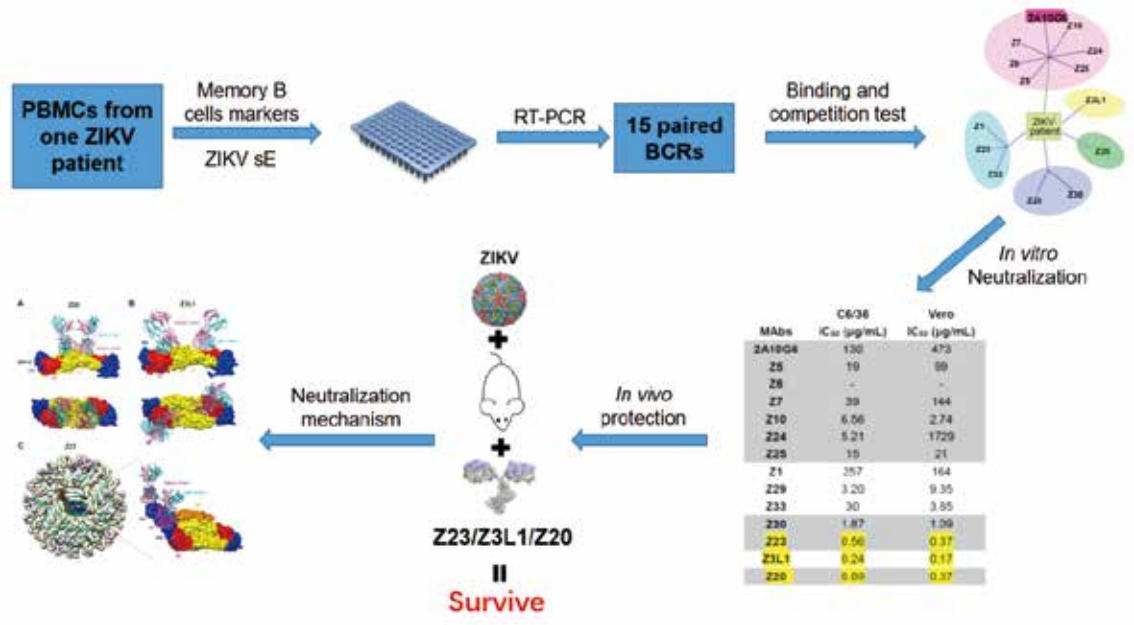
Life Science

Molecular Determinants of Human Neutralizing Antibodies Isolated from a Zika Patient

Zika virus (ZIKV), a flavivirus, is causing global concern, as accumulating evidence suggests that its infection is associated with microcephaly in newborns and neurological complications, such as Guillain-Barré syndrome, in adults; and currently no approved countermeasure against ZIKV infections is available. This concern is further emphasized by recent parallel studies by Dr. Michael Diamond from Washington University School of Medicine and Dr. George Fu Gao from the Institute of Microbiology, Chinese Academy of Sciences (IMCAS) that infection with ZIKV in mice could result in acute and chronic testicular damage and eventually lead to infertility. In accordance with this observation in mice, sexual transmission of ZIKV have been documented clinically, which has not been reported for other flaviviruses before.

Fortunately, newly isolated human neutralizing antibodies, as a result from more recent joint efforts by two research groups at IMCAS, leading respectively by Dr. YAN Jinghua from the CAS Key Laboratory of Microbial Physiological and Metabolic Engineering and Dr. George Fu Gao from the CAS Key Laboratory of Pathogenic Microbiology and Immunology, might mitigate this concern. The study was published, as a cover report, in *Science Translational Medicine* on December 14, 2016 and entitled "Molecular determinants of human neutralizing antibodies isolated from a Zika patient". In this study, Zika-specific human neutralizing antibodies with high potency



Human neutralizing antibodies isolated from a Zika patient and their molecular determinants. (Image by Dr. YAN Jinghua's lab)

were successfully isolated from a convalescent Zika patient, and their neutralization activities *in vitro* and protection efficacies *in vivo* were determined. The researchers also delineated the antibodies' neutralizing mechanisms through structural studies. Collectively, the results indicated the therapeutic potential of the isolated monoclonal antibodies against Zika infection, and provided a structure-based rationale for the design of future specific antivirals.

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The ZIKV envelope protein is known to facilitate virus entry and contains important epitopes for virus neutralization. In this study, they used a panel of memory B cell markers as well as soluble envelope (sE) to stain peripheral blood mononuclear cells isolated from a convalescent Zika patient. After cell sorting, 33 sE-specific memory B cells were obtained and 15 B cell receptors (BCRs) sequences were determined by RT-PCR. Through ELISA and SPR assay, 13 antibodies were confirmed to bind sE at variable affinities, targeting at least 5 different epitopes by competition test with Octet. Amongst these antibodies, three (Z20, Z23 and Z3L1) exerted potent neutralization activities against ZIKV.

Additionally, among the three, Z23 and Z3L1 showed no cross-binding or cross-neutralization to dengue virus 1-4, the closest phylogenetic relative to ZIKV. Both Z23 and Z3L1 conferred complete post-exposure protection *in vivo* against ZIKV infection in mice, whereas Z20 conferred partial protection. Structural studies revealed that Z20, Z23 and Z3L1 bound to tertiary epitopes on domains I, II and/or III of the envelope protein, and inhibited virus entry through different mechanisms.

Outbreaks of infectious disease in recent years, including the MERS-CoV in 2012, H7N9 influenza virus in 2013, Ebola virus in 2014, 2015 and 2016, and now Zika virus, have highlighted the shortage of therapeutics at hand to fight these infections. Filling this gap, in this study, the researchers developed a platform that can be used to isolate strongly neutralizing monoclonal antibodies against any viral pathogen from the B cells of convalescent patients within one month, providing a powerful tool to control and reduce the cases of infection for future outbreaks.

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