OSAKA IN FOCUS

Heritage For The Future

Science AAAS

Brought to you by the AAAS/*Science* Business Office

CONTENTS

2-Heritage for the Future Osaka builds on its legacy in the biosciences

EXCELLENCE IN RESEARCH

PAGE 4

INTEGRATING RESEARCH AND BUSINESS

PAGE 15

18 February 2011

Heritage for the Future

Osaka builds on its legacy in the biosciences

Leaders of the city of Osaka's academic, industry, and government sectors are implementing ambitious plans to make the Northern Osaka Biomedical Cluster one of the top five bioscience regions worldwide within the next 10 years. **Reporting from Japan, Adarsh Sandhu takes a closer look.**

Osaka has been at the center of Japan's pharmaceuticals industry since the 17th century when the Doshomachi district was a hub for merchants trading herbal medicines. The area has been an incubator for global companies like Takeda Pharmaceutical Co., Ltd. and Shionogi & Co., Ltd, as well as the predecessor of Osaka University's School of Medical Sciences.

"Osaka has a rich history of research in the life sciences and is a base for major pharmaceutical companies," says former president of Osaka University and immunologist **Tadamitsu Kishimoto,** currently a professor at the Graduate School of Frontier Biosciences, Osaka University. "Biomedicine has tremendous potential here. We want to realize the dream of former president Yuichi Yamamura, who envisaged Northern Osaka as an international hub for life sciences."

Indeed, Osaka-based scientists have made outstanding contributions to the life sciences including the discovery by Kishimoto of interleukin-6 (IL-6), a protein governing the immune response. This led to the development and commercialization of the IL-6-inhibiting drug, tocilizumab, for the treatment of Castleman's disease and rheumatoid arthritis. Kishimoto donates the profits from the sale of tocilizumab to the Kishimoto Foundation to support research. "I want to contribute to nurturing the next generation of researchers in the life sciences," says Kishimoto.

In the area of infectious diseases, the discovery of *Vibrio parahaemolyticus*—a bacterium that causes food poisoning—was made at the university's Research Institute for Microbial Diseases (RIMD), and its brother institute, the Research Foundation for Microbial Diseases (BIKEN), Japan's largest manufacturer of vaccines for diseases such as chickenpox. Notably, scientists at RIMD are also developing vaccines to fight malaria, a so-called neglected disease, which affects about 40 percent of the world's population, mostly in poorer countries.

The tradition of pioneering work in immunology, initiated by the late Yuichi Yamamura, is being continued by Osaka University's Kishimoto and by **Shizuo Akira,** director of the Immunology Frontier Research Center (IFReC) whose research on Toll-like receptors, innate immunity, and viral recognition has made him one of the most highly-cited immunologists.

Breakthroughs have also been made in transplant surgery at Osaka University Medical School, where surgeons performed Japan's first kidney transplant in 1964 and the first simultaneous heart-lung transplant in 2009.

So what are the plans for Osaka's return to center stage?

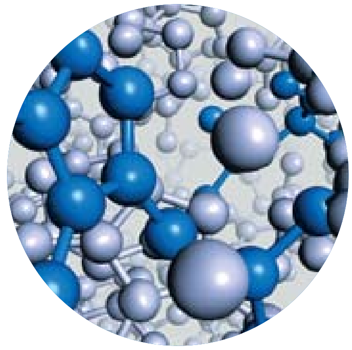
Developing a Strategy

The core goals, which are contained in the so-called Osaka Bio Strategy, involve accelerating the development of new drugs and medical devices; promoting constructive alliances between industry, academia, and government throughout the Kansai area (which includes the cities of Osaka, Kyoto, and Kobe); and strengthening support for venture capital companies (via the Osaka Bio Fund's ¥1.1 billion ($13 million) in capital assets). The establishment of a Comprehensive Global Strategic Special Zone of the Japanese government is included, with two core priority areas: the biomedical industry, and environment and new energy.

Participation is being sought from some of the world's largest electronics, chemical, and precision instrument companies, such as Panasonic and Sharp, both of which are headquartered in Osaka.

"The biomedical industry relies on medical devices," says **Yasushi Sugimoto**, director general of the Department of Commerce, Industry and Labor, Osaka Prefecture. "The

Tadamitsu Kishimoto



Kansai region is Japan's largest manufacturer of lithium ion batteries, generating ¥22 billion ($260 million) in revenue in 2009, and batteries are a critical component of medical equipment."

To promote interdisciplinary and cross-sector collaboration, the Osaka Bio Headquarters has been set up to bridge the gap between research and commercial entities. "The Bio Headquarters consists of members from industry, academia, and government," says Kishimoto, president of the organization. "Members of this organization devise plans to achieve our goals as part of the Osaka Bio Strategy framework."

To provide support for venture companies, the Osaka Bio Strategy includes the launch of a biotalent matching service catering to the human resource needs of start-up companies.

Promoting Research, Fostering Business

To reduce both the time and cost of performing clinical trials, Osaka plans to make available the expert services of institutions such as the five hospitals of the Osaka Prefectural Hospital Organization to the pharmaceutical industry. A clinical trials website has also been set up, offering up-to-date information about trial results. On the policy side, a request has been made by the Osaka Bio Headquarters to the central government and the Pharmaceutical and Medical Devices Agency to make positive reforms to clinical trial regulations and practices.

Knowledge of the properties of proteins is extremely important for fundamental research on immunology, cancer treatment, and drug discovery. Osaka is renowned for its expertise in protein research, exemplified by more than 50 years of research conducted at Osaka University's Protein Research Institute (PRI). Now, in an innovative development, the biomedical cluster launched the Protein Mall in May 2009 as an open access platform for drug discovery. It aims to create a 'drug development value chain' to foster business opportunities based on protein-related research.

Knowledge is essential, but collaboration is also critical to achieve Osaka's goals. As such, the Drug Seed Alliance Network Japan—managed by the Osaka Chamber of Commerce and Industry—is actively promoting partnerships between industries both within Japan and overseas. Recent international agreements include memoranda of understanding signed with France, Australia, Belgium, and the BioBusiness Alliance of Minnesota.

A central and important facility in the Northern Osaka Bio Cluster is the National Institute of Biomedical Innovation (NIBIO), which the government set up in 2005 to act as a stepping stone for commercializing ideas from the laboratory and bringing them into the clinic. Research at NIBIO ranges from developing adjuvants for more effective vaccines to maintaining an ancestry database of cynomolgus monkey colonies, which is openly available to researchers.

The strength of Osaka's expertise in life sciences is based on decades of basic research conducted by imaginative and highly motivated scientists, historically from within Japan but now also from overseas. Shizuo Akira, director of IFReC—launched in October 2007 as one of only five World Premier Institutes chosen by the Japanese government—says that approximately 30 percent of its principle investigators are foreign, a rare situation in Japan, but made possible through extensive support provided by IFReC staff for foreign scientists to help them overcome language and cultural barriers.

Looking to the Future

There are some disturbing trends among young Japanese researchers that worry their senior counterparts. "Youngsters are reluctant to go overseas these days," notes Kishimoto. "It's probably because Japanese universities now offer world class research environments. But research is not only about equipment and clean rooms; meeting people from different backgrounds and developing international networks is equally, if not more, important."

Only time will tell how these trends will affect Japan's research prowess, but the new research programs have attracted many bright researchers from overseas, which may compensate for the decreased willingness of Japanese scientists to travel internationally.

Osaka and the Kansai region have a lot to offer the biomedical industry with new projects in neuroscience, human-machine interface research, cancer treatment, and robotic assistance in hospitals, all of which build on the legacy of Osaka's pharmaceutical and electrical industries.

On balance, the important fact is that Osaka is still an energetic and forward-looking location for pursuing research and business in the biosciences.

Adarsh Sandhu holds joint professorships at the Tokyo Institute of Technology and Toyohashi University of Technology, Japan.

Establishing a Comprehensive Global Strategic Special Zone in Osaka

The last half of the 20th century saw Japan's automobile industry lead the nation to become a powerful first-world economy. But this 'unipolar economic structure' has seen its day and the realities of the new millennium dictate different approaches for further economic growth.

Osaka: Traditional Enterprising Spirit Is Still Alive

CREDIT: © OSAKA CONVENTION & TOURISM BUREAU

To pull Japan out of the current economic malaise, prominent members from academia, industry, and government of Osaka Prefecture—the heart of the Kansai region of Western Japan incorporating the cities of Kyoto, Kobe, and Nara—are devising new economic models based on the historical strengths of the region's electronics, chemical, biomedical, and precision instruments sectors. In particular, a strategy that makes full use of Osaka's current expertise in the biomedical, and environment and new energy industries will be the driving force, with a potential economic upside of ¥700 billion ($8.3 billion).

The history of Osaka's biomedical industry goes back to the 17th century when the Doshomachi district in Osaka City was the national hub for the distribution of herbal medicine and related materials. Centered on Doshomachi, the Northern Osaka Biomedical Cluster covers an area 40 km in diameter, and includes university startups and pharmaceutical companies as well as the world's leading research institutes. In recent years, the Northern Osaka Biomedical Cluster has enjoyed a reputation as one of the top biomedical clusters in Japan.

Osaka Prefecture's Proposal for the Comprehensive Global Strategic Special Zone

One of the pillars of the Japanese government's strategy for economic growth is founded on a vision of so-called Life Innovation for becoming a leader in research and providing exceptional health care. Now, Osaka Prefecture will help to realize this national goal by integrating the unique potential of Northern Osaka with the world-class biomedical industries and abundance of highly-skilled employees available in this area.

In September 2010, Osaka proposed a draft of the Comprehensive Global Strategic Special Zone to the national government. With a formal government designation as a biomedical industry area in this region, Osaka could act as a catalyst to initiate the spread of ideas for life innovation throughout the rest of Japan. Osaka will submit a formal application in 2011.

The proposal includes:

(1) Establishment of a PMDA (Pharmaceuticals and Medical Devices Agency) office in the Osaka region to accelerate the development of pharmaceuticals and medical devices, and resolve issues related to 'drug-lag and device-lag' (delays in drug and device development and approval due to stringent government regulations);

(2) Extending the function of the National Cerebral and Cardiovascular Center (NCVC) by constructing new buildings to expand the Research and Development Initiative Center and related medical clusters;

(3) Setting up a Comprehensive Special Zone

Midosuji: Main Business and Shopping Street in Downtown Osaka

Osaka's Bay Area as the New Administrative Center

based on the achievements of Osaka University, NCVC, and the Osaka Medical Center for Cancer and Cardiovascular Diseases to promote clinical trials and treatment of cancer and cardiovascular diseases;

(4) Setting up a multidisciplinary medical and welfare robot demonstration experiment zone by bringing together local small and medium enterprises (SMEs) as well as global corporations such as Panasonic for the development of robot-assisted patient beds, automated drug mixing for injections under aseptic conditions, and autonomous delivery robots for transporting medical supplies and medicine;

(5) Creation of a unified industry-academic-government approach to support the development of antibody and nucleic acid medicines based on shared 'good manufacturing practice' (GMP) facilities maintained at the Saito Life Science Park in the Northern Osaka Biomedical Cluster. In addition to contract-based manufacture of cutting-edge biomedical products, the GMP facilities would strengthen the research and development activities of startup companies by offering consultation, development of human resources, and collaborative research;

(6) Increasing efforts to attract new vaccine-related industries—the growth engines of medical industries—to form a strong foundation for the research, development, and manufacture of biomedical products. This policy takes advantage of Osaka University's research institutes—the Immunology Frontier Research Center, the Research Institute for Microbial Diseases, and the Institute for Protein Research—and the National Institute of Biomedical Innovation (NIBIO), located in the Saito Life Science Park, all world leaders in vaccine research.

New Energy and Biomedicine

The Comprehensive Global Strategic Special Zone also includes an area that addresses environmental and new energy industries. Osaka Prefecture hopes that the inclusion of academic and industrial initiatives on new energy as well as the integration of biotechnology will provide the impetus to improve Osaka's economic potential and create a positive ripple effect throughout the rest of Japan.

Osaka has a rich history of innovative contributions to the development of new energy resources. For example, Osaka is recognized globally for manufacturing 34 percent of the world's supply of lithium ion batteries. In the area of photovoltaics, industries in Osaka manufacture 11 percent of solar cells sold worldwide.

The Research and Development Initiative for Scientific Innovation of New Generation Batteries, or RISING, program aims to understand the nature of the chemical reactions governing the lifespan of lithium ion batteries, and develop batteries with five times greater energy storage capacity than current technology. Future applications include not only automobiles, but also portable devices for improved health care.

Taking the lead in the development and adoption of new energy technologies, Osaka will be hosting the Osaka New Energy Forum 2011, scheduled for 24–26 March, at the Osaka International Convention Center. Chaired by Osaka Governor Toru Hashimoto, the theme of the conference will be to review the role of electric vehicles in society. The organizers expect about 10,000 participants at the event.

Panasonic's In-Hospital Delivery Robot, "HOSPI"

MORE INFO

The Osaka New Energy Forum
www2.convention.co.jp/oneforum/en/

Unsurpassed Pedigree in Translational Medicine

Osaka University Medical School and affiliated facilities set the example for a comprehensive approach towards taking cutting-edge research from the laboratory to the clinic, and into the home.

The Medical School at Osaka University, a part of the Faculty of Medicine within the Graduate School of Medicine, is the oldest in Japan, with roots going back to the Tekijuku school established in 1838 by Ogata Koan, pioneer of Western medicine in Japan, and the first person in Japan to encourage a systematic approach to smallpox vaccination.

"Our medical school has played a pivotal role not only in the development of medicine in this country but also in the growth of Osaka University as a whole," says **Toshio Hirano,** dean of the Graduate School of Medicine.

In the early days the Medical School was renowned for the treatment of infectious diseases such as smallpox and pulmonary tuberculosis. A high standard of both innovative treatments and cutting-edge research continues today.

The Medical School later evolved into an immunology hub as the result of breakthroughs including the discovery of interleukin-6 (IL-6)—a key immune stimulatory molecule—by Tadamitsu Kishimoto and Toshio Hirano. This led to the development of Japan's first humanized monoclonal antibody therapy, tocilizumab, which blocks the action of IL-6 and is used to treat rheumatoid arthritis, joint inflammation, and Castleman's disease.

Recently, the impact of the discovery of IL-6 and tocilizumab was acknowledged by the joint award of the 2009 Crafoord Prize by the Royal Swedish Academy of Science to Kishimoto and Hirano as well as Charles Dinarello, who discovered IL-1.

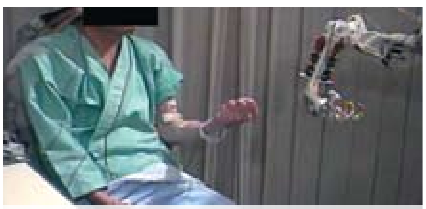
Osaka University Medical School

Toshio Hirano

"The discovery of IL-6 and more recent clarification of the signal pathways involving Toll-like receptors by Shizuo Akira of the Immunology Frontier Research Center are two examples of the research that have made Osaka University a world-class center for immunology," says Hirano.

The Medical School also has world-class medical imaging resources including an ultrahigh resolution semiconductor positron emission tomography (PET) system commissioned in July 2010, the world's first permanent magnet PET/MRI (magnetic resonance imaging), a real-time positron imaging system for monitoring the kinetics of drugs inside the body, a compact cyclotron system for the generation of radioisotopes and labeled compounds, and a 11.7 Tesla MRI facility at the Graduate School of Frontier Biosciences. In new developments, a 7 Tesla functional-MRI system will be available at the National Institute of Information and Communications Technology on the campus.

"Osaka will use these imaging facilities to focus on the treatment of degenerative diseases—such as Alzheimer's disease—and malignant diseases," says Hirano. "In addition, we are working on clarifying the mechanisms governing the onset of other ailments such as cardiovascular and autoimmune diseases in order to develop better drugs and treatments."



Robotic Arm Operated by Electrocorticogram

Masahiro Fukuzawa

The Osaka University Medical School is also recognized for pioneering transplant surgery, performed at Osaka University Hospital, starting with Japan's first kidney transplant in 1964, the first heart transplant in 1999 (following the 1997 passage of new legislation on organ transplants by the Japanese government allowing the harvest of organs from brain dead patients), and the first simultaneous heart-lung transplant in 2009.

Osaka University Hospital is the largest hospital in the Kansai region. "We have about 2,000 staff, including 800 doctors," says **Masahiro Fukuzawa,** director of the hospital. "In 2009, we had about 620,000 outpatients, 340,000 inpatients, and performed 8,700 operations. We are an information technology-oriented hospital, with a heliport on the roof, and a world-class trauma and acute critical care center."

In 2008 an oncology center was set up at the hospital where cancer surgery is performed and clinical research is carried out on different therapy modalities, including drugs, radiation, and relaxation. Furthermore, as part of the Cancer Professional Training Program first launched in 2007, education courses for patients and the general public were initiated on these same therapies.

At the heart center, established in 2007, clinicians treat severe heart failure and intravascular disorders as well as perform heart surgery. "We are also developing advanced medical treatments for cancer and for partial organ transplants," says Fukuzawa.

The hospital collaborates with internal research groups including the Medical Center for Translational Research (MTR), set up in

CREDIT: (BOTTOM RIGHT) THIS WORK WAS SUPPORTED BY THE STRATEGIC RESEARCH PROGRAM FOR BRAIN SCIENCES OF MEXT.


Toshiki Yoshimine


Akira Myoui


Haruo Sugiyama


Kazuo Hayakawa

2002 to conduct research on topics including regenerative medicine, robotic surgery, and diagnostic imaging.

"Being located within the hospital enables us to have first-hand interaction with the patients and clinicians," says **Toshiki Yoshimine,** director of the MTR. Patient confidentiality and protection is a top priority. "Out of an abundance of caution we have established an ethics committee with whom we consult on decisions about exploratory clinical trials," says Yoshimine.

Innovative work is being done in tissue regeneration using a patient's own cells. Examples include the use of myoblast sheets produced from femoral muscle for the treatment of cardiomyopathy and engineered cell sheets composed of oral mucosal epithelium for corneal reconstruction. "With this technology there is no risk of immunological rejection," says MTR Vice Director **Akira Myoui.**

"One of our most challenging projects is on the brain-machine interface," says Yoshimine. "We are developing technologies to gauge human intent based only on brain activity as an alternative means of communication for people with severe motor impairments, such as ALS [Amyotrophic Lateral Sclerosis]." In recent trials, clinical researchers implanted electrodes directly onto the surface of the brains of patients with epilepsy or intractable pain in an attempt to treat these diseases. Analysis of information-based brain responses to simple grasp, pinch, and release hand movements in these patients has enabled them to control robots in real time. "These are very promising results," says Yoshimine. "Ultimately we want to develop a commercial, fully-wireless implantable system."

Kazutomo Ohashi is head of the Division of Health Sciences at the Medical School. "Our division is unique in Japan," says Ohashi. "Our students have backgrounds in nursing science and medical technology science. They are studying in one of our three unique interdisciplinary programs, which are based on informatics, mechanics, and life sciences."


Kazutomo Ohashi

Yuko Ohno and **Kenji Yamada** are in the Department of Robotics and Design for Innovative Healthcare. "This department reflects a collaboration between Osaka University and the robotics center at Panasonic Corporation," says Ohno. "Our nurses are working with robotics experts to develop a database of how robots could operate in hospitals." One exciting project being conducted at the Osaka University, in collaboration with other groups, is looking at the potential of robotic beds, which will enable patients to move from the bed to a wheelchair without human assistance. "This is a unique experiment fusing engineering and nursing," says Yamada. "Also, working directly with industry will enable rapid translation to actual applications in the future."

Immunology is another strong area of research at the Division of Health Sciences led by **Haruo Sugiyama,** developer of the WT1 (Wilms' Tumor Gene 1) peptide cancer vaccine. "We completed phase one clinical trials at Osaka University Hospital in 2002," says Sugiyama. "We are now pursuing phase 2 trials." The WT1 gene is highly expressed in both hematopoietic and solid tumors. Sugiyama demonstrated that WT1 plays an oncogenic role via its antiapoptotic function and promotion of cell motility, and is thus a promising target for cancer therapy.

The third major new program at the Division of Health Sciences is the Center for Twin Research, led by **Kazuo Hayakawa.** "This is the first center in Japan to focus on collecting data from twins


A Laboratory at Osaka University Medical School


Kenji Yamada and Yuko Ohno


Osaka University Hospital

aged 65 to 100 to clarify the effects of genetics and environment on health," says Hayakawa. "For example, why would one twin die at 70 and the other at 100?"

The twin research project, which is one of the Japanese government's 'Life Innovation' programs, will assess 1,000 twins separated in their youth who went on to live in different environments. Researchers will use NMR, PET, and other similar methods to examine the subjects. Results will be stored in a biobank accessible to scientists worldwide. "We want to use the results for preventative medicine, and perhaps even for anti-aging strategies," says Hayakawa.

MORE INFO

Osaka University Graduate School of Medicine
www.med.osaka-u.ac.jp/index-e.html

Osaka University Hospital
www.hosp.med.osaka-u.ac.jp/

Osaka University Hospital Medical Center for Translational Research
www.hp-mctr.med.osaka-u.ac.jp/

Graduate School of Medicine, Division of Health Sciences
sahswww.med.osaka-u.ac.jp/eng/welcome.html

World-Class Interdisciplinary Research on Imaging the Human Immune System

Scientists at the Immunology Frontier Research Center (IFReC) of Osaka University are using a large-scale, interdisciplinary approach to spatiotemporal imaging of the body's immune system.

The Osaka University Immunology Frontier Research Center (IFReC) was selected in 2007 by the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) as one of only five coveted WPI (World Premier International) research centers.

"IFReC is a unique interdisciplinary research center built on the foundations of our pioneering work in immunology," says **Shizuo Akira,** director of WPI-IFReC. "We are taking a spatiotemporal approach to obtain a complete picture of the immune response in the human body. Our projects are a fusion of expertise in immunology, imaging technology, and bioinformatics."

One of the ultimate goals of the research at WPI-IFReC is to craft methods for controlling the dynamics of immune cells for the development of tailor-made vaccines and immunotherapy treatments.

Research at WPI-IFReC is being conducted by approximately 170 specialists of whom one-third are non-Japanese researchers. "We have made a conscious effort to establish an international center," says Akira. "In fact, five of the principle investigators are from overseas."


Shizuo Akira


Cevayir Coban

In fiscal year 2009, the WPI-IFReC acquired funding totaling ¥1.35 billion ($15.9 million) and its researchers published 229 articles—statistics that underscore the high level of research activity at the center.

Takao Kodama is administrative director at WPI-IFReC, with responsibilities that include supporting overseas researchers living in Japan. "One of the unique administrative aspects of this WPI-IFReC research project is that we deal directly with MEXT and our decision-making process is top-down," says Kodama. "We do not have to hold unnecessary faculty meetings. This enables a highly efficient administrative process. In addition, the WPI-IFReC administration has made a conscious effort to enable a smooth transition for overseas researchers moving to Japan, and to offer them convenient housing near the campus as well as assistance with preparing applications for grants and other such matters."

IFReC Research Building

"I am quite satisfied with the support we receive from the administration staff," says **Nicholas Smith,** a principle investigator from Australia, who was attracted to the world-renowned immunology research program at Osaka.

"English is the de facto language for both administration and research," says **Cevayir Coban,** a principle investigator who moved to Osaka from the United States and the recipient of a $100,000 research grant from the Bill and Melinda Gates Foundation. "The Japanese language is not a hurdle for conducting research here."

In addition to partnerships within Japan, WPI-IFReC is collaborating with overseas research institutions, including the National Institutes of Health; the University of California, San Francisco; the California Institute of Technology; Harvard University; New York University; Stanford University; POSTECH in Korea; and the Indian Institute of Science Education and Research in Bhopal, India.

The research facilities of WPI-IFReC include the 10-story, 10,000 m^2 Integrated Life Science building completed in June 2009, the four-story 2,500 m^2 Animal Resource Center, and a new nine-story 8,000 m^2 research space—scheduled for completion in March 2011—connected to the main research building. Notably, the WPI-IFReC is strategically located adjacent to the Research Institute for Microbial Diseases (RIMD) and the

CREDIT: (BOTTOM) BY J. SAKANOUE

"Clarifying the mechanisms of the innate immune response is important for the development of strategies for the treatment and prevention of malaria."

Institute for Protein Research (IPR), forming a massive interdisciplinary research complex.

WPI-IFReC is keen to recruit highly motivated postdoctoral researchers from overseas, and offers WPI-IFReC Kishimoto Foundation Fellowships of about ¥4,400,000 ($52,600) per year. The Kishimoto Foundation was set up in 2008 in honor of Tadamitsu Kishimoto, ex-president of Osaka University.

To enhance its global visibility, WPI-IFReC organizes a wide range of international workshops and symposia to encourage further research and collaboration. "We organize a Winter School with colleagues in Singapore," says Akira. "Postdoctoral researchers from overseas can apply for the 40 or so places available. The next Winter School is on January 16–21, 2012 and will be held on Awaji Island, in the Seto Inland Sea."

As part of its outreach programs, WPI-IFReC holds regular science cafés in the Osaka city center. "These are very popular," says Kodama. "We have many regulars who attend."

In vivo imaging of cell movement is one of the central themes of research at WPI-IFReC. Principle investigator **Masaru Ishii** is an expert on intravital two-photon imaging of bone tissue in vivo. Ishii recently discovered a method for regulating the mechanism governing osteoclastogenesis by controlling the dynamics of movement of osteoclast precursors between blood and endosteum. "The significance of our research is that we perform experiments in living animals, thereby giving us a real-life view of the dynamics of osteoclast cells, which are involved in bone tissue destruction and resorption," says Ishii, who is one of the many physician-scientists at WPI-IFReC.

Two of the major goals of Ishii's research are to find alternatives to bisphosphonates and vitamins for the treatment of bone resorptive disorders, and to develop in vivo visualization techniques to clarify the migration and differentiation of hematopoietic stem cells, which give rise to all bone marrow-derived cell types in the blood.

"Our discovery that sphingosine-1-phosphate regulates the migration of osteoclast precursors is an important advance for the treatment of

Nicholas Smith

Masaru Ishii

rheumatoid arthritis and osteoporosis," says Ishii. "Bone biology will become even more important as the number of aged people increases worldwide."

Label-free imaging offers several advantages over widely-used fluorescent techniques, including a simpler protocol and elimination of spurious data related to nonspecific interactions between labels and targets. At WPI-IFReC, Smith focuses on label-free imaging of living cells using optical Raman scattering. "We record light scattered from a cell scanned with 532 nm laser light, which resonates with molecular states in a cell," says Smith. "The challenge is detecting extremely low-intensity scattered light. Our setup enables the extraction of well-defined 3D images of molecular changes in cells."

Smith is also pursuing the use of nanoparticles to enhance the local light field around these particles, allowing for ultrahigh-resolution laser imaging and even real-time modification of cells. For example, particles can be heated using laser light to potentially ablate subcellular compartments, or the laser beam itself can induce changes in the cell directly.

"Recently, we controlled the beating of heart muscles using pulsed laser irradiation," says Smith. "This effect is due to the release of calcium ions during laser irradiation, and demonstrates how lasers are now being used in new ways for in situ measurement or control of biological functions."

Vaccine development to prevent malaria is another high-priority research area at WPI-IFReC. "Clarifying the mechanisms of the innate immune response—that is the body's natural resistance to the *Plasmodium* parasite—is important for the development of strategies for the treatment and prevention of malaria," says Coban.

Coban is using mouse models of malaria to develop new vaccines to fight the disease, in particular DNA vaccines incorporating adjuvants for efficient immunogenicity. Specifically, Coban is studying hemozoin—a pigment produced by the malaria parasites as a byproduct of blood digestion and an essential compound for their survival—for use as an endogenous vaccine adjuvant against malaria. "We found that hemozoin binds directly to TLR9 [Toll-like receptor 9] and activates it," says Coban. "Synthetic hemozoin acts as an adjuvant in a canine anti-allergen vaccine, and we concluded that hemozoin affects immune responses to malaria infection." These results have important implications for the development of vaccine adjuvants for malaria treatment in humans.

The WPI-IFReC is aiming to break new ground in immunological research, and its staff are deeply committed to creating a unique and highly-imaginative research base in Japan.

MORE INFO

Immunology Frontier Research Center (IFReC), Osaka University
www.ifrec.osaka-u.ac.jp/index-e.php

'Brothers in Arms' in the Fight Against Infectious Diseases

RIMD and BIKEN are two of Osaka University's premier institutes with a common mission to eradicate infectious diseases.

Shigeharu Ueda

Hitoshi Kikutani

The Research Institute for Microbial Diseases (RIMD) and The Research Foundation for Microbial Diseases of Osaka University (BIKEN) were established as 'brother' organizations in 1934 following a donation from Gendo Yamaguchi, an Osaka entrepreneur.

"Our roots can be traced back to 1934 and microbiologist Tenji Taniguchi, who was convinced of the need for a counterpart to the Institute of Infectious Diseases at Tokyo Imperial University, now the University of Tokyo," says **Shigeharu Ueda,** director of BIKEN. Taniguchi strongly urged the head of the Osaka Imperial University to set up an institute in Osaka "to pursue basic and clinical medicine." Both RIMD and BIKEN were established using funds from Yamaguchi, who was extremely impressed with Taniguchi's ambitious suggestions. Profits from BIKEN are used to fund research at RIMD in addition to supporting other academic research on microbial diseases.

RIMD conducts research on microbiology, oncology, and molecular biology. "We have more than 200 researchers here," says **Hitoshi Kikutani,** RIMD director. Researchers at RIMD have made significant contributions to the life sciences, examples being the discovery of cell fusion, which led to the development of monoclonal antibodies—important tools for drug discovery and basic research—and the discovery of the bacteria known as *Vibrio parahaemolyticus,* which causes food poisoning.

Importantly, RIMD participates in international research and maintains collaborative research centers with the support of the Japanese government, including the Thailand-Japan Research Collaboration Center on Emerging and Re-emerging Infections (RCC-ERI), which was set up in Bangkok in 2005. "The RCC-ERI is a partnership with Thailand's National Institute of Health," says Kikutani. "The facilities include biosafety level 3 laboratories for research on HIV/AIDS and avian flu."

Building on its success with RCC-ERI, in 2010 RIMD was selected to be a member of the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID), a five-year program launched by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) as a successor to the RCC-ERI with the goal of establishing long-term research activities via further development of the RCC-ERI initiative. As one of activities of this program, RIMD set up the Mahidol-Osaka Center for Infectious Diseases (MOCID) at Mohidol University in Thailand in 2010. Specific objectives include finding treatment solutions for bacterial infections, HIV/AIDS, and mosquito-borne infectious diseases through collaborations with infectious disease research organizations from other countries.

BIKEN is known internationally as Japan's largest manufacturer of vaccines, and in line with government reforms of nonprofit foundations, it was restructured into a general incorporated foundation in April 2010. "The vaccines we manufacture are developed and produced based on the fundamental research conducted at RIMD," says Ueda. "Recently, we were at the front line in the fight against the pandemic H1N1 influenza virus and produced 5 million doses of the vaccine."

Historically, BIKEN has been at the forefront of the development of vaccines. Shortly after the construction of the Ishibashi production plant in 1935, BIKEN was given approval for the manufacture of seven vaccines, including those for cholera and pertussis. Then, at the end of World War II in 1945, BIKEN played a central role in restoring the health of the Japanese people by supplying large quantities of vaccines to fight cholera and smallpox. In 1952, BIKEN received approval for the first made-in-Japan influenza virus vaccine, followed by another first in 1961 for inactivated polio vaccine. Between 1965 and 1970, BIKEN began manufacturing several forms of the measles vaccine, as well as a vaccine for chickenpox. Just recently, in 2009, BIKEN obtained approval for the manufacture of cell culture-derived Japanese encephalitis vaccine.

"Cell cultured production is faster than procedures using eggs," says Ueda. "The rapid spread of diseases requires equally rapid responses. We continuously strive to improve the development and manufacture of vaccines."

BIKEN may be an unsung hero in the fight against measles, having supplied the CAM70 vaccine to UNICEF. "Over ten years we supplied about 200 million doses of CAM70," says Ueda. "This vaccine eliminated measles in Brazil. In cooperation with JICA, the Japan International Cooperation Agency, we helped Indonesia to set up a manufacturing plant in Bandon, which is

“Preventative medicine not only prevents the spread of disease but also reduces the cost of national health care budgets.”

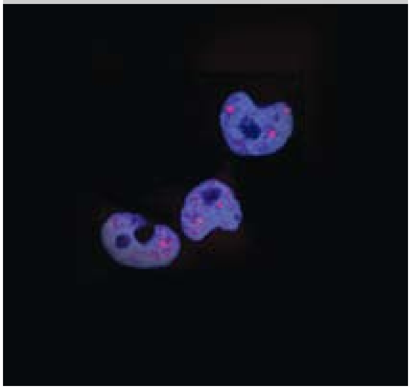
Malaria Testing Clinic

Keizo Tomonaga

being used to manufacture CAM70 for export.”

Ueda admits that, despite the success of CAM70, Japan still has not eliminated measles due to a lack of complete acceptance of vaccines by young mothers. In the 1990s, BIKEN transferred the know-how for the production of chickenpox vaccines to the U.S. company Merck & Co., Inc. “Our vaccines have had a dramatic effect on reducing chickenpox in the USA,” says Ueda. “Preventative medicine not only prevents the spread of disease but also reduces the cost of national health care budgets. For BIKEN the patent royalties from the vaccine for chickenpox raised about ¥10 billion ($120 million) over ten years, which was used to fund construction of a

Bornavirus



new production plant.” In addition to the manufacture of vaccines, BIKEN also offers JICA training courses on infectious disease-related topics approved by the World Health Organization.

Plans for the future include a major effort to develop a malaria vaccine. “About 40 percent of the world’s population lives in malaria-endemic regions,” says Ueda. “We have initiated clinical trials in Uganda for a malaria vaccine based on the serine repeat antigen [SERA], a protein produced by the *Plasmodium falciparum* parasite, which is responsible for malaria.” Phase 1 trials on vaccine safety were completed in December 2010. “Malaria is present only in the jungles of Asia, but is everywhere in Africa,” says Ueda. “About one million people die annually due to brain malaria alone.” RIMD researchers are administrating the SE36 SERA vaccine in Uganda. If approval is obtained, the vaccine will be manufactured at the Kanonji Institute of BIKEN, which complies with strict international good manufacturing practice (GMP) standards.

In a new initiative, BIKEN is funding a chair at RIMD to conduct research on dengue fever starting in April 2011, and will be building a laboratory at MOCID.

A recent highlight of research at RIMD is the discovery by **Keizo Tomonaga** and colleagues of DNA remnants of the nonretroviral bornavirus in mammalian genomes, including humans. These endogenous viruses are so called because they become integrated into the genome of their host. “About eight percent of the human genome is known to be composed of endogenous viruses,” says Tomonaga. “But this discovery was a case of serendipity.”

Bornaviruses cause neurological disorders in horses. The name originates from the city of Borna in Germany, where outbreaks of the disease were recorded to have occurred in 1885.

These findings imply that RNA viruses are extremely old, with analysis suggesting that bornaviruses have coexisted with primates for about 40 million years.

“This report generated a lot of international news coverage,” says Tomonaga. “In addition to newspaper reporters, the American Museum of Natural History contacted us about this discovery, and there is now a panel on display about so-called fossil viruses at the museum.”

MORE INFO

Research Institute for Microbial Diseases (RIMD)
www.biken.osaka-u.ac.jp/e/

Research Foundation for Microbial Diseases of Osaka University (BIKEN)
www.biken.or.jp/english/index.html

Critical Bridge For Drug Development

Located in the Saito Life Science Park in Northern Osaka, The National Institute of Biomedical Innovation fulfils the critical role of bridging the gap between basic research on drug discovery and drug development for commercialization.

Koichi Yamanishi

Tetsuji Naka

"NIBIO was set up by the Japanese government in April 2005 to act as a mediator between basic research at universities and commercialization by industrial corporations," says **Koichi Yamanishi,** director general of The National Institute of Biomedical Innovation (NIBIO). "Our institute plays a unique role in the development of drugs in this country."

The institute's three main functions are conducting basic research, sharing biological resources, and funding research. Furthermore, NIBIO's Tsukuba Primate Research Center houses a large scale breeding colony of about 2,000 monkeys—mostly cynomolgus macaques—whose family history has been recorded for over 30 years, making it a valuable resource available to researchers in pharmaceuticals research and development.

NIBIO's budget for fiscal 2010 is ¥11.20 billion ($133 million). "We actively support innovative ideas," says Yamanishi. "It is not widely known that NIBIO funded Shinya Yamanaka during the early stages of his research on induced pluripotent stem (iPS) cells." NIBIO also funds venture companies and offers grants and consultation on so-called orphan products—pharmaceuticals and medical devices for rare diseases—which large corporations can be reluctant to invest in because of the small numbers of affected patients and consequently limitations in recouping development costs.

In spite of the relatively small size of NIBIO, statistics underscore the significant scientific contributions of its 50 full-time researchers and their groups. For example, in fiscal year 2008 each NIBIO researcher received on average ¥16 million ($190,000) from competitive grants—the highest grants per person ratio for researchers at Japan's approximately 30 independent administration agencies. Furthermore, in 2009 each researcher published an average of three peer-reviewed papers—about twice the number in 2005.

In April 2010, NIBIO started its second phase of research (scheduled for completion in 2014) focusing on three areas:

(1) Next generation vaccines with an emphasis on the development and understanding of adjuvants to enhance efficacy;

(2) Drug toxicity testing systems including a new method to induce differentiation in a variety of stem cell types;

(3) Treatment of intractable or rare diseases by analyzing the molecular mechanisms governing these disorders and the development of relevant technologies for diagnosis and treatment.

Since 2008, NIBIO has been working on two industry-academia-government collaborative projects based on Super Special Consortia programs for the development of cutting-edge medical care. They are the Next Generation Infectious Disease Vaccine Innovation Program, and the Development of a Novel Drug Toxicity Testing System using human iPS cells. Notably, these projects were two of only 24 such programs approved by the government.

"The development of a drug takes about 15 to 20 years," says Yamanishi. "NIBIO was set up only five years ago, and during the second phase of research I want to push for actual commercialization of some of the drugs being studied in our projects." NIBIO also works with international groups including Cambridge University (on bioinformatics), as well as Peru and the Solomon Islands (on medicinal plants).

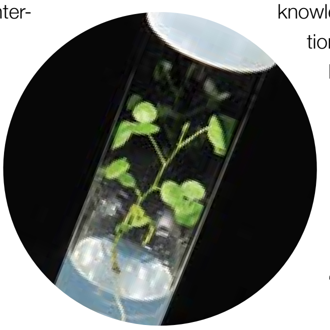
Medicinal Plant Research

Nobuo Kawahara is director of the Research Center for Medicinal Plant Resources (RCMPR). "Our center is the only comprehensive research facility in Japan conducting research on the cultivation and biochemical analysis of medicinal plants," says Kawahara.

The center cultivates and preserves more than 4,000 species and groups of medicinal plants, and supplies seeds and advice to other research institutes. Notably, only 12 percent of the medicinal plants used in Japan are produced in the country—the remainder being imported from China and other countries. "We want to expand the sources of these 'second type of rare-earths'—the first kind being metals such as lithium used in batteries—by working with other countries," says Kawahara.

Recently, a research group at RCMPR produced liquorice root by hydroponic culture—growing plants using mineral nutrient solutions in water and without soil. Liquorice root contains the sweet-tasting compound glycyrrhizin and is widely used as an herbal medicine, as well as a sweetener for food products.

Furthermore, another medicinal plants group has developed medicinal treatment for Leishmaniasis, a disfiguring disease transmitted by sand flies, based on screening of medicinal plants in countries including Myanmar, Peru, and the Solomon Islands. "We used the local knowledge to produce a solution for this disease," says Kawahara.



SOCS for Intractable Diseases

Tetsuji Naka is the project leader of the Immune Signaling Project. "We need to work on

"We hope that our research will enable a reduction in both time and cost of drug development, as well as the development of safer drugs."

Nobuo Kawahara

Tetsuro Urushidani

Ken Ishii

people," says Naka, "and not [only on] cells or lab animals. So we are working with colleagues at the Osaka University Graduate School of Medicine on the treatment of intractable diseases such as cancer using SOCS [suppressor of cytokine signaling] gene delivery."

SOCS is a family of genes involved in inhibiting the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signaling pathway. "Abnormal expression of SOCS molecules can cause dysregulated cytokine signaling, which leads to the development of disease," says Naka.

Recently, Naka and colleagues found over-expression of SOCS3 in cancer cells to be an effective new treatment for malignant pleural mesothelioma—a form of lung cancer caused by exposure to asbestos. This is an important development considering that asbestos-related diseases are expected to reach a peak in around 2030.

Predicting the Toxicity of Drugs

Tetsuro Urushidani is project leader of the Toxicogenomics/Informatics Project, which was recently awarded The President's Prize from the Science Council of Japan for the development of new biomarkers for human safety. "This is a large project involving academia, government, and 13 companies, including Astellas Pharma, Daiichi Sankyo, and Takeda Pharmaceutical Company," says Urushidani.

The project has yielded a toxicology database, called the Toxicogenomics Project-Genomics Assisted Toxicity Evaluation system (or TG-GATEs), containing millions of data points collected by observing in vitro changes in gene expression following administration of more than 150 drugs. The database can be applied in the early stages of drug development to predict toxicity risk and characterize the molecular mechanism of this toxicity, without the need for expensive animals testing.

"We hope that our research will enable a reduction in both time and cost of drug development, as well as the development of safer drugs," says Urushidani.

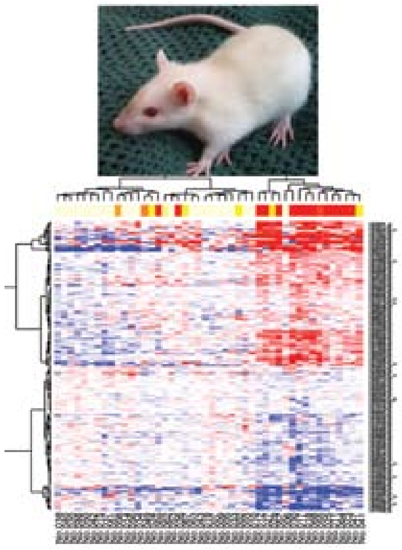
Vaccines and Innovative Adjuvants

Ken Ishii is the project leader of the Laboratory for Adjuvant Innovation. He is developing vaccines and their adjuvants—substances added to vaccines to increase the response of the immune system. Ishii joined NIBIO because he wanted to take his ideas from the lab to real world applications, and "not just write high-impact papers."

"We lack a fundamental understanding of the mechanisms by which viral preparations affect the immune response of the body," says Ishii. "In October 2010, we established the Next Generation Adjuvant Research Group to address these issues." Notably, the Adjuvant Group includes members from vaccine manufacturers and venture capital companies.

Recently, Ishii reported on why some influenza vaccines work better than others, and determined that a rare immune system cell type, plasmacytoid dendritic cells, modulate the effect of inactivated flu virus vaccines, but not live virus vaccines. "These results highlight the importance of our research," says Ishii. "We need a scientific approach to understanding adjuvants, otherwise interest in adjuvant research may dwindle, similar to the demise of gene therapy with viral vectors, which saw a dramatic decrease in activity following the death of patients on this therapy."

Treatment of malignant pleural mesothelioma



Hierarchical clustering of genes and chemicals

MORE INFO

National Institute of Biomedical Innovation
www.nibio.go.jp/english

"One plus one equals three and a little more" at the National Cerebral and Cardiovascular Center

The NCVC launches the Research and Development Initiative Center for an integrated approach to translational research in the 21st century.


Nobuo Hashimoto


Yoshiyuki Taenaka


Hiroaki Naito


Kazuo Minematsu

The National Cerebral and Cardiovascular Center (NCVC) was established in 1977 by the Japanese government for the treatment of cardiovascular disease and to investigate its causes. "Our founding fathers had great foresight in setting our mission as being the treatment of both cerebral and heart diseases," says **Nobuo Hashimoto,** president of the center, "because a malfunction of, say, the heart can lead to a stroke due to clogged blood vessels in the brain." Invoking a common Japanese expression, Hashimoto further illustrates the benefit of the center's broad mission: "Our integrated approach to treatment utilizes all our extensive resources, where one plus one equals three and a little more."

The NCVC is internationally renowned for its scientific contributions, including the discovery of bioactive peptides such as atrial natriuretic peptide and brain natriuretic peptide, the development of artificial hearts and lungs, and research into the rapid treatment of acute cerebral thrombosis using the thrombolytic drug tissue plasminogen activator (t-PA) in combination with, or without, catheter procedures.

In April 2010, the Japanese government reorganized the NCVC into an independent administrative institution, thereby giving Hashimoto and his staff greater autonomy to hire specialists—especially from industry—and initiate new wide-ranging collaborative research activities.

The NCVC has continued to evolve. "We set up the Research and Development Initiative Center (RDIC) in April 2010," says **Yoshiyuki Taenaka,** director of the RDIC. "This center was set up by the NCVC and offers a one-stop approach for translating basic research and clinical trials into real-life applications."

Notable areas covered by the RDIC include preventative medicine and epidemiologic informatics, a biological and clinical data bank, and intellectual asset management. "We want to share our wealth of assets with the public and industry," says Taenaka, "including our knowledge of how to prepare healthy diets for patients suffering from specific ailments. We also have research facilities for drug and medical device trials, which we are willing to share with industry."

These resources include the NCVC Hospital. "Our hospital has 640 beds of which about 30 percent are for treatment of diseases requiring intensive care," says **Hiroaki Naito,** director general of the hospital.

Staff at the RDIC are committed to Director Taenaka's vision. "My mission is to support clinical trials," says **Haruko Yamamoto,** director, Department of Advanced Medical Technology Development. "We are testing drugs for efficacy against so-called orphan diseases, which large pharmaceutical companies often ignore because they are not commercially viable."

An important mission of the RDIC is the secure collection, storage, and analysis of data on cardiovascular disease for preventative medicine. "Clarifying the cause of stroke and cardiovascular disease is important as a first step in prevention," says **Yoshihiro Miyamoto,** director, Department of Preventative Medicine and Epidemiologic Informatics. Studies of residents in highly populated Japanese cities show higher occurrences of heart disease compared with other Japanese cohorts. "This reflects the possible effects of modern urban life in Japan," says Miyamoto.

When prevention fails, rapid treatment is essential. "We established the first stroke care unit and earliest coronary care unit in Japan," says **Kazuo Minematsu,** deputy director general of the NCVC Hospital.

The NCVC multidisciplinary team, including **Takeshi Nakatani,** director, Department of Transplantation, has made tremendous contributions to heart transplants and clinical applications of the ventricular assist device (VAD) including the NCVC-type, for long-term circulatory support.

In addition to reducing treatment time during emergencies, the NCVC is initiating trials of a 'mobile telemedicine' system that will transmit essential medical data from ambulance to hospital, aiding physicians in their diagnosis prior to the patient reaching the hospital. Recently, Hiroshi Nonogi, chairman of the Department of Cardiovascular Medicine was awarded the first International Collaboration in Resuscitation Science Award by the American Heart Association, underscoring the high quality of hyperacute care at NCVC.

But NCVC is not resting on its laurels. "We plan to integrate the hospital, research laboratories, and the new RDIC into a single building to create an environment even more conducive for translational research," says Hashimoto.

MORE INFO

National Cerebral and Cardiovascular Center

www.ncvc.go.jp/english/


Haruko Yamamoto


Yoshihiro Miyamoto


Takeshi Nakatani

Realizing the Potential for Life Sciences in Osaka

The Northern Osaka Biomedical Cluster consists of an area covering a 20 km radius, centered on the Doshomachi district, Osaka City. The origin of the district goes back to 17th century when it became the national center of pricing and distribution of raw materials for herbal medicines.

Saito Life Science Park and Nearby Research Institutes

The cluster was established based on the ambitious vision of Yuichi Yamamura, former president of Osaka University, to make Northern Osaka a destination for the life sciences.

This vision is now coming to fruition. A significant development was the opening in September 2008 of the Osaka Bio Headquarters at the Senri Life Science Center building to act as a bridge in coordinating bioscience projects involving academic, industrial, and governmental organizations. Additionally, a number of startup companies have been established in the area, over 300 Osaka Pharmaceutical Manufacturers Association (OPMA) member companies are conducting business around Doshomachi, and world-class research is being carried out at institutes such as the National Institute of Biomedical Innovation, the National Cerebral and Cardiovascular Center, Osaka University, Osaka Prefecture University, and the National Institute of Advanced Industrial Science and Technology (AIST).

In the cluster, the Saito Life Science Park (LSP) is becoming increasingly important as a place to conduct biotechnology research and business, with 40 companies and approximately 1,300 researchers and support staff working on site. Small and medium sized companies and university startups will be able to expand their business at the Saito Bio Incubation Facilities, which include wet labs and animal research facilities.

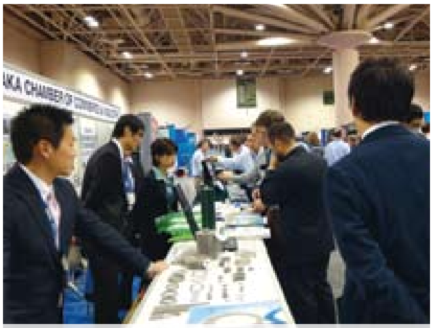
Additionally, a new industrial park neighboring the Saito LSP is scheduled to begin operation in the spring of 2014. It is expected that innovative industries, including those in the life sciences, will move to this area and join those already established in the Saito LSP.

To accelerate biotechnology development in the Osaka region, an ambitious set of goals called the Osaka Bio Strategy has been laid out. These goals—including that the Osaka Bio Cluster should rank at least 5th worldwide in the biomedical field within 10 years—were devised by the Osaka Bio Strategic Promotion Conference, headed by Toru Hashimoto, governor of Osaka, and chaired by Tadamitsu Kishimoto, former president of Osaka University.

The Osaka Bio Strategic Promotion Conference consists of 10 organizations (listed on page xv). The policies of the Conference are implemented by the Osaka Bio Support Group, made up of 20 members from the front line of the biotechnology field, led by Isao Teshirogi, president and representative director of Shionogi & Co., Ltd.

In an effort to support startup companies, the Osaka Bio Strategy made provisions for the Osaka Bio Fund—¥1.1 billion ($13 million) in assets to provide finance for new continued »

"World Medical Polis, Minnesota" Event in Osaka



Osaka Booth at MD&M in Minneapolis

Institut Pasteur has signed an MOU with OCCI

Osaka Bio Strategic Promotion Conference Member Organizations

Ministry of Economy, Trade and Industry (METI), Kansai Bureau

National Cerebral and Cardiovascular Center

National Institute of Biomedical Innovation

Osaka Bioscience Institute

Osaka Chamber of Commerce and Industry

Osaka Pharmaceutical Manufacturers Association

Osaka Prefectural Government

Osaka Prefecture University

Osaka University

Senri Life Science Foundation

MORE INFO

Osaka Bio Headquarters
www.osaka-bio.jp/en/

ventures in pharmaceutical products and medical devices.

Making the most of another of Osaka's advantages—a highly-skilled biotech workforce from world-class universities—Osaka Bio Headquarters provides human resources matching programs to introduce postdoctoral researchers and senior specialists to startup companies.

On the clinical side, Osaka Bio Headquarters organizes the Osaka Clinical Trials website in cooperation with OPMA. The website releases the results of clinical trials run by Osaka's 13 highly specialized hospitals.

Established in May 2009, the Protein Mall Kansai (PMK, protein-mall.osaka-bio.jp/en/) is Japan's largest assembly of protein-related research institutes and companies, organized by the Osaka Bio Headquarters and the Senri Life Science Foundation.

The 75 members of PMK aim to create commercial opportunities through the practical application of protein-related research, the promotion of collaborative research, and the support of contract research, all of which contribute to innovative technology and new business in the Kansai region, which includes Osaka and five other Prefectures.

The Osaka Chamber of Commerce and Industry (OCCI) promotes open innovation by providing business-matching programs. Specific programs include the Drug Seeds Alliance Network Japan (DSANJ, www.dsanj.jp/e/) with OPMA as a co-organizer, formed to accelerate technology transfer in the following areas: drug candidates and targets; foods and cosmetics; biomarkers, diagnostics, and reagents; and platform technologies.

OCCI maintains the DSANJ database and conducts partnering events categorized by disease area, country, or region. There are already 164 organizations networked as technology providers, and 55 pharmaceutical companies with a presence in Japan have registered as technology searchers. DSANJ is active internationally, having organized successful meetings for European and Korean companies on Alzheimer's disease.

The Medical Device Forum holds regular monthly meetings where professional medical researchers and doctors from medical institutions propose joint projects for industry to develop, such as medical devices, biomedical protocols, and equipment. OCCI conducts the World Forum for BIO/MEDICAL Device in Kansai for stimulating alliances between Japanese and overseas companies in medical device fields. Utilizing the Kansai region's strengths in developing advanced medical platforms, these initiatives are seen as economic models that can be applied nationwide in the drug discovery and the medical device industries.

International Partnerships

In February 2010, OCCI signed a memorandum of understanding (MOU) with the Bio Business Alliance of Minnesota, United States—one of the top medical device clusters in the world—with the goal of forming an alliance between Japanese and Minnesota-based companies to promote the development and commercialization of medical devices.

Furthermore, an MOU between OCCI and Institut Pasteur in Paris, France in the field of drug development was signed June 2010. Institut Pasteur maintains a presence on the DSANJ database, posting technology information that serves to promote alliances with Japanese pharmaceutical companies.

The Kansai Bio Promotion Conference has also signed MOUs with partners in France, Belgium, and the State of Queensland in Australia.

These alliances are possible because of the historical accomplishments of the life sciences community in Osaka. This community plans to continue building upon this strong foundation, creating greater potential for life science-related research and business in the future.

Dynamic and Evolutionary Research on Protein Science

The Institute for Protein Research was set up in 1958 as a joint-use research facility of Osaka University and has played a central role in protein science both in Japan and around the globe.

"In the early days this institute was addressing issues related to nutrition," says **Toshiharu Hase,** director of the Institute for Protein Research (IPR). "Now we conduct fundamental research on protein science—P450 was discovered here. We also support the development of the Worldwide Protein Database and the Protein Data Bank of Japan [PDBj, www.pdbj.org]."

The IPR has state-of-the-art research facilities, including equipment for X-ray analysis and a powerful 950 MHz nuclear magnetic resonance spectrometer. There are also plans to install a cryo-electron microscope. Notably, IPR has a dedicated beamline at the SPring-8 synchrotron facility in Hyogo, which is available for collaborative research.

IPR has inter-faculty agreements with a number of academic institutions, including Peking University in China, Yonsei University and Seoul National University in South Korea, National Tsing Hua University in Taiwan, Indian Institute of Chemical Biology in India, and the University of Manchester in the United Kingdom. The institute also often welcomes international scientists, for example it hosted eight researchers from seven overseas countries in 2009.

IPR is also the source of new, enabling technologies. **Junichi Takagi** is a structural biologist at the Laboratory of Protein Synthesis and Expression. "Our group has developed a high purity recombinant protein expression/purification system for a wide range of proteins," says Takagi. "We have created an inexpensive and fast affinity purification method, which has played a vital role in many structural biology projects." Recently, Takagi was the focus of international attention when he clarified the 3D structure governing semaphorin signaling through the plexin receptor. "We used X-ray analysis to determine the 3D structure of Semaphorin 6A and Plexin A2, before and after signal transmission," says Takagi. "Our discovery will contribute to the understanding of the mechanism underlying many serious diseases and the development of new drugs." Indeed, this report resolves the structural mechanism governing receptor activation, namely the transmission of signals across membranes.

Toshiharu Hase

Junichi Takagi

Takagi is also conducting research on the structure of proteins that are implicated in neuronal synapse functions through ultrastructural analysis of proteins using electron microscopy and tomography.

"I want to use our know-how to tell the whole biological story based on the 3D structures of proteins," says Takagi.

Also interested in structural biology is **Akira Shinohara** at the Laboratory of Genome and Chromosome Functions, who is investigating the molecular mechanisms of homologous recombination using molecular, genetic, and biochemical methods.

Akira Shinohara

"Malfunction of homologous recombination leads to cancer and infertility in humans," says Shinohara. "My research interests are to clarify the mechanism of homologous recombination in eukaryotes and the mechanism of meiotic recombination."

Shinohara is studying the role of protein/genes in the RAD52 family both in vivo and in vitro, and in particular, researching Rad51—a homolog of bacterial RecA. Notably, Rad51/RecA is known to form a right-handed helical filament on single-stranded (ss) DNA and carry out homology search and strand exchange during the recombination process. Since the Rad51-mediated exchange event is inefficient in vitro, other factors must be required to promote this reaction, including Rad52-mediated formation of a ring-like structure on the ssDNA, which facilitates the binding of Rad51 to the DNA.

"We are also studying recombination and chromosome dynamics during meiosis—a type of cell division that occurs during the production of gametes [eggs and sperm]," says Shinohara.

Recent work has implicated the Csm4 protein in the specific movement of DNA ends during recombination. "Our results imply that chromosome movement promotes a variety of biochemical reactions on chromosomes including meiotic recombination," says Shinohara. "More recent experiments indicate that physical forces may be regulating chromosome functions—that is, physics may regulate biochemistry."

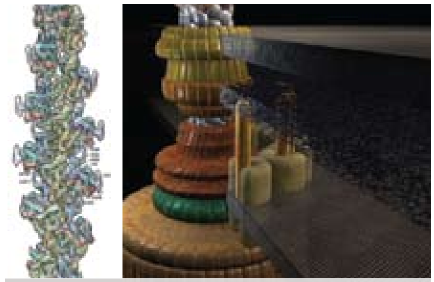
MORE INFO

Institute for Protein Research,
Osaka University
www.protein.osaka-u.ac.jp

Excellence in Interdisciplinary Research and Education

Osaka University's Graduate School of Frontier Biosciences offers a stimulating environment for cutting-edge interdisciplinary research on biological system dynamics.

Keiichi Namba



Structure of F-actin and Flagellar Motor

The Graduate School of Frontier Biosciences (FBS) at Osaka University was established in 2002. "Our mission is to educate graduate students in an interdisciplinary environment," says **Keiichi Namba,** dean of FBS. "Our 70 or so faculty members are from diverse backgrounds including mathematics, physics, chemistry, medicine, and information science. And our approximately 250 graduate students interact with these specialists. It's a unique graduate school, and very popular with students from both Japan and overseas."

Doctoral students at FBS receive support from the prestigious Global Center of Excellence (GCOE) program running from 2007 to 2011. As part of this program, students spend one month doing their research in the laboratory of another research group. "This enables students to gain firsthand experience in interdisciplinary research," says Namba.

The graduate school entrance examination at FBS is flexible, offering applicants the choice of sitting exams in physics/mathematics, biology, or chemistry. "We welcome students from overseas with appropriate TOEFL [test of English as a foreign language] and GRE [Graduate Record Examination] scores," says Namba.

In addition, the FBS holds annual symposia, biannual summer schools, and annual retreats—which are open to overseas participants—and supports collaborative visits of students and postdocs to universities and research institutes in the United States, Europe, and Asia.

Namba is a biophysicist specializing in biological nanomachines. "We analyze the structure and dynamics of macromolecular assemblies using techniques including electron cryomicroscopy and X-ray diffraction," says Namba. "Recently, we used cryomicroscopy to successfully visualize the structure of F-actin in a few days." F-actin is the helical polymer of a protein, actin, which is an essential component of muscle fibers and cell cytoskeletons. These results offer a deeper understanding of the cellular mechanisms governing life. Namba is also investigating the source of energy for the torque of the bacterial 'flagellar motor'—a rotary nanomachine composed of assemblies of proteins—and how the tiny helical propellers connected to the rotary motor propel bacteria through liquids.

Toshio Yanagida, who is the leader of the Soft Biosystems Group at Osaka University and a pioneer of single molecule imaging, is now focused on the dynamics of living cells. "Molecular machines use fluctuations such as Brownian motion," says Yanagida. "A deeper understanding of how living cells use such fluctuations—or *yuragi*—to process enormous amounts of information will enable the design of more energy-efficient and robust machines."

In 2011 and 2012, Yanagida is launching two major interdisciplinary projects. One is the Quantitative and Computational Biology Center (QBiC), which begins in April 2011 and aims to develop a comprehensive understanding of biological system dynamics. "This is a multi-institute project with Osaka University and RIKEN," says Yanagida. "We will focus on the basic elements regulating biological systems while developing new experimental and theoretical techniques. The infrastructure for the project includes a new 7000 square meter building, 15 principle investigators, 60 postdoctoral researchers, 20 technicians, and more than 20 graduate students. We aim to double this manpower by 2013," says Yanagida.

Toshio Yanagida

The other initiative is the Brain Information Transmission Interdisciplinary Research Center, to be launched in 2012 in collaboration with the National Institute for Communication Technology (NICT, in Hyogo) and the Advanced Telecommunications Research Laboratory (ATR, in Kyoto). "This project focuses on how the brain processes internal and external information, and how to transmit this data to a computer. This could revolutionize human-machine communication and network system technologies," emphasizes Yanagida. The project is based on three main pillars: heart-to-heart science (HHS), brain–machine interface (BMI), and brain-function installed information network (BFI).

The aim of these collaborations is to analyze the flow of information, energy, and materials within living organisms and interface them with an external control system. "We will start with single molecules and work up towards the whole brain," explains Yanagida. "Ultimately, such studies are expected to lead to the construction of highly energy-efficient machines and advanced medical diagnostics."

MORE INFO

Graduate School of Frontier Biosciences, Osaka University
www.fbs.osaka-u.ac.jp

CREDIT: (TOP RIGHT) PROFESSOR KEIICHI NAMBA, OSAKA UNIVERSITY

Pharmaceutical Approach to Alleviating Human Disorders

Scientists at the Graduate School and School of Pharmaceutical Sciences of Osaka University are dedicated to investigating a range of pharmaceutical and health sciences, including cancer and psychiatric disorders. Here, we talk to two prominent members devoted to translational research.

Kazutake Tsujikawa

Hitoshi Hashimoto

Kazutake Tsujikawa is known for the discovery of prostate cancer antigen-1 (PCA-1), a gene highly expressed in prostate cancer and pancreatic cancer. "Prostate cancer is one of the biggest killers in the world," says Tsujikawa. "We are using mouse models to study whether this gene can act as a molecular marker, a biomarker, for this type of cancer, which may allow early diagnosis."

Currently the biological roles of this novel gene remain unclear. Tsujikawa and colleagues found that in vitro silencing of PCA-1 induced apoptosis in cancer cell lines and significantly reduced tumor formation in vivo. They concluded that PCA-1 may serve as a promising molecule target for prostate cancer and pancreatic cancer therapy.

Tsujikawa has recently developed an enzyme-based assay for PCA-1 activity to aid in screening possible therapeutic agents. "PCA-1 is a member of the hABH [human AlkB homologs] family," says Tsujikawa. "We have also discovered that the expression of hABH family proteins may correlate with specific cancers. The hABH family of molecules could be targets for cancer therapy. We are working on a joint industry-academia-government project to clarify the cancer mechanisms for translational research."

This research is being conducted in collaboration with the medical school of Osaka University, Nara Medical University, Kagoshima University, and Hyogo University of Health Sciences. Tsujikawa is also pursuing research as part of the Ministry of Education, Culture, Sports, Science and Technology's Knowledge Cluster Initiative (second stage) and the Program for Promotion of Fundamental Sciences in Health Sciences of the National Institute of Biological Innovation.

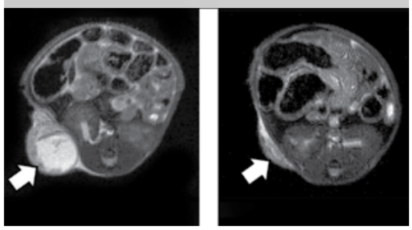
Tsujikawa is also working on calcitonin gene-related peptide (CGRP) that is released from sensory nerve endings. CGRP is known to play a central role in migraine and diseases such as heart failure. "We have generated mice deficient in RAMP-1 [receptor activity modifying protein 1], a specific subunit of CGRP receptors. Interestingly, RAMP-1-deficient mice showed recovery from experimental allergic encephalomyelitis. The result indicates that CGRP plays a crucial role in controlling the body's immune system," says Tsujikawa. The research is supported by the Japan Chemical Industry Association as part of the International Council of Chemical Associations Long-Range Research Initiative.

Hitoshi Hashimoto is at the Laboratories of Molecular Neuropharmacology where he investigates the molecular mechanisms for psychiatric disorders and drugs for their treatment. "We are using molecular biology and animal models to identify new molecular targets for the development of drugs," says Hashimoto.

Hashimoto is investigating the molecular pharmacology of pituitary adenylate cyclase-activating polypeptide (PACAP); identifying and evaluating hyperplasia-associated gene of beta cell (HPGB), regenerating islet-derived protein 3 (RegIII), and prostaglandin receptor CRTH2 as molecular targets for drug discovery; and developing methods to differentiate embryonic stem cells into neurons.

"In 1993, we successfully cloned the cDNA of the PACAP-selective receptor, PAC1, in rat brain," says Hashimoto. "Since then we have investigated the role of PACAP in the nervous system."

MRI images of diminished tumor growth in PCA-1-knockdown prostate cancer cells in a xenograft system (left, control; right, PCA-1 knockdown). The arrow indicates a tumor.



Hashimoto's research includes in vivo studies on PACAP signaling, which led to the development of mice lacking the PAC1 receptor gene and/or PACAP gene and a transgenic mouse line overexpressing the PACAP gene. Notably, mice lacking PACAP (PACAP-/-) exhibited behavioral abnormalities, including explosive jumping, suggesting that PACAP has a role in the regulation of psychomotor functions.

Furthermore, clinical genetic experiments showed variants of the genes encoding PACAP and PAC1 receptor to be associated with schizophrenia, implicating PACAP-mediated signaling pathways in psychiatric disorders.

Recently, Hashimoto used PACAP-deficient mice as a model to study how light intensity affects resetting of the circadian clock when light cycles are altered. Intriguingly, PACAP-deficient mice also showed depression-like behavior, making them potentially useful for studies on the mechanistic association between an altered biological clock and depression.

Hashimoto's research has an international perspective. "I collaborate with David Vaudry at INSERM, France; Herbert Meltzer at the Vanderbilt University Psychiatric Hospital; Dóra Reglödi at University of Pécs, Hungary; and many colleagues elsewhere."

MORE INFO

Graduate School and School of Pharmaceutical Sciences, Osaka University
www.phs.osaka-u.ac.jp/en/

Breaking the Mold: Changing Traditional Views of Dentistry

The Graduate School of Dentistry at Osaka University plans to introduce ambitious new programs for a molecular biology-based approach to training dentists in the 21st century.

Graduate School of Dentistry

Approach for Periodontal Tissue Regeneration

"What is a dentist?" asks **Toshiyuki Yoneda,** dean of the Graduate School of Dentistry at Osaka University. "I am afraid that dentistry is still viewed as a surgical-based vocation involving filling cavities and pulling teeth. We want to destroy this antiquated view because we believe that the future skill sets of dentists must cross many disciplines, including pharmacology, law, and even the arts."

The heart of the problem in Japan is the rapidly aging population. "The majority of patients in Japan are middle-aged or above, and traditional ailments such as tooth decay are no longer the main issues for dentists," says Yoneda. "For example, periodontal disease in an elderly patient can be linked to other diseases such as diabetes and cardiovascular disease, so dentists must be able to understand these other systemic disorders. We must revise the education curricula for dental schools to include a deeper understanding of molecular biology and pathophysiology."

Yoneda also says that he wants Osaka University—a comprehensive university with schools of medicine, pure sciences, engineering, and arts—to introduce new curricula for training dentists. As a first step, Yoneda has submitted a proposal to the Ministry of Education, Culture, Sports, Science and Technology to establish a program on 'Life Innovation'. The six-year program would focus on intractable diseases of the mouth and their relationship with other diseases of the body. Distinctive features of the program include: the awarding of a Master of Oral Diseases to graduates of a post-residence course, introduction of special lectures on 'biodentistry,' creation of a personal genome database using 'oral bioinformatics,' and the establishment of an 'intractable diseases international station.'

In addition to these plans, Yoneda and his colleagues are also involved in cutting-edge research. Recent highlights include studies on bone biology in which the researchers discovered a link between stress signals in the endoplasmic reticulum (ER)—an important cellular compartment in which protein folding occurs—and activation of vesicular trafficking out of the ER.

In an equally high-impact contribution, Yoneda's group conducted experiments in an attempt to quantify pain. "Pain is a subjective experience, but our experiments show promise as a means of producing an objective view," says Yoneda. Experiments on inflammatory pain in rats showed the importance of proton sensing receptors, such as TRPV1, in the transmission of pain. When activated, TRPV1 appears to upregulate calcitonin gene-related peptide (CGRP) expression, a scenario associated with inflammatory pain.

"We have also been working on using drugs to treat oral diseases, instead of periodontal surgery," says Yoneda. "We have convincing results showing that teeth weakened by periodontal problems can be made stronger by drug therapy using fibroblast growth factor-2 [FGF-2]."

At the Cell Processing Center, the group led by **Shinya Murakami,** head of the Department of Periodontology, is extracting fat cells to generate periodontal tissue. "This is the first such center in a dental school in Japan and, although we are still in the early stages, we have had encouraging results that indicate the possibility of producing periodontal tissue from fat cells," says Yoneda.

The Osaka University Graduate School of Dentistry holds many joint symposia with universities and institutes in the United States, United Kingdom, Korea, and Thailand. Osaka students can go to the United States for two–month 'home stays' to improve their English.

The dental school holds regular community outreach forums to emphasize the importance of dentistry, and its evolution, for the young and old.

Surgery at the Translational Research Center

Osaka University was the first government-run comprehensive university to establish a school of dentistry. "We pioneered dentistry in Japan," says Yoneda. "I am confident that our new initiatives based on a molecular biology approach will inspire education and research at dental schools in Japan and globally."

MORE INFO

Graduate School of Dentistry, Osaka University
www.dent.osaka-u.ac.jp/english

Evolution from Molecular Biology to Atomic Biology

Seiki Kuramitsu believes that thermophilic bacteria, which live in water temperatures close to boiling, offer an excellent model for creating a new system biological field of life sciences that predicts biological function through atomic-level analysis.

"In spite of the tremendous advances in the life sciences, it is still not possible to accurately predict the results of medical treatment," says **Seiki Kuramitsu,** professor in the Department of Biological Sciences, Graduate School of Science, Osaka University. This department was established in 1949 for education and research in the biological sciences, based on advances in science at the boundary of chemistry and physics. "I believe that it is necessary to construct a new field of life science whereby we can predict the response of an organism based on chemistry."

Kuramitsu's laboratory and many research groups are investigating whether biological phenomena underlying different environmental stimuli can be defined in single cells by studying the 3D structure and function of all the intracellular molecules at an atomic level.

Seiki Kuramitsu

"*Thermus thermophilus* HB8, an extremely thermophilic bacterium that thrives at 80°C, is an excellent model for structural and functional studies. Its constituent proteins are stable, and most of its approximately 2,200 genes are common to many other organisms, including humans," says Kuramitsu.

The four aspects required for understanding the whole cell system are: (1) structural genomics, (2) functional genomics, (3) functional analysis of each system, and (4) simulation and prediction of all biological phenomena in the cell.

"The goal of our so-called Whole Cell Project is prediction, as opposed to explanation," says Kuramitsu. "I want to move from molecular biology to atomic resolution biology."

"This is a *human* project, not just an *Osaka* project," adds Kuramitsu. "Also, this is not a subject just for medical school researchers; it is an interdisciplinary subject. We welcome the world's scientists to join us."

MORE INFO

The Whole Cell Project
www.thermus.org/e_index.htm

Cognitive Neuroscience Robotics at Osaka

Osaka University launches an innovative program in cognitive neuroscience robotics, supporting education and development of technology at the human-machine interface.

The goal of the Global Center of Excellence Program (GCOE) based on cognitive neuroscience robotics is to develop new information and robot technology systems to provide information and services based on cognitive neuroscience. "This highly competitive five-year GCOE program was launched in 2009," says **Hiroshi Ishiguro,** leader of the program. "I believe that we were awarded the project because of our interdisciplinary approach towards cognitive science and robotics."

The project involves experts from robotics, neuroscience, and human sciences. "Cognitive neuroscience is related to meta-level brain functions such as memory and reasoning," says Ishiguro. "Conventional information and robot technology, IRT, has produced a more convenient world but without regard for effects on our cognitive functions. We want to establish new paradigms based on cognitive neuroscience for safe and adaptable IRT systems."

One of the goals of the program is to establish a new graduate school department for students to study cognitive neuroscience robotics. "There are many hurdles to overcome to achieve this goal, with the highest being the need to scrap old and low-performing research areas," says Ishiguro. "The big question is whether Osaka University can do this."

The research and educational activities of the GCOE program are coordinated with the Advanced Telecommunications Research Institute International (in Kyoto) and the National Institute of Information and Communications Technology (in Hyogo) in Japan, and institutes overseas including the Italian Institute of Technology and Bielefeld University in Germany.

"We welcome doctoral candidates from overseas to join us to create human-friendly robots based on cognitive neuroscience," says Ishiguro.

Professor Hiroshi Ishiguro and his Android

"We welcome doctoral candidates from overseas to join us to create human-friendly robots based on cognitive neuroscience."

MORE INFO

Global COE Program "Center of Human-friendly Robotics Based on Cognitive Neuroscience"
www.gcoe-cnr.osaka-u.ac.jp/english/

Innovative Approaches to Neuroscience and Microfluidics

AIST Kansai continues to excel in producing ideas for a sustainable society of the future.

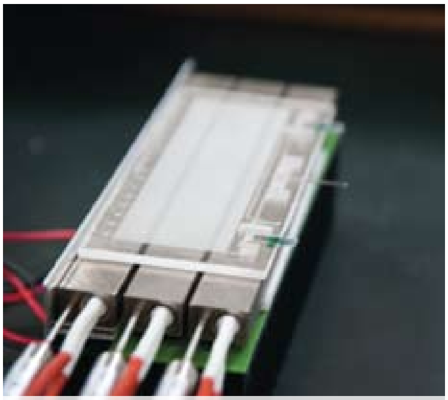
The National Institute of Advanced Industrial Science and Technology (AIST) is one of Japan's largest public research organizations with about 3,000 researchers working at nine locations throughout Japan.

Takahisa Taguchi is the director of AIST Kansai. "Our activities here are focused on three areas: energy, life sciences, and information communications technology," says Taguchi. "One of our main goals is to commercialize our research for the benefit of society."

Researcher **Hidenori Nagai** is focusing on creating compact analytical devices using microfabrication technology. "I am working on technology for the rapid and highly sensitive detection of target genes," explains Nagai. "I have developed a new method for detecting DNA based on rapid amplification." Compared with amplification by polymerase chain reaction (PCR), which can take several hours, Nagai's approach enables DNA amplification in just two to five minutes. "This is the fastest method reported to date," says Nagai. "Our compact and fast approach will enable point of care testing [POCT] on a tailor-made basis." Nagai is collaborating with academia to develop a commercial POCT system for genome assays.

The new high-speed PCR system consists of a pressure sensitive polyolefin film and cyclo-olefin polymer substrate containing microfluidic channels. During operation, the device is placed onto heated aluminum blocks maintained at 95°C (denaturation), 72°C (extension), and 55°C (annealing). When the sample is injected into the device, differences in vapor pressure due to the thermal gradient generate sufficient driving forces to move droplets of the sample through the various zones in the microcapillary network. "We successfully used this device to detect anthrax down to a concentration of 10 cells per microliter after a five-minute amplification," says Nagai.

Hidenori Nagai



Microfluidic Device for High-Speed PCR

Masami Kojima is studying the effect of brain-derived neurotrophic factor (BDNF) on brain function. "In 2003, I was with the group at the National Institutes of Health [in the United States] that identified BDNF as playing a role in memory formation," says Kojima. "We found that a common polymorphism [Val66Met] in the BDNF gene affects human memory and the secretion mechanism of the growth factor."

More recently, Kojima and colleagues reported that BDNF regulates cholesterol synthesis for synapse development. Specifically, they showed that BDNF induces de novo cholesterol biosynthesis in cultured cortical and hippocampal neurons, thereby indicating a role for BDNF in cholesterol metabolism.

"Depression is a serious illness affecting millions of people worldwide, and BDNF may have a role to play," says Kojima. "So, recently I have been working with clinicians on a national project [JST/CREST] on mental illnesses—including depression—focused on molecular dysfunction of BDNF."

Kojima works with many groups overseas, including those in the United States and China. "One of the major goals of AIST is to find applications for our research," says Kojima. "I often discuss my work with colleagues at AIST and at other institutes to achieve this goal, which would be difficult to accomplish by myself."

Masami Kojima

MORE INFO

National Institute of Advanced Industrial Science and Technology (AIST), Kansai
www.aist.go.jp/index_en.html

Cancer Research at Osaka Prefecture University

Five contrasting and innovative approaches to diagnosing and curing cancer.

Osaka Prefecture University (OPU) is one of the largest public universities in Japan. Established about 130 years ago to train veterinarians, the university employs 707 faculty who teach the approximately 8,000 students—164 from overseas—attending classes at three campuses: Nakamozu, Habikino, and Rinku.

Here, we introduce the research activities of five members of the OPU faculty who are actively involved in the Osaka Prefecture University Bio Strategy Committee on the development of bio-industries in the Osaka Bay area.

Kikuya Sugiura, a veterinarian at the School of Life and Environmental Sciences explains his research: "I am developing immunology-based therapy for tumors using dendritic cells [DC]. The function of DC is to present antigens to T lymphocytes, activating the immune response. We are obtaining these cells in culture by inducing the differentiation of monocytes isolated from blood, which can then be used to fight cancers."

This method alone, however, is not effective in completely destroying tumors. In a novel approach, Sugiura injects interferon γ (IFNγ)—a potent inducer of the T lymphocyte-mediated immune response—along with DC into dogs with naturally occurring tumors, brought to the OPU veterinary school for cancer therapy. "This treatment induced complete healing in the dogs," says Sugiura. "They are an almost perfect model for these experiments because breast cancer, lymphoma, and osteosarcoma occur spontaneously. So if the treatment is effective in dogs, there is a very high probability that it will work in humans."

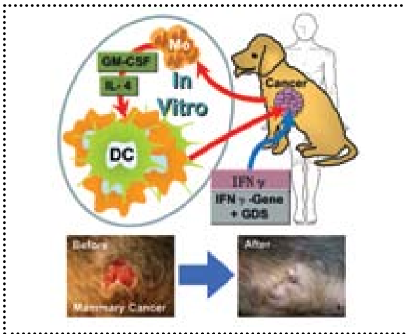
Sugiura is also testing drug delivery directly into the tumor microenvironment by introducing cytokine genes into tumor cells using a gene delivery system. Applying IFNγ and DC together appears to create a strong synergistic immune response against tumors, providing hope for the development of a similar treatment in humans.


Kikuya Sugiura

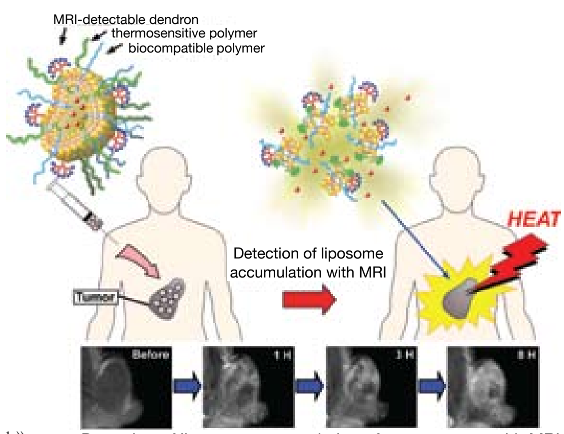
Ikuo Fujii, based at the Graduate School of Science, is an active member of the Osaka Prefecture Bio Strategy Committee and is committed to making Osaka a center for life sciences. Fujii has recreated in the laboratory the process by which the immune system makes antibodies and is developing low molecular weight peptides known as microantibodies. This will allow him to "contribute to molecular–targeted medicine and advanced medical diagnostics," says Fujii.

In particular, Fujii is addressing problems associated with antibody medicine. These problems include antigenicity, manufacturing costs, and cell membrane permeability issues. "I am reproducing the functions of antibodies using small peptides," says Fujii. "I have developed a unique phage-display peptide library of peptide surfaces, which are stable against proteases in the blood, show high binding activity and specificity, and are highly membrane permeable." These exciting results are expected to contribute to the development of the next generation of antibody-based therapeutics and diagnostics for the detection and treatment of cancer.

The precise and reproducible delivery of bioactive molecules to specific targets is essential for the development of medical treatment protocols. Chemist **Kenji Kono** is developing biofunctional nanomaterials for the delivery of drugs to treat cancer. "The development of accurate drug delivery technology is critical for personalized chemotherapy," continued »



Using dendritic cells (DC) developed from peripheral blood monocytes (Mo) by granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin (IL)-4, DC-based immunotherapy has provoked immune responses against cancer in human patients. However, improvements are necessary in order for the immune response to be sufficient for a satisfactory clinical outcome. Interferon-gamma (IFNγ), a potent inducer for DC maturation and T helper type 1 response, is an important tool for achieving such improvements. Inoculation of canine IFNγ with DC into the microenvironment of canine tumors significantly improved the clinical outcome, including complete remission of mammary carcinomas. For obtaining local-limiting and long-lasting effects of IFNγ, methods are being developed for in vivo transfection of the canine IFNγ gene into tumor cells using a gene delivery system (GDS). Results from the study of dogs with common human tumor types may provide useful information for the development of human cancer therapies.



Detection of liposome accumulation of mouse tumor with MRI

"We are aiming to lead research in the field of high-precision, liposome- and dendrimer-based drug delivery."

says Kono. "We are aiming to lead research in the field of high-precision, liposome- and dendrimer-based drug delivery."

In one set of experiments, Kono and colleagues loaded anticancer drugs into temperature-sensitive 100 nm-diameter liposome capsules that are designed to break down at elevated temperatures. They injected the capsules into a tumor, applied an RF microwave to locally heat the capsule to about 45°C, and monitored the delivery of the anticancer drugs using magnetic resonance imaging. "Having a way to visibly monitor the delivery, release, and spread of drugs is important for the development of safe procedures," says Kono. Other drug delivery systems developed by Kono and his team include nanoparticles made up of dendrimers, artificially-created branched molecules, that can respond to stimuli by virtue of surface modifications or loading of gold nanoparticles. These can be used for stimulus-induced drug release or heat generation upon laser light irradiation. Kono also created drug-carrying liposomes composed of a new type of functional, dendron-bearing lipid.

Boron neutron capture therapy (BNCT) is a high-energy physics approach to cancer therapy that combines two treatments that individually are virtually harmless, but together can be lethal. A beam of low-energy (or thermal) neutrons directed at a tumor interacts with boron-10 isotopes injected into the patient and targeted to tumor cells using specialized antibodies. "This interaction produces boron-11 particles, which rapidly decay to produce alpha particles and lithium-7 ions," says OPU's **Mitsunori Kirihata.** "This reaction is local and destroys cancer cells without harming adjacent healthy ones."

Kirihata has developed a method for the mass production of highly concentrated boron-10 compounds (in collaboration with locally-based Stella Chemifa Corporation), as well as the synthesis of boron-10-antibody compounds, which can be injected into patients and directed to specific tumor sites. Kirihata is also investigating further applications of BNCT by developing a new method for synthesizing fluoride-labeled boronophenylalanine that can be used in positron emission tomography imaging of BNCT-treated tumors.


Ikuo Fujii


Takashi Inui

"We have set up a consortium to make the Osaka Bay Area an international center for BNCT research and treatment," says Kirihata. "The new, compact, and relatively inexpensive accelerator for BNCT at Kyoto University is a major step towards the proliferation of BNCT treatment."

The drug development process is both time consuming and expensive, with many compounds being shelved during early testing due to difficulties in handling, and in many cases because the compound is simply not sufficiently soluble in water. These unused compounds could be potentially useful therapies if modified to improve solubility and therefore more easily reach target cells. **Takashi Inui** at the Graduate School of Life and Environmental Sciences has developed a new method of drug delivery that makes use of previously abandoned therapeutic compounds. "I spent many years in the pharmaceuticals industry and am aware of the vast number of unused compounds," says Inui. "I have successfully loaded low-solubility drugs inside L-PGDS [lipocalin-type prostaglandin D synthase] carrier cavities. I call this a drug delivery system based on intelligent-type artificial proteins."


Kenji Kono

The drug molecules exhibit selective molecular biorecognition and can be used for targeting cancer tissues. Inui used mass spectroscopy, SAXS (small-angle X-ray scattering), and NMR to identify that the drug was indeed inside and bound to the carrier capsule. "This is a world first, and I expect these results will have a tremendous effect on drug discovery," says Inui.


Mitsunori Kirihata

MORE INFO
Osaka Prefecture University
www.osakafu-u.ac.jp/english/index.html

AAAS/*Science* would like to express our appreciation and thanks to the following sponsors of this booklet:

AIST Kansai, National Institute of Advanced Industrial Science and Technology

Graduate School of Dentistry, Osaka University

Graduate School of Engineering Science, Osaka University

Graduate School of Frontier Biosciences, Osaka University

Graduate School of Medicine, Osaka University

Graduate School of Pharmaceutical Sciences, Osaka University

Graduate School of Science, Osaka University

Immunology Frontier Research Center (IFReC), Osaka University

Institute for Protein Research, Osaka University

National Cerebral and Cardiovascular Center

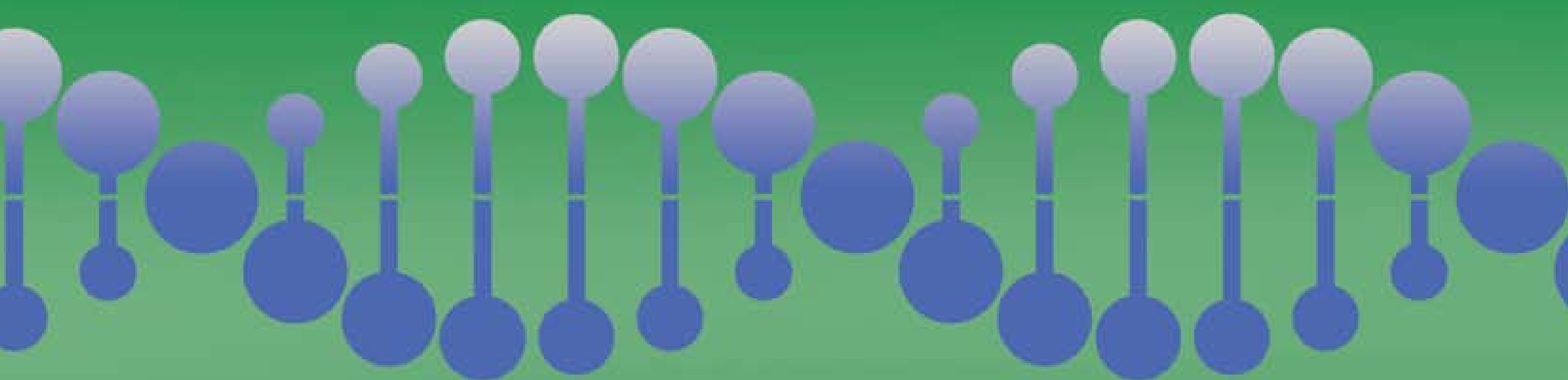
National Institute of Biomedical Innovation

Osaka Bio Headquarters (Osaka Prefectural Government)

Osaka Prefecture University

Research Institute for Microbial Diseases, Osaka University

Senri Life Science Foundation



Science

AAAS

1200 New York Ave., NW
Washington, DC 20005