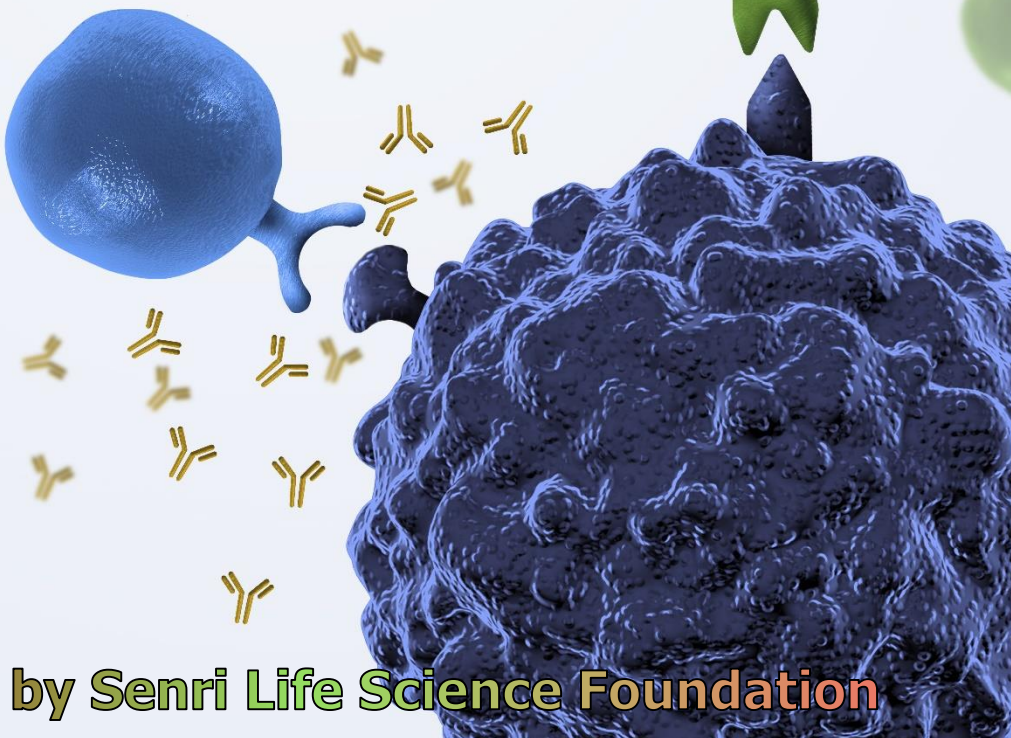
2018 Senri Life Science International Symposium on

"A New Horizon of Cancer Immunotherapy"

Date : January 19th (Fri), 2018, 10:00-17:00
Venue : Senri Life Science Center Building 5th floor
"Yuichi Yamamura Memorial Life Hall"

Coordinated by
Nagahiro Minato & Keiya Ozawa



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Description of cover view ;
A conceptual image of cancer immunotherapy - immune checkpoint blockade and CAR-T cell therapy.

Created by Evo Devo Design.

2018 Senri Life Science International Symposium

"A New Horizon of Cancer Immunotherapy"

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10:00- 10:10 Opening address

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

Chair : Keiya Ozawa (The University of Tokyo, Japan)

10:10-10:30 Introduction

Nagahiro Minato (Kyoto University, Japan) p.4

10:30-11:10 "Tumor and host factors regulating anti-tumor immunity and immunotherapy efficacy"

〈**Talk 1**〉 **Thomas F. Gajewski** (University of Chicago, USA) p.6

11:10-11:50 "Donor-derived immunity in cancer immunotherapy"

〈**Talk 2**〉 **Johanna Olweus** (Oslo University Hospital Radiumhospitalet, Norway) p.10

11:50-12:30 "Immune Checkpoint Blockade and Beyond in Cancer Immunity"

〈**Talk 3**〉 **Nagahiro Minato** (Kyoto University, Japan) p.12

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

Chair : Nagahiro Minato (Kyoto University, Japan)

13:40-14:20 "Response and Resistance to PD-1 Blockade Therapy"

〈**Talk 4**〉 **Antoni Ribas** (Jonsson Comprehensive Cancer Center at UCLA, USA) p.14

14:20-15:00 "Recent trends of clinical gene therapy, focusing on CAR-T cell therapy"

〈**Talk 5**〉 **Keiya Ozawa** (The University of Tokyo, Japan) p.18

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

15:20-16:00 "CAR T cell therapy beyond the CD19 paradigm"

〈**Talk 6**〉 **Michel Sadelain** (Memorial Sloan Kettering Cancer Center, USA) p.22

16:00-16:40 "Developing effective adoptive T cell therapy for solid tumors"

〈**Talk 7**〉 **Daniel J. Powell Jr.** (University of Pennsylvania, USA) p.26

16:40-16:50 Closing remarks

Keiya Ozawa (The University of Tokyo, Japan) p.30

Described time includes questions and answers.

Opening Address

Tadamitsu Kishimoto, MD., PhD.

Title:

Guest Professor, Immunology Frontier Research Center, Osaka University
3-1 Yamada-oka, Suita City, Osaka 565-0871, Japan
URL: http://www.ifrec.osaka-u.ac.jp/en/laboratory/immuneregulation/index.php

Chairman of the Board of directors, Senri Life Science Foundation
Level 20, Senri Life Science Center Building
1-4-2, Shinsenri-Higashimachi, Toyonaka-City, Osaka 560-0082, Japan
URL: http://www.senri-life.or.jp/index.html

Educational History:

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

Professional History:

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

Honors & Awards:

1982 Behring-Kitasato Prize
1983 Osaka Science Prize
1986 Erwin von Bälz Prize
1988 Takeda Prize
1988 Asahi Prize
1990 Prize of The Japanese Medical Association
1990 Person of Cultural Merit, Japan
1991 Foreign Associate, The US National Academy of Science
1991 Scientific Achievement Award from the International Association of Allergology and Clinical Immunology
1992 Honorary Member, the American Association of Immunologists
1992 Imperial Prize from the Japan Academy
1992 Sandoz Prize for Immunology from International Union of Immunology Society
1992 Honorary Citizen, Tondabayashi City
1995 Member, the Japan Academy
1996 The Avery-Landsteiner Prize from the German Immunology Society
1997 Foreign Associate member, the Institute of Medicine of the National Academy of Science, USA
1997 Honorary member, the American Society of Hematology
1998 The Order of Culture from Emperor
1999 The Donald Seldin Award from the International Society of Nephrology
2000 ISI Citation Laureate Award
2001 Honorary Member, International Association of Dental Research
2002 Honorary Professor, the forth Military Medical University, Xi'an, China
2002 Honorary Member, World Innovation Foundation
2003 Doctor of Science, Honoris Causa, Mahidol University
2003 Robert Koch Gold Medal
2004 Clemens von Pirquet Distinguished Professor, Medicine and Immunology, University California, Davis
2005 Member, Deutsche Akademie der Naturforscher Leopoldina
2006 Honorary Lifetime Achievement Awards, International Cytokine Society
2009 The Crafoord Prize from the Royal Swedish Academy of Sciences
2010 CIS (Clinical Immunology Society, USA) President's Award
2011 The Japan Prize
2012 Bestowed with the Royal Decoration from Thai Kingdom
2017 King Faisal International Prize from Saudi Arabia

〈 Introduction 〉
“A new horizon of cancer immunotherapy”

Nagahiro Minato, MD., PhD.

Discovery of immune checkpoint mechanism in cancer and subsequent clinical success of the checkpoint blockade therapy have drastically changed the landscape of current cancer treatment in humans.

A main lesson from it is that endogenous immunity can have powerful potential and impact on cancer much more than previously thought, if it operates adequately.

The checkpoint blockade therapy is now followed by emerging, similarly promising immunotherapy with elegant genetic strategies, including gene-modified T cell therapy such as CAR-T.

In this symposium, current state of art on cancer immunity and immunotherapy is discussed.

<MEMO>

〈Talk 1〉
"Tumor and host factors regulating anti-tumor immunity and immunotherapy efficacy"

Thomas F. Gajewski, MD., PhD.

Title:

Professor, Departments of Pathology & Medicine. The University of Chicago
Gordon Center for Integrative Science
929 E. 57th Street, Room W-436
Chicago, IL 60637

Educational History:

1980-1984	University of Chicago B.A., Biology - June, 1984
1986-1989	University of Chicago Ph.D., Immunology, with Dr. Frank Fitch - December, 1989
1984-1991	University of Chicago, Pritzker School of Medicine M.D. - June, 1991

Postdoctoral Training:

1989-1993	Postdoctoral Research (Part time) Dr. Frank Fitch University of Chicago
1991-1993	Intern and Resident Department of Internal Medicine University of Chicago
1993-1995	Postdoctoral Research Dr. Thierry Boon Ludwig Institute for Cancer Research Brussels, Belgium
1993-1997	Fellow, Section of Hematology/Oncology, Clinical Investigator Pathway Department of Medicine University of Chicago

Professional History:

2017-	Abbvie Professor in Cancer Immunotherapy
2009-	Professor with Tenure, Department of Pathology, Department of Medicine Section of Hematology/Oncology, and the Ben May Institute
2004-	Associate Professor with Tenure, Department of Pathology, Department of Medicine Section of Hematology/Oncology, and the Ben May Institute
2000-	Assistant Professor, Ben May Institute

1999-	Committee on Cancer Biology member, University of Chicago
1998-	Investigator, Cancer Research Center, University of Chicago
	• UCCRC Immunology Program Leader (2002-)
	• Director, Human Immunologic Monitoring Facility (2001-)
1997-	Committee on Immunology member, University of Chicago
1997-2004	Assistant Professor, Department of Pathology, University of Chicago
1997-2004	Assistant Professor, Department of Medicine, Section of Hematology/Oncology, University of Chicago
	• Director, Melanoma Oncology
1993-1995	Investigator, Ludwig Institute for Cancer Research, Brussels Branch, Brussels, Belgium

Honors & Awards:

1984	Garber Summer Research Fellowship
1984	B.A. with Honors
1985	NIH Summer Research Grant
1984-1986	Achievement Reward for College Scientists (ARCS)
1986-1991	Growth and Development Training Grant (M.D./Ph.D.)
1991	Dr. Harold Lamport Biomedical Research award, for the best dissertation in biomedical research
1991	M.D. with Honors
1993-1995	Fellowship award, International Institute for Cellular and Molecular Pathology (ICP, Brussels)
1995-1997	Scholar Award, V-Foundation for Cancer Research
1996	Central Society of Clinical Investigation Trainee Award
1997-2000	Clinical Associate Physician Award (General Clinical Research Center, NIH; predecessor to K08)
1997-2000	McDonnell Scholar Award for Molecular Oncology
1998-2002	Clinical Investigator Award, Cancer Research Institute
2000-2005	Burroughs Wellcome Fund Clinical Scientist Award for Translational Research
2006-	Inducted into ASCI (American Society for Clinical Investigation)
2007-	Elected into Henry Kunkel Society
2010-2012	President, Society for Immunotherapy of Cancer (SITC)
2015	SITC Top Volunteer Award
2015	SITC Spirit Award for the band “The Checkpoints”
2016	American Cancer Society-Jules L. Plangere Jr. Family Foundation Professorship in Cancer Immunotherapy
2016	Weir Lectureship, Texas Tech University, Amarillo, TX
2016	Distinguished Professor, University of Chicago
2016	Melanoma Research Foundation Humanitarian Award
2017	Chicago’s Best Doctors
2017	Staffileno Memorial Lectureship, NorthShore University Health
2017	Kimura Memorial Lectureship, Nagoya, Japan
2017	Hickam Endowed Lectureship, CSCTR, Chicago, IL
2017	Miller Memorial Lectureship, South Dakota State University

2017	Emily Frederick DiMaggio Lectureship, Dana Farber Cancer Center
2017	Giants of Cancer Care “Immuno-oncology”, ASCO
2017	Abbvie Endowed Professorship in Cancer Immunotherapy
2017	William B. Coley Award

Abstract

Two major phenotypes of human melanoma metastases have been observed based on gene expression profiling and confirmatory assays. One subgroup of patients has a T cell-inflamed phenotype that includes expression of chemokines, T cell markers, and a type I IFN signature. In contrast, the other major subset lacks this phenotype and appears to display immune “exclusion”. The mechanisms of immune escape are likely distinct in these two subsets, and therefore the optimal immunotherapeutic interventions necessary to promote clinical responses may be different.

The T cell-inflamed tumor microenvironment subset shows the highest expression of negative regulatory factors, including PD-L1, IDO, and FoxP3+ Tregs. Deep analysis of tumor antigen-specific T cells in the tumor microenvironment has identified additional mechanisms of immune dysfunction and new potential therapeutic targets.

Treatment strategies targeting several pathways have been translated back into the clinic, including anti-PD-1/PD-L1 mAbs and IDO inhibitors, and combinations of these agents also look promising. In contrast to the T cell-inflamed melanomas, non-T cell-inflamed tumors are largely immunotherapy resistant with current approaches. Natural innate immune sensing of tumors appears to occur via the host STING pathway, type I IFN production, and cross-priming of T cells via CD8α+ DCs, and these factors are absent in non-T cell-inflamed tumors.

New strategies are being developed to engage or mimic this pathway as a therapeutic endeavor, including STING agonists. The molecular mechanisms that mediate the absence of the T cell-inflamed tumor microenvironment in patients are being elucidated using parallel genomics platforms. The first oncogene pathway identified that mediates immune exclusion is the Wnt/β-catenin pathway, which argues that new pharmacologic strategies to target this pathway should be developed to restore immune access to the tumor microenvironment. Recent evidence has indicated that host factors, including the intestinal microbiota, are also critical.

We recently have identified commensal bacteria in mouse models that augment spontaneous anti-tumor immunity and increase efficacy of anti-PD-L1 therapy. Similar analyses in human melanoma patients have been performed, and commensal bacteria have similarly been identified that correlate with anti-PD-1 efficacy. These results have prompted the pursuit of new probiotics that may improve spontaneous immune infiltration and expand immunotherapy efficacy in the clinic.

〈Talk 2〉
“Donor-derived immunity in cancer immunotherapy”

Johanna Olweus, MD., PhD.

Title:

Professor, University of Oslo
Head, Department of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Ullernchausséen 70, 0310 Oslo, Norway
URL: http://ous-research.no/olweus/
www.med.uio.no/klinmed/english/research/centres/kgj-cancer-immunotherapy

Educational History:

Dec. 1992	MD degree, Faculty of Medicine, University of Bergen, Norway
May 1998	PhD degree, Faculty of Medicine, University of Bergen, Norway
2006	Specialist, Immunology and Transfusion Medicine (Clinical Immunology)

Professional History:

1993- 97	PhD fellowship from Norwegian Research Council, work performed at Becton Dickinson Immunocytometry Systems, San José, CA, USA
1997-98	Intern, Drammen Hospital – Vestre Viken (internal medicine and surgery)
(1998-99	Maternity leave, 1yr)
1999-00	Intern, General Practice (Kristiansand and Oslo)
(2000-01	Maternity leave, 1yr)
2001-06	Resident in Immunology and Transfusion Medicine (Clinical immunology), Oslo University Hospital Rikshospitalet and Ullevål Hospital - Specialist 2006
(2005-06	Maternity leave, 1yr)
2006-08	Senior Consultant, Group Leader and Head, Section for Medical Immunology, Institute for Immunology, Oslo University Hospital Rikshospitalet, Norway
2006-08	President, Norwegian Society for Immunology
2008-present	Professor, University of Oslo
2008-present	Head, Department of Cancer Immunology, Institute for Cancer Research, Oslo University Hospital Radiumhospitalet, Oslo, Norway
2013-present	Director, K.G. Jebsen Center for Cancer Immunotherapy, University of Oslo, Norway (www.med.uio.no/klinmed/english/research/centres/kgj-cancer-immunotherapy)

Honors & Awards:

2004	The Medinnova Innovation Award
2004	Birkeland Innovation Award
2011	Inven2 Innovation Award

Abstract

Patient T cell responses to cancer cells can induce dramatic clinical responses when enhanced by immunotherapy, such as checkpoint inhibition. However, most patients eventually relapse.
By contrast, T cells from human leukocyte antigen (HLA)-matched donors can cure leukemia. Donor T-cell repertoires are unbiased by thymic central tolerance, and by the immunosuppressive environment of the tumor and are easily accessible. We have demonstrated that naïve T cells from healthy individuals are able to respond to neoantigens that are ignored by the T cells of melanoma patients in vivo. T-cells re-directed with T-cell receptors identified from such donor T cells are capable of mediating killing of patient tumor cells harbouring the relevant mutation. This approach was recently utilized to generate a T-cell receptor that targets a recurrent mutation in leukemia. The data provide a rationale for the use of “outsourced” T-cell receptors in cancer immunotherapy. Non-synonymous mutations are highly attractive therapeutic targets as they are tumor-specific. Most neoantigens are, however, private, and therapeutic application of T-cell receptor-mediated targeting therefore requires identification of T-cell receptors for every patient. A major hurdle for widespread therapeutic application is thus lack of cost-efficient and rapid methods for gene transfer. In contrast, targeting of shared antigens has the obvious advantage that a single immune receptor can be used in many patients, as for CAR19. A major limitation for extension of the success of CAR therapy to other cancers than B-cell leukemia is the scarcity of suitable cell-type restricted cell surface targets. T-cell receptors have the advantage over CARs and therapeutic antibodies that they can recognize antigens from any cellular protein. T-cells that recognize self-antigens in context of self-HLA with high affinity are, however, depleted during negative selection in the thymus. We have demonstrated that donor T cells can provide a source of T-cell receptors that specifically and efficiently recognize shared cell-type specific peptides in the context of mismatched HLA. I will discuss the possibility that donor-derived T-cell receptor repertoires can overcome some of the limitations of host T-cells in cancer immunotherapy and potential therapeutic contexts for such T-cell receptors.

〈Talk 3〉
“Immune Checkpoint Blockade and Beyond in Cancer Immunity”

Nagahiro Minato, MD., PhD.

Title:

Provost, Executive Vice President, Kyoto University
Project-leading Professor, Graduate School of Medicine, Kyoto University
Yoshida Sakyo-ku, Kyoto 606-8501, Japan
URL: http//www.kyoto-u.ac.jp

Educational History:

1975	Graduated from School of Medicine, Kyoto University.

Professional history:

1975-1977	Resident of the Chest Disease Research Institute Hospital, Kyoto University
1977-1980	Research Associate of Department of Immunology and Microbiology, Albert Einstein College of Medicine, New York, USA.
1980-1989	Assistant Professor of Department of Medicine, Jichi Medical School, Japan.
1984	Doctorate of Medicine (MD, PhD) from Kyoto University
1989-1992	Associate Professor of Department of Medicine, Jichi Medical School, Japan.
1992-2015	Professor of Department of Immunology and Cell Biology, Graduate School of Medicine, Kyoto University
1998-2009	Professor of Department of Bioregulation, Graduate School of Biostudies, Kyoto University (Joint appointment).
2011-2014	Dean of Graduate School of Medicine, Kyoto University
2014–	Executive Vice President of Kyoto University
2017–	Provost of Kyoto University

Honors & Awards:

2014	JCA-CHAAO Prize
2015	SGH Cancer Special Prize
2016	JPS Drug Science Prize

Abstract

Although PD-1 discovered by Dr. Honjo at Kyoto University was initially found to play an important role in peripheral self-tolerance serving as a checkpoint for autoimmunity, our subsequent studies revealed that PD-1 expressed on effector T cells could significantly affect a potential immunity of host against cancer.

We found that cancer cells expressing PD-1 ligands could mimic normal self cells and avoid a potential immune attack, and that the inhibition of PD-1/PD-L interaction could lead to a remarkable augmentation of potential host tumor immunity and significant therapeutic effects in animal models.

A decade later, the idea, currently called PD-1 checkpoint blockade therapy, was substantiated by successful clinical trials in human cancer patients with humanized anti-PD-1 or anti-PD-L1 antibody, and current efforts are directed to the improvement of the therapeutic efficacy as well as the search for predictive biomarkers of the therapy. The clinical success of immune checkpoint blockade therapy confirmed a potential importance of host immunity in controlling cancers.

Incidentally, accumulating evidence in large-scale clinical studies also indicates that the accessibility of immune effectors to cancer cells in tissue microenvironment, on which efficacy of immune checkpoint blockade and other immunotherapies may count, shows a significant correlation with a better prognosis of cancer patients. Nonetheless, the mechanism assuring the immune accessibility to cancer in tissue involves apparently complex cellular processes and may be hampered by various conditions and factors.

In this talk, I will briefly summarize the history of PD-1 checkpoint and then introduce a unique animal model of chronic myelogenous leukemia (CML), in which the effective access of memory T cells to tumor cells in tissue is remarkably promoted via coordinated interplay with mesenchymal stroma cells and is capable of eradiating CML-initiating cells that otherwise cause lethal CML development.

〈Talk 4〉
"Response and Resistance to PD-1 Blockade Therapy"

Antoni Ribas, MD., PhD.

Title:

Professor of Medicine with tenure
Professor of Surgery
Professor of Molecular and Medical Pharmacology
University of California Los Angeles (UCLA)

Division of Hematology-Oncology, 11-934 Factor, UCLA Medical Center
10833 Le Conte Ave. Los Angeles, CA 90095
Clinic Address:
100 UCLA Medical Plaza, Suite 550 Los Angeles, CA 90095

Educational History:

1984-90	School of Medicine, University of Barcelona, Barcelona, Spain.
1990	M.D. Medical Doctor [Licenciado en Medicina y Cirugia]. University of Barcelona, Barcelona, Spain.
1997	Ph.D. Doctoral Thesis Dissertation: Interleukin-2 Gene Therapy for Cancer Suma Cum Laude and Extraordinary Prize Autonomous University of Barcelona, Barcelona, Spain

Professional History:

1993	Sidney Kimmel Cancer Center, San Diego, CA.
1994-95	Clinical Instructor in Medical Oncology, Vall d'Hebron University Hospital
1996-98	Postdoctoral Researcher, Division of Surgical Oncology, UCLA, Los Angeles, CA.
1998-2001	Hematology/Oncology Fellow and Clinical Instructor in Internal Medicine Department of Medicine, Division of Hematology/Oncology, UCLA.
2001-2006	Assistant Professor in Residence of Medicine and Surgery, Department of Medicine, Division of Hematology/Oncology, and Department of Surgery, Division of Surgical Oncology, UCLA.
2006-2008	Associate Professor in Residence of Medicine and Surgery, Department of Medicine, Division of Hematology/Oncology, and Department of Surgery, Division of Surgical Oncology, UCLA
2008-2011	Associate Professor of Medicine and Surgery (with tenure). Department of Medicine, Division of Hematology/Oncology, and Department of Surgery, Division of Surgical Oncology, UCLA
2011-Present	Professor of Medicine (with tenure). Department of Medicine, Division of Hematology/Oncology. Professor of Surgery. Department of Surgery, Division of Surgical Oncology. Professor of Molecular and Medical Pharmacology, UCLA.

Honors and Awards:

1997	Extraordinary Prize and Suma Cum Laude, Doctoral Thesis, Autonomous University of Barcelona
2000	Fellow Teaching Award, UCLA
2000	Amgen Oncology Fellow Award
2000	Clinical Research Career Development Award, American Society of Clinical Oncology (ASCO)
2002	K23 CA93376 Career Development Award
2002	Stop Cancer Career Development Award
2005	Melanoma Research Foundation Junior Researcher Award
2008	New Faculty Award from the California Institute of Regenerative Medicine (CIRM)
2009	Elected member of the American Society of Clinical Investigation (ASCI)
2013	Physician of the Year, Melanoma International Foundation
2013	Outstanding Research Award, Society for Melanoma Research (SMR)
2015	Member of the Royal Academy of Medicine of Catalonia
2015	Lila and Murray Gruber Cancer Research Award, American Academy of Dermatology (AAD)
2015	NCI R35 Outstanding Investigator Award
2016	AACR Richard and Hinda Rosenthal Memorial Award
2017	Doctor Honoris Cause from the University of Buenos Aires, Argentina

Abstract

Blockade of the PD-1/L1 negative immune checkpoint interaction with therapeutic antibodies leads to unprecedented numbers of long lasting responses in patients with multiple metastatic cancers, thereby rapidly becoming standard of care treatment for patients with metastatic melanoma, carcinomas of the head and neck, lung, kidney and bladder, Merkel cell carcinoma and Hodgkin's disease, among a rapidly growing list.

Primary resistance to PD-1 blockade therapy is most frequently mediated by a lack of intratumoral tumor antigen-specific T cell infiltration {Tumeh, 2014 #6520;Ribas, 2015 #6482}. Furthermore, biopsy of metastatic melanomas lesions taken from patients who did not l respond to PD-1 blockade had a transcriptome that was dominated by mesenchymal, regeneration and stemness gene expression which collectively we termed innate anti-PD-1 resistance signature (IPRES) {Hugo, 2016 #6574}.

In occasional cases we have been able to map a genetic mechanism of primary resistance to PD-1 blockade therapy. A putative pre-existing immunoediting process had led to the cancer cells being genetically unable to respond to interferons through biallelic loss of function mutations in *JAK1* and *JAK2*. These two kinases control signaling downstream of the interferon gamma receptor, which would then prevent PD-L1 upregulation on melanoma cells upon interferon gamma exposure {Shin, 2017 #6661}. Therefore, in these cases it would not be useful to try to block PD-1:PD-L1 interactions with antibody therapy as the cancer cells cannot express PD-L1 due to the *JAK* mutations.

Furthermore, approximately 25-30% of patients with metastatic melanoma who initially had an objective tumor response to therapy, being cases of acquired resistance. Using genetic analyses approaches we described that similar loss of function mutations in the interferon gamma signaling pathway (*JAK1* or *JAK2*) and the antigen presentation pathway (*beta-2 microglobulin – B2M-*) can allow the relapse of acquired resistant lesions {Zaretsky, 2016 #6647}.

We have modeled these mutations in syngeneic mouse cancer systems that have a response to anti-PD-1/L1 therapy. Indeed, CRISPR/Cas9 knock out of *JAK1* or *JAK2* or *B2M* results in complete abrogation of anti-PD-1 responses in the MC38 high mutational load colon carcinoma and in the YUMM2.1 *BRAFV600E* mutated melanoma models syngeneic to C57BL/6 mice.

We hypothesize that modeling these resistance mechanism will allow us to understand their mechanisms and test combination therapies that may prevent or overcome resistance.

<MEMO>

〈Talk 5〉
"Recent trends of clinical gene therapy, focusing on CAR-T cell therapy"

Keiya Ozawa, MD., PhD.

Title:

Director, IMSUT Hospital
Director, Center for Gene & Cell Therapy (CGCT)
Professor, Division of Genetic Therapeutics, The Advanced Clinical Research Center
The Institute of Medical Science, The University of Tokyo (IMSUT)
4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, JAPAN

Visiting Professor
Division of Immuno-Gene & Cell Therapy (Takara Bio), Jichi Medical University
3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

Educational History:

1977 M.D. Faculty of Medicine, University of Tokyo
1984 Ph.D. (Doctor of Medical Science) Faculty of Medicine, University of Tokyo

Professional History:

1980-1982 Research Associate, Department of Hemopoiesis,
Institute of Hematology, Jichi Medical School, Tochigi
1984-1987 Research Associate, The Third Department of Internal Medicine,
Faculty of Medicine, University of Tokyo, Tokyo
1985-1987 Research Fellow, Clinical Hematology Branch,
National Heart, Lung, and Blood Institute, National Institutes of Health, U.S.A.
1987-1990 Senior Assistant Professor, Department of Hematology-Oncology,
The Institute of Medical Science, The University of Tokyo, Tokyo
1990-1994 Associate Professor, Department of Hematology-Oncology,
The Institute of Medical Science, The University of Tokyo, Tokyo
1994-1998 Professor, Department of Molecular Biology, Institute of Hematology,
Jichi Medical School, Tochigi
1998-2014 Professor and Chairman, Division of Hematology, Department of Medicine
Professor, Division of Genetic Therapeutics, Center for Molecular Medicine
(formerly Department of Molecular Biology, Institute of Hematology)
Jichi Medical University, Tochigi
2008-2014 Director, Center for Molecular Medicine, Jichi Medical University, Tochigi
2011-2014 Professor, Division of Immuno-Gene & Cell Therapy (Takara Bio)
Jichi Medical University, Tochigi
2014-present Current Positions (See above)

Honors and Awards:

1985-1987	Fogarty Fellow, NIH, U.S.A
1986-	Member, The New York Academy of Sciences
1991-	Listed in the Who's Who in the World
1992-	Listed in the Who's Who in Science and Engineering
1995	16th Research Grant from the Japanese Foundation for Multidisciplinary Treatment of Cancer
1995	Research Grant from the Uehara Memorial Foundation
1997-	Listed in the Who's Who in Medicine and Healthcare
1999	Grant-in-Aid of The Japan Medical Association
2000	Research Grant on Bioscience from the Takeda Science Foundation
2010	Research Grant from the Uehara Memorial Foundation

Abstract

Gene therapy research remained stagnant for many years due to serious side effects. However, clinical gene therapy has been revived in Western countries, because a number of successful clinical trials have been reported recently, including hematopoietic stem cell gene therapy and AAV-vector gene therapy mainly for hereditary disorders. Regarding cancer gene therapy, there has been increasing focus on gene-modified T cell therapy, which is divided into CAR (chimeric antigen receptor)-T and TCR (T cell receptor)-T cell therapy. These technologies have different characteristics and are used depending on the type of target molecules. CARs are hybrid proteins consisting of an extracelluar single chain fragment of variable region (scFv) fused to intracellular lymphocyte signaling domains CD28 or 4-1BB, coupled with CD3ζ to mediate T cell activation. Recent clinical trials of CD19-targeted CAR-T cell therapy have achieved a great success in the treatment of relapsed/refractory B cell malignancies, including ALL, CLL, and non-Hodgkin lymphoma (NHL).

In Japan, we have started clinical study of CD19-CAR-T cell therapy for NHL at Jichi Medical University Hospital, in collaboration with Memorial Sloan Kettering Cancer Center and Takara Bio Inc. Multi-institutional clinical trials of CD19-CAR-T cell therapy for ALL are also being conducted. As for the unique side effects of CAR-T cell therapy, there are cytokine release syndrome (CRS) and neurological toxicities (including cerebral edema). Depletion of normal B cells is called “on-target, off-tumor reaction” and causes immunoglobulin deficiency in the late phase.

On August 30, 2017, the U.S. FDA (Food and Drug Administration) approved tisagenlecleucel (KYMRIAH®, CD19-CAR-T cell therapy; Novartis Pharmaceuticals Corp.) for the treatment of pediatric and young adult patients with relapsed/refractory B-ALL. The FDA also approved tocilizumab (ACTEMRA®, an interleukin-6 receptor antagonist; Genentech Inc.) for the treatment of CRS. In the near future, CAR-T cell therapy will be expanded to treat the other hematological malignancies and solid tumors. As for solid tumors, the other strategies will be needed to get efficacy in combination with CAR-T. Applications of gene-editing technologies are also exciting topics. Allo (universal) CAR-T cells can be produced by knockout of TCR gene, and PD-1 gene knockout will enhance the efficacy of CAR-T cell therapy by local immune checkpoint blockade. Gene-modified T cell therapy is now becoming one of the major treatments to conquer intractable cancer.

<MEMO>

〈Talk 6〉
"CAR T cell therapy beyond the CD19 paradigm"

Michel Sadelain, MD., PhD.

Title:

Center for Cell Engineering
Memorial Sloan Kettering Cancer Center
New York, NY, USA

Educational History:

Baccalaureat (Mathematiques), 1976
Lycee Jehan Ango, Dieppe, France
M.D., 1984
University of Paris–Pierre et Marie Curie, Paris, France
(Thesis Advisor: Gabriel Richet)
M.S. (Physiology), 1984
University of Paris–Rene Descartes, Paris, France
Ph.D. (Immunology), 1989
University of Alberta, Edmonton, Canada
(Thesis Advisor: Thomas Wegmann)
Postdoctoral Fellow 1989-94
Whitehead Institute for Biomedical Research,
Massachusetts Institute of Technology,
Cambridge, MA (Laboratory of Richard Mulligan)

Research Positions:

1994 Assistant Member, Immunology Program, Sloan-Kettering Institute
2000 Associate Member, Immunology Program, Sloan-Kettering Institute
2004 Member, Immunology Program, Sloan-Kettering Institute
2007 Member, Molecular Pharmacology & Chemistry Program, Sloan-Kettering Institute
Academic and Hospital Appointments
1994 Assistant-Attending Geneticist, Department of Human Genetics and Hematology/ Oncology and Bone Marrow Transplant Services, Departments of Medicine and Pediatrics, Memorial Hospital
1995 Assistant Professor, Graduate School of Medical Sciences, Cornell University Medical College
1997 Director, Gene Transfer and Somatic Cell Engineering Facility,
Memorial Sloan Kettering Cancer Center
1998 Assistant Professor, Department of Medicine, Weill College of Medicine at Cornell University
2000 Associate-Attending Geneticist, Department of Human Genetics and Hematology/ Oncology and Bone Marrow Transplant Services, Departments of Medicine and Pediatrics, Memorial Hospital
2001 Associate Professor, Graduate School of Medical Sciences, Cornell University
2004 Attending Geneticist, Department of Medicine, Hematology/Oncology and Bone

Marrow Transplant Services, Departments of Medicine and Pediatrics, Memorial Hospital

2004 Professor, Immunology Program and Microbial Pathogenesis, Weill Cornell Medical College and Graduate School of Medical Sciences, Cornell University

2007 Director, Center for Cell Engineering, Memorial Sloan Kettering Cancer Center

Honors & Awards:

1976 Baccalaureat Mathematiques, "Mention Tres Bien" (Top 1%, national).

1984 These d'Etat de Docteur en Medecine, awarded with thesis medal and mention "honorable". Thesis President: Pr. Gabriel Richet.

1984 Concours de l'Internat des Hopitaux (Elite French Residency Program)

1989 Centennial Fellowship from the Medical Research Council of Canada

1995 McDonnell Scholar Award in Molecular Medicine in Cancer Research

2003 Elected to the American Society for Clinical Investigation (ASCI)

2004 Alliance for Cancer Gene Therapy Investigator Award

2005 V Foundation Award in Honor of Mayor Rudolph Giuliani

2007 Incumbent of the Stephen and Barbara Friedman Chair

2012 Recipient of the Coley Award of the Cancer Research Institute for Distinguished Research in Tumor Immunology – CD19 CAR therapy

2013 Antonio Cao Award for Research in Thalassemia or Hemoglobinopathies, Palermo, Italy

2013 Elected, Vice President of the American Society for Gene and Cell Therapy (ASGCT)

2013 Sultan Bin Khalifa International Thalassemia Awards (SITA) International Award for Innovative Medical Research on Thalassemia

2013 Highlighted in Science for "Breakthrough of the Year, Cancer Immunotherapy"

2014 President Elect, American Society for Gene and Cell Therapy (ASGCT)

2014 Inventor of the Year Award from the New York Intellectual Property Law Association (NYIPLA)

2015 President, American Society for Gene and Cell Therapy (ASGCT)

2016 Sir Galton Memorial Research, Hammersmith Hospital, London, UK

2016 Visiting Professor, Soochow University, Suzhou, PR China

Abstract

Chimeric antigen receptors (CARs) are synthetic receptors that redirect and reprogram T cells to mediate tumor rejection. The most successful CARs used to date are those targeting CD19, which offer the prospect of complete remissions in patients with chemorefractory/ relapsed B cell malignancies, especially acute lymphoblastic leukemia (ALL). To broaden the applicability of CAR therapy, we are investigating novel CAR designs, novel CAR targets and alternative T cell engineering modalities. To enhance the intrinsic (function, persistence) and extrinsic (action on the tumor microenvironment) potency of adoptively transferred T cells, we are studying the impact of constitutive 4-1BBL expression on therapeutic efficacy.

To identify new CAR targets, we rely on integrated proteomics and transcriptomics to address the challenges of tumor heterogeneity and on-target/off-tumor toxicity based on combinatorial targeting. Using CRISPR/Cas9, we found that directing a CAR to the T cell receptor alpha chain (TRAC) locus not only results in uniform CAR expression in human peripheral blood T cells, but enhances T cell potency by attenuating T cell exhaustion, vastly outperforming conventionally transduced CAR T cells. Using gene editing, we are further inquiring whether allogeneic T cell sources, including induced pluripotent stem cell-derived T cells, can be harnessed to produce therapeutic T cells on a large scale.

<MEMO>

〈Talk 7〉
“Developing effective adoptive T cell therapy for solid tumors”

Daniel J. Powell Jr., PhD.

Title:

Professor, University of Pennsylvania
3400 Civic Center Blvd.
Bldg. 421, TRC Rm 8-103
Philadelphia, PA 19104-5156 USA

Educational History:

1991	A.A.	Delaware County Community College (Liberal Arts)
1993	A.S.	Delaware County Community College (Natural Science)
1995	B.S.	Cabrini College (Biology / Pre-Medicine)
2002	Ph.D.	Thomas Jefferson University (Immunology)
2002-2007		Research Fellow, Surgery Branch, National Cancer Institute, NIH

Professional History:

2007-2013	Research Assistant Professor of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine
2008-2013	Assistant Professor of Obstetrics and Gynecology, University of Pennsylvania School of Medicine (Secondary)
2013-2016	Research Associate Professor of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine
2013-present	Associate Professor of Pathology and Laboratory Medicine in Obstetrics and Gynecology, University of Pennsylvania School of Medicine (Secondary)
2016-present	Associate Professor of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine

Hospital and/or Administrative Appointments:

2007-2012	Deputy Director, Clinical Cell and Vaccine Production Facility

Other Appointments:

2010-present	Director, Cellular Therapy Tissue Facility

Honors & Awards:

1995	Beta Beta Beta Biological Honor Society
1995	Sigma Zeta Honorary Science Society
2000	Keystone Symposia Scholarship
2001	Thomas Jefferson Alumni Fellowship
2001	Kimmel Cancer Institute Training Committee Representative, Thomas Jefferson University
2003	NCI Fellows Award for Research Excellence
2005	NCI Exceptional Pay Increase Award

2005 NCI Postdoctoral Research Fellow Representative to the AAAS

2007 NCI Exceptional Pay Increase Award

2007 NCI CCR Fellows & Young Investigators Award

2007 Member, Strategic Planning Committee for Translational Research, Department of Obstetrics and Gynecology, University of Pennsylvania

2008 Full Member, American Association for Cancer Research

2009 University Nominee and Recipient of the W.W.Smith Charitable Trust Award

2010 Election to International Society for Biological Therapy of Cancer (ISBTc)

2010 The Philadelphia Antique Show, selection of the Cellular Therapy Tissue Facility to receive $650K in construction-related funds.

2010 The International Society for Biological Therapy of Cancer (iSBTc) Presidential Travel Award; ISBTc (Ph.D. candidate Evripidis Lanitis to present)

2011 Society for Immunotherapy of Cancer (SITC); Travel Award; (Ph.D. candidate Evripidis Lanitis)

2014 Outstanding New Investigator Award, American Society of Gene & Cell Therapy (ASGCT)

2015 The Teal Trailblazer Award, The Sandy Rollman Ovarian Cancer Foundation

Abstract

The clinical application of gene-modified T cell therapy has revolutionized the treatment of hematologic malignancy, as highlighted by the FDA approval of CD19-specific chimeric antigen receptor (CAR) T cell therapy for acute lymphoblastic leukemia; however this success is not readily translated to the solid tumor setting where additional barriers of immunosuppression and limited penetrance may exist. Still, it is clear that T cells play a central role in the control of a wide range of solid tumors, as evidenced by the correlation between T cell infiltration in tumors and favorable prognosis. Further supporting this notion is the finding that in select tumor, such as melanoma, the adoptive transfer of autologous tumor infiltrating lymphocytes (TILs) can mediate dramatic and durable tumor regression in treatment refractory patients. Findings from these studies highlighted the importance of antigen specificity, differentiation status and patient pre-conditioning for effective treatment of solid tumor. To broaden this therapy for other cancers, we and others have genetically modified T cells to endow them with tumor reactivity using a T cell receptor (TCR) with HLA-restricted tumor antigen specificity, sometimes derived from TILs that have mediated objective clinical responses in patients. T cells engineered to express TCRs specific for shared tumor associated antigen have demonstrated the reproducible capacity to mediate solid tumor regression, and in some cases, toxicity against normal tissue expressing the target antigen, emphasizing the importance of antigen selection. Unlike TCR engineered T cells, CAR T cells recognize surface tumor antigens in an HLA-independent manner, thereby potentially providing a universal approach to solid cancer treatment. While clinical trials are ongoing, the earliest reports of CAR T cell therapy for solid tumor have shown limited clinical responses, yet with the risk for on-target toxicity. To improve the efficacy and safety of CAR T cell therapy for solid tumor, we and others have identified safer tissue-specific target antigens and developed novel approaches to enhance tumor penetrance, reduce immunosuppression and address the challenge of tumor antigen heterogeneity, whilst instilling CAR T cells with synthetic system that permit orthogonal control of T cell activity. These novel approaches represent the cutting edge of gene-engineered T cells and the next wave of synthetically engineered T cells for solid tumor.

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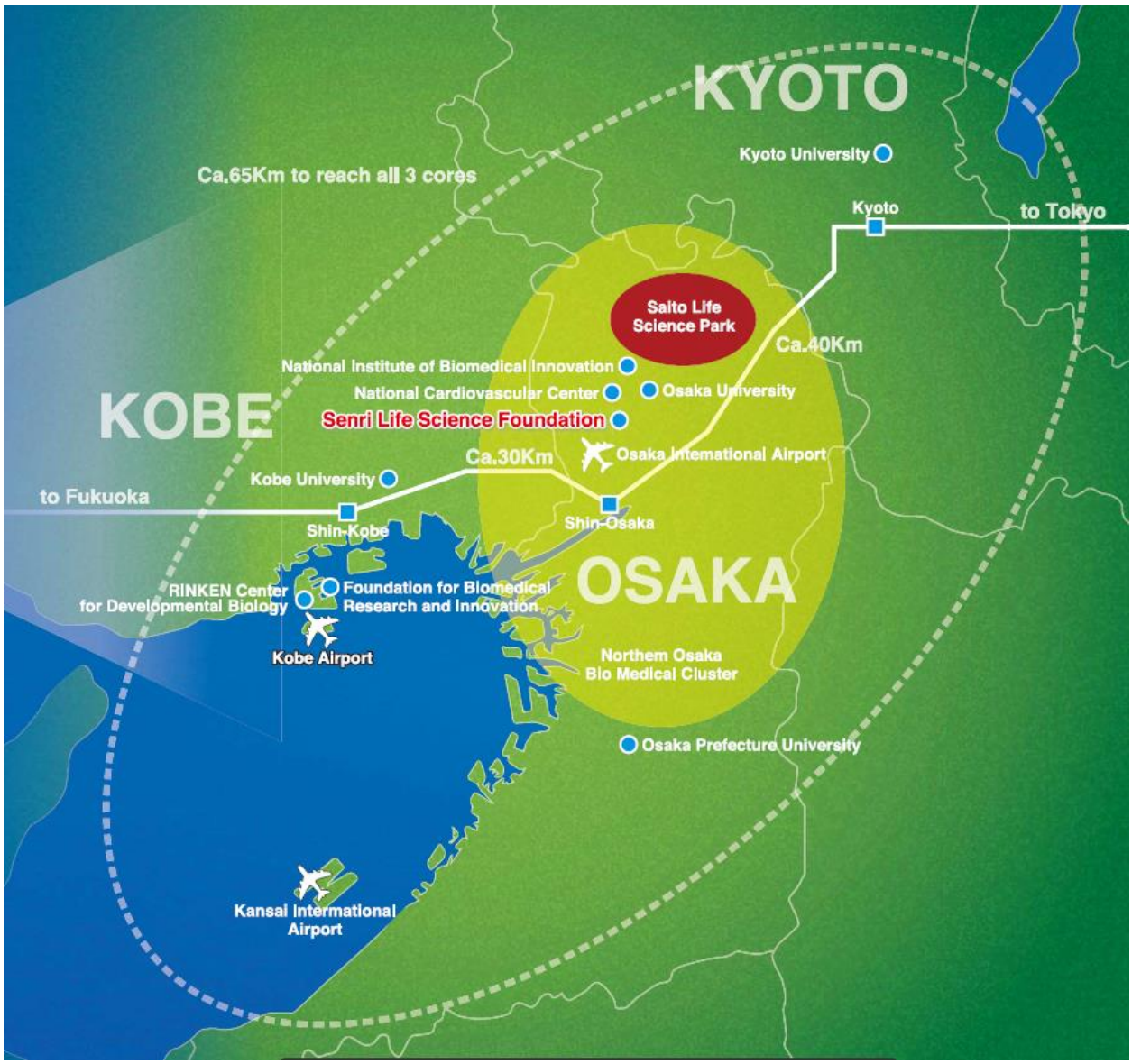
Closing Remarks

Keiya Ozawa, MD., PhD.

<MEMO>



SENRI LIFE SCIENCE FOUNDATION

Foundation Overview

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

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

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

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

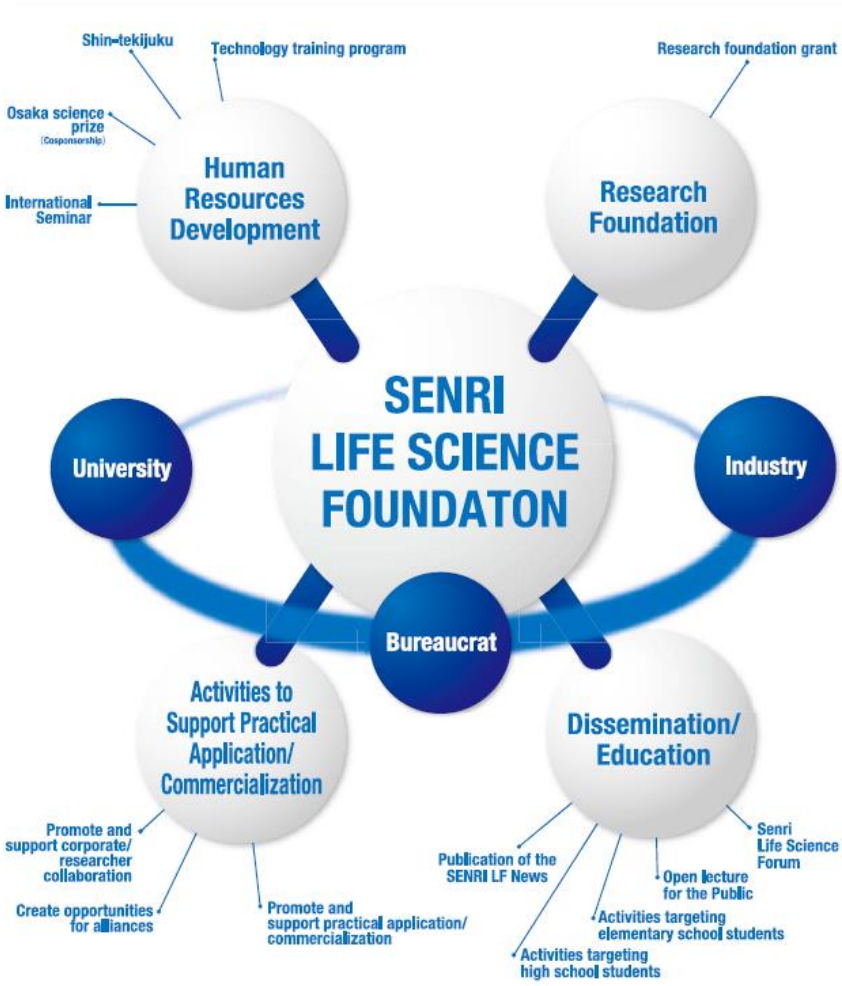
As a "center for intelligent exchange" in life sciences, it has contributed to the advancement and promotion of life sciences through active efforts, e.g., developing excellent researchers, subsidizing and aiding research, supporting practical applications of research through exchanges with industry,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

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

We would greatly appreciate your active and enthusiastic cooperation.

President of
Senri Life Science Foundation

Tadamitsu Kishimoto



SENRI LIFE SCIENCE FOUNDATION INITIATIVE

Senri Life Science Foundation

Level 20, Senri Life Science Center Building
1-4-2, Shinsenri-Higashimachi, Toyonaka-City,
Osaka 560-0082, Japan
Phone: 06-6873-2001, Fax: 06-6873-2002
E-mail: sng@senri-life.or.jp
URL: http://www.senri-life.or.jp