FY2022 Financial Results

Company

HEALIOS K.K. (TSE 4593)

Date

February 14, 2023

Important Note on Future Events, etc

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Contents

Focus pipeline and maximize investment efficiency

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—

Research & Development Funding Needs

New 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 and U.S. 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	AMD	RPE	Japan				Co-development with Sumitomo Pharma Co., Ltd.: Plan to initiate clinical trial by March, 2023.
	–	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.

Pipeline Development Policy

New Healios

Inflammatory Conditions — **HLCM051**

Ischemic stroke	・In response to the results of our domestic study, Athersys intends to propose modifications of primary and secondary endpoints in the ongoing U.S. study*, to reflect the best potential benefit. ・Based on the discussion results with FDA, we will consider utilizing the U.S. trial data.

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

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

Immuno- Oncology — **eNK®（HLCN061）CAR-eNK®**

Solid tumors	・In-house manufacturing and R&D aimed at global expansion ・Establishment of an effective eNK® platform for solid tumors

＊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.

Streamlining the Management System

Strengthening leadership team

Streamlining executive officer members and strengthening the eNK® development structure in North America

Establishment of CSO (Chief Scientific Officer) to strengthen the research activities

Finance

The projected budget for FY23 is expected to be approximately 2.7 billion yen.

Carving-out organ bud technology to accelerate R&D and efficiently advance the program

Active use of external funds without dilution of the Company's shares
—License revenue, project finance, domestic and overseas subsidies, etc.—

Highlights

Update

Healios

Inflammatory Conditions	Ongoing discussions with regulatory authorities in relation to Multistem for both ARDS and ischemic stroke LOI with Mitsubishi UFJ Capital for Joint Development of HLCM051 for ARDS Ongoing discussions with potential partners
Immuno-Oncology	Non-clinical studies are underway to start clinical trials using eNK® cells Ongoing discussions with potential partners Six posters on eNK® cells will be presented at the 22nd Congress of the Japanese Society for Regenerative Medicine in March
Replacement Therapies	HLCR011 AMD: Plan to initiate clinical trial by March Using Healios UDCs, Sumitomo Pharma plans to conduct research to study the potential use in three areas, including the ophthalmology area. Carve-out organ bud technology to accelerate its R&D and efficiently advance the program. One poster on UDCs will be presented at the 22nd Congress of the Japanese Society for Regenerative Medicine in March
Finance	Completed fundraising process in January (approx. 2.26 billion yen) Japan Investment Corporation made a $30 million commitment as a limited partner in our venture fund consolidated subsidiary, Saisei Bioventures, L.P.

Presentation of the Research Results of Healios' eNK® Cells and UDCs at the 22nd Congress of the Japanese Society for Regenerative Medicine

New Healios

We will present 6 posters for eNK® cells and 1 poster for UDCs.

【 eNK® cells】

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)

Date of presentation: Thursday, March 23 16:50-17:50 Venue: Kyoto International Conference Center, 1F (Event Hall)

【UDC】

Poster No.: P-21-3 Clinical grade genetically engineered hypoimmunogenic human induced pluripotent stem cell line

Date of presentation: Saturday, March 25 16:50-17:50 Venue: Kyoto International Conference Center, 1F (Event Hall)

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

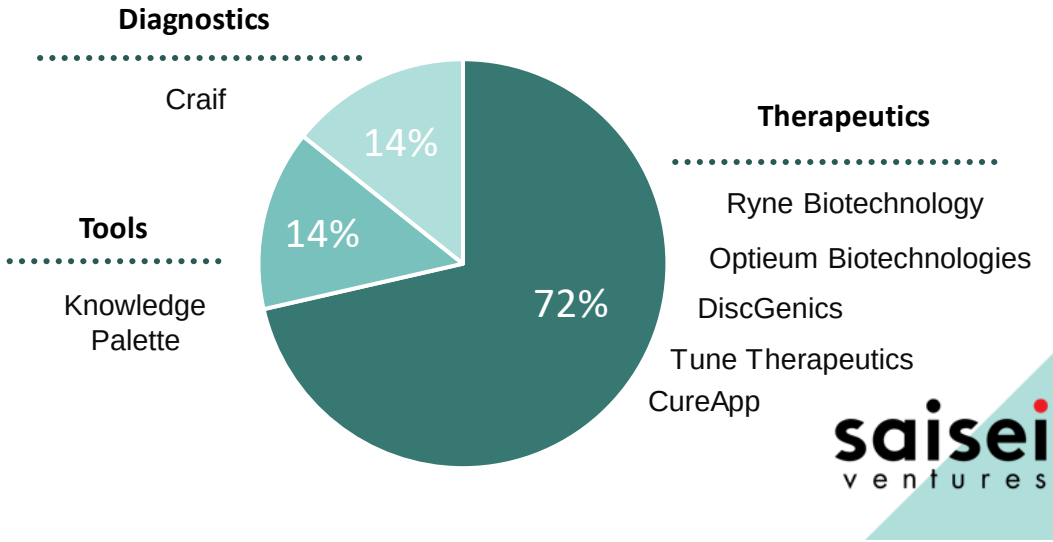
Engage deeply with regenerative medicine innovation around the world through our venture fund activities

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)

Compounds	
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)

Program Overview

Update

Healios

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

Near term revenue & Commercial capabilities

Innovative best in class programs

Partnering → **Carve-out**

[1]Future migration to UDC platform

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 the regulatory authorities SAKIGAKE designation
	HLCM051	ARDS	MultiStem®	Japan			Phase 2	Ongoing consultations with the regulatory authorities Orphan designation
Immuno-Oncology	HLCN061	Solid tumors	eNK	Global				Pre-IND: 2022, IND: 2024 Joint research with National Cancer Center Japan, Hiroshima University and Hyogo Medical University
	–		CAR-eNK	Global				
Replacement Therapies	HLCR011	AMD	RPE	Japan				Co-development with Sumitomo Pharma Co., Ltd. Pending trial initiation Sumitomo Pharma: plan to initiate clinical trial by March, 2023.
	–	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

Financial Highlights

Consolidated Statement of Income

Update

Healios

R&D expenses in the second half of 2022 were 1,471 million yen (R&D expenses of approximately 63% of the first half of 2022). Continue to advance R&D activities while optimizing expenses.

(Units: millions of yen)

	FY2021	FY2022		
			YoY variance	Main reasons for increase/decrease
Revenue	41	90	49	Increase due to provision of universal donor cell (UDC), etc.
Operating profit	-5,384	-5,179	205	Decrease in SG&A expenses ＋273 Increase in R&D expenses -107
Profit	-4,911	-5,170	-259	Decrease in finance income -1,382 Decrease in finance costs +302 (Primarily non-cash activity; please refer to the next page for details)
R&D expenses	3,700	3,808	107	The quarterly R&D expenses for the period were as follows: Q1 1,087, Q2 1,249 , Q3 690, and Q4 781 R&D expenses in the second half of fiscal year decreased compared to those in the first half of the year.
Number of employees	116	**70**	-46	Due to the implementation of a voluntary retirement program and other factors, the number of our employees was 70 as of December 31, 2022.

(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 fiscal year ended December 31, 2022, we recorded finance income of ¥346 million and finance costs of ¥500 million.

Finance income was mainly due to the recording of ¥183 million in gain on remeasurement of derivatives [*1] and ¥ 162 million in gain on remeasurement of investment securities.

Finance costs were mainly due to the recording of ¥375 million in interest expenses on bonds [*2], ¥53 million in loss on remeasurement of warrants, ¥44 million in interest expenses and ¥18 million in profit or loss transferred to equity interests held by external investors in the Saisei Fund [*3].

*1. Gain on remeasurement of derivatives

Gain on remeasurement of derivatives is the net unrealized gains/losses on the convertible bond-type bonds with subscription rights to shares, which our company issued to overseas investors in July 2019, at fair value. These are non-cash items. The convertible bond-type bonds with subscription rights to shares were redeemed during the nine months ended September 30, 2022.

Supplemental Explanation of Finance Income and Finance Costs

Update

Healios

*2. Interest expenses on bonds

Of the total interest on bonds of 375 million yen posted in the fiscal year ended December 31, 2022, 335 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.

*3. 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.

Consolidated Statement of Financial Position

Update

Healios

(Units: millions of yen)

	December 31, 2021	December 31, 2022		
			Variance	Main reasons for increase/decrease
Current assets	16,429 (68.5%)	8,462 (56.3%)	-7,967	Decrease in cash and cash equivalents -7,879 (Cash and cash equivalent balance at 12/31/22 was 7,247) Redemption of 5,000 million yen of convertible bonds
Non-current assets	7,543 (31.5%)	6,571 (43.7%)	-972	Decrease in other financial assets -870
Total assets	23,971 (100.0%)	15,033 (100.0%)	-8,939	
Current liabilities	6,042 (25.2%)	3,808 (25.3%)	-2,234	Redemption of 5,000 million yen of convertible bonds Reclassification of loans payable from non-current liabilities to current liabilities + 3,000
Non-current liabilities	9,284 (38.7%)	6,842 (45.5%)	-2,442	Change in presentation classification of loans payable due within one year from the end of the fiscal year -3,000
Total liabilities	15,326 (63.9%)	10,650 (70.8%)	-4,676	
Total equity	8,645 (36.1%)	4,382 (29.2%)	-4,263	Recording of loss -5,170
Total liabilities and equity	23,971 (100.0%)	15,033 (100.0%)	-8,939	

(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

Development plan

April 2019
First patient enrolled

March 2021
Patient enrollment completed

August 2021
Announcement of top-line results

March 2022
Regenerative medicine product pre-application consultation with the PMDA was conducted.

(Current)
Healios was advised that when making a future application for approval for the ARDS indication, it needs to add certain supporting data to the proposed application data package. Consultations with the regulator are ongoing to confirm the design of an additional study and the final approach to advance the program.

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.)

HLCM051 ARDS: Target Disease

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 7,000 to 12,000 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.

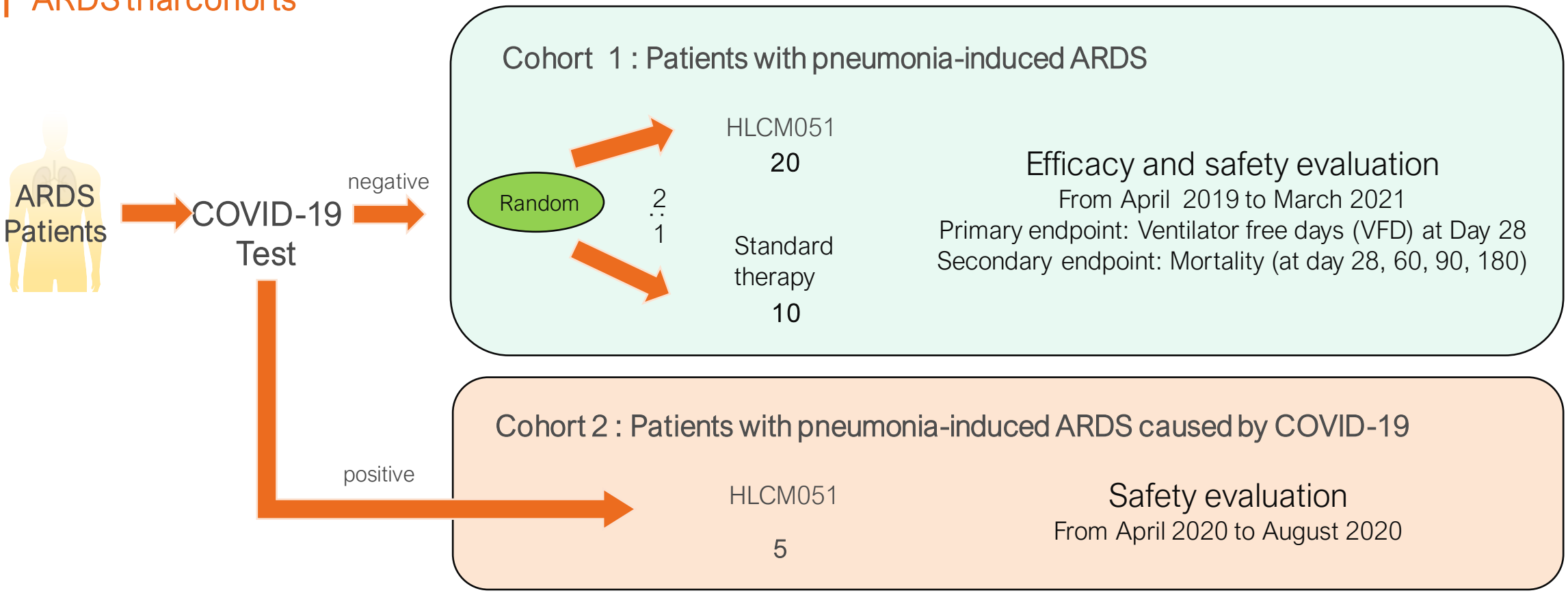
The only symptomatic treatment for respiratory failure includes artificial respiration.

(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%**

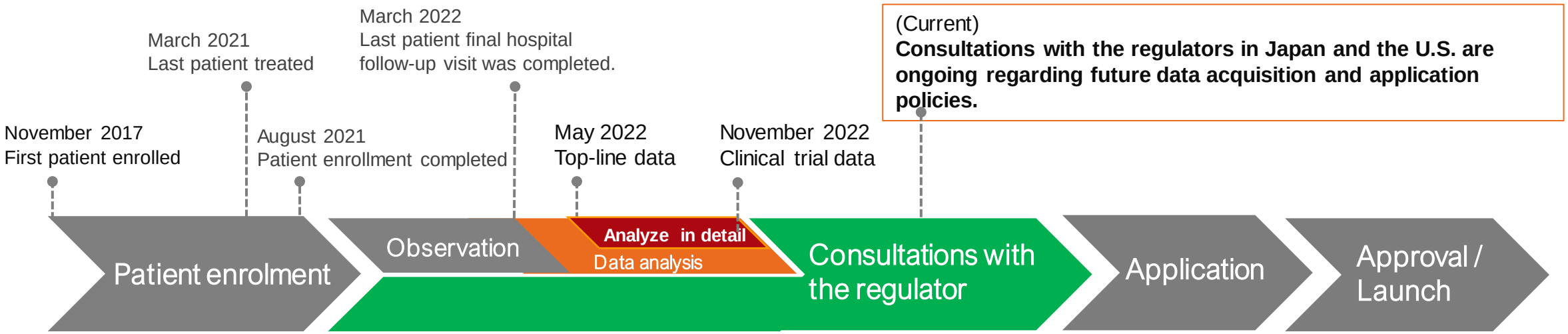
	Cohort 2
	HLCM051
Primary Endpoint	
Safety	**No safety issues**
Secondary Endpoint	
VFD	**25 days**
Mortality (180 days after administration)	**0%**

TREASURE Study: Development Status

Update

Healios

TREASURE study



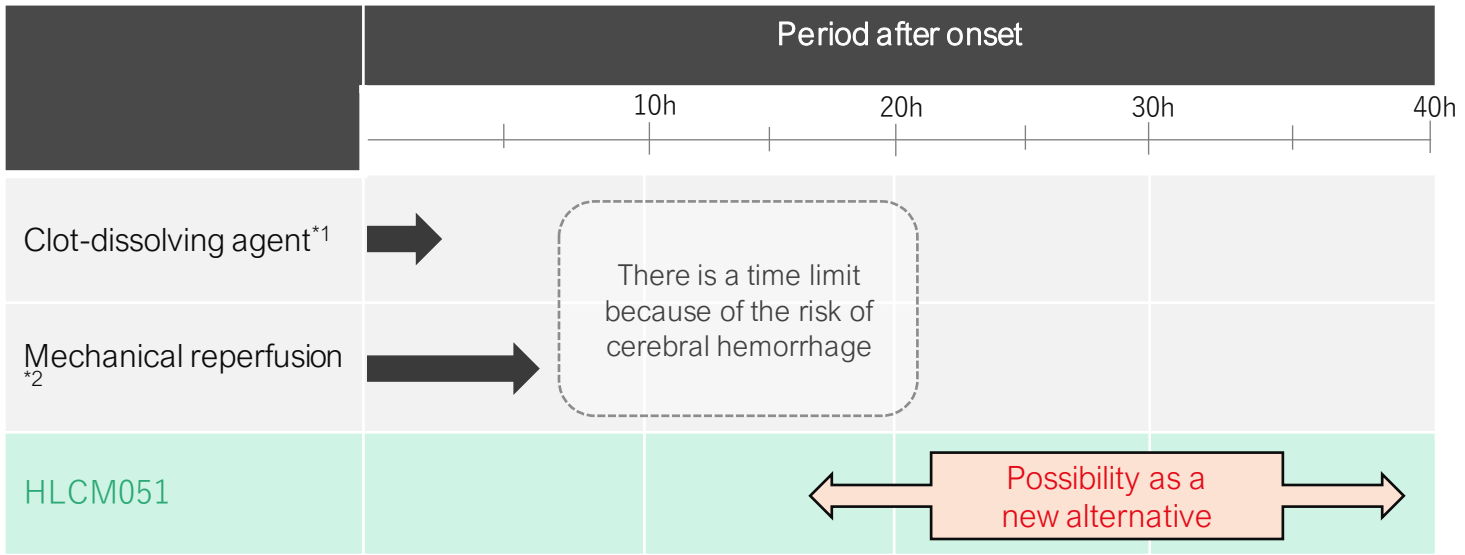
・HLCM051 is designated for SAKIGAKE Designation System

We are in discussions with the regulatory authorities in relation to the path forward for the product, including potential filing and approval, leveraging the framework of the 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

Summary: HLCM051

Update

Healios

- TREASURE Study (Ischemic Stroke)

Results of TREASURE Study were presented at scientific conferences in October and November. Consultations with the regulators in Japan and the U.S. are ongoing regarding future data acquisition and application policies.

- ONE-BRIDGE Study（ARDS）

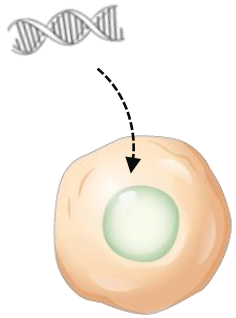
In a face-to-face meeting with the regulatory authorities in March, we were advised that it is necessary to add certain supporting data to the proposed application data package. We are continuing to discuss with the regulatory authorities to confirm the design of an additional study and the final approach to advancing the program.
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

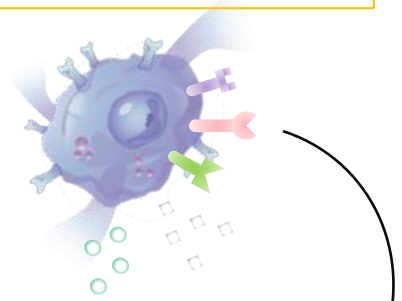
Master cell banks established for eNK cell production

eNK cells differentiation

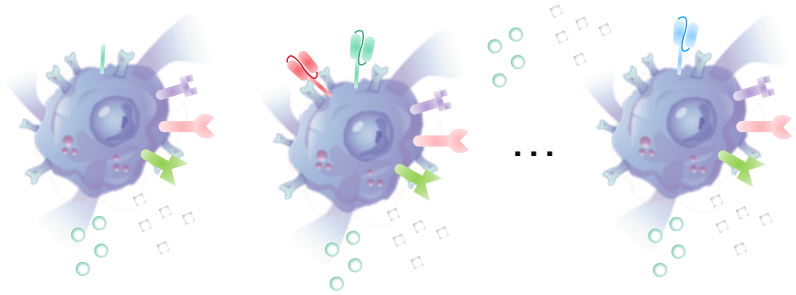
Technology Platform

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*

+

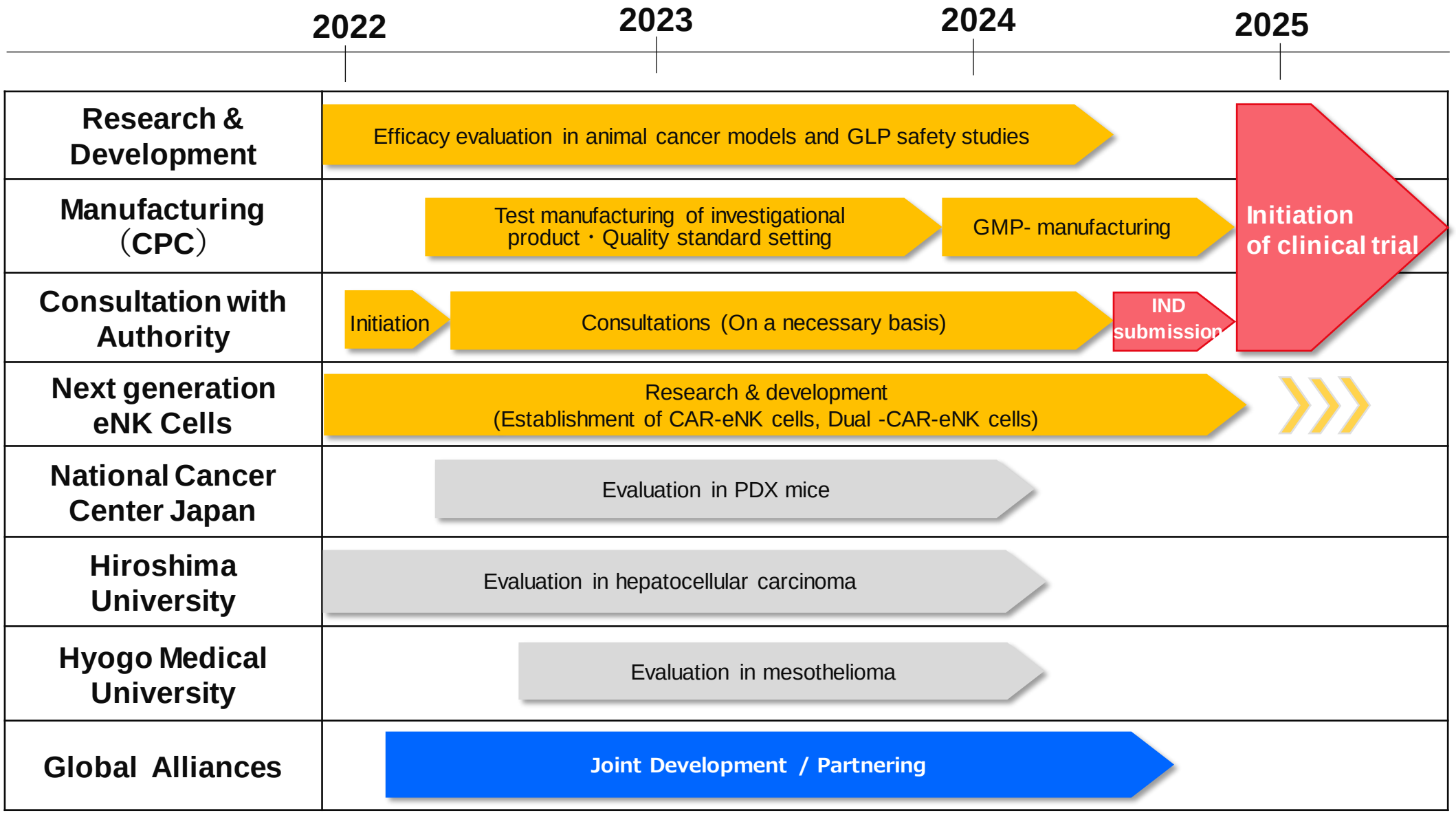
eNK combination therapies with immune checkpoint inhibitors

=

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

R&D Roadmap of eNK Cells (HLCN061)



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

Healios

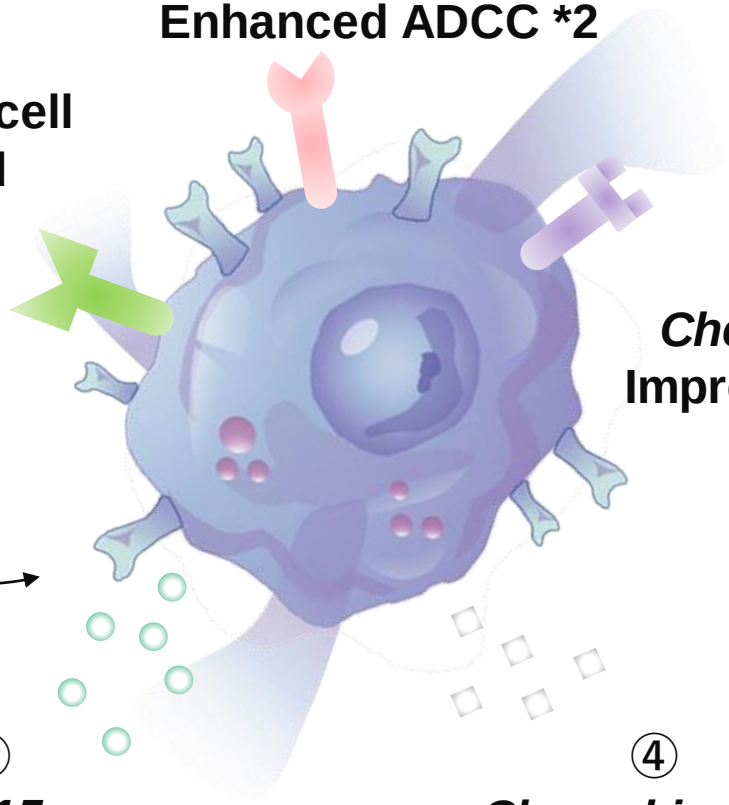
Healios' eNK Cells key features

Healios proprietary gene-edited iPS cells line

eNK cell differentiation

① ***Activator A***[*1] **Enhanced cancer cell recognition and cytotoxicity**

② ***CD16*** **Enhanced ADCC *2**



③ ***Chemokine B Receptor***[*1] **Improved migration to solid tumors**

④ ***Chemokine C***[*1] **Recruitment of host' immune cells**

⑤ ***IL-15*** **Prolonged survival**

*1 Not disclosed
*2 ADCC: antibody-dependent cellular cytotoxicity
Attack activity to pathogens by an immune cell though an antibody

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

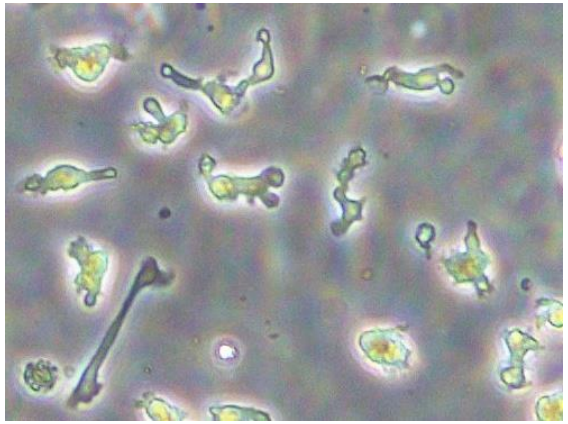
-GMP facility fully operational and being advanced in preparation for clinical trials
-In-house manufacturing enables control of the schedule and quality of clinical production

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

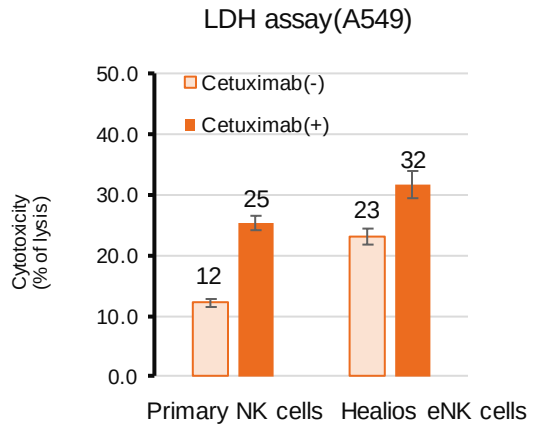
Fully-closed, feeder free, 3D perfusion bioreactor system

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

Summary: iPSC eNK Immuno-Oncology

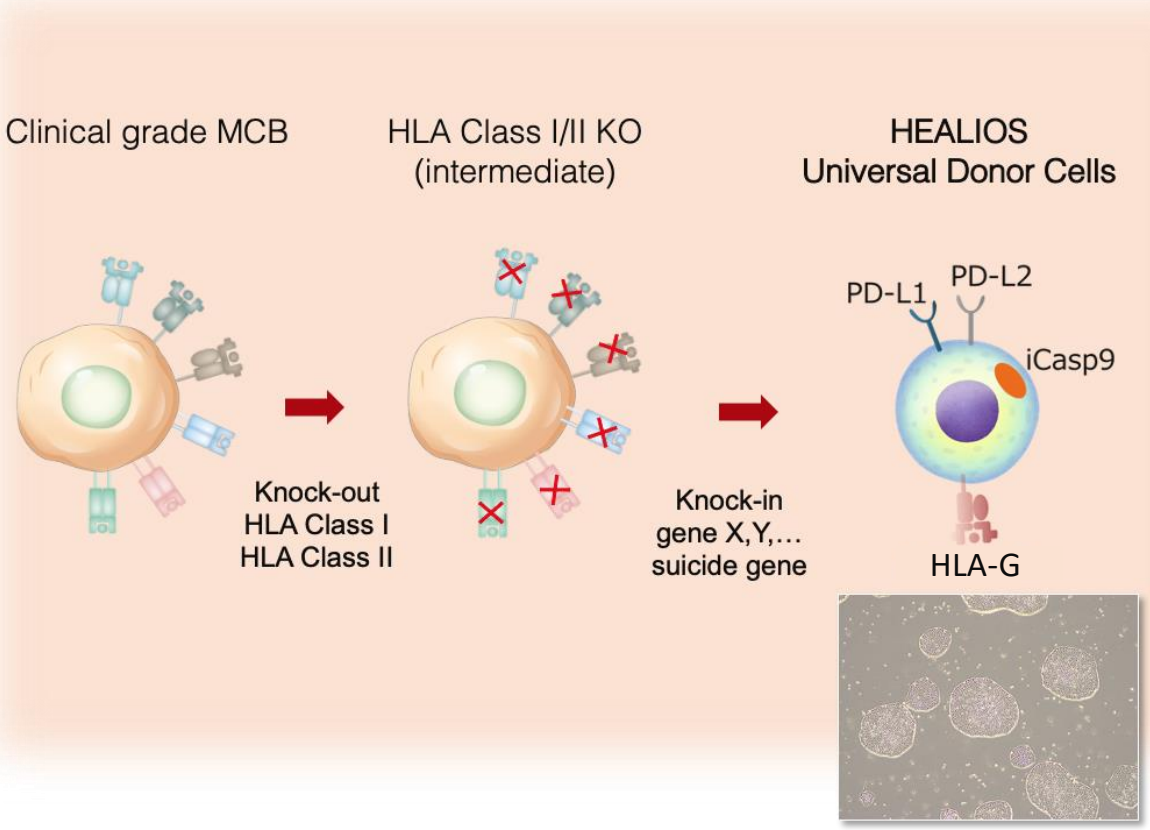
- **Years of Experience have Yielded a Best-In-Class Platform:** Healios' iPSC therapy leadership has led to the development of a functionally enhanced natural killer cell platform which provides for multiple pipeline product opportunities
- **Unique Approach**: Our eNK cell platform has enhanced recognition, 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 E*vidence** demonstrating robust cancer elimination
- **Initial Target Indications**: Lung cancer, liver cancer, mesothelioma, other non-disclosed
- **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

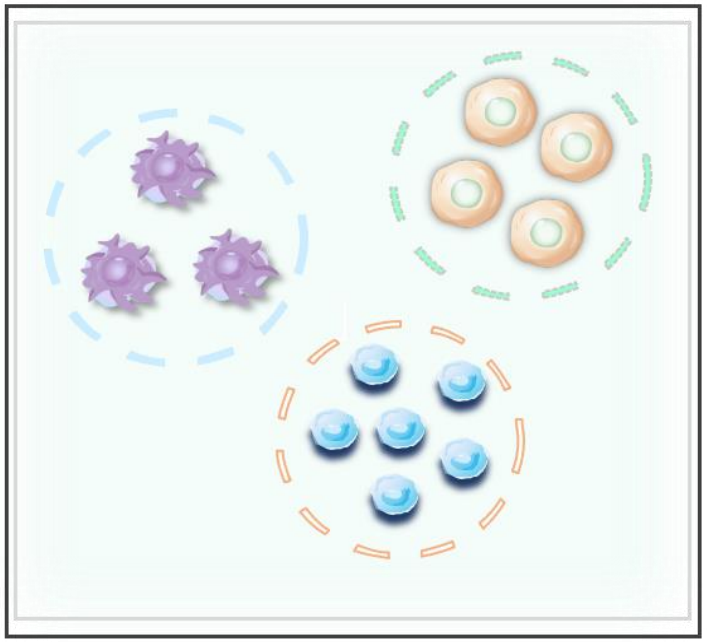
Universal Donor Cell (UDC) Replacement Therapies

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

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

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

(Source) in-house data

iPSC Platform: UDC and iPS Cell Line Collaborations

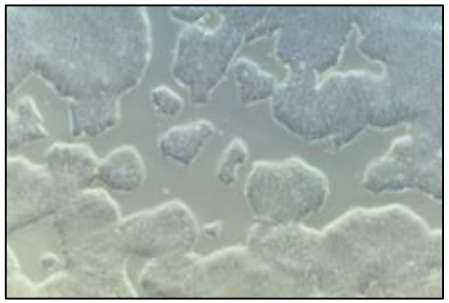
Update

December 2022: Signed Material Transfer Agreement with Sumitomo Pharma to study the potential use of UDCs in three areas, including the ophthalmology area.

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

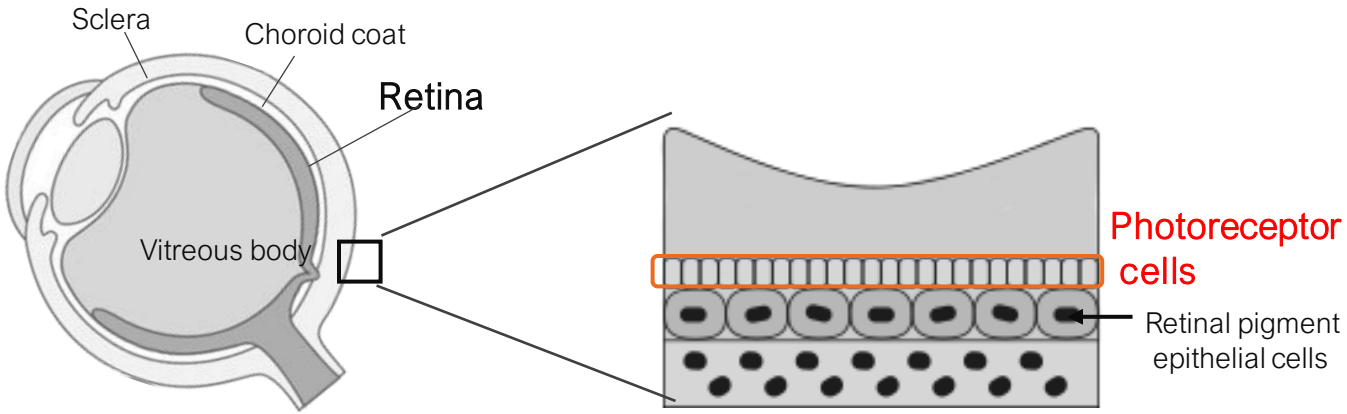
Photoreceptor cells



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

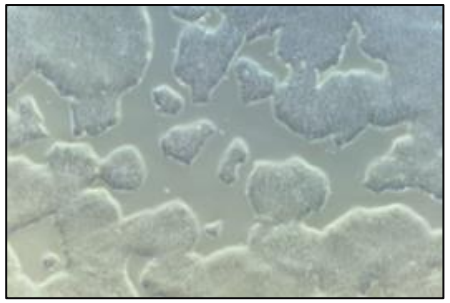
* Photoreceptor cells are one of the cells that compose the retina and are particularly responsive to light.

(Source) Joint research data

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

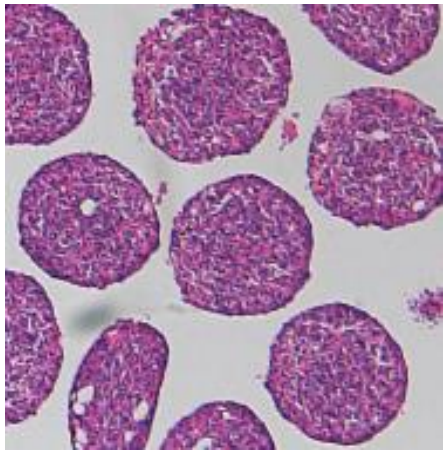
Joint research with the Department of Regenerative Medicine at the National Center for Global Health and Medicine in Tokyo

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.

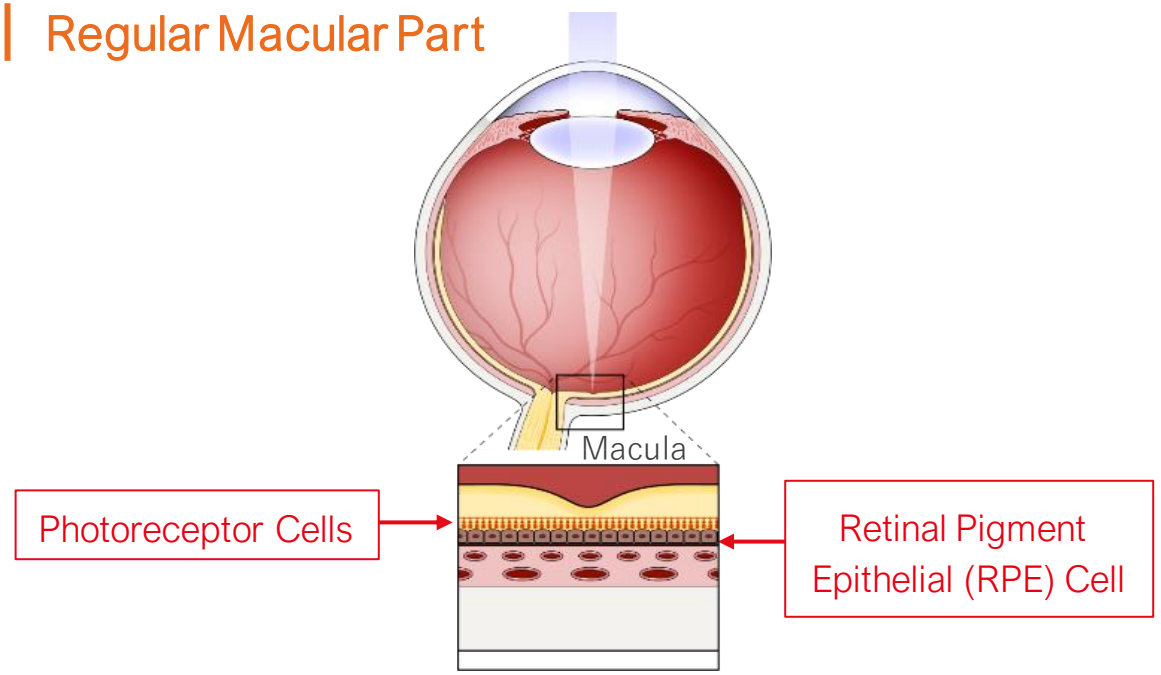
In our joint research with the Department of Regenerative Medicine at the National Center for Global Health and Medicine in Tokyo, **we have successfully confirmed the differentiation of UDCs into pancreatic β-cells.**

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

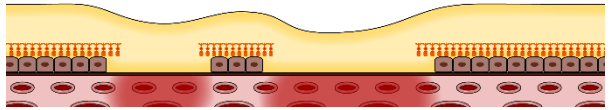
Age-related Macular Degeneration (AMD) causes Retinal Pigment Epithelial (RPE) cells to degenerate, which damages function

Regular Macular Part



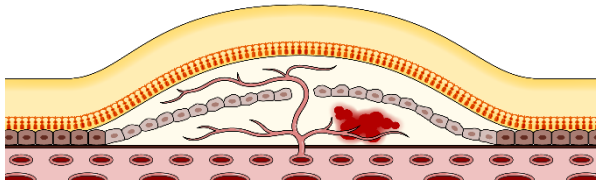
Developed Dry-AMD

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.

Sumitomo Pharma: Plan to initiate clinical trial by March, 2023.

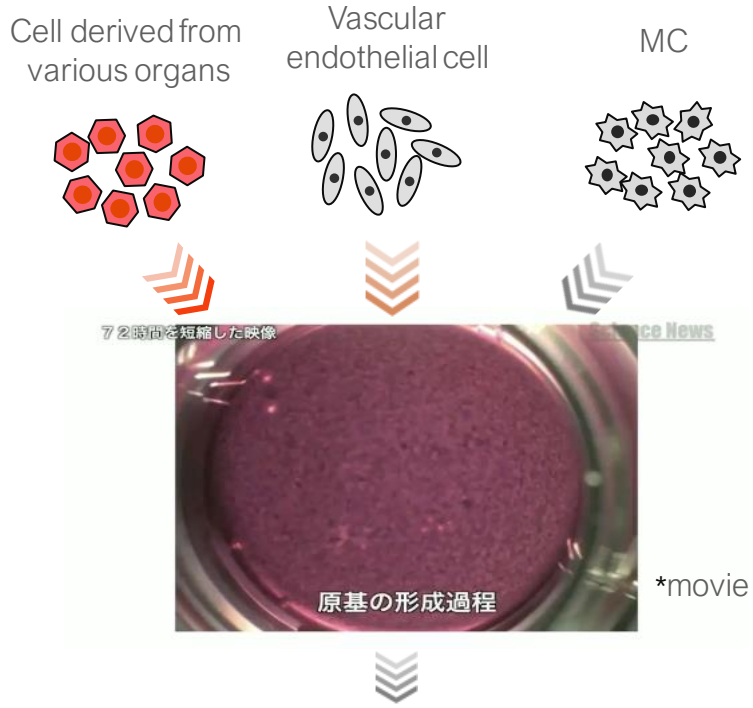
HLCL041: Liver Organ Bud Platform

Update

Healios

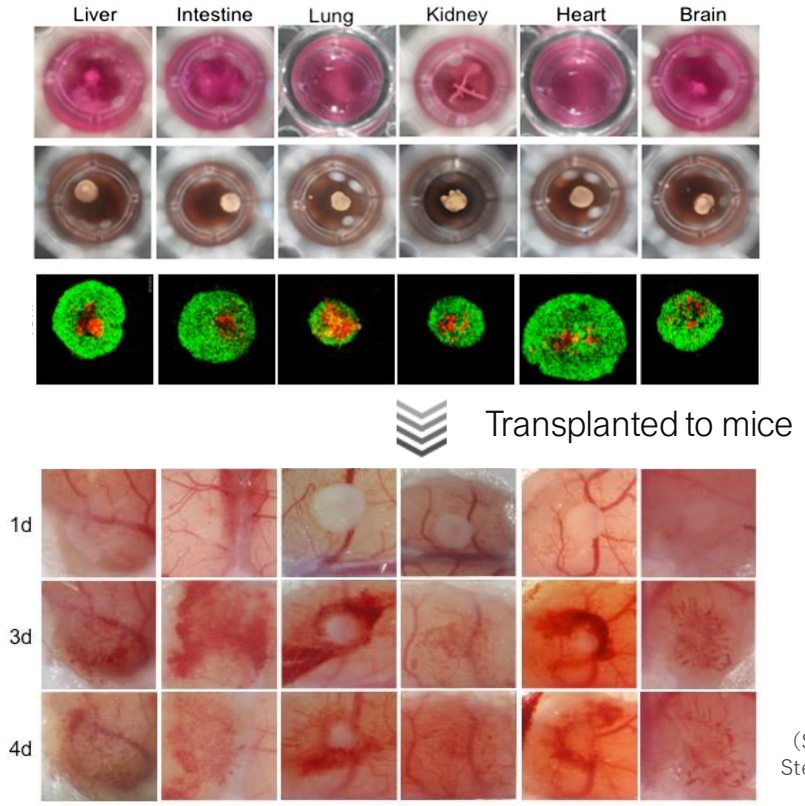
By creating an "Organ Bud" of each organ with iPS cells, we have laid the groundwork for paradigm shifting therapies to emerge for various severe diseases.

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.
- Continuing to progress the regulatory process for Multistem ARDS and ischemic stroke
- Driving forward eNK program R&D towards the clinic while pursuing partnerships with global pharmaceutical companies
- Expanding UDC and IPS cell line collaboration activities
- Ongoing implementation of cost management measures

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	4.566 million yen (As of December 31, 2022)
Head office	Yurakucho Denki Bldg. North Tower 19F, 1-7-1 Yurakucho, Chiyoda-ku ,Tokyo 100-0006, Japan
Number of Employees	70 (As of December 31, 2022)
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

Large number of researchers (more than 30 Ph.D.'s) 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

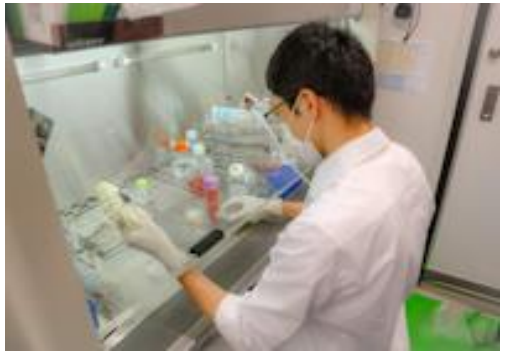
2. QC
- I. Functional evaluation of various cells
- II. Development of evaluation protocols

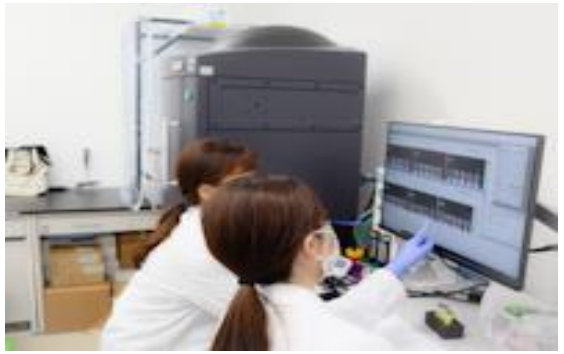
3. Genetic Recombination Experiments
- I. Construction of plasmids
- II. Construction of viral vectors
- III. Creation of transgenic cells

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

MultiStem®
Inflammatory Conditions

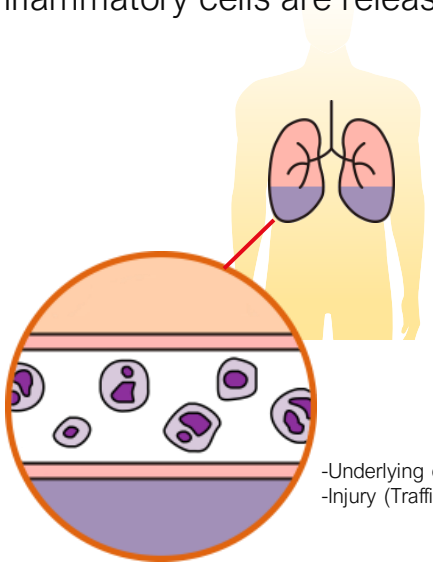
Somatic Stem Cell	iPSC Platform	
Inflammatory Conditions	**Immuno-Oncology**	**Replacement Therapies**
Multistem® • Ischemic stroke • ARDS	**iPSC eNK** iPSC-derived, gene-engineered NK cells for: • Lung cancer • Liver cancer • Other non-disclosed	**Universal Donor Cell (UDC)** • UDC-pancreatic islets 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

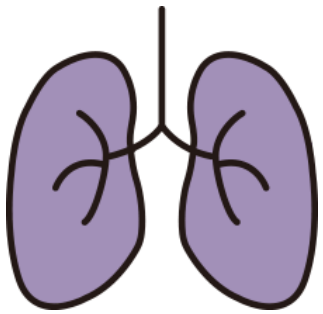
Inflammatory cells are released



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

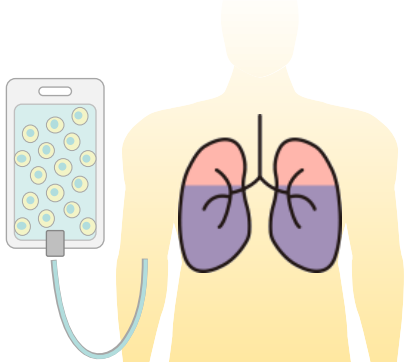
When the tissue is damaged, inflammatory cells are released in large quantities.

Inflammatory cells attack the lungs



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

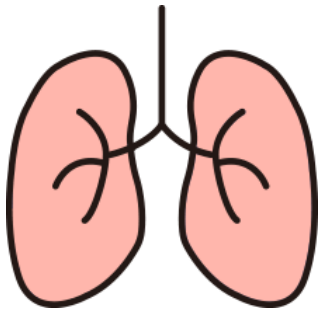
HLCM051 administered



- 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

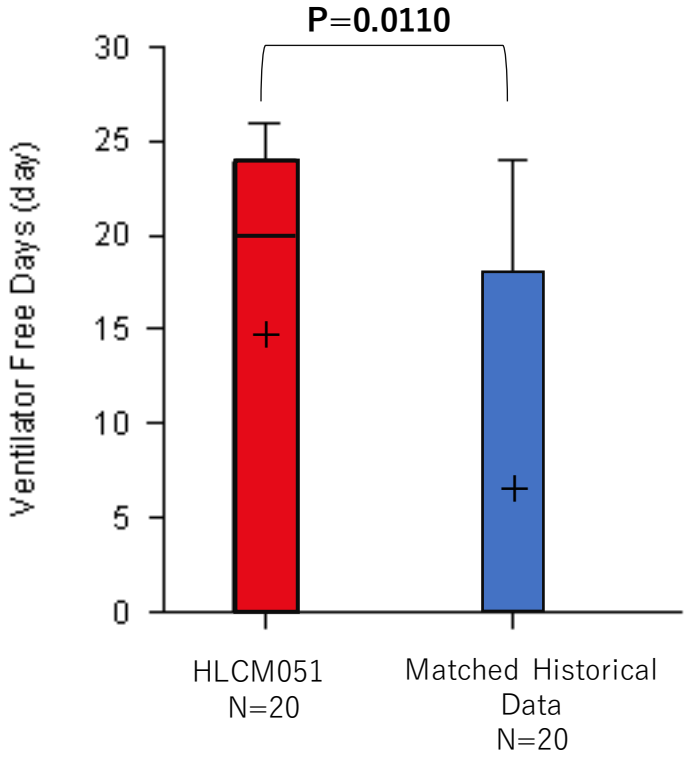


We can anticipate earlier ventilator removal and a lower mortality rate.

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.

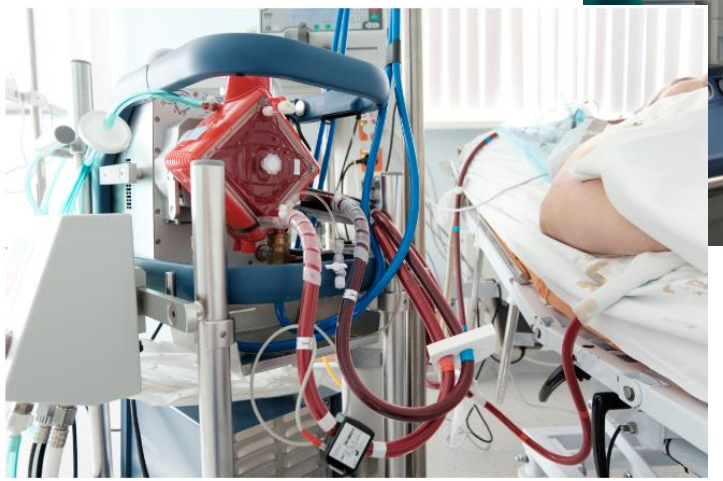
Contribution to patients ⇒ Providing new treatment
Improvement of mortality and QOL

- 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

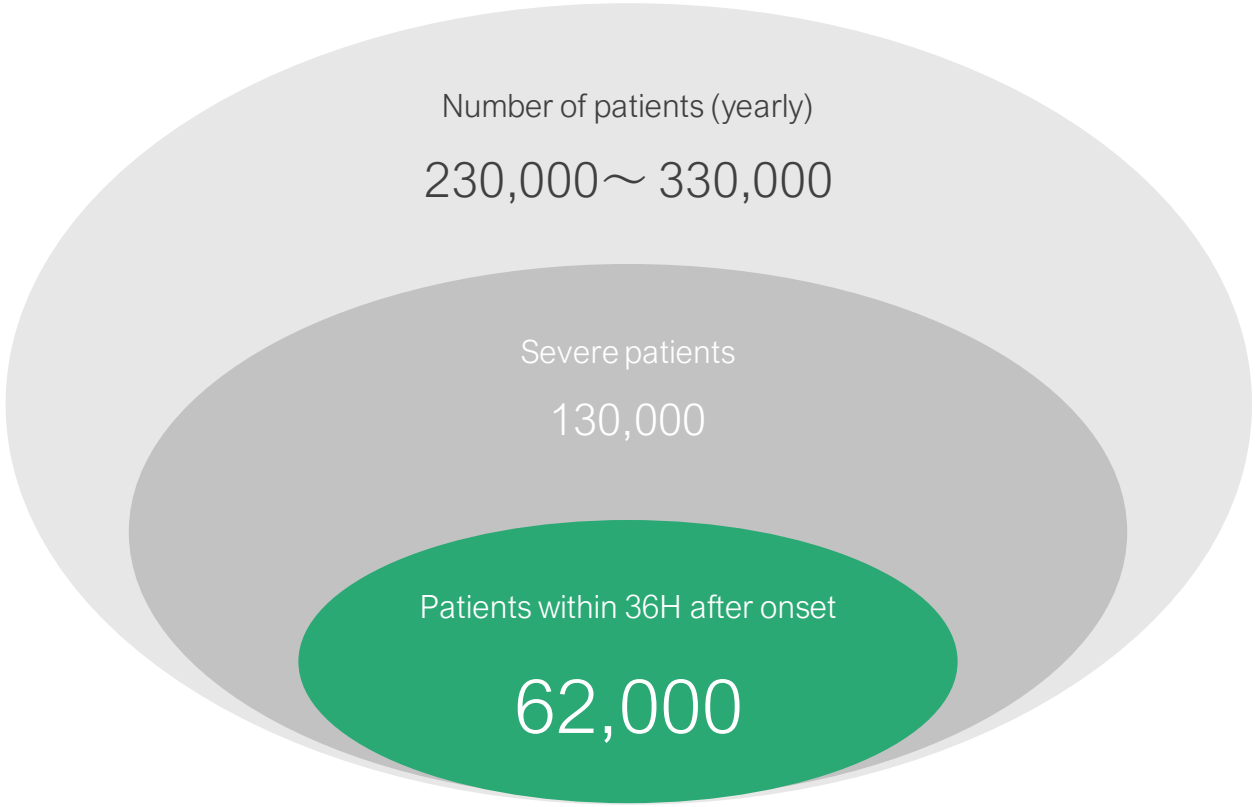
ECMO



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)

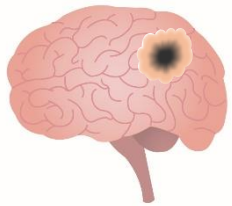
Severe patients （atherothrombotic and cardiogenic cerebral infarction)

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.

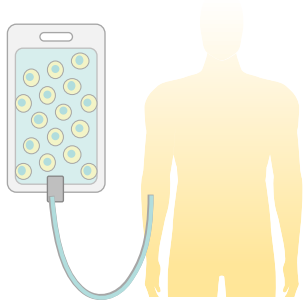
HLCM051 Stroke: Mechanism of Action

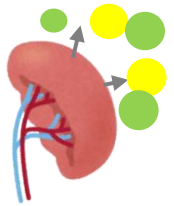
Stroke-induced neuronal damage



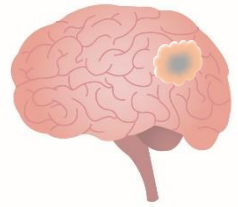
Primary Damage

With HLCM051





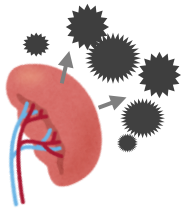
HLCM051
-suppress the mobilization/ release of inflammatory cells (lymphocytes, cytokines)
-activate the mobilization/ release of anti-inflammatory cells



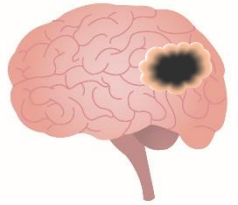
Attenuate neuronal damage in the acute phase of stroke caused by inflammatory cells

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.

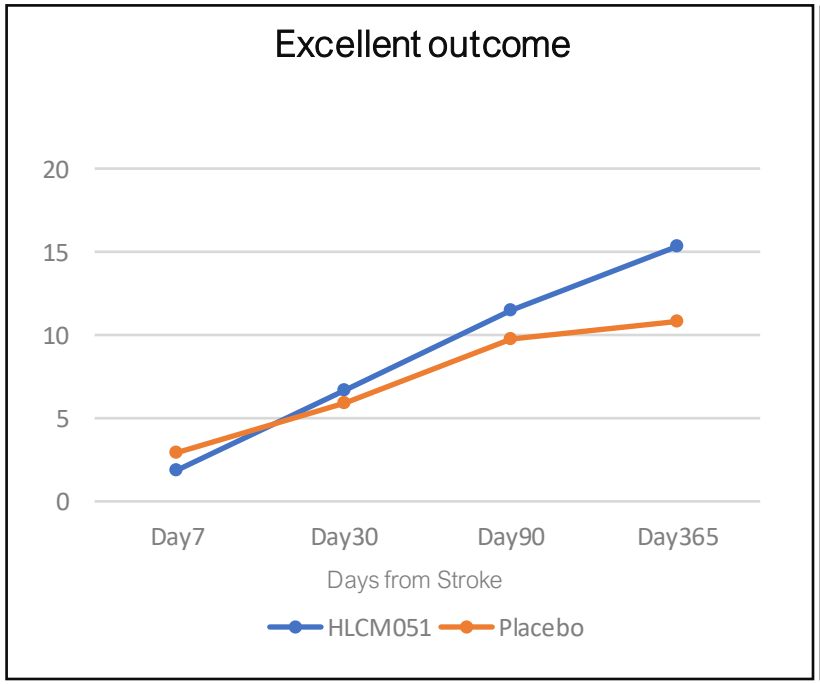
Secondary Damage

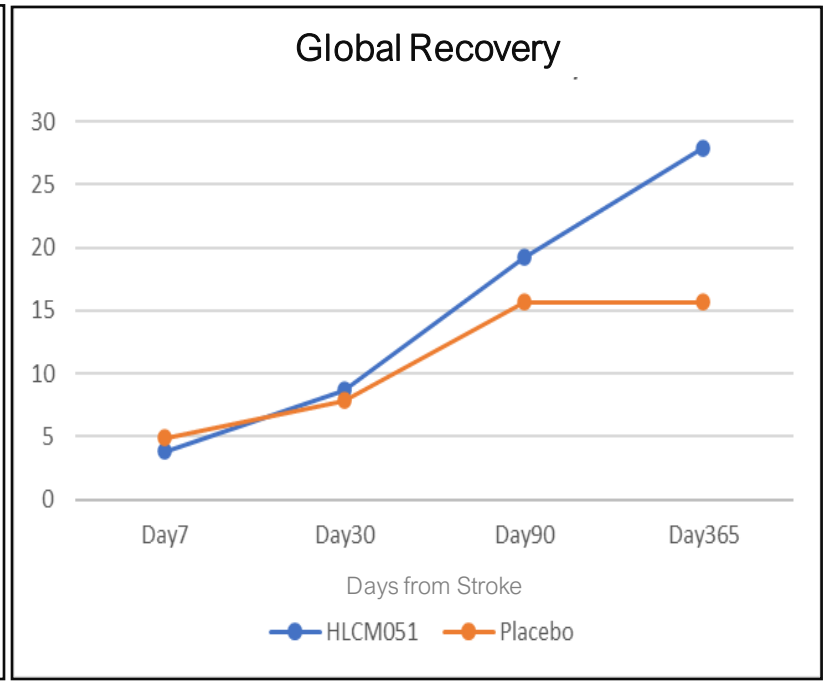
(Source) This figure was based on Stroke. 2018 May;49(5):1058-1065.Fig.2

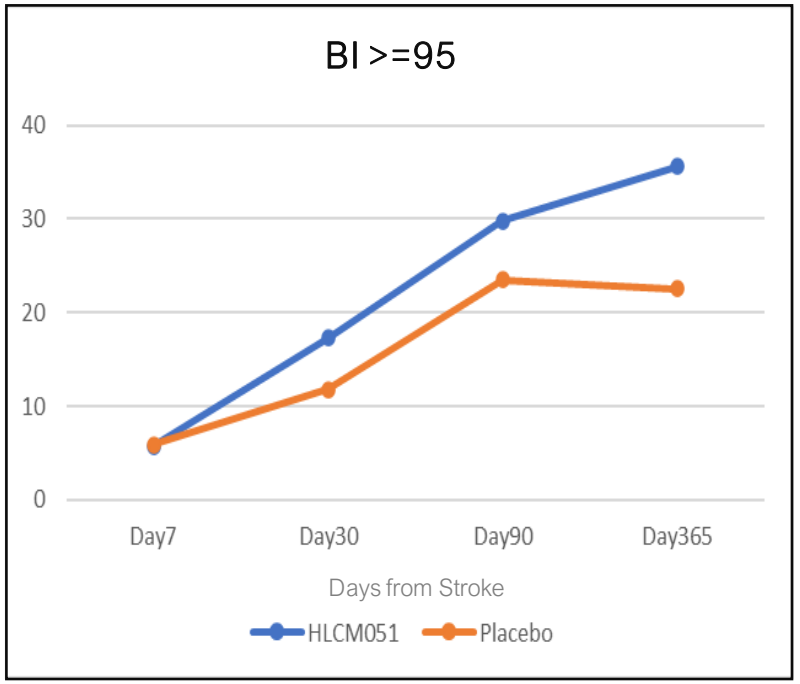
Update

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

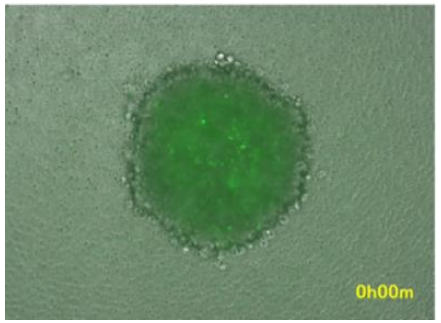
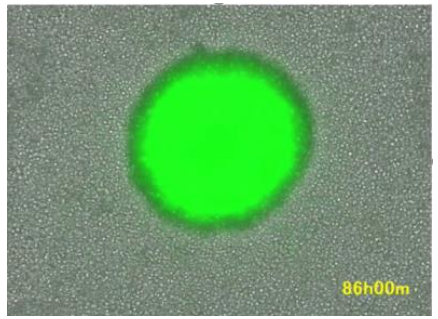
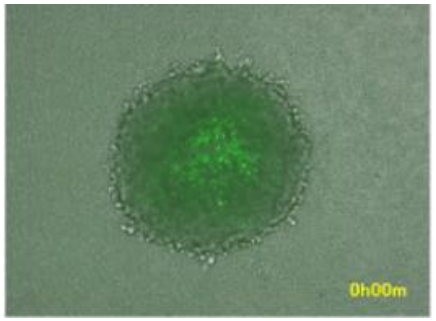
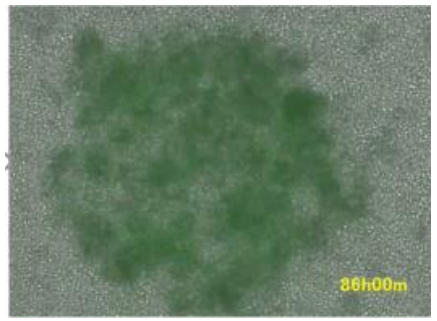
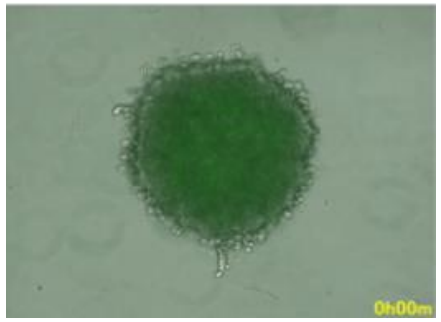
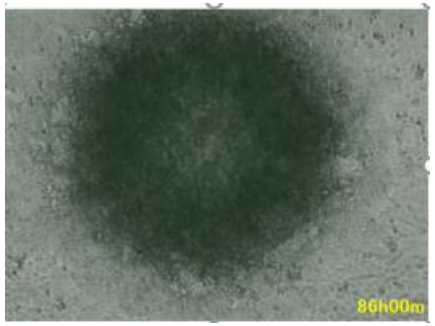
Alliances & Collaborations

- **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)

Bright green: apoptotic cells

	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.

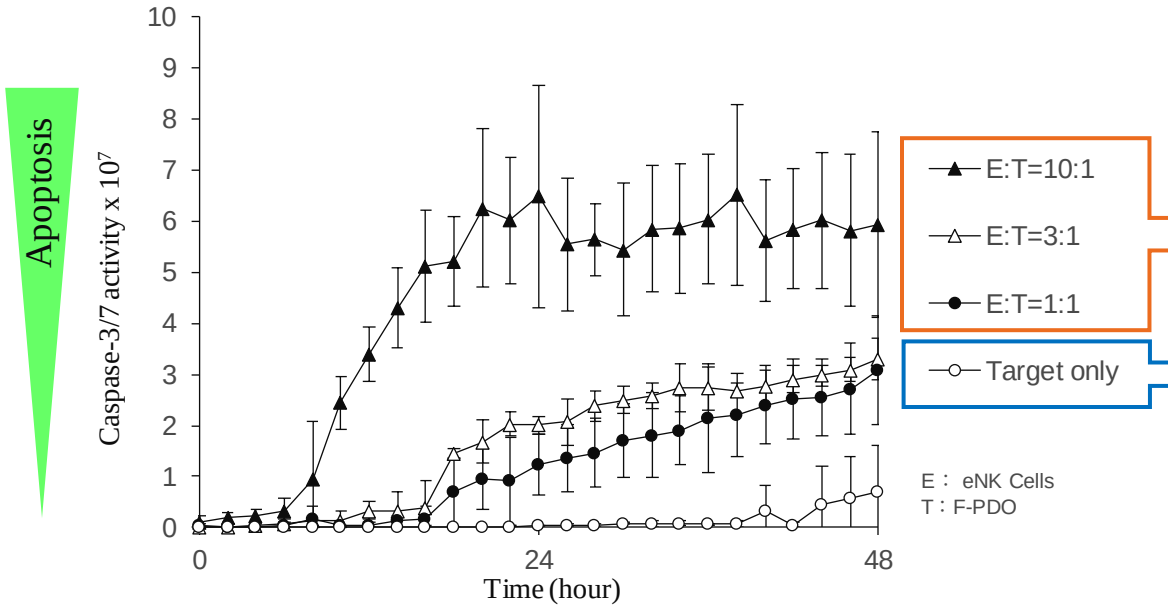
(Source) in-house data

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.

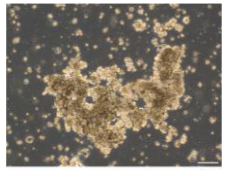
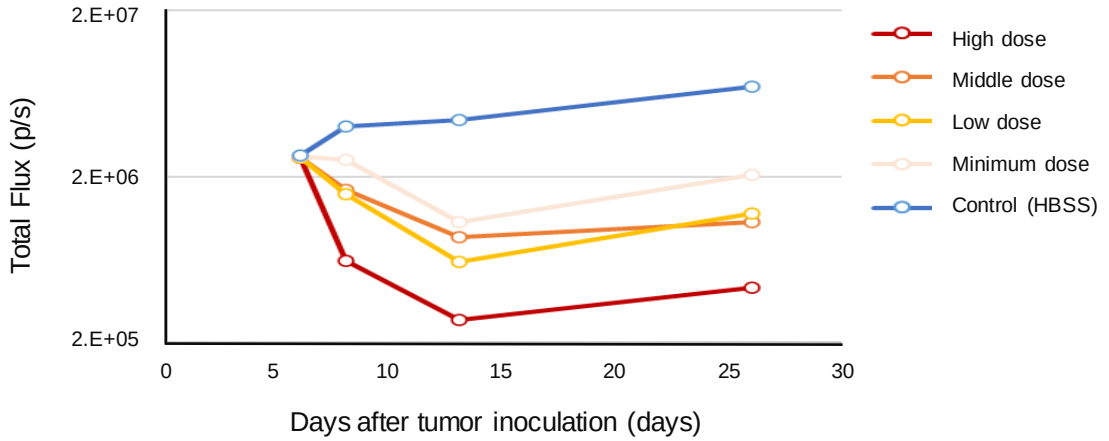


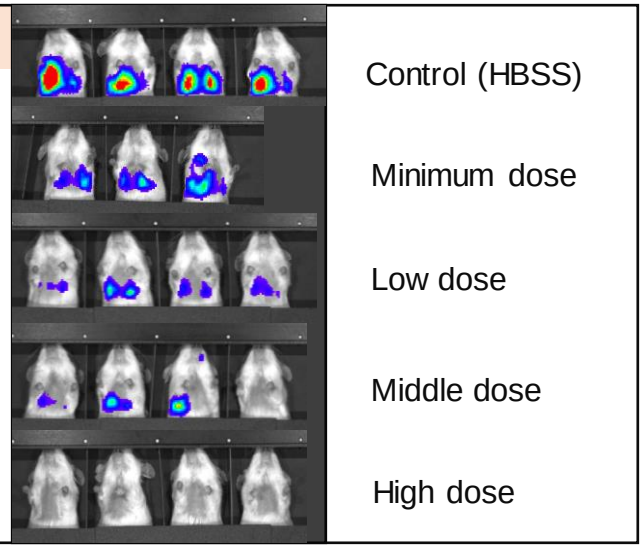
Photo by Fukushima Medical University

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

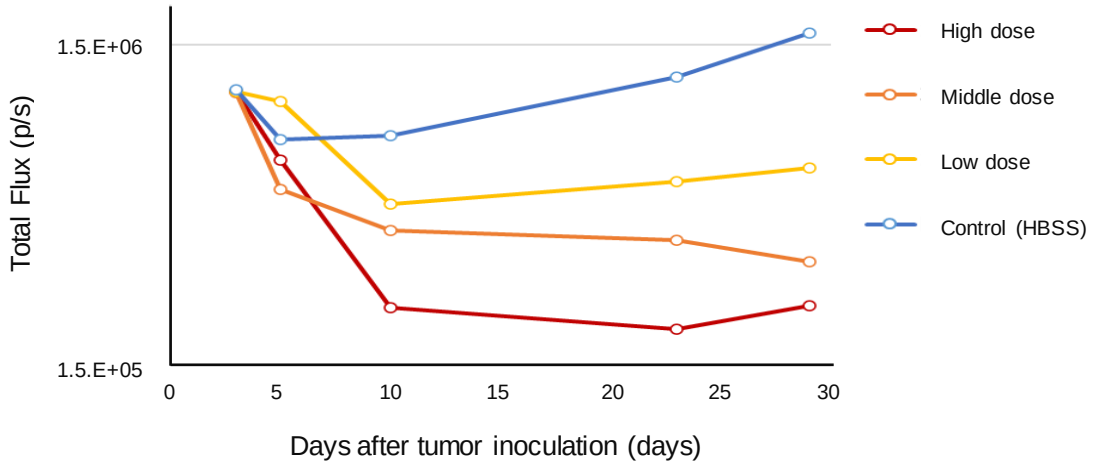
HLCN061 In Vivo: Healios' eNK Cells Show Robust Anti-Tumor Activity Against Lung Cancers

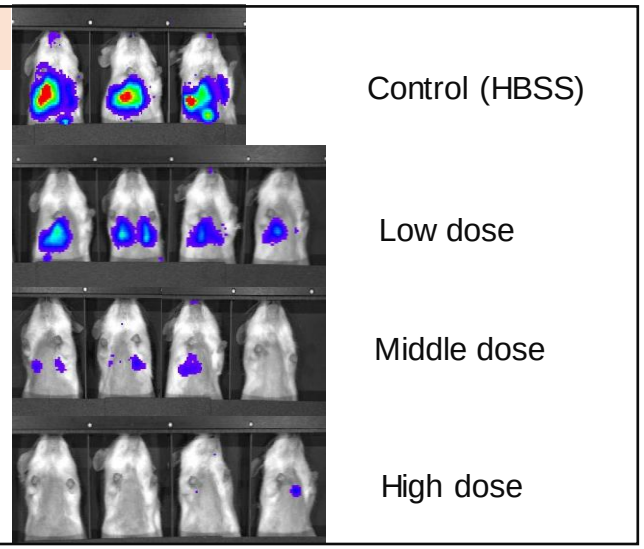
HCC827-Luc





H1975-Luc





(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.

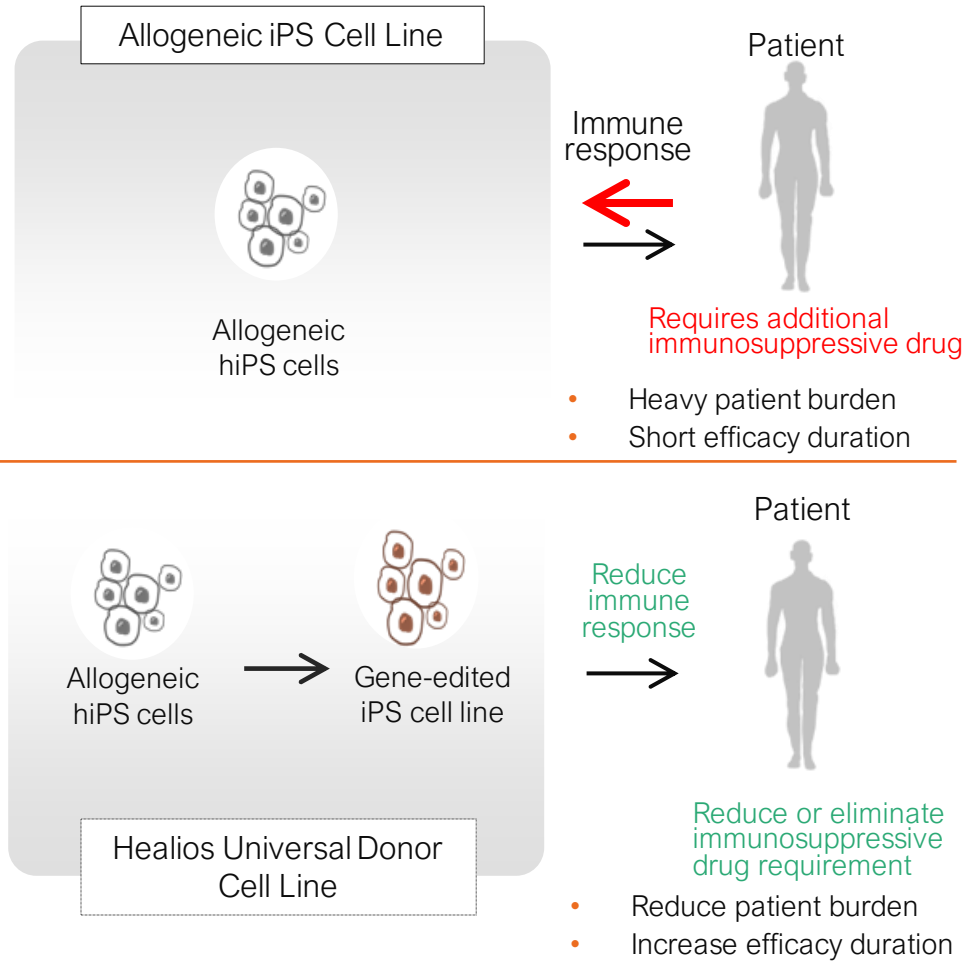
We aim to accelerate our research and development to deliver new immuno-oncology therapies using eNK cells to patients as soon as possible.

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”

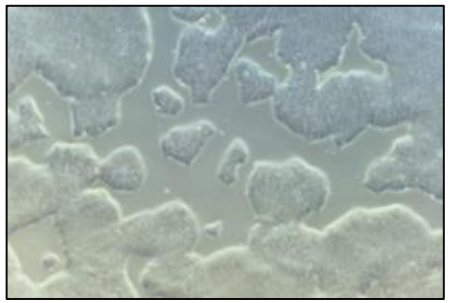


Targeted cell programming through gene-editing

- 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.).

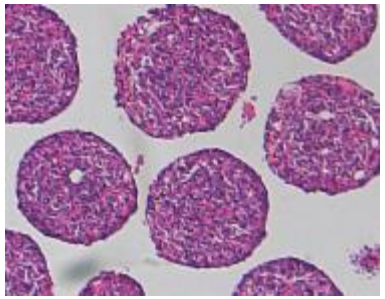
Hypo-immune UDC: Examples Of Cell Therapies

Universal Donor Cells (UDC)

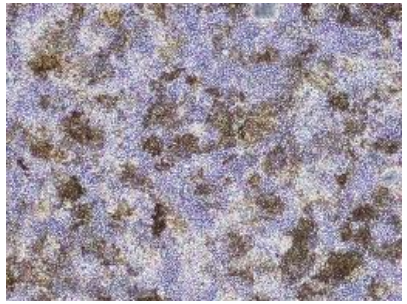


Photoreceptor cells

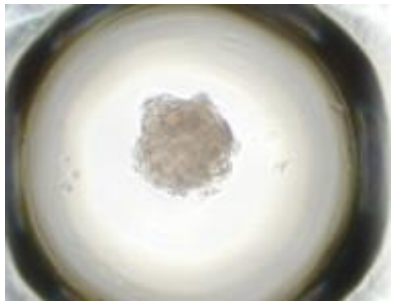
Pancreatic β cells



RPE cells



Liver buds



Successfully differentiated from UDCs

Future migration to UDC platform

(Source) in-house data and Joint research data

Healios

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