

Engineering a potential treatment for all four dengue serotypes

SINGAPORE, 17 July 2015 – A multinational research team comprising scientists, engineers and drug developers have joined forces to develop a viable dengue therapeutic that targets all dengue serotypes¹. This is welcome news as dengue now spans the entire tropical world and an estimated 400 million people are infected each year. Despite the numbers, there remains no licensed treatment for dengue patients. However, this problem may soon be solved by promising findings published in the prestigious journal, *Cell*.

Researchers from the Singapore-MIT Alliance for Research and Technology (SMART), Duke-NUS Graduate School of Medicine (Duke-NUS), National University of Singapore (NUS) and Nanyang Technological University (NTU) have collaborated with the Massachusetts Institute of Technology (MIT) and a biotechnology company, Visterra, to develop a single treatment.

The team started with a naturally occurring antibody that reacted only against limited number of types of dengue virus. Using that antibody as a scaffold, the team engineered a new antibody that reacts against all four types of dengue virus. The engineering was made possible by computational methods developed in MIT and SMART. This was then confirmed and validated using a detailed crystal structure of the antibody-virus protein complex obtained at NTU, which also provided insights into how the antibody engaged the virus to produce the desired effect. Using a variety of systems developed in the SMART laboratories in the Campus for Research Excellence And Technological Enterprise (CREATE) (e.g. the SMART humanised mouse model), Duke-NUS and NUS, the team then showed that this novel antibody has the potential to neutralise dengue virus and prevent signs of disease.

Another important feature of this antibody is that it acts on a part of the virus that is not normally targeted by the normal human immune response. This is important as the antibody would not need to compete with but would instead augment the overall natural immune response against dengue virus.

“This interdisciplinary, transnational team has enabled us to address this problem in unique ways,” said Prof Ram Sasisekharan, SMART Principal Investigator (PI) of the Infectious Diseases Interdisciplinary Research Group (ID IRG), and MIT Professor of Biological Engineering and Health Sciences & Technology, who led the team. “A single laboratory would not have the breadth of expertise to solve this problem on its own.”

“We have each been working on our own areas of interests for years,” added Assoc Prof Eng Eong Ooi, Deputy Director of the Emerging Infectious Diseases Programme at Duke-NUS and SMART Co-Lead PI of ID IRG. “To be able to take what we have built over the years and put it

¹ Dengue virus has four serotypes (DENV1-4) circulating in nature. To have complete protection against the dengue infection, a vaccine has to simultaneously stimulate an equally strong antibody response against all four serotypes.

together to solve a critical medical need, has been very rewarding personally and professionally.”

Prof Peter Dedon, SMART PI of ID IRG and current Resident PI, said: “This is the goal of SMART ID IRG – to bring together interdisciplinary teams of scientists from MIT and Singapore to solve the biggest problems in infectious disease. Computer scientists, engineers, molecular biologists, immunologists, virologists – all bringing their expertise and technology to develop a new therapy for dengue. This synergy could not have happened without the National Research Foundation (NRF)-funded SMART programme.”

This antibody is now being developed by Visterra, which has incorporated a branch in Singapore, Visterra Singapore International Pte Ltd, to develop this antibody, in partnership with D3 of A*STAR for clinical trials next year.

This research took the team three years to achieve this significant breakthrough. Each piece of the technology that enabled this translational work was developed independently of one another but the team was able to assemble the expertise within a short time to fulfil this collective goal.

Prof Edward Holmes, former Executive Deputy Chairman, Biomedical Research Council, A*STAR Distinguished Professor, University of California Vice Chancellor/Dean Emeritus of Health Sciences, UCSD CEO/President of Sanford Consortium for Regenerative Medicine said: "With the global incidence of dengue epidemics in the Americas and Asia on the rise in the recent decades, and no specific treatment for dengue, this important breakthrough has significant implications for dengue in Singapore and around the world. This progress is another excellent example of how collaboration between research institutes, academia, hospitals and industries can result in such spectacular findings that can translate to a possible cure for dengue.”

This research is based on the paper ‘Structure-Guided Design of an Anti-dengue Antibody Directed to a Non-immunodominant Epitope’ and was funded by the the National Research Foundation Singapore under its Campus for Research Excellence and Technological Enterprise (CREATE) programme; and the U.S. National Institutes of Health.

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About Singapore-MIT Alliance for Research and Technology (SMART)

[新加坡-麻省理工学院科研中心]

Singapore-MIT Alliance for Research and Technology (SMART) is a major research enterprise established by the Massachusetts Institute of Technology (MIT) in partnership with the National Research Foundation of Singapore (NRF) since 2007. It is the first entity in the Campus for Research Excellence and Technological Enterprise (CREATE) developed by NRF.

SMART serves as an intellectual hub for research interactions between MIT and Singapore. Cutting-edge research projects in areas of interest to both Singapore and MIT are undertaken at SMART. SMART comprises an Innovation Centre and five Interdisciplinary Research Groups (IRGs): BioSystems and Micromechanics (BioSyM), Center for Environmental Sensing and Modeling (CENSAM), Infectious Diseases (ID), Future Urban Mobility (FM) and Low Energy Electronic Systems (LEES).

For more information, please visit - <http://smart.mit.edu>

About SMART Infectious Diseases Interdisciplinary Research Group

[跨学科感染疾病研究中心]

SMART Infectious Diseases IRG (ID IRG) seeks fundamental understanding of host-pathogen interactions as well as direct impact on human health through translational research. The ID IRG focuses on infectious diseases that have major impact on human health, including dengue fever, malaria and tuberculosis. The strategy of the IRG is to develop enabling technologies, including humanised mouse model, high resolution proteomics, glycomics, metabolomics and cellular mechanics platforms, to study infectious diseases using novel approaches and from new angles. The ID IRG has developed an integrated, cutting-edge research program with participation of both MIT faculty and investigators from Singapore universities and research institutes.

About Duke-NUS Graduate Medical School

The Duke-NUS Graduate Medical School Singapore (Duke-NUS) was established in 2005 as a strategic collaboration between the Duke University School of Medicine, located in North Carolina, USA, and the National University of Singapore (NUS). Duke-NUS offers a graduate-entry, 4-year MD (Doctor of Medicine) training programme based on the unique Duke model of education, with one year dedicated to independent study and research projects of a basic science or clinical nature. Duke-NUS also offers MD/PhD and PhD programmes. Duke-NUS has five Signature Research Programmes: Cancer and Stem Cell Biology, Neuroscience and Behavioural Disorders, Emerging Infectious Diseases, Cardiovascular and Metabolic Disorders, and Health Services and Systems Research.

2015 marks Duke-NUS' 10th anniversary. In this time, Duke-NUS and SingHealth have established a strategic partnership in academic medicine that will guide and promote the future of medicine, tapping on and combining the collective strengths of SingHealth's clinical expertise and Duke-NUS' biomedical sciences research and medical education capabilities.

For more information, please visit www.duke-nus.edu.sg

About CREATE [早越研究与科技企业学园]

CREATE is an international collaboratory housing research centres set up by top universities. At CREATE, researchers from diverse disciplines and backgrounds work closely together to perform cutting-edge research in strategic areas of interest, for translation into practical applications leading to positive economic and societal outcomes for Singapore. The interdisciplinary research centres at CREATE focus on four areas of interdisciplinary thematic areas of research, namely human systems, energy systems, environmental systems and urban systems. More information on the [CREATE programme](http://www.create.edu.sg) can be obtained from www.create.edu.sg