Preface to this Special Issue on Yokogawa's Life Science Business

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INTRODUCTION

About thirty years ago, Mr. Shouzo Yokogawa, the then chairman of Yokogawa Electric Corporation, asked the R&D department to try to measure something "soft." This unprecedented request led to Yokogawa becoming involved in biotechnology research, and marked the start of Yokogawa's life science business.

The R&D department studied several "soft" things to be measured, such as the octane number of oil (which was closely related to Yokogawa's business at that time), the freshness of foods, the ripeness of fruits, the taste of water, the rice-polishing ratio of Japanese *sake*, odor index, and so on. Among them, researchers picked cells.

The technological trend at that time may have convinced Yokogawa's researchers of the promising prospects of cell measurement. In 1987, Dr. Susumu Tonegawa, Ph.D., became the first Japanese laureate of the Nobel Prize in Physiology and Medicine. His discovery of the genetic mechanism that produces antibody diversity stimulated global interest in biotechnology.

However, life science was a minor business in Yokogawa, and the engineers assigned to this task faced bigger hurdles than those in other sectors.

At last, the trend has changed. The 21st century is the age of life science. Huge, epoch-making projects are carving out the future for humankind. Such projects include regenerative medicine using ES and iPS cells, drug discovery, and precision medicine that analyses gene information of cells and offers the optimum treatment to each patient. Yokogawa's technologies for cell measurement have the potential to enhance these projects greatly.

Life science now covers wider categories, from medical drugs and drug discovery to various activities that help humans live healthy, rich lives such as healthcare, food, agriculture, and cosmetics. Yokogawa has to rediscover and redefine its life science business, and so in this preface, we review the history of Yokogawa's life science business over the past thirty years.

CSU AND DRUG DISCOVERY SUPPORT SYSTEMS

Yokogawa chose cells as an object to be measured. Engineers were sure that Yokogawa's optics and servo control technologies could be successfully used to observe the quick movement of cells. However, biotechnology was a completely new business for Yokogawa and the engineers did not know what customers needed and what equipment was required to meet such needs.

A manager of the development team sent some staff to universities and research institutions and made them join autopsies and cell culturing experiments in order to identify the needs of researchers. As a result, they found that researchers wanted to observe the behavior of living cells in real time with high sensitivity and high definition, not through still images.

It was already known that confocal microscopes with fluorescent staining offer clearer images than ordinary fluorescence microscopes. Thus, the goal of developing high-speed confocal microscopes for observing living cells was set.

Ten years later (1996), the CSU10 Nipkow disk type confocal scanner unit, which was Yokogawa's first product for cell measurement, was released. However, the CSU10 attracted little attention in the market except among a few researchers because Yokogawa was a newcomer to this field with no experience of marketing and no sales channels for biotechnology products.

The engineers did not give up though; they travelled all over Japan to visit researchers and demonstrate the CSU, and their steady efforts gradually increased awareness of the CSU.

Meanwhile, Yokogawa decided to work with microscope makers to increase the sales of the CSU, because although it was effective to build relationships with researchers both in and outside Japan, it was not efficient. The CSU

engineers developed adapters that enable the unit to be easily attached to the microscopes of any maker, and expected microscope makers to sell the CSU as a package with their microscopes. These early engineers were pioneers in the field of biotechnology, full of originality and ingenuity and from whom we have much to learn.

Fortunately, the peripheral technologies of biological microscopes made progress around the same time as the release of the CSU. In particular, the green fluorescent protein (GFP) made it possible to observe any living cells. Although the CSU originally targeted cerebral and cardiovascular cells, GFP enabled the unit to observe any cells. GFP was discovered by Dr. Osamu Shimomura, Ph.D., and in 2008 he won the Nobel Prize in Chemistry for his work.

There were other major technological progresses. Microscope light sources to excite fluorescent protein shifted from massive, heavy gas lasers to small, inexpensive diode lasers. Microscope sensors were switched from film cameras to digital cameras, dramatically improving performance. In line with the development of digital technology, various software programs were released which made it much easier to acquire and process (image processing, analysis, display, and recording) cell images. Colorful images accompanied research papers and made them much more convincing. Thanks to such progress, high-performance microscopes became a vital tool for biotechnology researchers.

The CSU successfully rode a wave of technological progress. By leveraging fluorescent proteins including GFP, the CSU was able to observe living cells, which led to a new method of observing live cell images. The CSU did not damage living cells during observation over a long period, making the unit the de-facto standard for live cell imaging.

Although the CSU was a high-end product for a niche market, cumulative shipments reached 1,000 units in 2006, and are now approaching 3,000 units in 2017. This success was thanks to our predecessors who had real insight: they set a clear goal, used the progress in peripheral technologies and the subsequent market expansion, and strived to achieve the goal. This shows that to succeed in a new business, it is crucial to correctly assess the technological trend and business environment.

Images taken by the CSU appeared on the cover of *Nature* in 2002 and 2003. *Science* described Yokogawa's live cell imaging as a major method for biotechnology. In Japan, the CSU received various awards including the Okochi Memorial Prize and the Education, Culture, Sports, Science and Technology Minister's Award.

Yokogawa set up the Life Science Business Headquarters in 2005 and then the Kanazawa Office as core facilities for the life science business, and started developing drug discovery support systems. A major aim was to expand the business from the niche area of basic cell research to the downstream sector with larger markets.

Drug discovery support systems need some core technologies. These are a confocal unit for observing cells, positioning (mechatronics) technology for high throughput, and software for analyzing cell reactions. Yokogawa had to develop new element technologies for positioning control and software. Fortunately, the development staff had an opportunity to participate in a national project sponsored by the New Energy and Industrial Technology Development Organization (NEDO) which aimed to develop confocal laser microscopes with the world's highest performance, and Yokogawa was able to acquire necessary elemental technologies through this project.

Yokogawa has developed and released the CellVoyager series cytological discovery system and the CQ1 confocal quantitative image cytometer, which are selling steadily mainly in Europe. In 2017, Yokogawa released the latest model of the CellVoyager series and a new software product using AI technology.

Although Yokogawa is a latecomer in this field, the advantage of low damage to cells is highly regarded by customers. Yokogawa is working together with Group companies overseas and strengthening its global sales structure. The company is also striving to improve software and services not only to sell products but also to offer derivative solutions to customers.

FUTURE OF YOKOGAWA'S LIFE SCIENCE BUSINESS

In FY2016, Yokogawa's life science business fell into the red, mainly due to the expiration of patents and the departure of major distributors. The fundamental reason is, however, that Yokogawa just continued selling equipment for thirty years and failed to evolve the business. Another reason may be that although the environment has drastically changed, structural reform of the organization remained a low priority because the life science business used to be a minor sector for Yokogawa.

Today, the business trend has changed again and the age of life science has come. In 2018, Yokogawa will operate under a new mid-term business plan. For Yokogawa's life science business, the next year is not a thirty-first year but a fresh, first year to grow further.

CONCLUSION

Our founder, Dr. Tamisuke Yokogawa, wrote about organisms in his book "*Kaku-no-gotoku Shinzu* (My Thoughts)" as follows: "The only tools available for germ research are microscopes with a magnification of a mere several thousand. Moreover, the method is not ideal; kill germs, dye them, and you can only see their shape. I wonder what their real structure and behavior are."

If we could tell him about subsequent scientific advances, he would surely be amazed. "Now everyone can see the structure and behavior of living cells, thanks to your company."

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