Sustaining momentum in iPSC-derived allogeneic cell therapies

Drug Target Review **connects with Dr Stefan Braam, co-founder and CTO of Cellistic, and Andy Holt, CCO of Cellistic, for a rundown on today's landscape for allogeneic cell therapies.**

We are beginning to see more and more first patient-dosed milestones with induced pluripotent stem cell (iPSC)-based therapies in Phase I clinical trials. What makes those developments so important and exciting today?

Stefan: We are just 17 years forward from the invention of the core technology, so it did not take long to achieve broad acceptance. But what has been difficult is to really understand what it takes to differentiate an iPSC into a cell of interest. Fortunately, we now understand how to do that. We know how to control them and scale them and, as a result, we are seeing iPSC therapies progressing into clinical trials.

Andy: It is something to be celebrated, to be sure. The simple truth is that somebody has got to be first. You cannot have an approved therapy until you have a clinical trial, and now that we have clinical trials, we are ideally positioned to see how it will all playout.

Are there any myths or misperceptions about iPSC-based cell therapies that industry keeps coming up against?

Andy: Not so much myths or misperceptions, but we do tend to run into questions that we have a good "Version 1" answer for, but not yet the final answer for. For example; *how do we modulate immune response? What is the right starting cell type? What is the right reprogramming technology?* There is a lot of "pursuit of perfection" going on when we have sufficient information with which to make a start.

Stefan: I agree with Andy. We are seeing that the first programmes moving into the clinic have multiple gene edits, with the aim to make a cell that is fully fit-for-purpose to, for example, attack a tumour. It is essentially combining iPSC technology and synthetic biology to achieve the most potent cell that is well equipped to attack a tumour cell. There are still questions around that – basically, which set of gene edits is required – and it will take clinical trials to figure that out.

How have conversations around autologous and allogeneic cell therapies shifted or evolved over recent years? What factors are driving those discussions?

Stefan: There are niche applications where autologous approaches will be the best choice, like the CAR T-cell therapies currently on the market. But autologous remains process-centric, ie, it is still difficult to reach enough patients to make the economics work. At some point, supply comes exhausted as you go to larger indications. To get the cost down and the access up, you have to go to allogeneic.

Andy: There is a history of allogeneic therapy in the market, but iPSCs coming to the fore in allogeneic is really the new conversation taking place. And as autologous cell therapy gets more and more clinical and progresses towards commercial validation, it is nice to see the conversation evolve around the realisation that there is room for numerous different approaches. No modality has entirely supplanted another. And for the first time in the last few years, we're starting to hear: "I am not going to stay with autologous. If I do not see it [my approach] working in autologous, I am going to switch to allogeneic." And that is huge.

Let us say I am interested in exploring an iPSC-based allogeneic cell therapy. What attributes should be on my short list in identifying the ideal manufacturing partner?

Stefan: From my viewpoint, it is expertise, expertise, expertise. If you think cell manufacturing is difficult, iPSC-based approaches are even more so. You are starting with a stem cell that can become any cell in the body, so controlling the biology is a lot more sophisticated than a process where you simply care about transfecting something in or expanding cells. Here, you are instructing the cell to become the right cell type, which is

one of the core reasons it took so long to get to clinical trials.

Andy: Exactly. You would want a high level of expertise, given the complexity of the tasks. You would want experience in iPSC-derived allogeneic cell therapies. And you would want a team quite knowledgeable about scale-up with the facilities to tolerate it. On that final point, it is really more about how well the manufacturing is optimised for fit-for-purpose programmes; how efficiently it is run; and whether you have an understanding of how to roll with the punches when things get interesting, which they inevitably will as you bring one of these therapeutics forward into good manufacturing practice (GMP).

How do you see Cellistic's growth contributing to the industry's growth? Where does the company fit naturally in the larger industry landscape?

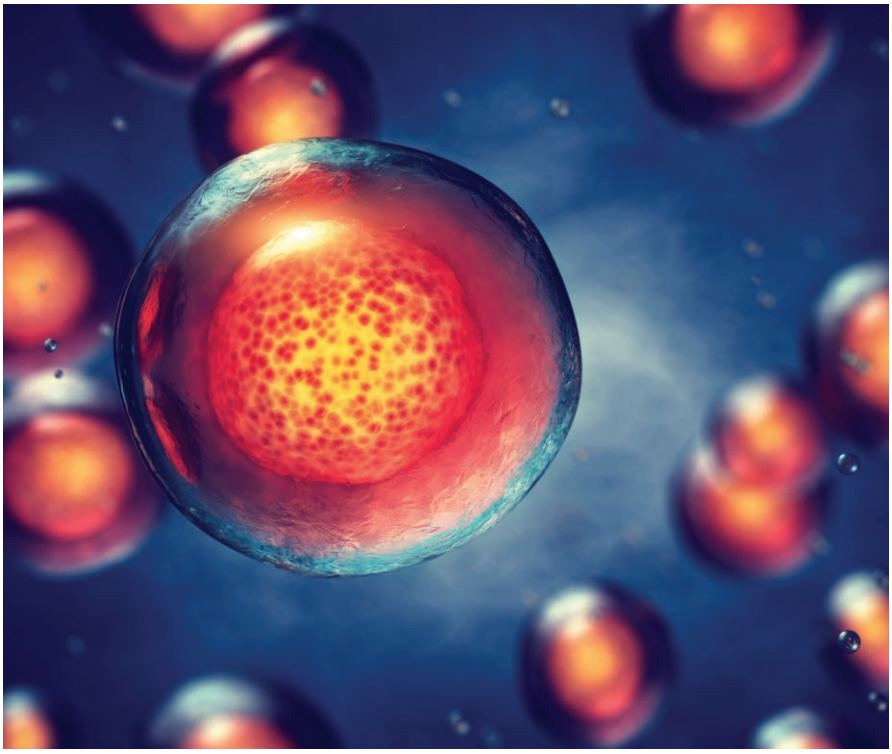
Andy: We are a speciality player. If we are going to succeed, we need iPSC allogeneic cell therapy to be viable and, of course, we believe it is. That is where our expertise lies and what we're here to do exclusively. In the larger contract development and manufacturing organisation (CDMO) and cell therapy landscape, we are a narrow and deep player, which is a bit unusual. We are hoping that we can fit into a rising tide around iPSC-derived cell therapies and accelerate them – ie, help them reach more people faster.

Stefan: And our model is a little different. We facilitate allogeneic cell therapy by making our technologies broadly accessible to therapeutic developers. We are not necessarily only working with people who are committed to iPSC, but we are primarily focused right now on companies that are working on autologous, but already considering how to make their next product allogeneic. We want to disrupt the industry by making the technology broadly accessible, and with that model we can secure a seat at the table to make iPSC-based allogeneic cell therapy a success and a reality.

Last year (in 2022), Cellistic purchased the manufacturing arm of Celyad Oncology. What opportunities – near-term and long-term – do you foresee the manufacturing capacity and capability will bring to the market?

Stefan: For me, it is all about credibility. We can only call ourselves a CDMO when we have all the capabilities required to develop and manufacture a product. In our case, we essentially looked across the globe for the right opportunity. With new technologies moving the way they are into manufacturing, I think you need your research and development (R&D) experts sitting very close to your manufacturing experts. That is why we are consolidating the whole team in one location, with our R&D team being 50 metres away from our GMP facility. I think that is the best way to de-risk the manufacturing of the novel therapies we are going after.

Andy: It opens up immediate opportunities to move into allogeneic in a way that did not exist before and grants a bit of a different finish line. We can get you to the clinic now. We can get you all the way into GMP and into a clinical trial; whereas before we were really focused on development. Now we can be a development company and a manufacturing company, which was always the vision, but now is real. Our sole focus on iPSC-derived allogeneic cell therapy makes us an ideal partner for those that want to be in the allogeneic space; think iPSC is the way forward; but do not yet know how to get it done and do not want to invest the capital in their own facility. We have an answer for that now. We can take your therapeutic concept and take it all the way to the clinic in our hands.



Dr Stefan Braam

Co-Founder and Chief Technical Officer

Dr Stefan Braam is the co-founder, patent-holder and visionary who blazes Cellistic's scientific trails. He co-founded Pluriomics/Ncardia (a sister company of Cellistic) in 2011 and, as the inventor of its core technologies, has been instrumental in the growth of both organisations. Stefan has been published in leading scientific journals, is an inventor on multiple patent families, secured multiple grants and commercial research collaborations, and was instrumental in Ncardia pre-seed, seed, Series A and B financing rounds.

Andy Holt

Chief Commercial Officer

At Cellistic, Andy leverages his experience in scaling up cell and gene therapy platforms to help Cellistic clients reach their goals in allogeneic cell therapy. When he joined Cellistic in 2022, Andy brought more than 15 years of experience in cell and gene therapy to the company. In his prior roles, he held business development, corporate development and management positions for CDMOs, driving commercial strategy and growth in adeno-associated virus (AAV) gene therapy manufacturing.

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