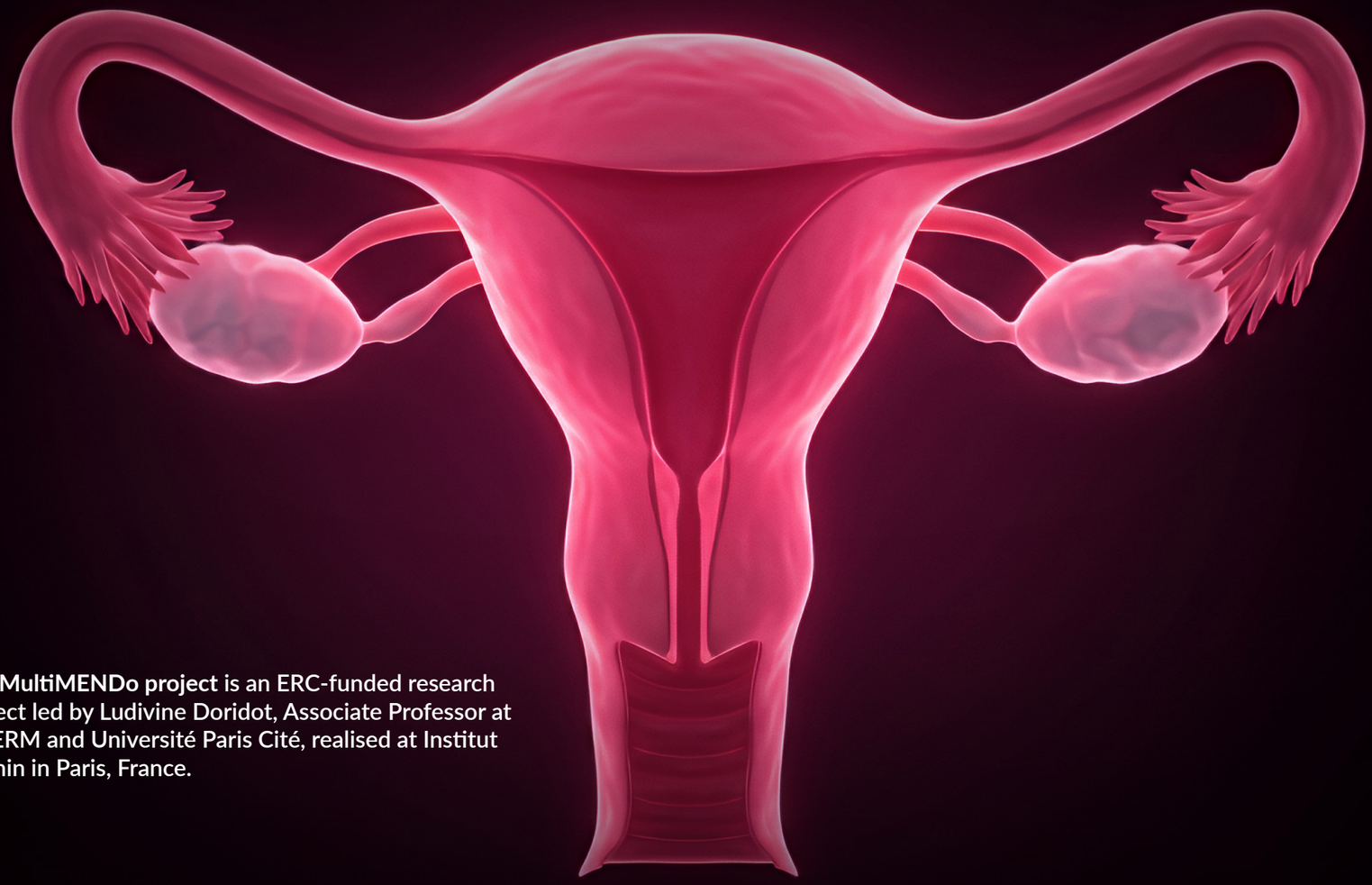
DISSEMINATION
MultiMENDo

MultiMENDo at midpoint: a researcher's reflections on progress and purpose



The MultiMENDo project is an ERC-funded research project led by Ludivine Doridot, Associate Professor at INSERM and Université Paris Cité, realised at Institut Cochin in Paris, France.

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This five-year project, which began in May 2023, has now reached its mid-point. This article provides an update on its progress and shares the coordinator's personal reflections on the journey so far.

The aims of the MultiMENDo project

The MultiMENDo project has two clear objectives:

1. Find diagnostic biomarkers and/or prognostic biomarker candidates for endometriosis in menstrual blood.
2. Establish a relevant 3D model from menstrual blood cells to investigate new therapeutic approaches for endometriosis.

The setting up of the observational clinical study to collect menstrual blood

In order to collect menstrual blood from willing participants, whether affected by endometriosis or not, a clinical study with clear objectives had to be established. To achieve this, the coordinator received support from the INSERM clinical research department. Following the provided template, the coordinator had to understand what was expected and how to design a clinical research protocol. This proved challenging and took longer than anticipated. Once the protocol and additional documentation were written, the whole file was submitted to an ethics committee. Their feedback led to a few minor changes, but also to a justification for not implementing some of their recommendation. Indeed, some suggestions were not relevant in the context of menstrual blood collection—for example requiring participants to wear gloves during collection, which is not something they normally do when managing their menstrual hygiene, or concerns about the bacterial contamination of the sample (something that cannot be avoided in the context of an intra-vaginal collection with the use of a menstrual cup).

Finally, the clinical study was validated, and since July 2024, we have had an ongoing clinical trial (NCT06245512) allowing the recruitment of willing participants.

The recruitment started slowly, and we did not attempt to accelerate it right away, as we needed to fine-tune the menstrual blood processing within the lab (more on that in the next paragraph). Once we were confident with this processing, we used several channels to improve the enrolment rate (for example, we talk about the study in university courses related to endometriosis, we made a LinkedIn post about our ongoing research and clinical study which led to more than 50 000 impressions, 25 000 members reached, more than 230 reposts—notably by a patient's association). So far, we have already included more than 50 women who provided one to three samples (this number has doubled since May 2025, indicating a significant improvement in the recruitment rate). As the goal is to enrol 250 participants, most of whom are affected by endometriosis, we are progressing well; however, we still have some way to go. We allowed for several menstrual blood collections per patient (up to three samples) to refine the protocols with the first samples and still be able to analyse each patient appropriately, and to assess the potential stability of the measured parameters over time. This is important in order to design rigorous and useful tools for endometriosis care.

The menstrual blood processing: a challenge

While this was not unexpected, the quality and quantity of the samples were quite heterogeneous between participants. We have not yet been able to assess potential predictive factors for this heterogeneity. However, we are collecting data to identify such factors and refine the method for collecting this overlooked biological fluid in reproducible and standardised conditions. Furthermore, we are trying to design a protocol that is as simple and rapid as possible in order to boost its potential usefulness in future clinical practice, while adapting to the observed heterogeneity of the samples. However, since we don't know which part of the sample will be the most useful (for example, a specific cell type or the cell-free portion), we are trying to extract as much information as possible from these samples.

Update on the transcriptomic data from menstrual blood

The first single-cell proteogenomics datasets that we generated were of poor quality, so we had to optimise our protocols and identify key factors to know when a sample is usable or not. Following this initial setback, we made progress and successfully generated our first good-quality datasets of single-cell

proteogenomics from the menstrual blood of women with and without endometriosis. We could detect the expected cell types and are currently diving into the data to identify the most promising biomarkers, while expanding the number of assessed patients. In parallel, for the major cell populations, we set apart enriched cell type fractions in order to perform bulk RNAseq. This will complement the single-cell data and hopefully facilitate a more cost-effective validation of the identified biomarkers.

Update on the 3D culture models from menstrual blood

Concerning the establishment of 3D models (notably organoids with epithelial cells), we are able to obtain successful cultures for most of the menstrual blood samples. We are currently mostly cryopreserving them in order to use a standardised protocol on a reasonable set of samples from women with and without endometriosis. In parallel, we are cryopreserving stromal and immune cells to construct a complex model that examines how cells interact and defines new therapeutic approaches.

In parallel with these organoids, we began developing an endometrium-on-chip model that provides a more controlled structure and environment for modelling the endometrium.

Personal perspectives on obtaining the funding and coordinating this project

The obtained funding is an European Research Council (ERC) Starting Grant (StG), awarded to early-career researchers within ten years of completing a PhD. This eligibility window can be extended by up to 18 months in the event of pregnancy or maternity leave; a provision I could have benefited from with my two children, but did not actually need, as my PhD was obtained in 2013. I responded to the 2022 call (submitting my written application in January 2022 and attending an interview in September 2022).

Before submitting my application, I spent several years getting started. I had initially sought national funding (ANR JCJC), however, my application was not successful. The amount available through the ERC calls allowed me to aim higher and design a more ambitious project. However, I had to convince myself to go for it. The testimonials I had heard during information sessions on these calls had rather discouraged me, giving me the impression that I wasn't up to the task. Little by little, my project matured, and the objectives became clearer.

The first projects I participated in or led in my laboratory resulted in publications. I also obtained initial funding through an internal call for projects at Université Paris Cité (emergence call), which enabled me to launch the first single-cell transcriptomic manipulations and become more comfortable with the technological aspects of my project. All of this gave me the confidence I needed.

Then I worked hard and read extensively to position the project in relation to the literature, emphasising the limitations of previous studies and how my proposal would go further or complement them by offering a new perspective. I also had numerous discussions to gather the views of people from diverse backgrounds, including doctors and researchers (both young and not so young), as well as administrative staff with a background in biology. And although I sometimes thought, "This feedback isn't relevant because this person doesn't really understand the subject," I forced myself to take all the feedback into account, to question myself, to tell myself, "If this person didn't understand, it's because I'm not being clear enough."

I also received advice from previous laureates (a big thank you to Leila Périé and Camille Berthelot), whose feedback on their experiences and some more specific advice on my project helped me improve both the project and the application. To accomplish all this, I worked on my application for approximately four months, albeit not full-time, but with a significant investment of time (one day a week at the beginning, three days a week at the end). These intermittent work sessions allowed me to take a step back and reread my work with a 'fresh' perspective. I also received support from my institution (Université Paris Cité) for the budgetary part and feedback on the scientific part, as well as the curriculum part (thanks, Elise Viola).

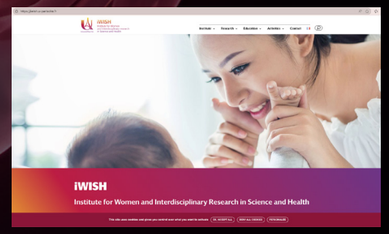
In June, I received notification of a videoconference audition scheduled for September. The task was to present the five-year project in eight minutes flat. I considered taking a training course designed to prepare candidates for these interviews, but after discussing the cost and actual benefits with my institution, we decided against it. Once again, the help and advice of previous laureates proved invaluable (another thank you to Camille Berthelot). I had two mock interviews organised by my institution (thank you, Giuliana Victoria!) and a group of national institutions, with former laureates or jury members as evaluators. I also organised a dozen other rehearsals with everyone around me (researchers, doctors, administrators). I recorded a version, and some friends shared it with trusted Anglo-Saxon researchers. And here too, I forced myself to listen and take notes of all the feedback, some of which might even seem contradictory, so it wasn't necessarily a matter of integrating it as suggested by these selected jurors, but rather an effort to clarify, to take a step back from the comments, to find a way to emphasise certain points. I also noted and prepared responses to all the questions that had been asked of me during these rehearsals. I was very stressed before the interview, but I had prepared as well as I possibly could.

The interview itself was intense, with a panel of about 15 people remotely sitting in front of me. The eight-minute presentation went well. I knew every word by heart and had worked on my speech so that every idea and every detail was essential and flowed clearly. It was the questions that worried me. I was asked about ten questions that focused on my mastery of the different aspects of the project: my knowledge of the field from a clinical point of view (endometriosis and its subtypes), statistics and bioinformatics tools, and my technical skills in cell biology (particularly organoids). I also had an open question on a subject outside my field of expertise (the microbiome) and the possibility of incorporating this dimension into the project. I had to defend the project and the way I had designed it, demonstrating that I had thought beyond the defined project (and considered potential collaborations, such as studying the microbiome, for example). At the end of the interview, I was sure I had not convinced the jury. The announcement that the funding had been granted a few weeks later came as a big surprise to me. As I truly believed in this project, I had already started working on a resubmission (due in October), trying to consolidate all the project's limitations. These reflections have already enabled me to improve the project, and I was ultimately able to incorporate some of them.

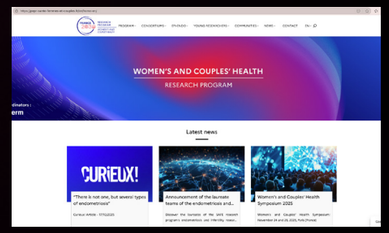
The project took longer than expected to get off the ground, mainly due to administrative procedures, despite the request to postpone the start of the project by several months in order to move forward with the procedures for setting up the clinical study. There were, therefore, moments of doubt during the first period, as it was impossible to obtain the biological samples of menstrual blood for over a year, which was the cornerstone of the project. However, thanks to the good relations and collaboration with the clinical team at Cochin Hospital, we were able to make progress on the technical developments. I feel extremely fortunate to work in an environment where researchers and clinician-researchers work hand in hand. Nevertheless, this delay caused a setback in the project's progress, and other developments took place in the meantime.

The project is now making great strides, and it is exciting to see the theory put into practice. The first experiments are nearing completion, and data are being generated and analysed. Additionally, numerous collaborations have been established, allowing me to broaden my vision and integrate new dimensions into my research. This journey has been enriching, but it has not been smooth sailing. It is also a great responsibility. Doubt remains, and it is easy to put pressure on ourselves to prove that the jury was right to place their trust in us. This helps us grow as researchers and opens up many new horizons. However, the difficulty now lies in realising that we cannot pursue everything, even if we have wide interests and a lot of curiosity, which must always remain a driving force.

Among the major projects I have chosen to get involved in, there is a rather local and multidisciplinary initiative focus on women's health: the Institute for Women and Interdisciplinary Research in Science and Health (iWISH) at Université Paris Cité, which provides an integrated view of women's health with many covered topics (**https://iwish.u-pariscite.fr/**),



and a nationwide initiative focused on endometriosis: the InEndo consortium of the women's and couples' health priority research programme (**https://pepr-sante-femmes-et-couples.fr/en/endometriosis/**).



PROJECT SUMMARY

The MultiMENDo project focuses on endometriosis, a gynaecological disorder affecting approximately 10% of women of childbearing age. This complex disease is notably associated with chronic pelvic pain and infertility, leading to a reduced quality of life. There is a huge diagnostic delay and a lack of curative therapies. The project aims to find diagnostic and prognostic biomarkers and investigate new therapeutic approaches using menstrual blood, a relevant and easily accessible yet overlooked biological fluid.

PROJECT LEAD PROFILE

Ludivine Doridot is a researcher at INSERM (French National Institute of Health and Medical Research) and an Associate Professor at Université Paris Cité (Paris, France). She obtained her PhD in Genetics from Université Paris Descartes in 2013 for her studies on preeclampsia, a hypertensive disease of pregnancy. She then performed a postdoc in Beth Israel Deaconess Medical Center, a Harvard-affiliated hospital in Boston (USA), where she studied genetic-environment interaction in the context of metabolic syndrome. Since 2017, she has focused on endometriosis and reproductive immunology.

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