A bright future for the production of a new dengue vaccine?

A candidate dengue vaccine has been found to be both safe and able to stimulate a strong immune response in most vaccine recipients in an early-stage clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH. "The global burden of dengue is enormous – and it is growing," commented Anthony S Fauci, director of NIAID. The vaccine developed by scientists at the NIH is a promising new hope for the control of dengue virus, for which no effective antiviral treatment currently exists.

Responsible for hundreds of millions of infections every year, with over 3.5 billion people at risk in over 100 countries, dengue has also become a leading cause of morbidity in American and European travelers and military. With prevention largely relying on ineffective mosquito control, the critical need for safe and effective dengue vaccines has been recognized by policy makers. However, the development of a vaccine against the infection has been inhibited by the multiple serotypes of dengue virus, and the fact that previous infection with one serotype is known to increase the risk of severe or life-threatening disease with a second serotype. Therefore, a multivalent dengue vaccine including all four dengue serotypes is required.

> "The vaccine … is a promising new hope for the control of dengue virus, for which no effective antiviral treatment currently exists."

The recent Phase I clinical trial, led by principal investigator Anna Durbin (Johns Hopkins Bloomberg School of Public Health, MD, USA), was a randomized, placebo-controlled study designed to evaluate four versions of the live-attenuated tetravalent dengue vaccine. The safety and immunogenicity of the four different mixtures of the vaccine were measured in 113 adults aged 18–50 years who had not been previously exposed to dengue or related viruses. Participants received a single 0.5-ml injection of one of the vaccine combinations, and serum neutralizing antibody levels to all four dengue viruses were measured on days 0, 28, 42 and 180.

The results demonstrated that all four candidate vaccine combinations induced antibody responses against each of the dengue viruses. In 75–90% of vaccinees, one dose of each vaccine mixture induced a trivalent or better neutralizing antibody response, with one vaccine combination, TV003, appearing to induce a more balanced antibody response. No adverse events were noted other than rash, which correlated with non-black race and trivalent or better response.

The researchers note that the inexpensive production cost of TV003 will be crucial to its potential use in developing countries. Further studies are being conducted to evaluate its safety and ability to stimulate an immune response in both healthy volunteers and in those who have been previously infected by either dengue or other related viruses. Phase II trials will soon begin in Brazil and Thailand.

– Written by Jenaid Rees

Sources: Durbin AP, Kirkpatrick BD, Pierce KK *et al.* A single dose of any of four different live attenuated tetravalent dengue vaccines is safe and immunogenic in flavivirus-naive adults: a randomized, double blind clinical trial. *J. Infect. Dis.* doi:10.1093/infdis/jis936 (2013) (Epub ahead of print); Edelman R. Unique challenges faced by the clinical evaluation of dengue vaccines. *Expert Rev. Vaccines* 10(2), 133–136 (2011); NIAID press release: www.niaid.nih.gov/news/newsreleases/2013/Pages/DengueVax.aspx

Epidemiological–phylodynamic model may suggest future directions for tackling HCV spread

The spread of any communicable disease is closely linked to the social patterns, distribution and interactions of infected and high-risk groups. While this spread is relatively simple to document for diseases that spread rapidly, are quickly apparent and are not associated with any socially stigmatized behaviors (e.g., influenza), this is not the case for diseases that do not fulfill these criteria. Two prime examples of such diseases are HIV and HCV, which are indeed difficult to 'track' through a population.

> "…we may now have an improved method for modeling the spread of certain diseases through populations."

Improving our capabilities in this area has the potential to be very useful, owing to the often extreme variance in transmission potential between infected individuals. Although high-risk group categorization tells us how an individual came to be infected, it does not then reliably predict the likelihood (and degree) of further transmission. HCV epidemics, for example, involve 'superspreaders', specific individuals who pass on the disease many times. In order to gain a realistic picture of viral evolution, it is necessary to model and account for this.

It is this topic that has been the focus of investigation by a group including

researchers from the Oxford University (UK), the University of Athens (Greece) and Imperial College (UK). Led by Gkikas Magiorkinis (Oxford University), the group developed a model for estimating the variation in transmissibility of rapidly evolving viral epidemics, and then tested it against data from several HCV epidemics in Greece.

Using 943 patient samples obtained between 1995 and 2000, and approximately 100 viral sequence samples obtained between 1996 and 2006, the researchers used their model to estimate the variance of secondary infection, viral generation times and superspreading events, suggesting that we may now have an improved method for modeling the spread of certain diseases through populations.

– Written by Jacob McCarthy

Sources: Magiorkinis G, Sypsa V, Magiorkinis E *et al.* Integrating phylodynamics and epidemiology to estimate transmission diversity in viral epidemics. *PLoS Comput. Biol.* 9(1), e1002876 (2013); University of Oxford press release: Target 'super-spreaders' to stop hepatitis C: www.ox.ac.uk/media/news_releases_for_journalists/130201.html

Priority Paper Alerts

León AJ, Banner D, Xu L *et al.* Sequencing, annotation, and characterization of the influenza ferret infectome. *J. Virol.* 87(4), 1957–1966 (2013).

Ferrets are an extremely useful model for influenza virulence and pathogenesis, and will only become more useful as a result of this paper's publication of their influenza virus infectome. Divided according to stage of infection and immune experience, this characterization was generated via the next-generation sequencing and analysis of RNA extracted from lung and lymph node tissue of both infected and uninfected ferrets. Gene expression profiles were generated following exposure to H1N1 influenza, demonstrating the initial innate immune reaction giving way to the adaptive response by day 5 postinfection, and the expected diminished innate, enhanced adaptive response to subsequent exposure. This fully annotated infectome information is likely to be very useful in characterizing the mechanisms regulating disease interactions and outcomes in both seasonal and pandemic influenzas.

Nanni P, Gatta V, Menotti L *et al.* Preclinical therapy of disseminated HER-2$^+$ ovarian and breast carcinomas with a HER-2-retargeted oncolytic herpesvirus. *PLoS Pathog.* 9(1), e1003155 (2013).

Although oncolytic viruses show great promise in the treatment of cancer, a central challenge has always been the correct targeting of their activity. This paper details the preparation and use of an oncolytic herpesvirus against ovarian and breast cancer, specifically targeting the HER-2 oncoprotein. Researchers modified the viral sequence encoding its receptor-binding glycoprotein, inserting sequences from anti-HER-2 antibodies. This resulted in the specific targeting of the resulting virus to HER-2-expressing cells, such as HER-2$^+$ carcinoma cells. Tested in a mouse model of progressive peritoneal carcinomatosis, compatibility with both local and systemic delivery allowed the modified virus to demonstrate inhibitory effectiveness against disseminated and metastatic cancer. Following treatment, 60% of mice were free from peritoneal diffusion, and a 95% reduction in the total weight of neoplastic nodules was observed.

US FDA approval for novel darunavir formulation

Jannsen Therapeutics (NJ, USA) has recently announced the US FDA approval of its novel darunavir (Prezista®) 800 mg once-daily tablet for the treatment of HIV. This will allow HIV sufferers without darunavir resistance-associated mutations currently taking darunavir 400 mg to reduce the number of the tablets they take by half.

Darunavir is a protease inhibitor recommended by the Office of AIDS Research Advisory Council for both treatment-naive and treatment-experienced adults and adolescents. This new 800-mg tablet is twice as potent as the previous darunavir 400-mg tablet, which required two tablets to be taken daily in combination with ritonavir and other HIV medications.

Current HIV treatment can often involve a complicated dosing regime, involving multiple drugs taken at different times of the day with and without food. Since strict adherence is required to help avoid the development of resistance, being able to reduce the number of pills to be taken could help patients better comply with their treatment. "The single 800-mg tablet provides an option for a reduced pill burden and reflects our ongoing commitment to offer more treatment options for the diverse population of people living with HIV," stated Bryan Baugh, Medical Director at Janssen Therapeutics.

Jannsen plans to discontinue the production of darunavir 400 mg, as the introduction of this new-strength version will render it obsolete. The darunavir 800-mg tablet is expected to be made available shortly.

> "The single 800-mg tablet provides an option for a reduced pill burden..."

This approval may help to bring simpler dosing regimens to HIV patients, and may encourage further formulation studies in order to allow similarly effective but less-complicated treatment in the future.

– Written by Georgina Askeland

Source: Janssen Therapeutics press release: www.janssentherapeutics.com/news-center/fda-approves-new-800mg-prezista-darunavir-tablet