COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2023/2024

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Unravelling signaling pathways regulating lineage specification during human preimplantation development**		3 keywords: Human preimplantation, IVF, bioinformatics
Unit / team: **CR2TI / Team 2**		
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Socio-economic and scientific context (approximately 10 lines):

In France, 15% of couples are consulting for infertility problems. 2014 European activity report of the reproductive biology hospital units reports that IVF babies represent 2.3% of birth (De Geyter et al., 2018). However, the success rate is only about 20 to 30% per attempt. Improving the effectiveness of IVF procedures is a major medical and societal challenge for ensuring a healthy pregnancy and increase the live birth rates of infertile couples. We think there is a large gain that can be achieved at the embryo level. Indeed, in countries allowing egg donation, embryos obtained from egg donation can implant and lead to pregnancies in menopaused women. This hints that egg/embryo quality might be able to overcome physiologically poor implantation environment. However, we have to understand what drives proper development of embryos in order to improve embryonic development during IVF cycles. Our team has initiated ground work aiming at understanding IVF to improve more than 10 years ago, and we have now a multi-skilled team working together to achieve this aim: reproductive biologists, clinicians, stem cell biologists, developmental biologist, bioinformaticians in image analysis and transcriptomics.

Working hypothesis and aims (approximately 8 lines):

Hypothesis

We can deduct from the analysis of our actual datasets what are the putative improvements of culture media that would improve the quality of embryos and their ability to implant.

Aims

1/ Identify putative signaling pathways involved and their effect.
2/ Evaluate effect of treatments on human embryos, based on integrated analysis of time-lapse images and transcriptomic data. Infer single cell composition based on single-embryo sequencing.
3/ Integrate transcriptomic and proteomic data to refine our assessment of embryo potential to implant.

Most of the data have already been generated. The bioinformatics challenge lies in our ability to perform multimodal analysis. We rely on a state-of-the-art network of collaborators to achieve our aims.

Main milestones of the thesis (approximately 12 lines):

The work will start by the analysis of the preliminary data obtained by the team: 10 different treatments have been performed on human embryos The first step of the thesis will be to stratify embryos based on morphokinetic features and associate with each feature the odd of proper implantation and pregnancy success rate.
The second step will be to match transcriptomic signatures obtained after treatment of each individual embryo with the activation of signaling pathways. This has 3 goals: 1/ check that the treated embryos still have "normal" signatures, 2/ infer cellular composition of each embryos by deconvolution, 3/ identify signatures that are robustly found associated with specific morphological states vs more variable signatures, less robust.
Finally, the previous steps will give us a great correlation of molecular signatures, morphological features and potential for implantation. This will give us the perfect opportunity to add a proteomic layer (currently being acquired by mass spectrometry) to our analysis, consolidating correlations previously made and potentially identifying candidates that could refine our assessment of implantation/pregnancy potential of human embryos.

Scientific and technical skills required by the candidate (2 lines):

We look for candidates highly motivated by an academic career. We are a dynamic team that brings together experts in bioinformatics, human embryology and stem cell biology. We aim to develop competitive projects. Skills in multimodal data integration are particularly appreciated.

3 publications from the team related to the topic (last 5 years):

- Unraveling hallmark suitability for staging pre- and post-implantation stem cell models.
Onfray C, Chevolleau S, …., David L. Cell Rep. 2024, *in press*

- Integrated pseudotime analysis of human pre-implantation embryo single-cell transcriptomes reveals the dynamics of lineage specification.
Meistermann D, Bruneau A, Loubersac S, ... Bourdon J, Fréour T, David L. Cell Stem Cell. 2021

- Induction of Human Trophoblast Stem Cells from Somatic Cells and Pluripotent Stem Cells.
Castel G, Meistermann D, ... Okae H, Fréour T, David L. Cell Rep. 2020

National and international collaborations :

Fr : Damien Eveillard (Nantes)

Europe : Antonio Scialdone (Munich), Stefan Semrau (New York), Hilde van de Velde (UZ Brussels)