INTERVIEW

Capacity or capability? Getting your priorities right in viral vector manufacturing

JAN THIRKETTLE is Chief Development Officer at Freeline, a Syncona-funded start-up focussed on liver-directed AAV gene therapy. Jan has extensive experience in the development and deployment of novel platforms including natural product and enzyme derived NCEs, biologics and gene therapies. Prior to joining Freeline Jan led the establishment of GSK's Cell & Gene Therapy platform and was responsible for CMC/supply for Strimvelis, the first *ex vivo* gene therapy to receive an EU Marketing Authorisation Application. He has held industry positions spanning from discovery to commercial manufacturing, but is most passionate about late-state development, new technology introduction and project delivery. Jan holds an MA in Chemistry and a PhD in Biological Chemistry from Oxford University.

FREELINE **Q** The capacity crunch in viral vector manufacture is one of the dominant talking points in gene therapy, following a significant 12 months for the commercial prospects of the field – how does a biotech such as Freeline approach and plan around this challenge with future success in mind?

JT: At Freeline we decided to make very early investment in manufacturing because it was clear to us that we had a technology and a lead product that would be clinically effective, and so we had to ensure we had a manufacturing platform that wouldn't just enable us to get into early clinical development, but rather that could take us through to commercialisation with minimal changes along the way. To put it another way, there is a crunch in gene therapy

manufacturing capacity at the moment – however, the main issue is not getting access to capacity, to a factory with people in it. The problem is instead more about getting access to the right manufacturing capability – the technology and expertise that you need to make the vectors. Technology that is viable to use at large scale and which enables you to make products of consistently high quality isn't just out there ready to access, it has to be built.

Whilst there are CMOs offering capacity out there, this is still a new field, so the majority of them are themselves very new to cell and gene therapy and they can't offer a mature capability – whether that be technology or a long history of making these products – and developing these manufacturing platforms requires a deep understanding of the products and of virology.

So the most important first step for companies like us is to invest in the manufacturing technology early on to ensure that we have the ability to produce product at high quality, and a scale that can meet commercial supply needs.

The second step does then relate to securing the physical manufacturing capacity; the GMP facility and associated quality capabilities in which to deploy that manufacturing platform. However, there are still relatively few CMOs who can offer just the capacity for viral work, even if you provide the expertise, so there is a real squeeze. This brings with it the associated high costs and requirement to commit to capacity a long way in the future.

Those constraints are particularly impactful in early phase development where there is a need for agility on technical issues and timing of manufacture as you move from preclinical to clinical activities. Having flexibility is critical and it's very hard to achieve in the current environment on the basis of a 'standard' CMO relationship. This is what is driving many companies like us to take on the task of establishing their own GMP facilities to support clinical development. Keeping it in-house also brings important benefits of protecting manufacturing know-how and ensuring you have a strong feedback loop between process development and operational experience.

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When it comes to securing capacity for late-phase and commercialization, it's much more of a balanced question in terms of 'outsource' versus 'do it yourself'. At late-phase and commercial stages there's: a) a greater ability to commit funds ahead; b) your production plans are much more fixed; and c) the facility and quality systems requirements are much more demanding, which calls for a different sort of operation. These factors then weigh much more heavily against the

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flexibility side of the equation. That said, the need for long-term supply security is critical, so a tactical CMO relationship isn't going to cut it, either.

Q Can you expand on trends in the gene therapy CMO sector – how do you see them developing?

JT: Within the past couple of years the CMO sector has clearly woken up to the fact that gene therapy is here to stay, and there is now definite demand there. However, building capacity – and even more so, building capability – is not a quick process hence the capacity crunch. The field is clearly responding to the demand, though, and thinking increasingly about meeting the needs of late-phase companies. More recently, we have seen the more committed CMOs starting to invest in developing their own manufacturing platforms to offer. As I said earlier, I don't see these offerings meeting the commercialization needs of product companies with significant production needs, but CMOs being able to offer scalable manufacturing platforms will be important in enabling the next wave of product companies to get into early clinical development more quickly and securely.

The other trend I see relates to addressing the business model for those companies who are weighing up how to best secure long-term commercial capacity. The more forward thinking CMOs are recognizing the need to support product companies who have their own technology, and who want to remain very close to their technology when its deployed. Such companies are offering business relationships that are much more customized; this relates to everything from the IP terms to support for customer involvement on-plant, to models such as facility sharing and build-to-buy. I think we'll see quite a range of different partnering models and more bespoke deals in the coming years, particularly with the bigger players.

Q This month's Spotlight focuses in part on overcoming challenges in viral vector bioprocess tech transfer and scale up – what are the key considerations for each area, for you?

JT: Whilst we are lucky to be able to leverage the principles of tech transfer established in the biologics field (and indeed, at Freeline, we're able to benefit from many individuals who have that experience) there are some significant challenges we face because these viral products are not the same as historical biologics. Given that the viral experience of most CMOs is limited, there is a

substantial familiarisation task to ensure that those nuances are understood and practices evolved as needed. There are no short cuts here – you need to invest in lots of face-to-face time, training and good documentation. The willingness of the partner/CMO to invest in this sort of training and upskilling is for me a really important differentiating point when selecting a partner.

On the scale up side of things, it's very similar. We are able to pull in manufacturing technologies and development strategies that we have inherited from the biopharma space. That's great because it's allowing us to move a lot quicker than the biopharma field was able to in the '80s. Again, gene therapy products have their own subtleties and that requires different approaches, often different technology choices. What may have been important for quality of a biologic may well not be important for a viral product and often those differences are not well understood unless you are really familiar with these products; this particularly affects cell culture and analytics.

So we still have to invest a lot of time and energy with the equipment companies, with the providers of reagents, and in particular, with the analytical providers; either to help them really understand the intricacies of what our product needs, or to work with them to develop new technologies. This is where you see real differentiation between companies – those that have 'got it' and are investing in that development and time to understand the technology, and those who are just trying to repackage their current biopharma offering for a new customer base.

Q In addition, we explore emerging non-viral approaches such as exosome- and DNA-based delivery platforms – what excites you in particular about that field, currently?

JT: For me, this field is still at a very early phase. You just need to look at how long it's taken to get viral gene therapies to a point where we've got a good enough understanding to use them as effectively and safely as therapies, and to make them at scale – decades.

That said, there are clearly limitations with all the current viral systems. For instance, AAV has limitations on the size of the transgene, and lentivirus is very difficult to make and to control how and where they integrate their payload. So whilst I'm sure we will see significant progress on the viral manufacturing front, some of these limitations are intrinsic, which means there is opportunity to address them, no question about it. That said, whilst there is a clear opportunity for non-viral systems, the challenge will be addressing those limitations whilst not losing what the viral systems do so

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well. The viral systems have set the bar really quite high in terms of expression level, copy number and transduction efficiency – and now safety, too.

Q A further trend we examine this month is the evolving relationship between gene editing and vectors – what are your thoughts on likely future developments there?

JT: This is very much linked to the previous point, however do I think that many outside the field see gene editing and gene therapy as two different things. In reality, gene editing technologies are just one part of the evolution of the integrating gene therapy vectors, and it's very likely that they are going to need viral systems like AAV to actually deliver them for the foreseeable future

There's clearly opportunity there; to integrate your target gene into a specific, designated location as opposed to it being delivered randomly could have real benefits in some areas. However, as I said, the bar has been set quite high by the latest generation of viral systems as regards the efficacy and safety they are delivering – viruses have had an awful long time to get good at delivering DNA, after all!

As I alluded to, the gene editing systems themselves need to be delivered into the target cell. If you like, they are not a complete vector in their own right, but a very sophisticated enhancement of the integration machinery of a viral vector. A big challenge is how you deliver them into the cell without damaging that cell or eliciting an immune response. There are clearly a range of ways to do this, including non-viral systems, but I would expect that for the mid-term at least, viral systems will be used to deliver gene editing tools – so more a case of evolution than revolution.

Q It's been a huge past 12 months for gene therapy. What are your hopes and expectations for the year ahead?

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JT: Within Freeline we are really excited about the year ahead. We are all about getting transformational cures to patients and without giving too much away we are looking forward to taking some big steps towards that in more than one therapeutic area. For the

field as a whole, I am looking forwards to seeing more commercial approvals, but I think what will be just as exciting will be seeing compelling clinical outcomes in a broader range of therapy areas. Within the past few years, we've seen transformational efficacy in a number of rare monogenetic diseases and in oncology. More recently, we've seen product approvals in those areas. These have shown that there is both a regulatory path and a reimbursement pathway – i.e,. shown that these therapies can be commercialized. With that trail-blazing done, for me the next phase is all about showing that gene therapies can be delivered to large numbers of patients and that the modality can deliver safety and efficacy in a broader range of indications, not just cancer and monogenetic disorders. I have no doubt that this will happen and at Freeline we're working towards exactly that. The momentum is there and the understanding of the technology in building exponentially, but seeing those steps achieved will be what the 'second chapter' of gene therapy is all about.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

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