“Creating an Environment for Bio/Medical Innovation in Japan

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One of Japan’s biggest current challenges is the transition to a dynamic market for innovation and entrepreneurship. The medical industry is a prime example of this transition.

- The first iPS treatment to human body has been succeeded in the world on 12th SEP 2014.
- From last April 2015, Japan has totally changed in Medical Innovation Environment.
- Most effective platform for medical innovation has been prepared in terms of Legislation and organization
  - Promotion Act of Heath industries and advancement of healthcare technologies
  - Promotion Act of Regenerative Medicine (RM)
  - Safety Act of regenerative Medicine
  - Revised Pharmaceutical Affairs Law (including medical device + Regenerative Medicine)
  - Start of administrative agency of Japan medical research and development (AMED)
  - Promotion Act of Special Zone for Medical Innovation
    - Kansai area, Kanagawa and Tokyo
  - Start of clinical research core hospitals system
Why medical innovation is important?

Drug industry $1T (2010) → $1.5T (2020)

The Medical Industry is experiencing a paradigm shift similar to what the IT industry experienced in the mid 1990's.

After emerging of Windows 95 OS and many private Internet Service Providers, many people have started to use their own PCs connected to the Internet.

Many people have become to do a large amount of data information processing and digital communication personally without using host computers.

It & iPS

After emerging of human genome sequencing and regenerative medical technologies (iPS etc), people will be able to enjoy the benefits of personalized medicine.

People have just started to be treated with personal identification of specific genome type and personal cell processing technologies without using blockbuster drugs.
Paradigm Shift & Epoch making

- 20th century Medicine
  - Drug discovery + Medical Devices
- 21st century Medicine
  - Regenerative Medicine
  - Genomic medicine & Personalized medicine
- It & iPS also change 20th century medicine
  - Innovation of clinical trial process and protocol of investigating drugs
    - In the case of chemical compounds, the current success probability of drug discovery is approximately 1/30000 (a one-30000th)
  - R&D of New methods for Evaluating Cardio toxicity using iPS and genome sequencing technologies
    - Using human tissues and organs instead of animal’s
    - Pre specification of similar genome type patients
    - Pre screening of the patients who serious side effects will be concerned about, using their tissues and organs from their iPS cells
Series of plan and legislation

2010/6 Cabinet Decision
  「New growth Strategy Plan through Healthcare and Life Innovation」
2010/11 Start of national Conference of Medical Innovation by MHLW, MEXT and METI.
2011/1 Start of Medical Innovation Promotion Office in Prime minister Secretariat
2011/3 Tohoku Earthquake
2012/6 Formulation and cabinet decision of Five-year Plan of Medical Innovation
2013/4 Enactment : Promotion Act of Regenerative Medicine by Congressmen League
2013/6 Cabinet Decision : Strategy of Healthcare and Medicine
2013/11 Enactment
  Safety Act of regenerative medicine
  Revised Pharmaceutical affairs Act

2014/5 Enactment ( Enforcement 2014/6)
Act on Promotion of Healthcare Industries and Advancement of Healthcare Technologies
Act of administrative agency of Japan Medical Research and Development

2014/6 Legal establishment of headquarter of healthcare policy in PM Secretariat
2014/11 Enforcement
  Safety Act of regenerative medicine , Revised Pharmaceutical affairs Act
2015/4 Start of Japan agency of Medical Research and Development AMED
Distinguished points by recent reforms

- Concerning RM, Introduction of **Early approval system** with a condition of post market surveillance
  - Compare with US-FDA, Japanese industries have more advanced regulation system. ⇒ Many companies will be able to do clinical research more effectively in Japan.
  - Full cost of each drug discovery has been approximately 1~3 billion US$. ⇒ Half
  - In Kansai area, early approval system will be introduced in the field of medical devices.

- Medical institutions have been permitted to **outsource** cells / tissue processing operation to external businesses

- Research funding scheme has been renewed by establishing **Independent Administrative Agency of Japan Agency for Medical Research and Development (AMED)**
Regenerative medicine in Japan
-Two tracks to provide new technologies

Medical Practitioner Act / Medical Service Act
- Medical treatment at own expense
- Aesthetic Surgery
- Immune Cell Therapy

Clinical research
- Regenerative medicine for clinical use

Clinical trials
- Regenerative medicine products

Promotion Act for Regenerative Medicine
- Responsibility for each player
- Organize security and other standards
- Organize a system that allows medical institutions to outsource cells/tissue processing operation to external businesses
- Introduction of an Early Approval System

Safety Act for Regenerative Medicine
- Introduce safety guaranteed systems related to each risks of regenerative medicine (introduce approval/notification system)
- Organize a system that allows medical institutions to outsource cell/tissue processing operation to external businesses

Revised Pharmaceutical Affairs Law
- Define "regenerative medicine"
- Introduce Early Approval System
- Post-marketing monitoring

Source: The excerpt with permission from Yoshihide Esaki, Promoting Practical Use Of Regenerative Medicine, Ministry of Economy Trade and Industry (METI), Sep. 2014
Approval system corresponding to an implementation of regenerative medical industry (Approval with condition and deadline)

Conventional route to approval (total cost: 1B$)

<Problem in the case which one applies conventional approval system to regenerative medical industry>
Since human’s cell is necessary, the quality will be heterogeneous reflecting individual variation. Therefore, it takes long time for gathering and assessment of data to confirm its efficacy

Approval system corresponded with early implementation of regenerative medical industry

※Earlier access to patients

- Earlier estimation of efficacy than conventional way, from limited cases
- Able to assess acute phase side effect in a short period

Clinical research
Clinical Trial (estimating the efficacy and confirming the safety)
Approval with condition and deadline
Clinical trial
(Confirming efficacy and safety)
Approval
Come onto the market

Request for the approval again by the due date
Approval or lapse of the approval with condition or deadline
Continue to be on the market

Explain the risk to patient, get the consent and employ post-marketing safety measure
High Expectations for Regenerative Medicine

<Characteristics of Stem Cells>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cultivation Methods</th>
<th>Pros / Cons</th>
<th>Principal Usages</th>
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</thead>
<tbody>
<tr>
<td>ES Cells (embryonic stem cells)</td>
<td>From <strong>fertile eggs</strong> (destroy fertile egg)</td>
<td><strong>Pros</strong>: Reproduce semi-permanently</td>
<td>Basic research</td>
</tr>
<tr>
<td>iPS Cells (induced pluripotent stem cells)</td>
<td>From <strong>somatic cells</strong> (inject genes)</td>
<td><strong>Pros</strong>: No ethical aspects; <strong>Cons</strong>: Risks of malignant transformation</td>
<td><strong>1)</strong> Clinical application for treatments w/ low malignant transformation risks; <strong>2)</strong> Application for drug discovery &amp; pathology research</td>
</tr>
<tr>
<td>MSCs (mesenchymal stem cells)</td>
<td><strong>Present in bodies</strong> (procure from tissues)</td>
<td><strong>Pros</strong>: No need of specific manipulation (gene injections, etc.); No aberrant cell growth; <strong>Cons</strong>: Limited cell fission (some dozen times)</td>
<td>Clinical application for regenerate tissues &amp; organs (Mainstream of today’s regenerative medicine)</td>
</tr>
</tbody>
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High Potential to Bring Significant Benefits

1) Improves QOL of patients AND their caregivers & families
2) Reduce social cost of long-term conditions such as Diabetes and Kidney Disease
METI estimates the market size for regenerative medicine at about $25 billion in 2050 (Japan), and $380 billion (global), which promises enormous economic benefits.
Creating Value-Added Supply Chains

Regenerative Medicine is supported by a range of related industries.

Consumable Supplies and Materials
1) Mediums
2) Reagents
3) Culture vessels

Supporting Industries
1) Design, construction
2) Maintenance

Cell Processing Center (CPC)

Drug Evaluation System / Appliances
IPS cells
Cardiac cells
Drug evaluation system w/ cardiac cells

Innovative Drug Discovery

Leading companies on regenerative medicine products / services
Japan Tissue Engineering Co. (skin, cartilage)
Terumo Co., Cell Seed Inc. (cardiac cell sheet)
Hexilos K.K. (retina cell sheet processed by iPS cell)

Cell Culture Devices
1) Incubators
2) Auto-culturing devices

Regenerative Medicine

Transportation Services
1) Transportation of cultured cells

Cell Assessment Devices
1) Flow cytometers
2) Image analysis devices

Transportation of cultured cells
Setting Common Standards for Regenerative Medicine

Quick development of the forum standard

Standardization and packaging between devices

Packaging of devices, consumable supplies and services

Value-added increase by the packaging
  The spread of domestic products

Transportation, transplantation

Inspection equipment

Culture flask

Centrifugal tube

SOP of transportation

Transport container

Temperature logger

Reagents

Culture bags

Packaging

Transportation container

Insulator

Conservation unit

Inspection equipment

Packaging of devices, consumable supplies and services

De facto strategy

Reinforce international competitiveness

Domestic standardization

International standardization

Packaging of devices, consumable supplies and services

Entry from different industries (electric equipment, IT, chemical ...)

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Laboratory study

Researchers in pharmaceutical companies and doctors conduct detailed research on the “cause of disease” and search for the “origin of medicine”.

Preclinical experiment research (Animal experiment)

“Origin of medicine”, after being subjected to various experiments, is tested on animals and cells to examine its effects carefully. After the experiment, the “elements of medicine” which are expected to be effective against disease and confirmed not to have side effect become a “nominated medicine”.
Clinical trial

“nominated medicine” is tested on human beings. For “nominated medicine” to become “medicine”, they have to be tested on humans for effectiveness and side-effects (safety).

Phase 1

“Nominated medicine” is given to mainly healthy adults. Starts from small amount, with the amount then being increase to look into side-effects. Also, they examine how fast “nominated medicine” is absorbed in the body, what kind of effect is occurred and how much time it takes before it is excreted.

Phase 2

“Nominated medicine” is tested on small number of patients to examine its effectiveness, side-effects (safety) and effective use (amount, interval, period)

Phase 3

At last, they examine if effectiveness and side-effects (safety) of “nominated medicine” found in experiments above can be applied to other patients. Also, depending on “nominated medicine”, they check if it works better than existing medicine, how small side-effect is and effectiveness and side-effects when they use it for a long time.
- Application approval
  - Results above are presented to PMDA and examined if it works as “medicine”.

- Check after production and sale
  - After “medicine” is on sale and used by many patients, they examine its effectiveness, safety and side-effects which they have not found.
Conclusion: Japan has a potential for new paradigm of medical innovation

- Healthcare industry in Japan has been not strong in terms of finding blockbusters which global mega pharmaceutical companies have been strong at.

- High level of regenerative medicine research + Personalized Medicine
  - iPS and stem cell Treatment
    - Prof. Shinya Yamanaka (Kyoto Univ.), prof. Sawa (Osaka Univ.), Prof. Okano (Keio Univ.), Prof. Masayo Takahashi (Riken)
  - TOHOKU Medical Mega Bank (100,000 ~ 150,000 bio and gene samples)

- High Level of Japanese manufacturing and IT industries

- Japanese Companies can continue to invest Medial innovation
  - Medical treatment needs 10 years from research and development to applying to human body
  - The first iPS treatment to human body has been succeeded in the world on 12th SEP 2014.
  - Approval of Cell Sheet 2nd Sep 2015
Road map: Application of iPS cell to human

- Sep 2014: Retina, eye, first case in the world by Dr. Masayo Takahashi RIKEN KOBE
- 2016〜2017: Parkinson syndrome
- 2016〜2017: Blood platelet
- 2017; Heart (cardiac) muscle
- 2017〜2018: Spinal Cord
- 2017〜2018: Natural Killer T Cell
- 2019: Liver organ
- 2019〜2020: Hair
- 2022〜: Teeth
- 2025〜: Kidney
the public health insurance for all the people.
> Everyone join the public insurance.

Free Access
> One can go to the hospitals he or she wants, regardless of symptoms and disease’s type.

Top Ranking of medical service in the world (WHO)

Healthcare spending is more than 10% of the annual budget and has been increasing

Medical expenditure is about 40 trillion yen in (FY2013)
> 1/3 from national budget, 1/3 from public insurance, 1/3 from patients

With aging society, not life expectancy but healthy life expectancy became more valued