Our Trial on Biomedical Engineering Research and Education System Related to Medical Regulatory Science

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Abstract— **I would like to introduce our new biomedical engineering research and education system related to medical regulatory science. This system has been operated in TWIns, which is an abbreviation for Tokyo Women's Medical University and Waseda University Joint Institution for Advanced Biomedical Sciences. TWIns opened in 2008 as the first collaborative research institute between a school of medicine and a school of science and engineering in Japan. The present number of residents at TWIns is 600, including 300 graduate students.**

I personally had a critical experience on "First in Human (FIH)" twice throughout my 40-year developmental life on ventricular assist devices. Therefore, I strongly believed an importance to establish a practical environment to cultivate human resources on medical regulatory science. As for a biomechanical engineering research, we have established dry-laboratories to provide practical tools to assess safety and effectiveness of medical treatments and to set up reliable test platforms for assessing the performances of keep-coming new medical devices. In addition, in 2010 we opened a joint graduate school that offers the first government-approved PhD degree program in Medical Regulatory Science. We hope this unique environment will contribute to the future success of those who experience our new concept, called another EBM: Engineering-Based Medicine.

Keywords— **Medical regulatory science, Biomedical engineering, First in Human, Dry laboratory, Engineering-Based Medicine**

I. Introduction

TWIns was opened in 2008 as the first collaborative research institute between a school of medicine(Tokyo Women's Medical University) and a school of science and engineering (Waseda University) in Japan. TWIns is an abbreviation for Tokyo Women's Medical University and Waseda University Joint Institution for Advanced Biomedical Sciences. [1]Waseda University had following two synergistic objectives to construct TWIns; 1) As research laboratories for life science, biomedical engineering and biology had been broadly dispersed in different campuses, we tried to consolidate facilities in one place. 2) As there is no medical faculty in Waseda, it was a great opportunity to be in official partnership with Tokyo Women's Medical University to create new fields of innovative medical treatments. It was not a hard job to create a synergetic philosophy, because we had a 50-year history on biomedical engineering collaboration between both universities. TWIns new building is constructed next to Tokyo Women's Medical University Hospital with a total floor area of 20,000 square meter.

Present number of residents at TWIns is 600; 450 from Waseda University and 150 from Tokyo Women's Medical University, including 300 graduate students.

I originally belong to a faculty member of the department of "Modern Mechanical Engineering" for Undergraduate program and "Integrative Bioscience and Biomedical Engineering" for Master program. There are three mechanical-engineering based laboratories at TWIns, and total number of academic staffs and graduate students with a background of biomedical engineering and bio-robotics are 100.

Fig. 1 Front view and Map (upper), and side view (bottom) of TWIns building

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Ⅱ. SET UP AN IDEAL ENVIRONMRNT OF "ANOTHER EBM; ENGINEERING BASED MEDICINE"

A. Background to establish dry laboratories

I personally had a critical experience on "First in Human (FIH)" twice throughout my 40-year developmental life on ventricular assist system (VAS). The first FIH was experienced with our original device in 1981 at the National Cardiovascular Center, Osaka, Japan. [2]The technology of our pulsatile device was transferred to Toyobo Company and commercialized later (now distributed by Nipro Corporation). It was approved as a medical product of short term use (less than one month) by the Japanese government in 1991. Toyobo pumps have already been used over 900 cases in Japan to restore patients with poor blood circulatory condition. Due to a limited number of cardiac transplantation donors in Japan, an average waiting duration to receive a donor heart was over two years. So, it was strongly required to maintain a high quality of life during a usage of LVAS. Toyobo VAS is placed at the outside of the chest wall using two large diameter conduits, which may be a major part to induce infection problem for a long-term use. To solve the problem, several trials to install a pump inside of the body were conducted in 1980's. Finally, the development of non-pulsatile VAS was considered to be the most realistic method for long-term use. EVAHEART is one of compact centrifugal pumps which enable to implant into a small thoracic cavity for better quality of life. Sun Medical Research Corporation, Tokyo Women's Medical University, and Waseda University worked together to create a mechanical circulatory support device for patients with end-stage heart failure [3]. In 2005, the FIH with EVAHEART, that was my 2nd FIH experience, was conducted at Tokyo Women's Medical University Hospital. After eighteen clinical trials that included pivotal and pilot studies, the Japanese Ministry of Health, Labor and Welfare finally approved the first commercial implantable ventricular assist device. Those experiences led us to conclude that bioengineering laboratories should be established to design, construct, test, and perfect prototype medical devices including robots. Complex devices manufactured with precision components could be brought to market with a high degree of confidence in their reliability and durability. Unexpected problems with commercial products could be solved by computer modeling and simulation technologies. Academic team members, especially students, would gain hands-on experience and real-world responsibilities to prepare them for successful careers.

Therefore, I strongly believed an importance to establish a practical environment to cultivate human resources on medical regulatory science. As for a bio-mechanical engineering research, we have established dry-laboratories to provide practical tools to assess safety and effectiveness of medical treatments and to set up reliable test platforms for assessing the performances of keep-coming devices.

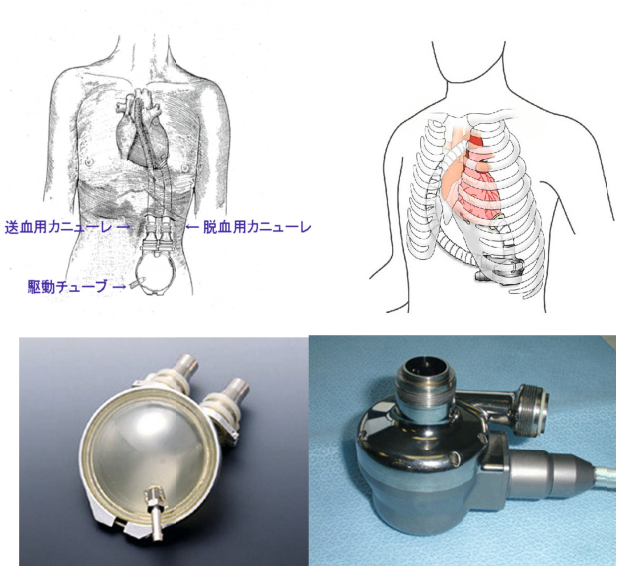

Fig. 2 Schematic drawings of para-corporeal, pneumatically-driven pulsatile VAS (upper left) and implantable, motor-driven non-pulsatile VAS (upper right)
Bottom two photographs are indicated commercial VAS pumps; Toyobo (Nipro) pulsatile VAS (left) and Non-pulsatile EVAHEART (right)

B. Establishment of a practical facilities

The dry-laboratories based on a philosophy of "Another EBM"are dedicated to three purposes [4] (Fig.3-6):

1) Testing medical devices such as artificial heart, prosthetic heart valves and vascular stents for safety and effectiveness. For this purpose, we also assemble mock circulatory systems to test the basic performance, durability and biocompatibility of devices. Fig.3 shows anti- thrombogenicity test circuits.

2) Training surgeons to implant or to control new medical devices to achieve the best performance of the devices. Fig.4 shows a training machine to improve a surgical skill on coronary bypass surgery and mitral valve repair.(Fig.4,5)

3) Analyzing to select the most effective patient with new medical devices using flow visualization method and/or computer fluid dynamics (CFD). We devise instruments that enable clinicians and surgeons to visualize blood flow and compute hemodynamics to help them determine optimal patient-specific treatments. We are studying cerebral aneurysms (Fig.6) to validate engineering, pathological, and clinical data.

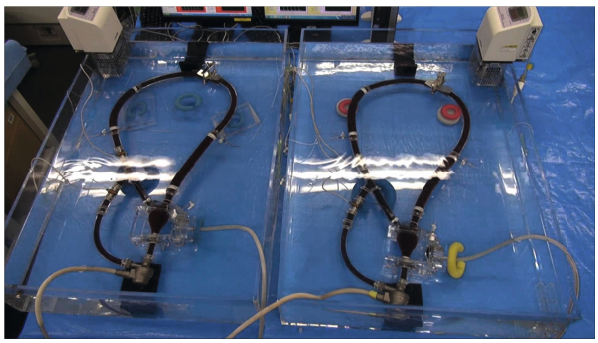

Fig.3 Experimental set up to evaluate the anti- thrombogenicity of medical devices under the same hemodynamic condition. This study is conducted to clarify the effect of surface roughness on thrombogenicity, using two identical blood circuits with different inlet cannula of EVAHEART.

Fig. 4 Beating heart simulator for coronary bypass surgery (left) OPCAB Boot camp(right)

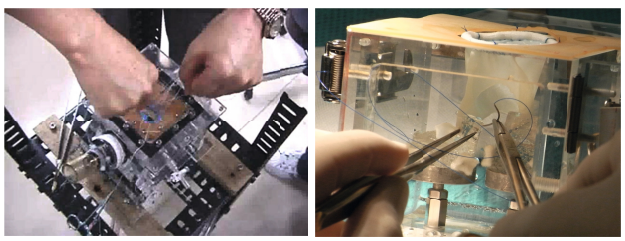

Fig. 5 Practical surgical training simulator for mitral valve repair and/or replacement

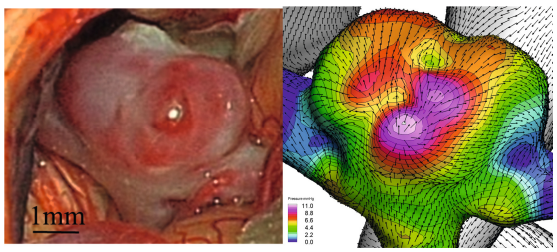

Fig. 6 Cerebral aneurysms of a patient (left) and CFD result to indicate thickness distribution of the aneurysms (right)

III. New Graduate School Program on Medical Regulaory Science (MRS)

A. *Background and Concept to propose a new PhD program*

Medical regulatory science (MRS) within the healthcare industries pertains to governmental regulation of pharmaceuticals, medical devices, in vitro diagnostics, biologics, and nutritional products. Professional responsibilities in these areas include monitoring research and development, clinical trials, premarket approval, manufacturing, labeling, advertising, and post-market surveillance. MRS aims to improve decision-making in in vitro tests, animal experiments, and clinical trials of drugs, diagnostics, devices, and therapy protocols based on previous experience.

Post-approval proper use is another issue MRS seeks to clarify.

B. *Approach*

To strengthen the foundation of this new subject, we propose to consolidate MRS with three other academic disciplines: evaluation, prediction, and determination. [4] Gaining approval of a product can be a lengthy, tedious, and costly process. Regulatory agencies and their procedures vary widely between different countries, and efforts are underway to establish global standards. Regulatory affairs departments within healthcare companies are evolving and expanding to ensure the delivery of safe products to market in a reasonable time. So, professionals in regulatory affairs are increasingly in demand. Financial compensation for their employment also is increasing.

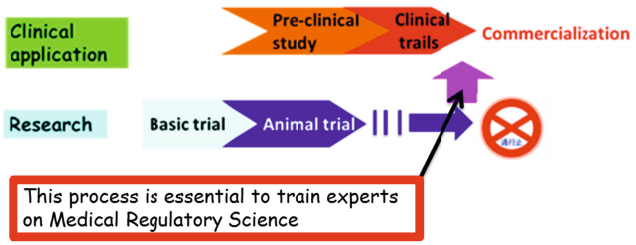

Fig. 7 Relationship between Basic medical science and clinical application towards commercialization

C. *Cooperative Major in Advanced Biomedical Sciences*

In 2010, Tokyo Women's Medical University and Waseda University opened a joint graduate school department that offers the first government approved PhD degree program for students of MRS. The program is called Cooperative Major in Advanced Biomedical Sciences. The number of students proposed for this doctoral degree course is limited to ten, five from each university. Candidates must earn at least thirty credits and pass a thesis review. Fourteen credits must be earned from the following subjects:

1) Biostatistics
2) Clinical Studies
3) Bioethics
4) Introduction to GLP/GCP/GMP
5) Medical Regulatory Science
6) Seminar in the Bioscience and Biomedical Laboratories
7) Practical training in the Advanced Medical Institute

Thesis titles of the first PhD recipients, who completed their work at the end of 2013 are as follows:
a) Study on Global Harmonization Initiatives for Medical Device Regulation
b) Study on International Radiation of High-intensity Therapeutic Ultrasound Devices
c) Study on Post-market Risk Assessment of Implantable Arrhythmia Devices in Japan
d) Study on Visualization and Evaluation of Medical Device Development using System Dynamics[5]
e) Study on Optimization of Therapeutic Parameters for Photodynamic Therapy
f) Study on Hemodynamic Evaluation Method of the Vascular Grafts by Computational Fluid Dynamics[6]
g) Study on the Current Status and Challenges of Premarket Clinical Trials for Medical Devices in Japan
h) Study on Health Technology Assessment in Japan and Cost-Utility Analysis of Molecular Targeting Agents
j) Study on Regulation and Clinical Evaluation for Human Cells and Tissue Products

Up to now, total number to pass the entrance examination of this PhD program is 66 for these six years, and 18 completed a PhD course, then successfully received PhD. (Fig.8) Students with a degree in MRS will have a decided advantage in competing for jobs in this specialty. We want to reduce or supplant traditional reliance on animal tests with in vitro experiments to make final decisions with government approval. So, we are working to create new guidelines by holding periodic meetings with government regulators, academic researchers, clinicians, and MRS section members in the healthcare industries.

Fig. 8 Memorial photograph of the first PhD students, received on 26 March 2013. Their background, occupation and ages are different, but all became Medical Regulatory Science experts.

IV. Final Remarks

I expect our synergistic strategy and trial at TWIns will help us create the next generation of new medical treatments for future applications in medicine: this approach is named "Another EBM: Engineering Based Medicine". We hope the unique experience of Engineering-Based Medicine at TWIns will help them contribute to the future success of the medical instrument and pharmaceutical industries in Japan.

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Conflict of Interest

The author declare that he has no conflict of interest.

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