OSAKA UNIVERSITY

RESEARCH PROFILE 2017

Foreword

Yasushi Yagi
Executive Vice President for Research

I am pleased to present the *Osaka University Research Profile 2017,* which is a compilation of outstanding research projects conducted by our distinguished researchers. Osaka University is a comprehensive research university, and thus this booklet covers a full repertoire from life science and medicine, natural science, engineering, and humanities and social sciences. This compilation also introduces globally collaborative research projects which are promoted and supported by the university's own funding project called the International Joint Research Promotion Program.

Looking towards the 90th anniversary of the university in 2021, we set out Osaka University Vision 2021 last year and have embarked on open research revolution from a high position amongst the World's Most Innovative Universities selected by Reuters in 2015 and 2016. Our ability to innovate from the stage of fundamental research and through the creation of useful technology with economic impact stems from our long history of determination and broad disciplinary spectrum. With roots in *Kaitokudo* and *Tekijuku* – schools in the 18th and 19th centuries that produced a number of Japan's luminaries – the university has become a place where future leaders can rise above fixed social standings to engage in solving social issues.

Osaka University has been selected as an excellent institution by the Japanese government in their significant funding projects such as the World Premier International Research Center Initiative (WPI) in immunology, the Program for Promoting the Enhancement of Research Universities, and the Top Global University Project. We will continuously endeavor to contribute to the advancement of knowledge that leads to the betterment of our society.

Life Science and Medicine

Shizuo Akira
Immunology Frontier Research Center

Categorizing macrophages by disease

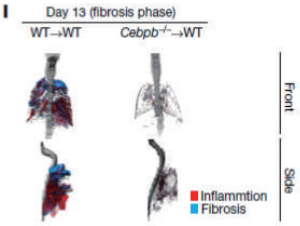
Previously, scientists had divided macrophages into two conditions, M1 and M2. M1 macrophages are involved in acute inflammation and M2 macrophages are associated with chronic inflammation, but research has progressively shown that this classification is an oversimplification. Rather than basing macrophage categories on function, a more clinically relevant approach may be to categorize them based on disease. Dysfunctional macrophages contribute to disparate illnesses such as cancer, allergies and even obesity. Thus, study of the activation of these different macrophages has promise for new therapies.

Using this new approach, the Shizuo Akira lab has identified the effects of a number of key factors that contribute to macrophage activation. One example is jumonji domain containing-3 (Jmdj3), a type of demethylase. Jmdj3 is critical for the activation of macrophage responses to allergic stimuli. Trib1 is an adaptor protein involved in lipid metabolism. It regulates tissue residential macrophage differentiation, and its dysfunction is associated with exacerbated metabolic syndrome. Most recently, CCAAT/enhancer binding protein β was found to regulate a newly discovered type of monocyte, segregated-nucleus-containing atypical monocyte (termed SatM), and this regulation was found to have a critical role in fibrosis development.

Dysregulation of the immune system contributes to a vast range of diseases. By typing macrophages not to their function, but to their disease association, the lab aims to uncover new therapies that are both highly effective and highly specific.

References:

1) Satoh T, Takeuchi O, Vandenbon A, Yasuda K, Tanaka Y, Kumagai Y, Miyake T, Matsushita K, Okazaki T, Saitoh T, Honma K, Matsuyama T, Yui K, Tsujimura T, Standley DM, Nakanishi K, Nakai K, Akira S. The Jmjd3-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection. ***Nature Immunology*** 2010 Oct; 11(10): 936-44.
2) Satoh T, Kidoya H, Naito H, Yamamoto M, Takemura N, Nakagawa K, Yoshioka Y, Morii E, Takakura N, Takeuchi O, Akira S. Critical role of Trib1 in differentiation of tissue-resident M2-like macrophages. ***Nature*** 2013 Mar 28; 495(7442): 524-8.
3) Satoh T, Nakagawa K, Sugihara F, Kuwahara R, Ashihara M, Yamane F, Minowa Y, Fukushima K, Ebina I, Yoshioka Y, Kumanogoh A, Akira S. Identification of an atypical monocyte and committed progenitor involved in fibrosis. ***Nature*** 2017 Jan 5; 541(7635):96-101.



MRI analysis: Lack of SatM resulted in resistance to fibrosis.

Shimon Sakaguchi
Immunology Frontier Research Center

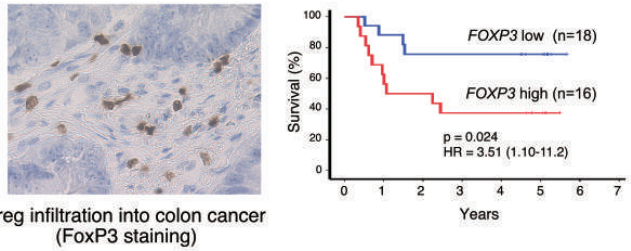
Tregs and self-tolerance

Regulatory T cells (Tregs) have an important role in discriminating between self and foreign antigens for immune cells. They are responsible for preventing autoimmunity, and their dysfunction is associated with autoimmune diseases like arthritis. At the same time, evidence has shown that they infiltrate into tumors and deflect away an effective immune response against cancer cells. Thus, the strategy to control Treg activity is of strong medical interest.

Tregs can be identified most reliably by the expression of the transcription factor FOX3. Tregs can be further divided based on the expression level of FOX3 and surface receptors into subpopulations with different functions. Continuing research in the Shimon Sakaguchi lab has shown particular Treg subpopulations that infiltrate cancer cells can be used for predicting prognosis. The investigation also identified cytokines that could alter the subpopulations to favorable ratios for better prognosis.

Other work has shown that CTLA-4, which is highly expressed in Tregs, is essential for Treg function. Its conditional deletion specifically in Tregs resulted in fatal autoimmune disease while it enhanced tumor immunity. The study is in progress to differentially control autoimmunity and tumor immunity via targeting Tregs.

Reference: Saito T, Nishikawa H, Wada H, Nagano Y, Sugiyama D, Atarashi K, Maeda Y, Hamaguchi M, Ohkura N, Sato E, Nagase H, Nishimura J, Yamamoto H, Takiguchi S, Tanoue T, Suda W, Morita H, Hattori M, Honda K, Mori M, Doki Y, & Sakaguchi S. Two FOXP3+CD4+ T-cell subpopulations distinctly control the prognosis of colorectal cancers. ***Nature Med.*** 2016 Jun;22(6):679-84.



Tumor infiltration of FOXP3+ Tregs indicate poor prognosis.

Tadamitsu Kishimoto
Immunology Frontier Research Center

Understanding of IL-6-associated inflammatory disease

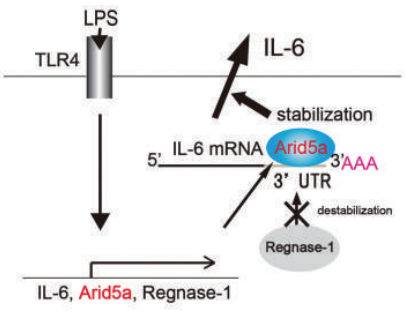
IL-6 is a pluripotent cytokine, which is responsible for host defense, and whose dysregulation is associated with a wide range of diseases. Anti-human IL-6 receptor monoclonal antibody tocilizmab is a blockbuster drug for inflammatory diseases such as rheumatoid and juvenile arthritis. Since continuously secreted IL-6 is often associated with inflammatory disease, further understanding of the factors involving in IL-6 expression can promote the clarification of its pathogenesis.

Arid5a is an RNA-binding protein that stabilizes the mRNA of IL-6. Its deficiency has led to lower IL-6 levels in a mouse model of multiple scrlerosis. In addition, modulating Arid5a levels has been shown to switch helper T cell behavior from pro-inflammatory to anti-inflammatory by destabilizing the mRNA of STAT3, whose activation is dependent on IL-6.

Consistent with its role in diseases, mice in which Arid5a was knocked out show a resistance to a number of ailments. These mice were protected from endotoxin shock that caused an increase in serum levels of IFN-γ, which along with IL-6 is a pro-inflammatory cytokine. Preliminary study has also indicated knockout mice are less susceptible to pulmonary fibrosis.

A deeper investigation has identified key functions in the regulation of Arid5a expression. When its protein levels come at peak, Arid5a protein is phosphorylated and ubiquitinated, which in turn promotes its protein degradation. Understanding the regulation of gene expression of Arid5a and proteins levels can be useful for the treatment of chronic inflammatory disease.

Reference: Masuda K, Ripley B, Nyati KK, Dubey PK, Zaman MM, Hanieh H, Higa M, Yamashita K, Standley DM, Mashima T, Katahira M, Okamoto T, Matsuura Y, Takeuchi O, Kishimoto T. Arid5a regulates naive CD4+ T cell fate through selective stabilization of Stat3 mRNA. ***J. Exp. Med.*** 2016 Apr 4;213(4):605-19.



Arid5a may play an important role in autoimmune disease through control of IL-6 levels in vivo.

Shigekazu Nagata
Immunology Frontier Research Center

Flippases and scramblases

Phosphatidylserine (PtdSer) is exclusively localized in the inner leaflet of eukaryotic plasma membranes. This asymmetrical distribution of PtdSer is maintained by an ATP-dependent flippase that translocates PtdSer from outer to inner leaflets.

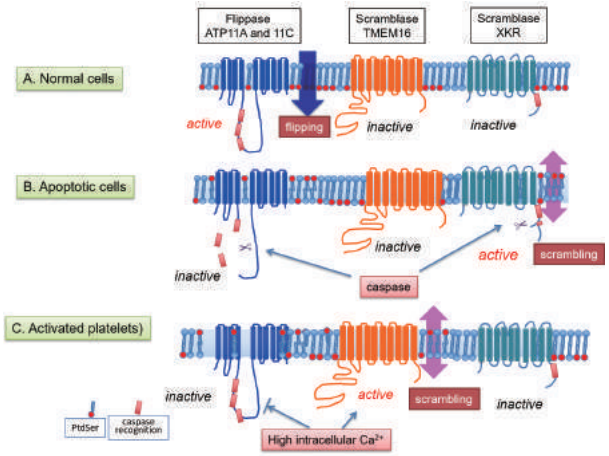
When cells undergo apoptosis, or platelets are activated, the asymmetrical distribution of PtdSer is disrupted by a scramblase that non-specifically scrambles phospholipids between the leaflets. PtdSer, thus exposed to the cell surface, works as an "eat me" signal of apoptotic cells, and as scaffolds on activated platelets for clotting factors.

Nagata's group identified two P4-type ATPases as flippases, five TMEM16 family members as Ca^{2+}-dependent scramblases, and three Xkr family members as caspase-activated scramblases.

Patients of Scott syndrome, a rare congenital bleeding disorder, carry mutation in a member of TMEM16, and their platelets cannot expose PtdSer, leading to the reduced thrombin production for blood clotting.

When cells undergo apoptosis, the P4-ATPases are destroyed by proteases called caspase. At the same time, a member of the Xkr family is cleaved by caspase and functions as a scramblase. PtdSer, thus exposed on the dead cell's surface, is recognized by macrophages for engulfment. If this process does not proceed properly, dead cells are not cleared from our bodies, and activate the immune system, leading to autoimmune disease.

Reference: Nagata, S., Suzuki, J., Segawa, K., and Fujii, T. Exposure of phosphatidylserine on the cell surface. ***Cell Death Differ.*** 2016 Jun;23(6):952-61.



Flippase and Scramblase. In normal cells, flippases translocate phosphatidylserine (PtdSer) from outer to inner leaflets to confine PtdSer to the inner leaflet. Caspase in apoptotic cells or a high concentration of Ca^{2+} in activated platelets inactivates flippase, and activates scramblase, causing the quick PtdSer-exposure to the cell surface.

Mucosal Immunology

Kiyoshi Takeda
Graduate School of Medicine

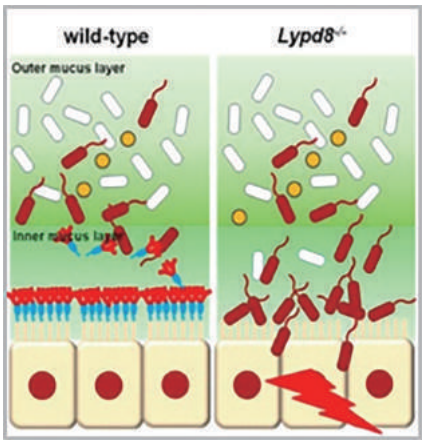
Bacteria-free zones in the intestine

The intestine by its very nature is exposed to a large number of microbes. The high potential for infection is mitigated by several types of barriers. Two types of mucous layers form one type of barrier by covering the epithelial cells that line the intestine. Bacteria can be found in the outer layer, but not in the inner layer. Indeed, function of the inner layer associates with intestinal inflammation such as colitis.

Researchers have identified specialized cells in the small intestine that secrete anti-microbial peptides to separate bacteria from the epithelial cells, but no comparable cell type is known in the large intestine. It therefore remains unknown if the large intestine operates by a similar or distinctive method as the small intestine.

The Kiyoshi Takeda lab has discovered the Ly6/Plaur domain containing 8 (Lypd8) protein is highly and selectively expressed in the large intestine and that its deficiency in mice compromises the bacteria-free space layering the epithelia allowing invasion of intestinal bacteria. The invasion was made by Gram-negative rod bacteria, which possess multiple flagella. Lypd8 was found to preferentially bind to the flagella to suppress the motility of the bacteria, thereby contributing to the maintenance of intestinal homeostasis.

Reference: Okumura R, Kurakawa T, Nakano T, Kayama H, Kinoshita M, Motooka D, Gotoh K, Kimura T, Kamiyama N, Kusu T, Ueda Y, Wu H, Iijima H, Barman S, Osawa H, Matsuno H, Nishimura J, Ohba Y, Nakamura S, Iida T, Yamamoto M, Umemoto E, Sano K, Takeda K. Lypd8 promotes the segregation of flagellated microbiota and colonic epithelia. ***Nature*** 2016 Apr 7;532(7597):117-21.



Ly6/PLAUR domain containing 8 (Lypd8), which is a highly glycosylated GPI-anchored protein, is highly and selectively expressed in epithelial cells on the uppermost layer of the intestinal gland and shed into the intestinal lumen. Lypd8 inhibits intestinal bacterial invasion of the colonic mucosa by binding to the intestinal bacteria, and thereby regulates the intestinal inflammation.

Immunopathology

Atsushi Kumanogoh
Graduate School of Medicine

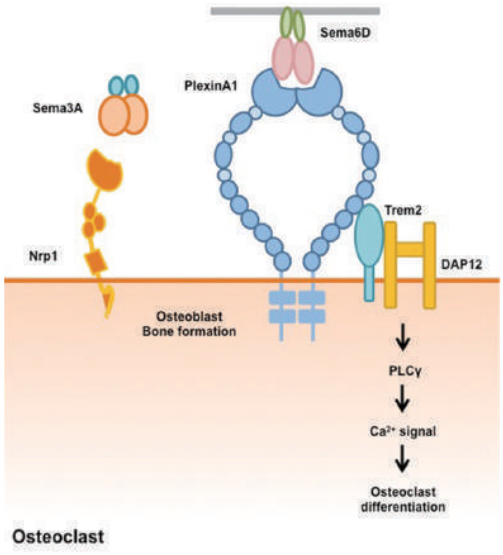
Semaphorins and immune diseases

Semaphorins were originally described as proteins that contribute to axon guidance, but have since been found to have far more versatile roles in multiple systems. In immunity, semaphorins have been found to influence immune cell interactions, activation and differentiation. Furthermore, they have diagnostic and therapeutic potential. Class IV semaphorins show promise because of their roles in the differentiation of cytotoxic T cells and helper T cells. Accordingly, the Atsushi Kumanogoh lab has been investigating the molecular mechanisms through which these semaphorins operate.

Although it has been established that mTOR signaling regulates helper T cell activity, it was only recently shown by the lab that mTOR signaling regulates cytotoxic T cells in a Sema4A-dependent manner. Mice deficient of Sema4A had dysfunctional mTOR signaling, which could be ameliorated with treatment of recombinant Sema4A protein. The same study showed that among plexins, which along with neuropilin is the main receptor for semaphorins, plexin B2 is the functional receptor for this effect.

Sema4A may also be useful as alternative treatment for multiple sclerosis patients resistant to standard IFN-β therapy. Treatment in mice with a monoclonal antibody for Sema4A may indicate a promising alternative target. Similarly, Sema4D is associated with rheumatoid arthritis, and mice treated with an antibody against Sema4D showed reduced inflammation.

Reference: Kimura T, Nada S, Takegahara N, Okuno T, Nojima S, Kang S, Ito D, Morimoto K, Hosokawa T, Hayama Y, Mitsui Y, Sakurai N, Sarashina-Kida H, Nishide M, Maeda Y, Takamatsu H, Okuzaki D, Yamada M, Okada M, Kumanogoh A. Polarization of M2 macrophages requires Lamtor1 that integrates cytokine and amino-acid signals. ***Nature Commun.*** 2016 Oct 12;7:13130.



Masahiro Yamamoto
Research Institute for Microbial Diseases

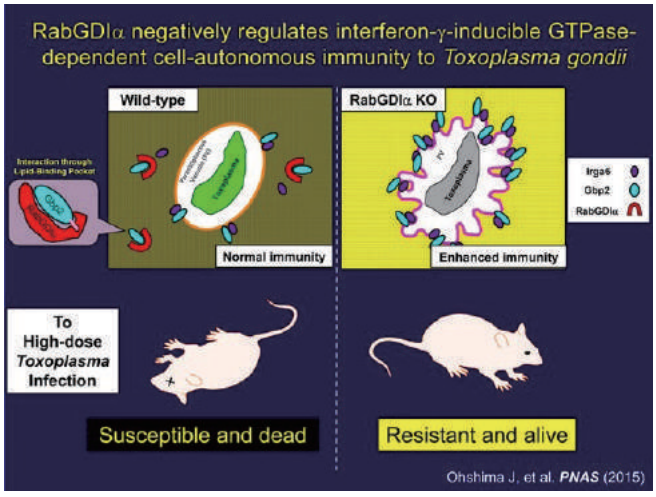
Immunity against toxoplasmosis

IFNγ is an essential cytokine for both the innate and adaptive immune systems. It induces a number of proteins, including GTPases, which in turn suppress the replication of viruses and vacuole formation of bacteria. Another target of IFNγ-induced GTPases is the parasite *T. gondii*, which is the cause of toxoplasmosis, which can have severe effects in patients suffering from diseases with weakened immune systems such as AIDS.

Crucial for the survival of *T. gondii* in a host cell is the formation of the parasitophorous vacuole, a structure that is disrupted by IRGs and GBPs, two specific types of IFNγ-induced GTPases. However, little is known about the signals that recruit these molecules to the PV, including those that negatively regulate the recruitment.

RabGDIα, a GTPase inhibitor, binds with GBP2 to prevent the latter from acting out their immune function against *T. gondii*. Its absence in mice led to stronger resistance against increasing doses of *T. gondii* infection. This effect was the result of higher levels of recruitment to parasitophorous vacuoles of both GBPs and IRGs, the latter of which was dependent on GBP activity. The discovery of RabGDIα as a negative regulator for GTPase interaction with *T. gondii* provides a possible therapeutic target against infection.

Reference: Ohshima J, Sasai M, Liu J, Yamashita K, Ma JS, Lee Y, Bando H, Howard JC, Ebisu S, Hayashi M, Takeda K, Standley DM, Frickel EM, Yamamoto M. RabGDIα is a negative regulator of interferon-γ-inducible GTPase-depen dent cell-autonomous immunity to Toxoplasma gondii. ***PNAS*** 2015 Aug 18;112(33):E4581-90



Masaru Ishii
Graduate School of Frontier Biosciences

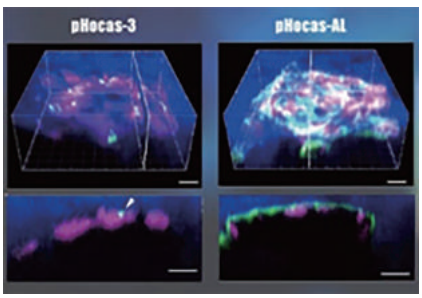
Controlling bone production

Innovations in microscopy now allow scientists to watch molecular and cellular events in a live body in real time. These observations have given a whole new understanding of the dynamics of multiple cellular systems, including bone development and immune responses. Intravital multiphoton microscopy suffers from less scattering and phototoxicity than other microscopy systems, making it a preferable system for studying animal bodies.

The Masaru Ishii lab has created an intravital multiphoton microscopy that they used to observe osteoclasts migrating and functioning in mice. Osteoclasts are responsible for bone resorption, but although several signaling molecules and receptors had been previously identified, how osteoclasts interact with bone had never been directly visualized. The researchers found that osteoclasts could be divided into two groups based on their motility. Less motile osteoclasts strongly adhered to and devoured bone, whereas more motile osteoclasts had less affinity for bone and circulated until bone destined for resorption was encountered, causing a change in the osteoclast state. New molecular probes made by the collaboration with the Kazuya Kikuchi lab at the Graduate School of Engineering have allowed for spatio-temporal quantification of the osteoclast activity, including morphological changes and molecular fluctuations. These findings have provided a more precise description of the different states.

These studies have led to the discovery that RANKL promotes switching to the less motile state, and that a subpopulation of Th17 cells expressed RANKL, providing a potential mechanism for bone inflammation. RANKL was also found to promote a metabolic shift to oxidation that caused osteoclast differentiation and an increase in SAM production. This finding revealed Dnmt3a has an important role in bone loss, and Dnmt3 deficiency results in higher bone mass in mice. This mechanism could be a therapeutic target for bone disorders.

Reference: Maeda H, Kowada T, Kikuta J, Furuya M, Shirazaki M, Mizukami S, Ishii M, Kikuchi K. Real-time intravital imaging of pH variation associated with cell osteoclast activity and motility using designed small molecular probe. ***Nature Chem. Biol.*** 2016 Aug; 12(8):579-85.



Tamotsu Yoshimori
Graduate School of Medicine/
Graduate School of Frontier Biosciences

Autophagy

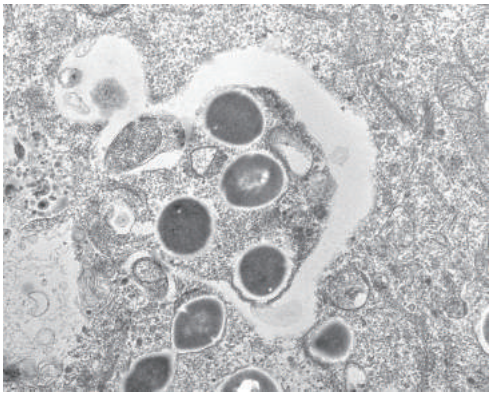
Autophagy describes an elaborate system that traffics bulk components inside a cell for degradation or recycling. It is essential for homeostasis, which is why it requires strict regulation. Indeed, over the years in increasing number of diverse diseases have been attributed to dysfunction in autophagy. The Tamotsu Yoshimori lab is investigating key molecular events that control autophagy.

Necessary for autophagy is the formation of the autophagosome, a double membrane structure that surrounds the content to be processed. The autophagosome then transports the material to and binds with a lysosome. From where inside the cell the double membrane is formed has remained in dispute. Imaging experiments by the lab have shown conclusively that the autophagosome first appears at contact sites between the endoplasmic reticulum and mitochondria.

This and other recent discoveries by the lab have identified new proteins that play large roles in autophagy. In the past couple of years, for example, the lab found that INPP5E regulates fusion between the autophagosome and lysosome, most likely by stabilizing actin filaments that connect the two structures. A new signaling pathway dependent on Syntaxin17 for the formation of autophagy was reported. Finally, Rubicon, a factor thought to play a role in late-stage autophagy, was found to be associated with liver diseases due to dysfunctional autophagy.

These results suggest that controlling autophagy could have therapeutic applications. Accordingly, the lab is investigating the role of autophagy in obesity-related diseases like diabetes and in the population of misfolded proteins, like those common to Alzheimer's and Creutzfeldt-Jakob disease.

Reference: Hasegawa J, Iwamoto R, Otomo T, Nezu A, Hamasaki M, Yoshimori T. Autophagosome-lysosome fusion in neurons requires INPP5E, a protein associated with Joubert syndrome. ***EMBO J.*** 2016 Sep 1;35(17):1853-67.



Autophagosome engulfs bacteria invading cells

Sachiko Tsukita
Graduate School of Medicine/
Graduate School of Frontier Biosciences

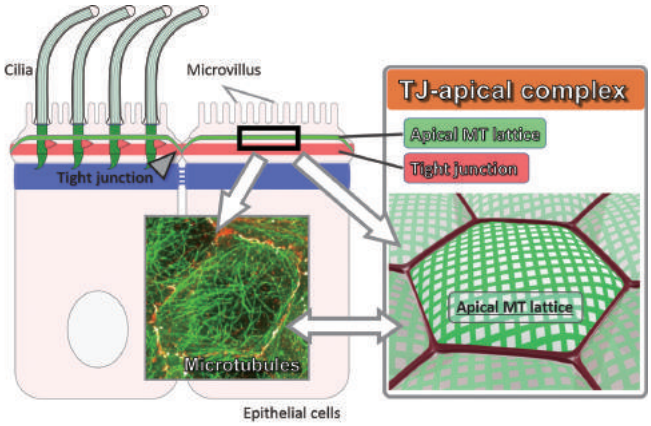
Tight junctions and biological systems

Tight junctions (TJs) are cell-cell adhesions that physically connect different cells to form epithelial cell sheets. They serve a number of functions, including the creation of a paracellular barrier between cells. These barriers can include pores, such as paracellular channels for ions and solutes, which represent a new category of biological channels. TJs serve a number of functions as an organizing center for extra- and intra-cellular events in biological systems. In particular, this group recently discovered a specific cytoskeletal structure linked to TJs, and defined it as the "TJ-apical complex." TJs and this complex are proposed to regulate the functions of TJs, apical membranes, and biological systems.

The main component of TJs, claudin, is a large family of proteins with at least 27 members in humans and mice. Claudins are the major component of paracellular barriers and channels. In early work, this lab isolated the TJ fractions in association with apical membranes, which led to the discovery of many TJ components, including claudin, other membrane proteins such as occludin and tricellulin, and cytoskeletal proteins such as ZO1. The Sachiko Tsukita lab has identified and investigated the molecular aspects of claudins and other TJ proteins, and the functions of TJ-based biological systems, the disorders of which lead to various disease states, including disordered metabolism, gastrointestinal tract inflammation, and atopic dermatitis.

This group has recently identified the "TJ-apical complex" and focused on its roles in epithelial morphogenesis and biological systems by exploring the responsible proteins for it. Collectively, these studies will reveal new structural and functional aspects of TJ-based epithelial cell sheets in flexible and complex biological systems.

Reference: Herawati E, Taniguchi D, Kanoh H, Tateishi K, Ishihara S, Tsukita S. 2016. Multiciliated cell basal bodies align in stereotypical patterns coordinated by the apical cytoskeleton. ***J. Cell Biol.*** 2016 Aug 29;214(5):571-86.



Toshihiro Horii
Research Institute for Microbial Diseases

Vaccines for malaria

Malaria is not a common disease in Japan, but as the most common parasite-borne disease in the world and the cause of a half million deaths annually, the government has recognized that research in this field will make a large global impact. One of the leaders in the field is Toshihiro Horii, whose group is developing a vaccine for tropical malaria along with the mechanism of the malaria infection and evasion from host immune system.

The malaria pathogen is able to evade the immune system through vast polymorphisms and redundant functions in its proteins. Collaborations have collected a large and diverse set of isolates of Plasmodium falciparum, providing study on the genetic diversity of serine repeat antigens 5 (SERA5) and inroads on vaccines. Studies in models of several animal species have demonstrated that experimental vaccines can promote antibodies against SERA that inhibit growth of the parasite. These studies have led to clinical trials for a vaccine that includes SE36 protein and reported good efficacy, especially in children.

Reference: Yagi M, Palacpac NM, Ito K, Oishi Y, Itagaki S, Balikagala B, Ntege EH, Yeka A, Kanoi BN, Katuro O, Shirai H, Fukushima W, Hirota Y, Egwang TG, Horii T. Antibody titres and boosting after natural malaria infection in BK-SE36 vaccine responders during a follow-up study in Uganda. ***Scientific Reports*** 2016 Oct 05;6:34363

The vaccine was produced under GMP (Good Manufacturing Procedure) conditions at the Kanonji Institute of the Research Foundation for Microbial Diseases of Osaka University.

Yoshiki Sawa
Graduate School of Medicine

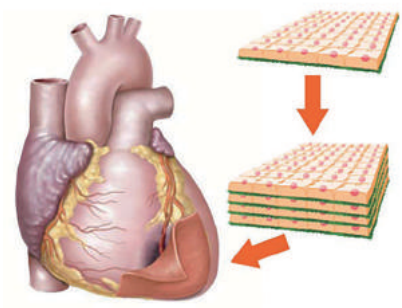
Stem cell therapies for heart failure

Heart disease remains the number one cause of death in industrial countries. Patients can be treated with drugs or implanted devices, but in the most severe cases, new heart tissue, typically from a transplant, is needed. The lack of donors has pushed forward cell regeneration research for the creation of cardiac tissue.

The Yoshiki Sawa lab is using stem cells to produce cardiac sheets for surgical treatment. The sheets are grafted over the damaged areas of the heart and have been shown to recover cardiac function. This strategy involves preparing skeletal myoblast cells from the patient into sheets ready for transplantation. Already, several patients have benefited from this technology, but the number of cells available for treatment remains low and the molecular mechanisms that lead to the recovery remain controversial. It is possible the transplanted cells do not replace the dead cells, but rather stimulate the secretion of regenerating factors. Discovery of these factors could lead to new pharmaceutical therapies and potentially avoid the risky and traumatic nature of transplantation.

It is for this reason that the same experiments are being tested with induced pluripotent stem cells (iPSCs). These cells can be prepared from blood cells, which means they can be acquired through blood donors, and then differentiated into various heart cell types. iPSC-derived cardiomyocytes have already shown good outcomes in mouse and pig models. However, the creation of iPS cells requires manipulation of the genome, which risks cancerous and other deleterious effects. Therefore, exhaustive safety evaluation is necessary before any of their products can be used for clinical therapies. However, because they can be acquired in principle from blood donations, confirmation of their safety would in principle suggest patients now on waiting lists for new hearts only need a matching blood donor.

Reference: Kawamura T, Miyagawa S, Fukushima S, Maeda A, Kashiyama N, Kawamura A, Miki K, Okita K, Yoshida Y, Shiina T, Ogasawara K, Miyagawa S, Toda K, Okuyama H, Sawa Y. Cardiomyocytes Derived from MHC-Homozygous Induced Pluripotent Stem Cells Exhibit Reduced Allogeneic Immunogenicity in MHC-Matched Non-human Primates. ***Stem Cell Reports*** 2016 Mar 8;6(3):312-20.



Natural Science

Michio Murata
Graduate School of Science

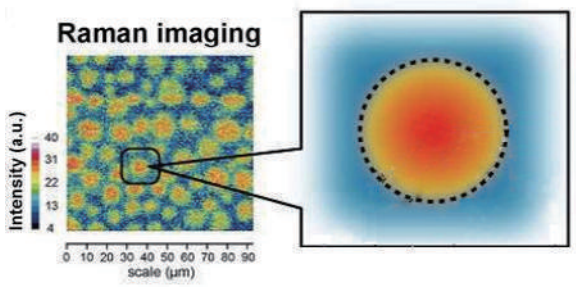
Observing the cell membrane in action

The cell membrane is an arbiter that determines how the cell interacts with its environment. Understanding how membrane components and structures respond to environmental signals is crucial for understanding how a cell adapts to changes in its environment. The Michio Murata lab has been using various spectroscopy modalities to study the dynamics of membranes.

Lipid rafts are self-assembling structures in the membrane that regulate a number of phenomena, such as signal transduction and protein shuttling. They are also considered the entry point for a number of pathogens, including HIV. Lipid rafts consist of sphingomyelin and cholesterol, but little is known about how these lipids self assemble. The lab has been using NMR spectroscopy to study how these two lipids interact in order to form lipid rafts. Studies have identified key moieties in the molecular structure and different domains that have challenged standard models, which have depended on bulky fluorophores that could have steric effects on the interactions.

Many antibiotics and antifungal agents form ion channels in the membrane by interacting with cholesterol and other lipids. The lab has been using the above technologies to investigate the dynamics behind the formation of these pores and using these findings to develop compounds with stronger therapeutic effects.

Reference: Ando J, Kinoshita M, Cui J, Yamakoshi H, Dodo K, Fujita K, Murata M, Sodeoka M. Sphingomyelin distribution in lipid rafts of artificial monolayer membranes visualized by Raman microscopy. ***PNAS*** 2015 Apr 14;112(15):4558-63.



Akira Harada
Graduate School of Science

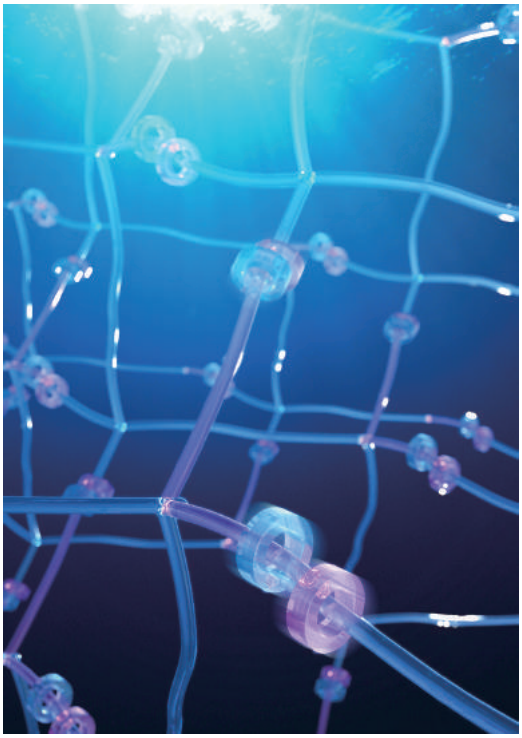
Smart Materials

Biological materials show intelligence in that they adapt to their environments in order to maintain or enhance function. Synthetic material with similar intelligence would make the material more robust and longer lasting. Such adaptivity is possible in supramolecular materials that show molecular recognition through host-guest interactions.

For this purpose, the Akira Harada lab is using cyclodextrin, a ring-shaped oligosaccharide that is ideal for host-guest interactions with hydrophobic molecules. Cyclodextrin can be assembled into a macromolecular structure in which ring structures of the cyclodextrin molecule are assembled along an axle. The ring can then physically move along the axle to adapt to stimuli (physical response). Furthermore, the hydrocarbon nature of cyclodextrin and its guests allows for noncovalent bonding, which permits reversible interactions (chemical response).

Taking advantage, the lab has prepared smart materials that respond to various stimuli including but not limited to light, pH, and temperature with self-assembly, self-healing, and actuation. The combination of physical and chemical responses allows the material to exercise these capabilities in both wet and dry states.

Reference: Iwaso K, Takashima Y, Harada A. Fast response dry-type artificial molecular muscles with [c2]daisy chains. ***Nature Chem.*** 2016 Jun;8(6):625-32.



Toshio Yanagida
Graduate School of Frontier Biosciences

Biological principles for ultra-energy saving

Go-playing Artificial Intelligence (AI) AlphaGo (Google DeepMind), which recently beat a world-class player Lee Se-dol, uses 200,000 Watts. While, human brains are estimated to use only 1-20 Watts based on brain temperature measurements. The Toshio Yanagida lab endeavors to understand what accounts for this vast difference. First, his team developed single molecule nano-technology to study biological molecular machines such as molecular motors and cellular signaling networks. Results from these studies clearly indicate that, biological machines harness thermal noise for function, additivity and flexibility. This is in sharp contrast to man-made machines, such as AI, that must filter noise from the signal for function, which uses a large amount of energy. Furthermore, the Yanagida lab studies emergent recognition of visual objects hidden in degraded figures. The rate of recognition was expressed by a simple equation equivalent to the Arrhenius equation, suggesting that recognition is caused by spontaneous fluctuation. Actually, fMRI measurements of brain activity indicate that the human brain evokes several possible answers and searches by spontaneous fluctuation before recognition. Based on these results, Yanagida argues that a common principle using fluctuation (noise) works from molecular machine to human brain for ultra-energy saving. Now, in collaboration with industry partners, this principle is to be applied to control of complex computer networks and so far has shown 100X energy savings in simulations.

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1) Nishikawa S, Arimoto I, Ikezaki K, Sugawa M, Ueno H, Komori T, Iwane AH, Yanagida Switch between large hand-over-hand and small inchworm-like steps in myosin VI. ***Cell*** 2010 Sep 17;142(6):879-88.
2) Karagiannis P, Ishii Y, Yanagida T. Molecular machines like myosin use randomness to behave predictably. ***Chem. Rev.*** 2014 Mar 26;114(6):3318-34.
3) Fujita K, Iwaki M, Yanagida T. Transcriptional bursting is intrinsically caused by interplay between RNA polymerases on DNA. ***Nature Commun.*** 2016 Dec 7; 7:13788.

Keiichi Namba
Graduate School of Frontier Biosciences

Structure and function of nanomachines

To an engineer, the biological body is a miraculous energy transducer that inputs the chemical energy of food to output the mechanical energy of movement. This ability is crucial for survival and is fundamental to evolution, as even single cell organisms possess the capacity to transduce energy at extremely high efficiency. In many ways, this ability makes nature a model for the construction of energy efficient machines.

One of the most basic of these biomachines is the flagellar motor. The flagellum appears in prokaryotes and eukaryotes and is essential for mobility, allowing a cell to move from an area of low nutrition to one of high nutrition. Although nanoscopic in size, the flagellar motor has a remarkable number of components that coordinate to convert the energy expired from cation translocation across the cell membrane into motility.

The Keiichi Namba lab is using a number of molecular imaging technologies, such as x-ray diffraction and cryoelectron microscopy, to study the structure-function relationship in the flagellar and actomyosin motors. Of particular interest are questions that ask how the component proteins self assemble, how they coordinately conform for the energy transduction, and how they achieve such remarkable dynamic feats, as a flagellar motor can utilize energy of an extremely low level as low as that of thermal noise for directional motions.

Answering these questions is expected to provide a new paradigm for the design of future nanotechnologies.

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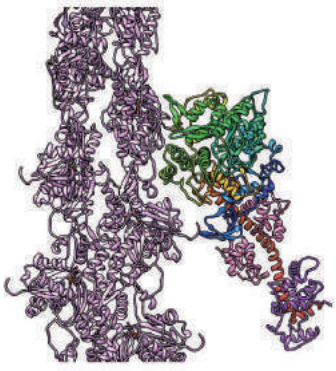
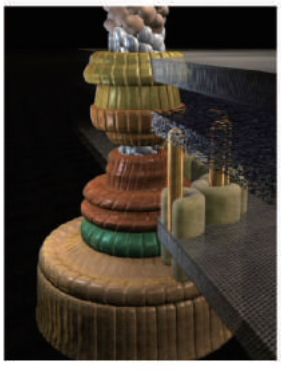
1) Fujii T. and Namba K. Structure of actomyosin rigor complex at 5.2-Å resolution and insights into the ATPase cycle mechanism. ***Nature Commun.*** 2017 Jan 09;8.13969.
2) Fujii T, Kato T, Hiraoka K, Miyata T, Minamino T, Chevance F, Hughes K, Namba K. Identical folds used for distinct mechanical functions of the bacterial flagellar rod and hook. ***Nature Commun.*** 2017 Jan 25;8.14276.





Takeharu Nagai
The Institute of Scientific and Industrial Research

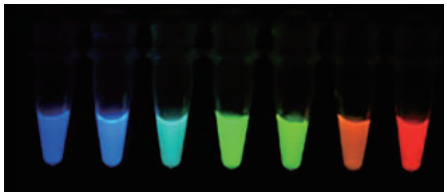
Watching molecules in action inside a cell

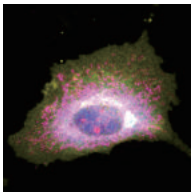
Molecular events inside a cell can have tremendous impact on the function of an entire body. An increase in the production of one protein could be enough to trigger a series of events that signal a cell to grow, multiply or die. Bio-imaging technologies have made it possible to watch molecular events inside a living body in real time.

These technologies depend on probes that release light in response to specific activity inside a cell. However, current probes are disruptive to the cell or demand complicated optical setup for the microscopy, thus limiting the number of molecular events observable.

The Takeharu Nagai lab has been innovating new technologies that relax these limitations. For example, they have developed a fast photoswitchable fluorescent protein that allows biocompatible superresolution imaging in living cells. On the other hand, they have also developed bioluminescent probes such as Nano-lantern and LOTUS-V enabling bioimaging in conjunction with optogenetic manipulation of cellular functions. The lab has also reported novel microscopy systems including a light absorption microscope and a fluorescence polarization microscope, which could measure absorption spectrum of non-labeled cell and multiple cellular functions reported by homo-FRET probes expressing in live cells, respectively.

Reference: Nakano M, Arai Y, Kotera I, Okabe K, Kamei Y, Nagai T. Genetically encoded ratiometric fluorescent thermometer with wide range and rapid response. ***PLOS ONE*** 2017 Feb 17;12(2). e0172344.





Tatsuo Kakimoto
Graduate School of Science

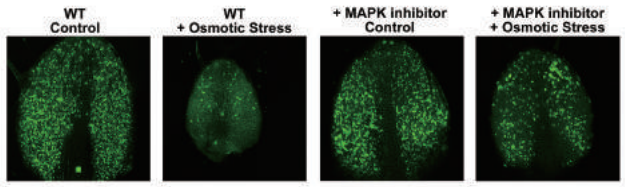
Cytokinenins, hormones for plant growth

Like animals, plants respond to environmental cues to grow. However, whereas animals can move from an area of low resources to one of high resources, plants are immobile and therefore require a larger repertoire for adaptation. Thus, unlike many animals, which have a determined final body shape, such as the number of limbs, the number of leaves and other appendages in plants is much more plastic.

Plant hormones and hormone-like materials mediate internal and environmental signals to regulate growth. The Tatsuo Kakimoto lab is studying biosynthesis, perception, and signal transduction of these signaling molecules. These include the discovery of biosynthetic enzymes and receptors of cytokinins, which are important class of plant hormones, discovery of a number of new peptide hormones, and gene networks that regulate plant development.

These studies are expected to give insights on how to improve crop yields, especially as climate change happens at more rapid and extreme levels.

Reference: Kumari A, Jewaria PK, Bergmann DC, Kakimoto T. Arabidopsis Reduces Growth Under Osmotic Stress by Decreasing SPEECHLESS Protein. ***Plant Cell Physiol.*** 2014 Dec;55(12):2037-46.



Kensuke Kobayashi
Graduate School of Science

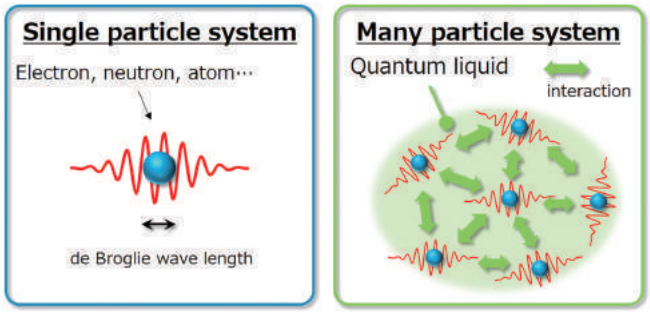
Mesoscopic physics and noise

Recent progress in nanotechnology enables us to directly address quantum transport of electrons in nano-devices made of metal or semiconductor. For example, researchers can control electrons one by one in nano-devices called quantum dots. Also, the wave nature of electrons is accessible in small electron interferometers. The advantage of this research field, namely "mesoscopic physics", lies in the controllability and the versatile degrees of freedom in the device design.

In mesoscopic systems, noise, or non-equilibrium fluctuations, can convey valuable essential information. For example, the Kensuke Kobayashi lab has shown that the noise induced by spin accumulation in spintronic devices is proportional to the spin current. The noise was also used to probe dynamical aspects of the Kondo effect in quantum dots.

Their several studies of noise have provided experimental evidence that further clarifies how electrons transport in mesoscopic systems quantum-mechanically. Recently, the lab for the first time demonstrated the evidence of fluctuation theorem in quantum regime and the universality of quantum liquid in the non-equilibrium regime. These achievements have established that noise is a unique tool to uncover interesting aspects of various nonequilibrium systems.

Reference: Ferrier M, Arakawa T, Hata T, Fujiwara R, Delagrange R, Weil R, Deblock R, Sakano R, Oguri A, Kobayashi K. Universality of non-equilibrium fluctuations in strongly correlated quantum liquids. ***Nature Phys.*** 2016 Nov 23;12:230-35.



Ryosuke Kodama
Graduate School of Engineering

State behavior at extreme conditions

How materials respond to high pressures and temperatures provides insightful information on planetary formation along with being a fundamental issue in condensed matter and other disciplines of physics. Several models that explain the different reactions have been used to predict the different interior structures of planets. However, confirming these theories by recapitulating the conditions in the laboratory requires advanced laser technologies.

Lasers have created pressures of over 100 GPa in experimental settings, but these remain too weak to give the necessary details about the physical processes that must occur. The Ryosuke Kodama lab is studying ways to control of plasma behavior at high laser intensities. This control allows for shock wave compression experiments that achieve unprecedented pressures to subject materials to unique states that could show precise pressures at which phase transitions occur.

Forsterite is a rock-forming mineral common to many planets including earth, and there is large interest in the field on how high-speed collisions of fosterite produce molten layers and magnetic fields. This research has since been extended to dynamically compress iron, which comprises a large part of the core of the earth. These experiments are providing new details about essential phase transition for planetary formations and also the resulting magnetic fields emitted by the planets.

Crucial to these discoveries by the lab is the control of plasma behavior at high laser intensities.

References:
1) Monden Y. and Kodama R. Enhancement of Laser Interaction with Vacuum for a Large Angular Aperture. ***Phys. Rev. Lett.*** 2011 Aug 12;107(7).073602.
2) Sekine T, et al. Shock Compression Response of Forsterite above 250 Gpa. ***Sci. Adv.*** 2016 Aug 2;8.e1600157.
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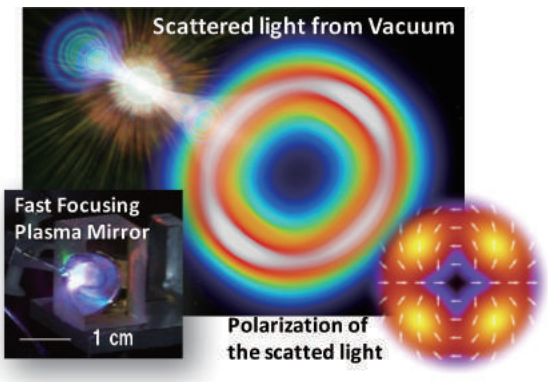


Hiroshi Tsunemi
Graduate School of Science

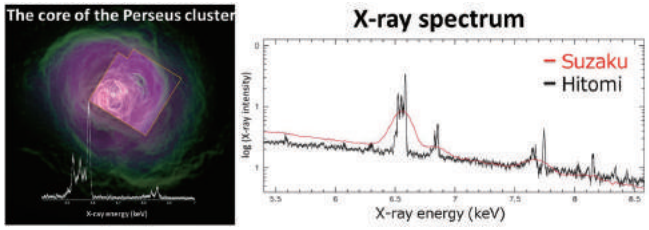
Watching X-rays to watch the universe

Almost all the celestial bodies generate hot plasma producing several millions to hundreds of millions of degrees or more. They usually radiate X-rays with which we can study the dynamics of the universe. The signals, however, are relatively faint, thus cameras with superior sensitivity are required. In addition, these cameras are mounted on flying apparatus, such as balloons and satellites, meaning that they also need to be extraordinary robust.

The Hiroshi Tsunemi lab is building equipment for this purpose. So far, they have been working for Japanese X-ray satellites, including MAXI that is set on the International Space Station. All the instruments are widely used for research whole through the world, studying from stellar flares to galaxies in the distance. In addition, they have described a new type of X-ray interferometer that produces fringes on an X-ray detector from irradiating a parallel x-ray beam on a grating.

The latest satellite, Hitomi, was launched in 2016. It was unfortunately lost in one month in orbit. JAXA decided to re-start a new project to recover it. Since it should be prepared as soon as possible, they will again concentrate on the re-production of the camera.

Reference: The Hitomi collaboration. The quiescent intracluster medium in the core of the Perseus cluster. ***Nature*** 2016 Jul 07;535:117-121.



Engineering

Minoru Asada
Graduate School of Engineering

Hiroshi Ishiguro
Graduate School of Engineering Science

Robot empathy [1]

The self-other relationship is the basis of all our social interactions. Understanding how the brain translates its sensory stimuli into awareness of the self and the other is essential for building empathetic robots. Robots offer an excellent way to model how empathy and other social behavior develop, because unlike an animal model, the robot can be reset. Cognitive developmental robotics aims at understanding human cognitive developmental processes by utilizing synthetic or constructive approaches [2]. Minoru Asada, as a pioneer in this research field, joined the study investigating brain behavior in different social contexts and attempts to apply them to the construction of new robotics. His current project entitled "Constructive developmental science based on understanding the process from neuro-dynamics to social interaction" focuses on the artificial empathy as a symbolic goal of the project.

Awareness of the self begins at the very early stages of infancy, which are also the most difficult to study, because of the infant's inability to communicate. Moreover, this period determines a great deal about social behavior for the rest of the child's life. Robotics provides an attractive model for studying infant cognitive development, especially for irregularities that can lead to cognitive disorders like autism. His joint team has recently reported distinctive brain activities in autistic kids when non-verbally interacting with their mothers.

One way in which infants show this awareness is through mimicry (smiling is one example). Therefore, the lab is also creating computational models that convert social perception into motor mimicry. By incorporating models of infant social cognition, the lab aims to produce algorithms that enhance human-robot interactions.

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1) Asada M. Towards artificial empathy. ***Int. J. Soc. Robot.*** 2015 Feb;7(1):19-33.
2) Asada M, Hosoda K, Kuniyoshi Y, Ishiguro H, Inui T, Yoshikawa Y, Ogino M, Yoshida C. Cognitive developmental robotics: a survey. ***IEEE TAMD.*** 2009 May;1(1):12-34.

Baby robot "Affetto"

Android Science

Social interactions are essential to well being, and there is increasing awareness that social isolation can have severe effect on one's health. This isolation is more likely to happen in people with social disorders, exasperating the problem. The Hiroshi Ishiguro lab is developing anthropomorphic robots that can be used both to study and treat these populations.

The lab has combined neural modeling of social behavior with advanced robotics to mimic human interactions. Human-robot interactions are rarely engaging, because the user is unable to perceive the intention of the robot. The lab is therefore studying social cues from which the robot can engage in verbal and non-verbal interactions that the user finds fulfilling and worth sustaining. These robots are so adept at mimicking human behaviors, including minute details in facial expressions, that they have been used as performers in theatre.

The lab is finding that providing empathetic interactions to isolated individuals can enhance not only the latter's health, but also creativity and confidence, helping the individual contribute positively to his or her community. Furthermore, the ability to program empathetic robots is contributing to understanding the mental cognition involved in interpersonal relationships.

Reference: Mahzoon H, Yoshikawa Y, Ishiguro H. Social skill acquisition model through face-to-face interaction: local contingency for open-ended development. ***Front. Robot. AI.*** 2016 Mar 24.3(10).

Masahiro Miura
Graduate School of Engineering

Naoto Chatani
Graduate School of Engineering

Mamoru Tobisu
Graduate School of Engineering

Cross-coupling reactions

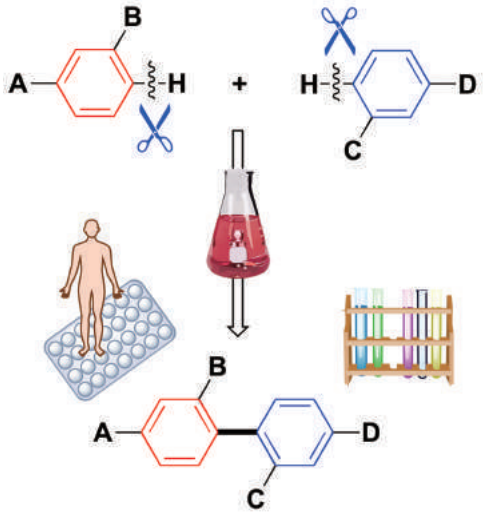
Cross-coupling reactions are used to produce complex organic molecules. Before this Nobel Award winning invention, scientists struggled to synthesize much more than the most basic carbon-based compounds. The invention of cross-coupling reactions using palladium as a catalyst has made a significant impact on the production of a variety of valuable substances including new drugs, agrochemicals and organic electronic materials.

Yet many reactions remain difficult to achieve or require multistep sequences. The Masahiro Miura lab is looking at ways to simplify and cheapen cross-coupling reactions, with particular interest in reducing synthetic steps and waste byproducts in obtaining target molecules.

The group has developed various direct aromatic coupling reactions via carbon-hydrogen bond cleavage, in which the preactivation of reacting substrates such as halogenation and metalation can be avoided, and importantly, the principal byproduct is only harmless water in some cases. The methods allow to efficiently prepare a wide range of electron-conjugated aromatic materials.

Other developments by the lab include new reaction protocols involving the utilization of copper, a relatively cheap metal, as a catalyst. The group has shown that the copper-based direct coupling methods are particularly effective for the synthesis of a variety of nitrogen-containing heterocyclic compounds of interest in the field of medicinal chemistry.

Reference: Miura M, Satoh T, Hirano K. Development of direct aromatic coupling reactions by transition-metal catalysis. ***Bull. Chem. Soc. Jpn.*** 2014; 87(7):751-64.

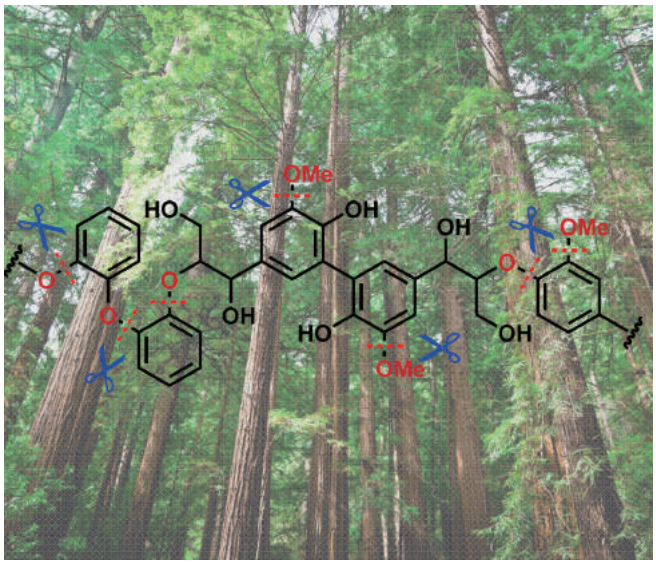


New organic chemistry processes

Benzene-based structures can be found in a wide variety of organic compounds that have pharmaceutical, agricultural and other applications. However, the number of benzene-containing compounds that can be synthesized in the laboratory is limited because of the formation of undesirable byproducts and the high cost. Naoto Chatani and Mamoru Tobisu are currently investigating new cross-coupling processes that are intended to address this problem.

These researchers are using transition metal catalysts to cleave bonds with carbon atoms in molecules (C-H, C-O, etc.) that are normally unreactive. These reactions have been shown to be especially efficient for modifying the sp^2 bonds that are present in benzene moieties. A wide range of products can be synthesized using simple and readily available materials such as hydrocarbons and ethers. In addition, the mechanisms through which these reactions operate are helping to identify essential molecules for these types of reactions and are providing new insights regarding how organic chemical bonds can be exploited to synthesize a larger library of compounds.

Reference: Tobisu M, Takahira T, Morioka T, Chatani N. Nickel-catalyzed alkylative cross-coupling of anisoles with Grignard reagents via C-O bond activation. ***J. Am. Chem. Soc.*** 2016 Jun 1;138(21):6711-4.



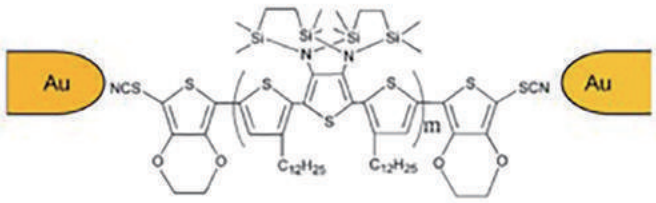
Hirokazu Tada
Graduate School of Engineering Science

Nanocircuits

To the engineer, because molecules can transmit electrical information, they could be used as components in nanocircuits. Their innate energy fluctuations and thermal instability make for a new paradigm in signal processing. Taking advantage, the Hirokazu Tada lab is assembling molecules to construct organic nanosized semiconductors.

Using molecules whose structure and functions are precisely designed, the goals are to gain knowledge related to carrier and spin injection characteristics through the differences in connection modes between non-magnetic and magnetic electrodes and molecules. The group has established a method for controlling carriers and spin injection and transport in a single molecule and derive a design guideline for switching elements.

Reference: See Kei Lee, Tatsuhiko Ohto, Ryo Yamada, and Hirokazu Tada. Thermopower of benzenedithiol and C60 molecular junctions with Ni and Au electrodes. ***Nano Letters*** 2014, 14 (9), 5276–5280.



Yasufumi Fujiwara
Graduate School of Engineering

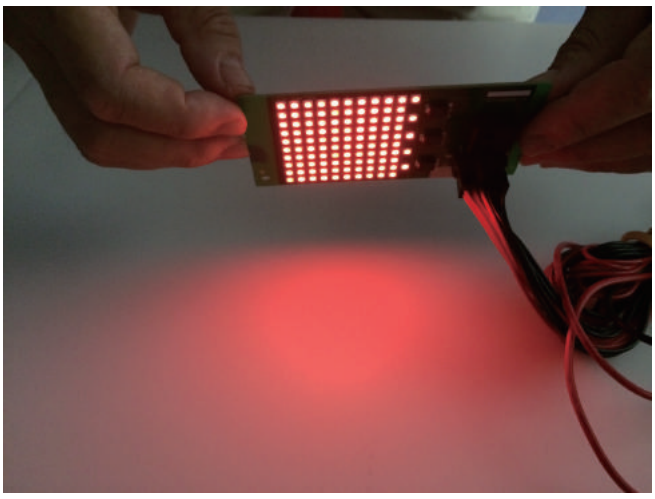
Environmentally Friendly Red LED

Rare-earth doped semiconductors are promising materials for opto-electronic devices. Most LEDs using III-nitride semiconductors have attained high performance at shorter wavelengths in the visible light spectrum, but red light has remained elusive. Adding these longer wavelengths would help realize integrated full-color displays. Europium-doped gallium nitride (GaN:Eu) has the special property of red light emission.

Vital to these applications is the ability to control energy transfer from the excited GaN host to Eu ions. One example is the construction of GaN:Eu structures by organometallic vapor phase epitaxy, which can significantly enhance the emission intensity to levels feasible for monolithic full-color LED displays. This improvement comes from manipulating Eu ion transitions in the intra-4f shell by codoping with impurity ions such as magnesium or oxygen or by embedding GaN:Eu into microcavities that shorten the lifetime of the Eu emission. Experiments observing the temperature dependence of photoluminescence-excitation spectra showed that the thermal dissociation of photogenerated excitons contribute to the energy transfer process. Further study found that the brightness of the red light depended not on radiative transitions but on the excitation of the emission centers.

Continued research on the incorporation, excitation and emission of Eu ions is expected to lead to future light technologies of better brightness and lower energy demands.

Reference: Mitchell B, Timmerman D, Poplawsky J, Zhu W, Lee D, Wakamatsu R, Takatsu J, Matsuda M, Guo W, Lorenz K, Alves E, Koizumi A, Dierolf V & Fujiwara Y. Utilization of native oxygen in Eu(RE)-doped GaN for enabling device compatibility in optoelectronic applications. ***Scientific Reports*** 2016 Jan 4;6:18808.



GaN-based red LED - unique in the world

Masateru Taniguchi
The Institute of Scientific and Industrial Research

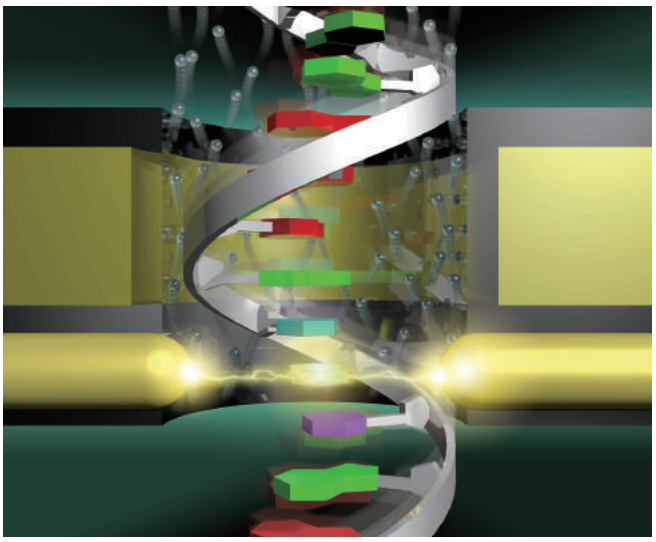
Single molecule sequencing

Single molecule technology has great promise for revealing the function of genes and proteins. This information can then be translated into the creation of drugs and diagnostics.

Next-generation sequencers are continuously resolving the minutest details about nucleic acids, proteins and other fundamental cellular molecules at unprecedented speeds. These gains are in part by exploiting specific properties of the molecules. Using nanoelectrodes, the Masateru Taniguchi lab has demonstrated that electron transport between single nucleotides occurs through tunneling. This feature allows researchers to identify single nucleotides by current measurement only. Furthermore, they are sensitive to post-translational modifications, adding additional information about the epigenome to the data.

Developments in imaging and other photonics have realized single molecule imaging in live cells. These studies have revealed how abnormal function can lead to pathological conditions. However, the resolution limits which phenomena can be detected. Ion channels are often compromised upon infection, but their dynamics is too fast to be analyzed at the single molecule level. The lab has established new nano-sized electromechanical sensors that overcome this problem.

Reference: Tanaka S, Tsutsui M, Theodore H, Yuhui H, Arima A, Tsuji T, Doi K, Kawano S, Taniguchi M, Kawai T. Tailoring particle translocation particle via dielectrophoresis in pore channels. ***Scientific Reports*** 2016 Aug 16;6.31670.



Tsuyoshi Sekitani
The Institute of Scientific and Industrial Research

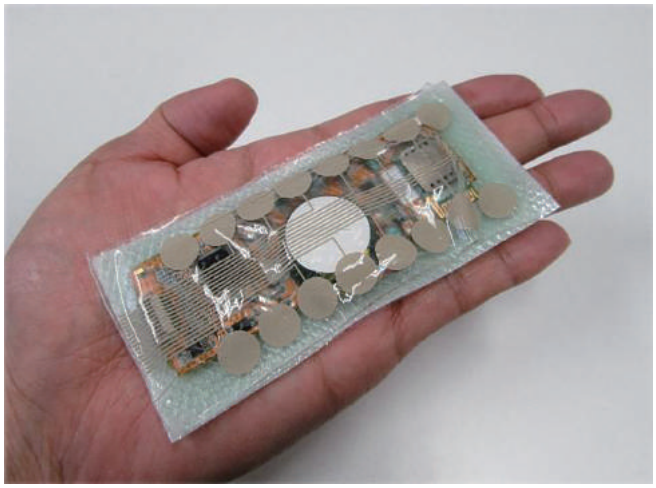
Organic detectors

Many organic materials have flexibility and other features that allow them to adapt to a changing environment. In addition, unlike their inorganic counterparts, they possess a capacity for self-assembly. These features can be incorporated into the design of nanoscopic electronic and photonic devices. Doing so provides not only artificial devices of wider application and superior function, but also gives new insights on molecular and cellular phenomena operating in our body.

This approach has led to a number of new technologies including foldable transistors with fast response time and high heat resistance and been used to detect all sorts of environmental parameters such as moisture, temperature and pressure. Moreover, they can be crumpled like paper and stretched more than twice their length without compromising their function. In terms of patient diagnostics, these sensors are much less invasive. Much of this development is dependent on advances in nanotechnologies like carbon nanotubes that are integrated into elastomers.

The added organic properties of these sensors allows them to function beyond ordinary detection systems by acting as artificial skin that can be used in robotics or medicine. They could even potentially provide sensation to currently imperceptible stimuli, such as magnetoception, which many species use but is absent in humans.

Reference: Sekitani T, Yokota T, Kuribara K, Kaltenbrunner M, Fukushima T, Inoue Y, Sekino M, Isoyama T, Abe Y, Onodera H, Someya T. Ultraflexible organic amplifier with biocompatible gel electrodes. ***Nat Commun.*** 2016 Apr 29;7.11425.



A palm-sized patch-type brain sensor

Tomoo Ushio
Graduate School of Engineering

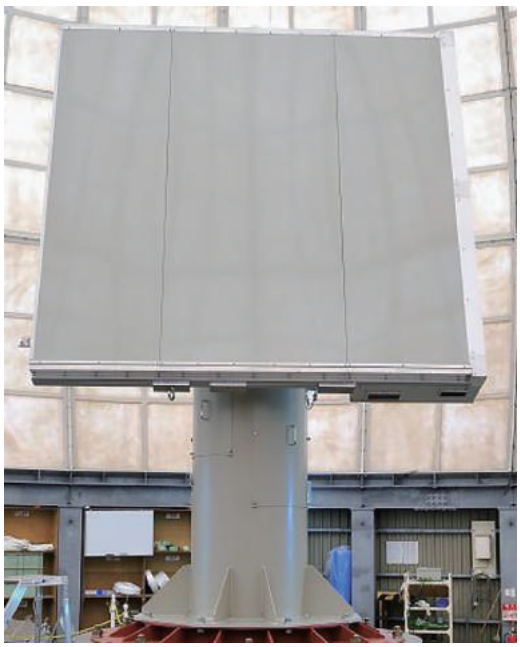
New radar systems for rainfall

With the increase of extreme weather events, demand and need for the prediction of intense thunderstorms are rising. Tomoo Ushio's group is constructing a network of remote devices that detect lightning and rainfall for this purpose.

Examples include the Phased Array Radar (PAR) system, which has superior spatio-temporal resolution to sense the rapid events that often lead to severe thunderstorms. This system is operated by transmitting a broad beam and sharpening the receiving beam on the digital beam forming technique.

The group's technology is also being used for the Global Lightning and sprIte MeasurementS (GLIMS) on the International Space Station to make the first lightning and TLE observations by optical and electromagnetic wave technologies. These measurements are further expected to bring clarity to the relationship between TLE and lightning discharges.

Reference: Miyoshi T, Kunii M, Ruiz J, Lien G-Y, Satoh S, Ushio T, Bessho K, Seko H, Tomita H, Ishikawa Y. "Big data assimilation" revolutionizing severe weather prediction. ***BAMS*** 2016 Aug 31:1347-54.



Atsuko Miyaji
Graduate School of Engineering

Cryptography

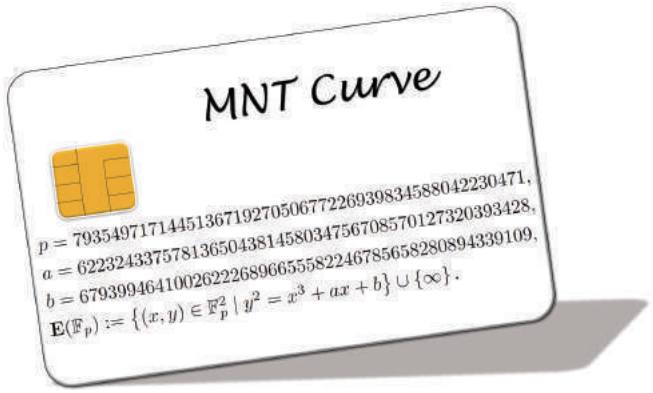
With seemingly the whole world online, information security is of interest to individuals, corporations and entire nations. Accordingly, there has been increasing efforts to build new algorithms and other cryptographic tools. These innovations need to consider a number of factors, including vulnerabilities and countermeasures, but also computing power. Furthermore, for their universal implementation, international standards are required.

New methodologies include (n,n)blockcipher compression function schemes for short and variable message encryption, and mutual authentication protocols that depend on subspace learning parity from noise problems and pseudo-inverse matrix properties.

Oblivious random access machines (ORAM) are good at hiding access patterns from an untrusted server, but are not practical for devices with limited storage space. A recursive version of Matrix ORAM can significantly reduce the storage space.

Finally, elliptic curve cryptography (ECC) uses the algebraic structure of elliptical curves to provide equivalent security to non-ECC methods on smart cards but with fewer key bits. It is further advanced to be secure to side-channel attacks.

Reference: "Variable message encryption through block cipher compression function", Concurrency and Computation: Practice and Experience, Wiley Publisher, 2016



MNT-curve, constructed by Miyaji-Nakabayashi-Takano, can be applied ID-based encryption

Humanities and Social Sciences

Global History

Shigeru Akita
Graduate School of Letters

Global history from a global perspective

The British Empire has had a tremendous impact on East Asia. Conventional history describes this impact as exploitative and having negative influence on economic growth in Asia. Yet the Empire brought an order to East Asia that could be seen as having accelerated the region's industrialization. In many ways, regardless of any imbalance in power, trade with the West created an invigorated East.

It can be argued that rather than a strictly confrontational relationship, economically the relationship was more complementary, in a way that can be described as "Gentlemanly Capitalism" from British point of view, which shifted the economic interests of all parties.

In the case of Japan, whereas some scholarship would argue that the country's industrialization was a reaction to Western encroachment, Gentlemanly Capitalism of Great Britain promoted Japanese industrialization. Gentlemanly Capitalism is seen in the importance of trade with British colonies like India and the transition of the UK from the "Workshop of the World" to the "Banker and Clearing House of the World" that promoted the industrialization of Japan.

Most of history has had a Eurocentric perspective. Studying countries that are thought to have had a lesser role, such as those in Asia, is expected to bring a new outlook on global history.

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Linguistics

Satoshi Kinsui
Graduate School of Letters

Role language

Role language is a type of speech that can be associated with a general character. In Japanese, the expression, "I know (that topic)", will be said by an elderly man as "washi ga shitteoru no ja", whereas a noble lady will say, "watakushi ga zonji teorimasu ha", demonstrating how language changes with status. Role language can be defined by phonetic boundaries and psychological traits given to a character and therefore is heavily based on social and cultural stereotypes.

The concept of role language only took hold in linguistics at the turn of the century. Despite its novelty, it has interdisciplinary applications, as role language research has been conducted under the purview of history, sociology, and literature among other humanities. From a stylistic perspective, role language has a tremendous presence in Japanese fiction and is used by minor characters to provide insights about main characters. From a practical perspective, role language is believed to improve the quality of translations. Accordingly, comprehension of role language should provide nuanced understanding of a foreign language.

Reference: Kinsui S, Yamakido H. Role language and character language. ***ALA.*** 2015;5(2):29-42.

Fumio Ohtake
Institute of Social and Economic Research

Income inequality

Since the 1980's, there has been a trend of widening inequality in the distribution of incomes and wages in the United States, the United Kingdom, and a few other countries, and an apparently similar trend has been observed in Japan. In the U.S., the main causes of this trend are seen to be increasing wage differentials among employees with different educational backgrounds and skills, brought about in the process of the revolution of information technologies and economic globalization. In Japan, however, wage differentials due to educational background, age, or firm size have not widened. Fumio Ohtake sought to solve this puzzle of why there has been a trend towards increasing wage and income differentials despite an almost stable pattern of wage differentials between groups of different educational background, age, and so on. He found the answer to lie in the aging of the entire population of Japan. Income variances within an age cohort are generally small in younger generations, but these variances become larger in older generations in Japan. Because of these distributional characteristics, the aging of the population is about the most important factor behind increasing inequality in income distribution.

Recently, he empirically examined the effects of school curricula on subsequent preference formation. The estimation results, using Japanese data, show that the actual curriculum at public elementary schools varies widely from area to area and is associated with preference formation. Specifically, pupils who have experienced participatory/cooperative learning practices are more likely to be altruistic, cooperative with others, reciprocal, and have national pride. In contrast, the influence of education emphasizing more on anti-competitive practices is negatively associated with these attributes. Such contrasts can also be seen for other preferences regarding government policies and a market economy. The findings imply that elementary school education, as a place for early socialization, plays an important role in the formation of life-long social preferences.

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Yoshiyasu Ono
Institute of Social and Economic Research

Combating stagnation and unemployment

An affluent economy is a permanent goal of any national government. In developing countries the remedy is productivity improvement. Developed countries, however, already have very high productivity and nevertheless suffer from secular stagnation. It is due to deficiency of aggregate demand, which describes the total demand for goods and services at a given time.

Modern theories consider stagnation to be induced by low productivity or imperfections of commodity, labor and financial markets. They recommend monetary expansion and structural reform as remedies. However, recent experience of developed countries shows that they have hardly been effective. Yoshiyasu Ono has focused on an essential human nature, viz. wealth preference, and mathematically presented a quite different mechanism of secular demand stagnation. Policy options listed above are found to be ineffective or rather harmful. Government purchases and public services should be increased.

His policy recommendation sounds similar to Keynesian economics but in fact entirely differs. Keynesians emphasize stimulus of increasing income and asset to consumption and investment. They recommend tax cuts, deficit spending and monetary expansion. Ono has proved that neither tax cuts nor increases in financial assets stimulate them. He recommends increases in public services financed by balanced budget because they not only yield direct benefits but also expand employment, moderate deflation and stimulate consumption. As a consequence, income expands.

References:

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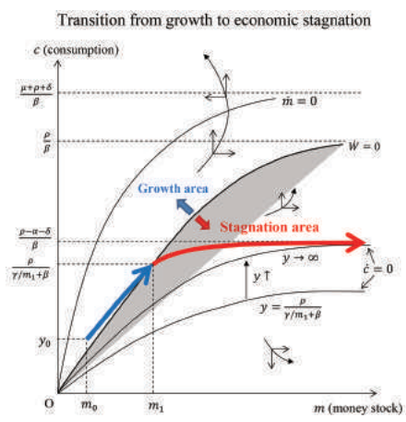
2) Murota R, Ono Y. Fiscal policy under deflationary gap and long-run stagnation: reinterpretation of Keynesian multipliers. ***Econ. Model.*** 2015 Dec;51:596-603.



Noriko Okubo
Graduate School of Law and Politics

Green Access Project

Societies have increasingly recognized the need for policies and laws that consider environmental issues. While governments ultimately make the final vote, stakeholder opinions are recognized as vital. Japan is unusual in that voluntary efforts by the general public and businesses have been relatively effective for preserving the environment.

One area that participation has been influential is river management. Classically, Japan's policy for disaster risk resulted in large infrastructure projects, such as dams and river embankments. The environmental impacts of these measures have been often ignored because of the absence of other stakeholders in the decision-making process. Recently, a participatory system has been introduced for the river management field. Although that represented a remarkable progress, one cannot say that the participation right is now definitively established. In addition, access to justice for protecting nature is still very limited.

Therefore, an effective legal system that coheres with the Aarhus Convention and encourages public participation is recommended. Models that satisfy these criteria along with integrating seamlessly into Japanese society are being explored. This research is performed by the Green Access Project, which aims to provide a global paradigm for the guarantee of environmental rights through citizen participation for a sustainable society.

Reference: Okubo N. The development of the Japanese legal system for public participation in land use and environmental matters. ***Land Use Policy*** Mar 2016;52:492-500.

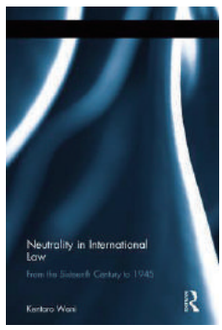
Kentaro Wani
Osaka School of International Public Policy

War and law

In war, legalese defines neutrality as the relationship between one state in war (belligerent State) with another not in war (neutral State). In this condition, the neutral State is obliged to treat the belligerent State impartially, but provide no military assistance to any belligerent States. In the past, international law permitted sovereign states to declare war with extraordinary liberty, which brought heightened attention to the role of neutrality. Modern international law has restricted this freedom, putting question into contemporary definitions of neutrality. One aspect of research by Kentaro Wani considers how neutrality has evolved from the 16th Century to 1945 and how this evolution is relevant today.

Another issue regarding war in international law is armed conflict. Currently, the use of armed conflict during war falls under the euphemism "international humanitarian law". In reality, this law defines the conditions under which it is acceptable to kill during conflict. Prior to World War I, there were very few guidelines on how war could be declared, and many warring nations took brutal measures to kill people and seize property. Wani is also investigating the application of this law to present war.

Reference: Wani K. *Neutrality in international law: from the sixteenth century to 1945.* Routledge. 2017.



GLOBAL COLLABORATION

Osaka University established the International Joint Research Promotion Program in 2013 in order to further enhance research quality and promote globalization of the university. We support advanced research between researchers overseas and at Osaka University to establish an international joint lab on campus. This program will give added impetus to the globalization of our education and research.

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Yasushi Sakata
Graduate School of Medicine

Osamu Yamaguchi
Graduate School of Medicine

Out with the old: mitochondrial quality control protein identified

The protein responsible for the disposal of aging mitochondria in humans has been revealed, with important implications for heart and neurodegenerative diseases

The protein that initiates the destruction of old and diseased mitochondria — small, cellular 'power plants' — has been identified for the first time by researchers at Osaka University and King's College London. Malfunctions in clearing damaged mitochondria are implicated in a number of disorders, including metabolic diseases, heart failure, and debilitating neurodegenerative diseases such as Alzheimer's and Parkinson's.

Mitochondria power the essential cellular processes that keep us healthy, but old and diseased mitochondria release reactive molecules that can damage cellular proteins and DNA. In normal cells, these damaged mitochondria are broken into small pieces (mitochondrial fragmentation) and gobbled up by killer vesicles (mitophagy) so that they can be replaced with fresher mitochondria. When the processes of mitochondrial quality control go wrong, very serious and often life-threating complications arise.

Scientists have known for some time that the protein Atg32 is essential for mitophagy in yeast, but have been unable to track down its functional equivalent in humans and other mammals.

Osamu Yamaguchi, Yasushi Sakata and co-workers at the Department of Cardiovascular Medicine in Osaka University, with collaborators elsewhere in Japan and Kinya Otsu, a professor of cardiology at King's College in the United Kingdom, have identified the functionally equivalent protein of Atg32 in mammals, called Bcl-2-like protein 13 (Bcl2-L-13).

Previous attempts had largely relied on searching for proteins in human cells that have similar amino acid sequences to Atg32. Yamaguchi and co-workers adopted a different tactic of basing their search on the molecular features of Atg32. By screening a public database for proteins with similar features, they uncovered Bcl2-L-13, a transmembrane protein found in the mitochondria that shares amino acid structural arrangements with Atg32. Unsurprisingly, the amino acid sequence of Bcl2-L-13 had little in common with that of Atg32.

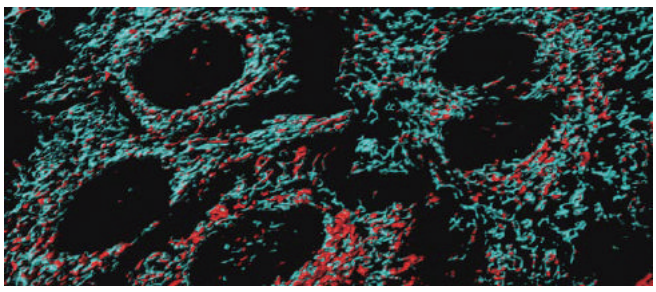
The researchers confirmed the role of Bcl2-L-13 in mitochondrial destruction through cell culture experiments. They found that blocking the expression of Bcl2-L-13 in human embryonic kidney cells reduced mitochondrial fragmentation and mitophagy of damaged mitochondria. Furthermore, introducing Bcl2-L-13 to yeast cells deficient in Atg32 induced mitophagy.

Their finding is a major step in the fight against diseases associated with the persistence of damaged mitochondria. Yamaguchi says: "If we can efficiently eliminate abnormal mitochondria by mitophagy via controlling the activity of Bcl2-L-13, we will be able to intervene in such diseases."

The team now intends to discover how Bcl2-L-13 is activated and functions in the body.

Reference: Murakawa T, Yamaguchi O, Hashimoto A, Hikoso S, Takeda T, Oka T, Yasui H, Ueda H, Akazawa Y, Nakayama H, Taneike M, Misaka T, Omiya S, Shah AM, Yamamoto A, Nishida K, Ohsumi Y, Okamoto K, Sakata Y, Otsu K. Bcl-2-like protein 13 is a mammalian Atg32 homologue that mediates mitophagy and mitochondrial fragmentation. ***Nat Commun.*** 2015 Jul 6;6.7527.

This research project was supported by the Osaka University International Joint Research Promotion Program. Associate Professor Yamaguchi and Professor Sakata jointly conducted this research with the following researcher: Professor Kinya Otsu, King's College London, United Kingdom



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Mitochondria (black ovals) need to be regularly replenished to power essential cellular processes. The protein responsible for initiating this mitochondrial turnover has been discovered in humans.

Shumei Murakami
Graduate School of Dentistry

Simple 3D glasses show a positive effect on dental education

Researchers show that 3D glasses are effective at teaching the spatial intricacies of the mouth to dental students

Of all clinical practices, dentistry is unusual in the time a doctor spends with the patient. Almost all appointments involve a detailed look inside the mouth, which is why good understanding of the spatial structure of the mouth is essential for good patient care. Researchers at Osaka University and University of Copenhagen, Denmark, have collaborated to find a cheap tool that effectively provides this education to dentistry students, preparing them for a promising practice immediately upon graduation.

"Study of the oral and maxillofacial region (OMR) is fundamental to all dentistry programs," says Dr. Shumei Murakami of Osaka University and leader of the study.

Dentistry students learn about the 3D structure of the OMR through hands-on practicals with patients and in the classroom by analyzing 3D images provided by CT and MRI scanning. However, these images have limitations.

"Sometimes stereoscopic information is hard to gather from 3D images, like when two structures are superimposed," said Professor Sven Kreiborg, an invited professor from Copenhagen University who, like Murakami, is interested in improving dentistry education.

Three-dimensional printings are one option, but cost makes it impractical, especially in poorer nations.

Murakami, Kreiborg and colleagues came up with a simple and somewhat archaic solution to the problem. 3D glasses – not the modern high-tech type, but rather those that were used in movie theatres half a century ago – recapitulate well the depth of the OMR.

"3D glasses have already proven effective in the classroom for other subjects that depend on spatial awareness like architecture," said Murakami.

While 3D glasses may seem crude compared with the images acquired from expensive CT and MRI machines, Murakami remarked that students are usually looking at printed 2D images in the classroom.

In their method, Murakami explains, "We use CT and MRI to make anaglyph images. The 3D glasses recapture the stereoscopic information lost when printing the CT and MRI images."

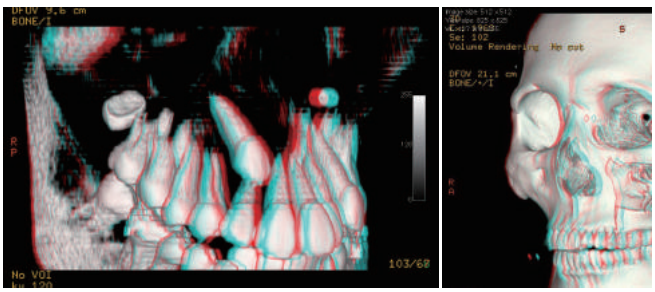
The study showed that students gathered more stereoscopic information when using the 3D glasses.

"Our goal was not to create revolutionary technology, but to find a cheap way that would have an impact on student education," said Murakami.

Indeed, as a pair of 3D glasses only costs 50 yen (U.S. 50¢), there is little reason for students and universities not to experiment with this approach.

Reference: Murakami S, Verdonschot RG, Kreiborg S, Kakimoto N, Kawaguchi A. Stereoscopy in dental education: an investigation. ***J. Dent. Educ.*** 2017;81(3).

This research project was supported by the Osaka University International Joint Research Promotion Program. Associate Professor Murakami jointly conducted this research with the following researchers: Professor Sven Kreiborg, Dr. Per Larsen and Dr. Tron Darvann at University of Copenhagen, Denmark



Left: Impacted tooth in maxillary teeth arch
Right: Face bones fracture

Genji Kurisu
Institute for Protein Research

Modified enzymes for bio-hydrogen production

Changing the cofactors that help proteins work in a search for hybrid enzymes that could fuel the hydrogen economy

A collaboration between researchers at Osaka University in Japan and Ruhr-Universität Bochum in Germany is investigating enzymes that can catalyze fast and efficient production of hydrogen. The researchers are exploring how these enzymes might be modified and adapted to produce hydrogen on an industrial scale.

"The enzymes we are studying might be used to produce bio-hydrogen," explains Genji Kurisu of Osaka University's Institute for Protein Research. This would mean tweaking photosynthesis in algae to optimize the process of using sunlight to split water into oxygen and hydrogen. However, Kurisu cautions that years of basic research will probably be necessary before their work could move to an industrial scale.

The enzymes, known as [FeFe]-hydrogenases, are found in simple organisms such as bacteria and algae and are nature's fastest catalysts for producing hydrogen. Kurisu is collaborating with the research group in Germany, led by Thomas Happe, to learn more about the chemistry of these natural enzymes, and also how semi-synthetic modified forms could be made more stable and effective.

[FeFe]-hydrogenases are 'metalloproteins' that must have a small chemical cofactor containing iron bound to the protein molecules to allow them to perform their impressive feats of catalysis. Kurisu has been working with metalloproteins since his doctoral research project in the 1990s. With colleagues at Osaka, he has become skilled in determining their precise three-dimensional structures.

Kurisu's interests in the fundamental structure and basic science of the enzyme activity perfectly complements Happe's particular interest in the effects of replacing natural cofactors with synthetic ones toward applications for modified enzymes. "This is a really good collaboration for us," says Kurisu.

In their most recent investigation, the collaborators examined the precise structural changes that occur when synthetic cofactors are incorporated into the enzymes (see image). They achieve this by making crystals of the semisynthetic enzymes and using a beam of X-rays to reveal their structure — a technique called X-ray crystallography. "Osaka has opened protein crystallography as an important technique for me, which will influence the topics I can work on," comments Happe.

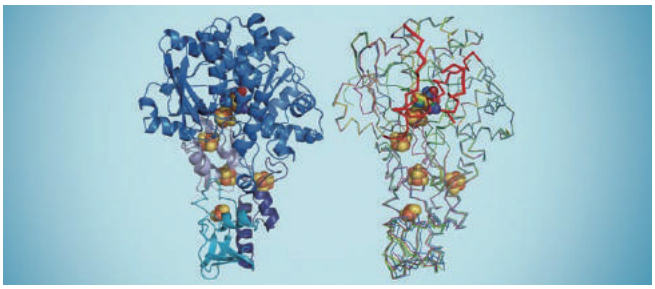
Through their investigation the team identified the essential parts of the cofactors needed for enzyme activity.

This is difficult work, because the enzymes come from organisms that function under anaerobic conditions. "Purifying and crystallizing the enzymes using an oxygen-free glove box can be very stressful," says Kurisu.

With the ever-increasing interest in hydrogen as a renewable fuel, clearing all these hurdles may eventually help to build a clean and sustainable hydrogen-based economy.

Reference: Esselborn J, Muraki N, Klein K, Engelbrecht V. Metzler-Nolte N. Apfel UP, Hofmann E, Kurisu G, Happe T. A structural view of synthetic cofactor integration into [FeFe]-hydrogenases. ***Chem. Sci.*** 2016;7:959-68.

This research project was supported by the Osaka University International Joint Research Promotion Program. Professor Kurisu jointly conducted this research with the following researcher: Professor Thomas Happe, Ruhr-Universität Bochum, Germany



Schematic representations of semisynthetic proteins that can catalyze the production of hydrogen with the help of metallic cofactor atoms (colored spheres).

Miki Shinohara
Institute for Protein Research

Protein Complex Prevents Genome Instability

Structural and organizational roles for key protein complex in yeast model of DNA repair

An international collaboration between Osaka University and the Friedrich Miescher Institute for Biomedical Research (FMI) in Switzerland is investigating the repair process of a serious form of DNA damage that can lead to instability of genetic material and tumor formation. The researchers are studying the roles of groups of proteins that control the repair of double-stranded breaks (DSBs) in DNA that occur from internal or external sources, such as UV irradiation.

The yeast Saccharomyces cerevisiae, also known as baker's or brewer's yeast, is being used by the team as a model organism to study the repair protein functions. This yeast is an ideal model because it shares many similarities with plants and animals, all of which are made up of cells with nuclei, yet its genetics are sufficiently simple to allow it to be easily manipulated in the lab. Yeast is therefore an excellent tool to study the different types of genomic mutations that characterize human cancers.

The researchers found that the MRX complex of three yeast proteins plays a vital structural role during early DSB repair and when overcoming delays in the replication of partially separated DNA double helices [1]. "MRX is introduced to the DNA damage site or stalled replication fork through its interaction with yeast replication protein A," says Susan M. Gasser of FMI. "We used super-resolution microscopy to show that this interaction behaves like a linchpin to stabilize broken ends of DNA."

Crucially, their research revealed that this structural role did not require the presence of another protein, cohesin, as was commonly thought.

The Xrs2 member of the MRX complex interacts with other proteins to ensure that the correct molecules are present at repair sites of DNA damage. Strong similarities between regions of yeast proteins and related human proteins are a sure sign that the sequences are functionally important enough not to have changed during evolution. Nbs1, the human equivalent of Xrs2, shares a similar role, and mutations at one end of this protein cause an inherited disease with a high risk of cancer and immunodeficiency.

In a related study, the team found that mutations in the part of Xrs2 equivalent to the disease-causing region of Nbs1 caused the build-up of a protein, Ku, which controls the structure of chromosome ends [2]. "This reduced the precision of the joining of damaged DNA ends, akin to that seen in the human disease," explains Miki Shinohara of the Osaka University Institute for Protein Research, Department of Integrated Protein Functions. "The same part of Xrs2 was also needed to sustain high activity levels of a key enzyme involved in the DNA damage response."

These findings offer an insight into how cells can develop genomic instabilities, leaving them susceptible to cancer.

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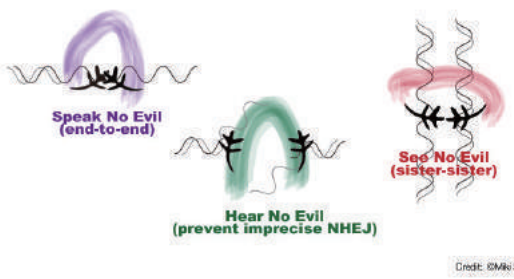
This research project was supported by the Osaka University International Joint Research Promotion Program. Associate Professor Shinohara jointly conducted this research with the following researcher: Professor Susan M. Gasser, Friedrich Miescher Institute for Biomedical Research, Switzerland



Three wise monkeys showing multiple functions of Mre11-Rad50-Xrs2 complex at different types of DNA break.

Kentaro Nagamine
Graduate School of Science

Simulating supermassive black holes

Cutting-edge simulations explain how supermassive black holes and galaxies formed from collapsing gas clouds in the early Universe

Near the edge of the visible Universe are some of the brightest objects ever observed, known as quasars, which are believed to contain supermassive black holes of more than a billion times the mass of our Sun. Simulations by Kentaro Nagamine at Osaka University's Department of Earth and Space Science, Isaac Shlosman at the University of Kentucky and co-workers have revealed for the first time exactly how these black holes formed 700 million years after the Big Bang.

"The early Universe was a dense, hot and uniform plasma," explains Nagamine. "As it cooled, fluctuations in the mass distribution formed seeds around which matter could gather due to gravity." These are the origins of the first stars. Similar processes might have later seeded the growth of bigger structures such as supermassive black holes.

Until recently, many researchers thought supermassive black holes were seeded by the collapse of some of the first stars. But modeling work by several groups has suggested that this process would only lead to small black holes. Nagamine and co-workers simulated[1,2] a different situation, in which supermassive black holes are seeded by clouds of gas falling into potential wells created by dark matter — the invisible matter that astronomers believe makes up 85% of the mass of the Universe.

Simulating the dynamics of huge gas clouds is extremely complex, so the team had to use some numerical tricks called 'sink particles' to simplify the problem.

"Although we have access to extremely powerful supercomputers at Osaka University's Cybermedia Center and the National Astronomical Observatory of Japan, we can't simulate every single gas particle," explains Nagamine. "Instead, we model small spatial scales using sink particles, which grow as the surrounding gas evolves. This allows us to simulate much longer timescales than was previously possible."

The researchers found that most seed particles in their simulations did not grow very much, except for one central seed, which grew rapidly to more than 2 million solar masses in just 2 million years, representing a feasible path toward a supermassive black hole. Moreover, as the gas spun and collapsed around the central seed it formed two misaligned accretion discs, which have never been captured in other numerical simulations before.

In other recent work, Nagamine and co-workers described the growth of massive galaxies that formed around the same time as supermassive black holes[3]. "We like to push the frontier of how far back in time we can see," says Nagamine. The researchers hope their simulations will be validated by real data when NASA's James Webb Space Telescope, due to be launched in 2018, observes distant sources where direct gas collapse is happening.

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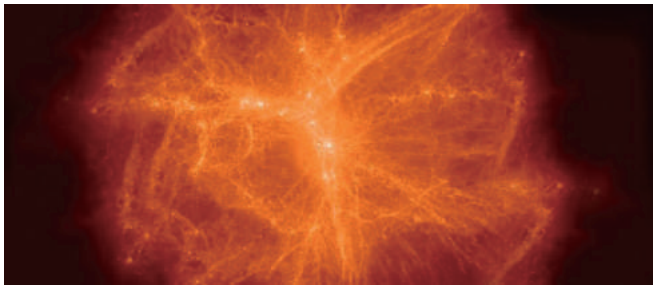
This research project was supported by the Osaka University International Joint Research Promotion Program. Professor Nagamine jointly conducted this research with the following researcher: Professor Isaac Shlosman, University of Kentucky, United States



Simulation of a network of dark matter filaments in a high-density region of the early Universe. Each dense bright spot is a dark matter halo into which gas collapses to form large galaxies and supermassive black holes.

Kazushi Mashima
Graduate School of Engineering Science

Realizing Industrial-scale Alkene Metathesis at Low Temperature

Catalyst activation process that facilitates low-temperature alkene metathesis

Alkene metathesis involves the cleavage and formation of carbon–carbon double bonds and is attractive in organic synthesis because it often creates fewer undesired by-products and less hazardous waste than alternative reactions. Alkene metathesis is used industrially for propene synthesis, reforming of petroleum oil, and drug manufacture. In 2005, Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock were awarded the Nobel Prize in Chemistry for their work on alkene metathesis. However, the catalysts used in industrial alkene metathesis only operate at high temperature (>350°C), limiting the scope of this reaction in industrial settings.

An international research collaboration between Osaka University and ETH Zürich in Switzerland recently developed a low-temperature activation process to extend the scope of industrial alkene metathesis.

"We used an organosilicon reductant to activate silica-supported tungsten and molybdenum oxo catalysts, generating a large amount of active species at just 70°C," says Kazushi Mashima of the Osaka University Graduate School of Engineering Science, Department of Chemistry.

A typical industrial catalyst for alkene metathesis is tungsten trioxide supported on silica. This catalyst requires a high temperature to form the active oxo alkylidene groups needed for alkene metathesis. The researchers developed a way to prepare a silica-supported tungsten oxo catalyst that was active in alkene metathesis at low temperature. First, they fabricated isolated tungsten(VI) oxo surface sites on silica by grafting and heat treatment. Second, the tungsten(VI) oxo surface sites were reduced using an organosilicon reductant, which was chosen to minimize the formation of salts and metal species. The resulting material displayed promising catalytic activity in alkene metathesis, reacting with 1000 equivalents of *cis*-4-nonene at 70°C in 6 h. The poisoned catalyst could be reactivated by reaction with the organosilicon reductant.

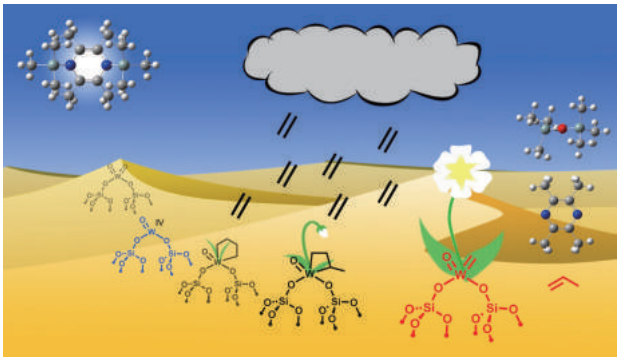
"The unprecedented reactivation of the poisoned catalyst reveals that it may be suitable for use under flow conditions," says Christophe Copéret of ETH Zürich. The researchers then used the organosilicon reductant to activate traditional industrial catalysts for alkene metathesis, achieving promising results. The importance of the team's findings has been noted by Schrock: "The work by Copéret and Mashima may revolutionize the synthesis and use of inexpensive supported metathesis catalysts for hydrocarbons on an industrial scale by allowing the use of much lower temperatures than currently employed." [R. R. Schrock, Reducing Them Down To Charge Them Up: Low Temperature Catalyst Activation, *ACS Central Science,* **2016,** 2 (8), 495–496, DOI: 10.1021/acscentsci.6b00223]

The ability to perform alkene metathesis at low temperature on an industrial scale will provide important materials more efficiently and at lower cost.

Reference: Mougel V, Chan KW, Siddiqi G, Kawakita K, Nagae H, Tsurugi H, Mashima K, Safonova O, Copéret C. Low temperature activation of supported metathesis catalysts by organosilicon reducing agents. ***ACS Cent. Sci.*** 2016 Aug 24;2(8):569-76.

This research project was supported by the Osaka University International Joint Research Promotion Program. Professor Mashima jointly conducted this research with the following researcher:

Christophe Copéret
Department of Chemistry and Applied Biosciences, ETH Zürich, Switzerland



Katsuro Inoue
Graduate School of Information Science and Technology

Detecting License Inconsistencies in Large-scale Open Source Projects

Empirical study exposes license infringements in open source software and identifies the reasons behind these inconsistencies

Reduce, reuse, and recycle is a popular approach for conserving resources, and this can extend to the world of technology in the form of free and open source software (FOSS) distributed under OSS licenses. Katsuro Inoue at Osaka University's Graduate School of Information Science and Technology and Daniel. M. German at University of Victoria's Department of Computer Science have used Ninka, a sentence-based license detection tool, to analyze source code files and identify inconsistencies between OSS licenses with the same origin.

FOSS can be freely used, modified, and redistributed by anyone. It offers the benefits of reducing development time while increasing product quality, security, and stability. Android, Apache, Firefox, and Linux are all familiar examples of FOSS.

In their recent study, Inoue and his team conducted an empirical evaluation of the evolution of software licenses over the development of the open source project Debian 7.5. This large-scale FOSS system comprises thousands of source code files, each containing software license descriptions that generally reside in the header comment. These licenses describe the requirements and conditions that should be followed when the code is reused, and they should not be changed without the copyright owner's permission, or unless permitted under the terms of the license.

"It is important that FOSS developers check licenses so that they do not commit an infringement; but this is not a trivial task," Inoue explains. "License violation may occur when developers misunderstand the license of source files, which could result in legal disputes."

After identifying files that shared an origin, as demonstrated by their identical language and logic, the researchers applied Ninka, which Inoue and colleagues developed in 2010. Ninka can identify 110 licenses with 93% accuracy, and processes 600 files/minute. The research team found that license inconsistencies were not uncommon: out of 74,848 file groups, 5,359 (7.2%) contained at least one inconsistency.

The team performed a manual examination of the files' repository history to categorize these inconsistencies into those caused by legitimate changes by the copyright owner and additions, modifications, or choices made by reusers. The highest proportion of inconsistencies, at 98.4%, resulted from the license changing during the process of license evolution.

"Our analysis exposes the difficulty of discovering license infringements, and highlights the usefulness of determining and maintaining source code provenance," Inoue says.

The research team intends to improve Ninka and develop new methods to analyze the history of each source file to improve the assessment of whether license inconsistencies are legitimate.

References:
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2) German DM, Manabe Y, Inoue K. A sentence-matching method for automatic license identification of source code files. ***ASE '10 Proceedings of the IEEE/ACM International Conference on ASE.*** 2010;437-46.

This research project was supported by the Osaka University International Joint Research Promotion Program. Professor Inoue jointly conducted this research with the following researcher: Professor Daniel M. German, University of Victoria, Canada

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Yoneyuki Sugita
Graduate School of Language and Culture

Japan in the spotlight

Two books comprehensively examining Japan's international relations from many angles provide a thorough analysis of a notoriously complex dynamic

Two books edited by an Osaka University researcher shine an interdisciplinary light on the complex and sometimes bewildering subject of Japan's international relations. The books are published at a significant juncture in Japan's history with the commemoration of the 70th anniversary of the end of World War II in 2015 and the recently increased agitation between Japan and its neighbors. They address, among other subjects, the experiences of Japanese–American soldiers in the Korean War, the personalization of Buddhist funeral practices after the collapse of the 'bubble economy', and the integrating effect on the region of Asian popular culture such as manga and animation.

Both books were edited by Yoneyuki Sugita, a history professor at Osaka University's Graduate School of Language and Culture. The first book — *Japan Viewed from Interdisciplinary Perspectives* — evaluates the history and future of Japan from a wide range of perspectives under three broader themes; globalization, Japan's relations with its Asian neighbors and its relationship with the United States[1]. Under these subjects, chapters look at President Obama's foreign policy focus on Asia, Japan's development aid to Myanmar while the country was being ostracized by the West, and the Asia-Pacific Economic Cooperation forum's role in settling disputes and providing trade security for Japan.

The second book — *Toward a More Amicable Asia-Pacific Region* — considers how Japan might contribute toward realizing a more peaceful and prosperous Asia-Pacific region[2]. It addresses questions such as "Is a strong regional power needed to stabilize the region?", "How should countries in the region deal with the problem of disputed islands?" and "What role has the nuclear crisis in North Korea played in Japan's relations with the United States?" It evaluates the continued dominance of the United States in the politics and security of the region and recommends that countries seek a mediating position regarding sovereignty in territorial disputes. It asserts that the United States has used the nuclear crisis to foster a greater dependence on it by Japan.

The books were the result of a series of international symposia hosted at Osaka University in 2014 and 2015 on Japan and its interactions with the world. Authors include Japanese and foreign specialists in sociology, history, Japan studies, religious studies, economics and international politics. The chapters were also informed by extended discussions between the contributors prior to and during the symposia. "This discussion was very valuable for helping the presenters turn their papers into chapter manuscripts," says Sugita.

Sugita has recently published *Social Commentary on State and Society in Modern Japan* (Springer), which analyzes societal and cultural aspects of modern Japan.

References:
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2) Sugita Y (ed.). *Toward a more amicable Asia-Pacific region: Japan's roles.* University Press of America. 2015. [ISBN-13: 978-0761866787; ISBN-10: 0761866787] https://rowman.com/ISBN/9780761866787/Toward-a-More-Amicable-Asia-Pacific-Region-Japan%E2%80%99s-Roles
3) Sugita Y (ed.). *Social commentary on state and society in modern Japan.* Springer. 2016. [ISBN 978-981-10-2395-8] http://www.springer.com/gp/book/9789811023941

This research project was supported by the Osaka University International Joint Research Promotion Program. Professor Sugita jointly conducted this research primarily with the following researchers:
Senior Research Fellow Bart Gaens, The Finnish Institute of International Affairs, Finland
Professor Laura Hein, Northwestern University, United States
Director Marie Söderberg, European Institute of Japanese Studies, Sweden
Senior Lecturer Nissim Otmazgin, The Hebrew University of Jerusalem, Israel
Professor Paul Midford, Norwegian University of Science and Technology, Norway

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Japan and its regional and global interactions from an interdisciplinary perspective are the subject of two recent books.

Osaka University Facts and Figures

Students

Undergraduate 15,479

Graduate 7,892

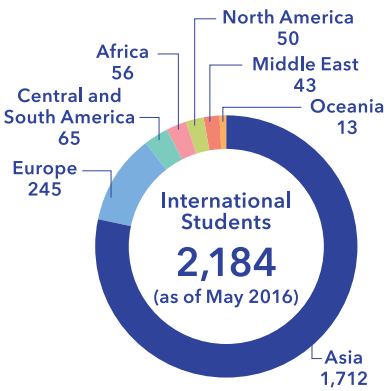
Academic Staff

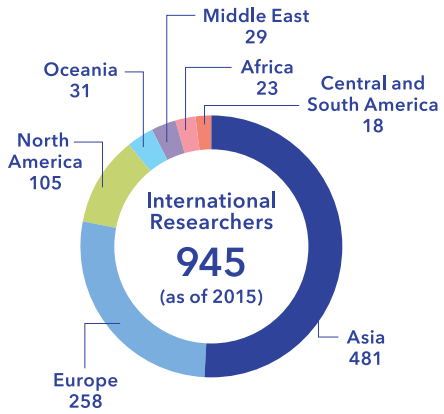
Academic Staff 3,196

Researchers 292

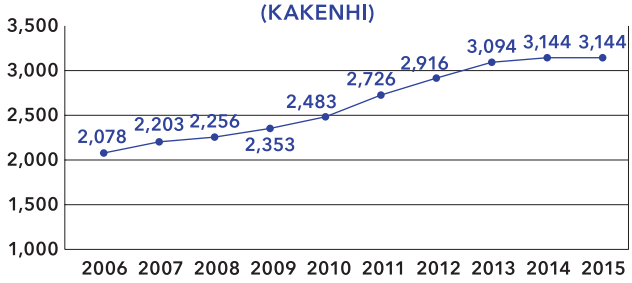
*Figures above are as of May 1, 2016

International Students and Researchers

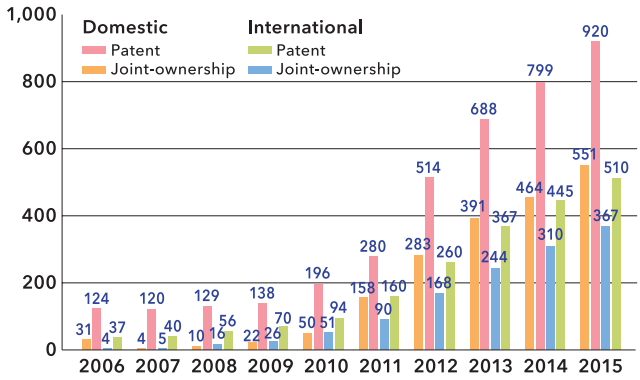




The Number of Projects Selected for Grants-in-Aid for Scientific Research (KAKENHI)

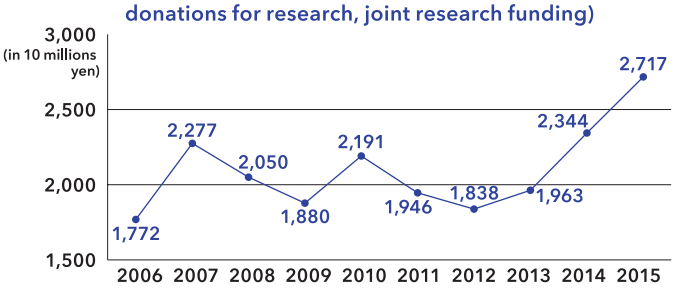


The Number of Patents



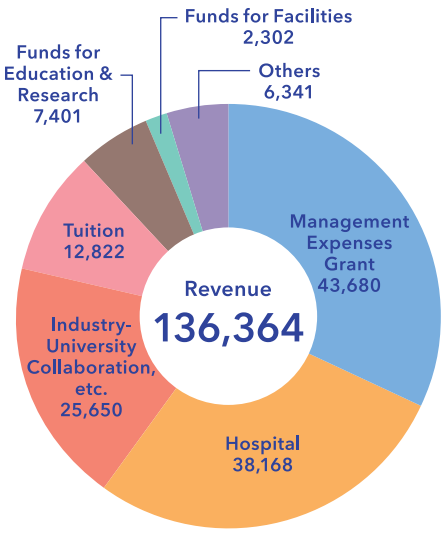
External Funding

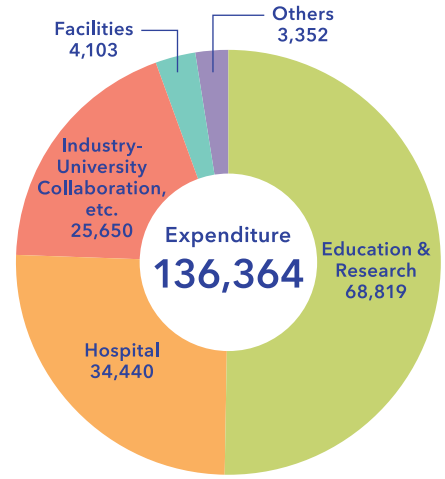
(including commissioned research, donations for research, joint research funding)



Budget

FY2016, in millions of yen
(1 USD=112 JPY as of April 1, 2016)





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