Launching the Biomedical Imaging Center Platform of Juntendo University

Yasuo Uchiyama
M.D. & Ph.D.
Institute Director and Specially Appointed Professor
Research Institute for Diseases of Old Age
Graduate School of Medicine, Juntendo University

The ability to perceive forms has advanced along with the development of morphological analysis instruments. Organizing what you see just as it is can be surprisingly difficult. In my research in the fields of life sciences and medicine, I have analyzed the cells of humans and other mammals. Over half a century ago as a medical student, I observed human tissue sections under an optical microscope during histology practice. Even now, I still remember looking at tissue sections stained with hematoxylin-eosin (the most commonly used stain) under an optical microscope and being amazed at the fine detail of the structures. When I heard that the late Professor Toshio Ito (who discovered and reported the fat-storing cells in the sinusoid of the liver in 1956, known as Ito cells) could differentiate over 100 colors even with Eosin staining, I became even more eager to learn about the structures and molecules within cells. Later, when I entered the laboratory and observed tissue sections for a student histology practice with a high-resolution optical microscope, I felt as though I was looking at completely different images. While it is important to use better equipment in research activities, it is also true that the tissue sections for histology practice I used at that time were of high quality and could be suitable for observation even with an upgraded microscope. In retrospect, I realize that improving the quality of tissue sections for student practice is also crucial in education.

When engaging in research activities, having an environment where various equipment can be used is highly important. When starting as a researcher, it is unusually impossible to immediately obtain an environment where you can freely pursue your interests. Typically, you would start working in a laboratory that is already researching what you are interested in. I wanted to know about the morphological formation of tissue cells—the site of vital activity—that I had seen as a student, so I began regularly joining embryology labs. After graduating, I trained in pediatrics, where the processes of highly dynamic growth are evident. I then started my research in embryology.

Our faces are given form primarily by the processes of the head, upper jaw, and lower jaw. The surface of each process is covered with epithelial cells, but these cells are not required for fusion between processes and must disappear. Similarly, in finger formation, the interdigital mesenchymal cells die and superficial epithelial cells are also keratinized and lost in the interdigital regions. The development of these structures thus involves not only cell proliferation but also cell death. This fascinating phenomenon is known as programmed cell death.

My research then took me to Hannover Medical School (Medizinische Hochschule Hannover, MHH) in former West Germany, where I studied not embryology but the 24-hour rhythms of structures and functions in tissue cells. The amount of glycogen in the liver fluctuates significantly within a 24-hour period, and in response to these fluctuations, the amount of endoplasmic reticulum involved in glycogen metabolism in hepatocytes also changes. The liver receives nutrients taken up from the digestive tract and transported via the portal vein. Within the liver, blood flows through sinusoids receiving branches of the portal vein and hepatic artery towards the central veins. Hepatocytes are arranged along these sinusoids, thus presenting a radial arrangement of hepatocytes around the central veins. The periphery of this radial arrangement has a highly oxygenated and nutrient-rich blood flow, leading to the accumulation of glycogen granules and rough endoplasmic reticulum in hepatocytes. On the other hand, hepatocytes contain a low amount of glycogen granules and instead, abundant fat droplets around the central veins. This radial arrangement of hepatocytes is called the hepatic lobule. Hepatocytes in the peripheral (or periportal) region of the hepatic lobules are glycogeniclipolytic, while those in the perivenous region are glycolytic-lipogenic. Unlike hepatocytes in the periportal region, those in the perivenous region are rich in smooth endoplasmic reticulum, which is heavily involved in detoxification. Despite having these characteristics, the morphology of hepatocytes undergoes dynamic changes. Indeed, it has been shown that cell morphology undergoes significant changes reflecting its functions, and these changes are interconnected among tissues and cells. It is natural for function and morphology to be coordinated with each other, but it is also true that the extent of morphological changes can be surprising. I analyzed and understood the fluctuations in morphology and function of cells from various tissues within the 24-hour period.

During my research, I was able to set up my laboratory and create my research environment. However, for an individual to arrange the imaging equipment necessary for research activities was impossible in those days and is difficult even now. At the age of 29, I started my study of chronobiology by studying abroad in West Germany. Upon returning to Japan, I became an assistant in the Department of Anatomy at Tohoku University School of Medicine, where I dedicated myself to both research and education. While there, I could not expand my research funding and tools. However, the professor in charge supported my wish to pursue my research independently, and young students began to visit my laboratory and assist me with my research. The staff at Nissei Sangyo in Tokyo provided me with opportunities to use electron microscopes for observation, which was very helpful in advancing my research. When I moved to the Institute of Basic Medical Sciences at the University of Tsukuba, my research environment improved and the number of research colleagues increased. Looking back on my research career, I see that establishing my position as an independent researcher at an early stage worked to my advantage in my subsequent research activities. I have been involved in research and education in the medical field at many universities, including the University of Tsukuba, Iwate Medical University, Osaka University, and Juntendo University. These experiences have led me to think about how best to train young people who wish to get into research.

Indeed, revitalizing local universities has become a prominent topic of discussion in recent times. There are several key pillars of university reform such as training young researchers, setting up positions for PIs (principal investigators who have independent laboratories where they conduct research, manage laboratory budgets, etc.), introducing a cross-appointment system, increasing the number of female researchers, and so on. These are important issues for universities, and in light of this, local universities are attempting to revitalize themselves by working in partnership with each other. This has promoted cooperation that addresses a variety of issues while compensating for each university’s weaknesses. Partner universities hold presentations by PIs and young researchers (younger than 35 years and in postgraduate, post-doctoral, or assistant professor positions) at their respective universities, which can serve as springboards for the presenting researchers. For young researchers to develop, they must be under a suitable system of guidance with a mentor who can support them and discuss the content of the research. Such mentors are never named as research collaborators, and yet they have done outstanding international research. It is also important to create a system that enables young scientists to become independent researchers early on in their careers.

Based on my experience, one needs a suitable research setting, research funding, research colleagues, and a support system to progress freely with one's research. In recent years, there seems to have been a significant decline in the number of young people who can access these resources and support systems. One reason why few young people consider entering the fields of basic medicine and life sciences is that following a pathway in basic research does not seem to open up a future for them. If we can create an environment that opens doors for graduate students, post-doctoral students, or assistant professors, and there are well-established career paths after graduation, more young people are likely to enter these fields. Furthermore, it is not just limited to young researchers, but it is also crucial to establish a platform equipped with the necessary equipment for research, including high-cost instruments.

It was fortunate that the infection and immunology, neurology, and cancer project teams working under the Japan Science and Technology Agency’s Moonshot Program arranged for high-end equipment to be gathered in one place, and set up imaging platforms at Juntendo University in the Kanto region and at the National Cerebral and Cardiovascular Center in the Kansai region. The instruments installed at Juntendo are a scanning electron microscope + elemental analyzer (EDX), transmission electron microscope, confocal laser microscope, high-speed confocal microscope system, lattice light-sheet microscope, and super-resolution microscopes (STORM, STED). Essentially, these instruments can be used by researchers participating in the Moonshot program, but it is fine if the platforms equipped with these instruments are opened up to all researchers, and there is no concern that these platforms will become unavailable to researchers participating in Moonshot. Also, these instruments are introduced with clear explanations using movies, making them easy to operate. Currently, teaching staff affiliated with the Juntendo University Biomedical Research Core Facilities (Morphological Imaging Centre) and the Research Institute for Diseases of Old Age are responsible for running the center. Consultation on the skills and experience required in the morphological sciences (scanning laser microscopy, super-resolution microscopy, electron microscopy) is available, and staff also provide technical assistance in three-dimensional image analysis (FIB-SEM and serial sectioning equipment), immunoelectron microscopy, and correlative light and electron microscopy (CLEM and In-resin CLEM).

Further development of this platform will require not only the provision of technical assistance, but also the introduction of systems that enable remote operation, and the creation of a consultation system for advancing the understanding of morphology in the images that are obtained. In particular, technical staffs need to be employed and trained to provide technical assistance and to conduct morphological analysis. From my perspective, the most important thing is the participation of companies manufacturing imaging equipment in our platform. There needs to be a forum for mutual discussion about what users want, what innovations in equipment are needed, and what new information companies should provide. If young company employees can work collaboratively as interns, this will also lead to the fostering of that company’s human resources. Regular information exchange meetings, seminars, and so forth also need to be established.

Cultivating young researchers and finding and developing the skills of mid-career PIs are desirable for the life sciences sector in the future. Such calls have been repeated for many years, but there has been little substantial movement from academia. Our platform is taking its first steps, and we hope to develop it into an open platform for rapid mutual progress.