FY2020 Financial Results

Company

HEALIOS K.K. (TSE 4593)

Date

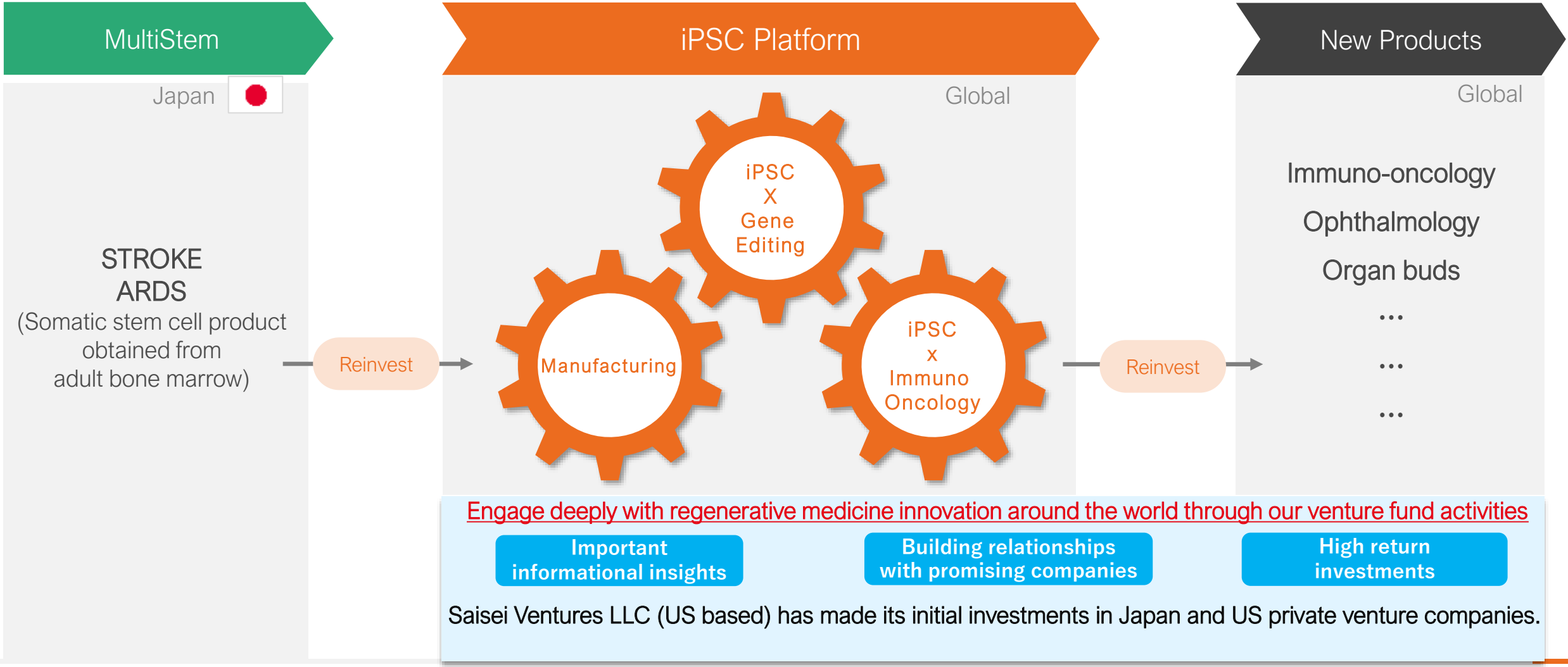
February 12, 2021

Hybrid Strategy

Update

Healios

- Generate near term profits in stroke and ARDS indications
- Reinvest profits in our world-leading engineered IPSC platform to create next generation therapies for the global market



Pipeline in Inflammatory Conditions, Immuno-oncology, and Replacement Therapies

Update

Healios

Inflammatory Conditions

Development Code	Indication	Country / Region	Pre-clinical test	Clinical trial (Regenerative medical products)	Preparation for application	Apply/ Approved	On Market	Progress status
HLCM051	Ischemic Stroke	Japan		Phase2/3		SAKIGAKE Designation System		Patient enrollment progress exceeds 90%
	ARDS	Japan		Phase2		Orphan regenerative medicine product		Patient enrollment progress exceeds 90%

Immuno-Oncology

Development Code	Indication	Country / Region	Pre-clinical test	Phase 1 trial	Phase 2 trial	Phase 3 trial	Preparation for application	Apply/ Approved	On Market	Progress status
HLCN061	Solid Tumors	Japan US/EU	→							Research and development of genetically modified NK cells(*1) Joint research with the National Cancer Center Japan

Replacement Therapies

Development Code	Indication	Country / Region	Pre-clinical test	Phase 1 trial	Phase 2 trial	Phase 3 trial	Preparation for application	Apply/ Approved	On Market	Progress status
HLCR011	Wet AMD	Japan	→							Undergoing preparation for clinical trial Joint development with Sumitomo Dainippon Pharma
HLCR012	Dry AMD	US/EU	→							
HLCL041	Metabolic Liver Disease	Japan	→							Joint research with Yokohama City University

*1) NK Cells: Natural Killer Cells

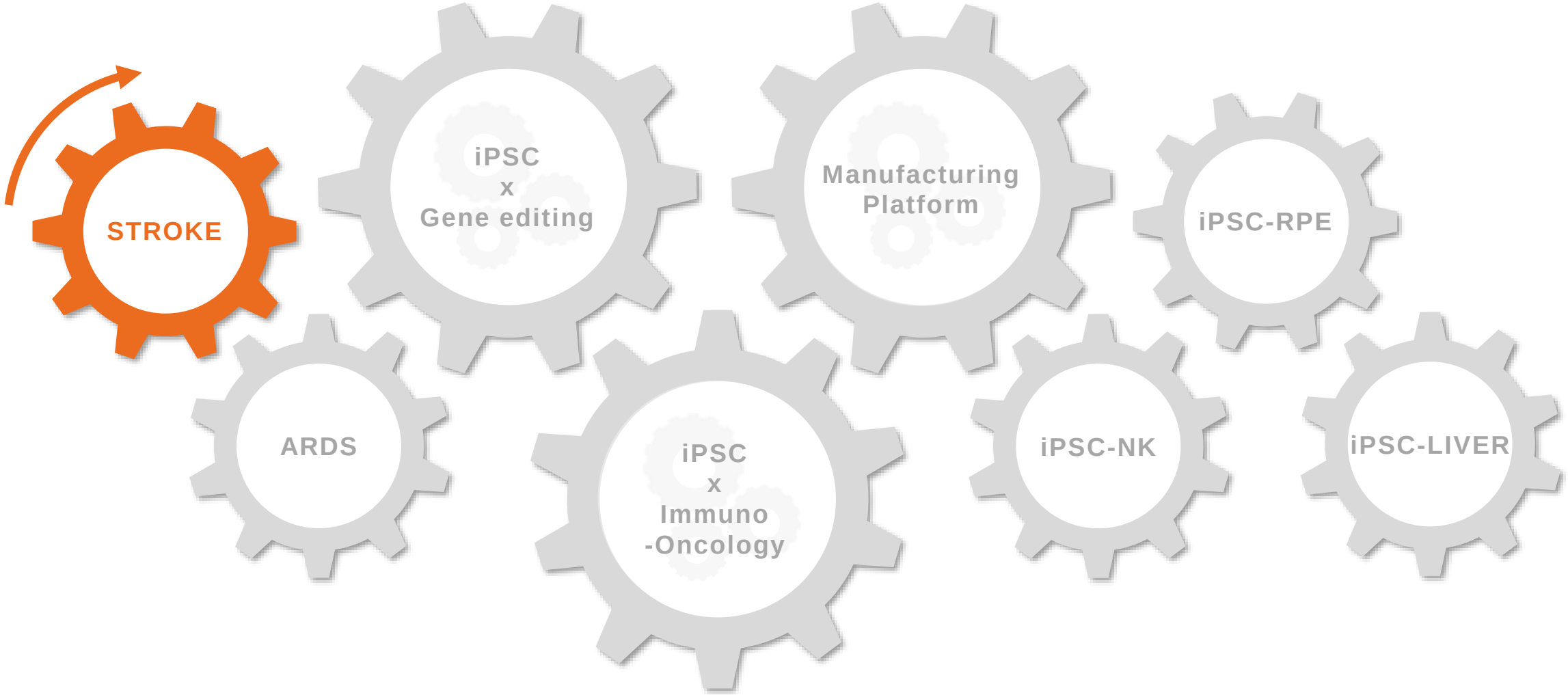
Preparation in advance of potential approval applications

① Basic business agreement with SPLine Corporation※ regarding the sale of pharmaceuticals

※SPLine Corporation is a wholly-owned subsidiary of MEDIPAL HOLDINGS CORPORATION ("MEDIPAL"). The MEDIPAL Group has storage facilities and delivery systems capable of distributing specialty drugs, including regenerative medicine products. Its notable achievements in cell medicine distribution include establishing the first wholesale distribution system in Japan for cells pharmaceuticals.

② Healios applied for and obtained “GYOSHA Code” from the Ministry of Health, Labor and Welfare.

HLCM051 Stroke



HLCM051 Stroke: TREASURE Study Ongoing

Update

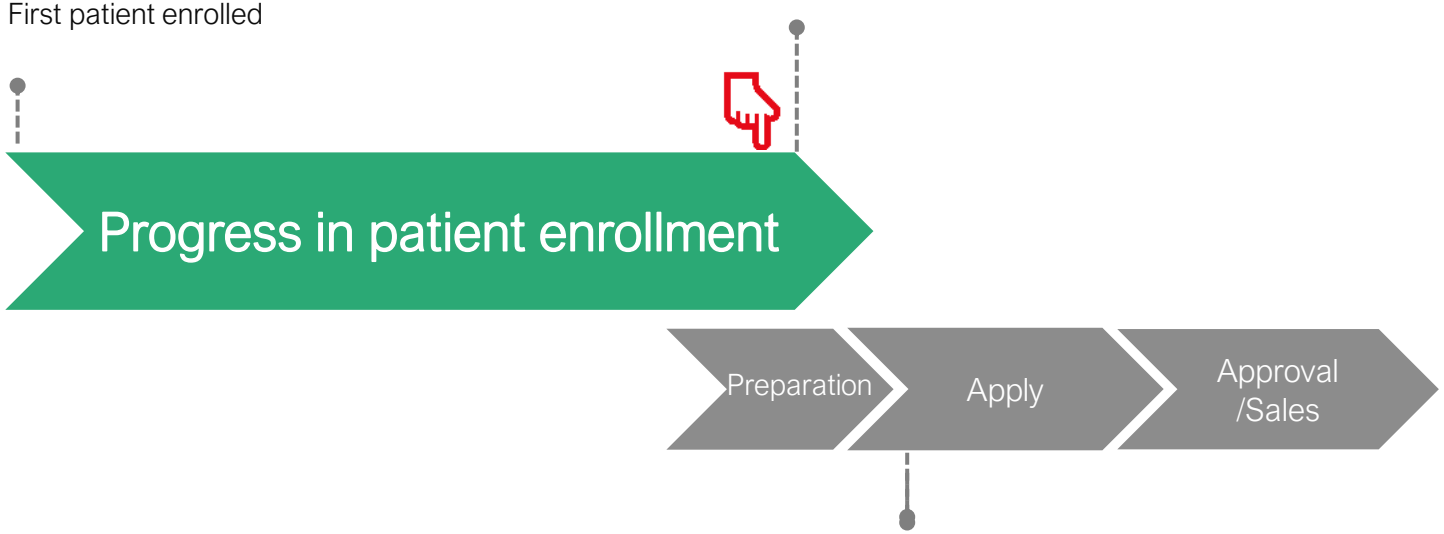
Healios

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

Development Plan

Due to the increase in COVID-19 infections in Japan, recent patient enrollment progress has been slower than expected. The current enrollment progress exceeds 90%.

November 2017
First patient enrolled



The approval period may be shortened from 12 months to 6 months by the SAKIGAKE Designation System

Overview of TREASURE study

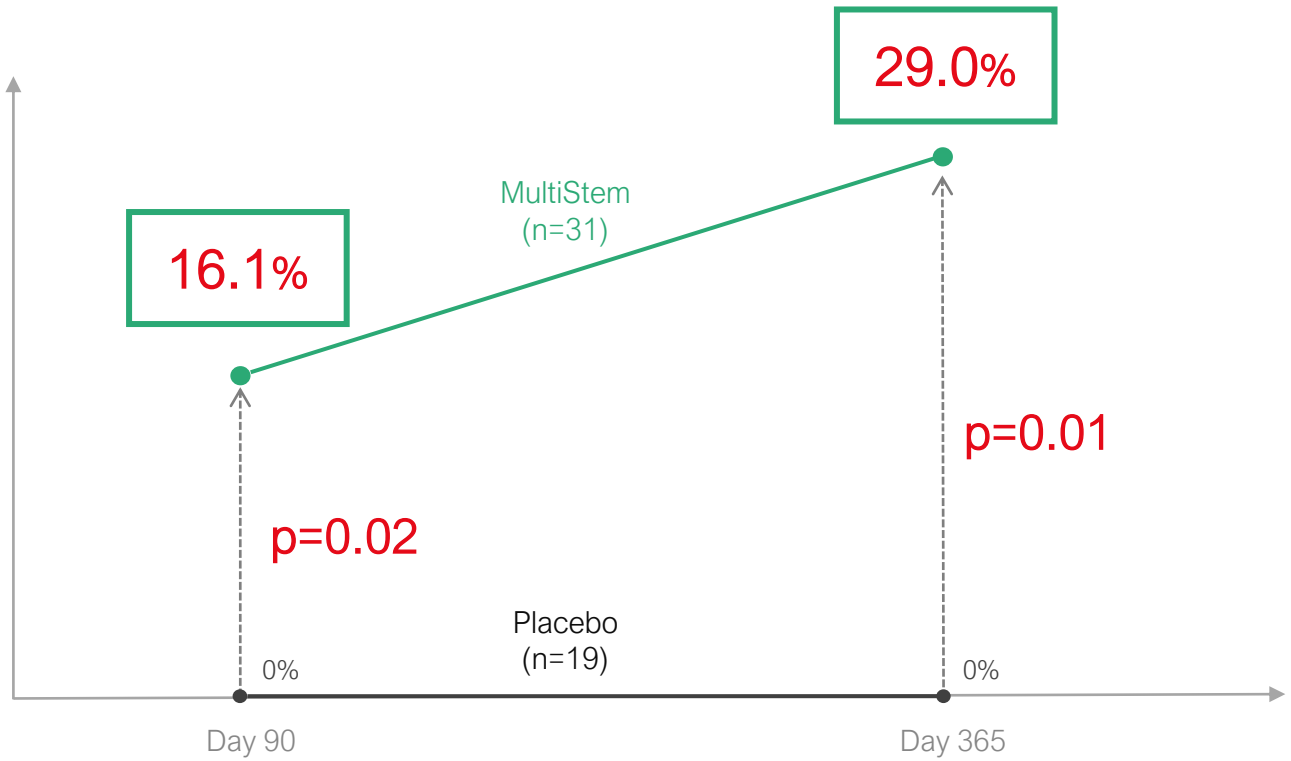
Trial	Placebo-Controlled, Double-Blind, Phase 2/3 Efficacy and Safety Trial of HLCM051 (MultiStem®) in Patients With Ischemic Stroke （TREASURE study）
Subjects	Ischemic stroke within 18 to 36 hours
Conditions	Placebo-Controlled, Double-Blind
Enrollment	220 (HLCM051 [n=110], placebo [n=110], randomized)
Primary Endpoints	Proportion of subjects with an excellent outcome defined by functional assessments [Time Frame: Day 90]

- “Excellent Outcome” is defined as achieving mRS ≤1, NIHSS ≤1, and BI ≥95. mRS, NIHSS, and BI are the three major indices of functional assessment for stroke patients.

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

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

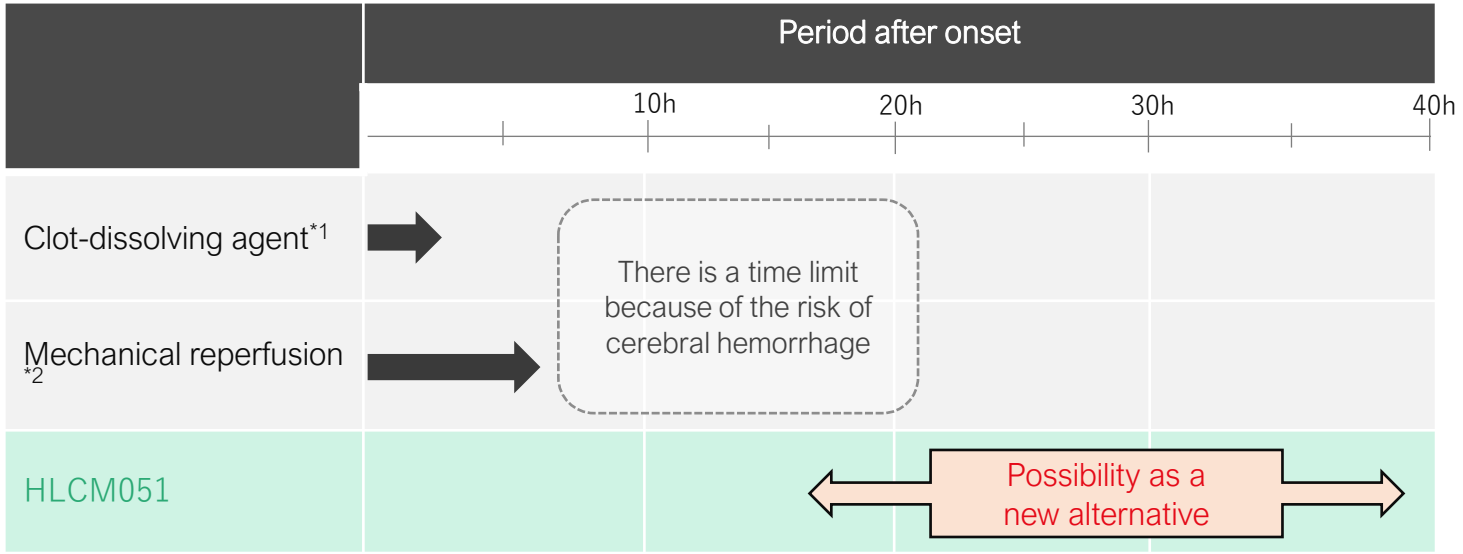
Trial	The placebo-controlled double-blind Phase 2 study conducted by Athersys in the US and the UK （MASTERS study)
Subjects	Administered MultiStem or Placebo within 36 hours of the onset of stroke
Endpoint	Proportion of subjects with an Excellent Outcome on Day 90 and Day 365

*<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 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

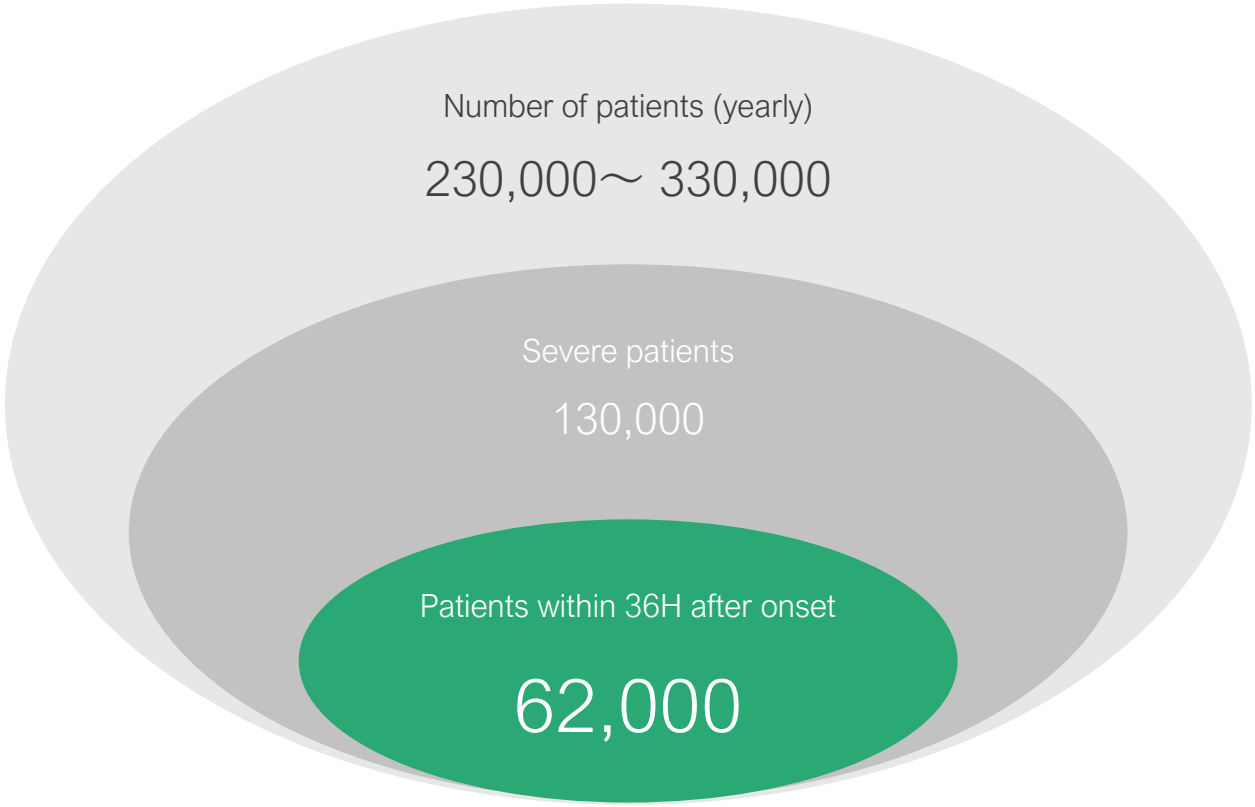
Ischemic stroke, which represents the most common form of stroke (70 - 75% of cases in Japan), is caused by a blockage of blood flow in the brain that cuts off the supply of oxygen and nutrients, resulting in tissue loss.

(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.

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)

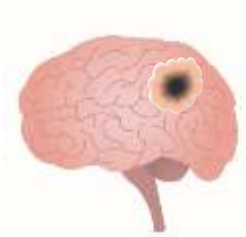
Severe patients （atherothrombotic and cardiogenic cerebral infarction)

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.

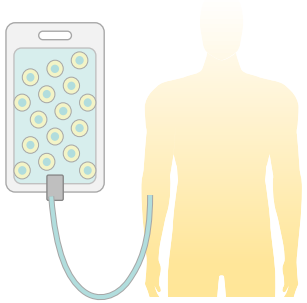
HLCM051 Stroke: Mechanism of HLCM051 Treatment

Stroke-induced neuronal damage

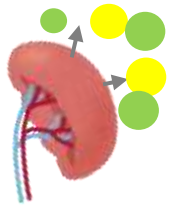


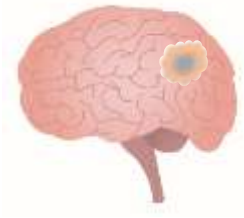
Primary Damage

With HLCM051



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



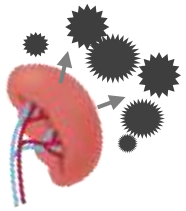


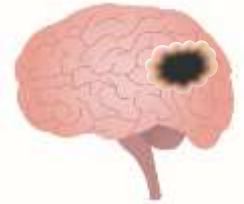
Attenuate neuronal damage in the acute phase of stroke caused by inflammatory cells

Secondary Damage mitigation

Without HLCM051

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



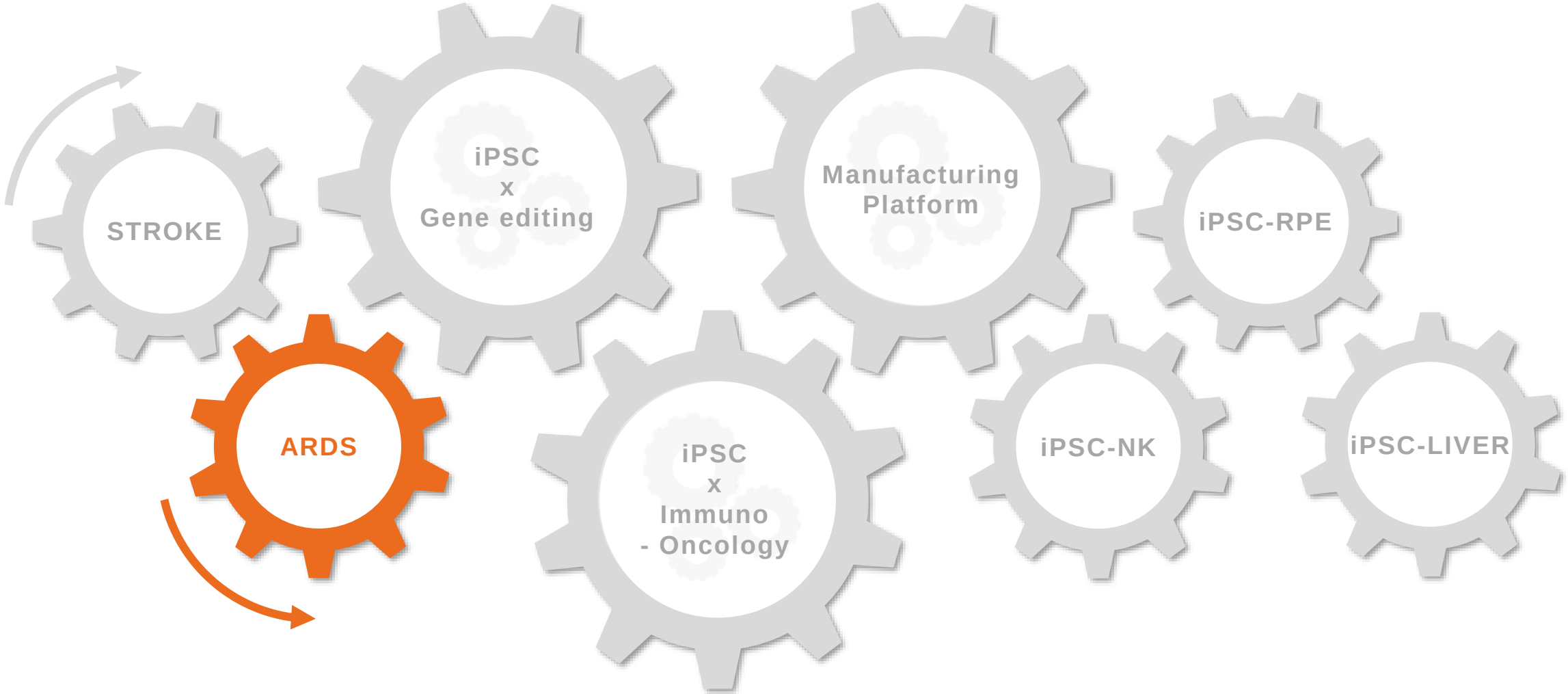


Neuronal damage exacerbated by inflammatory chemokines/cytokines
Inflammatory cells are released from the spleen and exacerbate the neuronal damage of the ischemic site.

Secondary Damage

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

HLCM051 ARDS



HLCM051 ARDS: ONE-BRIDGE Study Ongoing

Update

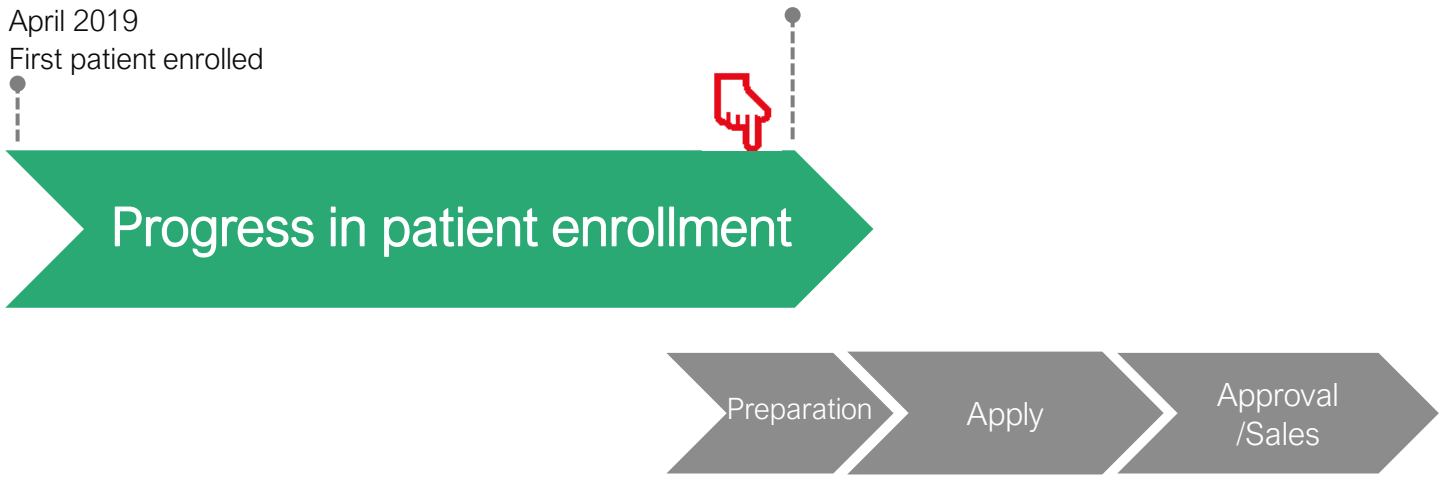
Healios

Ongoing Phase 2 trial for patients with pneumonia induced ARDS in Japan (ONE-BRIDGE study)

Cohort for COVID-19 induced ARDS patients was initiated and full enrollment was completed in August 2020

Development Plan

Due to the increase in COVID-19 infections in Japan, recent patient enrollment progress has been slower than expected. The current enrollment progress exceeds 90%.



Overview of ONE-BRIDGE study

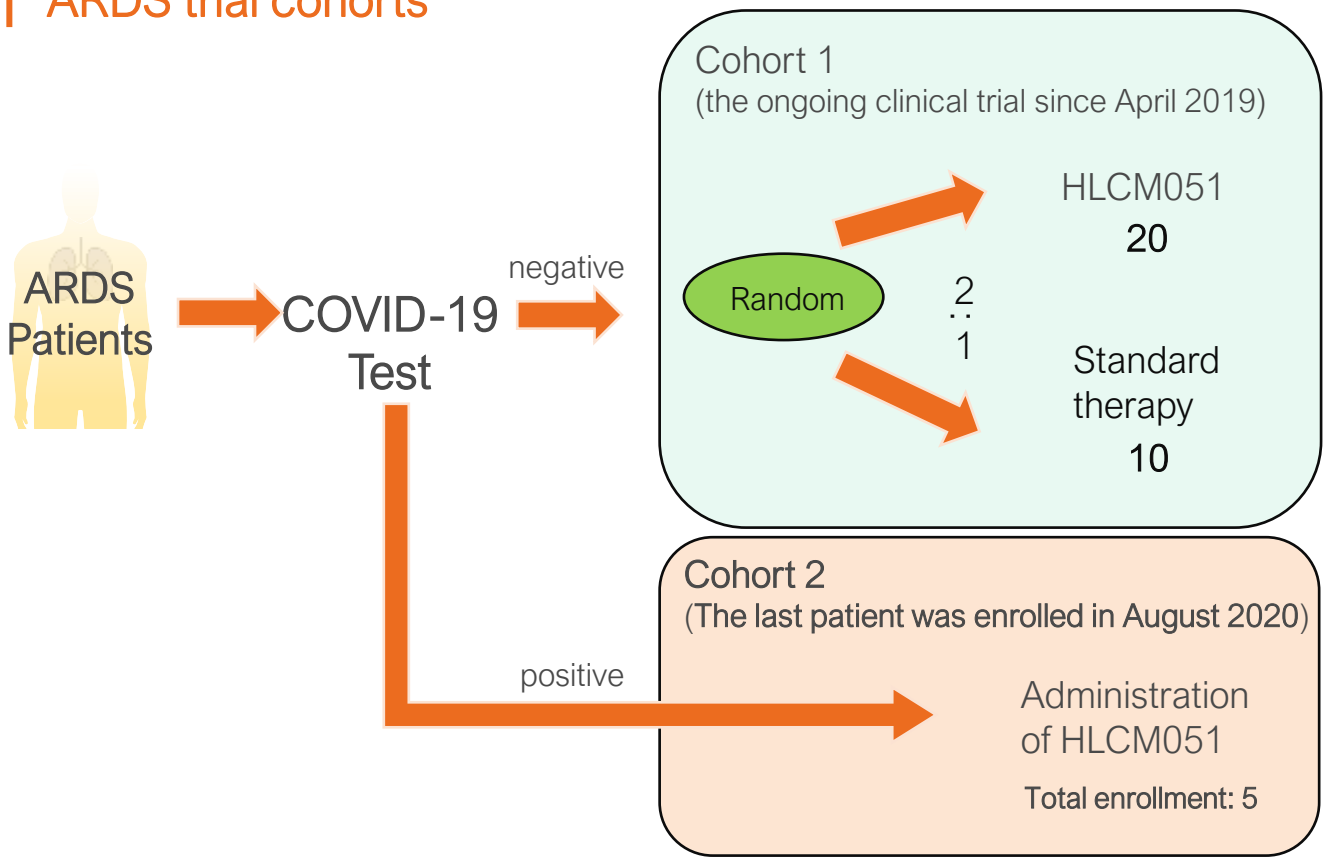
Clinical Trial	Efficacy and Safety Study of HLCM051 (MultiStem®) For Pneumonic Acute Respiratory Distress Syndrome (ONE-BRIDGE)
Subjects	Patients with pneumonia induced ARDS
Conditions	Open label, Standard therapy-controlled
Enrollment	30 (HLCM051: 20, Standard therapy: 10） Randomized
Primary Endpoint	The number of days out of 28 in which a ventilator was not used for the patient (i.e. ventilator free days)

HLCM051 has been designated as an orphan regenerative medicine product for use in the treatment of ARDS.

HLCM051 ARDS: New Cohort for COVID-19 Induced ARDS Patients

The new group of patients with COVID-19 pneumonia (Cohort 2) is separated from the ongoing treatment group (Cohort 1). The addition of this COVID-19 cohort should not effect the originally planned clinical trial.

ARDS trial cohorts



Overview of the ARDS trial

	Cohort1	Cohort 2
Initiation of the trial	April 2019	Started in April 2020 Enrollment completed in August 2020
Subjects	Patients with pneumonia induced ARDS	Patients with pneumonia-induced ARDS caused by COVID-19
Enrollment	30 (HLCM051: 20, Standard therapy: 10)	Approximately 5 (HLCM051: 5)
Objective	Efficacy and safety evaluation	Safety evaluation

Cohort 2 was conducted at more than 15 facilities in the ONE-BRIDGE trial

HLCM051 ARDS: About Acute Respiratory Distress Syndrome (ARDS)

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

About ARDS

Acute Respiratory Distress Syndrome (ARDS) is **a general term for the symptoms of acute respiratory failure** suddenly occurring in all seriously ill patients. The major causes are severe pneumonia, septicemia, trauma etc.
Inflammatory cells are activated in response to these diseases or injuries, **causing damage to the tissue of the lungs**. As a result, water accumulates in the lungs, leading to acute respiratory failure.

（Source）Athersys

Typically, ARDS is said to occur within 24 to 48 hours of the onset of the illness or injury that caused it. **The mortality rate is approximately 30 to 58%*.**

(* ARDS treatment guideline 2016)

Current Treatment

Artificial respiration using an endotracheal tube or mask is used to treat for respiratory failure in an intensive care unit (ICU).
However, it is known that prolonged use of a ventilator worsens a patient's prognosis.

At present, **there are no therapeutic drugs** that can make a direct improvement to a patient's vital prognosis when ARDS develops.
There is demand for new treatments for ARDS that will lead to improvements in patients' symptoms and prognosis.

HLCM051 ARDS: Number of ARDS Patients

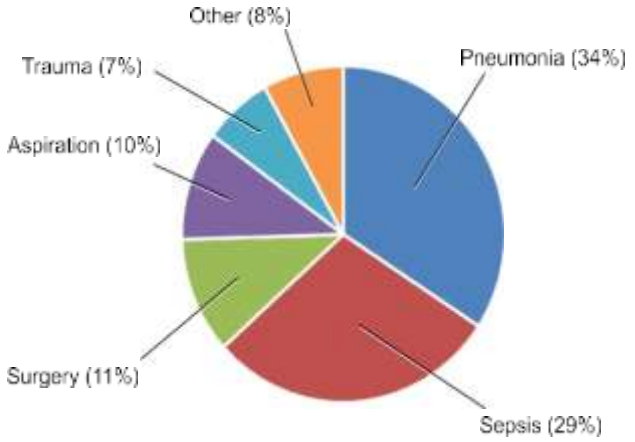
Number of ARDS patients in Japan estimated approximately **7,000～12,000 per year**

Approximately 1/3 of ARDS cases caused by pneumonia

Epidemiological data

Epidemiological data	Incidence rate	The estimated number of ARDS patients in Japan＊1
Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. Source：JAMA.2016; 315(8): 788-800	・0.42 cases per ICU bed ・10.4% of ICU admissions ・23.4% of patients requiring mechanical ventilation	11,937
Epidemiology of Acute Lung Injury (ALI) / Acute Respiratory Distress Syndrome (ARDS) in Chiba Prefecture Source：Journal of Japanese Association for Acute Medicine 2007; 18(6): 219-228	6.1 per 100,000 persons	7,320

Underlying diseases of ARDS



(Source) Respiratory Investigation; 55(4): 257-263

Approximately one-third of ARDS cases are caused by pneumonia. Seasonal infections may progress from pneumonia to ARDS. Some data indicate that approximately 71%[*2] of avian-origin influenza A (H7N9) infections result in ARDS.

＊1（Source）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（Source）Gao HN. et al., *N Engl J Med.* 2013 Jun 13;368(24):2277-85.

HLCM051 ARDS: Relationship between COVID-19 and ARDS

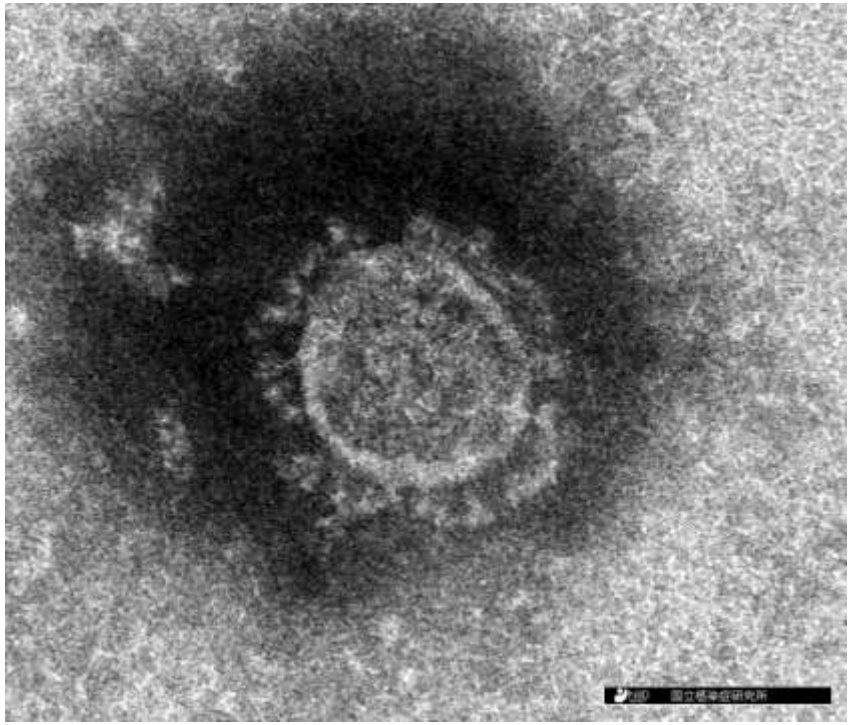
・In 2019, an outbreak of SARS-CoV-2 was first identified near Wuhan City, China, followed by a COVID-19 pandemic.

・According to the data published on the initial group of cases of the new coronavirus (COVID-19) in Wuhan, **31 to 41.8%** of hospitalized patients developed ARDS and ARDS complications were confirmed in **54 to 93% of fatal cases※1※2, indicating that ARDS is a major cause of mortality in COVID-19 patients.**

(Note) As the above two reports studied the initial group of patients, the incidence rate and mortality of ARDS patients is expected to fluctuate depending on the current situation in each country.

・Athersys, Inc., our partner company based in the United States, has initiated a Phase II/III clinical trial evaluating MultiStem for COVID-19 induced ARDS. On May 5, 2020 (local time), the first patient was enrolled in this trial.

Electron micrograph of SARS-CoV-2



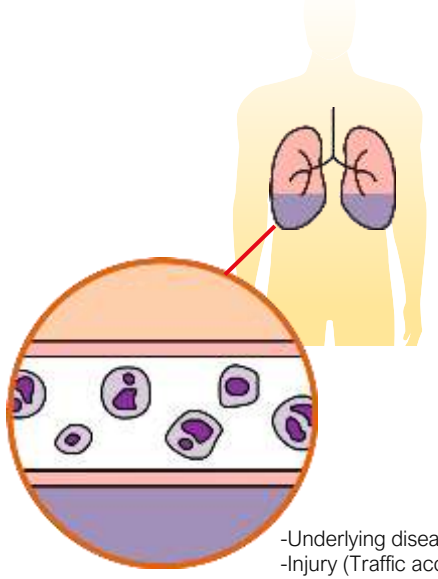
(Source) The National Institute of Infectious disease

(Source) *1 Zhou F, et al. Lancet. 2020 Mar 11. pii: S0140-6736(20)30566-3
(Source) *2 Wu C , et al. JAMA Intern Med. 2020 Mar 13. doi: 10.1001

HLCM051 ARDS: Pathological Process and HLCM051 Expected Mechanism of Action

Following intravenous administration after ARDS, HLCM051 accumulates in the lungs and controls excessive inflammation, protects damaged tissue and promotes restoration.

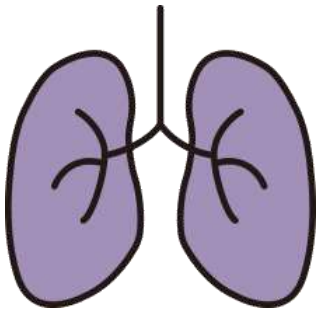
Inflammatory cells are released



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

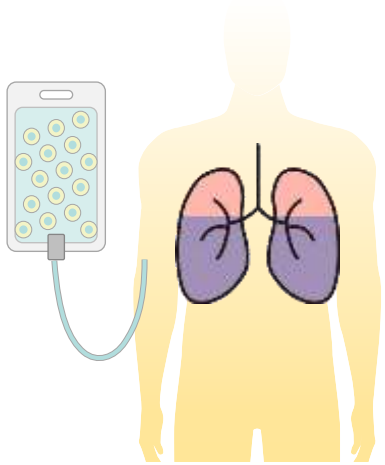
When the tissue is damaged, inflammatory cells are released in large quantities.

Inflammatory cells attack the lungs



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

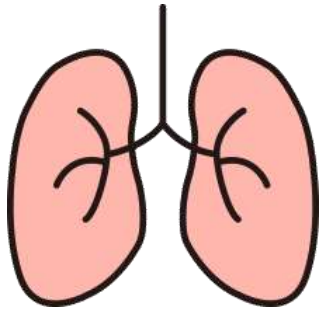
HLCM051 Administered



- 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.

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

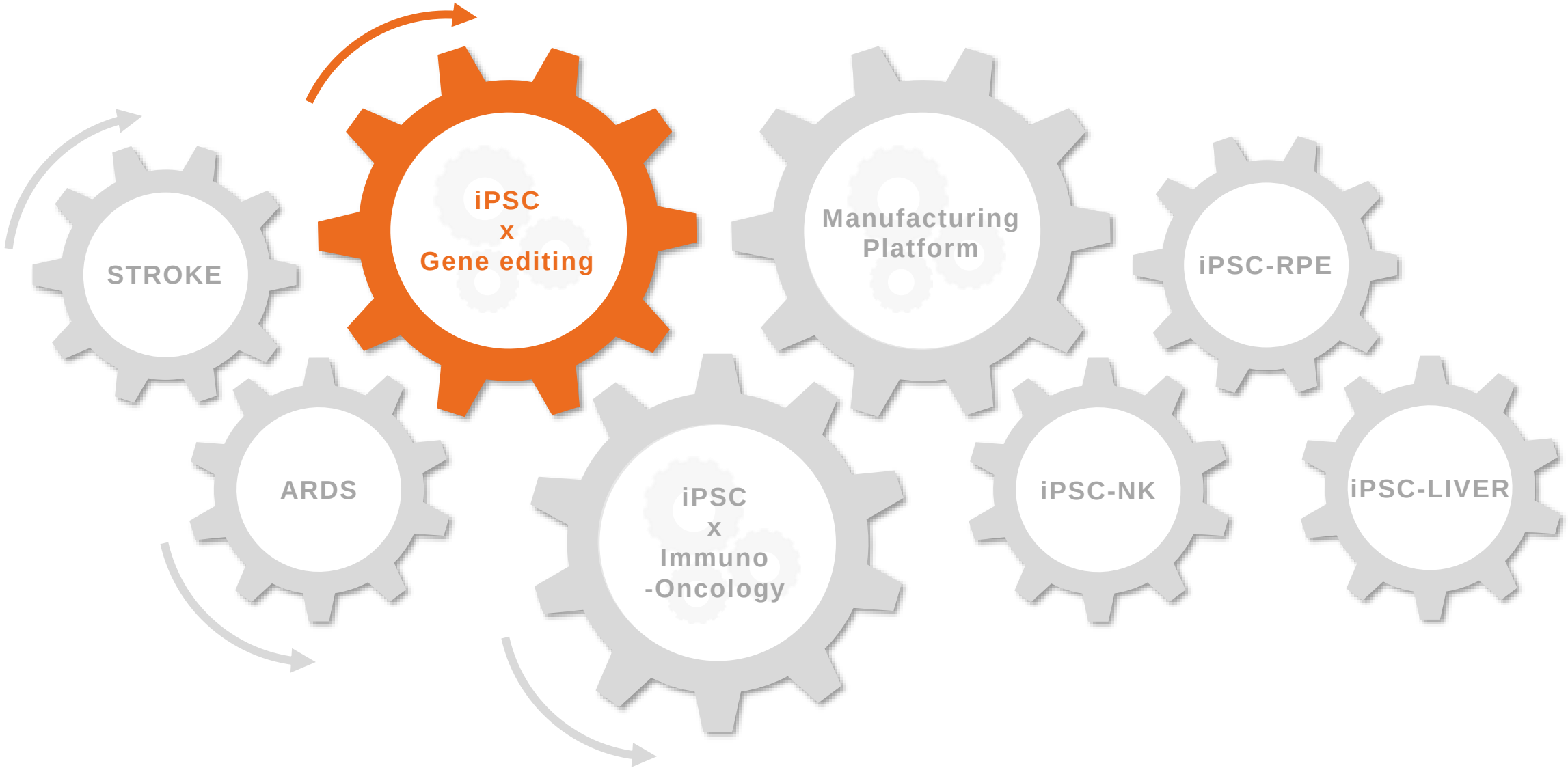
In the above analysis based on data obtained 90 days after administration, the mortality rate and the number of ventilator-free days (VFD) within a 28-day post-administration period et al. tended to improve in the MultiStem group compared with the placebo group. The results of the 1-year follow-up after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

（Source）Athersys

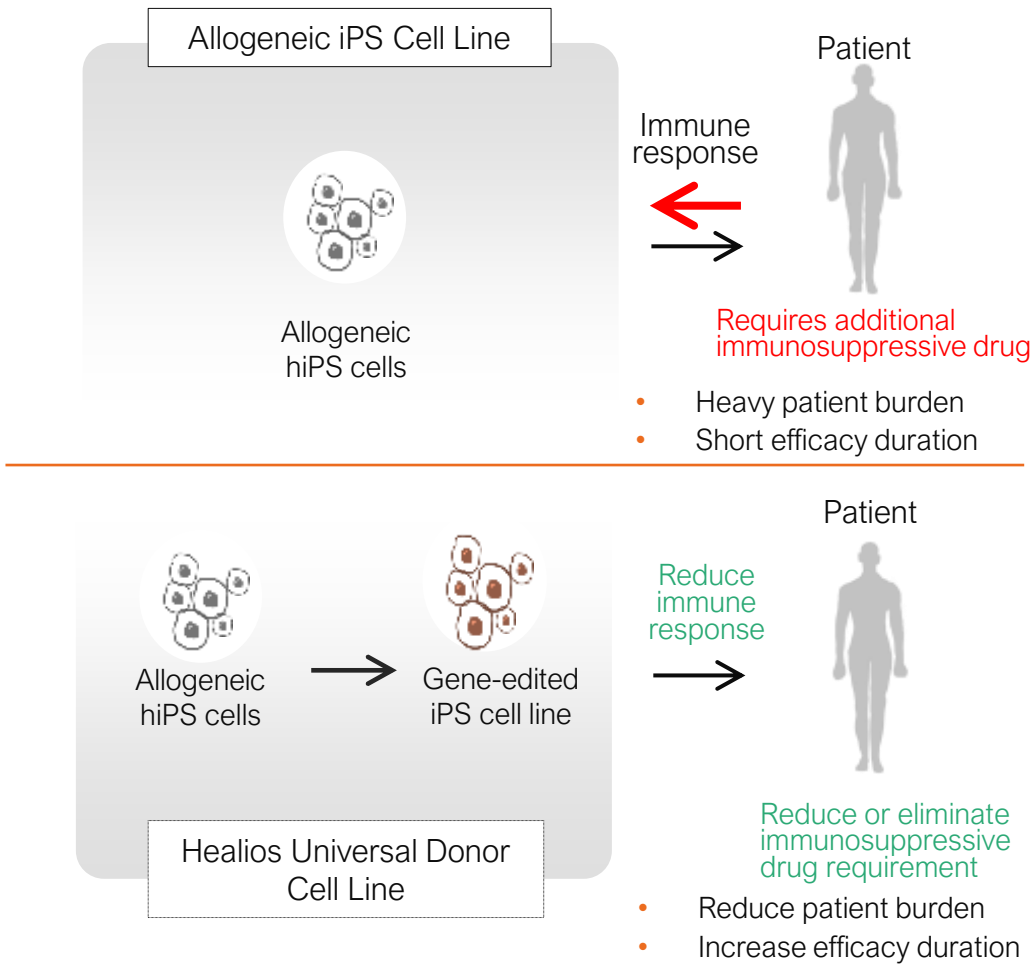
iPSC Platform



iPSC Platform

Update

World-leading engineered “universal” iPSC platform: “Universal Donor Cells” / “UDC”



Targeted cell programming through gene-editing

- In October 2020, Healios established a clinical grade line that can be clinically applied to humans in each of Japan, the United States and Europe.
- 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.

iPSC Platform

Update

Healios

	Autologous iPS cells	Allogeneic iPS/ES cells	UDC
Immune rejection	None	Occurs (Immunosuppressive drugs are required)	None
Manufacturing term	Several months to 1 year (Need to make from each patient)	Off-the-shelf (Single line)	Off-the-shelf (Single line of gene-edited cells)
Cost	Very high	Low	Low

iPSC Platform: Production of Eengineered, Universal iPS Cells

Update

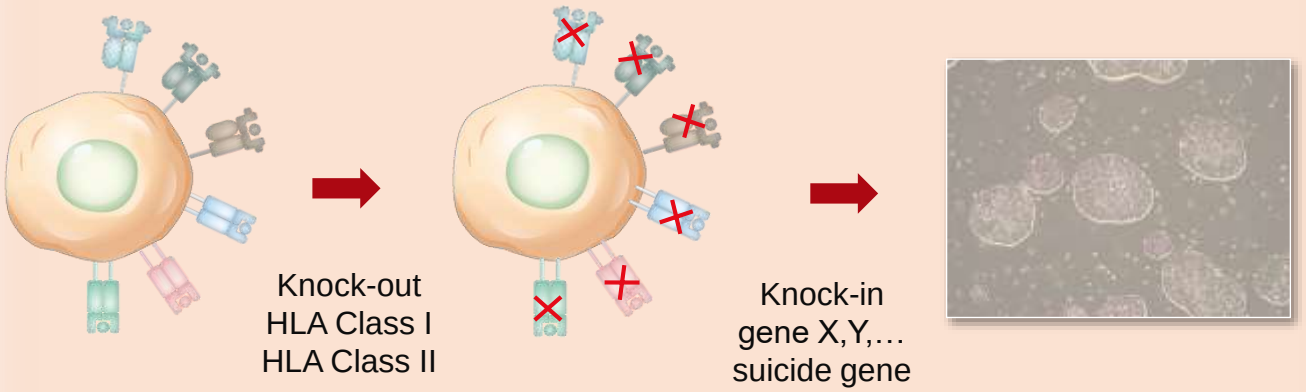
Healios

Engineered, universal iPS cells unlock full potential of iPSC therapies

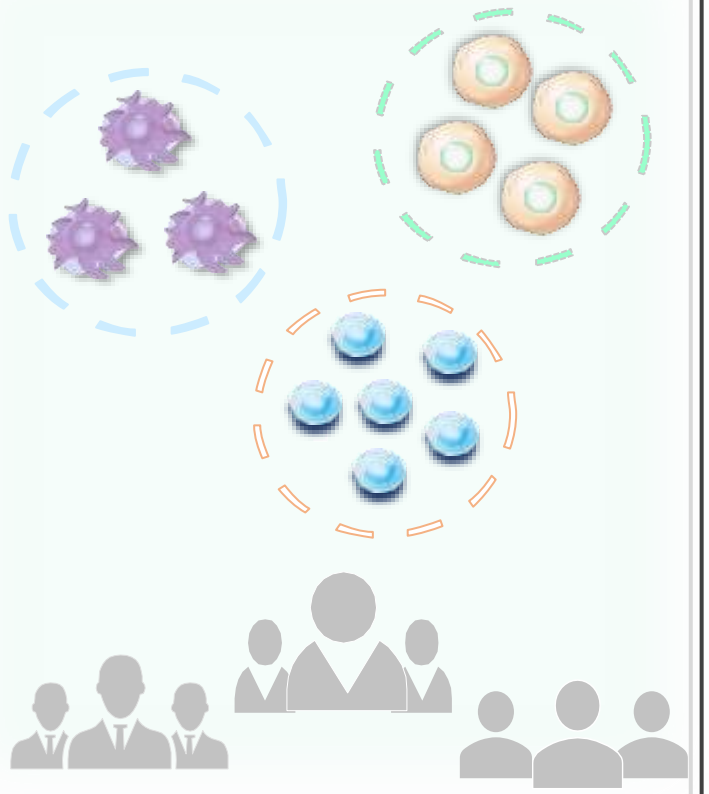
Clinical grade MCB

HLA Class I/II KO (intermediate)

HEALIOS Universal Donor Cells



Universal iPSC regenerative medicines



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

（Source）in-house data

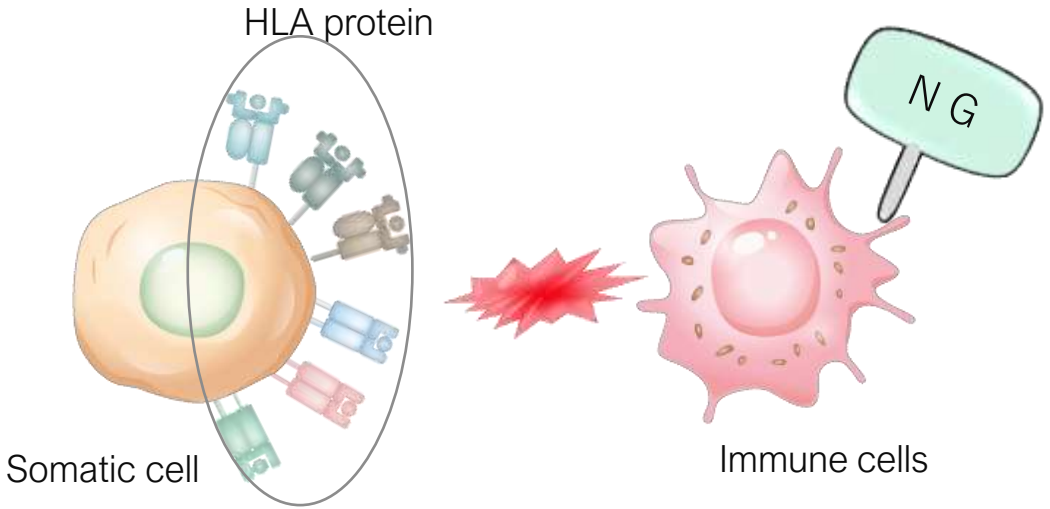
iPSC Platform: Self-recognition of HLA Protein and UDC

HLA (human leukocyte antigen) protein:

・ HLA is a group of cell-surface proteins that are encoded by the MHC (major histocompatibility complex) gene and responsible for the regulation of the immune system.

・There are a myriad of HLA variations

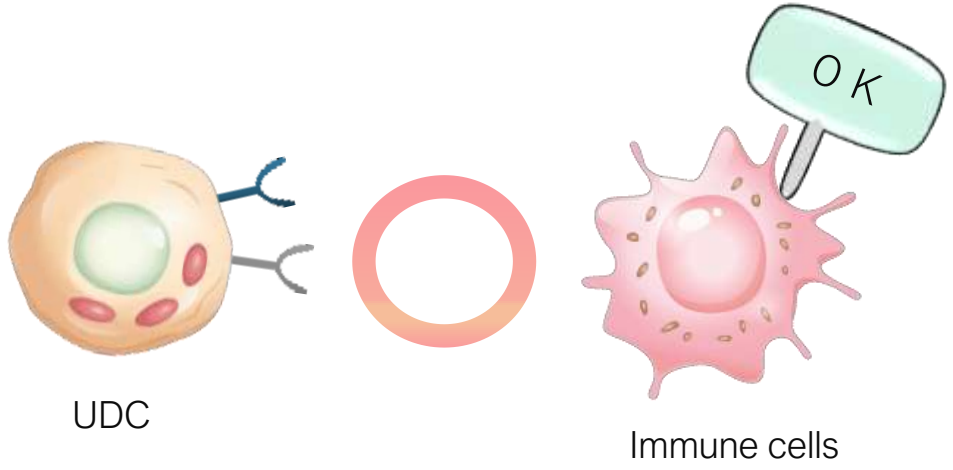
・Immune cells distinguish between autologous and allogeneic cells and tissue.



HLA protein mismatch causes immune rejection

UDC:

- Deletion of HLA protein
- Introduction of immunosuppression-related molecules
- Introduction of suicide genes as a safety mechanism

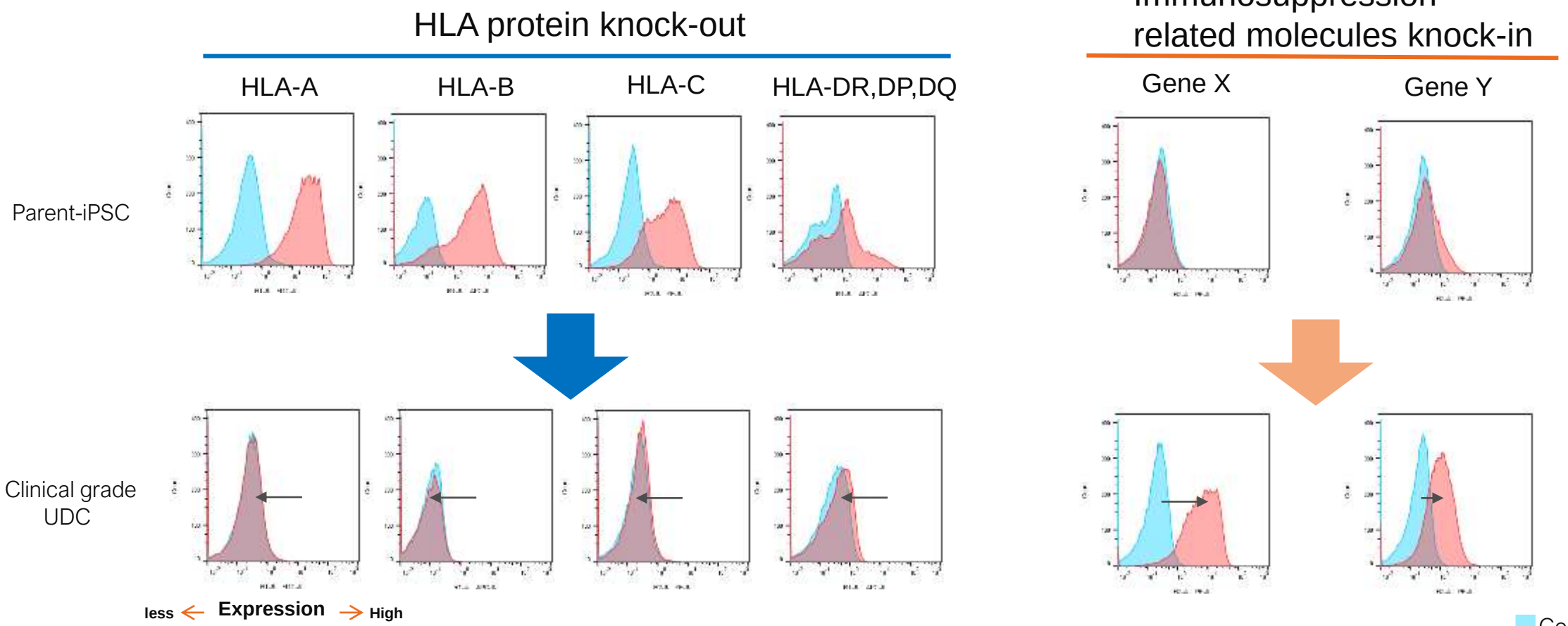


UDC is a safer and more versatile iPS cell

iPSC Platform: Removal of HLA Proteins and Addition of Immunosuppression-related Molecules

New Healios

Results of gene editing in clinical grade UDC



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

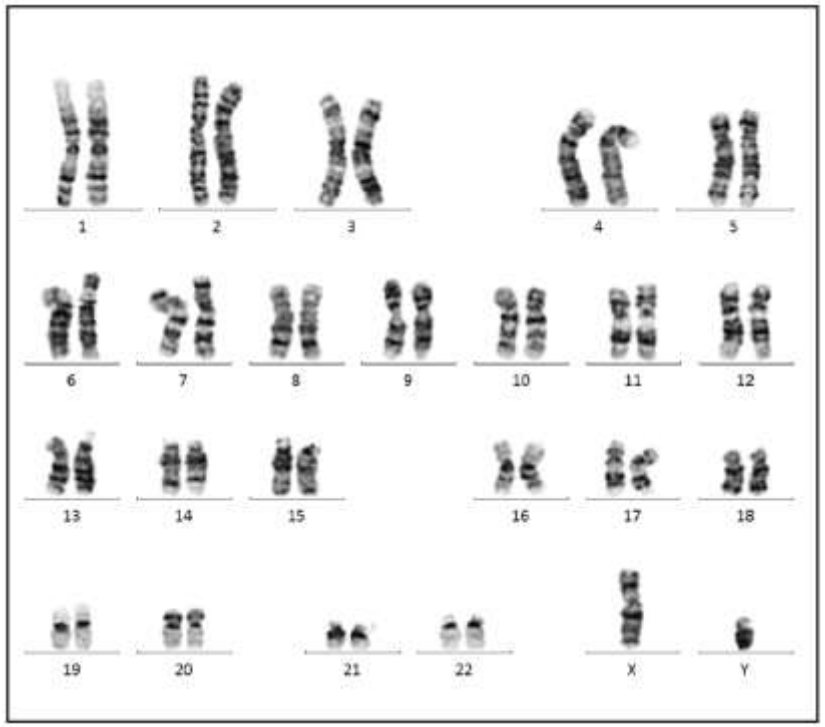
(Source) in-house data

iPSC Platform: Safe and Versatile iPS Cells

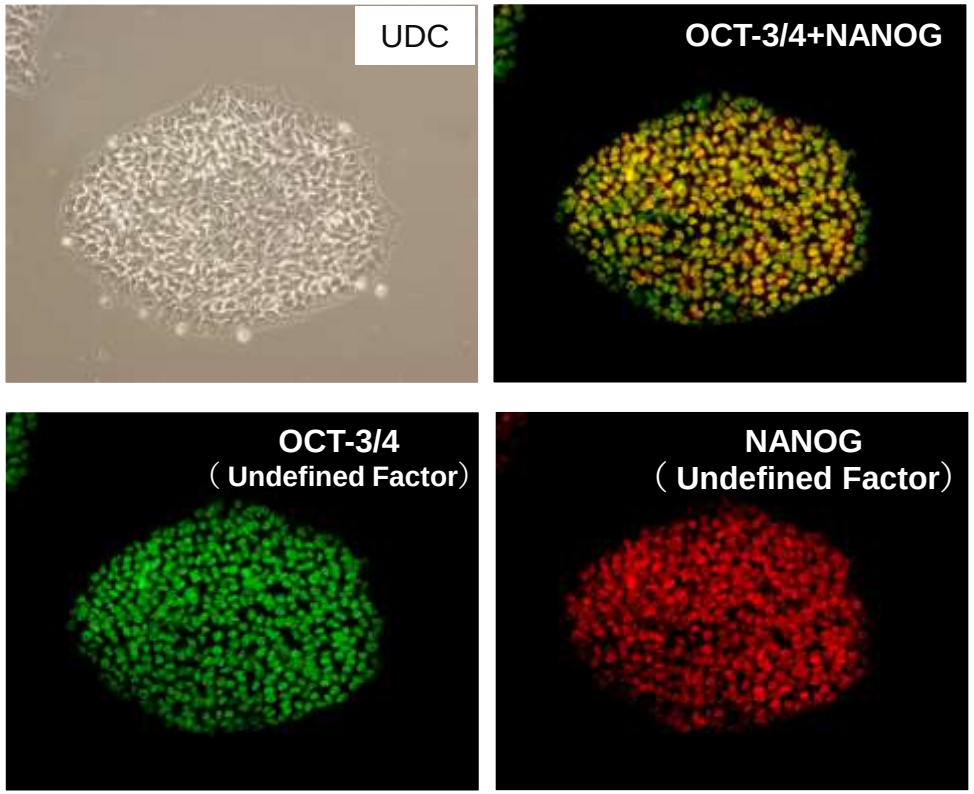
New Healios

Characteristics of Clinical grade UDC

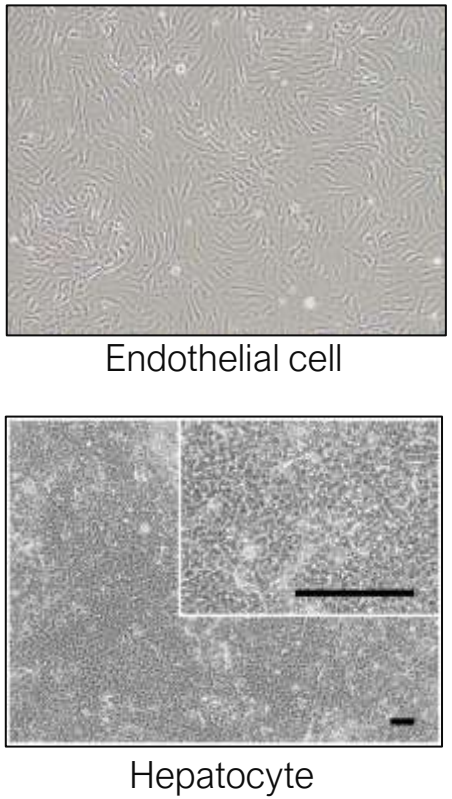
46 (X,Y)



Expression of Pluripotency Markers



Differentiation

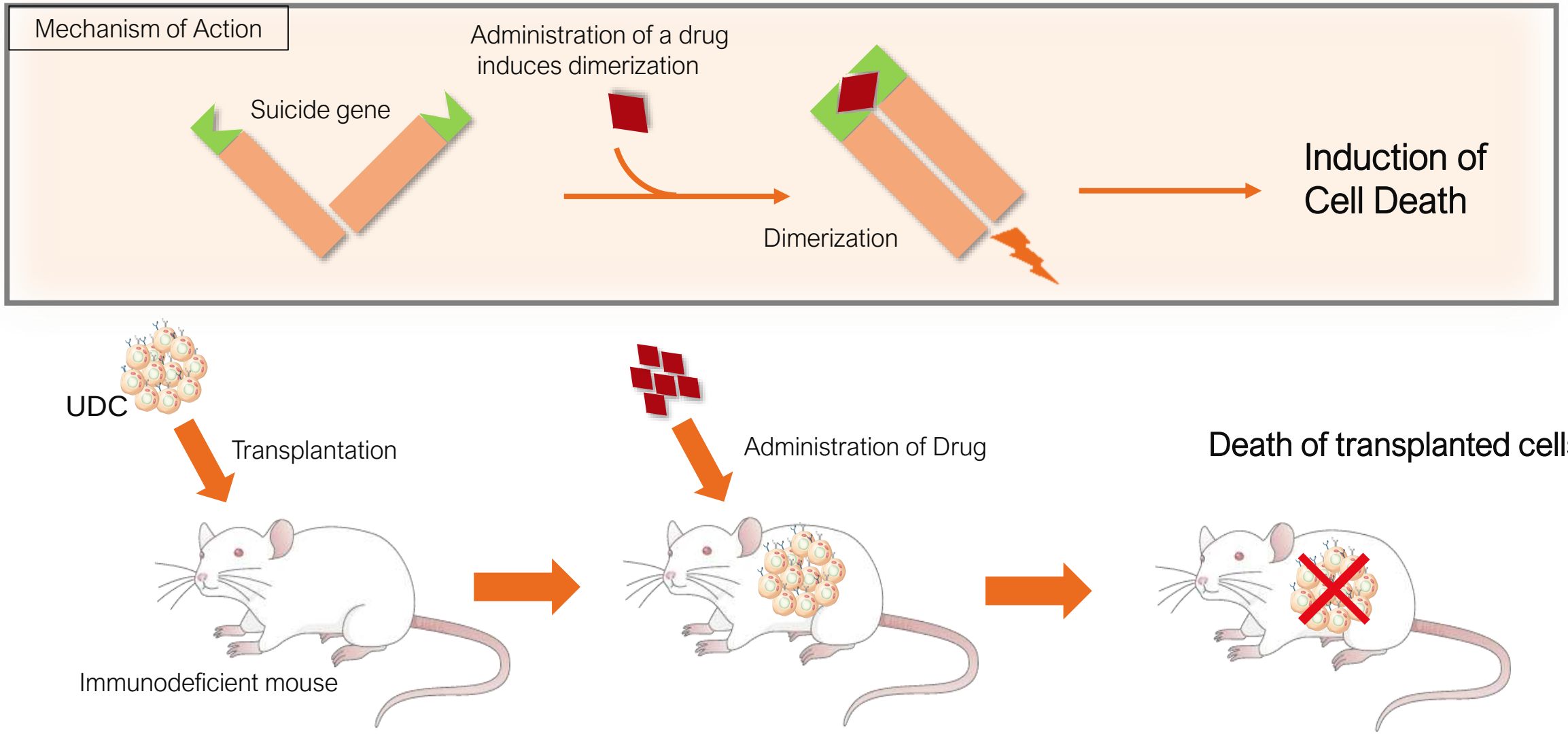


No post gene-editing karyotypic aberrations

iPSC pluripotency maintained

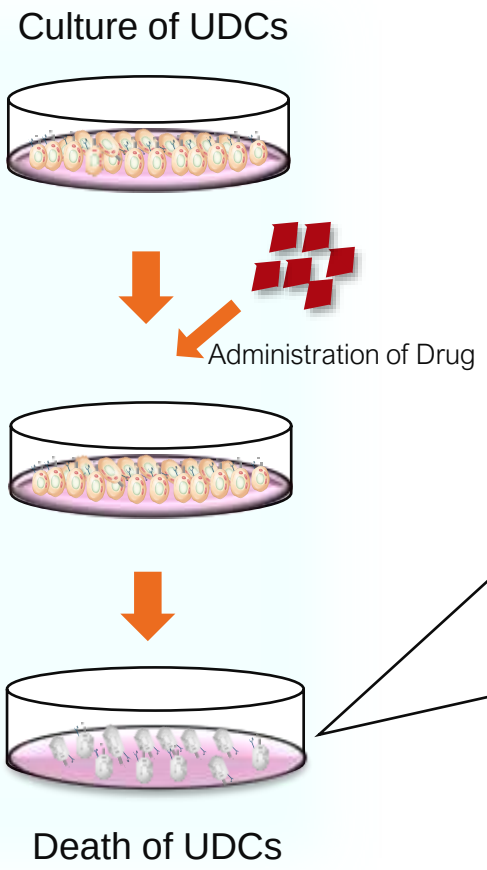
（Source）in-house data

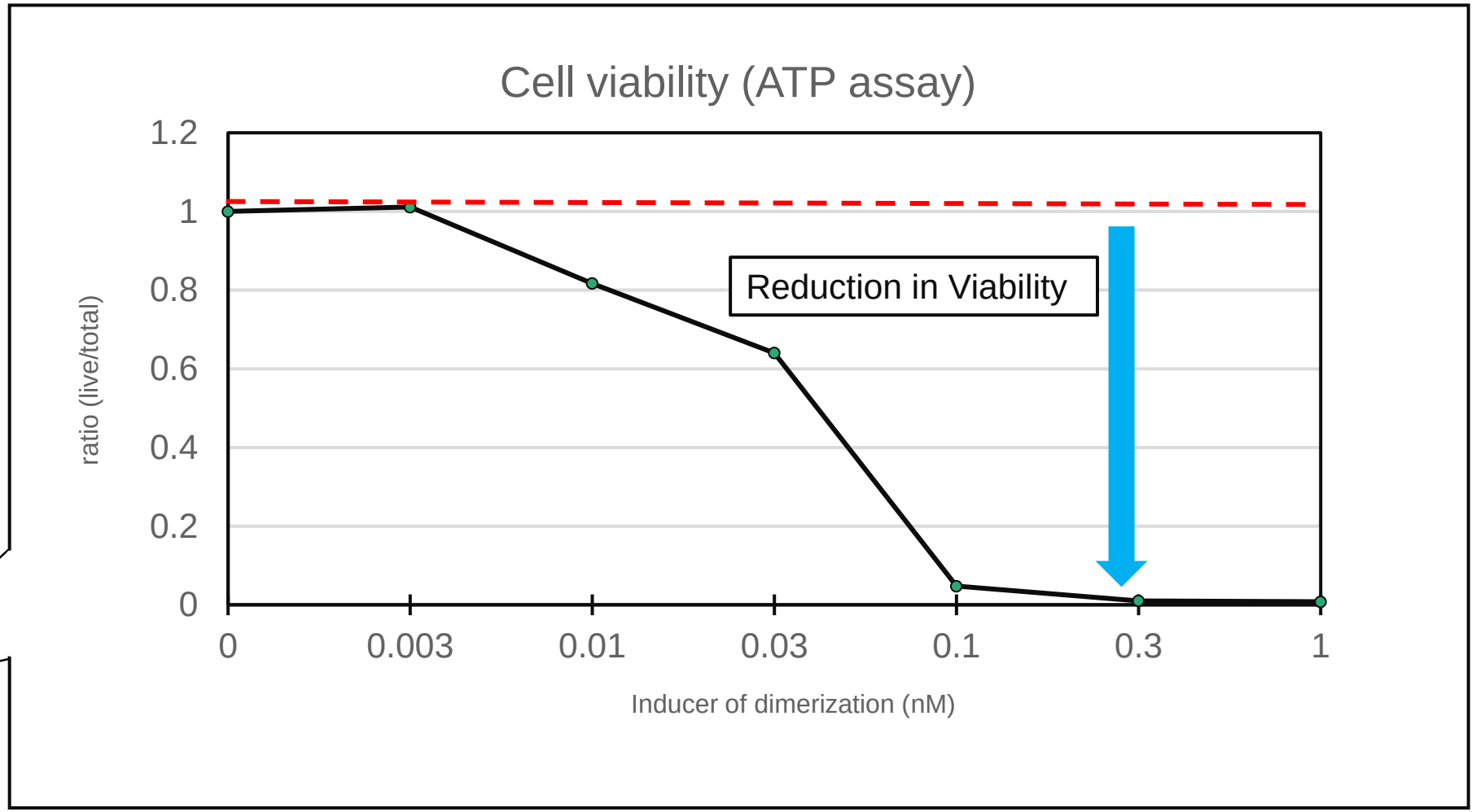
iPSC Platform: Evaluation of UDC Inducible Suicide Genes *In Vivo*



Confirmed suicide gene activity in immunodeficient mice

iPSC Platform: Evaluation of UDC Inducible Suicide Genes *In Vitro*



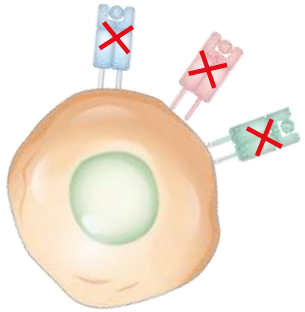


After induction of suicide genes, target cells die by apoptosis

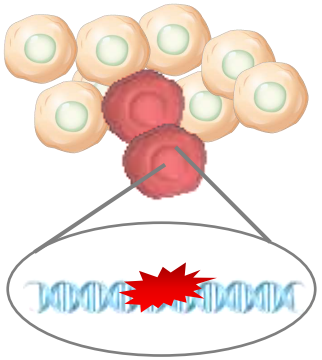
（Source）in-house data

iPSC Platform: UDC Production Process Checklist (Excerpt)

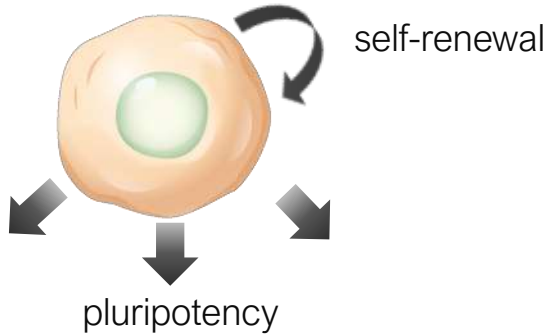
①Confirmation of gene editing



②Absence of malignant mutations



③ Retention of iPS cell properties

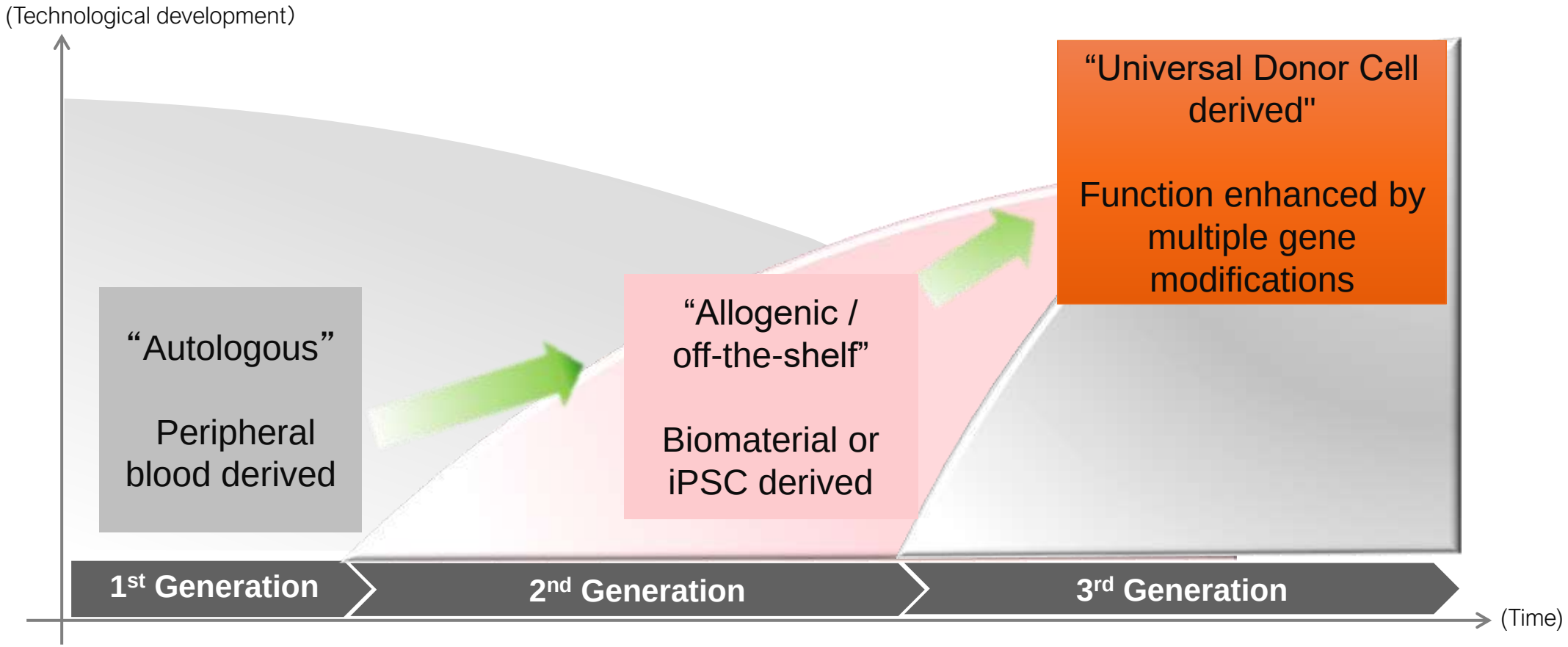


Quality check item	Contents
Confirmation of gene editing	Identification of target region sequence
Expression level of HLA proteins	Loss of HLA Class I expression
	Loss of HLA Class II expression
Transgene expression	Expression of immune suppression associated molecules
	Expression of suicide genes
Gene 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 (triploblastic differentiation)
	Absence of immunogenicity
	Function of suicide genes

iPSC Platform: Unlocking the Full Potential of iPS Cells

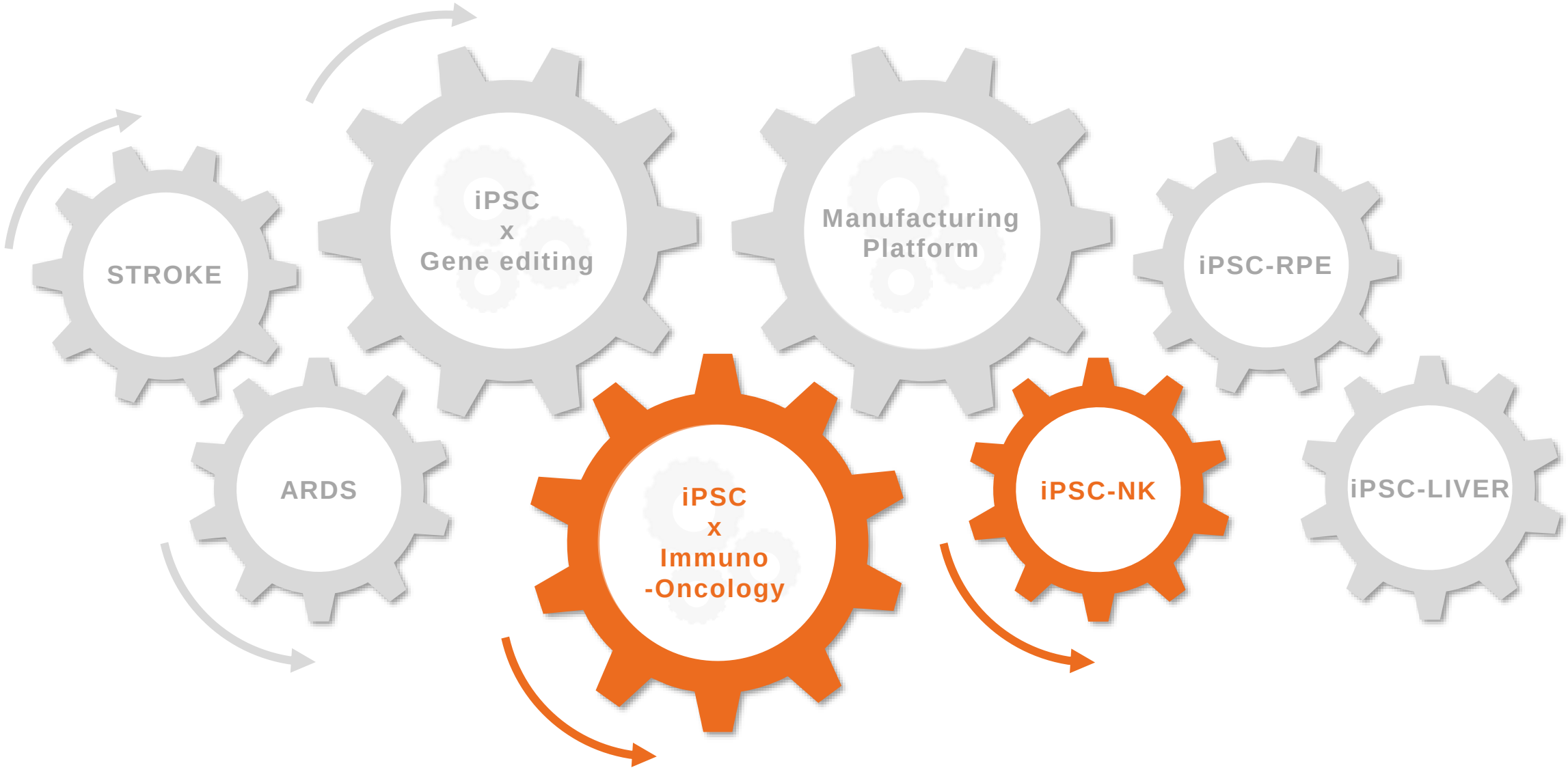
By using UDCs, graft rejection may be avoided, and sustained efficacy may be expected.

Target an off-the-shelf product: stable production and quality with lower cost of goods.

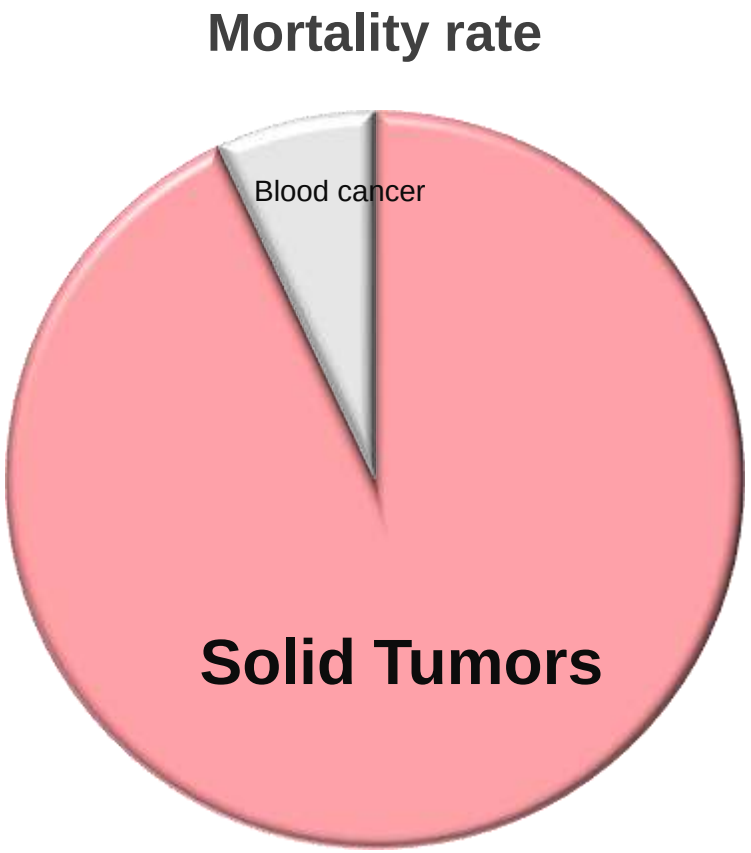


＊See Appendix for additional explanation.

HLCN061



The No.1 cause of death in Japan is cancer (approximately 90% of which are caused by solid tumors)



（Source） data from National Cancer Center, Center for Cancer Control and Information Service, 2018

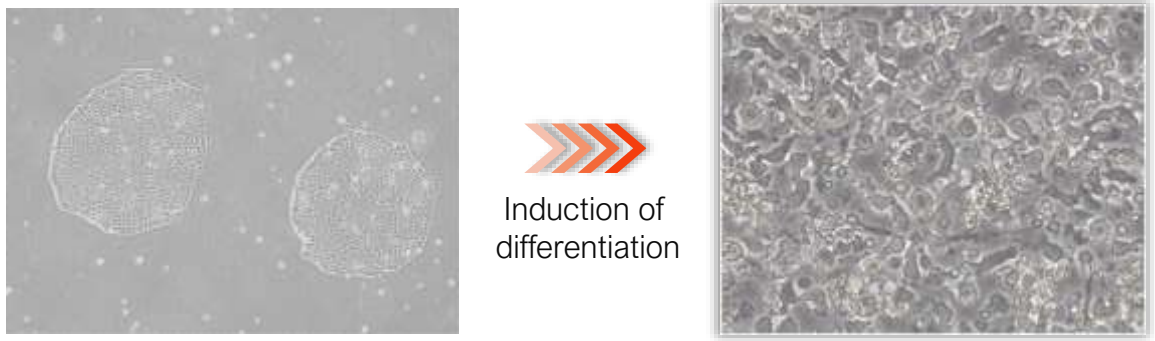
HLCN061: Leading the Development of iPSC Derived Gene-Modified NK Cells

Update

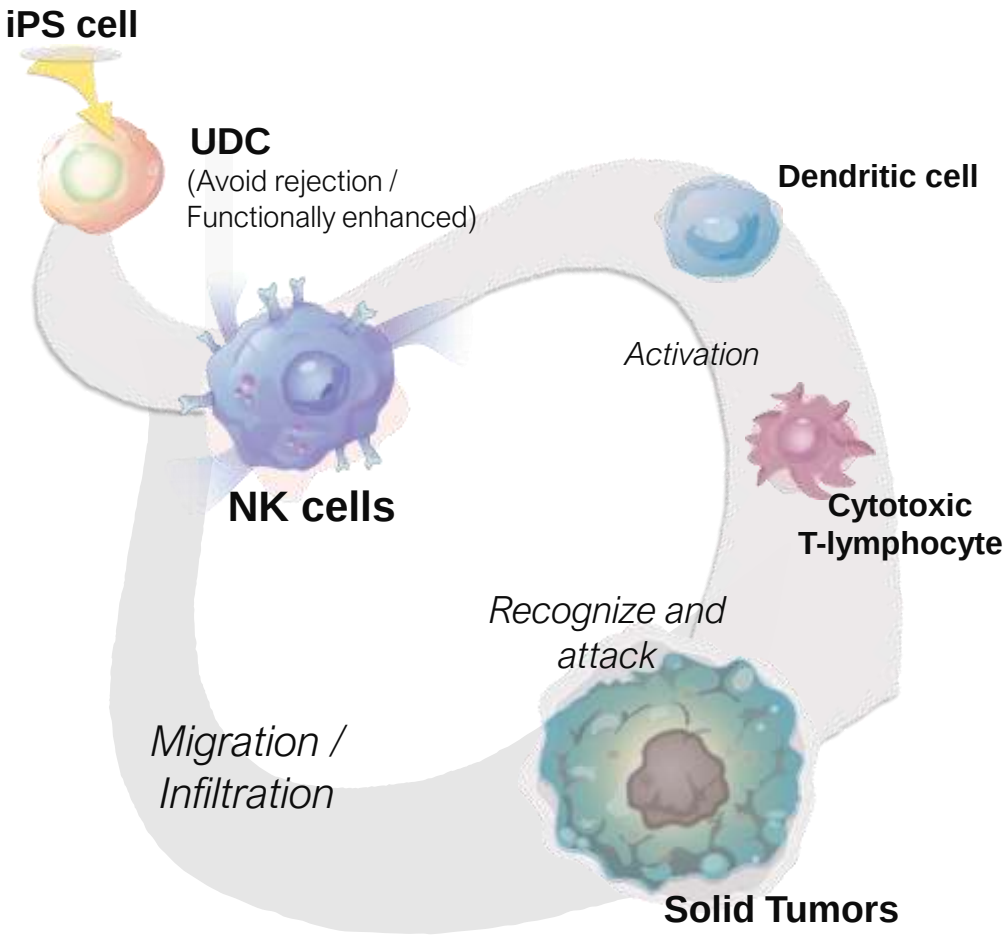
Natural killer (NK) cells, a type of white blood cell, play a central role in a cell mediated defense system that human bodies naturally have, and attack cancer cells and virus-infected cells.

- Best in class, enhanced anti-tumor efficacy by introducing/modulating various factors related to NK cells killing activity
- Broad applicability across tumor types irrespective of specific cancer antigens

Production of NK cells



UDC　　NK cells

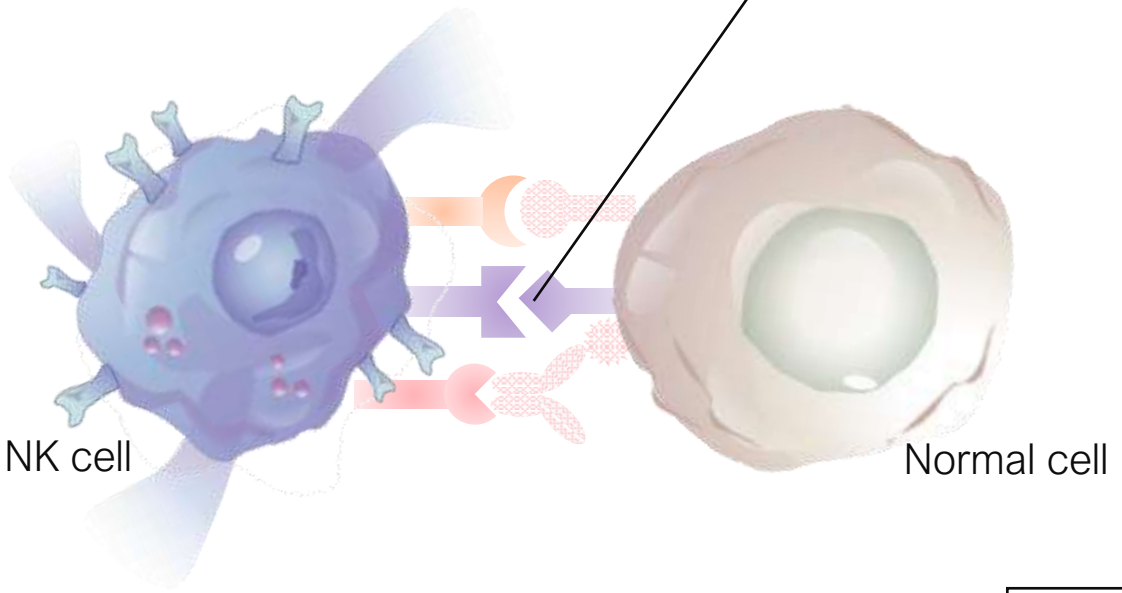


（Source）in-house data

HLCN061: Mechanism of NK Cell Attack of Cancerous or Virus-Infected Cells

Normal cells

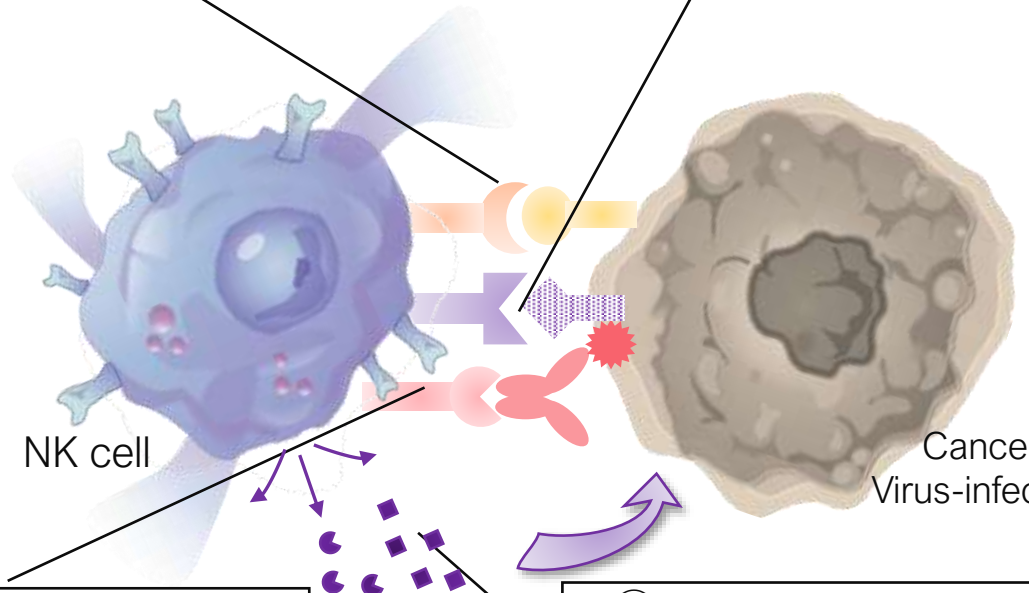
NK cells do not attack normal cells by recognizing normal marker



Cancerous or virus-infected cells

① Activated by abnormal markers

② Release the brake allowing for the attack



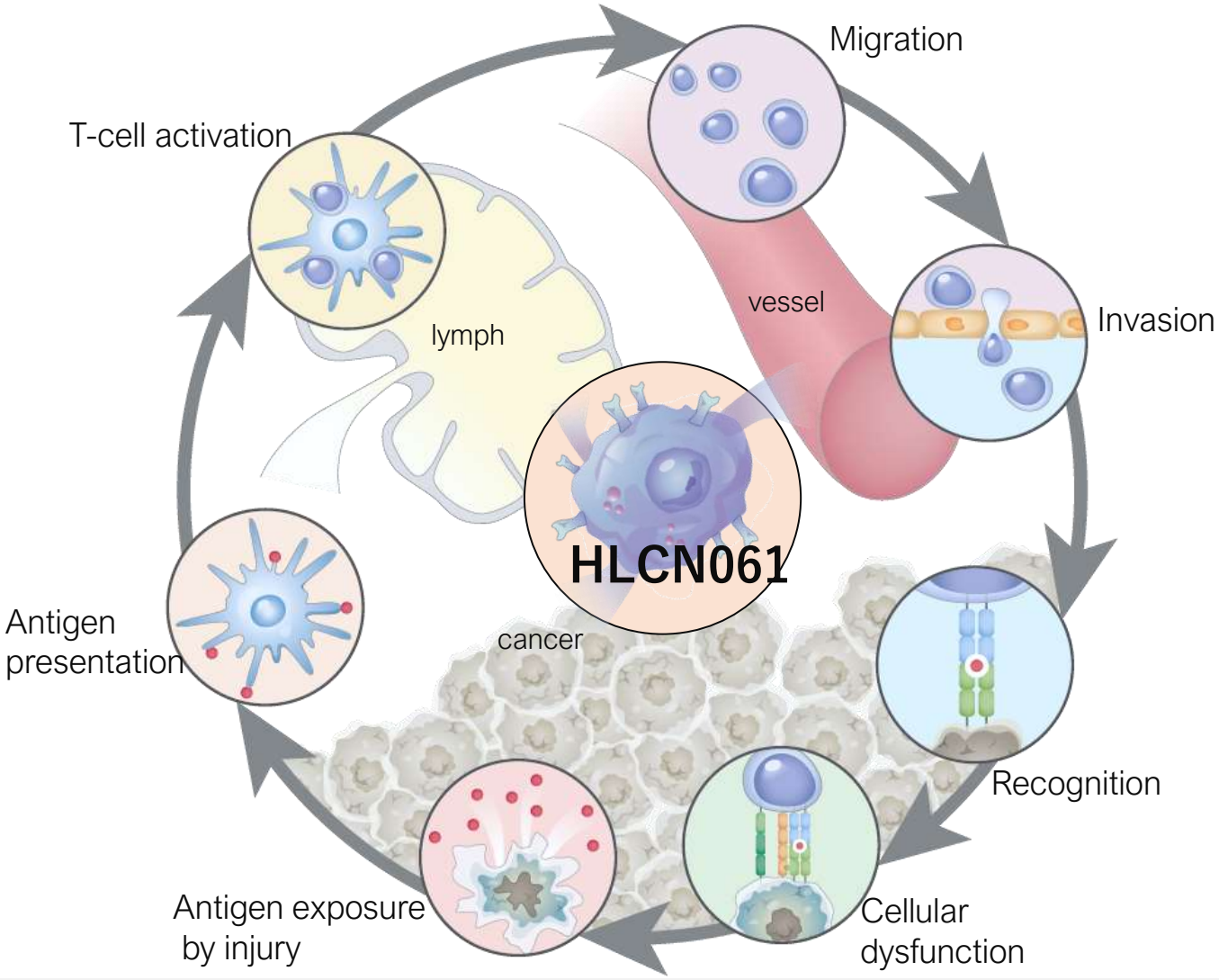
③ Recognize the antibodies that are attacking the cancer and further activate.

④ Release the degrading enzymes and destroy cancer cells

HLCN061: Enhancement of Anticancer Functions through Gene Modification

New Healios

Enhancing Anticancer Function at Each Stage of the Cancer-Immunity Cycle



Cancer-Immunity Cycle

NK cells recognize and kill cancer cells

↓

Exposed to cancer antigen

↓

Activation of the cancer immunity cycle and induction of cytotoxic T-lymphocytes

↓

Degeneration of cancer

(Source) This material was based on Daniel S.Chen and Ira Mellman.,Immunity. 2013;39(1):1-10.

HLCN061: Market Leading Range of Functional Enhancements

	HEALIOS	Company-A		Company-B		Company-C
	iPS Cell	iPS Cell①	iPS Cell②	Cell①	Cell②	Cord blood
Recognizes cancer cells	✓		✓		✓	✓
Enhanced function in combination with antibodies	✓	✓	✓	✓	✓	
Migrates to cancer cells	✓					
Attracts host immune cells	✓					
Activates surrounding T-cells and dendritic cells	✓		✓			✓
Self-activation and maintenance of survival	✓		✓			✓
Avoids immune rejection in patients	✓					

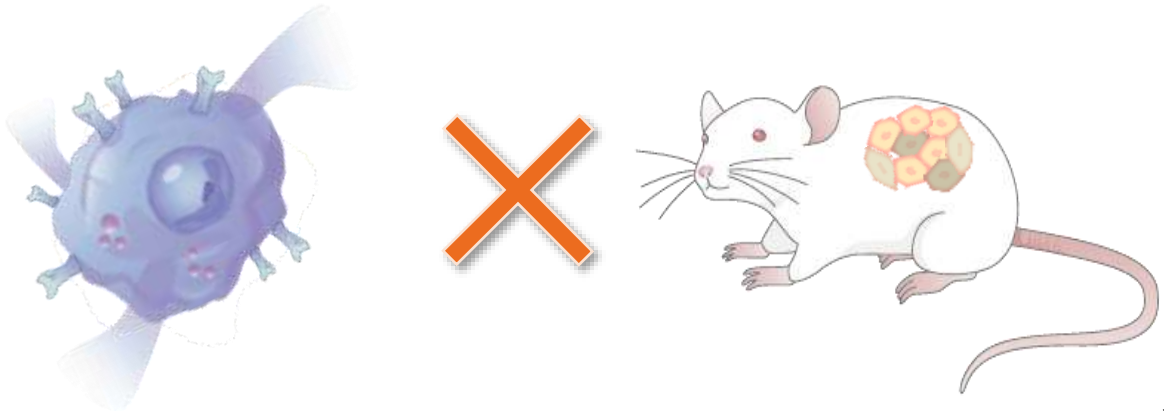
（Source） Adapted by Healios from public information

HLCN061: Joint Research with the National Cancer Center Japan

Healios

Healios

The National Cancer Center Japan



Gene edited NK cells

PDX

Research utilizing PDX（Patient-Derived Xenograft）

・Investigate the expression of several molecules recognized by HLCN061

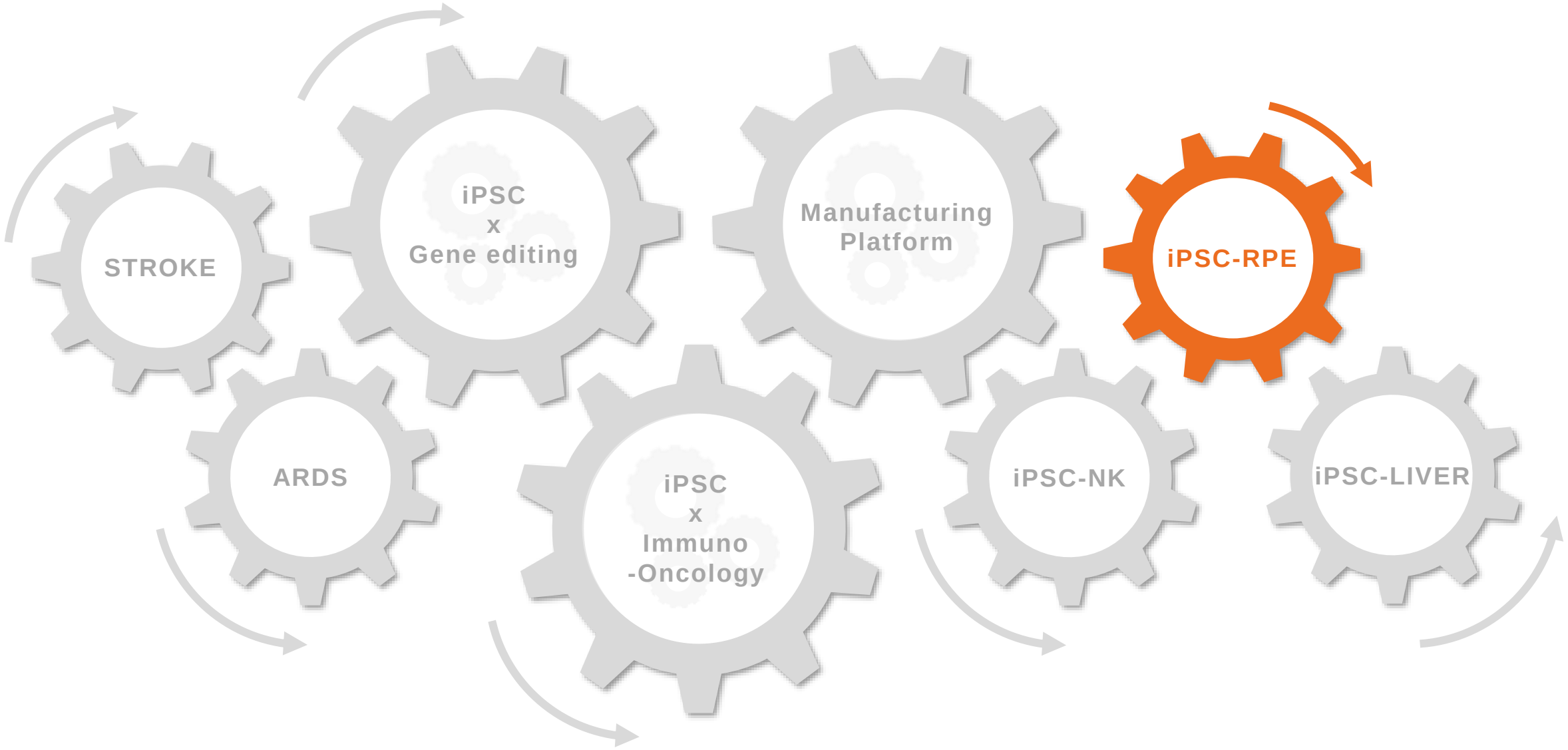
・Clarify the characteristics of solid cancers to which HLCN061 exerts antitumor effects

Based on the results of these studies

PDX models ＊1 will be used to consider what solid cancers we should target with our therapy.

*1 PDX models
Transplant human patient cancer tissue into immunodeficient mice
Dramatically improves the predictability of clinical response

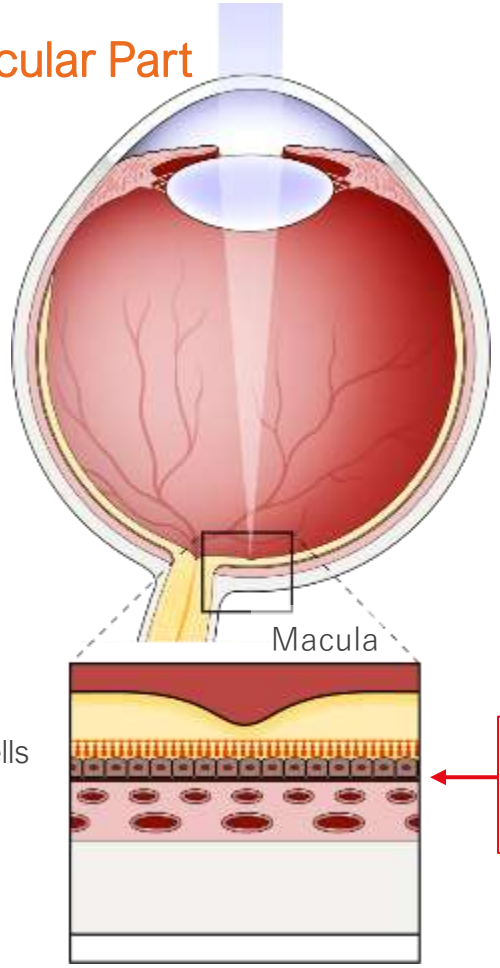
HLCR011 AMD



HLCR011 AMD: Pathological Conditions

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

Regular Macular Part

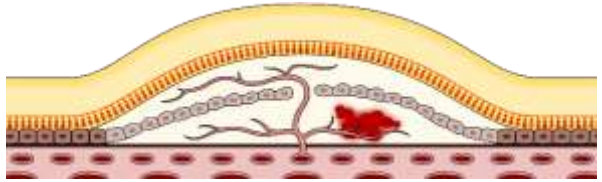


Developed Dry-AMD

Immunity barrier maintained
→ Degeneration of photoreceptor→ Dry AMD

Wet AMD

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



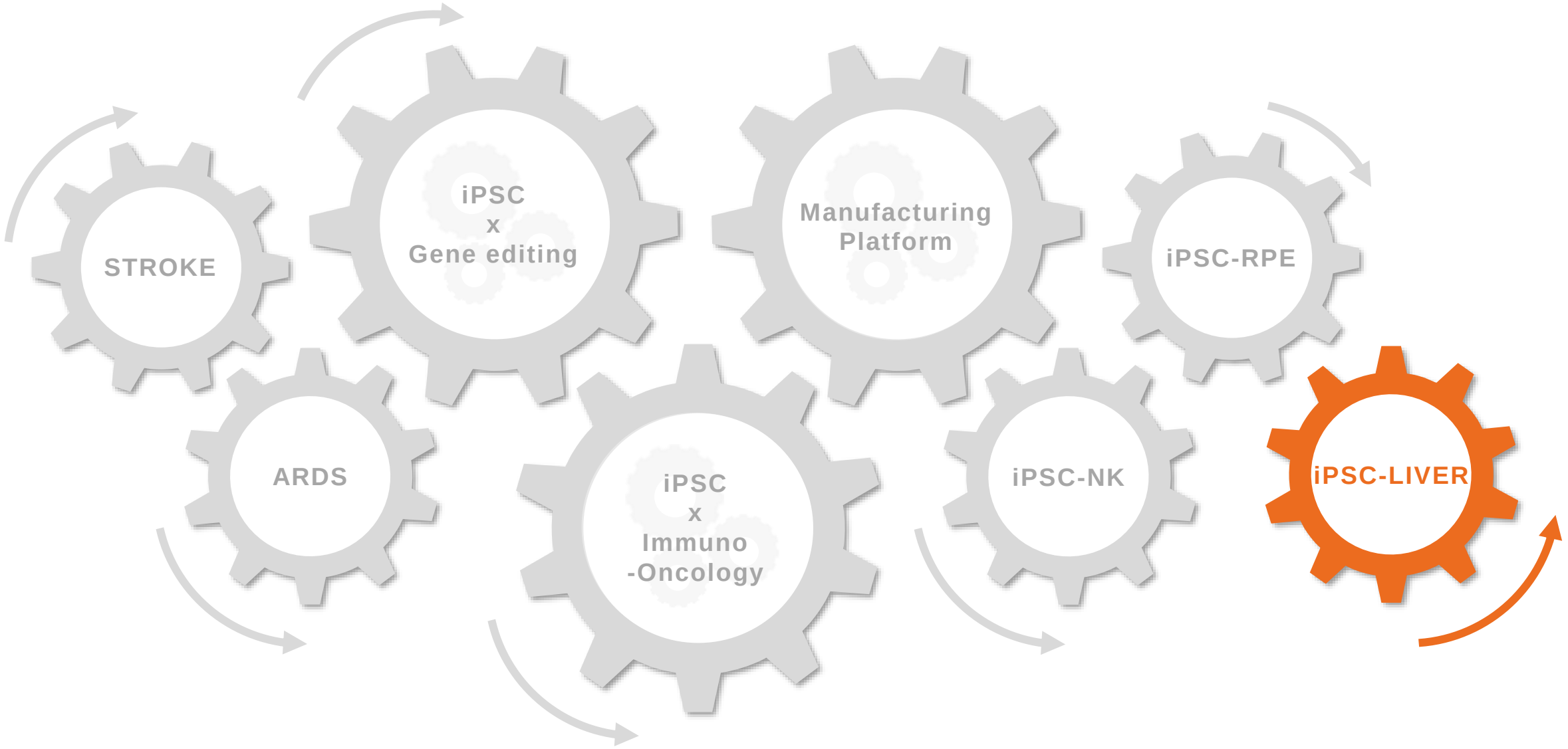
HLCR011 AMD: Manufacturing for iPSC-derived RPE Products

In Japan, HEALIOS and Dainippon Sumitomo Pharma jointly develop a treatment using iPS cell-derived RPE cells.

Sighregen, a joint venture with Sumitomo Dainippon Pharma, is establishing a manufacturing facility

> “SMaRT”, the Manufacturing Plant for Regenerative Medicine & Cell Therapy by Sumitomo Dainippon Pharma
>
> Sighregen rents the facility in SMaRT and is establishing the iPSC-RPE manufacturing system and facility for iPSC-RPE cell products

HLCL041 Liver Organ Bud Platform



HLCL041: Liver Organ Bud Platform

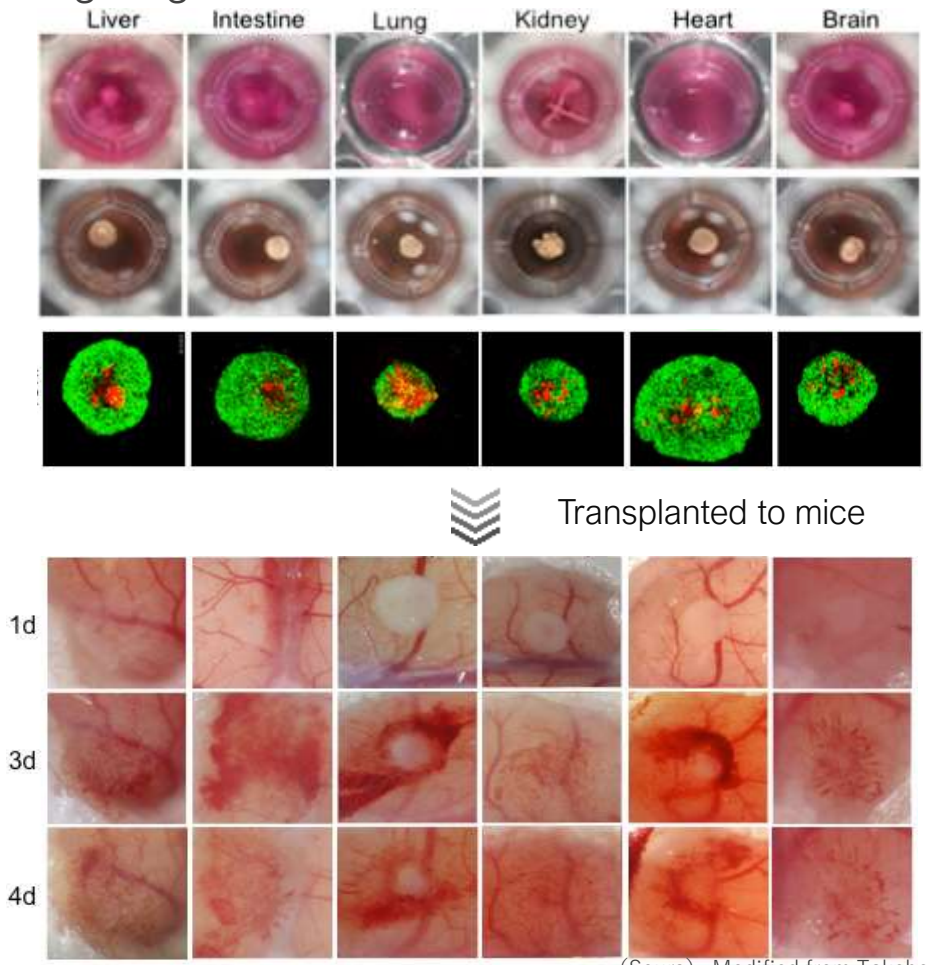
By creating an "Organ Bud" of each organ with iPS cells, we have laid the groundwork for paradigm shifting therapies to emerge for various severe diseases.

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

*movie

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



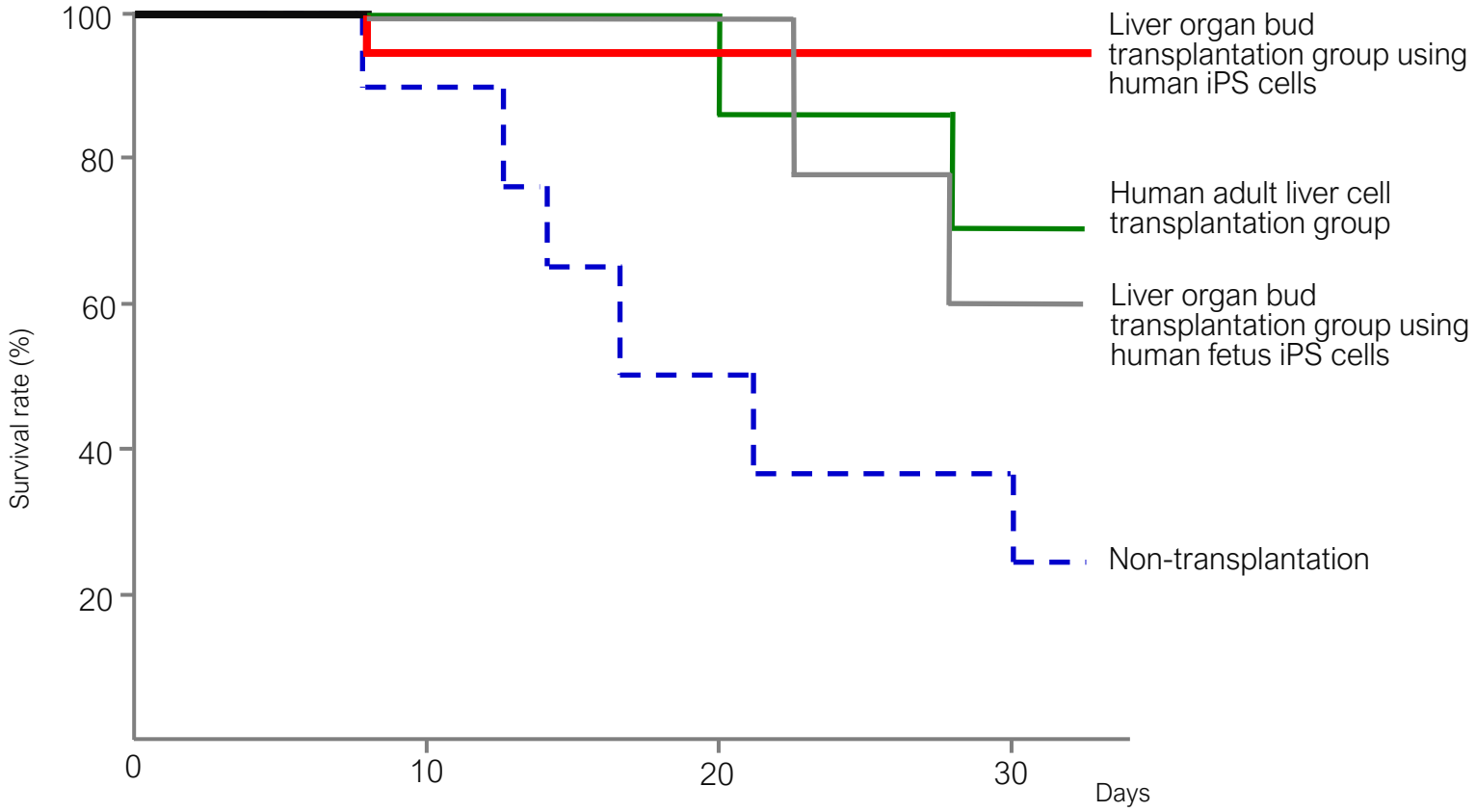
Green：Cells of each organ
Red：Vascular endothelial cell
Black：MSC

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

HLCL041: Liver Organ Bud Platform: Survival Rate of Liver Failure in Mouse Model

Survival rate improves significantly in transplantation experiments

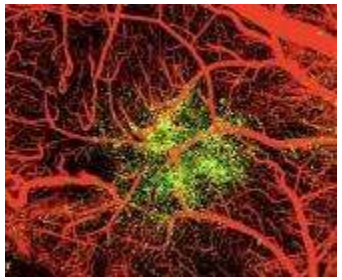
Treatment effects of liver bud transplantation to mouse using hiPSC



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

Process

Process by which organ forms from organ bud links mouse‘s vascular network autonomously



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

Financial Highlights

Voluntary Adoption of International Financial Reporting Standards (IFRS)

HEALIOS K.K. (the “Company”) hereby announced that, at the executive officers meeting held on February 13, 2020, it has resolved to voluntarily adopt International Financial Reporting Standards (“IFRS”) as its accounting standard for its consolidated financial statements instead of the Japanese Generally Accepted Accounting Principles (“J-GAAP”) from the fiscal year ending December 31, 2020 as follows.

The Company decided to adopt IFRS voluntarily in order to improve the international comparability of its financial information in the capital markets.

The disclosures for the fiscal year ending December 31, 2020 are as follows:

Accounting period		Disclosure materials	Accounting standards
Fiscal year ending December 31, 2020	1st to 3rd quarters	Quarterly Earnings Report	IFRS
		Quarterly Report	IFRS
	Year end	Earnings Report	IFRS
		Consolidated Financial Statements (Note	IFRS
		Annual Securities Report	IFRS

(Note) The Company discloses the information in its consolidated financial statements from the fiscal year ending December 31, 2020.

Statement of income

(Units: one million US dollar)

	FY2019	FY2020		
			YoY variance	Main reasons for increase/decrease
Revenue	0.81	0.26	-0.56	Milestone revenue was recorded only in the first quarter of the previous year, resulting in a decrease in revenue compared to the same period last year.
Operating profit	-39.42	-39.18	0.24	Mainly due to increase in SG&A expenses −$1.00mn and decrease in R&D expenses +$1.52mn.
Profit	-44.09	-51.64	-7.55	Mainly due to increase in finance costs -$8.77mn as a result of change in fair value of derivatives embedded in convertible bonds (non-cash) -$5.88mn and increase in the carrying amount of bonds by the amortized cost method (non-cash) -$2.82mn.
R&D expenses	29.49	27.97	-1.52	
Number of employees	109	113	4	

(Note) * Financial figures for the fiscal year ended December 31, 2019 are presented in accordance with IFRS.
* For details of the financial figures, please refer to the summary of the financial results announced today.
* Adopt average exchange rate (JPY/USD) over respective 12-month periods for P&L; FY2019 109.02 yen per dollar and FY2020 106.76 yen per dollar.

Supplemental explanation of financial expenses

Details of financial expenses

In the fiscal year ending December 2020, we recorded financial expenses of ¥1,182 million. This was mainly due to the recording of ¥637 million in loss on valuation of derivatives*1, ¥502 million in interest on bonds*2, and ¥36 million in interest expenses.

*1 Gain or loss on valuation of derivatives

Gain or loss on valuation of derivatives are 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 as of the end of December 2020. These are non-cash items booked in accordance with the International Financial Reporting Standards (IFRS), which was introduced by in the first quarter of the fiscal year ending December 2020.

*2. Interest on bonds

Of the total interest on bonds of ¥502 million, ¥461 million was charged to income using the amortized cost method. As in *1 above, this is a non-cash expense recorded in accordance with the International Financial Reporting Standards (IFRS), which was introduced in the first quarter of the fiscal year ending 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.

Balance sheet

Update

Healios

（Units: one million US dollar）

		December 31, 2019	December 31, 2020		
				Variance	Main reasons for increase/decrease
	Current assets	176.86 (75.7%)	144.99 (64.8%)	-31.87	Mainly due to decrease in cash equivalents −$32.47mn. (cash equivalent balance at 12/31/20 was $134.53mn)
	Non-current assets	56.75 (24.3%)	78.89 (35.2%)	22.14	Mainly due to increase in other financial assets +$14.45mn as a result of the acquisition of additional shares of Athersys, Inc. and a rise in Athersys shares.
Total assets		233.61 (100.0%)	223.88 (100.0%)	-9.73	
	Current liabilities	17.93 (7.7%)	25.95 (11.6%)	8.02	Mainly due to increase in other financial liabilities +$6.77mn.
	Non-current liabilities	103.01 (44.1%)	122.07 (54.5%)	19.06	Mainly due to increase in bonds and loans payable +$14.68mn and lease obligations +$1.60mn.
Total liabilities		120.94 (51.8%)	148.02 (66.1%)	27.08	
Total equity		112.67 (48.2%)	75.86 (33.9%)	-36.81	Mainly due to net loss -$51.64mn and increase in other components of equity +$4.44mn as a result of a rise in Athersys shares.
Total liabilities and equity		233.61 (100.0%)	223.88 (100.0%)	-9.73	

(Note) * Financial figures for the fiscal year ended December 31, 2019 are presented in accordance with IFRS.
* For details of the financial figures, please refer to the summary of the financial results announced today.
* Adopt spot rate (JPY/USD) at end of fiscal period for B/S ; FY2019 109.56 yen per dollar and FY2020 103.50 yen per dollar.

Appendix

Overview of Healios

Update

Company Overview

About us

Company Name	HEALIOS K.K.
Representative	Hardy TS Kagimoto, MD, Chairman and CEO
Establishment	February 24, 2011
Paid in Capital	4,991 million yen(As of December 31, 2020)
Head office	Yurakucho Denki Bldg. North Tower 19F, 1-7-1 Yurakucho, Chiyoda-ku ,Tokyo 100-0006, Japan
Number of Employees	113 (As of December 31, 2020)
Business	Research, development and manufacturing of cell therapy/ regenerative medicine products
Research Institution	Kobe (77：(Ph.D. Holders :Over 30 people) As of December 31, 2020) Yokohama
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)

Company History

Update

Healios

	Company	In the field of iPSC Regenerative Medicine	In the field of Somatic Stem Cell Regenerative Medicine
2011	Establishment of the company		
2012	Tokyo office opened		
2013		A patent licensing agreement concluded with RIKEN Joint Development Agreement with Sumitomo Dainippon Pharma Co., Ltd.	
2014		Joint research with Yokohama City University on Organ buds	
2015	Listed on Tokyo Stock Exchange (MOTHERS)		
2016		Start universal donor cell research	HLCM051 license agreement with Athersys, Inc. Clinical trial for ischemic stroke initiated
2017	A business and capital alliance with Nikon BBG250 Business transfer		
2018	Establishment of Healios NA, Inc. in the US Establishment of Organoid Neogenesis Laboratory Inc	CRADA with National Eye Institute Sighregen establishes a manufacturing facility in SMaRT	Strategic investment and collaboration expansion with Athersys ARDS development & clinical trial initiated
2019	Expansion of alliance with Nikon	Changes in joint development framework with Sumitomo Dainippon Pharma	
2020	Establishment of Sales and Marketing Department Establishment of a new Healios research facility	In-house development of gene-modified natural killer cells（HLCN061） Establishment of UDC research line and clinical grade line Joint research with the National Cancer Center Japan	COVID-19 induced ARDS clinical trial cohort enrollment completed

HEALIOS K.K. Leadership

Management Team

Since July 2019

Jun Narimatsu	Richard Kincaid	David Smith	Michael Alfant	Gregory Bonfiglio	Yoshinari Matsuda	Seigo Kashii
Accountant Supporting various venture companies in the field of IT/ Healthcare	**Executive Officer CFO** Experienced at Nezu Asia Capital Management (hedge fund)	Served at Lonza Extensive experience in cell manufacturing	Group Chairman & CEO, Fusion Systems, Co., Ltd. Presidents Emeriti, ACCJ	Founder & Managing Partner of Proteus, LLC. (Investment in RM ventures)	Attorney-at-Law, Senior Management Partner of Uruma Law Offices Legal Professional Corporation	Ex-corporate auditor of Astellas Pharma

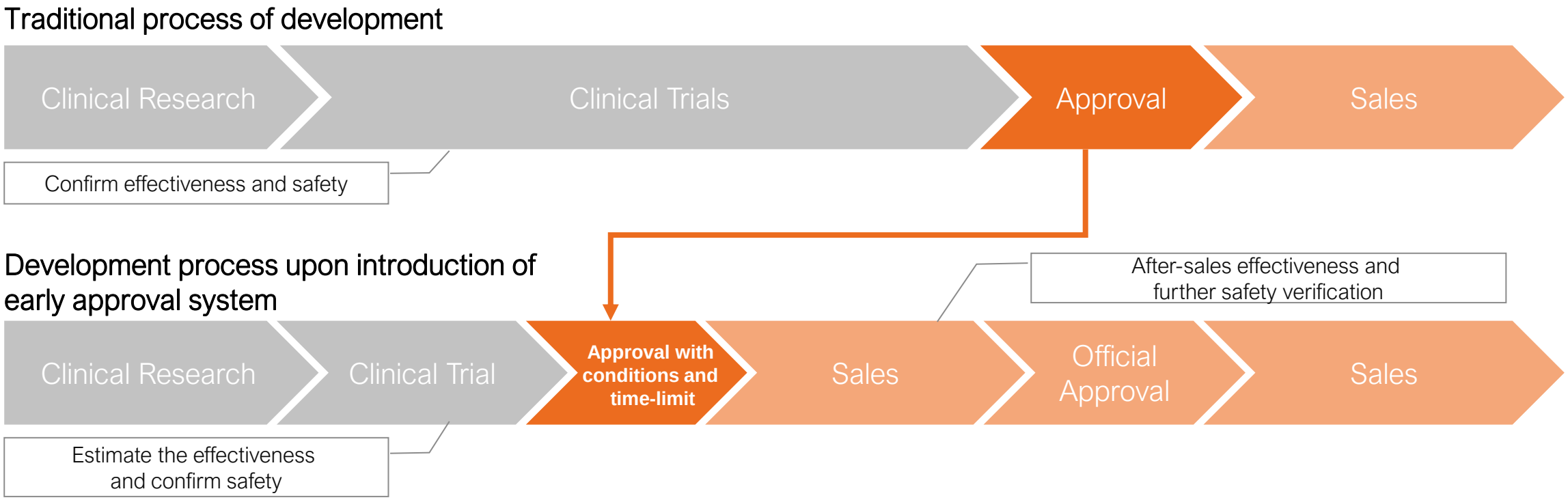
Masanori Sawada	Hardy TS Kagimoto	Kouichi Tamura	Michihisa Nishiyama	Koji Abe
Executive Vice President, CMO (Chief Medical Officer) MD, PhD, MBA	**Chairman and CEO** MD, Founder	**Executive officer Research and Manufacturing field** Ex-Astellas US Director of Laboratories Expertise in Immunosuppressant Research	**Executive Officer Development field** Constructed network for Tacrolimus approval and sales at Astellas in the US and Europe	**Executive Officer HR & GA field** Over 30 years experience in HR

Historical Relaxation of Japanese Regulations

Drastic reduction in the trial time period and number of patients with “Conditional and Time-limited Authorization System.”

Insurance is listed at ‘Conditional and Time-limited Authorization’ stage.

Conditional and Time-limited Authorization System



About Orphan Regenerative Medicine Designation

Orphan regenerative medicine designation is available in cases of rare diseases with small patient numbers and no existing direct treatments.

【Criteria for designation as a rare disease】

1． Number of patients with this disease in Japan is lower than 50,000

2． Unmet medical needs

- A serious target disease with very high medical needs
- No alternative drug, medical device, regenerative medicine, or therapy exists
- A significantly higher efficacy and safety than that of existing drugs, medical devices, or regenerative medicines can be expected

3． A theoretical basis for using regenerative medicines exists and the developmental plan is considered appropriate

【Benefits of receiving orphan designation】

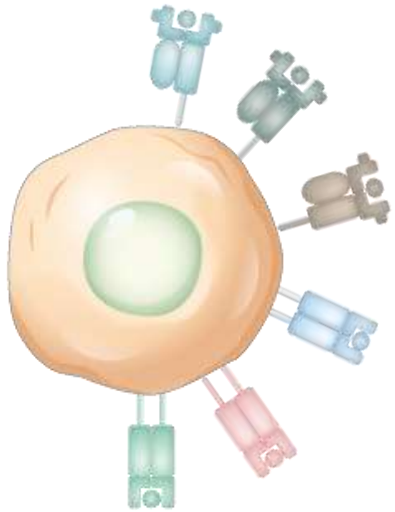
- Granting of subsidies to reduce development expenses
- Tax measures, priority advice and consultations and priority review
- Longer Reexamination period

ARDS is also a rare disease with an estimated incidence of 7,000 to 12,000 patients per year.

((source)Definition of the Ministry of Health, Labour and Welfare：https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000068484.html

iPSC Platform

iPSC Platform: Universal Donor Cell



iPS cell
(pluripotent stem cell)

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Gene-Editing

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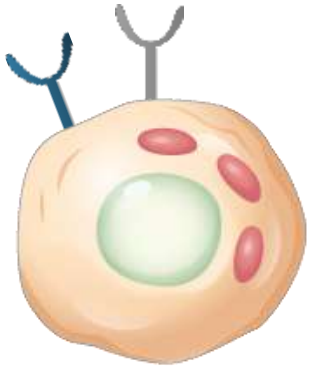
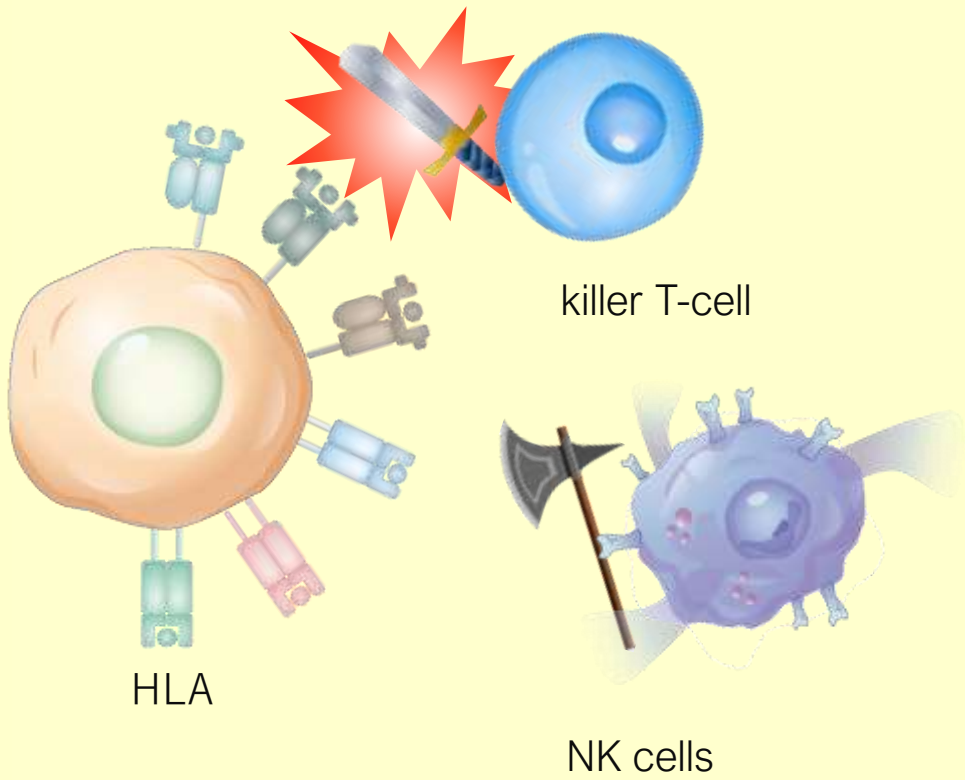


Universal Donor Cell
(Safe and versatile stem cells)

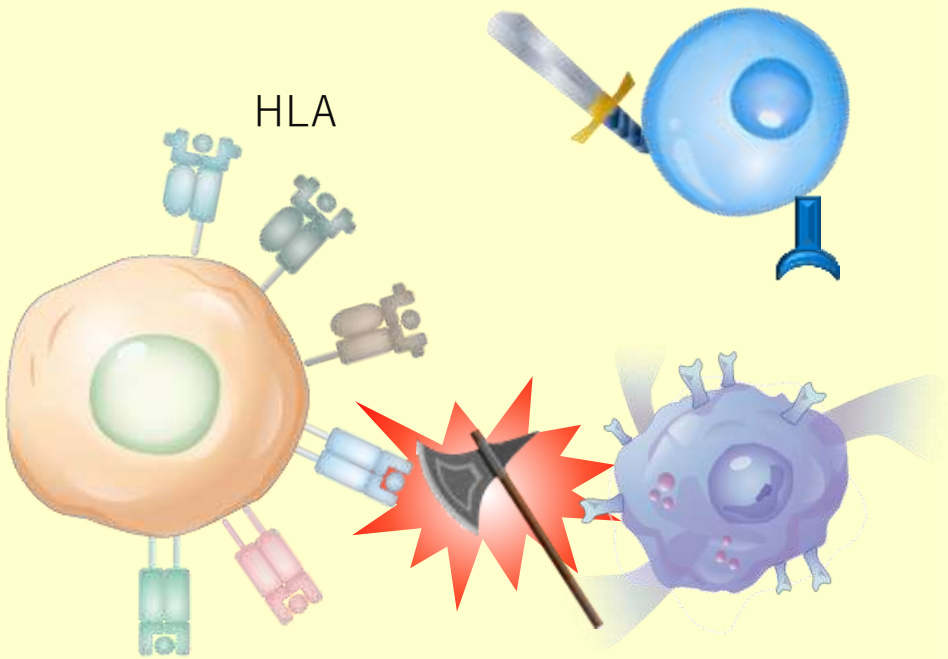
By using gene editing technology to produce iPS cells that avoid immune rejection, it is possible to realize universal iPS cells that can respond to the need for “one cell for all patients."

iPSC Platform: Rejection of Cell Transplant

HLA type mismatch

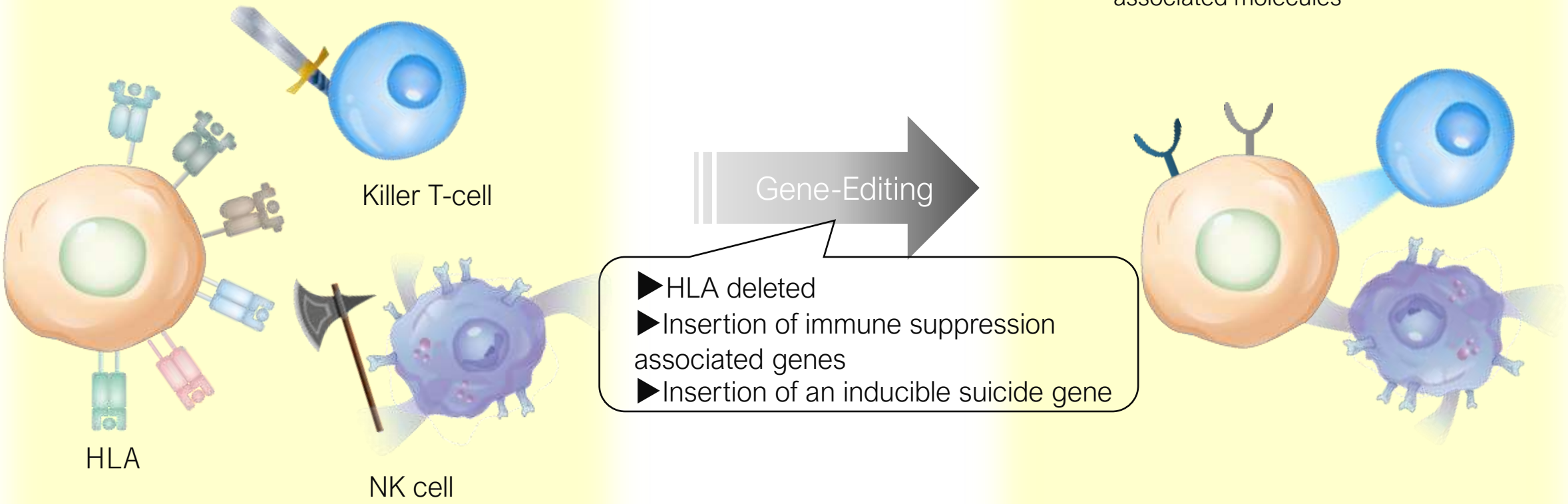


HLA protein deletion



Immune response

iPSC Platform: Avoid Rejection Due to Immune Response

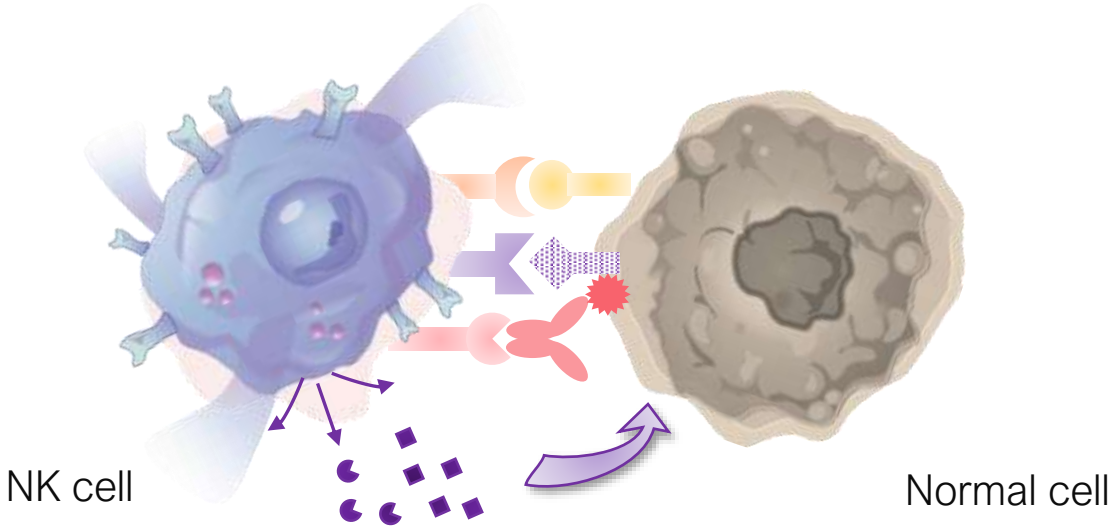


We produce immune rejection free iPS cells to realize safe and universal cell therapies.

NK Cells

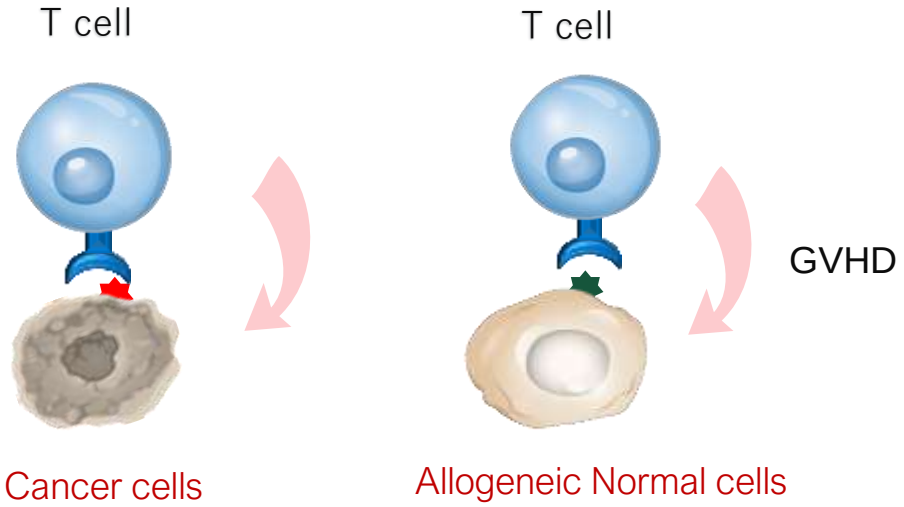
HLCN061: NK Cells

NK Cells：



・NK cells are large granular lymphocytes (LGL) and critical to the innate immune system. The role of NK cells is to recognize and attack abnormal cells, such as cancer cells and virus-infected cells.

Superiority of NK cells to T cells

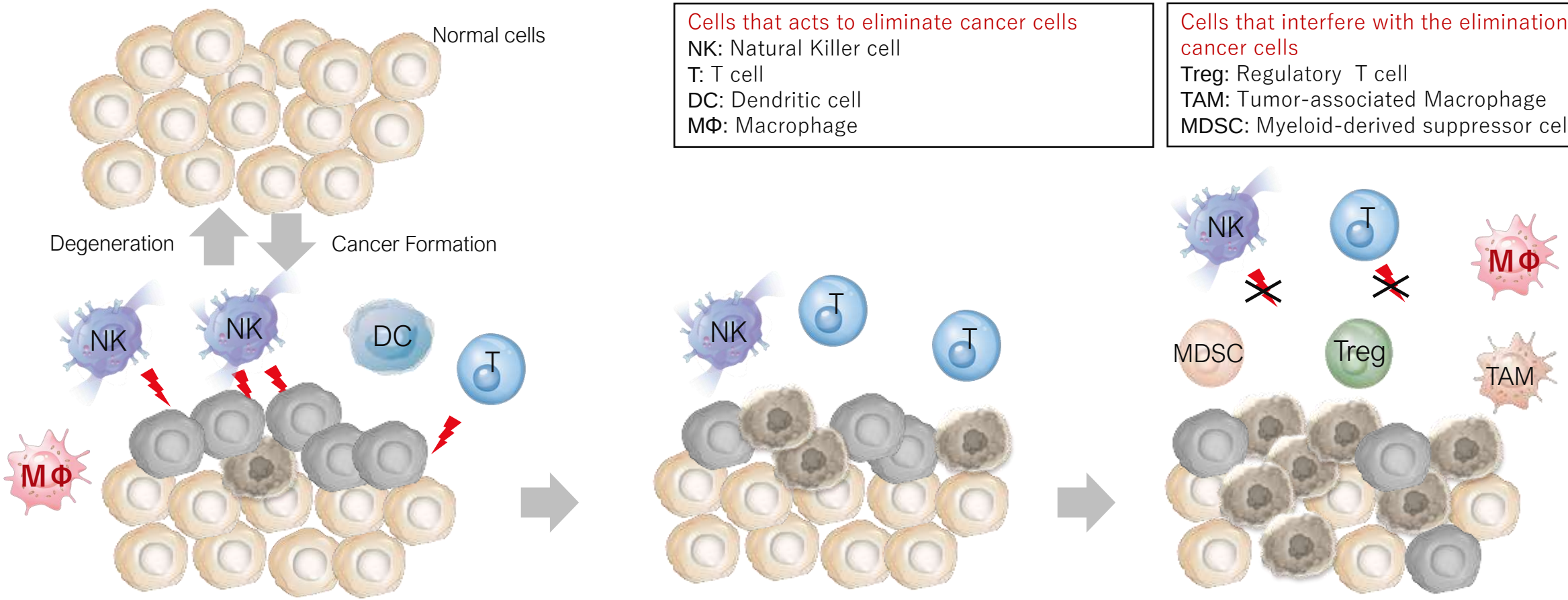


- Graft-versus-host disease (GVHD) occurs with allogeneic T cells
- Solid cancers are heterogeneous and have few relevant targets of cancer antigens
- Cytokine syndrome occurs with T cells

HLCN061: Theory of Cancer Immunoediting

Cells that acts to eliminate cancer cells
NK: Natural Killer cell
T: T cell
DC: Dendritic cell
MΦ: Macrophage

Cells that interfere with the elimination of cancer cells
Treg: Regulatory T cell
TAM: Tumor-associated Macrophage
MDSC: Myeloid-derived suppressor cell



Elimination

- NK and T cells attack and eliminate cancerous cells

Equilibrium

- Equilibrium between cancer growth and clearance by immune system

Escape

- Cancer cells avoid immunity
- Appearance of immune suppressive cells

(Source) modified from Schreiber et al., Science 2011, 331 (6024): 1565

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