Ncardia
Stem cell experts

Mass production with iPSCs: an interview with Stefan Braam

Stefan Braam (Ncardia; Gosselies, Belgium) discusses how his company has pushed the boundaries with high-throughput iPSC research.

Can you introduce yourself and tell us a little bit about your role in the establishment of Ncardia?

My name is Stefan Braam. I studied biomedical sciences before doing a PhD in the Christine Mummery Lab (Leiden University; Netherlands) in the field of stem cell biology. At that point, I started to look at drug discovery and I realized that although it's interesting to do academic research, I wanted to generate an impact on society with stem cell biology. With that idea in mind, I started a company called Pluriomics (Gosselies, Belgium). After some years, we acquired another company in 2017 and renamed ourselves Ncardia. Today, we are one of the leading companies offering services with stem cells, in the areas of drug safety and efficacy assessment, and cell therapy.

Ncardia are leaders in induced pluripotent stem cell (iPSC) work. Can you give us a brief overview of what your company provides in this field?

We are a solution-orientated company and in different domains we provide different solutions. For drug safety assessments we mainly focus on cardiovascular safety and see a lot of demand for healthy cell models that closely recapitulate human biology. In this space we deliver cells, cryopreserved in a vial or live in ready-to-use assay plates. We also run those safety assays at our Services Department in Leiden (Netherlands) for our clients.

For drug efficacy and cell therapy projects, it's very different since it's much more customized. Typically, we run those projects as service or partnering projects, for which we develop custom cell models, design phenotypic assays, screen on compound libraries, and enable process development and large-scale manufacturing. Basically, everything that is needed to solve the client's problem.

You have managed to create a large-scale system with differentiations of human iPSC-derived cells, which is incredibly impressive – what were the major issues in designing such a strategy and why did you invest in this?

Looking at iPSC technology and the literature around it, you will notice a lot of low-throughput applications in 6-well and 12-well plates. Our ambition was to use iPSC technology in drug discovery to support high-throughput screening, which needed a significant increase in the number of cells. We struggled for years and years to facilitate the scaling up of the processes and, fortunately, now we've

really got that under control. The key thing in solving that was changing the culturing methodology to suspension culture in bioreactors. With bioreactors, we have now reached sizes of approximately 20 billion cardiomyocytes in a single batch. The billion is the new million.

Ncardia utilizes iPSC technology for drug discovery. How does that work and what are the advantages of this type of drug screening?

At Ncardia, we bridge the gap between clinical trials and preclinical work. We're doing that by developing human disease models that closely recapitulate the key features of a disease.

What that typically means, is that for targeting genetic diseases, we go back to the patients that carry that disease. We can generate iPSC models from that patient and manufacture the relevant cells at scale. In our case, these are typically cells in the central nervous system and cardiovascular space, but we also make combinations of various cell types to build a model with the relevant biology.

We have also developed quite extensive assay capabilities, ranging from electrophysiology to high-content imaging and biomarker expression. With these functional assays we can measure the relevant disease phenotype and thus the effect of drug candidates on this disease.

Simultaneously, we always have screening in mind too. Almost all of our assays are in 96- or 384-well plates to enable testing of large sets of molecules to identify those that might work in the patient population. Part of our drug discovery platform is the actual screen of compound libraries on these disease models for our clients.

The iPSC-based disease models are really key in phenotypic screening, but what should be considered when selecting the model for a specific application?

The first critical step is to make the right cell type. Secondly, the assay has to actually measure the disease biology. Our Pfizer (NY, USA) colleagues have published a paper discussing the 'phenotypic rule of three', which talks about the system, the stimulus and the readout.

In our case, the system is always of high value: it's the iPSC model. We try not to modulate our system too much. But if we need to, we will use physiological relevant stimuli – something that is intrinsic to the disease pathology such as genetic variants, growth factors or altered metabolism such as glucose levels. Then, in terms of readouts, we look at biomarkers that are, as much as possible, translational and could be realistically measured in the clinic.

You also develop custom assays to identify disease phenotypes. What are some of the complications that can occur in this phase and how have you tried to tackle them?

The key challenge is to find an assay system that is relevant and scalable, and for that you need knowledge about the disease biology and a well-equipped laboratory.

Once we start projects there is always quite a long list of things that we could potentially measure, so there's always a trade-off between keeping it simple but still relevant. At that point, insight into the

biology is needed to make sure to select the appropriate assay. It is quite intensive to do these kinds of projects and iPSC biology is not the easiest biology.

Another key challenge is to be able to manufacture at scale. The way we approach this is by generating large batches of cells and cryopreserve them. We do it this way to enable the usage of the same batch of cells for development as for the actual screen, to minimize iPSC variability and enhance assay reproducibility.

Why do you feel being able to have these large-scale screenings is so important?

Imagine the classical drug discovery funnel: a lot of drugs are coming in at the top and maybe one comes out at the bottom. What companies are doing – for good reasons – is to screen on the target in immortalized cells, identify a molecule and optimize it. Only at that late stage, at the bottom of the funnel, the molecule will be tested on more complex biology in animals.

What happens is that the most relevant biology is only tested close to the clinical trials, which is counterintuitive. And in addition, an animal does not always translate well to humans. In fact, what would be way more efficient is to put the most relevant biology on top of the funnel and make the best decisions early on, in order to avoid later stage failures due to safety or efficacy reasons.

We're trying to reverse these steps by bringing that human biology early into the funnel where you can have maximal impact and accelerate the process.

What prompted your entry into the cell therapy market?

When I started my PhD iPSCs were still undiscovered, but everybody was hoping to have cell replacement therapies using human embryonic stem cells instead. There was a big hype around 2005–2006 and people were saying “it will take another 10 years”. Clearly, it didn't take another 10 years.

I believe that manufacturing of sufficient batch sizes has been a key bottleneck. But we solved that issue during our drug efficacy screening projects for which a lot of cells were needed. Once we had tackled this key problem in drug discovery, we realized this was also key in cell therapy and started working with cell therapy companies.

What is really interesting is that with manufacturing a cell for a drug discovery project you are somewhat low in the value chain – you're still making a raw material for a screen. But by making a cell for a cell therapy company, you're making the actual drug product. Fitness wise, it is a very interesting direction for Ncardia.

What are the unique opportunities in using iPSCs for cell therapy?

I would say the fascinating thing about an iPSC is that it can become anything. So, the real opportunity for the cells is to move into the allogeneic space and create – from a well-characterized stem cell bank, with the appropriate immune escape strategies and at large scale – an allogeneic cell

product that can be used to treat a patient population. I think the move into this allogenic space in cell therapy is going to be critical.

What are the challenges in translating an advanced therapy and how are you addressing them?

I think what is pretty unique about the iPSC field is that we have always worked with highly compliant materials. Looking at other advanced therapeutic products, people talk a lot about removing serums from processes. That kind of noncompliant materials were effectively banned from the iPSC field quite a while ago. I would say the real challenge is gone.

So far, our entrance into the cell therapy market is surprisingly smooth.

What is needed to accelerate uptake of stem cell technologies in cell therapy and where could Ncardia play a role in that?

Let's be honest: the field is still quite young. The most advanced players are starting out with Phase I clinical trials. There are drug products in development where everybody is still struggling with the questions “is this the right cell” and “how can it be used therapeutically?”

If you analyze Ncardia from the highest level, we do three things. We work in iPSC technology, we manufacture cells at scale and we develop assays with those cells. We have learned over the past 10 years, while performing iPSC safety assessments and efficacy screens, that each of these three things are directly applicable to cell therapy. What a cell therapy developer really wants is to manufacture a cell at scale and understand that cell inside out. This is where Ncardia can really help.

What are Ncardia's goals for the next one to five years?

We are around 50 people now, all working on very exciting iPSC projects. We are seeing a lot of traction in the market, both in drug efficacy and safety assessment, as well as in cell therapy. We would like to enhance our position, to really grow with the field. Right now, our expertise in drug discovery is focused on cardiovascular and the central nervous system but we want to extend beyond that. We hope to maintain a position as the leading iPSC technology company in this space.

Questions?

support@ncardia.com

www.ncardia.com