Zika antibodies identified with therapeutic and diagnostic potential

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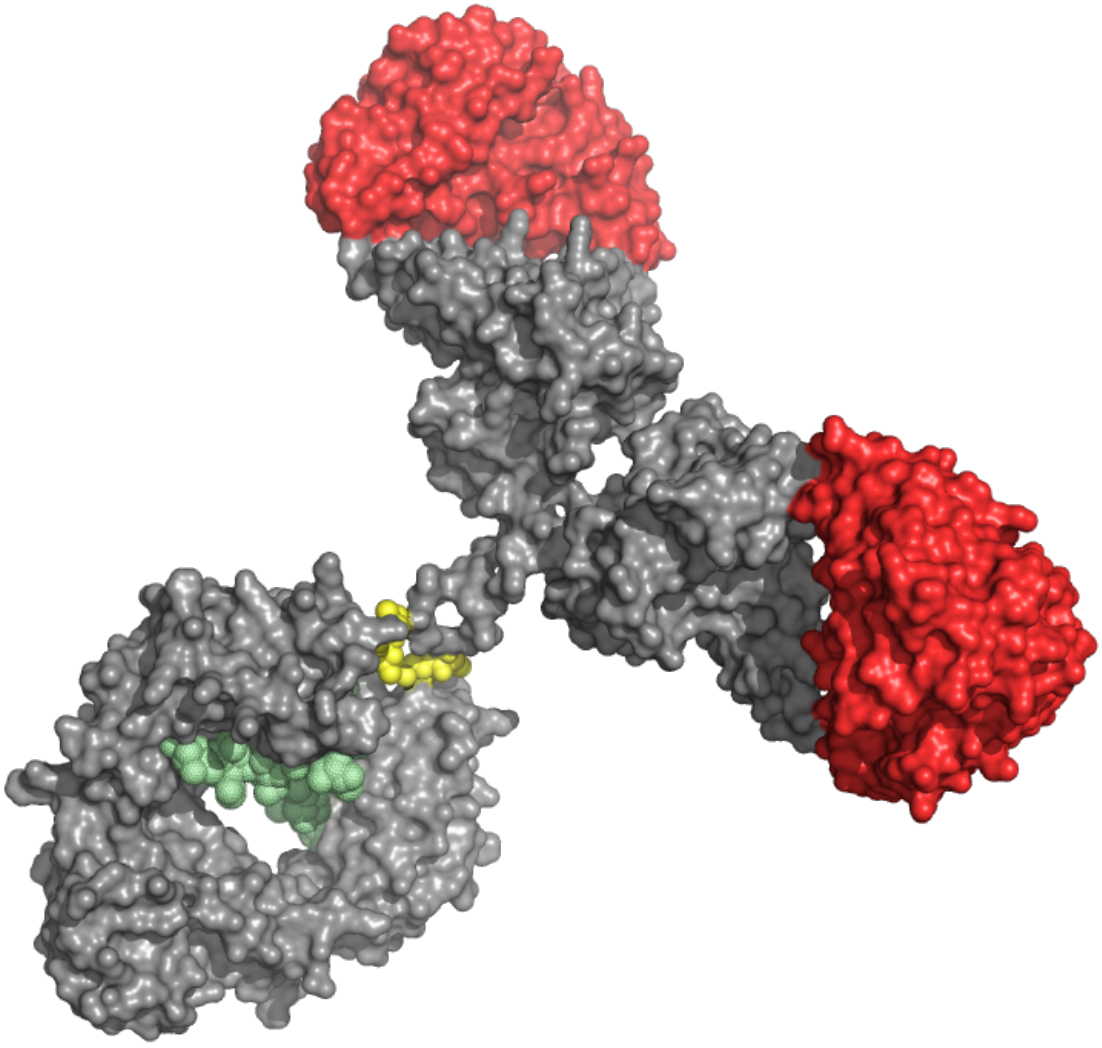


In red the part that binds to the virus, in grey the "tail" of the antibody (named Fc) that binds the receptors of the antibodies present on the different types of cells, and in yellow the LALA mutation that blocks the binding of the antibody to such receptors. Credit: Universita della Svizzera Italiana

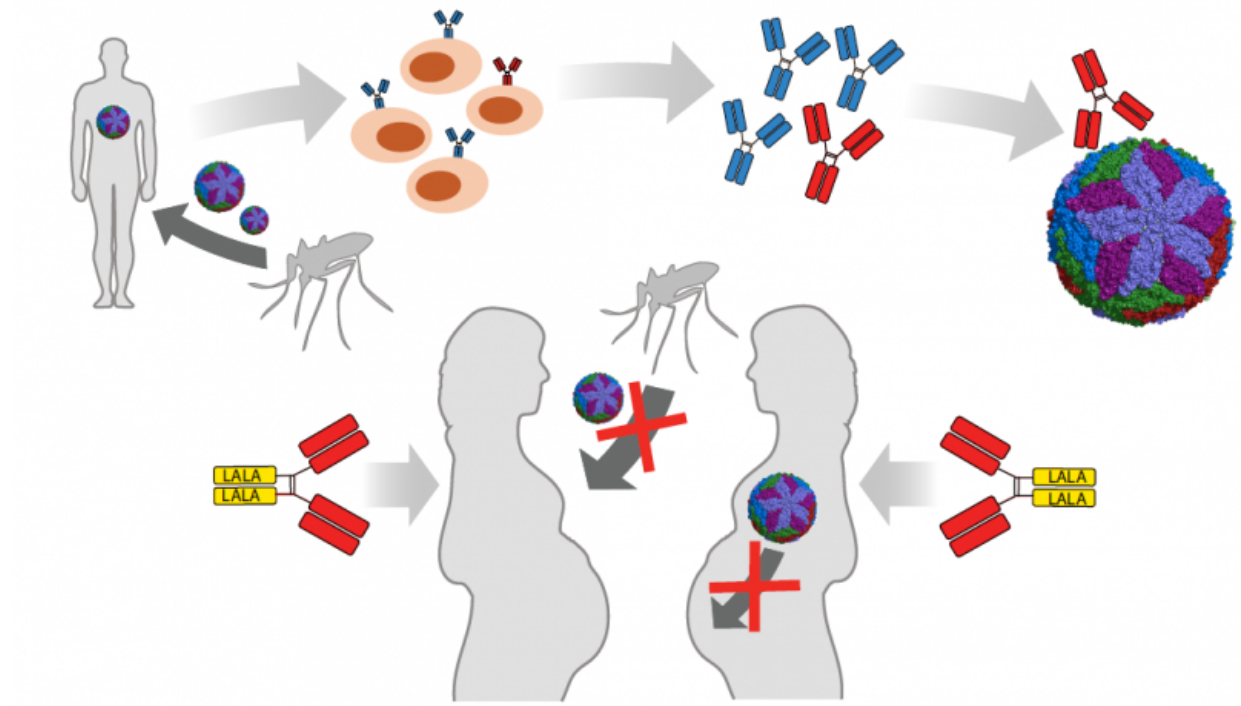
A team of researchers has identified novel therapeutic monoclonal antibody candidates isolated from Zika-infected patients and new strategies for Zika virus diagnostics. An article published today in the renowned scientific journal *Science* describes for the first time an in-depth analysis of the human antibody and T cell immune response to the Zika virus infection with important implications for differential diagnostics and for the development of vaccines and new treatments.

The study is the result of an international collaboration with the University of California, Berkeley (US), Public Health England, Porton Down (UK), the Policlinico San Matteo IRCCS, Pavia (IT), the Swiss Tropical and Public Health Institute, Basel (CH), and the Centre for Tropical Medicine, Ho Chi Minh City (VN). The study was partially funded by the Swiss National Science Foundation, the European Research Council, the US National Institute of Health and the Italian Ministry of Health.

Zika virus is a mosquito-borne flavivirus with homology to Dengue virus. After its introduction into Brazil in 2015, Zika virus has spread rapidly in Latin America and in February 2016, the World Health Organization (WHO) declared it a Public Health Emergency of International Concern. While the main route of Zika virus infection is through bites by mosquitos, the virus may also be spread sexually and vertically from mother to child during the first months of pregnancy. Most of the Zika virus infections are asymptomatic or cause only mild symptoms. However, Zika virus infection can lead to congenital birth

defects such as microcephaly. As of today, there is no preventive vaccine or specific therapy available.

The study published in *Science* reports the first characterization of the human immune response to Zika infection, showing that most of the antibodies elicited by Zika virus infection cross-react with Dengue virus. These cross-reactive antibodies are poorly neutralizing, and can increase the severity of subsequent infection with Zika or Dengue virus. The study shows in experimental models that cross-reactive antibodies induced by infection with Zika virus are capable of provoking lethal Dengue virus infections. These findings, which are subject to validation by prospective epidemiological studies, should be taken into consideration in the context of the development of vaccines.



from the top left, the Zika virus infection that can occur by mosquito bite in the centre, the human immune response to the infection, and to the right, the isolation of the specific Zika antibody and the relative target virus. Below, the

LALA “super antibody” that restrains the infection either by mosquito-human infection (to the left) or towards the foetus (to the right). Credit: Universita della Svizzera Italiana

It took only four months to functionally select, clone and characterize more than 100 anti-Zika virus antibodies from the initial screening of human B cells derived from four convalescent patients. The most potent antibody capable to neutralize Zika virus is now being developed by Humabs to prevent congenital infections."I believe that our discoveries will also have a significant impact on the development of novel diagnostic to differentiate between a Zika or a Dengue infection" said Davide Corti, CSO and senior VP, Humabs. "This study represents another example of the rapid pathway established at Humabs for the isolation and characterization of large numbers of antibodies directed against infectious agents and for the development of the best in class antibodies as potential new therapies against emerging pathogens," said Filippo Riva, CEO of Humabs.

"In contrast to the broad cross-reactivity observed with antibodies, we found that the T cell response is to a large extent Zika-specific, a finding that may decrease the risk of Dengue infection in Zika-immunized individuals," said Federica Sallusto, Director of the Center of Medical Immunology at the IRB.

The study also illustrates the use of some of the Zika virus-specific antibodies isolated in serological diagnostic tests in large cohort clinical and epidemiological studies to investigate the risk of Zika virus disease enhancement in subjects pre-immunized with other flavivirus such as the Dengue virus and the real incidence rate of Zika virus congenital infection in Zika infection endemic areas.

A highly potent neutralizing antibody was identified and engineered into the "LALA" form to not bind the Fc receptors, which is normally the pathway to promote the infection and multiplication of the virus. This LALA antibody showed to inhibit the increase of Zika virus infection caused by antibodies present in the serum of subjects immune to Dengue or Zika virus and showed prophylactic and therapeutic efficacy in a lethal infection model of Zika virus. This class of highly potent engineered LALA antibodies holds the promise of preventing congenital Zika virus infection in pregnant women at risk, and also to serve as potential inhibitors of disease enhancement and transplacental infection by pre-existing cross-reactive antibodies.

More information: K. Stettler et al. Specificity, cross-reactivity and function of antibodies elicited by Zika virus infection, *Science* (2016). DOI: 10.1126/science.aaf8505

Provided by Universita della Svizzera Italiana