Division of Biochemistry
- Chemical Biology -

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Visitors

Instructor JUNG, Dongju	Baylor College of Medicine, USA, 26 March–5 April 2008
Assoc Prof TSAI, Francis TF	Baylor College of Medicine, USA, 11 November 2008

Scope of Research

In human history, small organic molecules have been utilized for improving human health and for revealing secrets of life. Discovery or design of small organic molecules with unique biological activity permits small-molecule-initiated exploration of biology and further understanding of human diseases. Our laboratory has been discovering small organic molecules that modulate transcription or differentiation to use them as tools to explore biology. Such chemistry-initiated biology is recently called chemical biology, an emerging field of biology and medical sciences. Although our chemical biology is a basic one, it may "catalyze" future drug discovery.

Research Activities (Year 2008)

Presentations

Special Lecture: Organic Chemistry of Life, Uesugi M, Ewha Womans University, Korea, 7–11 January 2008.

Target Identification of Bioactive Small Molecules, Uesugi M, Medical Chemistry Symposium, Singapore, 23 January 2008.

Chemical Biology of Synthetic Small Molecules, Uesugi M, International Symposium on Hierarchy and Holism (ISHH): Bridging across Different Hierarchies in Natural Sciences, Okazaki, 23 February 2008.

Small-Molecule-Initiated Biology and Beyond in iCeMS, Uesugi M, AICT First International Conference on Convergence Technologies, Korea, 21 May 2008.

Chemical Biology of Synthetic Small Molecules, Uesugi M, SSF/JST-PRESTO Joint Symposium, Sweden, 27 May 2008.

Isolating and Identifying the Targets of Bioactive Small Molecules, Uesugi M, 10th Chinese International Peptide Symposium (CPS-2008), China, 2 July 2008.

Isolating and Identifying the Targets of Bioactive Small Molecules, Uesugi M, 22nd Naito Conference on Chemical Biology, Sapporo, 11 September 2008.

Small Molecule Activators of Transcription, Uesugi M, 2008 Riken Conference, Narita, 13 November 2008.

Grants

Uesugi M, Small-molecule Initiated Analysis of Cellular Signaling, Grant-in-Aid for Scientific Research (B), 1 April 2006–31 March 2008.

Uesugi M, Methods for Isolating Target Proteins of Small Molecules, Grant-in-Aid for Scientific Research on

Small-molecule-initiated Biology

Knowledge about bioactive small molecules is a treasure of the humankind. Small organic compounds that the human being have discovered or synthesized from natural resources have been utilized for improving human health and for revealing secrets of life. The major goal of our research programs has been to expand the treasure by discovering and analyzing novel organic compounds with unique biological activities and to use them as tools to explore biology.

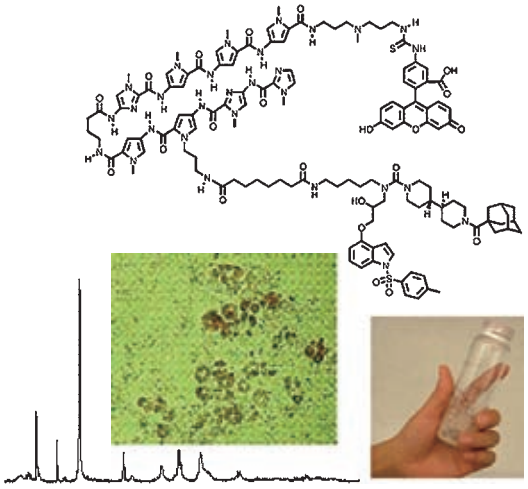
Our current research programs focus on discovering and using small organic molecules that modulate gene transcription or cell signaling. Regulation of gene transcription and cell signaling often induces drastic phenotypic changes in living organisms. Precise, external control over these endogenous processes through small organic molecules represents a challenge of chemistry to nature. The latest achievements are summarized below.

Discovery of synthetic small molecules that modulate transcription. Our group has discovered by screening chemical libraries a unique small-molecule modulator of transcription. The synthetic molecule we named "adamanolol" represents the first small molecules that modulate gene transcription by targeting transcription factor-coactivator interaction. Our group, as a collaboration with another laboratory, synthesized adamanolol and its derivatives and obtained structure-activity relationship, which enabled the design of the second-generation compound named "wrenchnolol." The wrench-shaped compound is now recognized in the field as a highly unique synthetic molecule that controls gene expression.

Wrenchnolol mimics an alpha-helical activation domain of transcription factor ESX: it may serves as a small-molecule activation module when coupled with a DNA binding molecule. Our group, as a collaboration with Prof. Dervan in Caltech, has recently succeeded in designing a completely organic, synthetic transcription factor that activates transcription. This work demonstrates that it is possible to generate a transcription factor out of organic compounds.

Discovery of small molecules that modulate cell signaling. Our group has developed an interesting method of screening chemical libararies for the discovery of bioactive molecules. In this unique method, synthetic small molecules were first profiled by their effects on phenotypic fat cell differentiation and pre-selected for more focused secondary assays. This approach enabled us to discover a number of bioactive compounds with a range of biological activities, including anti-proliferation of selective cell types and inhibition of lipogenesis. These molecules are now used for elucidation of new biological pathways in our group. For example, we recently discovered a new signaling pathway to control insulin/IGF pathways by utilizing the compound we call chromeceptin.

Our group also discovered small organic molecules that differentiate mouse embryonic stem (ES) cells into dopaminergic neurons. Our approach to discovering such molecules is rooted in the logic of asymmetric catalysts in chemistry. This work might be a good demonstration of applying the logic in chemistry to the biological field.



Priority Areas, 1 April 2006–31 March 2008.

Uesugi M, Intracellular Imaging of Small Molecules, Industrial Technology Research Grant Program by NEDO, 1 June 2006–31 May 2008.

Uesugi M, Small Molecule Transcription Factors for Biological Investigations, PRESTO, Japan Science and Technology Agency, 1 October 2005–31 March 2009.

Uesugi M, Small Molecules that Promote the Production of iPS cells, The Project for Realization of Regenerative Medicine, Japan Science and Technology Agency, 1 April 2008–31 March 2013.

Kawazoe Y, Small Molecules that Modulate Cell Differentiation, Grant-in-Aid for Young Scientists (B), 1 April 2006–31 March 2008.

Kawazoe Y, Chemical Genetic Analysis of Vacuole Formation, Grant-in-Aid for Scientific Research (C), 1 April 2008–31 March 2011.