

Healios

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

HEALIOS K.K. (TSE 4593)

FY2017 2Q Financial Results

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1. Financial Highlights

Statement of income

(Million yen)

	FY 2016 2Q	FY 2017 2Q		
			YoY change	Main reasons for increase/decrease
Sales	41	27	▲14	
Operating income	▲2,602	▲935	+1,667	Research & Development Cost decreased ＋1,696
Ordinary income	▲2,647	▲981	+1,665	-
Net income	▲2,650	▲342	+2,307	Gain on Business transfer +641

R&D	2,322	626	▲1,696	▲1,809 (Due to MultiStem License-in in FY2016)
Amortization of goodwill	50	33	▲16	-
Number of employees	52	67	+15	-

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Balance sheet

(Million yen / %)

		December 31, 2016	June 30, 2017		
				Change	Main reasons for increase/decrease
	Current assets	8,073 (88.0%)	16,329 (97.6%)	+8,255	Cash and deposit ＋8,238 (Cash and deposit balance 16,065)
	Non-current assets	1,101 (12.0%)	404 (2.4%)	▲696	Goodwill ▲691
Total assets		9,174 (100.0%)	16,734 (100.0%)	+7,559	
	Current liabilities	772 (8.4%)	1,239 (7.4%)	+466	
	Non-current liabilities	2,408 (26.2%)	2,316 (13.8%)	▲91	
Total liabilities		3,180 (34.7%)	3,555 (21.2%)	+375	
Total equity		5,994 (65.3%)	13,178 (78.8%)	+7,183	Capital etc. ＋7,490 Earned surplus ▲342
Total assets		9,174 (100.0%)	16,734 (100.0%)	+7,559	

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2. Updates in FY2017 2Q

Issuance of stock acquisition rights

Total fund raising originally estimated: Approximately 13 billion yen
(Amount could change depending on the share price trend going forward.)

[As of the end of July 2017]

Number of exercised shares : 4,350,000 common shares (60.9%)
Total fund raising : 6.15 billion yen
Number of unexercised latent shares : 2,795,700 common shares

* In the case of the final financing amount being less than the estimated amount, Healios will screen and make judgments on projects based on their short-term business potential and strategic importance, and will prioritize investment them accordingly.

[Purpose of the funds]

Disclosed on March 2, 2017

	Billion yen
Development for HLCM051 (Ischemic stroke in Japan)	4.63
Development for HLCR012 (iPSC-derived RPE cells for Dry AMD in US and Europe)	1.01
Development for HLCL041 (Organ bud)	0.78
License fee to introduce new seeds and development fee	4.81
Debt repayments	2.5

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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										Business transfer completed on April 30, 2017

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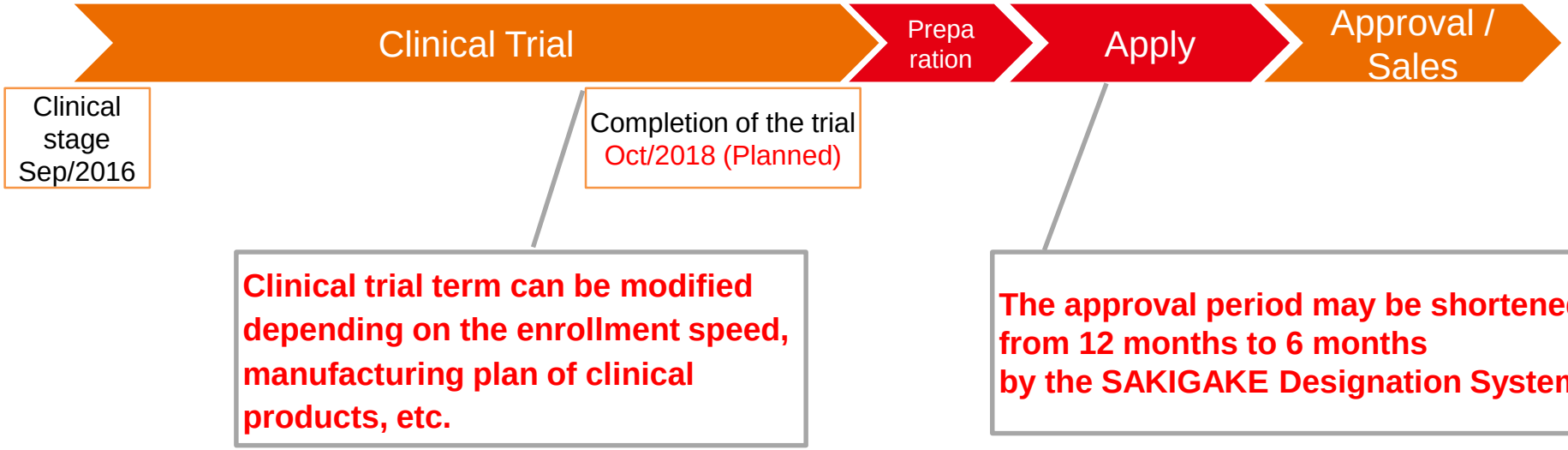
HLCM051: Clinical trial status

Somatic stem cell regenerative medicine

HLCM051
MultiStem®

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

The start of this trial was originally planned for January 2017
https://clinicaltrials.gov/ct2/show/NCT02961504
▼This is our first trial of cell products and we have prepared carefully
▼It has taken time to ship and manufacture our clinical products due to conditions of the manufacturing contractor in the United States



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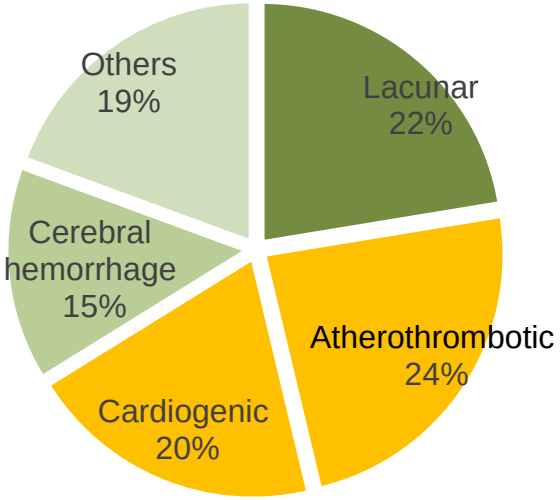
TREASURE study enrollment criteria

【Primary Criteria to enroll patients in TREASURE study】

- ✓ **Atherothrombotic or cardiogenic cerebral infarction by brain magnetic resonance imaging (MRI) demonstrating an acute lesion measuring ≥ 2.0 cm of longest diameter;**
- ✓ **NIHSS score of 8 to 20 at the baseline assessment （Moderate to Severe)**
- ✓ **Patients who can be administered HLCM051 within 36 hours after onset**

Severity at hospitalization and evaluation with NIHSS score by subtype of acute stroke patients of 101,165 patients (2000 - 2012) registered in the acute stroke data bank in Japan

（Source）Stroke Data Bank 2015



Subtype	%	NIHSS at hospitalization（Average ± standard deviation)
Lacunar	22	3.76±3.95
Atherothrombotic infarction	24	6.82±7.79
Cardiogenic cerebral infarction	20	12.7±11.0
Cerebral hemorrhage	15	15.5±13.1
Others	19	ND

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Universal Cells, Inc's Gene Editing Technology Published in Nature Biotechnology

iPSC Regenerative medicine

Universal Donor Cells

Our collaborative research partner, Universal Cells Inc' s research accomplishment has been published in the journal Nature Biotechnology



"HLA-E-expressing pluripotent stem cells escape allogeneic responses and lysis by NK cells"

Dr. Russell Group
Nature Biotechnology (May, 2017)

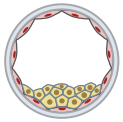
- Normal human embryonic stem cells were engineered by Universal Cells' gene editing technology to be able to escape immune rejection.
- These gene edited normal human embryonic stem cells can differentiate into pigment epithelium (RPE) cells.
- The RPE cells can also escape immune rejection.

Conducting collaborative research toward application of this technology to iPS cells

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Stem cell source

ES Cells

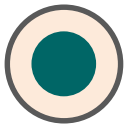


ES cells

iPS Cells



Autologous iPS cells



Allogeneic iPS cells



HLA matched iPS cells

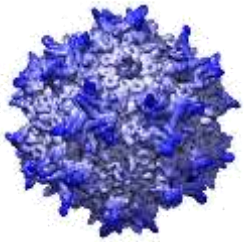


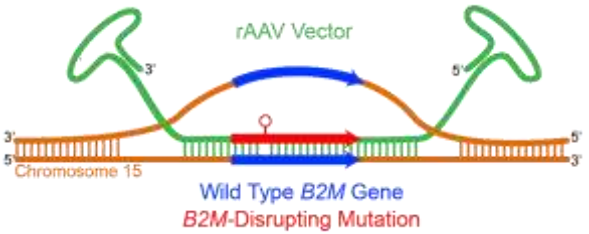
✓Collaborative research to manufacture Universal Donor iPSC, which can escape immune rejection

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Universal Cells

✓ rAAV mediated gene editing
✓ Suicide gene introduced
Thymidine Kinase suicide gene to allow for in vivo elimination of transplanted cells





ES Cells

HLA matched iPS cells
Allogeneic iPS cells

Autologous iPS cells

rAAV-Mediated Gene Editing

Nuclease free

lowest possible genotoxicity, no off-target cutting, no error-prone repair, no risk of immune response to foreign nucleases

Endogenous promoters

Only endogenous promoters are utilized, removing the risk of off-target gene activation

Simple delivery

rAAV vectors efficiently enter cells in vivo and ex vivo

Clinical validation

rAAV extensively tested in humans

(Source) Prepared by Healios based on data provided by Universal Cells

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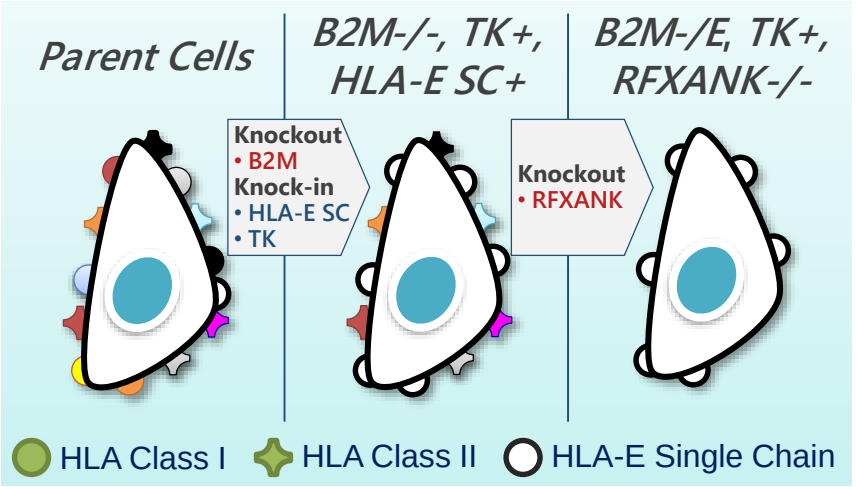
Rejection

Autologous iPS cells

Universal Cells ✓ HLA Class I, Class II engineered

HLA matched iPS cells

ES Cells
Allogeneic iPS cells



Knockout

Beta-2 Microglobulin

Common subunit essential for cell surface expression of all HLA **class I** heterodimers

RFXANK

Transcription factor gene
Required for **class II** expression

Knock-in

HLA-E Single Chain

Heavy chain of the non-polymorphic HLA-E gene
Provides a class I-positive signal to **inhibit NK cells**

Suicide gene (TK)

Thymidine Kinase (TK) suicide gene

(Source) Prepared by Healios based on data provided by Universal Cells

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Cost-effective

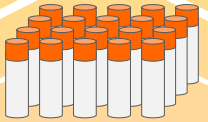
Universal Cells ✓ Histocompatible single cell line

ES Cells
Allogeneic iPS cells

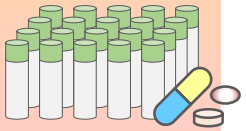
HLA matched iPS cells

Autologous iPS cells

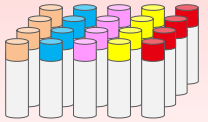
Cost effective



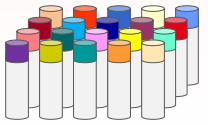
Single cell line



Single cell line
+ immunosuppression cost



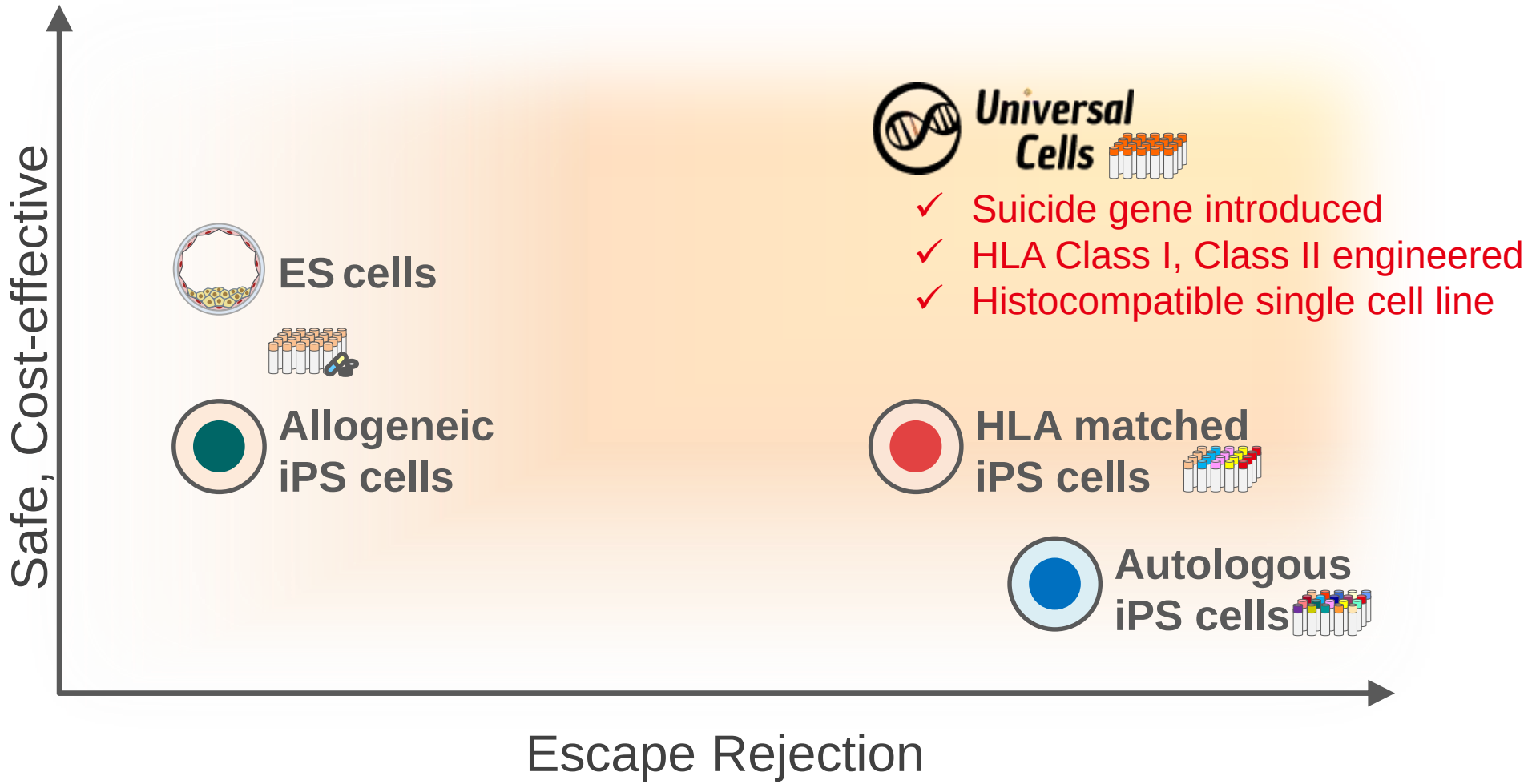
Multiple cell lines



Tailor-made cell lines

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Choice of stem cell source



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3. Future Business Development

Status of existing pipelines

Indications	Stage	Outline	Development funds
Wet AMD	Pre clinical	• About 600,000 patient subjects in Japan • Differentiation and transplant RPE cells from iPSC (aim is to outgrow symptomatic treatment using anti-VEGF medication) • In joint development with DSP	Financing based on joint development with DSP. (Milestone and development fee: total 6.8 bil Yen). Fundraising completed with 2015 listing.
Dry AMD	Pre clinical	• About 5 million patient subjects all over the world • Treatment of transplantation using iPSC derived RPE cells • No effective medication • Selection of development partner in process	Plan to prepare subsequent development costs through alliances, etc.
Metabolic Liver Disease	Pre clinical	• About 30 patient subjects in Japan; over 400 in the world • Mini-liver transplant for patients with congenital abnormalities in specific liver enzymes • Existing treatments cost more than ¥30 million / year • Yokohama City University plans to start clinical research in FY2019	Partial research costs already raised. Plan to prepare subsequent development costs through alliances, etc.
Ischemic Stroke	Clinical stage	• About 60,000 patient subjects in Japan • Cellular medication that improves post-stroke prognosis by suppressing immunoreaction • Hopes are for efficacy during 18-36 hours post-stroke, when there is no existing medication • In clinical trials since 2016. Testing assumed to take place for about two years	License fees and partial development funding already raised through loans. Next milestone is slated payment of about US$30 million.
ILM Peeling, etc. (BBG)	Business transfer	• Business transfer to DWTI completed on April 30, 2017 • Received a lump sum fee of 1.3 billion yen. There is also the possibility of receiving milestone payments.	-

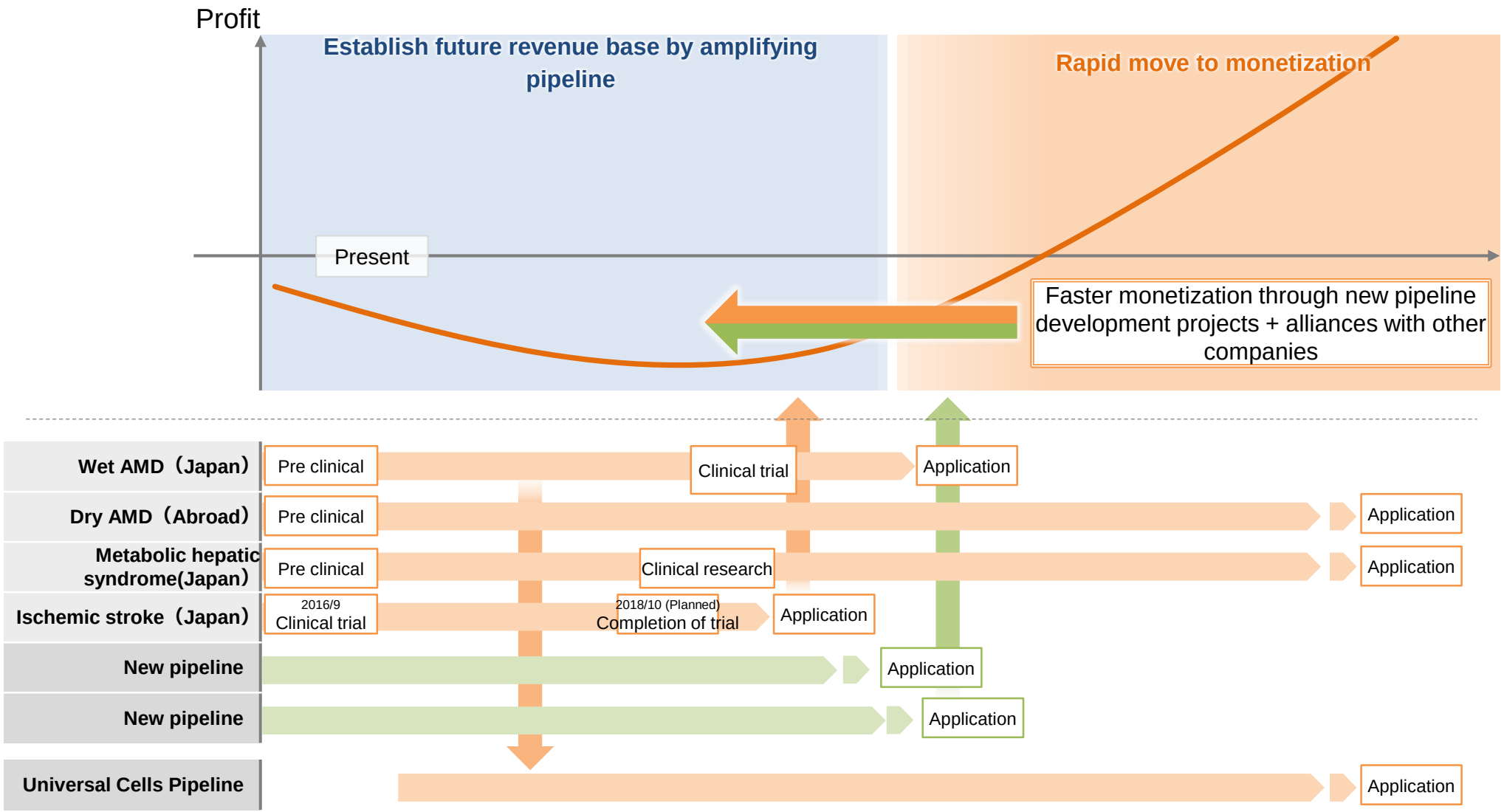
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Introducing new seeds

Introducing new pipelines	Priority is given to bringing in projects with an early expected payoff and synergy with existing pipeline projects.
	Selection of new and unique pipeline projects with no competition on the market, not just iPS cell-related, but including clinical pipeline projects and technology optimal for realistic fulfillment of select unmet patient medical needs.
	Next generation iPS cells with Universal Cells' technology to avoid transplant rejection are to be established as defacto standard, replacing predecessor ES / iPSC products on the market.
Enforce of organization	Further strengthen R&D and manufacturing, looking into partnerships or M&A with other companies as options.

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Development & revenue planning



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4. Details of Somatic Stem Cell Regenerative Medicine

Introduced new pipeline: HLCM051 in January 2016

Athersys inc.



（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 frozen in a stable condition 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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Outline of ischemic stroke in Japan

Ischemic stroke

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

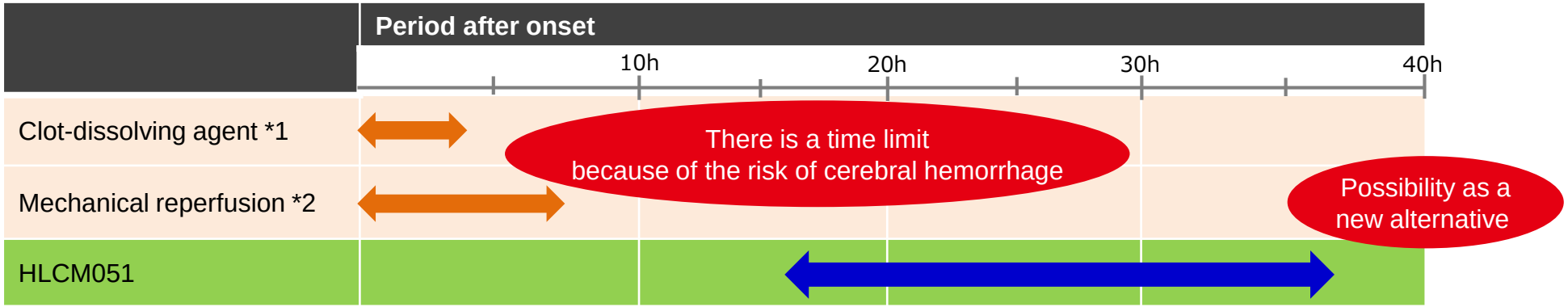
It is estimated that 37.9% of bedridden patients and 21.7% of persons who were in need of care were affected by ischemic stroke



（Source）Athersys

Treatment in accordance with the period after onset

■ Expected development of a new therapy that can be applied in a longer treatment widow period following 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 recovery of 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 (yearly)	**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**	

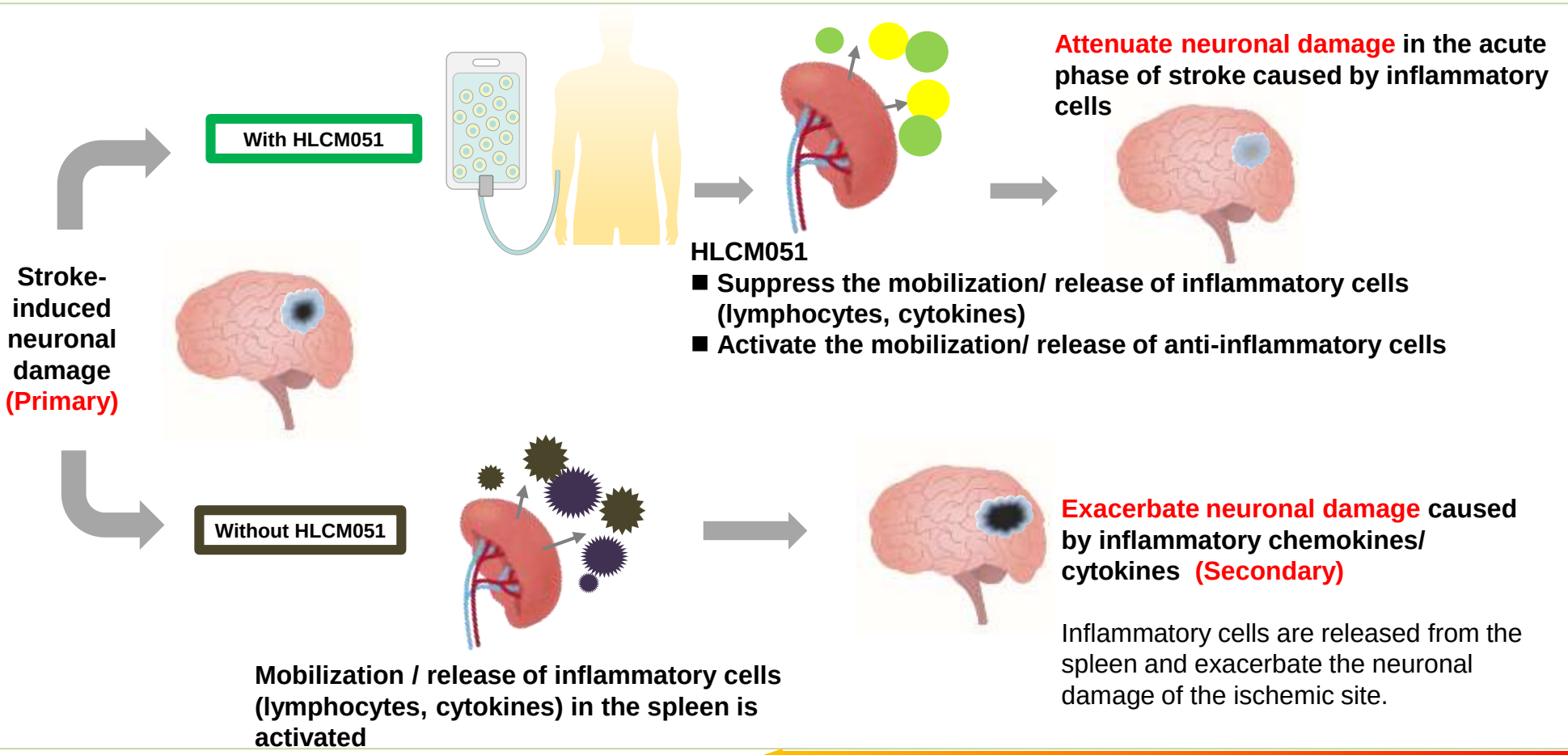
(Source) Healios estimated the annual number of new patients with ischemic stroke in Japan according to materials issued by the Fire and Disaster Management Agency, the Ministry of Internal Affairs and Communication, and the Ministry of Health, Labour and Welfare – DATAMONITOR epidemiological estimates 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 results of its market research.

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

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Mechanism of HLCM051 treatment

- 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.



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HLCM051 Clinical trial

Somatic stem cell regenerative medicine

HLCM051
MultiStem®



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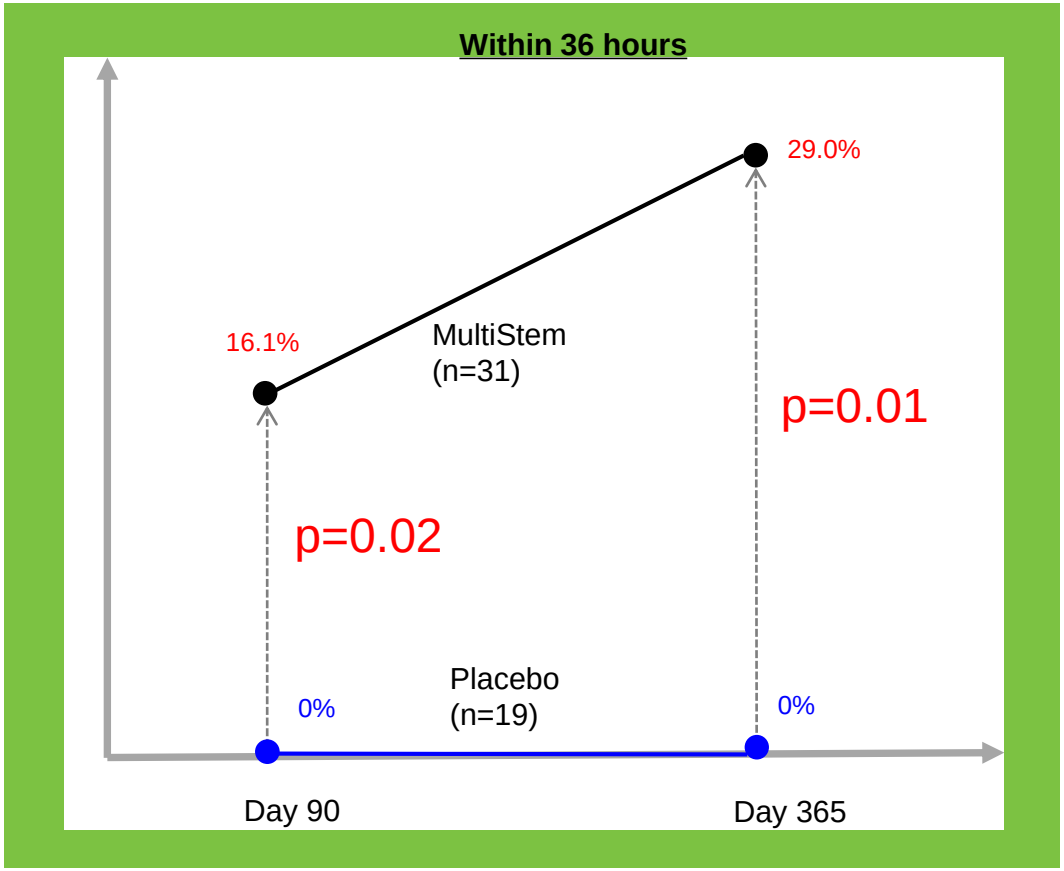
Study Design Based on the Result of the Phase II Study by Athersys in Europe and America

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.

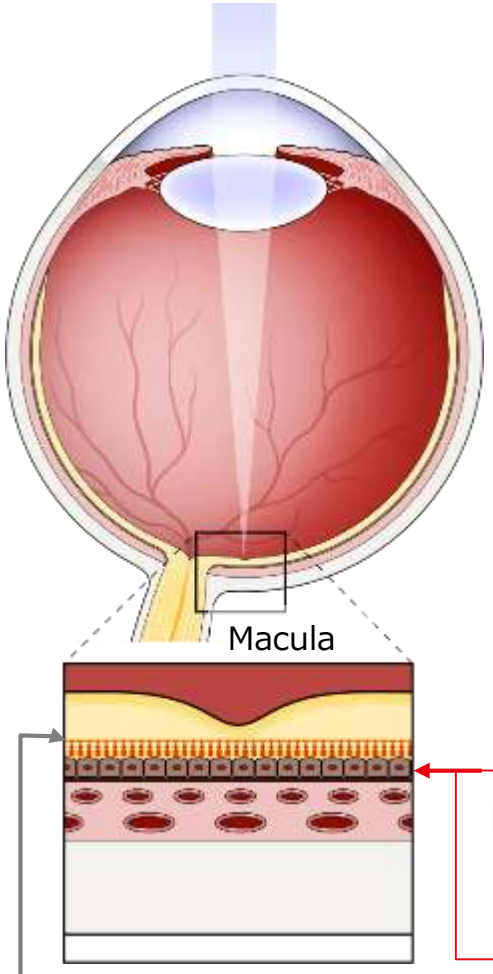
(Note) Excellent outcome = All of the following: mRS ≤ 1, NIHSS ≤ 1, and BI ≥ 95)

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5. Details of iPSC Regenerative Medicine

Explanation of AMD pathological condition

AMD causes RPE Cells to degenerate, which will damage functions



Regular Macular Part

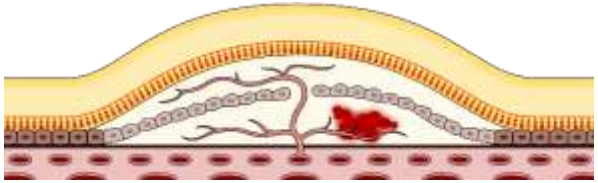
Developed Dry AMD

Immunity Barrier Maintained
→ Degeneration of photoreceptor→ Dry AMD



Wet AMD

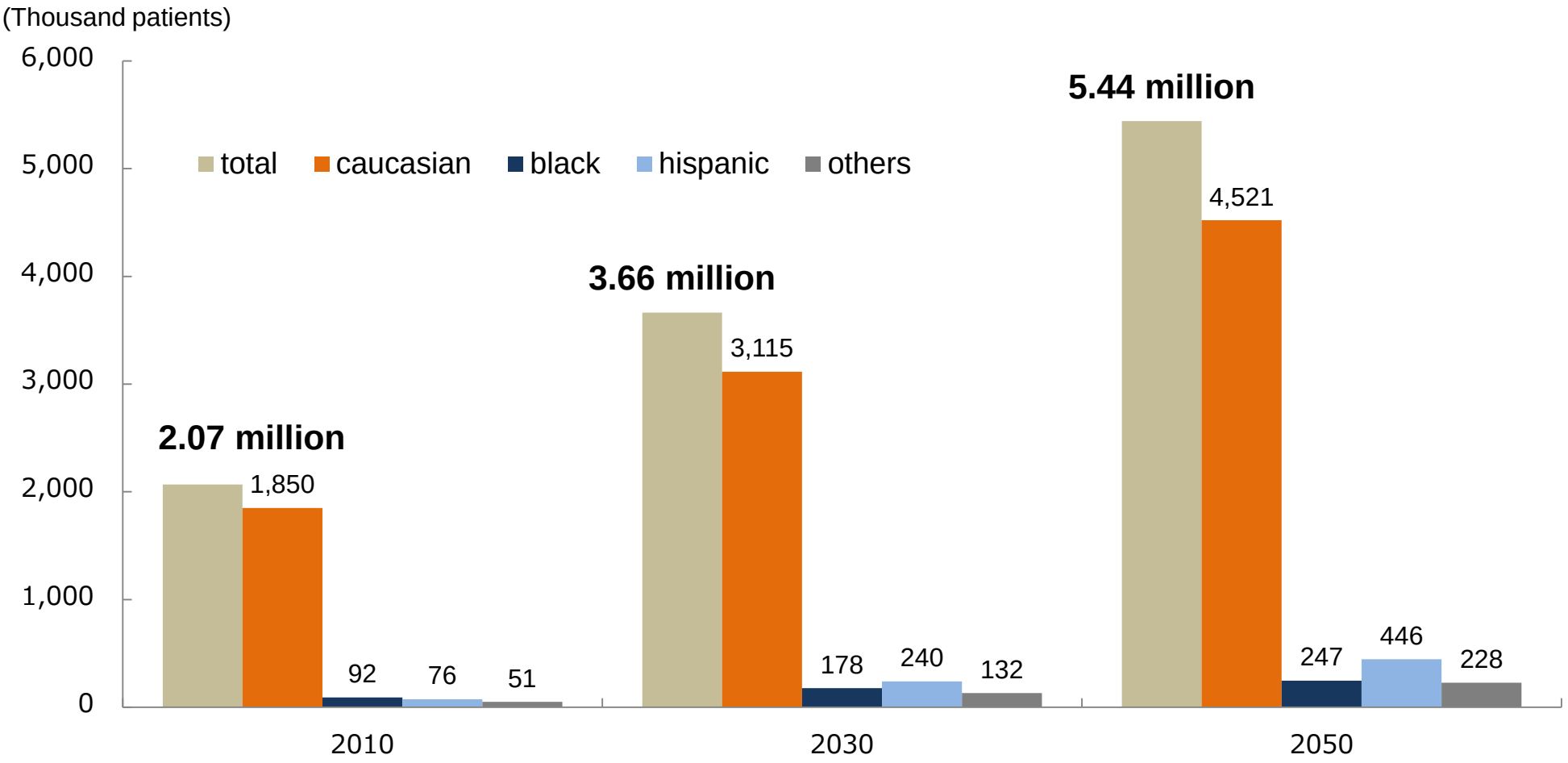
Destruction of Immunity Barrier → Invasion of Immune Cells
→ Inflammation → Wet AMD



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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
Number of AMD Patients	**10,000**	**9,230**	**13,000**
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: 8.44billion USD.
No medicine for Dry AMD.

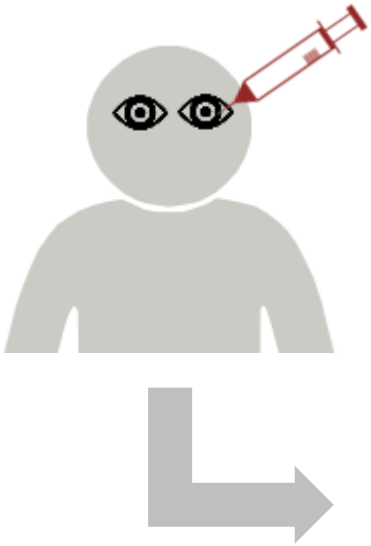
Condition	Medicine / Effect	Year	America	Japan	Others	Total
Wet	Anti-VEGF Medicine/ Restraint of New Blood Vessels	2016	**4,729 million USD**	**580 million USD**	**3,127 million USD**	**8,436 million USD**
Dry			**No Medicine**			

(source) Market scale was calculated using official materials from drug companies (Roche Diagnostic, Novartis, Regeneron, Bayer HealthCare, Santen Pharmaceutical Co., Ltd). Calculated using 2016 fiscal year-average exchange rates.

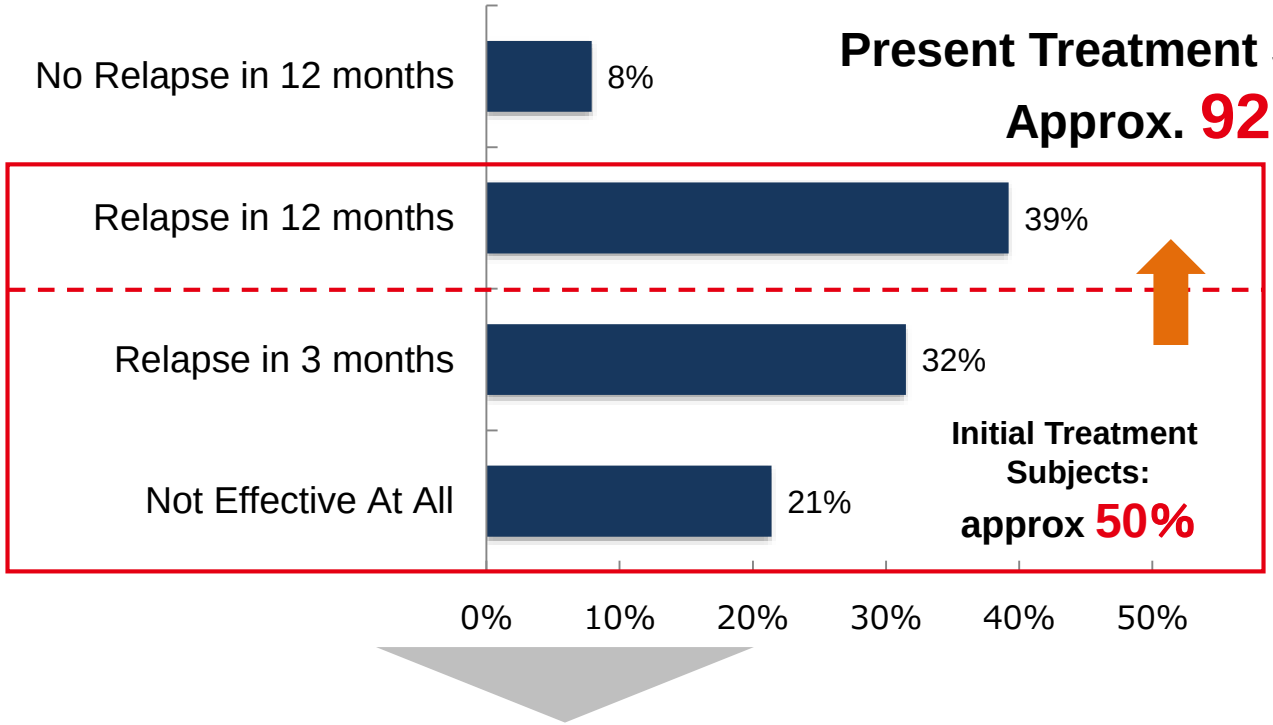
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Treatment subjects for Wet AMD

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%

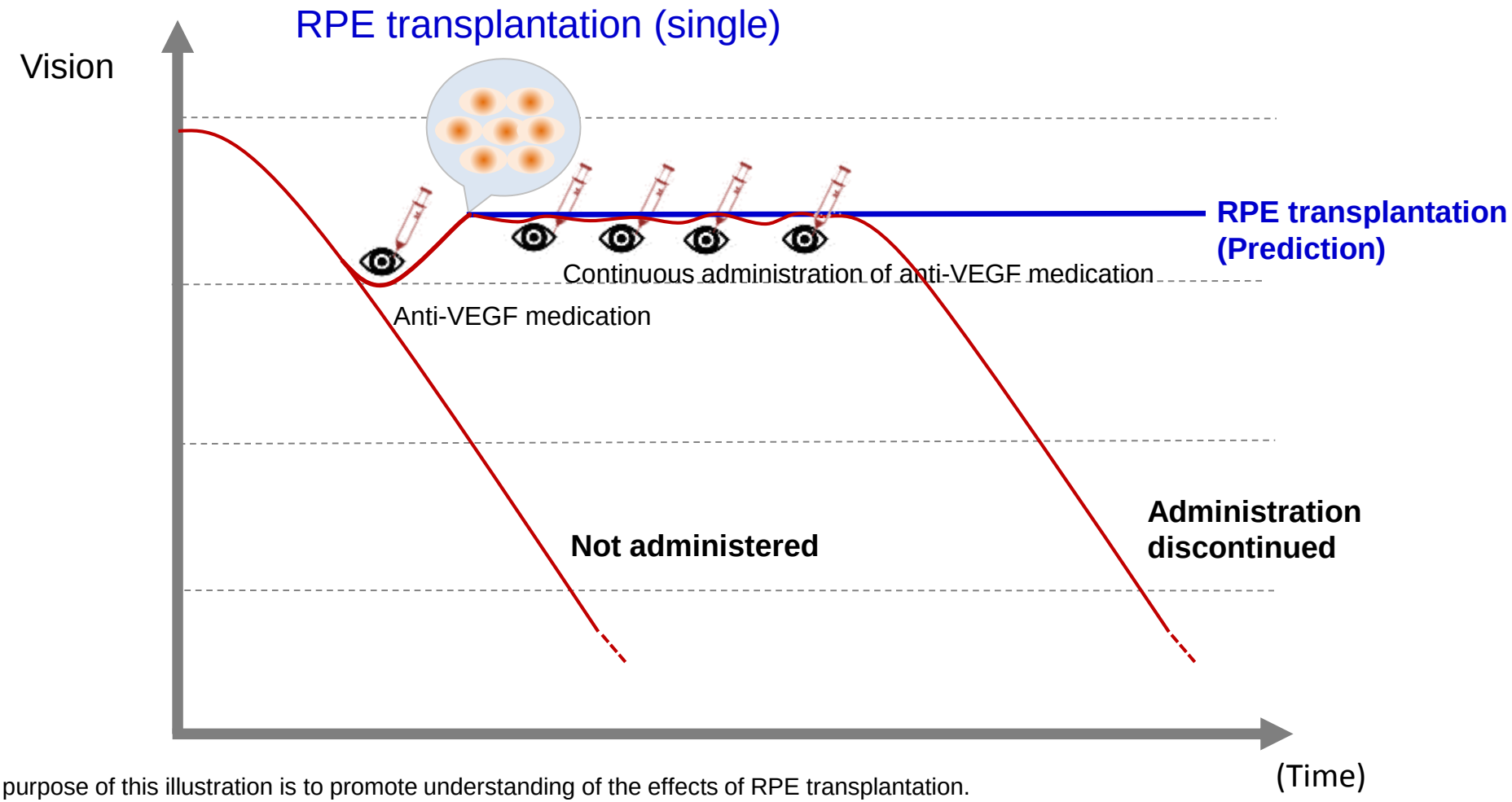
Initial Treatment Subjects:
approx 50%

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 vary 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 treatment until 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**

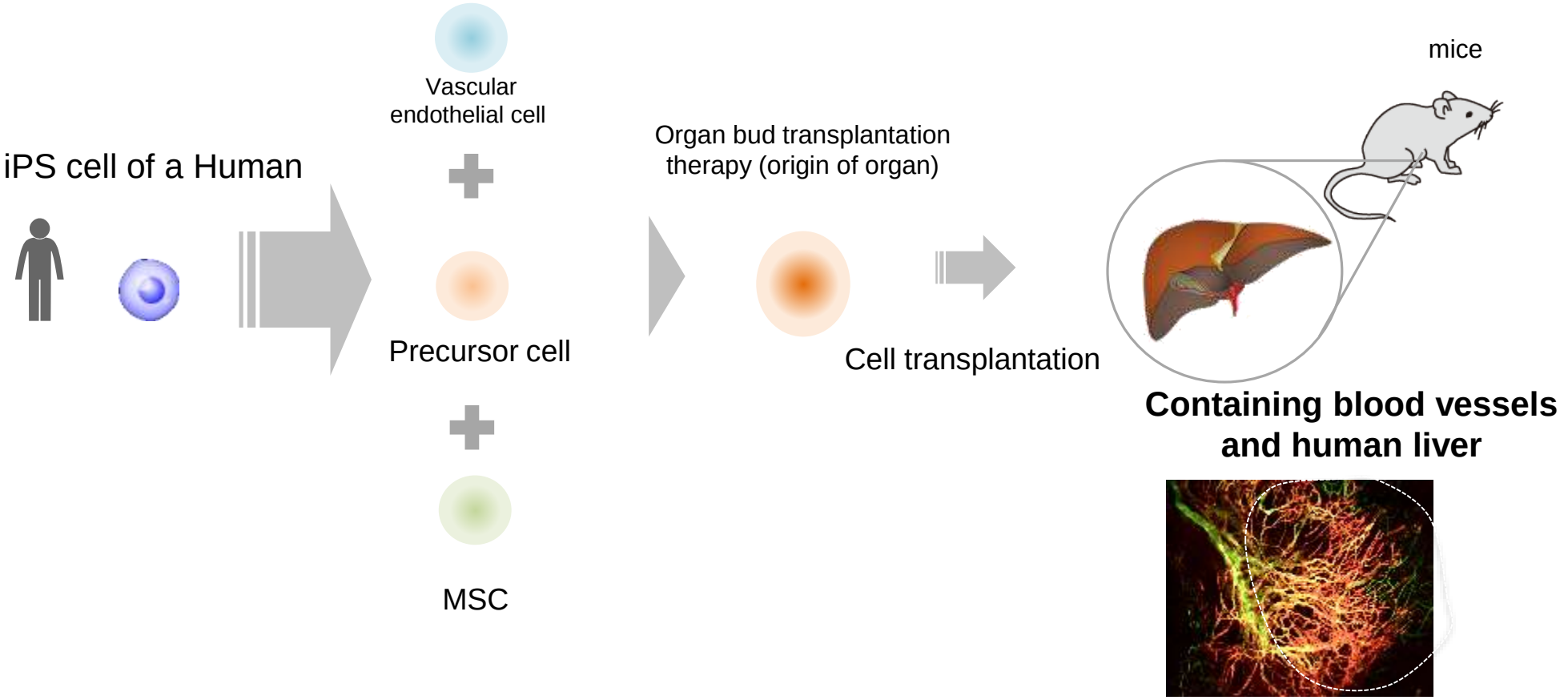
(source) Onset Data: National Eye Institute; Average Life Span: The Ministry of Health, Labor and Welfare; Annual Recommended Medication Protocol: Materials Presented by Institute of Physical and Chemical Research

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6. Expansion to 3D Organs (Liver)

3D organ generation mechanism

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



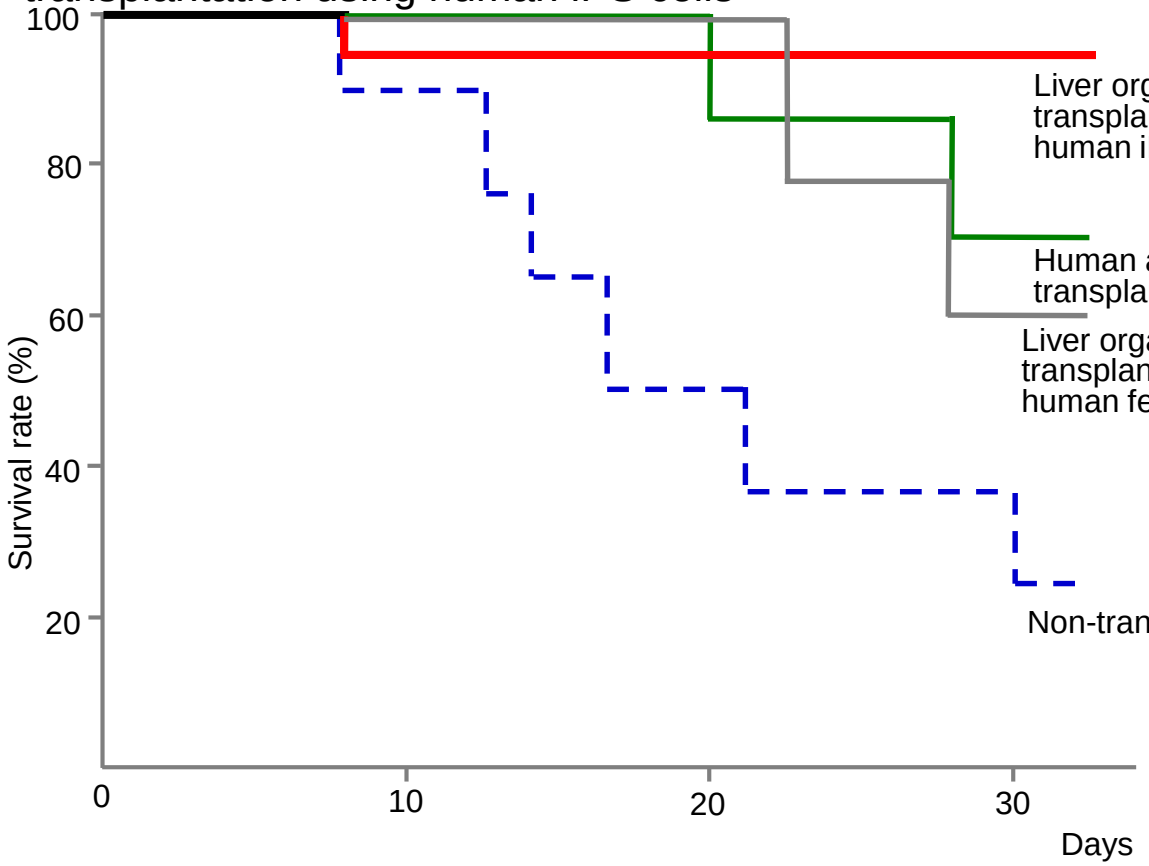
（Source）Takebe,T., et al. Nature Protocols, 9, 396–409 (2014)

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Survival rate of liver failure model mouse

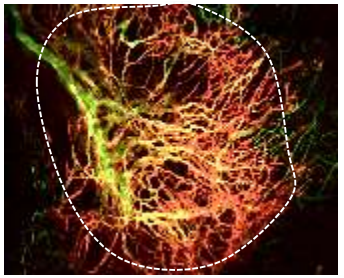
Survival rate improves significantly in transplantation experiments

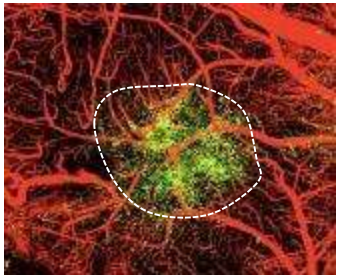
Treatment effects of liver organ bud transplantation using human iPS cells



(Source) Adapted by 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 (yearly)	**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 and incidence rate.

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8. 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	9,139 million yen (As of end of June, 2017)
Research Institution	Kobe and Yokohama
Number of Employees	67　(As of end of June, 2017)
Affiliated Company	SighRegen Co., Ltd. (Joint Venture with Sumitomo Dainippon Pharma Co., Ltd.)

Our Experienced Team

President and CEO
Hardy TS　Kagimoto, MD



- Succeeded in Developing BBG and Realized Sales in Europe

Director of Overseas Development
Al Reaves, Ph.D



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

Director of Laboratories in Kobe, Research and Manufacturing
Kouichi Tamura, Ph.D



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

Director of Domestic Development
Michihisa Nishiyama

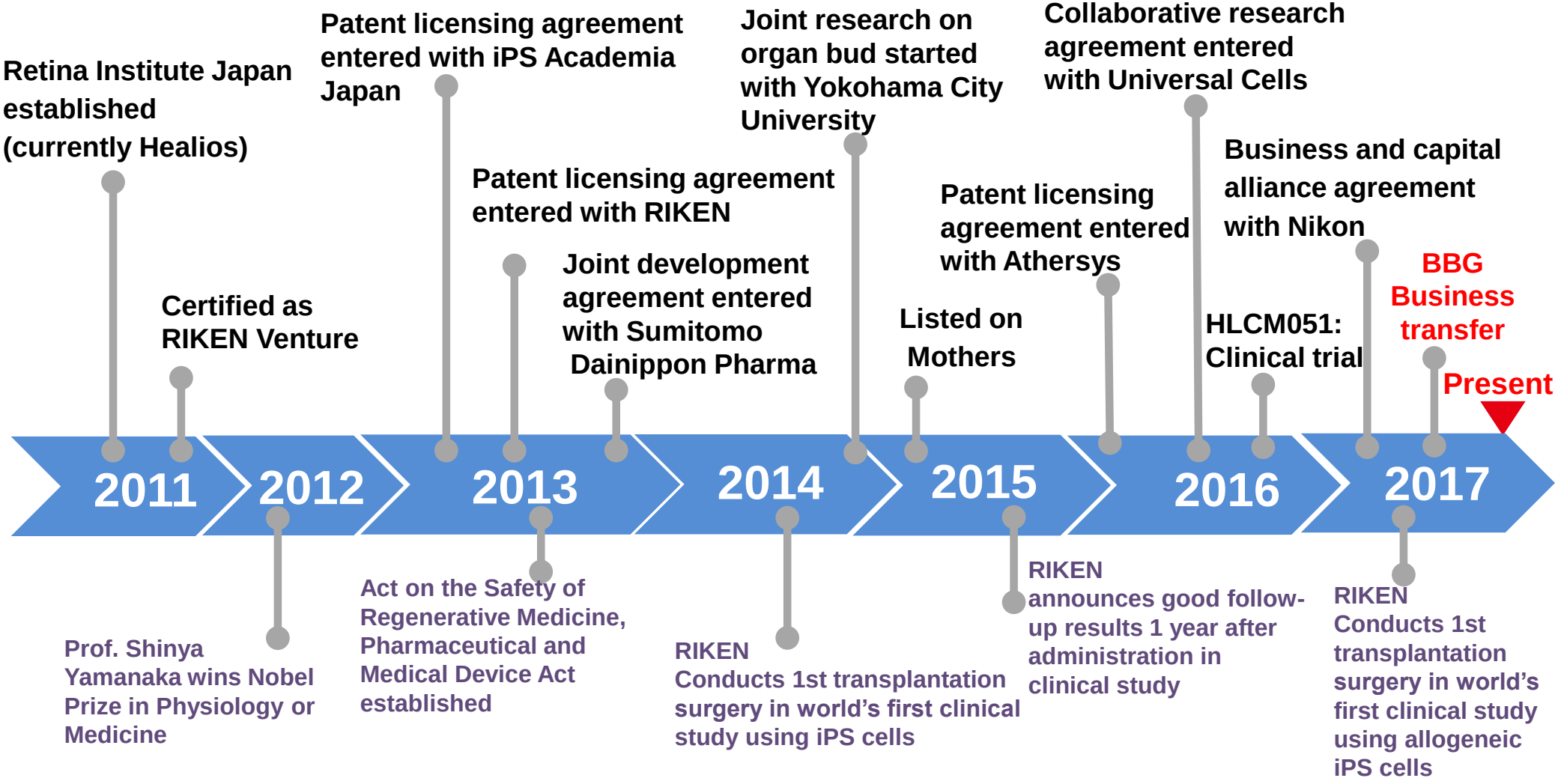


- Constructed network for Tacrolimus approval and sales at Astellas in the US and Europe

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Company History and Social Trends

Pioneer of iPSC regenerative medicine development



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8. Circumstance of Regenerative Medicine

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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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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