Interview: Jos Joore and Paul Vulto â?? Co-Founders, Mimetas, The Netherlands

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OrganoPlatesâ?¢ serve as a highly useable platform for 3D cell cultures, are completely compatible with existing lab equipment, and can be used to develop true â??organ-on-a-chipâ?? models. Co-founders of the developer and manufacturer, Mimetas, discuss the impact this product is already having on the drug development process, and its potential to replace animal-testing in pre-clinical research in the future.

Having worked abroad, how do you feel the Netherlands compares as an environment to innovate and be an entrepreneur?

Paul Vulto (PV): I am very positive about this region, and think that it is an excellent place to start your own business. The density of the life science industry here is a consequence of the environment in many respects, being a multi-core region with ancient cities, a longstanding tradition of academic and scientific excellence, a strong entrepreneurial spirit, fantastic public transport, robust transport infrastructure and easy access to airports, state of the art telecommunications networks, and a very high quality of life complete with plentiful green space, despite being a very densely populated region. What you see here is that even though the local market is very small, people can still create businesses here, and doing so requires that you internationalize your business immediately; Mimetas was incorporated in January 2013 and by September 2013 we had opened our US office.

There are also a few disadvantages to the Netherlands, especially that big pharma has been leaving the country slowly in many respects, so we have to work much harder than a competitor based in Basel or Boston, because there the big pharmaceutical institutes are around the corner and you end up meeting people on a regular basis. We are very lucky here at the Leiden Bioscience Park, which is the biggest concentration of life science companies in the Netherlands, and we are now seeing the larger biotech companies really start to explode, like Galapagos, Prosensa and ProQure, so it really

seems that weâ??re catching up, but itâ??s still not like having Roche around the corner.

Has having Astellas next-door and Janssen Biologics around the corner fueled Mimetasâ??s development so far?

Jos Joore (JJ): Itâ??s very good to see that what we have lost on the big pharma front, primarily being Organon, which became Schering-Plough and then MSD before all of the R&D activities were faded out, is being replaced through new investment. Itâ??s very promising that Astellas chose this location, and Janssen is expanding their unit here tremendously by setting up a huge innovation center here on top of the former Crucellâ??s facilities, even though they originally began with only a production facility here in the Netherlands. Aside from the Crucell integration, what they are doing now is taking their existing business here as a core and building onto this strong knowledge base with the prevention center that they just opened for example; this is a facility geared towards developing products for healthy people, largely because the market is much larger. So the Netherlands is on a bit of a roll in this sense, which is a strong positive after we saw a ten-year period during which Organon closed down and the financial crisis occurred that caused some companies to pull out of the Netherlands to some extent, but now over the last three years we have seen a return of investment and a wave of young companies like us that are really exploding.

How well have you been able to ride this wave of growth and investment from big pharma, and does the proximity of these large knowledge bases really help in terms of networking and finding applications?

PV: Definitely. Galapagos for instance was our founding customer, and historically speaking your first customer is always your most important. However, we also have to stress the importance of the international thinking that is so normal here in Leiden and the Netherlands, because while Janssen has a site just down the road we do most of our business with them in Belgium, and for Astellas we visited each site that they have in Japan before we visited their lab here in Leiden. We went straight for the core of these companies meaning the laboratories around their headquarters, and in the case of Astellas the facility here only opened fully this year, so we travelled to meet the scientists in Japan before we met our colleagues two buildings over; of course, we now know them quite well.

Could you please introduce your OrganoPlateâ?¢ technology, and explain what differentiates your product from other organ-on-a-chip products and other organ-modeling technologies?

JJ: The OrganoPlateâ?¢ is based on the common interface that everyone uses in labs at present, the microtiter plate, and we use this to access the microfluidics which are on the bottom of the plates. Each plate has 96 individual microfluidic culture units that can be accessed through the 384-well top plate that is compatible with most automated laboratory equipment. This is something that in any other technology that we know of would take up a couple cubic meters of space and equipment to make it run with pumps, tubes, making it highly incompatible with standard lab equipment. That is the core of what we do; we bring microfluidics and organ-on-a-chip cultures in a form that any biologist will recognize and know how to work with.

PV: From a user perspective, what makes it a better predictive tool for better predictive models, is that we embrace the paradigm of 3D cell cultures, meaning extracellular-matrix-embedded cell culture (ECM), such that cells have their natural adhesion substrates, they can cluster together and form very stable spheroids. It is a huge simplification over techniques like hanging drop type cultures, with the capability to do far more. The microfluidics make it easy to perfuse the cell culture, suspended in an ECM gel, with growth media via elegant gravity-leveling flow.

The chip aspect is of course is in the microfluidics, and I think this is a revelation for everyone who has been working with these technologies. A perfused proximal tubule in the kidney or a perfused

blood vessel has a diameter on the scale of 100 micrometers, and the only way to perfuse such a structure is using microfluidics.

The trick in all of this is finding, and patenting, a way to keep the cell-culture gel, or gels if you have multiple cell-types, in place, so there is the space and access to perfuse, and to do this in such a way that the distances between the cells and the media remain physiologically relevant. We accomplish this feat using our PhaseGuide technology, which are not a wall or membrane, but a very small ridge that helps to form a freestanding liquid-air meniscus such that there is no membrane or wall holding it in place. This allows us to fill a channel with cells in an ECM, and then fill the channel next to it with media such that the two liquids directly interface with no barrier between them; we can also build more complex models with more than two channels to model multiple layers of tissue, for example a layer of brain endothelial cells, with neurons on one side and growth media on the other.

JJ: Moreover, the cells can also be seeded on the surface of gels such that we can grow complex cell structures like capillaries, kidney and gut tubules, and other structures allowing us to model higher level organ functionality. We can keep these models alive for weeks or even months, which is remarkable for any cell culture, by just exchanging the media in the one channel, as the culture gel will remain undisturbed in the PhaseGuide channel.

If you look at any disease tissue or healthy tissue it consists of multiple cell types, there are boundaries, compartments that are separated by cellular boundaries, blood vessels that perfuse the tissue, and there is ECM which surrounds the cells. To model any piece of any organ tissue, you have to provide all of these elements; we can do this, and our product allows you to easily layer multiple types of cells, and provides the microfluidics necessary to perfuse the model in one easily useable package. Doing this in the past wouldâ??ve taken a room full of equipment, a handful of postdocs, and would have been less stable and have less functionality than our product; we took this to a different level, which is the combination of usability and biological complexity in a package that can truly be called an organ-on-a-chip.

How disruptive is this technology in your opinion in terms of the impact on the drug development cycle?

JJ: There are two disruptive impacts that we foresee. The first is that at a very basic level we think this technology will replace standard 2D cell cultures; itâ??s cool to study processes in cells growing on flat surfaces, but completely useless when itâ??s about any predictive statement about tissue function and higher functionalities. You need the 3D culture aspect to take a step up in terms of biology, and we think that a lot of the standard 2D cell culture will be replaced by OrganoPlatesâ?¢ and 3D cultures in general.

However, most importantly, because it is what is driving our revenue at the moment, is that several pharmaceutical companies perceive this technology to be the next step up in terms of model development. OrganoPlatesâ?¢ completely disrupt existing alternatives in this regard, which are still 2D cell cultures, but also animal testing which is something that is still part of any drug development project, but is not an effective predictive model; the translation to humans is horrible, with maybe 10 to 20 percent of the data translating well to humans. There is a definite need to develop a more effective and predictive model for developing human therapies than the use of lab mice and the like, and growing fully human tissues using human cells in an OrganoPlateâ?¢ has the potential to do that in almost any application.

PV: On the usability side, one plate produces 96 data points and fits in the palm of your hand. Lab mice are not usually that large, but they take up substantially more space and resources to support and monitor.

However, the more major impact is the quality of the predictive model. Our early customers really had a need for an effective kidney model because there are no good kidney models that predict toxicity effects. There are similar needs for models of brain tissue, the blood-brain barrier, etc. There was a real market gap in existence that we have been able to fill.

Looking towards our next applications, we have already had in-depth discussions of doing high volume screenings of candidate molecular entities using our organ-on-a-chip models. This would be a completely new way of approaching how we will discover our new drug candidates, and they are probably going to be much better since you are checking them on a complex system of human cells.

How has the quality of findings developed using your technology been perceived so far by regulatory institutions?

JJ: As usual, the regulatory bodies tread carefully, but they have followed our developments very closely and are very interested. We see that they are visiting our booths everywhere, and the EMA and FDA have both become involved in organ-on-a-chip type projects before, but we are all aware that we have not yet brought this technology up to a level where we can say it is clinically validated.

PV: In the drug development cycle there are a few end responsibilities, and it is the pharmaceutical company that is making the decisions in the lead optimization and pre-clinical phases, and weâ??re seeing strong adoption of our technology in this setting. Then you have pre-clinical testing, and at this stage the main benefactor is still the pharmaceutical company. At some point when we can actually show that complex 3D cell culture tests are better than animal tests, then it would be time to discuss replacing, or at least complementing, animal tests.

Eventually, there will be one further level where OrganoPlatesâ?¢ could play a role in impacting drug development, and that would be in the clinical testing phase as a tool for helping to stratify patients into sub-populations, because not all humans are affected the same way by the same medications.

JJ: We have a product that can be used to build models of specific diseases to screen drugs, but what Paul is saying is that we could potentially take a biopsy from a patient, seed it across perhaps as many as 100 OrganoPlatesâ?¢. Then we can test all of the different drugs that could potentially work for a patient on that patientâ??s own cells and select the most effective drug. That is a game changer, because the current state of the art technique for personalized medicine is sequencing the DNA or RNA of the tumor, which is rather limited in scope on its own. At the very least, OrganoPlatesâ?¢ will certainly be an extremely useful tool for further developing personalized medicine approaches.

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