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– Chemical Biology –

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KRUNGCHANUCHAT, Saowalak Chiang Mai University, Thailand, 1 September 2018–28 February 2019

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

Perron, A.; Nishikawa, Y.; Iwata, J.; Shimojo, H.; Takaya, J.; Kobayashi, K.; Imayoshi, I.; Mbenza, N. M.; Takenoya, M.; Kageyama, R.; Kodama, Y.; Uesugi, M., Small-molecule Screening Yields a Compound That Inhibits the Cancer-associated Transcription Factor Hes1 via the PHB2 Chaperone, *J. Biol. Chem.*, **293,** 8285-8294 (2018).

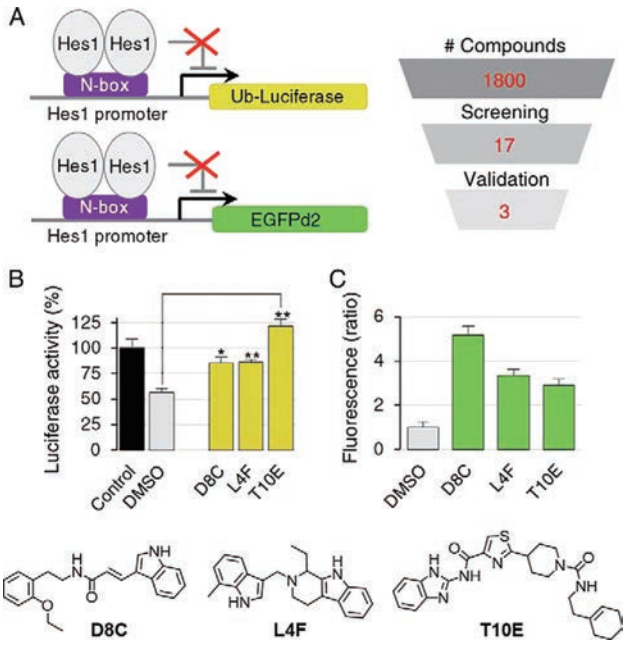
Mao, D.; Ando, S.; Sato, S.; Qin, Y.; Hirata, N.; Katsuda, Y.; Kawase, E.; Kuo, T. F.; Minami, I.; Shiba, Y.; Ueda, K.; Nakatsuji, N.; Uesugi, M., A Synthetic Hybrid Molecule for Selective Removal of Human Pluripotent Stem Cells from Cell Mixtures, *Angew. Chem. Int. Ed.*, **56,** 1765-1770 (2017).

Asano, L.; Watanabe, M.; Ryoden, Y.; Usuda, K.; Yamaguchi, T.; Khambu, B.; Takashima, M.; Sato, S.; Sakai, J.; Nagasawa, K.; Uesugi, M., Vitamin D Metabolite, 25-Hydroxyvitamin D, Regulates Lipid Metabolism by Inducing Degradation of SREBP/SCAP, *Cell Chemi. Biol.*, **24,** 207-217 (2017).

Katsuda, Y.; Sato, S.; Asano, L.; Morimura, Y.; Furuta, T.; Sugiyama, H.; Hagihara, M.; Uesugi, M., A Small Molecule That Represses Translation of G-quadruplex-containing mRNA, *J. Am. Chem. Soc.*, **138,** 9037-9040 (2016).

Small-molecule Screening Yields a Compound That Inhibits the Cancer-associated Transcription Factor Hes1 via the PHB2 Chaperone

The transcription factor Hes family basic helix-loop-helix transcription factor 1 (Hes1) is a downstream effector of Notch signaling and plays a crucial role in orchestrating developmental processes during the embryonic stage. However, its aberrant signaling in adulthood is linked to the pathogenesis of cancer. In the present study, we report the discovery of small organic molecules (JI051 and JI130) that impair the ability of Hes1 to repress transcription. Hes1 interacts with the transcriptional corepressor transducing-like enhancer of split 1 (TLE1) via an interaction domain comprising two tryptophan residues, prompting us to search a chemical library of 1,800 small molecules enriched for indole-like π-electron–rich pharmacophores for a compound that blocks Hes1-mediated transcriptional repression. This screening identified a lead compound whose extensive chemical modification to improve potency yielded JI051, which inhibited HEK293 cell proliferation with an EC50 of 0.3 μM. Unexpectedly, using immunomagnetic isolation and nanoscale LC-MS/MS, we found that JI051 does not bind TLE1 but instead interacts with prohibitin2 (PHB2), a cancer-associated protein chaperone. We also found that JI051 stabilizes PHB2's interaction with Hes1 outside the nucleus, inducing G2/Mcell-cyclearrest. Of note, JI051 dose-dependently reduced cell growth of the human pancreatic cancer cell line MIA PaCa-2, and JI130 treatment significantly reduced tumor volume in a murine pancreatic tumor xenograft model. These results suggest a previously unrecognized role for PHB2 in the regulation of Hes1 and may inform potential strategies for managing pancreatic cancer.



Chemical Decontamination of iPS Cell-derived Neural Cell Mixtures

This report describes the design and evaluation of phosphorylated 7-ethyl-10-hydroxycamptothecin (SN38-P), which selectively eliminates tumor-forming proliferative stem cells, including human induced pluripotent stem cells (hiPSCs) and neural stem cells, from iPSC-derived neural cell mixtures. Results of the present study demonstrate that simple phosphorylation of an anticancer drug can provide a safe, cost-effective, and chemically-defined tool for decontaminating hiPSC-derived neuron.