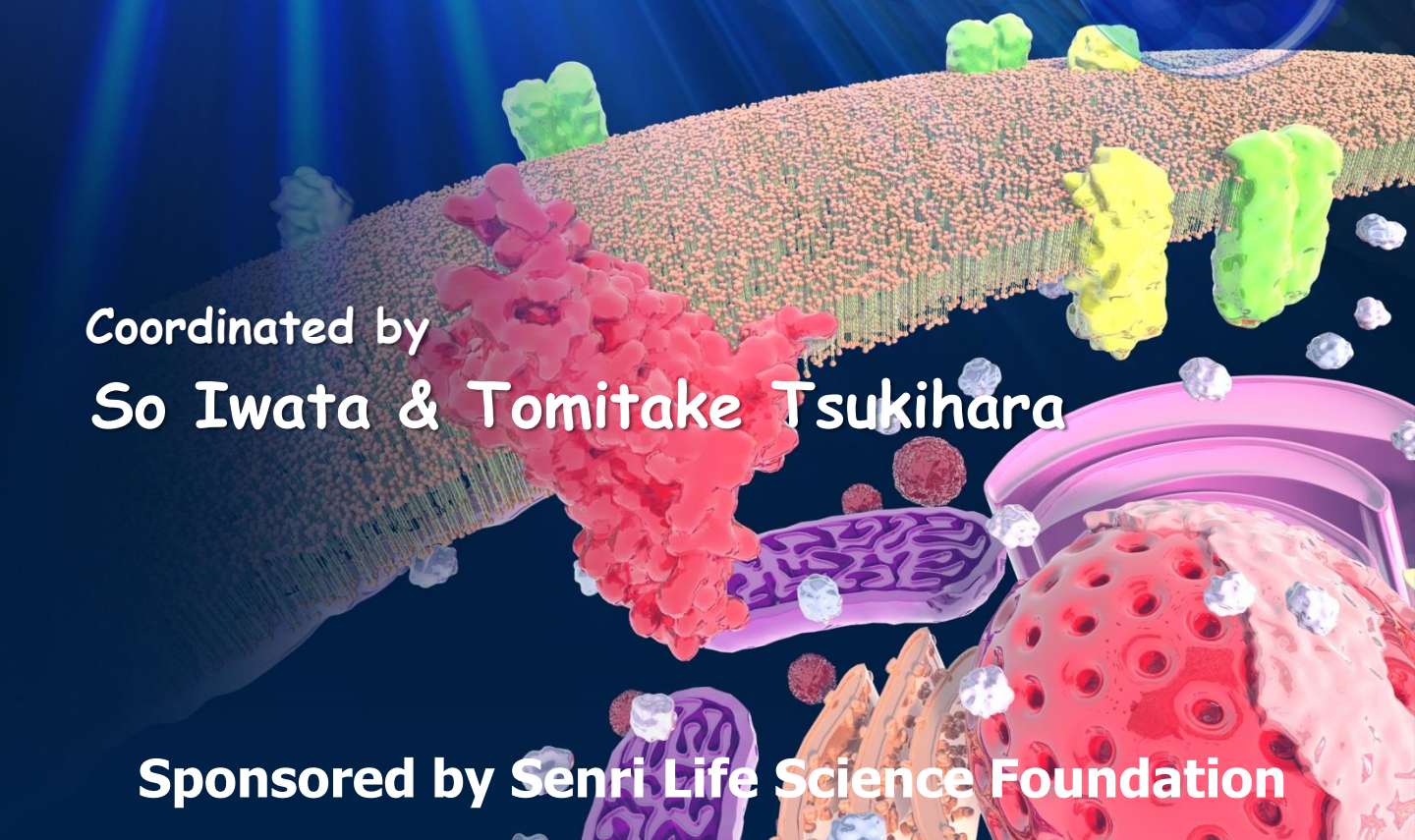
2016 Senri Life Science International Symposium on

"Frontiers in Structural Biology - - - X-ray Free Electron Laser and Drug Discovery"

Date : January 22nd (Fri), 2016, 10:00-17:00
Venue : Senri Life Science Center Building
5th floor "Yuichi Yamamura Memorial Life Hall"



Coordinated by
So Iwata & Tomitake Tsukihara

Sponsored by Senri Life Science Foundation

Description of cover view ;
This conceptual figure, inspired by the title of this symposium “Free electron laser and drug discovery”, shows cellular components illuminated by a bright light.

2016 Senri Life Science International Symposium
“Frontiers in Structural Biology - - - - -
X-ray Free Electron Laser and Drug Discovery ”
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10:00- 10:10 Opening address

Tadamitsu Kishimoto (President of Senri Life Science Foundation) p.2

Chair : Tomitake Tsukihara (University of Hyogo/Osaka University)

10:10-10:30 Introduction

So Iwata (Kyoto University, RIKEN SPring-8 Center, Japan) p.4

10:30-11:10 “New Frontier in Structural Biology: Free Electron Laser”

〈Talk 1〉 **So Iwata (Kyoto University, RIKEN SPring-8 Center, Japan)** p.6

11:10-11:50 “Beyond Crystallography: Diffractive Imaging Using Coherent X-ray Source”

〈Talk 2〉 **Jianwei (John) Miao (UCLA, USA)** p.10

11:50-12:30 “GPCR crystallography with X-ray lasers”

〈Talk 3〉 **Vadim Cherezov (University of Southern California, USA)** p.14

12:30-13:40 **Lunch**

Chair : So Iwata (Kyoto University, Japan)

13:40-14:20 “Structural and functional studies of bovine cytochrome oxidase by X-ray free electron laser and synchrotron radiation X-ray”

〈Talk 4〉 **Tomitake Tsukihara (University of Hyogo/Osaka University, Japan)** p.18

14:20-15:00 “Molecular and structural insights into opioid receptor activation”

〈Talk 5〉 **Aashish Manglik (Stanford University School of Medicine, USA)** p.22

15:00-15:20 **Coffee break**

15:20-16:00 “The application of Free Electron Lasers to biology: a new age of time resolved crystallography”

〈Talk 6〉 **Gebhard F.X. Schertler (Paul Scherrer Institute, Switzerland)** p.26

16:00-16:40 “Understanding the Complete GPCR Superfamily”

〈Talk 7〉 **Raymond C. Stevens (University of Southern California, USA)** p.30

16:40-16:50 Closing remarks

Tomitake Tsukihara (University of Hyogo/Osaka University, Japan) p.34

Described time includes questions and answers.

Opening Address

Tadamitsu Kishimoto, MD.,PhD.

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Educational History:

1964	Graduated from Osaka University Medical School
1970-1973	Research Fellow, Department of Medicine, Johns Hopkins University, School of Medicine

Professional History:

1973-1974	Assistant Professor in the Department of Medicine, Johns Hopkins University, School of Medicine
1974-1979	Assistant Professor, Department of Medicine III, Osaka University Medical School
1979-1983	Professor, Department of Pathology and Medicine, Osaka University Medical School
1983-1991	Professor, Institute for Molecular and Cellular Biology, Osaka University
1991-1998	Professor and Chairman, Department of Medicine III, Osaka University Medical School
1995-1997	Dean, Osaka University Medical School
1997-2003	President, Osaka University
2003-2011	Professor of Immunology, Graduate School of Frontier Biosciences, Osaka University
2004-2006	Member, Council for Science and Technology Policy, Cabinet Office
2007-Present	Chairman of the Board of directors, Senri Life Science Foundation
2011-Present	Guest Professor, Immunology Frontier Research Center, Osaka University

Honors & Awards:

1982 Behring-Kitasato Prize
1983 Osaka Science Prize
1986 Erwin von Bälz Prize
1988 Takeda Prize
1988 Asahi Prize
1990 Prize of The Japanese Medical Association
1990 Person of Cultural Merit, Japan
1991 Foreign Associate, The US National Academy of Science
1991 Scientific Achievement Award from the International Association of Allergology and Clinical Immunology
1992 Honorary Member, the American Association of Immunologists
1992 Imperial Prize from the Japan Academy
1992 Sandoz Prize for Immunology from International Union of Immunology Society
1992 Honorary Citizen, Tondabayashi City
1995 Member, the Japan Academy
1996 The Avery-Landsteiner Prize from the German Immunology Society
1997 Foreign Associate member, the Institute of Medicine of the National Academy of Science, USA
1997 Honorary member, the American Society of Hematology
1998 The Order of Culture from Emperor
1999 The Donald Seldin Award from the International Society of Nephrology
2000 ISI Citation Laureate Award
2001 Honorary Member, International Association of Dental Research
2002 Honorary Professor, the forth Military Medical University, Xi'an, China
2002 Honorary Member, World Innovation Foundation
2003 Doctor of Science, Honoris Causa, Mahidol University
2003 Robert Koch Gold Medal
2004 Clemens von Pirquet Distinguished Professor, Medicine and Immunology, University California, Davis
2005 Member, Deutsche Akademie der Naturforscher Leopoldina
2006 Honorary Lifetime Achievement Awards, International Cytokine Society
2009 The Crafoord Prize from the Royal Swedish Academy of Sciences
2010 CIS (Clinical Immunology Society, USA) President's Award
2011 The Japan Prize

〈 Introduction 〉
“Membrane protein structures and drug discovery”

So Iwata, Ph.D.

The results of genome sequencing projects have shown that up to 30% of human proteins occur in cell membranes. Membrane proteins play crucial roles in many biological functions, including the capture of energy from sunlight by plants, the use of energy in cells, and the movement of molecules across cell membranes. They are particularly important in medicine, since ~over 50% of commercially available drugs (such as antihistamines, beta blockers, antipsychotic drugs, morphine) target membrane proteins. We need to understand membrane protein structures to provide a basic understanding of life at the molecular level and for computer aided rational design of new drugs, which could reduce the number of animal experiments and unwanted side effects. In my talk, I would like to summarise the current status and the recent advances in structural biology on membrane proteins and its effect on drug discovery.

I will also discuss new technical development in membrane protein crystallography. Radiation damage of crystals is one of the most hampering problems in the current macromolecular crystallography. The X-ray beams at the latest beamlines are so intense that the crystals suffer serious radiation damage during even very-short exposure-time. The problem is particularly severe for crystals of membrane proteins, which are extremely radiation sensitive. X-ray free electron laser (XFEL) could provide a solution to this problem. In my talk, I will present some recent results on membrane protein crystallography at the Japanese XFEL facility, SACLA.

<MEMO>

〈Talk 1〉
"New Frontier in Structural Biology: Free Electron Lasers"

So Iwata, Ph.D.

Title:

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Educational History:

1986	B.Sc., Undergraduate at the University of Tokyo
1988	M.Sc., University of Tokyo.
1991	Ph.D., University of Tokyo.

Professional History:

1991-1992	Research fellow with Prof. Noriyoshi Sakabe at the Photon Factory, National Laboratory for High Energy Physics, Tsukuba
1992-1996	Postdoctoral fellow at Max-Planck-Institute for Biophysics, Frankfurt am Main, Germany
1996-1999	Lecturer at Uppsala University, Department of Biochemistry
1999-2000	Professor of Biochemistry at Uppsala University
2000-2015	Division of Molecular Biosciences, Imperial College, London
2004-2015	Diamond Fellow, Diamond Light Source, UK
2005-2008	Director of Centre for Structural Biology, Division of Molecular Biosciences, Imperial College London
2005-2011	Research Director, Japan Science and Technology Agency, ERATO(Exploratory Research for Advanced Technology) IWATA Human Receptor Crystallography Project
2005-2012	Senior Visiting Scientist, Riken Yokohama Institute
2007- present	Professor, Graduate School of Medicine, Kyoto University
2012-present	Group Director, SACLA Science Research Group, RIKEN SPring-8 Center

Honors & Awards:

Prize

1998 The Svedberg prize from the Swedish society for biochemistry and molecular biology

1999 Lindbom prize from the Royal Swedish Academy of Science

2007 Japan Academy Medal from the Japan Academy
Japan Society for Promoting Science Prize

2010 The Gregori Aminoff Prize, Sweden

2012 The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology

Other awards

1992 Fellowship from the Japanese Society for the Promotion of Science

1996 Human Frontier Science Project Fellowship

2002 BBSRC Japan Partnering Award 2002

2004 BBSRC Japan Partnering Award 2004

2005 Japan Science Technology Agency, ERATO award

2009 BBSRC Diamond Professorial Fellowship

Abstract

X-ray free-electron lasers (XFELs) are revolutionary X-ray sources. Very short X-ray pulses duration (a few tens of femtoseconds) , high intensity delivering up to 10^{12} photons per pulse, sub-micrometre beam-seize are unique for this new X-ray source.

Radiation damage of crystals is one of the most hampering problems in the current macromolecular crystallography. The X-ray beams at the latest beamlines, including microfocus beamlines, are so intense that the crystals suffer serious radiation damage during even very-short exposure-time. The problem is particularly severe for crystals of membrane proteins or macromolecular assemblies, which are extremely radiation sensitive. X-ray Free Electron Laser could provide a solution to this problem. Very high dose rates delivered by the intense femtosecond pulses of XFELs reduce the amount of damage suffered by a crystal during its irradiation. Single shot diffraction patterns are collected from a series of small crystals and by combining them, we could swiftly complete the dataset without any serious radiation damage. At the Japanese XFEL facility, SACLA, we are currently developing a data collection system focusing on drug-target protein crystals including those from membrane proteins and flexible multi-modular proteins. The system is composed of a diffraction chamber with a sample injector and a fast readout multiport CCD (mpCCD) detector. The sample injector is optimized for the data collection from crystals in the lipidic cubic phase (LCP), which are common for membrane proteins. The injector is also capable to handle the crystals obtained from solutions by making the solution viscous using additives including gels and grease. The system requires only several 100 micrograms of proteins to complete the dataset. The system can dramatically accelerate the structure determination of membrane proteins.

The SFX system is also suitable for time-resolved crystallography including visualization of ultrafast protein structural dynamics on the femtosecond to picosecond time-scale, as well as time-resolved diffraction studies of non-cyclic reactions. I am convinced that this will lead to a revolution of time-resolved protein crystallography. In my talk, I will present some recent results of pump and probe experiments at SACLA.

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〈Talk 2〉
“Beyond Crystallography: Diffractive Imaging Using Coherent X-ray Source”

Jianwei (John) Miao, PhD.

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Educational History:

12/1999	Ph. D., Physics, the State University of New York, Stony Brook,
5/1999	M. S., Computer Science, the State University of New York, Stony Brook,
5/1999	Advanced Graduate Certificate, Biomedical Engineering, the State University of New York, Stony Brook,
7/1994	M. S., Physics, Chinese Academy of Sciences,
7/1991	B. S., Physics, Hangzhou University, P. R. China,

Professional History:

7/2009-Present	Professor, Department of Physics and Astronomy & California NanoSystems Institute, University of California, Los Angeles
7/2007-7/2009	Associate Professor, Department of Physics and Astronomy & California NanoSystems Institute, University of California, Los Angeles
8/2004-7/2007	Assistant Professor, Department of Physics and Astronomy & California NanoSystems Institute, University of California, Los Angeles
1/2000-7/2004	Staff Scientist, Stanford Synchrotron Radiation Laboratory, SLAC, Stanford University

Honors and Awards:

2015	The University of Strasbourg Institute for Advanced Study (USIAS) Fellowship, France.
2013	Microscopy Today Innovation Award.
2013	Theodore von Kármán Fellowship, RWTH Aachen University, Germany.
2012-2013	Outstanding Teaching Award, Dept. of Physics & Astronomy, UCLA.
2010	Kavli Frontiers Fellow.
2009 – Present	Guest Professor, Zhejiang University, China.
2006-2007	Outstanding Teacher of the Year Award, Dept. of Physics & Astronomy, UCLA.
2006-2008	Alfred P. Sloan Research Fellow.
2004 – Present	Guest Scientist, RIKEN, Japan.
1999	Werner Meyer-Ilse Memorial Award.
1997-1999	Whitaker Foundation Scholarship.
1990-1991	Outstanding Student of the Year Award, Physics Department, Hangzhou University.

Abstract

The discovery and analysis of X-ray diffraction from crystals by Max von Laue, William Henry Bragg and William Lawrence Bragg in 1912 marked the birth of X-ray crystallography. Over the last century, X-ray crystallography has been fundamental to the development of many fields of science. However, many biological and physical science samples are difficult to be crystallized and thus their three-dimensional structures are presently not accessible to X-ray crystallography. Overcoming these obstacles requires the development of new X-ray sources and methodologies.

Recently, the X-ray science community has witnessed two revolutionary developments. First, large-scale coherent X-ray sources, such as X-ray free electron lasers (XFELs) and advanced synchrotron radiation, have been under rapid development worldwide. Compared with previous generation X-ray sources, the new sources increase the X-ray brilliance by several orders of magnitude. Second, the methodology of X-ray crystallography was extended to allow the structure determination of non-crystalline specimens or nanocrystals in 1999, which is known as coherent diffraction imaging (CDI) or lensless imaging.

In CDI, the diffraction pattern of a non-crystalline sample or a nanocrystal is first measured and then directly phased to obtain an image. The well-known phase problem is solved by combining the oversampling method with iterative algorithms.

In this talk, I will discuss the principle of CDI, illustrate some biological applications using synchrotron radiation and XFELs, and present my future perspectives of biological imaging with coherent X-ray sources.

<MEMO>

〈Talk 3〉
"GPCR crystallography with X-ray lasers"

Vadim Cherezov, PhD.

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Educational History:

1987-1993	M.S., Summa Cum Laude, Moscow Institute of Physics and Technology, Russia
1993-1997	PhD, Moscow Institute of Physics and Technology, Russia
1995	Internship in the Laboratory Leon Brillouin, Saclay, France.
1998 – 2000	PostDoctoral fellow, The Ohio State University, Columbus, OH.

Professional history:

1991 – 1995	Junior Research Fellow, Joint Institute for Nuclear Research, Dubna, Russia.
1995 – 1998	Research Fellow, Joint Institute for Nuclear Research, Dubna, Russia.
2000 – 2006	Research Associate, The Ohio State University, Columbus, OH.
2006 – 2007	Scientific Associate, The Scripps Research Institute, La Jolla, CA.
2008 – 2009	Staff Scientist, The Scripps Research Institute, La Jolla, CA.
2009 – 2013	Assistant Professor, The Scripps Research Institute, La Jolla, CA.
2013 – 2014	Associate Professor, The Scripps Research Institute, La Jolla, CA.
2014 – present	Head of Laboratory, Moscow Institute of Physics and Technology, Russia.
2015 – present	Associate Director, The Bridge Institute @ USC, Los Angeles, CA.
2015 – present	Professor, University of Southern California, Los Angeles, CA.

Honors & Awards:

1996	Frank Laboratory award for junior researcher, Joint Institute for Nuclear Research, Dubna, Russia
2013	John Karling distinguished lecture award, Purdue University, IN
2015	Thomson Reuter's highly cited researcher in category "Pharmacology and Toxicology"

Abstract

Structural studies of G protein-coupled receptors (GPCRs), and other biomedically relevant membrane proteins and complexes, are hampered by challenges related to growing sufficiently large crystals capable of withstanding radiation damage and yielding high-resolution data. We have developed a new approach of using a membrane mimetic gel-like matrix known as lipidic cubic phase (LCP) for growth and delivery of membrane protein microcrystals for data collection by serial femtosecond crystallography (SFX) at X-ray free electron lasers (XFEL) [1]. Microcrystals are delivered to the intersection point with an XFEL beam using a specially designed LCP injector [2], allowing to adjust LCP flow-rate and minimize crystal consumption. LCP-SFX uses highly intense 40-fs XFEL pulses to minimize radiation damage and collect room temperature high-resolution data from sub-10 μm crystals. Protein consumption is reduced by 2-3 orders of magnitude compared to a liquid injector, making the LCP-SFX method attractive for structural studies of challenging membrane and soluble proteins, and their complexes [3]. Recent applications of this method led to solving difficult structures of the human δ-opioid receptor in complex with a bi-functional peptide ligand [4], a blood pressure regulator - angiotensin receptor [5], and a major GPCR signaling complex between rhodopsin and arrestin [6].

References

1. Liu, W., Wacker, D., Gati, C., Han, G.W., James, D., Wang, D., Nelson, G., Weierstall, U., Katritch, V., Barty, A., Zatsepin, N.A., Li, D., Messerschmidt, M., Boutet, S., Williams, G.J., Koglin, J.E., Seibert, M.M., Wang, C., Shah, S.T.A., Basu, S., Fromme, R., Kupitz, C., Rendeck, K.N., Grotjohann, I., Fromme, P., Kirian, R.A., Beyerlein, K.R., White, T.A., Chapman, H.N., Caffrey, M., Spence, J.C.H., Stevens, R.C., Cherezov, V. (2013). Serial Femtosecond Crystallography of G Protein-Coupled Receptors. Science 342: 1521-1524.
2. Weierstall, U., James, D., Wang, C., White, T.A., Wang, D., Liu, W., Spence, J.C.H., Doak, R.B., Nelson, G., Fromme, P., Fromme, R., Grotjohann, I., Kupitz, C., Zatsepin, N.A., Liu, H., Basu, S., Wacker, D., Han, G.W., Katritch, V., Boutet, S., Messerschmidt, Williams, G.J., Koglin, J.E., Seibert, M.M., Klinker, M., Gati, C., Shoeman, R.L., Barty, A., Chapman, H.N., Kirian, R.A., Beyerlein, K.R., Stevens, R.C., Li, D., Shah, S.T.A., Howe, N., Caffrey, M., Cherezov, V. (2014) Lipidic cubic phase injector facilitates membrane protein serial femtosecond crystallography. Nat Commun 5: 3309.
3. Liu, W., Ishchenko, A., Cherezov, V. (2014) Preparation of microcrystals in lipidic cubic phase for serial femtosecond crystallography. Nat Protoc 9: 2123-2134.

4. Fenalti, G., Zatsepin, N.A., Betti, C., Giguere, P., Han, G.W., Ishchenko, A., Liu, W., Guillemyn, K., Zhang, H., James, D., Wang, D., Weierstall, U., Spence, J.C.H., Boutet, S., Messerschmidt, M., Williams, G.J., Gati, C., Yefanov, O.M., White, T.A., Oberthuer, D., Metz, M., Yoon, C.H., Barty, A., Chapman, H.N., Basu, S., Coe, J., Conrad, C.E., Fromme, R., Fromme, P., Tourwe, D., Schiller, P.W., Roth, B.L., Ballet, S., Katritch, V., Stevens, R.C., Cherezov, V. (2015) Structural basis for bi-functional peptide recognition at human delta-opioid receptor. Nat Struct Mol Biol 22: 265-268.
5. Zhang, H., Unal, H., Gati, C., Han, G.W., Liu, W., Zatsepin, N.A., James, D., Wang, D., Nelson, G., Weierstall, U., Sawaya, M.R., Xu, Q., Messerschmidt, M., Williams, G.J., Boutet, S., Yefanov, O.M., White, T.A., Wang, C., Ishchenko, A., Tirupula, K.C., Desnoyer, R., Coe, J., Conrad, C.E., Fromme, P., Stevens, R.C., Katritch, V., Karnik, S.S., Cherezov, V. (2015) Structure of the Angiotensin Receptor Revealed by Serial Femtosecond Crystallography. Cell 161: 833-844.
6. Kang, Y., Zhou, X.E., Gao, X., He, Y., Liu, W., Ishchenko, A., Barty, A., White, T.A., Yefanov, O., Han, G.W., Xu, Q., de Waal, P.W., Ke, J., Tan, M.H., Zhang, C., Moeller, A., West, G.M., Pascal, B.D., Van Eps, N., Caro, L.N., Vishnivetskiy, S.A., Lee, R.J., Suino-Powell, K.M., Gu, X., Pal, K., Ma, J., Zhi, X., Boutet, S., Williams, G.J., Messerschmidt, M., Gati, C., Zatsepin, N.A., Wang, D., James, D., Basu, S., Roy-Chowdhury, S., Conrad, C.E., Coe, J., Liu, H., Lisova, S., Kupitz, C., Grotjohann, I., Fromme, R., Jiang, Y., Tan, M., Yang, H., Li, J., Wang, M., Zheng, Z., Li, D., Howe, N., Zhao, Y., Standfuss, J., Diederichs, K., Dong, Y., Potter, C.S., Carragher, B., Caffrey, M., Jiang, H., Chapman, H.N., Spence, J.C., Fromme, P., Weierstall, U., Ernst, O.P., Katritch, V., Gurevich, V.V., Griffin, P.R., Hubbell, W.L., Stevens, R.C., Cherezov, V., Melcher, K., Xu, H.E. (2015) Crystal structure of rhodopsin bound to arrestin by femtosecond X-ray laser. Nature 523: 561-567.

<MEMO>

〈Talk 4〉
“Structural and functional studies of bovine cytochrome oxidase by X-ray free electron laser and synchrotron radiation X-ray”

Tomitake Tsukihara, Ph.D.

Title:

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Professor Emeritus, Osaka University
Visiting Professor, Institute for Protein Research, Osaka University,
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Educational History:

1967	BA, Phar. Osaka University, Osaka, Japan
1969	M. Sc., Macromolecular Science, Osaka University, Osaka, Japan
1974	Ph.D., Science Osaka University, Osaka, Japan

Professional History:

1971-1973	Assistant Professor, Tottori University
1973-1978	Instructor, Tottori University
1978-1991	Associate Professor, Tottori University
1978-1980	Research Associate, Purdue University
1991-1995	Professor, Tokushima University
1995-2008	Professor, Institute for Protein Research, Osaka University
2006-2008	Director of Institute for Protein Research, Osaka University
2008-Present	Professor Emeritus, Osaka University
2008-Present	Visiting Professor, Institute for Protein Research, Osaka University
2008-Present	Specially Appointed Professor, Graduate School of Life Science, University of Hyogo
2010	Visiting Chair Professor, Institute of Biotechnology, National Cheng Kung University, Taiwan
2011-Present	Distinguished Visiting Scholar, National Synchrotron Radiation Research Center, Taiwan

Honors and Awards:

1987	Award from the Crystallographic Society of Japan
1996	Protein Society (USA) Amgen Award
2004	Award from the Minister of Education, Culture, Sports, Science and Technology
2010	S. Nishikawa Award of the Crystallographic Society of Japan
2013	The Naito Foundation Merit Award for Advancement of Science

Abstract

Cytochrome c oxidase (CcO), the terminal oxidase of the respiratory chain, resides in the mitochondrial inner membrane or the bacterial cytoplasmic membrane. The enzyme reduces O_2 to H_2O and pumps protons to generate the electrochemical proton gradient across the membrane. Bovine CcO consists of 13 different protein subunits and four redox-active metal centers. The locations of the redox-active sites (heme a, heme a_3, Cu_A, and Cu_B) within the CcO complex were determined by X-ray crystallography (1). The Fe_{a3}–Cu_B site catalyzes the reduction of molecular oxygen to two water molecules. Electrons are transmitted to the dioxygen-reduction site from cytochrome c on the positive-side surface of CcO through the Cu_A site and heme a, whereas protons are taken up from the negative side and transferred through specific hydrogen-bond networks in the transmembrane region (2). In addition to the protons used for water production, additional protons are transferred through CcO across the membrane, generating the proton gradient. We proposed a proton-pumping path, later named the H-path (3), which is distinct from the path proposed for bacterial CcO. The H-path theory is supported by site-directed mutagenesis studies and computational analyses (4-6).

We conducted high-resolution X-ray analyses of the structures of the reaction intermediate analogs in order to refine the H-path. The H-path consists of a tandem water channel on the negative side and a hydrogen-bond network on the positive side. Bovine CcO pumps four proton equivalents per catalytic cycle. Protons are transferred by H_3O^+ through the water channel on the negative side into the proton pool linked to the hydrogen-bond network of the H-path. A gate to block backward transfer of protons is controlled by a conformational change of helix X. The gate is opened in the R-state of the reaction cycle. Four protons accumulate in the proton pool in the R-state, and the gate is subsequently closed during the following states of the reaction cycle. Each of the four protons is pumped when an electron is transferred from Cu_A to Fe_{a3}-Cu_B via Fe_a.

Among the high-resolution structures of reaction intermediates, the structure of fully oxidized CcO suggested that a peroxide moiety bridges between Fe^{3+} and Cu^{2+}. The O–O distance of 1.7 Å (7) is significantly longer than the analogous O–O bond distance in typical model compounds (1.55 Å). Because X-ray exposure could affect the long bond distance, and other structures have been proposed for the structure of the compound at the Fe_{a3}-Cu_B site, we performed a radiation damage–free structure determination at the SPring-8 angstrom compact free-electron laser (SACLA) facility. This approach was based on combined use of a large crystal and femtosecond X-ray pulses from an X-ray free-electron laser (XFEL). The X-ray

analysis indicated that the O–O distance was 1.55 Å (8). Consequently, the compound in the Fe_{a3}-Cu_B site of the fully oxidized state was deduced to be a peroxide. The femtosecond X-ray pulses of an XFEL provides time-resolved crystal structure analysis. We are currently working on a time-resolved crystal structure analysis of bovine CcO aimed at elucidating the proton pumping mechanism.

References

1. T. Tsukihara, H. Aoyama, E.Yamashita, T. Tomizaki, H. Yamaguchi, K.Shinzawa-Itoh, R. Nakashima, R. Yaono and S.Yoshikawa, Structure of Metal Sites of Oxidized Bovine Heart Cytochrome c Oxidase at 2.8 A Resolution. *Science*, **269**, 1069-1074 (1995).
2. T. Tsukihara, H. Aoyama, E.Yamashita, T. Tomizaki, H. Yamaguchi, K.Shinzawa-Itoh, R. Nakashima, R. Yaono and S.Yoshikawa, The Whole Structure of the 13-Subinit Oxidized Cytochrome c Oxidase at 2.8 A. *Science*, **272**, 1136-1144 (1996).
3. S. Yoshikawa, K. Shinzawa-Itoh,, R. Nakashima, R. Yaono, E. Yamashita, N. Inoue, M. Yao, M. Fei, C. Peters Libeu, T. Mizushima, H. Yamaguchi, T. Tomizaki and T. Tsukihara, Redox-Coupled Crystal Structural Change in Bovine Herart Cytochrome c. *Science*, 280, 1723-1729 (1998).
4. T. Tsukihara, K. Shimokata, Y. Katayama, H. Shimada, K. Muramoto, H. Aoyama, M. Mochizuki, K. Shinzawa-Itoh, E. Yamashita, M. Yao, Y. Ishimura and S. Yoshikawa. The low-spin heme of cytochrome c oxidase as the driving element of the proton-pumping process. *Proc. Natl. Acad. Sci. U.S.A.* **100**, 15303-15309 (2003).
5. K. Shimokata, Y. Katayama, H. Murayama, M. Suematsu, T. Tsukihara, K. Muramoto, S. Yoshikawa, and H. Shimada, The Proton-Pumping Pathway of Bovine Heart Cytochrome *c* Oxidase. *Proc. Natl. Acad. USA,* **104**, 4200-4205 (2007).
6. K. Kamiya, M. Boero, M. Tateno, K. Shiraishi, and A. Oshiyama, Possible Mechanism of Proton Transfer through Peptide Groups in the H-Pathway of the Bovine Cytochrome c Oxidase. *Journal of Ammerican Chemical Society*, **129**, 9663-9673 (2007).
7. H. Aoyama, K. Muramoto, K. Shinzawa-Itoh, K. Hirata, E. Yamashita, T. Tsukihara, T. Ogura and S. Yoshikawa. A peroxide bridge between Fe and Cu ions in the O2 reduction site of fully oxidized cytochrome c oxidase could suppress the proton pump. *Proc. Natl. Acad. Sci. USA*. **106**, 2165-2169 (2009).
8. Hirata K, Shinzawa-Itoh K, Yano N, Takemura S, Kato K, Hatanaka M, Muramoto K, Kawahara T, Tsukihara T, Yamashita E, Tono K, Ueno G, Hikima T, Murakami H, Inubushi Y, Yabashi M, Ishikawa T, Yamamoto M, Ogura T, Sugimoto H, Shen JR, Yoshikawa S, Ago H., Determination of damage-free crystal structure of an X-ray-sensitive protein using an XFEL. *Nat Methods.* **11**, 734-736 (2014).

<MEMO>

〈Talk 5〉
“Molecular and structural insights into opioid receptor activation”
Aashish Manglik, MD.

Title:

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Educational History:

2004-2008	B.A. in Chemistry and Biology, summa cum laude, Washington University in St. Louis, St. Louis, USA
2008-Present	M.D./Ph.D. candidate, Stanford University School of Medicine, Palo Alto, USA
2010-2014	Ph.D., Program in Biophysics, Stanford University Advisor: Brian K. Kobilka

Professional History:

2015-Present	Stanford Distinguished Faculty Fellow

Honors and Awards:

2008	Spector Award for Best Undergraduate Biology Honors Thesis, Washington University
2011	American Heart Association Predoctoral Fellowship
2013	Selected to attend the 2013 Lindau Meeting

Abstract

G protein coupled receptors (GPCRs) conduct the majority of transmembrane responses to hormones and neurotransmitters, and mediate the senses of sight, smell and taste. Among the hundreds of GPCRs within the human genome, the opioid receptors represent particularly important targets for the alleviation of pain. Despite over two centuries of medicinal chemistry since the isolation of morphine from the opium poppy, the ideal opioid analgesic devoid of key liabilities like addiction and respiratory depression remains elusive. I will describe our efforts to understand the structural and biophysical basis of opioid receptor function using X-ray crystallography as well as NMR and fluorescence spectroscopy. Additionally, I will describe the structure-guided discovery of a novel opioid analgesic with reduced side effects.

References:

1. Huang W*, Manglik A*#, Venkatakrishnan AJ, Laeremans T, Feinberg EN, Sanborn AL, Kato HE, Livingston KE, Thorsen TS, Kling R, Granier S, Gmeiner P, Husbands SM, Traynor JR, Weis WI,Steyaert J, Dror RO, Kobilka BK. Structural insights into μ-opioid receptor activation. Nature. In Press (2015)
2. Sounier R, Mas C, Steyaert J, Laeremans T, Manglik A, Huang W, Kobilka BK, Demene H, Granier, S. Propagation of conformational changes during μ-opioid receptor activation. Nature. In press (2015)
3. Manglik A*, Kim TH*, Masureel M, Altenbach C, Yang Z, Hilger D, Lerch MT, Kobilka TS, Thian FS, Aashish Manglik, CV 3 Hubbell WL, Prosser RS, Kobilka BK. Structural Insights into the Dynamic Process of β2-Adrenergic Receptor Signaling. Cell. 161(5):1101-11 (2015)
4. Granier S, Manglik A*, Kruse AC*, Kobilka TS, Thian FS, Weis WI, Kobilka BK. Structure of the δ-opioid receptor bound to naltrindole. Nature. 485(7398): 400-4 (2012).
5. Manglik A, Kruse AC, Kobilka TS, Thian FS, Mathiesen JM, Sunahara RK, Pardo L, Weis WI, Kobilka BK, Granier S. Crystal structure of the μ-opioid receptor bound to a morphinan antagonist. Nature. 485(7398): 321-6 (2012).

<MEMO>

〈Talk 6〉
“The application of Free Electron Lasers to biology: a new age of time resolved crystallography”
Gebhard F.X. Schertler, PhD.

Title:

Head of Biology and Chemistry Department, Paul Scherrer Institute (PSI), Villigen, Switzerland
Professor for Structural Biology, D-BIOL, Swiss Federal Institute of Technology (ETH) Zurich, Switzerland

Educational History:

University of Munich, PhD, 1989, Biochemistry
University of Innsbruck, Diploma, 1984, Chemistry

Research Positions:

Member of Directorial Board, Paul Scherrer Institute (PSI), 2011
Head of Department of Biology and Chemistry, PSI, 2010
Head of Laboratory of Biomolecular Research, PSI, 2010
Full Professor of Structural Biology, ETH Zürich, 2010
Group Leader, MRC-LMB Cambridge, 1998
Staff Scientist, MRC-LMB Cambridge, 1991
EMBO fellow, MRC-LMB Cambridge, 1989

Honors & Awards:

Research fellowship, Clare Hall, 1996
EMBO long term fellowship, Richard Henderson,1989

Memberships and Professional Activities:

Editor of Membrane Protein Section, Current Opinion in Structural Biology 2011
Chair, International Retinal Protein Conference 2012
Chair, Gordon Conference, Ligand Recognition and Molecular Gating, 2002
Member of Directorial Board, Paul Scherrer Institute, Villigen
Scientific Advisory Board, Heptares Pharmaceuticals
International Retinal Protein Conference
Scientific advisory committee of MAX IV Laboratory, Sweden

Abstract

Free electron lasers (FELs) are relatively new, highly brilliant and coherent x-ray sources. During the last five years their extraordinary potential in structural biology has been convincingly demonstrated. De novo structures from nanometer sized crystals as well as structures of large complexes were obtained; in addition, first room temperature structures of reaction intermediates were determined. The strongest advantage of the short x-ray pulses with extreme intensity that can be generated with a XFEL is the fact that we can observe the diffraction patterns from nano crystals before significant radiation damage can set in.

Switzerland is building its own free electron laser (SwissFEL) to support a broad range of basic research in quantum physics, material science, biology, and structure based drug discovery. It will be an excellent tool for dynamics on an atomic length scale. We will achieve major insights in quantum computing and engineering and we will gain a deeper understanding of the principles that make proteins the universal tools of life. The timing of the free electron laser pulse in the femtosecond range is coinciding with the time it takes to make or break the chemical bond. That is why XFEL free electron lasers will become the prime tools to study heterogeneous catalysis in hard matter, soft matter and enzymes. Time-resolved diffraction methods and crystallography are a major key to all these questions.

The development of fast liquid jets and the sample-saving viscose jets (e.g. LCP jets) have standardized the sample application for protein crystallography with XFELs. The development of powerful software packages to deal with millions of diffraction patterns is now enabling serial crystallography as a powerful method. This is particularly interesting for dynamic crystallography. There are currently several light-activatable systems where a reaction can be triggered with a short laser pulse and a variable delay time between the light pulse and the x-ray probe pulse. In this way, we can collect a series of data sets obtained at different time points from thousands of single crystals. This data can be analysed in a more objective way because the changing amplitudes are not influenced by radiation damage. Another very important property of this method is that we obtain still diffraction patterns. To obtain structure factors we have to reconstruct the amplitudes from many partial reflections collected by serial femtosecond crystallography (SFX). At first, this seems like a complication but for membrane protein crystals it is a real advantage. Most crystals of interesting samples like membrane proteins have significant mosaicity which leads to a smearing out of the intensities in reciprocal space. This prevented the use of Laue-methods for many systems because all intensities in the collected diffraction patterns overlap significantly. By collecting stills and having only partial reflections in the pattern, the overlap is minimized. Now, time resolved crystallography becomes possible for a large number of biological systems because the impact of mosaicity is less severe.

Therefore I think free electron lasers will open a new era of dynamic crystallography, which will lead to a new level of understanding complex biological systems.

Selected publications

1 Time-resolved structural studies with serial crystallography: A new light on retinal proteins.
Panneels V, Wu W, Tsai C, Nogly P, Rheinberger J, Jaeger K, Cicchetti G, Gati C, Kick LM, Sala L, Capitani G, Milne C, Padeste C, Pedrini B, Li XD, Standfuss J, Abela R, and Schertler GF.
Struct. Dyn. 2, 041718 (2015).

2 Lipidic cubic phase serial millisecond crystallography using synchrotron radiation
Nogly P, James D, Wang D, White TA, Zatsepin N, Shilova A, Nelson G, Liu H, Johansson L, Heymann M, Jaeger K, Metz M, Wickstrand C, Wu W, Bath P, Berntsen P, Oberthuer D, Panneels V, Cherezov V, Chapman H, Schertler GF, Neutze R, Spence J, Moraes I, Burghammer M, Standfuss J and Weierstall U.
IUCrJ 2, (2015).

3 Conformational activation of visual rhodopsin in native disc membranes
Malmerberg E, Bovee-Geurts PHM, Katona G, Deupi X, Arnlund D, Wickstrand C, Johansson LC, Westenhoff S, Nazarenko E, Schertler GF, Menzel A, de Grip WJ and Neutze R.
Sci Signal 8, ra26 (2015).

4 7 Å resolution in protein two-dimensional-crystal X-ray diffraction at Linac Coherent Light Source
Pedrini B, Tsai CJ, Capitani G, Padeste C, Hunter MS, Zatsepin NA, Barty A, Benner WH, Boutet S, Feld GK, Hau-Riege SP, Kirian RA, Kupitz C, Messerschmitt M, Ogren JI, Pardini T, Segelke B, Williams GJ, Spence JC, Abela R, Coleman M, Evans JE, Schertler GF, Frank M and Li XD.
Philos Trans R Soc Lond B Biol Sci 369, 20130500 (2014).

5 Femtosecond X-ray diffraction from two-dimensional protein crystals
Frank M, Carlson DB, Hunter MS, Williams GJ, Messerschmidt M, Zatsepin NA, Barty A, Benner WH, Chu K, Graf AT, Hau-Riege SP, Kirian RA, Padeste C, Pardini T, Pedrini B, Segelke B, Seibert MM, Spence JC, Tsai CJ, Lane SM, Li XD, Schertler GF, Boutet S, Coleman M and Evans JE.
IUCrJ 1, 95-100 (2014).

6 Crystallization scale preparation of a stable GPCR signaling complex between constitutively active rhodopsin and G-protein
Maeda S, Sun D, Singhal A, Foggetta M, Schmid G, Standfuss J, Hennig M, Dawson RJ, Veprintsev DB, Schertler GF.
PLoS One;9(6):e98714 (2014).

7 Structural basis for recognition of synaptic vesicle protein 2C by botulinum neurotoxin A
Benoit RM, Frey D, Hilbert M, Kevenaar JT, Wieser MM, Stirnimann CU, McMillan D, Ceska T, Lebon F, Jaussi R, Steinmetz MO, Schertler GF, Hoogenraad CC, Capitani G, Kammerer RA.
Nature 505, 108-111 (2014).

8 Production of GPCRs and GPCR complexes for structure determination
Maeda S and Schertler GF.
Curr Opin Struct Biol 23, 381-392 (2013).

9 Insights into congenital stationary night blindness based on the structure of G90D rhodopsin
Singhal A, Ostermaier MK, Vishnivetskiy SA, Panneels V, Homan KT, Tesmer JJ, Veprintsev D, Deupi X, Gurevich VV, Schertler GF, Standfuss J.
EMBO Rep 14, 520-526 (2013).

10 Molecular signatures of G protein-coupled receptors
Venkatakrishnan AJ, Deupi X, Lebon G, Tate CG, Schertler GF, Babu MM.
Nature; 494(7436):185-94 (2013).

11 Two distinct conformations of helix 6 observed in antagonist-bound structures of a beta1-adrenergic receptor
Moukhametzianov R, Warne T, Edwards P C, Serrano-Vega MJ, Leslie AG, Tate CG, Schertler GF.
Proc Natl Acad Sci U S A, 108:8228-8232 (2011).

12 The structural basis for agonist and partial agonist action on a beta1-adrenergic Receptor
Warne T, Moukhametzianov R, Baker JG, Nehme R, Edwards PC, Leslie AG, Schertler GF, Tate CG.
Nature, 469, 241-244 (2011).

13 Crystal structure of constitutively active rhodopsin: How an agonist can activate its GPCR
Standfuss J, Edwards PC, D'Antona A, Fransen M, Xie G, Oprian DD, Schertler GF.
Nature, 471:656-660 (2011).

14 Stabilized G protein binding site in the structure of constitutively active metarhodopsin-II
Deupi X, Edwards P, Singhal A, Nickle B, Oprian D, Schertler GF, Standfuss J.
Proc Natl Acad Sci U S A, 109, 119-124 (2011).

15 Structure of a beta1-adrenergic G-protein-coupled receptor
Warne T, Serrano-Vega MJ, Baker JG, Moukhametzianov R, Edwards PC, Henderson R, Leslie AGW, Tate CG, Schertler GF.
Nature, 454:486-491 (2008).

16 Crystal structure of a thermally stable rhodopsin mutant
Standfuss J, Xie G, Edwards P, Burghammer M, Oprian DD, Schertler GF.
J Mol Biol, 372:1179-1188 (2007).

〈Talk 7〉
"Understanding the Complete GPCR Superfamily"
Raymond C. Stevens, PhD.

Title:

Provost Professor of Biological Sciences and Chemistry, University of Southern California
Founding Director, Bridge Institute, University of Southern California, Los Angeles, California, USA
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Educational History:

1986	B.A., Chemistry, University of Southern Maine
1988	Ph.D., Organic Chemistry, University of Southern California
1989 – 1992	Postdoctoral Fellow: Chemistry Department, Harvard University

Professional History:

1992 – 1999	Assistant Professor of Chemistry, University of California, Berkeley
1994 – 1999	Assistant Professor of Neurobiology, University of California, Berkeley
1993 – 2001	Senior Principal Investigator, Lawrence Berkeley National Laboratory
1999 – 2014	Professor, Department of Integrative Structural and Computational Biology (formerly Department of Molecular Biology) and Department of Chemistry, The Scripps Research Institute
1999 – 2002	Founding Scientist and Director of Science and Technology, Syrrx.
1999 – 2005	Syrrx Scientific Advisory Board. Syrrx Acquired by Takeda Corporation March, 2005.
2002 – 2004	Founding Scientist, MemRx/Sagres Corporation. Acquired by Chiron/Novartis, July, 2004.
2008 – 2012	Founding Scientist and Board of Directors, Receptos, Inc. IPO May, 2013.
2011 – 2013	Chinese Academy of Sciences Senior Distinguished Visiting Professor, Shanghai Institute of Materia Medica, Shanghai, China
2011 – present	Founding Scientist and Chairman Board of Directors, RuiYi, Inc (Shanghai, China).
2012 – present	Founding Director, iHuman Institute (Shanghai, China)
2014 – present	Provost Professor of Biological Sciences and Chemistry, University of Southern California, Dornsife College of Letters, Arts and Sciences; Professor of Physiology and Biophysics, Keck School of Medicine; Professor of Chemical Engineering and Materials Science, Viterbi School of Engineering
2014 – present	Founding Director, The Bridge Institute, University of Southern California

Honors & Awards:

1987 Walter C. Hamilton Memorial Scholarship for research in neutron diffraction
1987 International Travel Award from U.S. National Committee for Crystallography and National Science Foundation
1989 National Institute of Health Postdoctoral Fellowship
1992 Sidhu Award from Pittsburgh Diffraction Society
1994 National Science Foundation Young Investigator Award
1994 Beckman Foundation Young Investigator Award
1995 Lawrence Berkeley Laboratory Outstanding Performance Award
1997 Society of Bioinorganic Chemistry Award, "Metals in Biology" Gordon Conference
2002 R&D Magazine R&D 100 Award
2003 Jouan Robotics Award
2005 Distinguished Alumni Award, University of Southern California
2008 Honorary Doctorate of Science, University of Southern Maine
2012 Qian Ren Award, Chinese Academy of Sciences (Shanghai, China)
2012 Max T. Rogers Distinguished Lectureship in Chemistry, Michigan State University
2013 National PKU Alliance, Outstanding Service Award
2014 Distinguished Lecturer, The 25th Annual Frontiers in Chemistry Symposium, The Scripps Research Institute
2014 Zhao Chenggu SIMM Award for International Drug Discovery

Abstract

G protein-coupled receptors (GPCRs) constitute one of the largest protein families in the human genome and play essential roles in normal cell processes, most notably in cell signaling.

The human GPCR family contains of more than 800 members, recognizes thousands of different ligands and activates a number of signaling pathways through interactions with a small number of binding partners. Unfortunately, an understanding of these receptors has been hampered by a lack of solid structure-function data.

After 20 years of technology innovation by researchers globally, the benefits of the technology efforts are now paying off, particularly in the area of understanding human GPCRs. Delivering GPCR structure-function data in close collaboration with the community on specific receptor systems is of immense value to the basic science community interested in cell signaling and molecular recognition, as well as the applied science community interested in drug discovery.

To date, we have determined high resolution structures of 19 of the 30 (19 of the 21 human) GPCRs– notably the adrenergic, adenosine, angiotensin, chemokine, dopamine, glucagon, glutamate, histamine, lysophosphatidic, opioid, purinergic, serotonin, sphingolipid, and smoothened receptors, and representing class A, B, C and F receptor systems with new structures continuing to be deposited at a strong rate.

Crystallographic studies alone are only a part of the picture, and we have been following this work up with NMR, HDX, EM, and other biophysical techniques to understand the activation mechanism, including examining receptor-intracellular partner complexes such as the first view of the rhodopsin-arrestin complex structure. The use of the technology platform for drug discovery is now being established through an industry-academia open source GPCR Consortium, Receptos, a small molecule GPCR drug discovery company, and RuiYi, an antibody-GPCR company.

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Closing Remarks

Tomitake Tsukihara,PhD.

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Foundation Overview

Since its establishment in 1990, the foundation has enjoyed success and developed as an unprecedented foundation in Japan, for which universities/research institutions, pharmaceutical companies, and the like jointly engage in endeavors and enterprises. As of April 2010, the foundation took on status as a Public Interest Incorporated Foundation, legally certified as a facility engaging in public services, effectively further raising expectations toward its activities. The foundation primarily develops individuals and subsidizes research in the life science field. These activities are conducted using management gains from assets of over 4 billion yen including the foundation's basic fund and Specified Assets as well as endowments by contributors who are in agreement with the focus of the public service efforts in which the foundation engages. It also uses subsidies from the government to actively engage in activities to support practical applications of research, based on the underlying efforts of industry-academia collaborations.

These fruits should be borne via the steady accumulation of rich and diverse research conducted on a solid scientific base.

Our foundation was established in 1990 in the Kita-Osaka (northern Osaka), Senri region, in the middle of Greater Osaka (including Kyoto and Kobe), which features a concentration of universities/research institutions and pharmaceutical companies, via an integration of human resources from industry/academia/government and funds, for the purpose of creating a life science hub in Japan.

Since its establishment, the foundation has garnered not only domestic but also international-level participation.

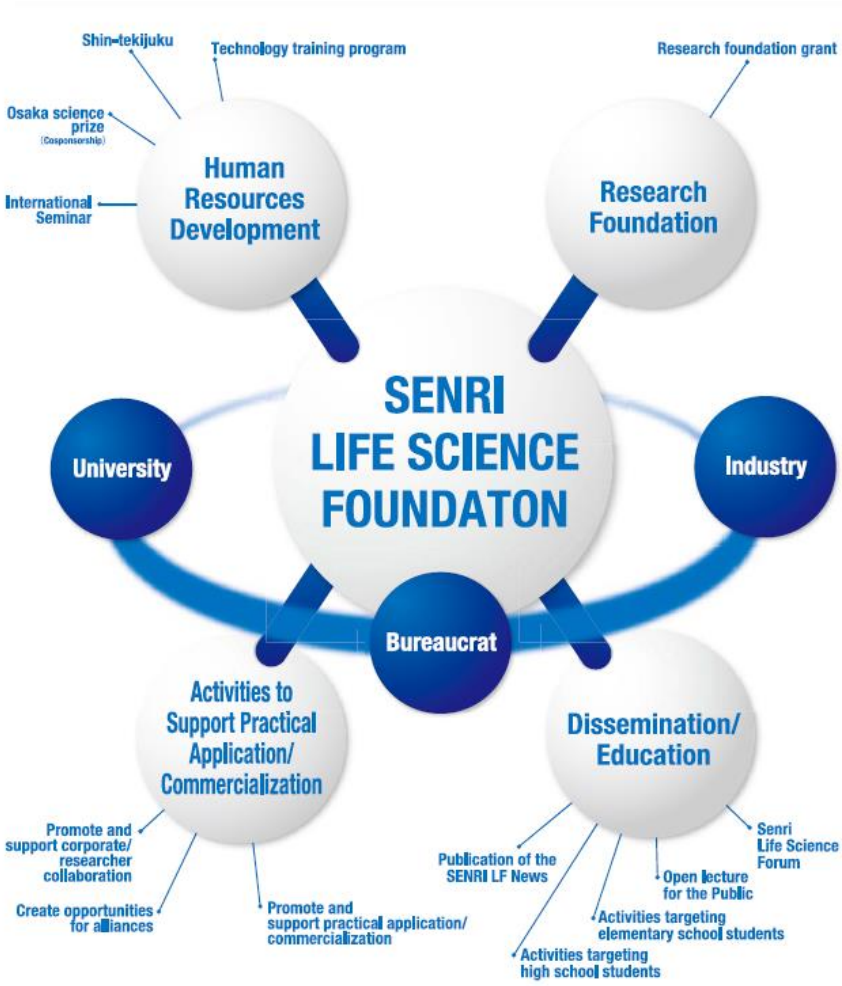
As a "center for intelligent exchange" in life sciences, it has contributed to the advancement and promotion of life sciences through active efforts, e.g., developing excellent researchers, subsidizing and aiding research, supporting practical applications of research through exchanges with industry, and educational/dissemination activities.

Looking ahead to the future, we pledge to further enrich these activities, contributing to society via the advancement and promotion of life sciences.

We would greatly appreciate your active and enthusiastic cooperation.

President of
Senri Life Science Foundation

Tadamitsu Kishimoto



SENRI LIFE SCIENCE FOUNDATION INITIATIVE

Senri Life Science Foundation

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