Shinya Yamanaka

Director of the Center for iPS Cell Research and Application (CiRA) at Kyoto University, Professor at the Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University, Senior Investigator at the Gladstone Institute of Cardiovascular Disease in San Francisco and Professor of Anatomy at the University of California, San Francisco

2010 Balzan Prize for Stem Cells: Biology and Potential Applications

For the discovery of a method to transform already differentiated cells into cells presenting the characteristics of embryonic stem cells.

Institution Administering Research Funds: Kyoto University

Adviser for the Balzan General Prize Committee: Nicole Le Douarin

Molecular Basis During iPS Cell Generation and Its Application

Shinya Yamanaka will use half of his prize to support a research project on molecular mechanisms and application of induced pluripotent stem (iPS) cells at the Center for iPS Cell Research and Application (CiRA), Kyoto University, lasting 5-6 years. iPS cells were originally generated from mouse and human fibroblasts by retroviral introduction of four factors, Oct3/4, Sox2, c-Myc, and Klf4. iPS cells are similar to embryonic stem (ES) cells in morphology, proliferation, gene expression, and most importantly, pluripotency. It is important to develop a method to differentiate various target cells from iPS cells with high efficiency and safety. Synthetic RNA technologies have a promising outlook for controlling such cell-fate conversion. For example, direct injection of synthetic mRNAs into mammalian cells could serve as a powerful tool for gene therapy and regenerative medicine because transfected mRNAs do not integrate into the genome, eliminating the risk of cellular damage such as tumor formation. Furthermore, the injection being irrelevant to transfer to the nucleus and nuclear events enables rapid and homogenous gene expression in cell clusters. However, precise control of protein production from directly transferred synthetic RNAs has yet to be attained. Thus, elucidating the design principle of functional RNA molecules could be particularly useful for the next generation of stem cell research.

The Center for iPS Cell Research and Application (CiRA) hired one young faculty member, Dr. Saito, on 1st July 2011, to promote the research to control cell fate using synthetic

RNA-based gene manipulation technologies. Dr. Saito attempts to take a synthetic biology approach that leads to understand and control cells through the process of 'artificially creating' biomolecules and biological systems. Creating artificial biomolecules that freely control the functions of cells and applying them to examinations and medical treatments is one of the research goals of this new field. His laboratory will use the unique technology of synthetic biology that designs RNA and/or RNA-protein complexes (RNP) artificially and experimentally evolve them in order to control fate of target cells depending on cellular environment. In concrete terms, he will engage in the following research projects:

1. Developing a technique to control cell fate with high safety and purity using artificial RNA/RNP molecular complexes.
2. Developing artificial RNA/RNP-based genetic switches that can detect specific protein and/or RNA expression and control ON/OFF of the translation of target genes.

Researcher:
Hirohide Saito, Associate Professor CiRA

Publications:
* corresponding author
- James A. Stapleton, Kei Endo, Yoshihiko Fujita, Karin Hayashi, Masahiro Takinoue, Hirohide Saito*, and Tan Inoue*, *Feedback Control of Protein Expression in Mammalian Cells by Tunable Synthetic Translational Inhibition,* "ACS Synthetic Biology", 1: 83-88, 2012.

Other Relevant Information
References for the RNA-based gene synthetic biology technologies developed by Dr. Saito:

- Hirohide Saito*, Yoshihiko Fujita, Shunnichi Kashida, Karin Hayashi, and Tan Inoue*, *Synthetic human cell fate regulation by protein-driven RNA swiches,* "Nature Communications", 2, 160 (2011).
- Hirohisa Ohno, Tetsuhiro Kobayashi, Rinko Kabata, Kei Endo, Takuma Iwasa, Shige Yoshimura, Kunio Takeyasu, Tan Inoue*, and Hirohide Saito*, *Synthetic RNA-protein complex shaped like an equilateral triangle,* "Nature Nanotechnology", 6: 116-120 (2011).
- Hirohide Saito*, Tetsuhiro Kobayashi, Tomoaki Hara, Yoshihiko Fujita, Karin Hayashi, Rie Furushima, and Tan Inoue* *Synthetic Translational Regulation by an L7Ae-Kink-turn RNP Switch* "Nature Chemical Biology", 6: 71-78 (2010).