Definition and Regulation on Regenerative Medicine (or Cell Therapy Product)

Case Study:
The experience of the industrialization for autologous cell based products in JAPAN.
Japan Tissue Engineering Co., Ltd. (J-TEC)

- Only J-TEC has approved QMS/GMP facilities in Japan, among biotech companies.

Foundation: Feb. 1, 1999
HQ location: Gamagori
Capital: 7,785 mil yen
Employee: 218

QMS/GMP facilities
Regenerative Medicine for skin
Cultured epidermis
Clinical Research : BURNS

Chukyo Hospital burn center

Left thigh

Right thigh

After 4 weeks
The 1st Tissue-Engineered Medical Product Approved in Japan

- **Category**: Medical device
- **Indication**: Severe burn (DDB + DB ≥ 30%)
- **Regulatory Status**: Approved : Oct. 2007
- **Reimbursement price**: JPY 314,000 / sheet ($3,140 / sheet)
JACE Business Model

- From a stamp-sized sample of a patient’s own healthy skin, J-TEC cultures enough epidermis to cover the patient’s entire body within 3 weeks.
Regenerative Medicine for Cartilage
Tissue-Engineered Cartilage

Prof. Ochi (Hiroshima University)

- Improve inadequacies of ACI by 3-D Cultivation (prevent de-differentiation of chondrocytes and retain in implant site after operation)
- Existence of chondrocytes having proliferation potency
- Production of cartilage matrices
Transplantation of Tissue-engineered Cartilage

Uchio Y. and Ochi M,
3875 Nihon Iji-Shinpou 1998.
Clinical Research: Damaged knee cartilage

Lysholm score: pre-operation 70.6 → post-operation 96.7
Arthroscopic assessment: excellent / good 96%


Case Report

13-yr-old boy, a cartilage defect in the medial femoral condyle

pre-operation

2 yrs after operation
Clinical Trial

Evaluation by MRI

Pre-operative finding 12 months after ope.
About 40 patients participated in the clinical trial. J-TEC monitored their results after surgery for 1 year.

J-TEC submitted an application for mfg & sales in Aug. 2009, but excluded the elbow from its indication.
Long term follow up results

According to these results, the efficacy of cultured cartilage grafting lasted during extra follow up period (1-5 years).
2nd RM Product Approved in Japan

[Category] Medical device

[Indication]
Traumatic cartilage defects and osteochondritis dissecans (OCD) exclu. osteoarthritis (OA) for knee joints.
Defect area: 4 cm² +

[Regulatory Status] Approved: July 2012

[Reimbursement price] JPY 2,130,000 / knee ($21,300 / knee)
Evaluation of Safety and Efficacy

How do you know it’s safety?

- No infectious factor such as pathogenic organism
- No anticipated immune reaction such as allergy
- No risk of transformation after grafting

Objective evaluation of TEMPs

How do you know it’s efficacy?

- Efficacy of the treatment
- Efficacy of the product
To develop tissue-engineered regenerative medicine products using autologous cells

1. Establishment of cell banks for research and development.
   ※Skin 249 (2)  Cartilage 295 (6)  Cornea 128 (2)

2. Standardization of cell culture procedure for production.
   /Age  /Biopsy site  /Doctors technique  /Uncontrolled etc.

3. Evaluate product characterization.
   /cell survival rate  /cell content  /impurities etc.

4. Establishment of standards for product safety and efficacy

5. Development of product packages and delivery system
   /avoiding reduce(increase) cell viability  /easy to handle etc.

6. Construction of GMP compliant facilities

We have a lot of work to achieve ‘from Bench to Bedside”
Ensuring safety for cell based products

Implemented for ensuring the product safety.

<table>
<thead>
<tr>
<th></th>
<th>Choice of raw materials Process of manufacture</th>
<th>Animal experiments</th>
<th>Clinical trials</th>
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<tbody>
<tr>
<td>Pathogenic organisms</td>
<td>• Microbe clearance • Aseptic manipulation</td>
<td>Evaluation pathogen infectious disease</td>
<td>Evaluation pathogen infectious disease (Long term follow up in some cases)</td>
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<tr>
<td>Immune reaction (allergy)</td>
<td>• Immunogenicity of raw materials • Removal by washing</td>
<td>Evaluation of immunological reaction</td>
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<td>Tumorigenecity (Carcinogenicity)</td>
<td>• Soft-ager colony formation assay • Karyotype analysis • Carcinogenicity test for medium.</td>
<td>Evaluation of neoplasia</td>
<td>Evaluation of neoplasia (Long term follow up in some cases)</td>
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<tr>
<td>Others</td>
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</table>
Growth Potential Cells in Cultured Epidermis

A Ki67 / TO-PRO®-3

①Initial Colony  ②Subconfluent  ③Confluent

④Final Product
The analysis for the cell contents in cultured epidermis

**Main active component**
- Keratinocyte

**Process-Related Impurities**
- Feeder cell (3T3-J2)

**Raw material-Related Impurities**
- Epidermis
  - Melanocyte
  - Langerhans cell
  - Merkel cell
- Dermis
  - Fibroblast

**Subcutaneous tissue**
- Adipocyte
The analysis for the cell contents in cultured epidermis

- **Keratinocyte**
- **Feeder cell**
- **Fibroblast**
- **Adipocyte**
- **Melanocyte**
- **Langerhans cell**
- **Merkel cell**
The analysis for the cell contents in cultured epidermis

<table>
<thead>
<tr>
<th>P0</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>Final Product</th>
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<tbody>
<tr>
<td>Keratinocyte</td>
<td>98.3</td>
<td>97.2</td>
<td>95.3</td>
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<td>Feeder cells</td>
<td>0.8</td>
<td>1.0</td>
<td>2.7</td>
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<td>Adipocyte</td>
<td>0.9</td>
<td>1.4</td>
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<td>fibroblast</td>
<td>1.6</td>
<td>0.5</td>
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<td>9.0</td>
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<td>Langerhans cell</td>
<td>9.0</td>
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</tbody>
</table>

**Shipping inspection**

**Keratinocyte**

「Content rate of keratinocyte in final product」

**Feeder cells**

「Residual ratio of feeder cells in final product」
4. Establishment of standards for product safety and efficacy (JACE)

**Receiving inspection**
- #1 Transport condition of biopsy tissue
- #2 Appearance of biopsy tissue

**Process inspection**
- #1 Morphology of cultured 3T3-J2
- #2 Morphology of 3T3-J2 feeder
- #3 Morphology of cultured keratinocyte
- #4 Intensity of sheet by detachment and washing
- #5 Proliferative potential of cultured keratinocyte
- #6 Viability of frozen-thawed keratinocyte
- #7 Number of collected cells on 3T3-J2 subculture
- #8 Preservation period of biopsy tissue

**Shipping inspection; judge until shipping**
- #1 Sterility 5 days before shipping
- #2 Mycoplasma-negative [PCR] 2 days before shipping
- #3 Appearance and morphology of cultured epidermis
- #4 Endotoxin
- #5 Appearance of final product package
- #6 Intensity of keratinocyte sheet
- #7 Viable cell density of keratinocyte sheet
- #8 Viability of keratinocyte sheet
- #9 Residual bovine-serum albumin in keratinocyte sheet
- #10 Content rate of feeder cell in keratinocyte sheet
- #11 Content rate of keratinocyte in keratinocyte sheet

**Shipping inspection; judge after shipping**
- #1 Mycoplasma-negative [DNA-statining]; judge 5 days after shipping
- #2 Sterility of final product; judge 14 days after shipping
5. Development of product packages and delivery system

Product packaging assures the preservation stability. Designing logistics, with temperature control and maintaining expiration date, is very important.

Storage temperature: 10 – 25°C
Expiration: 56 hrs
6. Construction of GMP compliant facilities

- The environment within our production facilities is controlled by air conditioning and room pressure control systems.
- The flow of people and objects is also controlled to maintain the environment in its highly clean state.
Technology and Know-How (1)

- Productization and optimization of TEMPs
  - Optimization of culture conditions
    (Medium preparation, Culture environment, Container design, etc.)
  - Combined culture with scaffolding
  - Cell freezing technology
    (Cell banking, Cell freezing in ultracold storage, Quality control)
  - Quality inspection
    - Setting cell quality endpoint and standard value
    - Setting safety evaluation items
      (Microbial contamination examination, Cell character evaluation, Residual test, etc.)
Technology and Know-How (2)

- Systematization of production and logistics of TEMPs

  - Managing schedule in cooperation with Hospital
    (Planning- Receiving order-Tissue biopsy-Culture-Shipping-Logistics -Grafting)

  - Raw material management system
    (Selection, Procurement, Storage, Information-gathering)

  - Packaging cell culture product
    - Defining storage conditions (temperature range, preservative solution)
    - Designing product container, Selecting material, Conditions for sterilization

  - Information control
    (Identification management, Prevention of misidentification, Traceability)

  - Training system
    (Education of operatives, Recognition of skills)

  - Developing logistics for order-made cell product
    (Special logistics system with temperature control)
Key point to achieve TE Industry

GMP Facility

HQ

Educational system for Employee

SOP and documentation

More!
- Delivery (Package, Logistics etc.)
- Post-marketing Surveillance
- Training system for Drs. etc.
The training system for Doctors

Contents

- What is JACC® (configuration, indication, clinical efficacy and safety etc)
- How to use (pre-operative screening, biopsy, graft procedure, Rehabilitations etc)
- Account for patient and informed consent
- About post marketing surveillance
- Hand’s on course (Training by Simulation kit)

Simulation Kit

Text for
- Doctor
- Comedical staff
- Patient
Thank you for your attention.

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