Division of Biochemistry
– Chemical Biology –

https://www.scl.kyoto-u.ac.jp/~uesugi/

Prof
UESUGI, Motonari
(D Pharm Sc)

Assoc Prof
SATO, Shinichi
(D Eng)

Senior Lect
PERRON, Amelie
(Ph D)

Assist Prof
TAKEMOTO, Yasushi
(D Eng)

Program-Specific Assist Prof
ABO, Masahiro
(D Pharm Sc)

PD
TAKEMOTO, Misao
(D Eng)

Students

NODA, Naotaka (D4)
ADO, Genyir (D3)
JIN, Shuyu (D3)
NISHIO, Kosuke (D3)
TOH, Kohei (D2)
SINGH, Vaibhav Pal (D2)
CRUZADO, Kevin Tan (M2)
TSERENDAGVA, Manchir (M1)
FARRAG, Asmaa Mostafa Abdelbari Soliman (RS)
TRAN, Mai Chi (RS)

Assist Techn Staff

JUNG, Yejin

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 that these basic studies open new avenues for small-molecule applications in a range of fields.

KEYWORDS

Chemical Biology
Chemical Genetics
Small Molecules
Immunology
Chemical Library

Recent Selected Publications

Mendoza, A.; Takemoto, Y.; Cruzado, K. T.; Masoud, S. S.; Nagata, A.; Tantipanjaporn, A.; Okuda, S.; Kawagoe, F.; Sakamoto, R.; Odagi, M.; Mototani, S.; Togashi, M.; Kawatani, M.; Aono, H.; Osada, H.; Nakagawa, H.; Higashi, T.; Kittaka, A.; Nagasawa, K.; Uesugi, M., Controlled Lipid β-Oxidation and Carnitine Biosynthesis by a Vitamin D Metabolite, *Cell Chem Biol.*, (2021) (in press).

Takemoto, Y.; Kadota, S.; Minami, I.; Otsuka, S.; Okuda, S.; Abo, M.; Punzalan, L. L.; Shen, Y.; Shiba, Y.; Uesugi, M., Chemical Genetics Reveals a Role of Squalene Synthase in TGFβ Signaling and Cardiomyogenesis, *Angew. Chem. Int. Ed.*, **60,** 21824-21831 (2021).

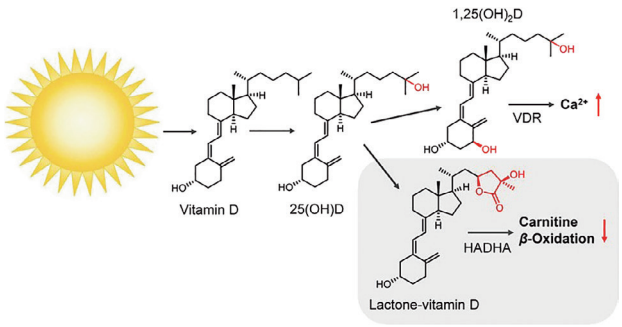
Jin, S.; Vu, H. T.; Hioki, K.; Noda, N.; Yoshida, H.; Shimane, T.; Ishizuka, S.; Takashima, I.; Mizuhata, Y.; Pe, K. B.; Ogawa, T.; Nishimura, N.; Packwood, D.; Tokitoh, N.; Kurata, H.; Yamasaki, S.; Ishii, K. J.; Uesugi, M., Discovery of Self-Assembling Small Molecules as Vaccine Adjuvants, *Angew. Chem. Int. Ed.*, **60,** 961-969 (2021).

Hakariya, H.; Takashima, I.; Takemoto, M.; Noda, N.; Sato, S.; Uesugi, M., Non-Genetic Cell-Surface Modification with a Self-Assembling Molecular Glue, *Chem. Commun.,* **57,** 1470-1473 (2021).

Takemoto, Y.; Mao, D.; Punzalan, L. L.; Götze, S.; Sato, S.; Uesugi, M., Discovery of a Small-Molecule-Dependent Photolytic Peptide, *J. Am. Chem. Soc.*, **142(3),** 1142-1146 (2020).

Controlled Lipid β-Oxidation and Carnitine Biosynthesis by a Vitamin D Metabolite

Lactone-vitamin D3 is a major metabolite of vitamin D3, a lipophilic vitamin biosynthesized in numerous life forms by sunlight exposure. Although lactone-vitamin D3 was discovered 40 years ago, its biological role remains largely unknown. Chemical biological analysis of its photoaffinity probe identified the hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha (HADHA), a mitochondrial enzyme that catalyzes β-oxidation of long-chain fatty acids, as its selective binding protein. Intriguingly, the interaction of lactone-vitamin D3 with HADHA does not affect the HADHA enzymatic activity but instead limits biosynthesis of carnitine, an endogenous metabolite required for the transport of fatty acids into the mitochondria for β-oxidation. Lactone-vitamin D3 dissociates the protein-protein interaction of HADHA with trimethyllysine dioxygenase (TMLD), thereby impairing the TMLD enzyme activity essential in carnitine biosynthesis. These findings suggest a heretofore undescribed role of lactone-vitamin D3 in lipid β-oxidation and carnitine biosynthesis, and possibly in sunlight-dependent shifts of lipid metabolism in animals.



Chemical Genetics Reveals a Role of Squalene Synthase in TGFβ Signaling and Cardiomyogenesis

KY02111 is a widely used small molecule that boosts cardiomyogenesis of the mesoderm cells derived from pluripotent stem cells, yet its molecular mechanism of action remains elusive. The present study resolves the initially perplexing effects of KY02111 on Wnt signaling and subsequently identifies squalene synthase (SQS) as a molecular target of KY02111 and its optimized version, KY-I. By disrupting the interaction of SQS with cardiac ER-membrane protein TMEM43, KY02111 impairs TGFβ signaling, but not Wnt signaling, and thereby recapitulates the clinical mutation of TMEM43 that causes arrhythmogenic right ventricular cardiomyopathy (ARVC), an inherited heart disease that involves a substitution of myocardium with fatty tissue. These findings reveal a heretofore undescribed role of SQS in TGFβ signaling and cardiomyogenesis. KY02111 may find its use in ARVC modeling as well as serve as a chemical tool for studying TGFβ/SMAD signaling.