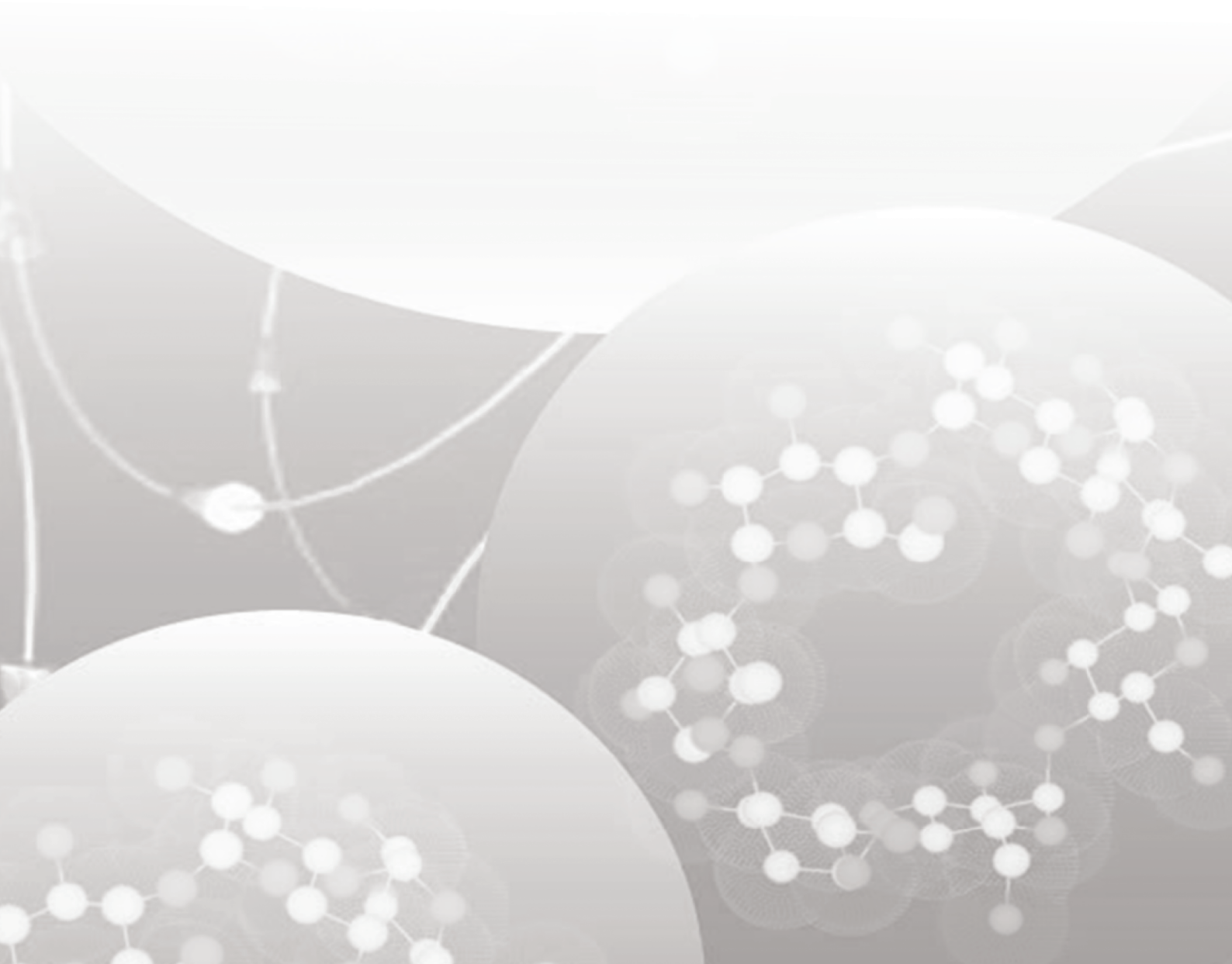
The 3rd GCOE International Symposium on Signal Transduction Medicine in the Coming Generation

Program and Abstracts

December 10-11, 2012 ◆ Kobe Portopia Hotel



Program

Kobe University Global COE Program
The 3rd International Symposium on Signal Transduction Medicine in the Coming Generation

Day 1st: Monday, December 10, 2012 (13:30-18:20)

Venue: Room "Kairaku", B1F Main Building, KOBE PORTOPIA HOTEL

*Presentation: 35 min (Guest Speaker)/20 min (In-house Speaker), Discussion: 5min

13:30-13:35 Opening Address
Hideki Fukuda *(President, Kobe University)*

13:35-13:50 Brief Summary of the Global COE Program
Takeshi Azuma *(Leader for Global COE Program "Global Center of Excellence for Education and Research on Signal Transduction Medicine in the Coming Generation")*

Chairperson: Masaru Yoshida

13:50-14:30 Invited Lecture
"Gastrokines: stomach-specific regulators of homeostasis and tumour suppression."
Andrew Giraud *(Professor, The Royal Children's Hospital, Australia)*

14:30-14:55 "Application of metabolomics of pancreatic beta-cell biology"
◎***Susumu Seino*** *(Professor, Kobe University)*

14:55-15:20 "Wnt5a-Ror signaling under physiological and pathological conditions"
◎***Yasuhiro Minami*** *(Professor, Kobe University)*

Coffee Break

Chairperson: Yoshiyuki Rikitake

15:35-16:00 "Identification of novel drug targets for the treatment of neovascular eye diseases"
◎***Akiyoshi Uemura*** *(Assistant Professor, Kobe University)*

16:00-16:25 "*Helicobacter pylori* infection and gastric cancer."
◎***Takeshi Azuma*** *(Professor, Kobe University)*

16:25-17:05 Invited Lecture
"Understanding Brain Control of Glucose Homeostasis: Implications for Diabetes Pathogenesis and Treatment"
Michael W. Schwartz *(Robert H Williams Endowed Chair in Medicine Professor and Director, Diabetes and Obesity Center of Excellence, University of Washington)*

17:20-17:50 Poster presentation (Odd number posters)
17:50-18:20 Poster presentation (Even number posters)

18:20-20:30 *Mixier*

◎Global COE Program member to be evaluated.

Day 2nd: Tuesday, December 11, 2012 (8:40-9:25)

Venue: Room "Nunobiki-Kitano", Main Building B1F, KOBE PORTOPIA HOTEL

*Presentation: 35 min (Guest Speaker), Discussion: 5min

8:40-8:45 Opening Address
Takeshi Azuma *(Global COE Program leader)*

Chairperson: Yasuhiro Minami

8:45-9:25 Invited Lecture
"Wnt/ß-catenin Signaling in Acute Injury and Chronic Disease"

Randall T. Moon *(Investigator, HHMI, Director and William and Marilyn Conner Professor, Institute for Stem Cell and Regenerative Medicine, University of Washington School of Medicine, HHMI and Department of Pharmacology)*

Lectures

Andrew Giraud

Professor, Director
Infection and Immunity Research Theme
Group Leader,
Gastrointestinal Research in Inflammation and Pathology (GRIP)
Murdoch Childrens Research Institute, The Royal Childrens Hospital Australia

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“Gastrokines: stomach-specific regulators of homeostasis and tumour suppression.”

The gastrokines are a family of 3 stomach-specific proteins that are synthesised by gastric mucous -secreting cell lineages. Gastrokines have a highly conserved disulfide-linked tertiary structure, and emerging data suggests convergent roles in the maintenance of normal gastric mucosal function and suppression of inflammation. While highly expressed in normal stomach, total suppression of gastrokine synthesis in chronic *H.pylori* infection and gastric cancer progression, coupled with their demonstrated anti-proliferative activity, suggest putative tumour suppressor roles. Precise modes of action remain unsolved, but the recent demonstration of a gastrokine 2/trefoil factor (TFF)1 heterodimer suggests an interactive function for these proteins. This talk will give an overview of gastrokine biology, concentrating on the rapidly accumulating evidence supporting roles in maintaining gastric mucosal homeostasis and promoting tumour suppression. This will be illustrated by data derived from knockout and knockin mouse models and from human tissue samples.

◎Susumu Seino

Professor
Divisions of Diabetes and Endocrinology/Cellular and Molecular Medicine,
Kobe University Graduate School of Medicine

“Application of metabolomics to pancreatic beta-cell biology”

Insulin secretion from pancreatic β-cells plays a central role in glucose homeostasis and impaired insulin secretion contributes to the development of diabetes. Metabolic signals in β-cells are crucial in regulation of insulin secretion. For example, ATP generated by glucose metabolism is a key signal in glucose-induced insulin secretion (GIIS), which is the most important mechanism of insulin secretion. In addition to GIIS, potentiation of GIIS also is required for normal regulation of insulin secretion. cAMP is a well-known second messenger in β-cells that potentiates insulin secretion in a glucose-dependent manner. Utilizing this effect, incretin (gut hormones that increase cAMP in the β-cells)-related anti-diabetic drugs have been developed recently. However, the mechanism of the glucose-dependency of cAMP action in insulin secretion remains unknown. Using metabolome-based analysis, we find that glutamate generated through the malate-aspartate (MA) shuttle, an NADH shuttle linked to glycolysis, is essential for potentiation of insulin secretion by incretin/cAMP signaling and that glutamate transport into insulin granules through vesicular glutamate transporter 1 (VGLUT1) is required in this process. Thus, glutamate is an essential signal linking glucose metabolism and cAMP action in the β-cell and mediates the glucose-dependent effect of cAMP in insulin. Metabolomics is a powerful approach to identification of novel metabolic signals and potential therapeutic targets in insulin secretion.

◎Yasuhiro Minami

Professor
Division of Cell Physiology, Kobe University Graduate School of Medicine

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“Wnt5a-Ror signaling under physiological and pathological conditions”

Wnt5a and its cognate receptors, the Ror-family of receptor tyrosine kinases, Ror1 and Ror2, have been shown to play crucial roles in the developmental morphogenesis by regulating convergent extension (CE) movements and planar cell polarity (PCP). Studies with cultured cells have revealed that Wnt5a-Ror signaling plays important roles in the regulation of various cellular functions, including cell polarity, migration/invasion, proliferation, differentiation, and stemness.

In this talk, first of all, I will give a brief background of the roles of Wnt5a-Ror signaling in the developmental morphogenesis, and will then present evidence showing that constitutively activated Wnt5a-Ror2 signaling in osteosarcoma cells (mesenchymal origin) and in cancer cells (epithelial origin) following epithelial-mesenchymal transition (EMT) can confer invasive properties on these malignant cells. More recently, we have found that Wnt5a-Ror2 signaling plays important roles in the kidney morphogenesis by regulating GDNF-Ret signaling during the ureteric bud formation. In fact, both *Wnt5a*$^{-/-}$ and *Ror2*$^{-/-}$ mice exhibit duplicated ureters & kidneys. We have also shown by using an organ culture of the developing kidneys that proper Wnt5a-Ror2 signaling is required for the development of the ureters & kidneys. Finally, I will show our present findings showing the role of Wnt5a-Ror signaling during kidney inflammation using a mouse unilateral urinary obstruction (UUO) model. I would like to discuss the functions of Wnt5a-Ror signaling under physiological and pathological conditions and the possible development of our findings to clinical applications.

◎Akiyoshi Uemura

Assistant Professor
Divisions of Vascular Biology/Division of Ophthalmology, Kobe University
Graduate School of Medicine

“Identification of novel drug targets for the treatment of neovascular eye diseases”

In diabetic retinopathy and retinopathy of prematurity, retinal ischemia following capillary obstruction induces formation of new blood vessels which grow out of the retinal surfaces. Because the extra-retinal angiogenesis directly causes vision-threatening hemorrhage, anti-angiogenic therapies, such as laser photocoagulation and anti-VEGF drugs, are administered to treat ischemic retinopathy. Nonetheless, in order to fundamentally resolve the disease pathogenesis, regeneration of functional vessels in ischemic retinas would be of great benefit. By contrast to ischemic retinopathy, new blood vessels grow into hypoxic retinas during development. By utilizing developmental angiogenesis model in postnatal mouse retinas, we showed that binding of neuron-derived Sema3E to the endothelial PlexinD1 receptor suppressed disoriented projections of endothelial filopodia, thereby facilitating intra-retinal angiogenesis. Furthermore, we found that a small GTPase RhoJ mediates Sema3E-induced contraction of endothelial cells (ECs), whereas VEGF inactivates RhoJ via an EC-specific Rho guanine nucleotide exchange factor, Arhgef15. In a mouse model of ischemic retinopathy, ECs of extra-retinal vessels intensively expressed PlexinD1 and RhoJ, which contributed to suppress abnormal angiogenesis. By targeting the PlexinD1, intraocular injections of Sema3E proteins selectively suppressed extra-retinal angiogenesis without affecting intra-retinal vascular regeneration. Thus, we proposed that Sema3E-PlexinD1-RhoJ signals can be potential targets for vascular regeneration therapy in ischemic retinopathy.

◎Takeshi Azuma

Professor
Divisions of Gastroenterology, Kobe University Graduate School of Medicine

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"*Helicobacter pylori* infection and gastric cancer"

Helicobacter pylori is a group I carcinogen in human. CagA is a most important virulent factor of *H. pylori* associate with gastric cancer. CagA is directly injected from the *H. pylori* into the cells via the bacterial type IV secretion system and undergoes tyrosine phosphorylation in the host cells. We previously discovered that translocated CagA forms a physical complex with SHP-2, and stimulates phosphatase activity. SHP-2 is known to play an important positive role in mitogenic signal transduction. Deregulation of SHP-2 by CagA may induce abnormal proliferation and movement of gastric epithelial cells. In addition, the CagA protein is polymorphic. We discovered that predominant CagA proteins isolated in East Asia, where gastric cancer is prevalent, have a distinct sequence at the phosphorylation site of CagA. East Asian-specific sequence confers stronger SHP-2 binding and transforming activities to Western CagA. We examined the CagA diversity of *H. pylori* isolated from chronic gastritis and gastric cancer patients in Asian countries. The prevalence of East Asian CagA was significantly higher in patients with gastric cancer than in patients with chronic gastritis. The much greater magnitude of risk observed with East Asian CagA-positive *H. pylori* infection. Therefore, patients harboring East Asian CagA-positive *H. pylori* are at a higher risk for developing gastric cancer than those infected with Western CagA-positive strains. In addition, we sequenced whole genome of 4 Japanese strains. Phylogenetic analysis revealed greater divergence between the East Asian (hspEAsia) and the European (hpEurope) genomes in proteins in host interaction, specifically virulence factors and outer membrane proteins. A phylogenetic tree of concatenated well-defined core genes supported divergence of the East Asian lineage (hspEAsia; Japanese and Korean) from the European lineage ancestor, and then from the Amerind lineage ancestor. These results demonstrate dramatic genome evolution within a species, especially in likely host interaction genes, and provide essential information for understanding gastric carcinogenesis induced *H. pylori* infection.

Michael W. Schwartz

Robert H Williams Endowed Chair in Medicine Professor and Director,
Diabetes and Obesity Center of Excellence, University of Washington

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"Understanding Brain Control of Glucose Homeostasis: Implications for Diabetes Pathogenesis and Treatment"

The unanswered question of whether the brain plays a physiological role in glucose homeostasis has been a source of controversy for many years. Our current, islet-based understanding of glucose homeostasis originated with the discovery of insulin in 1921 and the subsequent identification of liver, muscle and adipose tissue (but not the brain) as the principal targets of insulin's glucoregulatory effects. The islet's pre-eminent position was secured with the finding that defective insulin secretion and action are strongly implicated in diabetes pathogenesis.

Current diabetes treatment options reflect this islet-centered view, consisting principally of recombinant human insulin preparations, insulin secretogogues (some of which also inhibit glucagon secretion), and drugs that increase insulin sensitivity. While these drugs enjoy wide use and are effective in controlling hyperglycemia, the primary manifestation of type 2 diabetes (T2D), their efficacy is limited by the fact that they address the consequences of diabetes but not the underlying cause. Recent, compelling evidence that unlike traditional medical therapy, bariatric procedures commonly induce diabetes remission (at least in part independently of weight loss, and potentially involving a central mechanism) justifies a reconsideration of how glucose homeostasis is achieved by the body and the respective roles of islet and brain in this process.

Here, we offer evidence of a brain-centered glucoregulatory system (BCGS) that plays an unexpectedly important and previously unrecognized role in both glucose homeostasis and diabetes pathogenesis. This role appears to be complementary to that of pancreatic islets, such that activation of the BCGS is capable of controlling blood glucose levels even when islet function fails, and may also contribute to the mechanism whereby bariatric procedures induce T2D remission. To more effectively confront the diabetes epidemic, future studies must clarify the role of the BCGS in glucose homeostasis and determine whether *1)* defective BCGS function contributes to the pathogenesis of T2D, and *2)* therapies that target the BCGS have potential in the treatment of T2D.

Randall T. Moon

Investigator, HHMI
Director and William and Marilyn Conner Professor
Institute for Stem Cell and Regenerative Medicine, University of Washington
School of Medicine, HHMI and Department of Pharmacology

"Wnt/ß-catenin Signaling in Acute Injury and Chronic Disease"

Wnts are a family of secreted proteins that activate receptor-mediated signal transduction pathways, leading to modulation of cell proliferation, cell fate, cell behavior, and the self-renewal of stem cells. Constitutive activation of the pathway via mutations is linked to cancer while attenuated signaling is linked to neurodegenerative disease, bone density disease, and other conditions. Our lab focuses on three goals: identifying the normal roles of Wnt signaling in embryos and adults, dissecting the molecular and cellular mechanisms by which this signaling occurs, and leveraging this knowledge to identify candidate therapies for acute and chronic medical conditions that involve aberrant Wnt signaling. This talk will cover both published and unpublished studies on the observed elevation of Wnt signaling in tissue repair and regenerative processes following acute injury, on hints that Wnt signaling may be attenuated in some degenerative processes, and data consistent with the idea that Wnt/ß-catenin signaling has different roles in different cancers. Implications for current and potential therapies will be discussed.

Posters

Poster Titles and Abstracts

	Poster Title	*Name/JobTitles*
P1	Analysis of Wnt5a-Ror signaling in renal fibrosis using a mouse model	Kaoru Yamagata GCOE Research Associate Cell physiology
P2	The establishment of metabolic proteome analysis by stable isotope labeling methods	Naoya Hatano GCOE Research Associate The Integrated Center for Mass Spectrometry
P3	The regulation of UVB/ROS-induced versican expression and inflammatory response associating with skin tumorigenesis	Makoto Kunisada GCOE Research Associate Dermatology
P4	Persistent cortical plasticity by upregulation of chondroitin 6-sulfation	Shinji Miyata GCOE Postdoc Pharmacokinetics
P5	Molecular mechanisms of hepatitis C virus-induced glucose metabolism disorder	Deng Lin GCOE Postdoc Microbiology
P6	ROLES OF IMMUNOGLOBULIN-LIKE CELL ADHESION MOLECULES IN THE HOMEOSTASIS OF THE BRAIN	Muneaki Miyata GCOE Postdoc Signal Transduction
P7	Characterization of neutralizing antibody for human herpesvirus 6	Akiko Kawabata GCOE Postdoc Clinical Virology
P8	Roles for sumoylation in regulation of the xeroderma pigmentosum group C protein	Masaki Akita GCOE Postdoc Biosignal Research Center
P9	Anti-CXCL13 antibody can protect against gastric lymphoid follicles induced by *Helicobacter* infection	Koji Yamamoto GCOE Postdoc Gastroenterology
P10	Development of therapeutic and preventive vaccines against Hepatitis C virus	Jiang Dapeng GCOE Postdoc Microbiology
P11	Establishment of experimental methodology to analyze of the membrane-mediated reactions of amyloidogenic peptides and influenza virus	Kenji Sasahara GCOE Postdoc Zoonosis
P12	Arhgef15 Promotes Retinal Angiogenesis by Mediating VEGF-Induced Cdc42 Activation and Potentiating RhoJ Inactivation in Endothelial Cells	Yoko Fukushima GCOE Postdoc Vascular Biology
P13	Establishment of metabolomics-based diagnostic system for pancreatic diseases	Takashi Kobayashi GCOE JSPS Student Gastroenterology
P14	Expression and function of chondroitin sulfate N-acetylgalactosaminyltransferase 2 in the development of atherosclerosis	Dyah Samti Mayasari GCOE Student Cardiovascular Medicine

	Poster Title	*Name/JobTitles*
P15	Isolation and Characterization of Novel Secreted Protein, SCUBE2 In Neointimal Formation	Hirowati Ali GCOE Student Cardiovascular Medicine
P16	Endothelial lipase modulates pressure overload-induced heart failure through alternative pathway for fatty acid uptake	Hideto Nakajima GCOE Student Cardiovascular Medicine
P17	Skin Lymphatic Capillary Role on Blood Pressure Maintenance of High Salt Treated Hyperaldosteronism Mice	Dwi Aris Agung Nugrahaningsih GCOE Student, Cardiovascular Medicine
P18	Analysis of human herpesvirus-6-induced cell signaling and immune suppression	Mayuko Hayashi GCOE Student, Clinical Virology
P19	Altered Cell Surface Heparan Sulfate (HS) Expression Induces Osteoblastic Differentiation and Attenuates Phagocytosis Activity of Human Aortic Smooth Muscle Cells (HAoSMC).	Eko Purnomo GCOE Student, Cardiovascular Medicine
P20	Roles of vascular endothelial protein tyrosine phosphatase (VE-PTP) in endothelial cells	Kemala Mantilidewi GCOE Student Molecular and Cellular Signaling
P21	A novel combination therapy with anti-CD3 antibody and IL-2 complexes against atherosclerosis targeting effector T cells and regulatory T cells	Kazuyuki Kasahara GCOE Student Cardiovascular Medicine
P22	The inhibitory effect of *Spirulina platensis* on UVB-induced skin carcinogenesis: anti-inflammatory and antioxidant mechanisms	Flandiana Yogianti GCOE Student Dermatology
P23	Elucidation of pancreatic beta-cell fate after birth using inducible Cre/loxP system	Kanako Tamura GCOE Student Cellular and Molecular Medicine
P24	Hair bundle misorientation and dysmorphology of aberrantly attached cochlear hair cells in nectin-3 knockout mice	Terunobu Fukuda GCOE Student Molecular and Cellular Biology
P25	Hepatitis C virus (HCV) infection induces lysosomal degradation of hepatocyte nuclear factor 1α via interaction with the HCV NS5A protein	Chieko Matsui GCOE Student Microbiology
P26	Unraveling the mechanisms of inflammation and immunity in aortic aneurysm formation	Keiko Yodoi GCOE Student Cardiovascular Medicine
P27	Interferon-γ induces the formation of gastric lymphoid follicles after *Helicobacter suis* infection	Yang Lin GCOE Student Gastroenterology
P28	The interaction between hepatitis C virus NS5A protein and histone methyltransferase SMYD3	Ming Chen GCOE Student Microbiology
P29	Genetic dissection of cell competition that regulates tumorigenesis	Kei Kunimasa GCOE Student, Genetics

Organizer

Kobe University Global COE Program

「Global Center of Excellence for Education and Research

on Signal Transduction Medicine in the Coming Generation」

- Bringing up clinician-scientists in the alliance between basic and clinical medicine -