Current status of stem cell research and clinical trials for cell therapy in Korea

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1. Research of ESCs
2. Translational research projects using ASC
3. Cord blood banks and CBT
4. Investigational GMP
5. KFDA regulation for cell therapy
1. Research of ESCs
Overview of Stem Cell Research

- ES cell banking for 44 hES cell lines at a national level is undergoing.

- Korean scientific community and government are working hard to implement new research integrity infrastructures and bioethics guidelines.

- The Ministry of Health and Welfare is revising the Law for bioethics and safety.

- Several International stem cell symposia were held in Korea to make an international research network and collaboration.
### Recognition of the Important Funding by Government

(Million US$/year)

<table>
<thead>
<tr>
<th>Source</th>
<th>Embryogenic Stem Cells</th>
<th>Adult Stem Cells</th>
<th>Bioethics Infrastructure</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min.Sci.Tech</td>
<td>5.9</td>
<td>10.9</td>
<td>1.2</td>
<td>18.1</td>
</tr>
<tr>
<td>Min. Health Welfare</td>
<td>0</td>
<td>9.5</td>
<td>0.5</td>
<td>10.0</td>
</tr>
<tr>
<td>Min Com. Ind. Ener</td>
<td>0</td>
<td>3.1</td>
<td>0</td>
<td>3.1</td>
</tr>
<tr>
<td>Min Edu</td>
<td>0.1</td>
<td>0.4</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Min Agric Forestry</td>
<td>0</td>
<td>0</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>S M Bus. Adm.</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Rural Dev. Adm.</td>
<td>0</td>
<td>0.5</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Korea FDA</td>
<td>0</td>
<td>1.2</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>6.0</strong></td>
<td><strong>25.6</strong></td>
<td><strong>2.6</strong></td>
<td><strong>34.2</strong></td>
</tr>
</tbody>
</table>

Kim DW, 2007, SCRC annual report
# Objectives in Stem Cell Research Center (SCRC)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Establishment of the basic platform for stem cell research</td>
</tr>
<tr>
<td>(2002-2005)</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>Development of core techniques for stem cell research</td>
</tr>
<tr>
<td>(2005-2008)</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>Clinical and industrial application of stem cells</td>
</tr>
<tr>
<td>(2008-2012)</td>
<td></td>
</tr>
</tbody>
</table>
Fund management (SCRC)

Research field

Distribution of PIs

Embryonic stem cells 41%
Adult stem cell 38%
Infrastructure 21%
University 75%
Research institute 9%
Industry 16%
Achievement of SCRC (2\textsuperscript{nd} Phase)

- Identification of Dppa 5, a human ES cell specific marker
- Establishment of parthenogenic ES cell lines from immature oocytes
- Efficient induction of oligodendrocytes from human ES cells and therapeutic application in animal models
- Development of PBSC based cellular therapeutics for cardiovascular disorders
- Gene regulating NK cell differentiation from HSC
2. Translational research projects using ASC

- BM processing for BMT
- BM derived MNCs for Buerger’s disease
- BM derived MNCs in MI, spinal cord injury
- G-CSF mobilized MNCs in MI
- MSC injection in stroke and SCI
- Human neural stem cells in SCI and Hypoxic encephalopathy
- BM derived MNCs in Liver cirrhosis

Allogenic
Buerger’s disease

Bone marrow harvest

- under general anesthesia from iliac crest
- harvested volume: ~ 600 ml

Cell Injection:

- 30 mL volume in 50~60 injections (26 gauge needle)
- intramuscular (~1.5 cm depth)
- calf & plantar area
- with 3 cm-distance

DH CHOI, 2002
Case: M/31 # 3388290

C.C: Pain & gangrenous change at Lt. great toe
D: 3 months
PHx: Hypertension (-), DM (-)
Smoking: 15 PYs
Alcohol: moderate

DITI (Digital Infrared Thermographic Imaging)
CABG combined with Stem Cell Therapy

Preop

Postop 6 month

Operation

-Transplanted area and cell No.-

<table>
<thead>
<tr>
<th>Graft</th>
<th>Cell Tx</th>
<th>T.cell($10^9$)</th>
<th>CD 34+$($10^9$)</th>
<th>AC 133+ ($10^9$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 LAD, OM1</td>
<td>I, L, Apex</td>
<td>2.39</td>
<td>6.24</td>
<td></td>
</tr>
<tr>
<td>2 LAD, D</td>
<td>I, L, Apex</td>
<td>1.15</td>
<td>4.59</td>
<td>1.22</td>
</tr>
<tr>
<td>3 LAD, D</td>
<td>I, L, Apex</td>
<td>1.67</td>
<td>10.75</td>
<td>8.29</td>
</tr>
<tr>
<td>4 LAD, OM1</td>
<td>I, L, Apex</td>
<td>1.98</td>
<td>5.7</td>
<td>1.38</td>
</tr>
<tr>
<td>5 LAD, D</td>
<td>I, L, Apex</td>
<td>0.87</td>
<td>5.2</td>
<td>1.51</td>
</tr>
<tr>
<td>6 RV branch</td>
<td>A, L, Apex</td>
<td>0.82</td>
<td>5.1</td>
<td>0.99</td>
</tr>
<tr>
<td>7 No graft</td>
<td>A, L, Apex</td>
<td>1.25</td>
<td>5.3</td>
<td>1.13</td>
</tr>
</tbody>
</table>

Yoo KJ, 2003
MAGIC Cell Program in SNUH

2003 2004 2005 2006 2007

MAGIC Cell-1: G-CSF vs. Cell infusion vs. control in elective PCI

MAGIC Cell-2: G-CSF vs. control in AMI who underwent primary PCI

MAGIC Cell-3-DES: Cell infusion vs. control in AMI and OMI with DES

G-CSF and endothelial function
Effect of Cell infusion on LV dyssynchrony
G-CSF and Restenosis, coronary remodeling

MAGIC Cell-4-ICMP: Cell infusion in ischemic CMP without PCI

MAGIC Cell-5

1st generation stem cell therapy
1.5th generation stem cell therapy
2nd generation stem cell therapy

MAGIC Cell: Myocardial Infarction with G-CSF and Intra-Coronary Stem Cell Infusion

Presented by Kang HJ at KSBT, 2007
Allogenic Human Neural Stem Cells

- Clinical trial of transplantation of allogenic human neural stem cells in Patients with spinal cord injury
- Clinical trial of transplantation of allogenic human neural stem cells in neonates with severe perinatal hypoxic ischemic encephalopathy
- Source: fetal neural stem cell
- Location: Yonsei Univ. Severance hospital (PI: Park KI)
- Clinical outcome: promising

Personal communication with Prof. Park
Examples of What Cell Processing Laboratories Now Do

Basic Processing
- Plasma removal
- Red cell removal
- Washing
- Volume reduction

More Advanced Processing
- CD34+ cell isolation
- DLI in BMT
- DC in renal cell cancer, colon cancer, and melanoma

Cord blood
Bone marrow
Peripheral Blood
A South Korean woman paralyzed for 20 years is walking again after scientists say they repaired her damaged spine using stem cells derived from umbilical cord blood.

Hwang Mi-Soon, 37, had been bedridden since damaging her back in an accident two decades ago.

Last week her eyes glistened with tears as she walked again with the help of a walking frame at a press conference where South Korea researchers went public for the first time with the results of their stem-cell therapy.

They said it was the world's first published case in which a patient with spinal cord injuries had been successfully treated with stem cells from umbilical cord blood.
3. Cord blood banks
and CBT
CB Banks in Korea 2007

- Company-based: 11 banks
- University (Hospital)-based: 5 banks
- Regional: 2 bank

- For Private: 8
- For Both: 3
- For public: 5
- For public: 2

Total 18 CB Banks
Cumulative CB units for public banks in Korea

Lee YH (2007)
Double Unit UCBT

**Establish safety of the model**
(engraftment and GVHD)

**Assess feasibility**

**Characterize pattern of**
*double chimerism*

- HLA ≤ 2 ag mm CD34
  >0.85 x 10^5/kg

- HLA ≤ 2 ag mm
CD34 >1.7 x 10^5/kg

Cytoreductive Therapy

- UCB 1
- UCB 2

BMBx BMBx

Speed of PMN Recovery

TIME

Presented by Koo HH at KSBT, 2007
<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>Median age (years)</th>
<th>Conditioning regimen</th>
<th>Median TNC dose, $\times 10^7$ cells/kg (range)</th>
<th>Median CD34+ dose, $\times 10^5$ cells/kg (range)</th>
<th>Media time to ANC Recovery, days (range)</th>
<th>Grade 3-4 Acute GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myeloablative conditioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Minnesota</td>
<td>50</td>
<td>24 (11-60)</td>
<td>Flu/Cy/TBI</td>
<td>3.6 (1.7-7.4)</td>
<td>4.4 (1.2-14.5)</td>
<td>24 (5.41)</td>
<td>20%</td>
</tr>
<tr>
<td>SMC + SNUCH, Korea</td>
<td>49</td>
<td>10 (1-17)</td>
<td>Bu or TBI</td>
<td>5.4 (0.7-16.5)</td>
<td>-</td>
<td>18 (12-34)</td>
<td>8%</td>
</tr>
<tr>
<td>Hyogo College Of Medicine, Japan</td>
<td>11</td>
<td>33 (19-52)</td>
<td>Cy/TBI±Ara-C</td>
<td>3.9 (2.8-4.8)</td>
<td>1.1 (0.6-2.6)</td>
<td>21 (16-26)</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Reduced-intensity conditioning</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Minnesota</td>
<td>93</td>
<td>52 (17-69)</td>
<td>Flu/Cy/TBI</td>
<td>4.8 (2.5-6.5)</td>
<td>4.9 (0.7-16.6)</td>
<td>12 (0-32)</td>
<td>23%</td>
</tr>
<tr>
<td>Dana Farber Cancer Institute</td>
<td>21</td>
<td>49 (24-63)</td>
<td>Flu/Mel</td>
<td>4.0 (3.0-5.3)</td>
<td>2.0 (0.6-10.0)</td>
<td>20 (15-34)</td>
<td>5%</td>
</tr>
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</table>

*Note: SMC = Saudi Medical College.*
Isolation and ex vivo expansion of EPC from UCB

Morphology of MSC derived from cord blood
4. Investigational GMP
Cell processing is not equivalent to the production of conventional pharmaceutical drugs.

Academic institution is not equivalent to a pharmaceutical company.

Cited from the presentation slides by Maekawa 2006 ISLM symposium.
The medicines for investigational trial should be manufactured in the GMP facility and only used for patients with strict indication for therapeutic trials.
iGMP facility at YCTC
5. KFDA regulation for cell therapy
Definition of cell therapeutics
- Manipulated cells and tissues in ex vivo
- Genetically modified cells
- Tissue and cells complex
- Government regulation by law for safety of human derived tissues, which are using for cell therapy
<table>
<thead>
<tr>
<th>Mission</th>
<th>Approval processing</th>
<th>Expectation of Company provision or Preliminary data</th>
<th>Clearrness in Law</th>
<th>Scientific requirement for processing with rapidity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basic search/ toxicity test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prediscussion system in preclinical trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IND request</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase I (1-2 yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phase II (2-3 yr)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Phase III (1-2 yr)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>NDA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Test for safety and effectiveness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>approval</td>
<td></td>
<td></td>
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</tbody>
</table>
### Cellular therapeutics approved for commercialization license by KFDA

<table>
<thead>
<tr>
<th>Co. name</th>
<th>Product name</th>
<th>Indication</th>
<th>Approved date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celontech</td>
<td>Chondron (autologous derived cartilage)</td>
<td>Cartilage defect</td>
<td>2001. 1. 30</td>
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<tr>
<td>Duplogen</td>
<td>Articell (autologous derived cartilage)</td>
<td>Cartilage defect</td>
<td>2002. 9. 9</td>
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<tr>
<td>Taego Science</td>
<td>Holoderm (autologous skin fibroblast)</td>
<td>2nd, 3rd degree burn</td>
<td>2002. 12. 10</td>
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<td>Taego Science</td>
<td>Kaloderm (autologous skin keratinocytes)</td>
<td>Deep, 3rd degree burn</td>
<td>2005. 3. 21</td>
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<td>MCTT</td>
<td>Keraheal (autologous keratinocyte)</td>
<td>2nd, 3rd degree burn</td>
<td>2006. 5. 3</td>
</tr>
</tbody>
</table>
Encourage system for production of the BT cellular drugs

pre-IND : meeting with KFDA officers before the development of new BT therapeutics

- Open the problem solving window
- investigation clinical trial (experimental trial for small cases)

Fast Track

- Manufactured medicine

  - new drugs for AIDS, cancer, intractable life threatening disease
  - need for rapid introduction due to develop the resistant of drugs
  - cellular therapeutics etc

☞ commercial product release before complete paper works
☞ rapid approval firstly
Investigational clinical trials

✓ The cellular therapeutics (more than minimal manipulation) are regulated under the Medicine law.

1. Emergency clinical trial: There is no therapeutic treatment for life saving except cell therapy
   ✓ Individual base (case base), a medical certificate
   ✓ Patient’s medical record and physician’s opinions
   ✓ Patients’ consent, IRB approval
   ✓ Company cell supply with free charge

2. Investigational clinical trial:
   Before confirmation of the cellular drug effectiveness and safety fully, the physician/scientists try the clinical trial in patients with intractable diseases in the institutions.
<table>
<thead>
<tr>
<th>No</th>
<th>Title</th>
<th>PI</th>
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<tbody>
<tr>
<td>1</td>
<td>Clinical trial of transplantation of allogenic human neural stem cells in Patients with spinal cord injury</td>
<td>Park, KI</td>
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<tr>
<td>2</td>
<td>Clinical trial of transplantation of allogenic human neural stem cells in neonates with severe perinatal hypoxic ischemic encephalopathy</td>
<td>Park, KI</td>
</tr>
<tr>
<td>3</td>
<td>Autologous Dendritic Cell-based Immunotherapy of Malignant Melanoma Patient</td>
<td>Lee, MG</td>
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<tr>
<td>4</td>
<td>Immune Cell Therapy with Epstein-Barr virus specific T cells for Epstein-Barr virus associated far advanced gastric adenocarcinoma</td>
<td>Song SY</td>
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<td>5</td>
<td>Autologous transplantation of bone marrow stromal cell in traumatic acute and subacute spinal cord injury patients</td>
<td>Yoon, DH</td>
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<td>6</td>
<td>Therapeutic angiogenesis with autologous bone marrow cell transplantation in patients with ischemic heart disease and critical limb ischemia</td>
<td>Choi, DH</td>
</tr>
<tr>
<td>7</td>
<td>Clinical trial of autotransplantation of oral mucosal keratinocyte in the patient with oral mucosal defect</td>
<td>Cha, IH</td>
</tr>
</tbody>
</table>
Acknowledgement

• DW Kim, Ph.D. (Yonsei Univ.) : Director of Stem cell Research Center
• KI Park, MD.Ph.D.(Yonsei Univ.)
• HJ Kang, MD.,Ph.D (Seoul National Univ.)
• HH Koo, MD, Ph.D (Sungkyunkwan Univ)
• Staffs KFDA and Min. of Science & Technology