KUIS-11 : Frontier Bioscience in Modern Medicine — Report —

The 11th Kyoto University International Symposium 2008 （KUIS-11）

Frontier Bioscience in Modern Medicine

REPORT

Oct. 9 –11, 2008

Reporting Hall, Mingdao Building,
Shanghai Medical College, Fudan University

KYOTO UNIVERSITY 2008

Organized by
Kyoto University

With special support from
Fudan University

In association with
AEARU
（The Association of East Asian Research Universities）

Sponsored by
The Kyoto University Foundation

In collaboration with
Global COE Program,
Graduate School of Medicine,
Kyoto University

AEARU

KYOTO UNIVERSITY MISSION STATEMENT

Kyoto University states its mission to sustain and develop its historical commitment to academic freedom and to pursue harmonious coexistence within the human and ecological community on this planet.

Research

1. Kyoto University will generate world-class knowledge through freedom and autonomy in research that conforms with high ethical standards.
2. As a university that comprehends many graduate schools, faculties, research institutes and centres, Kyoto University will strive for diverse development in pure and applied research in the humanities, sciences and technology, while seeking to integrate these various perspectives.

Education

3. Within its broad and varied educational structure, Kyoto University will transmit high-quality knowledge and promote independent and interactive learning.
4. Kyoto University will educate outstanding and humane researchers and specialists, who will contribute responsibly to the world's human and ecological community.

Relationship with society

5. As a university committed to a broad social engagement, Kyoto University will encourage cooperation with local and national society, and will disseminate knowledge informed by the ideals of freedom and peaceful coexistence.
6. As an international institution, Kyoto University will promote foreign academic exchange and thereby strive to contribute to the well-being of the world.

Administration

7. In order to enhance the free development of learning, Kyoto University will pay due respect to the administrative independence of each of its component institutions, while promoting cooperation among them.
8. Kyoto University will conduct its administration with regard for the environment and respect for human rights and will be accountable to society at large.

The 11th Kyoto University International Symposium 2008 (KUIS-11)

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Preface

A fundamental understanding of biological phenomena is a major driving force behind the advancement of medicine. Recent advances in bioscience and biotechnologies are having an unprecedented impact on modern medicine. Parallel to these advances, the integration of such fields as molecular biology, genetic engineering, biological informatics and nanotechnologies is expected to bring about increasingly efficient strategies for controlling diseases and promoting human health and welfare.

For over a century, Kyoto University has made significant contributions to the advancement of modern medicine, and it continues to do so through its Graduate School of Medicine, Institute for Frontier Medical Science, Institute for Virus Research and newly established Institute for Integrated Cell-Material Sciences (iCeMS) and its Center for Induced Pluripotent Stem (iPS) Cell Research and Application. Recent research achievements include the establishment of a number of valuable genetically-engineered animal models for various human diseases; regeneration technology including embryonic stem (ES) and iPS cells; research into the molecular biology of viruses and other infectious diseases; integrated brain research including the bioimaging of brain function; genetic epidemiology for human diseases and new methods of translational research.

Through this symposium, we intended to introduce an outstanding selection of Kyoto University's current medical research activities to students and researchers in China, a country which is emerging as a global leader in advanced medicine. Close international cooperation is increasingly important to the field of medical sciences and medicine. In this aspect, we believe that the 11th Kyoto University International Symposium (KUIS-11) successfully held in cooperation with our long-term partner Fudan University at its Shanghai Medical College, including the participation of several of China's leading experts in the biomedical field has provided a significant contribution to the opening of new avenues of cooperation between China and Japan.

KUIS-11 was sponsored by the Kyoto University Foundation and also by the Global COE Program at the Graduate School of Medicine. Finally, Kyoto University highly appreciates the enormous efforts made by Fudan University to make this Symposium a success.

Toshio YOKOYAMA
Vice-President for International Relations
Kyoto University

Nagahiro MINATO
Chair, Symposium Organizing Committee
Vice Dean, Graduate School of Medicine
Kyoto University

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Welcome

Since its foundation at the turn of the 19th century, Kyoto University has continually endeavored to contribute to the well-being of the world. In its Mission Statement of 2001, the university put forth its intention to pursue harmonious coexistence within the human and ecological community on this planet. This lofty idea of doing something good for such an expansive community – including non-humans – has been a source of inspiration throughout the university's campuses. As President of Kyoto University, I am eager to promote our international academic exchange efforts, as they are vital to our success in such a mission of global significance.

In the field of medicine, Kyoto University has made historical contributions to the advancement of modern medical sciences and human welfare, and it continues to do so through its Graduate School of Medicine, Institute for Frontier Medical Science, Institute for Virus Research and the newly launched Institute for Integrated Cell-Material Sciences (iCeMS) and the Center for Induced Pluripotent Stem Cells (iPS) Research and Application. Medical science is entering a new stage of development, in which recent achievements in biosciences, genetic engineering, nanotechnology and public health studies will be closely integrated. It is to be hoped that this situation will bring forth new strategies for enriching the lives of the people of the world.

During these ever-changing times of great innovation, close international co-operation is becoming more important than ever. In this context it is significant that Kyoto University has maintained long-standing and fruitful interactions with the academia of China, and this is particularly notable in the field of medicine. I believe that China is emerging as one of the most reputed countries for advanced bioscience and biotechnologies. I am happy, therefore, that the 11th Kyoto University International Symposium is to be held on the campus of Fudan University, an institution with which we have an enduring friendship, with the special understanding and support of President Wang Shenghong and his colleagues. I believe that this symposium will open a new page in the history of academic co-operation between China and Japan, and further promote creative joint endeavors among students and researchers across the ever-narrowing sea between our two countries.

Dr. Hiroshi MATSUMOTO
President
Kyoto University

Program

October 9 (Thursday)

18:00 – Registration

18:30 – 20:30 Reception at Hilton Shanghai (Top Floor)

October 10 (Friday)

8:00 – 9:00 Registration

9:00 – 9:10 Opening Remarks
Hiroshi MATSUMOTO, President of Kyoto University
Weiping WANG, Executive Vice-President of Fudan University

9:10 – 18:00 Symposium Sessions

Session I Chair : Nagahiro MINATO / Shu NARUMIYA

9:10 – 9:40 **Shuh NARUMIYA**
Physiology and Clinical Application of the Prostanoid Receptors

9:40 – 10:10 **Hitoshi NAGAOKA**
Molecular Mechanism for Generation of Antibody Memory

10:10 – 10:40 **Zhi-Li HUANG**
Genetic Dissection of Histaminergic Roles in Sleep-Wake Regulation

10:40 – 11:10 Coffee Break

11:10 – 11:40 **Yo-ichi NABESHIMA**
The Discovery of α-klotho and FGF23 Unveiled New Insight into Calcium and Phosphate Homeostasis

11:40 – 12:10 **Ping ZHENG**
Neuroactive Steroid Dehydroepiandrosterone Sulphate Inhibits 5-HT-evoked Glutamate Release via Activation of Sigma-1 Receptors and Inhibition of 5-HT_3 Receptors in Rat Prelimbic Cortex

12:10 – 12:40 **Hidenao FUKUYAMA**
Frontiers in Neuroimaging

12:40 – 14:00 Lunch Break

Session II Chair : Takashi SHINOHARA / Fumihiko MATSUDA

14:00 – 14:30 **Shimon SAKAGUCHI**
Regulatory T Cells for Immune Tolerance and Homeostasis

14:30 – 15:00 **Takashi NAGASAWA**
The Chemokine CXCL12 and Bone Marrow Niches for Hematopoietic Stem Cells and B Lymphocytes

15:00 – 15:30 **Takashi SHINOHARA**
Culture and Genetic Modification of Spermatogonial Stem Cells

15:30 – 16:00 Coffee Break

16:00 – 16:30 **Fumihiko MATSUDA**
Genomic Study of Human Multigenetic Disorders

16:30 – 17:00 **Qi-Qun TANG**
Understanding the Mechanism of Adipogenesis

17:00 – 17:30 **Yunzeng ZOU replaced by Yuhong NIU**
Heat Shock Transcription Factor 1 Prevents Cardiac Dysfunctions Induced by Pressure Overload in Mice

17:30 – 18:00 **Masanori FUKUSHIMA**
The Newer Clinical Trial Infrastructure and Paradigm in Japan — the Role of the Translational Research Informatics Center (TRI)

18:00 – 19:00 Refreshments at Mingdao Building

October 11 (Saturday)

8:00 – 9:00 Registration

9:00 – 15:00 Symposium Sessions

SessionIII Chair : Makoto Mark TAKETO

9:00 – 9:30 **Shigekazu NAGATA**
Engulfment of Apoptotic Cells

9:30 – 10:00 **Makoto Mark TAKETO**
A Novel Mechanism of Colon Cancer Invasion: Role of Bone Marrow-Derived Cells

10:00 – 10:30 **Nagahiro MINATO**
Rap Signaling in Lymphohematopoietic Cell Development and Leukemia

10:30 – 11:00 Coffee Break

11:00 – 11:30 **Ryoichiro KAGEYAMA**
Oscillations in Notch Signaling Regulate Proliferation and Differentiation of Neural Progenitor Cells

11:30 – 12:00 **Masato NAKAGAWA**
Generation of Induced Pluripotent Stem (iPS) Cells by Sox2, Oct4, Klf4, and c-Myc Transcription Factors and their Family Genes

12:00 – 13:30 **Lunch Break**

SessionIV Chair : Yoshio KOYANAGI

13:30 – 14:00 **Masao MITSUYAMA**
Mycobacterium Tuberculosis, Listeria Monocytogenes and the Host Cytokine Response

14:00 – 14:30 **Takashi FUJITA**
Mechanism of Foreign RNA Recognition in Cytoplasm

14:30 – 15:00 **Yoshio KOYANAGI**
HIV-1 Pathogenesis: Productive Infection in CD4⁺ Effecter Memory T Lymphocytes and CD4⁺ Depletion in Humanized Mice

15:00 – 15:10 **Closing Remarks**
Xiaoyuan FENG, Dean of Shanghai Medical College
Toshio YOKOYAMA, Vice-President of Kyoto University

Overview

Prof. Nagahiro MINATO
Chair, Symposium Organizing Committee
Vice Dean, Graduate School of Medicine
Kyoto University

The 11th Kyoto University International Symposium (KUIS-11) entitled "Frontier Bioscience in Modern Medicine" was held with great success at the Mingdao Reporting Hall on the campus of Shanghai Medical College, Fudan University, Shanghai on Oct 10th to 11th, 2008. In the autumn of 2007, an agreement of student exchange was signed between Kyoto University Graduate School of Medicine and Fudan University. It was during that signing ceremony that it occurred to us that it would be a good idea to have an academic symposium to introduce our activities in the field of bioscience to young researchers and students in China. In order to substantially promote academic exchange between Kyoto University and Fudan University, we thought it essential that each side be aware of the activities of the partner institution. Professor Xiaoyuan Feng, Dean of Shanghai Medical College, instantly accepted the idea and promised us all the cooperation necessary.

We planned the symposium program so that we could present the most representative current activities in the fields of basic bioscience and medicine at Kyoto University, including the Graduate School of Medicine, Institute of Virus Research and Institute for Frontier Medical Sciences. I believe that this is the first time an event of this scale has been attempted in the history of biomedical research at Kyoto University. The scientific program eventually involved the participation of 21 leading scientists – 17 from Kyoto University and 4 from Fudan University.

A welcome reception, hosted by the President of Kyoto University, was held on the evening of Oct 9th, prior to the scientific sessions. More than 50 guests attended the reception, including the President of Fudan University, major figures from as many as seven other universities and medical schools around the Shanghai area, and most of the symposium speakers. This was actually more than we initially expected, and it was a welcome surprise to have guest delegates from so many universities in China. The reception had a very relaxed and friendly atmosphere which allowed the participants to engage in substantial and frank discussions on science, culture and many other issues. We were eagerly invited by several other universities to hold similar symposia in coming years at different locations in China.

The next two days of the symposium were also very successful. The proceedings were held in the Mingdao Reporting Hall, a beautiful hall on the campus of Shanghai Medical College. We were happy to see that the hall's 300 seats were filled with young researchers and students from many universities and institutions in Shanghai, Nanjing, Wuhan, Shaanxi and many other parts of China. There were enthusiastic questions and discussion among the audience after each presentation, and during the coffee breaks the speakers were often encircled by inquisitive audience members. We were told that the total audience for the scientific sessions exceeded 700 people over the two days.

Overall, the symposium was an even greater success than we had initially expected. I believe that the original intention of this symposium – to introduce the current activities of Kyoto University in the field of biomedicine to China – has been achieved. And perhaps more importantly, I believe that we contributed to the opening of a new arena for real friendship and future cooperation with China in the academic fields of bioscience and medicine. Through this symposium, we also learned about the scientific advances made in the bioscience and medicine fields in China, and are convinced that substantial interaction and collaboration with China will become increasingly important. Regular symposia on this scale involving leading academics of both sides will make an important contribution to the establishment of sustainable scientific interaction between China and Japan.

Finally, I would like to stress that the symposium would not have been so successful without the strong support and collaboration of the Foreign Affairs Office at Shanghai Medical College, particularly Dr. Chouwen Zhu. I visited Shanghai several times during the preparation of this symposium, and during those visits Dr. Zhu always kindly responded to any requests promptly and efficiently. I would also like to express my sincere appreciation for the efficient cooperation and friendship of the staff of the Foreign Affairs Office at Fudan University.

Opening Remarks

Dr. Hiroshi MATSUMOTO
President
Kyoto University

It is my great pleasure and honor to be able to hold the 11th Kyoto University International Symposium here in Shanghai with the strong support of Fudan University. Since its foundation at the turn of the 19th century, Kyoto University has continually endeavored to contribute to the well-being of the world.

We believe that promoting international academic exchange is vital to that globally significant mission. For that reason, we have been holding Kyoto University International Symposia on various emergent topics every year in different cities around the world, including cities in West Europe, North America and Asia. This, the 11th Symposium, is one of the most ambitious meetings to comprehensively cover the frontiers of medical science on Kyoto University campuses.

Medical science is entering a new stage of development, in which recent achievements in biosciences, genetic engineering, nanotechnology and public health studies are to be closely integrated. These developments are expected to produce new strategies for enriching the lives of the people of the world. For over a century Kyoto University has made historical contributions to the advancement of modern medical sciences and human welfare, and it continues to do so. This is exemplified by our recent breakthroughs in the study of iPS cells, which are anticipated to have a clinical application in the near future.

I believe that China is emerging as one of the most reputed countries for advanced bioscience and biotechnologies. Kyoto University has maintained a long-standing and fruitful relationship with the academia of China, particularly in the field of medicine. It is significant and timely, therefore, that we are holding this symposium here in China. I believe that this symposium represents the beginning of a new chapter in the history of academic cooperation between China and Japan.

Lastly, I would like to express my sincere thanks to Fudan University and the Shanghai Medical College for their enormous support in making this symposium possible, and also my heart-felt welcome to the distinguished guests and promising young scholars from eminent medical schools in China.

Opening Remarks

Prof. Weiping WANG
Vice-President
Fudan University

Dear President Matsumoto; Dear guests, ladies and gentlemen, it is a great honor and pleasure for me to welcome you, on behalf of Fudan University, to the 11th Kyoto University International Symposium.

As the proud host location of this year's Kyoto University International Symposium, we appreciate the vision and wisdom of Kyoto University, which has successfully staged its International Symposiums in cities outside of Japan and thereby expanded the scope of academic exchange to a more global level. Thanks to this international strategy, we can also have the honor of welcoming fellow researchers from Chinese universities including Huazhong University of Science and Technology, Zhejiang University and Nanjing University to the Medical Center of Fudan University.

Kyoto University is one of our most valuable friends in Asia. Last year, Kyoto University was one of our distinguished guests at the 80th anniversary of the establishment of Shanghai Medical University. It was on that occasion that a comprehensive cooperative agreement between the medical colleges of Kyoto University and Fudan University was signed. We are convinced that co-hosting the 11th Kyoto University International Symposium is a fine way for us to initiate further and more fruitful collaboration in the future.

Shanghai Medical College of Fudan University is happy both to facilitate the conference and to share our knowledge and visions in the field of Frontier Bioscience in modern medicine with renowned researchers from Japan and China. I notice with happiness that in the forthcoming sessions, four presentations will be delivered by Fudan University professors. It's my sincere hope that the students and faculties of Fudan University will take full advantage of this opportunity to learn about and discover the recent advances in bioscience and biotechnologies and their unprecedented impact on modern medicine. I also hope all the researchers here find this conference interesting and inspiring for their future careers.

I wish the 11th Kyoto University International Symposium great success, and all our guests an enjoyable stay in Shanghai.
Thank you !

Abstracts

Physiology and Clinical Application of the Prostanoid Receptors

Shuh NARUMIYA

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Graduate School of Medicine
Kyoto University

Prostanoids including prostaglandin (PG) D_2, PGE_2, $PGF_2\alpha$, PFI_2 and thromboxane (TX) A_2 are a group of lipid mediators formed and released in response to various, often noxious, stimuli. They exert their actions by acting on a family of G-protein-coupled receptors, which include PGD receptor (DP), EP1, EP2, EP3 and EP4 subtypes of PGE receptor, PGF receptor (FP), PGI receptor (IP) and TX receptor (TP). We have generated mice deficient in each of these prostanoid receptors individually, and examined the roles each receptor plays in the body under various physiological and pathophysiological conditions. Since non-steroidal anti-inflammatory drugs (NSAIDs) exert their actions by inhibiting COX, prostanoids have generally been believed to be pro-inflammatory mediators. However, our results have disclosed that these receptors play both positive and negative roles in disease initiation and development. For example, the PGE_2-EP2/EP4 pathway and the PGI_2-IP pathway together facilitate elicitation of arthritic response in collagen-induced arthritis, while the PGE_2-EP4 pathway exerts anti-inflammatory action in dextran sodium sulfate-induced colitis. In ovalbumin-induced allergic asthma, the PGD_2-DP signaling mediates and the PGE2-EP3 signaling suppresses allergic reactions. Interestingly, micro-array analysis for gene expression in these models has revealed that the prostanoid signaling often regulates disease development by modulating expression of disease-associated genes such as chemokines, cytokines, and tissue remodeling factors. Our KO mouse studies have also revealed functions of prostanoids that had not been anticipated by the effects of NSAIDs. One of the unexpected findings is a variety of actions prostanoids exert in the immune response. Here, in contrary to what was previous believed, we have recently found that the PGE_2-EP2/EP4 signaling facilitates Th1 differentiation and Th17 expansion. In addition, in hapten-induced contact hypersensitivity, the PGD_2-DP signaling inhibits and the PGE_2-EP4 signaling facilitates mobilization and activation of Langerhans cells (LCs) in the skin, the TXA_2-TP signaling negatively modulates activation of naive T cells by LCs, and the PGE_2-EP1 signaling facilitates Th1 differentiation. Furthermore, in the brain, inhibition of the PGE_2-EP1 signaling blunts stress-induced ACTH release, while enhancing behavioral stress responses, and the PGE_2-EP3 signaling mediates febrile response. These results demonstrate that prostanoids act on the respective receptors and critically regulate many steps of disease initiation and progression in both positive and negative ways. This knowledge can be exploited to develop clinically useful drugs that provide context-dependent therapeutic intervention in a variety of diseases.

Supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan, and the National Institute of Biomedical Innovation of Japan.

Molecular Mechanism for Generation of Antibody Memory

Hitoshi NAGAOKA

Hitoshi NAGAOKA and Tasuku HONJO

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Boehring and Kitasato discovered that vaccination depends on memory in neutralizing substances in sera, which turn out to be antibodies. Extensive studies in the past century elucidated not only antibody structure but also the molecular nature of antibody memory, which consists of somatic hypermutation (SHM) and class switch recombination (CSR). At the very end of the 20th century, a molecule that regulates SHM and CSR was identified. The 198-residue protein called activation-induced cytidine deaminase (AID) is specifically expressed in activated B cells and responsible for DNA cleavage in SHM and CSR. Mutations in the AID gene cause hyper IgM syndrome type II with severe immune deficiency due to the absence of all the isotypes except for elevated IgM without SHM. The critical questions about the function of AID are: a) how AID cleaves DNA to trigger recombination and mutation; and b) how it can distinguish the V region for SHM and the switch region for CSR. There are two contrasting hypotheses to explain DNA cleavage by AID. One, originally proposed by our group, is the RNA editing hypothesis. In this model, AID edits unknown target mRNA, and edited mRNA encodes a putative endonuclease. The other hypothesis, namely the DNA editing model, claims that AID directly attacks cytidine in DNA and generates GU mismatches on DNA. The resultant mismatch pairs are recognized by the base excision repair pathway that can introduce DNA cleavage. A major finding to support the DNA editing hypothesis is the *in vitro* DNA deamination activity of AID. We provide the evidence that the DNA deamination activity is not required for CSR *in vivo* by an extensive study with AID mutants. Our studies strongly indicate that AID cleaves target DNA not through DNA deamination but probably through RNA editing.

Genetic Dissection of Histaminergic Roles in Sleep-Wake Regulation

Zhi-Li HUANG

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Shanghai Medical College of Fudan University

The histaminergic neurons are confined to the tuberomammillary nucleus (TMN) of the posterior hypothalamus, and send their fibers to almost all regions of the brain. A growing body of evidence has implicated histamine as a crucial player in mediating wakefulness in mammals. Presumed histaminergic neurons discharge tonically and specifically during wakefulness, and the central release of histamine exhibits circadian variation associated with wakefulness. Based on the findings from gene-manipulated mice, we provide several lines of evidence showing the roles of the histaminergic system in the somnogenic effects of prostaglandin (PG) D_2 and adenosine, and in the arousal effects of PGE_2 and orexin.

PGD_2 and adenosine are potent endogenous somnogenic substances. PGD_2 is produced by the action of PGD synthase dominantly localized in the leptomeninges and choroid plexus, and circulates in the CSF. It activates DP_1 receptors (R) to promote sleep by stimulating them to release adenosine. The released adenosine activates adenosine $A_{2A}R$ and subsequently excites the ventrolateral preoptic area (VLPO), one of the sleep centers in the anterior hypothalamus. VLPO neurons then send inhibitory signals to downregulate the histaminergic TMN, which contributes to arousal. Conversely, both endogenous PGE_2 and orexin activate the histamiergic system through EP_4R and OX-2R, respectively, to promote the wakefulness via histamine H_1R. Furthermore, the arousal effect of the ciproxifan, H_3R antagonist, depends on the activation of histaminergic systems, which may provide a potential approach for the treatment of narcolepsy.

These findings indicate that VLPO and TMN regulate sleep and wakefulness, by means of a ‘ flip-flop ’ mechanism, operating in an anti-coincident manner during sleep-wake state transitions.

The Discovery of α-Klotho and FGF23 Unveiled New Insight into Calcium and Phosphate Homeostasis

Yo-ichi NABESHIMA

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Graduate School of Medicine
Kyoto University

α-Klotho was first identified as the gene responsible for premature ageing-like phenotypes, particularly those features involving abnormalities and characteristic symptoms of calcium metabolism. Recent advances indicate that α-Klotho (α-Kl) and FGF23 are key players that integrate the multi-step regulatory system of calcium homeostasis that rapidly adjusts the extracellular calcium concentration and continuously maintains its concentration within a narrow physiological range. α-Kl and FGF23 have also been identified as major players in the regulatory system of phosphate homeostasis.

The clarified molecular functions of α-Kl and FGF23 can be summarized as follows; (i) α-Kl binds to Na^+,K^+-ATPase, and Na^+,K^+-ATPase is recruited to the plasma membrane by a novel α-Kl dependent pathway correlated with cleavage and secretion of α-Kl in response to extracellular Ca^{2+} fluctuation. (ii) The increased Na^+ gradient created by Na^+,K^+-ATPase activity drives the transepithelial transport of Ca^{2+} in the choroid plexus and the kidney, this is defective in α-$kl^{-/-}$ mice. (iii) The regulated PTH secretion in the parathyroid glands is triggered via recruitment of Na^+,K^+-ATPase to the cell surface in response to extracellular Ca^{2+} concentrations. (iv) α-Kl, in combination with FGF23, regulates the production of $1,25(OH)_2D$ in the kidney. In this pathway, α-Kl binds to FGF23, and α-Kl converts the canonical FGF receptor 1c to a specific receptor for FGF23, enabling the high affinity binding of FGF23 to the cell surface of the distal convoluted tubule where α-Kl is expressed. (v) The FGF23 signal down-regulates serum phosphate levels, due to decreased NaPi-IIa abundance in the apical membrane of the kidney proximal tubule cells. (vi) α-Kl in urine increases TRPV5 channel abundance at the luminal cell surface by hydrolyzing the N-linked extracellular sugar residues of TRPV5, resulting in increased Ca^{2+} influx from the lumen. (vii) Human α-kl mutations cause tumoral calcinosis. (viii) The symptoms of a gain of function mutation in humans is the opposite to that found in a loss of function mutation in human and mice. (ix) Discoveries of human α-kl mutations provide a compelling evidence that α-Kl is a pivotal regulator of calcium and phosphate homeostasis not only in mice but also in humans.

The unveiling of the molecular functions of α-Klotho and FGF23 has recently given new insight into the field of calcium and phosphate homeostasis.

Neuroactive Steroid Dehydroepiandrosterone Sulphate Inhibits 5-HT-evoked Glutamate Release via Activation of Sigma-1 Receptors and Inhibition of 5-HT_3 Receptors in Rat Prelimbic Cortex

Ping ZHENG

State Key Laboratory of Medical Neurobiology
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Dehydroepiandrosterone sulphate (DHEAS) is one of the most important neuroactive steroids. We studied the effect of DHEAS on spontaneous and evoked glutamate release in the pyramidal cells of the layers V-VI of rat prelimbic cortex using whole-cell patch-clamp in slices and further studied its mechanism. The results showed that DHEAS at 1 μM had no effect on spontaneous glutamate release, but inhibited 5-HT-evoked presynaptic glutamate release. The concentration-response relationship of this effect of DHEAS was bell-shaped with the maximum at 1 μM and this inhibition appeared to have some degree of selectivity because it had no effect on high K^+, electrical stimulus or dopamine-evoked stimuli. Further mechanism study showed that the effect of DHEAS on 5-HT-evoked glutamate release was canceled by the sigma-1 receptor blocker; DHEAS had no effect on 5-$HT_{2A/2C}$ receptor agonist-evoked glutamate release, but inhibited 5-HT_3 receptor agonist-evoked glutamate release, and 5-HT_3 receptor antagonist blocked the effect of DHEAS on 5-HT-evoked glutamate release; sigma-1 receptor agonist inhibited 5-HT_3 receptor agonist-evoked presynaptic glutamate release and intrasynaptosomal Ca^{2+} concentration increase. These results suggest that DHEAS inhibits 5-HT-evoked presynaptic glutamate release via activation of sigma-1 receptors and then inhibits of 5-HT3 receptors in the pyramidal cells of rat prelimbic cortex.

Frontiers in Neuroimaging

Hidenao FUKUYAMA

Human Brain Research Center
Graduate School of Medicine
Kyoto University

Functional MRI (fMRI) has been utilized to investigate the functional localization of the brain. The basic concept was derived from a paper by Roy and Sherrington in 1890 [1]. Brain activities were reflected in the increase of cerebral blood flow (CBF). MRI and positron emission CT (PET) detect such areas as neurons are activated. We are looking for a new technology to detect areas in which neuronal activities are truly elevated. Activated neural systems show an increase in water content and this phenomenon enables the acquisition of diffusion weighted images with a fast acquisition sequence.

Neurochemical and neuropharmacological researchers have been developing drugs that decrease beta-amyloid in the brain. To evaluate the drugs' efficacy, it is important to visualize beta-amyloid in the brain of Alzheimer's disease patients in vivo. Pittsburg compound B is one of the standard imaging tracers used to detect beta-amyloid by PET. According to neuropathological research, beta-amyloid accumulated in the early stage of the disease compared to the development of dementia. In order to treat or protect dementia, early detection by scientific tools is essential. Amyloid imaging is currently considered to be an effective tool for the early diagnosis of Alzheimer's disease.

[1] Roy CS, Sherrington CS.On the Regulation of the Blood-supply of the Brain. J Physiol. 1890 Jan;11(1-2):85-158.

Regulatory T Cells for Immune Tolerance and Homeostasis

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Naturally arising $CD25^+CD4^+$ regulatory T cells (Tregs) are engaged in the maintenance of immunological self-tolerance and immune homeostasis by suppressing aberrant or excessive immune responses, such as autoimmune disease and allergy. Tregs specifically express the transcription factor Foxp3, a key regulator of Treg development and function. Ectopic expression of Foxp3 in conventional T cells is sufficient to confer suppressive activity on naive T cells, repress production of cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-γ), and up-regulate Treg-associated molecules such as CD25, and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4). How Foxp3 controls these molecular events has, however, yet to be elucidated. We have shown that the transcription factor AML1/Runx1, which is crucially required for normal hematopoiesis including thymic T cell development, activates IL-2 and IFN-γ gene expression in conventional $CD4^+$ T cells through binding to their respective promoters. In natural Tregs, Foxp3 physically interacts with AML1/Runx1, thereby conferring suppressive activity on them. Further, Treg-specific conditional knockout of AML1/Runx1, and also CTLA-4, which natural Tregs constitutively express at a high level, impairs Treg function and results in the development of autoimmune disease. Based on these and other findings on the molecular basis of Treg development and function, it will be discussed how Tregs contribute to the maintenance of immunological self-tolerance and immune homeostasis, and how they can be exploited to control physiological and pathological immune responses.

The Chemokine CXCL12 and Bone Marrow Niches for Hematopoietic Stem Cells and B Lymphocytes

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All types of blood cells including lymphocytes arise from hematopoietic stem cells (HSCs) and develop within a microenvironment in bone marrow. It has been assumed that the special microenvironments known as niches, where HSCs, hematopoietic cells and leukemia stem cells reside, supply the requisite factors and play an essential role in their maintenance and regulation. It has been reported previously that HSCs reside near bone surfaces and/or near the vasculature and that a population of osteoblasts and/or endothelial cells might function as niches for HSCs. However, the nature and molecular regulatory mechanism of the niches have been a long-standing unresolved issue. Chemokines are a family of small structurally related chemoattractive cytokines and CXCL12-abundant reticular (CAR) cells are a small population of bone marrow stromal cells expressing high amounts of a chemokine CXCL12 (also known as SDF-1 and PBSF), which is essential for the colonization of bone marrow by HSCs during ontogeny and the development of B lymphocytes. Our recent studies have shown that the induced deletion of CXCR4, a receptor for CXCL12 in adult mice results in severe reduction of HSC numbers and that most cells in HSC fractions are found in contact with the processes of CAR cells, some of which surround sinusoidal endothelial cells or are located near the endosteum in bone marrow. These findings indicate that CXCL12-CXCR4 signaling plays an essential role in maintaining the HSC pool, and suggest that CAR cells are a key component of niches for HSCs and B lymphocytes. We expect these studies to provide a novel basis for understanding the spatiotemporal regulation of lymphohematopoiesis by environmental niches within bone marrow.

Culture and Genetic Modification of Spermatogonial Stem Cells

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Spermatogenesis depends on a population of cells called spermatogonial stem cells. These cells can undergo self-renewing division and support male reproduction throughout life. In 2003, we succeeded in the long-term culture of the spermatogonial stem cells of mice. In the presence of a glial cell line-derived neurotrophic factor, germline stem (GS) cells were established from postnatal mouse testis. These cells can restore fertility to congenitally infertile recipient mice following transplantation into the seminiferous tubules. Unlike other germline cells that often acquire genetic and epigenetic changes in vitro, GS cells retained the euploid karyotype and androgenetic imprint during the 2-year experimental period. In this culture condition, we also succeeded in the establishment of ES-like cells (multipotent germline stem cells, mGS cells) from postnatal mouse testis. These mGS cells were phenotypically similar to ES/EG cells except in their genomic imprinting pattern. They differentiated into various types of somatic cells in vitro under conditions used to induce the differentiation of ES cells. Both GS and mGS cells can be used to produce knockout animals, which opens up a new possibility of genetic manipulation of male germline lineage. These cells will be useful for understanding the spermatogenesis mechanism, and have important implications for developing new technology in transgenesis or medicine.

Genomic Study of Human Multigenetic Disorders

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Advances in the characterization of DNA variation have led to increasingly effective approaches to identifying the genetic determinants of many multifactorial diseases, providing a new understanding of the pathogenesis of these conditions, diagnostics and potentially individual-based therapy (personalized medicine). Although a number of publications have reported the genes or polymorphisms responsible for various human multigenetic diseases, the area is still controversial; only a small number of genes were confirmed as significant by independent reproduction studies or in other ethnicities. One of the important tools in this regard is the study of multi-ethnic populations (trans-ethnic disease mapping) as a means to validate a gene-disease relationship, and as a powerful method of identifying functionally relevant genetic variants through comparative analysis of linkage disequilibrium (LD) and disease-association patterns.

In light of this, Kyoto University Graduate School of Medicine has established a number of significant collaborations with European and Asian scientists on human multigenetic diseases. The collaborations include extensive genomics programs in trans-ethnic genetic analyses of inflammatory disorders, infectious diseases, cancers and cardiovascular diseases. Comparison of genotypes between cases and controls in different ethnic groups leads to fine-mapping of disease-related genetic variants, restricting the number of candidate polymorphisms that require functional investigation to establish their roles in disease. To explore the genetics of the target diseases, we perform systematic genome-wide association studies (GWAS) using SNP arrays containing several hundred thousand SNP markers along the human genome. As an example of such studies, a trans-ethnic GWAS analysis of Japanese and European populations with rheumatoid arthritis was presented.

Understanding the Mechanism of Adipogenesis


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Obesity results from the increase of both adipocyte number and size. This increase in the number of adipocytes is due to the recruitment of pluripotent stem cells that reside in the vascular stroma of adipose tissue. These stem cells have the potential to commit and then differentiate into adipocyte, as well as myocyte, osteocyte and chondrocyte. The adipocyte developmental pathway can be classified into three stages: 1) stem cell; 2) preadipocyte; 3) adipocyte and can be studied in two distinct steps: 1) adipocyte lineage commitment; and 2) terminal differentiation into adipocytes.

By using the established 3T3-L1 preadipocyte cell lines the mechanism of terminal adipocyte differentiation has been well characterized: CCAAT enhancer-binding protein (C/EBP) family members and peroxisome proliferator activated receptor (PPAR)γ act sequentially during adipogenesis, while C/EBPβ is an activator for C/EBPα and PPARγ, the pleiotropic activators of genes that produce the adipocyte phenotype. Recently we found that when growth-arrested 3T3-L1 preadipocytes are induced to differentiate, C/EBPβ is rapidly expressed but still lacks DNA-binding activity. After a long (14-hour) lag, glycogen synthase kinase (GSK) 3β enters the nucleus, which correlates with the hyperphosphorylation of C/EBPβ and acquisition of DNA-binding activity. Concurrently, 3T3-L1 preadipocytes synchronously enter the S phase and undergo mitotic clonal expansion, a prerequisite for terminal differentiation. Ex vivo and in vitro experiments with C/EBPβ show that C/EBPβ is phosphorylated on Thr-188 by mitogen activating protein kinase (MAPK), and on Ser-184 /Thr-179 by GSK 3β during 3T3-L1 adipocyte differentiation, phosphorylation of Thr-188 by MAPK "primes" C/EBPβ for subsequent phosphorylation on Ser-184 and Thr-179 by GSK3β.

While MAPK activity is down-regulated before the S phase is completed, it is necessary to identify the kinase that maintains C/EBPβ in the primed phosphorylated state throughout the S phase and MCE. Our further investigation indicates that cdk2/cyclinA, whose expression is activated at the onset of the S phase, functions in this capacity. Ex vivo and in vitro experiments show that cdk2/cyclinA catalyzes this delayed priming phosphorylation. Mass spectrometric analysis revealed that cdk2/cyclinA phosphorylates C/EBPβ on Thr-188 and is required for phosphorylation (on Ser-184 or Thr-179) of C/EBPβ by GSK3β and maintenance of DNA binding activity. Suppression of cdk2 activity by RNA interference or pharmacologic inhibitor disrupts subsequent events in the differentiation program. Thus, MAPK and cdk2/cyclinA act sequentially to maintain Thr-188 of C/EBPβ in the primed phosphorylated state during MCE and thereby progression of terminal differentiation. C/EBPβ gains its DNA-binding activity and transactivates of the C/EBPα and PPARγ genes after it is fully phosphorylated on Thr-188, Ser-184 and Thr-179. The delayed transactivation of the C/EBPα and PPARγ genes in the adipocyte differentiation program by C/EBPβ appears necessary to allow mitotic clonal expansion, which would otherwise be prevented, because C/EBPα and PPARγ are antimitotic.

We recently identified a factor and developed conditions that cause 10T1/2 stem cells to commit to the adipocyte lineage in cell culture. Moreover, this process can be recapitulated in vivo. Treatment of 10T1/2 stem cells with our usual adipocyte differentiation protocol does not provoke commitment or differentiation, as indicated by failure to express cytoplasmic triglyceride or adipocyte markers. Only after initial exposure to BMP4, followed by treatment with differentiation inducers, do C3H10T1/2 stem cells enter the adipose development pathway and give rise to cells that express the adipocyte phenotype. We interpret this dependence on BMP4 as evidence for commitment. We have been able to verify these findings in an in vivo context. Thus, when 10T1/2 stem cells are first treated with BMP4 in cell culture and then implanted subcutaneously (at a site lacking adipose tissue) into athymic mice, the implanted cells develop into tissue indistinguishable from adipose tissue in normal fat depots of the same animal. The goal of this research is to identify the genes and proteins that trigger commitment to the adipocyte lineage.

Heat Shock Transcription Factor 1 Prevents Cardiac Dysfunctions Induced by Pressure Overload in Mice


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Heat shock transcription factor 1 (HSF1) can protect myocardium from ischemic injury, but its role in prevention of heart failure is unknown. In the present study, we examined the effects of HSF1 on heart failure by using a pressure overload model in both HSF1 transgenic (TG) and knockout (KO) mice. Pressure overload was produced by constriction of the transverse aorta (TAC), which caused a similar elevation of the blood pressure (BP) in wild type (WT), TG and KO mice. There were no significant differences in BP, heart rate, heart weight and body weight among the three types of mice at basal condition. After TAC, however, echocardiography demonstrated that cardiac performance was well preserved in HSF1 transgenic mice up to 4 weeks, but it began to decrease after 1 week in HSF1-deficient mice and after 2 weeks in wild-type ones. Constitutive activation of HSF1 in the heart significantly stimulated angiogenesis, and thereby maintained cardiac function and also reduced mortality for 4 weeks after TAC, while TAC failed to induce angiogenesis in HSF1-deficient mice and thus promoted cardiac dysfunction in response to pressure overload and enhanced mortality, suggesting a protective role of HSF1 probably through stimulating angiogenesis. We also injected an angiogenic inhibitor, TNP, into the heart of TG mice which resulted in a significant cardiac dysfunction at 4 weeks after TAC. Moreover, the expression of hypoxia-inducible factor-1 (HIF-1) was more strongly increased in the TG hearts and decreased in the heart of KO mice as compared to WT ones, whereas p53 was suppressed in the TG hearts and enhanced in the KO ones as compared to WT hearts after TAC. These results indicate that HSF1 preserves cardiac function after pressure overload through stimulating angiogenesis, which is mediated, at least in part, by upregulation of HIF-1 and downregulation of p53.

The Newer Clinical Trial Infrastructure and Paradigm in Japan—the Role of the Translational Research Informatics Center (TRI)

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The Translational Research Informatics Center (TRI)

Japan has long lagged behind the West in carrying out high quality clinical trials. The reason for this is that Japanese scientists, physicians, and clinical investigators understood neither the infrastructure prerequisite for clinical trials nor clinical science. It took some time, therefore, for the government to come to understand the importance of clinical trials as a basis of new drug development, and to invest money into clinical trials.

However, in 2001 our government decided to invest some money in the field of translational research, i.e. early phase clinical trials for new drugs, devices and other technologies, and a budget of 2 million dollars per year for 5 years was allocated to the Kyoto University Hospital. The following year, in 2002, 25 million dollars was allocated to build the TRI in Kobe City, as a national data center for supporting academia based clinical trials. The TRI provides full support for investigator sponsored trials, and any doctor can submit an application for support for clinical study through our web site: http://www.tri-kobe.org.

After the establishment of the institute many important clinical trials and research undertakings were launched and are now ongoing. The subject of this research includes cancer, strokes, CVD, neurological disorder, and also diagnostics including PET screening. Several projects have already been completed and have already been published in leading journals such as JCO (the Journal of Clinical Oncology), The Lancet Oncology, Circulation and others.

In 2004 the government began a 5 year project of cancer translational research under TRI supervision with a budget allocation of 10 million dollars per year. And out of 11 projects 1 project was launched as an Investigational New Drug (IND) registered trial and another is now being prepared for registration by the IND. Furthermore in 2007 the government started a 5 year project of TR infrastructure development. Under this project, 14 million dollars per year are allocated to 5 universities and 1 institute (the Biomedical Research Institute in Kobe which is the sister institute of TRI). Again the TRI is supervising the projects and support trials which are carried out by those institutes and related hospitals. This project will dramatically change the Japanese R&D and clinical trial system in the coming decades.

Engulfment of Apoptotic Cells

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Apoptosis is triggered by a variety of stimuli, and dying cells are swiftly phagocytosed by macrophages. Apoptosis is mediated by a cascade of caspases, which eventually activates a specific DNase (CAD: caspase-activated DNase). *CAD*-deficient cells do not undergo apoptotic DNA fragmentation, but the DNA of dead cells is degraded by DNase II in macrophages after they are engulfed. Using this knowledge, we established an assay for the engulfment of apoptotic cells, and identified several hamster monoclonal antibodies that inhibit the engulfment of apoptotic cells. Characterization of the antigens that are recognized by these mAbs indicated that different subsets of macrophages use different molecules (MFG-E8 and Tim-4) to recognize phosphatidylserine on apoptotic cells for engulfment. MFG-E8 is a soluble protein present on a subset of macrophages such as tingible-body macrophages in the spleen, and thioglycollate- elicited peritoneal macrophages. Lack or excess of MFG-E8 blocks the engulfment of apoptotic cells *in vitro* and *in vivo*, and causes SLE-type autoimmune disease. Using ELISA for human MFG-E8, we found that some SLE patients carry a significant level of MFG-E8 in their blood samples, suggesting an involvement of aberrant expression of MFG-E8 in the pathoetiology of human SLE in some cases. With the MFG-E8-mediated engulfment system, we monitored the engulfment of apoptotic cells at the a single cell level, and found that apoptotic cells are engulfed successively at the specific location of the phagocytes, suggesting the presence of portals for apoptotic cells.

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A Novel Mechanism of Colon Cancer Invasion: Role of Bone Marrow-Derived Cells

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Most colorectal adenomas are initiated by the *APC* gene inactivation, and progress to malignant adenocarcinomas through additional mutations in the genes encoding RAS, TGF-β type II receptor, p53, etc.

To investigate the role of impaired TGF-β family signaling in colon cancer progression, we earlier constructed the compound mutant mouse strain "*cis-Apc*$^{+/\Delta 716}$ *Smad4*$^{+/-}$ (*cis-Apc/Smad4*)" that carried a knockout allele of the *Smad4* gene on the same chromatid as that of *Apc* (*Apc*$^{\Delta 716}$) [1]. In the compound mutant, loss of the SMAD4-dependent TGF-β family signaling turns the intestinal adenomas into invasive adenocarcinomas, although SMAD4-independent signaling remains unaffected. Because polyp adenomas are initiated by a loss of heterozygosity (LOH) of *Apc* that is caused by recombination at the centromeric rDNA cluster on chromosome 18, the tumor epithelial cells in the *cis-Apc/Smad4* mice carry homozygous mutations in both *Apc* and *Smad4* genes.

Recently much attention has been paid to the role of the stromal cells such as fibroblasts and inflammatory cells in tumor development. However, the precise roles of the stromal cells in tumor invasion are not fully understood. It also remains unclear how genetic lesions in the tumor epithelial cells, such as inactivation of the TGF-β family signaling, induce stromal cell accumulation and activation.

Focusing on the tumor-stromal interactions, we have investigated here the mechanism of intestinal tumor invasion in the *cis-Apc/Smad4* mice. We demonstrate here that a novel type of immature myeloid cells (iMCs) is recruited from the bone marrow to the tumor invasion front. These CD34^{+} iMCs express MMP9/2 and CC-chemokine receptor 1 (CCR1), and migrate toward its ligand CCL9. In the adenocarcinomas, expression of CCL9 is increased in the tumor epithelium. By knocking out the *Ccr1* gene in the *cis-Apc/Smad4* mutant mice, we further demonstrate that lack of CCR1 prevents the accumulation of CD34^{+} iMCs at the invasion front and suppresses tumor invasion. Analysis of human colon cancer specimens that carried a mutant TGF-β type II receptor showed similar iMCs expressing CCR1 and MMP9/2. These results indicate that loss of the TGF-β family signaling in the tumor epithelium causes an accumulation of iMCs that helps tumor invasion [2], and shows therapeutic implications in treating invasive colon cancer.

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Rap Signaling in Lymphohematopoietic Cell Development and Leukemia

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Human lymphohematopoietic malignancies are caused by diverse genetic alterations including chromosomal translocations; however, molecular mechanisms for them to lead to the eventual leukemia genesis remain unknown in most cases. Rap belongs to the Ras family GTPases and plays crucial roles in regulating homeostatic hematopoiesis as well as normal lymphocyte development (Adv. Immunol, 2007, Blood 2008). With the use of various gene-engineered mice, we have shown that deregulated activation of endogenous Rap signal in the lymphohematopoietic system causes diverse types of leukemia of multiple cell lineages. For instance, constitutive activation of Rap signal in marrow hematopoietic progenitors in mice deficient in Spa-1(Rap GTPase-activating protein) results in a spectrum of myeloproliferative disorders (MPD) including chronic myeloid leukemia (CML) in the chronic phase, its blast crisis and myelodysplastic syndrome (MDS) (Cancer Cell, 2003, Cancer Res., 2006). The MPDs resemble human CML, and indeed human Bcr-Abl oncogene has been shown to potently activate Rap signal (Oncogene 2006). A minor proportion of SPA-1-/- mice also develop B1 cell chronic lymphocytic leukemia (CLL) associated with systemic autoimmunity, highly reminiscent of human B-CLL (Immunity 2006). Rap signal is crucial for B-cell receptor editing of autoreactive marrow B cells, and constitutive Rap signaling results in aberrant editing leading to the expansion of autoreactive B1 cells. Deregulated Rap activation in T-lineage cells results in the Notch-dependent T cell acute lymphoblastic leukemia (T-ALL) with characteristic Notch gene mutation similar to human T-ALL (Blood 2008). Preleukemic Spa-1-/- mice are hypersensitive to X-ray irradiation, implying that genetic instability may underlie the eventual leukemia genesis. Altogether, it is suggested that Rap signal may play crucial roles not only in normal hematopoiesis but also in leukemia genesis of multiple cell lineages in manners highly dependent on the specific contexts of lymphohematopoietic cell lineages. Rap signaling pathway may provide a common target for controlling various leukemia types in humans (Trend Mol Med 2004).

Oscillations in Notch Signaling Regulate Proliferation and Differentiation of Neural Progenitor Cells

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Expression of the Notch effector gene Hes1 is required for maintenance of neural progenitor cells in the embryonic brain, but persistent and high levels of Hes1 expression inhibit the proliferation and differentiation of these cells. By using a real-time imaging method, we found that Hes1 expression dynamically oscillates in neural progenitors. Furthermore, sustained overexpression of Hes1 down-regulates the expression of proneural genes, Notch ligands and cell cycle regulators, suggesting that their proper expression depends on Hes1 oscillation. Surprisingly, the proneural gene Neurogenin2 (Ngn2) and the Notch ligand Delta-like1 (Dll1) are also expressed in an oscillatory manner by neural progenitors, and inhibition of Notch signaling, a condition known to induce neuronal differentiation, leads to down-regulation of Hes1 and sustained up-regulation of Ngn2 and Dll1. These results suggest that Hes1 oscillation regulates Ngn2 and Dll1 oscillations, which in turn leads to the maintenance of neural progenitors by mutual activation of Notch signaling. Our data also suggests that oscillatory expression of Ngn2 is not sufficient but sustained up-regulation is required for neuronal differentiation and that Ngn2 oscillation is advantageous for the activation of Notch signaling by inducing Dll1 expression without promoting neuronal differentiation.

Generation of Induced Pluripotent Stem (iPS) Cells by Sox2, Oct4, Klf4, and c-Myc Transcription Factors and their Family Genes


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Although human ES cells could be used in cell transplantation therapy, their clinical application faces ethical objections against utilizing human embryos. One solution is to generate pluripotent cells directly from somatic cells. We have recently shown that retrovirus-mediated transfection of four factors (Sox2, Oct3/4, Klf4, and c-Myc) induced pluripotent stem cells, which we designated induced pluripotent stem (iPS) cells, directly from human and mouse fibroblasts.

Mouse iPS cells are indistinguishable from ES cells in many characters and produce germline-competent chimeras. However reactivation of the c-Myc retrovirus results in an increased tumorigenicity in the chimeras and progeny mice. In this study, we developed a new protocol for the generation of iPS cells without the c-Myc retrovirus. The iPS cells generated without the c-Myc retrovirus were high quality. Furthermore, we could generate human iPS cells from adult dermal fibroblasts without the c-Myc retrovirus. These findings are important for the clinical application of this iPS cell technology. Human iPS cells provide patient-specific stem cells, which could be useful in drug discovery, toxicology, and regenerative medicine.

However, integration of viral genes into the host genome increases the risk of tumorigenicity. To resolve this problem, we generated mouse iPS cells without retrovirus infection. Repeated transfection of a single plasmid containing the cDNAs of Sox2, Oct3/4, and Klf4, together with a c-Myc expression plasmid, into mouse embryonic fibroblasts resulted in integration-free iPS cells, which produced teratomas and adult chimera mice. The generation of integration-free mouse iPS cells addresses a critical safety concern for the use of iPS cells in regenerative medicine.

The introduction of the three or four factors into fibroblasts can produce iPS cells, however, the molecular mechanisms of the production of iPS cells remain to be resolved. To resolve this question, we examined whether the four factors can be replaced by their family genes. We found that some, but not all, of the family genes were capable of inducing iPS cells instead of one of the four factors from mouse and human fibroblasts. We are now examining the pluripotency of these iPS cell clones and the functions of reprogramming genes during the generation of iPS cells.

Mycobacterium Tuberculosis, Listeria Monocytogenes and the Host Cytokine Response

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M. tuberculosis (Mtb) and *L.monocytogenes* (LM) are the causative agents for tuberculosis and listeriosis, respectively, and both bacterial species are typical facultative intracellular bacteria that can resist intracellular killing in infected macrophages. We have been interested in the molecular mechanism by which these particular types of bacteria exhibit virulence and induce a vigorous cytokine response and Th1-type of acquired immunity in infected hosts.

Though the virulence mechanism of Mtb has not yet been fully elucidated, RD1, a genomic region missing in BCG, appears to be responsible for host cell necrosis and cytokine induction in Mtb- infected macrophages. In our recent study using an RD1-deficinet mutant strain of Mtb, it has been shown that the RD1 region is involved in the induction of necrosis in infected RAW264 cells via mitochondrial membrane damage and ATP depletion. It also seems that the RD1 region is engaged in the host's inflammatory cytokine response.

The major virulence factors of LM are encoded by LIPI-1 locus consisting of *prfA* and 5 other structural genes. Among them, *hly* gene coding for listeriolysin O (LLO) is the most important virulence gene as the *hly*-deficient mutant becomes incapable of growing inside macrophage. LLO is a cytolysin that enables LM to escape from the phagosomal compartment into cytosolic space inside infected macrophages. In a series of our recent studies, we have found that the N-terminus domain of LLO is responsible for the induction of caspase-dependent cytokines including IL-1beta and the active form of IL-18. By using various recombinant LM strains harboring the genes for truncated LLO or allied cytolysin, it was clearly shown that the 1-3 domain of LLO is responsible for the activation of caspase-1 after the evasion of LM into the cytosol of macrophages.

The relationship between virulence-associated genes and cytokine induction was presented.

Mechanism of Foreign RNA Recognition in Cytoplasm

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A DExD/H protein, RIG-I, is critical in innate antiviral responses by sensing viral RNA. Here we show that RIG-I recognizes two distinct viral RNA patterns: double-stranded (ds) and 5′ppp-single-stranded (ss) RNA. The binding of RIG-I with dsRNA or 5′ppp-ssRNA in the presence of ATP produces a common structure, as suggested by protease digestion. Further analyses demonstrated that the C-terminal domain of RIG-I (CTD) recognizes these RNA patterns and CTD coincides with the auto-repression domain. Structural analysis of CTD by NMR spectroscopy in conjunction with mutagenesis revealed that the basic surface of CTD with a characteristic cleft interacts with RIG-I ligands. Our results suggest that the bipartite structure of CTD regulates RIG-I on encountering viral RNA patterns.

HIV-1 Pathogenesis: Productive Infection in $CD4^+$ Effecter Memory T Lymphocytes and $CD4^+$ Depletion in Humanized Mice

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Human immunodeficiency virus type 1 (HIV-1) is a retrovirus that explicitly infects humans and chimpanzees. Cost effective and readily accessible small animal infection models have been generated by means of transplanting human cells into immunodeficient mice and studies on HIV-1 infection in these models greatly contribute to the understanding of HIV-1 pathogenesis. We infected $CD34^+$ human cells-transplanted NOD/SCID/IL2Rγ^{null} mice with CCR5-tropic or CXCR4-tropic HIV-1. The CXCR4-tropic HIV-1-infected mice were depleted in $CD4^+$ thymocytes and peripheral blood $CD4^+$ T lymphocytes, while preferential depletion of $CD45RA^-$ $CD4^+$ memory T lymphocytes was found in CCR5-tropic HIV-1-infected mice. Within memory T lymphocytes, $CD45RO^+CCR7^-$ effecter memory T lymphocytes (T_{EM}) were preferentially infected and consumed by CCR5-tropic HIV-1. The majority of CCR5-tropic HIV-1-infected cells in the spleen were $Ki67^+CD69^+$ proliferating cells, while a fraction of HIV^+ cells were $hKi67^-hCD69^-$ resting T lymphocytes. This work gives a detailed analysis on the impact of HIV-1 infection on human immune cells and HIV-1 productive infection, thus providing a foundation on which to build therapeutic strategies.

Closing Remarks

Prof. Xiaoyuan FENG
Dean
Shanghai Medical College
Fudan University

Dear Vice-President Toshio Yokoyama, dear guests, students, ladies and gentlemen, it gives me great honor and pleasure to be here today at the closing ceremony of the 11th Kyoto University International Symposium. Over the past two days, the finest scholars in the fields of bioscience and medicine from Japan and China have explored the topic of "Frontier Bioscience in Modern Medicine" at Fudan University, the local host of this event.

In recent years, the latest advances in bioscience and biotechnologies have had an unprecedented impact on the development of modern medicine. Shanghai Medical College of Fudan University, as one of the leading medical colleges in China, shares Kyoto University's vision that breakthroughs in biological research will the one of the essential driving forces for the advancement of medicine. Bearing this in mind, researchers from all over the world have endeavored to broaden our knowledge of advanced bioscience and biotechnologies.

The 11th Kyoto University International Symposium successfully served as a platform for the exchange of visions and ideas in the field, and I believe the achievements made here will lead to further research and discoveries in the future.

I'd like to take this opportunity to express our gratitude towards Kyoto University, which has the vision to find overseas partners with which to co-host international symposiums. Once again, this strategy proves to be successful and insightful.

We are delighted to see our discussions reach a wide audience in China and involve researchers from not only Kyoto University and Fudan University, but also other Chinese universities including Huazhong University of Science and Technology 华中科技大学, Zhejiang University 浙江大学, Nanjing Medical University 南京医科大学, the 4th Military Medical University 第四军医大学, Suzhou University 苏州大学, and locally in Shanghai, Shanghai University 上海大学, Shang hai Jiaotong University 上海交通大学, Tongji University 同济大学, the 2nd Military Medical University 第二军医大学, East China Science and Technology University 华东理工大学, East China Normal University 华东师范大学, Shanghai Normal University 上海师范大学 and Shanghai Academy of Sciences 中科院上海分院. I'm pleased to announce that over 700 people attended the symposium during its two-days.

I'd like to offer my sincere congratulations to both Kyoto University for successfully organizing this event and to my colleagues, the staff of Fudan University, for their effective and efficient support. I believe that both sides look forward to further expanding our collaboration and exchange in the future.

Ladies and gentlemen, I hope that you found the time you spent with your colleagues and co-researchers at Fudan University interesting and rewarding, and your stay in Shanghai enjoyable. Thank you !

Raising Afresh the Eternal Question: a few remarks at the end of KUIS-11

Prof. Toshio YOKOYAMA
Vice-President
Kyoto University

Ladies and Gentlemen, it is my pleasure to announce, with my thanks to every participant, that these two days of intense reports and discussions have now successfully come to a close.

It was early this year, at the inauguration reception for the Center for iPS Cell Research and Application, that I asked Professor Shinya Yamanaka the following question: ‘ If this new technology has become applicable to humans, can we really die properly ? ’ He answered in his usual conscientious manner, ‘ You need not worry for another ten years, as we have to examine many things beforehand. ’ A strange answer to a strange question – but this kind of sharp exchange is not uncommon on the campus of Kyoto University !

Listening to the concisely presented essence of world-class bioscience achievements in modern medicine, the following general impression has come into my mind: The scientists gathered here have been sharing their precious time, collaborating to raise afresh the eternal question from ancient times, that is: ‘ What is Life ? ’

We are certainly living in an age of profound change, in which conventional notions of nature and humanity are themselves undergoing change. Now, any new knowledge obtained in laboratories or in any actual on-site situations, must be reconsidered in terms of its meaning for the entire global community. Specialists cannot decide such meaning by themselves alone, and for this very reason, inter-disciplinary and international discussions ought to be continued.

Kyoto University has been reputed for its historical commitment to academic freedom, dialogue, and originality. On our campus, anyone can notice the distinctive trait of talkativeness among our members. This characteristic will prove to be the indispensable background for any future contribution to the development of world academia and the global civilization with a new human civility at its core, shijie wenming. The promising students who have participated in this event are most welcome to join us in Kyoto in whatever way possible.

Now, I am having great difficulty to find the proper words to express my renewed thanks to all the organizations that have extended their enormous support to realize this symposium. But to mention only a few: Fudan University under President Wang Shenhong; its Foreign Affairs Office under the direction of Pro Vice-President Chen Yinzhang; and Shanghai Medical College under Dean Feng Xiaoyuan; and AEARU, the Association of East Asian Research Universities; then, Kyoto University Department of International Affairs headed by Director Masao Tsukamoto; the Kyoto University Foundation; the Global Center of Excellence Program at Kyoto University Graduate School of Medicine, represented by Professor Shu Narumiya.

I would also like to thank various institutions that kindly sent important delegations to this symposium. If I dare mention only six among them, they are: the Fourth Military Medical University; Zhejinag University; Sichuan University; Nanjing University; Huazhong University of Science and Technology; and Nanjing Medical University. In addition, I must mention the kind support and understanding of Kitano Hospital led by President Yoshio Yamaoka, Professor Emeritus of Kyoto University.

Lastly, to mention only a few individual names among our colleagues: Professor Nagahiro Minato, Chair of the Organizing Committee of this symposium and his occasional secretary Ms. Emiko Hatanaka, member of the administrative staff of Kyoto University Graduate School of Medicine; and Mr. Ainslie Kerr, Specialist Administrator of Kyoto University Division of International Affairs, who is also currently Secretary of AEARU. To close, I must mention two more names: Associate Professor Zhu Chouwen, Director of the Medical Center Office and Deputy Director of the Foreign Affairs Office, Fudan University; and Assistant Professor Han Liyou of Kyoto University International Center, who is a holder of a Kyoto University PhD in agricultural science. Without these two capable scholars ’ intermediary roles between Fudan and Kyoto, this symposium could not have been so well realized.

I conclude here by expressing my warmest good wishes for every participant ’s well-being and creativity.

Photographs

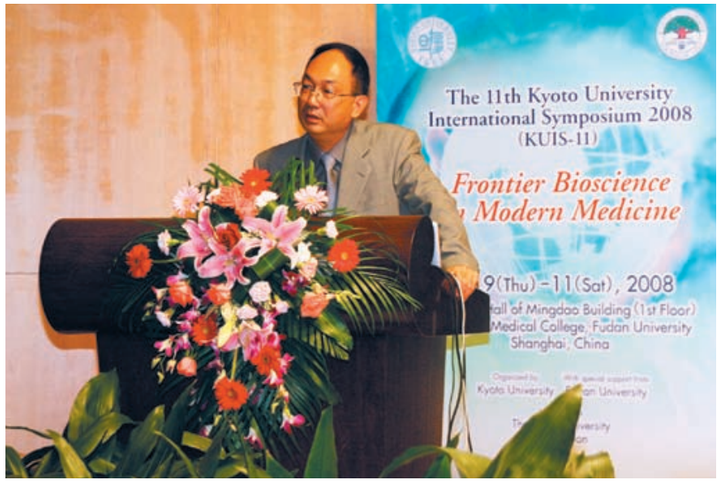
President Shenhong Wang (Fudan University) and President Hiroshi Matsumoto (Kyoto University) exchange greetings at the reception.

Symposium participants engage in animated discussions during the reception.

The symposium venue: Mingdao Building, Shanghai Medical College, Fudan University

Staff greet the symposium participants at the reception desk.

President Hiroshi Matsumoto, Kyoto University



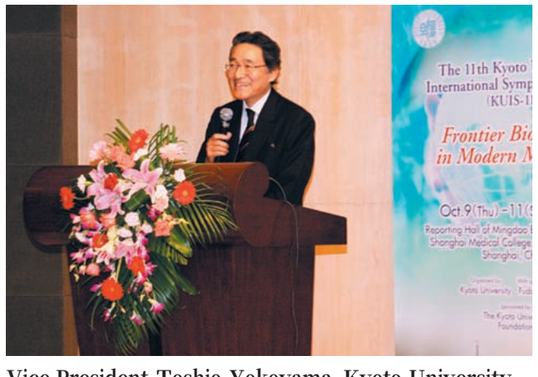
Executive Vice-President Weiping Wang, Fudan University

Professor Atsushi Hiraide explains Kyoto University's student exchange programs to interested Chinese students.

The presentations were followed by lively question-and-answer sessions.

The auditorium was filled to capacity throughout the symposium.

Professor Xiaoyuan Feng, Dean of Shanghai Medical College Fudan University



Vice-President Toshio Yokoyama, Kyoto University

Professor Xiaoyuan Feng, and Professor Nagahiro Minato, Chair of the Symposium Organizing Committee

Participation Report

Prof. Ryoichiro KAGEYAMA
Institute for Virus Research
Kyoto University

It was a great pleasure to represent Kyoto University as a speaker at the 11th Kyoto University International Symposium at Fudan University. It was my first opportunity to visit Shanghai, but I had heard that it was a large, vibrant city. The symposium was held across two days on October 10th to 11th, following a reception on the 9th. Faculty members from Kyoto University's Graduate School of Medicine, Institute for Frontier Medical Sciences and Institute for Virus Research, as well as faculty members from Fudan University gave presentations on their research findings. It is rare – in Japan or elsewhere – to find an academic meeting involving so many researchers of such caliber, and the presentations and discussion sessions were of an extremely high standard. The symposium drew faculty members, graduate and undergraduate students not only from Fudan University, but also from universities and research institutes in the surrounding areas, and the auditorium was filled with an air of excitement. The positive attitude of the Chinese researchers was very evident during the lively question-and-answer sessions which followed each presentation. My own presentation prompted many questions, each of which was related to a pertinent point which I was very keen to discuss. My presentation was greatly enhanced by the question-and-answer session, and it was evident that the scholars who asked questions were very well-versed in the field. The level of expertise demonstrated was the same as can be found at academic meetings in Japan, Europe and the US. It seems that any difference that existed between the level of research being undertaken in those regions and that being undertaken in China (or at least in Shanghai) has vanished. Rather, in contrast to Japan, which is currently facing a dearth of graduate students, when I witnessed the large number of active and passionate Chinese students, I felt that in the near future Japan could well be surpassed by China in the field of fundamental medicine.

I feel that the symposium created a link between Kyoto University and the Chinese students, and I am hopeful that many of them will come to study in Kyoto. Whether or not this hope is realized, however, is likely to depend on efforts made from now on. According to what I have heard, universities from

all over the world are visiting Fudan University and other institutions in China, and holding similar symposia. It is likely that the students of Fudan University, having listened to presentations by scholars visiting from various countries, are considering where best to continue their studies. I think that this symposium provided an excellent opportunity to raise awareness about Kyoto University, however in order to continue to attract outstanding graduate students, we must also be seen to be enhancing graduate school education in other ways, and must provide laboratory opportunities in Japan for accomplished researchers regardless of their nationality. Currently, the International Young Scientists Career Development Organization (ICDO), the activities of which are focused on Kyoto University's Graduate School of Medicine, is actively trying to recruit international scholars. It is my hope that effective use of such systems will make Kyoto University appealing to international researchers.

In closing, I would like to sincerely thank Professor Nagahiro Minato, who worked tremendously hard for this symposium; Professor Toshio Yokoyama, Director of the Organization for the Promotion of International Relations and those who work with him; as well as Kyoto University president Dr. Hiroshi Matsumoto, who delivered an opening speech for the symposium despite being in midst of a very busy period, directly following his assumption of office. I sincerely hope that this symposium will lead increased interaction between Fudan University and Kyoto University.

Report

Prof. Xiaoyuan FENG
Dean
Shanghai Medical College
Fudan University

From October 9–11, in the autumn of 2008, the 11th Kyoto University International Symposium (KUIS-11): Frontier Bioscience in Modern Medicine was held on our campus, Shanghai Medical College of Fudan University, in the city center of Shanghai, China. This was a historic occasion because it was the first time for a Kyoto University International Symposium to be held in China, having been held at various venues around the world since 2000. As the proud local host of this year's symposium, we appreciate the vision and wisdom shown by Kyoto University in successfully staging international symposia in cities around the world, and thereby expanding the scope of knowledge exchange to a more global level.

As one of the China's top higher education institutions, Fudan University has achieved worldwide fame throughout its venerable past. Shanghai Medical College boasts both a long history and a rich heritage of learning and scholarship. It is our pleasure to share in Kyoto University's distinctive research achievements, and to promote the advancement of academic research on a global scale through this symposium. As we know, recent advances in bioscience and biotechnologies are having an unprecedented impact on modern medicine. Newly emerging paradigms in medical science are expected to bring about efficient strategies for promoting human health at the global level. At present, Kyoto University is a world leader in research into regeneration technology including ES and iPS cells. The symposium presented and ideal opportunity for Kyoto University to introduce its medical research activities to students and researchers in China.

President Wang Shenghong and other professors from Fudan University participated in the welcome reception party. Prof. Wang Weiping, Executive Vice President and Director of the Medical Center, Fudan University delivered an address in the opening ceremony of the symposium. Four professors from Fudan University, along with fourteen professors from Kyoto University and gave keynote speeches in a total of four sessions. In each session, two professors served as excellent chairpersons and the discussions which followed were lively and fruitful. Over 700 participants attended the symposium over the course of the two days. In addition to students and researches from Fudan University and Kyoto University, students and

scholars from many institutes and universities throughout China (including the Shanghai Institute for Biological Science, Shanghai JiaoTong University, the Second Military Medical University, Zhejiang University, Huazhong University of Science and Technology and Nanjing Medical University) enthusiastically participated in the symposium and engaged in academic discussions. Recent advances and ideas in the field of frontier bioscience in modern medicine were shared by renowned young researchers from Japan and China.

A great deal of preparatory work was done over the preceding year to ensure the smooth convocation of the symposium. In September 2008, Professor Zhu Chouwen, Deputy Director of the Foreign Affairs Office of Fudan University, Professor Qian Ruizhe, Vice Dean of Shanghai Medical College of Fudan University, and myself, Dean of Shanghai Medical College of Fudan University, had a meeting with Professor Minato, Vice Dean of the Graduate School of Medicine, Kyoto University to conclude the arrangements and preparations for the symposium. We then held a special meeting to make detailed preparations for the symposium and arranged for Dr. Liu Jinye, Director of the Dean's Office of Shanghai Medical College and Dr. Liu Qiong, Foreign Affairs Assistant of Shanghai Medical College, to specially prepare for the symposium. Many other meetings were also held to refine the details of the symposium.

We also vigorously promoted the symposium. Notices and information about the symposium were posted on the home page of Shanghai Medical College of Fudan University. At the same time, we prepared a Chinese version of the poster and posted them around our campus. We also published the documentation of the conference with the help of post-graduate working groups and the students union. Students and researchers in the Medical College of Shanghai Jiao Tong University, Shanghai Institute for Biological Science and other institutions and universities in Shanghai were also invited to attend the conference. To muster the enthusiasm of the participants, our foreign affairs staff communicated with the staff of those institutions by telephone and email, and also met in person. We made the symposium known to almost every biomedical researcher and student in Shanghai – a fact that was later reflected in the large number of active participants.

Over 25 volunteers played an active role not only in the preparatory work but also during the symposium. These volunteers expertly handled the task of welcoming the Japanese scholars and staff. We also had a group of volunteers who served the almost 700 participants during the symposium's coffee break. They took a great deal of care in managing the budget, selecting food and soft-drinks, and arranging the room for the coffee break. There was also a group who had the job of registering the participants and assisting in the survey after the symposium. These volunteers arranged the lunches for both the VIP guests in the professor's restaurants and the almost 700 participants in the student dining room. Without the hard work of these volunteers from our college, we could not have organized such an important event.

Our university attached great importance to details such as transportation, lunch, coffee breaks, promotion, the layout of the conference hall in the Mingdao Building, leasing the conference hall and so on. To make the layout perfect, we hired an advertising company to arrange the meeting place, including the placement of the flowers, inspection of the lights, projector and loudspeakers, and the arrangement of the VIP rooms and lounges.

Altogether, the conference was successful and mutually-beneficial. It is well-known that communication and development are key themes in promoting human health at the global level. For over a century, Kyoto University has made significant contributions to the advancement of modern medicine and its research achievements are widely recognized. Recently, Fudan University has also made considerable contributions to the development of biomedicine. The 11th Kyoto University International Symposium stands as an example of successful cooperation between Fudan University and Kyoto University, and will further the academic exchange between the two institutions. This in turn will contribute to the development of China-Japan education and research exchanges. We are convinced that co-hosting the 11th Kyoto University International Symposium will lead to further fruitful collaborations in the future.

The 11th Kyoto University International Symposium (KUIS-11)

Frontier Bioscience in Modern Medicine — Report

Shanghai, China, Oct. 9 − 11 , 2008

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京都大学基本理念

京都大学は、創立以来築いてきた自由の学風を継承し、発展させつつ、多元的な課題の解決に挑戦し、地球社会の調和ある共存に貢献するため、自由と調和を基礎に、ここに基本理念を定める。

研　究

1. 京都大学は、研究の自由と自主を基礎に、高い倫理性を備えた研究活動により、世界的に卓越した知の創造を行う。
2. 京都大学は、総合大学として、基礎研究と応用研究、文科系と理科系の研究の多様な発展と統合をはかる。

教　育

3. 京都大学は、多様かつ調和のとれた教育体系のもと、対話を根幹として自学自習を促し、卓越した知の継承と創造的精神の涵養につとめる。
4. 京都大学は、教養が豊かで人間性が高く責任を重んじ、地球社会の調和ある共存に寄与する、優れた研究者と高度の専門能力をもつ人材を育成する。

社会との関係

5. 京都大学は、開かれた大学として、日本および地域の社会との連携を強めるとともに、自由と調和に基づく知を社会に伝える。
6. 京都大学は、世界に開かれた大学として、国際交流を深め、地球社会の調和ある共存に貢献する。

運　営

7. 京都大学は、学問の自由な発展に資するため、教育研究組織の自治を尊重するとともに、全学的な調和をめざす。
8. 京都大学は、環境に配慮し、人権を尊重した運営を行うとともに、社会的な説明責任に応える。