Kymouse success in steps to developing HIV vaccine

A new approach to developing a human vaccine against HIV has been developed by researchers at Kymab, a UK therapeutic antibody platform Company, The Scripps Research Institute (TSRI) of San Diego, California, and the International AIDS Vaccine Initiative (IAVI). HIV is one of the most intransigent targets for vaccine development, and no effective vaccine has been developed in thirty years of global research.

The research, which tested the first step in an approach to develop effective vaccines against the range of HIV variants existing worldwide, is published in Science and was supported by funding from the International AIDS Vaccine Initiative and the US National Institutes of Health.

The results show that Kymouse, which is a mouse that has been modified to mimic human antibody responses, is an effective platform for discovering and testing possible vaccines and suggest ways in which testing of vaccine candidates can be improved.

"We increasingly recognize that traditional vaccine strategies will not be successful against all viruses, especially not HIV," says Dennis Burton, chair of the TSRI Department of Immunology and Microbial Science and scientific director of the International AIDS Vaccine Initiative (IAVI) Neutralizing Antibody Center (NAC) at TSRI and the National Institutes of Health (NIH) Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery (CHAVI-ID). "Together with the Kymab team, we have taken a novel approach in which have induced human antibodies in Kymouse that are at the beginning of the pathway to protective antibodies and which is a huge boost to our mission to develop an HIV vaccine."

The work is based on the observation that a fraction of people who become infected by HIV develop broadly neutralizing antibodies against diverse HIV strains. Such antibodies would be ideal to protect against or possibly treat HIV infection - if a vaccine could be made to elicit them.
However, these antibodies originate from a limited number of precursor antibody-producing cells in the body and acquire their unusual and protective properties only during a long course of infection. Moreover, although these cells have been activated when immunizing certain biased animal models, this is the first time it has been achieved through immunization of an immune system, as in the Kymouse, that resembles the human.

The researchers injected Kymouse strains with a nanoparticle formed of 60 copies of a small protein that mimics HIV and was designed to bind and stimulate the specific precursor cells for one class of broadly neutralizing antibody.

They expected to find just one such precursor cell (among tens of millions of such cells) in each immunized mouse.

The research team then looked to see whether or not the mice had mounted an antibody response to this injection. Given the combined challenges of a complex immunogen structure and the rarity of the right antibodies, an effective response against the HIV immunogen was elicited remarkably efficiently.

"Our phenomenal results with the teams at TSRI and IAVI came from work at the boundaries of protein engineering, immunology and vaccine technology," explains Professor Allan Bradley, Chief Technical Officer at Kymab and Director Emeritus of the Wellcome Trust Sanger Institute, who developed the Kymouse platform. "Using Kymouse, we show how an advanced vaccine candidate can search out the one cell among tens of million antibody-producing cells and make it proliferate.

"Kymouse can deliver antibody responses that we need to build effective HIV vaccines."

The team validated their antibody response by sequencing genes from more than 10,000 cell samples, and showed that genes from responding mice had the
expected sequence for precursors to broadly neutralizing antibodies against the HIV target.

"It is a big step forward in this branch of HIV vaccine development," says William Schief, TSRI Professor and Director of Vaccine Design for the IAVI Neutralizing Antibody Center at TSRI, in whose lab the vaccine nanoparticle was developed. "We have the first proof of principle that this HIV vaccine strategy and our vaccine candidate can work in a human immune system and trigger the first step in the pathway to developing broadly neutralizing and protective antibodies against the virus.

"It is the very sort of response we'd want to see as we test components of a future vaccine."

HIV has proved an extremely difficult challenge in vaccine development. The new research shows that Kymouse can produce antibodies of the type that could evolve to confer protection, suggests ways in which the immunization regime can be improved and indicates that Kymab's technologies will support and accelerate the search for other, rarer and perhaps even more effective antibodies.

"About 35 million people have died of HIV/AIDS and 36 million are currently infected. Although a vaccine is the most likely way to stem this loss, no successful vaccine has been found in more than thirty years of HIV research," says Professor Paul Kellam, Vice President of Infectious Diseases and Vaccines at Kymab. "This is a pressing need and these results show that our Kymouse technologies can serve a vital part in the search for effective vaccines that help to protect against this most challenging disease."

"This dramatic proof of concept gives us hope we can find better broadly effective vaccines for HIV and, indeed, for other infections, using the human immune system to help guide us along the best path."