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A New Wave of Chemical Genomics

～From Biological Investigation to Drug Discovery～

2011/09/24

Multi-media room (10F) of the B building, Kinki University E campus

13:00-13:10 **Opening Remark** (Dr. Kakehi)

13:10-14:10 **Keynote Lecture: Dr. James Chen** Chaired by Dr. Tanaka
Department of Chemical and Systems Biology Stanford School of Medicine
Chemical probes of embryonic signaling and patterning.

14:10-14:20 **Tea break**

14:20-15:00 **Dr. Minoru Yoshida** Chaired by Dr. Sugiura
Chemical Genomics Research Group, RIKEN Advanced Science Institute
Chemical genomics based on fission yeast collections expressing yeast and human ORFeomes

15:00-15:30 **Dr. Reiko Sugiura** Chaired by Dr. Yoshida
Laboratory of Molecular Pharmacogenomics, Kinki University
A powerful genetic strategy to screen for inhibitors of MAPK signaling and its application to genomic drug discovery

15:30-15:40 **Tea break**

15:40-16:20 **Dr. Motonari Uesugi** Chaired by Dr. Nakanishi
Institute for Integrated Cell-Material Sciences, and
Institute for Chemical Research, Kyoto University
Small molecule tools for cell biology and cell therapy

16:20-16:25 **Concluding Remark** (Dr. Sugiura)

JAMES KENNETH CHEN
Associate Professor
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EDUCATION

Harvard College, Cambridge, MA 1987 – 1991
A. B. degree in Chemistry, *Summa cum laude*
Research Advisor: George M. Whitesides

Harvard University, Cambridge, MA 1991 – 1998
Ph.D. degree in Chemistry and Chemical Biology
Research Advisor: Stuart L. Schreiber

Marine Biological Laboratory, Woods Hole, MA Summer 1998
Embryology: Concepts and Techniques in Modern Developmental Biology

Johns Hopkins School of Medicine, Baltimore, MD 1999 – 2003
Postdoctoral Fellow, Department of Molecular Biology and Genetics
Research Advisor: Philip A. Beachy

PROFESSIONAL EXPERIENCE

Assistant Professor, Department of Molecular Pharmacology and Department of Chemistry (by courtesy), Stanford University, Stanford, CA 2003 – 2006

Executive Director, High-Throughput Bioscience Center, Stanford University, Stanford, CA 2003 – present

Assistant Professor, Department of Chemical and Systems Biology and Department of Chemistry (by courtesy), Stanford University, Stanford, CA 2006 – 2010

Associate Professor, Department of Chemical and Systems Biology and Department of Chemistry (by courtesy), Stanford University, Stanford, CA 2010 – present

HONORS AND AWARDS

Harvard University Certification of Distinction in Teaching	1991
National Science Foundation Predoctoral Fellowship	1991 – 1994
American Chemical Society Organic Chemistry Predoctoral Fellowship	1994 – 1995
Damon Runyon-Walter Winchell Postdoctoral Fellowship	1999 – 2002
American Cancer Society Postdoctoral Fellowship	2002 – 2003
W. Barry Wood, Jr. Research Award, Johns Hopkins School of Medicine	2003
Kimmel Scholar Award, Sidney Kimmel Foundation for Cancer Research	2004 – 2006
Basil O'Connor Starter Scholar Research Award, March of Dimes Foundation	2005 – 2007
Terman Fellow, Stanford University	2005 – 2008
Astellas USA Foundation Award	2005
Faculty Fellow, Stanford University School of Medicine	2006
Brain Tumor Society/Rachel Molly Markoff Research Chair	2006 – 2008
American Cancer Society Research Scholar Award	2008 – 2011
NIH Director's Pioneer Award	2008 – 2013

PROFESSIONAL SERVICE AND MEMBERSHIPS

Member, American Chemical Society	1989 – present
Member, Bio-X, Stanford University	2003 – present
Associate Member, Stanford Institute for Stem Cell Biology and Regenerative Medicine	2003 – present
Consultant, Infinity Pharmaceuticals	2004
Member, Stanford University School of Medicine Faculty Diversity Committee	2004 – 2005
Member, Quantitative Chemical Biology Program Steering Committee, Stanford University School of Medicine	2004 – 2009
Member, Medical Scientist Training Program Admissions Committee, Stanford University School of Medicine	2004 – present
Departmental Representative, Stanford University School of Medicine Faculty Senate	2005 – 2006
Member, Stanford Comprehensive Cancer Center	2005 – present
Adhoc Reviewer, NIH Study Section (Innovative Technologies for	2005 – 2006

the Molecular Analysis of Cancer)	
Member, Advisory Committee for the Scholarly Concentrations Program in the Molecular Basis of Medicine, Stanford University School of Medicine	2006 – 2011
Discussion Leader, Bioorganic Gordon Research Conference	2007
Consultant, Fate Therapeutics	2008 – present
Editorial Board Member, *Zebrafish*	2008 – present
Workshop Co-Chair, 8th International Conference on Zebrafish Development and Genetics	2008
Departmental Representative, Stanford University School of Medicine Faculty Senate	2009 – present
Associate Member, Stanford Digestive Disease Center	2009 – present
Member, Society for Developmental Biology	2009 – present
Editorial Board Member, *Chemistry & Biology*	2009 – present
Adhoc Reviewer, NIH Study Section (PAR-08-138: Zebrafish Screens)	2010
Adhoc Reviewer, NIH Study Section (PAR-08-139: Tools for Zebrafish Research)	2010
Faculty Mentor, Stanford Clinical and Translational Networking Program	2010
Member, NIH Study Section (DEV-1: Development)	2010 – 2012
Director, Advisory Committee for the Scholarly Concentrations Program in the Molecular Basis of Medicine, Stanford University School of Medicine	2011 – present

SELECTED PUBLICATIONS (PEER-REVIEWED)

1. Taipale, J., **Chen, J. K.**, Cooper, M. K., Wang, B., Mann, R. K., Milenkovic, L., Scott, M. P., and Beachy, P. A. (2000) The effects of oncogenic mutations in Smoothened and Patched can be reversed by cyclopamine. *Nature* 406: 1005-1009.
2. Berman, D. M., Karhadkar, S. S., Hallahan, A. R. Pritchard, J. I., Eberhart, C. G., Watkins, D. N., **Chen, J. K.**, Cooper, M. K., Taipale, J., Olson, J. M., and Beachy, P. A. (2002) Medulloblastoma growth inhibition by Hedgehog pathway blockade. *Science* 297: 1559-1561.
3. **Chen, J. K.**, Taipale, J., Cooper, M. K., and Beachy, P. A. (2002) Inhibition of Hedgehog signaling by direct binding of cyclopamine to Smoothened. *Genes Dev.* 16: 2743-2748.

4. **Chen, J. K.**, Taipale, J., Young, K. E., Maiti, T., and Beachy, P. A. (2002) Small molecule modulation of Smoothened activity. *Proc. Natl. Acad. Sci. U. S. A.* 99: 14071-14076.
5. Chen, W., Ren, X., Nelson, C. D, Barak, L. S., **Chen, J. K.**, Beachy, P. A., de Sauvage, F., and Lefkowitz, R. J. (2004) Activity-dependent internalization of Smoothened mediated by beta-Arrestin 2 and GRK2. *Science* 306: 2257-2260.
6. Sinha, S. and **Chen, J. K.** (2006) Purmorphamine activates the Hedgehog pathway by targeting Smoothened. *Nat. Chem. Biol.* 2: 29-30.
7. Meloni, A. R., Fralish, G. B., Kelly, P., Salahpour, A., **Chen, J. K.**, Wechsler-Reya, R. J., Lefkowitz, R. J. and Caron, M. G. (2006) Smoothened signal transduction is promoted by Gprotein coupled receptor kinase 2. *Mol. Cell. Biol.* 26: 7550-7560.
8. Esengil, H., Chang, V., Mich, J. K., and **Chen, J. K.** (2007) Small-molecule regulation of zebrafish gene expression. *Nat. Chem. Biol.* 3: 154-155.
9. Shestopalov, I. A., Sinha, S., and **Chen, J. K.** (2007) Light-controlled gene silencing in zebrafish embryos. *Nat. Chem. Biol*. 3: 650-651.
10. Esengil, H. and **Chen, J. K.** (2008) Gene regulation technologies for zebrafish. *Mol. BioSystems* 4: 300-308.
11. Shestopalov, I. A. and **Chen, J. K.** (2008) Chemical technologies for probing embryonic development. *Chem. Soc. Rev.* 37: 1294-1307.
12. Low, W.-C., Wang, C., Pan, Y., Huang, X.-Y., **Chen, J. K.**, and Wang, B. (2008) The decoupling of Smoothened from G-alpha-i proteins has little effect on Gli3 protein processing and Hedgehog-regulated chick neural tube patterning. *Dev. Biol.* 321: 188-196.
13. Stanton, B. Z., Peng, L. F., Maloof, N., Nakai, K., Wang, X., Herlihy, K. M., Duffner, J. L., Taveras, K. M., Hyman, J. M., Lee, S. W., Koehler, A. N., **Chen, J. K.**, Fox, J. L., Mandinova, A., and Schreiber, S. L. (2009) A small molecule that binds Hedgehog and blocks its signaling in human cells. *Nat. Chem. Biol.* 5: 154-156.
14. Cupido, T., Rack, P. G., Firestone, A. J., Hyman, J. M., Han, K., Sinha, S., Ocasio, C. A, and **Chen, J. K.** (2009) The imidazopyridine derivative JK184 reveals dual roles for microtubules in Hedgehog signaling. *Angew. Chem. Intl. Ed*. *Engl.* 48: 2321-2324.
15. Mich, J.K., Blaser, H., Thomas, N. A., Firestone, A. J., Yelon, D., Raz, E., and **Chen, J. K.** (2009) Germ cell migration in zebrafish is cyclopamine-sensitive but Smoothenedindependent. *Dev. Biol.* 328:342-354.
16. Yang, H., Xiang, J., Wang, N., Zhao, Y., Hyman, J., Jiang, J., **Chen, J. K.**, Yang, Z., and Lin, S. (2009) Converse conformational control of Smoothened activity by

structurally related small molecules. *J. Biol. Chem.* 284: 20876-20884.

17. Hyman, J. M., Firestone, A. J., Heine, V. M., Zhao, Y., Ocasio, C. A., Han, K., Sun, M., Rack, P. G., Sinha, S., Wu, J. J., Solow-Cordero, D. E., Jiang, J., Rowitch, D. H., and **Chen, J. K.** (2009) Small-molecule inhibitors reveal multiple strategies for Hedgehog pathway blockade. *Proc. Natl. Acad. Sci. U. S. A*. 106: 14132-14137.
18. Ouyang, X., Shestopalov, I. A., Sinha, S., Zheng, G., Pitt, C. L. W., Li, W.-H., Olson, A. J., and **Chen, J. K.** (2009) Versatile synthesis and rational design of caged morpholinos. *J. Am. Chem. Soc.* 131: 13255-13269.
19. Firestone, A. J. and **Chen, J. K.** (2010) Controlling destiny through chemistry: Smallmolecule regulators of cell fate. *ACS Chem. Biol.* 5: 15-34.
20. Shestopalov, I. A. and **Chen, J. K.** (2010) Oligonucleotide-based tools for studying zebrafish development. *Zebrafish* 7: 31-40.
21. Ouyang, X. and **Chen, J. K.** (2010) Synthetic strategies for studying embryonic development. *Chem. Biol.* 17: 590-606.
22. Clanton, J.A., Shestopalov, I., **Chen, J.K.**, and Gamse, J. T. (2011) Lineage labeling of zebrafish cells with laser uncageable fluorescein dextran. *J. Vis. Exp.* doi: 10.3791/2672
23. Sakata, T. and **Chen, J. K.** (2011) Chemical 'Jekyll and Hyde's: Small-molecule inhibitors of developmental signaling pathways. *Chem. Soc. Rev.* 40: 4318-4331.
24. Park, K.-S., Martelotto, L. G., Peifer, M., Sos, M. L., Karnezis, A. N., Mahjoub, M. R.,Bernard, K., Conklin, J., Szczepny, A., Yuan, J., Guo, R., Opsina, B., Falzon, J., Bennett, S., Brown, T. J., Markovic, A., Devereux, W. L., Ocasio, C. A., **Chen, J. K.**, Stearns, T., Thomas, R. K., Dorsch, M., Buonamici, S., Watkins, D. N., Peacock, C. D., and Sage, J. (2011) A cell-autonomous requirement for Hedgehog signalling in small cell lung cancer. *Nature Med.*, in press.

Chemical probes of embryonic signaling and patterning

James K. Chen

Embryonic development can be described as a series of chemical interactions and reactions that are executed with spatial and temporal precision. While molecular biology and genetics have been the primary tools of developmental biologists, chemistry can provide a unique window into embryological processes. Unconstrained by Nature's molecular architecture, synthetic compounds can control these events with cellular resolution and within seconds.

Here I describe two examples of how chemical tools can be used to interrogate the signaling pathways that regulate embryonic development. First, by conducting a highthroughput screen for Hedgehog pathway inhibitors, we have identified a small molecule that blocks Gli transcription factor function and primary cilia formation.

Through cell-based and *in vitro* studies, we have established that this compound targets the AAA+ ATPase cytoplasmic dynein, which is required for retrograde ciliary trafficking and therefore Gli regulation. Using this molecular probe, we have also interrogated other dynein-dependent processes, such as mitotic spindle assembly and organelle transport. Second, we show how temporal, tissue-specific changes in transcription factor function can be discerned by integrating caged antisense oligonucleotides, photoactivatable fluorophores, fluorescence-activated cell sorting, and microarray technologies. As a proof of principle, we have dynamically profiled No tail-a (Ntla)/Brachyury-dependent genes at different stages of axial mesoderm development in zebrafish.

These studies have identified discrete sets of Ntla-dependent transcripts that are coincident with notochord cell fate commitment or differentiation, revealing a surprising degree of transcription factor plasticity within a single cell lineage.

Minoru Yoshida

Education and Professional Career:

1981: B.Sc. University of Tokyo
1983: M.Sc. University of Tokyo
1986: Ph.D. University of Tokyo
1986-94: Assistant Professor, Department of Biotechnology, University of Tokyo
1995-02: Associate Professor, Department of Biotechnology, University of Tokyo
2002-: Chief Scientist, Chemical Genetics Laboratory, RIKEN
2008-: Group Director, Chemical Genomics Research Group, RIKEN ASI

Award and Honors:

1986: Japan Society for Bioscience, Biotechnology, and Agrochemistry Award for the Encouragement of Young Scientists (Japan Society for Bioscience, Biotechnology, and Agrochemistry)
1998: Sumiki-Umezawa Memorial Award (Japan Antibiotics Research Association)
2009: Japan Bioindustry Association Award (Japan Bioindustry Association)
2010: Prizes for Science and Technology, The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology
2011: Japan Society for Bioscience, Biotechnology, and Agrochemistry Award (Japan Society for Bioscience, Biotechnology, and Agrochemistry)

Present Position and Address:

Group Director, Chemical Genomics Research Group, RIKEN Advanced Science Institute
Chief Scientist, Chemical Genetics Laboratory, RIKEN Advanced Science Institute
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Recent Selected Publications:

1. Nishimura, S., Arita, Y., Honda, M., Iwamoto, K., Matsuyama, A., Shirai, A., Kawasaki, H., Kakeya, H., Kobayashi, T., Matsunaga, S., and Yoshida, M. Marine antifungal theonellamides target 3β-hydroxysterol to activate Rho1 signaling. **Nature Chem. Biol**., 6: 519-526, 2010.
2. Sasaki, K., Ito, T., Nishino, N., Khochbin, S., and Yoshida, M. Real-time imaging of histone H4 hyperacetylation in living cells. **Proc. Natl. Acad. Sci. U.S.A**., 106: 16257-16262, 2009.
3. Ho, C. H., Magtanong, L., Barker, S. L., Gresham, D., Nishimura, S., Natarajan, P., Koh, J. L. Y., Proter, J., Gray, C. A., Andersen, R. J., Giaever, G., Nislow, C., Andrews, B., Botstein, D., Graham, T. R., Yoshida, M., and Boone, C. A molecular barcoded yeast ORF library enables mode-of-action analysis of bioactive compounds. **Nature Biotechnol**., 27: 369-377, 2009.
4. Kaida, D., Motoyoshi, H., Tashiro, E., Nojima, T., Hagiwara, M., Ishigami, K., Watanabe, H., Kitahara, T., Yoshida, T., Nakajima, H., Tani, T., Horinouchi, S., and Yoshida, M. Spliceostatin A targets SF3b and inhibits both splicing and nuclear retention of pre-mRNA. **Nature Chem. Biol**., 3: 576-583, 2007.
5. Matsuyama, A., Arai, R., Yashiroda, Y., Shirai, A., Kamata, A., Sekido, S., Kobayashi, Y., Hashimoto, A., Hamamoto, M., Hiraoka, Y., Horinouchi, S., and Yoshida, M. ORFeome cloning and global analysis of protein localization in the fission yeast *Schizosaccharomyces pombe*. **Nature Biotechnol**., 24: 841-847, 2006.

Chemical genomics based on fission yeast collections expressing yeast and human ORFeomes

Minoru Yoshida
Chemical Genomics Research Group, RIKEN Advanced Science Institute

The discovery of chemical compounds that can inhibit functions of specific proteins has had a significant impact on developments in the biological sciences. An essential but challenging step in the development of small molecules into biochemical tools or therapeutic drugs is target identification. The major approach to target identification has been the detection of physical interaction between the small molecule and its target. However, such interactions are not always detectable, because of their varied strength and stability as well as the constraints on complex formation *in vitro*. Here we show a novel approach using a genome-wide overexpression screen of fission yeast *Schizosaccharomyces pombe* ORFs for systematic target identification of bioactive small-molecules. We succeeded in cloning all the ORFs (ORFeome) of *S. pombe*, and expressed them under the control of an inducible promoter. Using this ORFeome collection, we generated a chemical-genomic profile of theonellamide F, a marine sponge-derived fungicide, using a collection of fission yeast strains in which each introduced ORF can be overexpressed, and showed that the target is associated with membrane-associated molecules showing polarized distribution. Indeed, theonellamide F bound ergosterol and induced β-glucan synthesis by activating Rho1. However, the induced phenotypic changes were totally different from those by known sterol-binding molecules such as polyene antibiotics. Thus, theonellamides represent a novel class of sterol-binding molecules that activates the Rho1 pathway, and the fission yeast ORFeome provides a useful platform to predict the mode of action of bioactive compounds. Furthermore, we expressed a human ORFeome in *S. pombe*, and found more than 1,000 human genes that inhibit the yeast growth by overexpression. Such the "Humanized" yeast collection provides an effective screening method to identify compounds that control human disease-related genes. A specific inhibitor is expected to restore the growth arrest by gene overexpression. We screened the RIKEN NPDepo chemical library, identified chemicals that recovered the lethality of poly(ADP-ribose) polymerases, PARP10 and tankyrase 1, and examined specific inhibitory activity of the hit compounds using mammalian and yeast cells. Thus the yeast cells expressing the yeast and human ORFeomes will serve as a living test tube for a variety of chemical genomics.

MEMO

Reiko Sugiura

Professor
Laboratory of Molecular Pharmacogenomics
Kinki University
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Education

Keio University, Faculty of Letters,	B. A.	1982	Literature
Keio University, Faculty of Law and Political Science,		1985	Law Science
Kobe University School of medicine.	M. D.	1992	Medicine
Kobe University School of medicine.	Ph. D.	1998	Pharmacology

Honors:

The 1998 Kobe Medical Award for Excellence in Research.
The 1999 Kobe Medical Award for Excellence in Research.
The 2000 Japanese Pharmacological Society Young Investigator Award.
The 2003 Kobe Medical Award for Excellence in Research.

Research and Professional Experience:

Resident, Department of Psychiatry, Kobe University Hospital, Kobe, Japan. 1992-1993.

Resident, Division of Psychiatry and Internal Medicine, Saiseikai Nakatsu Hospital, Osaka, Japan. 1993-1994.

Graduate Fellow, Department of Pharmacology, Kobe University School of Medicine, Kobe, Japan. 1994-1996.

Assistant Professor, Department of Pharmacology, Kobe University School of Medicine, Kobe, Japan; 1996-1999.

Lecturer, Department of Pharmacology, Kobe University School of Medicine, Kobe, Japan; 1999-2000.

Associate Professor, Department of Pharmacology, Kobe University School of Medicine, Kobe, Japan; 2000-2004

Professor, Laboratory of Molecular Pharmacogenomics, School of Pharmaceutical Sciences, Kinki University: 2004 to present

Selected Publications

The Cell Surface Protein Gene *ecm33*$^{+}$ Is a Target of the Two Transcription Factors Atf1 and Mbx1 and Negatively Regulates Pmk1 MAPK Cell Integrity Signaling in Fission Yeast.
Takada, H., Kita, A., & **Sugiura R**.
Mol. Biol. Cell 2010; 21(4):674-85.

The Role of the RNA-Binding Protein Nrd1 and Pmk1 MAPK in the Regulation of Myosin mRNA Stability in Fission Yeast
Satoh, R., Kita, A., & **Sugiura R.**
Mol. Biol. Cell 2009; 20(9): 2473-2485.

Atf1 Is a Target of the MAP Kinase Pmk1 and Regulates Cell Integrity in Fission Yeast. Takada, H., Kita, A., **Sugiura R**.
Mol. Biol. Cell**,** 2007; 18(12): 4794-4802

Rho2 is a Target of the Farnesyltransferase Cpp1 and Acts Upstream of Pmk1 MAP Kinase Signaling in Fission Yeast.
Ma Y, Kita A, and **Sugiura R**.
Mol. Biol. Cell, 17(12):5028-5037. (2006)

Feedback regulation of MAPK signalling by an RNA-binding protein.
Sugiura R, *et al*.,
Nature, 424： 961-965. (2003)

The MAPK kinase Pek1 acts as a phosphorylation-dependent molecular switch.
Sugiura R, *et al.,*
Nature 399: 479-483, 1999

pmp1^{+}, a suppressor of calcineurin deficiency, encodes a novel MAP kinase phosphatase in fission yeast.
Sugiura R, *et al.,*
EMBO-J. 17: 140-148, 1998

A Powerful Genetic Strategy to Screen for Inhibitors of MAP Kinase Signaling and its Application to Genomic Drug Discovery

Reiko Sugiura

Mitogen-activated protein kinases (MAPKs), found in all eukaryotes, are signal-transducing enzymes playing a central role in a variety of biological processes. The Pmk1 MAPK signaling pathway regulates cytokinesis and cell integrity in fission yeast. We have demonstrated that MAPK and calcineurin phosphatase act antagonistically in the Cl^- homeostasis in fission yeast and developed a genetic screen that aims to identify negative regulators of the Pmk1 MAPK signalling.

Our genetic screen based on the functional interaction between calcineurin and Pmk1 MAPK has efficiently isolated negative regulators of the Pmk1 MAPK pathway. These include *pmp1*$^+$ encoding a dual-specificity MAPK phosphatase, *ptc1*$^+$ and *ptc3*$^+$ encoding a serine/threonine protein phosphatase, *pek1*$^+$ encoding a MAPK kinase and *rnc1*$^+$ encoding a KH-type RNA-binding protein. We also demonstrated that Rnc1 plays a crucial role in negative feedback regulation of MAPK signalling, by binding and stabilizing the mRNA of a MAPK phosphatase at the post-transcriptional level (Sugiura *et al*., *Nature* 2003). Most recently, we also identified several targets of Pmk1 MAPK, including *ecm33*$^+$ encoding a cell surface protein, *nrd1*$^+$ encoding an RRM-type RNA-binding protein (Satoh *et al.*, Mol. Biol. Cell 2008), and *atf1*$^+$ encoding a transcription factor, and developed an *in vivo* real-time monitoring system of the Pmk1 MAPK activation (Takada *et al.*, Mol. Biol. Cell 2007, 2010).

As MAPK signal transduction pathways are one of the most attractive targets for cancer therapy, inhibitors that target this signaling appear to be promising drug candidates for the treatment of cancer. Here, I first give an overview of the use of fission yeast as a model system for drug discovery and then, I introduce our molecular genetic strategy to identify regulators of MAPK signaling and the application of this approach to drug discovery (Sugiura *et al*., Drug Discovery; *Sourcebook of Models for Biomedical Research*, 2008).

MEMO

Motonari Uesugi, Ph. D.

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A. Personal

a. Name: Motonari Uesugi
b. Date of Birth: January 25, 1967, Osaka, Japan.
Nationality: Japanese (Permanent Resident of The United States)

B. Education

1986-1990 *Kyoto University*, Kyoto, Japan.
B.S. degree in Pharmaceutical Sciences

1990-1995 *Kyoto University*, Kyoto, Japan.
Institute for Chemical Research
Ph.D. degree in Pharmaceutical Chemistry and Biochemistry

1995-1998 *Harvard University*, Cambridge, MA, USA.
Department of Chemistry and Chemical Biology
Postdoctoral Training in Chemical Biology

C. Academic Appointments

1998-2005 *Assistant Professor*, Department of Biochemistry, Baylor College of Medicine, Houston, TX.

2005-2009 *Associate Professor (tenured)*, Department of Biochemistry, Baylor College of Medicine, Houston, TX.

2005-present ***Professor***, Institute for Chemical Research, Kyoto University, Kyoto, Japan.

2007-present ***Professor***, Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto, Japan

2009-present ***Adjunct Associate Professor***, Department of Biochemistry, Baylor College of Medicine, Houston, TX.

E. Honors or Awards

1992-1995 Predoctoral Fellow Award, The Japan Society for the Promotion of Science.

1995-1996 Postdoctoral Fellow Award, The Naito Foundation.

1996-1999 Postdoctoral Fellow Award, The Leukemia Society of America.

2001-2002 Lymphoma Research Foundation Junior Faculty Award.

2003 American Cancer Society Research Scholar Award.

2006 Gold Medal Award, Tokyo TechnoForum 21.

2011 The Pharmaceutical Society of Japan Award for Divisional Scientific Promotions '11.

2011 German Innovation Award Gottfried Wagener Prize.

F. Professional Activities

2009- present Member, Editorial Board, *Chemistry & Biology*

2010-present Member, Editorial Board, *MedChemCom*

G. Selected Publications

・A mitochondrial surface-specific fluorescent probe activated by bioconversion. Kawazoe, Y., Shimogawa, H., Sato, A., Uesugi, M. Angew. Chem. Int. Ed. 50(24), 5478-81 (2011).

・A Dumbbell-Shaped Small Molecule that Promotes Cell Adhesion and Growth. Yamazoe, S., Shimogawa, H., Sato, S., Esko, J. D., Uesugi, M. Chem. Biol. 16 (7), 773-782 (2009).

Small Molecule Tools for Cell Biology and Cell Therapy

MOTONARI UESUGI

Institute for Integrated Cell-Material Sciences, and Institute for Chemical Research,

Kyoto University, Japan

In human history, bioactive small molecules have had three primary uses: as medicines, agrochemicals, and biological tools. Among them, what our laboratory has done in the past was the discovery and use of biological tools. Our laboratory has been discovering and designing small organic molecules with unique activities, and using them as tools, we have been understanding and controlling cell physiology.

In addition to tool discovery, our laboratory has recently become interested in exploring another application of small molecules: small molecule tools for cell therapy. Although small molecule drugs will continue to be important, cell therapy will be a powerful approach to curing difficult diseases that small molecule drugs are unable to handle. However, there are a number of potential problems in bringing cell therapy technologies to the clinic, including high cost, potential contamination, low stability, and tumorigenesis. Stable, completely defined small molecule tools, which are usually amenable to cost-effective mass production, may be able to help the clinical use of cell therapy.

Through screening chemical libraries, we have been discovering unique synthetic molecules that modulate or detect fundamental characteristics of human cells useful for cell therapy. Some of such molecules may serve as tools for cell engineering or cell therapy as well as basic cell biological research. This presentation provides a quick overview of our recent research programs with a special emphasis on the discovery and utilization of “adhesamine.” This dumbbell-shaped synthetic molecule enhanced attachment and growth of cells by binding to heparan sulfate on cell membrane and thereby clustering syndecan. Using this molecule as a lead, we were able to design small synthetic molecules with fibronectin-like properties, which boost culture, expansion, and transplantation of clinically useful cells.

Other small-molecule tools we newly discovered may be discussed in the presentation.