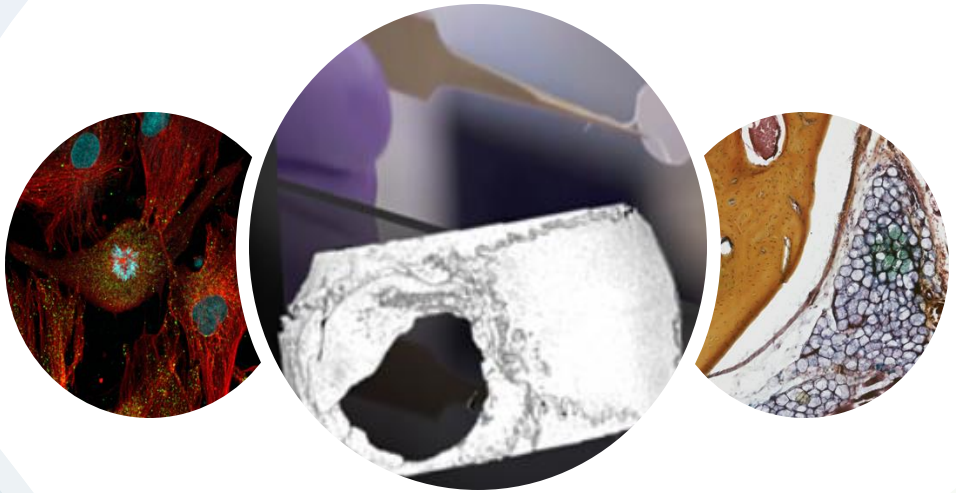
Clinical Impact of Stem Cells

Prof. Shukry James Habib

Department of Biomedical Sciences, UNIL

www.habiblab.org



Learning Objectives

1. **Pluripotent vs Adult Stem Cells:**
    - Differentiate between pluripotent and adult stem cells.
    - Explore their applications in regenerative medicine.

2. **Clinical Trials Unveiled:**
    - Understand the fundamentals of clinical trials.

3. **Stem Cells in Action:**
    - Examine real-world examples of stem cell use in clinical trials.
    - Discover their applications in treating various medical conditions.

4. **Innovative Bone Repair Technologies:**
    - Explore cutting-edge technologies transforming bone repair.

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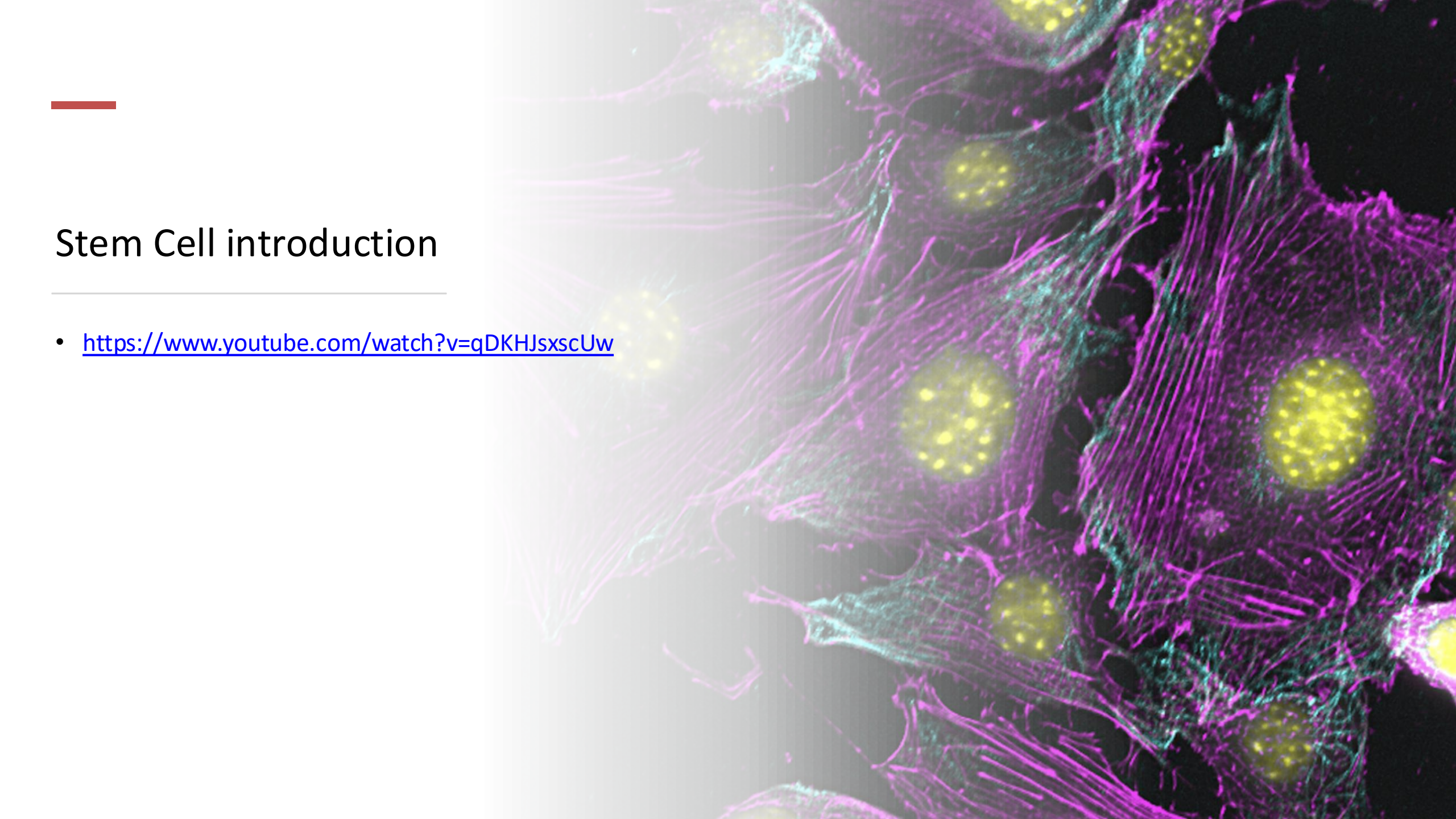
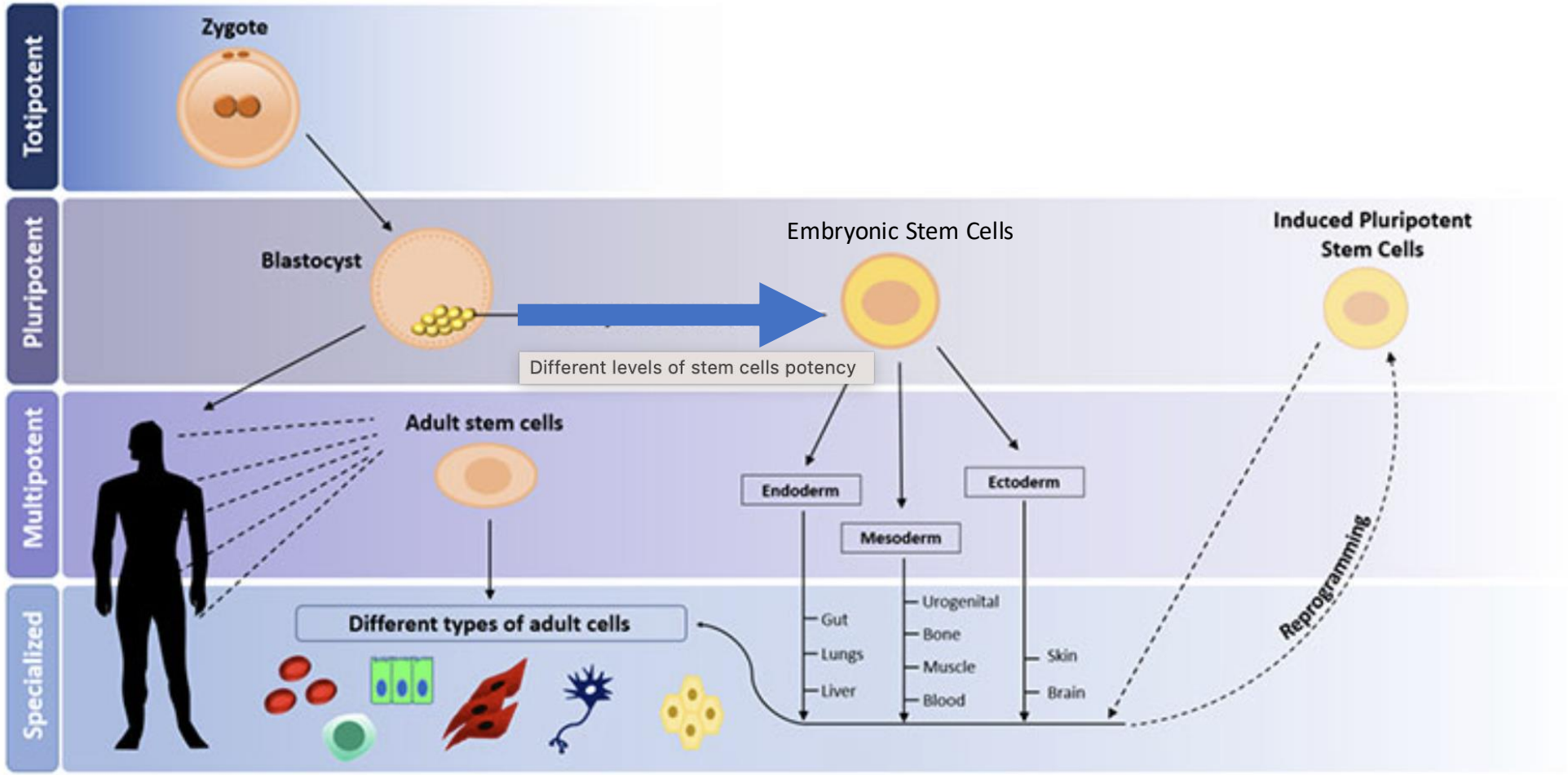
Stem Cell introduction

- https://www.youtube.com/watch?v=qDKHJsxscUw



Stem cells

- What characteristics do stem cells typically possess?
- What are the different types of stem cells?
- What are the division modes of stem cells?


Totipotent
Pluripotent
Multipotent
Specialized
Zygote
Blastocyst
Embryonic Stem Cells
Induced Pluripotent Stem Cells
Different levels of stem cells potency
Adult stem cells
Endoderm
Mesoderm
Ectoderm
Gut
Lungs
Liver
Urogenital
Bone
Muscle
Blood
Skin
Brain
Different types of adult cells
Reprogramming

Stem cells

- What characteristics do stem cells typically possess?
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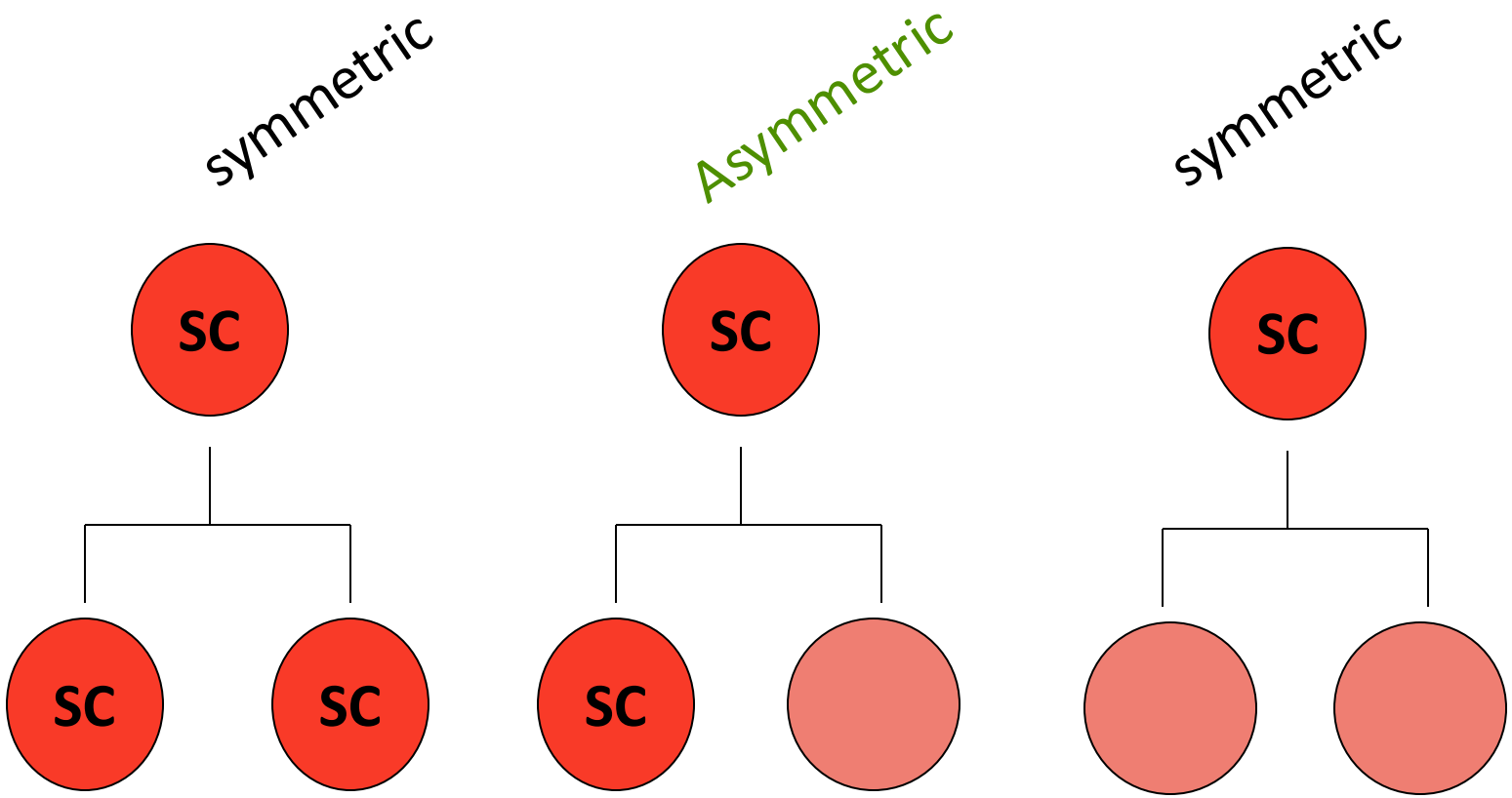
- What are the division modes of stem cells?

Mechanisms of stem cell division



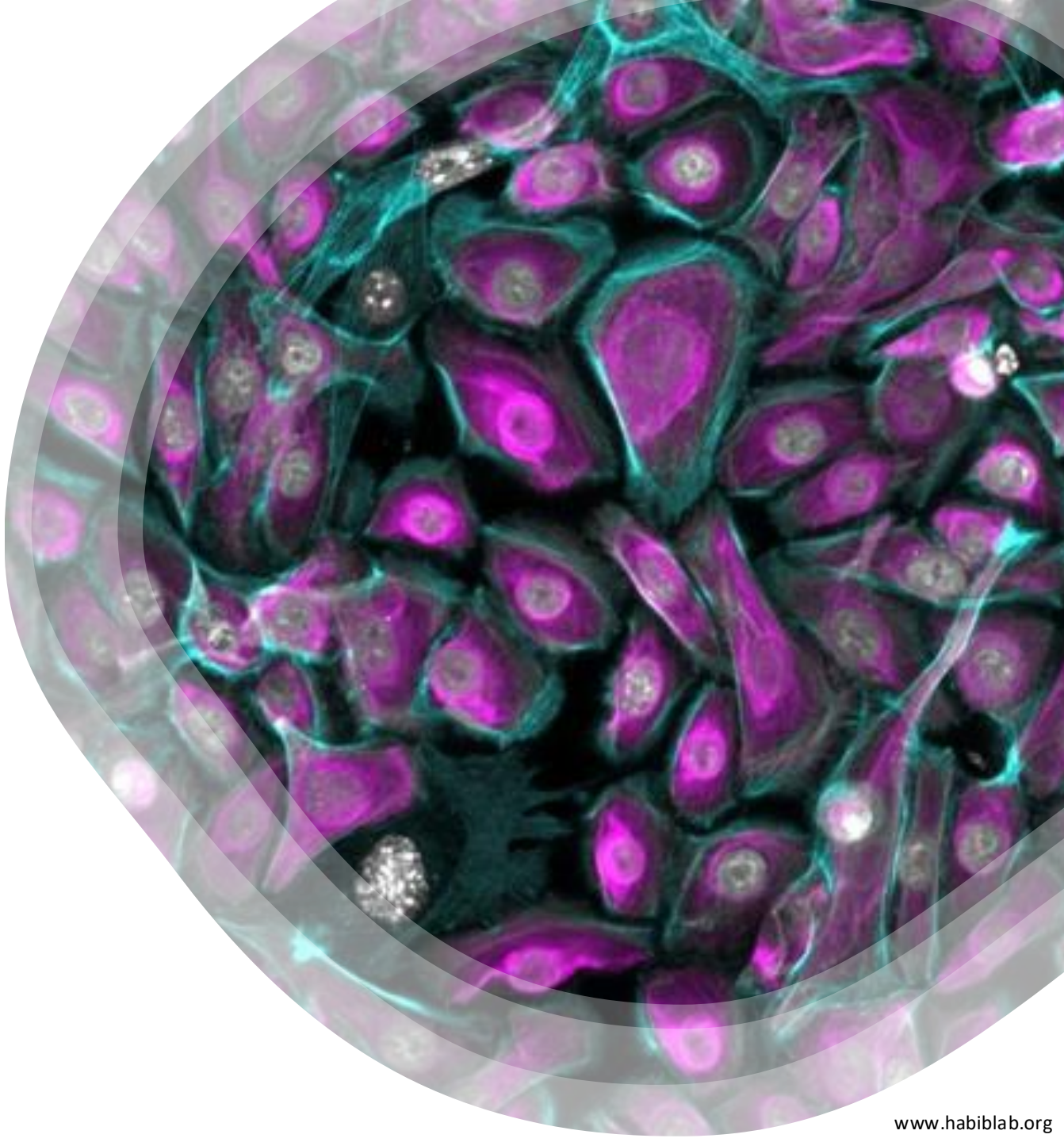
SC=Stem Cell

Adult Stem Cell Expansion *in vitro*

- Adult stem cells are not immortal.

- Expansion often requires:

1. Wnt/β-catenin signalling sustains stem cell undifferentiation.
2. Factors like FGF and EGF, signalling through tyrosine kinase pathways, control cell proliferation



Advantages of Adult Stem Cells:

- Can be isolated from the patient (autologous) and are thus immune-compatible.
- Differentiation potential is limited to the tissue of origin.

Disadvantages of Adult Stem Cells:

- Some sources are impractical (e.g., neural stem cells from the adult brain).
- The number of adult stem cells obtained from certain sources is often insufficient for treatment (e.g., bone marrow autologous transplantation).
- In vitro expansion is limited.

Which of the following are pluripotent?

1. Adult stem cells from the patient
2. Adult stem cells from a HLA-compatible donor (*e.g.* cord blood)
3. Induced Pluripotent stem cells (iPSCs) from patient or bank
4. HLA-compatible embryonic stem cells lines from fertilised embryos (fresh, frozen or low quality).

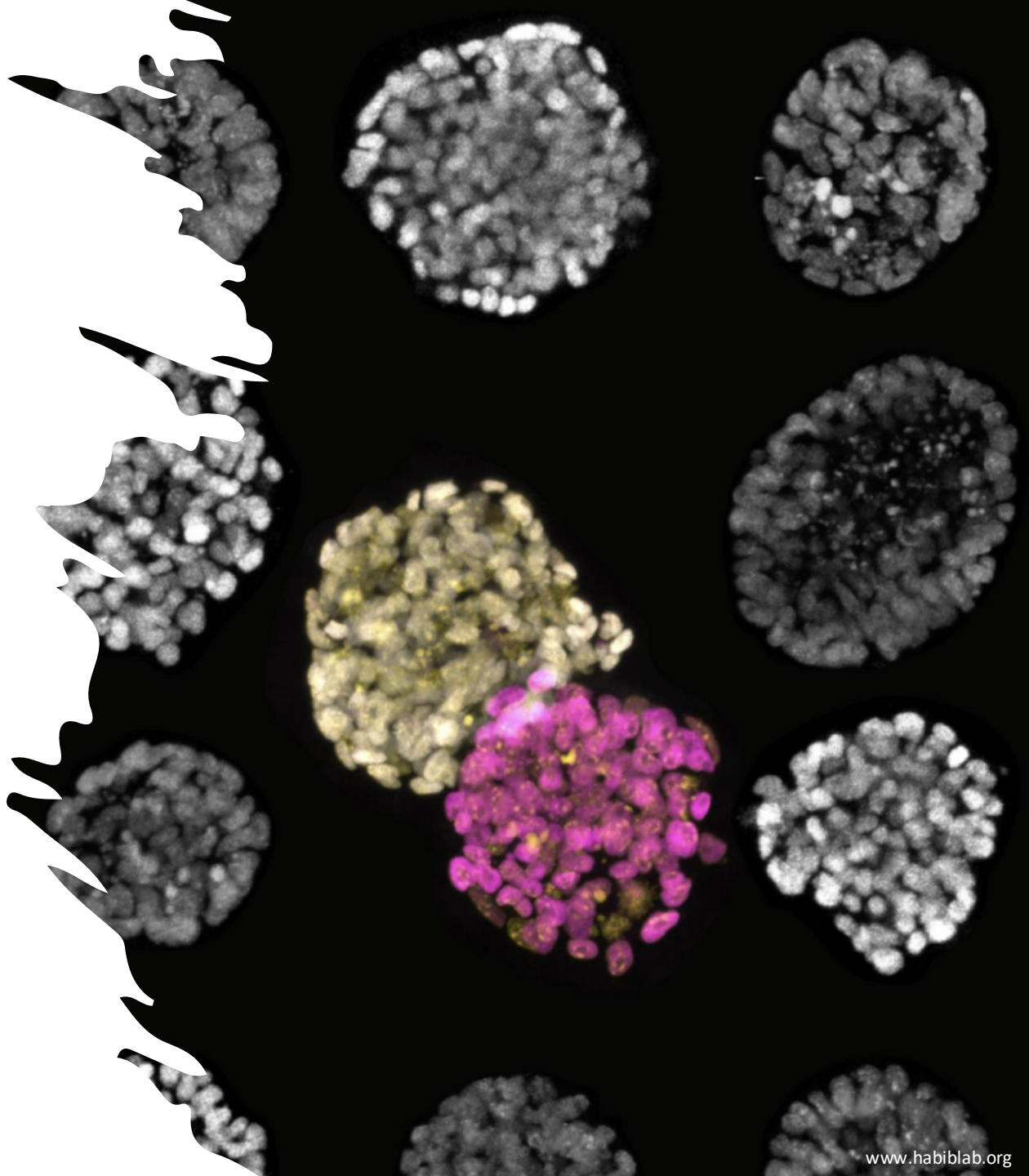
Pluripotent stem cells

Advantages:

- Potential for indefinite expansion
- Plasticity
- Homologus recombination for gene repair.

Distadvantages:

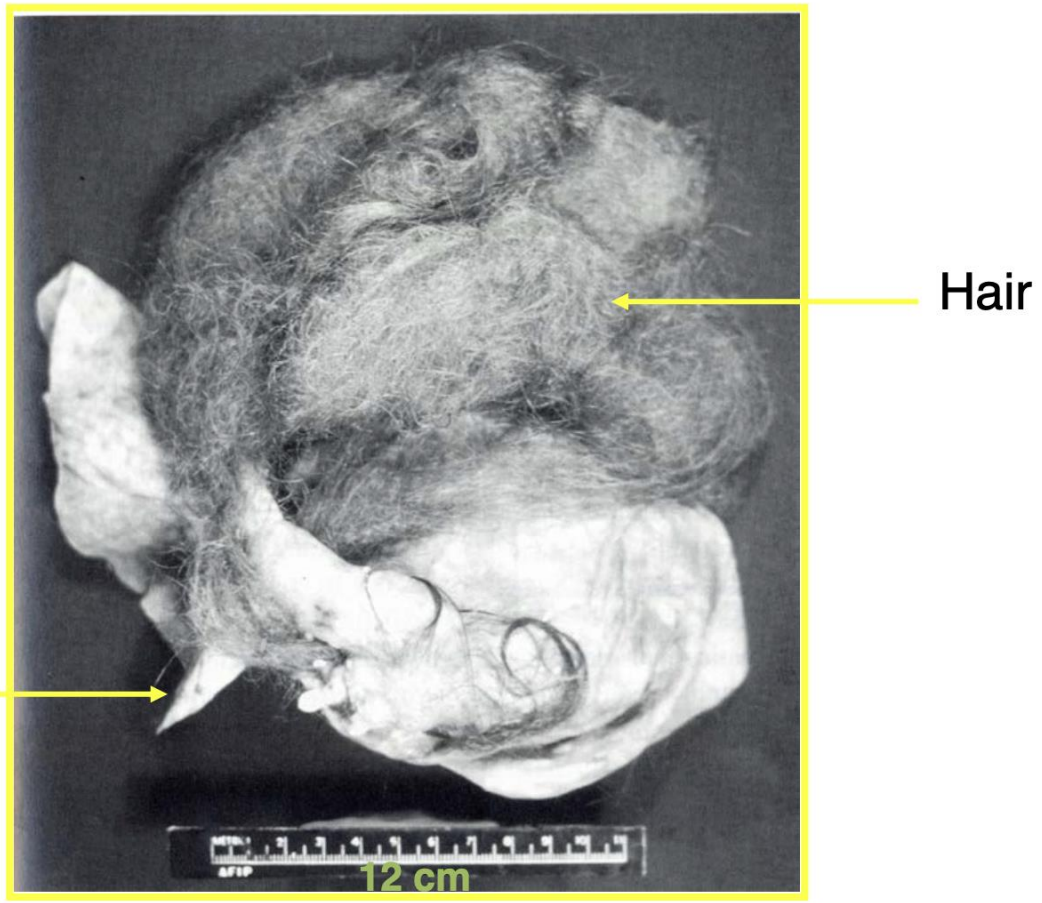
- Expensive
- Challenging differentiation protocols (*but are improving*)
- Immunosuppression is required for therapy.



The Rule of Stem Cell Therapy

All pluripotent stem cells need to be differentiated before they can be transplanted into patients.

OTHERWISE…



Human teratoma

Mechanisms of stem cell-based therapies

- **Regeneration and Differentiation Mechanism:**
  - Transplanted stem cells exhibit differentiation into specific cell types by homing to the damaged area.
- **Paracrine Mechanism:**
  - Stem cells release factors such as cytokines, fostering a paracrine effect with neurotrophic, anti-inflammatory, and angiogenic factors.
- **Immune Regulation Mechanism:**
  - Transplanted stem cells modulate the immune system, actively regulating responses and inhibiting abnormalities.

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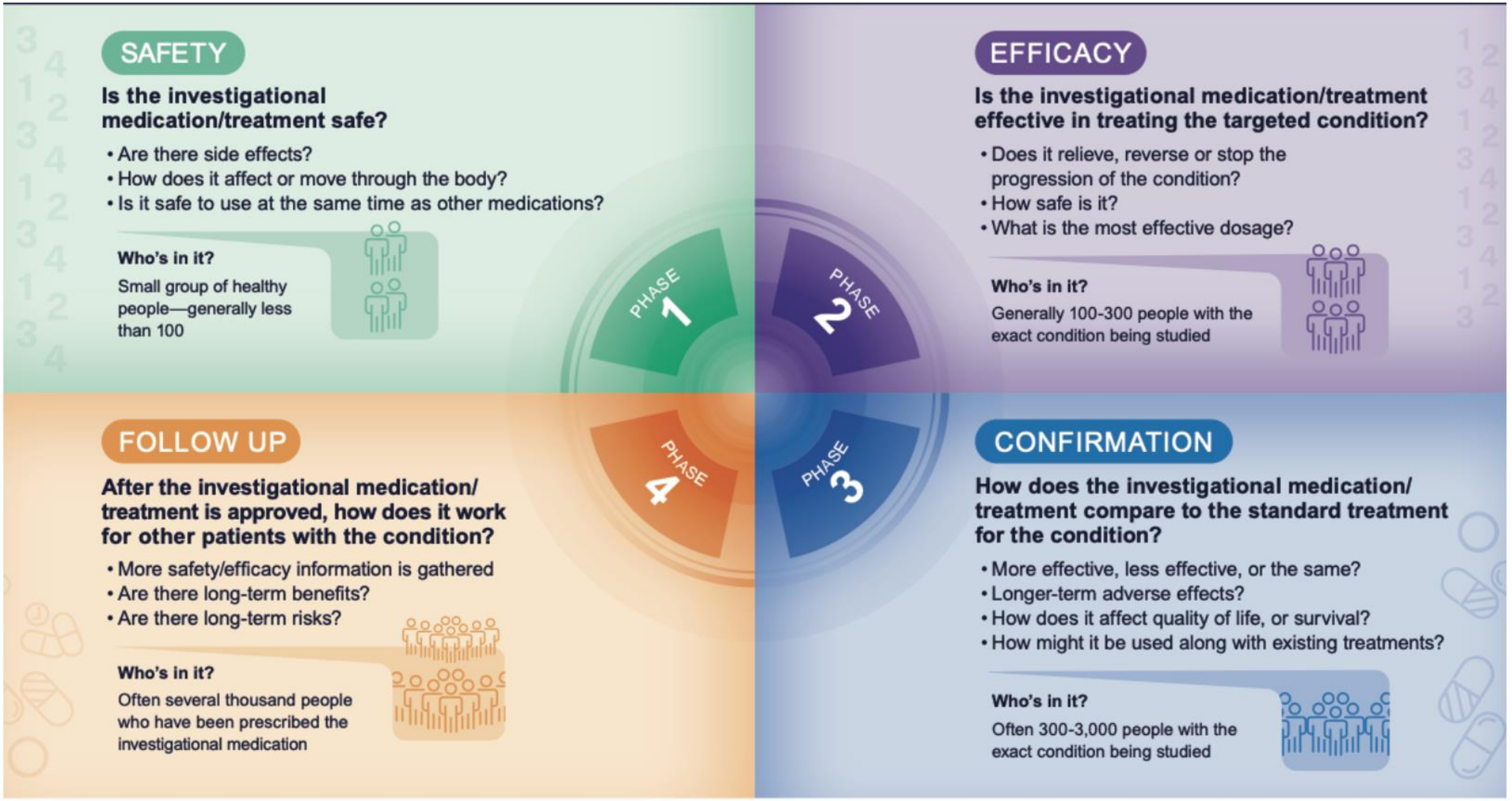
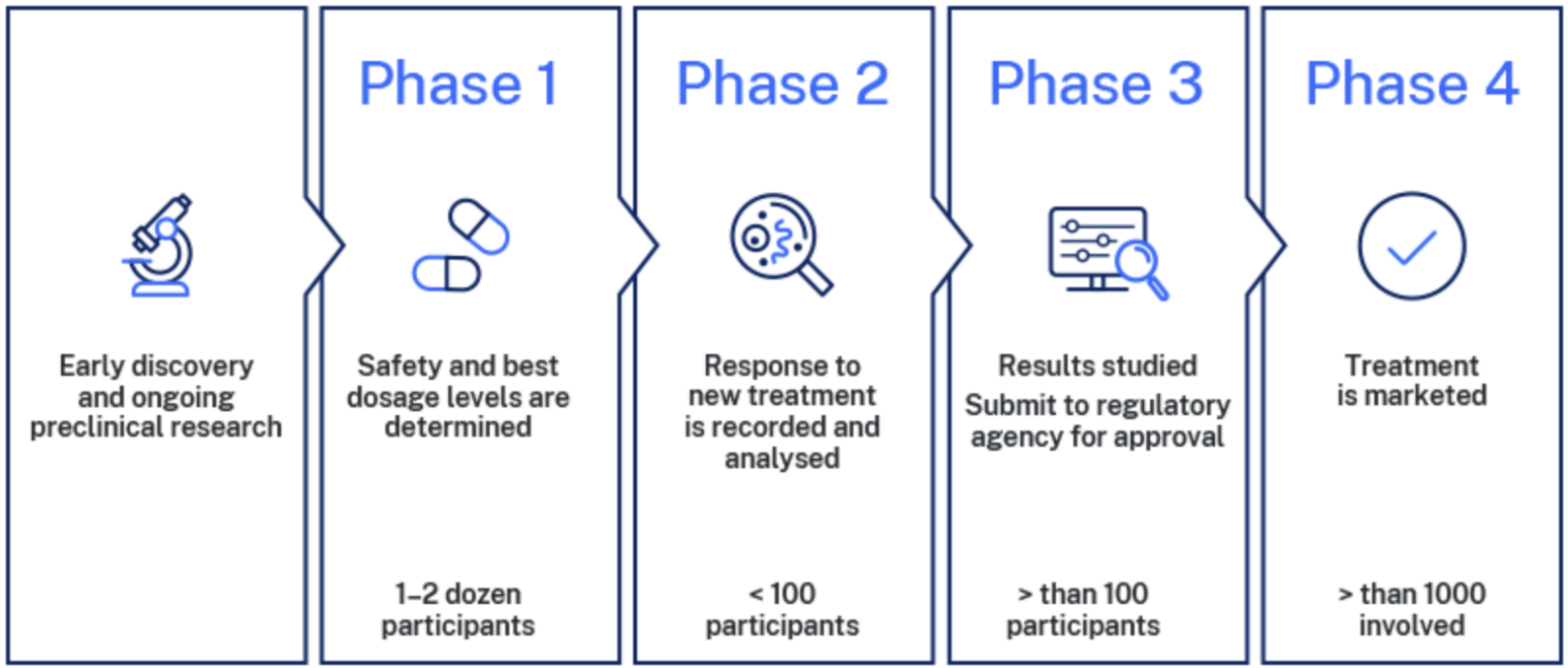
https://www.uemo.eu/european-health-union-new-rules-to-improve-clinical-trials-in-the-eu/

Clinical trials



Clinical trials



isscr.org/treatment-guide

Submit an abstract and register for The Global Stem Cell Event. **ISSCR 2024 is Open!**

INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

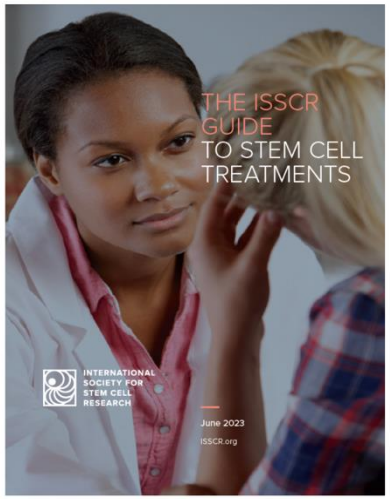
Discovery Advocacy Education Leadership English Membership

The ISSCR Guide to Stem Cell Treatments

+ Frequently Asked Questions

+ About Stem Cells | Public Education Web Site

Download the Guide



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ClinicalTrials.gov API

API Home

If you are looking for information about clinical studies, please visit ClinicalTrials.gov.

ClinicalTrials.gov main site

Notice to API users:

Traffic from legacy API endpoints has been moved to the new domain https://classic.clinicaltrials.gov/. For more information:

- View the Migration Guide
- Read the Modernization Transition Top Questions

The ClinicalTrials.gov application programming interface (API) provides a toolbox for programmers and other technical users to use to access all posted information on ClinicalTrials.gov study records data. The API is designed for encoding simple and complex search expressions and parameters in URLs. Clicking on query URLs retrieves study records from ClinicalTrials.gov. Use of ClinicalTrials.gov data is subject to these Terms and Conditions.

Documentation

Use the following links to learn about the ClinicalTrials.gov API.

Link	Description
API URLs	List of info URLs for accessing information about the API and query URLs with parameters.
Query URL Responses	Description of information returned by query URLs.
Search Expressions and Syntax	Types and syntax of search expressions used in query URLs.
Search Operators	List of operators with examples and descriptions of search expressions used in query URLs.
Data Element-to-API Field Crosswalks	List of ClinicalTrials.gov data elements and their corresponding API fields.
Study Structure and Fields	Organization of API fields within a ClinicalTrials.gov study record and other information.
Search Areas	List and description of ways to specify the portions of a study record to search, ranging from multiple API fields (e.g., BasicSearch, ConditionsSearch) to a single field (e.g., Acronym).
Download Content for All Study Records	URLs for downloading all content for all study records available on ClinicalTrials.gov as a single zip file.

Interactive Demonstrations

Use the following demonstrations to explore and develop the three types of query URLs available for accessing different levels of API data from ClinicalTrials.gov. After specifying the parameter values in the Request section on a demonstration page and clicking on "Send Request," the Response section will display the resulting URL that was sent to ClinicalTrials.gov to generate the response.

Query URL Type	Description	Example
Full Studies	Retrieves all content from the first study record returned for a submitted query by default. Returns up to 100 study records per query when the minimum rank and maximum rank parameters are set in a query URL and up to 10,000 records using the Full Studies interactive demonstration.	https://ClinicalTrials.gov/api/query/full_studies?expr=heart+attack
Study Fields	Retrieves the values of one or more fields from up to all study records returned for a submitted query by default. Returns up to 1,000 study records per query when the minimum rank and maximum rank parameters are set in a query URL and up to all study records using the Study Fields interactive demonstration.	https://ClinicalTrials.gov/api/query/study_fields?expr=heart+attack&fields=NCTId,Condition,BriefTitle
Field Values	Retrieves a unique list of values for one study field from all study records returned for a submitted query.	https://ClinicalTrials.gov/api/query/field_values?expr=heart+attack&field=Condition

Good Manufacturing Practice (GMP)

On GMP:

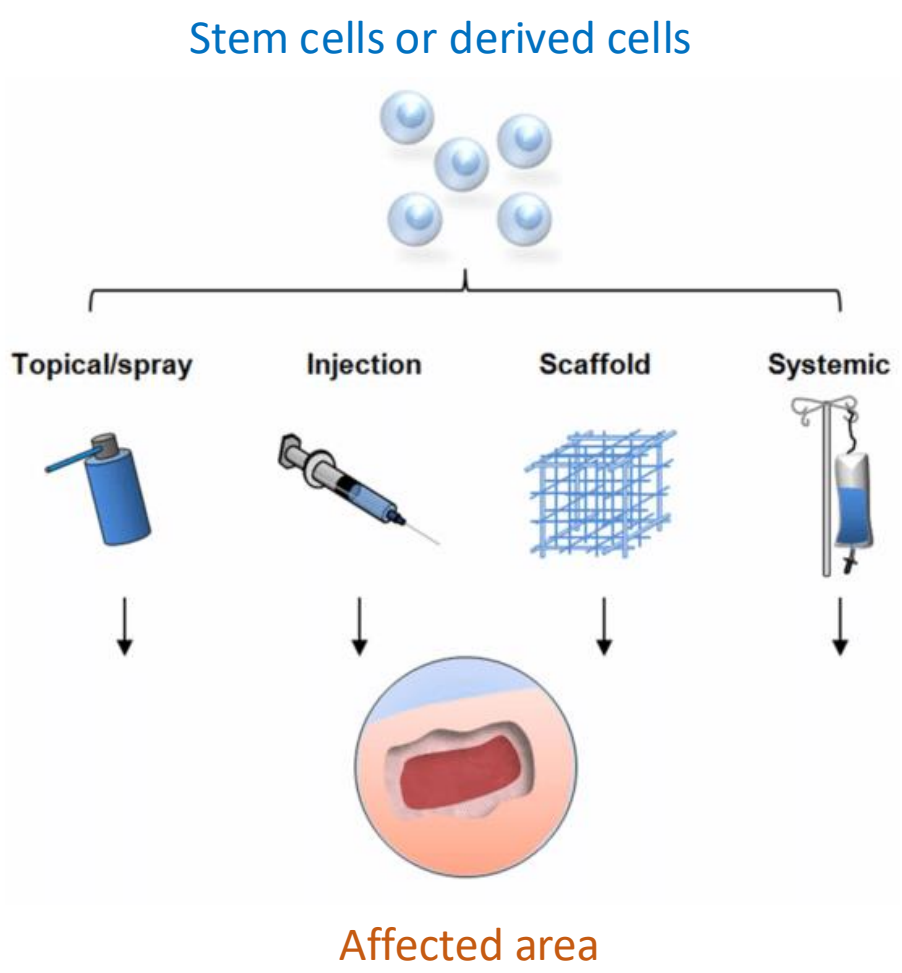
- GMP ensures quality control in pharmaceuticals, food, diagnostics, and medical devices.
- Strictly defined and well-controlled processes to meet predefined specifications.
- Ensures proper testing, dosing, and adherence to regulations for optimal product effectiveness.
- FDA oversees GMP regulations in the US.

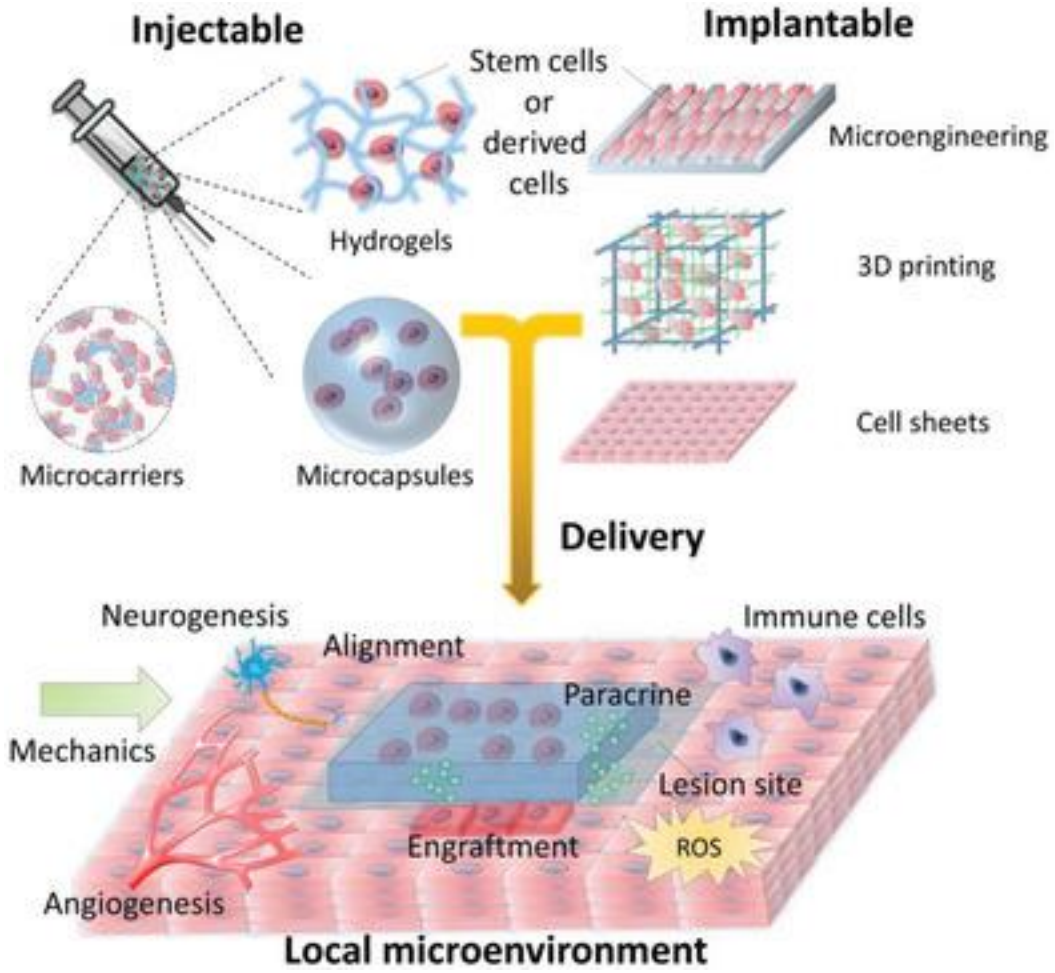
https://www.linkedin.com/pulse/why-good-manufacturing-practice-gmp-so-important-john-van-der-worp/

What Constitutes Current Sources of Stem Cells for Clinical Applications?

1. Adult stem cells isolated from patient (+/- gene therapy) or from a healthy donor.
2. iPSCs derived from patients (+/- gene therpay) or from a healthy donor.
3. Embryponic stem cells.
4. Partially reprogrammed cells.
5. All the above.

Delivering Stem Cells or Derived Cells to the Affected Site





Source: DOI: 10.3389/fimmu.2012.00192

https://doi.org/10.1002/adfm.201809009

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Pluripotent Stem Cells as a Source for Regenerative Medicine

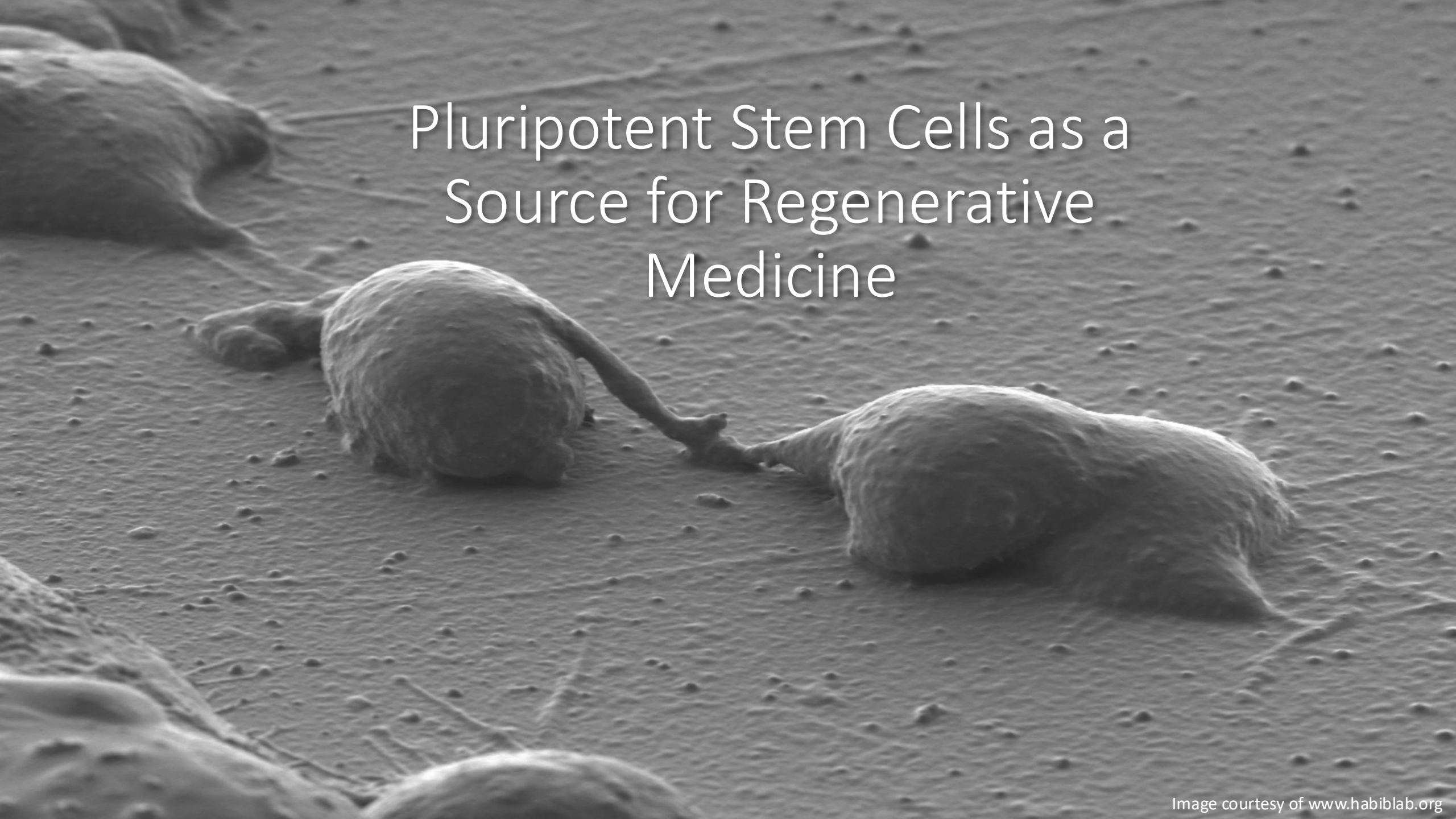
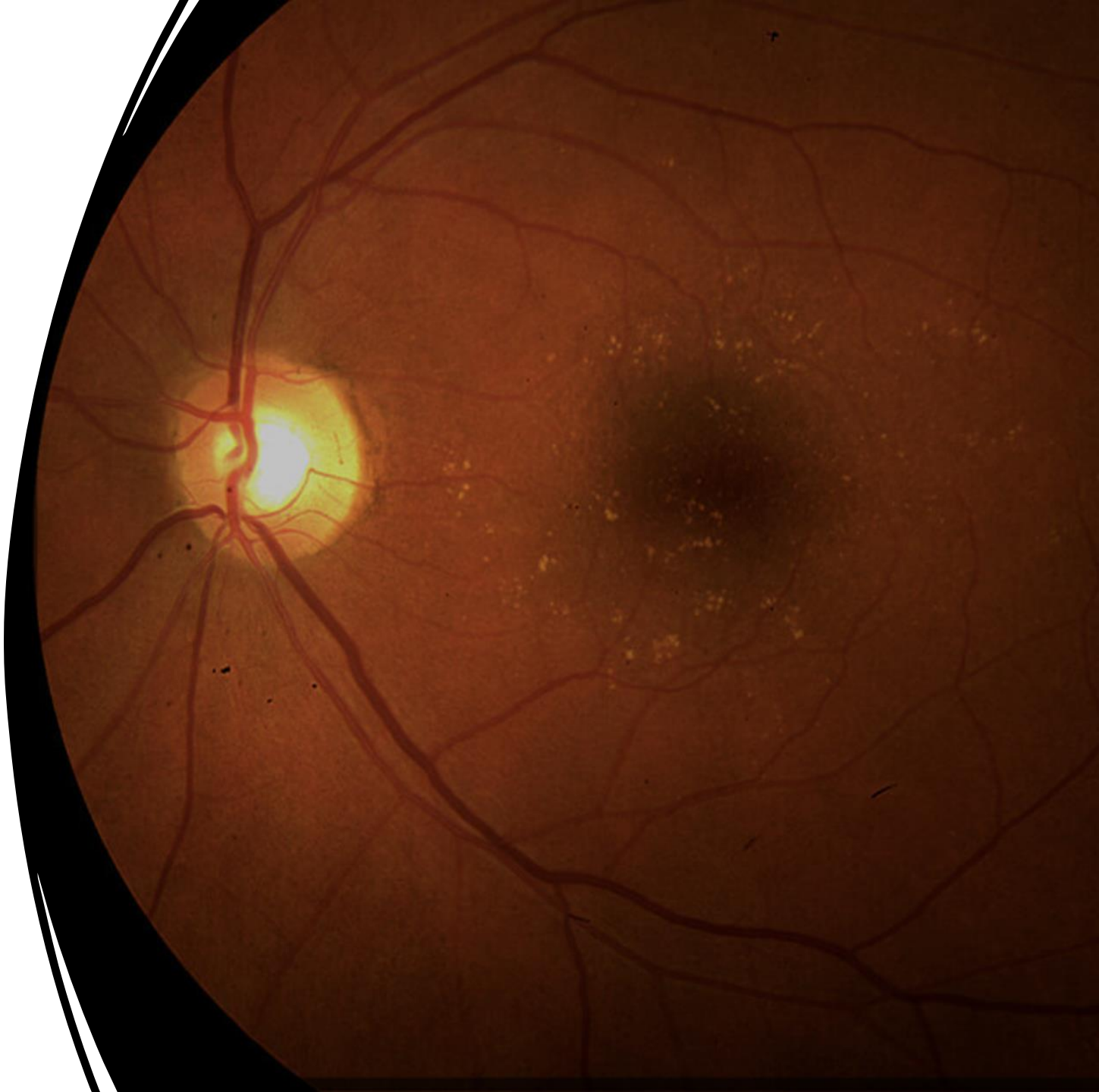
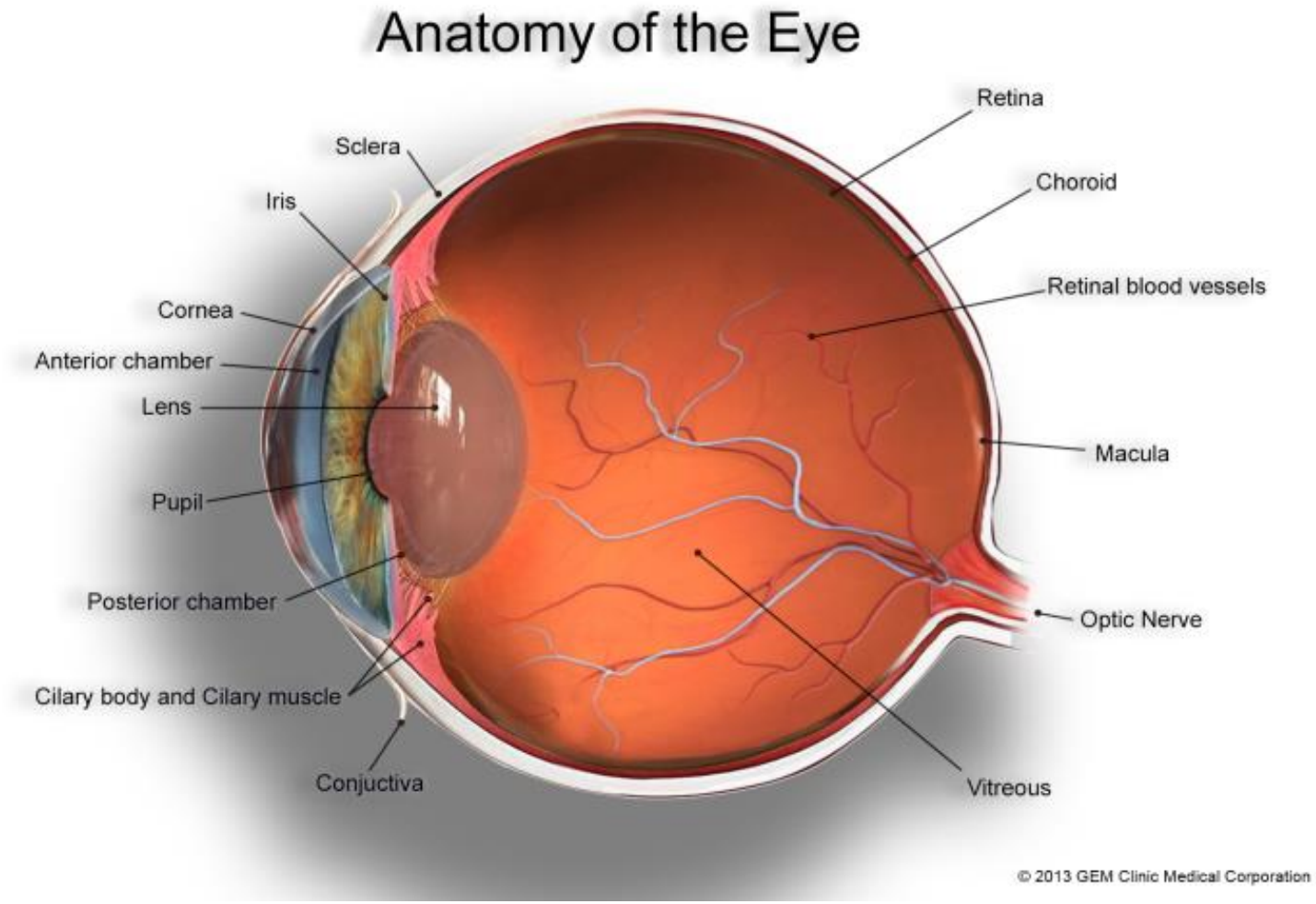


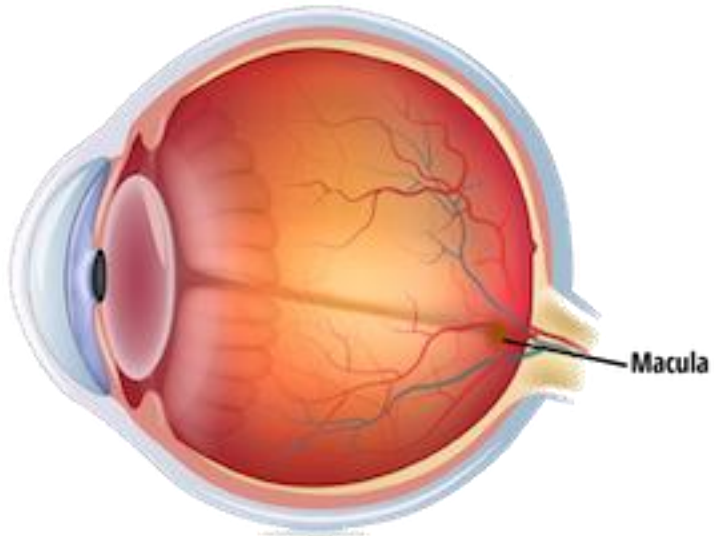
Image courtesy of www.habiblab.org

Macular degeneration

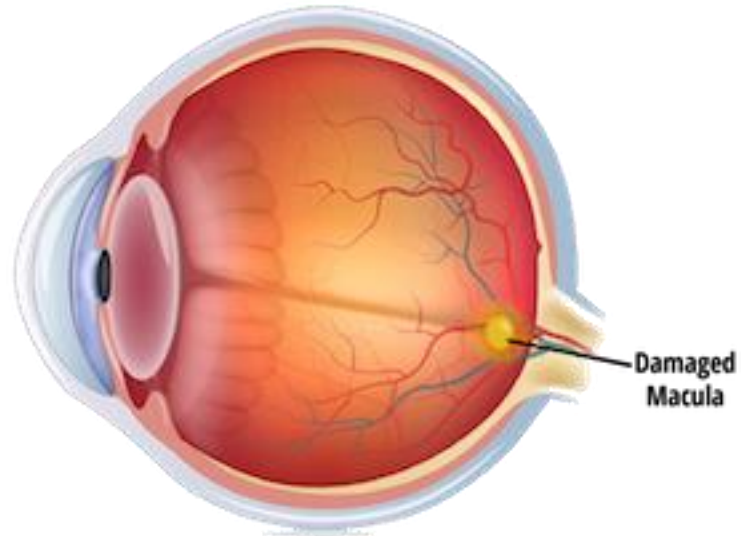




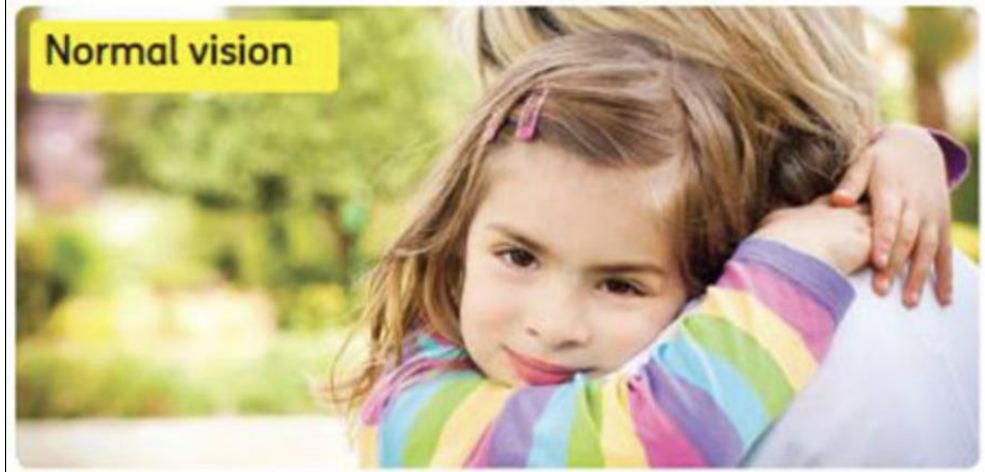
https://www.youtube.com/watch?v=8gRpjwmbdJQ

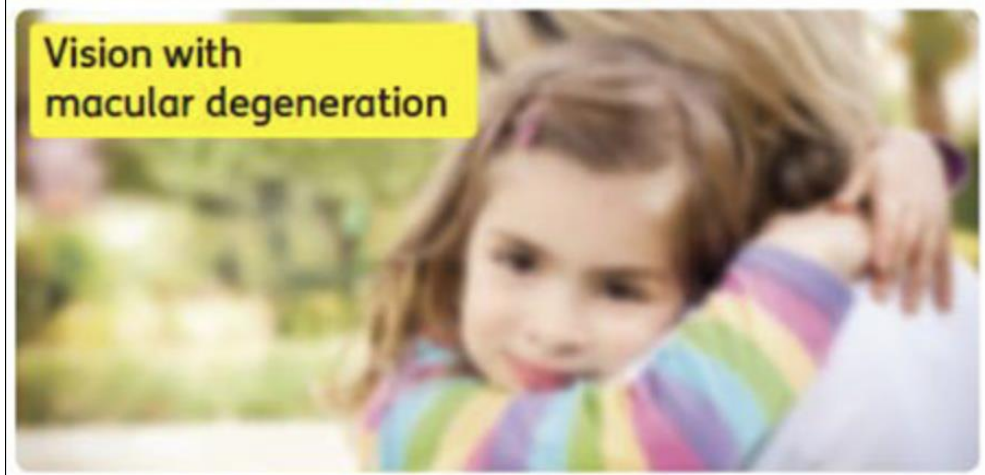


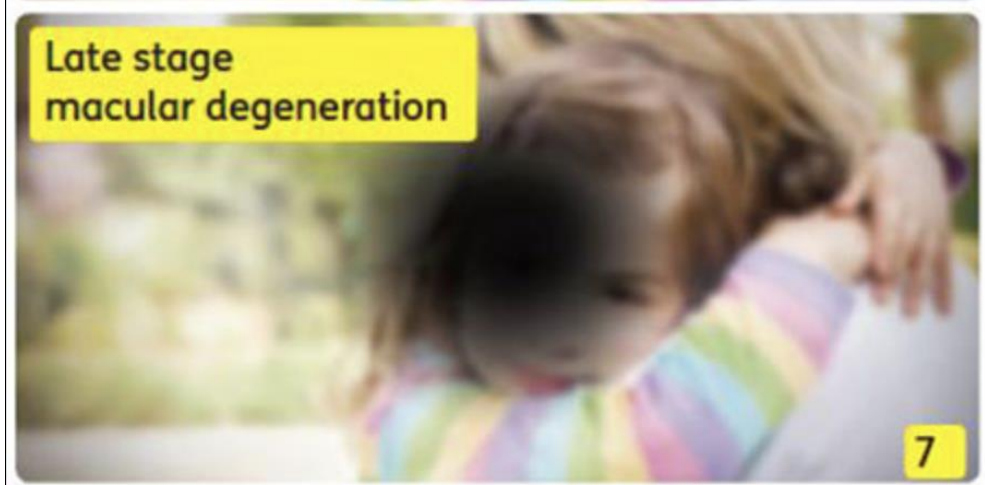
Healthy Eye



Macular Degeneration


Normal vision


Vision with
macular degeneration


Late stage
macular degeneration

doi:10.1038/nbt.4114

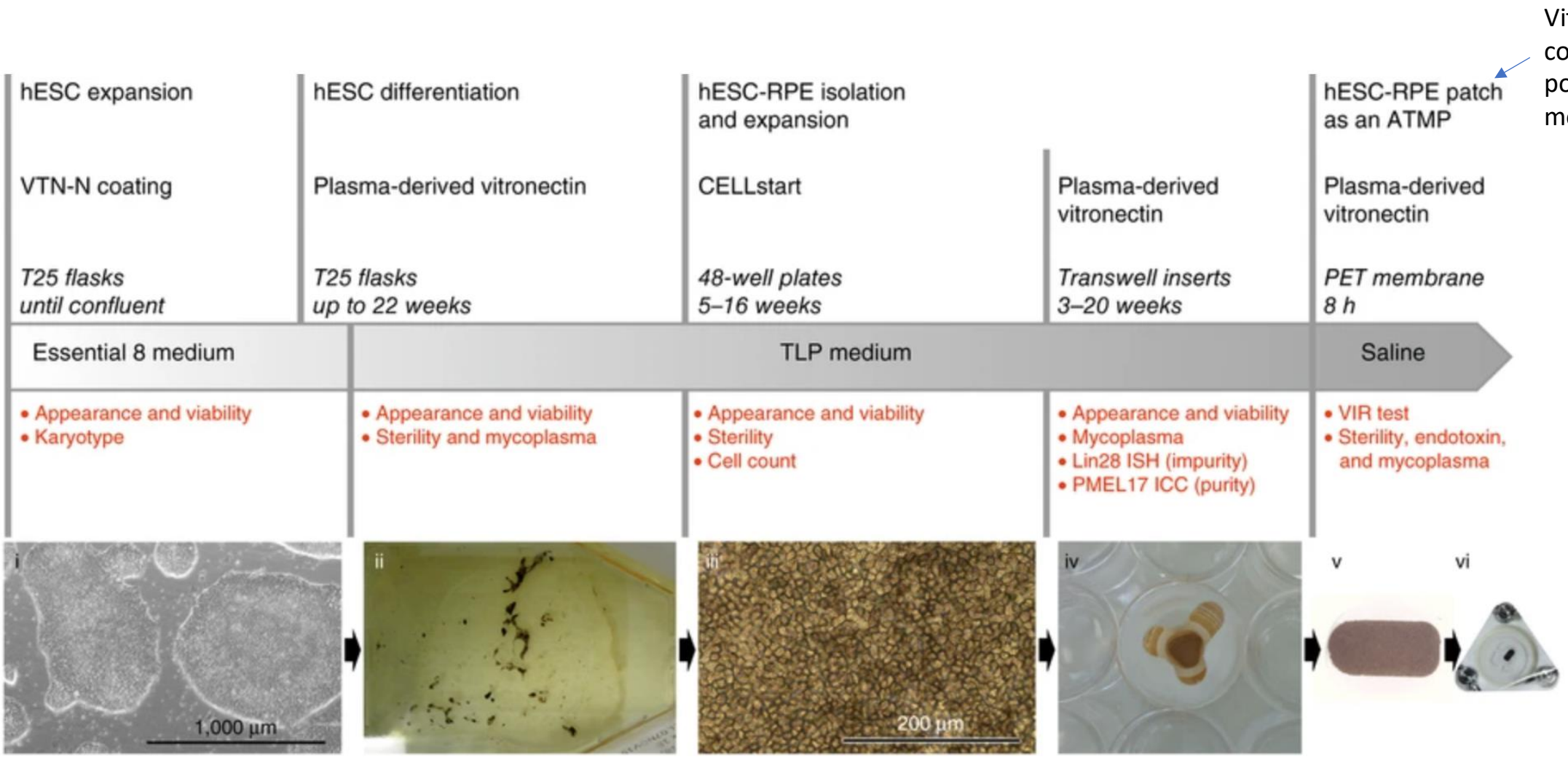
nature biotechnology

Phase 1 clinical study of an embryonic stem cell–derived retinal pigment epithelium patch in age-related macular degeneration

Lyndon da Cruz[1–4], Kate Fynes[1], Odysseas Georgiadis[1–3], Julie Kerby[5,6], Yvonne H Luo[1–3], Ahmad Ahmado[1], Amanda Vernon[7], Julie T Daniels[7], Britta Nommiste[1], Shazeen M Hasan[1], Sakina B Gooljar[1], Amanda-Jayne F Carr[1], Anthony Vugler[1], Conor M Ramsden[1,3], Magda Bictash[5], Mike Fenster[5], Juliette Steer[5], Tricia Harbinson[5], Anna Wilbrey[5], Adnan Tufail[2,3], Gang Feng[5], Mark Whitlock[5], Anthony G Robson[2,3], Graham E Holder[2,3], Mandeep S Sagoo[2,3], Peter T Loudon[5], Paul Whiting[5,8] & Peter J Coffey[1,2,9]

Age-related macular degeneration (AMD) remains a major cause of blindness, with dysfunction and loss of retinal pigment epithelium (RPE) central to disease progression. We engineered an RPE patch comprising a fully differentiated, human embryonic stem cell (hESC)–derived RPE monolayer on a coated, synthetic basement membrane. We delivered the patch, using a purpose-designed microsurgical tool, into the subretinal space of one eye in each of two patients with severe exudative AMD. Primary endpoints were incidence and severity of adverse events and proportion of subjects with improved best-corrected visual acuity of 15 letters or more. We report successful delivery and survival of the RPE patch by biomicroscopy and optical coherence tomography, and a visual acuity gain of 29 and 21 letters in the two patients, respectively, over 12 months. Only local immunosuppression was used long-term. We also present the preclinical surgical, cell safety and tumorigenicity studies leading to trial approval. This work supports the feasibility and safety of hESC-RPE patch transplantation as a regenerative strategy for AMD.

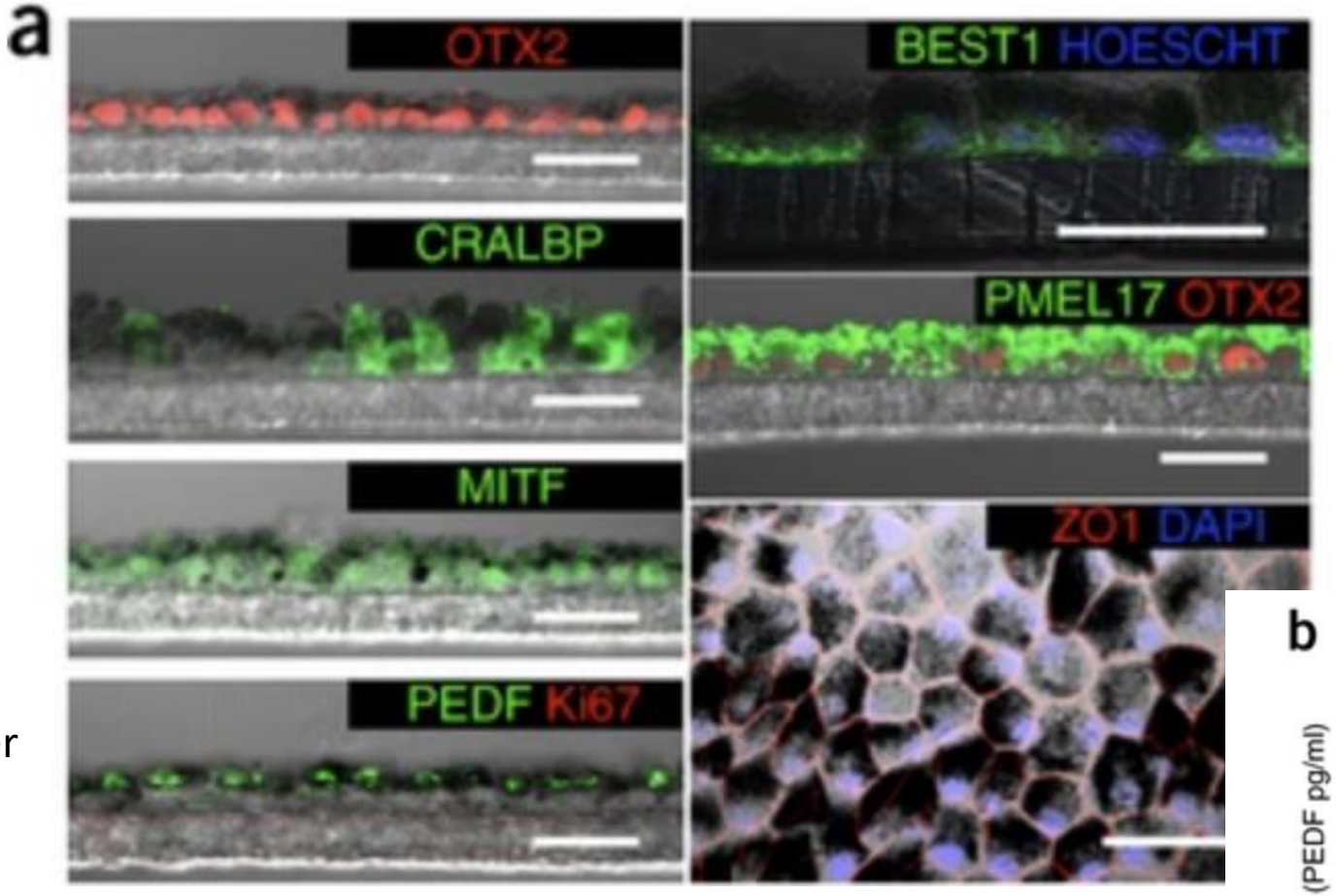
Generation of hESC-derived retinal pigment epithelium (RPE)



Chractirisation of hESC-derived retinal pigment epithelium (RPE)

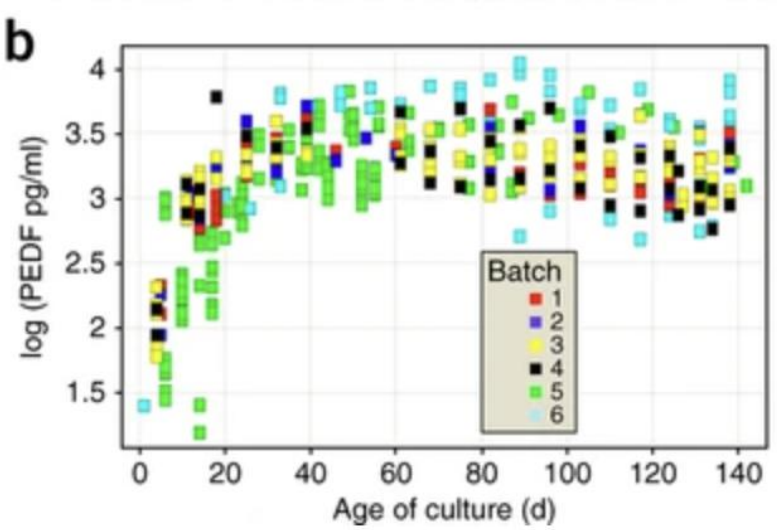
RPE markers

Apical marker



Basal marker

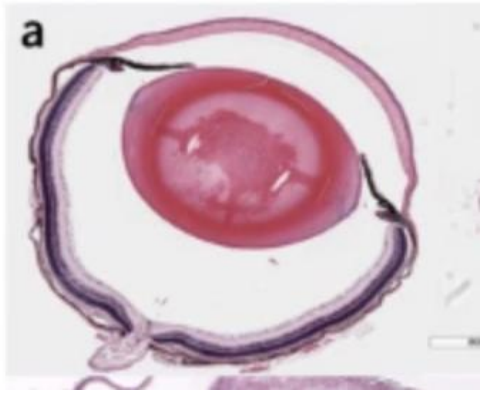
Premilanocytes



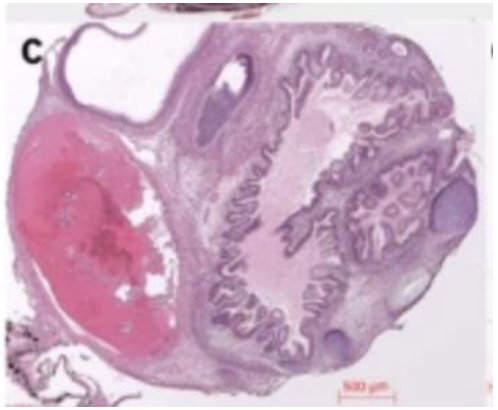
PEDF: Pigment epithelium-derived factor

Safety of hESC derived RPE

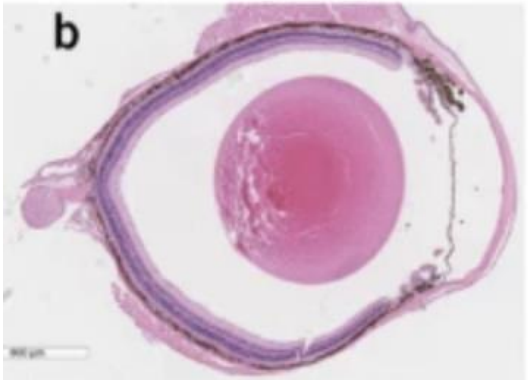
Control eye



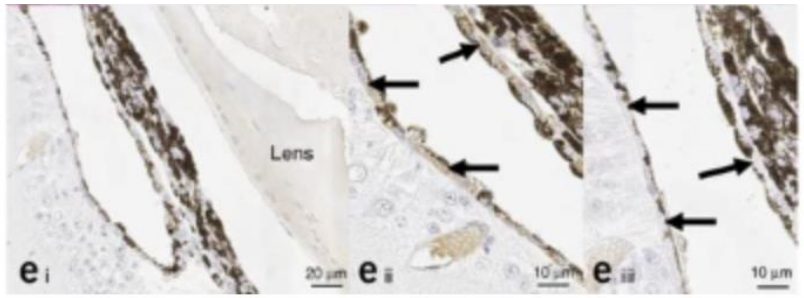
hESCs injection



2 weeks post injection
hESC-derived RPE



Anti human mitochondria IHC-
26 weeks post injection

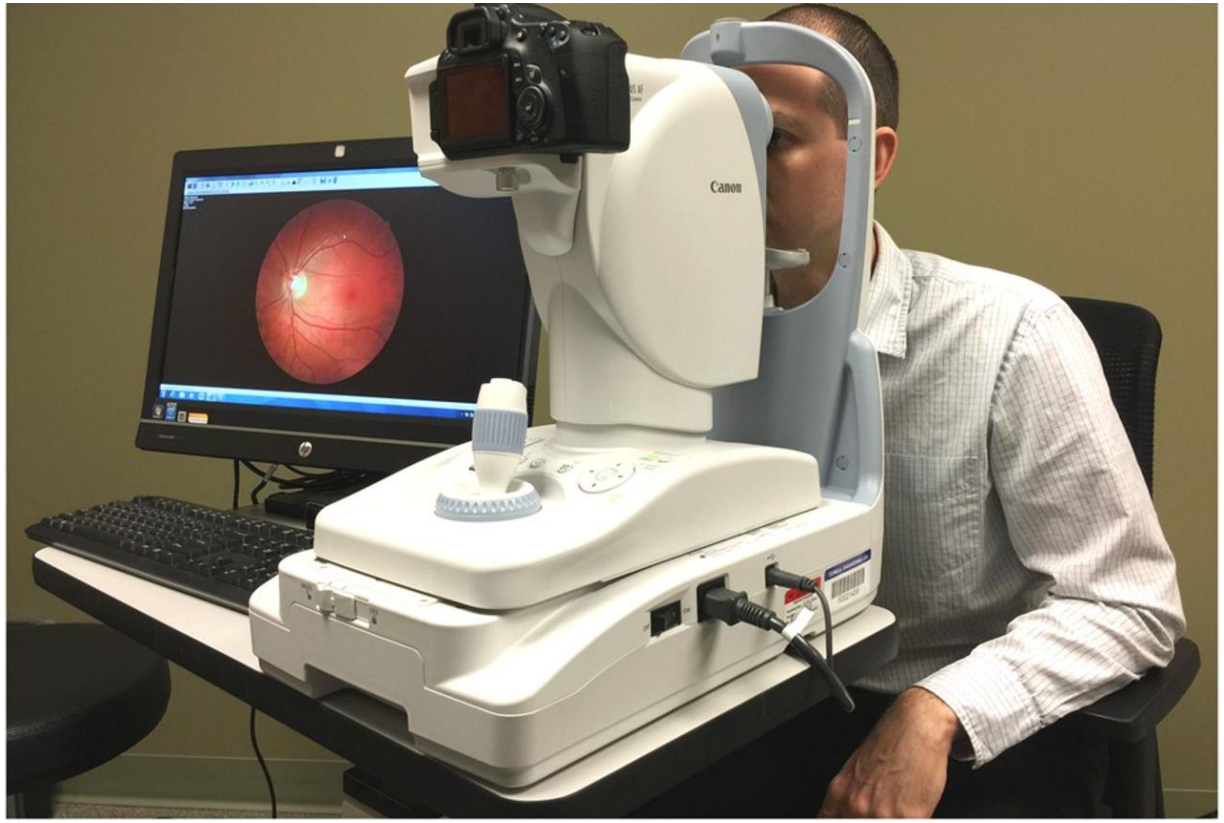


80 mice

Machines

Spectral domain optical coherence tompgraphy

Provides high-resolution, optical cross-sectional, and en face analysis of the retina, RPE, and choroid with *depth-resolved* segmentation.

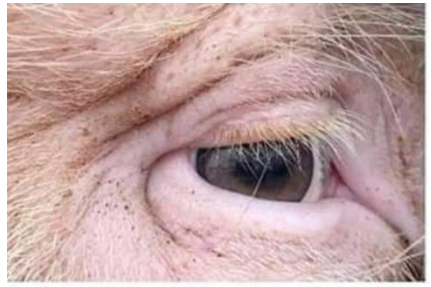


Colour Fundus photograph

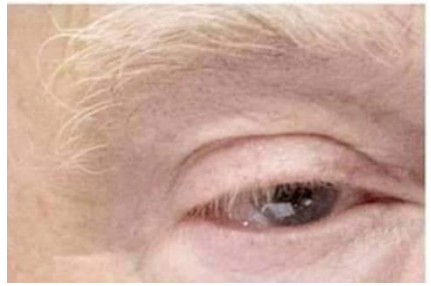
captures the images of the retina, optic nerve head, macula, retinal blood vessels, choroid, and the vitreous.

Safety of patch delivery

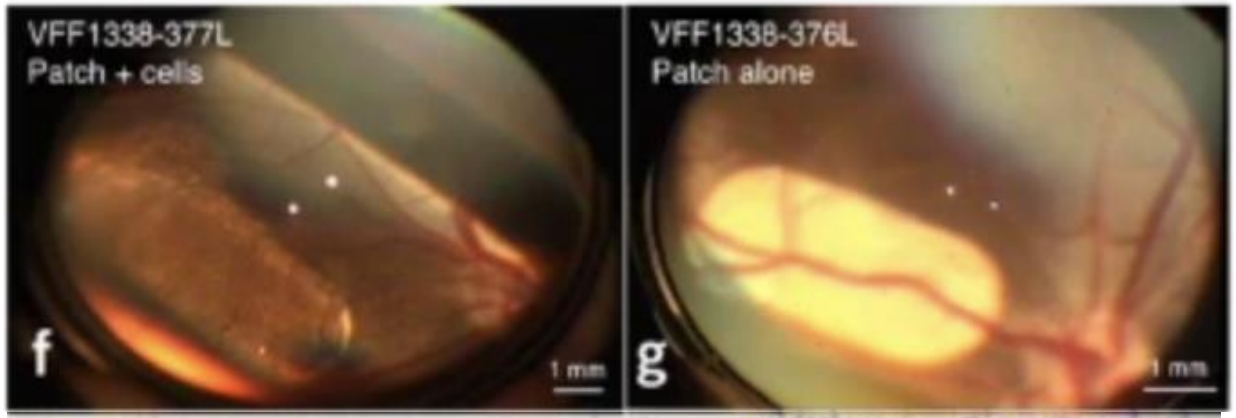
Pig

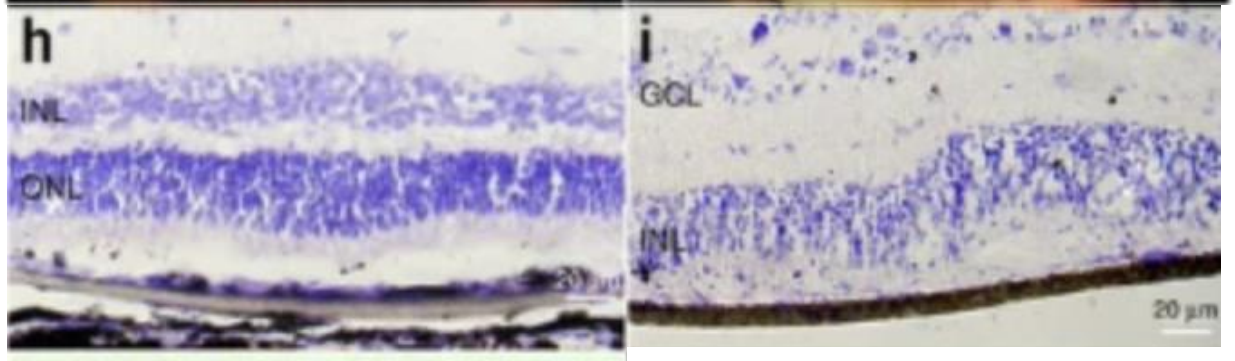


Human



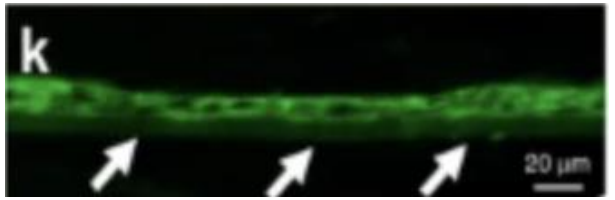
6weeks post surgery: Patch in subretinal space





Unstained RPE

TRA-1-85 human marker



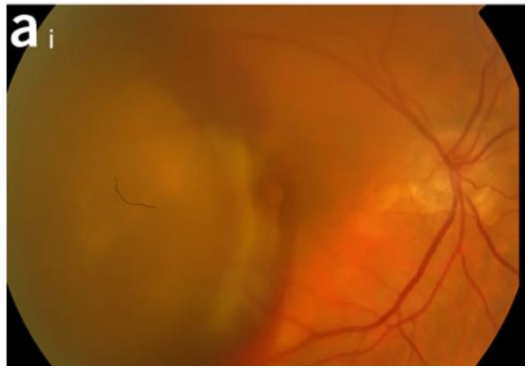
Sample size: 20 pigs.

Oral prednisolone- immune suppressive.

Clincal trial phase I

Pre-clincal study on mice and pigs: Saftey and tumorogencity studies.

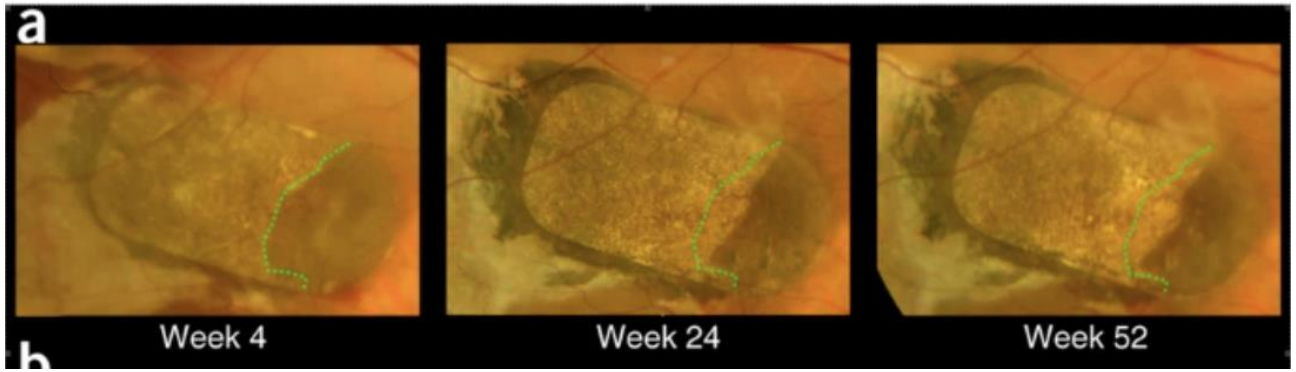
Patient I



Sub RPE and hemorrhage

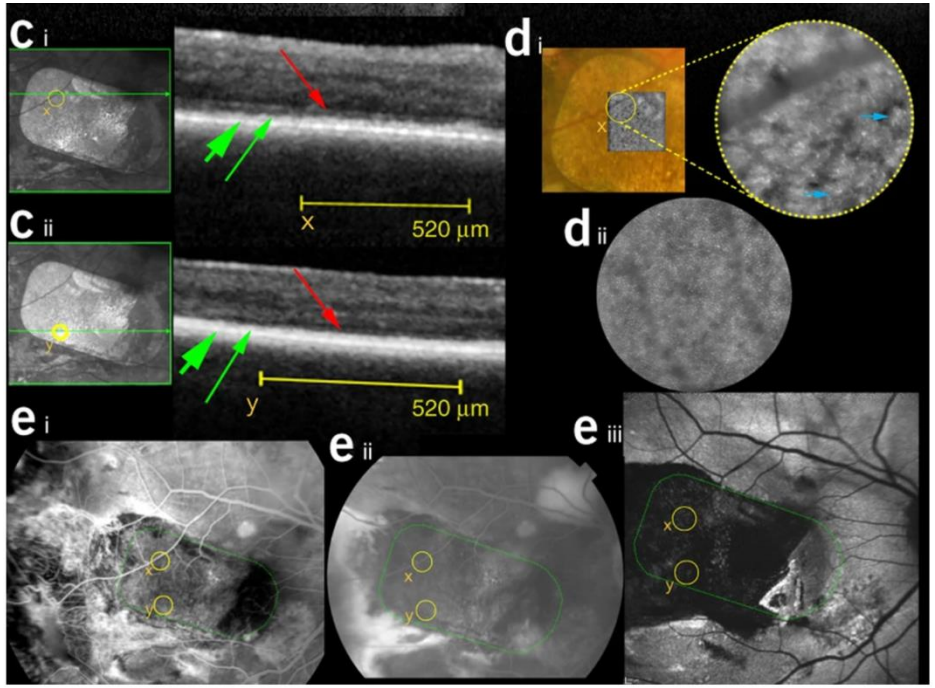
(Colour Fundus photograph)

Cells survival over 6 months and spreading

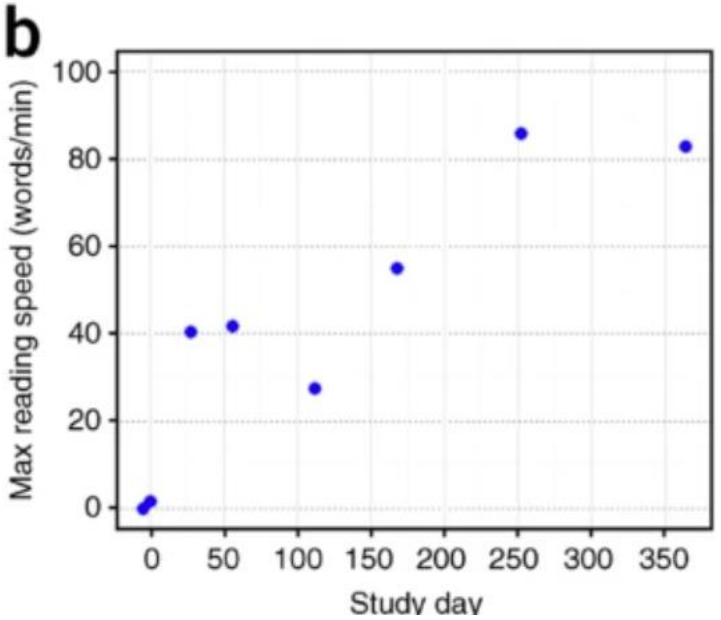


Patient I

12 months: Spectral domain optical coherence tompgraphy



angiogram

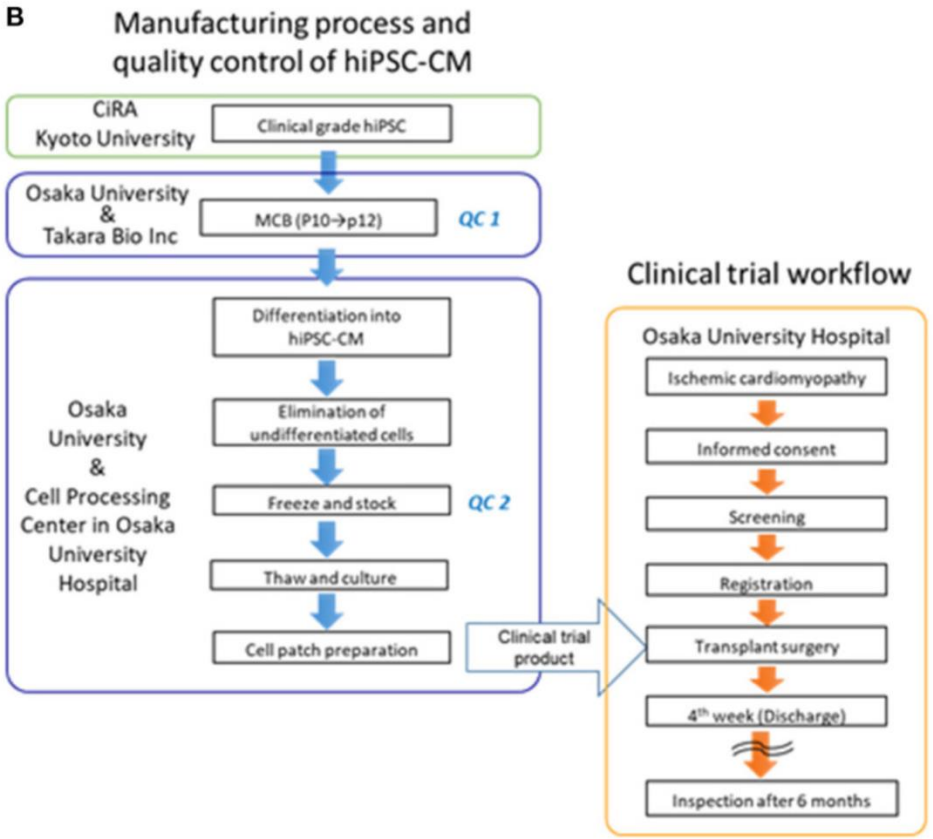


Heart Failure

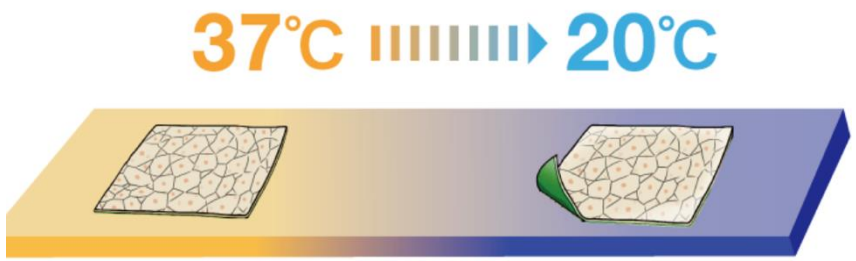
- 60 million people affected.
- With current treaments one out of five patients will die within 12 months.

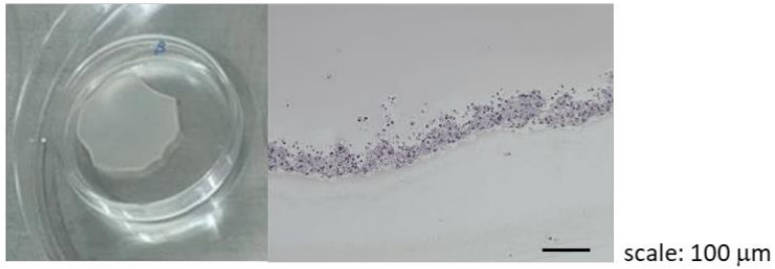
jRCT2052190081 Clinical trial (PMID: 36051285)

Event/Date	symptoms and treatment
2019.3 1st attack	• Chest pain on exertion • CAG revealed lesions on RCA, LCX and LAD, • and PCI was performed
2019.9 (Day 0) 2nd attack	• Recurrence of chest pain • A new lesion of LMT and stenosis of 4AV were found on CAG. Diagonised to be in ACS state. • Intubation and IABP management. • When the PCPS flow level is lowered, the blood pressure becomes 50 units and the hemodynamics are not stable. It was considered to change to circular support with Impella.
(Day 4)	• The IABP and PCPS were removed and the Impella was attached. Since the hemodynamics were maintained, the cardiac stimulant could be gradually reduced.
(Day 20)	• Impella extraction
(Day 21)	• Successful extubation
(Day 22)	• ACE administration
2020.1	• hiPSC-patch transplantation

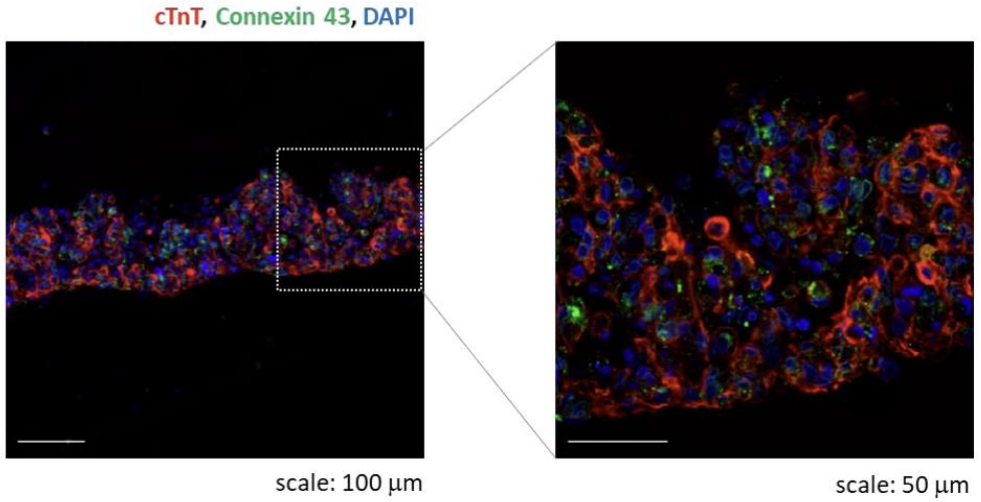


jRCT2052190081 Clinical trial (PMID: 36051285)





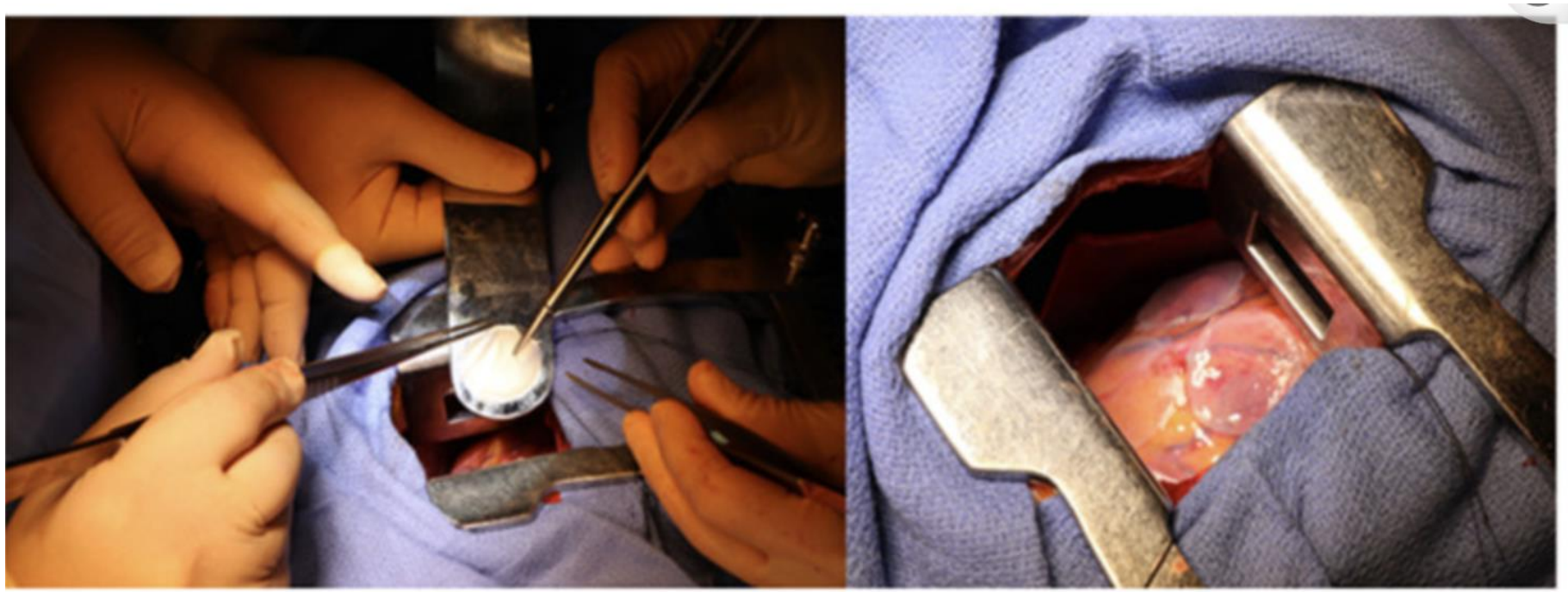
(C)



Supplementary Figure 1. Characteristic properties of hiPSC-CM patch.

- Cardiac Troponin T (cTnT)
- Connexin (Cx) 43 is the predominant protein forming gap junctions and non-junctional hemichannels in ventricular myocardium.

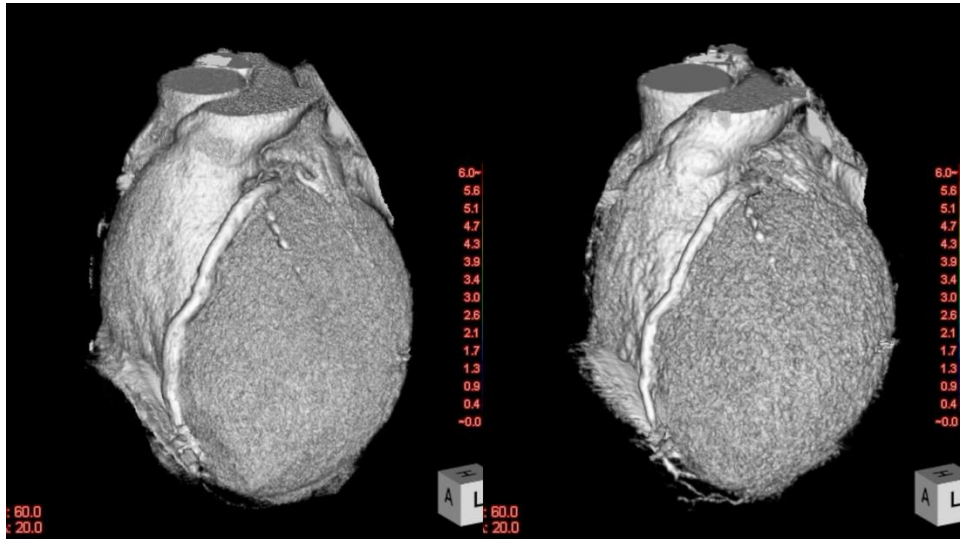
jRCT2052190081 Clinical trial (PMID: 36051285)

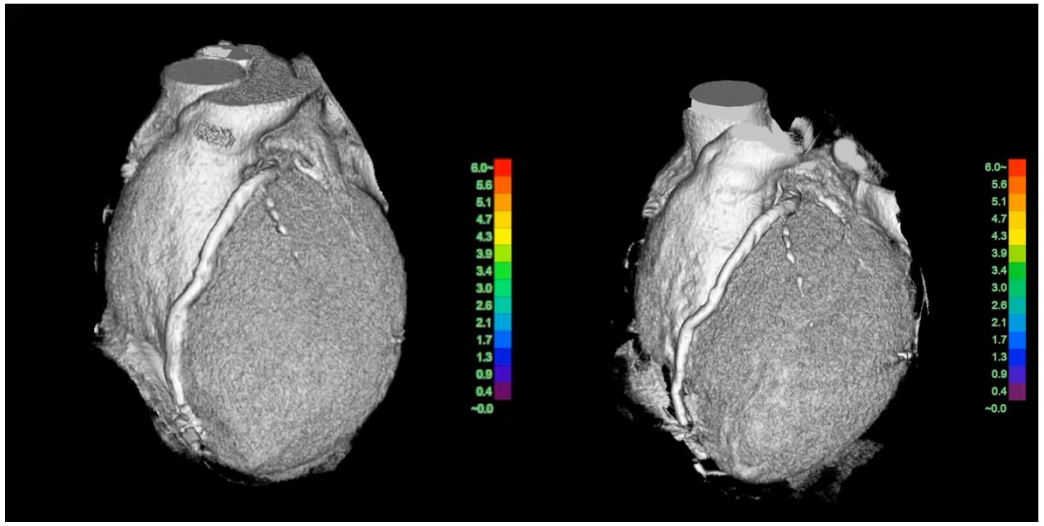


Patch transplantation of the left ventrical

jRCT2052190081 Clinical trial (PMID: 36051285)

4D-CT

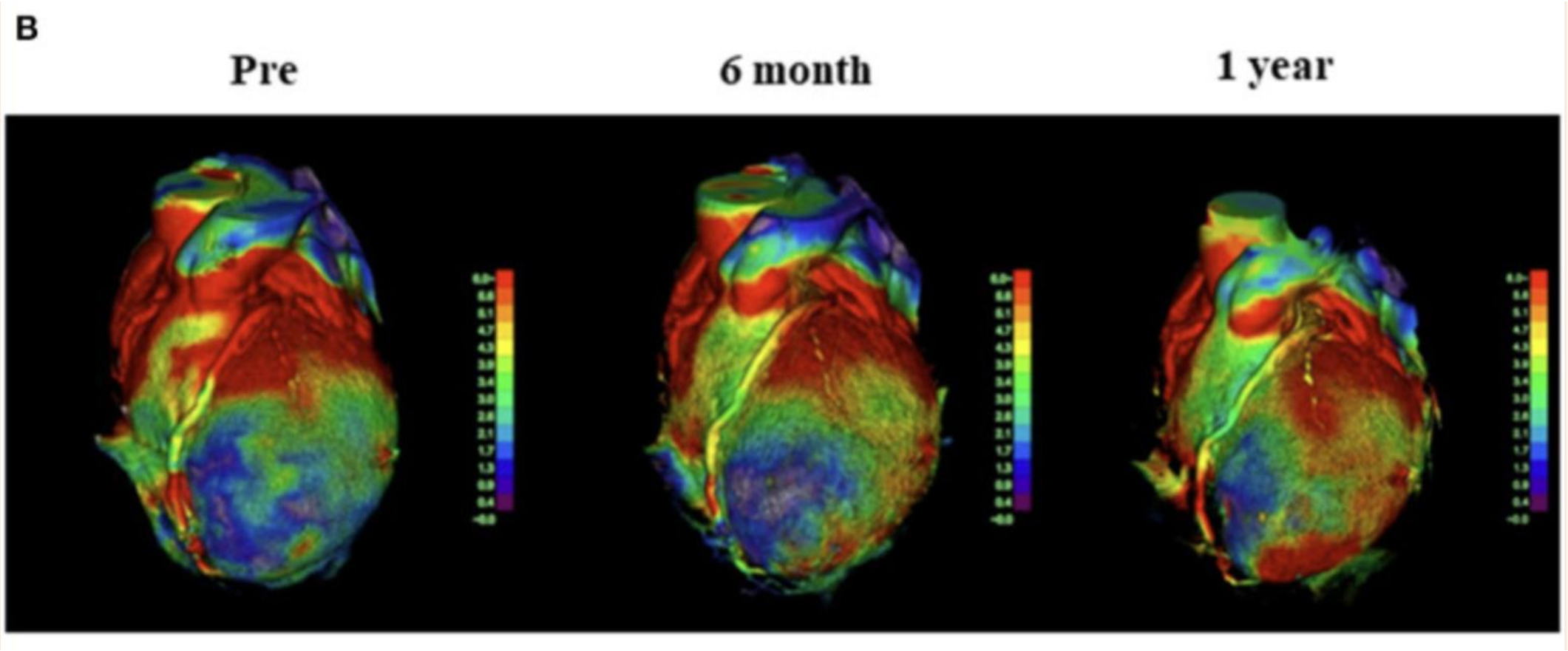




Colours were set so that red indicated a good dynamic area; the darker the colour, the lower the movement.

jRCT2052190081 Clinical trial (PMID: 36051285)

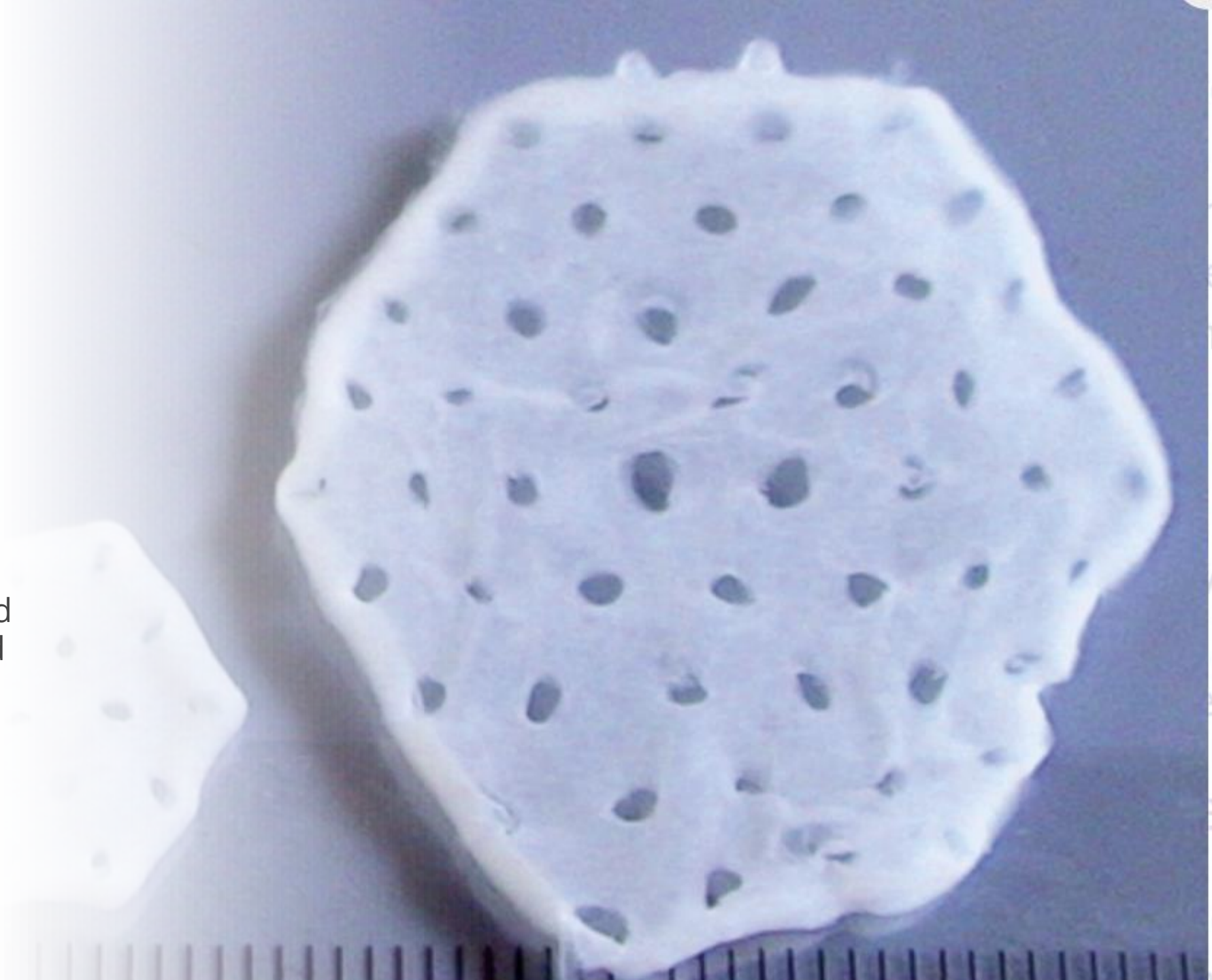
4D-CT

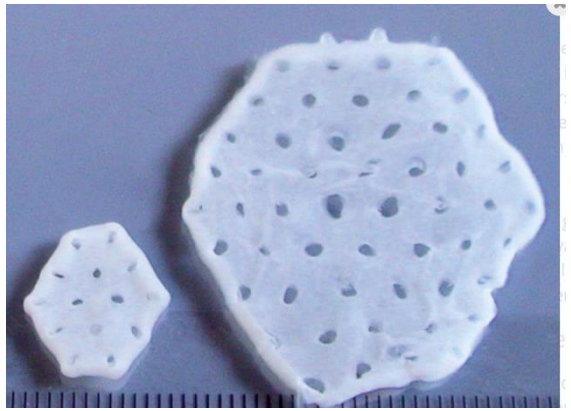


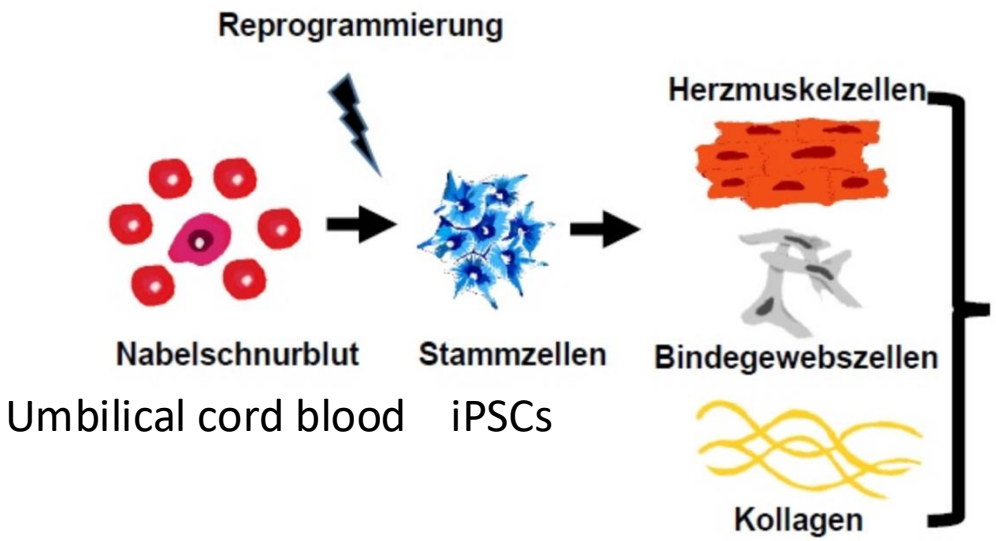
Colours were set so that red indicated a good dynamic area; the darker the colour, the lower the movement.

BioVAT-HF trial

Safety and Efficacy of Induced Pluripotent Stem Cell-derived Engineered Human Myocardium as Biological Ventricular Assist Tissue in Terminal Heart Failure

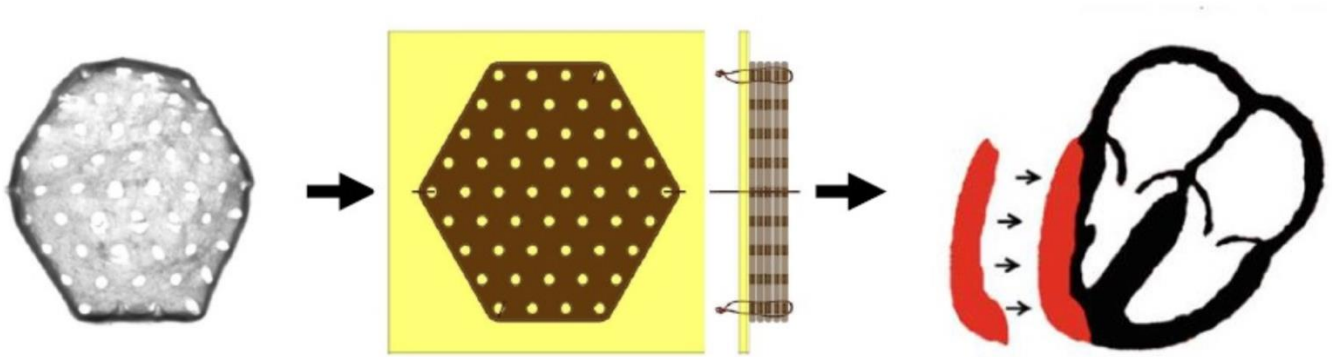






Umbilical cord blood iPSCs

200,400, 800 million cell patches

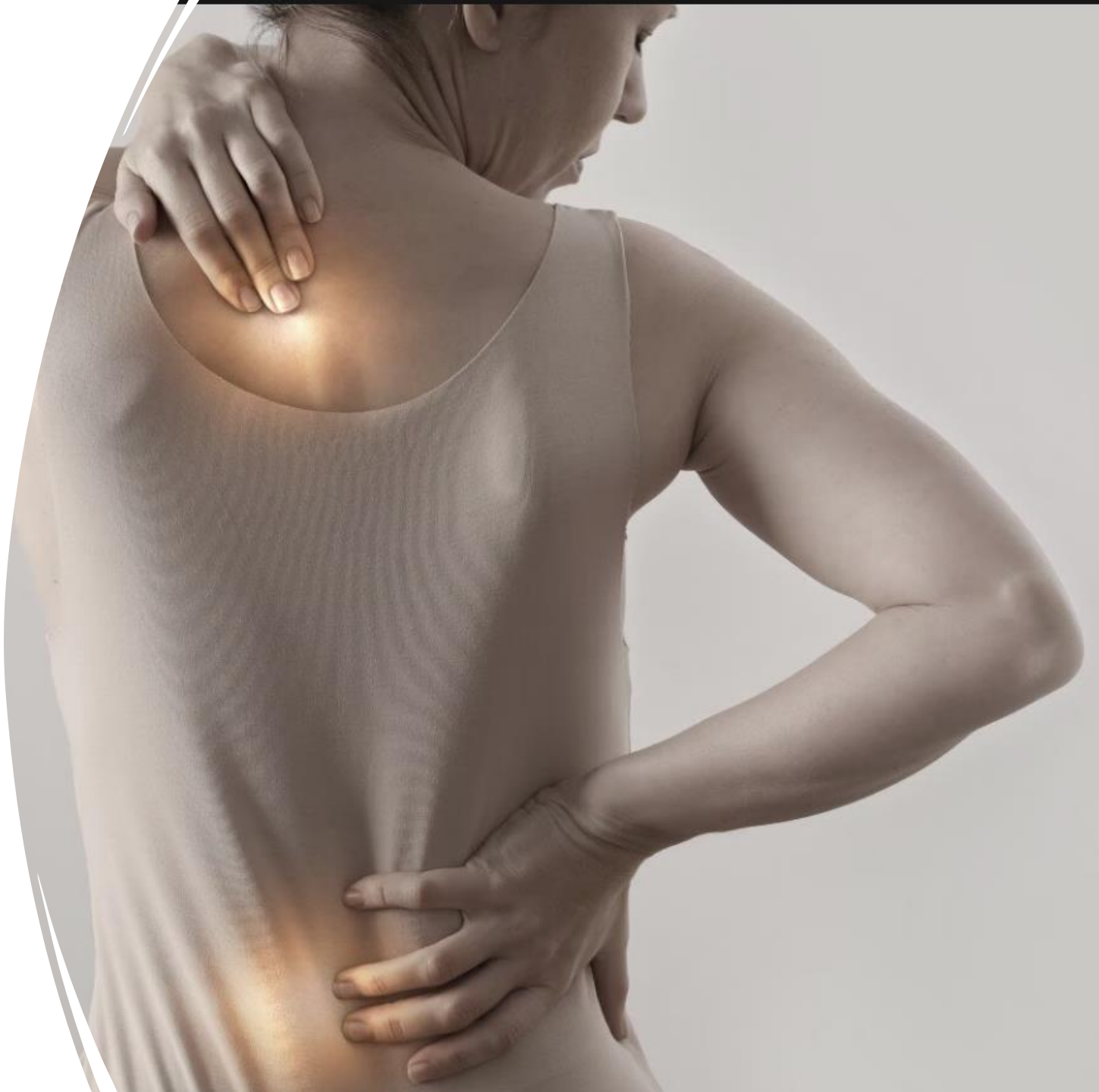


Engineered Heart Muscle (Herzpflaster)

Reparatur durch Herzpflaster Implantation

Phase I (10 patients): Started 09/02/2021 completed 04/04/2023: “For the first time, we are seeing the development of real heart muscle tissue in the human heart with severe heart muscle weakness and are eagerly awaiting the results of the BioVAT-HF study," says Prof. Dr. Gerd Hasenfuß, Chairman of the Heart Centre at the University of Göttingen.

Spinal cord injury



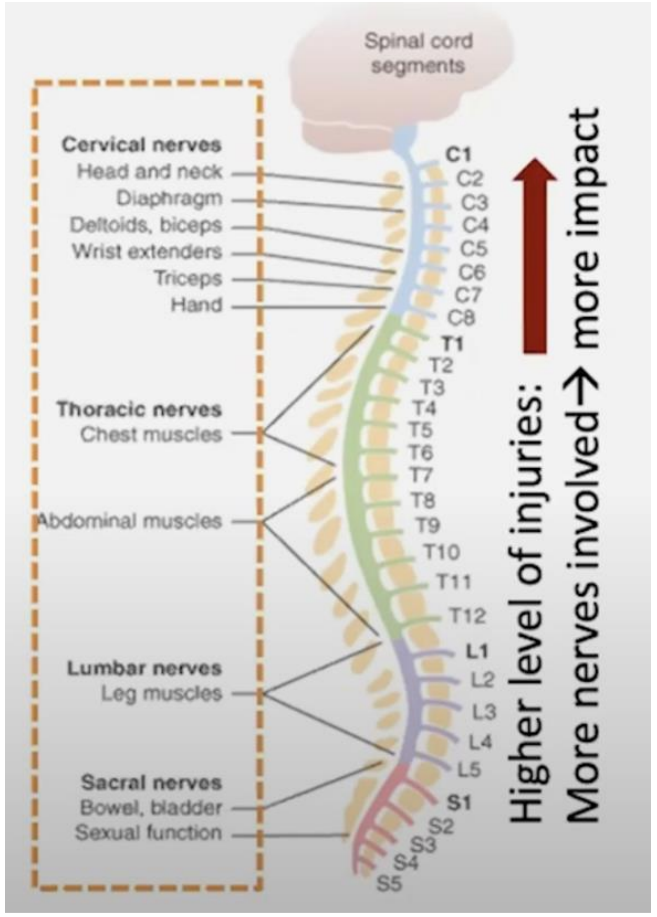
Spinal Cord Injury (SCI)

- Life time imparirments:

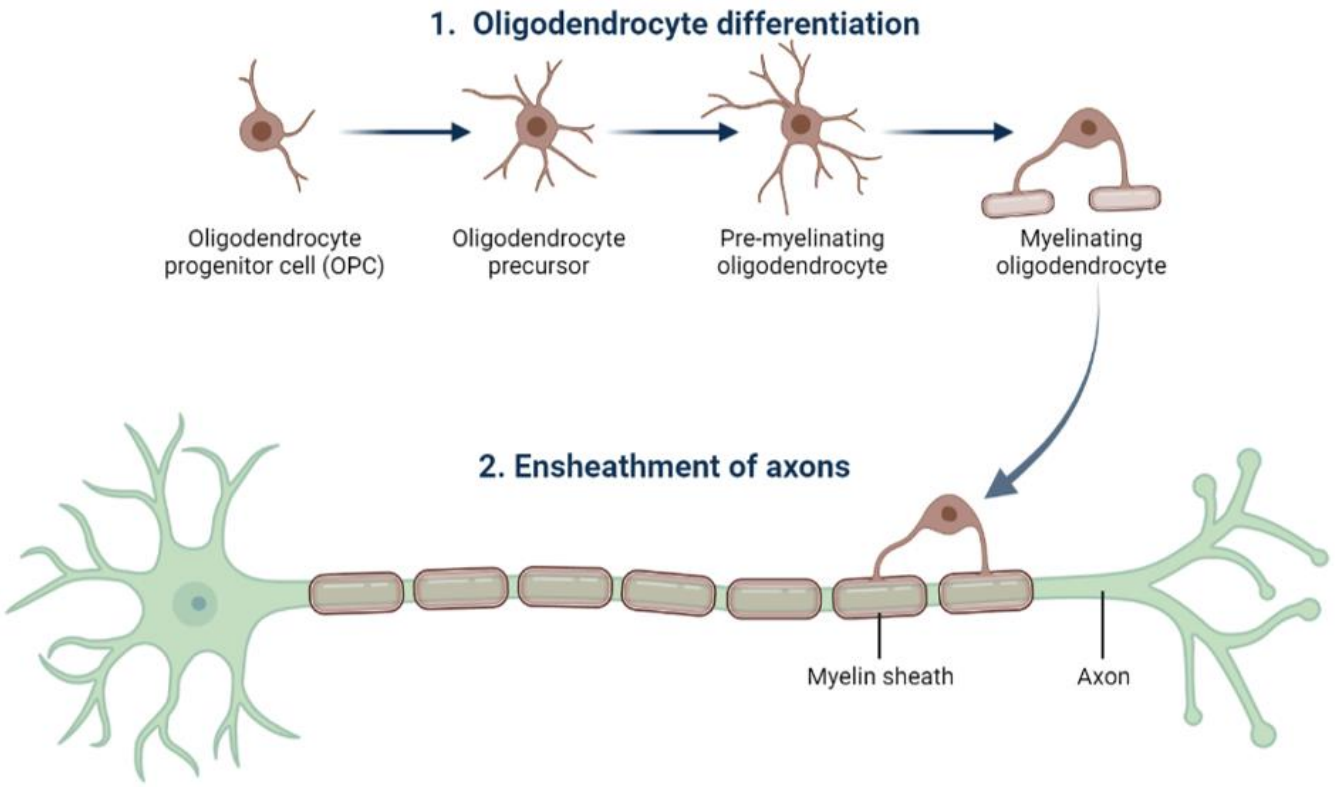
- Wheelchair
- Pain
- Re-hospitilisation
- Infection
- Ventilator
- Shortened life expectancy

- 67% of patients are uneplpyed 10 years post-injury.

- Lifetime healthcare costs can reach $5 million/ patient.



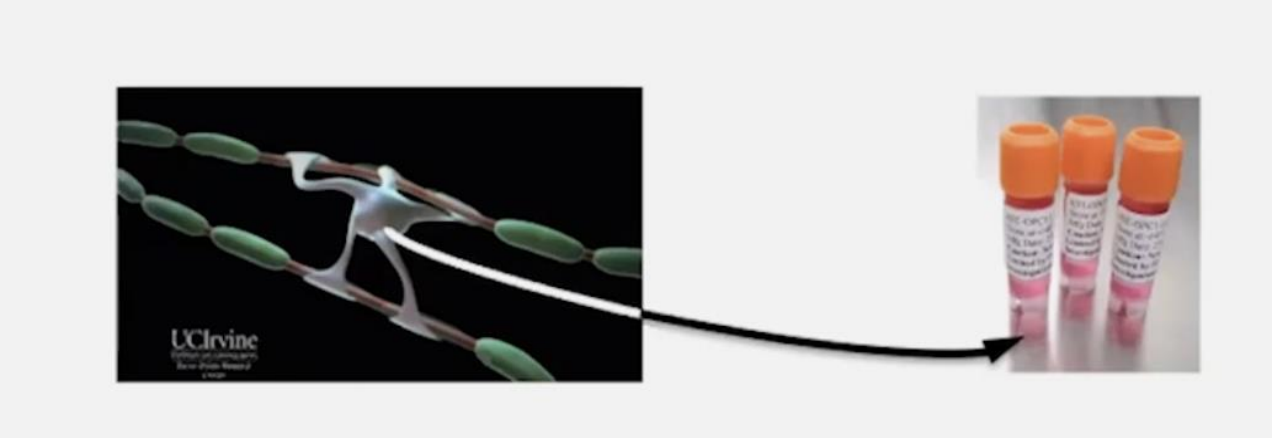
Myelination



OPCs can be damaged and lost due to inflammtory resoponse post injury

OPC1 and SCI

- OPC1: Oligodendrocyte progenitor cells derived NIH-approved pluripotent stem cell line.



- OPC1 has been shown to:

- Remyelinate axons
- Promote neurite growth
- Improve motor function

Ten-year safety of pluripotent stem cell transplantation in acute thoracic spinal cord injury

1. Objective:

- Evaluate safety of LCTOPC1 in T3 to T11 neurologically complete SCI patients, administered 7-14 days post-injury.

2. Methods:

- Participants (n = 5) received a single 2 × 10^6 LCTOPC1 injection with 60 days of tacrolimus immunosuppression.
- Follow-up included annual in-person examinations and MRI for 5 years.
- Telephone questionnaires for 6 to 15 years post-injection.

3. Endpoints:

- Primary: Safety – adverse events.
- Secondary: Neurological function (sensory and lower-extremity motor scores).

4.Results:

- No serious adverse events reported in 98% follow-up through the first 10 years.
- No neurological decline, spinal cord damage, or syrinx formation.
- MRI showed 80% with T2 signal changes consistent with tissue matrix formation.

5.Conclusions:

- Crucial safety data supports future embryonic stem cell–derived therapies.
- LCTOPC1 well-tolerated for up to 10 years, prompting a cervical dose escalation trial (NCT02302157).

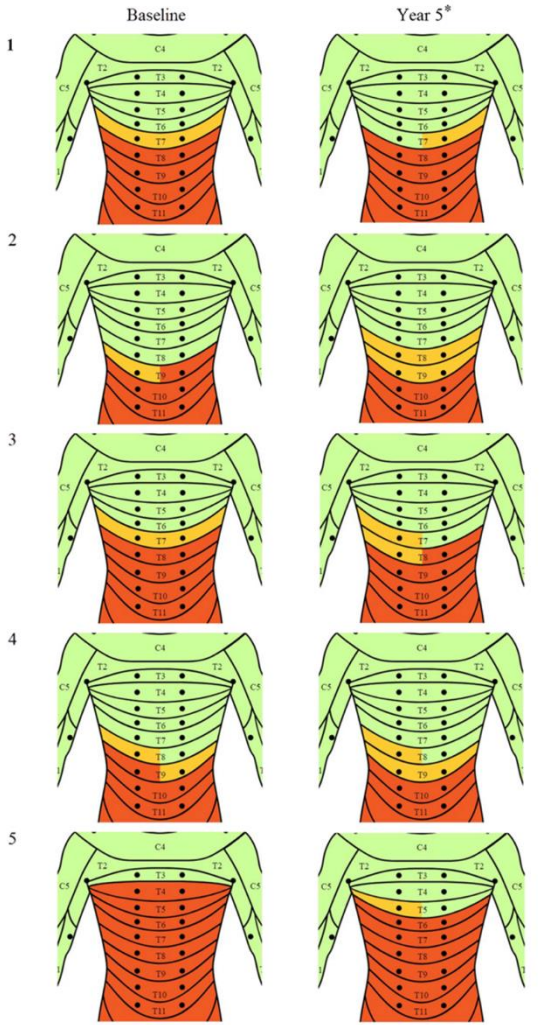
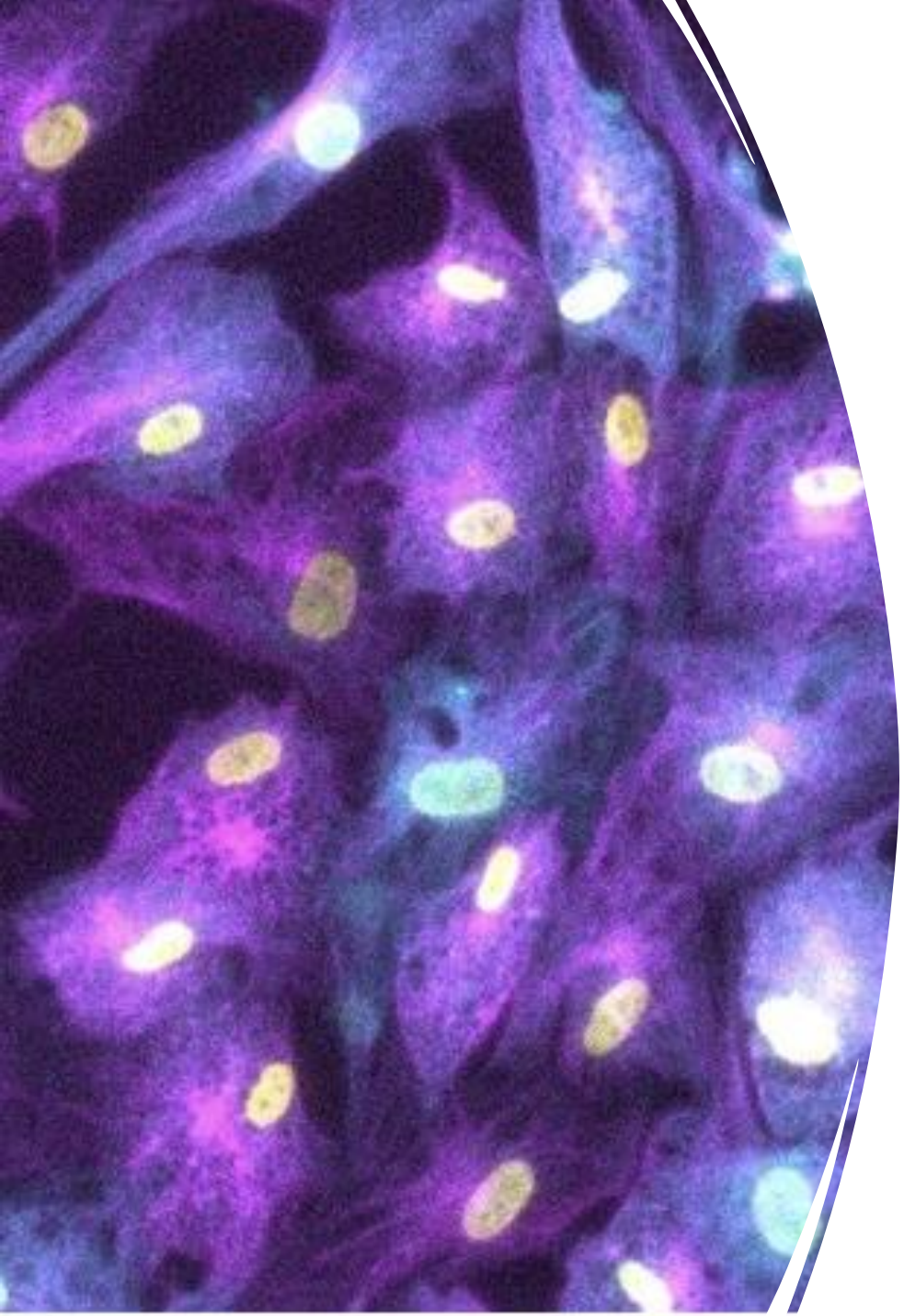


FIG. 3. ISNCSCI pretransplantation (baseline) and at year 5 for each of the 5 study patients. *Green* represents areas with normal motor and/or sensation, *red* represents areas with absent motor and/or sensation, *orange* areas represent sensation that is present but abnormal. *Participant 3 did not participate in year 5 follow-up; year 4 data are presented.

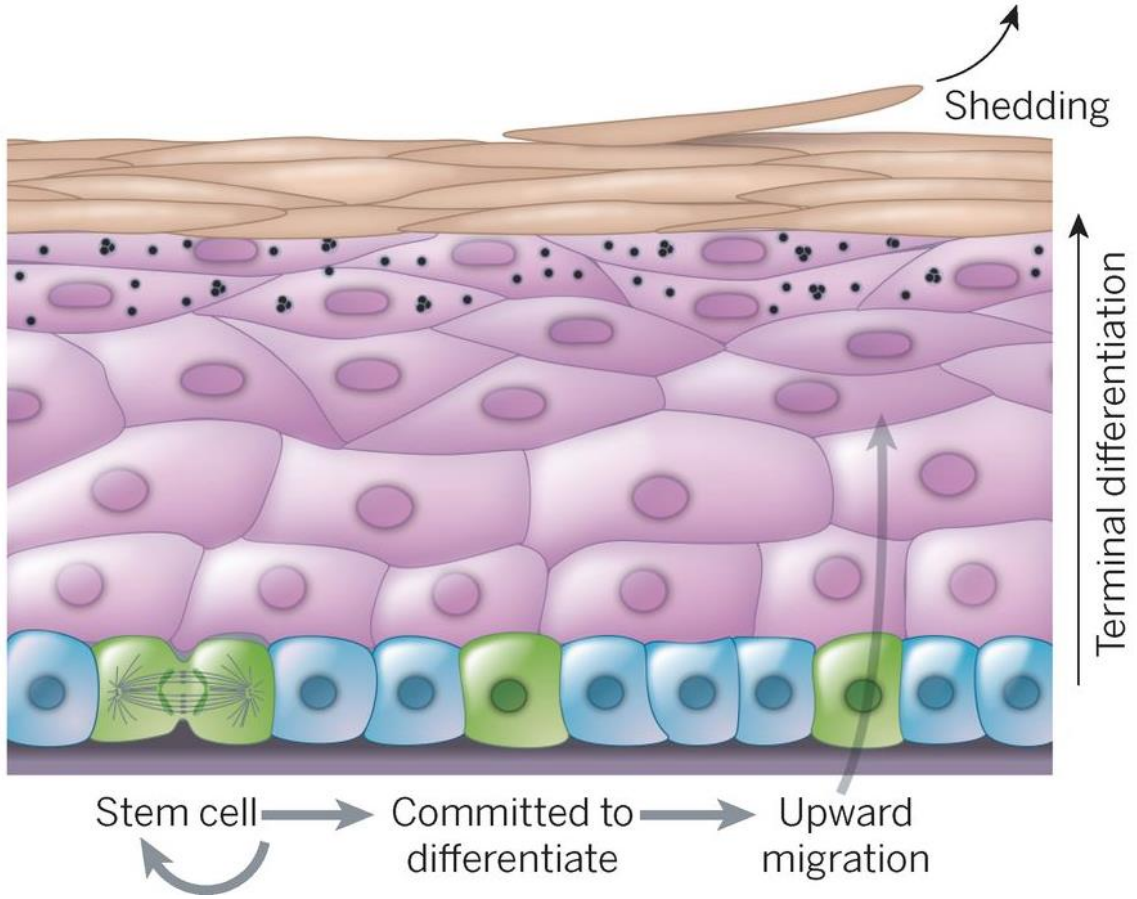
PMID: 35364569

- https://www.youtube.com/watch?v=k3EvdEGEopU



Adult Stem Cells as a Source for Regenerative Medicine

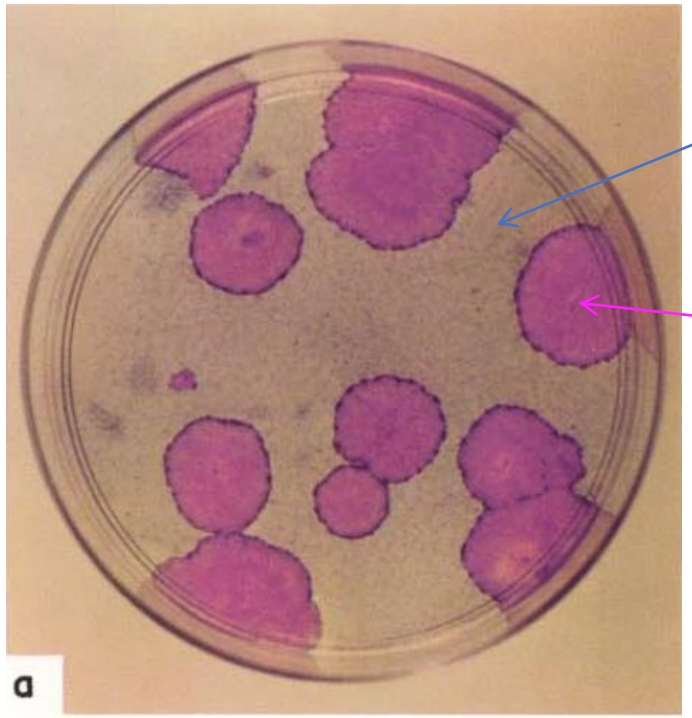
The interfollicular epidermis



Adopted from Fiona M Watt *Science* 2014

Skin in a dish

Cell 1975: James Reinwald and Howard Green:

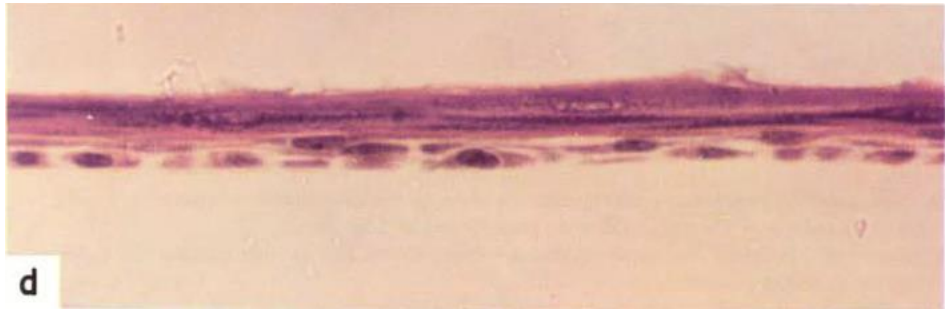


Irradiated mouse fibroblasts

Human Epidermal Keratinocyte Colony (KC)

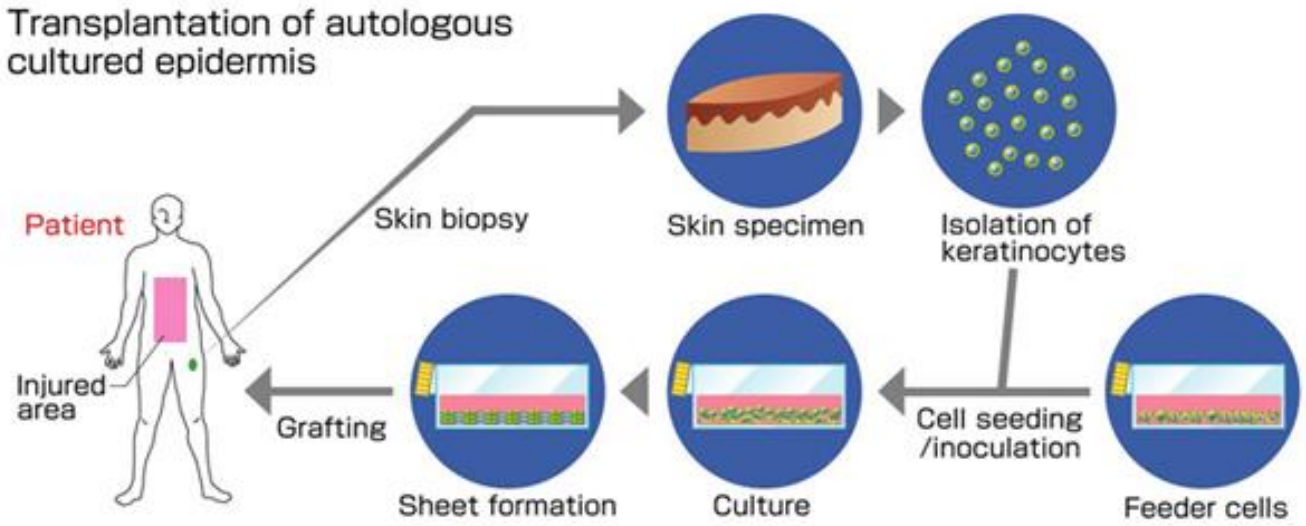
Culture lifetime: 20-50 cell generation

Vertical sections through KC showing their stratified appearance



Skin in a dish

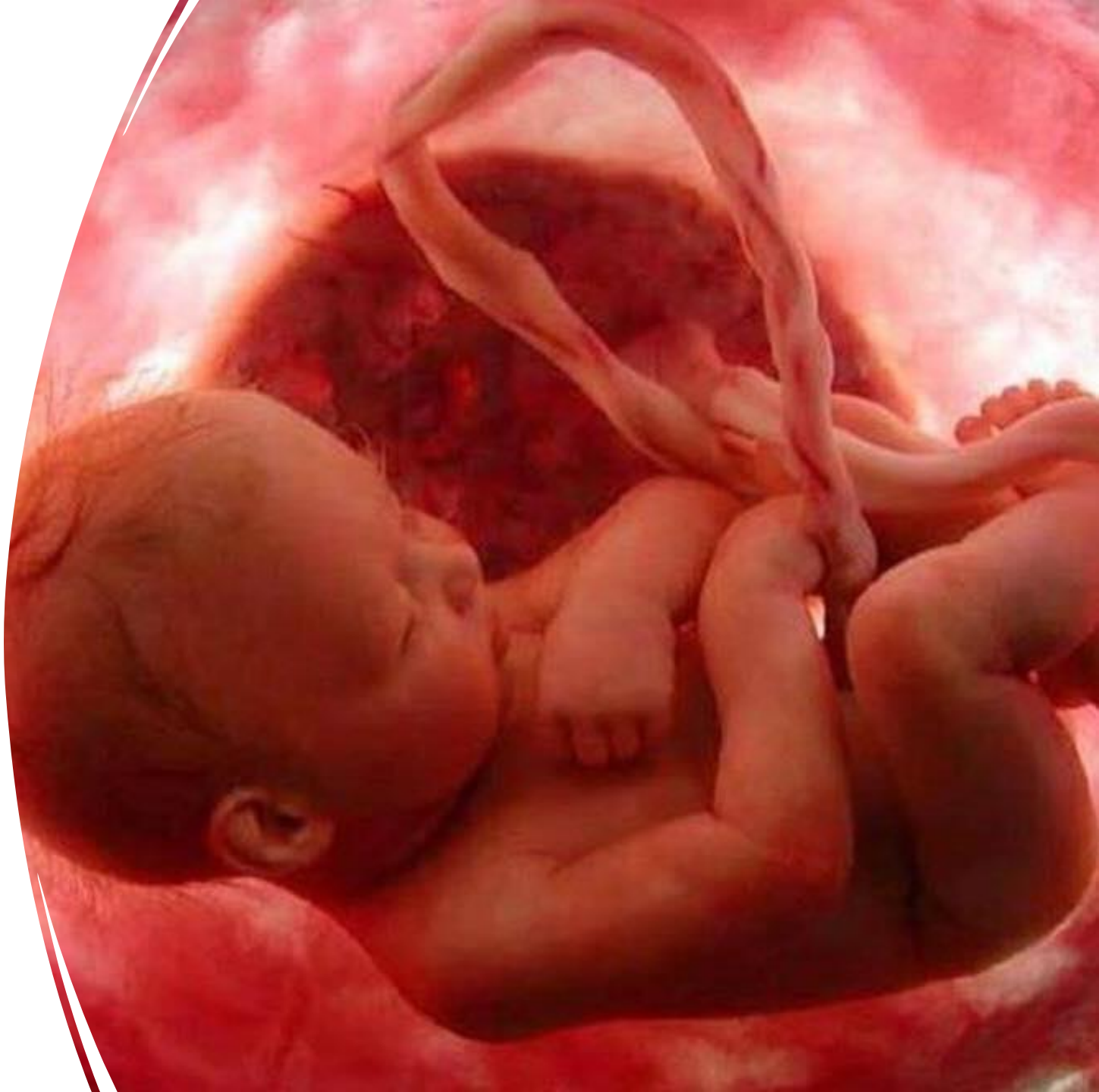
The Lancet 1981: Nicolase E. O'Connor *et al* and Howard Green:



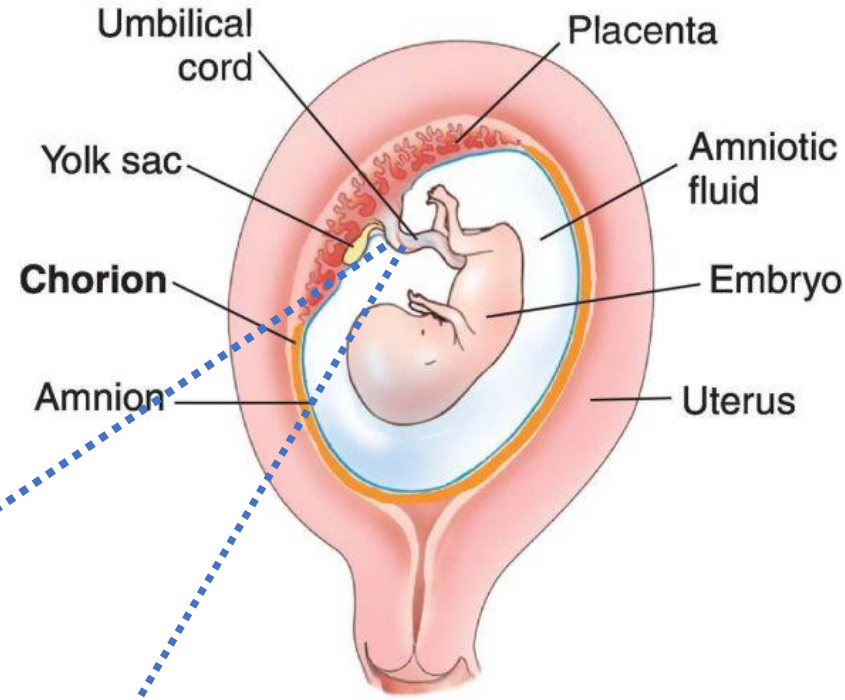
In the summer of 1983 this approach was demonstrated to be life-saving for the 5-year-old Jamie Selby and his 6-year-old brother Glen, who had both sustained burns over >95% of their body surface

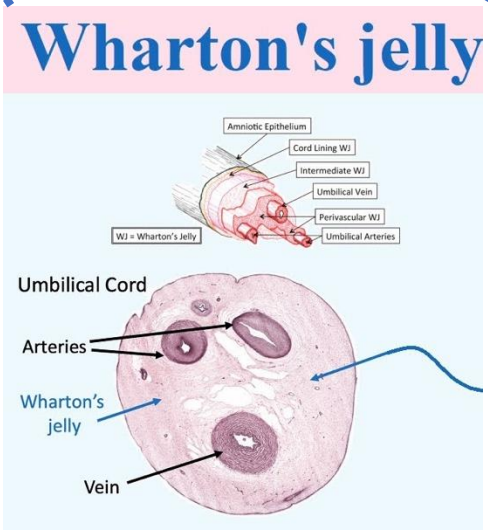
* https://www.youtube.com/watch?v=zstKQhnt8dM

Perinatal Mesenchymal Stem Cells/ Skeletal Stem Cells



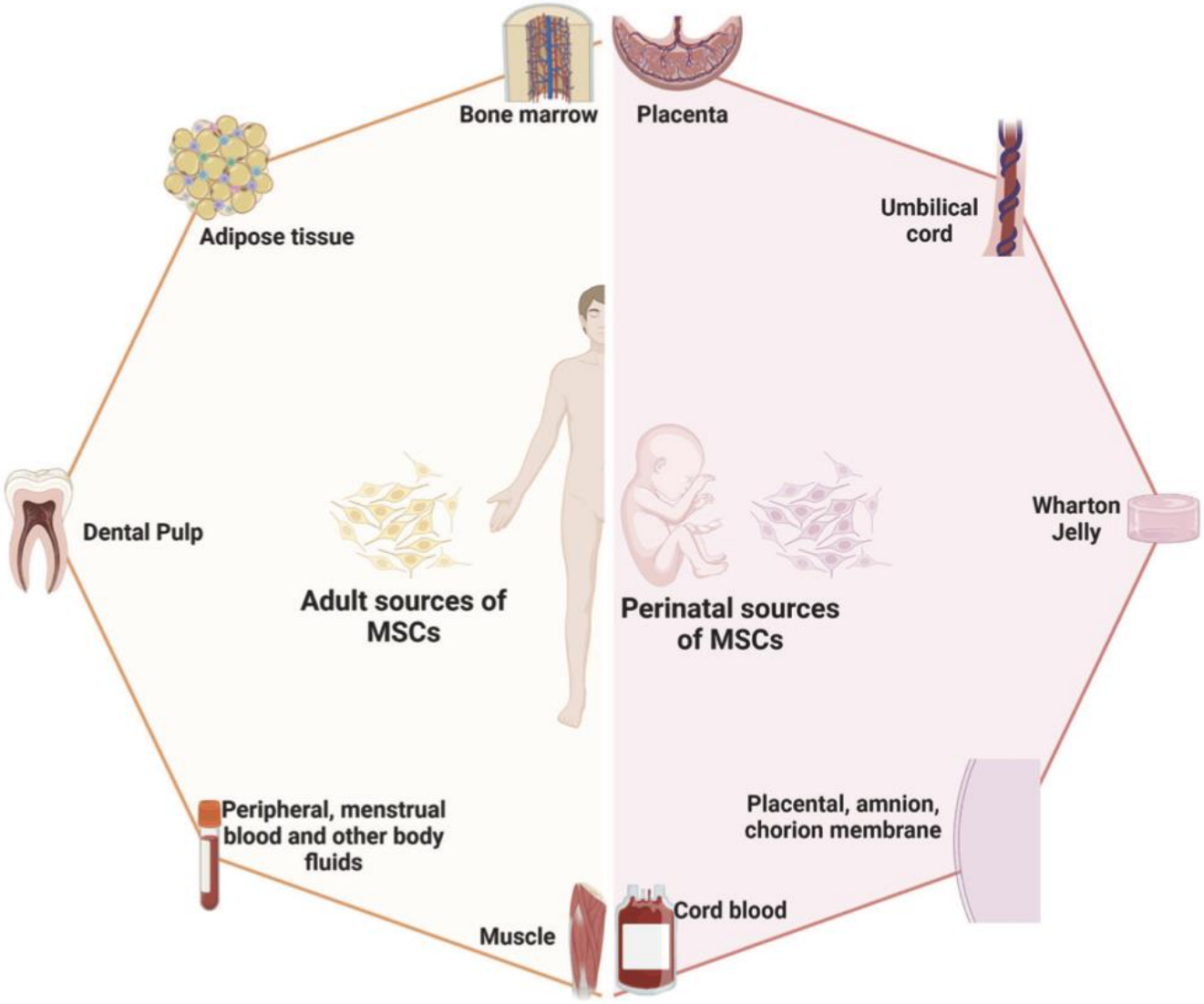
Perinatal Mesenchymal Stem Cells/ Skeletal Stem cells





Source: https://vaidyanamah.com/the-fetal-membranes/

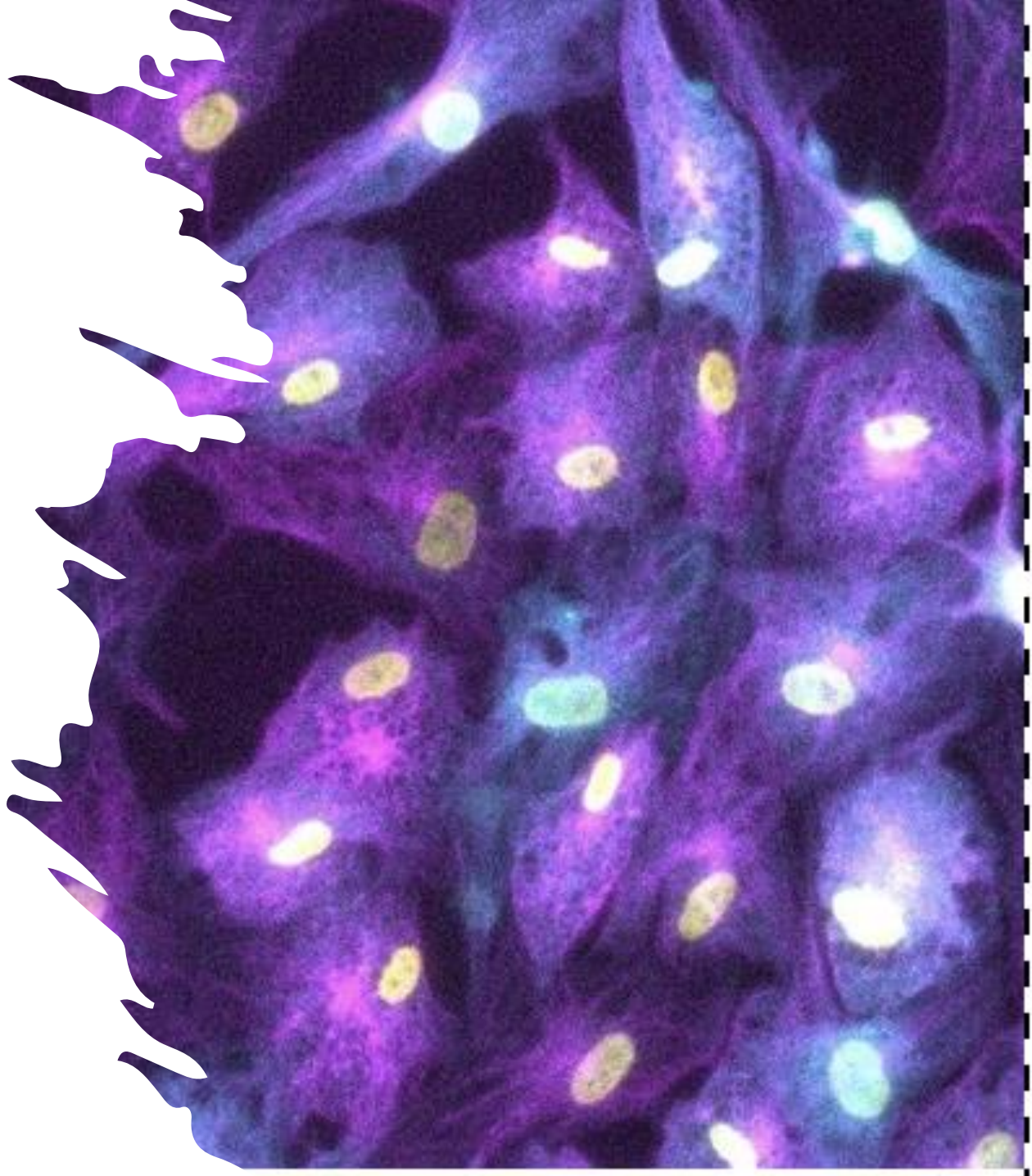
Mesenchymal Stem Cells/ Skeletal Stem cells

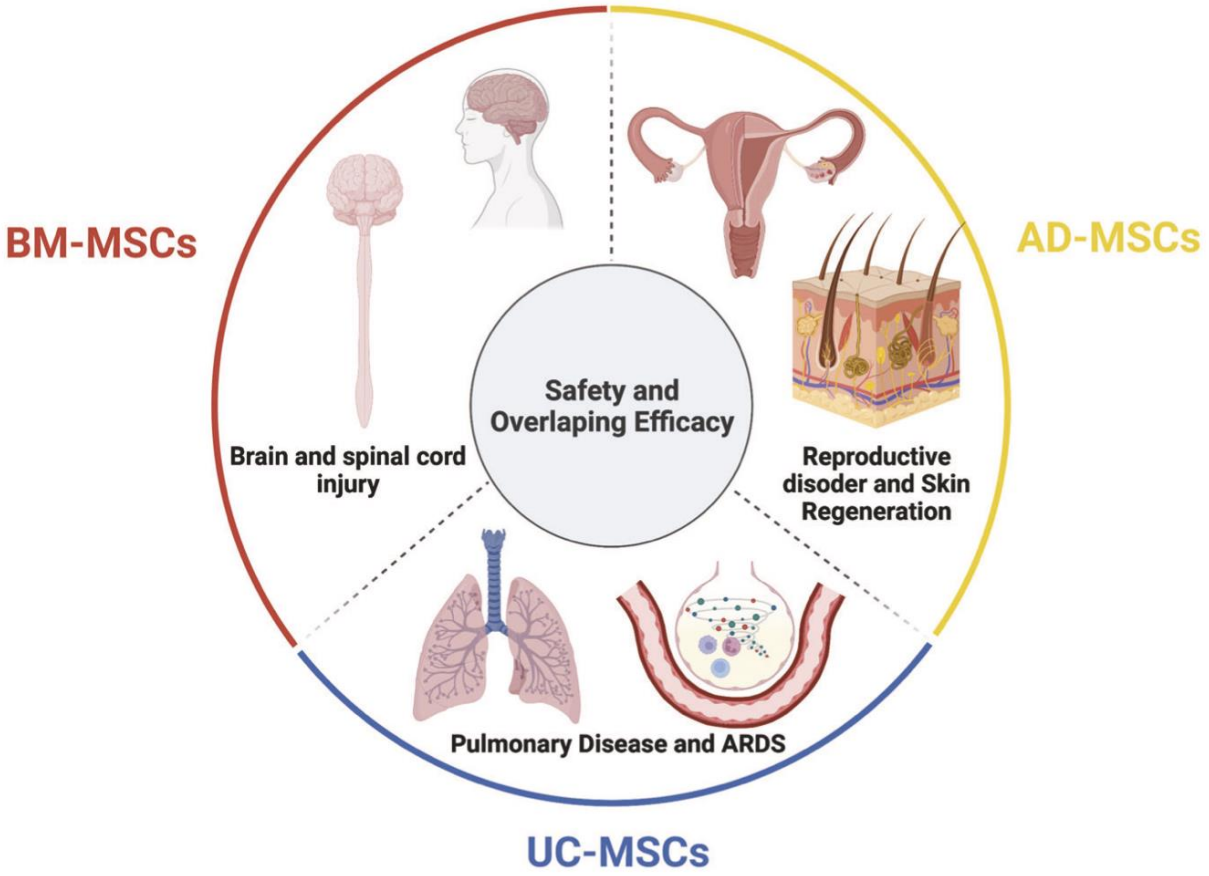


PMID: 35933430

MSC/SSC

- MSC surface markers (95% positive) for CD73, CD90 and CD105.
- Less than 2% negative for CD11, CD13, CD19, CD34, CD45, and HLR-DR).
- Differentiation ability into chondrocytes, osteocytes, and adipocytes.
- Variability in the marker and expression across BM-MSC, AT-MSC and UC MSC
- Differentiation potential varies between BM-MSC, AT-MSC. UC-MSC shows stronger differentiation capabilities to osteogenic than BM-MSC.
- Immunomodulation: inhibit proliferation of peripheral blood mononuclear cells.
- Injected MSCs are attracted to injured sites in the body.





2022: 1462 registered clinical trials using MSCs

PMID: 35933430

BM-MSCs for Deep Skin Burns (PMID: 16142297)

Case Overview:

- Female patient S., 45 years old, admitted on May 9, 2003
- Diagnosis: Thermal burn (I-II-IIIAB degree), covering 40% body surface

Treatment Progress:

- Challenges: Poor blood supply, infection (Pseudomonas aeruginosa), limited success with traditional methods
- Sequential therapy, including BM-MSCs transplantation and autodermoplasty (ADP)

Cell Transplantation Success:

- Application of allogenic BM-MSCs on June 7, 2003, led to significant improvement
- Enhanced epithelial growth, pain relief, and improved patient contact observed
- Visual indicators: Appearance of bright red vessels, indicative of improved vascularization
- First skin grafts applied on June 11, 2003, covering 60% of burn surface
- Second ADP on June 24, 2003, with SG from first donor sites, achieving complete healing by July 7, 2003
- Visual indicators: Neoangiogenesis, rapid epithelialization, favourable biochemical responses

Fig. 1. Profuse bleeding from new capillaries during dressing 3 days after application of fibroblast-like mesenchymal stem cells (FMSC).

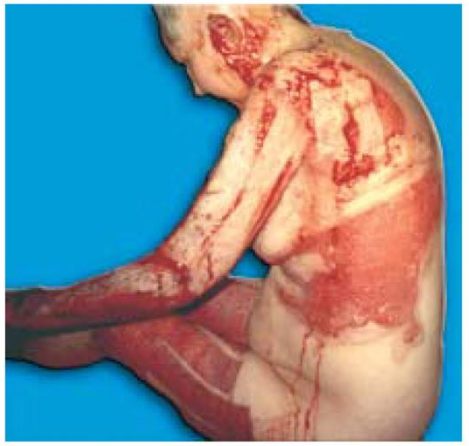


Fig. 2. Transplantation areas and degree of skin graft take after autodermoplasty (ADP) following application of FMSC.

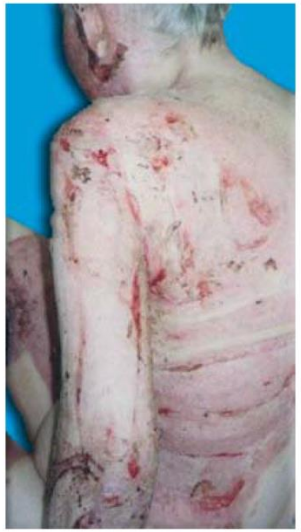


Fig. 5. Surface of burns on day 32 after application of FMSC and ADP.

Conclusion:

•Integrated approach led to successful burn wound healing

•Patient discharged on July 9, 2003, resumed work on August 1, 2003

•Demonstrates the effectiveness of combined therapies for comprehensive recovery in severe burn cases.

Harnessing the Potential of BM-MSCs Across Neurological Disorders

1. Stroke Rehabilitation with BM-MSCs:

- Promising results: Enhanced safety profile observed.
- Motor impairment scale scores exhibit notable improvement.

e.g.: PMID: 15929052, 20506226, 21493695, 31495331

2. BM-MSCs and UC-MSCs in Spinal Cord Injuries:

- Small non-randomized studies conducted.
- Encouraging findings:
  - Improved Spinal Injury Association Impairment Scale Grade.
  - Enhanced sensory scores.
  - Positive impact on bladder function.

e.g.: PMID: 28235424, 30362373

3. BM-MSCs in Multiple Sclerosis Treatment:

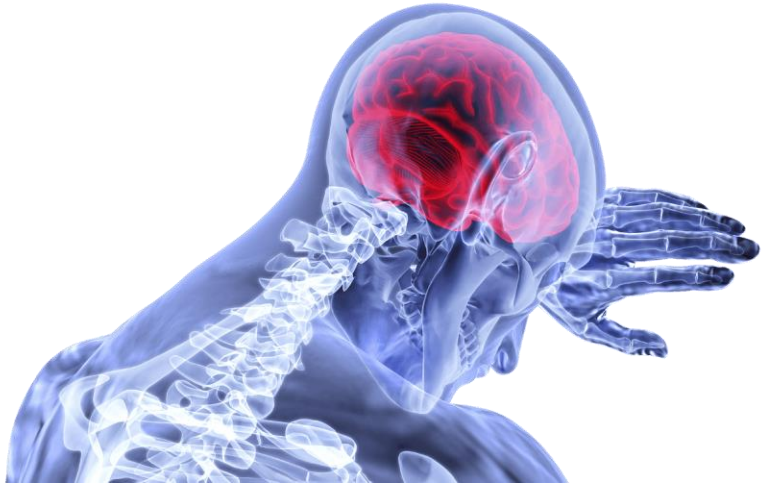
- Significant progress in fine and gross motor function measures.
- Prolonged improvement observed up to 12 months.

e.g.: PMID: 28235424

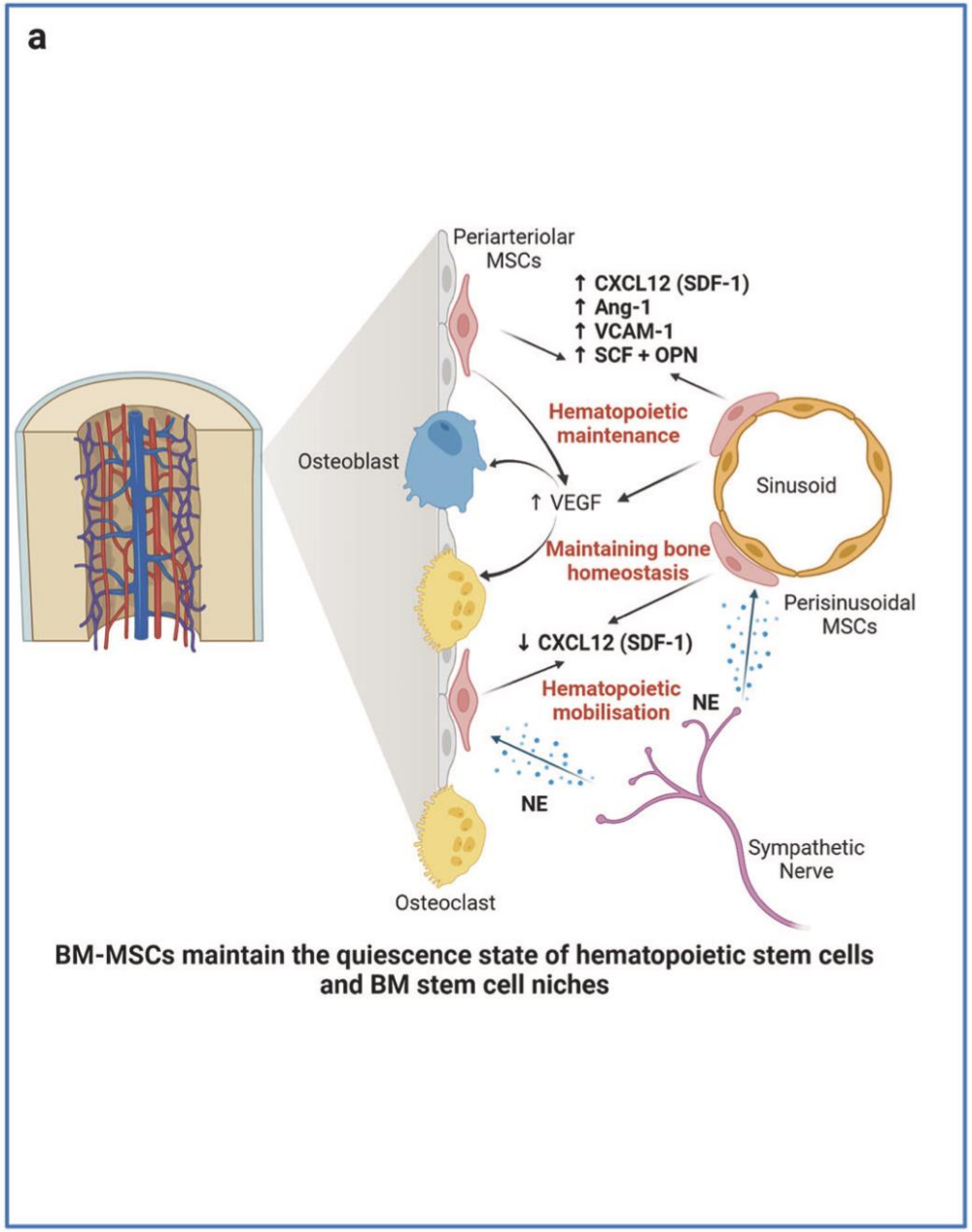
4. BM and UC-MSCs in Autism Spectrum Disorders:

- 90% improvement among 254 children treated with BM-MSCs.
- Positive outcomes on the Indian Scale for Assessment of Autism and Childhood Autism Rating Scale.

e.g.: PMID: 33489466, PMID: 32531111



Mechanisms

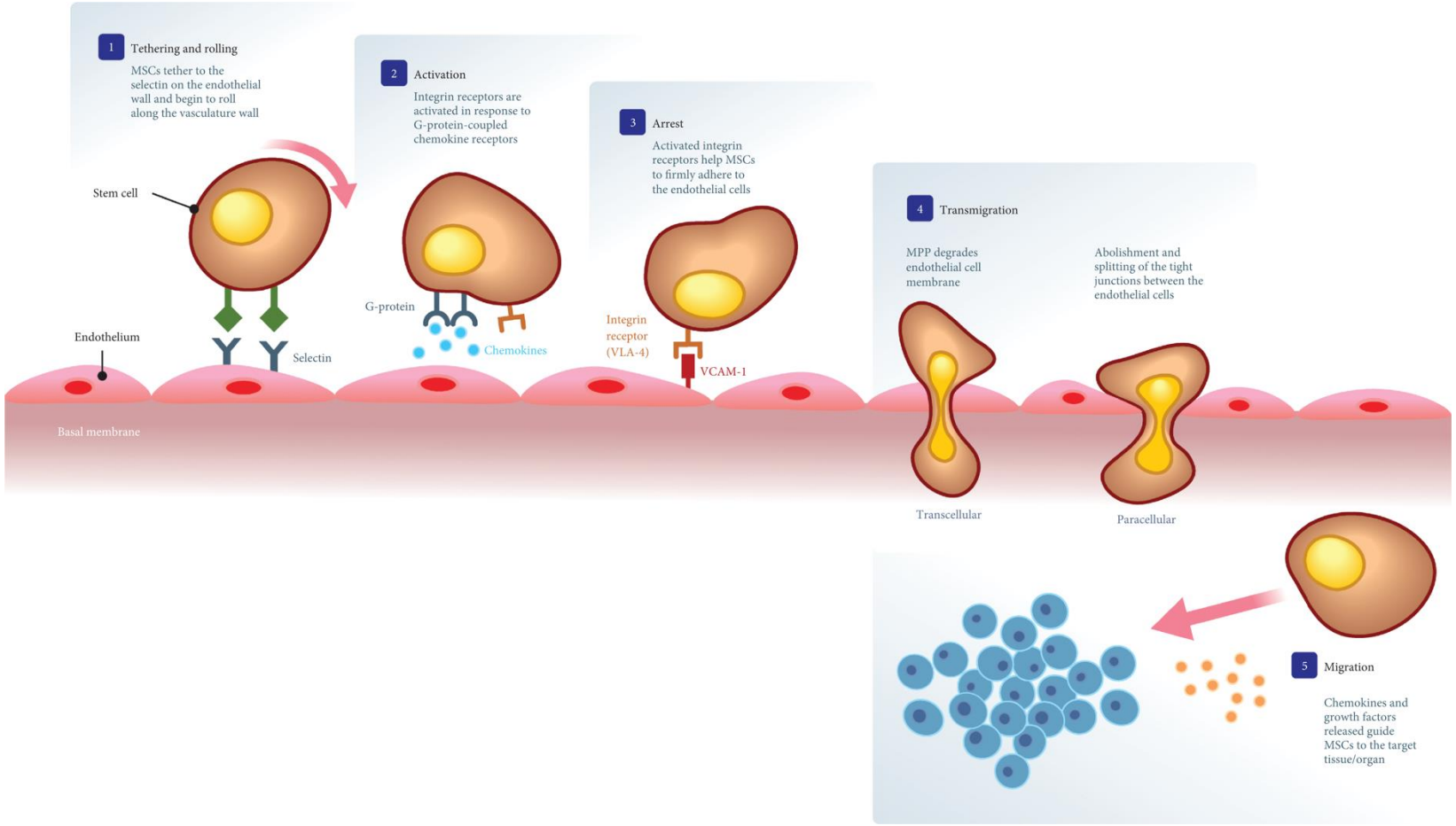


NE:Norepinephrine
SDF-1: Stromal cell-derived factor/C-X-C-chemokine 12
Ang-1: angiopoietin-1
VCAM-1: vascular cell adhesion molecule 1

PMID: 35933430

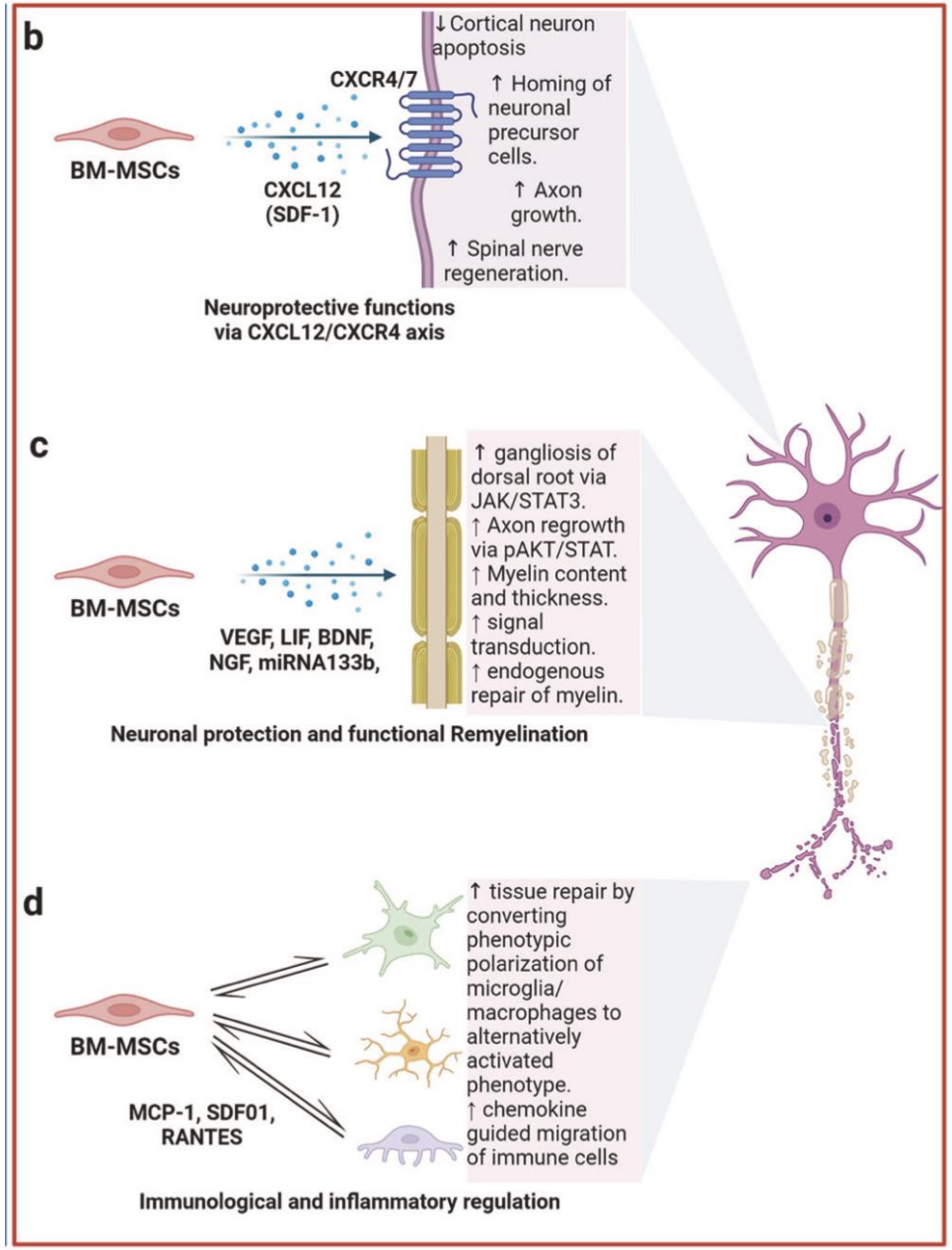
Mechanisms

Blood
Brain
Barier



https://doi.org/10.1155/2020/8889061

Mechanisms



NE:Norepinephrine
SDF-1: Stromal cell-derived factor/C-X-C-chemokine 12

PMID: 35933430

Challenges in MSC-based therapy

1. Post-Administration Concerns:

- Long-term allogeneic cell survival, especially in disease treatment, raises concerns.
- Caution needed for potential embolism events linked to MSC-induced inflammatory reactions.

2. Homing Success:

- Successful homing of infused cells to targeted tissues is vital for lasting patient benefits.

3. Dead Cells and Immunomodulation:

- Studies suggest dead MSCs retain immunomodulatory properties.
- Questions arise about the impact of dead cells in cell-based products on patient health.

4. MSC Source Impact:

- Review poses a challenge: "What is the downstream impact of MSC sources on their application?"

Conclusion

and efficacy of MSCs in the treatment of various diseases. The major conclusion of these studies and trials is that MSC-based therapy is safe, although the outcomes have usually been either neutral or at best marginally positive in terms of the clinically relevant endpoints regardless of MSC tissue origin, route of infusion, dose, administration duration, and preconditioning.[136] It

PMID: 35933430

Learning Objectives

1. **Pluripotent vs Adult Stem Cells:**
    - Differentiate between pluripotent and adult stem cells.
    - Explore their applications in regenerative medicine.

2. **Clinical Trials Unveiled:**
    - Understand the fundamentals of clinical trials.

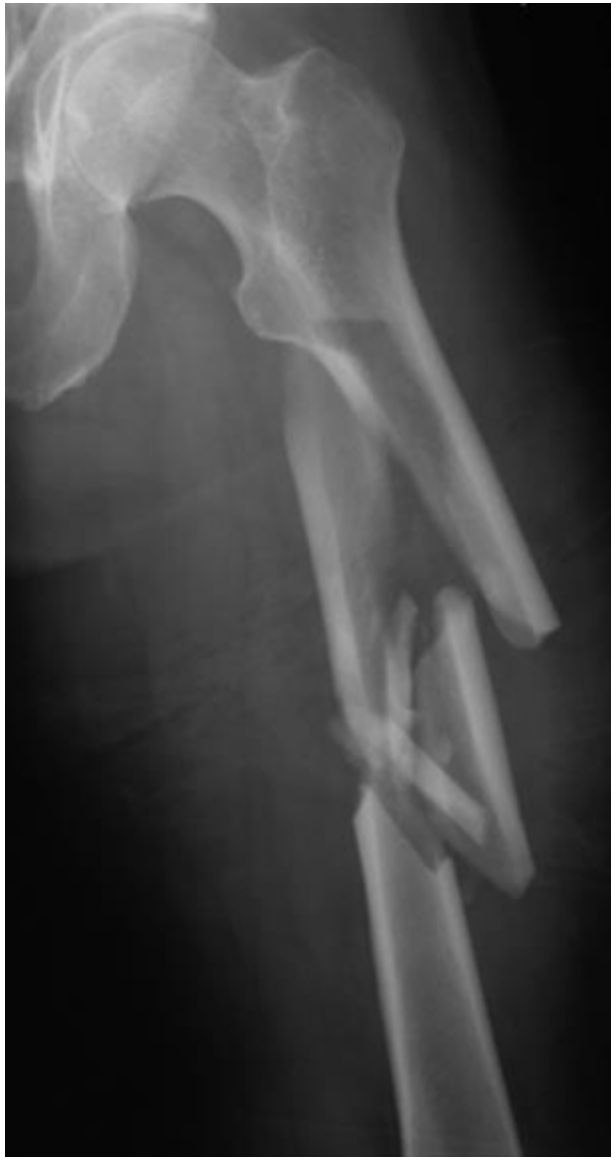
3. **Stem Cells in Action:**
    - Examine real-world examples of stem cell use in clinical trials.
    - Discover their applications in treating various medical conditions.

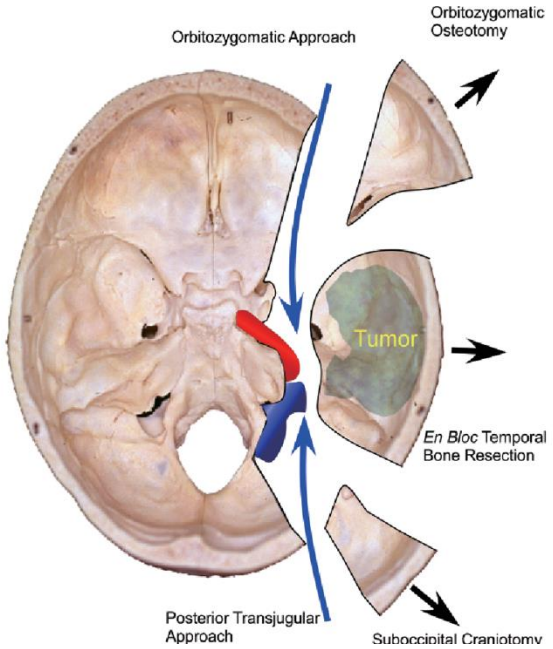
4. **Innovative Bone Repair Technologies:**
    - Explore cutting-edge technologies transforming bone repair.

Significance

Half of all people suffer a broken bone in their lifetime

- Globally aging population
- Bone fractures are 61% non fatal care cost in >65 age

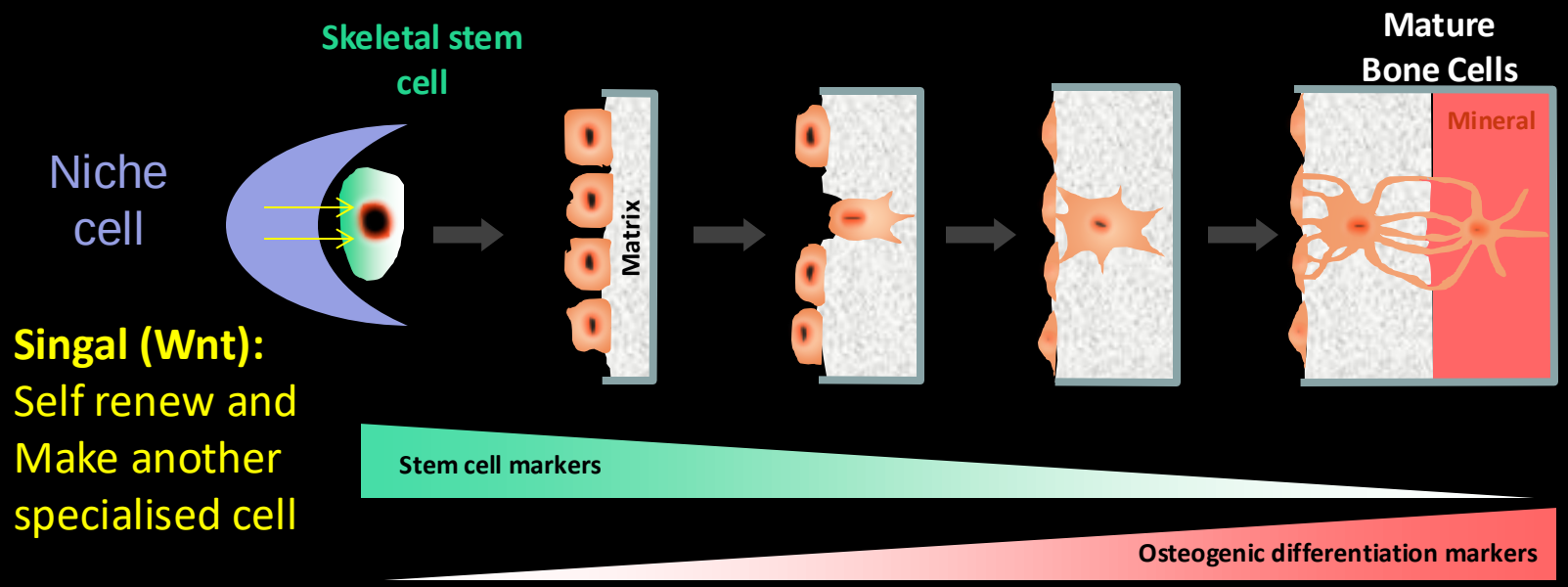




- Radical bone resection.
- Damaged stem cells after Radio Therapy.
- Existence of cancer stem cells

Engineering scalable healthy bone tissues for transplantation

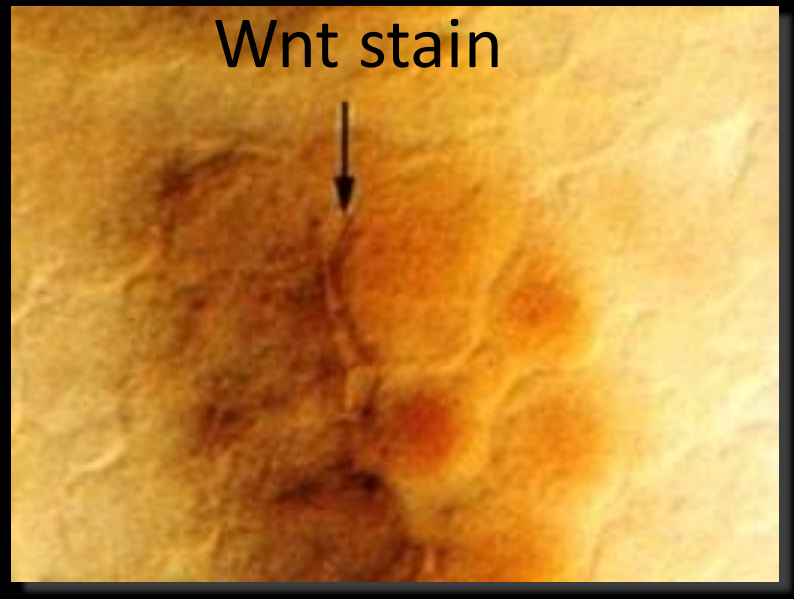
Osteocytogenesis



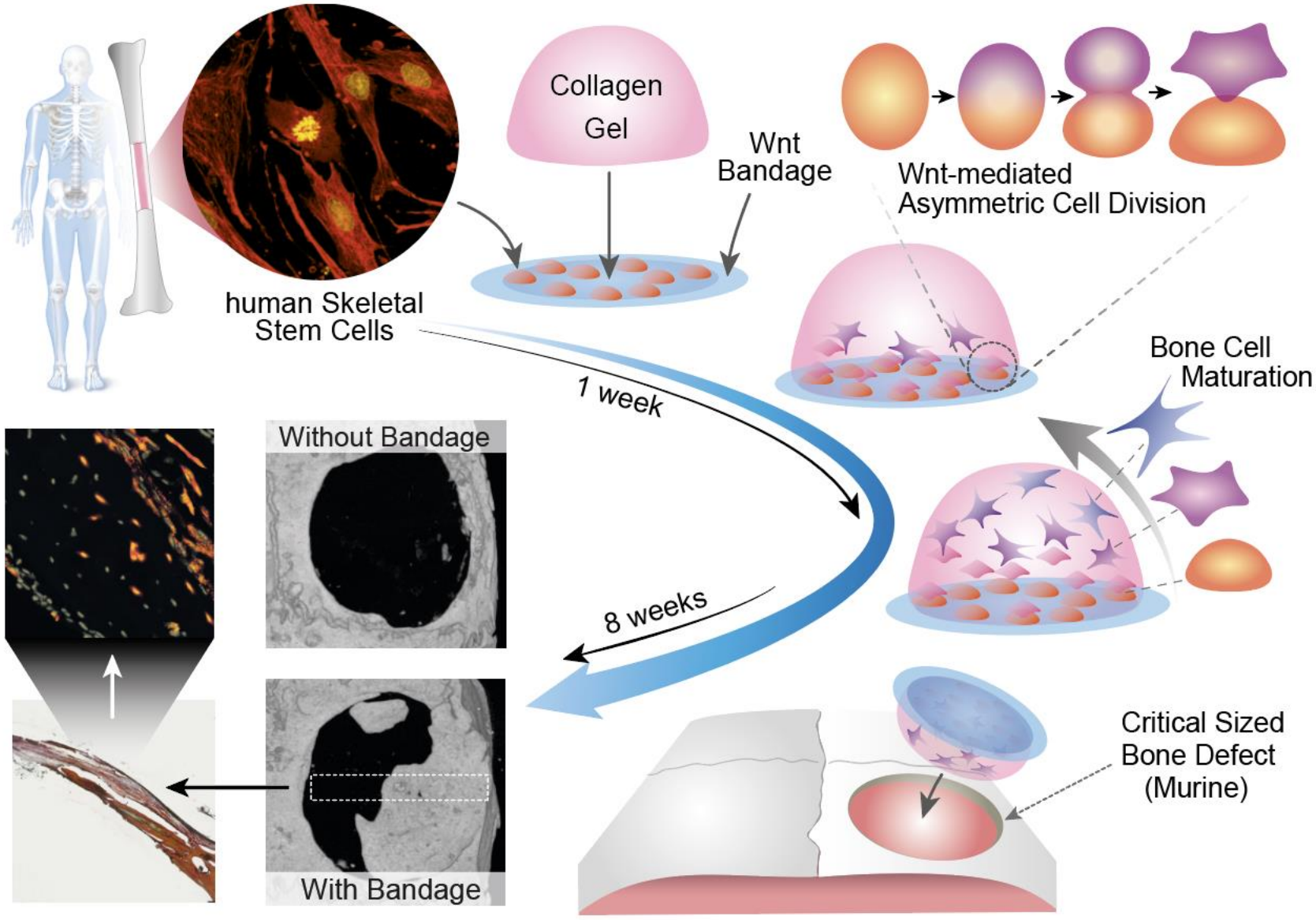
Can we engineer this bone niche *in vitro*?

In vivo, hydrophobic Wnt signals are mostly local and asymmetric

Drosophila embryo



(Van den Heuvel et al., Cell 1989)



Wnt-Induced Osteogenic Model (WIOTM)

Okuchi et al. *Nature Materials* 2021

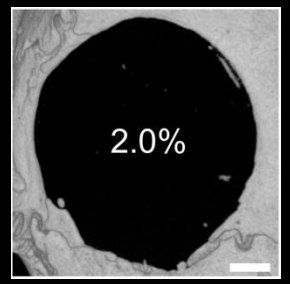
Lowndes M., et al Stem Cell Reports 2016

Lowndes M., et al Nature Protocols 2017

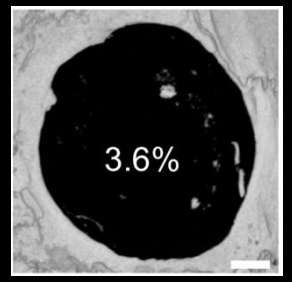
After 8 weeks…µCT

Survival of hSSCs and generation of the first humanized bone in SCID mice

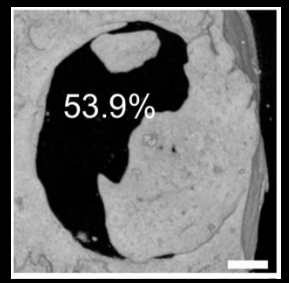
Defect Only

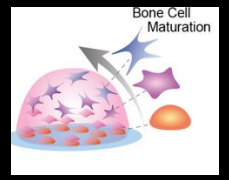


Control-bandage

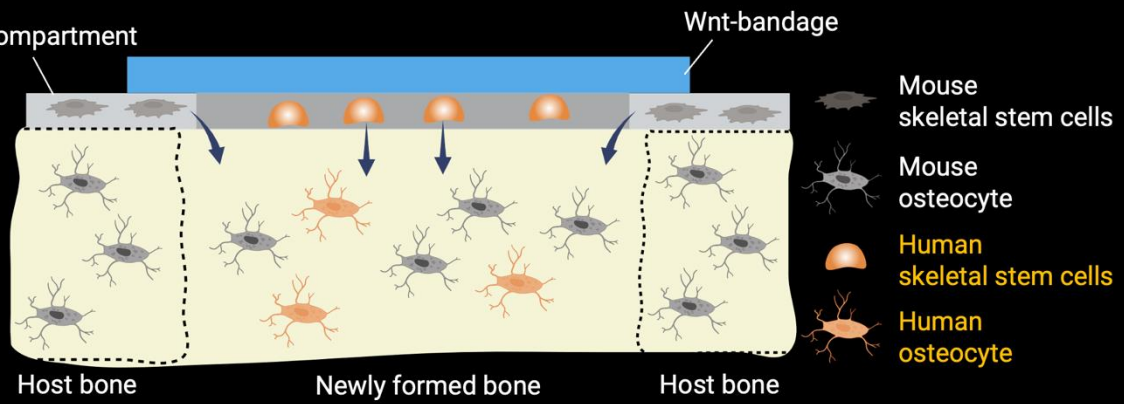


WIOTM-bandage





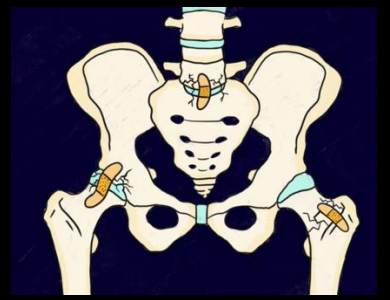
10K cells



Okuchi et al. *Nature Materials* *2021*

Independent.ie

Bandage-like material that can mend broken bones developed by researchers



NOTÍCIASAOMINUTO

Cientistas criam compressa 'milagrosa' que repara ossos partidos

Patent

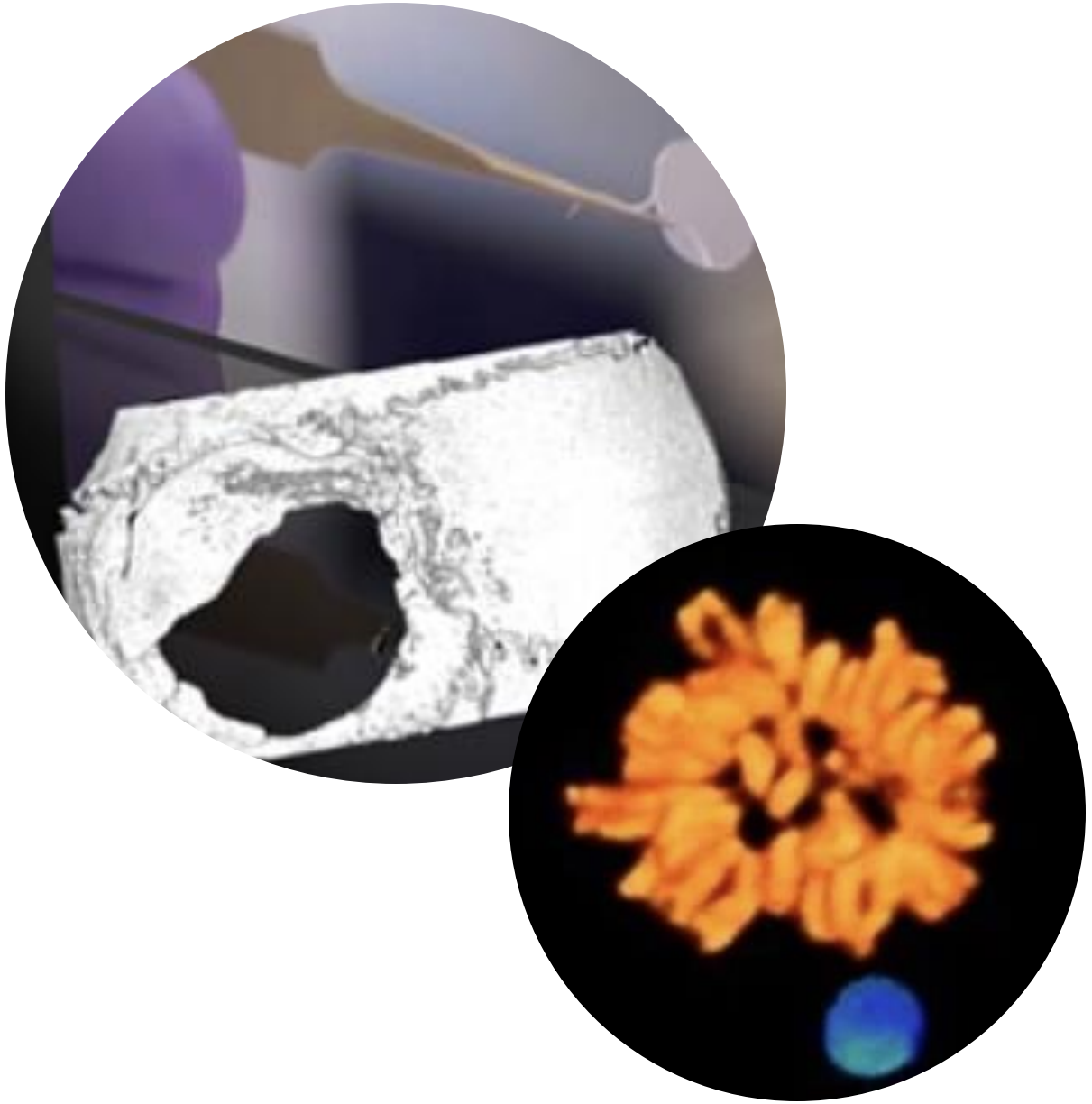
> 107 News Articles

Televised Coverage CBS-News

Preparation for Clinical trials

From Basic Discoveries to Translational Innovations

Exploring Aging

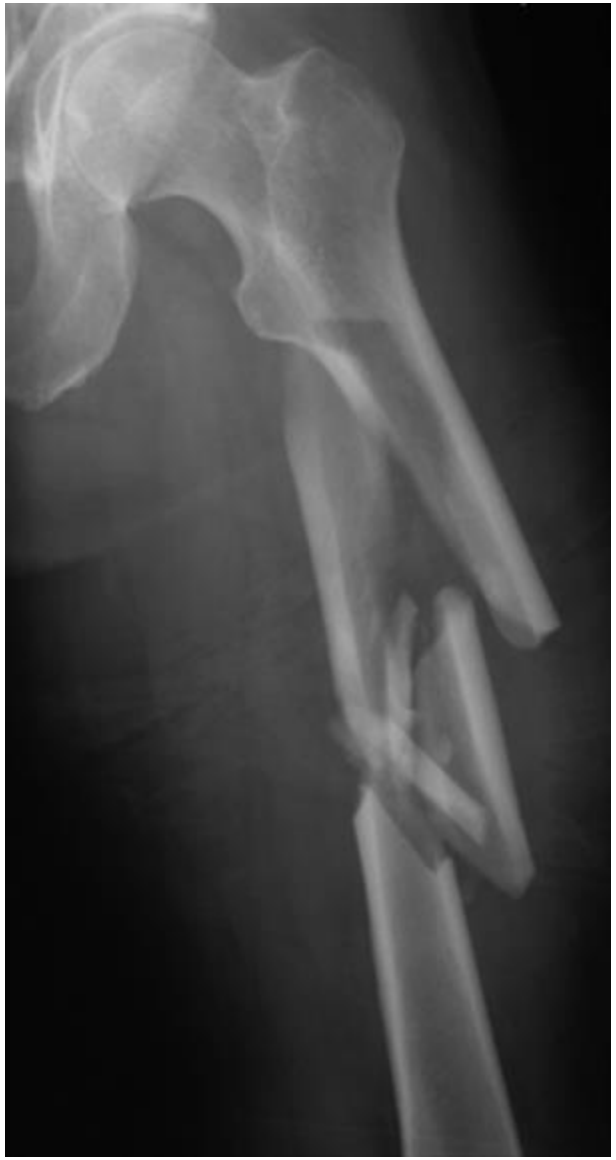


Significance

Half of all people suffer a broken bone in their lifetime

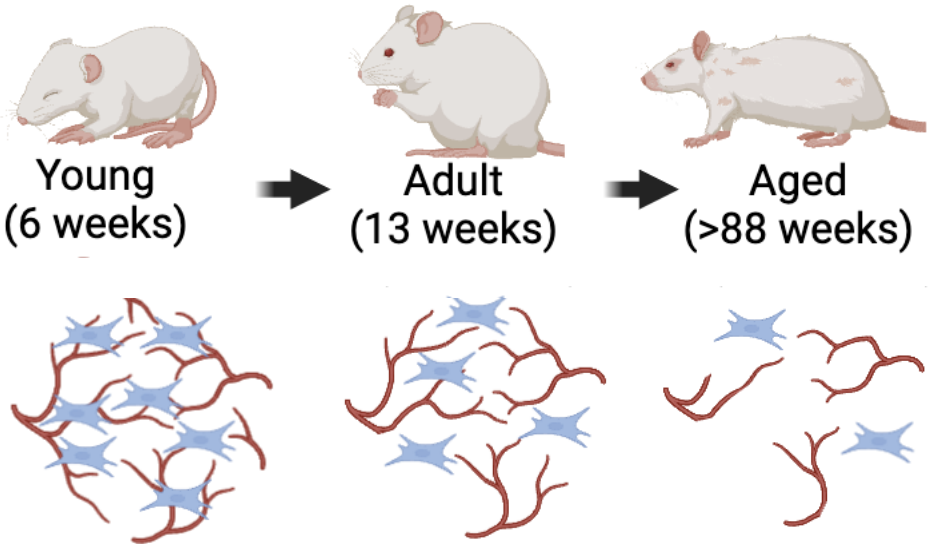
Fractures in children heal fast
Fractures in the elderly heal slowly

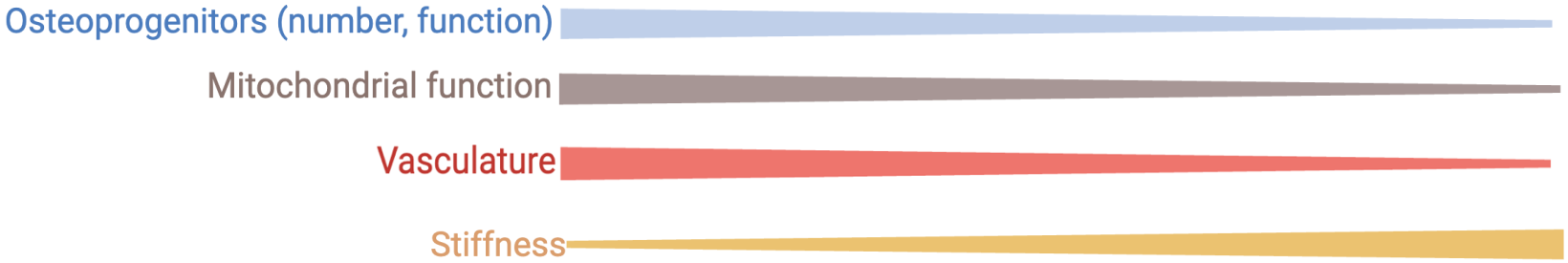
- Globally aging population
- Bone fractures are 61% non fatal care cost in >65 age



Calvarial bone

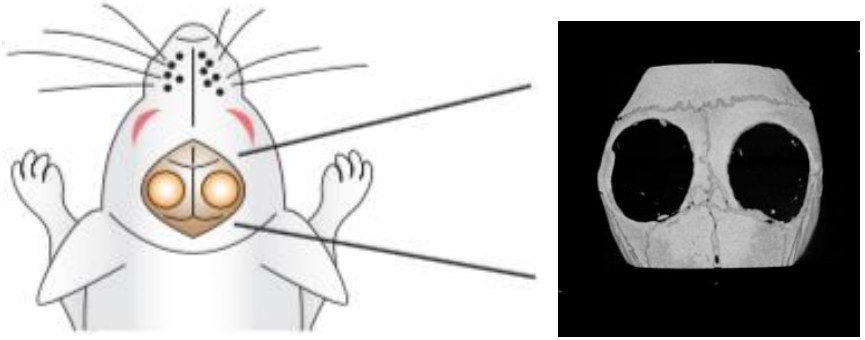
Osteoprogenitors compartments

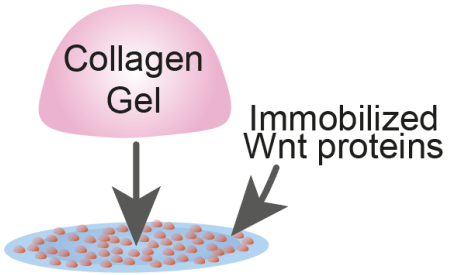


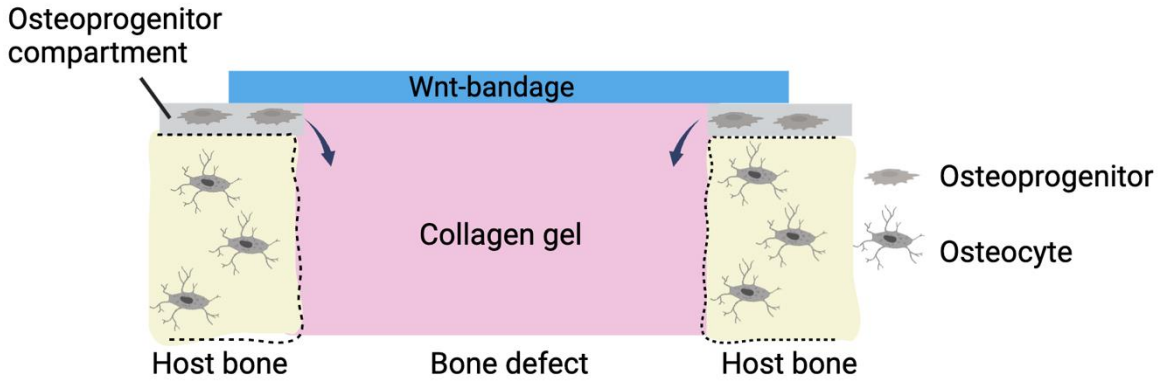


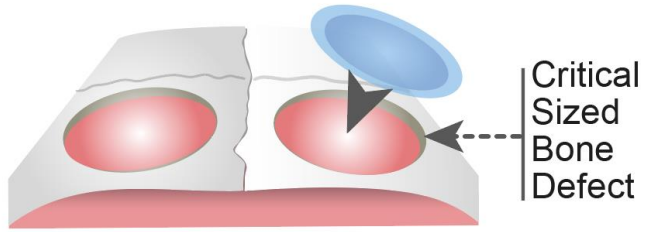
How do aging Osteoprogenitor compartments respond to injury?

Calvarial critical size-defect



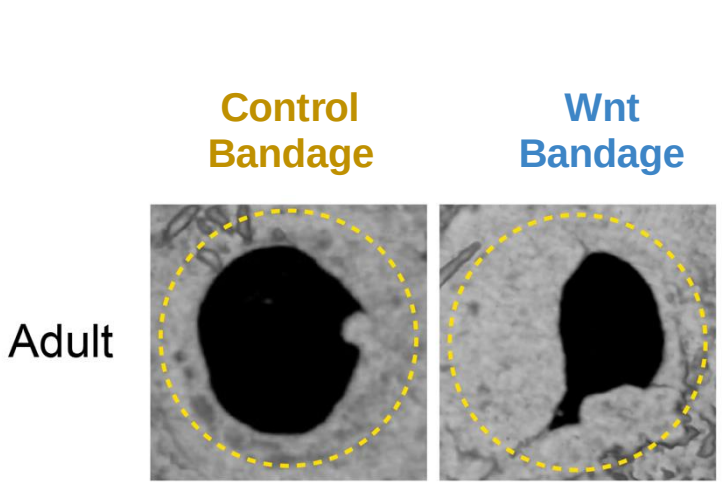


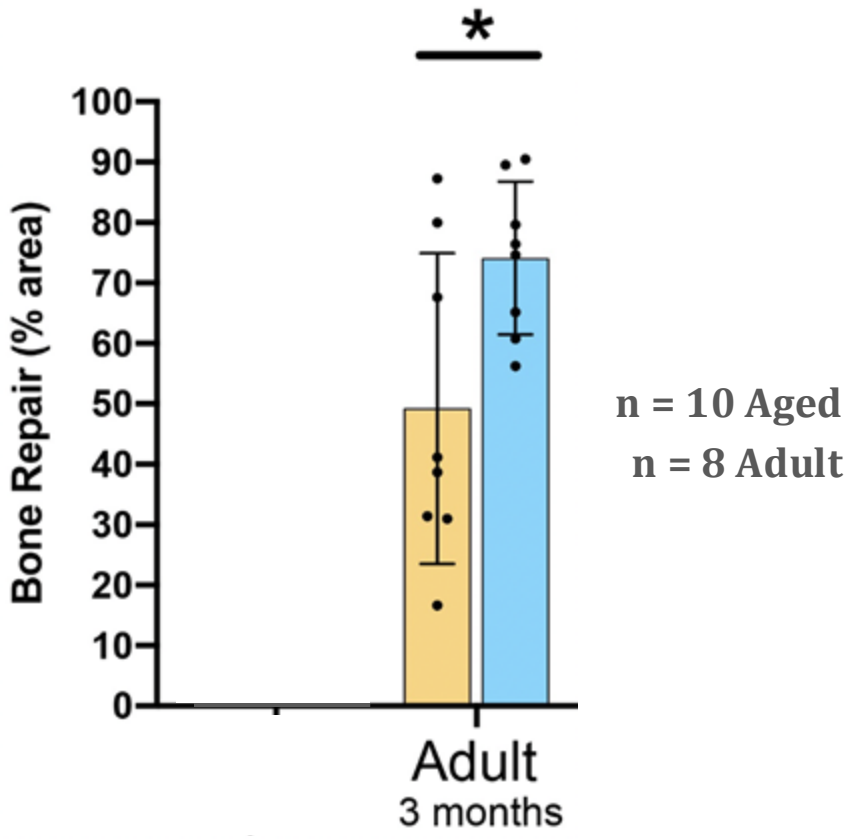




Calvarial critical size defect

Wnt-bandages can improve bone repair in Aged mice

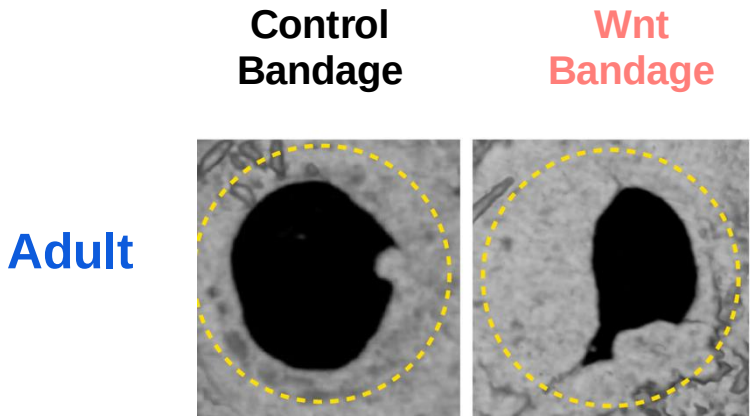


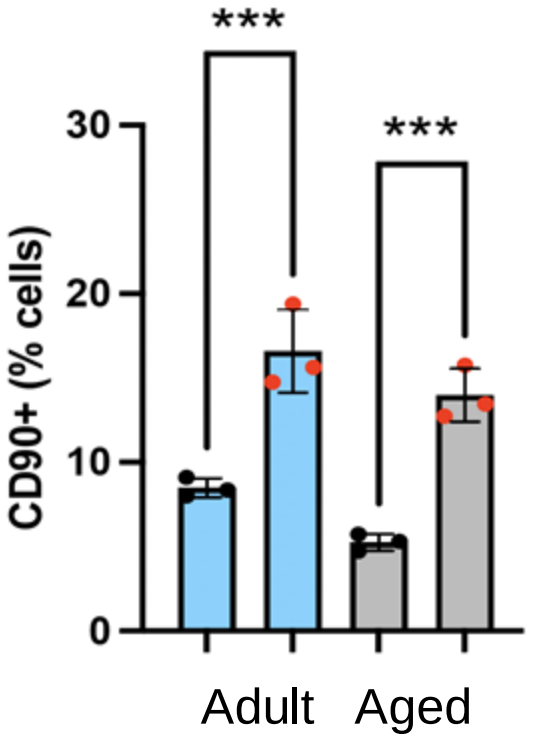


n = 10 Aged
n = 8 Adult

Wnt-bandage improves bone repair in Adult and Aged mice

Wnt-bandages increases the number of SSCs in Aged mice

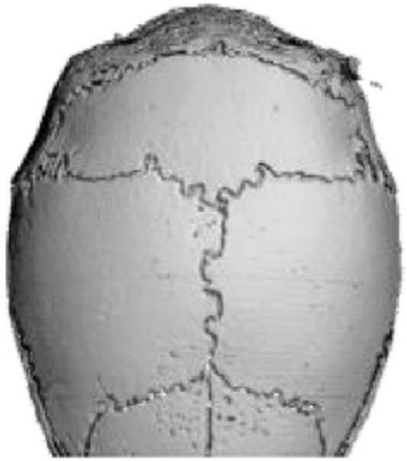




But SSC/progenitor number alone is <u>insufficient</u> to efficiently rejuvenate bone repair in Aged mice

Can the SSC compartments in Aged mice be rejuvenated ?

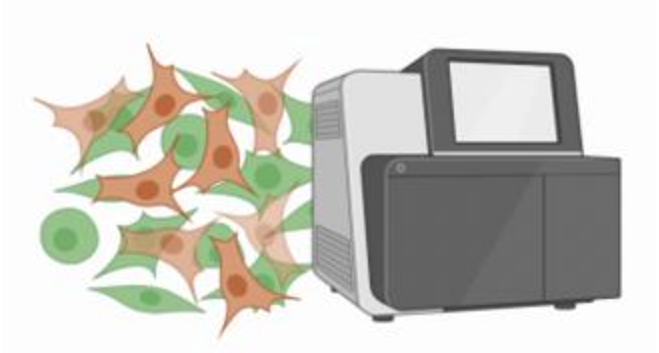
Single RNAseq of osteoprogenitor cell compartments



Young

Adult

Aged



Aging

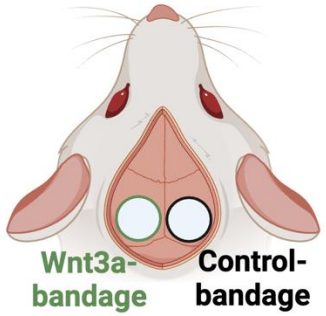
Mitochondrial complex II, NAD+ biosynthesis → **Energy metabolism**

How to improve whole body energy metabolism?

Aging

Mitochondrial complex II, NAD+ biosynthesis → **Energy metabolism**

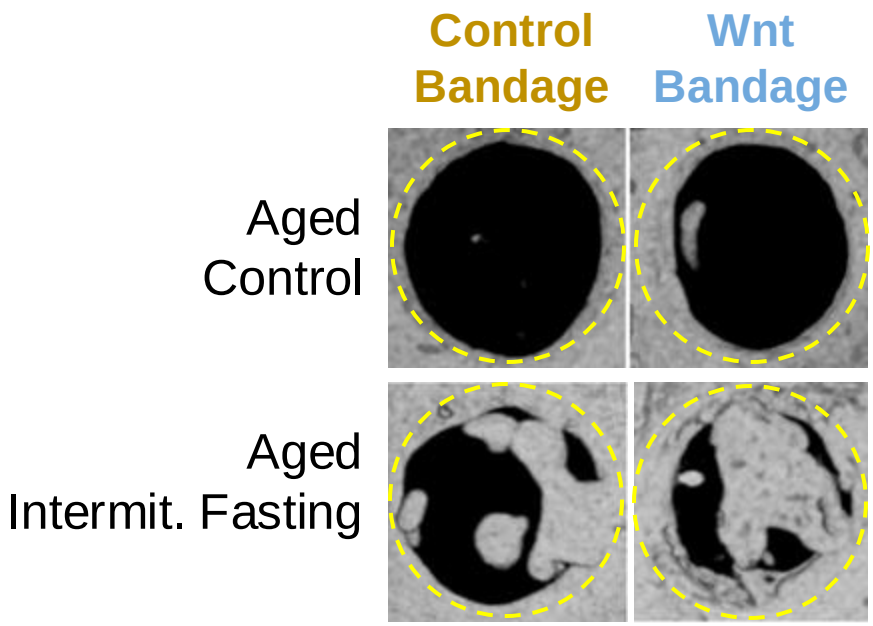
Intermittent fasting

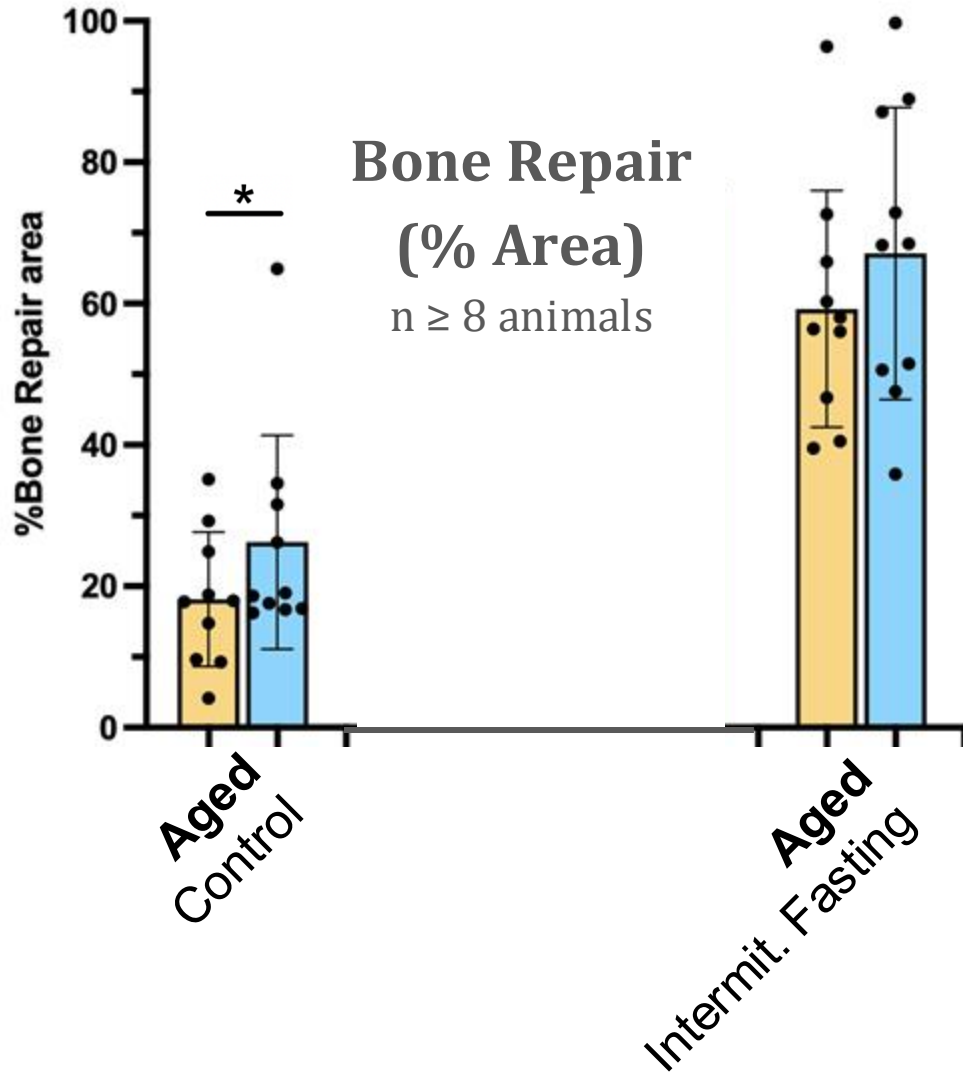


Alternating Fed/Fasting 24hr

Hu, D et al (2020) Hepatobiliary Surg Nutr
Sbierski-Kind, J. et al (2022) Microbiome
Zou, H. et al (2020) Nutrients
di Francesco, A et al (2018) Science

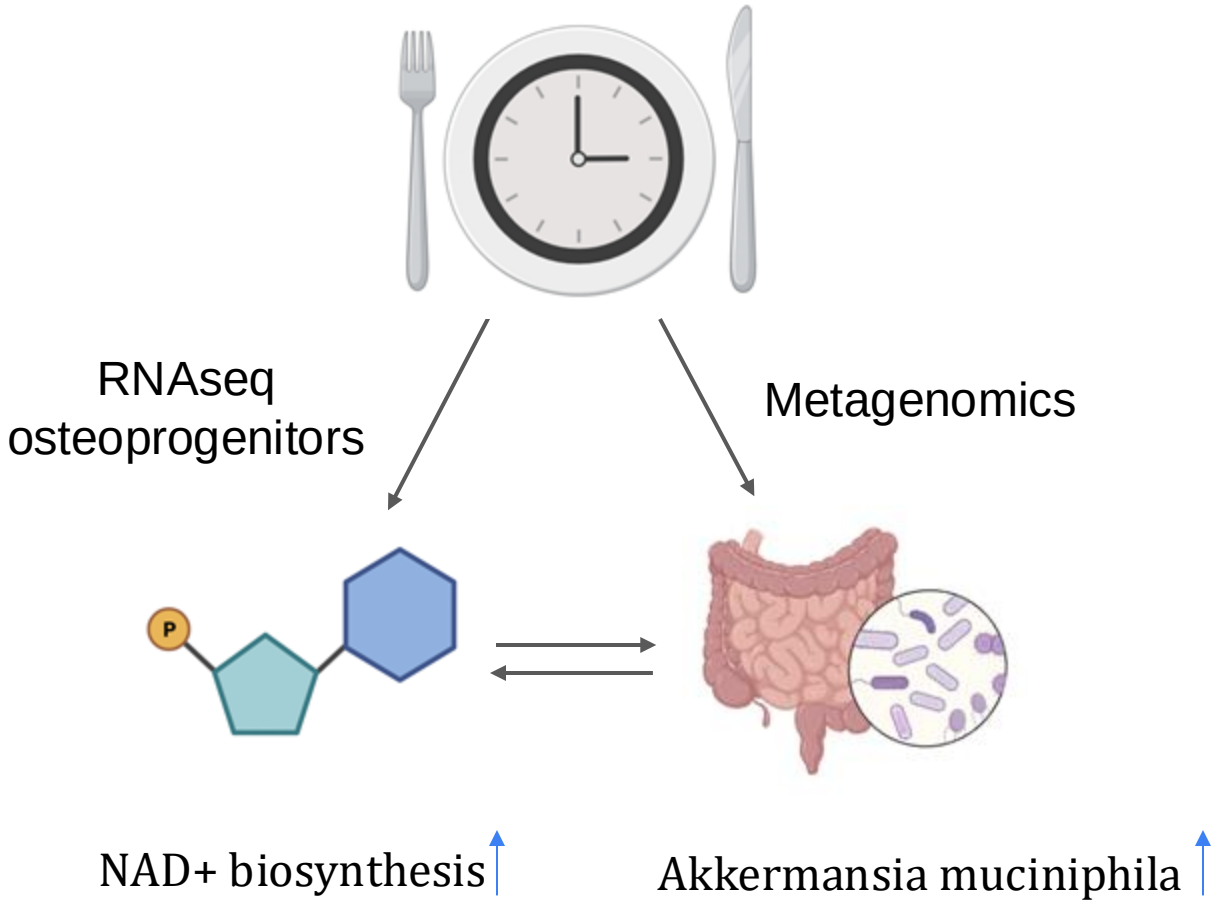
Bone repair improved in Aged mice





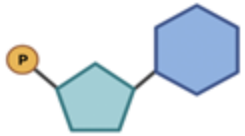
Intermittent fasting

Alternating Fed/Fasting 24hr
Equal calories to standard diet



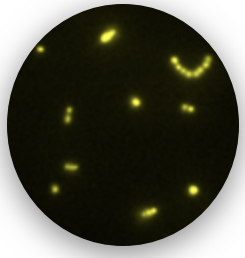
Short term supplementation of NMN or AKK

NAD⁺ precursor (NMN)



or

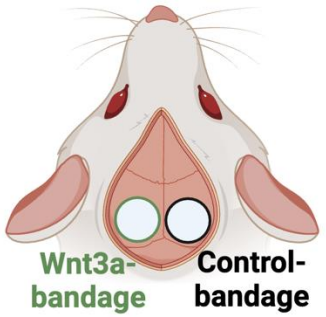
Akkermansia muciniphila



Treatment

2 weeks

Calvarial defect



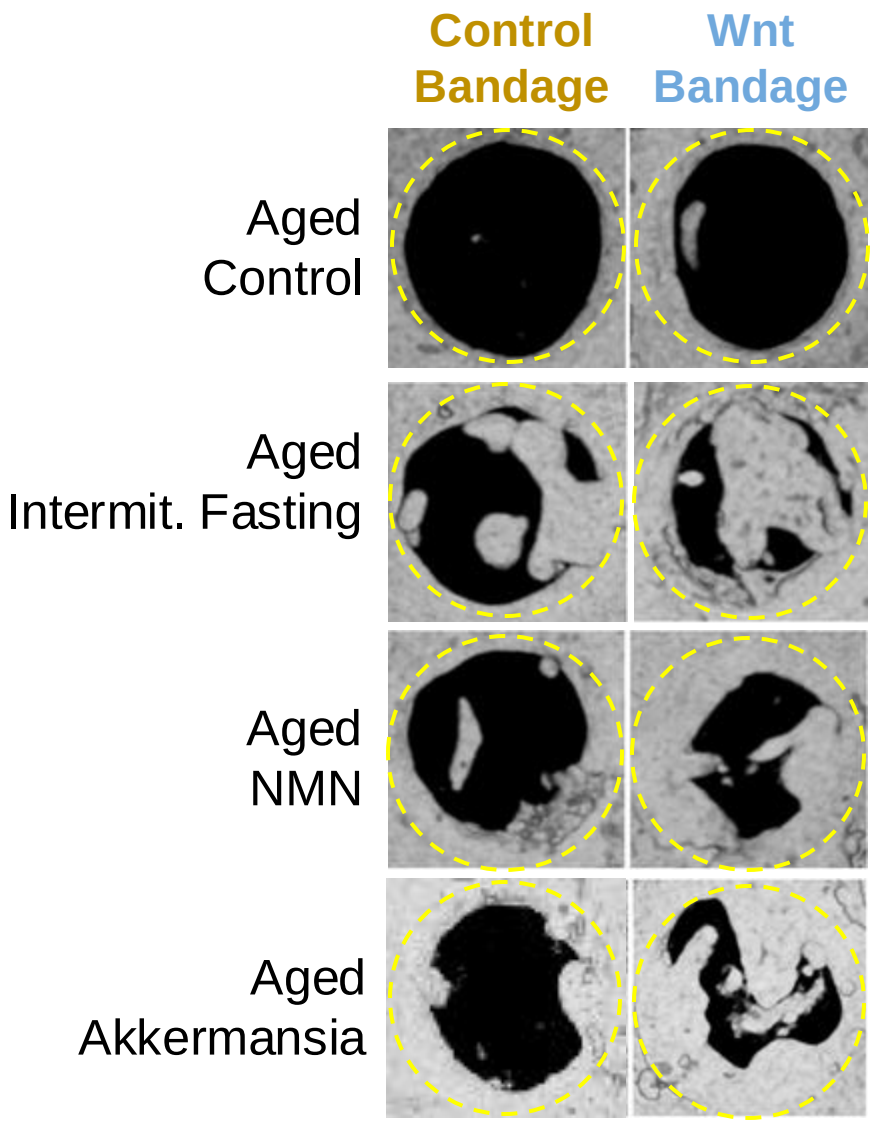
Treatment

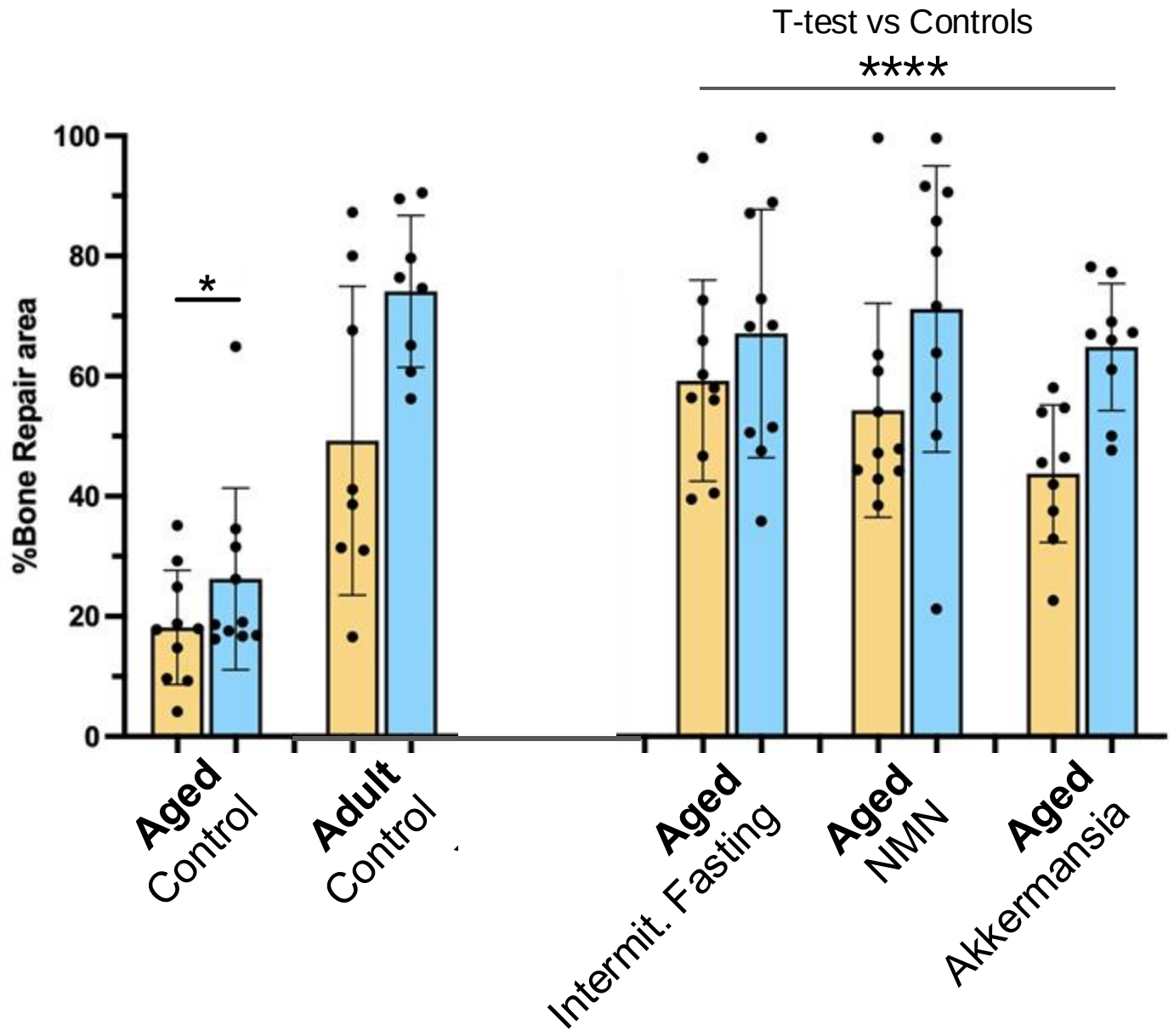
2 weeks

8 weeks

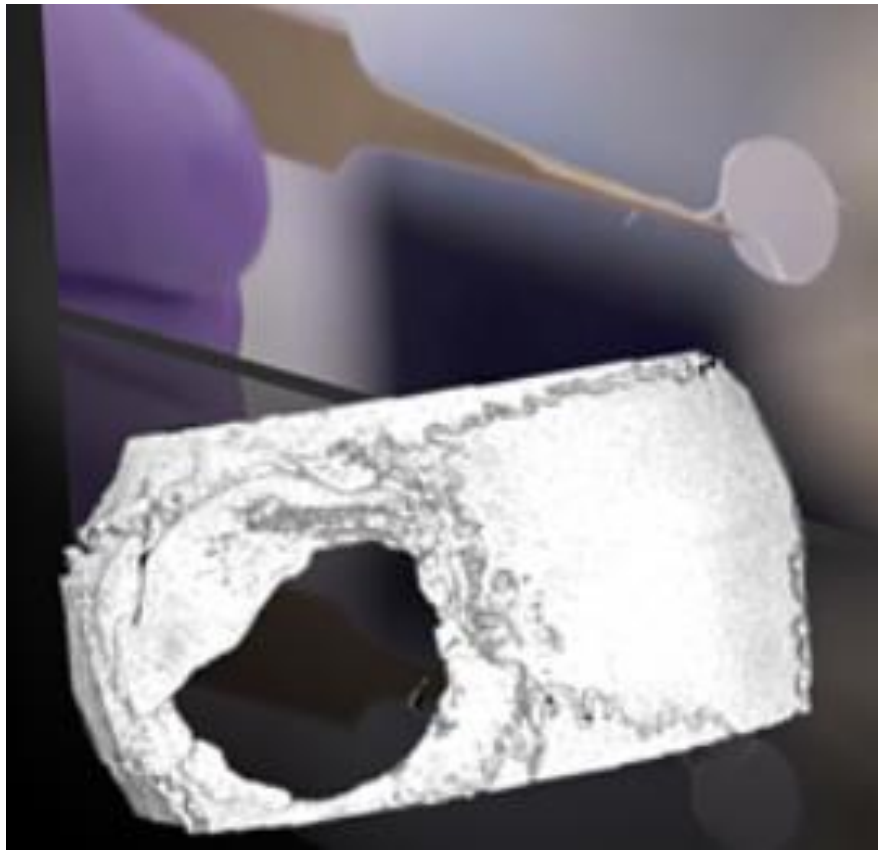
μCT

Short term supplementation of NMN or AKK rejuvenate aged bone repair

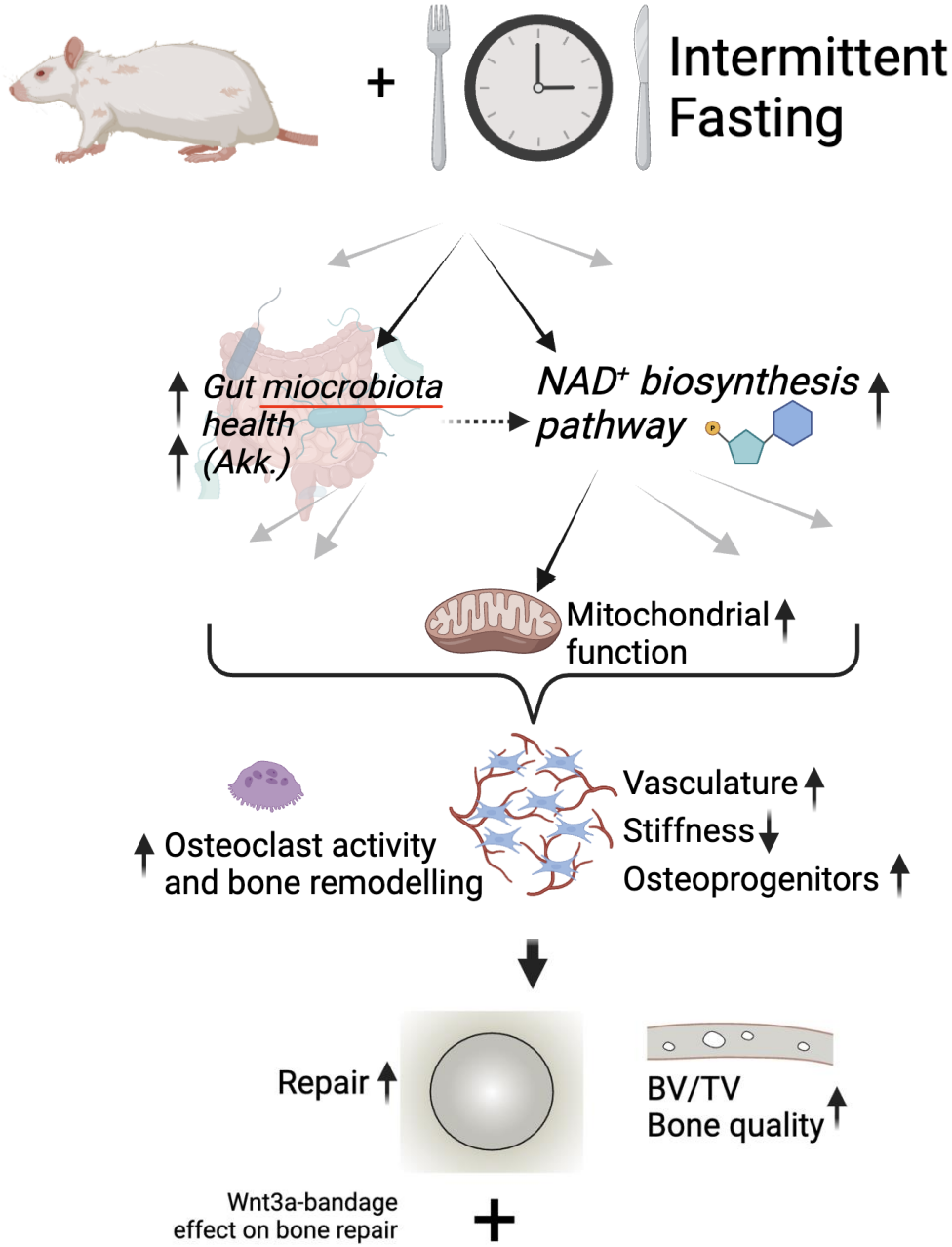




Conclusions

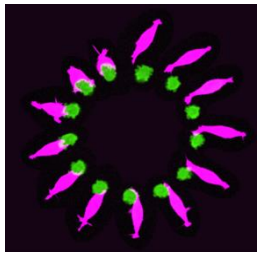


- Wnt-bandge promotes bone repair.
- Wnt-bandage increases the number of SSCs/progenitors.
- Increase of SSCs/progenitors alone is insufficient to promote efficient bone repair in aged mice.

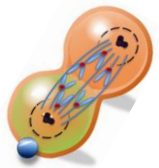

Intermittent Fasting
Gut miocrobiota health (Akk.)
NAD+ biosynthesis pathway
Mitochondrial function
Osteoclast activity and bone remodelling
Vasculature
Stiffness
Osteoprogenitors
Repair
BV/TV
Bone quality
Wnt3a-bandage effect on bone repair

Localized Wnts:

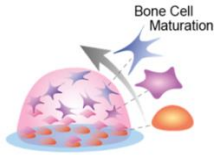
- Coordinate cell-cell interactions and drive morphogenesis.

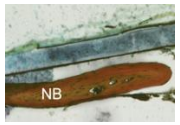


- Mediate asymmetric stem cell division.

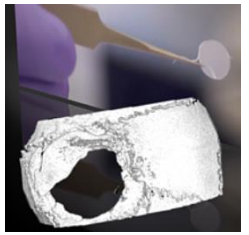


- Direct organized formation of organoids (in vitro) and tissues (in vivo).





- Promote tissue repair.



- In combination with whole-body energy metabolism, can rejuvenate aged osteoprogenitors for bone repair.

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Habib Lab

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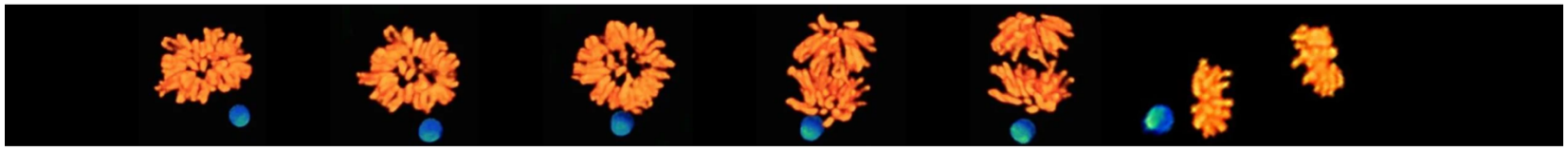
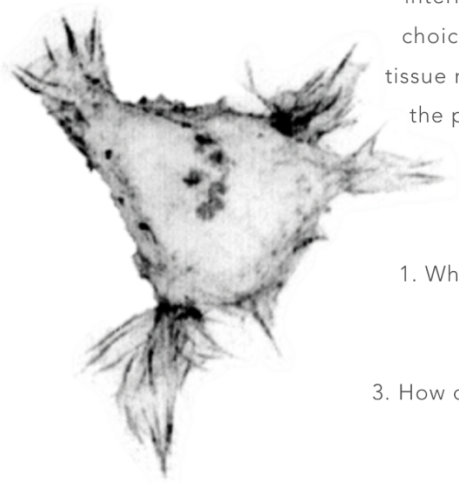
Homeostasis | Regeneration | Tumorigenesis

Department of Biomedical Sciences
Université de Lausanne



About Our Lab



Stem cells have the ability to make more stem cells (self-renew) and also to give rise to differentiated cells. We are interested in the external and internal cues that regulate mammalian stem cell division and cell fate choice. We aim to study and compare these cues during homeostasis, tissue regeneration and tumorigenesis. Additionally, we are interested in the parallels between cellular mechanisms in adult regeneration and embryonic development.

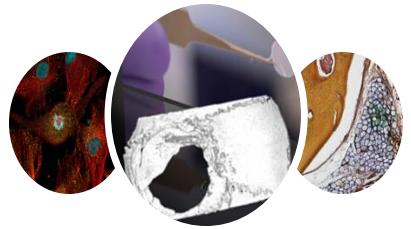
Many questions about tissue formation:

1. What intracellular and extracellular molecular cues control stem cell division and fate specification?
2. How do cells sort and self-organise to generate tissues?
3. How can we direct stem cell division to engineer organised human tissue models *in vitro* for regenerative medicine applications?

We are also especially interested in the interaction between ageing and metabolism, and the effect of both on stem cell function & regenerative potential.

https://www.habiblab.org/

Open MSc thesis positions



Open PhD positions

https://www.youtube.com/watch?v=qDKHJsxscUw
https://www.youtube.com/watch?v=8gRpjwmbdJQ
https://www.youtube.com/watch?v=k3EvdEGEopU
https://www.youtube.com/watch?v=zstKQhnt8dM