
بسم الله الرحمن الرحيم

Biologic Therapy With Emphasis on Stem Cells and Their Derivatives in Azoospermia Disorder

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Nanobiothecnology Research Center,
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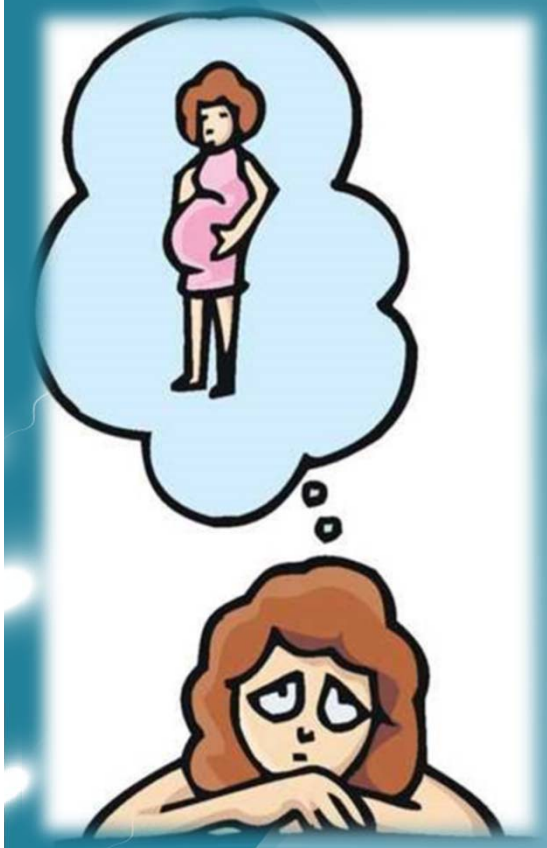
January 2022

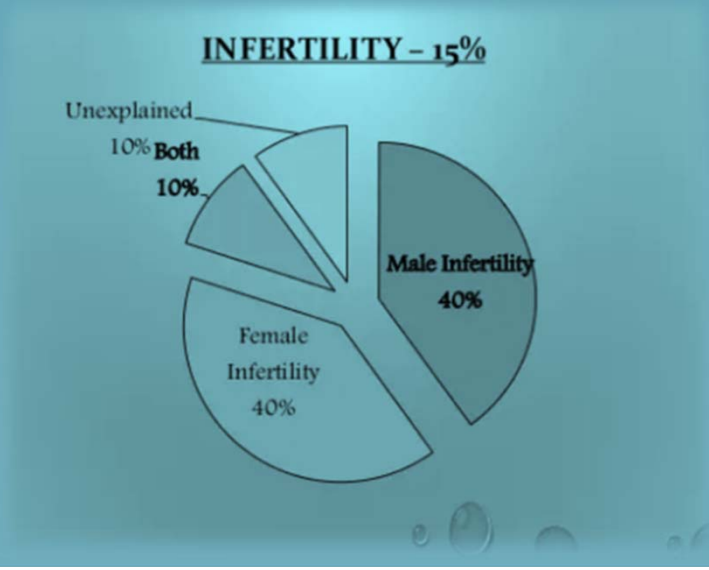


Infertility

The inability to conceive following unprotected and regular sexual intercourse

– 1 year (age < 35) or 6 months (age >35)

– Affects 15% of reproductive couples

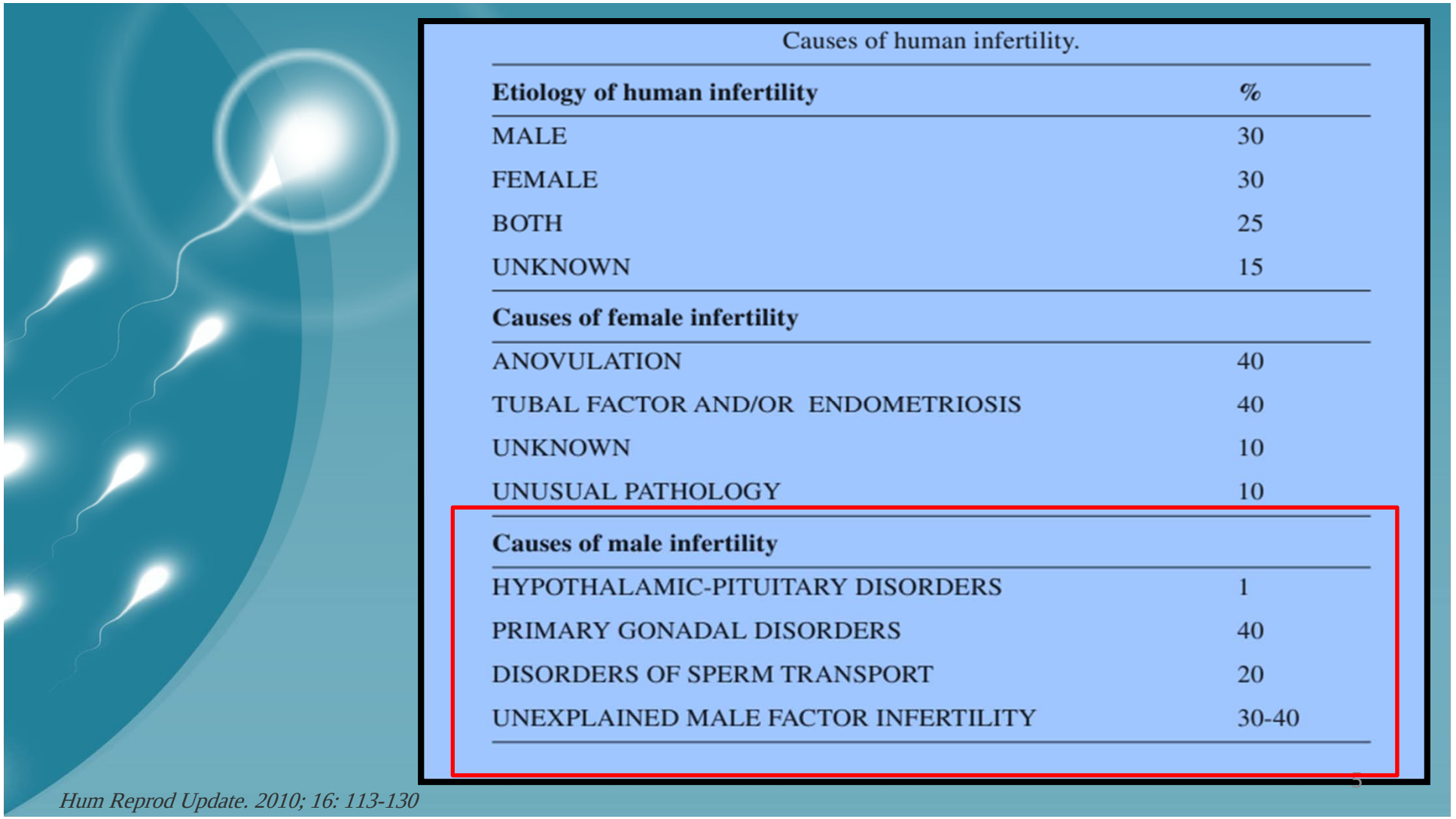


Fertil Steril. 2017 Sep; 108(3):393-406

Classification

- **Primary infertility**
  - a couple that has never conceived
- **Secondary infertility**
  - infertility that occurs after previous pregnancy regardless of outcome

Popul Health Metr. 2012; 10: 17.



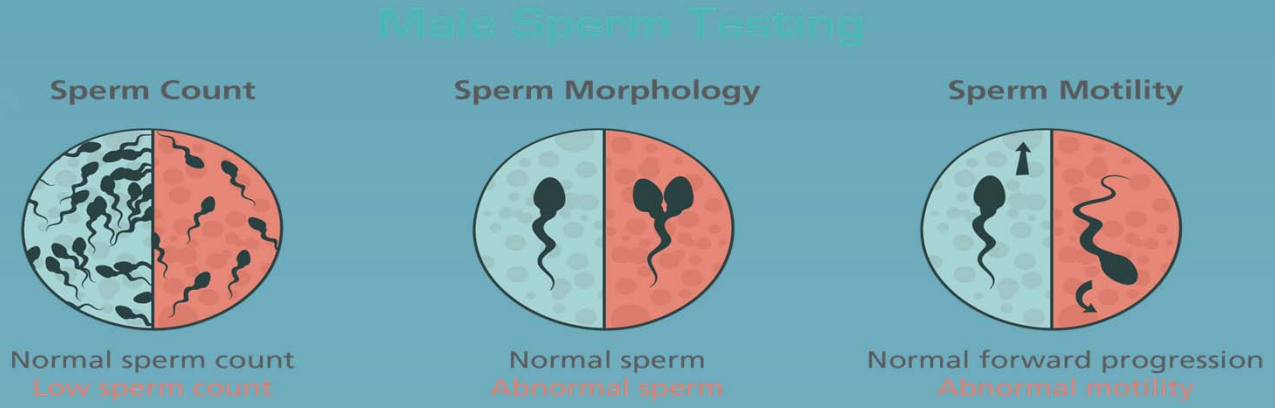
Causes of human infertility.

Etiology of human infertility	%
MALE	30
FEMALE	30
BOTH	25
UNKNOWN	15
Causes of female infertility	
ANOVULATION	40
TUBAL FACTOR AND/OR ENDOMETRIOSIS	40
UNKNOWN	10
UNUSUAL PATHOLOGY	10
Causes of male infertility	
HYPOTHALAMIC-PITUITARY DISORDERS	1
PRIMARY GONADAL DISORDERS	40
DISORDERS OF SPERM TRANSPORT	20
UNEXPLAINED MALE FACTOR INFERTILITY	30-40

Hum Reprod Update. 2010; 16: 113-130

Sperm disorders

It is due to disorders in the sperm, whether they affect their morphology, motility or count.



Semen Analysis Test - Normal Values

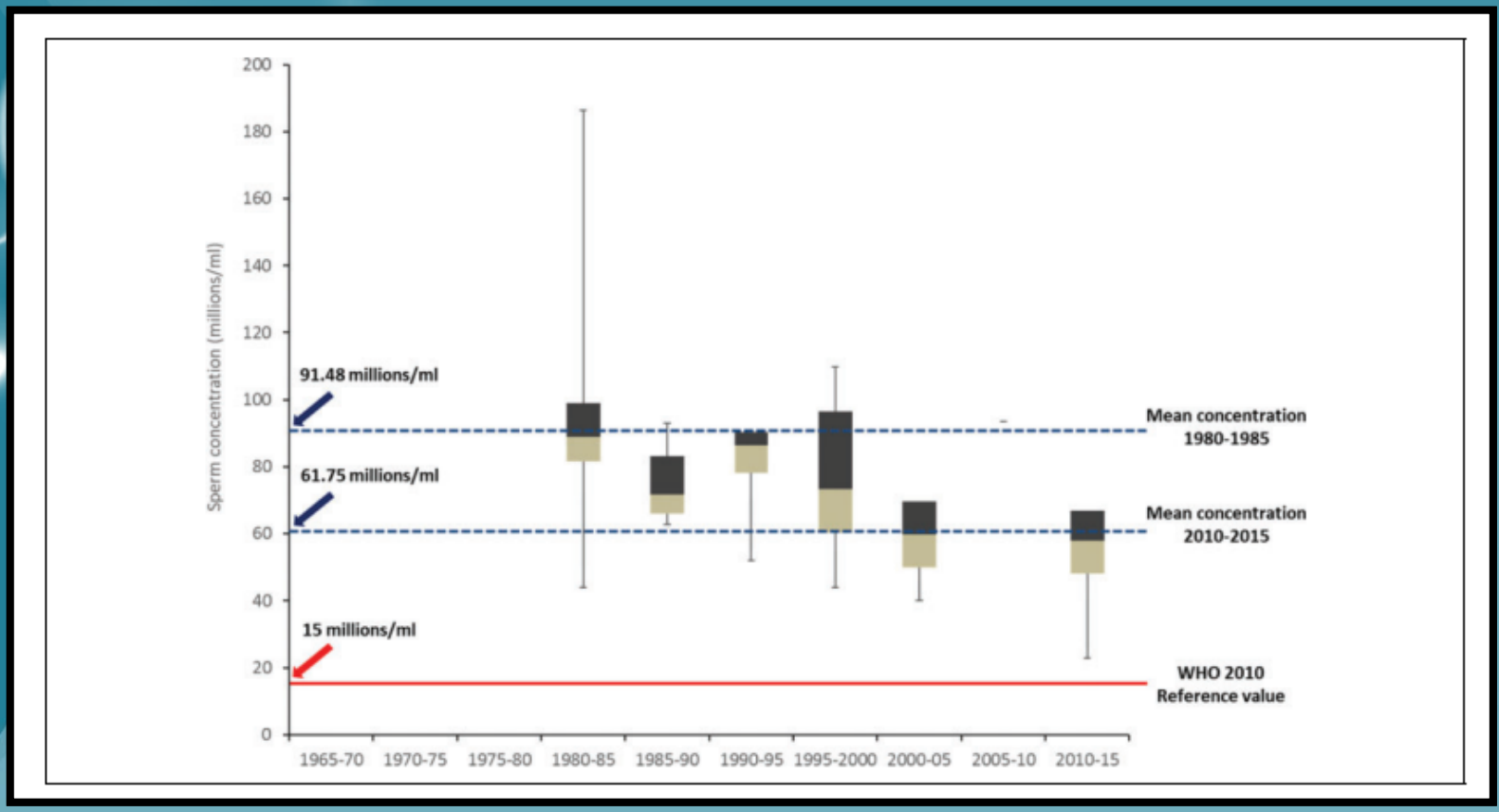
Parameter	Reference Range
Semen Volume	>= 1.5 mL
Sperm Count	>= 15 million per mL
Total Sperm Number	>= 39 million
Sperm Motility	Total motility >= 40% motile sperms within 60 minutes of ejaculation. Progressive motility >= 32%
Sperm Viability Or Vitality	>= 58%
Sperm Morphology	>= 4%
White Blood Cells	< 1 million per mL
Semen pH	>= 7.2

JBRA Assisted Reproduction 2020;24(1):82-86

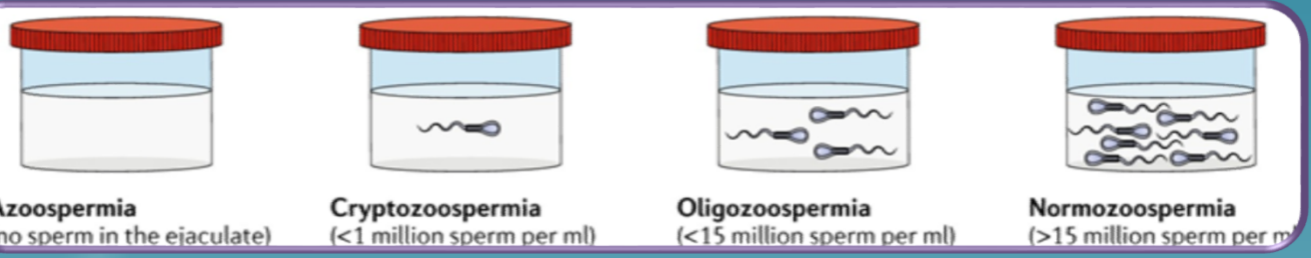
Semen parameter	WHO 1980	WHO 1987	WHO 1992	WHO 1999	WHO 2010
Volume (mL)	ND	≥2	≥2	≥2	1.5
Sperm count (10^6/mL)	20–200	≥20	≥20	≥20	15
Total sperm count (10^6)	ND	≥40	≥40	≥40	39
Total motility (% motility)	≥60	≥50	≥50	≥50	40
Progressive motility (%)	≥2	≥25	≥25 (grade a)	≥25% (grade a)	32 (grade a+b)
Vitality (% alive)	ND	≥50	≥75	≥75	58
Morphology (% normal forms)	80.5	≥50	≥30	14	4

WHO: World Health Organization; ND: not defined.
Adapted from the article of Esteves et al (Urology 2012;79:16-22) [28] with original copyright holder's permission.

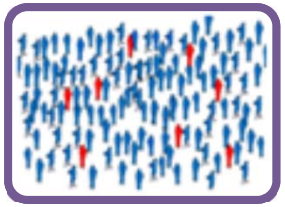
World J Mens Health. 2021 Apr; 39(2): 172–185



Human and Experimental Toxicology 2017; 1–9.



Absence of spermatozoa in the ejaculate both in a neat semen sample and in a centrifuges suspended semen sample.



1-3% of male population
10 % infertile male associated with infertility

Obstructive
Non obstructive

Pre testicular
Testicular
Post testicular

Research in Medicine 2017, 41(1): 1-9

What exactly is Azoospermia?

No sperm seen in semen sample ⇨ centrifuged the semen sample at 3000g for 15 minutes ⇨ the pellet formed must be examined for presence of any sperm

- If any sperm is found in the pellet ⇨ Cryptozoospermia

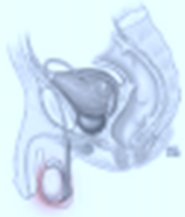
- If no sperm is found even after centrifugation ⇨ repeat analysis must be done after 2-4 weeks

Pre-testicular

Hypothalamic disease:
- Gonadotropin deficiency (Kallmann syndrome)
- Isolated LH deficiency ("fertile eunuch")
- Isolated FSH deficiency
- Congenital hypogonadotropic syndromes

Pituitary disease:
- Pituitary insufficiency
- Hyperprolactinemia
- Exogenous hormones
- Growth hormone deficiency

Testicular



Chromosomal:
- Klinefelter syndrome
- XX male (sex reversal syndrome)
- XYY male
- Others

Non-chromosomal:
- Varicocele
- Cryptorchidism
- Sertoli-cell-only syndrome
- Chemo/radiotherapy
- Others

Post-testicular

Other causes:
- Congenital blockage of the ductal system
- Cystic fibrosis
- Acquired blockage of the ductal system
- Antisperm antibodies
- Ejaculatory duct obstruction

World J Mens Health. 2020 Jul;38(3):308-322.

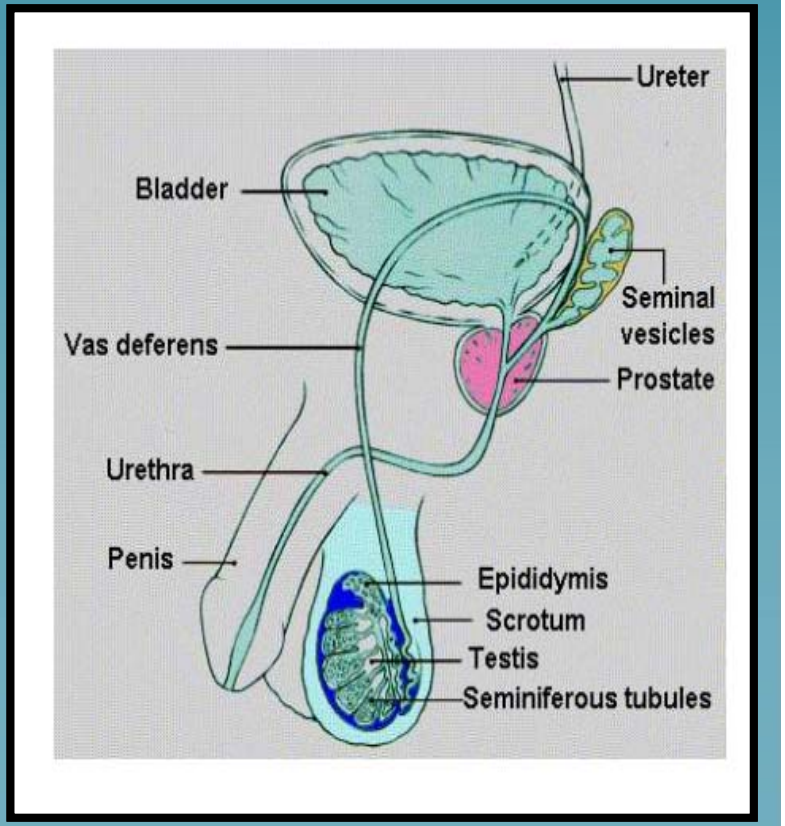
Obstructive azoospermia

- **Sites of Obstruction**

– Epididymis
– Vas deferens
– Ampulla of the vas
– Ejaculatory duct

Can be congenital or acquired

– CBAVD
– Vasectomy
– Infections
- Incomplete patency of the vas deferens
- Slow maturation of spermatozoa in the epididymis



Fertil sterile 2019;111(5):873-880.

Non obstructive Azoospermia

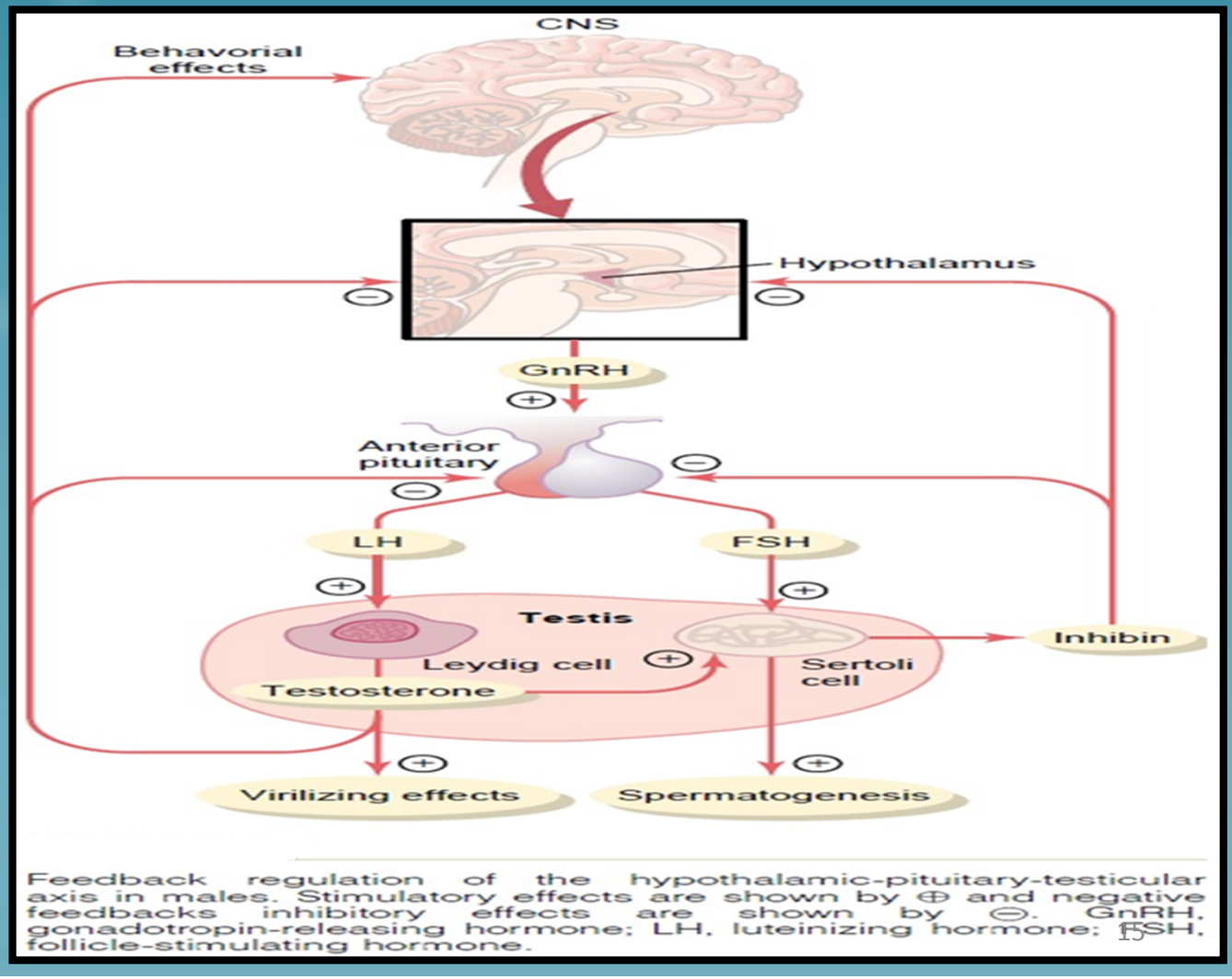
- **Primary Testicular Failure or Hypergonadotropic hypogonadism**

– defect in production of sperm by testes themselves

- **Secondary Testicular Failure or Hypogonadotropic hypogonadism (pre-testicular)**

– due to defect at the level of pituitary gland or the hypothalamus

American Journal of Men's Health, 2020:1–16.



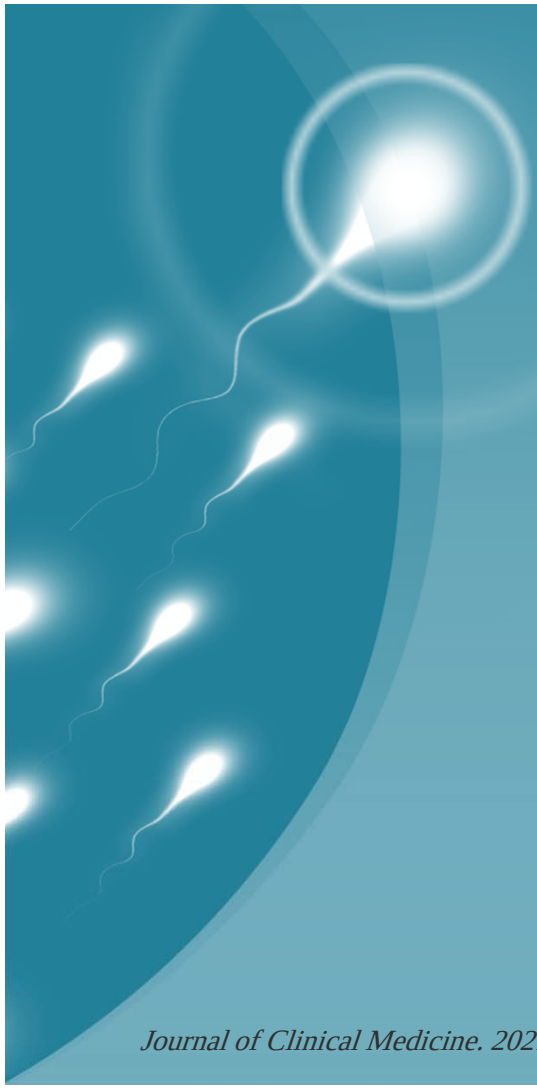
Feedback regulation of the hypothalamic-pituitary-testicular axis in males. Stimulatory effects are shown by ⊕ and negative feedbacks inhibitory effects are shown by ⊖. GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

Journal of Occupational Health and Epidemiology 2016, 5(1):53-62

Gonadotropin, Testosterone, and Testis Volume Changes with OA and NOA

Etiology	Subtype	FSH	LH	Testosterone	Testis Volume
Obstructive Azoospermia		↔	↔	↔	↔
Non-obstructive Azoospermia	Primary Testicular Failure	↑	↑	↓	↓
	Hypogonadotropic Hypogonadism	↓	↓	↓	↓

Spermatogenesis. 2014; 4: e28218.



Clinical management in NOA

For men faced with nonobstructive azoospermia (NOA),

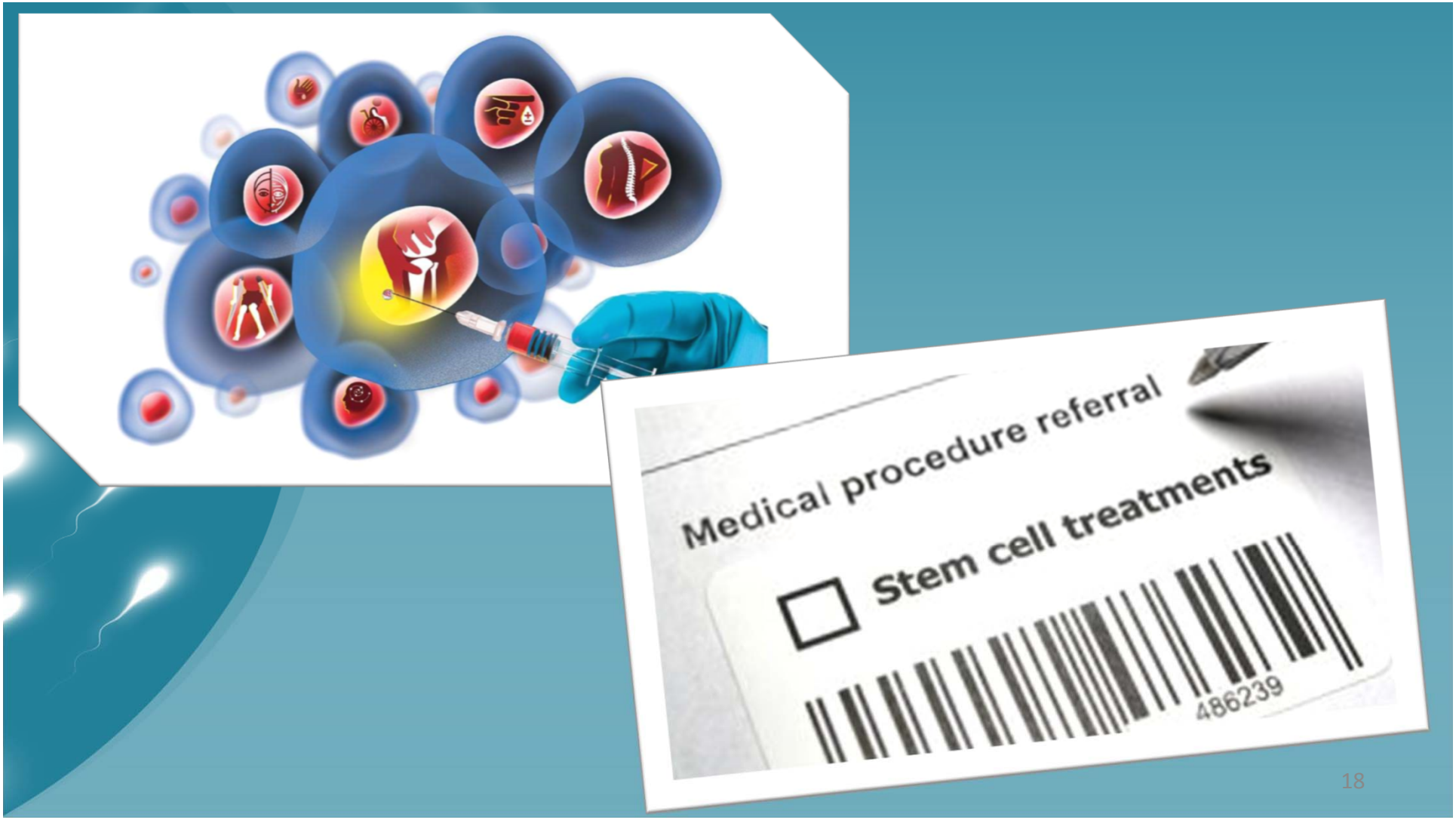
the most severe form of male infertility, have limited options for reproduction.

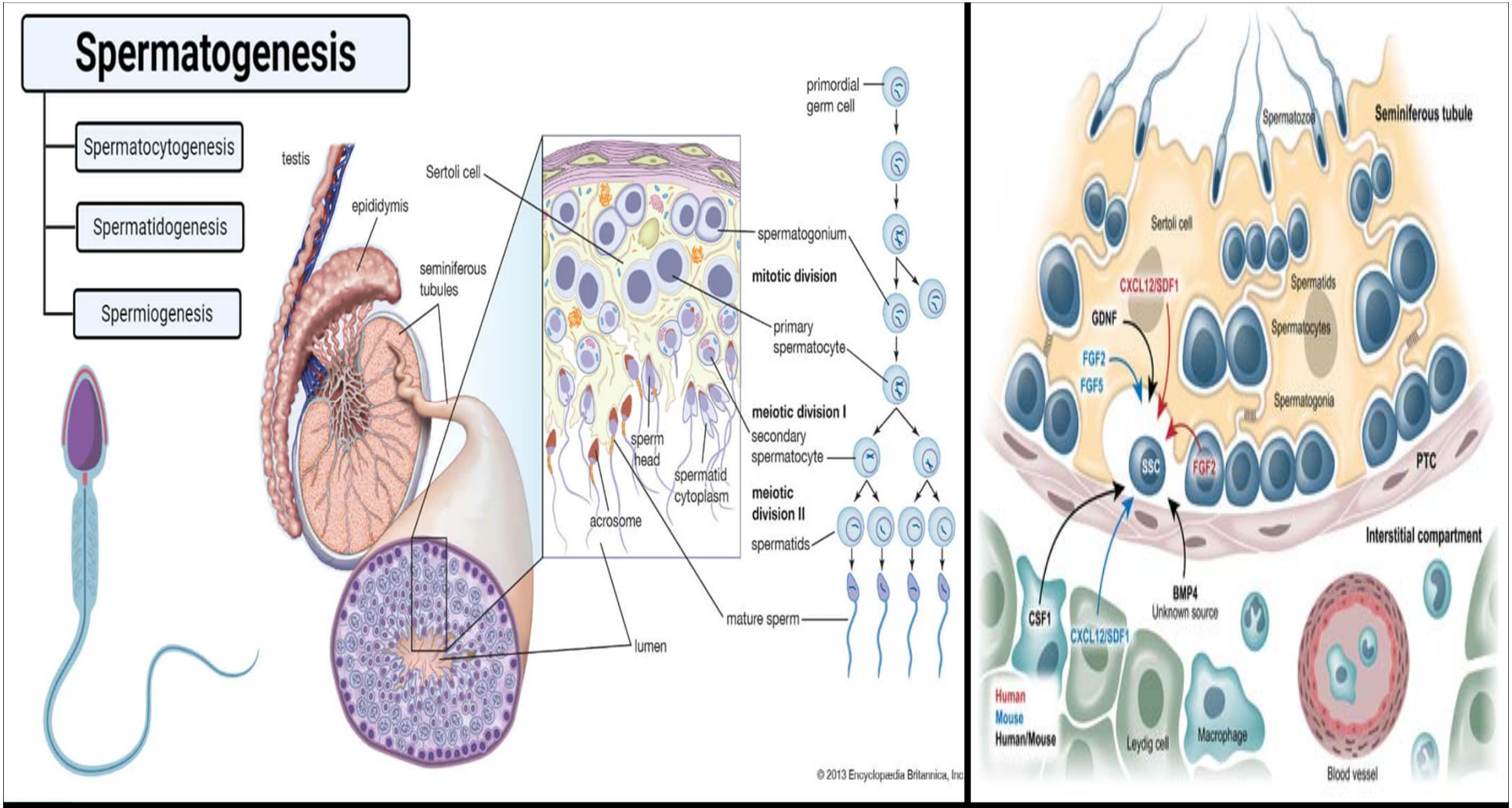
The only treatment option for conceiving genetically their own children is TESE with intracytoplasmic sperm injection (ICSI).

However, TESE–ICSI has a limited success rate in men with NOA, as the sperm retrieval rate per TESE cycle is 56% , and during the first TESE cycle, sperm is found about 50% of cases, and the subsequent live birth rate of ICSI is 41%, resulting in a 23% chance to father a child.

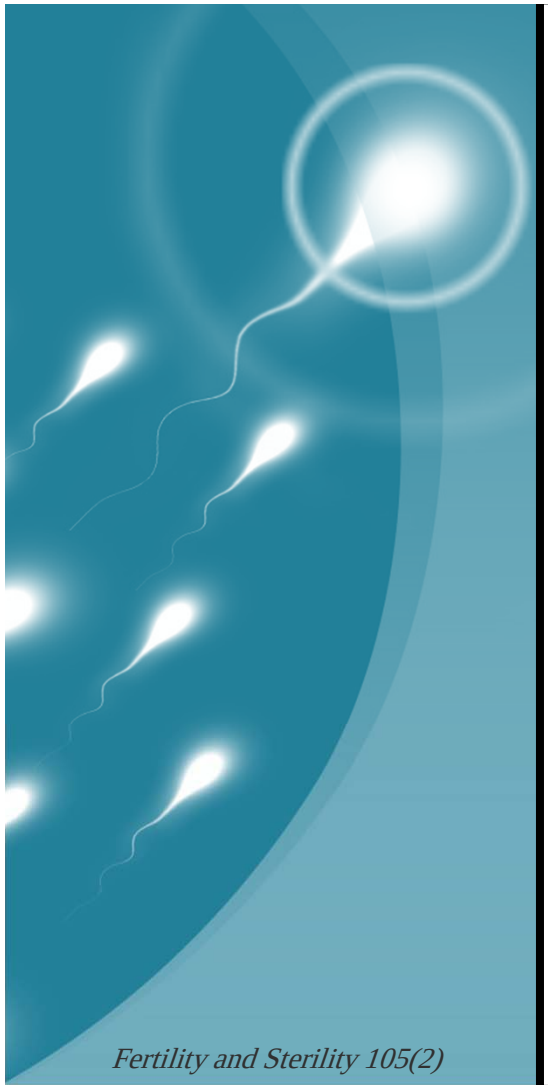
If sperm cannot be retrieved by testicular sperm extraction, there are no current options to maintain the reproductive potential of these individuals.

Journal of Clinical Medicine. 2021-12-23

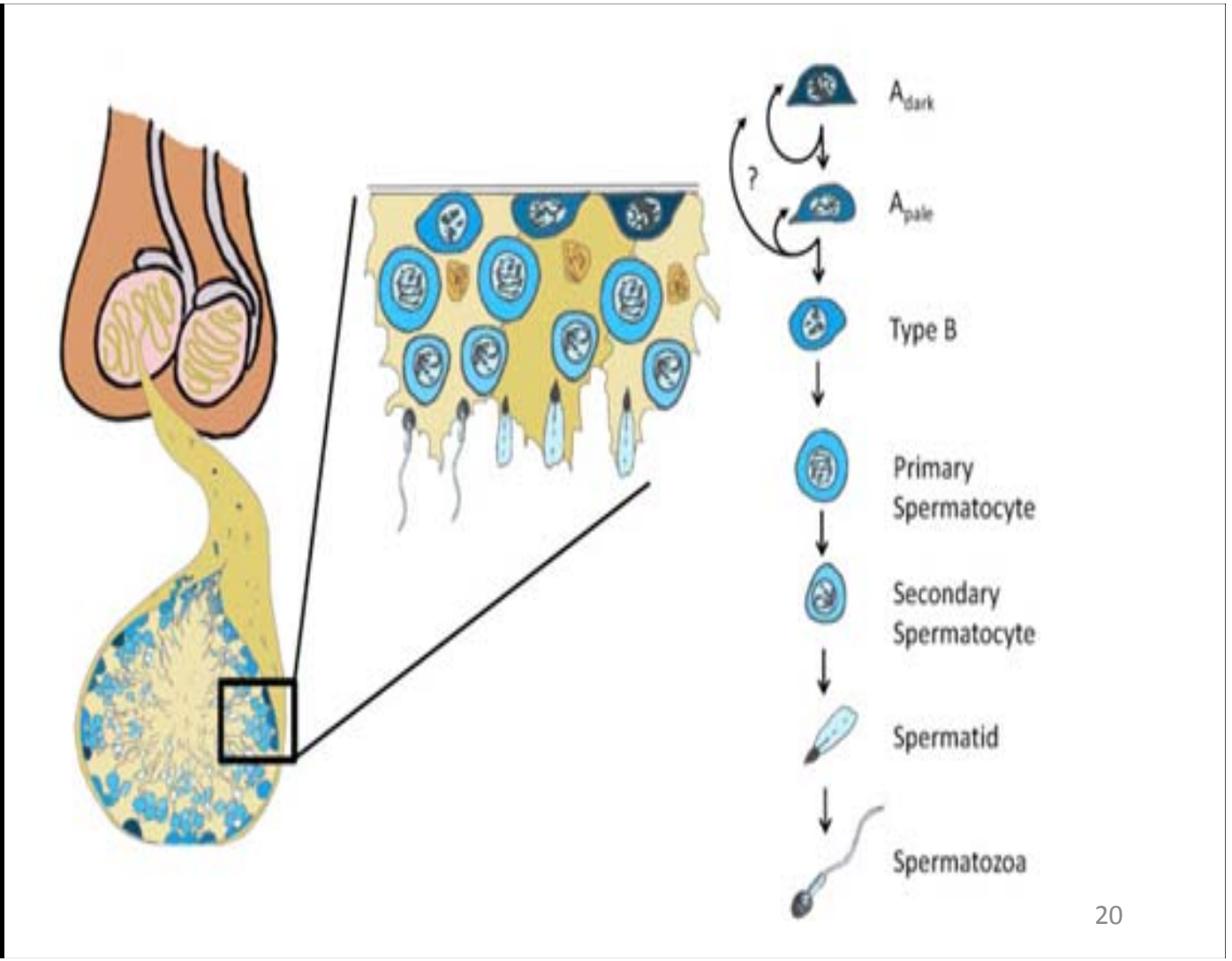

Medical procedure referral
Stem cell treatments
486239

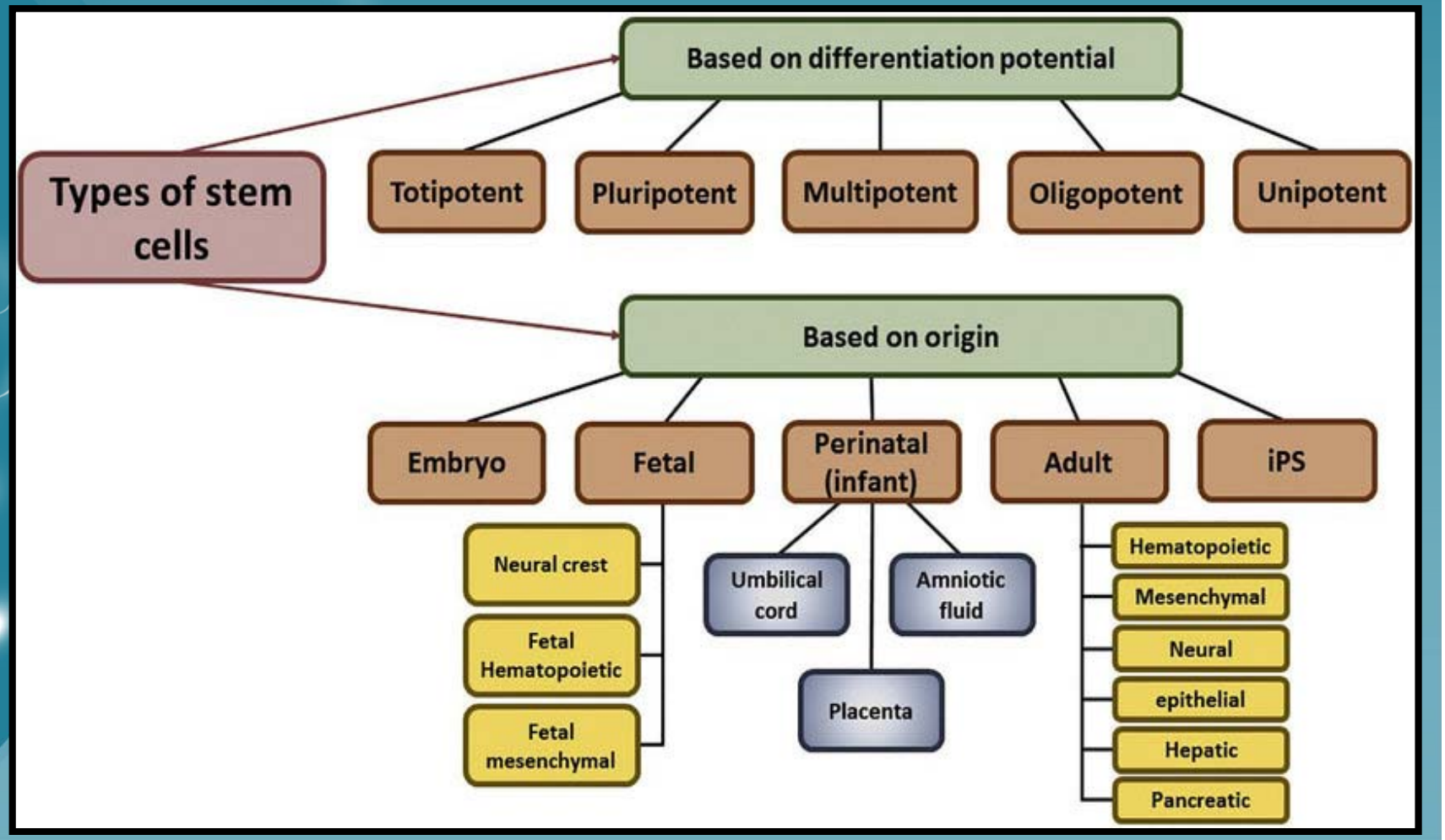


https://microbenotes.com/spermatogenesis/

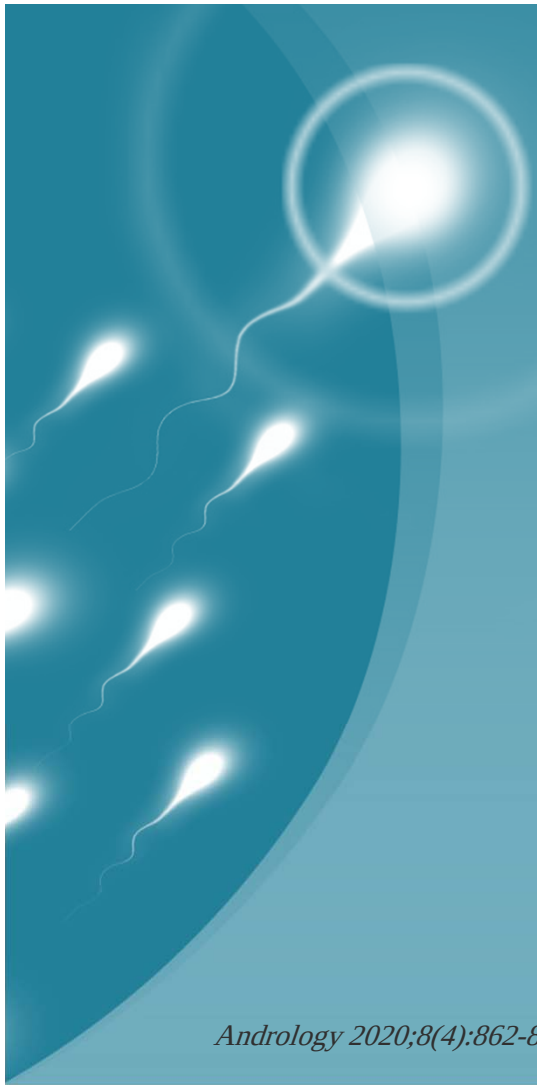


Fertility and Sterility 105(2)





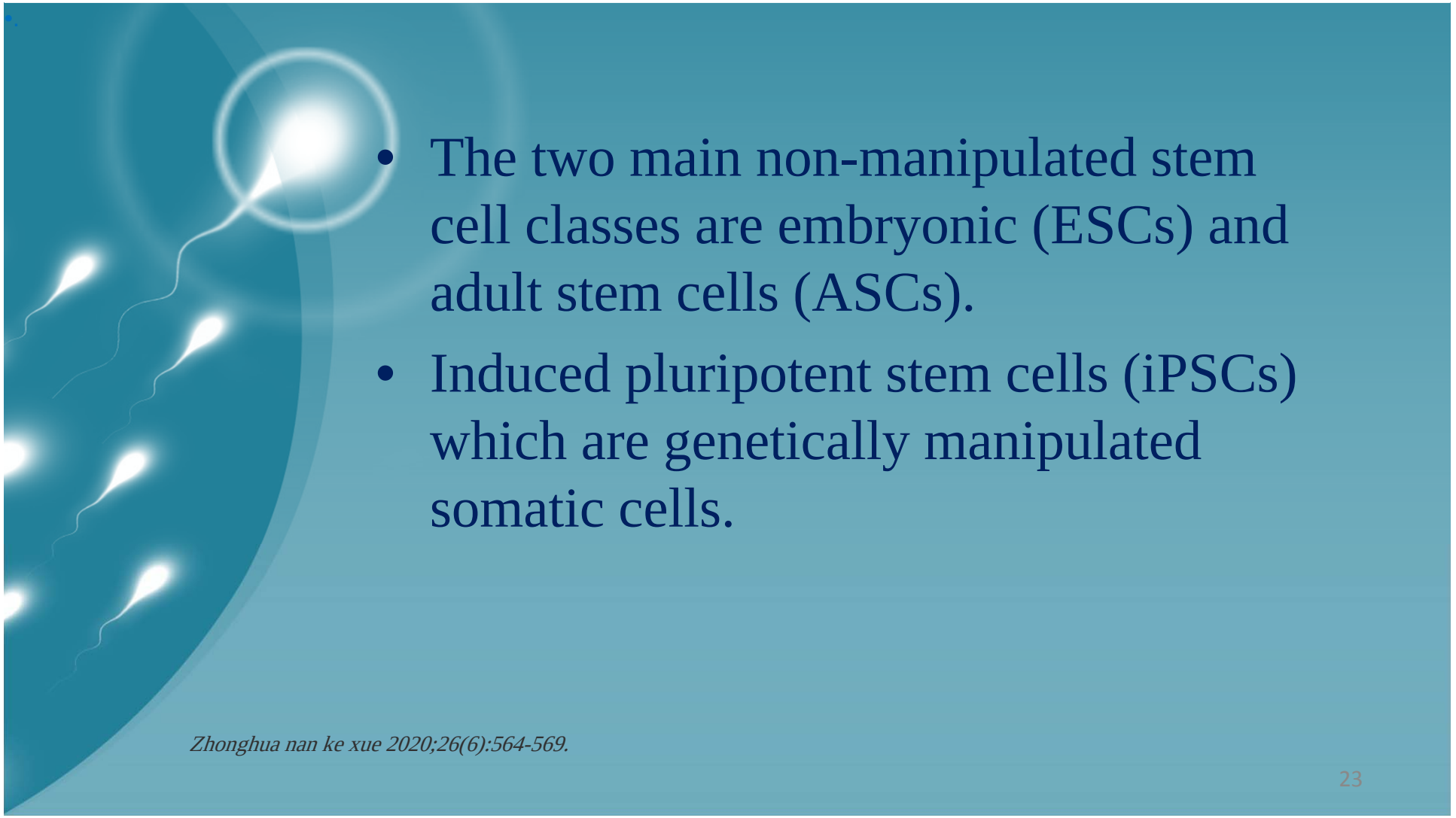
Stem Cell Research 37:101421



There are currently multiple avenues of research involving at least four types of stem cells for use in male fertility preservation.

Strategies that have been extensively investigated involve **(i)** spermatogonial stem cells; **(ii)** embryonic stem cells; **(iii)** induced pluripotent stem cells; **(iv)** adult stem cells.

Andrology 2020;8(4):862-878.



- The two main non-manipulated stem cell classes are embryonic (ESCs) and adult stem cells (ASCs).
- Induced pluripotent stem cells (iPSCs) which are genetically manipulated somatic cells.

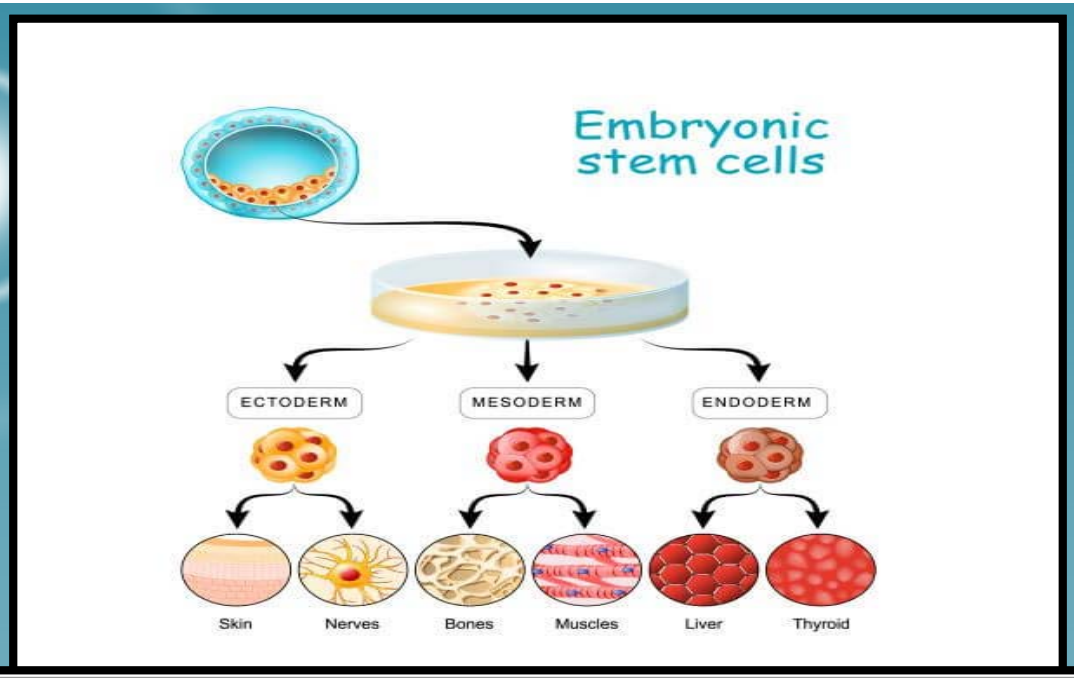
Zhonghua nan ke xue 2020;26(6):564-569.

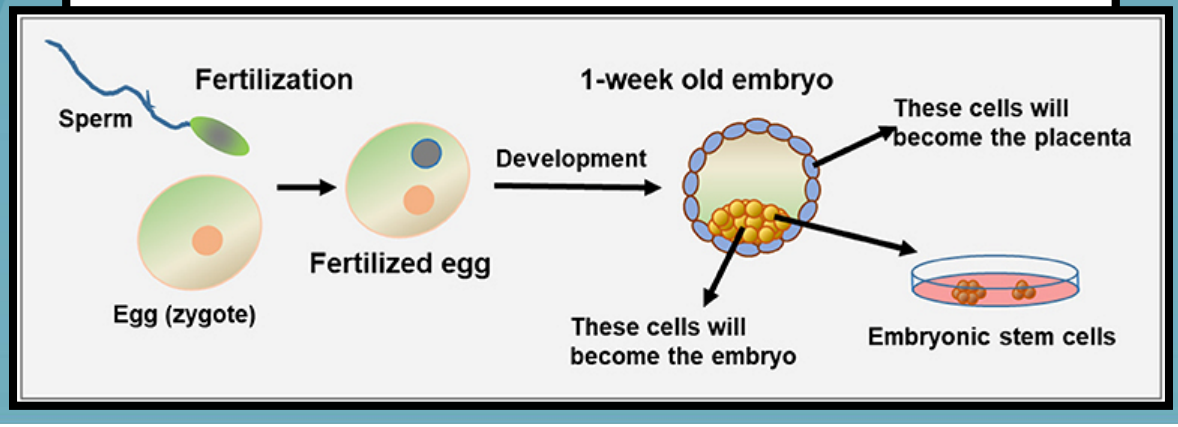
SCs	MSCs	Stem cell from extraembryonic tissues	iPSCs	Spermatogonial stem cells
Derived from inner cell mass of the blastocyst	Derived from bone marrow, adipose tissues, bone, Wharton's jelly, umbilical cord blood, and peripheral blood	Derived from amnion, chorion, placenta, and umbilical cord	Derived from somatic cells	Derived from testicular tissues
Pluripotent	Multipotent	Multipotent	Pluripotent	Pluripotent
These cells can differentiate into cell types of all three germ layers	These cells can differentiate into mesoderm-derived tissues (adipose tissues, bon, cartilage, and muscle)	These cells can differentiate into adipocytes, endothelial cells, hepatocytes, osteocytes, myocytes, and neurons	These cells can differentiate into cell types of all three germ layers	These cells can differentiate into cell types of all three germ layers
Prolonged proliferation	Degree of proliferation depends on the tissue from which these cells were isolated	Degree of proliferation depends on the tissue from which these cells were isolated	Prolonged proliferation	Difficult to be maintained in cultures
Indefinite self-renewal potential	Limited self-renewal	Limited self-renewal	Indefinite self-renewal potential	Self-renewal ability to go through numerous cell divisions while maintaining the undifferentiated state
High telomerase activity	Low telomerase activity	Low telomerase activity	High telomerase activity	High telomerase activity
Immortal; cell lines remain intact for long periods of time and produce endless numbers of cells	Production of limited number of cells	Production of limited number of cells	Immortal; cell lines remain intact for long periods of time and produce endless numbers of cells	—
These cells are not immune privileged	These cells have immunomodulatory characteristics	—	These cells are not immune privileged	These cells are not immune privileged

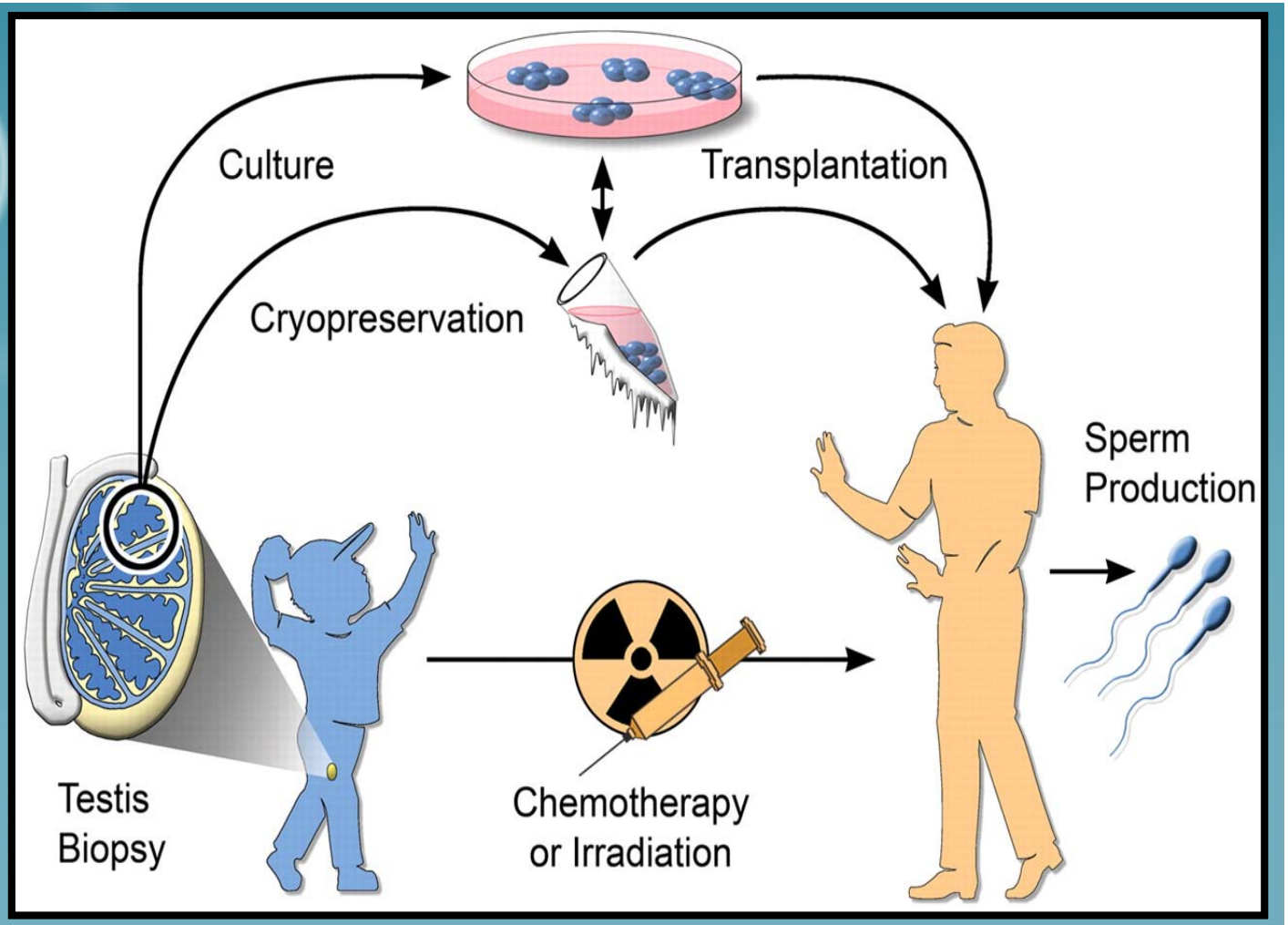
Potential advantages and disadvantages of stem cells in regenerative medicine

Stem cells	Advantages	Disadvantages
ESCs	Pluripotent; high telomerase activity	Ethical concerns; malignant potential; difficult to control; may require many steps to differentiate into desired cell type; immune rejection
MSCs	No ethical or moral concerns; low malignant potential; avoiding allogeneic immune rejection	Limited flexibility; multipotent; difficulty to be maintained in cell culture for long periods
Stem cell from extraembryonic tissues	No ethical or moral concerns; reducing risk of tumorigenicity	Limited flexibility; multipotent
iPSCs	No ethical or moral concerns; patient-specific cells	Use of viral vectors to introduce genes; malignant potential
Spermatogonial stem cells	No ethical or moral concerns	Relatively small numbers in testis; difficulty to be maintained in cultures; immune rejection

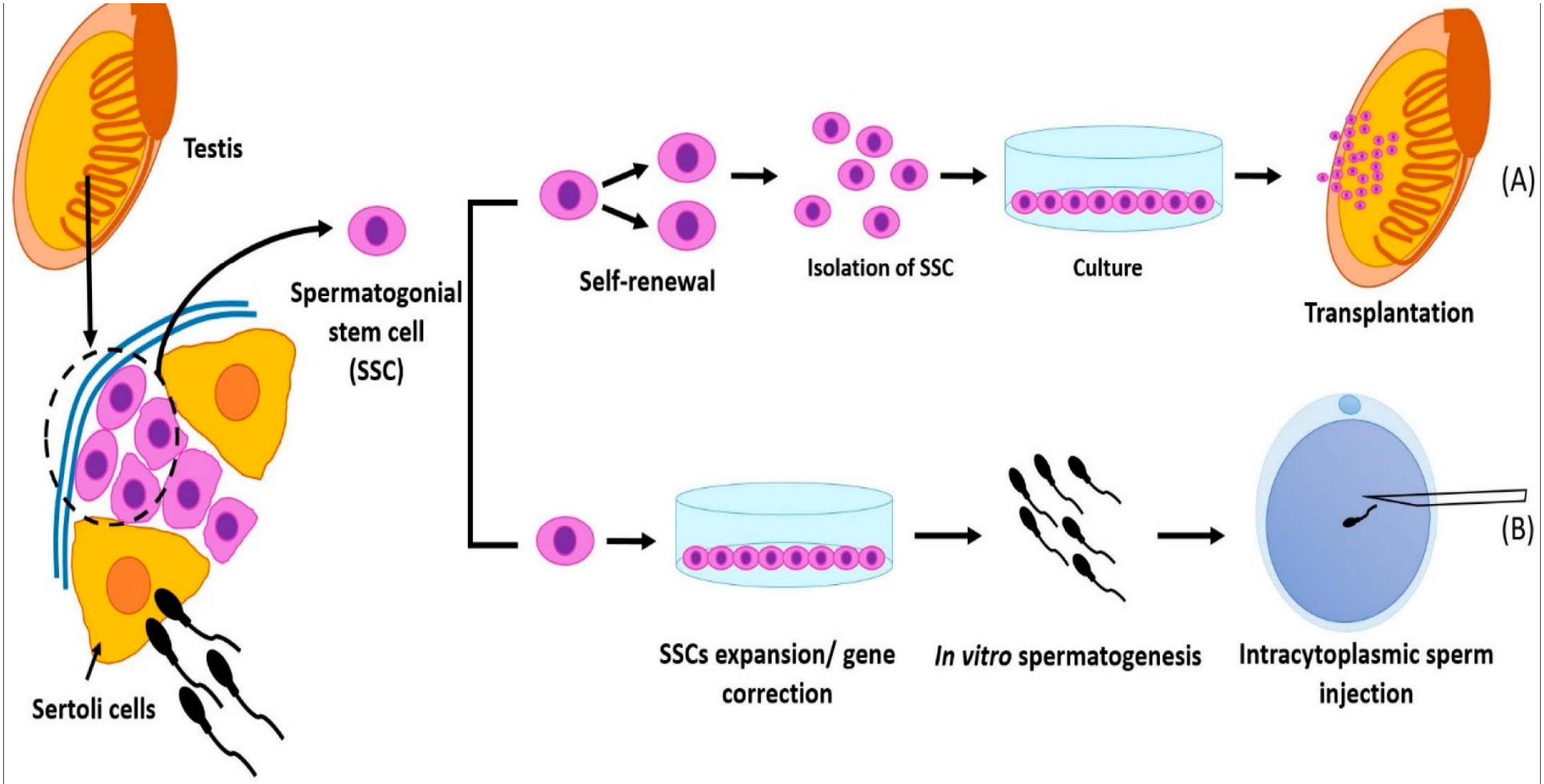
BioMed Research International;2014:507234.


Embryonic stem cells
ECTODERM
MESODERM
ENDODERM
Skin
Nerves
Bones
Muscles
Liver
Thyroid

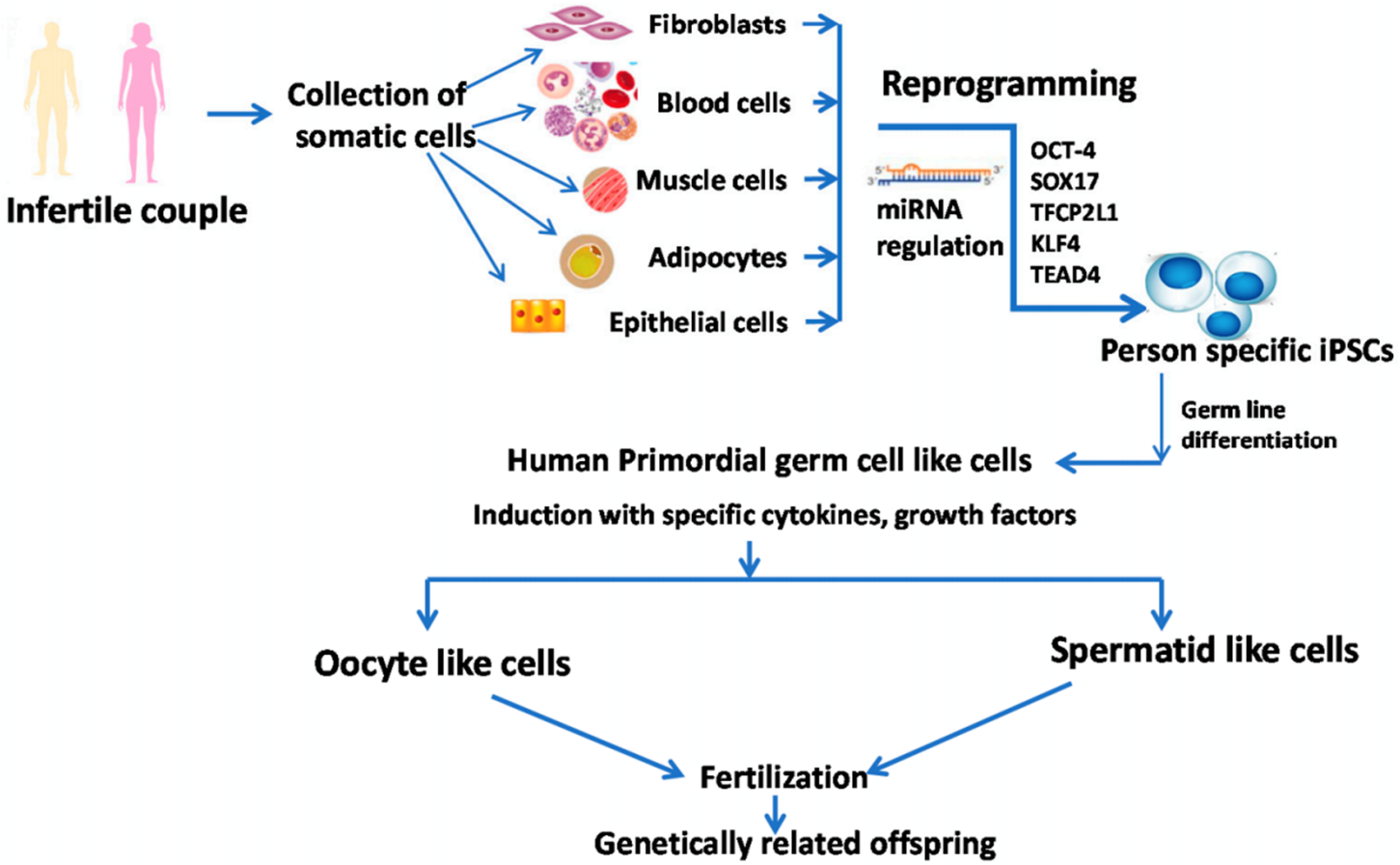

Fertilization
Sperm
Egg (zygote)
Fertilized egg
Development
1-week old embryo
These cells will become the placenta
These cells will become the embryo
Embryonic stem cells



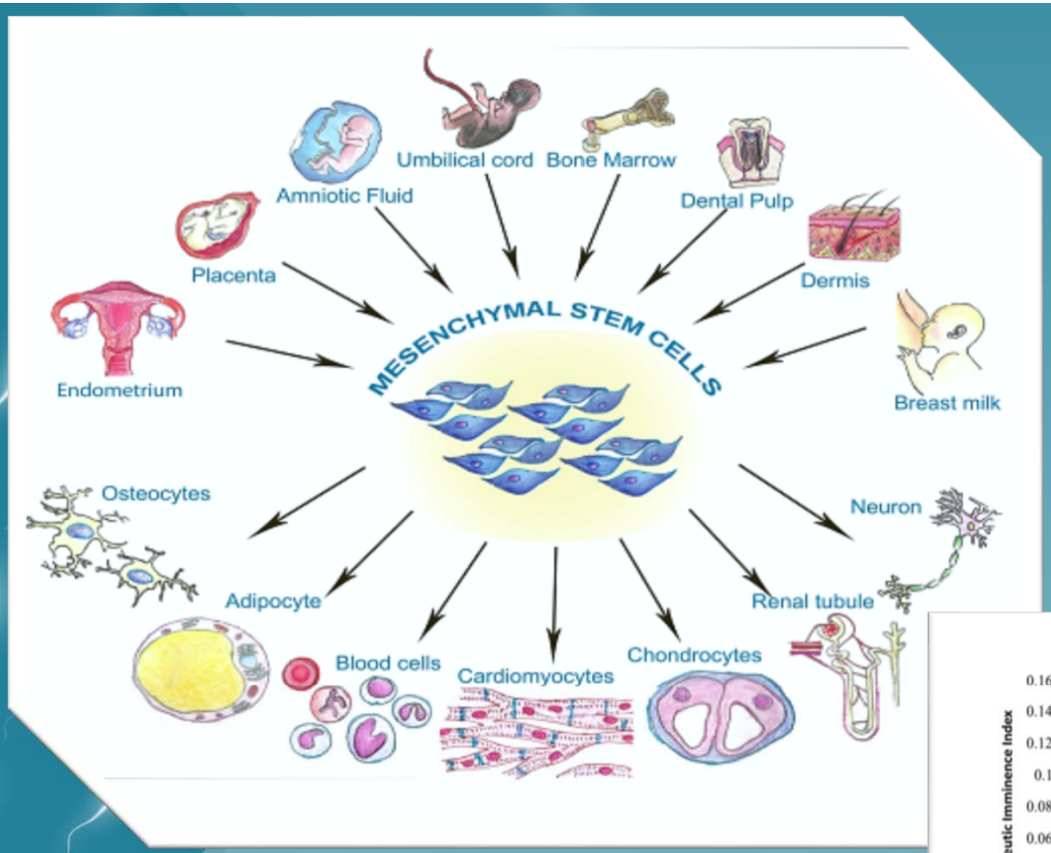
Chimera Research 2019; 205-220

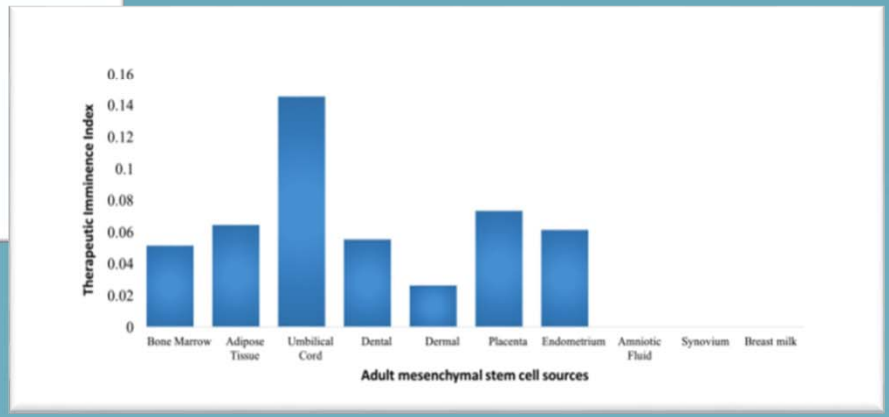


Cells 2021, 10(7), 1779; https://doi.org/10.3390/cells10071779

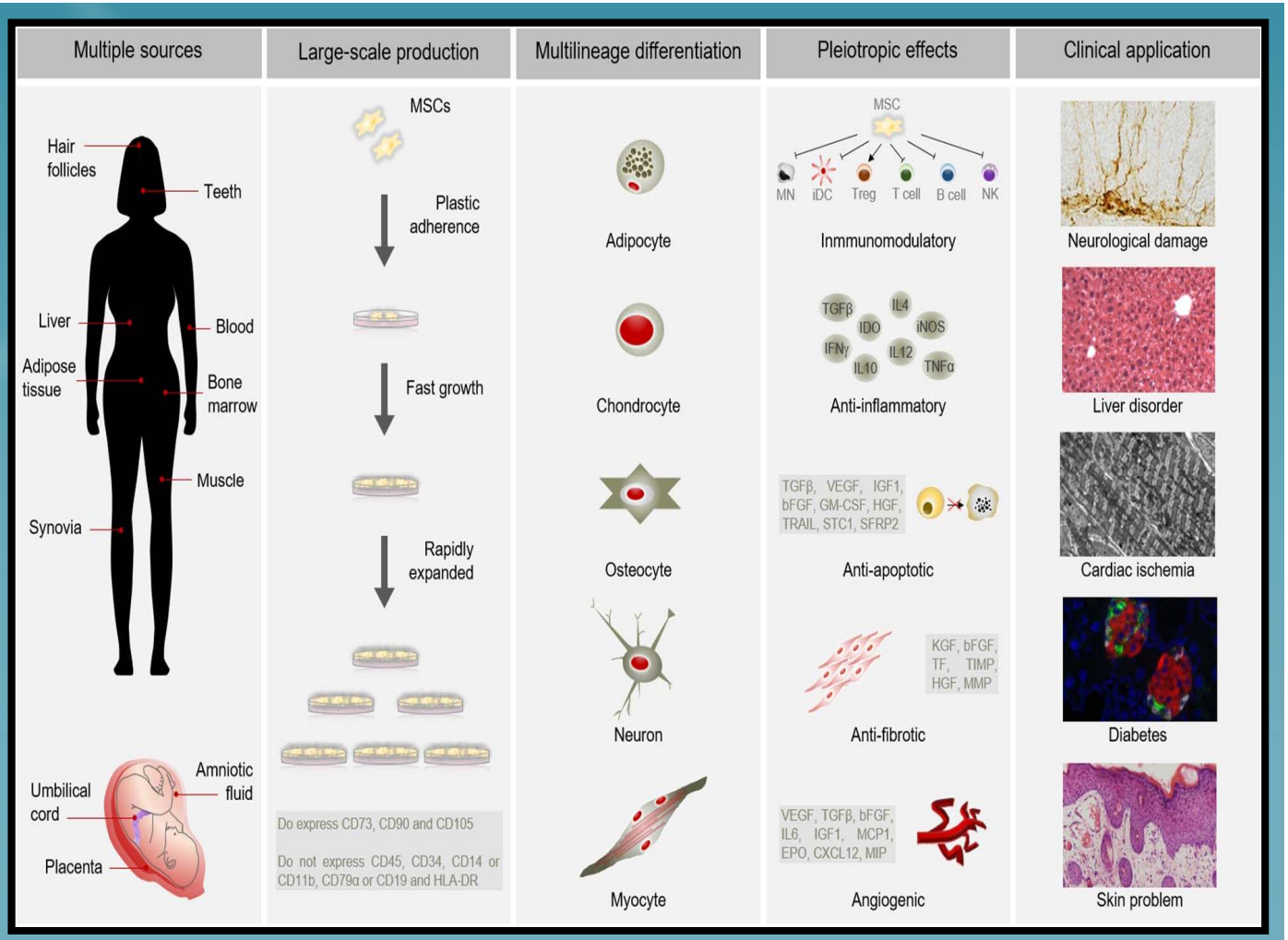

Infertile couple
Collection of somatic cells
Fibroblasts
Blood cells
Muscle cells
Adipocytes
Epithelial cells
Reprogramming
miRNA regulation
OCT-4
SOX17
TFCP2L1
KLF4
TEAD4
Person specific iPSCs
Germ line differentiation
Human Primordial germ cell like cells
Induction with specific cytokines, growth factors
Oocyte like cells
Spermatid like cells
Fertilization
Genetically related offspring

Cell type	Advantage	Disadvantage
MSC	Availability Easy to isolate and expand Multilineal differentiation Immunosuppressive Both of the autograft and allograft are possible Free from ethical issues Limited replicative lifespan (safe from malignant formation)	Limited replicative lifespan (alteration of various functions including multipotency)
ESC	Pluripotent (can differentiate into almost all types of cells)	Ethical / political issues Risk of teratoma formation after transplantation
iPSC	Pluripotent as ESCs Can be derived from somatic cells	Risk of teratoma formation after transplantation



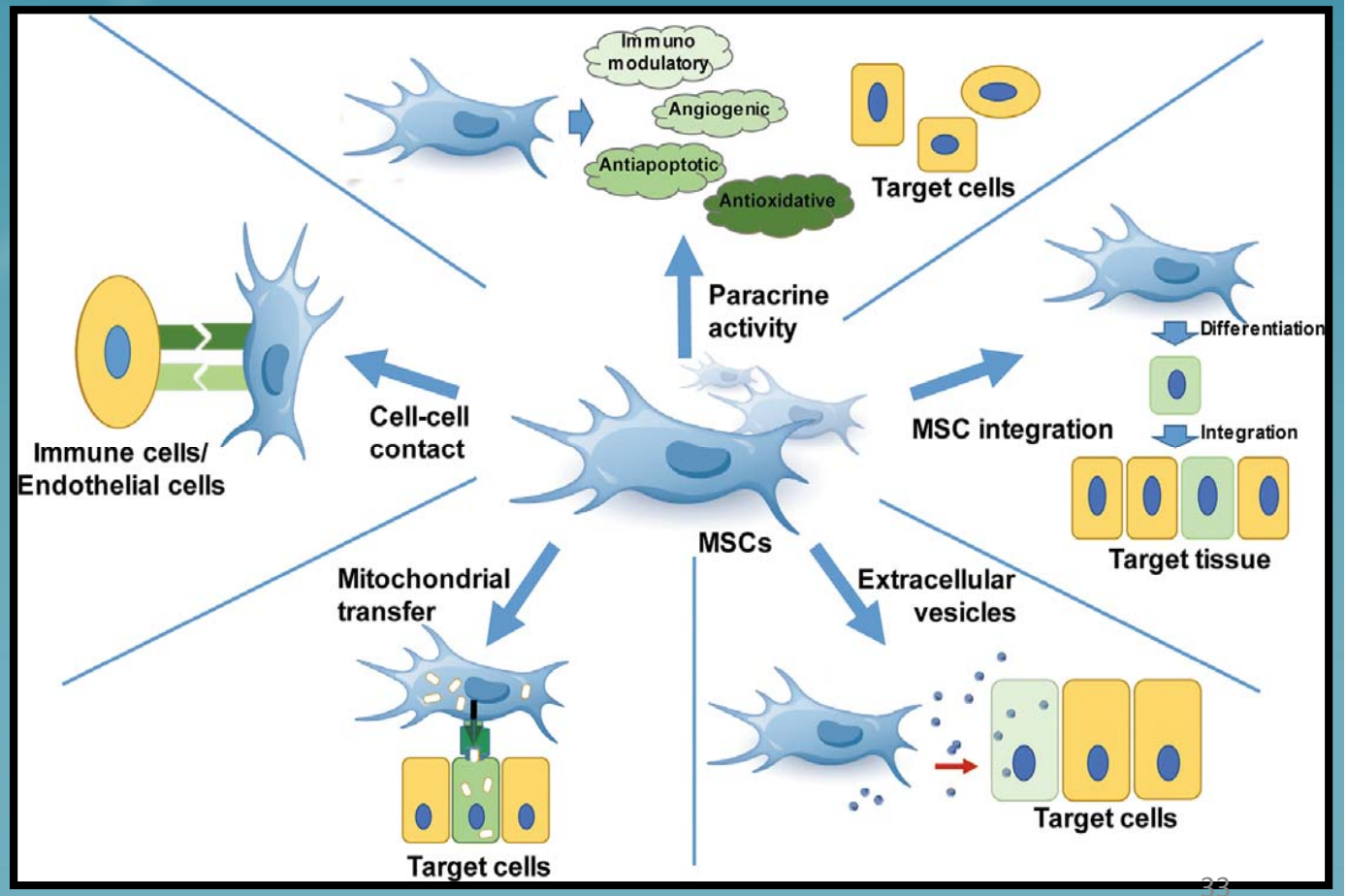


Stem Cell Reviews and Reports 2017; doi:10.1007/s12015-017-9759-8

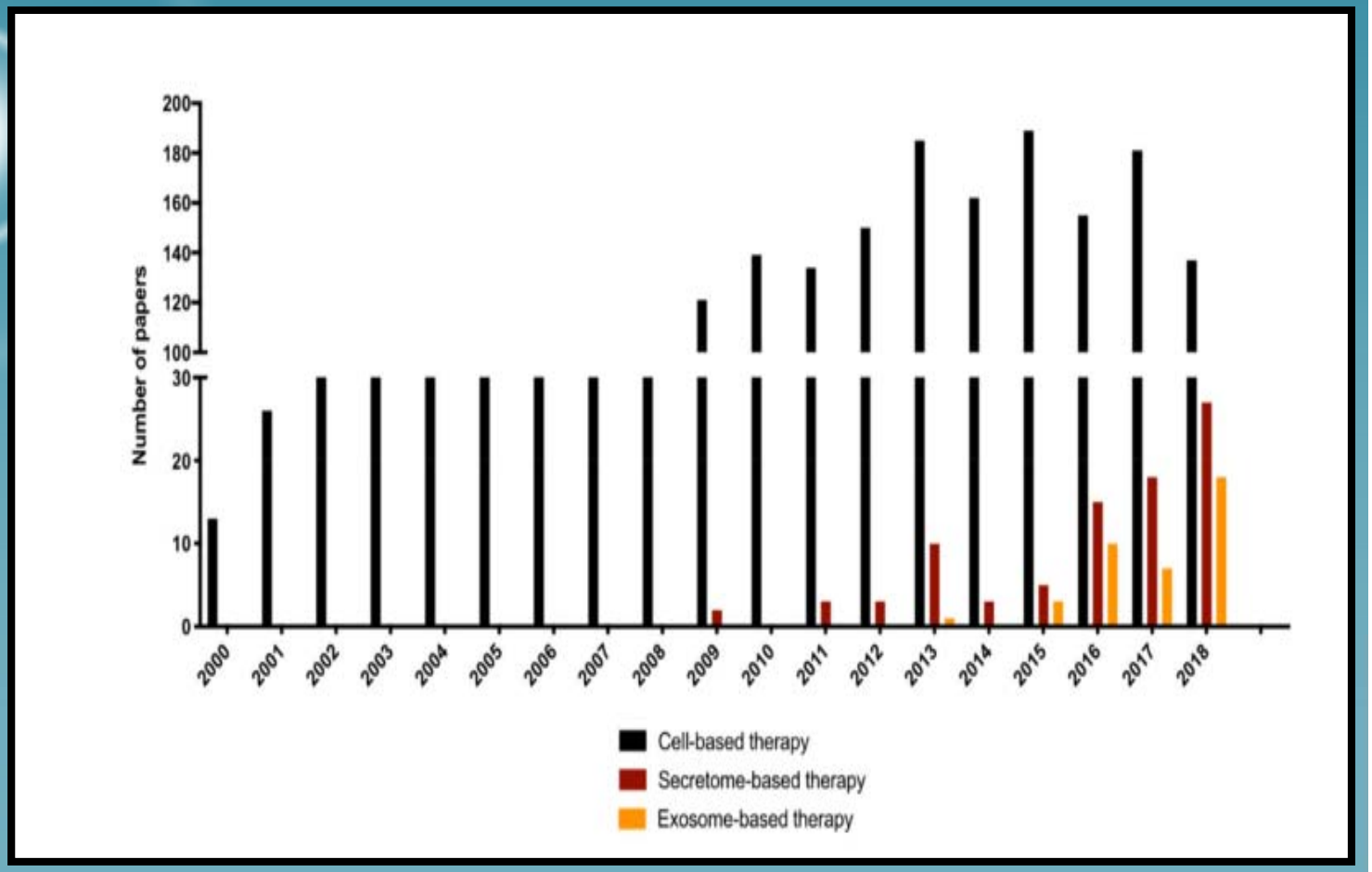


Stem cell Rev Rep 2017;13(6):741-756

Mechanisms underlying the effects of MSC-based therapy

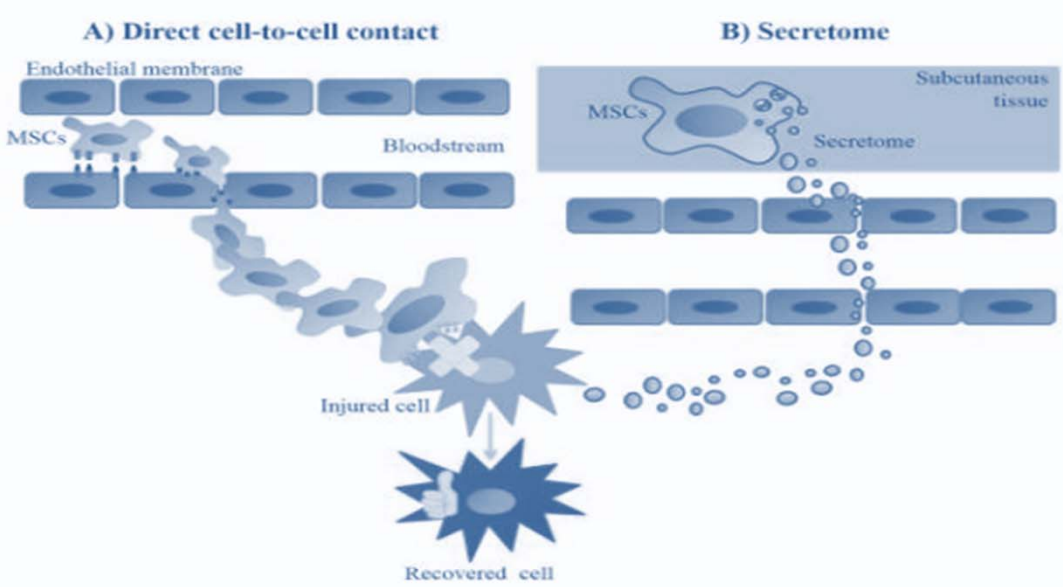


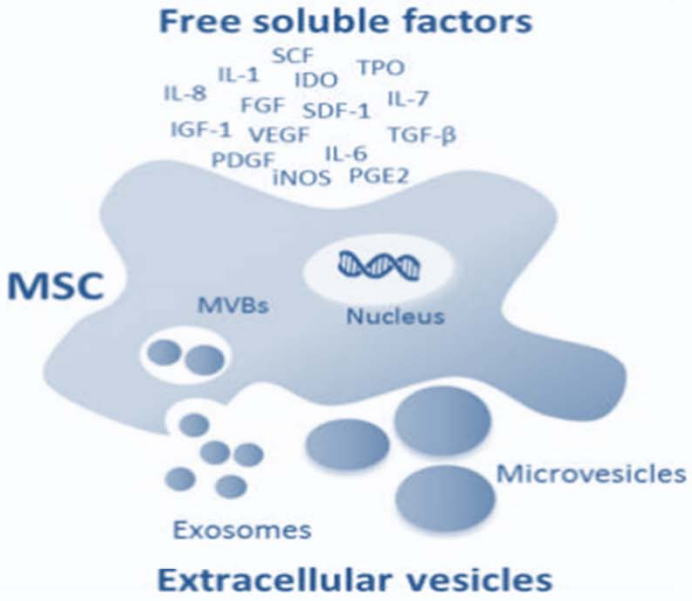
Cellular and Molecular Life Sciences 2020; 77, 2771–2794



Pharmaceuticals 2020 13(2):31

MSC secretome and tissue regeneration

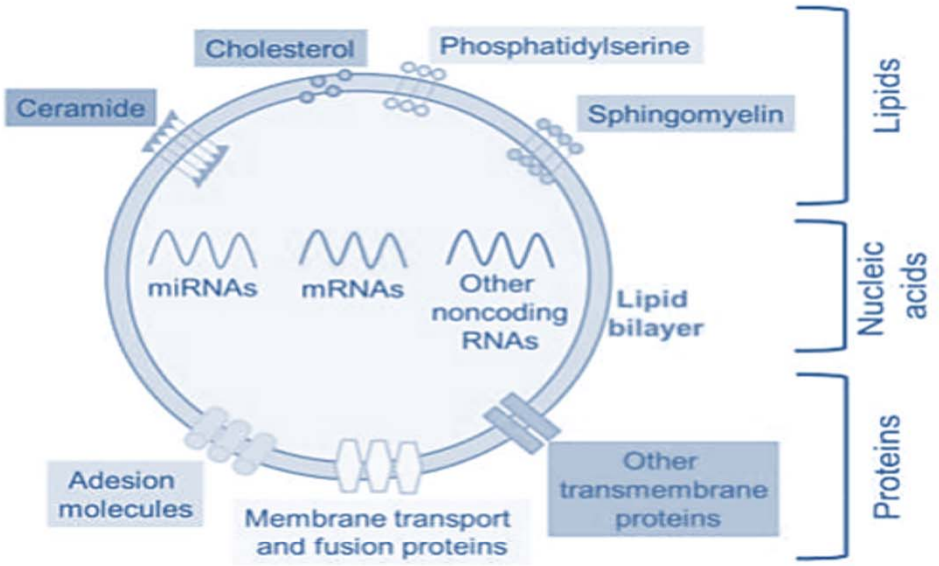


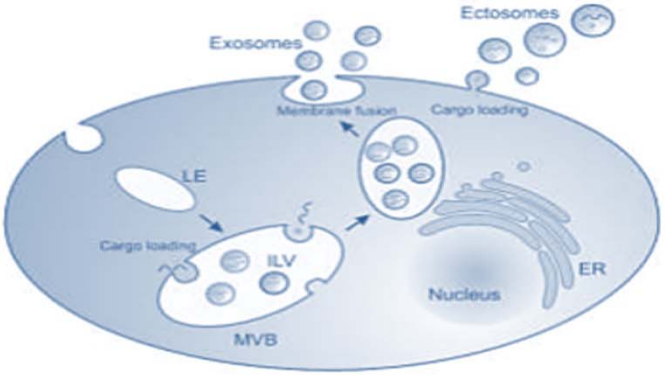


*"The **multipotency** of MSCs **is not the key** aspect for their current therapeutic use"*

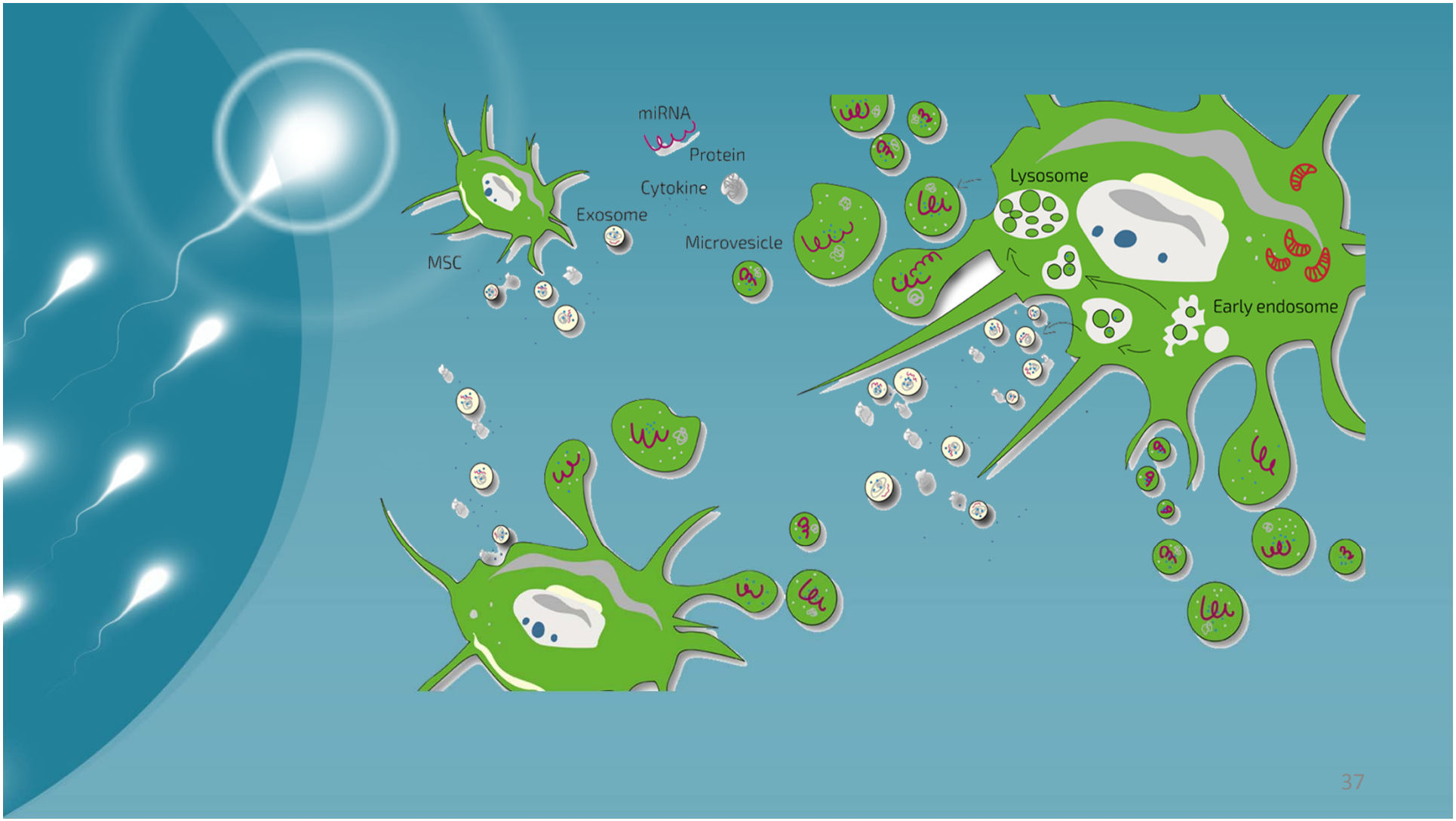
*"MSCs are powerful **site-regulated DRUG STORES** that may serve as modulatory or curative agents for a variety of human maladies"*

MSC secretome contains extracellular vesicles (EVs)





	EXOSOMES	MICROVESICLES (OR ECTOSOMES)
Size (nm)	40 – 150	150 – 600
Biogenesis	Multivesicular bodies (MVBs) fusion with cell membrane	Outward budding of cell membrane


miRNA
Protein
Cytokine
Exosome
Microvesicle
MSC
Lysosome
Early endosome

Secretome can replace MSC regenerative therapy

MSCs

Secretome

Ability to adapt and respond to the microenvironment

Safer (non-living, lower immunogenicity, no vascular clotting)
Nanoscale (enhanced permeability and retention effect)
Physiological mediators of tissue regeneration
Effectively **cross biological membrane**
Scalable production process

MSC-secretome shows fewer limitations than its parental cells

❖ *In vitro* studies on MSC and spermatogenesis

- A certain combination of growth factors, chemical components, genetic manipulations, and/or co-culture with other cells can be used to induce the differentiation of MSCs into the germ cell epithelium.
- The results of *in vitro* studies have been published demonstrating that NOA can be restored through MSC transplantation.

Stem Cell Res Ther 2021; 6;12(1):229.

MSC source	Source age	Species	Inducer
Adipose tissue	Adult	Dog	BMP4
Adipose tissue	Adult	Dog	CD61 overexpression
Adipose tissue	Adult	Goat	BOULE overexpression DAZL overexpression STRA8 overexpression
Adipose tissue	Adult	Human	Retinoic acid
Adipose tissue	Adult	Mouse	BMP4 EGF GDNF LIF Retinoic acid
Adipose tissue	Adult	Mouse	Sertoli cells co-culture Retinoic acid Testosterone
Adipose tissue	Adult	Mouse	Testicular cell conditioned medium Retinoic acid
Amniotic membrane	Fetal	Human	Retinoic acid
Amniotic membrane	Fetal	Mouse	BMP4 Retinoic acid
Bone marrow	Adult	Goat	BMP4 Retinoic acid
Bone marrow	Adult	Human	Retinoic acid Sertoli cell-conditioned medium
Bone marrow	Adult	Human	Retinoic acid
Bone marrow	Adult	Mouse	BMP4
Bone marrow Adipose tissue	Adult	Mouse	BMP4 Retinoic acid
Bone marrow	Adult	Mouse	BMP4 Retinoic acid
Bone marrow	Adult	Mouse	Retinoic acid
Bone marrow	Adult	Mouse	Sertoli cell-condition medium
Bone marrow	Adult	Mouse	Static magnetic field BMP4
Bone marrow	Adult	Mouse	Retinoic acid Testicular cell co-culture
Bone marrow	Adult	Rat	bFGF LIF Retinoic acid
Bone marrow	Adult	Rat	Retinoic acid
Bone marrow	Adult	Rat	Sertoli cell co-culture

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Cont…

Bone marrow	Adult	Sheep	Inorganic zinc (sulfate) Organic zinc (acetate) Retinoic acid
Bone marrow	Adult	Sheep	Retinoic acid TGF-β1
Bone marrow	Adult	Sheep	Retinoic acid
Bone marrow	Adult	Sheep	TGFb1 BMP4 BMP8b
Bone marrow	Fetal	Human	Retinoic acid Testicular extracts
Lung	Fetal	Human	Retinoic acid
Umbilical cord	Fetal	Human	BMP4 Retinoic acid
Umbilical cord	Fetal	Human	BMP4
Umbilical cord	Fetal	Human	pCD61-CAGG-TRIP-pur (oCD61) plasmid
Umbilical cord	Fetal	Human	Testicular cell co-culture
Wharton's jelly	Fetal	Human	BMP4 Testicular cell-conditioned medium Placental cell-conditioned medium Retinoic acid
Wharton's jelly	Fetal	Human	BMP4 Placenta cell co-culture Retinoic acid
Wharton's jelly	Fetal	Human	Retinoic acid Testosterone Testicular cell-conditioned medium
Wharton's jelly	Fetal	Human	Retinoic acid
Wharton's jelly	Fetal	Human	Sertoli cell co-culture

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❖MSC therapy in animal model of azoospermia

- MSCs transplanted into the testes of NOA animal models showed both induction of spermatogenesis and/or differentiation of MSCs into germ cells.

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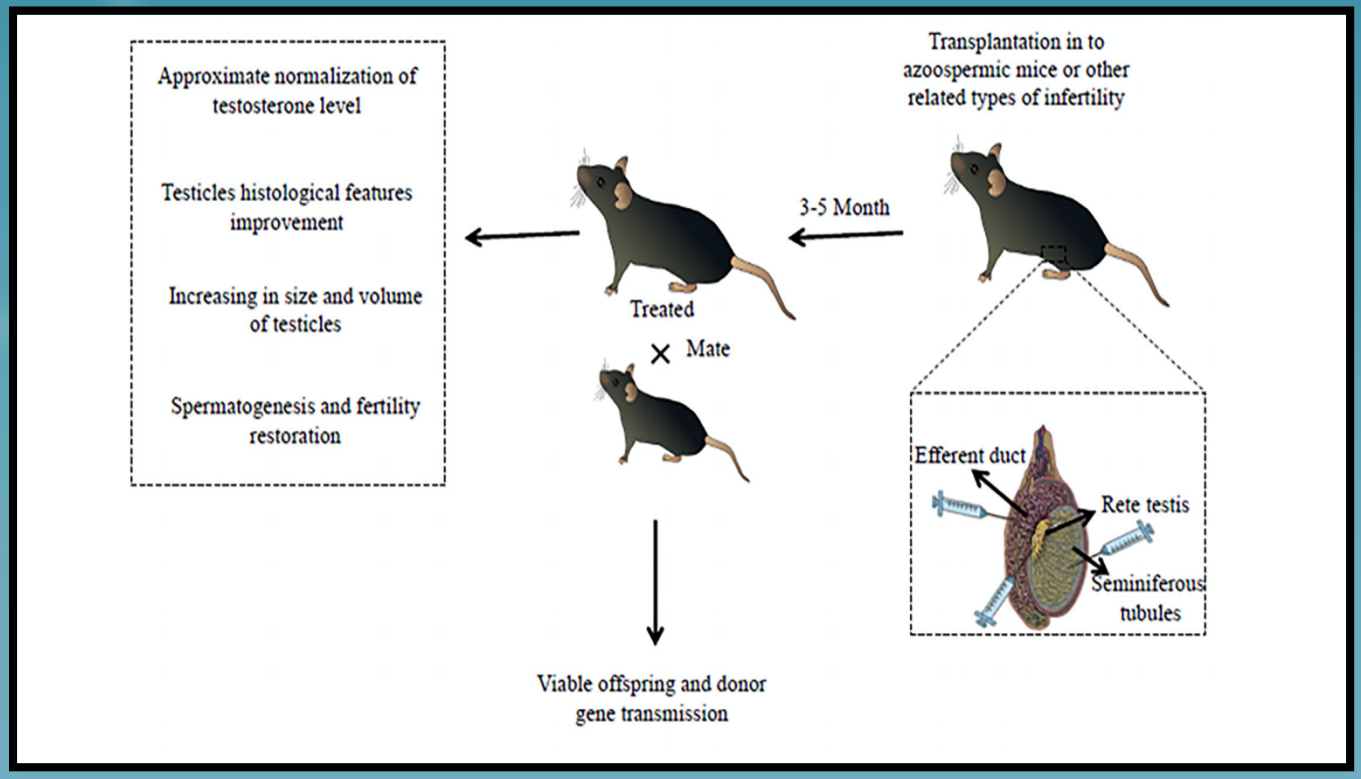
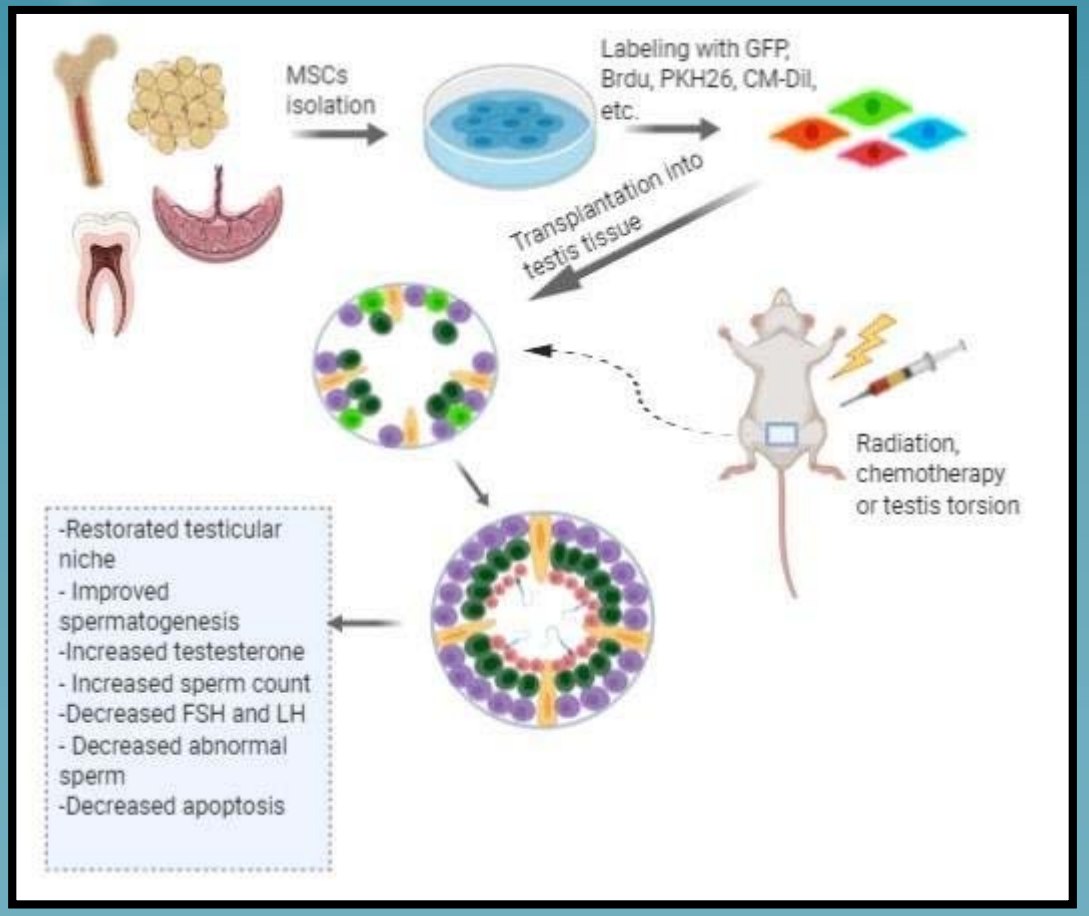
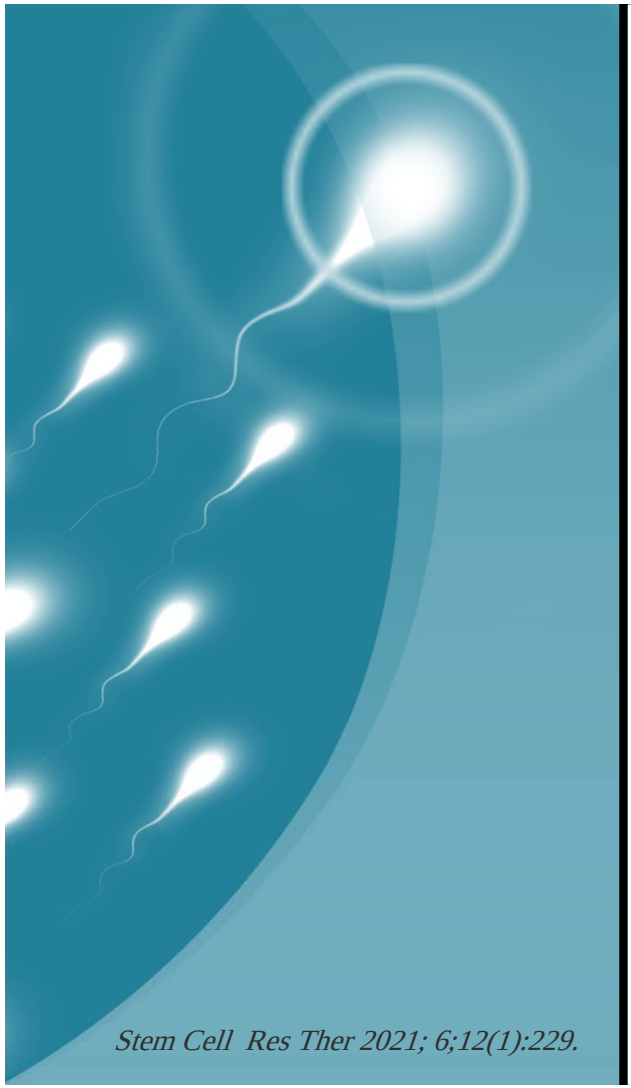


J Cell Physiol 2018;233(10):6455-6469.


MSCs isolation
Labeling with GFP, Brdu, PKH26, CM-Dil, etc.
Transplantation into testis tissue
Radiation, chemotherapy or testis torsion
-Restorated testicular niche
- Improved spermatogenesis
-Increased testesterone
- Increased sperm count
-Decreased FSH and LH
- Decreased abnormal sperm
-Decreased apoptosis

Recent in vivo studies of MSCs application for male infertility

MSC Source	Number of cells	Used animals	Disease model	Period of MSCs Treatment	Results
Rat ADMSC	$1x10^6$ cells	Rat	Busulfan induced azoospermia	12 weeks	$GFP^{+}/Vasa^{+}$ and $GFP^{+}/SCP1^{+}$ cells were determined. Full spermatogenesis recovery and proliferation
Rat BMMSCs	$1x10^6$ cells	Rat	Lead (Pb) induced gonado-toxicity	21, 30 and 60 days	BMMSCs can differentiate into germ cells and Leydig cells. BMMSCs modulated testosterone levels and DNA apoptosis
Human UCMSC	$2,5x10^5$ cells	Mice	Busulfan induced infertility	3,9,18 and 20 days	HUCMSCs differentiated into germ cells and restored tubules
Induced BM-MSCs by co-culture with testicular cell conditioned medium	$1 x10^5$ cells	Rat	Busulfan induced azoospermia	8 weeks	BMMSCs can transdifferentiate into spermatogenic cells but after 8 weeks meiosis was not determined
Rat BMMSCs	$2,5x10^5$ cells	Rat	Busulfan induced infertility	4, 6 and 8 weeks	BMMSCs migrated to the germinal epithelium and expressed spermatogonia markers so these cells differentiated into spermatogonia
Human UCMSCs	$1 x10^5$ cells	BALB/c mice	Busulfan induced azoospermia	12 weeks	After transplantation of UCMSCs, increased expressions of meiosis-associated genes. UCMSCs (CD34-) restored testicular injury and decrease FSH and LH levels.
Rat BMMSCs	$5x10^6$ cells	Rat	Cadmium-induced testis injury	2 weeks	BMMSCs can prevent mitochondrial apoptosis and repair testis injury
Rat BMMSCs	$1x10^6$ cells	Rat	Doxorubicin-induced testicular toxicity	8 weeks	BMMSCs reduced rate of abnormal sperm and testicular oxidative stress
Human orbital fat tissues (OFSC)	$3x10^4$ cells	Rat	3 hours 720^0 torsion and detorsion	7 days	OFSCs can prevent intrinsic apoptosis and oxidative stress



Source	Transplantation	Donor species	Therapeutics	Recipient species	Modeling
Adipose tissue	Allotransplant	Hamster	Cell	Hamster	Busulfan
Adipose tissue	Allotransplant	Mouse	Cell Exosome	Mouse	Busulfan
Adipose tissue	Allotransplant	Rat	Cell	Rat	Busulfan
Adipose tissue	Allotransplant	Rat	Cell	Rat	Cisplatin
Adipose tissue	Xenotransplant	Human	Cell	Rat	Torsion
Amnion	Allotransplant	Mouse	Cell	Mouse	Busulfan
Bone marrow	Allotransplant	Guinea pig	Cell	Guinea pig	Busulfan
Bone marrow	Allotransplant	Hamster	Cell	Hamster	Busulfan
Bone marrow	Allotransplant	Mouse	Cell	Mouse	Busulfan
Bone marrow	Allotransplant	Mouse	Cell Exosome	Mouse	Busulfan
Bone marrow	Allotransplant	Mouse	Cell	Mouse	Cisplatin
Bone marrow	Allotransplant	Rat	Cell	Rat	Busulfan
Bone marrow	Allotransplant	Rat	Cell	Rat	Doxorubicin
Bone marrow	Allotransplant	Rat	Cell	Rat	Lead nitrate
Bone marrow	Allotransplant	Rat	Cell	Rat	Torsion
Bone marrow	Xenotransplant	Goat	Cell	Mouse	Busulfan
Umbilical cord	Xenotransplant	Human	Cell	Mouse	Busulfan
Urine	Allotransplant	Mouse	Cell Exosome	Mouse	Busulfan

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Model of Disease	Therapeutic Intervention/Route of Administration	Core Findings
Busulfan-induced NOA mice model	Urine-derived stem cells -derived EVs/Intratesticular	spermatogenic genes (*Pou5f1*, *Prm1*, *SYCP3*, and *DAZL*) and the spermatogenic protein UCHL1 were significantly increased after 36 days of injection
Busulfan-induced NOA rats model	Amniotic fluid-derived EVs/Intratesticular	DAZL and VASA were increased significantly. Sperm parameters and spermatogenesis index were significantly improved. OCT-3/4+ cells were increased in NOA rats after AF-Exos injection, showing the restoration of spermatogenesis.
Cyclophosphamide-induced testicular spermatogenic dysfunction	Bone marrow mesenchymal stem cell-derived EVs/intravenous	Increased spermatogonia cell proliferation and reduced apoptosis. Phosphorylated levels of ERK, AKT, and p38MAPK proteins were reduced
Electromagnetic field-induced oxidative stress in mouse spermatogonial stem cells (in vitro)	Sertoli cells-derived EVs	down-regulation of the apoptotic gene (Caspase-3), and oxidative stress. Up-regulation of SSCs specific gene (GFRα1).
Testicular ischemia-reperfusion injury in rats	Bone marrow mesenchymal stem cell-derived EVs/Intratesticular	Reduced HMGB1, caspase-3, and cleaved caspase-3

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❖MSC therapy of azoospermia patients

- Various clinical trials for the treatment of infertility in reproductive diseases in both women and men have been recorded or completed.

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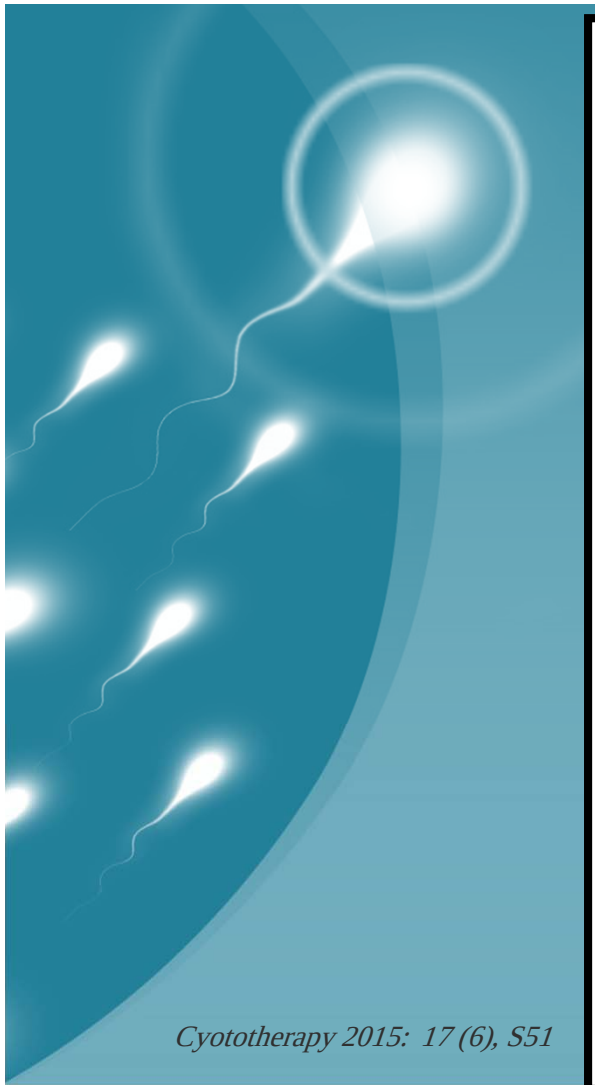

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AUTOLOGOUS MSC THERAPY FOR AZOOSPERMIA: A PILOT CLINICAL

H Gabr, WA Elkheir
Clinical Pathology, Cairo University, Cairo, Egypt

Infertility affects 10—15% of the couples, male factors accounting for about 50% of causes. Azoospermia has been observed in 10—15% of male infertility and 1% of general population, and non-obstructive azoospermia been diagnosed in 60% of azoospermic men.

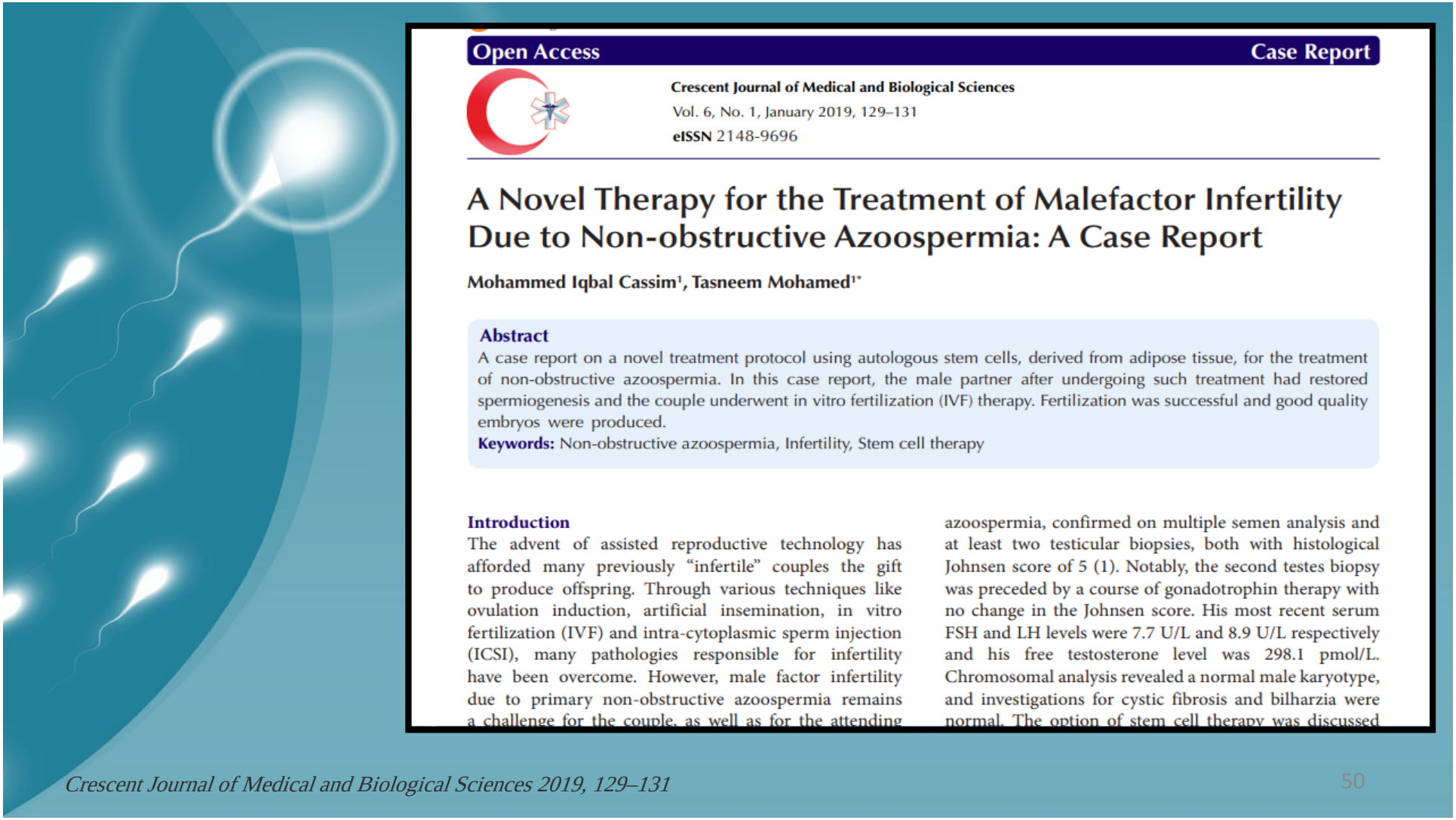
For male infertility with a normal genetic background, stem cell therapy to generate male gametes may represent a promising treatment strategy.

Experimental animal studies have proven the fact that resumption of normal spermatogenesis can be achieved in a testicular atrophy mouse model after stem cell injection.

Subjects and Methods: This clinical trial (clinical trial identifier NCT02025270)will recruit 60 azoospermia patients with normal karyotype. Patients received 20million autologous, bone marrow derived MSCs intratesticular. Follow up was done for one year using hormonal profile, semen analysis and testicular biopsy.

Results and Conclusions: Preliminary results of the clinical trial initiated for MSC for treatment of azoospermia showed that 60% of patients showed increase in testicular size, elevation of testosterone level and reduction of FSH level. 3 patients(5%) showed appearance of sperms in the ejaculate, 12 patients (20%) showed sperm in needle aspiration, 8 (13.4%) patients showed sperms in testicular biopsy, and 15(25%) patients showed round/elongated spermatids in ejaculate, while 22 (36.6%) patients showed no sperms or spermatids.

Cytotherapy 2015: 17 (6), S51



Open Access Case Report

Crescent Journal of Medical and Biological Sciences
Vol. 6, No. 1, January 2019, 129–131
eISSN 2148-9696

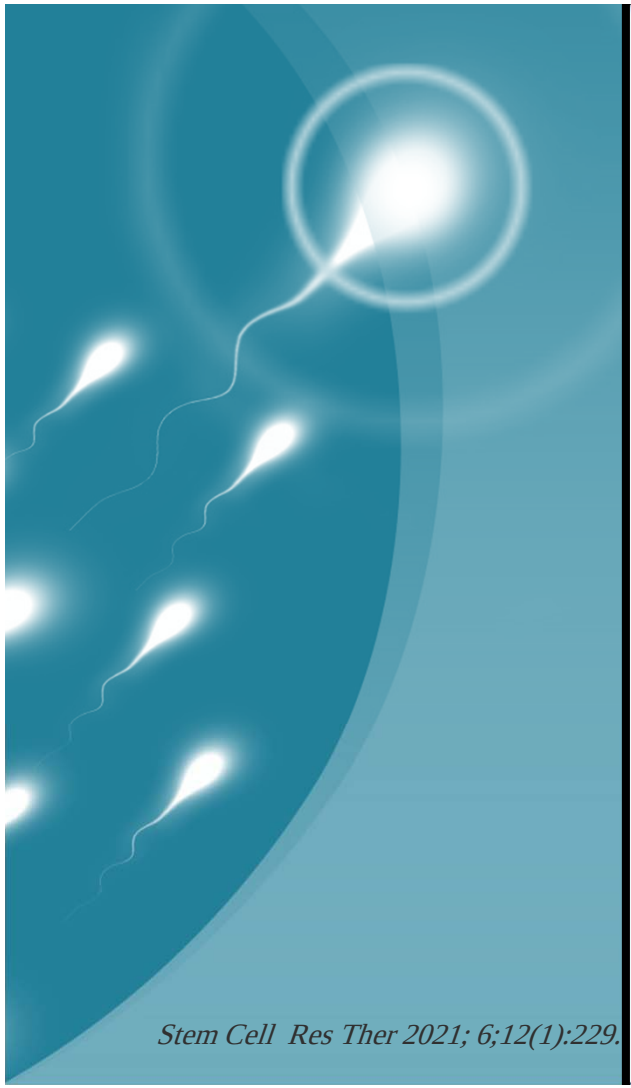
A Novel Therapy for the Treatment of Malefactor Infertility Due to Non-obstructive Azoospermia: A Case Report

Mohammed Iqbal Cassim[1], Tasneem Mohamed[1*]

Abstract
A case report on a novel treatment protocol using autologous stem cells, derived from adipose tissue, for the treatment of non-obstructive azoospermia. In this case report, the male partner after undergoing such treatment had restored spermiogenesis and the couple underwent in vitro fertilization (IVF) therapy. Fertilization was successful and good quality embryos were produced.
Keywords: Non-obstructive azoospermia, Infertility, Stem cell therapy

Introduction

The advent of assisted reproductive technology has afforded many previously "infertile" couples the gift to produce offspring. Through various techniques like ovulation induction, artificial insemination, in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), many pathologies responsible for infertility have been overcome. However, male factor infertility due to primary non-obstructive azoospermia remains a challenge for the couple, as well as for the attending azoospermia, confirmed on multiple semen analysis and at least two testicular biopsies, both with histological Johnsen score of 5 (1). Notably, the second testes biopsy was preceded by a course of gonadotrophin therapy with no change in the Johnsen score. His most recent serum FSH and LH levels were 7.7 U/L and 8.9 U/L respectively and his free testosterone level was 298.1 pmol/L. Chromosomal analysis revealed a normal male karyotype, and investigations for cystic fibrosis and bilharzia were normal. The option of stem cell therapy was discussed



Clinical trials related stem cell therapy performed or underway for improvement of infertility.

Trial Identifier	Est. # of Subjects	Status	Site	Conditions	Interventions	Outcome of Trial
NCT04706312	12	Not yet recruiting	Nanjing Medical University	Diminished Ovarian Response	Human Amniotic Mesenchymal Stem Cells (Hamscs) Transplantation	No results posted
NCT04676269	40	Recruiting	Indonesia University	Thin Endometrium Infertile Patients	Amnion Bilayer and Stem Cell Combination Therapy	No results posted
NCT03207412	20	Unknown	Chongqing Medical University, China	Premature Ovarian Failure	Human Amniotic Epithelial Cells	No results posted
NCT02696889	3	Active	University of Illinois at Chicago	Primary Ovarian Insufficiency, Low Ovarian Reserve	Autologous Stem Cell Therapy	Report of 2 cases revealed a significant improvement in clinical features related to POI. There was an increase in size as well as estrogen production in the MSC engrafted ovary [174]
NCT02713854	240	Recruiting	The University of Hong Kong	Subfertility	Human Embryonic Stem-Cell-Derived Trophoblastic Spheroid (Bap-Eb) as a Predictive Tool	No results posted
NCT03592849	50	Enrolling by invitation	Nanjing Drum Tower Hospital, China	Infertile Women with Thin Endometrium or Endometrial Scarring	Procedure: Collagen Scaffold Loaded with Umbilical-Cord-Derived Mesenchymal Stem Cells Therapy	No results posted
NCT03166189	46	Completed	D.O. Ott Research Institute of Obstetrics, Gynecology, Russian Federation	Infertility of Uterine Origin Asherman Syndrome	Biological: Bone Marrow-Derived Msc and Hrt Other: Hormonal Replacement Therapy	No Results Posted
NCT02313415	26	Completed	Nanjing Drum Tower Hospital, China	Infertility with Intrauterine Adhesions	Procedure: Umbilical Cord Mesenchymal Stem Cells	Phase 1 trial revealed that transplantation of clinical grade human UC MSC could improve the proliferative and differentiation efficiency of endometrium [175]
NCT02025270	100	Unknown	Al Azhar University, Egypt	Azoospermic Patients	Bone-Marrow-Derived Mesenchymal Stem Cells	No results posted
NCT02641769	50	Recruiting	Stem Cells of Arabia, Amman, Jordan	Non-obstructive Azoospermia	Intratesticular Transplantation of Autologous Stem Cells	No results posted
NCT02414295	1	Completed	Man Clinic for Andrology and male infertilit, Cairo, Egypt	Klinefelter Syndrome Azoospermia	Mesenchymal Stem Cell Injection	No Results Posted
NCT02062931	60	Unknown	Al-Azhar University hospitals, Egypt	Premature Ovarian Failure	Biological: Stem Cell Preparation and Injection	No results posted
NCT02603744	9	Unknown	Royan Institute	Premature Ovarian Failure	Intraovarian Injection of Adipose-Derived Stromal Cells (Adscs)	Intraovarian engrafting of ADSCs were found to be safe and feasible and linked to reduction in FSH level [176]
NCT02204358	30	Unknown	Nanjing University Medical School	Intrauterine Adhesions, Endometrial Dysplasia	Collagen Scaffold Loaded with Autologous Bone Marrow Stem Cells Testicular Injection of Autologous Human Bone Marrow	No results posted
NCT02041910	60	Unknown	Hesham Saeed Elshaer, El-Rayadh Fertility Centre	Azoospermia	Derived Stem Cells	No results posted
NCT02151890	10	Completed	Al Azhar University, Cairo, Egypt	Premature Ovarian Failure	Biological: Stem Cell	No results posted
NCT02372474	112	Completed	Al Azhar University, Cairo, Egypt	Premature Ovarian Failure	Biological: Stem Cell	No results posted

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Trial Identifier	Est. # of Subjects	Status	Site	Conditions	Interventions	Outcome of Trial
NCT04009473	100	Enrolling by invitation	Multicenter	Ovarian Failure Premature Ovarian Failure	Combination Product: SEGOVA Procedure Includes Stem Cell Therapy, Growth Factor, and Platelet Plasma Rich Therapy	No results posted
NCT02240823	30	Unknown	Odense University Hospital	Erectile Dysfunction After Prostatectomy	Adipose-Derived Stem Cells (ADMSC)	Intracavernous injection of ADMSC is a safe procedure and resulted in improvement of erectile function [178]
NCT02414308	20	Unknown	Man Clinic for Andrology, Male Infertility, and Sexual Dysfunction	Erectile Dysfunction Peyronie' Disease	Adipose Tissue Stem Cell Injection	No results posted
NCT02008799	20	Recruiting	Man Clinic for Andrology, Male Infertility, and Sexual Dysfunction	Azoospermia	Intratesticular Artery Injection of Bone Marrow Stem Cell	No result posted

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Protocol summary
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Health conditions studied
Primary outcomes
Secondary outcomes
Intervention groups
Recruitment centers
Sponsors / Funding sources
Person responsible for general inquiries
Person responsible for scientific inquiries
Person responsible for updating data
Sharing plan

Intra-testicular Injection of Autologous Adipose Derived Mesenchymal Stem Cell (ADMSC) in Non-obstructive Azoospermia Patients: Clinical Trial, Phase I, Non-Randomized

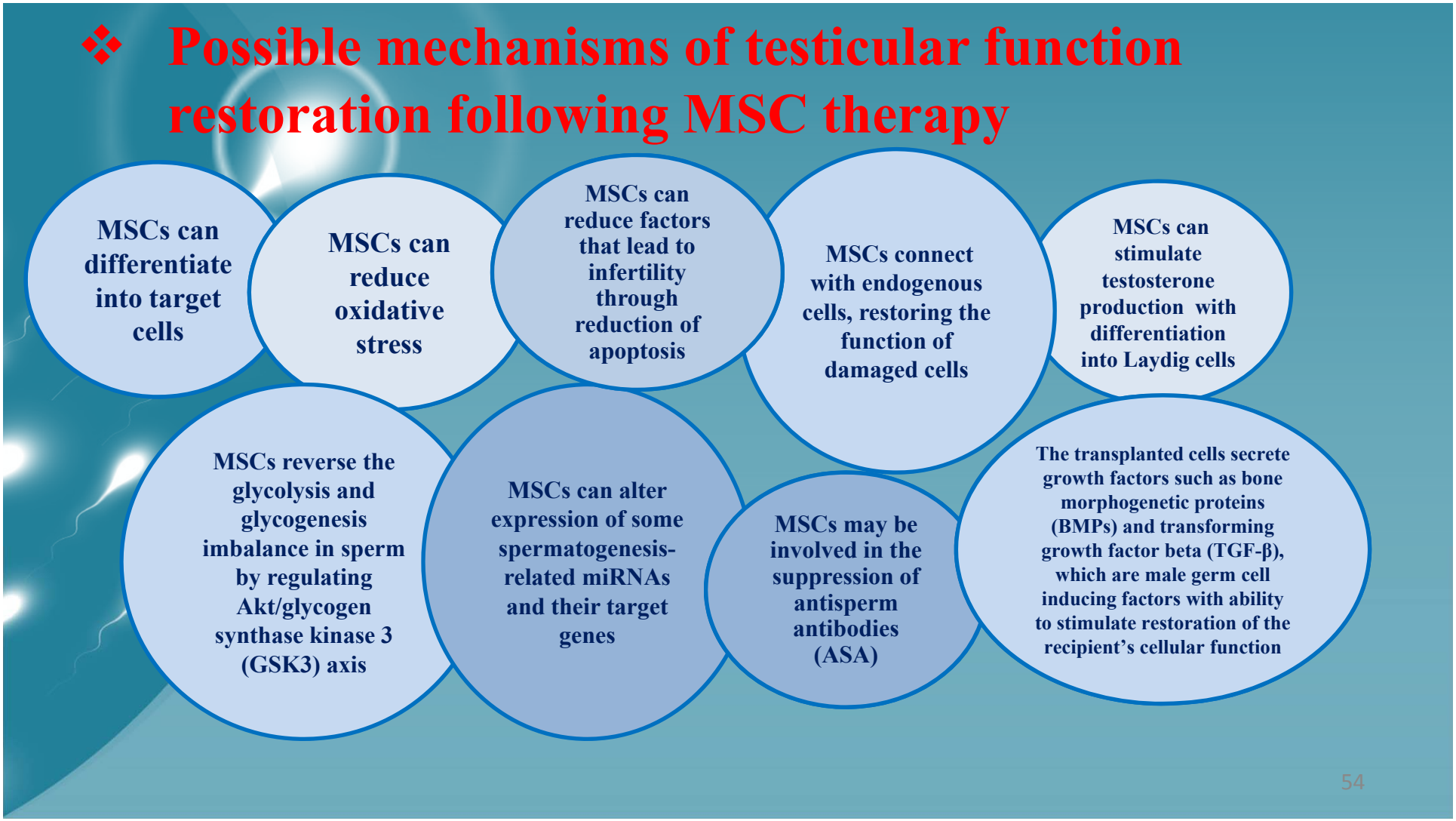
More options

Protocol summary

Study aim	Aim 1 (Primary End Point include): Safety and Tolerability: [Time Frame: 6 months] Incidence and severity of Adverse events and Severe Adverse Events Vital signs Physical examination Clinical chemistries, hematology, and urinalysis Safety and tolerability assessments will be done 2 weeks, 1,2,3,4,5 and 6 months after the cell injection. Aim 2: (Secondary End Point include): Efficacy [Time Frame: 6 months] Sperm retrieval rate (SRR) [Time Frame: 6 months] By Semen analysis every month until any sperm is found in the semen. If no sperm is found at the end of the 3rd month, testicular sperm extraction (TESE/TESA) will be performed and the tissue will be used for histological assessment. Sperm density Sperm motility Total serum Testosterone level (TH) Number spermatogonia Number of spermatocytes Total serum estradiol level Total serum follicle stimulating hormone level (FSH) Total serum luteinizing hormone level (LH) Inhibin B hormone Prolactin Improvement in sexual function will be assessed using a questionnaire
Design	non randomized non blinded phase I clinical trial
Settings and conduct	Field: Cell therapy Place: JSC Astana Medical University, Astana, Kazakhstan Method: Autologous intratesticular MSC transplantation
Participants/Inclusion and exclusion criteria	Inclusion criteria: 20-50 years infertile males seeking fertility treatment with confirmed diagnosis of Non-obstructive azoospermia (NOA) and all items

Expected recruitment start date	2019-12-22, 1398/10/01
Expected recruitment end date	2021-12-22, 1400/10/01
Actual recruitment start date	2019-12-22, 1398/10/01
Actual recruitment end date	2021-12-22, 1400/10/01
Trial completion date	2022-02-20, 1400/12/01

❖ Possible mechanisms of testicular function restoration following MSC therapy




Thank you
for your
attention