IMSUT Distinguished Professor Unit

Division of Stem Cell Therapy
幹細胞治療部門

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We are working on uncovering new diseases, elucidating the causes of disease, and developing therapeutic modalities by connecting the knowledge and methodology of basic science including immunology, molecular biology, cell biology, and developmental engineering with clinical medicine. Our ultimate goal is to contribute to establishing new frontiers of stem cell therapy and to make clinical applications of stem cells a reality.
Current work in the Nakauchi Lab includes;
1. Elucidation of heterogeneity and hierarchy in hematopoietic stem cells
2. Rejuvenation of antigen specific T cells for efficient immunotherapy
3. Generation of organs from iPS cells by way of blastocyst complementation
With respect to education, we aim to establish an environment where individuals can make the utmost use of their interests, personalities and abilities in order to foster potential researchers, as a human resource, with a succession of creative studies in the field of bioscience.

1. Interspecies organogenesis generates autologous functional islets

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Islet transplantation is an established therapy for diabetes. However, lack of donor islets precludes its broader application. We previously showed that functional pancreata can be created from rat pluripotent stem cells (PSCs) in mouse by inter-species blastocyst complementation (BC). Although the resulting pancreata were functional and made of rat PSC-derived cells, they were of mouse size, making them insufficient for isolating the number of islets needed to treat diabetes in a rat model.

We performed the reverse experiment, injecting mouse PSCs into Pdx-1 deficient rat blastocysts. The generated pancreata were composed of mouse PSC-derived cells but were of rat size. Islets prepared from these mouse-rat (mouse[R]) chimaeric pancreata were transplanted into mice with streptozotocin (STZ)-induced diabetes. The transplanted islets successfully normalized and maintained host blood glucose levels for over 370 days without immunosuppression except for the first 5 days post-

transplant to avoid hyper acute rejection from residual rat cells. These data provide proof-of-principle evidence for the therapeutic potential of PSC-derived islets generated by BC in a xenogeneic host.

2. Interspecies chimeras for human stem cell research

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Interspecies chimeric assays are a valuable tool for investigating the potential of human stem and progenitor cells, as well as their differentiated progeny. This Spotlight article discusses the different factors that affect interspecies chimera generation, such as evolutionary distance, developmental timing, and apoptosis of the transplanted cells, and suggests some possible strategies to address them. A refined approach to generating interspecies chimeras could contribute not only to a better understanding of cellular potential, but also to understanding the nature of xenogeneic barriers and mechanisms of heterochronicity, to modeling human development, and to the creation of human transplantable organs.

3. 'Off-the-shelf' immunotherapy with iPSC-derived rejuvenated cytotoxic T lymphocytes.

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Adoptive T-cell therapy to target and kill tumor cells shows promise and induces durable remissions in selected malignancies. However, for most cancers, clinical utility is limited. Cytotoxic T lymphocytes continuously exposed to viral or tumor antigens, with long-term expansion, may become unable to proliferate ("exhausted"). To exploit fully rejuvenated induced pluripotent stem cell (iPSC)-derived antigen-specific cytotoxic T lymphocytes is a potentially powerful approach. We review recent progress in engineering iPSC-derived T cells and prospects for clinical translation. We also describe the importance of introducing a suicide gene safeguard system into adoptive T-cell therapy, including iPSC-derived T-cell therapy, to protect from unexpected events in first-in-humans clinical trials.

4. In Vivo Generation of Engraftable Murine Hematopoietic Stem Cells by Gfi1b, c-Fos, and Gata2 Overexpression within Teratoma.

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Generation of hematopoietic stem cells (HSCs) from pluripotent stem cells (PSCs) could potentially provide unlimited HSCs for clinical transplantation, a curative treatment for numerous blood diseases. However, to date, bona fide HSC generation has been largely unsuccessful in vitro. We have previously described proof of concept for in vivo HSC generation from PSCs via teratoma formation. However, our first-generation system was complex and the output low. Here, we further optimize this technology and demonstrate the following: (1) simplified HSC generation using transcription factor overexpression; (2) improved HSC output using c-Kit-deficient host mice, and (3) that teratomas can be transplanted and cryopreserved. We demonstrate that overexpression of Gfi1b, c-Fos, and Gata 2, previously reported to transdifferentiate fibroblasts into hematopoietic progenitors in vitro, can induce long-term HSC formation in vivo. Our in vivo system provides a useful platform to investigate new strategies and re-evaluate existing strategies to generate HSCs and study HSC development.

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