FY2020 Q1 Financial Results

Company

HEALIOS K.K. (TSE 4593)

Date

May 14, 2020

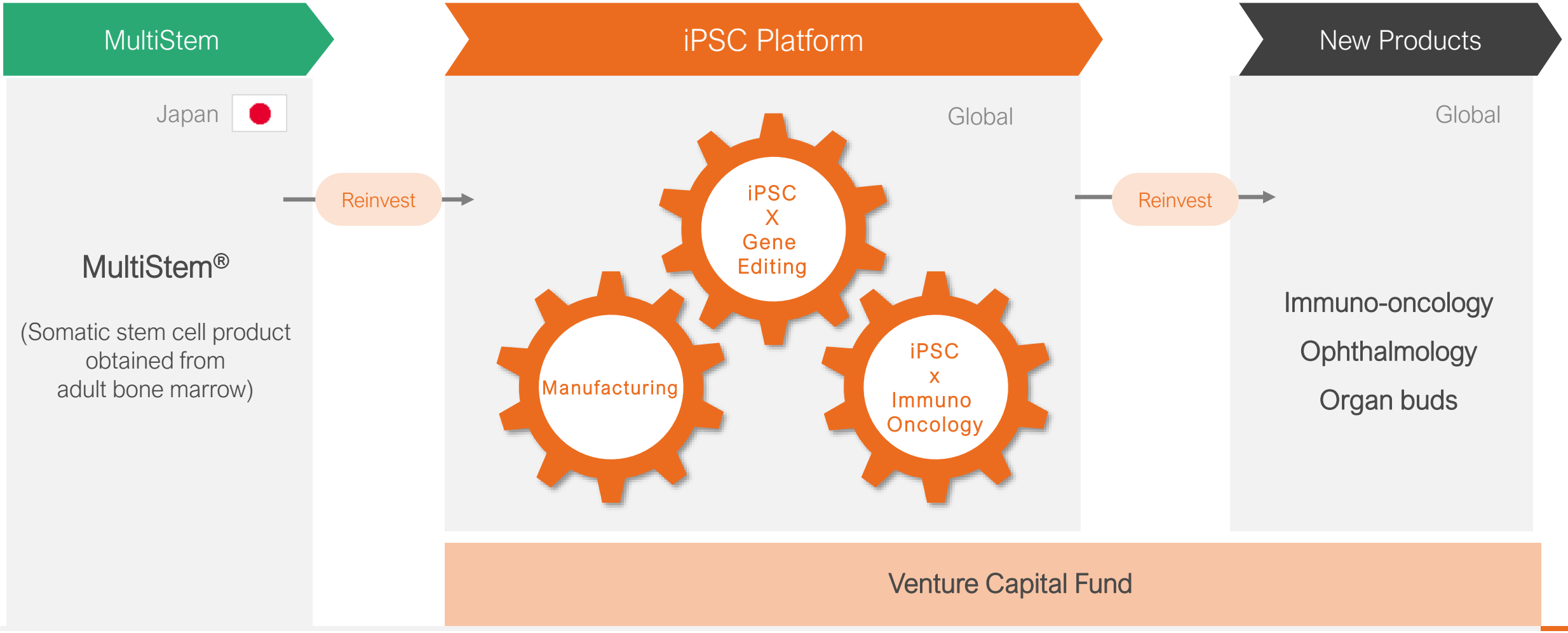


1. Strategy/Updates | 02
2. HLCM051 Stroke | 06
3. HLCM051 ARDS | 12
4. iPSC Platform | 18
5. HLCN061：Immuno-oncology(NK Cells) | 21
6. HLCR011 AMD | 25
7. HLCL041 Liver Organ Bud Platform | 31
8. Financial Highlights | 36
9. Appendix | 40

Strategy

Reinvest somatic stem cell product earnings to establish next-generation stem cell platform

Expect synergistic benefit from venture capital fund



© HEALIOS K.K. All rights reserved.

Pipeline

Update

Healios

Market	Field	Development Code	Indication	Pre-clinical test	Clinical trial	Apply-approve	On Market	Progress status
Japan	Somatic Stem Cell Regenerative Medicine	HLCM051	Ischemic Stroke	→	→			With the continued COVID-19 pandemic, the pace of clinical trial has slowed
			ARDS	→	→			Assessing impact on clinical trial progress
	iPSC Regenerative Medicine	HLCR011	Wet AMD	→				Undergoing preparation for clinical trial Joint development with Sumitomo Dainippon Pharma
		HLCL041	Metabolic Liver Disease	→				Joint research with Yokohama City University
		HLCN061	Solid Tumors	→				Research and development of genetically modified NK cells(*1)

Market	Field	Development code	Indication	Pre-Clinical test	Phase 1 trial	Phase 2 trial	Phase 3 trial	Apply-approve	On Market	Progress status
US EU	iPSC Regenerative Medicine	HLCR012	Dry AMD	→						CRADA with NEI
US		HLCN061	Solid Tumors	→						Research and development of genetically modified NK cells(*1)

*1) NK Cells：Natural Killer Cells

© HEALIOS K.K. All rights reserved.

HLCM051 ARDS: ONE-BRIDGE Study Ongoing

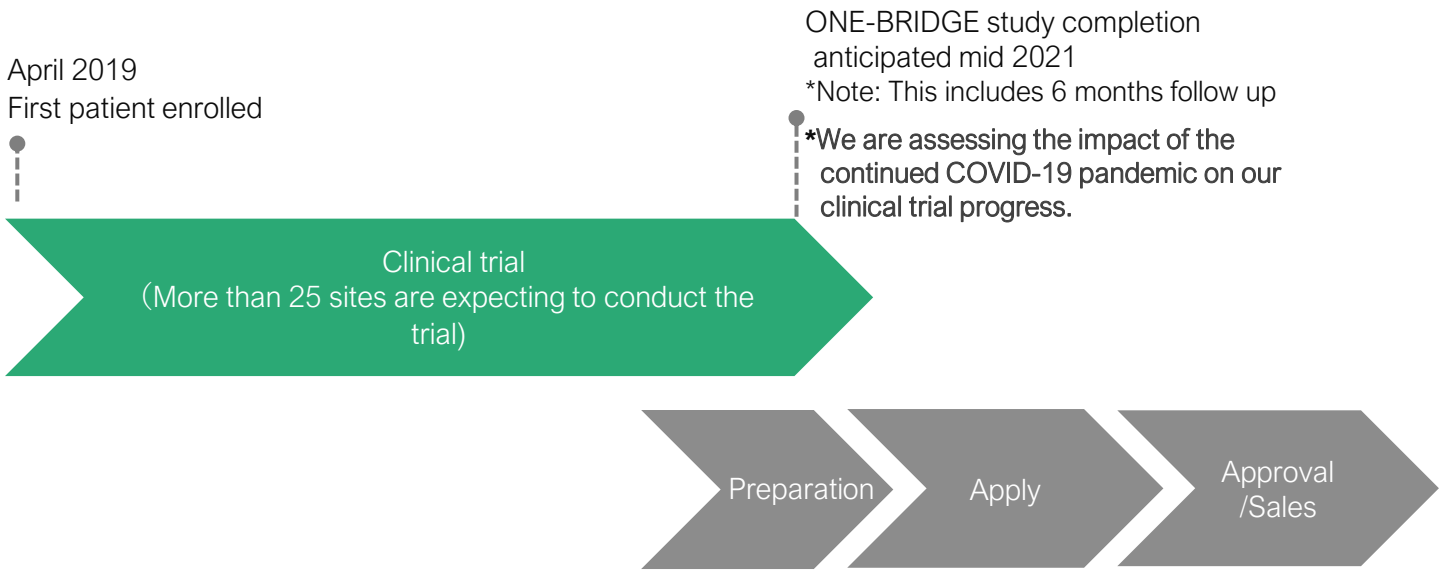
Update

Healios

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

Development Plan

We have decided to make a protocol change to the ONE-BRIDGE study to include COVID-19 induced ARDS patients as a separate cohort in the ongoing trial.



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)

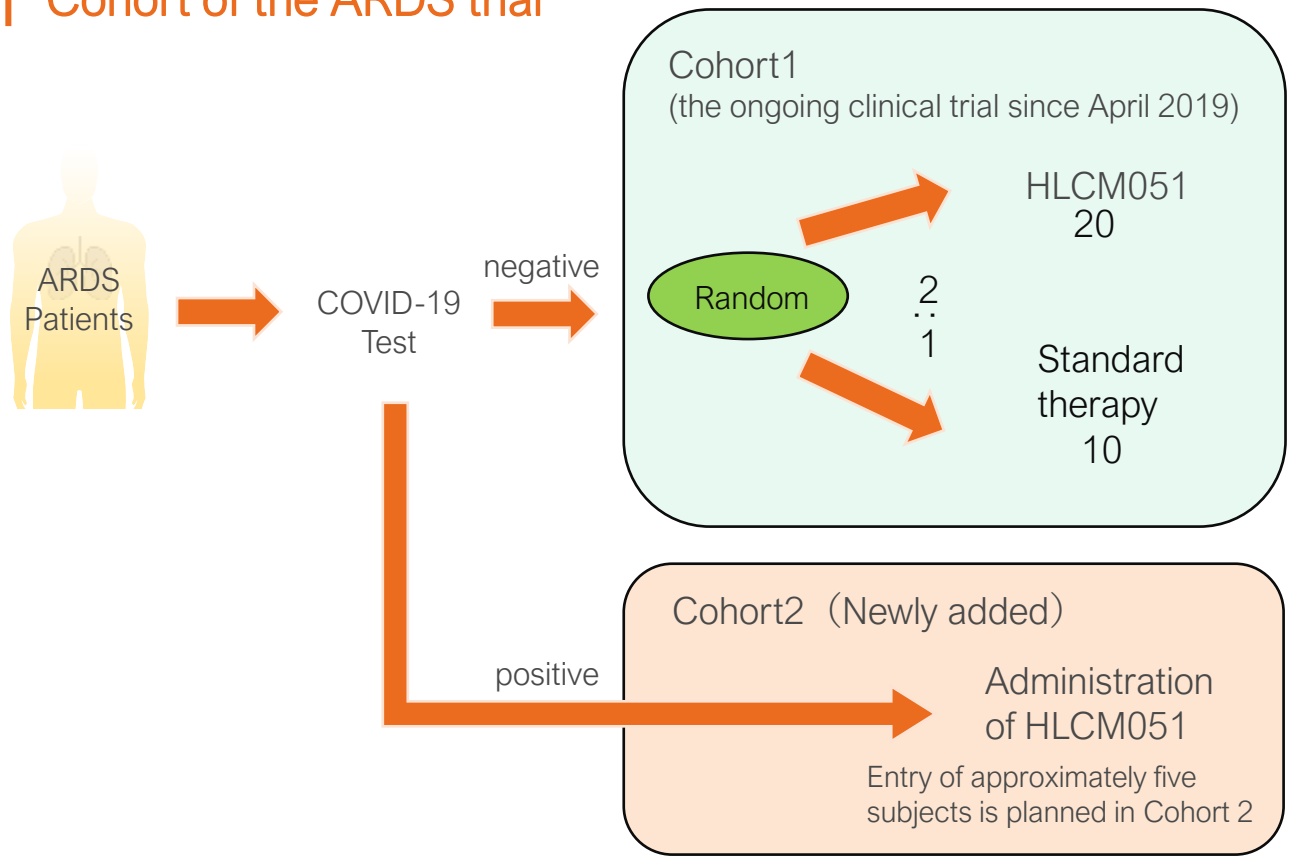
HLCM051 has been designated as an orphan regenerative medicine product for use in the treatment of ARDS.

© HEALIOS K.K. All rights reserved.

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

The new group of patients with COVID-19 pneumonia (Cohort2) is separated from the ongoing treatment group (Cohort1). The addition of this COVID-19 cohort should not effect the progress of the originally planned clinical trial.

Cohort of the ARDS trial

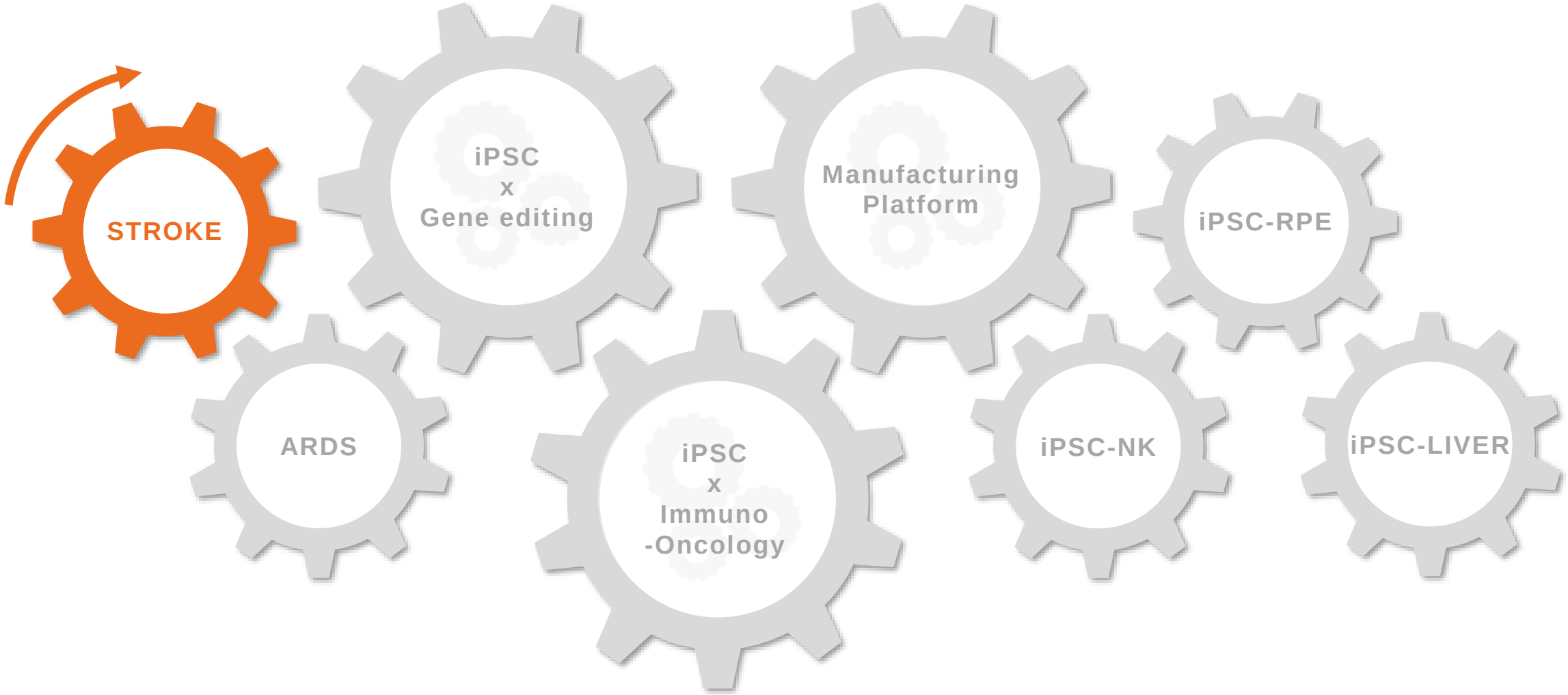


Overview of the ARDS trial (on April 13, 2020～)

Subjects	Patients with pneumonia induced ARDS	Patients with pneumonia-induced ARDS caused by COVID-19
Enrolment	30 (HLCM051: 20, Standard therapy: 10)	Approximately 5 (HLCM051: 5)
Objective	Efficacy and safety evaluation	Safety evaluation

© HEALIOS K.K. All rights reserved.

HLCM051 Stroke



© HEALIOS K.K. All rights reserved.

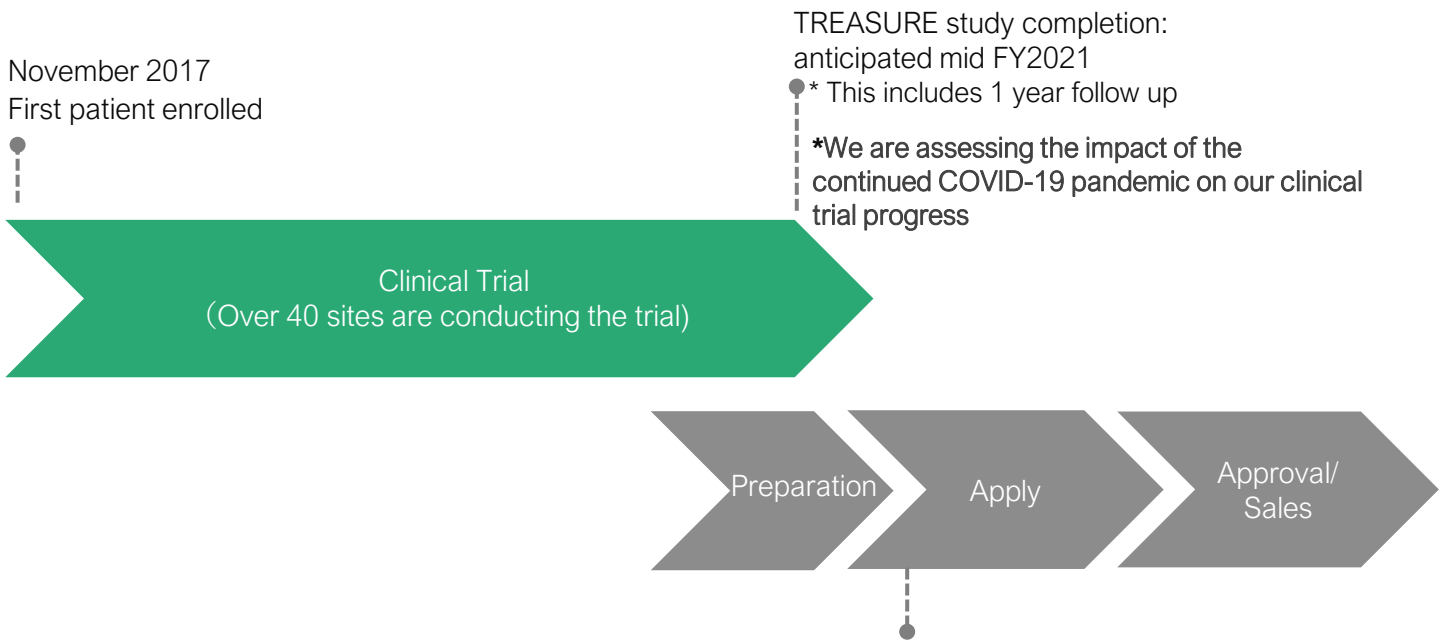
HLCM051 Stroke: TREASURE Study Ongoing

Update

Healios

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

Development Plan



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]

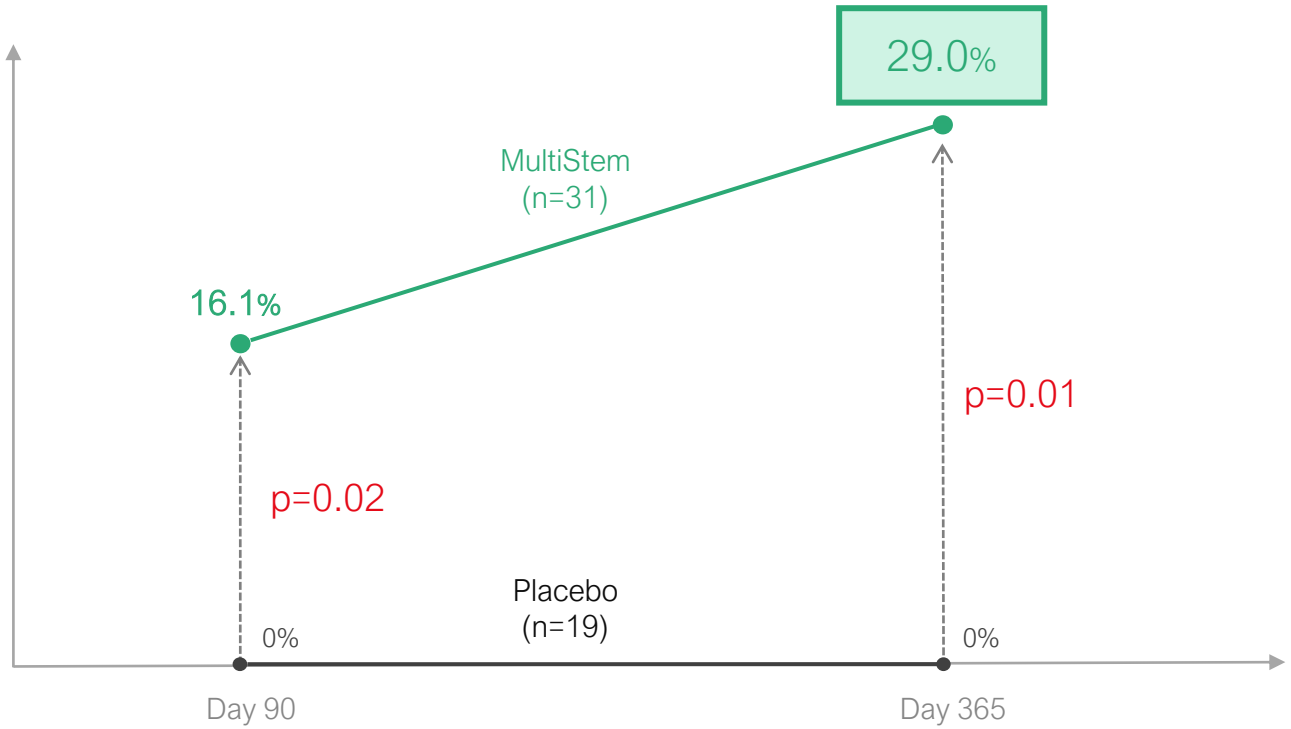
- “Excellent Outcome” is defined as achieving mRS ≤1, NIHSS ≤1, and BI ≥95. mRS, NIHSS, and BI are the three major indices of functional assessment for stroke patients.

© HEALIOS K.K. All rights reserved.

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

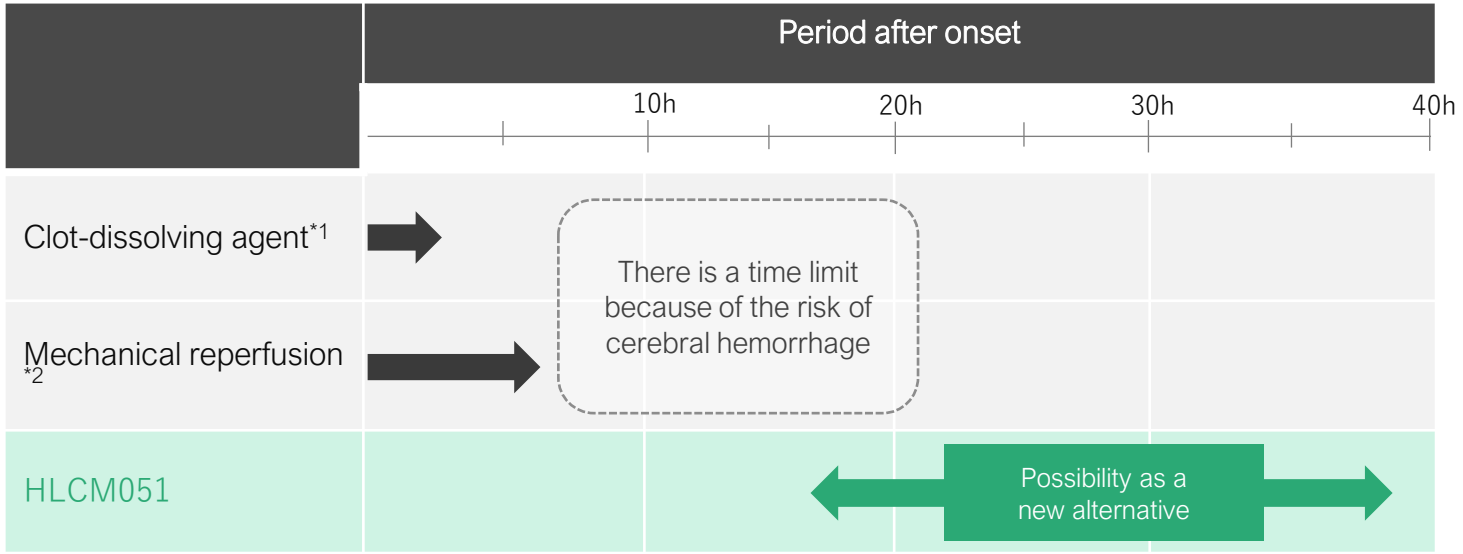
*<Excellent Outcome> is defined as mRS score of ≤1 (scale, 0 to 6), NIHSS score of ≤1 (scale, 0 to 42), and BI score of ≥95 (scale, 0 to 100).

© HEALIOS K.K. All rights reserved.

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.



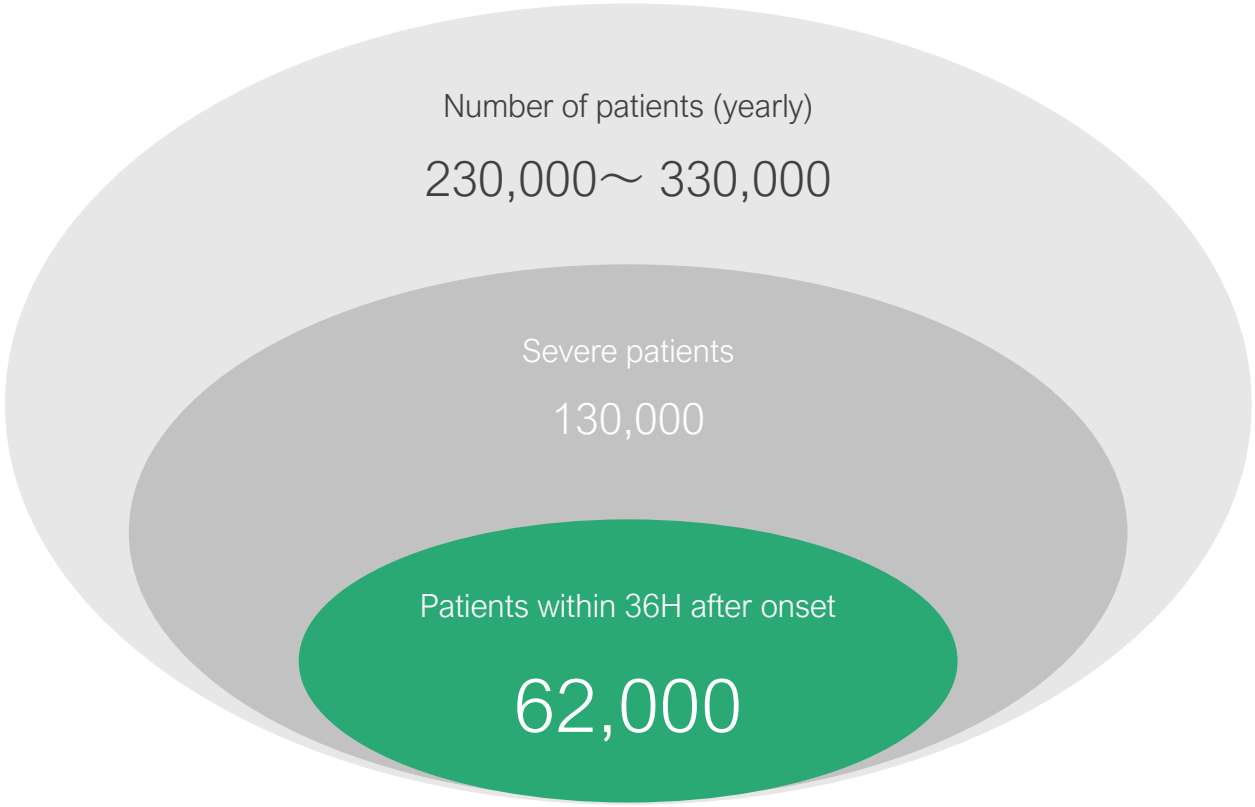
(Source) Athersys

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.

© HEALIOS K.K. All rights reserved.

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)

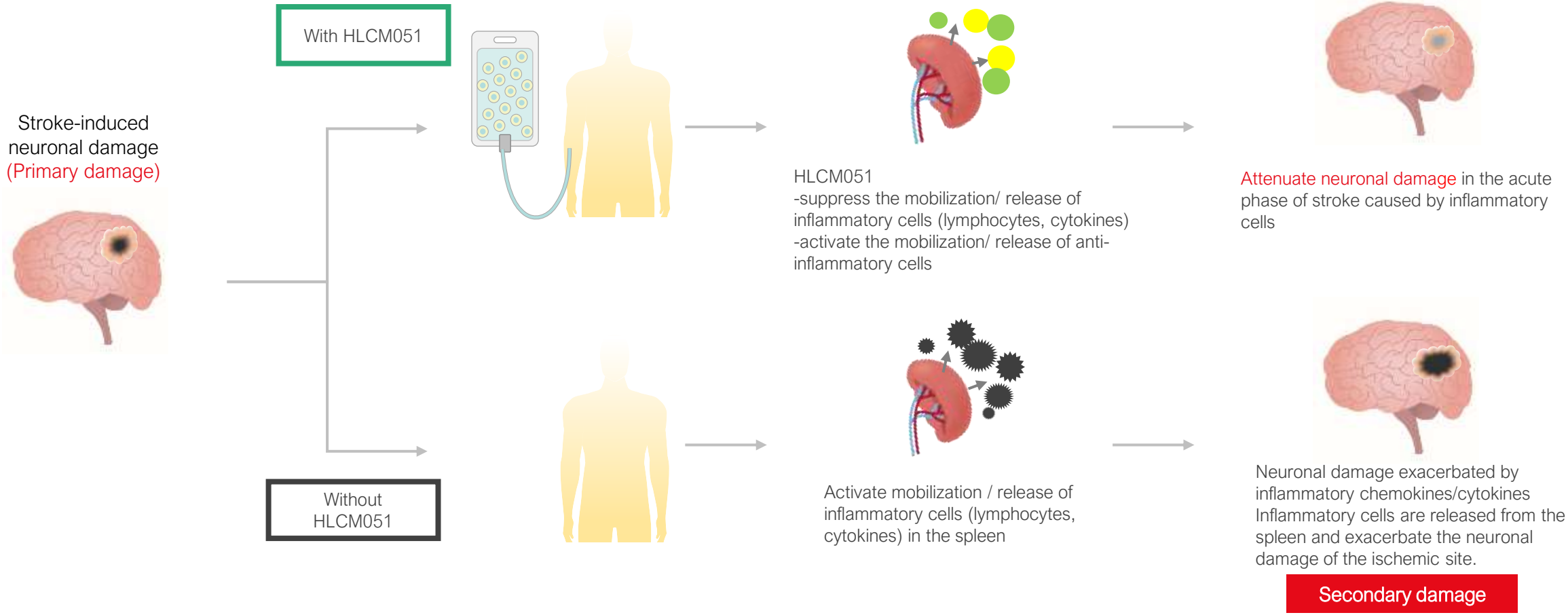
Patients within 36 hour after onset

(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.

© HEALIOS K.K. All rights reserved.

HLCM051 Stroke: Mechanism of HLCM051 Treatment

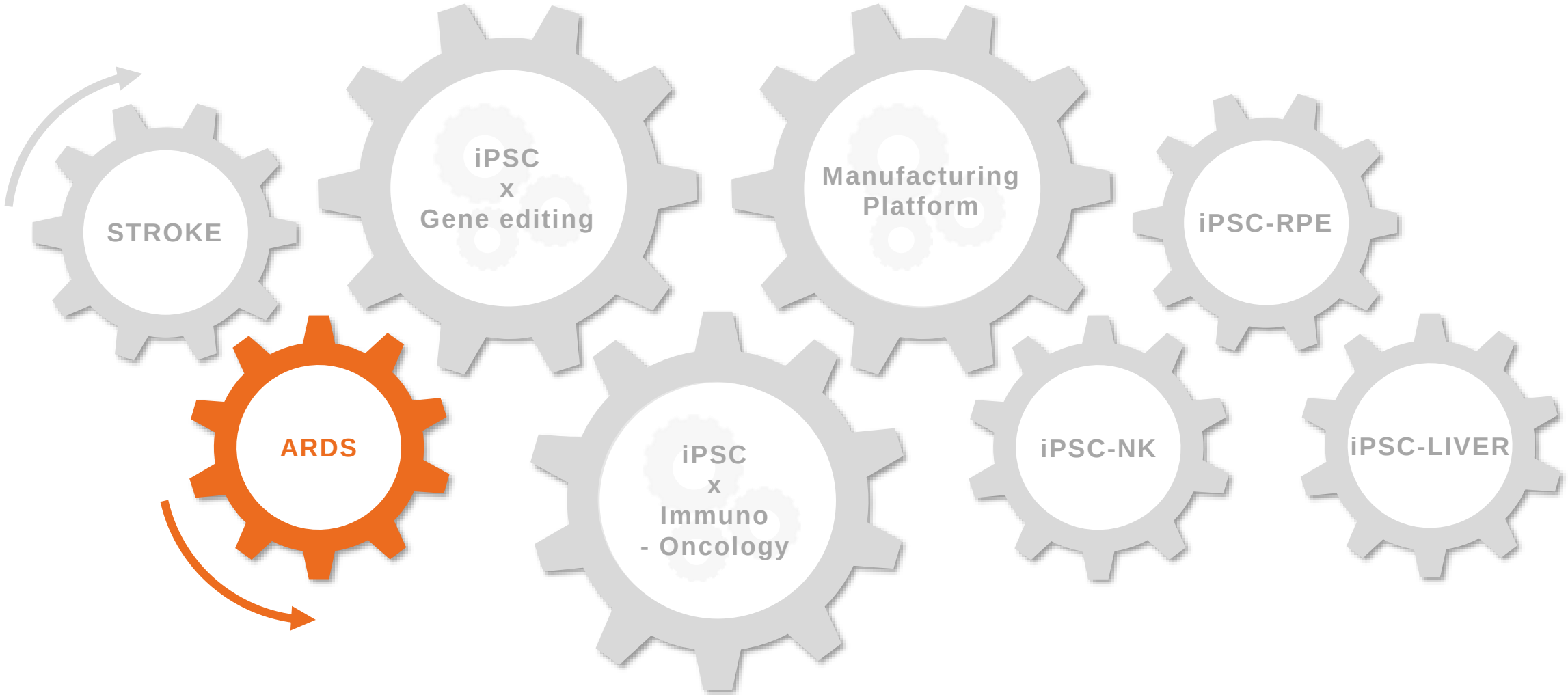
Administrated intravenously, HLCM051 distributes to the spleen downregulating the hyperinflammatory response and promotes a neuroprotective effect by releasing various cytokines and growth factors.



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

© HEALIOS K.K. All rights reserved.

HLCM051 ARDS



© HEALIOS K.K. All rights reserved.

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.

© HEALIOS K.K. All rights reserved.

HLCM051 ARDS: Number of ARDS Patients

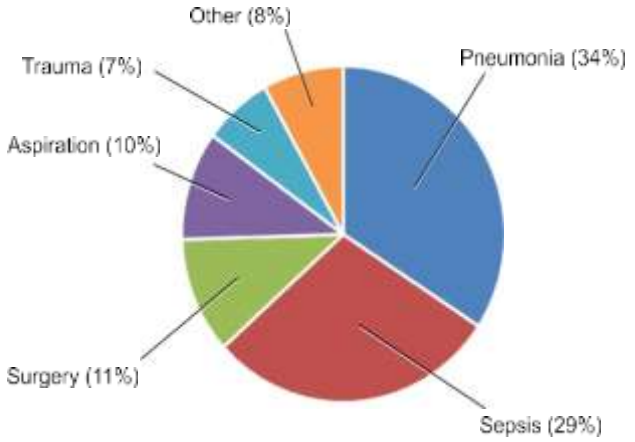
Number of ARDS patients in Japan estimated approximately 7,000～12,000 per year

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.

© HEALIOS K.K. All rights reserved.

HLCM051 ARDS: Relationship between COVID-19 and ARDS

New Healios

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

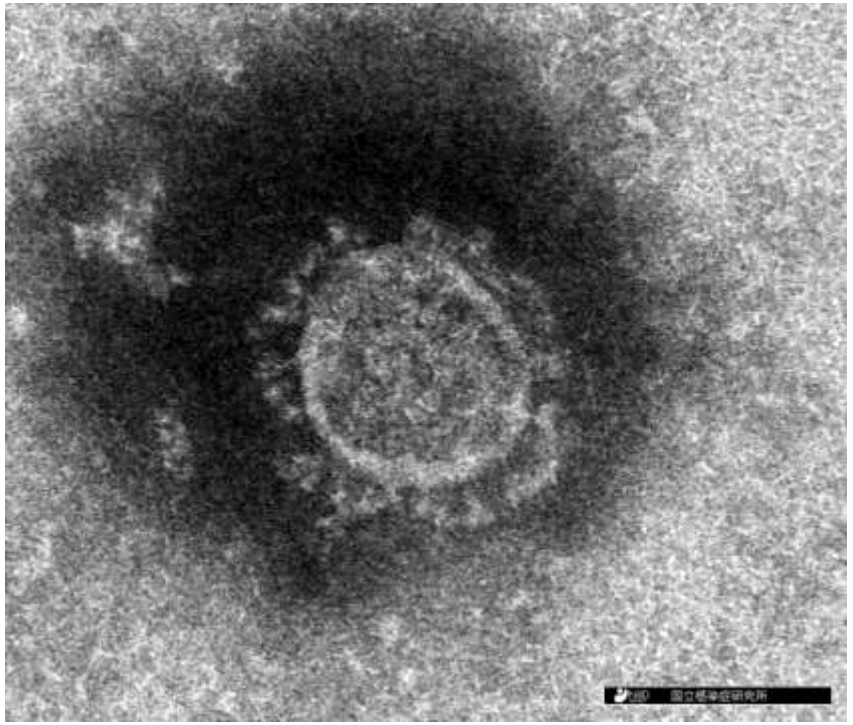
・According to the data published on the initial group of cases of the new coronavirus (COVID-19) in Wuhan, 31 to 41.8% of hospitalized patients developed ARDS and ARDS complications were confirmed in 54 to 93% of fatal cases※1※2, indicating that ARDS is a major cause of mortality in COVID-19 patients.

(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 (local time), the first patient was enrolled in this trial.

・In China, several clinical trials using mesenchymal stem cells in patients with COVID-19 are in progress.

Electron micrograph of SARS-CoV-2



(Source) The National Institute of Infectious disease

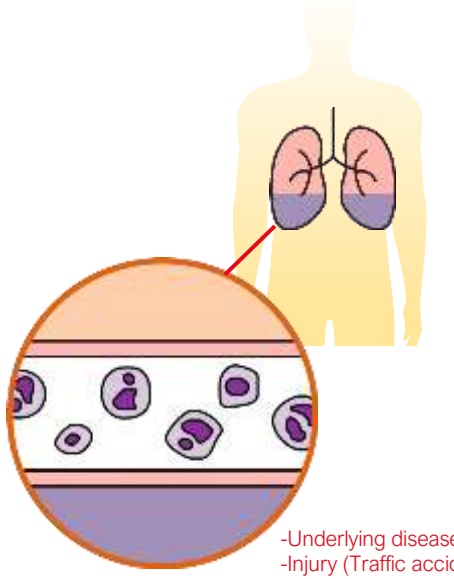
(Source) *1 Zhou F, et al. Lancet. 2020 Mar 11. pii: S0140-6736(20)30566-3
(Source) *2 Wu C , et al. JAMA Intern Med. 2020 Mar 13. doi: 10.1001

© HEALIOS K.K. All rights reserved.

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.

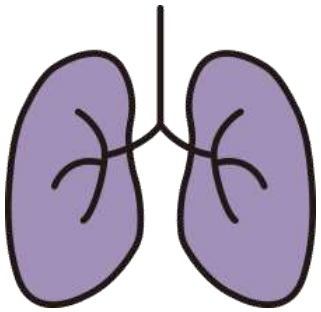
Inflammatory cells are released



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

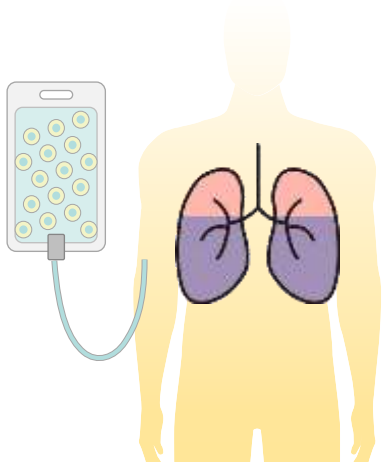
When the tissue is damaged, inflammatory cells are released in large quantities.

Inflammatory cells attack the lungs



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

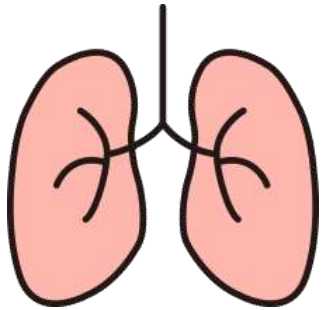
HLCM051 Administered



- 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.

© HEALIOS K.K. All rights reserved.

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.

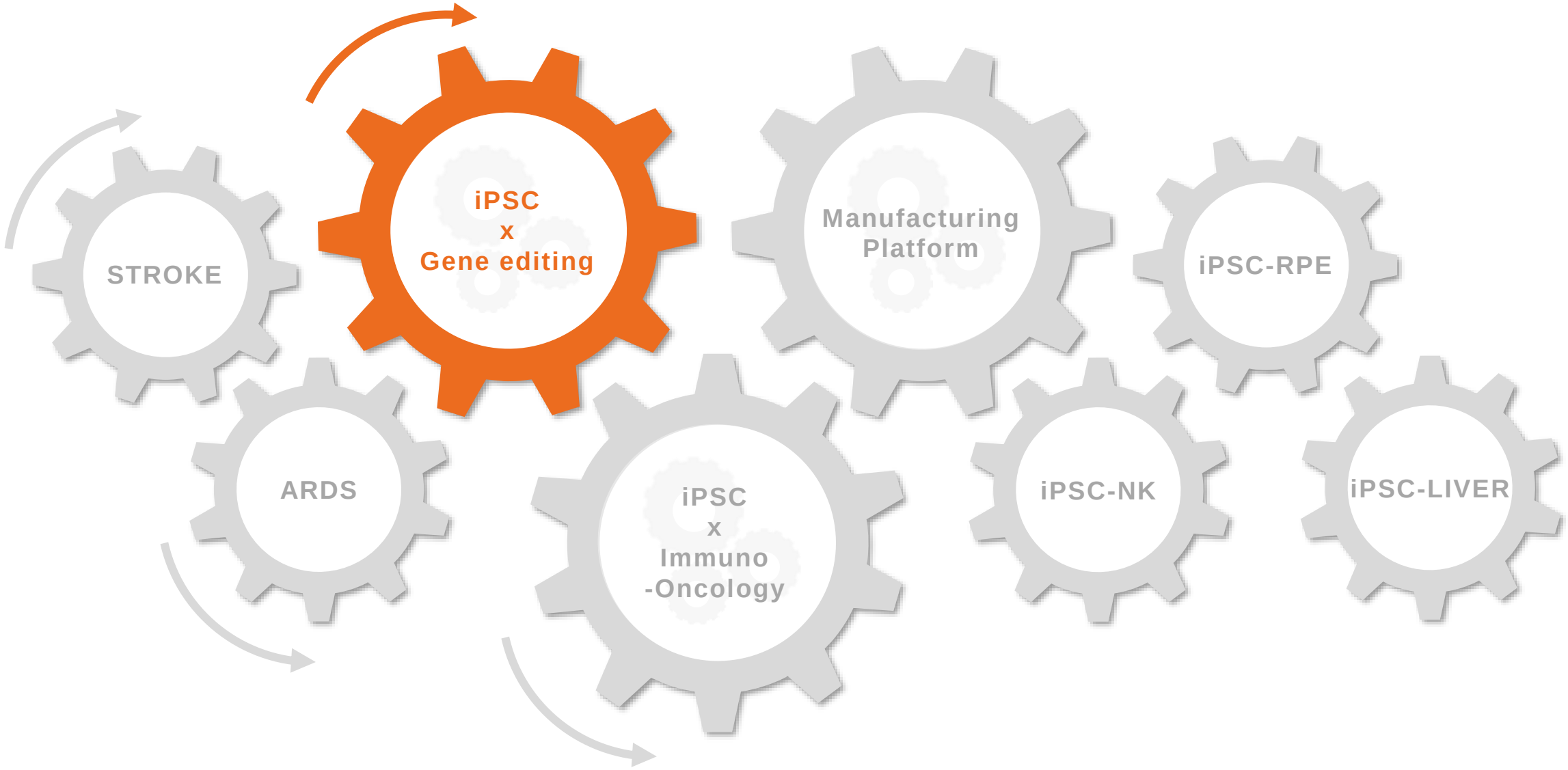
Overview of the Analysis

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

© HEALIOS K.K. All rights reserved.

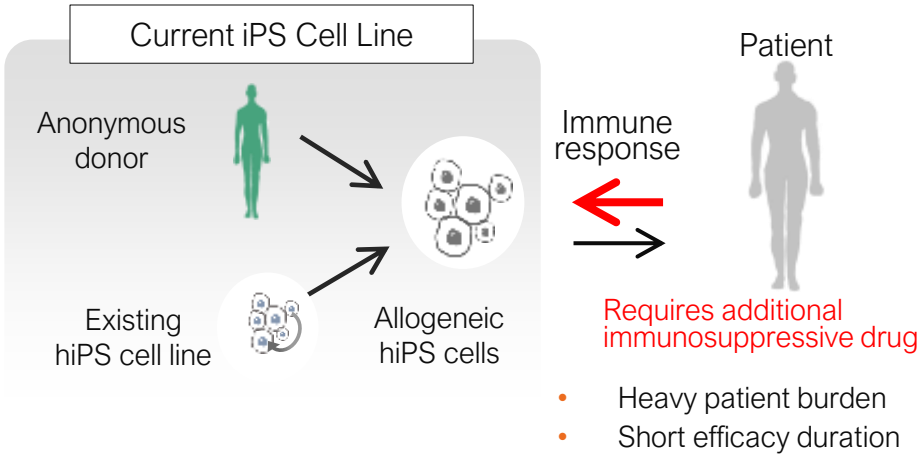
iPSC Platform



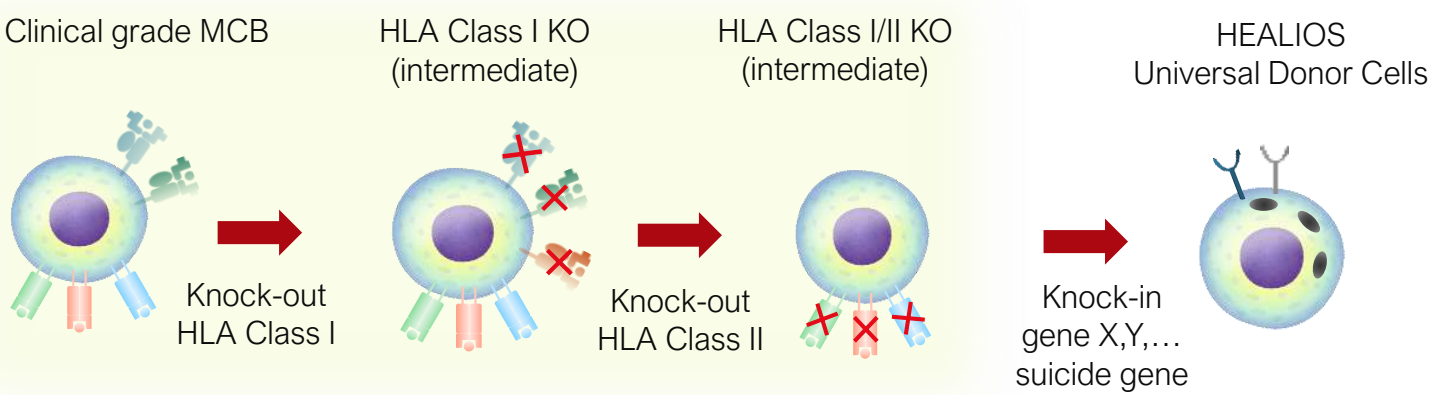
© HEALIOS K.K. All rights reserved.

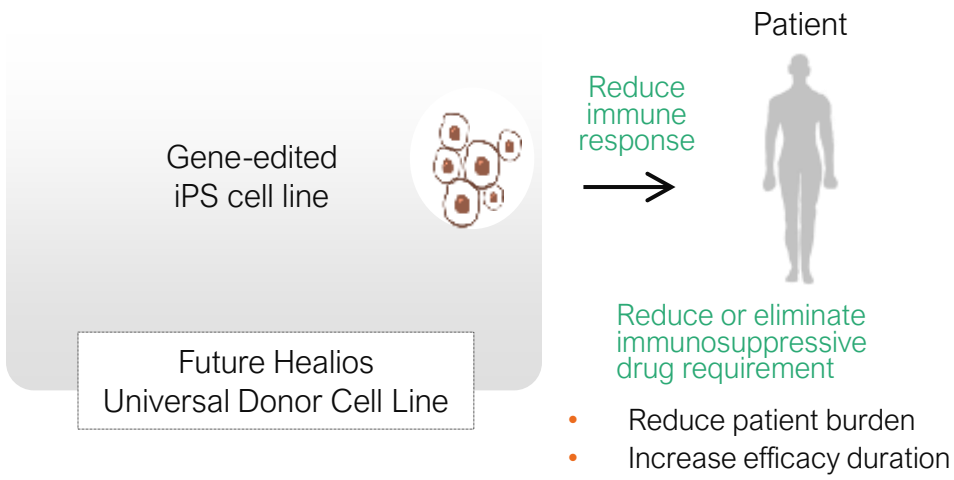
Proprietary gene-edited iPSC platform: “Universal Donor Cells”

- Generating hypoimmunogenic human pluripotent stem cells (universal donor cells or UDCs) as a starting material for allogenic transplantation
- Accelerates progress towards next-generation therapies in ophthalmology, organ buds, and immuno-oncology
- Leading the development of a clinical grade universal donor cell line in accordance with global standards.
- Initiated FDA and PMDA consultation and will distribute research cell line in the near future.



HLA knockout procedure to generate HEALIOS Universal Donor Cells





© HEALIOS K.K. All rights reserved.

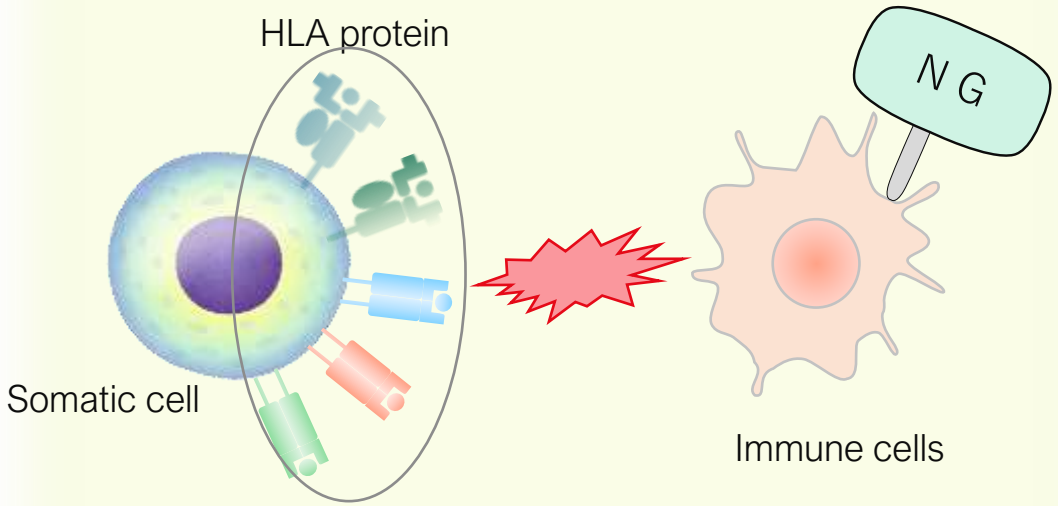
iPSC Platform: Self-recognition of HLA Protein and UDC

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.



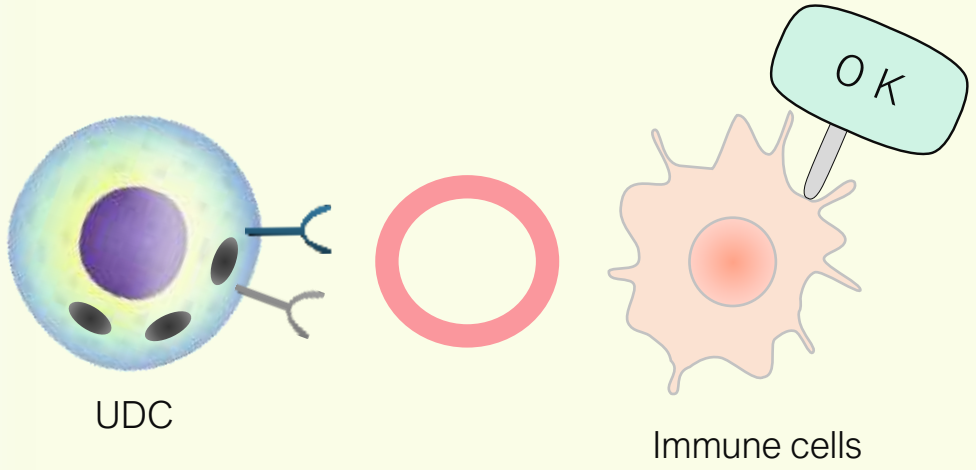
HLA protein mismatch causes immune rejection

UDC:

・Deletion of HLA protein

・Introduction of immunosuppression-related molecules

・Introduction of suicide genes as a safety mechanism

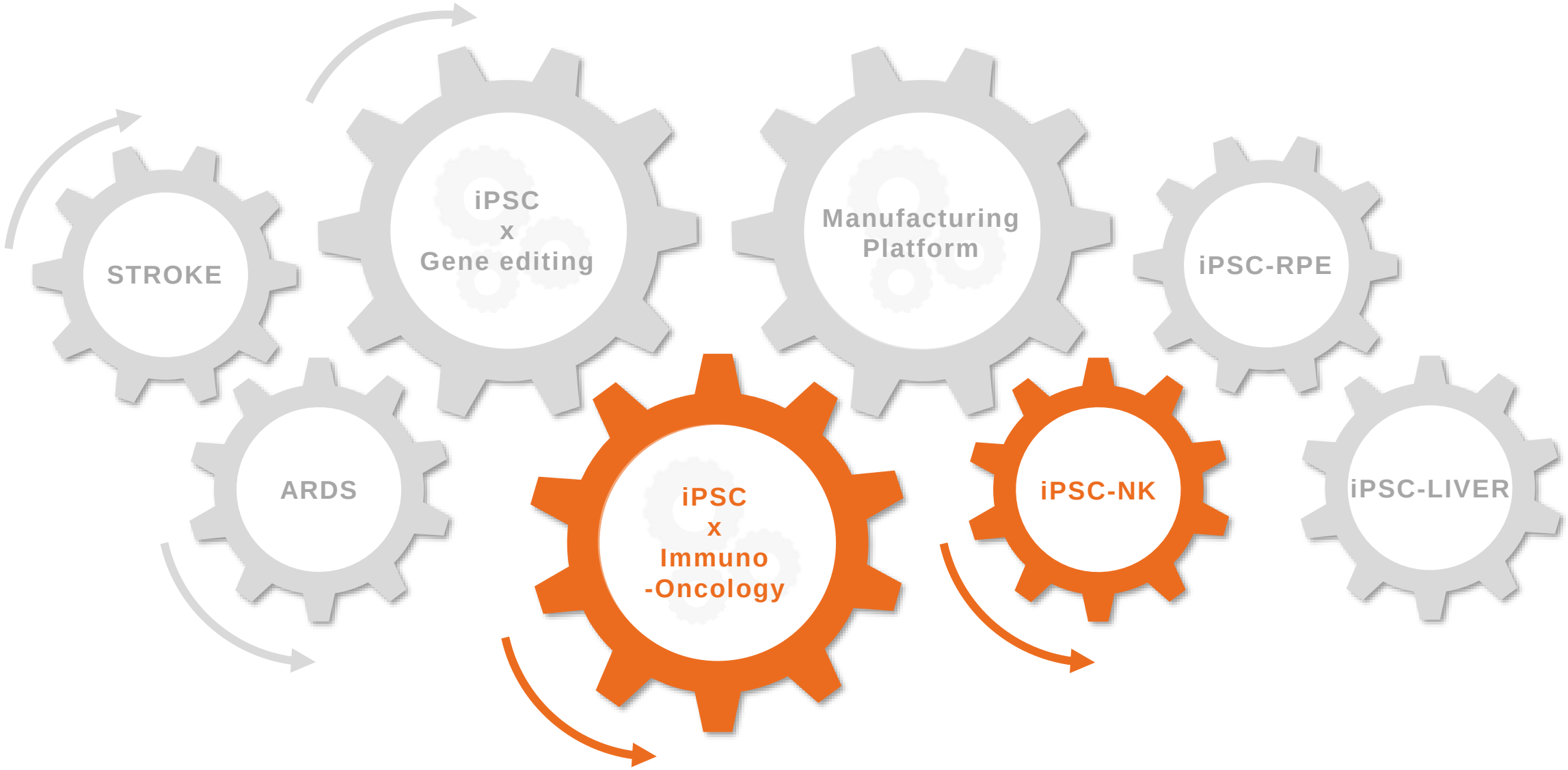


UDC is a safer and more versatile iPS cell

＊See Appendix for additional explanation.

© HEALIOS K.K. All rights reserved.

HLCN061

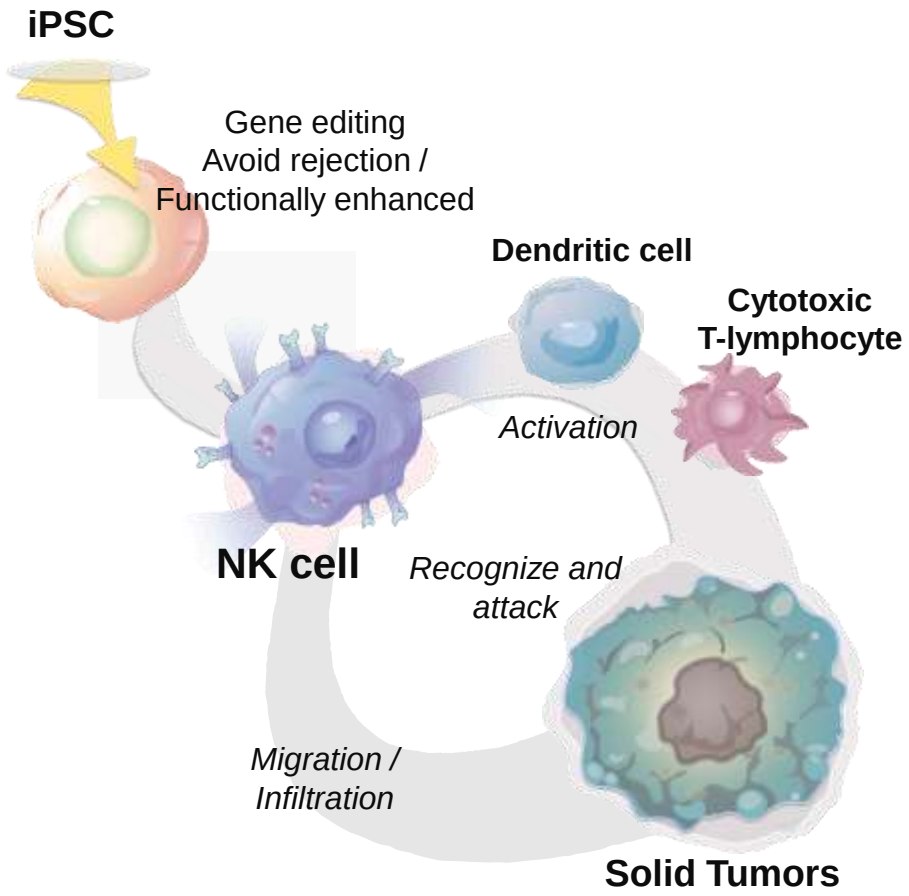


© HEALIOS K.K. All rights reserved.

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

Natural killer (NK) cells are a subset of lymphocytes, a type of white blood cell. NK cells 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
- The expected efficacy of treatments using NK cells includes life-extension, promotion of healing, relief of symptoms, and improvement of quality of life.

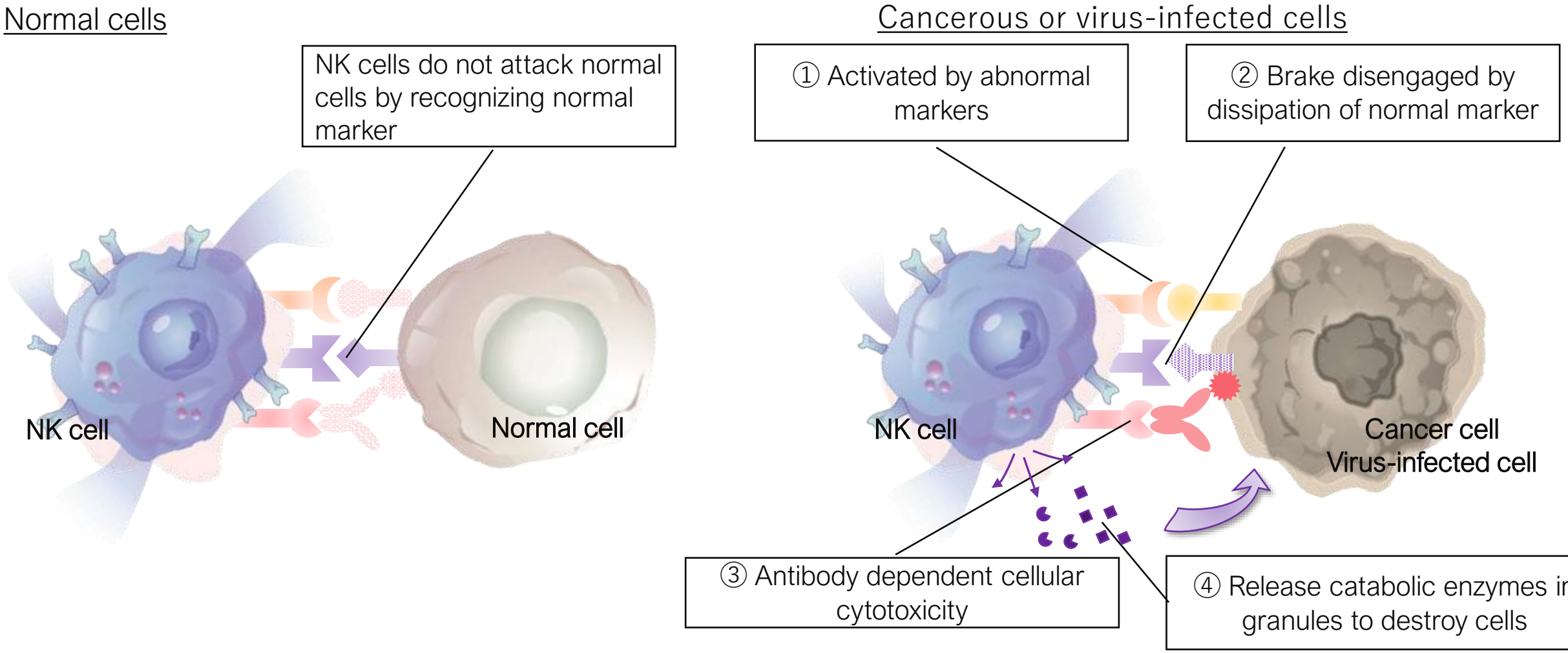


© HEALIOS K.K. All rights reserved.

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

New Healios

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.

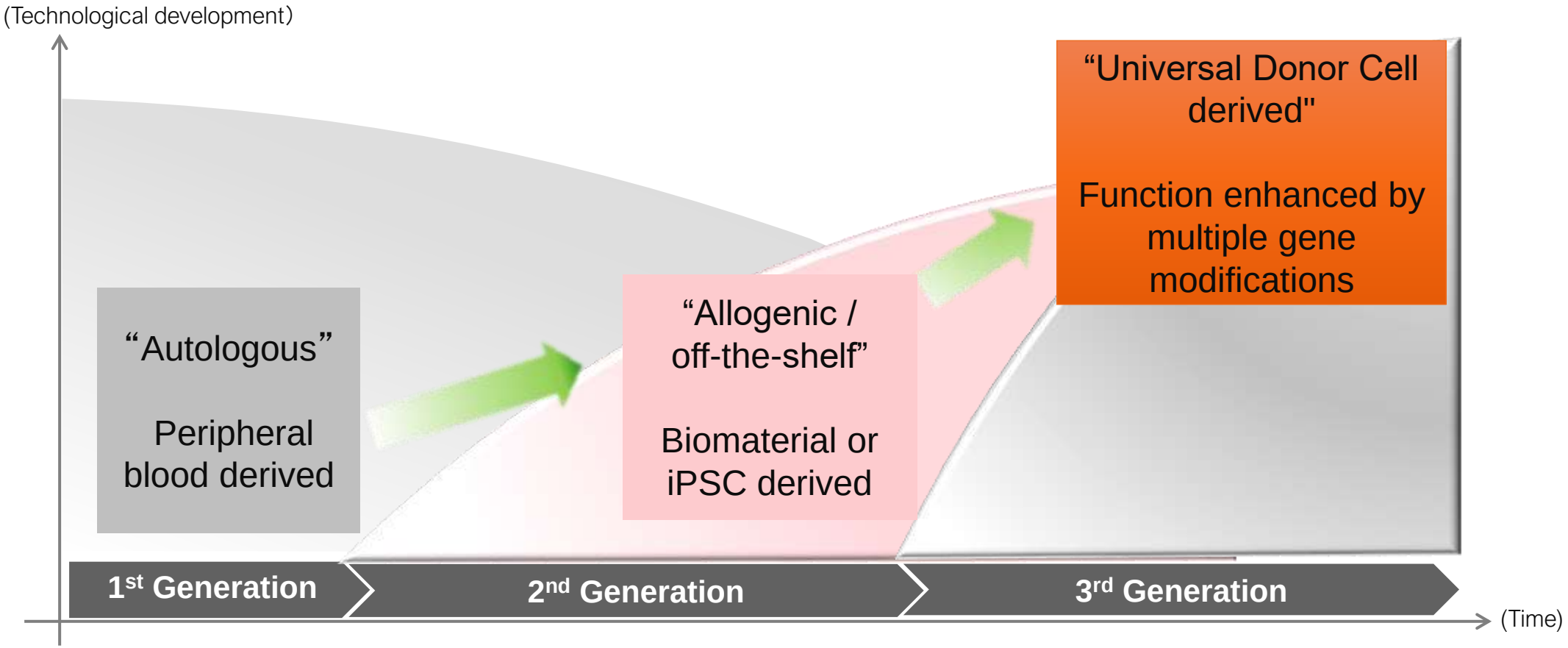


© HEALIOS K.K. All rights reserved.

HLCN061: iPSC Derived Gene-Modified NK Cells

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

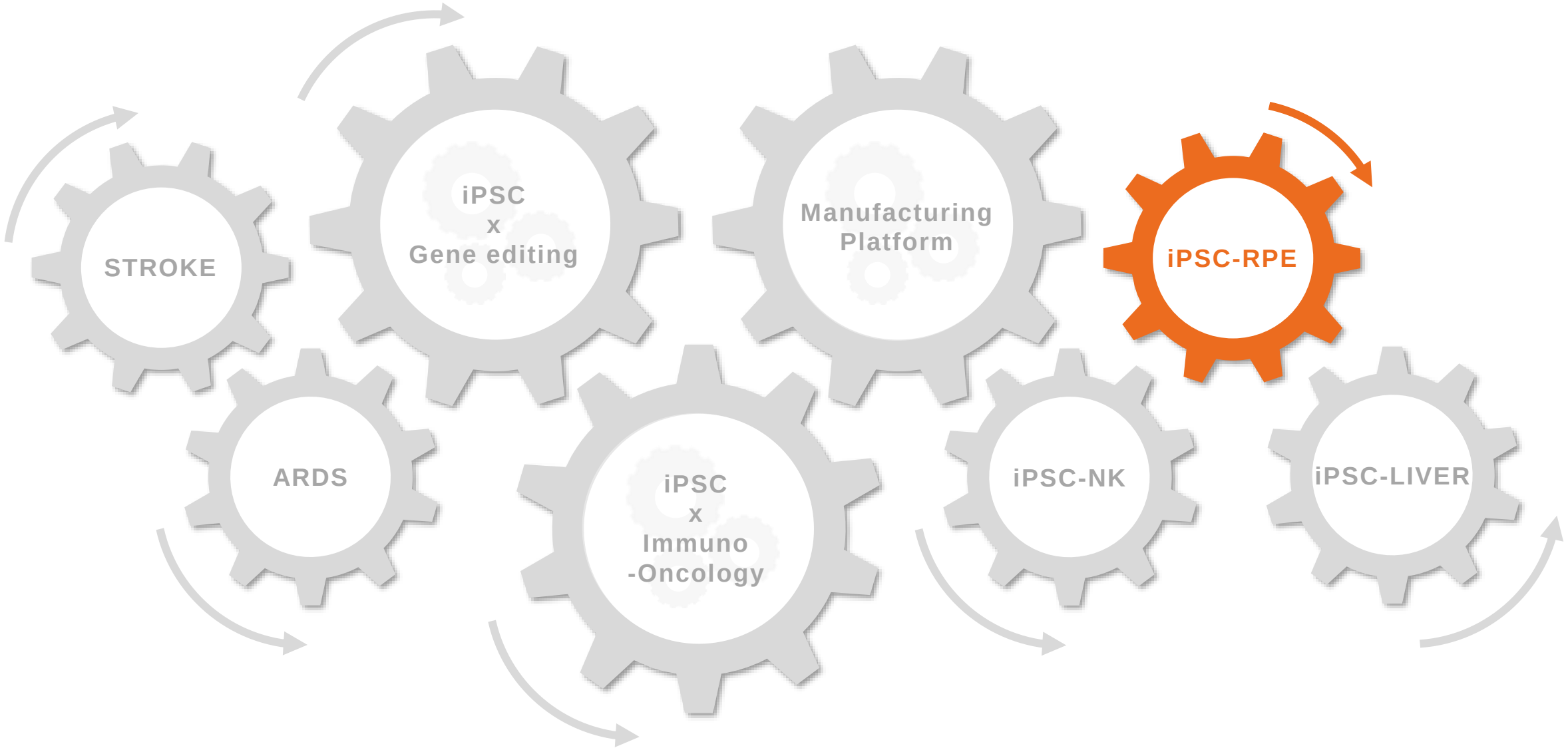
Target an off-the-shelf product: stable production and quality with lower cost of goods.



＊See Appendix for additional explanation.

© HEALIOS K.K. All rights reserved.

HLCR011 AMD

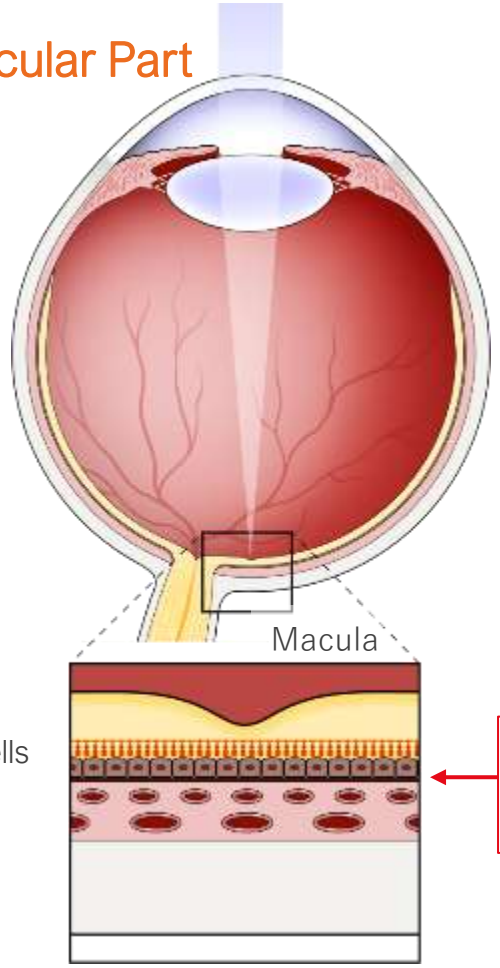


© HEALIOS K.K. All rights reserved.

HLCR011 AMD: Pathological Conditions

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

Regular Macular Part



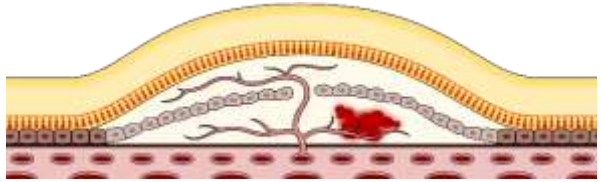
Developed Dry-AMD

Immunity barrier maintained
→ Degeneration of photoreceptor→ Dry AMD



Wet AMD

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



© HEALIOS K.K. All rights reserved.

HLCR011 AMD: Number of AMD Patients

Large number of both Wet and Dry AMD patients (including mild cases)

（Thousand patients）

	US	Japan	Others
Number of AMD Patients	10,000	9,230	13,000
Number of AMD Patients in Serious Cases	2,000	690	2,600～3,220
Wet-AMD patients in serious cases	1,000～1,500	630	1,300～1,950
Dry-AMD patients in serious cases	850～900	60	1,100～1,170

(Source) According to research by Hisayama Kyushu University Graduate School of Medicine in Fukuoka (based on a comprehensive study), the total number of patients in Japan is calculated, estimating the total number of first-stage age-related macular degeneration and latter stage of age-related macular degeneration based on population statistics (2007). Also, the Disease Information Center announced that the number of patients suffering serious cases is approximately 690,000. The total number of patients in the US, which the National Eye Institute reports, includes the total number of age-related macular degeneration patients in mild cases and patients with visual field defects. Also, our company calculated the total number of Dry/Wet patients based on the incidence rates presented by AMDF (2010). Our company calculated the total number of patients in Europe based on incidence rates in each grade of European population statistics （2010)

(Source)Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE).Source: Arch Ophthalmol. 2006 Apr;124(4):529-35

© HEALIOS K.K. All rights reserved.

HLCR011 AMD: Market scale of anti-VEGF treatment

Sales of anti-VEGF treatment are increasing every year

No medicine for Dry AMD

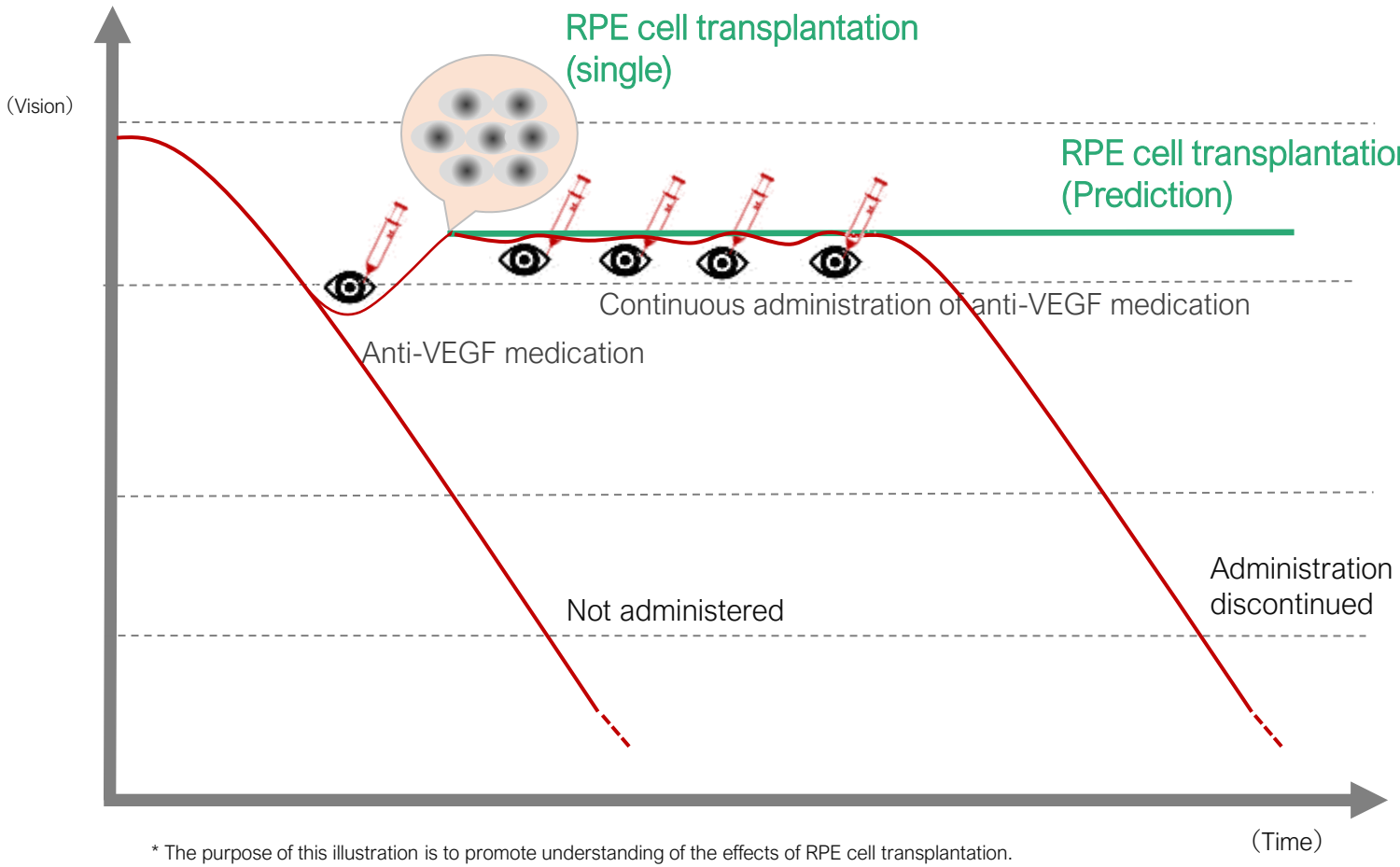
Indication	Medicine/Effect	Year	US	Japan	Others	Total
Wet AMD and other 3 diseases	Anti-VEGF treatment/ Restraint of New Blood Vessels	2016	4.729 billion USD	580 million USD	3.127 billion USD	8.436 billion USD
		2017	5.116 billion USD	632 million USD	3.483billion USD	9.231 billion USD
		2018	5.735 billion USD	713 million USD	4.001billion USD	10.45 billion USD
Dry AMD	No Medicine					

(Source) Market scale was calculated using official materials from drug companies (Roche Diagnostic, Novartis, Regeneron, Bayer HealthCare, Santen Pharmaceutical Co., Ltd).
Calculated using 2015,2016,2017 fiscal year-average exchange rates. (FY2016: $1=¥110, FY2017: $1=¥112, FY2018:$1=¥110)

© HEALIOS K.K. All rights reserved.

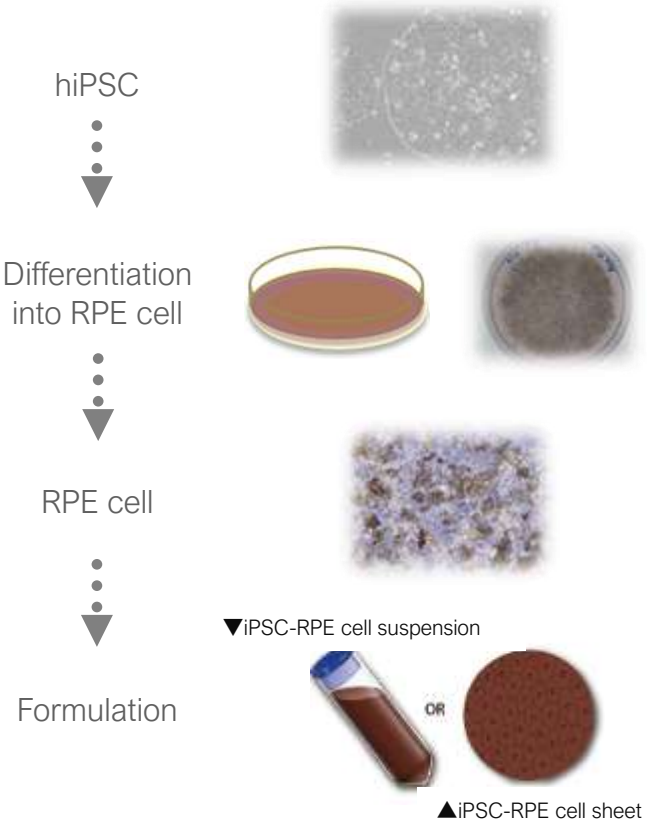
Expected Changes in Vision with iPSC-RPE Cell Products Treatment

Good vision can be maintained with early treatment



* The purpose of this illustration is to promote understanding of the effects of RPE cell transplantation.
Changes in vision with the administration of anti-VEGF medication vary according to patient symptoms and administration frequency.

iPSC-RPE Cell Differentiation



© HEALIOS K.K. All rights reserved.

HLCR011 AMD: Manufacturing for iPSC-derived RPE products

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

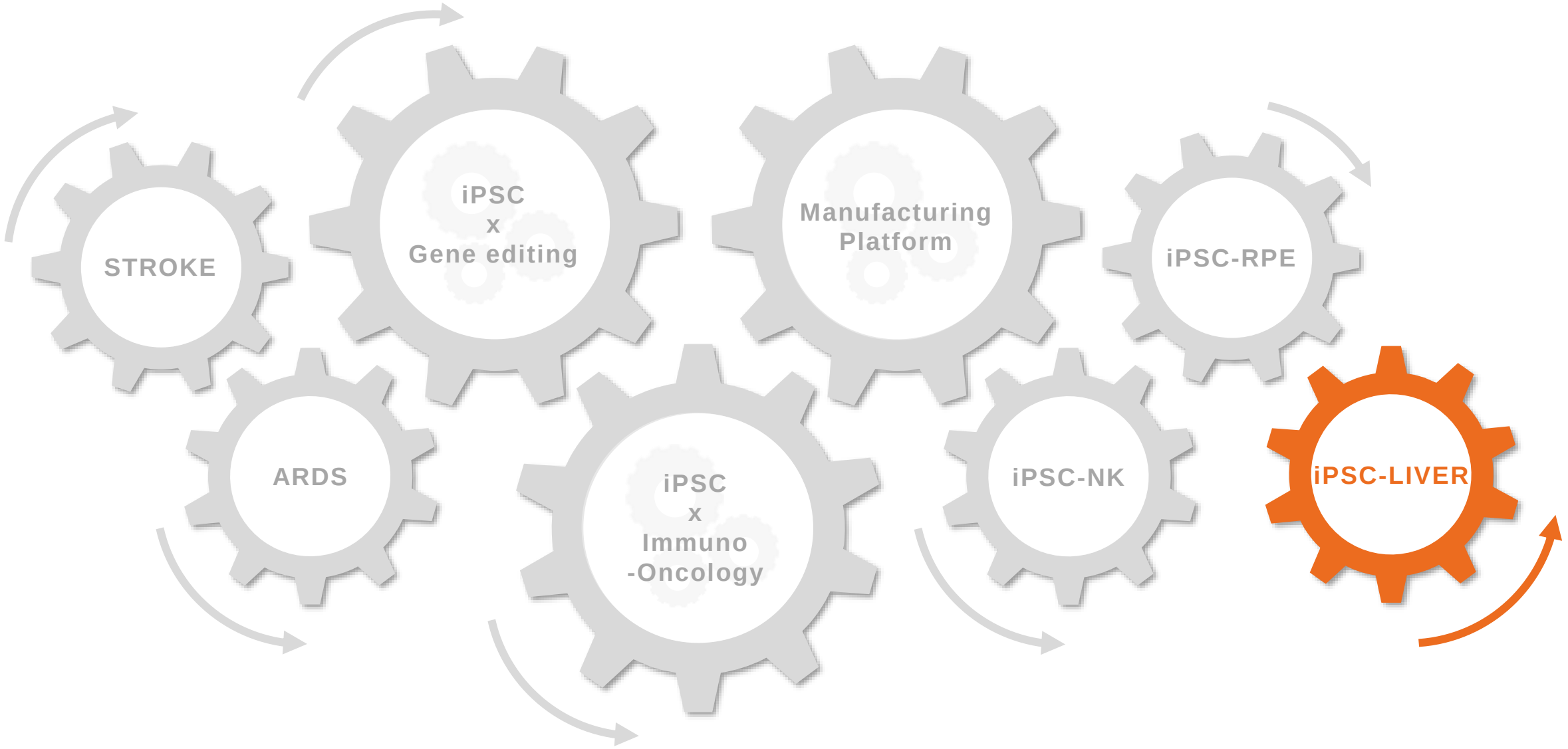
Sighregen rents the facility in SMaRT and is establishing the iPSC-RPE manufacturing system and facility for iPSC-RPE cell products





© HEALIOS K.K. All rights reserved.

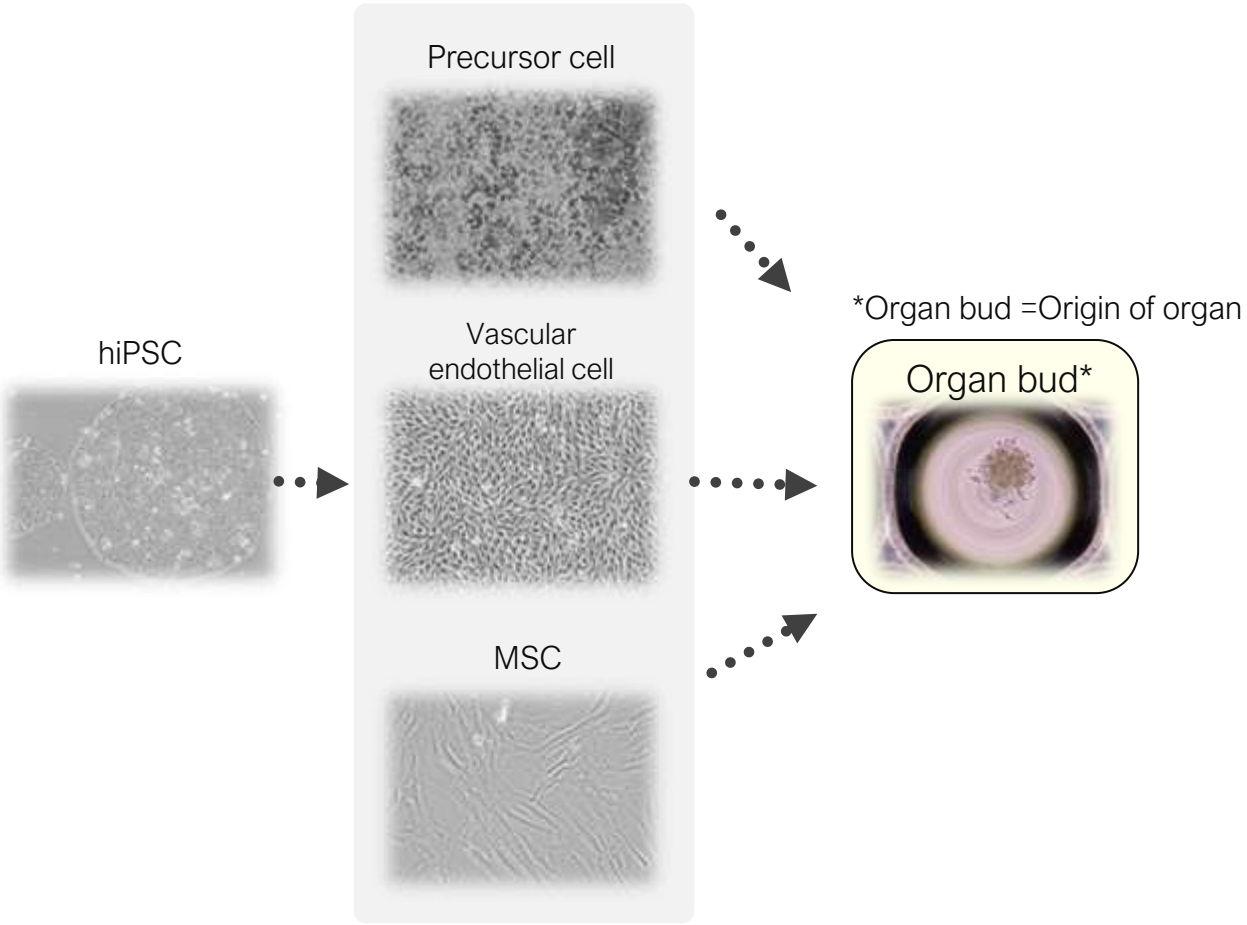
HLCL041 Liver OrganBud Platform

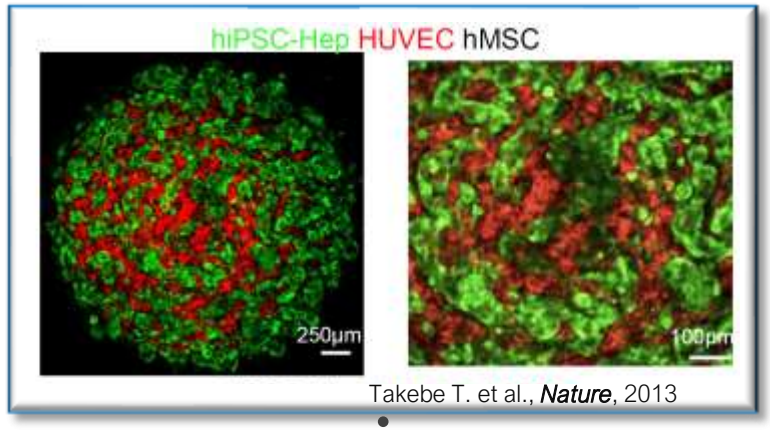


© HEALIOS K.K. All rights reserved.

HLCL041: Liver Organ Bud Platform: 3D Organ Generation Mechanism

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





Cell Transplantation

Containing blood vessels and human liver



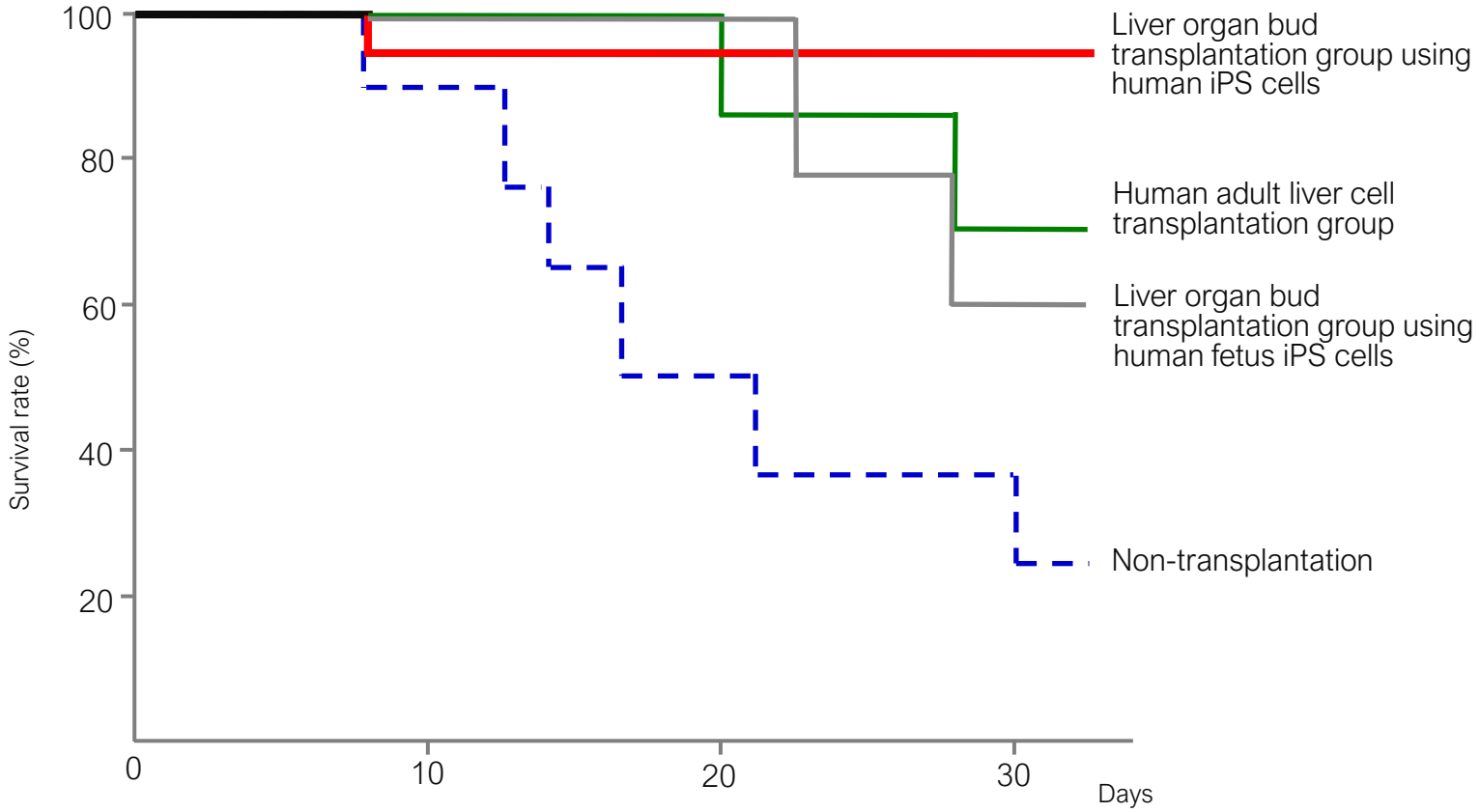
(Source) Takebe T. et al., *Nature Protocols*, 2014

© HEALIOS K.K. All rights reserved.

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

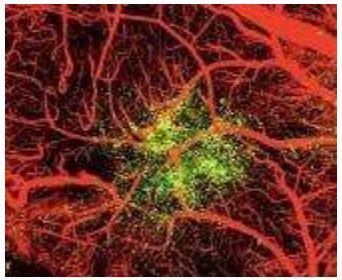


（Source） Adapted by Healios from Takebe. T, et al. Nature, 499 (7459),（2013）

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)

© HEALIOS K.K. All rights reserved.

HLCL041: Liver Organ Bud Platform: Market Opportunity

Prospecting R&D for alternative treatment for liver transplantation

Liver disease drawing attention in the future is cirrhosis

Liver Transplantation

	Liver transplantation			Total
	US	Japan	Europe	
Number of patients undergoing treatment (Annual)	Approx. 6,000	Approx. 400	Approx. 4,000	Approx. 10,000
Number of patients on waiting list (Annual)	Approx. 15,000	Approx. 400	Approx. 4,000	Approx. 20,000

（Source）Compiled by Healios based on materials disclosed by Japanese Liver Transplantation Society, UNOS, Eurotransplan, UK Transplant, Agence de la biomédecine, and Scandia Transplant.

Patients with Cirrhosis

Cirrhosis	Number of Patients in Japan
Estimated patients with cirrhosis	400,000~500,000
Number of patients receiving treatment at medical facilities.	Approx. 56,000
Annual deaths in Japan	Approx. 17,000

（Source）Patient Survey 2011 Liver Cancer White Paper 2015

Progress of liver disease

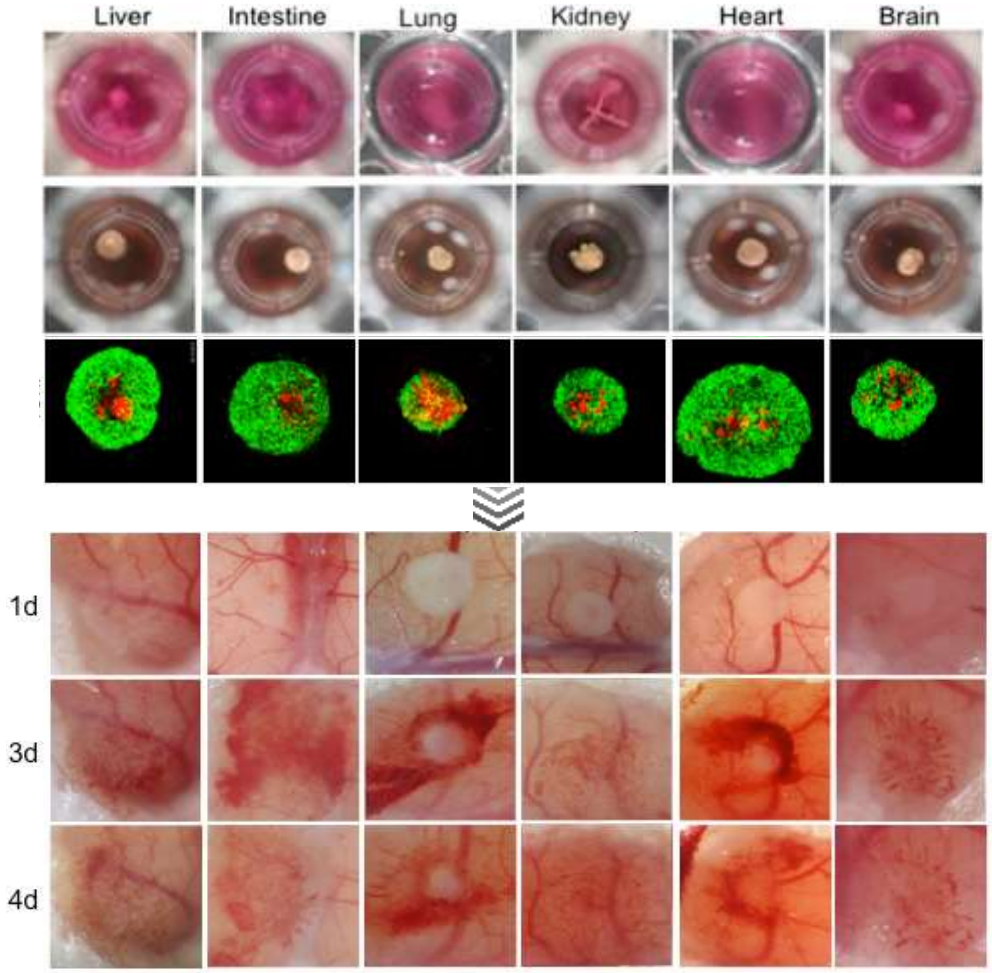


© HEALIOS K.K. All rights reserved.

HLCL041: Liver Organ Bud Platform

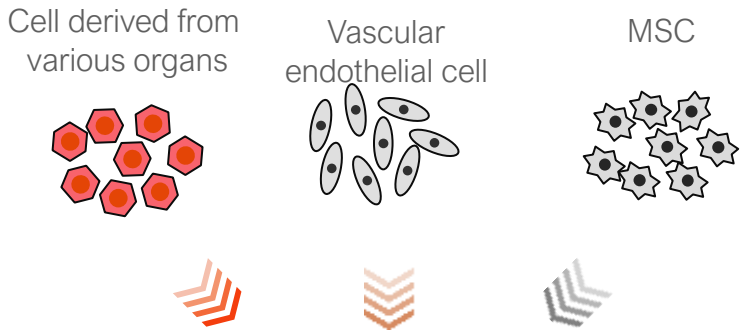
Inducing progenitor cells from iPSC will expand the possibility of development across various organs

Potential application for various organs



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

Transplanted to mice



Using cells derived from various organs, vascular endothelial cells and mesenchymal stem cells, achieved construction of vascularized 3D organ buds.

The vascularization was confirmed in vivo by transplantation to mice.

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

© **HEALIOS K.K.** All rights reserved.

Financial Highlights

© HEALIOS K.K. All rights reserved.

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.

© HEALIOS K.K. All rights reserved.

Statement of income

(Units: one million US dollar)

	FY2019 Q1(YTD)	FY2020 Q1(YTD)		
			YoY variance	Main reasons for increase/decrease
Sales	0.99	0.06	-0.92	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 income	-8.38	-8.55	-0.17	Mainly due to decrease in revenue −$0.92mn and R&D expenses +$1.11mn.
Net income	-8.50	-11.61	-3.11	Mainly due to increase in finance costs -$2.94mn.
R&D expenses	7.10	5.99	-1.11	
Number of employees	98	107	9	

(Note) * Financial figures for the first quarter of 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 for the first quarter announced today.
* Adopt average exchange rate (JPY/USD) over respective 3-month periods for P&L; FY2019 Q1 110.21 yen per dollar and FY2020 Q1 108.85 yen per dollar.

© HEALIOS K.K. All rights reserved.

Balance sheet

Update

Healios

（Units: one million US dollar）

		December 31, 2019	March 31, 2020		
				Variance	Main reasons for increase/decrease
	Current assets	176.86 (75.7%)	168.34 (64.2%)	-8.52	Mainly due to decrease in cash equivalents −$7.12mn. (cash equivalent balance at 03/31/20 was $159.88mn)
	Non-current assets	56.75 (24.3%)	93.87 (35.8%)	37.12	Mainly due to increase in other financial assets +$33.86mn: as a result of the acquisition of additional shares of Athersys, Inc. and a rise in Athersys shares.
Total assets		233.61 (100.0%)	262.21 (100.0%)	28.60	
	Current liabilities	17.93 (7.7%)	26.04 (9.9%)	8.11	Mainly due to increase in trade and other payables +$6.40mn and other financial liabilities +$1.93mn.
	Non-current liabilities	103.01 (44.1%)	113.41 (43.3%)	10.39	Mainly due to increase in deferred tax liabilities +$6.04mn and lease liabilities +$2.35mn.
Total liabilities		120.94 (51.8%)	139.44 (53.2%)	18.50	
Total equity		112.67 (48.2%)	122.77 (46.8%)	10.10	Mainly due to net loss -$11.61mn and increase in other components of equity +$19.91mn as a result of a rise in Athersys shares.
Total liabilities and equity		233.61 (100.0%)	262.21 (100.0%)	28.60	

(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 for the first quarter announced today.
* Adopt spot rate (JPY/USD) at end of fiscal period for B/S ; FY2019 Q4 109.56 yen per dollar and FY2020 Q1 108.83 yen per dollar.

© HEALIOS K.K. All rights reserved.

Appendix

© HEALIOS K.K. All rights reserved.

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	12,868 million yen (As of March 31, 2020)
Head office	World Trade Center Building 15F 2-4-1 Hamamatsucho Minato-ku, Tokyo Japan 105-6115
Number of Employees	107 (As of March 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 March 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)

© HEALIOS K.K. All rights reserved.

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	In-house development of gene-modified natural killer cells	Decided to include COVID-19 induced ARDS patients in ongoing clinical trial

© HEALIOS K.K. All rights reserved.

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)	**Executive Officer Manufacturing field** 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

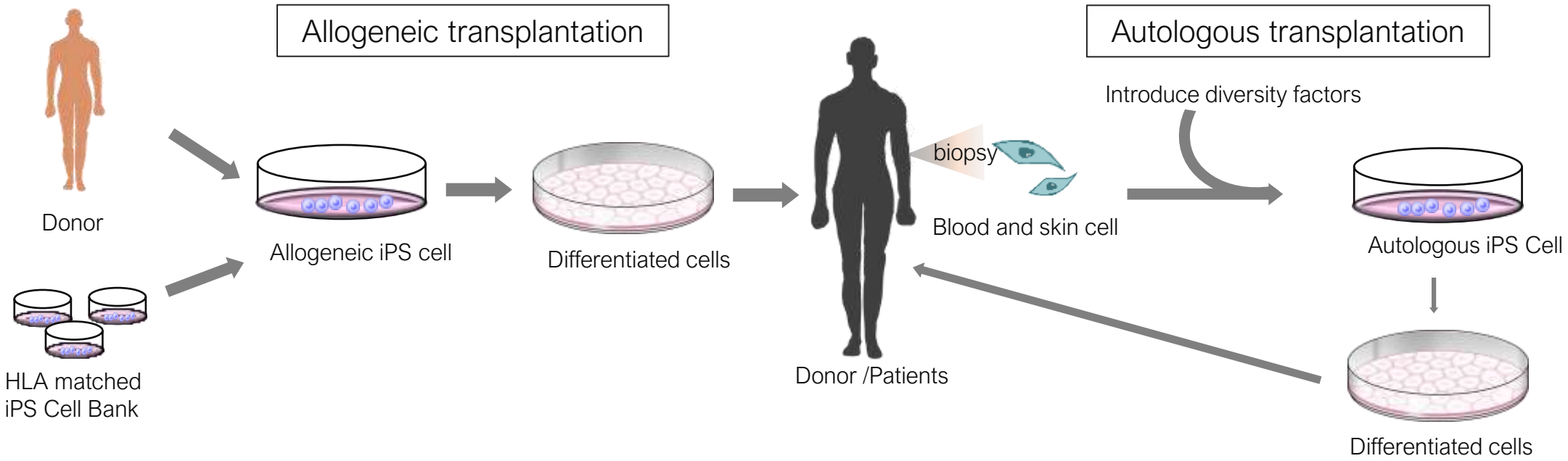
Masanori Sawada	Hardy TS Kagimoto	Kouichi Tamura	Michihisa Nishiyama	Koji Abe
Executive Vice President, CMO (Chief Medical Officer) MD, PhD, MBA	**Chairman and CEO** MD, Founder	**Executive officer Research field** Ex-Astellas US Director of Laboratories Expertise in Immunosuppressant Research	**Executive 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

© HEALIOS K.K. All rights reserved.

iPSC Platform

© HEALIOS K.K. All rights reserved.

iPSC Platform: Allogeneic iPS cells（Universal Donor Cell: UDC）that suppress immune rejection



（Source）modified from Sackett et al, Transplant Rev, 2016

	Autologous iPS Cell	Existing iPS/ES cell lines	HLA matched iPS Cell Bank	UDC
Immune rejection	None	Occur (Immunosuppressive drugs are required)	Under consideration	None
Manufacturing term	Several months～1 year (Need to make from each patient)	Ready-to-use (One line)	Ready-to-use (Multiple lines required)	Ready-to-use (One line of gene-edited cell)
Cost	Very high	Low	High	Low

© HEALIOS K.K. All rights reserved.

iPSC Platform: Universal Donor Cell



iPS cell
(pluripotent stem cell)

Gene-Editing

Universal Donor Cell
(Safe and versatile stem cells)

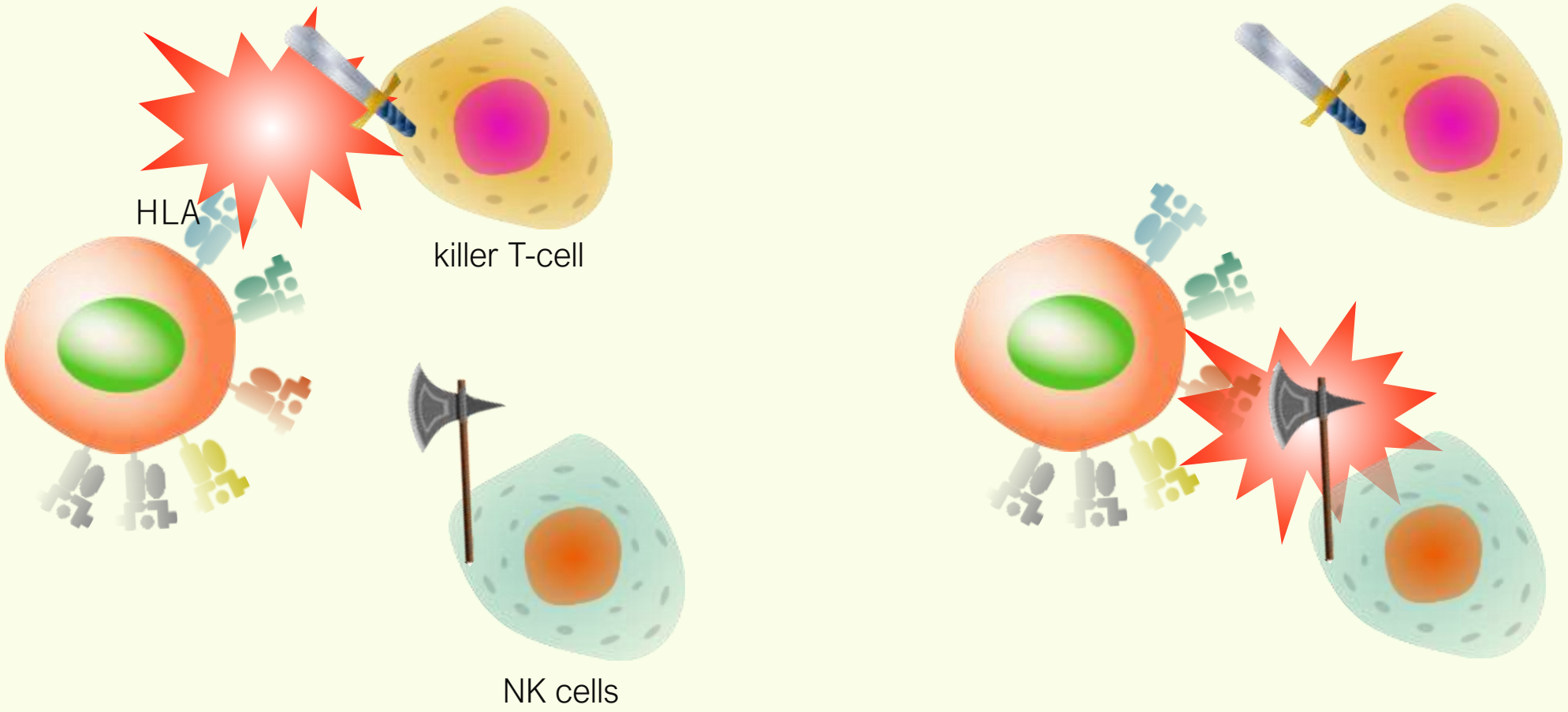
By using gene editing technology to produce iPS cells that avoid immune rejection, it is possible to realize universal iPS cells that can respond to the need for “one cell for all patients."

© HEALIOS K.K. All rights reserved.

iPSC Platform: Rejection of cell transplant

HLA type mismatch

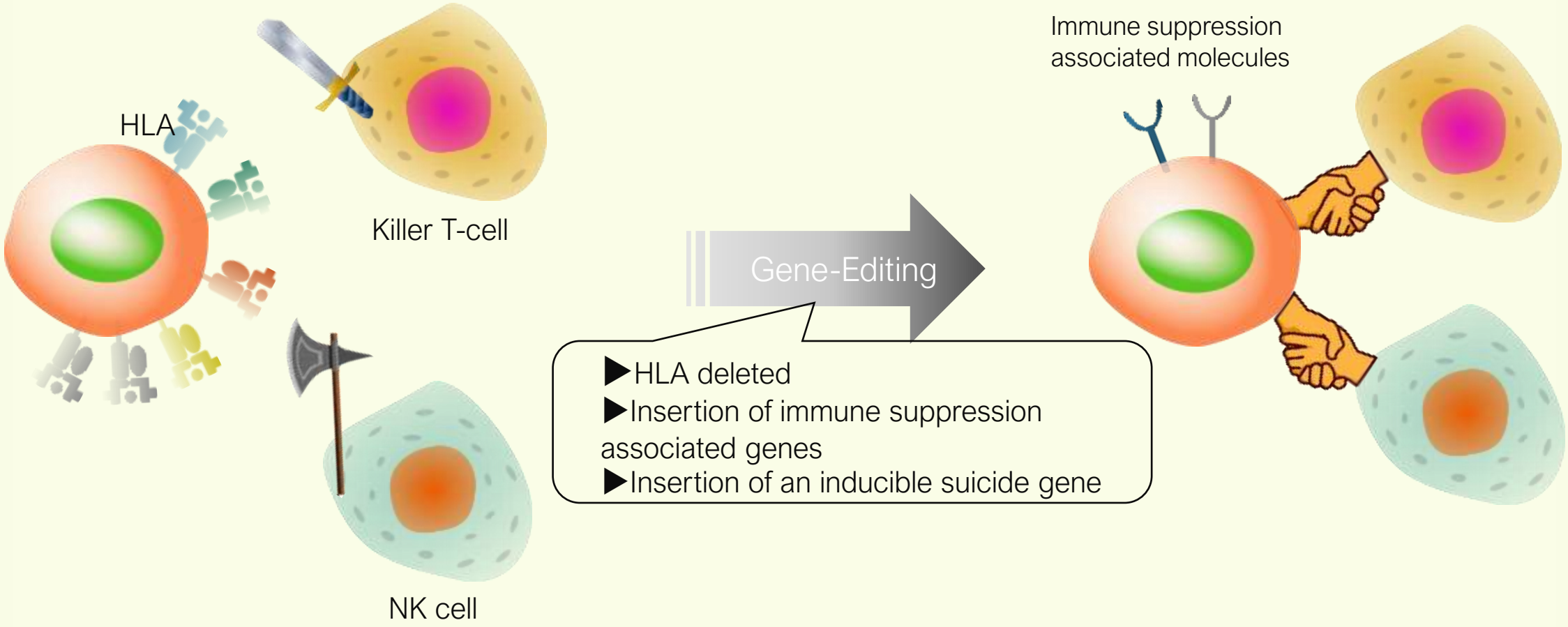
HLA protein deletion



Immune response

© HEALIOS K.K. All rights reserved.

iPSC Platform: Avoid rejection due to immune response

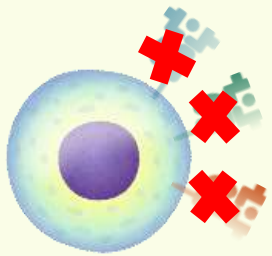


We will produce the immune rejection free iPS cell and realize the safe and universal cell therapy.

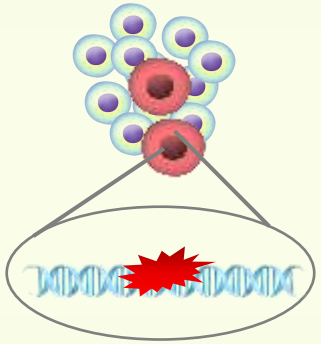
© HEALIOS K.K. All rights reserved.

iPSC Platform: UDC production process check items and quality checks

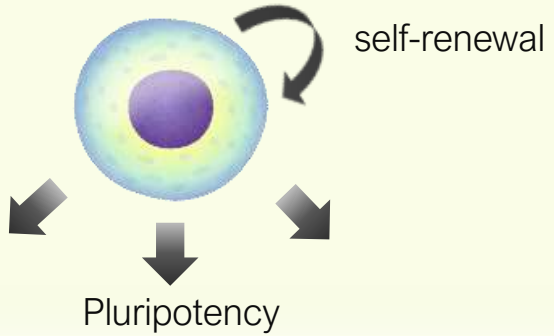
①Check of Gene editing



②Absence of malignant mutations



③ Retain the properties of iPS cells



Quality check item	Contents
Check 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
	None of cancer associated gene
Attribution	Sterility
	Endotoxin free
	Mycoplasma free
	Gene expression analyses (Comparison with the parent cell line)
	Expression of undifferentiated markers
	Pluripotency（triploblastic differentiation）
	None of immunogenicity
	Function of suicide genes

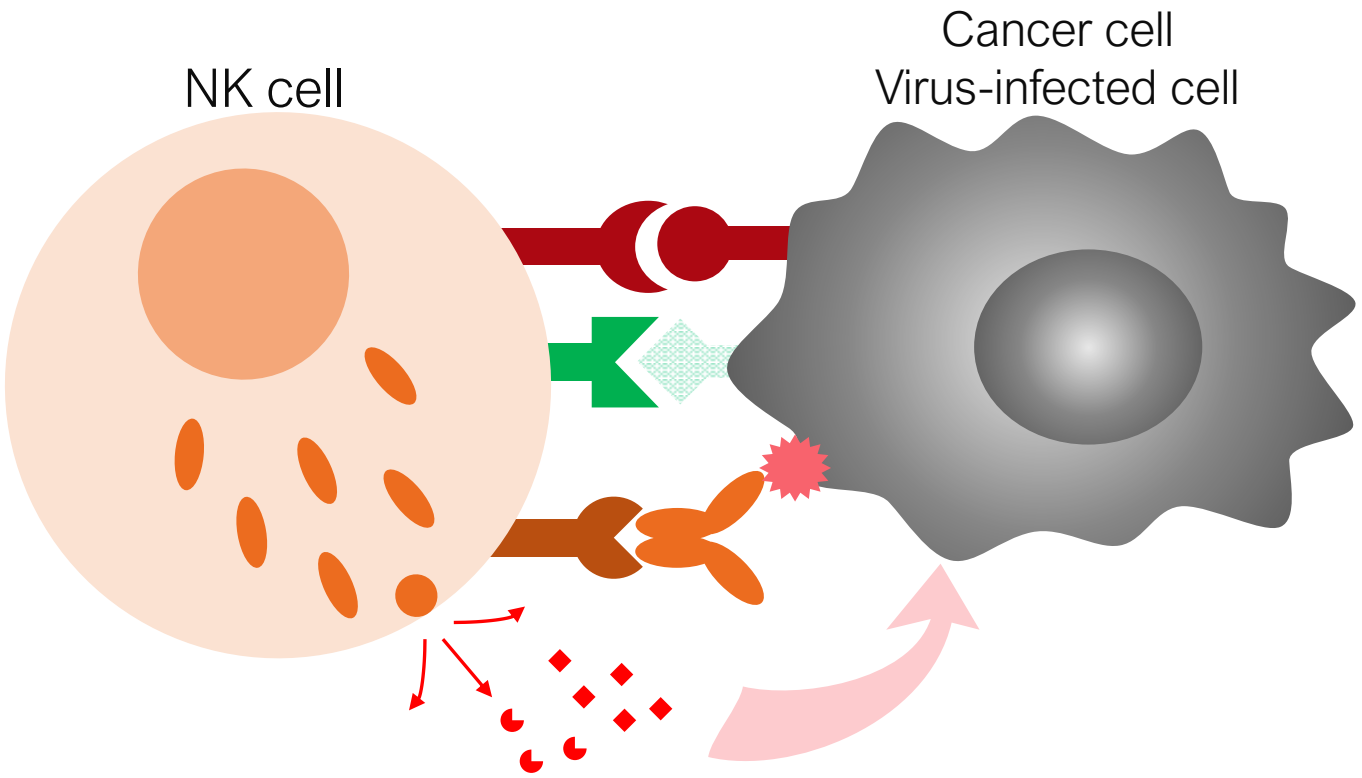
© HEALIOS K.K. All rights reserved.

NK Cells

© HEALIOS K.K. All rights reserved.

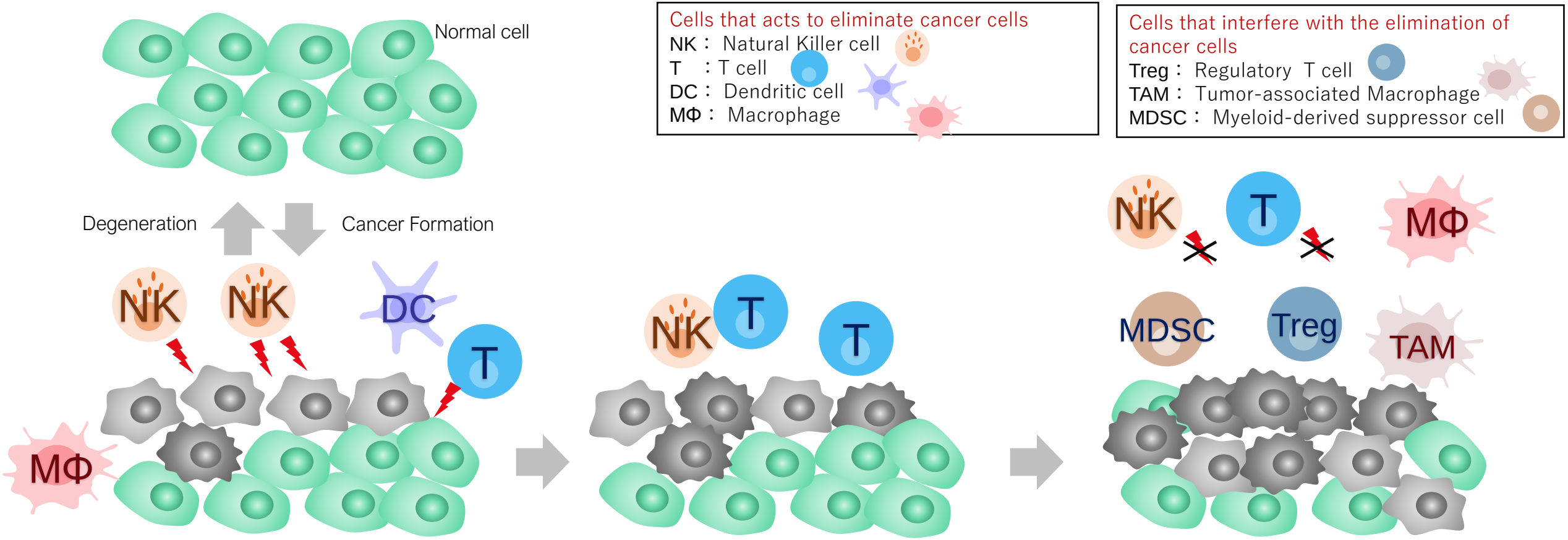
HLCN061: NK Cells

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.



© HEALIOS K.K. All rights reserved.

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

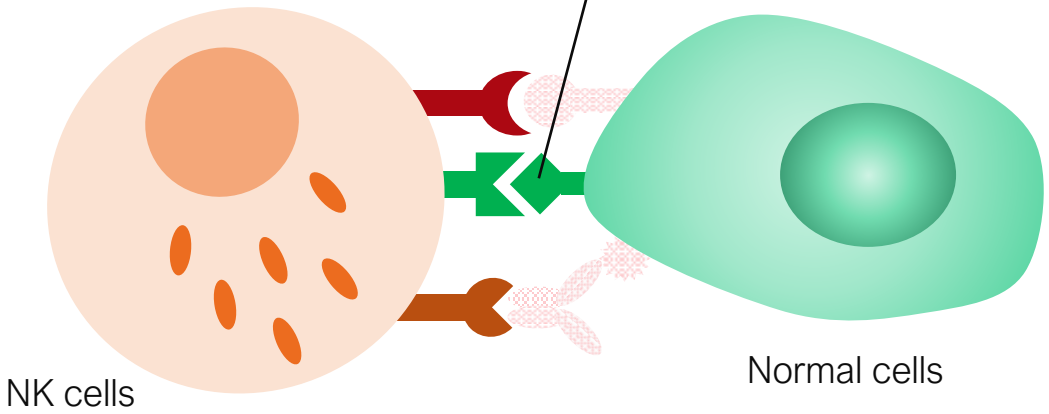
Elimination	Equilibrium	Escape
• NK and T cells attack and eliminate cancerous cells	• Equilibrium between cancer growth and clearance by immune system	• Cancer cells avoid immunity • Appearance of immune suppressive cells

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

© HEALIOS K.K. All rights reserved.

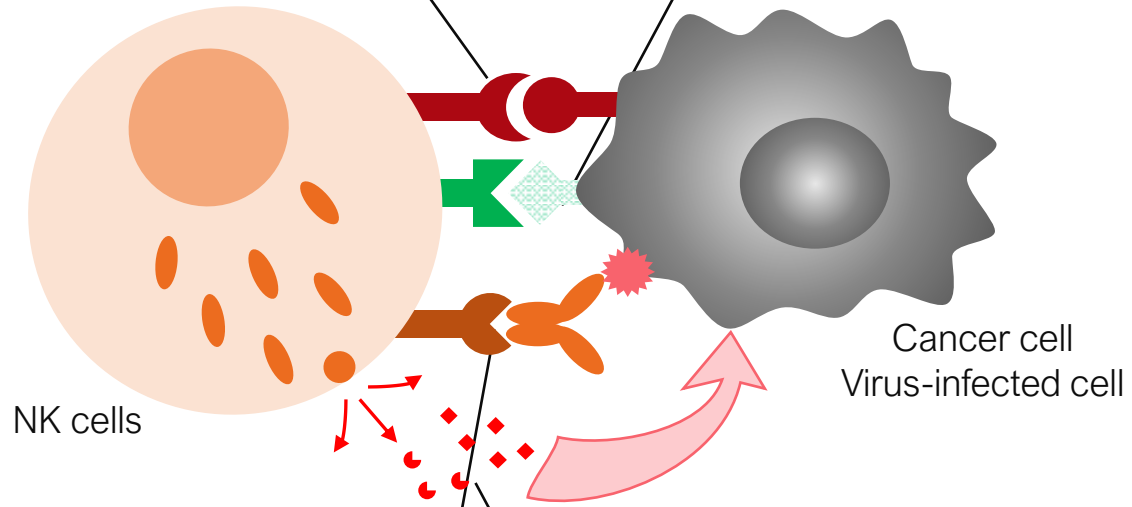
HLCN061: Mechanism of NK Cell Attack of Cancerous or Virus-Infected Cells

NK cells do not attack normal cells by recognizing normal marker



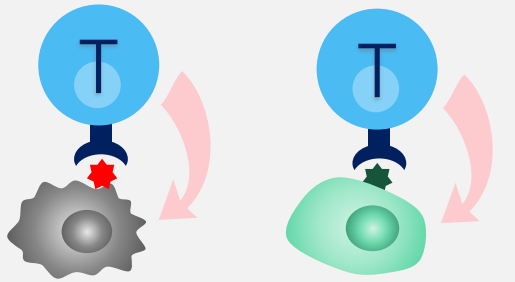
① Activated by abnormal markers

② Brake disengaged by dissipation of normal marker



③ Antibody dependent cellular cytotoxicity

④ Release perforin and granzymes to destroy cells

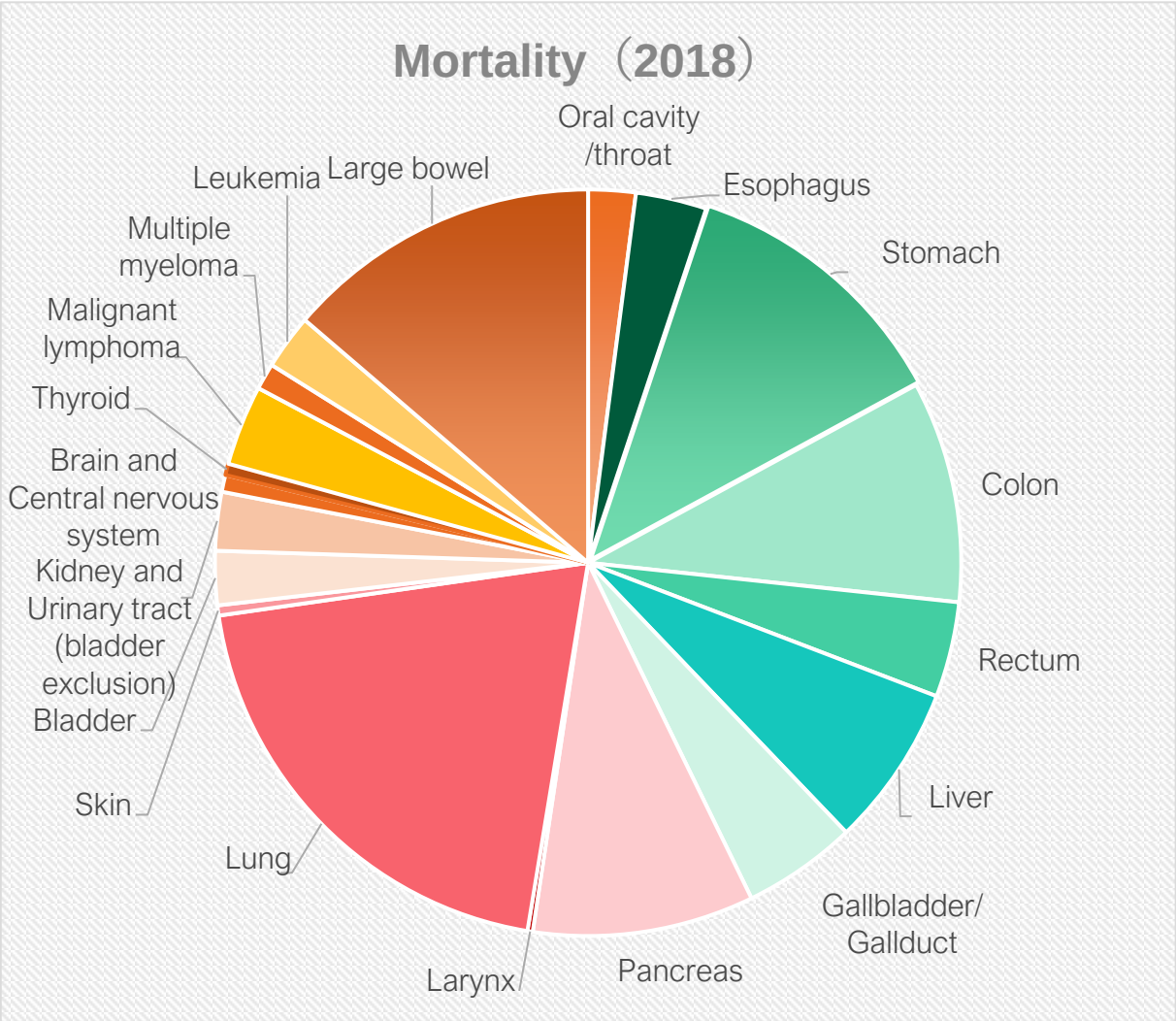


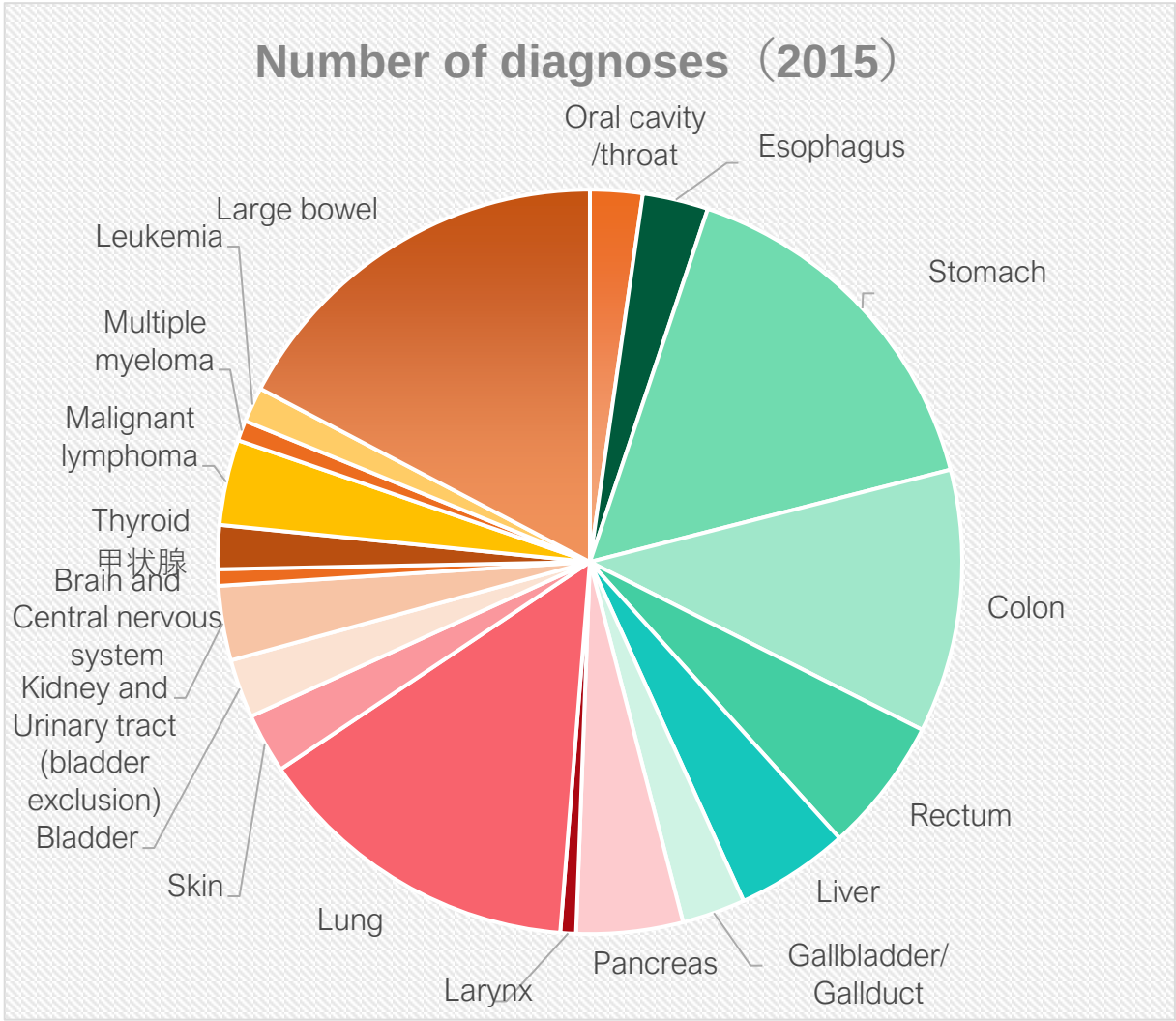
Superiority of NK cells to T cells

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

© HEALIOS K.K. All rights reserved.

HLCN061: Number of cancer deaths and diagnoses by site





（Source） National Cancer Center Cancer Information Service "cancer registry and statistics" （ vital statistics ）

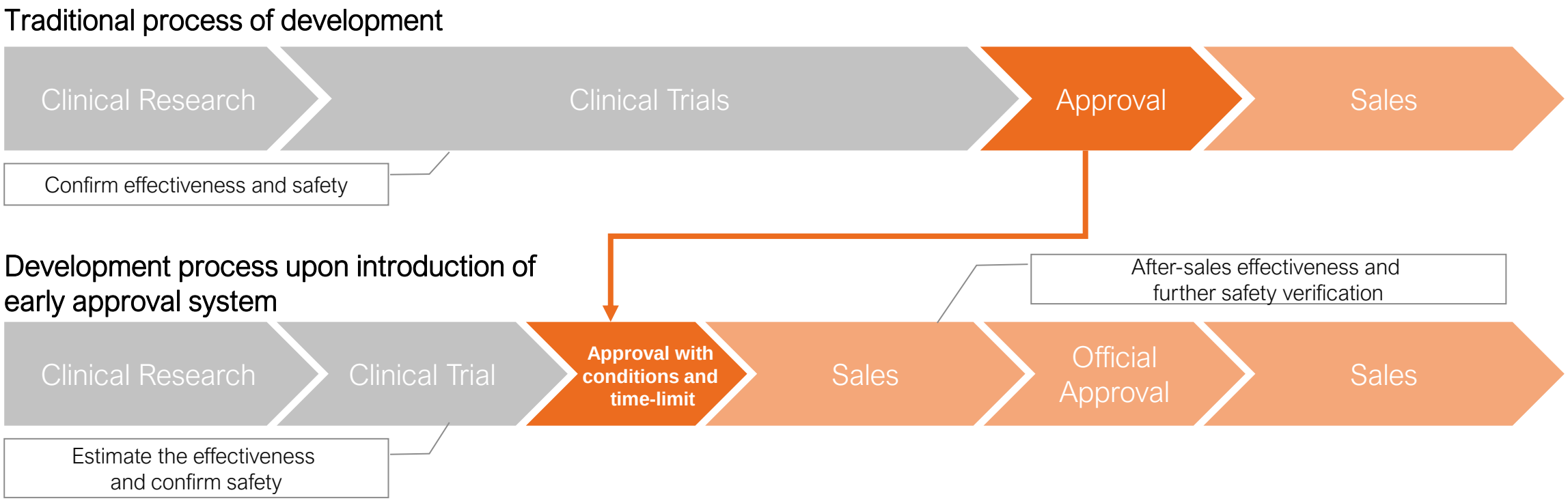
© HEALIOS K.K. All rights reserved.

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



© HEALIOS K.K. All rights reserved.

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.

© HEALIOS K.K. All rights reserved.

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

Important note on future events, etc

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

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

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

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

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

© HEALIOS K.K. All rights reserved.



＜Contact information＞
Corporate Communications
HEALIOS K.K.

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