April 6, 2022

Company Name: HEALIOS K.K.
Representative: Hardy TS Kagimoto, Chairman & CEO
(TSE Growth Code: 4593)

Business Briefing for Institutional Investors

HEALIOS K.K. held a webinar to present an update on its business to institutional investors in Japan. The meeting agenda is provided below, and the presentation materials are available for viewing.

HEALIOS K.K. Business Briefing for Institutional Investors

Date and Time: Tuesday April 5, 2022, 10:00-12:00

Description:

1. Introduction	Chairman and CEO Hardy TS Kagimoto, MD
2. Overview and Current Status of HLCM051 Clinical Trials	Executive Vice President CMO (Chief Medical Officer) Masanori Sawada, MD, PhD, MBA
3. iPSC Regenerative Medicine eNK cells & UDC	Executive Officer Research field Kouichi Tamura, Ph.D

Briefing materials: attached

Contact: Department of Corporate Communications, HEALIOS K.K.
E-mail: ir@healios.jp

Overview and Current Status of HLCM051 Clinical Trials

Company
HEALIOS K.K.

Date
April 5, 2022

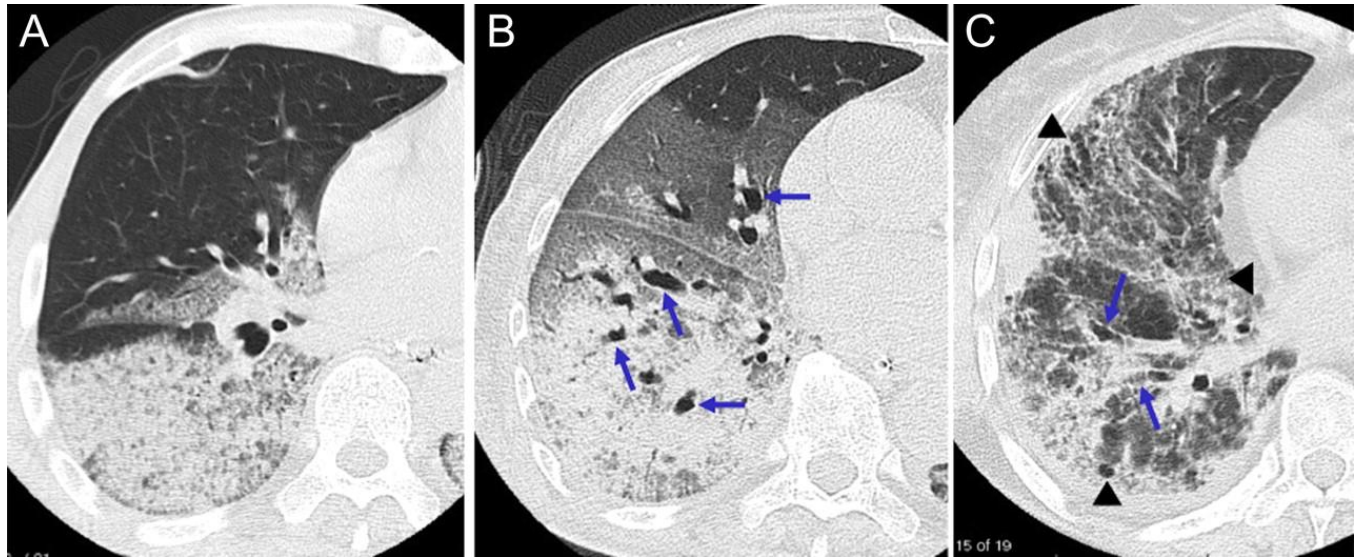
Executive Vice President CMO (Chief Medical Officer)
Masanori Sawada, MD, PhD, MBA

HLCM051 ARDS: Target Disease

Acute Respiratory Distress Syndrome or ARDS is a collective term for respiratory failure that occurs suddenly in critically ill patients (mainly due to severe pneumonia, sepsis, trauma, etc.). Activated inflammatory cells run amok and attack the lungs. It is a disorder with a very high mortality rate (30 ~ 58%) and a poor prognosis, for which there is a need for novel therapies that can improve patient outcomes.

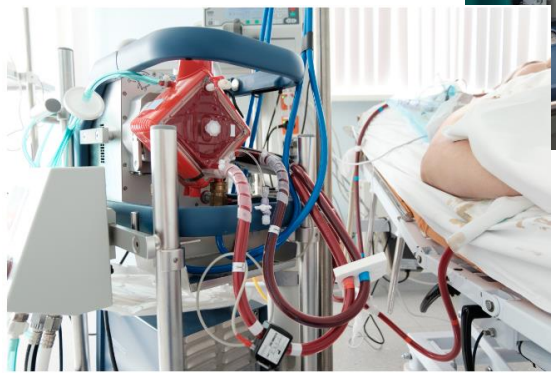
At present, there are no therapeutic drugs that can make a direct improvement to a patient's vital prognosis when ARDS develops. The only symptomatic treatment for respiratory failure includes artificial respiration.

Time-dependent change in CT image in ARDS affected lung



（出所） Ichikado K　BMJ Open. 2012 Mar 1;2(2):e000545

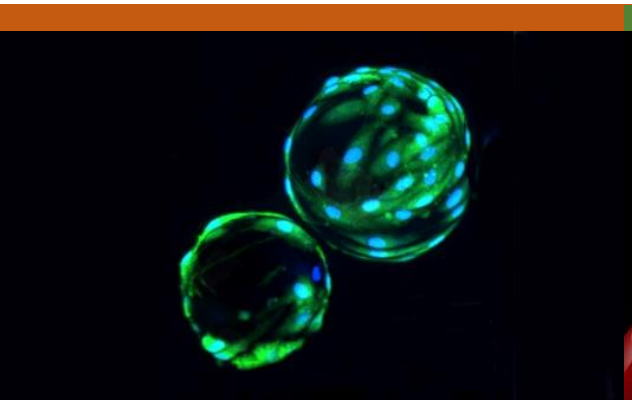
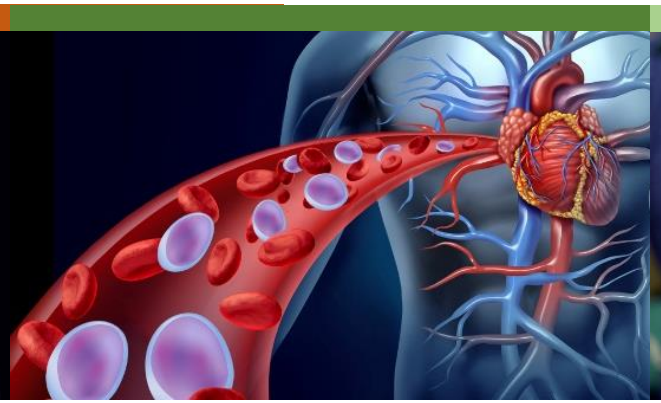
ECMO

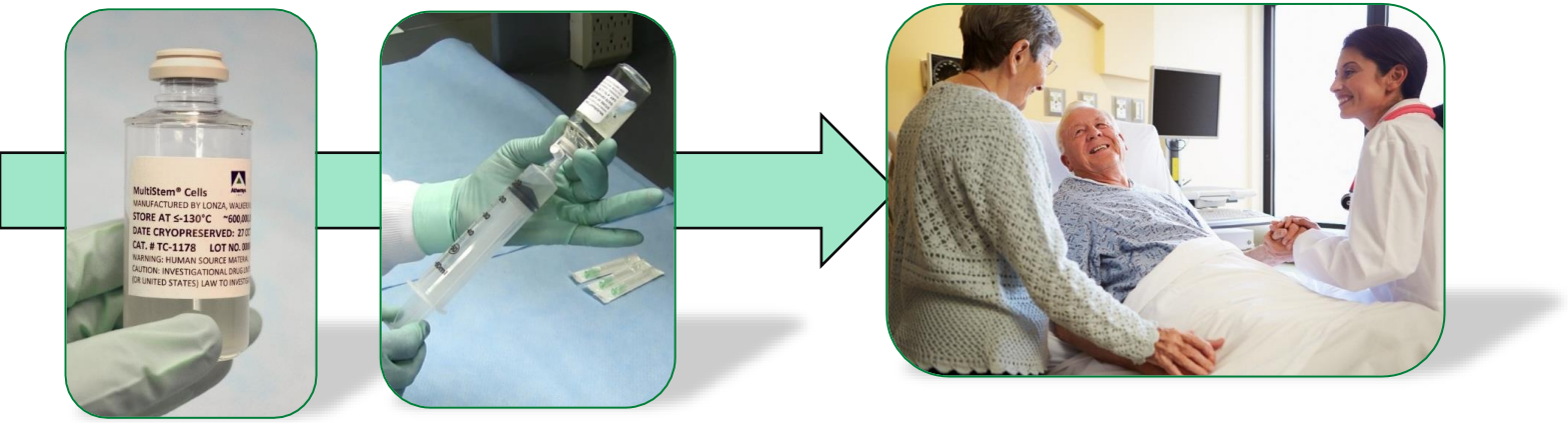


Artificial Respiration

HLCM051 ARDS: Overview of Cell Therapy

The allogeneic bone marrow-derived Multipotent Adult Progenitor Cell product (HLCM051) is expected to restore damaged lung tissue and improve respiratory function by reducing inflammation, regulating immune function, promoting angiogenesis, and protecting and repairing damaged cells and tissues.

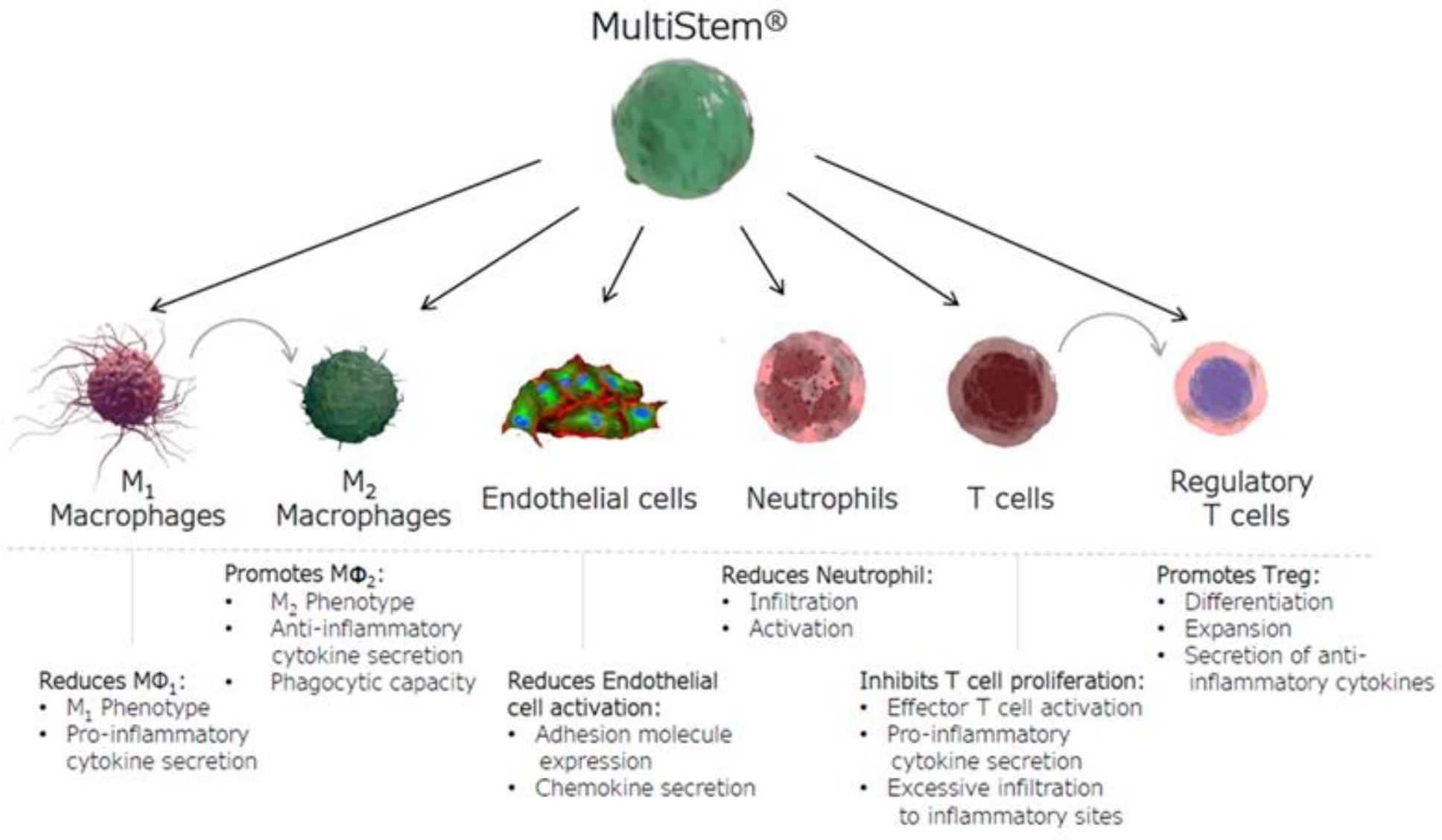


Partner Company: Athersys, Inc.

Head Office	Cleveland, Ohio (U.S.A.) NASDAQ：ATHX
Developed Products	Stem cell product: MultiStem® （proprietary）

(Source) Based on materials provided by Athersys

HLCM051 ARDS: Multiple Mechanisms of Action



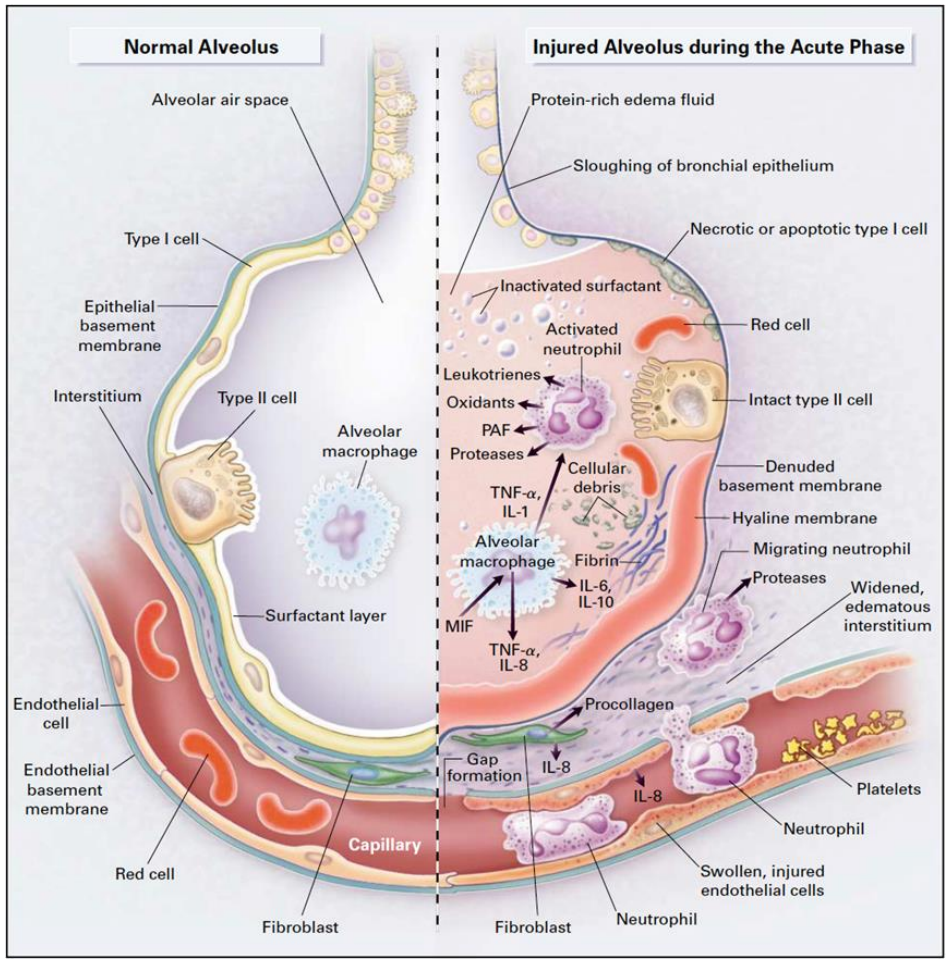
(Source) Athersys

HLCM051 ARDS: Multiple Mechanisms of Action

Intravenous HLCM051 first reaches the lungs. It restores lung tissue and improves respiratory function by promoting inflammation reduction, immune regulation, and protection and repair of damaged cells and tissues.

Recovery of Multipotent Progenitors from the Peripheral Blood of Patients Requiring Extracorporeal Membrane Oxygenation Support

Kim Chi T. Bui[1]*, Dinithi Senadheera[2,3], Xingchao Wang[2,3], Benjamin Hendrickson[3], Philippe Friedlich[4], and Carolyn Lutzko[2,3]

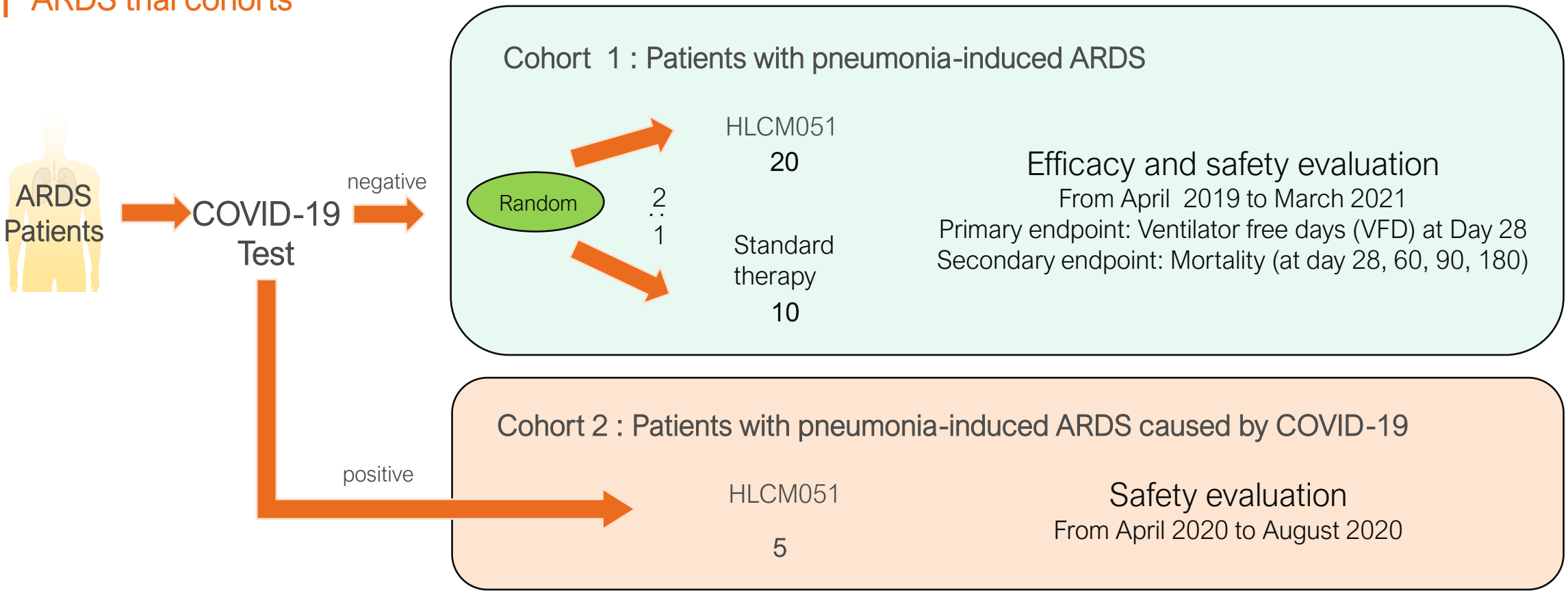


(Source) Ware et al. NEJM 2000; 342: 1334

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%**

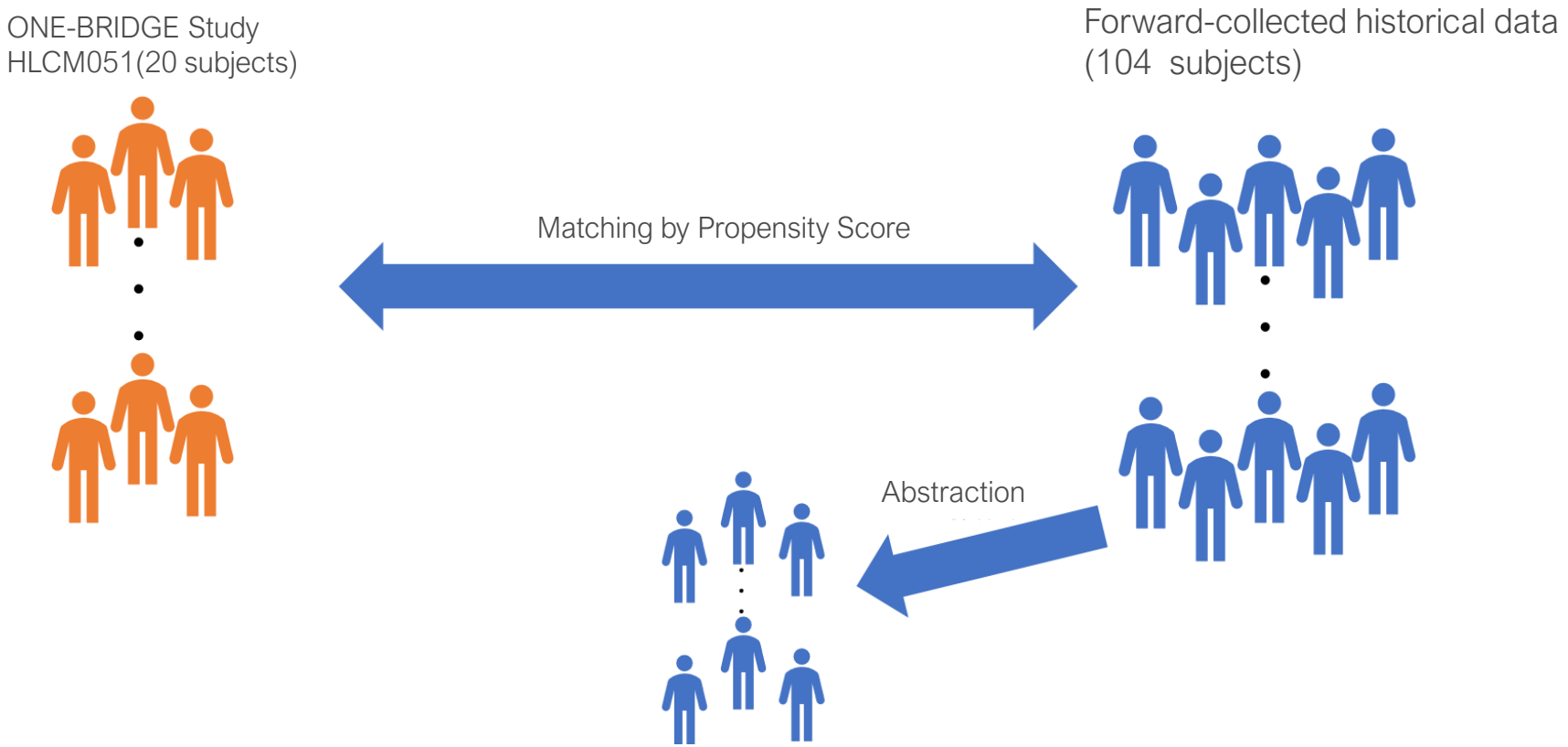
	Cohort 2
	HLCM051
Primary Endpoint	
Safety	**No safety issues**
Secondary Endpoint	
VFD	**25 days**
Mortality (180 days after administration)	**0%**

（Source）in-house data

HLCM051 ARDS: Comparison with Historical Data

Comparison with historical data was a secondary efficacy endpoint of the study protocol

- Data source reported in Scientific Reports (Sci Rep. 2021; 11: 20051.) in October 2021
- Matching comparison was performed with the data from the paper on which the study design is based.

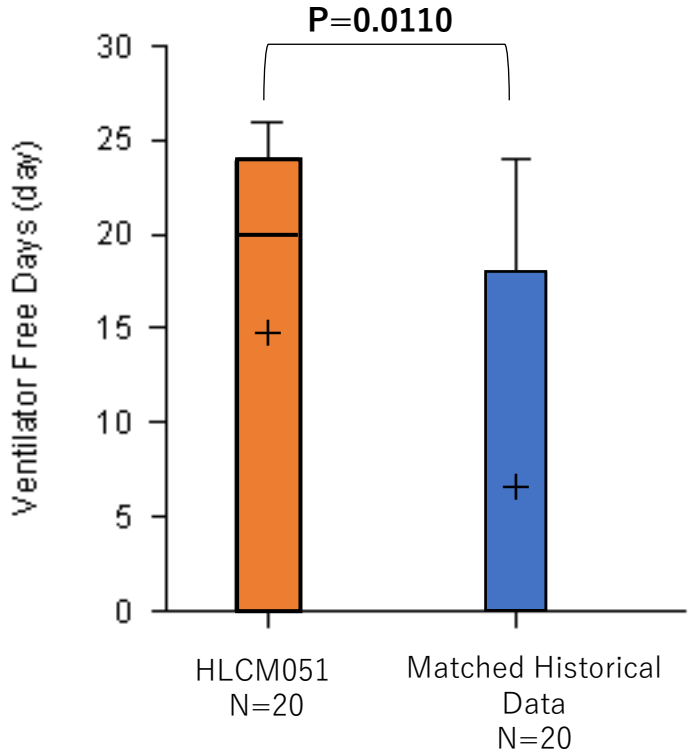


HLCM051 ARDS: Comparison with Historical Data

Consistent with the ONE-BRIDGE study, VFD was prolonged and mortality improved.

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日 days**
Secondary Endpoint	**P=0.0536**	
Mortality (180 days after administration)	**26.3%**	**60.0%**



(Source) in-house data

HLCM051 ARDS: Development Status

ONE-BRIDGE Study

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

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.

April 2019
First patient enrolled

March 2021
Patient enrollment completed

August 2021
Announcement of top-line results

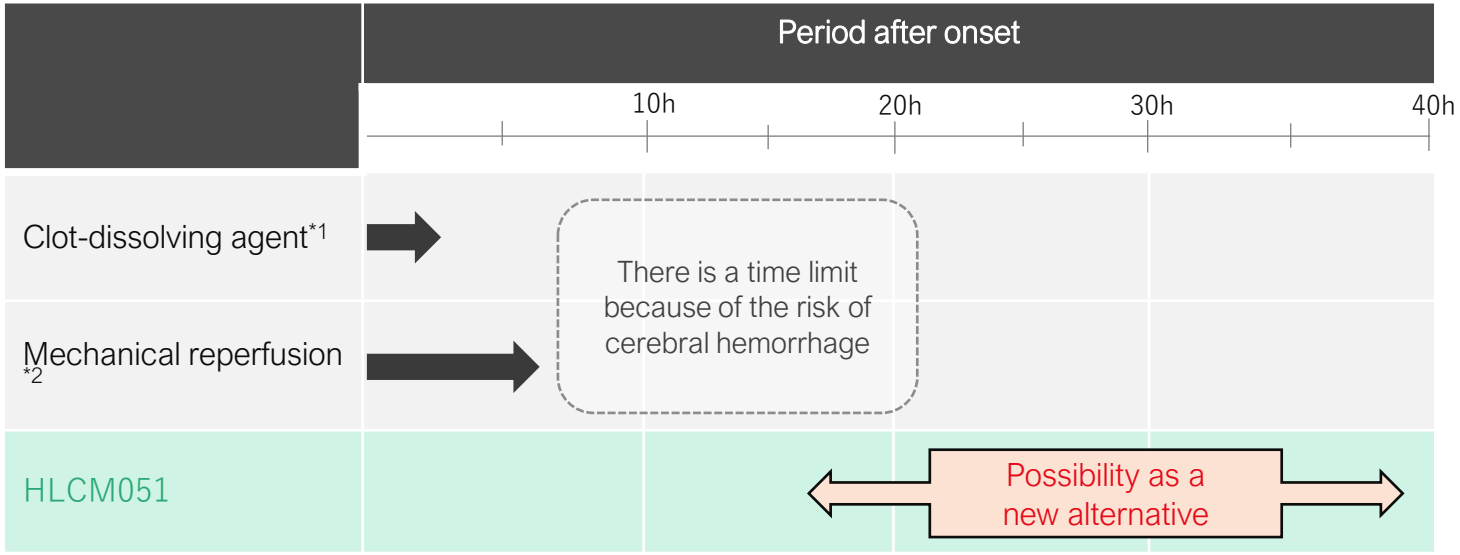
*HLCM051 has been designated as an **orphan regenerative medicine product** for use in the treatment of ARDS by the Ministry of Health, Labor and Welfare.

HLCM051 Ischemic Stroke: Overview

Ischemic stroke is caused by a blockage of blood flow in the brain that cuts off the supply of oxygen and nutrients, resulting in tissue loss.
The annual number of cases in Japan ranges from 230,000 to 330,000
It is estimated that 37.9% of bedridden patients and 21.7% of persons who were in need of care were affected by ischemic stroke.

(Source) Athersys

Treatment in Accordance with the Period After Onset



※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.

HLCM051 Therapy Could Greatly Extend the Treatment Window for Stroke Patients

(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.

HLCM051 Ischemic Stroke: Mechanism & Neuroprotective Effects in Cerebral Infarction

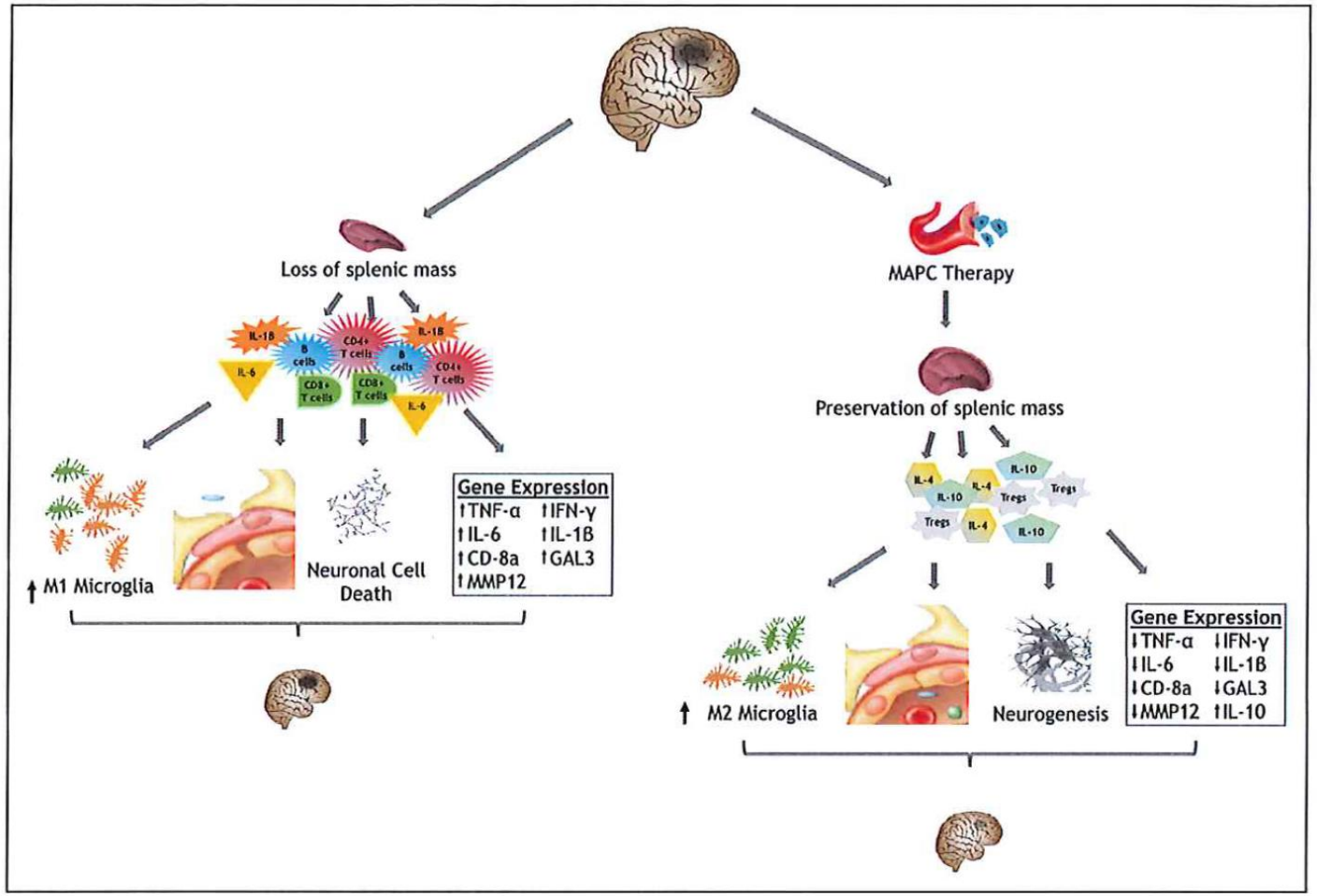


Figure 2. A model hypothesis for how multipotent adult progenitor cells (MAPC) enhance recovery after stroke. In the untreated scenario, ischemic stroke leads to the activation of the peripheral immune system, including spleen reduction and the release from the spleen of proinflammatory cells and cytokines. These proinflammatory mediators contribute to worsening blood–brain barrier (BBB) disruption and central nervous system (CNS) inflammation mediated by M1 microglia. An intravenous administration of MAPC reverses splenic atrophy, promotes the release of anti-inflammatory mediators from the spleen, which ultimately leads to less BBB disruption and less CNS inflammation, and the promotion of a proregenerative environment. IL indicates interleukin; and Tregs, T regulatory cells.

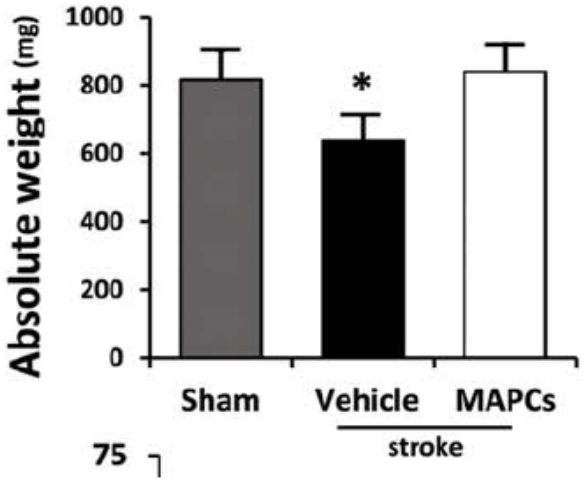
M1 Microglia： injurious properties
M2 Microglia： Protection

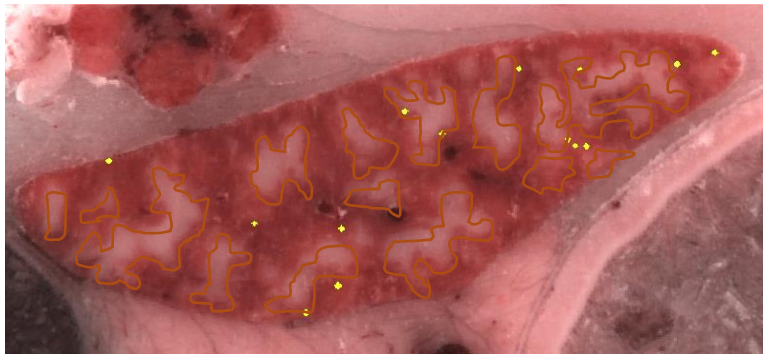
(Source) Stroke. 2018 May;49(5):1058-1065

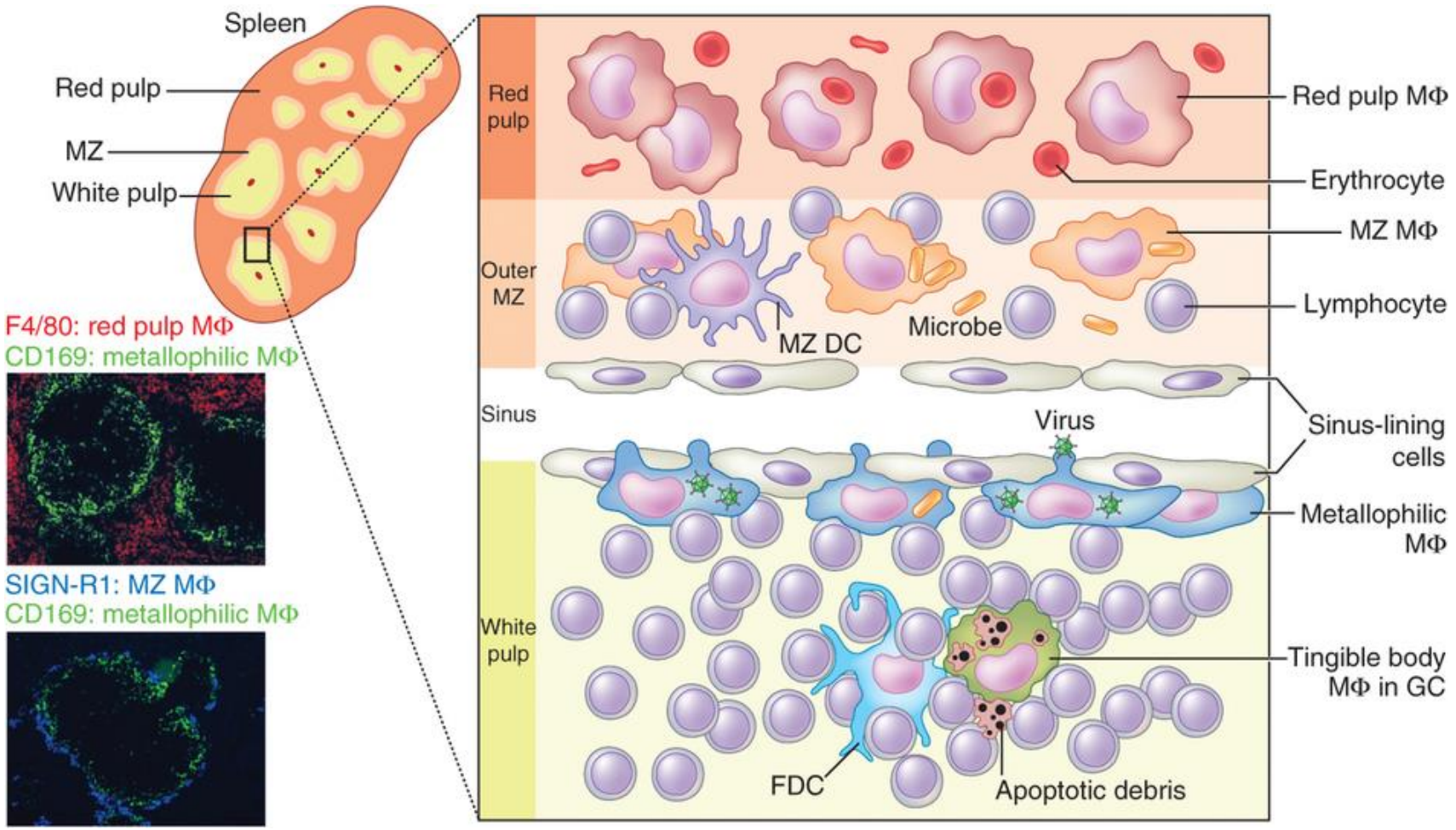
- ✓ Cerebral infarction leads to activation of the peripheral immune system and release of proinflammatory cells and cytokines from the spleen (atrophy of the spleen).
- ✓ Spleen-induced proinflammatory mediators contribute to exacerbation of blood-brain barrier (BBB) disruption and central nervous system (CNS) inflammation mediated by injurious microglia (M1).
- ✓ Intravenously administered HLCM051 reduces the destruction of the BBB by promoting the release of anti-inflammatory mediators from the spleen while suppressing atrophy of the spleen, and reduces inflammation of the CNS by promoting the environment for nerve cell regeneration.

HLCM051 Ischemic Stroke: Mechanism Involving the Spleen

Offner et al. focused on the peripheral immune system (especially the spleen) and involvement of the peripheral immune system after acute central nervous system injury and stroke.
Offner et al. (2009) found that peripheral immune organs, including the spleen, shrank by about 20 ~ 40% within 72 ~ 96 h of the onset of stroke in rodents.



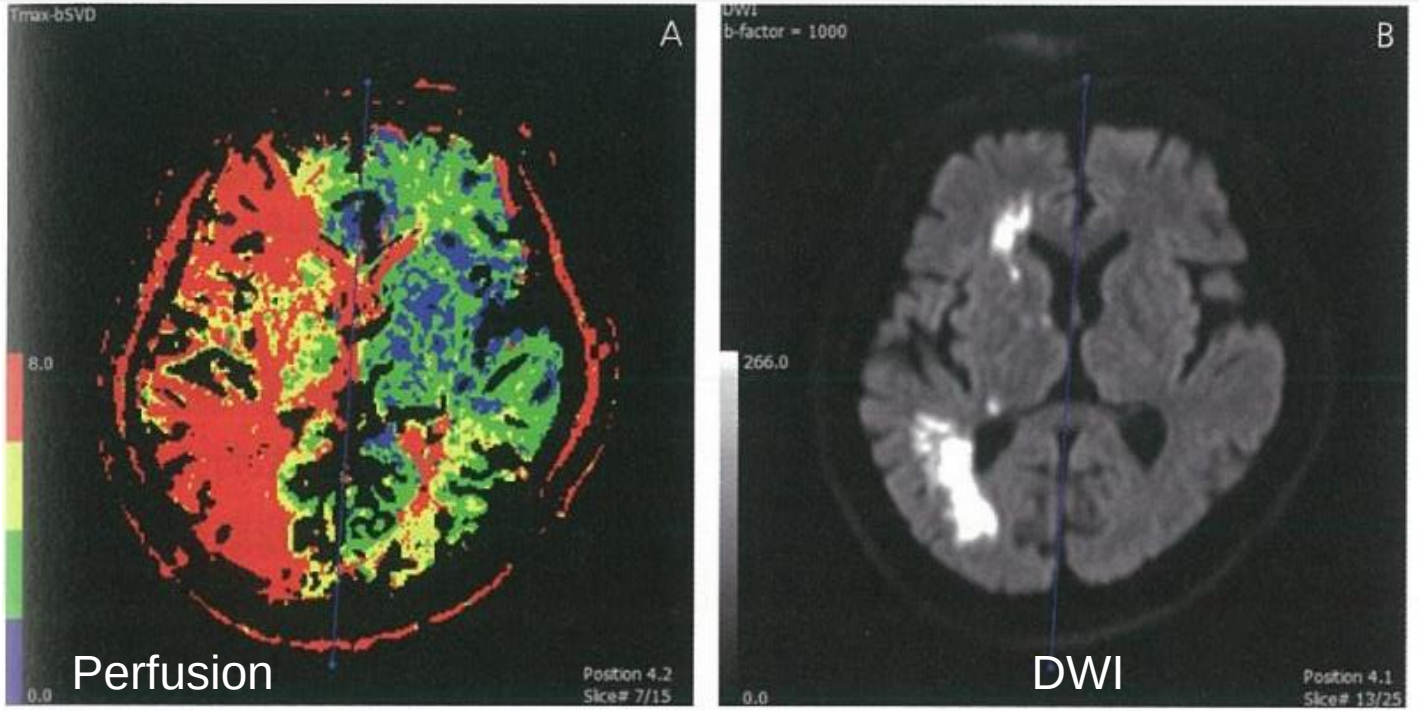


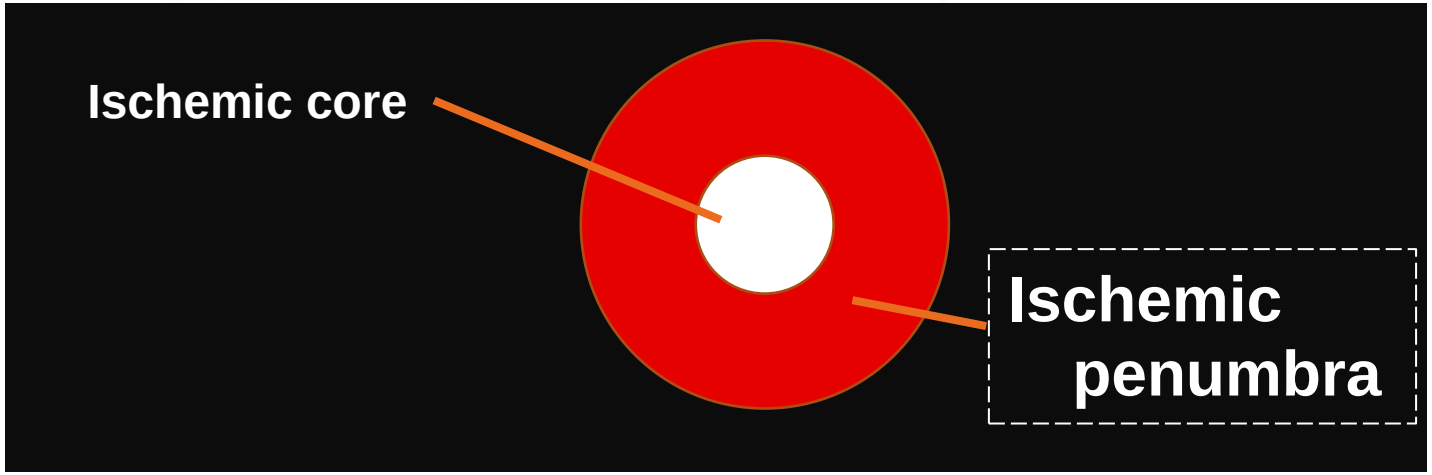


(Source) Offner et al.（2009）

(Source) Walker P., et al., Exp Neurology, 2010

HLCM051 Ischemic Stroke: The Importance of Protecting the Penumbra Region in the Treatment of Cerebral Infarction





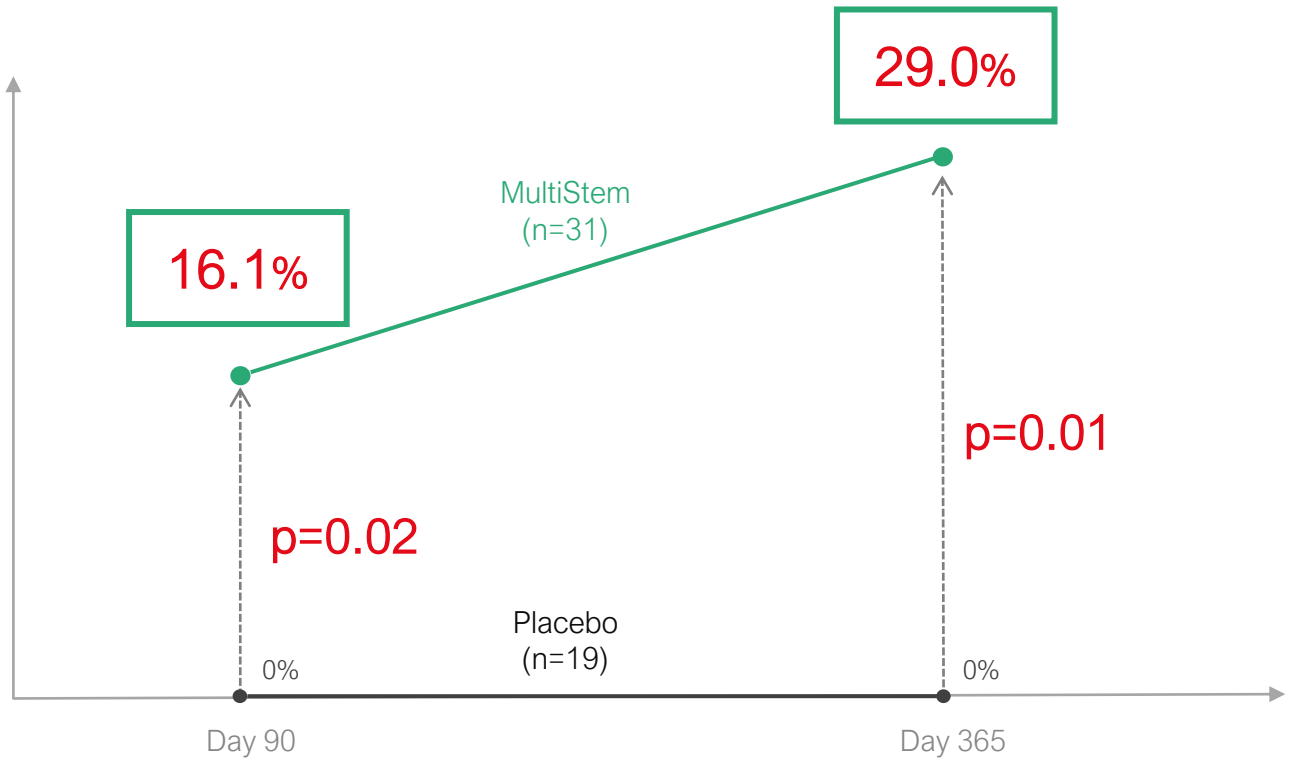
The penumbra is an area of the brain in the early stage after the onset of cerebral infarction in which blood flow is reduced and the brain is in a state of ischemia, but cells are not necrotized.

(Source) Neurology Handbook Differential Diagnosis and Treatment (5th ed.)

HLCM051 Ischemic Stroke: Results of Double-blind Study Conducted by Athersys

The proportion of patients who achieved Excellent Outcome was statistically significant in the group of patients who received MultiStem within 36 hours of the onset of cerebral infarction

Analysis of the Double-blind study conducted by Athersys



(Source) This material was based on *Lancet Neurol*. 2017 May;16(5):360-368; 16 360–68 Supplementary appendix Table 5

Overview of the Analysis

Trial	The placebo-controlled double-blind Phase 2 study conducted by Athersys in the US and the UK （MASTERS study)
Subjects	Administered MultiStem or Placebo within 36 hours of the onset of stroke
Endpoint	Proportion of subjects with an Excellent Outcome on Day 90 and Day 365

*<Excellent Outcome> is defined as mRS score of ≤1 (scale, 0 to 6), NIHSS score of ≤1 (scale, 0 to 42), and BI score of ≥95 (scale, 0 to 100).

HLCM051 Ischemic Stroke: TREASURE Study Overview

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

TREASURE: TReatment Evaluation of Acute Stroke Using REgenerative cells

Acute ischemic stroke (within 36 hours)

Estimated Enrollment: 220 subjects

Main Inclusion Criteria:

- ✓ Clinical diagnosis of cerebral cortical ischemic stroke
- ✓ 20 years of age or older
- ✓ NIHSS 8 – 20 at baseline
- ✓ tPA or mechanical thrombectomy allowed
- ✓ A modified Rankin Scale (mRS) of 0 or 1 prior to the onset of ischemic stroke

Randomized(1 : 1)

- **HLCM051 (N=110)**
- **Placebo (N=110)**

Primary Endpoint

・Efficacy
Proportion of subjects with an **excellent outcome** defined by functional assessment [Day 90]

・Safety
Comparison between the HLCM051 and placebo groups in key adverse events

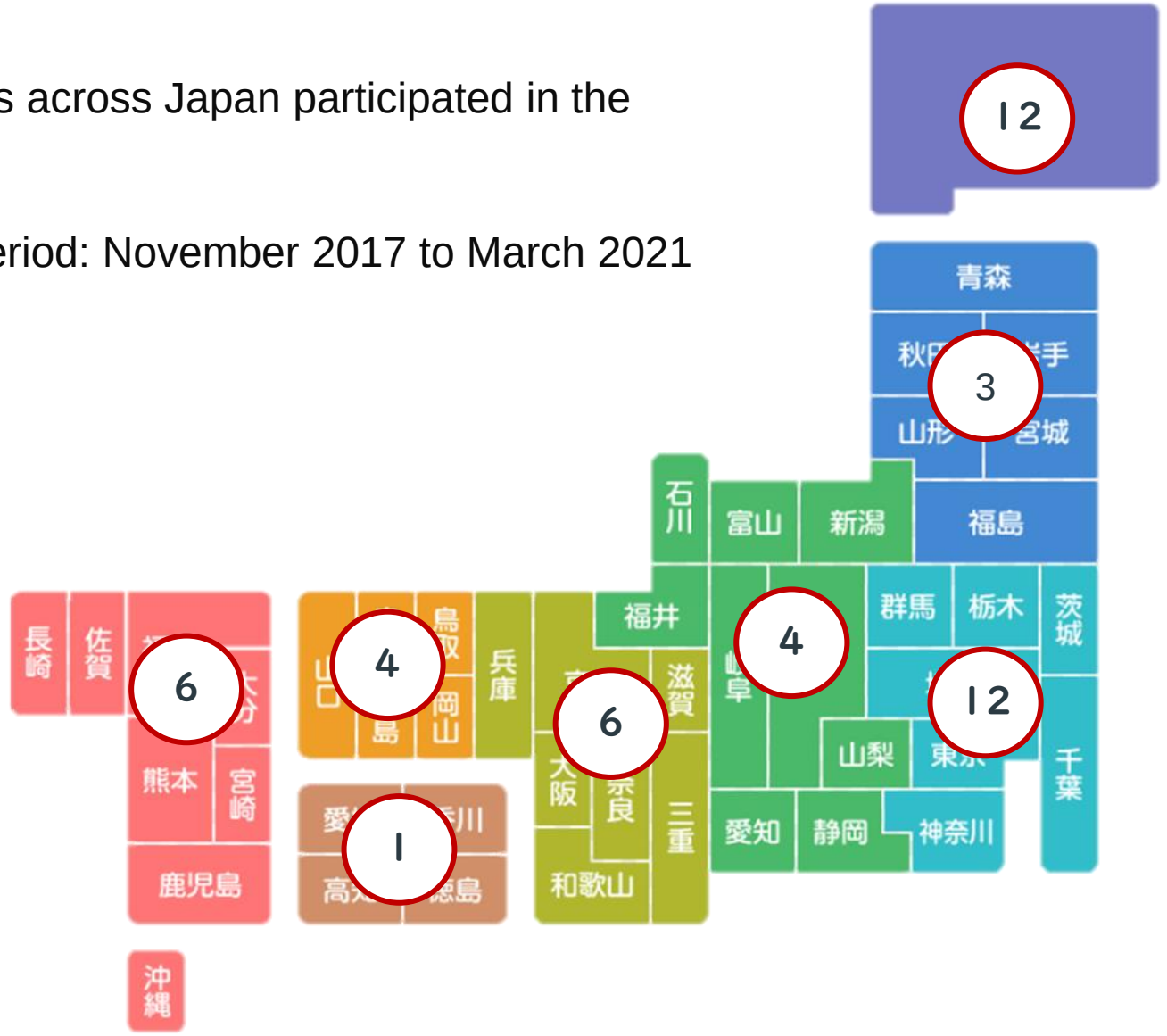
Secondary Endpoints (examples)

・Proportion of subjects with an **excellent outcome** defined by functional assessments [Day 365]

・Proportion of subjects exhibiting functional outcome throughout the range of **mRS scores by shift analysis** [Days 90 and 365]

HLCM051 Ischemic Stroke: TREASURE Study Implementation System

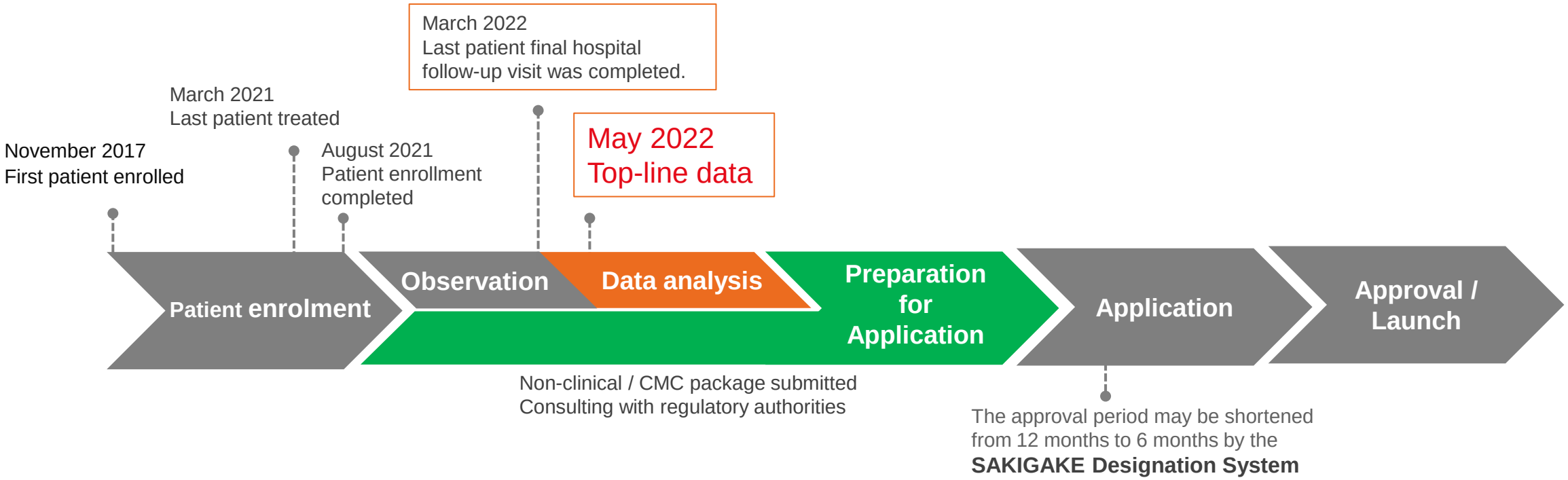
- ✓ 48 medical institutions across Japan participated in the TREASURE study
- ✓ Subject enrollment period: November 2017 to March 2021



HLCM051 Stroke: Topline Results in May 2022

90 and 365-day top-line results of the TREASURE study planned for May 2022.

Development Plan



iPSC Regenerative Medicine
eNK Cells & UDC

Company

Healios K. K.

Date

April 5, 2022

Executive Officer Research field
Kouichi Tamura, Ph.D

Program Overview

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**	

[1]Future migration to UDC platform

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]

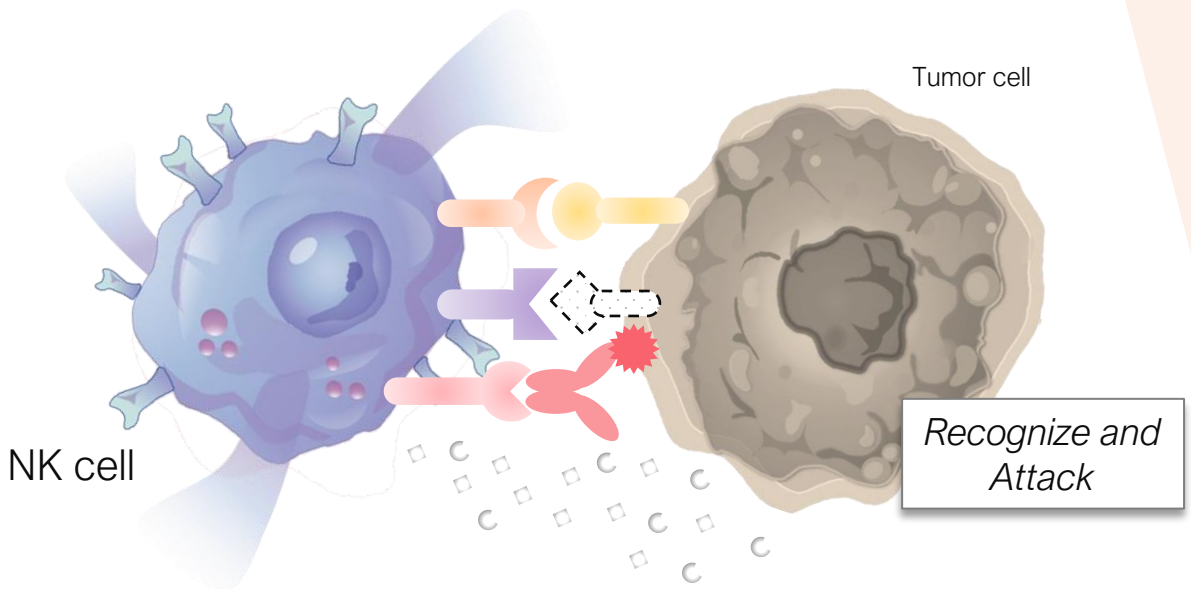
The Potential for Natural Killer (NK) Cells

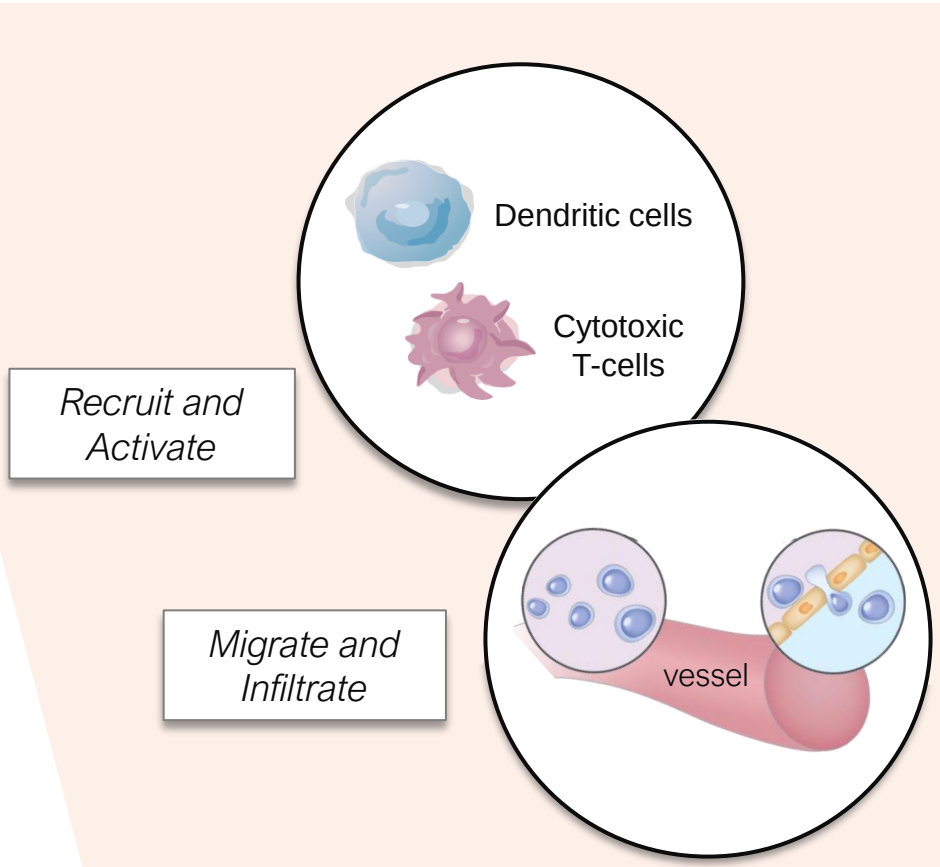
- Offer tremendous promise as a new therapeutic approach to treating solid tumors.
- Innate, central role in a cell mediated defense system in humans, and attack cancer cells and virus-infected cells.
- Reported advantages over T cell-based therapies:
  - Broad mechanism to recognize tumor cells
  -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

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

Healios' Three-Pronged NK Cell Therapy Approach

A gene-engineered iPSC-NK cell platform designed not only with enhanced cytotoxicity but also with recruitment and trafficking properties



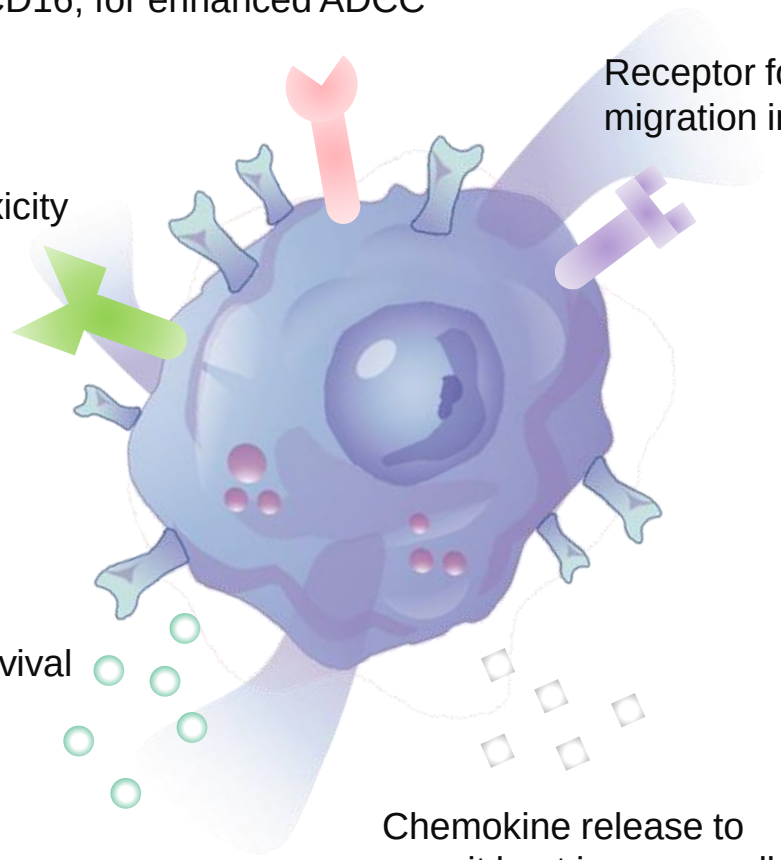


Key Characteristics of the Healios iPSC eNK Cell Platform

CD16; for enhanced ADCC

Receptor for improved migration into solid tumors

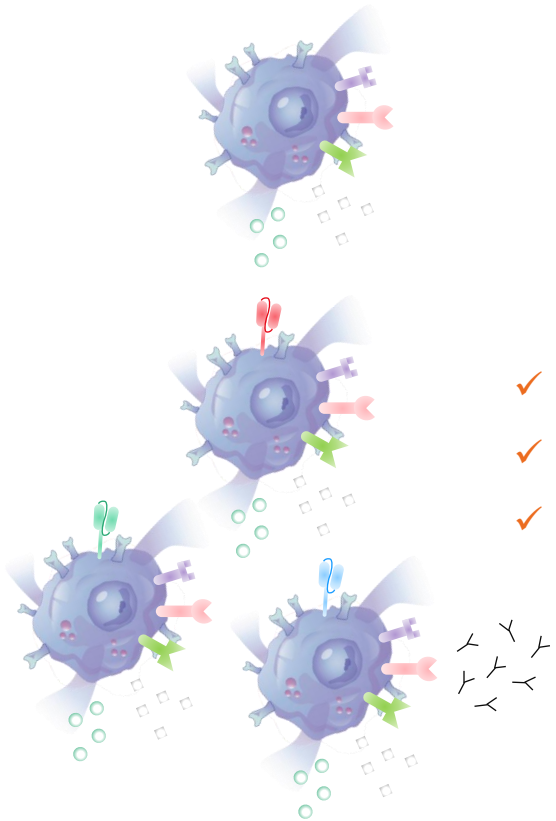
Receptor for enhanced recognition and cytotoxicity



IL-15; for improved persistence and survival

Chemokine release to recruit host immune cells

Multiple Product Candidates



Stand-alone eNK product

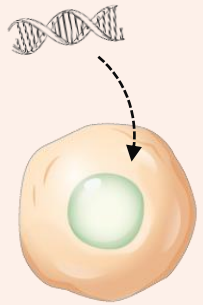
CAR-eNK products against specific targets

- ✓ **CAR eNK cell therapy**
- ✓ **Dual CAR eNK**
- ✓ **Bispecific CAR eNK**

In combination with antibody therapies

Core eNK Platform Technologies & Competencies

Engineered iPSC Lines



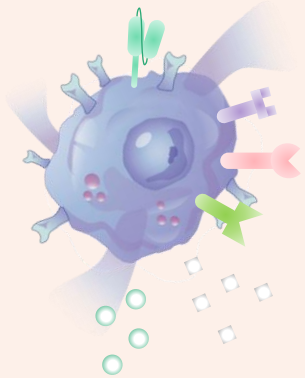
NK differentiation

Proprietary, engineered iPSC lines

- ✓ Enhanced cytotoxic activity
- ✓ Enhanced proliferative potential and prolonged survival
- ✓ Recruitment of patient immune cells
- ✓ Migration and invasion of solid tumors

Master cell banks established for NK cell production

Differentiation of NK Cells With Enhanced Functionality



eNK

- Optimization of differentiation induction conditions
- Confirmation of killing function, maintenance of proliferation and survival, migration and invasion
- Ability to attract immune cells
- Efficacy and safety in animal models
- Quality standards strategy

Process Optimization, Scale Up & Manufacturing

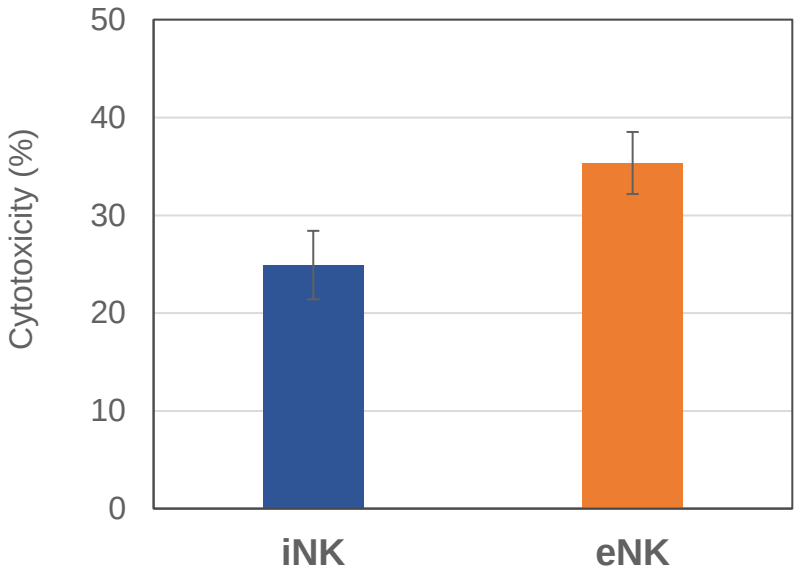
GCTP/GMP Manufacturing
@ HEALIOS Facility
in Kobe, Japan

Validated CARs for Multiple Products

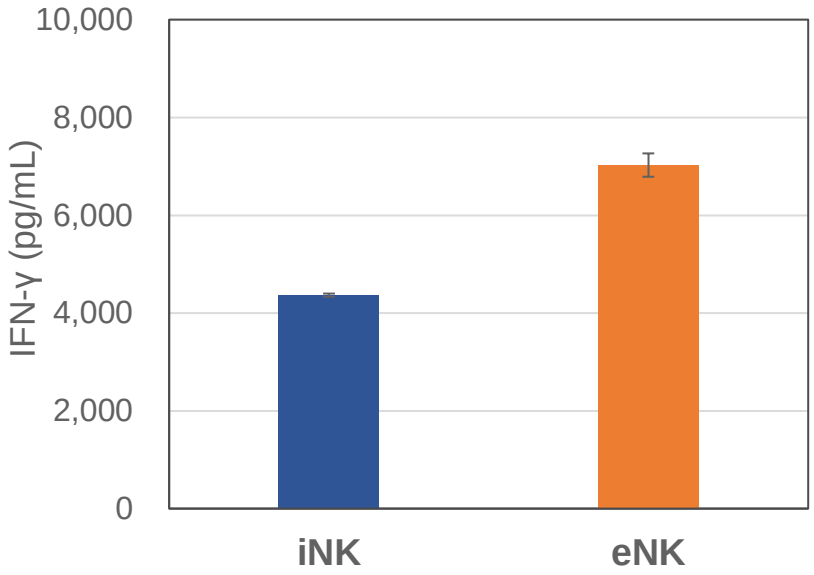
Product 1 Product 2 ... Product n

Cytotoxicity and Cytokine Production of eNK Against A549 (Lung Cancer)

Cytotoxicity (LDH assay)



Cytokine Production (co-cultured with A549)

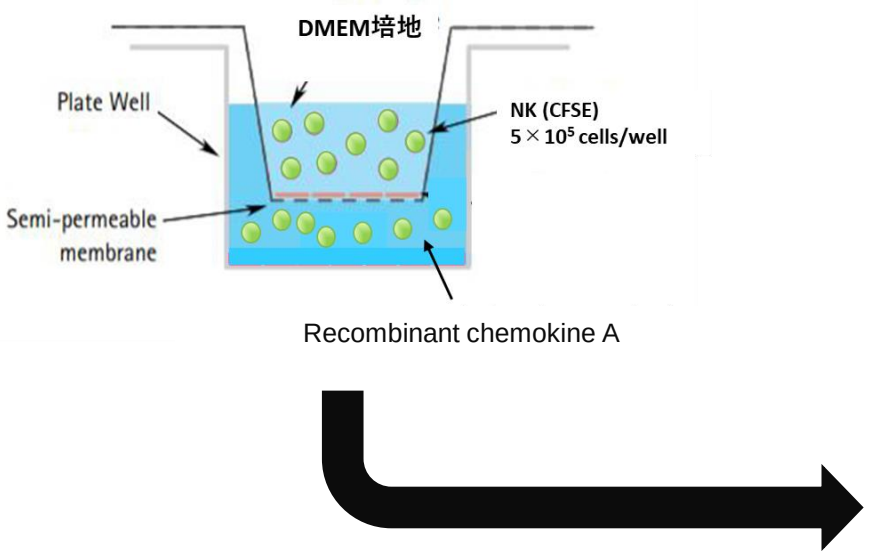


eNK: gene-edited and functionally enhanced NK cells derived from iPSC
iNK: gene un-edited iPSC derived NK cells

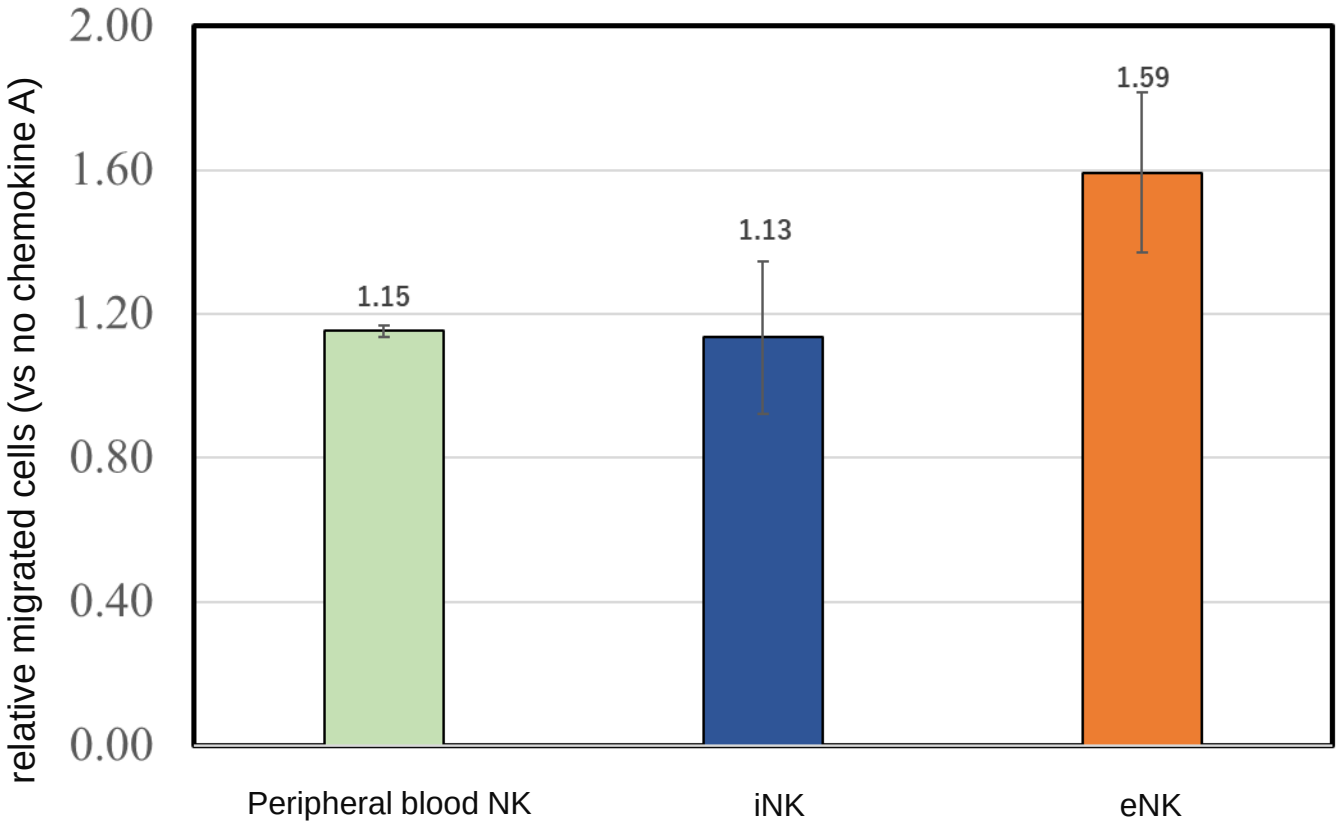
Enhanced cytotoxicity and IFN-γ production were observed with eNK

(Source) in-house data

Enforced Expression of Chemokine Receptor A for Migration



Measure the relative migration as the ratio of the number of cells that migrated to the lower chamber with and without chemokine A.

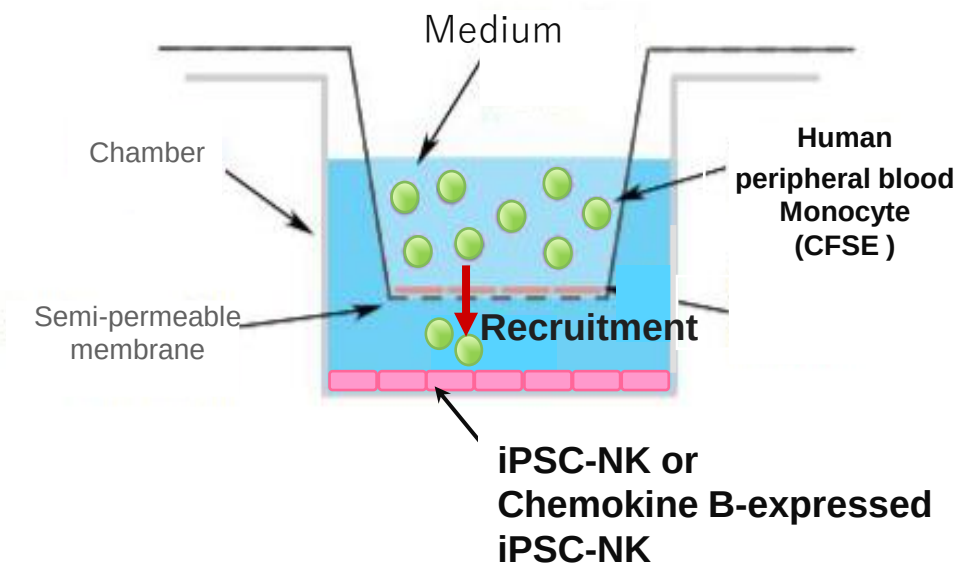


eNK efficiently migrates to chemokine A

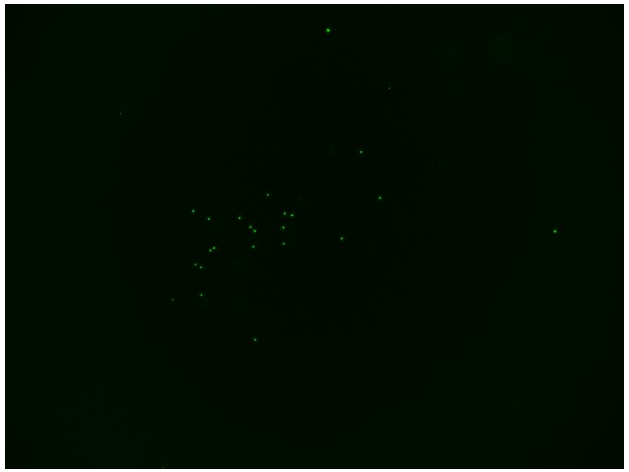
（Source）in-house data

Recruitment of Immune Cells by Forced Expression of Chemokine B

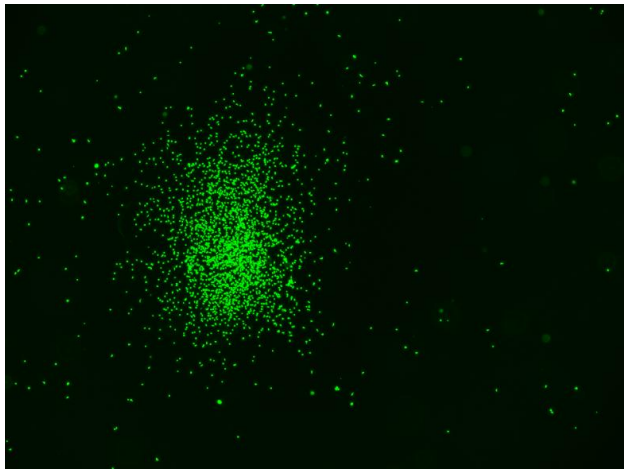
Recruitment Assessment



iPSC-NK



Chemokine B-expressed iPSC-NK



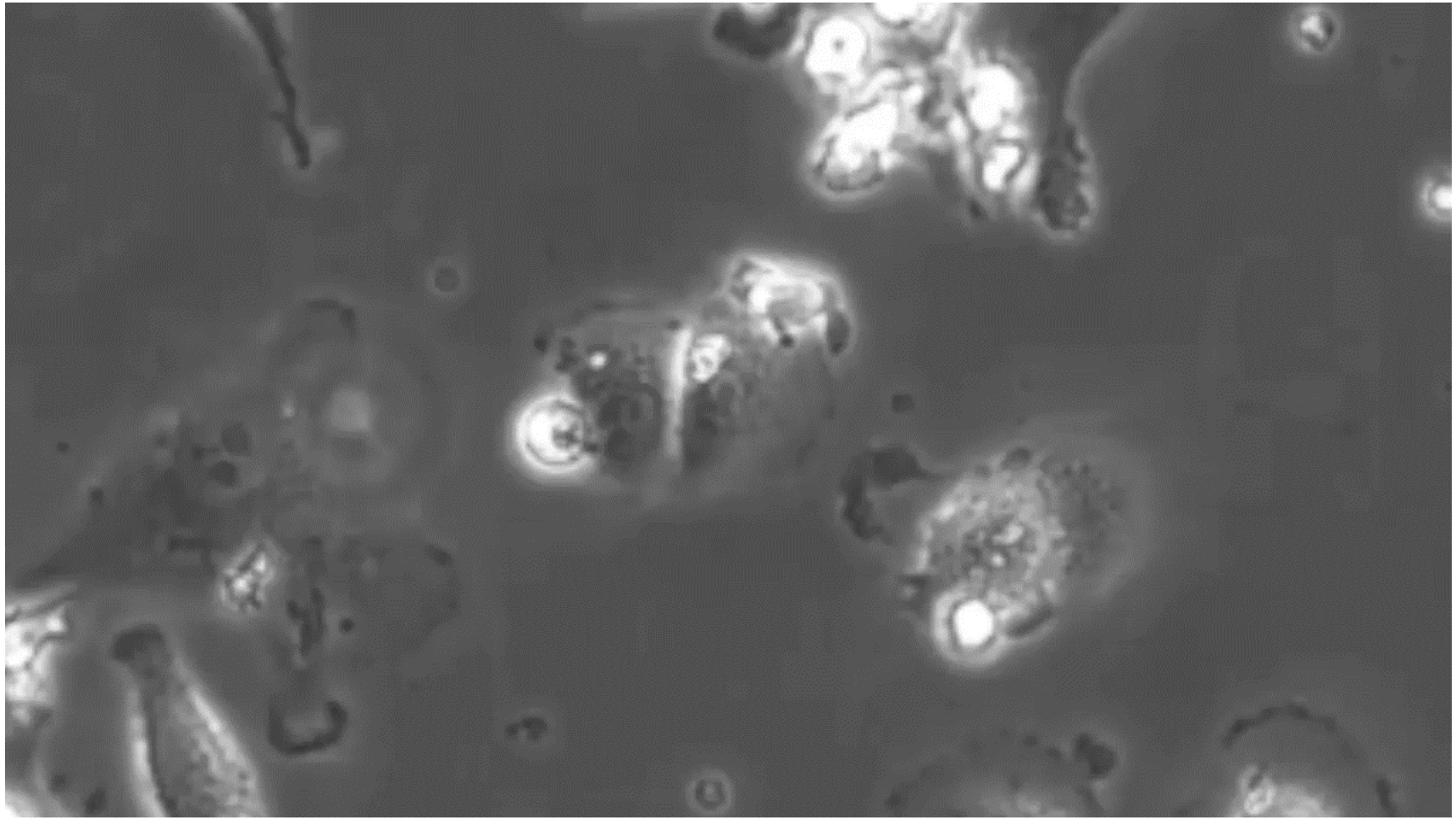
- ✓ Chemokine B is an attractant for T cells and dendritic cells expressing their receptors.
- ✓ Chemokine B-expressing iPSC-NKs recruit human immune cells.

eNK shows the potential to recruit T-cells and Dendritic cells.

(Source) in-house data

Time Lapse Imaging of Cancer Cell Attack by Healios iPSC-NK cells

iNK killing lung cancer cells (A549)



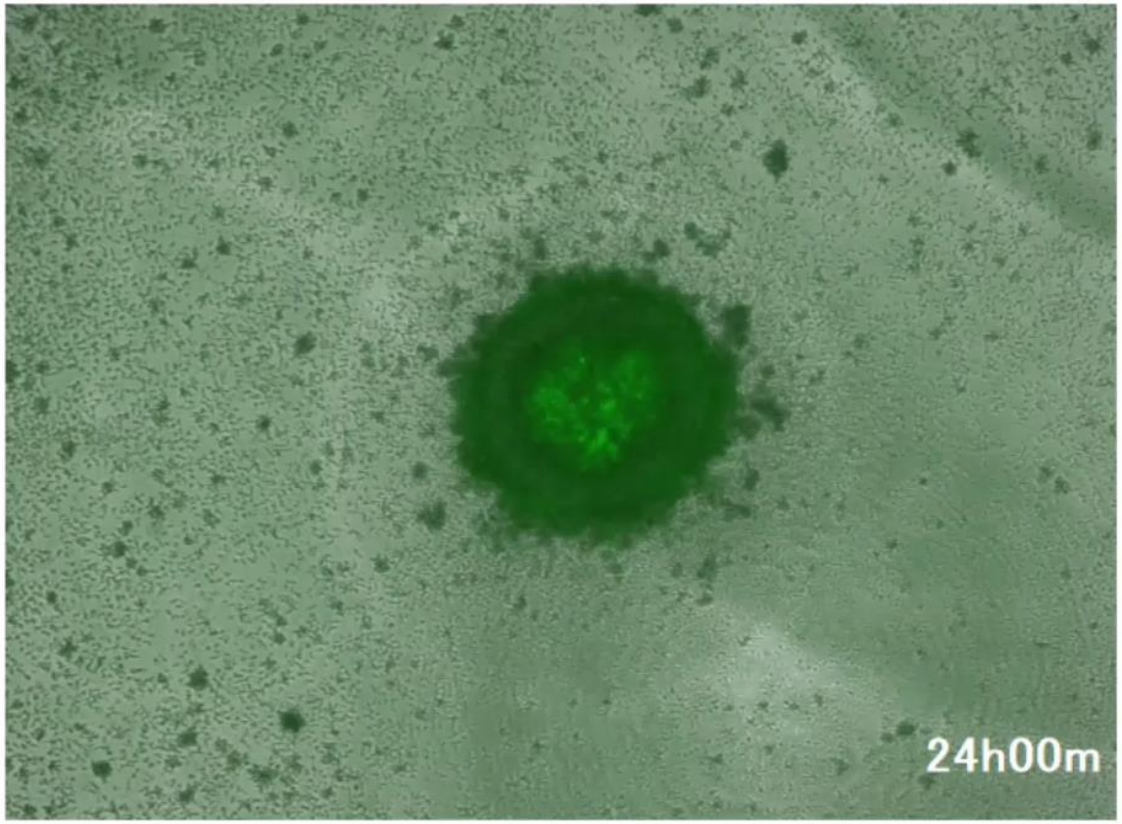
(Source) in-house data

Time Lapse Imaging of Cancer Spheroid Co-cultured with iPSC-NK Cells: Cytotoxicity and Destruction of the Spheroid

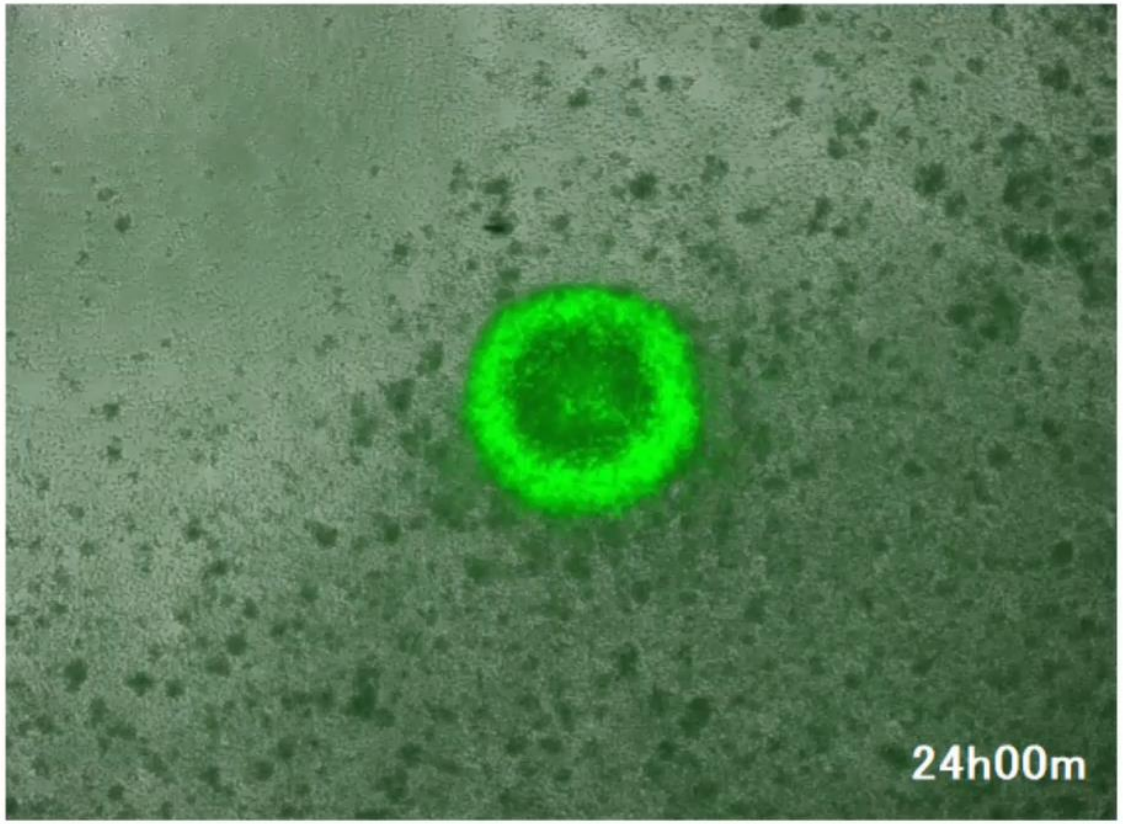
From 24 hours until 85 hours after co-culture

Green: apoptotic cells

iNK



eNK

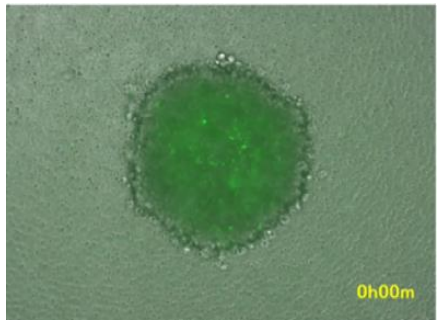
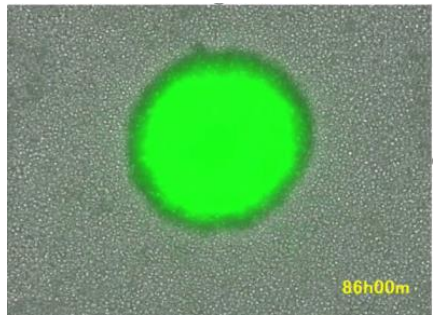
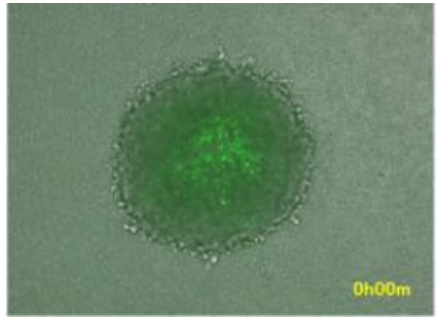
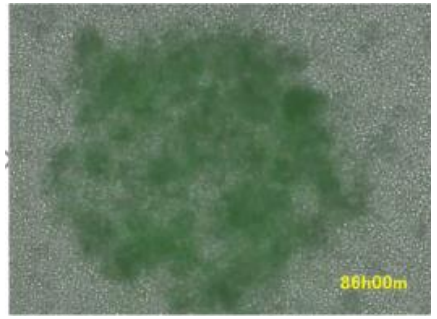
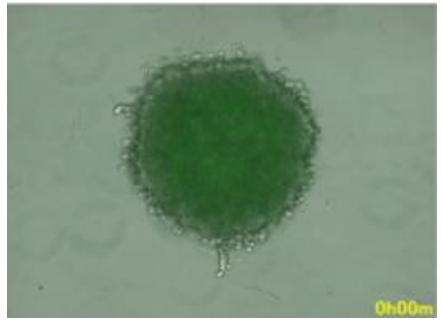
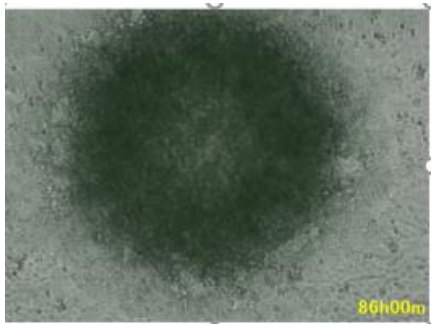


eNK more rapidly killed cancer cells and destroyed the spheroid

（Source）in-house data

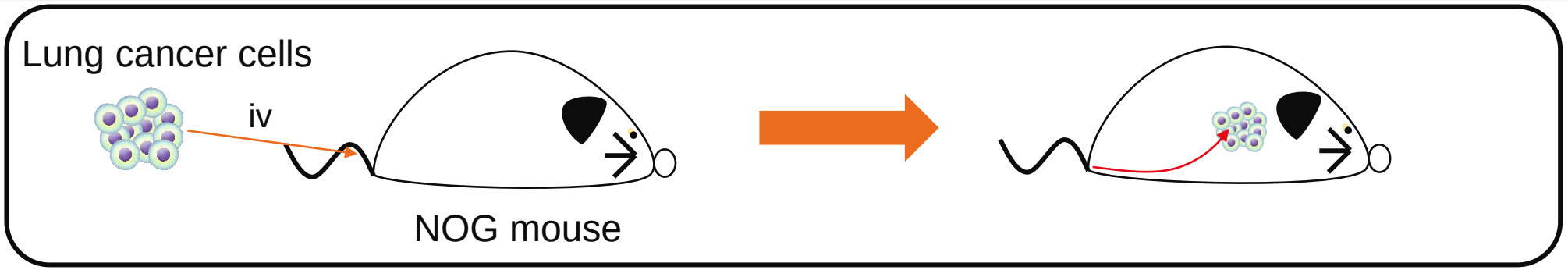
In Vitro Evidence of Anti-tumor Effect as Mono- and Combination Therapy (Lung, A549)

Green : apoptotic cells

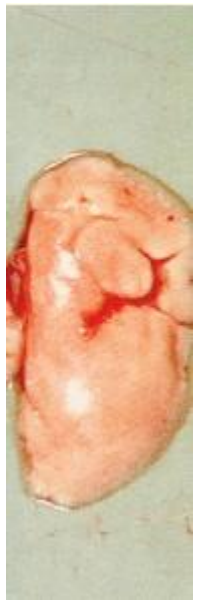
	0h	86h (3.5 days)	
eNK only			eNK cells have killed the cancer cells
eNK with anti-EGFR antibody			The lung cancer cells were efficiently killed and the lung cancer cell spheroid was destroyed.
Anti-EGFR antibody only			The cancer cells survived and the cancer cell spheroid expanded for 86 hours.

（Source）in-house data

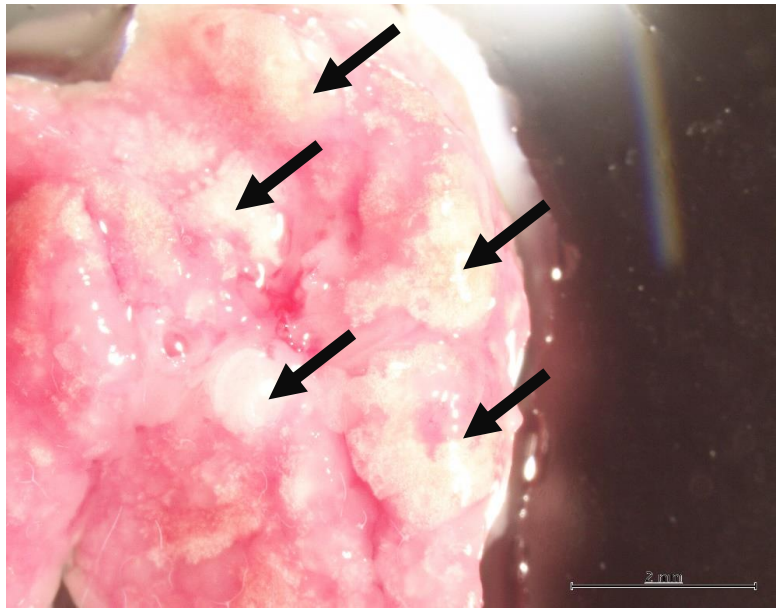
Establishment of Orthotopic Lung Cancer Mouse Model

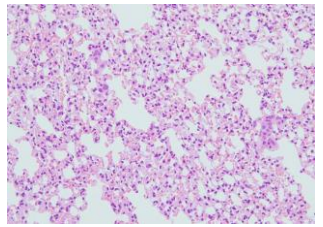
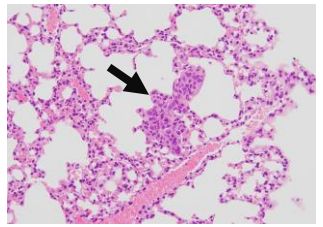
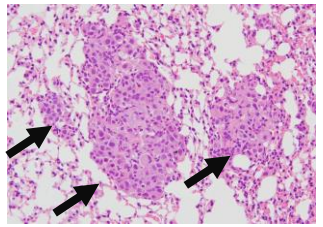


Normal lung



A549 transplanted lung



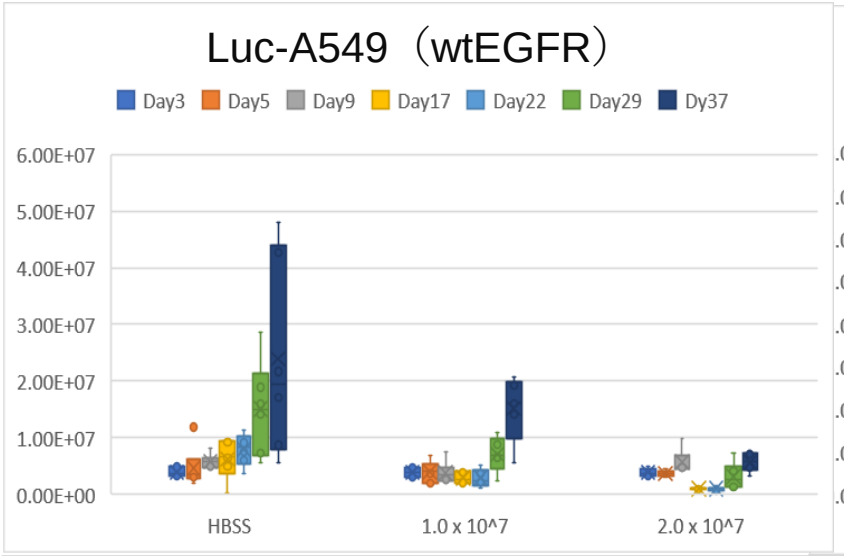
Transplanted cell number	Tissue section
1x10^4 cells	
1x10^5 cells	
1x10^6 cells	

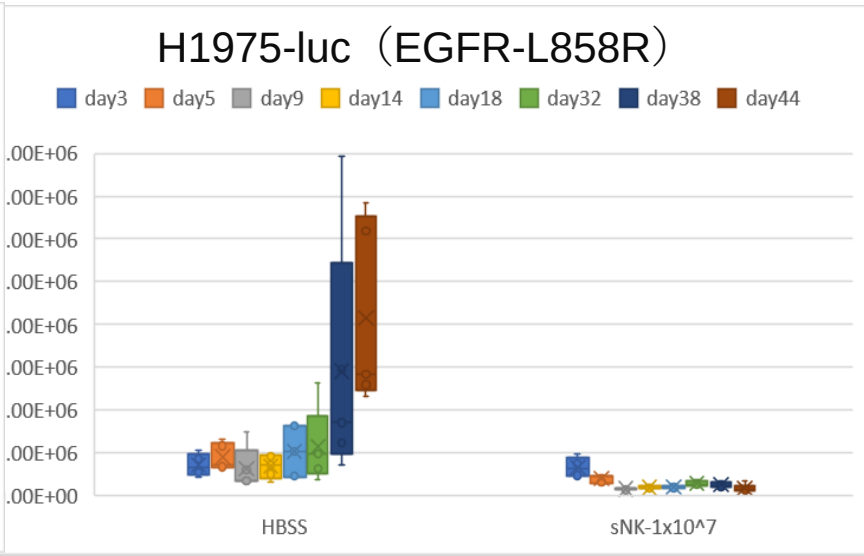
The cancer nodules were observed in lung tissue

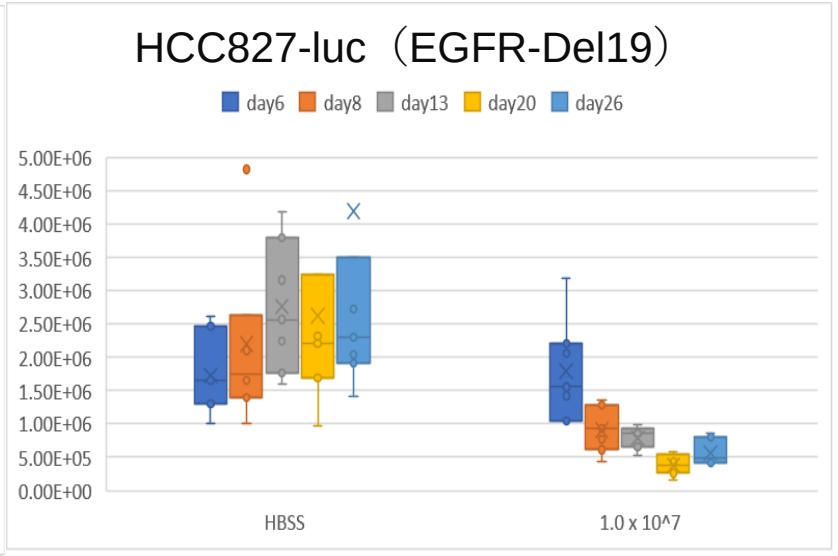
The cancer nodules were diffusely observed throughout the lung

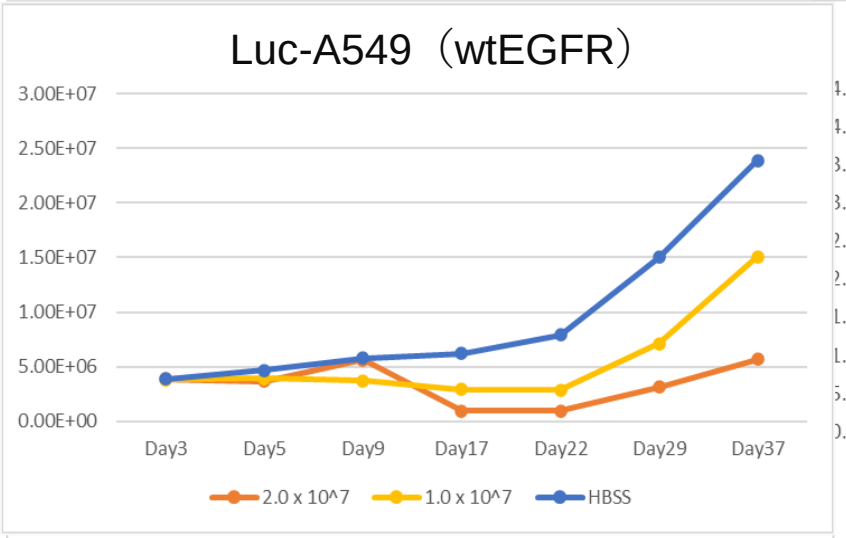
(Source) in-house data

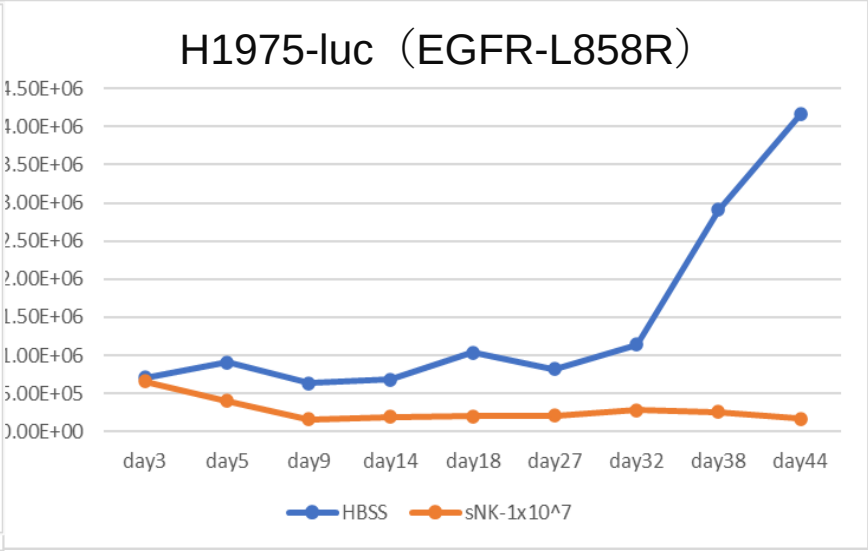
Anti-tumor Effect of eNK Cells in Tumor Bearing Mice (Lung)

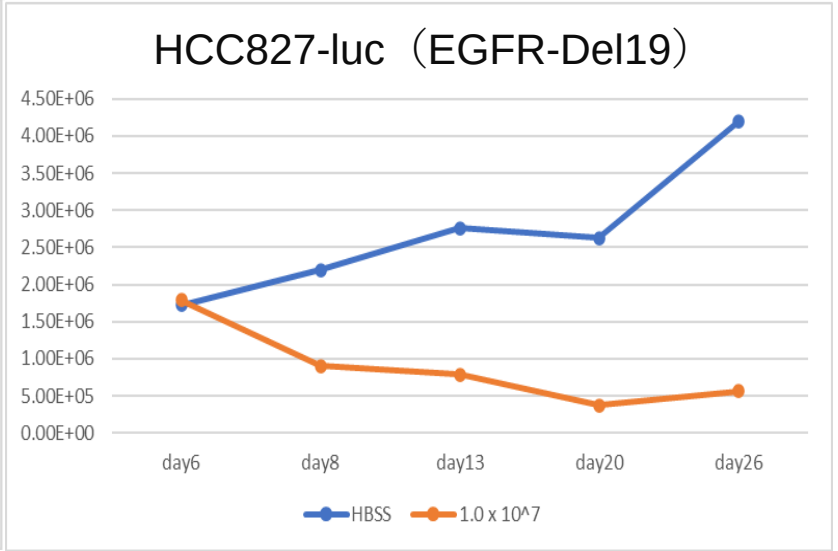








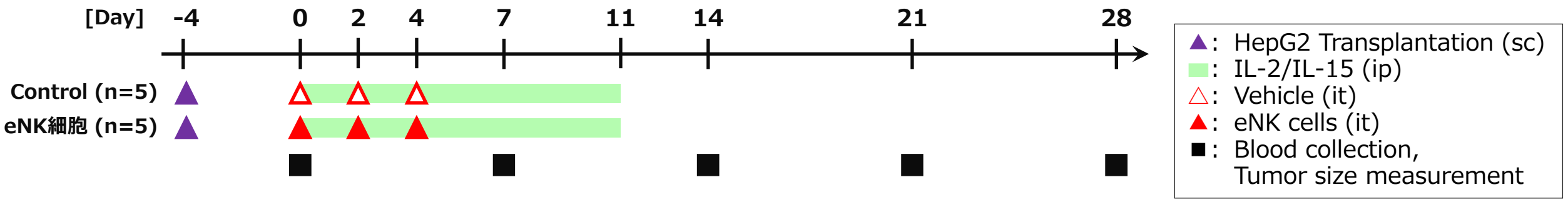


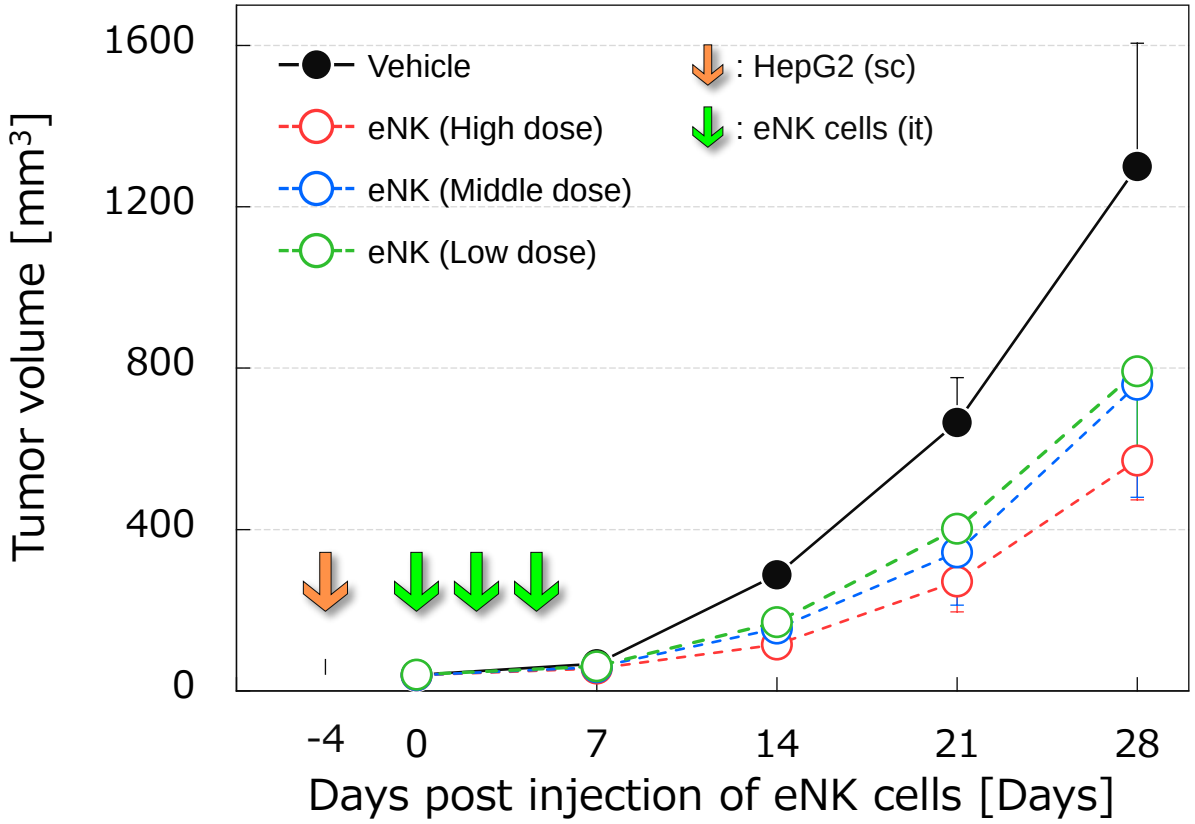


eNK can suppress the tumor growth (A549) or eliminate the tumor (H1975, HCC827)

（Source）in-house data

Anti-tumor Effect of eNK Cells in Tumor Bearing Mice *(Hepatocellular Carcinoma; HCC, sc)*





Intra-tumor injection of eNK cells suppressed tumor growth

(Source) in-house data

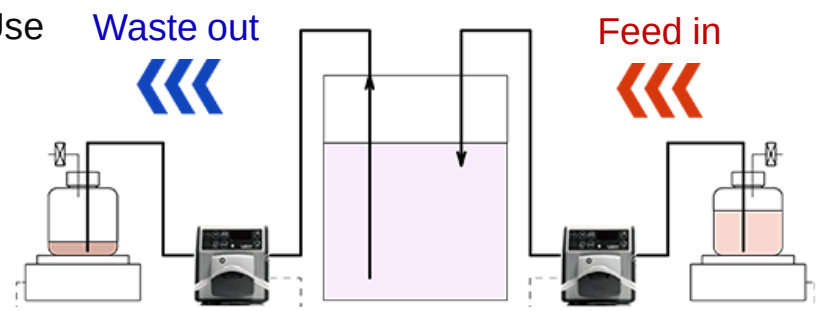
eNK Cell Production Method: Upstream Process

① Upstream Process: Preclinical scale 3D Perfusion Bioreactor System

iPSC Sphere Formation → **HPC Differentiation Induction** → **NK cell Differentiation Induction** → **NK cell Expansion**

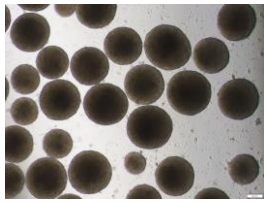
500mL Single Use Bioreactor

Perfusion System Based Automatic Medium exchange

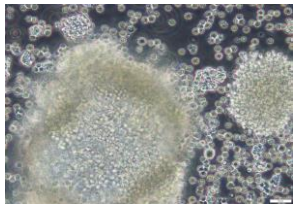


3L Single Use Bioreactor

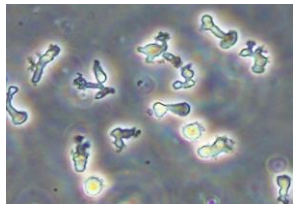
＊Illustration of Perfusion System (adopted from homepage of SATAKE MultiMix)



iPSC Sphere



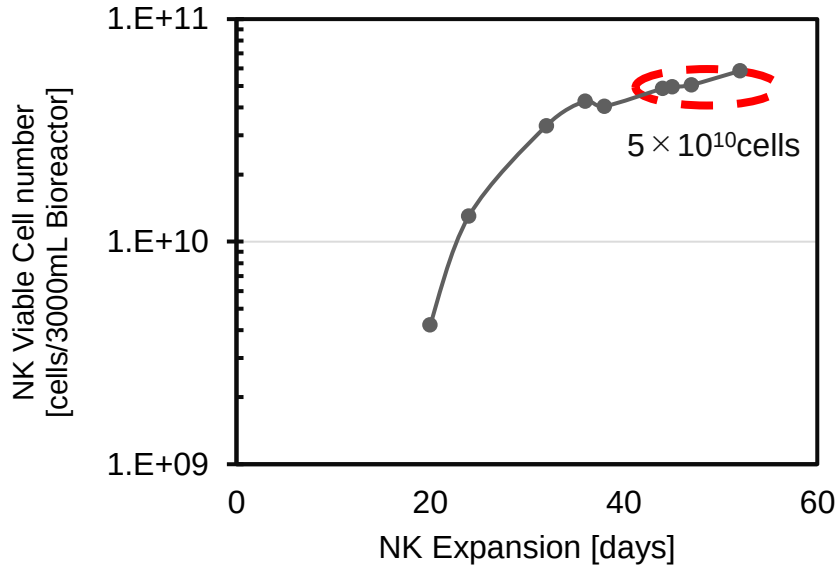
HPC



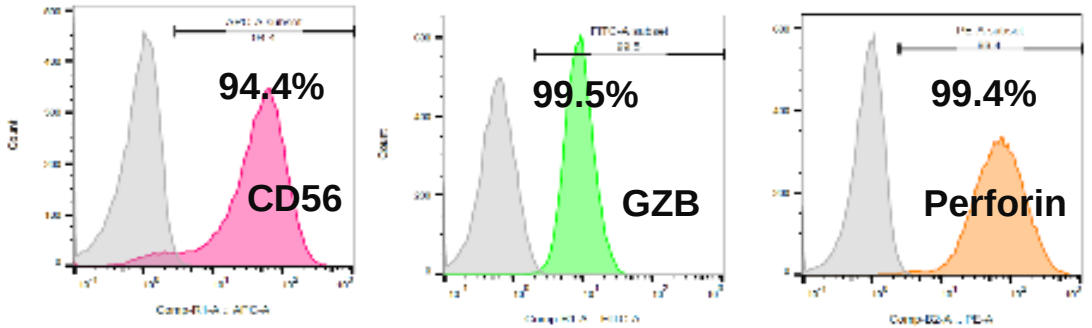
NK cell

Mass production using 3L Bioreactor

Production of 100 billion NK cells using two 3L-bioreactors



Flow Cytometric Analysis of NK Cell



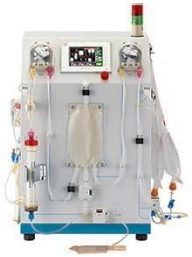
(Source) in-house data

eNK Cell Production Method: Downstream Process

② Downstream Process: Cell Harvest, Aseptic Filling and Finish, Cryopreservation

Upstream Process → **Cell Harvest: Concentrate・Wash Cryoprotectant Mixing** → **Aseptic Filling and Finish** → **Cryopreservation** → **Storage Cold chain**

3L Single Use Bioreactor



Closed system: Automatic Cell Washing Concentration System

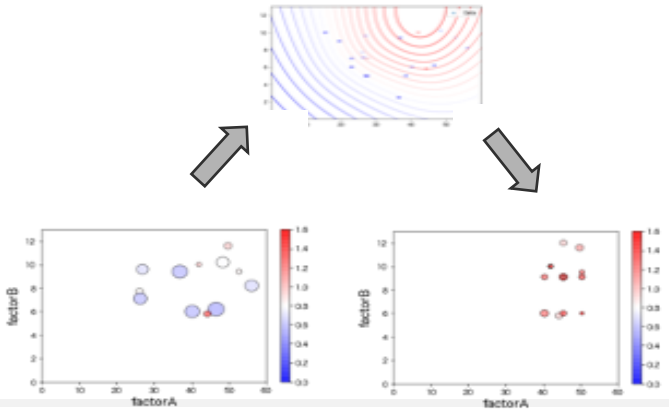
Cryoprotectant Design (Healios KK Original)

Automatic Filling and Finish Machine (Healios KK Original)

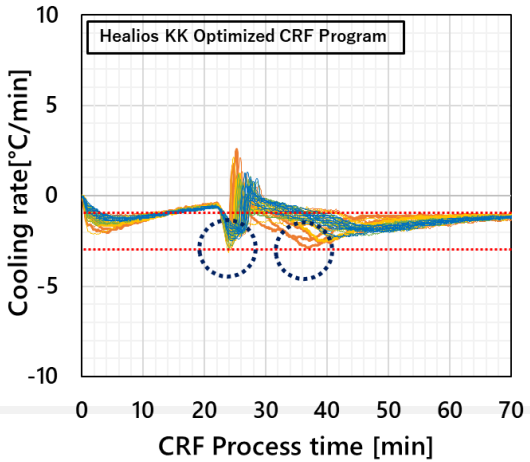
Controlled Rate Freezer

Storage: Liquid Nitrogen Tank

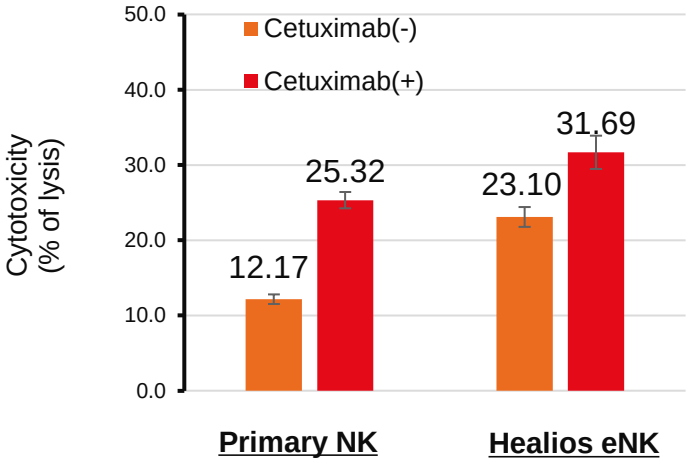
Composition Optimization: Design of Experiments by AI Analysis



CRF Program Optimization



LDH assay(A549)



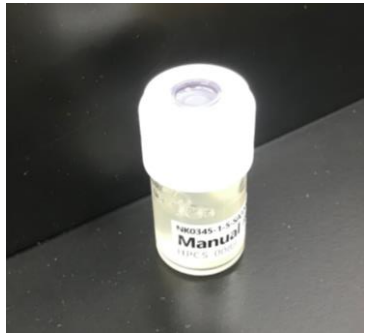
In this process, cryopreserved samples show high cytotoxicity

(Source) in-house data

iPSC-Derived Product Manufacturing: A New and Dedicated GMP Facility

To control the schedule and quality of clinical trial product manufacturing,
Healios established a new facility for cell processing and manufacturing (CPC) in Kobe, Japan.

Proprietary, automated 3D perfusion bioreactor system for eNK production



3D manufactured eNK finished product

Market Leading Range of Functional Enhancements

	Healios		A社			B社	C社
Enhanced Function	**HLCN061 (eNK)**	**HLS CAR eNK**	**iPS cell ①**	**iPS cell ②**	**iPS cell ③**	**iPS cell A**	**ー**
Migration into solid tumor	✓	✓					
Recruitment of host immune cell	✓	✓					
Enhancement of NK cell function and survival	✓	✓		✓	✓	✓	✓
CAR	-	✓		✓	✓	✓	✓
Antibody Dependent Cell Cytotoxicity	✓	✓	✓	✓	✓	?	?
Clinical Stage	-	-	P1	-	-	-	-

HLCN061 (eNK) is expected to have an advantageous effect by enhancing tumor infiltration and immune cell recruitment through the introduction of chemokine receptor A and chemokine B

（Source） Adapted by Healios from public information

Summary: iPSC eNK Immuno-Oncology

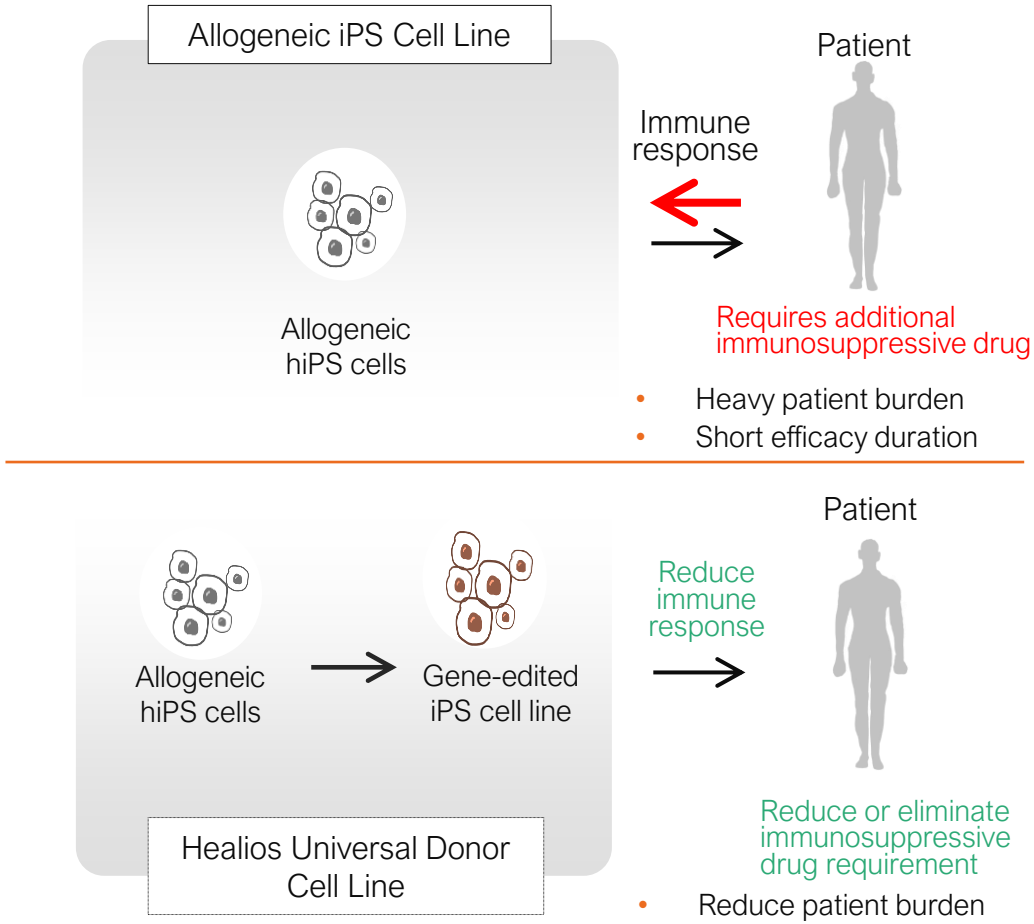
- **Unique Approach**: A gene engineered iPSC-NK cell platform designed not only with enhanced cytotoxicity but also with recruitment and trafficking properties
- **Initial Target Indications**: Lung cancer, liver cancer, other non-disclosed
- Promising *in vitro* and *in vivo* evidence
- Robust and advanced manufacturing processes and infrastructure in place
- Multiple strong collaborations
- Near-term regulatory milestones: Pre-IND: 2022, IND: 2024

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”

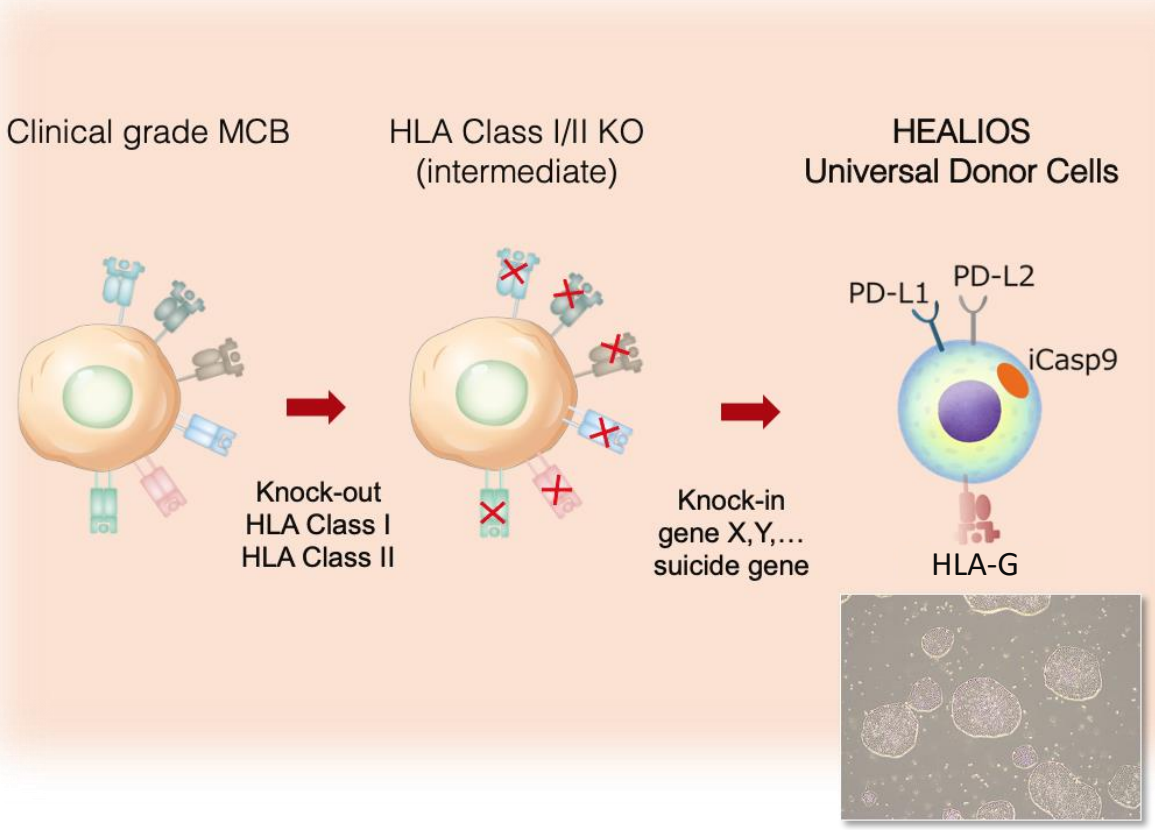


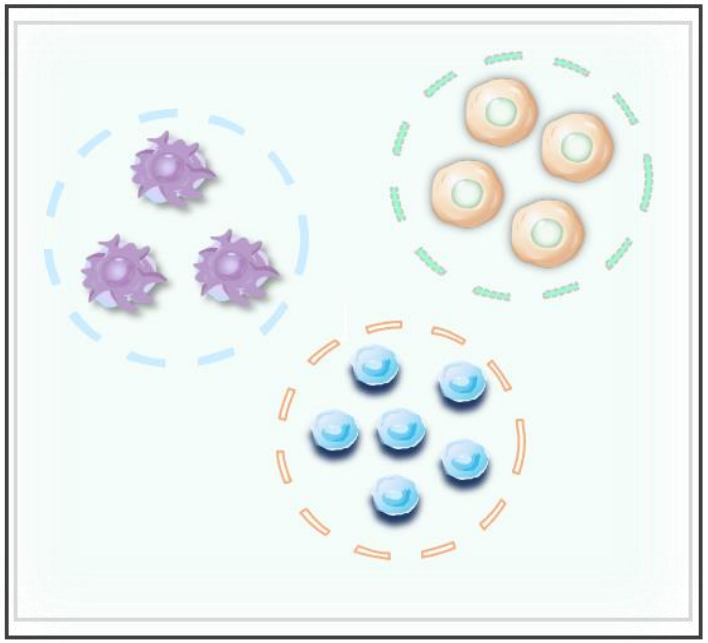
Targeted cell programming through gene-editing

- 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.).
- Active discussions with several companies and academic institutions in relation to use with various therapeutic candidates.

Hypo-immune UDC: Engineered Genetic Profile

Gene Editing Procedure for Healios UDC





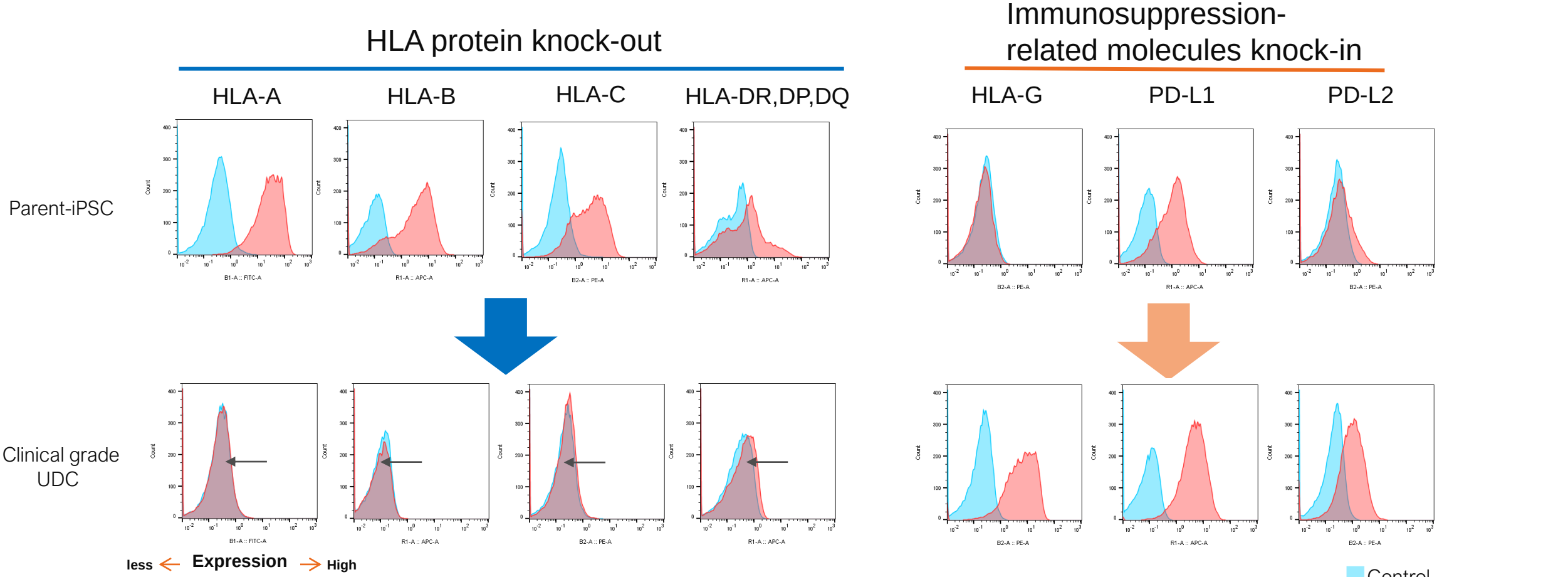
- Off-the-shelf, scalable and cost-efficient
- Address broadest population with single product
- Enhanced level and duration of efficacy

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

（Source）in-house data

Removal of Polymorphic HLAs and Addition of Immunosuppressive Genes

Results of gene editing in clinical grade UDC

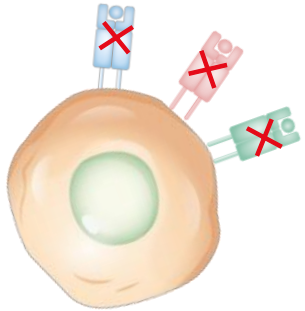


Post-gene editing disappearance of HLA proteins and enhanced expression of immunosuppression-related genes

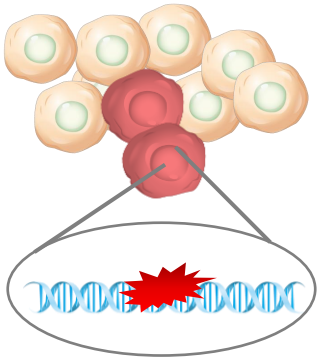
（Source）in-house data

UDC Production Process Checklist

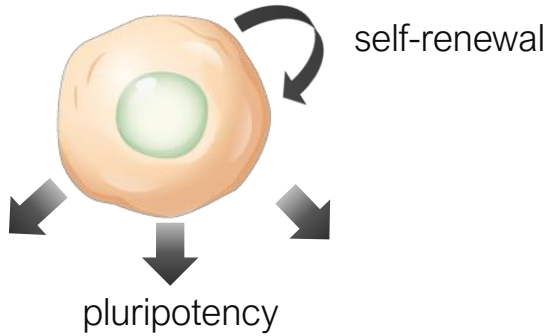
①Confirmation of gene editing



②Absence of malignant mutations



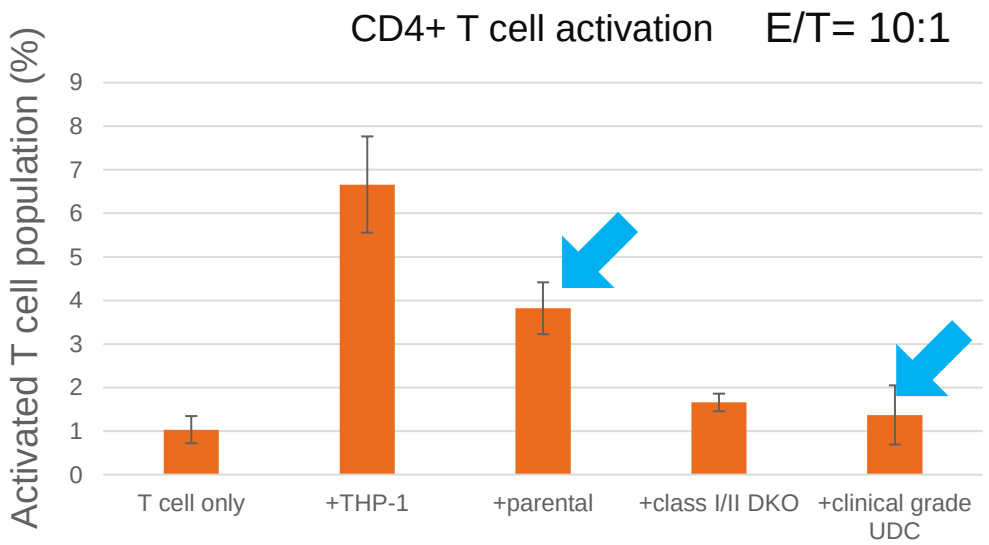
③ Retention of iPS cell properties

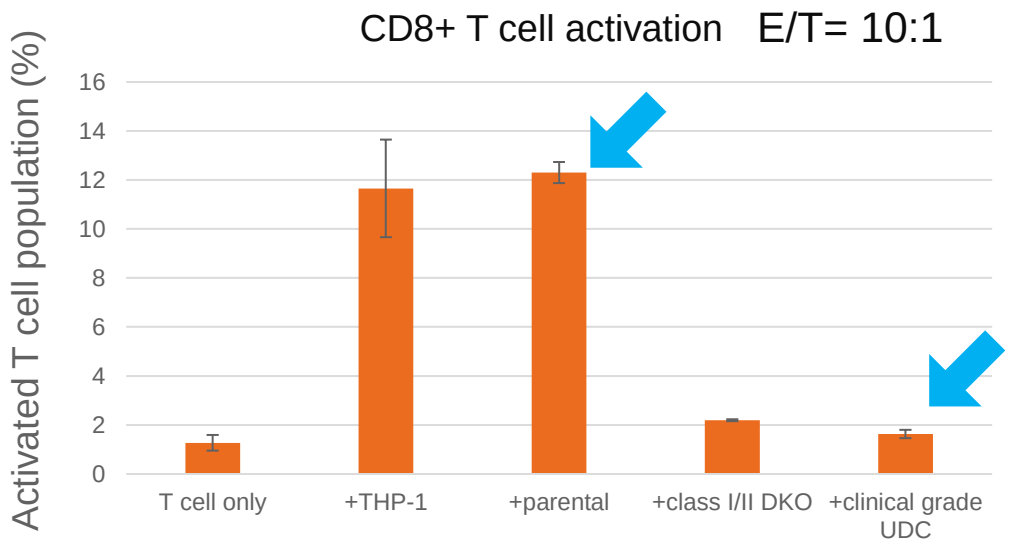


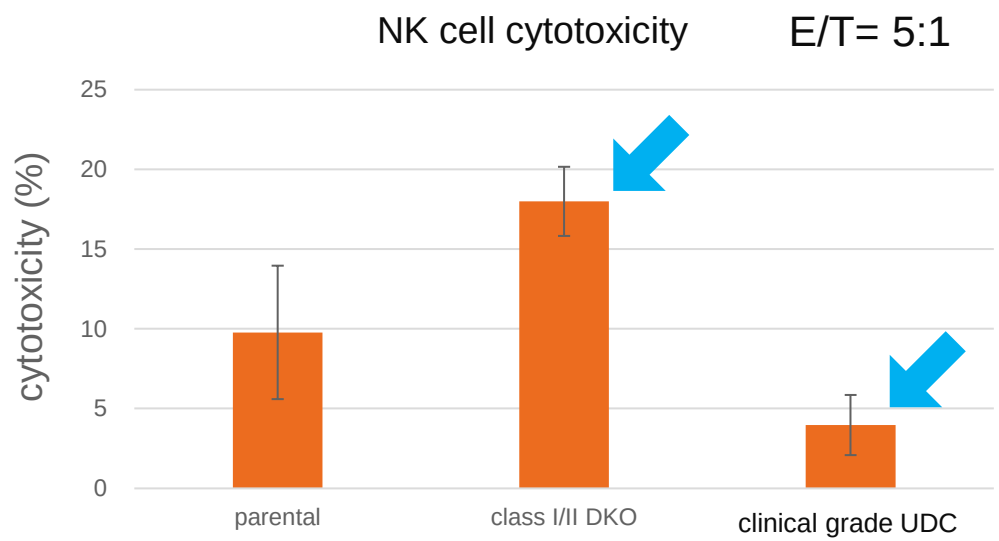
Quality check item	Contents
Confirmation of gene editing	Confirmation of target region sequence
Expression level of HLA proteins	Loss of HLA Class I expression
	Loss of HLA Class II expression
Transgene expression	Expression of immune suppression associated molecules
	Expression of suicide genes
Gene mutation	No off target issues
	Normal karyotype
	No cancer associated genes
Attribution	Sterility
	Endotoxin free
	Mycoplasma free
	Gene expression analyses (Comparison with the parent cell line)
	Expression of undifferentiated markers
	Pluripotency (three germ layer differentiation)
	Absence of immunogenicity
	Function of suicide genes

（Source）in-house data

Confirmation of Hypo-immunity



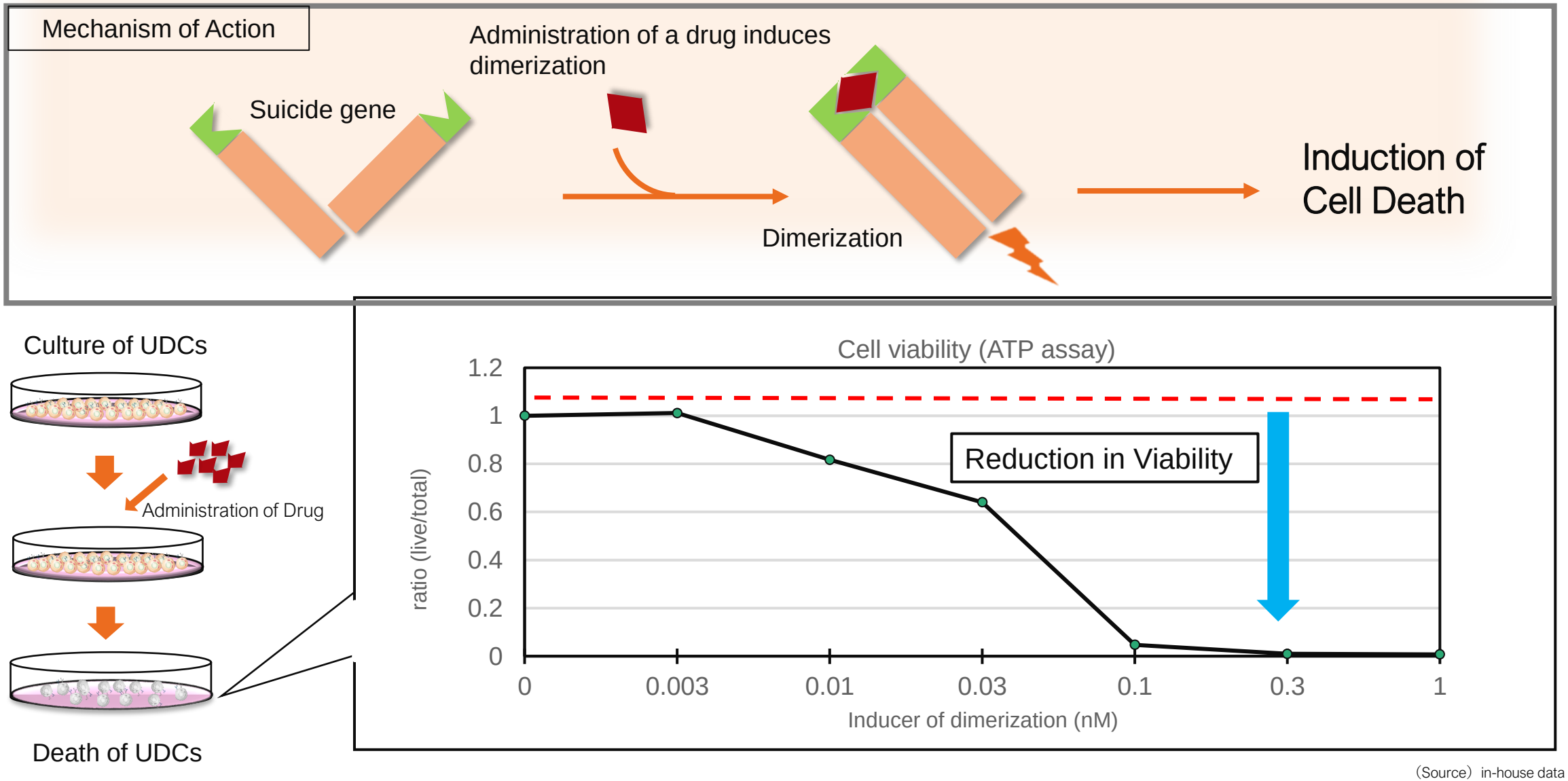




Clinical grade UDC did not show any activation of T or NK cells

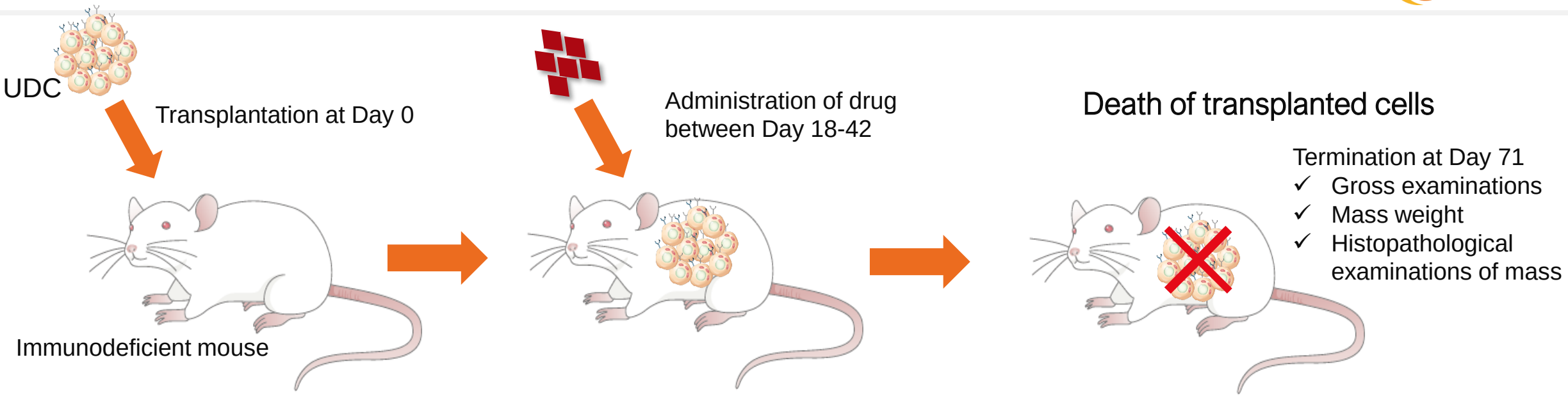
（Source）in-house data

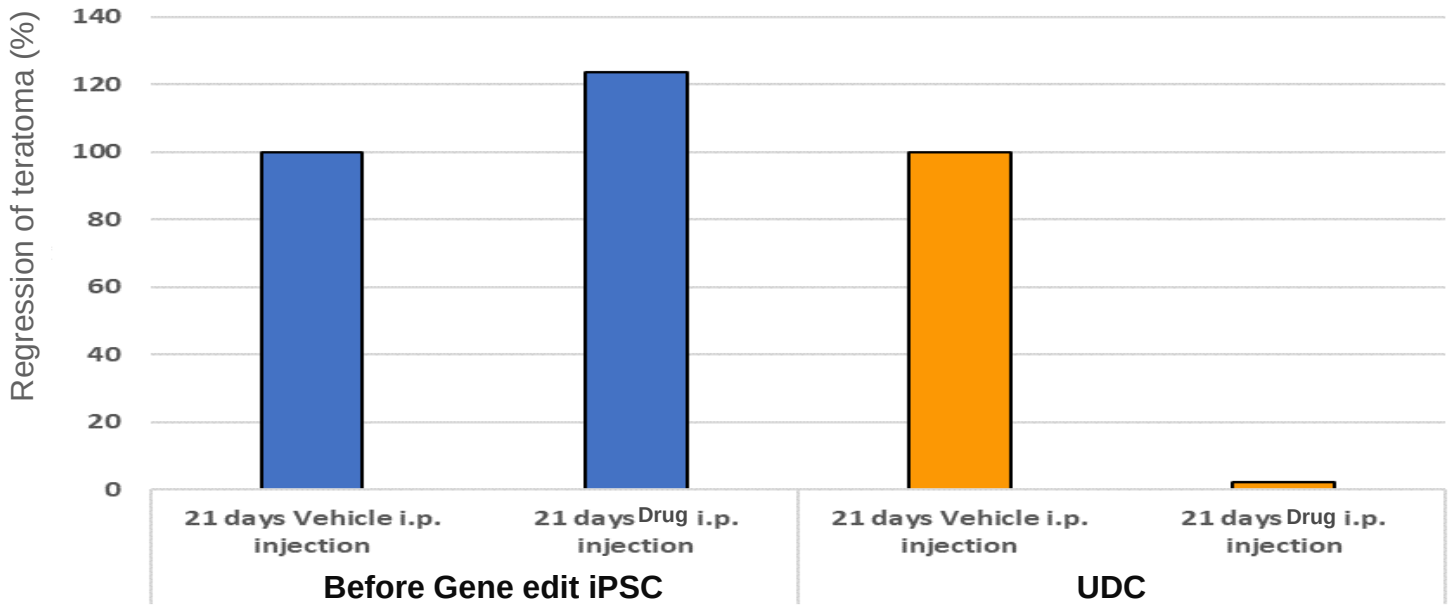
Evaluation of UDC Inducible Suicide Gene (In Vitro)



（Source）in-house data

Suicide Gene Function In Vivo

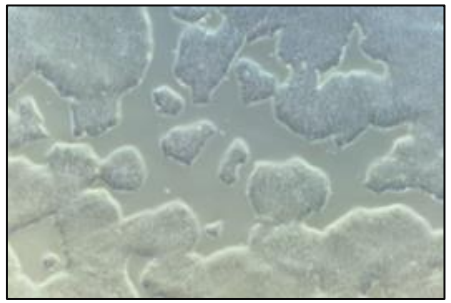




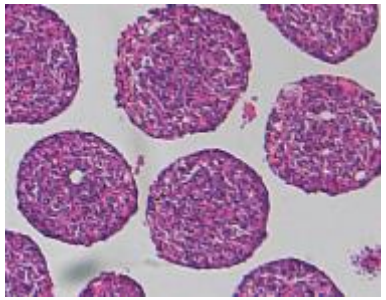
（Source）in-house data

Hypo-immune UDC: Examples Of Cell Therapies

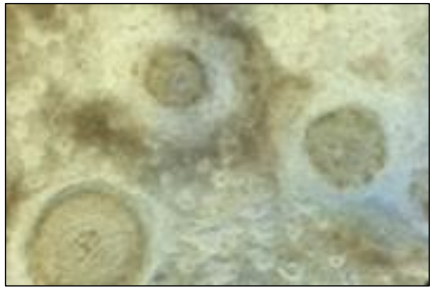
Universal Donor Cells (UDC)



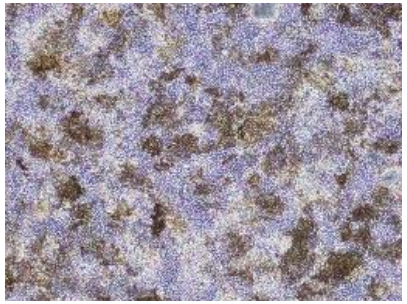
Pancreatic β cells



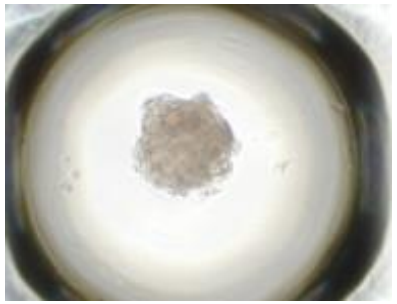
Photoreceptor cells



RPE cells



Liver buds



Successfully differentiated from UDCs

Future migration to UDC platform

（Source）in-house data and Joint research data

Conclusion

- Continued pioneering in cell therapy
- Uniquely positioned to leverage strong Japanese proficiencies
- Substantial infrastructure to support multiple programs across development stages
- Global strategy
  - Building a commercial organization to launch MultiStem® for ARDS & stroke in Japan
  - Accelerating innovative iPSC platform development for immuno-oncology & cell replacement therapies
    - Focus on clinical development of engineered-NK (eNK) cells for solid tumors in Japan and US
    - Advancement of therapies derived from proprietary hypo-immune Universal Donor Cell (UDC) line
  - Continued investment in precision manufacturing capabilities and strengths in Japan to support future global supply

Committed to transforming the lives of patients by

creating, developing and commercializing cutting edge cell therapy technologies

Healios

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