Kymouse™, Kymab's human antibody discovery platform, successfully demonstrates steps to developing HIV vaccine

Kymab, The Scripps Research Institute and International AIDS Vaccine Initiative collaboration improves discovery and testing of promising HIV vaccine strategies

Cambridge, UK, 9 September 2016: Kymab, the Cambridge-based antibodies-to-medicines company, announces today a publication of a new approach to developing a human vaccine against HIV in the internationally renowned scientific journal Science. The publication presents new findings from a collaboration between researchers at Kymab, 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 paper is entitled "Priming HIV-1 broadly neutralizing antibody precursors in human Ig loci transgenic mice".

The research, which tested the first step in an approach to develop effective vaccines against the range of HIV variants existing worldwide, was published in *Science* on Thursday 8 September, 2016, 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 recognise that traditional vaccine strategies will not be successful against all viruses, especially not HIV. Together with the Kymab team, we have taken a novel approach in which we 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 a HIV vaccine" 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).

The work is based on the observation that a fraction of people who become infected by HIV develop broadly neutralising 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 immunising certain biased animal models, this is the first

time it has been achieved through immunisation 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 neutralising antibody. They expected to find just one such precursor cell (among tens of millions of such cells) in each immunised 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 neutralising 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 neutralising 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 immunisation 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."

Kymab has raised more than $120m in equity funding from partners including Bill & Melinda Gates Foundation, the Wellcome Trust, Malin Corporation plc and the Woodford Patient Capital Trust plc to fund its unique antibody development platform in therapeutic development and vaccine discovery. Kymab is building a rich pipeline of assets in four main therapeutic spaces: infectious disease, such as HIV and malaria, as well as immuno-oncology, inflammation and haematology.

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Notes to Editors

About Kymab

Kymab is a leading biopharmaceutical company focused on the discovery and development of fully human monoclonal antibody drugs using its proprietary Kymouse™ antibody platform.

Kymouse™ has been designed to maximise the diversity of human antibodies produced in response to immunisation with antigens. Selecting from a broad diversity of fully human antibodies assures the highest probability of finding that rare drug candidate with best-in-class characteristics. The Kymouse™ naturally matures these molecules to highly potent drugs obviating the need for further time-consuming modifications. Kymab is using the platform for its internal drug discovery programmes and in partnership with pharmaceutical companies. Kymab commenced operations in 2010 and has raised over US$120m of equity financing which includes $90m Series B financing. It has an experienced management team with a successful track record in drug discovery and development and has numerous therapeutic antibody programmes in immune-oncology, auto-immunity; hematology, infectious disease and other areas.

http://www.kymab.com

Publication

Sok D, Briney B, Jardine JJ, Kulp DW *et al*. (2016) Priming HIV-1 broadly neutralizing antibody precursors in human Ig loci transgenic mice. This paper will be published online by the journal Science on THURSDAY, 8 September, 2016.

Participating Centres

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- Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA, USA
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- Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery, The Scripps Research Institute, La Jolla, CA, USA
- Ragon Institute of MGH, MIT, and Harvard, Cambridge, MA, USA

About The Scripps Research Institute

The Scripps Research Institute (TSRI) is one of the world's largest independent, not-for-profit organizations focusing on research in the biomedical sciences. TSRI is internationally recognized for its contributions to science and health, including its role in laying the foundation for new treatments for cancer, rheumatoid arthritis, hemophilia, and other diseases. An institution that evolved from the Scripps Metabolic Clinic founded by philanthropist Ellen Browning Scripps in 1924, the institute now employs more than 2,500 people on its campuses in La Jolla, CA, and Jupiter, FL, where its renowned scientists—including two Nobel

laureates and 20 members of the National Academy of Science, Engineering or Medicine—work toward their next discoveries. The institute's graduate program, which awards PhD degrees in biology and chemistry, ranks among the top ten of its kind in the nation. For more information, see www.scripps.edu.

About International Aids Vaccine Initiative (IAVI)

The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996 and operational in 25 countries, IAVI and its network of collaborators research and develop vaccine candidates. IAVI was founded with the generous support of the Alfred P. Sloan Foundation, The Rockefeller Foundation, The Starr Foundation, and Until There's A Cure Foundation. Other major supporters include the Bill & Melinda Gates Foundation, the Foundation for the National Institutes of Health, The John D. Evans Foundation, The New York Community Trust, the James B. Pendleton Charitable Trust; the Governments of Canada, Denmark, India, Ireland, Japan, The Netherlands, Norway, Spain, Sweden, the United Kingdom, and the United States, the Basque Autonomous Government (Spain), the European Union as well as the National Institute of Allergy and Infectious Diseases and The City of New York, Economic Development Corporation; multilateral organizations such as The World Bank and The OPEC Fund for International Development; corporate donors including BD (Becton, Dickinson & Co.), Bristol-Myers Squibb, Continental Airlines, Google Inc., Pfizer Inc, and Thermo Fisher Scientific Inc.; leading AIDS charities such as Broadway Cares/Equity Fights AIDS; and many generous individuals from around the world. For more information, see www.iavi.org.