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– Chemical Biology –

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KEYWORDS

Cell Therapy
Chemical Biology
Small Molecules
Chemical Library
Chemical Genetics

Scope of Research

Chemical biology is an interdisciplinary field of study that is often defined as “chemistry-initiated biology.” As biological processes all stem from chemical events, it should be possible to understand or manipulate biological events by using chemistry. Our laboratory has been discovering or designing unique organic molecules that modulate fundamental processes in human cells. Such synthetic organic molecules often serve as tools for basic cell biology. Discovery or design of small molecules with unique biological activity permits small-molecule initiated exploration of complex cellular events. Our mission is to create a new world of bioactive synthetic molecules: their new way to use, their new shapes, and their new sizes. We hope to open new avenues for small-molecule applications in a range of fields, including future concepts in drug discovery and use of small molecules for cell therapy.

Selected Publications

Sato, S.; Watanabe, M.; Katsuda, Y.; Murata, A.; Wang, D. O.; Uesugi, M., Live-cell Imaging of Endogenous mRNAs with a Small Molecule, *Angew. Chem. Int. Ed*., accepted (in press).

Frisco-Cabanos, H. L.; Watanabe, M.; Okumura, N.; Kusamori, K.; Takemoto, N.; Takaya, J.; Sato, S.; Yamazoe, S.; Takakura, Y.; Kinoshita, S.; Nishikawa, M.; Koizumi, N.; Uesugi, M., Synthetic Molecules that Protect Cells from Anoikis and Their Use in Cell Transplantation, *Angew. Chem. Int. Ed*., **126 (42),** 11390-11395 (2014).

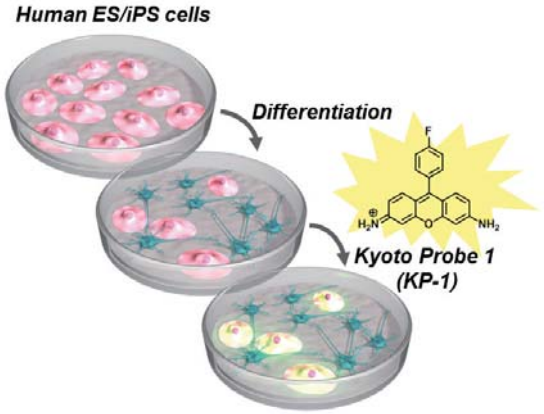
Kuo, T. F.; Mao, D.; Hirata, N.; Khambu, B.; Kimura, Y.; Kawase, E.; Shimogawa, H.; Ojika, M.; Nakatsuji, N.; Ueda, K.; Uesugi, M., Selective Elimination of Human Pluripotent Stem Cells by a Marine Natural Product Derivative, *J. Am. Chem. Soc*., **136 (28),** 9798-9801 (2014).

Hirata, N.; Nakagawa, M.; Fujibayashi, Y.; Yamauchi, K.; Murata, A.; Minami, I.; Tomioka, M.; Kondo, T.; Kuo, T. F.; Endo, H.; Inoue, H.; Sato, S.; Ando, S.; Kawazoe, Y.; Aiba, K.; Nagata, K.; Kawase, E.; Chang, Y. T.; Suemori, H.; Eto, K.; Nakauchi, H.; Yamanaka, S.; Nakatsuji, N.; Ueda, K.; Uesugi, M., A Chemical Probe That Labels Human Pluripotent Stem Cells, *Cell Reports*, **6,** 1165-1174 (2014).

Sakano, D.; Shiraki, N.; Kikawa, K.; Yamazoe, T.; Kataoka, M.; Umeda, K.; Araki, K.; Mao, D.; Matsumoto, S.; Nakagata, N.; Andersson, O.; Stainier, D.; Endo, F.; Kume, K.; Uesugi, M.; Kume, S., VMAT2 Identified as a Regulator of Late-stage β Cell Differentiation, *Nat. Chem. Biol*., **10,** 141-148 (2014).

A Chemical Probe That Labels Human Pluripotent Stem Cells

A small-molecule fluorescent probe specific for human pluripotent stem cells would serve as a useful tool for basic cell biology research and stem cell therapy. Screening of fluorescent chemical libraries with human induced pluripotent stem cells (iPSCs) and subsequent evaluation of hit molecules identified a fluorescent compound (Kyoto probe 1 [KP-1]) that selectively labels human pluripotent stem cells. Our analyses indicated that the selectivity results primarily from a distinct expression pattern of ABC transporters in human pluripotent stem cells and from the transporter selectivity of KP-1. Expression of ABCB1 (MDR1) and ABCG2 (BCRP), both of which cause the efflux of KP-1, is repressed in human pluripotent stem cells. Although KP-1, like other pluripotent markers, is not absolutely specific for pluripotent stem cells, the identified chemical probe may be used in conjunction with other reagents.



Synthetic Molecules That Protect Cells from Anoikis and Their Use in Cell Transplantation

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 present study reports on the chemical synthesis and biological evaluation of water-soluble molecules that protect suspended cells from anoikis. The synthetic molecules bind to and induce clusters of integrins and heparan-sulfate-bound syndecans, two classes of receptors that are important for extracellular matrix-mediated cell survival. Molecular biological analysis indicates that such molecules prolong the survival of suspended NIH3T3 cells, at least in part, by promoting clustering of syndecan-4 and integrin β1 on the cell surface, leading to the activation of small GTPase Rac-1 and Akt. In vivo experiments using animal disease models demonstrated the ability of the molecules to improve cell engraftment. The cluster-inducing molecules may provide a starting point for the design of new synthetic tools for cell-based therapy.