

DEZAWA MUSE CELL™: From Science To Clinical Breakthroughs

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University of Regensburg

University of Geneva

MuseCell Innovations PTE Ltd



Therapeutic Potential of Progenitor Cells

Mesenchymal Progenitor Cells



Topical/spray



Injection

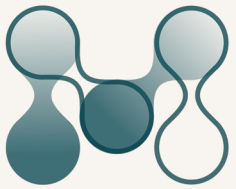


Scaffold



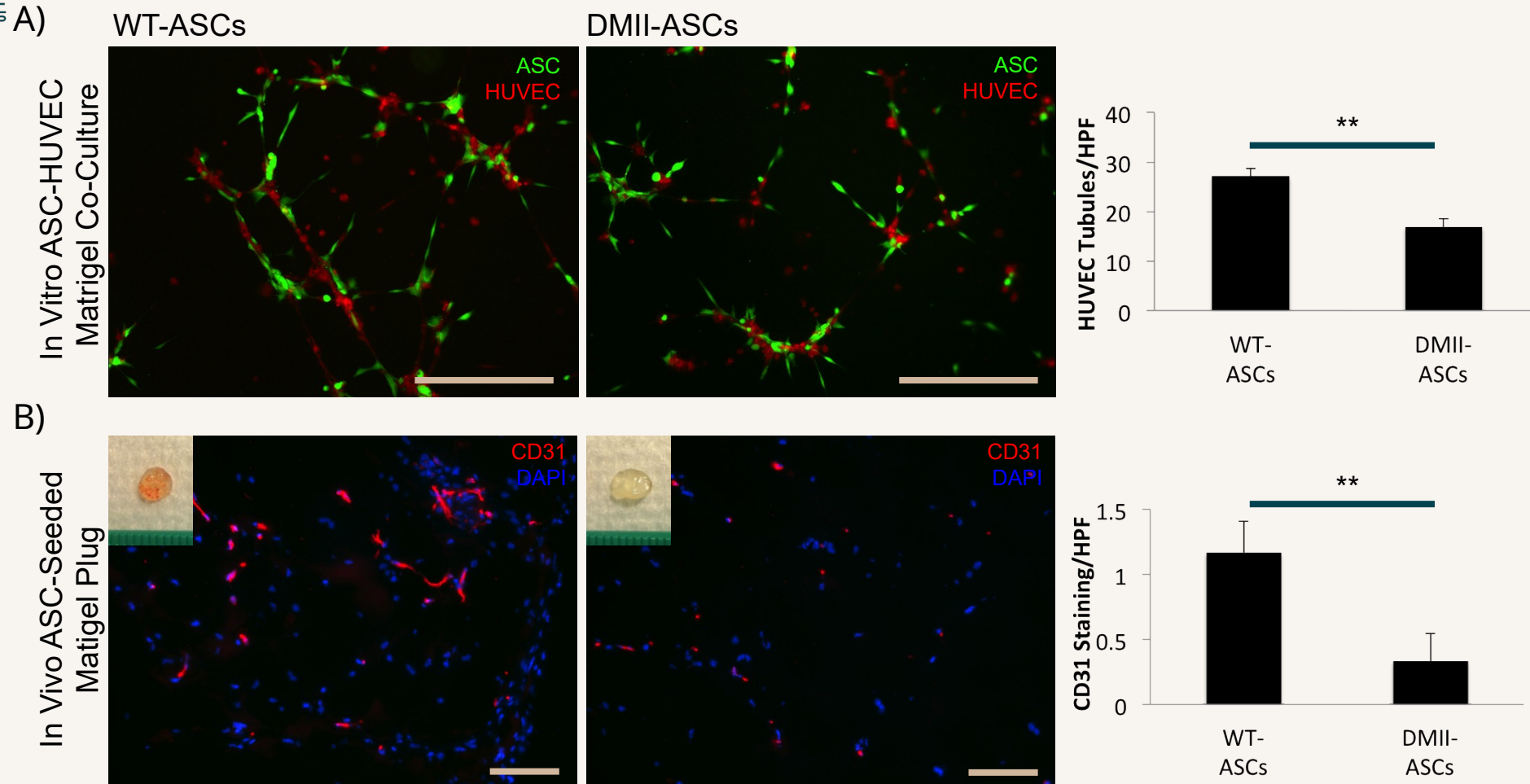
Systemic

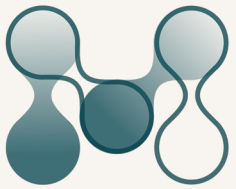




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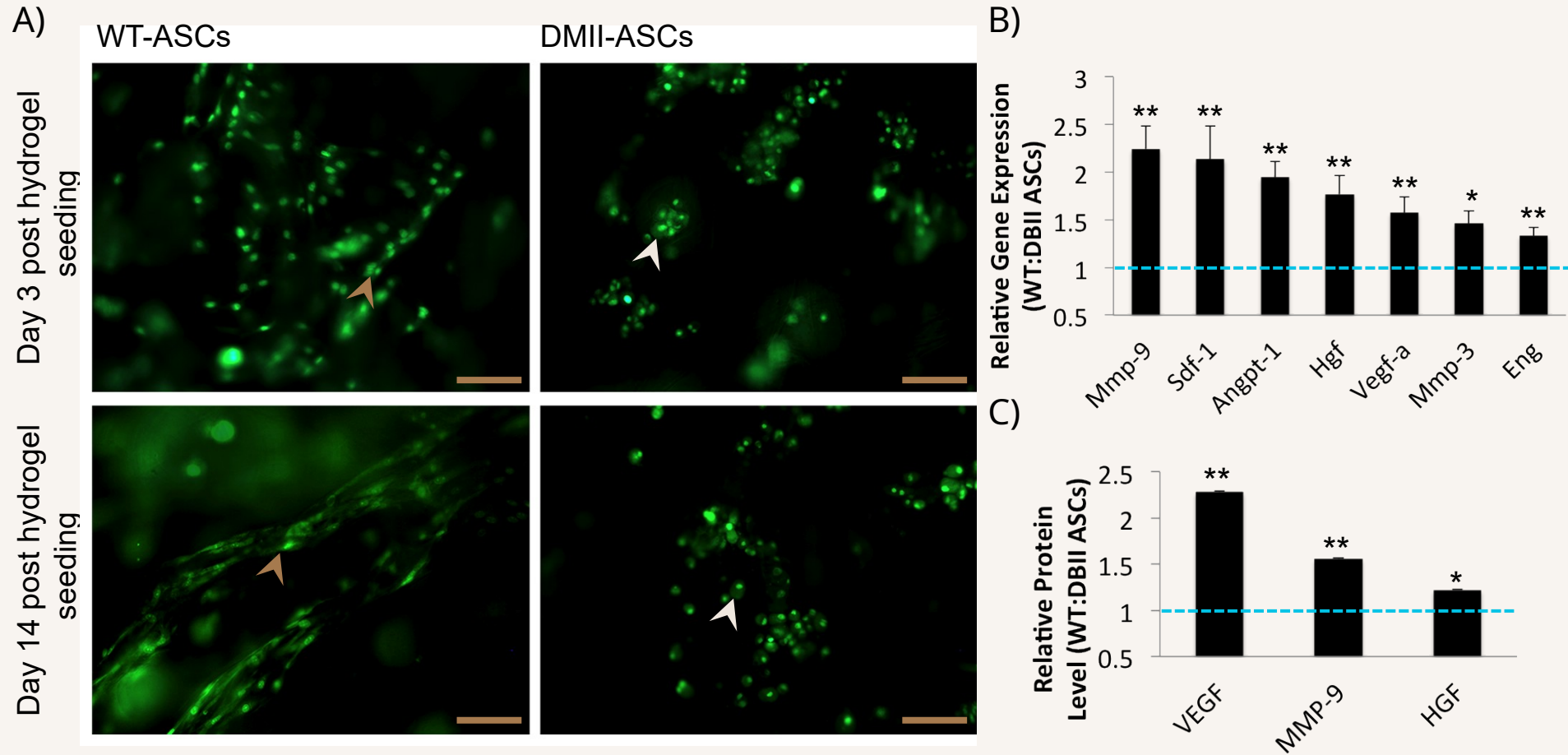
Diabetic ASCs Display A Reduced Neovascular Potential





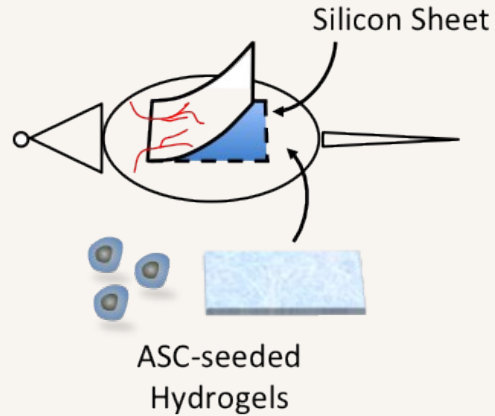
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Diabetic ASCs Remain Impaired Following Regenerative Hydrogel Scaffold Seeding

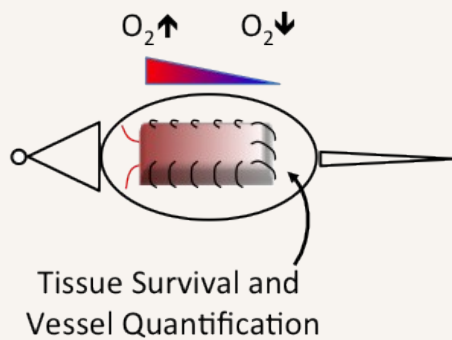


Diabetes Impairs the Regenerative Potential of ASCs In Vivo

A)

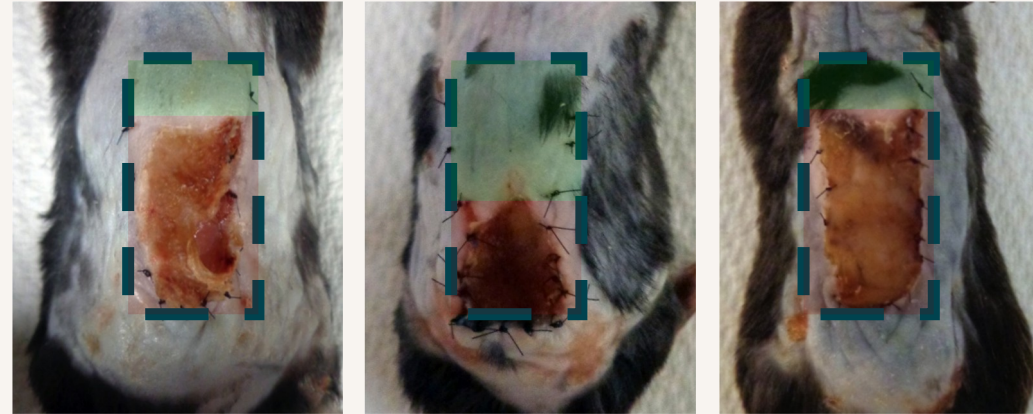


Day 0



Day 10

B)

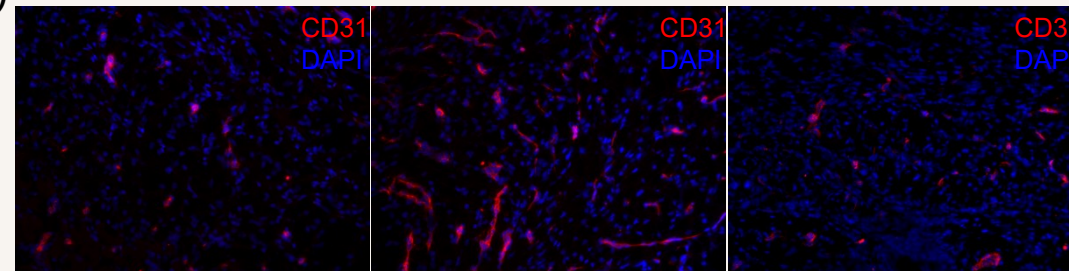


No Cells

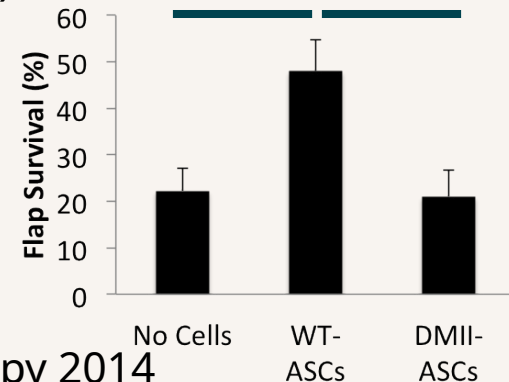
WT-ASCs

DMII-ASCs

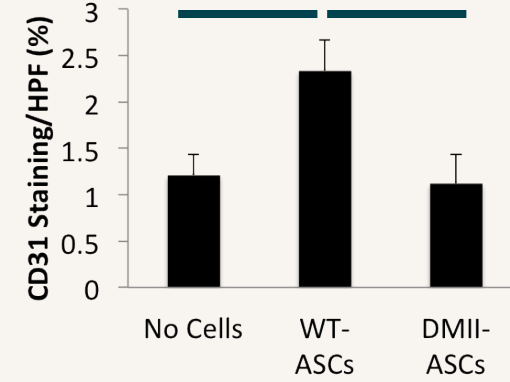
C)

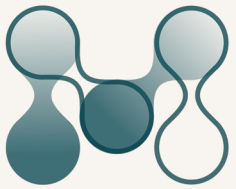


D)



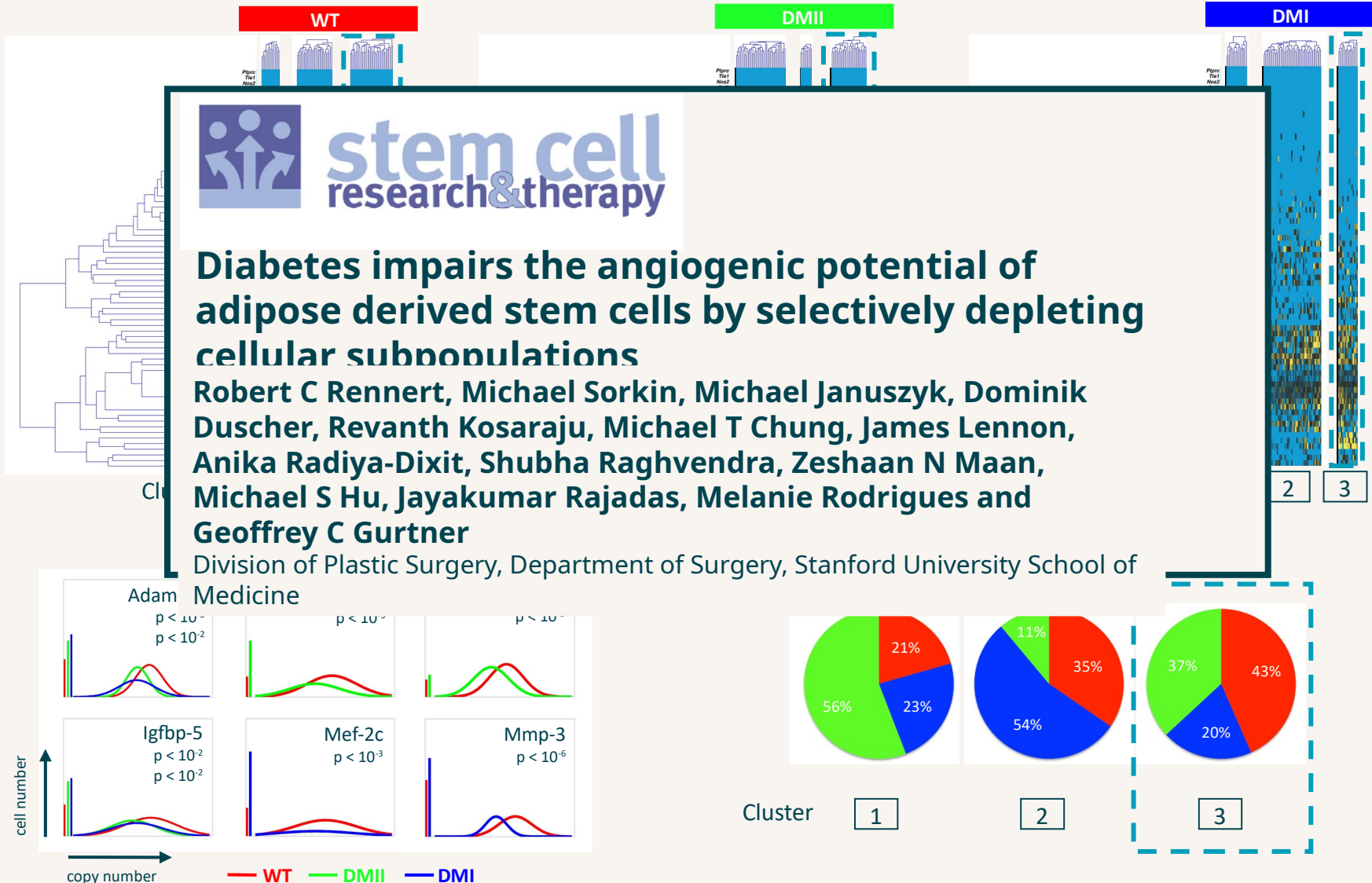
E)



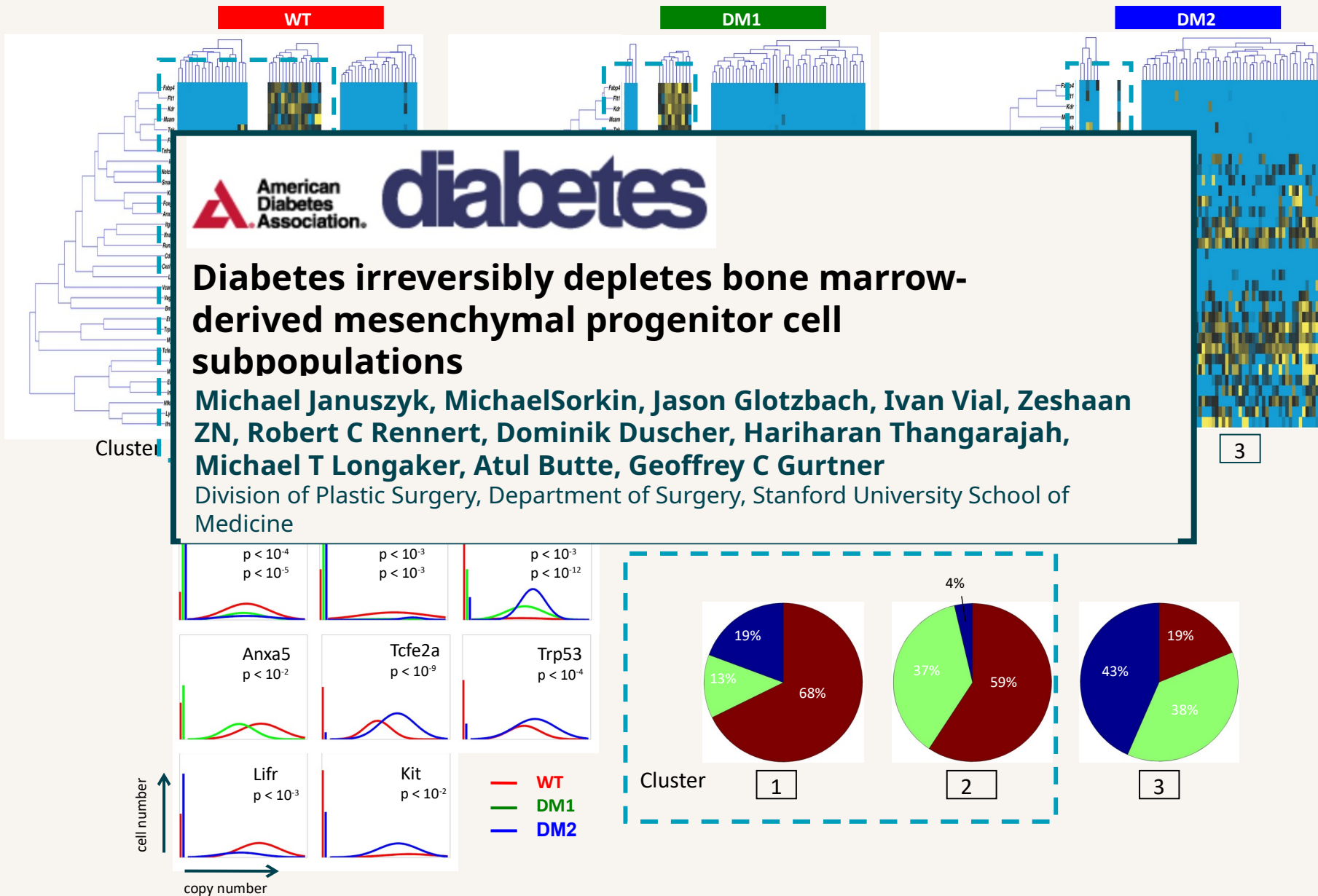


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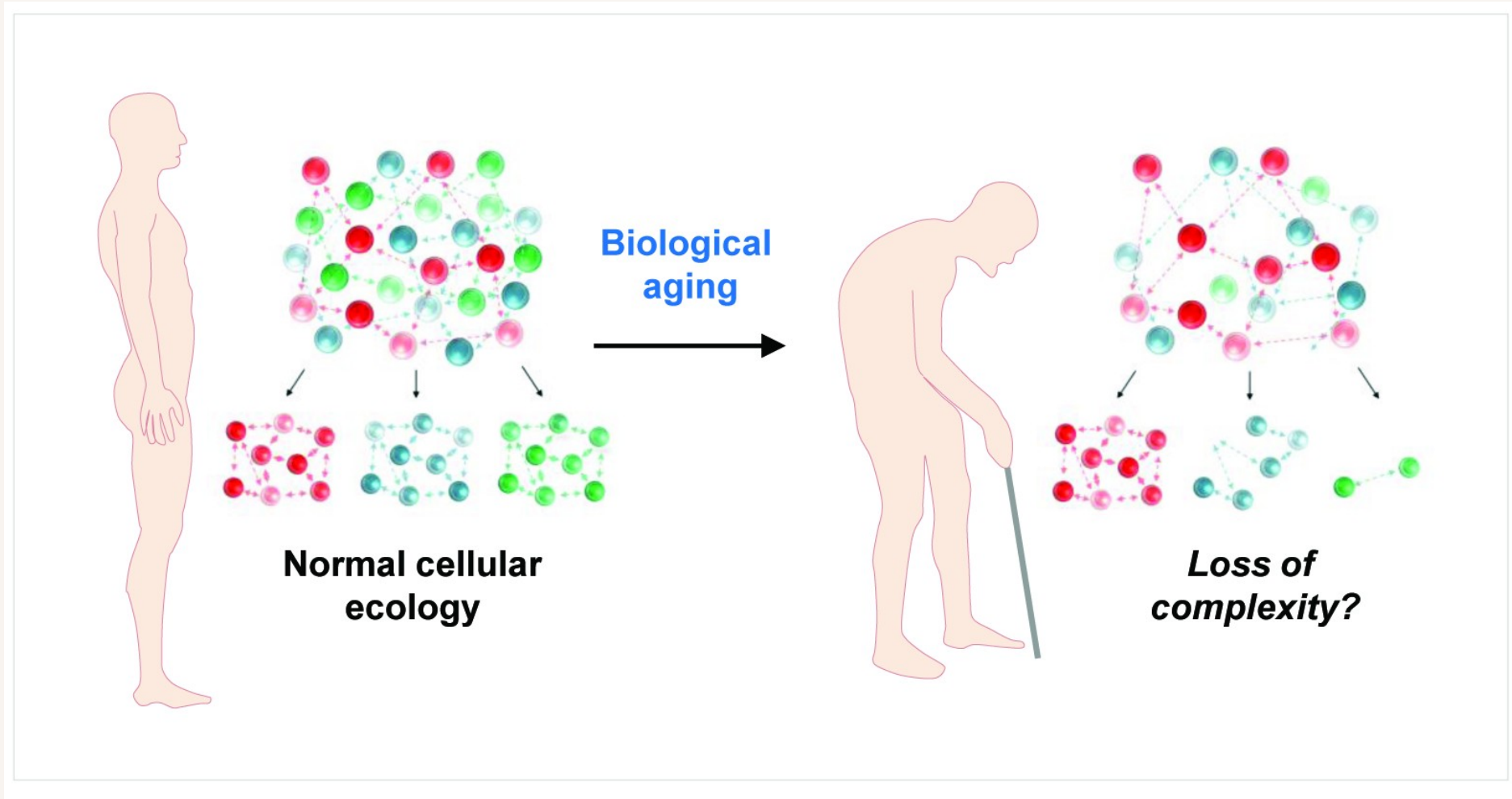
Diabetes Selectively Depletes ASC Subpopulations



Diabetes Selectively Depletes BM-MSC Subpopulations



Are Similar Depletions Happening in Aged Tissues?



Aging diminishes the function of ASCs

Figure 1

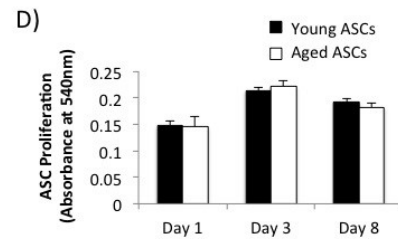
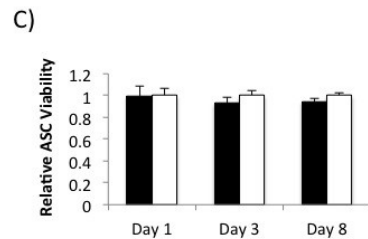
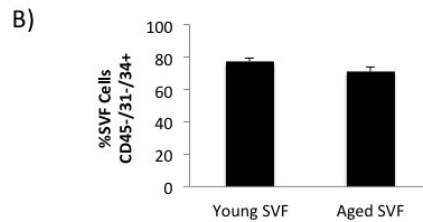
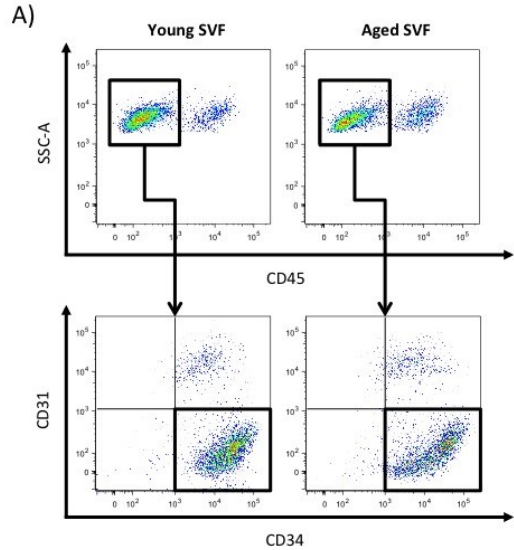
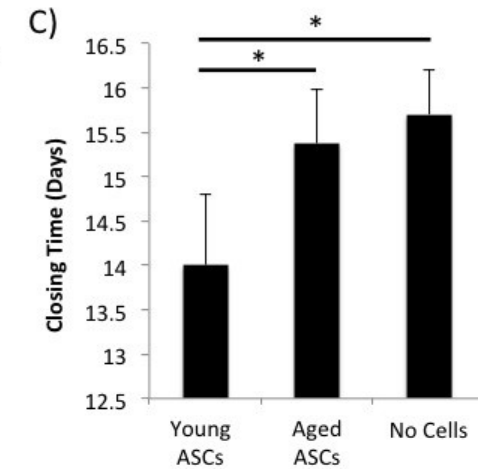
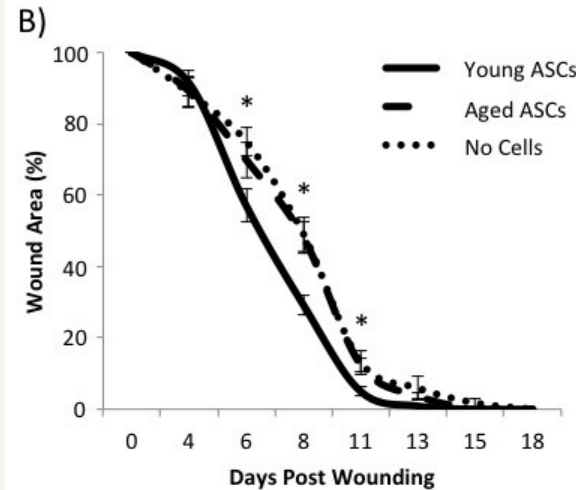
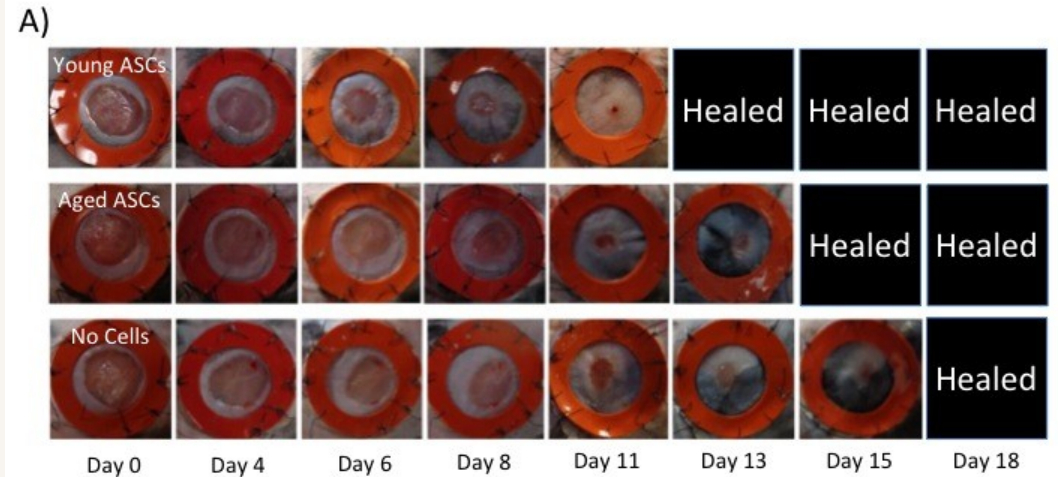


Figure 5



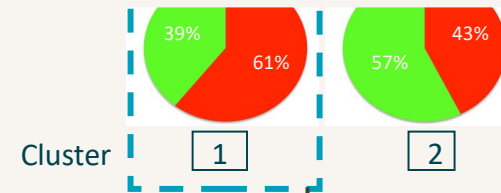
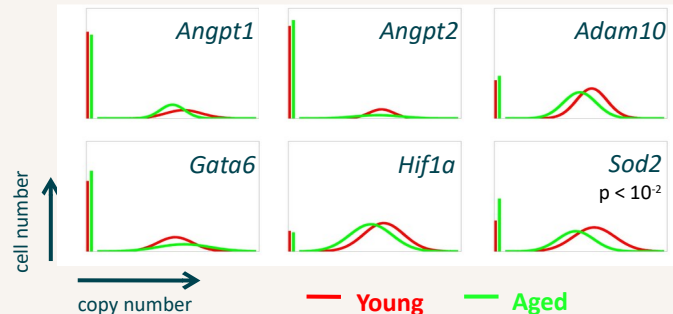
Aging Selectively Depletes ASC Subpopulations

nature SCIENTIFIC
REPORTS

Aging disrupts cell subpopulation dynamics and diminishes the function of mesenchymal stem cells

Dominik Duscher, Robert C Rennert, Michael Januszyk, Ersilia Anghel, Zeshaan N Maan, Alexander J Whittam, Marcelina G. Perez, Revanth Kosaraju, Michael S Hu, Graham G Walmsley, Melanie Rodrigues, David Atashroo, Sacha Khong, Atul J Butte, and Geoffrey C Gurtner

Division of Plastic Surgery, Department of Surgery, Stanford University School of Medicine



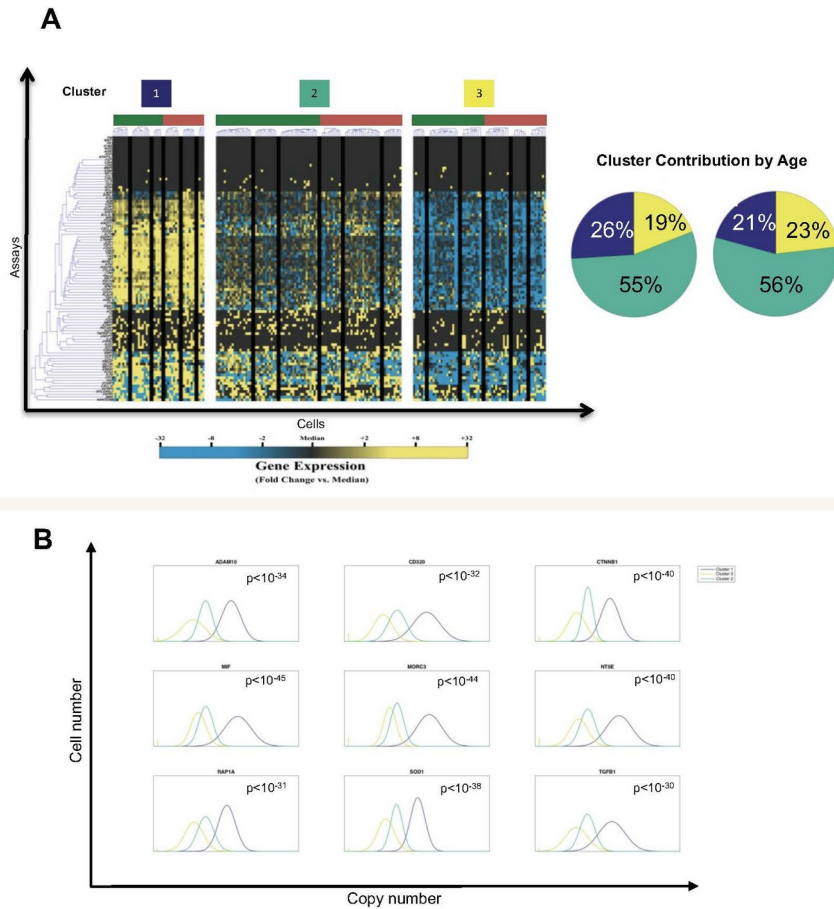
Selected Cluster 1 Defining Genes:

<i>Hif1a</i>	$p < 10^{-07}$	<i>Adam10</i>	$p < 10^{-03}$
<i>Mef2c</i>	$p < 10^{-04}$	<i>Sod2</i>	$p < 10^{-02}$
<i>Bmp2</i>	$p < 10^{-03}$	<i>Cxcl12</i>	$p < 10^{-02}$
<i>Ccl2</i>	$p < 10^{-03}$		

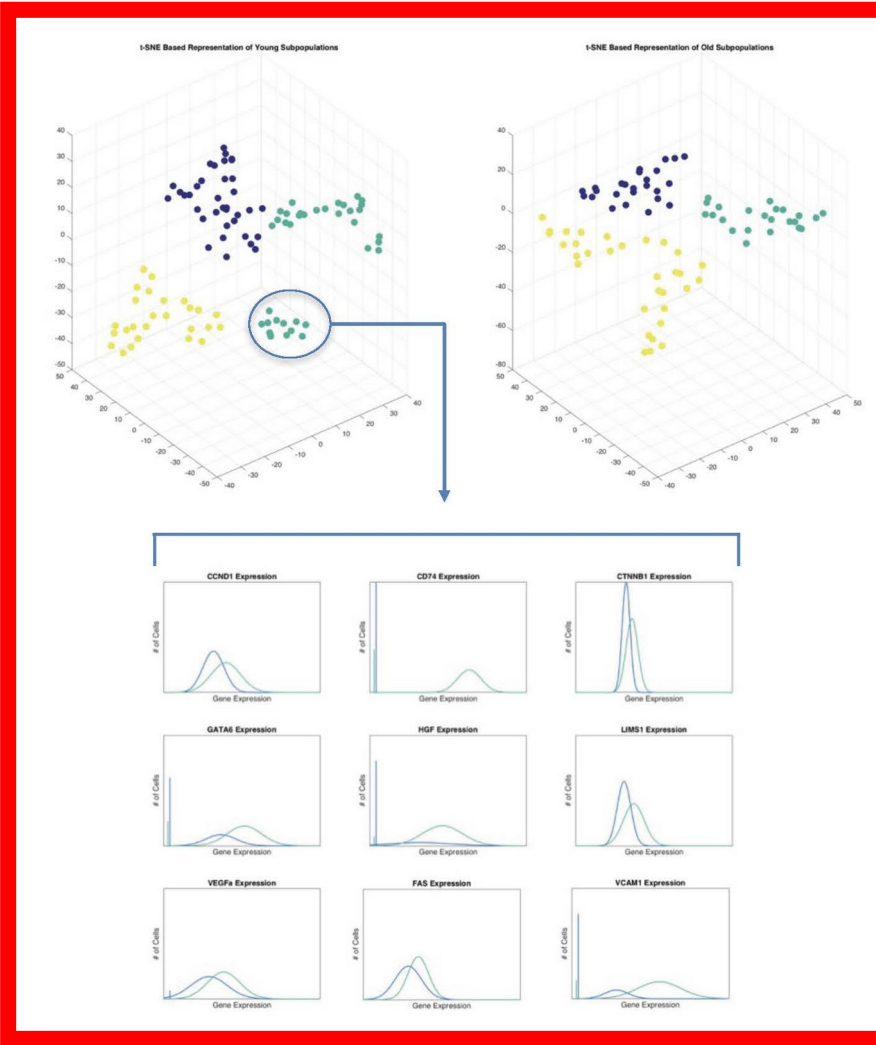
Aged

Aging Selectively Depletes BM-MSC Subpopulations

Figure 2: Young BM-MSCs contain a higher proportion of cells belonging to a subpopulation correlated with a more regenerative molecular phenotype



E



Khong SM... **Duscher D.** ... Gurtner GC. Single Cell Transcriptomics of hMSCs Reveal Age-Related Cellular Subpopulation Depletion and Impaired Regenerative Function. *Stem Cells* 2018

Diabetes and Aging Cause Ubiquitous Alterations in Progenitor Cell Subpopulation Dynamics

> [Stem Cells Transl Med.](#) 2014 Sep;3(9):1079–89. doi: 10.5966/sctm.2014-0007. Epub 2014

Capillary force seeding of hydrogels for adipose-derived stem cell delivery in wounds

Ravi K
Laure
Jayak

> [Tissue Eng Part A.](#) 2016 Feb;22(3–4):295–305. doi: 10.1089/ten.tea.2015.0277.

Adipose-Derived Stem Cell-Seeded Hydrogels Increase Endogenous Progenitor Cell Recruitment and Neovascularization in Wounds

Revanth > [JCI Insight.](#) 2017 Oct 5;2(19):e96260. doi: 10.1172/jci.insight.96260.

Alexand
Geoffre

Delivery of monocyte lineage cells in a biomimetic scaffold enhances tissue repair

Mic > [Stem Cells Int.](#) 2018 Dec 19;2018:1353085. doi: 10.1155/2018/1353085. eCollection 2018.

Rob
War
Rya
H P

Fibrin Glue Enhances Adipose-Derived Stromal Cell Cytokine Secretion and Survival Conferring Accelerated Diabetic Wound Healing

> [Handchir Mikrochir Plast Chir.](#) 2018 Apr;50(2):74–82. doi: 10.1055/s-0043-118596.

Epub 2018 Apr 19.

[Comparison of the regenerative cytokine profile of adipose-

abdominal and ultrasonic-assisted adipose-derived stromal cell Single-Cell Gene Expression Analysis and Evaluation of the Therapeutic Function of Murine Adipose-Derived Stromal Cells (ASCs) from the Subcutaneous and Visceral Compartment

[Article in Germ
Matthias Michal

> [J Plast Reconstr Aesthet Surg.](#) 2020 Sep;73(9):1738–1746. doi: 10.1016/j.bjps.2020.02.045. Epub 2020 Mar 17.

Deferoxamine enhances the regenerative potential of diabetic Adipose Derived Stem Cells

Ursula Hopfner¹, Zeshaan N
Maximilian Zaussinger¹, Mar

Affiliations + expand

PMID: 32418841 DOI: 10.1016/j.bjps.2020.02.045

> [Clin Hemorheol Microcirc.](#) 2021;77(1):27–36. doi: 10.3233/CH-200852.

Erythropoietin can partially restore cigarette smoke induced effects on Adipose derived Stem Cells

Haydar Kükrek¹, Matthias Aitzetmüller¹, Mateja Vodišek¹, Dorian Mogg¹
Hans-Günther M > [Transl Res.](#) 2019 Mar;205:51–63. doi: 10.1016/j.trsl.2018.10.006. Epub 2018 Nov 2.

Affiliations + e

PMID: 32651309

Small molecule inhibition of dipeptidyl peptidase-4 enhances bone marrow progenitor cell function and angiogenesis in diabetic wounds

> [J Cell Physiol.](#) 2019 Dec;234(12):23097–23110. doi: 10.1002/jcp.28873. Epub 2019 May 23.

Exosomes from human adipose-derived stem cells promote sciatic nerve regeneration via optimizing Schwann cell function

> [Stem Cell Res Ther.](#) 2019 Jan 31;10(1):47. doi: 10.1186/s13287-019-1152-x.

Microvesicles from human adipose stem cells promote wound healing by optimizing cellular functions via AKT and ERK signaling pathways

Sen Ren¹, Jing Che
Hewei Xiong¹, Peng
Zhenbing Chen³

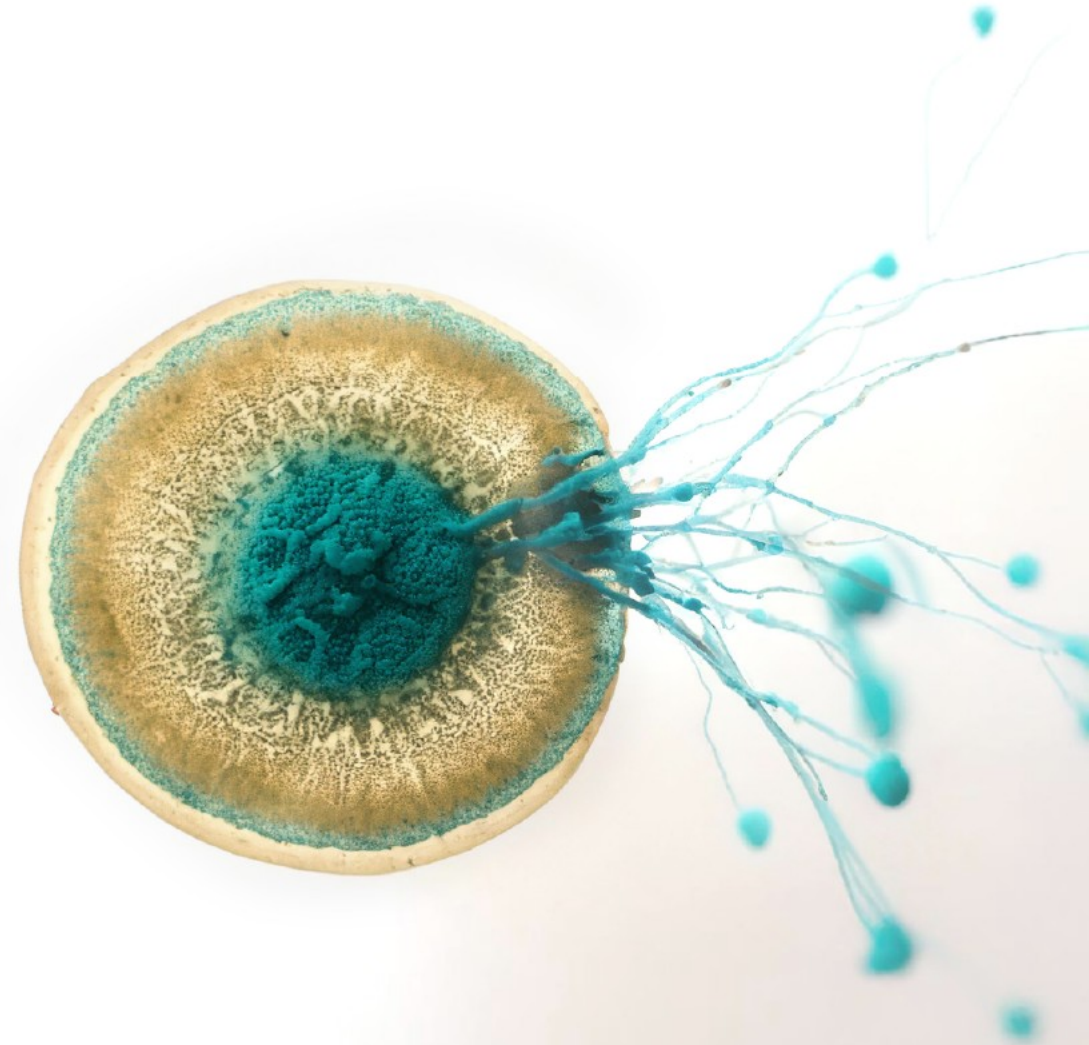
> [Arthrosc Tech.](#) 2023 Nov 20;12(12):e2265–e2271. doi: 10.1016/j.eats.2023.07.055. eCollection 2023 Dec.

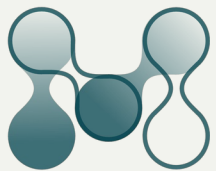
Arthroscopy with Lipoaspirate and Plasma Infiltration Using Adipose-Derived Stem Cells Plus Platelet-Rich Plasma: Harvesting and Injection for Arthroscopic Treatment of Cartilage Defects of the Knee



The Basic Characteristics of the

DEZAWA MUSE CELL™



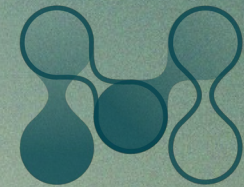


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● Live

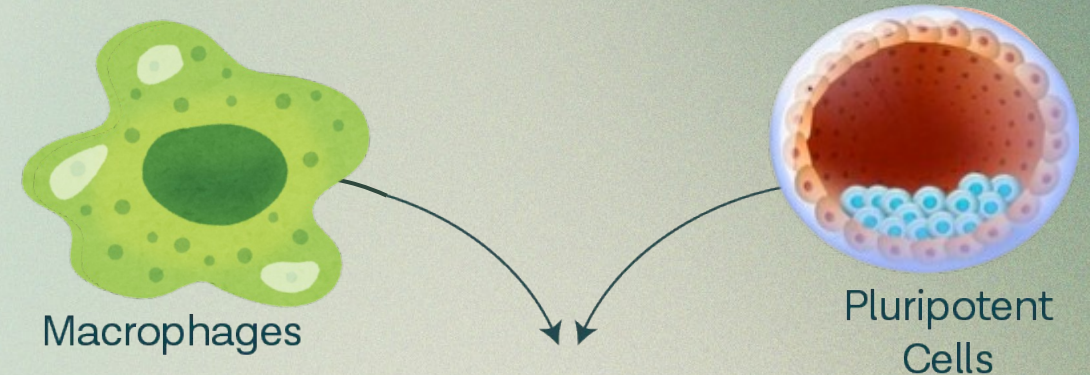
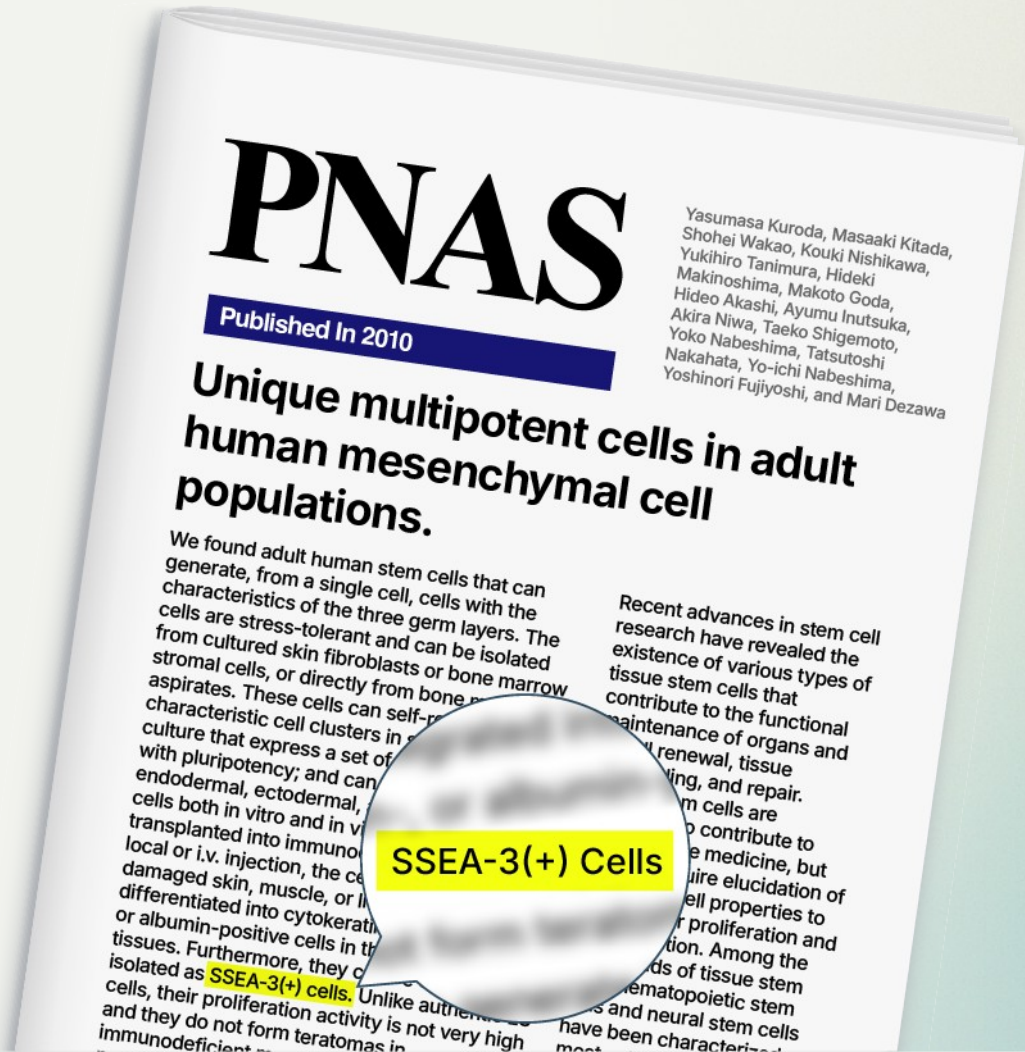


制作 **8** CROWN FACTORY



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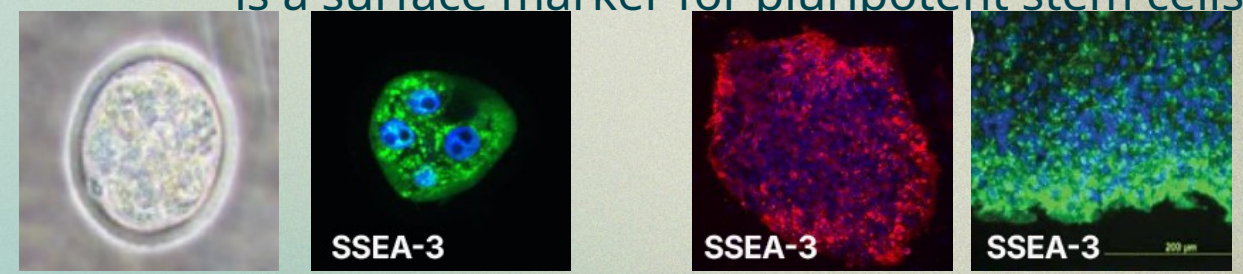
Multilineage-differentiating stress-enduring (DEZAWA MUSE CELLS™)
Pluripotent reparative endogenous stem cells



DEZAWA MUSE CELLS™
have dual features of Macrophages
and Pluripotent cells

SSEA-3(+)

SSEA-3 (Stage-Specific Embryonic Antigen 3)
is a surface marker for pluripotent stem cells



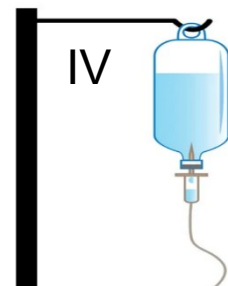
Fertilized egg → inner cell mass ES Cells iPS cells



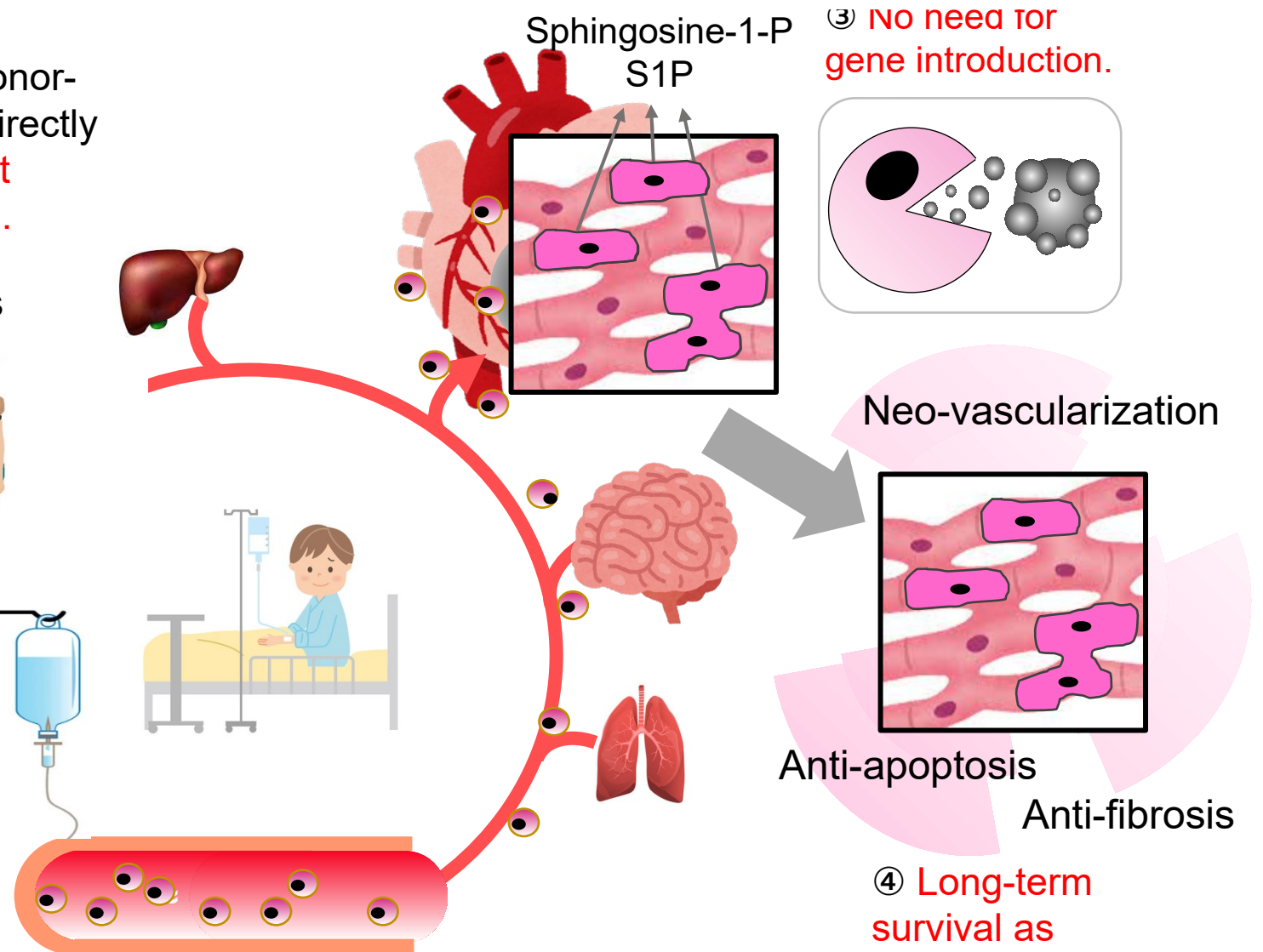
This strategy is available for various diseases because Muse cells are pluripotent.

① **HLA-mismatch** donor-
Muse cells can be directly
administered **without**
immunosuppression.

Donor Muse cells

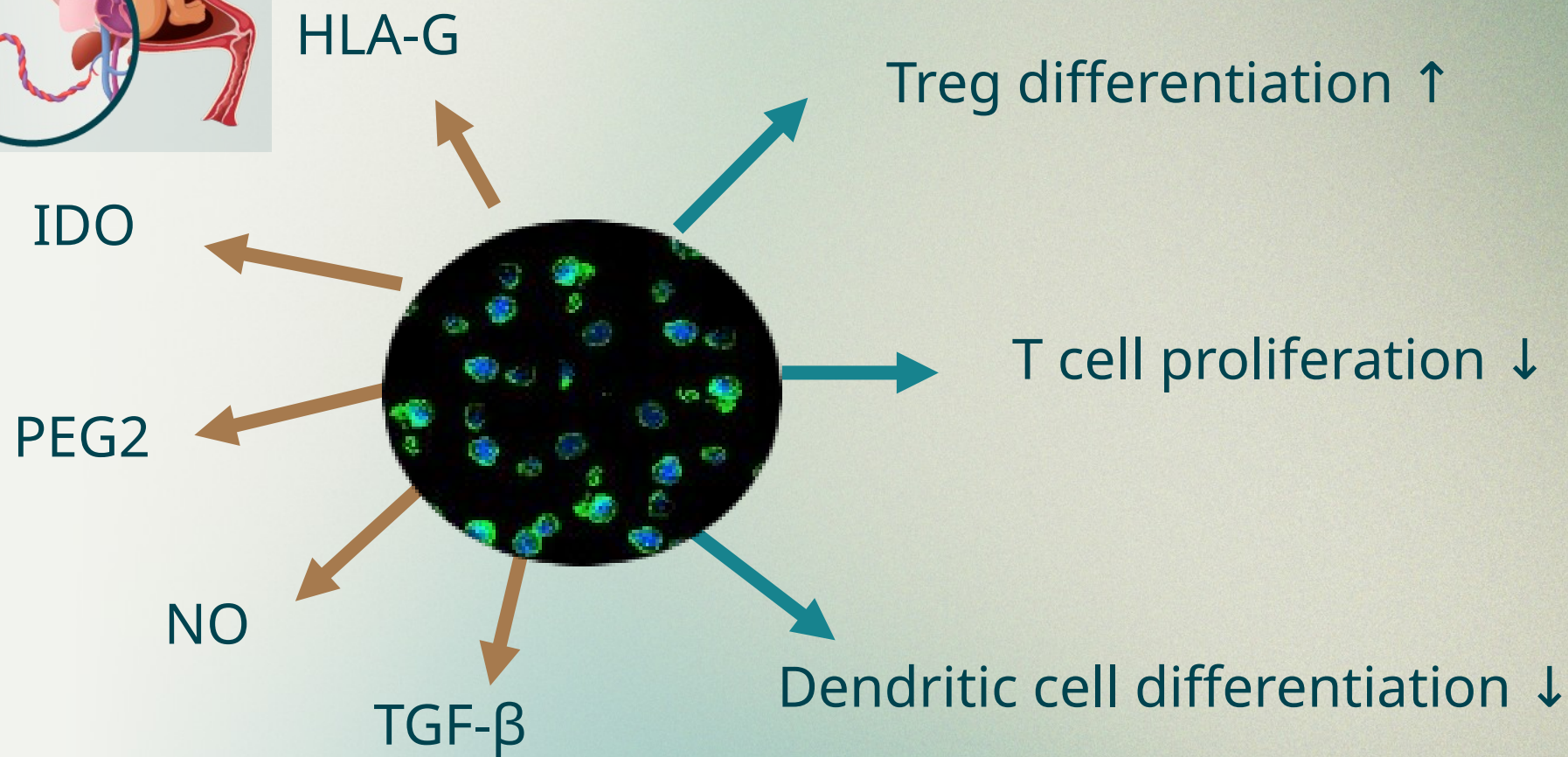
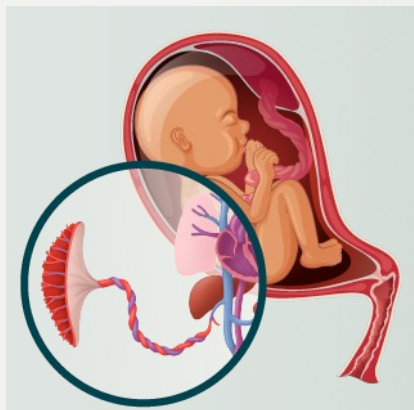


② **Administered**
intravenously. No need for



③ **No need for**
gene introduction.

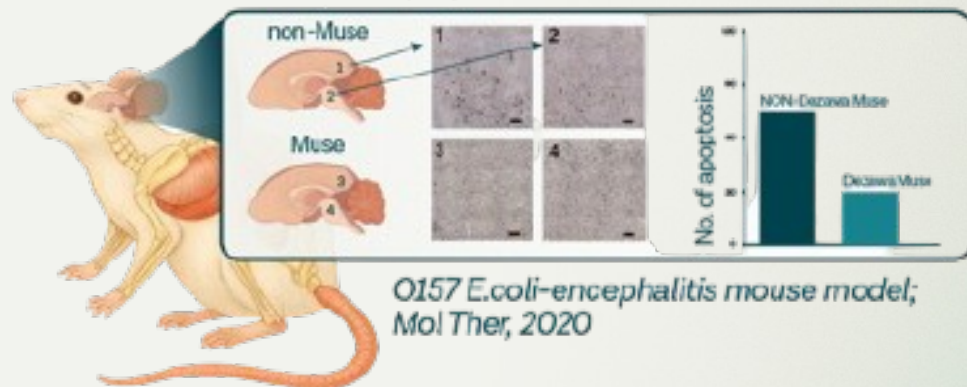
④ **Long-term**
survival as
functional cells
without rejection.



Pleiotropic effects of DEZAWA MUSE CELLS™ are long-lasting in vivo.

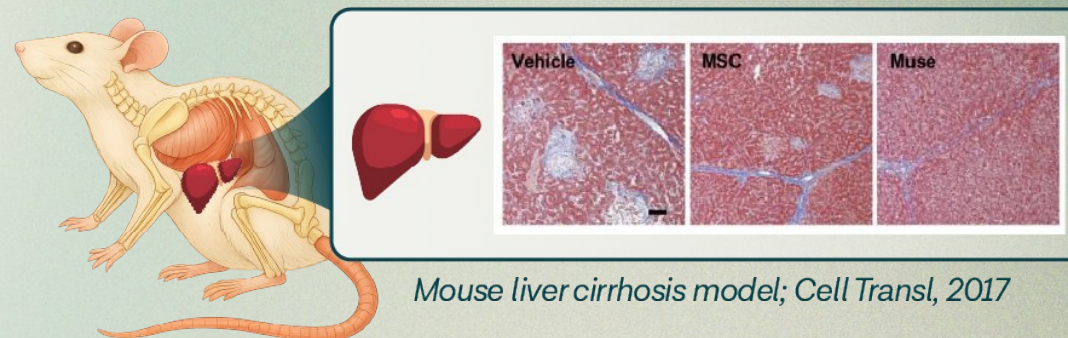
01. Anti-apoptosis

G-CSF, KGF, IL-6, etc.



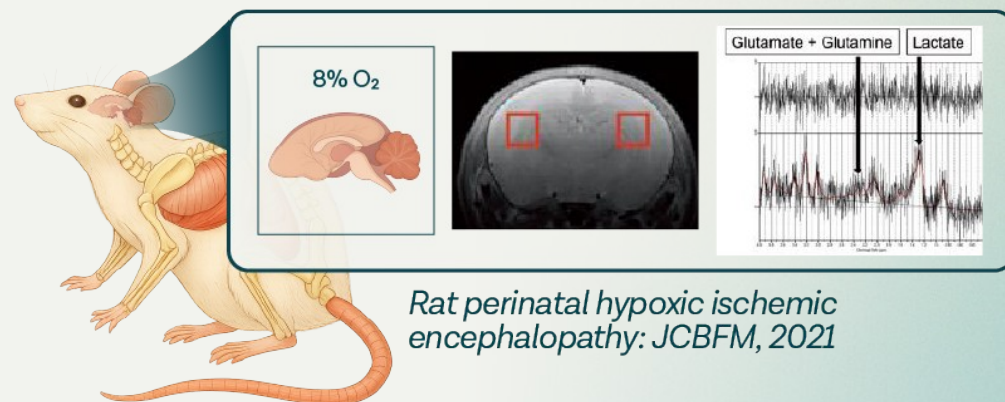
02. Anti-fibrosis

MMP-1, MMP-2, MMP-9, PGE2, etc



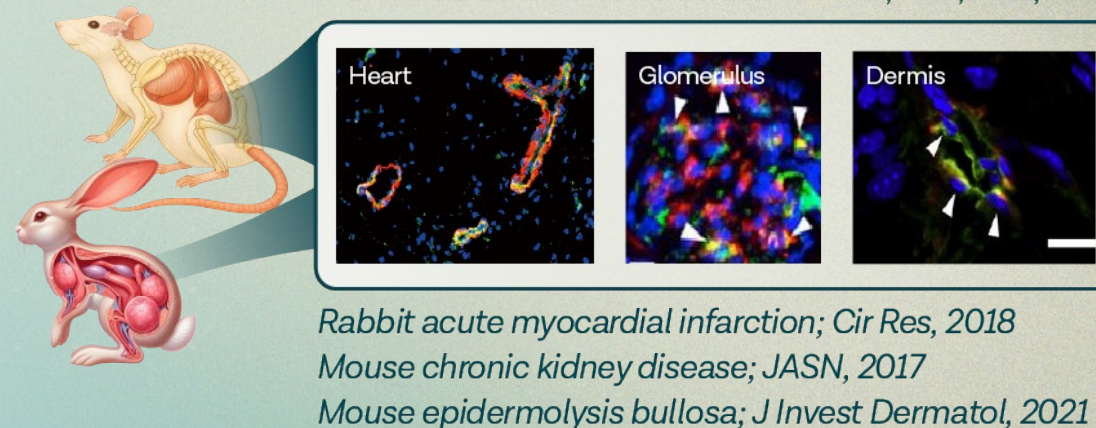
03. Tissue protection

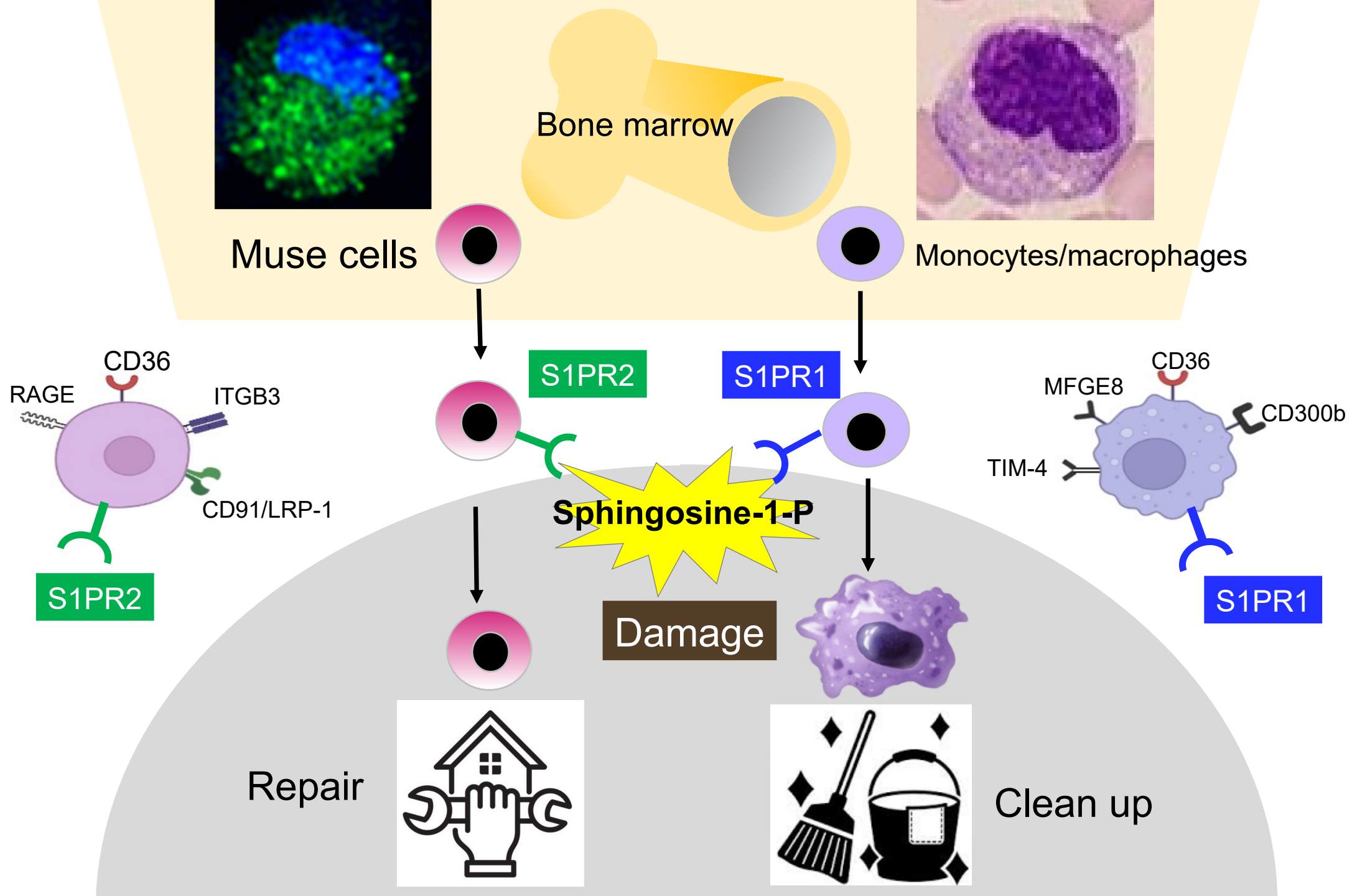
HGF, VEGF, IGF, PDGF, PGE2, IL-1, G-CSF, etc.



04. Vascular Protection

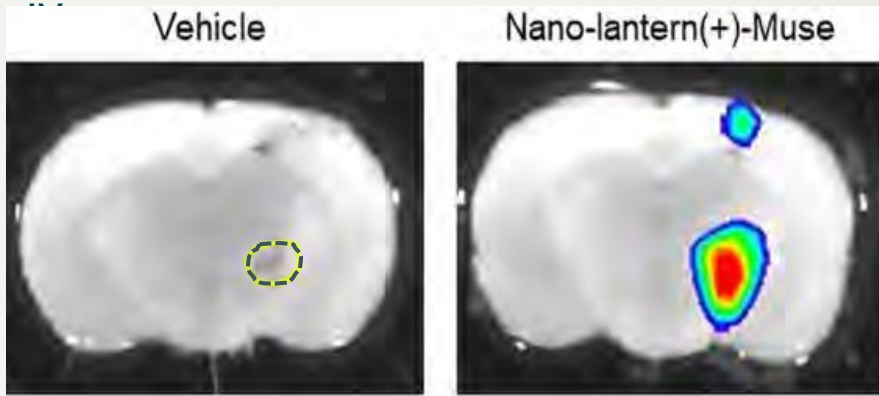
HGF, VEGF, PGE2, KGF...





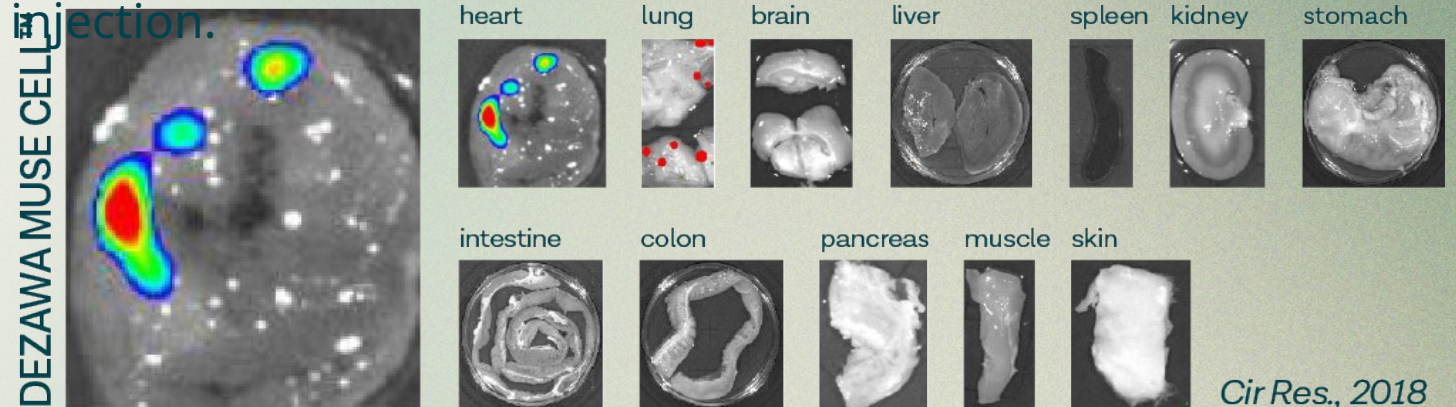
DEZAWA MUSE CELLS™ accurately migrate to damaged sites by sensing sphingosine-1-P, a universal damage signal common to all organs.

Mouse lacunar stroke: 1 day after



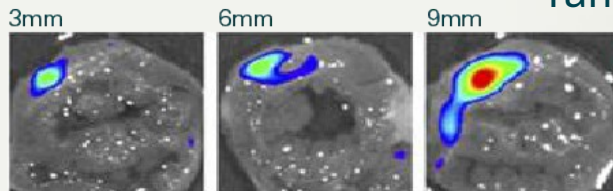
Abe et al., Stroke, 2020

Rabbit acute myocardial infarction: 3 days after intravenous injection.

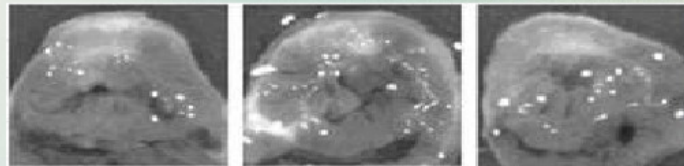


Cir Res., 2018

Distance from occlusion

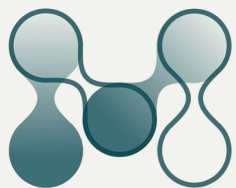


Yamada et al., Cir Res, 2018



DEZAWA MUSE CELLS™ → DEZAWA MUSE CELLS™ + JTE-013
(S1P receptor antagonist)

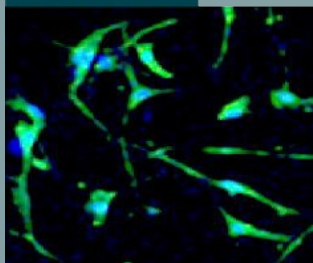
S1P receptor was blocked in **DEZAWA MUSE CELLS™** (2 weeks).



MUSECELL™
INNOVATIONS

Pluripotent DEZAWA MUSE CELL™ differentiate into a broad spectrum of
in vitro and *in vivo*.

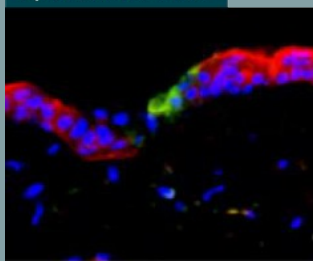
Neural Cells



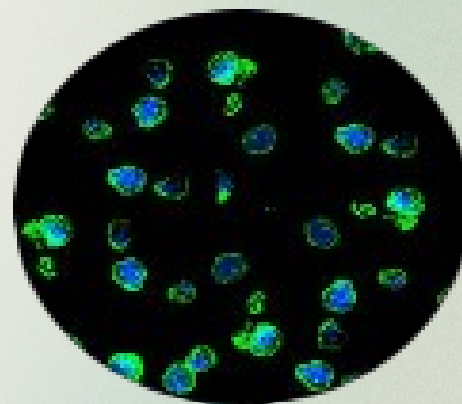
Melanocytes



Epidermal Cells

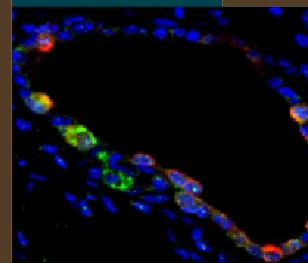


Ectodermal

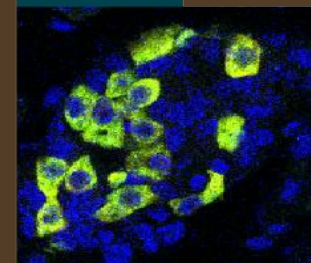


DEZAWA MUSE CELL™

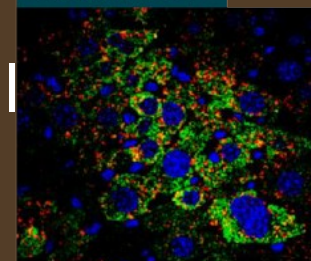
Bile Duct Cells



B Cells



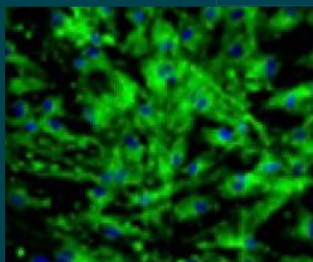
Hepatocytes



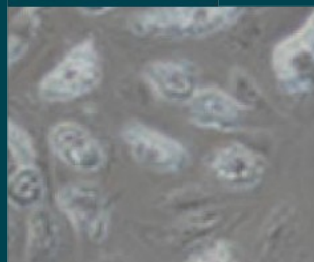
Endodermal

Mesodermal

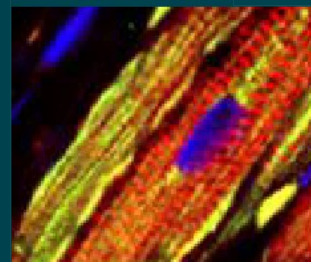
Osteocytes



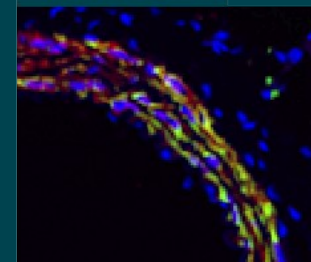
Adipose Cells



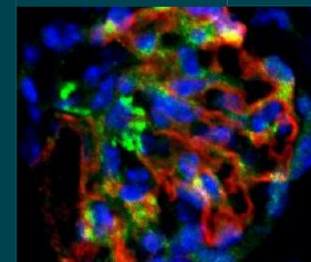
Cardiomyocytes



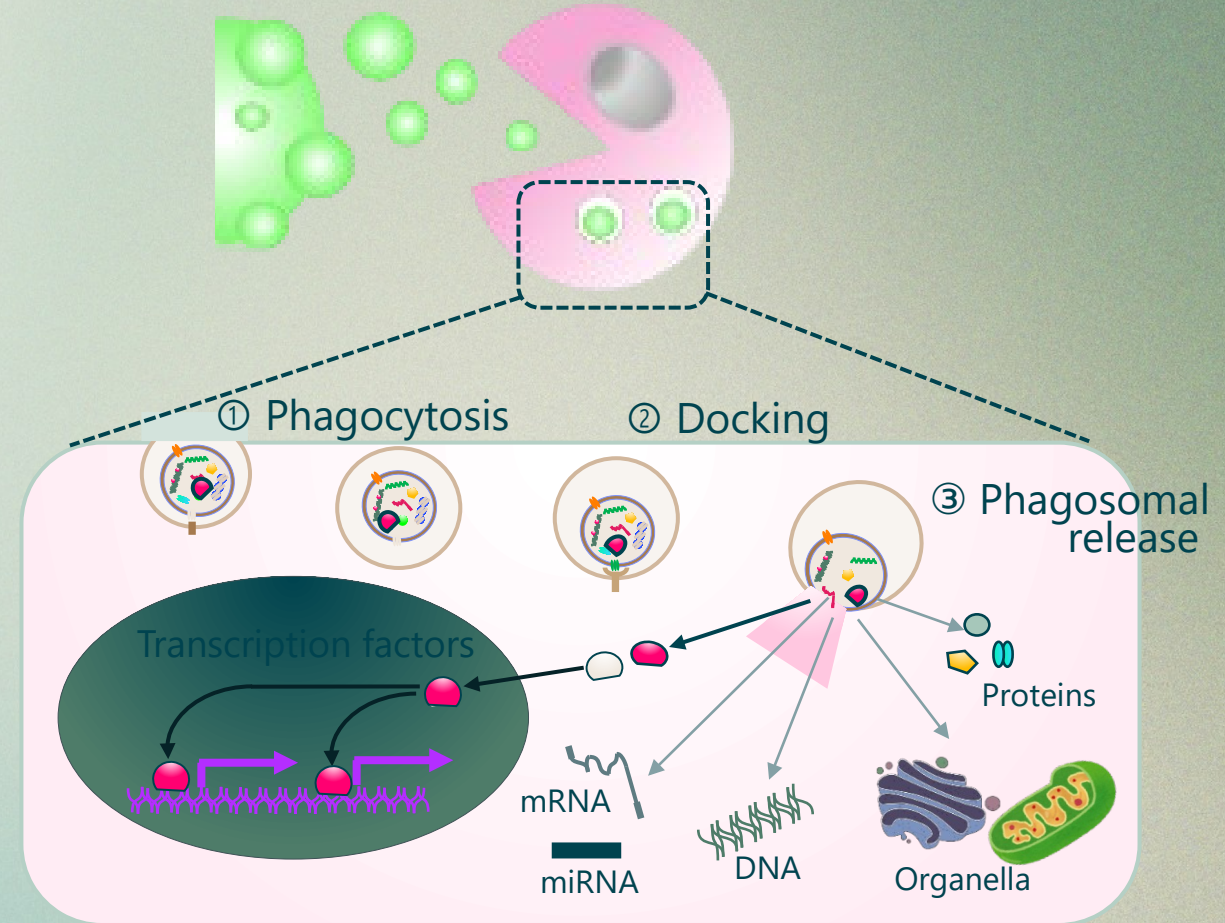
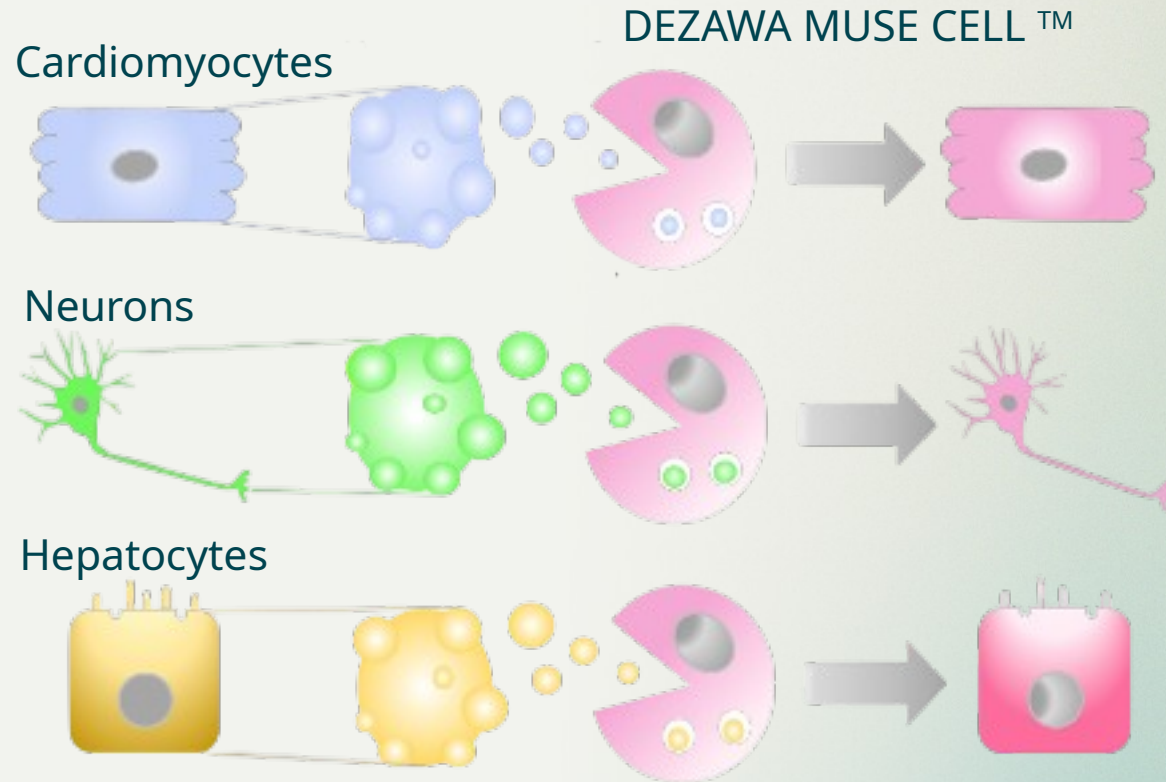
Vascular Cells



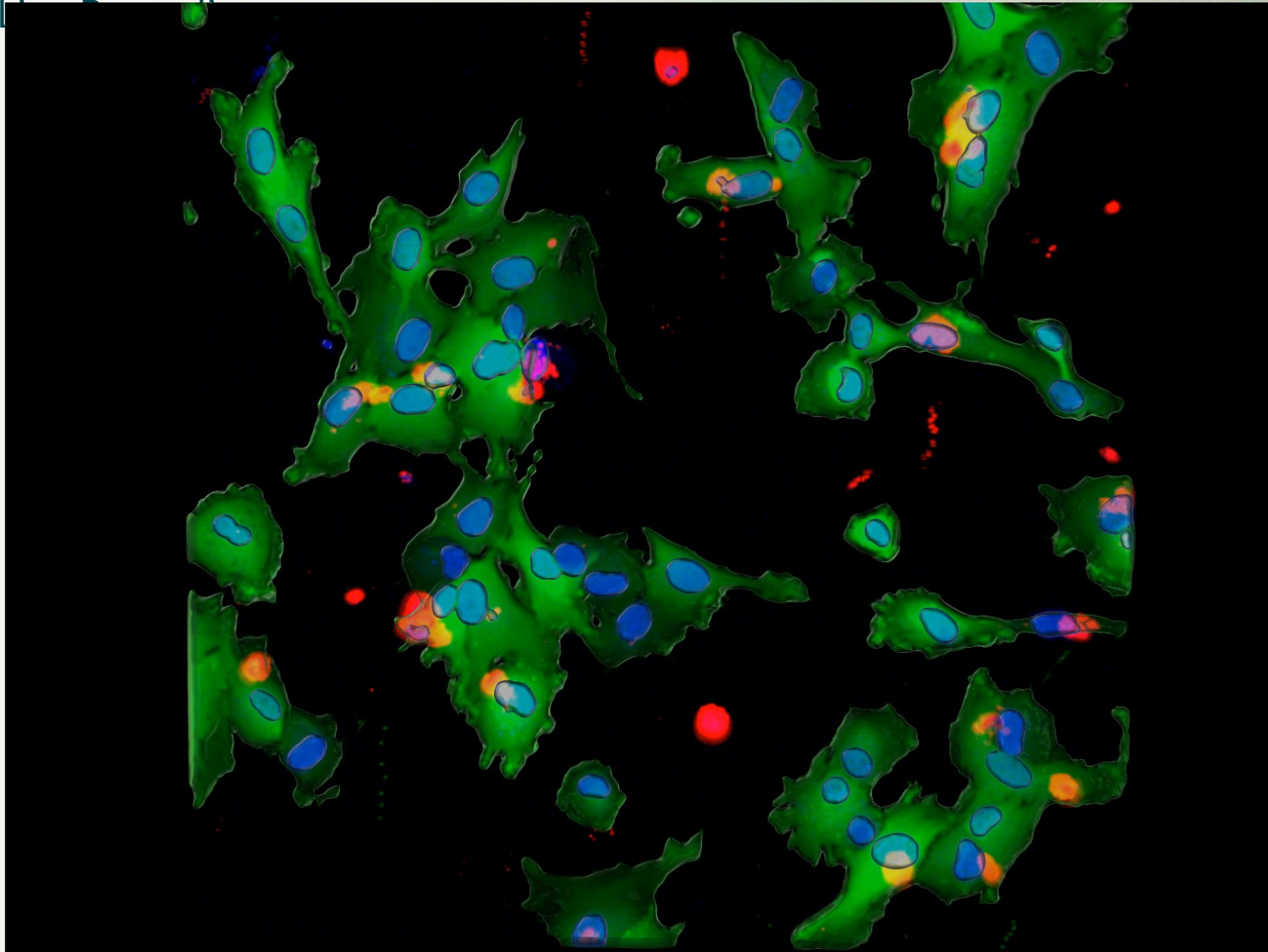
Renal Cells



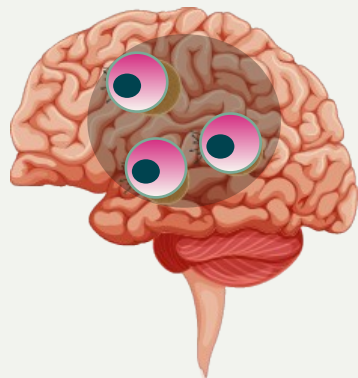
DEZAWA MUSE CELL™ differentiates into target cell types by phagocytosing apoptotic cells.



Human DEZAWA MUSE CELL™ : mouse apoptotic liver fragments 24-h



Differentiation of **DEZAWA MUSE CELLS™** in the brain proceeds in days.

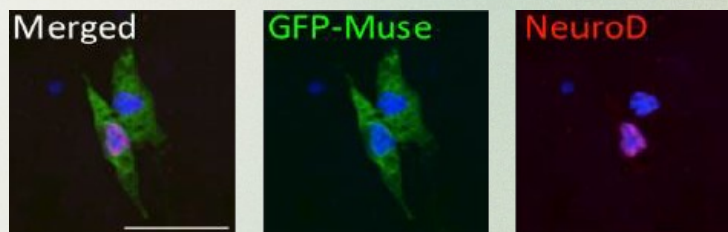


Human-DEZAWA MUSE CELL™
(GFP+) in rat post infarct tissue,
2015

● Live

Stem Cells, 2015

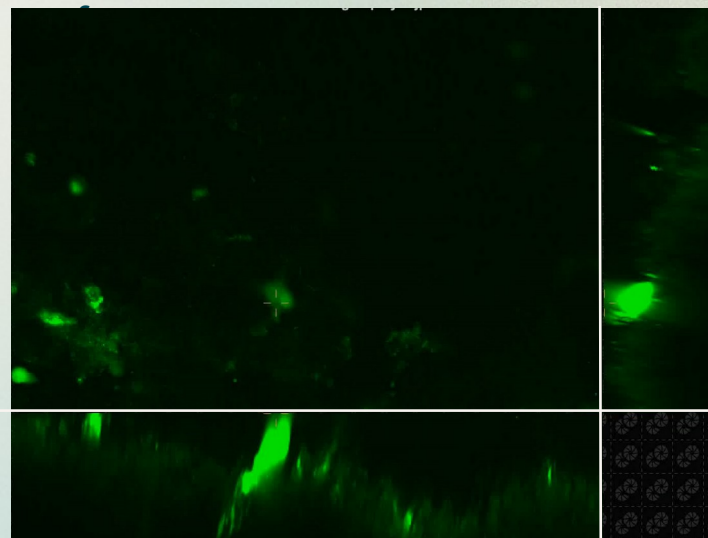
Day 3: NeuroD
(Neural precursor marker)



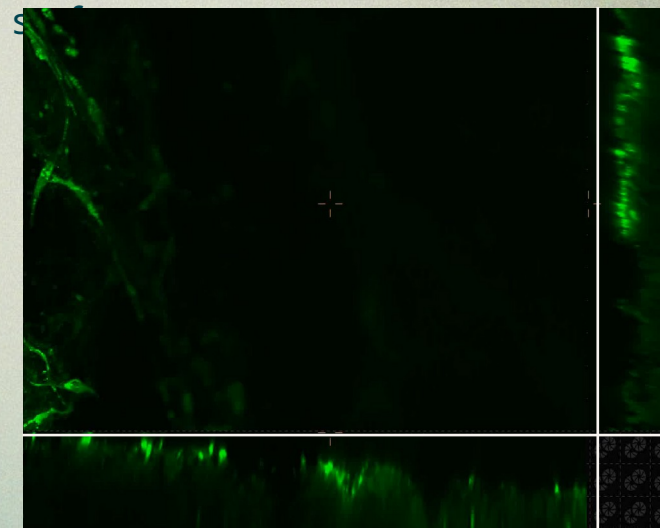
Day 7: MAP2
(Mature neuronal marker)

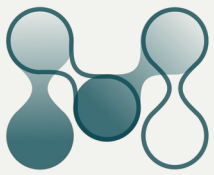


Brain Deep site



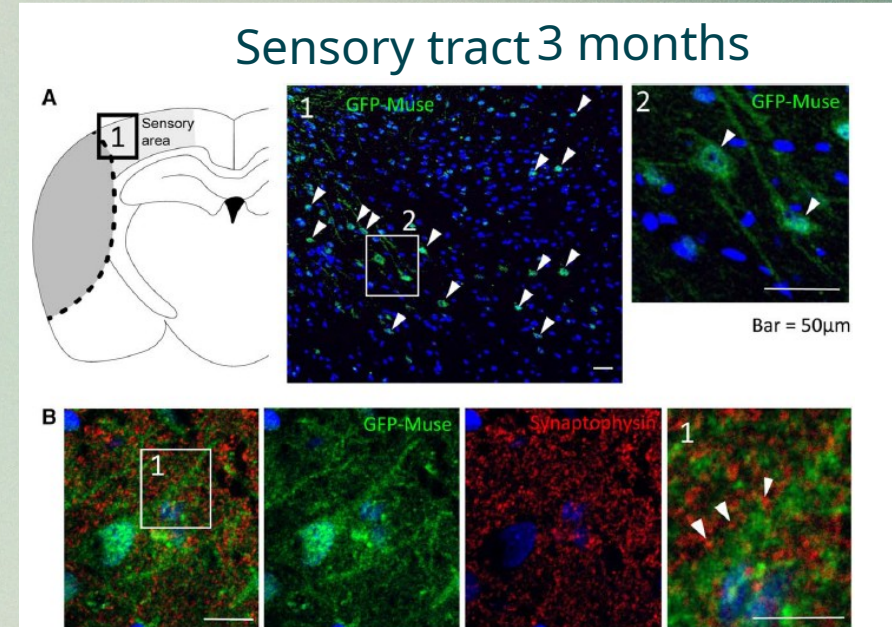
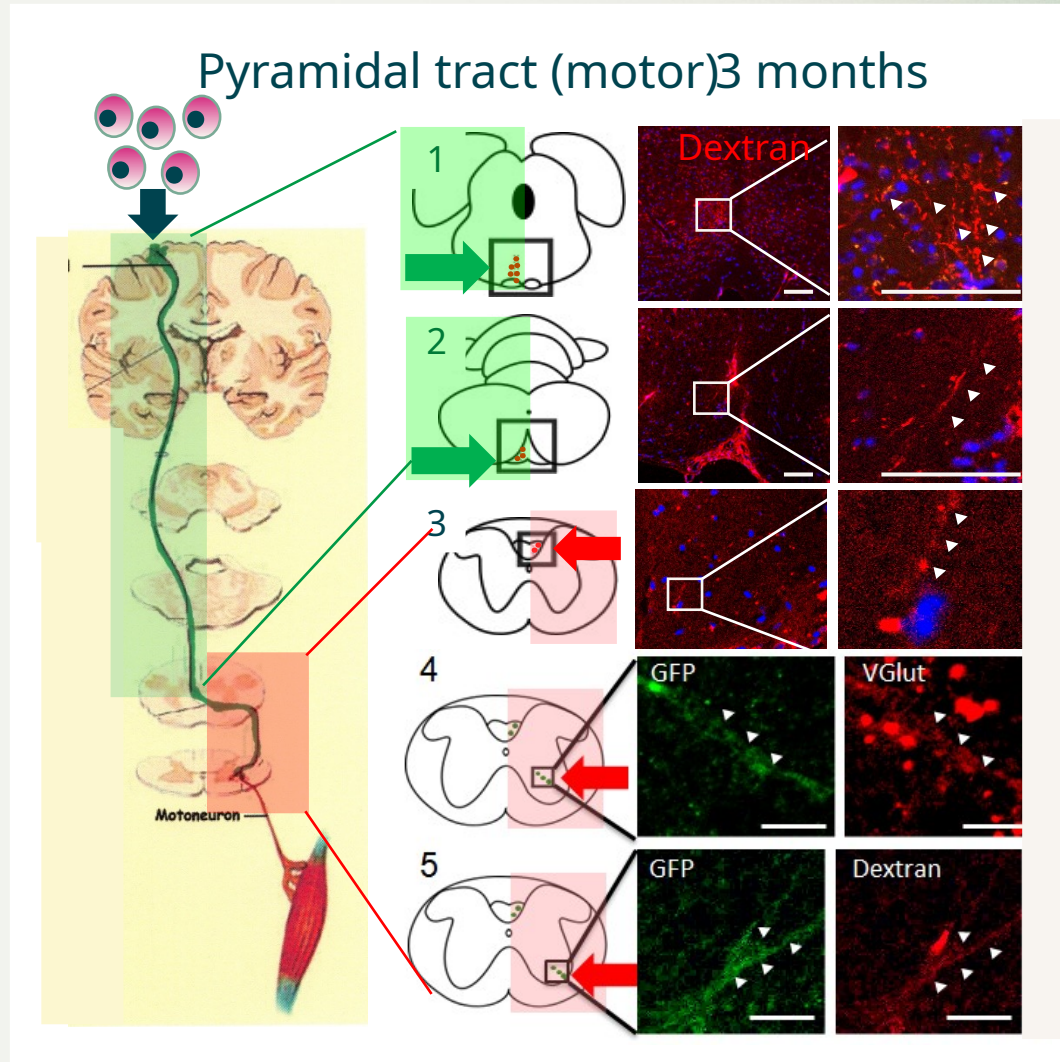
Brain Deep site



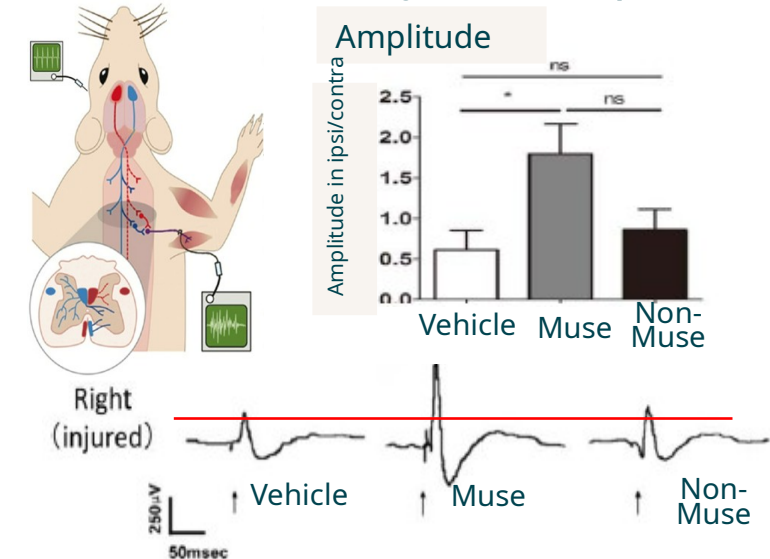


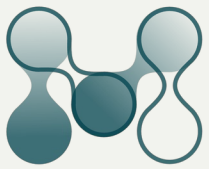
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INNOVATIONS

DEZAWA MUSE CELLS™ reconstructed the neural circuit in rat stroke model

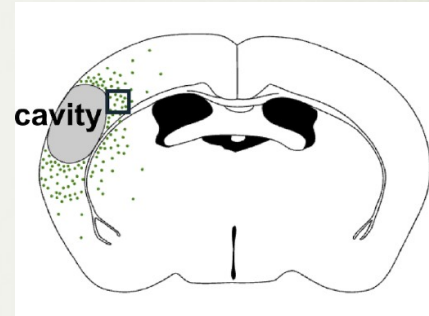
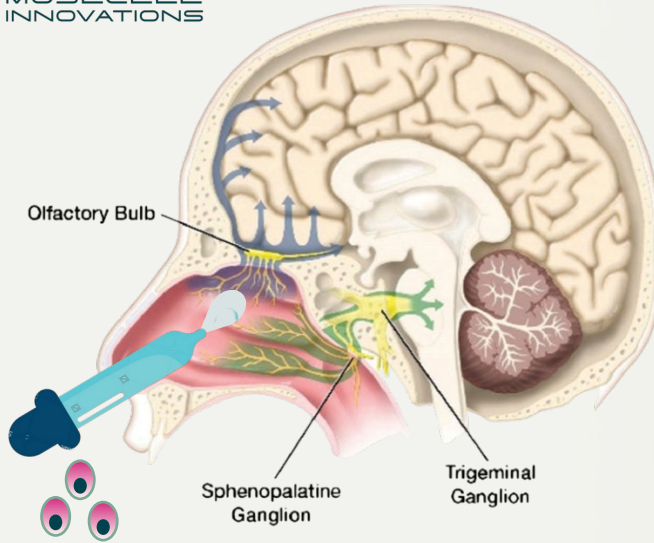


Somatosensory evoked potential

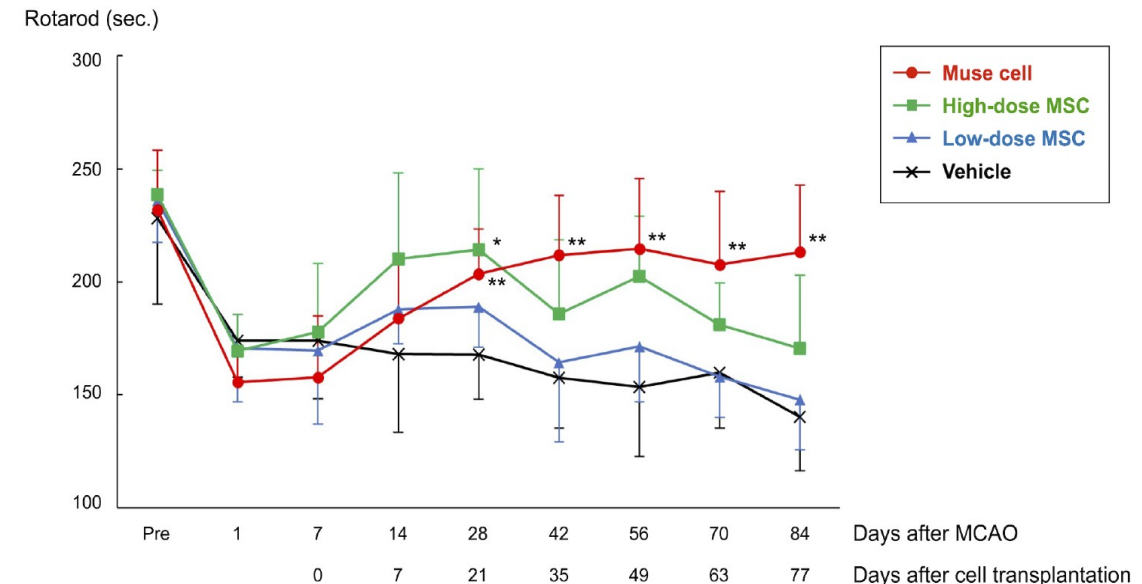
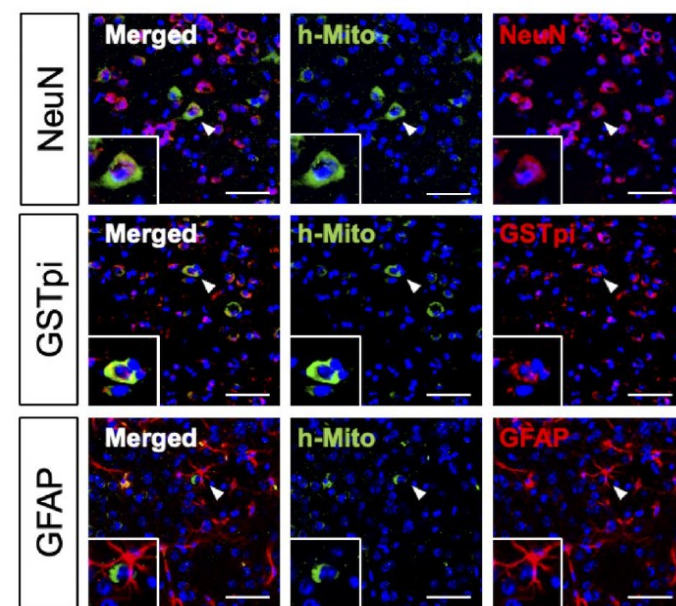
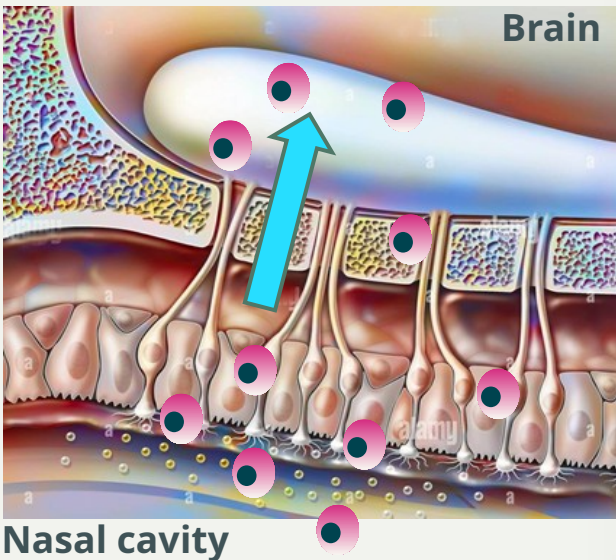
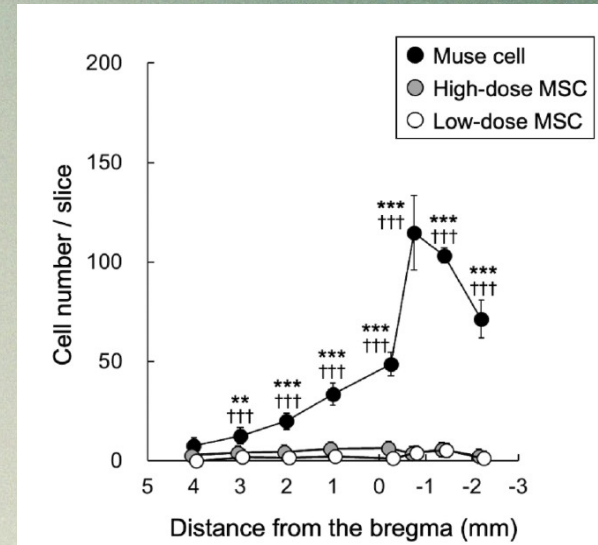
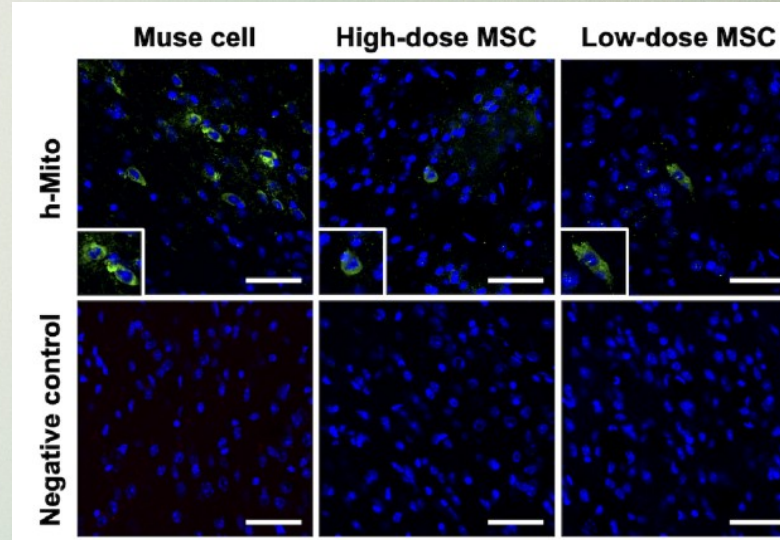




MUSECELL™
INNOVATIONS



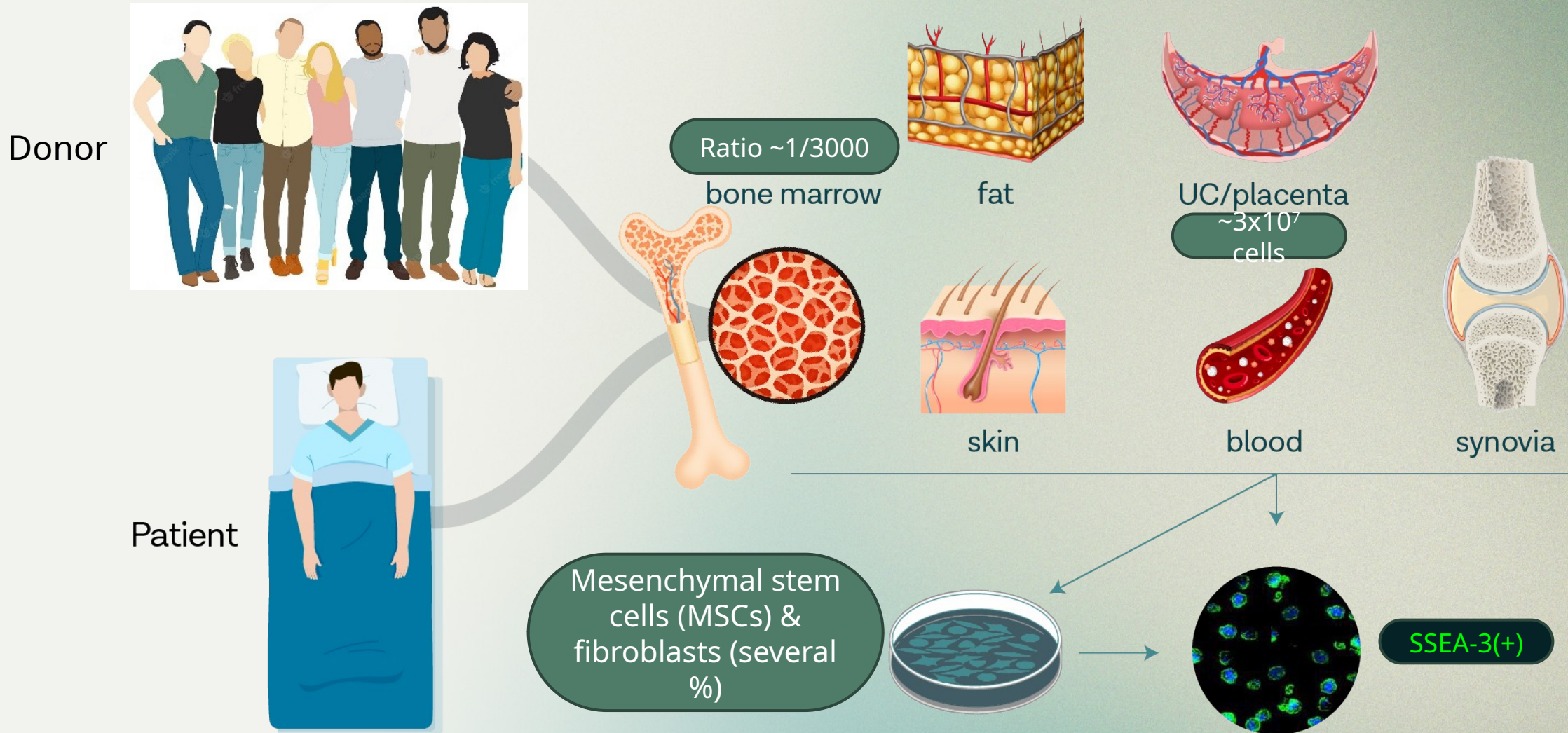
DEZAWA MUSE CELLS™ can be treated by nasal administration for brain diseases. Yamamoto et al., Sci Rep, 202



Clinical Trials



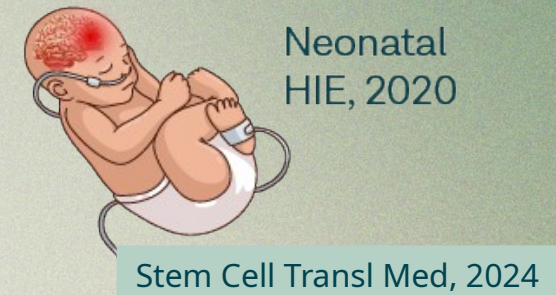
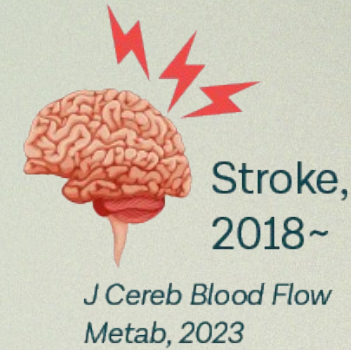
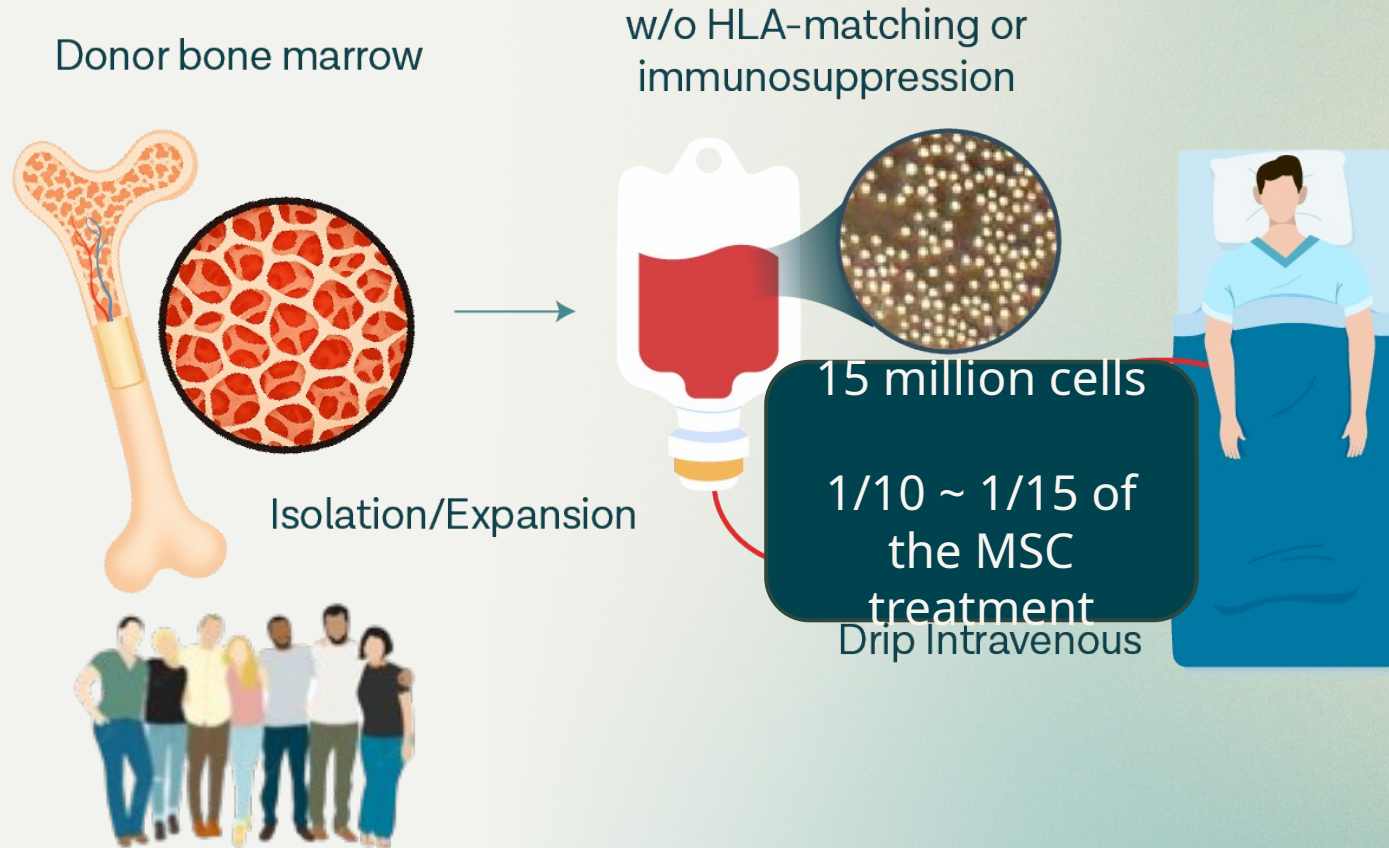
DEZAWA MUSE CELLS™ can be purified from various tissues.



~200 Patients

Donor **DEZAWA MUSE CELLS™** have not been rejected for over 7 yrs.

DEZAWA MUSE CELL™ preparation



Epidermolysis Bullosa, 2018~



Open-label clinical trial for acute myocardial infarction: ~12% recovery of left ventricular ejection fraction at 12 weeks after treatment

Noda et al., Cir J, 2020

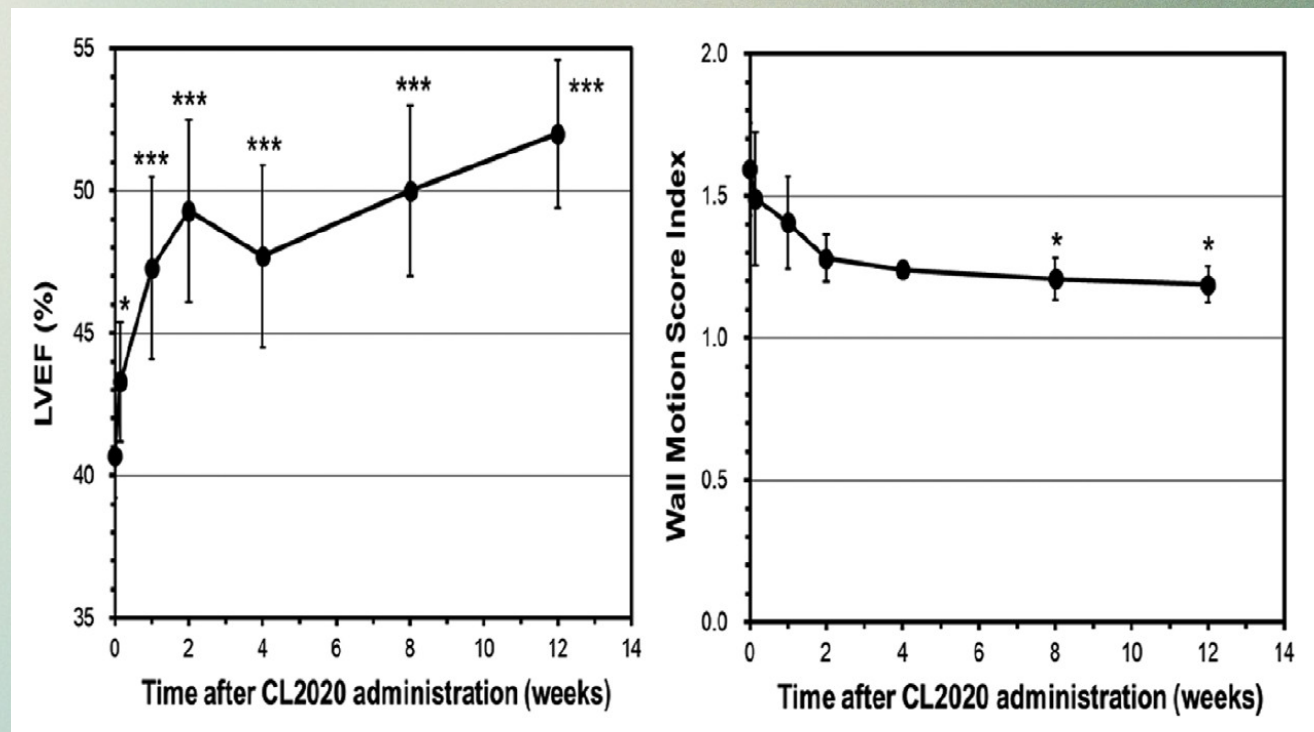
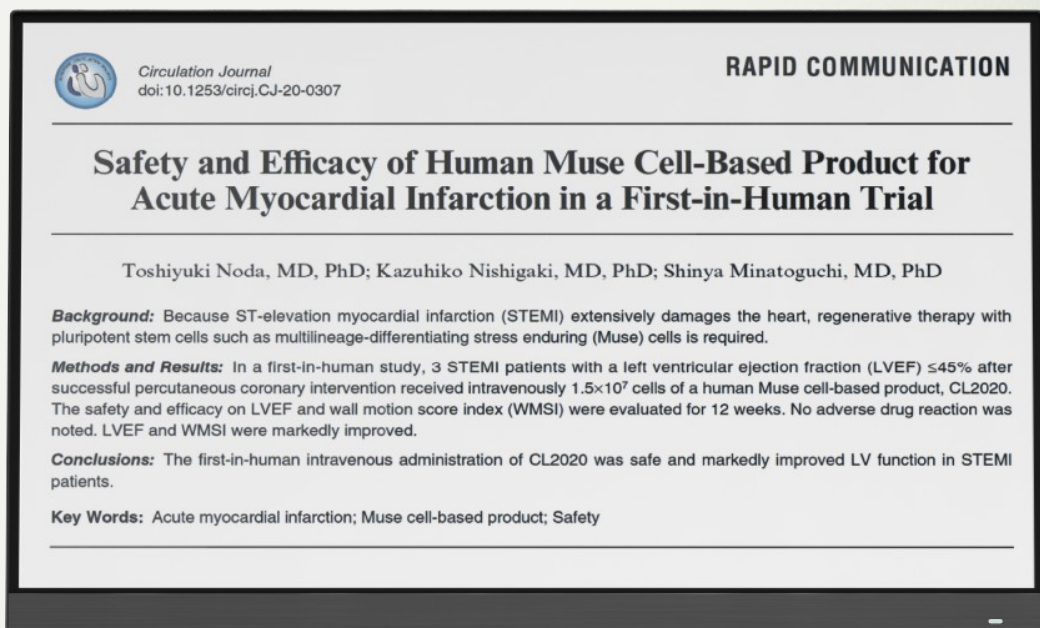
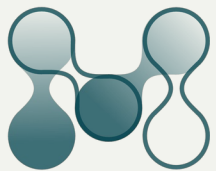


Figure. Changes in cardiac function before and after the administration of CL2020.

(a) Left ventricular ejection fraction (LVEF)

(b) Wall motion score index (WMSI) before 24h, 8 days, and 2, 4, 8, and 12 weeks after administration of CL2020.

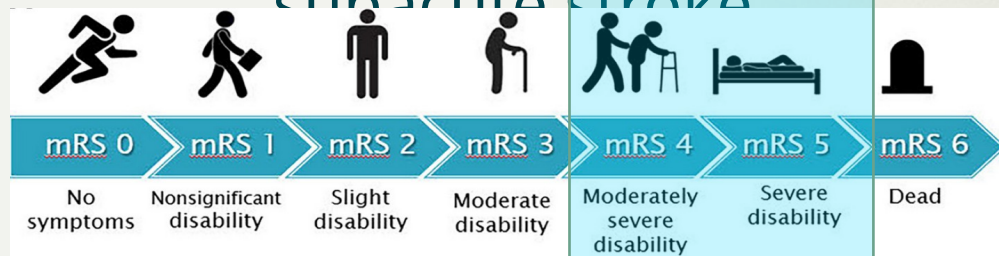
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$



MUSECELL™
INNOVATIONS

Niiziuma et al., J Cereb Blood Flow Metab, 2023

Randomized placebo-controlled double-blind clinical trial for subacute stroke



modified Ranking Scale (mRS)

Patient baseline

Severe disability (modified Rankin Scale [mRS] 4–5)

Bedridden, incontinent, or needing help for walking, eating, and toilet use

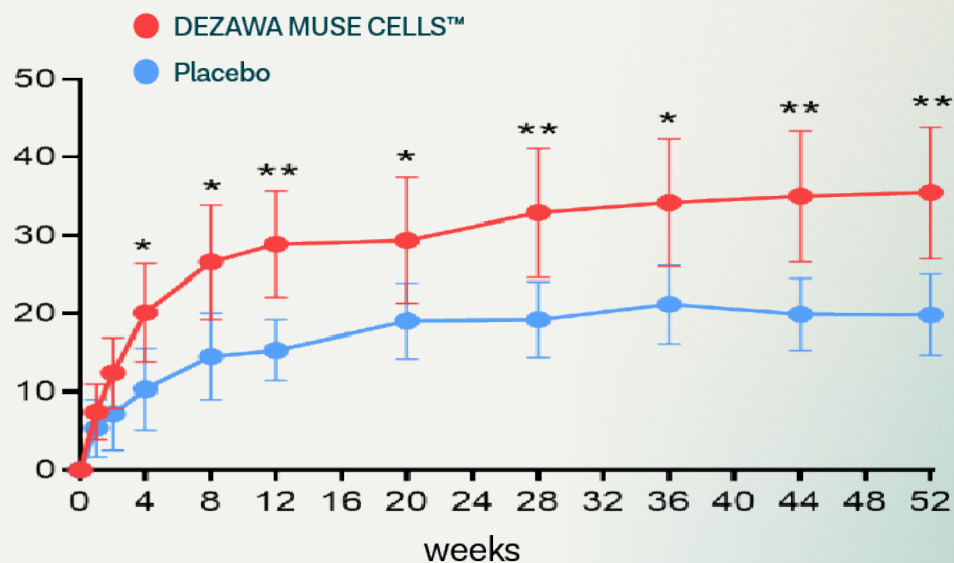
Intervention

A single dose of **donor-DEZAWA MUSE CELLS™** at 2~4 weeks after onset.

At 52 weeks

HLA-matching test or immunosuppressant

FMMS Total



DEZAWA MUSE CELL™ Group

~70% became independent when using trains, walking, toilet, and eating.

~30% of the patients regained their pre-stroke function and returned to work.

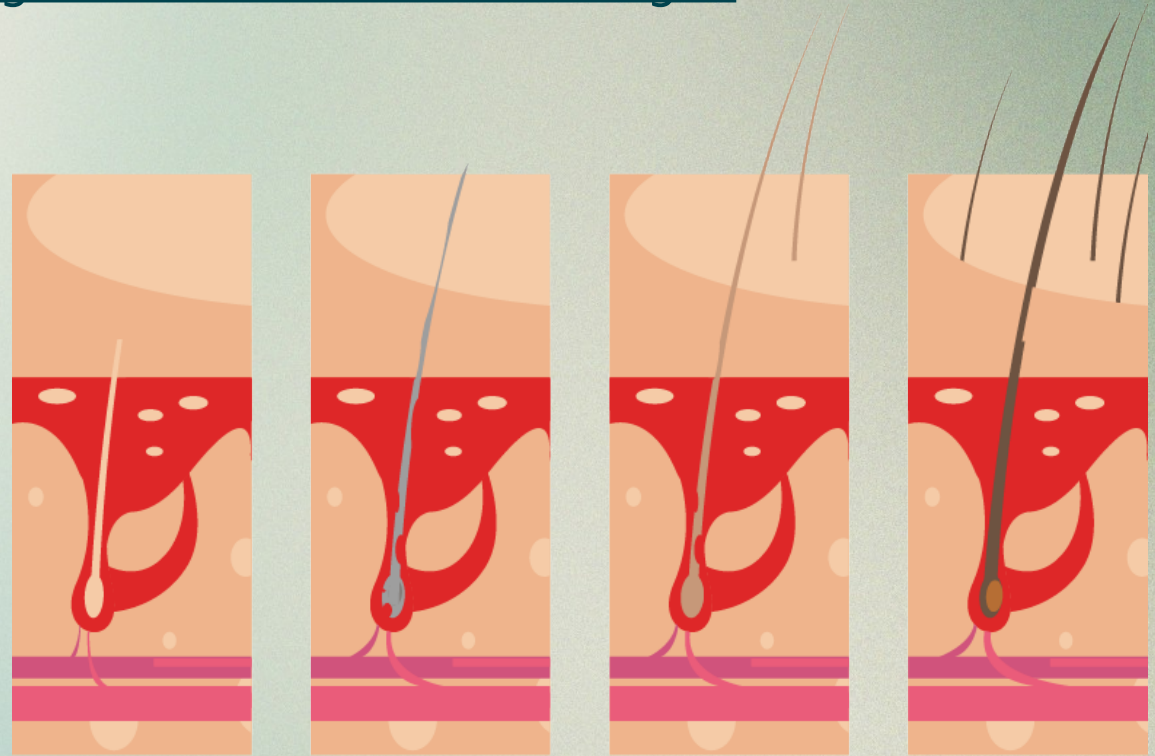
Placebo Group

None recovered to the point where they could return to work.

In the clinical trial for ischemic stroke, around 24% of the DEZAWA MUSE CELL™ group patients had **happy side effects**: hair growth and hair color change.

J Cereb blood Flow Metab, 2023

tion (CL2020, 24%, placebo, 60%) (Table 2). The occurrence of psychiatric disorders (CL2020, 16%; placebo, 70%; $P=0.004$) and insomnia (CL2020, 16%; placebo, 60%; $P=0.016$) were significantly low in the CL2020 group compared with the placebo group. Up to week 12, ARs occurred in 7 (28%) patients in the CL2020 group and 1 (10%) patient in the placebo group. In the CL2020 group, 3 (12%) patients had hair discoloration from gray/white to black by week 12, and 3 additional patients had hair discoloration between week 12 and week 52, for a total of 6 patients (24%); no patients in the placebo group had this AR.



Gray hair turned black, and hair growth occurred.

ALS mouse model (17 week-old)

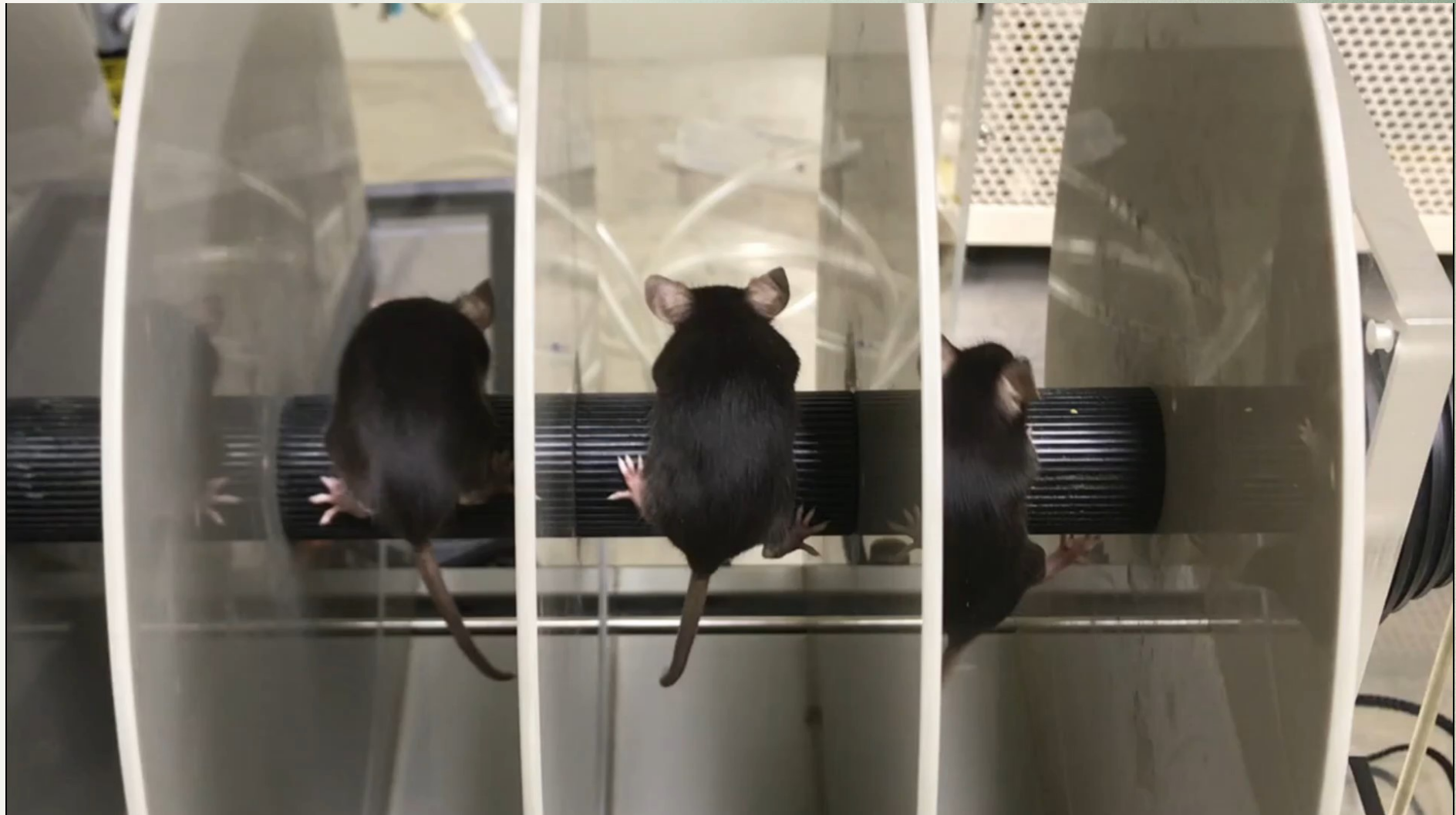
Yamashita et al., Sci Rep, 2021

MSC

DEZAWA MUSE CELLS™

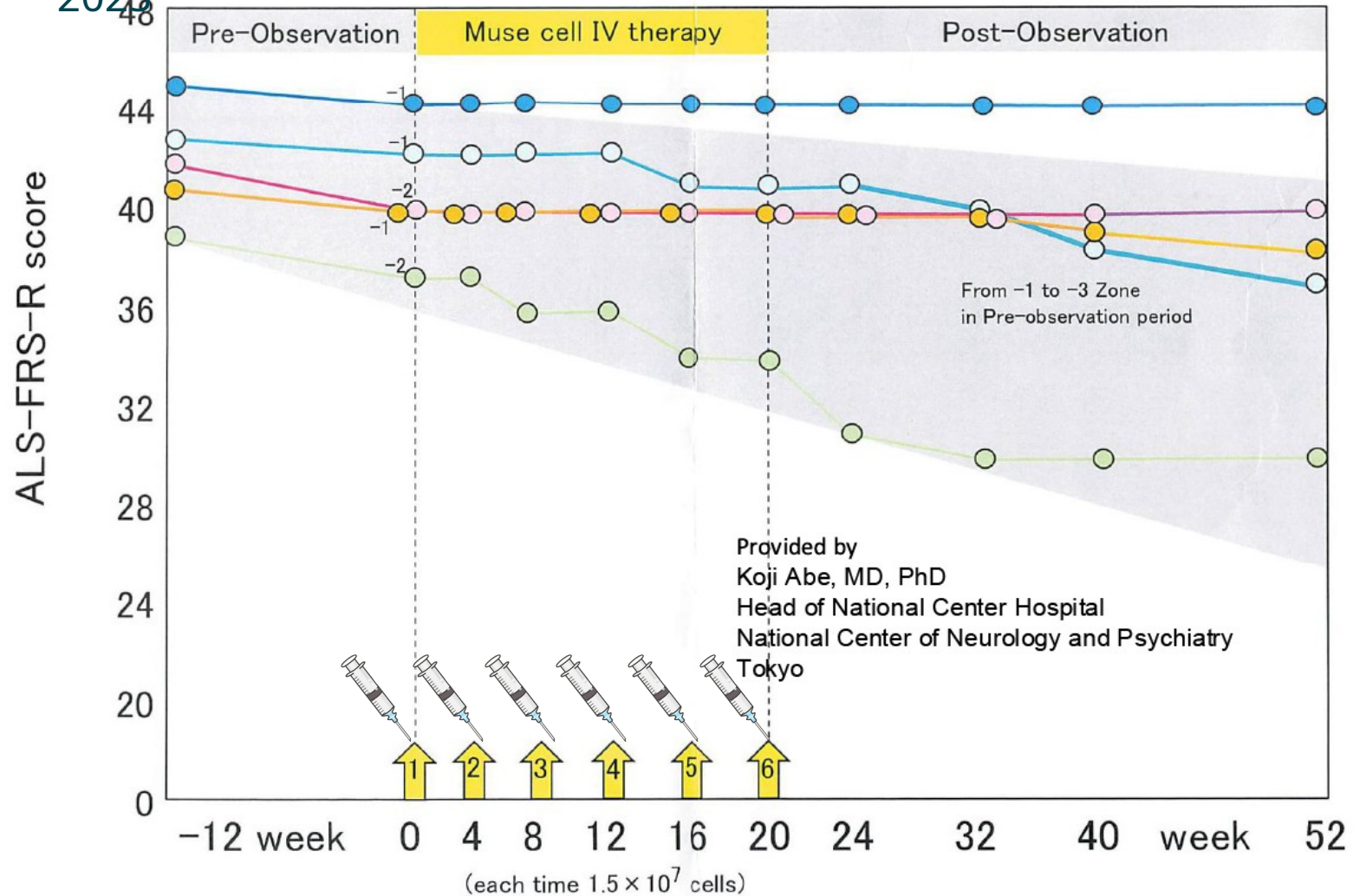
Vehicle

● Live

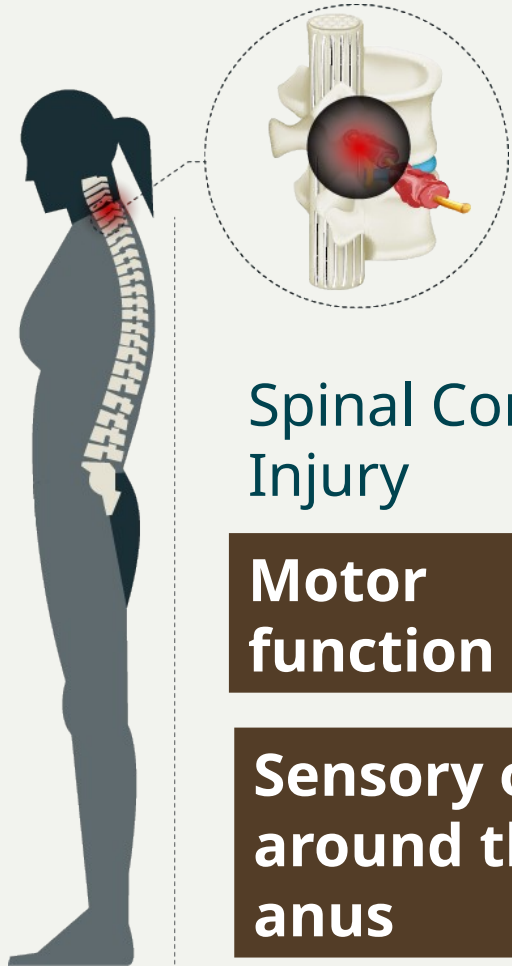


Phase II open-label clinical trial for ALS: Six doses of **donor-DEZAWA MUSE CELLS™ iv** without immunosuppression

Yamashita et al., Cell Transpl,
2023



Phase I/IIa clinical trial for cervical (C4~C7) spinal cord injury: **donor-DEZAWA MUSE CELL™** intravenous drip without immunosuppressant.

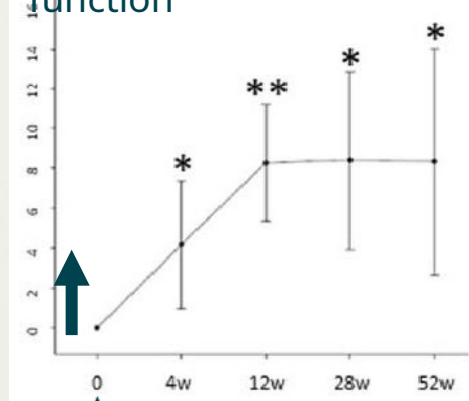


Spinal Cord Injury

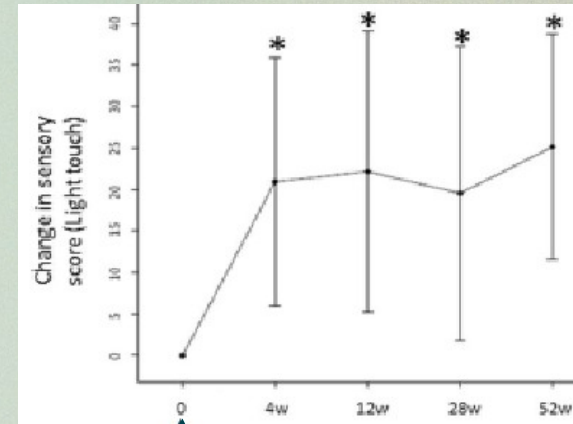
**Motor
function loss**

**Sensory only
around the
anus**

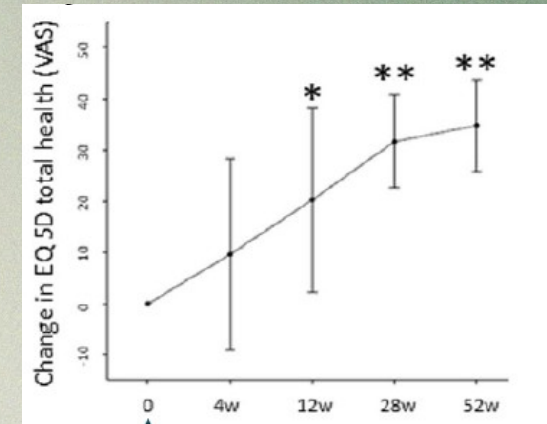
Recovery of motor
function



Touch sensory



Activities of daily living

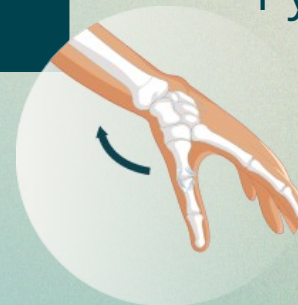


DEZAWA MUSE
CELL™
iv 3 weeks after
injury

1 year after



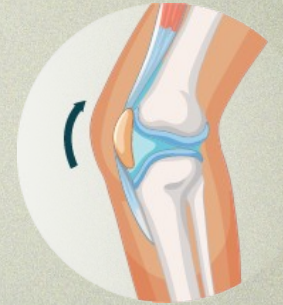
shoulder
movement



wrist
movement



elbow
movement



knee
support

Phase I Open-label clinical trial for neonatal hypoxic-ischemic encephalopathy:
donor-DEZAWA MUSE CELLS™ intravenous drip without immunosuppressant.



Hypoxic Ischemic Encephalopathy



Hypothermia For 3 days



DEZAWA MUSE CELL™ iv (5-14 days after birth)

Sato et al., Stem Cell Transl Med, 2024

*including 42 patients, who died.

1.5 yr	Donor Muse cell treatment		Baby Cooling Japan data base
	Low dose (1.5M cells)	High dose (15M cells)	
Survival	100.0% (3/3)	100.0% (6/6)	91.5% (451/493)
Respiratory support	0% (0/3)	0% (0/6)	17.7% (87/493) *
Development at a normal level (KSPD)	66.7% (2/3)	66.7% (4/6)	33.1% (57/172) *

KSPD: Kyoto Scale of Psychological Development
Assesses a child's development in 3 domains:



Cognition & Adaptation



Language & Society



Posture & Exercise

„In a clinical trial for neonatal hypoxic-ischemic encephalopathy in Japan, a single dose of donor-Muse cells was administered to very severe neonates. The results showed remarkable therapeutic outcomes that far exceeded those of existing treatments, and the findings have been published in an international journal. With standard treatment, approximately 10% of children remain bedridden and require mechanical ventilation. However, all the babies who received Muse Cells have not needed mechanical ventilation, and many have developed to a normal level and are even attending kindergarten.“



Mari Dezawa, MD, PhD

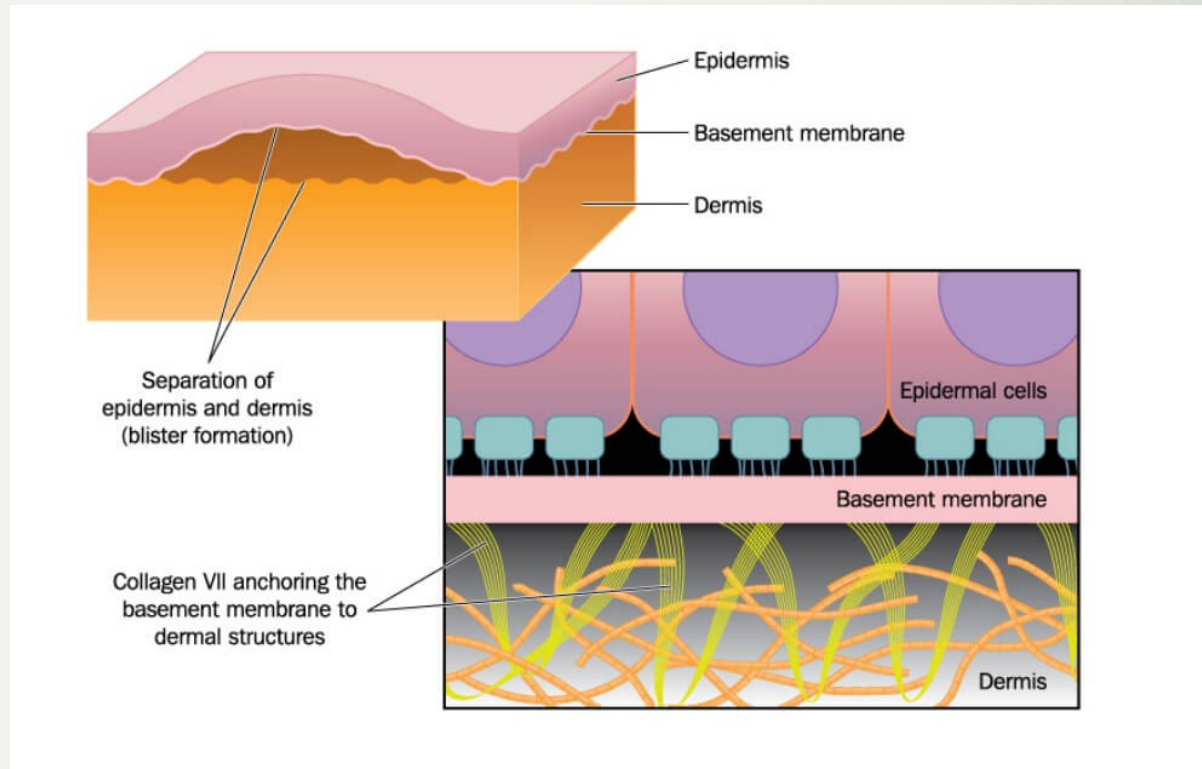
Tohoku Univ Graduate School Of Medicine
MuseCell Innovations PTE Ltd

Epidermolysis bullosa (EB): Caused by mutations of the epidermis-dermis junctional complex. There is no cure.

Prof. Katsuto Tamai, 2018, Igaku-no-ayumi



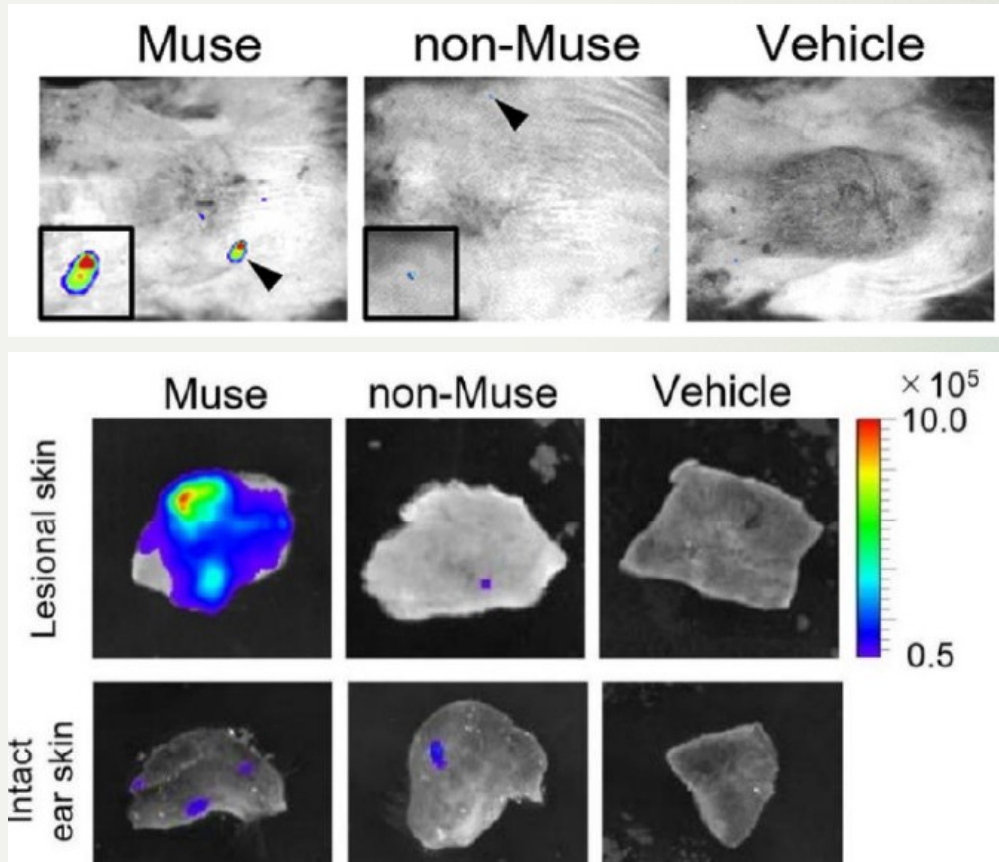
American Academy of Dermatology Association



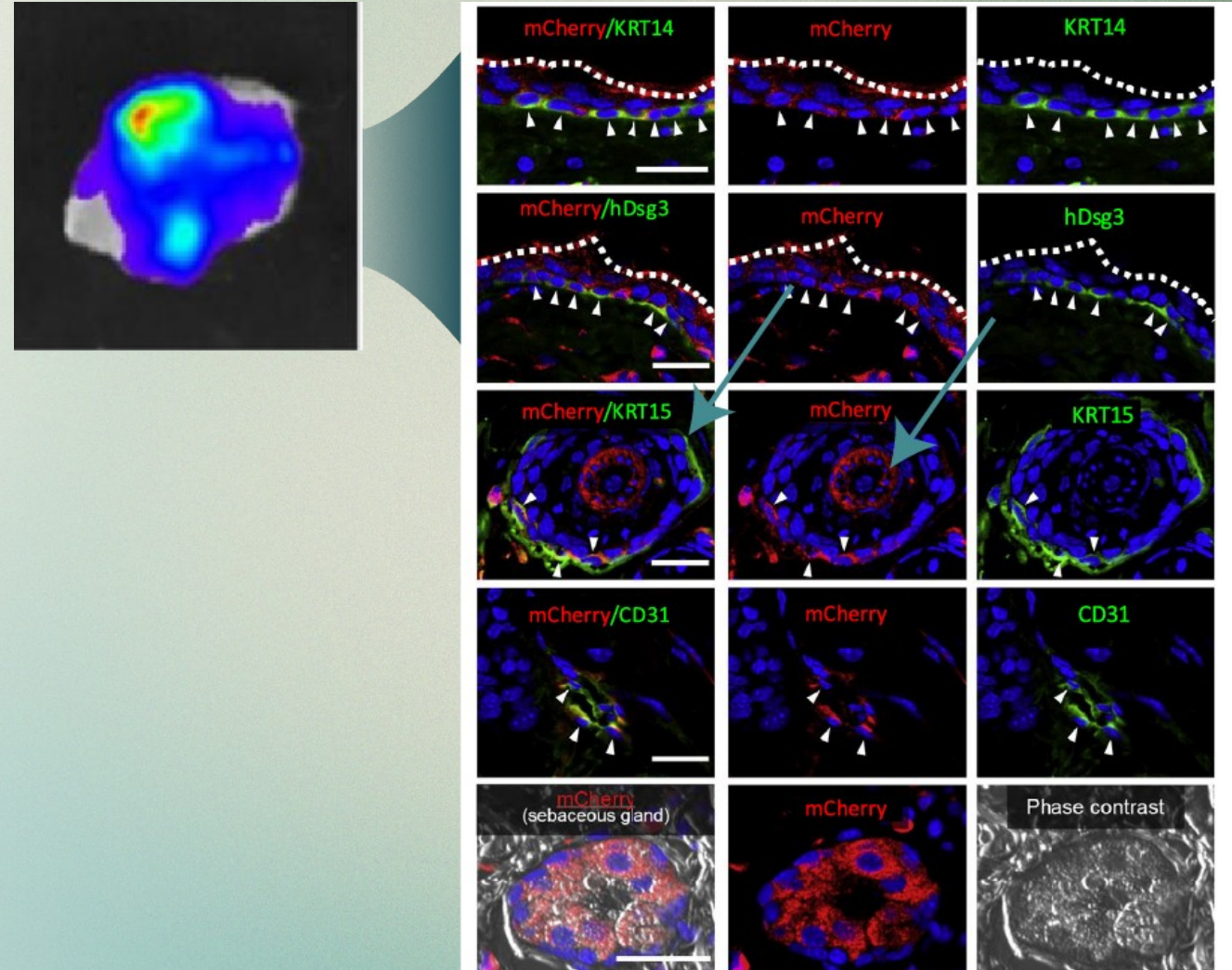
Human **DEZAWA MUSE CELLS™** were maintained integrated as epidermal and dermal cells in the mouse Col-17-/- EB model without immunosuppression for 6 months.

Fujita et al., J Invest Dermatol,
2020

1 Week after iv admin



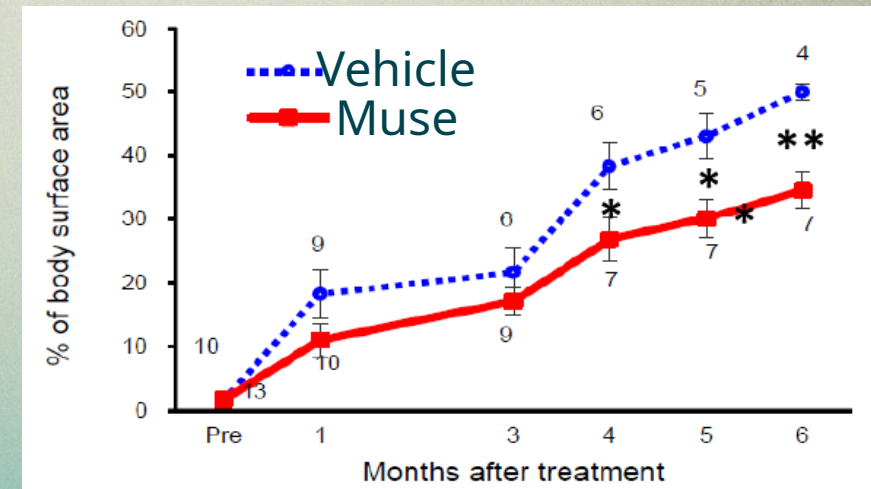
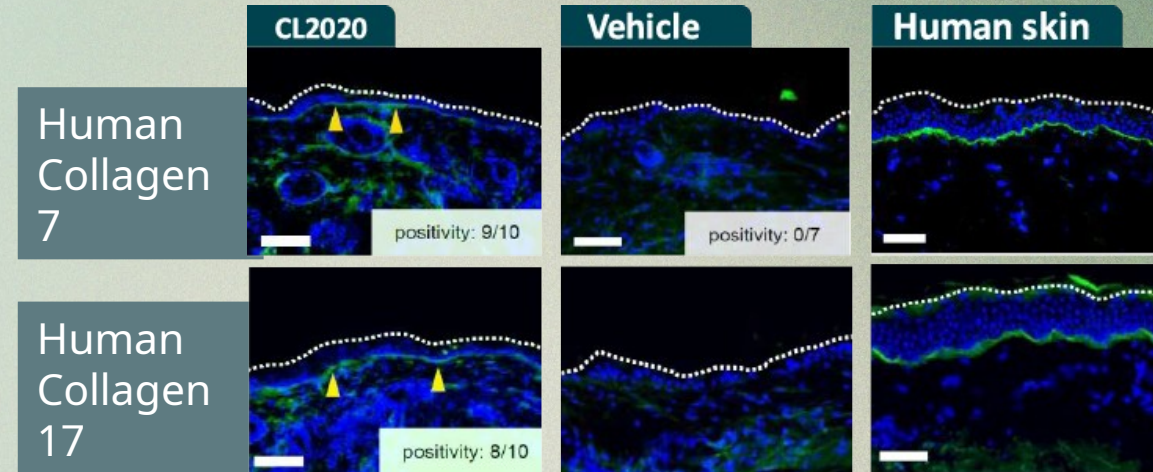
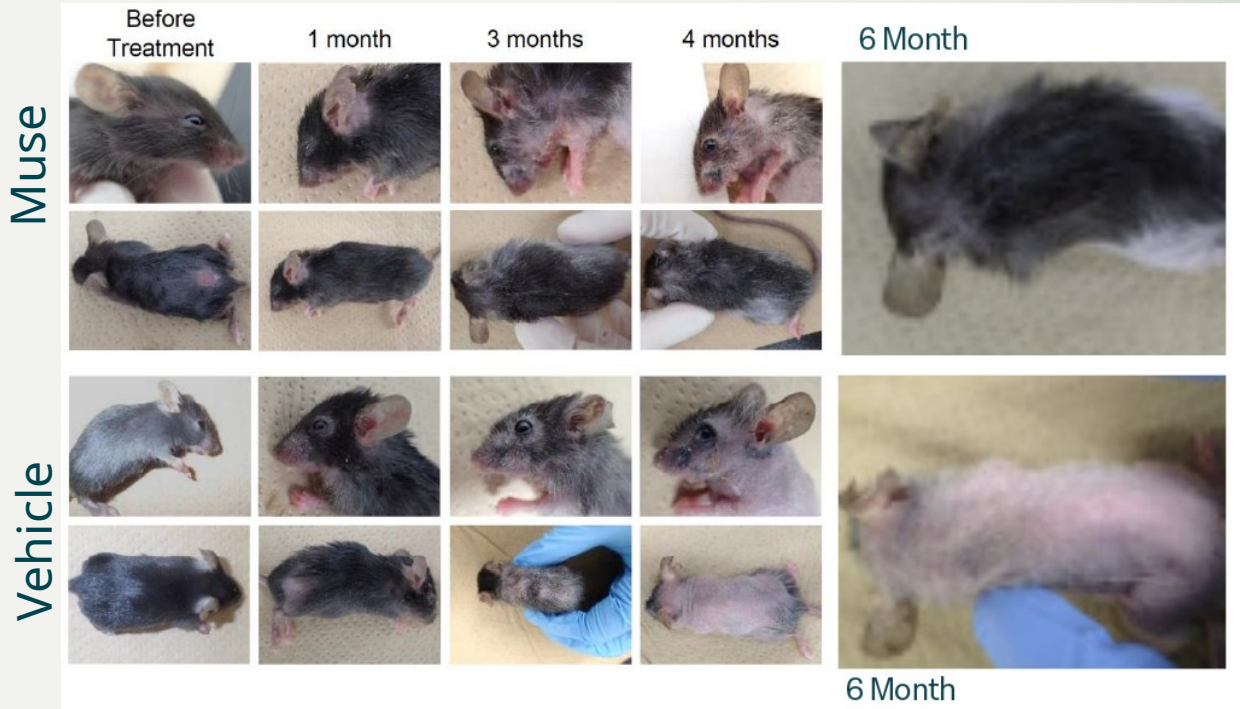
4 Weeks after iv admin, Muse Group



Human **DEZAWA MUSE CELLS™** were maintained integrated as epidermal and dermal cells in the mouse Col-17-/- EB model without immunosuppression for 6 months.

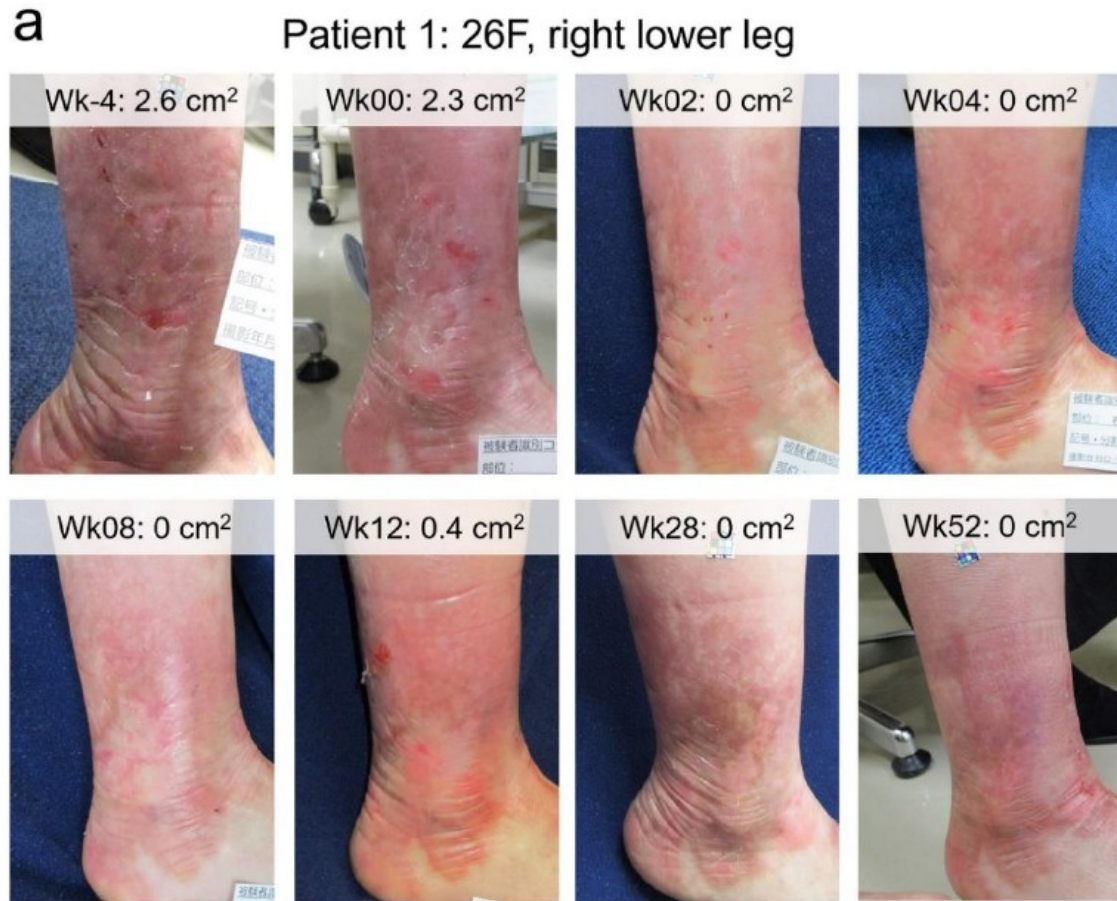
Fujita et al., J Invest Dermatol, 2020

Human col7, col17 detected in the mouse skin

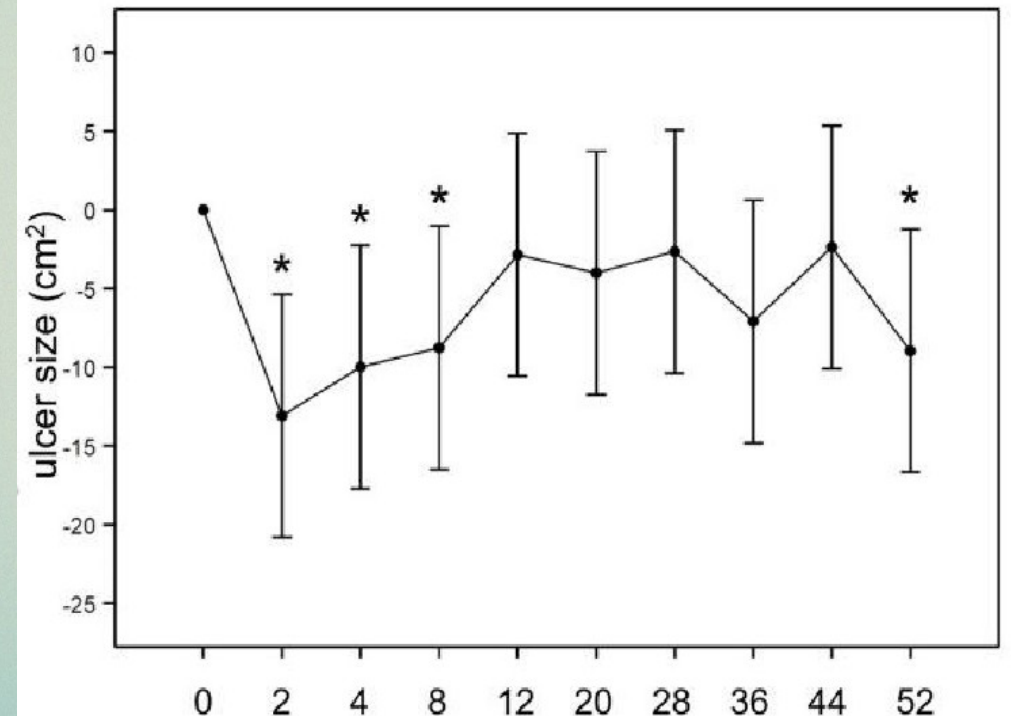


Open-label phase 1/2 clinical trial for epidermolysis bullosa: Single iv of donor-DEZAWA MUSE CELLS™

Fujita et al., J Eur Acad Dermatol Venereol 2021

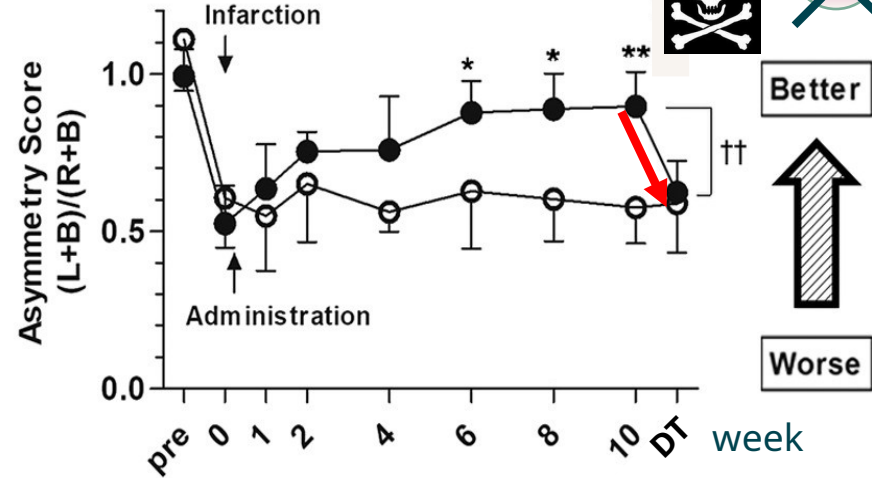


A statistically significant reduction in skin ulcer area was observed for the first 3 months and at 1 year



The rejection of engrafted DEZAWA MUSe CELLS™ causes the loss of functional recovery.

① Uchida et al., Stroke, 2017

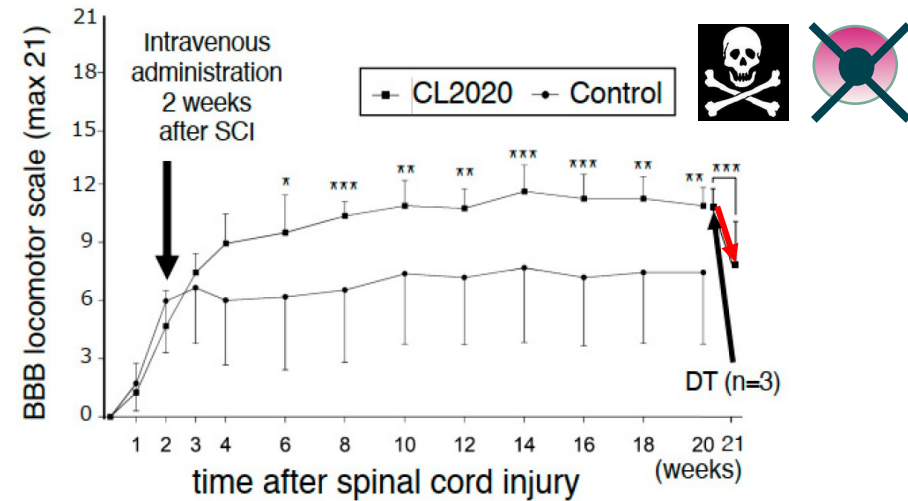
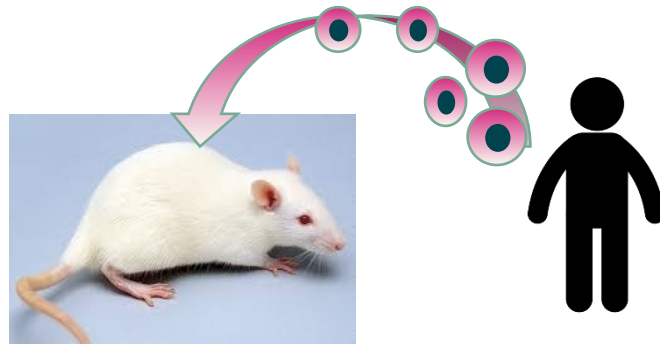


Mouse lacuna stroke model



② Rat mid thoracic spinal cord injury

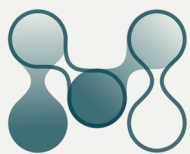
Int J Mol Sci, 2023



cases of improved function worsening were observed even after 7 years in clinical trial

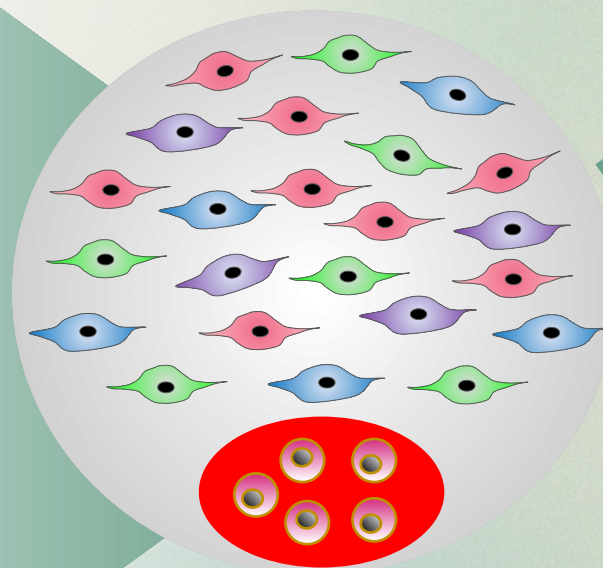
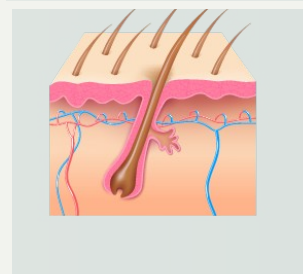
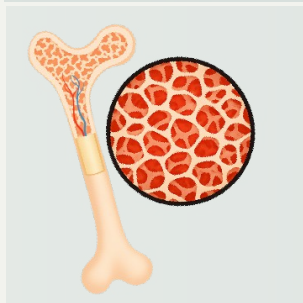
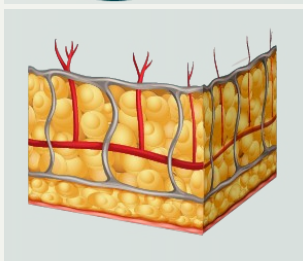
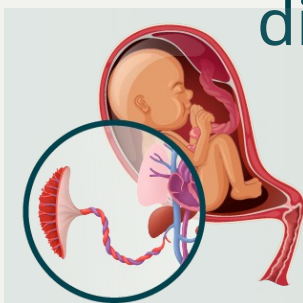
Fundamental difference between
DEZAWA MUSE CELLS™
and MSCs



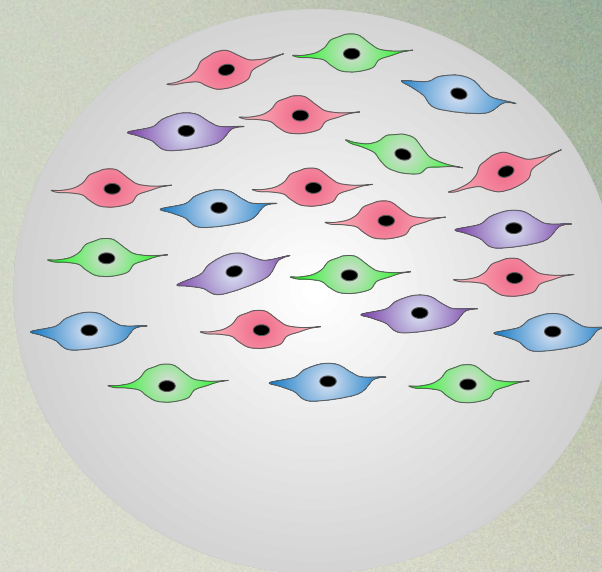


MUSECELL™
INNOVATIONS

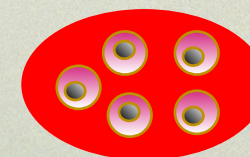
The character of **DEZAWA MUSE CELLS™** and non-Muse MSCs is different.



MSCs

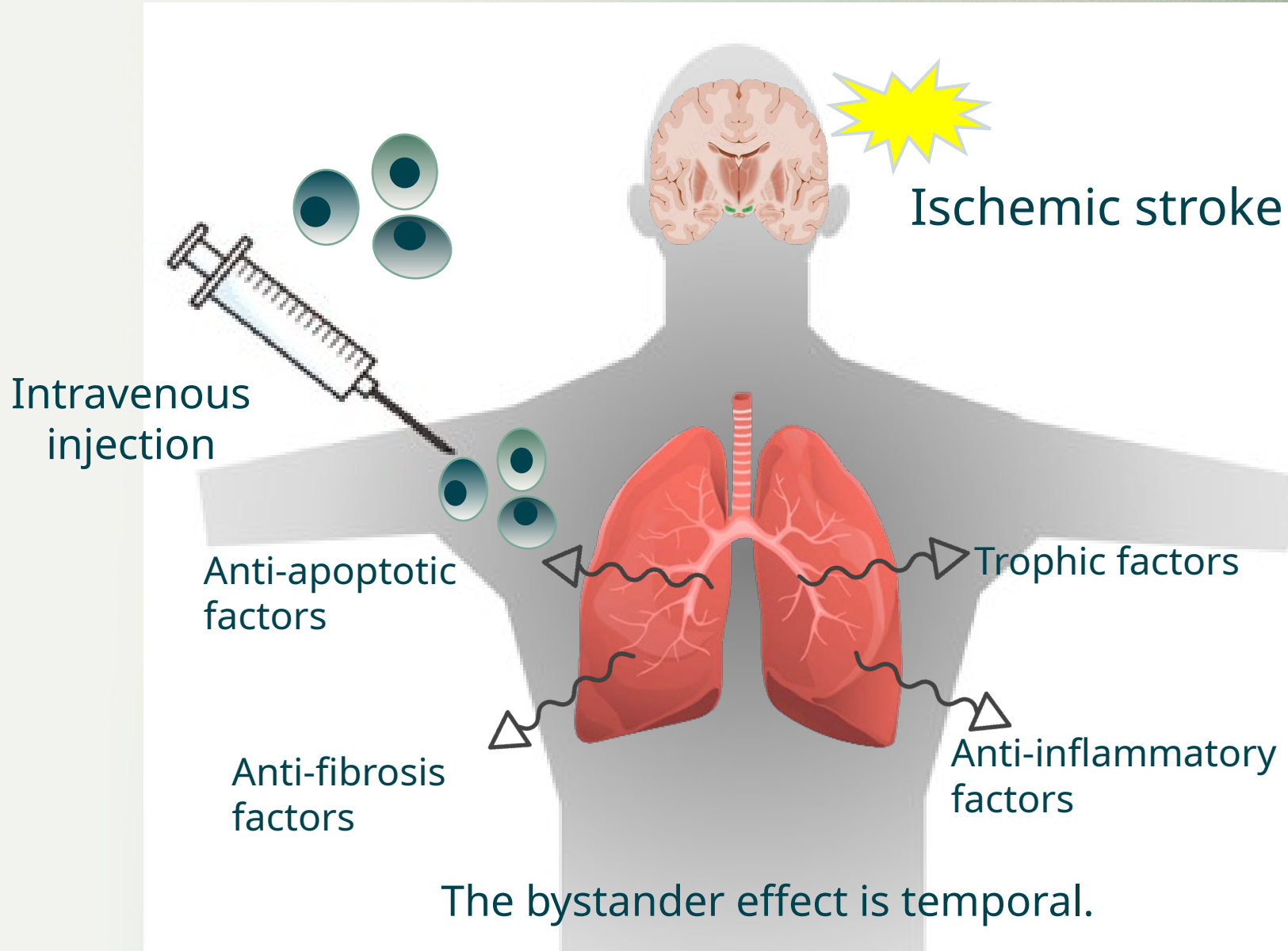


Non-Muse MSCs



DEZAWA Muse

In the case of Mesenchymal stem cells (MSCs)



DEZAWA MUSE CELLS™ are clinically superior to MSCs because...

1. Under intravenous injection: In clinical trials:

~15% of Muse cells home to the site of damage.

Fewer than 1% of MSCs, if any, home to the site of damage. (Freyman et al., Eur Heart J, 2006)

2. 15 million DEZAWA MUSE CELLS™ were used per patient:

MSCs requires 0.1~1 billion cells, a 10-fold greater number.

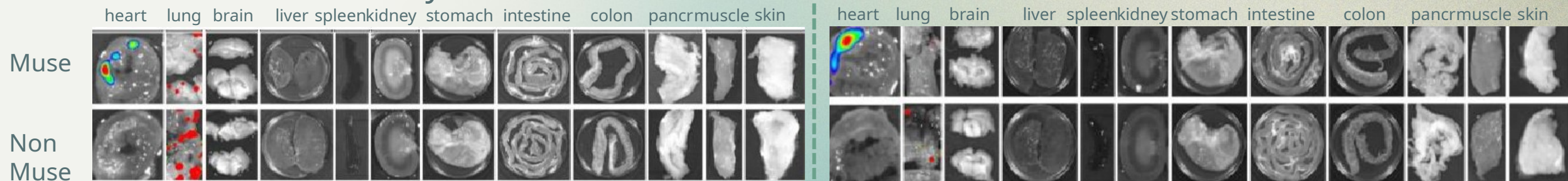
3. DEZAWA MUSE CELLS™ migrate to sphingosine-1-P, a universal damage.

MSCs respond to CXCR4 and SDF-1, not specific for damage.

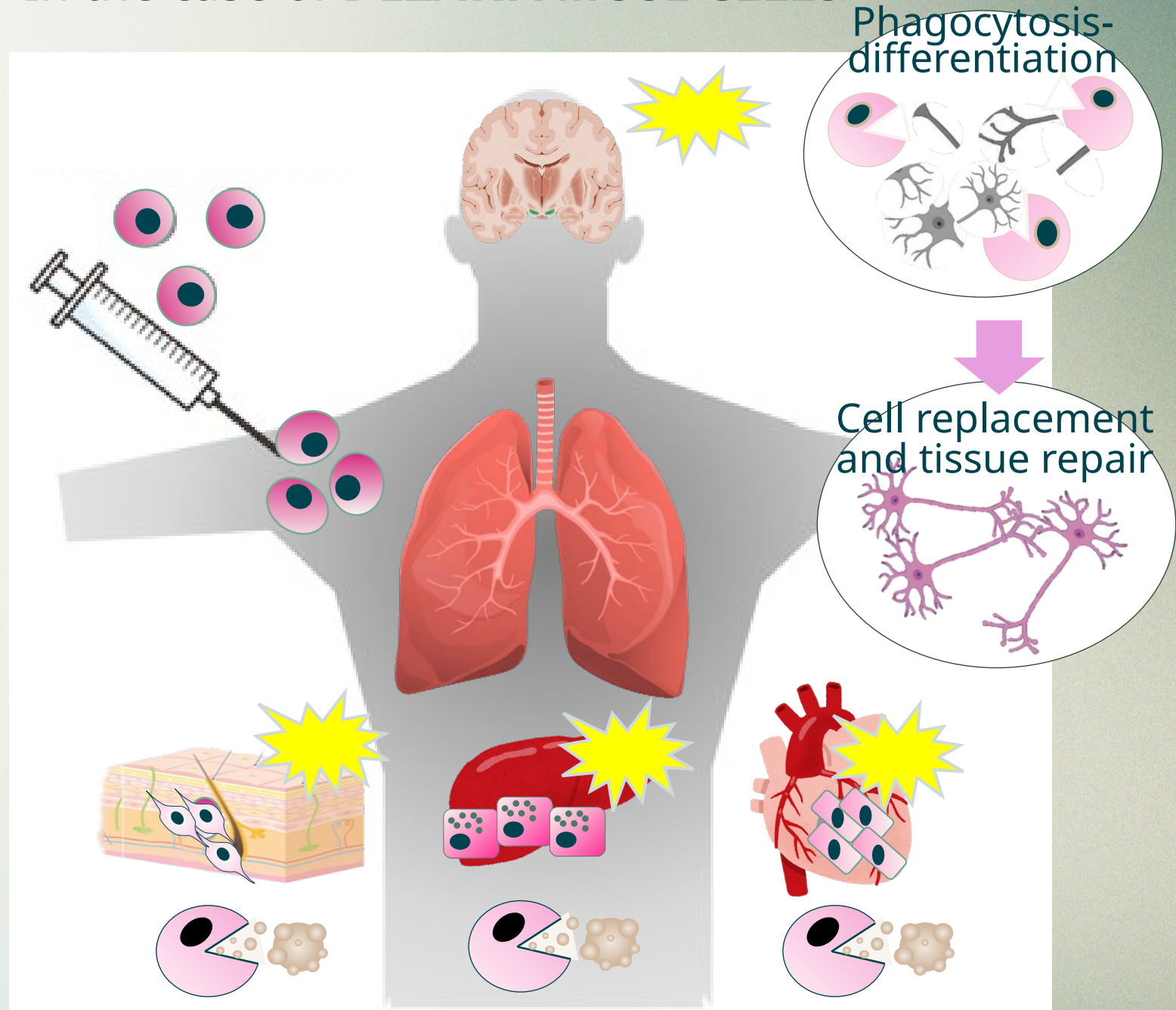
Rabbit acute myocardial infarction model (Cir Res

2018)
3 days IV

2 Weeks IV



In the case of **DEZAWA MUSE CELLS™**



Muse cells are naturally existing non-tumorigenic reparative pluripotent stem cells

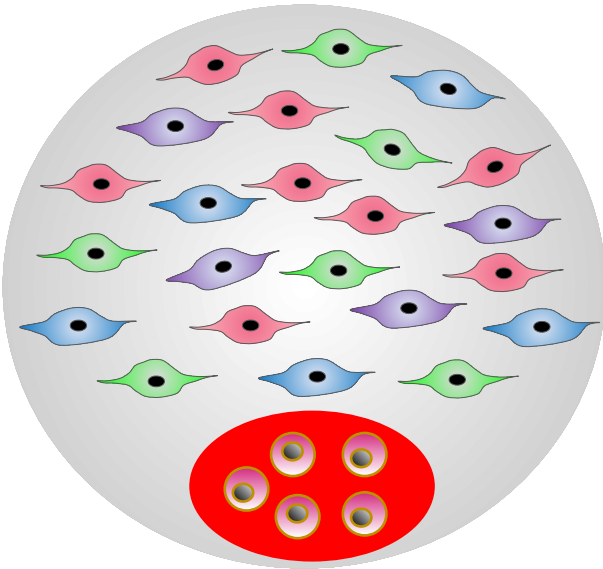
There is no need for

- surgical approaches
- gene introduction for rendering pluripotency
- differentiation induction into the target cell type
- HLA-matching test for donor cell use
- Immunosuppressant treatments

THANK YOU !

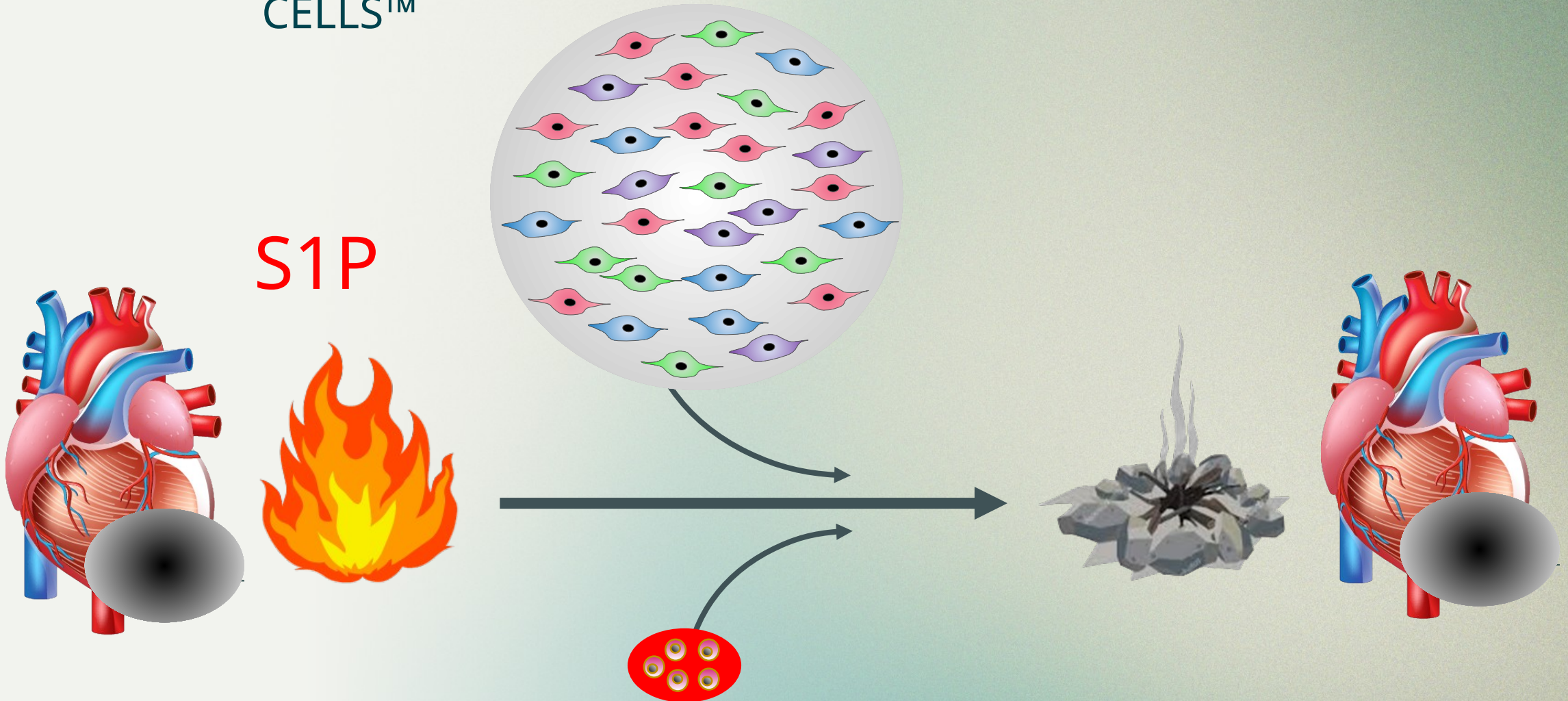


DEZAWA MUSE CELLS™ are contained in MSCs at several percent.

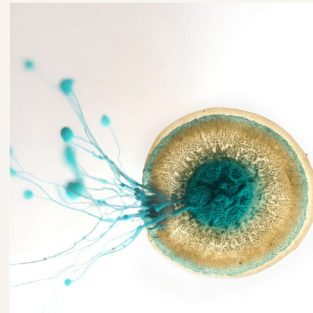
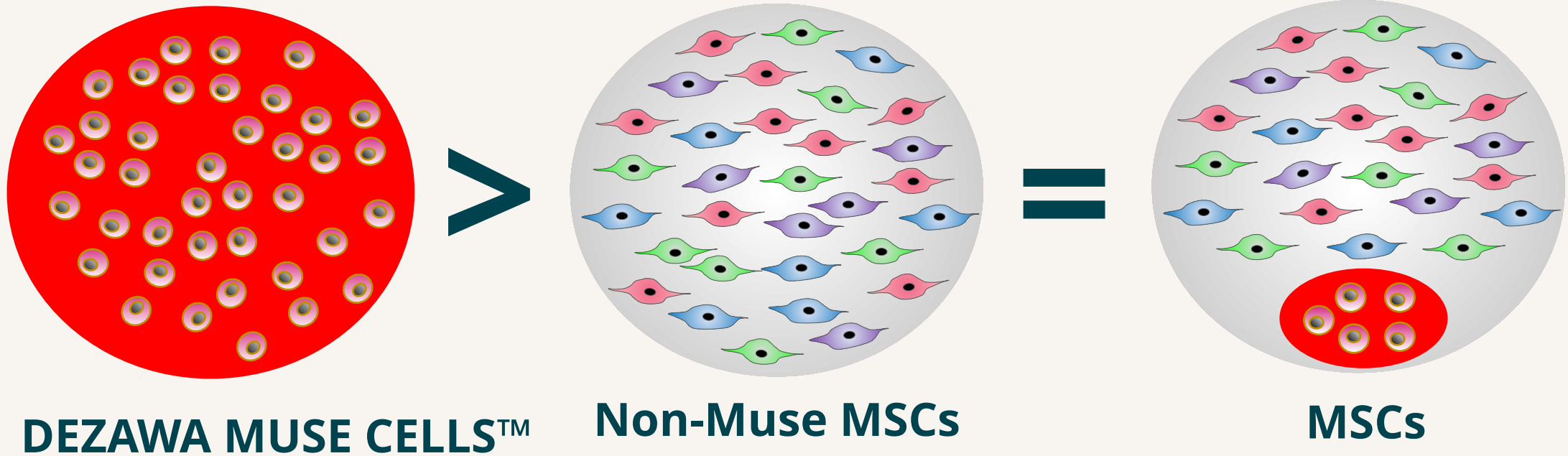


- Could administering large amounts of MSCs have the same effect as administering DEZAWA MUSE CELLS™?
- Is there any merit in purifying DEZAWA MUSE CELLS™?

Why **DEZAWA MUSE CELLS™** in MSCs are not effective?
Because a large number of Non-Muse MSCs disturb DEZAWA MUSE CELLS™

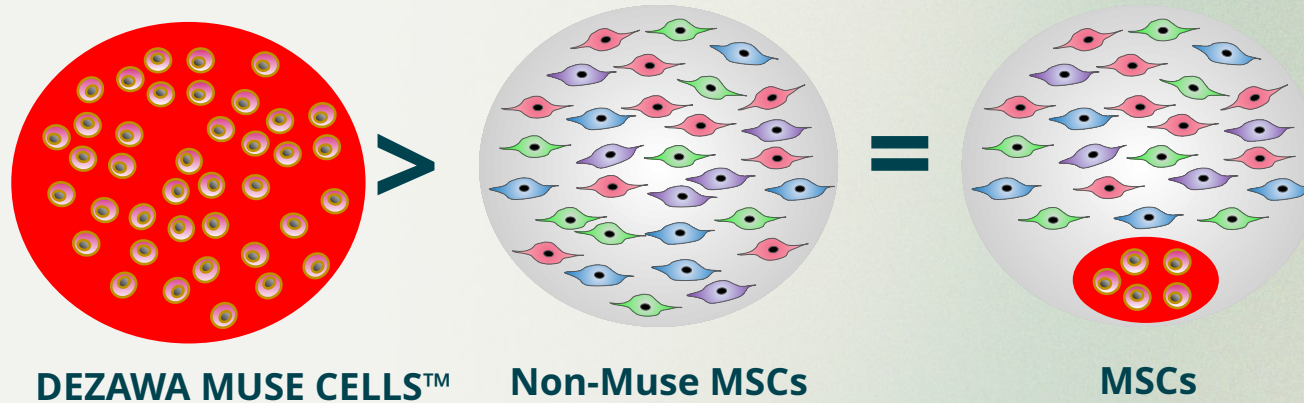


Therapeutic effects under the same number of cells

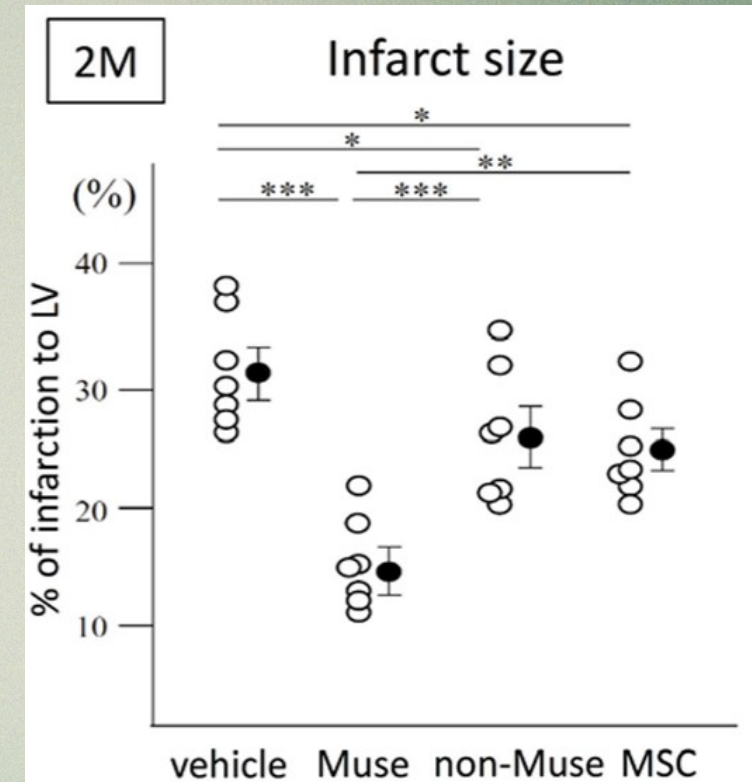
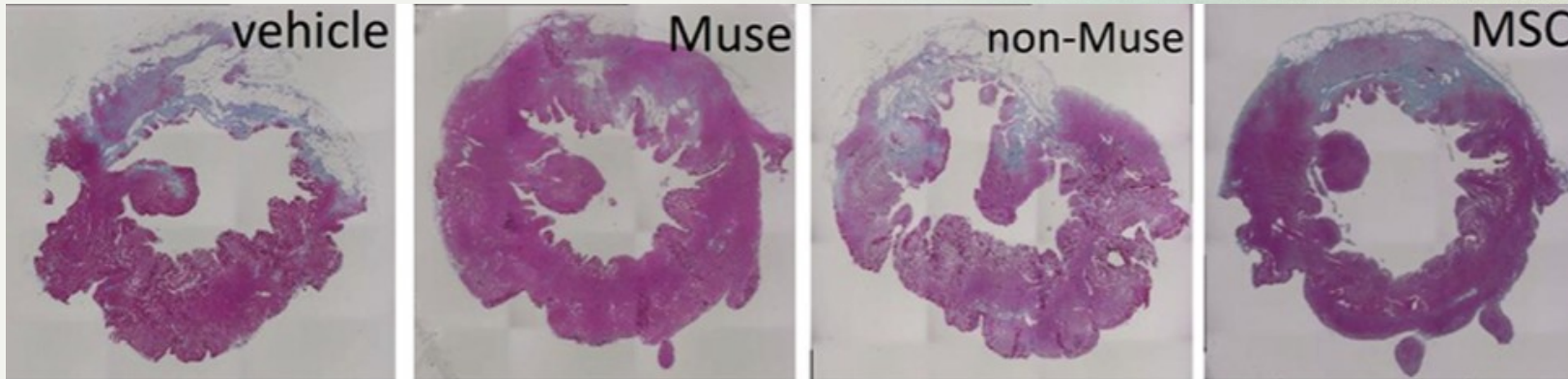


The same number of non-Muse MSCs and MSCs has a lesser therapeutic effect than **DEZAWA MUSE CELLS™**.

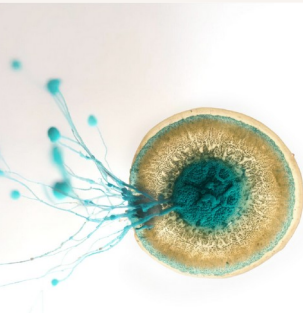
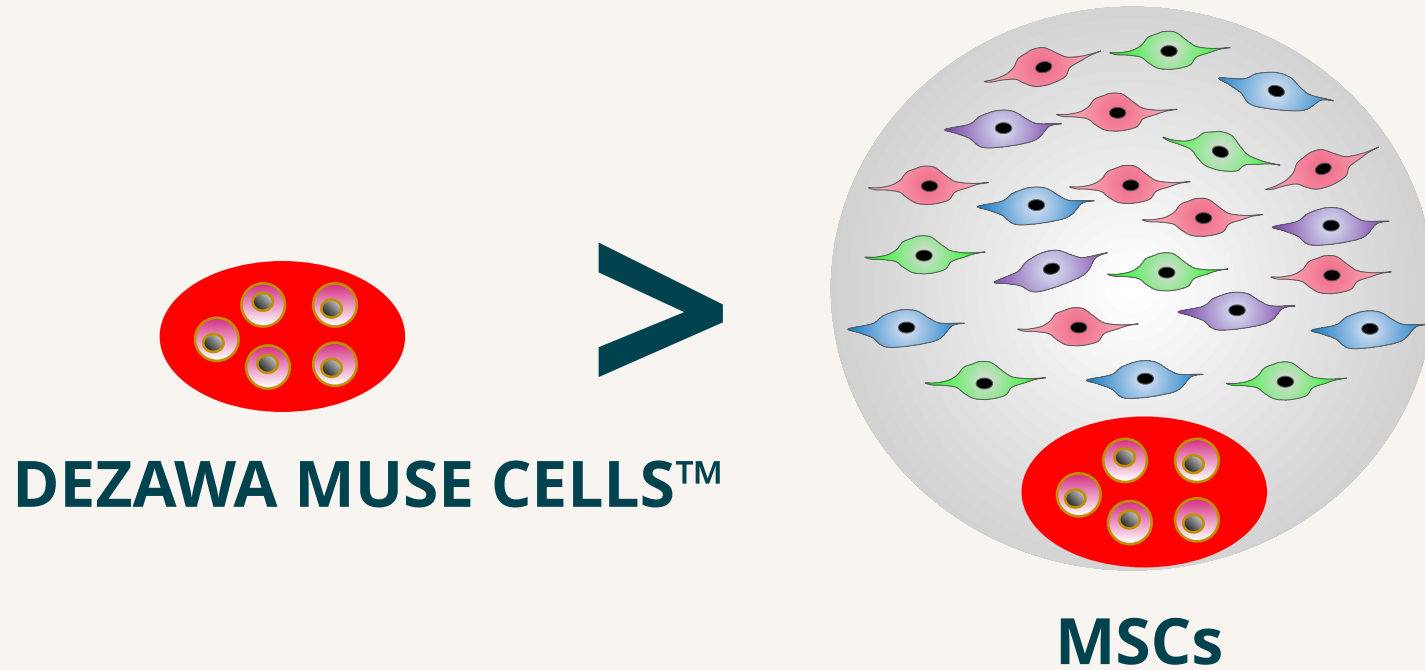
Yamada et al., Cir Res
2018



2 month 0.3 million cells iv



Therapeutic effects in MSCs vs purified DEZAWA MUSE CELLS™



Comparison of efficacy between a purified small number of **DEZAWA MUSE CELLS™** vs. MSCs containing the same number of Muse cells.

