthetic, computer-generated sequences of proteins that can prompt the immune system to respond to a wide variety of circulating HIV strains.

Mosaic vaccines have already been studied in animals and have shown some success in enhancing the breadth of immune responses. According to Dr. Barton Haynes, director of the Duke Human Vaccine Institute (Durham, NC) and the Center for HIV/AIDS Vaccine Immunology (CHAVI), the newly formed research coalition has begun designing an early phase safety trial to assess mosaic vaccines in humans. The trial will test the mosaic concept and could possibly lead to the next generation of HIV vaccine candidates.

Dr. Bette Korber, senior scientist at Los Alamos National Laboratory (NM) and leader of the team that developed the mosaic genes, noted: "HIV's diversity is vast, and the mosaic gene design represents a novel

vaccine design to directly tackle HIV diversity in human clinical trials. Based on computational models, mosaic vaccines were predicted to perform better than natural HIV genes; experimental studies in animals that directly compared mosaic to natural vaccines supported that prediction. We are excited to test this concept in humans."

The mosaic HIV candidate vaccine is based on the NYVAC vaccinia vector (derived from the vaccine to protect against smallpox) and DNA that contains a new set of artificial computer-designed HIV genes. It is being provided by Sanofi-Pasteur, which is a collaborator in the study. The Phase I clinical trial will be supported by the Bill & Melinda Gates Foundation and the National Institutes of Health (NIH).

New Center for Systems Vaccinology

Recently, the National Institute of Health (NIH) has awarded a five-year, \$15.5 million grant to the Emory Vaccine Center (Atlanta, GA) to study human immune responses to vaccination in the newly established Center for Systems Vaccinology. The modern analytical tools of systems biology will be employed to understand the immune responses vaccines stimulate in humans and this knowledge will be used to guide design of vaccines against HIV, malaria and other global pandemics.

A major challenge in the development of vaccines is the fact that the effectiveness of vaccination can only be ascertained after vaccinated individuals have been exposed to

infection. This issue will be addressed using a multidisciplinary approach developed by Dr. Bali Pulendran, Principal Investigator of the new center.

The center will comprise a highly integrated and interdisciplinary team of researchers and clinicians.

Pulendran's approach, published in *Nature Immunology* in November 2008, involves immunology, genomics and bioinformatics to predict the immunity of a vaccine without exposing individuals to infection. This systems biological approach permits researchers to observe a global picture of all the nearly 30,000 genes, proteins and cells participating

in immune responses to vaccination. Using this approach, the investigators were able to identify signatures of gene expression in the blood a few days after vaccination that could predict with up to 90 percent accuracy the strength of the immune response to the yellow fever vaccine, one of the most successful vaccines ever developed.

Researchers and clinicians working in areas as diverse as immunology, vaccinology, clinical medicine, computational modeling and mathematics will work together at the new Center for Systems Vaccinology to determine whether Pulendran's approach can be used to predict the effectiveness of other

vaccines, including common vaccines against influenza, pneumococcal disease and shingles. With each of these vaccines, a substantial proportion of elderly individuals do not launch protective immunity. Researchers aim to identify gene signatures that would identify such individuals. Successful prediction

of immunity and efficacy of vaccines would facilitate the rapid evaluation of new vaccines as well as the identification of individuals who are unlikely to be protected by a vaccine.

“We anticipate our collaborative research at the Center for Systems Vaccinology will

address an important public health challenge in identifying novel biomarkers of vaccine efficacy. Such research will also synergize with studies in animal models to help understand the nature of the human immune response with an exquisite degree of depth and resolution,” said Dr. Pulendran.

Novartis and Venter collaborate to develop next generation vaccines

The company Synthetic Genomics Inc. (SGI) and the not-for profit research organization J. Craig Venter Institute (JCVI) recently announced the formation of a new company, Synthetic Genomics Vaccines Inc. (SGVI). The new San Diego (CA) headquartered company is dedicated to the development of new vaccines using the advanced tools and technologies of synthetic genomics.

In a three-year collaboration with Novartis, SGVI will apply synthetic genomics tools to accelerate the production of the influenza seed strains required for vaccine manufacturing. The seed strain is the starter culture of a virus, and is the base from which larger quantities of the vaccine virus can be grown. Currently, Novartis and other vaccine companies rely on the World Health Organization (WHO) to identify and distribute live reference

viruses to create seasonal or pandemic vaccines. Novartis and SGVI plan to develop a bank of synthetically constructed seed viruses ready to go into production as soon as WHO identifies the flu strain. The technology could reduce the vaccine production time by as much as two months, which is particularly critical in the event of a pandemic.

“We are excited to apply our advanced synthetic genomics technologies to revolutionize vaccine production. We look forward to working with Novartis, a world leader in vaccine development and production, on our first application area in influenza,” said Dr. Fernanda Gandara, President of SGVI.

Novartis has been working with JCVI for more than a decade to apply their findings in the genomics field to develop novel vaccines that prevent disease. The last

collaboration introduced the use of genomics in vaccines research, a technology today known as “reverse vaccinology,” as first applied to the development of a serogroup B meningococcal vaccine.

In May 2010 researchers at JCVI published results in the journal *Science* describing the construction of the first self-replicating, synthetic bacterial cell. This cell is the proof of principle that genomes can be designed in the computer, chemically made in the laboratory and transplanted into a recipient cell to produce a new self-replicating cell controlled only by the synthetic genome. Using these same synthetic genomic advances it is conceivable that more universal vaccines could be developed to target a wide range of infectious disease agents in addition to new influenza vaccines.

Cancer Research UK funds brain cancer vaccine trial

A promising cancer vaccine to treat glioblastoma has been advanced to first clinical trials by the charity Cancer Research UK and the German company Immatix Biotechnologies.

The trial includes about 45 patients newly diagnosed with glioblastoma and takes place at different sites across the UK. Patients will receive a number of doses of the vaccine IMA950 together with the standard treatments of surgery, radiotherapy and chemotherapy. IMA950 contains 11 peptides that are found on the surface of glioblastoma tumours but not on healthy cells. When incorporated into the vaccine, these peptides train

T cells in the immune system to recognize and destroy cancer cells.

The launch of the trial resulted from Cancer Research UK's innovative Clinical Development Partnerships (CDP) scheme. CDP is a joint initiative between Cancer Research UK's Drug Development Office and Cancer Research Technology—the charity's development and commercialization arm—to put drugs that otherwise cannot be developed by pharmaceutical companies through early phase clinical trials. Trials of experimental vaccines such as IMA950 may have not been possible without this initiative, which strives to deliver the latest potential treatments to cancer patients.

Under the terms of the partnership, Cancer Research UK is funding the trial and after the trial, the German biotech company Immatix will have an option to further develop and commercialize the drug in exchange for future milestone payments to Cancer Research UK.

“This is a truly collaborative deal between our world-class scientists and Immatix Biotechnologies to ensure promising therapeutic programs reach patients,” said Cancer Research Technology's licensing manager, Dr. Ian Walker.