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Promotion of Technological Innovation through Medicine-Engineering Collaboration in Japan — Industry-Academia-Government Collaboration in OCT Technology as a Case Example —

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1 Introduction

The Third Science and Technology Basic Plan[1], initiated in fiscal year 2006, primarily emphasizes the importance of technological innovation. It also emphasizes the importance of interdisciplinary and consolidated research, also emphasized in the previous term, and holds the collaboration between medicine and engineering to be a high-priority issue.

In Japan, the rapid aging of the population and the declining birthrate will eventually create a serious social issue: the lack of a young labor force. To address this issue, the "Revised Law concerning Stabilization of Employment of Older Persons" was enacted in fiscal year 2006, extending the mandatory retirement age to slow the reduction of the labor force and reduce national pension expenses. The success of this policy relies on the health and longevity of older people so that they can continue on the job. Moreover, the maintenance of people's good health, regardless of their age and sex, should reduce the nation's continuously increasing medical expenditure. Most of all, if we consider the basics of life, to stay healthy, i.e. to be free of diseases, is a fundamental need for anyone who seeks to live a happy life.

Over the past few decades, Japan has maintained its strong international competitiveness as a nation excelling at "manufacturing things" such as automobiles, machinery, electric and electronic appliances and materials[1, 2]. The country is already equipped with a high technology development capacity, which is one of the requirements for satisfying the social need for developing medical equipment. Today, the global and Japanese markets for medical equipment are estimated as approximately twenty trillion yen and two trillion yen, respectively. The values of Japanese imports and exports in this area were about the same in fiscal year 1992, but the value of imports has increased rapidly since then, reaching 955 billion yen in 2004 and far exceeding the value of exports (430 billion yen) for the same year[3].

In domestic and international road maps, the development of molecular imaging technology is regarded as the next step after the completion of the Human Genome Project, a step that should contribute to the establishment of molecular libraries and ultimately to the promotion of molecular therapy and preventive medicine[4, 5]. The promotion of collaborative innovation between medicine and engineering is crucial to the implementation of this road map and should be regarded as a top-priority issue in Japan.

The present report focuses on OCT (Optical Coherence Tomography)[6], a growing technology whose development illustrates the perils and promises of this trend. The first patent for such an invention was applied for in Japan by a local university at the peak of the bubble economy in the late 1980s[7]. Even back then, the technology gave a glimpse of its potential to create business opportunities through its application to medical equipment, but Europe and the U.S., although

latecomers in OCT invention, have unfortunately gone far ahead of us in commercialization of the technology.

In Japan, the Law for Promoting University-Industry Technology Transfer (TLO law) went into force in 1998. The Third Science and Technology Basic Plan[1], approved at a Cabinet meeting in March 2006, notes that "S&T system reforms enabled steady progress in industry-academia-government collaboration such as: increase in the numbers of industry-academia joint research, technology transfers by technology licensing organizations (TLOs), and university-derived ventures (the total number of such ventures has reached 1,000)," and that "in order for the activities of industry-academ ia-government collaboration to achieve sufficient results, it is necessary to further revitalize the activities of university intellectual property centers and TLOs and make them more effective," suggesting that measures for promoting university startups have already been taken. However, if such measures had been taken a decade earlier, i.e. before the bubble economy in late 1980s, and the significance of public investment in technological innovation had been recognized earlier, Japan would have had an advantage over Europe and the U.S. in the development and commercial exploitation of medical equipment.

Given these situations, we have reaffirmed the significance of the TLO Law and recognized the necessity of examining the current and future state of technology development in Japan, i.e. whether the development of technology (including OCT) synchronizes with the trend of technology transfer promotion and whether there is any obstacle to its future progress. Moreover, as is pointed out by the Ministry of Health, Labour and Welfare[8], we need to expose any operational problems in the clinical trial system or other systems related to the Pharmaceutical Affairs Law that are part of the approval process for new medical equipment products, as such problems may demotivate entrepreneurs and ultimately impair Japan's global competitiveness in medical equipment development.

The Third Science and Technology Basic Plan[1] envisions that "the core strategies are: development of human resources who can produce excellent research findings, creation of a competitive environment, promotion of science, and creation of persistent innovations through strategic investment; and removal of systematic or operational obstacles to return the R&D benefits to society. Science and technology has a mission to address a broad range of these policy issues for the next five years," emphasizing the importance of evaluating success in terms of concrete results.

From these standpoints, this report focuses on the application of OCT to ophthalmic diagnostic imaging systems and chronologically compares its developmental process in Japan and in western countries, from its invention to its commercialization. Moreover, this report introduces the attempt of industry-academia-g overnment cooperation in Japan to recover the initiative, not only in first-generation but also in second- and third-generation OCT technology, and proposes some measures to promote collaborative innovation between medicine and engineering in Japan.

2 Principles underlying OCT and the course of its development

2-1 Principles underlying OCT

OCT is a technology derived from the Michelson interferometer, and its mechanism is roughly described in Figure 1[6]. The light source is a current-injection type semiconductor light source called an SLD (Super Luminescent Diode), which is an infrared light with a wavelength of around 780 nm, 830 nm, 1.3 μm or 1.5 μm that

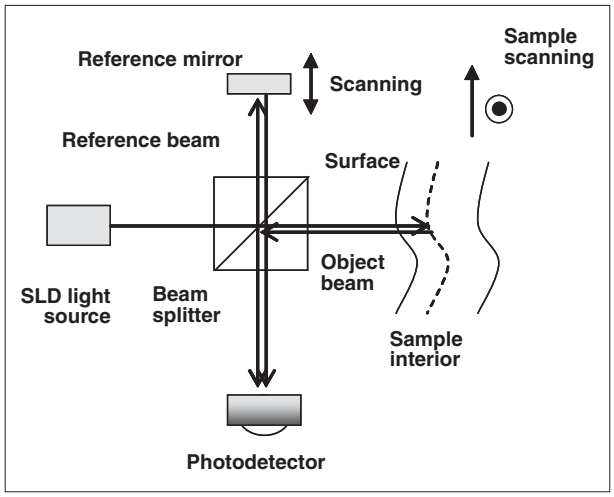

Figure 1 : Mechanism of OCT

Prepared by the STFC based on Reference[6]

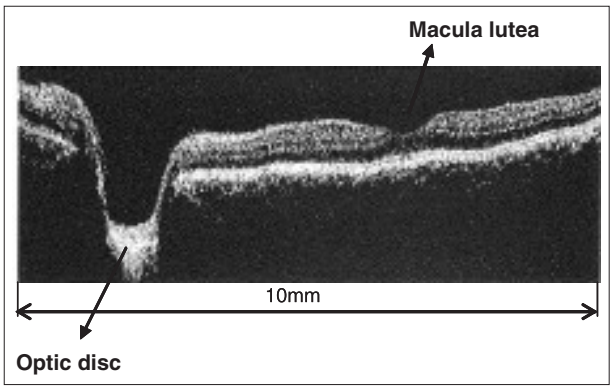

Figure 2 : Example of a retinal tomogram taken by OCT
Photograph provided by Microtomography Co., Ltd.

can penetrate 1-2 mm deep into a living body and that has a sufficiently high spatial coherence but a low temporal coherence. The beam is divided in two by a beam splitter; the transmitted beam reaches the surface of the test sample, enters the test sample and is reflected or scattered by any scattering object or by any boundary between materials with different refractive indices. This reflected or scattered beam returns to the beam splitter, where it is reflected to the photodetector as the object beam. Meanwhile, the beam initially reflected by the beam splitter is reflected by the reference mirror surface, passes through the splitter this time and reaches the photodetector interfering with the object beam based on the superposition principle.

When the path lengths (the distance traveled by the individual beams after being divided by the beam splitter until being combined again) of the object and reference beams are equal to each other (i.e. at zero path-length difference), the two waves intensify each other, and the intensity of the light received by the photodetector is greater than when the path-length difference is not zero. By performing such measurements with multiple reference-mirror positions and scanning the sample two-dimensionally and perpendicularly to the axis of the incident light, the laminar structure (boundaries of refractive indices) inside the sample can be displayed in a three-dimensional manner.

If light with a high temporal coherence, e.g. a laser beam, is used as the light source, intensification of interference occurs irrespective of the path-length difference, making it difficult to see the laminar structure of the sample. Thus, the use of a light source with lower temporal coherence gives a higher depth resolution. This is the key to this invention, and the depth resolution can be 10-20 μm, depending on the spectral bandwidth (about 50 nm) of the light source.

2-2 Process of development in Japan

The first patent on the principle of OCT was applied for in 1990 by Naohiro Tanno, who was then a Professor at Yamagata University[7]. An application was filed only for a Japanese patent and not for a U.S. or any other foreign patent. Meanwhile, the first research paper on OCT, titled "Backscattering Optical Heterodyne Tomography"[9] was prepared for the 14th Laser Sensing Symposium in 1991, and was written in Japanese and not in English. This reminds us of the famous story of Koichi Tanaka, the winner of the Nobel Prize for chemistry in 2002. Since Mr. Tanaka had never published any paper in English except for one that he wrote for a symposium held in China, his research had not received much international attention until he won the Prize. In earlier times, researchers did not have enough funds to publicize their discoveries to the world or to claim their intellectual property rights, and the importance of publishing research papers in English is here reacknowledged.

At that time, Professor Tanno was one of the key members of Biophotonics Information Laboratories, Ltd. (capitalized by the former Ministry of International Trade and Industry) led by Humio Inaba, who was then a professor at Tohoku University. The project was launched by researchers who were inspired by the idea of X-ray CT (Computer Tomography (theory by Allan Cormack, apparatus by Godfrey Hounsfield)), which was awarded the Nobel Prize in Physiology or Medicine in 1979. They were seeking techniques to view the interior of human bodies or other organisms by detecting transmitted light using laser beams instead of X-rays.

In this project, professor Tanno proposed the idea of using in an interferometer a light source that retains one advantage of a laser light source, i.e. low spatial coherence, but has an intentionally reduced temporal coherence compared with a laser. Traditional interferometers

used light sources with low coherence in both temporal and spatial domains, such as incandescent lamps. However, an incandescent lamp is not a point source; it has width, i.e. has a low spatial coherence, and is thus incapable of providing a high resolution at the object plane. In practice, the resolution can be improved by placing a pinhole behind the incandescent lamp; however, this lowers the intensity, preventing the photodetector from catching enough light. OCT employs an interferometric measurement that takes advantage of the high spatial coherence and low temporal coherence of an SLD light source, which is the key feature of this invention.

Unlike X-ray CT that detects photons transmitted through an object, OCT detects the reflected light and enables non-invasive, in-vivo imaging of the tissues in layers close to the surface of a living body. Since this concept appeared to be too different from the original idea of utilizing the coherence of laser beams, which was the dominant focus in the Biophotonics Information Laboratories, Ltd., it was not accepted by some project members. As a result, the concept of OCT was never regarded as fundamental to the project, and a high priority was not placed on investigating potential applications of OCT such as medical equipment development. Nevertheless, immediately after inventing OCT, Professor Tanno and his colleagues approached the Faculty of Medicine of Yamagata University and gave seminars several times a year to regularly introduce their technology seed from the engineering side.

The development process of OCT technology in Japan, from its invention to its application in medical equipment, is chronologically shown in Table 1 along with that in Europe and the U.S. Professor Tanno continued to spread his technology seed by introducing OCT technology at the Yamagata Technopolis Foundation and suggesting to local companies the potential application of semiconductors to testing apparatus. However, in terms of actual research activity, since Yamagata University had no doctoral program then, he taught his master' s students the methods of simulation and other calculation techniques. Although he published his first English paper[10] in 1994, he could not perform a full-scale demonstration experiment.

While Japan was in the middle of this "blank period", in 1996, Zeiss-Humphrey Systems, Inc. (Humphrey), a U.S. subsidiary of the well-established German optical firm Carl Zeiss Meditec AG (Carl Zeiss), released a test model of the industry's first OCT equipment. Professor Shoji Kishi and his colleagues in the Faculty of Medicine of Gunma University showed an interest in this product and purchased the first model. They became the first group to collect clinical data in Japan and demonstrated its utility in the diagnosis of diseases of the ocular fundus[11].

Hearing this news, Professor Tanno noticed that the principle used in the OCT equipment was just what he had invented, and notified Carl Zeiss of this fact. With governmental support based on the Law for Promoting University-Industry Technology Transfer (TLO law) enacted in May 1998, he received financial aid from JST (Japan Science and Technology Agency) and started to make a prototype in 2000. In 2001, he received a visit from the CEO of Carl Zeiss for patent negotiation and persuaded the CEO to accept that his Japanese patent had preceded Carl Zeiss's use of the technique. Carl Zeiss agreed to pay him a royalty on the use of the patent in Japan and to mark their domestically sold products with the Japanese patent number. Fueled by the success of the patent negotiation, Professor Tanno further promoted the development of the product; in 2001, the project was approved under the Temporary Law concerning Measures for the Promotion of the Creative Business Activities of Small and Medium Enterprises and received grants from the Tohoku Bureau of Economy, Trade and Industry and a Yamagata Prefecture New Industry Creative Type Technology R&D Grant. In 2002, then Professor Tanno, who had become the Chairman of the Cooperative Research Center of Yamagata University, founded Microtomography Co., Ltd., a venture capital firm jointly established by a semiconductor-manufacturing equipment manufacturer, MTEX Matsumura Corporation. He was appointed the director of the venture capital firm, and Sumio Matsumura and Michiro Hasegawa were appointed the CEO and the director, respectively. In 2003, the product was

Table 1 : Comparison of OCT development processes in Japan, Europe and the U.S.

Year	Japan		Europe-U.S.
	Engineering	Medicine	Medicine-engineering collaboration
1990	Professor Tanno applied for Japanese patent		
1991	Professor Tanno introduced his idea at the Yamagata Technopolis Foundation, and taught the associated calculation methods in a master's-level course, because the university offered no doctoral program		Professor Fujimoto applied for a patent, published an angiotomogram in Science.
1992	Biophotonics Information Laboratories, Ltd. was founded		Professor Fujimoto received $6 million from Zeiss-Humphrey Systems Inc. (a subsidiary of CZ in U.S.) for promoting collaboration with an image processing group and the Eye Center of the Lincoln Laboratory. He published a fundus photograph in '93 Opt. Lett.
1993			
1994	Professor Tanno et al. published their first English paper		
1995			
1996			Professor Fujimoto et al. published a collection of clinical data. CZ made the first shipment of a test model of funduscopy equipment
1997		Professor Kishi purchased the first model manufactured by CZ	
1998	The TLO Law was enacted	Professor Kishi et al. reported clinical cases.	G. Hausler et al. of the University of Erlangen published the principle of high-speed OCT
1999			
2000	Professor Yasuno et al. of University of Tsukuba published the FD-OCT method. Professor Tanno et al. took part in a regional collaborative research project and received grants from JST (MTEX Matsumura Corporation (MTEX), the parent company of the current MT)		Speed-up and multifunctionality of OCT were pursued. Development of next-generation OCT was promoted, e.g. blood flow measurement utilizing the Doppler effect
2001	Professor Tanno received a visit from the CEO of CZ for patent negotiation. MTEX was approved under the Temporary Law concerning Measures for the Promotion of the Creative Business Activities of Small and Medium Enterprises and received a Yamagata Prefecture New Industry Creative-type Technology R&D Grant		
2002	MTEX received grants from the Tohoku Bureau of Economy, Trade and Industry. Microtomography Co., Ltd. was founded		
2003	MT received approval under the Pharmaceutical Affairs Law		
2004	MT shipped the first domestic funduscopy equipment. Professor Yatagai et al. launched the "ultrahigh-speed Fourier optical radar microscope for biometrics" project funded by JST		
2005	NEDO project "eye fundus blood flow, internal disease examination project" (Kyoto University, Yamagata Technopolis Foundation, Topcon, Nidek, Hamamatsu Photonics) was launched. Professor Yatagai et al. launched "the study concerning application of OCT to ophthalmology" through technological cooperation with Topcon Corporation.		CZ's market share of first-generation OCT equipment reached 90%
2006	MT proposed the application of spectroscopic OCT to 3D tomography to in vivo oxygen saturation in cooperation with Professor Hidetoshi Yamashita of the Yamagata University Faculty of Medicine and Professor Tetsuya Yuasa of the Faculty of Engineering		

MT: Microtomography Co., Ltd. CZ: Carl Zeiss Meditec AG

approved under the Japanese Pharmaceutical Affairs Law, and in 2004, 14 years after the technology was invented and eight years later than its commercialization in Europe and the U.S., Japan's first OCT equipment was finally put on the market.

2-3 Process of development in Europe and the U.S.

For comparison with the process described in Japan, this section explains the process of OCT development in Europe and the U.S., using Table 1. Professor J. Fujimoto and his colleagues at MIT[12], an institute famous as a base of industry-academia collaboration in the U.S., independently invented a principle similar to Professor Tanno's invention. In 1991, they applied for a U.S. patent and published the world's first English paper on OCT titled "Optical Coherence Tomography" in Science[13]. The term OCT currently used among experts around the world is derived from this paper. Professor Fujimoto launched a medicine-engineering collaboration project with an image processing group within MIT and medical scientists at the Eye Center of the Lincoln Laboratory. In 1993, they made the world's first in vivo tomographic observation of the retina[14]. The professor received $6 million as a grant from Humphrey and vigorously worked on the commercialization of OCT equipment. In 1996, he took the initiative in publishing a 5-cm-thick book of clinical data collected in trials of optical coherence tomographic imaging[15], which astonished ophthalmologists around the world. At about the same time, Humphrey released the world's first test model of the equipment. Today, a decade after the product was first released, three companies are engaged in the production and distribution of the equipment, including the above-mentioned two companies and a latecomer, OPI (Opthalmic Technologies Inc.) of Canada. Carl Zeiss and its subsidiary Humphrey command 90% of global market share.

The speedy process of OCT development in Europe and the U.S. can be compared to a football game; the players cooperated in passing the ball (OCT) efficiently, from the defender, to the mid-fielder to the forward player, to take the shortest distance from the invention to the ultimate goal of market domination. The players comprehensively maintained a good balance between work-sharing and cooperation and worked swiftly to bring the university-launched innovation to practical use. The U.S. is already equipped with dynamic systems to facilitate collaborative innovation between medicine and engineering, i.e. the creation of technology seeds and swift technology transfer, and for collecting clinical data, systems that actually operate night and day. Researchers in Japanese universities and public institutions should learn from the smooth cooperation among industry, academia and government in the U.S. and should strongly support Japan's original dynamic systems for facilitating collaborative innovation between medicine and engineering.

3 Institutional and operational problems of the system

This chapter focuses on the legal process in Japan that affects the speed of the collaborative innovation between medicine and engineering. Regarding the developmental process of medical equipment, i.e. R&D (invention) → prototype → clinical data collection → application → screening under the Pharmaceutical Affairs Law → commercialization → shipment, the TLO Law is applied to the first half of the process; in the second half of the process, i.e. clinical data collection and subsequent steps, the Pharmaceutical Affairs Law is applied to screen the products to be put on the market[16]. Although OCT is medical equipment, it is regarded as a pharmaceutical product and must be approved under the Pharmaceutical Affairs Law.

This also applies to the development of OCT equipment; preliminary clinical trials must be performed to collect clinical data demonstrating that the equipment is clinically effective and has no adverse effects. Clinical trials are accompanied by risks, which gives rise to issues of liability for accidents. Thus, screening must be performed with deliberation, requiring a vast amount of time and money. In the U.S., it only took five years for Professor Fujimoto and his colleagues to succeed

in the commercialization of the equipment; in Japan, it took 14 years from the invention to commercialization of the same technology. From now on, innovation based on collaboration between medicine and engineering must be advanced through comprehensive consideration of a variety of issues, e.g. those surrounding the facilitation of technology transfer from universities and the operational differences of the Pharmaceutical Affairs Law as it applies in Japan and the corresponding regulations in the U.S. For example, physicians and professors in the U.S have larger discretionary powers in the clinical trial process. If the physicians or professors consider that trials can be conducted safely, they are authorized to take the initiative in collecting clinical data on their own responsibility. This is why they can accumulate a large amount of clinical data to demonstrate the safety and efficacy of medical equipment within a short time.

In the case of this OCT equipment, Carl Zeiss submitted an application for approval under the Pharmaceutical Affairs Law, first in the U.S. and Europe and then in Japan. Following its successful development of the OCT equipment, the company also succeeded in commercializing OCT-based equipment for measuring the length of the eyeball and received approval under the Japanese Pharmaceutical Affairs Law before any other company. Meanwhile, Microtomography Co., Ltd. of Japan also developed a similar product and applied for the approval under the Pharmaceutical Affairs Law in November 2004 as a generic machine using OCT equipment. However, the light source in Microtomography's product had a wavelength of 830 nm[17], which was different from that in the Carl Zeiss product (780 nm), so the company withdrew the application in March 2005 and re-applied for the machine as a new product in November 2005, and it still has not been approved as of June 2006.

Another typical case of medicine-engineering collaboration is a physician's report of a therapeutic method for an intractable auditory disease[18]. The disease involves impairment of the cochlear duct, which is found between the eardrum and the auditory brain stem and which converts sound vibrations into neural signals. One technique to restore the auditory capability of patients affected by this disease is the transplantation of an artificial cochlea into the patient's cochlear duct, which involves medical technology developed through medicine-engineering collaboration. The artificial cochlea comprises a receiver and an electrode, which are placed inside the body, and a microphone, speech processor and a battery, which are placed outside the body. This procedure has been performed on more than sixty thousand people worldwide and more than four thousand people in Japan. Regarding this therapeutic method, Japan led the world at the development stage; however, it is reported that today the global market for the artificial cochlea is dominated by Australian, U.S., Austrian and French companies. This was reported in the 10th memorial lecture titled "Fusion between different fields and new research trends" given in the ME Forum hosted by the Science Council of Japan in cooperation with the Japanese Society for Medical and Biological Engineering (held on January 23, 2006 in Sanjo Conference Hall at the University of Tokyo).

In this lecture, Mr. Yasuhiro Suzuki of the Health Policy Bureau, Ministry of Health, Labour and Welfare reported that "in cutting-edge basic technology, Japan is a world leader, along with the U.S. and European countries. Meanwhile, with respect to exploratory research on the application of such basic technology to novel medical equipment that satisfies clinical needs, as well as the infrastructure of clinical tests and trials using this equipment and the equipment screening system under the Pharmaceutical Affairs Law, Japan confronts many more problems than Europe and the U.S."[8] These countries have many judges for screening and approving new drugs or medical equipment. For instance, the U.S. FDA (Food and Drug Administration) has 9,000 judges, while its Japanese counterpart has only 300. In his report, Mr. Suzuki also acknowledged that "it is urgent that we improve the environment not only for basic and translational research but also for the clinical studies and trials that lie ahead. For

a long while the clinical trials system in our country has been "hollowed-out", and as the environment for conducting clinical trials in other Asian countries is rapidly improving, the number of clinical trials conducted in our country is steadily decreasing. This not only deprives Japanese citizens of opportunities to benefit from leading-edge medical equipment but also directly decreases the global market share of domestic manufacturers." He also acknowledged that "with the aim of drastically reforming the infrastructure for conducting clinical trials and studies in fiscal year 2006, the Ministry of Health, Labour and Welfare launched a 'Research project for promoting establishment of infrastructure for clinical research' with MHLW Grants-in-Aid for Scientific Research and performs a model project of a physician-driven clinical trial for improving the environment for secure accomplishment of clinical trials," reflecting the Ministry's active stance toward the operational improvement of the systems.

New drugs and medical equipment must all be approved under the Pharmaceutical Affairs Law, which reflects the strong public demand for product safety[19-21]. In the White Paper on Labour Economy 2005[22], the Ministry declared its determination to "be deeply aware of our important duty to supply safe and effective drugs to the public and to protect people's life and health from adverse effects of drugs or from defective drugs, and to exert our best efforts so that the disastrous health damage caused by such drugs will never occur again".

Such assurance of safety seems incompatible with the swift action required for innovation. However, dealing with this severe contradiction is a top-priority issue confronted by every country, and Japan is no exception. In this sense, the above-mentioned report[8] from the Ministry of Health, Labour and Welfare suggests that "domestic development of superior medical equipment, collection of clinical data, swift screening of products and their clinical application are essential for the development of medical equipment. However, each of these steps is accompanied by risks and liabilities, and the quickest way to solve the problem of medical equipment development is to obtain a national consensus on how to deal with such risks and liabilities." The primary purpose of medical equipment or drug development is the recovery and maintenance of health for patients and potential patients. The medical institutions and manufacturers are constantly demanded that they recognize their roles as suppliers of health, and without confusing the means with the ends, find transparent solutions acceptable to all.

To promote future collaborative innovation between medicine and engineering, we must explore measures to improve the operation of systems, such as expanding the discretionary powers of judges and ensuring the transparency of the screening process by giving access permission to research centers and research sites and bringing about more extensive disclosure of information concerning the screening process, etc., in addition to increasing the number of judges and building physician-driven, highly transparent systems for clinical trials. This would require an increase in the budget allocation to support the relevant departments in industry, universities and government. Moreover, for the mid- and long-term, we need to establish an interdisciplinary human resource development system between humanities and science to foster the development of people who are qualified both in the law and medicine or engineering and who are capable of making decisions at higher levels. Then we should be able to assign such people to the R&D of medical equipment or the screening process under the Pharmaceutical Affairs Law.

4 Next-generation OCT

4-1 Second-generation high-speed OCT

As discussed above, Japan can be credited as the first country in which OCT technology was patented. However, Japan lagged far behind others in the commercialization of OCT and is in a weak business position, at least for first-generation OCT. This section discusses the potential for Japan to catch up in the second and later generations of OCT.

Figure 3 can be compared to Moore's Law for

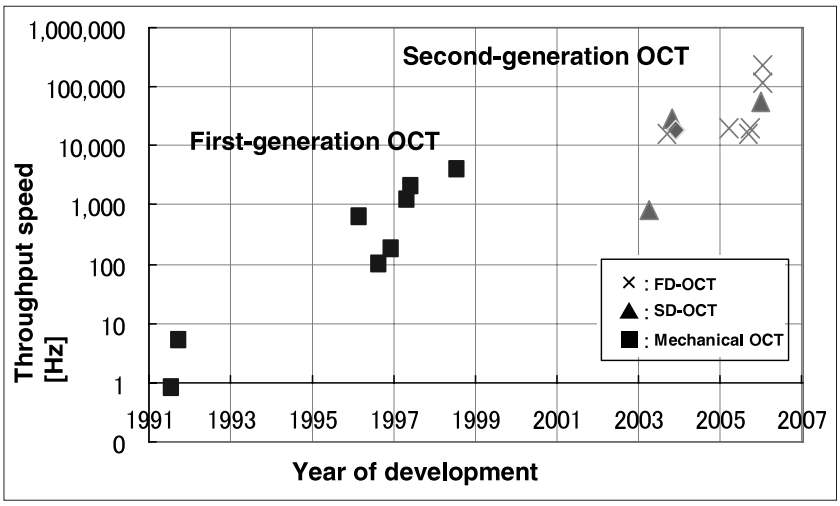

Figure 3 : Annual progress in the performance of OCT equipment

Prepared by the STFC based on reference data by Professor Yatagai

semiconductors; it shows the annual progress in performance of OCT equipment, using the throughput speed of OCT as an index. The throughput speed in first-generation OCT was about 1Hz in 1991 at the laboratory level but increased to 4 kHz by 1999. However, after this 4,000-fold increase, the throughput speed seemed to reach a saturation point. Meanwhile, regarding the medical application of OCT equipment, there is a strong need to collect in vivo real-time tomograms as video data. As a result, the development of second-generation OCT involved a technology race to improve the throughput rate. The throughput rate has reached 200 kHz in recent models, and real-time recording and replay of 3D video data at video rates has been achieved at the product level.

The two most interesting technologies for speeding up the equipment are FD-OCT (Fourier Domain OCT)[23, 24] and SD-OCT (Spectral Domain OCT)[25], in which the number of moving parts in the equipment is reduced. First-generation OCT provided three-dimensional tomograms by mechanically moving the reference mirror and the movable head comprising the optical interferometer, which limited measurement speed. Meanwhile, FD-OCT enables data gathering in the depth direction of the sample with the reference mirror fixed. The interference light obtained from the interferometer shown in Figure 1 is divided into wavelength spectra by a grating spectrometer and detected by a CCD (Charge Coupled Device) array, and the detected signal is subjected to real-time Fourier transformation by a computer to acquire the entire reflection intensity distribution in the depth direction substantially within one measurement[25]. Therefore, mechanical movement of the reference mirror can be omitted. Moreover, by exploiting the features of spatial collective parallel processing, which is an advantage of the optical system, and adopting one-dimensional imaging optics using a cylindrical lens, the uniaxial scanning of the sample plane can also be omitted. Furthermore, using a wavelength-tunable SLD light source means that spectrometers are no longer needed, which enables both speed-up and miniaturization of the equipment.

The use of such high-speed OCT that takes advantage of the more subtle features of light waves makes practical the real-time, three-dimensional observation of blood flow in the ocular fundus. Such R&D, exploiting the key characteristics of optical techniques, is being actively conducted by the Computational Optics Group led by Toyohiko Yatagai of University of Tsukuba. During fiscal years 2004 through 2007, the group is promoting research titled the "ultrahigh-speed Fourier optical radar microscope for biometrics" with support from JST (Japan Science and Technology Agency). The group is also engaged in technology transfer under industry-academia

collaboration and started a study of the application of OCT to ophthalmology in fiscal year 2005 to promote commercialization of the next-generation high-speed OCT equipment through technological cooperation with Topcon Corporation. Topcon Corporation has retained the largest share of the global market for conventional funduscopy equipment developed before OCT. The industry-academia collaboration in this case is similar to the relationship between Professor Fujimoto of MIT and Humphrey. With engineering-medicine collaboration, the university takes charge of the basic design of the equipment, the development of know-how for instrumentation and the patent application, while the company takes charge of the marketing and the legal process required for clinical trials and Pharmaceutical Affairs Law approval, utilizing its long-term experience and performance. The collection of clinical data in the university must be approved by the university's ethics committee, as has become obligatory since fiscal year 2005. Under the provisions of the TLO Law, University of Tsukuba sold the patent and the technical know-how concerning high-speed OCT to Topcon Corporation and shared the profit from the sale with the inventor. In the case of high-speed OCT, the TLO Law functioned effectively, and the perils of the "Valley of Death" and the "Darwinian Sea" were successfully navigated through industry-academia collaboration. In June 2006, the first high-speed OCT was commercialized by Topcon Corporation, and it is attracting attention for its potential to capture part of Carl Zeiss's share of the entire OCT market in the future. Unfortunately, however, therapies using this equipment are not covered by insurance.

4-2 Various applications of OCT and the situation abroad — toward the third generation —

It is well known that the progress of diabetes results in visual impairment. Microtomography Co., Ltd. has proposed a method for measuring the oxygen saturation in hemoglobin in the capillaries exposed on the retina by using OCT. Moreover, the Department of Ophthalmology of Kyoto University Hospital is cooperating with Yamagata Technopolis Foundation, Hamamatsu Photonics K.K., Topcon Corporation and Nidek Co., Ltd. to develop equipment for measuring the blood flow in the ocular fundus. The project has received a grant from the New Energy and Industrial Technology Development Organization (NEDO), and its success is expected to have a large impact. With the aim of improving the resolution of the ocular fundus tomogram up to the diffraction limit, the group is planning to adopt a method for collecting data while performing real-time measurement and correction of ocular aberration, utilizing the adaptive optics techniques of Hamamatsu Photonics K.K., i.e. a liquid crystal spatial phase modulator.

So far, OCT technology has mainly been used in funduscopy equipment, but as the technology shifts into the third generation, its potential areas of application seem to be increasing, e.g. dermatology, dentistry, dental surgery, digestive surgery, cardiovascular surgery etc., in addition to its current implementation in ophthalmology. As an example of such new OCT technology, Professor Masamitsu Haruna of Osaka University[26] is developing an OCT that uses a light source with a wavelength of 1.3 or 1.5 μm. These wavelengths are absorbed by moisture and thus cannot be used for funduscopy, but can be applied to corneous or skin tomography or facial tomography applied to cosmetic product development, or can be combined with an endoscope for non-invasive tomography of the stomach wall. Moreover, with the attempt to understand the physiology of the living body, high-speed OCT is used to perform time-lapse photography, permitting dynamic observation of sweat glands and secretory glands[27]. Since this wavelength range is also used in optical fiber communication, companies including the former NTT have made a vast investment in relevant R&D. Achievements in cutting-edge devices such as light sources and photodetectors may be transferable to OCT equipment, including optical amplification by the multi-wavelength method or rare-earth-doped optical fibers.

The U.S. NIH (National Institutes of Health)

has drawn a road map in which the development of molecular imaging technology, which should contribute to the establishment of molecular libraries and ultimately to the promotion of molecular therapy and preventive medicine, is regarded as the next step following the completion of the Human Genome Project. Professor Fujimoto currently holds an additional post at NIH to explore the extension of OCT applications to molecular imaging. Meanwhile, Professor deBore and his colleagues, who left Professor Fujimoto's group and moved to MGH (Massachusetts General Hospital), are working on the facilitation of medicine-engineering collaboration by taking advantage of high-speed OCT technology. Moreover, the University of California at Irvine has integrated the Schools of Medicine and Engineering and founded a medicine-engineering collaboration center, a facility similar to MGH. The establishment of such institutions in universities reflects the acceleration of medicine-engineering collaboration in the U.S. Meanwhile, in Europe, Professor Fercher and his colleagues at the Medical University of Vienna, Austria, and Professor Drexler and his colleagues who left this group and moved to Imperial College, U.K., are actively engaged in the R&D of high-speed OCT technology.

As can be seen, the global competition to speed OCT innovation through medicine-engineering collaboration is becoming more and more intense. The competition is not only in the technical realm but also in the area of establishing systems to support industry-academia-government collaboration and the implementation of local equivalents of the Pharmaceutical Affairs Law. In the modern era of technology and business globalization, it is unavoidable that Japanese companies first perform clinical trials and receive product sales approval in the U.S. or Europe and then release the products in Japan. In order to stop this hollowing-out of clinical trials, as mentioned in the report by the Ministry of Health, Labour and Welfare[8], "we are working on the establishment of a registration system for clinical studies and an information disclosure system, following a global trend in which the contents of human studies such as clinical trials, clinical studies, etc., must be notified to a third-party organization beforehand." To further facilitate collaborative innovation between medicine and engineering in Japan, it will be more important than ever to further exploit the TLO Law, and safely, swiftly and transparently implement the Pharmaceutical Affairs Law.

5 Conclusion

This report focused on OCT technology to illustrate the issues involved and the measures required to promote collaborative innovation between medicine and engineering from the standpoint of "strategic investment for the creation of innovations and removal of systematic or operational obstacles to return the benefits to society," as required for the Third Science and Technology Basic Plan.

Funduscopy equipment typifies products developed with medicine-engineering collaboration, and has demonstrated its power in the diagnosis of glaucoma and retinal separation. The underlying principle, OCT (Optical Coherence Tomography) technology, was patented for the first time in Japan by Yamagata University in the late 1980s. As the first case of medicine-engineering collaboration, OCT had the potential to take a startup launched by a Japanese local university to success. In this sense, the technology transfer pattern in this case was different from that observed during 1970s and 1980s, in which Europe and the U.S. created research breakthroughs, based on which Japan did the commercialization and formed profitable business.

However, in the case of OCT technology, from its invention to commercialization, Europe and the U.S. preceded Japan in commercialization by eight years and together hold a 90% share of the global market as of 2006. In order to make up for the loss, Japan not only needs to resolve issues of technology transfer but also needs to revise the screening process under the Pharmaceutical Affairs Law, a procedure specifically involving medicine-engineering collaboration. For instance, we should establish a physician-driven, highly

transparent system for clinical trials where safety can be ensured, by expanding the discretionary powers of physicians, professors and ethics committees in the clinical trial process so that they can collect clinical data on their own responsibility in trials they consider safe.

Currently, intense competitions in product development are taking place, both domestically and internationally, involving second-generation, high-speed OCT technology. In this second generation, Japanese industry, academia and government have cooperated in exploiting the TLO Law appropriately, and Japan, which once lagged behind Europe and the U.S., has caught up with these countries and is ready to take the lead. OCT technology is advancing toward the third generation and, in addition to its current ophthalmologic application, is seeing wider use in, e.g. dermatology, dentistry, dental surgery, digestive surgery, and cardiovascular surgery, which is creating fresh global competition. Such global competition, involving collaboration between medicine and engineering in such areas as OCT innovation, is becoming more and more intense, not only in the technical realm but also in the area of transforming systems to support industry-academia-government collaboration and the operation of clinical trial systems.

In the modern era of technology and business globalization, as the Ministry of Health, Labour and Welfare points out, if the Japanese legal system continues to consume an unnecessarily long time compared to other countries, Japanese companies will continue to receive approval for clinical trials or product sales in Europe or the U.S. before releasing the products in Japan. Such a situation would hinder the progress of Japanese medicine and destroy our self-reliance in the development of medical equipment.

In order to improve this situation, and following the global trend in which the contents of clinical trials and clinical studies must be notified to a third-party organization beforehand, Japan must work on the establishment of a registration system for clinical trials and a system for disclosing related information to the public and increase the budget to achieve this. Moreover, we must reinforce and expand medicine-engineering collaboration centers that integrate areas of medicine and engineering and, in the mid- and long -term, must establish an interdisciplinary human resource development system between humanities and science to foster the development of people who are qualified both in the law and medicine or engineering and who are capable of making decisions at higher levels so that we will be able to assign such people to the R&D of medical equipment or the operation of the legal system.

For further facilitation of the collaborative innovation between medicine and engineering in Japan, it will be more important than ever to further exploit the TLO Law and safely, swiftly and transparently implement the Pharmaceutical Affairs Law so that "those that need to be advanced are swiftly advanced, and those that need to be withdrawn are withdrawn at early stages." It is urgent that we design a highly transparent, comprehensive strategy to promote collaborative innovation between medicine and engineering. Such policies are expected to result in further improvement in Japanese medicine and reinforcement of our global competitiveness in medical equipment development.

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