Division of Biochemistry
– Chemical Biology –

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

Prof
UESUGI, Motonari
(D Pharm Sc)

Assist Prof
SHIMOGAWA, Hiroki
(D Sc)

Proj Res*
SATO, Shinichi
(D Eng)

Proj Res**
HIRATA, Nao
(D Eng)

Proj Res***
WATANABE, Mizuki
(D Pharm Sc)

Proj Res**
JIN, Guihua
(D Med Sc)

Proj Res**
KUO, Ting-Fang
(D Sc)

Proj Res**
KATSUDA, Yousuke
(D Sc)

Proj Res***
TAKENOYA, Mihoko
(D Eng)

Proj Res (PD, iCeMS)**
PERRON, Amelie
(Ph D)

Researcher

OTSUKA, Shinya****

Assist Res Staff

NAKASHIMA, Mitsue****

Students

FRISCO, Heidie Laya (D2)
MAO, Di (D1)
TAKAYA, Junichiro (D1)
RYODEN, Yuta (M2)

* Program-Specific Research Center Assist Prof of iCeMS
** PD (NEXT Program) of iCeMS
*** Res (WPI) of iCeMS
**** iCeMS

Visitors

Assoc Prof HOW, Siew Eng	Universiti Malaysia Sabah, Malaysia, 4 April
Prof LEI, Xiaoguang	National Institute of Biological Sciences, China, P.R., 31 October–1 November
Prof SCHÄRER, Orlando D.	Stony Brook University, U.S.A., 29 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. 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.

KEYWORDS

Cell Therapy
Chemical Biology
Small Molecules
Chemical Library
Chemical Genetics

Selected Publications

Minami, I.; Yamada, K.; Otsuji, T. G.; Yamamoto, T.; Shen, Y.; Otsuka, S.; Kadota, S.; Morone, N.; Barve, M.; Asai, Y.; Tenkova-Heuser, T.; Heuser, J. E.; Uesugi, M.; Aiba, K.; Nakatsuji, N., A Small Molecule That Promotes Cardiac Differentiation of Human Pluripotent Stem Cells under Defined Cytokine- and Xeno-free Conditions, *Cell Reports*, (in press) (2012).

Jung, D.; Abu-Elheiga, L.; Ayuzawa, R.; Gu, Z.; Shirakawa, T.; Fujiki, Y.; Nakatsuji, N.; Wakil, S. J.; Uesugi, M., Mis-localization and Inhibition of ACC1 by a Synthetic Small Molecule, *Biochem J.*, **448 (3),** 409-416 (2012).

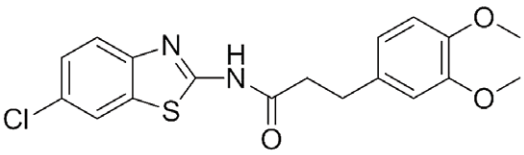
Kamisuki, S.; Shirakawa, T.; Kugimiya, A.; Abu-Elheiga, L.; Choo, H. Y.; Yamada, K.; Shimogawa, H.; Wakil, S. J.; Uesugi, M., Synthesis and Evaluation of Diarylthiazole Derivatives That Inhibit Activation of Sterol Regulatory Element-binding Proteins, *J. Med. Chem.*, **54(13),** 4923-4927 (2011).

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).

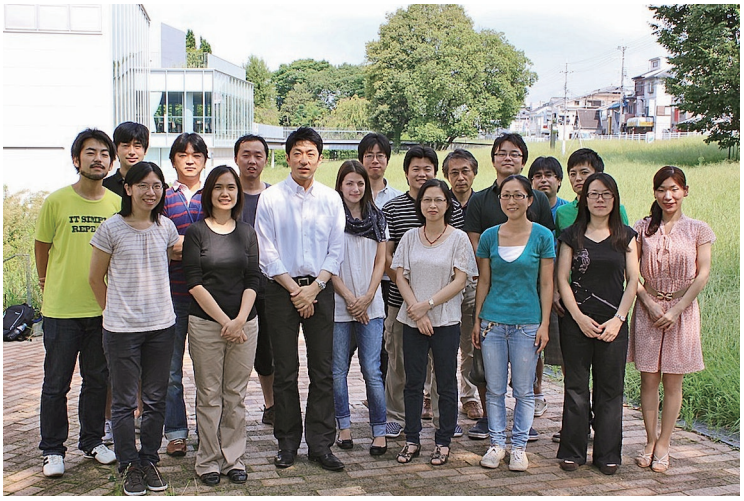
Shirakawa, T.; Kawazoe, Y.; Tsujikawa, T.; Jung, D.; Sato, S.; Uesugi, M., Deactivation of STAT6 through Serine 707 Phosphorylation by JNK, *J. Biol. Chem.*, **286,** 4003-4010 (2011).

A Small Molecule That Promotes Cardiac Differentiation of Human Pluripotent Stem Cells under Defined Cytokine- and Xeno-free Conditions

Human pluripotent stem cells (hPSCs), including embryonic stem cells and induced pluripotent stem cells, are potentially useful in regenerative therapies for heart disease. For medical applications, clinical-grade cardiac cells must be produced from hPSCs in a defined, cost-effective manner. Cell-based screening led to the discovery of KY02111, a small molecule that promotes differentiation of hPSCs to cardiomyocytes. Although the direct target of KY02111 remains unknown, results of the present study suggest that KY02111 promotes differentiation by inhibiting WNT signaling in hPSCs but in a manner that is distinct from that of previously studied WNT inhibitors. Combined use of KY02111 and WNT signaling modulators produced robust cardiac differentiation of hPSCs in a xeno-free, defined medium, devoid of serum and any kind of recombinant cytokines and hormones, such as BMP4, Activin A, or insulin. The methodology has potential as a means for the practical production of human cardiomyocytes for regeneration therapies.

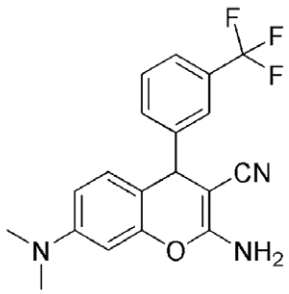


KY02111



Mis-localization and Inhibition of ACC1 by a Synthetic Small Molecule

Chromeceptin is a synthetic small molecule that inhibits insulin-induced adipogenesis of 3T3-L1 cells and impairs the function of insulin-like growth factor 2 (IGF2). The molecular target of this benzochromene derivative is multifunctional protein 2 (MFP-2). The interaction between chromeceptin and MFP-2 activates the signal transducer and activator of transcription 6 (STAT6), which subsequently induces IGF inhibitory genes. It was not previously known how the binding of chromeceptin with MFP-2 blocks adipogenesis and activates STAT6. Results of the present study showed that the chromeceptin/MFP-2 complex binds to and inhibits acetyl-CoA carboxylase 1 (ACC1), an enzyme important for the de novo synthesis of malonyl-CoA and fatty acids. The formation of this ternary complex removes ACC1 from the cytosol and sequesters it in peroxisomes through guidance of Pex5p. As a result, chromeceptin impairs fatty acid synthesis from acetate where ACC1 is a rate limiting enzyme. Overexpression of malonyl-CoA decarboxylase or siRNA knockdown of ACC1 resulted in STAT6 activation, suggesting a role of malonyl-CoA in STAT6 signaling. The molecular mechanism of chromeceptin may provide a new pharmacological approach to selective inhibition of ACC1 for biological studies and pharmaceutical development.



Chromeceptin