

Healios

“To be the change in an ever evolving world
through enrichment of living”

FY2016 3Q Financial Results

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1. Financial Highlights

Statement of income

(Million yen)

	FY 2015 3Q	FY 2016 3Q		
			YoY change	Reasons for increase/decrease
Sales	76	57	▲19	
Operating income	▲705	▲3,053	▲2,347	Research & Development Cost ▲2,269
Ordinary income	▲611	▲3,099	▲2,488	-
Net income	▲582	▲3,103	▲2,521	-
R&D	375	2,644	+2,269	Multistem License-in +1,809
Amortization of goodwill	75	75	–	-
Number of employees	42	53	+11	-

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Balance sheet

(Million yen / %)

	December 31,2015	September 30, 2016		
			Change	Main reasons for increase/decrease
Current assets	9,325 (88.9%)	8,665 (88.4%)	▲660	
Non-current assets	1,162 (11.1%)	1,138 (11.6%)	▲24	
Total assets	10,487 (100.0%)	9,803 (100.0%)	▲684	
Current liabilities	1,080 (10.3%)	1,052 (10.7%)	▲28	
Non-current liabilities	29 (0.3%)	2,451 (25.0%)	+2,422	Long-term debt +2,414
Total liabilities	1,110 (10.6%)	3,504 (35.7%)	+2,394	
Total equity	9,377 (89.4%)	6,299 (64.3%)	▲3,078	Earned surplus ▲3,103
Total assets	10,487 (100.0%)	9,803 (100.0%)	▲684	

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2. FY2016 3Q Updates

HLCM051 to Clinical Stage

Somatic stem cell regenerative medicine

HLCM051
MultiStem®



Clinical trial protocol notification was submitted to PMDA. A 30-day review period was completed for the clinical study initiation.

"Placebo-Controlled, Double-Blind, Phase 2/3 Efficacy and Safety Trial of HLCM051 (MultiStem®) in Patients With Ischemic Stroke"

Study Design

Subjects: Patients with onset of ischemic stroke within 18 to 36 hours prior to the start of the administration of the investigational product

Enrollment: 220 (HLCM051 group [n=110], or placebo group[n=110], randomized)

Study period: Approximately 2 years

Primary Endpoint: Proportion of subjects with an excellent outcome defined by the functional assessments on Day 90.

*Excellent Outcome

"Excellent Outcome" is defined as achieving mRs ≤1, NIHSS ≤1, and BI ≥95 in mRS, NIHSS, and BI, the three major indices of functional assessments for stroke patients.

(Source) Image: prepared by Healios based on the materials provided by Athersys

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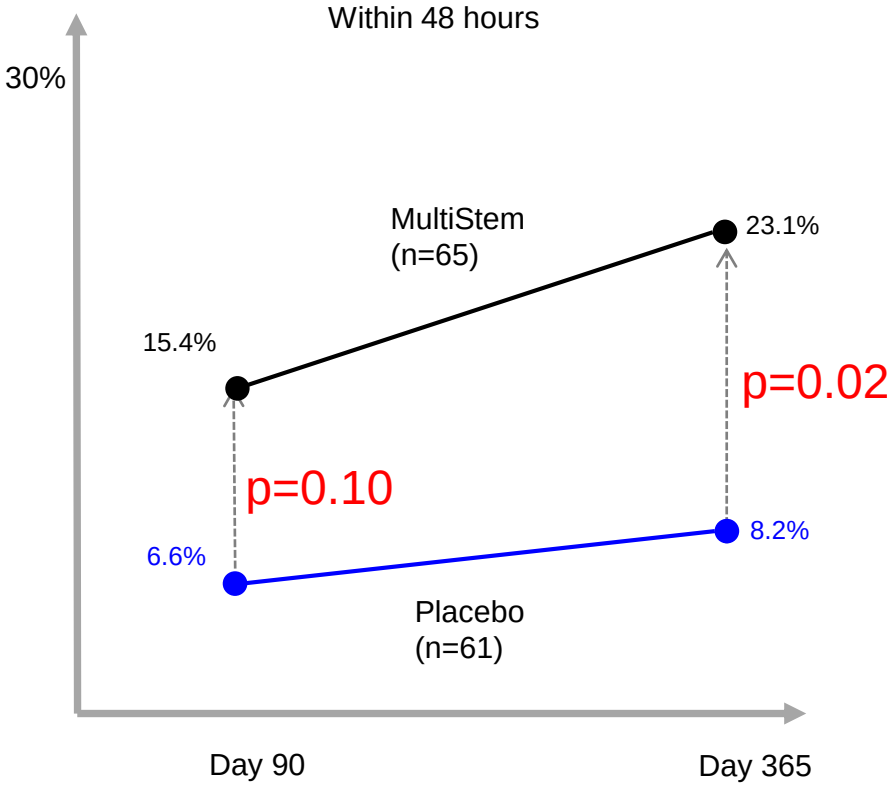
Study Design Based on the Result of the Phase II Study by Athersys in Europe and America

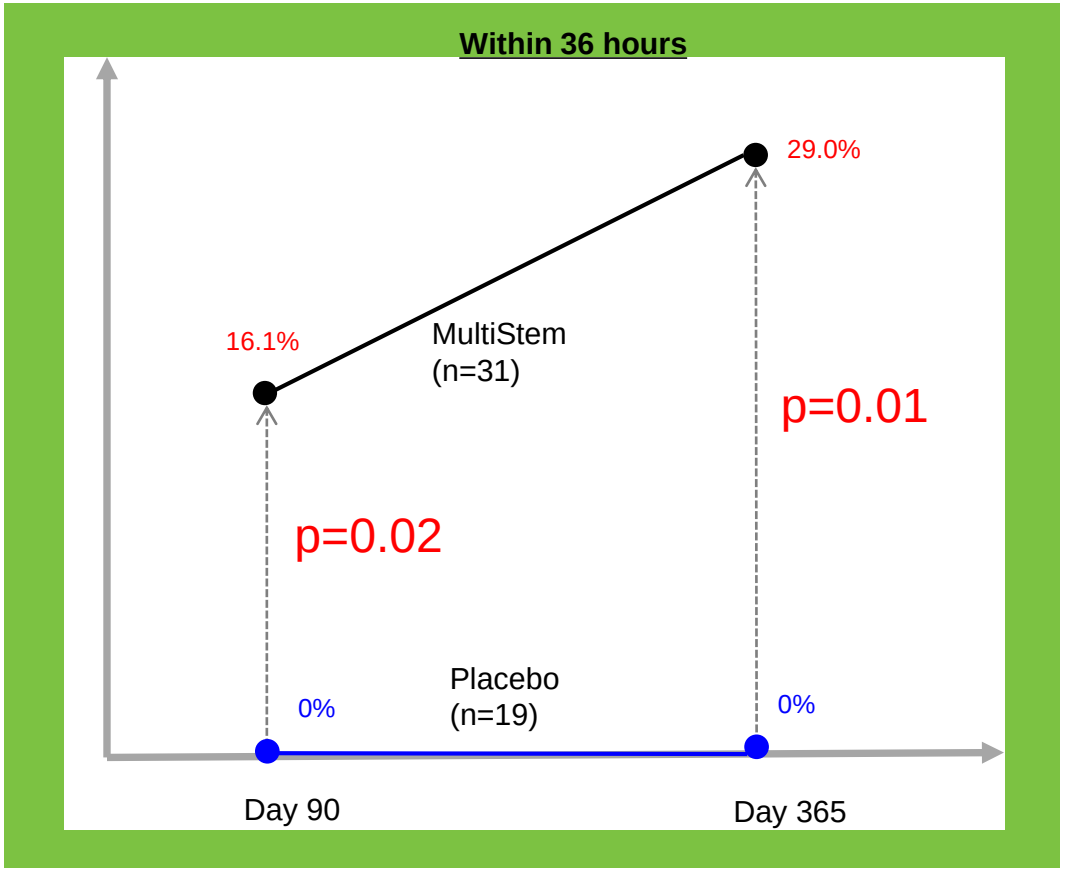
Somatic stem cell regenerative medicine

HLCM051
MultiStem®



The proportion of patients who achieved Excellent Outcome was statistically significant (compared with the placebo group) both at Day 90 and Day 365 in the group of patients who had received MultiStem within 36 hours of the onset of cerebral infarction.





(Source) Prepared by Healios based on the data provided by Athersys.

(Note) Excellent outcome = All of the following: mRS ≤ 1, NIHSS ≤ 1, and BI ≥ 95)

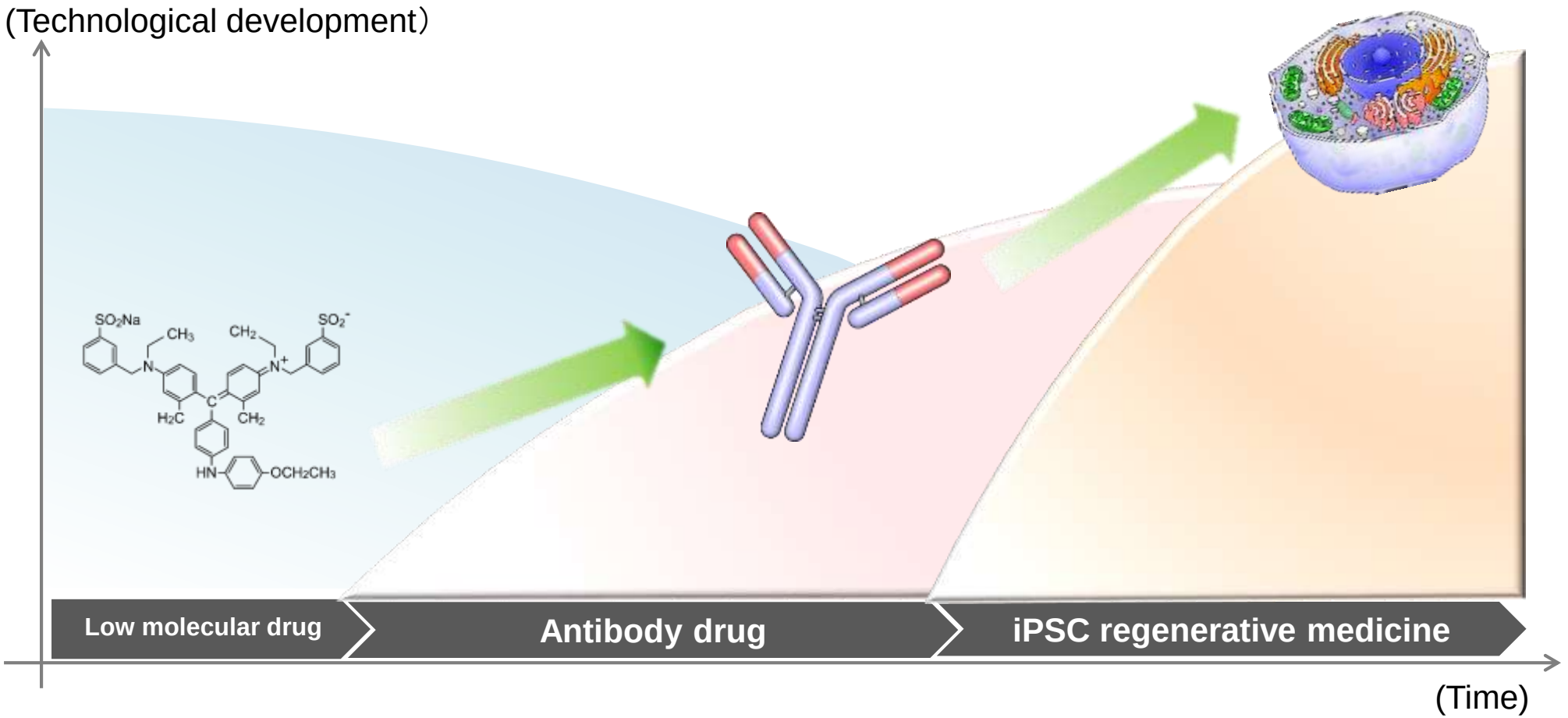
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Pipeline

Field	Development Code	Indication	Market	Pre-clinical test	Phase I Trial	Phase II Trial	Phase III Trial	Apply-approve	On the Market	Progress Status
Somatic stem cell Regenerative Medicine	HLCM051	Ischemic Stroke	Japan	→	→	→				**To Clinical stage**
iPSC Regenerative Medicine	HLCR011	Wet AMD	Japan	→						Start of clinical studies originally scheduled in 2017 may be delayed
	HLCL041	Metabolic Liver Disease	Japan	→						Joint research with Yokohama City University
	HLCR012	Dry AMD	US	→						Technical transfer
	HLCR012	Dry AMD	EU	→						Global Trial Under Consideration based on US Phase III Trial
Compound drug	HLM0021	Vitreous surgery	Japan	→	→	→	→			Under development at WAKAMOTO Co., Ltd.
	HLM0021	Cataract surgery	Japan	→	→	→				Development will be advanced immediately after licensee is determined.
	HLM0022	ILM Peeling	EU	→	→	→	→	→	→	Launched
	HLM0023	ILM Peeling	US	→	→	→	→			Under development at D.O.R.C.

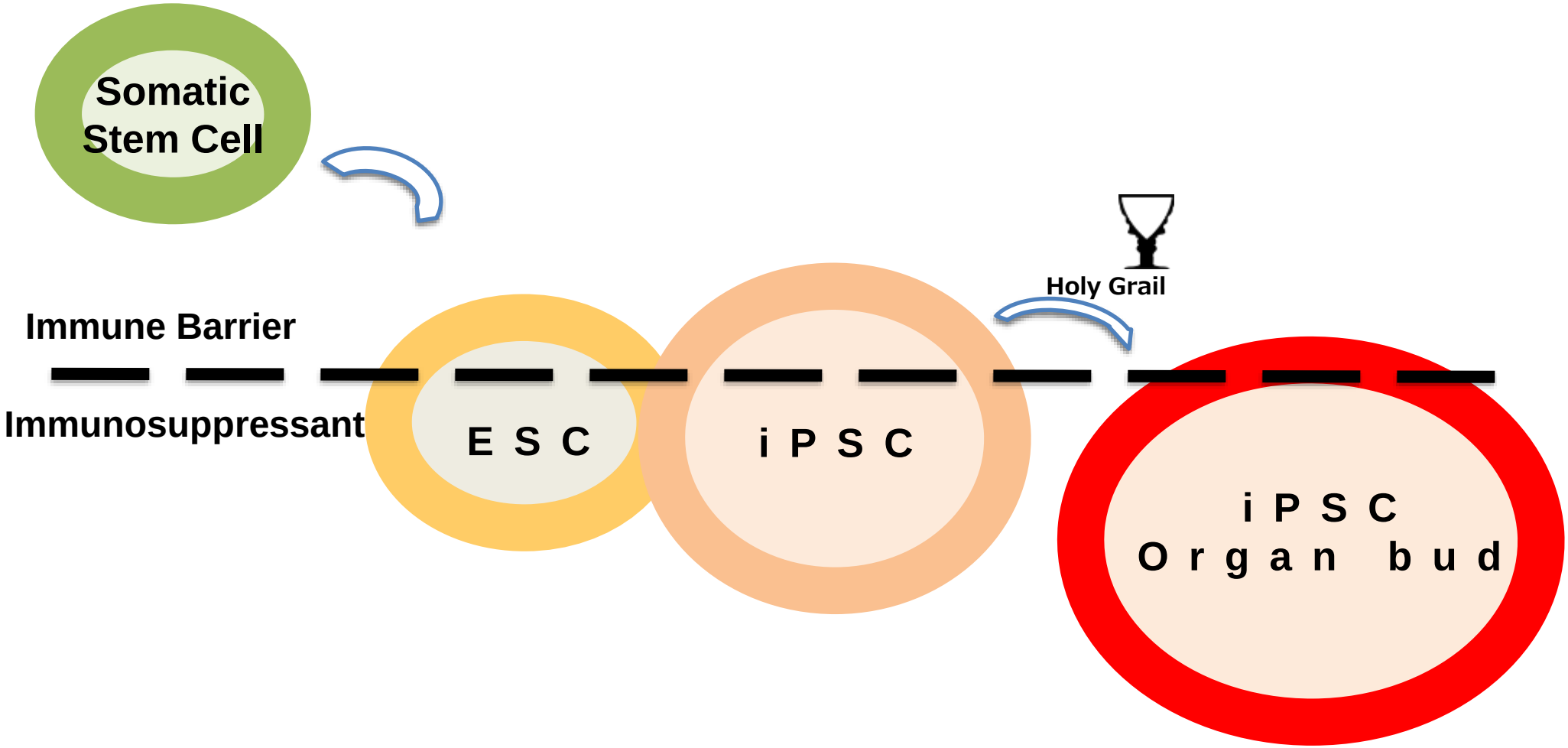
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Technological development from low molecular drug to antibody drug to iPSC regenerative medicine, etc.



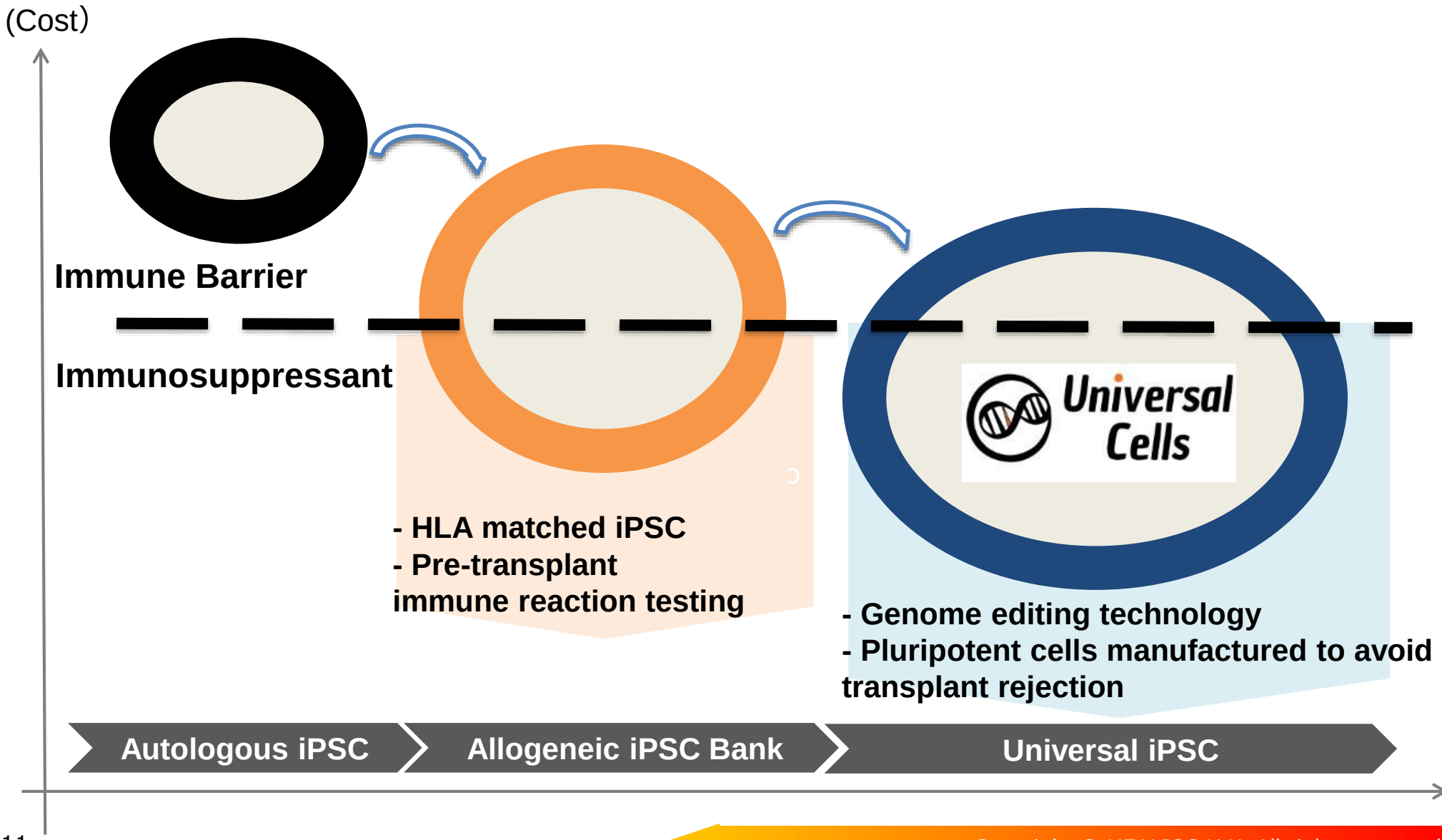
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Image of the Transition of Cellular Medicine Products



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Healios' approach for Technology for Immune Reaction



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3. Details of Somatic Stem Cell Regenerative Medicine

Introduced New Pipeline: HLCM051 in January 2016

Healios and Athersys, Inc. (“Athersys”) entered into a license agreement over products for regenerative medicine marketed in Japan, making use of the stem cell product MultiStem® and related technology, whose patent right and patent licensing authority are held by Athersys.

① An exclusive license for the development and distribution of MultiStem cell therapy for ischemic stroke in Japan and

② An exclusive license for the research and development of MultiStem as a material for manufacturing products for regenerative medicine (targeting metabolic liver diseases) now under joint research and development by Healios and the Public University Corporation Yokohama City University.

About Athersys, Inc

Company name	Athersys, Inc. （NASDAQ:ATHX）
Representative	Gil Van Bokkelen, Ph.D. Chairman and CEO
Head Office	3201 Carnegie Avenue, Cleveland, Ohio
Paid in Capital	$323 million (As of end of December 2015）
Number of Employees	60 (As of end of December 2015）
Research Institution	Cleveland, Ohio (U.S.A.) and Leuven, Belgium (E.U.)
Major Share Holders	Pappas Ventures, Sabby Management, The Vanguard Group, M&G IM

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Outline of Ischemic Stroke in Japan

Ischemic stroke

Ischemic stroke, which represents the most common form of stroke (70–75% in Japan), is caused by a blockage of blood flow in the brain that cuts off the supply of oxygen and nutrients and results in tissue loss

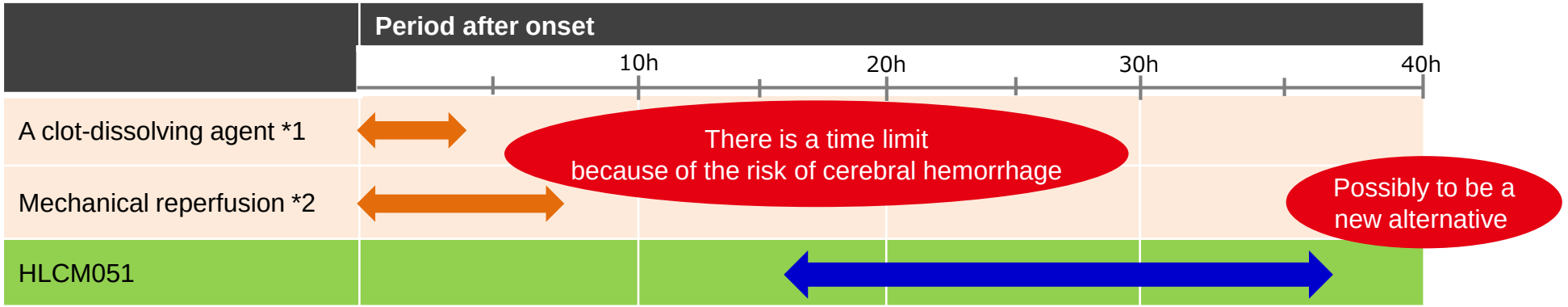
It is estimated that 37.9% of bedridden patients and 21.7% of persons who were in need of care were affected by ischemic stroke



（Source）Athersys

Treatment in accordance with the period after onset

■ Expected development of a new therapy that can be used during a longer period after the onset of ischemic stroke (ability to help more patients)



*1: Dissolves blood clots in the brain vessels. *2: Insertion of the catheter into a blood vessel and recovering the thrombus directly with a wire

(Note) This material was prepared to explicitly describe the major therapeutic options for ischemic stroke and their treatment window periods after onset. Appropriate treatments are conducted according to patients' conditions and classification of their symptoms. Experimental or investigational treatments not included in the above are also performed.

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Annual number of new patients with ischemic stroke in Japan

Target population

	Japan	Note
Number of patients (year)	**230,000 – 330,000**	Annual medical costs for ischemic stroke estimated at 1070.7 billion yen（2009）
Severe patients（atherothrombotic and cardiogenic cerebral infection)	**130,000**	
patients within 36 h after onset	**62,000**	

(Source) Healios estimated the annual number of new patients with ischemic stroke in Japan according to the materials issued by the Fire and Disaster Management Agency, the Ministry of Internal Affairs and Communication, and the Ministry of Health, Labour and Welfare – DATAMONITOR epidemiological estimate also shown as upper end of range.
(Source) Healios estimated the percentage of patients who reach the hospital within 36 hours after onset at 47% according to the result of its market research.

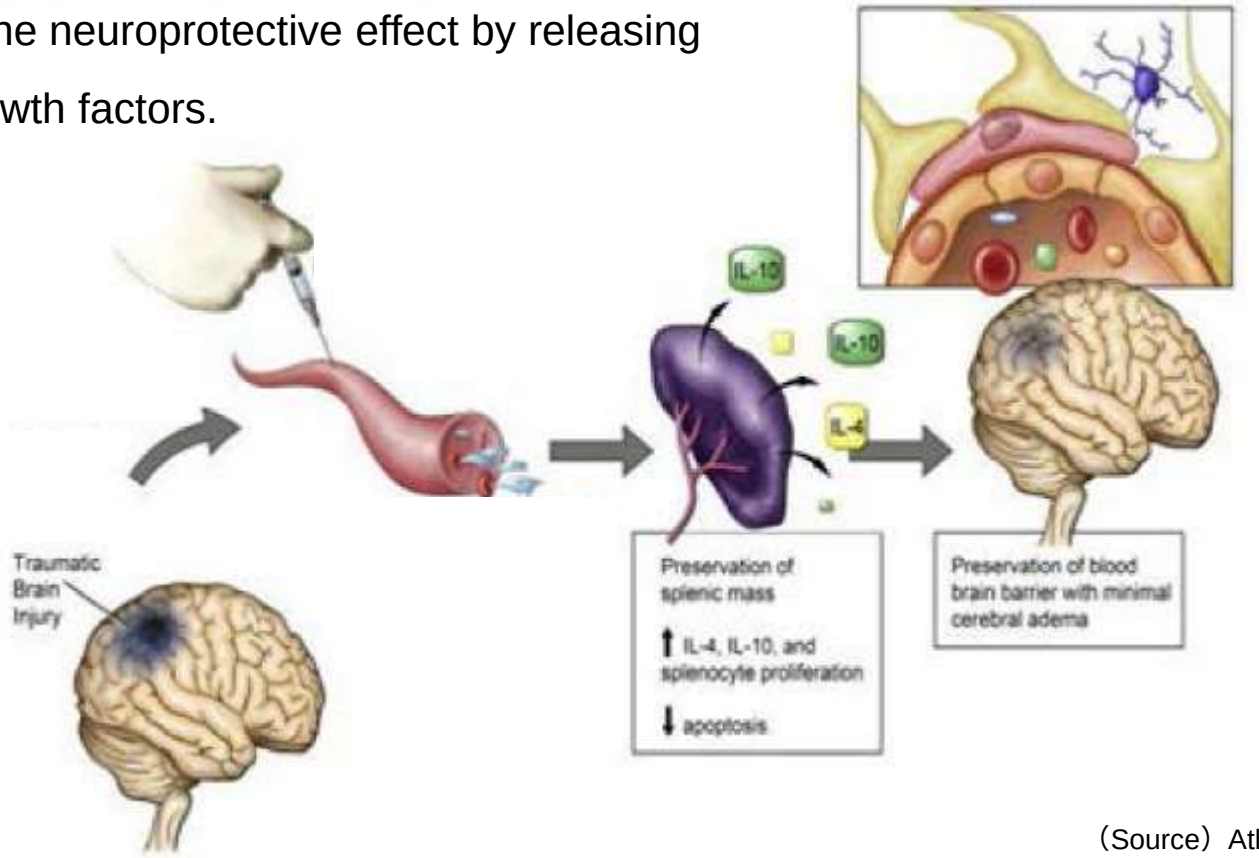
(Note)Calculated using 2013 and 2014 fiscal year-end exchange rates.

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Mechanism of treatment using HLCM051

Exhibits its therapeutic efficacy by suppressing inflammation and immune reactions and stimulating the formation of neuroprotective substances

- Following intravenous administration after acute neurological injury, HLCM051 distributes to spleen, downregulating hyperinflammatory response
- HLCM051 promotes the neuroprotective effect by releasing various cytokines and growth factors.



（Source）Athersys

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HLCM051 Product Profile



（Source）Athersys

- Cell therapy product based on patented technology
- Developing for “off-the-shelf” administration: no tissue matching needed
- Long shelf life: can be kept stably frozen for years
- Consistent safety profile
- Promotes healing and tissue repair through multiple mechanisms of action
- Not a permanent transplant: cells cleared from the body over time

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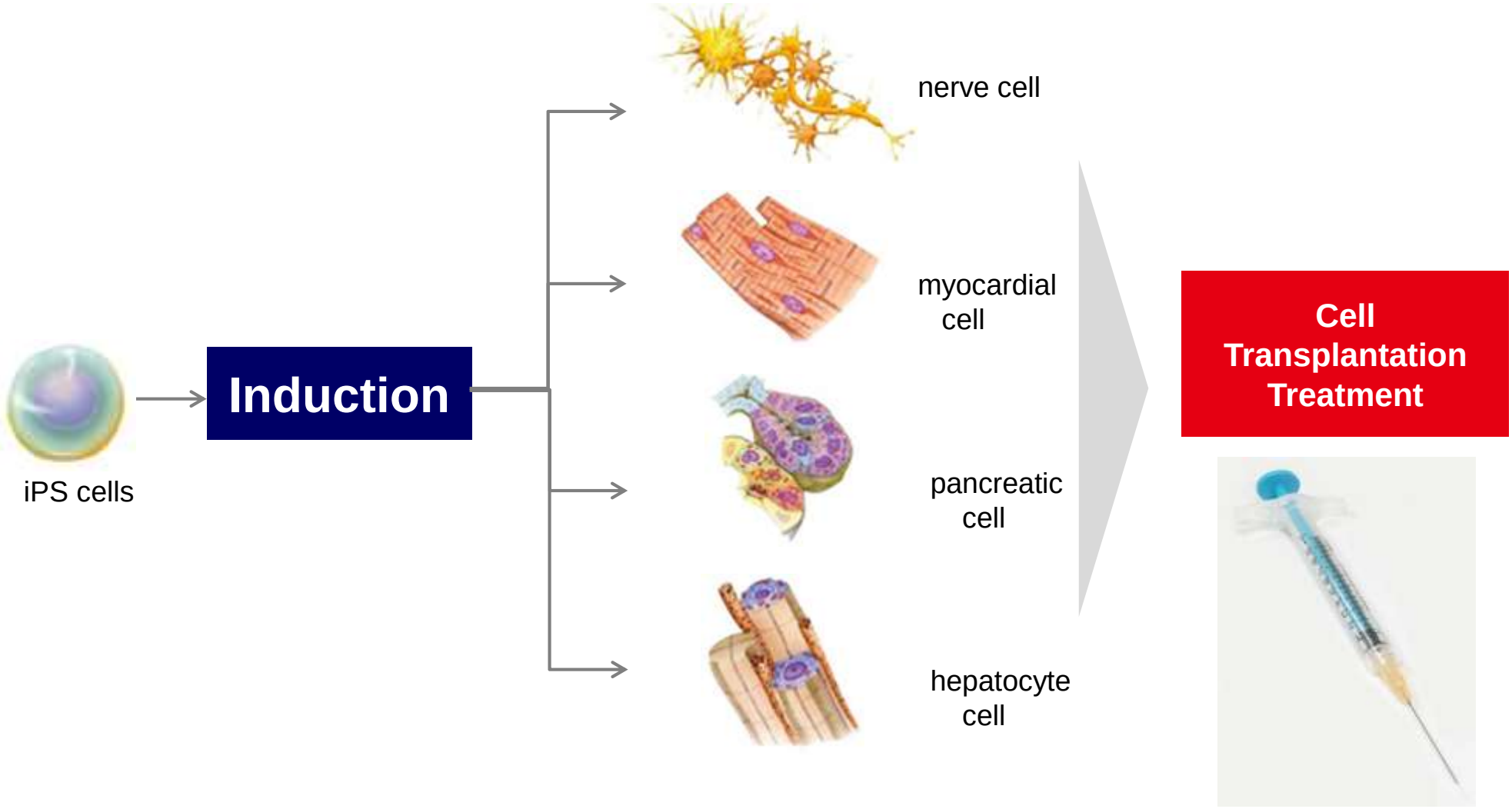
4. Details of iPSC Regenerative Medicine

Step 1 Treat diseases with iPS Cells

Step 2 About AMD and Profitability

Step 3 Strategy for Placing RPE Cell Medicine on the Market

Make “Regular Cells” from iPS Cells



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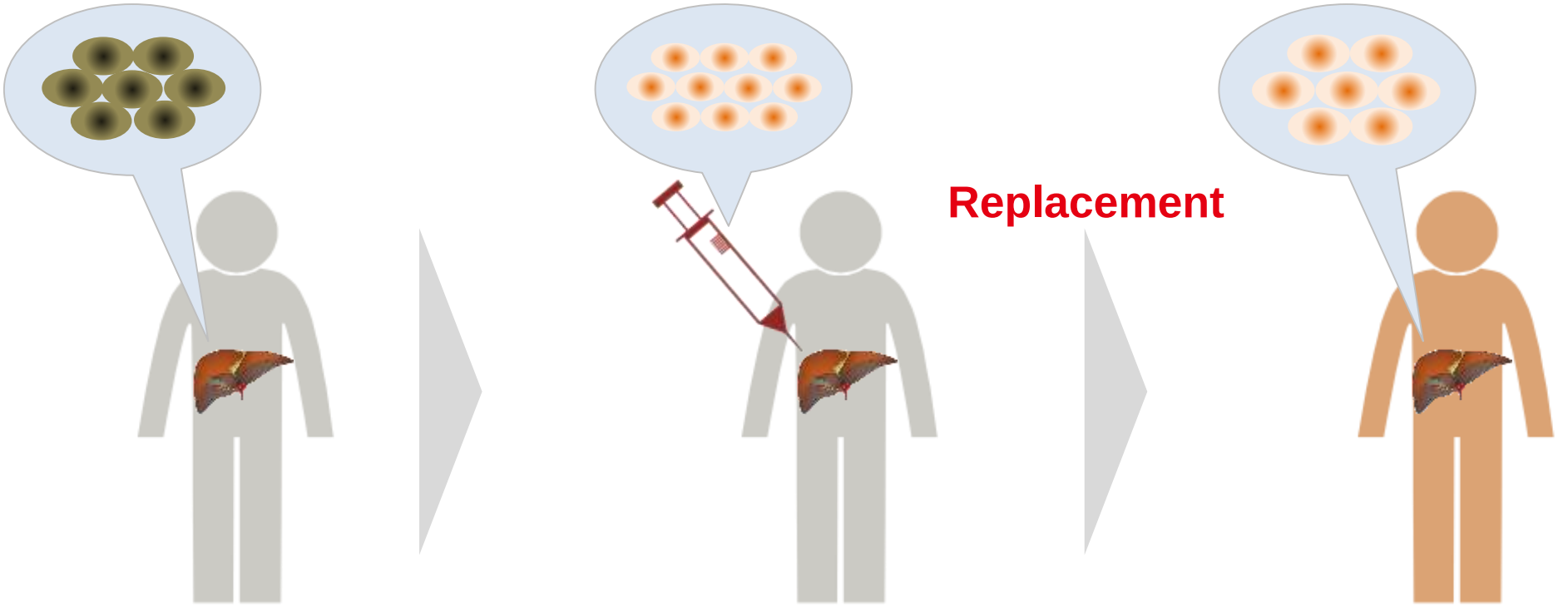
Mechanism of iPSC Regenerative Medicine

Replace damaged cells with regular cells

Tissue (cells) Damaged by Aging, Disease or Accident

iPSC Regenerative Medicine
Target Cells made from iPS cells

Replace Damaged Tissue (cells) with regular cells



Patient

Recovery of Organ Function

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4. Details of iPSC Regenerative Medicine

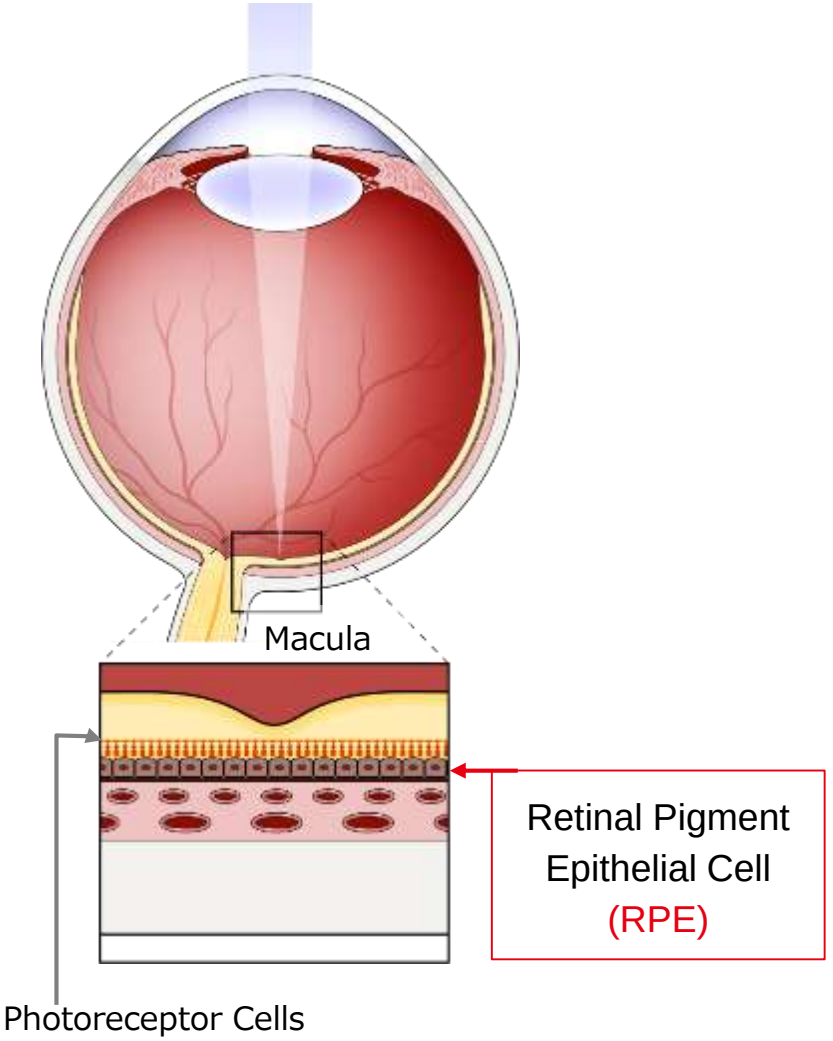
Step 1 Treat diseases with iPS Cells

Step 2 About AMD and Profitability

Step 3 Strategy for Placing RPE Cell Medicine on the Market

Explanation of AMD Pathological Condition

AMD causes RPE Cells to degenerate, which will damage functions



Regular Macular Part

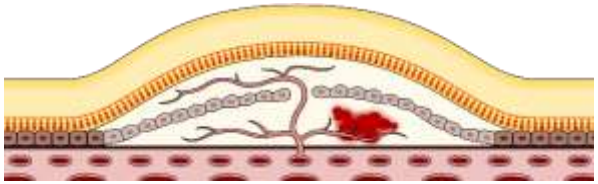
Developed Dry AMD

Immunity Barrier Maintained → Visual Cell Degenerative Disease → Dry AMD



Wet AMD

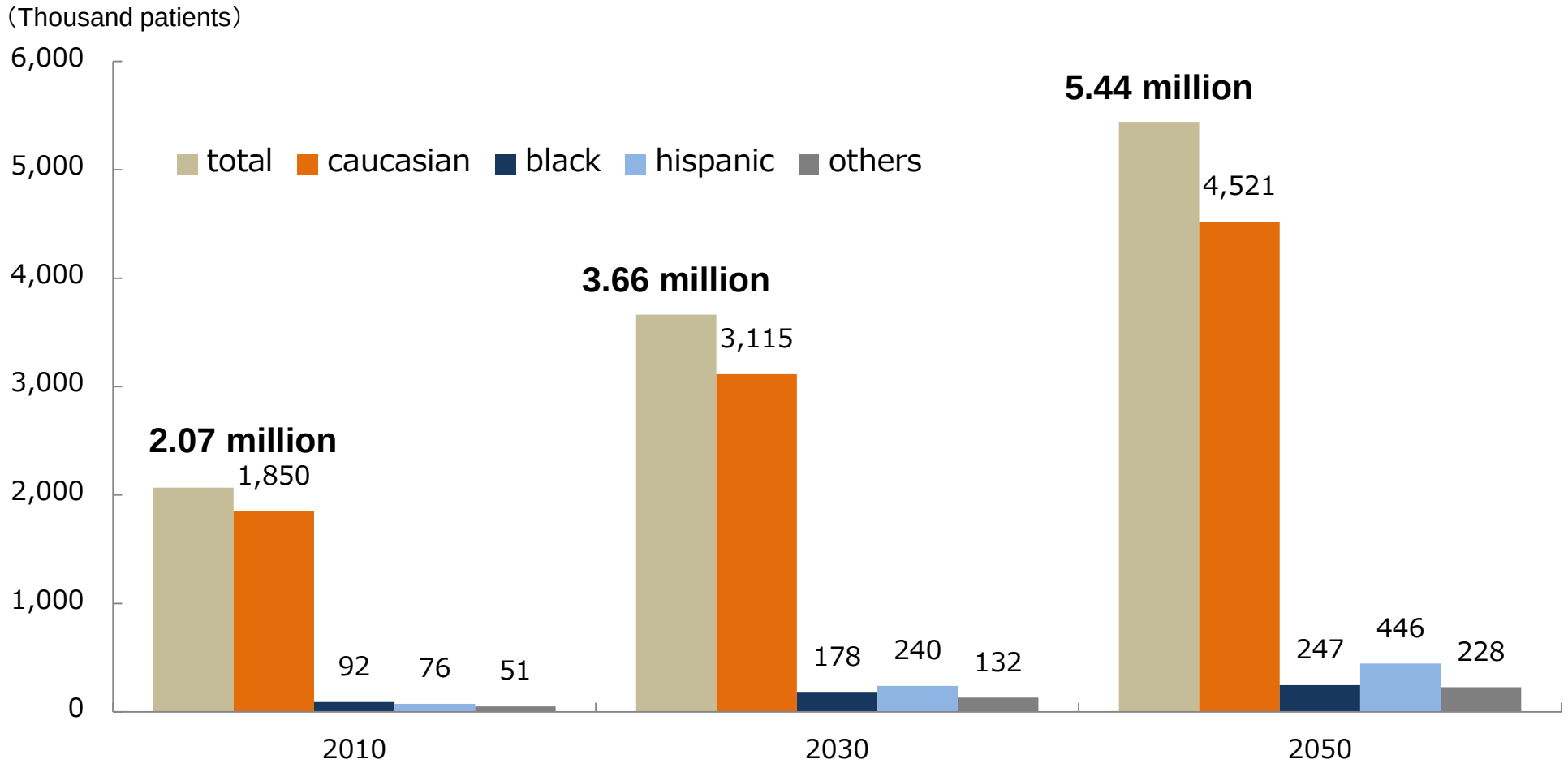
Destruction of Immunity Barrier → Invasion of Immunity Cells → Inflammation → Wet AMD



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Estimated Number of AMD Future Patients in Serious Cases in US

Expected to Increase over Medium to Long Term as Society Ages



（source）National Eye Institute

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Number of AMD Patients

Number of both Wet and Dry patients (including mild cases)

（Thousand patients）

	America	Japan	Others
The Number of AMD Patients	**10,000**	**9,230**	**13,000**
The Number of AMD Patients in Serious Cases	**2,000**	**690**	**2,600-3,220**
Wet-Patients in serious cases	**1,000-1,500**	**630**	**1,300-1,950**
Dry-Patients in serious cases	**850-900**	**60**	**1,100-1,170**

※According to research by Hisayama Kyushu University Graduate School of Medicine in Fukuoka (based on a comprehensive study), the total number of patients in Japan is calculated, estimating the total number of first-stage age-related macular degeneration and latter stage of age-related macular degeneration based on population statistics（2007）Also, the Disease Information Center announced that the number of patients suffering serious cases is approximately 690,000. The total number of patients in the US, which the National Eye Institute reports, includes the total number of age-related macular degeneration patients in mild cases and patients with visual field defects. Also, our company calculated the total number of Dry/Wet patients based on the incidence rates presented by AMDF (2010). Our company calculated the total number of patients in Europe based on incidence rates in each grade of European population statistics （2010）

※source: Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE).Source: Arch Ophthalmol. 2006 Apr;124(4):529-35

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Market Scale of AMD

Annual Sales of Medicinal Treatments of Wet AMD: 831.6 billion yen. No Medicine for Dry AMD.

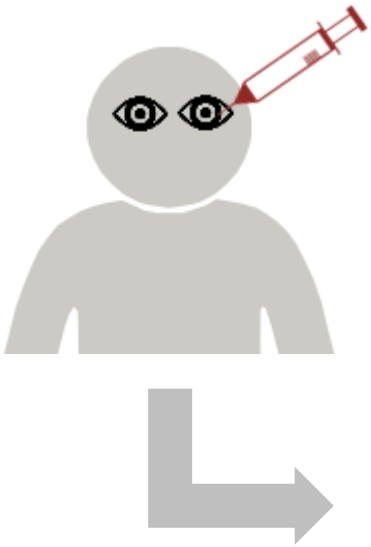
Condition	Medicine/Effect	Year	America	Japan	Others	Total
Wet	Anti-VEGF Medicine/ Restraint of New Blood Vessels	2013	**363.6 billion yen**	**38.0 billion yen**	**294.7 billion yen**	**696.3 billion yen**
		2014	**414.1 billion yen**	**55.7 billion yen**	**361.8 billion yen**	**831.6 billion yen**
Dry	**No Medicine**					

(source)Market scale was calculated using official materials from drug companies (Roche Diagnostic, Novartis, Regeneron,Bayer HealthCare, Santen Pharmaceutical Co., Ltd). Calculated using 2013 and 2014 fiscal year-end exchange rates.

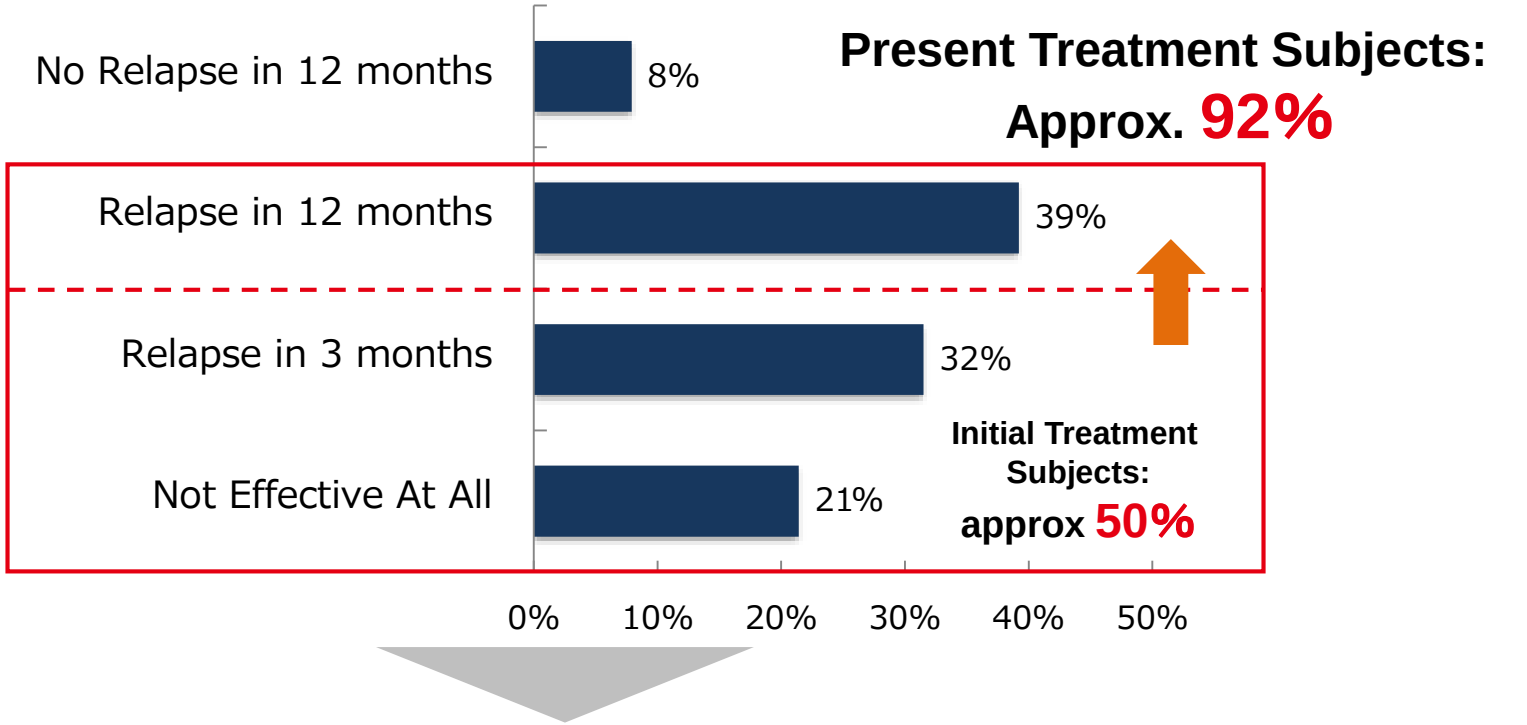
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Treatment Subjects for Wet AMD

Patients recurring within 1 Year, which is the case of approx. 92% of Wet AMD Patients, are the candidates for treatment.



Recurrence frequency after receiving anti-VEGF medication



Present Treatment Subjects: Approx. 92%

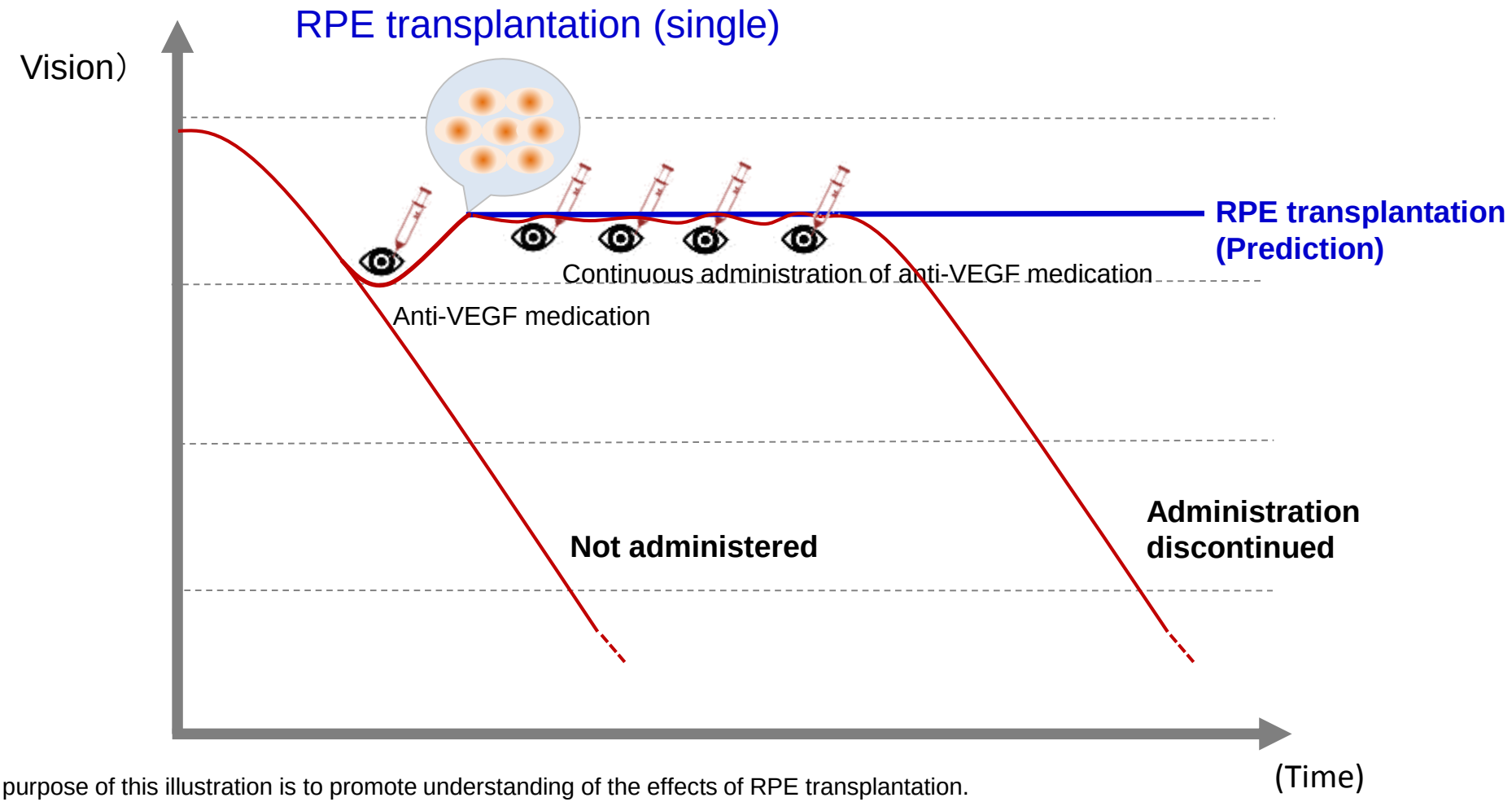
Initial Treatment Subjects: approx 50%

QOL of Continuously Medicated Patients is not High.

(source) 13th Annual Meeting of The Japanese Society for Regenerative Medicine March 19th Thurs, 12:00～12:50
Approach to Clinical Application of iPS cells Institute of Physical and Chemical Research, Mandai Michiko

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Good vision can be maintained with early treatment



* The purpose of this illustration is to promote understanding of the effects of RPE transplantation.
Changes in vision with the administration of anti-VEGF medication are not the same as the above according to patient symptoms and administration frequency.

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Guide to Medicine Price – Approach from Medical Expense of Existing Health Care

Anti-VEGF Medicine mostly Continues From the Beginning of the Treatment to Death

Annual Medical Expense

Unit Price of Anti-VEGF
170,000 yen

✖

Annual Recommended Medication Protocol
6 Times

＝

Annual Medical Expense
1,020,000 yen

Estimate of Lifetime Medical Expense

On the Assumption of Average Life Span (Japan): 80years old (Male) / 86 years old (female)

Estimate of Lifetime Medical Expense

Continuous Treatment for **50-year old Patient Onset** ＝approx. **30years** ✖ **1.02 million yen** ＝ **Approx. 30 million yen**

60-year old Patient Onset ＝approx. **20years** ✖ **1.02 million yen** ＝ **Approx. 20 million yen**

(source) Onset Data: National Eye Institute; Average Life Span: The Ministry of Health, Labor and Welfare; Annual Recommended Medication Protocol: Materials Presented by Institute of Physical and Chemical Research

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4. Details of iPSC Regenerative Medicine

Step 1 Treat diseases with iPS Cells

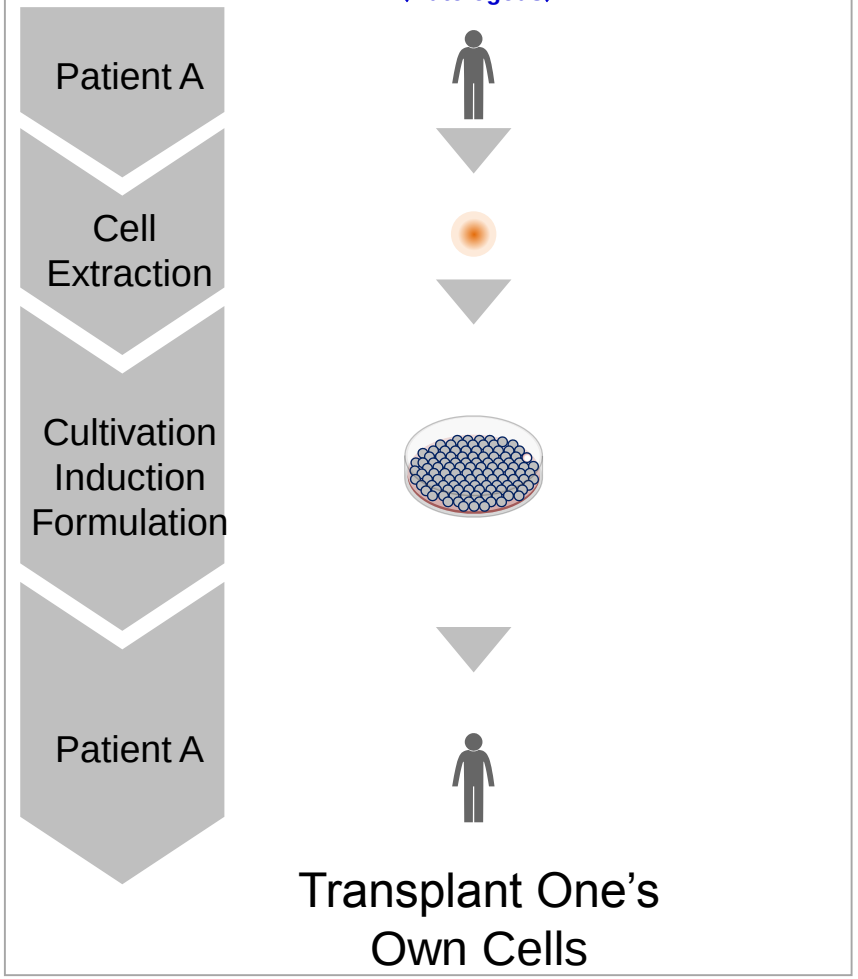
Step 2 About AMD and Profitability

Step 3 Strategy for Placing RPE Cell Medicine on the Market

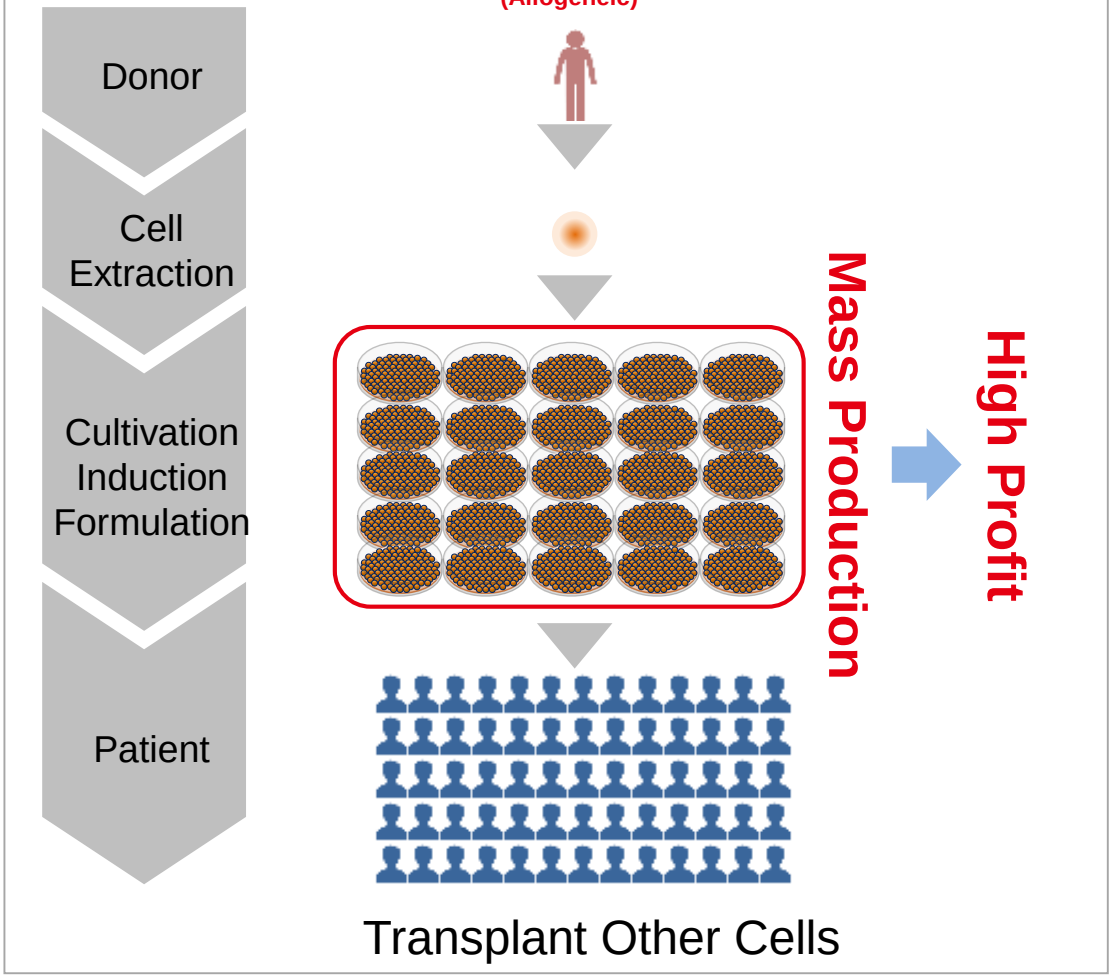
Autologous and Allogeneic Transplantation

We Handle Cross-Regenerative Medical Treatment , with High Profit Margins

iPSC Regenerative Medicine
(Autologous)



iPSC Regenerative Medicine
(Allogeneic)



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Project System

Arranged Domestic Value Chain by Cooperation with Sumitomo Dainippon Pharma Co., Ltd

Development → Production → Marketing → Sales

Can Build Up Developing, Sales and Manufacturing in Japan

Development	Production	Marketing	Sales	
Healios 6.8 billion yen by Collaborative Development with Sumitomo Dainippon Pharma Co., Ltd	**SighRegen**(※) Secured Personnel Structure for Pharmaceutical Manufacturing	**SighRegen** Approved Sales Promotion	**Healios** Sales	Medical Institution

(※) Joint Venture with Sumitomo Dainippon Pharma Co., Ltd

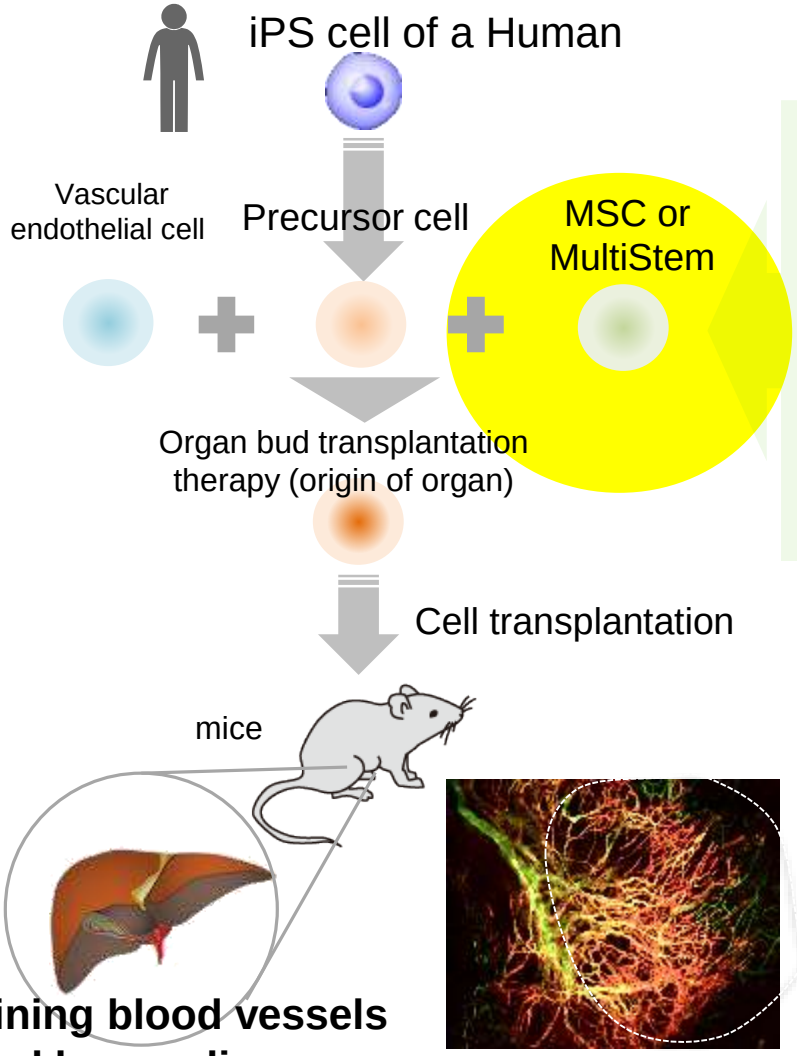
Flexibly Examine Collaborative Development, Prioritizing Self-Manufactured Sales

Development	Production	Marketing	Sales	
Healios Initial POC in Japan	**Healios** Contract Manufacturing to Lonza	**Under Consideration** (Under Consideration)	**Under Consideration** (Under Consideration)	Medical Institution

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5. Expansion to 3D Organs（Liver）

Generating “Orgun bud” by co-culturing 3 types of cells



Containing blood vessels and human liver

Consideration of the availability of MultiStem

Consideration of the large supply of MultiStem



(Source) Athersys

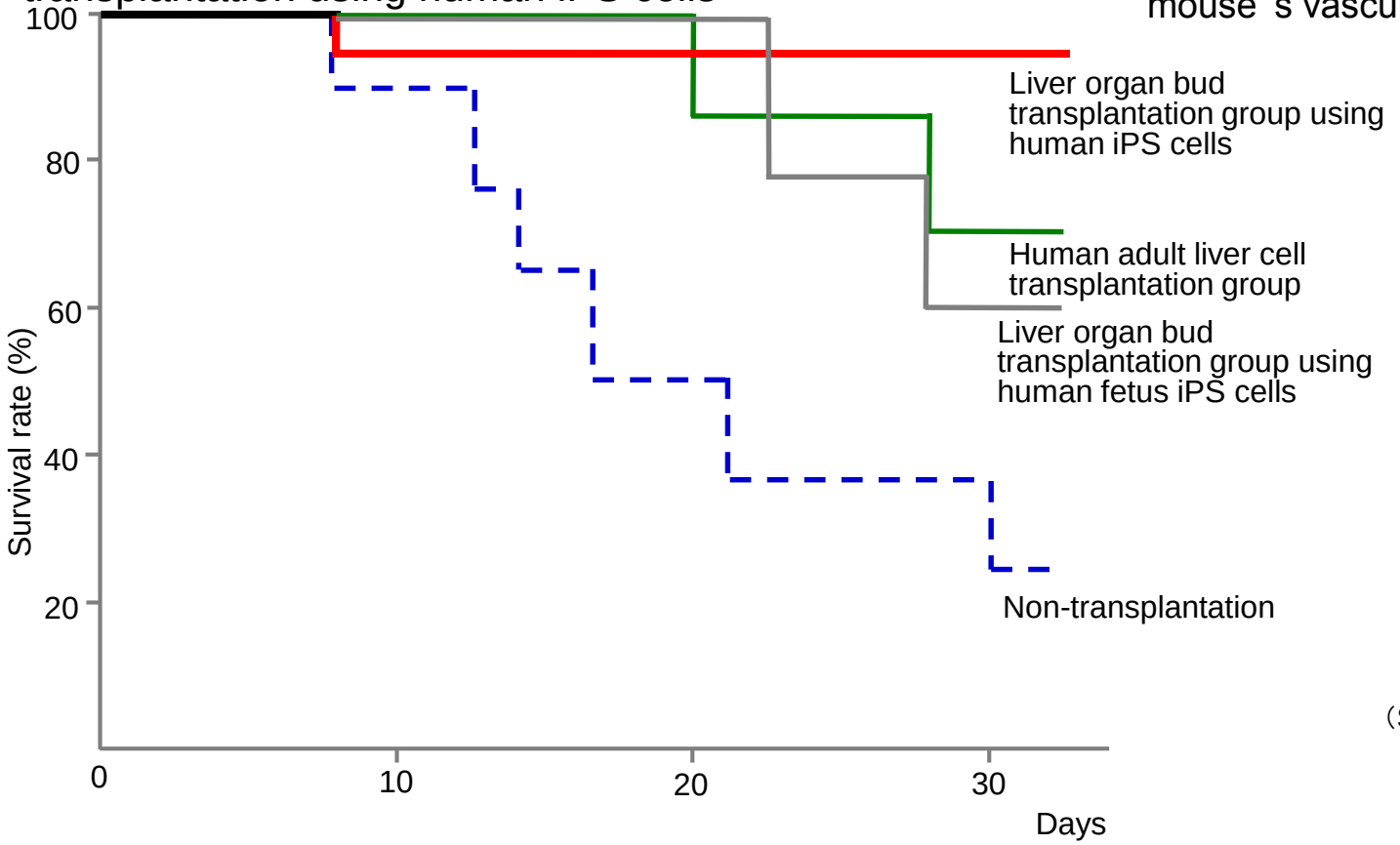
（Source）Takebe, T., et al. Nature Protocols, 9, 396–409 (2014)

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Survival Rate of Liver Failure Model Mouse

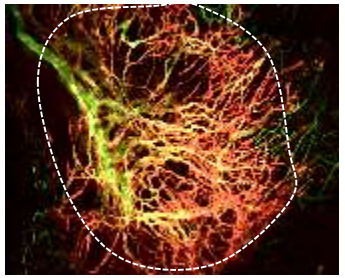
Survival rate improves significantly in transplantation experiments

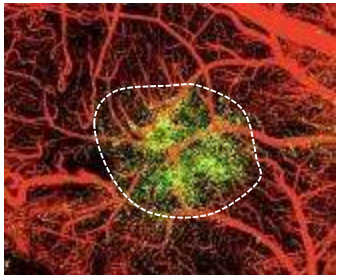
Treatment effects of liver organ bud transplantation using human iPS cells



（Source） Adapted bu Healios from Takebe. T, et al. Nature, 499 (7459),（2013）

Process in which organ formed from organ bud links mouse ‘s vascular network autonomously





（Source）Takebe,T., et al.
Nature Protocols, 9, 396–409 (2014)

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Yokohama City University planning to start clinical study in 2019

Urea cycle defect

Disease caused by congenital abnormality of enzyme functioning in metabolic pathway (urea cycle) which detoxifies ammonia in the liver and produces urea. Presently, the only definitive treatment available is liver transplantation.

* Even patients with minor conditions require treatment combining food treatment and medication to lower ammonia levels throughout their lives.

Estimated market size of metabolic liver disease in newborns

	US	Japan	Europe	Total
Number of patients (year)	**Approx. 160**	**Approx. 30**	**Approx. 230**	**Approx. 420**
Treatment costs (Annual) Enzyme replacement therapy	**30 million yen – 50 million yen**			
Estimated annual market scale	**5 –8 billion yen**	**1 –1.5 billion yen**	**6 –11.5 billion yen**	**12 –21 billion yen**

∗ Number of patients and market size are estimated by Healios based on number of newborns, incidence rate.

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Expansion of Marketability (Alternative Treatment for Replacing Liver transplantation)

Prospecting R&D for alternative treatment for liver transplantation

	Liver transplantation			Total
	US	Japan	Europe	
Number of patients undergoing treatment (Annual)	**Approx. 6,000**	**Approx. 400**	**Approx. 4,000**	**Approx. 10,000**
Number of patients on waiting list (Annual)	**Approx. 15,000**	**Approx. 400**	**Approx. 4,000**	**Approx. 20,000**

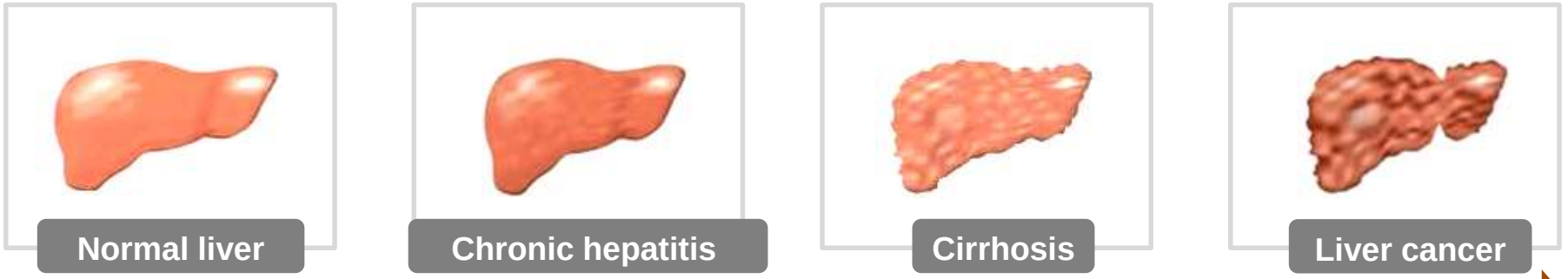
（Source） Compiled by Healios based on materials disclosed by Japanese Liver Transplantation Society, UNOS, Eurotransplant, UK Transplant, Agence de la biomédecine, and Scandia Transplant.

Liver disease drawing attention in future is cirrhosis

Estimated patients with cirrhosis in Japan: 400,000 to 500,000. About 56,000 receive treatment at medical facilities.
Annual deaths in Japan: 17,000 patients.

（Source） Patient Survey 2011 Liver Cancer White Paper 2015

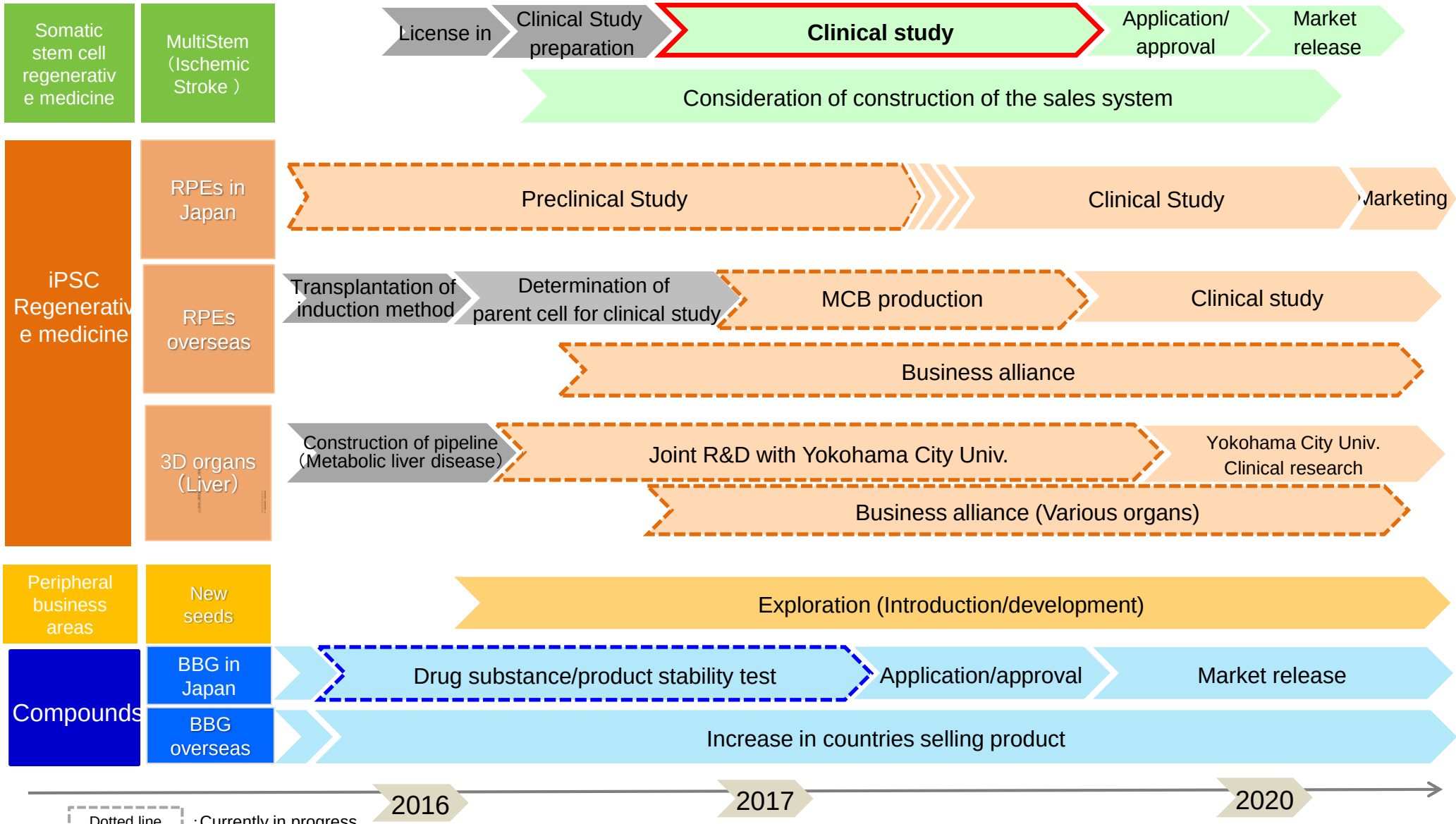
Progress of liver disease



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6. News Follow-Up

Summary of Main News Follow-Up



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7. Company Overview

Healios Overview

About Us

Company Name	HEALIOS K.K.（TSE: 4593）
Representative	Hardy TS Kagimoto,MD　President and CEO
Head Office	World Trade Center Building 15F 2-4-1 Hamamatsucho Minato-ku, Tokyo　Japan 105-6115
Paid in Capital	5,387million yen(As of end of September, 2016)
Research Institution	Kobe and Yokohama
Number of Employees	53　(As of end of September, 2016)
Affiliated Company	SighRegen Co., Ltd. (Joint Venture with Sumitomo Dainippon Pharma Co., Ltd.)

How it was founded

- Started business to establish treatments for age-related macular degeneration and determined to build up a pharmaceutical company which can provide treatments for intractable diseases.
- Founded Aqumen Biopharmaceuticals K.K. (later transferred business to Healios), succeeded in developing BBG250, entered into a contract with DORC, and started selling across Europe.
- Appraised by RIKEN, targeted the very first iPSC regenerative medicine based on iPS cells, which have the potential to be a complete cure for age-related macular　degeneration, and we are responsible for putting retinal pigment epithelial cells to practical use.

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Our Experienced Team for Development

Lineup to Develop in Japan, US, and Europe

Ophthalmology Expert



President and CEO

Hardy TS Kagimoto, MD

- Succeeded in Developing BBG and Realized Sales in Europe

Expert in Age-related Macular Degeneration



Director Overseas Development

Al Reaves, Ph.D

- Responsible for innovative clinical programs for wet & dry AMD - Lucentis (X-US); Visudyne (global)

Experts in Immunosuppressant Development



Director of Laboratories in Kobe , Research and Manufacturing

Kouichi Tamura, Ph.D

- Astellas US Director of Laboratories
- Well-acquainted with Immunosuppressant Research



Director Domestic Development

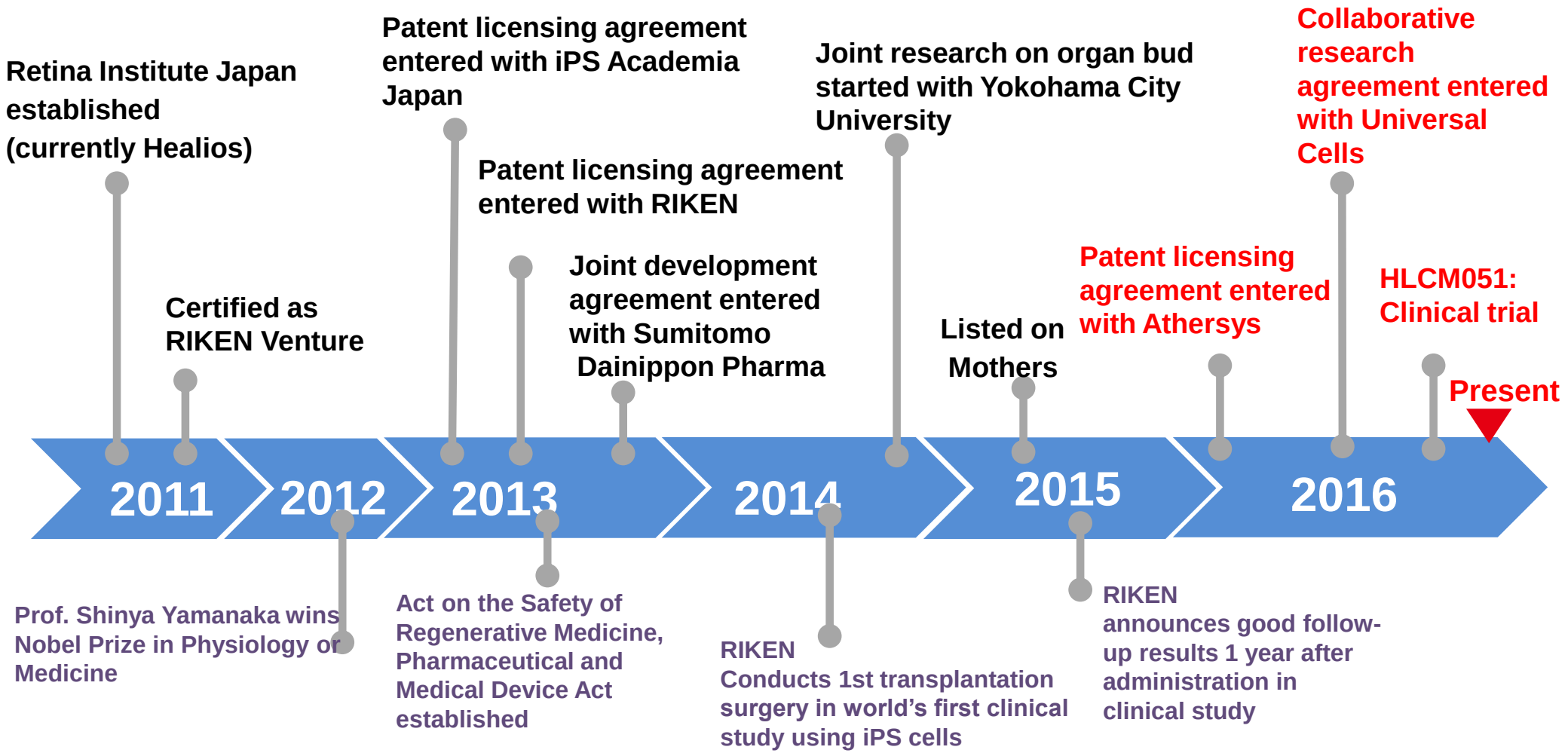
Michihisa Nishiyama

- Constructed Network for Tacrolimus Approval and Sales at Astellas in the US and Europe

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Company History and Social Trends

Pioneer of iPSC regenerative medicine development



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8. Appendix

Rapid Impact of Modified Regulations

Approval of regenerative medicine products, September 2015

Product Name	Temcell® HS Injection	Heart Sheet
Company	JCR Pharmaceuticals	Terumo
Indications	Acute GVHD after hematopoietic stem cell transplantation	Severe heart failure due to ischemic heart disease
Price	13.9 million yen	14.76 million yen
Important Point	First allogeneic cell-based regenerative product	First conditional approval

(note)Calculated using 2013 and 2014 fiscal year-end exchange rates.

Price calculation method prospects

Cost accounting system

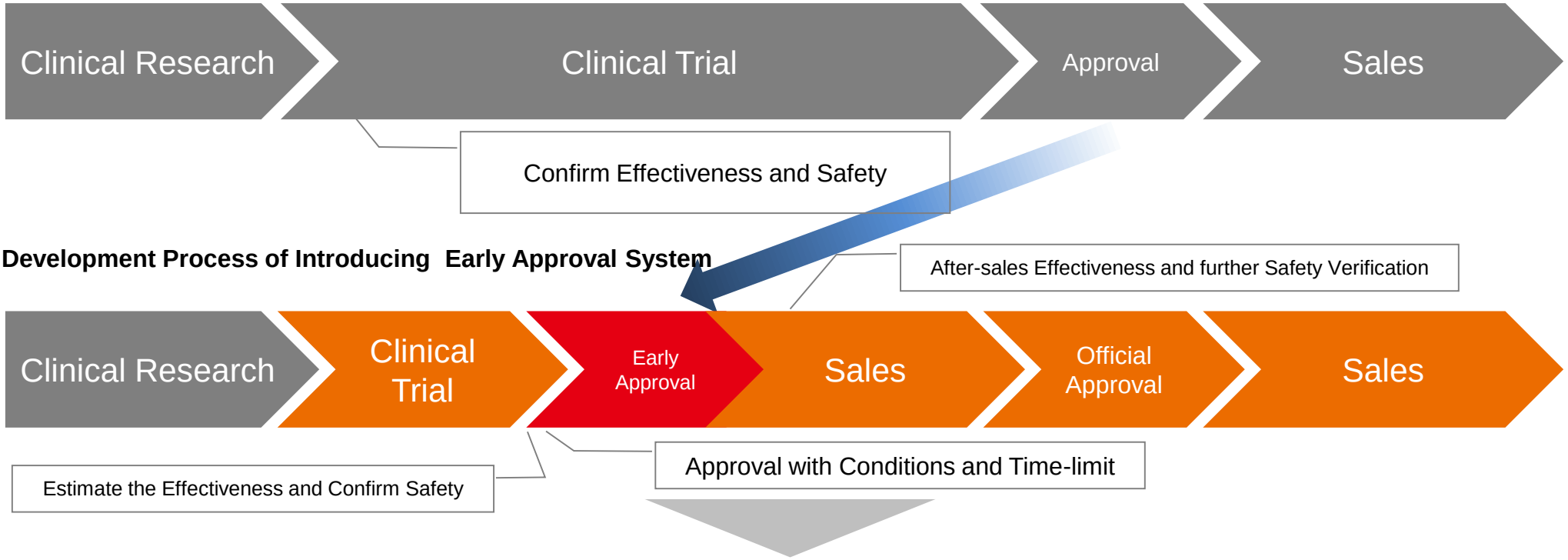
* The price of new drugs is basically calculated according to the prices of official articles with similar efficacy (price determination by comparable drug). However, if there are no appropriate similar official articles, required costs are added in the calculation of prices (cost accounting system).

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Historical Alleviation of Regulations

Japanese Government Revises Regulations to Put Japan at the Forefront

Process of the Development So Far



- Drastic reduction in the treatment period and number of patients (several dozen) with ‘Early Approval System’ .
- Insurance is listed at ‘Early Approval’ stage

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Descriptions on future events, etc. in this document include Healios' assumptions, prospects, etc. based on information which could be acquired at the time this document was presented. For this reason, actual performance, development progress, etc. may differ from those described in this document according to the outcome of R&D in the future, the actions of regulatory authorities, etc. in the future, and uncertain/pending factors as of this point.

Also, this document contains information on regenerative medicine and medical equipment that are currently under development or already on the market. Such information is not intended for promoting advertising or providing medical advice.

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Healios

＜Contact information＞
Corporate Communication Group
Personnel and Administration Department
HEALIOS K.K.

Phone: +81-(0)3-5777-8308
For the press: pr@healios.jp
For the investors: ir@healios.jp