Current status and future direction of the regulatory framework for gene therapy in Japan

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COI: The author have no financial conflicts of interest to disclose concerning the presentation.
Our Strategy

Report from Advisory Panel for Promotion of Medical Ventures
Innovation is a “key trigger” for Japan’s economic growth, and venture company is a driving force which is definitely important for the success in innovation. Especially, progress of drugs and medical devices is significant as an investment for the future. This report shows a guiding principle of MHLW’s promotion policy for medical ventures.

※ Medical ventures; Venture companies for drugs, medical devices and cellular and tissue-based products

1. Importance and necessity of promotion of medical ventures

◆ There is a very high growth potential in healthcare.
  - Healthcare is a huge growing market all over the world.
  - In Japan, it is necessary to respond to problems for extension of healthy life expectancy and building sustainable healthcare system.

◆ Venture companies are at the center of the innovation of drugs and medical devices.
  - Many new drugs of the biggest US & EU pharmaceutical companies are come from venture companies.
  - Japan’s fundamental research and manufacturing technology is good enough. However, it doesn’t work effectively for development of medical devices etc.

◆ Promotion of medical ventures is necessary right now in Japan.
  - Venture companies must play an important role when predicting future R&D trends of medicine.

◆ Three types of Medical ventures

<table>
<thead>
<tr>
<th>Grow by itself</th>
<th>Acquired by large company</th>
<th>Enter from different industry</th>
</tr>
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<tbody>
<tr>
<td><img src="image1" alt="Grow by itself" /></td>
<td><img src="image2" alt="Acquired by large company" /></td>
<td><img src="image3" alt="Enter from different industry" /></td>
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</table>


Features of medical venture projects

Medical ventures have the following business features (and therefore they face many challenges):

1. **High scientific and technological level and high development risk**
   - Innovating in the medical field requires high levels of science and technology and involves high development risk.

2. **Long period of time to approval and large amount of funding required**
   - Require a long period for development and need a large amount of capital.

3. **Understanding of and response to medical, pharmaceutical affairs and medical insurance regulations**
   - Sufficient understanding of pharmaceutical affairs and public insurance is essential to overcome this obstacle to entry.

4. **Difficult to secure talent knowledgeable about these features**
   - Development of talent requires time and cost. Difficult for new entrepreneurs to emerge or be fostered.

By making use of strengths and overcoming weaknesses, there is great potential for growth and significance in promoting medical ventures.

<table>
<thead>
<tr>
<th>Japan’s strengths</th>
<th>Japan’s weaknesses</th>
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<tr>
<td>- High level of seeds, even by global standards, at universities and research institutes</td>
<td>- Few entrepreneurs and difficult for ventures to secure talent</td>
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<tr>
<td>- Spread of clinical research in hospitals</td>
<td>- Venture funding is scarce and weak support for financial side</td>
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<tr>
<td>- SMEs have excellent manufacturing technologies</td>
<td>- Weak ties with overseas in terms of funding or talent</td>
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<td>- Fast approval review process (Ex.: regenerative medicine)</td>
<td>- Medical system does not consider ventures</td>
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<td></td>
<td>- Few model cases</td>
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Japan’s strengths and weaknesses (Compared to Europe and the U.S.)

Japanese ventures need to consider overseas deployment to raise efficiency of high capital investment.
 III. Promotion policy and measures for medical ventures

“The Goal of Policy”

- The Goal of Policy
- The Vision of Policy

- Medical ventures play a leading role in making innovation.
- Development of health and medical care in Japan & the world
- Economic growth in Japan
- To the center of innovation

- Japan should be the country with the brightest business environment in the world.
- Good cycle of innovation

“Three principles” & “Three pillars” of promotion measures

- Proper regulation from the venture business point of view
- Support from MHLW
- Promotion measures with a sense of urgency
- Support corresponding to the characteristics of each company
Two Acts
Regulating
Regenerative Medical
Technology & Product
New Legislative Framework

• Revision of the Pharmaceutical Affairs Law: The Act on Pharmaceuticals and Medical Devices (PMD Act)
• The Act on the Safety of Regenerative Medicine

These two acts were enacted on 25 November 2014

Other related governmental policy:
• Healthcare and Medical Strategy Promotion Act (2014.5)
• Japan Medical Research Development Institution Act (2014.5)
Two acts regulating regenerative medicine & cell therapy

MHLW process

Regenerative Medicine

All medical technologies using processed cells which safety and efficacy have not yet been established

PMDA process

Production and marketing of regenerative and cellular therapeutic products by firms

The Act on the Safety of Regenerative Medicine (ASRM)

Medical Care or Academic Research Purpose

The Act on Pharmaceuticals and Medical Devices (PMD Act)

Commercial Product Marketing Authorization Purpose
Outsourcing Cell Culturing and Processing under the Act on the Safety of Regenerative Medicine (ASRM and PMD Act)

**Clinical study, private practice**

**ASRM**
- Corporate factory, etc.
  - *Licensed facility
- Medical institution
  - *Notified facility

**Processing, storage**
- Collection
- Practice (transplanting)

**Regenerative medical products**

**PMD Act (Revised PAL)**
- Corporate factory, etc.
  - *Licensed facility
- Acquisition of cells
- Processing, storage
- Purchase of licensed product

Scope of application:
- ASRM
- PMD Act
The Act on Pharmaceuticals and Medical Devices (PMD Act)
Additions for regenerative medicine products
- Definition and independent chapter for regenerative medicine products
- Introduction of conditional/time limited approval system
Expeditioed approval system under PMD Act

[Traditional approval process]

Clinical study → Phased clinical trials (confirmation of efficacy and safety) → Approval → Marketing

Approval or Revocation of the conditional approval

Marketing continues

Follow-up submission within stipulated time period (max. 7yrs)

[New scheme for regenerative medicine products]

Clinical study → Clinical trials (likely to predict efficacy, confirming safety) → Conditional/time-limited approval → Marketing (Further confirmation of efficacy and safety)

Approval or Revocation of the conditional approval

Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients

< Drawback of traditional PAL approval system >

Long-term data collection and evaluation in clinical trials, due to the characteristics of cellular/tissue-based products, such as non-uniform quality reflecting individual heterogeneity of autologous donor patients
Enhancing the R&D of Regenerative Medicines
SAKIGAKE Designation System

MHLW assigns and supports the world’s first products currently being developed with high expectation on a trial basis since 2015.

Assignment criteria
- Prominent effectiveness and dire medical needs for the therapy
- Technological innovativeness
- World’s first submission for approval in the future (incl. simultaneous submissions)

Priorities and advantages

1. Prioritized consultation
   [Waiting time: 2 months → 1 month]

2. Substantialized pre-submission assessment and 3. Prioritized review

4. Review partner
   [PMDA manager as a concierge]

5. Substantial post-marketing safety measures
   [Extension of re-examination period]
Lead the world in the practical application of innovative medical products

Accelerate R&D through supporting each stage

Strengthen the structure of PMDA
(consultation, review, safety measures in terms of quality and quantity)

Promotion of Regulatory Science
(Developing guidelines/assessment for the state-of-the-art technology)
### SAKIGAKE Assignment for RM products
(Feb. 2016(#1-3), Feb.2017(#4-6))

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Proposed indication</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>#1</td>
<td><strong>STR01</strong> (Autologous bone marrow-derived mesenchymal stem cell)</td>
<td>Nerve syndrome and dysfunction caused by spinal cord injury</td>
<td>NIPRO Medical Co., Ltd. / Sapporo Medical Univ.</td>
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<td>#2</td>
<td><strong>G47Δ</strong> (Growth-controlled oncolytic herpes simplex virus type 1)</td>
<td>Malignant glioma</td>
<td>Daiichi Sankyo Co., Ltd. / Institute of Medical Sciences, University of Tokyo</td>
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<tr>
<td>#3</td>
<td><strong>JRM-001</strong> (autologous cardiac progenitor/stem cells)</td>
<td>Pediatric congenital heart disease (single ventricle physiology)</td>
<td>Japan Regenerative Medicine Co., Ltd. / Okayama University</td>
</tr>
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<td>#4</td>
<td><strong>CLS2702C/D</strong> (Oral mucosa-derived esophageal cell sheet)</td>
<td>Extensive endoscopic submucosa dissection (ESD) in esophageal cancer</td>
<td>CellSeed / Tokyo Women’s Medical University Hospital</td>
</tr>
<tr>
<td>#5</td>
<td><strong>Dopamine neural precursor cell derived from allogenic iPS cell</strong></td>
<td>Parkinson’s disease</td>
<td>Sumitomo Dainippon Pharma Co., Ltd. /CiRA, Kyoto University</td>
</tr>
<tr>
<td>#6</td>
<td><strong>Pluripotent progenitor cell derived from allogeneic adult bone marrow</strong></td>
<td>Acute brain infarction.</td>
<td>Healios K.K. / Athersys</td>
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<td>#7</td>
<td><strong>TBI-1301</strong> (cancer antigen (NY-ESO-1) specific TCR Gene-transduced T Lymphocytes (autogenous))</td>
<td>Treatment of synovial sarcoma</td>
<td>Otsuka Pharmaceutical Co., Ltd.</td>
</tr>
<tr>
<td>#8</td>
<td><strong>CLBS12</strong> (autogenous CD34+ cells)</td>
<td>Improvement of Severe lower limb ischemia</td>
<td>Caladrius Biosciences, Inc.</td>
</tr>
<tr>
<td>#9</td>
<td><strong>AVXS-101</strong> (recombinant AAV containing human SMN (survival motor neuron) gene)</td>
<td>Treatment of spinal muscular atrophy (Type I)</td>
<td>Novartis Pharma K.K.</td>
</tr>
<tr>
<td>#10</td>
<td><strong>OBP-301</strong> (gene-modified oncolytic adenovirus)</td>
<td>Unresectable, chemotherapy-intolerant/-resistant locally advanced esophageal cancer</td>
<td>Oncolys BioPharma Inc.</td>
</tr>
<tr>
<td>#11</td>
<td><strong>SB623</strong> (adult bone marrow-derived mesenchymal stem cells)</td>
<td>Improvement of motor impairment after traumatic brain injury (Moderate to severe)</td>
<td>SanBio Co., Ltd.</td>
</tr>
</tbody>
</table>
Approved Products
2018-2019
Under The PMD Act
New therapy for spinal cord injuries gets fast-tracked

By MASATOshi TODA/ Staff Writer
November 22, 2018 at 14:30 JST

Therapy using mesenchymal stem cells for patients with spinal cord injury

Mesenchymal stem cells
- Contained in bone marrow and fat and work to replace damaged cells. Can turn into bone, nerve and other cells.

1. Extract bone marrow fluid from the patient
2. Separate mesenchymal stem cells and cultivate them
3. Create cell- and tissue-based products and give the patient an intravenous drip injection
4. Mesenchymal stem cells concentrate in damaged parts and promote recovery
5. Rehabilitate the patient to regain walking capability

The Asahi Shimbun

Treatment using stem cell regenerative medicine to restore damaged nerve connections in patients with spinal cord injuries, whose only course of treatment is rehabilitation, may be available by year-end.
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**INDICATION**
KYMRIA® (tisagenlecleucel) is indicated for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

https://www.novartis.co.jp/news/media-releases/prkk20180423-1
Press release in Japanese)
AnGes Obtains Conditional Approval in Japan for HGF Gene Therapy to Treat Critical Limb Ischemia

AnGes, Inc., a biopharmaceutical company focused on developing innovative gene-based medicines for treating serious diseases, announced today that they have obtained conditional approval (“Approval with Conditions and Time Limit”) from the Japanese Ministry of Health, Labour and Welfare (MHLW) for HGF plasmid to treat patients with critical limb ischemia (CLI).

HGF plasmid is the first gene therapy product to be approved in Japan, for the improvement of ulcers in patients suffering from chronic arterial occlusion (arteriosclerosis obliterans and Buerger’s disease) who have had an inadequate response to standard pharmacotherapy and who experience difficulty in undergoing revascularization. AnGes applied for marketing approval to the MHLW in January 2018 based on positive results from the randomized, placebo-controlled phase three trial and investigator-led clinical study conducted in Japan. HGF plasmid is one of the first gene therapy products to be approved for a non-genetic disease with chronic and progressive symptoms.

Indication:
Ulcer healing for Critical Limb Ischemia patient
Benefit and Risk Balance Assessment

• Discussion of acceptable level of clinical effectiveness vs. patient access to the new therapy

• Weighing acceptable risk against expected benefit

• Based on Regulatory Sciences
Thank you
for your attention