Current Status of Advanced Therapy in Japan

Regulatory aspect and trends

GBC2017 Symposium in Seoul

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New Act on Advanced Therapy

- clinical research and clinical trail for development of advance therapy

Current approved advance therapy in Japan

Cell therapy

	Indication	Auto／Allo	Company	Approved year	Approved condition
cultured epithelial cells (JACE)	Severe burn	Auto	J-TEC	2009	
Cultured Cartilage (JACC)	traumatic cartilage defects and osteochondritis dissecans	Auto	J-TEC	2009	
Mesenchymal stem cells (Temcell)	GVHD	Allo	JCR	2015	
Skeletal myoblast sheet (HeartSheet)	severe heart failure	Auto	Terumo	2015	Conditional and time-limited approval

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 advance therapy

Cell Therapy

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

Gene Therapy

Guideline for gene therapy clinical research (1995, revision 2015)

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

Guideline for ensuring quality and safety of gene therapy products (1995, revision 2013)

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

Clinical Research

Governing Rule/Regulation

- The Act on the Safety of Regenerative Medicine
- Medical Care Act

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

108 clinical research protocols were approved under the **former legislation**.

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

Devices Act (PMD. Act)

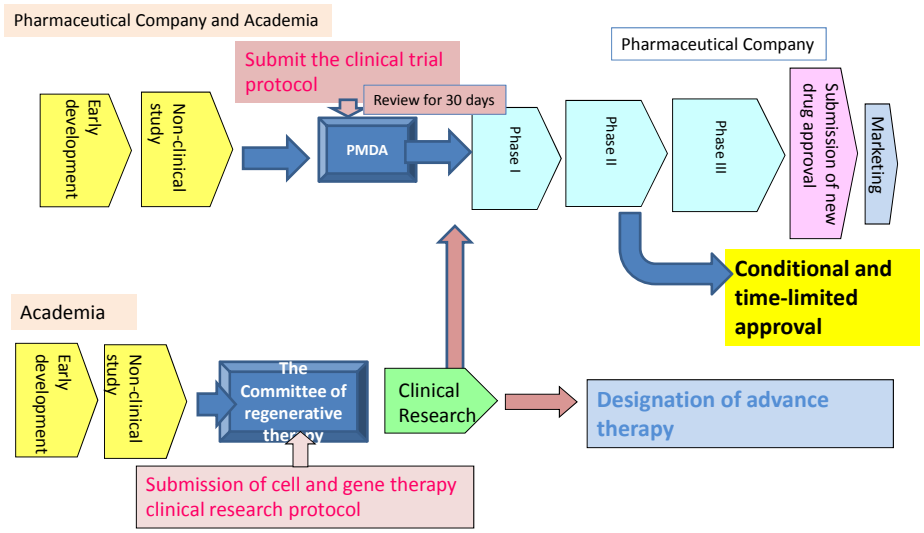
- 3 Products were approved, and 1 Product was conditionally approved
- No gene therapy product have been approved in Japan

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

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

Process for development of advance therapy medicinal products

【Process of advance therapy medicinal products】



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

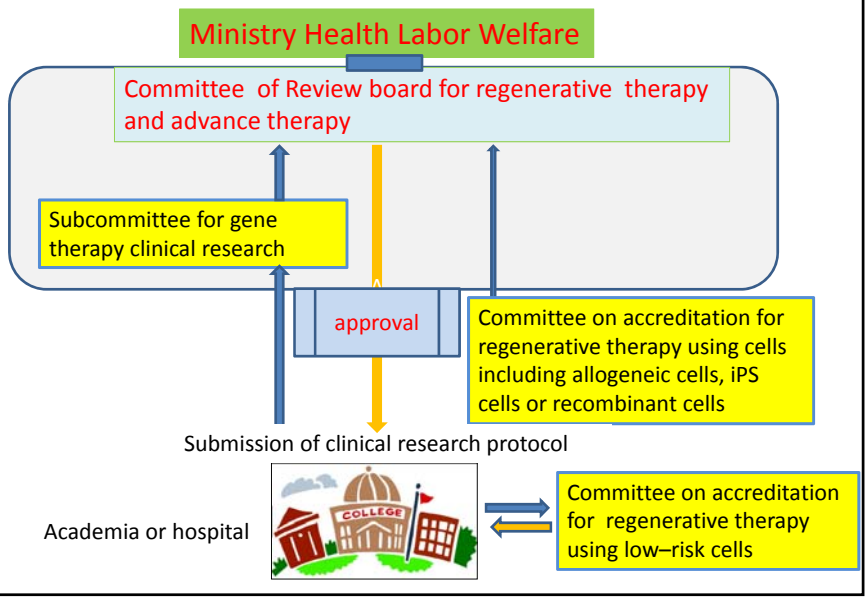
	Indication	Auto／	Company	Approve ar	Approved condition
cultured epithelial cell (JACE)	Severe burn			09	
Cultured Cartilage (JACC)	traumati… and osteochondritis dissecans			09	
Mesenchymal stem cells (Temcell)	GVHD	Allo	JCR	2015	
Skeletal myoblast sheet (HeartSheet)	severe heart failure	Auto	Terumo	2015	Conditional and time-limited approval

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



Key issues of quality and safety of cell therapy products from standard and guidelines

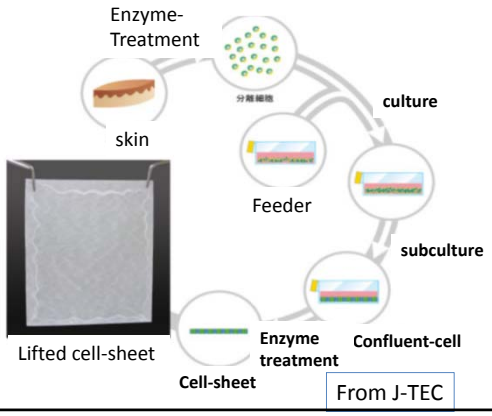
- AS the ingredient of cell therapy products is living cell, sterilization process could not applied to these products. Therefore, it is very important to enhance the safety of cell therapy products to use raw materials free from adventitious agents
- Serum, growth factor, and/or blood-fractionated protein 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.



From J-TEC

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

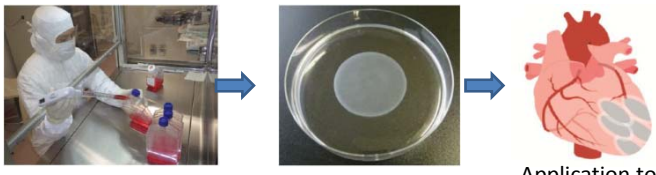
No.	Sex	Age	Cause	Inhalation Injury	% Total Body Surface Area	Result	Operation Times	% Cultured Epithelial Autograft Graft Take	Length of Stay
1	Male	46	Flame	–	54	Living	4	90	120
2	Male	75	Flame	+	58	Deceased	3	–	
3	Male	62	Chemical	–	70	Living	2	80	71
4	Male	60	Flame	+	40	Living	3	80	138
5	Female	20	Flame	+	37	Living	4	70	82
6	Female	45	Flame	+	45	Living	7	90	95
7	Male	58	Flame	+	45	Living	5	70	126
8	Female	85	Scald	–	64	Living	6	80	114
9	Male	63	Flame	+	40.5	Living	4	95	116
10	Male	55	Flame	+	48	Deceased	3	—	
11	Male	46	Flame	–	37	Living	3	50	74
12	Male	56	Flame	+	31.5	Living	4	30	147
13	Female	54	Flame	–	33	Living	4	80	76
14	Female	64	Flame	+	35.5	Living	4	80	100

Hayashi et al: Changes in the Dermal Structure during cultured Epidermal Autograft Engraftment Process. www.PRSGlobalOpen.com p.1-7 (2016)

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



Skeletal myoblast sheet

Application to patient heart

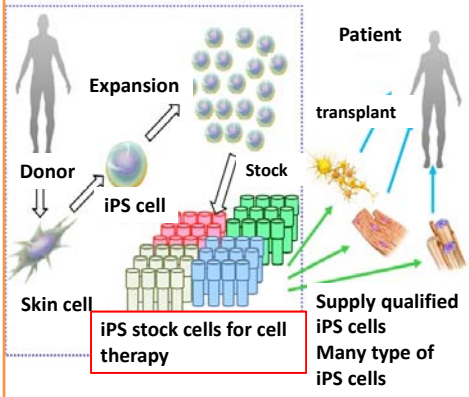
From Terumo Co.

Development of iPS cell-derived cell therapy in Japan

From Kyoto Univ. CiRA Institute

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.



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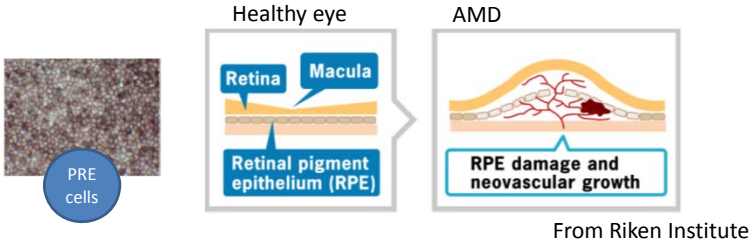
Pilot safety study of iPSC-based intervention for wet-type AMD

- 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).



From Riken Institute

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

List of Gene Therapy Clinical Study Protocols Approved in Japan from 2012

Year of Approval	Institute, Company	Target Disease	Gene	Vector/ Methods
2014	kyushu Univ. Hospital	Intermittent claudication	Fibroblast growth factor-2 （FGF-2)	Sendai viral vector／in vivo
2014	Jichi Medical Univ.	Parkinson's disease	Aromatic L-amino acid Decarboxylase (AADC)	Adeno associated vector／in vivo (intra-putamen)
2014	Jichi Medical Univ.	Aromatic L-amino acid Decarboxylase deficiency	AADC	Adeno associated vector type-2／in vivo (intra-striatum)
2014	Tokyo Univ. Research Hospital	Glioblastoma	β-galactosidase (Lac-Z) as a marker	*Oncolytic herpes simplex virusesG47Δ in vivo (intra-tumor)
2014	Osaka Univ. Hospital	Chronic arterial occlusion (arteriosclerosis obliterans; Buerger's disease)	Hepatocyte Growth Factor （HGF)	Plasmid vector／in vivo （intra-muscular)
2014	Okayama Univ. Hospital	Malignant pleural mesothelioma	REIC（Reduced Expression in Immortalized Cells) /Dickkopf-3（Dkk-3)	Adenoviral Type 5／in vivo (intra-thoracic、intra-tumor)
2014	Jichi Medical Univ.	Refractory B cell Non-Hodgkin Lymphoma	CD19-specific chimeric antigen receptor(CAR)	Retroviral vector/ex vivo (Peripheral blood mononuclear cell)
2013	Tokyo Univ. Research Hospital	olfactory esthesioneuroblastoma	β-galactosidase (Lac-Z) as a marker	*Oncolytic herpes simplex virusesG47Δ in vivo(intra-tumor)
2013	Tokyo Univ. Research Hospital	Glioblastoma	β-galactosidase (Lac-Z) as a marker	*Oncolytic herpes simplex virusesG47Δ in vivo (intra-tumor)

List of Gene Therapy Clinical Study Protocols Approved in Japan from 2012

Year of Approval	Institute, Company	Target Disease	Gene	Vector/ Methods
2013	Mie Univ. Hospital	Esophageal cancer	MAGE-A4 antigen specific T cell receptor (TCR) α-chain and β-chain	Retroviral vector/ex vivo (syngeneic T cell)
2012 ++	Anges-MG	primary lymphedema	Hepatocyte Growth Factor （HGF)	Plasmid vector／in vivo (intra-muscular)
2013	Mie Univ. + (multiple collaboration study, 4 institution)	Acute myeloid leukemia (AML) myelodysplastic syndrome	WT1 antigen specific T cell receptor α-chain and β-chain. siRNA gene against TCR.	Retroviral vector/ex vivo (Peripheral blood mononuclear cell)
2012	Okayama Univ. Hospital	cervicofacial・thoracic malignant tumor	-	*Oncolytic Adenoviral Type 5, Telomelysin/in vivo (intra-tumor)
—	Chiba Univ. Hospital	Malignant pleural mesothelioma	NK4	Adenoviral vector/ in vivo (intra-thoracic)
2012	National Center of Child Health and Development	X-linked （X-Chronic granulomatous disease)	human cytochrome b heavy chain（CYBB)	Retroviral vector/ex vivo （Hematopoietic stem cell)
2012	Tokyo Univ. Hospital	Prostate cancer	β-galactosidase (Lac-Z) as a marker	*Oncolytic herpes simplex virusesG47Δ in vivo (intra-tumor)
2012	kyushu Unuv. Hospital	Retinitis pigmentos	Pigment epithelium-derived factor（hPEDF)	simian immunodeficiency viral vector (SIV)／in vivo (subretinal injection)
2013	Chiba Univ. Hospital	familial LCAT deficiency	Lecithin cholesterol acyltransderase（LCAT)	Retroviral vector／ex vivo (pre-adipocyte)

List of Gene Therapy Clinical Study Protocols Approved in Japan from 2012

Year of Approval	Institute, Company	Target Disease	Gene	Vector/ Methods	Condition
2015	Novartis Pharma	Diffuse Large B cell lymphoma（DLBCL）	CART19 Cells	autologous T cell transfected by Lentivirus vector(CTL019)	Phase II
2015	Novartis Pharma	Acute B cell lymphoblast	CART19 Cells	autologous T cell transfected by Lentivirus vector(CTL019)	Phase II
2015	Astellas Pharma	Malignant melanoma	GM-CSF	Oncolytic virus using HSV1（talimogene laherparepvec）	Phase I
2015	Kagoshima Univ	Progressive solid cancer	–	Survivine-promoter-dependent oncolytic adenovirus （Surv.m-CRA-1）	Phase I
2015	kyorin Pharmceuticals	Malignant mesothelioma	Reduced Expression in Immortalized Cells）/Dickkopf-3（Dkk-3）	adenovirus vector（Ad5-SGE-REIC/Dkk-3）／	Phase I/II
2015	Mie University + Multi-hospital trials	Solid tumor	NY-ESO-1-specific TCR-expressed T-cell 、siTCR	Retrovirus vector (MS3II-NYES01-siTCR)／ex vivo autologous T cell	on going
2012	Anges-MG	primary lymphedema	Hepatocyte Growth Factor（HGF）	Plasmid vector／	[Terminated]
2012	Astellas pharma Inc.	Cytomegalovirus	antigen of cytomegalovirus (2 kind)	Plasmid vector	[Terminated]

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

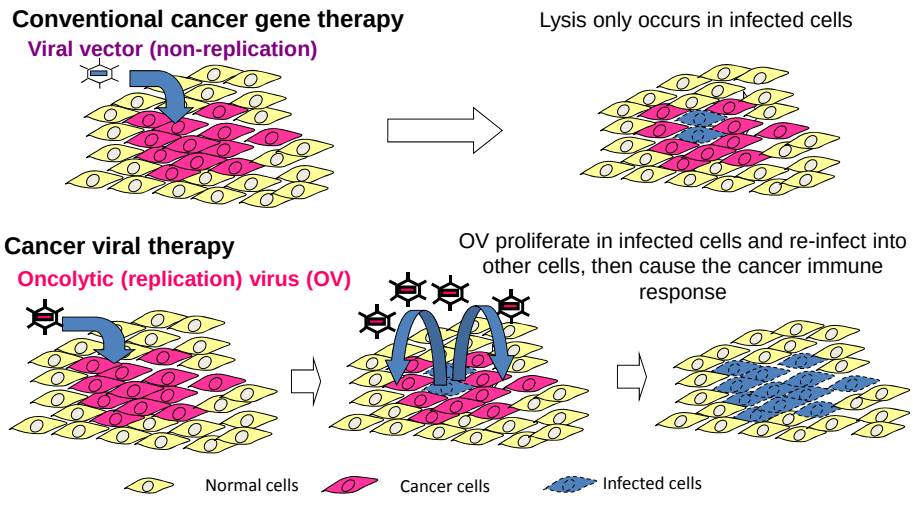
- ICH Considerations - General Principles to Address Virus and Vector Shedding
- ICH Considerations - Oncolytic Viruses
- ICH Considerations - Non-Clinical testing for Inadvertent Germline transmission of Gene Transfer Vectors

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



Development of oncolytic virus in Japan

	Company/Univ	Name	Gene	Indication
Clinical Research	Nagoya Univ	attenuated HSV-1; HF-10 TBI- 1401		Recurrent Brest Cancer, Recurrent Head and Neck Cancer
	Mie Univ	attenuated HSV-1; HF-10		Solid tumor
	Tokyo Univ	Recom.HSV-; G47Δ		Prostate Cancer, Progressive glioblastoma,
	Okayama Univ	Recom. Adenovirus; Telomelysin (OBP-301)	hTERT Promotor	Head and Neck Cancer, Lung Cancer, esophageal neoplasm
Clinical Trial	Oncolysis BioPharma	Recom. Adenovirus; Telomelysin (OBP-301)	hTERT Promotor	Progressive Solid Cancer
	Takara Bio	attenuated HSV-1; HF-10		Head and Neck Cancer, Malignant Melanoma,
	Tokyo Univ	Recom.HSV-; G47Δ		Progressive Glioblastoma
	Kagoshima Univ	recom. Adenovirus; Surv.m-CRP-1	Survivine Promoter	osteosarcoma
	Astellas-Amgen BioPharma	HSV1（talimogene laherparepvec）	GM-CSF	Malignant Melanoma

CART cell and TCR-CTL

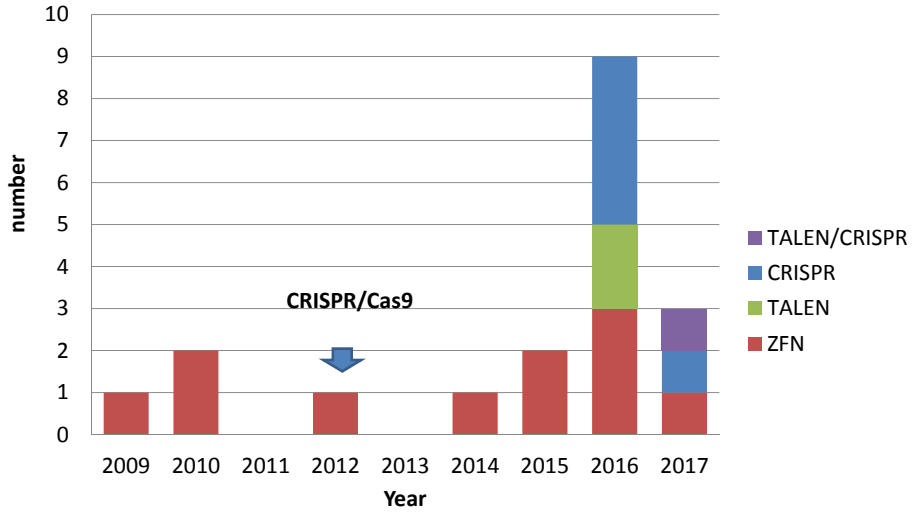
- Tumor-specific cytotoxic T cell gene therapies are developed not only by pharmaceutical company but also by academia.
- CART clinical trials (CTL019) are expected to become new tools to treat patients with intractable cancer, because of their high response rate.

- 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.

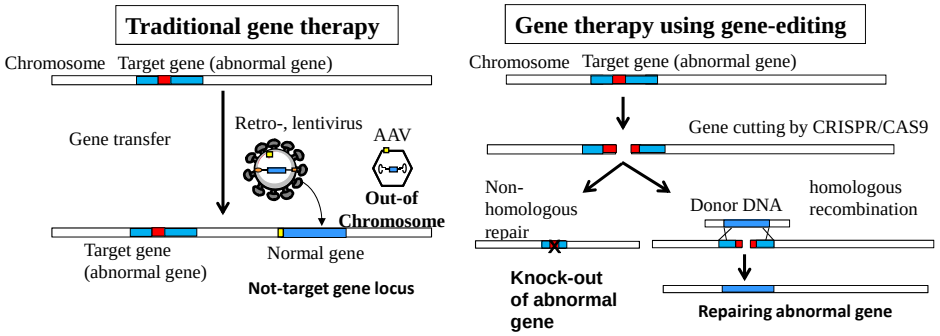
Whereas from their high responsibility, CART cell therapy will be expected to provide breakthrough therapy for many cancers, it should be very important to control the severe adverse effects.

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



- 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)

Clinical protocol using gene-editing in Clinicaltrial.gov

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

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 βtalathemia
  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 105 containing a genetic construct engineered to express a specific therapeutic sequence or protein 106 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.

- **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-threating diseases : Designation of “Sakigake” (like breakthrough therapy)

Sakigake-designation

Japan Revitalization Strategy Revised in 2014
– Japan's challenge for the future –

June 24th, 2014

Assessment Criteria

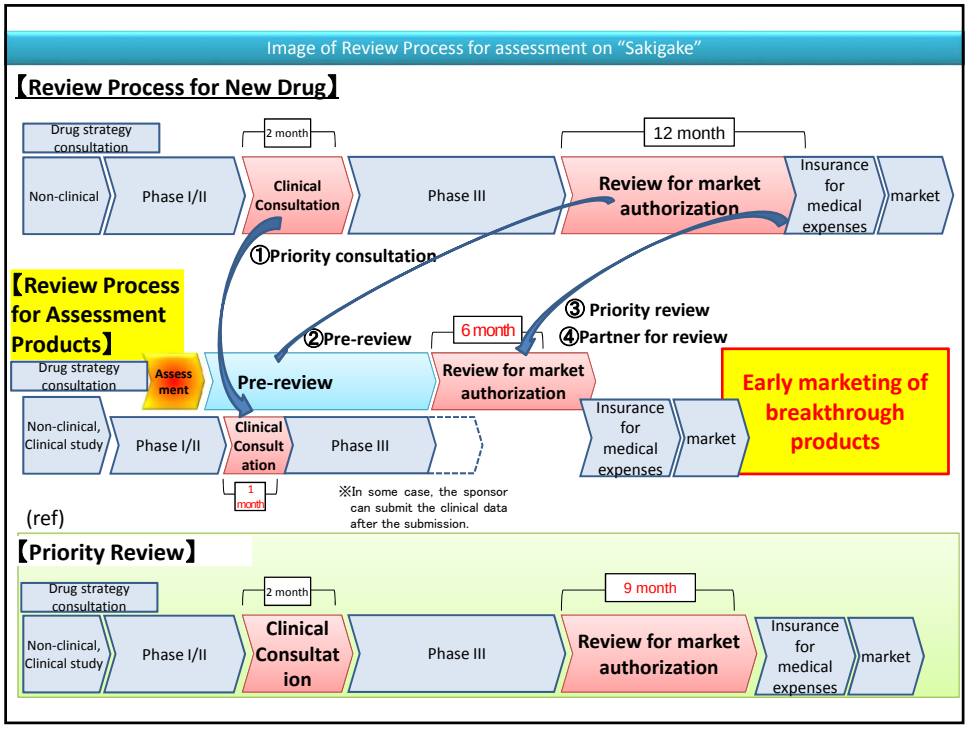
Section 2 Three Action Plans II. Strategic Market Creation Plan
Theme 1: Extending the nation's "healthy life expectancy"
(3) Specific new measures to be taken
v) Others
2) Promoting world-leading commercialization of innovative drugs and medical devices
("Strategy of SAKIGAKE as a Package")

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

Date	Name	indication and treatment	Name of applicant
2016/2/10	STR01autologous bone-marrow-derived MSC	cultured MSC for neurological disorder and/or dysfunction due to spinal cord injury	NIPRO Medical Co., Ltd. /Sapporo Medical Univ.
2016/2/10	G47Δ(oncolytic virus)	restrictive replicative recombinant herpes virus1- for malignant brain tumor (Glioma)	Daiichi Sankyo Co., Ltd. / Institute of Medical Sciences, University of Tokyo
2016/2/10	autologous heart stem cell	cultured heart stem cell for congenital children heart disease (functional single ventricular disease)	Japan Regenerative Medicine Co., Ltd. /Okayama University
2016/2/28	CLS2702C/D (cell sheet derived from oral mucosa)	cultured epithelial cell sheet for stricturestenosis derived from surgery for esophageal cancer	CellSeed Co.Ltd.
2016/2/28	dopamine-produce progenitor cell derived from iPS cell	dopamine-produce progenitor cells differentiated from allogeneic iPS cells for Parkinson disease	Sumitomo Dainippon Pharm. Kyoto Univ
2016/2/28	allogeneic bone-marrow-derived MSC	cultured allogeneic bone-marrow-derived MSC for the acute-phase cerebral infarction (after 18-36h)	Healios Co.Ltd.

Designation of SAKIGAKE (like breakthrough therapy)



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.