Division of Biochemistry
– Chemical Biology –

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

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Visitors

Assoc Prof CHANG, Young-Tae	National Univeristy of Singapore, Singapore, 14 May
Prof PARK, Hea-Young Choo	Ewha Womans University, Korea, R., 28 June–19 July
Assoc Prof DORE, Timothy	University of Georgia, USA, 2 July
Prof PIEL, Joern	University of Bonn, Germany, 2 September
Assoc Prof PARK, Seung Bum	Seoul National University, Korea, R., 7–9 October
Prof QUIOCHO, Florante A.	Baylor College of Medicine, USA, 29 November–10 December

Scope of Research

Chemical biology is often defined as “chemistry-initiated biology,” in which scientists start with chemistry and end up understanding biology by utilizing chemical tools. Our laboratory has been discovering or designing small-molecule tools that modulate fundamental processes in human cells. Such small organic molecules often serve as tools for basic cell biology and/or for cell therapy. Discovery or design of small molecules with unique biological activity permits small-molecule initiated exploration of complex cellular events, and may also contribute to the realization of cell therapy. Although our primary goal is to provide chemical tools for biological investigations, we also hope to open new avenues for small-molecule applications in a range of fields.

KEYWORDS

Cell Therapy
Chemical Biology
Small Molecules
Chemical Library
Chemical Genetics

Selected Publications

Shirakawa T, Kawazoe Y, Tsujikawa T, Jung D, Sato S, Uesugi M: Deactivation of STAT 6 through Serine 707 Phosphorylation by JNK, *J. Biol.Chem.*, (in press).

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.*, (in press).

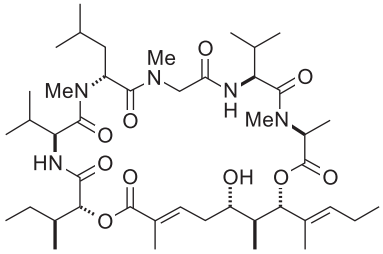
Kamisuki S, Mao Q, Abu-Elheiga L, Gu Z, Kugimiya A, Kwon Y, Shinohara T, Kawazoe Y, Sato S, Asakura K, Choo H, Sakai J, Wakil SJ, Uesugi M: A Small Molecule that Blocks Fat Synthesis by Inhibiting the Activation of SREB, *Chem. Biol.*, **16 (8),** 882-892 (2009).

Yamazoe S, Shimogawa H, Sato S, Esko JD, Uesugi M: A Dumbbell-Shaped Small Molecule that Promotes Cell Adhesion and Growth, *Chem. Biol.*, **16 (7),** 773-782 (2009).

Jung D, Shimogawa H, Kwon Y, Mao Q, Sato S, Kamisuki S, Kigoshi H, Uesugi M: Wrenchnolol Derivative Optimized for Gene Activation in Cells, *J. Am. Chem. Soc.*, **131(13),** 4774-4782 (2009).

Mechanism of Action of Marine Natural Product Aurilide

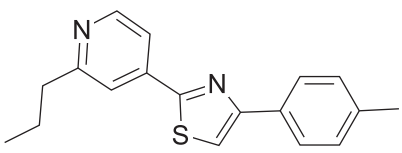
Aurilide is a potent cytotoxic marine natural product that induces apoptosis in cultured human cells at the pM to nM range; however, its mechanism of action has been unknown. Results of the present study showed that aurilide selectively binds to prohibitin 1 (PHB1) in the mitochondria, activating the proteolytic processing of optic atrophy 1 (OPA1), and resulting in mitochondria-induced apoptosis. The mechanism of aurilide cytotoxicity suggests that PHB1 is an apoptosis-regulating protein amenable to modulation by small molecules. Aurilide may serve as a small-molecule tool for studies of mitochondrion-induced apoptosis.



Aurilide

Fatostatin, A Small Molecule that Blocks Fat Synthesis

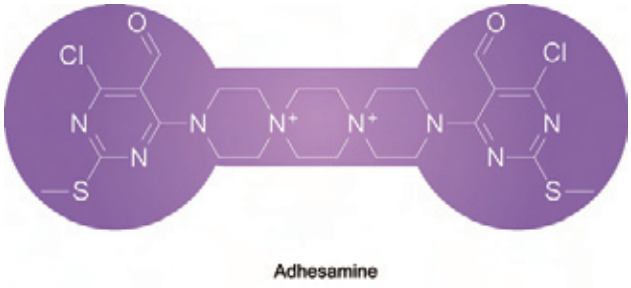
Sterol regulatory element binding proteins (SREBPs) are transcription factors that activate transcription of the genes involved in cholesterol and fatty acid biosynthesis. In the present study, we show that a small synthetic molecule we previously discovered to block adipogenesis is an inhibitor of the SREBP activation. The diarylthiazole derivative, now called fatostatin, impairs the activation process of SREBPs, thereby decreasing the transcription of lipogenic genes in cells. Our analysis suggests that fatostatin inhibits the ER-Golgi translocation of SREBPs through binding to their escort protein, the SREBP cleavage-activating protein (SCAP), at a distinct site from the sterol-binding domain. Fatostatin blocked increases in body weight, blood glucose, and hepatic fat accumulation in obese ob/ob mice, even under uncontrolled food intake. Fatostatin may serve as a tool for gaining further insights into the regulationof SREBP.



Fatostatin

Adhesamine, A Dumbbell-Shaped Small Molecule that Promotes Cell Adhesion and Growth

During an image-based phenotype screening of our chemical library, we noted a small molecule that boosts the adhesion and growth of human cells. Chemical and cell biological experiments suggest that the diaryldispiro-tripiperazine derivative (adhesamine) targets selective cell-surface glycosaminoglycans, especially heparan sulfate, for increasing cell adhesion and growth. The addition of adhesamine to the culture medium enables the adhesion of even floating lymphocytes to cell culture plates and the microinjection into them. Unlike poly-Llysine, adhesamine induces apparently normal cell adhesion accompanied by organized actin structures and activation of focal adhesion kinase and ERK1/2 mitogen-activated protein kinases. Adhesamine may be useful as a cell-attaching reagent for cell engineering and basic cell biology.



Adhesamine

Wrenchnolol Derivative Optimized for Gene Activation in Cells

Naturally occurring transcription factors usually have two independent domains, a DNA-binding domain and an activation domain. In designing a synthetic small molecule that mimics a transcription factor,each of the two domains needs to be replaced by small-molecule counterparts. Results of the present study show that derivatives of wrenchnolol, a synthetic molecule that interacts with Sur-2 coactivator, serve as activation modules and stimulate gene transcription in vitro and in cells when tethered to a DNA-binding molecule. Thirteen derivatives of wrenchnolol were chemically synthesized and tested for their ability to activate transcription in vitro and in cells. When tethered to the GAL4 DNA-binding domain, one derivative increased transcription of a GAL4-responsive reporter gene in cells 9-fold. This optimized derivative also induced up to 45% myogenesis of C2C12 cells when tethered to the DNA-binding domain of myogenic transcription factor MyoD. This optimized derivative may serve as a starting point for designing biological tools or components of fully synthetic transcription factors that permit selective up-regulation of genes.