

Next stop

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CHAPTER 8

Summary

One of the efforts made to fill the gap of knowledge about placenta is the development of physiologically relevant *in vitro* models to study the organ, its development, the onset or mechanism behind pathological conditions. Recently different on-a-chip models capable of resembling *in-vivo* like features of the placenta were developed. These models are very interesting for the drug development field which is in need of relevant *in vitro* placenta models to test new or already developed therapeutics. In fact, for only an inconsistent percentage of drugs are available safety assessments regarding their administration during pregnancy; anyway drugs are prescribed during pregnancy when there is no alternative, even if there are no information about the safety of the mother or the fetus.

There is a clear urgency in assessing the safety of these drugs and the development of placenta-on-a-chip models is a first step in that direction. To proceed further the on-a-chip models should be scalable to be applied in high-throughput testing and relevant and scalable assays should be developed in parallel. The aim of this thesis is to demonstrate that on-a-chip models and assays can be applied in high-throughput content and the advantage of this application.

Scalability is generally implemented as a second step both to establish the models and for the assays. Scalable assays rely on optimized control conditions to maximize the signal window of it. In Chapter 2 we reported the implementation of the data analysis for the barrier integrity assay. This implementation allows to quantify permeability in control conditions in on-a-chip systems with highly permeable membrane and to increase scalability by encountering of the experimental time off-set.

An assay can also be developed to be scalable-friendly as we described in Chapter 3 where we reported the ROS-cell viability assays. Data acquisition and analysis were optimized to achieve high throughput scale. We showed that the assay is reliable to characterize on-a-chip models, to screen for antioxidant based on their capability to inhibit reactive oxygen species (ROS) accumulation, to capture different ROS levels in different phenotypes of cells. In Chapter 4 we applied the ROS-cell viability assay to the placenta-on-a-chip to characterize the model in terms of ROS content as it has never been done even if oxidative signaling plays a crucial role in the development of physiological and pathological placental barriers. As a first step to help developing a disease placental model we investigate how prolonged culture, stimulation of trophoblasts with pro-syncytialization media and perfusion settings affect the ROS baseline and the way the placenta-on-a-chip model experience ROS accumulation upon a chemically triggered an oxidative

stress insult. The short-term culture and the switch to static conditions which could mimic early placenta development and impaired perfusion, have the strongest effect of increasing the ROS accumulated, which resemble a pathological oxidative profile.

In the last experimental chapter (Chapter 5) we reported the first screening-on-a-chip where we combined highly physiological and complex biology, resembled in the vasculature-on-a-chip models and in the sprouting initiation assay, with the scalability required for a screening (more than 4000 chips used). Qualitative indexes quantified to evaluate for the suitability of both the model and assay to be used in screening, the fact that in the list of hits there were compounds with already known antiangiogenic effect, validate the use of on -a-chip in screening; the fact that a compound that with the traditional screening was selected and then withdrawn in later phases of the development due to toxic reasons, in our screening-on-a-chip was not selected as hit due to the safety reason even if it had a strong anti-angiogenic effect, indicate the more predictability of the screening-on-a-chip which place them as valid alternative to traditional 2D screening.

This study is an example of standardization of on-a-chip models and assay, showcases the possibility of using on-a-chip in early-stage of drug development; The advantages of this type of screening are reflected in the complex analysis that can be accomplished where we could gain information on efficacy and toxicity of the compounds, already at the screening phase, for a more conscious selection of hits.

In the general discussion (Chapter 6) we discuss the major findings of the chapters, link them together and compared with the literature already present.