News Release

SMART Researchers Develop Mice with Complete Human Blood System Cells

Breakthrough will help advance both basic and applied research in infectious diseases, blood cell cancers and autoimmune diseases

Singapore, 1 December 2010 – A team of researchers at the Singapore-MIT Alliance for Research and Technology (SMART) has successfully developed humanised mice with complete human blood system cells. The study addresses the use of humanised mice in research applications and the improvement of the representation of cells of the human blood system that were previously low in number or missing in the mice. The results were published in this week's PNAS Early Edition. PNAS is the official journal of the US National Academy of Sciences and an authoritative source of high-impact, original research that broadly spans the biological, physical, and social sciences. The team, from SMART's Infectious Diseases Interdisciplinary Research Group (IRG), includes Postdoctoral Associate Dr. Chen Qingfeng, Postdoctoral Associate Dr. Maroun Khoury and Lead Investigator Professor Chen Jianzhu.

The existing humanised mouse model provides an important tool to study infection by human pathogens, especially those that infect human blood lineage cells (different cells that constitute the blood). They also allow investigations of human immune responses to pathogens in a small animal model. However, current models are far from optimal. For example, repopulation of Natural Killer (NK) cells, myeloid blood lineage cells and red blood cells in the mouse is generally poor or undetectable. NK cells and myeloid cells play important roles in innate immune responses. They are responsible for the rejection of tumors and cells infected by viruses in the human body.

Lead author of the paper, Chen Qingfeng said, "The poor reconstitution and function of these cell types in humanised mice are attributed largely to the lack of specific human cytokines which play an important role in NK cell activation in our bodies. Cytokines are protein molecules that help to regulate the immune system and are critical in the development and maintenance of the NK and myeloid cells in humanised mouse experiments."

Lead author of the paper, Chen Qingfeng said, "The development of humanised mice with adequate levels of reconstitution of NK and myeloid cells is critical for realising the full potential of the humanised mouse models in infectious disease research and other research involving blood lineage cells," he explained.

The team developed a simple and efficient method to improve the reconstitution of specific human blood lineage cells, namely NK and myeloid cells, in humanised mice. In their study, human DNA molecules (IL-15 and FLT-3/FLK-2 Ligand) were injected into humanised mice by

high pressure-tail vein injection (hydrodynamic delivery). Using this method, the human cytokine in the mice lasted two to three weeks and stimulated a dramatically increased production of NK cells that lasted more than a month. The generated human NK cells in mice were fully functional, both in vitro and in vivo, as they reacted to virus infections the same way as the ones found in the normal human body.

The team tested another group of human cytokines using the same high pressure-tail vein injection. The team was again successful in enhancing the numbers of other human immune cells such as dendritic cells, monocytes/macrophages and more importantly red blood cells.

Professor Chen Jianzhu, lead principle investigator of the Infectious Diseases IRG at SMART said, "Although the hydrodynamic injection by itself has been widely used in mice, we are the first to use this technique in the humanised mice model, and also the first to show we can obtain human red blood cells in vivo as well as improve the other human cells. This is an important breakthrough for studying human immune responses and disease progression in a small animal model. The team has developed an efficient model that will help advance the study of human immune responses to pathogens."

This method of producing human blood lineage cells in humanised mice provides a good model to study blood related infectious diseases of major interest in South-East Asia such as Dengue, Malaria and HIV. This method also offers an opportunity to develop more accurate human blood cell disease models, which can be used for basic study of human diseases as well as therapeutic development.

This study was funded primarily by SMART and done entirely at the SMART laboratories in Singapore.

Note to Editor:
The published paper titled "Expression of Human Cytokines Dramatically Improves Reconstitution of Specific Human Blood Lineage Cells in Humanised Mice" can be found on PNAS Early Edition at http://www.pnas.org/content/early/recent and will be available in the next print issue of PNAS.

About SMART
SMART is a major new research enterprise established by the Massachusetts Institute of Technology (MIT) in partnership with the National Research Foundation of Singapore (NRF) in 2007. It is the first entity in the Campus for Research Excellence and Technological Enterprise (CREATE) being developed by NRF. Serving as an intellectual hub, cutting-edge research projects in areas of interest to both Singapore and MIT are undertaken at the SMART and interdisciplinary, experimental, computational and translational research are conducted.

Four interdisciplinary research groups (IRG) have been established to date: they are BioSystems and Micromechanics (BioSym), Centre for Environmental Sensing and Modelling (CENSAM), Future Urban Mobility and Infectious Disease (ID). The SMART Innovation Centre, similar to MIT's Desphande Centre, has also been established to identify and nurture

ideas for emerging technologies and accelerate their migration from laboratories to the marketplace.

About SMART's Infectious Disease Interdisciplinary Research Group

The SMART Infectious Diseases IRG (ID-IRG) seeks fundamental understanding of host-pathogen interactions as well as direct impact on human heath through translational research. The ID-IRG focuses on infectious diseases that have major impact on human health, including influenza, RSV, dengue fever, malaria and tuberculosis. The strategy of the IRG is to develop enabling technologies, including humanised mouse model, high throughput single cell assay, high resolution proteonomics, glycomics, metabolomics and cellular mechanics platforms, to study infectious diseases using novel approaches and from new angles. The ID-IRG has developed an integrated, cutting-edge research program with participation of both MIT faculty and investigators from Singapore universities and research institutes.

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