World’s First Tetravalent Dengue Vaccine in Clinical Trial

by V.K. Sanjeed

Sanofi Pasteur, the vaccines division of sanofi-aventis Group, announced in April this year the start of clinical studies of its investigational tetravalent dengue vaccine in Singapore and Vietnam. Sanofi pasteur is expanding its global dengue vaccine clinical study program in Asia where trials are already ongoing in Thailand and the Philippines. In Singapore, Sanofi Pasteur is collaborating with the Communicable Disease Centre to conduct a clinical study in 4 hospitals. The aim is to collect useful information about the first tetravalent dengue vaccine candidate to reach the clinical phase and evaluate the incidence of disease among trial participants. Sanjeed finds out more from Dr Melanie Saville, Associate Vice President and Head, Clinical Dengue Programme in Sanofi Pasteur and Dr Ng Lee Ching, Head of Environmental Health Institute, National Environment Agency.

APBN: Tell us about the challenges faced when Sanofi Pasteur started the development of a dengue vaccine in the 90’s.

MELANIE SAVILLE: There are a number of challenges in terms of development of a dengue vaccine. No vaccine is available despite over 60 years of research. There is no animal model for the disease which can be a useful method for screening candidate vaccines. A dengue vaccine is complex as there are four serotypes circulating. With a theoretical risk of immunopotentiation after sequential monovalent infections with the dengue serotypes there is a need to have a combined tetravalent vaccine to ensure an immune response against all 4 serotypes. As part of the clinical development, there is a need to perform efficacy trials as unlike many other vaccines, no immune correlate of protection currently exists for dengue. In addition, it is important that one can industrialize the production process of the vaccine strains and demonstrate consistent large-scale manufacturing.

Thus the classical live attenuated approach was used to develop the first generation of dengue vaccine. However this approach was abandoned in 2004 due to reactogenicity and under-attenuation of the serotype 3 virus in the vaccine.
APBN: Tell us about the challenges faced when Sanofi Pasteur started the clinical studies with the tetravalent candidate vaccine in the 2000’s.

MELANIE SAVILLE: There are many challenges in developing a tetravalent dengue vaccine. In the 2000s we are now developing a second generation of tetravalent dengue vaccine based on using recombinant technology with the immunogenic properties of each of the four dengue serotypes (determined by the proteins expressed on the surface of the viral particles) being combined with the well characterized attenuated profile of the YF-17D vaccine strain used for the yellow fever vaccine.

The main challenge for clinical studies is to demonstrate the safety, immunogenicity and efficacy of the tetravalent dengue vaccine. Phase I clinical trials have been conducted in adults and children from non-endemic and endemic countries (US, Mexico, Philippines). Overall, a balanced immune response was observed against all four serotypes after three doses of the tetravalent dengue vaccine. The vaccine also appears to be well tolerated with a similar profile after each dose of vaccine. These results have set the foundation for further development including the initiation of the first efficacy trial for a tetravalent dengue vaccine that is being conducted in Thailand and a number of clinical trials in Asia and Latin America including the trials in Singapore and Vietnam.

APBN: Dengue is an RNA virus. How fast does it mutate? Will this affect the duration of immunity conferred by the vaccine?

MELANIE SAVILLE: The dengue vaccine strain (based on the well characterized attenuated profile of the YF-17D vaccine strain) has been shown to be genetically very stable.

APBN: How is the vaccine currently manufactured?

MELANIE SAVILLE: The vaccine is manufactured using cell culture. The process for production is suitable for industrialization and consistent large-scale manufacturing.

APBN: Is it a sub-unit vaccine / live-attenuated vaccine / killed / RNA/DNA vaccine?

MELANIE SAVILLE: This is a live-attenuated vaccine.

APBN: Are novel vaccine types like RNA/DNA based and carbohydrate based catching on in the industry? Why or why not?

MELANIE SAVILLE: A number of approaches are under investigation other than the live attenuated approach. These are believed to be in the preclinical phase of development.

APBN: What are some of the questions you are trying to answer with the clinical trials in Singapore and Vietnam?

MELANIE SAVILLE: The objectives of the trials in Singapore and Vietnam are to evaluate the bodies immune response to the vaccine and follow the safety of the vaccine in adults, adolescents and children in these countries.
APBN: Why did you choose Singapore and Vietnam in addition to U.S, Mexico and Philippines for the clinical trials? What about Indonesia, Malaysia, and other South-East Asian countries?

MELANIE SAVILLE: Sanofi Pasteur is expanding its global dengue vaccine clinical study program to evaluate the tetravalent dengue vaccine in endemic areas such as Singapore and Vietnam. In addition, an efficacy trial is underway in Thailand where again, dengue is endemic. As the program continues to expand we are discussing with additional countries the possibility of further evaluation of the vaccine.

APBN: Tell us why the Western Pacific Region might be heading for a major dengue outbreak.

DR NG LEE CHING: Dengue is a complex disease, with outbreaks hard to predict. However, we do see an increasing trend in disease incidence in the Western Pacific Region. Firstly Aedes aegypti is a very efficient vector of dengue, as demonstrated by Singapore’s dengue situation. We continue to see dengue transmission even though the vector population has been brought down to a low level, where house index is below 1% (less than 1% of homes are found breeding mosquitoes). Secondly Aedes aegypti has expanded its territory. Due to urbanization and increased travel (across borders and within countries), we see the vector emerging in new territories like rural areas and secluded islands, and in countries with no previous record of the vector.

For example, Thailand, Indonesia and India have reports of spread of transmission to rural areas, and around 2004 Nepal saw their first local transmission of dengue which was attributed to establishment of the vector in the southern part of the country. The development has brought the vector into a immunologically naive population, which is very susceptible to a dengue outbreak, if a virus is introduced through an infected human. In the same light, increased travel has also increased the risk of viral introduction and viral exchange, which has resulted in co-circulating of all multiple
serotypes in specific locations. As immunity conferred by one serotype does not protect against infection of another serotype, having multiple serotypes circulating in a location can increase the frequency of outbreaks.

**APBN:** Despite the best efforts of countries in the region to contain dengue, the virus has continued to infect millions of people every year. Why is this so and what is lacking?

**DR NG LEE CHING:** In the absence of a vaccine or any prophylactic treatment, the only effective means of dengue control is through suppression of the vector population. Unfortunately, the vector is well adapted to our homes, especially urban homes. They breed in our man-made containers, and predominantly feed on humans. In other words, they are “well provided for” in our homes by us.

To break their life cycle, we need to deprive them of breeding opportunities, and this can only be done by a concerted environmental management effort involving all premise owners, the government and all stakeholders. People, including premise owners, architects and civil engineers must be educated about dengue and the potential habitats of its vector. Premise owners need to make dengue prevention a way of life – which entails proper housekeeping and maintenance of premises. Urban planners (developers, architects etc) need to take dengue prevention into consideration in their design and buildings. Companies must take responsibility for any undesirable consequences of their businesses (e.g. used tires, construction sites etc). Government needs to put in place a system that supports good field and laboratory surveillance, and coordinate and champion the effort. In summary, everyone must play a role in dengue control. We need effective education, coordination, a robust system and adequate resources to make this work. It is a daunting task and the effort will be limited by the weakest link in the system.

**APBN:** Tell us about the impact of dengue in the region and potential impact globally.

**DR NG LEE CHING:** Overall, the disease is a potential threat for almost half the world’s population. Of the estimated 230 million people infected annually, two million, mostly children, develop dengue hemorrhagic fever (DHF), a severe form of the disease. DHF is a leading cause of hospitalization in South-East Asia, placing tremendous pressure on strained medical resources.

**APBN:** Recently, an Australian team successfully transferred a life-shortening strain of the bacteria Wolbachia, into Aedes aegypti. It halved the adult life span under laboratory conditions. The association is stable, and the Wolbachia strain is maternally inherited at high frequency. Comment on the feasibility of this strategy in containing dengue.

**MELANIE SAVILLE:** These are interesting results that warrant further evaluation. However it is difficult for us to comment on the feasibility. All efforts at dengue prevention should obviously be encouraged.
APBN: Lastly if you could have 1 wish for vaccine development, vaccine production or vaccination programs, what would it be?

**MELANIE SAVILLE:** Dengue fever is a major public health concern with the global prevalence of dengue continuing to increase dramatically. Sanofi Pasteur’s goal is to develop a safe and effective tetravalent dengue vaccine as rapidly as possible, accessible in all regions of the world where dengue is a public health issue.

**DR NG LEE CHING:** An effective and safe vaccine will be much appreciated. As the burden of dengue is high in developing countries, I would wish for a vaccine that is very affordable, and nobody will be denied a vaccine because of unaffordability. However, we should note that the availability of dengue vaccine does not eliminate the need for Aedes mosquito control. Aedes is also vector of other diseases like Chikungunya and Yellow Fever.

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**About Dr Melanie Saville (MBBS)**

Dr. Melanie Saville is the Head of the Clinical Dengue Program at Sanofi Pasteur, the vaccines division of sanofi-aventis Group, the largest company in the world devoted entirely to human vaccines.

Since joining the company in France in 2004, she has led the clinical development for influenza vaccines and is now managing the tetravalent dengue vaccine program.

Dr. Saville has been involved in vaccines clinical research since 2000. Before joining Sanofi Pasteur, she worked on several vaccine projects in Phase One to Three when with Wyeth in the United Kingdom (UK). Between 1998 and 2000, Dr Saville also conducted research in the field of respiratory viruses and Herpes Simplex Virus when she served at the Health Protection Agency in the UK. Prior to that, she was a clinical virologist at St Mary’s and the Hammersmith hospitals in London.

Dr Saville has a medical degree from the University College London as well as a master’s degree in Medical Virology from the Royal Free Hospital Medical School, UK.

**About Dr Ng Lee Ching**

Dr Ng Lee Ching obtained her PhD at the Dept of Microbiology at NUS, before doing a postdoctoral fellowship at Umea University, Sweden. She has more than 15 years of experience in molecular biology and microbiology, including 9 years committed to Biological Defence and Infectious Diseases at DSO National Laboratories and Defence Science and Technology Agency. Dr Ng joined the National Environment Agency in December 2004, and is currently the Head of the Environmental Health Institute (EHI), which is the research arm within the Division of Public Health.