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)

Program-Specific Assist Prof
MAO, Di
(D Med Sc)

PD
TAKEMOTO, Misao
(D Eng)

Students

HAKARIYA, Hayase (D3)
NODA, Naotaka (D3)
ADO, Genyir (D2)
JIN, Shuyu (D2)
NISHIO, Kosuke (D2)
TOH, Kohei (D1)
SINGH, Vaibhav Pal (D1)
ZHAI, Peihong (M2)
CRUZADO, Kevin Tan (M1)
FARRAG, Asmaa Mostafa Abdelbari Soliman (RS)
TSERENDAGVA, Manchir (RS)
PINEDA ARISTA, Karla Mariel (RS)

Assist Techn Staff

JUNG, Yejin PUNZALAN, Louvy Lynn Calvelo MANDAL, Sathi MENDOZA, Aileen De-Leon

Guest Res Assoc

QI, Zhiyuan Fudan University, China, P.R., 31 January–28 February
XUE, Zian Fudan University, China, P.R., 31 January–28 February

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, including future concepts in drug discovery and use of small molecules for immunotherapy.

KEYWORDS

Chemical Biology Small Molecules Chemical Library
Chemical Genetics Immunology

Selected Publications

Jin, S.; Vu, H. V.; 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(2),** 961-969 (2021).

Punzalan, L. L.; Jiang, L.; Mao, D.; Mahapatra, A. D.; Sato, S.; Takemoto, Y.; Tsujimura, M.; Kusamori, K.; Nishikawa, M.; Zhou, L.; Uesugi, M., Chemoproteomic Profiling of a Pharmacophore-Focused Chemical Library, *Cell Chem. Biol.*, **27,** 708-718 (2020).

Zhang, X.; Jiang, L.; Huang, K.; Fang, C.; Li, J.; Yang, J.; Li, H.; Ruan, X.; Wang, P.; Mo, M.; Wu, O.; Xu, Y.; Peng, C.; Uesugi, M.; Ye, D.; Yu, F.-X.; Zhou, L., Site-Selective Phosphoglycerate Mutase 1 Acetylation by a Small Molecule, *ACS Chem. Biol.*, **15(3),** 632-639 (2020).

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).

Topics

Discovery of Self-Assembling Small Molecules as Vaccine Adjuvants

Immune potentiators, termed adjuvants, trigger early innate immune responses to ensure the generation of robust and long-lasting adaptive immune responses of vaccines. Presented here is a study that takes advantage of a self-assembling small-molecule library for the development of a novel vaccine adjuvant. Cell-based screening of the library and subsequent structural optimization led to the discovery of a simple, chemically tractable deoxycholate derivative (molecule 6, also named cholicamide) whose well-defined nanoassembly potently elicits innate immune responses in macrophages and dendritic cells. Functional and mechanistic analyses indicate that the virus-like assembly enters the cells and stimulates the innate immune response through Toll-like receptor 7 (TLR7), an endosomal TLR that detects single-stranded viral RNA. As an influenza vaccine adjuvant in mice, molecule 6 was as potent as Alum, a clinically used adjuvant. The studies described here pave the way for a new approach to discovering and designing self-assembling small-molecule adjuvants against pathogens, including emerging viruses.

Discovery of a Small-Molecule-Dependent Photolytic Peptide

We accidentally found that YM-53601, a known small-molecule inhibitor of squalene synthase (SQS), selectively depletes SQS from mammalian cells upon UV irradiation. Further analyses indicated that the photodepletion of SQS requires its short peptide segment located at the COOH terminus. Remarkably, when the 27 amino acid peptide was fused to green fluorescent protein or unrelated proteins at either the NH_2 or COOH terminus, such fusion proteins were selectively depleted when the cells were treated with both YM-53601 and UV exposure. Product analysis and electron spin resonance experiments suggested that the UV irradiation promotes homolytic C-O bond cleavage of the aryl ether group in YM-53601. It is likely that the radical species generated from UV-activated YM-53601 abstract hydrogen atoms from the SQS peptide, leading to the photolysis of the entire protein. The pair of the SQS peptide and YM-53601 discovered in the present study paves the way for the design of a new small-molecule-controlled optogenetic tool.