【Grant-in-Aid for Scientific Research (S)】

Integrated Disciplines (Complex Systems)

Title of Project : Control and Analysis of Cells by Synthetic Small Molecules

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Research Area : Complex Systems
Keyword : Chemical probes

【Purpose and Background of the Research】

This research project proposes a new way of using synthetic small molecules, in which small chemical compounds serve as tools for improving the efficacy and productivity of cell therapy by manipulating and detecting fundamental biological processes in human cells. The proposed research includes proof-of-concept experiments that develop and use small molecule tools for cell therapy. Specific goals are the discovery, understanding, and use of (i) small molecule anoikis inhibitors, (ii) small molecules that promote cardiomyogenesis, (iii) chemical probes that visualize human stem cells, (iv) small molecules that eliminate human pluripotent stem cells. Through the proposed research, we hope to open a new field of synthetic bioactive molecules.

【Research Methods】

Aim 1: Discovery, understanding, and use of small molecule anoikis inhibitors. One of the major problems encountered in cell transplantation is the low level of survival of transplanted cells due to detachment-induced apoptosis, called anoikis. The aim of this project is to design an anoikis inhibitor by mimicking fibronectin, a large 440KDa extracellular protein.

Aim 2: Discovery, understanding, and use of small molecules that promote cardiomyogenesis. Stem cell therapy requires differentiation of iPS or ES cells into specific, clinically useful cell types after expansion. The aim of this project is to understand molecular mechanism of KY02111, the most potent small molecule promoter of cardiomyogenesis that we previously discovered. We also plan to design even more potent small molecule inducers based on the molecular understanding.

Aim 3: Discovery, understanding, and use of chemical probes that visualize human stem cells. One of the current problems of stem cell therapy is the tumorigenic risk of residual undifferentiated cells. Fluorescent compounds that selectively labels residual pluripotent stem cells would permit convenient detection and purification of residual stem cells. Screening of fluorescent chemical libraries with human iPS cells, and subsequent evaluation of hit molecules, identified a fluorescent compound (Kyoto Probe 1; KP-1) that selectively labels human pluripotent stem cells. However, its selectivity is not perfect. The aim of this project is to improve its selectivity.

Aim 4: Discovery, understanding, and use of small molecules that eliminate human pluripotent stem cells. KP-1 is capable of detecting human pluripotent stem cells but not eliminating them. The aim of this project is to develop small molecules that eliminate residual pluripotent stem cells from cell mixtures for safer transplantation. We previously revealed the selectivity mechanism of KP-1. Based on its mechanism, we search for stem-cell-eliminating molecules.

【Expected Research Achievements and Scientific Significance】

Cell therapy will play an essential role in the future practice of medicine. One of the problems of cell therapy is high cost. Small molecules offer the advantage of cost-effective mass production. Success of the concept of the proposed research will eventually reduce the cost of therapy.

【Publications Relevant to the Project】

・Takemoto, N., 20 others, *Uesugi, M. Small Molecule-induced Clustering of Heparan Sulfate Promotes Cell Adhesion. ***J. Am. Chem. Soc.*** 135 (30), 11032-11039 (2013).
・Hirata, N., 23 others, *Uesugi, M. A Chemical Probe that Labels Human Pluripotent Stem Cells. ***Cell Reports*** 6(6), 1165-1174 (2014).

【Term of Project】 FY2014-2018

【Budget Allocation】 150,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.scl.kyoto-u.ac.jp/~uesugi/