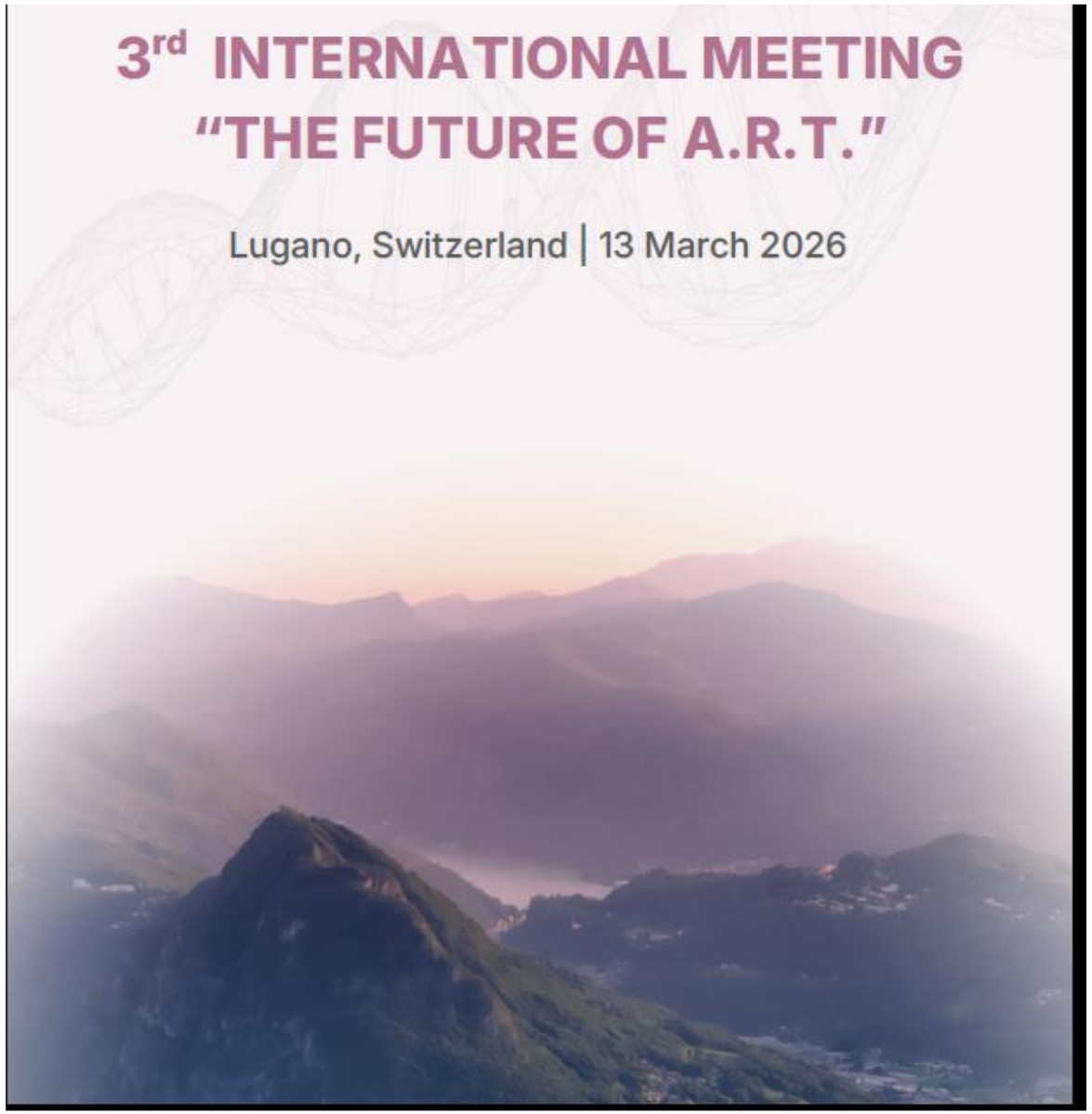

Innovations in the field of male infertility: the future looks bright!

ASL Bari
PugliaSalute

Ettore Caroppo
Andrology Outpatients Clinic
PTA «F. Jaia», Conversano (Ba), Italy

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES OPEN ACCESS

Sperm and offspring production in a nonobstructive azoospermia mouse model via testicular mRNA delivery using lipid nanoparticles

Daisuke Mashiko[a], Chihiro Emori[a], Yuki Hatanaka[a], Daisuke Motooka[b], Chen Pan[a], Yuki Kaneda[a], Martin M. Matzuk[c,1], and Masahito Ikawa[a,d,e,f,1]

Reproduction

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RESEARCH

Monoclonal antibody potentiating gonadotropin activity *in vitro* and *in vivo* in male and female rats and in ewes

Elodie Kara[1], Jérémy Decourtye[1], Laurence Dupuy[1], Sophie Casteret[1], Philippe Bouchard[2], René Frydman[2] and Marie-Christine Maurel[1]

https://doi.org/10.1038/s41585-026-01128-9

Fathers matter too: sperm-borne epigenetic messages link paternal exposures to next-generation health

Sergio Pecorelli, Roberto Lucchini, Luca Lambertini & Giuseppe Novelli

A systematic review of the validated monogenic causes of human male infertility: 2020 update and a discussion of emerging gene–disease relationships

Brendan J. Houston[1,*], Antoni Riera-Escamilla[2], Margot J. Wyrwoll[3], Albert Salas-Huetos[4,5], Miguel J. Xavier[6], Liina Nagirnaja[7,8], Corinna Friedrich[3], Don F. Conrad[7,8,9], Kenneth I. Aston[4,8,9], Csilla Krausz[8,9,10], Frank Tüttelmann[3,9], Moira K. O'Bryan[1,8,9], Joris A. Veltman[6,9], and Manon S. Oud[11,*]

Human Reproduction Update, Vol.28, No.1, pp. 15–29, 2022

Table 1 Numbers of genes that are at least moderately linked to male infertility or abnormal genitourinary development phenotypes.

Description	AR	AD	XL	YL	Total
Isolated infertility	**27**	**5**	**4**	**0**	**36**
Acephalic sperm	3	0	0	0	3
Globozoospermia	1	0	0	0	1
Macrozoospermia	1	0	0	0	1
Multiple morphological abnormalities of the sperm flagella	13	1	0	0	14
Non-obstructive azoospermia or oligozoospermia	7	4	3	0	14
Congenital bilateral absence of the vas deferens	1	0	1	0	2
Fertilisation failure	1	0	0	0	1
Syndromic infertility	**13**	**3**	**1**	**0**	**17**
Primary ciliary dyskinesia	7	0	1	0	8
Other syndromes	6	3	0	0	9
Endocrine disorder/Reproductive system syndrome	**28**	**30**	**7**	**2**	**67**
Disorders of sexual development	14	13	4	2	33
Hypogonadotropic hypogonadism*	14	17	3	0	34

Genetic determinants of testicular sperm extraction outcomes: insights from a large multicentre study of men with non-obstructive azoospermia

Antoni Riera-Escamilla[1,2,*,†], Mohamed M. Arafa[3,4,5,†], Ginevra Farnetani[6,†], Miguel J. Xavier[7], Manon S. Oud[8], Ahmad A. Majzoub[3,4], Liliana Ramos[9], Chiara Abrardo[1], Matilde Spinelli[6], Daniel Moreno-Mendoza[1,10], Giuseppe Defazio[6,11], Elisabet Ars[12], Marc Pybus[12], Josvany R. Sánchez Curbelo[1], Haitham T. Elbardisi[3,4,13], Shoaib Nawaz[14,15], Najeeb Syed[15], Eduard Ruiz-Castané[1], Godfried W. van der Heijden[9], Khalid A. Fakhro[15,16,17], Joris A. Veltman[7,18], and Csilla Krausz[6,*]

Human Reproduction Open, 2025, **2025(3)**, hoaf049

Table 1. Summary of the comparisons performed on carriers of LP/P variants according to two different ACMG-AMP variant classification methods; comparisons were performed in function of TESE outcome or testis phenotype.

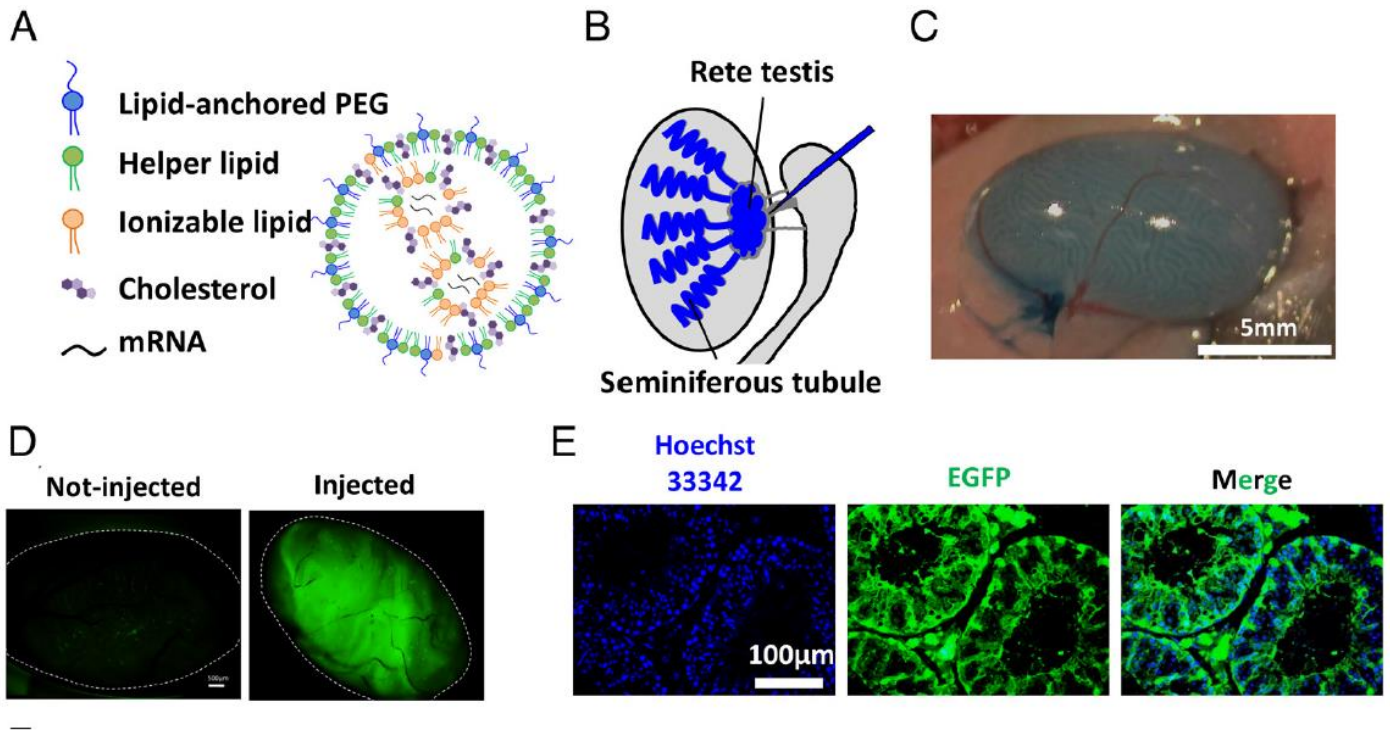
		Carriers of LP/P variants according to different classification methods n (%)	
	Entire cohort (n = 571)	Variant classification I (n = 64)	Variant classification II (n = 35)
TESE outcome	Negative (n = 329, 57.6%)	53 (16.11)	30 (9.11)
	Positive (n = 242, 42.4%)	11 (4.51)	5 (2.06)
	Negative vs positive P-value, OR (CI 95%)	**6.03×10^{-8}*****, 4.13 (2.11–8.08)	**1.29×10^{-5}*****, 4.99 (1.89–12.9)
Testis phenotype	MA (n = 171)	34 (19.9)	20 (11.7)
	SCO (n = 238)	22 (9.2)	11 (4.6)
	HSG (n = 143)	8 (5.6)	4 (2.8)
	MA vs SCO P-value, OR (IC 95%)	**0.0158***, 2.31 (1.26–4.29)	0.0680, 2.48 (1.12–5.75)
	MA vs HSG P-value, OR (IC 95%)	**0.0011****, 4.2 (1.83–10.89)	**0.0173***, 4.62 (1.5–19.03)

PNAS RESEARCH ARTICLE | MEDICAL SCIENCES OPEN ACCESS

Sperm and offspring production in a nonobstructive azoospermia mouse model via testicular mRNA delivery using lipid nanoparticles

Daisuke Mashiko[a], Chihiro Emori[a], Yuki Hatanaka[a], Daisuke Motooka[b], Chen Pan[a], Yuki Kaneda[a], Martin M. Matzuk[c,1], and Masahito Ikawa[a,d,e,f,1]

PNAS 2025 Vol. 122 No. 42 e2516573122



- Pathogenic variants in human pyruvate dehydrogenase E1 subunit alpha 2 (*PDHA2) gene* have been identified in NOA patients
- *Pdha2-KO* mice exhibit meiotic arrest due to impaired pyruvate dehydrogenase (PDH) complex structure. *Pdha2* encodes the testis-specific E1α subunit of the PDH complex, and its mRNA expression peaks in pachytene spermatocytes. LNP injection into the rete testis enabled efficient Pdha2 mRNA delivery to both male germ cells and Sertoli cells.
- LNP-mediated delivery of Pdha2 mRNA enabled the resumption and completion of meiosis, restored sperm production, and facilitated the generation of healthy fertile offspring via ICSI.
- Whole-genome sequencing of the offspring confirmed the absence of large-scale genomic abnormalities.
- LNP-mediated mRNA delivery opens a new era for the treatment of male infertility in the clinic.

Testicular mRNA-LNP Delivery: A Novel Therapy for Genetic Spermatogenic Disorders

Chenwang Zhang[1,2] | Nan Liang[3] | Wenbo Li[1] | Shuai Xu[1] | Peng Li[1] | Wanze Ni[1,4] | Na Li[1] | Sha Han[1] | Ningjing Ou[1,2,3,5] | Haowei Bai[1] | Yuxiang Zhang[1] | Furong Bai[1] | Yifan Sun[1] | Dewei Qian[1,4] | Xinjie Bu[1,4] | Erlei Zhi[1] | Ruhui Tian[1] | Yuhua Huang[1] | Jingpeng Zhao[1] | Fujun Zhao[1] | Hao Chen[3] | Zheng Li[1,2,4] | Chencheng Yao[1]

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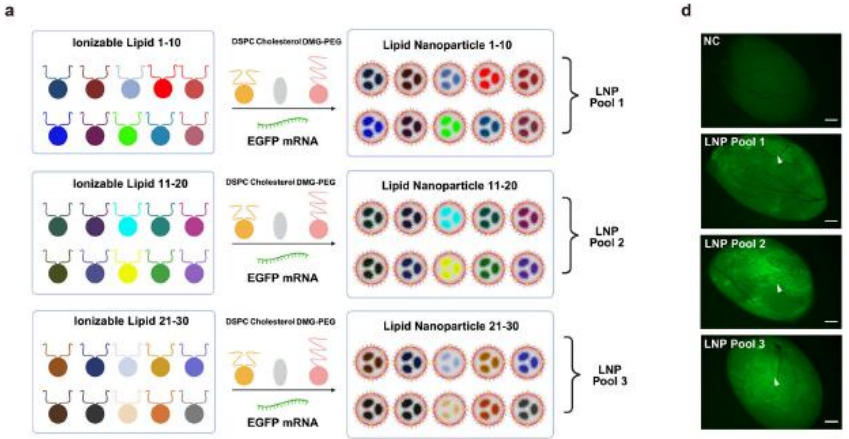
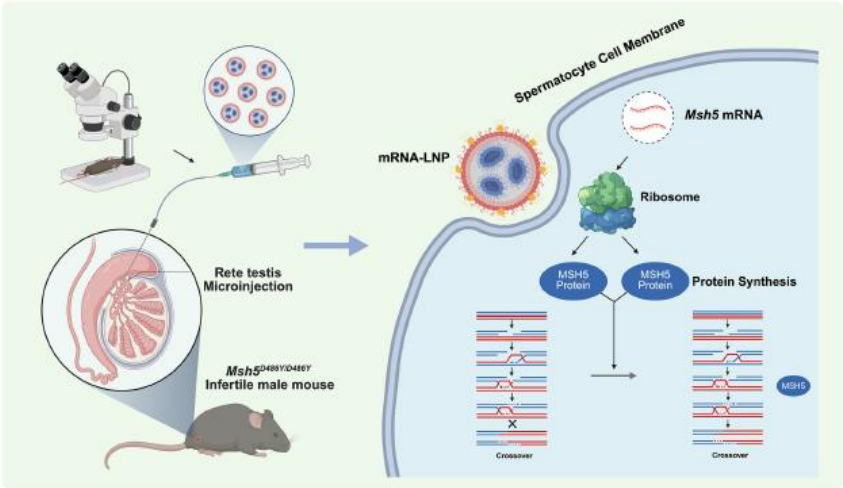
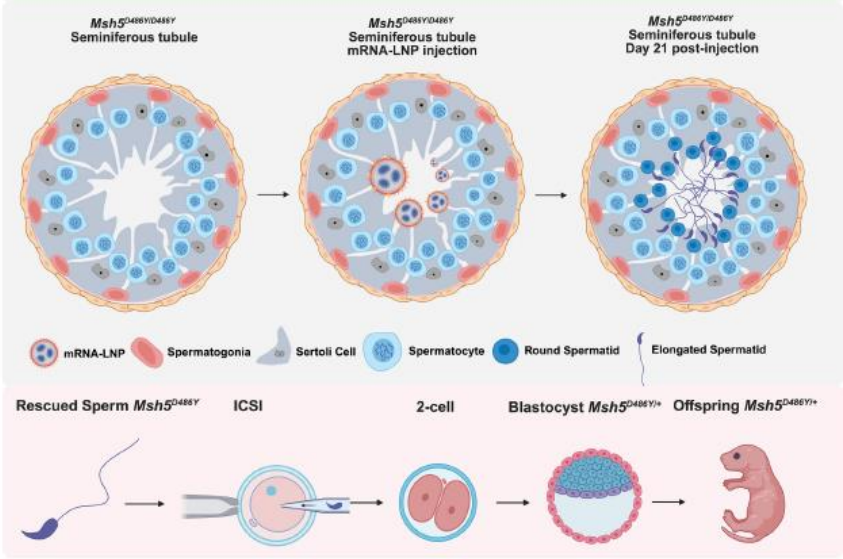
Advanced Science, 2026; 0:e09855







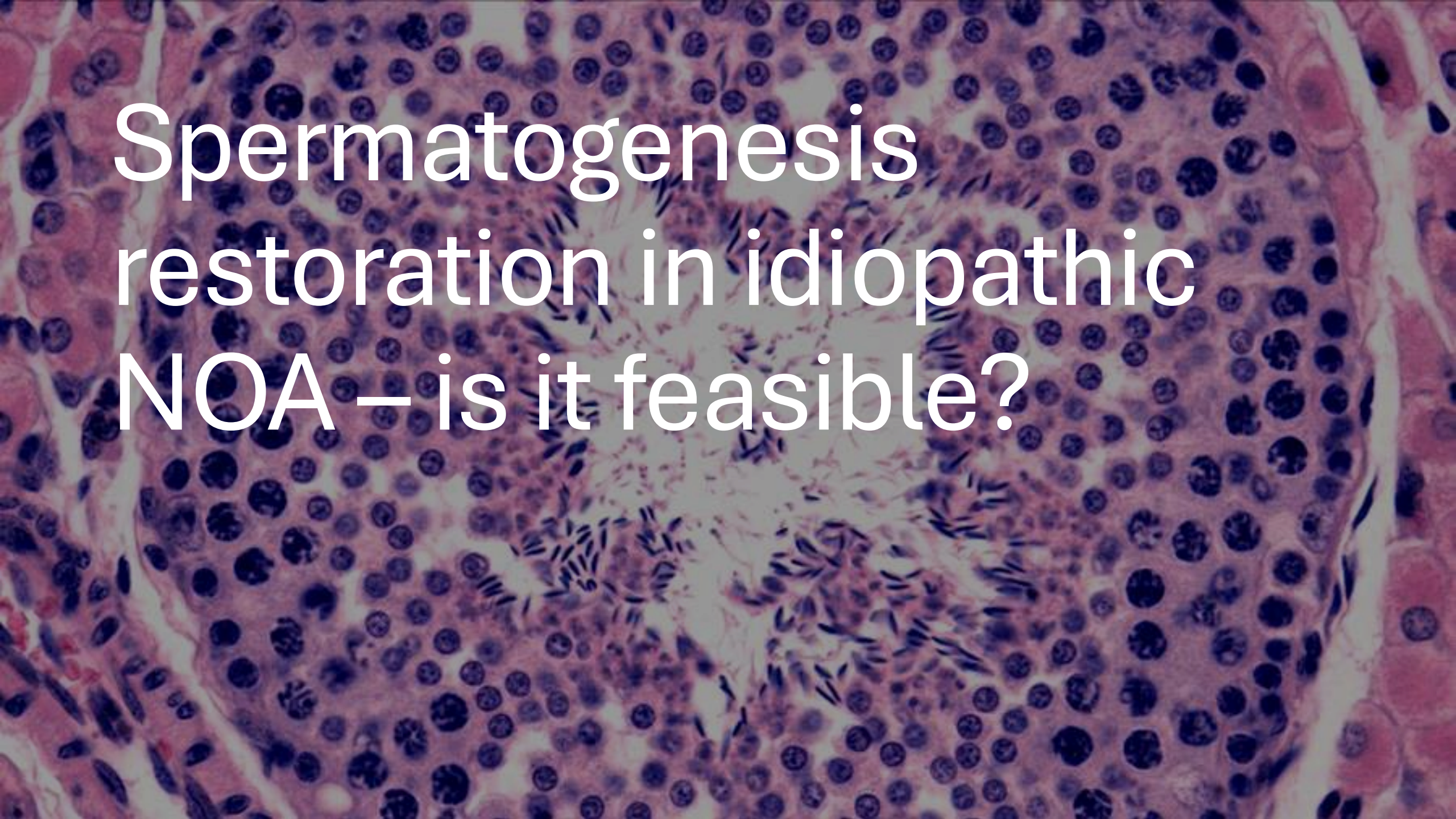
MutS Homolog 5(Msh5) genetic variant is associated with meiotic arrest and NOA in mice and in men.

Maps KO mice display complete spermatogenic arrest at the spematocyte stage

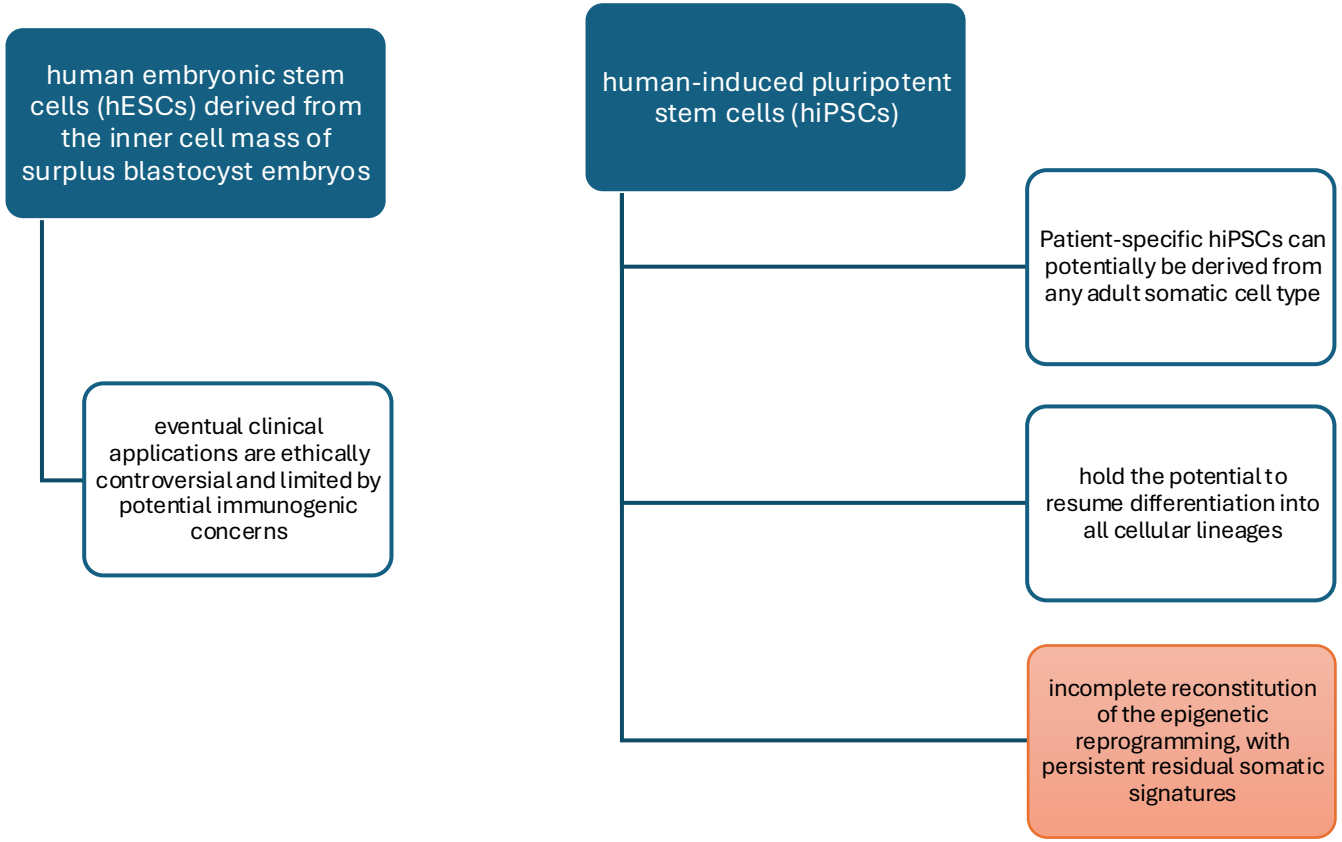
In vivo delivery of Pool1-LNP3 encapsulating Msh5 mRNA could promote crossover formation and restore spermatogenesis in **Msh5D486Y/D486Y mouse models.**

The ICSI offspring were healthy.

Maps mRNA-LNP3 recovered spermatogenesis in **Maps KO mouse with meiotic arrest**.



Spermatogenesis restoration in idiopathic NOA – is it feasible?



Macedo and Alves-Lopes, Hum Reprod Update 2025 10.1093/humupd/dmaf029

- In mice, the generation of fertile offspring from induced pluripotent stem cells-derived gametes was achieved over a decade ago

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] and Mitinori Saitou[1,2,3,*]

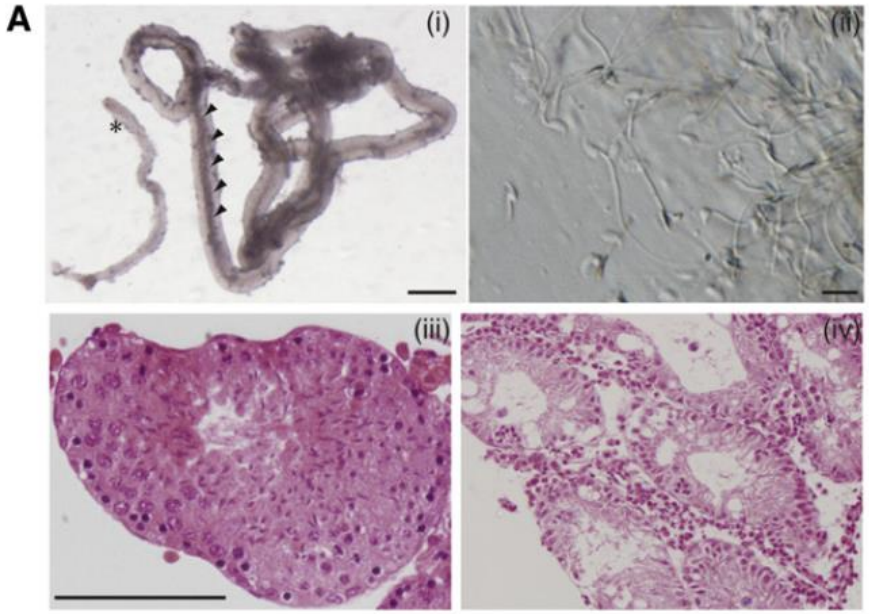
Cell *146*, 519–532, August 19, 2011

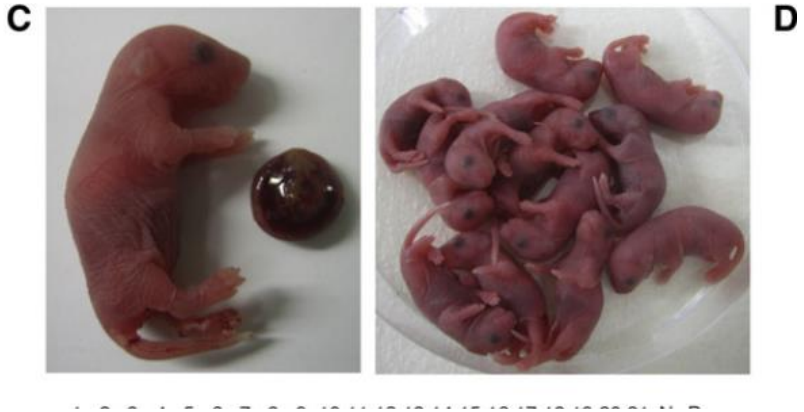
Primordial germ cell-like cells (PGCLCs) in mice with robust capacity for spermatogenesis.

PGCLCs were generated from embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) through epiblast-like cells (EpiLCs), a cellular state highly similar to pregastrulating epiblasts but distinct from epiblast stem cells.

PGCLCs were transplanted into seminiferous tubules (STs) of neonatal W/W mice lacking endogenous spermatogenesis through the efferent ducts

STs were isolated from the recipient testis at 8-10 weeks after transplantation and dissected to retrieve sperm, then used for ICSI





ARTICLE

https://doi.org/10.1038/s41467-018-07740-7 OPEN

Differentiation of primate primordial germ cell-like cells following transplantation into the adult gonadal niche

Enrique Sosa[1], Di Chen[1], Ernesto J. Rojas[1], Jon D. Hennebold[2,3], Karen A. Peters[4], Zhuang Wu[5], Truong N. Lam[5], Jennifer M. Mitchell[6], Meena Sukhwani[4], Ramesh C. Tailor[7], Marvin L. Meistrich[5], Kyle E. Orwig[4], Gunapala Shetty[5] & Amander T. Clark[1]

nature COMMUNICATIONS

NATURE COMMUNICATIONS | (2018)9:5339

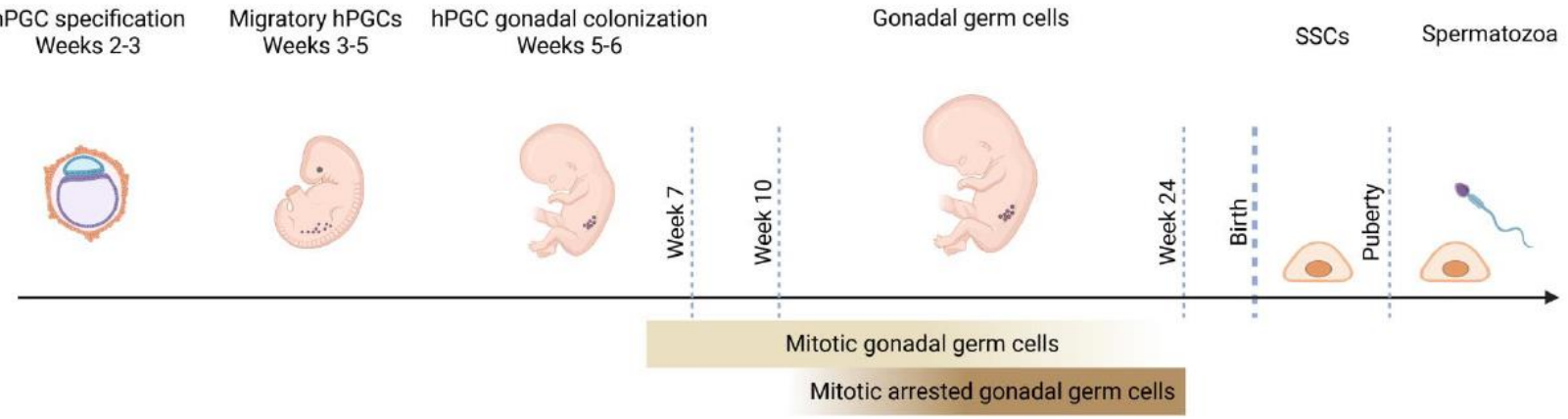
Xenotransplantation (monkey to mouse) and homologous transplantation (monkey to monkey) to validate an in vitro protocol for differentiating male rhesus macaque PGCLCs (rPGCLCs) from induced pluripotent stem cells (riPSCs). Immature rPGCLCs once transplanted into an adult gonadal niche **commit to differentiate towards late rPGCs** that **initiate epigenetic reprogramming** but **do not complete the conversion into ENO2-positive spermatogonia**.

What about humans?

- At present, attempts at maturating patient germ cells beyond the human primordial germ cell-like cells state remain limited

Macedo and Alves-Lopes, Hum Reprod Update 2025 10.1093/humupd/dmaf029

In vivo germline development



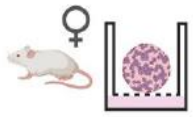
In vitro maturation of hPGCLCs

Human hindgut organoids

Alves-Lopes et al., 2023, 2024

25 days

some cells expressed DAZL and DDX4 and **progressively lowered genomic methylation markers** after 25 days in culture

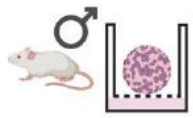


Co-culture with mouse fetal ovarian cells

Yamashiro et al., 2018

77 days

These germ cells expressed DAZL and DDX4 and **reached levels of DNA methylation close to 10%,** mostly **resembling embryonic mitotic gonocytes observed from Week 7 onwards**

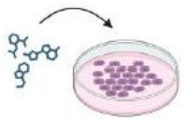


Co-culture with mouse fetal testicular cells

Hwang et al., 2020

81-120 days

These germ cells showed similar evidence of DAZL and DDX4 expression and an overall transcriptomic signature **resembling mitotic pro- spermatogonia**. However most testicular tubular-like structures disaggregated by Day 80



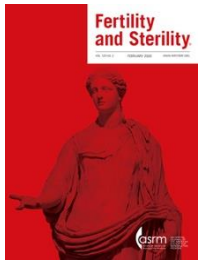
Molecular supplementation

Murase et al., 2024

90-140 days

a medium supplemented with SCF, forskolin, and FGF2 robustly propagates hPGCLCs for 30days on mouse feeder cells

Ethical considerations of in vitro gametogenesis: an Ethics Committee opinion



ASRM Ethics Committee

Received January 13, 2026; accepted January 15, 2026.

Significant biological and methodological barriers remain before IVG from mouse models can be translated to humans

These **challenges** include:

1) low efficiency
2) genetic and epigenetic abnormalities
3) chromosomal errors in in vitro-derived gametes
4) incomplete or improper imprinting
5) the need for human gonadal somatic cells to be used as a matrix for proper gamete development

Key **biological safety concerns** include:

1) the risk of genetic and epigenetic abnormalities, incomplete or improper imprinting, and mutations arising during reprogramming or differentiation. These abnormalities may not be immediately apparent, necessitating long-term follow-up of offspring for developmental, metabolic, and reproductive outcomes.
2) preclinical models must evaluate the risk of tumorigenicity, especially when using iPSCs, which have inherent risks of reversion or uncontrolled growth

Monoclonal anti-human FSH antibodies

A promising tool for non-hormonal stimulation of spermatogenesis?

FSH treatment of male idiopathic infertility improves pregnancy rate: a meta-analysis

D Santi[1,2], A R M Granata[2] and M Simoni[1,2]

Endocrine CONNECTIONS

2015 Sep;4(3):R46-58

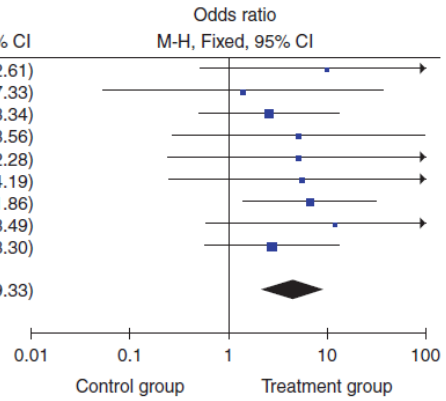
Spontaneous pregnancies

B

Reference	FSH treatment Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
(12)	4	39	0	39	5.0	10.01 (0.52, 192.61)
(37)	1	23	0	10	7.3	1.40 (0.05, 37.33)
(39)	6	62	2	50	22.7	2.57 (0.50, 13.34)
(42)	4	57	0	30	6.8	5.13 (0.27, 98.56)
(13)	2	31	0	30	5.3	5.17 (0.24, 112.28)
(43)	2	19	0	19	5.0	5.57 0.25, 124.19)
(44)	10	68	2	80	17.8	6.72 (1.42, 31.86)
(16)	4	15	0	15	4.1	12.13 (0.59, 248.49)
(45)	10	70	2	35	26.0	2.75 (0.57, 13.30)
Total (95% CI)		384		308	100.0	4.50 (2.17, 9.33)
Total events	43		6			

Heterogeneity: χ^2=2.29, df=8 (P=0.97); I^2=0%

Test for overall effect: Z=4.04 (P<0.0001)



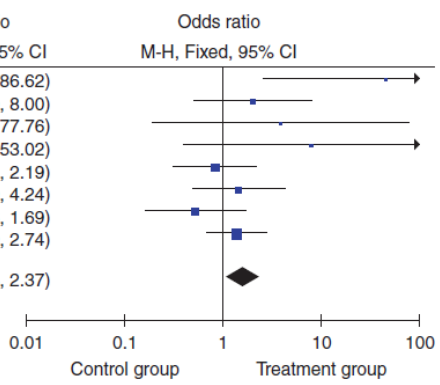
ART pregnancies

C

Reference	FSH treatment Events	Total	Control Events	Total	Weight (%)	Odds ratio M-H, Fixed, 95% CI
(12)	14	39	0	39	0.8	44.92 (2.57, 786.62)
(14)	8	24	4	20	7.2	2.00 (0.50, 8.00)
(36)	3	40	0	20	1.5	3.83 (0.19, 77.76)
(37)	6	23	0	10	1.2	7.80 (0.40, 153.02)
(39)	10	56	10	48	22.0	0.83 (0.31, 2.19)
(42)	14	53	6	30	14.0	1.44 (0.49, 4.24)
(13)	6	29	10	30	19.4	0.52 (0.16, 1.69)
(44)	26	58	29	78	33.9	1.37 (0.69, 2.74)
Total (95% CI)		322		275	100.0	1.60 (1.08, 2.37)
Total events	87		59			

Heterogeneity: χ^2=12.22, df=7 (P=0.09); I^2=43%

Test for overall effect: Z=2.36 (P=0.02)



From 10 to 18 infertile men
should be treated to achieve one additional pregnancy…

Treatment of idiopathic oligozoospermia with recombinant human follicle-stimulating hormone: a prospective, randomized, double-blind, placebo-controlled clinical study in Chinese population

Clinical Endocrinology (2015) **83**, 866–871

Yin-man Ding*,[1], Xin-ji Zhang†,[1], Jing-Ping Li‡, San-san Chen§, Ren-tao Zhang*, Wan-long Tan§ and Xiao-Jun Shi*

Table 2. Sperm parameters (before and after) and pregnancy rates after treatment with different doses of rhFSH or placebo for 3 months. Data are presented as mean ± SD

	Seminal parameters				Pregnancy rates	
	Sperm count (×106)	Sperm concentrations (×106/ml)	Forward motility (%)	Normal morphology (%)	Spontaneous pregnancy rate	ART pregnancy rate
Placebo group (n = 30)						
Before	12·1 ± 4·1	4·1 ± 3·3	25·8 ± 9·1	29·7 ± 9·2	6·7% (2/30)	25% (7/28)
After	15·2 ± 3·9	5·0 ± 2·3	27·1 ± 3·2	31·9 ± 10·4		
50 IU group (n = 36)						
Before	13·3 ± 5·6	4·3 ± 2·1	25·4 ± 5·1	29·4 ± 6·2	8·3% (3/36)	27·2% (9/33)
After	16·9 ± 3·5	5·9 ± 3·9	27·7 ± 4·7	28·2 ± 3·7		
100 IU group (n = 38)						
Before	16·2 ± 6·2	5·2 ± 4·3	24·8 ± 5·1	30·7 ± 3·2	7·9% (3/38)	31·4% (11/35)
After	18·2 ± 5·7	6·9 ± 7·9	28·7 ± 12·9	35·8 ± 9·7		
200 IU group (n = 41)						
Before	15·8 ± 7·7	4·8 ± 5·2	24·8 ± 10·1	29·7 ± 9·2	9·7% (4/41)	**37·1% (13/35)**
After	**29·7 ± 9·9***	**14·9 ± 7·2***	30·7 ± 7·1	35·8 ± 12·8		
300 IU group (n = 40)						
Before	14·1 ± 5·7	5·1 ± 3·3	23·8 ± 10·1	31·7 ± 9·2	**15% (6/40)**	**41·1% (14/34)**
After	**44·1 ± 12·4***	**19·1 ± 10·2***	29·7 ± 11·8	36·1 ± 12·8		

*P < 0·05 vs. Placebo-control group. The bold values means significance.

Table 3. Sperm parameters at the different time intervals after treatment with rhFSH (300 IU). Data are presented as mean ± SD

	Seminal parameters			
	Sperm count (×106)	Sperm concentrations (×106/ml)	Forward motility (%)	Normal morphology (%)
Placebo group (n = 29)				
3 months after therapy	13·5 ± 4·5	3·1 ± 2·1	26·2 ± 10·2	28·1 ± 11·1
Treated group (n = 40)				
Basal	14·7 ± 5·2	3·7 ± 3·2	23·5 ± 8·3	26·6 ± 6·2
The first month	15·9 ± 7·4	6·8 ± 4·9	25·7 ± 8·7	29·4 ± 11·7
The second month	19·2 ± 8·5	10·9 ± 2·9	26·1 ± 7·7	31·7 ± 9·8
The third month	**32·1 ± 10·3***	**15·8 ± 9·8***	29·7 ± 11·8	32·1 ± 12·8
The fourth month	**55·1 ± 18·8***	**21·3 ± 10·9***	**33·8 ± 10·1***	**39·6 ± 17·6***
The fifth month	**62·9 ± 21·2***	**30·8 ± 10·4***	**41·7 ± 12·1***	**51·8 ± 13·5***
3 months after therapy	**76·8 ± 25·6***	**33·4 ± 13·2***	**44·6 ± 11·5***	**53·2 ± 14·1***

*$P < 0·05$ vs. Placebo-control group.

Reproduction

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RESEARCH

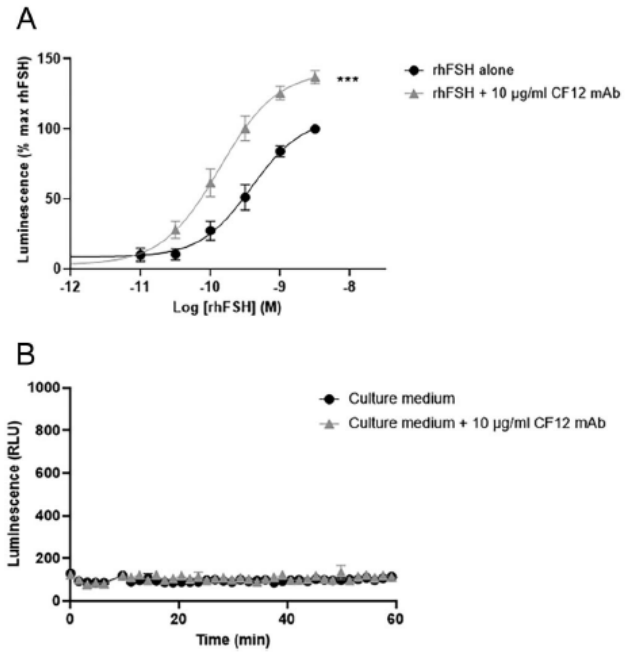
Monoclonal antibody potentiating gonadotropin activity *in vitro* and *in vivo* in male and female rats and in ewes

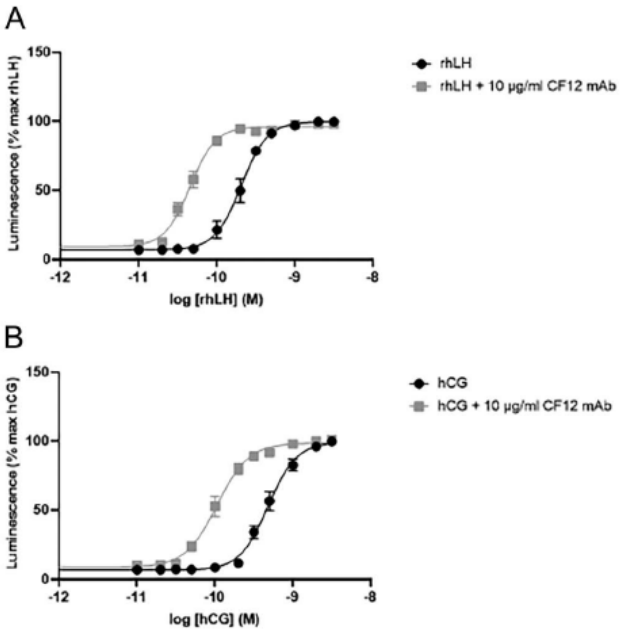
Elodie Kara[1], Jérémy Decourtye[1], Laurence Dupuy[1], Sophie Casteret[1], Philippe Bouchard[2], René Frydman[2] and Marie-Christine Maurel[1]

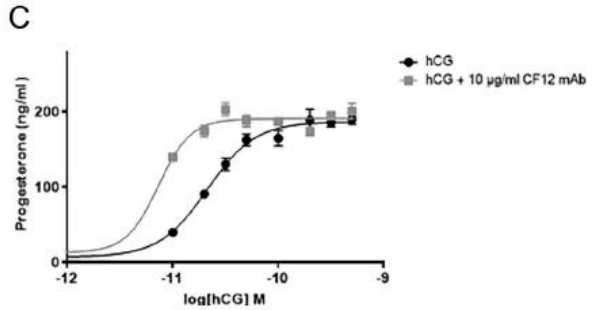
- Equine CG (eCG), which binds only to LH receptor in equines but exhibits dual FSH- and LH-like activity in other species, is used to induce ovulation in livestock such as ewes, goats, cows, and sows, but it's highly immunogenic.
- Interestingly, these anti-eCG Abs exhibit different types of modulating activity: whereas most females develop anti-eCG Abs that decrease fertility, some females develop anti-eCG Abs resulting in enhanced fertility, reaching a 100% birth rate, sometimes with hyperprolificity
- Enhancing anti-eCG Abs collected from goat plasma were purified and their action in combination with eCG on the FSH-R downstream signaling studied in vitro; compared to eCG alone, the enhancing complexes activate protein kinase A and betaarrestin pathways and increase extracellular signal regulated kinase phosphorylation in HEK293 cells expressing the FSH-R
- To develop a **monoclonal antihuman-FSH** enhancing mAb a mouse was immunized against rhFSH. The activity of antibodies secreted by the generated clones was compared based on in vitro FSH bioassays using bovine granulosa cells prepared from ovaries collected from a local slaughterhouse or HEK293 cells expressing FSH-R and on male mouse Leydig tumor cells (mLTC-1) expressing LH/CG-R

Activity of CF12 mAb in vitro on gonadotropins

- The effect of CF12 mAb on FSH and its receptor was shown by examining cAMP production in HEK293 cells overexpressing hFSH-R stimulated with increasing doses of rhFSH alone
- mLTC-1 expressing endogenous LH/CG-R were stimulated with increasing doses of either rhLH or hCG, then CF12mAB was added and cAMP production was assessed.

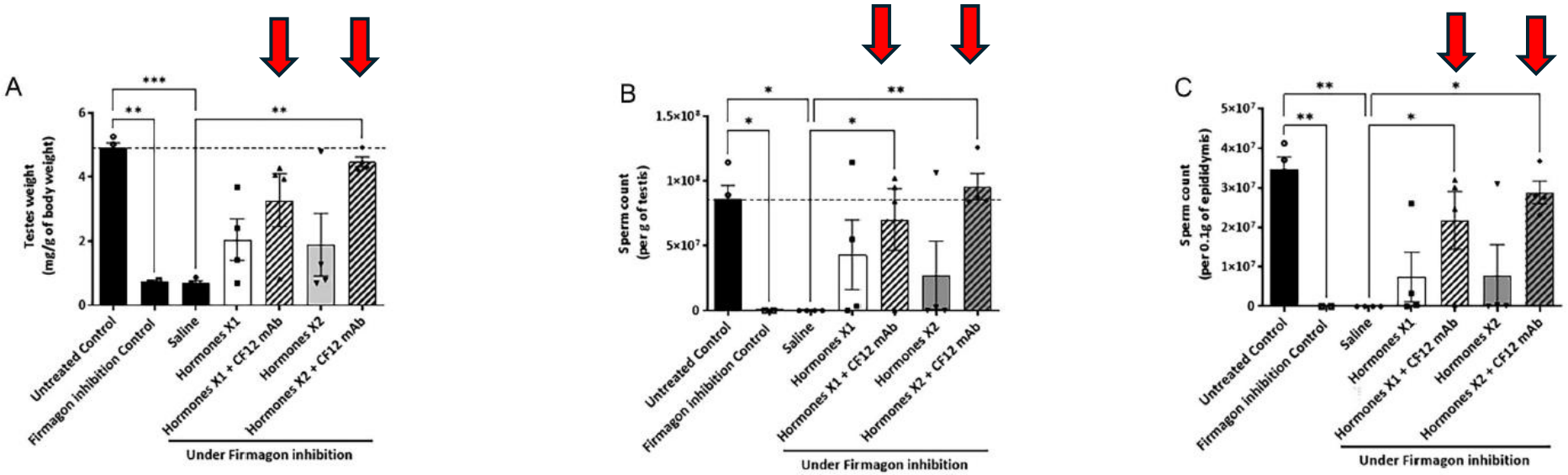






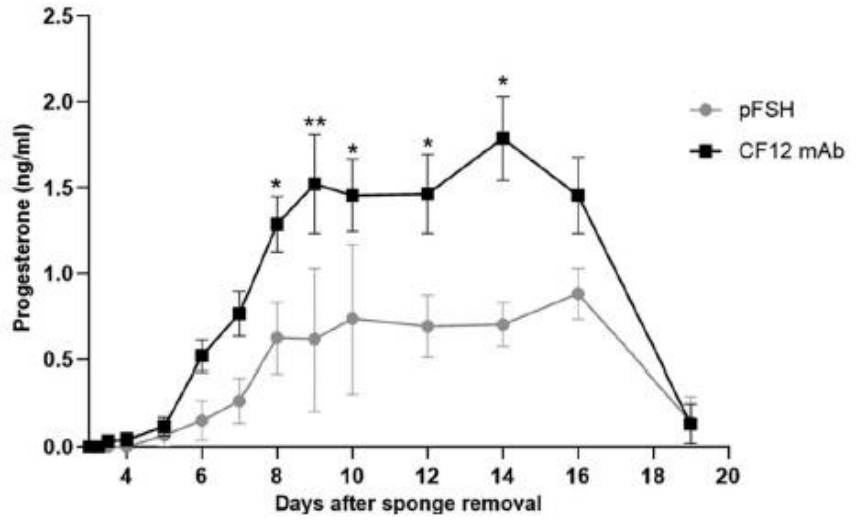
Exploration of CF12 mAb effect on spermatogenesis in hypogonadal adult rats

- Inhibition of endogenous gonadotropin secretion in Wistar Han rats with a long-acting GnRH antagonist created an azoospermic adult rat model



In vivo effect of CF12 mAb administration on ovulation induction in adult ewes

- CF12 mAB ovulation rate (laparoscopy): 100%
- pFSH ovulation rate (laparoscopy): 36%



Conclusions

- CF12 mAb combined with rhFSH enhances in vitro FSH-R-mediated intracellular cAMP production, achieving the same effect as rhFSH alone but with a **five-fold lower dose of rhFSH**, and increasing the maximal effect by **40%**
- A similar five-fold enhancing effect was observed on LH/CG-R mediated intracellular cAMP production with **rhLH or hCG**, although the maximal effect remained unchanged
- CF12 mAb **potentiates endogenous hormones** (ewes) by potentially enhancing the bioactivity of gonadotropins produced naturally
- It is hoped that this potentiating antibody could represent a significant advance in reproductive medicine, enabling improvements in the treatment of infertility:
  - A) less frequent injections
  - B) broaden the range of infertility care strategies

https://doi.org/10.1038/s41585-026-01128-9

Fathers matter too: sperm-borne epigenetic messages link paternal exposures to next-generation health

nature reviews urology

Published online: 04 February 2026

Sergio Pecorelli, Roberto Lucchini, Luca Lambertini & Giuseppe Novelli

- The mature spermatozoon delivers a compact but potent information suite, comprising DNA methylation, retained histones, small non-coding RNAs and mitochondrial RNAs. These molecules are sensitive to the paternal metabolic state and, in mouse models, have been shown to influence offspring metabolism, suggesting a regulated, non-genetic form of mitochondrion–nucleus crosstalk at fertilization
- although reprogramming is extensive, it is strategically incomplete. Key genomic regions, particularly those that harbour imprinted genes and developmental regulators, resist erasure, enabling parent-of-origin epigenetic information to persist through embryogenesis
- The epididymis acts not just as a conduit, but as a dynamic signalling environment, in which epididymosomes (extracellular vesicles) post-testicularly remodel the RNA cargo of the sperm. Furthermore, organelle-to-epigenome signalling emerges as a key pathway
- A hopeful corollary of the responsiveness of sperm is their potential malleability. Research highlights the epididymal phase as a key window during which sperm RNA profiles are susceptible to environmental inputs. This window provides a potentially actionable preconception window: dietary interventions, heat-stress mitigation or reduced toxicant exposure could recalibrate sperm epigenetics before conception
- Sustained lifestyle modifications hold promise for positive reshaping. Thus, preconception health becomes a shared, modifiable responsibility

ENVIRONMENTAL EPIGENETICS

Environmental Epigenetics, 2025, 11(1), 1–14
DOI: https://doi.org/10.1093/eep/dvaf033
Advance Access Publication 2 December 2025
Research Article

Generational stability of environmentally induced epigenetic transgenerational inheritance of adult-onset disease over ten mammalian generations

Alexandra A. Korolenko, Eric E. Nilsson, Sarah De Santos, Michael K. Skinner*

Epigenetic changes persisted over multiple generations of ancestral exposure rather than disappearing. Epigenetic changes persisting for 10 generations challenge views of epigenetic alterations being erased or reset at each generation

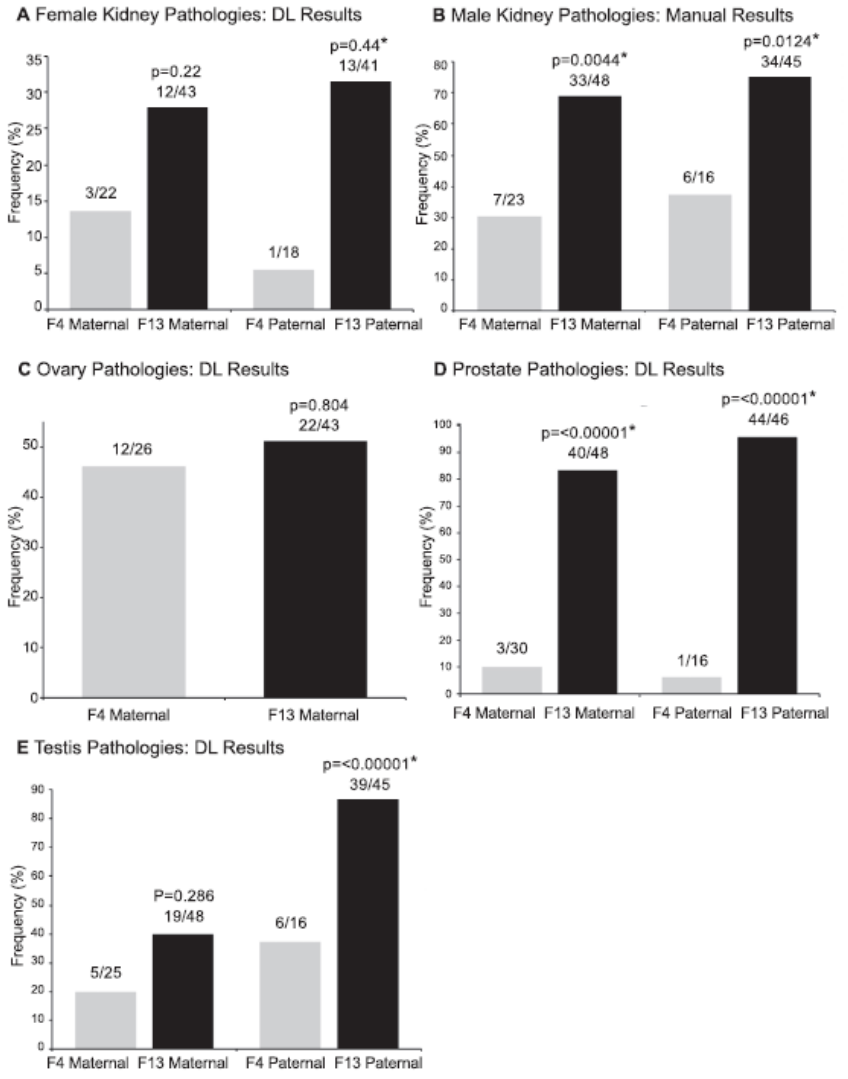


Figure 9. Pathology DL and manual results. (A) Female kidney disease. (B) Male kidney disease. (C) Ovary disease. (D) Prostate disease. (E) Testes disease. Statistical differences were determined by Fisher's exact tests. F13 maternal and paternal lineages compared to F4 control maternal and paternal lineages, *— $P < .05$.

RESEARCH ARTICLE

Tertiary Epimutations – A Novel Aspect of Epigenetic Transgenerational Inheritance Promoting Genome Instability

John R. McCarrey[1]*, Jake D. Lehle[1], Seetha S. Raju[1], Yufeng Wang[1], Eric E. Nilsson[2], Michael K. Skinner[2]

PLOS ONE

December 19, 2016

Possible link between ancestral exposure and neurodevelopmental disorders in offspring and grand offspring

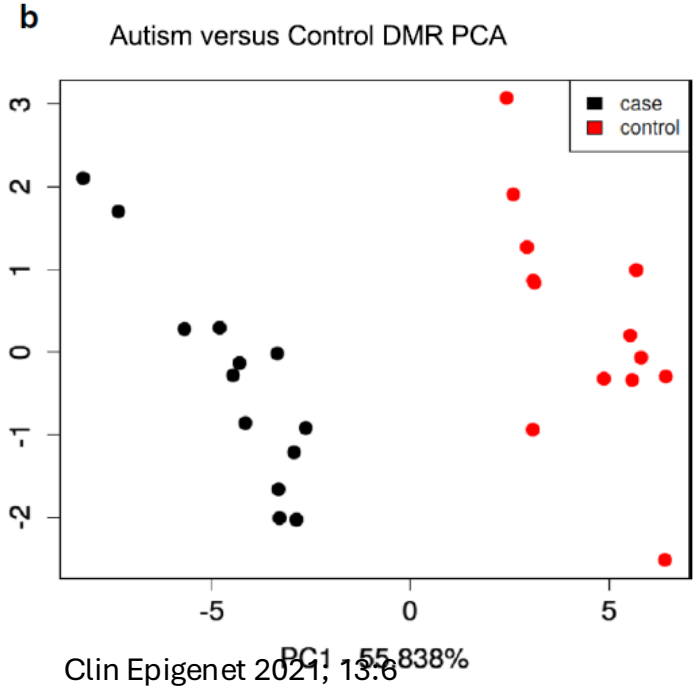
In sperm from DDT-exposed Indigenous Greenlandic and South Africanmen, H3K4me3 enrichment was altered in a dose-like response at young transposable elements, neurodevelopmental genes, and putative embryonic enhancers

Environ Health Perspect. 2024; 132: 17008

Children born in DDT-exposed populations exhibit higher rates of attention deficit and hyperactivity disorders, autism and neurodevelopmental delays

Am. J. Psychiatry 2018; 175: 1094–1101
Mol. Autism 2020; 11: 69
Environ. Health Perspect 2009; 117: 1359–1367
Environ. Health Perspectm2018; 126: 047004

Sperm of fathers of children with autism showed 805 DMR compared to sperm of fathers of healthy children.
Of 805, 303 were hypermethylated and 502 were hypomethylated



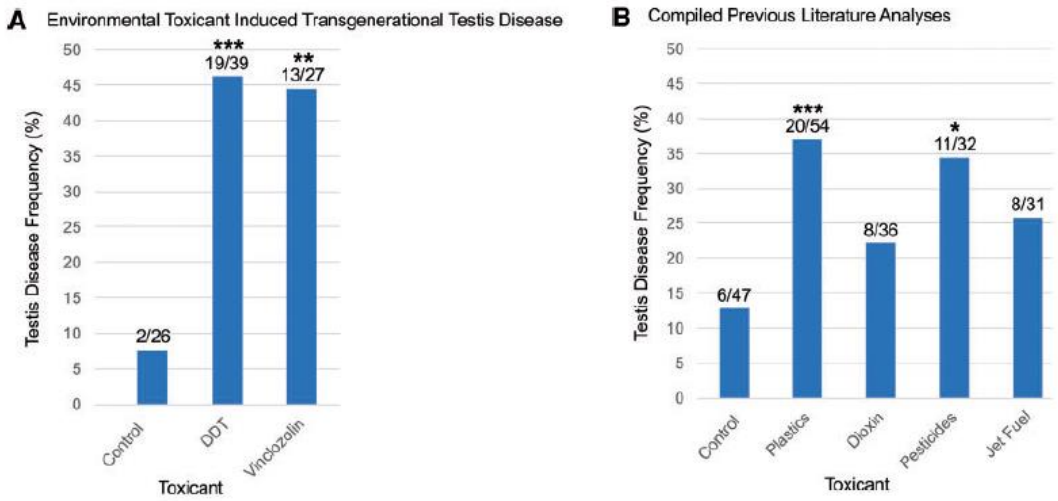
Clin Epigenet 2021; 13:6

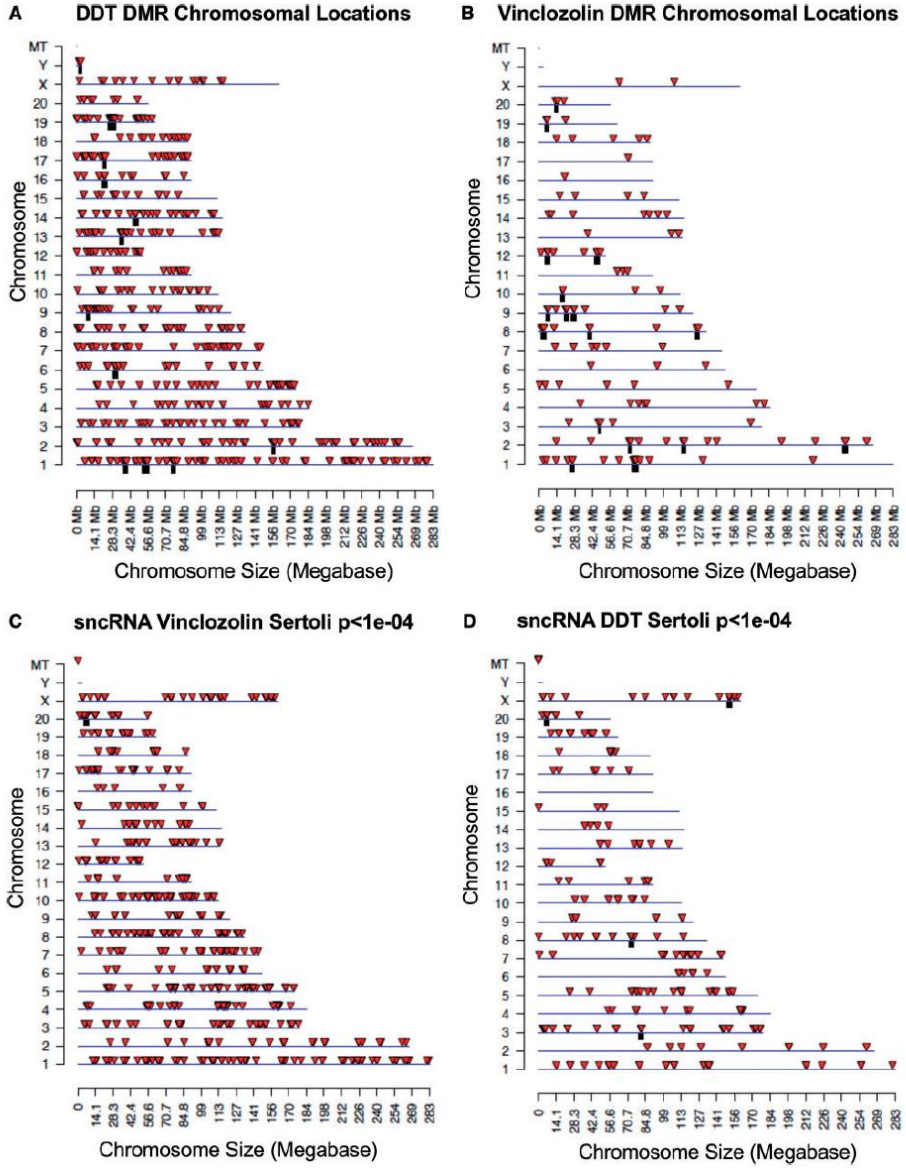
RESEARCH ARTICLE

Epigenetic transgenerational inheritance of testis pathology and Sertoli cell epimutations: generational origins of male infertility

Environmental Epigenetics, 2019, 1–18

Ingrid Sadler-Riggleman[1,†], Rachel Klukovich[2,†], Eric Nilsson[1], Daniel Beck[1], Yeming Xie[2], Wei Yan[2,‡] and Michael K. Skinner[1,*,‡]

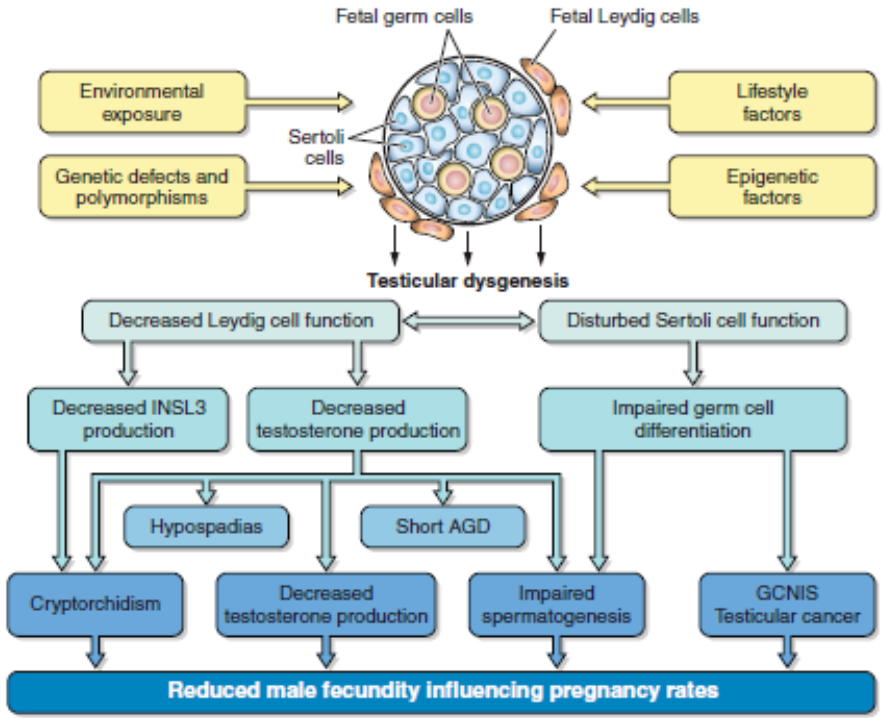




Physiol Rev 96: 55–97, 2016
Published November 18, 2015; doi:10.1152/physrev.00017.2015

MALE REPRODUCTIVE DISORDERS AND FERTILITY TRENDS: INFLUENCES OF ENVIRONMENT AND GENETIC SUSCEPTIBILITY

Niels E. Skakkebaek, Ewa Rajpert-De Meyts, Germaine M. Buck Louis, Jorma Toppari, Anna-Maria Andersson, Michael L. Eisenberg, Tina Kold Jensen, Niels Jørgensen, Shanna H. Swan, Katherine J. Sapra, Søren Ziebe, Lærke Priskorn, and Anders Juul

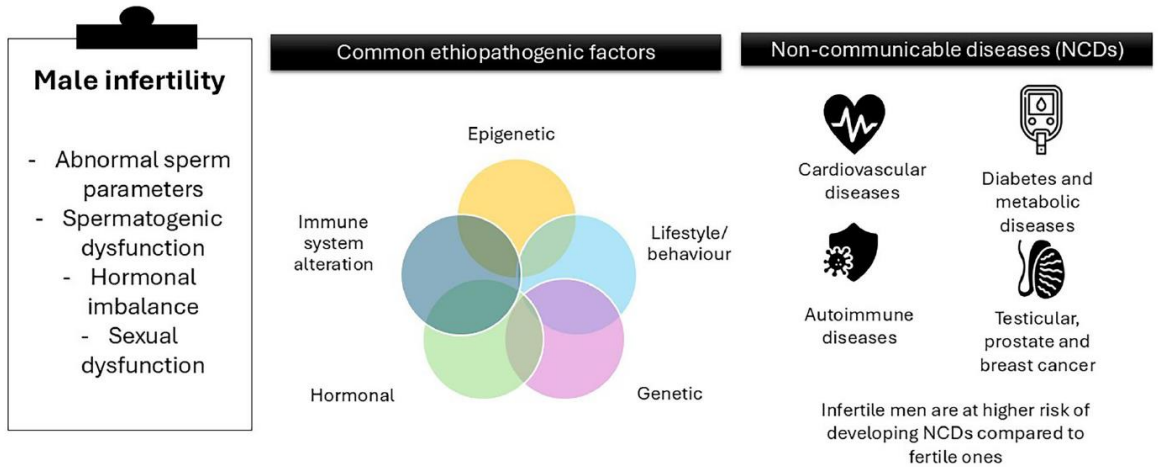


Developments in reproductive biology and medicine

Are infertile men at a higher risk of morbidity and early mortality?

Ettore Caroppo [1,*] and Michael L. Eisenberg [2]

Human Reproduction, 2026, **41(2)**, 148–158



male infertility as harbinger of broader health issues

Epigenetic mechanisms within the sperm epigenome and their diagnostic potential

Chad A. Pollard, Research Technician,
Tim G. Jenkins, Assistant Professor *

Best Practice & Research Clinical Endocrinology & Metabolism 34 (2020) 101481

Developments in reproductive biology and medicine

Could the sperm epigenome become a diagnostic tool for evaluation of the infertile man?

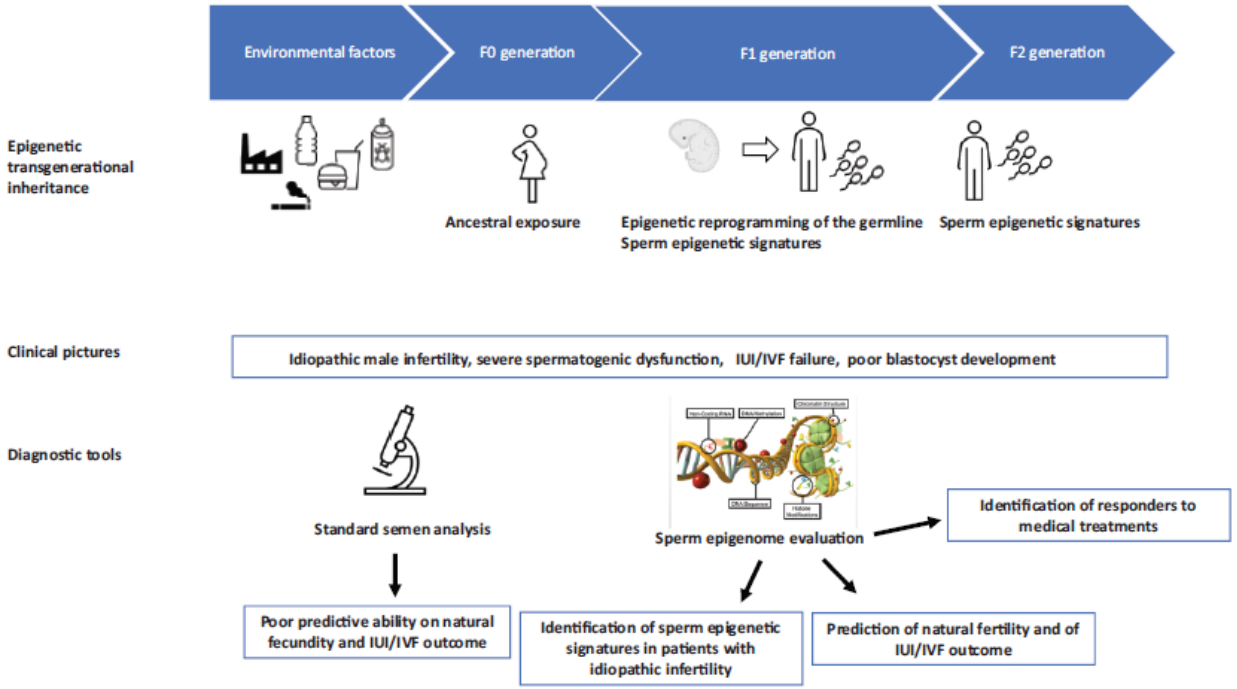
Ettore Caroppo [1,*] and Michael K. Skinner [2]

Human Reproduction, 2024, **39(3)**, 478–485

Spermatozoa from normozoospermic fertile and infertile individuals convey a distinct miRNA cargo

[1]A. Salas-Huetos, [1]J. Blanco, [1]F. Vidal, [2,3]M. Grossmann, [2]M. C. Pons, [3]N. Garrido and [1,*] E. Anton

Andrology, 2016, 4, 1028–1036



Environmentally responsive sperm epigenome signatures as a diagnostic tool for male factor infertility.

nature communications

Perspective

https://doi.org/10.1038/s41467-023-37820-2

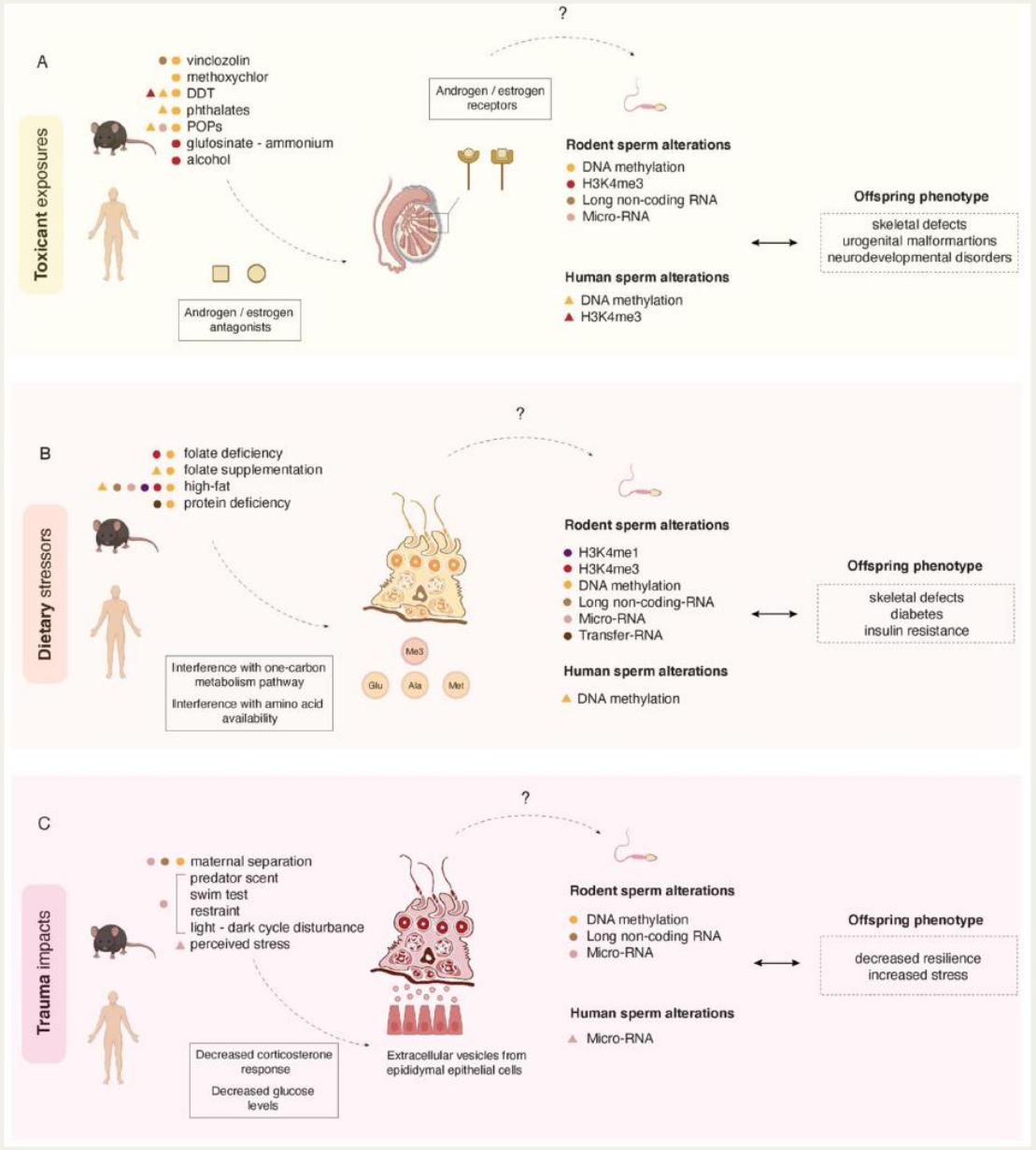
Emerging evidence that the mammalian sperm epigenome serves as a template for embryo development

Ariane Lismer[1] & Sarah Kimmins[1,2]

- Even robust proof of transmission of DNA methylation and / or chromatin states from sperm to the embryo is insufficient to provide causal links to alterations in embryonic gene expression at single-locus resolution.
- Little is known regarding how certain marks in sperm may promote splicing variants, alternative promoters, and enhancer-specific transcription, in the embryo.
- It remains unclear how specific levels of change in DNA methylation and histone modifications alter post-fertilization gene expression

BOX 3

The sperm epigenome is sensitive to environmental stress at functional regions that correlates with phenotypes in the offspring



Infertility

The Past, Present, and Future of Male Reproductive Health

Rene Almeling*

Sociology Department, Yale University, New Haven, CT 06520

Received 1 September 2025; Accepted 1 December 2025

HISTORICAL INATTENTION TO MALE REPRODUCTIVE HEALTH

"The gap in knowledge about male fertility is not natural or inevitable. Based on my historical research, I argue that it can be traced back to the earliest days of medical specialization, when doctors positioned the male body as a neutral medical "standard" and the female body as "reproductive"—leaving us with a "missing science" of male reproductive health"

"In part, this is the result of a cultural belief that sex is binary: traditional views of male and female as distinct and even "opposite" categories meant that since female bodies were defined as reproductive, male bodies were defined as not reproductive".

"The topic of male reproductive health continues to hover around the edges of multiple specialties, including urology and endocrinology, without serving as the focus of any one in particular"

"There are few research dollars for those who want to study male reproductive health"

"Nevertheless, there are exciting developments in this field, including research that is starting to fill in crucial details about the relationship between male bodily health, sperm, and risks to offspring"

Conclusions

Research in the field of male infertility is making significant efforts to introduce innovations in both diagnostics and therapy

Unfortunately, at present it is premature to translate these findings into clinical practice

The future of male reproductive science will look brighter when greater attention (and funding) will be dedicated to male reproductive health