J-TEC's perspective:

The clinical development of the autologous cell/tissue-based medicinal products

Ken-ichiro Hata  D.D.S  Ph.D
Managing Director, R&D Department
Japan Tissue Engineering Co., Ltd.
Transition in study of Regenerative Medicine in Japan

- **1981** Clinical Application of Cultured Epidermis
- **1980 - early 90’s**
  - Development of Medical Treatment using human tissue under medical practitioners law
- **1990 – 2000**
  - Beginning of new era of “Tissue Engineering” (1993) and “Regenerative Medicine”
  - “Medical Investigation” ≈ “Regenerative Medicine”
  - Kyoto University’s Institute for Frontier Medical Sciences (since 1998)
  - “Millennium Project : national commitment “ (1999) and University-launched Venture company
Transition in study of Regenerative Medicine in Japan

- Big wave of Bio-tech Business including the field of Regenerative Medicine
  - “Major Plan for Development of New Industry and Job Creation” (2001)
  - Institute of Biomedical Research and Innovation (IBRI) in Kobe (since 2003)
- Discussion of CPC at the university
  - Proposal of iGMP
- Sept. 1st, 2006
  - Issuance of Guideline of treatment for human stem cell
- Establishment of preparing human iPS cells (2007)
- Revision of MHLW Guideline of No.1314 (2008)
Autologous Cultured Epidermis

1975: Prof. H. Green of Harvard Medical School developed a method that involved culturing keratinocytes together with mouse fibroblasts to form a keratinocyte sheet, a method known as Green’s technique for culturing epidermis.


1981: World first report: Grafting Green-type autologous cultured epidermis (ACE) for the treatment of severe burn patients (First case of medical treatment of TEMPs)


1984: The lives of two severely burned children were saved by Green-type ACE cultured from 2 cm² skin remained to them.


1985: Japan first report: Green-type ACE were used for the treatment of severe burn patients in Japan by Prof. N. Kumagai of St. Marianna University of Medicine.

Indications of Cultured Epidermis

- Burn wound
- Vitiligo
- Epidermolysis bullosa
- Nevus
- Scar
- Donor site of skin graft

etc….
Tissue-Engineered Cartilage

Prof. Ochi (Hiroshima University)

- Improve inadequacies of ACI technique by 3-D Cultivation (prevent de-differentiation of chondrocytes and retain their phenotype)
- Existence of chondrocytes having proliferation potency
- Production of cartilage matrices
About 40 patients participated in the clinical trial. J-TEC monitored their results after surgery for 1 year.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbow) Chef</td>
<td>No improvement</td>
</tr>
<tr>
<td>Elbow) Building constructor</td>
<td>No improvement</td>
</tr>
<tr>
<td>Knee) Physical education teacher</td>
<td>Excellent</td>
</tr>
<tr>
<td>Knee) Farmer</td>
<td>Very excellent</td>
</tr>
<tr>
<td>Knee) 68 year-old senior</td>
<td>No improvement</td>
</tr>
<tr>
<td>Knee) 120kg weight female</td>
<td>Excellent</td>
</tr>
<tr>
<td>Knee) Aerobics instructor</td>
<td>Very excellent</td>
</tr>
<tr>
<td>Knee) Nurse</td>
<td>Efficacy</td>
</tr>
</tbody>
</table>

No improvement

Excellent

Very excellent

NA
J-TEC is the only bio-tech company in Japan with approved GMP facilities.

Foundation: Feb. 1, 1999
HQ location: Gamagori
Capital: 5,553 mil yen
Employee: 117
Regulation for cell/tissue-based medicinal products

- Japanese pharmaceutical law “Yakuji-ho” requires TE & RM products an extra-step of application for starting clinical trial.

![Diagram showing the regulatory process with stages: Basic research, Pre-clinical study, Application for starting clinical trial, Clinical trial, Application for mfg & sales, Health insurance listing, Post-marketing surveillance.]

GOAL
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.
Autologous Culture Epidermis JACE

- JACE, J-TEC’s Autologous Cultured Epidermis is a keratinocyte sheet cultured together with 3T3-J2 cells (derived from mouse) as feeder cell, and FBS.
- JACE is a skin-like sheet with the keratinocyte and it is strength enough to suspend with career sheet.

**[Indication]**

Severe burn; DDB + DB >= 30%

Approval code: 21900BZZ00039000
Autologous Culture Epidermis JACE

Storage temperature: 10~25°C

Expiration: 50 hrs +α
10 Years to Launch

Founded & Started JACE R&D (1999.2)

- Submitted (2000.12)
- Approved (2002.3)
- Plan registered (2002.10)
- Completed (2004.10)
- Submitted (2004.10)
- Approved (2007.10)
- Health insurance listing requested (2007.1)
- Listed (2009.1)

- Basic research
- Pre-clinical study
- Application for starting clinical trial
- Clinical trial
- Application for mfg & sales

Health insurance listing

Post-marketing surveillance

GOAL
# Pipelines

<table>
<thead>
<tr>
<th>Product outlook</th>
<th>Autologous Cultured Epidermis</th>
<th>Autologous Cultured Cartilage</th>
<th>Autologous Cultured Corneal Epithelium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alliance</strong></td>
<td>Prof. Howard Green, Harvard Univ., USA</td>
<td>Prof. Mitsuo Ochi, Hiroshima Univ., JP</td>
<td>Veneto Eye Bank, IT Prof. Michele De Luca &amp; Prof. Graziella Pellegrini, Modena Univ., IT</td>
</tr>
<tr>
<td><strong>Business territory</strong></td>
<td>Japan</td>
<td>Worldwide</td>
<td>Asia</td>
</tr>
<tr>
<td><strong>Indication</strong>*</td>
<td>Severe burn: DDB + DB &gt;= 30%</td>
<td>- Traumatic cartilage deficiency</td>
<td>-Chemical burn</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Osteochondrosis dissecans</td>
<td>-Stevens-Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Osteoarthritis</td>
<td>-Relapsed pterygium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-Pemphigus, others</td>
</tr>
</tbody>
</table>

*Indication for autologous cultured cartilage & corneal epithelium: J-TEC’s Projection.
## Approval for Starting a Clinical Trial

<table>
<thead>
<tr>
<th>Products</th>
<th>Category</th>
<th>Company</th>
<th>Approval date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immuno-therapy for cancer by dendric cells</td>
<td>Drag</td>
<td>KYOWA HAKKO KIRIN</td>
<td>2001.10</td>
<td>Suspended</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KYOWA KIRIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cultured epidermis</td>
<td>Medical Device</td>
<td>J-TEC</td>
<td>2002.03</td>
<td>Approved for M&amp;S (2007.10)</td>
</tr>
<tr>
<td>HGF gene therapy</td>
<td>Drag</td>
<td>Anges MG</td>
<td>2003.10</td>
<td>Submitted application for M&amp;S (2008.03)</td>
</tr>
<tr>
<td>Cultured cartilage</td>
<td>Medical Device</td>
<td>J-TEC</td>
<td>2004.02</td>
<td>Submitted application for M&amp;S (2009.08)</td>
</tr>
<tr>
<td>Heart regeneration by myoblast</td>
<td>Drag</td>
<td>TERUMO</td>
<td>2006.04</td>
<td>Preparing for clinical trial</td>
</tr>
<tr>
<td>Treatment for GVHD by MSC</td>
<td>Drag</td>
<td>Japan Chemical Research</td>
<td>2007.05</td>
<td>Preparing for clinical trial</td>
</tr>
<tr>
<td>HSV-TK gene therapy</td>
<td>Drag</td>
<td>TAKARA BIO</td>
<td>2007.09</td>
<td>Preparing for clinical trial</td>
</tr>
<tr>
<td>FGF gene therapy</td>
<td>Drag</td>
<td>Sanofi-aventis</td>
<td>2007.11</td>
<td>Preparing for clinical trial</td>
</tr>
<tr>
<td>Cultured skin</td>
<td>Medical Device</td>
<td>BCS</td>
<td>2007.12</td>
<td>Preparing for clinical trial</td>
</tr>
<tr>
<td>Cultured corneal epithelium</td>
<td>Medical Device</td>
<td>Arblast</td>
<td>2009.06</td>
<td>Preparing for clinical trial</td>
</tr>
</tbody>
</table>
TEMPs has less products/experiences than Pharmaceutical/Medical device industry.
The Aim of Autologous Cell Therapy

- Recovery from previously untreatable disorders
- Minimized physical strain of patient
- Avoiding uncertainty of treatment and operation
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
Chapter 7 Clinical trial

On application for starting clinical trial, the safety should be evaluated under considerations of clinical usefulness, and the design of domestic clinical trial for cell-based medicinal products also should be evaluated about the point as mentioned below.

1. Indication
2. Inclusion criterion and exclusion criteria in treatment protocol
3. Therapeutic regimen
4. Adequacy for clinical trial
5. Assumed risks and benefits, content of informed consent

Guideline on Ensuring Quality and Safety of Products Derived from Processed Human (autologous) Cells/Tissues
(MHLW Notification No. 0208003 8 Feb. 2008)
Dilemma of Clinical Studies using autologous tissue

- **Primary Endpoint**
  - Clinical improvement vs. Histological regeneration
    - No objective indication such as clinical test values

- **Evaluation method**
  - Established method vs. Original method
    - Few established method, because Regenerative Medicine is the novelty field

- **Controlled trial / Blind trial**
  - Are Controlled trial and Blind trial actual?
    - Because of the surgical operation, it’s difficult to set the control group and blind trial.

- **Stratified analysis**
  - How to do stratified analysis? How to set appropriate indication?
    - Difficult to justify the classification for stratified analysis
    - Limited cases
Controlled Trial / Blind Trial

Microfracture
- Palliative treatment: Aiming short-term improvement by restoration of cartilage. Its performance and limitation are well-known.
- Ethical adequacy of invasive examination such as arthroscopy or biopsy as controlled trial.

<table>
<thead>
<tr>
<th>JACC</th>
<th>Microfracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthroscopic biopsy</td>
<td>Equivalent procedure losses the blindness</td>
</tr>
</tbody>
</table>
| Grafting  
  - Open Surgery | Operation  
  - Arthroscopy (loss the blindness, discrepancy of operation scale)  
  - Open Surgery (ethical issue) |
| Follow-up assessment  
  - Arthroscopy  
  - Biopsy | Follow-up assessment  
  - Arthroscopy (ethical issue)  
  - Biopsy (ethical issue) |
| Necessity of Retreatment | Necessity of Retreatment  
  - Negative impact of the treatment using cultured cartilage |
Stratified analysis

Assumed category

Causes of disease, damaged area, age, sexuality, duration of disease, Primary disease etc.

Category 1

Category 2

Tasks of categorization by background factor

- No rational marker of categorization
  (Level of details for analyze the categorization)
- Meanings of categorization for efficacy evaluation not for safety evaluation.
- Depending on operative procedure, background factor might not be disclosed.
**Boutique**
Manufacturer of pharmaceutical products/medical devices/TEMPs using allogeanic tissues

**Laundry**
Manufacturer of TEMPs using autologous tissues
Hospital

High quality product

Appropriate technique
From Human Treatment to Organ Treatment.

**in-vivo Medicine**
- Tumor removal
- Chemotherapy/Hyperthermia
- Stimulation for Hepatocytes etc..

**ex-vivo Medicine**
- preservation/restoration ex-vivo technique of tissue or organ
- techniques of substitutional artificial organ
- grafting technique etc.
Reimbursement policy of JACE

【facility criterion】
Institute that has special intensive-care unit (ICU) for burn care.

notification (24*1)

Not notification (150)

reimbursement

No reimbursement

No reimbursement

1~20 sheets ← More than 21 sheets
Supplying for one patient

【Reimbursement limits】
20 sheets are limits

*1: Hokkaido 0、Tohoku 3、Kanto 9、Chubu 5、Kinki 5、Chugoku 0、Shikoku 1、Kyushu 1 (1 Oct 2009)
The launch of autologous cultured cartilage (JACC) is projected in FY2011.
Experience is important to make the guideline for safety.

Thank You!

ken-ichiro_hata@jppte.co.jp