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Bringing Blue Sky Research Down to Earth:  
Translational Medical Research at the University of Tokyo

The University of Tokyo—also known as Todai (東大), a contraction of Tokyo daigaku (東京大学)—is one of the world’s premier research universities, conducting world-class interdisciplinary research across a wide spectrum of fields, and internationally acknowledged for major contributions in the arts and humanities, natural sciences, engineering, and medicine. The University, established in 1877, currently comprises approximately 5,800 academic staff and 28,000 students, located on campuses centered around Tokyo and in facilities throughout Japan. Its excellence in education and research is exemplified by the success of its alumni, which includes seven Nobel Laureates in the past half century.

Novel Approaches to Translational Medical Research

Translational research has recently become a stronger focus for the University, with the goal of solving real-life problems that positively impact society as a whole. “To complement our successes in interdisciplinary research we are initiating major programs to transfer the seeds of our basic research into devices, protocols, and products for the benefit of society,” explains Takao Shimizu, a biochemistry professor at Todai’s Medical School and executive vice president of the University. Examples of internationally acclaimed and innovative programs and infrastructure for translational research include the Translational Research Initiative (TRI) and Open Innovation Center for Drug Discovery (OCDD).

The Translational Research Initiative

The TRI aims to bring about a paradigm shift in health care technologies. “Our mission is to translate basic research at Todai into practical healthcare applications,” says Takashi Kadowaki, the director of the University of Tokyo Hospital and head of TRI. “We have experts from the arts, sciences, engineering, and medicine, all collaborating at the 22nd Century Medical and Research Center [CMRC].”

Twenty departments make up the CMRC, each with an endowment of US$500,000 per year for 10 years. “This is the largest concentration of endowed departments in Japan,” says Kadowaki.

From Diabetes to Biomedical Engineering

Kadowaki, who manages the TRI and treats hospital patients, also conducts research on diabetes and metabolic diseases. “Changes in dietary habits since the mid-1950s have led to a 35-fold increase in diabetic patients in Japan,” he says. “In 2007, Japan had an astonishing 8.9 million confirmed diabetes cases.” In 2003, Kadowaki’s group discovered that downregulation of the so-called adiponectin receptor (Adipor) was a major cause of obesity-related insulin resistance in type 2 diabetics. “We are now in the preclinical stage of translational medical research on ‘adiponectin receptor activators’ (ARAs) to counteract insulin resistance. Treating diabetes will also reduce the impact of associated ailments such as kidney disease, stroke, and ischemic heart disease.”

Engineers also play an important role in research at TRI. “Our teams of leading biomedical engineers interact frequently with their counterparts in translational medicine research,” says Ichiro Sakuma, a leading researcher at the Center for Medical System Innovation (CMSI) at TRI.

Other research at CMSI includes the fabrication of supramolecular nanocarriers for drug delivery (Kazunori Kataoka), the synthesis of artificial polymer-based cell membranes (Kazuhiko Ishihara), the regeneration of bone and cartilage for oral and maxillofacial surgery (Tsuyoshi Takato), the synthesis and medical applications of photo-responsive biomolecules (Teruyuki Nagamune), and the development of lab-on-a-chip and other microfluidic devices (Takehiko Kitamori).

New Research Facilities

Research infrastructure is critical for effective translational medical research. The ‘Phase One Unit,’ a new treatment and research unit, has recently been added to the University of Tokyo Hospital Clinical Research Support Center (UT-CresCent). The unit has 12 beds, magnetic resonance imaging and positron emission tomography-computed tomography scanners, and state of the art medical diagnostic equipment. “These facilities will enable us to reduce the time taken to test potential drugs for the treatment of ailments including Alzheimer’s disease,” explains Takashi Moritoyo, head of the new unit.
Preventative Medicine: Predicting Alzheimer’s Disease
Japan—like many other industrial nations—is dealing with a rapidly aging population. In particular, the limitations of present-day medical care and social support infrastructure make coping with increases in Alzheimer’s disease (AD) a challenge. Takeshi Iwatsubo in the Department of Neuropathology is the principle investigator of the Japanese Alzheimer’s Disease Neuroimaging Initiative (J-ADNI). “J-ADNI was launched in 2007 to establish a complete set of biomarkers to predict the onset of AD, in particular the progression from mild cognitive impairment to AD,” explains Iwatsubo. “The goal is to develop disease-modifying drug treatments.”

As of 2012, J-ADNI had tested approximately 600 subjects at 38 clinical sites throughout Japan and has collected a plethora of MRI, brain activity, pathology, and biomarker data. These results will be analyzed for patterns indicative of disease progress and also used to track patient response to treatment.

Researchers at J-ADNI are collaborating with 11 major drug manufacturers to identify and test promising therapies, including Japan’s Takeda Pharmaceutical Company Limited, from which Todai obtained the license for TAK-070—a β-secretase inhibitor—for phase 1 clinical trials scheduled to start in March 2013. “There are at least two million AD patients in Japan alone,” says Iwatsubo. “We expect preemptive medical diagnosis in preclinical AD to improve the quality of life for millions of people worldwide.”

The Open Innovation Center for Drug Discovery
Hidenori Ichijo is director of the Open Innovation Center for Drug Discovery (OCDD) and with his colleagues, Takayoshi Okabe and Hirotatsu Kojima, manages the OCDD, a central facility for drug screening in Japan. In contrast to other institutions providing complete screening services, the OCDD offers facilities and training but requires researchers to conduct screening themselves, giving them more control over their own research.

“We store a huge range of chemical compounds—approximately 210,750 as of 2012—that are available for screening to identify new drugs, including so-called orphan drugs for treating rare diseases,” explains Ichijo. In addition to shipping samples to researchers around Japan, the OCDD also provides advice and the use of its facilities. “Through the end of 2012, we have accepted 646 applications for use of the OCDD library, provided 3.6 million samples, and held 629 advisory meetings,” says Okabe.

A recent research highlight is an important finding by Ichijo concerning amyotrophic lateral sclerosis (ALS). “The discovery that it can regulate glial-initiating cells to produce tumors in the brain. Importantly, Miyazono and colleagues found that TGF-β receptor inhibitors could act as effective antitumor agents.”

Looking Ahead and Abroad
“Education and research are evolving at Todai,” states executive vice president Shimizu. “President Junichi Hamada has stated the need to ‘change the whole education system’,” he continues. “So we will start our academic year in September to synchronize with overseas universities.” This shift symbolizes the emphasis that Todai places on internationalization, taking an outward-looking stance as the University meets, in Shimizu’s words, “the daunting challenges facing the next generation.” Shimizu also strongly believes “that student and faculty diversity and mobility are vital for the university to nurture students able to take on those challenges.”

Basic Research Seeds for Translational Medical Research

Kohei Miyazono  
Department of Molecular Pathology
Research into the autocrine signaling of the cytokine transforming growth factor beta (TGF-β) has led to the discovery that it can regulate the ability of so-called glioma-initiating cells to produce tumors in the brain. Importantly, Miyazono and colleagues found that TGF-β receptor inhibitors could act as effective antitumor agents.

Yasutera Urano  
Department of Chemical Biology and Molecular Imaging
Urano has developed a method for rapid in vivo cancer detection using a novel γ-glutamyltranspeptidase-activated fluorescent probe. The probe ‘switches on’ when taken up by tumor cells. His research was featured on the 23 November 2011 cover of Science Translational Medicine.

Hiroshi Takayanagi  
Department of Immunology
Takayanagi and colleagues initiated osteoimmunological studies into the molecular mechanisms of bone destruction in arthritis. They found that an antibody against the proangiogenic semaphorin-4D molecule promoted bone formation, but did not impact resorption. Related patents have been licensed to a U.S. company that plans to perform clinical trials on its use for the treatment of arthritis, osteoporosis, and cancer.
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2012 Cozzarelli Prize Recipients

**Class I: Physical and Mathematical Sciences**

*Water, plants, and early human habitats in eastern Africa*
Clayton R. Magill, Gail M. Ashley, and Katherine H. Freeman
(2013) PNAS 110:1175–1180

**Class II: Biological Sciences**

*Eight pairs of descending visual neurons in the dragonfly give wing motor centers accurate population vector of prey direction*
Paloma T. Gonzalez-Bellido, Hanchuan Peng, Jinzhu Yang, Apostolos P. Georgopoulos, and Robert M. Olberg
(2013) PNAS 110:696–701

**Class III: Engineering and Applied Sciences**

*Point process modelling of the Afghan War Diary*
Andrew Zammit-Mangion, Michael Dewar, Visakan Kadirkamanathan, and Guido Sanguinetti

**Class IV: Biomedical Sciences**

*Robust cardiomyocyte differentiation from human pluripotent stem cells via temporal modulation of canonical Wnt signaling*
Xiaojun Lian, Cheston Hsiao, Gisela Wilson, Kexian Zhu, Laurie B. Hazeltine, Samira M. Azarin, Kunil K. Raval, Jianhua Zhang, Timothy J. Kamp, and Sean P. Palecek

**Class V: Behavioral and Social Sciences**

*Evolution of music by public choice*
Robert M. MacCallum, Matthias Mauch, Austin Burt, and Armand M. Leroi

**Class VI: Applied Biological, Agricultural, and Environmental Sciences**

*Arabidopsis synchronizes jasmonate-mediated defense with insect circadian behavior*
Danielle Goodspeed, E. Wassim Chehab, Amelia Min-Venditti, Janet Braam, and Michael F. Covington

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See the full story on page 1633.

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