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PREIMPLANTATION GENETIC DIAGNOSIS INTERNATIONAL SOCIETY

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PGT and BEYOND...

Maternal spindle transfer coupled with hyperspectral imaging: a personalized solution for infertility treatment

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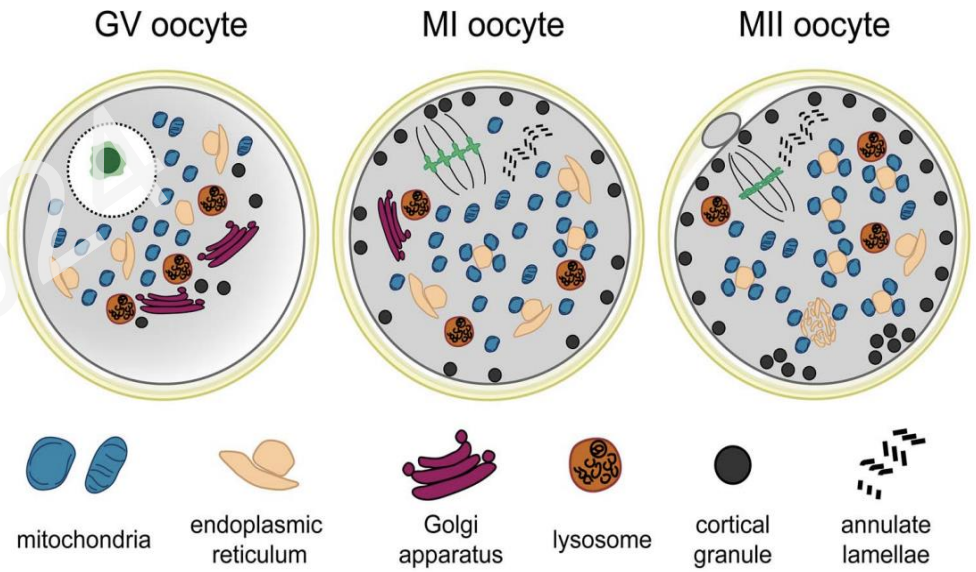
PGT and BEYOND...

embryotools

Oocyte quality

Oocyte quality refers to the ability of an oocyte to develop into a chromosomally normal embryo with chances to implant and sustain a pregnancy.

The developmental competence is mainly dictated by the chromosomal status and cytoplasmic factors (e.g. organelles, mRNAs, ribosomes) of the oocyte [1-4].



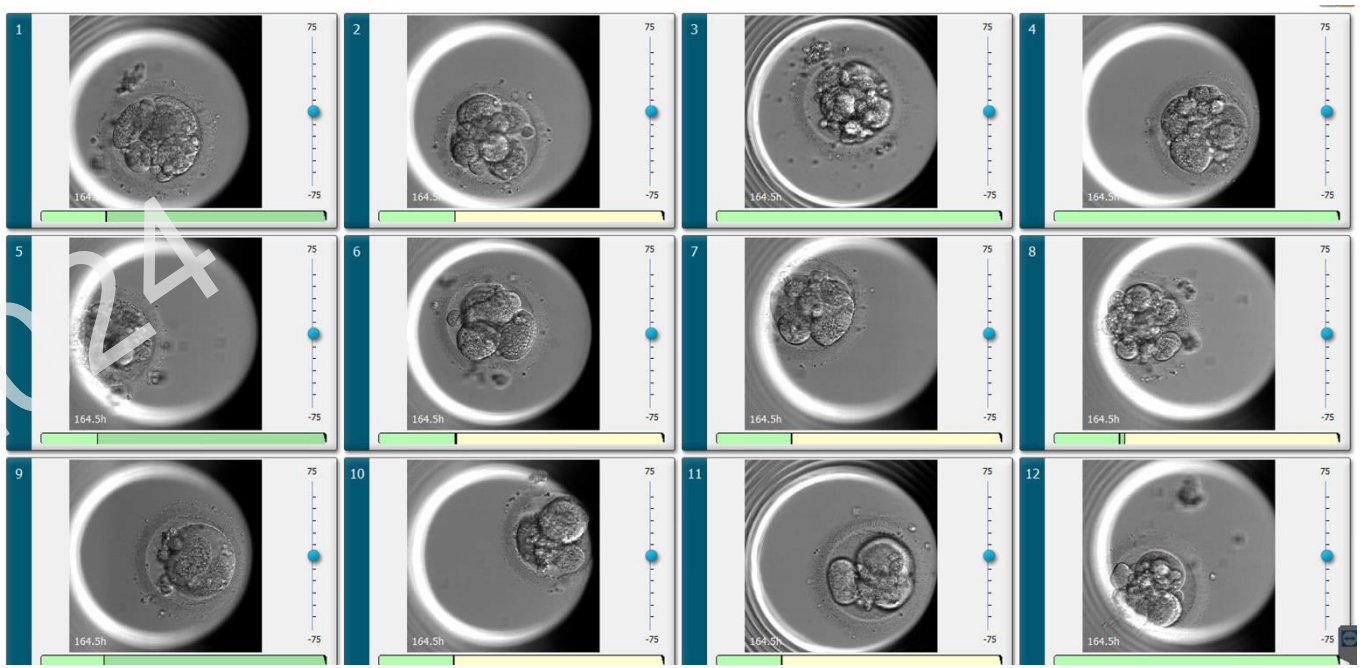
Z. Trebichalská et al., 2021, Vol. 104, No. 1

[1]Conti M, Franciosi F. ***Hum Reprod Update 2018**:245-266* | [2] Wolf DP, Hayama T, Mitalipov S. ***EMBO J. 2017.*** 36(17):2659 | [3]Van Blerkom, J. (2004). **Reproduction,** 128(3), 269–280. | [4]*Cohen J.* (1998) . ***Mol Hum Reprod*** (3):269-80.

Oocyte quality

Cytoplasmic dysfunction (including, but not limited to mitochondria) is a major cause of impaired oocyte quality and embryo development. [1-4]

Low fertilization and/or poor embryo development in repeated IVF cycles.



[1]Conti M, Franciosi F. ***Hum Reprod Update 2018***:*245-266* | [2] Wolf DP, Hayama T, Mitalipov S. ***EMBO J. 2017.*** 36(17):2659 | [3]Van Blerkom, J. (2004). **Reproduction,** 128(3), 269–280. | [4]*Cohen J.* (1998) . ***Mol Hum Reprod*** (3):269-80.

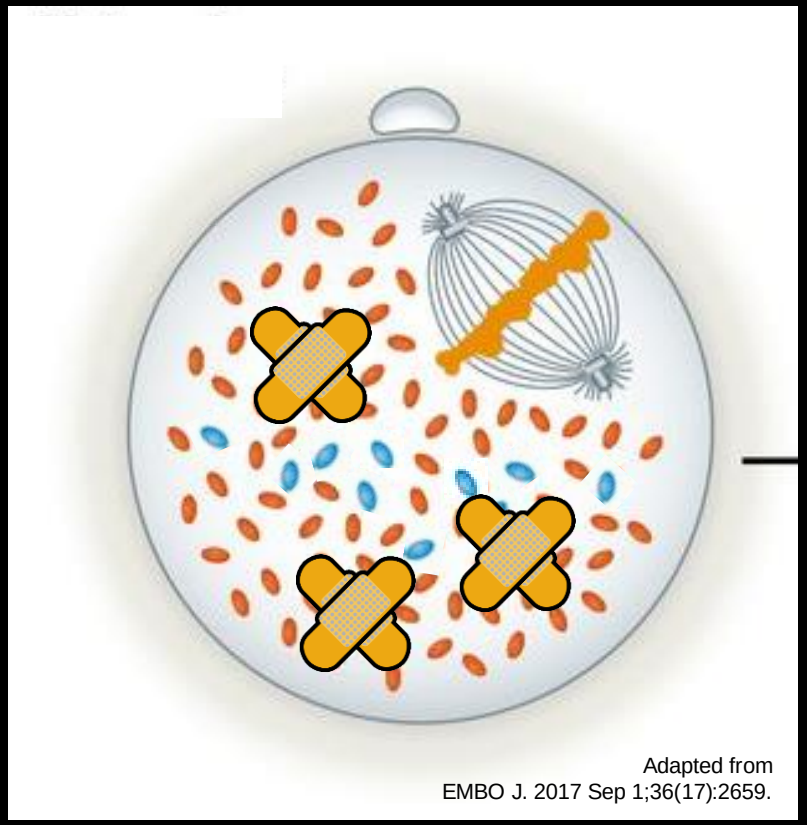
Proposed strategies to improve oocyte quality

Cytoplasmic transfer[1]
Mitochondrial transfer[2]

Antioxidants supplementation[3]
Metabolites supplementation[4]

Main limitations:

- Could ameliorate development, but not likely to repair all dysfunctions in severe phenotypes.
- Defective elements still passed down to the embryo.
- Organelles different than mitochondria (e.g., maternal transcripts) cannot be repaired.



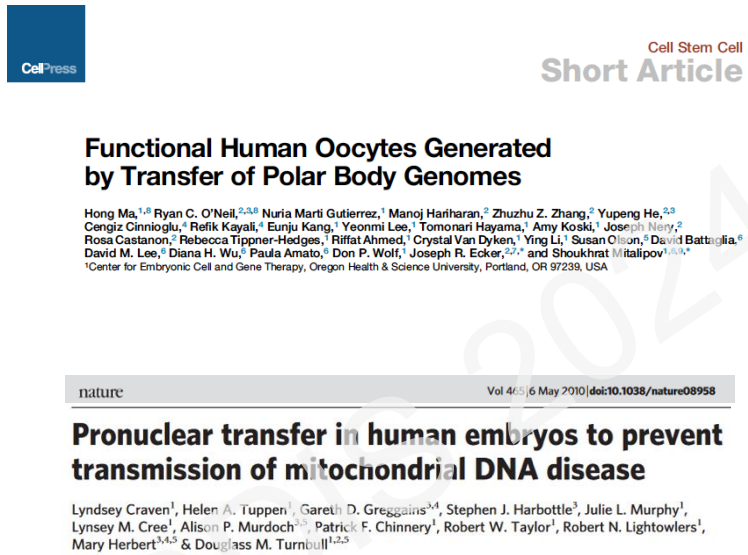
Adapted from
EMBO J. 2017 Sep 1;36(17):2659.

[1]J Cohen et al., Molecular Human Reproduction vol 4, pp 269-280, 1998 | [2]Fakih et al., JFIV Reprod Med. Genet. 2015 | [3]Bertoldo et al., Cell Repor 11: 30(6): 1670-1681. [4]Zhang et al., Nature Aging. Online 2023.

How can poor quality oocytes be repaired?

An approach that offers promise to **improve oocyte quality** is the **transfer of the nuclear genome** from an affected oocyte/zygote into a new healthier cytoplasm - **Mitochondrial replacement therapies (MRTs).**

GV transfer | Polar body transfer | Spindle transfer | Pronuclear transfer


Cell Stem Cell
Short Article

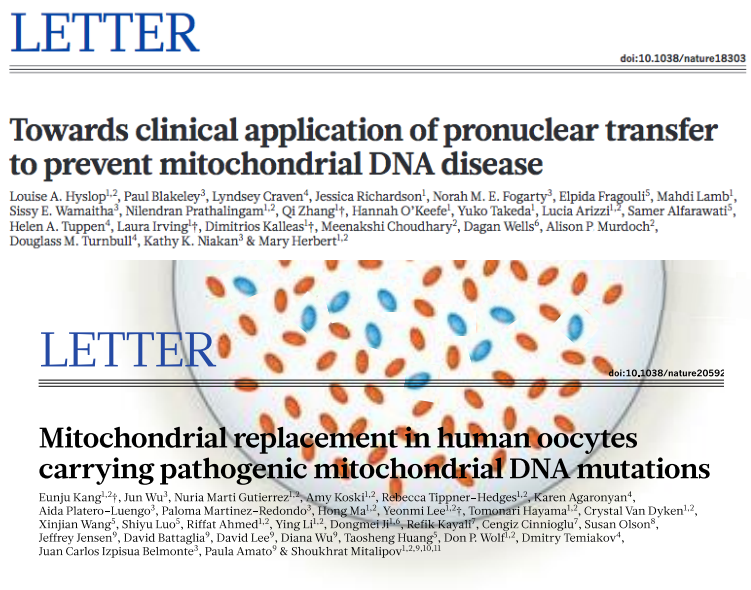
Functional Human Oocytes Generated by Transfer of Polar Body Genomes

Hong Ma,[1,8] Ryan C. O'Neil,[2,3,8] Nuria Marti Gutierrez,[1] Manoj Hariharan,[2] Zhuzhu Z. Zhang,[2] Yupeng He,[2,3] Cengiz Cinnioglu,[4] Refik Kayali,[4] Eunju Kang,[1] Yeonmi Lee,[1] Tomonari Hayama,[1] Amy Koski,[1] Joseph Ney,[2] Rosa Castanon,[2] Rebecca Tippner-Hedges,[1] Riffat Ahmed,[1] Crystal Van Dyken,[1] Ying Li,[1] Susan Olson,[5] David Battaglia,[6] David M. Lee,[6] Diana H. Wu,[6] Paula Amato,[6] Don P. Wolf,[1] Joseph R. Ecker,[2,7,*] and Shoukhrat Mitalipov[1,4,9,*]
[1]Center for Embryonic Cell and Gene Therapy, Oregon Health & Science University, Portland, OR 97239, USA

nature Vol 465|6 May 2010|doi:10.1038/nature08958

Pronuclear transfer in human embryos to prevent transmission of mitochondrial DNA disease

Lyndsey Craven[1], Helen A. Tuppen[1], Gareth D. Greggains[3,4], Stephen J. Harbottle[3], Julie L. Murphy[1], Lynsey M. Cree[1], Alison P. Murdoch[2,5], Patrick F. Chinnery[1], Robert W. Taylor[1], Robert N. Lightowlers[1], Mary Herbert[3,4,5] & Douglass M. Turnbull[1,2,5]


LETTER doi:10.1038/nature18303

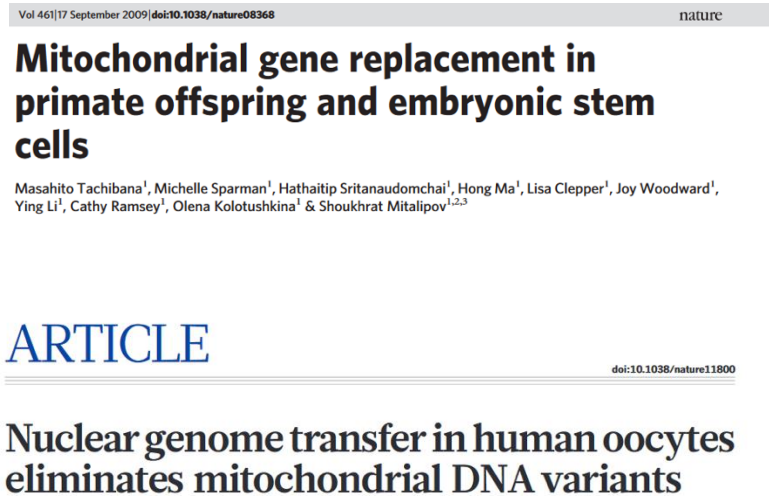
Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease

Louise A. Hyslop[1,2], Paul Blakeley[3], Lyndsey Craven[4], Jessica Richardson[1], Norah M. E. Fogarty[3], Elpida Fragouli[5], Mahdi Lamb[1], Sissy E. Wamaitha[3], Nilendran Prathalingam[1,2], Qi Zhang[1]†, Hannah O'Keefe[1], Yuko Takeda[1], Lucia Arizzi[1,2], Samer Alfarawati[5], Helen A. Tuppen[4], Laura Irving[4]†, Dimitrios Kalleas[1]†, Meenakshi Choudhary[2], Dagan Wells[6], Alison P. Murdoch[2], Douglass M. Turnbull[4], Kathy K. Niakan[3] & Mary Herbert[1,2]

LETTER doi:10.1038/nature20592

Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations

Eunju Kang[1,2]†, Jun Wu[3], Nuria Marti Gutierrez[1,2], Amy Koski[1,2], Rebecca Tippner-Hedges[1,2], Karen Agaronyan[4], Aida Platero-Luengo[3], Paloma Martinez-Redondo[3], Hong Ma[1,2], Yeonmi Lee[1,2]†, Tomonari Hayama[1,2], Crystal Van Dyken[1,2], Xinjian Wang[5], Shiyu Luo[5], Riffat Ahmed[1,2], Ying Li[1,2], Dongmei Ji[1,6], Refik Kayali[7], Cengiz Cinnioglu[7], Susan Olson[8], Jeffrey Jensen[9], David Battaglia[9], David Lee[9], Diana Wu[9], Taosheng Huang[5], Don P. Wolf[1,2], Dmitry Temiakov[4], Juan Carlos Izpisua Belmonte[3], Paula Amato[9] & Shoukhrat Mitalipov[1,2,9,10,11]


Vol 461|17 September 2009|doi:10.1038/nature08368 nature

Mitochondrial gene replacement in primate offspring and embryonic stem cells

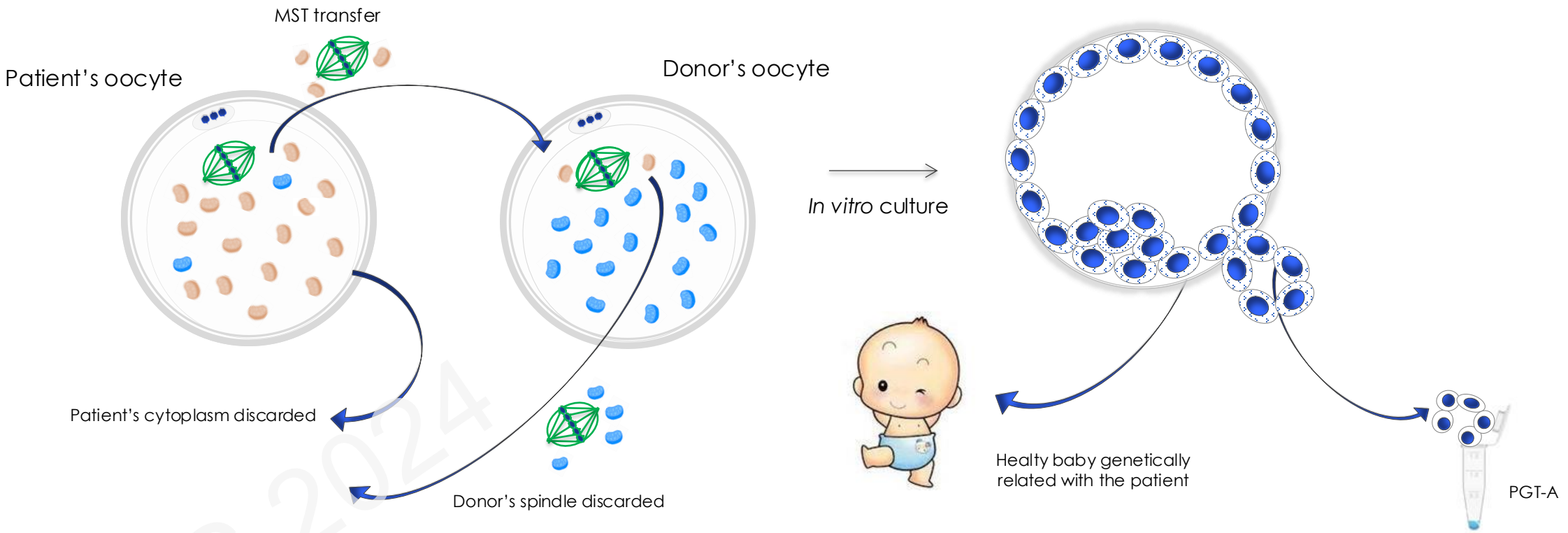
Masahito Tachibana[1], Michelle Sparman[1], Hathaitip Sritanaudomchai[1], Hong Ma[1], Lisa Clepper[1], Joy Woodward[1], Ying Li[1], Cathy Ramsey[1], Olena Kolotushkina[1] & Shoukhrat Mitalipov[1,2,3]

ARTICLE doi:10.1038/nature11800

Nuclear genome transfer in human oocytes eliminates mitochondrial DNA variants

Daniel Paull[1], Valentina Emmanuele[2], Keren A. Weiss[1], Nathan Treff[3], Latoya Stewart[1], Haiqing Hua[1,4], Matthew Zimmer[1], David J. Kahler[1], Robin S. Goland[4], Scott A. Noggle[1], Robert Prosser[5], Michio Hirano[2], Mark V. Sauer[5,6]* & Dieter Egli[1]*

Maternal spindle transfer (MST)



Technically very demanding | low mtDNA carryover | Manipulation of oocytes before fertilization | Easier to coordinate the spindle donor oocyte and the recipient cytoplast

Research Project

Proof of concept in the mouse model

eLife RESEARCH ARTICLE

Maternal spindle transfer overcomes embryo developmental arrest caused by ooplasmic defects in mice

Nuno Costa-Borges[1]*, Katharina Spath[2,3], Irene Miguel-Escalada[4], Enric Mestres[1], Rosa Balmaseda[5], Anna Serafín[5], Maria Garcia-Jiménez[1], Ivette Vanrell[1], Jesús González[5], Klaus Rink[1], Dagan Wells[2,3], Gloria Calderón[1]

[1]Embryotools, Parc Cientific de Barcelona, Barcelona, Spain; [2]Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom; [3]Juno Genetics, Winchester House, Oxford Science Park, Oxford, United Kingdom; [4]Genomics and Bioinformatics, Centre for Genomic Regulation, Barcelona, Spain; [5]PCB Animal Facility, Parc Cientific de Barcelona, Barcelona, Spain

- **MST feasible without impairing embryo development in both fresh and vitrified oocytes;**
- **Overcomes embryo development arrest in NZB oocytes;**
- **Low (2-3%) heteroplasmy levels in embryos and organs;**
- **MST healthy and fertile mice followed up to 5 generations (F5);**
- **No heteroplasmy detected after F2;**
- **Normal histological examinations;**

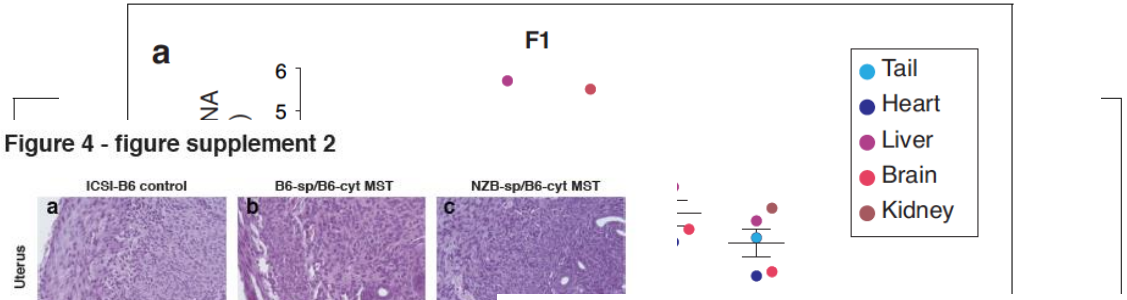


Figure 4 - figure supplement 2

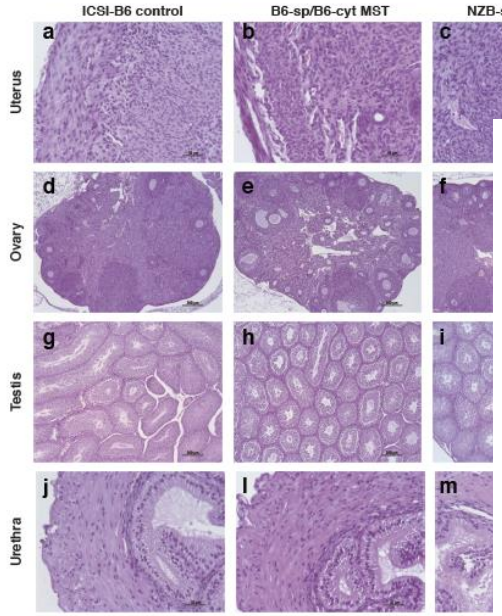


Figure 4-figure supplement 2. Hematoxylin and eosin (H&E) stained sect organs of adult mice generated from B6 ICSI control embryos, B6 recipr NZB-sp/B6-cyt MST embryos. Representative images from uterus (**a-c**), ova male urethra (**j-m**). All analyzed sections showed the typical morphology of a

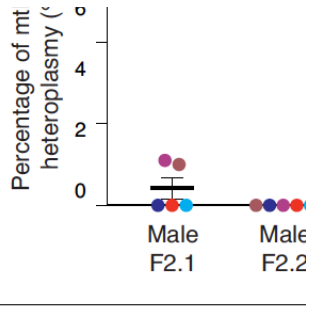


Figure 4 - figure supplement 1

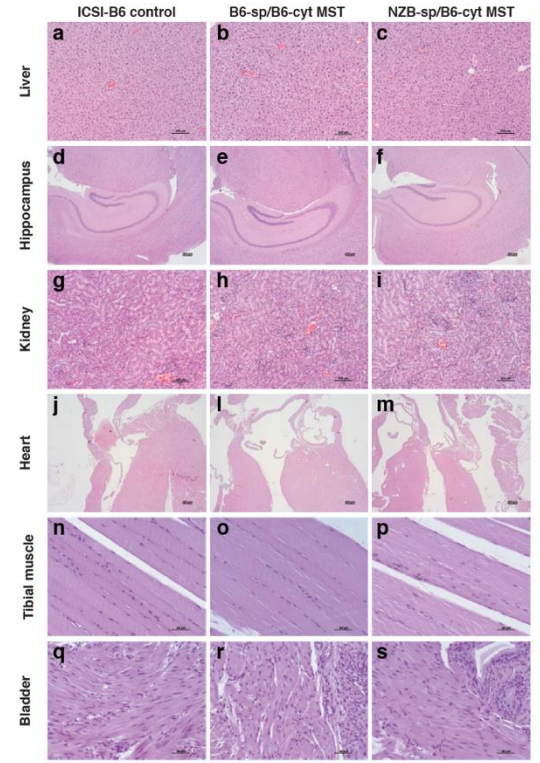


Figure 4-figure supplement 1. Hematoxylin and eosin (H&E) stained sections of adult mice generated from B6 ICSI control embryos, B6 reciprocal MST and NZB-sp/B6-cyt MST embryos. Representative images from liver (**a-c**), hippocampus (**d-f**), kidney cortex (**g-i**), heart (**j-m**), skeletal muscle from the tibia (**n-p**) and smooth muscle from the bladder (**q-s**). All analyzed sections showed the typical morphology of a healthy tissue.

Figure 4. Analysis of mitochondrial heteroplasmy levels in adult mice born by MST. (**a**) Mitochondrial heteroplasmy levels in several organs

Costa-Borges *et al.* eLife 2020;9:e48591. DOI: https://doi.org/10.7554/eLife.48591

MST translational project

Pre-clinical validation in human donor oocytes

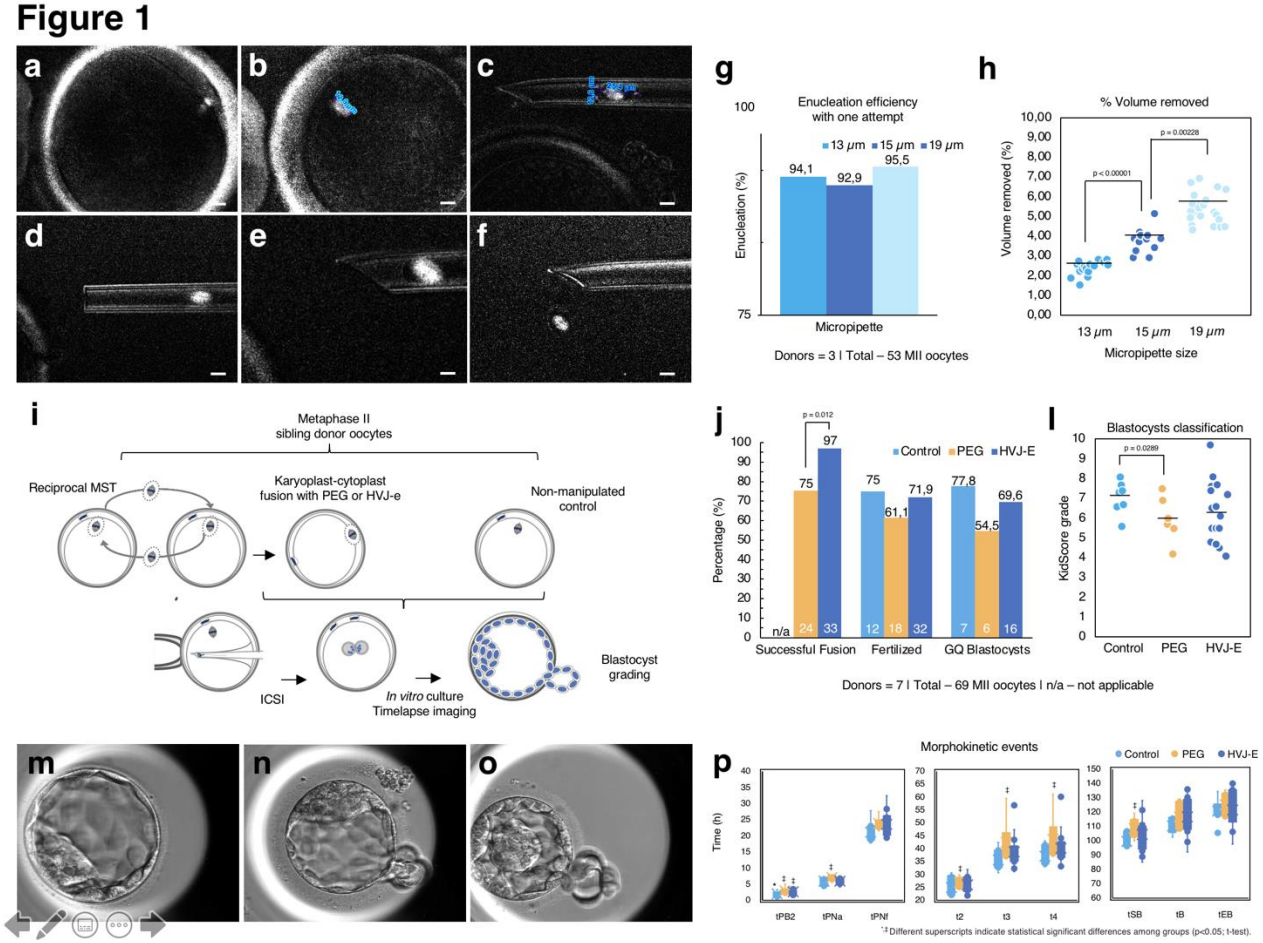
CYTOPLASM REPLACEMENT BY SPINDLE TRANSFER DEMONSTRATES ENHANCED EMBRYO DEVELOPMENT WITHOUT COMPROMISING EUPLOIDY RATES: PRE-CLINICAL STUDY WITH DONOR OOCYTES.

N. Costa-Borges,[a] K. Spath,[b] E. Nikitos,[c] L. Ribustello,[d] I. Miguel-Escalada,[a] K. Rink,[a] K. Kostaras,[c] P. Psathas,[c] D. Wells,[e] G. Calderon.[a] [a]Embryotools, Barcelona, Spain; [b]CooperGenomics, Oxford, United Kingdom; [c]IOLIFE, Athens, Greece; [d]CooperGenomics, Livingston,

CONCLUSIONS: This study shows that cytoplasm replacement by ST can enhance the potential of developmentally compromised oocytes to develop up to the blastocyst stage without compromising euploidy rates. This opens up the possibility of providing new treatment options for patients with certain forms of infertility refractory to current clinical strategies.

Supported by: This study was financially supported by the Institute of Life (Athens, Greece).

- **Optimization of the enucleation and fusion protocols in human oocytes donated for research;**
- **Enucleation and fusion rates over 90%;**
- **Euploidy and developmental competence comparable to controls;**
- **Feasible with fresh or vitrified oocytes, but better results achieved with fresh cytoplasts;**
- **mtDNA carryover <1% (n=30);**

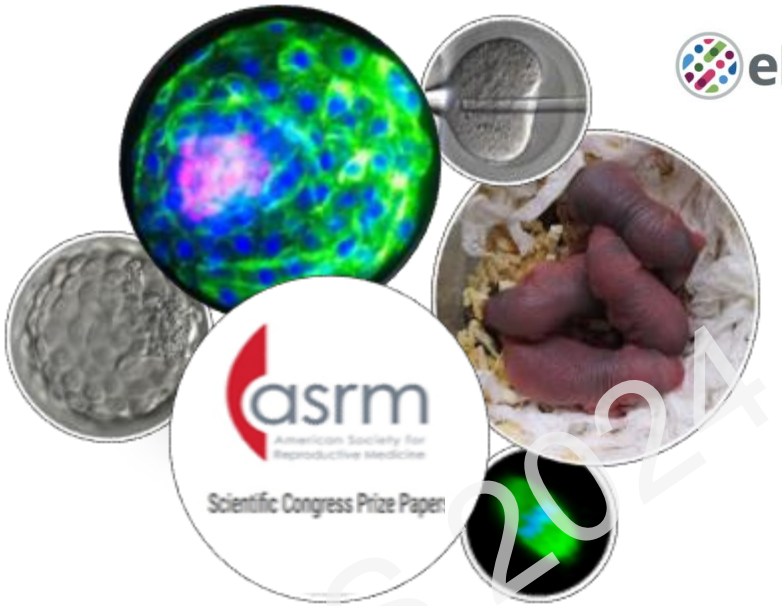


Costa-Borges et al., Fertil&Steril, Vol. 110, Supplement, Sept 2018

MST translational project

Proof of concept in the mouse model

Pre-clinical validation in human donor oocytes



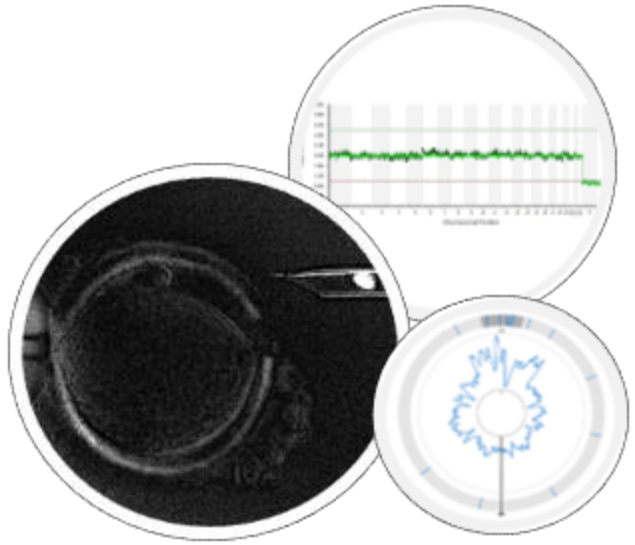
eLife

RESEARCH ARTICLE

Maternal spindle transfer overcomes embryo developmental arrest caused by ooplasmic defects in mice

Nuno Costa-Borges[1]*, Katharina Spath[2,3], Irene Miguel-Escalada[4], Enric Mestres[1], Rosa Balmaseda[5], Anna Serafín[5], Maria Garcia-Jiménez[1], Ivette Vanrell[1], Jesús González[5], Klaus Rink[1], Dagan Wells[2,3], Gloria Calderón[1]

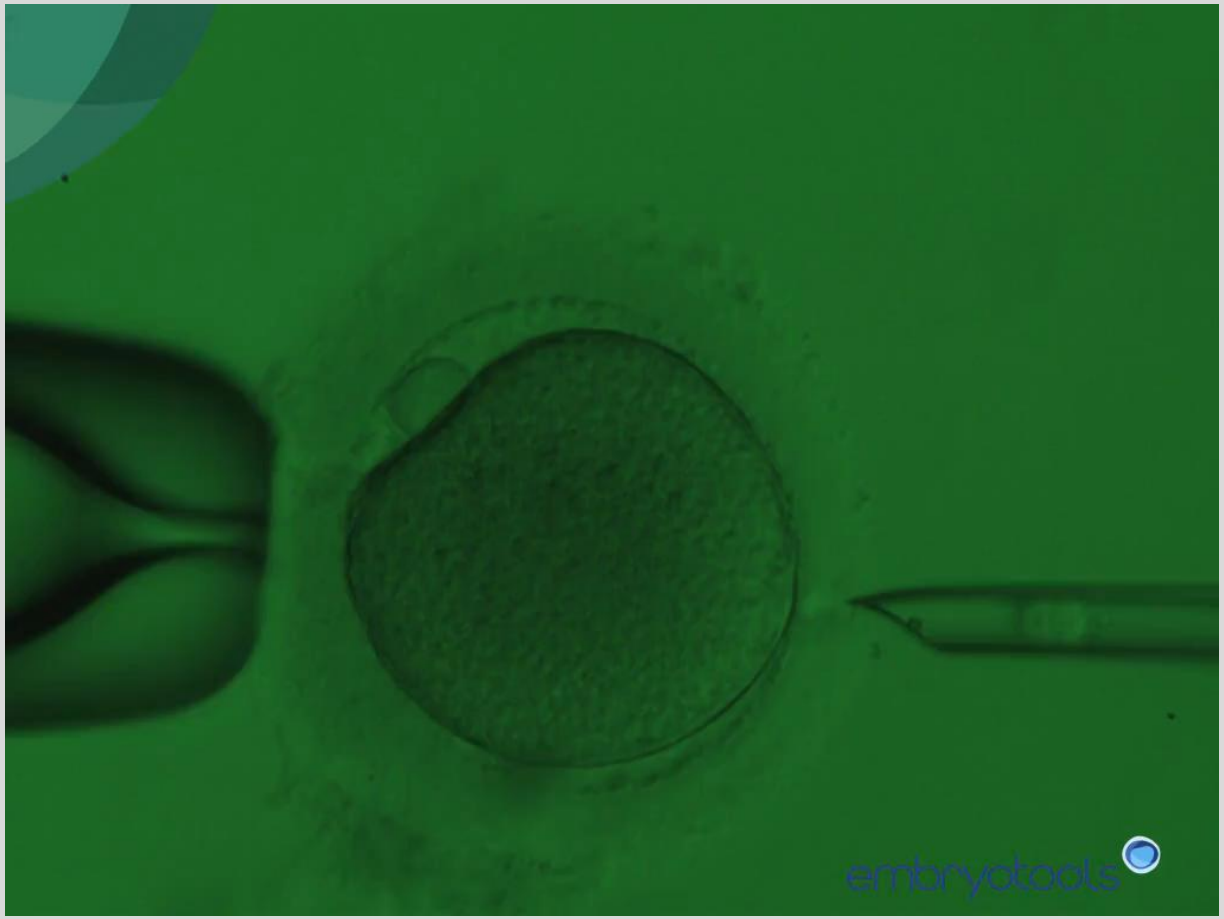
[1]Embryotools, Parc Cientific de Barcelona, Barcelona, Spain; [2]Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom; [3]Juno Genetics, Winchester House, Oxford Science Park, Oxford, United Kingdom; [4]Genomics and Bioinformatics, Centre for Genomic Regulation, Barcelona, Spain; [5]PCB Animal Facility, Parc Cientific de Barcelona, Barcelona, Spain



The studies in the mouse and in human oocytes donated for research allowed to confirmed the technical feasibility of MST and provided reassurance data concerning safety.

Costa-Borges et al., Fertil&Steril, Vol 110, No. 4, Supplement, September 2018 | Costa-Borges et al., Fertil&Steril. Vol 112, No. 3, Supplement, September 2019 | Costa-Borges et al., 2020. Elife, 9:e48591.

Enucleation and reconstruction techniques



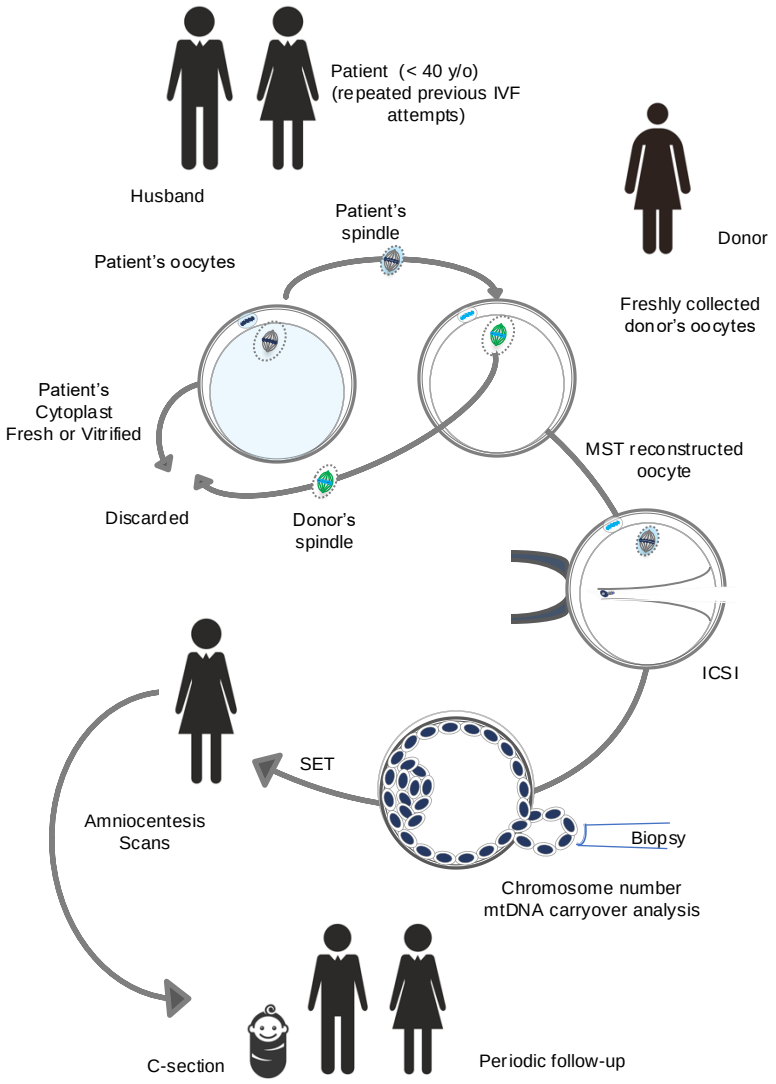
Pilot trial | Design

First pilot study of maternal spindle transfer for the treatment of repeated in vitro fertilization failures in couples with idiopathic infertility

Nuno Costa-Borges, Ph.D.,[a,1] Eros Nikitos, M.Sc.[b,1] Katharina Späth, Ph.D.[c,1] Irene Miguel-Escalada, Ph.D.[a]* Hong Ma, Ph.D.,[d] Klaus Rink, Ph.D.,[a] Clement Coudereau, Ph.D.,[c] Hayley Darby,[d] Amy Koski, M.Sc.,[d] Crystal Van Dyken, Ph.D.,[d] Enric Mestres, Ph.D.,[a] Evmorfia Papakyriakou, M.Sc.,[b] Dominique De Ziegler, M.D.,[b] George Kontopoulos, M.D.,[b] Themistoklis Mantzavinos, M.D.,[b] Ioannis Vasilopoulos, M.D.,[b] Stylianos Grigorakis, M.D.,[b] Thomas Prokopakis, M.D.,[b] Konstantinos Dimitropoulos, M.D.,[b] Panagiotis Polyzos, M.D.,[b] Nikolas Vlachos, M.D.,[b] Konstantinos Kostaras, M.D.,[b] Shoukhrat Mitalipov, Ph.D.,[d] Gloria Calderón, Ph.D.,[a] Panagiotis Psathas, M.D.,[b] and Dagan Wells, Ph.D.[c,e]

[a] Embryotools, Parc Cientific de Barcelona, Spain; [b] Institute of Life, IASO Maternity Hospital, Athens, Greece; [c] Juno Genetics, Winchester House, Oxford Science Park, Oxford, UK; [d] Center for Embryonic Cell and Gene Therapy, Oregon Health & Science University, Oregon; and [e] University of Oxford, Nuffield Department of Women's and Reproductive Health, Winchester House, Oxford, UK

Figure 1



Costa-Borges et al., 2023

Pilot trial | results

No. of patients recruited: 25 | **Average age:** 37.1 (min 32 and max 40)
Average no. of previous failed IVF cycles: 6.4 (min 3 and max 11, total = 159)

Mean no. of MII oocytes used MST/patient: 4.4 (min 1 and max 10, no. total = 123)

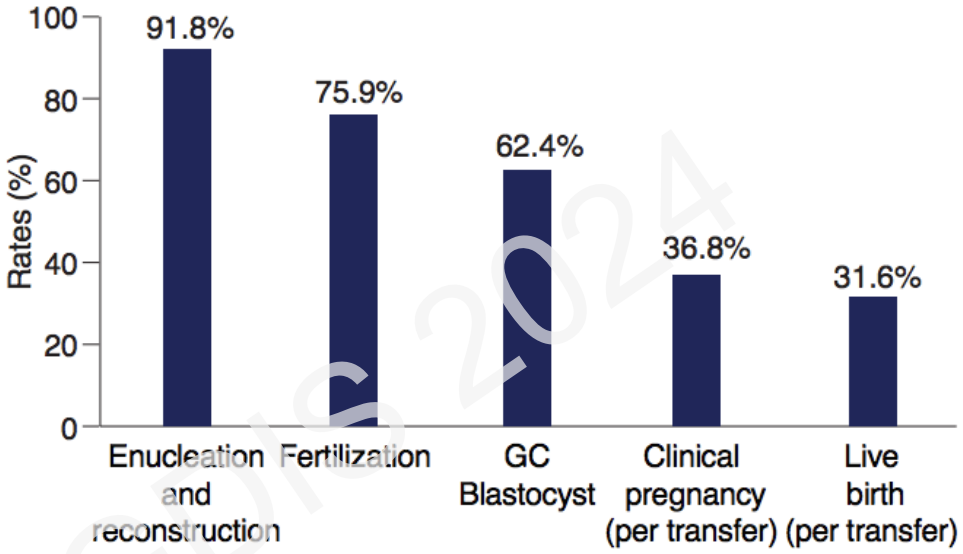
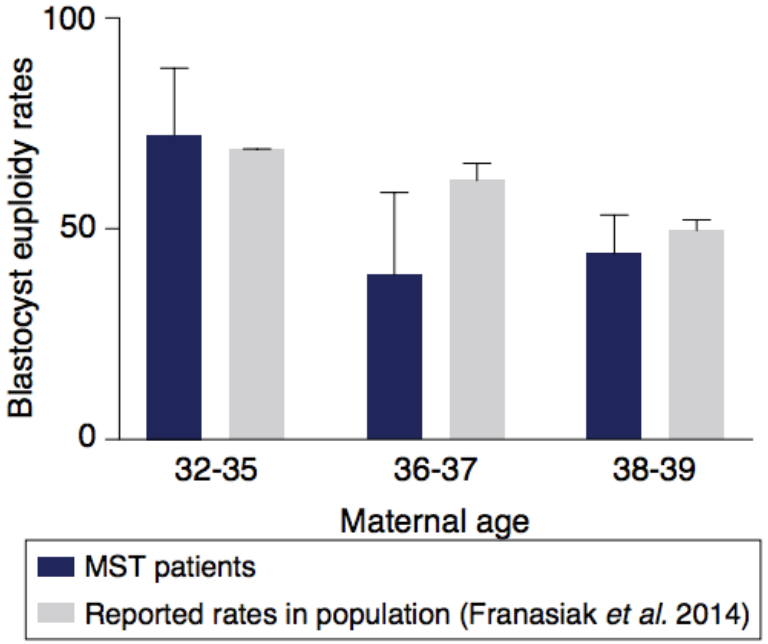


Figure 2. Summary of MST pilot study outcomes



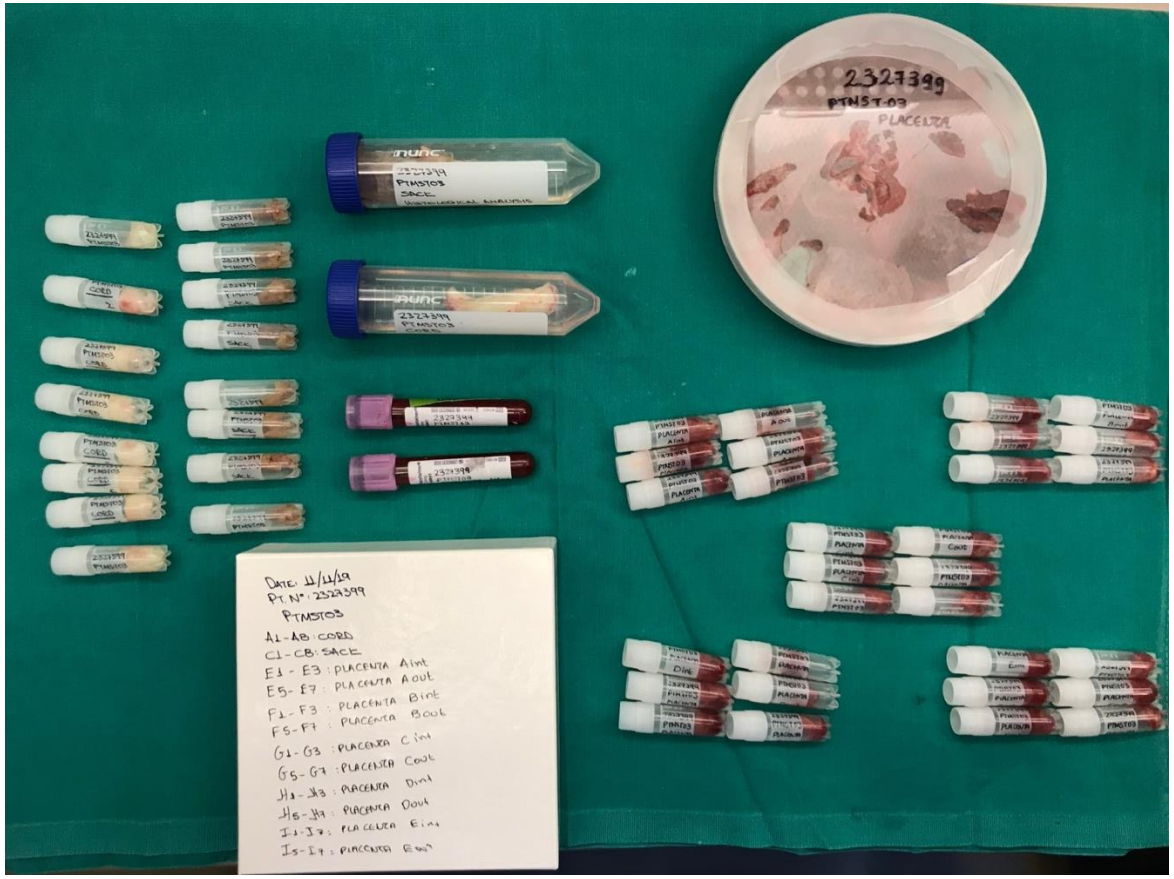
Summary

- No. of patients with at least 1x GQ blastocyst**: 21/25**
- No. of patients with at least 1x GQ euploid blastocyst: **16/25**
- No. of patients with all blastocysts aneuploid: **5/25**
- No. of patients w/o fertilized oocytes or blastocyst development: **4/25**

Costa-Borges et al., 2023

Pilot trial | follow-up

Molecular analysis confirmed all babies were resultant from MST independently by two different labs (Dr. Dagan Wells' and Dr. Mitalipov's Oregon).
All have been followed-up and are healthy.



Pilot trial | follow-up

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All have been followed-up and are healthy.

Current research

Accurate diagnostic tools for oocyte quality assessment are lacking.

Novel light-based microscopy approaches have been proposed to classify oocytes based on their metabolic profile.

Metabolites critical for embryo development (e.g., NADH, FAD, retinol, retinoic acid, flavins) present auto-fluorescence when excited at specific wavelengths.

Hyperspectral imaging allows to collect non-invasively metabolic information from live cells based on intrinsic autofluorescence signals.

IBEC
Institute for Bioengineering of Catalonia

Institutional news July 20, 2022

IBEC researchers are part of the European ATTRACT Project to develop a diagnostic device to improve embryo selection for in vitro fertilization procedures

Bioengineering in reproductive health

European Projects

HSMe-ImPredict - Development of non-invasive imaging methodology for improving embryo implantation prediction, via hyper-spectral metabolic profiling (2022-2024)	Marie Curie Individual Fellowship	Samuel Ojosnegros

National projects

HYSPLANT - Selección de embriones para fecundación in vitro: predicción del éxito de implantación mediante clasificación metabólica de embriones (2020-2023)	MINECO Retos investigación: Proyectos I+D	Samuel Ojosnegros
Prediction of implantation success by hyperspectral metabolic profiling of human embryos obtained by in vitro fertilization (2020-2022)	AGAUR Beatriu de Pinós 2018	Samuel Ojosnegros

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Head of Bioengineering in Reproductive Health

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Researcher profile

Current research

Institute for Bioengineering of Catalonia

PI: Samuel Ojosnegros

O-208 Maternal spindle transfer restores the developmental competence of in vitro aged oocytes with diminished metabolic activity identified by hyperspectral imaging FREE

N Costa-Borges, A Parra, E Mestres, M Acacio, C Castello, A Seriola, S Ojosnegros, G Calderón

Human Reproduction, Volume 38, Issue Supplement_1, June 2023, dead093.254,
https://doi.org/10.1093/humrep/dead093.254
Published: 22 June 2023

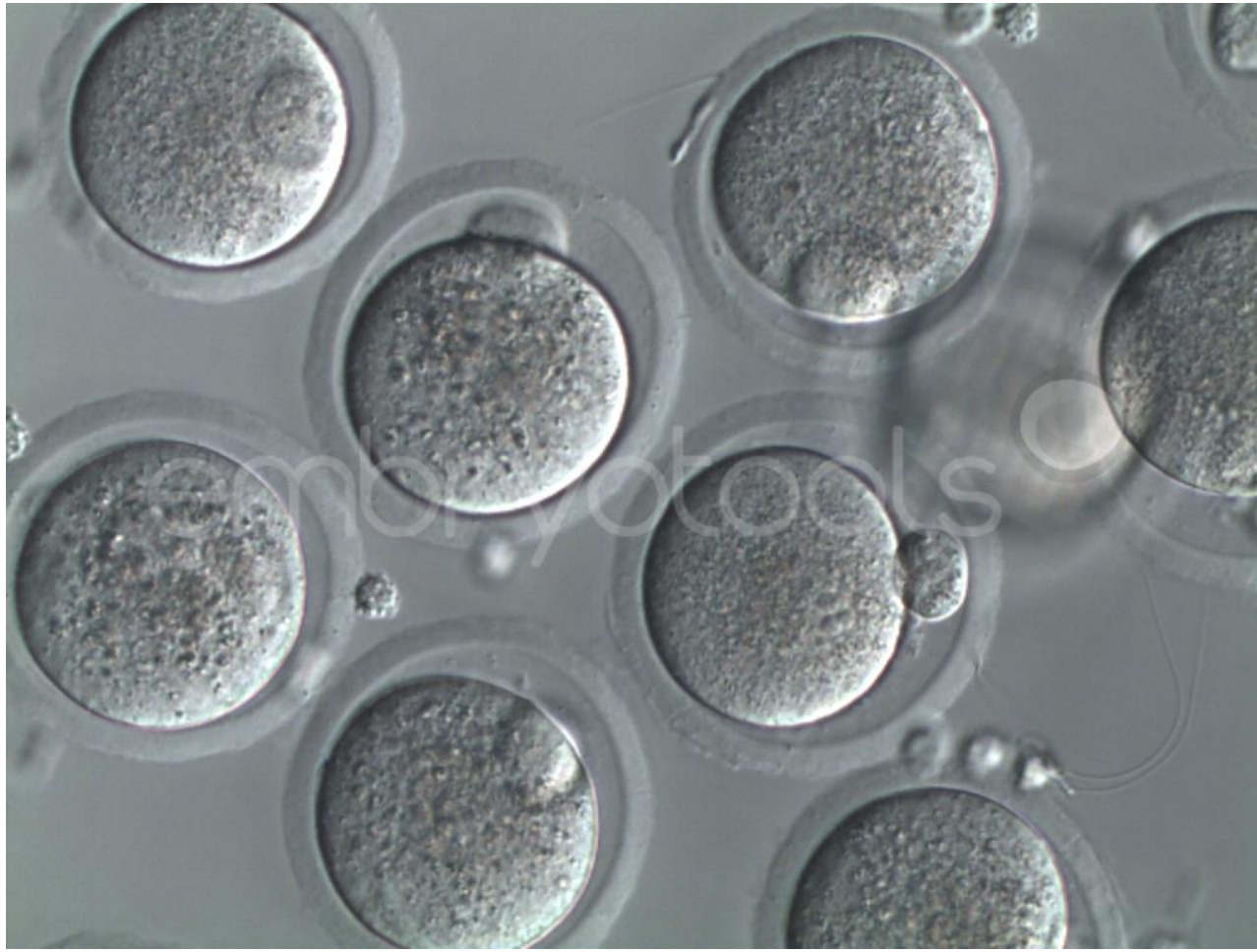
Fertility and Sterility asrm

ABSTRACT | VOLUME 120, ISSUE 4, SUPPLEMENT , E215, OCTOBER 2023

MATERNAL SPINDLE TRANSFER RESTORES THE EMBRYO DEVELOPMENTAL COMPETENCE OF POOR-QUALITY OOCYTES IDENTIFIED NON-INVASIVELY BY HYPERSPECTRAL IMAGING: PROOF OF CONCEPT IN THE MOUSE MODEL

Nuno Costa-Borges, PhD • Enric Mestres, PhD • Mònica Acacio, MSc • ... Anna Seriola, PhD • Samuel Ojosnegros, PhD • Gloria Calderon, PhD • Show all authors

DOI: https://doi.org/10.1016/j.fertnstert.2023.08.975 • Check for updates



Study question

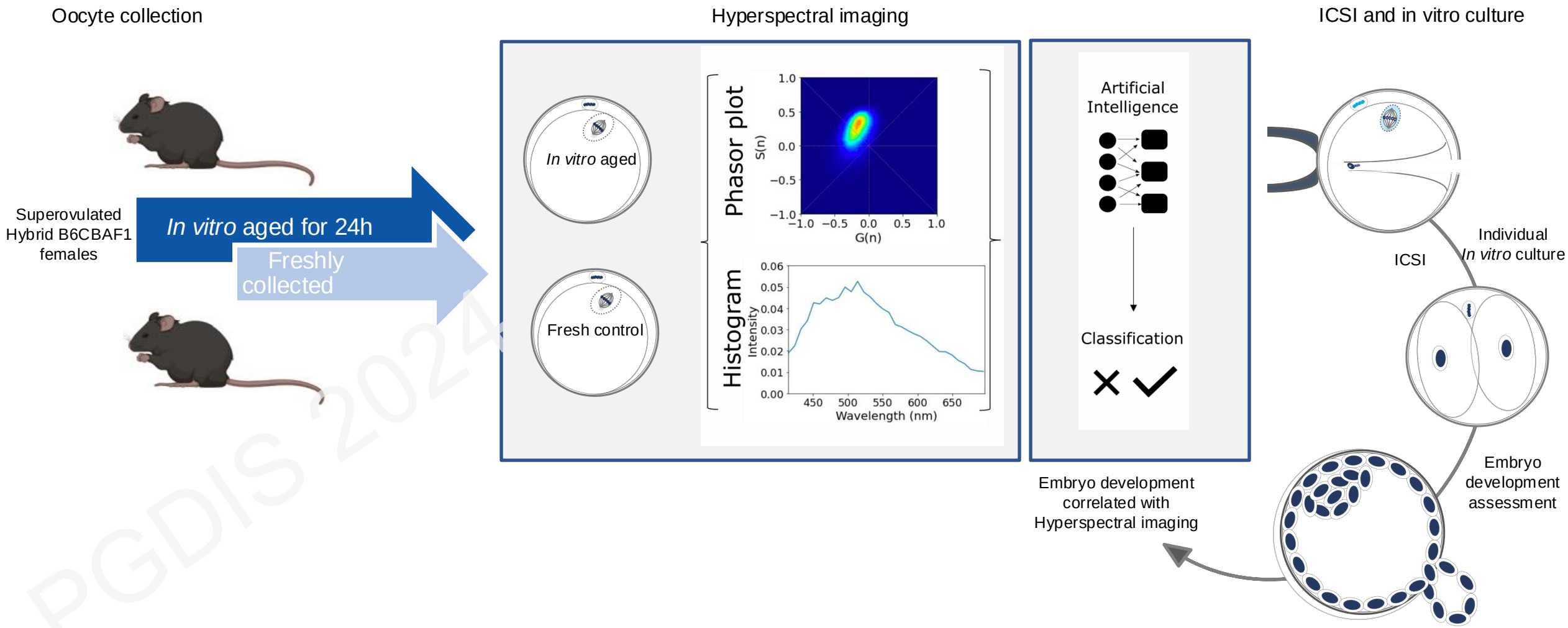
1. Can hyperspectral imaging identify among a co-hort of morphologically identical oocytes those with altered metabolic activity?

2. Can the developmental competence of poor-quality oocytes identified by hyperspectral imaging be restored after maternal spindle transfer?

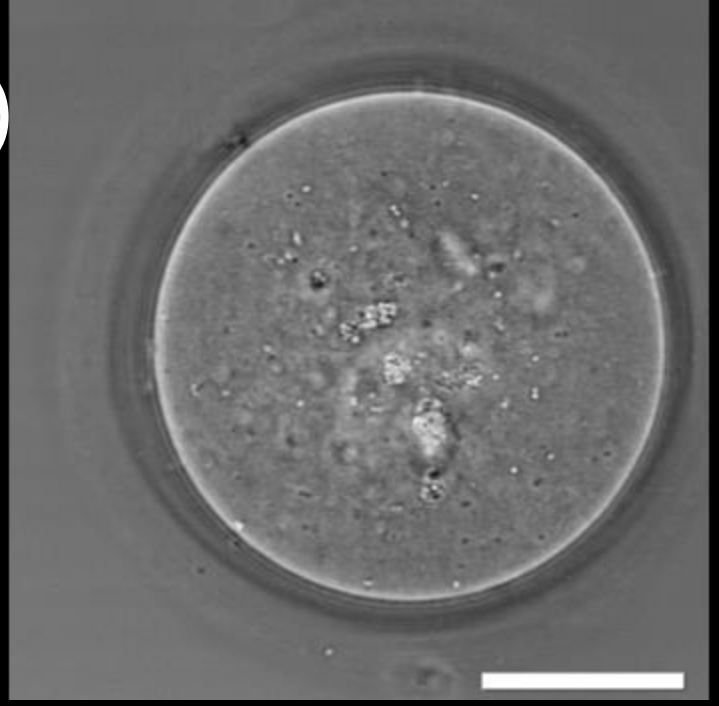
Study design (I)

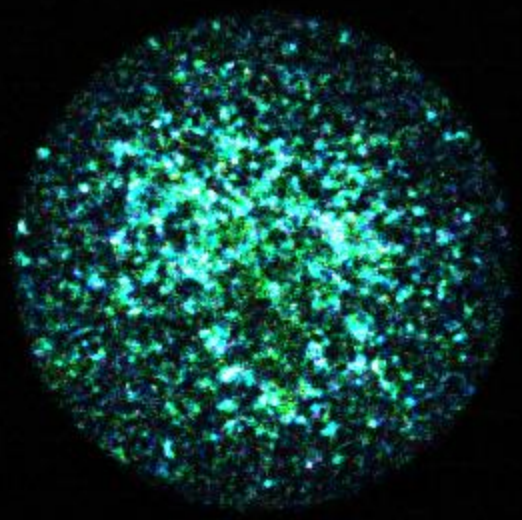
IBEC
Institute for Bioengineering of Catalonia

PI: Samuel Ojosnegros

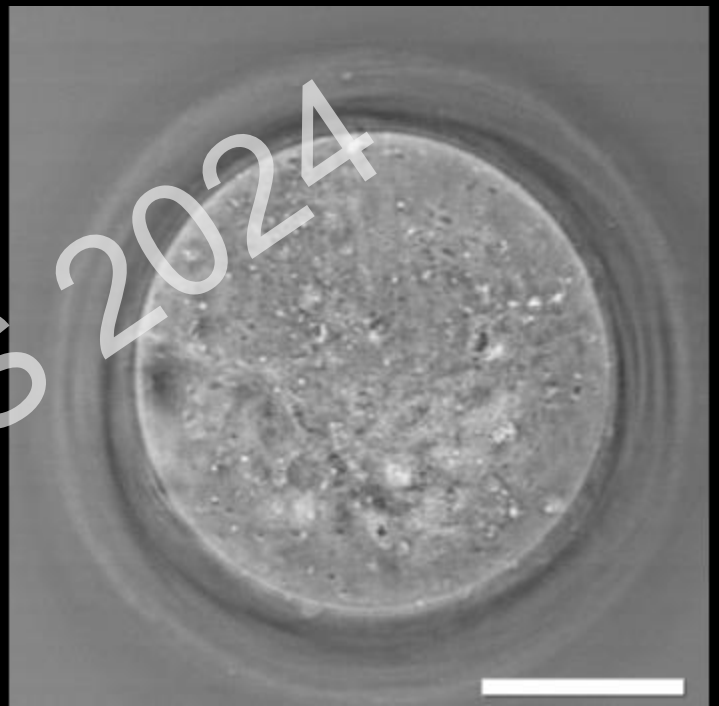


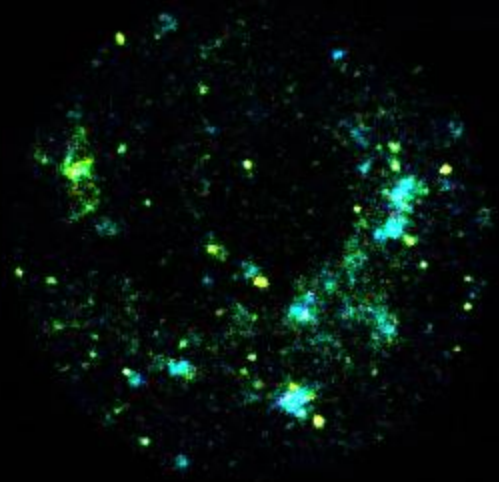
Results (I)





Fresh controls





in-vitro aged oocytes

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PI: Samuel Ojosnegros

Results (I)

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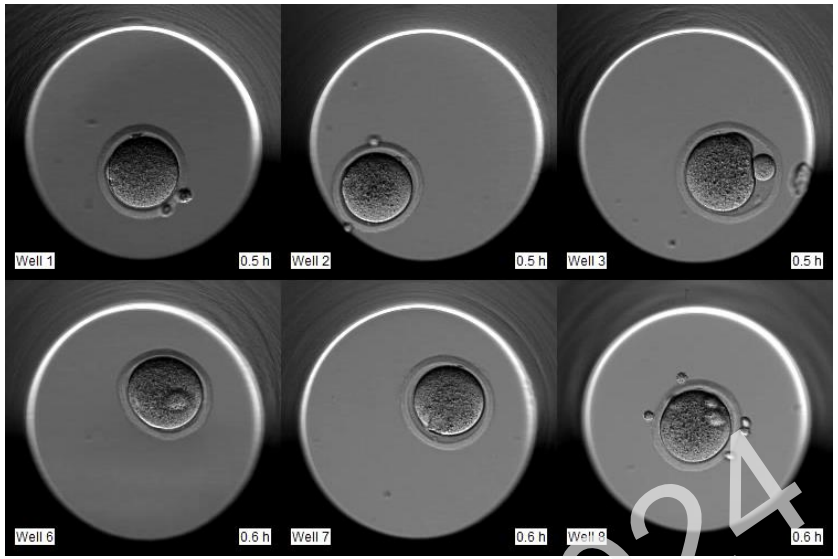

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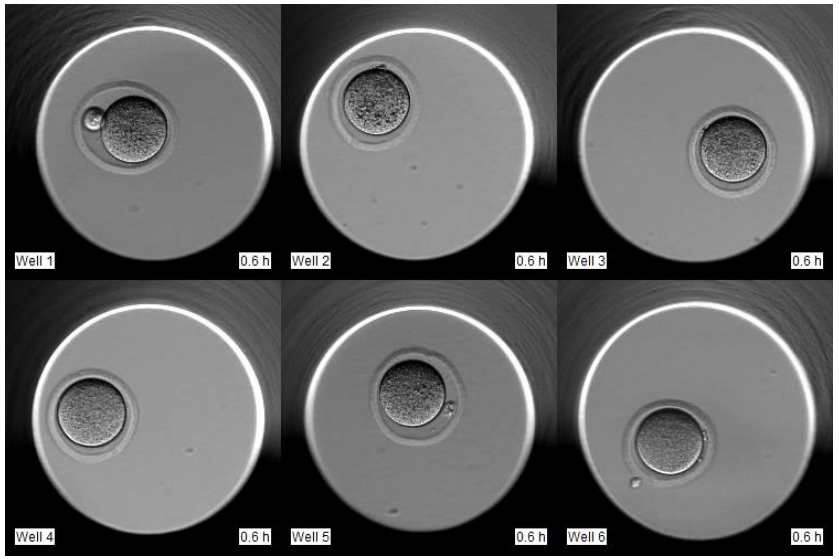
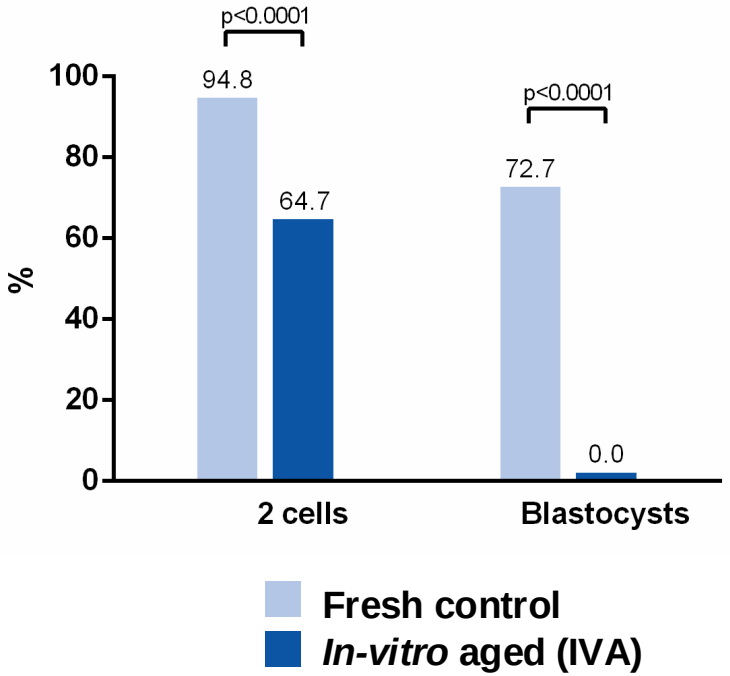


In-vitro aged (IVA)



Embryo development severely compromised in the *in vitro* aged (IVA) group with no blastocyst formation.

Study design (II)

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Oocyte collection

Supervoulated Hybrid B6CBAF1 females

In vitro aged for 24h

Freshly collected

MST *in vitro* aged spindle /fresh cytoplast

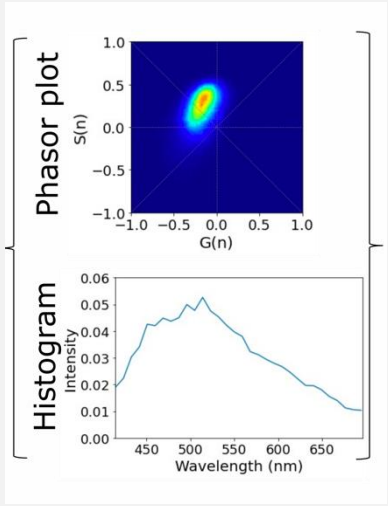
Maternal spindle transfer

In vitro aged

Fresh control

MST

Hyperspectral imaging



ICSI and in vitro culture

ICSI

Individual *In vitro* culture

Embryo development assessment

Embryo transfers

Results (II)

embryotools

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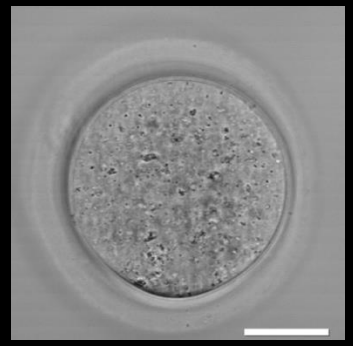
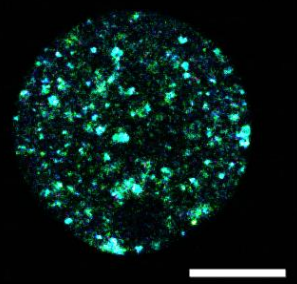
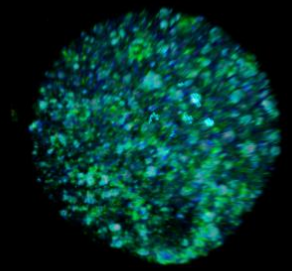
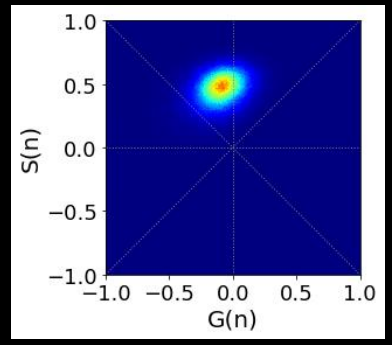
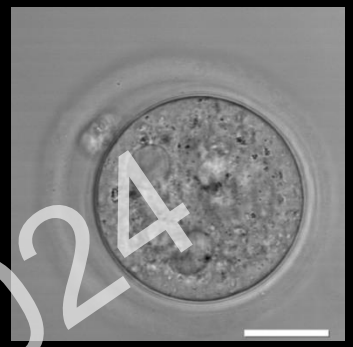
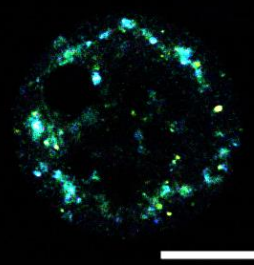
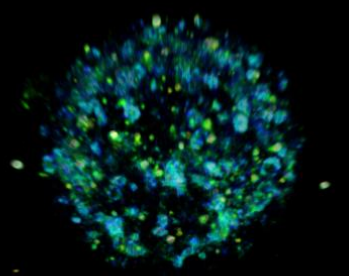
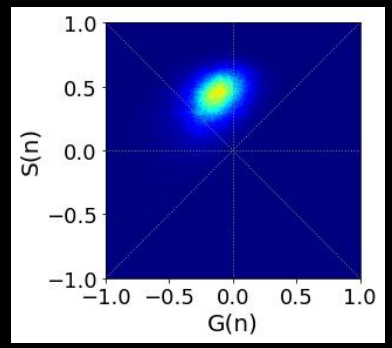
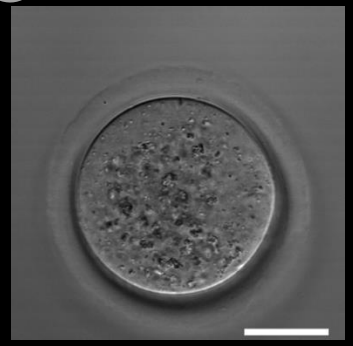
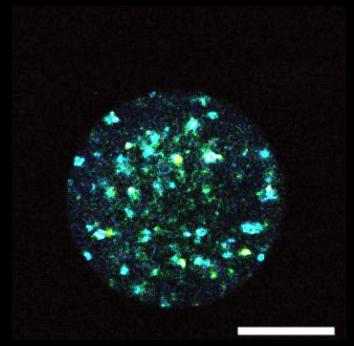
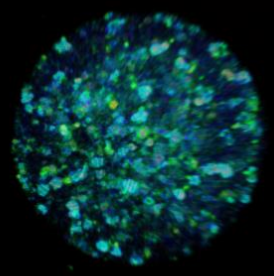
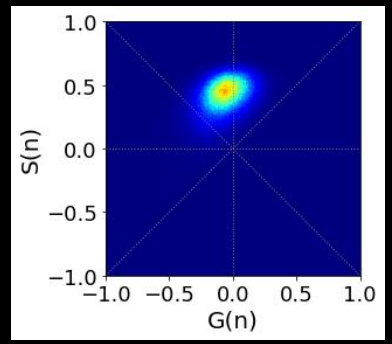
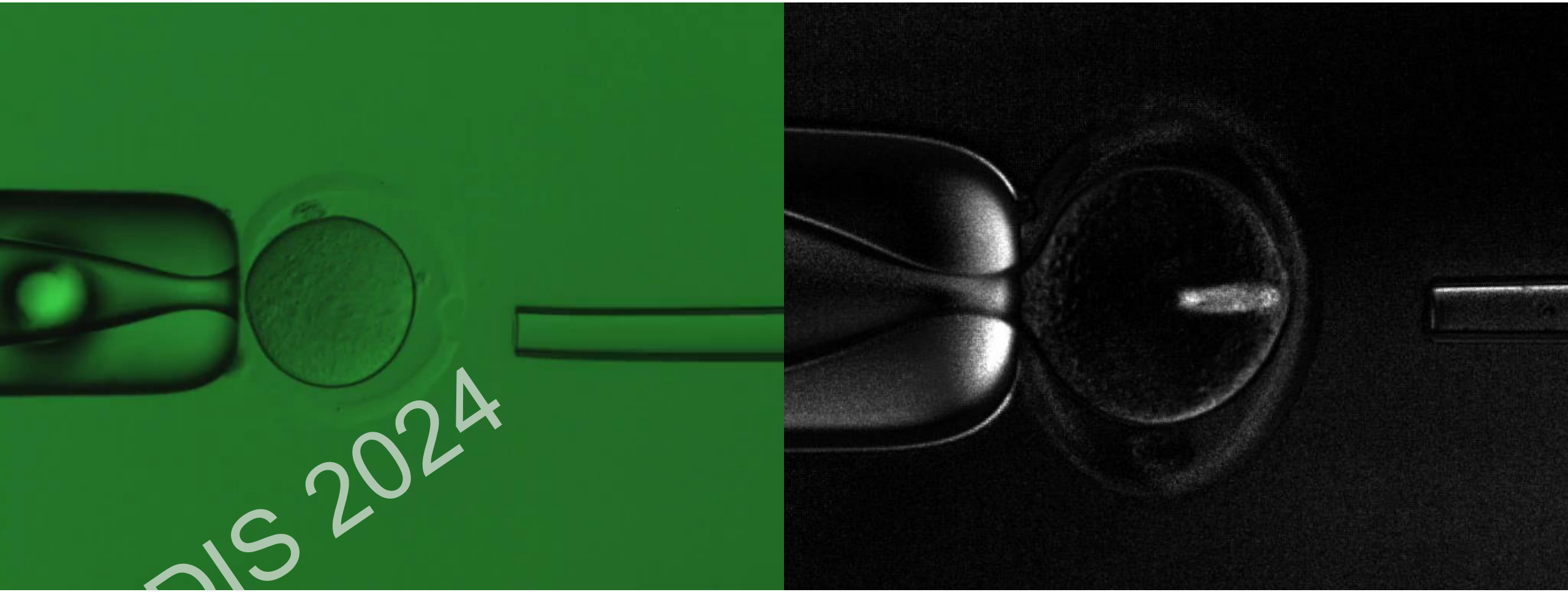
PI: Samuel Ojosnegros

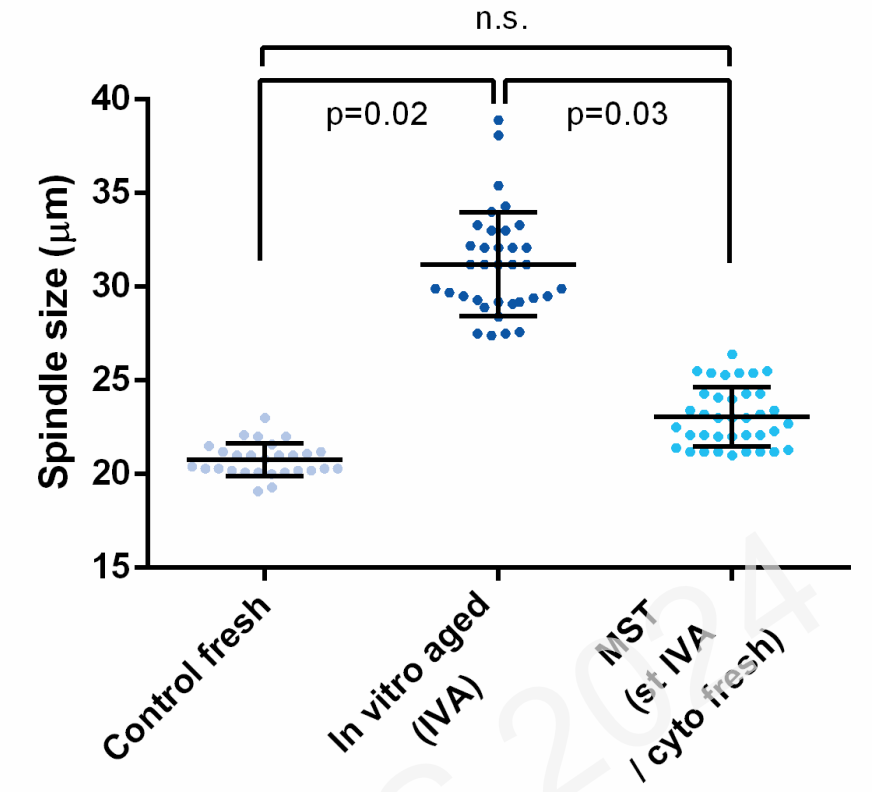
	Brightfield image	Z slide view	3D view	Phasor plot
Fresh control				
In-vitro aged (IVA)				
MST *IVA*/fresh cyto				

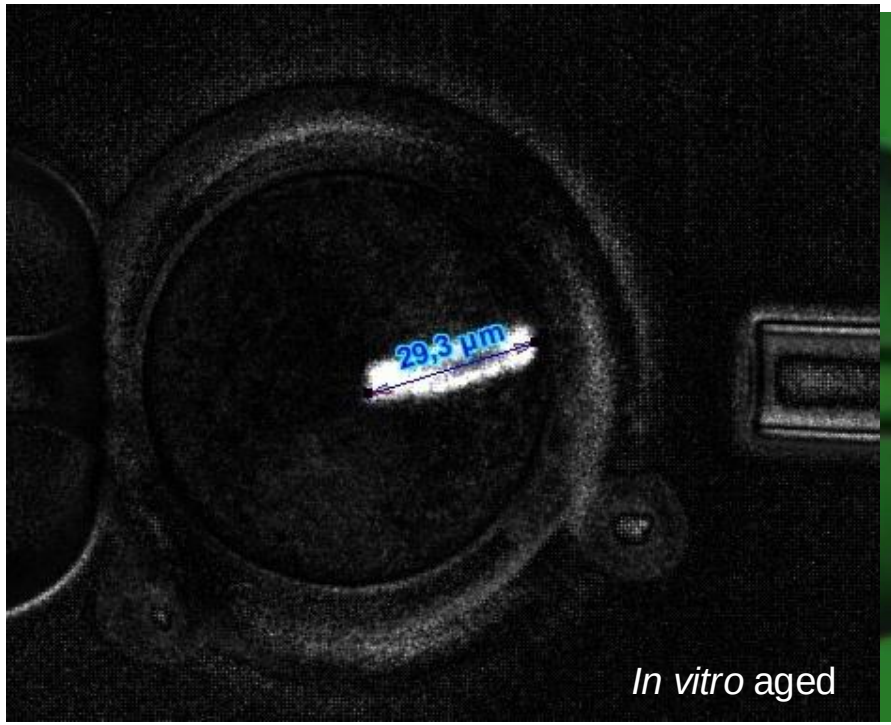
Results (II)

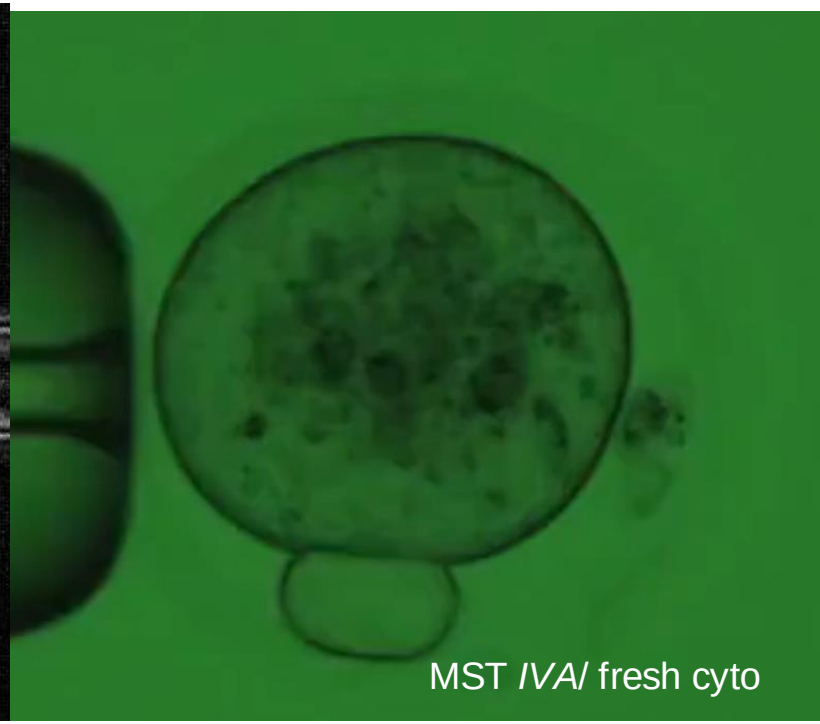


Abnormal spindles observed in 100% of the *in vitro* aged oocytes.

Results (II)

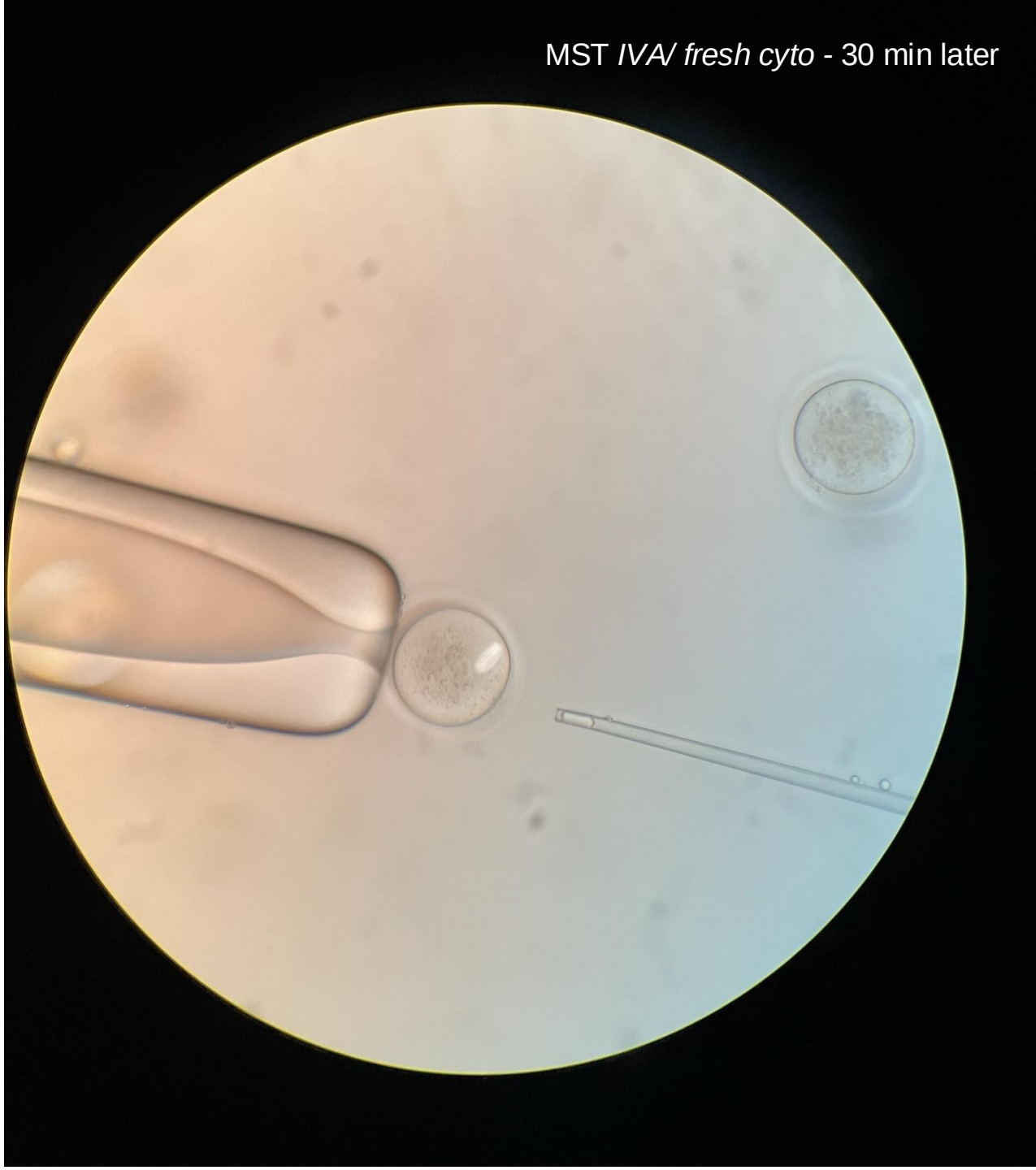




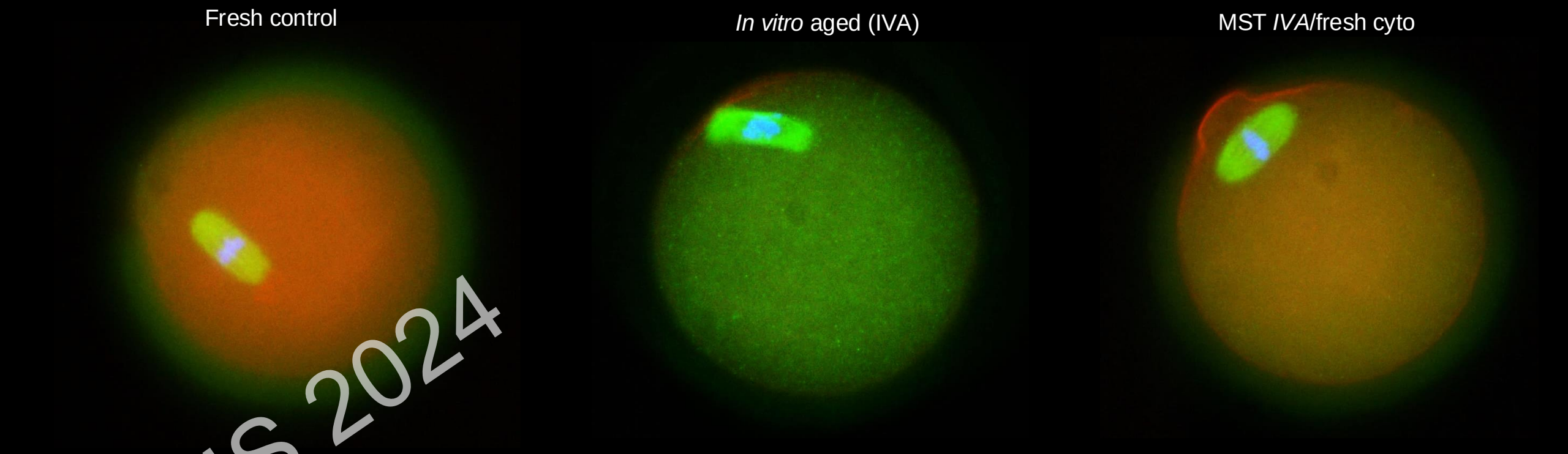


In-vitro aged oocytes show abnormally elongated and oversized spindles, which are restored to a normal barrel shape within 30 min after MST.


MST *IVA/ fresh cyto*
PGDIS 2024


MST *IVA/ fresh cyto* - 30 min later

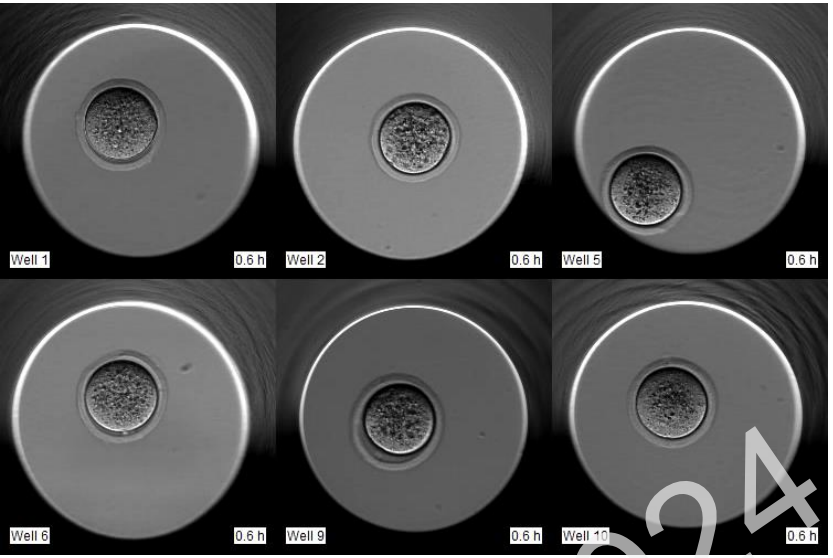
Results (II)



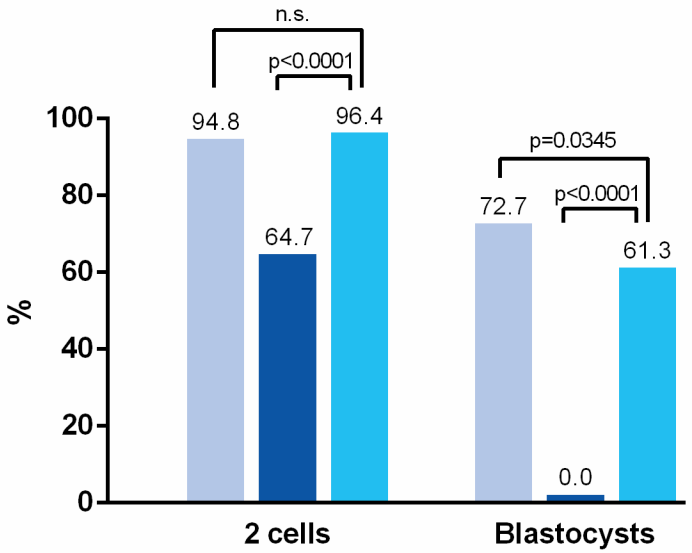
In-vitro aged (IVA) oocytes presented misaligned chromosomes, whereas the control fresh and MST groups showed spindles with a normal barrel shape and chromosomes aligned in a metaphase plate.

Results (II)

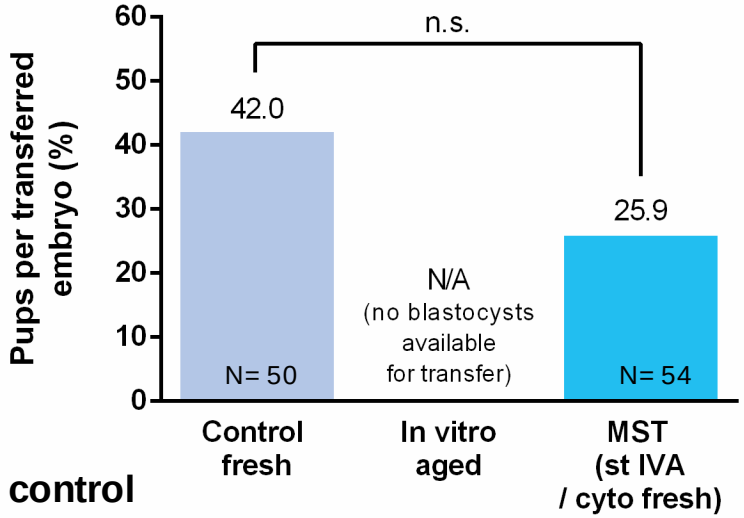
IVA/fresh-cyto



In vitro development



In vivo development



Enhanced embryo developmental competence in the MST IVA/fresh cyto group, in terms of blastocyst and full-term developmental rates.

Conclusions

- MST does not adversely affect the spindle apparatus, early embryonic development or euploidy rates.
- MST has the potential to rescue embryonic development from poor-quality oocytes.
- First pilot trial indicates that MST derived embryos can implant and sustain a healthy pregnancy to term.
- All MST children born so far appear to be healthy, but we need long-term follow-up.
- More carefully controlled clinical trials are needed to provide more insights into the efficacy and safety of the MST for clinical indications.
- MST can also be advantageous for donors – reduced psychological or/and anonymity concerns – as resultant children would not be genetically related to them.
- Hyperspectral imaging coupled with MST can represent a valuable strategy to identify and restore the developmental competence of oocytes with metabolic defects, paving the way for personalized IVF techniques.

Multidisciplinary-team work

embryotools

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Unió Europea
Fons Europeu
de Desenvolupament Regional

This study was partially financed by the Acció-Generalitat de Catalunya and the European Regional Development funds (ERDF) Ref. RD 15-1-0011, Embryotools and the Institute of Life.

Thank you for your attention

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