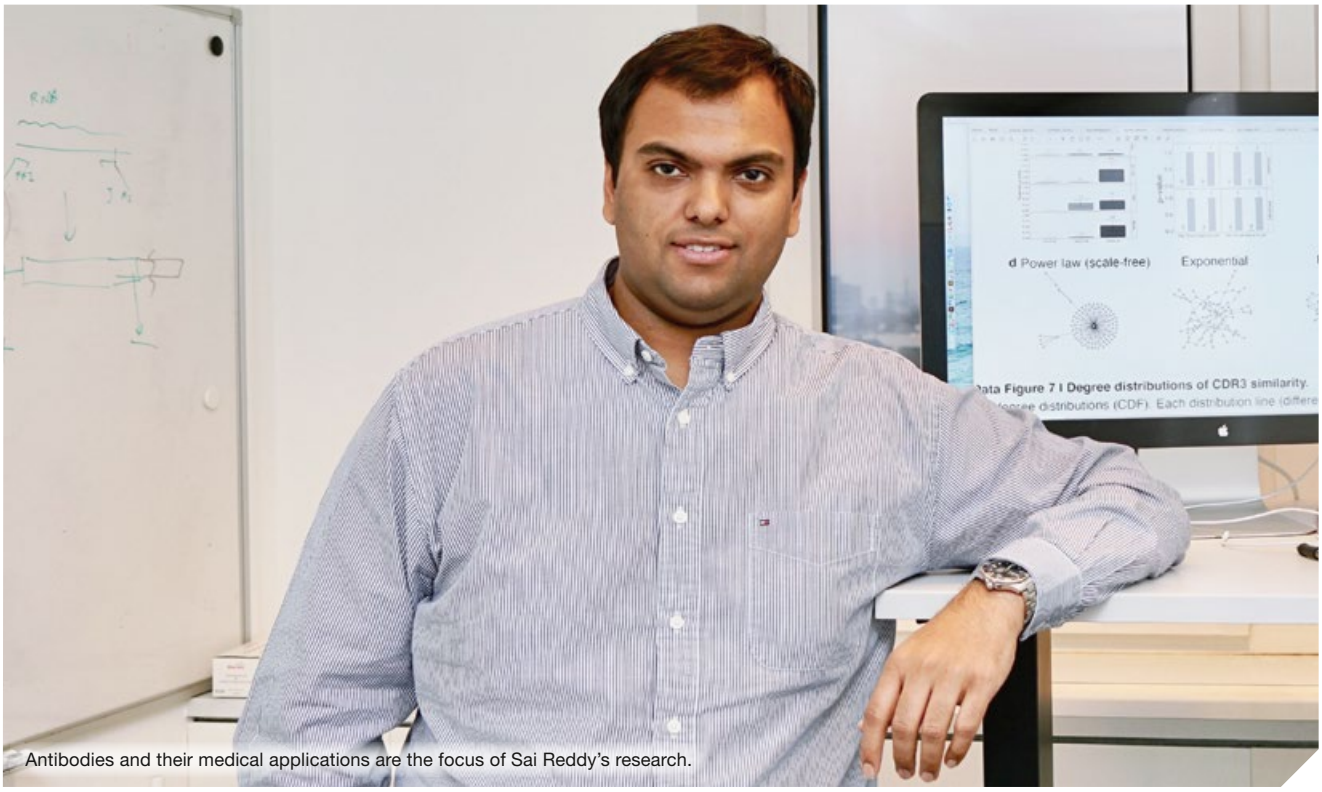
Systems biology of humoral immunity (AntibodyX)

Exploring the antibody repertoire in acute and chronic infections

Worldwide, scientists are exploring new ways of using potent antibodies for disease prevention and the treatment of acute and chronic infections, and even against cancer. Sai Reddy and his team are developing their own analytical methods to do just this and are applying them in order to understand the immune response to pathogens in detail.



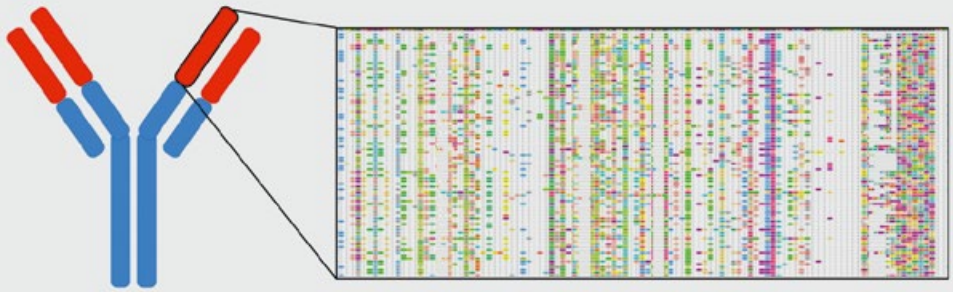
Antibodies and their medical applications are the focus of Sai Reddy's research.

Every antigen contact leaves a trace on the host organism, at least on an immunological level. "The main goal of our project is to be able to determine the antibody pattern of a given organism," says Sai Reddy, principle investigator of the Research, Technology and Development (RTD) Project AntibodyX. An extremely complex task, since there are millions of these plasma proteins within a single organism. The AntibodyX team is not only looking to find out which antibodies are present in a blood or tissue sample. They also want to be able to measure them quantitatively. But that's easier said than done. The methods enabling such analysis with high throughput and precision didn't even exist at the start of the RTD Project. "Thanks to AntibodyX, we've managed to make great progress in this area," explains the bioengineer Reddy. The team has succeeded in optimizing existing methods for the measurement of antibodies to meet even their own high requirements. "We've also developed several analytical tools to help us quickly filter out the information we're looking for from the enormous amounts of generated data," says Reddy. These methods incorporate novel concepts from the areas of mathematical ecology, statistical genetics, machine learning and network theory.

Looking for a needle in a haystack

"The search for a particular antibody in a blood or tissue sample was initially rather like looking for a needle in a haystack," says Sai Reddy. In order to make this search easier, and therefore more feasible in practice, the scientists exploited the fact that antibodies can be identified by particular genetic sequences. "The advantage of this method is that the distribution pattern of these sequences serves as a marker, allowing us to determine the immunological health of an organism," explains Reddy. In other words, the more of a particular antibody an individual has, the more efficient its body's defenses against the corresponding antigen are.

But that's not all. Every filtered-out antibody can be characterized in detail thanks to the team's new customized biochemical methods. "For example, we can also ascertain which of an antigen's molecular structures the antibody can dock onto," explains the researcher – information that the AntibodyX team needs in order to address further interesting problems. Among these is the question of why, after infection, the course of the disease can vary widely from patient to patient.



High-throughput sequencing of antibodies is providing new insight into immune responses and enabling the discovery of new vaccines and immunotherapies. © Sai Reddy

Super-antibodies as therapy

"After an HIV infection, a small number of patients exhibit a low concentration of the virus in their blood over a long time," describes Reddy. The clinical symptoms are also correspondingly milder. These patients are known as super controllers. They possess antibodies that can efficiently neutralize different strains of the HIV pathogen. "Thanks to spontaneous mutations, antibodies that are particularly effective against a particular pathogen can arise, which increase the survival chances of the affected individual," explains the researcher. The benefit of these findings is clear: "Such super-antibodies could be used for therapy or prevention." Two examples demonstrate just how promising this approach is.

Scientists at the Rockefeller University in New York have managed to extract some of these highly effective antibodies from super controller patients and synthesize them millions of times over. They then administered them to other HIV patients with considerable success. In some of the subjects a reduction in viral replication was observed over a certain period of time. Experts believe that a combination of different super-antibodies would significantly increase the effect. This hypothesis was given weight by experiences from the latest Ebola epidemic in humans, where treatment with the ZMAPP preparation was trialed. This therapeutic agent contained three types of Ebola-neutralizing antibodies. These plasma proteins were obtained from infected mice, which had produced the super-antibodies through spontaneous mutations. The success of this trial gained worldwide attention, as all of the patients treated with this method survived. "The administered antibodies kept the virus in check until the body was able to build its own immune response," Sai Reddy explains. Conversely, the Ebola pathogen damaged the bodies of untreated patients so severely within a matter of days that their immune systems were no longer able to build a defensive strategy.

Tailor-made vaccinations

The possible uses of such tailor-made vaccinations spur Sai Reddy and his team on. "Another goal of our RTD Project is to use the methods we've developed to explore the evolution of an antibody repertoire in both acute and chronic infections in detail." In order to reach this goal as quickly as possible, three groups within the AntibodyX team are investigating different problems. While the group led by Alexandra Trkola is focusing on the immune response of people with HIV, the research in Lars Hangartner's group concerns defenses against the influenza virus, and Annette Oxenius is examining the immune response to infection with the lymphocytic choriomeningitis virus (LCMV) in mice. The overarching goal of this research is to analyze the immunological processes that occur during acute and chronic infection in the hope of finding potential new vaccines. Sai Reddy can also imagine another promising use for these findings: "The application of neutralizing antibodies could also lead to a breakthrough in cancer therapy."

AntibodyX at a glance

AntibodyX
Systems Biology of Humoral Immunity

Principal investigator: Prof. Sai Reddy

Research groups:

- Prof. Sai Reddy, Laboratory for Systems and Synthetic Immunology, D-BSSE, ETH Zurich – Experimental and computational methods
- Prof. Lars Hangartner, Institute of Medical Virology, University of Zurich – Immunology, virology
- Dr. Roland Regoes, Institute of Integrative Biology, ETH Zurich – Bioinformatics, computational biology
- Prof. Alexandra Trkola, Institute of Medical Virology, University of Zurich – Immunology, virology
- Prof. Annette Oxenius, Institute of Microbiology, ETH Zurich – Immunology, virology

Total budget (2013–2017): CHF 2.9 million, including CHF 1.4 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project