How to foster the development of regenerative medicine?
The experience in Japan

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TWIns
Regenerative medicine & cell therapy in Japan

Medical Care Act (MCA) = The Act on the Safety of Regenerative Medicine. NEW!

Pharmaceuticals and Medical Devices Act. (PMD Act.) NEW!

**Academic Research Purpose**

Medical care

Clinical Research using human stem cells

108 protocols approved
(as of November 2014 - before new legislation)

Cancer immunotherapy

6 types of therapy are currently provided in approved university hospitals as “advanced care”
* Partially covered by national health insurance

**Commercial Product Marketing Authorization Purpose**

Cellular/Tissue based Products

2 marketed products
- JACE (autologous cultured epidermis)
- JACC (autologous cultured cartilage)

19 clinical trials initiated (including 6 gene therapy products)
(≈March 2015)

Covered by MHLW

Covered by MHLW and PMDA
Starting Points to foster top science regenerative medicine from Japan/Asia for the world patients

- **Round Table (Mode2) R&D efforts** among stakeholders; Bio-Engineering-Medical, Internist-Surgeon, Academia-Industry, Science-Art, “Bench to Bedside and Back”...

- **Innovative clinical applications** to int’l standard therapy (not local GOD HAND treatment) with device & material

- **Technology & System fusion** across Cell Imaging, Tissue Engineering, Automation Control and Modular Platform System for large production (from semiconductor to RM)

Two keys for Success from Japan: iPS cell (cell source), and Cell Sheet Engineering (tissue engineering and therapy)
Development of Advanced Therapy in 21st century

20th century Clinical Practice
- Connoisseur & God Hand

21st century Clinical Practice
- Nano-bio interface
- Nano machine therapy

TE Advanced therapy
- Cardiac RM
- Cure Therapy
  - Liver
  - Teeth
  - Cartilage

Cluster for Dynamic Integration

Evidenced Based Treatment

Drug delivery
- Chip & Sensing technologies
- Gene therapy

Bio Materials

Chemical IC

TE & Regen. Medicine
Cell Sheet Regenerative Medicine
Key Driver of Medicinal Innovation

From Symptom Treatment to Advanced “Cure” Therapy

Small Molecules  Bio Drug  Gene Medicine  Cell Medicine  Cell Sheet, Tissue Medicine

Pain, Fever  Insulin  RNAi  Adult Stem Cell  DDS
Flu, Factor VIII  Plasmid DNA  ES Cell  Bio Material

Pharmaceutics  Genetic Engineering  Cell Engineering  Stem Cell Biology  Regenerative Medicine
Chemistry  Cell Sheet Engineering  Tissue Engineering  DDS  Robotics

Fusion of Biology and...  New Business Model
Cell Sheet Tissue Engineering Regenerative Medicine

Teruo OKANO, Ph.D.
Ex Vice-President (Research Strategy) and Professor, Director of Institute of Advanced Biomedical Engineering and Science, Tokyo Women’s Medical University
Adjunct Professor, Univ. of Utah

- Leader of TWIns (TWMU & Waseda Joint Research Institute of Advanced Biomedical Science) with 400 scientists, medical doctors & industry researchers.
- Project Leader of CSTEC (Cell Sheet Tissue Engineering Center) “Innovation Core program of Regenerative Medicine with Industry” (2006-2016)
- Leader of FIRST (top 30 scientists) program
- Innovative research and 700+ publications in Biomaterials, DDS, and Regenerative Medicine

Disrupt cell-cell junction and adhesive protein
Maintain structure and Functions
Temp. Responsive Polmer Poly(N-isopropylacrylamide) (PIPAAm)

Cell Sheet formation On Culture Dishes

Enzyme Treatment
T Changes (37→20℃)

Hydrophobic Surfaces
Hydrophilic Surfaces

Clinical Application
Esophagus
Cornea
Heart
Middle Ear
Liver
Pancreas

Cell Sheets (thin layered)
Stem Cells
Thick Tissues (vascularized)
Periodontium
Lung
Cartilage

Cell sheet

20 nm
Intelligent 3D cell sheet engineering management

Multi-layering Tissue Engineering

“structural & functional”

System Integration
Clinical Studies of Cell Sheet Engineering RM

1. Corneal Epithelium by oral mucosa
   - 2003 Clinical Study started at Osaka Univ. (26)
   - 2007-2010 25 Clinical Trial in France (Cellseed)
   - 2011 PMA of Cellseed accepted by EMA
   - 2013 Approved as Advanced Therapy in Japan
   - 2015 Physician initiated Clinical Trial started

2. Cardiomyopathy by myoblast
   - 2007 Clinical Study started at Osaka Univ. (24)
   - 2011 Clinical Trial started in Japan (Terumo)(7)
   - 2015 MPA submitted for approval

3. Esophageal by oral mucosa
   - 2008-2010 Clinical Study at TWMU (10)
   - 2012 Clinical Study at Karolinska started (10)
   - 2013 Nagasaki-TWMU joint Clinical Study

4. Periodontal Disease
   - 2008-2010 Clinical Study at TWMU (10)

5. Cartilage
   - 2008-2010 Clinical Study at TWMU (10)
   - 2011 Clinical Study started at Tokai Univ (7)
Clinical Application starting now

Lung Air Leakage Treatment by Fibroblast Cell Sheet

Middle Ear Treatment after Removal of Pearl Tumor by Nasal Mucosa Cell Sheet

Middle Ear Cavity Measure by CT
Nagasaki Univ Hospital

Oral Surgery Outpatient

1. Biopsy of Patient
Oral mucosa tissue

5 ~ 6mmΦ

Cell isolation

3. Cell isolation

1,200km
7 hours at most

Cell culture by
thermo responsive
culture insert

4. Cell culture by
thermo responsive
culture insert

1 day incubation
at CPC before
transplantation

7. 1 day incubation
at CPC before
transplantation

Cell Sheet
transplantation

20℃

2. Shipment to TWMU

3. Cell culture by thermo responsive culture insert

4. Cell culture by thermo responsive culture insert

5. Culture 15 days, Pre-shipping Quality Test of cell sheet

Ope Room

Shipment to TWMU

6. Shipment to Nagasaki

Shipment to
Nagasaki

Multi-center clinical study to ship cell sheet for 1,200km distance in Japan
International Biomedical Clinical Networking to realize RM

Building “Global High Way” for patients and industry to offer standard RM therapy
Innovate Cell Culture Method for global cell biology researchers to change practice

Venture Co CellSeed Inc (supported by TWMU) to tie up with World giant Thermo
“Large Scale & Low Cost” Stem Cell Expansion Method

Establishment of Dominant Technologies for large 3D Organ Fabrication

Conventional Stirring

Stirring Optimized for Human iPS Cells

Ratio of Differentiation (myocardial Cells)

Breakthrough Technology
Large scale Expansion of myocardial cells in the lowest cost & highly stable method

equivalent to myocardial cells of human left ventricle (1×10⁹)

100mL bottle can culture cells equivalent to 50 culture dishes “10cm dia.”
From costly “manual cell culture” at cGMP CPC to Automated Cell Sheet Manufacturing System

Cell Processing Center (GMP)

Automated Culture System to generate cell sheets

Quality by Design and Process Analysis Technology is essential to reduce cost and gain sustainability

1. Space reduction 1/50 ~ 1/200
   X 2 ~ 5 times effective full utilization
   100 ~ 1000 times production capability

2. Avoid human error by automation

2U · CPC requires 280 m²
Maximum 48 sheets/year · 2U · CPC

1. Huge Space cost
2. Huge HR related cost to cover GMP manual process
3. Risk of human error
Innovatively integrated **Cell Aseptic Processing** "T-Factory"

**Development of Tissue Factory**

A novel process assembly method, **"flexible modular platform (fMP)"** has been developed and patented by combining one processing unit with individual aseptic isolators.

**Prototype**

Current methods of manual processing

- **cleanroom**
- **isolator**
Japanese way to foster regenerative medicine and industry

- Round Table (Mode 2) R&D efforts among stakeholders (vs traditional Linear model R&D) & int’l voicing
- METI coop with MHLW clarifying complicated regulations (from adaptive industrialization point of view)
- Timely legislation of RM Promotion Act (May 2013) (switch from “negative” to “positive” regulations)
- Japan Society of Regenerative Medicine committees (Frontiers understand medical business and industry)
- FIRM: Forum for Innovative Regenerative Medicine (100+ companies working on industrialization issues)
Promotion Act of Regenerative Medicine passed the Diet on April 26th 2013

USD1.2 Billion budget for iPS Cell based R&D efforts and...

Highway Program for Realization of Regenerative Medicine

Achieve regenerative medicine and drug discovery as rapidly as possible through collaboration between MEXT, MHLW, and METI

<table>
<thead>
<tr>
<th>Expansion of regenerative medicine market (domestic)</th>
<th>2012</th>
<th>2020</th>
<th>2030</th>
</tr>
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<tbody>
<tr>
<td>Regenerative medicine</td>
<td>¥9 billion</td>
<td>¥9.5 billion</td>
<td>¥1 trillion</td>
</tr>
<tr>
<td>Peripheral industries</td>
<td>¥1.7 billion</td>
<td>¥9.5 billion</td>
<td>¥550 billion</td>
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Source: Report on the Commercialization and Industrialization of Regenerative Medicine (METI, February 2013)
MHLW Grants-in-Aid for Scientific Research
(Regenerative Medicine Commercialization Research Projects)

- Support for research toward the commercialization of regenerative medicine
  - Research to establish storage methods, etc. for human stem cells
  - Research concerning the assurance of safety with respect to the tumorigenic risk posed by stem cells and other risks, etc.

- Support for research toward drug discovery and application
  - Research on drug discovery using iPS cells

<table>
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<tr>
<th>FY</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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<tr>
<td>Budget</td>
<td>¥570 million</td>
<td>¥1.3 billion</td>
<td>¥1.51 billion</td>
<td>¥2.13 billion</td>
<td>¥2.98 billion</td>
</tr>
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</table>

More than 5-fold increase over 5 years
Market Size for Regenerative Medicine will get to Yen 2,500 Billion Yen (domestic) and 3,800 Billion Yen (Overseas) in 2050.
市場規模の算出方法

「市場規模」=「装置類の市場規模」 + 「消耗品類の市場規模」 + 「サービスの市場規模」

予測市場規模の推移（国内）

FY2012 17bil. (yen)  →  2012年 17bil. (yen)
FY2015 95bil.  →  2015年 95bil.  
FY2020 550bil.  →  2020年 550bil. 
FY2030 1,300bil.  →  2030年 1,300bil.
FY2050 1,300bil.  →  2050年 1,300bil. (yen)

予測市場規模の推移（海外）

FY2012 240bil. (yen)  →  2012年 240bil. (yen)
FY2020 1,100bil.  →  2020年 1,100bil.  
FY2030 5,200bil.  →  2030年 5,200bil.
FY2050 15,000bil.  →  2050年 15,000bil. (yen)

市場規模は2050年までに億円で1,300億（国内）と15,000億（海外）に達する。これ以降では市場拡大が見込まれています。
Two Acts to regulate regenerative medicine & cell therapy in Japan

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

Production and marketing of regenerative and cellular therapeutic **products** by firms

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* Two laws were enacted in November 2014
Overview of the Act on the Safety of Regenerative Medicine

I. Obligate hospitals and clinics to submit plans in advance and report

II. Enable commissioning cell processing to licensed enterprises

III. Obligate CPCs to notify or obtain licence/accreditation

- Notification (Hospitals / Clinics)
- Application for a license (Firms)
EMA (European Medicinal Agency) is preparing Adaptive Licensing System.

Outsourcing of processing/manipulation of cell/tissues in the new laws

Clinical Trials, Private Practice

New Regenerative Medicine Law

- Standards for medical facilities and processing/manipulation plants applicable to regenerative medicine as medical practices

Regenerative Medicine Products

Pharmaceutical Affairs Law

- Manufacturing Standards for regenerative medicine product plants

Company Plants (with permission)

Medical facilities (with notification)

Collection

Processing

Transplant

Processing

Company Plants (with permission)

Processing

New Law

PAL
Two acts regulating regenerative medicine & cell therapy

Regenerative Medicine

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

The Act on the Safety of Regenerative Medicine

Production and marketing of regenerative and cellular therapeutic products by firms

The Act on Pharmaceuticals and Medical Devices (PMD Act)*

* Two laws were enacted in November 2014
The Pharmaceuticals and Medical Devices Act (PMD Act)

◆ New category and definition of “regenerative medical products”

Difficult to gather and evaluate the data for efficacy of regenerative medical products in a short time due to heterogeneity of cells

To secure timely provision of safe regenerative medicines, a new regulatory framework is needed

Expedit ed approval system for regenerative medical products

After the safety is confirmed and the results predict likely efficacy, the product will be given conditional, time-limited marketing authorization in order to enable timely provision of the products to patients.
Expedited approval system under PMD Act

[Traditional approval process]

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

< 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.

[New scheme for regenerative medical products]

Clinical study → Clinical trials (likely to predict efficacy, confirming safety) → Conditional term-limited authorization → Marketing (Further confirmation of efficacy and safety) → Re-application within a period (max. 7 yrs) → Marketing authorization or Revocation → Marketing continues

Post-marketing safety measures must be taken, including prior informed consent of risk to patients.
Voicing for Regenerative Medicine Promotion Act (and other laws) (2006-2014) /“JSRM Ethics” for regenerative medicine participants

New casualty insurance development for “clinical study” (FIRM to design casualty insurance for “cell culture outsourcing “)

Certificate for regenerative medicine physicians to involve clinics

Certificate for cell culture technicians for qualified cell processing

Public symposium and media communication to improve literacy

Avoidance of asymmetry of information among stakeholders
JSRM activity to be more allied with TERMIS-AP or TERMIS-Int’l
FIRM established in July 2012
Starting from study meeting at TWIns in 2011, now more than 120 company members joining.

- Voicing outside to promote RM industry
- Tackling with conventional issues within industry

<table>
<thead>
<tr>
<th>Chairman</th>
<th>Yuzo Toda (Fujifilm Corporation)</th>
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<tr>
<td>Vise-chairman</td>
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<tr>
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<td>Akihiko Iwai (Astellas Pharma Inc.)</td>
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<td></td>
<td>Masahiro Kitano (Hitachi, Ltd.)</td>
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<td></td>
<td>Kunihiko Suzuki (MEDIINE Co., Ltd.)</td>
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<td>Directors</td>
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<td>Masafumi Nakao (Asahi Kasei Corporation)</td>
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<td>Toshiki Sugimoto (Dai Nippon Printing Co., Ltd.)</td>
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<td></td>
<td>Masahide Konno (Tokio Marine &amp; Nichido Fire Insurance Co., Ltd.)</td>
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Remaining key issues to be solved from now...

- Methodology of Insurance Coverage and Patient Access (Health Technology Assessment vs Budget Impact)
- Allogeneic cell & tissue - Banking and Supply system (for treating large number of patients properly)
- Innovative PPP Cluster set up to realize RM as industry (to generate S&Ts and “positive” regulations at one place)
- Global Standardization based on stakeholders’ consensus (frontiers of medical industry to collaborate)
- Securing longer term career plan for fusion specialists (Leaving from Inflexible doctorate program at university)
Challenges for Value-based Evidence and Decisions in Healthcare

Embarking on New Era from Asia
Maybe in 10 year time...

you may say “Who moved my cheese ? ” or “How great to regenerate industry and contribute to the World ! “

Let’s take actions to realize “Healthy Active Aging Society” !

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