EXPLORING PATIENT-DERIVED ORGANOID DRUG DISCOVERY

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Sylvia F Boj received her PhD in 2006 at the University of Barcelona, Spain for her work at IDIBAPS on functional genetic analysis for deciphering the transcriptional role of MODY genes in pancreatic beta cells.

With a long term EMBO fellowship, she subsequently joined the Hubrecht Institute (Utrecht, the Netherlands) as a postdoctoral fellow. In the laboratory of Prof. Hans Clevers she first studied the role of TCF7L2 regulating metabolism. Then, she established an in vitro organoid model for human pancreatic cancers. In 2014, she moved to the HUB foundation for Organoid Technology (Utrecht, the Netherlands) as a group leader for Cystic Fibrosis and Cancer programs. More recently, in 2016, she was appointed as scientific director of the HUB foundation, with the ultimate goal of transferring scientific advances of the organoid technology to the development of new drugs, by interacting with pharmaceutical companies, and developing clinical trials to validate the predictive value of the organoids for the response of patients to certain treatments.

What are the key benefits of patient derived organoids drug discovery?

There are two main benefits. With tumor organoids, we can better represent the heterogenous population of patients that need to be treated, since organoids can keep the genomic and phenotypic heterogeneity present in the tumour. Also, we can generate organoids from normal tissue from the same patient. So, in terms of toxicity and other type of studies, we have a very relevant control.

Could you tell us more about your novel system to study the effects of immune modulating drugs?

What we've been able to develop an assay that allows to screen hundreds of wells. We have developed with engineer T cells versus cancer and normal organoid cells from different type of tumours (colorectal, pancreatic or breast tumors). In this assay, we have been able to see a response from the T cells (IFN-γ secretion) and their capacity to kill specifically the tumour cells. Now we are developing the assay using naïve T cells and other cell types from the immune system to provide a platform for testing immune modulating drugs.

What innovations have advanced your research in oncology and immuno-oncology drug discovery and development?

Well, I think that the fact that we can run screens with tumour and normal cells from the same patient can give confidence to the drug developers to explore the toxicity effects not only on the specific tissue in which the drugs can be targeted, but also in other tissues, since we have living biobanks from many healthy tissue. Furthermore, the scalability of screenings for oncology or immune-oncology drugs in hundreds of organoid cultures, offers an indication of how broad the effect can be of a specific drug, or combinations of drugs, in patient populations.

What are the main challenges that you're currently facing in this work?

In terms of the organoids, one of the main challenges we are facing is having access to high quality material to generate the organoid model. Right now, we are third or fourth in line when a biopsy or resection is taken because of diagnostic purposes or other clinical trials. So, we are working very hard to prove the predictive value of organoids to really convince authorities that organoids could be one of the first destinations of patient material to develop organoids and organoid-based assay test for drug response. In terms of cancer, we are aware of how heterogenous the tumours are. Therefore, we are also exploring how we can improve the representation of the complexity when we stablish organoid model from biopsied tumors.

What do you feel are the next steps for your company's work in this field?

There are already patients in the world with cystic fibrosis that are receiving treatment because of organoids predicted a clinical benefit for them, so we are now running retrospective clinical trials for colorectal and lung cancers to examine to what extent, tumour organoids have a predictive response of the patient response. We believe that after clinical validation of the organoid models, many company will adopt the use of organoids as their preferred in vitro platform for drug screening, drug development or patient stratification in order to run clinical trials.

What are the top three takeaways from your presentation here today?

That with our technology, it is possible to generate organoids from any endoderm-derived tissue (small and large intestine, lung, breast, liver, pancreas, etc) from almost any patient, since they can be generated either from resected tissue or biopsies. In the terms of oncology and immuno-oncology, how well organoids represent genetic and phenotypic characteristics of the disease model they have been generated from. And on the process of the clinical validation of organoid models for different type of tumours, we already have cases for few patients in which the organoid tumours predicted the response of the patients to a specific treatment.

What do you look to get out of attending events such as this?

Being a spin off company from an academic group, at the beginning, we were presenting mainly in academic-focused meetings. In meetings like this one, that are more dedicated to companies and pharma, we can present our technology while also learning what the needs and challenges of the industry are in terms of 3D in vitro models.

What do you consider the most important technologies impacting genome and cell-based drug discovery?

In terms of genome drug discovery, I think that the capacity we have now to deep sequence, ensuring time- and cost-efficiency and with limited amount of material, even at single cell level, is very important and provides very relevant data. And it's something that will pay once we understand the complexity of the data that is generated by all the deep sequencing. In case of organoids, we believe we have developed an in vitro model that brings the patient back to the lab.