

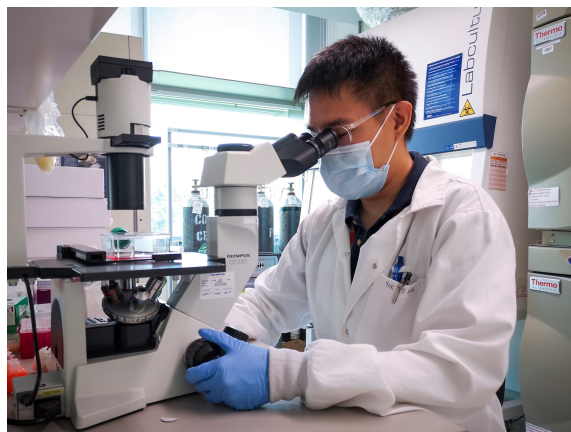
## Media Release

### SMART Researchers Develop Potential Antibody Treatment for Yellow Fever in Seven Months

- *The Rapid Response Strategy, which can be extended to other infectious disease indications, has allowed researchers to drastically reduce the time taken to develop candidate treatment for yellow fever within 7 months, Zika within 9 months, and COVID-19 within 4 months.*
- *Yellow fever vaccines pose risks for particular groups of people and only supportive care can be administered as no treatment is currently available.*
- *Same species of mosquito that spreads dengue is also capable of transmitting yellow fever, extending the risk of a yellow fever outbreak even to non-endemic regions including Asia and parts of USA.*

**Singapore, 30 July 2020** - Yellow fever, an acute viral haemorrhagic disease transmitted by infected mosquitoes, infects about 200,000 people and causes an estimated 30,000 deaths each year. While currently endemic in 47 countries in Africa and Central and South America, the potential for large urban outbreaks is still present in other regions where the mosquitoes capable of transmitting yellow fever exist, especially in Southeast Asia due to the favourable ecology for the *Aedes aegypti* mosquito species. This is particularly worrying in Singapore, where the same mosquito species is on track to cause the worst dengue outbreak in its history, with 18,000 cases and 19 deaths so far in 2020. Although a safe and effective vaccine has been developed for use in most cases, to date, there have been no licensed treatment options available against the disease.

Researchers from [Antimicrobial Resistance](#) (AMR), an interdisciplinary group at [Singapore-MIT Alliance for Research and Technology](#) (SMART), MIT's research enterprise in Singapore, have developed TY014, a potential antibody treatment for yellow fever. SMART AMR collaborated with researchers from Massachusetts Institute of Technology (MIT), and local institutions such as the Singapore General Hospital, Duke-NUS and Tysana Pte Ltd to develop the antibody treatment within only seven months using a Rapid Response Strategy, a feat that usually takes several years.



SMART AMR researcher Yok Teng Chionh evaluating cells producing TY014 antibody

In a paper titled "[Phase 1 Trial of a Therapeutic Anti-Yellow Fever Virus Human Antibody](#)" published in the New England Journal of Medicine, the researchers describe the methods and results of Phase 1 of



the first-in-human TY014 study. The study has demonstrated the potential for yellow fever treatment using TY014, a fully engineered, human manufactured IgG1 monoclonal antibody that targets the yellow fever virus, with success in early-stage clinical trials in Singapore. The paper also explains the Rapid Response Strategy that accelerated the development of candidate treatment to only seven months; with the clinical batch of TY014 produced within five months from the initial transfection, and the completion of Phase 1a and 1b of clinical trials two months later.

### **Reducing the time to make new drugs and therapeutics**

Monoclonal antibodies hold promise for treating a variety of infectious diseases including cancers, but these usually take several years to develop and test. The condensed timeline for TY014 was facilitated by a development process that carefully monitored product quality and correlated them with safety toxicology and pharmacokinetic studies using redundant orthogonal analytics; performing many of the steps necessary for drug development in parallel. The quick turnaround was also enabled by adapting an advanced proprietary computational platform technology<sup>1</sup>, first developed at SMART and MIT, to identify and engineer the TY014 antibody.

“Traditional drug development processes are very linear, and they take many years. If you’re going to get something to humans fast, you can’t do it linearly, because then the best-case scenario for testing in humans is a year to 18 months. If you need to develop a drug in six months or less, then a lot of these things need to happen in parallel,” says Professor Ram Sasisekharan, Principal Investigator at SMART AMR, and Professor of Biological Engineering and Health Sciences & Technology at MIT.

The Rapid Response Strategy dramatically reduces the time it takes to make new therapeutics from years to months. Using this strategy, the researchers have also developed a Zika candidate treatment within nine months. This was followed by the yellow fever programme which took seven months.

It can be extended to other infectious disease indications and reduce timelines for antibody biologics which are important in potential pandemic responses, as seen in the current COVID-19 pandemic. Most recently, a COVID-19 antibody treatment (named TY027) was developed by this team in just four months using this approach. Preliminary results from the Phase 1 trials show that no adverse events have been observed after the infusion of TY027 in healthy volunteers. Phase 3 clinical trials are expected to start in August in Singapore.

“The COVID-19 pandemic has exposed the need for a rapid response to infectious diseases. Leveraging off the experience and foundation documented in this study, and previous research, we were able to respond quickly to COVID-19 and will be able to adapt and improve the rapid response strategy for future pandemic responses,” added Professor Sasisekharan.

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<sup>1</sup> The design process uses computational methods to target functionally important, and evolutionarily stable, regions on the virus. The key is to select “building blocks” from a database of all known antibody elements based on several criteria, including their functional importance, to build candidate antibodies to evaluate. Testing these candidates provides valuable feedback, and the design-build-test loop continues until an optimised antibody that fully neutralizes the target virus is identified.



With further anticipated advancements, a rapid response platform that can go from sequence to clinical testing of promising antibody biologics within three months is entirely feasible.

In a third-party review of the study, Dr Rahul Singhvi, CEO of US-based manufacturing technology company, National Resilience Inc. said, “This is a very important study that demonstrates the critical importance of innovation, process design, sophisticated analytics, and progressive regulatory thinking in the drug development process; bringing an antibody therapeutic to patients within months of a deadly disease. Thanks to the rigorous characterisation of the materials used at different stages of the programme, the reduction in timelines did not compromise any safety or efficacy requirements in clinical trials. The authors have set a new benchmark for the timeline from discovery to treatment. This is not only transformational but essential to combat the increasing risks from current and emerging infectious disease threats.”

### **The lack of therapeutics for yellow fever**

Large epidemics of yellow fever occur when infected people introduce the virus into heavily populated areas with high mosquito density and where most people have little or no immunity. To prevent an epidemic, it is important to vaccinate 80% or more of the population at risk. However, the global manufacturing capacity is unable to meet a surge in demand, especially during an outbreak.

Furthermore, the vaccine is contraindicated in infants and those above 60 years old, as well as in immunocompromised persons, due to the increased likelihood of severe adverse effects. Management of yellow fever in these groups is usually through supportive care.

“Following reports of urban yellow fever outbreaks in Africa in 2016 followed by Latin America in 2017 and 2018, we were convinced that a yellow fever therapeutic is urgently needed for potential international spread and outbreaks. Other regions, while currently not endemic for yellow fever, remain at risk of unprecedented yellow fever outbreaks, as the vector responsible for the disease, the *Aedes aegypti* mosquito, is prevalent throughout the tropics and subtropics including Asia. While there is a highly effective vaccine, the vaccine production is limited with vaccination coverage often incomplete. It is also contraindicated for subgroups of population. An antibody treatment will not only plug these gaps but could also prepare global healthcare systems for potential outbreaks” says Associate Professor Jenny Low, lead author of the study and Senior Consultant with the Department of Infectious Diseases, Singapore General Hospital, and Principal Investigator at SMART AMR.”

Researchers used a computational approach to develop the TY014 antibody to specifically target an epitope on the yellow fever virus envelope (E) protein in post-infection therapy. This will help alleviate the stress on global healthcare systems in managing a yellow fever outbreak, and also fill the current gaps in healthcare that cannot be safely addressed by vaccination alone. This is especially important in regions with an imposing footprint of the *Aedes aegypti* mosquito, the species responsible for current dengue infections and also capable of transmitting yellow fever, in places such as Asia and even in parts of the United States of America - where healthcare systems are ill-equipped for widespread yellow fever vaccination.



### **Testing for safety and efficacy**

The clinical trial was conducted at the SingHealth Investigational Medical Unit in Singapore in healthy human volunteers. Researchers found that following TY014 treatment, the virus was undetectable in blood samples from people who received the antibodies. The treatment also reduced inflammation following vaccination, compared to people who received the vaccine but not the antibody treatment.

With the phase 1b trial completed in July 2019, the researchers will perform phase 2 clinical trials in patients infected with the disease.

This research was supported by the National Research Foundation Singapore, under its Campus for Research Excellence and Technological Enterprise (CREATE) programme, and Tysana Pte. Ltd.

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### **About Singapore-MIT Alliance for Research and Technology (SMART) [新加坡-麻省理工学院研究中心]**

Singapore-MIT Alliance for Research and Technology (SMART) is MIT's Research Enterprise in Singapore, established by the Massachusetts Institute of Technology (MIT) in partnership with the National Research Foundation of Singapore (NRF) since 2007. SMART is the first entity in the Campus for Research Excellence and Technological Enterprise (CREATE) developed by NRF. SMART serves as an intellectual and innovation 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 currently comprises an Innovation Centre and five Interdisciplinary Research Groups (IRGs): Antimicrobial Resistance (AMR), Critical Analytics for Manufacturing Personalized-Medicine (CAMP), Disruptive & Sustainable Technologies for Agricultural Precision (DiSTAP), Future Urban Mobility (FM) and Low Energy Electronic Systems (LEES).

SMART research is funded by the National Research Foundation Singapore under the CREATE programme.

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

### **About Antimicrobial Resistance Interdisciplinary Research Group (AMR IRG)**

The AMR IRG is a translational research and entrepreneurship program that tackles the growing threat of antimicrobial resistance. By leveraging talent and convergent technologies across Singapore and MIT, we aim to tackle AMR head-on by developing multiple innovative and disruptive approaches to identify, respond to, and treat drug-resistant microbial infections. Through strong scientific and clinical collaborations, our goal is to provide transformative, holistic solutions for Singapore and the world.

For more information, please log on to: <http://amr.smart.mit.edu/#home>

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