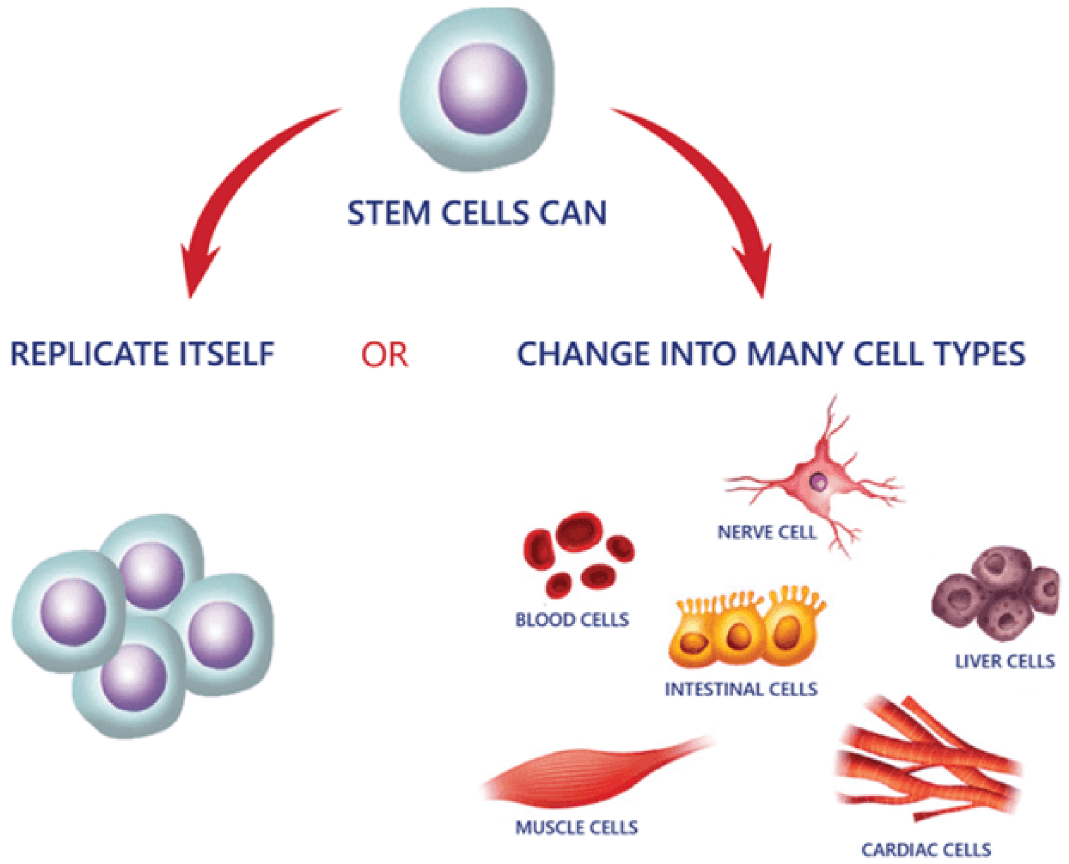
Advances in Bioengineering & Stem Cell-Based Strategies for Fertility Preservation

보라매병원 산부인과

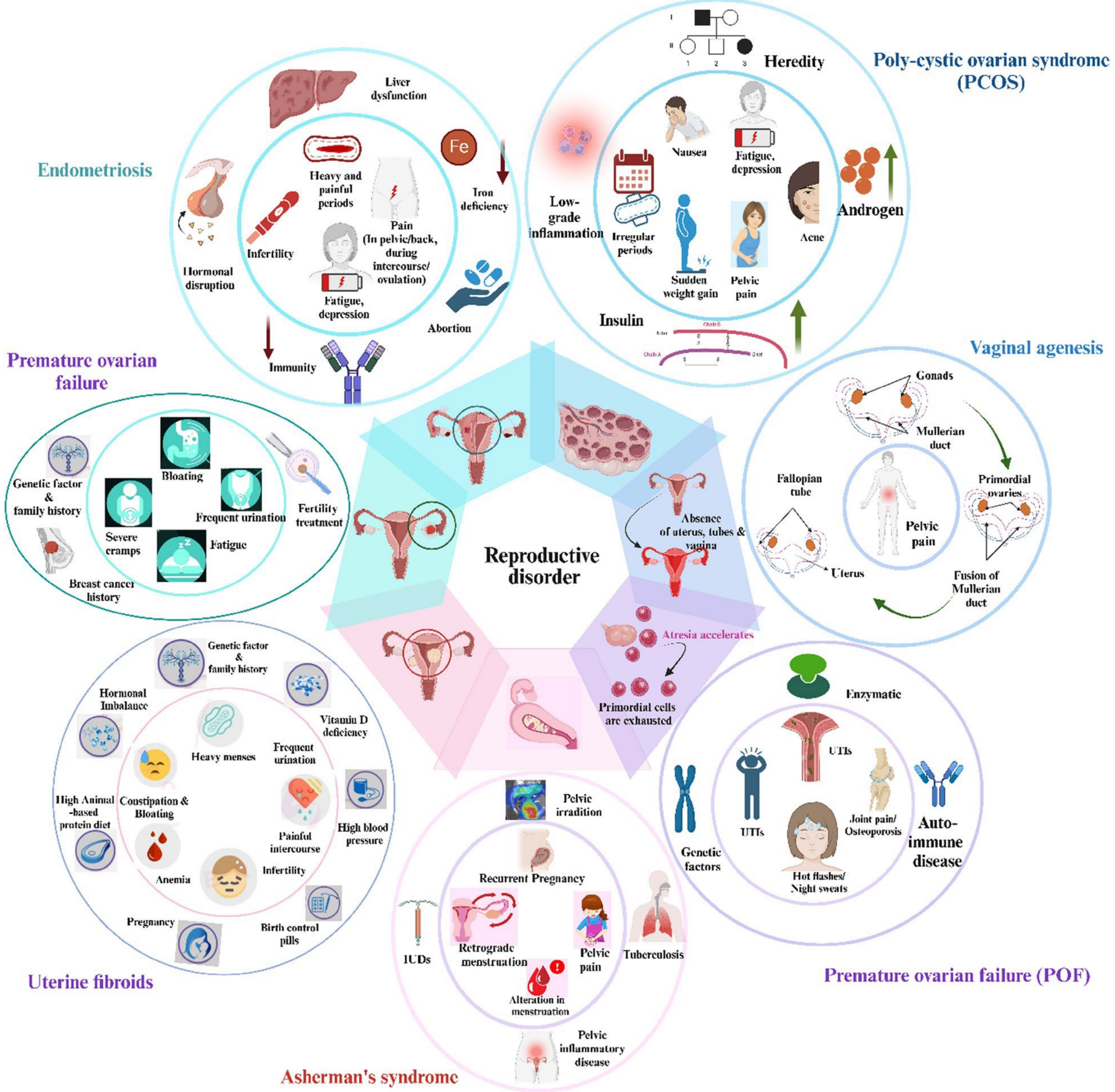
이다용

What are Stem Cells?

- Stem cells are the body's raw materials
  - can divide & renew through cell division for long periods of time
- Stem cells are an unspecialized population
- Stem cells can give rise to specialized cells after division in a process called differentiation



Stem Cells for Female Reproductive Disorders

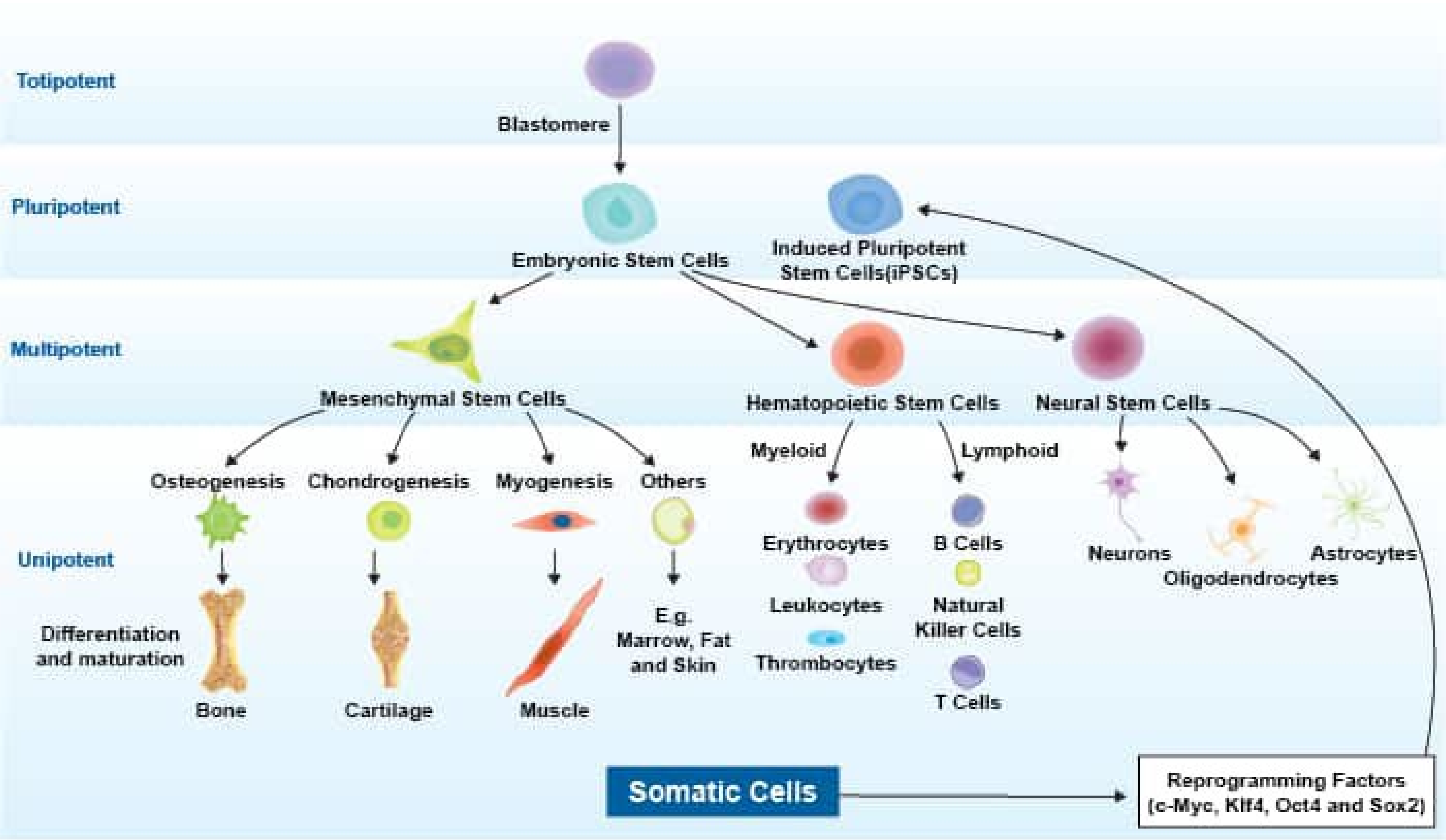


Potency of Stem Cells

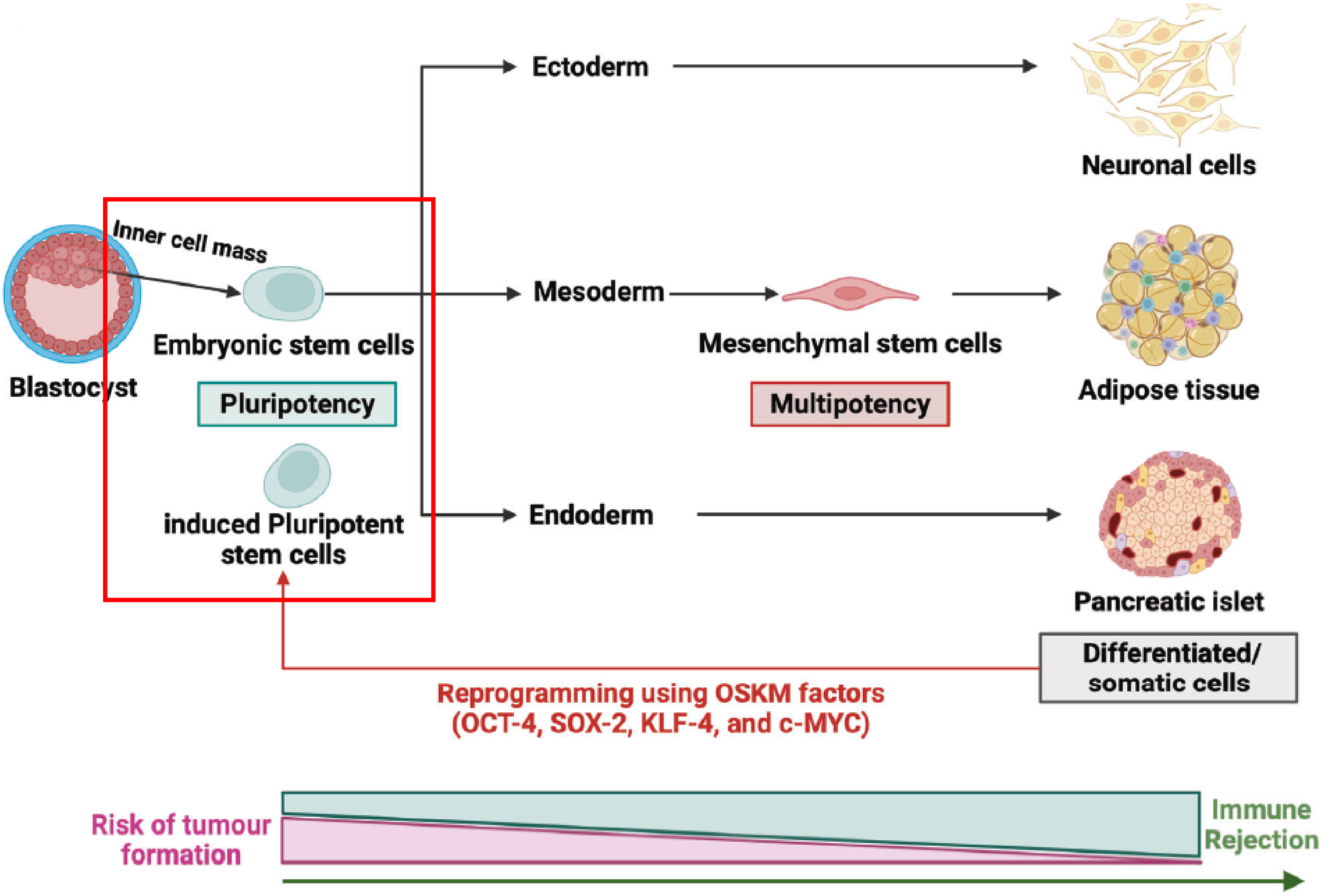
전능성

만능성

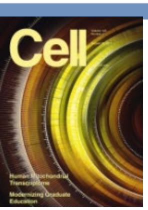
다능성



Pluripotent Stem Cells



Embryonic Stem Cells Based Therapy

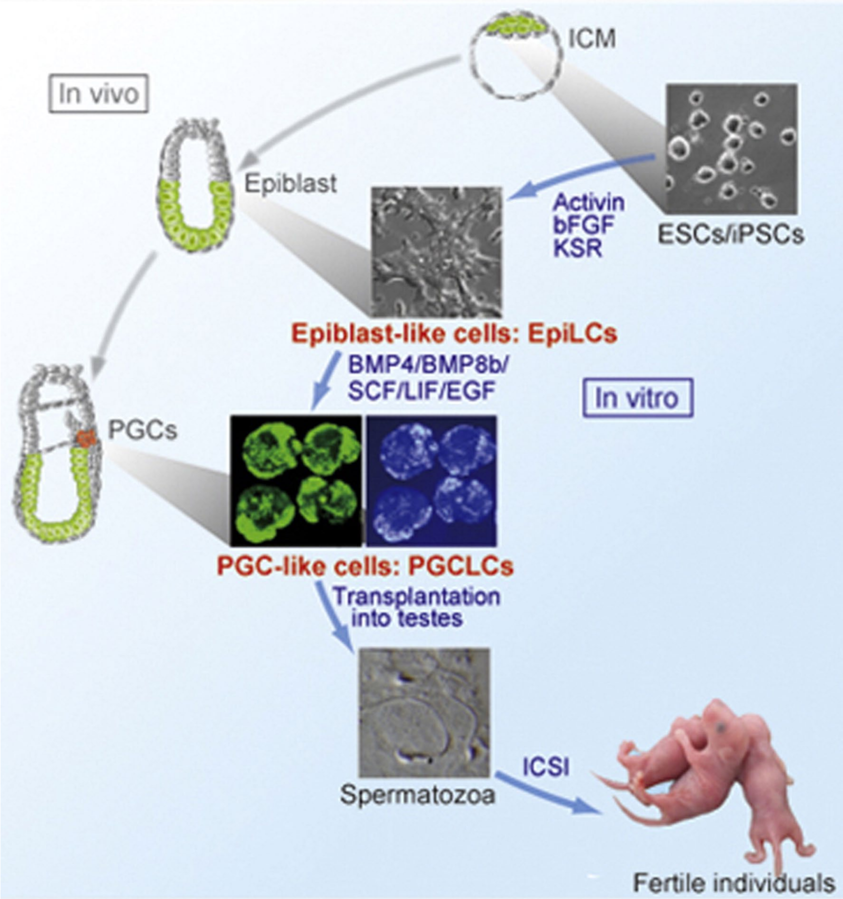


ARTICLE · Volume 146, Issue 4, P519-532, August 19, 2011 · *Open Archive* Download Full Issue

Reconstitution of the Mouse Germ Cell Specification Pathway in Culture by Pluripotent Stem Cells

Katsuhiko Hayashi [1,3] · Hiroshi Ohta [1,3] · Kazuki Kurimoto [1,3] · Shinya Aramaki [1] · Mitinori Saitou [1,2,3]

- Mouse ESCs are converted into primordial germ cells and epiblast like cells, by various growth factors

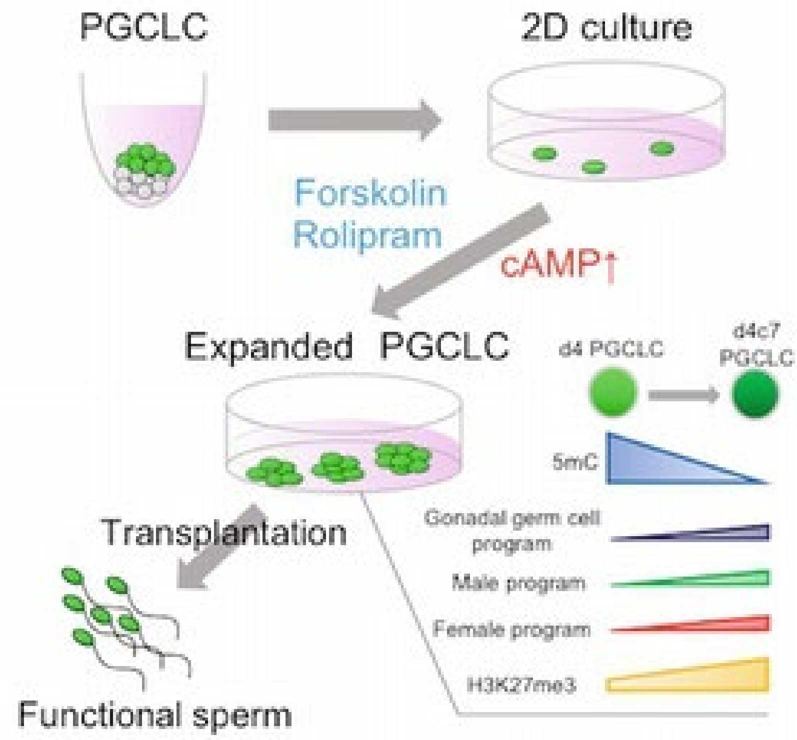


Home › The EMBO Journal › Article

In vitro expansion of mouse primordial germ cell-like cells recapitulates an epigenetic blank slate

Article | Published: 30 May 2017

Hiroshi Ohta, Kazuki Kurimoto, Ikuhiro Okamoto, Tomonori Nakamura, Yukihiro Yabuta, Hidetaka Miyauchi, Takuya Yamamoto, Yukiko Okuno, Masatoshi Hagiwara, Kenjiro Shirane, Hiroyuki Sasaki & Mitinori Saitou



Embryonic Stem Cells Based Therapy

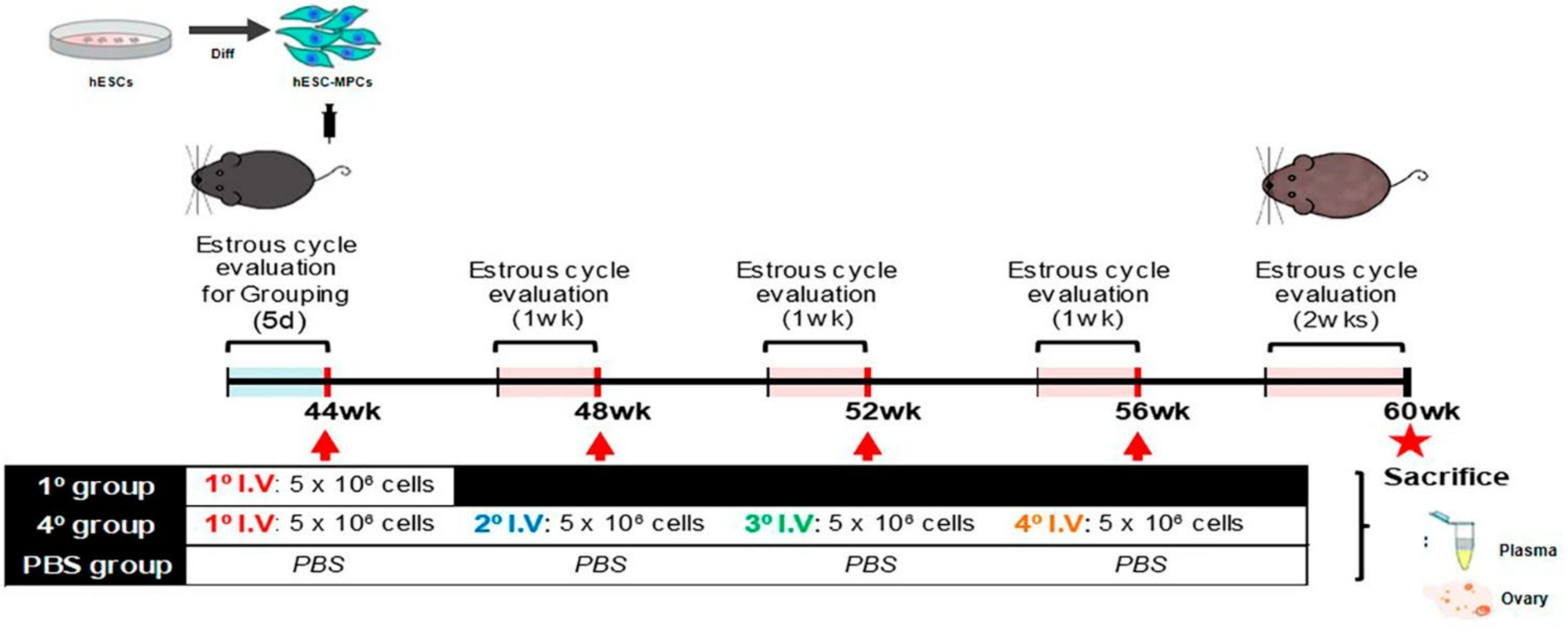
Home > Stem Cell Research & Therapy > Article

Multiple treatments with human embryonic stem cell-derived mesenchymal progenitor cells preserved the fertility and ovarian function of perimenopausal mice undergoing natural aging

Research | Open access | Published: 03 March 2024

Eun-Young Shin, Suji Jeong, Jeoung Eun Lee, Dong Seok Jeong, Dong Keun Han, Seok-Ho Hong & Dong Ryul Lee

- No approved stem cell-based therapies for preserving ovarian function during aging
- Human CHA-hES15 ESCs (Korea Stem Cell Registry No. hES12010028) → human ESC-MPCs
- Natural perimenopausal mouse model, 10 months of age



Embryonic Stem Cells Based Therapy

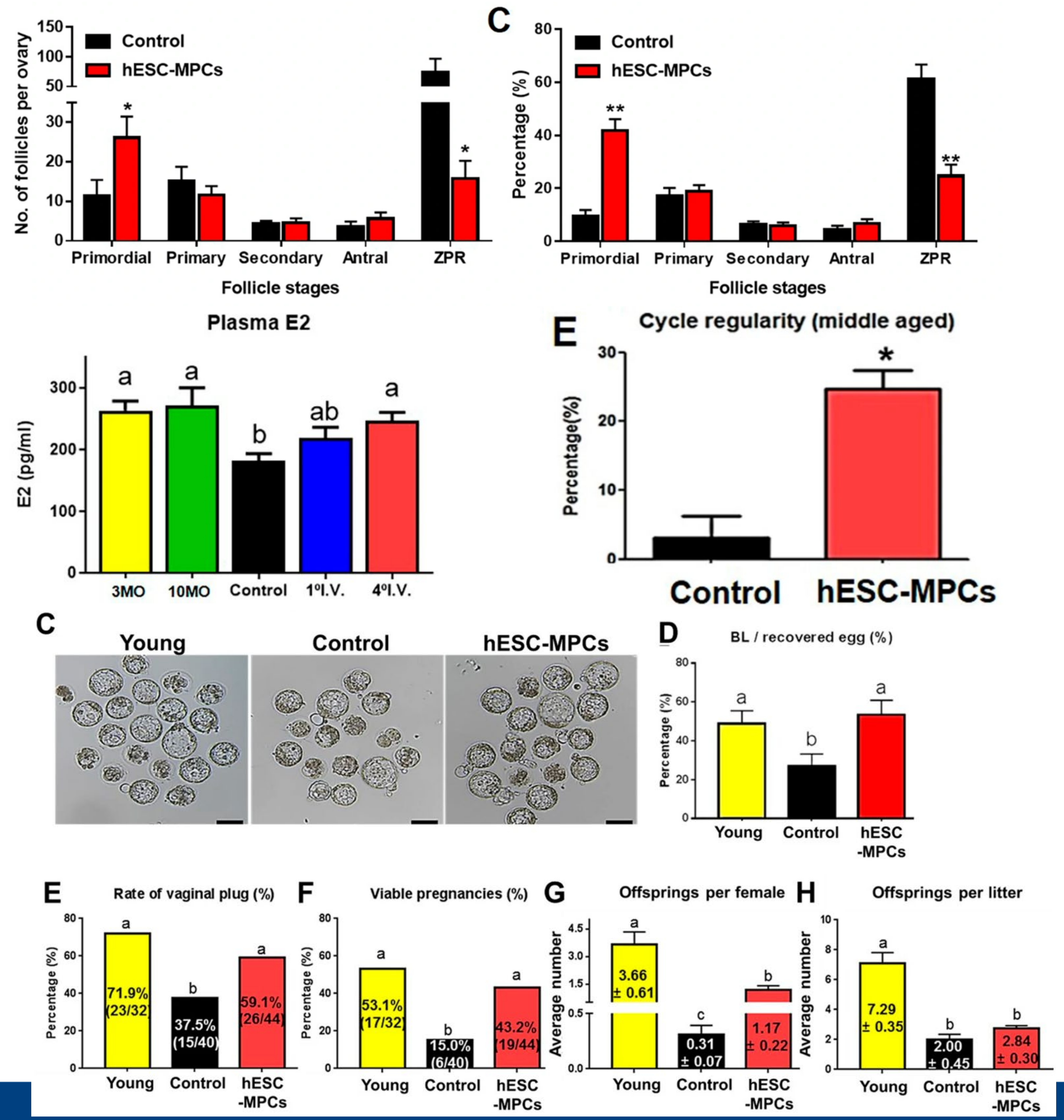
Home > Stem Cell Research & Therapy > Article

Multiple treatments with human embryonic stem cell-derived mesenchymal progenitor cells preserved the fertility and ovarian function of perimenopausal mice undergoing natural aging

Research | Open access | Published: 03 March 2024

Eun-Young Shin, Suji Jeong, Jeoung Eun Lee, Dong Seok Jeong, Dong Keun Han, Seok-Ho Hong & Dong Ryul Lee

- Increased primordial follicles
- Normalized estradiol levels
- Restored estrous cycles
- Higher embryonic development & live birth rates



Embryonic Stem Cells Based Therapy

Home > Stem Cell Research & Therapy > Article

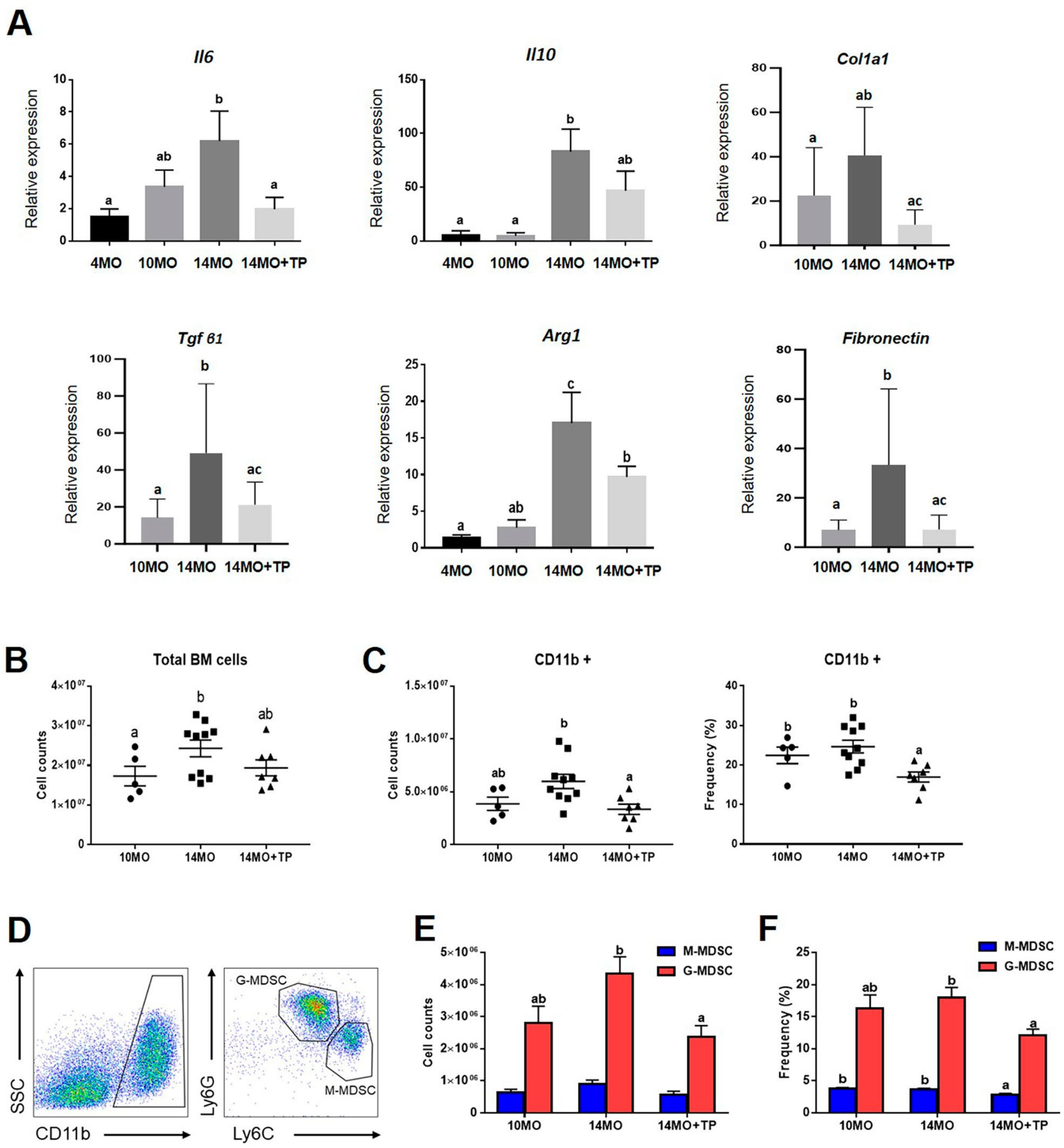
Multiple treatments with human embryonic stem cell-derived mesenchymal progenitor cells preserved the fertility and ovarian function of perimenopausal mice undergoing natural aging

Research | Open access | Published: 03 March 2024

Eun-Young Shin, Suji Jeong, Jeoung Eun Lee, Dong Seok Jeong, Dong Keun Han, Seok-Ho Hong & Dong Ryul Lee

- Reduced ovarian fibrosis by downregulating inflammation & fibrosis-related genes via the suppression of myeloid-derived suppressor cells (MDSCs) produced in the bone marrow

pro-inflammatory cytokines / pro-fibrotic macrophage / pro-fibrotic genes



Induced Pluripotent Stem Cells Based Therapy

Home > Clinical Epigenetics > Article

Epigenetic regulation and factors that influence the effect of iPSCs-derived neural stem/progenitor cells (NS/PCs) in the treatment of spinal cord injury

Review | Open access | Published: 21 February 2024

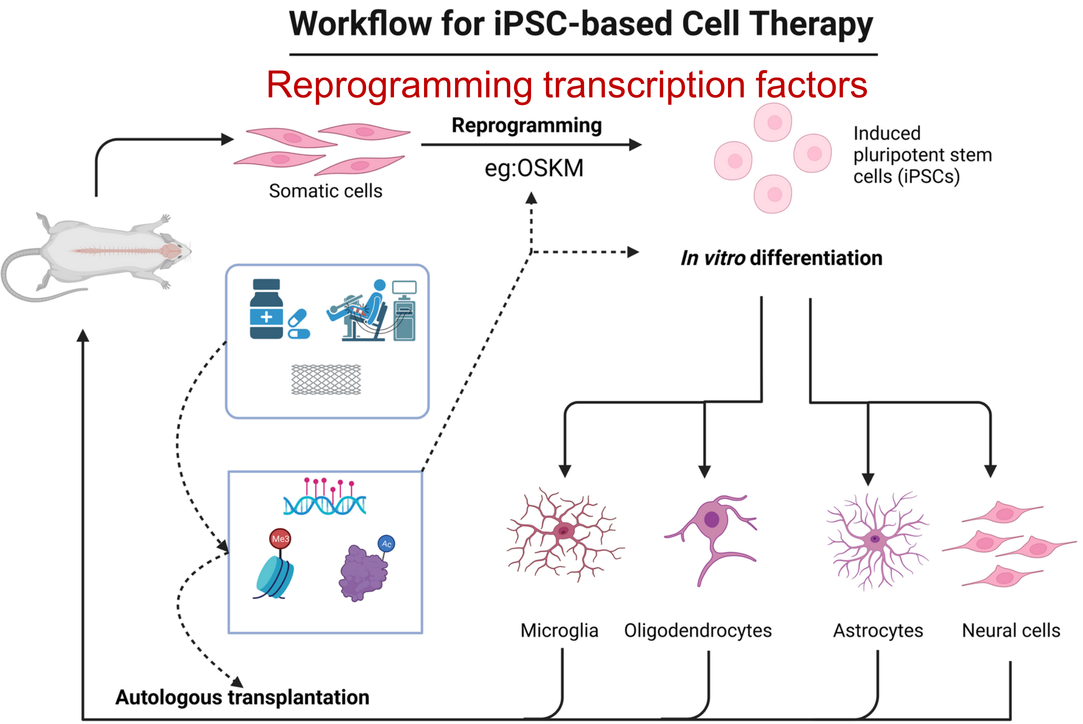
Yubiao Yang, Boyuan Ma, Jinyu Chen, Derong Liu, Jun Ma, Bo Li, Jian Hao & Xianhu Zhou

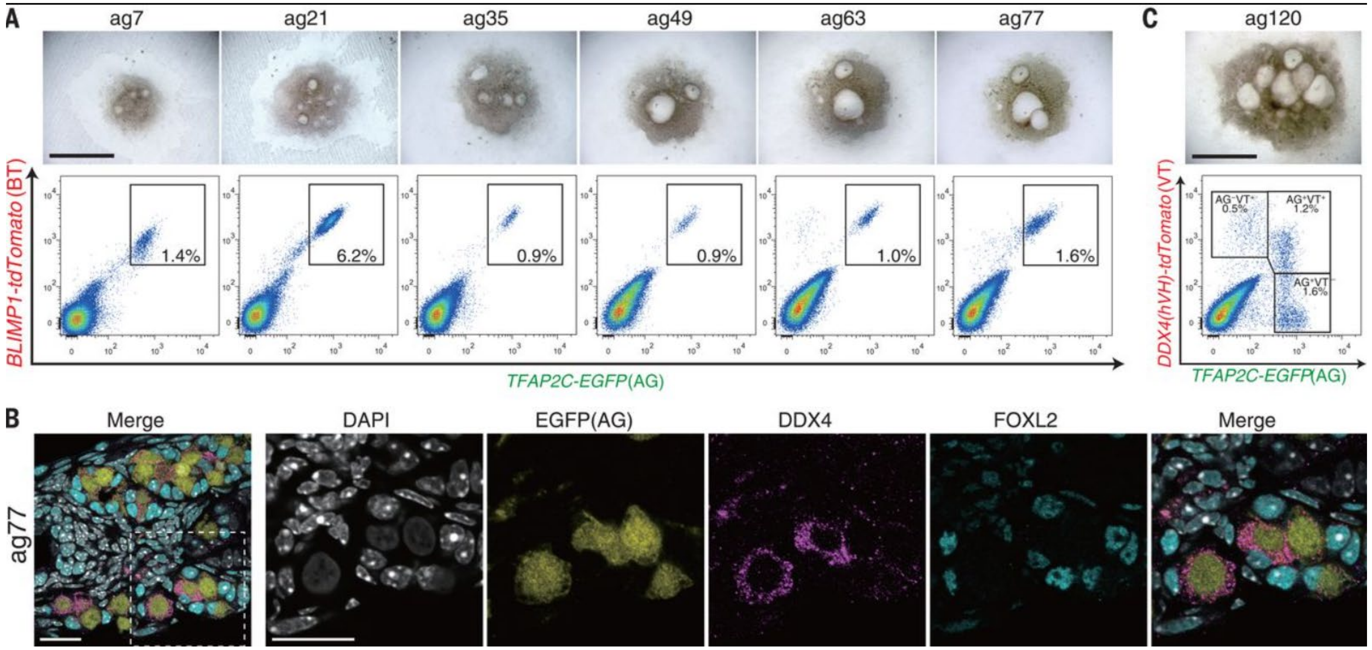
Generation of human oogonia from induced pluripotent stem cells in vitro

CHIKA YAMASHIRO, KOTARO SASAKI, YUKIHIRO YABUTA, YOJI KOJIMA, TOMONORI NAKAMURA, IKUHIRO OKAMOTO, SHIHORI YOKOBAYASHI, YUSUKE MURASE, YUKIKO ISHIKURA, [...], AND MITINORI SAITOU +3 authors Authors Info & Affiliations

SCIENCE · 20 Sep 2018 · Vol 362, Issue 6412 · pp. 356-360 · DOI: 10.1126/science.aat1674

- Induced Human pluripotent stem cells (hPSCs)
  → primordial germ cell–like cells (hPGCLCs)
  → oogonia-like cells during a long-term in vitro culture (4 months) in xenogeneic reconstituted ovaries with mouse embryonic ovarian somatic cells





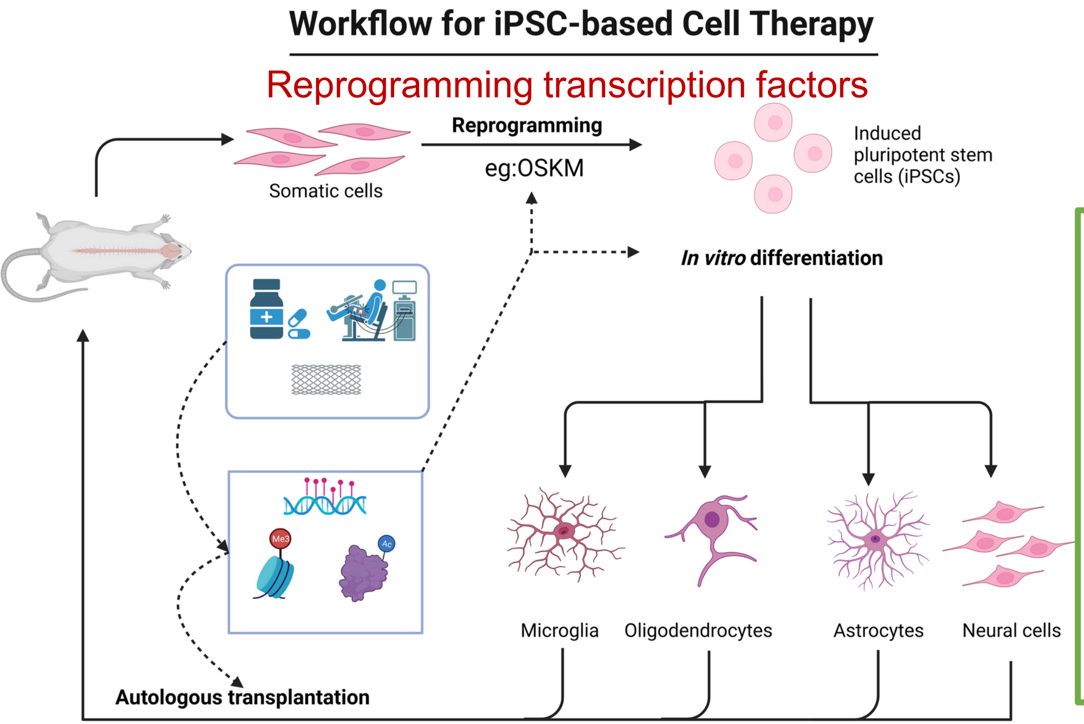
Induced Pluripotent Stem Cells Based Therapy

Home › Clinical Epigenetics › Article

Epigenetic regulation and factors that influence the effect of iPSCs-derived neural stem/progenitor cells (NS/PCs) in the treatment of spinal cord injury

Review | Open access | Published: 21 February 2024

Yubiao Yang, Boyuan Ma, Jinyu Chen, Derong Liu, Jun Ma, Bo Li, Jian Hao & Xianhu Zhou



Generation of human oogonia from induced pluripotent stem cells in vitro

CHIKA YAMASHIRO, KOTARO SASAKI, YUKIHIRO YABUTA, YOJI KOJIMA, TOMONORI NAKAMURA, IKUHIRO OKAMOTO, SHIHORI YOKOBAYASHI, YUSUKE MURASE, YUKIKO ISHIKURA, [...], AND MITINORI SAITOU +3 authors Authors Info & Affiliations

SCIENCE • 20 Sep 2018 • Vol 362, Issue 6412 • pp. 356-360 • DOI: 10.1126/science.aat1674

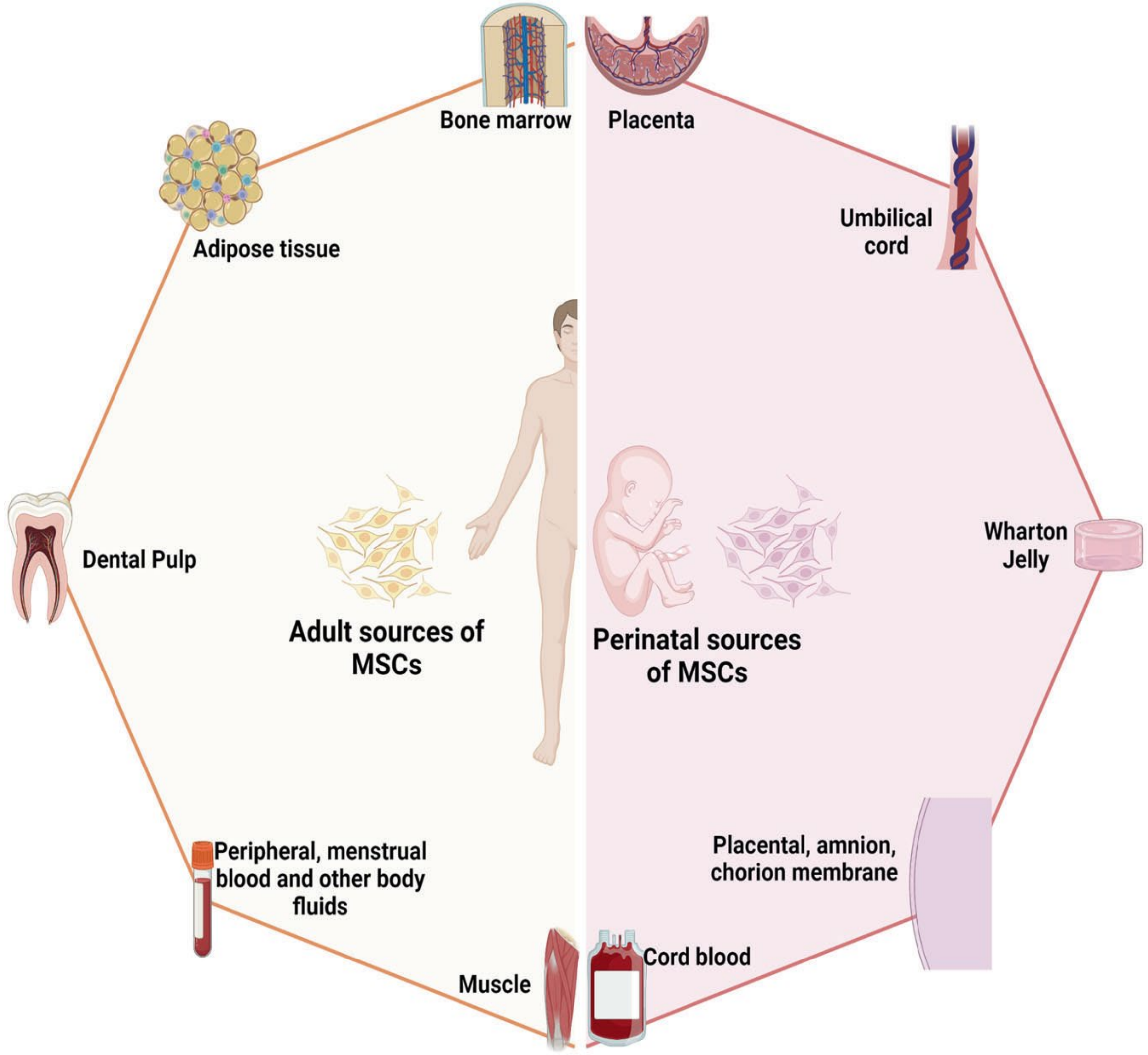
- Induced Human pluripotent stem cells (hPSCs)
  → primordial germ cell–like cells (hPGCLCs)
  → oogonia-like cells during a long-term in vitro culture (4 months) in xenogeneic reconstituted ovaries with mouse embryonic ovarian somatic cells

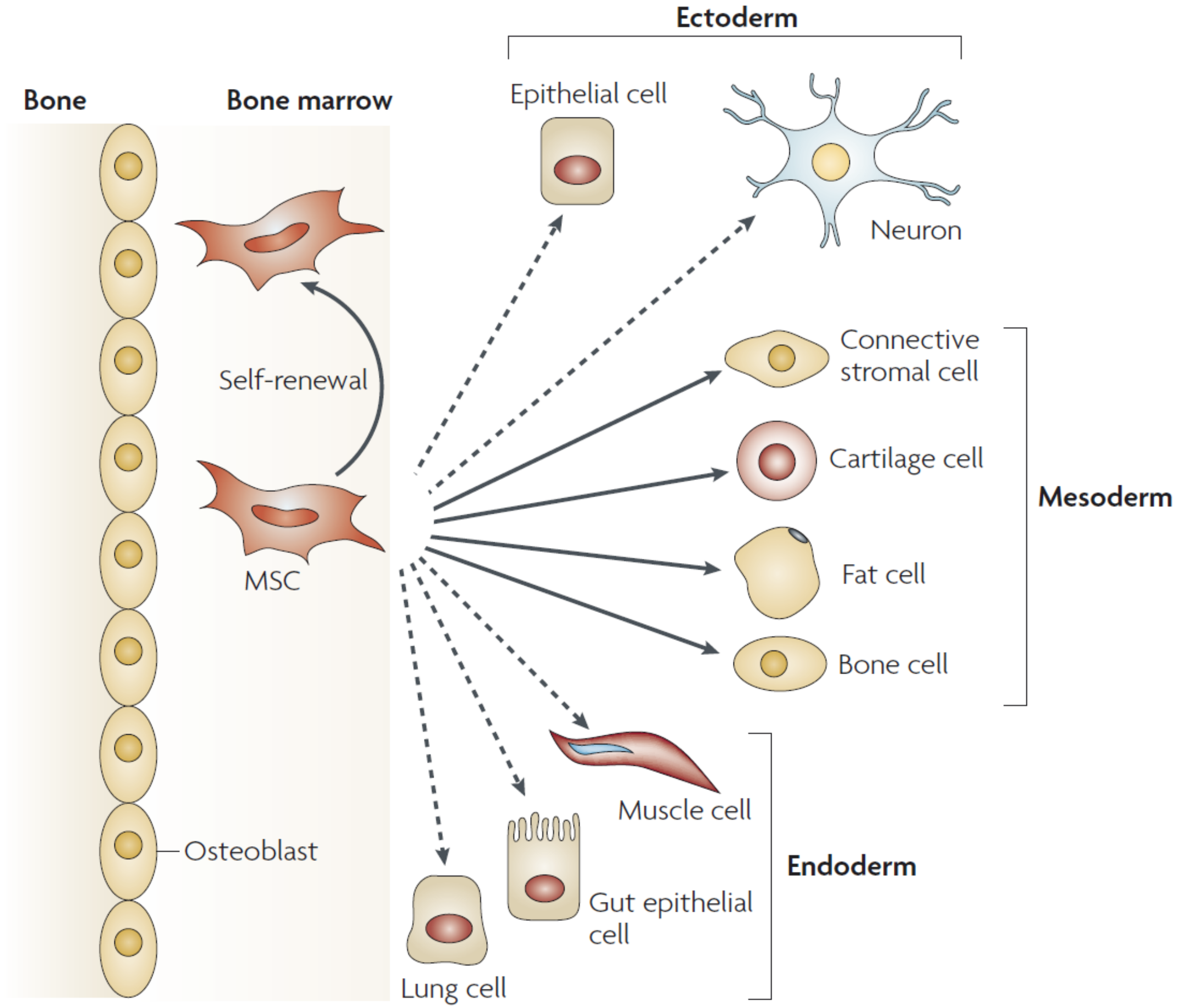
- Genomic instability
- Potential residual epigenetic memory
- Teratoma formation
- Low germ cell differentiation
- Incomplete meiotic progression

Mesenchymal Stem Cells

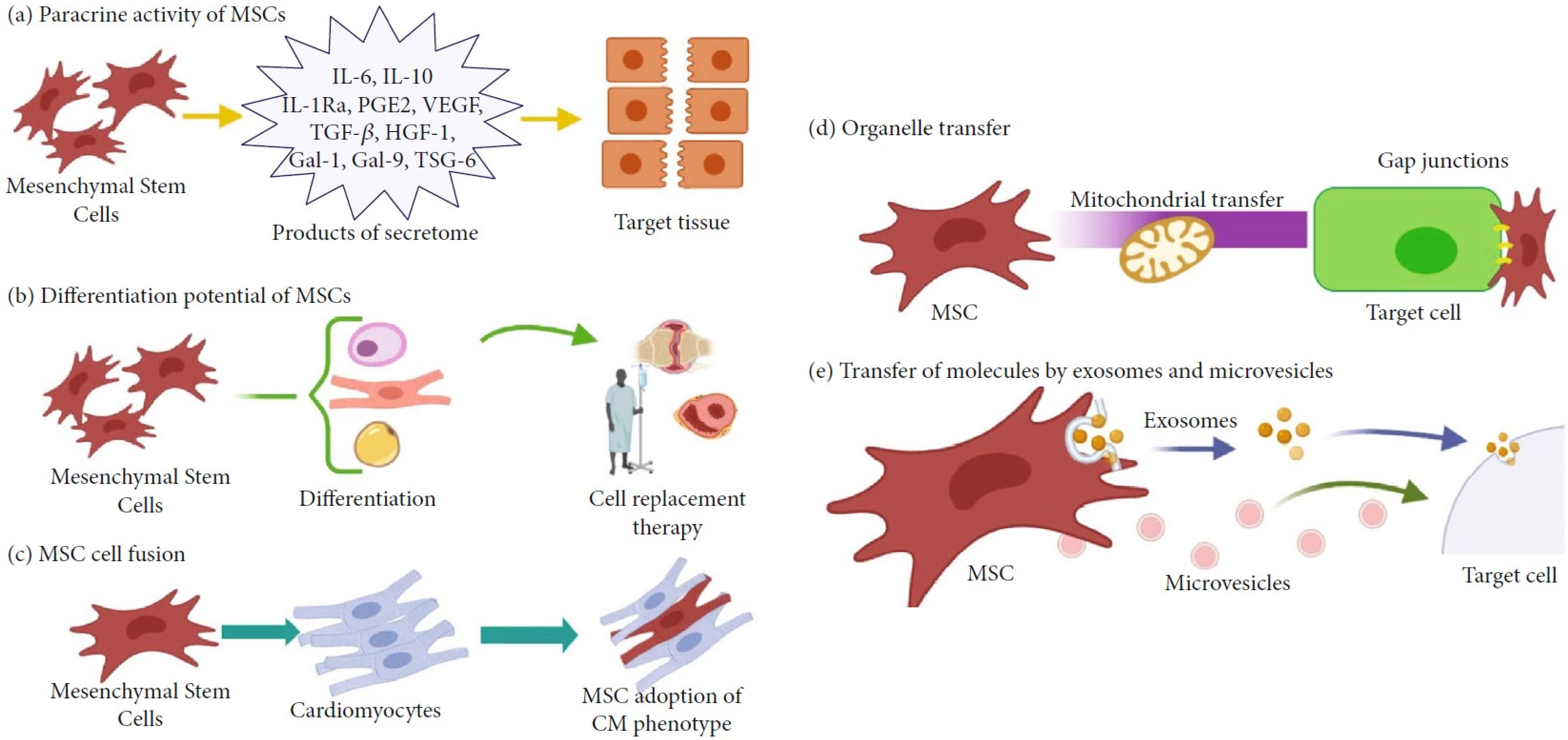
- MSCs can be derived from different adult tissues
  - originating from the mesodermal layer of adult tissues

- Proliferative
- Self-renewal
- Differentiation to different lineages





Mesenchymal Stem Cells Based Therapy



MSC = (Multipotent) Mesenchymal Stromal Cells ?

> Cytotherapy. 2006;8(4):315-7. doi: 10.1080/14653240600855905.

Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement

M Dominici [1], K Le Blanc, I Mueller, I Slaper-Cortenbach, Fc Marini, Ds Krause, Rj Deans, A Keating, Dj Prockop, Em Horwitz

- Investigators report studies of multipotent mesenchymal stromal cells using different methods of isolation and expansion, and different approaches to characterizing the cells
  - First, MSC must be plastic-adherent when maintained in standard culture conditions
  - Second, MSC must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19 and HLA-DR surface molecules
  - Third, MSC must differentiate to osteoblasts, adipocytes and chondroblasts in vitro

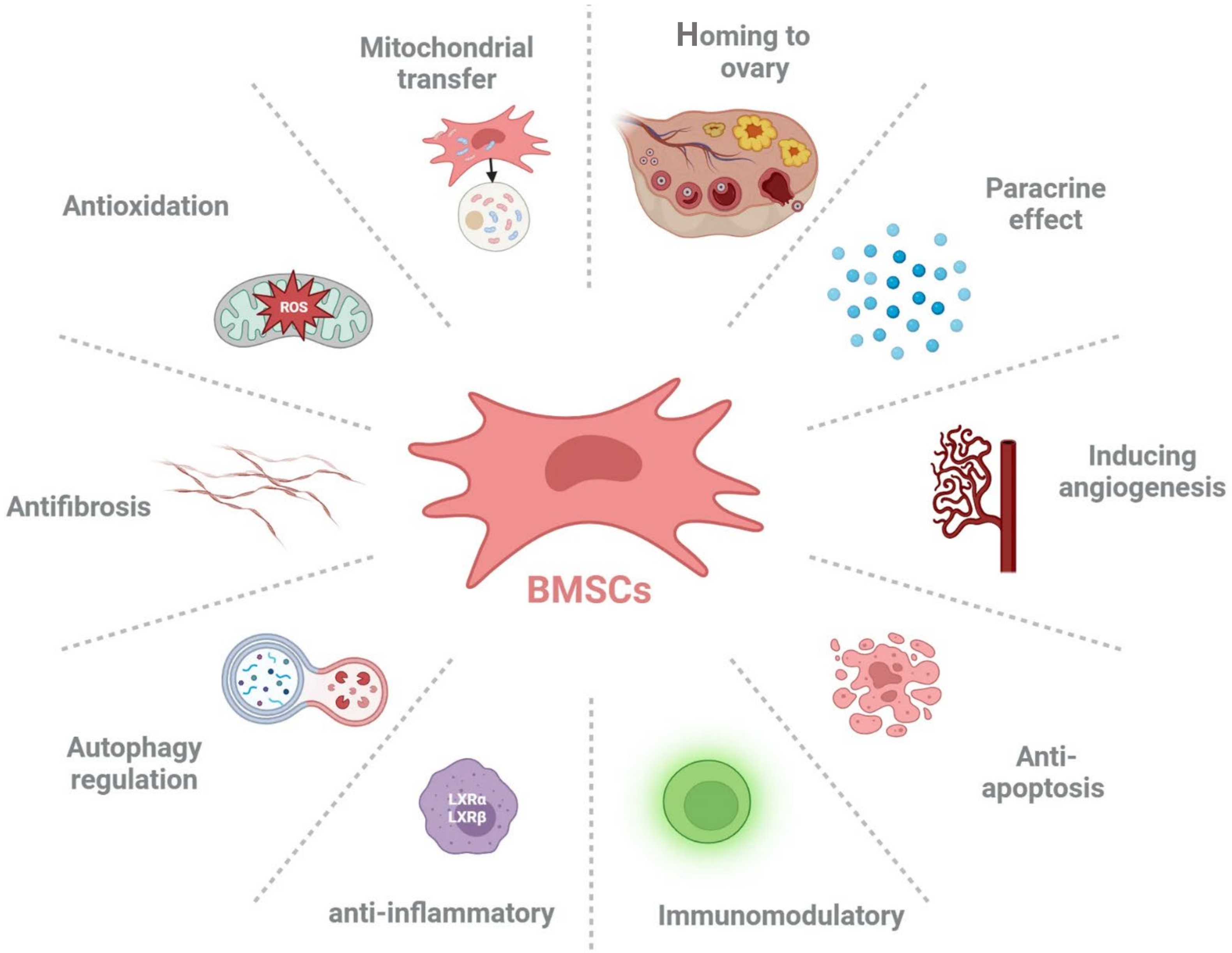
구분	Mesenchymal Stem Cell	Mesenchymal Stromal Cell
의미	진정한 줄기세포	기능적/표현형 기반 세포 집단
self-renewal	기대됨	제한적/불명확
분화능	multipotent	일부 subset만 해당

Mesenchymal Stem Cells on Ovary

SYSTEMATIC REVIEW article
Front. Immunol., 27 October 2022
Sec. Alloimmunity and Transplantation
Volume 13 - 2022 | https://doi.org/10.3389/fimmu.2022.997808

Bone marrow mesenchymal stem cells in premature ovarian failure: Mechanisms and prospects

Yanjing Huang [1] Mengdi Zhu [1] Zhuo Liu [1] Runan Hu [1] Fan Li [1]



Mesenchymal Stem Cells on Ovary – Homing to Ovary

SYSTEMATIC REVIEW article
Front. Immunol., 27 October 2022
Sec. Alloimmunity and Transplantation
Volume 13 - 2022 | https://doi.org/10.3389/fimmu.2022.997808

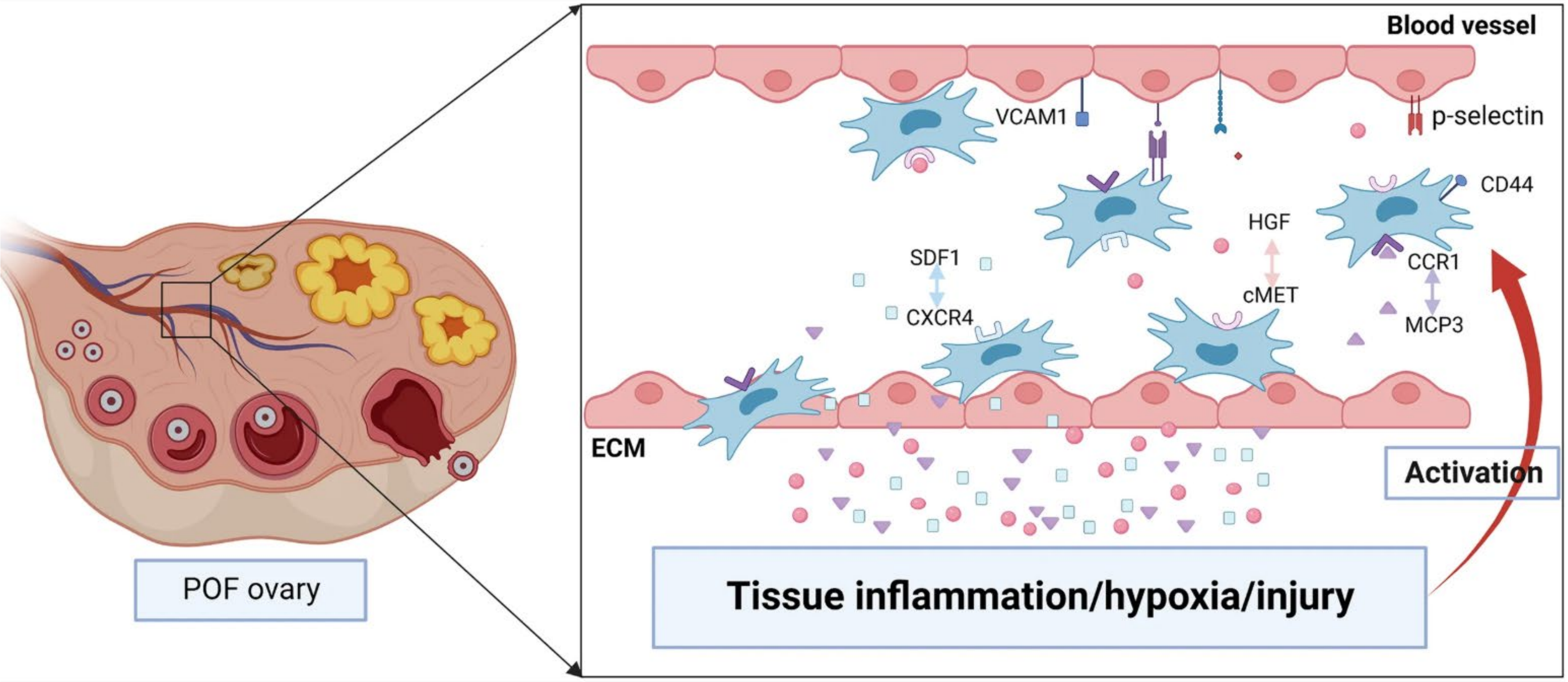
Bone marrow mesenchymal stem cells in premature ovarian failure: Mechanisms and prospects

Yanjing Huang [1] Mengdi Zhu [1]

- Tissue inflammation, hypoxia or injury

  → chemokines including stromal cell derived factor 1 (SDF1), hepatocyte growth factor (HGF), monocyte chemotactic protein-3 (MCP3)

  → express BM-MSC specific receptors such as CXC chemokine receptor 4 (CXCR4), cMET, CC chemokine receptor 1(CCR1)



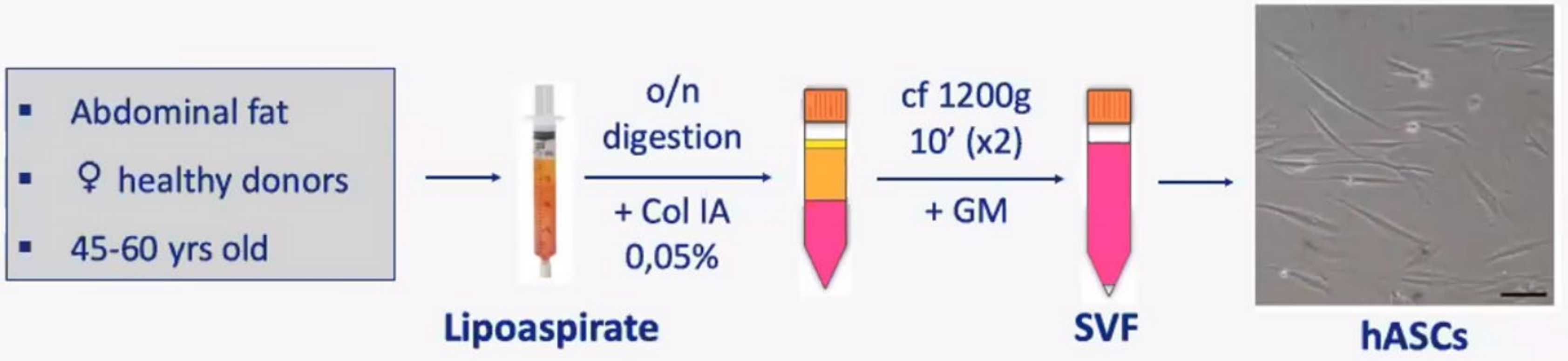
Effects of Stem Cell Ovarian Transplant – Animal Study

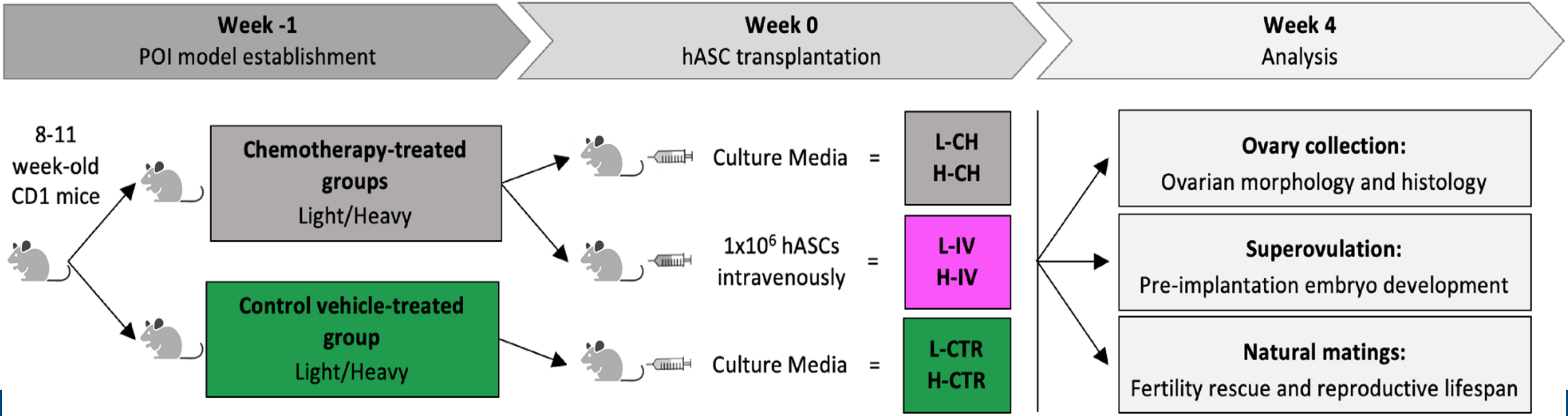
Human adipose-derived stromal cells transplantation prolongs reproductive lifespan on mouse models of mild and severe premature ovarian insufficiency

Giulia Salvatore, Massimo De Felici, Susanna Dolci, Cosimo Tudisco, Rosella Cicconi, Luisa Campagnolo, Antonella Camaioni & Francesca Gioia Klinger

Stem Cell Research & Therapy **12**, Article number: 537 (2021)

- 1×10^6 hASCs were transplanted systemically through the tail vein





Effects of Stem Cell Ovarian Transplant – Animal Study

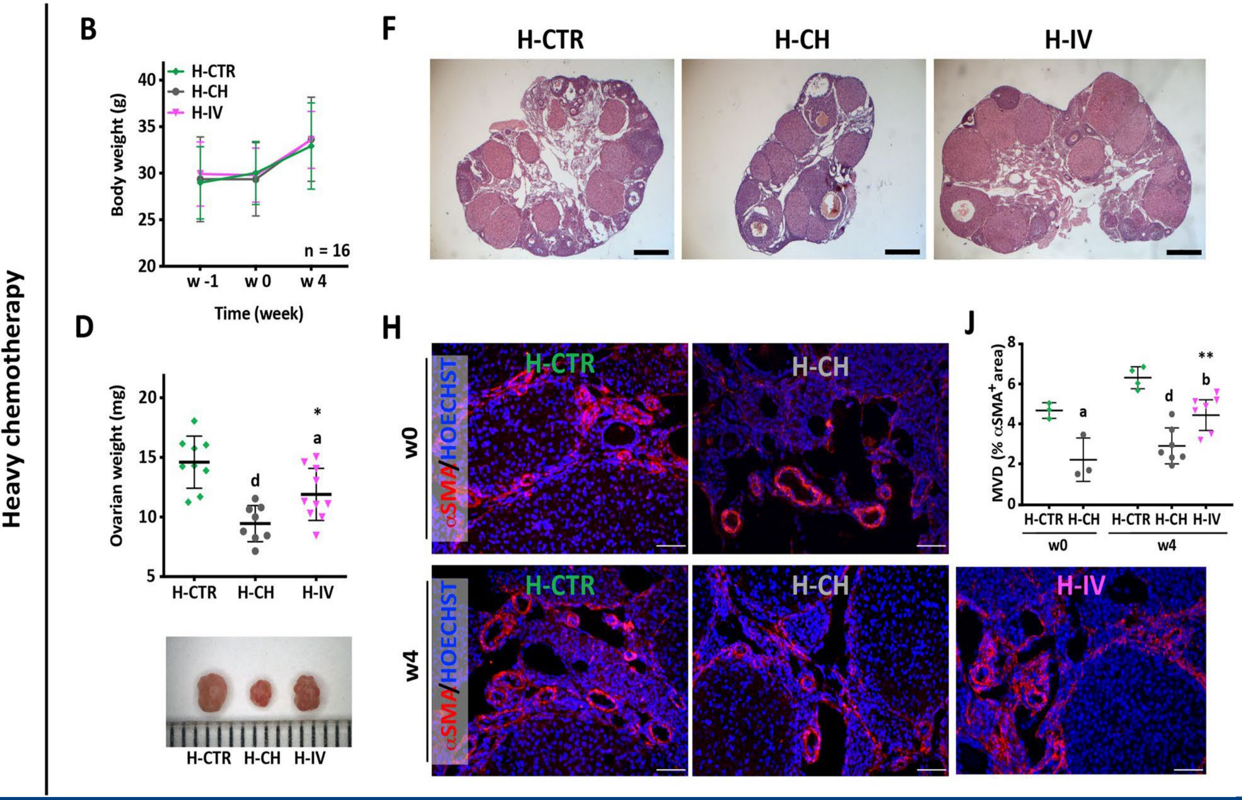
Human adipose-derived stromal cells transplantation prolongs reproductive lifespan on mouse models of mild and severe premature ovarian insufficiency

Giulia Salvatore, Massimo De Felici, Susanna Dolci, Cosimo Tudisco, Rosella Cicconi, Luisa Campagnolo, Antonella Camaioni & Francesca Gioia Klinger

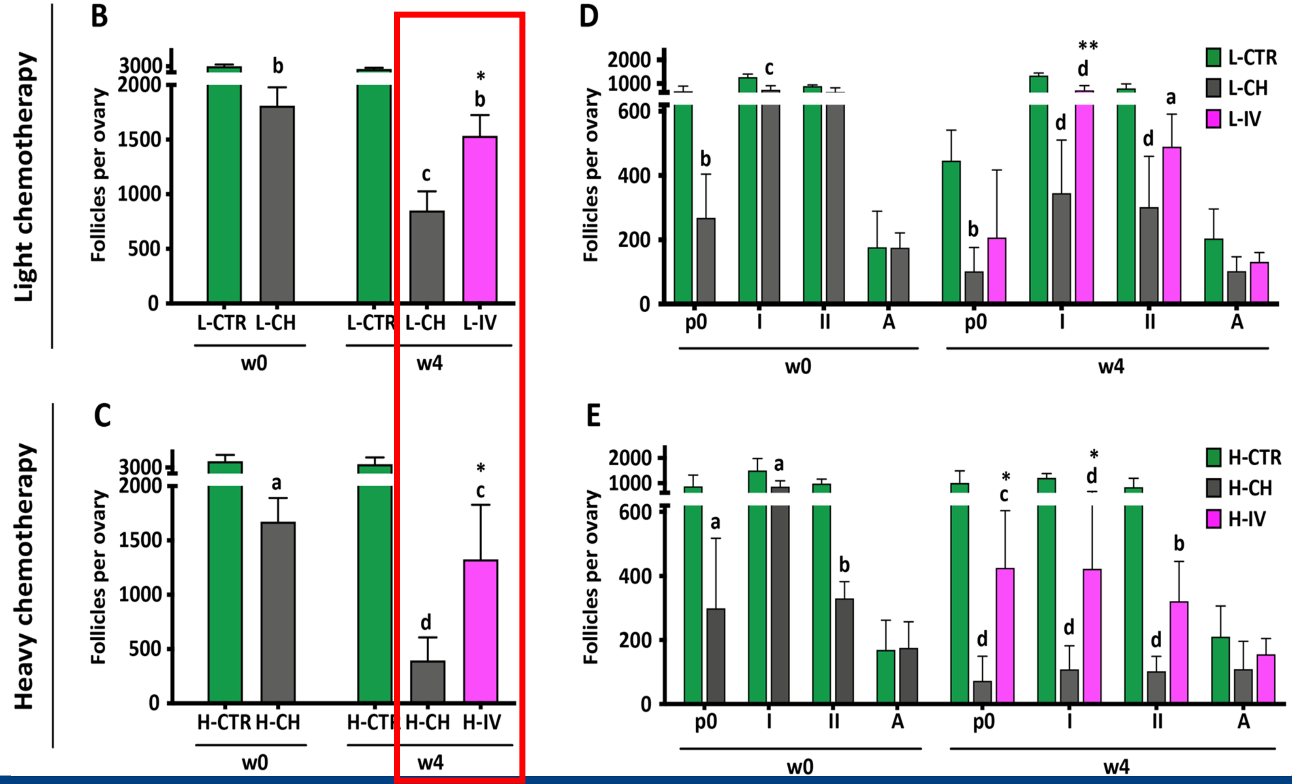
Stem Cell Research & Therapy **12**, Article number: 537 (2021) | Cite this article

- hASC transplantation preserve ovarian weight, vascularization & reserve

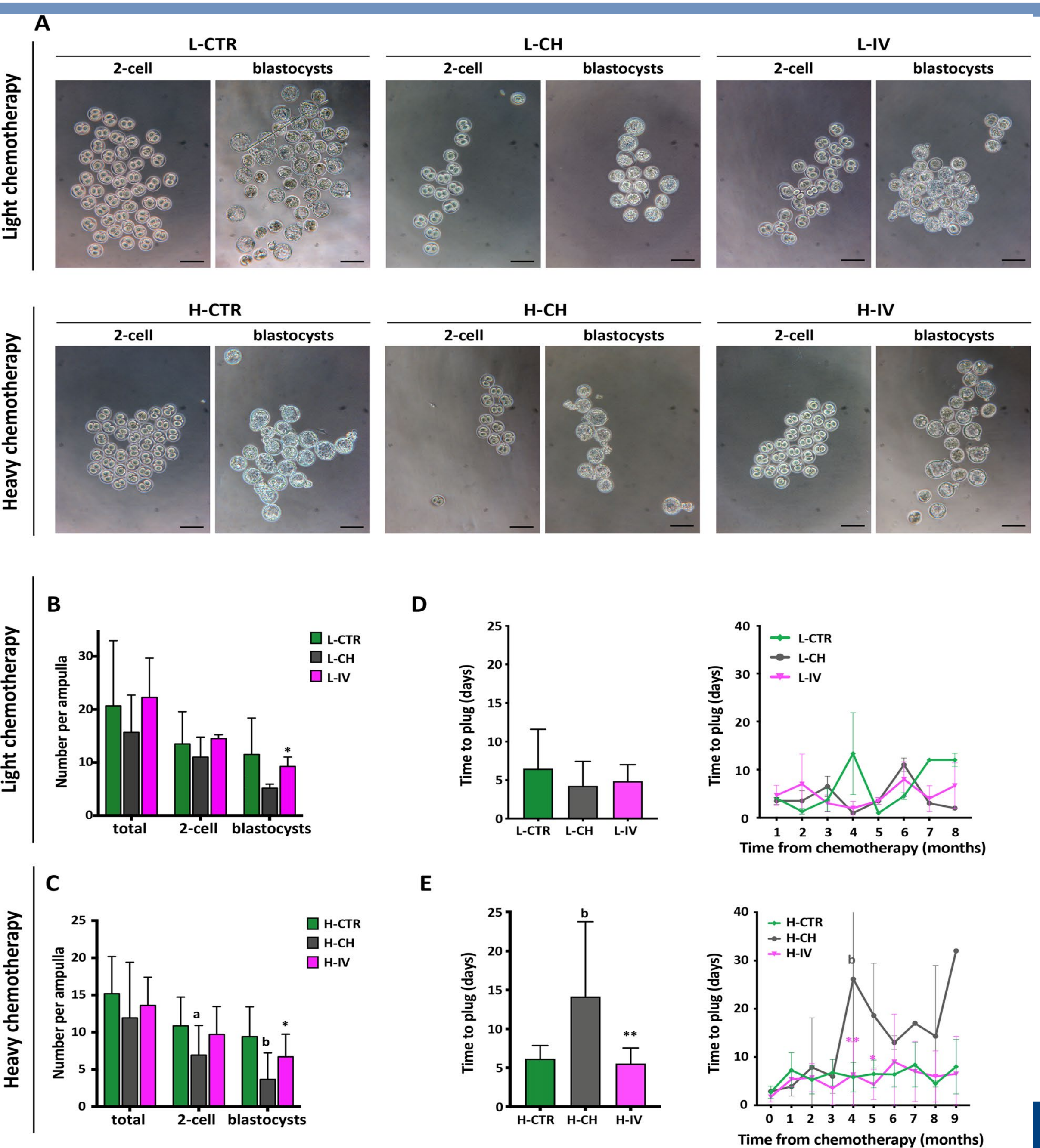
Control CTx CTx-IV infusion



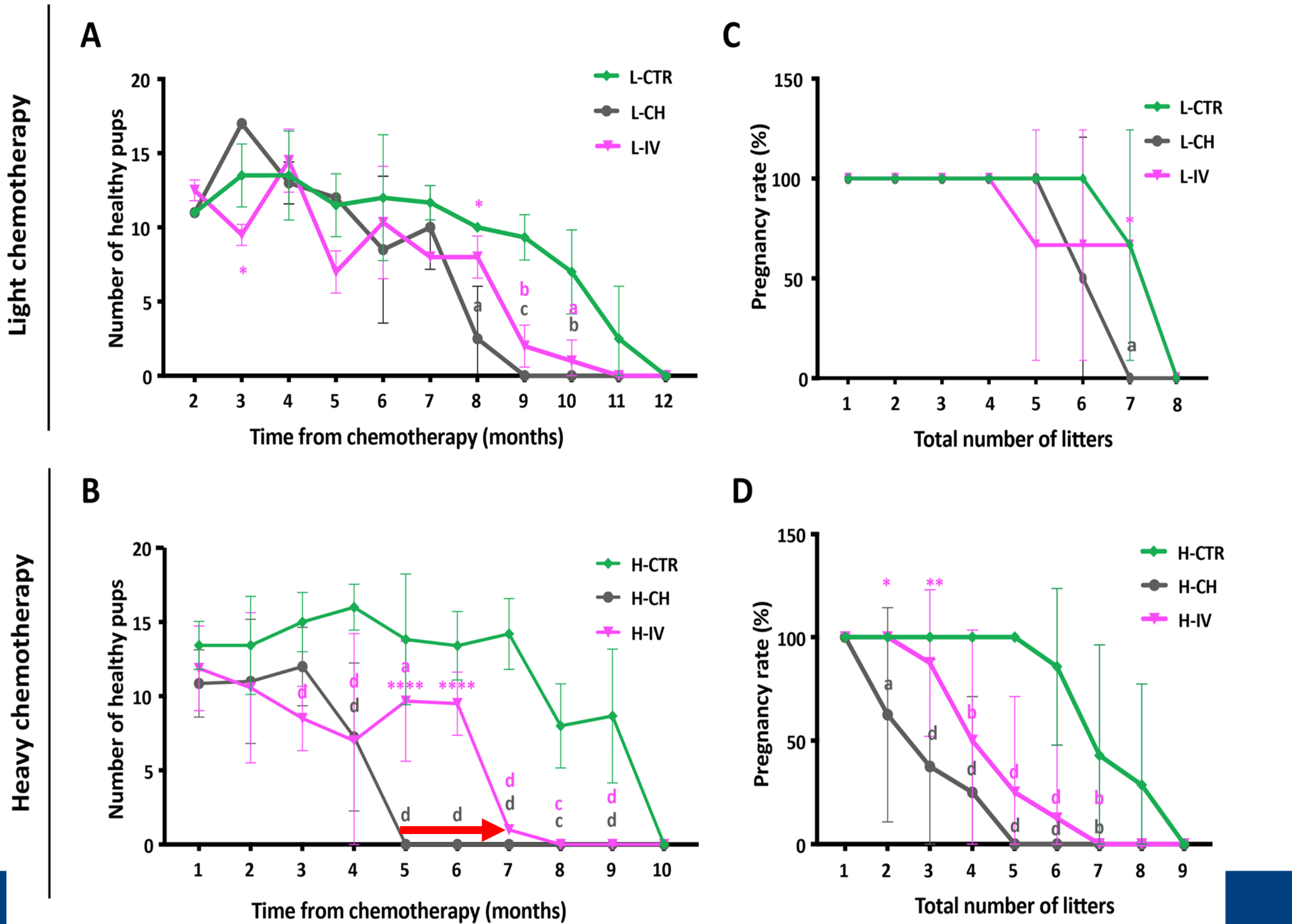
Follicle number per ovary



Effects of Stem Cell Ovarian Transplant – Animal Study



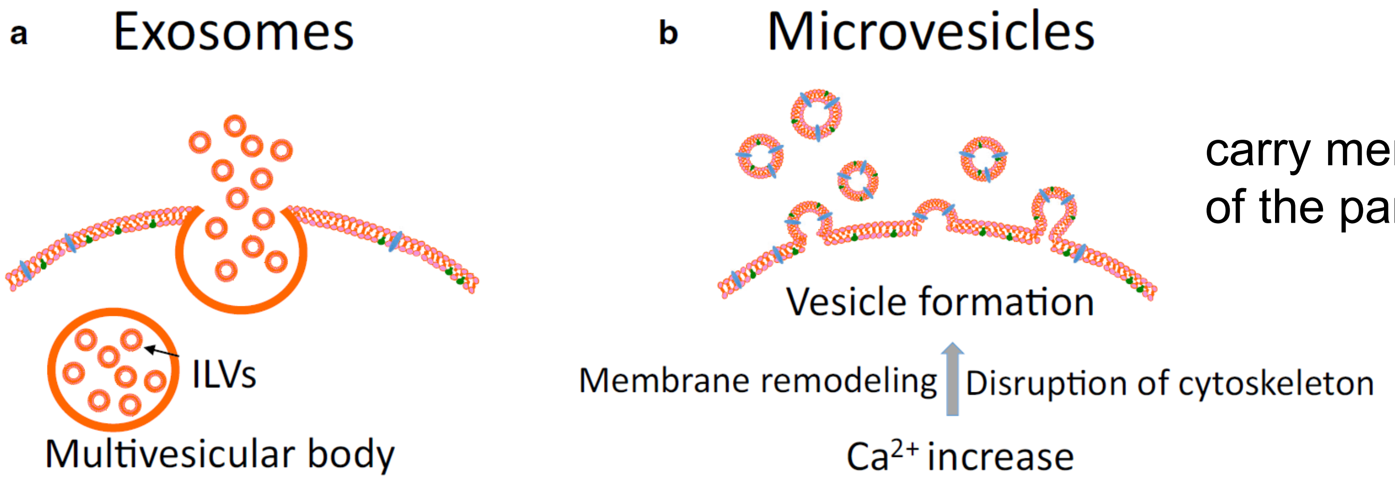
- IV-hASC transplantation improves early post-fertilization development & slows POI



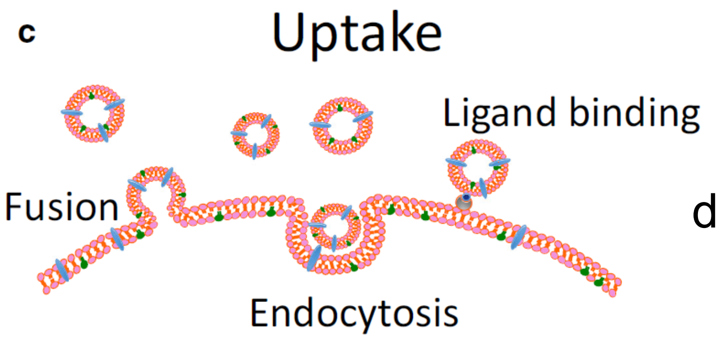
Mesenchymal Stem Cells Based Therapy - Exosome

- Exosome
  - class of membranous vesicles with diameters of 30–200 nm
  - mediate local cell-to-cell communication by transferring microRNAs & proteins

Intraluminal vesicles (ILVs) released are termed exosomes



carry membrane markers of the parent cell



direct fusion to the plasma membrane, receptor-dependent endocytosis, phagocytosis

Mesenchymal Stem Cells Based Therapy - In Vitro

SCIENTIFIC REPORTS

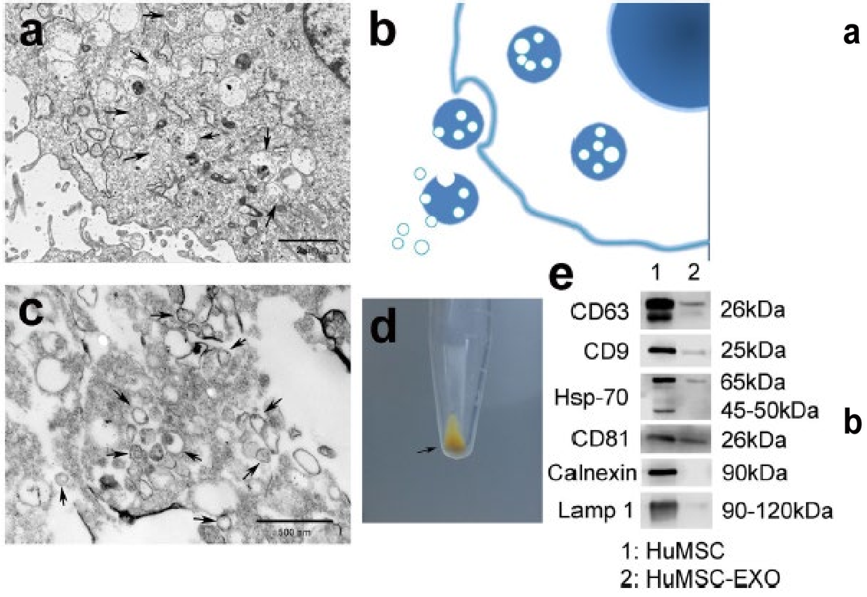
OPEN

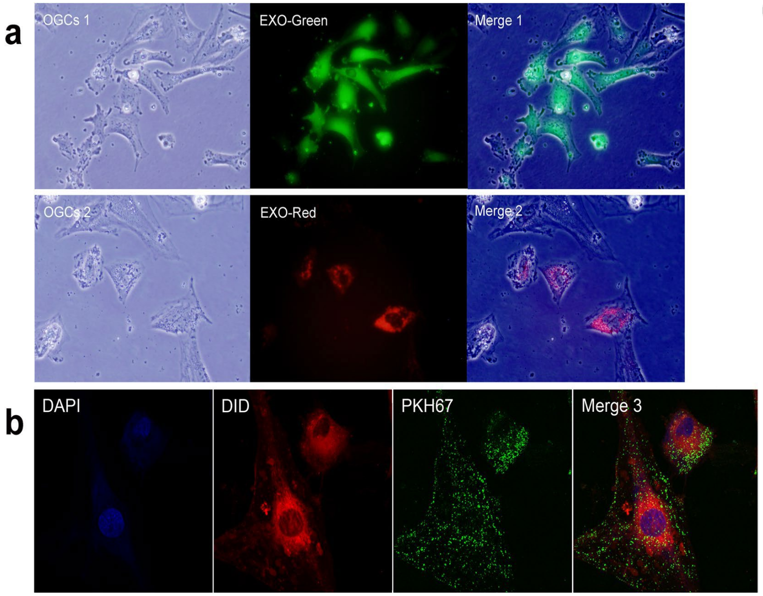
Exosomes derived from human umbilical cord mesenchymal stem cells protect against cisplatin-induced ovarian granulosa cell stress and apoptosis *in vitro*

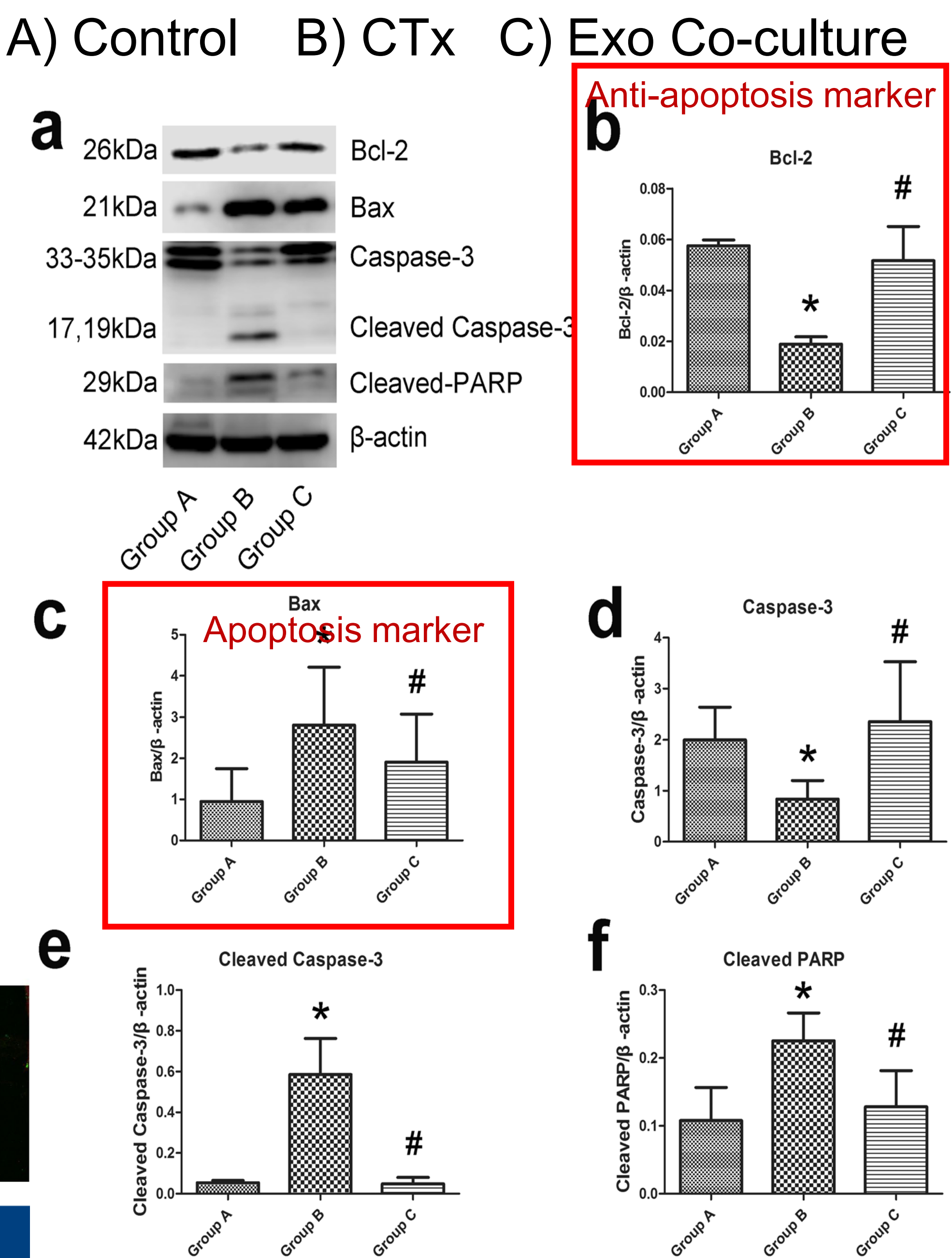
Received: 18 November 2016
Accepted: 20 April 2017
Published online: 31 May 2017

Liping Sun[1], Dong Li[2], Kun Song[1], Jianlu Wei[3], Shu Yao[1], Zhao Li[4], Xuantao Su[5], Xiuli Ju[2], Lan Chao[1,6], Xiaohui Deng[1,6], Beihua Kong[1] & Li Li[1,6]

- Uptake of exosomes of hUC-MSC by ovarian granulosa cells







Mesenchymal Stem Cells Based Therapy - In Vitro

scientific reports

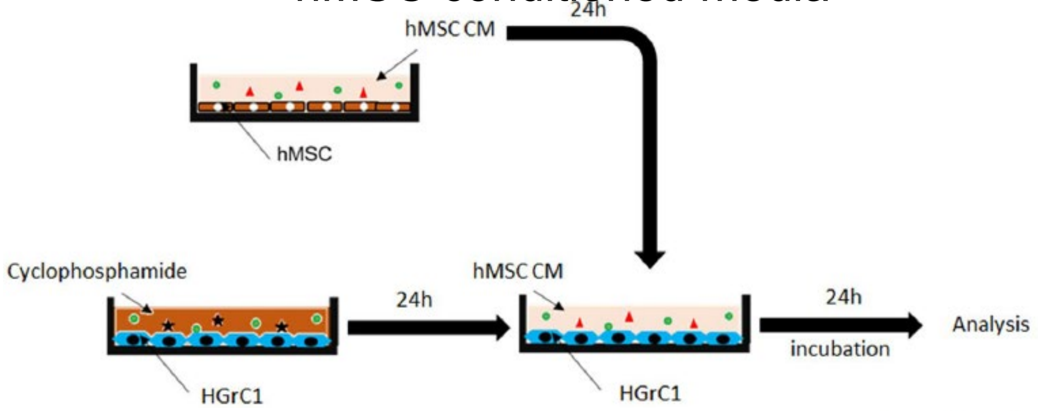
Check for updates

OPEN **Human BM-MSC secretome enhances human granulosa cell proliferation and steroidogenesis and restores ovarian function in primary ovarian insufficiency mouse model**

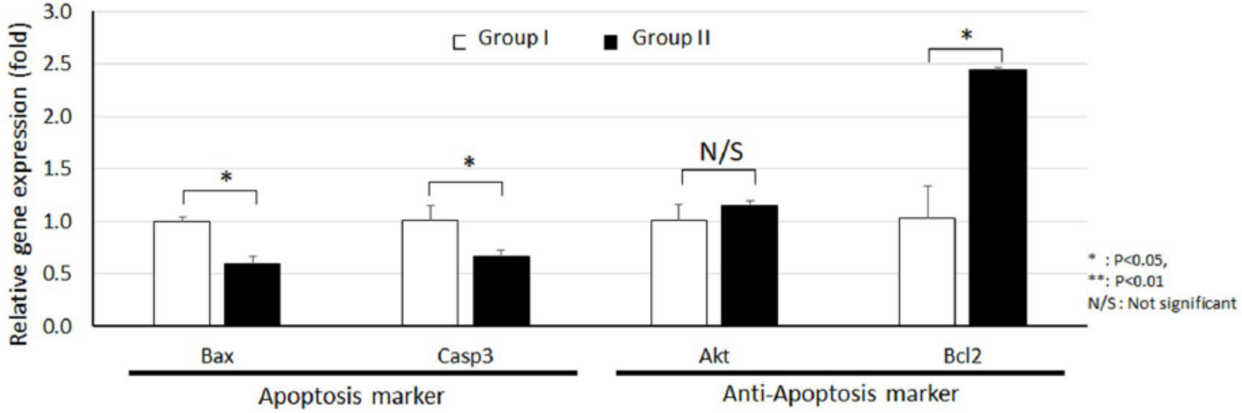
Hang-soo Park[1,6], Rishi Man Chugh[2,6], Abdeljabar El Andaloussi[3,6], Elie Hobeika[4], Sahar Esfandyari[2], Amro Elsharoud[2], Mara Ulin[2], Natalia Garcia[2], Mahmood Bilal[5] & Ayman Al-Hendy[1]✉

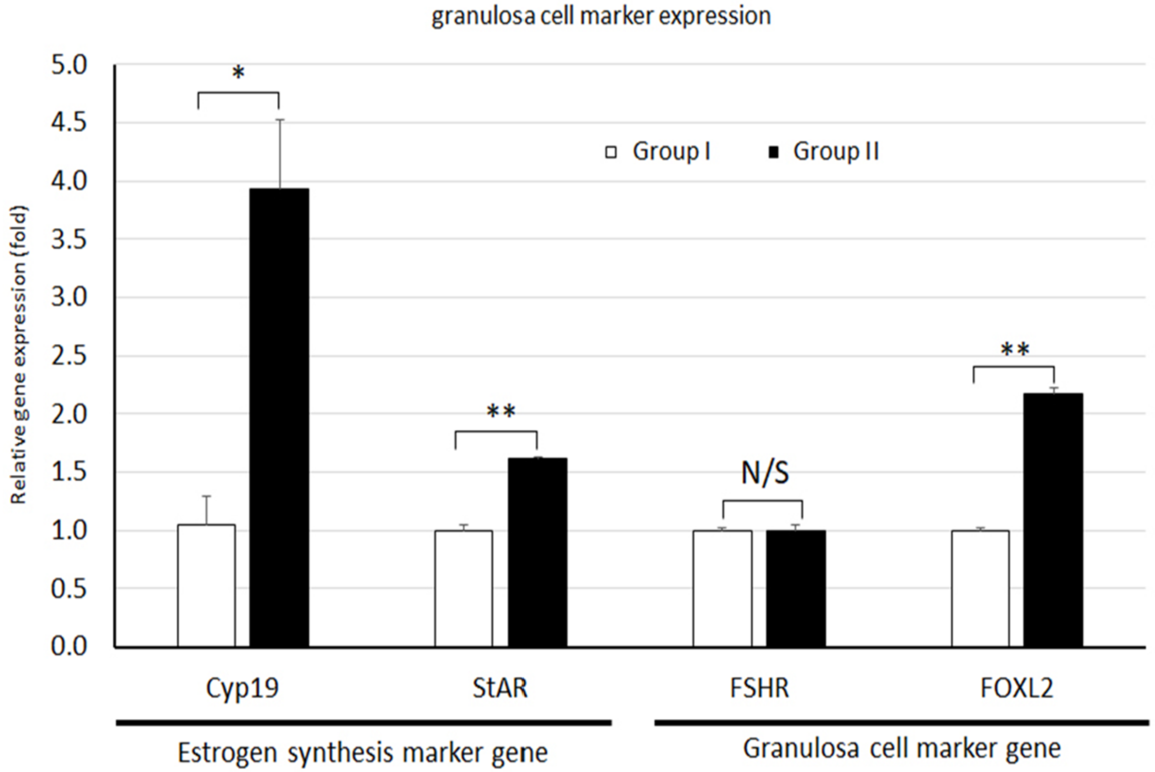
Published: 25 February 2021

hMSC conditioned media



Control hMSC-CM





Mesenchymal Stem Cells Based Therapy - In Vitro

scientific reports

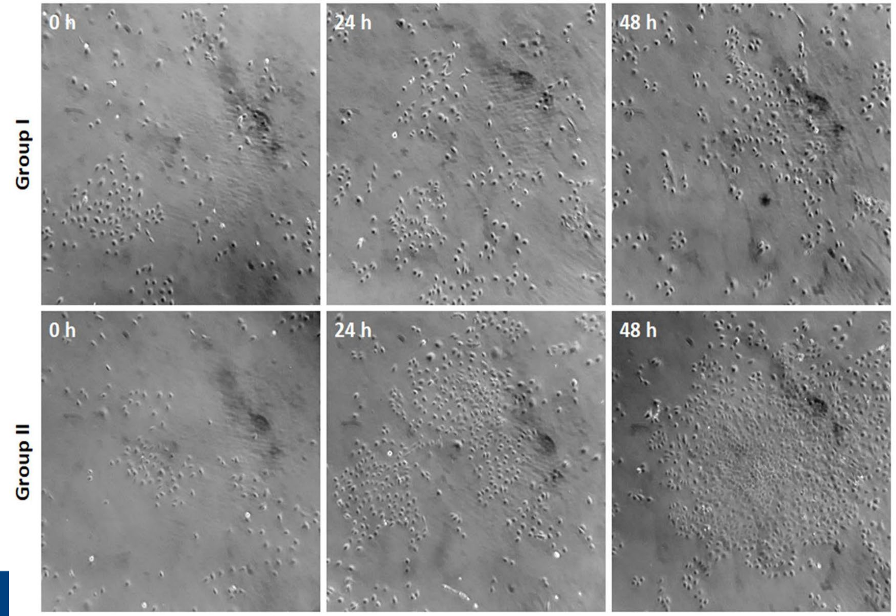
Check for updates

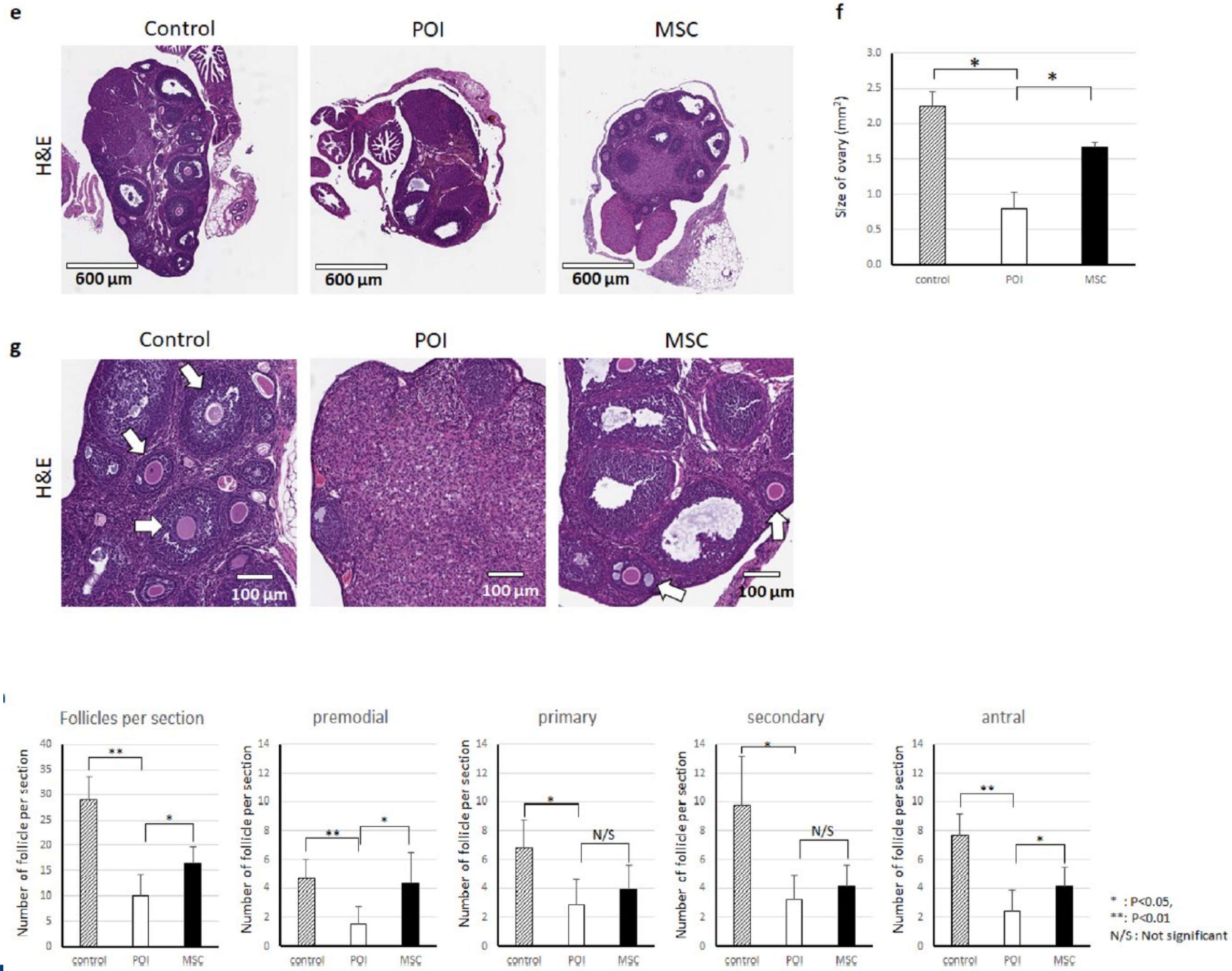
OPEN **Human BM-MSC secretome enhances human granulosa cell proliferation and steroidogenesis and restores ovarian function in primary ovarian insufficiency mouse model**

Hang-soo Park[1,6], Rishi Man Chugh[2,6], Abdeljabar El Andaloussi[3,6], Elie Hobeika[4], Sahar Esfandyari[2], Amro Elsharoud[2], Mara Ulin[2], Natalia Garcia[2], Mahmood Bilal[5] & Ayman Al-Hendy[1]✉

Published: 25 February 2021

- hMSC-conditioned media stimulates GC proliferation





Mesenchymal Stem Cells Based Therapy - In Vivo

Molecular Therapy

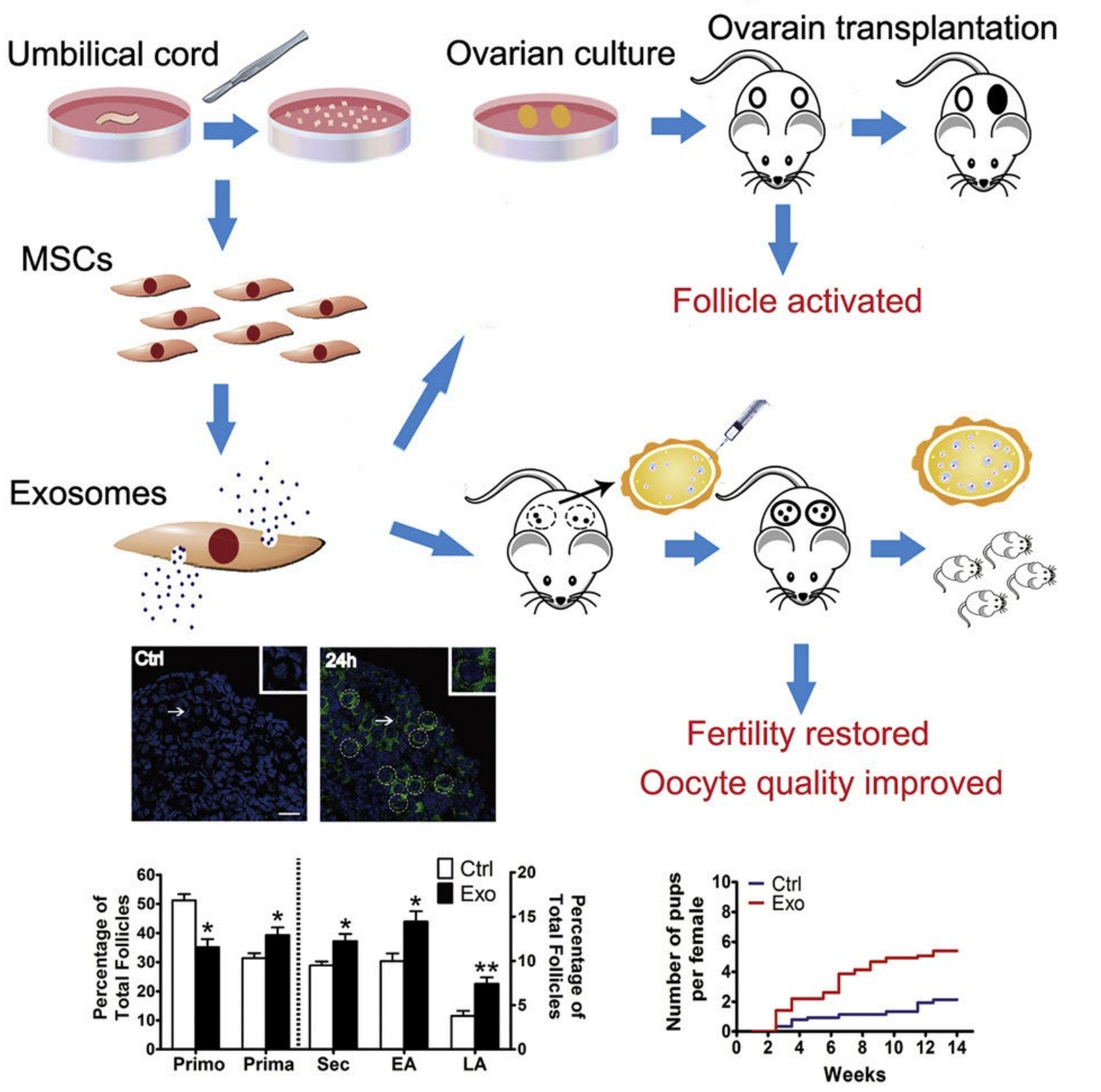
Volume 28, Issue 4, 8 April 2020, Pages 1200-1213

Original Article

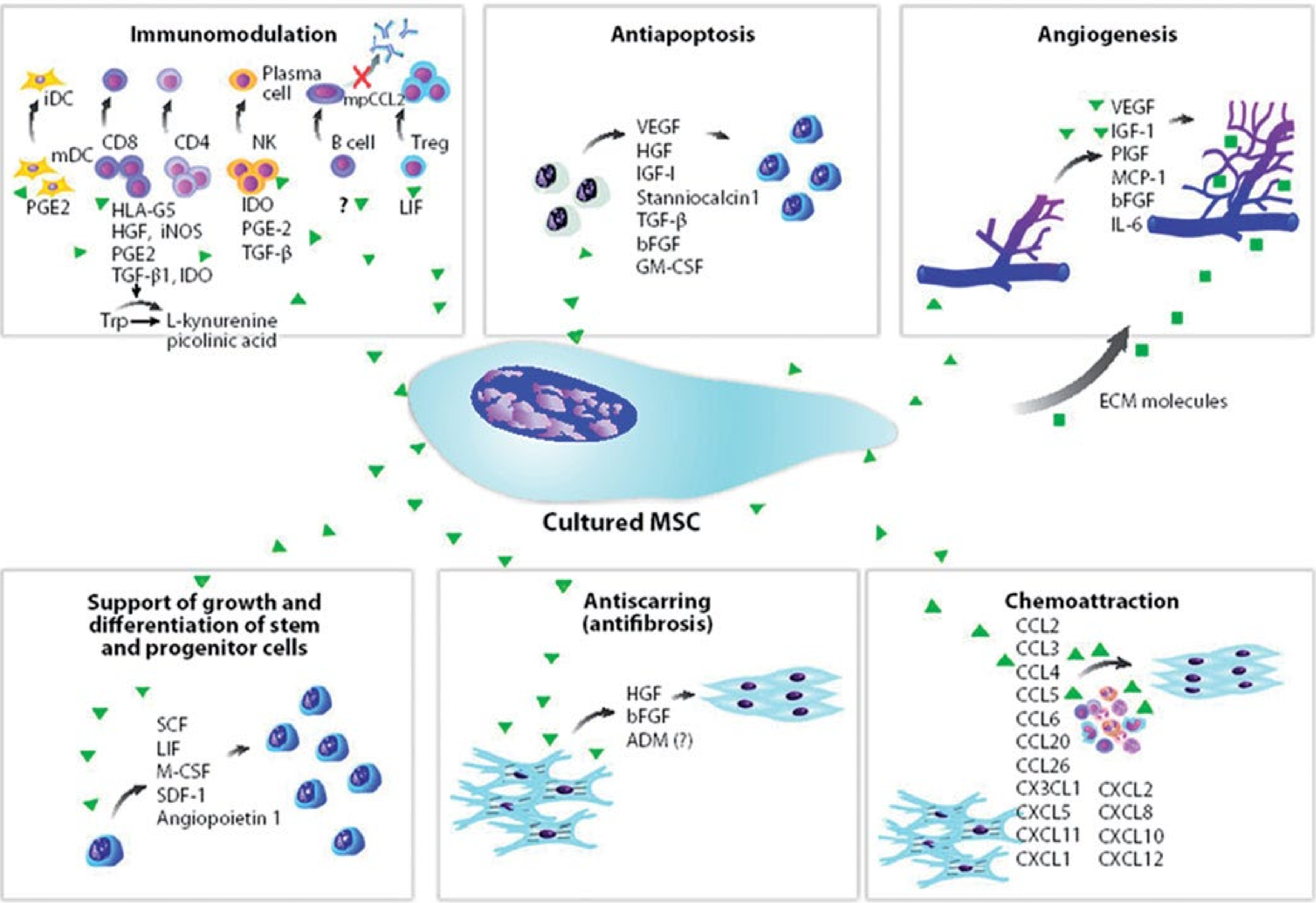
HucMSC-Derived Exosomes Mitigate the Age-Related Retardation of Fertility in Female Mice

Weijie Yang [1 2 6], Jing Zhang [1 6], Boqun Xu [3 6], Yuanlin He [1], Wei Liu [1], Jiazhao Li [1], Songying Zhang [2], Xiaona Lin [2], Dongming Su [4], Tinghe Wu [5], Jing Li [1]

- Uptake of HucMSC-exos by cultured newborn ovaries of mice
- Activation of the oocyte phosphatidylinositol 3-kinase (PI3K)/mTOR signaling pathway & acceleration of follicular development
- Stimulatory effects of HucMSC-exos on primordial follicles were through carrying functional microRNAs, such as miR-146a-5p or miR-21-5p



Mesenchymal Stem Cells Based Therapy



Autologous BM-MSC Ovarian Transplant

Igboeli *et al. Journal of Medical Case Reports* (2020) 14:108
https://doi.org/10.1186/s13256-020-02426-5

Journal of
Medical Case Reports

CASE REPORT **Open Access**

Intraovarian injection of autologous human mesenchymal stem cells increases estrogen production and reduces menopausal symptoms in women with premature ovarian failure: two case reports and a review of the literature

Prosper Igboeli[1], Abdeljabar El Andaloussi[2], Ujalla Sheikh[1], Hajra Takala[1], Amro ElSharc
Larisa Gavrilova-Jordan[3], Steven Levy[4] and Ayman Al-Hendy[1*]

- Autologous bone marrow-derived MSC injected into the POF patient's right ovary

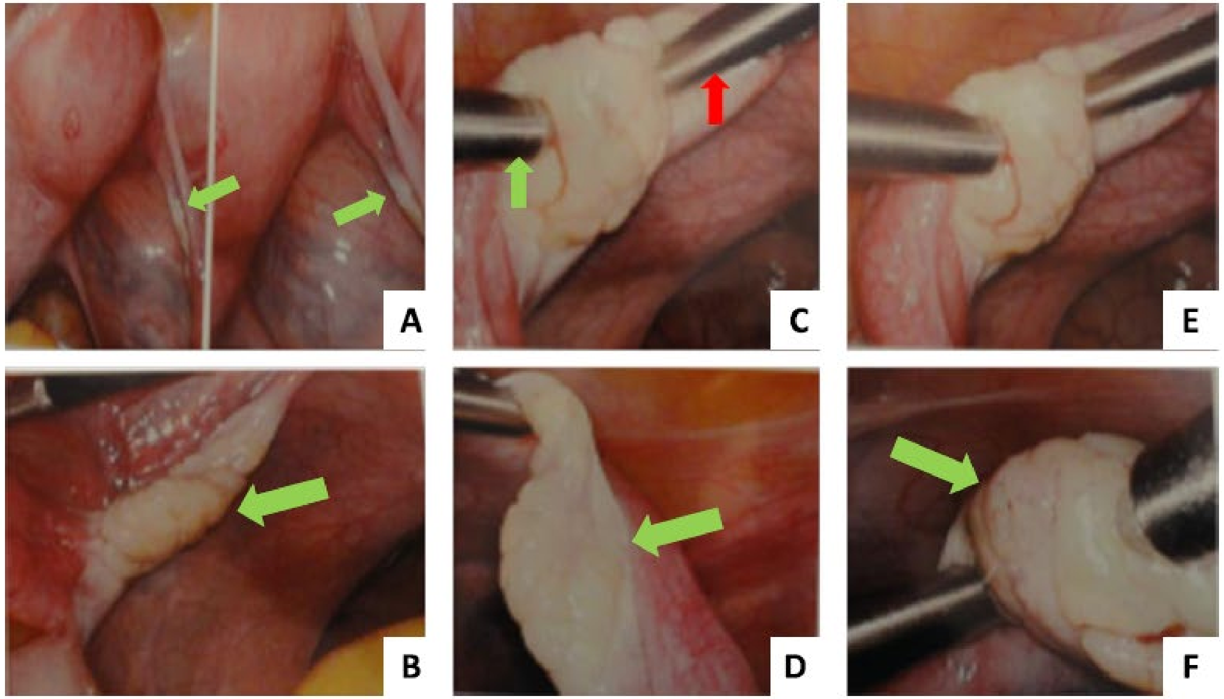


Fig. 1 Ovarian morphologic changes after mesenchymal stem cell injection. **a** Atrophic ovary before injection (*green arrows*) (low magnification). **b** Atrophic ovary before injection (*green arrow*) (zoom-in). **c** Laparoscopic grasper (*green arrow*) to stabilize the ovary during injection process via stem cell injector (*red arrow*). **d** Atrophic ovary (*green arrow*) stabilized in place just before injection process. **e** Injection of the stem cells. **f** Ovary (*green arrow*) near end of injection process (Notice the swelling and apparent increase in ovarian size.)

Autologous BM-MSC Ovarian Transplant

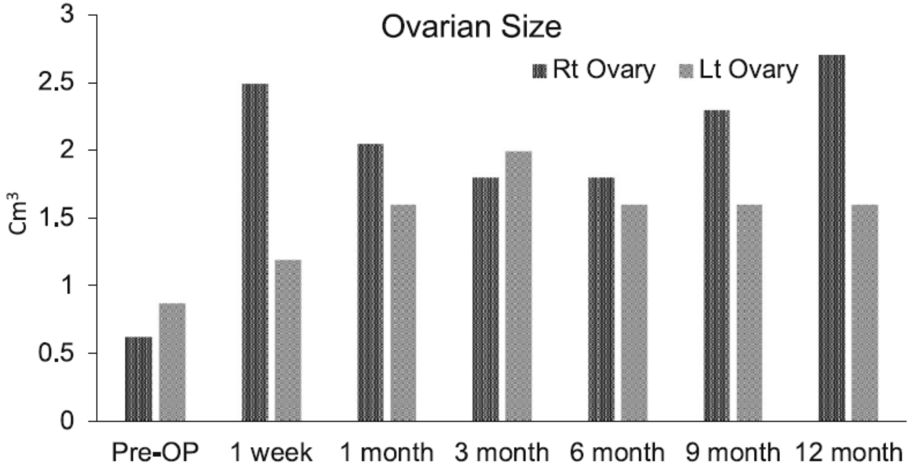


Fig. 2 Ovarian volume measured in cubic centimeters after mesenchymal stem cell implantation into ovary of patient 1

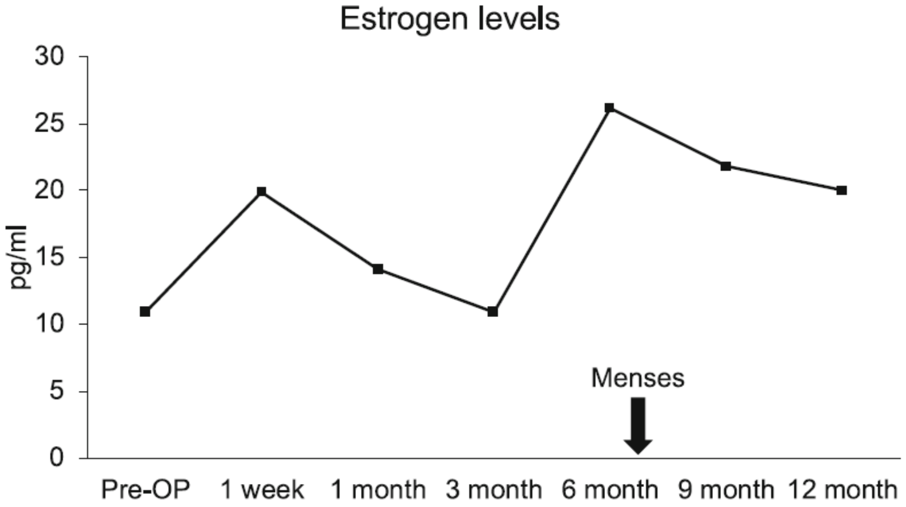


Fig. 3 Serum estrogen level quantified at pre– and post–mesenchymal stem cell ovarian implantation. The *arrow* indicates the menses that resume within 7 months following mesenchymal stem cell engraftment

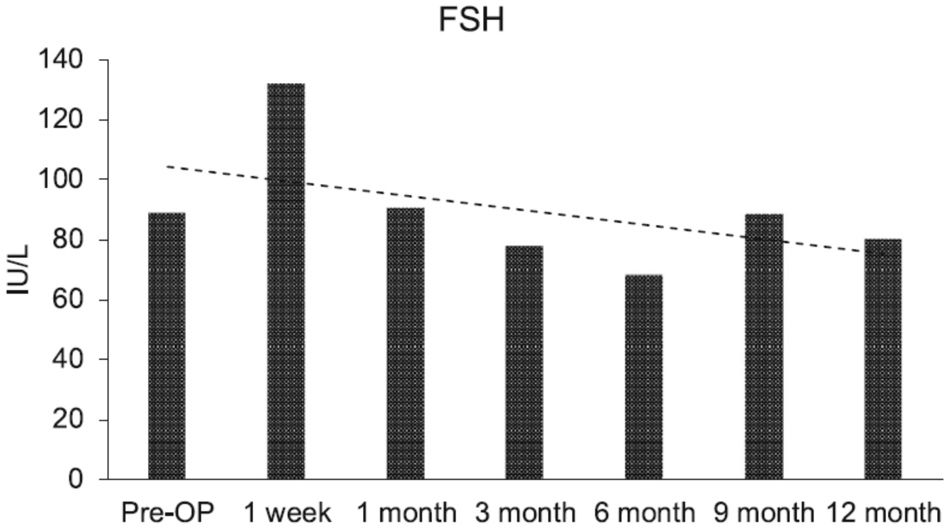


Fig. 4 Serum follicle-stimulating hormone (FSH) level reported pre– and post–mesenchymal stem cell ovarian implantation

Autologous BM-MSC Ovarian Transplant

Autologous Stem Cells Therapy, The First Baby of Idiopathic Premature Ovarian Failure

Acta Medical International 2016

M. Edessy[1], Hala N. Hosni[2], Y. Shady[1], Y. Waf[1], S. Bakr[3] and M. Kamel[1]
[1]Department of Gynocology and Obstetrics, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, [2]Department of Pathology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt, [3]Department of Zoology, Faculty of Science, Al-Azhar University, Cairo, Egypt

- Autologous bone marrow-derived MSC, injected directly into the ovaries
- Among 10 patients
  - 2 cases resumed menstruation after 3 months
  - one of them got pregnancy after 11 months and delivered a healthy full term baby

Table 8: Hormonal profile of the pregnant case before and after transplantation (months)

Case	Before				After													
	Basal				1 month after injection			2 months after injection			6 months after injection				10 months after injection			
	FSH	LH	E2	AMH	FSH	LH	E2	FSH	LH	E2	FSH	LH	E2	AMH	FSH	LH	E2	AMH
Case	58	31	11	<0.1	120	35	50	97	65	13	64	35	20	3	13	17	150	5

Autologous BM-MSC Ovarian Transplant

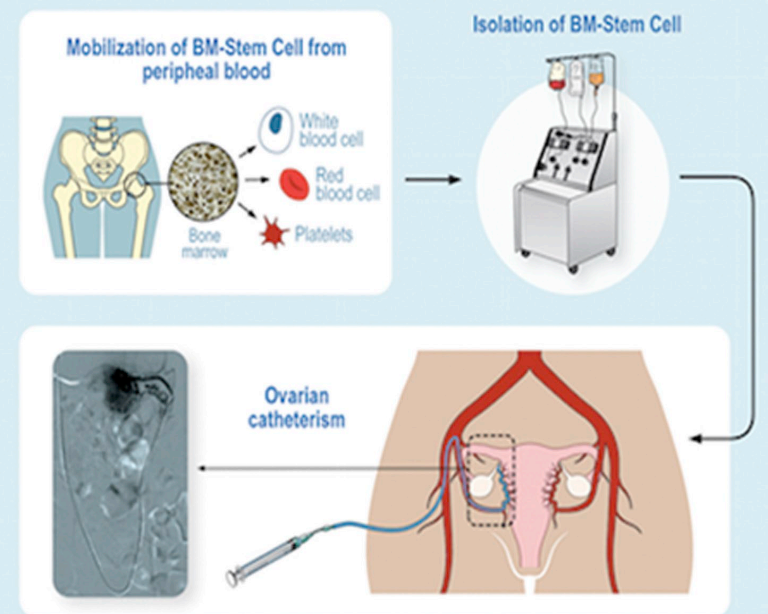
Autologous stem cell ovarian transplantation to increase reproductive potential in patients who are poor responders

Fertil Steril 2018

Sonia Herraiz, Ph.D.,[a,b,c] Mónica Romeu, M.D.,[c,d] Anna Buigues, B.Sc.,[a,c,e] Susana Martínez, M.D.,[d] César Díaz-García, M.D.,[f] Inés Gómez-Seguí, M.D.,[g] José Martínez, M.D.,[h] Nuria Pellicer, M.D.,[d] and Antonio Pellicer, M.D.[a,c,i]

[a] Fundación IVI, [b] IVI-RMA Valencia, [c] Reproductive Medicine Research Group, IIS La Fe, [d] Women's Health Area, [g] Hematology Department, and [h] Radiology Department, La Fe University Hospital; [e] Department of Pediatrics, Obstetrics and Gynecology, University of Valencia, Valencia, Spain; [f] IVI-RMA London, London, United Kingdom; and [i] IVI-RMA Rome, Rome, Italy

- 17 patients, G-CSF 5 days, then stem cell collection
- Intra-arterial catheterization procedure
- Five pregnancies were achieved: 2 after ET, 3 by natural conception



Reproductive outcomes before and after autologous stem cell ovarian transplant.

Characteristics	Previous	After ASCOT	P Value
FSH dose (IU)	3,623 ± 1,444	4,201 ± 1,342	NS
Days of stimulation	10.5 ± 2.7	9.9 ± 3.8	NS
E_2 day hCG administration	1,079.4 ± 736.5	720.7 ± 512.2	NS
Antral follicles (total)	4 ± 1.9	5.8 ± 1.7	.036
Control ovary	2.5 ± 1.0	2.8 ± 1.5	NS
Infused ovary	1.9 ± 0.7	2.9 ± 1.4	.026
Follicles >16 mm (total)	2.6 ± 1.8	2.9 ± 1.2	.05
Control ovary	1.2 ± 1.0	1.5 ± 1.1	NS
Infused ovary	1.2 ± 1.5	1.5 ± 1.2	NS
Punctured follicles (total)	4.0 ± 3.1	4.7 ± 1.9	NS
Control ovary	2 ± 2.1	1.9 ± 1.0	NS
Infused ovary	1.5 ± 1.8	2.1 ± 1.7	NS
Retrieved MII (total)[a]	2.3 ± 2.0	2.6 ± 1.6	NS
0	4	2	
1	4	10	
2	1	4	
3	5	5	
≥4	3	3	
No oocyte pick-up	7	3	
Retrieved MII (control ovary)	0.5 ± 1.0	1.4 ± 1.0	NS
Retrieved MII (infused ovary)	0.3 ± 0.5	1.2 ± 1.0	NS
Total embryos by cycle[a]	1.7 ± 1.5	2.1 ± 1.6	NS
0	4	4	
1	5	12	
2	4	2	
≥3	3	5	
Embryos (control ovary)	—	1.0 ± 1.2	
Embryos (infused ovary)	—	1.1 ± 0.9	
Canceled COS	4/15 (26.6%)	1/15 (6.6%)	NS

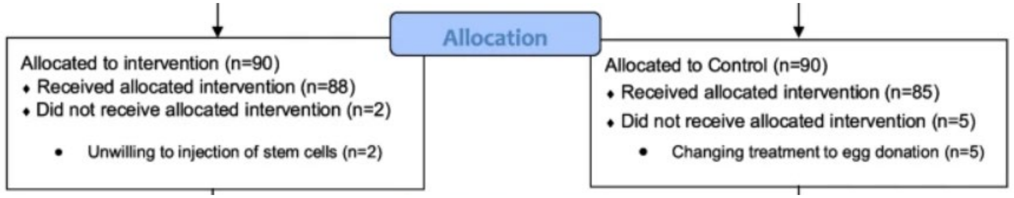
Autologous Men-MSC Ovarian Transplant

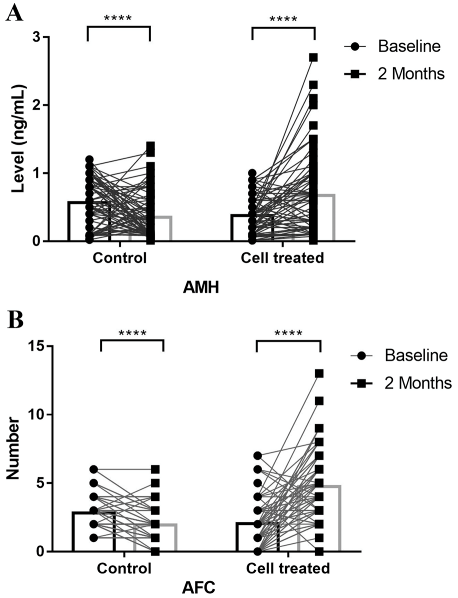
Home > Stem Cell Research & Therapy > Article

The effects of intraovarian injection of autologous menstrual blood-derived mesenchymal stromal cells on pregnancy outcomes in women with poor ovarian response

Research | Open access | Published: 15 November 2023

Simin Zafardoust, Somaieh Kazemnejad, Mina Fathi-Kazerooni, Maryam Darzi, Mohammad Reza Sadeghi, Ali Sadeghi Tabar & Zahra Sehat





- Autologous Men-MSC treatment: quicker, safer and less invasive method of collection and no ethical issues
  - improvement in AMH levels & AFC
  - higher rate of spontaneous pregnancy
  - greater number of mature oocytes & embryos in IVF
  - subgroup analysis: only among individuals <40y

Parameters	In ≤ 40years old group			In > 40years old group		
	MenSC	Control	*P*-value	MenSC	Control	*P*-value
Spontaneous pregnancy	12/44 (27.3%)	4/44 (9.1%)	0.01	6/36 (16.6%)	2/37 (5.4%)	NS
Pregnancy after ICSI	8/26 (27.6%)	2/14 (4.8%)	0.009	0/23 (0%)	2/18 (5.6%)	NS
Clinical pregnancy	20/44 (50%)	6/44 (13.6%)	< 0.001	6/36 (16.7%)	4/37 (10.8%)	NS
Live birth rate	11/44 (25.0%)	4/44 (9.1%)	0.02	5/36 (13.9%)	2/37 (5.4%)	NS

Other Source of Stem Cells for Ovarian Transplant

Home > Journal of Ovarian Research > Article

Evaluation of safety, feasibility and efficacy of intra-ovarian transplantation of autologous adipose derived mesenchymal stromal cells in idiopathic premature ovarian failure patients: non-randomized clinical trial, phase I, first in human

Research | Open access | Published: 06 January 2021

Volume 14, article number 5, (2021) Cite this article

Results

Participants had not shown any early-onset possible side effects and secondary complications during follow-up. The menstruation resumption was observed in four patients which established for several months. In the 15×10^6 group, two POF patients had a return of menstruation second months after the intervention. Two other POF patients in 5×10^6 and 10×10^6 cell groups reported menstruation resumption at 1 month after the intervention. We observed decreased serum FSH levels of less than 25 IU/l in four patients. In two patients in 5×10^6 and 10×10^6 cell groups, serum FSH showed an inconsistent decline during a 1 year follow up after ADSCs transplantation. The ovarian volume, AMH, and AFC were variable during the follow-up and no significant differences between cell groups ($p > 0.05$).

Conclusions

We showed the intra-ovarian embedding of ADSCs is safe and feasible and is associated with an inconsistent decline in serum FSH. This should be further investigated with a large RCT.

Home > Science China Life Sciences > Article

Transplantation of UC-MSCs on collagen scaffold activates follicles in dormant ovaries of POF patients with long history of infertility

Research Paper | Published: 13 March 2018

Premature ovarian failure (POF) is a refractory disease for clinical treatment with the goal of restoring fertility. In this study, umbilical cord mesenchymal stem cells on a collagen scaffold (collagen/UC-MSCs) can activate primordial follicles *in vitro* via phosphorylation of FOXO3a and FOXO1. Transplantation of collagen/UC-MSCs to the ovaries of POF patients rescued overall ovarian function, evidenced by elevated estradiol concentrations, improved follicular development, and increased number of antral follicles. Successful clinical pregnancy was achieved in women with POF after transplantation of collagen/UC-MSCs or UC-MSCs. In summary, collagen/UC-MSC transplantation may provide an effective treatment for POF.

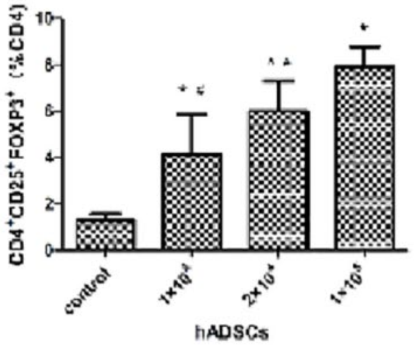
Mesenchymal Stem Cells Based Therapy – Immune Modulation

International Immunopharmacology
Volume 55, February 2018, Pages 257-262

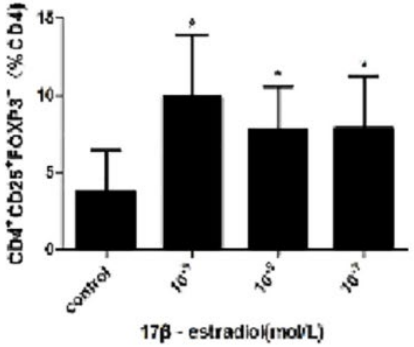
Effects of human adipose-derived mesenchymal stem cells combined with estrogen on regulatory T cells in patients with premature ovarian insufficiency

Kaijing Song [a], Huihua Cai [b], Dongmei Zhang [a], Ruichun Huang [a], Donghua Sun [a], Yuanli He [a]

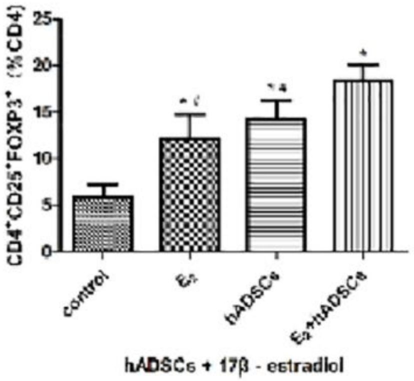
- hAD-SCs increase the proportion of CD4+ CD25+ Foxp3+ Tregs by upregulating the expression level of Foxp3
- 17β-estradiol significantly increases the proportion of CD4+ CD25+ Foxp3+ Tregs in the PBMCs population
- hAD-SCs & 17β-estradiol can exert a synergistic effect on promoting immunomodulation of Tregs
- The combination treatment with hAD-SCs and estrogen may be effective way to improve immune-induced POI



hADSCs

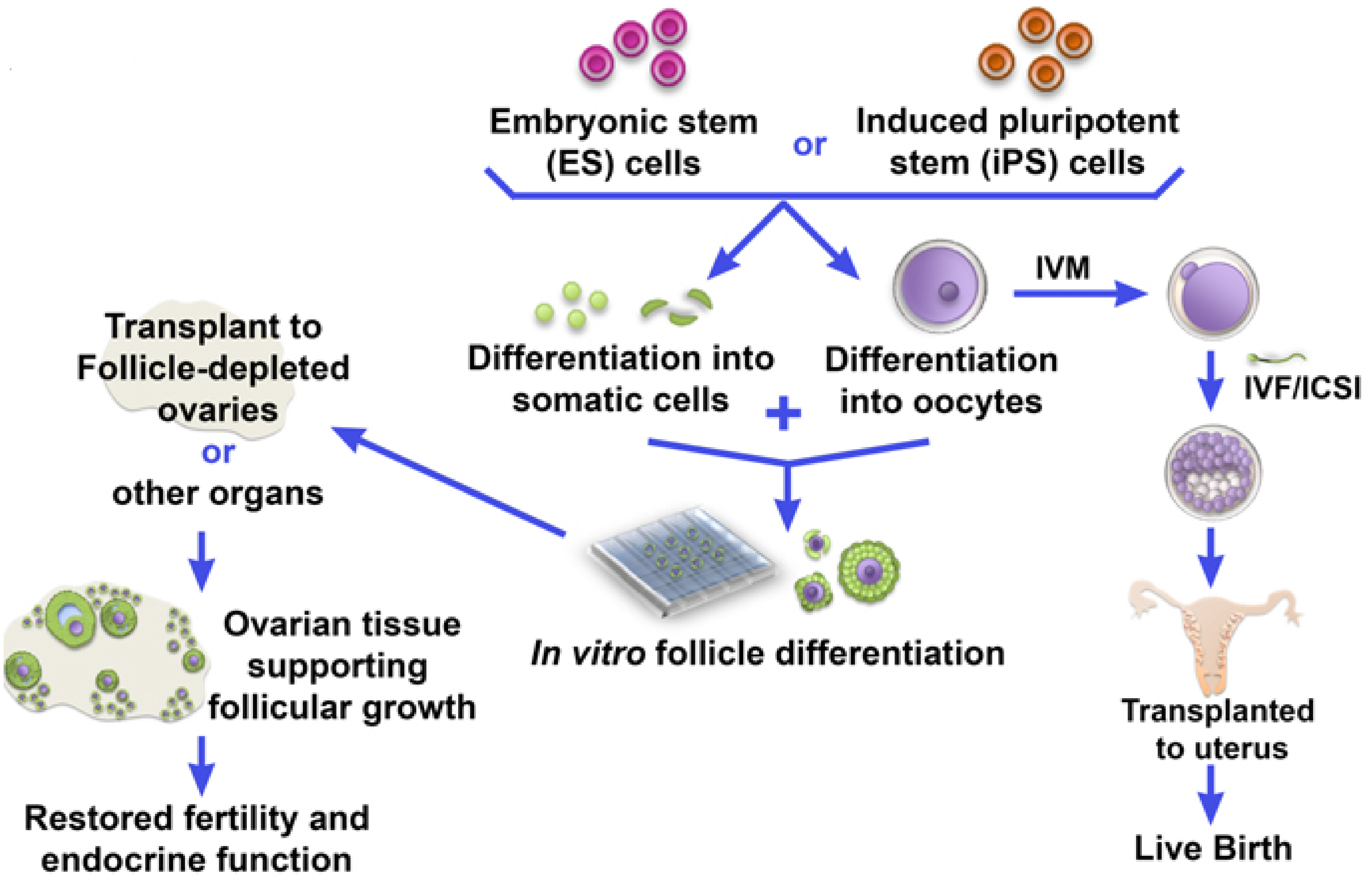


17β-estradiol



hADSCs+17β-estradiol

Making New Gametes from PSCs



Mouse Artificial Gametes

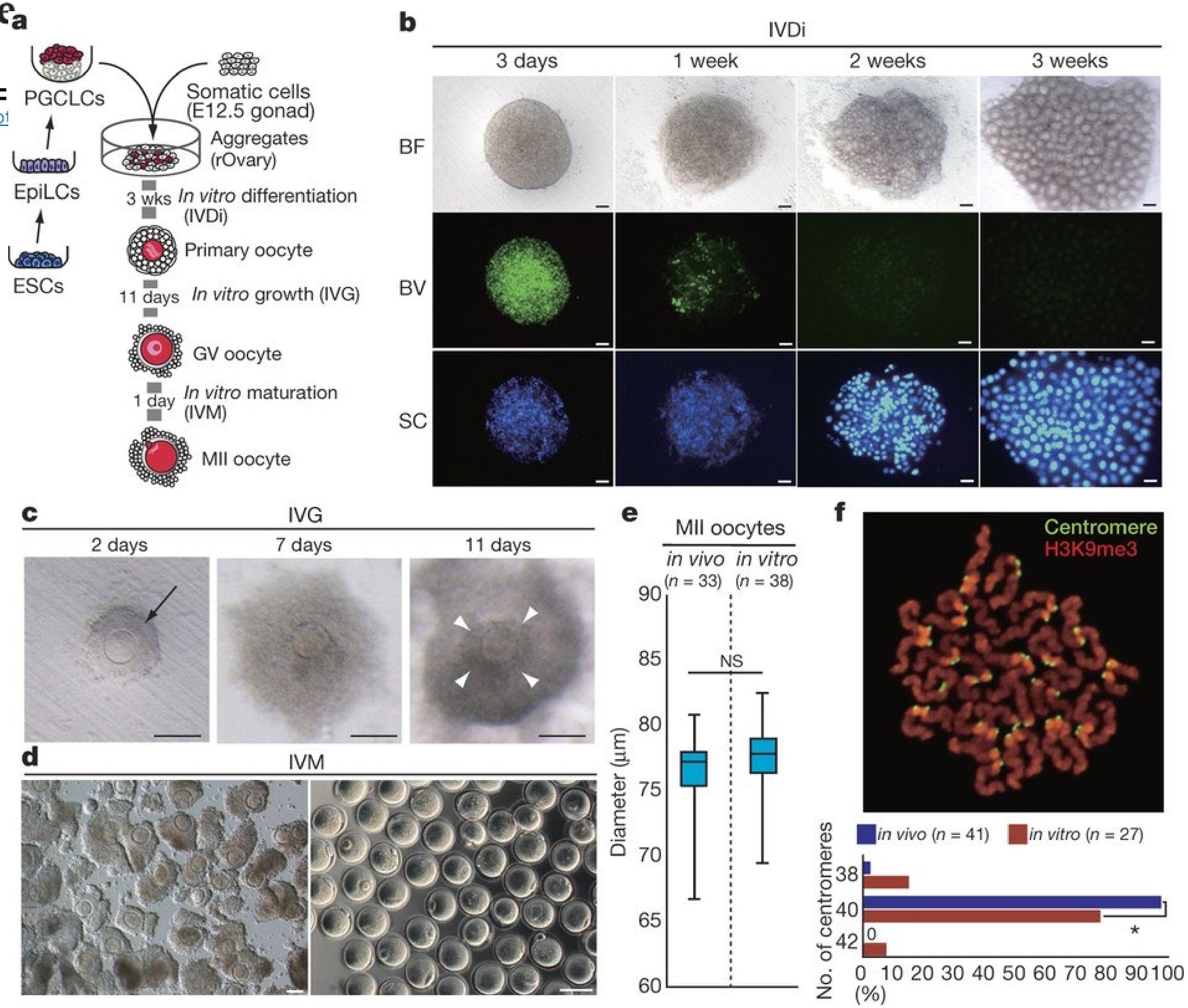
Reconstitution *in vitro* of the entire cycle of the mouse female germ line

Orie Hikabe, Nobuhiko Hamazaki, Go Nagamatsu, Yayoi Obata, Yuji Hirao, Norio Hamada, So Shimamot
Takuya Imamura, Kinichi Nakashima, Mitinori Saitou & Katsuhiko Hayashi

Nature **539**, 299–303 (2016) | Cite this article

primordial germ cell like cells =

epiblast-like cells =



- Fully potent mature oocytes were generated in culture from embryonic stem cells and from induced pluripotent stem cells derived from both embryonic fibroblasts and adult tail tip fibroblasts

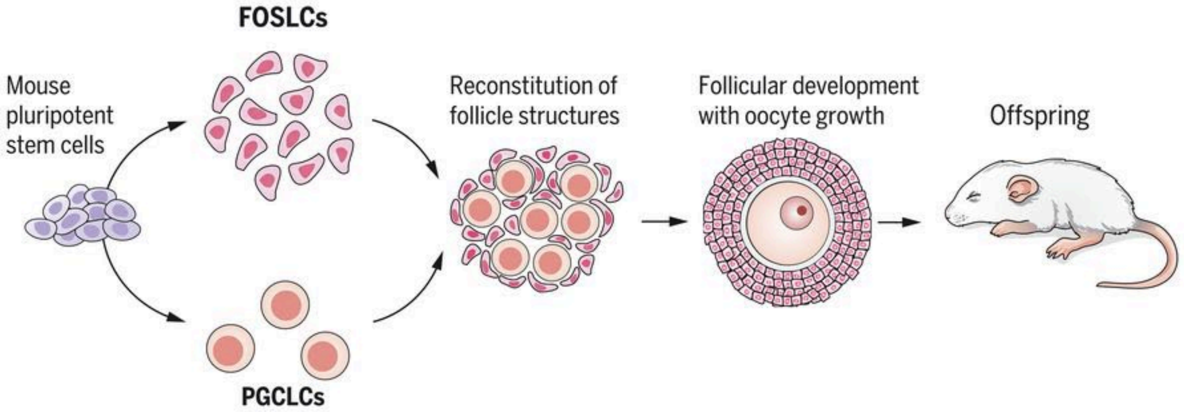
Generation of Ovarian Follicles from Mouse PSCs

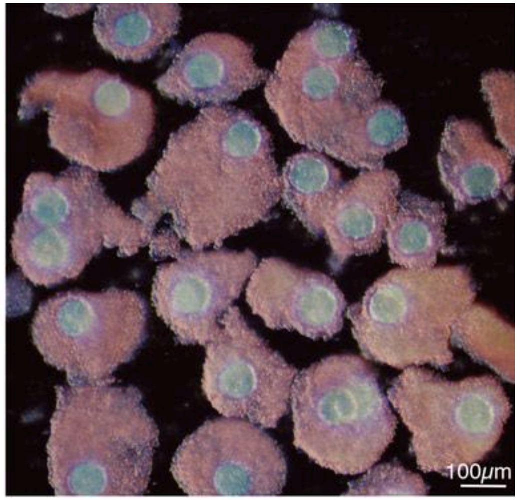
Generation of ovarian follicles from mouse pluripotent stem cells

TAKASHI YOSHINO, TAKAHIRO SUZUKI, GO NAGAMATSU, HARUKA YABUKAMI, MIKA IKEGAYA, MAMI KISHIMA, HARUKA KITA, TAKUYA IMAMURA, KINICHI NAKASHIMA, [...], AND KATSUHIKO HAYASHI +5 authors Authors Info & Affiliations

SCIENCE • 16 Jul 2021 • Vol 373, Issue 6552 • DOI: 10.1126/science.abe0237

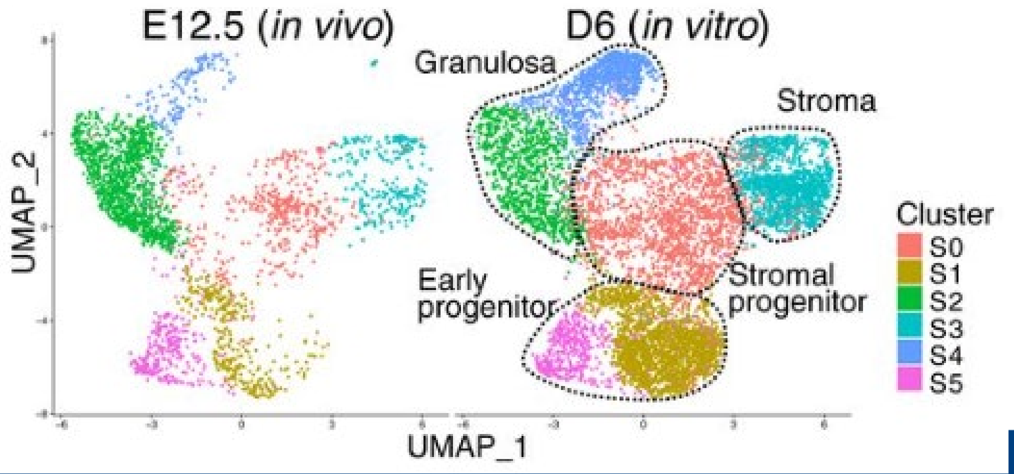
fetal ovarian somatic cell–like cells





- When the embryonic stem cell–generated ovarian gonadal tissue was combined with early primordial germ cells or in vitro–derived primordial germ cell–like cells, germ cells developed into viable oocytes within the reconstituted follicles
- They could be fertilized and result in viable offspring

Gene expression profiles between gonadal somatic cells



Generation of Ovarian Follicles from Human iPSCs

eLife

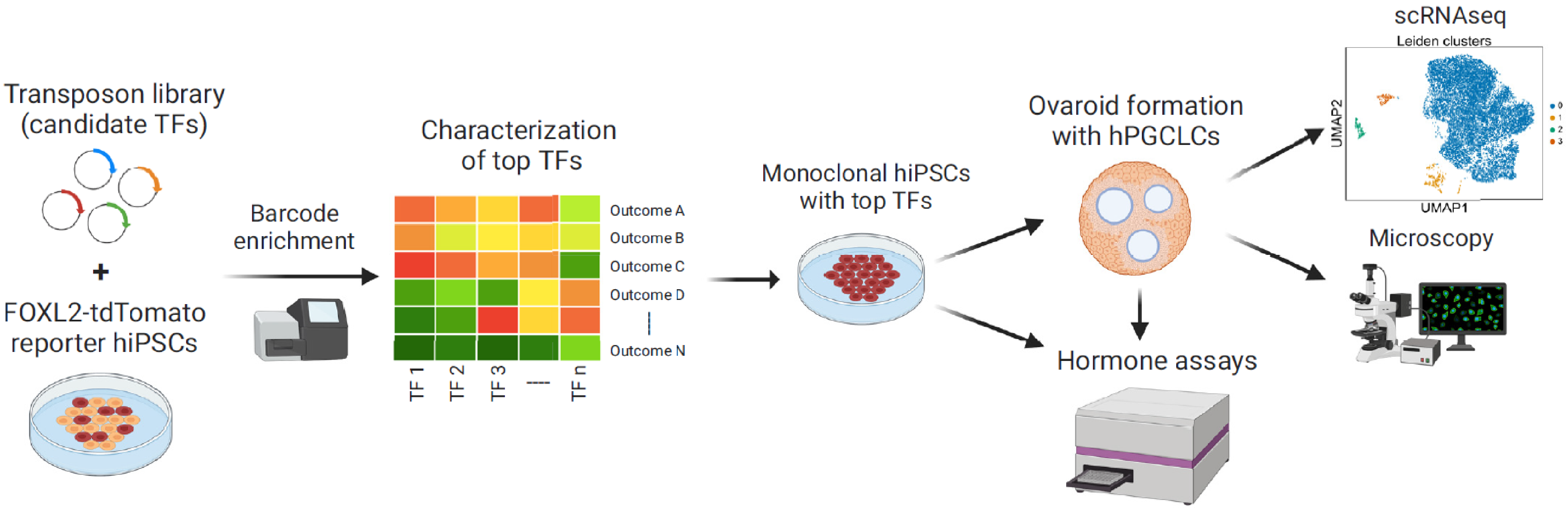
Directed differentiation of human iPSCs to functional ovarian granulosa-like cells via transcription factor overexpression

Merrick D Pierson Smela, Christian C Kramme, Patrick RJ Fortuna, Jessica L Adams, Rui Su, Edward Dong, Mutsumi Kobayashi, Garyk Brixi, Venkata Srikar Kavirayuni see all »

Wyss Institute, Harvard University, United States; Department of Genetics, Harvard Medical School, United States; Massachusetts General Hospital Center for Cancer Research, Harvard Medical School, United States; Department of Biomedical Engineering, Duke University, United States; Department of Computer Science, Duke University, United States

Feb 21, 2023 · https://doi.org/10.7554/eLife.83291

- Generating human primordial germ cell-like cells (hPGCLCs) from human induced pluripotent stem cells (hiPSCs)
- Simultaneous overexpression of two transcription factors (TFs) can direct the differentiation of hiPSCs to granulosa-like cells
  - overexpression of NR5A1 and either RUNX1 or RUNX2



Generation of Ovarian Follicles from Human iPSCs

eLife

Directed differentiation of human iPSCs to functional ovarian granulosa-like cells via transcription factor overexpression

Merrick D Pierson Smela, Christian C Kramme, Patrick RJ Fortuna, Jessica L Adams, Rui Su, Edward Dong, Mutsumi Kobayashi, Garyk Brixi, Venkata Srikar Kavirayuni see all »

Wyss Institute, Harvard University, United States; Department of Genetics, Harvard Medical School, United States; Massachusetts General Hospital Center for Cancer Research, Harvard Medical School, United States; Department of Biomedical Engineering, Duke University, United States; Department of Computer Science, Duke University, United States

Feb 21, 2023 · https://doi.org/10.7554/eLife.83291

- Aggregated with hPGCLCs,

  granulosa-like cells form ovary-like organoids

  (ovaroids)

  and support hPGCLC development

  from the premigratory

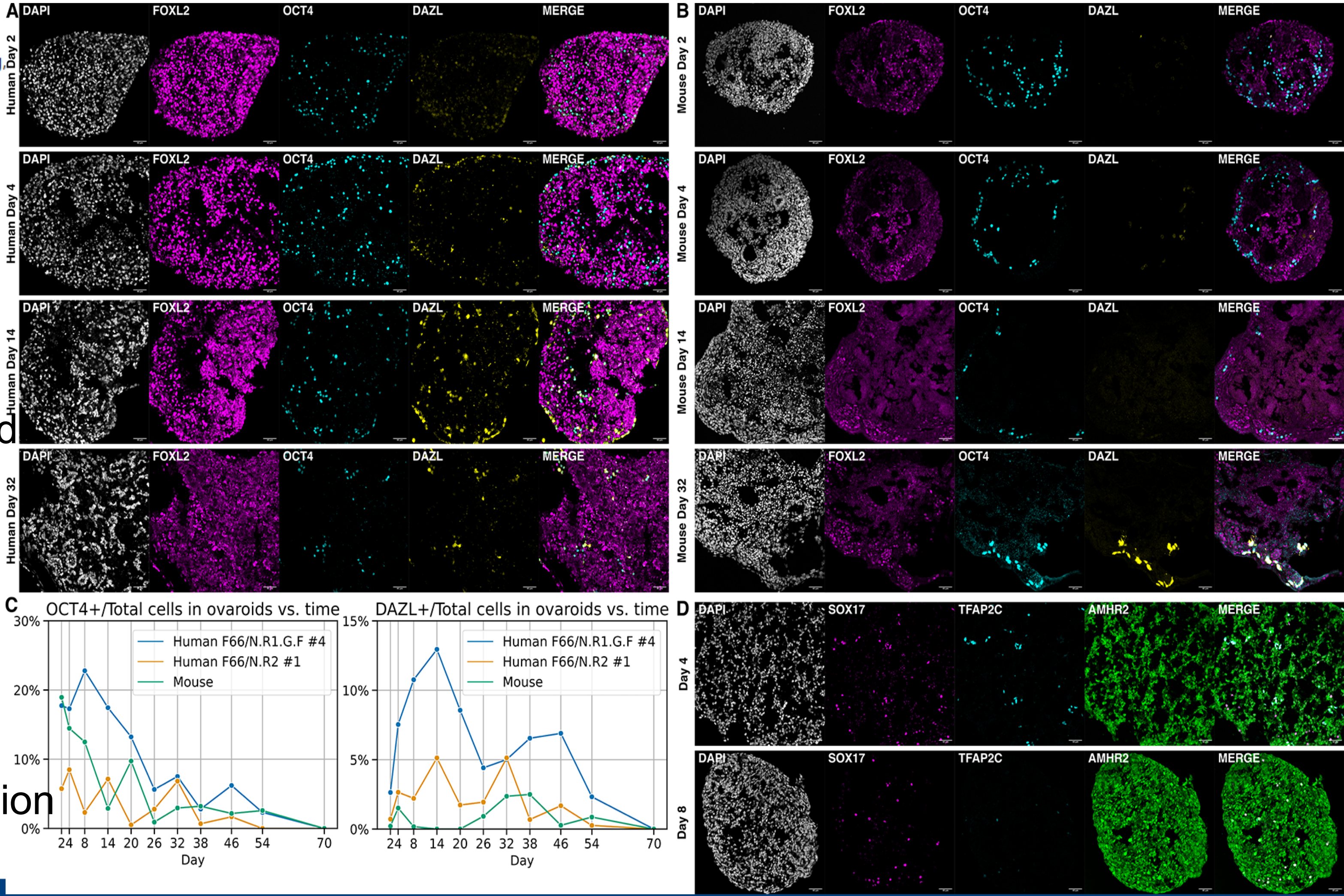
  to the gonadal stage

  as measured by induction of DAZL expression

granulosa

germ cell/pluripotent

Mature germ cell



Generation of Ovarian Follicles from Human iPSCs

eLife

Directed differentiation of human iPSCs to functional ovarian granulosa-like cells via transcription factor overexpression

Merrick D Pierson Smela, Christian C Kramme, Patrick RJ Fortuna, Jessica L Adams, Rui Su, Edward Dong, Mutsumi Kobayashi, Garyk Brixi, Venkata Srikar Kavirayuni see all »

Wyss Institute, Harvard University, United States; Department of Genetics, Harvard Medical School, United States; Massachusetts General Hospital Center for Cancer Research, Harvard Medical School, United States; Department of Biomedical Engineering, Duke University, United States; Department of Computer Science, Duke University, United States

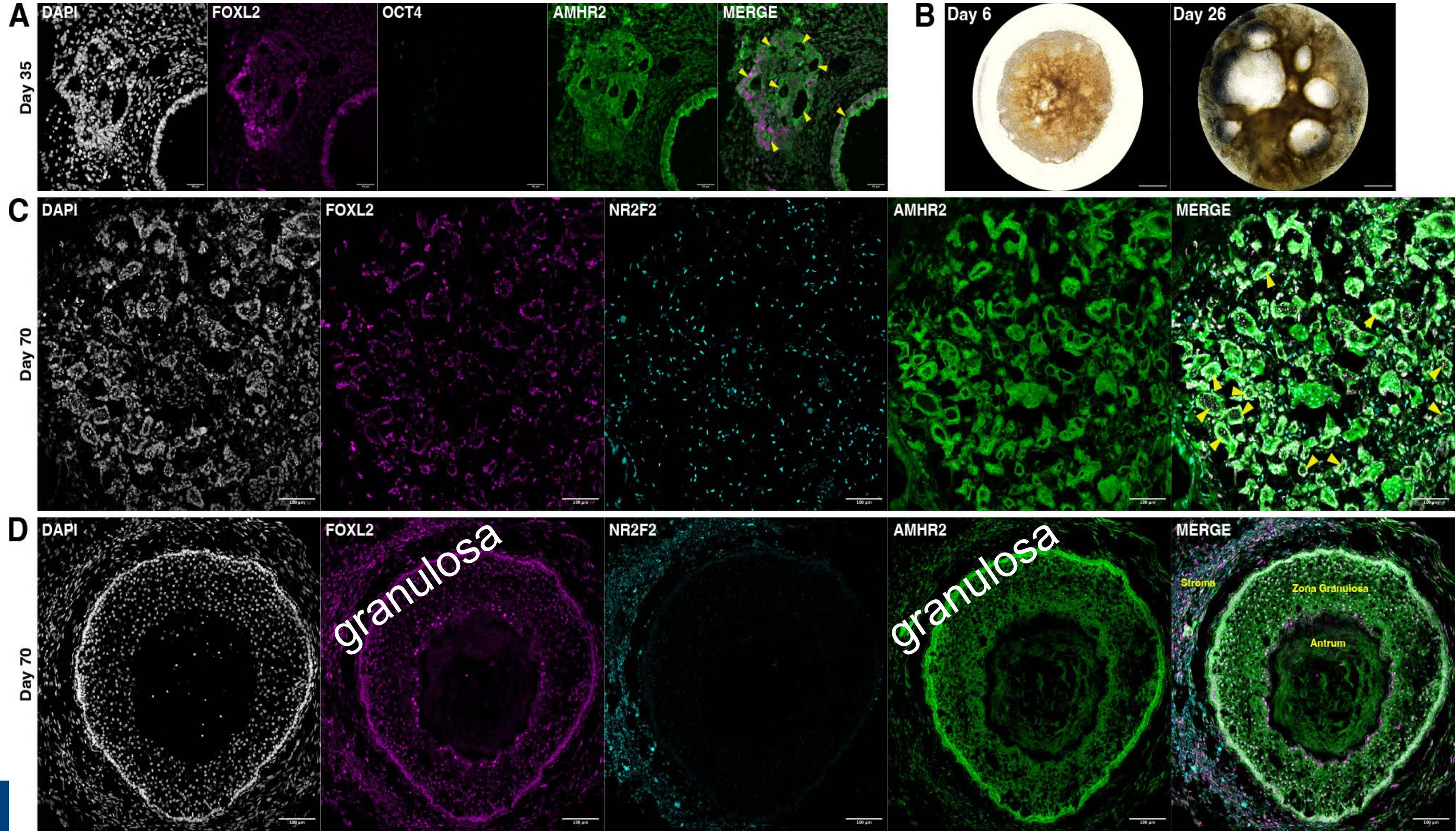
Feb 21, 2023 · https://doi.org/10.7554/eLife.83291

- Novel tool for understanding the molecular mechanism about the differentiation of somatic cells
- Enable to address the interaction between germ cells and somatic cells
- Apply in vitro gametogenesis in various mammalian species

- Whole-ovaroid foaming follicle-like structures after culture

  → Single layers of FOXL2+AMHR2+ cells

  → Antral follicle consisting of FOXL2+AMHR2+ granulosa-like cells arranged in several layers around a central cavity



Summary

- Stem cell therapy in FP

  - POI

  - Ovarian aging

- ESC & iPSC based therapy is ongoing

- Mesenchymal stem cells based therapy is on clinical trial

  - various source of stem cell

  - various mechanism: immune modulation, exosome

- Use of stem cells to produce new oocytes and stromal cell to create follicles

  → artificial ovary or reconstructed ovary