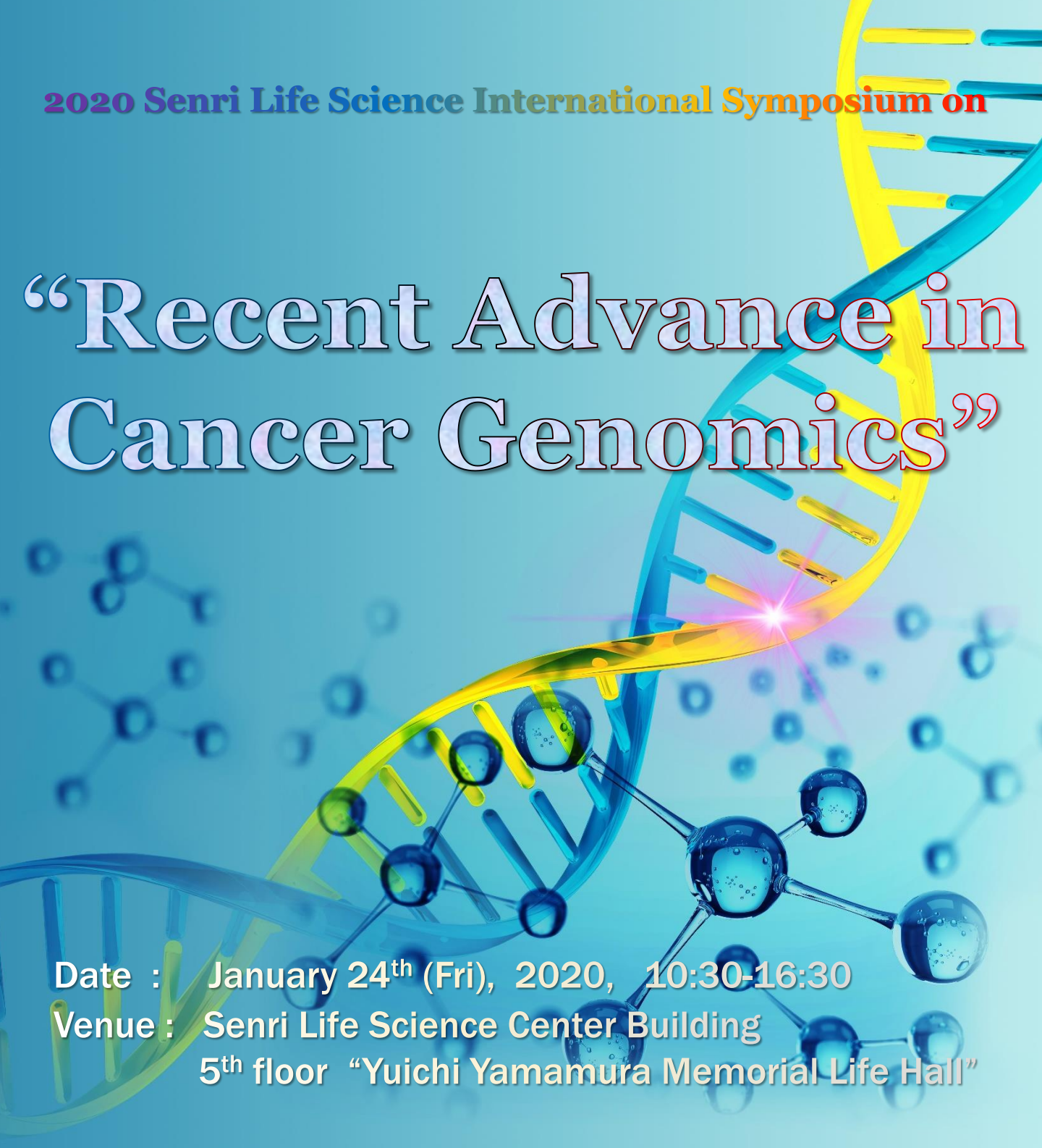
2020 Senri Life Science International Symposium on

# "Recent Advance in Cancer Genomics"



Date : January 24th (Fri), 2020, 10:30-16:30

Venue : Senri Life Science Center Building
5th floor "Yuichi Yamamura Memorial Life Hall"

Coordinated by

Hiroyuki MANO & Seishi OGAWA

Sponsored by Senri Life Science Foundation

Description of cover view ;
A conceptual image of cancer genomics –
The dramatic progress of comprehensive genome analysis technology has led to the achievement of innovative pathophysiology and cancer therapy.

Created by Evo Devo Design.

## 2020 Senri Life Science International Symposium

# “Recent Advance in Cancer Genomics”

## -------- Program -------

10:30- 10:35 Opening address

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

Chair : Seishi Ogawa (Graduate School of Medicine Kyoto University, Japan)

10:35-10:50 Introduction

**Hiroyuki Mano** (National Cancer Center Research Institute, Japan) p.4

10:50-11:30 “Cancer Genomics and Precision Medicine”

〈**Talk 1**〉 **Hiroyuki Mano** (National Cancer Center Research Institute, Japan) p.6

11:30-12:10 “(Epi)Genomic Predictors of Disease Progression in Gastrointestinal Cancer”

〈**Talk 2**〉 **Patrick Tan** (Duke-NUS Medical School, Singapole) p.10

12:10-13:20 **Lunch**

13:20-14:00 “Single-cell multi-omics chart the topology of normal and malignant blood cell development”

〈**Talk 3**〉 **Dan A. Landau** (New York Genome Center, USA) p.14

Chair : Hiroyuki Mano (National Cancer Center Research Institute, Japan)

14:00-14:40 “Clonal Origin of cancer”

〈**Talk 4**〉 **Seishi Ogawa** (Graduate School of Medicine Kyoto University, Japan) p.18

14:40-15:00 **Coffee break**

15:00-15:40 “The new taxonomy of ALL”

〈**Talk 5**〉 **Charles Mullighan** (St. Jude Children’s Research Hospital, USA) p.20

15:40-16:20 “Cancer modeling in the CRISPR era”

〈**Talk 6**〉 **Andrea Ventura** (Memorial Sloan Kettering Cancer Center, USA) p.24

16:20-16:30 Closing remarks

**Seishi Ogawa** (Graduate School of Medicine Kyoto University, Japan) p.28

*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
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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
2019 Keio Medical Science Prize

# 〈 Introduction 〉
## "Recent Advance in Cancer Genomics"
**Hiroyuki Mano, MD., PhD.**

Cancer genomics has revolutionized the way we diagnose and treat cancer patients with. Discovery of molecular targets has substantially prolonged patients' survival with corresponding inhibitors, and prognostic biomarkers has further sophisticated therapeutic intervention. Identification of the same oncogenes across a wide array of cancers also paved the way to genomic medicine. Further understanding of cancer provides a variety of cancer models with better prediction of clinical efficacy for drugs than conventional cell lines. This symposium will discuss these hot issues with the world-leading scientists.

<MEMO>

# 〈Talk 1〉
# “Cancer Genomics and Precision Medicine”

**Hiroyuki Mano, MD., PhD.**

**Title:**

Executive Director
Director, Research Institute
Director, Center for Cancer Genomics and Advanced Therapeutics
Division Head of Cellular Signaling, Research Institute
National Cancer Center
5-1-1 Tsukiji, Chuoku, Tokyo 104-0045, Japan

**Educational History:**

1984 MD degree from School of Medicine, Faculty of Medicine, The University of Tokyo
1992 PhD degree from Graduate School of Medicine, The University of Tokyo

**Professional History:**

| | |
|---|---|
| 1984–1986 | Medical Intern, The University of Tokyo Hospital, Tokyo, Japan |
| 1986–1989 | Fellow, The Third Department of Internal Medicine, Faculty of Medicine, The University of Tokyo, Tokyo, Japan |
| 1989–1991 | Postdoctoral Researcher, Department of Biochemistry, St. Jude Children’s Research Hospital, Memphis, TN |
| 1991–1993 | Assistant Professor, The Third Department of Internal Medicine, Faculty of Medicine, The University of Tokyo, Tokyo, Japan |
| 1993–2001 | Associate Professor, Department of Molecular Biology, Jichi Medical University, Tochigi, Japan |
| 2001–2013 | Professor, Division of Functional Genomics, Jichi Medical University, Tochigi, Japan |
| 2009–2013 | Project Professor, Department of Medical Genomics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan |
| 2013–2018 | Professor, Department of Cellular Signaling, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan |
| 2016–present | Executive Director, Director of Research Institute, National Cancer Center, Japan |
| 2018–present | Director, Center for Cancer Genomics and Advanced Therapeutics, National Cancer Center, Japan |

**Honors & Awards:**

1993 Incitement Award from Japanese Cancer Association
2008 The Medical Award from The Japan Medical Association
2009 The Princess Takamatsu Cancer Research Fund Prize
2010 The Academic Award of the Mochida Memorial Foundation
2010 The Takeda Prize for Medical Science from Takeda Science Foundation
2011 The Uehara Prize from The Uehara Memorial Foundation
2011 The Prize for Science and Technology from The Ministry of Education,

Culture, Sports, Science and Technology, Japan

2011 The David Jablon's "Asclepios Award" from The Bonnie J. Addario Lung Cancer Foundation

2012 The Takamine Memorial Daiichi Sankyo Prize from The Daiichi-Sankyo Foundation of Life Science

2012 The Keio Medical Science Prize from The Keio University Medical Science Fund

2012 The Medal with Purple Ribbon from The Japanese Emperor

2013 The Shiono Prize from The Cell Science Research Foundation

2013 JCA-CHAAO Award from Japanese Cancer Association

2015 The Bälz Prize from Boehringer Ingelheim

2019 The Yamazaki Teiichi Prize from The Foundation for Promotion of Material Science and Technology of Japan

# Abstract

Our discovery of EML4-ALK oncogene in lung cancer brought highly effective ALK inhibitors to the patients carrying this fusion gene. Identification of other ALK fusions in various cancer subtypes further led to realize the importance of beyond-organ, gene-based cancer classification scheme (Cancer Discov 2:495-502), ushering in the “cancer genomic medicine” to the clinics. To assist clinical sequencing of cancer specimens, we developed the “Todai OncoPanel (TOP)” multigene test that can sensitively and reliably detect gene fusions in addition to single nucleotide variations from formalin-fixed specimens (Cancer Sci 110:1464-1479). Further, to functionally annotate variants of unknown significance (VUS) in the cancer genome, we have created the MANO method that screen hundreds of VUSs in a high-throughput manner (Sci Transl Med 9, eaan6556).

Japan planned to adapt gene-panel testing to optimize cancer treatments under the national health insurance system. To discuss a necessary platform to perform such cancer genomic medicine in a nation-wide manner, The Expert Meeting for Cancer Genomic Medicine Promotion Consortium was held in the Spring of 2017 in The Ministry of Health, Labour and Welfare (MHLW). The Expert Meeting recommends a step-wise adaptation of genomic medicine, i.e. such medicine should be first conducted only in designated hospitals, and the number of these hospitals shall be increased gradually. Another important proposal from the Expert Meeting is to set a central datacenter to aggregate genomic as well as clinical information of gene-panel tests. MHLW accordingly designated, in the Spring of 2018, eleven Core Hospitals for Cancer Genomic Medicine and 156 of Cooperative Hospitals for Cancer Genomic Medicine. The Ministry also established, in June 2018, The Center for Cancer Genomics and Advanced Therapeutics (C-CAT) to store and utilize genomic/clinical information.

The genomic medicine platform in Japan, consisting of these hospitals and C-CAT, officially started at June 1st 2019 with two approved cancer gene panels, “OncoGuide NCC Oncopanel” and “FoundationOne CDx”. We are preparing the “C-CAT Cloud” system so that such genomic and clinical information shall become available to academia and third parties.

<MEMO>

# 〈Talk 2〉
# “(Epi)Genomic Predictors of Disease Progression in Gastrointestinal Cancer”

**Patrick Tan, MD., PhD.**

**Title:**

Professor, Duke-NUS Medical School Singapore
Executive Director, Genome Institute of Singapore
Director, SingHealth Duke-NUS Institute of Precision Medicine (PRISM)
EMAIL: gmstanp@duke-nus.edu.sg and tanbop@gis.a-star.edu.sg

**Educational History:**

1986 - 1987 National Junior College, Singapore, GCE 'A' Level
1988 - 1992 Harvard University, B.A. (Biochemistry)
1992 - 2000 Stanford University School of Medicine, M.D., Ph.D (Developmental Biology)

**Professional History:**

2019 - Present Executive Director, Genome Institute of Singapore
2015 - Present Director, SingHealth Duke-NUS Institute of Precision Medicine (PRISM)
2012 - Present Professor (Tenured), Cancer and Stem Cell Biology, Duke-NUS Medical School
2012 - Present Senior Principal Investigator, Cancer Science Institute of Singapore (NUS)
2009 - Present Director, Duke-NUS Genome Biology Facility
2006 - Present Principal Investigator (Adjunct), National Cancer Centre, Singapore
2012 - Present Professor (Adjunct), Dept of Physiology, National University of Singapore
2016 – 2019 Deputy Executive Director, Biomedical Research Council, A*STAR
2014 - 2016 Associate Director (Genomic Medicine), Genome Institute of Singapore
2013 - 2016 Senior Group Leader, Genome Institute of Singapore
2009 - 2014 Research Associate Professor, Duke University, USA
2004 - 2013 Senior Research Fellow (Adjunct), Defence Medical and Environmental Research Institute, Defence Science Organization (DMERI@DSO), Singapore
2003 - 2012 Associate Professor (Adjunct), Dept of Physiology, NUS
2008 - 2012 Program Leader, Genomic Oncology, Cancer Science Institute of Singapore
2004 - 2013 Group Leader, Genome Institute of Singapore
2006 - 2012 Associate Professor (Awarded Tenure in 2009), Cancer and Stem Cell Biology, Duke-NUS Medical School Singapore
2005 - 2008 Associate Professor (Adjunct), School of Computer Science, Nanyang Technological University, Singapore
2002 - 2007 Chief Scientific Officer, Agenica Research Pte Ltd (Joint Venture with NCCS, Mitsui Corp, and Shimadzu Corp)
2002 - 2006 Principal Investigator, National Cancer Centre, Singapore
2003 - 2004 Senior Research Fellow, Defence Medical and Environmental Research Institute (DMERI@DSO), Singapore

2004 Visiting Scientist, Broad Institute, Cambridge, MA
2000 - 2003 Research Scientist, Defence Medical Research Institute, Singapore

**Honors & Awards:**

1987 President's Scholarship, Singapore
1987 Loke Cheng Kim Scholarship, Singapore
1988 Detur Prize for Academic Excellence, Harvard University
1991 Signet Society, Harvard University
1992 Graduated summa cum laude (Highest Honors), Harvard University
1992 Phi Beta Kappa Society
1992 Fairchild Fellowship (for MSTP training), Stanford University
1998 Charles Yanofsky Award for Most Outstanding Graduate Thesis (Physics, Biology, Chemistry), Stanford University
2001 Young Scientist Award (Singapore National Academy of Sciences)
2001 NCC Academic Award for Best Intellectual Property Filing
2002 NCC Academic Award for Best New Research Programme
2002 Singapore Youth Award (National Youth Council)
2002 Best Business Plan and Executive Summary (Systome Therapeutics), Startup@Singapore National Techno-Venture Competition
2004 SingHealth Investigator Excellence Award
2005 AACR-ITO EN Scholar in Training Award, AACR 96th Annual Meeting (for graduate student Amit Aggarwal)
2008 Singapore Youth Award, Medal of Commendation (National Youth Council)
2010 AACR-Bristol-Myers Squibb Oncology Scholar-in-Training Award (for graduate student Iain Tan)
2010 ASCO Young Investigator Award (for graduate student Iain Tan)
2011 Singapore General Hospital Scientist Award
2011 Duke-NUS Pioneer Award (Faculty Award for Contributions to Medical Curriculum Development)
2011 Swee Liew Wadsworth Lectureship. Department of Physiology, National University of Singapore
2013 Duke-NUS Pioneer Award (Faculty Award for Contributions to Establishing Duke-NUS)
2013 Chen New Investigator Award, Human Genome Organization
2013 American Society for Clinical Investigation (elected member)
2015 President’s Science Award 2015 (Team)
2016 Japanese Cancer Association International Award
2018 JP Kim Memorial Lecture, Korean International Gastric Cancer Week
2018 AACR Team Science Award (Team Leader)

# Abstract

Stomach cancer (gastric cancer) is a leading cause of global cancer mortality. Particularly prevalent in Asia, previous genomic studies have shown that gastric tumors are high intra-tumor and inter-tumor molecular heterogeneity. In this talk, I will outline recent studies attempting to dissect this heterogeneity at the genetic and epigenetic level, revealing new potential strategies for treatment.

<MEMO>

# 〈Talk 3〉
# “Single-cell multi-omics chart the topology of normal and malignant blood cell development”

**Dan A. Landau, MD., PhD.**

**Title:**

Assistant Professor of Medicine, Division of Hematology and Medical Oncology
Assistant Professor of Physiology and Biophysics
Member, Institute of Computational Biomedicine
Weill Cornell Medicine
Belfer Research Building
413 East 69th Street, BB-1428
New York, NY 10021

**Educational History:**

| | |
|---|---|
| 1995–1998 | Tel Aviv University<br>B.S.- 1998 |
| 1998-2002 | Sackler School of Medicine, Tel Aviv University<br>M.D.- 2002 |
| 2010-2013 | Paris Diderot University<br>Ph.D.- 2013 |

**Postdoctoral Training:**

| | |
|---|---|
| 2007-2008 | Internal Medicine Intern<br>Yale New Haven Hospital |
| 2008-2009 | Internal Medicine Resident<br>Yale Cancer Center<br>Yale University |
| 2009-2014 | Hematology and Medical Oncology Fellow<br>Yale Cancer Center<br>Yale University |
| 2011-2014 | Post-Doctoral Research Fellow<br>Dana Farber Cancer Institute and The Broad Institute of Harvard and MIT |

**Professional History:**

| | |
|---|---|
| 2016-Present | Member, Institute of Computational Biomedicine, Weill Cornell Medicine<br>Core member, New York Genome Center |
| 2015-Present | Assistant Professor of Medicine, Division of Hematology and Medical Oncology<br>Assistant Professor of Physiology and Biophysics<br>Weill Cornell Medicine |

**Honors & Awards:**

1998 Dean’s Award for Outstanding Academic Achievement, Tel Aviv University

2006 HIV Research Award, French National Agency for HIV

2011 Research Training Award for Fellows, American Society of Hematology

2012 Plenary scientific session, Annual meeting, American Society of Hematology

2012 Post-Doctoral Fellow, American Cancer Society

2014 Big Data to Knowledge K01 Award, NIH

2014 Theodore T. Puck Award, Aspen Cancer Conference

2014 Scholar Award, American Society of Hematology

2014 Yale Cancer Center Award for Outstanding Contribution in Hematology

2015 Career Award for Medical Scientist, Burroughs Wellcome Fund

2016 Young Physician-Scientist Award, American Society of Clinical Investigation

2016 Kimmel Scholar, Sydney Kimmel Foundation

2016 Junior Faculty Scholar Award, American Society of Hematology

2017 The Levy Memorial Award for Outstanding Achievement, American Society of Hematology

2017 Next Gen Innovators, HemOnc Today

2018 SU2C Philip A. Sharp Award for Innovation in Collaboration

2018 The Pershing Square Sohn Prize for Young Investigators in Cancer Research

2018 ASPIRE (Accelerating Scientific Platforms and Innovative Research) Award, Mark Foundation

2018 Lung Cancer Discovery Award , American Lung Association

2018 NIH Director's New Innovator Award, NIH Common Fund

2019 Young Investigator Award, Weill Department of Medicine

# Abstract

Cancer progression, relapse and resistance are the result of an evolutionary optimization process. Vast intra-tumoral diversity provides the critical substrate for cancer to evolve and adapt to the selective pressures provided by effective therapy. Our previous work has shown that genetically distinct subpopulations compete and mold the genetic makeup of the malignancy [1, 2]. Additionally, we have shown that epigenetic changes in cancer may be similar to the process of genetic diversification, in which stochastic trial and error leads to rare fitness enhancing events [3]. These studies demonstrate the need to integrate genetic, epigenetic and transcriptional information in the study of cancer evolution, specifically at the single-cell resolution – the atomic unit of somatic evolution. To enable this work, we have developed a single-cell multi-omics toolkit, and apply it to chart the evolutionary history and developmental topographies of normal and malignant blood cells.

First, we have applied single-cell multi-omics to chronic lymphocytic leukemia (CLL), a highly informative model for cancer evolution [4]. We applied multiplexed single-cell reduced-representation bisulfite sequencing to healthy B and CLL cells, and demonstrated that epimutations serve as a molecular clock. Heritable epimutation information therefore allows to infer high-resolution lineages with single-cell data, directly in patient samples. CLL tree topography showed earlier branching and longer branch lengths than normal B cell trees. These features reflect rapid drift after malignant transformation and CLL's greater proliferative history. Multi-omic single-cell Integration of methylome sequencing with whole transcriptome and genotyping capture validated tree topology inferred solely on the basis of epimutation information. To examine potential lineage biases during therapy, we profiled serial samples during ibrutinib-associated lymphocytosis, and identified clades of cells that were preferentially expelled from the lymph node after treatment, marked by distinct transcriptional profiles involving TLR pathway activation. The single-cell integration of genetic, epigenetic and transcriptional information thus charts the lineage history of CLL and its evolution with therapy.

Second, charting the transcriptomes of clonally mutated cells is challenging in the absence of surface markers that distinguish cancer clones from one another, or from admixed non-neoplastic cells. To tackle this challenge, we developed Genotyping of Transcriptomes (GoT), a technology to integrate genotyping with high-throughput droplet-based single-cell RNA sequencing [5]. With GoT we profiled thousands of CD34+ cells from patients myeloproliferative neoplasms to study how somatic mutations corrupt the process of human hematopoiesis. These data allow to

superimpose the two differentiation trees; the native wildtype tree and the one corrupted by mutation. High-resolution mapping of malignant versus normal progenitors showed increased fitness with myeloid differentiation with CALR mutation. We identified the unfolded protein response as a predominant outcome of CALR mutations, with dependency on cell identity. Notably, stem cells and more differentiated progenitors show distinct transcriptional programs as a result of somatic mutation, suggesting differential sensitivity to therapeutic targeting. We further extended the GoT toolkit to genotype multiple targets and loci that are distant from transcript ends. Together, these findings reveal that the transcriptional output of somatic mutations in blood neoplasms is dependent on the native cell identity.

**Reference:**


1. Landau, D. A., Carter, S. L., Stojanov, P. et al., Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. Cell 152, 714-726 (2013).
2. Landau, D. A., Tausch, E., Taylor-Weiner, A. N. et al., Mutations driving CLL and their evolution in progression and relapse. Nature 526, 525-530 (2015).
3. Landau, D. A., Clement, K., Ziller, M. J. et al., Locally disordered methylation forms the basis of intratumor methylome variation in chronic lymphocytic leukemia. Cancer Cell 26, 813-825 (2014).
4. Gaiti, F., Chaligne, R., Gu, H. et al., Epigenetic evolution and lineage histories of chronic lymphocytic leukaemia. Nature 569, 576-580 (2019).
5. Nam, A. S., Kim, K. T., Chaligne, R. et al., Somatic mutations and cell identity linked by Genotyping of Transcriptomes. Nature 571, 355-360 (2019).

# 〈Talk 4〉

# “Clonal Origin of cancer”

**Seishi Ogawa, MD., PhD.**

**Title:**

Professor of Pathology and Tumor Biology,
Graduate School of Medicine, Kyoto University
Yoshida-konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan
Phone : +81-75-753-9283
URL: http://plaza.umin.ac.jp/kyoto_tumorpatho/

**Educational History:**

1989 –1993: MD, PhD program, University of Tokyo
1983 –1988: Undergraduate/MD program, School of Medicine, University of Tokyo

**Professional History:**

2017 - Present: Guest Professor, Department of Molecular Hematology, Karolinska Institute.
2013 - Present: Professor, Department of Pathology and Tumor Biology, Kyoto University
2008 - 2013: Associate Professor, Cancer Genomics Project, University of Tokyo
2006 - 2008: Associate Professor, The 21st century COE program, Graduate School of Medicine, University of Tokyo
2002 - 2006: Associate Professor, Department of Regeneration Medicine for Hematopoiesis, Graduate School of Medicine, University of Tokyo
1996 –2002: Assistant Professor of Medicine, University of Tokyo
1995 –1996: Research fellow of Japan Society for the Promotion of Science
1994 –1995: Clinical Associate, University of Tokyo
1988 –1989: Postgraduate clinical training in internal medicine

**Honors and Awards:**

1996 Erwin von Bälz Prize
1997 Incitement Award of the Japanese Cancer Association
2010 Mauverney Prize of the Japanese Cancer Association
2012 Nice STEP researcher 2011
2013 Award of the Japanese Society of Hematology
2013 Medical Award of The Japan Medical Association
2014 Mochida Memorial Award
2014 Sagawa Special Award
2016 Uehara Prize
2016 Princes Takamatsu Cancer Research Fund Prize
2017 Culture, Sports, Science and Technology Minister's Commendation
2017 Takamine Prize
2017 Takeda Prize
2018 Medal with Purple Ribbon
2019 Erwin von Bälz Prize

# Abstract

Cancer is thought to comprise a heterogeneous population of neoplastic cells showing a complex hierarchical structure in terms of gene mutations. According to recent studies, the entire cancer hierarchy by itself might be further embedded in higher level hierarchies that are recursively generated by multiple rounds of positive selections, where acquisition of driver mutations plays a central role. Thus, before a cancer develops, many independent, precancerous populations of clones are presumed to be present within apparently or physiologically normal tissues. However, it is poorly understood how those clones evolve from early infancy to the end of the life span in terms of their frequency and size and how its dynamics is affected by environmental/genetic factors to contribute to cancer. In this study, we investigated clonal expansion in physiologically normal tissues and those exposed to chronic inflammation by collecting a large number of micro-scale samples from aged esophagus as well as inflamed colorectal tissues from patients with ulcerative colitis, followed by an unbiased detection of somatic mutations and copy number abnormalities (CNAs) using whole-exome sequencing (WES). We demonstrated pervasive expansion of clones in aged esophageal tissues and inflamed colorectal epithelium in UC patients. Driver genes mutated in these expanded clones showed significant overlaps to those involved in cancer development of corresponding tissues, suggesting that these expanded clones represent the origin of cancer. Nevertheless, the frequency and patterns of mutations were substantially different between normal and cancer tissues, likely reflecting discrete underlying mechanism of clonal selection between both conditions. Thus, a mutation which is positively selected in non-cancerous expansion might not promote clonal selection but even negatively affect cancer development. For example, NFKBIZ mutations are highly prevalent in UC epithelia but rarely found in both sporadic and colitis-associated cancer, suggesting negative selection of NFKBIZ-mutated cells during colorectal carcinogenesis, which was further supported by significantly attenuated colitis-induced tumor formation in Nfkbiz-deficient mice and compromised cell-competition of NFKBIZ-disrupted colorectal cancer cells. To summarize, our results disclosed discrete mechanisms of clonal selection and remodeling between aged or inflamed tissues and cancer development, which may unmask novel cancer vulnerability potentially utilized for therapeutics of colorectal cancer.

# 〈Talk 5〉

# “The new taxonomy of ALL”

## Charles Mullighan, MD., PhD.

**Title:**

Member, Department of Pathology, St Jude Children’s Research Hospital
Co-leader, Hematologic Malignancies Program, St Jude Children’s Research Hospital
Deputy Director, St Jude Children’s Research Hospital Comprehensive Cancer Center
William E. Evans Endowed Chair, St Jude Children’s Research Hospital
Medical Director, Biorepository, St. Jude Children's Research Hospital
Professor, Department of Pathology, College of Medicine, University of Tennessee

**Professional History:**

| | |
|---|---|
| 1993 | Intern, Royal Adelaide Hospital, South Australia |
| 1994-1997 | University of Adelaide George Murray Scholar and Immunology Registrar, Departments of Immunology and Transplantation Immunology, University of Oxford, United Kingdom |
| 1998-2000 | Physician Trainee (Internal Medicine Resident), Royal Adelaide Hospital, South Australia |
| 2001 | Chief Medical Resident, Royal Adelaide Hospital |
| 2001-2003 | Haematology/Haematopathology Trainee, Institute of Medical and Veterinary Science |
| 2004-2008 | NH&MRC (Australia) CJ Martin Travelling Postdoctoral Fellowship; Physician Scientist Postdoctoral Fellow, Department of Pathology, St. Jude Children's Research Hospital |
| 2008- | Assistant Member, Department of Pathology, St. Jude Children's Research Hospital |
| 2008- | Medical Director, Biorepository, St. Jude Children's Research Hospital |
| 2011- | Associate Member, Department of Pathology, St. Jude Children’s Research Hospital |
| 2011- | Co-leader, Hematologic Malignancies Program, St Jude Children’s Research Hospital |
| 2014- | Member, Department of Pathology, St Jude Children’s Research Hospital |
| 2014- | Professor, Department of Pathology, College of Medicine, University of Tennessee |
| 2016- | William E. Evans Endowed Chair |
| 2019- | Deputy Director, St Jude Children’s Research Hospital Comprehensive Cancer Center |

**Honors and Awards:**

| | |
|---|---|
| 1992 | Deans List, Honors, University of Adelaide Medical School |
| 2001 | Royal Australasian College of Physicians (SA Branch) Professor John Chalmers Prize |
| 2001 | Haematology Society of Australia and New Zealand Albert Baikie Memorial Award |
| 2002 | Royal Australasian College of Physicians Pfizer Advanced Trainee Prize |
| 2002 | Royal College of Pathologists of Australasia D.S. Nelson Prize |
| 2003 | Royal College of Pathologists of Australasia Kanematsu Award |
| 2007 | American Society of Hematology Merit Award |
| 2007 | American Society of Hematology Scholar Award |
| 2007 | American Association of Cancer Research / Aflac Career Development Award |
| 2008 | American Society of Hematology Joanne Levy Memorial Award for Outstanding Achievement |
| 2009 | Society for Pediatric Pathology Lotte Strauss Prize |

2009 American Association for Cancer Research Team Science Award
2009 Pew Scholar in the Biomedical Sciences
2009 Memphis Business Journal “Health Care Heroes” Innovations Prize
2010 Founding Fellow, Faculty of Science, Royal College of Pathologists of Australasia
2012 Elected, American Society of Clinical Investigation
2012 Meyenburg Prize for Cancer Research
2015 United States and Canadian Academy of Pathology Ramzi Cotran Young Investigator Award
2015 Elected Fellow, Australian Academy of Health and Medical Sciences
2016 Elected, American Association of Physicians
2016 Inaugural St. Baldrick’s Foundation Robert J. Arceci Innovation Award
2016 American Society of Hematology William Dameshek Prize
2017 NCI R35 Outstanding Investigator Award
2018 Clarivate Highly Cited Researcher
2019 Society of Hematology and Oncology Distinguished Lecturer

# Abstract

Acute lymphoblastic leukemia is the commonest childhood tumor, a leading cause of cancer death in the young, and associated with poor prognosis in adults. Karyotyping of ALL has enabled a degree of risk stratification and tailoring of therapy, and has demonstrated the potential of risk adapted therapy in which leukemic features at presentation and early response have enabled modulation of therapeutic intensity to optimize outcomes. However, the full range of leukemia subtypes and their drivers have been poorly understood. This has been transformed with the application of sequencing approaches in large cohorts of childhood and adult ALL samples. Such studies have examined thousands of patients with ALL and have provided several key insights relevant to ALL and cancer in general that will be reviewed in this presentation. These include the power of transcriptome sequencing to integrate multimodal genomic data to define ALL subtypes and their driving genetic alterations; the notion that ALL subtypes may be defined by heterogeneous alterations of multiple partners of rearrangement to a single driver; the recurring theme that perturbation of chromatin modifying genes and transcription factors is central to multiple subtypes of ALL, and that specific transcription factor mutations exert primacy in defining ALL subtypes. Moreover, studies across cohorts of ALL, AML and lineage ambiguous leukemias have demonstrated that specific genetic alterations arising in early progenitors can define leukemia subtypes that transcend a single lineage. These findings have important implications for therapeutic targeting. While several subtypes have logical targets for therapeutic repurposing (e.g. Ph-like ALL) these studies have also begun to reveal additional vulnerabilities, including HDAC inhibitors, BCL2 inhibitors, and FLT3 inhibitors. Mutational profiling also offers the opportunity to track disease in real time an detect relapse-promoting mutations and modify therapy to avoid treatment failure. These concepts that exemplify ALL as a paradigm of genomically-informed precision medicine will be reviewed.

<MEMO>

# 〈Talk 6〉
# “Cancer modeling in the CRISPR era”
## Andrea Ventura, MD., PhD.

**Title:**

Member, Cancer Biology and Genetics Program.
Memorial Sloan Kettering Cancer Center
1275 York Avenue. New York, NY, 10065

**Educational History:**

1997 Medical Degree
Catholic University Medical School, Rome, Italy.
1998 Internship and Medical Board Certification

2003 PhD in molecular and cellular biology
Open University, London, UK.
European Institute of Oncology, Milan, Italy

**Postdoctoral training:**

2003-08 Postdoctoral Fellow
MIT
Center for Cancer Research, Cambridge, MA
Laboratory of Tyler Jacks

**Professional History:**

2018-present Member
Cancer Biology and Genetics Program
Memorial Sloan Kettering Cancer Center, NY 10065
2018-present Professor
Cell & Developmental Biology
Weill Cornell Medicine, NY 10065
2014-2018 Associate Member
Cancer Biology and Genetics Program
Memorial Sloan Kettering Cancer Center, NY 10065
2014-2018 Associate Professor
Cell & Developmental Biology
Weill Cornell Medicine, NY 10065
2008-2014 Assistant Member
Cancer Biology and Genetics Program
Memorial Sloan Kettering Cancer Center, NY 10065
2008-2014 Assistant Professor
Cell & Developmental Biology
Weill Cornell Medicine, NY 10065

**Awards, Honors and Patents**

| | |
|---|---|
| 2016 | Pershing Square Sohn Cancer Research Alliance Award |
| 2013 | Lumera d'argento award, Roccalumera, Italy |
| 2009 | Sidney Kimmel Scholar Award |
| 2008-2013 | Geoffrey Beene Junior Investigator Chair |
| 2007 | Forbeck Scholar Award |
| 2004-5 | Postdoctoral Fellowship American Italian Cancer Research Foundation |
| 2000-2 | Research fellowship from Italian Association for Cancer Research |

# Abstract

Chromosomal rearrangements are common cancer-associated mutations that often result in the generation of therapeutically actionable gene fusions. Unfortunately, until recently this class of mutations has proven challenging to recapitulate using conventional gene targeting methods. To overcome this limitation, we have recently developed a CRISPR-based strategy to model a broad range of chromosomal rearrangements, including inversions, deletions, translocations, and tandem duplications (Maddalo et al., 2014). Since this strategy can be used to induce the desired chromosomal rearrangement in somatic cells—ex vivo or directly in vivo—of adult animals, it enables the rapid and cost-effective generation of novel mouse models of human cancer. As proof of concept, we have applied this strategy to generate a novel model of EML4-ALK driven lung adenocarcinoma, and to show that a novel gene fusion observed in a few human gliomas is a potent oncogenic driver and a therapeutic target (Cook et al., 2017; Maddalo et al., 2014; Ventura and Dow, 2018).

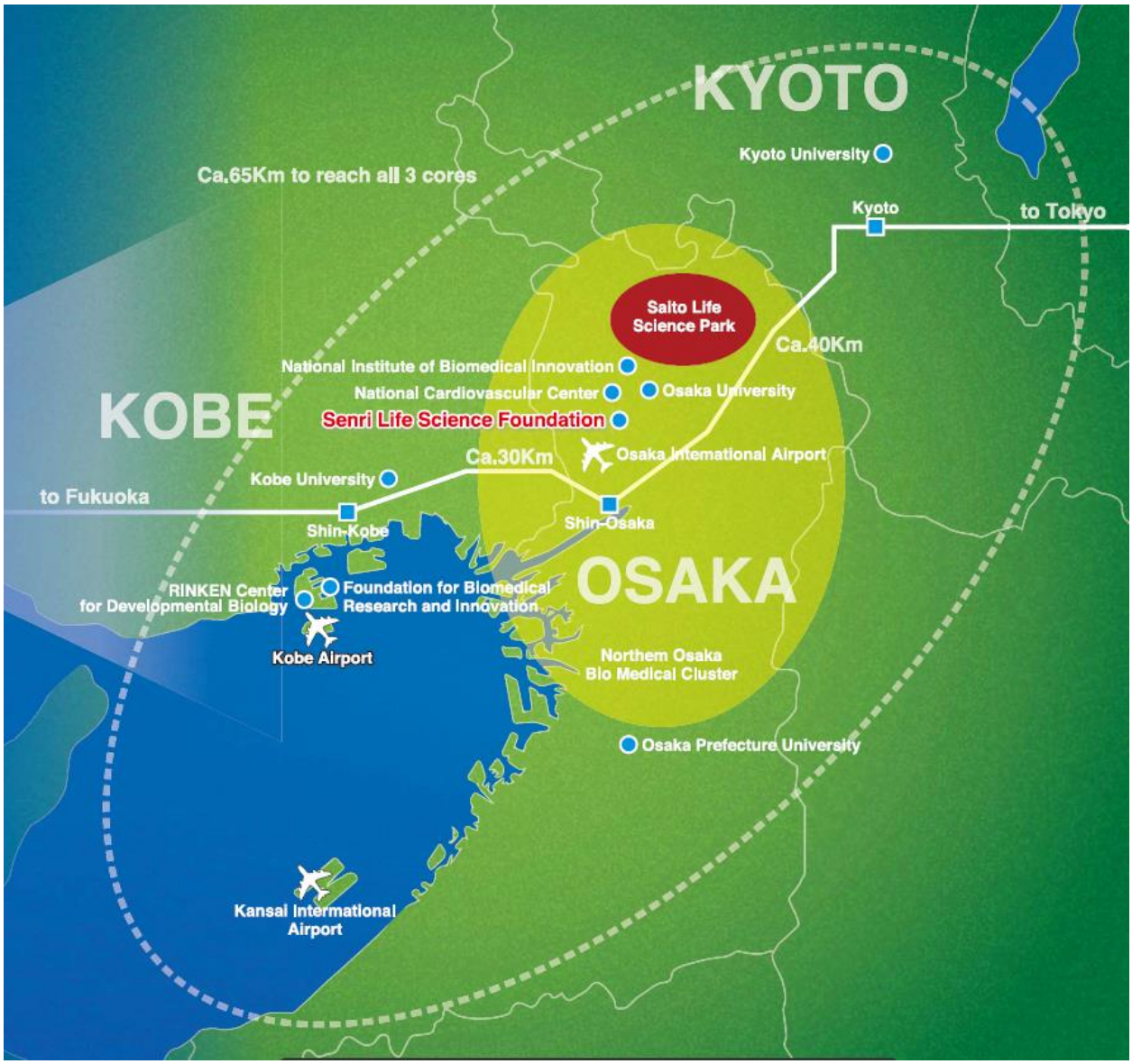
In my presentation, I will discuss how my group is using these novel technologies, as well as conventional gene targeting methods, to recapitulate the genetic complexity of human cancers in vivo. I will present new and unpublished models of pediatric brain cancers driven by BRAF gene fusions we have recently generated using in vivo and ex vivo CRISPR-mediated chromosomal engineering and show how we are using these models to test novel therapeutic strategies and to gain insights into the molecular pathogenesis of human cancers.

<MEMO>

## Closing Remarks

**Seishi Ogawa, 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.

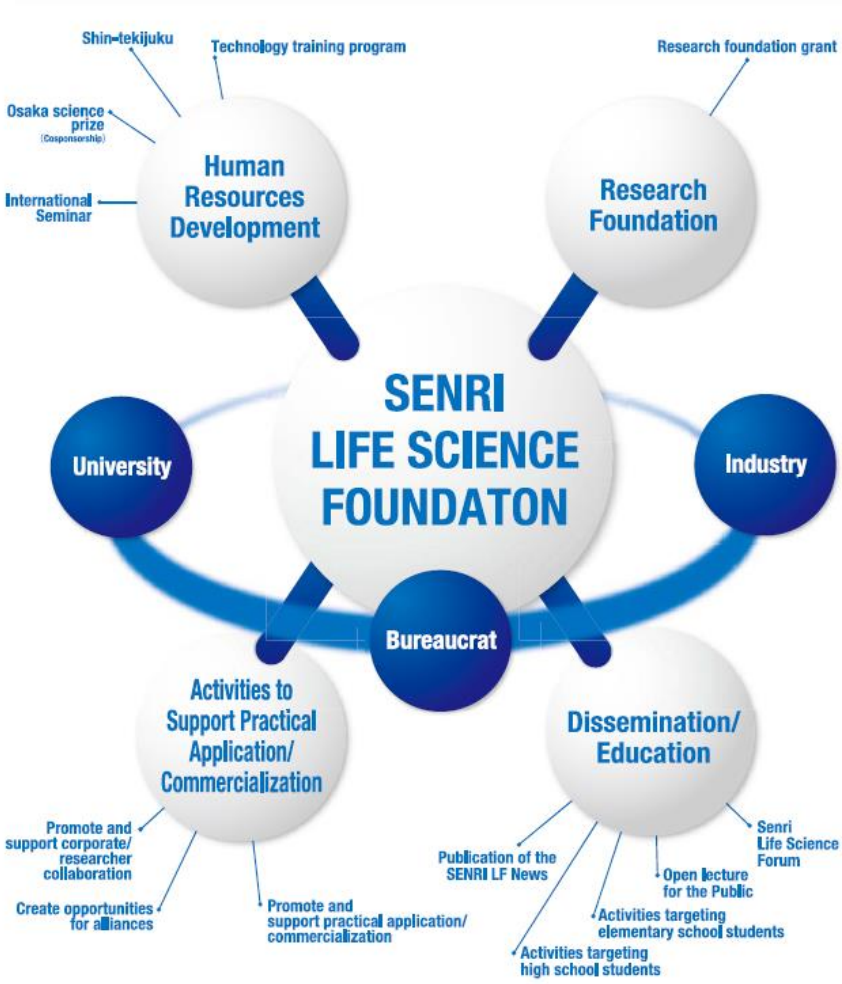
As a "center for intelligent exchange" in life sciences, it has contributed to the advancement and promotion of life sciences through active efforts, e.g., developing excellent researchers, subsidizing and aiding research, supporting practical applications of research through exchanges with industry,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

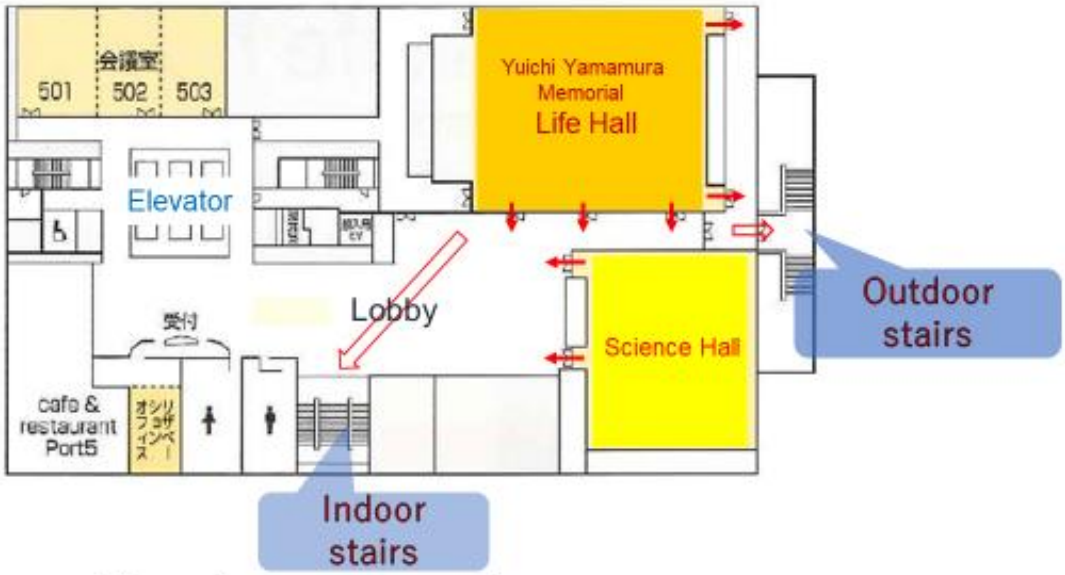
President of
Senri Life Science Foundation

*Tadamitsu Kishimoto*



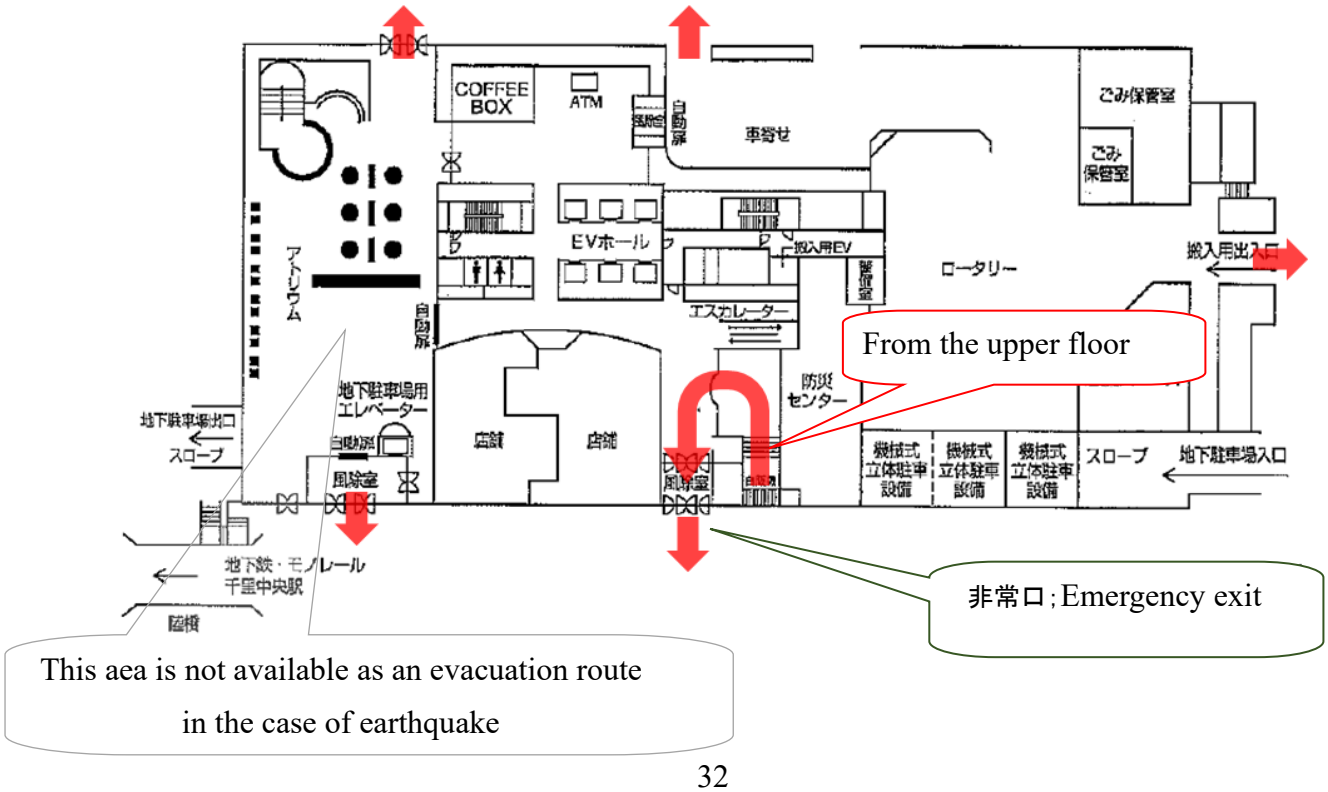

*SENRI LIFE SCIENCE FOUNDATION INITIATIVE*

# Emergency evacuation routes of Senri Life Science Building 5th floor




There is an announce in an emergency.
Follow the instructions, please evacuate calmly.
When evacuating, please exit the route indicated by the red arrow.
Don't use the elevators

## Evacuation route on the 1st floor of the building



Announcement of coming seminar

# 線維症をもたらす炎症細胞社会

開催日時： **2020年2月14日(金)　10:30～17:00**

コーディネータ：
松島 綱治
東京理科大学研究推進機構　生命医科学研究所　教授

小川　佳宏
九州大学大学院　医学研究院　教授

開催場所：
大阪府豊中市新千里東町１－４－２
千里ライフサイエンスセンタービル　５階
山村雄一記念ライフホール

## 応募要領

・定　員：２００名
（お申込み順に受付け、定員になり次第締め切らせて頂きます。）
・参加費：無料（要事前申し込み）
・主　催：公益財団法人千里ライフサイエンス振興財団

## E-mailの場合

メール件名：**千里LFセミナー　Ｎ５　申込み**　として下さい。

1. 氏名
2. 勤務先、所属、
3. 郵便番号、所在地（住所）
4. 電話番号

後日、事務局より送信する参加証(e-mail送信)を印刷し、セミナー開催当日、受付でご提出ください。入場引換券になります。

【E-mail送信先】　tkd-2019〔ａｔ〕senri-life.or.jp
（↑〔at〕を半角の＠アットマークに置き換えて送信してください。）

## FAXの場合

ＦＡＸ件名：**千里LFセミナー　Ｎ５　申込み**　として下さい。

1. 氏名
2. 勤務先、所属、
3. 郵便番号、所在地（住所）
4. 電話番号・ＦＡＸ番号

後日、事務局より送信する参加証(FAX送信)を、セミナー開催当日、受付でご提出ください。入場引換券になります。

【FAX送信先】：　０６－６８７３－２００２


# Senri Life Science Foundation

**Level 20, Senri Life Science Center Building**
**1-4-2, Shinsenri-Higashimachi, Toyonaka-City,**
**Osaka 560-0082, Japan**
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**E-mail: sng-2019@senri-life.or.jp**
**URL: http://www.senri-life.or.jp**