THE UNIVERSITY OF TOKYO

NanoBio FIRST Seminar #4

『Engineering an HIV-resistant immune system with targeted nucleases 』

Paula Cannon, PhD

Associate Professor, Dept. of Molecular Microbiology and Immunology, University of Southern California Keck School of Medicine, Los Angeles, CA, USA.

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Venue: Auditorium,
1F, Fuculty of Engineering Bldg. 11,
The University of Tokyo

The chemokine receptor CCR5 is the major co-receptor used by HIV-1 to enter human CD4+ T cells. The absence of functional CCR5 in individuals homozygous for the CCR5Δ32 mutation is associated with profound resistance to HIV, and transplantation of hematopoietic stem cells (HSC) from a CCR5Δ32 donor into a single HIV+ leukemia patient led to the first reported case of an HIV cure in humans. These observations suggest that modification of a patient's own HSC to create CCR5-negative cells could be used to build an HIV-resistant immune system in subjects with HIV/AIDS. Using genome engineering tools such as zinc-finger nucleases (ZFNs) and TALENs, we are able to efficiently knock-out the CCR5 gene in human HSC, and pre-clinical studies using humanized mice have shown that these CCR5-negative stem cells generate mature human T cells in vivo that resist HIV infection.

Translating this to the clinic requires scale-up and adaptation of the technology for use with mobilized peripheral blood HSC, as well as selection of an appropriate patient population for such first-in-man clinical trials. Finally, targeted nuclease technologies can also be exploited to promote site-specific correction of genetic mutations, thereby allowing HSC engineering to be considered for other diseases of the blood and immune system that are currently only treatable by bone marrow transplantation.

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For Further Information Contact : NanoBio FIRST Research Support Office

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