Advancing Embryo Selection: Combined DNA and RNA Analysis in PGT

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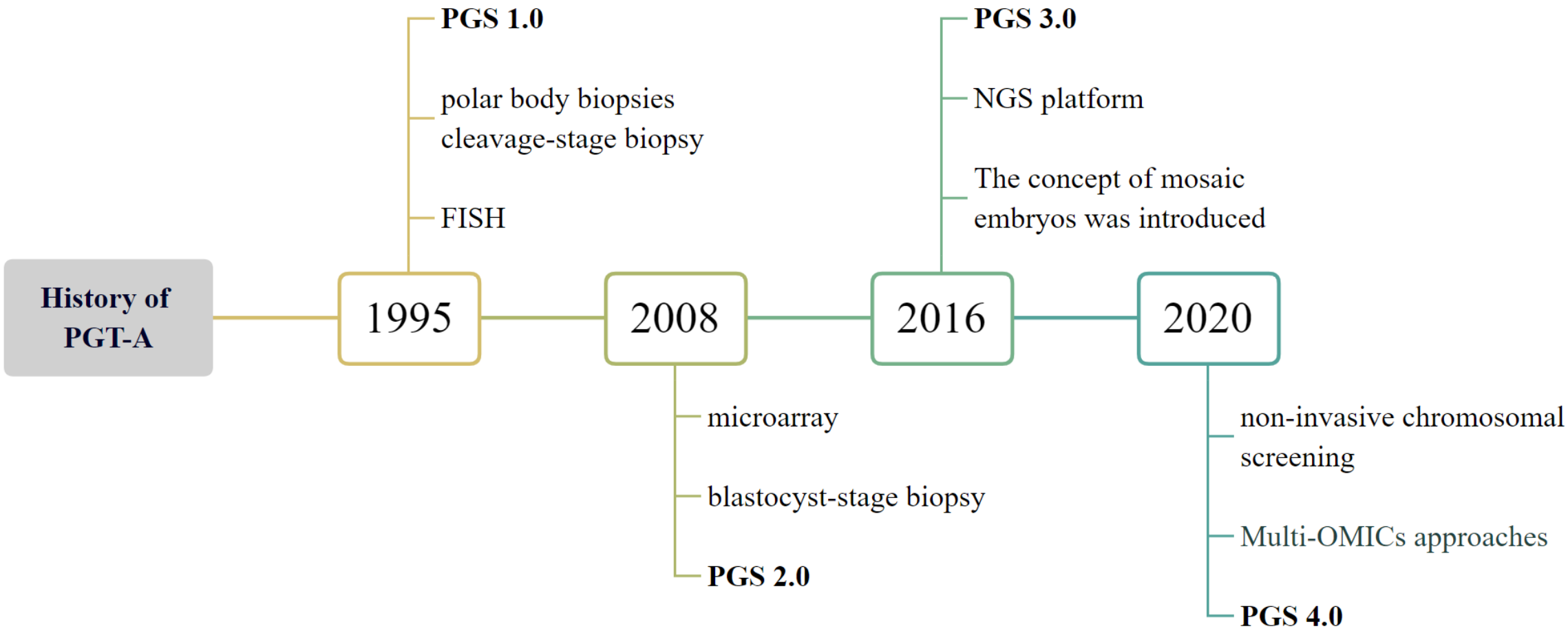
of Billions

Disclosure

- Dr. Taoli Ding
- Full-time employee, R&D project manager of Yikon Genomics

Thirty years development of PGT-A



Niederberger C, Pellicer A, Cohen J, et al. Forty years of IVF. Fertil Steril. 2018;110(2):185-324.e5.
Takeuchi K. Pre-implantation genetic testing: Past, present, future. Reprod Med Biol. 2020;20(1):27-40.

Current challenges faced by PGT-A

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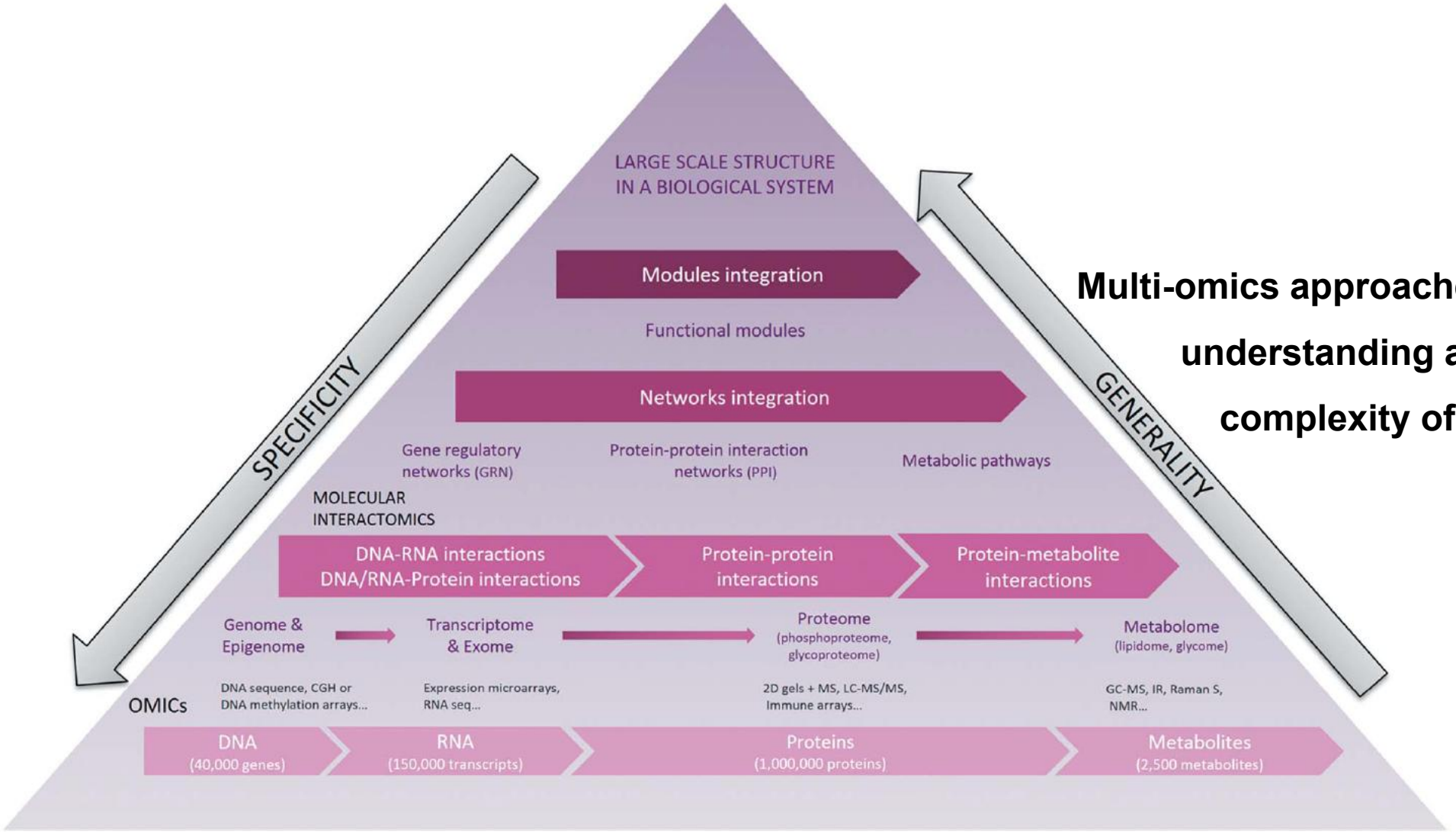

Multi-omics approaches are necessary in understanding and deciphering the complexity of biological systems

Hernández-Vargas P, et al. Identifying biomarkers for predicting successful embryo implantation: applying single to multi-OMICs to improve reproductive outcomes. Hum Reprod Update. 2020;26(2):264-301.

SCIENTIFIC REPORTS

OPEN

Human blastocysts of normal and abnormal karyotypes display distinct transcriptome profiles

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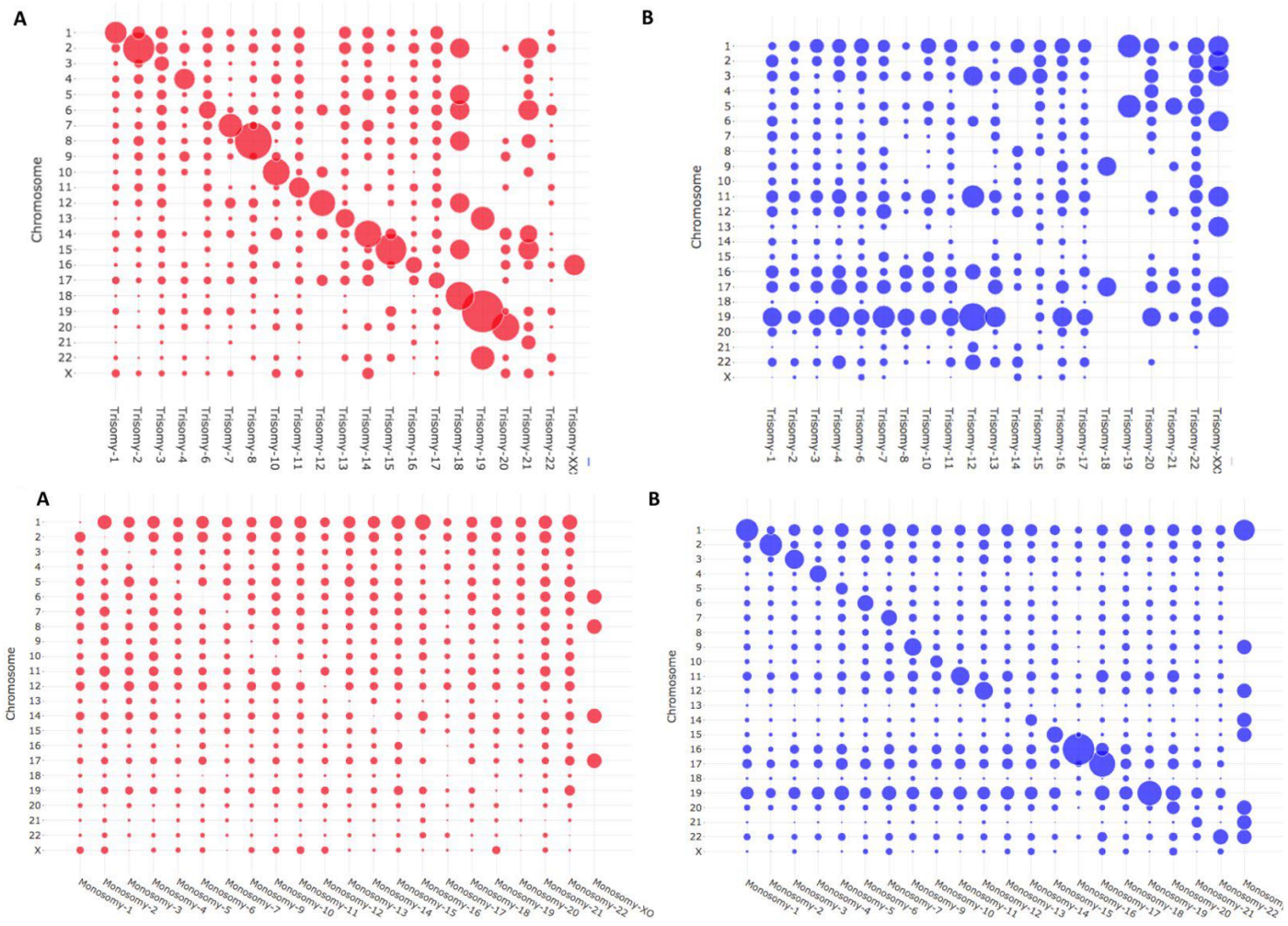
Frederick Licciardi[1], Tenzin Lhakhang[2], Yael G. Kramer[3], Yutong Zhang[4], Adriana Heguy[4,5,6] & Aristotelis Tsirigos[2,5,6]



Embryos with abnormalities of trisomies and monosomies display special characteristics of transcriptome profiles compared with normal embryos.

Licciardi F, et al. Human blastocysts of normal and abnormal karyotypes display distinct transcriptome profiles. Sci Rep. 2018;8(1):14906.

A proof-of-concept study for multi-omics PGT

OXFORD human reproduction

Human Reproduction, 2024, 00(0), 1–12
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Original Article

Reproductive genetics

Multi-omics PGT: re-evaluation of euploid blastocysts for implantation potential based on RNA sequencing

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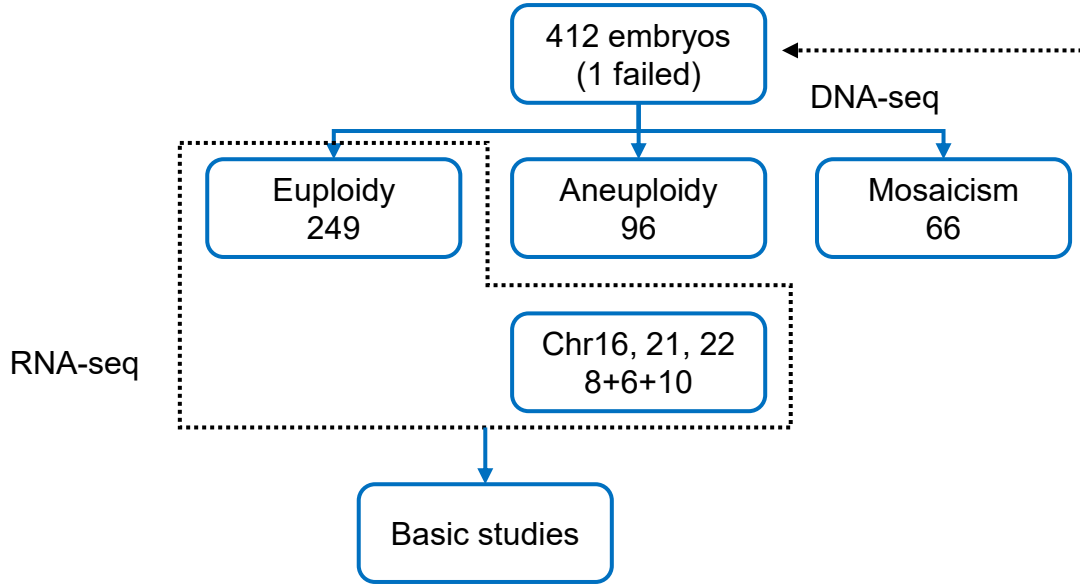
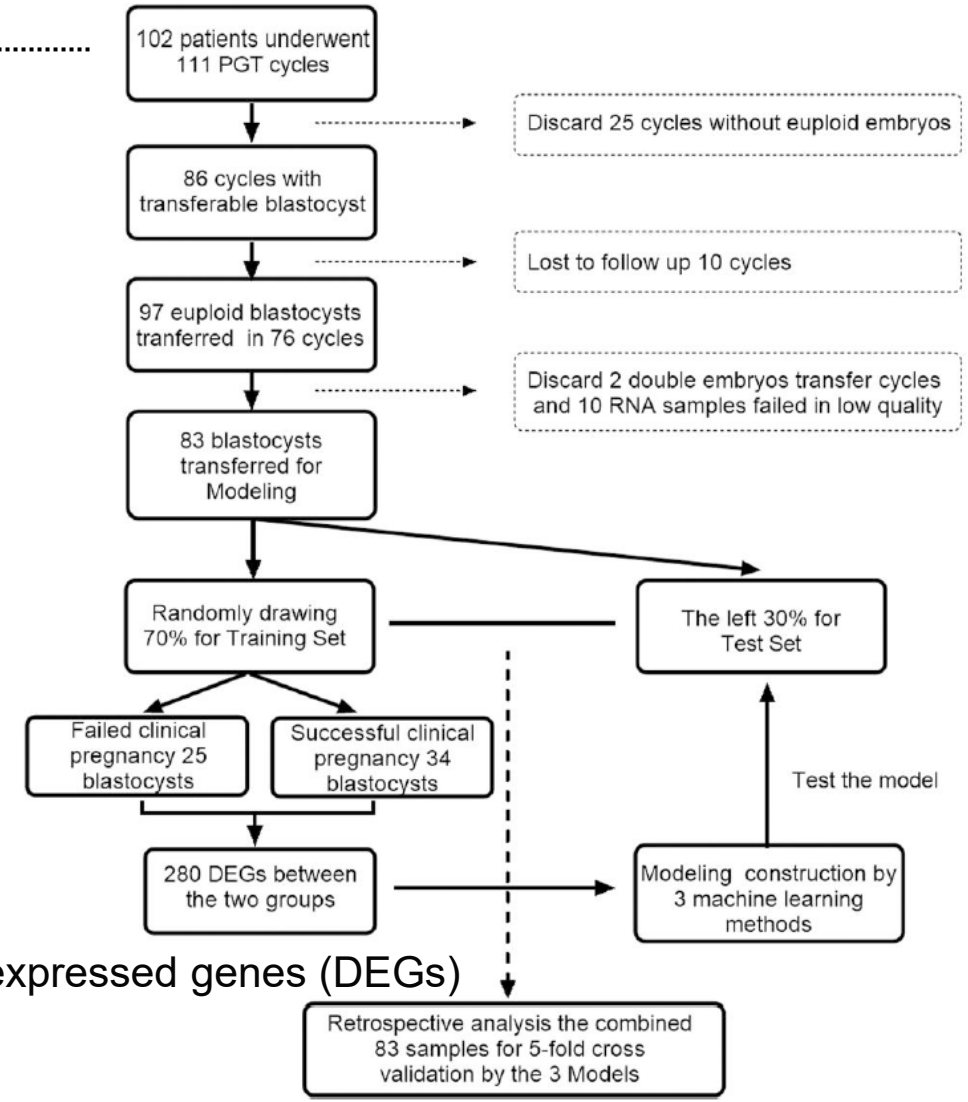
Study design



Transcriptome

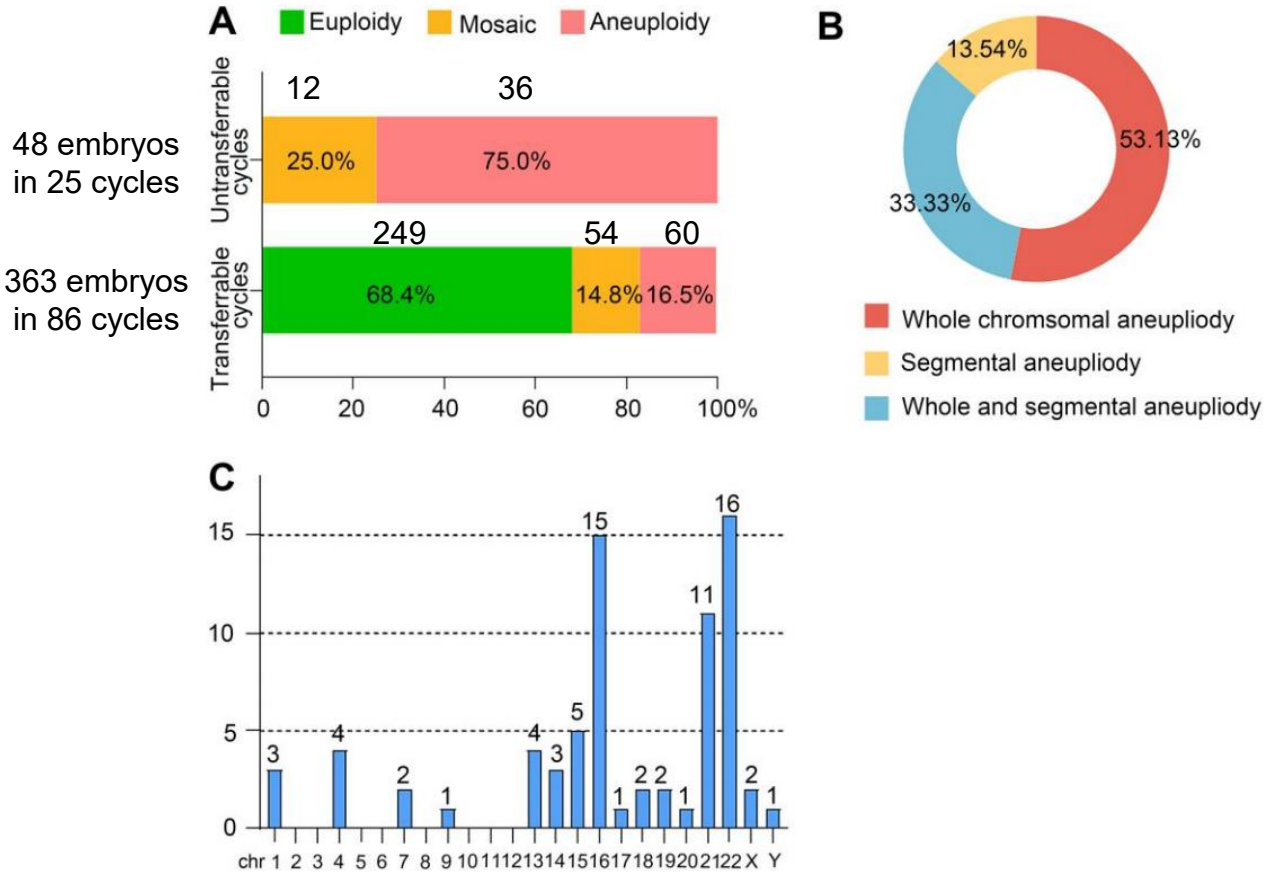
- ✓ aneuploidy vs. euploidy
- ✓ D5 embryos vs D6 embryos (high-quality)
- ✓ Protein–protein interaction network between embryos and endometrium



Results 1- Summary of PGT-A results

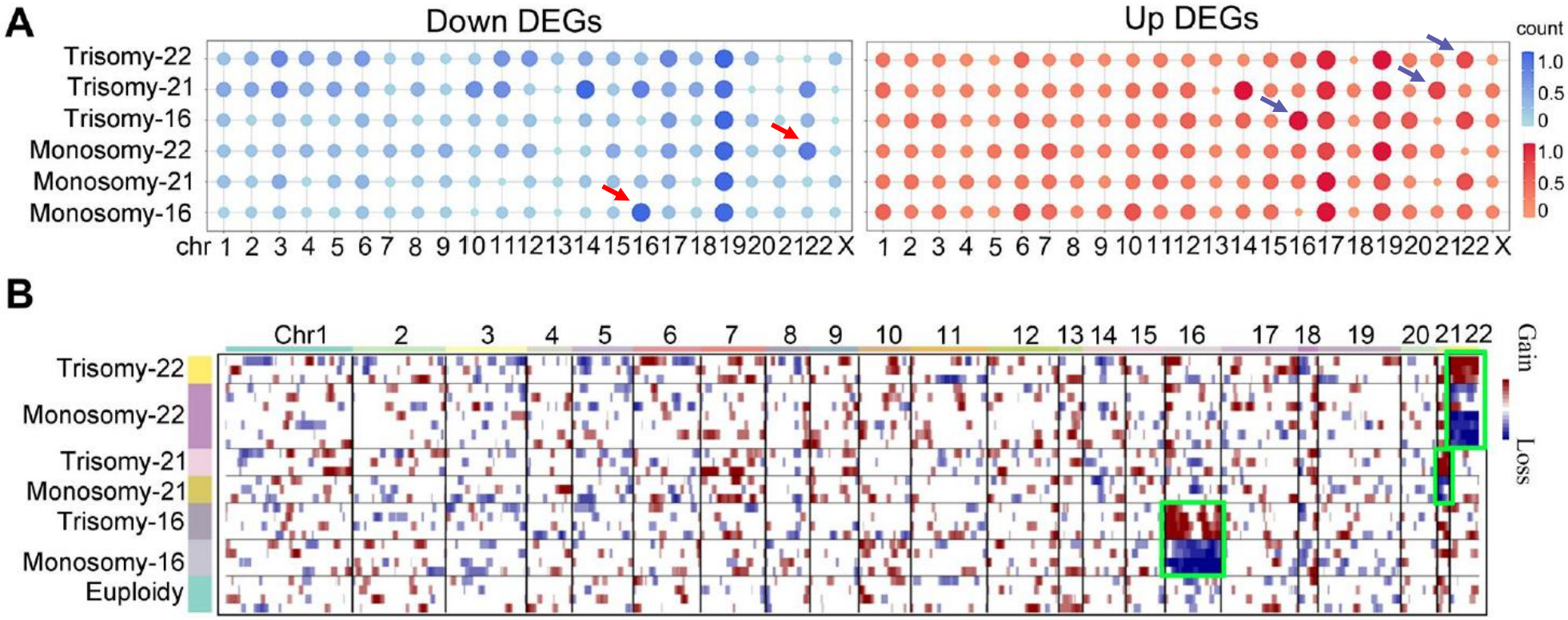
- CNVs were successfully detected in **99.8% (411/412)** of cases. Of the 412 blastocysts, **60.4% (249/412) tested as euploid embryos**.
- In the transferrable subgroup, the rates of euploidy, aneuploidy, and mosaicism among embryos were 68.4% (249/364), 16.5% (60/364), and 14.8% (54/364), respectively.
- Among the 96 aneuploidies (23.3% overall), the rates of whole chromosomal, segmental, and whole and segmental aneuploidies were 53.13%, 33.33%, and 13.54%, respectively.
- Furthermore, chromosomes 16, 21, and 22 were the top three whole chromosome aneuploidies.

Characteristic		P-value
No. of patients	102	
Oocyte retrieval cycles	111	
Maternal age (years)	33 (30, 36)	
Maternal BMI (kg/m^2)	20.90 (19.30, 23.10)	
Basal FSH (mIU/ml)	7.10 (5.90, 8.35)	
Basal LH (mIU/ml)	3.99 (3.17, 5.30)	
Basal E2 (pg/ml)	27.40 (20.95, 34.70)	
AMH (ng/ml)	3.35 (2.07, 4.55)	
No. oocytes	11 (6, 17)	
No. MII oocytes	10 (5, 14)	
No. 2PN zygotes	7 (4, 10)	
Biopsied blastocysts per cycle	3 (2, 5)	
High-quality rate of Day 5 blastocysts (%)	57.7% (146/253)	0.020
High-quality rate of Day 6 blastocysts (%)	46.6% (88/189)	
Embryos for PGT	412	
Success rate of PGT (%)	99.8% (411/412)	



Results 2- RNA-seq characteristics for aneuploidy

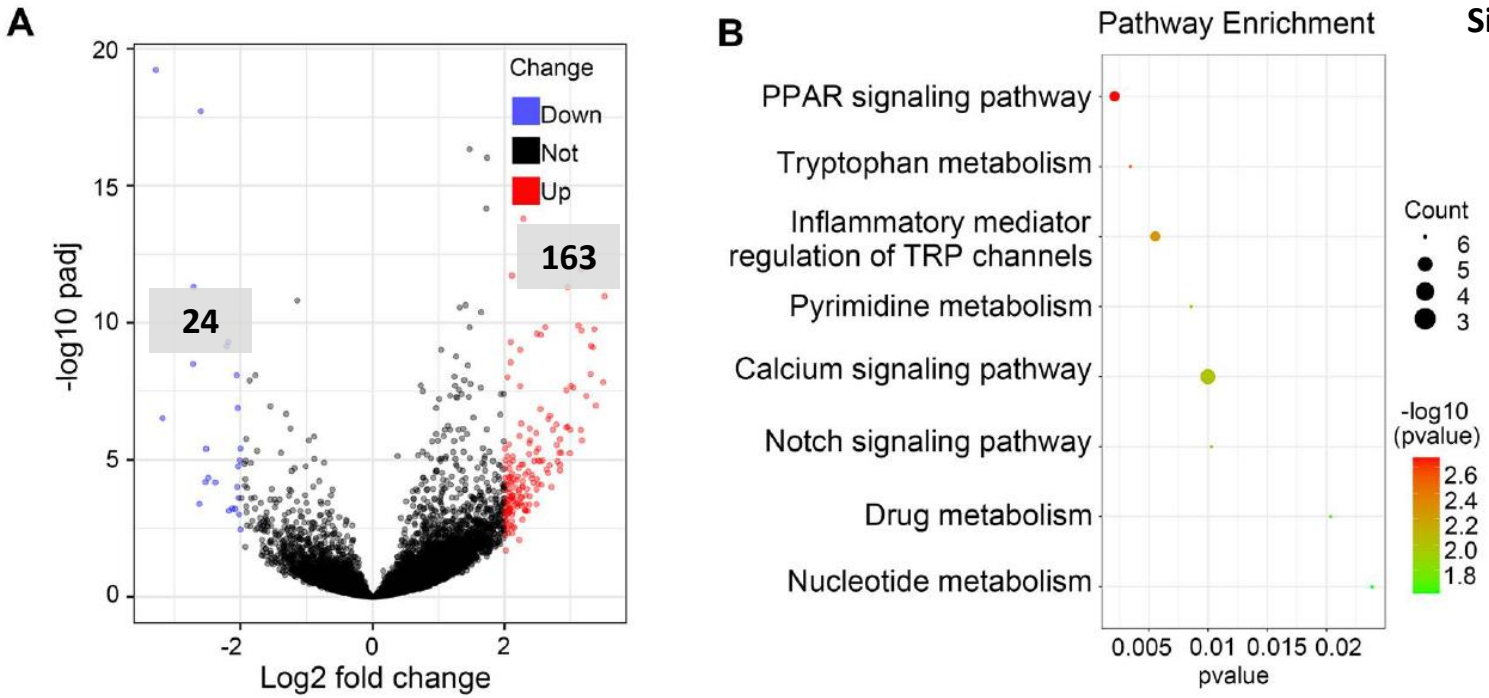
- The second fraction of each biopsy lysate was reverse-transcribed to cDNA, and the library was constructed. 10 M reads were obtained for each RNA library, in which the average exonic rate was 26.4%.
- We demonstrate a pronounced gene dosage effect, where genes tend to be under-expressed with the lost chromosomes in the case of monosomy, whereas in trisomy, genes in the extra chromosome show overexpression.
- CNVs inferred based on the fragments per kilobase million (FPKM) also showed the enriched gain (red region) or loss (blue region) panels in chromosomes 16, 21, and 22, which coincided with the CNVs of the PGT results.
- DEGs between aneuploidy and euploidy (chr 16) are essential for viability and fundamental for early embryonic development.



CNVs inferred based on the FPKM

Results 3- Transcriptome characteristics of blastocysts

- When comparing D5 euploid blastocysts with D6 euploid blastocysts, 163 over-regulated and 24 under-regulated genes were detected.
- Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and gene ontology (GO) analyses demonstrated that DEGs were mainly associated with the carboxylic acid transport, cell differentiation involved in embryonic placenta development, inflammatory mediator regulation of TRP channels, **PPAR signaling pathway (FABP3, PLIN5, EHHADH, and PPARG)**, and **Notch signaling pathway (HEY2, DLL4, and TLE6)** , of which the latter two pathways are associated with **trophoblast differentiation** and **placental formation**.



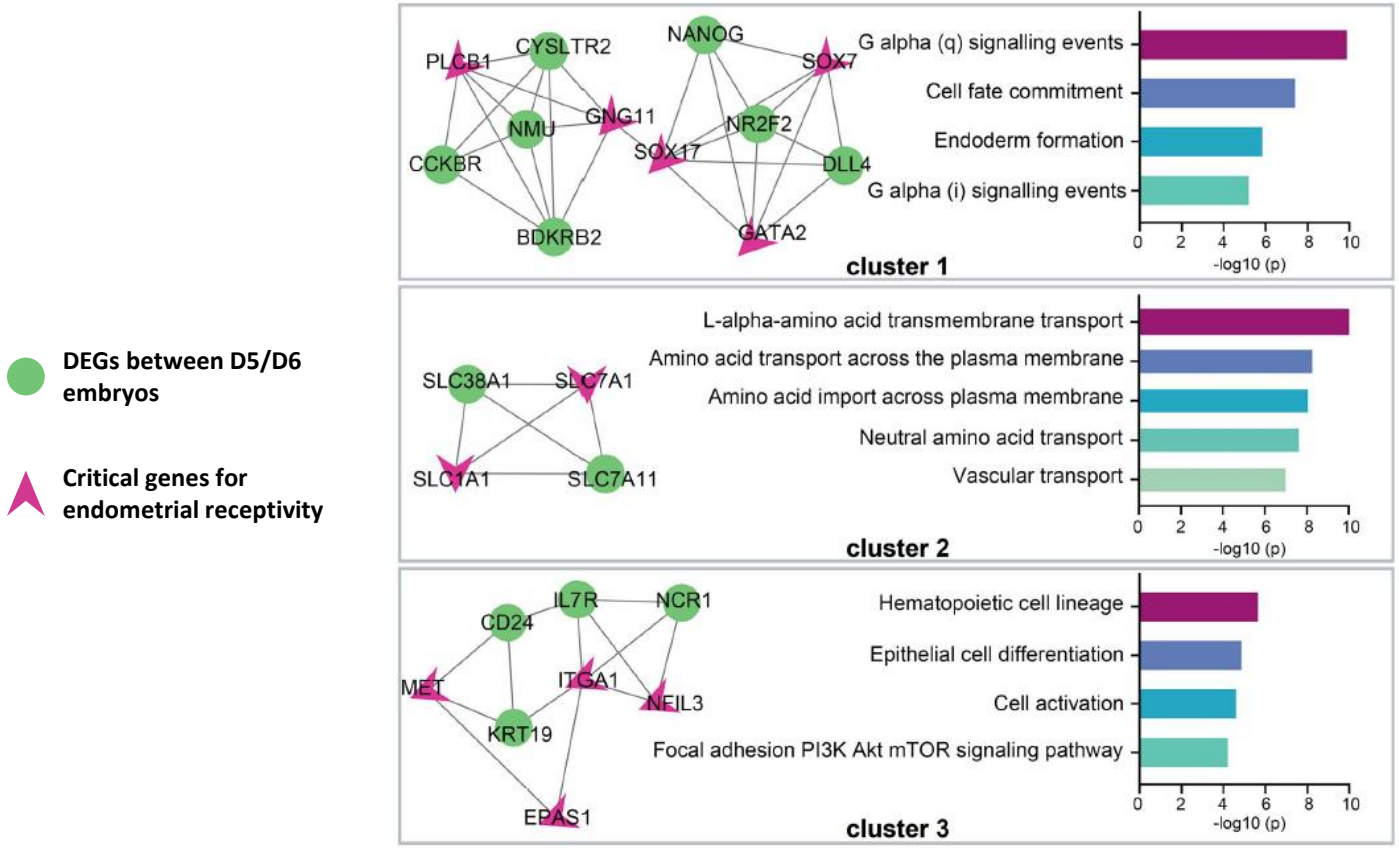
Significant DEGs in the KEGG pathway

FABP3, PLIN5, EHHADH, PPARG

HEY2, DLL4, TLE6

Results 4- Dialog between blastocysts and endometrium

- The protein-protein interaction network (PPIN) showed 185 nodes, 327 edges connecting 187 D5/D6 DEGs, and 199 critical genes for the receptive endometrium.
- Three clusters were involved in the implantation process.
- All three clusters implied that the **embryo was further differentiated for post-implantation development**, as **the endometrium was also undergoing epithelial cell differentiation to facilitate adhesion for the blastocysts**.



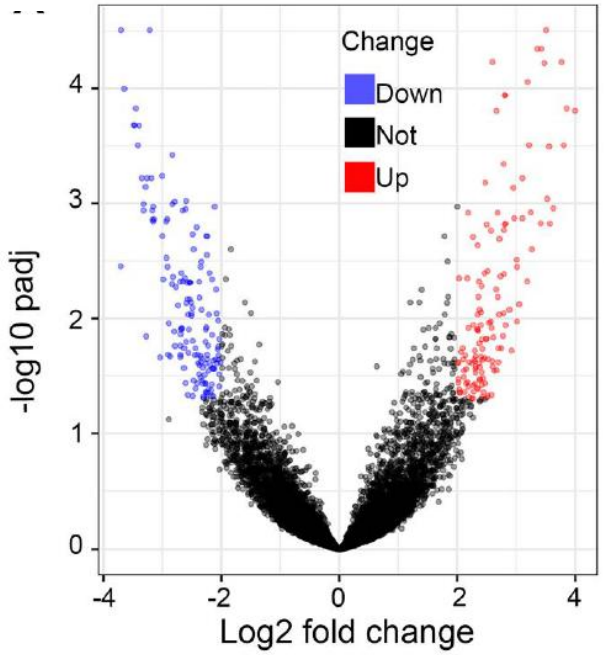
Blastocyst cell fate commitment and endoderm formation

Amino acid transmembrane transport and vascular transport between the endometrium and blastocyst

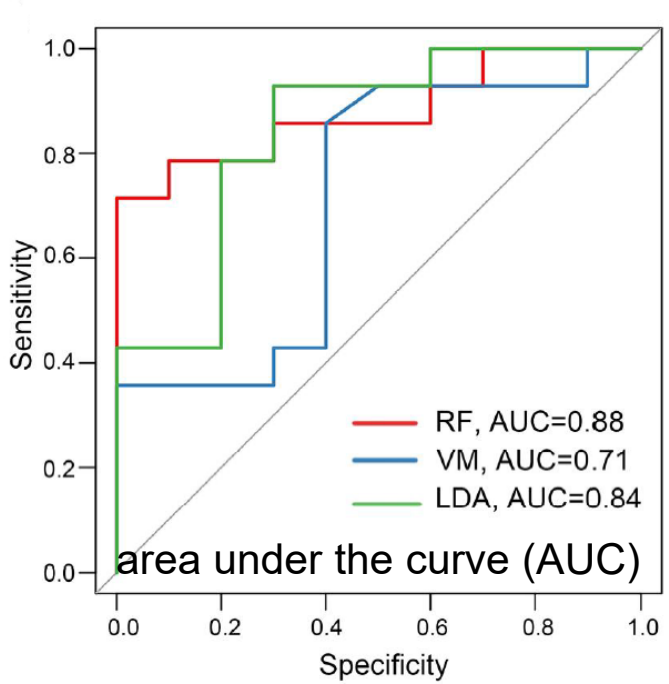
Endometrial preparation

Results 5- Ranking model for embryo implantation

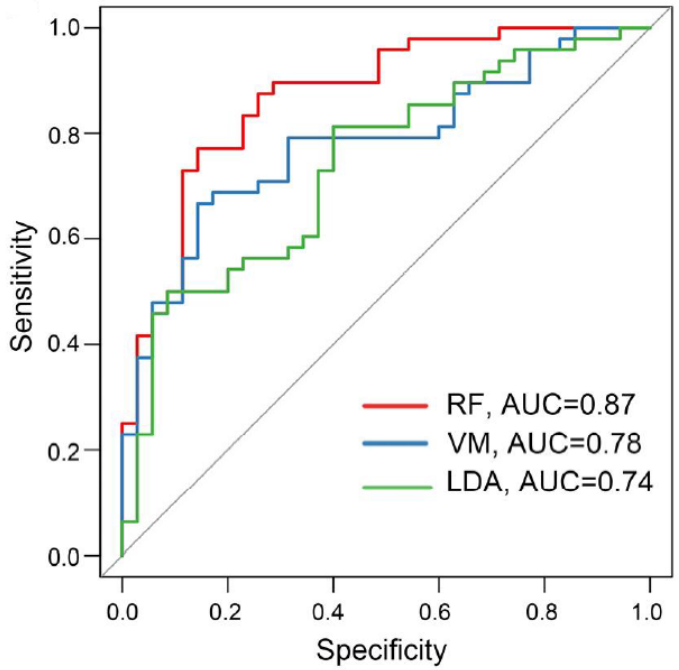
- 83 transferred embryos were left for the construction of an optimal predictive model based on the transcriptome changes associated with clinical pregnancy outcomes.
- Of all the 83 embryos, 59 embryos were randomly assigned to the training set and the remaining 24 embryos formed the test set for machine learning.
- There were **280 DEGs** identified between the successful clinical pregnancy group and failed clinical pregnancy groups.



280 DEGs identified from **34** successful clinical pregnancy embryos and **25** failed embryos



Predictive model test with three different machine learning models (**24** samples)

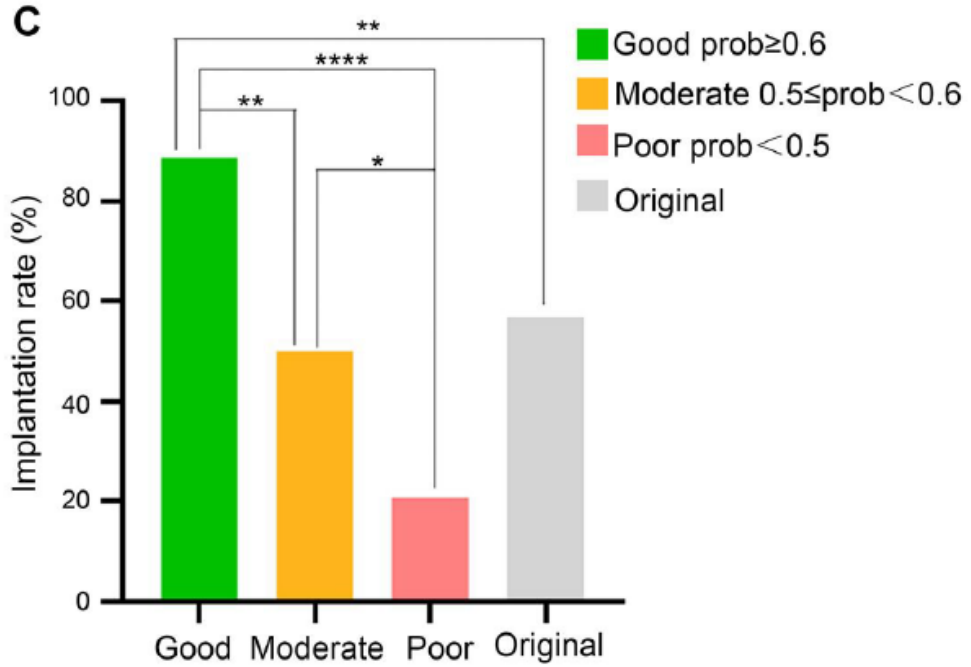


A retrospective analysis of all **83 euploidy blastocysts**

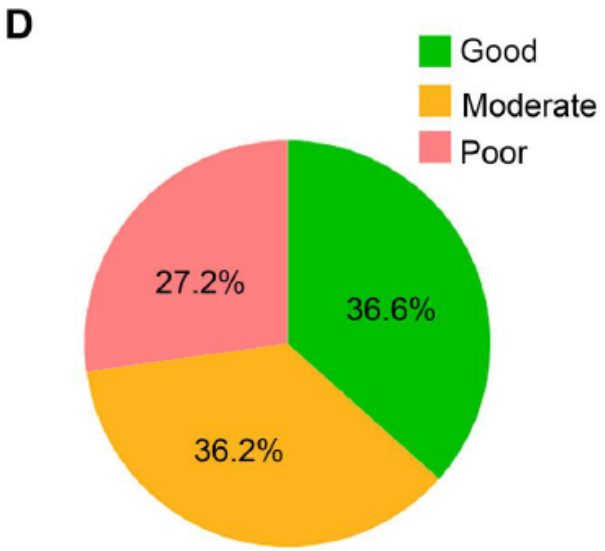
RF = random forest VM = support vector machine LDA = linear discriminant analysis

Results 5- Ranking model for embryo implantation

- Based on the probability (prob) of the RF prediction, 83 euploid blastocysts were divided into three groups: good (prob ≥0.6), moderate (0.5 ≤ prob < 0.6), and poor (prob < 0.5).
- The implantation rate was significantly higher in the good group than in the moderate group (88.6% vs 50.0%, P = 0.001). In addition, the implantation rate was higher in the moderate group than in the poor group (50.0% vs 20.8%, P = 0.035). Moreover, the implantation rate in the good group was significantly higher than the original implantation rate (88.6% vs 57.8%, P = 0.001).
- Among all of the 213 euploid blastocysts with RNA-seq results, 36.6%, 36.2%, and 27.2% were good, moderate, and poor blastocysts, respectively, based on the ranking model.
- These results indicate that the majority of euploid blastocysts were good and moderate and that the optimal sequence for transfer should be prioritized as good, followed by moderate and then poor blastocysts.



83 samples



213 euploid blastocysts

Conclusions

I. Transcriptomic analysis of blastocysts offers a novel approach for predicting embryo implantation potential, which can be utilized to optimize clinical embryo selection. The ranking system may be effective in reducing the times and costs involved in achieving a clinical pregnancy.

II. Machine learning models, built with DEGs from embryos with known pregnancy outcomes, achieved AUCs of 0.87 (RF), 0.78 (SVM), and 0.74 (LDA) in independent validation, indicating their predictive power.

III. The “Good prob” group, with an 88.6% implantation rate, demonstrates the potential of combined DNA and RNA analysis to enhance PGT clinical outcomes.

IV. Further validation is needed through larger, multi-center prospective studies; currently, two single-center clinical trials are underway to assess the model's clinical efficacy.

Acknowledgement

- All the patients who participated in this study.
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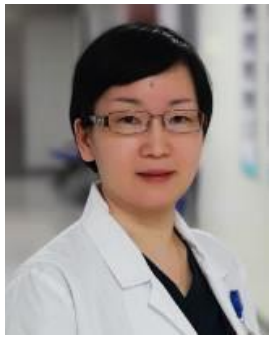
Dr. Jiamin Jin


Dr. Xiaomei Tong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Thank you for attention!

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