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– Chemical Biology –

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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 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 activities permits small-molecule-initiated exploration of complex cellular events. Our mission is to create a new world of bioactive synthetic molecules: new modes of activity, new shapes, and 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

Takaya, J.; Mio, K.; Shiraishi, T.; Kurokawa, T.; Otsuka, S.; Mori, Y.; Uesugi, M., A Potent and Site-Selective Agonist of TRPA1, *J. Am. Chem. Soc.*, **137,** 15859-15864 (2015).

Parvatkar, P.; Kato, N.; Uesugi, M.; Sato, S.; Ohkanda, J., Intracellular Generation of a Diterpene-Peptide Conjugate that Inhibits 14-3-3-Mediated Interactions, *J Am Chem Soc.*, **137,** 15624-15627 (2015).

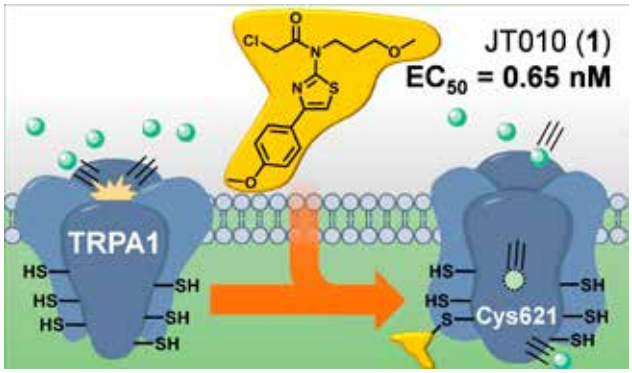
Sato, S.; Watanabe, M.; Katsuda, Y.; Murata, A.; Wang, D. O.; Uesugi, M., Live-cell Imaging of Endogenous mRNAs with a Small Molecule, *Angew. Chem. Int. Ed.*, **54,** 1855-1858 (2015).

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).

A Potent and Site-Selective Agonist of TRPA1

TRPA1 is a member of the transient receptor potential (TRP) cation channel family that is expressed primarily on sensory neurons. This chemo-sensor is activated through covalent modification of multiple cysteine residues with a wide range of reactive compounds including allyl isothiocyanate (AITC), the spicy component of wasabi. The present study reports on potent and selective agonists of TRPA1, discovered through screening 1,657 electrophilic molecules. In an effort to validate the mode of action of hit molecules, we noted a new TRPA1-selective agonist, JT010 (molecule 1), which opens the TRPA1 channel by covalently and site-selectively binding to Cys621 (EC50 = 0.65 nM). The results suggest that a single modification of Cys621 is sufficient to open the TRPA1 channel. The TRPA1-selective probe described herein might be useful for further mechanistic studies of TRPA1 activation.



Live-cell Imaging of Endogenous mRNAs with a Small Molecule

Determination of subcellular localization and dynamics of mRNA is increasingly important for understanding gene expression. A new convenient and versatile method is reported that permits spatiotemporal imaging of specific non-engineered RNAs in living cells. The method uses transfection of a plasmid encoding a gene-specific RNA aptamer, combined with a cell-permeable synthetic small molecule, the fluorescence of which is restored only when the RNA aptamer hybridizes with its cognitive mRNA. The method was validated by live-cell imaging of the endogenous mRNA of β-actin. Application of the technology to mRNAs of a total of 84 human cytoskeletal genes allowed us to observe cellular dynamics of several endogenous mRNAs including arfaptin-2, cortactin, and cytoplasmic FMR1-interacting protein 2. The RNA-imaging technology and its further optimization might permit live-cell imaging of any RNA molecule.