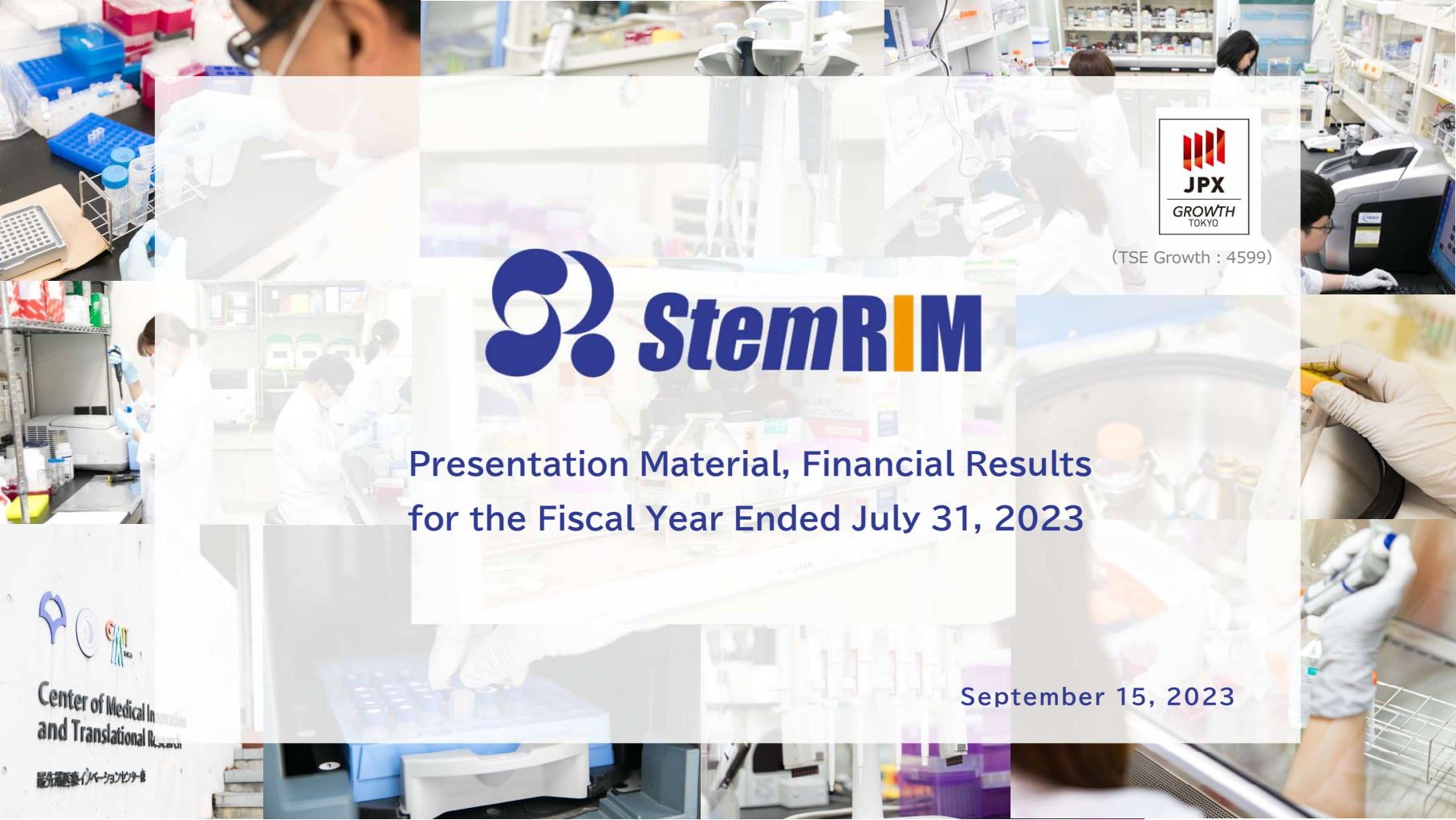


(TSE Growth : 4599)

StemRIM

Presentation Material, Financial Results for the Fiscal Year Ended July 31, 2023

September 15, 2023

StemRIM

Stem cell Regeneration-Inducing Medicine

Overcoming Refractory Diseases by "Regeneration-Inducing Medicine™"

StemRIM is a biotech company aiming to develop **"Regeneration-Inducing Medicine™ "** a next generation of regenerative medicine.

"Regeneration-Inducing Medicine™" is new class of medicine that induces functional regeneration of damaged tissues or organs by maximizing the patient's innate ability of tissue repairing.

We aim for a future in which **"Regeneration-Inducing Medicine™"** helps patients all over the world suffering from refractory diseases.

Mode of Action of “Regeneration-Inducing Medicine™”

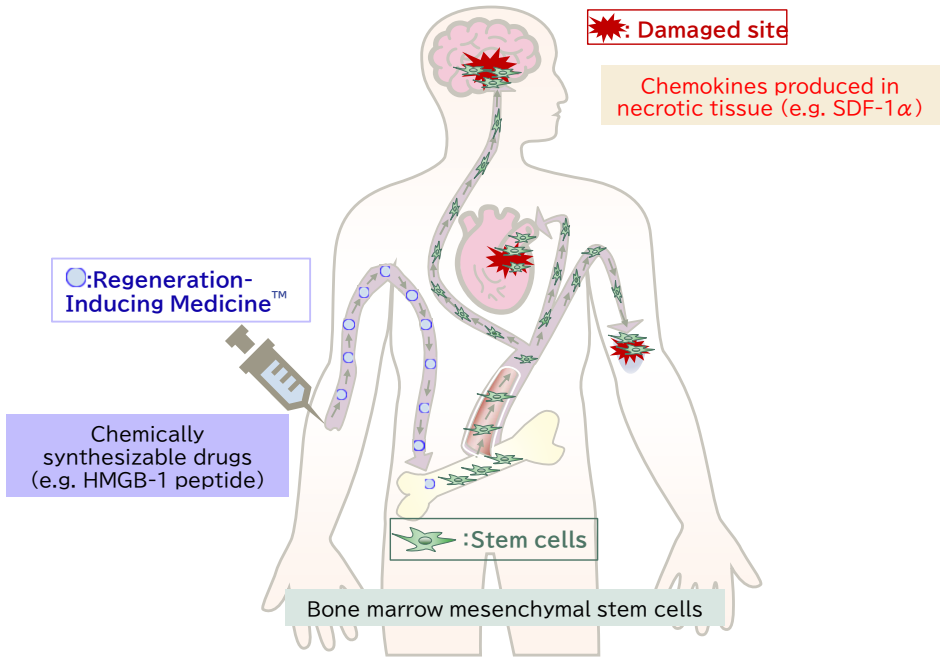
Bone marrow mesenchymal stem cells mobilized into the peripheral blood stream induce the tissue regeneration.

Administration of “Regeneration-Inducing Medicine™”

Mobilizing Stem cells from bone marrow into the blood stream

Stem cells accumulation in the damaged tissues

Functional tissue regeneration



Agenda

1 Summary of Financial Results for the Fiscal Year Ended July 31, 2023

2 Summary of Business Activities for the Fiscal Year Ended July 31, 2023

3 Future Growth Strategies

1. Summary of Financial Results for the Fiscal Year Ended July 31, 2023

Statements of Income

(Millions of yen)

	FY2021 (Ended July 31,2021)	FY2022 (Ended July 31,2022)	FY2023 (Ended July 31,2023)	Function (FY on FY)
Operating revenue	1,400	22	2,350	+2,327
R&D expenses	1,523	1,421	1,567	+145
SGA expenses	469	582	640	+57
Total operating expenses	1,993	2,003	2,207	+203
Operating Income (loss)	(593)	(1,980)	142	+2,123
Non-operating income	12	8	3	-5
Non-operating expenses	2	0	0	-0
Ordinary Income (loss)	(583)	(1,972)	145	+2,117
Extraordinary income	7	26	24	-1
Income (loss) before income taxes	(576)	(1,946)	170	+2,116
Total income taxes	6	2	1	-0
Net Income (loss)	△582	△1,948	168	+2,116

- **2.35 billion yen** in operating revenue from the development of PJ1-02 Redasemtide for acute ischemic stroke due to the achievement of development milestones in Japan, the U.S., Europe and China following the start of global Phase 2b clinical trials
- Investment in R&D equipment was promoted in line with progress in R&D. In addition, R&D expenses of 1.56 billion yen were recorded due to an increase in reagent consumables and subcontracting expenses for the evaluation of next-generation regenerative medicine. As a result, the company posted an **operating income of 140 million yen**.

Balance Sheet / Statements of Cash Flows

(Millions of yen)

	As of July 31, 2021	As of July 31, 2022	As of July 31, 2023	Function (FY on FY)
Current assets	9,940	9,262	10,440	+1,177
Of which cash and deposits	9,719	8,880	10,217	+1,337
Non-current assets	372	334	266	-68
Total assets	10,312	9,597	10,706	+1,109
Current liabilities	70	71	217	+145
Non-current liabilities	123	120	118	-2
Total liabilities	194	192	336	+143
Total net assets	10,118	9,404	10,370	+965
Total liabilities and net assets	10,312	9,597	10,706	+1,109

	As of July 31, 2021	As of July 31, 2022	As of July 31, 2023
Income (loss) before income taxes	△576	△1,946	170
Cash flows from operating activities	△519	△1,404	1,135
Cash flows from investing activities	△92	△0	△0
Cash flows from financing activities	109	112	202
Net increase (decrease) in cash and cash equivalents	△503	△1,292	1,337
Cash and cash equivalents at beginning of period	10,675	10,172	8,880
Cash and cash equivalents at end of period	10,172	8,880	10,217

- Cash and deposits increased due to the recording of 2.35 billion yen in business income. **10.2 billion yen in cash and deposits at the end of the period.**
- Estimated annual expenditures for the fiscal year ending July 2024 range from 1.43 to 1.91 billion yen (cash expenditures for R&D: 1.2 to 1.6 billion yen, cash expenditures for general and administrative expenses: 0.23 to 0.31 billion yen), **ensuring stable funds for R&D activities through 2028 at this time.**

2. Summary of Business Activities for the Fiscal Year Ended July 31, 2023

Summary of Business Activities for the Fiscal Year Ended July 31, 2023

Multiple Clinical Trials Progress to Next Stage for "Regeneration-Inducing Medicine™" Redasemtide

Clinical trial-related progress

Month/Year	History
Oct. 2022	Disclosure of Trial Data from Phase 2 Clinical Trial of Redasemtide for Acute Ischemic Stroke and Draft Protocol for Global Phase 3 Clinical Trial
March 2023	First administration of Redasemtide in an Additional Phase II Clinical Trial for the patients with Dystrophic Epidermolysis Bullosa
March	Preliminary Results from Phase 2 Clinical Trial of Redasemtide in Patients with Osteoarthritis of the Knee
April	Milestone Achievement in Development of Therapeutic Drug (Redasemtide) Targeting Acute Ischemic Stroke (Start of global phase 2b trials in Japan)
April	Preliminary Results from Phase 2 Clinical Trial of Redasemtide in Patients with Chronic Liver Disease
April	Milestone Achievement in Development of Therapeutic Drug (Redasemtide) Targeting Acute Ischemic Stroke (Start of global phase 2b trials in US)
May	Results from Phase 2 Clinical Trial of Redasemtide in Patients with Chronic Liver Disease (Additional Report)
May	Orphan Drug Designation of "Regeneration-Inducing Medicine ™" Redasemtide (HMGB1 peptide)
July	StemRIM Announces the Initiation of Global Late Phase 2 Clinical Trials for Redasemtide Targeting Acute Ischemic Stroke (Europe, China)
July	The First Administration of Global Late Phase 2 Clinical Trials for Redasemtide Targeting Acute Ischemic Stroke (Japan)

Other progress

Month/Year	History
Nov. 2022	Patent Registration (Japan) for the Use of the HMGB1 Fragment Peptide, Redasemtide, as an Additional Therapeutic Indication for Cardiomyopathy and Old Myocardial Infarction
Dec.	Patent Registration (Mexico) for the Use of the HMGB1 Fragment Peptide, Redasemtide, as an Additional Therapeutic Indication for Cardiomyopathy and Old Myocardial Infarction
Jan. 2023	Renewal of Tripartite Joint Research Agreement with Osaka University and Shiseido Co.,td
March	Patent Registration (Russia) for the Use of the HMGB1 Fragment Peptide, Redasemtide, as an Additional Therapeutic Indication for Cardiomyopathy and Old Myocardial Infarction
May	Patent Registration (Taiwan) for the Use of the HMGB1 Fragment Peptide, Redasemtide, as an Additional Therapeutic Indication for Cardiomyopathy and Old Myocardial Infarction
July	Patent Registration (Korea) for the Use of the HMGB1 Fragment Peptide, Redasemtide, as an Additional Therapeutic Indication for Cardiomyopathy and Old Myocardial Infarction

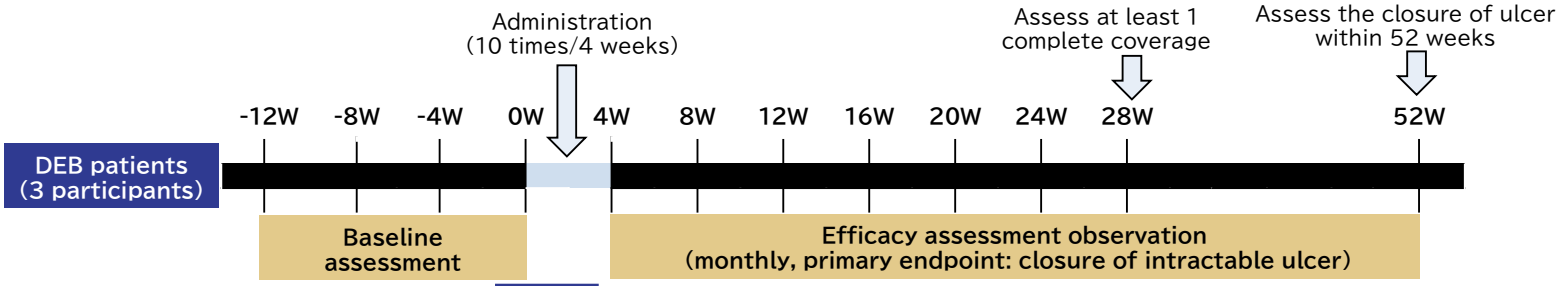
Overview of Development Pipeline

Project code	Development candidate	Indication	Investigator	Status	Development Stage	Out-license partner
PJ1-01	Redasemtide (HMGB1 cell mobilization domain peptides)	Epidermolysis bullosa	Shionogi & Co., Ltd.	Additional P2 Study Ongoing	Phase 2 study – Phase 3 study (*1)	Shionogi & Co. Ltd. (S-005151)
PJ1-02		Acute Ischemic Stroke	Shionogi & Co., Ltd.	Global P2b Study Ongoing	Phase 2 study	
PJ1-03		Cardiomyopathy (ischemic cardiomyopathy/ dilated cardiomyopathy)	Osaka University	Physician-Initiated P2 Study In preparation	Phase 2 study	
PJ1-04		Osteoarthritis of the knee	Hirosaki University	Physician-Initiated P2 Study Primary endpoint achieved	Phase 2 study	
PJ1-05		Chronic liver disease	Niigata University	Physician-Initiated P2 Study Primary endpoint achieved	Phase 2 study	
PJ2-01	TRIM3 (Novel Regeneration-Inducing peptide for Systemic administration)	Multiple tissue damage diseases	In-house (partnership is planned)	Pre-clinical	Research – Pre-clinical	-
PJ2-02	TRIM4 (Novel Regeneration-Inducing peptide for Systemic administration)	Multiple tissue damage diseases	In-house (partnership is planned)	Pre-clinical	Research – Pre-clinical	-
PJ3	TRIM5 (Novel Regeneration-Inducing peptide for Local administration)	Multiple tissue damage diseases	In-house (partnership is planned)	Pre-clinical	Research – Pre-clinical	-
PJ4	Autologous cell collection device for treatment	Multiple tissue damage diseases	In-house (partnership is planned)	Pre-clinical	Research – Pre-clinical; ND *2	-
PJ5	SR-GT1 (Stem cell gene therapy)	Epidermolysis bullosa	In-house (partnership is planned)	Under preparation for clinical trial	Research – Pre-clinical; P1/P2 study; None	-

*1: Application for approval is planed after Additional Phase2.
*2: The company is in the process of making adjustments in the direction of not conducting Phase 1 trials and beyond, but as this has not yet been finalized, it is listed as “ND”.

PJ1-01:Redasemtide(DEB)

Additional Phase 2 Protocol	
Study objectives	Evaluation of efficacy and safety of Redasemtide in patients with dystrophic epidermolysis bullosa having intractable ulcers
Study design	Single arm, multicenter, open label, uncontrolled
Intervention	Redasemtide (1.0 mg/kg) group: 3 participants
Regimen	30-minute intravenous infusion once a day, total 10 times/4 weeks [1st week of administration: 4 times/week, 2nd-4th weeks of administration: twice/week (once every 3-4 days)]
Primary endpoint	Closure of intractable ulcer



Status

February 2023: Initiated the administration to the first patient

* Shionogi & Co. Ltd., *Shionogi R&D Day 2022*, Oct. 12, 2022, pp.65
** jRCT2031220378

PJ1-01:Redasemtide(DEB)/Orphan Drug Designation

In May 2023, Redasemtide was designated by the Ministry of Health, Labour and Welfare as an orphan drug for the treatment of nutritional-type epidermolysis bullosa.

Orphan Drug, Orphan Medical Device, and Orphan Regenerative Medicine Product (Orphan Drug) Designation System

Designation Criteria

1. Less than 50,000 eligible patients (in Japan)
2. Intractable and other serious diseases are covered.
3. There is a high medical need for the drug and no suitable alternative drug or treatment is available.
4. There is a rationale for the use of the drug and the development plan is reasonable.

Public Assistance Measures

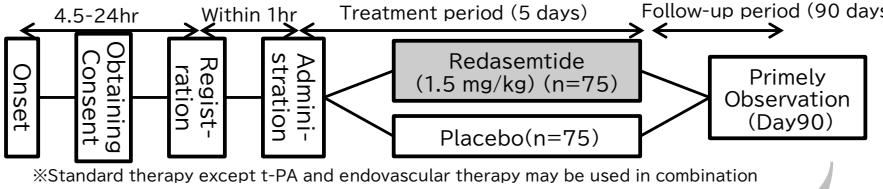
1. Grants for cost reduction in the development of orphan drugs
2. Guidance and advice from the Ministry of Health, Labour and Welfare, PMDA (Pharmaceuticals and Medical Devices Agency), and the Institute of Medical Science, Health, and Nutrition
3. Tax deductions for testing expenses incurred during the grant period
4. Priority in approval reviews compared to other pharmaceuticals, medical devices, regenerative medicine, and related products
5. Extension of the reexamination period for up to a maximum of 10 years

- Some Acknowledgment from the Ministry of Health, Labour and Welfare of the potential effectiveness of Redasemtide for nutritional disorders-type epidermolysis bullosa and the reasonableness of the development plan.
- Being eligible for priority review, it is expected to expedite the approval process, leading to early approval.

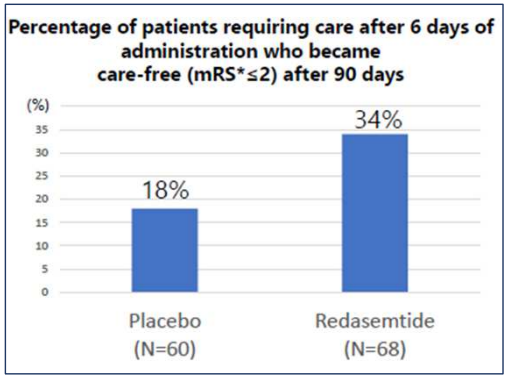
＊Ministry of Health, Labour and Welfare, "Overview of the Designation System for Orphan Drugs, Orphan Medical Devices and Orphan Regenerative Medicine Products".

PJ1-02:Redasemtide(Acute Ischemic Stroke)

Phase 2 Protocol	
Main purpose	To evaluate the efficacy of S-005151 compared to placebo in patients with acute ischemic stroke with respect to modified Rankin Scale (mRS) 90 days after the first dose.
Target patient	Acute ischemic stroke patients within 4.5 to 24 hours after the onset of cerebral infarction
Clinical trial design	Multicenter, randomized, double-blind, placebo-controlled, parallel-group
Dose	Intravenous administration once daily for 90 minutes for 5 days
Region	Japan



※Standard therapy except t-PA and endovascular therapy may be used in combination



・In the domestic Phase 2 trial, the proportion of patients who transitioned from needing assistance (mRS≧3) to care-free (mRS≦2) was 18% in the placebo group, while it was 34% in the Redasemtide group. This suggests the effectiveness of Redasemtide in acute ischemic stroke patients.

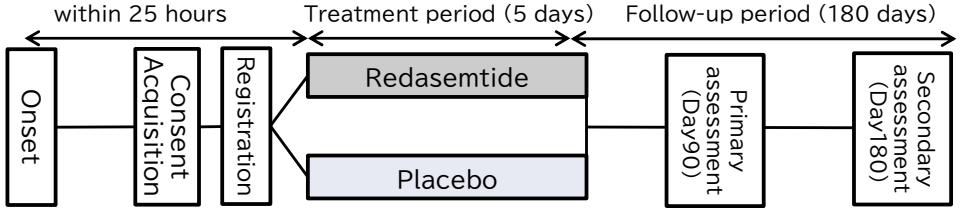
・The development plan has been partially revised, and it has been decided to conduct a global Phase 2b trial with the aim of dose optimization. After commencing the trial in Japan, trials will be sequentially initiated in the United States, Europe, and China. Following the acquisition of optimal dosage information, the plan is to transition to a global Phase 3 clinical trial for the purpose of applying for manufacturing and marketing approval.

・The impact on the application timeline due to changes in the development plan is expected to be minimal.

* modified Rankin Scale(mRS):General prognostic rating scale (degree of social reintegration) ``Score 0 (no symptoms) to score 6 (death)" in 7 grades
** Shionogi & Co. Ltd., *Shionogi R&D Day 2022,* Oct. 12, 2022, pp.63

PJ1-02:Redasemtide(Acute Ischemic Stroke)

Global Phase 2b Protocol	
Study objectives	Verification of efficacy of Redasemtide in patients with acute ischemic stroke
Subject population	• Can be administered within 25 hours from the onset of symptoms to the patients at age 18 or older • Baseline NIHSS score* between 8 and 22 • Intravascular recanalization therapy (t-PA treatment, endovascular treatment) is not applicable
Study design	Multicenter, randomized, placebo-controlled, double-blind
Intervention	• **Redasemtide (1.5 mg/kg) group** • **Redasemtide (0.75 mg/kg) group** • **Placebo group** **total 627 participants**
Regimen	90-minute intravenous infusion once a day for 5 days
Primary endpoint	Modified Rankin Scale (mRS) 90 days after administration
Country	**Japan, Europe, North America, China, etc.**



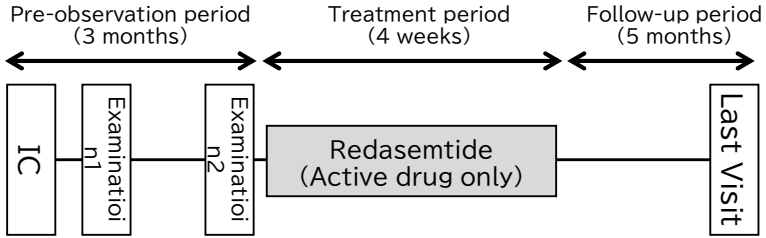
Status

Global Phase 2b study started in March 2023 in Japan and US, and in July 2023 in EU and China; the first patient was dosed in July (Japan).

* modified Rankin Scale(mRS):General prognostic rating scale (degree of social reintegration) "Score 0 (no symptoms) to score 6 (death)" in 7 grades
** National Institutes of Health Stroke Scale (NIHSS): Stroke Neurological Severity Rating Scale (42 points in total, the higher the score, the more severe)
*** Barthel Index (BI) : Evaluation scale for activities of daily living such as eating, bathing, and toileting (total 100 points, the higher the score, the more independent the person is, and the guideline for complete independence is 95 points)
**** Shionogi & Co. Ltd., *Shionogi R&D Day 2022,* Oct. 12, 2022, pp.64

PJ1-05:Redasemtide(Chronic Liver Disease)

Phase 2 Protocol	
Main purpose	Evaluate the safety and exploratory efficacy in patients with chronic liver disease
Clinical trial design	Single arm study, Open label, Uncontrolled
Target patient	Patients with chronic liver disease with liver hardness test results of 4 kPa or greater by MR elastography.
Administration group/number of cases	1.5 mg/kg (free form), 90minutesintravenous infusion •Cohort A: 4 times / 4 weeks [once a week] •Cohort B: 7 times / 4 weeks [Week 1: 4 days, Week 2-4: once a week (1 dosage/3-4 days)]
Endpoint	**Rate of change in liver stiffness, rate of change in liver stiffness using ultrasound elastography, and rate of change in Child-Pugh score, etc.**
Site	Division of Gastroenterology and Hepatology, Niigata University Medical and Dental Hospital



Status

Preliminary results in April 2023

* MR elastography: Magnetic Resonance Elastography (MRE) is one test that can quantitatively evaluate liver fibrosis.
** Child-Pugh score: Child-Pugh score is an assessment method mainly used to evaluate liver reserve function in patients with chronic liver diseases such as liver cirrhosis. It scores the severity of liver dysfunction using hepatic encephalopathy, ascites, serum bilirubin level, serum albumin level, and prothrombin activity, and classifies it into three stages, A to C.
*** jRCT2031200232

PJ1-05:Redasemtide(Chronic Liver Disease)

Primary endpoint evaluation

Safety endpoints: Presence or absence of adverse events and percentage of the presence

- No serious adverse events or adverse reactions related to Redasemtide
  - ✓ 1 patient experienced a serious adverse event (bleeding during liver biopsy) .
  - ✓ 2 patients experienced adverse events (one case of hoarseness and one case of fever, both mild) that could not be definitively attributed to the drug.

Secondary endpoint evaluation

Efficacy endpoints: Change ratio of liver stiffness, Variation of Child-Pugh score.

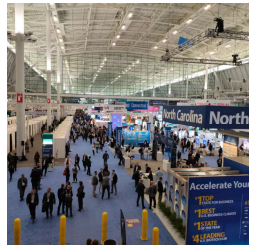
- Change ratio of liver stiffness by MR elastography (which is the most reliable method for evaluating liver fibrosis in chronic liver disease) :
  - ✓ 8–12% reduction in liver stiffness

Out-licensing activities for new “Regeneration-Inducing Medicine™”

Participation in multiple conferences both domestically and internationally as part of the derivation activities for the next generation of “Regeneration-Inducing Medicine™” following Redasemtide.

BioJapan
2022.10.11~13 @Yokohama, Japan

BIO International Convention 2023
2023.6.5~8
@Boston, MA, USA



EU-Japan Biotech & Pharma Partnering Conference 2022
2022.10.11 @Osaka, Japan

Yokohama
Osaka
San Francisco
New York
Boston

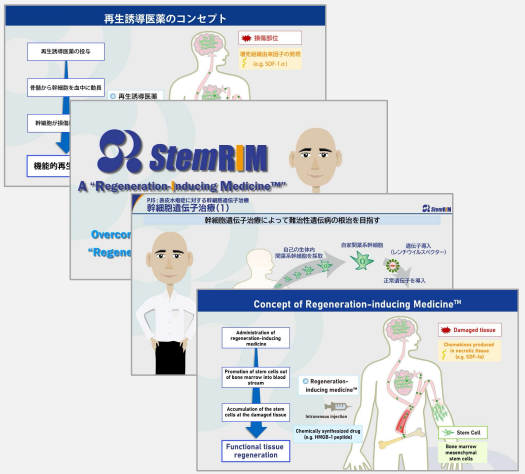
41st Annual J.P. Morgan Healthcare Conference
2023.1.9~12 @San Francisco, CA, USA

Jefferies 2023 Global Healthcare Conference New York
2023.6.7~9 @New York, NY, USA

Enhanced Investor Relations and Public Relations activities

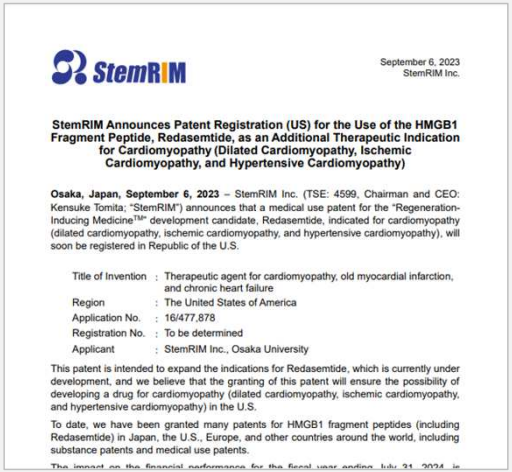
Global outreach and expanded coverage for information dissemination to individual and institutional investors both domestically and internationally.

Enhanced video contents



・Our company website.
https://stemrim.com/video/

Timely Disclosure



StemRIM

September 6, 2023
StemRIM Inc.

StemRIM Announces Patent Registration (US) for the Use of the HMGB1 Fragment Peptide, Redasemtide, as an Additional Therapeutic Indication for Cardiomyopathy (Dilated Cardiomyopathy, Ischemic Cardiomyopathy, and Hypertensive Cardiomyopathy)

Osaka, Japan, September 6, 2023 – StemRIM Inc. (TSE: 4599, Chairman and CEO: Kensuke Tomita; "StemRIM") announces that a medical use patent for the "Regeneration-Inducing Medicine™" development candidate, Redasemtide, indicated for cardiomyopathy (dilated cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy), will soon be registered in Republic of the U.S.

Title of Invention	:	Therapeutic agent for cardiomyopathy, old myocardial infarction, and chronic heart failure
Region	:	The United States of America
Application No.	:	16/477,878
Registration No.	:	To be determined
Applicant	:	StemRIM Inc., Osaka University

This patent is intended to expand the indications for Redasemtide, which is currently under development, and we believe that the granting of this patent will ensure the possibility of developing a drug for cardiomyopathy (dilated cardiomyopathy, ischemic cardiomyopathy, and hypertensive cardiomyopathy) in the U.S.

To date, we have been granted many patents for HMGB1 fragment peptides (including Redasemtide) in Japan, the U.S., Europe, and other countries around the world, including substance patents and medical use patents.

・TDnet Company Announcements Service
https://www.release.tdnet.info/index e .html

Sharing information on X

Our Twitter account is @StemRIM Inc.
https://twitter.com/StemRIM Inc

3. Future Growth Strategies

Future Growth Strategies

We will continue to pursue our growth strategy and aim to maximize the potential value of “Regeneration-Inducing Medicine™”

・Facilitate out-licensing activities for new compounds with significant activity in non-clinical studies.

・Expanding out-licensing activities with a focus on global development

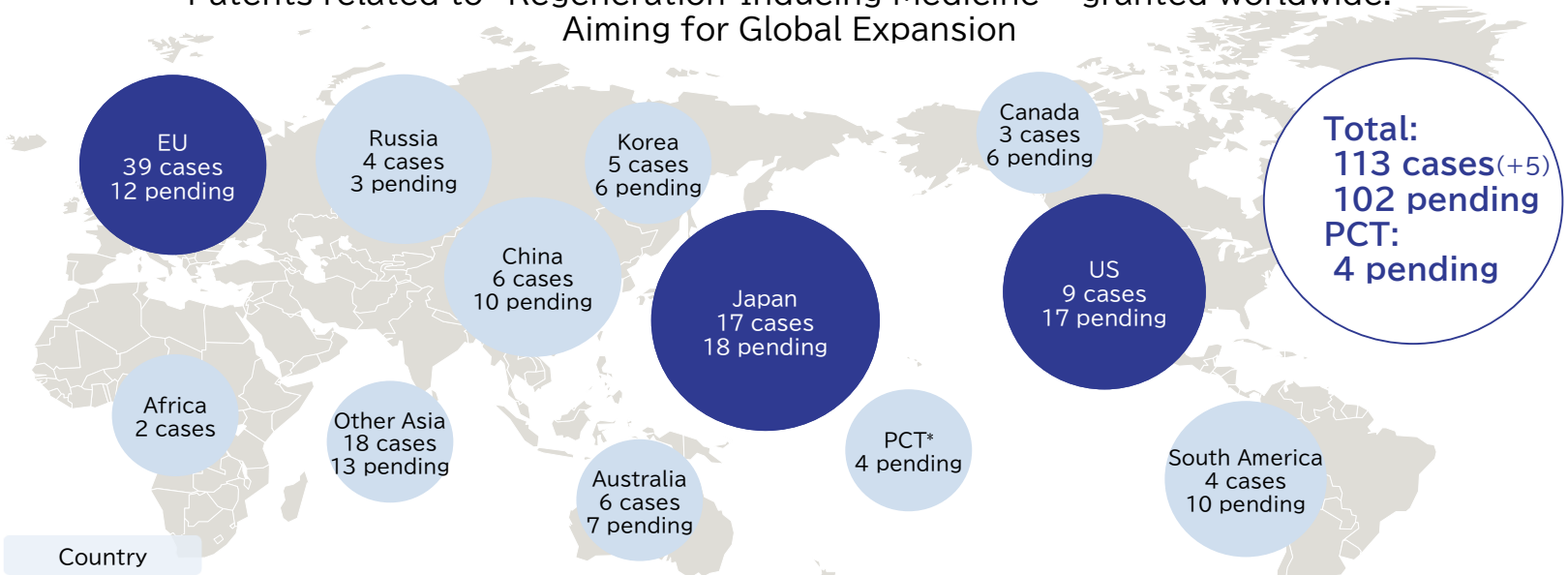
・Continued to provide lateral support for ongoing clinical trials in Redasemtide and continued progress in joint research and development with Osaka University.

・Continued to identify multiple development candidates through rapid confirmation of animal drug efficacy and formulation of regulatory strategies.

・Collaboration with various universities in the Collaborative Research Institute to conduct multifaceted non-clinical studies for the in-licensing of new “Regeneration-Inducing Medicine™”.

IP Strategy

Patents related to “Regeneration-Inducing Medicine™” granted worldwide.
Aiming for Global Expansion



Country

JPN USA CHN GER KOR IND ESP POL SWD RUS BEL IDN BRA MEX ZAF

ISR HKG GBR FRA AUS CAN ITA IRL NLD CHE DNK FIN TUR SGP TWN

*PCT: Members of the Patent Cooperation Treaty
** As of July 31, 2023

SDGs: Achieving a Sustainable Future

Health and Well-Being for All

StemRIM is dedicated to achieving a sustainable future by providing therapeutic solutions to people worldwide suffering from refractory diseases through the realization of “Regeneration-Inducing Medicine™”.
We aim to support healthy and prosperous lives for all.

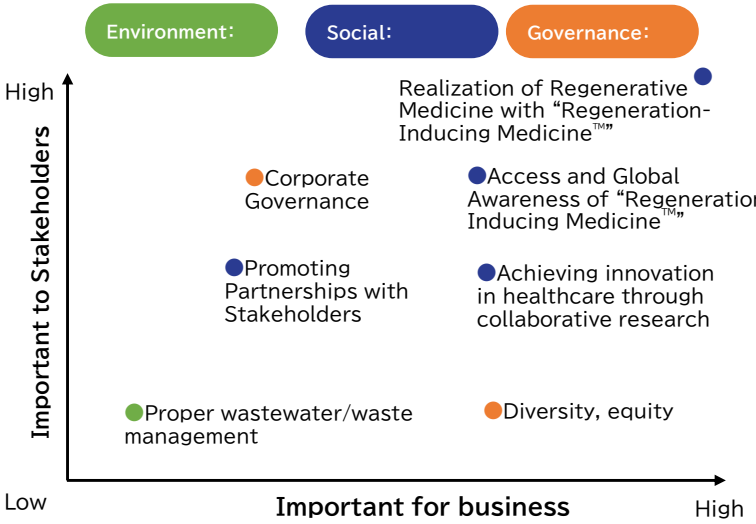
We aim to bring smiles to patients suffering from rare diseases worldwide in the future.

Target

3.4/3.8

SDGs: Identification of Materiality

Our company has identified key material issues (Materiality) with the aim of achieving sustained growth while contributing to the resolution of global societal challenges, including the Sustainable Development Goals (SDGs).
Out of the 17 Sustainable Development Goals (SDGs), our company places the highest priority on Goal 3, which is directly related to our business characteristics. To achieve this goal, we are focusing on six foundational objectives that serve as the basis for our goals and business operations.
We are committed to these six goals, aligning them with our business activities, in order to not only achieve sustainable growth but also contribute to the sustainable development of society through addressing global social issues such as the SDGs.



3	Materiality	Related SDG Development Goals
Increase in Positive Impact	・Realization of Regenerative Therapy with "Regeneration-Inducing Medicine™". ・Increase global awareness with access to "Regeneration-Inducing Medicine™". Supporting healthy and affluent lives by providing therapeutic drugs to people suffering from intractable diseases around the world through our business ・Achieving innovation in healthcare through collaborative research ・Promoting Partnerships with Stakeholders	3.4/3.8 8.2 17.17
Managing and Controlling Negative Impacts	・Corporate Governance ・Diversity, Equity	16.b 5.1/5.5
	・Establishment of a sustainable research system (Proper wastewater, Waste management)	6.3/6.b 12.4

SDGs: Activities for the Fiscal Year Ended July 31, 2023

● Donation to “Towards a Society Where Women with Pelvic Organ Prolapse Can Seek Treatment with Ease”.

We contributed to the Osaka University Graduate School of Medicine’s crowdfunding project, ”Towards a Society Where Women with Pelvic Organ Prolapse Can Seek Treatment with Ease,” in support of its mission. This condition, pelvic organ prolapse, affects approximately half of women who have given birth. However, due to low awareness and a lack of accurate knowledge, many women hesitate to seek medical attention.
We believe in the importance of women with pelvic organ prolapse receiving appropriate treatment and support to lead active lives. Therefore, We made a donation to contribute towards creating a society where women can readily access the care they need.

Message of support from our company

Our company is dedicated to the development of pharmaceuticals aimed at eradicating and improving the quality of life for those with the rare disease, epidermolysis bullosa. Regarding pelvic organ prolapse, we understand that, despite the availability of treatment methods, many individuals do not seek treatment for various reasons. Through this project, we hope that pelvic organ prolapse becomes better understood, and that numerous women will receive appropriate treatment without hesitation, leading to an improved quality of life and expanded opportunities. We believe that this initiative aligns with our company’s values, and we are pleased to support it.

Sincerely,
Masatsune Okajima
President and CEO
StemRIM Inc.

Appendix.

Discovery of in-vivo mechanism inducing tissue regeneration

Differences between normal skin and epidermolysis bullosa skin

In normal skin (Figure A), type 7 collagen functions like an adhesive, bonding the epidermis and dermis, the superficial layers of skin. In epidermolysis bullosa congenita (Figure B), the epidermis and dermis are easily detached with the slightest irritation due to abnormal type 7 collagen.Since epidermal stem cells, which are responsible for supplying epidermal cells, reside in the epidermis, the epidermal stem cells are lost from the skin of patients with epidermolysis bullosa, and the epidermis loses its regenerative capacity.

Fig. A

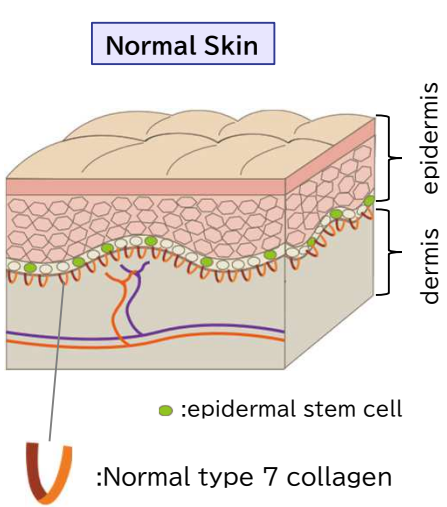
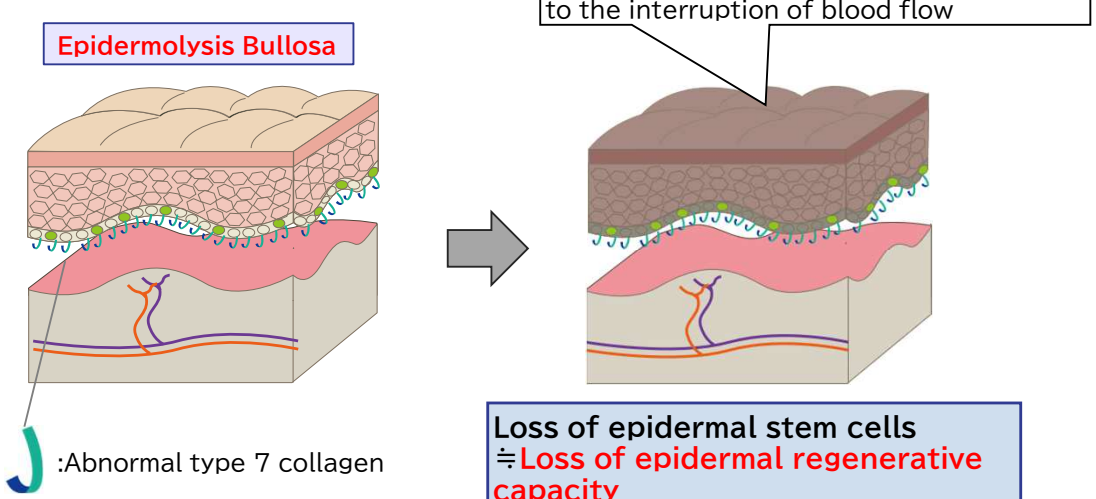
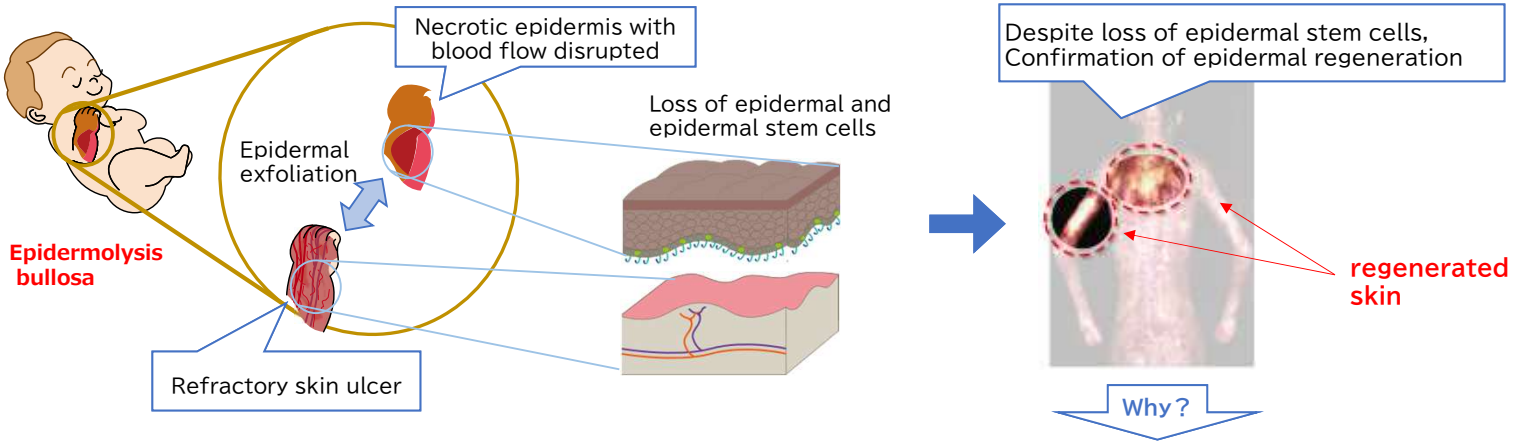


Fig. B



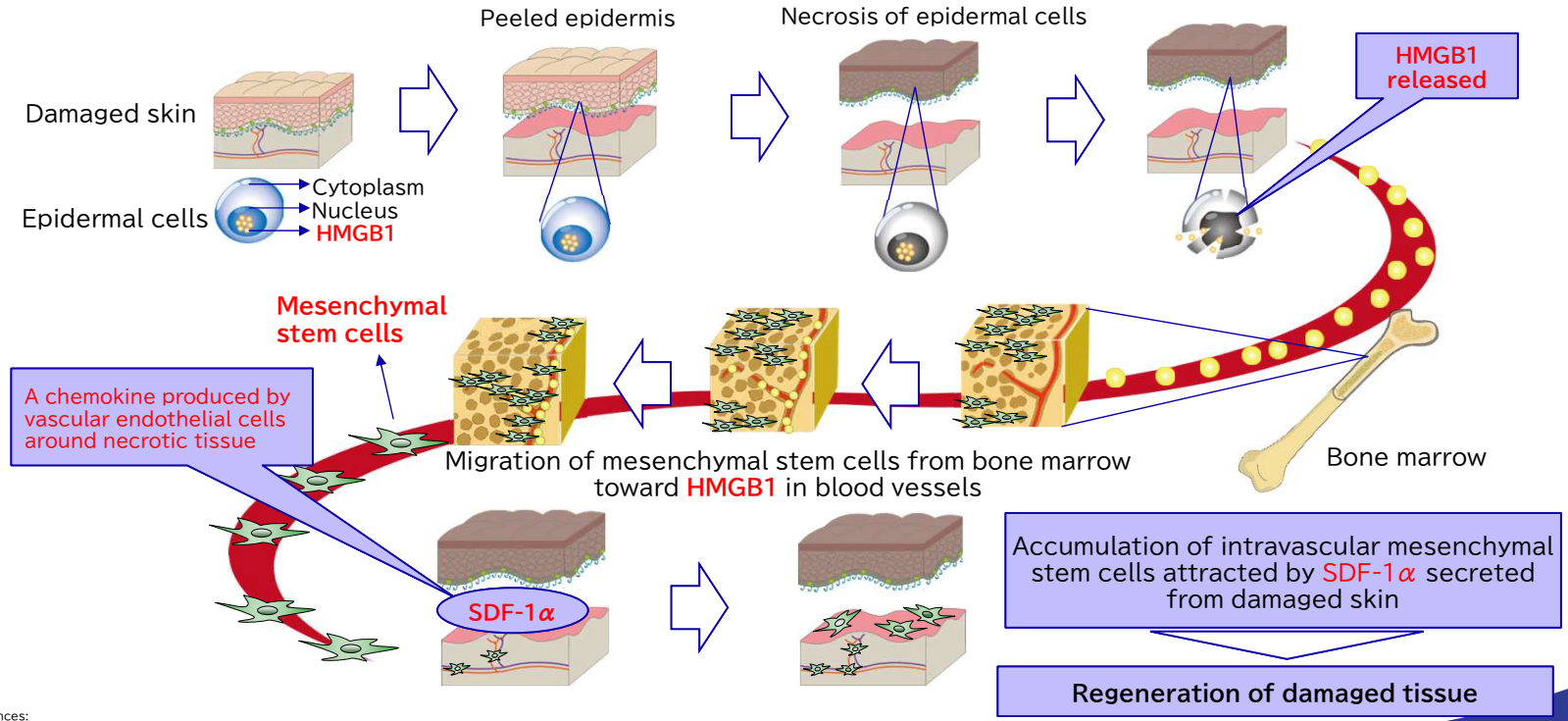
Discovery of in-vivo mechanism inducing tissue regeneration

The beginning of the research and development on “Regeneration-Inducing Medicine™” : Hypothesis of stem cell recruitment mechanism from bone marrow to damaged skin.



Discovery of in-vivo mechanism inducing tissue regeneration

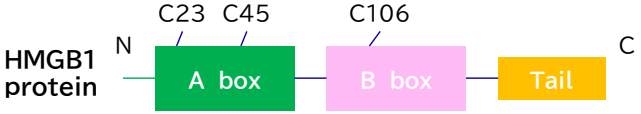
Discovery of crosstalk mechanism between damaged skin and bone marrow mesenchymal stem cells via necrotic tissue-derived factor



References:
J Immunol. 2015 Feb 15;194(4):1996-2003
Proc Natl Acad Sci U S A. 2011 Apr 19;108(16):6609-14.

HMGB1 peptide drugs with improved safety

Designing highly safe, chemically synthesized peptide drug from A-Box domain of HMGB1 protein

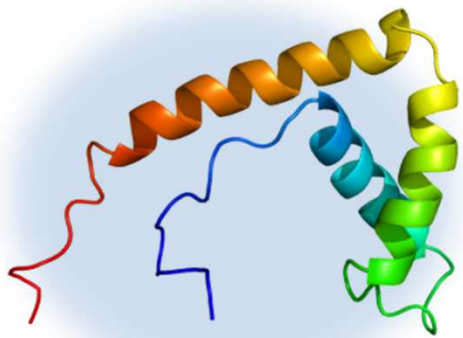


- An Important in vivo molecule that activate tissue regeneration

Identifying the function of protein domains

Prof. Katsuto Tamai
Osaka University

A box	Bone marrow mesenchymal stem cell activating domain, named "KOI2-domain"
B box	Innate immune response-activating domain that induces inflammation

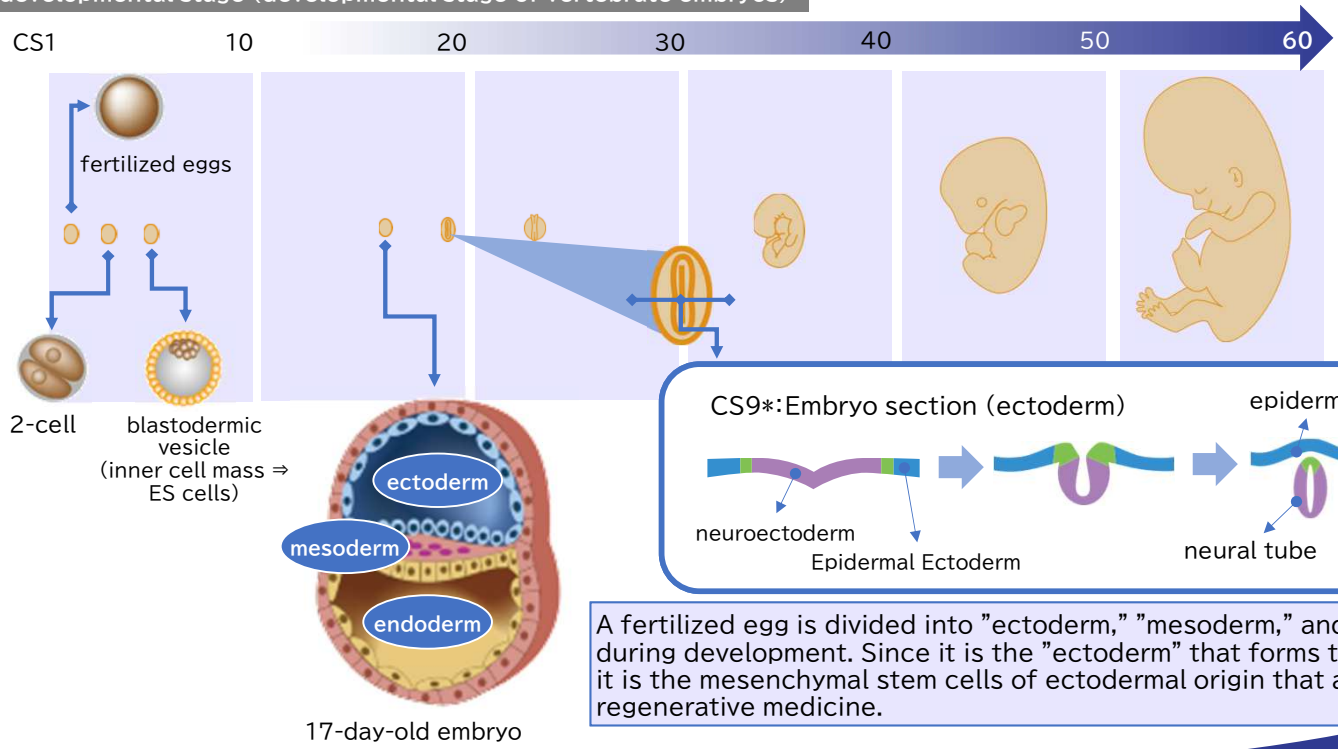


HMGB1 peptide drug excluding the domains causing side effects in HMGB1 protein

Advantages of “Regeneration-Inducing Medicine™”

Epidermis formation during human development

Carnegie developmental stage (developmental stage of vertebrate embryos)



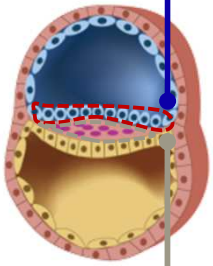
A fertilized egg is divided into ”ectoderm,” ”mesoderm,” and ”endoderm” during development. Since it is the ”ectoderm” that forms the epidermis, it is the mesenchymal stem cells of ectodermal origin that are induced by regenerative medicine.

Advantages of “Regeneration-Inducing Medicine™”

Ectodermal mesenchymal stem cells have high pluripotency and differentiation ability to various tissues.

Tissues into which differentiation has been confirmed in our collaborative research with Osaka University

Tissues into which differentiation is thought to occur embryologically



17-day old embryo (Cross-section)

Ectoderm

Differen-tiation

Ectodermal Mesenchymal stem cells

Differen-tiation

Nerves	Epi-dermis	Follicles
Bone	Cartilage	Fat
Blood vessels	Dermis	Muscle
Ligament	Heart	Heart

Mesoderm

Differen-tiation

Cellular medicine from other companies

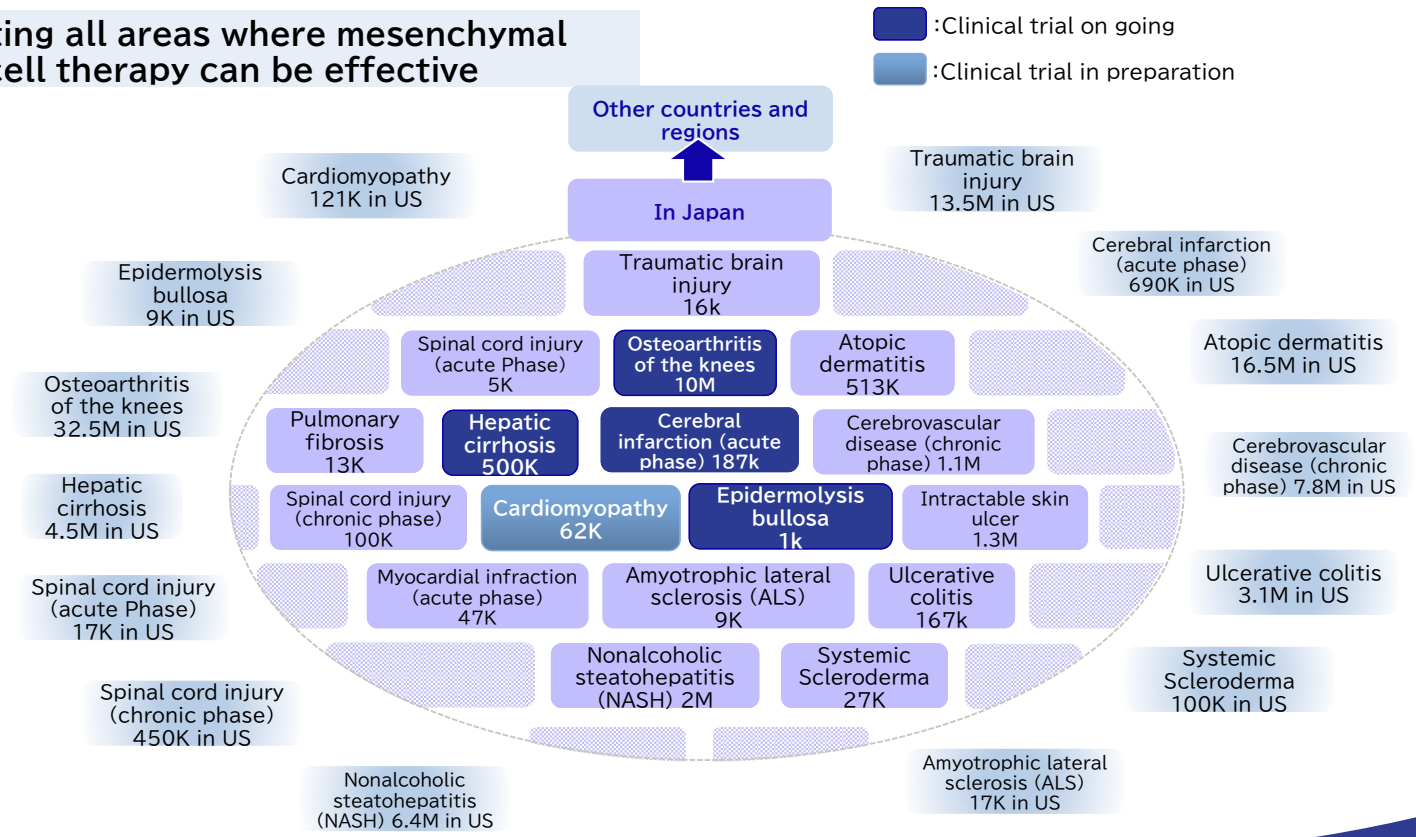
Mesenchymal stem cells (Derived from mesoderm)

Differen-tiation

Bone	Cartilage	Fat
Blood vessels	Dermis	Muscle
Ligament	Heart	Heart

Expanding Indications and Markets

Targeting all areas where mesenchymal stem cell therapy can be effective

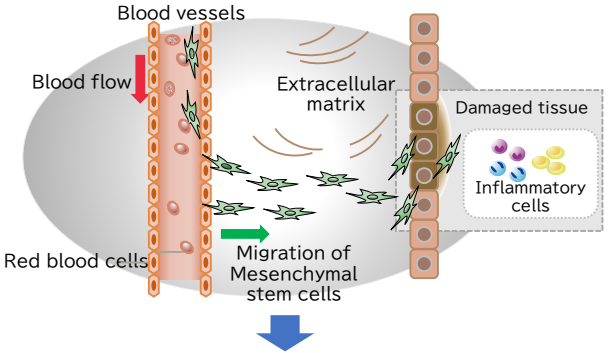


Functions of mesenchymal stem cells

In-vivo mesenchymal stem cells have 5 distinctive capabilities

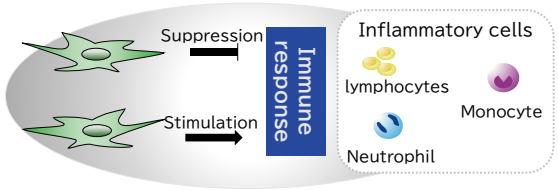
1. Cell migration ability

Mesenchymal stem cells migrate to damaged tissue via the bloodstream



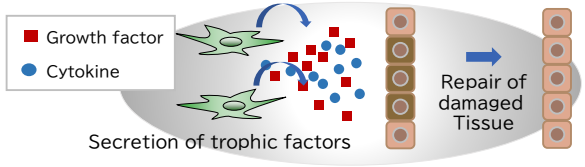
2. Immunomodulatory ability

Modulates immune response and inhibits the spread of tissue damage caused by excessive inflammation



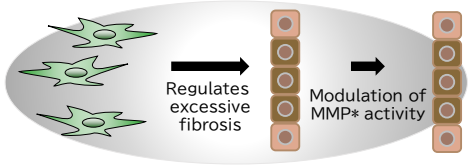
3. Trophic factor secretion ability

Promotes cell proliferation and tissue repair by secreting growth factors and cytokines to cells in damaged tissue



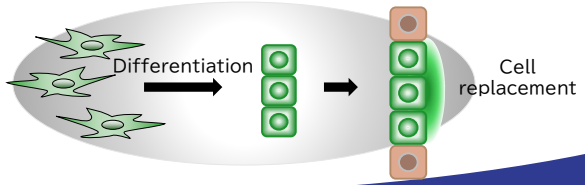
4. Fibrosis regulation ability

Regulates and inhibits excessive fibrosis of damaged tissue



5. Tissue regeneration ability

Mesenchymal stem cells themselves differentiate into various cell types to Replacing cells in damaged tissues and regenerating tissues

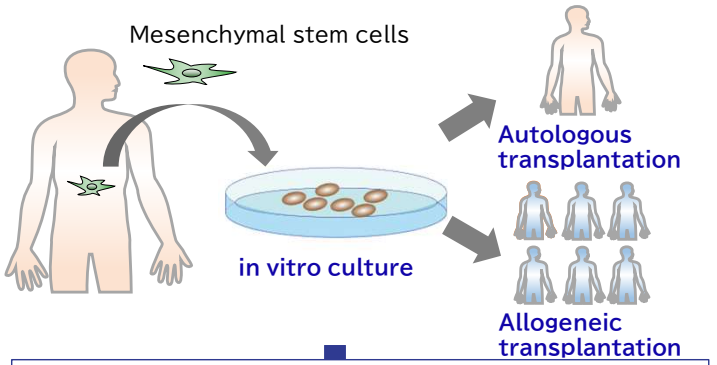


* MMP:Matrix metalloproteases

In vitro culture reduces the functions of MSCs

"Regeneration-Inducing Medicine™" can avoid functional degradation of mesenchymal stem cells due to in vitro culture

Manufacturing process of conventional cellular medicine

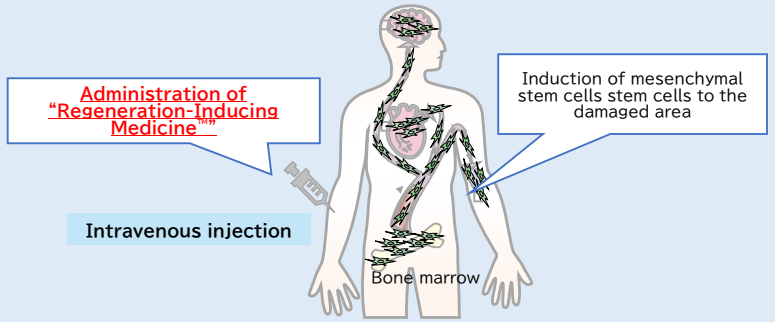


Mesenchymal stem cells lose their functions during in vitro culture

Source: Stem Cell Research & Therapy2018,9:131

Cell Migration ability | Immuno-modulatory ability | Trophic factor Secretion ability | Fibrosis regulation ability | Tissue Regene-ration ability

Induction of MSC in "Regeneration-Inducing Medicine™"



Induction of mesenchymal stem cells into damaged tissues while retaining their native functions

Cell Migration ability | Immuno-modulatory ability | Trophic factor Secretion ability | Fibrosis regulation ability | Tissue Regene-ration ability

"The effects of MSC cell therapy are limited to inflammation suppression and supply of growth factors to the remaining cells", reported by Caplan AI

「Mesenchymal Stem Cells: Time to Change the Name!」 Arnold Caplan June 2017

Source: Stem Cells Transl Med. 2017 Jun;6(6):1445-1451. doi: 10.1002/sctm.17-0051. Epub 2017 Apr 28.

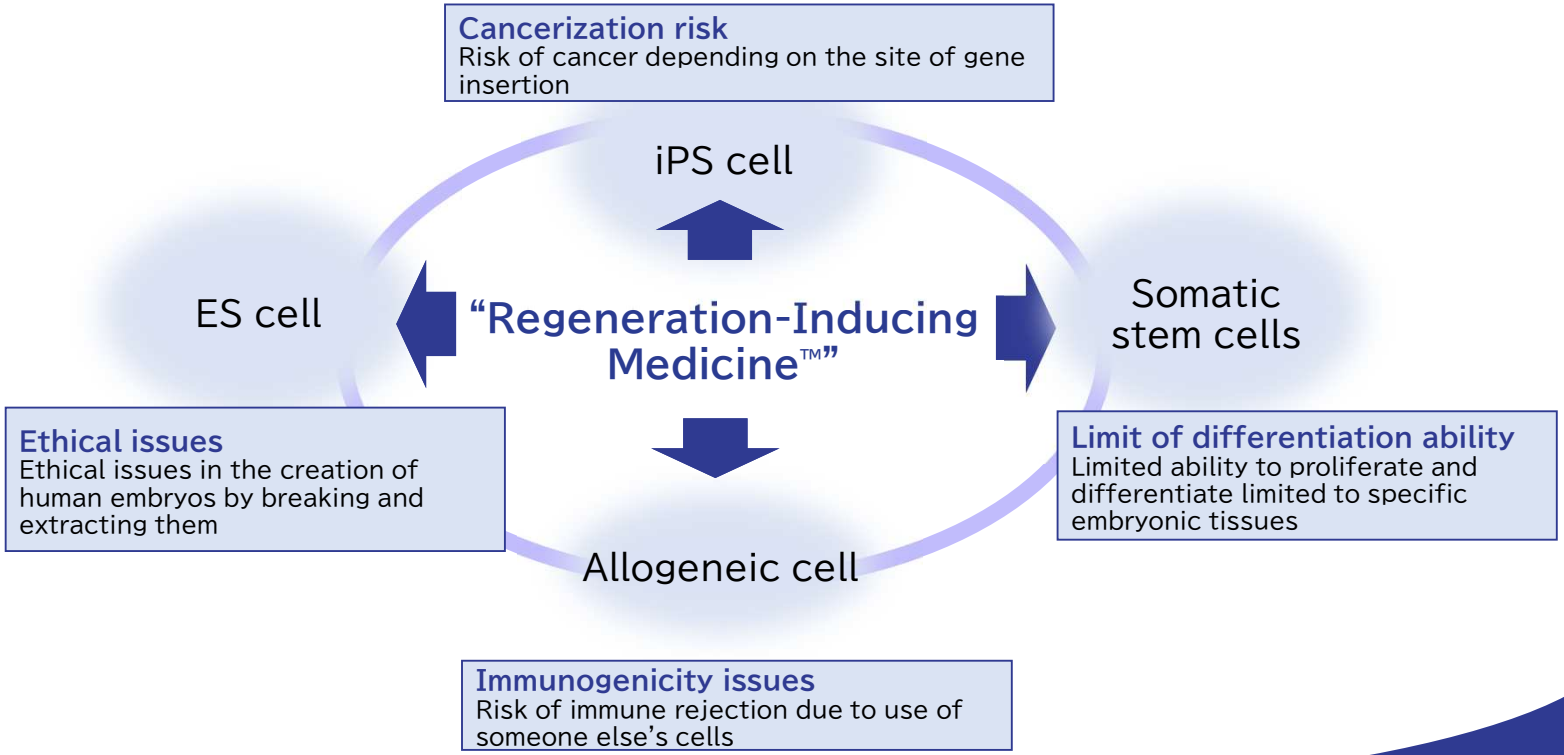
Summary of advantages of “Regeneration-Inducing Medicine™”

“Regeneration-Inducing Medicine™” includes advantages in both cell therapy and chemicals

		“Regeneration-Inducing Medicine™”	Cell therapy	Chemicals
Efficacy	Tissue regeneration	○ Applicable for large-scale tissue damage	▲ Applicable for large tissue damage with large number of cells	↓ No regeneration
	Mechanism of action	○ Use in vivo native regeneration mechanism	○ Cellular physiological activity	↓ Targeting molecules often including side-effect and off-target
	Indications	○ Same compound can cover a wide range of indications	○ Same platform can cover a wide range of indications	↓ In general, targeting limited indications caused by same mechanism
Safety	Noninvasive	○ Compound mobilizes the patient’s cells in vivo and no rejection	↓ Invasive in cell collection Immune-rejection in allogenic case	○ Low noninvasive
Quality	Quality control	○ Easy quality control and stable production	↓ Cell culture includes risk of cellular change	○ Easy quality control and stable production
Other benefit	Cost	○ Normal industrial drug production	↓ CPC and cell collection and transplantation facility is required	○ Affordable and large-scale production
	Regulatory affairs	○ Same as general compound drugs	↓ No standard, and case-by-case regulation is required	○ Standardized regulation

Summary of advantages of “Regeneration-Inducing Medicine™”

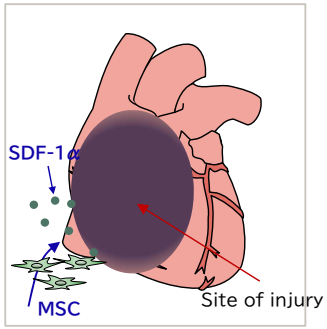
“Regeneration-Inducing Medicine™” can solve the four major problems of conventional cell therapy



PJ3 Novel Regeneration-Inducing Peptide for Local Administration

Developing protein drugs that accumulate mesenchymal stem cells at the site of injury

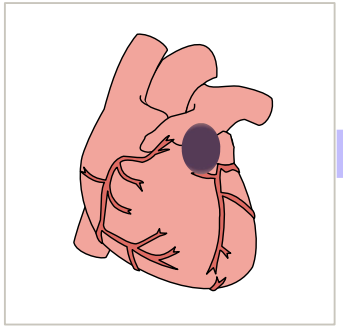
Large injury



- SDF1-a is released, and mesenchymal stem cells mobilized in the blood accumulates at the injury

=Mechanism of action in PJ1, PJ2 is effective

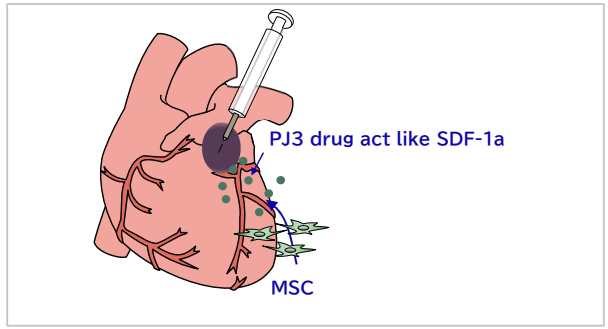
Small injury or chronic phase



- SDF1-a is not released, and mesenchymal stem cells cannot accumulate efficiently

=Combination therapy that maximizes the effects of "Regeneration-Inducing Medicine™" is effective

Efficient accumulation of mesenchymal stem cells by topical administration of PJ3 drug



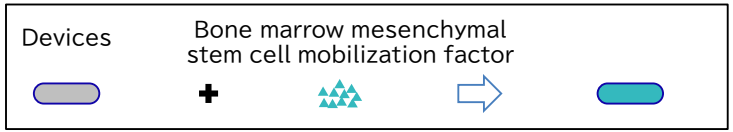
- Effective accumulation of mesenchymal stem cells at the site of injury by topical administration or intravenous injection

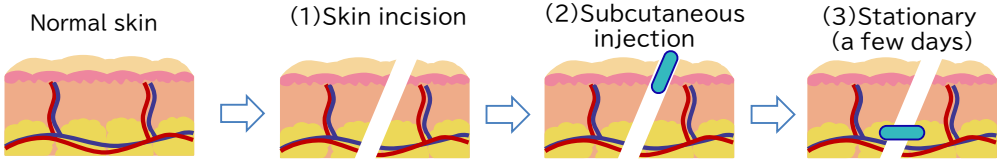
=Maximize damage repair effect of mesenchymal stem cells

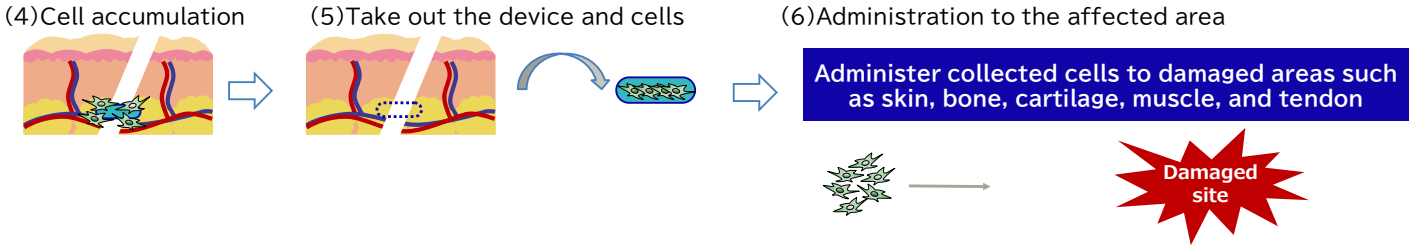
- ✓ Multiple candidate proteins have been identified so far
- ✓ Confirmed good results in animal experiments
- ✓ Currently, the most suitable indication is being selected through multiple animal model experiments

PJ4 Autologous cell collection device for treatment

Developing devices to collect mesenchymal stem cells mobilized in vivo



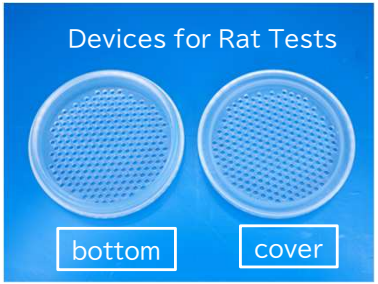




- ✓ Animal testing confirms that the device has good stem cell recovery capability
- ✓ The most suitable indication is being selected through experiments with several disease model animals
- ✓ Conducting non-clinical trials needed to start clinical trials

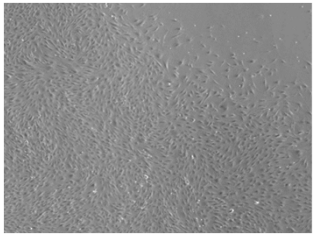
PJ4 Autologous cell collection device for treatment

Confirmation of mesenchymal stem cell harvesting in a rat model



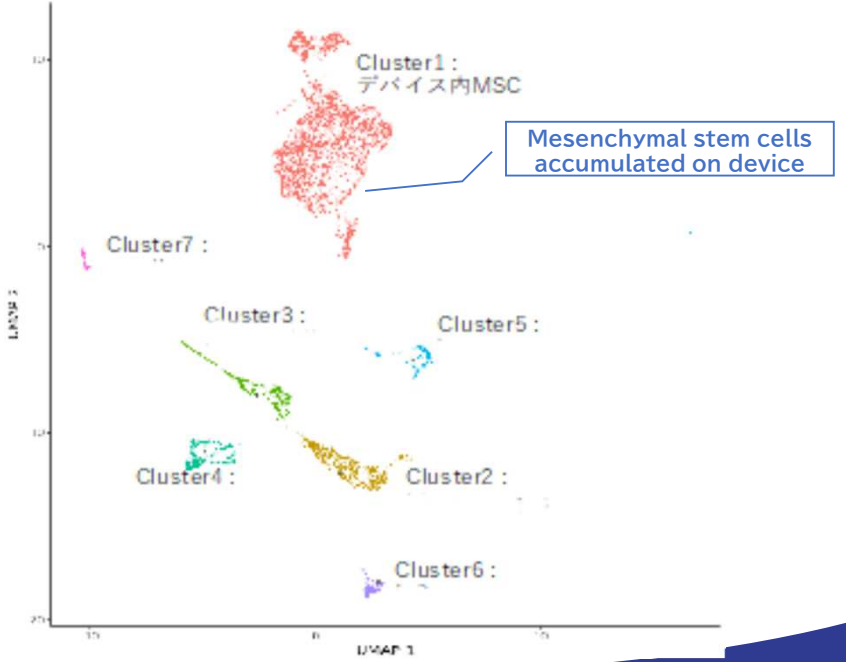
Devices after cell harvesting

Aggregated cell mass



Confirmation of the presence of MSC-like cells by culture of accumulated cells

Single-cell transcriptome analysis by next-generation sequencers for cells accumulated on the device

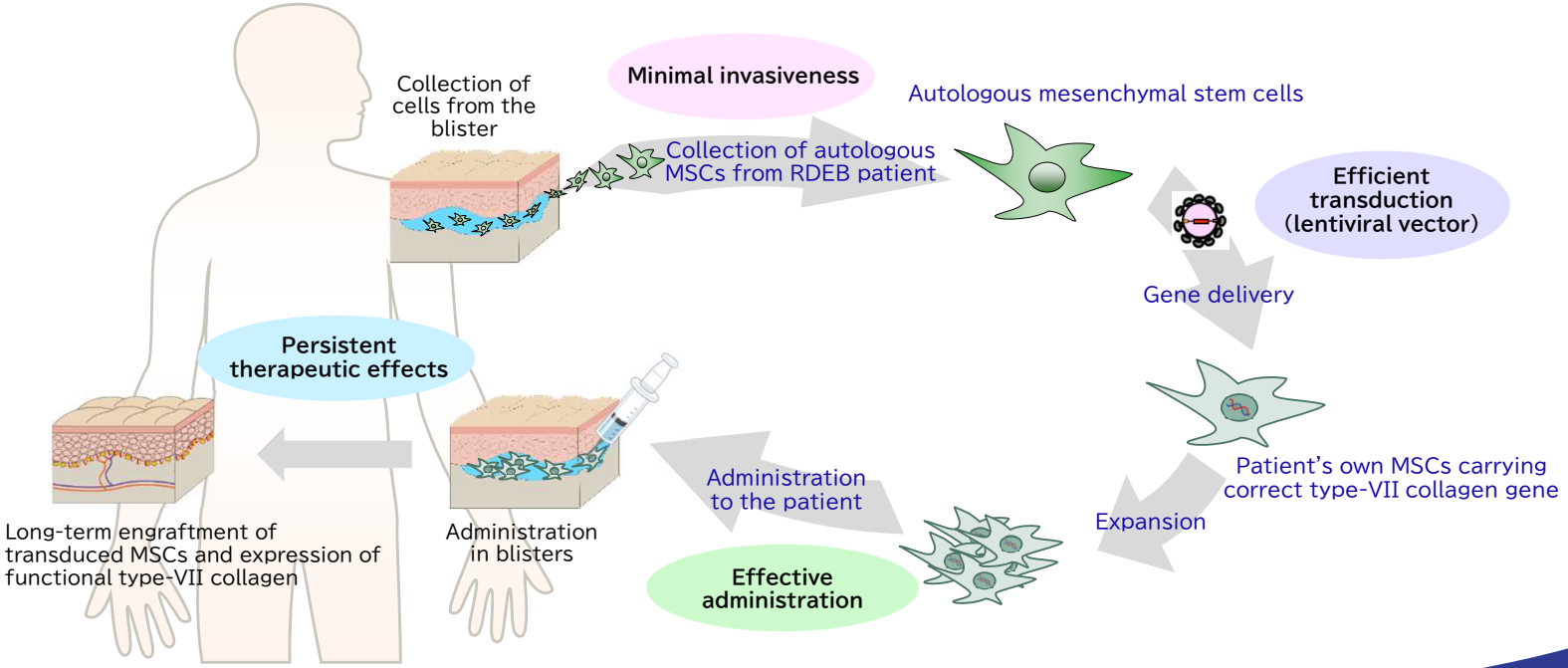


PJ5 Stem cell gene therapy

Aim to cure intractable genetic disease by stem cell gene therapy

Concept

Ex vivo gene therapy involving the introduction of correct type VII collagen gene into autologous mesenchymal stem cells (MSCs) and administration of the cells in the blisters of the patient.



PJ5 Stem cell gene therapy

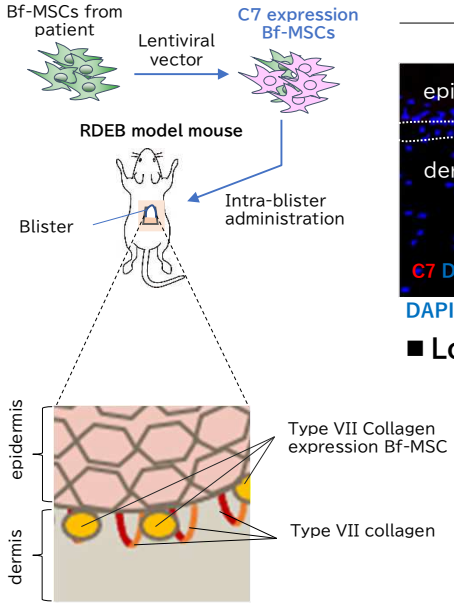
Ex vivo gene therapy with minimal invasiveness, high efficacy, and persistent effect
This therapy employs a novel method of isolating Bf-MSCs from a patient, efficient delivery of functional type VII collagen gene to the cells, and novel administration method to the patient with minimal invasiveness.

Company	Brand, Generic or Code name	*in/ex vivo*	Target cell	Formulation	Administration route	Comparison with StemRIM			
						Area	Patient's burden	Effective length	Efficacy
StemRIM	SR-GT1	*ex vivo*	Mesenchymal stem cells	Cell suspension	Intra-blister administration	Non-ulcer surface	Low	Long-term (sustained)	High
Krystal Biotech	Vyjuvek	*in vivo*	-	Virus containing gel	Local application	Ulcer surface	Low	Long-term (limited)	High
Abeona Therapeutics	prademagene zamikeracel	*ex vivo*	Skin keratinocytes	Epidermal Sheet	Epidermal sheet transplantation	Ulcer surface	High	Long-term (limited)	High
Castle Creek Biosciences	dabocemagene autoficel	*ex vivo*	Dermal fibroblasts	Cell suspension	Intradermal administration	Ulcer surface	High	Long-term (limited)	Low
Amryt Pharma	AP-103	*in vivo*	-	Protein solution	Intravenous administration	Whole body	Low	Short-term	High

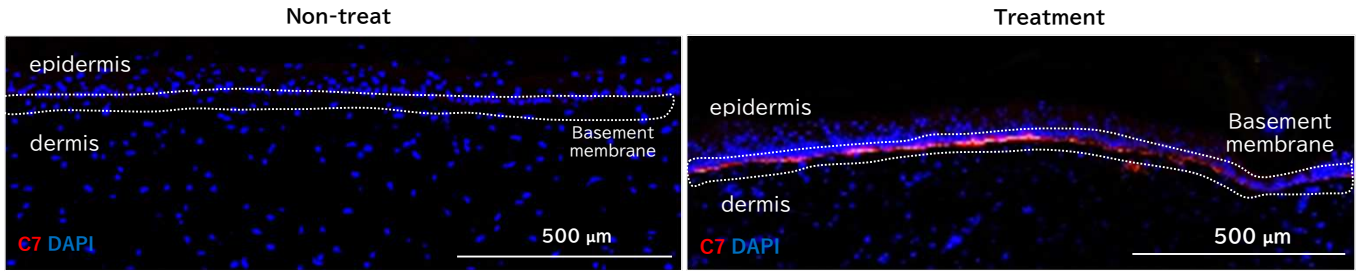
PJ5 Stem cell gene therapy

Verification of therapeutic efficacy and duration of drug effect of this treatment using RDEB model mice

■ Restoration of the type-VII collagen protein (C7) at the basement membrane on RDEB model mouse



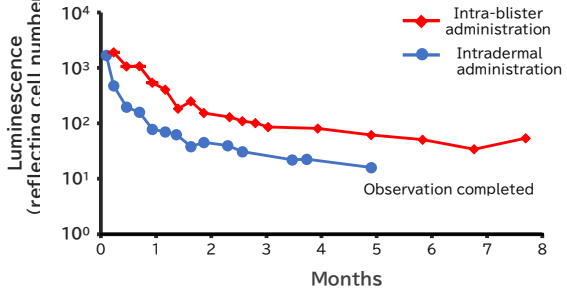
Skin tissue of RDEB model mouse after administration



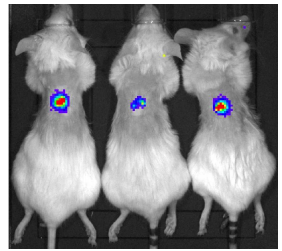
DAPI:

■ Long-lasting strong signal compared to the intradermal administration

Number of Bf-MSCs grown by route of administration



Intra-blister (5 months)



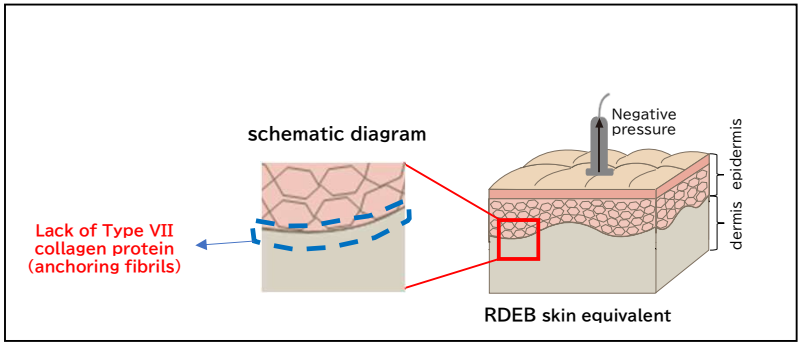
*Joint research between and Osaka University

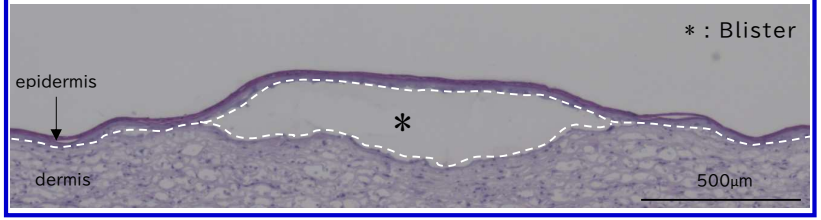
PJ5 Stem cell gene therapy

Therapeutic effects on RDEB skin model

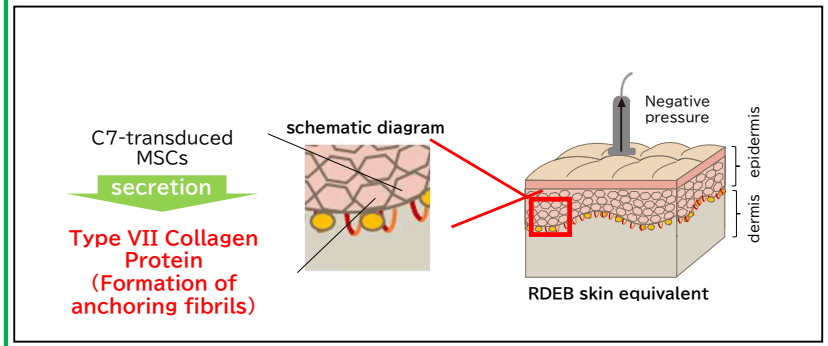
- We confirmed the effect of gene therapy using patient-derived Bf-MSCs by RDEB skin model and artificially forming blisters by suction method.

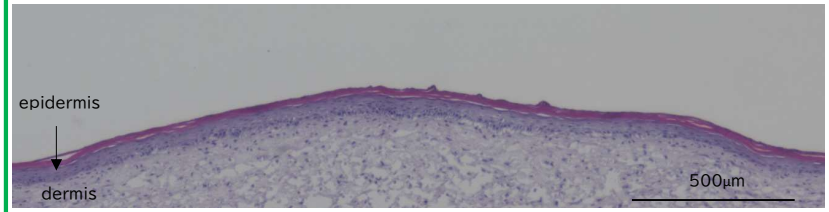
RDEB skin equivalents





RDEB skin equivalents with gene transduced Bf-MSC





Joint research between and Osaka University

Corporate information

Company name	StemRIM Inc.
Chief Executives	Kensuke Tomita（Representative Director） Masatsune Okajima（Representative Director）
Address	Saito Bio-Incubator 3F, 7-7-15 Saito-Asagi, Ibaraki City, Osaka, 567-0085 Japan
Established	October 30, 2006
Shareholders' equity	9,195 million yen(as of July 2023)
Number of Employees	75 (as of July 2023)
Number of R & D staff	58 research staff  *26 staff with Ph.D, including MD and Veterinarian *In-house patent attorney and pharmacist *Numbers as of July2023

Month/ Year	History
Oct. 2006	Established a company aiming to develop new drugs based on the discovery of bone marrow multi-potent stem cell mobilization factors identified by Professor Katsuto Tamai of the Graduate School of Medicine, Osaka University.
Apr. 2010	Transferred our head office to Saito Bio Incubator (Ibaraki City, Osaka Prefecture) and set up a laboratory there. Signed joint research agreement with Shionogi & Co., Ltd. on bone marrow-derived stem cell mobilization factors
Nov. 2014	Signed a license agreement with Shionogi & Co., Ltd. regarding Redasemtide (HMGB1 peptides)
Jan. 2018	An investigator-initiated phase 2 clinical trial of Redasemtide for dystrophic epidermolysis bullosa patients started at Osaka University. (to be completed in March 2020)
Apr. 2019	A company-initiated phase 2 clinical trial of Redasemtide for cerebral infarction patients started at Shionogi & Co., Ltd. (to be completed in December 2021)
Aug. 2019	Listed on the Tokyo Stock Exchange Mothers
June 2020	Established a new R&D base, "StemRIM Institute of Regeneration-Inducing Medicine, Osaka University".
Nov. 2020	An investigator-initiated phase 2 clinical trial of Redasemtide for Osteoarthritis of the knee patients started at Hirosaki University.
Nov. 2020	An investigator-initiated phase 2 clinical trial of Redasemtide for Chronic liver disease patients started at Niigata University.
Feb. 2021	Signed joint research agreement with Shiseido Co., Ltd. and Osaka University on anti-aging skin.
July 2022	An investigator-initiated additional phase 2 clinical trial of Redasemtide for DEB* patients started.
Mar. 2023	Notification of Preliminary Results of Data Analysis of Physician-Initiated Clinical Trial (Phase 2) on Redasemtide in Patients with Knee Osteoarthritis
April 2023	A global Phase 2b clinical trial of Redasemtide for Acute Ischemic Stroke started in Japan and US.
April 2023	Notification of Preliminary Results of Data Analysis of Physician-Initiated Clinical Trial (Phase 2) on Redasemtide in Patients with Chronic Leaver Disease.
July 2023	A global Phase 2b clinical trial of Redasemtide for Acute Ischemic Stroke started in EU and China.

StemRIM Management

Director

Kensuke Tomita, Chairman and CEO

Chairman and CEO, StemRIM Inc. (March 2019 – Present)
President, StemRIM Inc. (April 2018 - March 2019)
Director, StemRIM Inc. (July 2013 - April 2018)
External director, MEDINET Co., Ltd. (Oct. 2014 – Jan. 2016)
Advisor, StemRIM Inc. (April 2012 – June 2013)
President and CEO, OncoTherapy Science, Inc.
(April 2003 – June 2012)
President and CEO, Anges MG (currently Anges Inc.)
(June 2000 – March 2003)
Vice president, Rhône Poulenc Roller Inc.(currently Sanofi S.A.)
(Aug. 1994 – March 2000)
Sandoz KK (currently Novartis Pharma KK) (Nov. 1991 – July 1992)
Roller Japan Inc.(currently Sanofi S.A.) (July 1989 – Sep. 1991)
Eli Lilly Japan KK (July 1987 – April 1989)
Sankyo Co., Ltd.(currently Daiichi Sankyo Co., Ltd.)
(April 1974 – July 1987)

Masatsune Okajima, President

President, StemRIM Inc. (March 2019 – Present)
Vice president, Medicinova Inc. (Sep. 2006 – March 2019)
Deputy General Manager, Daiwa Securities SMBC Co., Ltd.(April 2002 – Aug. 2006)
Manager, Daiwa Securities SB Capital Markets Co., Ltd. (currently Daiwa Securities SMBC Co., Ltd.) (April 1999 – March 2002)
Sumitomo Capital Securities Co., Ltd. (Oct. 1996 – April 1999)
Sumitomo Bank, Ltd. (currently Mitsui Sumitomo Bank) (April 1991 – Oct. 1996)

Katsuto Tamai, Founder, Director

Director, StemRIM Inc. (Oct. 2022 – Present)
Professor, Endowed course of Regeneration-Inducing Medicine Graduate School of Medicine/ Faculty of Medicine, Osaka University (Oct. 2009 – Present)
Director, StemRIM Inc. (Feb. 2007 – Aug. 2010)
Associate professor, Department of Gene Therapy, Graduate School of Medicine/ Faculty of Medicine, Osaka University (May 2003 – Sep. 2009)

Noriko Sawai, External director

Head of healthcare team, Social Innovation and Investment Foundation (Aug. 2022 – present)
Impact Officer, Social Innovation and Investment Foundation (Feb. 2020 – July 2022)
External director, StemRIM Inc. (Oct. 2019 – Present)
DeNA Co. (June 2014 – Jan. 2020)
CSK Venture Capital Co. (April 1995 – May 2014)

Hirotada Nagai, External director

President, HyakusanSoken KK (July 2022 - Present)
External directors, StemRIM Inc. (Oct. 2020 - Present)
Auditor, Regional Fish Institute, Ltd. (May 2020 – Present)
Director, PRDM Co., Ltd. (March 2018 – Present)
Director, PorMedTec Co., Ltd. (Dec. 2017 – Present)
Director, Kyoya KK (Dec. 2017 - Present)
Pharmaceuticals and Medical Devices Agency (PMDA) (Sep. 2012 – July 2014)
Pharmaceutical and Food Safety Bureau of Ministry of Health, Labour and Welfare (April 2001 – Sep. 2017)

External Audit & Supervisory Board Member

Yoji Kudo, External audit

Akihiro Mizukami, External audit

Yoichiro Shimada, External audit