Innovating to Create Value through New Perspectives and Synthesis

With the corporate mission of “Contributing to Society through Healthcare,” the Terumo Group has brought valuable innovation to medical settings by thoroughly seeking out new perspectives and combining existing concepts.

We will continue to flexibly incorporate diverse perspectives and take on challenges in order to create and deliver innovations of value to both recipients and providers of healthcare.

**CASE 1**
From Japan, the World’s First Cellular and Tissue-based Product designed for the Treatment of Severe Heart Failure: HeartSheet™
Providing a New Alternative to Patients Awaiting Treatment

**CASE 2**
Percutaneous Coronary Intervention via the Radial Artery in the Wrist: Transradial Intervention (TRI)
Contributing to Improvement of Patients’ QOL and Medical Cost Efficiency

**CASE 3**
Japan’s First Intradermal Injection Device with Unique Needle Design: Immucise®
Making Difficult Intradermal Injections Simpler and More Certain

**Strengthening of Innovation-Producing Research and Development**

**Seeking Innovation of Value by Understanding the Perspectives of Medical Settings**
- “Terumo Fellows” Drive Innovation through Outstanding Expertise
- Developing Medical Devices through the Biodesign Program
CASE 1

From Japan, the World’s First Cellular and Tissue-based Product Designed for the Treatment of Severe Heart Failure: HeartSheet™

Providing a New Alternative to Patients Awaiting Treatment
**Seeking to Provide a New Treatment Alternative**

HeartSheet is a product designed for the treatment of severe heart failure resulting from ischemic heart disease. In September 2015, Terumo obtained approval* for the manufacture and sale of the world’s first cellular and tissue-based product for severe heart failure, and launched HeartSheet in May 2016.

Treatment using HeartSheet consists of collecting muscle tissue from the patient’s own body, culturing cells from that tissue, forming the cells into sheets, and transplanting the sheets onto the surface of the patient’s heart. The product is intended for use with patients who have seen insufficient efficacy from the conventional treatments of medication or coronary artery bypass surgery. The new HeartSheet treatment is expected to restore heart function. One major benefit of the product is that because the cultured cells are collected from the patient’s own body, there is no adverse reaction to the cells.

*Conditional and time-limited approval

**Breakthrough Achieved by a Change in Thinking**

HeartSheet was developed by a project started in 2002 with the goal of using regenerative medicine to restore heart muscle function in treating severe heart failure, which has few treatment options. At that time, the expected treatment method was administration of the cultured cells through injection. In 2007, however, the method was shifted to sheets for transplant, which were expected to increase the efficacy. This transition in thinking to find a new combination provided a breakthrough in development. Following successful clinical trials that started in 2012, Terumo applied for manufacture and sale approval in 2014, and received conditional and time-limited approval just under a year later.

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**Achievement through Cooperation of Industry, Academia, and Government**

HeartSheet is the result of collaboration by industry, academia, and government. The product’s development and manufacturing incorporate “cell sheet engineering” methods established by Professor Teruo Okano of Tokyo Women’s Medical University; the autologous myoblast cell sheet technology and transplantation method of Professor Yoshiki Sawa of Osaka University; and the cellular product manufacturing and quality control technology of Terumo. In addition, Terumo used the new approval review system provided for cellular and tissue-based products in Japan’s 2014 Pharmaceutical and Medical Device Act. HeartSheet is the first product that obtained conditional and time-limited approval within the new system.

**HeartSheet Will be a Breakthrough in Accelerating the Commercialization of Regenerative Medicine**

HeartSheet is important not only because of its value as a new treatment alternative; it is also a breakthrough in accelerating the commercialization of regenerative medicine. It was previously very difficult to definitively show the efficacy of cellular and tissue-based products, meaning that getting products to market took a long time. With the introduction of a new regulatory system for quickly approving these products, and HeartSheet obtaining the first conditional and time-limited approval within that system, we expect that numerous other cellular and tissue-based products will be more rapidly developed and commercialized. Progress in the commercialization of regenerative medical products will expand the range of effective treatments for illnesses that have no effective treatment, providing enormous value to society. Terumo intends to further expand the potential of heart muscle regenerative medicine in order to bring valuable, effective treatments to the patients awaiting them.

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**Providing new treatment alternative**

Heart failure treatments

<table>
<thead>
<tr>
<th>Existing treatments</th>
<th>New treatment</th>
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</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Restoration of heart function using HeartSheet</td>
</tr>
<tr>
<td>Percutaneous coronary intervention*</td>
<td>Prepared cell sheet</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Heart transplant</td>
<td></td>
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<tr>
<td>Ventricular assist device</td>
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*Used for the treatment of ischemic heart disease, which is considered to be one of the causes of heart failure
**CASE 2**

Percutaneous Coronary Intervention via the Radial Artery in the Wrist: Transradial Intervention (TRI)

**Contributing to Improvement of Patients’ QOL* and Medical Cost Efficiency**

*Quality of life

**TRI Increasingly Used Globally**

Transradial intervention (TRI) is an interventional procedure for treating coronary artery disease. In TRI, a catheter is inserted into the radial artery, a blood vessel in the wrist, in order to access and treat lesions in the coronary artery. Previously, catheters were commonly inserted through the femoral artery. TRI results in fewer complications and greatly shortens patient hospital stays, contributing to improved patient QOL and greater medical cost efficiency. As increasing healthcare costs become a more significant challenge mainly in developed nations, TRI is expanding throughout the world. Just eight years ago, TRI accounted for less than 5%* of coronary interventional procedures in the United States. However, now it accounts for 30%* of such procedures, and is expected to reach 50%* by 2020.

*Terumo estimates

**Device Developed by Innovating Multiple Terumo Technologies**

Because the blood vessels in the wrist are difficult to puncture due to their narrowness, and the blood vessels leading from there to the heart are winding, it was previously difficult to access through the wrist to the location of a lesion in the coronary artery. Terumo succeeded in developing an introducer sheath (a product that enables access into a blood vessel) with sufficient internal diameter to accept existing catheters, while also having a reduced outer. These achievements allow elderly and female patients with narrow blood vessels to undergo TRI. Additionally, Terumo improved the guidewire used to guide the catheter to the lesion, making it travel more smoothly through winding blood vessels by using shape-memory metal alloy and applying a coating on the outer surface to increase lubricity. The fusion of multiple Terumo technologies has enabled the previously challenging TRI and contributed to its expansion.

**Spreading Expertise from Physician to Physician through Trainings**

New medical treatments are only effective when medical professionals are able to perform them appropriately; this requires education and training. Terumo Medical Pranex, Terumo’s own training facility for medical professionals, has cath labs that simulate medical settings and enable training and seminars on proper product use. Terumo Medical Pranex is capable of providing systematic education programs for TRI as well. There, physicians can use Terumo’s exclusively developed blood vessel model to receive training in radial artery puncture and catheter manipulation. Terumo has also invited physicians from outside of Japan to receive TRI training from Japanese physicians, leading to steady expansion of understanding and utilization of the technique globally.

**Creating Social Innovation**

In order to further spread medical treatments that benefit society, great efforts are needed to convince patients and medical professionals to accept the value of the technologies coupled with developing the valued products. Terumo has provided training and seminars to promote global expansion of TRI, and will continue to create innovation that brings value to society through vascular interventional therapy for various parts of the body as well.
Guidewire
Smooth travel through winding blood vessels

Placement of sheath in wrist blood vessel

Conventional sheath
TRI sheath

Same inner diameter
Narrower outer diameter

Maintains the same inner diameter while enabling approach through narrow blood vessels in the wrist
Injection is simple:
Bring the needle vertically to the skin, and press

Intradermal Injection
Device: Immucise

Upper layer of skin (epidermis and dermis)

Limiter:
Stretches the skin taut, assisting the vertical injection

Flange:
Confirms that the device is pressed with appropriate pressure on the skin

A uniquely developed needle structure that aims to make an intradermal injection administered into upper layer of skin (the epidermis and the dermis) simpler and more certain

A thin and short needle with a diameter of 33G (0.2mm) and length of 1.15mm
Making Difficult Intradermal Injections Simpler and More Certain

Intradermal Injection Considered to Have Great Potential

The location where an injection is made varies, depending on the medication and purpose; it could be intradermal, subcutaneous, intravenous, or intramuscular. Normally, vaccines for influenza and other infectious diseases have been administered subcutaneously or into muscle. However, the upper layers of the skin—the epidermis and dermis—contain a large amount of the cells related to immunity: immunocytes. In recent years, it has been found that intradermal injections of vaccines produce immunological effects rapidly and require less vaccine than subcutaneous or muscular injections to acquire the same level of effect. Intradermal injection can also give immunity to people such as the elderly, who may have weakened immune systems. Intradermal injection is performed using a thin needle that has been accurately positioned against the skin. However, one weakness of intradermal injection has been that because these skin layers are only about two millimeters thick, variability in the skill of the physician giving the injection can affect effectiveness.

Pursuit of a Shape for Simple, Certain Injection

Terumo began development with the concept of a design that could perform intradermal injection in a simple, certain way; this was the beginning of Immucise. Starting in 2010, Terumo collaborated with the pharmaceutical company Daiichi Sankyo Co., Ltd. to jointly research an intradermal seasonal influenza vaccine. During development of Immucise, Terumo studied the method of a vertical “press injection” to enable simple, certain insertion of the needle into the thin upper skin layer. As development progressed, it became clear that the structure of the syringe that touched the skin and the length of the needle were critical design elements. Terumo studied various syringe structures for stretching the skin taut in order to insert the needle easily, and explored multiple needle shapes for reaching the ideal depth in the upper layer of skin, and then carefully evaluated the optimal combination of structure and shape in a lengthy trial-and-error process. This work successfully resulted in a new device capable of intradermally injecting, even into thin upper layer of skin, simply and with certainty.

Expanding Development and Applications through Collaboration with Pharmaceutical Companies

Through development projects including Japan’s first plastic prefilled syringe and the world’s thinnest pen needle for insulin self-injection created to reduce patient pain, the NANOPASS 34, Terumo has accumulated a wealth of expertise and achievement in the field of syringes and needles. Terumo brought this vast expertise to bear in the development of Immucise. The development and mass production of vaccines using Immucise also represents a fusion of this Terumo expertise with the vaccine development and production know-how of pharmaceutical companies.

In September 2015, the Immucise intradermal injection needle was approved for manufacture and sale in Japan. Immucise will be used for the influenza vaccine, but further application of the product is expected with other vaccines going forward. Terumo also looks to expand the use of Immucise beyond Japan and into the global market, and will continue working to bring the value of intradermal injection to more medical settings.
Strengthening of Innovation-Producing Research and Development

Seeking Innovation of Value by Understanding the Perspectives of Medical Settings

At the Terumo Group, we pursue innovation in every work process. We believe that the source of creating innovation to bring value to medical settings is research and development capabilities and the people who sustain those activities.

In a changing healthcare environment, the Terumo Group is applying new perspectives and methodologies to cultivating the people who sustain our research and development. This will accelerate and increase the amount of high-quality innovation we can achieve to serve the needs in medical settings.

Bringing New Value to Medical Settings through Innovative Technology

“Terumo Fellows” Drive Innovation through Outstanding Expertise

In April 2016, Terumo created the “Terumo Fellow” Program to recognize and appoint as “Terumo Fellows” associates with expertise and experience in their fields, and who have made outstanding contributions leading to innovation in medical settings around the world, and in technology, research, and clinical development.

The following four individuals achieved outstanding innovation and brought new value to medical settings by demonstrating tireless effort and determination to incorporate new perspectives and synthesize existing concepts. All of these individuals have embodied the Terumo global vision of “Innovating at the Speed of Life,” long before it was officially set as our vision. In doing so they have made enormous accomplishments benefitting medical settings in a variety of fields.

Terumo Fellows will continue to drive research and development in their fields, both by personally innovating and by advising the young engineers who will sustain Terumo Group growth into the future.

Atsuhiko Nogawa
Terumo Fellow
Vice President, CV Division R&D, Cardiac and Vascular Company, Terumo Corporation
Outstanding Achievements
– Developed and commercialized oxygenator and related devices for use in cardiac surgery
– Developed endoscopic blood vessel harvesting devices

Dragica Paunovic, M.D.
Terumo Fellow
Chief Medical Officer, Vice president Clinical, Terumo EMEA
Outstanding Achievements
– Led the global deployment of medical device technologies developed in Japan, especially by initiating and conducting early and late stage clinical trials in Europe and other continents.
– Enabled global deployment of interventional systems products including drug-eluting stents and OFDI (Optical Frequency Domain Imaging) instruments, and many others.

Hiroyuki Yagami
Terumo Fellow
Chief Researcher, TIS Division R&D, Cardiac and Vascular Company, Terumo Corporation
Outstanding Achievements
– Developed the first intravascular coronary ultrasound diagnosis device produced in Japan
– Developed sensors, catheters, and materials for use with intravascular coronary ultrasound diagnosis

Dennis Hlavinka
Terumo Fellow
Director of Engineering, Terumo BCT, Inc.
Outstanding Achievements
– Developed a centrifugal method for the removal of contaminating leukocytes from platelets as they are being harvested for transfusion
The Biodesign Program is a program at Stanford University that links the three fields of medicine, engineering, and business. Its purpose is to systematically and practically cultivate the way of thinking and skills necessary to perform problem-solving innovation in medical device development.

In the Biodesign process, participants carefully observe to identify the potentially hidden clinical needs, and then select the highest-priority needs. Based on these identified needs, product concepts are generated and screened from feasibility and market perspectives, coupled with the result of early verification using prototypes. Development strategies and business plans are then formulated with the aim of successful commercialization. This process of screening the highest-priority needs and clarifying product concepts enables more rapid and market-targeted product development.

Terumo uses the Biodesign methodology widely to develop its research and development human resources as well as improve the real process of medical devices development. In 2013, R&D headquarters adopted the Biodesign process as a method of human resource development for acquiring its way of thinking and skills to create further innovation. Furthermore, in 2014, Terumo organized the “Medtech Design Team” for medical device development using the Biodesign process with the aim of achieving more innovation for solving clinical needs at increased speed.

### Developing Medical Devices through the Biodesign Program

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**Biodesign: The process of innovating medical technologies**

- **Needs finding**
  - Observe and carefully clarify the clinical needs
  - Select the highest-priority needs

- **Needs screening**
  - Generate product concept
  - Screen concepts from feasibility and market perspectives, coupled with the result of verification using prototypes

- **Concept generation**
  - Examine development strategy related to intellectual property, regulatory, etc.

- **Concept selection**
  - Develop business plans

- **Development strategy and planning**

- **Business plan development**

- **Into commercialization**