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Kobe Biomedical Innovation Cluster at Port Island
From Rubble to Pioneering Research

Hiroo Imura is the president of the Foundation for Biomedical Research and Innovation and one of the chief scientific architects responsible for rebuilding Kobe after the 1995 earthquake that razed the port city to the ground. Professor Imura developed and oversaw a biomedically inspired strategy for rebuilding one of the most international cities in Japan, the success of which is exemplified by two prominent scientists, whose work is highlighted here, who relocated to Kobe’s Port Island to take advantage of its excellent research facilities.

A massive tremor measuring 7.3 on the Richter scale struck the port city of Kobe at 5:46 am on Tuesday 17 January 1995. The 20-second trembler—later named the Great Hanshin-Awaji Earthquake—killed over 4,000 people, displaced over 300,000 more from their homes, and caused damage estimated at over $100 billion. Global news coverage highlighted the resulting fires that destroyed the downtown and quayside, the destruction of the elevated Hanshin Expressway, and the sharp 1000-point drop in the Nikkei 225 stock market index. Kobe city planners were left with the formidable task of rebuilding Japan’s sixth-largest city.

**FINDING A NEW DIRECTION**

“Creating a blueprint for reconstructing Kobe was a daunting mission,” says Hiroo Imura, a medical doctor and president of the Foundation for Biomedical Research and Innovation (FBRI), who was one of the central figures given a mandate to rebuild the city. “At the time of the earthquake I was president of Kyoto University, and did not have any direct association with Kobe. However, in 1998 I was appointed director of Kobe City General Hospital, and it was at this time that Kobe city officials asked me for suggestions for the reconstruction. I decided to base the rebuilding of the city on biomedical research and industry because I was convinced that, at the time, Japan was behind the West in translational research in spite of having a rapidly aging society.”

In 1999, Imura proposed setting up an organization to link industry, government, and academic institutions to collaborate on clinical research and the development of medical devices for cutting-edge medical treatment. Imura’s ‘all Kansai plan’ received solid support from the deans of the medical schools at the universities of Kyoto, Osaka, and Kobe as well as the National Cardiovascular Center in Osaka and the Kobe Medical Association. Then in 2000, Imura established the FBRI and the Kobe Medical Industry Development Project to form the Kobe Biomedical Innovation Cluster (KBIC). Its mission was to revitalize Kobe’s economy, provide health care for the local community, and support the development of medical technology in Asia.

“The FBRI on Port Island has three main objectives,” explains Imura. “First, to support clinical trials for pharmaceutical research carried out at the Translational Research Informatics Center, where we have about 50 projects in progress. The second is to promote cutting-edge research on regenerative medicine being conducted at the RIKEN Center for Developmental Biology (CDB) and the KBIC; and the third, to conduct and support research on medical technologies being done by RIKEN, the KBIC, or other organizations.”

The complex also includes the Kobe City Medical Center General Hospital, which opened in July 2011 and offers researchers direct interaction with patients for a firsthand insight into ailments and the effectiveness of treatments. According to Imura, there are plans afoot to increase the number of hospitals at the cluster.

In addition to the government-funded research facilities operated by RIKEN, the cluster is also home to about 200 companies including Nippon Boehringer Ingelheim Co., Ltd. and Asubio Pharma Co., Ltd.

Imura notes that recent trends in the pharmaceutical industry indicate a move to relocate to growing markets, such as China. “Companies are prone to focus on the size of a market in a country, and have a tendency to overlook the importance of the depth of basic research there,” says Imura. “In Japan we have an excellent record of basic research in the life sciences. For example, Osaka University is renowned for immunology and nearby Kyoto University for the pioneering research performed by Shinya Yamanaka on induced pluripotent stem [IPS] cells.” Imura also emphasizes the importance of basic research into preemptive treatment for major diseases in Asia, such as diabetes.

“I hope that the successful rebuilding of Kobe in the form of the biomedical cluster on Port Island will inspire and give hope to other disaster-inflicted regions, including the Tohoku region of Japan,” says Imura.

**ABOUT KOBE**

Modern day Kobe, population ~1.5 million, is a port city located about 500 km west of Tokyo. Kobe is an international city with about 40,000 foreign residents from more than 100 countries. Its long history of internationalization is exemplified by the eight international schools, foreign industry, and wide selection of international culinary choices in areas such as the vibrant Sannomiya district of downtown Kobe.

Kobe is less than three hours from Tokyo and Nagoya by train and Sapporo by air. Kobe Airport is only 17 minutes from downtown, offering easy connections within Japan as well as international links via the nearby Kansai Airport.

Port Island at the Port of Kobe has excellent hotels, convention centers, and world-class universities. The Port Liner monorail system links Port Island and Kobe Airport to Sannomiya on the mainland.
CLEAR VISION: REGENERATIVE APPROACH FOR DEGENERATIVE RETINAL DISEASE

Masayo Takahashi is team leader at RIKEN’s Laboratory for Retinal Regeneration at the CDB. “After obtaining my M.D. and Ph.D. from Kyoto University and working at the ophthalmology department of Kyoto University Hospital, I went to the Salk Institute in 1996,” says Takahashi. “My stay at the Salk triggered my interest in the possibility of using stem cells for retinal degenerative diseases.”

Degenerative diseases of the retina—such as age-related macular degeneration—is the fourth largest cause of vision loss in the developed world, with associated health care costs of approximately $255 billion. “This is an unmet medical need,” explains Takahashi. “The worldwide pharmaceutical market alone is about $2.5 billion.”

On returning to Japan, Takahashi was able to successfully induce human embryonic stem (ES) cells and IPS cells to differentiate into photoreceptor cells, with the help of Dr. Sasai’s laboratory in the same institute. Takahashi and her group have also described the generation of IPS cells from the skin fibroblasts of retinitis pigmentosa patients, thereby opening the way for potential patient-based retinal therapy.

Takahashi stresses how important the facilities available at the KBIC are for her research. “Degenerative retinal disease research requires close collaboration between experts in a wide range of fields,” says Takahashi. “Here at the KBIC we have RIKEN’s CDB for regeneration of cells such as retinal pigment epithelium. Equally important is the nearby Kobe General Hospital and the Innovation Hospital, where I can actually meet and treat patients. This combination of basic research facilities and a top-class hospital has been critical for our clinical trials and translational research.”

Until Takahashi’s pioneering research using stem cells, regeneration of the retina in an adult was thought to be impossible. Now, the generation and the possibility of transplantation of retinal cells demonstrated by Takahashi and her colleagues gives hope to millions of patients worldwide suffering from degenerative retinal diseases.

In spite of recent successes, however, Takahashi cautions about over-hyping this type of therapy. “This treatment is still in its infancy,” says Takahashi. “Transplantation of generated cells does not lead to total recovery of vision yet; to achieve that we need to know more about the disease. But one thing is certain: Regenerative therapy of retinal degenerative disease is not a dream. It is a definite reality.”

SYSTEMS BIOLOGY: SLEEPING ON THE JOB

Advances in computer processing power and in technologies such as genome sequencing have enabled scientists to generate and analyze vast amounts of data in order to understand the complex interactions found in biological processes—a relatively new and intriguing area of research referred to as systems biology.

“Systems biology is an extension of molecular biology,” says Hiroki Ueda, head of the Laboratory for Systems Biology, at the CDB. “We could say it’s the biology that comes after the identification of key genes.”

Ueda, who has M.D. and Ph.D. degrees from the University of Tokyo, became leader of the laboratory in 2003, and head of the Functional Genomics Unit at the CDB in 2004. Ueda and his colleagues are developing concepts and strategies to address disorders related to “biological time,” such as sleep and circadian rhythms.

“Over the last few years we have focused our research on understanding dynamic biological systems, in particular the mammalian circadian clock,” says Ueda.

A deeper understanding of how the circadian clock functions is important because it governs metabolism and hormone cycles, and the malfunction of this system can lead to sleep disorders and depression. Ueda and colleagues are developing systems biology-based models to answer a number of questions, including elucidating the underlying mechanism of the circadian periodicity, how external stimuli such as light can affect the endogenous clock, the mechanism by which environmental temperature affects our internal clock, and how multiple cellular clocks are synchronized.

Ueda’s goal is to understand biological time and the unique facilities at CDB are a tremendous asset to achieve this goal. “I want to study time from the atomic to the macroscopic level,” says Ueda. “Here, we have experts from many different fields including mathematics, chemistry, and biology. We also have animal facilities and access to RIKEN’s new supercomputer, named ‘K,’ only one stop away on the monorail. This environment is highly conducive to cutting-edge research.”

Laboratory for Retinal Regeneration
www.riken.go.jp/engn/r-world/research/lab/cdb/retinal/index.html

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Western blot analysis on 3T3 cell lysates using anti-Phospho-Akt1 (pS473) RabMAb (Cat. #2118-1, 1:10,000 dilution). Cells were either (1) untreated or (2) treated with PDGF.

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