OSAKA BIO HEADQUARTERS

Creating the world's best business environment for life science innovation

With the generous support of special economic zone designations from the Japanese government, major tax breaks from the Osaka Prefectural Government and strengthened assistance for the development of drug discovery, Osaka has become the most rewarding location in Japan for innovation-driven life science companies.

Finding a competitive advantage is critical for turning a business opportunity into a lasting and profitable enterprise. Over the past two decades, however, such advantages have been hard to come by in Japan. Drastic times call for drastic measures: the recent package of reforms and incentive schemes launched by the Japanese government promises far-reaching and revolutionary changes to the business environment in ways previous reforms and stimuli have been unable to achieve.

The greater Kansai region, including Osaka, Kyoto and Hyogo prefectures, has been singled out by the central government as a pillar for the country's economic growth, being granted two 'special zone' designations that provide not only generous tax incentives but also a range of special measures aimed at reducing red tape and regulatory hurdles, and increasing international competitiveness and cooperation.

The first of these designations, the Kansai Innovation Comprehensive Global Strategic Special Zone, which will soon enter its fourth year of operation, offers businesses in the region lower corporate tax, monetary as well as financial support measures and special regulatory exceptions to promote innovation in life science.

In May 2014, Osaka also became a National Strategic Special Zone. Osaka has taken up the challenge of implementing breakthrough deregulatory forms to promote private sector business. The scale of these micro-reforms is unprecedented, and they are part of the central government's goal of eliminating accumulated barriers to business.

Together with renowned academic and research institutions such as Osaka and Kyoto universities, the National Cerebral and the Cardiovascular Center and the National Institute of Biomedical Innovation, the region represents the largest and densest science cluster in Japan.

To enhance the competitive advantage that businesses in the region enjoy through the synergies resulting from the Kansai Innovation Comprehensive Global Strategic Special Zone, the Osaka Prefectural Government in collaboration with cities in the region now offer waivers of up to 100% for five years on local taxes for businesses relocating into this special economic zone, and up to 50% off levied tax for the next five years. The cumulative benefit of these tax incentives together with the special tax benefits offered by the central government brings the effective corporate tax rate down to levels equivalent to those of other Asian countries.

While lowering the cost of business is in itself a distinct advantage for new and expanding enterprises, the region also offers major advantages specifically for life science innovation through intensive assistance and streamlined product approval processes. So significant are the advantages realized through the special zone reforms that there are now no vacancies at the biocluster's flagship business centre in northern Osaka, the Saito Life Science Park.

To promote the development of medical devices and the translation of clinical trials into practice, in 2013, Japan's Pharmaceuticals and Medical Devices Agency (PMDA) opened an office in central Osaka—the first outside Tokyo. The Osaka Chamber of Commerce and Industry also facilitates the development of medical devices through direct business support. Further, the Osaka Prefectural Government is building a virtual network of over 10,000 hospital beds to facilitate clinical trials. These measures, in addition to the Kansai Innovation Comprehensive Global Strategic Special Zone reforms and incentives, have significantly boosted Osaka's business standing in the life sciences.

Through the National Strategic Special Zone, the government has designated Osaka University Hospital and the National Cerebral and Cardiovascular Center as a hub to promote the research and development of innovative medicine and medical equipment as well as regenerative medicine. With the lead of these two medical institutes, Osaka has accelerated the development of advanced medical treatments and pharmaceuticals.

The range of incentives, support and expertise on offer in Osaka for life science innovation is unprecedented and represents a once-in-a-generation opportunity for businesses and entrepreneurs seeking an international competitive advantage. The region's venture culture and will to succeed make Osaka one of the most attractive areas for life science innovation in the world.

Building innovation on tradition

Japan's epicentre of pharmaceutical medicine since the Edo period, Osaka continues to lead life science and biotechnology innovation with the Osaka Bio Headquarters initiative, which is headed by one of Japan's leading life scientists, Tadamitsu Kishimoto.

Born and raised in Osaka, Kishimoto has strong ties to his hometown and great aspirations for its future. Even in the 1940s, when Kishimoto was a child, Osaka had a long history as a national hub for medicinal ingredients. As early as the 1600s, domestic and imported herbs, roots and bark were produced and traded in the district of Osaka known as Doshomachi. The Tokugawa shogunate formalized and regulated the industry in the 1700s and granted the Doshomachi merchants exclusive rights to supply medicinal ingredients throughout the country. When Western medicine was introduced at the beginning of the twentieth century, Doshomachi embraced this alternative approach to medicine with the establishment of the Osaka Pharmaceutical School, which today is known as the Osaka University School of Pharmaceutical Sciences.

This centuries-old tradition in pharmaceutical medicine is a source of pride for Osaka and acts like a beacon for life-science companies throughout Japan. Today, the historical Doshomachi district and surrounds host hundreds of drug developers, pharmaceutical wholesalers and manufacturers, and innovative biotechnology developers, along with electrical, chemical and precision equipment manufacturers, which make technological advancement possible. Seeing the vast potential of his hometown as an international centre for pharmaceutical, life-science and biotechnology innovation, Kishimoto has devoted his efforts to establishing the Osaka Bio Headquarters, which seeks to boost the life-science industry through facilitating collaboration between industry, academia and government.

Kishimoto is no stranger to innovation, and while he has spent most of his research career in Osaka, his discoveries have had a worldwide impact. In the 1970s, he made the first of a rush of discoveries that were to shed new light on the mechanics of the human immune system. His most widely lauded discovery is that of interleukin-6 (IL-6), a crucial but previously unknown component of the immune system.

T-cells and their role in antibody production had been known since the late 1960s, around the time that Kishimoto was completing his doctoral studies at Osaka University, but just how T-cells stimulated immune responses remained a mystery. After spending four years as a visiting professor at John Hopkins University in the USA, Kishimoto returned to Osaka to take up the challenge of unravelling the secrets of the human immune system. By the mid-1980s, he had successfully isolated the soluble T-cell-derived factor responsible for inflammatory responses, a factor now known as IL-6. Since then, he has continued his pioneering research, revealing the multifaceted functionality of IL-6 in immune regulation, the formation of blood cell components, inflammation and even oncogenesis.

"I have been studying immunology for over 50 years, since I was 25 years old," says Kishimoto. "Why have I studied immunology so long? Because it is a fascinating field. We continue to make many new findings, and each raises new questions."

After a six-year tenure as president of Osaka University and service on the National Council for Science and Technology Policy, the highly awarded Kishimoto turned his sights to his hometown and the possibilities it represented. "Osaka's Doshomachi district has a history of medicine production and renowned medical experts going as far back as Kouan Ogata in the 1800s, who founded the Tekijyuku school of medicine—the predecessor of Osaka University," says Kishimoto. "I am very fond of the adage of my mentor and one of our country's greatest immunologists, the late Professor Yuichi Yamamura, who said, 'Embrace your precious time, your historical place and the harmony of your people.' He saw a future in which northern Osaka (the Hokusetsu district) would become a global mecca for life science. This, too, is my vision."

Using the broad reach of the Osaka Bio Headquarters, Kishimoto aims to make the Hokusetsu district a world-class bio cluster that fosters innovation and the development of top-researchers and innovators.

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



GRADUATE SCHOOL OF MEDICINE/FACULTY OF MEDICINE, OSAKA UNIVERSITY

Continuing a long tradition of medical innovation

The Graduate School of Medicine and the Faculty of Medicine at Osaka University can trace their ancestry to the birthplace of modern medicine in Japan. But far from dwelling on the past, they have grand plans for advancing the frontiers of medical research and education.

Nurturing great physicians

Osaka University is the sixth oldest national university in Japan. Its origin can be traced back to Tekijyuku, a school established by the physician and scholar Koan Ogata in the late Edo period over 175 years ago. Ogata was a specialist in treating smallpox and is regarded by many as the father of modern medicine in Japan. Students flocked to him to study *rangaku*—principally scientific subjects introduced to Japan by the then more technologically advanced Western countries. In this way, he nurtured many talented minds, thereby laying the foundations of Osaka University.

An inside view of the new Center of Medical Innovation and Translational Research, which opened in May 2014.

"We have a responsibility to continue the long history of medical study that our predecessors have handed down to us," says dean of the faculty and graduate school, Yasufumi Kaneda. "This tradition of high-quality education and research will continue generation after generation." The school is well known for its many outstanding research achievements, particularly in the areas of biochemistry, cell and molecular biology, and immunology. But far from resting on its laurels, it has many plans to further stimulate both the academic and medical communities in Osaka.

Under one roof

In May 2014, the university opened the Center of Medical Innovation and Translational Research to develop cutting-edge medical technologies through collaboration between Osaka University's schools and medical enterprises. The centre has two principal focuses — immunology and regenerative medicine — and it has already become a hive of activity. "We have 30 fully functioning laboratories at the centre, and I see a good flow of people and knowledge as a result of our efforts," says Kaneda. The centre houses advanced facilities, including equipment for genome analysis, protein analysis, cell sorting and molecular imaging. Furthermore, around 25 administrators provide vital support to researchers.

Learning from patients

Across from the medical school complex on the Suita campus of the university is Osaka University Hospital. "It is crucial for us to work closely with the hospital," says Kaneda. "Ultimately, our goal in pursuing education, research and clinical practice is to cure intractable human diseases."

In 2002, the hospital also established the Medical Center for Translational and Clinical Research. This government-funded centre seeks to apply high-quality findings in basic research to clinical research. The medical school has developed a system for assessing whether newly discovered drugs and medical therapies are in need of more basic research, can go into animal testing or are ready for clinical trials. "It is important for physicians who are on the front line in the battle against diseases to be able to reliably assess the current status of new treatments," says Kaneda.

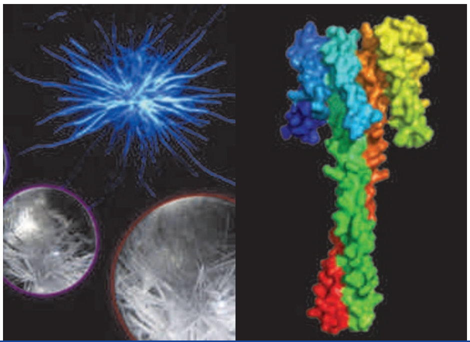
New courses for medical innovation

From this October, the medical school will offer several new courses for first- and second-year undergraduate students, including one on the latest developments in international medicine. These courses seek to improve medical literacy and foster a 'hands-on' approach. Kaneda nostalgically recalls the moment when he first saw a fluorescently labelled live cell under a microscope. "I have learned a lot about the mechanisms of life from observations of live cells," he says. "Our definition of medical study has always been one that emphasizes scientific inquiry."

Graduate School of Medicine
Faculty of Medicine, Osaka University

Graduate School of Medicine/Faculty of Medicine, Osaka University

www.med.osaka-u.ac.jp/index-e.html



INSTITUTE FOR PROTEIN RESEARCH, OSAKA UNIVERSITY

A fascination with proteins

The Institute for Protein Research is accelerating the worldwide effort to understand biology and disease by using its world-class facilities and research ingenuity to explore the structure and function of proteins.

Founded in 1958, the Institute for Protein Research (IPR), through its Protein Data Bank of Japan, has provided structural and other data for a whopping 30% of proteins catalogued in the Worldwide Protein Data Bank. As a Japanese-government-approved Joint Usage/Research Center, IPR hosts a histology database, operates a dedicated synchrotron beamline at SPring-8, and runs ten nuclear magnetic resonance (NMR) systems. Those include Asia's only, and one of the world's few, 950 MHz NMR systems, which can analyse proteins in solution with unprecedented precision. In addition to being a boon for IPR scientists, these formidable facilities are used each year by some 60 research groups from other Japanese institutions and another dozen from overseas.

"Japan has put all these resources into the global effort to transform protein research," says IPR's Yuji Goto.

Scientists at IPR conduct their own transformative research. Goto, for example, is opening a new path to understanding and treating Alzheimer's disease. Whereas conventional Alzheimer's research focuses on the molecular changes in amyloid during disease development, Goto studies folding dynamics—a broader view, which could revolutionize our understanding of a whole class of protein-folding diseases.

Goto conjectures that all the misfolding happens at once, in much the same way a supersaturated solution suddenly precipitates when triggered by a nucleation event. He has shown that ultrasound can trigger such an event in a supersaturated amyloid solution. "The body creates that state to avoid gradual accumulation, which is beneficial," he hypothesizes. "The problem is that you then have the dangerous supersaturated state."

He says the same theory could explain how a small number of pathogenic prions introduced from a cow infected with bovine spongiform encephalopathy (BSE or mad cow disease) can trigger the sudden accumulation of misfolded prions in Creutzfeldt–Jakob disease patients.

He illustrates his theory using strings of wooden pieces representing proteins as they loosen from their folded, functional state and adopt elongated structures that characterize their crystallized, dysfunctional state—an aggregation event first discovered from the hardening of egg white. His research has renewed interest in protein aggregation. "I hope that looking from a different perspective will undercover a different rule. If we can find that rule, we'll have a key to treatment," says Goto.

IPR's Kiyotoshi Sekiguchi is also setting new trends with his discovery of a culture process for induced pluripotent stem (iPS) cells. It is taking the stem cell world by storm, because it is safe, stable and efficient.

The culture system allows the cells to be dissociated without killing them or causing common problems in cell culture, such as mutations or chromosomal abnormalities. Whereas previously an iPS cell colony could only generate three or four new colonies, now one colony can easily produce 100 new ones. Not only is that more than a 20-fold increase in efficiency, it is also faster and less labour intensive.

Furthermore, unlike conventional cell culture systems that use animal feeder cells to nourish the growing cells, Sekiguchi's system is based on an artificial protein called laminin. This 'feeder-free' system means clinical use will have fewer risks, making it much easier to be approved by regulators. In fact, Kyoto University's Jun Takahashi has adopted the system to derive neurons from iPS cells for a Parkinson's disease study that he hopes will be approved this year.

"It is the best and strongest binding substrate for iPS cells," says Sekiguchi. "I don't think there will be anything better."

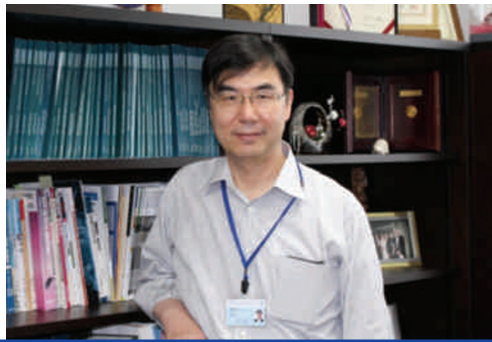
Sekiguchi was especially gratified when Nobel laureate Shinya Yamanaka started using his feeder-free culture system. Now, after the two co-published an article on it, iPS cell researchers in Japan and other countries are adopting this system.

Sekiguchi is addressing the one downside—its high cost—by trying to better understand how the system works. Both he and Goto hope to take advantage of IPR's unique facilities to understand their respective phenomena, opening up the next stages of applied research in their fields.

INSTITUTE for PROTEIN RESEARCH
OSAKA UNIVERSITY

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





IMMUNOLOGY FRONTIER RESEARCH CENTER, OSAKA UNIVERSITY

A stimulating environment for immunology

The Immunology Frontier Research Center (IFReC) at Osaka University is a prestigious research community directed by Shizuo Akira, a very highly cited immunologist. Designated one of the nine World Premier International Research Centers by the Japanese government, IFReC is a hub for researchers eager to extend the frontiers of immunology.

Innate and acquired immunity

Akira's team is focusing on two main areas of research — identifying the mechanisms of messenger-RNA regulation by analysing phenotypes that cause inflammation and immune responses; and studying differentiation in several macrophage subsets. The team made the fascinating discovery of a 'metabolic' mouse, which was simultaneously thin and had lipodystrophy (a disproportionate distribution of body fat) as a result of defective differentiation of a specific type of macrophage. This finding demonstrates the role of these macrophages in maintaining peripheral tissue, such as fat cells.

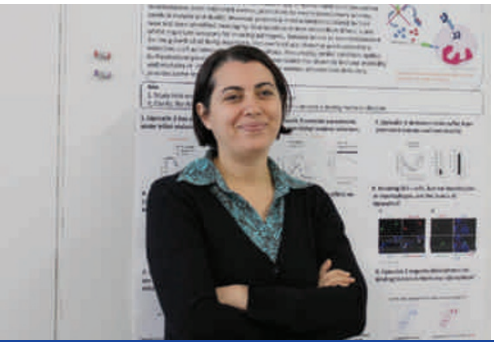
In contrast to Akira, whose research interests lie in innate immunity, Shimon Sakaguchi, a professor at IFReC, is interested in acquired immunity and specializes in a type of lymphocyte known as regulatory T cells. Sakaguchi's quest is to discover how to control the acquired immune system for cases such as allergies, autoimmune disorders and organ transplantation. He is also investigating how effective immune responses against cancer cells can be evoked in cancer patients by reducing regulatory T cells. Very recently, this investigation has reached the stage of clinical application, which will be conducted at Osaka University Hospital. "The antibodies will hopefully be approved for cancer drug development in Japan within this year; this is similar to the approval time frames of other countries, for example, those of the Food and Drug Administration in the USA," says Sakaguchi. "The process of drug discovery in this country is improving and becoming much smoother."

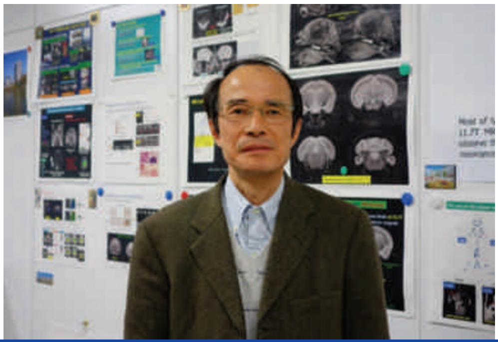
IFReC is located at the centre of medical and bioscience research in Osaka.

Real-time imaging of immunological processes

Researchers at IFReC are interested in integrating the areas of immunology, imaging and informatics as much as possible. "It is amazing to observe in real time the processes of immunological systems, which we have conceptualized," enthuses Akira. In terms of research facilities, IFReC has several two-photon microscopes for observing cellular activities related to the immune response and an 11.7-tesla magnetic resonance imaging (MRI) system for analysing pathological changes associated with the early stages of immunological diseases in mice.

Unlike 'wet' *in vivo* or *in vitro* experiments, MRI analysis has the advantage of enabling researchers to image the immune system both spatially and temporally. Yoshichika Yoshioka, a professor of biofunctional imaging at IFReC, used ultrahigh-field MRI to obtain sequential images of a macrophage in living mice every ten minutes without invasion. "After visualizing





the behaviour of a macrophage using *in vivo* MRI, I can analyse the excised tissues by using *ex vivo* micro MRI to look at the scattered cells, which are 20 to 30 micrometres in size," Yoshioka explains. He is also using an MRI system to observe small-scale but important processes that occur during the early stages of infections and to identify variations between individuals — processes that have never been imaged before.

Another notable example of how imaging can provide insights into biological processes is the work of Cevayir Coban, an associate professor and malaria immunologist at IFReC. She analysed high-resolution images of a mouse brain to investigate the impaired sense of smell in malaria infection. "The images we obtained revealed that T cells and malaria parasites are concentrated in the olfactory bulb in the brain, which also exhibited massive bleeding. Nobody suspected this," says Coban excitedly. "We were able to discover this using the technique of multiphoton imaging."

An 11.7-tesla MRI system — just one of the excellent facilities that researchers have access to at IFReC.

Supporting young and overseas researchers

IFReC supports its students and young researchers by facilitating scientific discourse and interactions between researchers and providing advanced educational programmes. It encourages young researchers to become principal investigators, and already several researchers have gone on to become principal investigators in the imaging and informatics sections. Other examples of ways in which IFReC supports its young researchers are a grant designed to encourage collaborative research and a training programme that provides researchers with opportunities to study and investigate other specializations in addition to immunology.

"One key ingredient for excellent scientific research is forums where you can participate in academically stimulating conversations," Akira explains. "Great discussion makes scientists tick." Opportunities for interaction broaden scientists' horizons, believes Akira. "A good community is critical for generating new scientific ideas." IFReC considers such opportunities to be a valuable part of the research process and so organizes colloquia and closed seminars for researchers to exchange ideas founded on unpublished research data. "These events provide opportunities to learn from each other and to think much deeper about our own research. Osaka University has a long tradition of open discussion, especially among excellent immunologists, such as Tasuku Honjo and Tadamitsu Kishimoto."

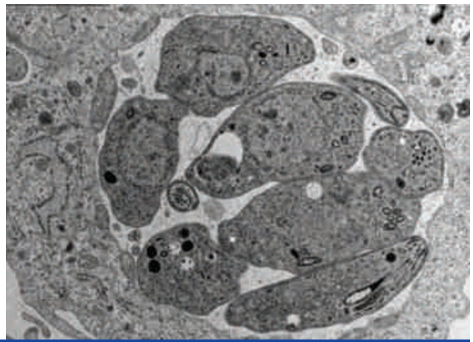
IFReC also welcomes international students and researchers. Currently, about 30 per cent of its members are from overseas (including three principal investigators). The institute provides overseas students and researchers with many forms of support, including assistance with completing paperwork, opportunities to improve their Japanese, and help in finding housing and childcare. Coban from Turkey, who is an associate professor and a mother of two, says of the centre, "It is a great place to work. I really enjoy it. If you want to study immunology, IFReC is at the top of the list."

Adopting a long-term outlook

Regarding the future of immunology, Sakaguchi emphasizes that it is important for society to adopt a long-range view. "It takes time for scientists to complete each project. One generation spends about three decades doing research, but it can sometimes take over a century for a research community to make a scientific discovery."

Akira adds, "If researchers design their scientific projects to be completed within only several years, the scale of academic projects will inevitably be small." Permitting scientists to conduct research over longer periods, such as one or two decades, however, could stimulate their creativity and their generation of wide-ranging scientific ideas. Evidence of this is provided by the fact that it took Akira's group nine years to finally discover two important transcriptional factors — nuclear factor for IL-6 expression (NF-IL6) and signal transducer and activator of transcription 3 (STAT3). The group is now investigating post-transcriptional regulation of phenotypes.

"Our country often tends to prioritize obtaining good results promptly rather than being patient and waiting for serendipity. Many things have been implemented to improve this situation," elaborates Sakaguchi. "I am confident that things will be better from now on." And among those laying the groundwork is IFReC, points out Akira. "IFReC is striving to produce a stimulating environment for talented scientists."



RESEARCH INSTITUTE FOR MICROBIAL DISEASES, OSAKA UNIVERSITY

Both sides of the microbial infection equation

Since its establishment in 1934, the Research Institute for Microbial Diseases (RIMD) has pursued a comprehensive study of microbes, focusing particularly on the complex interactions between microbes and their hosts. That has proved to be a fertile field, allowing RIMD to stay at the cutting edge and to contribute greatly to both clinical and basic research.

RIMD's history illustrates their success in that mission. "Tsunesaburo Fujino's discovery of *Vibrio parahaemolyticus* and Michiaki Takahashi's development of a chickenpox vaccine helped put the institute on the map," says RIMD's director Eisuke Mekada. "Yoshio Okada's elaboration of the mechanism by which the Sendai virus fuses established the virus as a standard research tool around the world. Kumao Toyoshima's discovery of oncogenes launched what became one of the hottest fields in cancer research."

The RIMD continually reinvents itself. It differs from most Japanese research organizations in that when principal investigators leave, rather than promoting the next in line, the RIMD employs new principal investigators who contribute new ideas and offer fresh perspectives.

RIMD's Masahiro Yamamoto's world-leading research on *Toxoplasma gondii*, a protozoan that may infect up to one in every three people, demonstrates the benefits of the institute's emphasis on studying microbiology and immunology together.

The immune system normally keeps *T. gondii* in check. However, in chemotherapy patients and other immunocompromised people, the protozoan can cause encephalitis, chorioretinitis and other debilitating disorders.

Yamamoto uses avirulent parasite strains to analyse the immune reaction at the molecular level and virulent parasites to examine how the host's immune system is targeted. Looking at both sides of the equation has allowed Yamamoto to begin evaluating how over 2,000 genes respond to infection. He says, "I can knock out genes in both mice and the parasite, allowing me to analyse in depth what is happening."

In a string of published studies, Yamamoto identified the specific amino acid substitution in the parasite's ROP16 kinase that allows only some strains to successfully infect. He also pinpointed a transcription factor in the host, ATF6-beta, as a cellular target. Through a laborious knocking out of genes, Yamamoto's group found a cluster of p65 GTPases that play a crucial role in disrupting the vacuoles where the parasite proliferates in the cell.

In the future, he intends to look at malaria and other parasites, focusing on how vacuole formation is involved. "I want to elucidate principles guiding the interaction between host and parasite in order to identify the determining factors of endosymbiosis in the parasites' life cycle," he explains.

In the true spirit of RIMD's mission to connect fundamental and applied science, Yamamoto will tackle the development of anti-toxoplasma and anti-malaria drugs.

While Masahito Ikawa's research does not directly involve microbes, a shared tool—genetic engineering—has made him one of the hottest names in reproductive studies.

In the 1990s, Ikawa engineered mice with a fluorescent protein expressed throughout the body; green glowing mice became one of the most iconic scientific images of the past decades. Researchers everywhere adapted his system to their own research.

Ikawa himself used it to examine the mammalian reproductive system. After knocking out 14 genes related to a sperm's ability to fertilize an egg, in 2005 he made the breakthrough discovery of Izumo, a sperm membrane protein that initiates fusion with the egg. "This has been my biggest contribution," he says.

Last year, Ikawa rapidly adopted the CRISPR/Cas gene-editing technology. Within a year he produced some 100 lines of knockout mice—a fantastic advance on the average of 15 mice produced per year over the previous two decades.

Half the new strains will go to collaborators, while the others will be used in his own experiments on reproduction. He will make 200 strains of mice with altered reproduction-related genes. With CRISPR/Cas and nine micromanipulators, he can approach problems of infertility with an efficient systematic approach.

"These new techniques are changing the world of research," Ikawa notes.

RIMD

Research Institute for Microbial Diseases, Osaka University

www.biken.osaka-u.ac.jp/english/index.html

THE RESEARCH FOUNDATION FOR MICROBIAL DISEASES OF OSAKA UNIVERSITY

Better and more vaccines for a safer world

The Research Foundation for Microbial Diseases of Osaka University (BIKEN) recently celebrated its 80th anniversary. Koichi Yamanishi, director general of BIKEN, talks about the past, present and future of vaccine development at the foundation.

Successful vaccine development in Japan

BIKEN recently celebrated its 80th year, a very special occasion for the newly appointed director general, Koichi Yamanishi, who is also professor emeritus and former dean of the Faculty of Medicine at Osaka University. Yamanishi spent most of his life working as a researcher next door at the Research Institute for Microbial Diseases, where most of the groundwork takes place for the vaccines that BIKEN later develops, produces and supplies worldwide. "BIKEN is the first successful venture in vaccine development originating from academia in Japan," he says.

Specializing in the research and development of vaccines, BIKEN has the highest market share of vaccines produced in Japan. BIKEN's vaccine production facility is a large-scale operation, bringing in annual sales of 30 billion yen (about US$275 million) and employing 850 people.

Some well-known vaccines developed at BIKEN include one for measles, produced in 1966, and another for chickenpox, developed in 1974 and the only vaccine strain in the world providing protection against chicken pox.

"We often describe our work by using the example of wheels on either side of a car. On the one side we have development, while on the other side we have production — both activities are complementary and indispensable," explains Yamanishi.

Fresh wind

One of the first things Yamanishi did after being appointed to his current position was assign new members to BIKEN's management team from both academia and the pharmaceutical industry. "A fresh wind has been blowing since Yamanishi started as the director general here," says a member of staff. "A major difference he has made is to enhance the decision-making ability of the management board, so that BIKEN can develop new vaccines more smoothly." BIKEN and its management team, led by Yamanishi, are keen to become a better organization by learning from research foundations and institutes worldwide.

Meeting the high demand for vaccines

As the recent Ebola virus outbreak in Africa so powerfully demonstrates, society demands that vaccines for infectious diseases are developed, produced and distributed. To meet this strong demand, Yamanishi decided to expand the capacity of the Seto Center over the next five years to increase the availability of vaccines for influenza, chicken pox and shingles. Increased stock of these vaccines will ensure that future global demand for them is met.

BIKEN is also keen to develop the next generation of vaccines. Research and development of vaccines is a long-term undertaking, often requiring one to two decades to come to market. To realize this goal, BIKEN has recently established a new research organization, the BIKEN Center for Innovative Vaccine Research and Development, to promote cooperative development. BIKEN has received many ideas of interest from researchers eager to work in this new centre.

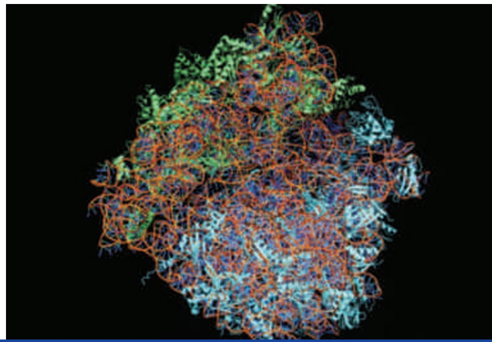
Researchers at BIKEN, while focused on vaccines, conduct research in diverse areas. "My research is focused on optimizing vaccines related to drug delivery systems and safety science," explains Yasuo Yoshioka, a project leader at the centre. "In addition, I am working on the development of a biomarker for predicting the efficacy and safety of vaccines."

Another project leader, Taiki Aoshi, is also focusing on vaccine safety. "We would like to understand the interaction between immune cells in lymphoid tissue to establish the protective immune response. Combined with appropriate antigen and adjuvant delivery, we believe this knowledge will contribute to the development of safe and effective next-generation vaccines."

And finally, Shintaro Sato intends to "make all possible efforts to establish and provide several useful tools for screening and evaluating mucosal vaccines and mucosal adjuvants."

"Effort and enthusiasm are essential for developing vaccines," says Yamanishi. "I will continue to do all that I can to inspire young investigators."





GRADUATE SCHOOL OF PHARMACEUTICAL SCIENCES, OSAKA UNIVERSITY

How academia can spur biomedical innovation

In a country determined to remake itself as a biomedical powerhouse and in a city that has long been at the forefront of Japan's pharmaceutical research and development, Osaka University's Graduate School and School of Pharmaceutical Sciences has spawned an array of pioneering science and technology. Below are just a few examples of the school's researchers who are taking up the challenge of making academia a driving force in drug innovation.

Taking sides

Chemical compounds are naturally synthesized as mixtures of mirror-image left- and right-handed 'chiral' forms by chemical reactions. This is a headache for those designing drugs, since often only one of the two forms has a favourable biological effect, while the other can be ineffective or even toxic.

Organic chemist Shuji Akai wants to ensure that this does not keep promising chemical compounds from reaching their clinical potential. To this end, he is investigating ways to produce 'optically pure' chemical compounds, rather than mixtures of right- and left-handed forms. Many catalysts have been devised for selectively preparing optically pure forms, but most of them contain rare metals at their active centres. Akai has developed a completely different strategy that exploits the cooperative action of a natural enzyme (lipase) and an abundant metal (vanadium).

Lipases strictly distinguish between left- and right-handed forms and have been widely used to separate 50/50 mixtures to provide the desired form while leaving the same amount of the other form as waste.

To eliminate this wastage, Akai has produced a new vanadium-containing cocatalyst, which can convert either form into the other form. By the combined use of lipase and the vanadium catalyst, he realized complete conversion of the 50/50 mixture into a single form without producing any waste.

However, this 'cooperative catalysis' approach soon ran into a problem: vanadium and lipase are incompatible. "They cancel each other out," says Akai.

Akai's breakthrough came when he devised a way to separate the two reactions using mesoporous silica with three-nanometre-diameter pores. Covalent bonds keep vanadium immobilized on the surfaces of the pores, which are too narrow for the larger lipase to enter. The vanadium reaction occurs in the pores, whereas the lipase is active outside the pores; in this way, only the desired pure form was obtained quantitatively. "This strategy will be used in combination with other enzymes and other cocatalysts to efficiently synthesize new drug candidates." says Akai.

As a synthetic chemist, Akai has collaborated with a pharmaceutical company to produce a diabetes drug candidate. He is now looking for biologists in academia to collaborate on other biomedical problems.

"It's vital for organic chemists and biologists to work together for biomedical innovation," says Akai.

The real thing

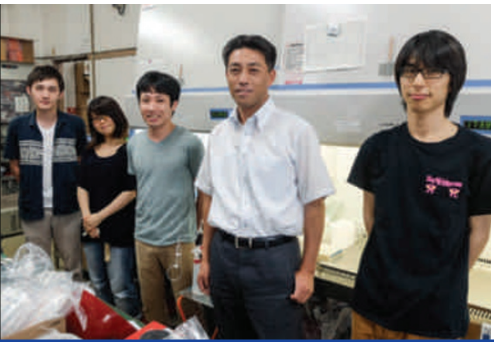
A drug can work like a dream, but if it is too toxic, it is useless. A crucial stage of drug development is toxicity testing, which pharmaceutical companies like to conduct early in the process to avoid squandering precious resources on dead ends. The crucial test is whether liver cells can process the drugs. But where can you obtain good liver cells?

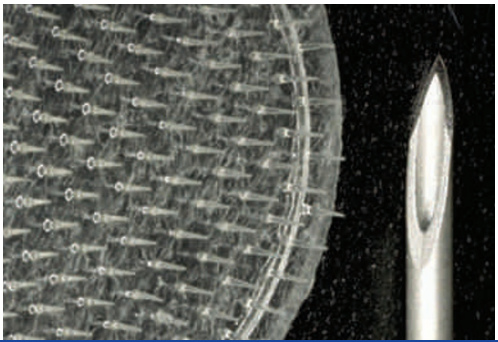
The advent of induced pluripotent stem (iPS) cells has offered an exciting new opportunity. These embryonic-like stem cells can be differentiated into any of the body's cell types, including liver cells. They thus offer a potentially endless supply of genetically identical, standardized cell types for testing. Also, as human cells, they will be more reliable indicators of potential efficacy and side effects than the mouse models that are generally used now. Furthermore, they can be made from patients with particular genetic backgrounds for tailor-made testing and, potentially, therapy.

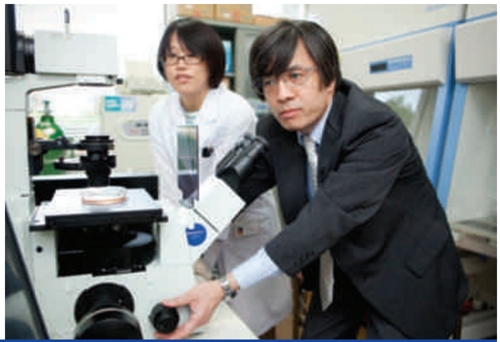
But making high-quality liver cells in sufficient quantity from iPS cells has so far proved a challenge. Hiroyuki Mizuguchi set out to rectify this.

Mizuguchi developed a technology to mass expand iPS-derived liver cells with high efficiency. The key is timing. "Everybody uses a variety of growth factors and other media to derive liver cells," says Mizuguchi. "The unique aspect of this method is that I add genes at specific stages of the development process to get them closer to the real thing."

He knew he was on the right track when he compared cells he had produced with those that had been removed from a human liver and cultured for 48 hours—the time range that pharmaceutical companies often use for







testing. "We saw incredible levels of activity in our cells—the same amount as in cultured cells," Mizuguchi says.

The cells, first created in 2012, produce what Mizuguchi describes as "the most mature artificial liver cells available."

Hundreds of tiny pinpricks

About 4,000 children die each day from diseases that are preventable by vaccination. Many developing countries lack cold storage and cold transportation for vaccines, and hence access is a problem. Furthermore, lack of medical expertise for administering the vaccines in isolated villages compounds the problem.

Shinsaku Nakagawa and his collaborator, Naoki Okada, have developed a prickly solution to the problem—vaccination through easily administered, dissolvable microneedles. Their idea was inspired by previous work on a cancer vaccine, which introduced them to the challenges of drug delivery systems.

Nakagawa's group has created a small round patch about the size of a little-finger nail and fitted with some 200 needles that are 800 micrometres long. This length is perfect for delivering vaccines to the right spot. Whereas conventional shots go deep beneath the skin, the microneedles inject the vaccine right into the top layers where Langerhans cells and dermal dendritic cells, which are involved in the immune response, reside. "That's exactly where we want it," declares Nakagawa.

Such microneedles have been previously proposed for transcutaneous administration, but developers have always got stuck because the tiny needles break off, leaving metallic pieces in the skin. Nakagawa's group overcame this problem by using needles made of hyaluronic acid, a compound that naturally occurs in the body and is used in cosmetics and wound repair. The needles melt into the skin within two hours, carrying the vaccine with them.

In addition, Nakagawa's group has already made preliminary diphtheria and tetanus microneedle vaccines that do not require refrigeration. (Currently, the influenza microneedle vaccine still does.) Subjects who have received influenza vaccine by microneedle have experienced a little redness, which disappears in three weeks, but no serious side effects. Furthermore, the microneedle vaccination was as effective or more effective than vaccination by conventional injection.

Radical new techniques always require time to prove themselves. "It is critical for us that the drug industry enthusiastically participates in clinical trials and commercialization of our microneedle vaccine," says Nakagawa.

But with an eye on the end user, he is confident that microneedle vaccination will spread. "This is a patch that anyone can apply. People can even apply it to themselves," he says.

Choose your weapon

Japanese academia has often been criticized for being unable to make its discoveries clinically relevant. Kazutake Tsujikawa disagrees, and he is staking his career on a belief in 'academic drug innovation'.

To prove his point, Tsujikawa has aligned a variety of molecular approaches to create pioneering cancer drugs. Supported by the Ministry of Education, Culture, Sports, Science and Technology's Platform for Drug Discovery, Informatics, and Structural Life Science and another translational medicine grant awarded to Osaka University, Tsujikawa already has three promising targets. All three approaches have been verified in animals and are progressing towards clinical testing.

The most exciting, for Tsujikawa, is a prostate cancer antigen-1, PCA-1, that his group discovered and has since been demonstrated to be a target for prostate and pancreatic cancer therapy. PCA-1 demethylates methylated DNA and RNA bases; Tsujikawa designed a small compound to inhibit this activity. "This molecule wasn't known to exist," he says. "Ours will be the first-in-class molecular-targeted therapy using it as a target."

Tsujikawa is also taking aim at urothelial and lung cancer. His group identified a micro RNA molecule that plays a role in the development and progression of both cancers and has since identified an inhibitor for the molecule.

To develop a therapy for bladder cancer, Tsujikawa is taking yet another approach. A protein known as ALKBH8 is known to be involved in bladder cancer. Tsujikawa developed a bridged nucleic acid—modified RNA molecules that are very selective for the target molecule—to inhibit this molecule.

Small compounds are simple to synthesize, but they have a low specificity, meaning they disturb other pathways besides those being targeted and sometimes produce debilitating side effects. Nucleic acids, by contrast, have specificity conferred by genetic sequences and thus, presumably, fewer side effects. "But that specificity is something that has yet to be proved true," cautions Tsujikawa.

The bridged nucleic acid antisense therapeutic approach is so cutting edge that Japan's regulatory body is still trying to catch up, he says. There are few examples of its use in solid carcinoma treatment anywhere in the world. Still, with the approach's effectiveness proved in animals and the promise of a cancer therapy having few side effects, Tsujikawa is preparing for the clinic. "This has the most potential for future medicines," he says.

OSAKA UNIVERSITY

Graduate School of Pharmaceutical Sciences, Osaka University
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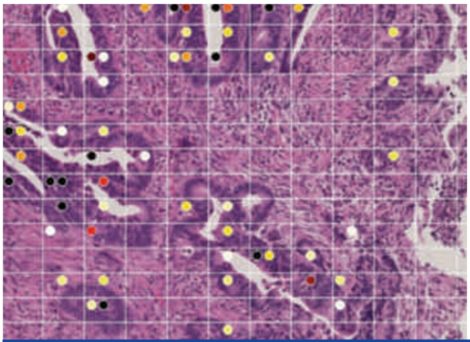


GRADUATE SCHOOL OF ENGINEERING SCIENCE, OSAKA UNIVERSITY

The mathematics of cancer

Despite the giant strides that have been made in cancer research in recent years, much still remains to be done. Many molecules initially hailed as potential game changers, flop in clinical trials. Early diagnosis remains a distant goal. Cancer researchers are searching for new approaches that will allow them to take the next leap forward. Takashi Suzuki, who has pioneered a new field called 'mathematical oncology', is one researcher to follow.

Suzuki adopts an innovative approach to diagnosis. Doctors currently have to examine histological slides of biopsied tumour samples, which requires a level of medical expertise that is often lacking in rural areas and developing countries. "Currently, if you are not a well-trained doctor, you cannot easily diagnose whether a given sample is a cancer," explains Suzuki.

Suzuki's solution is to employ automated cancer-tissue modelling software. Suzuki compared homologous cancerous growths, applying mathematical tools and formulating rules based on observations of how cells touch each other, their topology and their variegation.

The system is still under development, and hence the diagnosis of breast cancer, for example, often misses the mark. But using it, Suzuki can now identify intestinal cancer with an accuracy approaching 100%. Once optimized, the automatic diagnostic system "will be fast, large scale and accurate," claims Suzuki.

Suzuki developed the system in collaboration with cancer biologists at Osaka University. They have licensed the patent to a software company, and he is optimistic it will be improving health care soon. "This has a huge potential to contribute to society in the near future," he predicts.

Suzuki is also involved in a simulation project that, in the longer term, is likely to accelerate the hunt for cancer therapeutics.

He targeted the process by which cancer cells degrade the extracellular matrix and commence metastasizing. Previous biological experiments had revealed that three molecules—membrane type-1 matrix metalloproteinase (MT1-MMP), tissue inhibitor of metalloproteinase (TIMP-2) and metalloproteinase-2 (MMP-2)—are involved in the regulation of this pathway. But the experiments could not illuminate how this happens. "Biologists want to see the whole picture, but with biological experiments alone they cannot," Suzuki explains. "They can knock down or knock out, and they know the input and output, but they can't see what happens in the middle. It's a limitation."

Biological modelling overcomes this obstacle, letting researchers observe what happens over time. "Biological modelling is a very rational way to look at this," says Suzuki.

Whereas biologists would consider only a handful of possible combinations, Suzuki exploited the power of computer simulations to show that only one specific assemblage—two MT1-MMP molecules, one TIMP-2 molecule and one MMP-2 molecule—could explain the observed pattern of activity. Wet experiments subsequently confirmed that this configuration was indeed correct.

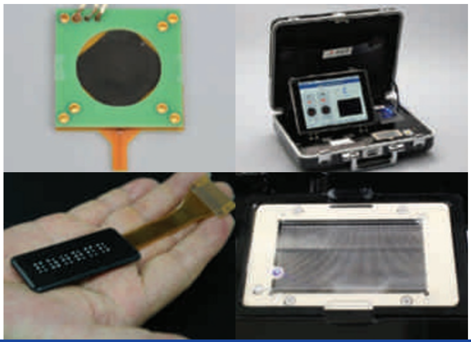
Using a computational model, Suzuki studied the dynamics of the early stage of metastasis when cancer cells first invade the extracellular matrix. He found that MT1-MMP activity reaches a peak before dropping and stabilizing.

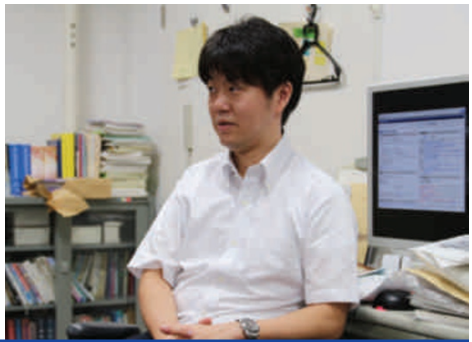
Suzuki's work has helped resolve an enigma that has shrouded the field since the discovery of MMP in 1994. It also offers clues for developing effective therapeutic intervention strategies. "It tells us where we have to hit to try to correct things," he says. "It opens up many paths."

Mathematical models are an essential link in a feedback loop that illuminates cancer biology: biological experiments lead to a mathematical model, which drives simulation experiments, the creation of a new biological model and new biological experiments based on the model.

Suzuki, who spends half his time on mathematics and half on applications in cancer biology, says his modelling could open up numerous dead ends in research. Taking a more rational approach in experimental design will make research more efficient, cheaper and faster—and save a lot of mice, he says. "I want that to happen in the near future," he says.

Many research projects—about half of the biology presentations Suzuki sees when visiting conferences—potentially stand to benefit from mathematical modelling. "I believe that anything we see in the physical world, we can understand mathematically," he states.





NATIONAL INSTITUTE OF ADVANCED INDUSTRIAL SCIENCE AND TECHNOLOGY (AIST)

Technology for evaluating health in society

The National Institute of Advanced Industrial Science and Technology (AIST) pursues knowledge and technology with the aim of benefiting society. To this end, the Kansai branch of the Health Research Institute of AIST is developing medical devices that can be used at hospitals and the research and development departments of medical companies.

Redefining health

Although commonplace in many contexts, the term 'health' has become a keyword in the life sciences. Adopting a definition that goes beyond the treatment of solely physical ailments, researchers at the AIST Health Research Institute are developing technologies that address the individual's physical, psychological and social well-being.

Nanotube actuator for medical devices

Among them is Kinji Asaka, leader of the Artificial Cell Research Group, who has recently developed a carbon-nanotube actuator — a device that generates movement on the application of a low voltage. Its small size and low-power requirements mean that it can be used to operate micropumps, molecular motors and nanoscale robots (known as nanorobots). Asaka got the inspiration for his actuator from the soft texture of human muscles.

Asaka has used the actuator to create prototype medical devices that promote health and assist people with disabilities. One example is an extremely lightweight and thin Braille display, which can assist people with poor or no vision to operate household electrical appliances.

Another example is a micropipette developed in collaboration with scientists in Germany that can efficiently suck ten microlitres of liquid. Currently, Asaka is actively pursuing international collaborations with the aim of using the micropipette to practically benefit society (for example, for microdosing in medical and biochemical analysis).

"I plan to launch it within five years," says Asaka. "To realize that goal, we have to mass produce actuator films and facilitate the commercialization of the production system." He obtained a patent for the carbon-nanotube actuator in 2003 and has subsequently been enjoying the long-term development process, which requires him to draw on a wide range of different fields, including materials science, polymer science and robotics engineering as well as physics, chemistry and electronic engineering. "It takes a lot of time and input from many individuals to develop improved medical devices," says Asaka, "but that is why I really enjoy the process."

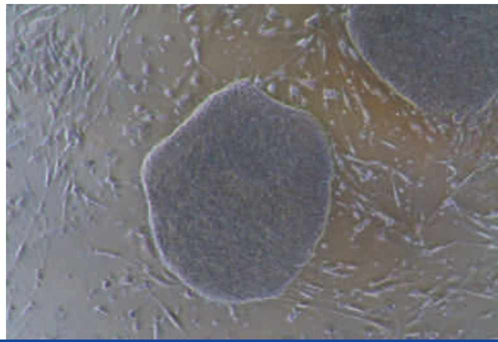
> ***"It takes a lot of time and input from many individuals to develop improved medical devices, but that is why I really enjoy the process."***

Rapid diagnosis of infectious diseases

Hidenori Nagai, a senior researcher in the Stress Signal Research Group, is also developing technologies to improve health. He is currently working on an advanced clinical sensor, which he hopes will one day become as commonplace as the humble thermometer. This sensor is called GeneSoc™ (gene sensor on a chip), a name that is derived from the Japanese word *jinsoku*, which means rapid. It comes in a small attaché case and permits medical practitioners at hospitals to promptly analyse samples from patients exhibiting symptoms associated with infectious diseases.

"The sensor employs a biochemical technique known as a polymerase chain reaction, which enables up to ten copies of target genes to be taken from a patient in about five to eight minutes," says Nagai. "That length of time is acceptably short for hospital-based doctors to diagnose infectious diseases such as flu, tuberculosis and norovirus."

The project was initially started as a national countermeasure to bioterror, but its focus has now shifted towards disease diagnosis. Nagai joined the venture this year. He hopes to develop GeneSoc™ so that it can be sold globally at a reasonable price. Nagai's dream is to rapidly diagnose infectious diseases to permit immediate treatment. "I am interested in using this device to improve public health, for example by using it in the fight against malaria."



NATIONAL INSTITUTE OF BIOMEDICAL INNOVATION (NIBIO)

A multifaceted drug-discovery institute

Spread throughout the Japanese archipelago, the National Institute of Biomedical Innovation (NIBIO) wields tremendous influence in the world of drug discovery. Its research laboratories approach drug discovery from a wide range of angles, while its experimental resource hubs supply cells and animals to researchers around the globe. It operates under a simple philosophy—bring the best people and resources together to make drugs that help people.

"Our mission," says the NIBIO Director General Yoshihiro Yoneda (middle photograph on this page), "is to help people create drugs."

Now in its tenth year, the NIBIO oversees the Tsukuba Primate Research Center, a vital resource for late-stage preclinical drug development, along with three branches of the Research Center for Medicinal Plant Resources in Nayoro City, Kagoshima and Tsukuba, which together hold more than 4,000 species and groups of medicinal plants. Its Japanese Collection of Research Bioresources Cell Bank contains cell lines from healthy donors and patients, including luciferase stably expressing cancer cell lines (which are useful for bioimaging), human induced pluripotent stem (iPS) cell lines, patient cell lines from cancer-prone families and 2,100 B lymphocyte cell samples from the Japanese population. There are over 200,000 types of genetic clones, including more than 100,000 *Cynomolgus macaque* cDNA clones and more than 15,000 chimpanzee cDNA clones.

In 2013 alone, the NIBIO provided 3,067 tubes to 1,870 research projects within Japan and another 1,210 tubes to 471 research projects in 32 countries, including the USA, China, Germany and the UK.

'Ship' molecule

The institute also supports over 300 researchers and research staff who are pushing the envelope of drug development. Yoneda, for example, pioneered research on importin-α, a molecule that acts as a 'ship' that ferries 'cargo'—critical signaling molecules—into the nucleus. "We found it, and then we discovered its function," he says.

Subsequent research has revealed an interesting twist. As people age, importin-α becomes less active, except in cancerous tumours, where it becomes more active. Understanding what goes wrong in one process might shed light on what happens in the other. "We're trying to understand the connection," says Yoneda. "Importin-α might help us understand both phenomena."

While research has focused on the more than 5,000 'cargo' molecules that get transported into and out of the nucleus, the roughly 25 'ships' have not been adequately studied. "The simplicity of the transport mechanism has discouraged people," says Yoneda. It's something he hopes to remedy and, in so doing, glean new clues into what goes wrong in the human body. "We want to find more 'ships', what kind of 'cargo' they carry and how they operate in specific types of cells."

Monkey collection

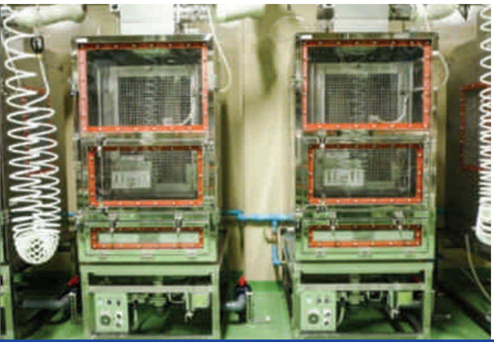
Yasuhiro Yasutomi, director of the Tsukuba Primate Research Center, approaches drug development from a radically different perspective, using a unique resource. His centre has 1,600 monkeys, which it supplies to 500 registered users, and currently manages 40 research projects. For example, the NIBIO supplies primates for research on mucosal tuberculosis vaccines. "Such research is difficult to carry out in other countries because of restrictions and cost issues," Yasutomi says. "And the NIBIO is the only place in Japan that offers non-human primates for medical research." Furthermore, it has the world's only collection of 100% *Cynomolgus macaque* iPS cell lines.

The centre is the only organization to have been awarded grants from the Global Health Innovative Technology Fund in three consecutive years.

A unique resource of the centre is its population of around 80 monkeys over 30 years old. Monkeys are usually used for research by the time they are five. But as they age, monkeys experience numerous disorders that have parallels in humans, including hyperlipidemia, macular degeneration and dilated cardiomyopathy, making them a great naturally occurring model.

Some 20 of the centre's aged monkeys are also being used for research into H7 avian influenza, which seeks to understand why the virus has such a large impact on the elderly.

Some 15 years ago, for example, it was discovered that almost all monkeys over 25 years exhibit dementia. "We want to see if there's anything we can do to improve awareness among the aged," says Yasutomi. He is particularly excited by research with his monkeys showing that some of these disorders



(for example, diabetes and Alzheimer's disease) are connected. Preliminary research shows the link may be through metabolic problems stemming from faulty motor proteins; a deeper understanding could help develop therapies for both conditions. "This will definitely lead to new drug targets," he says.

Data warehouse

Kenji Mizuguchi approaches drug discovery from a completely different angle. Having spent 10 years in Cambridge, UK, where he created a method for predicting protein structures from their amino acid sequences—a method still widely used by pharmaceutical companies and academia today—he became more interested in systems biology.

In the pursuit of therapeutic molecules, researchers usually determine a signalling molecule, a pocket in that molecule, and something that will fill the pocket. "But that is still just the beginning," says Mizuguchi. Since a drug targeting one pathway will often disrupt others, "you need to understand how they interact with each other." So he now uses his computational and systems approach to predict protein–protein and protein–drug interactions.

Much of the data he uses is publicly available. The challenge is knowing how to integrate it. When done successfully, "We can understand why one drug works in a particular situation whereas another does not."

"More than a database, it's a 'data warehouse'," says Mizuguchi. Its purpose is to prioritize potential targets. High-throughput analyses might produce hundreds of candidates, but it's too costly to look at these candidates one by one. Mizuguchi looks at various parameters—how they interact with each other, where they are found, genomic data, structural data—and then ranks them. "We say 'these five are potentially more interesting'."

Already one integrated database he created, TargetMine, has led to several promising candidates, including some for treating hepatitis C virus (HCV) infection and chronic inflammatory diseases. In the case of HCV, in a collaboration with Osaka University, TargetMine predicted that the human gene alpha-enolase would be a regulator of HCV replication and release; a prediction that has subsequently been verified experimentally. Mizuguchi and his collaborators also identified BIG3, a key signaling molecule in breast cancer cells, and then went on to find an inhibitor (ERAP) that hampers the interaction between BIG3 and its partner PHB2. By doing so, the inhibitor makes the cells more susceptible to chemotherapy. "The protein was too big—it was impossible for biologists to work with," says Mizuguchi. "But through the modelling, we could see how it works, we could narrow in on the interaction site."

Vaccine search

Mizuguchi's approach is well suited for taking advantage of the biology expertise in Osaka. "We won't have a big computer, but being here gives me contact with people involved in real-life applications and with people still developing new methods. I know what my biologist collaborators need, and I can develop that," he says.

The NIBIO's Ken Ishii is involved in real-life applications, and one of Mizuguchi's databases helps Ishii predict the potential efficacy and safety of vaccine and vaccine adjuvants.

Working with Shizuo Akira at Osaka University, Ishii spent 15 years looking at the immune responses caused by nucleic acids. "It's really fun. It is sequence dependent, structure dependent and modification dependent, so you can direct the immune response with precision by adding nucleic acids," he says. "Nucleic acids are signatures of the stress we experience."

He now works with pathogen-associated and damage-associated molecular patterns, learning how to fine-tune an immune response to prevent or treat immune disorders. And Ishii was at the centre of the race to discover tumour rejection antigens. "I came to look at the field as a form of therapeutics, looking for immunotherapy," he says.

Ishii just finished a phase-I clinical trial for a malaria vaccine. In the future, he plans to take on other increasingly important problems, including the immune response to pollutants, such as particulate matter 2.5 (PM2.5). Just how do such environmental factors interact with the complex system of intercellular communication among exosomes, nucleic acids and other molecules? "What happens is a truly interesting area of immune response," Ishii says. "It's possible that introduced particulate matter disrupts the communication."

The primate resources were a huge attraction for Ishii when deciding to come the NIBIO. They made it possible do to research that would have been prohibitively expensive elsewhere. "It's a huge advantage over the USA and Europe," he says, noting that powerful overseas pharmaceutical companies and researchers are also drawn by the primate centre. "It's a unique place with which to collaborate."

Ishii also likes NIBIO's philosophy. As a former a member of the group regulating vaccines at the US Food and Drug Administration, Ishii stands at the crossroads of basic research, pharmaceutical development and regulatory agencies—a traditional weak point for Japan. "In the USA, it's natural for these three to work together. In Japan, we have to struggle to overcome traditional hierarchical thinking," he explains. "The NIBIO is thinking this way, and that's why I wanted to come here."



CENTER FOR INFORMATION AND NEURAL NETWORKS (CINET), NICT

Brain imaging sheds light on neural processes

Emotion and perception have been mainly gauged using psychological criteria and tests, but now researchers at the Center for Information and Neural Networks (CiNet) can evaluate them more objectively by using images of the brain.

Brain imaging

CiNet conducts interdisciplinary research at the intersection between neuroscience and information science. One of the dozen research centres of the National Institute of Information and Communications Technology (NICT) in Japan, CiNet focuses on four areas: understanding and applying knowledge of how the brain determines the meaning of a message; building a low-energy information and communication network based on human brain function; developing brain–machine interfaces to provide better care and produce advanced communication technologies; and establishing technologies for measuring brain function.

CiNet is well equipped for this research. It possesses several advanced bioimaging systems, including a magnetoencephalogram and a 7-tesla magnetic resonance imaging (MRI) system (CiNet is one of only about 40 research institutes worldwide to have this technology).

In addition to its world-class facilities, CiNet promotes cross-discipline research through collaborating with researchers in quite different academic fields. One example is the partnership with Fumio Ohtake, a professor at the Institute of Social and Economic Research of Osaka University, which extends to the increasingly popular fields of neuromarketing and neuroeconomics.

Quantitative analysis of neural responses

"Researchers at CiNet quantitatively analyse the neural responses of individuals to unique environments using bioimaging and bioinformatics technologies," says Toshio Yanagida, director of CiNet. For example, they use images of neural networks in the brain to evaluate how people respond to their personal surroundings and social situations. "We obtain a variety of neuroinformatics data, such as the way in which the brain reacts on entering a room that is a comfortable temperature and has pleasant lighting," explains Yanagida. This information can be used by hospitals and pharmaceutical companies to make patients with mental and neurological disorders feel more at ease during hospitalization and rehabilitation. It can also provide companies with insights into factors that influence people's choices when purchasing products. "Companies can then use the data to improve the satisfaction levels of consumers," adds Yanagida.

Masahiko Haruno, a principal investigator in the Computational and Social Neuroscience Laboratory at CiNet, researches the individual differences in decision-making during social activities. Subconscious intuition and primitive sensory processing in social contexts originate from neural networks in the brain. According to Haruno, people can be categorized into three groups in terms of decision-making: those who seek to be prosocial by minimizing differences; those who maximize individual benefit; and those who are competitive when evaluating outcomes. "The use of imaging techniques to see such differences helps clarify the brain dynamics, which determine when our minds react emotionally or logically," says Haruno.

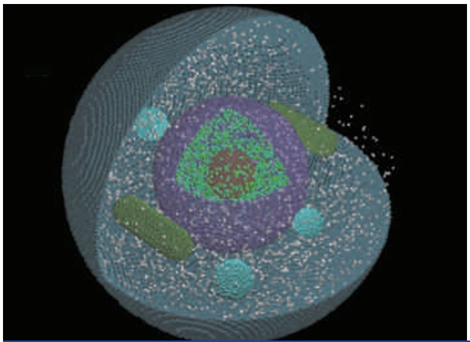
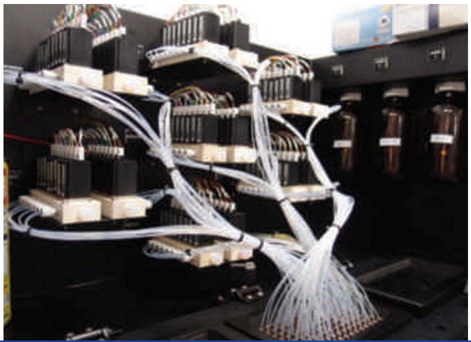
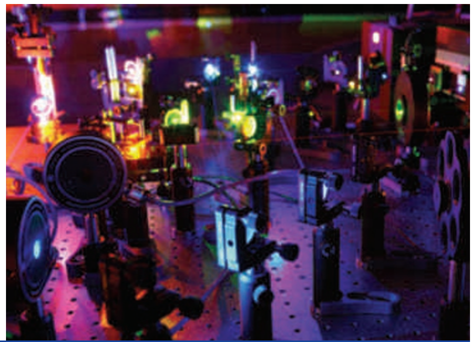
Visualizing brain cubes

Eiichi Naito, a principal investigator in the Human Sensorimotor Manipulative Laboratory of CiNet, is extracting information about the brain from massive data sets to determine the underlying patterns of different activities. For instance, brain images obtained from a person playing a piano vary depending on the mood and even the composer of the music. "Looking at brain voxels (three-dimensional units similar to pixels in a photograph) allows us to evaluate the most important brain regions for different activities," Naito says. "We can then estimate which areas of the brain will require functional assistance in special situations such as rehabilitation."

Minding the future

CiNet welcomes researchers from overseas and seeks to extend its research network. For example, CiNet will host its first conference on new directions in the neuroscience of pain in December 2014, which will feature an exciting range of national and international speakers.

Yanagida also hopes to explore the exceptional efficiency of the human body. "The energy consumed by cells is miniscule compared to the huge amounts of energy expended by artificial computers," he says. "Determining why this is so will usher in a new era in scientific exploration."

RIKEN QUANTITATIVE BIOLOGY CENTER

Unravelling the molecular secrets of living cells

One of RIKEN's newest research centres, the Quantitative Biology Center (QBiC) brings together a range of disciplines with the ambitious goal of observing, modelling and ultimately understanding living cells in all their complexity.

Biological systems are incredibly complex, involving direct and indirect cascades of interactions among molecules that can be as simple as individual ions and as elaborate as folded protein complexes; these interactions occur both within and outside organelles of all shapes, sizes and functions. Understanding how the cell operates on a macroscopic level by accounting for the dynamics of these biomolecular interactions requires the expertise and combined efforts of molecular biologists from all specializations, as well as chemists, physicists, computer scientists and even engineers. Although a daunting task, future advancements in medicine, agriculture and biotechnology will hinge on how well we understand these cellular processes and their broader interactions. This is the challenge that the RIKEN Quantitative Biology Center has taken up.

QBiC's triple strategy

Research at QBiC is approached from three perspectives with the aim of developing a holistic understanding of the living cell. "Our researchers conduct quantitative investigations of molecules and cells in three main areas: measuring cell dynamics, computational modelling of those dynamics, and eventually redesigning molecular and cellular processes," explains QBiC director Toshio Yanagida, a biophysicist renowned for his pioneering work in single-molecule biology.

In addition to being director of QBiC, Toshio Yanagida is also director of the Center for Information and Neural Networks and deputy director of the Osaka University Immunology Frontier Research Center, both of which are similarly focused on complex systems.

The Cell Dynamics research team develops new imaging and detection techniques for quantitatively measuring intracellular molecular processes, such as real-time observations of gene expression and protein translation. These techniques include high-resolution microscopy of living cells, single-cell mass spectrometry analysis, and nuclear magnetic resonance imaging of the entire cell.

The measurements made by the Cell Dynamics research team are then used by the Computational Biology research team to develop accurate computational models of biological systems. Using the world-class supercomputing resources available to RIKEN, which include the K computer, the team simulates and predicts interactions among macromolecules within the cell and among cells within the body.

Once a viable model of cellular dynamics has been developed, the synthetic biologists from the Cell Design research team design and generate artificial systems that mimic the living cell using technologies such as genome engineering and cell-free protein synthesis.

Bringing together the world's best minds

QBiC hosted the inaugural international symposium "Towards Whole-Cell Modeling" in 2012, and it will host the second one in the summer of 2015 in Osaka. In addition to lectures by world-leading scientists in the field, there will be oral and poster sessions welcoming participants from a wide range of fields in quantitative biology.

As well as holding regular international symposia and seminars from leading quantitative biologists from around the world, QBiC actively promotes itself as an international research centre through programs such as RIKEN's International Program Associate (IPA) initiative, which allows doctoral students from participating universities worldwide to conduct their studies with one of QBiC's research teams.

Facilitating the exchange of ideas among leading scientists and attracting fresh young talent from around the world are important strategies of QBiC, bringing together great minds to develop suitable quantitative techniques for probing living organisms in all their dynamic complexity.

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