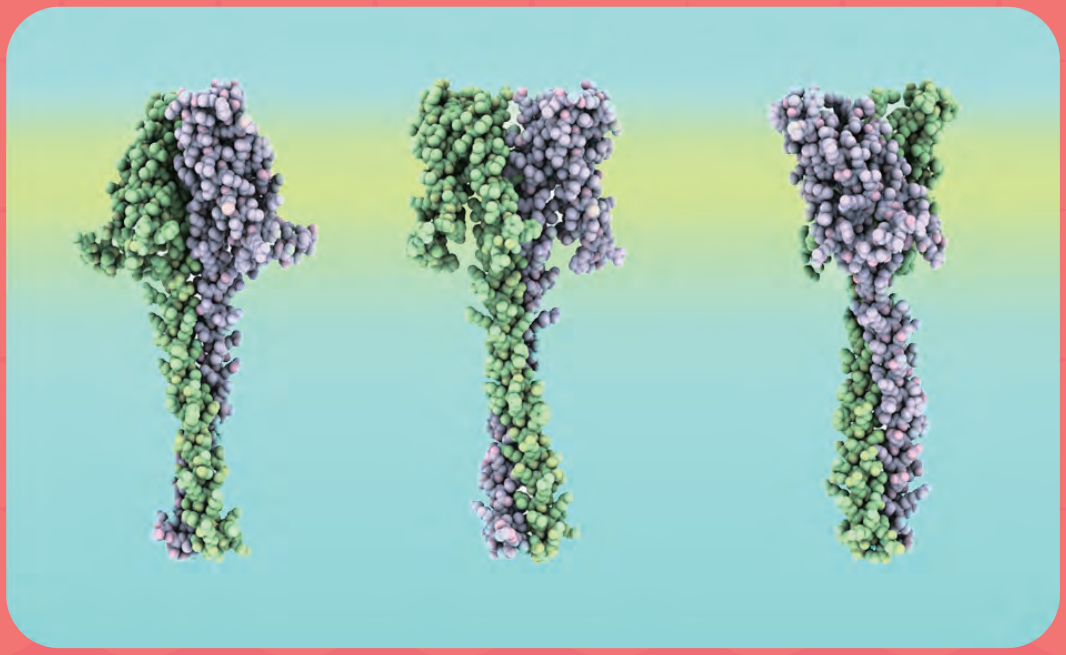
Prospectus
Institute for Protein Research
Osaka University

2015



INSTITUTE for PROTEIN RESEARCH

Contents

Greetings from Director

Haruki Nakamura, D.Sci., Director

The machinery of life on the earth has been made of proteins, which are expressed from the corresponding genes in genome, and the complicated molecular activities are provided by huge number of interactions among those proteins. In 1958, Institute for Protein Research (IPR) was founded by members in Faculty of Science and Medical school of Osaka University, covering different fields of sciences, such as chemistry, physics, biology and medicine. Since then, protein research in IPR has made a remarkable progress by elucidating structures and functions of proteins, and by understanding their biological roles from the molecular level to the cellular and the higher levels. Through wide and strong supports from the community, IPR has expanded over time after 57 years. Now, it has four divisions (16 labs) with an attached center, Research Center for State-of-the-Art Functional Protein Analysis (7 labs), which develops its original techniques and applies them to reveal protein structures and functions.

IPR had worked as an inter-university joint-use facility attached to Osaka University since its foundation. In April 2010, IPR was qualified as one of the Joint Usage/Research Centers in Japan by MEXT, Ministry of Education, Culture, Sports, Science and Technology in Japan. In particular, IPR offers the usages of its own synchrotron beam line at SPring-8 and of the Nuclear Magnetic Resonance (NMR) spectrometers with ultra-high sensitivities, to domestic and foreign protein researchers. In addition, IPR has constructed protein structural database (PDB: Protein Data Bank) as PDBj (PDB Japan), one of the four members of the wwPDB (worldwide PDB), by annotating the deposited data from structural biologists in Asian and Oceania region and by providing several original services and derived databases. PDBj-BMRB also constructs NMR experimental database, collaborating with BMRB (BioMagResBank) in U.S.A. IPR has also organized many international collaborative researches with foreign protein scientists.

Professors and staffs in IPR (about 40 members) work hard for their own researches, as well as for educational activities to undergraduate students at Faculty of Science and that of Medicine, and Ph. D. students at Graduate school of Science, Medicine, and Frontier Biosciences. From those Faculties and Graduate schools, nearly 100 students always study at laboratories in IPR, and about 70 postdoctoral fellows make their own original investigations with various national and international research projects. Those students and postdocs gather from many different places in the world, and global human interactions are common in IPR.

Paradigm of protein research has been rapidly changed from previous analysis of individual protein molecules to understanding of the protein complex that expresses biological activities and to revealing the biological information from protein interactions, still based on the structures and functions of individual proteins. Namely, protein structural analysis is not a goal as the previous structural biology, but it is a starting point for a novel scientific field, Structural Life Science, where life science is investigated at multi-scale based on the protein network. IPR is going forward to this Structural Life Science as the basic science, promoting the principle of Osaka University, "To discover the true essence of things". In addition, IPR is going to cooperate with the public and the industries through activities at Open Space Laboratory for Advanced Protein Science where an industry researcher is invited as a guest professor, and support program for industries with database construction and its release to the public. All of those activities will appear on our web page (http://www.protein.osaka-u.ac.jp).

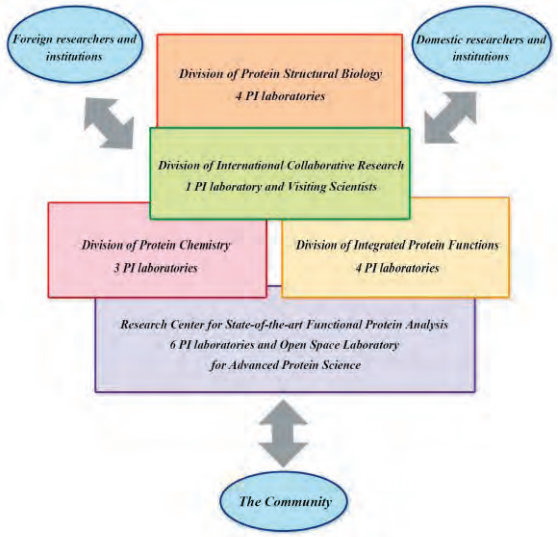
Concept and Future

The processes of life, mediated by a large variety of proteins, are very complex. Elucidation of these processes through molecular studies of proteins can be well achieved by efficient cooperation of researchers in various fields of natural sciences. Another requisite is the establishment of suitable infrastructures that allow close collaborations among scientists across the country. The Institute for Protein Research (IPR) was founded as a joint-use research organization attached to Osaka University to fulfill these needs, and thus to play a central role in protein science in Japan. Now, IPR works as one of the Joint Usage/Research Centers authorized by Japanese Government.

Thus, the mission of IPR does not change at all during the long history, and it is summarized as the following two concepts:

1) With tight collaborations by researchers in IPR having various backgrounds such as chemistry, physics, biology and medicine, basic studies are performed on the structure and function of proteins and their biological significance at the molecular level, as well as at the cellular level.

2) As the Joint Usage/Research Center, IPR provides the resources for research, databases such as PDB, and scientific communication for domestic and international collaborational studies, promoting protein science for the scientific community and society.



Based on the above mission, IPR has so far made various projects on structural biology, neurobiology, proteomics, and molecular and cellular biology, and produced many excellent results. Although IPR started as a domestic center, it is now widely recognized as an international center of excellence for protein research. For instance, IPR operates the Worldwide Protein Data Bank (wwPDB) as one of four worldwide centers, mainly covering Asia-Oceania region. Because of its high level scientific activity, it has attracted many researchers from abroad and will continue to do so in the future. IPR will continue to make essential contributions to revealing the structure and function of proteins and their networks for the elucidation of life.

History

Osaka University was active in the study of proteins and enzymes since its foundation in 1931, and it was a long-standing desire of the university authorities to promote further this facet of the university's activities by establishing a research institute specialized for protein science. In 1955 an official plan was drafted to establish such an institute as a part of Osaka University and submitted to the Ministry of Education, Science and Culture. The Ministry agreed to open a new laboratory for organic chemistry of proteins and amino acids in the Faculty of Science. The new laboratory was opened in 1956, and Professor Shiro Akabori, who had played a pivotal role in protein research, was appointed as its supervisor.

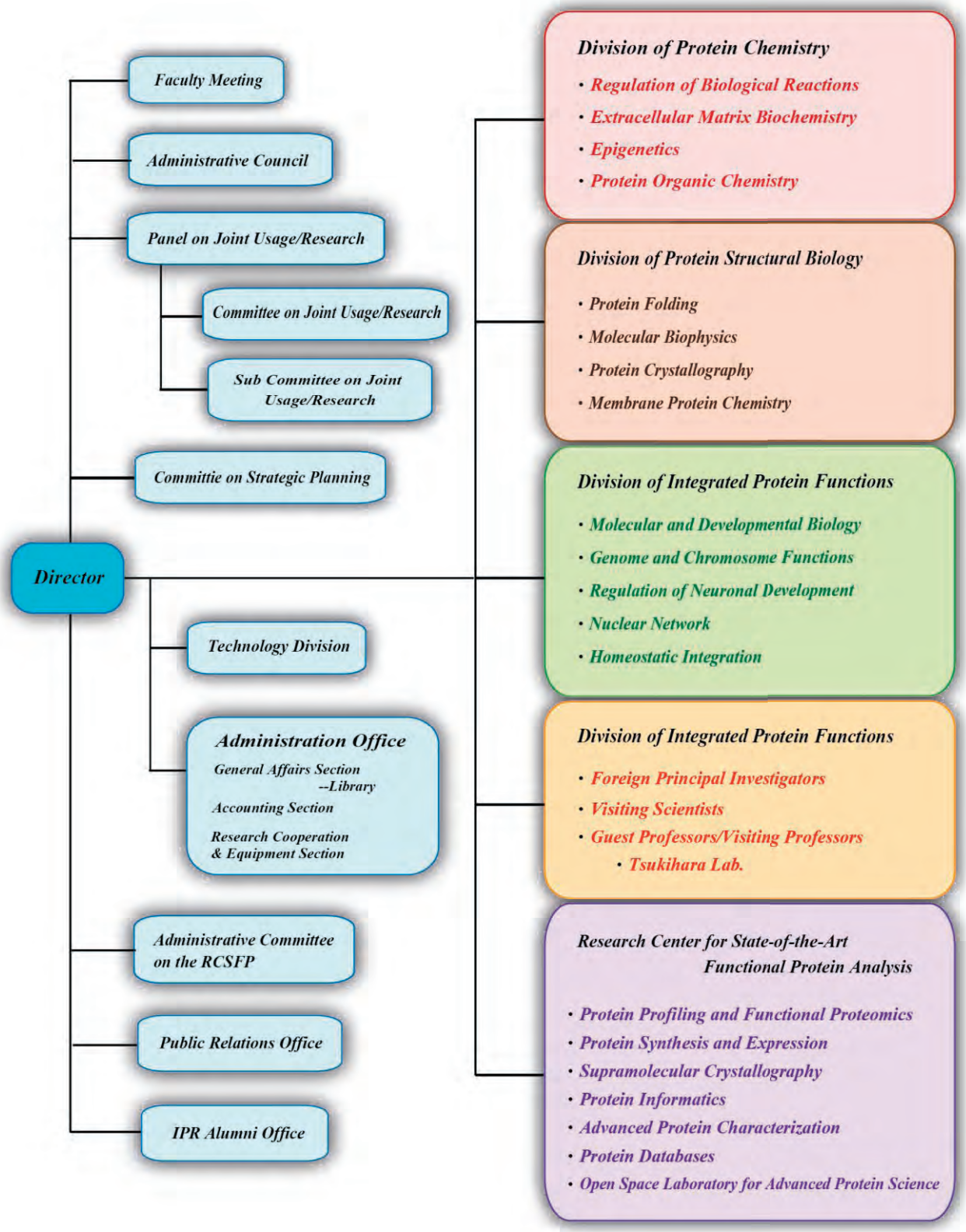
In the meantime, among scientists in the relevant fields had continuously grown a strong desire for the establishment of a central institute for protein research, with the aim of facilitating close cooperation among researchers from a wide variety of scientific fields. In 1957, the Science Council of Japan urged the Government to

consider the foundation of such an institute somewhere in the country. The Government decided to establish a research institute for protein science attached to Osaka University. The Institute for Protein Research (IPR) was thus founded formally on April 1, 1958, as a part of Osaka University, and Professor Shiro Akabori was appointed as its first director. The IPR has developed significantly in terms of its scientific activity and infrastructures. Now, the IPR comprises four divisions with 14 laboratories and an attached research center (Research Center for State-of-the-art Functional Protein Analysis) with 7 laboratories, serving as a joint usage/research institute for the community in the fields of protein and related sciences.

Chronological table

1956	Set up of a new laboratory in Faculty of Science, Osaka University, for organic chemical studies of proteins and amino acids (the forerunner of Institute for Protein Research) supervised by Prof. Shiro Akabori.
1958	Establishment of Institute for Protein Research as a Joint-use Research Organization, composed of three Divisions (Organic Chemistry, Physical Chemistry and Protein Metabolism). Advisory Committee on Administration was also founded.
1959	Divisions of Enzymology and Protein Crystallography were added.
1960	Divisions of Protein Chemistry, Physiology and Protein Biosynthesis were added.
1961	The main building (4,130 m^2) was completed in the former campus at Nakanoshima.
1962	Set up of the Peptide Center
1964	Division of Molecular Biophysics was added.
1965	Set up of a Branch Division (569 m^2) in Torii Memorial Hall
1967	Division of Plasma Proteins was added.
1971	Main building (7,873 m^2) of Institute for Protein Research was completed at Suita Campus.
1972	Relocation to new building at Suita campus
1977	Division of Plasma Proteins was renamed to Division of Regulation of Macromlecular Functions
1978	Establishment of Crystallographic Research Center
1979	Buildings of Research Center for Crystal analysis (1,505 m^2) and NMR Research Laboratory (267 m^2) were completed.
1988	Reorganization of the Peptide Center and Crystallographic Research Center as Research Center for Protein Engineering.
1998	Establishment of Center for Structural Biology
2002	Establishment of Research Center for Structural and Functional Proteomics
2004	Transformed into the Research Institute of Japanese national universities by the National University Corporation Law
2005	Reorganization of the Research Divisions to 4 Research Divisions with 12 Laboratories. Laboratory of Foreign Principal Investigators and Endowed Research Division of Molecular Recognition by Takara Bio Inc. were added.
2006	Set up of Endowed Research Division of Disease Proteomics by Shimadzu
2008	Building of Collaborative Research Facility (1,149 m^2) was completed.
2009	Construction of Main building for Earthquake-resistance was completed.
2010	Certified as Joint Usage/Research Center by MEXT.
2012	Establishment of Research Center for State-of-the-Art Functional Protein Analysis.

Organization



Former Directors

1st	*Shiro AKABORI*	1 April 1958	～	30 November 1961
2nd	*Toshizo ISEMURA*	1 December 1961	～	30 November 1965
3rd	*Tomoji SUZUKI*	1 December 1965	～	14 August 1969
4th	*Kouzo NARITA*	15 August 1969	～	14 August 1971
5th	*Masao KAKUDO*	15 August 1971	～	1 April 1982
6th	*Yoshiharu IZUMI*	2 April 1982	～	31 March 1985
7th	*Ryo SATO*	1 April 1985	～	31 March 1987
8th	*Takekazu HORIO*	1 April 1987	～	31 March 1989
9th	*Yukiteru KATSUBE*	1 April 1989	～	31 March 1993
10th	*Hachiro NAKAGAWA*	1 April 1993	～	31 March 1995
11th	*Fumio SAKIYAMA*	1 April 1995	～	31 March 1997
12th	*Yoshimasa KYOGOKU*	1 April 1997	～	31 March 1999
13th	*Yasutsugu SHIMONISHI*	1 April 1999	～	31 March 2000
14th	*Katsuya NAGAI*	1 April 2000	～	31 March 2004
15th	*Hideo AKUTSU*	1 April 2004	～	31 March 2006
16th	*Tomitake TSUKIHARA*	1 April 2006	～	31 March 2008
17th	*Saburo AIMOTO*	1 April 2008	～	31 March 2010
18th	*Toshiharu HASE*	1 April 2010	～	31 March 2014
19th	*Haruki NAKAMURA*	1 April 2014	～	Present

Professors Emeriti

Yoshiharu IZUMI, D. Sci.
Hachiro NAKAGAWA, M. D., D. Med.
Toshio TAKAGI, D. Sci.
Yasutsugu SHIMONISHI, D. Sci.
Hideo AKUTSU, D. Sci.
Yukiteru KATSUBE, D. Sci.
Akira ASANO, D. Sci.
Fumio SAKIYAMA, D. Sci.
Katsuya NAGAI, M. D., D. Med.
Tomitake TSUKIHARA, D. Sci.

Administrative Council

As of 1 April 2015

Outside of Osaka University

Professor Fuyuki ISHIKAWA	*Graduate School of Biostudies, Kyoto University*
Professor Tohru KATAOKA	*Graduate School of Medicine, Kobe University*
Professor Akihiko NAKANO	*Graduate School of Science, The University of Tokyo*
Director Yoichi NABESHIMA	*Foundation for Biomedical Research and Innovation*
Professor Yoshinori FUJIYOSHI	*Graduate School of Pharmaceutical Sciences・Cellular and Structural physiology Institute, Nagoya University*
Professor Kiyoshi KITA	*The Institute of Medical Science, The University of Tokyo*
Professor Kiyoko FUKAMI	*School of Life Science, Tokyo University of Pharmacy and Life Sciences*

Inside of Osaka University

Professor Koichi FUKASE	*Graduate School of Science*
Professor Tsuyoshi INOUE	*Graduate School of Engineering*
Professor Akira KIKUCHI	*Graduate School of Medicine*
Professor Masato OKADA	*Research Institute for Microbial Diseases, Osaka University*
Professor Kenji NAGAI	*Institute of Scientific and Industrial Research*

In IPR

Professor Atsushi NAKAGAWA	*Institute for Protein Research*
Professor Toshifumi TAKAO	*Institute for Protein Research*

Staff List

Director	*Professor*	*Haruki NAKAMURA, D. Sci.*
Vice Directors	*Professor*	*Atsushi NAKAGAWA, D. Sci.*
	Professor	*Akira SHINOHARA, D. Sci.*
Director of the Research Center		*Professor Junichi TAKAGI, D. Sci.*

Division of Protein Chemistry

Laboratory of Regulation of Biological Reactions

Professor	*Toshiharu HASE, D. Sci.*
Associate Professor	*Masato NAKAI, D. Sci.*
Assistant Professor	*Yoko KIMATA-ARIGA, Ph. D.*

Laboratory of Extracellular Matrix Biochemistry

Professor	*Kiyotoshi SEKIGUCHI, D. Sci.*
Assistant Professor	*Masashi YAMADA, Ph. D.*
Technical Staff	*Naoko NORIOKA, Ph. D.*

Laboratory of Epigenetics

Professor	*Shoji TAJIMA, D. Sci.*
Associate Professor	*Isao SUETAKE, Ph. D.*
Guest Associate Professor	*Nobuyasu MAKI, Ph. D.*
Assistant Professor	*Hironobu KIMURA, Ph. D.*
Technical Staff	*Naoyuki ABE, M. Sci.*

Laboratory of Protein Organic Chemistry

Professor	*Hironobu HOJO, D. Sci.*
Associate Professor	*Toru KAWAKAMI, Ph. D.*
Associate Professor	*Takeshi SATO, Ph. D.*
Assistant Professor	*Yuya, ASAHINA, Ph. D.*

Division of Protein Structural Biology

Laboratory of Protein Folding

Professor	*Yuji GOTO, D. Sci.*
Associate professor	*Young-Ho LEE, Ph. D.*
Assistant Professor	*Masatomo SO, Ph. D.*

Laboratory of Molecular Biophysics

Professor	*Toshimichi FUJIWARA, D. Sci.*
Visiting Professor	*Akira NAITO, D. Sci.*
Associate Professor	*Chojiro KOJIMA, Ph. D.*
Assistant Professor	*Yoh MATSUKI, Ph. D.*
Assistant Professor	*Toshihiko SUGIKI, Ph. D*

Laboratory of Protein Crystallography

Professor	*Genji KURISU, Ph. D.*
Associate Professor	*Hideaki TANAKA, Ph. D.*
Assistant Professor	*Risa MUTO, Ph. D.*

Laboratory of Membrane Protein Chemistry

Independent Associate Professor	*Joji MIMA, Ph. D.*

Division of Integrated Protein Functions

Laboratory of Genome and Chromosome Functions

Professor	*Akira SHINOHARA, D. Sci.*
Associate Professor	*Miki SHINOHARA, Ph. D.*
	Masahiro TERASAWA, Ph. D.

Laboratory of Regulation of Neuronal Development

Professor	*Kazuaki YOSHIKAWA, M.D., D. Med.*
Assistant Professor	*Koichi HASEGAWA, Ph. D.*
Assistant Professor	*Kazushiro FUJIWARA, Ph. D.*

Laboratory for Molecular and Developmental Biology

Professor	*Takahisa FURUKAWA, M.D., D. Med.*
Associate Professor	*Yoshihiro OMORI, Ph. D.*
Assistant Professor	*Rikako SANUKI, Ph. D.*
Technical Staff	*Toshinori TSUJI*

Laboratory of Nuclear Network

Independent Associate Professor	*Junko KANOH, Ph. D.*

Laboratory of Homeostatic Integration

Associate Professor	*Nobuaki OKUMURA, Ph. D.*

Division of International Collaborative Research

Laboratory of Foreign PI

Visiting Professor	*Matthias RÖGNER, Ph. D.*
Visiting Professor	*Thomas HAPPE, Ph. D.*
Specially Appointed Associate Professor	*Damien R. HALL, Ph.D.*

Laboratory of Visiting Scientists

Guest Professor	*Toshio YAMAZAKI, D. Sci.*

Laboratory of Guest Professors/Visiting Professors

Tsukihara Laboratory

Visiting Professor	*Tomitake TSUKIHARA, D. Sci.*

Research Center for State-of-the-art Functional Protein Analysis

Laboratory of Protein Profiling and Functional Proteomics

Professor	*Toshifumi TAKAO, D. Sci.*
Specially Appointed Assistant Professor	*Caroline D. REREIRA, Ph. D.*

Laboratory of Protein Synthesis and Expression

Professor	*Junichi TAKAGI, D. Sci.*
Associate Professor	*Kenji IWASAKI, Ph. D.*
Assistant Professor	*Yu KITAGO, Ph. D.*
Specially Appointed Assistant Professor	*Yukiko MATSUNAGA, Ph. D.*
Specially Appointed Assistant Professor	*Masataka UMITSU, Ph.D.*
Technical Staff	*Keiko KAWAKAMI*

Laboratory of Supramolecular Crystallography

Professor	*Atsushi NAKAGAWA, D. Sci.*
Associate Professor	*Mamoru SUZUKI, Ph. D.*
Assistant Professor	*Mayumi AMANO, Ph.D.*
Assistant Professor	*Eiki YAMASHITA, Ph. D.*
Specially Appointed Assistant Professor	*Kohei TAKESHITA, Ph. D.*
Specially Appointed Assistant Professor	*Akifumi HIGASHIURA, Ph. D.*

Laboratory of Protein Informatics

Professor	*Haruki NAKAMURA, D. Sci.*
Associate Professor	*Akira KINJO, Ph. D.*
Assistant Professor	*Yuko TSUCHIYA, Ph. D.*
Visiting Professor	*Junichi HIGO, D. Sci.*
Guest Associate Professor	*Takeshi KAWABATA, Ph.D.*
Guest Associate Professor	*Narutoshi KAMIYA, Ph. D.*
Guest Associate Professor	*Ikuo FUKUDA, Ph.D*
Technical Staff	*Takashi KOSADA, M. Sci.*

Laboratory of Advanced Protein Characterization

Professor	*Atsushi NAKAGAWA, D. Sci.*
Professor	*Junichi TAKAGI, D. Sci.*
Professor	*Toshifumi TAKAO, D. Sci.*
Associate Professor	*Kenji IWASAKI, Ph. D.*
Associate Professor	*Takeshi SATO, Ph. D.*
Assistant Professor	*Eiki YAMASHITA, Ph. D.*
Assistant Professor	*Naotoshi MIMURA, D. Sci.*
Assistant Professor	*Toshihiko SUGIKI, Ph.D.*
Assistant Professor	*Risa MUTO, Ph.D.*
Specially Appointed Assistant Professor	*Akifumi HIGASHIURA, Ph. D.*
Technical Staff	*Keiko KAWAKAMI*
Technical Staff	*Naoko NORIOKA, Ph. D.*
Technical Staff	*Naoyuki ABE, M. Sci.*

Laboratory of Protein Databases

Professor	*Haruki NAKAMURA, D. Sci.*
Professor	*Toshimichi FUJIWARA, D. Sci.*
Professor	*Kiyotoshi SEKIGUCHI, D. Sci.*
Associate Professor	*Akira KINJO, Ph. D.*
Associate Professor	*Chojiro KOJIMA, Ph. D.*
Technical Staff	*Takashi KOSADA, M. Sci.*
Technical Staff	*Reiko YAMASHITA*

Open Space Laboratory for Advanced Protein Science

Visiting Professor	*Midori UEMURA,*

Administration Office

Head	*Ichiro YASUGUCHI*

General Affairs Section

Chief	*Shinichi MATSUNAGA*
Deputy Chief	*Yoko TANAKA*
Clerk	*Noriko YOSHIMURA*

Accounting Section

Chief	*Takashi SHIRAI*
Deputy Chief	*Yasuhiro NAKATA*
Deputy Chief	*Hiroharu MICHIKI*
Clerk	*Yutsuki KITADA*
Clerk	*Hiroko NAKATA*

Research Cooperation & Equipment Section

Chief	*Toshizumi MATSUSHITA*
Deputy Chief	*Sadahiro KURIBAYASHI*
Deputy Chief	*Naoko ARAKI*
Clerk	*Kazuaki NAGAMI*

Staff & Students /Closing Accounts /Education & Research Activities

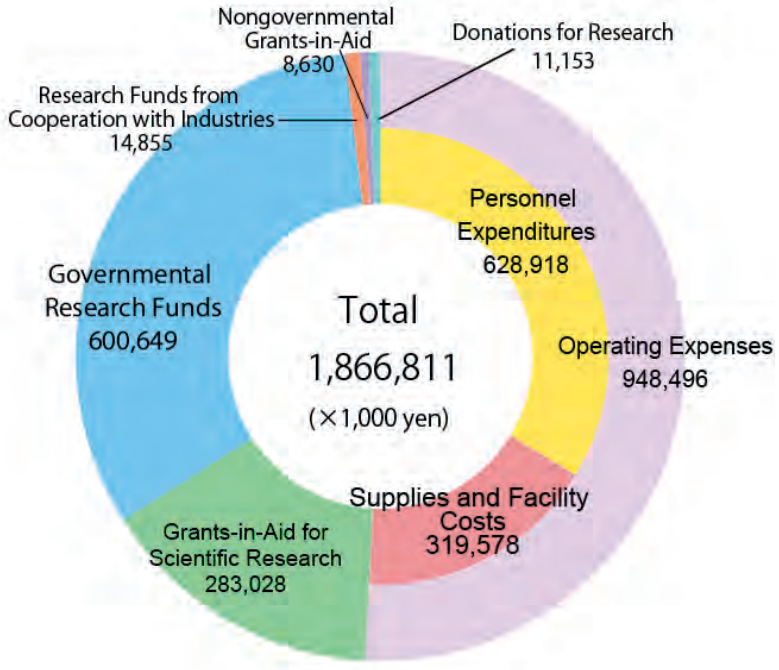
Number of Members

As of 1 April 2015

Staff	*Professor*	14
	Visiting(Guest) Professor	5
	Associate Professor	13
	Visiting(Guest) Associate Professor	3
	Associate Professor (Lecturer)	2
	Assistant Professor	16
	Specially Appointed Assistant Professor	5
	Technical Assistant	6
	Administrative Staff	14
	Technical Supporter	25
	Administrative Assistant	16
	Total	119
Researcher	*Post Doctoral Fellow*	66
	Foreign Post Doctoral Fellow	2
	JSPS Postdoctoral Fellow	10
	Joint Research Collaborator	136
	(Regular: 59 Beamline: 69 NMR:10)	
	International Joint Research Collaborator	12
	Total	226
Student	*Undergraduate Student*	10
	Graduate Student(doctor course)	37
	Graduate Student(master course)	56
	Research Student	4
		107

Closing Accounts

The Year 2014



Periodical Publications

1. *Memoirs of the Institute for Protein Research, Osaka University (Annual)*
2. *Annual Report of the Institute for Protein Research (Annual)*

Education Activities

Members of this Institute participate in graduate course education in cooperation with the Graduate Schools of Science, Medicine, and Frontier Biosciences.

Course in Charge

Biological Science ,Graduate School of Science

Professor	Associate Professor	Assistant Professor
Toshiharu HASE	*Toru KAWAKAMI*	*Yoko KIMATA-ARIGA*
Kiyotoshi SEKIGUCHI	*Masato NAKAI*	*Masashi YAMADA*
Shoji TAJIMA	*Isao SUETAKE*	*Hironobu KIMURA*
Yuji GOTO	*Chojiro KOJIMA*	*Yoh MATSUKI*
Toshimichi FUJIWARA	*Miki SHINOHARA*	*Rikako SANUKI*
Genji KURISU	*Yoshihiro OMORI*	*Koichi HASEGAWA*
Takahisa FURUKAWA	*Nobuaki OKUMURA*	*Kazushiro FUJIWARA*
Akira SHINOHARA	*Kenji IWASAKI*	*Yu KITAGO*
Kazuaki YOSHIKAWA	*Mamoru SUZUKI*	*Eiki YAMASHITA*
Toshifumi TAKAO	*Akira KINJO*	
Junichi TAKAGI	*Junko KANOH*	
Atsushi NAKAGAWA	*Joji MIMA*	
Haruki NAKAMURA	*Hideaki TANAKA*	Specially Appointed Assistant Professor
Hironobu HOJO	*Young-Ho LEE*	*Akifumi HIGASHIURA*
	Takeshi SATO	

Chemistry, Graduate School of Science

Professor	Associate Professor	Assistant Professor
Toshimichi FUJIWARA	*Toru KAWAKAMI*	*Yoh MATSUKI*
Toshifumi TAKAO	*Chojiro KOJIMA*	*Yuya ASAHINA*
Haruki NAKAMURA	*Akira KINJO*	
Hironobu HOJO	*Takeshi SATO*	

Macromolecular Science, Graduate School of Science

Professor	Associate Professor	Assistant Professor
Yuji GOTO	*Mamoru SUZUKI*	*Eiki YAMASHITA*
Genji KURISU	*Hideaki TANAKA*	
Atsushi NAKAGAWA	*Young-Ho LEE*	Specially Appointed Assistant Professor
		Akifumi HIGASHIURA

Medical Biosignaling, Graduate School of Medicine

Professor	Assistant Professor
Kazuaki YOSHIKAWA	*Koichi HASEGAWA*
Takahisa FURUKAWA	*Kazushiro FUJIWARA*

Graduate School of Frontier Biosciences

Professor	Associate Professor
Toshifumi TAKAO	*Mamoru SUZUKI*
Junichi TAKAGI	*Kenji IWASAKI*
Atsushi NAKAGAWA	*Akira KINJO*
Haruki NAKAMURA	
Takahisa FURUKAWA	

Number of Students

	Undergraduate	Master Course	Doctor Course
School of Science	7	46	31
School of Medicine	3	1	1
Graduate School of Frontier Biosciences	0	5	3

Research Activities

Number of Publications

2010 ～2014

	2010	2011	2012	2013	2014
Original Paper	132	127	128	128	108
Review	23	22	27	31	20
Presentation at Meeting	327	278	279	277	306

Large Project Researches

No.	Grant / Program Name / Subject	(study period)

As the Project Leader

1	CREST, Japan Science and Technology Agency Structural studies of the proteins working in novel cell membrane potential signal	2014-2019
2	Program for coordination toward integration of related databases, Japan Science and Technology Agency Enhancement of functionality and integrative management of PDB	2014-2016
3	Japan Science and Technology Agency/Research Center Network for Realization of Regenerative Medicine Feeder-free culture substrates for stem cells	2013-2017
4	JST-CREST, Japan Science and Technology Agency Structural Studies on the transient macromolecular complexes formed upon photoacclimation	2013-2018
5	Grant-in-Aid for Scientific Research (A), Japan Society for the Promotion of Science Elucidation of the atomic structures and molecular networks for understanding of infection and multification mechanism of Reoviridae	2013-2015
6	Platform for Drug Discovery, Informatics, and Structural Life Science: correlative structural analysis Development and application of a correlative structural analysis by a primary use of EM	2012-2014
7	X-ray Free Electron Laser Priority Strategy Program, Ministry of Education, Culture, Sports, Science and Technology Development of X-ray single particle analysis technique for structure determination of biological macromolecular assemblies using spherical particle	2012-2013
8	Grant-in-Aid for Scientific Research on Innovative Areas, The Ministry of Education, Culture, Sports, Science and Technology Structural basis for the cell-cell communication at the neuro-immune interface	2012-2016
9	Platform for Drug Discovery, Informatics, and Structural Life Science Project Development of highly efficient recombinant protein production pipeline using mammalian expression system	2012-2016

10	Strategic research program for XFEL science Structural analyses of multi-module proteins using XFEL	2012-2016
11	Grant-in-Aid for Scientific Research on Innovative Areas, The Ministry of Education, Culture, Sports, Science and Technology Integral Understanding of the Mechanism of Transcription Cycle through Quantitative, High-resoution Approaches	2012-2016
12	Grant-in-Aid for Young Scientists (A), Japan Society for the Promotion of Science, Japan Society for the Promotion of Science Elucidation of the vault function based on its whole structure	2012-2014
13	X-ray Free Electron Laser Priority Strategy Program, Ministry of Education, Culture, Sports, Science and Technology Development of X-ray single particle analysis technique for structure determination of biological macromolecular assemblies using spherical particle	2012-2013
14	Grant-in-Aid for Scientific Research on Innovative Areas, The Ministry of Education, Culture, Sports, Science and Technology Genome-wide networks via non-coding DNA regions	2011-2015
15	Program for coordination toward integration of related databases, Japan Science and Technology Agency Global Construction and Integration of PDB	2011-2013
16	Grant-in-Aid for Scientific Research on Innovative Areas, The Ministry of Education, Culture, Sports, Science and Technology Systematic analysis of Genome adaptation	2010-2014
17	Grant-in-Aid for Scientific Research on Innovative Areas, The Ministry of Education, Culture, Sports, Science and Technology Structure analysis of nuclear transport machinery and improvement of data collection system using synchrotron radiation	2010-2014
18	Funding Program for Next Generation World-Leading Reseachers, Japan Society for the Promotion of Science Identification of the molecule regulating intracellular Mg^{2+} and its importance in cancer malignancy	2010-2013
19	Funding Program for Next Generation World-Leading Researchers, Japan Society for the Promotion of Science Structural analysis of the entire electron transfer network of photosynthetic energy transduction for light-driven bio-hydrogen production	2010-2013
20	Funding Program for Next Generation World-Leading Reseachers, Japan Society for the Promotion of Science Molecular study on the formation of anueploidy in gamates for evaluation on risk of miscarriage	2010-2013
21	Grant-in-Aid for Scientific Research (A), Japan Society for the Promotion of Science Structural analysis of lipoprotein receptor family proteins	2010-2012
22	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Structural and functional analysis of ATP synthesis related membrane proteins	2010-2011
23	Coordination, Support and Training Program for Translational Research, The Ministry of Education, Culture, Sports, Science and Technology Feeder-free culture substratum for human pluripotent stem cells	2009-2013
24	Grant-in-Aid for Young Scientists (S), Japan Society for the Promotion of Science Role of PIP3 Transport in Regulation of Cell Polarity	2008-2012
25	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Solid-state NMR investigation on functional and irregular structures of H^+-ATPsynthase Fo	2007-2011
26	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Structural Analysis of Membrane Protein Complexes by Solid-State NMR	2007-2009
27	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Development of “Target” tag system for the next generation structural biology	2007-2009
28	Grant-in-Aid for Creative Scientific Research, Japan Society for the Promotion of Science Structural basis of functional coupling between transcription and cellular metabolism	2006-2010
29	Grant-in-Aid for Scientific Research (A), Japan Society for the Promotion of Science Crystal structure of hexameric membrane protein connexon and elucidation of gap junction structure and function	2006-2008
30	Inter-University Collaborative Project (with NINS Center for Integrative Bioscience), The Ministry of Education, Culture, Sports, Science and Technology International Frontier for Elucidation of Structure and Function of Membrane Proteins (International Frontier in Membrane Protein Research)	2005-2010

31	Strategic Japan-UK Cooperative Program, Japan Science and Technology Agency In-silico Structural Interactome Study Based on Structural Genomics	2005-2008

As the Project member

32	AMED-CREST, Japan Agency for Medical Research and Development How gut microbiota shifts metabolites leading to neuro-endocrine disorders in mouse and men	2014~2019
33	Technology Research Association for Next generation natural products chemistry, Project focused on developing key technology of discovering and manufacturing drug for next-generation treatment and diagnosis. Development of innovative simulation softwares for in-silico drug screening	2013～2017
34	Platform for drug design, discovery and development, Japan Science and Technology Agency Development of the synchrotron beamlines dedicated to the measurement of micron-size protein crystals	2012～2016
35	Platform for Drug Discovery, Informatics, and Strucdtural Life Science Advances and Management of Data Cloud System for Structural Life Science	2012～2016
36	CREST, Japan Science and Technology Agency Mechanism of pluripotency in embryonic stem cells and three dimesional analyses of epigenome structure	2011～2016
37	Platform for drug design, discovery and development, Japan Science and Technology Agency Development of the synchrotron beamlines dedicated to the measurement of micron-size protein crystals	2011
38	Strategic Innovation Program, Japan Science and Technology Agency iPS cell-based regenerative medicine	2010～2013
39	Biomedical Kansai Research Program, Foundation for Biomedical Research and Innovation Realization of Cellular Treatment for Parkinson's disease patients	2010～2011
40	Grant-in-Aid for Scientific Research (S), Japan Society for the Promotion of Science X-ray crystallographic studies of intra- and inter-cellular transport	2009～2013
41	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Solid-state NMR investigation on functional and irregular structures of H^+-ATPsynthase Fo	2007～2011
42	Research and Development of the Next-Generation Integrated Simulation of Living Matter, The Ministry of Education, Culture, Sports, Science and Technology Dev. of Computational software for analysis of biochemical reactions	2007～2012
43	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Structural and functional analysis of gamma-secretase complex	2007～2011
44	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Structural studies of the cell-cell junctional proteins	2007～2011
45	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Structure and function of voltage-sensor domain proteins	2007～2011
46	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Structural analysis of molecules related to the innate immune system	2007～2011
47	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Structural biology on efflux transport machineries to understand multi-drug resistance	2007～2011
48	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Development of the synchrotron beamlines dedicated to the measurement of micron-size protein crystals	2007～2011
49	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Target Protein Research, Construction and Management of Information Platform	2007～2011
50	Target Protein Research Project, The Ministry of Education, Culture, Sports, Science and Technology Structural analysis of semaphorins and their receptors	2007～2009
51	CREST, Japan Science and Technology Agency Biomolecular Tomography with Molecular Labels in the Cell	2006～2011
52	New Energy and Industrial Technology Development Organization Development of Technology to Create Research Model Cells: Development of Technology for Selective Induction of ES Cell Differentiation by Artificial Basement Membranes with Customized Molecular Composition	2006～2009

53	Grant-in-Aid for Scientific Research on Priority Areas, The Ministry of Education, Culture, Sports, Science and Technology Dynamics of extracellular environments	2005～2009
54	CREST, Japan Science and Technology Agency Development of a novel high-speed imaging system to visualize protein nano-dynamics	2005～2009
55	BIRD, Bioinformatics Research and Development, Japan Science and Technology Agency Development of a practical macromolecular complex modeling system	2005～2008
56	CREST, Japan Science and Technology Agency Development of MM program for describing the effect of proteins surrounding the electron transfer system	2005～2008

Entrusted Researches

No.	Grant / Program Name / Subject	study period
1	New Energy and Industrial Technology Development Organization Development of cell manufacturing and processing systems for industrialization of regenerative medicine	2014～2018
2	New Energy and Industrial Technology Development Organization Development of biohearts with small-caliber blood vessels by rational cell positioning technology using a 3D printer	2014～2018
3	Program for coordination toward integration of related databases, Japan Science and Technology Agency Enhancement of functionality and integrative management of PDB	2014～2016
4	Ministry of Health, Labour and Welfare 2014～2016 Practical application project, the innovative cancer	2014～2016
5	Hamari Chemicals Ltd. Synthetic study of peptides under the microwave irraditation condition	2014～2014
6	Shared use of advanced research facilities and their platform formation (MEXT) Promotion of industrial use of advanced NMR facilities	2013～2015
7	Platform for Drug Discovery, Informatics, and Structural Life Science: correlative structural analysis Development and application of a correlative structural analysis by a primary use of EM	2012～2014
8	Nippon Syokubai Development of a new method for peptide synthesis	2013
9	Platform for drug design, discovery and development, The Ministry of Education, Culture, Sports, Science and Technology Development and supports for protein sample preparation and evaluation systems toward advanced NMR structural analysis	2012～2016
10	PRESTO, Japan Science and Technology Agency Structural elucidation of the intracellular transport machinery	2012～2014
11	Japan Space Forum Production of high quality protein crystals in space environment and high precision structure analysis	2012～2013
12	Strategic Basic Research Programs (Advanced Low Carbon Technology Research and Development Program), Japan Science and Technology Agency Generation of diatom factory through physiolomics toward a novel energy source	2011～2016
13	Japan Science and Technology Agency Promotion Project, the next generation cancer research strategy	2011～2015
14	Program for coordination toward integration of related databases, Japan Science and Technology Agency Global Construction and Integration of PDB	2011～2013
15	Japan Space Forum Production of high quality protein crystals in space environment and high precision structure analysis	2011～2012
16	New Energy and Industrial Technology Development Organization Validation and standardization of human pluripotent stem sells	2010～2015
17	PRESTO, Japan Science and Technology Agency Structural analysis of the electron transfer complexes for understanding entirely the photosynthetic energy transduction	2010～2014

18	New Energy and Industrial Technology Development Organization Development of cell-free devices for regenerative medicine	2010～2015
19	PREST, Japan Science and Technology Agency Role of neuronal cilia in development and function of the central nervous system	2010～2013
20	METI KANSAI (Kansai Bureau of Economy, Trade and Industry), Regional Innovation Creation R & D Program Research and Development of Rapid Detection System for Protein Aberrant Aggregations Associated with Diseases	2010～2012
21	Promotion of shared use of advanced research facilities (MEXT) Promotion of industrial use of advanced NMR facilities	2010～2011
22	CREST, Japan Science and Technology Agency Analysis of the synapse formation and the functional networks in the vertebrate retina	2009～2014
23	PRESTO, Japan Science and Technology Agency Development of structure-based Drug Delivery System (DDS) using vault particles.	2009～2012
24	Japan Aerospace Exploration Agency (JAXA) Production of high quality protein crystals in space environment and high precision structure analysis	2009

Joint Researches with Private Companies and Research Agencies

No.	Company / Subject	study period
1	Japan Aerospace Exploration Agency(JAXA) Production of high quality protein crystals in space environment (PCG#2-2) and high precision structure analysis	2014～2017
2	Chugai Pharmaceutical Co., ltd Epitope mapping of anti-plexin monoclonal antibodies	2014-2015
3	KRI, Inc. Cryo-EM Imaging of soft materials	2014-2015
4	Osaka Gas Chemicals, Co. Ltd. Cryo-EM Imaging of Biomaterials	2014-2015
5	KANEKA Corporation Structural analysis of biomaterials by EM imaging	2014-2015
6	Ajinomoto Co., lnc. Development of stem cell culture medium using modified laminins	2013～2014
7	Technology Research Association for Next generation natural products chemistry, Project focused on developing key technology of discovering and manufacturing drug for next-generation treatment and diagnosis. Development of innovative simulation softwares for in-silico drug screening	2013～2017
8	Japan Aerospace Exploration Agency(JAXA) Production of high quality protein crystals in space environment (PCG#2-2) and high precision structure analysis	2013～2015
9	Japan Aerospace Exploration Agency(JAXA) Production of high quality protein crystals in space environment (PCG#2-1) and high precision structure analysis	2013～2014
10	Japan Aerospace Exploration Agency (JAXA) Production of high quality protein crystals in space environment (NGCF#6) and high precision structure analysis	2013
11	Astellas Pharma Inc. Development of rational design technology of antibodies for basis of antibody medicine	2012～2014
12	Interprotein Corporation Drug discovery research of small molecule protein-protein interaction (PPI) inhibitors	2012～2013
13	Ajinomoto Co., Inc. Analysis of mechanical stress of E. coli cells during amino acid crystal fermentation	2012～2013

14	Panasonic Corporation	2012
	Research on structural prediction for protein-protein interaction	
15	Eisai Co.,Ltd	2011～2014
	Structure of drug-metabolizing enzyme cytochrome P450 in lipid bilayers	
16	Pharma Foods International Co., Ltd.	2011～2014
	Eisai Co.,Ltd	
17	Shimadzu Corporation	2011～2012
	Development of methodolgy for protein structural analysis	
18	Japan Aerospace Exploration Agency (JAXA)	2011～2012
	Production of high quality protein crystals in space environment and high precision structure analysis	
19	Ono Pharmaceutical Co.,Ltd.	2011～2012
	Recombinant protein production using FATT tag system	
20	Nippi Research Institute of Biomatrix	2011～2012
	Research on laminins, collagens, and related proteins.	
21	Sekisui Medical Co.,Ltd.	2011～2012
	Production of monoclonal antibody against native LR11	
22	Panasonic Corporation	2011
	Research on structural prediction for protein-protein interaction	
23	Japan Biological Informatics Consortium	2011
	Development of basic technology for precise in-silico drug screening	
24	Interprotein Corporation	2011
	Discovery research of small molecule medicines based on the analysis of protein function and structure	
25	Protein Wave Corporation	2011
	Studies on expression system construction and high efficiency large scale expression in some target proteins	
26	Mandam Corporation	2010～2014
	Identification of epidermal stem cells	
27	Daiichi Sankyo RD Associe Co., Ltd	2010～2011
	Recombinant protein production using FATT tag system	
28	Nippon Zoki Pharmaceutical Co., Ltd.	2010～2011
	Development of new Methods in virtual screening and structure optimization for G-protein coupled receptor (GPCR) models	
29	JST (Japan Science and Technology Agency), Riken	2010
	Development of NMR database	
30	Japan Aerospace Exploration Agency (JAXA)	2010
	Production of high quality protein crystals in space environment (NGCF#3) and high precision structure analysis	
31	Sysmex Corporation	2010
	Development protein crystallization monitoring technique using Malvern Instruments' Zetasizer Nano particle characterization system	
32	Interchange Association, Japan	2010
	Structure and dynamic investigation of interfacial enzyme	
33	Astellas Pharma Inc.	2009～2011
	Development of rational design technology of antibodies for basis of antibody medicine	
34	Panasonic Corporation	2009～2010
	Research on structural prediction for protein-protein interaction	
35	Interprotein Corporation	2009
	Discovery research of small molecule medicines based on the analysis of protein function and structure	

36	Japan Aerospace Exploration Agency (JAXA) Production of high quality protein crystals in space environment and high precision structure analysis	2009
37	Institute for Innovation, Ajinomoto Co., Inc. Structure and function of a transglutaminase from Streptomyces mobaraensis	2008～2011
38	Japan Clinical Laboratories, Inc. Development of monoclonal antibodies against human LRP6	2008～2010
39	JST (Japan Science and Technology Agency), Riken Development of NMR database	2008～2009
40	Theravalues Inc. Biomarker Discovery by Proteomics	2008～2009
41	Japan Institute of Leather Research Development of technology for reconstitution of artificial basement membranes with customized molecular composition	2007～2009
42	Astellas Pharma Inc. Development of a new methodology for antibody medicine by antibody informatics	2006～2008
43	Sysmex Corporation Development protein crystallization monitoring technique using Malvern Instruments' Zetasizer Nano particle characterization system	2005～2009
44	Hitachi High-Technologies Corporation Proteomics by a LC/MS^n system	2005～2009
45	Shimadzu Corporation Protein profiling analysis using the NBS method	2005～2008
46	Inter Cyto Nano Science Co. Ltd. Creation of low molecular medicine based on the analysis of biological function and structure of target protein	2005～2008

Other Outstanding Research Activities

	Program Name/Subject	(study period)
1	Management of Protein Data Bank Japan (PDBj)	2001～2014

Activities as a Joint-Usage/Research Center, and International Exchange

In order to fulfill its aim as a Joint-Usage/Research Center, the Institute carries out the following programs.

Joint Researchers and International Collaborative Research

A joint research program has been established to provide visiting scientists, who are engaged in studies on proteins, from outside the Institute with an opportunity to perform coordinated research at the Institute for up to 6 months. More than 50 scientists are selected yearly from applications of various domestic institutions.

The program covers the research and travel expense, and the Institute provides the facilities for accommodations. This program started in 1959, and total 2,217 researchers were so far admitted during the past 55 years. Researchers, who want to use big instruments such as the X-ray analysis facilities, the superconducting magnet NMR, and mass spectrometers, should apply for the visiting scientist program.

Number of Joint Researchers

	Regular		Beamline		NMR	
(Year)	Number	Month	Number	Theme	Number	Theme
2000	29	28	15	18		
2001	31	55	21	30		
2002	24	20	27	35		
2003	25	21	43	52		
2004	33	27	24	33		
2005	29	24	29	37		
2006	29	18	37	45		
2007	33	20	35	45		
2008	38	25	39	48		
2009	44	30	44	51		
2010	57	21	48	53	15	15
2011	51	35	48	52	15	15
2012	59	20	52	59	12	12
2013	69	22	58	63	14	14
2014	79	30	65	65	12	12

In addition, in 2005, the Institute started an international collaborative research program, inviting researchers widely from overseas countries. The research should be conducted in the form of a collaboration including at least one of the Principal Investigators at IPR, or it should use particular experimental facilities of IPR. So far, the researchers came from USA, UK, Sweden, Spain, New Zealand, Hungary, Poland, Bangladesh, India, Taiwan, China, Korea, France, Russia, Cuba, Germany, Malaysia, Indonesia, Netherlands, Singapore, Viet Nam and Italy using this program.

In the fiscal year of 2014, 17 overseas researchers visited the Institute from 12 countries, Germany, Korea, Thailand, USA, India, Malaysia, Taiwan, Australia, Hungary, Indonesia, UK and Sweden, ,and made collaborative researches with the Principal Investigators at the Institute.

Year	Number	Days
2005	6	305
2006	8	213
2007	4	44
2008	6	140
2009	8	252
2010	9	152
2011	9	431
2012	15	323
2013	13	224
2014	18	382

IPR Seminar

The Institute holds annually around 16 seminars on various topics. Applied topics are selected by the Advisory Committee on Research Programs. Speakers are supplied with travel expenses incurred in attending the seminar.

IPR Seminars from April 2014 to March 2015

	Title / Organizer	Date
1	Workshop on the Beamline for Biological Macromolecule Assemblies Atsushi NAKAGAWA (IPR, Osaka Univ.), Eiki YAMASHITA (IPR, Osaka Univ.), Akifumi HIGASHIURA (IPR, Osaka Univ.)	May 12-14, 2014
2	Practical Aspects of Non-uniform Sampling in Multi-dimensional NMR Spectroscopy and Application for Biological Systems Takahisa IKEGAMI (Yokohama City University), Koh TAKEUCHI (AIST)	June 18-19, 2014
3	Molecular mechanism of chromosome transmission: From replication to partitioning Toshiki TSURIMOTO (Kyusyu Univ.), Hisao Masukata (School of Science, Osaka Univ.) Hiroshi MASUMOTO (Kazusa DNA Res. Inst.)	September 25-26, 2014
4	Regulation and Environmental Adaptation of Photosynthesis: An Attractive Theme for Structural Life Science Toshiharu HASE (IPR, Osaka Univ.), Akira SUZUKI （Institut Jean- Pierre Bourgin,INRA Centre de Versailles), Genji KURISU （IPR, Osaka Univ.)	October 24, 2014
5	Genome stability and exchange of DNAs Susan GASSER (FMI), Akira SHINOHARA (IPR, Osaka Univ.)	November 14, 2014
6	Mechanism and regulation of aberrant protein aggregation Yuji GOTO (IPR, Osaka Univ.), Jozef KARDOS（Eotvos Larand Univ.) Eri CHATANI (Kobe Univ.), Hisashi YAGI (Tottori Univ.)	November 17-21, 2014
7	7th Retina Research Meeting Akira MURAKAMI (Juntendo Univ.), Takeshi IWATA (Tokyo Medical Center) Atsushi MIZOTA (Tokyo Univ.), Sumiko WATANABE (The Univ. of Tokyo)	November 22, 2014
8	Neural basis of information integration for decision making -Neural circuitry mechanism and its formational development- Makoto SATO (Faculty of Medicine, Osaka Univ.), Kazuaki YOSHIKAWA (IPR, Osaka Univ.)	November 27-28, 2014
9	The 5th symposium on “Fusion of neuronal science and structural biology” Michihiro IGARASHI (Niigata Univ.), Nobuyuki SHIINA (National Institute for Basic Biology) Tomoo NISHIOKA (Nagoya Univ.), Kozo KAIBUCHI (Nagoya Univ.) Junichi TAKAGI (IPR,Osaka Univ.), Atsushi NAKAGAWA (IPR, Osaka Univ.)	December 4-5, 2014
10	Looking to the future of Notch signaling Kenji MATSUNO (School of Science, Osaka Univ.), Junichi TAKAGI (IPR, Osaka Univ.) Yumiko SAGA (National Institute of Genetics)	December 18, 2014
11	-The 11th Japan-Korea Bilateral Symposium on Biological NMR- -International NMR Symposium on Pharmaceutical NMR- Toshimichi FUJIWARA (IPR, Osaka Univ.), Chojiro KOJIMA (IPR, Osaka Univ.) Bong-Jin LEE（Seoul National Univ.)	December 19-20, 2014
12	Molecular Crowding and Macromalecular Association Yuji GOTO (IPR, Osaka Univ.), Damien HALL (Australian National Univ.)	February 5, 2015

13	Joint workshop by PDBj & Platform for Drug Discovery, Informatics, and Structural Life Science Haruki NAKAMURA (IPR, Osaka Univ.)	February 20, 2015
14	Cutting edge of Structural biology and biochemistry of anaerobic proteins HGenji KURISU (IPR, Osaka Univ.), Yuichi FUJITA (Nagoya Univ.)	March 5, 2015
15	Analysis and prediction of protein assembly structures by bioinformatics Haruki NAKAMURA (IPR, Osaka Univ.), Kei YURA (Ochanomizu Univ.)	March 5, 2015
16	Photomovement responses, photosensor proteins, optgenetics. ~ Watanabe In Memoriam~ Kenji IWASAKI (IPR, Osaka Univ.), Mineo ISEKI (Toho Univ.)	March 6, 2015

International Exchange

The post of Visiting Professor from foreign countries or regions is provided at the Research Center for State-of-the-art Functional Protein Analysis. The Institute also accepts foreign scientists through programs sponsored by the Japan Society for the Promotion of Science, or through other programs when financing is guaranteed from outside the Institute. More than two hundred visiting foreign scientists have participated in research activities since the establishment of the Institute. In 2005, the Institute has started a new program, the International Collaborative Research, for overseas researchers who perform coordinated research at the Institute and use particular experimental facilities of IPR, including a synchrotron beam line for biological macromolecular assemblies at SPring-8, as well as in a joint research program for Japanese researchers. The Institute has also accepted the international exchange students through the program called FrontierLab@OsakaU. To promote further cooperation in research, the Institute has concluded Inter-Faculty Academic Exchange Agreements as follows.

Peking University, Institute of Physical Chemistry (China) from 1987
Center for Genetic Engineering and Biotechnology (Cuba) from 2003
National Synchrotron Radiation Research Center (Taiwan) from 2007
Indian Institute of Chemical Biology (India) from 2009
Seoul National University, College of Pharmacy (Korea) from 2009
Airlangga University, Institute of Tropical Disease (Indonesia) from 2014
National Center for Protein Science, Shanghai (China) from 2014
Peking University, Center of Protein Science (China) from 2014
The Australian National University, College of Physical and Mathematical Sciences (Australia) from 2014

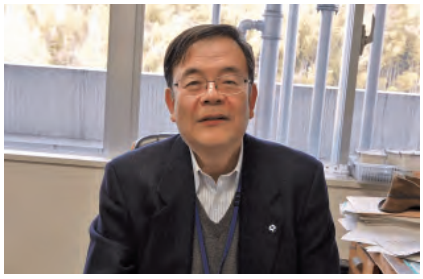
Collaborations with Foreign Institutions

	Representative/Institution/Coutry/Project Title
1	Prof. Zengyi Chang, Center of Protein Science, Peking University, China ・Promotion of Protein Science
2	Prof. Ming Lei, National Center for Protein Science Shanghai ・Promotion of Structural Biology
3	Dr. Akira Suzuki, INRA, Versailles, France ・Molecular physiology of plant amino acid synthesis
4	Dr. Guy T. Hanke, Osnabrueck University, Germany ・Redulation of redox metabolisms in chloroplast
5	Prof. Peter F. Stadler, University Lipzig, Department of Computer Science, Bioinformatics, Lipzig, Germany ・Bioinformatics of DNA methylation
6	Dr.Norimasa Iwanami, Max Planck Institute of Immunobiology and Epigenetics, Freiburg, Germany ・Analysis of Dnmt1 mutation in zebrafish
7	Dr. Jorge Fernandez-de-Cossio, Center for Genetic Engineering and Biotechnology, Cuba ・Development of Analytical Software for Interpretation of Mass Spectral Data
8	Prof. Luca Tamagnone, University of Torino, Italy ・Development of function-modulating antibodies against human plexin D1.
9	Prof. Gregory A. Petsko,Cornell University, USA ・Development of pharmacological chaperone for sorLA.
10	Director, Prof. Shangjr Gwo, Taiwan ・Structure biology research using synchrotron radiation
11	Prof. Chun-Jung Chen, National Cheng Kung University ・Crystal structures of key proteins and complexes involved in two-component regulatory systems in Pseudomonas aeruginosa for the regulatory mechanism

12	Prof. Janos Hajdu, Uppsala University, Sweden ・Studies of coherent X-ray imaginf for virus particles
13	Prof. Thomas Happe, Ruhr University Bochum, Germany ・X-ray structural analysis of [FeFe]-hydrogenase from green alga
14	Prof. Matthias Rögner, Ruhr University Bochum, Germany ・Crystallization of NDH1 from Thermophilic cyanobacterium
15	Prof. Michael Hippler, University of Münster, Germany ・Structural dynamics of calredoxin, a novel EF-hand and thioredoxin domain protein from Chlamydomonas reinhardtii
16	Prof. James R. Ketudat-Cairns, Suranaree University of Technology, Thailand ・Structural studies of a glycoside hydrolase family 116 beta-glycosidase from a thermophilic bactera
17	Prof. Jozsef Kardos, Etovos Lorand University, Hungary ・Understanding the mechanism of protein abberant aggregation and amyloid formation
18	Prof, Gennaro Esposito, University of Udine, Italy ・Amyloid fibril formation of β2-microglobulin
19	Prof. Alexey Merz, University of Washington School of Medicine ・Functions of yeast Sec1/Munc18 (SM) -family proteins in SNARE-mediated membrane docking and fusion
20	Prof. William Wickner, Dartmouth Medical School ・Membrane tethering mediated by the HOPS complex in ・SNARE-dependent membrane fusion
21	Prof. András Per c zel, Etovos Lorand University, Hungary ・Protein misfolding and early stage aggregates
22	Prof. Masayori Inouye, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, USA ・Isotope labeling by single protein production systems
23	Prof. John L. Markley, University of Wisconsin-Madison, USA ・Databank for biological NMR
24	Prof. Praveen Ballabh, New York Medical College, USA ・Mechanisms of neurogenesis in human fetal brain
25	Prof. Zhengang Yang, Fudan University, China ・Molecular mechanism of cortical interneuron development
26	Prof. Neil Hunter, University of California Davis, USA ・Study on mechanisms of meiotic recombination
27	Prof. Susan Gasser, Friedrich Mericier Institute, Switzerland ・Molecular mechanism of chromosome dynamics

Division of Protein Chemistry

Laboratory of Regulation of Biological Reactions



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The plant organelles collectively referred as plastids play a diverse set of physiological functions represented by photosynthesis, and soluble and membrane-bound proteins, localized in certain subplastidal compartments, are involved in the organelle functions. We have been studying the function and biogenesis of plastids and plastidal proteins with techniques of biochemistry, genetics and cell biology using higher plants and cyanobacteria. Current projects are as following. i) Reducing power necessary for carbon, nitrogen and sulfur assimilation are utilized by combination of an electron carrier protein, ferredoxin and ferredoxin-dependent enzymes, enabling plants to assimilate inorganic raw materials to organic compounds such as sugar and amino acid. The structure of electron transfer complex and catalytic mechanisms of ferredoxin and partner redox enzymes are studied. ii) Cytosolically synthesized polypeptides are transported into chloroplasts and converted to functional mature proteins. The mechanisms of protein translocation across the envelope membranes of chloroplasts and involvements of molecular chaperones are studied. Recently, a new multi-protein complex with a size of one-megadalton was discovered, and its structure and function are under investigation. iii) Malaria cells contain an organelle called apicoplast, in which redox metabolisms for parasite vitality take place. We are studying malaria ferredoxin and its partner redox enzymes to explore how redox cascade is operative in apicoplasts.

【Current Research Programs】

1) Electron partitioning in redox metabolisms of photosynthetic and non-photosynthetic plastids
2) Reaction mechanism of ferredoxin-dependent enzymes
3) Molecular mechanism of chloroplast biogenesis
4) Structure and function of chloroplast protein translocons
5) Structure and reaction mechanism of ferredoxin and its oxidoreductase of malaria apicoplast

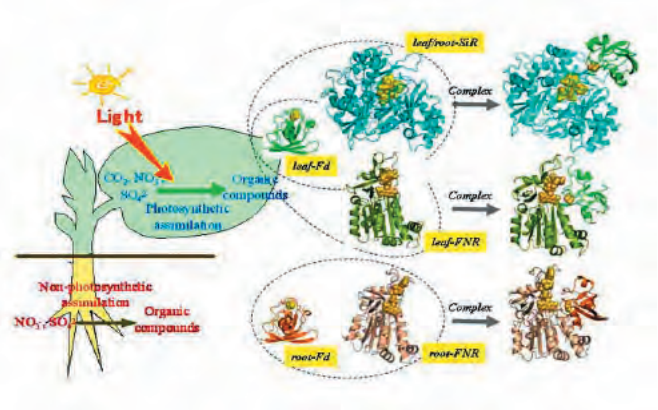

Fig.1. Electron transfer complex of ferredoxin and ferredoxin-dependent enzymes in chloroplasts and root plastids.

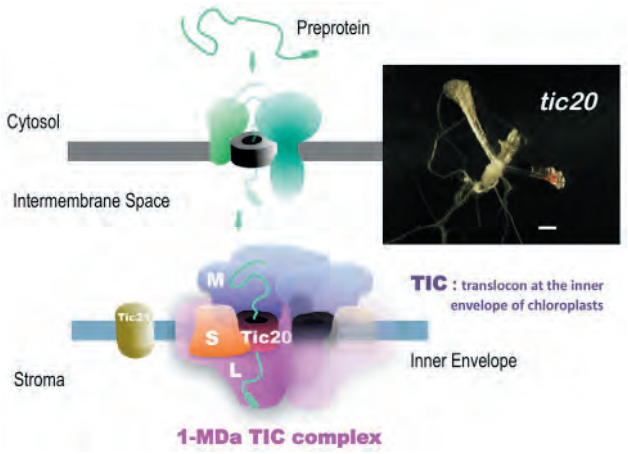

Fig.2. A novel one-megadalton protein translocation machinery at the inner envelope of chloroplasts.

【References】

1. Unconvering the Protein Translocon at the Chloroplast Inner Envelope Membrane. Kikuchi S, Nakai M, et al. (2013) *Science* **339**, 571-574.
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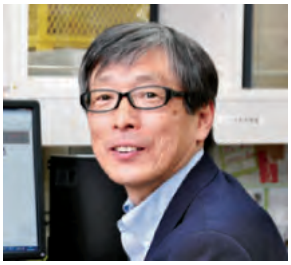
3. N-terminal structure of maize ferredoxin:NADP$^+$ reductase determines recruitment into different thylakoid membrane complexes. Altmann B, Twachtmann M, Muraki N, Voss I, Okutani S, Kurisu G, Hase T, and Hanke GT. (2012) *Plant Cell* **24**, 2979-2991
4. Electron Transfer of Site-specifically Cross-linked Complexes between Ferredoxin and Ferredoxin-NADP+ Reductase. Kimata-Ariga Y, Sakakibara Y, Ikegami T, and Hase T. (2010) *Biochemistry* **49**, 10013-10023.
5. A 1-megadalton translocation complex containing Tic20 and Tic21 mediates chloroplast protein import at the inner envelope membrane. Kikuchi S, Oishi M, Hirabayashi Y, Nakai M, et al. (2009) *Plant Cell* **21**, 1781-1797.
6. Molecular interaction of Ferredoxin and Ferredoxin-NADP$^+$ reductase from human malaria parasite. Kimata-Ariga Y, Hase T, *et al.* (2007) *J. Biochem.* **142**, 715-720.

Laboratory of Extracellular Matrix Biochemistry



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The goal of our laboratory is to understand the molecular basis of tissue architecture and cellular functions in multi-cellular organisms based on the cell-extracellular matrix (ECM) interaction. ECM is not a mere scaffold between cells but rather an information-rich supra-molecular structure that provides cells with signals that regulate cell growth, differentiation, and apoptosis. Cells read the barcode-like signals written in the ECM with a variety of cell surface receptors and determine whether they should grow or differentiate. The composition of the ECM is spatiotemporally regulated during embryonic development and differs from one cell type to another. We performed a comprehensive immunohistochemical survey of more than 40 basement membrane proteins in mouse embryos. The immunohistochemical data was compiled into a high-resolution digital image database ("Mouse Basement Membrane Bodymap"), which is available on the internet at http://www.matrixome.com/bm/.

【Current Research Projects】

1) Purification and characterization of laminins and other basement membrane proteins.
2) Studies on spatiotemporal customization of basement membrane composition during development.
3) Mechanisms of integrin-mediated cell-substratum adhesion and signal transduction.
4) Regulation of cell-cell and cell-substrate interactions by tetraspanin CD151.
5) Regulation of stem cell proliferation and differentiation through engineering of extracellular environment.

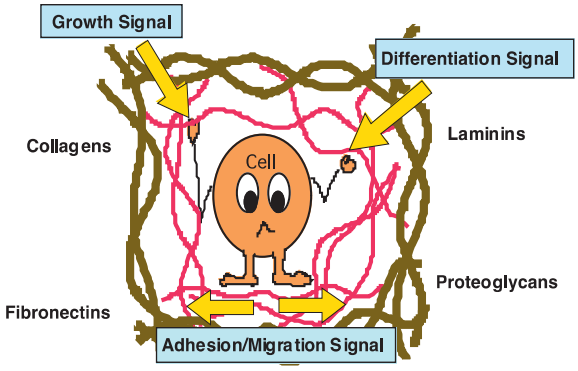

Fig. 1. Regulation of cell growth, differentiation, and survival by extracellular matrix. *Cells have their own customized extracellular matrix.*

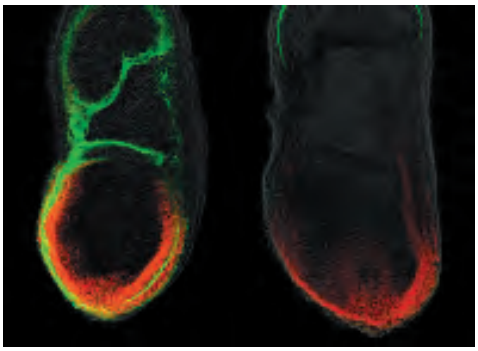

Fig. 2. Localization of laminin alpha 5 (left; green) and alpha 1 (right; green) chains in E7 mouse embryos, double-stained with anti-Oct-3/4 (red). *Laminin alpha 5 was detected along the entire basement membrane, while laminin alpha 1 was localized at the extraembryonic basement membrane.*

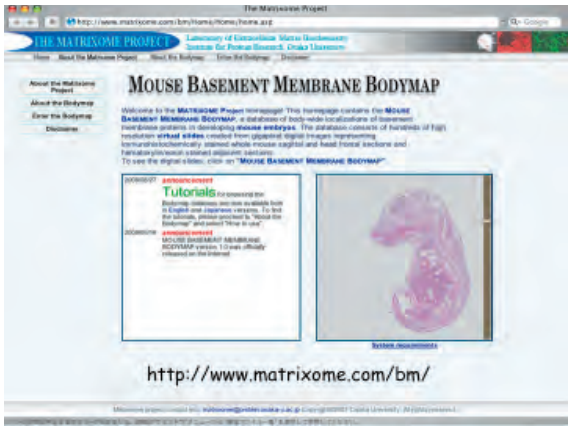

Fig. 3. Mouse Basement Membrane Bodymap database. *More than 90% of basement membrane components have been localized within E16.5 mouse embryos by means of immunohistochemistry.*

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Laboratory of Epigenetics

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In vertebrates, genomic DNA is packaged into chromatin, of which fundamental structure is a nucleosome. The methylation modification of cytosine in the sequence of CpG and the posttranslational modifications of core histones affect packaging of chromatin. These modifications are crucial for gene expression. We are specially focusing on DNA, histones H3 lysine 9 and 27, and H4 lysine 20 methylations, which are known to contribute to gene silencing *via* forming heterochromatin. The methyl groups are transferred from *S*-adenosyl-L-methionine by methyltransferases. Our final goal is to elucidate the mechanisms how DNA methylation state are regulated, and the silencing marks on the lysine residues in histone H3 and H4 are affecting the DNA methylation state.

【Current Research Programs】

1) Effect of methylation and histone modification on chromatin structure
2) Mechanism of creation and inheritance of the DNA methylation patterns
3) Identifying the factors interacting with DNA methyltransferases

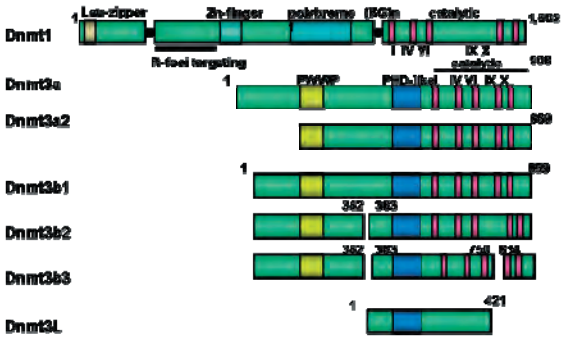

Fig.1. Schematic illustration of the members of DNA methyltransferase family Dnmts. *Up to present, 4 genes, Dnmt1, Dnmt3a, Dnmt3b, and Dnmt3L, are identified.*

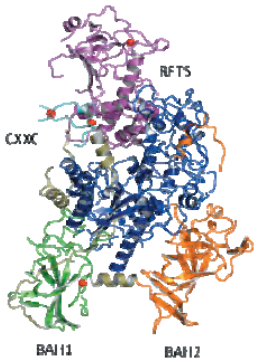

Fig. 2. Multi-domain structure of mouse Dnmt1. *Figure shows ribbon model of mouse Dnmt1. The C-terminal catalytic domain are surrounded by the RFTS, CXXC motif, and two BAH domains (BAH1 and BAH2). Four zinc ions are shown in red spheres. All of the zinc ions are in a motif similar to Zn-finger motif. The KG-repeat linker connecting the N-terminal region and the C-terminal catalytic domain is in a flexible structure.*

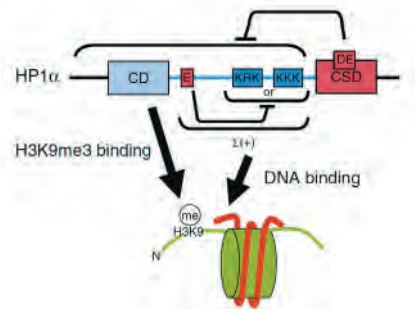

Fig.3. Recognition of histone H3K9me3 in nucleosome structure by HP1α. *The selective binding to histone H3K9me3 in nucleosomes via the chromodomain (CD) is cooperatively enhanced by the balance of net positive charge [Σ(+)] of the hinge (HR) and the suppressive effect of the chromoshadow domain (CSD). The delicate charge balance of the HR and CSD allows the selective binding of HP1α to histone H3K9me3 in nucleosomes. (ref. 4)*

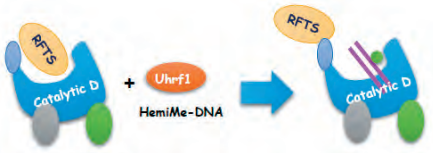

Fig. 4. The RTS domain plugging the catalytic pocket of Dnmt1 is removed by direct interaction with Uhrf1 (SRA), and thus the DNA can access to the catalytic center. *(ref. 6)*

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Laboratory of Protein Organic Chemistry

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Chemical methods enable the synthesis of proteins, which can not be prepared by the recombinant method, such as site-specifically labeled, glycosylated and phosphorylated proteins. Laboratory of Protein Organic Chemistry is aiming to promote new protein researches using these synthetic proteins. Thus, our laboratory is developing facile methods for protein synthesis based on ligation chemistries. In addition, the synthetic method is applied for the preparation of membrane proteins and their partial sequences to elucidate the signal transduction mechanism by solid state NMR and IR. Modified histones and their partial sequences, glycosylated proteins are also being synthesized for the functional analyses.

【Current Research Programs】

1) General studies on a chemical protein synthesis
2) Development of methods for peptide ligation
3) Development of methods for site-specific modification of peptides and proteins
4) Synthetic studies of membrane proteins
5) Structural and functional studies of membrane proteins
6) Synthetic studies of modified histones, and elucidation of the role of modifies

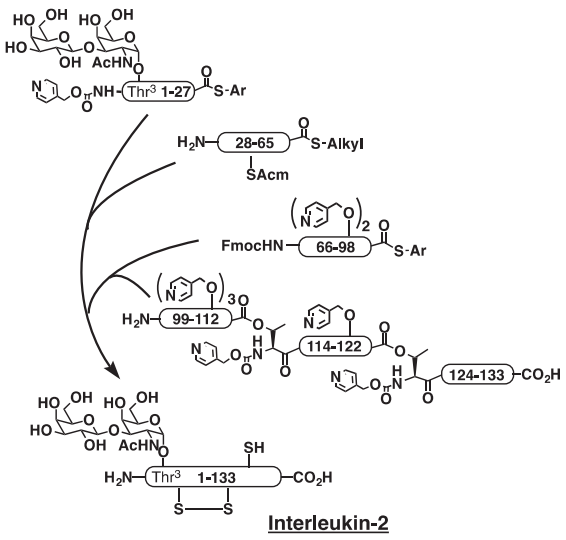

Fig. 1. Synthetic route of human interleukin-2 as a example of chemical protein synthesis. The key compound of the method is a peptide thioester which is prepared by the solid-phase method. The thioester group is then chemoselectively reacted with the terminal amino group of the other segment to give a peptide bond. The reaction is repeated until the entire sequence of the desired protein is assembled. After deprotection and folding, the correctly folded functional protein is obtained.

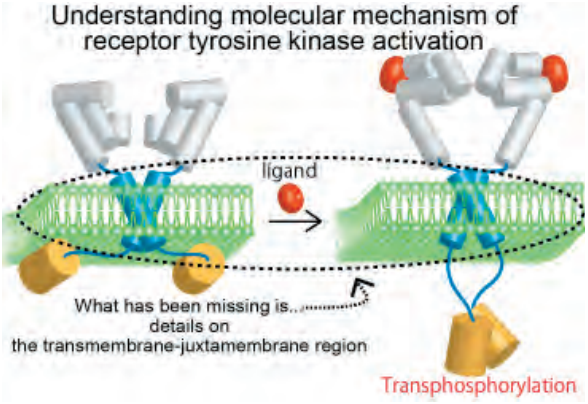

Fig. 2. Concept for our research on activation mechanism of receptor tyrosine kinase. Our research focuses on structure of the transmembrane and the juxtamembrane regions to understand how these regions involve in the activation mechanism.

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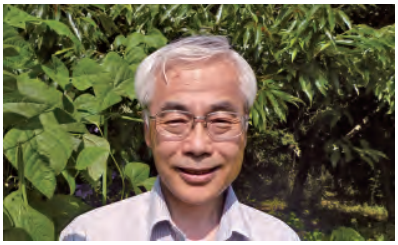
Division of Protein Structural Biology

Laboratory of Protein Folding



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Protein folding is a process in which an extended polypeptide chain acquires a unique folded conformation with biological activity. Clarifying the mechanism of protein folding is essential to improve our understanding of the structure and function of proteins. It is also important because many critical biological processes and disease states involve protein misfolding and aggregation reactions. We study the conformational stability and the mechanisms of protein folding and misfolding with various approaches including spectroscopies (NMR, fluorescence, CD), physicochemical measurements (calorimetry, analytical ultracentrifugation) and fluorescence microscopy.

【Current Research Programs】

1) Observation of folding processes and clarification of the mechanism of protein folding
2) Structural stability and formation of amyloid fibrils
3) Comprehensive understanding of protein folding and misfolding on the basis of solubility and supersaturation

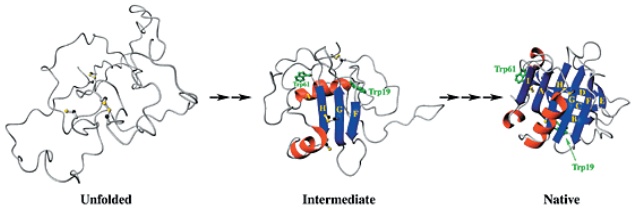

Fig. 1. Schematic presentation of folding pathway of bovine β-lactoglobulin with non-native α-helical intermediate.

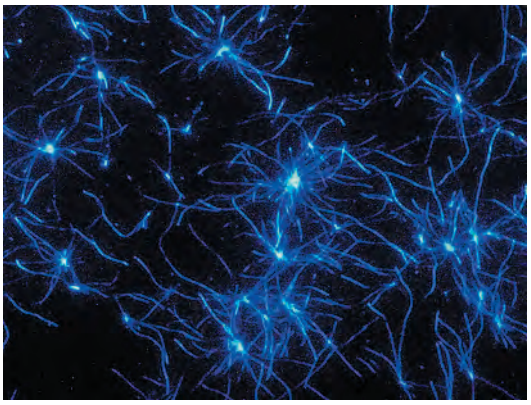

Fig. 2. Real time observation of the growth of amyloid-β fibril using total internal reflection fluorescence microscopy.

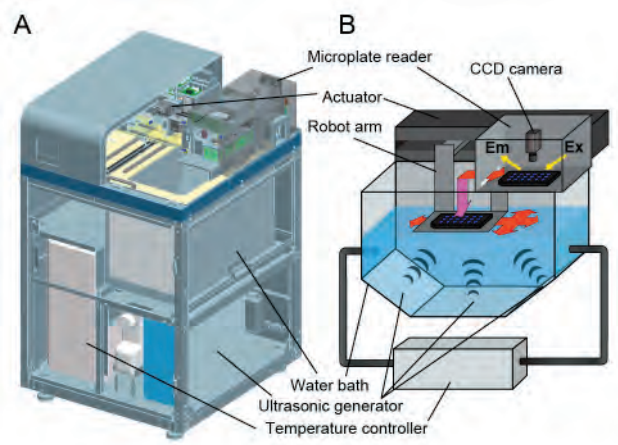

Fig. 3. Overview (A) and schematic illustration (B) of the a HANdai Amyloid Burst Inducer (HANABI) system. HANABI performs a high-throughput analysis of ultrasonication-forced amyloid fibrillation. (Ref.3)

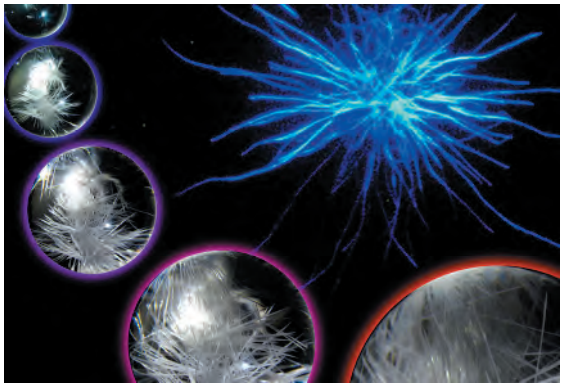

Fig. 4. Comparison of crystallization of sodium acetate and amyloid fibrillation of amyloid β. (Ref.4)

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Laboratory of Molecular Biophysics

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Laboratory of molecular biophysics is engaged in studying the biological macromolecular structure and their intermolecular interactions mainly by using nuclear magnetic resonance (NMR). NMR provides information on the protein structure at work with atomic resolution even in cells. Taking this advantage, we can understand the biological activities for signal transduction and energy conversion from structures. Structures of F_o *c*-ring, light-harvesting Bchl *c* complex, β_2-microglobulin amyloid, florigen, interacting ubiquitin, and membrane-bound mastoparan-X have been elucidated. Since supramolecular systems such as membrane protein complexes play important roles in biological systems, we are also developing new methodologies in NMR to analyze those challenging structures. One of our programs for solid-state NMR features high-field dynamic nuclear polarization (DNP) for a 1000-fold signal enhancement by using high-intensity terahertz light source, gyrotron. These developments aim to contribute to not only academic but also industrial NMR applications such as drug discovery.

【Current Research Programs】

1) NMR analysis of proteins and their interactions
2) Sensitivity enhancement of high-resolution NMR by hyperpolarization
3) New methodologies in biological NMR including isotope-labeled sample preparation and data analysis

Fig. 1. NMR magnet for 600-MHz solid-state NMR on the left and 395-GHz gyrotron for high-intensity light source of terahertz-wave on the right. Hyperpolarization generated with these instruments increases the NMR sensitivity of proteins. This DNP-NMR spectrometer was developed in Institute for Protein Research. (Ref. 4)

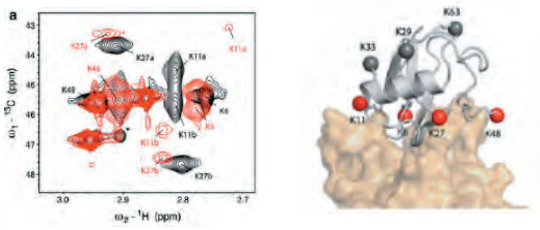

Fig. 2 ^{1}H–^{13}C HSQC spectra of methylated ubiquitin and methylated ubiquitin interacting with protein YUH1 shown on the left. Ubiquitin and YUH1 are shown in the complex (1CMX) by the ribbon and surface representation, respectively. Larger and smaller chemical shift changes are colored red and gray, respectively. This simple post-methylation method gives strong CH_3 NMR signals for detecting the protein interactions. (Ref. 2)

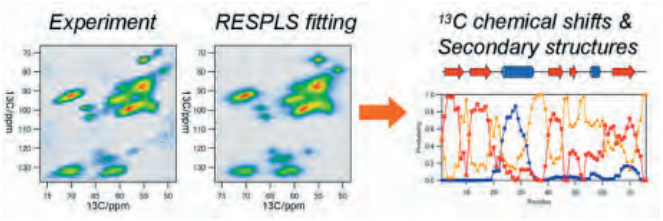

Fig. 3 Automatic solid-state NMR structural analysis of protein. ^{13}C-NMR spectra of proteins in solids often show unresolved signals. Our spectral fitting softwane RESPLS enables chemical shift assignments and secondary structure prediction based on the databases PDBj and BMRB. This method simplifies the structural analysis by providing reliable information even for lyophilized states. (Ref. 3)

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Laboratory of Protein Crystallography

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Protein crystallography is the best method to determine atomic structure of protein molecules, in order to elucidate the molecular mechanism of the highly organized biological systems. The main aim of our group is the X-ray structure determination of the biological macromolecular assemblies including membrane protein complexes. We are focusing on macromolecular assemblies around photosystem I, and dynein motor including the possible cargo such as huge vault complex.

【Current Research Programs】

1) Structural studies of photosynthetic energy-transducing membrane protein complex and related redox enzymes
2) Crystal structure analyses of dynein motors
3) High resolution structural analysis of rat liver vault

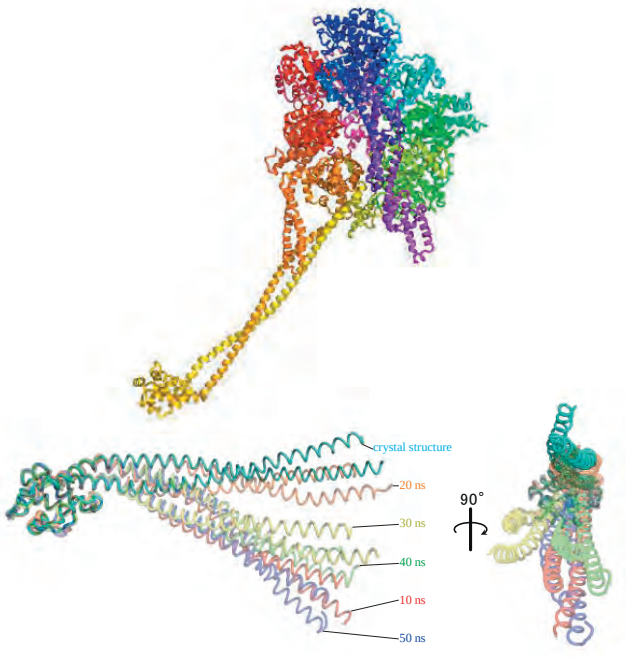

Fig. 2. Overall structure of the dynein motor domain (upper panel) and the swing motion of the stalk region (lower panel). Dynein is a microtubule-based motor protein, whose motor activity is located in the motor domain of the heavy chain. (Upper) A crystal structure of the motor domain is drawn as a ribbon model showing linker, six AAA modules constituting ring, stalk–strut coiled-coils and C-sequence at the outside of the ring. (Lower) Crystal structure is superimposed with the models of five simulated structures derived from the molecular dynamics simulation. The orientation of the swing is parallel to the AAA ring and is consistent with a diffusive search-like motion for the next step along a microtubule.

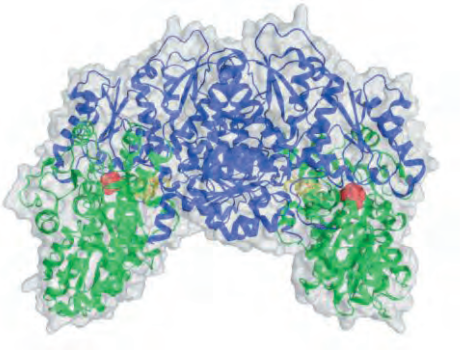

Fig. 1. Crystal structure of the hetero-tetrameric catalytic component NB-protein of DPOR (Dark-operative Protochlorophyllide OxidoReductase). The [4Fe-4S] clusters are shown in CPK model, and the Pchlide molecules in stick model. The BchN and BchB subunits in one dimer are colored in green and blue.

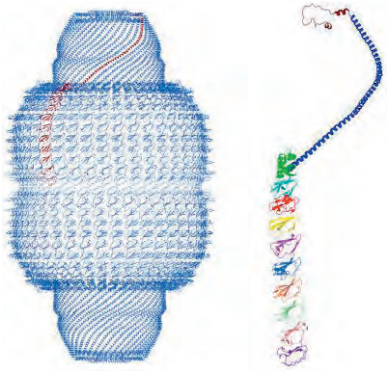

Fig. 3. Overall structure of the vault shell. (Left) The whole vault shell comprises a 78-mer of MVP molecules. One molecule of MVP is colored in red, and the others are colored in blue. (Right) The MVP monomer is folded into nine structural repeat domains, a shoulder domain, a cap-helix domain, and a cap-ring domain. Each domain is depicted in a different color.

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Laboratory of Membrane Protein Chemistry

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Laboratory of Membrane Protein Chemistry is working on *in vitro* reconstituted proteoliposomal studies to understand the molecular machineries of membrane tethering, docking, and fusion processes in the endomembrane organelle systems of eukaryotic cells (from yeast to human). Intracellular membrane tethering, docking, and fusion events are fundamental and conserved biological reactions, which are vital for vesicle trafficking between subcellular organelle membrane compartments and plasma membranes, organelle morphology, hormone secretion, and also synaptic neurotransmission. Earlier seminal studies have revealed that membrane tethering, docking, and fusion are temporally and spatially regulated in cells by the diverse sets of key protein components, which include SNARE-family proteins, SNARE-interacting chaperone proteins such as Sec1/Munc18-family proteins, Rab-family small GTPases, Rab-interacting effector proteins, and tethering multisubunit complexes. However, it has still remained enigmatic how those essential protein factors cooperate to specifically and efficiently mediate membrane tethering, docking, and fusion events. In our group, we explored the vital tethering/docking/fusion machineries by *in vitro* reconstitution with purified recombinant proteins (SNAREs, Rabs, and so on) and synthetic lipid bilayers with defined lipid compositions. Using homotypic yeast vacuole membrane fusion as a model, we found that the functional synergy of SNARE chaperones (Sec17p, Sec18p, and the HOPS complex) and phosphoinositides is essential to trigger rapid SNARE-dependent membrane fusion. Next, by comprehensively studying 14 purified SNAREs in yeast, which localize at not only vacuoles but also endosomes, Golgi, and endoplasmic reticulum (ER), for their capacity to assemble into QabcR-SNARE complexes and initiate reconstituted proteoliposomal fusion, we uncover the novel concept that SNAREs employ multiple and distinct strategies to confer the specificity of membrane fusion. Moreover, we recently have developed the *in vitro* assays to quantitatively analyze membrane tethering of synthetic liposomes in the presence of the protein factors related to physiological tethering processes. Our reconstitution studies now establish that membrane-anchored human Rab GTPases, including ER/Golgi Rab2a, endosomal Rab5a, and lysosomal Rab7a, directly and specifically catalyze membrane tethering in a guanine nucleotide-independent manner. This leads us to further study how exactly Rab GTPases and their effectors or tethering factors work together on membranes to mediate membrane tethering for ensuring the directionality of intracellular membrane trafficking.

【Current Research Programs】

1) Understanding the molecular machinery to catalyze membrane tethering, docking, and fusion events in eukaryotic endomembrane systems
2) Mechanisms by which miscellaneous sets of SNAREs, Rab GTPases, and their interacting proteins control the directionality of intracellular membrane trafficking

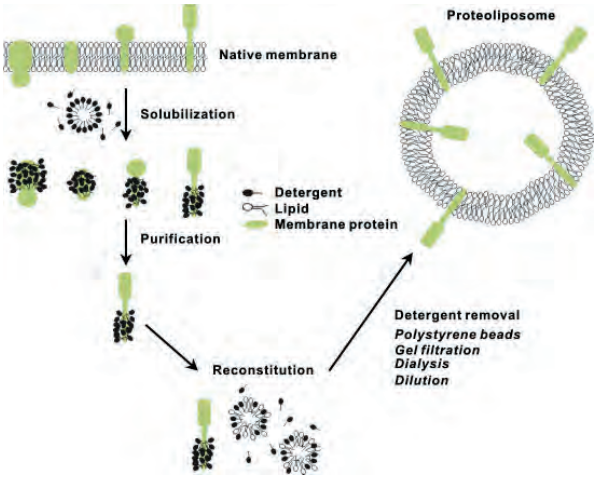

Fig. 1. Reconstituted proteoliposomes with purified membrane proteins and synthetic liposomes with defined lipid compositions.

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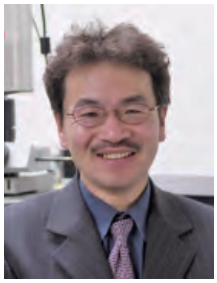
Division of Integrated Protein Functions

Laboratory of Genome and Chromosome Functions



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Laboratory of Genome-Chromosome Functions is engaged in the following chromosome and genome stability research. 1. Molecular mechanisms of recombination; homologous recombination and non-homologous end-joining. 2. Mechanism of genome stability and genome instability associated with cancer. 3. Mechanism of meiotic recombination which is essential for production of genome diversity and chromosome segregation. 4. Control of chromosome morphogenesis such as synaptonemal complex formation and chromosome dynamics in meiosis.

Errors in the recombination lead chromosome instability which results in turmorigenesis in somatic cells and miscarriage and aneuploidy diseases such as Down syndrome. The biological relevance to these diseases is also explored.

【Current Research Programs】

1) Analysis of proteins working with RecA homologues in recombination
2) Studies on chromosome morphogenesis
3) Analysis of the roles of chromatin modification in meiotic recombination
4) Mechanisms of choice of DSB repair pathways
5) Analysis of recombination in human cells

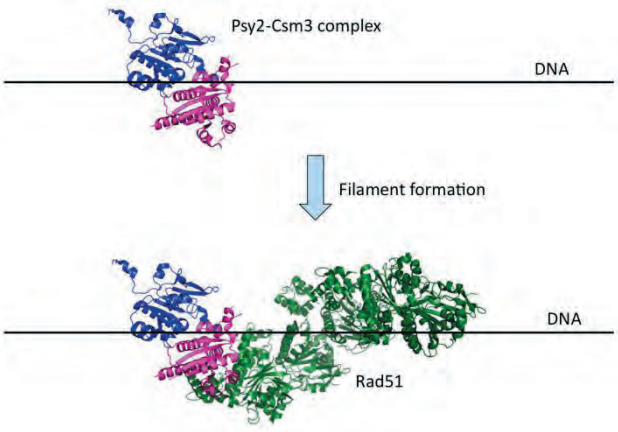

Fig. 1. Promotion of Rad51 filament formation by Psy3-Csm2 dimer. We identified a new protein complex involved in homologous recombination. This complex containing Psy3, Csm2, Shu1 and Shu2 promote the assembly of Rad51. X-ray structure analysis revealed that a core complex of Psy3-Csm2 is structurally similar to Rad51 dimer. Based on the structure of the complex, we propose a model in which Psy3-Csm2 (blue and red) dimer bound to single-stranded DNAs promotes the assembly of Rad51 filament (green) for homology search

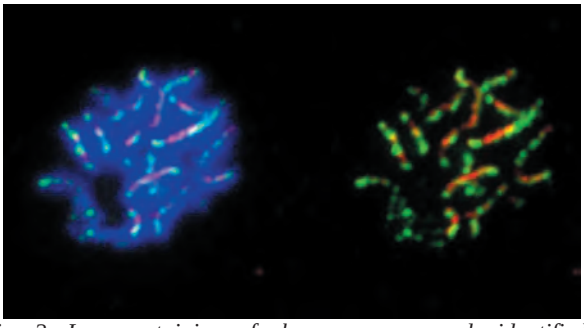

Fig. 2. Immunostaining of chromosome spreads identified a meiosis-specific chromosome structure, the synaptonemal complex (SC), in which paternal and maternal homologous chromosomes are synapsed along the chromosomes. Zip1 (green) is a component of the central element of the SC while Rec8 (red) is a cohesion component for the axial elements of the SC.

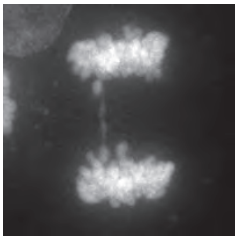

Fig. 3. Anaphase bridge formation in mitotic mammalian cells. When DNA double-strand breaks are introduced on mitotic chromosomes, anaphase bridges are formed, which, unless repaired, leads to chromosome instability.

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Laboratory of Regulation of Neuronal Development

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Laboratory of Regulation of Neuronal Development is engaged in studying the protein-protein interaction (PPI) networks that are involved in neuronal differentiation and survival. In 1991, we discovered the novel protein necdin (neurally differentiated embryonal carcinoma-derived protein) that was induced in neurally differentiated pluripotent stem cells. The necdin gene (*NDN*) is expressed only from the paternal allele through genomic imprinting, a placental mammal-specific epigenetic control of gene expression. Necdin is a member of the MAGE (melanoma antigen) family proteins that share a highly conserved domain known as the MAGE homology domain (MHD)(Fig. 1). Necdin binds to many regulatory proteins involved in the proliferation, differentiation, survival and death of mammalian neurons and neural stem/precursor cells. Thus, necdin serves as a hub of PPI networks for neuronal development (Fig. 2). We are also studying the possibilities that necdin deficiency causes abnormal brain development and neurodenerative disorders in humans.

【Current Research Programs】

1) Molecular mechanisms of neuronal differentiation
2) Molecular mechanisms of neuronal survival

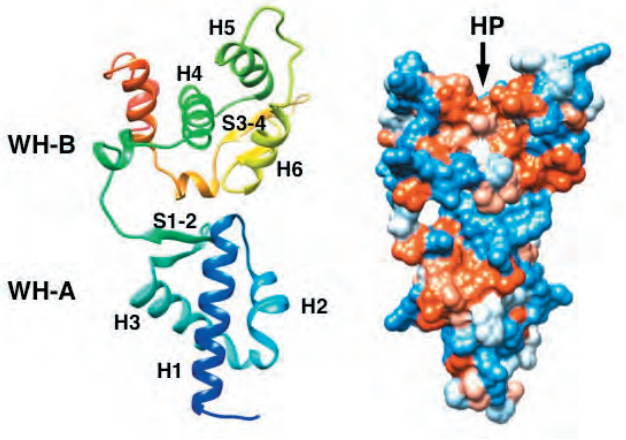

Fig. 1. A model structure of necdin MAGE homology domain.
A structural model of necdin MAGE homology domain (MHD) was predicted on the basis of structural data of necdin-like 2 (PDB 3NW0) using the Spanner program developed in our institute. Necdin MHD has a goblet-like appearance and consists of two winged helix motifs (WH-A, WH-B), which are often found in nuclear proteins that interact with DNA and proteins to form supramolecular complexes. Studies using necdin MHD mutants suggest that the hydrophobic pocket region (right, HP) including helices 4 and 5 (left, H4-H5) interacts with various regulatory proteins.

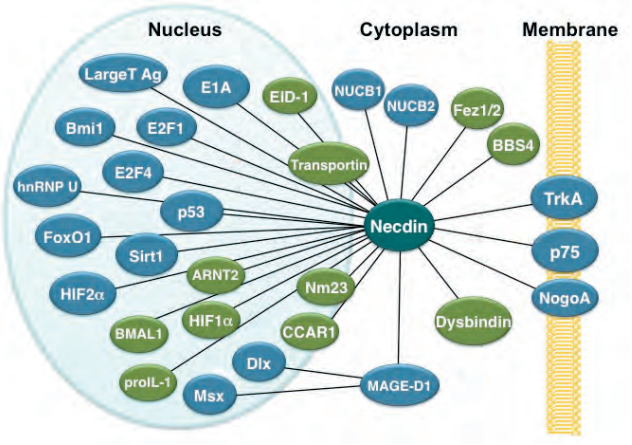

Fig. 2. Necdin as a hub of the protein-protein interaction (PPI) network for neuronal development. Necdin interacts with many proteins and forms PPI networks that are operative in mammalian neurons and neural stem/precursor cells. Necdin binds to nuclear proteins (p53, E2F, Sirt1, FoxO, HIF, Bmi1, etc.) and transmembrane receptor proteins (Trk, p75, etc.). These proteins also serve as hubs of the PPI networks involved in cell survival (death), cell proliferation, and energy metabolism. Thus, necdin is likely to integrate these PPI networks in neurons and neural stem/precursor cells. Presented are functionally relevant PPIs reported by us (light blue elements) and others (yellowish green elements). Necdin interacts physically with dozens of proteins other than these proteins.

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Laboratory for Molecular and Developmental Biology

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Our laboratory studies molecular mechanisms underlying the development and function of the vertebrate central nervous system (CNS) using various research methods of molecular biology, mouse genetics, biochemistry, cell biology and neural physiology. Our brain consists of more than 100 billions of neurons. To function as a brain, numerous numbers of neurons must be generated at right places and they must be interconnected each other. We use the retina as a model system to understand how DNA encodes programs to generate various neurons and glial cells, form precise neuronal circuits, and enable complicated neuronal function. We also focus on how abnormality of biological processes in development and maturation leads to human diseases. We are eager to contribute to development of diagnosis and cure of human diseases. Together, our lab aims to elucidate mechanisms and principles underlying the CNS development from DNA programs to physiological function and human diseases.

【Current Research Programs】

1) Molecular analysis of synapse formation in the CNS.
2) Elucidation of functional roles of microRNAs (miRNAs) in CNS development.
3) Analysis of molecular mechanisms underlying neuronal differentiation.
4) Functional analysis of cilium, an antenna of a cell, in the CNS.

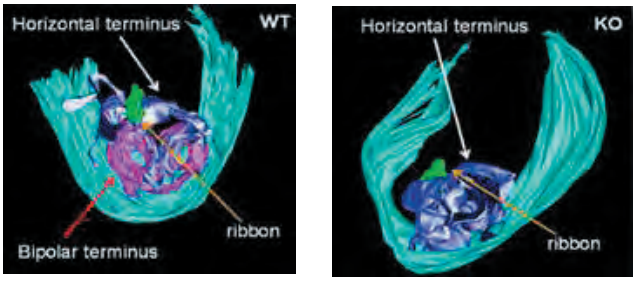

Fig. 1. Electron tomography of rod photoreceptor synapse terminals using ultrahigh-voltage electron microscopy. In the WT mouse retina, photoreceptor axonal terminus forms invagination to appose dendritic terminals of horizontal cells and bipolar cells to form the ribbon synapse. On the other hand, Pikachurin KO mice showed improper apposition of the bipolar cell dendritic tips to the photoreceptor ribbon synapses.

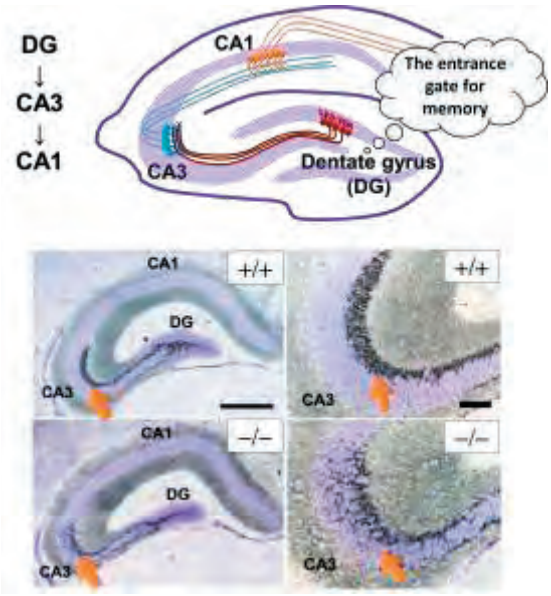

Fig. 2. Aberrant sprouting of mossy fibers in the miR-124a KO mouse. The mossy giver terminals were visualized by Timm staining with Nissl counterstaining at postnatal day 10. Scale bars represent 500 um.

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Laboratory of Nuclear Network

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Organisms promptly and appropriately respond to various environmental changes for their survival. In order to respond to various forms of stress, cells have developed signal transduction cascades for each stress. We will clarify the molecular bases for networks of proteins or cellular signals, focusing on the key proteins that are commonly involved in several distinct signal transductions. Our current interests are crosstalk of signal transductions for chromosome maintenance and those for nutrient recognition. Our study will contribute to understanding the mechanisms of chromosome disease, cancer or diabetes.

【Current Research Programs】

1) Analysis of molecular functions of telomere-binding proteins.
2) Analysis of functional networks among the chromosomal non-coding regions (including telomeres).
3) Analysis of molecular bases for Tel2-PIKK network.

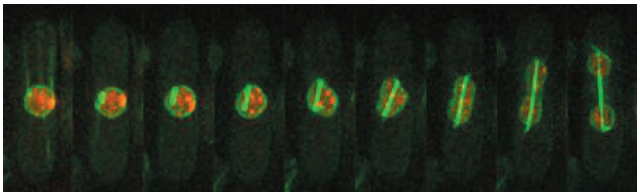

Fig. 1. Movement of telomeres in mitosis. A telomere-binding protein Taz1 (red), the nuclear envelope (green), and microtubule (green) were observed using the live cell-imaging microscope. Telomeres are transiently released from the nuclear envelope during mitosis.

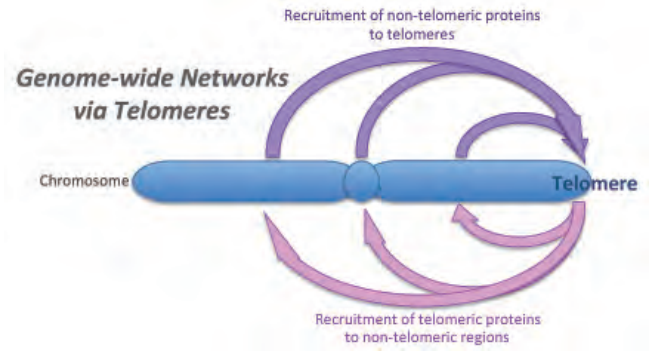

Fig. 2. Telomere-binding proteins are involved in various cellular phenomena. We focus on analyses of the functional networks among telomeres, nuclear architectures, and other chromosomal non-coding regions.

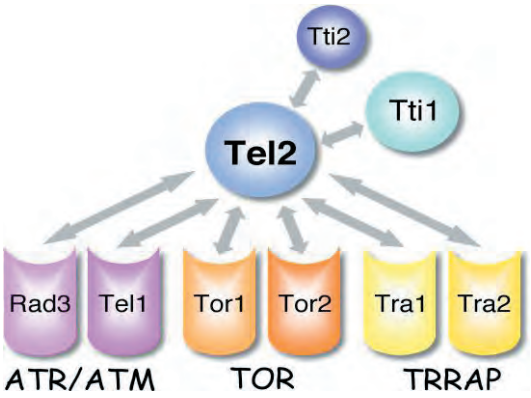

Fig. 3. Tel2-PIKK network. Tel2 protein interacts with all the PIKK (phosphoinositide 3-kinase-related kinase) family proteins and with Tti1 and Tti2 proteins. ATR/ATM proteins are involved in DNA damage/replication checkpoint. TOR proteins regulate uptake of nutrients and cell growth. TRRAP proteins are the common components of histone acetyltransferase, and regulate variety of cellular processes. How Tel2 regulates PIKK proteins is a big issue.

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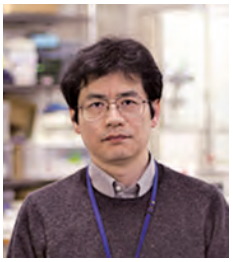
Laboratory of Homeostatic Integration



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Laboratory of Homeostatic Integration is engaged in studying animal metabolism and physiology based on protein sciences. We especially focus on the enzymes that are involved in dipeptide metabolism to elucidate the functional roles of dipeptides and their components. Recently we are studying non-covalent complexes of a dipeptidase, CN2, using ESI-TOF MS to analyze its reaction mechanism, metal affinity and substrate recognition. We are also trying to develop new proteomic techniques for researches in physiology, pathology and diagnosis. s

【Current Research Programs】

1) Studies on molecular mechanisms of biosynthesis and degradation of histidine dipeptides.
2) Analysis of non-covalent complexes of proteins using mass spectrometry.
3) Development of proteomic techniques and its application to physiology and pathology.
4) Development of procedures for evaluation of protein preparations for structural analysis and its application.

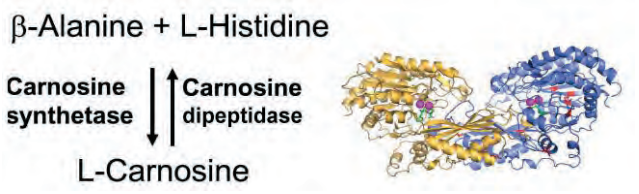

Fig. 1. Synthesis and degradation of carnosine *Carnosine is a naturally occurring dipeptide present at high concentrations in the skeletal muscles and the brain in mammals. This is synthesized from beta-alanine and histidine by carnosine synthetase, while degraded into these amino acids by carnosine dipeptidases. We found a Mn2+-dependent cytosolic dipeptidase, CN2, can hydrolyze carnosime and analyzed its primary and tertially structures (Ref. 6).*

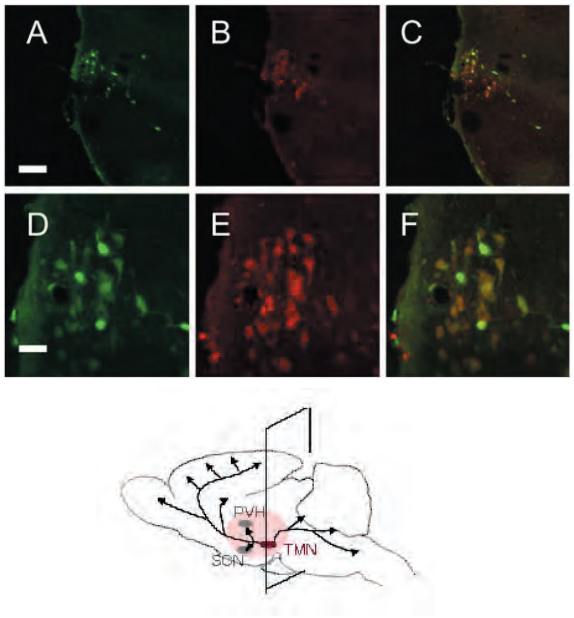

Fig. 2 Localization of carnosinase CN2 in the hypothalamus. *The carnosine-hydrolyzing dipeptidase, CN2, is expressed in a variety of tissues in mice, but its expression levels are highly variable depending on cell types. In the brain, CN2 (B, E) is highly expressed in histaminergic neurons in the tuberomammillary nucleus of the hypothalamus (TMN), where it is colocalized with the histamine-synthesizing enzyme, histidine decarboxylase (A, D)(Ref. 7).*

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Division of
International Collaborative Research

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Research in the laboratory of Matthias Rögner focuses on the structure, function, regulation and biogenesis of energy transducing membrane proteins from cyanobacteria. Topics involve dynamics and adaptations of bioenergetic processes in the thylakoid membrane in response to environmental signals both on the level of individual proteins, their (transient) interaction partners and on the level of membrane composition. First, inter-molecular interactions of the electron transfer complex between PhotosystemI and Fd from *Thermosynechococcus elongatus* were analyzed by the transferred cross-saturation method of NMR and X-ray crystallography. Most recently, a subtype of the NDH-1 complex from *Thermosynechococcus elongatus*, NDH-S, which is involved in a unique inorganic C-concentration mechanism, was crystallized in collab. with the Kurisu group (IPR). Additionally, the structure of recombinant CupS was solved by NMR in collaboration with T. Ikegami (IPR), including a model for its interaction with the transmembrane subunits of the complex (1, 2). Also, the solution structure of the Cyt. b_6f-complex subunit PetP, which is specific for cyanobacteria and red alga and regulates linear *vs.* cyclic photosynthetic electron transport, was determined for the first time by NMR.

The Happe group analyzes the anaerobic metabolism of the green alga *Chlamydomonas reinhardtii* in all its aspects. They also study structure-function relationships of Fe-Fe hydrogenases including a detailed characterization of the active center (H-cluster) and the catalytic turnover process. A novel *in vitro* maturation assay was established leading to semi-artificial hydrogenase with high catalytic activity (4-6). The structure of these novel biocatalysts was recently solved together with the Kurisu group (Fig. 1).

Both groups cooperate in the creation of a cyanobacterial design cell which combines the mechanism of photosynthetic water-splitting with hydrogen production *via* imported hydrogenase at the expense of CO_2-fixation (Fig. 2). Prerequsite is the re-routing of photosynthetic electrons by modifying interactions between Ferredoxin (Fd) and FNR on the one side and Fd with hydrogenase (H_2ase) on the other. For this purpose, various FNR-mutants have been designed in coop. with T. Hase (IPR) and characterized by *in vitro* activity assays and interaction studies (ITC, with the Ikegami-group, and SPR). The most promising mutants have recently been transformed into *Synechocystis* PCC 6803 and are now under evaluation.

【Current Research Projects】

1) Structural dynamics of cyanobacterial thermophilic NDH-1 complexes (Ref. 1+2) & Cyt. b_6f-complex.
2) Strategies for designing H_2-producing cyanobacterial model cells (Ref. 3).
3) Photobiological H_2 production in green algae, cell metabolism and signaling under anaerobiosis (Ref. 4).
4) Structure-function relationships of natural and semiartifical Fe-Fe hydrogenases, ferredoxins and maturases (Ref. 5+6).

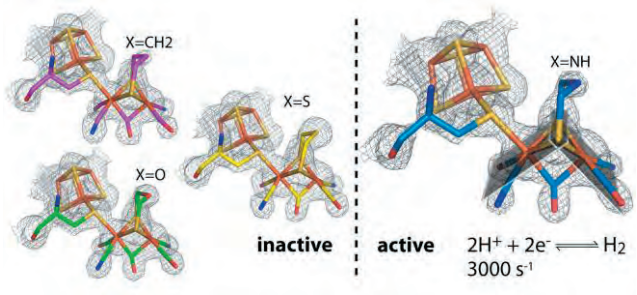

Fig.1. *Crystal structures of the catalytic center of active and inactive semiartifical [FeFe]-hydrogenase maturated* in vitro *with different synthetic 2Fe complexes of the kind* $Fe2[\mu\text{-}(SCH_2)_2X](CN)_2(CO)_4^{2-}$. *The central group of the dithiolate bridge is indicated next to the respective structure.*

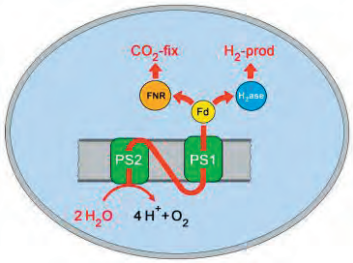

Fig. 2. *Cyanobacterial design cell for hydrogen production from water. Key elements are the water-splitting complex PS2 as source of electrons and the distribution of electrons at the acceptor side of PS1 between* CO_2*-fixation and* H_2*-production, guided by affinity design of Fd vs. FNR and hydrogenase, respectively. (3)*

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Laboratory of Foreign PI

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Research in the Hall laboratory is concerned with the physical study of important biochemical processes related to disease states. One example of this coupled science/medicine research program is the study of amyloid formation and its relationship to the spectrum of amyloidosis diseases [**1,2**]. Amyloid fibers are linear protein aggregates capable of being formed from various peptides and proteins [**2,3**]. In their most basic form, amyloid fibers have dimensions characterized by a width of 4-20 nm and a length in the nanometer to sub-millimeter range [**2,3**]. Peptide/protein monomeric units are joined by inter-peptide beta-sheets formed along the long axis of the fiber. The designation of amyloid is conferred upon a protein aggregate if, in addition to displaying fiber like structure, it possesses specific dye binding capabilities and a cross-beta X-ray fiber diffraction pattern [**1,2**]. Although amyloid formation is coming to be thought of as a potentially common property of most, if not all proteins, in medicine there are only twenty-seven distinct peptides that are known to be associated with an amyloidosis disease state [**1,4**]. These twenty-seven basic forms of amyloidosis (and their mutational variants) display a huge diversity in behaviors with respect to the pathophysiology of disease progression, with some showing tissue/organ specificity, while others tend towards non-specific dispersal of amyloid throughout the body. In general much of what we know (or think we know) about amyloid and its relationship to disease is based on qualitative experimental observation [**1,5**]. This is partly due to the general complexity of the systems studied, the difficulties of performing quantitative measurement in patients, and the limitations associated with the methodological approaches employed to study these processes. Work in the Hall laboratory is focused on sharpening up some of these foundations by approaching the topic from a biophysical perspective i.e. experiments interpreted through the lens of a constraining mathematical model [**1-8**]. Using a combination of experimental/computational approaches we would like to, in combination with Japanese colleagues at the IPR, explore the following topics,

【Current Research Programs】

1) Efficient means for fractionating and purifying heterogeneous amyloid fiber samples [**2,3**]
2) Non-subjective methods for characterizing gross amyloid structural properties using AFM and TEM **[3]**
3) Examine amyloid fiber breakage position effects as determinants of amyloid fiber behavior [**5,6**]
4) Placement effects of peptides within larger polypeptide chains as determinants of amyloid growth [**5,6**].
5) Spatial modeling of amyloidosis disease progression using computation and in vivo imaging data **[1,6,7].**
6) Elucidation of peptide structural precursor states of amyloid using NMR measurements.
7) Construction of an arc-length distance matrix data base for all proteins in the PDBj **[1,8]**.
8) Systematic application of a classification scheme for defining the surface chemical properties of amyloid **[1]**.

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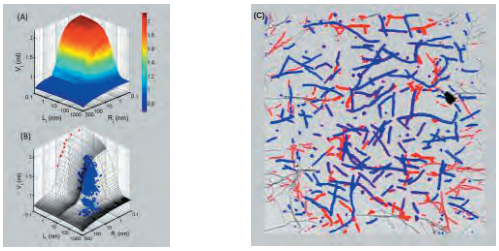

Fig. 1. *(A,B) Theoretical and experimental modeling of amyloid migration through a size-exclusion chromatography column.[3] (C) Semi-automated analysis of electron microscopy measurements of insulin derived amyloid fibers using the ADM software [2].*

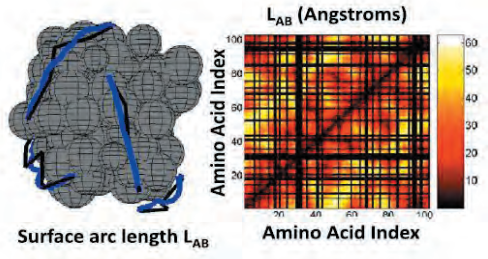

Fig. 2. *Description of a new protein distance matrix based on surface arc-length that is relevant to the interaction of non-structured polymers (such as intrinsically disordered proteins) with globular proteins [8]*

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Laboratory of Visiting Scientist

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We are investigating biomolecules using liquid-state and solid-state nuclear magnetic resonance (NMR) to understand their structure and function. We are also developing experimental methods for those purposes.

【Current Research Programs】

1) Solid-state NMR of biomolecules.
2) Solution-state NMR for detecting motion of molecules.
3) Solution-state NMR for structure and interaction of biomolecules.
4) Ultra-high field NMR.

Solid-state NMR is a suitable technique to investigate biomolecules in solid-like environment, such as membrane proteins. Comparing with the crystallographic study, their native environment can be kept in the NMR study. Heterogeneous system in terms of its environment or structure can be the target of solid-state NMR. Comparing with solution NMR, the difficulty coming from molecular size is less severe. Biomolecules in the large complex will be the anticipated target. Recently, by the development of instruments and methods, we can obtain fairly good spectra of complicated membrane proteins.

Aquaporin Z from E. coli is a water channel protein, consisting of 231 amino acids. This size is challenging for solid-state NMR. The molecule is fully labelled with 13C and 15N, and we can get assignments by connecting neighboring 13C and 15N atoms sequentially. The lack of 1H signals (comparing with solution NMR) brings about the problem poor separation. To get rid of overlaps of NMR signals, we record 3-dimensional spectra to separate signal in the 2 dimensions and connect to the next atom in the last dimension. We combine the following connections: N-CA-CO connection by NCACX, CA-CO-N connection by NCOCX, CO-N-CA connection by CANCO. Then, we can connect to the backbone signals 1 residue ahead.

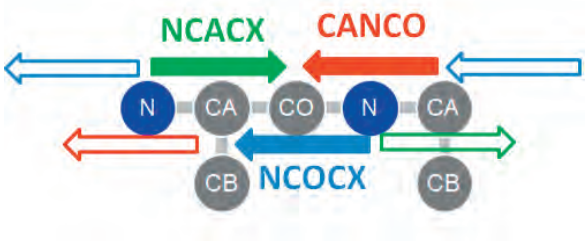

Fig. 1. Three 3-dimensional experiments for assignment

Actual analysis was hard. There are still many overlaps in 2 dimensional space. We also recorded spectra to connect 4 atoms, by which we skip the overlapped signal and connect to the next atom. Transmembrane helices are uniform in structure and amino acid composition, leading to failure of assignments. The assignments of other parts are promising. Soluble parts of membrane proteins are often important for function and binding of drugs. In the Aquaporin Z case, we can observe chemical shift perturbation by binding of drug. The determination of the binding site of drug is one of the purpose after the assignment.

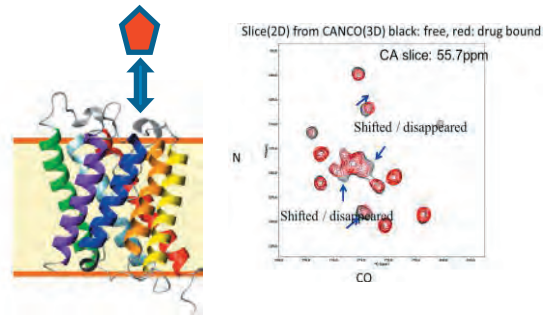

Fig. 2. Detecting binding of drug molecule to Aquaporin Z in 3D spectrum. Measured on 700MHz NMR with 3.2mm HCN probe.

Though the crystal structure of Aquaporin Z is known, A few of the chemical shifts observed in the current study showed unexpected values. This might be an indication of protein structure of native environment. We are closely analyzing them.

The current standard techniques presented here required high cost of sample and measurement time, because the sensitivity and resolution are not sufficient. New techniques of ultra-high field NMR(ref. 1) and 1H detection NMR will renew the efficiency of solid-state NMR. DNP is also most expected technique. In future, we will be able to apply solid-state NMR to variety of biomolecules with much low cost and time.

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Three-dimensional protein structure brings us the beautiful structural biology. X-ray crystallography that is the best method to determine atomic coordinates of protein molecules is a familiar tool of protein science. However, X-ray structure determinations of biological macromolecular assemblies and membrane proteins that have key roles in biological cells still contain difficulties to be conquered. The main aim of us is the X-ray structure determinations of respiratory complexes residing in the mitochondrial innermembrane in order to elucidate the molecular mechanism of the highly organized biological processes at atomic level.

【Current Research Programs】

1) Structural life science of mitochondrial inner membrane
2) Development of methods of high resolution and time-resolved structural analyses by XFEL for biological macromolecular assemblies

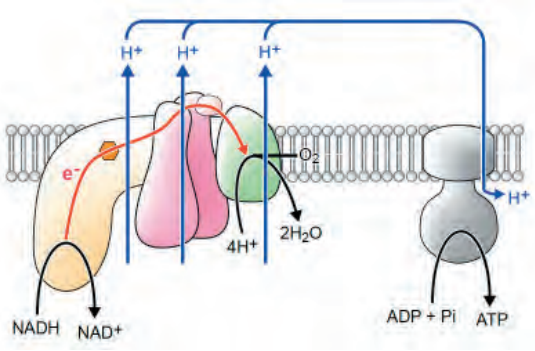

Fig. 1. A respiratory supper complex consisting of Complexes I, III and IV pumps proton to create efficiently an electrochemical proton gradient across the mitochondrial inner membrane and may reduce harmful superoxide production. Complex V generated ATP by using the electrochemical proton gradient. We are currently working on crystallization of the respiratory supper complexes from various organisms.

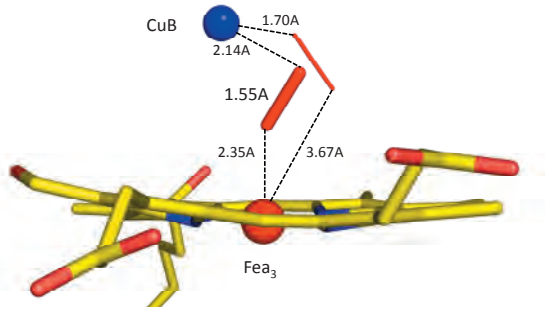

Fig. 2. The X-ray structural analysis of bovine cytochrome c oxidase using radiation damage free data at the SACLA indicates that a peroxide anion with an O-O distance of 1.55 Å exhibits multiple conformations in the binuclear center, in which the main component, with 95% occupancy, has O-CuB and O-Fea3 distances of 2.14 Å and 2.35 Å, respectively, and the minor component has analogous distances of 1.95 Å and 3.76 Å. Consequently, the compound in the dioxygen reduction center of the fully oxidized state is a peroxide anion.

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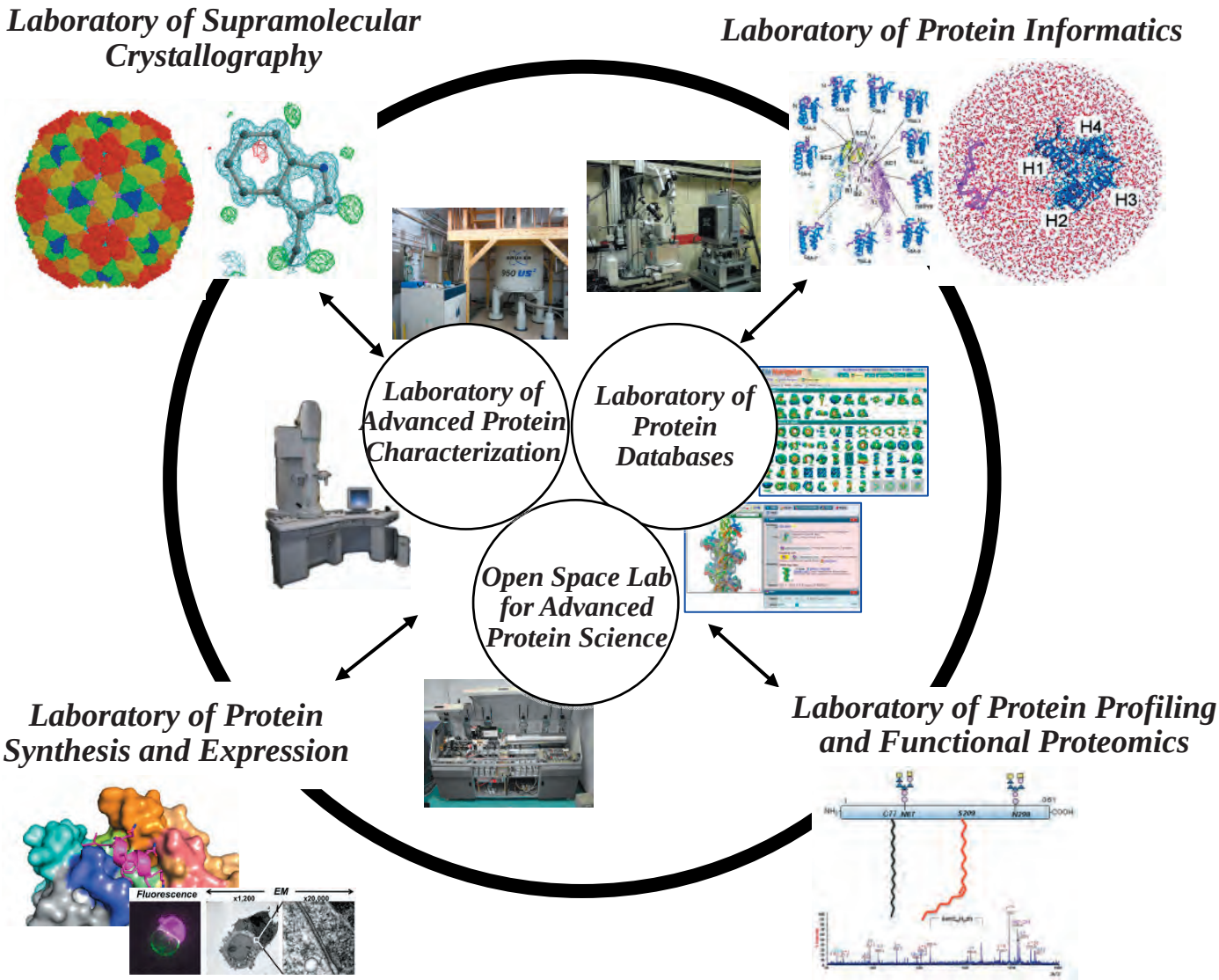
Research Center for State-of-the-Art Functional Protein Analysis

Research Center for State-of-the-art Functional Protein Analysis

The research Center for State-of-the-art Functional Protein Analysis (RCSFP) was established in 2012, inheriting the success of its predecessor The Research Center for Functional and Structural Proteomics. In recognition of the importance of expanding the scope of research outside the field of proteomics, the Center now aims to answer various scientific questions by incorporating a full range of cutting-edge technologies of protein analysis and world-class analytical instruments. The Center consists of six divisions and one open space laboratory and covers following research areas: protein profiling and functional proteomics, protein synthesis and expression, supramolecular crystallography, protein informatics, advance protein characterization, and database development.



Laboratory of Protein Profiling and Functional Proteomics

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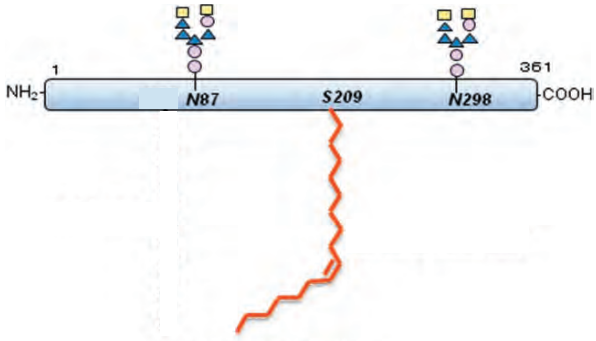
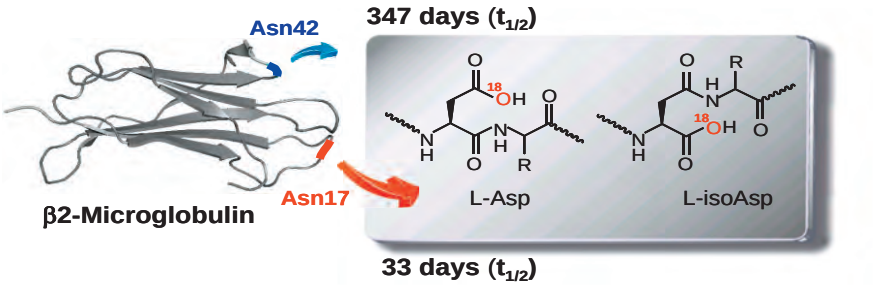
Mass spectrometry (MS) is well accepted technique for the analyses of chemical structures of biological compounds. For the last three decades, we have been working to develop methods for determining primary structures and post-translational modifications of proteins by using MS. In conjunction with accumulating protein and gene sequence databases, we are using state-of-the-art MS for large-scale protein identification which is indispensable for proteomics research. We apply the following developed methods to the structural analysis of micro quantities of peptides, proteins, and their related substances. We have found several novel post-translational modifications such as farnesyl moiety at the C-terminal Cys, heterogeneous fatty acids at the N-terminal Gly, ε-(γ-glutamyl)lysine in core histones, phosphatidylethanolamine linked to the C-terminal Gly, palmitoleoyl moiety at Ser, etc.

【Current Research Programs】

1) Development of chemical/analytical methods and software for analysis of protein primary structure by mass spectrometry
2) Mass spectrometric analysis of post-translational modifications
3) Development of chemical and analytical methods for proteomics
4) Study on fragmentation in mass spectrometry of peptides and carbohydrates
5) Hardware development for high-sensitivity and high-accuracy mass spectrometry



Posttranslational Modifications of Wnt Protein
-Wnt Lipid Modifications: Not as Saturated as We Thought-
(Takada R et al, 2006; Yamamoto H et al, 2013, 2015)



Quantitative Analysis of Deamidation and Isomerization in β2-Microglobulin by ^{18}O Labeling. (Fukuda M & Takao T, 2012)

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Laboratory of Protein Synthesis and Expression

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Assistant Professor	*Yu KITAGO*
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"How things work?" - This is the question most, if not all, scientists are eager to answer. Our passion is to unravel the mechanism of function of proteins in a living organism where they work as small "molecular machines" with a remarkable precision. This lab can be described as a "structural biology lab", but our goal is not the determination of three-dimensional structure of proteins. Rather, we FIRST solve the structure, THEN perform biochemical, biophysical, and cell biological experiments to draw novel pictures about molecular mechanism of proteins, taking advantage of the structural information that is not available to anybody else. We are mostly focused on the molecular interactions between cell surface receptors and their extracellular ligands implicated in the signal transduction in a wide variety of biological contexts, ranging from development, neurobiology, and immunity. Cellular response to the extracellular environment depends on the “sensing” the extracellular cues by use of the receptor-ligand system. Binding of ligands to the extracellular domain of the receptors transduces signals into cells that initiates various cellular events, ultimately changing the cell fate. In spite of a wealth of cell biological “signal transduction researches” conducted at every corner of today's biomedical arena, mechanism for the “signal transmission across the membrane”, the very first step in the signaling pathway is poorly understood. Our study focuses on questions such as how receptors recognize their specific ligands, how this recognition leads to structural change in the receptor complex, and how the information cross the plasma membrane without transporting chemical entity.

Our approach is multi-faceted. As the methodology for structural analysis, we utilize X-ray crystallography, which determines 3D structure of proteins at atomic resolution, and electron microscopy, which can derive structure of protein complexes too large for XRD or visualize the shape of proteins in their true biological environment (e.g., within cells). The latter expertise includes cutting-edge technologies such as cryoelectron microscopy and electron tomography. In order to back these structural efforts, we also develop an array of in-house technologies critical for the production of high-quality recombinant proteins using mammalian cell expression system.

【Current Research Programs】

1) Structure and function of extracellular ligands and their receptors implicated in cell adhesion and neural guidance/morphogenesis.
2) Structure-guided molecular design of novel proteins.
3) "Correlative" structural analysis by multidisciplinary approach.
4) Development of high-quality recombinant protein production system.
5) 3-D visualization of conformationally heterogeneous macromolecules using electron microscopy.

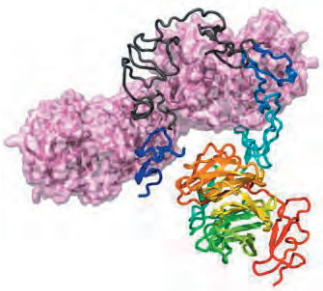

Fig. 1. Crystal structure of complex between reelin (pink) and its receptor (rainbow)

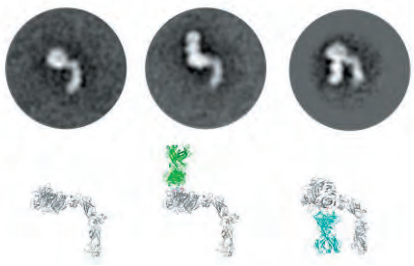

Fig. 2. Epitope mapping of antibody (green, cyan) against Plexin (gray) using negative stain EM imaging

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Assistant Professor	*Mayumi AMANO*
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There exist various biological macromolecular assemblies consisting of proteins, nucleic acids, sugars, lipids, and other substances in living cells. These macromolecular assemblies play key roles in all living system. Our laboratory works on structure determination of biological macromolecular assemblies, as well as proteins, which play important roles in biological system, using X-ray crystallography. Development of tools for X-ray crystal structure determination of biological macromolecular assemblies, including synchrotron radiation beamtime at SPring-8, is also one of our main works.

【Current Research Programs】

1) X-ray structure determination of macromolecular assemblies and proteins
2) Development methodologies for X-ray structure determination of biological macromolecular assemblies using synchrotron radiation and X-ray free electron laser
3) Development of data processing algorithm of diffraction data from micro-crystals

Fig. 1. Synchrotron radiation beamline for Biological Macromolecualr Assemblies (SPring-8 BL44XU). This beamline utilizes high-brilliant undulator radiation of SPring-8 to collect high quality diffraction data from biological macromolecular assembly crystals. About half of the user time is opened for the research groups outside of the IPR.

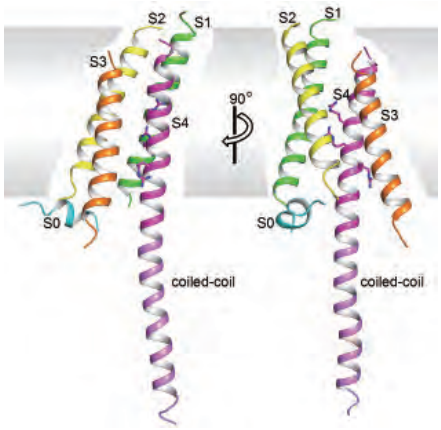

Fig. 2. Structure of Voltage-gated Proton Channel (VSOP/Hv1). We have succeeded to solve the atomic structure of the voltage-gated ion channel (VSOP/Hv1) by X-ray crystallography at 3.45 Å resolution. This is the first structure of the resting-state of the voltage-sensor protein family and it gave valuable information on the mechanism of voltage-sensor domain. In addition, the structure showed the inhibition mechanism by binding of zinc ion.

【References】

1. X-ray crystal structure of voltage-gated proton channel. Takeshita K, Sakata S, Yamashita E, Fujiwara Y, Kawanabe A, Kurokawa T, Okochi Y, Matsuda M, Narita H, Okamura Y, Nakagawa A (2014) *Nat. Struct. Mol. Biol.* **21**, 352-357.

2. High-resolution X-ray crystal structure of bovine H-protein using the high-pressure cryocooling method. Higashiura A, Ohta K, Masaki M, Sato M, Inaka K, Tanaka H, Nakagawa A (2013) *J. Synchrotron Rad.* **20**, 989-993.

3. A new protein complex promoting the assembly of Rad51 filaments. Sasanuma H, Tawaramoto MS, Lao JP, Hosaka H, Sanda E, Suzuki M, Yamashita E, Hunter N, Shinohara M, Nakagawa A, Shinohara A (2013) *Nat. Commun.* **4**, 1676.

4. Crystal structure of the C-terminal domain of Mu phage central spike and functions of bound calcium ion. Harada K, Yamashita E, Nakagawa A, Miyafusa T, Tsumoto K, Ueno T, Toyama Y, Takeda S (2013) *Biochim. Biophys. Acta: Protein Proteomics* **1834**, 284-291.

Laboratory of Protein Informatics

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Laboratory of Protein Informatics is engaged in the following protein informatics researches: (1) Structural bioinformatics studies covering molecular modeling and design, (2) Development of new databases and Web services, and (3) Large scale molecular simulations by parallel computers with GPGPUs to examine free energy landscapes of biomolecular systems to study the procedures of protein folding and of forming protein complexes.

【Current Research Programs】

1) Bioinformatics studies focused on protein structures and protein-protein interactions (Refs. 1-3)
2) Development of new algorithms for molecular simulations to examine the free energy landscapes on protein folding and formation of protein complexes (Refs. 3-6)

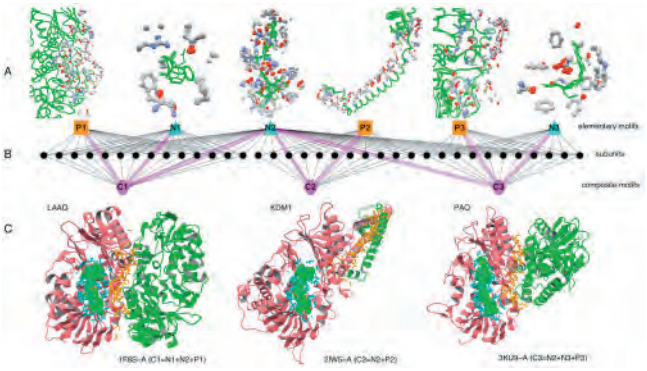

Fig. 1. Composite Structural Motifs of Binding Sites for Delineating Biological Functions of Proteins (C). *They are defined by integrating the elementary motifs (A) associated with individual subunits having binding sites for ligands including small molecules, proteins and nucleic acids. These 3 composite motifs share the same elementary motif for FAD binding (labeled N2 in B). (Ref. 1)*

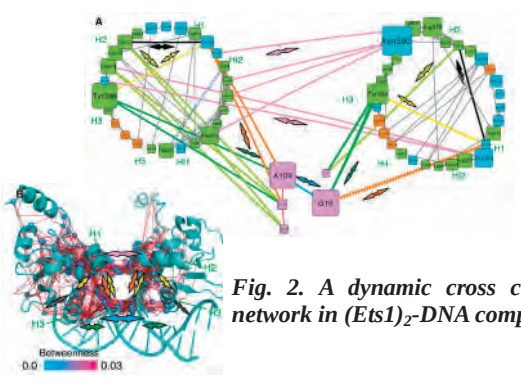

Fig. 2. A dynamic cross correlation network in (Ets1)$_2$-DNA complex.

A. The two circles correspond to the two Ets1 proteins and the pink nodes are the DNA. Each node indicates a residue and each edge indicates a proximal residue pair with a highly positive dynamic correlation observed during molecular dynamics simulation. B. A 3D representation of the core network. Each sphere shows the atom having large Betweenness value, which is a measure of the importance of each residue for the connection of the entire network. (Ref. 5)

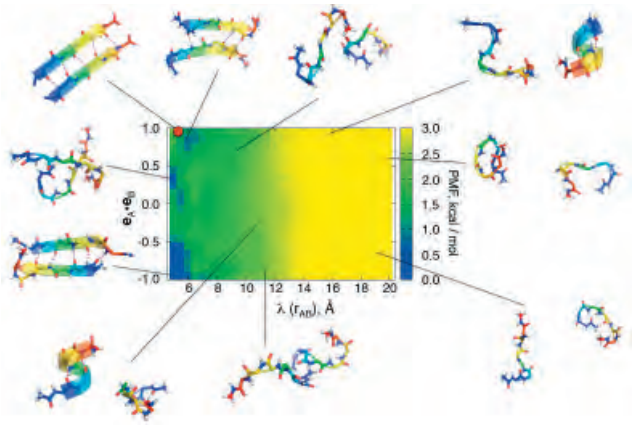

Fig. 3. Free energy landscape and corresponding structures at 300K for homo-dimer formation of two Alzheimer's peptides by V-AUS (Virtual-system coupled Adaptive Umbrella Sampling) method. *The horizontal axis is the distance between the centers of the two peptides, and the longitudinal axis is the inner product of the unit direction of each peptide. Graph colors correspond to the free energy, and the red circle at the upper left corresponds to the crystal structure. (Ref.6)*

【References】

1. Composite structural motifs of binding sites for delineating biological functions of proteins. Kinjo AR, Nakamura H (2012) *PLoS One* **7**, e31437.

2. 3D flexible alignment using 2D maximum common substructure: dependence of prediction accuracy on target-reference chemical similarity. Kawabata T, Nakamura H, (2014) *J. Chem. Info. Model.* **54**, 1850-1863.

3. High-resolution modeling of antibody structures by a combination of bioinformatics, expert knowledge, and molecular simulations. Shirai H, Ikeda K, Yamashita K, Tsuchiya Y, Sarmiento J, Liang S, Morokata T, Mizuguchi K, Higo J, Standley DM, Nakamura H, (2014) *Proteins* **82** 1624-1635.

4. The Zero-multipole summation method for estimating electrostatic interactions in molecular dynamics: analysis of the accuracy and application to liquid systems. Fukuda I, Kamiya N, Nakamura H (2014) *J. Chem. Phys.* **140**, 194307.

5. A Novel Approach of Dynamic Cross Correlation Analysis on Molecular Dynamics Simulations and its Application to Ets1 dimer–DNA Complex. Kasahara K, Fukuda I, Nakamura H, (2014) *PLoS One* **9**, e112419.

6. Virtual-system coupled adaptive umbrella sampling to compute free-energy landscape for flexible molecular docking. Higo J, Dasgupta B, Mashimo T, Kasahara K, Fukunishi Y, Nakamura H, (2015) *J. Comput. Chem.*, in press.

Laboratory of Advanced Protein Characterization

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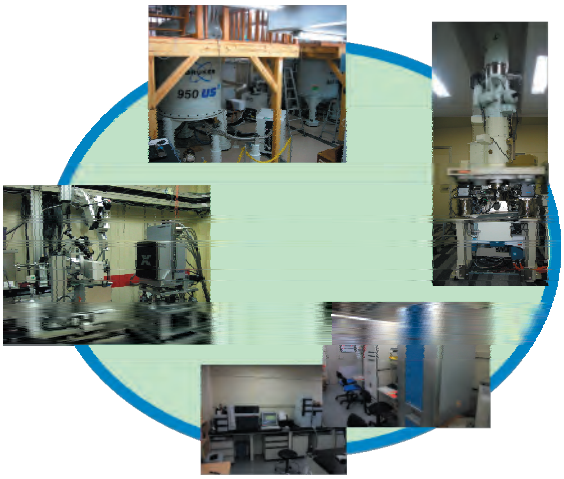

This laboratory is working on development and application of several important methodologies for advanced characterization of protein molecules and plays an important role in technical innovations for protein analyses and measurements. Faculty members in this laboratory are organized into three research groups, a group using NMR with super high magnet field, a group of X-ray crystallography using synchrotron radiation at SPring-8 and an electron microscopic imaging group, and one technical support group for chemical analyses of protein molecules.

Synchrotron Radiation Research Group

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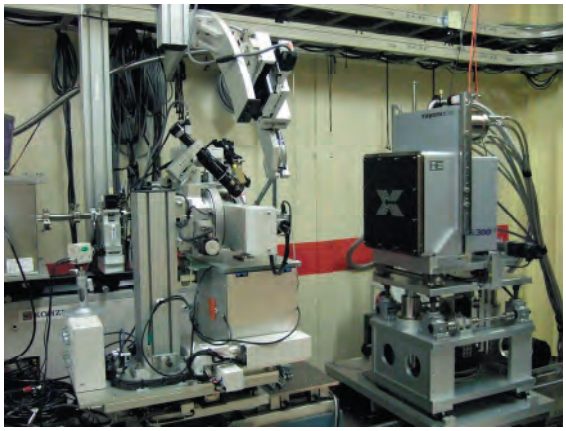
We are working on development of new methodologies for X-ray protein crystallography using synchrotron radiation beamline for biological macromolecular assemblies at SPring-8 (BL44XU). This beamline utilizes high-brilliant undulator radiation of SPring-8 to collect high quality diffraction data from biological macromolecular assembly crystals. About half of the user time is opened for the research groups outside of the IPR.



Synchrotron Radiation Beamline for Biological Macromolecular Assemblies at SPring-8 (BL44XU). This beamline utilizes high-brilliant undulator radiation of SPring-8 to collect high quality diffraction data from biological macromolecular assembly crystals. About half of the user time is opened for the research groups outside of the IPR.

【Current Reearch Programs】

1) Management of the Synchrotron Radiation Beamline for Biological Macromolecular Assemblies at SPring-8 (BL44XU)
2) Development of methodologies for X-ray crystal structure determination of biological macromolecular assemblies using synchrotron radiation
3) Structural studies on membrane proteins and macromolecular complexes

【References】

1. Determination of damage-free crystal structure of an X-ray-sensitive protein using an XFEL. 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 J-R, Yoshikawa S, Ago H (2014) *Nat. Methods* **11**, 734-736.
2. High-resolution X-ray crystal structure of bovine H-protein using the high-pressure cryocooling method. Higashiura A, Ohta K, Masaki M, Sato M, Inaka K, Tanaka H, Nakagawa A (2013) *J. Synchrotron Rad.* **20**, 989-993.

NMR Research Group

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We mainly determine the three-dimensional structures of proteins and peptides using nuclear magnetic resonance spectroscopy (NMR). In addition, we are studying the functions based on the interaction of a protein with another protein or its substrate. NMR is also suitable for analyses of flexibility, providing information as to which parts of proteins fluctuate. Furthermore, the developments of NMR methodologies to facilitate the above studies are also important tasks.

【Current Research Programs】

1) Development of new NMR methodology by applying amino acid-selective isotope labeling technique.
2) NMR analysis of the protein interaction between a small protein and macromolecular complexes with concomitant administration of X-ray crystallography.
3) Development of fundamental technology for successful, versatile, and reproducible In-cell NMR measurements.
4) Comprehensive structural analyses of variant Lamin proteins which causes severe hereditary disorders Laminopathy by NMR spectroscopy.

Fig. 1. The 950 and 800MHz NMR machines containing a superconducting magnet and cryogenic probe for each. The sensitivity of the 950MHz NMR reaches about 17-times the value that is exhibited by a normal 400MHz machine. Therefore, the measurement time can be saved by 1/300. The machines are also used for dilute samples within a shorter period, and for isotopically non-labeled samples. The superconducting is maintained by cooling the coil for the static magnetic field down to 2K with liquid helium.

【References】

1. Latest approaches for efficient protein production in drug discovery. Sugiki *et al.* (2014) *Expert Opin. Drug Discov.* **9**, 1189-1204.
2. The ATP-mediated regulation of KaiB-KaiC interaction in the cyanobacterial circadian clock. Mutoh *et al.* (2012) *PLoS ONE* **8**, e80200.

Electron Microscopy Group

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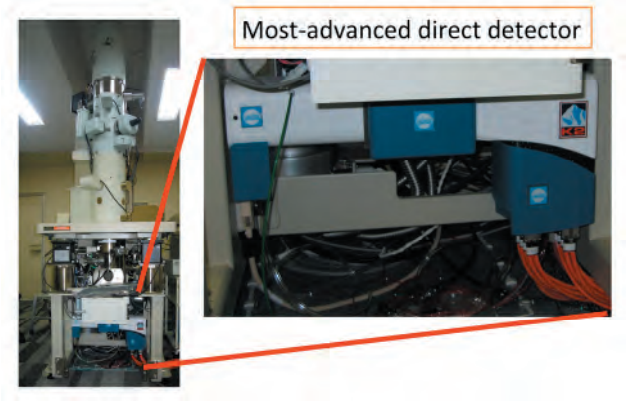
We set out to establish a road map for the development of EM techniques for structural analysis of purified proteins at functional state, and for the purpose of understanding the molecular architecture of subcellular structures, such as organelles, from the perspective of their atomic structures.

Our primary aims in this directive:

【1】Develop a single-particle reconstruction system for structural analysis of protein at atomic resolution using most advanced direct detection camera.

【2】Expand EM technology and its peripheral techniques for a wide range of applications, such as the three dimensional structure of pleomorphic objects in cells, and organic materials.

【3】Develop a hybrid approach that combines EM imaging with computer simulation, biochemistry, X-ray crystallography, optical microscopes and a variety of other cutting-edge methodologies to extract even further information from EM images and so as to enhance our understanding of protein function.



Cryo-electron microscope equipped with a most-advanced direct detector and energy filter.

【References】

1. Giant cadherins Fat and Dachsous self-bend to organize properly spaced intercellular junctions. Tsukasaki Y, Miyazaki N, Matsumoto A, Nagae S, Yonemura S, Tanoue,T, Iwasaki K, and Takeichi M. (2014) Proc. Natl. Acad. Sci.,111(45), 16011-16016.

Molecular Analysis Group

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This group is working on analysis of the primary structure of proteins and peptides by using conventional mass spectrometers and peptide sequencers. Nowadays we often use a variety of recombinant proteins for structural and functional study of target proteins. To obtain solid results, information on the chemical properties of recombinant proteins of experimental materials, such as terminal sequences and post-translational modifications, is very useful. This group is accumulating various data for such quality control of proteins to make them appropriate for molecular analysis.

MALDI-TOF Mass Spectrometer

Peptide Sequencer

Laboratory of Protein Databases

Professor *Haruki NAKAMURA*
Professor *Toshimichi FUJIWARA*
Professor *Kiyotoshi SEKIGUCHI*
Associate Professor *Akira R. KINJO*
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This Laboratory develops and manages several databases, which are freely and publicly available for a wide and global community of protein science: PDBj (Protein Data Bank Japan), for protein atomic structure database, BMRB (BioMagResBank) for NMR experimental data of biological molecules, Matrixome for mouse basement membrane bodymap, and a portal for CSD (Cambridge Structural Database).

Laboratory of Protein Databases

PDBj Group (Haruki NAKAMURA, Akira R. KINJO and Takashi KOSADA）

Correspondence Tel: 06-6879-4311; Fax: 06-6879-8636; E-mail: nahokoh@protein.osaka-u.ac.jp;
URL: http://pdbj.org/

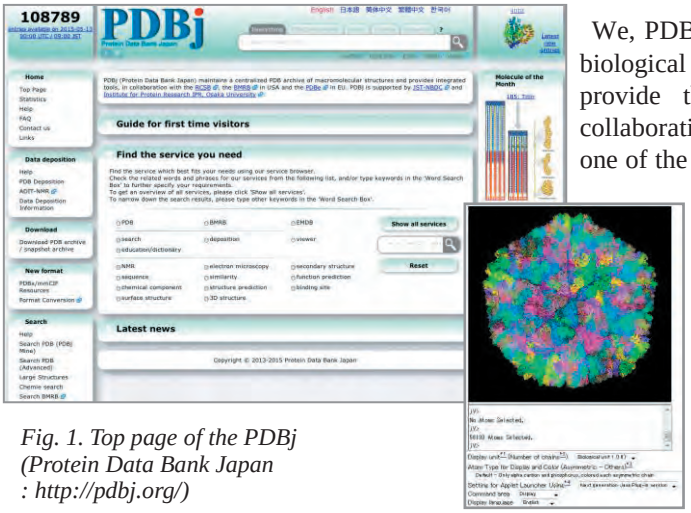

Fig. 1. Top page of the PDBj (Protein Data Bank Japan : http://pdbj.org/)

We, PDBj, curate, edit and process the 3D atomic structure data of biological macromolecules such as proteins and nucleic acids, and provide them freely and publicly from our own Web site, collaborating with wwPDB (worldwide PDB: http://wwpdb.org/) as one of the members of wwPDB. We also prepare various services for researchers and students, who are interested in structural biology. (Refs. 1, 2): Molecular graphics viewer, jV, molecular surface database for functional sites, eF-site, with the eF-seek service for the search of similar molecular surface, GIRAF, query service for the similar ligand binding sites, the navigation of the sequence and structure neighbours, Spanner, homology modeling server, and EM Navi, image viewer for the structures by electron microscopy.

【References】

1. Protein Data Bank Japan (PDBj): Maintaining a structural data archive and Resource Description Framework format. Kinjo AR, Suzuki H, Yamashita R, Ikegawa Y, Kudo T, Igarashi R, Kengaku Y, Cho H, Standley DM, Nakagawa A, Nakamura H. *Nucleic Acids Research* **40**:D453-D460 (2012)
2. PDBj Mine: Design and implementation of relational database interface for Protein Data Bank Japan. Kinjo AR, Yamashita R, Nakamura H. *Database* **2010**:baq021 (2010)

Laboratory of Protein Databases

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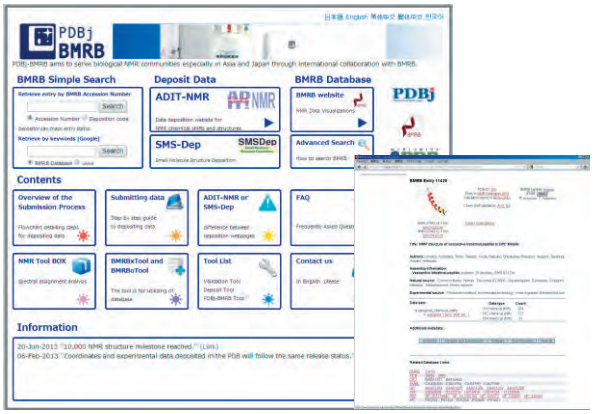
We, PDBj-BMRB, collect and process the NMR experimental data of biological molecules, and provide them from our Web site, collaborating with BMRB at University of Wisconsin-Madison in USA.

BMRB collects, annotates, archives, and disseminates (worldwide in the public domain) the important spectral and quantitative data derived from NMR spectroscopic investigations of biological macromolecules and metabolites. The goal is to empower scientists in their analysis of the structure, dynamics, and chemistry of biological systems and to support further development of the field of biomolecular NMR spectroscopy.



【Reference】

1. An automated system designed for large scale NMR data deposition and annotation: Application to over 600 assigned chemical shift data entries to the BioMagResBank from the RIKEN Structural Genomics/Proteomics Initiative internal database. Kobayashi N, Harano Y, Tochio N, Nakatani E, Kigawa T, Yokoyama S, Mading S, Ulrich EL, Markley JL, Akutsu H, Fujiwara T. *Journal of Biomolecular NMR* **53**:311-320 (2012)

Fig. 2. The home page of PDBj-BMRB (Protein Data Bank Japan - BioResMagBank: http:/bmrb.protein.osaka-u.ac.jp/).

Laboratory of Protein Databases

Matrixome Group (Kiyotoshi SEKIGUCHI)

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URL: http://www.matrixome.com/bm

We organize and maintain a web database "Mouse Basement Membrane Bodymap" which consists of hundreds of high resolution images representing the localization of more than 40 extracellular matrix proteins in whole mouse embryos analyzed by immunehistochemical technique. (Ref. 1)

【Reference】

1. Transcriptome-based systematic identification of extracellular matrix proteins. Manabe et al. *Proceedings of National Academy of Science U S A.* **105**:12849-12854 (2008)

Fig. 3. The Mouse Basement Membrane Bodymap database (http://www.matrixome.com/bm) consists of a panel of high resolution images of whole-body sections of mouse embryos immunostained for extracellular matrix proteins. Each image provides "virtual slide" on which users can zoom-in/out and move the view seamlessly online.

Laboratory of Protein Databases

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We support Academia researchers in Japan, who want to use CSD (Cambridge Structural Database system), which is a database for small organic chemical compounds constructed by CCDC (Cambridge Crystallographic Data Centre). We also provide a portal for CSD to researchers inside and even outside of Osaka University.

Open Space Laboratory for Advanced Protein Science

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Open space laboratory for advanced protein science has a role of bridging between academic and pharmaceutical drug discovery. The most important process of the small molecule drug discovery is (1) How to choose the hit compound ? (2) How to choose the drug target? (3) How to detect the interaction between hit compounds and drug targets? Finally these information are compiled as the protein-ligand interaction data base. We collaborate with related laboratories in the institute for Protein Research (Laboratory of Molecular Physics and Laboratory of Protein databases etc.). Under these collaborations, we develop the basic techniques which are necessary to complete above issues.

To figure out these problems, recently Fragment Based Drug Discovery (FBDD) method grows from the potential and low molecular weight compound (MW<250) to the clinical candidate. The key of the success is whether we can pick up a potential hit but weak compound at the beginning stage. Regarding the sensitivity, NMR is most appropriate method. But the problem is its low throughput. To avoid this problem, we focused on the fluorine compounds. 19F peak shows very characteristic peak by each compound and we can mix more than ten compounds at the same time by selecting appropriate compounds as a cocktail. Last year we selected 125 fluoride commercial available compounds. After water solubility check and examine the 19F peak profiling, based on last year experiments another new 125 compounds were added to our library as second fragment library. We selected two kinases (JAK3、GSK-3) as protein target. They are also attractive target for drug discovery field.
We did fragment screen by our soluble 250 fragment against two kinases by STDD method using 19F signals.
The fragment hits against two kinases are different. Even weak hits, They have selectivity for the each ATP site. We show hit fragments scaffold. It examined by competitive inhibition by known ATP site binding compound..This year, we will add other 250 fragments and increase fragment to 500 selected by Dr. Teruki Honnma (RIKEN)[1)]
strategy which is completely different from previous 250 fragments selection method. This year, I will try determing the orientation of hit fragments using QCI-F by RIKEN NMR facility under the collaboration with Prof. Kojima , IPR.
In addition to that, the protein targets would like to be also expanded to the membrane proteins.

On the other hand, some big public data base like ChEMBL contain the biological assay data between the ligands and some proteins involving ADME and TOX. But any systematic data base regarding reliable physico-Chemical interactions between ligands and drug targets is not found yet. If we can have such a DB with physicochemical interaction properties, they must be practically useful for both academic and industrial drug discovery. So we cooperate with related laboratories in Institute for Protein Research (Laboratory of Molecular Physics, Laboratory of Protein databases etc.) and would like to realize new approach with the physicochemical interaction DB between ligands and proteins.

【Current Research Programs】

Physicochemical interaction DB between ligands and drug target proteins

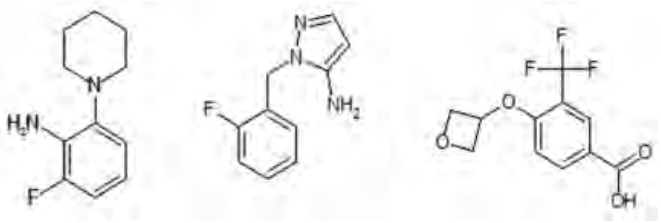


Fig.1. Fragment Hit example by 19F STDD

【Reference】

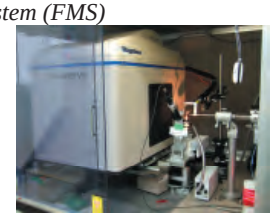
1)Homma T. et al (to be submitted)

Equipments

1. *General purpose computer system*

2. *Synchrotron radiation beam line for macromolecular assemblies*

3. *Ultra-high brilliant X-ray generator with a high performance imaging plate diffractometer & Free mounting system (FMS)*



4. *High-resolution NMR (400, 500, 600, 800, 950 MHz) & High-resolution solid-state NMR (500, 600, 700 MHz)*

5. *395GHz-600MHz DNP-NMR system*

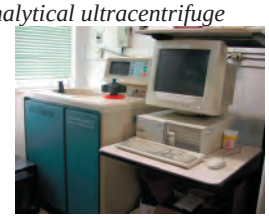
6. *Protein-protein interaction analyzer*

7. *Transmission electron microscope*

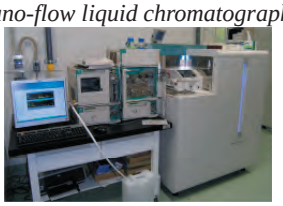
8. *Environmental control type vitrification device for TEM specimen*

9. *Ultra microtome system & High pressure freezer*

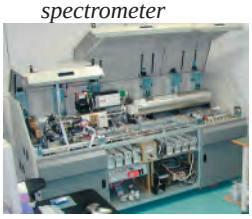
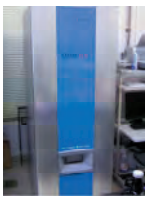

10. *Analytical ultracentrifuge*



11. *Nano-flow liquid chromatography*

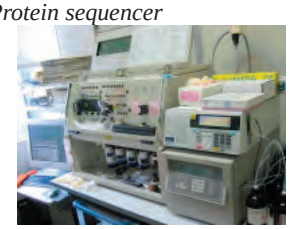


12. *Matrix-assisted laser desorption ionization tandem time-of-flight mass spectrometer*

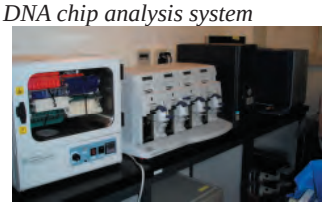
13. *microLC system/ MALDI plate spotter*

14. *Protein sequencer*



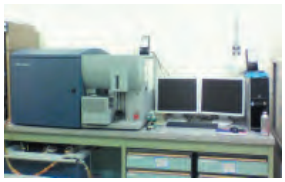
15. *Fluorescence and radioactivity imaging system*

16. *DNA chip analysis system*



17. *Time-lapse video microscope*

18. *Cell sorter*



19. *Differential scanning calorimeter & Isothermal titration calorimeter*

20. *Circular dichroism spectrometer*

21. *Fourier transform infrared absorption spectrometer*

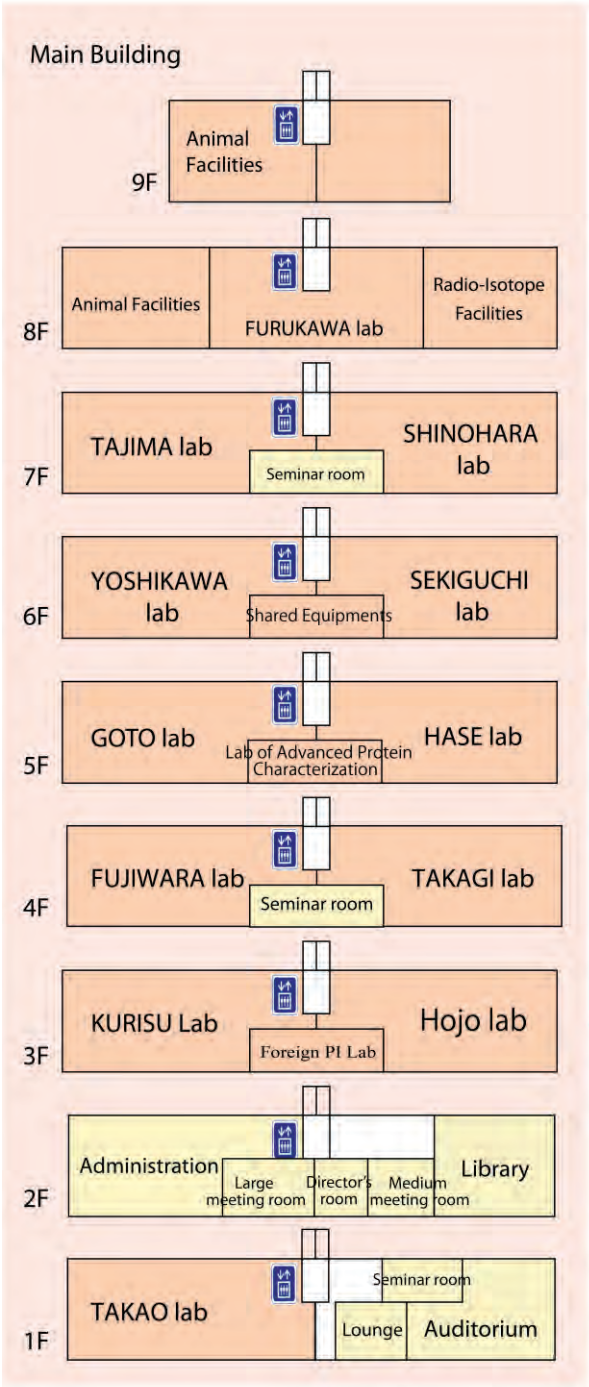
22. *PC cluster system with 28 GPGPUs*

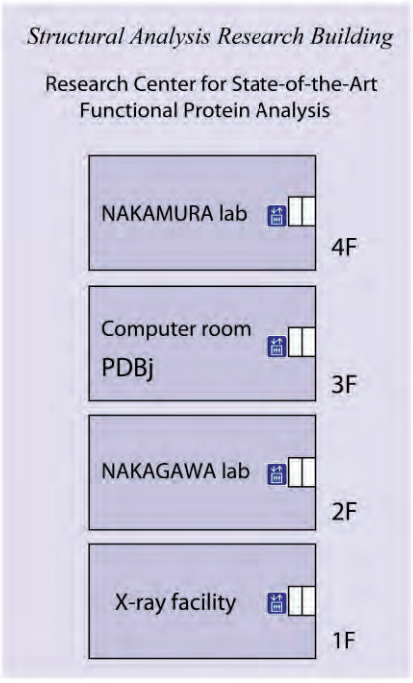
23. *Cryo-electron micoscope for biological imaging*

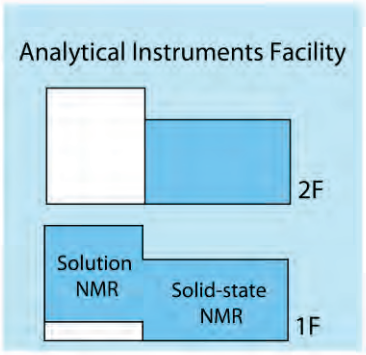
24. *Tandem Mass Spectrometer*

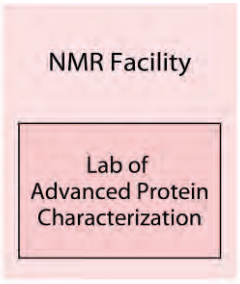
25. *Octet (Biolayer Interferometry device)*

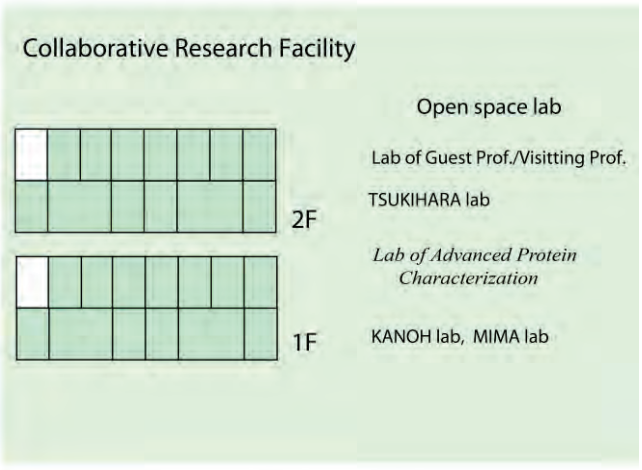
Floor Plan

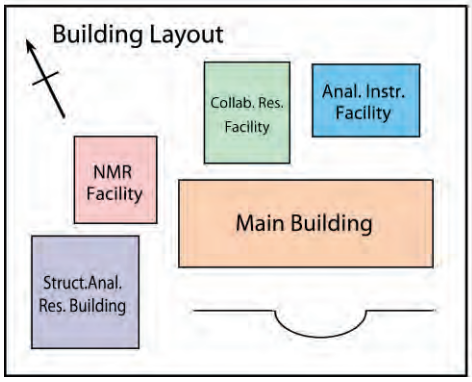






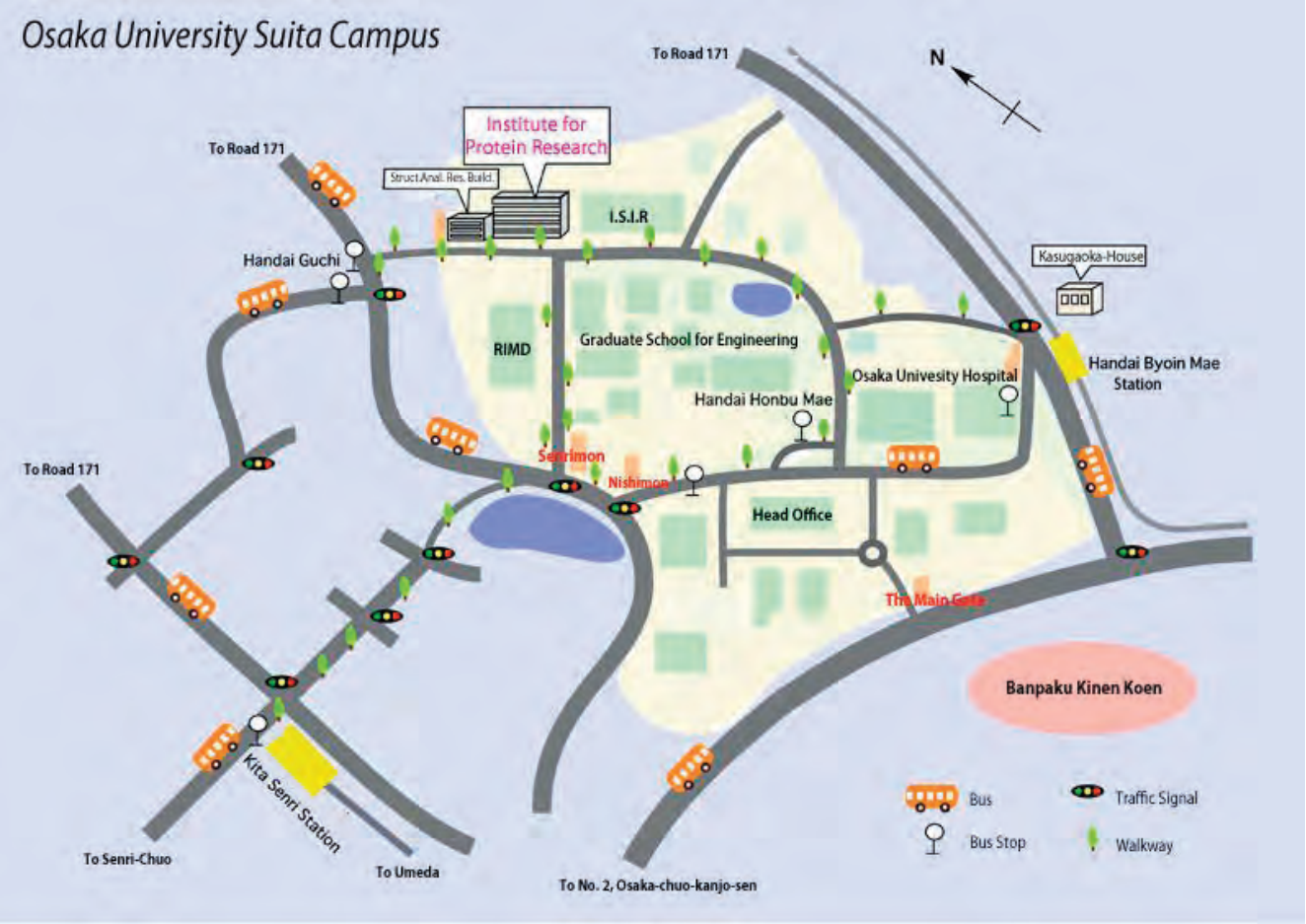






Laboratory of Homeostatic Integration is in the first floor of the Main building.

Access



Transportation to IPR from the nearest stations

■ *Hankyu Railways, Kita Senri Station: About 15 min walk. Or, by taxi a ride of about 5 min from Kita Senri Station*

■ *Subway, Midosuji-line, Senri Chuo Station: By taxi a ride of about 10 min. Or, take Hankyu-bus for "Onohara Higashi" and get off at "Handai Guchi", and then about 5 min walk. Take Hankyu-bus for "Handai Honbu Mae" and get off at "Handai Honbu Mae", and then about 15 min walk. Take Hankyu-bus for "Handai Igakubu Byoin Mae" and get off at "Handai Shigakubu Byoin Mae", and then about 15 min walk.*

■ *West Japan Railway (JR) Tokaido-line, Ibaraki Station: By taxi a ride of about 15 min. Or, take Kintetsu-bus for "Handai Honbu Mae" and get off at Handai Honbu Mae, and then about 15 min walk.*

■ *Osaka Monorail, Handai Byoin Mae Station: About 20 min walk.*

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