FY2023 Q1 Financial Results

Company

HEALIOS K.K. (TSE 4593)

Date

May 12, 2023

Important Note on Future Events, etc

This material has been prepared solely for the purpose of disclosing relevant information regarding HEALIOS K.K. (“HEALIOS”). This document does not constitute an offer to sell or the solicitation of an offer to buy any security in the United States, Japan or any other jurisdiction.

This presentation contains statements that constitute forward-looking statements, including estimations, forecasts, targets and plans, and such forward-looking statements do not represent any guarantee by management of future performance. [In many cases, but not all, HEALIOS uses such words as “aim,” “anticipate,” “believe,” “continue,” “endeavor,” “estimate,” “expect,” “initiative,” “intend,” “may,” “plan,” “potential,” “probability,” “project,” “risk,” “seek,” “should,” “strive,” “target,” “will” and similar expressions to identify forward-looking statements.] You can also identify forward-looking statements by discussions of strategy, plans or intentions. Any forward-looking statements in this document are based on the current assumptions and beliefs of HEALIOS in light of the information currently available to it, and involve known and unknown risks, uncertainties and other factors. Such risks, uncertainties and other factors may cause HEALIOS’s actual results, performance, achievements or financial position to be materially different from any future results, performance, achievements or financial position expressed or implied by such forward-looking statements.

This presentation is based on the economic, regulatory, market and other conditions as in effect on the date hereof, and HEALIOS does not guarantee that the information contained in this presentation is accurate or complete. It should be understood that subsequent developments may affect the information contained in this presentation, which HEALIOS is not under an obligation, or does not plan, to update, revise or affirm. The information in this presentation is subject to change without prior notice and such information may change materially. Neither this presentation nor any of its contents may be disclosed to or used by any other party for any purpose without the prior written consent of HEALIOS.

The information in connection with or prepared by companies or parties other than HEALIOS is based on publicly available and other information as cited, and HEALIOS does not have independently verified the accuracy and appropriateness of, nor makes any warranties with respect to, such information.

The information about regenerative medicine products (including products currently in development) which is included in this material is not intended to constitute an advertisement or medical advice.

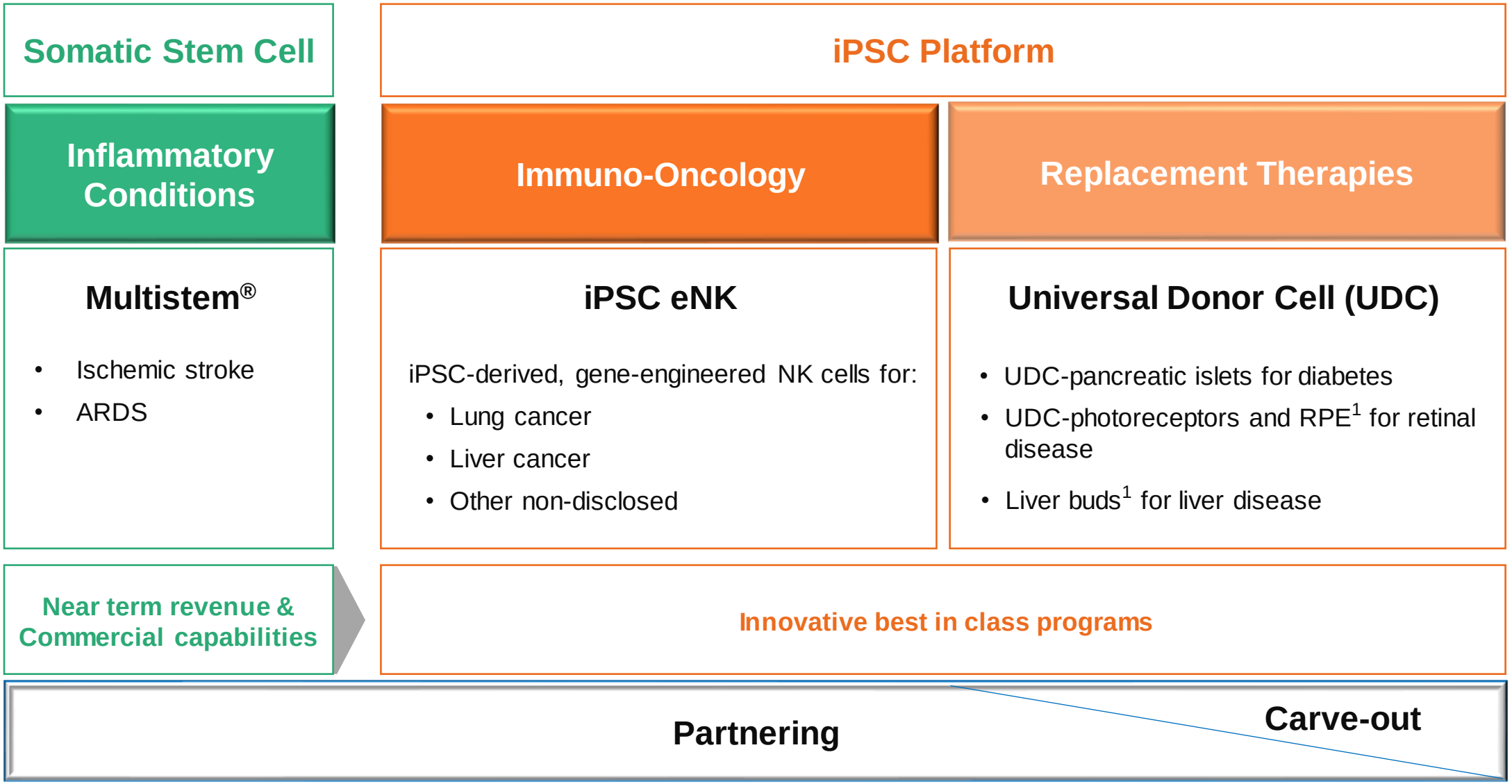
Contents

Vision

To become a global biopharma company committed to transforming the lives of patients by creating, developing and commercializing cutting edge cell therapy technologies.

Healios is leading the research and development of cellular medicines focused on major causes of death and areas of unmet medical need in developed countries
—oncology: solid tumors; CNS: ischemic stroke; respiratory: ARDS—

Program Overview



[1]Future migration to UDC platform

Pipeline Development Policy

Update

Healios

Inflammatory Conditions

HLCM051

Ischemic stroke

- In response to the results of our domestic study, Athersys proposed modifications of primary and secondary endpoints in the ongoing global study* and FDA accepted.
- Based on these results, we will consider to utilize clinical trial data / to participate in the global trial.

＊ Phase III study for stroke in the U.S conducted by Athersys. (MASTERS-2 study)

ARDS

- Additional study design (small-scale double-blind study) was discussed with PMDA and decided.
- Project finance and subsidies anticipated to be used for development funds.

Immuno- Oncology

eNK（HLCN061） CAR-eNK

Solid tumors

- Have established an effective eNK platform for solid tumors. Target 2024 IND.
- In-house manufacturing and R&D aimed at global expansion.

Replacement Therapies

HLCR011

RPE tear AMD

- Plan to initiate clinical trial imminently.
- Initial indication changed from AMD to RPE tear
- Scheduled to be launched in 2025 (announced by Sumitomo Pharma)

＊All pipeline programs are in discussion with potential partners

Note: Expectation based on the Company's current business situation and subject to change in the future.

Pipeline

Update

Healios

	Development Code	Therapeutic Area	Therapy	Region	Discovery	Pre-Clinical	Clinical	Comments
Inflammatory Conditions	HLCM051	Ischemic stroke	MultiStem®	Japan			Phase 2/3	Ongoing consultations with regulatory authorities based on the discussion results with FDA SAKIGAKE designation
	HLCM051	ARDS	MultiStem®	Japan			Phase 2	Preparing to start clinical trial Orphan designation
Immuno-Oncology	HLCN061	Solid tumors	eNK	Global				Pre-IND started IND: 2024 Joint research with National Cancer Center Japan, Hiroshima University and Hyogo Medical University
	–		CAR-eNK	Global				
Replacement Therapies	HLCR011	RPE tear AMD	RPE	Japan				Plan to initiate clinical trial with Sumitomo Pharma Co., Ltd. Scheduled to start clinical trial in FY2023 and to be launched in FY2025 (planed by Sumitomo Pharma)
	–	Retinal disease	UDC-photoreceptors & RPE*	Global				
	HLCL041	Liver disease	Liver buds	Global				Carve-out plan to accelerate R&D and efficiently advance the program
	–	Diabetes	UDC-pancreatic islets	Global				

* Future migration to UDC platform

Research & Development Funding Needs

Update

Healios

	Development Code	Therapeutic Area	Therapy	Region	Discovery	Pre-Clinical	Clinical	Funding Needs
Required								
Inflammatory Conditions	HLCM051	Ischemic stroke	MultiStem®	Japan			Phase 2/3	After consultation with Japanese regulators, development funding needs will be determined.
	HLCM051	ARDS	MultiStem®	Japan			Phase 2	Grants such as rare disease grants Project finance
Immuno-Oncology	HLCN061	Solid tumors	eNK	Global				Aiming for joint development FY2024 IND
	–		CAR-eNK	Global				Aiming for joint research and development
Not required								
Replacement Therapies	HLCR011	RPE tear AMD	RPE	Japan				Co-development with Sumitomo Pharma Co., Ltd. Plan to initiate clinical trial.
	–	Retinal disease	UDC-photoreceptors & RPE*	Global				
	HLCL041	Liver disease	Liver buds	Global				Carve-out plan to accelerate R&D and efficiently advance the program
	–	Diabetes	UDC-pancreatic islets	Global				

Note: Expectation based on the Company's current business situation and is subject to change in the future.

HLCR011 RPE tear

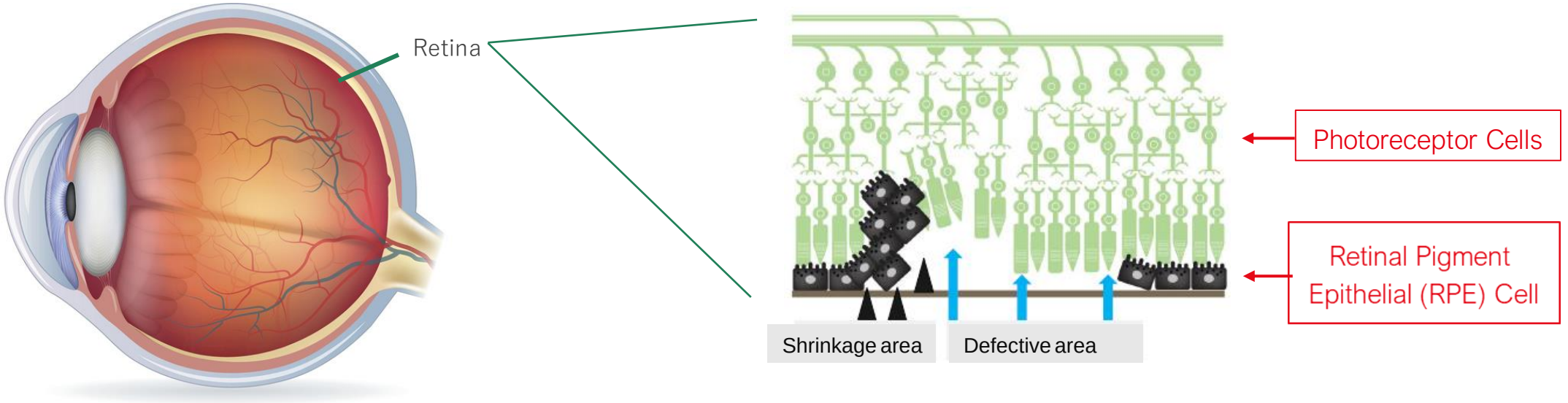
New

Healios

RPE (Retinal pigment epithelium) tear is a disease in which the sensory retina is detached from the RPE due to a tear in the retina (retinal tear). It causes visual field defects and vision loss.

If RPE is defective but photoreceptor function is preserved, pigment epithelial cell transplantation can restore vision.

RPE tear



Joint Development

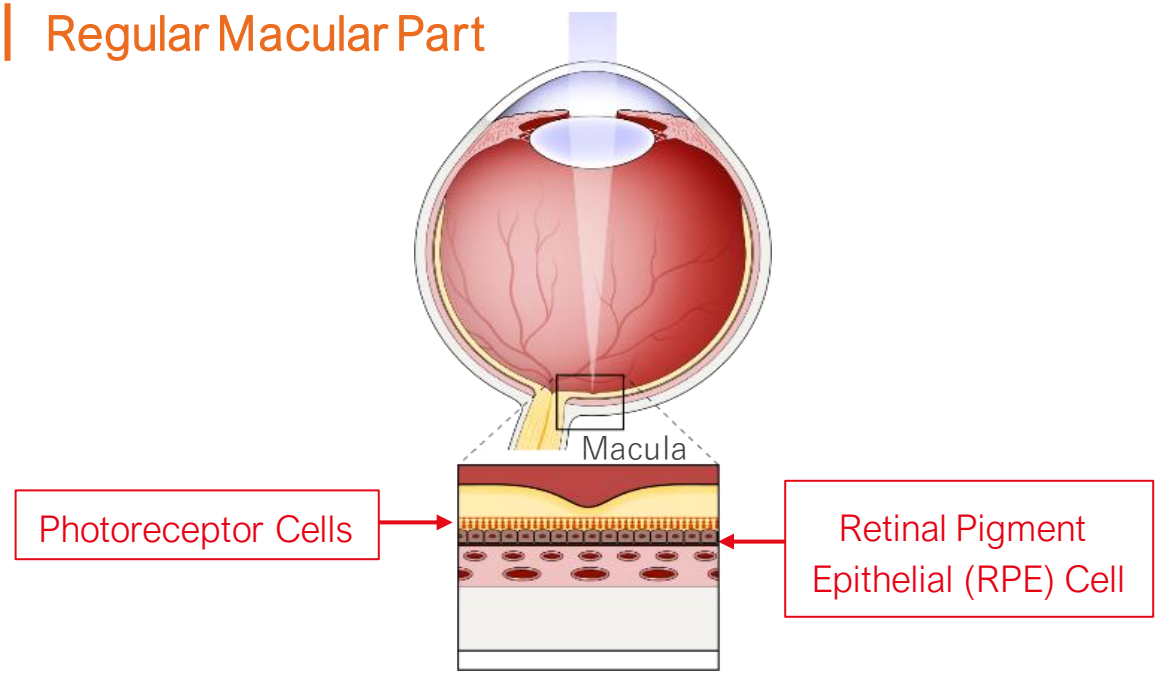
In Japan, HEALIOS and Sumitomo Pharma Co., Ltd. are jointly developing a treatment using iPS cell-derived RPE cells.

HLCR011 AMD

Update

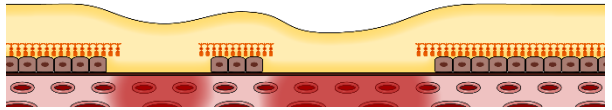
Age-related Macular Degeneration (AMD) causes Retinal Pigment Epithelial (RPE) cells to degenerate, which damages function

Regular Macular Part



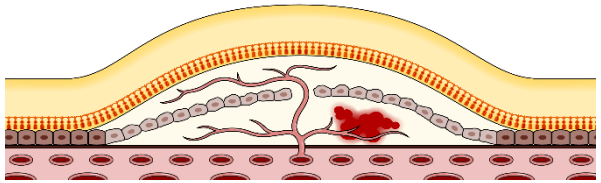
Developed Dry-AMD

Immunity barrier maintained
→ Degeneration of photoreceptor → Dry AMD



Wet AMD

Destruction of immunity barrier → Invasion of immune cells
→ Inflammation → Wet AMD



Joint Development

In Japan, HEALIOS and Sumitomo Pharma Co., Ltd. are jointly developing a treatment using iPS cell-derived RPE cells.

After confirming the efficacy of the treatment in RPE tear, Sumitomo Pharma will consider expanding the indication to include AMD.

Financial Highlights

Consolidated Statement of Income

Update

Healios

R&D expenses for the three months ended March 31, 2023 were 544 million yen (R&D expenses of approximately 50% of the same period of the previous year). Continue to advance R&D activities while optimizing investment efficiency and expense discipline.

(Units: millions of yen)

	FY2022 Q1(YTD)	FY2023 Q1(YTD)		
			YoY variance	Main reasons for increase/decrease
Revenue	11	7	-4	
Operating profit	-1,429	-888	541	Decrease in SG&A expenses ＋4 Decrease in R&D expenses +543
Profit	-1,461	-728	732	Decrease in finance income -3 Decrease in finance costs +147 (Primarily non-cash activity; please refer to the next page for details)
R&D expenses	1,087	544	-543	
Number of employees	115	**64**	-51	

(Note)
* For details of the financial figures, please refer to the summary of the financial results announced today.

Supplemental Explanation of Finance Income and Finance Costs

Update

Healios

Details of finance income and finance costs

In the three months ended March 31, 2023, we recorded finance income of ¥190 million and finance costs of ¥37 million.

Finance income was mainly due to the recording of ¥144 million in profit or loss transferred to equity interests held by external investors in the Saisei Fund [*1] and ¥ 29 million in gain on remeasurement of investment securities.

Finance costs were mainly due to the recording of ¥27 million in interest expenses on bonds [*2] and ¥10 million in interest expenses.

*1. Profit or loss transferred to equity interests held by external investors in the Saisei Fund

Profit or loss transferred to equity interests held by external investors in the Saisei Fund is the transfer amount of profits and losses of Saisei Bioventures, L.P., the consolidated subsidiary of our company, to limited partners other than our company. Saisei Bioventures, L.P. is a limited partnership established by Saisei Capital Ltd., the general partner and consolidated subsidiary of our company.

*2. Interest expenses on bonds

Of the total interest on bonds of 27 million yen posted for the three months ended March 31, 2023, 17 million yen was charged to income using the amortized cost method. This is a non-cash expense recorded in accordance with the International Financial Reporting Standards (IFRS), which was introduced in the 1st quarter of the fiscal year ended December 2020.

Under JGAAP, convertible bond issuances were accounted for as liabilities and issue fees were accounted for as expenses. Under IFRS, however, proceeds, after deducting issue fees from convertible bond issuances, are accounted for as liabilities and equity, based on a certain standard. As a result, the difference between the face value of convertible bonds and the amount recorded as liabilities is amortized (expensed) over the period.

Consolidated Statement of Financial Position

Update

Total assets as of March 31, 2023 were 15.2 billion yen (+0.2 billion yen from the end of the previous period).

Cash and cash equivalents decreased only 0.1 billion yen from the end of the previous year to 7.1 billion yen, mainly due to decrease in R&D expenses and proceeds from financing activities, etc.

(Units: millions of yen)

	December 31, 2022	March 31, 2023		
			Variance	Main reasons for increase/decrease
Current assets	8,462 (56.3%)	8,308 (54.7%)	-154	Decrease in cash and cash equivalents -98 (Cash and cash equivalent balance at 3/31/23 was 7,148)
Non-current assets	6,571 (43.7%)	6,882 (45.3%)	311	Increase in other financial assets +605 Decrease in investments accounted for using equity method -150
Total assets	15,033 (100.0%)	15,190 (100.0%)	157	
Current liabilities	3,808 (25.3%)	3,674 (24.2%)	-135	
Non-current liabilities	6,842 (45.5%)	7,652 (50.4%)	810	Increase in equity interests held by external investors in Saisei Fund +840
Total liabilities	10.650 (70.8%)	11,326 (74.6%)	675	
Total equity	4,382 (29.2%)	3,864 (25.4%)	-518	Recording of loss -728
Total liabilities and equity	15,033 (100.0%)	15,190 (100.0%)	157	

(Note) For details of the financial figures, please refer to the summary of the financial results announced today.

MultiStem®
Inflammatory Conditions

Somatic Stem Cell	iPSC Platform	
Inflammatory Conditions	**Immuno-Oncology**	**Replacement Therapies**
Multistem® • Ischemic stroke • ARDS	**iPSC eNK** iPSC-derived, gene-engineered NK cells for: • Lung cancer • Liver cancer • Other non-disclosed	**Universal Donor Cell (UDC)** • UDC-pancreatic islets for diabetes • UDC-photoreceptors and RPE[1] for retinal disease • Liver buds[1] for liver disease

HLCM051 ARDS: ONE-BRIDGE Study

Update

Healios

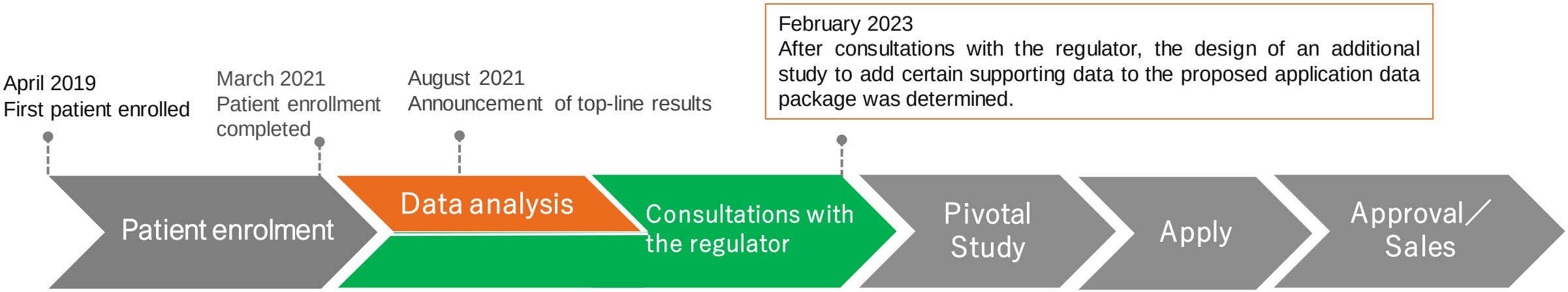
Development plan

Inflammatory Conditions

In discussion with potential partner companies

ARDS

- **Additional study design (small-scale double-blind study) was discussed with PMDA and decided.**
- **Project finance and subsidies anticipated to be used for development funds.**



HLCM051 has been designated as an **orphan regenerative medicine product** for use in the treatment of ARDS by the Ministry of Health, Labor and Welfare. (It has received SAKIGAKE status for ischemic stroke.)

Next Clinical Trial for HLCM051 for ARDS

Conditions	Placebo-Controlled, Double-Blind, Randomized
Subjects	Patients with pneumonia-induced ARDS *Including Patients with pneumonia-induced ARDS caused by COVID-19
Enrollment	80 (HLCM051 [n=40], placebo [n=40])
Primary Endpoint	VFD (the number of days out of 28 during which a ventilator was not used for the patient)
Secondary Endpoint (examples)	Mortality (180 days after administration)

The trial protocol will be finalized upon the submission of a future IND.

HLCM051 ARDS: Target Disease

Update

Healios

There is demand for new treatments for ARDS that will lead to improvements in patients' symptoms and prognosis

The number of ARDS patients in Japan is estimated at approximately 28,000 per year*1

About ARDS*2

Acute Respiratory Distress Syndrome (ARDS) is a general term for the symptoms of acute respiratory failure suddenly occurring in all seriously ill patients.

The mortality rate is approximately 30 to 58%*2.

Approximately 1/3 of ARDS cases are caused by pneumonia.

ARDS is a common cause of morbidity and mortality in severe COVID-19.

（Source）Athersys

Current Treatment

At present, there are no therapeutic drugs that can make a direct improvement to a patient's vital prognosis when ARDS develops.

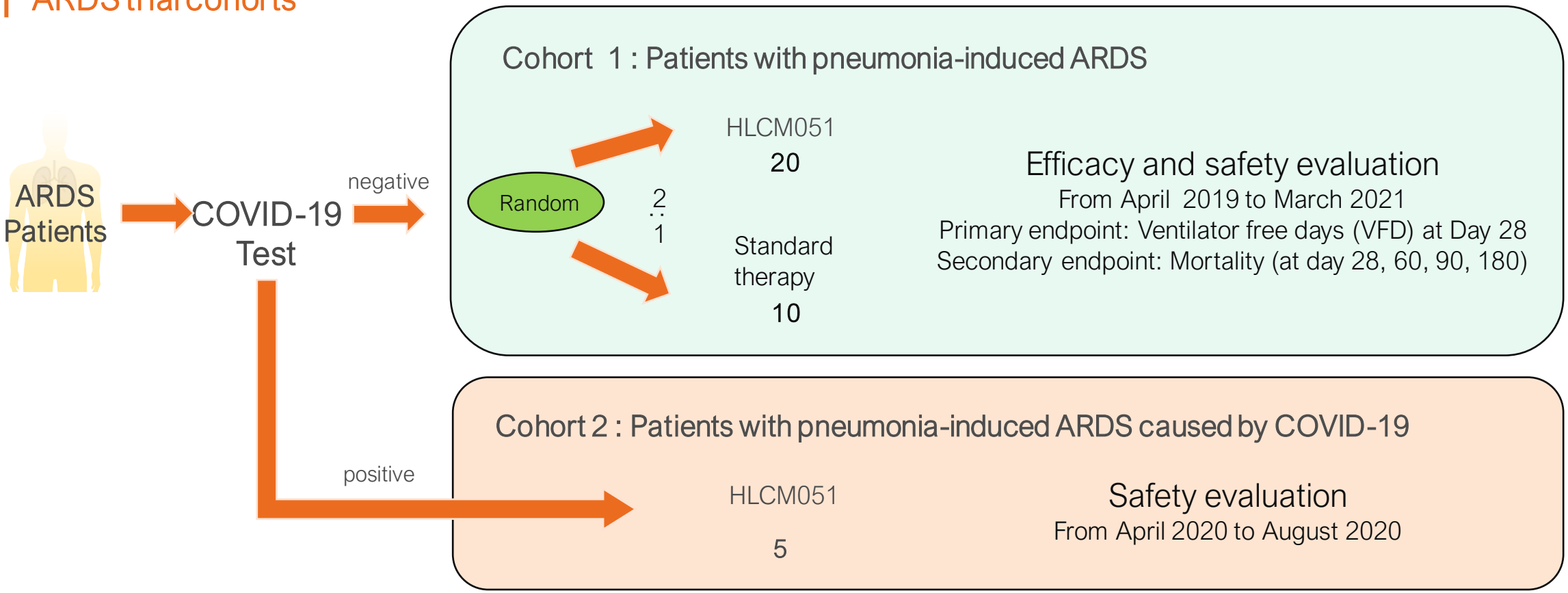
The only symptomatic treatment for respiratory failure includes artificial respiration.

(source)
＊1 The number of ARDS patients in Japan is estimated by Healios based on the incidence rate of epidemiological data and the total demographical population in Japan.
＊2 ARDS treatment guideline 2016

HLCM051 ARDS: ONE-BRIDGE Study

Phase II study investigating the efficacy and safety of HLCM051 in pneumonia induced ARDS patients

ARDS trial cohorts



Patient enrollment of COVID-19 pneumonia-derived cases (Cohort 2) was performed separately from the conventional clinical trial administration group (Cohort 1).

HLCM051 ARDS: ONE-BRIDGE Study Results at 180 Days Post Administration

Cohort 1

No safety concerns.

The HLCM051 treated group demonstrated a 9-day higher median VFD than the standard therapy group.

The treated group saw a 39% reduction in mortality as compared to patients treated with standard therapy.

Cohort 2

No deaths, no safety concerns.

The ventilator was withdrawn within 28 days for all five patients and in three days or less for three of these patients.

	Cohort 1	
	HLCM051	Standard therapy
Primary Endpoint		
VFD (the number of days out of 28 during which a ventilator was not used for the patient)	**20 days**	**11 days**
Secondary Endpoint		
Mortality (180 days after administration)	**26.3%**	**42.9%**

	Cohort 2
	HLCM051
Primary Endpoint	
Safety	**No safety issues**
Secondary Endpoint	
VFD	**25 days**
Mortality (180 days after administration)	**0%**

Presentation of the ONE-BRIDGE Study Results

New

Healios

The 63rd Annual Meeting of the Japanese Respiratory Society, April 28 in Tokyo (Poster Download)

PP115. Clinical efficacy and safety of mesenchymal stem cell（HLCM051）for acute respiratory distress syndrome caused by pneumonia: a randomized, open-label, standard therapy controlled, phase 2 domestic study.

PP116. A phase 2 clinical study of HLCM051 for acute respiratory distress syndrome caused by pneumonia: A comparison with historical control group using propensity score matching

Lead presenter: Kazuya Ichikado, M.D., Ph.D.,
Director, Division of Respiratory Medicine, Saiseikai Kumamoto Hospital

TREASURE Study: Development Status

Update

TREASURE study

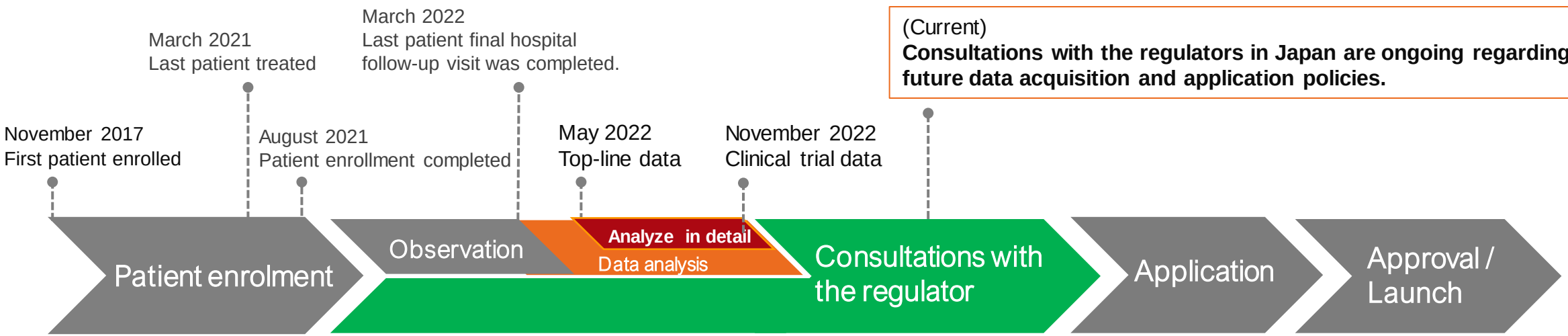
Inflammatory Conditions

Ischemic stroke

In discussion with potential partner companies

- **In response to the results of our domestic study, Athersys proposed modifications of primary and secondary endpoints in the ongoing global study* and FDA accepted.**
- **Based on these results, we will consider to utilize clinical trial data / to participate in the global trial.**

＊ Phase Ⅲ study for stroke in the U.S conducted by Athersys. (MASTERS-2 study)

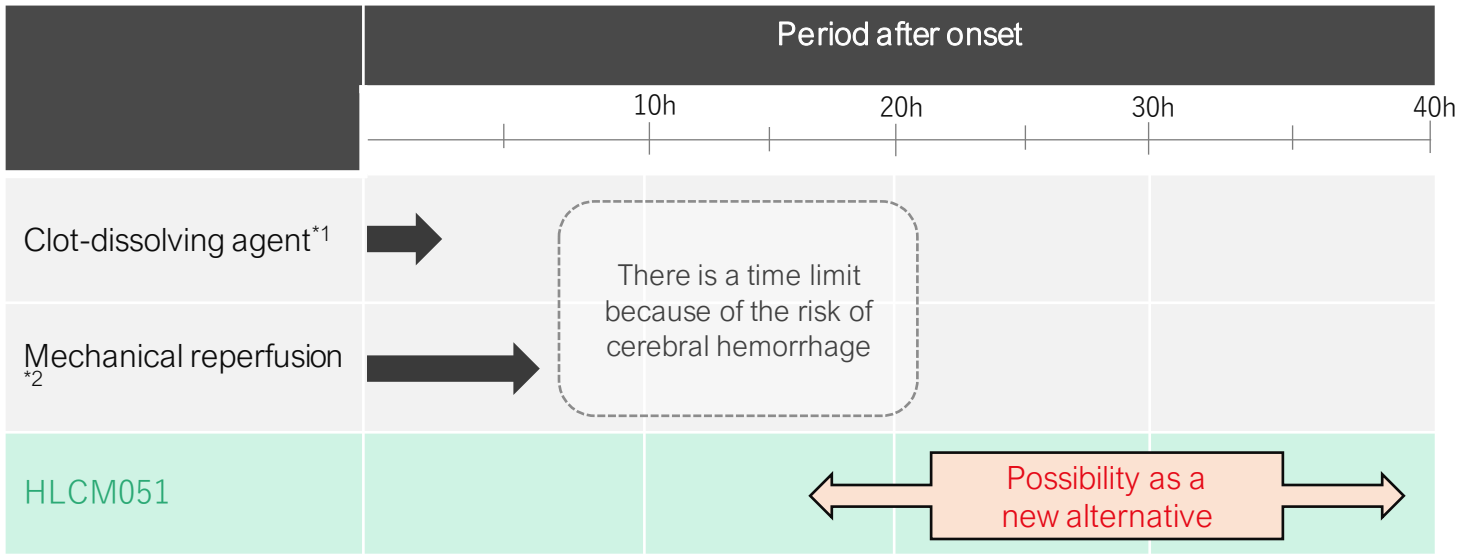


- HLCM051 is designated for SAKIGAKE Designation System

HLCM051 Stroke: Outline of Ischemic Stroke in Japan

Expected development of a new therapy that can be applied in a longer treatment window period following the onset of ischemic stroke (ability to help more patients)

Treatment in Accordance with the Period After Onset



※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.

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.

(Source) Athersys

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.

TREASURE Study: Overview

Trial	Placebo-Controlled, Double-Blind, Phase 2/3 Efficacy and Safety Trial of HLCM051 in Patients With Ischemic Stroke（TREASURE study）
Subjects	Ischemic stroke within 18 to 36 hours
Conditions	Placebo-Controlled, Double-Blind
Enrollment	220 (HLCM051 [n=110], placebo [n=110], randomized)
Outcome Measures (examples)	・Proportion of subjects achieving Excellent Outcome defined by functional assessments (primary endpoint at day 90) ・Global recovery (i.e., GEE) and dichotomous assessment ・Proportion of subjects with a BI score of ≥95

TREASURE Study: Results

Comparison of results between the HLCM051 group and the placebo group at 90 and 365 days

	90 days			365 days		
	HLCM051	**Placebo**	**p-value**	**HLCM051**	**Placebo**	**p-value**
Excellent Outcome*1	12 (11.5%)	10 (9.8%)	p=0.903	16 (15.4%)	11 (10.8%)	p=0.431
Global Recovery*2	20 (19.2%)	16 (15.7%)	p=0.762	29 (27.9%)	16 (15.7%)	p=0.037
BI >=95	31 (29.8%)	24 (23.5%)	p=0.437	37 (35.6%)	23 (22.5%)	p=0.045
Safety outcomes	There were no significant differences, including mortality and adverse events between the treatment and placebo groups.					

*1 Global Recovery (mRS<=2, NIHSS change >=75% and Barthel Index>=95).
*2 Excellent Outcome (mRS<=1, NIHSS<=1 and Barthel Index>=95)

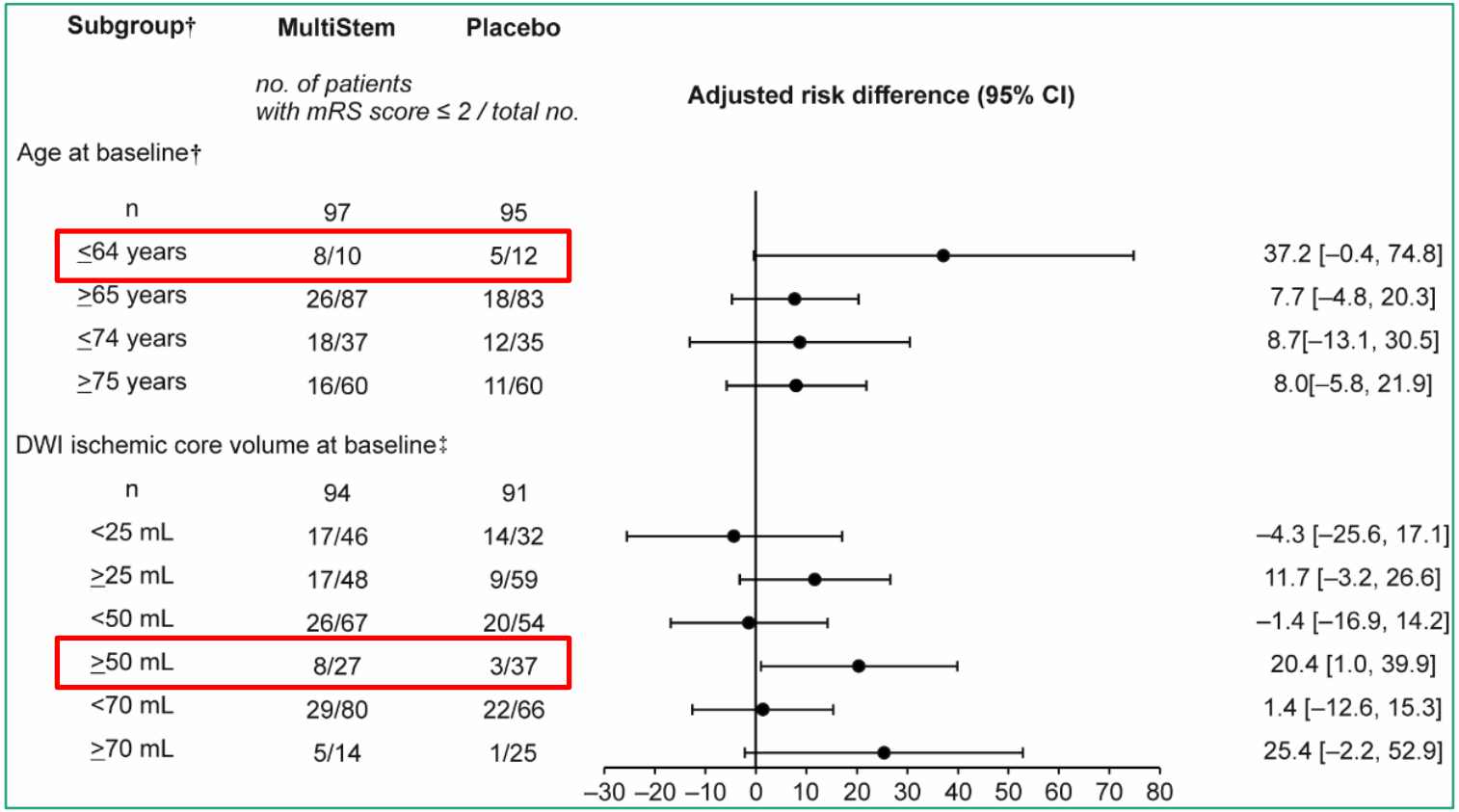
＊The above data was presented at the 14th World Stroke Conference and the 40th Annual Meeting of Japan Society of Neurological Therapeutics

TREASURE Study: Subgroup Analysis Results

New Healios

1 The results showed a trend toward efficacy as cerebral infarct volume increased from 25 mL to 50 mL and 75 mL. The efficacy was statistically significant, especially for volumes of 50 mL or greater.

2 Though a small sample size, patients under 64 years of age appear to achieve better results.



＊The subgroup analysis results were presented at the 48th Annual Meeting of the Japanese Stroke Association held on March 17, 2023.

Summary: HLCM051

- TREASURE Study (Ischemic Stroke)

Results of TREASURE Study were presented at scientific conferences in October and November, 2022. In response to the results of our domestic study, primary and secondary endpoints in the ongoing global study (MASTERS-2 study by Athersys) were changed. Consultations with the regulators in Japan are ongoing regarding future data acquisition and application policies.

- ONE-BRIDGE Study（ARDS）

In a face-to-face meeting with the regulatory authorities in 2022, we were advised that it is necessary to add certain supporting data to the proposed application data package. The design of an additional small-scale double-blind study was decided in February 2023 and agreed upon with the PMDA. We are preparing to start the clinical trial.

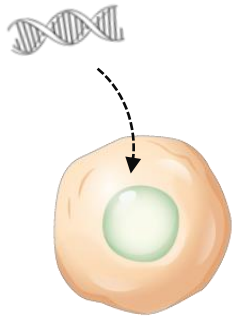
Healios and Mitsubishi UFJ Capital entered into a Letter of Intent for joint development for HLCM051 for ARDS.

iPSC eNK
Immuno-Oncology

Somatic Stem Cell	iPSC Platform	
Inflammatory Conditions	**Immuno-Oncology**	**Replacement Therapies**
Multistem® • Ischemic stroke • ARDS	**iPSC eNK** iPSC-derived, gene-engineered NK cells for: • Lung cancer • Liver cancer • Other non-disclosed	**Universal Donor Cell (UDC)** • UDC-pancreatic islets for diabetes • UDC-photoreceptors and RPE[1] for retinal disease • Liver buds[1] for liver disease

eNK Program Vision: eNK Platform

Gene-edited iPSC Line



Healios' proprietary iPS cells

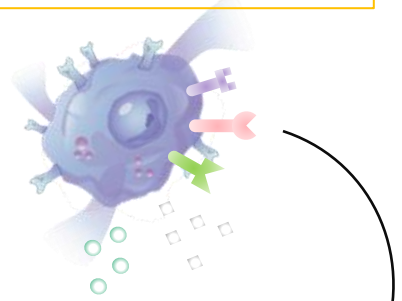
Master cell banks established for eNK cell production

eNK cells differentiation

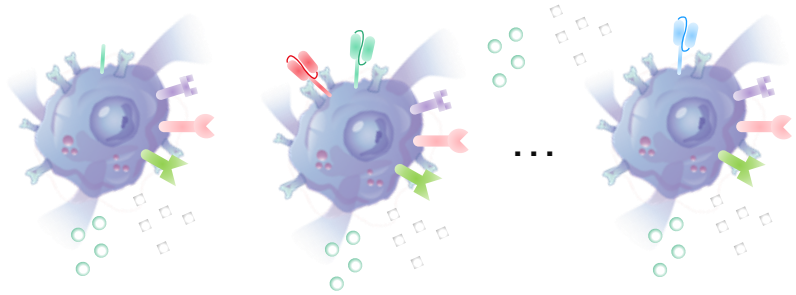
Technology Platform

Differentiation of eNK Cells with Enhanced Functionality

eNK Cells



Next Generation eNK Cells



CAR-eNK Cells *Dual CAR-eNK Cells*

Product Platform

eNK cells/CAR-eNK cells as monotherapies

+

eNK combination therapies with antibodies for ADCC*

+

eNK combination therapies with immune checkpoint inhibitors

=

Platform leading to numerous pipeline products and treatment approaches for various types of cancers

*ADCC: antibody-dependent cellular cytotoxicity
Attack activity to pathogens by an immune cell though an antibody

HLCN061: eNK Cells Enhanced Not Only with Improved Cytotoxicity and Persistence, but with Greater Migration to Tumors and Recruitment of Host Immune Cells

Update

Healios

Healios' eNK Cells key features

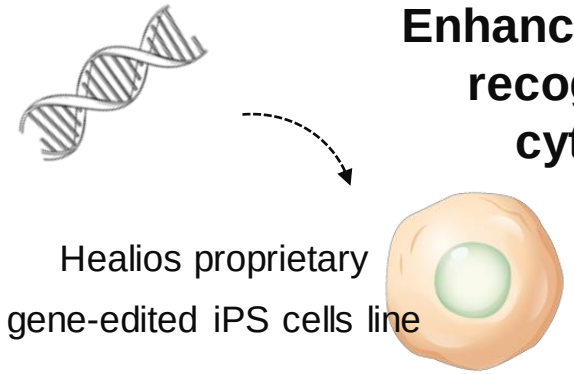
① ***NKG2D***
Enhanced cancer cell recognition and cytotoxicity

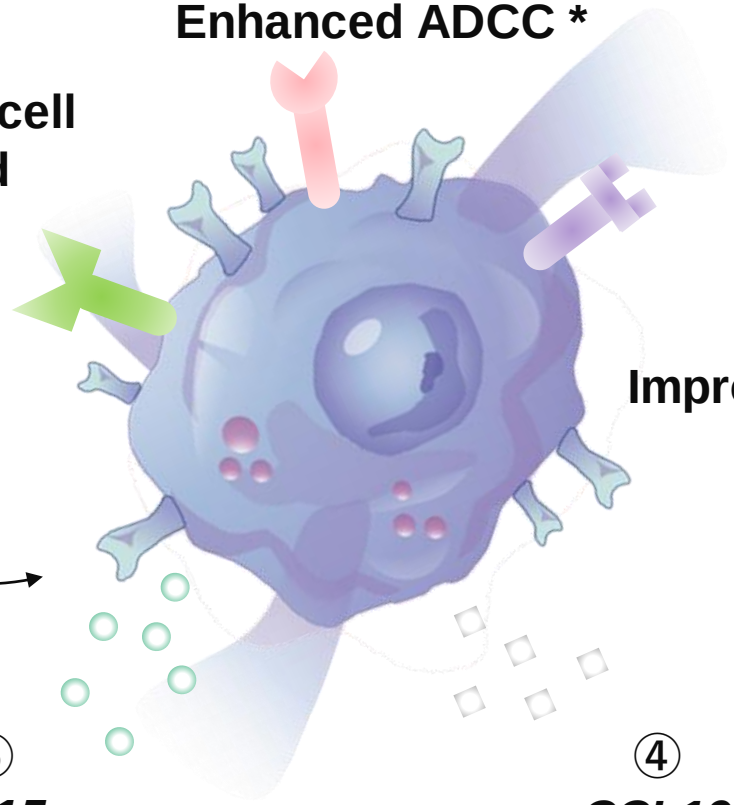
② ***CD16***
Enhanced ADCC *

③ ***CCR2B***
Improved migration to solid tumors

④ ***CCL19***
Recruitment of host immune cells

⑤ ***IL-15***
Prolonged survival





*ADCC: antibody-dependent cellular cytotoxicity
Attack activity to pathogens by an immune cell though an antibody

Presentation of the Research Results of Healios' eNK Cells and UDCs

New Healios

The 22nd Congress of the Japanese Society for Regenerative Medicine, March 23, in Kyoto

(Poster Download)

① Poster No.:P-03-1 Development of a method for mass production of transfected iPS cell-derived NK cells (HLCN061) using a 3D automated perfusion culture method

② Poster No.:P-03-3 Anti-tumor effect of iPSC-derived transgenic NK cells HLCN061 expressing high-affinity CD16 (F176V) on lung cancer and mesothelioma

③ Poster No.:P-03-4 Genetic engineering and quality control of clinical grade iPS cells as a source of HLCN061

④ Poster No.:P-03-5 Enhancement of anti-tumor effect against solid tumors by gene transfer in iPS cell-derived NK cells

⑤ Poster No.:P-03-6 Pharmacokinetic characteristics and antitumor effects of iPSC-derived transgenic NK cells (HLCN061)

⑥ Poster No.:P-03-7 Effect of IFN-γ on the anti-tumor effect of transgenic iPS cell-derived NK cells (HLCN061)

The 26th Annual Meeting of The American Society of Gene & Cell Therapy, May 19, in Los Angeles

Poster No.: 1576 HLCN061: An "Off-the-Shelf" Gene Engineered Human iPSC-Derived NK Cell Product for the Treatment of Solid Tumors

HLCN061: Advanced In-House GMP Grade, 3D Manufacturing Process & Facility

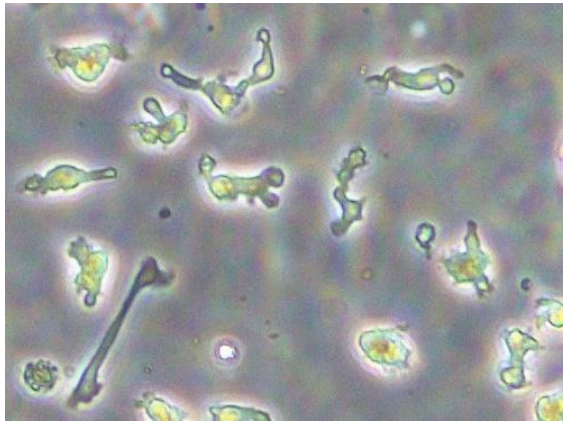
-GMP facility fully operational and being advanced in preparation for clinical trials
-In-house manufacturing enables control of the schedule and quality of clinical production

iPSC Sphere Formation → HPC Differentiation Induction → eNK Cells Differentiation Induction → eNK Cells Expansion

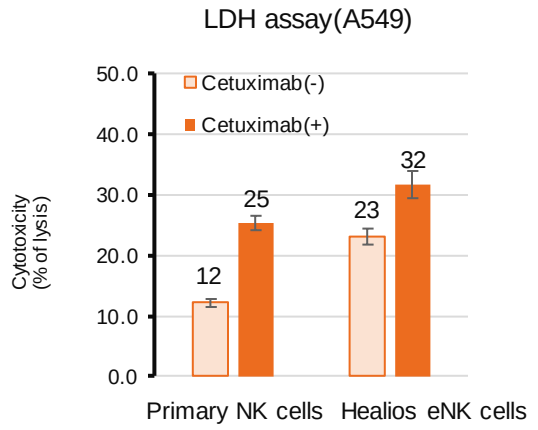
Fully-closed, feeder free, 3D perfusion bioreactor system

Cell Harvest: Concentration & Washing → Aseptic Filling and Finish → Cryopreservation → Storage

KCMI; Kobe Center for Medical Innovation
Photo by; OM Kobe (KCMI management company)



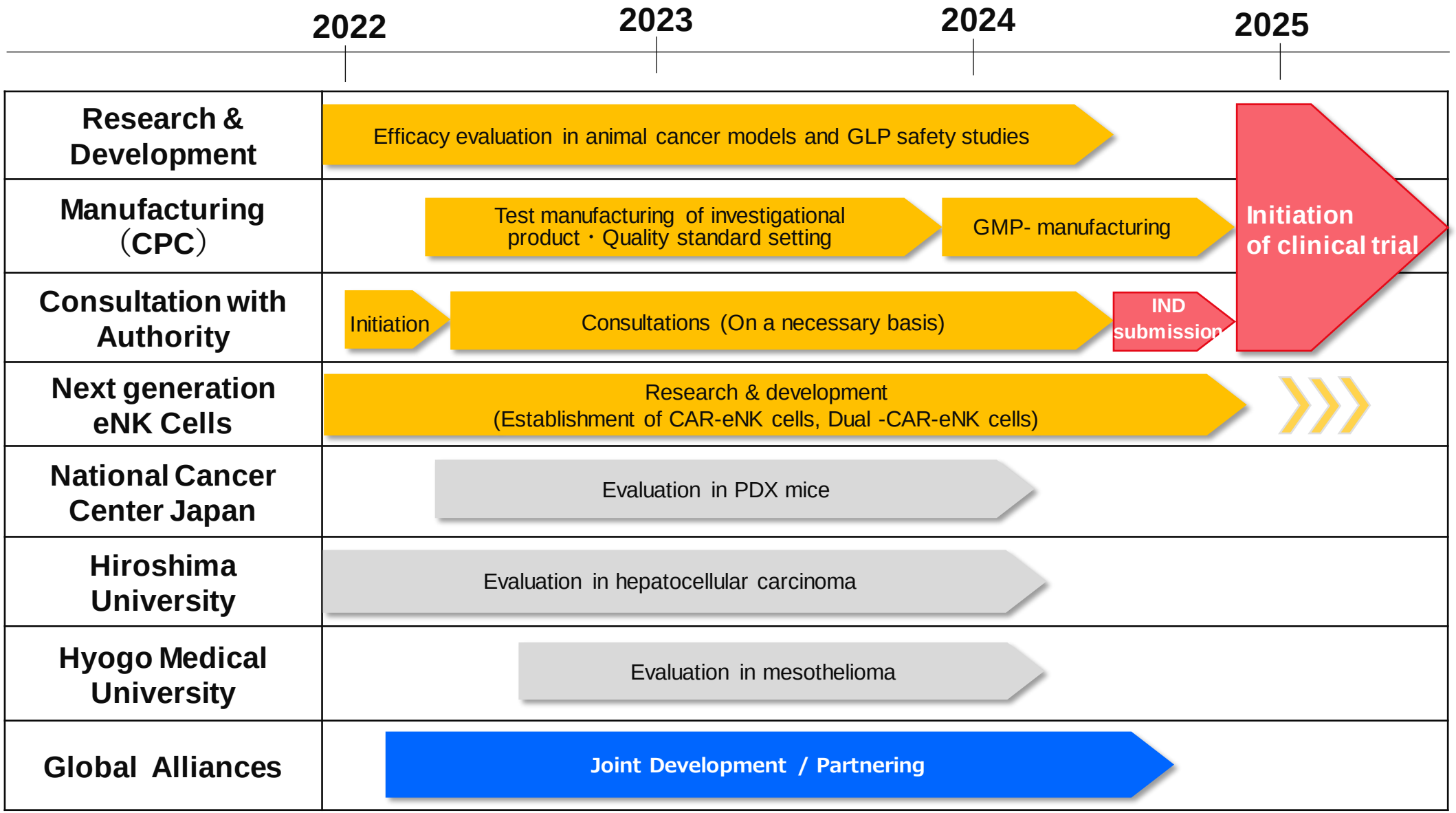
100 billion eNK cells per batch



Cryopreserved samples show high cytotoxicity post thaw

(Source) in-house data

R&D Roadmap of eNK Cells (HLCN061)



Summary: iPSC eNK Immuno-Oncology

Update

Healios

- **Years of Experience have Yielded a Best-In-Class Platform:** Healios' iPSC therapy leadership has led to the development of a functionally enhanced natural killer cell platform which provides for multiple pipeline product opportunities

- **Unique Approach**: Our eNK cell platform has enhanced recognition, cytotoxicity, and persistence, as well as unique recruitment and trafficking properties, designed to infiltrate solid tumors and mount a whole system immune cell attack

- **Promising *In Vitro* and *In Vivo* Evidence** demonstrating robust cancer elimination

- **Initial Target Indications**: Lung cancer, liver cancer, mesothelioma, other non-disclosed

Reference abstract: Development of a method for mass production of transfected iPS cell-derived NK cells (HLCN061) using a 3D automated perfusion culture method

- **Robust and Advanced Manufacturing** processes and infrastructure in place

- **Strong team** with near-term regulatory milestones: Pre-IND: 2022, IND: 2024

- **Pursuing partnerships** to bring new treatments to cancer patients as soon as possible

Universal Donor Cell (UDC) Replacement Therapies

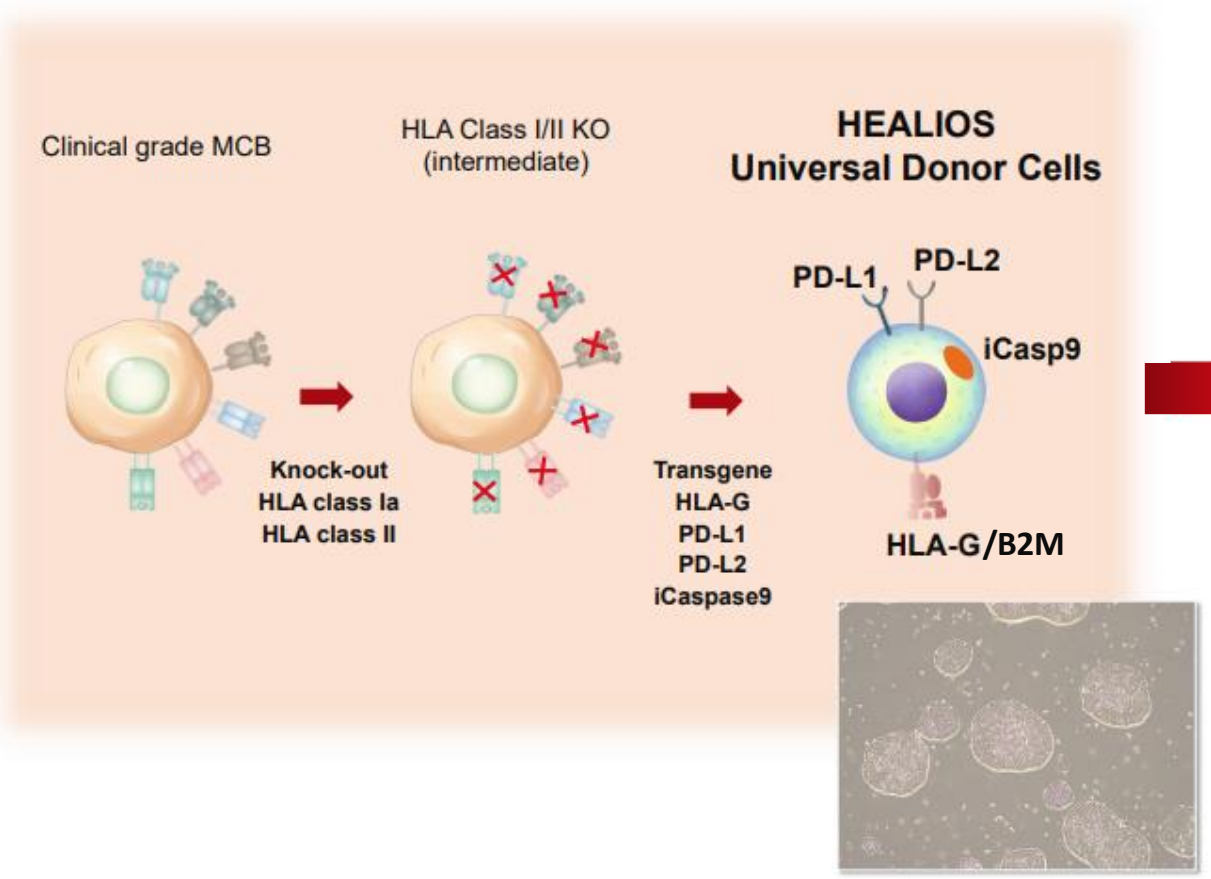
Somatic Stem Cell	iPSC Platform	
Inflammatory Conditions	**Immuno-Oncology**	**Replacement Therapies**
Multistem® • Ischemic stroke • ARDS	**iPSC eNK** iPSC-derived, gene-engineered NK cells for: • Lung cancer • Liver cancer • Other non-disclosed	**Universal Donor Cell (UDC)** • UDC-pancreatic islets for diabetes • UDC-photoreceptors and RPE[1] for retinal disease • Liver buds[1] for liver disease

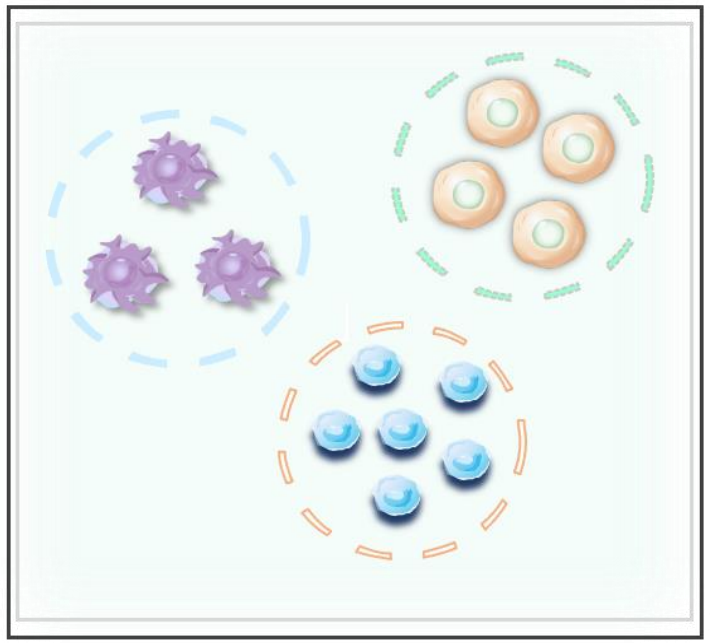
Hypo-immune UDC: Engineered Genetic Profile

Update

Healios

Gene Editing Procedure for Healios UDC





- Off-the-shelf, scalable and cost-efficient
- Address broadest population with single product
- Enhanced level and duration of efficacy

(Source) in-house data

Clinical grade line and Master Cell Bank established in 2020/2021

Reference abstract: Clinical grade genetically engineered hypoimmunogenic human induced pluripotent stem cell line
the 22nd Congress of the Japanese Society for Regenerative Medicine, March 23, in Kyoto

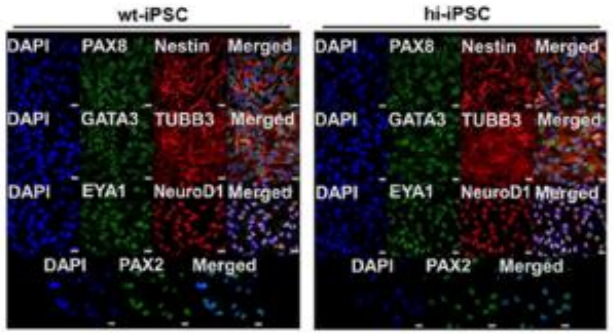
iPSC Platform: ONPs differentiated from UDCs

New

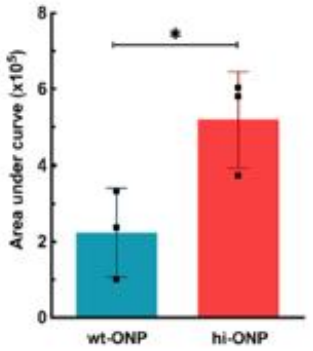
Healios

Healios UDC-derived otic neural progenitor cells (ONPs) demonstrate enhanced survival after transplantation into the cochlea confirmed by Northwestern University

Otic neural progenitor cells



Representative immunocytochemistry photomicrographs of iPSC-derived ONPs



Quantification of iPSC-derived ONPs 10 days following intracochlear transplantation

(Source: Northwestern University)

Left

Healios UDCs (hi-iPSCs) differentiated into late-stage ONPs as well as unedited cells (wt-iPSC) using multiple differentiation markers.

Right

More Healios UDC-derived ONPs (hi-ONPs) than unedited parental cell-derived ONPs (wt-ONPs) were viable after transplantation. In other words, immune rejection was reduced as expected.

The induction of differentiation into otic neural progenitor cells and the hypo-immune benefit upon transplantation into mice were confirmed

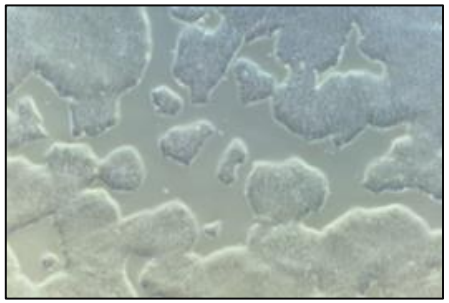
This approach may open a new avenue for experimental and clinical sensorineural hearing loss (SNHL) treatments

iPSC Platform: UDC and iPS Cell Line Collaborations

Supplying UDC and iPS cells to several companies and academic institutions (more than 10 facilities) and evaluating their potential for various diseases

Hypo-immune UDC: Differentiation and Induction of Photoreceptor Cells

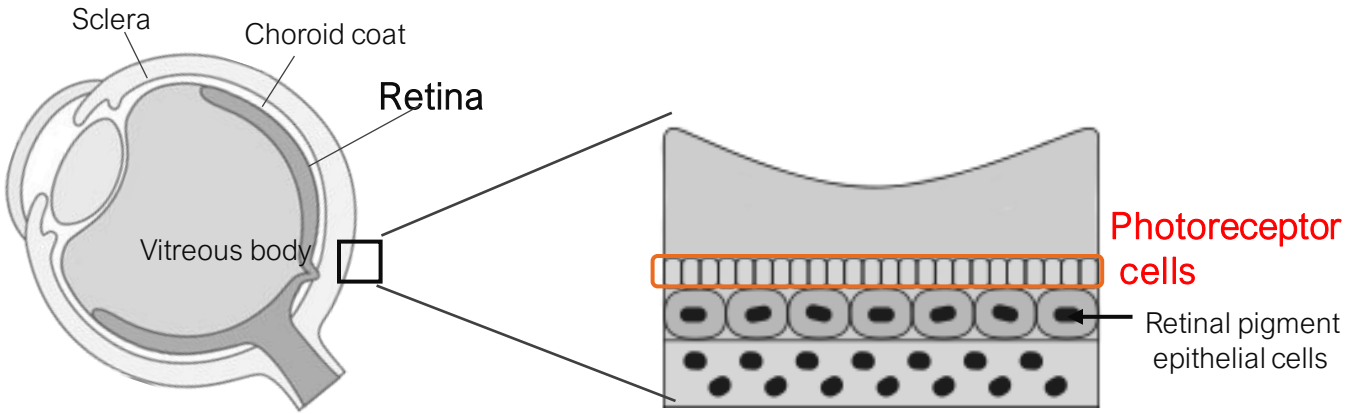
Photoreceptor cells



UDC

Differentiation and induction

Photoreceptor cells From UDC



Joint Research with STEMAXON

Confirmation of differentiation and culture from UDCs to photoreceptor cells* for retinal disease

-Cone cell dominant photoreceptor cell sheets with color-sensing

-Minimal contamination of unnecessary cells such as bipolar cells, which can be an obstacle to improving visual acuity

-Recovery of visual function confirmed in transplantation experiments using animal disease models

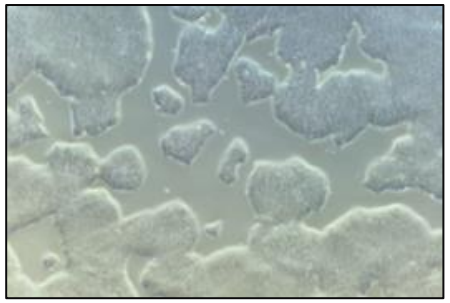
* Photoreceptor cells are one of the cells that compose the retina and are particularly responsive to light.

(Source) Joint research data

Hypo-immune UDC: Differentiation and Induction of Pancreatic β-cells

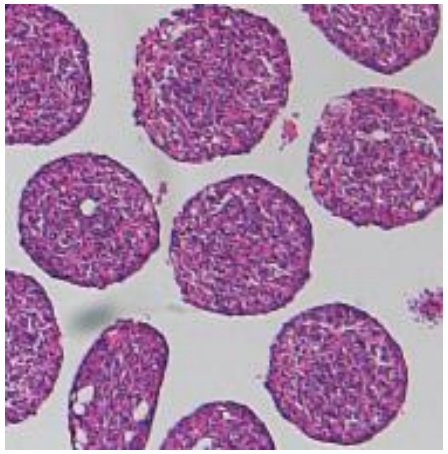
Joint research with the Department of Regenerative Medicine at the National Center for Global Health and Medicine in Tokyo

Pancreatic β-cells



UDC

Differentiation and induction



UDC-derived pancreatic β cells (HE staining)

(Photo provided by the National Center for Global Health and Medicine)

Pancreatic β-cells are a type of cell present in the islets of Langerhans within the pancreas. They produce and secrete insulin in response to blood glucose levels and serve to regulate the amount of glucose in the bloodstream.

In our joint research with the Department of Regenerative Medicine at the National Center for Global Health and Medicine in Tokyo, **we have successfully confirmed the differentiation of UDCs into pancreatic β-cells.**

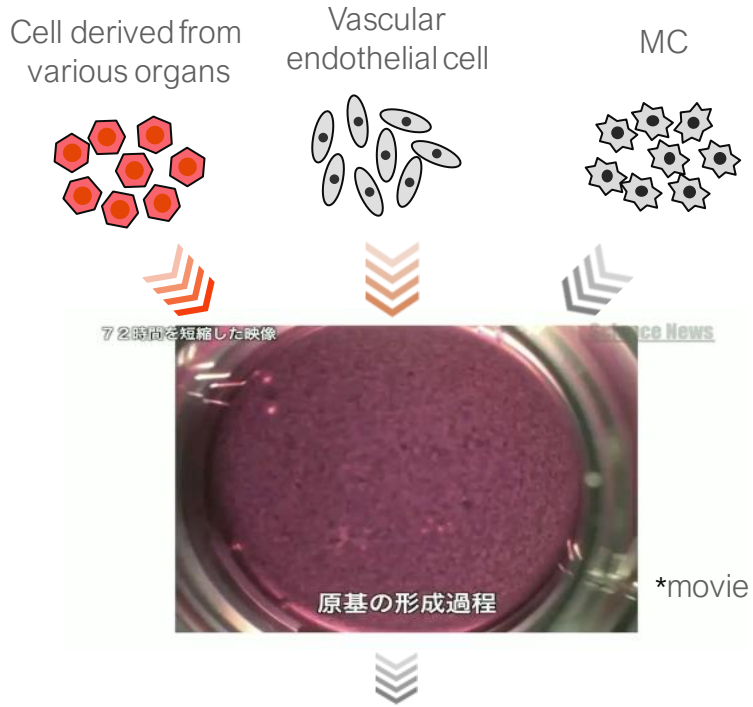
Moving forward, our joint research will work on optimizing the process and verifying the efficacy and safety of these cells in animal models of diabetes. Through this achievement, we hope to develop a new more effective therapeutic approach for diabetes and further expand the value and impact of our company's iPSC platform

(Source) Joint research data

HLCL041: Liver Organ Bud Platform

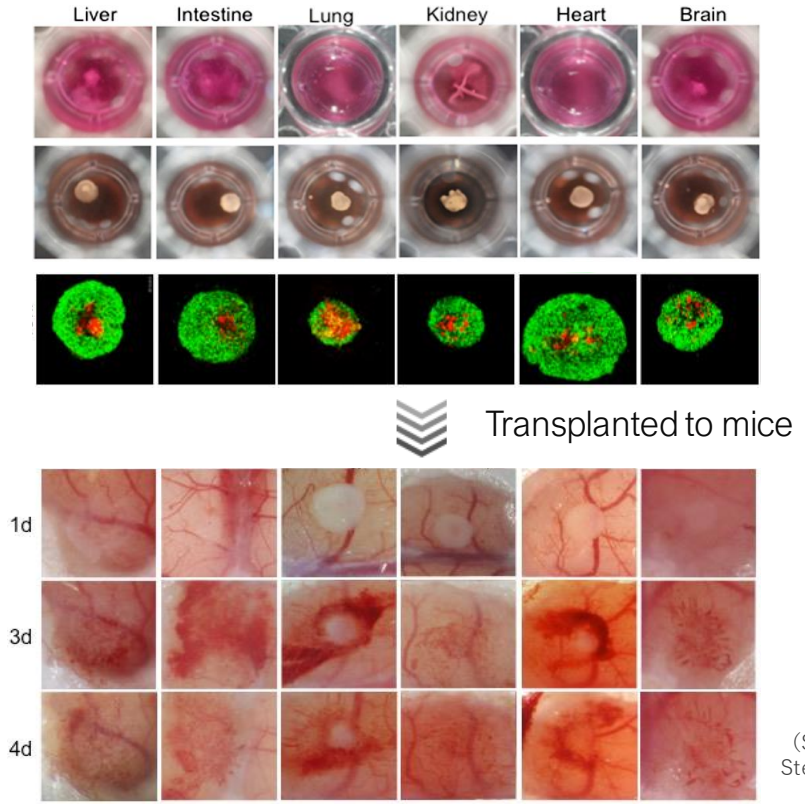
By creating an "Organ Bud" of each organ with iPS cells, we have laid the groundwork for paradigm shifting therapies to emerge for various severe diseases.

UDCs allow for the realization of organ replacement using organ buds.



The vascularization was confirmed in vivo by transplantation to mice.

（Sours） Japan Science and Technology Agency Science News “Diverse Approaches in Regenerative Medicine from Cell to Tissue/Organ” (Distributed October 3, 2013)
https://sciencechannel.jst.go.jp/M130001/detail/M130001005.html



Green：Cells of each organ
Red：Vascular endothelial cell
Black：MSC

（Sours） Modified from Takebe T. et al., Cell Stem Cell, 2015

We plan to carve out the technology to efficiently accelerate R&D in collaboration with external partners such as venture capital funds.

Conclusion

Update

Healios

- Focus pipeline and maximize investment efficiency.
  - Non-dilutive funding from project finance, carve outs, grants & partnering.
- Preparing for Multistem® ARDS trial; continuing to establish efficient path for ischemic stroke.
- Driving forward eNK program towards the clinic while pursuing partnerships with global pharmaceutical companies.
- Imminent RPE trial initiation by Sumitomo Pharma; projected 2025 product launch.
- Expanding UDC and IPS cell line collaboration activities.
- Ongoing cost discipline.

Committed to transforming the lives of patients by

creating, developing and commercializing cutting edge cell therapy technologies

Appendix

Vision

To become a global biopharma company committed to transforming the lives of patients by creating, developing and commercializing cutting edge cell therapy technologies.

Overview of Healios

Update

About us

Company Overview

Company Name	HEALIOS K.K.
Representative	Hardy TS Kagimoto, MD, Chairman and CEO
Establishment	February 24, 2011
Paid in Capital	119 million yen (As of April 30, 2023)
Head office	Hibiya Mitsui Tower 12F, 1-1-2 Yurakucho, Chiyoda-ku ,Tokyo 100-0006, Japan
Number of Employees	64 (As of March 31, 2023)
Business	Research, development and manufacturing of cell therapy/ regenerative medicine products
Affiliated Company	Sighregen Co., Ltd. (Joint Venture with Sumitomo Dainippon Pharma Co., Ltd.)
Subsidiary	・Healios NA Inc. (Established in February 2018) ・Organoid Neogenesis Laboratory Inc. (Established in June 2018 to promote the practical use of organ bud technology) ・Saisei Ventures LLC (Established in January 2021 as a venture fund investment advisor) ・Saisei Capital Ltd. (Established in January 2021 as a venture fund general partner) ・Saisei Bioventures, L.P. (Established in January 2021 as a venture fund limited partnership)

Advanced Technology at Healios' Kobe Research Institute

Update

Large number of researchers (24 Ph.D.'s as of Mar. 31) on staff and efficient, in-house implementation of everything from gene editing to process development

1. Exploratory Research
- I. Development of iPSC differentiation induction methods
- II. Functional evaluation of iPSC derived cells
- III. Functional evaluation of iPSC derived cells
- IV. Evaluation of gene-edited cells

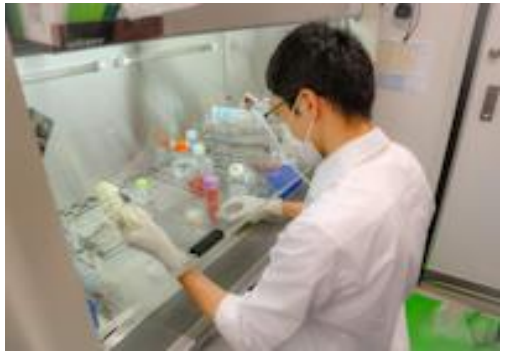
2. QC
- I. Functional evaluation of various cells
- II. Development of evaluation protocols

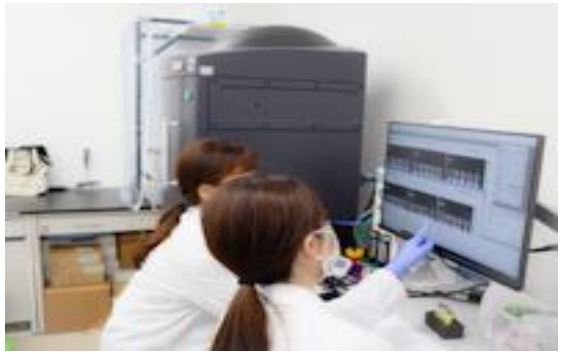
3. Genetic Recombination Experiments
- I. Construction of plasmids
- II. Construction of viral vectors
- III. Creation of transgenic cells

Healios' Kobe Institute Area(Photo by Kobe Urban Promotion Service Co.,Ltd.)

4. Experiments on animals
- I. Generation of disease mice models
- II. Evaluation of antitumor effects *in vivo*
- III. Evaluation of immune response *in vivo*
- IV. Evaluation: tissue section and immunostaining

5. Process Development Research
- I. Optimization of differentiation
- II. Development of mass production methods
- III. Development of freezing processes
- IV. Analysis of culture media





Healios Is Uniquely Positioned To Leverage Strong Japanese Proficiencies

Favorable External Environment In Japan

iPSCs Discovered in Japan

The Nobel Prize in Physiology or Medicine (2012) Shinya Yamanaka, M.D, Ph.D (Professor at Kyoto University)

Expedited Regulatory Framework

- Conditional and time limited authorization system
- SAKIGAKE (fast-track designation)

Precision Manufacturing in Cell Therapy

- Clinical and scale-up infrastructure for commercial purposes

Intrinsic Healios Strengths

Established Innovative R&D Expertise

- First in human iPSC technology in the world
- Proprietary hypo-immune universal donor iPSC platform technology
- Kobe Research Institute: > 30 Ph.D. holders
- Numerous high-profile R&D partnerships & JVs

Robust CMC Expertise & Foundational Alliances with Global Players

- GCTP/GMP manufacturing facility
- Automated 3D bioreactor system for eNK
- Advanced 3D organ manufacturing
- Long-standing alliances with Nikon & Sumitomo Pharma Co., Ltd.

Clinical Development Capabilities

- Completed enrolment in two major trials in 2021 including the largest Japanese cell therapy trial in history

Saisei Fund Accelerates Investment in Next-generation Therapeutics and Technologies

New Healios

January 2021 Saisei Bioventures, L.P. (Saisei Fund) established by Healios

Important informational insights

Building relationships with promising companies

High return investments

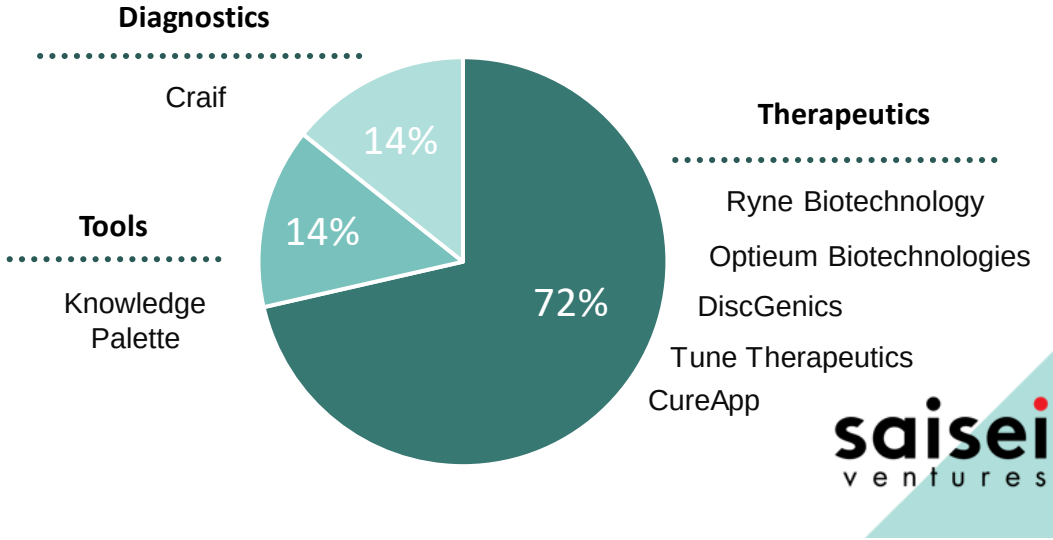
Engage deeply with regenerative medicine innovation around the world through our venture fund activities

Saisei Fund partners

Jonathan Yeh （Ph.D. MBA）
Founding Partner
Investment Committee
Board of Managers
Director of GP

Hikaru Saito （Ph.D.）
Japan representative partner
(Appointed in Jan 2023)
Formerly at Astellas Venture Management
Cell & gene specialist

Investment Portfolio



Japan Investment Corporation has made a $30 million commitment as a limited partner in the Saisei Fund, and in connection with this, Healios has decided to change its previously disclosed use of funds.

The decision by Japan Investment Corporation to invest in Saisei Bioventures, L.P. Change in the use of funds

Potential for Future Milestone Income

May 12, 2017, 1st Quarter Financial Results Briefing (page 7)

Comp ounds | BBG

Transfer our business relating to an ophthalmic surgical adjuvant containing BBG250

[The transferee] D. Western Therapeutics Institute, Inc.
[Transfer price] A lump sum fee of 1.3 billion yen at the time of transfer.

There is also the possibility of receiving milestone payments in line with the progress, etc., of development and out-licensing operations.

[Business transfer due date] April 30, 2017

Expected to receive milestone payments (amount undisclosed) as progress in development is expected in the medium term.

※February 13, 2023, D. Western Therapeutics Institute, Inc. “事業計画及び成長可能性に関する事項”(page.57 Japanese only)

MultiStem®
Inflammatory Conditions

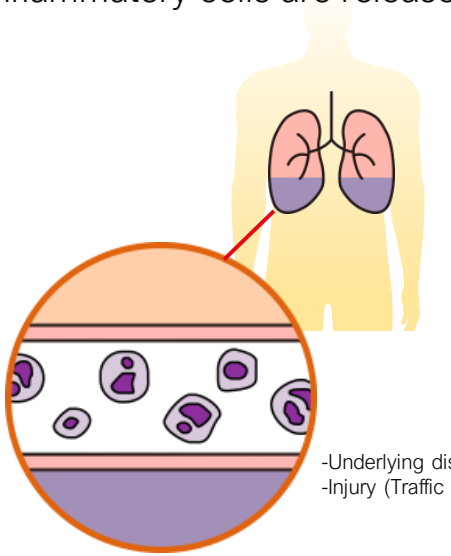
Somatic Stem Cell	iPSC Platform	
Inflammatory Conditions	**Immuno-Oncology**	**Replacement Therapies**
Multistem® • Ischemic stroke • ARDS	**iPSC eNK** iPSC-derived, gene-engineered NK cells for: • Lung cancer • Liver cancer • Other non-disclosed	**Universal Donor Cell (UDC)** • UDC-pancreatic islets for diabetes • UDC-photoreceptors and RPE[1] for retinal disease • Liver buds[1] for liver disease

HLCM051 ARDS: Mechanism of Action

Expected effects of HLCM051(MultiStem®), bone marrow-derived somatic stem cells

- Relief of inflammation, regulation of immune function
- Promotion of angiogenesis
- Promote protection and repair of injured cells and tissues
- Improvement of lung tissue and respiratory function

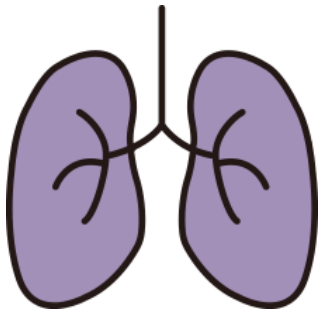
Inflammatory cells are released



-Underlying disease (pneumonia, etc.)
-Injury (Traffic accident, etc.)

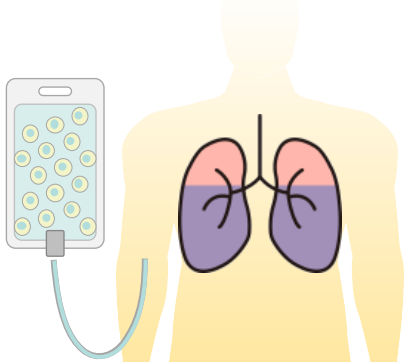
When the tissue is damaged, inflammatory cells are released in large quantities.

Inflammatory cells attack the lungs



The inflammatory cells attack the lungs. As a result, hypoxia develops and the patient falls into severe respiratory failure.

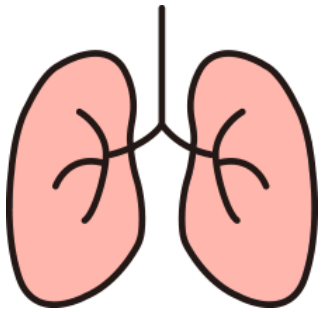
HLCM051 administered



- Suppresses excessive inflammation in the lungs.
- Protects damaged tissue and facilitates healing.

HLCM051 accumulates in the lungs as a result of intravenous administration.

Lung function improves

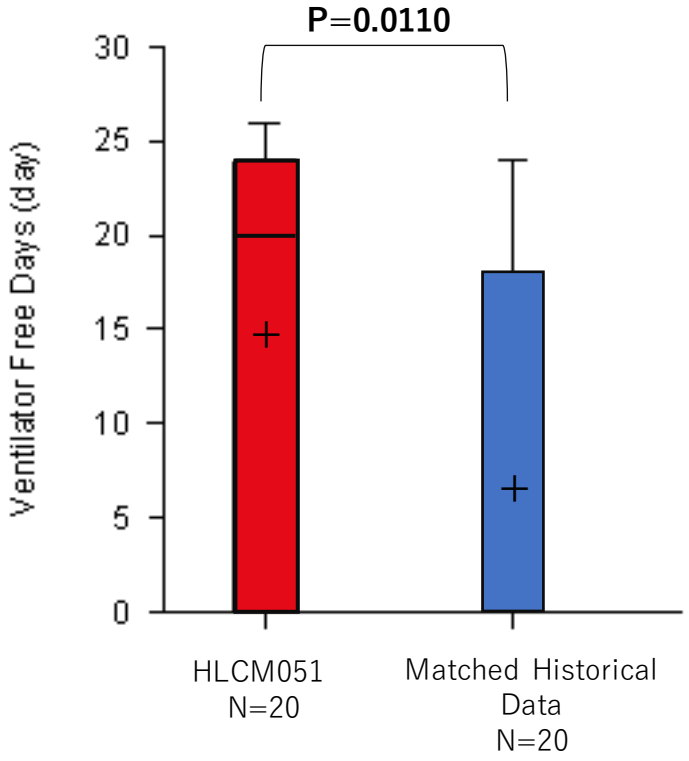


We can anticipate earlier ventilator removal and a lower mortality rate.

HLCM051 ARDS: Comparison with Historical Data

In the matched historical data comparison, the VFD was prolonged by 8.1 days (mean), and the mortality rate was 33.7% lower (reflecting a 56% decline in mortality as compared to the historical data group).

	Compared with historical data	
	HLCM051	Matched historical data
Primary Endpoint	**P=0.0110**	
VFD (the number of days out of 28 during which a ventilator was not used for the patient)	**14.8days**	**6.7 days**
Secondary Endpoint	**P=0.0536**	
Mortality (180 days after administration)	**26.3%**	**60.0%**



(Source) in-house data

Results of Double-blind Study Conducted by Athersys <ARDS>

Based on one-year follow-up summary results, an evaluation of quality-of-life suggests further potential benefits from MultiStem treatment including faster rehabilitation.

No serious adverse events were observed.

Analysis of the Double-blind study conducted by Athersys

	MultiStem	Placebo
Mortality	25%	40%
Ventilator-free (VF) days	12.9 days	9.2 days
Intensive Care Unit (ICU) free days	10.3 days	8.1 days

Post-hoc Analysis of patients in severe condition and pneumonia-induced ARDS

	MultiStem	Placebo
Mortality	20%	50%
Ventilator-free (VF) days	14.8 days	7.5 days
Intensive Care Unit (ICU) free days	12.0 days	5.0 days

In the above analysis based on data obtained 90 days after administration, the mortality rate and the number of ventilator-free days (VFD) within a 28-day post-administration period et al. tended to improve in the MultiStem group compared with the placebo group. The results of the 1-year follow-up after administration showed a similar trend.

Overview of the Analysis

Clinical trial	Exploratory clinical trial (Phase 1/2) conducted by Athersys in US and UK （MUST-ARDS study)
Subjects	ARDS patients administered MultiStem or Placebo intravenously (In Phase 2 trial, MultiStem 20, Placebo 10)
Endpoints	- Mortality - Ventilator Free days (The number of the days out of 28 in which a ventilator was not used for the patient) - ICU Free Days The number of the days out of 28 in which the patient was out of Intensive Care Unit

【Reference】

Research contents on MultiStem's mechanism of modulating the inflammatory response in critical care indications Published in Scientific Reports （Link to Athersys' Website June 30, 2021）

Report of Placebo-Controlled Clinical Trial Evaluating MultiStem Cell Therapy for ARDS Published in Intensive Care Medicine （Link to Athersys' Website November 30, 2021）

（Source）Athersys

HLCM051 can be the first available therapeutic medicine for ARDS

- Currently only artificial respiration and ECMO (Extracorporeal Membrane Oxygenation) are available as coping therapies.
- ECMO has a limited number of installations at medical institutions, requires multiple medical staff with special skills, and has a high cost of management.

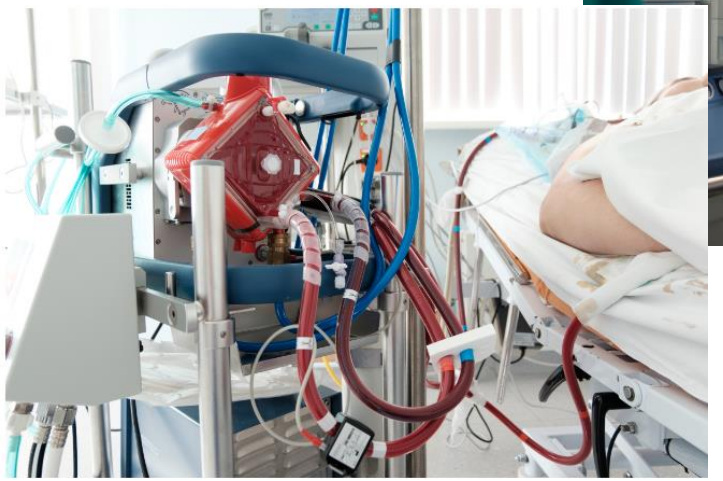
Contribution to patients ⇒ Providing new treatment Improvement of mortality and QOL

- Improving patient lifesaving rate and QOL
- Shortening the treatment period (ICU use, length of hospital stay, etc.)

Contribution to medical ⇒ Reducing the burden on medical staff and hospitals

- Improving effective use of artificial respiration including ECMO
- Curbing medical resources per patient

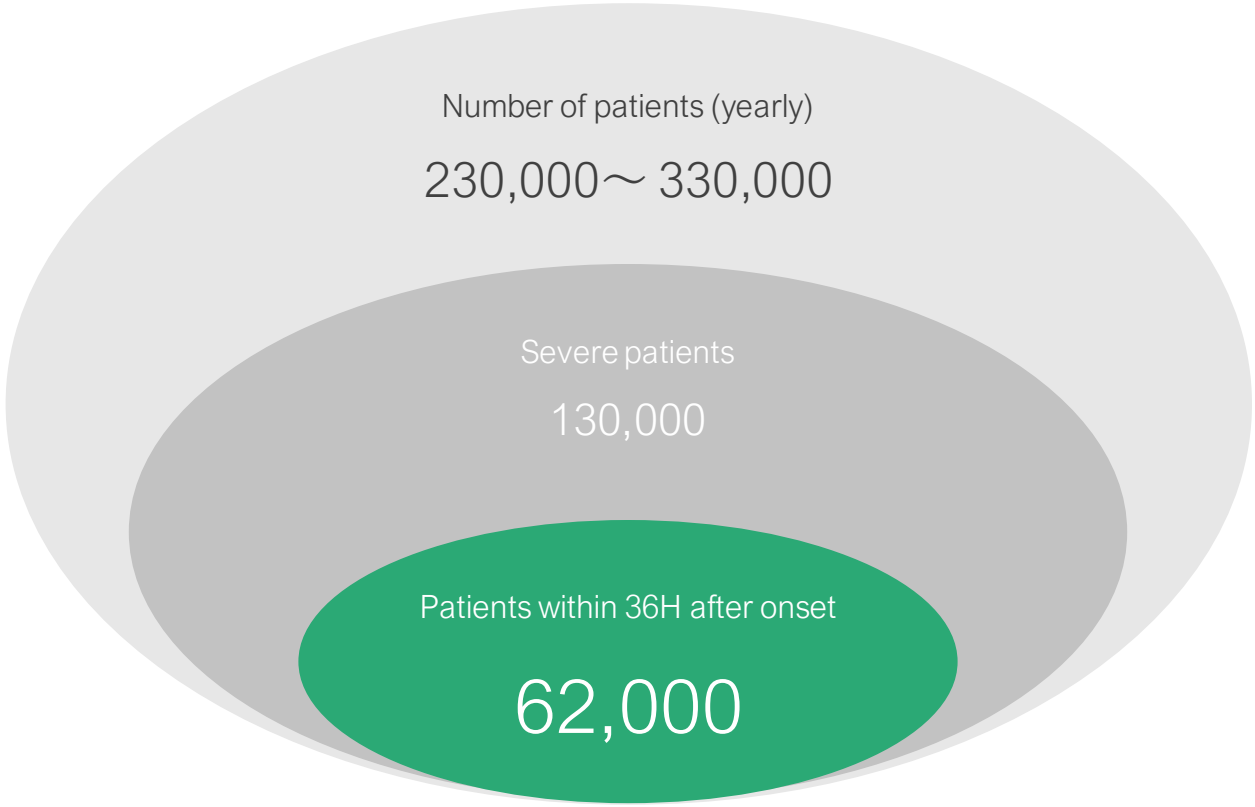
ECMO



Artificial Respiration

HLCM051 Stroke: Annual Number of New Patients with Ischemic Stroke in Japan

The number of patients in Japan targeted for HLCM051 is estimated to be 62,000 a year



Number of patients with ischemic stroke in Japan (yearly)

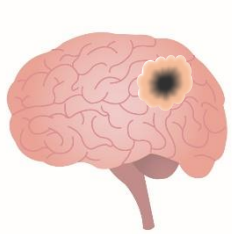
Severe patients （atherothrombotic and cardiogenic cerebral infarction)

Patients within 36 hour after onset

(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.

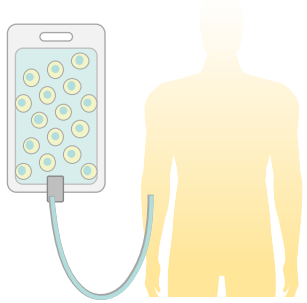
HLCM051 Stroke: Mechanism of Action

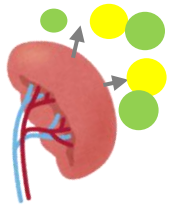
Stroke-induced neuronal damage



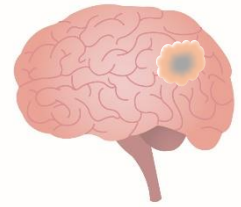
Primary Damage

With HLCM051





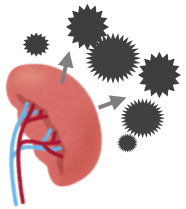
HLCM051
-suppress the mobilization/ release of inflammatory cells (lymphocytes, cytokines)
-activate the mobilization/ release of anti-inflammatory cells



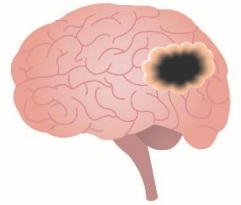
Attenuate neuronal damage in the acute phase of stroke caused by inflammatory cells

Secondary Damage mitigation

Without HLCM051



Activate mobilization / release of inflammatory cells (lymphocytes, cytokines) in the spleen



Neuronal damage exacerbated by inflammatory chemokines/cytokines
Inflammatory cells are released from the spleen and exacerbate the neuronal damage of the ischemic site.

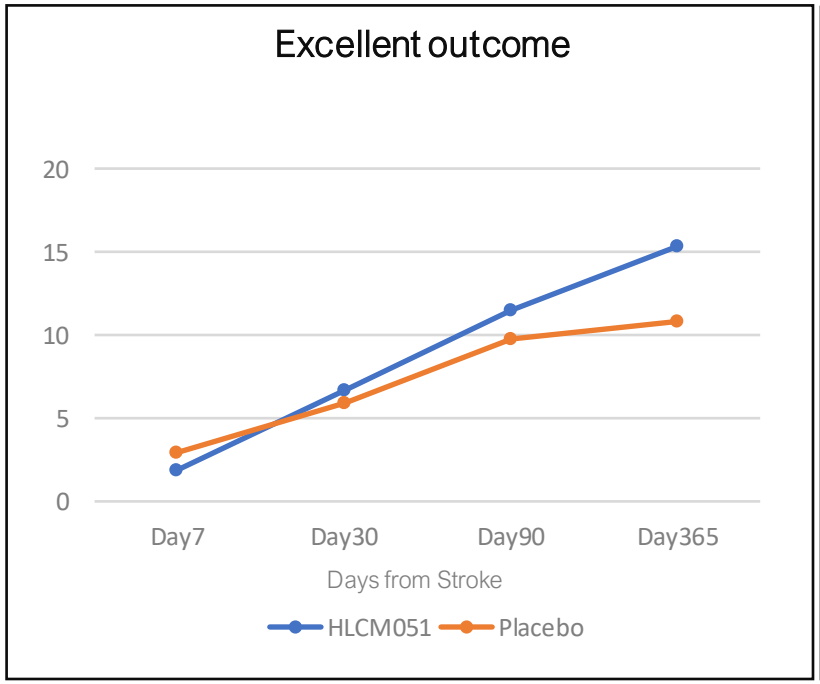
Secondary Damage

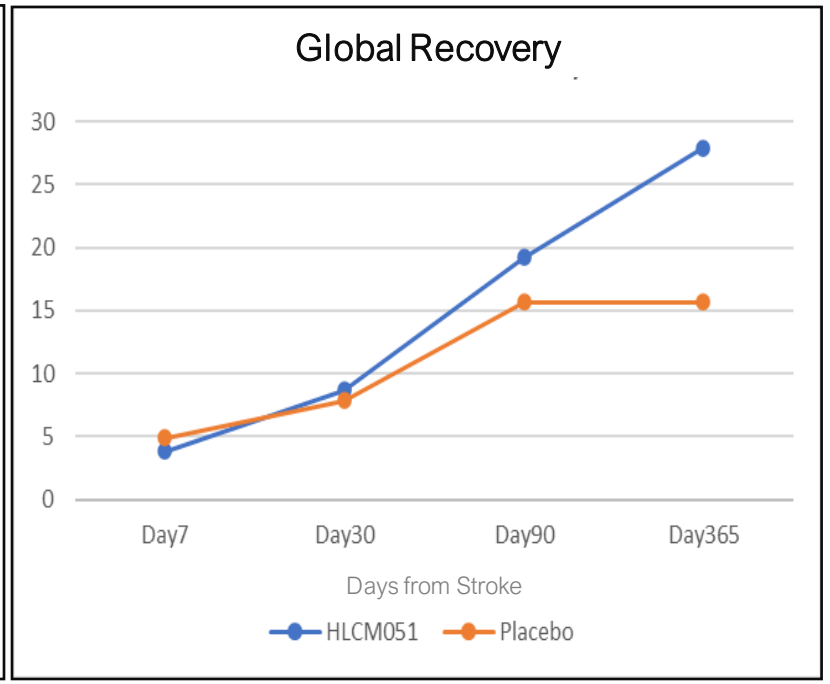
(Source) This figure was based on Stroke. 2018 May;49(5):1058-1065.Fig.2

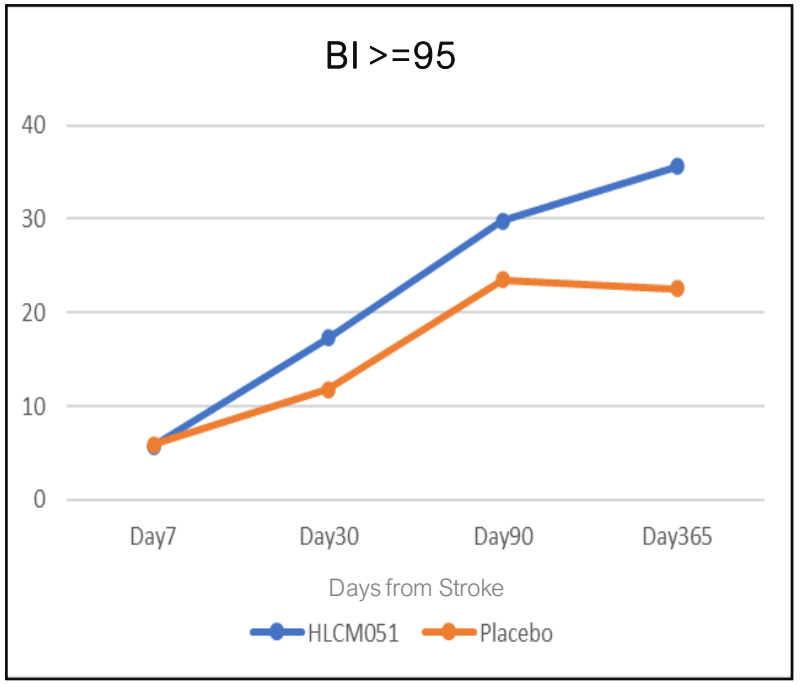
Update

Healios

Changes in the one year improvement rate in the HLCM051 and placebo groups







iPSC eNK
Immuno-Oncology

Somatic Stem Cell	iPSC Platform	
Inflammatory Conditions	**Immuno-Oncology**	**Replacement Therapies**
Multistem® • Ischemic stroke • ARDS	**iPSC eNK** iPSC-derived, gene-engineered NK cells for: • Lung cancer • Liver cancer • Other non-disclosed	**Universal Donor Cell (UDC)** • UDC-pancreatic islets for diabetes • UDC-photoreceptors and RPE[1] for retinal disease • Liver buds[1] for liver disease

The Promise of NK Cells as a Treatment for Solid Tumors

Key Facts about Cancer and the Unmet Need

- Solid tumors are the number one cause of death in Japan (~90% of cancer deaths)
- Cancer is the leading cause of death worldwide, accounting for nearly 10 million deaths in 2020[1]
- The economic impact of cancer is significant and increasing: The total annual economic cost of cancer in 2010 was estimated at US$ 1.16 trillion[1]

The Potential for Natural Killer (NK) Cells

- Offer tremendous promise as a new therapeutic approach to treating solid tumors.
- Innate, central role in a cell mediated defense system in humans, and attack cancer cells and virus-infected cells.
- Reported advantages over T cell-based therapies:
  - Broad mechanism to recognize tumor cells
  - Fewer adverse effects (e.g. CRS & GVHD)
  - Less exhaustion

[1]https://www.who.int/news-room/fact-sheets/detail/cancer

eNK Program Vision

Contribute to the eradication of solid tumors and other cancers by leveraging Healios' iPS cell expertise and augmenting the innate cancer killing ability of NK cells

Research & Development

- **Advanced technology at Healios' Kobe Research Institute**
  - In-house implementation from gene editing through to process development
- **Establishment of data for conducting clinical trials**
  - Generation and accumulation of efficacy and safety data

Manufacturing

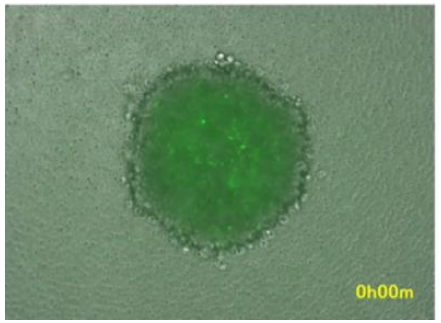
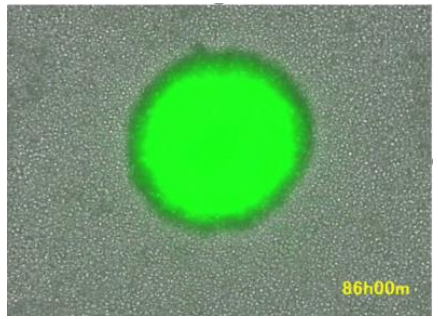
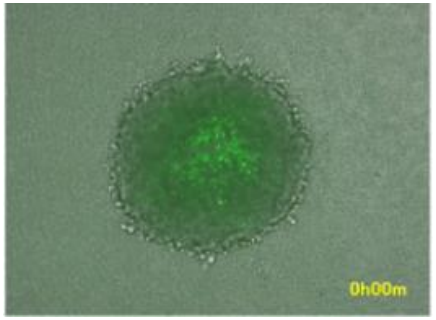
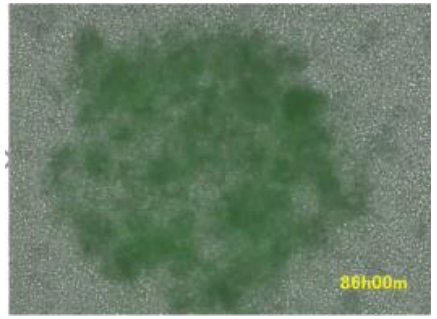
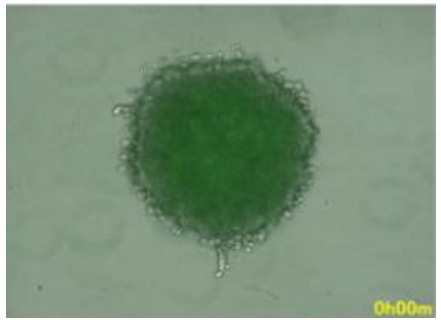
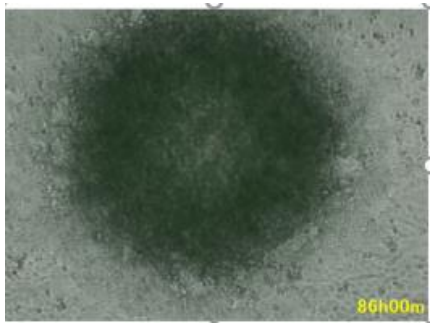
- **Manufacturing Capabilities**
  - In-house production of clinical product in proprietary 3D system

Alliances & Collaborations

- **Joint Development / Partnering**
  - Maximize the potential of the eNK cell program and platform

Accelerate activities in the above three areas

HLCN061 *In Vitro* Evidence of Anti-tumor Effect as Mono- and Combination Therapy (Lung, A549)

	0h	86h (3.5 days)	
eNK only			eNK cells have killed the cancer cells
eNK with anti-EGFR antibody			The lung cancer cells were efficiently killed and the lung cancer cell spheroid was destroyed.
Anti-EGFR antibody only			The cancer cells survived and the cancer cell spheroid expanded for 86 hours.

Bright green: apoptotic cells

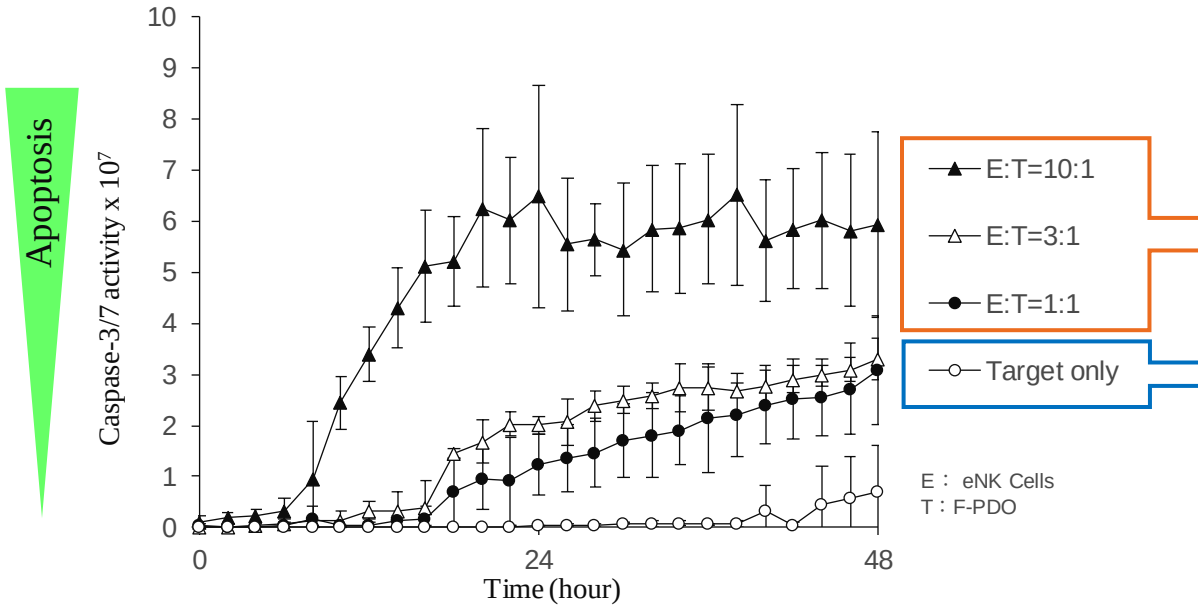
(Source) in-house data

HLCN061 *In Vitro*: Evidence of Anti-tumor Effect on Lung Cancer F-PDO®

New Healios

eNK cells have demonstrated a robust anti-tumor effect on lung cancer patient-derived tumor organoids (F-PDO®)

eNK cells were co-cultured with F-PDO® in effector/tumor cell (E:T) ratios of 1:1, 3:1 and 10:1. Cytotoxic activity was determined by measuring the apoptosis (cell death) of the cancer cells by caspase-3/7 activity.



eNK Cells effective against F-PDO ®

Under conditions of co-culture with eNK cells, F-PDO®cancer cell apoptosis was observed from 8 hours (E:T=10:1) and 18 hours (E:T=3:1 and 1:1)

Under conditions of co-culture without eNK cells, the apoptosis was not observed until 42 hours.

The above graph provides data for one example. In this study, several F-PDOs were examined and generally obtained similar results.

F-PDO® :
It stands for Fukushima Patients Derived Tumor Organoid, a cell mass established at Fukushima Medical University. The F-PDO is a cell mass consisting of multiple cell types derived from patient tumor tissue. Histological and genetic analysis have confirmed that they maintain the properties of patient cancer tissue. Due to their similarity to the original cancer, the results of the effect of anti-tumor drugs in models utilizing F-PDO can be evaluated as more reflective of the clinical situation.

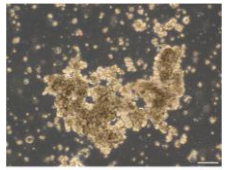
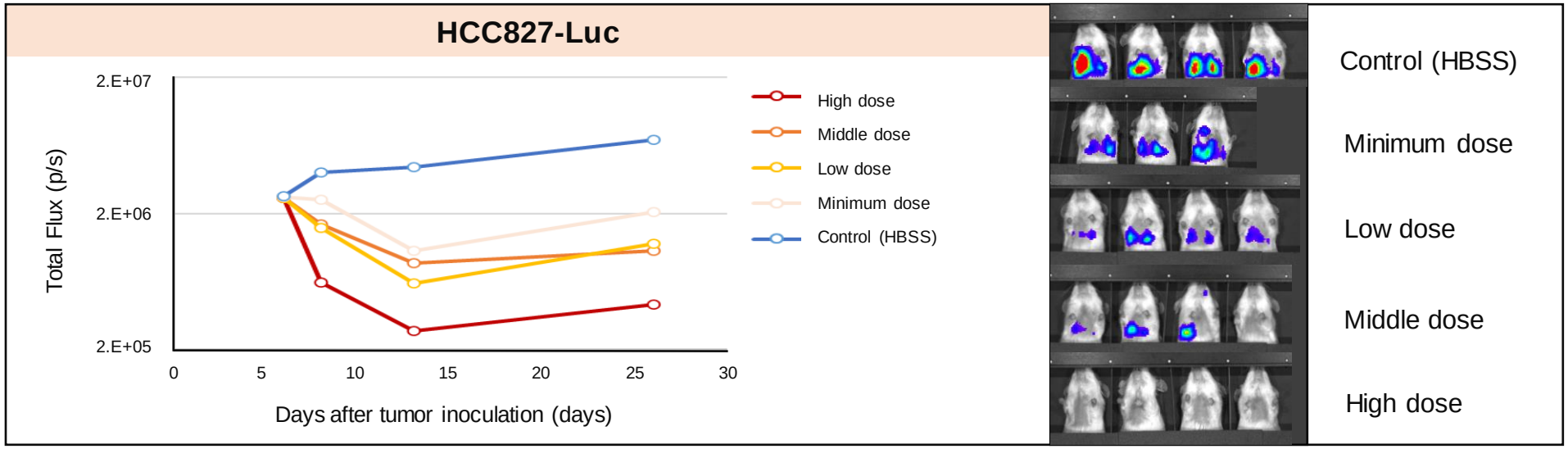
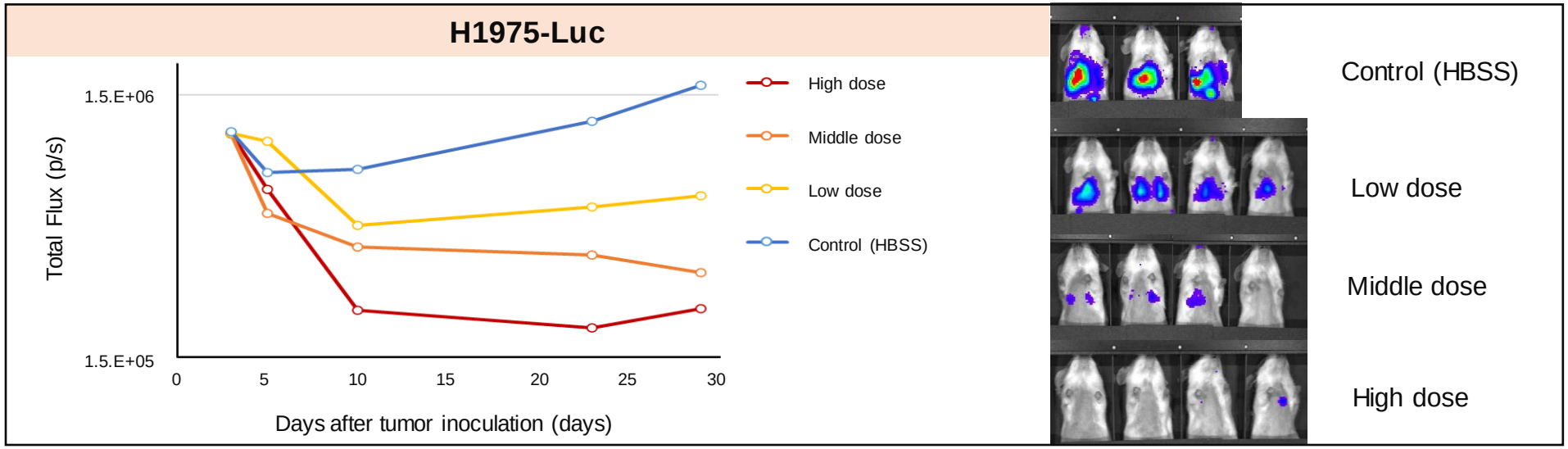


Photo by Fukushima Medical University

＊This examination was commissioned by Healios to the Fukushima Translational Research Foundation and conducted at FUJIFILM Wako Bio Solutions Corporation.

HLCN061 In Vivo: Healios' eNK Cells Show Robust Anti-Tumor Activity Against Lung Cancers





(Source) in-house data

Maximize the potential of the eNK cell program and platform

We are pursuing partnerships with pharmaceutical companies, to access financial and other resources as well as to leverage technological synergies.

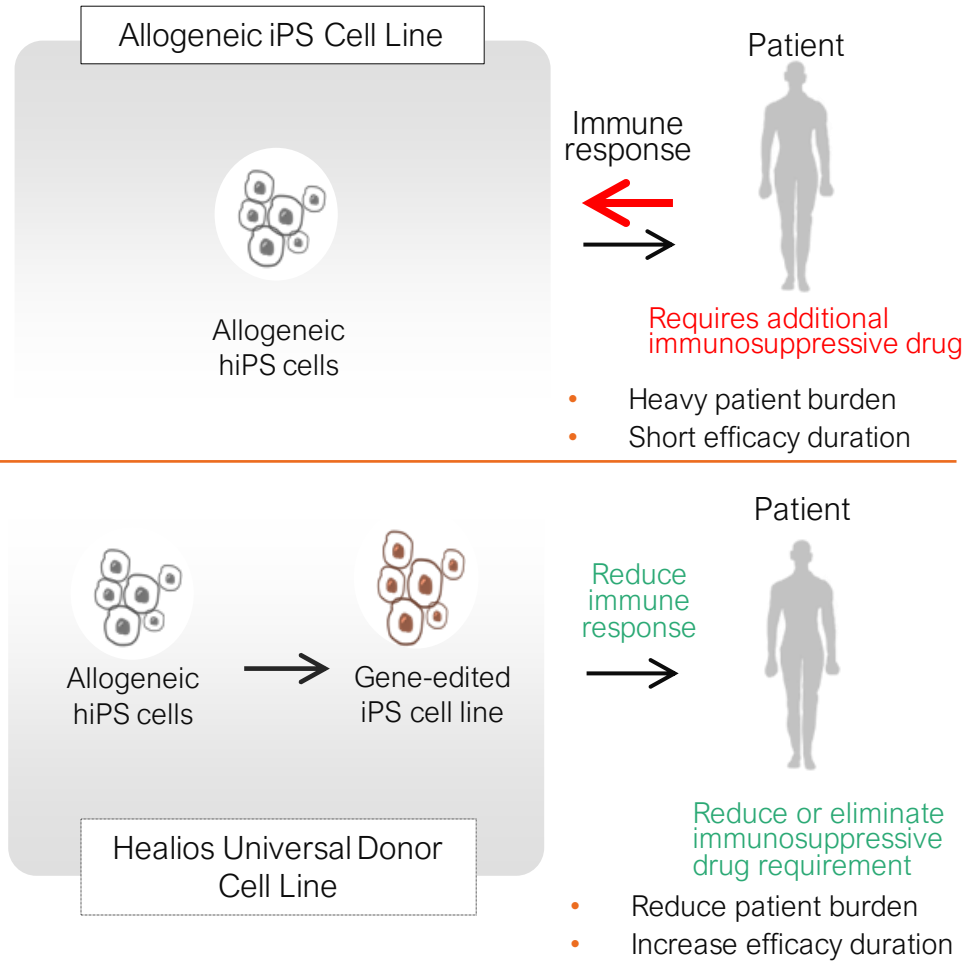
We aim to accelerate our research and development to deliver new immuno-oncology therapies using eNK cells to patients as soon as possible.

Universal Donor Cell (UDC) Replacement Therapies

Somatic Stem Cell	iPSC Platform	
Inflammatory Conditions	**Immuno-Oncology**	**Replacement Therapies**
Multistem® • Ischemic stroke • ARDS	**iPSC eNK** iPSC-derived, gene-engineered NK cells for: • Lung cancer • Liver cancer • Other non-disclosed	**Universal Donor Cell (UDC)** • UDC-pancreatic islets for diabetes • UDC-photoreceptors and RPE[1] for retinal disease • Liver buds[1] for liver disease

Hypo-immune Universal Donor Cell (UDC) Platform

World-leading engineered “universal” iPSC platform: “UDC”

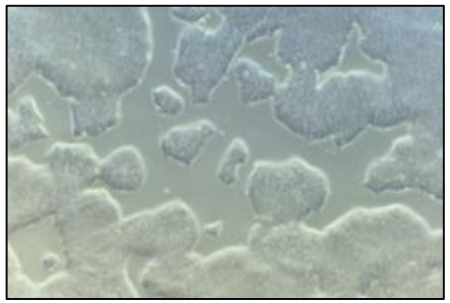


Targeted cell programming through gene-editing

- In October 2020, Healios established a clinical grade universal donor IPS cell line that can be clinically applied to humans in each of Japan, the United States and Europe.
- Master Cell Bank established in 2021
- Healios has led the development of high-quality, universal donor iPS cells in accordance with global standards.
- Consultations with the FDA and PMDA led to no concerns in relation to clinical use of UDC derived therapeutics.
- The UDC line differentiates readily into various in-house made cells (e.g. NK cells, liver progenitor cells, vascular endothelial cells, etc.).

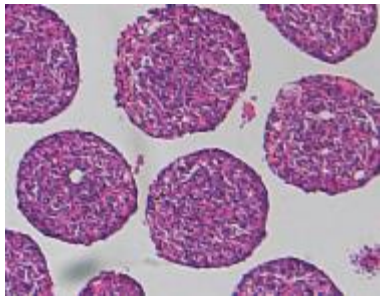
Hypo-immune UDC: Examples Of Cell Therapies

Universal Donor Cells (UDC)

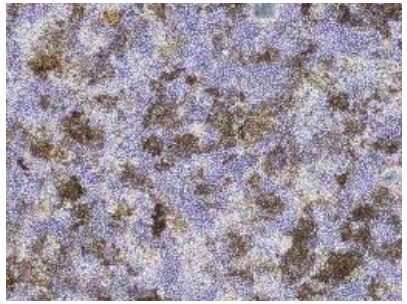


Photoreceptor cells

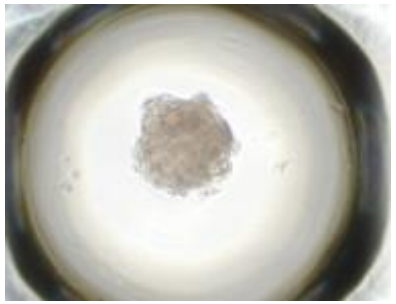
Pancreatic β cells



RPE cells



Liver buds



Successfully differentiated from UDCs

Future migration to UDC platform

(Source) in-house data and Joint research data

Healios

＜Contact information＞
IR & Finance and accounting Div.
HEALIOS K.K.

Press contact: pr@healios.jp
Investor contact: ir@healios.jp
https://www.healios.co.jp/contact/