دانشگاه علوم پزشکی
و خدمات بهداشتی درمانی تهران

EMRI
پژوهشگاه علوم غدد و متابولیسم
دانشگاه علوم پزشکی تهران

Revolutionizing Endocrinology: The Latest Breakthroughs in Cell Therapy

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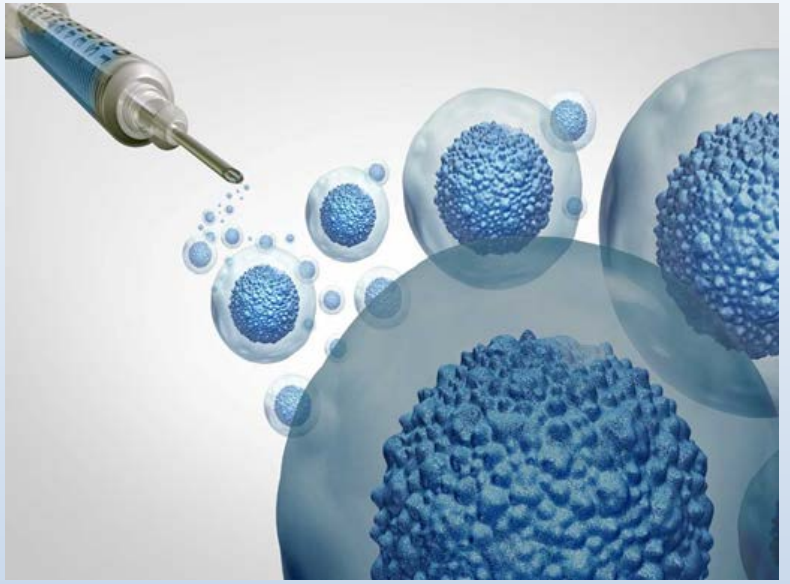
Endocrinology & Metabolism Research Center
Endocrinology & Metabolism Research Institute Tehran
University of Medical Sciences
22 November 2023

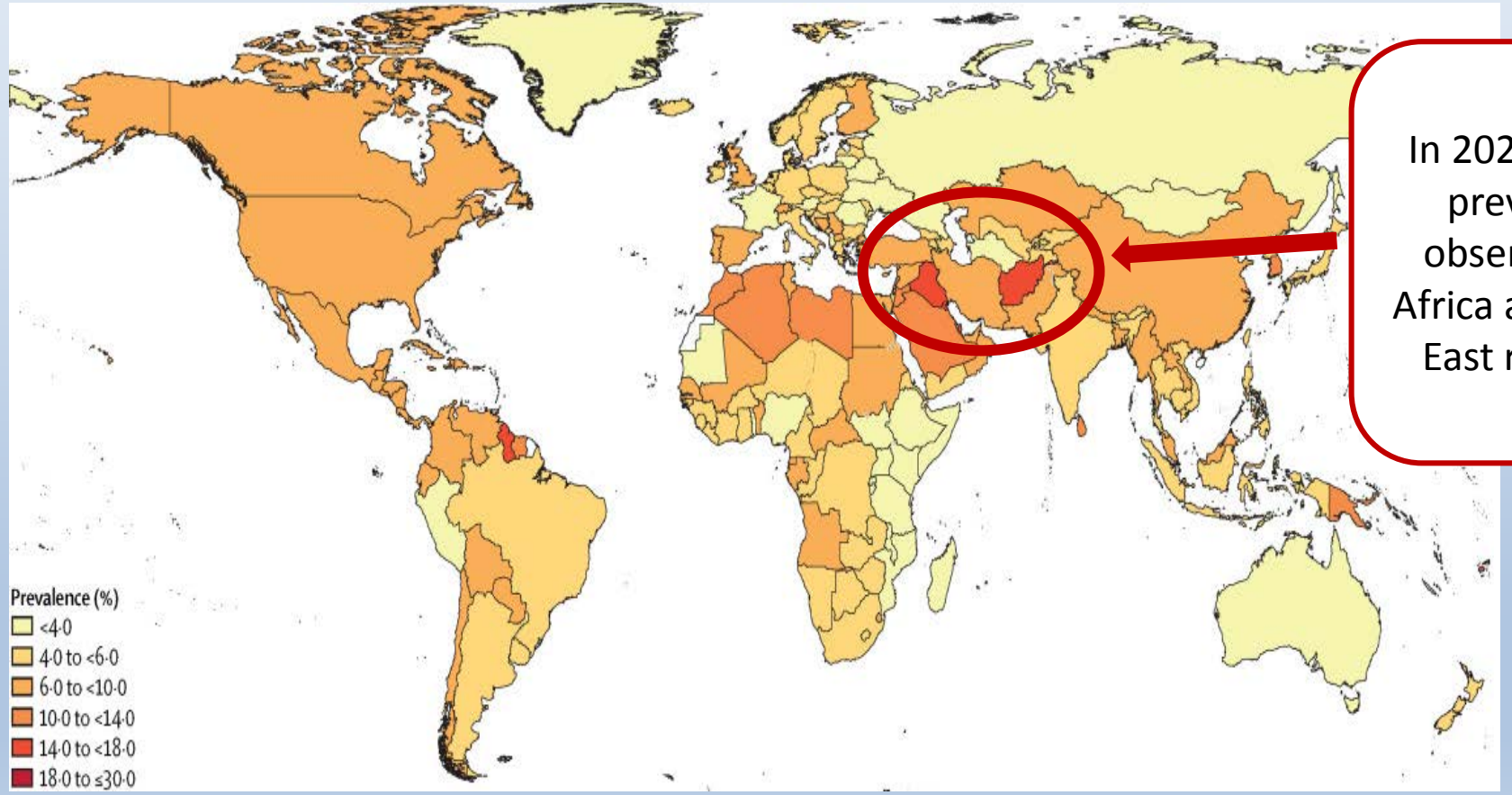
Outline



- A brief review of regenerative medicine
- New achievements in diabetes cell-based therapies
- Cell-based therapies in osteoporosis
- Our works & experiences in field of regenerative therapies for diabetes and its complications

Worldwide Age-Standardized Prevalence of Diabetes based on GBD 2021

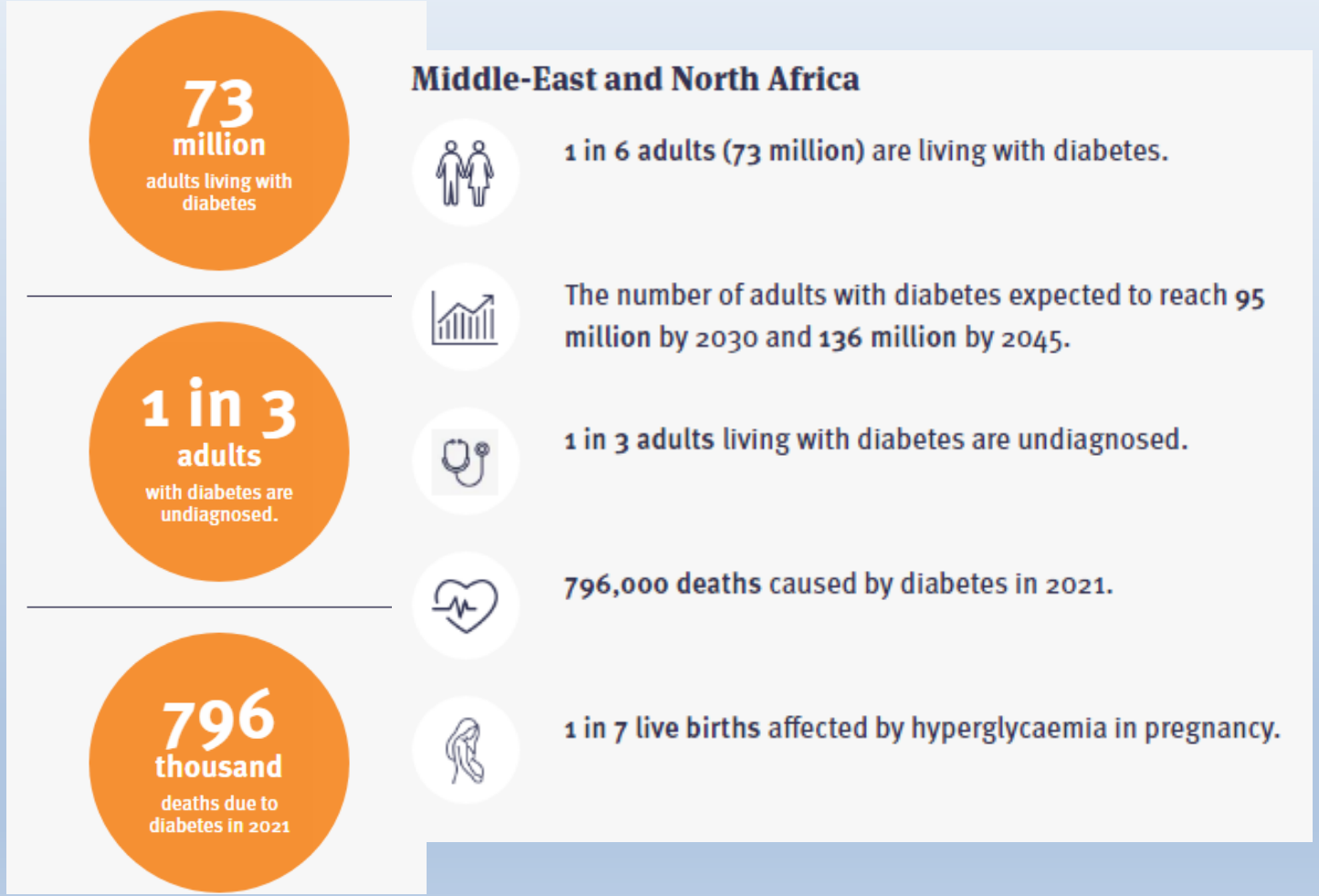
- The global prevalence of diabetes from 1990 to 2050: 3.2% to 6.1% (increased by 90.5%)



In 2021, the highest prevalence was observed in North Africa and the Middle East region = 9.3%

Ong, Kanyin Liane, **Larijani B**, et al. "Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021." *The Lancet* (2023).

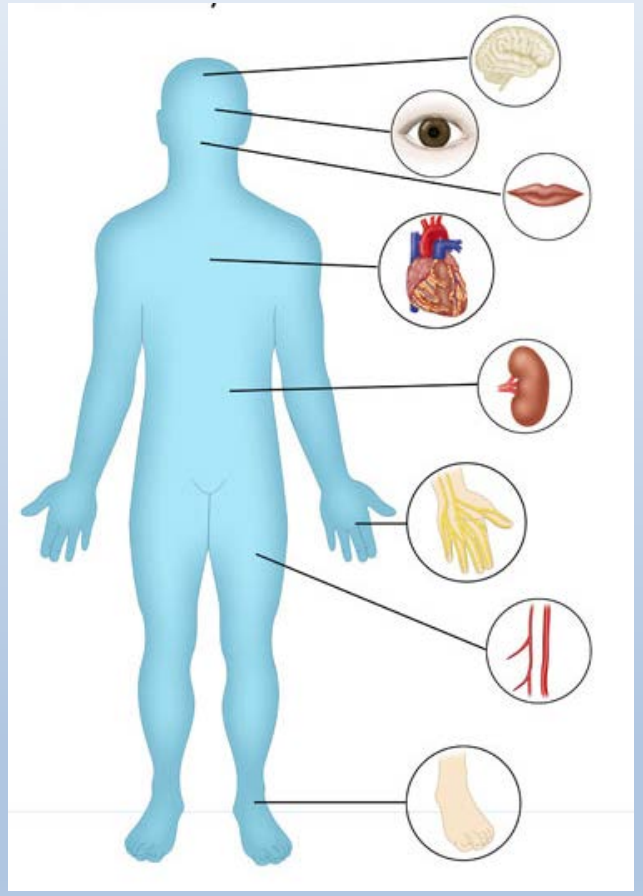
DM in MENA



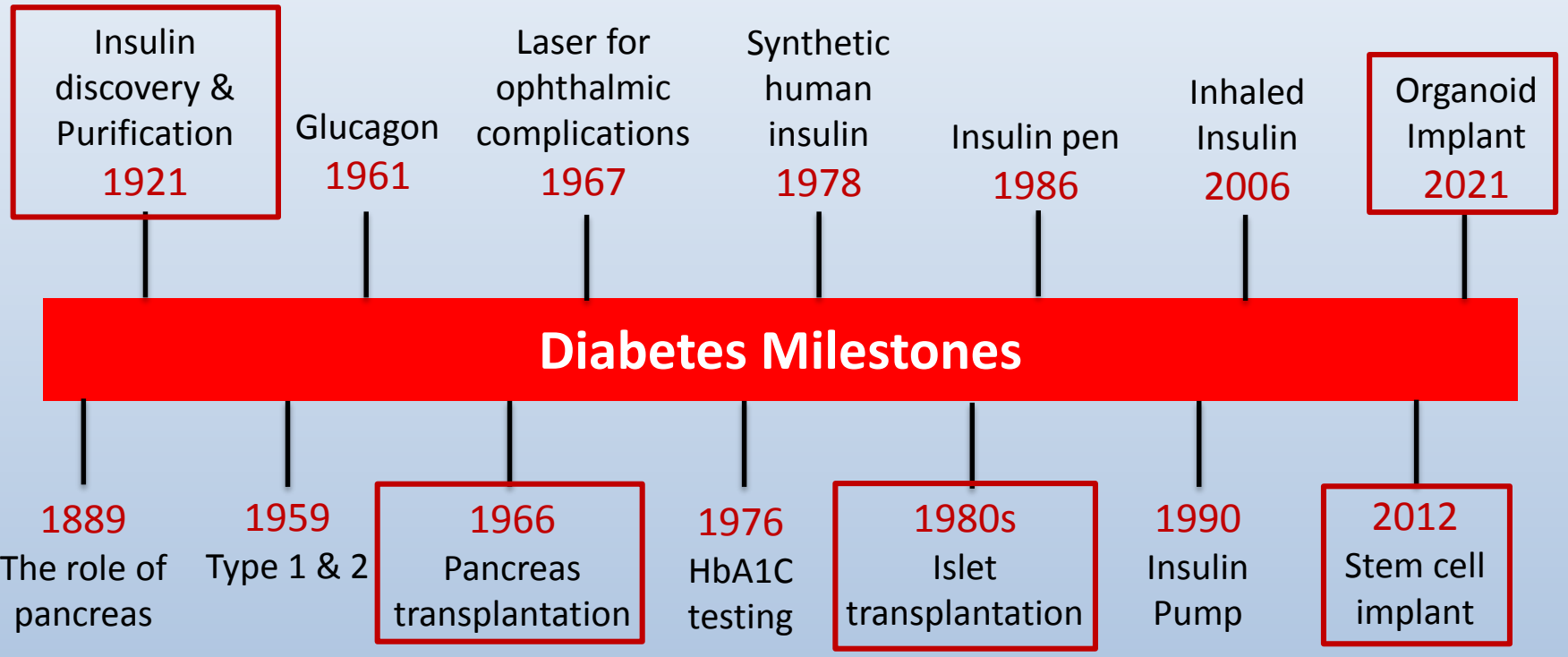
IDF Diabetes Atlas 10th edition: https://diabetesatlas.org/

Diabetes treatment

- Main objectives
  - Control of blood glucose level
  - Reduction of future complications
- Treatment modalities
  - Change in lifestyle
  - Alternative medicine
  - Pharmaceuticals
  - Insulin therapy
  - Surgical procedures
  - Regenerative medicine



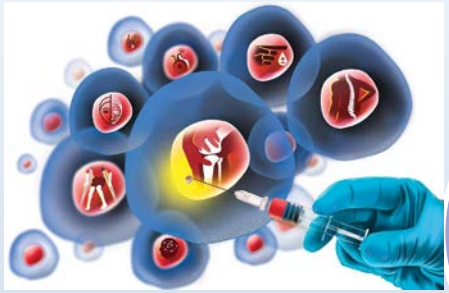
Diabetes timelines

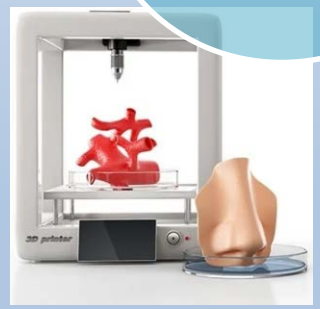


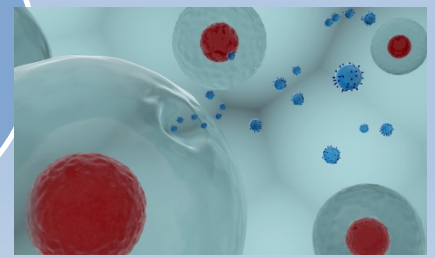
Hoang DM, et al.. Stem cell-based therapy for human diseases. Signal transduction and targeted therapy. 2022 Aug 6;7(1):272.

Regenerative medicine (RM)

Regenerative medicine may be defined as the process of replacing or "regenerating" human cells, tissues or organs to restore or establish normal function.







Arjmand B, Goodarzi P, Mohamadi-Jahani F, Falahzadeh K, **Larijani B**. Personalized Regenerative Medicine. Acta Med Iran. 2017 Mar;55(3):144-149. PMID: 28282715.

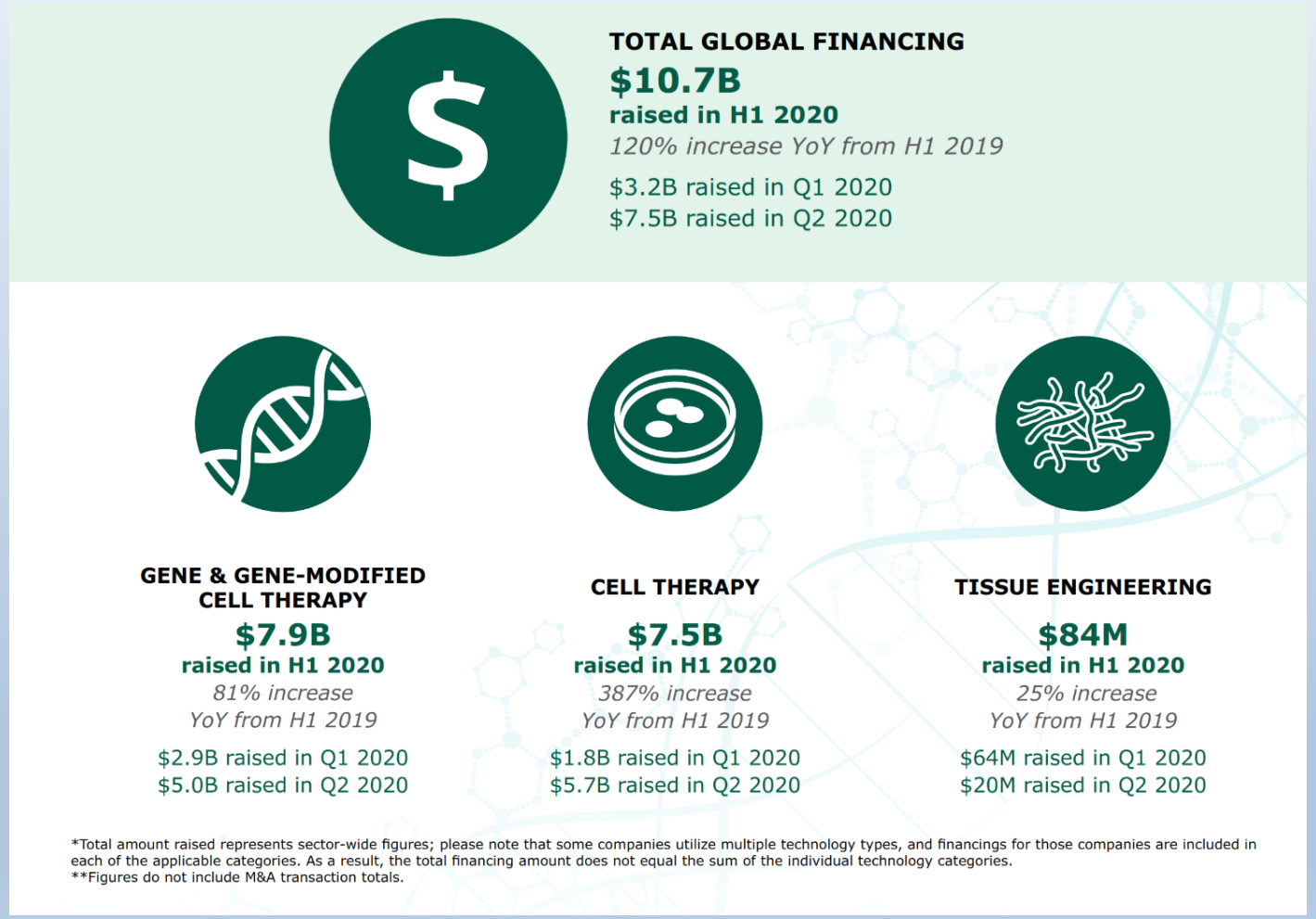
How cell therapy is a promising area of research for endocrine disorders

- Cell therapy replaces damaged or dysfunctional cells with healthy ones.
- It can be used to replace hormone-producing cells in endocrine disorders.
- Stem cells have been used to create functional beta cells in the lab, which improves blood sugar control.
- Cell therapy is a promising way to treat endocrine disorders by restoring hormonal balance and function.
- Advances in cell manipulation techniques, like gene editing and tissue engineering, may improve the effectiveness of cell-based therapies for endocrine disorders.

Alliance for Regenerative Medicine

ARM H1-2020 report

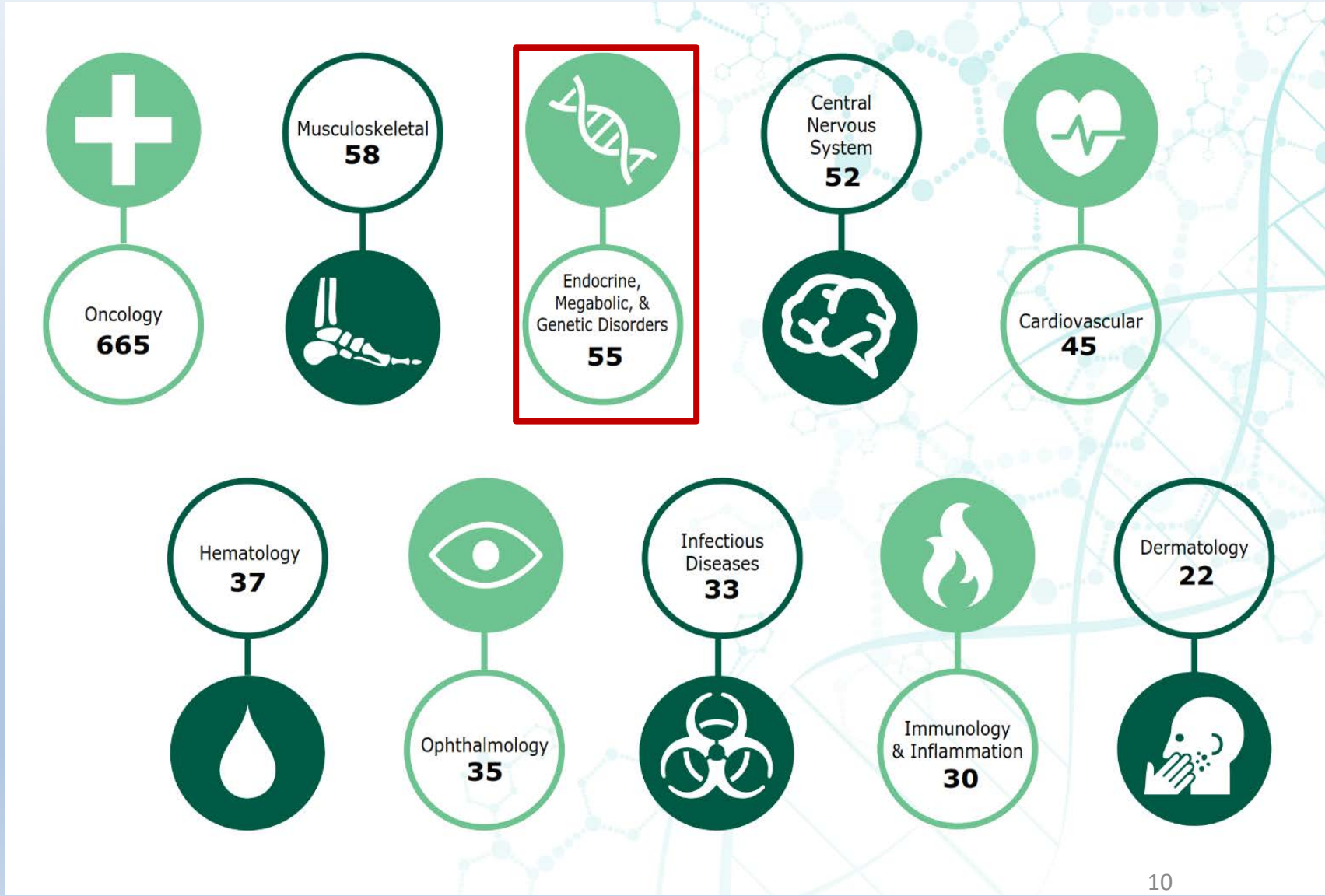
The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. You can see their financial report of first half of 2020 in this figure, which shows that total global financing in field of regenerative medicine had a $10.7B raise since 2019



Alliance for Regenerative Medicine

ARM H1-2020 report

1,078 Clinical Trials Currently Ongoing Worldwide. Of these, 55 clinical trials are in the field of endocrine, metabolic and genetic diseases.



RM products commercialization

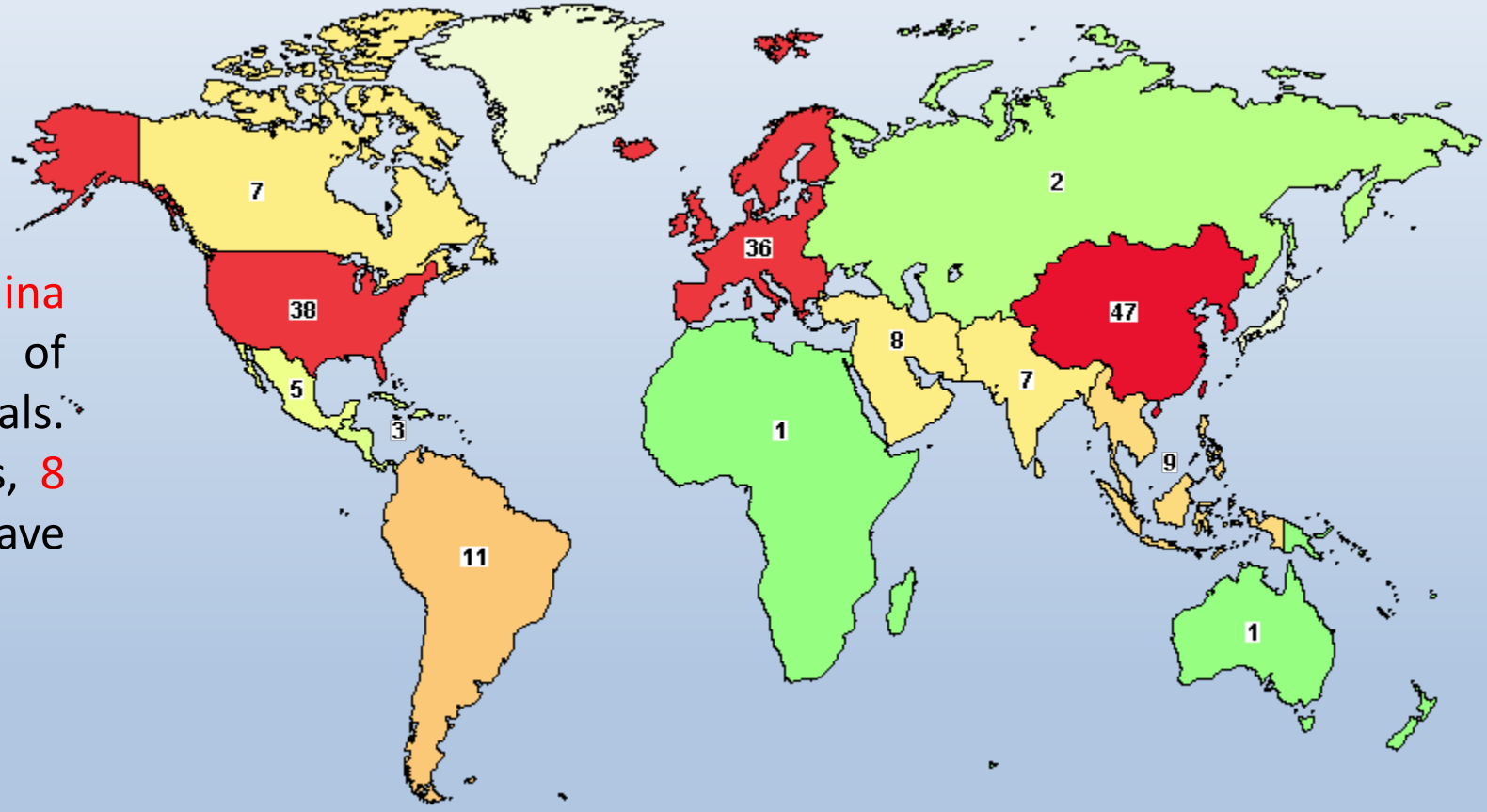
10 -12 years

Discovery (R&D) → **Preclinical** (GLP) → **Clinical** (GCP/GMP) → **Marketing**

Enhancing Tissue Engineering and Regenerative Medicine Product Commercialization: The Role of Science in Regulatory Decision-Making for the TE/RM Product Development. Timothy A. Bertram, Peter C. Johnson, Bill J. Tawil, Mark Van Dyke, and Kiki B. Hellman Tissue Engineering Part A 2015 21:19-20, 2476-2479

Registered clinical trials for DM cell therapy

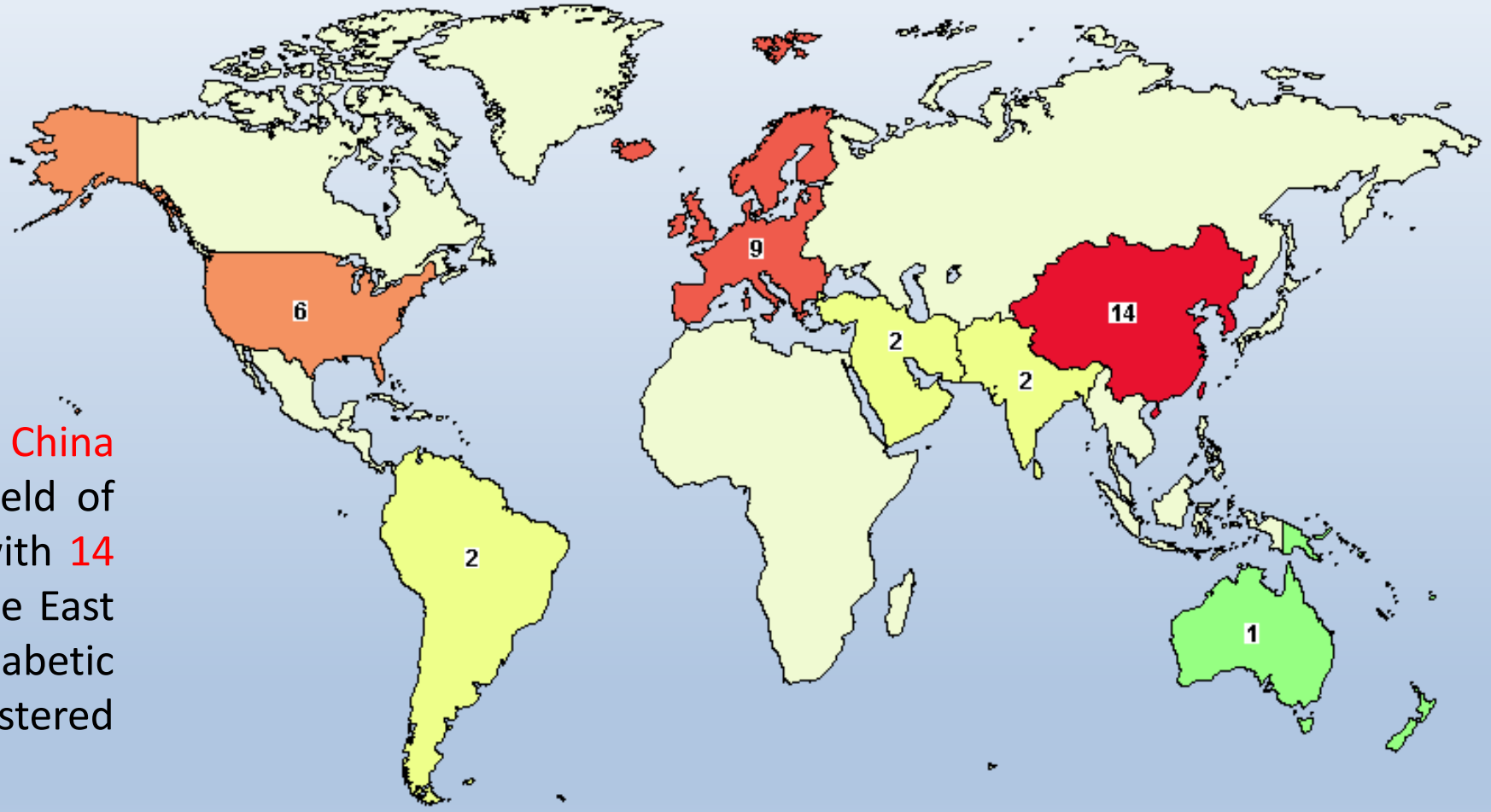
As you can see in the figure, China has the most activity in the field of DM cell therapy with 47 clinical trials. In Iran and Middle East countries, 8 clinical trials for DM cell therapy have been registered so far.



U.S. National Library of Medicine
ClinicalTrials.gov

Clinicaltrials.gov/accessed on 27 Aug 2023

Registered clinical trials for diabetic foot



As you can see in the figure, China has the most activity in the field of cell therapy for diabetic foot with 14 clinical trials. In Iran and Middle East countries, 2 clinical trials for diabetic foot cell therapy have been registered so far.

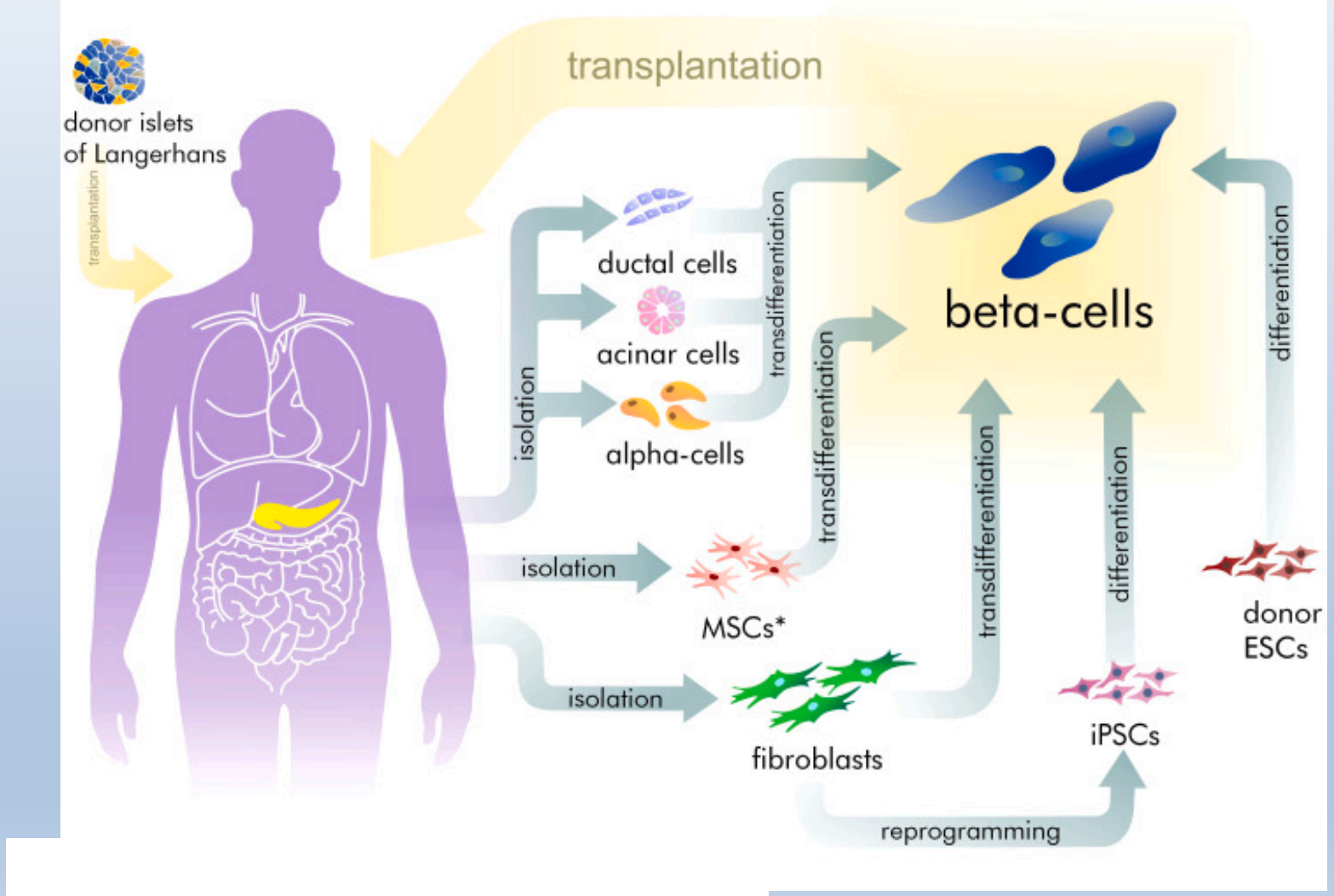
Clinicaltrials.gov/accessed on 27 Aug 2023

RM approaches for diabetes

- **Cell therapies**
  - Pancreatic islets transplantation
  - Immunomodulatory therapies (Telocytes (TCs), MSCs)
  - embryonic stem cells (ESCs) /induced pluripotent stem cells (iPSCs)-derived pancreatic progenitors
  - ESCs/iPSCs-derived β-like cells
- **Gene therapies**
  - Blockage of β-cells autoimmune destruction
  - Reprograming non-β cells into surrogate β cells
  - Replacement of β-cell function (insulin gene therapy)
  - Producing immune evasive allogenic IPCs/PPs (induced pluripotent stem cells/ Pancreatic progenitors)
- **Tissue engineering**
  - Skin substitutes / advance dressing
  - Bioartificial Pancreas

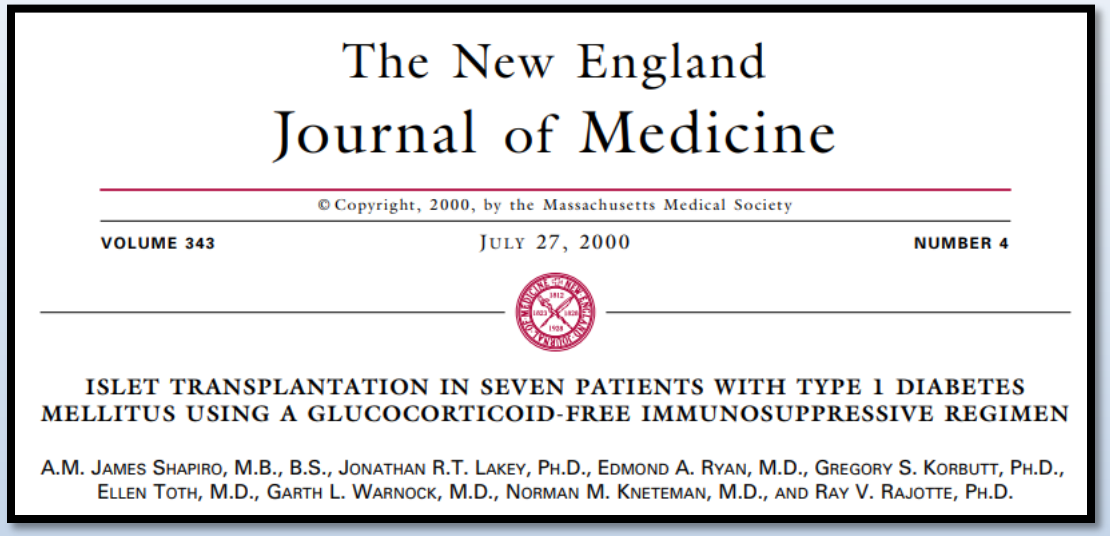
Advanced Therapy Medicinal Products in type I diabetes mellitus: technological and regulatory challenges Vigilância Sanitária em Debate, vol. 6, no. 1, pp. 41-55, 2018

Cell-based approaches



Brovkina O, Dashinimaev E. Advances and complications of regenerative medicine in diabetes therapy. PeerJ. 2020 Sep 8;8:e9746.

Edmonton's breakthrough



The New England
Journal of Medicine

VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

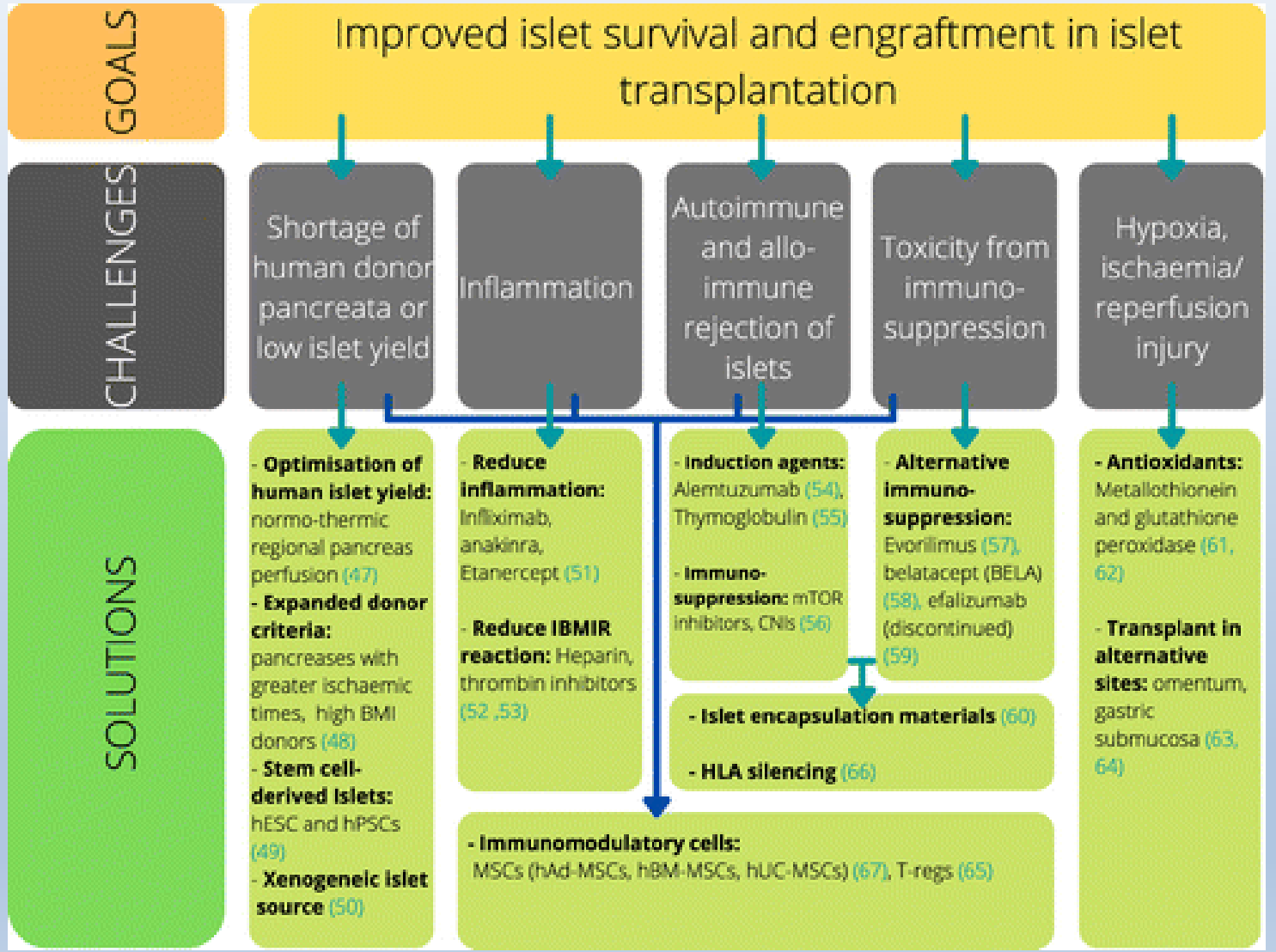
A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.

- Patients with type 1 diabetes and a history of severe hypoglycemia and metabolic instability underwent islet transplantation in conjunction with a **glucocorticoid-free immunosuppressive regimen** consisting of sirolimus, tacrolimus, and daclizumab. This study indicate that islet transplantation can result in insulin independence with excellent metabolic control when glucocorticoid-free immunosuppression is combined with the infusion of an adequate islet mass.

(Cited by 4471 up to 26 Aug 2023)

Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 2000

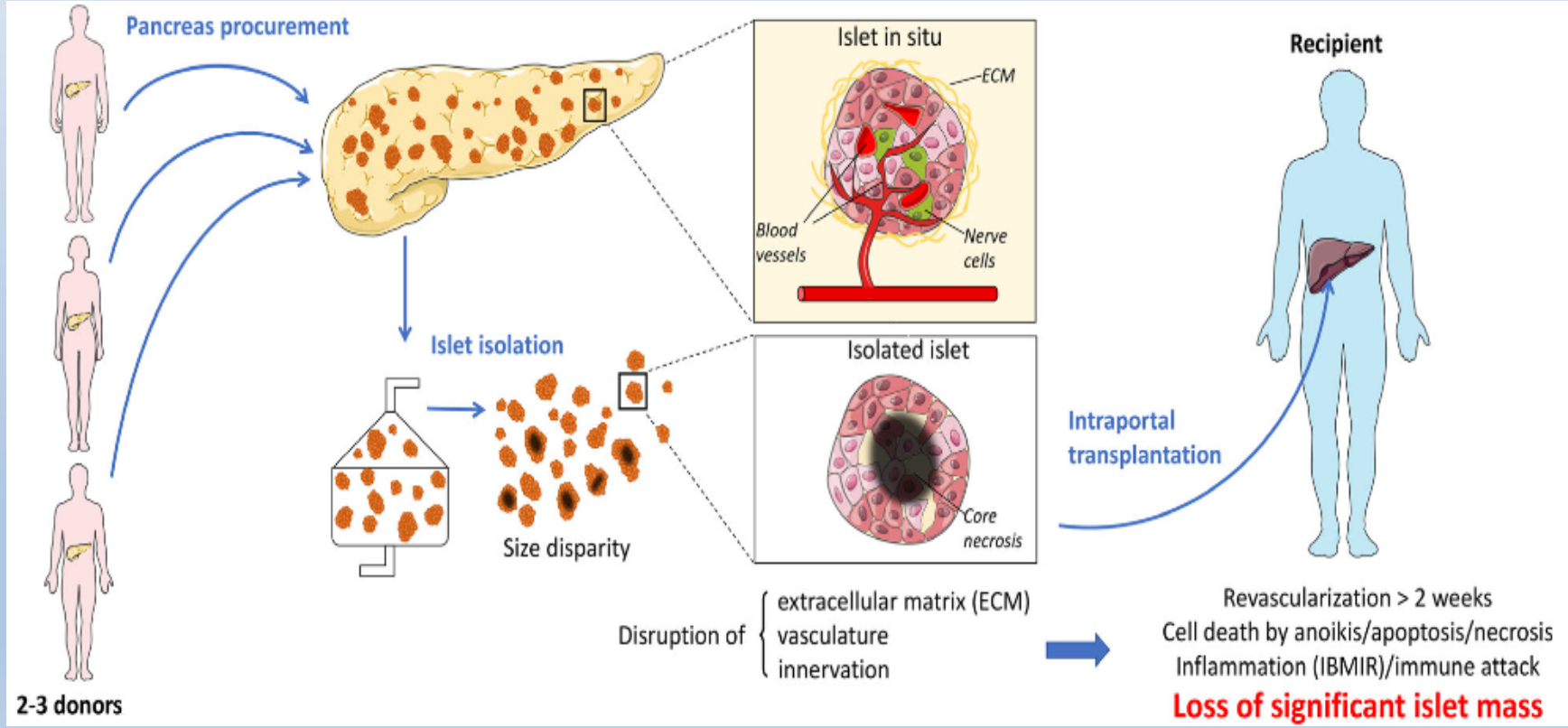
Limitations of islet transplantation



Walker, S., Appari, M., & Forbes, S. (2022). Considerations and challenges of islet transplantation and future therapies on the horizon. American journal of physiology. Endocrinology and metabolism, 322(2), E109–E117. https://doi.org/10.1152/ajpendo.00310.2021

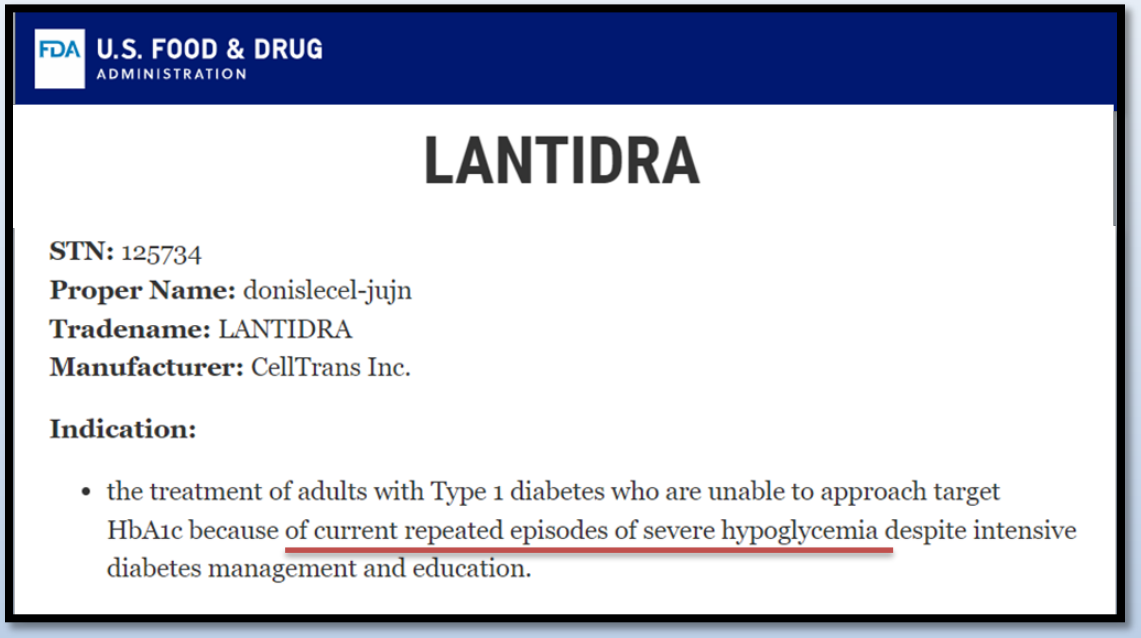
Limitations of islet transplantation

One of the most important limitations and unresolved problems in this field is **significant loss of insulin-producing tissue** during the isolation procedure and engraftment process, due to isolation-related damage, loss of vascularization, loss of extracellular matrix, and an inflammatory microenvironment at the site of implantation. These phenomena lead to the need for multiple donors in order to achieve insulin independence as well as to attrition of islet graft function over time.



Wassmer CH, Lebreton F, Bellofatto K, Bosco D, Berney T, Berishvili E. Generation of insulin-secreting organoids: a step toward engineering and transplanting the bioartificial pancreas. Transpl Int. 2020

FDA approves first cell therapy for type 1 diabetes



U.S. FOOD & DRUG ADMINISTRATION

LANTIDRA

STN: 125734
Proper Name: donislecel-jujn
Tradename: LANTIDRA
Manufacturer: CellTrans Inc.

Indication:

- the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

nature reviews drug discovery

Explore content | About the journal | Publish with us | Subscribe

nature > nature reviews drug discovery > news in brief > article

NEWS IN BRIEF 07 July 2023

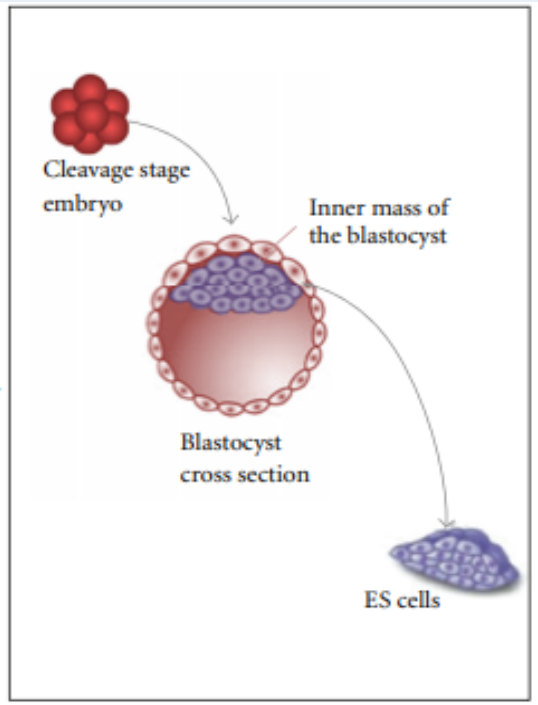
FDA approves first cell therapy for type 1 diabetes

- The U.S. Food and Drug Administration has approved Lantidra, the first allogeneic (donor) pancreatic islet cellular therapy made from **deceased donor pancreatic cells** for the treatment of type 1 diabetes. The primary mechanism of action of Lantidra is believed to be the secretion of insulin by the infused allogeneic islet beta cells. Lantidra is approved for the treatment of adults with type 1 diabetes who are unable to approach target glycated hemoglobin (average blood glucose levels) because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

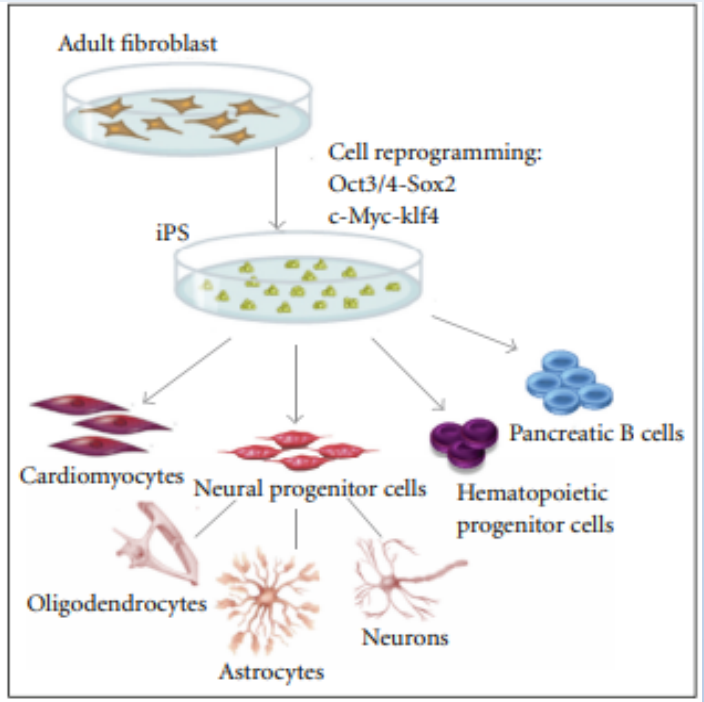
https://www.fda.gov/news-events/press-announcements/fda-approves-first-cellular-therapy-treat-patients-type-1-diabetes

Stem cell-based approach

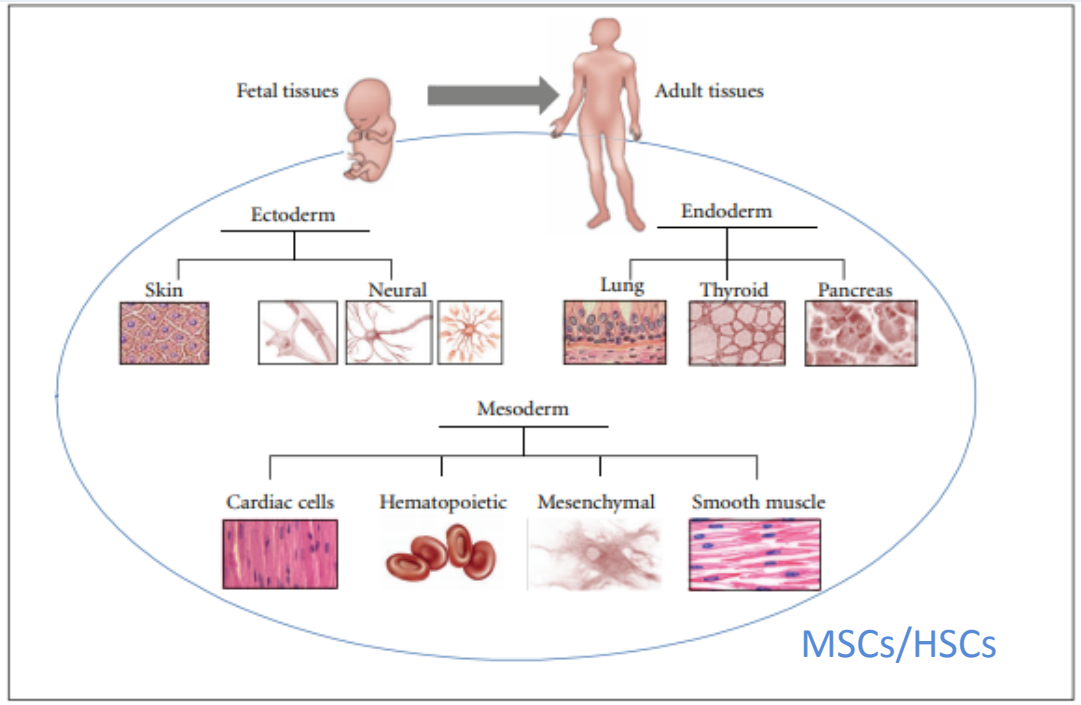
Embryonic stem cells



induced pluripotent stem cells



Tissue specific SCs



ES cells are derived from the inner mass of blastocyst and are considered as pluripotent stem cells.

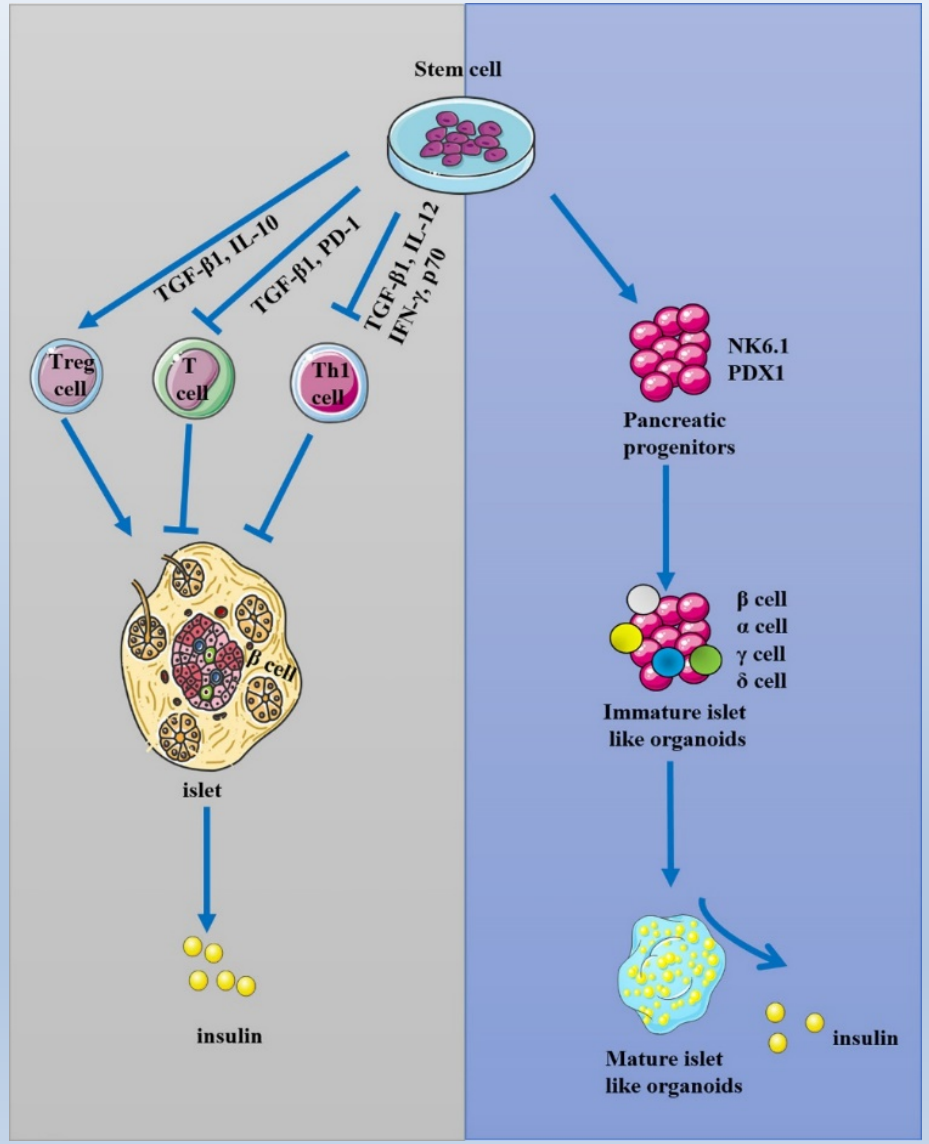
iPS cells are pluripotent stem cells that are derived from adult somatic cells such as skin fibroblasts and are genetically modified by introduction of four embryogenesis-related genes

tissue-specific stem cells known as somatic or adult stem cells are more restricted stem cells (multipotent stem cells) and are isolated from various fetal or adult tissues

Wislet-Gendebien, S., Laudet, E., Neirinckx, V., & Rogister, B. (2012). Adult bone marrow: which stem cells for cellular therapy protocols in neurodegenerative disorders?. *Journal of biomedicine & biotechnology*, *2012*,

Possible mechanisms of SCs

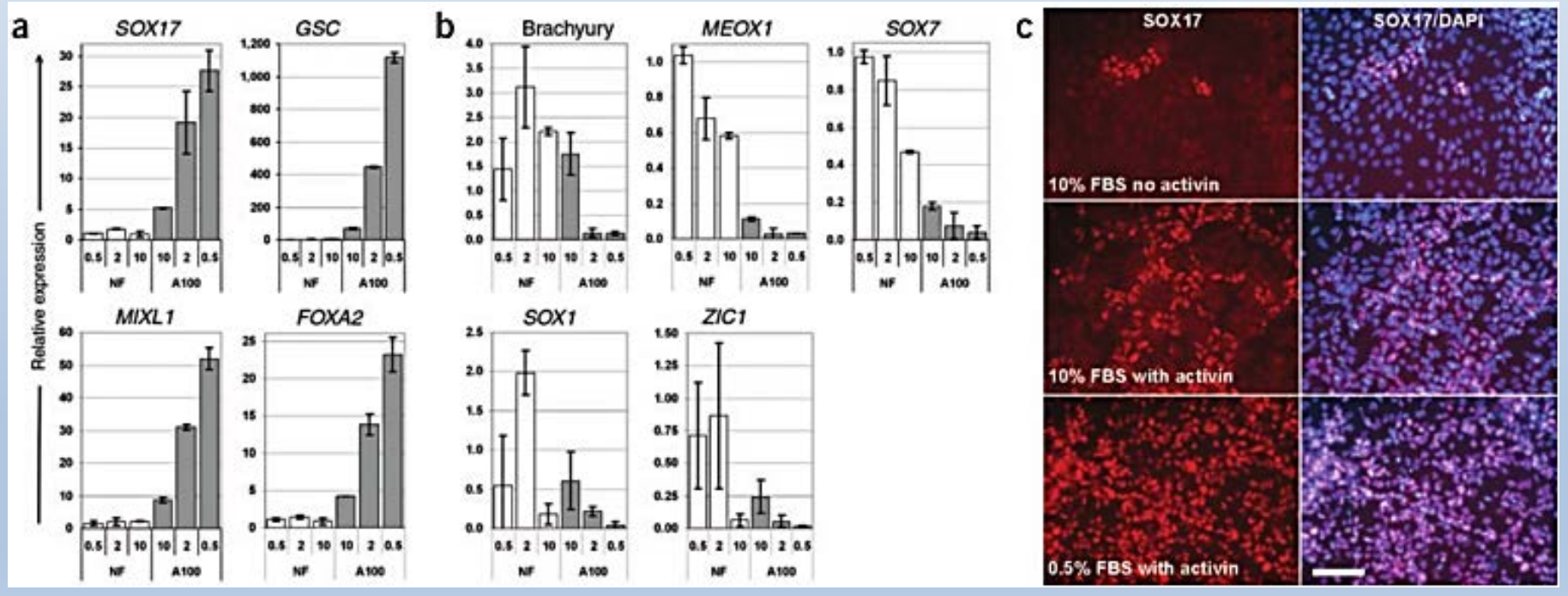
- Stimulate the replication of remaining β-cells
- Differentiate to β-cells-like cells
- Protect the remaining β-cells by immunomodulation and anti-inflammatory effects
- Produce exogenous insulin



Wan Xin-Xing et al, Stem Cell Transplantation in the Treatment of Type 1 Diabetes Mellitus: From Insulin Replacement to Beta-Cell Replacement, Frontiers in Endocrinology, VOLUME=13, 2022

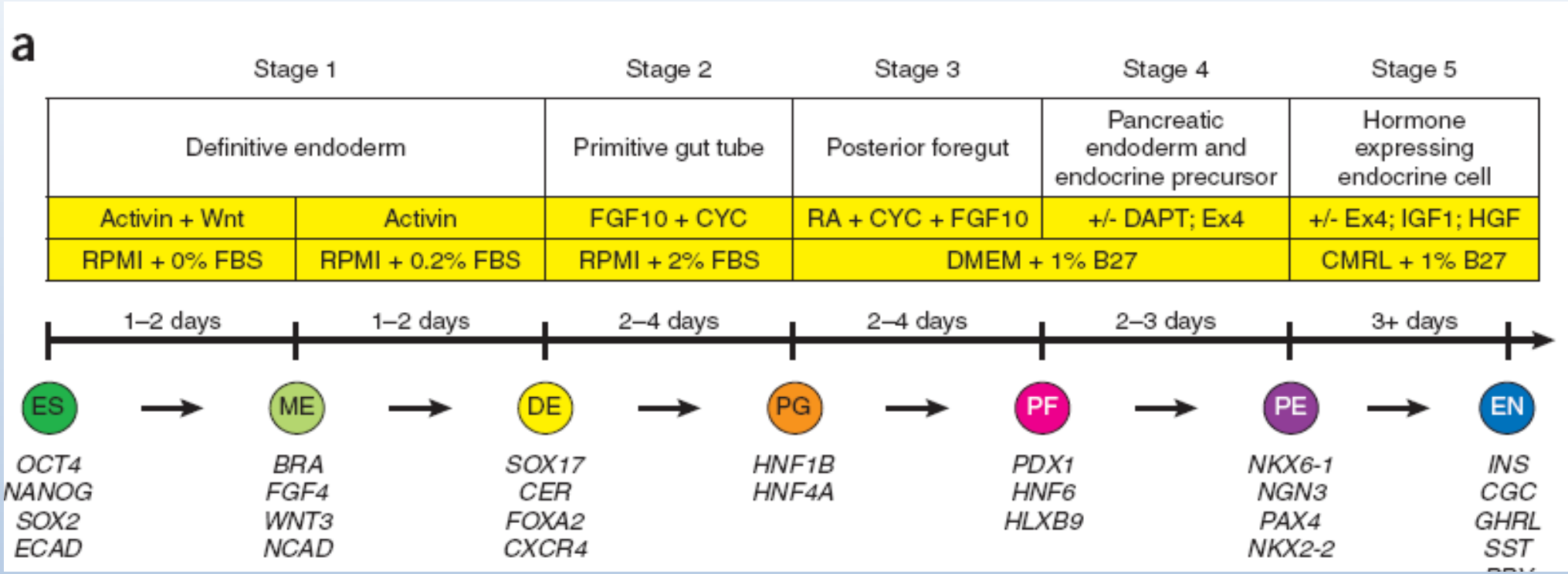
Embryonic stem cell-derived beta cells: 1st successful report in 2005

Findings of this study facilitated the use of human embryonic stem cells (HESCs) for therapeutic purposes and as in vitro models of development



D'Amour, K., Agulnick, A., Eliazer, S. et al. Efficient differentiation of human embryonic stem cells to definitive endoderm. Nat Biotechnol 23, 1534–1541 (2005). https://doi.org/10.1038/nbt1163

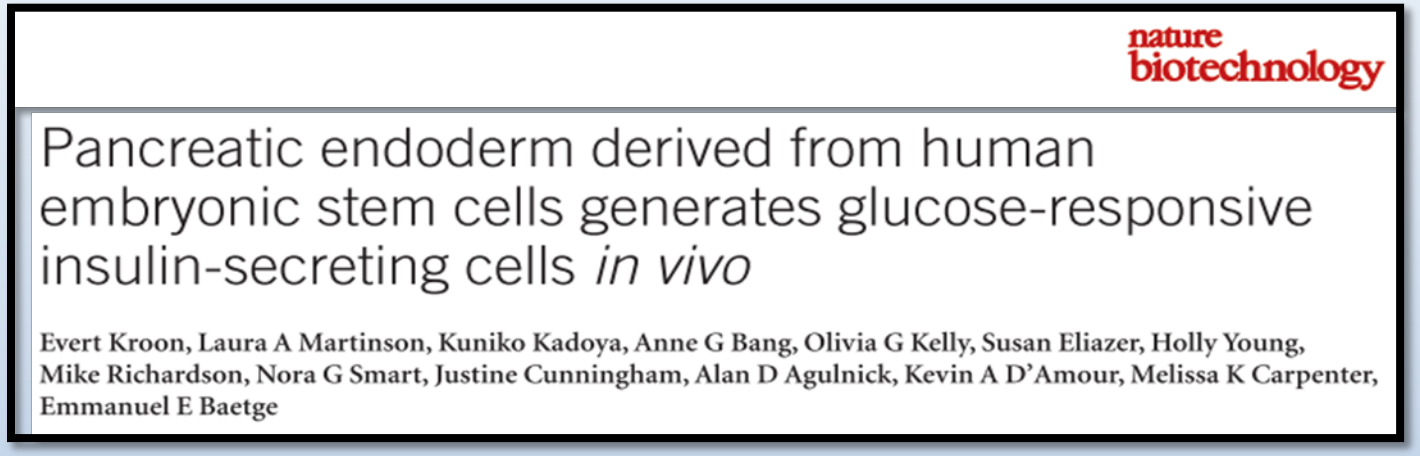
human embryonic stem cells to insulin producing cells (2006)



- Production of these human embryonic stem cell-derived endocrine cells in 2006 represented a critical step in the development of a renewable source of cells for diabetes cell therapy.
- You can see the schematic of differentiation procedure and protein expression for some key markers of pancreatic differentiation in the above picture.

D'Amour KA, Bang AG, Eliazer S, et al. Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. Nat Biotechnol. 2006;24(11):1392-1401. doi:10.1038/nbt1259

ESCs to glucose responsive endocrine cells (2008)



nature biotechnology

Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells *in vivo*

Evert Kroon, Laura A Martinson, Kuniko Kadoya, Anne G Bang, Olivia G Kelly, Susan Eliazer, Holly Young, Mike Richardson, Nora G Smart, Justine Cunningham, Alan D Agulnick, Kevin A D'Amour, Melissa K Carpenter, Emmanuel E Baetge

VIACYTE
Regenerating Health™

Data from this study provided definitive evidence that hES cells are competent to generate glucose-responsive, insulin-secreting cells.

Science	Leadership	Grants	Patents	Clinical
47	**27**	**>$85M**	**550**	**1st**
Peer-reviewed scientific publications	Average years of experience (Average of 9 years with ViaCyte)	From CIRM and JDRF $72.3M CIRM + $13.6M JDRF + more	Worldwide Patents 90 United States 400 Additional Pending Worldwide	ever clinical trials for a stem cell-derived cell replacement therapy for diabetes

Kroon E, Martinson LA, Kadoya K, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol. 2008;26(4):443-452. doi:10.1038/nbt1393

Recent clinical reports-1

Cell Stem Cell

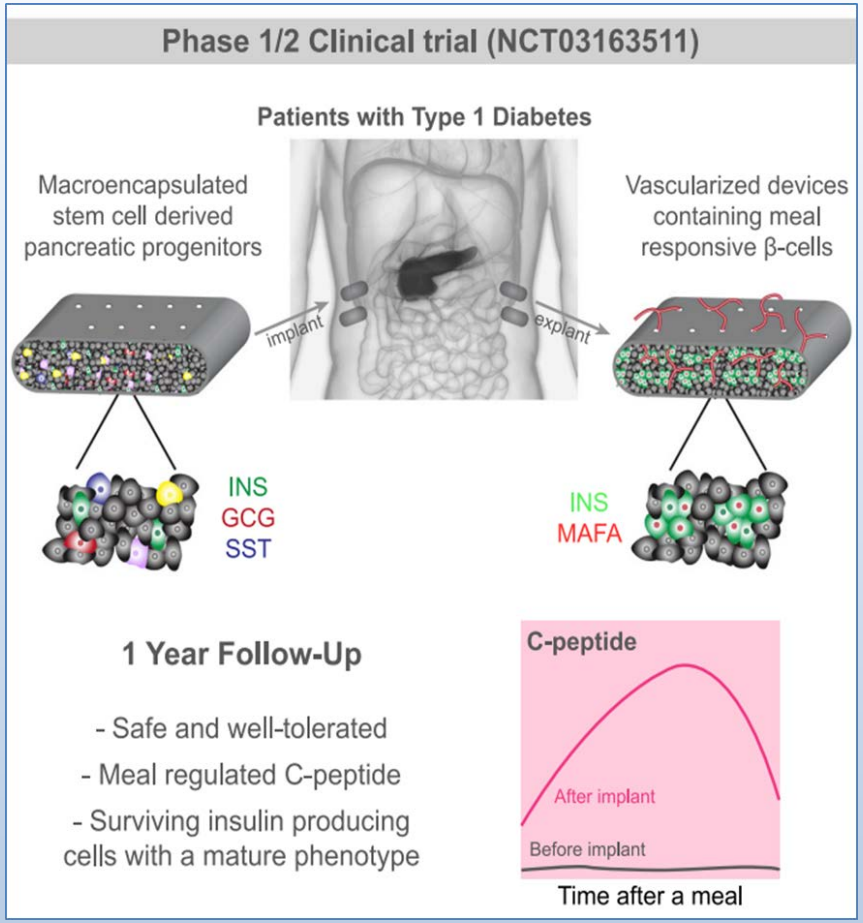
CellPress

Volume 28, Issue 12, 2 December 2021, Pages 2047-2061.e5

Clinical and Translational Report

Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes

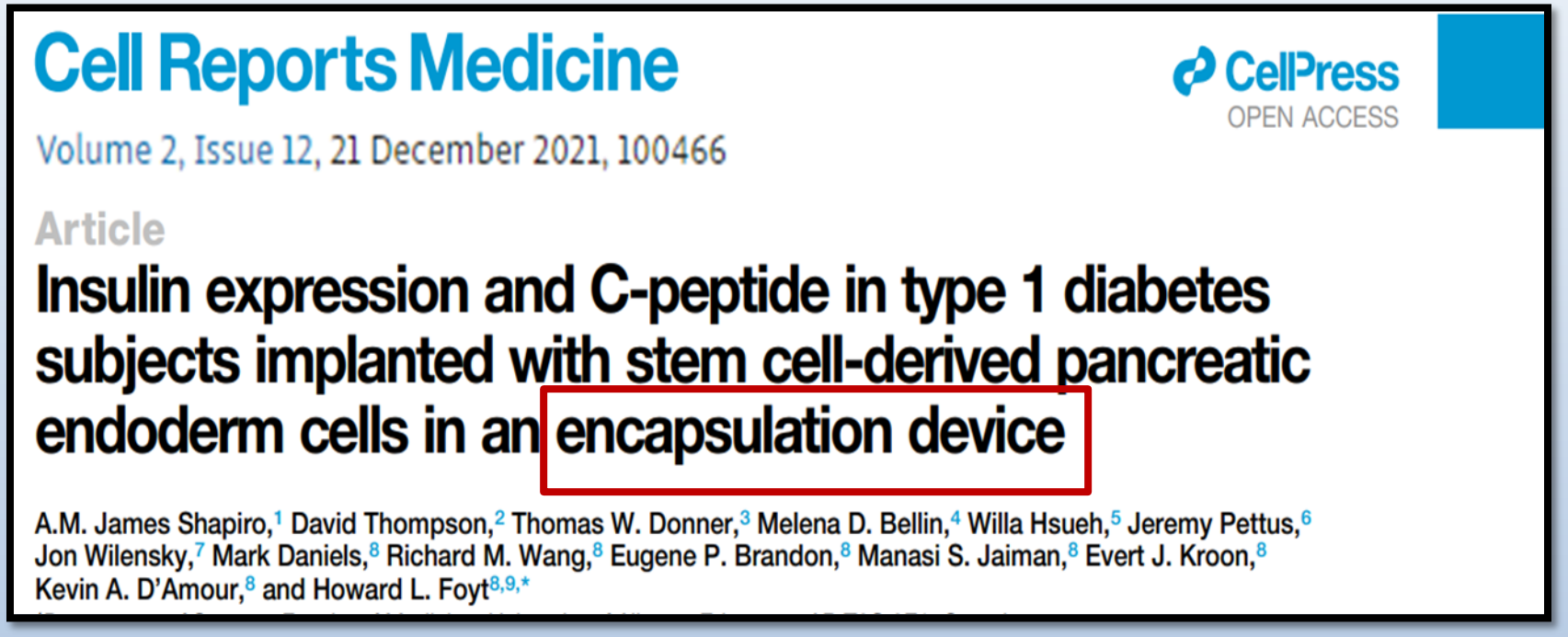
Adam Ramzy,[1] David M. Thompson,[2] Kirsten A. Ward-Hartstonge,[3,4] Sabine Ivison,[3,4] Laura Cook,[3,4] Rosa V. Garcia,[3,4] Jackson Loyal,[2] Peter T.W. Kim,[3] Garth L. Warnock,[3] Megan K. Levings,[3,4,5] and Timothy J. Kieffer[1,3,5,6,*]



- This study reports an analysis on 1 year of data from the first cohort of 15 patients that received subcutaneous implantation of cell products combined with an immunosuppressive regimen.
- Implants were well tolerated with no teratoma formation or severe graft-related adverse events. After implantation, patients had increased fasting C-peptide levels and increased glucose-responsive C-peptide levels and developed mixed meal-stimulated C-peptide secretion.

Ramzy A, Thompson DM, Ward-Hartstonge KA, et al. Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes. Cell Stem Cell. 2021;28(12):2047-2061.e5. doi:10.1016/j.stem.2021.10.003

Recent clinical reports-2



- These preliminary data from a first-in-human phase 1/2, open-label study provide proof-of-concept that pluripotent stem cell-derived pancreatic endoderm cells (PEC-01) engrafted in type 1 diabetes patients become islet cells releasing insulin in a physiologically regulated fashion.

Shapiro AMJ, Thompson D, Donner TW, et al. Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device. Cell Rep Med. 2021;2(12):100466. Published 2021 Dec 2. doi:10.1016/j.xcrm.2021.100466

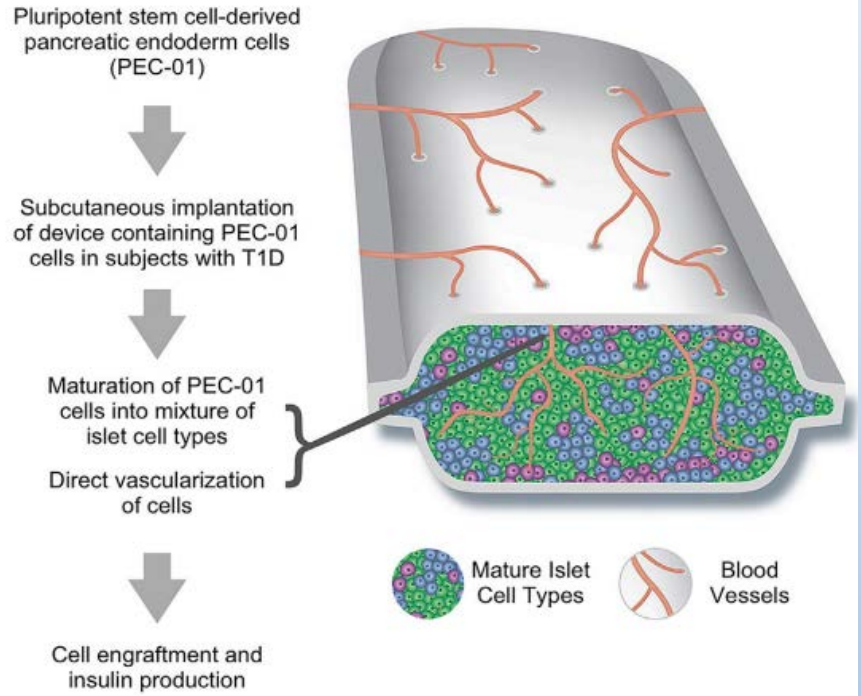
17 participants (9 male, 8 female)

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Men and non-pregnant women
Diagnosis of T1D for a minimum of 5 years
Hypoglycemia unawareness (Clarke score) or significant glycemic lability
Stable diabetic treatment
Willingness to use a continuous glucose meter
Acceptable candidate for surgical implantation
Exclusion criteria
History of islet cell, kidney, and/or pancreas transplant
Six or more severe, unexplained hypoglycemic events within 6 months of enrollment
Uncontrolled or untreated thyroid disease or adrenal insufficiency
Diabetic complications such as severe kidney disease or renal dysfunction, proliferative retinopathy, foot ulcers, amputations, and/or severe peripheral neuropathy
Detectable stimulated serum C-peptide during the screening period[a]

[a]C-peptide was assessed at two separate screening visits.

VC-02 Macroencapsulation Device (Phase 1/2 trial)

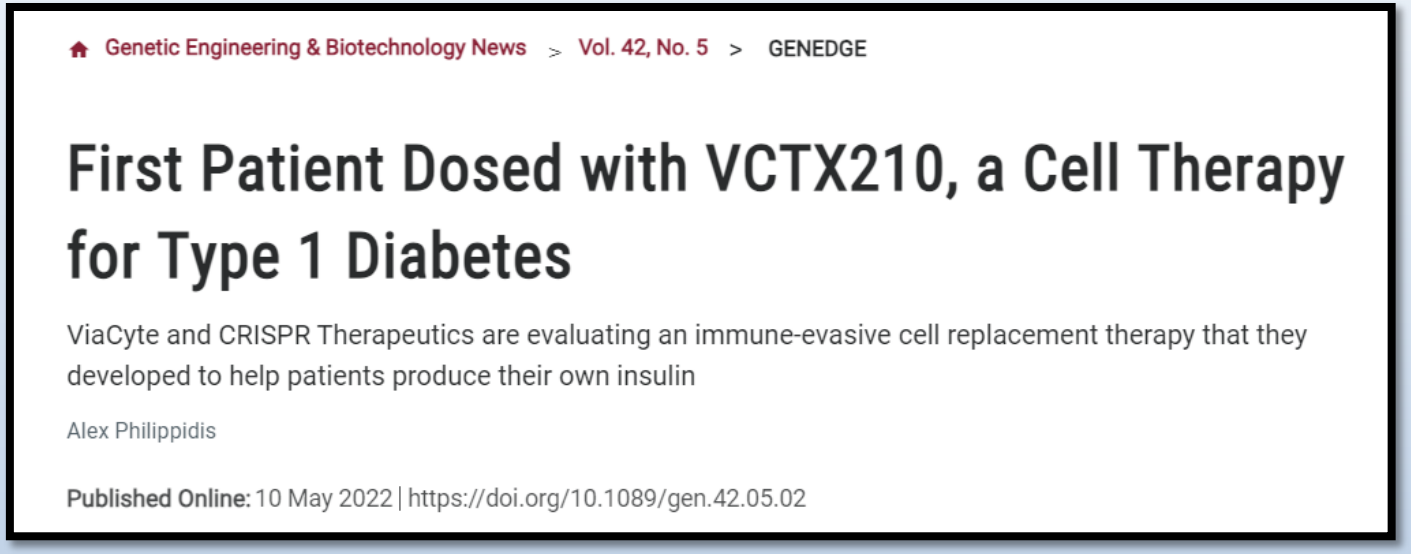


Outcome: Engraftment and insulin expression were observed in 63% of VC-02 units, 3–12 months post-implant

Shapiro AMJ, Thompson D, Donner TW, et al. Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device. Cell Rep Med. 2021;2(12):100466. Published 2021 Dec 2. doi:10.1016/j.xcrm.2021.100466

Many companies are engaged in research and activities in the field of regenerative medicine especially in the field of endocrine diseases.

Immune evasive pancreatic progenitors



Genetic Engineering & Biotechnology News > Vol. 42, No. 5 > GENEDGE

First Patient Dosed with VCTX210, a Cell Therapy for Type 1 Diabetes

ViaCyte and CRISPR Therapeutics are evaluating an immune-evasive cell replacement therapy that they developed to help patients produce their own insulin

Alex Philippidis

Published Online: 10 May 2022 | https://doi.org/10.1089/gen.42.05.02

Immune evasion: mechanisms to circumvent or suppress immune-mediated targeting and killing

This gene-editing cell replacement therapy for the treatment of type 1 diabetes (T1D), is developed by CRISPR Therapeutics and ViaCyte, Inc., using CRISPR/Cas9 technology to modify stem cells to avoid immune rejection.

First Patient Dosed with VCTX210, a Cell Therapy for Type 1 Diabetes, Alex Philippidis, Genetic Engineering & Biotechnology News 2022 42:5, 10-11

Semma Therapeutics is a biotechnology company that was founded by HSCI Co-Director Douglas Melton, Ph.D., to develop cell therapies for type 1 diabetes based on his groundbreaking research on stem cell-derived beta cells

HSCI and Semma Therapeutics have also collaborated with other institutions to establish the first area cell transplantation center in Boston, which aims to translate stem cell discoveries into treatments for diabetic patients.

Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells in vitro. Cell. 2014;159(2):428-439. doi:10.1016/j.cell.2014.09.040

semma THERAPEUTICS

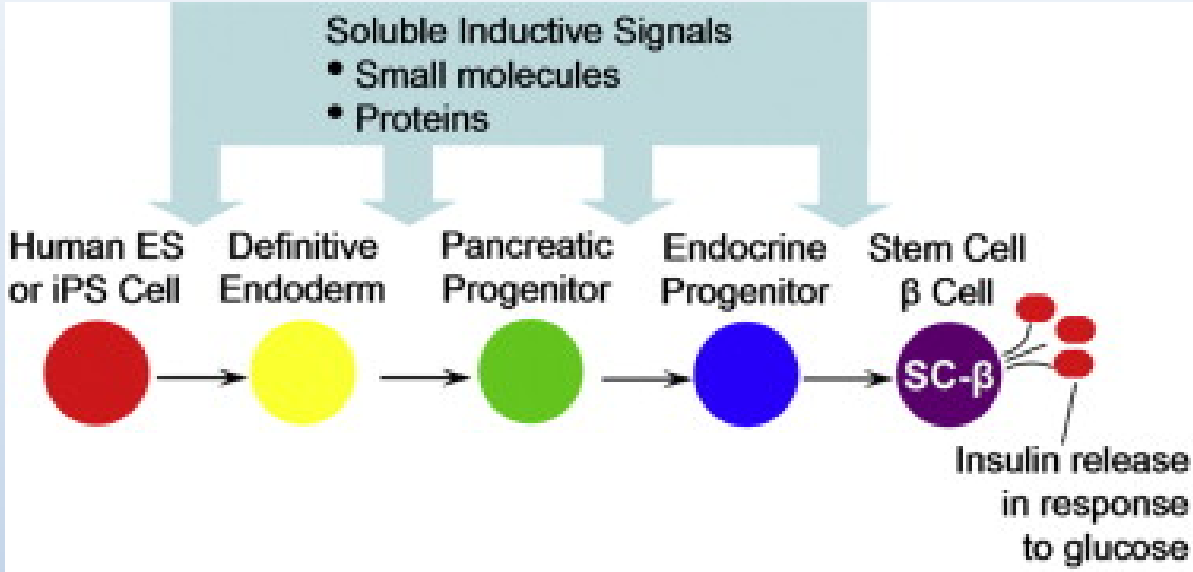
› Cell. 2014 Oct 9;159(2):428-39. doi: 10.1016/j.cell.2014.09.040.

Generation of functional human pancreatic β cells in vitro

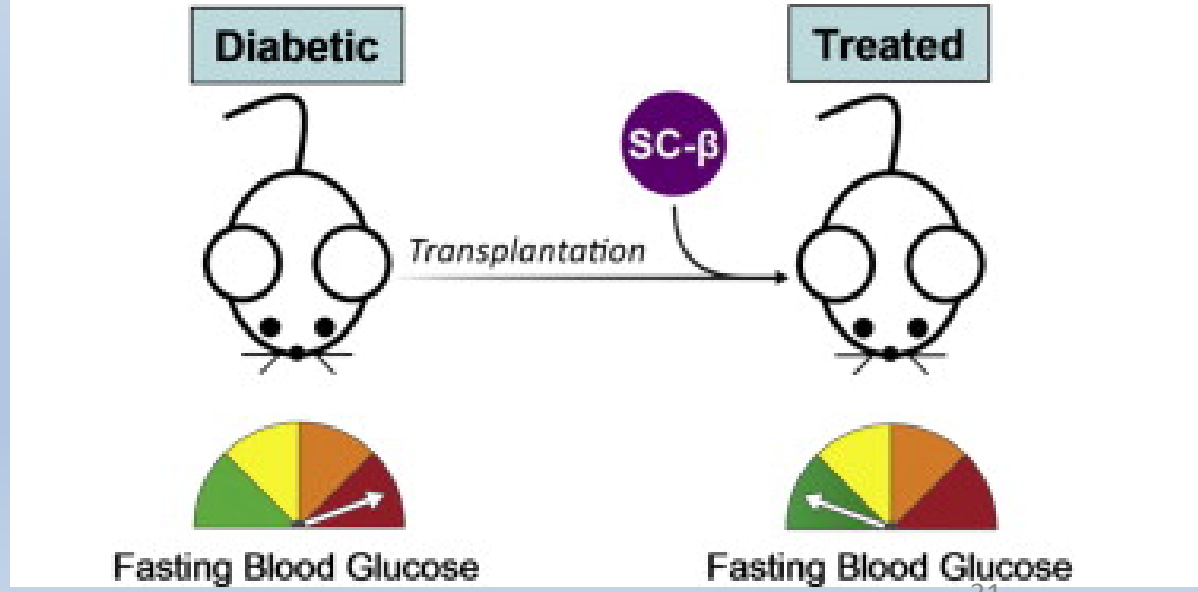
Felicia W Pagliuca [1], Jeffrey R Millman [1], Mads Gürtler [1], Michael Segel [1], Alana Van Dervort [1], Jennifer Hyoje Ryu [1], Quinn P Peterson [1], Dale Greiner [2], Douglas A Melton [3]

Affiliations + expand

PMID: 25303535 PMCID: PMC4617632 DOI: 10.1016/j.cell.2014.09.040



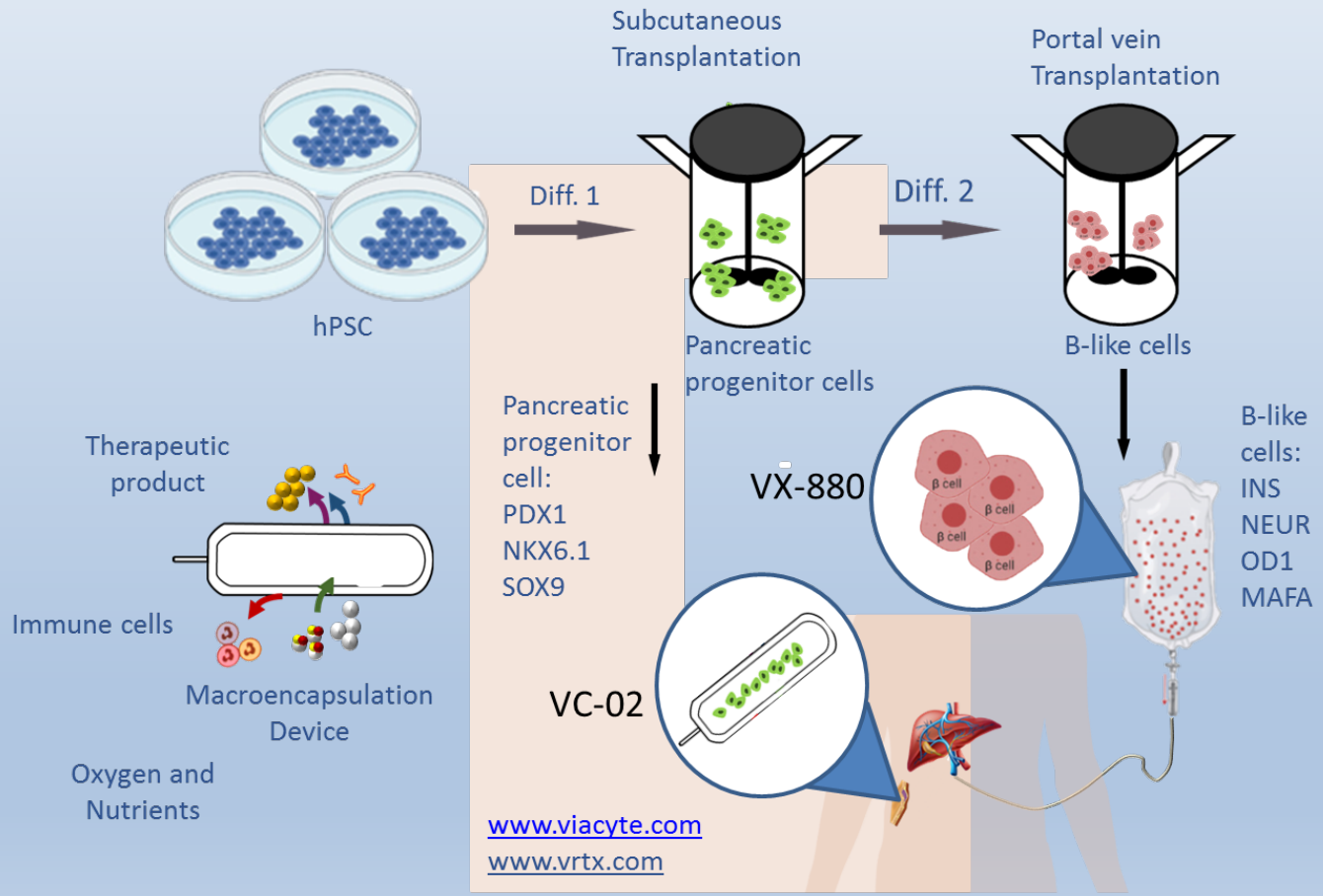
This article reports a scalable differentiation protocol that can generate hundreds of millions of glucose-responsive β cells from hPSC in vitro. These stem-cell-derived β cells (secrete quantities of insulin comparable to adult β cells in response to multiple sequential glucose challenges in vitro. Furthermore, these cells secrete human insulin into the serum of mice shortly after transplantation in a glucose-regulated manner.



Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells in vitro. Cell. 2014;159(2):428-439. doi:10.1016/j.cell.2014.09.040

Vertex: VX-880 project

- Vertex Pharmaceuticals is a biotechnology company that develops and commercializes medicines.
- One of its investigational products is **VX-880**, a stem cell-derived, fully differentiated islet cell therapy for people with type 1 diabetes. VX-880 is currently in a Phase 1/2 clinical trial, which has shown promising results in improving glycemic control and reducing or eliminating insulin use in patients with type 1 diabetes.
- VX-880 has also received **Fast Track Designation** from the U.S. Food and Drug Administration **(FDA)** .



Vertex Presents Positive VX-880 Results From Ongoing Phase 1/2 Study in Type 1 Diabetes at the American Diabetes Association 83rd Scientific Sessions June 23, 2023, https://news.vrtx.com/news-releases/news-release-details/vertex-presents-positive-vx-880-results-ongoing-phase-12-study

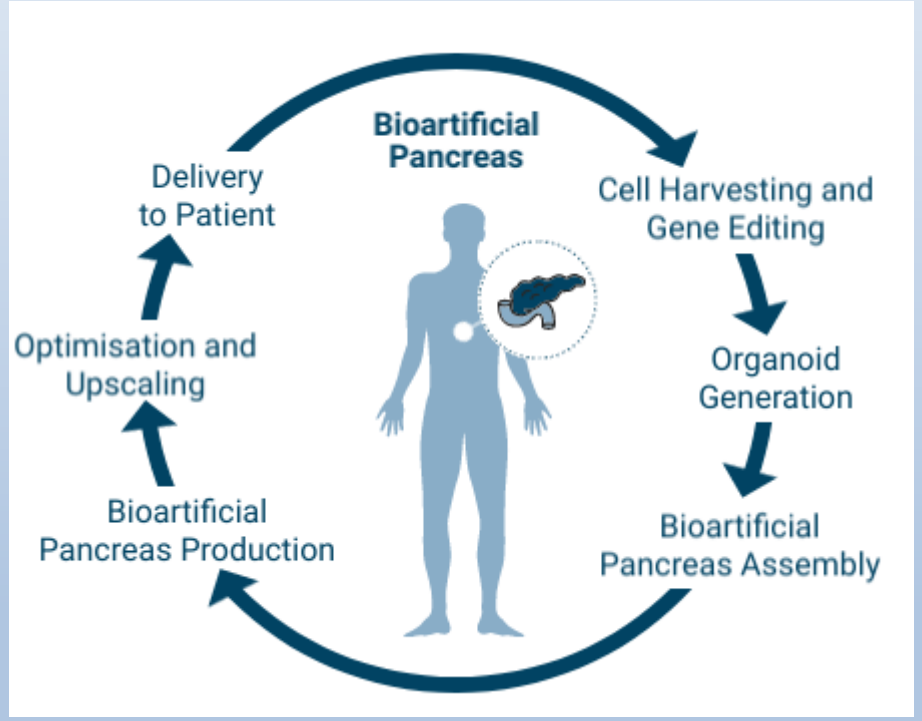
The involvement of insulin producing pharmaceutical companies in cell therapy research is proof that the future of diabetes treatment is tied to cell therapy.

The Novo Nordisk have two foundation for cell therapy research. (Foundation Center for Stem Cell Biology (DanStem) and Foundation Center for Stem Cell Medicine (reNEW))

Procyon collaborates with Novo Nordisk A/S on the development of a stem cell-based therapy for Type 1 diabetes

Bioartificial pancreas

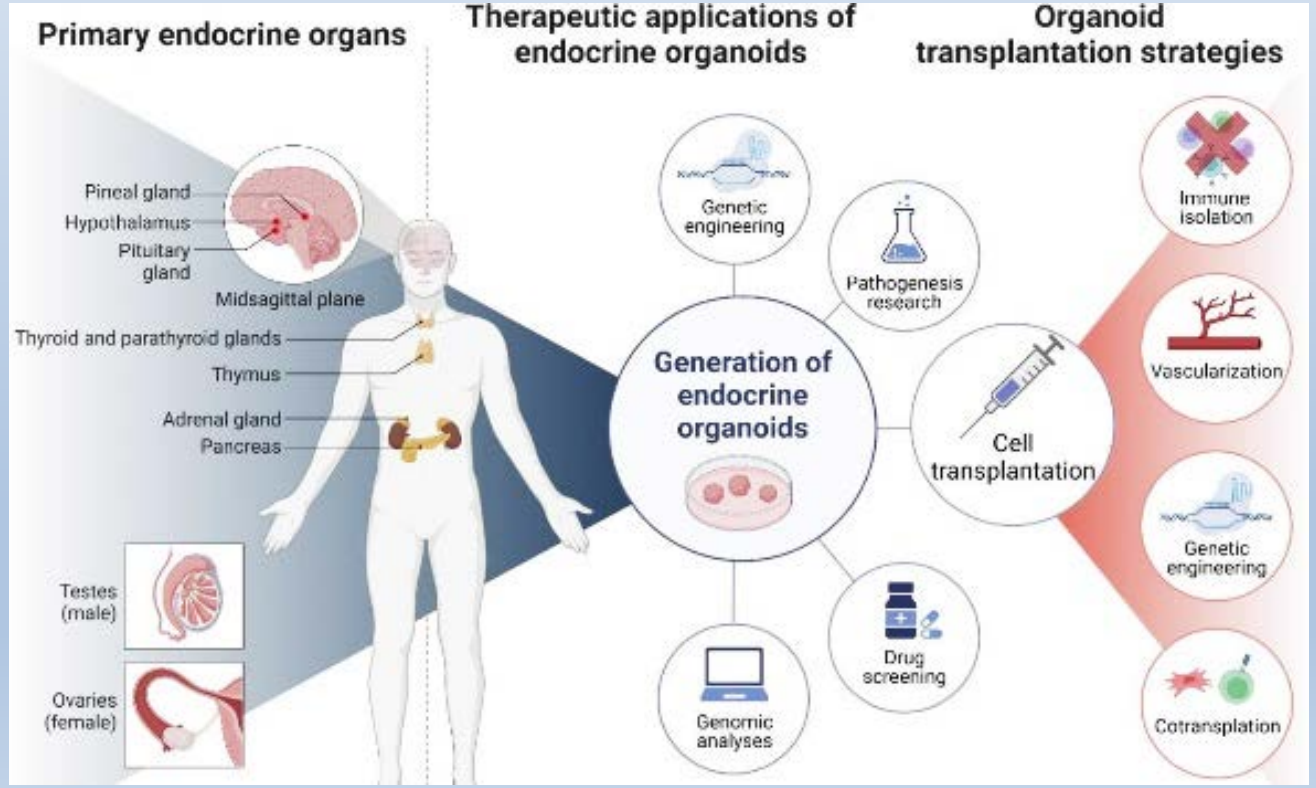
- European (EU) H2020 funded VANGUARD project is set to generate a tissue engineered bioartificial pancreas. The developed beta cell replacement therapy will be available to larger numbers of type 1 diabetic patients.
- The VANGUARD project aims to generate a vascularized and immune-protected bioartificial pancreas that can be transplanted into non-immuno-suppressed patients by combining advanced tissue engineering strategies.
- It involves nine project partners from seven European countries and has a budget of € 6.8 million.



https://vanguard-project.eu/

Endocrine organoids for therapeutic application

Organoids are 'in vitro mini-organs', in which cells (clusters) isolated from tissues or differentiated from stem cells form functional 3D structures to mimic the organ.
The advancement of endocrine organoids has been accelerated with evolving scientific tools such as gene editing, stem cell differentiation technology, and 3D culture system. Combined with marked improvements in the generation of high-quality organoids, various strategies for the transplantation of endocrine organoids were introduced and evaluated in both preclinical and clinical studies.



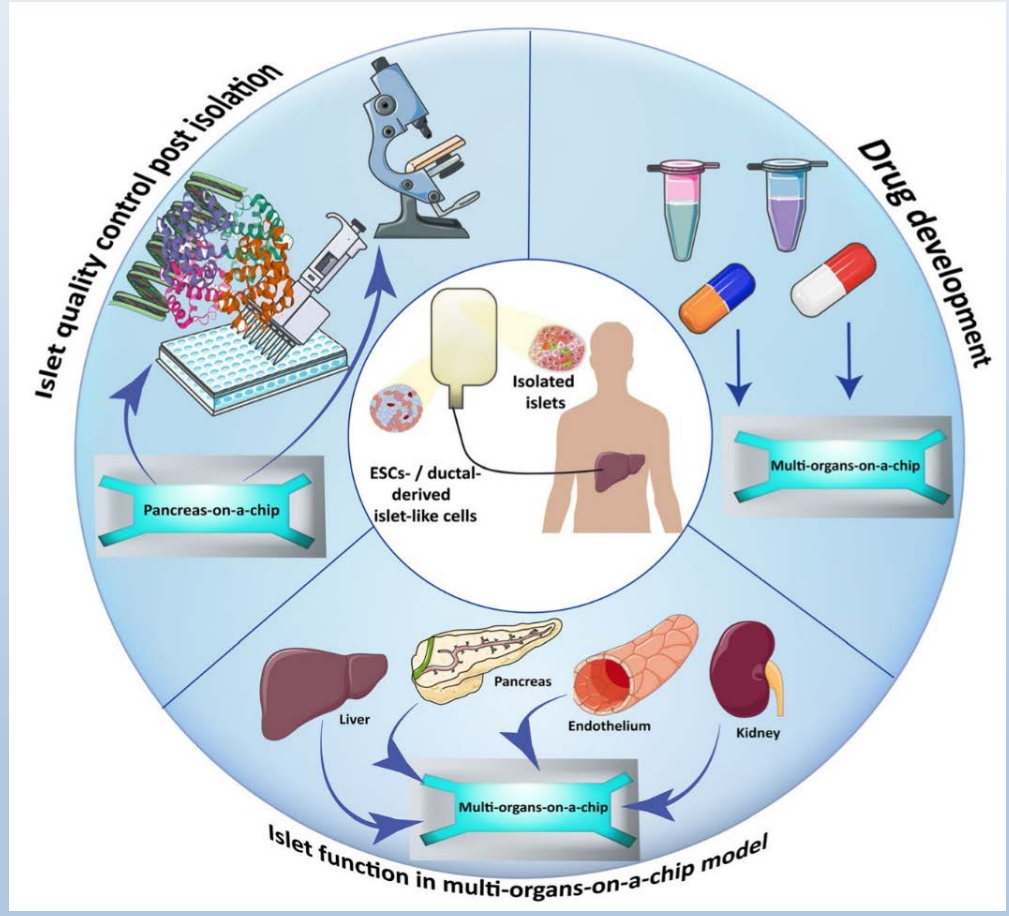
Jeon Set al. Recent advances in endocrine organoids for therapeutic application. Advanced Drug Delivery Reviews. 2023 Jun 8:114959.

Pancreas-on-a-chip

- Pancreas-on-a-chip (PoC), which refers to the study of endocrine part of the pancreas on microfluidic chip, may be used as a standardized and real-time assessment platform for evaluating islet potency and quality.

- Human pancreas-on-a-chip (PoC) technology is quickly advancing as a platform for complex in vitro modeling of islet physiology.

- In this picture you can see Pancreas-on-a-chip application for diabetes and islet transplantation research which includes:
    - islet quality control post-isolation procedure
    - stem cell-derived beta-like cell function assay
    - Drug development



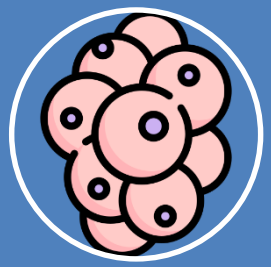
Abadpour S, et al. Pancreas-on-a-chip technology for transplantation applications. Current diabetes reports. 2020 Dec;20:1-3.

Challenges

Purity of the differentiated cells

Potency of the differentiated cells

Functionality after transplantation



Cell Survival after transplantation

Immune suppression

Mass production (scale up)

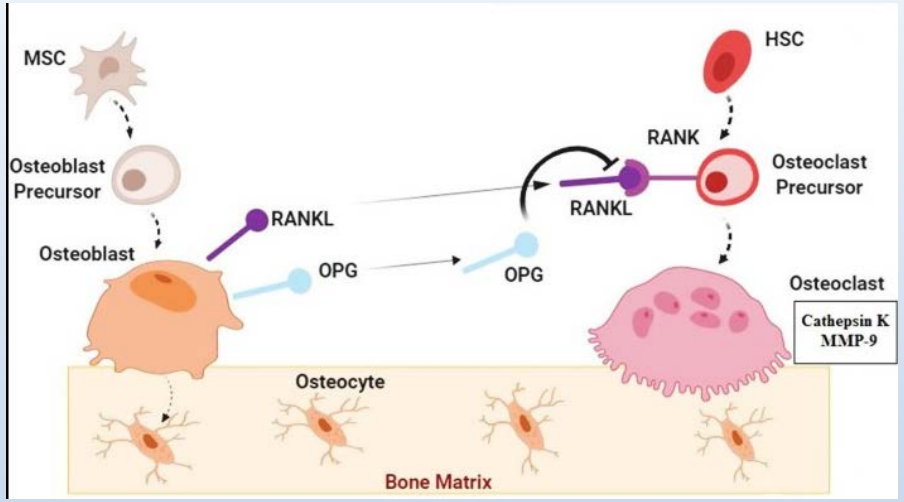
SCs therapies in osteoporosis

frontiers in Endocrinology

Front Endocrinol (Lausanne). 2020; 11: 430.
Published online 2020 Jul 3. doi: 10.3389/fendo.2020.00430
PMCID: PMC7347755
PMID: 32719657

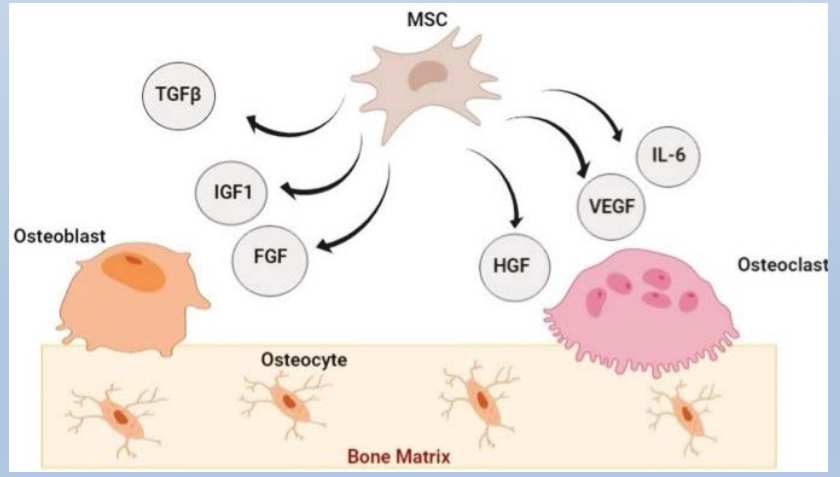
Prospect of Stem Cell Therapy and Regenerative Medicine in Osteoporosis

Babak Arjmand,[1,2,†] Masoumeh Sarvari,[2] Sepideh Alavi-Moghadam,[1] Moloud Payab,[3,†] Parisa Goodarzi,[4] Kambiz Gilany,[5,6,7,†] Neda Mehrdad,[8] and Bagher Larijani[9,*†]



Normal Bone Biology; Signaling Pathways

MSCs therapy is the most common technique of regenerative medicine in osteoporosis treatment. Moreover, using small molecules (e.g., PTH and oxytocin) which employ endogenous stem cells for osteoporosis treatment will be intertwined in future management

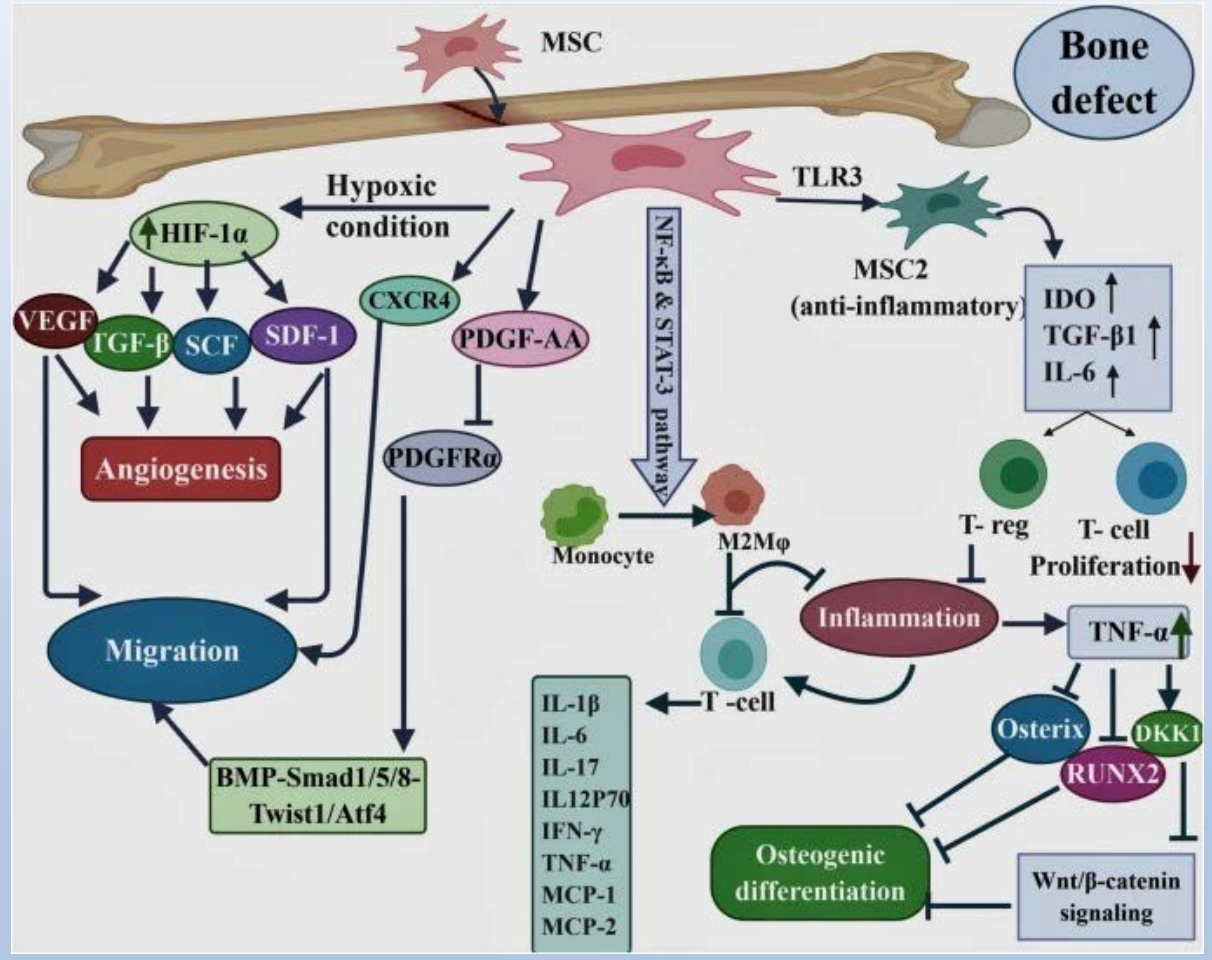


Paracrine Effects of Mesenchymal Stem Cells in Bone Regeneration

Arjmand B,…., Larijani B. Prospect of Stem Cell Therapy and Regenerative Medicine in Osteoporosis. Front Endocrinol (Lausanne). 2020 Jul 3;11:430.

The suggested SC sources

- Osteoporosis therapies can be carried out by exogenous introduction of mesenchymal stem cells (MSCs), typically procured from bone marrow, adipose, and umbilical cord blood tissues or through treatments with drugs or small molecules that recruit endogenous stem cells to osteoporotic sites.
- both adipose tissue and bone marrow seem to be promising stem cell sources for osteoarthritis therapy.
- HUCB-MSCs are less immunogenic and have the chondrogenic differentiation potential, therefore promoting cartilage repair without bone formation in a long period of time



Antebi B, Pelled G, Gazit D. Stem cell therapy for osteoporosis. Current osteoporosis reports. 2014 Mar;12:41-7.

Kangari P, et al. Mesenchymal stem cells: amazing remedies for bone and cartilage defects. Stem Cell Research & Therapy. 2020 Dec;11(1):1-21.

Regenerative medicine in Adrenal and Thyroid gland

- Glucocorticoids are secreted following a circadian rhythm, which is impossible to adequately recapitulate using current replacement therapies with synthetic glucocorticoids. Promising results have recently been obtained using cell replacement therapies. In particular, encapsulation of adrenocortical (stem) cells opens new prospects for successful transplantation. Furthermore, stem cells from the adrenal medulla might have the potential to be used for the treatment of neurodegenerative diseases.

- Regenerative medicine approaches, such as a bioengineered thyroid, have been proposed as potential therapeutic alternatives for patients with hypothyroidism. Some studies demonstrate the utility of a decellularized thyroid extracellular matrix scaffold system for the development of functional, bioengineered thyroid tissue, which could potentially be used to treat hypothyroidism.

Bornstein SR, Malyukov M, Heller C, Ziegler CG, Ruiz-Babot G, Schedl A, Ludwig B, Steenblock C. New horizons: novel adrenal regenerative therapies. The Journal of Clinical Endocrinology & Metabolism. 2020 Sep;105(9):3103-7.

Pan J, Li H, Fang Y, Shen YB, Zhou XY, Zhu F, Zhu LX, Du YH, Yu XF, Wang Y, Zhou XH. Regeneration of a bioengineered thyroid using decellularized thyroid matrix. Thyroid. 2019 Jan 1;29(1):142-52.

- Many researches have been conducted in the field of regenerative medicine in order to treat various endocrine diseases and the cure of chronic diseases is expected o be seen in the near future.

- Due to the high burden of diabetes all over the world, many researchers and pharmaceutical companies have focused on regenerative medicine in the field of diabetes, but researches are also being conducted on other endocrine diseases.

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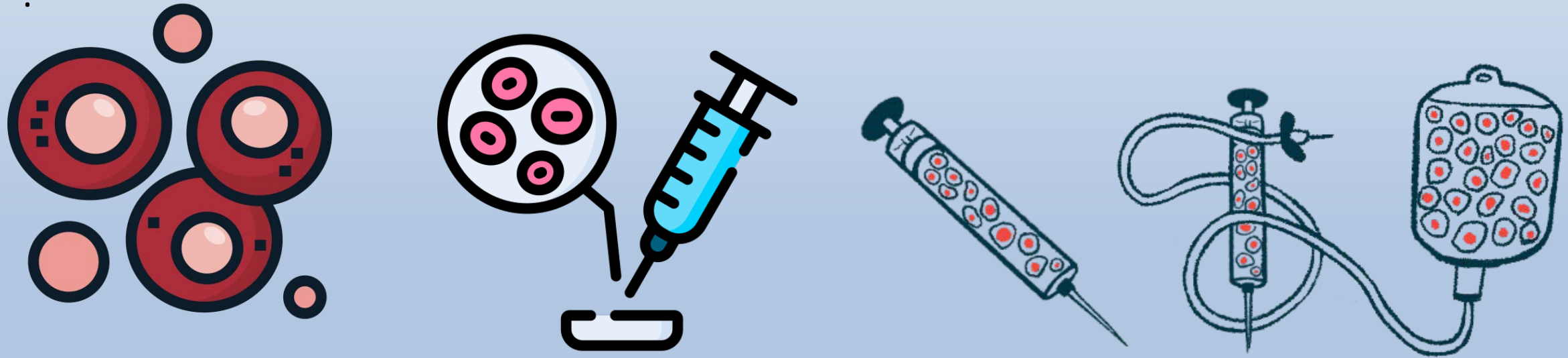


NASLI EE, Ghavamzadeh A, **Larijani B**. Therapeutic uses of stem cells in endocrinology-Review article.

Our works & experiences in the field

Good manufacturing practice (GMP) compliant

Good manufacturing practice (GMP) compliant in cell therapy is the adherence to the standards and regulations that ensure the quality, safety, and efficacy of cell-based products for human use. GMP compliance involves the establishment of a quality management system, the documentation of standard operating procedures, the validation of equipment and methods, the monitoring and control of manufacturing processes and facilities, and the training and auditing of personnel.

A lot of research has been done in Iran in order to make sure that regenerative medicine research is done according to GMP.

Sarvari M, Alavi-Moghadam S, **Larijani B**, Rezazadeh I, Arjmand B. Principles of good manufacturing practice. Biomedical product development: Bench to bedside. 2020:61-8.

Home > Cell and Tissue Banking > Article

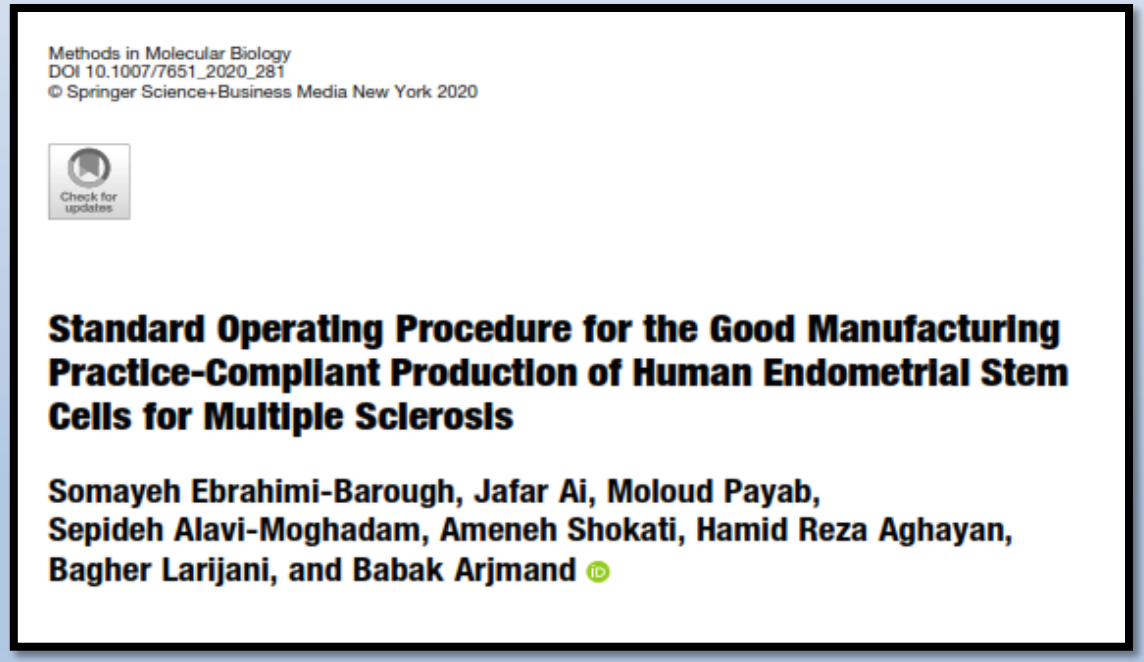
Springer

Published: 05 August 2011

Establishing a cGMP pancreatic islet processing facility: the first experience in Iran

Bagher Larijani, Babak Arjmand, Mahsa M. Amoli, Ziliang Ao, Ali Jafarian, Mitra Mahdavi-Mazdah, Hossein Ghanaati, Reza Baradar-Jalili, Sasan Sharghi, Abbas Norouzi-Javidan & Hamid Reza Aghayan

In this article we will briefly describe our experience in setting up a cGMP islet processing facility which can provide valuable information for regional countries interested to establish similar facilities.



Methods in Molecular Biology
DOI 10.1007/7651_2020_281
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Check for updates

Standard Operating Procedure for the Good Manufacturing Practice-Compliant Production of Human Endometrial Stem Cells for Multiple Sclerosis

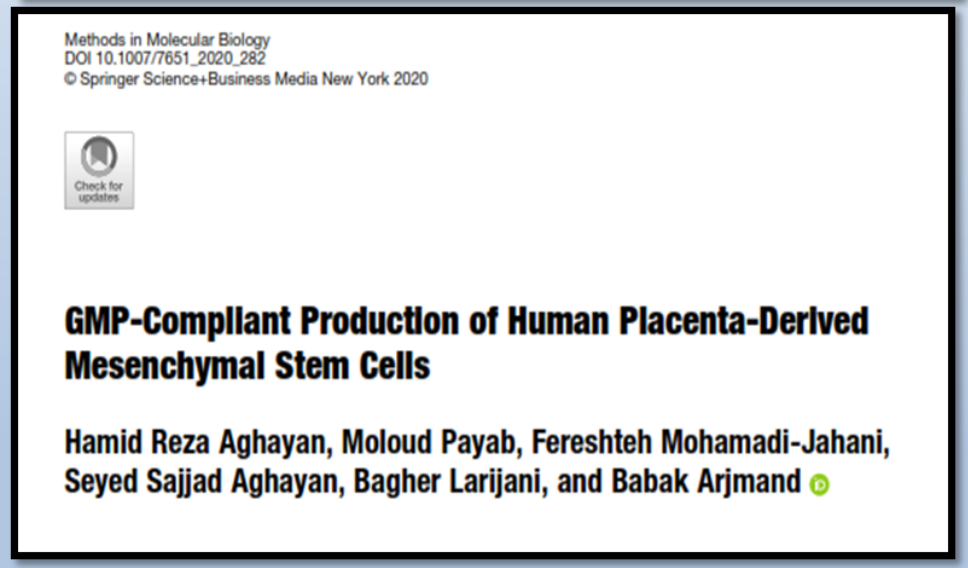
Somayeh Ebrahimi-Barough, Jafar Ai, Moloud Payab, Sepideh Alavi-Moghadam, Ameneh Shokati, Hamid Reza Aghayan, Bagher Larijani, and Babak Arjmand

Human endometrial stem cells as an invaluable source for cell therapy have introduced treatment for MS. In this respect, good manufacturing practice (GMP) has a pivotal role in clinical production of stem cells. This chapter tries to describe the protocol of GMP-grade endometrial stem cells for treatment of MS.

1. **Larijani, B**., Arjmand, B., Amoli, M.M. *et al.* Establishing a cGMP pancreatic islet processing facility: the first experience in Iran. *Cell Tissue Bank* **13**, 569–575 (2012).

2.Ebrahimi-Barough S,…, **Larijani B,** Arjmand B. Standard operating procedure for the good manufacturing practice-compliant production of human endometrial stem cells for multiple sclerosis. Stem Cells and Good Manufacturing Practices: Methods, Protocols, and Regulations. 2021:199-212.

In this chapter the authors have demonstrated the manufacturing of GMP-grade human fetal liver-derived mesenchymal stem cells.



the current chapter is to describe GMP-compliant production of human PLMSCs, which are suitable for clinical applications.

1. **Larijani B**, Aghayan HR, Goodarzi P, Arjmand B. GMP-grade human fetal liver-derived mesenchymal stem cells for clinical transplantation. Stem Cells and Good Manufacturing Practices: Methods, Protocols, and Regulations. 2015:123-36.

2. Aghayan HR, Payab M, Mohamadi-Jahani F, Aghayan SS, **Larijani B**, Arjmand B. GMP-compliant production of human placenta-derived mesenchymal stem cells. Stem cells and good manufacturing practices: Methods, protocols, and regulations. 2021:213-25.

Clinical studies

Islet transplantation

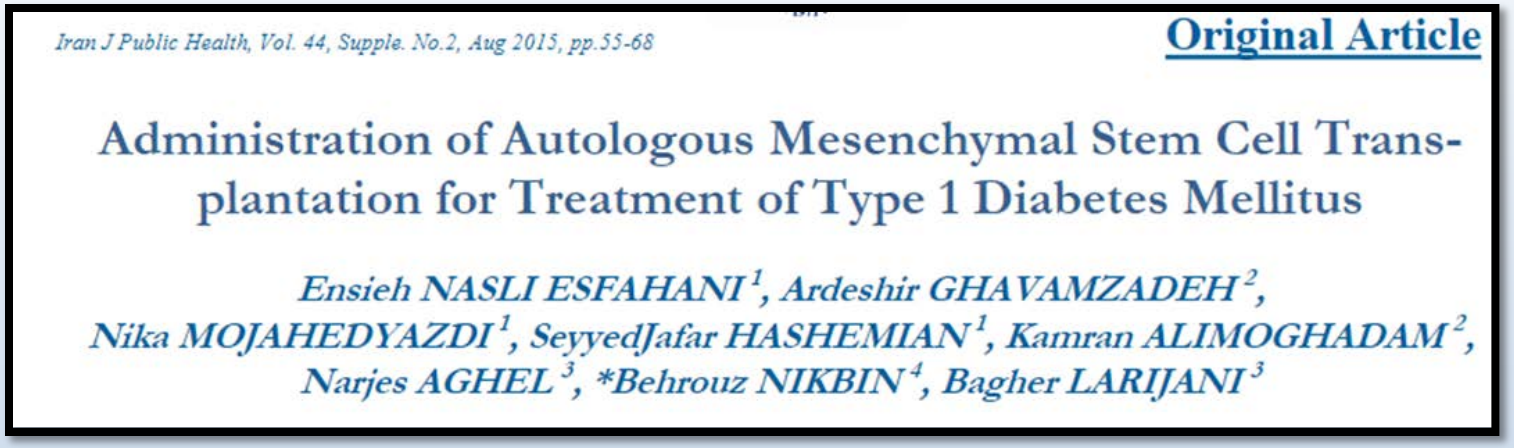
Cell Tissue Bank. 2012 Dec;13(4):569-75. doi: 10.1007/s10561-011-9273-1. Epub 2011 Aug 5.

Establishing a cGMP pancreatic islet processing facility: the first experience in Iran

Bagher Larijani [1], Babak Arjmand, Mahsa M Amoli, Ziliang Ao, Ali Jafarian, Mitra Mahdavi-Mazdah, Hossein Ghanaati, Reza Baradar-Jalili, Sasan Sharghi, Abbas Norouzi-Javidan, Hamid Reza Aghayan

In year 2005, the funding for establishing a current Good Manufacturing Practice (cGMP) islet processing facility by Endocrinology and Metabolism Research Center was approved by Tehran University of Medical Sciences and first successful clinical islet isolation and transplantation was performed in September 2010. This article can provide valuable information for regional countries interested to establish similar facilities.

Larijani B, Arjmand B, Amoli MM, et al. Establishing a cGMP pancreatic islet processing facility: the first experience in Iran. Cell Tissue Bank. 2012;13(4):569-575. doi:10.1007/s10561-011-9273-1



Iran J Public Health, Vol. 44, Supple. No.2, Aug 2015, pp.55-68

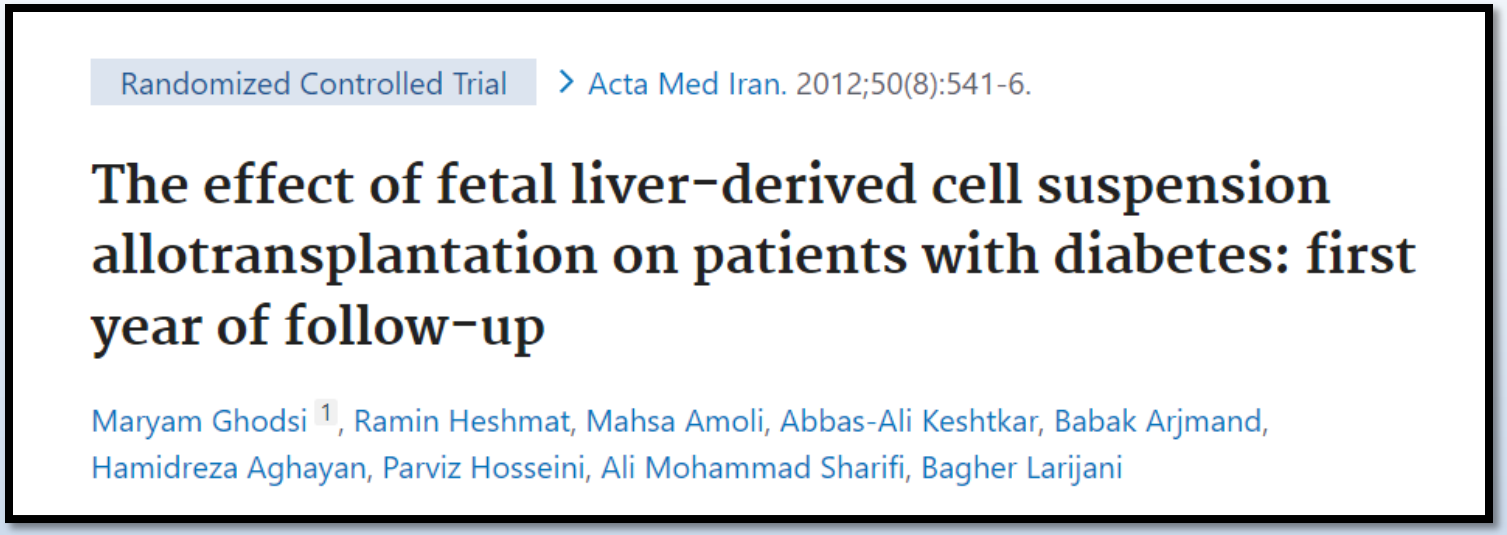
Original Article

Administration of Autologous Mesenchymal Stem Cell Transplantation for Treatment of Type 1 Diabetes Mellitus

Ensieh NASLI ESFAHANI[1], *Ardeshir GHAVAMZADEH*[2], *Nika MOJAHEDYAZDI*[1], *SeyyedJafar HASHEMIAN*[1], *Kamran ALIMOGHADAM*[2], *Narjes AGHEL*[3], **Behrouz NIKBIN*[4], *Bagher LARIJANI*[3]

- Twenty-three patients with T1DM, at 5 to 30 years of age and in both sexes, participated in this study. This trial consisted of two phases; In both phases, 100 milliliter of mixed mesenchymal stem cells and normal saline containing 2×10^6 autologous cells/kg for each patient was delivered to patients through cubital vein. All patients were evaluated at 1, 3, 6 and 9 months after the procedure.
- Mean levels of HbA1c and prescribed insulin dosage significantly decreased in comparison to the beginning of the study ($P<0.05$). Therefore, transplantation of BM-MSC can be viewed as a promising, simple, safe, and efficient therapeutic modality for T1DM.

NASLI ESFAHANI E,…, LARIJANI B. Administration of Autologous Mesenchymal Stem Cell Transplantation for Treatment of Type 1 Diabetes Mellitus. Iran J Public Health. 2015;44(Supple 2):55-68



- Fifty six patients with type one (n=30) and type two (n=26) diabetes, aged 10-58 years old (32.8 ± 16.3) were divided into the intervention and placebo group. The patients in the intervention group underwent fetal liver-derived hematopoietic stem cell transplantation while the patients in the placebo group received 5 ml of normal saline both via an intravenous route
- in this study, fetal liver-derived hematopoietic stem cell transplantation had no significant effects on glycemic control. The heterogeneity of our patients might account for the negative results.

Ghodsi, M., Heshmat, R., Amoli, M., Keshtkar, A. A., Arjmand, B., Aghayan, H., Hosseini, P., Sharifi, A. M., & Larijani, B. (2012). The effect of fetal liver-derived cell suspension allotransplantation on patients with diabetes: first year of follow-up. Acta medica Iranica, 50(8), 541–546.

> J Diabetes Metab Disord. 2015 Apr 22:14:33. doi: 10.1186/s40200-014-0126-x. eCollection 2015.

Evaluation of fetal cell transplantation safety in treatment of diabetes: a three-year follow-up

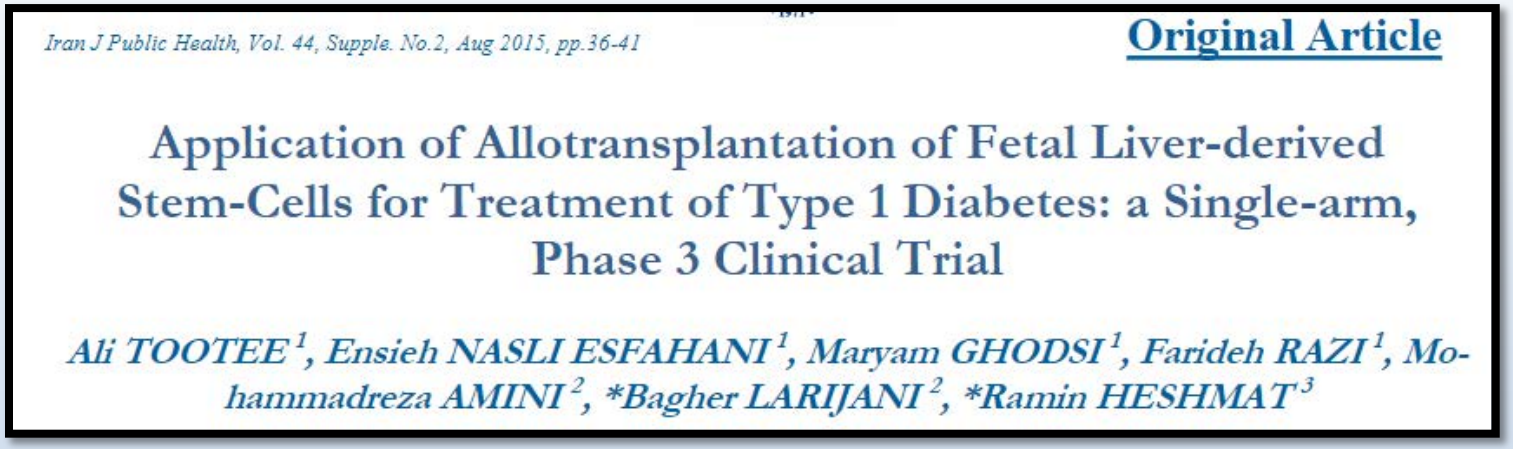
Ensieh Nasli-Esfahani [1], Maryam Ghodsi [2], Peyvand Amini [2], Abbas Ali Keshtkar [3], Somayeh Amiri [2], Nika Mojahed-Yazdi [2], Ali Tootee [3], Bagher Larijani [4]

Affiliations + expand

PMID: 26207222 PMCID: PMC4511990 DOI: 10.1186/s40200-014-0126-x

- 4 out of a total number of 56 patients who had undergone either fetal liver-derived cell suspension allotransplantation or placebo injection in 2007 (IRCT number: 138811071414 N10) were contacted and recruited for the evaluation of possible complications.
- There were no life-threatening complications nor significant differences in terms of evaluated diabetes complications (retinopathy, neuropathy, nephropathy and cardiovascular diseases) between the case and control groups. However, one case of meningioma was reported.

Nasli-Esfahani E, Ghodsi M, Amini P, Keshtkar AA, Amiri S, Mojahed-Yazdi N, Tootee A, **Larijani B**. Evaluation of fetal cell transplantation safety in treatment of diabetes: a three-year follow-up. J Diabetes Metab Disord. 2015 Apr 22;14:33. doi: 10.1186/s40200-014-0126-x. PMID: 26207222; PMCID: PMC4511990



Iran J Public Health, Vol. 44, Supple. No.2, Aug 2015, pp.36-41

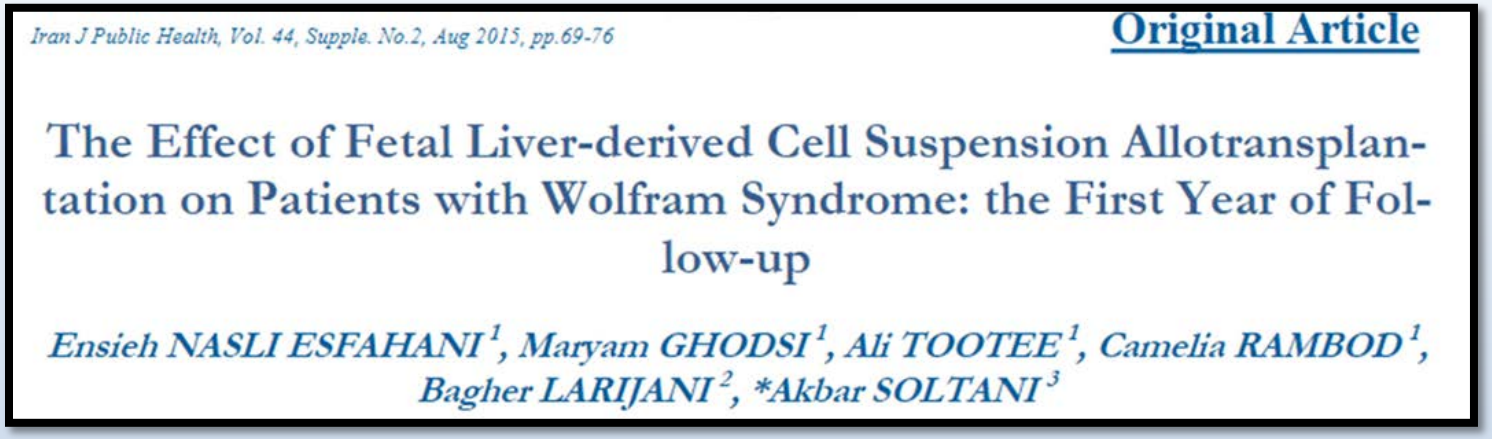
Original Article

Application of Allotransplantation of Fetal Liver-derived Stem-Cells for Treatment of Type 1 Diabetes: a Single-arm, Phase 3 Clinical Trial

Ali TOOTEE[1], *Ensieh NASLI ESFAHANI*[1], *Maryam GHODSI*[1], *Farideh RAZI*[1], *Mohammadreza AMINI*[2], **Bagher LARIJANI*[2], **Ramin HESHMAT*[3]

- 72 patients with recently diagnosed type 1 DM were recruited and fetal liver-derived cell suspension was administered by the means of intravenous injection. Anthropometric measurements and clinical data such as body mass index, duration of the disease, daily insulin requirement were recorded as well as some of laboratory indicators of favorable therapeutic response (hemoglobin A1c, c-peptide) before and after the intention at 0, 1, 3, 6 and 12 months following the intervention.
- Administration of fetal liver-derived fetal stem-cells resulted in significant changes in indicators of diabetes control in the patients. Required daily insulin dose and HbA1c showed significant changes, and c-peptide levels decreased significantly during the first three months of follow up period

TOOTEE A,…, LARIJANI B. Application of Allotransplantation of Fetal Liver-derived Stem-Cells for Treatment of Type 1 Diabetes: a Single-arm, Phase 3 Clinical Trial. Iran J Public Health. 2015;44(Supple 2):36-41



Iran J Public Health, Vol. 44, Supple. No.2, Aug 2015, pp.69-76

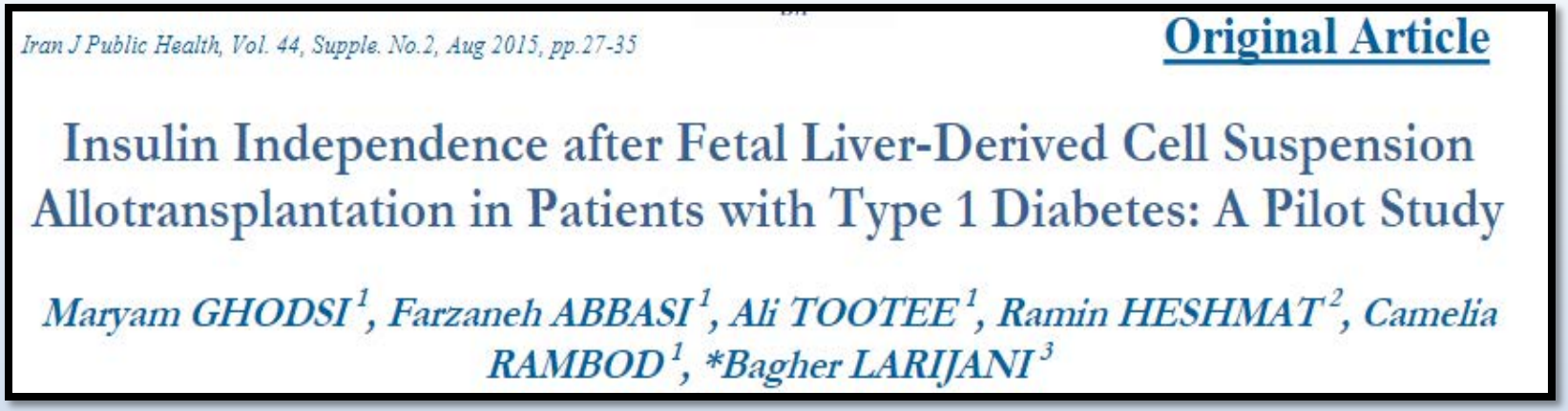
Original Article

The Effect of Fetal Liver-derived Cell Suspension Allotransplantation on Patients with Wolfram Syndrome: the First Year of Follow-up

Ensieh NASLI ESFAHANI [1], *Maryam GHODSI* [1], *Ali TOOTEE* [1], *Camelia RAMBOD* [1], *Bagher LARIJANI* [2], **Akbar SOLTANI* [3]

- Patients with type 1 diabetes (n=16) aged 6-30 years-old were included in the study. Fetal liver-derived cell suspension was transplanted by the means of intravenous injection patient.
- Findings of this study indicated that transplantation of fetal stem cells could, although not permanently, be an effective therapeutic intervention in patients with type 1 diabetes.

GHODSI M,…, LARIJANI B. Insulin Independence after Fetal Liver-Derived Cell Suspension Allotransplantation in Patients with Type 1 Diabetes: A Pilot Study. Iran J Public Health. 2015;44(Supple 2):27-35.



Iran J Public Health, Vol. 44, Supple. No.2, Aug 2015, pp.27-35

Original Article

Insulin Independence after Fetal Liver-Derived Cell Suspension Allotransplantation in Patients with Type 1 Diabetes: A Pilot Study

*Maryam GHODSI[1], Farzaneh ABBASI[1], Ali TOOTEE[1], Ramin HESHMAT[2], Camelia RAMBOD[1], *Bagher LARIJANI[3]*

- Six patients with WS aged 23-34 (mean: 29.50, SD: 4.76) were recruited for the current phase 3 single-arm clinical trial. The participants underwent fetal liver-derived hematopoietic stem cell transplantation. In order to evaluate the effectiveness of transplantation, glycemic control indexes were measured at regular follow-up sessions.
- One patient (out of six) experienced a 6 months insulin-free period with acceptable HbA1c levels. In another patient with history of recurrent hypoglycemic attacks, the frequency of bout of attacks remarkably decreased. It can be Concluded that Stem-cell therapy may represent a new method for treatment of patients with Wolfram Syndrome.

NASLI ESFAHANI E,.., LARIJANI B. The Effect of Fetal Liver-derived Cell Suspension Allotransplantation on Patients with Wolfram Syndrome: the First Year of Follow-up. Iran J Public Health. 2015;44(Supple 2):69-76

Med J Islam Repub Iran. 2022; 36: 34.
Published online 2022 Apr 13. doi: 10.47176/mjiri.36.34
PMCID: PMC9448473
PMID: 36128298

Clinical Outcomes of Fetal Stem Cell Transplantation in Type 1 Diabetes Are Related to Alternations to Different Lymphocyte Populations

Ali Tootee, [1] Behrouz Nikbin, [2] Ensieh Nasli Esfahani, [1] Babak Arjmand, [3] Hamidreza Aghayan, [3] Mostafa Qorbani, [4] Aziz Ghahari, [5] and Bagher Larijani[✉ 6,*]

In patients with diabetes, transplantation of stem cells increases C-peptide levels and induces insulin independence for some period. Today, this positive therapeutic outcome is widely attributed to the well-documented immunomodulatory properties of stem cells. The aim of this study was to report alternations in different lymphocyte populations in a stem cell clinical trial performed in our institute.

Our results demonstrated that transplantation of stem cells leads to significant positive therapeutic outcomes in one group of patients who showed totally distinct patterns of alternation to different groups of lymphocytes.

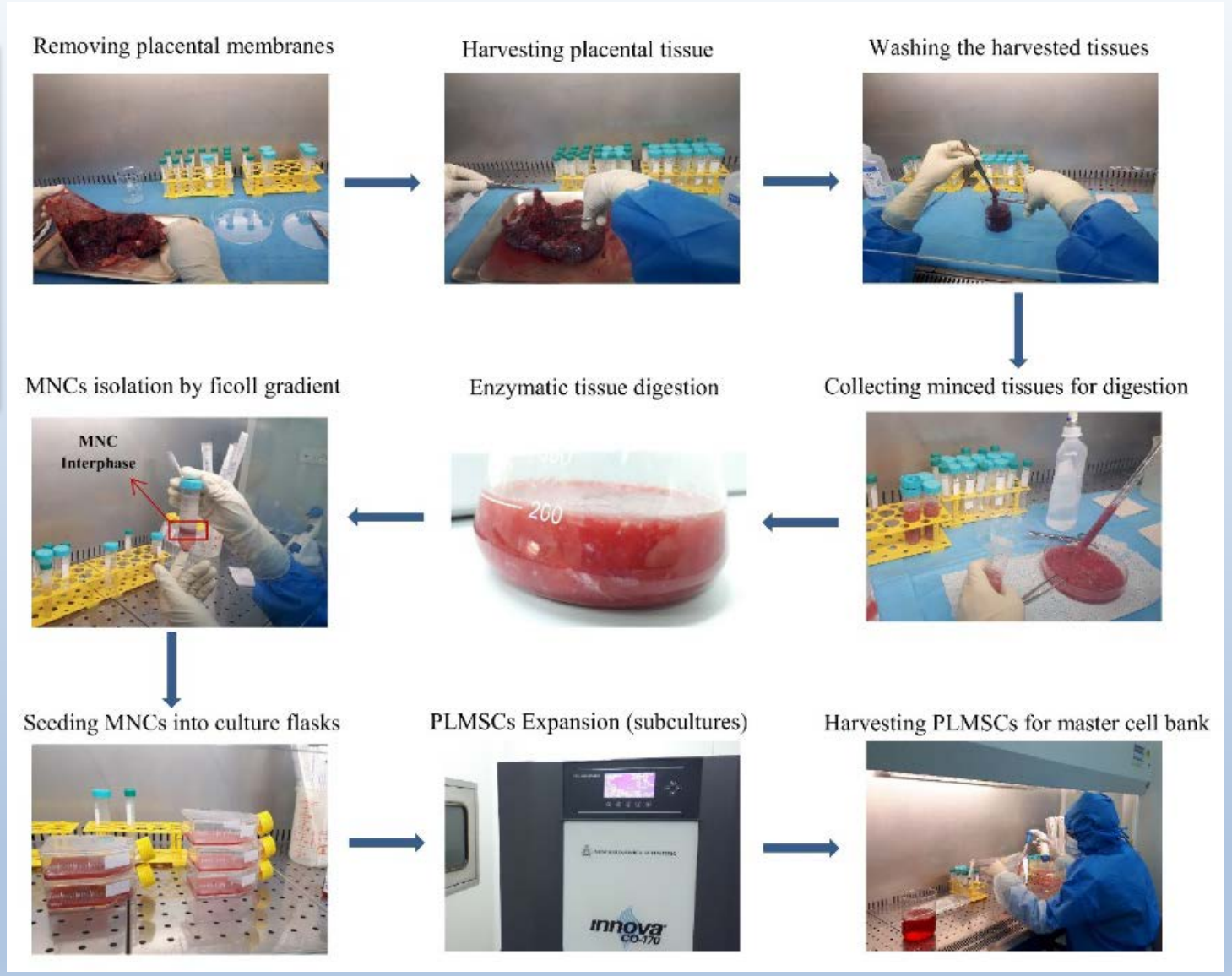
Tootee A, Nikbin B, Nasli Esfahani E, Arjmand B, Aghayan H, Qorbani M, Ghahari A, Larijani B. Clinical Outcomes of Fetal Stem Cell Transplantation in Type 1 Diabetes Are Related to Alternations to Different Lymphocyte Populations. Med J Islam Repub Iran. 2022 Apr 13;36:34.

J Diabetes Metab Disord. 2021 Jul 9;20(2):1179-1189. doi: 10.1007/s40200-021-00837-9. eCollection 2021 Dec.

Placenta derived Mesenchymal Stem Cells transplantation in Type 1 diabetes: preliminary report of phase 1 clinical trial

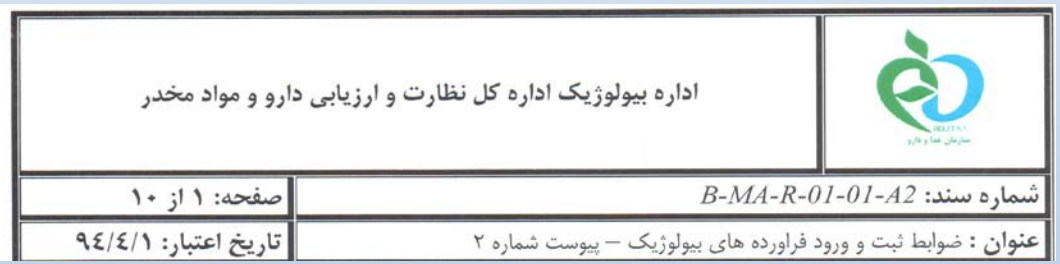
Sedighegh Madani [1], Aria Setudeh [2], Hamid Reza Aghayan [3], Sepideh Alavi-Moghadam [3], Mahtab Rouhifard [4], Negar Rezaei [4], Parastoo Rostami [2], Reihaneh Mohsenipour [2], Davoud Amirkashani [5], Fatemeh Bandarian [1], Babak Arjmand [3], Bagher Larijani [6]

To our knowledge; this is the first preliminary report of placenta derived MSCs (PLMSCs) transplantation in juvenile T1DM. This preliminary report of our phase I clinical trial demonstrated the short term safety of PLMSCs transplantation in juvenile T1DM.



Madani S,…, Larijani B. Placenta derived Mesenchymal Stem Cells transplantation in Type 1 diabetes: preliminary report of phase 1 clinical trial. J Diabetes Metab Disord. 2021 Jul 9;20(2):1179-1189.

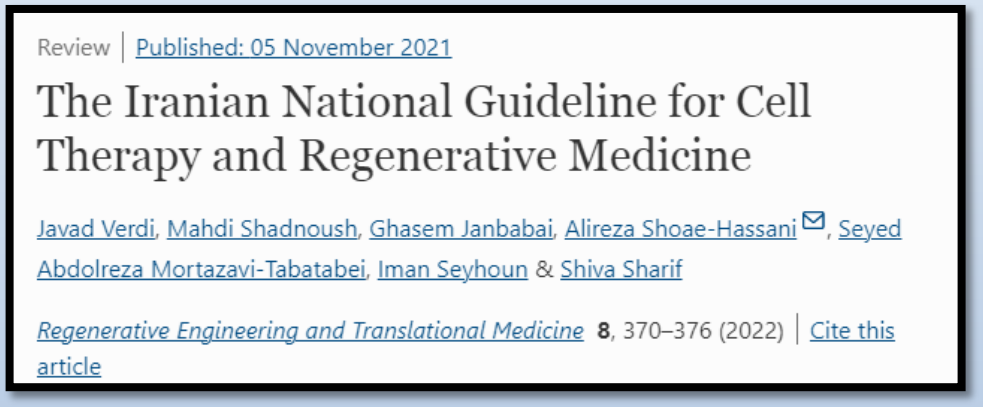
- Iran has many achievements and a good potential in the field of cell therapy and regenerative medicine, especially for the treatment of diabetes. In 2018, the Ministry of Health and Medical Education issued a national guideline for the establishment and operation of cell therapy and regenerative medicine departments in public and private therapeutic centers. This guideline aims to provide a regulatory framework and quality standards for the clinical application of stem cells and other cell-based therapies.


اداره بیولوژیک اداره کل نظارت و ارزیابی دارو و مواد مخدر

شماره سند: B-MA-R-01-01-A2	صفحه: ۱ از ۱۰
عنوان : ضوابط ثبت و ورود فراورده های بیولوژیک – پیوست شماره ۲	تاریخ اعتبار: ۹٤/٤/۱


ضوابط ثبت و ورود فراورده های بیولوژیک

پیوست شماره ۲ – ضوابط ثبت و ورود فراورده های بافت، سلول و ژن درمانی


Review | Published: 05 November 2021

The Iranian National Guideline for Cell Therapy and Regenerative Medicine

Javad Verdi, Mahdi Shadnoush, Ghasem Janbabai, Alireza Shoae-Hassani ✉, Seyed Abdolreza Mortazavi-Tabatabei, Iman Seyhoun & Shiva Sharif

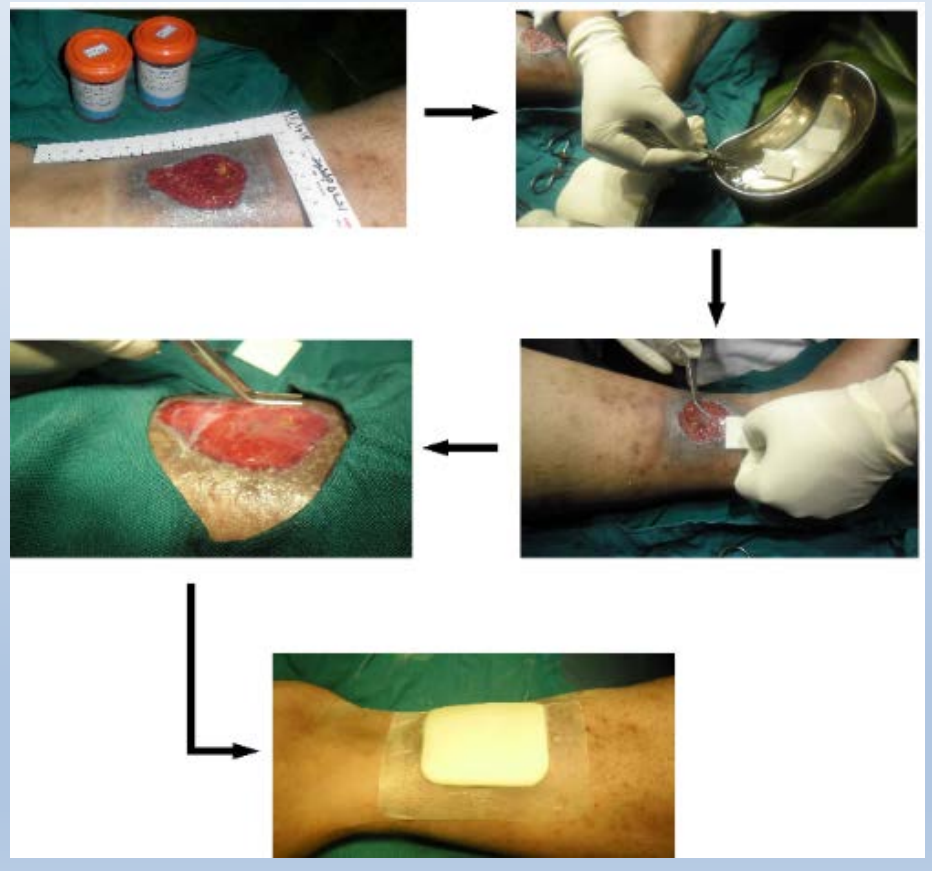
Regenerative Engineering and Translational Medicine **8**, 370–376 (2022) | Cite this article

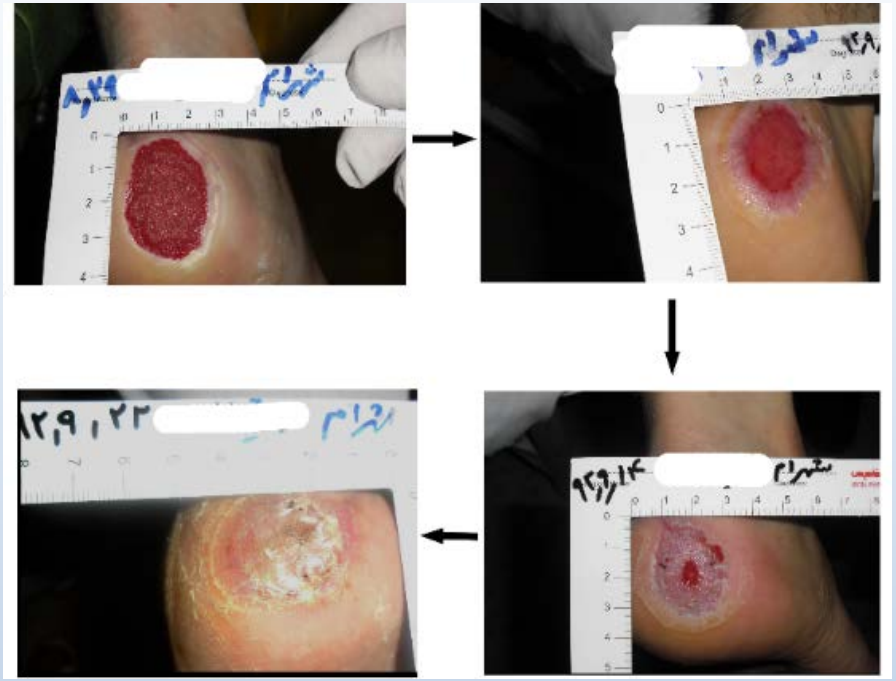
- Cell therapy is considered as a promising and cost-effective solution for the growing number of diabetic patients in Iran and worldwide, as it can potentially restore the function of the damaged pancreatic cells and regulate the blood glucose levels.

- Cell therapy is the future of diabetes control, as it offers a more personalized and effective treatment option than conventional therapies.

Aghayan HR, Arjmand B, Ahmadbeigi N, Vasei M. Draft of Iranian national guideline for cell therapy manufacturing. Archives of Iranian Medicine. 2017;20(8):0.

Our ongoing clinical trial: Investigating the effect of scaffold containing adipose tissue-derived stem cells in chronic wound healing in diabetic patients



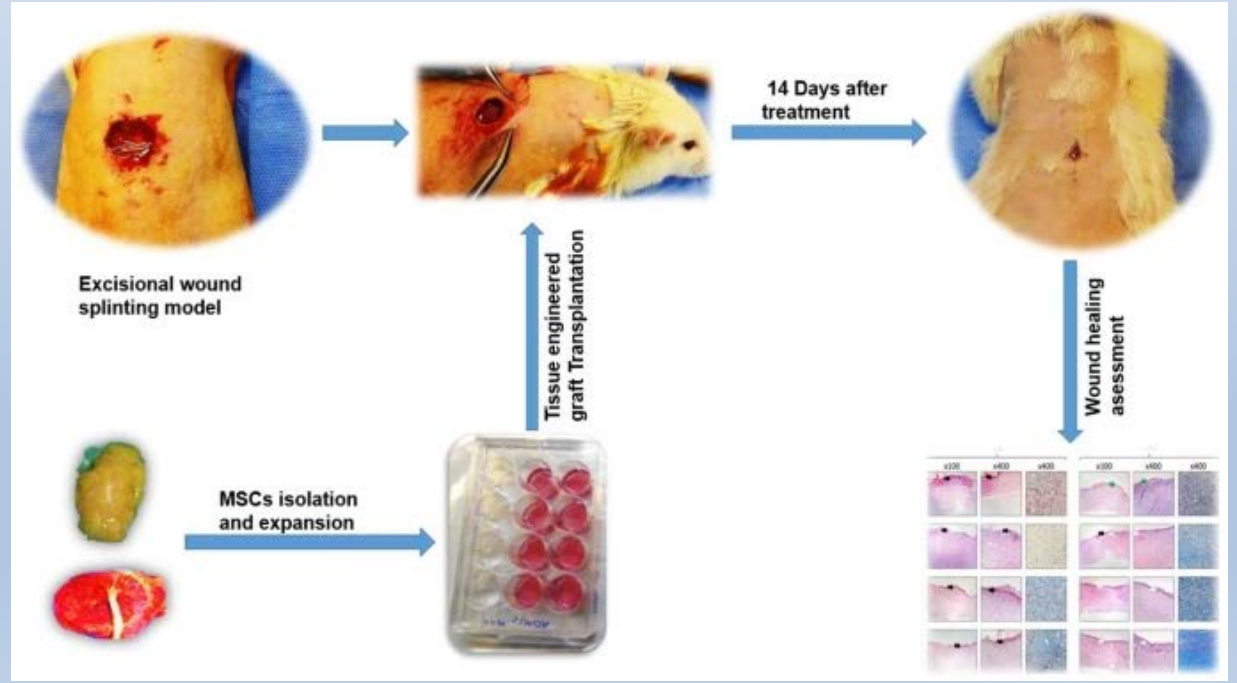


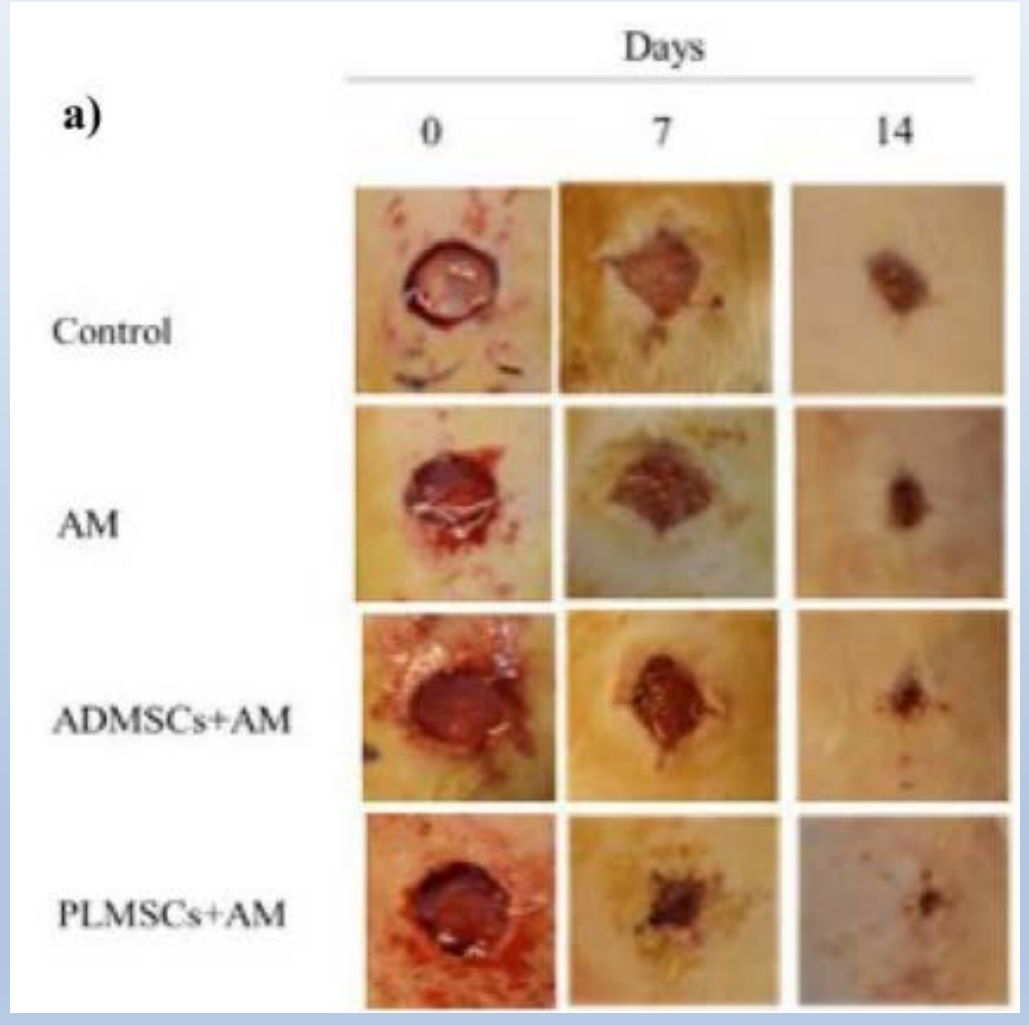
Unpublished data from our ongoing clinical trial which has been registered in Iranian Registry of Clinical Trials (IRCT)

Translational researches

MSCs' seeded amniotic membrane as a tissue-engineered dressing

The results of wound closure rate, re-epithelialization, angiogenesis, and collagen remodeling demonstrated that in comparison with the control groups, the MSC-seeded acellular amniotic membrane (AAMs) had superior regenerative effects in excisional wound animal model. We also found that PLMSCs had superior regenerative effects to ADMSc in the rat model of excisional wound.





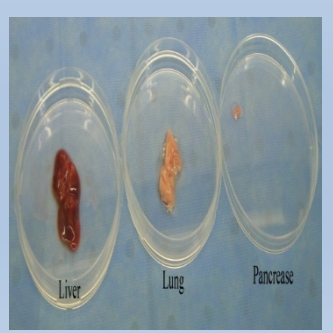
Aghayan HR, Hosseini MS, Gholami M, Mohamadi-Jahani F, Tayanloo-Beik A, Alavi-Moghadam S, Payab M, Goodarzi P, Abdollahi M, **Larijani B**, Arjmand B. Mesenchymal stem cells' seeded amniotic membrane as a tissue-engineered dressing for wound healing. Drug Deliv Transl Res. 2022 Mar;12(3):538-549.

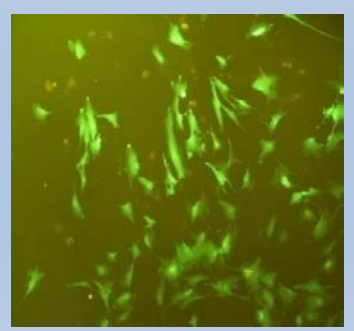
Front Endocrinol (Lausanne). 2019 Nov 6:10:761. doi: 10.3389/fendo.2019.00761. eCollection 2019.

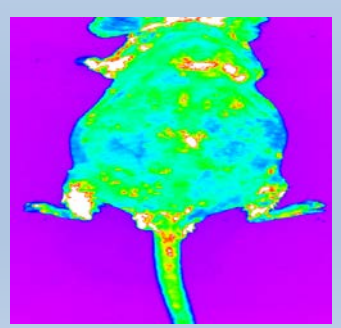
Co-transplantation of Human Fetal Mesenchymal and Hematopoietic Stem Cells in Type 1 Diabetic Mice Model

Babak Arjmand [1 2], Parisa Goodarzi [3], Hamid Reza Aghayan [1], Moloud Payab [4], Fakher Rahim [5], Sepideh Alavi-Moghadam [2], Fereshteh Mohamadi-Jahani [3], Bagher Larijani [6]

Based- on several studies human fetal mesenchymal and hematopoietic stem cells are ideal candidates for stem cell therapy. On the other hand, co-transplantation of them can improve their effects. Our results revealed that, co-transplantation of MSCs and HSCs has more therapeutic effects on T1D in comparison with MSCs transplantation. Also it was elucidated that, following cell transplantation, most of cells engrafted in the site of injury such as pancreas in T1D.







Arjmand B, …, Larijani B. Co-transplantation of Human Fetal Mesenchymal and Hematopoietic Stem Cells in Type 1 Diabetic Mice Model. Front Endocrinol (Lausanne). 2019 Nov 6;10:761.

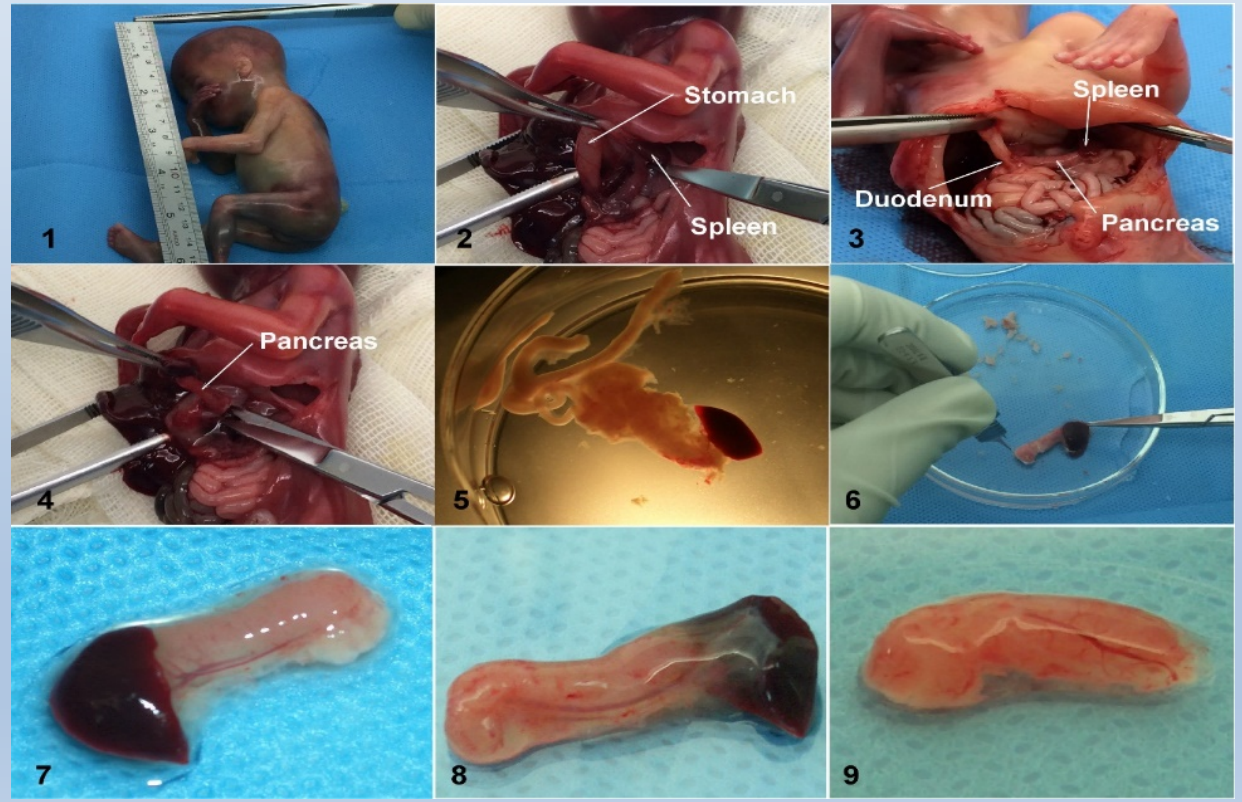
Original Article

A Simple and Cost-effective Method for Isolation and Expansion of Human Fetal Pancreas Derived Mesenchymal Stem Cells

Bagher Larijani MD[1], Babak Arjmand MD PhD[1], Naser Ahmadbeigi PhD[2], Khadijeh Falahzadeh MSc[3], Masoud Soleimani PhD[4], Forough Azam Sayahpour MSc[5], Hamid Reza Aghayan MD PhD Candidate•[1]

Previous studies have suggested mesenchymal stem cells (MSCs) as a suitable source for cell replacement therapy in diabetes.

The results of this study demonstrated that our simple and inexpensive method could yield a pure population of FPMSCs that might be suitable for transplantation.



Larijani B, Arjmand B, Ahmadbeigi N, et al. A simple and cost-effective method for isolation and expansion of human fetal pancreas derived mesenchymal stem cells. Arch Iran Med. 2015;18(11):770-775.

Jabbarpour *et al.*
Stem Cell Research & Therapy (2022) 13:268
https://doi.org/10.1186/s13287-022-02946-5

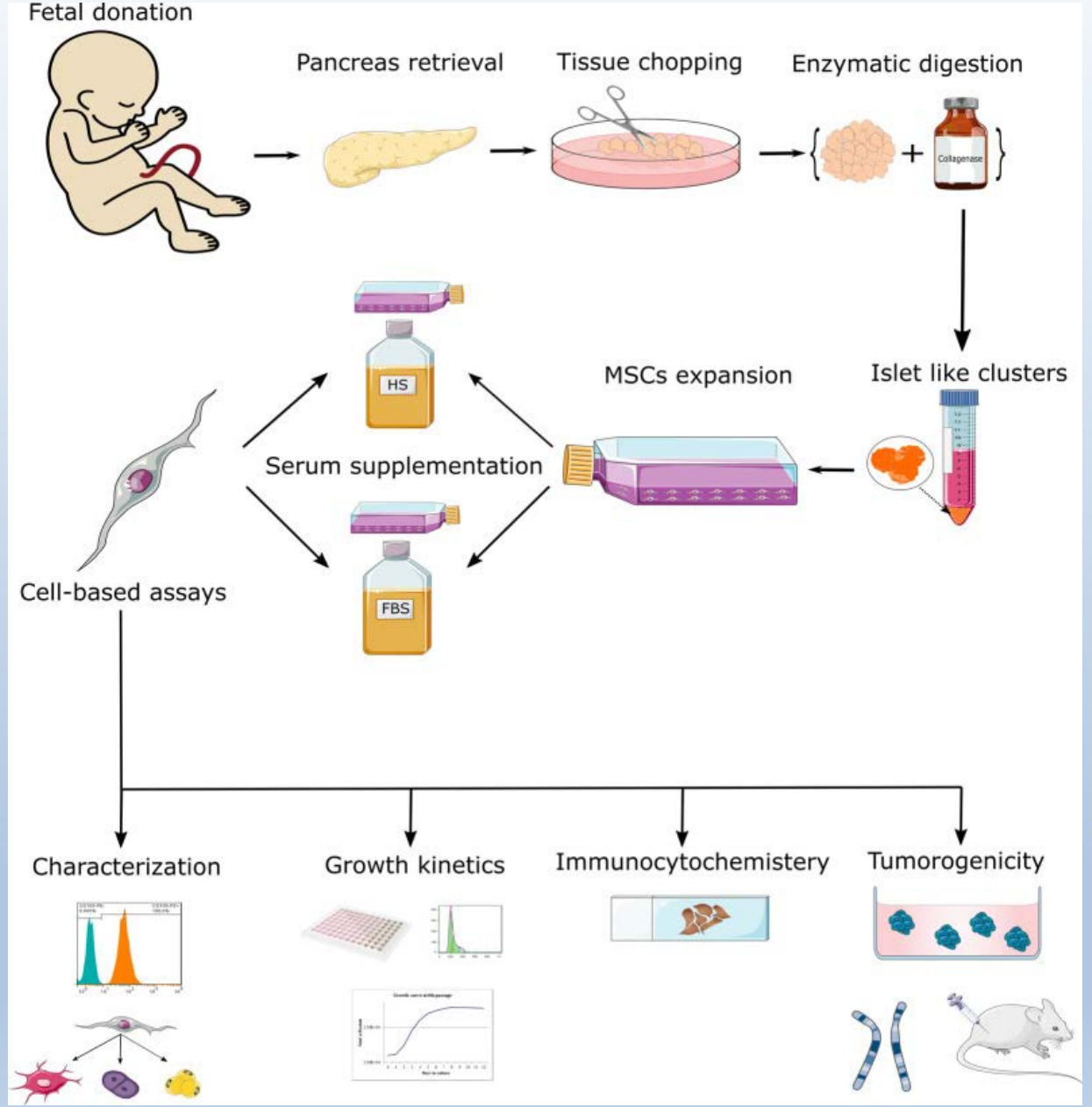
Stem Cell Research & Therapy

RESEARCH Open Access

Xeno-free protocol for GMP-compliant manufacturing of human fetal pancreas-derived mesenchymal stem cells

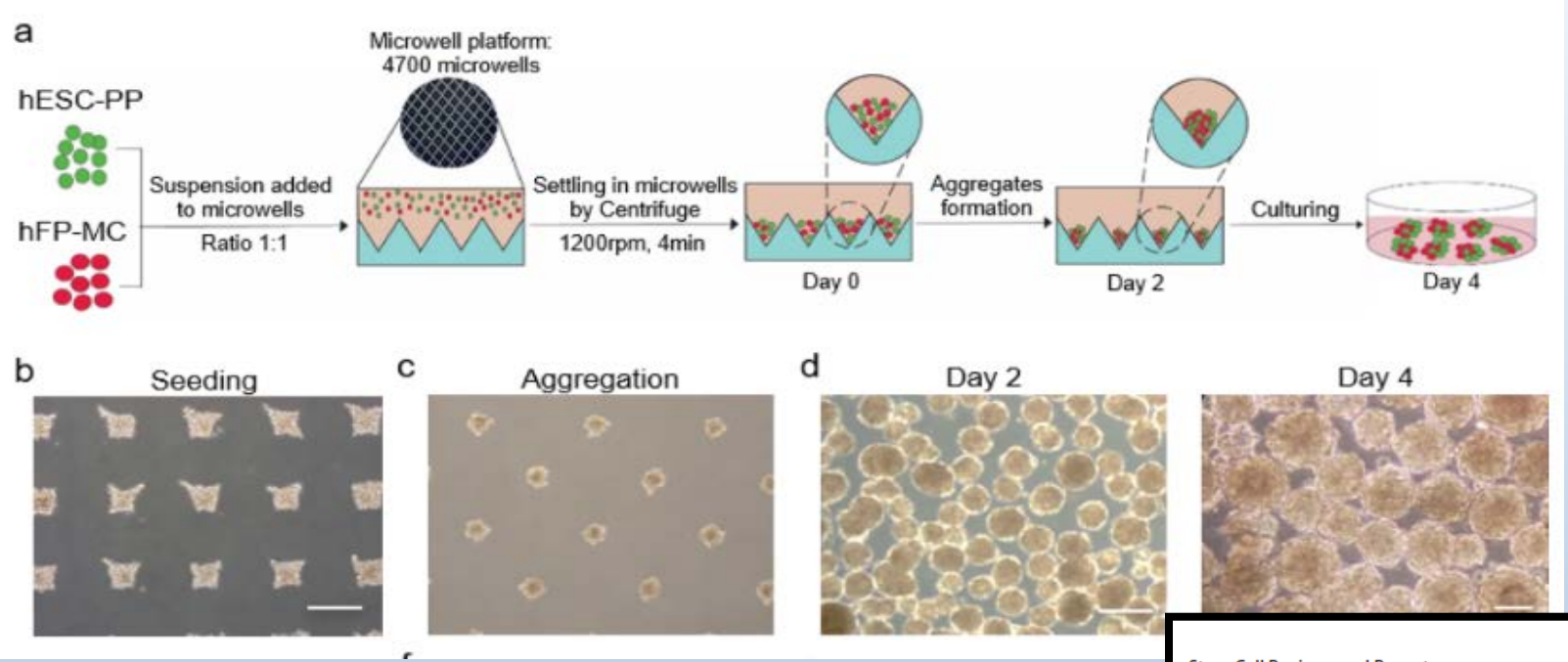
Zahra Jabbarpour[1†], Sajjad Aghayan[1†], Babak Arjmand[2], Khadijeh Fallahzadeh[2], Sepideh Alavi-Moghadam[2], Bagher Larijani[3] and Hamid Reza Aghayan[2*]

Our results demonstrated that human serum (HS) was a better serum alternative than fetal bovine serum (FBS) for in vitro expansion of fetal pancreatic-derived MSCs (FPMSCs). Compared with FBS, HS increased FPMSCs' proliferation rate and decreased their senescence. In conclusion, HS can effectively replace FBS for clinical-grade FPMSCs manufacturing.



Jabbarpour, Z., Aghayan, S., Arjmand, B., Fallahzadeh, K., Alavi-Moghadam, S., Larijani, B., & Aghayan, H. R. (2022). Xeno-free protocol for GMP-compliant manufacturing of human fetal pancreas-derived mesenchymal stem cells. Stem cell research & therapy, 13(1), 268. https://doi.org/10.1186/s13287-022-02946-5

ESC-derived endocrine progenitors



Pancreatic aggregates generated by forced aggregation through scalable AggreWell system showed similar features compared to the spheroids.

These aggregates, a combination of hFP-MCs and hESC-PPs, can be applied as an appropriate tool for assessing endocrine-niche interactions and developmental processes by mimicking the pancreatic tissue.

Stem Cell Reviews and Reports
https://doi.org/10.1007/s12015-021-10266-z

Check for updates

Improved Differentiation of hESC-Derived Pancreatic Progenitors by Using Human Fetal Pancreatic Mesenchymal Cells in a Micro-scalable Three-Dimensional Co-culture System

Zahra Ghezelayagh[1,2] · Mahsa Zabihi[2,3] · Ibrahim Zarkesh[4] · Carla A. C. Gonçalves[5] · Michael Larsen[5] · Newsha Hagh-parast[2] · Mohammad Pakzad[2] · Massoud Vosough[6] · Babak Arjmand[7] · Hossein Baharvand[1,2] · Bagher Larijani[8] · Anne Grapin-Botton[5,9] · Hamid Reza Aghayan[7] · Yaser Tahamtani[2,10]

Ghezelayagh Z,…, Larijani B. Improved differentiation of hESC-derived pancreatic progenitors by using human fetal pancreatic mesenchymal cells in a micro-scalable three-dimensional co-culture system. Stem cell reviews and reports. 2022 Jan 1:1-8.

Conclusion

- Diabetes is a common chronic disease that has a great burden on society. Many treatments have been provided for diabetes, but none of them have been able to cure it.
- Regenerative medicine and cell therapy are emerging fields that offer new possibilities for the treatment of endocrine disorders.
- By using stem cells, growth factors, and tissue engineering, these approaches aim to restore the function of damaged or diseased endocrine organs, such as the thyroid, pancreas, or adrenal glands.
- Several studies have shown the potential of these methods to improve the outcomes of patients with diabetes, osteoporosis, hypothyroidism, and other conditions.
- There are still many challenges and limitations that need to be overcome, such as the ethical and technical issues involved in the isolation, manipulation, and transplantation of stem cells.
- Therefore, more research and collaboration are needed to advance the field of regenerative medicine and cell therapy in endocrinology and to translate the findings from the bench to the bedside.

Thanks for your attention