STRATEGIES FOR SCALE-UP & SCALE-OUT

SPOTLIGHT

INTERVIEW

Importance of Innovation and Design in the Scalability of Cell & Gene Therapies

STEPHEN WARD **Chief Operating Officer, Cell and Gene Therapy Catapult.** Stephen was appointed Chief Operating Officer of the Cell Therapy Catapult in January 2013. He brings over 20 years of biological medicine research, development, and manufacturing experience to the organisation. Stephen enjoys bringing cutting edge technologies to patients, by developing commercially viable products and has developed and validated scaleable, commercial manufacturing processes for cell based medicinal products, vaccines, and recombinant biologicals.

JULIE KERBY **Head of Manufacturing Development, Cell and Gene Therapy Catapult.** Working closely with our collaborators she is responsible for the development and technical transfer of cell and gene therapy manufacturing processes ensuring they meet quality and regulatory requirements. Julie has more than 20 years' experience across large pharma, biotech and academic laboratories, including 7 years at Pfizer Ltd as Biology Lead for a cell replacement therapy for Age Related Macular Degeneration which achieved First-in-Human in 2015. Julie holds a BSc. Hons degree in Biology from the University of Southampton.

DAMIAN MARSHALL **Head of Analytical Development, Cell and Gene Therapy Catapult.** Joining the Cell and Gene Therapy Catapult in August 2013, Damian leads the assay development and validation team which underpins a diverse portfolio of cell therapy products at various stages of clinical maturity from pre-FiM to phase III. Damian has over 15 years of assay development experience in the cell therapy and life sciences fields having previously managed the R&D portfolios for both SMEs and LGC Ltd and has successfully managed a European life sciences business with an annual turnover in excess of £15million. Damian graduated with a degree in biological sciences and a PhD in developmental biology from Manchester University.

Q The current cell and gene therapies entering the market are for relatively small patient groups, as we move to larger indications what do you see as the critical issues around scaling?

SW: The key fundamental is to really understand the product that you're developing, and what you're working on. Without that, trying to produce that material/product at scale is an extremely challenging undertaking.

Our knowledge space around our products is really quite limited, and for some of these therapies they are still relatively immature, and that feedback loop from manufacturing, development, through to research, is still developing. However, one has to still capture more information as early as you can in the development cycle.

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This could mean better historical data packages, putting down some reference material, and really giving you options so that you can do more product comparability as you move through your development cycle and put an industrial process in place.

The second critical factor to think about early on is your raw material supply process. Changing key raw materials as you go through a development cycle can be challenging, often more impactful than an automation change. So really invest in your raw material supply chain as early as you can. Understand the quality of the materials, the variability of the material and also understand the robustness of supply of those materials.

Q Do you think that for cell and gene therapies to become part of mainstream healthcare, that the allogeneic model is the only way to achieve cost-effective and reimbursable products?

JK: No I don't - I think depending on the clinical indication the autologous model is entirely appropriate. The challenge is all about the scale-out as you move through your clinical development programme towards commercial manufacturing. As patient numbers increase, the logistics you have to overcome, thinking about the clean room footprint, the grade of that clean room – these are all key considerations in your scale-out strategy

The number of operators required can be really challenging: recruitment, training and retention of these skilled staff. And scheduling around

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the whole process – obtaining your starting material, putting it through your process and back out to clinic. These are all things that need to be thought about with a degree of care.

Equally your quality management system needs to be considered. The quality control burden for each of your batches, thinking about how you're going to release multiple batches, often simultaneously for multiple patients. And these all impact your cost of goods significantly and that's really where the concern lies around the autologous model: the need to drive down costs as we move to commercial scale.

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At some stage there's a tipping point in a manufacturing process in its clinical development, where automation and intensifying the process makes a lot of sense. This can be as early as thinking about modular automation with your existing equipment and controls, moving from say sampling testing to in-line testing. It could even be an integrated platform.

Q Where do you see the opportunities for innovation in the manufacturing pathway that will support the effective transition to commercial-scale manufacture?

JK: For me at the moment the biggest gap is with the cryopreservation technology we have available. Some of our therapies use quiescent, terminally differentiated cells, and at the moment the formulations and technologies for cryopreserving cells really don't work very well for those cell types. This really limits where those cell therapies can be manufactured, often having to be close to the point of care. If you're lucky you might have 24 hours stability of that product, so that limits your options.

SW: There are also several other opportunities we can go after as a sector. If one looks at it holistically the industry has really grown up in two ways. Firstly, certainly with small volume therapies, we're basically adapting systems that are coming out of the blood industry. So we're still looking at sterile tubing sets for example and ways of handling those relatively mid-sized volumes within those tubing sets and bags.

Secondly if you're in allogeneic cell therapy or gene therapy production you're looking more towards the established biopharma systems in terms of stirred tank reactors and downstream purification.

But I think there is a third way and that's the big opportunity for us as a sector. We can actually do our own innovation which is specific for cell and gene therapies. Certainly for the cells I think there's a rich seam which we can look to be mining in fluidic path disruptive technologies, so low volumes. How we are going to work with low volume products in the future as we increase the purity and knowledge of our therapies? There's some really interesting small volume fluidic work going on in terms of sorting as well.

In addition, looking at synthetic materials, not only in the production paths themselves, but also in the raw materials. Synthetic mimetics, driving down cost of goods, bringing up predictability and reproducibility in your product streams.

So I think those are really interesting areas for us to get into, to carve out a path that will actually feed innovation back into other sectors, such as biopharmaceuticals as they go down smaller batch sizes themselves.

DM: I also think there are some opportunities for looking at how we can put more of the product release testing back into the process. In particular the concept of looking at real time release or multistage release of products. This could overcome some of the limitations that some cell therapy products have in terms of low production volumes, limited manufacture times, or even short shelf life if you're working with freshly formulated products.

Over the last few years we've seen a lot of interest from companies looking to see how you can build more testing back into your process – and in particular rapid microbial methods.

Now there is a lot of work going on in this area, and in particular we've seen a lot of work looking at rapid mycoplasma testing as there are now validated kits available to do this. These kits are really good because they're reducing your testing time from 28-35 days, which is what you'd have to do if you were using a pharmacopeia test, down to less than a day. So there's obviously some real advantages in doing that.

The challenge then is how do you take that beyond mycoplasma? We've been working for a number of years looking at how we can start using nucleic acid based tests to look at things such as rapid sterility. Now it seems like an obvious step on to go from mycoplasma to sterility, but the actual challenges of doing that are pretty significant. In particular the challenges around avoiding false positives. It's just a fact that a lot of the materials we're using within our processing could have come from bacterial sources, and you could have residual carryover of nucleic acids. These have the potential to give a false positive test you wouldn't see on your standard pharmacopeia test which is growth based. So we've had to put a lot of effort

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into looking at how we can overcome those challenges in order to try to get more rapid microbial methods available for companies.

I also think going forward there are other opportunities to look at how we could get more of the final product testing built back into the process. This could be looking at areas such as purities or impurities, testing for these earlier within the process while providing enough assurance that by doing this testing you can have confidence it's not going to change in your final product.

Ultimately I also think we can look at how we build potency testing back into the process. Now that's probably the biggest challenge, because first of all you're going to need a very good potency test, it's going to have to be a very robust, and also have a relatively high level of sensitivity so that you can test within your process and still have enough confidence or assurance that it would hold with the potency of the final product.

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Q A critical part of your scaling strategy is to ensure product quality and comparability, how is the analytical toolkit evolving to support that process?

DM: That's a really good question. I guess the answer is the analytical toolkit is continually evolving. The challenge is to develop measurements which you can use as an anchor point to support your future scale up or scale out activities.

Firstly, it's important to have a good starting point to understand your product, to be able to show comparability. The normal way you would do this is to start off with your target product profile, from that you'd then be able to define your critical quality attributes and your critical process parameters, and then develop a control strategy around them.

Now these could be direct measurements if you know what you're going to measure, or it could be using screening technologies, and increasingly we're seeing more and more companies starting to use omic based approaches to try and understand their products. This is driven a little bit by the complexity of the manufacturing processes and the environment the cells are growing in, and it's also driven by a need to get a really good level of information to understand your product.

We're seeing a lot of interest in a whole range of 'omic' approaches. Transcriptomics and proteomics are the obvious ones, and have been around for a long time and companies are increasingly using these as screening tools. However, interestingly we're also see a lot of companies now start to adopt

metabolomics as an approach. Metabolomics is really interesting because metabolites are the end products of cellular processes and therefore metabolomics gives you a real functional read out of your cell. It's telling you how your cells are responding to their environment, it's telling you how your cells are behaving, and it's giving you indications of how you can actually control the way those cells are behaving.

If you look at how this is being used within the biopharmaceutical industry for example, they're using metabolomics to try and understand how they can drive higher cell numbers or higher titres of a product. Those are immediately transferable to what we're trying to do in cell and gene therapies in terms of trying to use the same approaches to control the growth environment. Now we may not necessarily always want to be driving higher numbers of cells, but it's about allowing us to get that higher level of control by understanding the way the cells are behaving and interacting with their environment.

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I think metabolomics also creates a number of opportunities to look at how we can come up with novel feeding strategies, and how we can come up with better ways of providing the things our cells require in a more timely and sophisticated way than just having fixed feeding regimes.

JK: I think all those analytical assays coming to the forefront now are incredibly exciting and going to offer real value. But often developers struggle with investing in new technologies, new analytics, when actually what they're trying to do is accelerate to the clinic as early as possible. So really the advice there is just try and do as much as you can as early as you can, even if it's something as simple as banking samples for later use.

DM: I couldn't agree with that more. We've seen this from people who have gone through the process of developing products, particularly companies that have got products through to phase 3 or are looking now at market authorisation. When you ask them about screening technologies they're all about the more information you can have, as early as you can get it within your process the better.

Another thing I'd like to touch on briefly is the opportunities for looking at process analytical technologies, or PAT. This is a concept of analysing and controlling your manufacturing processes through measurements of

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your critical attributes with a view of ensuring your final product quality, and I think there are a couple of opportunities we have here.

The first is to look at how we can build on what's been done in other industries such as the biopharmaceutical industry for inline measurements. For example, if you've already scaled up your product there may be opportunities for looking at how we can transfer some of the probe based technologies and embedding those within our cell and gene therapy manufacturing processes. Some of those of particular interest are the spectroscopic techniques that allow you to measure several parameters simultaneously. This could be measuring something simple like glucose consumption and lactic acid production. Now we can already do that using offline measurements, but by building these as in-line measurements we can do real time monitoring, giving us the opportunity to have a much finer level of control. With these probe based techniques and in-line technologies, we can also start to look at how the cells are using component that are more important for the quality of cell and gene therapies. This could be the interactions of the cells with particular cytokines or growth factors, measuring their depletion from the media.

I also think there are opportunities for looking at how biosensors could become more widely used within cell and gene therapy manufacture. Once we have a really good understanding about what it is that we need to measure then that could be a real driver for innovation in our field, looking at how biosensors and novel technologies could be developed and integrated within our manufacturing processes. Given the fact we're not using lockdown processes or platforms, I think the opportunity to embed these technologies into cell and gene therapy manufacture processes is pretty significant, and I think a lot of companies within this field will be willing to adopt these types of technologies to support their manufacturing.

Q What implications might these new tools have on the regulation of cell and gene therapies?

SW: We're not an expert regulatory panel here today, however there are several broad themes which I think are pertinent to comment on. Firstly something that is fairly obvious and self-explanatory but often forgotten about and overlooked, is when we're developing these therapies, CMC professionals need to work very closely with their regulatory colleagues. It's to ensure there's a smooth path through the development cycle, and to take away any pitfalls or problems that are going to pop up later as you go through the regulatory system.

And indeed as companies are looking to get accelerated approvals, then the role of the CMC professional and the scrutiny of development and manufacturing is more intense and comes even earlier in a development cycle than where it traditionally used to be. So it's all about the manufacturing, the development, and understanding the regulatory impacts of your choices as early as you can.

Another factor is the staging of product release. It's already changing, and I think it will continue to evolve as these products develop. The role of the Qualified Person or the equivalent to release this product, how is that being done, is it more automated rather than manual processes and systems we have today? I think that is an area of intense regulatory activity and interest.

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Finally, inevitably for these therapies, we are going to manufacture over multiple sites. It may be a handful of sites across the globe, or it may bemultiple sites in more regional or local centers. So how will that work from a regulatory perspective? Not only just from a GMP licencing aspect, but also the interactiom between the hospital pharmacist and pharmacies for example.

The UK Government has just released £30 million for example to set up these advanced therapy treatment centers to be test-beds to look at how to put these platforms in place so the end-to-end supply chain works in large healthcare systems. We also need to address how the pharmaceutical and administration elements come together, as well as perhaps some local manufacturing, to ensure that these products become mainstream clinical medicines that clinicians turn to rather than niche therapies which are difficult to administer, difficult to handle, which will ultimately limit their geographical use.

Q What do you envision the factory of the future will look like, and what do you see as the critical steps that need to be taken to get to this optimized manufacturing model?

SW: It's a really interesting question, and I'd like to answer this in three parts. Firstly, what drives factory design is scale. Often that's driven by the risk profile of the organization, and the therapy type – so batch size versus the cost of failure effectively. How big do you want your batch to be in terms of its impact of cost and clinical supply if that batch fails?

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From an allogeneic perspective that can be volume or number of cells. For autologous it's often the number of batches you want to do in parallel. And that will effectively drive your production room size. Also impacting room size are things such as operational excellence parameters, so the number of people you would like to have as an optimum. The optimized material flow, both incoming and outgoing within those rooms. All of which will start to set your foundation design of the type of production space you're looking to design.

The second thing is then the more detailed design. Now we're still a relatively immature industry, so the factories are, I would argue, more fully flexible than bespoke for the therapies we're developing. People are still going through an evolution chain on their processes, so factories which can be future-adapted are clearly essential. And indeed people reading this interview may well be aware of the Catapult cell and gene therapies manufacturing center north of London which has been designed to give segregated rooms, segregated production, all based on good design principles, to allow materials to move through in a unified way. Unidirectional flow of peoples and materials for example, all of which have functional importance for large-scale allogeneic processing as well as scaled-out automated and semi-automated autologous processing. So all of these allow one to not have to bet on the processes of the future but enable full flexibility to adapt as we scale.

And the third element is the critical mass of support that you need around a facility. This is often overlooked. People think about the immediate production space itself, but to support that space there's an awful lot of activity, often 4- or 5-fold the amount of production support staff needed compared to the actual production staff in the room.

So here I'm thinking of environmental monitoring capabilities, you're in process QC as well as end-stage QC, if that's on site or off site. QA group managing that GMP architecture and infrastructure. Engineering group facilities as well as equipment. Support teams in terms of clean room cleaning and wet area cleaning. All the way through to then managing your starting and raw materials, and liquid and solid waste, which can be quite considerable for large volume allogeneic processing.

So if one puts all that together then you end up with something that one could argue is a well-supported building which has sound operating and design principles in place to allow one to flex the processes that are intended to be run within that clean room environment.

And this type of factory is what we've designed at the Catapult and I think exemplifies what is needed over the next 10 years as more therapies move to commercial scale. This will realise the potential in the preclinical and clinical pipeline we've currently got across the globe. But there will be disruptive technologies that are going to be needed that will come on stream and make these factories even more advanced and different to what we have now.

JK: I think there are some really exciting technologies being developed at the moment which could make a significant step change to the field. I was lucky enough to recently see some augmented reality on gowning and the programme used facial recognition to tell the operator exactly what part of the gowning procedure they needed to do next, check they were doing those steps correctly. And then therefore allow them into the clean room appropriately gowned.

The idea is that by doing this daily checking you can actually reduce the training burden for those operators, because with that kind of documentation and the environmental monitoring checking the operators, QA can review and say those operators are trained.

So there are all sorts of ways that technology could impact. Another way new technology could support us is by looking at cleaning in the clean room, so by observing the operator and making sure the reagent has been used for the correct contact time, and coverage has been maintained, we can again reduce that QA burden and possibly some downtime of the clean room by not being cleaned adequately in that particular process.

> "this type of factory is what we've tried to do at the catapult, and these sort of exemplify, I think, what is needed over the next 10 years."

Another exciting area is the potential use of biocidal materials that could be incorporated into the build of our equipment and clean room surfaces. Again reducing some of that manpower and oversight burden.

So those are just a couple of examples of technologies which are coming very soon to our facilities. And I think are really exciting and could really change the way we do things in the future.

SW: If we look to the future, the graspable future, not the distant future, then I think one thing we're going to see that is very different to what we're looking at today is the size of these manufacturing facilities. I think the footprint per batch and complexity of the facilities we're currently working with is going to collapse dramatically. And that's going to be driven by two elements – process automation producing lower volume, higher potency, cell and gene therapies, being driven and controlled by an integrated smarter processing and release control set. All of which is going to take a lot of the complex engineering and a lot of the hands-on QA away from the factories of the future, to produce more cost effective but still efficacious and safe medicines.

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