Division of Biochemistry
– Chemical Biology –

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Visitors

Prof WANG, Ming-Wei — Chinese Academy of Sciences, China, P.R., 23 August
Prof KIM, Sunghoon — Seoul National University, Korea, R., 5 October
Prof LEE, Kyeong — Dongguk University, Korea, R, 28 November

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. Our mission is to create 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.

KEYWORDS

Cell Therapy
Chemical Biology
Small Molecules
Chemical Library
Chemical Genetics

Selected Publications

Kawazoe, Y.; Shimogawa, H.; Sato, A.; Uesugi, M., Mitochondrial Surface-specific Fluorescent Probe Activated by Bioconversion, *Angew. Chem. Int. Ed.*, **50(24),** 5478-5481 (2011).

Sumiya, E.; Shimogawa, H.; Sasaki, H.; Tsutsumi, M.; Yoshita, K.; Ojika, M.; Suenaga, K.; Uesugi, M., Cell-morphology Profiling of a Natural Product Library Identifies Bisebromoamide and Miuraenamide A as Actin-filament Stabilizers, *ACS Chem. Biol.*, **6(5),** 425-431 (2011).

Shirakawa, T.; Kawazoe, Y.; Tsujikawa, T.; Jung, D.; Sato, S.; Uesugi, M., Deactivation of STAT6 through Serine 707 Phosphorylation by JNK, *J. Biol. Chem.*, **286,** 4003-4010 (2011).

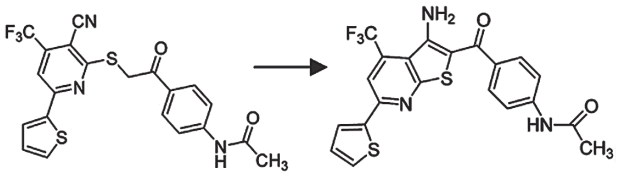
Sato, S; Murata, A.; Orihara, T.; Shirakawa, T.; Suenaga, K.; Kigoshi, H.; Uesugi, M., Marine Natural Product Aurilide Activates the OPA1-mediated Apoptosis by Binding to Prohibitin, *Chem. Biol.*, **18 (1),** 131-139 (2011).

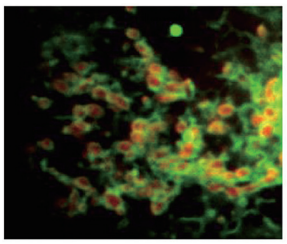
Kamisuki, S.; Shirakawa, T.; Kugimiya, A.; Abu-Elheiga, L.; Choo, H. Y.; Yamada, K.; Shimogawa, H.; Wakil, S. J.; Uesugi, M., Synthesis and Evaluation of Diarylthiazole Derivatives that Inhibit Activation of Sterol Regulatory Element-binding Proteins, *J. Med. Chem.*, **54(13),** 4923-4927(2011).

Murata, A.; Sato, S.; Kawazoe, Y.; Uesugi, M., Small-molecule Fuorescent Probes for Specific RNA Targets, *Chem. Comm.*, **47,** 4712-4714 (2011).

A Mitochondrial Surface-specific Fluorescent Probe Activated by Bioconversion

We carried out cell-based image screening of 12,000 small molecules enriched in aromatic groups and identified thirty-one that had potential as fluorescent probes for living cells. One of the candidates appeared to selectively stain mitochondrial surfaces. Results of spectroscopic analyses and chemical synthesis indicated that the molecule underwent metabolic cyclization to be fluorescent inside cells. To our knowledge, this molecule represents the first fluorescent probe specific for mitochondrial surfaces.





Cell-morphology Profiling of a Natural Product Library

Natural products provide a rich source of biological tools, but elucidating their molecular targets remains challenging. We carried out a cell morphological profiling of a natural product library, which permitted the identification of bisebromoamide and miuraenamide A as actin filament stabilizers. Automated high-content image analysis showed that these two structurally distinct marine natural products induce morphological changes in HeLa cells similar to those induced by known actin-stabilizing compounds. Bisebromoamide and miuraenamide A stabilized actin filaments in vitro, and fluorescein-conjugated bisebromoamide localized specifically to actin filaments in cells. Cell morphological profiling was also used to identify actin-stabilizing or -destabilizing natural products from marine sponge extracts, leading to the isolation of pectenotoxin-2 and lyngbyabellin C. Overall, the results demonstrate that high-content imaging of nuclei and cell shapes offers a sensitive and convenient method for detecting and isolating molecules that target actin.

Discovery of FGH10019

In 2009, our group reported the discovery and synthesis of "fatostatin," a small molecule that inhibits activation of sterol regulatory element-binding protein (SREBP). Fatostatin blocks biosynthesis and accumulation of fat in obese mice. We newly synthesized and evaluated a series of fatostatin derivatives. Our structure-activity relationships led to the identification of FGH10019 as the most potent drug-like molecule among the analogues tested. FGH10019 has high aqueous solubility and membrane permeability and may serve as a seed molecule for further development.

Small-molecule Fluorescent Probes for Specific RNA Targets

A method was developed that uses small molecules as fluorescent probes to detect specific mRNAs. In this approach, the fluorescence of fluorophore-quencher conjugates is restored by the binding of an mRNA aptamer tag to the quencher segment of the molecules. The method allows real-time detection of mRNA transcripts in vitro.