# Department of System Chemotherapy and Molecular Sciences

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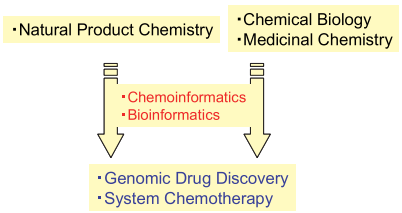
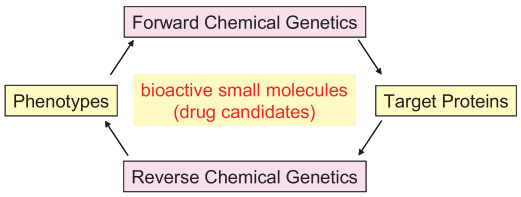
## Research Projects:

Chemical biology based on forward/reverse chemical genetics is a new research paradigm that accelerates drug development and the functional analysis of genes and proteins. Diversity of small molecules is one of the most important points to facilitate the success of chemical biology. As such, we have been screening two types of chemical libraries: a natural products library and a synthetic chemical library. After identifying bioactive small molecules, their modes of actions and targets are investigated using a chemical biology-based approach.




Recent major projects are as follows:

1. **Advanced chemical biology research for establishing system chemotherapy in order to cure multi-factorial diseases; e.g. cancer, heart failure, immunodeficiency, infectious diseases, diabetes, and neuronal diseases.**
2. **HCS (high-contents screening) and HTS (high-throughputs screening) for identifying useful small molecules (bioprobes).**
3. **Natural product chemistry and medicinal chemistry for mining novel bioactive small molecules.**
4. **Biosynthetic studies of natural products and their application to combinatorial biosynthesis.**

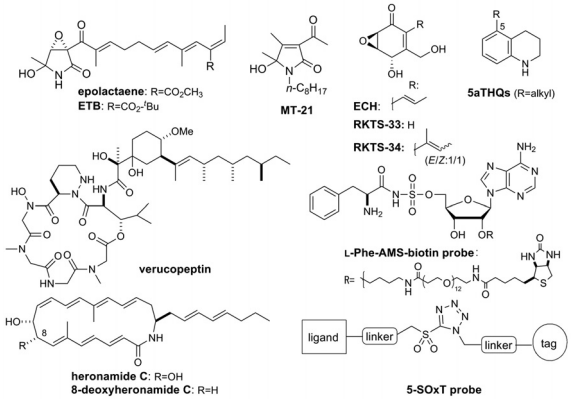



We have discovered epolactaene from *Penicillium* sp. to be a neuronal differentiation inducer, and have identified MT-21 and ETB (epolactene *tert*-butyl ester) as potent apoptosis inducers based on Structure-Activity Relationships (SAR) studies. Using a biotin-labeled probe of epolactaene/ ETB, human Hsp 60 (heat-shock protein 60) was identified as a binding protein of epolactaene/ ETB in vitro as well as in situ. Moreover, it was suggested that Cys442 of Hsp60 is responsible for the covalent binding with epolactaene/ETB as well as the inhibition of chaperone activity by epolactaene/ ETB. Epolactaene/ETB would be highly useful tools to understand the function of human Hsp60 and the mechanisms of molecular chaperones.

We have also found a small molecule, ECH, produced by a fungal strain that selectively inhibits apoptosis induced by the death-receptor system. Using chemical biology-based approaches, we revealed that ECH inhibits Fas-mediated apoptosis by blocking activation of procaspase-8 in the DISC (death-inducing signaling complex). In addition, ECH also inhibits Fas ligand-dependent apoptosis in CTL-mediated cytotoxicity. Based on the detailed SAR studies of ECH, RKTS-33&34 were developed as novel nonpeptide inhibitors targeting death receptor-mediated apoptosis.

Hypoxia-inducible factor (HIF) is deeply involved in cancer progression. During the course of our screening for HIF-signaling modulators, we re-discovered verucopeptin, produced by *Actinomodura*-like sp., as a new HIF-signaling inhibitor. We determined the absolute stereochemistry of verucopeptin by the spectroscopic analysis and synthetic approaches. Verucopeptin decreased the amount of HIF-1α protein, whereas it did not affect the level of HIF-1β protein. Further analysis of the inhibitory mechanism by verucopeptin is on going.

Irreversible modification is one of the most promising strategies to identify cellular receptors of bioactive small molecules. Recently we developed a 5-sulfonyl tetrazole probe, which enabled chemical tagging of binding proteins against a ligand. The studies on modes of action for antifungal molecules heronamides and 5aTHQs (5-alkyl-1,2,3,4-tetrahydroquinolines), as well as the development of an affinity probe to identify adenylation domain-containing modules in nonribosomal peptide synthetase (NRPS)-polyketide synthase (PKS) hybrids and NRPSs are also undertaken.




## Recent publications


- Sugiyama, R. *et al.* 5-Alkyl-1,2,3,4-tetrahydroquinolines, new membrane-interacting lipophilic metabolites, produced by combined culture of *Streptomyces nigrescens* and *Tsukamurella pulmonsis*. *Org. Lett.* **17**, 1918, 2015.
- Goto, Y. *et al.* UCHL1 provides diagnostic and antimetastatic strategies due to its deubiquitinating effect on HIF-1α. *Nat Commun.* **6**, 6153, 2015.
- Ishikawa, F. *et al.* Profiling nonribosomal peptide synthetase activities using chemical proteomic probes for adenylation domains. *ACS Chem. Biol.* doi: 10. 1021/acschembio. 5b00097, 2015.
- Sugiyama, R. *et al.* Structure and biological activity of 8-deoxyheronamide C from a marine-derived *Streptomyces* sp.: heronamides target saturated hydrocarbon chains in lipid membranes. *J. Am. Chem. Soc.* **136**, 5209, 2014.
- Otsuki, S. *et al.* Chemical tagging of a drug target using 5-sulfonyl tetrazole. *Bioorg. Med. Chem. Lett.* **23**, 1608, 2013.
- Fustin, JM. *et al.* RNA-methylation-dependent RNA processing controls the speed of the circadian clock. *Cell*, **155**, 793, 2013.
- Kishimoto, S. *et al.* Tumescenamide C, an antimicrobial cyclic lipodepsipeptide from *Streptomyces* sp. *Tetrahedron*, **68**, 5572, 2012.
- Nishimura, S. *et al.* Marine antifungal theonellamides target 3β-hydroxysterol to activate Rho1 signaling. *Nat. Chem. Biol.* **6**, 519, 2010.