Division of Biochemistry
- Chemical Biology -

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PD JUNG, Hye Jin — Yonsei University, College of Engineering, Department of Biotechnology, Chemical Genomics Laboratory, Korea, 28 January–6 February 2007

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 2007)

Publication

Sato S, Kwon Y, Kamisuki S, Srivastava N, Mao Q, Kawazoe Y, Uesugi M: Polyproline-rod Approach to Isolating Protein Targets of Bioactive Small Molecules: Isolation of a New Target of Indomethacin, *J. Am. Chem. Soc,* **129(4)**, 873-880 (2007).

Presentations

Chemical Biology of Gene Expression, Uesugi M, 32nd Lorne Conference on Protein Structure and Function, Australia, 4–8 February 2007.

Special Lecture: Chemical Biology of Gene Expression, Uesugi M, The University of Texas at Austin, TX, USA, 22 March 2007.

Chemical Biology of Gene Expression, Uesugi M, 87th Spring Meeting of the Chemical Society of Japan, Suita, Japan, 27 March 2007.

Special Lecture: Chemical Biology of Gene Expression, Uesugi M, School of Engineering, the University of Tokyo, Tokyo, Japan, 7 April 2007.

Chemical Biology of Gene Expression, Uesugi M, 19th FAOBMB Seoul Conference, Seoul, Korea, 27–30 May 2007.

Special Lecture: Chemical Biology of Gene Expression, Uesugi M, Ewha Womans University, Seoul, Korea, 30 May 2007.

Special Lecture: Chemical Biology of Gene Expression: Uesugi M, Kyung Hee University, Seoul, Korea, 31 May 2007.

Isolating and Identifying Protein Targets of Bioactive Small Molecules, Uesugi M, 4th Korea-Japan Young Scientist Meeting on Bioorganic and Natural Products Chemistry, Gyeongji, Korea, 29 August–1 September 2007.

Target Identification of Bioactive Small Molecules, Uesugi M, 2007 Chemical Genomics Symposium, Daejeon, Korea, 11 October 2007.

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.

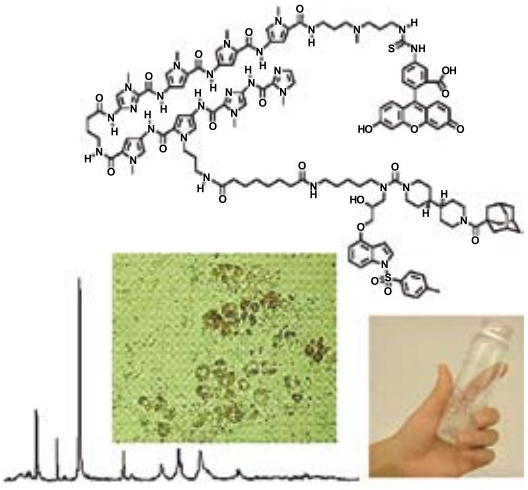
Our current research programs focus on discovering and using small organic molecules that modulate gene transcription or cell signaling. Regulation of gene transcription and cell signaling often induces drastic phenotypic changes in living organisms. Precise, external control over these endogenous processes 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.



Chemical Biology of Gene Expression, Uesugi M, 4th Japanese-German Frontiers of Sciences (JGFoS) Symposium, Kanagawa, Japan, 2–4 November 2007.

Grants

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

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

Uesugi M, Methods for Isolating Target Proteins of Small Molecules, Grant-in-Aid for Scientific Research on Priority Areas, 1 April 2006–31 March 2008.

Uesugi M, Intracellular Imaging of Small Molecules, Industrial Technology Research Grant Program by NEDO, 1 June 2006–20 March 2008.

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