Current Status of Advanced Therapy in Japan

Regulatory aspect and trends

GBC2017 Symposium in Seoul

Teruhide Yamaguchi
Kanazawa Institute of Technology (Japan)
New Act on Advanced Therapy
- clinical research and clinical trail for development of advance therapy
## Current approved advance therapy in Japan

### Cell therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Auto/Allo</th>
<th>Company</th>
<th>Approved year</th>
<th>Approved condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>cultured epithelial cells (JACE)</td>
<td>Auto</td>
<td>J-TEC</td>
<td>2009</td>
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<td>Cultured Cartilage (JACC)</td>
<td>Auto</td>
<td>J-TEC</td>
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<td></td>
</tr>
<tr>
<td>traumatic cartilage defects and osteochondritis dissecans</td>
<td>Auto</td>
<td>J-TEC</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Mesenchymal stem cells (Temcell)</td>
<td>Allo</td>
<td>JCR</td>
<td>2015</td>
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</tr>
<tr>
<td>Skeletal myoblast sheet (HeartSheet)</td>
<td>Auto</td>
<td>Terumo</td>
<td>2015</td>
<td>Conditional and time-limited approval</td>
</tr>
</tbody>
</table>

### Gene therapy

No gene therapy products is approved for market authorization in Japan.
Background for new legislations of cell and gene therapy

The Act on the Safety of Regenerative Medicine (including not only cell therapy but also gene therapy) (2013 published, 2014 adapted)

New legislation was needed to put regenerative medicine practices (e.g. cancer immunotherapies, cosmetic surgeries) under regulatory control to enhance their safety.

The Pharmaceuticals and Medical Devices Act (PMD Act)

Revision of the Pharmaceutical Affairs Law (renamed) to accommodate cellular product characteristics

The Goal is to benefit the patients with unmet medical needs
Guidelines for Advanced Therapy in Japan

Regulation of clinical Research for advanced therapy

Cell Therapy
- Guideline for stem cell therapy clinical research (published in 2013)

Gene Therapy

Advance therapy products under Pharmaceutical Affairs Law (PAL)

For Cell Therapy Products
- Guideline for ensuring quality and safety of products from processed cell/tissues (2008)
- For autologous cells (2008)
- For allogeneic cells (2008)
- For somatic stem cells (2012)
- For iPS cells (2012)
- For ES cells (2012)

For Gene Therapy Products

As the Act on the Safety of Regenerative Medicine, the regulation of advanced therapy has changed dramatically
Regenerative Medical Regulation

Clinical Research

Governing Rule/Regulation
- The Act on the Safety of Generative Medicine
- Medical Care Act

108 clinical research protocols had been approved under the former legislation.

Under the new legislation, 73 new clinical research protocol using stem cells have been approved.

Clinical Trial for Market Authorization

Governing Rule/Regulation
- The Act on the Safety of Generative Medicine
- The Pharmaceuticals, Medical Devices Act (PMD. Act)

- 3 Products were approved, and 1 Product was conditionally approved
- No gene therapy product have been approved in Japan

According to new ACT, the regenerative products (cell and gene therapy products) will be applied as conditional and time-limited approval.

According to new ACT, all cell therapy (regenerative therapy) clinical protocol should be evaluated by governmental committee or committee on accreditation for regenerative therapy.
Regenerative Medical Regulation

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According to the new ACT, all cell therapy (regenerative therapy) clinical protocols should be evaluated by governmental committee or committee on accreditation for regenerative therapy.

According to the new ACT, 3 products were approved, and 1 product was conditionally approved. No gene therapy product has been approved in Japan.

However, many regenerative therapy protocols have been conducted without evaluation by government or IRB.

According to new ACT, the regenerative products (cell and gene therapy products) will be applied as conditional and time-limited approval.
Process for development of advance therapy medicinal products

【Process of advance therapy medicinal products】

Pharmaceutical Company and Academia

Non-clinical study

Early development

Submit the clinical trial protocol

Review for 30 days

PMDA

Phase I

Phase II

Phase III

Submission of new drug approval

Marketing

Conditional and time-limited approval

Acadia

Early development

Non-clinical study

The Committee of regenerative therapy

Clinical Research

Designation of advance therapy

Submission of cell and gene therapy clinical research protocol
Cell Therapy (Regenerative Therapy)
Many advanced therapy protocols have been initiated as clinical researches in Japan

• Muscle stem cell sheet (Heart Cell) and cultured cartilage (JACC) have been originally developed as clinical research by academia.

• During clinical research and early clinical trails for advance therapy, academia and company are struggling to collaborate the development of these products.

• Enhancing translational research for cellular and gene therapy will provide useful seeds for advance therapy.
## Current approved advance therapy in Japan

### Cell therapy

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In Japan many cell therapy products are originally developed by academia. These seeds are translated to companies.

### Gene therapy

No gene therapy products is approved for market authorization in Japan.
Pathway for clinical research of advanced therapy using cellular and gene therapy

Ministry Health Labor Welfare

Committee of Review board for regenerative therapy and advance therapy

Subcommittee for gene therapy clinical research

Committee on accreditation for regenerative therapy using low-risk cells

Submission of clinical research protocol

Academia or hospital

Committee on accreditation for regenerative therapy using cells including allogeneic cells, iPS cells or recombinant cells
Key issues of quality and safety of cell therapy products from standard and guidelines

• AS the ingredient of cell therapy products is living cell, sterilization process could not applied to these products. Therefore, it is very important to enhance the safety of cell therapy products to use raw materials free from adventitious agents.

• Serum, growth factor, and/or blood-fractionated protein should be adopted to “Standard on Biologically-derived Raw Material and the Notification” which describes the criteria for the origin of raw materials and how evaluate and test the adventitious agents such virus or PrPsc.

• Since the specification of cell therapy products may be un-enough to evaluate quality attributes of cell therapy product, the consistency should be ensured by robust control of production process. (Quality and Safety Assurance of Cell/Tissue Pharmaceuticals and Cell/Tissue-derived Medical Devices)

• Concerning to non-clinical study of cell therapy, products, due to the species difference between cell therapy product and animal, the useful and meaningful data could not be always obtained, and then early phase study should be carefully conducted in the case of un-enough non-clinical safety data.
Safety issues for cell therapy products from iPS and ES cells (concept paper for clinical research)

• Gene stability during the establishment of iPS cells. ⇒ It is desirable to analyze no-mutation of cancer-related gene (Cosmic census + Shibata list) and chromosome.

• Tumorigenicity of final product produced manufactured from iPS or ES cells and contamination of undifferentiated cells in final product. ⇒ Either in vitro abnormal growth ability or in vivo tumorigenicity test are strongly recommended, and contamination of teratoma in final products should be conducted.

• New technology including the SGN could be utilize to analyze mutation and epigenome variation during the long-term culture.
JACE Review Report by PMDA

JACE consists of autologous cultured keratinocytes, produced using Dr. Green's technique, in which keratinocytes isolated from the patient’s own skin tissue are co-cultured with irradiated 3T3-J2 cells derived from mouse embryo as a feeder layer. This product is indicated for use in patients with serious, extensive burns who do not have sufficient donor skin available for autografting and is applied to the wound surface of deep dermal (deep second-degree) or full-thickness (third-degree) burns.

A multi-center, open-label, uncontrolled clinical study was conducted in 2 patients to confirm the efficacy and safety of the product in the treatment of severe burns. As a result, epithelialization of the wounds treated with JACE was observed and there were no particular safety problems. However, due to the very limited data obtained from the clinical study, it is considered necessary to impose the following conditions for approval: surveys in all patients treated with JACE.
Approval for additional Indication of JACE; Congenital giant pigmented nevus

To examine extensive burn wounds in 14 patients by using a combination of autograft and cultured epithelial autografts developed in Japan (JACE).

Table 1. Patient Information and Results

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Cause</th>
<th>Inhalation Injury</th>
<th>% Total Body Surface Area</th>
<th>Result</th>
<th>Operation Times</th>
<th>% Cultured Epithelial Autograft Graft Take</th>
<th>Length of Stay</th>
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<td>3</td>
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<td>4</td>
<td>80</td>
<td>100</td>
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</table>

HeartSheet: Restoring Cardiac function with skeletal myoblast sheets

[Classification] Human cellular/tissue-based products 2 Human somatic stem cell processed products
[Non-proprietary name] Human (autologous) skeletal myoblast-derived cell sheet
[Brand name] HeartSheet

[Conditions for approval]
1. The applicant is required to ensure that the product is used by physicians and surgeons with adequate knowledge and experience in severe heart failure and thoracotomy at medical institutions with capacity for emergency response under a system that ensures appropriate patient control through laboratory tests, etc.
2. The applicant is required to conduct an approval condition-based post-marketing evaluation in all patients transplanted with the product during the period between the conditional and time-limited approval and reapplication for marketing approval.

[Duration of approval] 5 years

From Terumo Co.
Development of iPS cell-derived cell therapy in Japan

iPS Cell Stock for Regenerative Medicine

The building of an iPS cell stock for regenerative medicine involves the collection of cells from healthy donors with homozygous HLA (human leukocyte antigen). The aim of the stock is to hold iPS cells of guaranteed quality which can be supplied quickly to medical care institutions and research institutions in Japan and overseas when required. The project is being led by the Medical Application Promoting Office, which is part of the CiRA Research Support Division, in collaboration with Facility for iPS Cell Therapy (FiT), a CiRA cell-processing facility.
Pilot safety study of iPSC-based intervention for wet-type AMD

- This site provides an introduction to a pilot safety study on the transplantation of autologous induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) cell sheets in patients with exudative (wet-type) age-related macular degeneration (AMD).

First clinical research was conducted using RPE cell from autologous iPS cells. Next clinical research will use RPE cells from allogeneic HLA-homo iPS cells.

As there was potential risk for Genome mutations during not only establishment of iPS cells but also manufacturing of RPE from iPS cell, whole genome analysis by NGS and in vivo tumorigenicity test have been conducted according to the concept paper.
Gene therapy
<table>
<thead>
<tr>
<th>Year of Approval</th>
<th>Institute, Company</th>
<th>Target Disease</th>
<th>Gene</th>
<th>Vector/ Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>kyushu Univ. Hospital</td>
<td>Intermittent claudication</td>
<td>Fibroblast growth factor-2 (FGF-2)</td>
<td>Sendai viral vector/in vivo</td>
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<td>Jichi Medical Univ.</td>
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<td>Aromatic L-amino acid Decarboxylase (AADC)</td>
<td>Adeno associated vector/in vivo (intra-putamen)</td>
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<tr>
<td>2014</td>
<td>Jichi Medical Univ.</td>
<td>Aromatic L-amino acid Decarboxylase deficiency</td>
<td>AADC</td>
<td>Adeno associated vector type-2/in vivo (intra-striatum)</td>
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<td>2014</td>
<td>Tokyo Univ. Research Hospital</td>
<td>Glioblastoma</td>
<td>β-galactosidase (Lac-Z) as a marker</td>
<td>*Oncolytic herpes simplex virusesG47Δ in vivo (intra-tumor)</td>
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<tr>
<td>2014</td>
<td>Osaka Univ. Hospital</td>
<td>Chronic arterial occlusion (arteriosclerosis obliterans; Buerger's disease)</td>
<td>Hepatocyte Growth Factor (HGF)</td>
<td>Plasmid vector/in vivo (intra-muscular)</td>
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<td>2014</td>
<td>Okayama Univ. Hospital</td>
<td>Malignant pleural mesothelioma</td>
<td>REIC (Reduced Expression in Immortalized Cells)/Dickkopf-3 (Dkk-3)</td>
<td>Adenoviral Type 5/in vivo (intra-thoracic, intra-tumor)</td>
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<td>2014</td>
<td>Jichi Medical Univ.</td>
<td>Refractory B cell Non-Hodgkin Lymphoma</td>
<td>CD19-specific chimeric antigen receptor(CAR)</td>
<td>Retroviral vector/ex vivo (Peripheral blood mononuclear cell)</td>
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<td>----------------</td>
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<tr>
<td>2013</td>
<td>Mie Univ. Hospital</td>
<td>Esophageal cancer</td>
<td>MAGE-A4 antigen specific T cell receptor (TCR) α-chain and β-chain</td>
<td>Retroviral vector/ex vivo (syngeneic T cell)</td>
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<td>2012 ++</td>
<td>Anges-MG</td>
<td>primary lymphedema</td>
<td>Hepatocyte Growth Factor (HGF)</td>
<td>Plasmid vector/in vivo (intra-muscular)</td>
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<tr>
<td>2013</td>
<td>Mie Univ. + (multiple collaboration study, 4 institution)</td>
<td>Acute myeloid leukemia (AML) myelodysplastic syndrome</td>
<td>WT1 antigen specific T cell receptor α-chain and β-chain. siRNA gene against TCR.</td>
<td>Retroviral vector/ex vivo (Peripheral blood mononuclear cell)</td>
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<td>*Oncolytic Adenoviral Type 5, Telomelysin/in vivo (intra-tumor)</td>
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<td>—</td>
<td>Chiba Univ. Hospital</td>
<td>Malignant pleural mesothelioma</td>
<td>NK4</td>
<td>Adenoviral vector/in vivo (intra-thoracic)</td>
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<td>human cytochrome b heavy chain (CYBB)</td>
<td>Retroviral vector/ex vivo (Hematopoietic stem cell)</td>
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<td>2012</td>
<td>Tokyo Univ. Hospital</td>
<td>Prostate cancer</td>
<td>β-galactosidase (Lac-Z) as a marker</td>
<td>*Oncolytic herpes simplex viruses G47Δ in vivo (intra-tumor)</td>
</tr>
<tr>
<td>2012</td>
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<td>Retinitis pigmentos</td>
<td>Pigment epithelium-derived factor (hPEDF)</td>
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<td>2015</td>
<td>Novartis Pharma</td>
<td>Diffuse Large B cell lymphoma (DLBCL)</td>
<td>CART19 Cells</td>
<td>autologous T cell transfected by Lentivirus vector (CTL019)</td>
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<tr>
<td>2015</td>
<td>Novartis Pharma</td>
<td>Acute B cell lymphoblast</td>
<td>CART19 Cells</td>
<td>autologous T cell transfected by Lentivirus vector (CTL019)</td>
</tr>
<tr>
<td>2015</td>
<td>Astellas Pharma</td>
<td>Malignant melanoma</td>
<td>GM-CSF</td>
<td>Oncolytic virus using HSV1 (talimogene laherparepvec)</td>
</tr>
<tr>
<td>2015</td>
<td>Kagoshima Univ</td>
<td>Progressive solid cancer</td>
<td>–</td>
<td>Survivine-promoter-dependent oncolytic adenovirus (Surv.m-CRA-1)</td>
</tr>
<tr>
<td>2015</td>
<td>kyorin Pharmaceuticals</td>
<td>Malignant mesothelioma</td>
<td>Reduced Expression in Immortalized Cells / Dickkopf-3 (Dkk-3)</td>
<td>adenovirus vector (Ad5-SEGE-REIC/Dkk-3)</td>
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<tr>
<td>2015</td>
<td>Mie University + Multi-hospital trials</td>
<td>Solid tumor</td>
<td>NY-ESO-1-specific TCR-expressed T-cell / siTCR</td>
<td>Retrovirus vector (MS3II-NYES01-siTCR) / ex vivo autologous T cell</td>
</tr>
<tr>
<td>2012</td>
<td>Anges-MG</td>
<td>primary lymphedema</td>
<td>Hepatocyte Growth Factor (HGF)</td>
<td>Plasmid vector</td>
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<tr>
<td>2012</td>
<td>Astellas Pharma Inc.</td>
<td>Cytomegalovirus</td>
<td>antigen of cytomegalovirus (2 kind)</td>
<td>Plasmid vector</td>
</tr>
</tbody>
</table>

Red: These clinical trials had been started as clinical research. Many clinical research will be expected to develop the clinical trial as a translational research.
Trend of gene therapy in Japan

• **Oncolytic virus therapy:** many oncolytic virus protocols have conducted as clinical research and clinical trial. Recently, OV therapy are considered to induce not only tumor-lysis but also immune reaction against tumor as a bystander effect.

• **CART and TCR-CTL therapy:** New trend of cancer therapy using these genetically modified T-cells are expected to cutting edge therapy.

• **New technology:** Genome editing technologies are expected as useful tools for repairing the abnormal gene, but it is difficult to exclude modification of undesired gene by off-target effects.
Guideline for gene therapy

- Guideline for gene therapy clinical research (revised 2015)
- Guideline for ensuring safety and quality of gene therapy products (revised 2013, under revision)

ICH
- ICH Considerations - General Principles to Address Virus and Vector Shedding
- ICH Considerations - Oncolytic Viruses
- ICH Considerations - Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors

IPRF GTDG
- Reflection paper: Biodistribution of gene therapy products
Oncolytic virus (Oncolytic Immunotherapy)

- Replication-competent virus and recombinant virus specific in tumor cells but not normal cells; Cancer virus therapy
- Cancer immunotherapy as a bystander effect of oncolytic virus

**Conventional cancer gene therapy**

Viral vector (non-replication)

Lysis only occurs in infected cells

**Cancer viral therapy**

Oncolytic (replication) virus (OV)

OV proliferate in infected cells and re-infect into other cells, then cause the cancer immune response

Normal cells  Cancer cells  Infected cells
### Development of oncolytic virus in Japan

<table>
<thead>
<tr>
<th>Company/Univ</th>
<th>Name</th>
<th>Gene</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagoya Univ</td>
<td>attenuated HSV-1; HF-10 TBI- 1401</td>
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<td>Recurrent Breast Cancer, Recurrent Head and Neck Cancer</td>
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<td>Mie Univ</td>
<td>attenuated HSV-1; HF-10</td>
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<td>Solid tumor</td>
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<td>Tokyo Univ</td>
<td>Recom.HSV-; G47Δ</td>
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<td>Prostate Cancer, Progressive glioblastoma,</td>
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<td>hTERT Promotor</td>
<td>Head and Neck Cancer, Lung Cancer, esophageal neoplasm</td>
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<td>Oncolysis BioPharma</td>
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<td>Takara Bio</td>
<td>attenuated HSV-1; HF-10</td>
<td></td>
<td>Head and Neck Cancer, Malignant Melanoma,</td>
</tr>
<tr>
<td>Tokyo Univ</td>
<td>Recom.HSV-; G47Δ</td>
<td></td>
<td>Progressive Glioblastoma</td>
</tr>
<tr>
<td>Kagoshima Univ</td>
<td>recom. Adenovirus; Surv.m-CRP-1</td>
<td>Survivine Promoter</td>
<td>osteosarcoma</td>
</tr>
<tr>
<td>Astellas-Amgen BioPharma</td>
<td>HSV1 (talimogene laherparepvec)</td>
<td>GM-CSF</td>
<td>Malignant Melanoma</td>
</tr>
</tbody>
</table>
CART cell and TCR-CTL

- Tumor-specific cytotoxic T cell gene therapies are developed not only by pharmaceutical company but also by academia.
- CART clinical trials (CTL019) are expected to become new tools to treat patients with intractable cancer, because of their high response rate.

- During CART(CTL019) clinical trials, several severe adverse effects were observed such as cytokine storm, cerebral edema, or swelling of the brain.
- The sponsor should correspond these adverse effects during the clinical studies.

Whereas from their high responsibility, CART cell therapy will be expected to provide breakthrough therapy for many cancers, it should be very important to control the severe adverse effects.
New technology such as gene editing have impact on regulation
Gene therapy clinical study using gene-editing technology  
(clinicaltrial.gov data 2017.3.15)
Comparison of gene-editing gene therapy with traditional gene therapy

**Traditional gene therapy**

Chromosome  Target gene (abnormal gene)

Gene transfer

Retro-, lentivirus

AAV

Out-of

Chromosome

Target gene (abnormal gene)

Normal gene

**Gene therapy using gene-editing**

Chromosome  Target gene (abnormal gene)

Gene cutting by CRISPR/CAS9

Non-homologous repair

Donor DNA

homologous recombination

**Knock-out of abnormal gene**

Repairing abnormal gene

- Gene addition or complement
- No change of abnormal gene
- Difficult to control the insertion site
  - Risk of insertional mutagenesis
- Difficult to control the expression of transgene

- Repair or knockout of abnormal/target gene (for congenital disease)
- Repair the abnormal gene
- Control the insertion site of target gene
- Control the expression of target gene

**Ultimate gene therapy for congenital chromosomal diseases**
**Risk of off-target genome editing (off target mutagenesis)**
<table>
<thead>
<tr>
<th>Phase</th>
<th>Title</th>
<th>Status</th>
<th>Method</th>
<th>Target</th>
<th>First received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>Autologous T cells genetically modified at the CCR5 gene by ZFN SB-728 for HIV</td>
<td>Completed</td>
<td>ZFN</td>
<td>ex vivo (T cell)</td>
<td>HIV 4-Feb-09</td>
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<tr>
<td>Phase 1</td>
<td>Phase I dose escalation study of autologous T cells genetically modified at the CCR5 gene by ZFN in HIV-infected patients</td>
<td>Completed</td>
<td>ZFN</td>
<td>ex vivo (T cell)</td>
<td>HIV 6-Jan-10</td>
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<tr>
<td>Phase 1/2</td>
<td>Study of autologous T cells genetically modified at the CCR5 gene by ZFN in HIV-infected subjects</td>
<td>Completed</td>
<td>ZFN</td>
<td>ex vivo (T cell)</td>
<td>HIV 29-Nov-10</td>
</tr>
<tr>
<td>Phase 1/2</td>
<td>Dose escalation study of cyclophosphamide in HIV-infected subjects on HAART receiving SB-728-T</td>
<td>Active</td>
<td>ZFN</td>
<td>ex vivo (T cell)</td>
<td>HIV 1-Mar-12</td>
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<tr>
<td>Phase 1/2</td>
<td>Repeat doses of SB728mR-T after cyclophosphamide conditioning in HIV infected subjects on HAART</td>
<td>Active</td>
<td>ZFN</td>
<td>ex vivo (T cell)</td>
<td>HIV 22-Aug-14</td>
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<tr>
<td>Phase 1</td>
<td>Safety study of ZFN CCR5-modified hematopoietic stem/progenitor cells in HIV-infected patients</td>
<td>Recruiting</td>
<td>ZFN</td>
<td>ex vivo (HSC)</td>
<td>HIV 16-Mar-15</td>
</tr>
<tr>
<td>Phase 1</td>
<td>A Phase I Study of T-Cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases SB-728mR in HIV-Infected Patients</td>
<td>Recruiting</td>
<td>ZFN</td>
<td>ex vivo (T cell)</td>
<td>HIV 24-Feb-15</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Ascending Dose Study of Genome Editing by ZFN Therapeutic SB-FIX in Subjects With Severe Hemophilia B</td>
<td>Recruiting</td>
<td>ZFN</td>
<td>in vivo</td>
<td>Hemophilia B 24-Feb-16</td>
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<tr>
<td>Phase 1</td>
<td>Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-318 in Subjects With MPS I</td>
<td>Not yet recruiting</td>
<td>ZFN</td>
<td>in vivo</td>
<td>MPS-I 29-Feb-16</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Dose Escalation Study to Evaluate the Safety, Tolerability and Biological Activity of a Single Dose of UCART19 in Patients With Relapsed / Refractory (R/R) B-cell Acute Lymphoblastic Leukemia (ALL) and Chronic Lymphocytic Leukemia (CLL) (CALM)</td>
<td>Recruiting</td>
<td>TALEN</td>
<td>ex vivo (T-cell:UCART19)</td>
<td>cancer 7-Mar-16</td>
</tr>
<tr>
<td>Phase 1</td>
<td>PD-1 Knockout Engineered T Cells for Metastatic Non-small Cell Lung Cancer</td>
<td>Recruiting</td>
<td>CRISPR</td>
<td>ex vivo(T cell)</td>
<td>cancer 30-May-16</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Study of Molecular-targeted Therapy Using Zinc Finger Nuclease in Cervical Precancerous Lesions</td>
<td>Not yet recruiting</td>
<td>ZFN</td>
<td>in vivo</td>
<td>HPV 1-Jun-16</td>
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<tr>
<td>Phase 1</td>
<td>Study of UCART19 in Pediatric Patients With Relapsed/Refractory B Acute Lymphoblastic Leukemia (PALL)</td>
<td>Recruiting</td>
<td>TALEN</td>
<td>ex vivo (T-cell: UCART19)</td>
<td>cancer 16-Jun-16</td>
</tr>
<tr>
<td>Phase 1</td>
<td>PD-1 Knockout Engineered T Cells for Muscle-invasive Bladder Cancer</td>
<td>Not yet recruiting</td>
<td>CRISPR</td>
<td>ex vivo(T cell)</td>
<td>cancer 1-Aug-16</td>
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<tr>
<td>Phase 1</td>
<td>PD-1 Knockout Engineered T Cells for Metastatic Renal Cell Carcinoma</td>
<td>Not yet recruiting</td>
<td>CRISPR</td>
<td>ex vivo(T cell)</td>
<td>cancer 11-Aug-16</td>
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<tr>
<td>Phase 1</td>
<td>PD-1 Knockout Engineered T Cells for Castration Resistant Prostate Cancer</td>
<td>Not yet recruiting</td>
<td>CRISPR</td>
<td>ex vivo(T cell)</td>
<td>cancer 11-Aug-16</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Ascending Dose Study of Genome Editing by the ZFN Therapeutic SB-913 in Subjects With MPS II</td>
<td>Not yet recruiting</td>
<td>ZFN</td>
<td>in vivo</td>
<td>MPS II 13-Jan-17</td>
</tr>
<tr>
<td>Phase 1</td>
<td>PD-1 Knockout EBV-CTLs for Advanced Stage Epstein-Barr Virus (EBV) Associated Malignancies</td>
<td>Not yet recruiting</td>
<td>CRISPR</td>
<td>ex vivo(T cell)</td>
<td>cancer 22-Jan-17</td>
</tr>
<tr>
<td>Phase 1</td>
<td>A Safety and Efficacy Study of TALEN and CRISPR/Cas9 in the Treatment of HPV-related Cervical Intraepithelial Neoplasia</td>
<td>Not yet recruiting</td>
<td>TALEN, CRISPR</td>
<td>in vivo</td>
<td>cancer 12-Feb-17</td>
</tr>
</tbody>
</table>

Red: Ongoing or Plan in 2015; Yellow: Ongoing  Blue: Plan in 2017
Gene editing of human fertilized eggs using CRISPR/Cas9

- Gene editing for human fertilized eggs
  (Protein Cell 2015, 6(5):363–372)
  model study for the treatment of βthalassemia
  cutting of β-globulin gene and introduce the mutation
  
  Cas9 mRNA, gRNA, GFP mRNA and oligo donor DNA were micro-injected

- Gene editing for human fertilized eggs
  (J. Assisted Reproduction and Genetics 2016, 33; 581–588)
  knock-out of CCR5 gene

  Cas9 mRNA, gRNA and donor oligo DNA were micro-injected

- Application of gene editing to fertilized human egg
  (Mol Genet Genomics: published online March 2017)
  βglobulin gene, G6PD gene

  Cas9 protein、Oligo-sgRNA and donor oligo DNA were micro-injected.
Definitions of Somatic Cell Therapy and Gene Therapy

- **Definition of Gene Therapy**
  - Gene therapy is a medical intervention based on modification of the genetic material of living cells (FDA)
  - Gene therapy is a medical treatment based on administration of gene or gene-transfected cells to patient (Japan)
  - Gene therapy medicinal products generally consist of a vector or delivery formulation/system containing a genetic construct engineered to express a specific therapeutic sequence or protein responsible for the regulation, repair, addition or deletion of a genetic sequence (EMA)
  - (Many guideline make a definition of gene therapy as transduce of a recombinant DNA materials to patients)

- Gene-knockout or gene deletion can be conducted by gene editing technology using protein or mRNA for CRISPR/CAS9 and guide RNA alone. From current guidelines, it may be possible to decide these gene-editing treatment will be out-of-focus of gene therapy.

- Even though using protein or mRNA for CRISPR/CAS9, there is a risk to cause genome editing of other than target gene by off-target effect.
In Japan, gene therapy guideline are now under revision, and the revised guideline will be published by the end of 2017 or early 2018.

- The revised guideline will cover the cutting-edge technology such as gene-editing.
- We believe EMA also is considering the revision of their gene therapy guideline.
- It is desirable to harmonize how to deal with the gene-editing technology as gene therapy.
In future

MHLW provide new pathway to enhance the development of cutting-edge-therapy to life-threatening diseases: Designation of “Sakigake” (like breakthrough therapy)
The Government will promote a package of measures, including the creation of a “priority examination designation system” that would halve the approval examination period before commercialization (from 12 months to 6 months) for drugs identified in the early clinical trial phase as being likely to be remarkably effective. Through these measures, the Government will aim to ensure that Japan leads the world in commercializing innovative drugs, medical devices, regenerative medicine products, and other items targeting fatal diseases (including orphan cancers, intractable diseases, and other serious conditions) for which effective remedies do not currently exist.
# Assignments on regenerative medical products

<table>
<thead>
<tr>
<th>Date</th>
<th>Name</th>
<th>indication and treatment</th>
<th>Name of applicant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016/2/10</td>
<td>STR01 autologous bone-marrow-derived MSC</td>
<td>cultured MSC for neurological disorder and/or dysfunction due to spinal cord injury</td>
<td>NIPRO Medical Co., Ltd. /Sapporo Medical Univ.</td>
</tr>
<tr>
<td>2016/2/10</td>
<td>G47Δ(oncolytic virus)</td>
<td>restrictive replicative recombinant herpes virus1- for malignant brain tumor (Glioma)</td>
<td>Daiichi Sankyo Co., Ltd. / Institute of Medical Sciences, University of Tokyo</td>
</tr>
<tr>
<td>2016/2/10</td>
<td>autologous heart stem cell</td>
<td>cultured heart stem cell for congenital children heart disease (functional single ventricular disease)</td>
<td>Japan Regenerative Medicine Co., Ltd. /Okayama University</td>
</tr>
<tr>
<td>2016/2/28</td>
<td>CLS2702C/D (cell sheet derived from oral mucosa)</td>
<td>cultured epithelial cell sheet for stricturestenosis derived from surgery for esophageal cancer</td>
<td>CellSeed Co.Ltd.</td>
</tr>
<tr>
<td>2016/2/28</td>
<td>dopamine-produce progenitor cell derived from iPS cell</td>
<td>dopamine-produce progenitor cells differentiated from allogeneic iPS cells for Parkinson disease</td>
<td>Sumitomo Dainippon Pharm. Kyoto Univ</td>
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<tr>
<td>2016/2/28</td>
<td>allogeneic bone-marrow-derived MSC</td>
<td>cultured allogeneic bone-marrow-derived MSC for the acute-phase cerebral infarction (after 18-36h)</td>
<td>Healios Co.Ltd.</td>
</tr>
</tbody>
</table>

Designation of SAKIGAKE (like breakthrough therapy)
【Review Process for New Drug】

1. **Priority consultation**
2. **Pre-review**
3. **Priority review**
4. **Partner for review**

【Review Process for Assessment Products】

- Drug strategy consultation
- **Assessment**
- Non-clinical, Clinical study

- Phase I/II
- **Clinical Consultation**
- Phase III
- **Review for market authorization**
- Insurance for medical expenses
- Market

Early marketing of breakthrough products

※ In some case, the sponsor can submit the clinical data after the submission.

【Priority Review】

- Drug strategy consultation
- **Clinical Consultation**
- Phase III
- **Review for market authorization**
- Insurance for medical expenses
- Market
Summary

- Many advanced therapy products have been developed at first as clinical research by academia in Japan.
- Cell and gene therapy clinical researches may play an important role on translational research to bring up seeds for advanced therapy.
- New Act for regenerative therapy carries out to enhance the safety of regenerative therapy and its rapid development.
- To develop oncolytic virus therapy and CART therapy, many clinical studies are ongoing and provide promising results. Gene-editing technology provide have a possibility of ultimate gene therapy, but there are remaining risk as off-target effects. Some gene editing technology are covered by the definition of gene therapy. We are now trying to revise the guideline to include these technology.
- Designation of “Sakigake” will be expected to progress a new therapy of advance therapy products for life-treating diseases.
Thank you for your attention