Next stop

CHAPTER 7

Impact paragraph

The results of this thesis indicate that on-a-chip technology can be standardized and scaled up for large-scale applications like screenings. These findings contribute to the incorporation of these on-a-chip models which closely resemble *in-vivo* like physiology into the pipeline of early-stage drug discovery to help coping with the difficulties faced since the 1990 for the release on the market of new drugs. The thesis also represents a first milestone to improve the availability of therapeutics during pregnancy by helping the development of new treatments for what at the moment are considered untreatable diseases and tested for safety concern the already approved drugs. Next to showing that on-a-chip models and assays are mature enough to be a valid alternative to traditional 2D cell culture for low and high-throughput applications this thesis also highlights the advantages of this new approach which could improve the way drug discovery is handled. In this chapter we described the impact of this PhD project in the research fields, for specific target group and how we disseminated the findings during the project.

Relevance

On-a-chip models have been developed to replace animal models in drug development due being expensive, time-consuming, ethically controversial and to the limited predictability of this model in human [1]. This is particularly true in the case of species-specific organs like placenta where the animal model does not recapitulate the structure of the human organ. There are already multiple examples of placenta-on-a-chip models and one which was used in a small screen to study permeability of drugs across the placental barrier. There are much more examples for other on-a-chip organs already used to study drug transport or effect [1]. Once these models have been established in low-throughout pre-clinical phases of drug development, the next challenge in on-a-chip technologies is to meet standardization and scalability required in drug discovery. This thesis helps in this direction by showing the first screening on-a-chip as an example of large-scale application of complex *in vitro* models. It also validates the on-a-chip as a better alternative of 2D cell culture, not only in the biology resembled but also in technical aspects like standardization, replicability and robustness.

The major impact of this thesis in the scientific community is the fact that we break the double pairs simplicity-high-throughput, complexity-low-throughput in favor of a new bond which brings together complexity and scalability. In addition to this, the new methodologies and analysis reported in this thesis could be used by other scientists in the field of on-a-chip to characterize or develop new models and to study the mechanism behind biological processes and diseases.

The implemented version of the barrier integrity assay could be used to run a screening to test permeability of the drugs on placenta-on-a-chip models and how they affect the barrier. It could be also used with other on-a-chip models, for instant to replace the Transwell absorption study in the intestinal track. The ROS-cell viability assay developed could be useful to test oxidative toxicity induced in the placenta by the administration of drugs, on the maternal and on the fetal side or to develop models with pathological phenotypes. Both these assays could be also applied in a future screening with already automated on-a-chip models like the vasculature reported in this thesis.

To conclude the main impact of this project is the possibility of broadening the knowledge about therapeutic and pregnancy, on one side by developing relevant and scalable models and assays to test for the already developed drugs to be used in pregnancy and on the other by developing disease models to study certain unknown diseases and develop new therapeutics to treat placental or pregnancy related conditions.

Target population

The results of this thesis are relevant for a few target groups on a short and long-term. The first and major impact is in the pharmaceutical industry which could integrate on-a-chip in screening to implement the way drug discovery and development is handled with the aim to reduce the amount of drugs withdraw by implementing the selection of compounds at early stages. This would be beneficial to improve the drug discovery and development workflow as with screening-on-a-chip is possible to gain more and more insightful information than with traditional screening where only efficiency is considered. This could speed up the process of developing new therapeutics but this improvement will be beneficial on a long-term as the time required to develop a drug is in the order of 10-2 years, therefore we did not envision a direct impact on the general population soon. Another long-term impact could be specific for pregnancy and the health care during maternity. Running a screening-on-a-chip with placenta models to test the suitability of approved drugs to be used in pregnancy or to develop new treatments specific for placental diseases will broaden the amount of information and drugs available for clinicians when they need to decide which treatments to prescribe under this particular circumstances. Before reaching this level some optimization is require, as placenta-on-a-chip needs to be established in high-throughput setting and validated in a screening setting, meaning that automation will be integrated in the way the models is established which will be more laborious than what we already

did with the vasculature models due to the higher degree in complexity of a co-culture than a mono-culture, next to this drugs will need to be tested for different safety concerns to investigate how does they affect the maternal side of the placenta, if they cross the placental barrier, and if this is the case how does it affect the fetal side, these are few of the countless questions for which it will be necessary to find an answer prior to decide if they are safety or not.

Implementing the health care during pregnancy has multiple advantages; it will improve the situation of the mother and fetus during the gestation and it will have a long-term impact considering that right treatments could avoid future comorbidities especially for the safety of new generations, as the newborn will have to cope with them for his/her entire life. We are still far away from this scenario but this thesis represents another step in this direction.

Dissemination

The research described in this thesis has been shared with the scientific community in international peer reviewed papers and at conferences. For instance, data reported in Chapter 2 were presented as poster during the Society for Reproductive Investigation (SRI) conference in Paris in 2019, at the Cell Culture under flow meeting at the biomedical center in Munich also in 2019, data in Chapter 3 and Chapter 4 were presented as poster at the virtual symposium “Novel perspectives in maternal and fetal health” organized by Dundee University in 2021, as an oral presentation at another virtual meeting the International Federation of Placenta Associations (IFPA) 2021, while Chapter 5 was presented as a poster at the virtual meeting Society for Laboratory Automation and Screening (SLAS) 2021, (EUROoCS) 2021 and as an oral presentation at the MPS world summit in 2021. Moreover as the PhD was part of a Marie Curie action H2020 funded project, the iPlacenta consortium, which includes 15 early stage researchers who are all focused on unravelling the placenta from different points of view, data reported in this thesis were also shared within this community composed by researchers and clinicians during different consortium meetings.

References

[1] D. E. Ingber, “Human organs-on-chips for disease modelling, drug development and personalized medicine,” *Nat. Rev. Genet.*, vol. 23, no. 8, pp. 467–491, 2022, doi: 10.1038/s41576-022-00466-9.