CREATING A LOGISTICS STRATEGY FOR COMMERCIALIZATION

SPOTLIGHT

INTERVIEW

Logistical considerations of the cell therapy supply chain at the point of care

KAREN COOPMAN has a background in pharmacology and has always had an interest in healthcare. The overarching theme of Karen's research is the manufacture of cellular therapies. The ultimate aim is to generate a viable stem cell bioprocess such that clinically relevant cell numbers can be generated whilst ensuring product potency, purity and safety. Developing scalable systems for stem cell growth and improving methods of cell preservation are the current focus of her group. A Reader in Biological Engineering at Loughborough University, she is the Director of the EPSRC/MRC Centre for Doctoral Training in Regenerative Medicine and is also on the Steering Group of BioProNET and Chair of ESACT UK, the UK Society for Cell Culture Biotechnology.

Q As the cell therapy industry is maturing and more products are entering the market, what do you see as the key bottlenecks for the cell therapy supply chain?

KC: Downstream processing and delivering the therapy in general are the key bottlenecks in the cell therapy supply chain. By delivery, I mean the decision as to whether cells can be delivered fresh or frozen. It's often a decision which is driven by practicality rather than an understanding of how preservation impacts cell function. Because a lot of cell types, like cancer cell lines, are frozen for research purposes, many people assume that these types of cells for clinical use could be frozen too. But it's not as easy as that when we need very high recovery rates of not only

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viable but functional cells. Getting people to understand the need to look at that problem very early on is one of the key challenges.

The other challenge that is a generic issue with manufacturing is quality control. It's a fact that in many cases we don't understand our products well enough to have good surrogate markers of quality or function that are easy and quick to test.

There's also lack of consistency in terms of how the cells are collected and processed initially. Compared to the manufacturing processes of monoclonal antibodies and other pharmaceutical products that are controlled incredibly tightly, the cell therapy manufacturing process has a lot of variability factors which are not controlled. In addition to the donor variability, or patient variability in the case of autologous therapies, there can also be variabilities in terms of how cells are collected, processed and stored before being taken to a processing plant.

Q What are the specific challenges associated with delivering final product to the patients?

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KC: In terms of administration to patients, there's some real questions that remain around dosing, and part of that is about retention of cells in the right location. Although a lot of clinical trials utilise high numbers of cells to start with, we know that many of those cells never make it to where they should, or they don't stay there for very long. There's a real need to develop new clinical or medical devices for cell delivery or administration to patients that will help that.

However, again, it comes down to how we first test the quality or function of those cells, and how do those change whether you're producing a fresh or frozen product as we may also be delivering damaged cells to the patient. For example, there are multiple conflicting studies from across the world, and from different cell types as well, that either show there are differences between fresh and frozen cells or that frozen cells perform with the same efficacy as fresh cells *in vitro*.

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People are getting a very mixed message and that's a real conundrum. Ultimately, people do need look at this early on for their specific product to see whether the cells perform differently when fresh or frozen. I suspect there is something about either cell type specificity in terms of how they behave in either hypothermic conditions or frozen conditions, or also how that relates in terms of function to the disease or disorder they are trying to treat.

The other concern which was overlooked for a long time, but I'm pleased to say there's now progress in that area, is controlled thawing. We've spent a long time developing measures and formulations for controlled freezing and there are many devices available now to do controlled freezing. But thawing often means just leaving a vial to thaw on the bench or in a waterbath for a few minutes. The fact that companies like Asymptote in the UK are actually tackling that with the development of controlled thawing devices is a really good step forward, because I think that would ease some of the challenges around actually getting the product into the clinic.

In terms of transport and logistics to the point of care, the challenges we face in the cell therapy logistics sector are not around the logistics necessarily but around the fact that fresh cell therapy products inevitably have a short shelf life. So even if we can maintain temperature under the right conditions while we do the transportation, the fact we need to transport and that inevitably incurs time means we're eating into that shelf life. This will remain a challenge unless we operate under redistributed manufacturing models and have a clinical manufacturing site together with or near to the clinic.

Q What are the possible routes of cell therapy delivery to clinical sites and what are the factors that decide the best suitable route for a product?

KC: There are 3 main delivery routes. Firstly, you can have a fresh product which is stored either at room temperature or refrigerated temperature. This method often has limitations in terms of shelf life. The formulations we use at the moment tend to be fine for a day or two, but not beyond that although there has been some progress being made in that area. Companies like Atelerix, a spin-out from Newcastle University has done a lot of work around encapsulating cells in alginate gels to improve their persistence during storage and transport, even at room temperature.

Secondly, you can have a frozen product which has both pros and cons. You could store the product for a longer period, but cell viability could be compromised due to freezing as I mentioned earlier. In addition to immediate cell death, there's also the possibility of delayed onset apoptosis

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which means that although initially the cells might appear viable, once you do your first release assay, the cells have started to die. That's a challenging issue in terms of putting it into the patient and there may be impacts on functions that we're not yet aware of because our quality control measures might not pick these up.

Thirdly, we have the interesting possibility of the mix of those two methods and I think that could be the best option moving forward. We store a frozen product because that enables a longer shelf life, and then, whether on-site or at the manufacturing site, thaw the product allowing some sort of controlled recovery period to effectively remove any debris, to allow us to say if there is any delayed onset apoptosis, because that's normally detectable within 12-24 hours. You do end up with that shorter shelf-life at the very end, but if you can coordinate when those cells need to be ready and know it's a 48-hour period, coordinating that with the patients and surgeon etc would be much easier than if you had a truly fresh product from start to finish.

What method you are going to adopt will to some extent also come down to whether you have an allogeneic or autologous therapy. Allogeneic therapies lend themselves much more to a cryopreserved type of product, because you want to create larger batches and store them for a longer shelf life. The method will also depend on what the options are in terms of either being able to manufacture the product at the clinical site, or whether that's something you'd have to do at a centralized location.

Q You mentioned about the possibility of manufacturing at the point of care. How geared up are many healthcare sites to deal with on-site cell therapy manufacture?

KC: Certainly, cell therapy products can be manufactured and processed at clinical sites. However, I don't think there are very many options available yet. Ahead of starting their own manufacturing centre, the Cell and Gene Therapy Catapult spent some time looking at the GMP manufacturing sites available in the UK, and actually it's a fairly small number and often focussed around a single therapy. One example of a hospital that is set up for GMP manufacture is the Robert Jones & Agnus Hunt Orthopaedic Hospital in Oswestry where they have been

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pioneering in the development of autologous chondrocyte implantation for cartilage defects and the use of mesenchymal stem cells for bone repair.

Now it's too early to tell what the preferred option in the future would be. We could either have hospitals that have the facility to do different types of therapies within a single facility, or we could end up in a situation where we have more specialised facilities such as that in Oswestry which focus on a treatment area, in their case orthopaedics. There are also discussions around decentralized manufacturing versus centralized manufacturing if the product can be made off site.

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Processing and manufacturing cells next to the patient is advantageous in that cells can be administered fresh without having the need to freeze them, and that could in many cases mean better quality (i.e. functionality) of cells.

Q At what point in the product development pathway should manufacturers begin supply chain planning? What are the factors to consider when developing a market viable supply chain?

KC: As early as possible in the product development pathway is my answer. Often people panic when they start seeing some clinical success in early trials because they know they may need to make changes in their manufacturing to accommodate the larger scales needed for later Phases. We don't want anyone to be in that situation. The sooner you assess whether your product can be supplied fresh or frozen, the better. That will have impact on the

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shelf life and therefore decide where you need to be located, and who will potentially have access to your therapy, how easily your process can be scaled, etc.

To leave that to the point where you've proven you have an effective therapy would be a bit naïve in a way. As you would have to do a lot of work to prove to any regulators that your product has stayed the same even though you've made this quite significant change as to how you do want to deliver the therapy. So understanding that as soon as possible is the absolute key. Our recent work here at Loughborough has also shown that making changes upstream, for example, what you are using in terms of your culture medium actually can impact how robust your cells are during the preservation process and so the industry needs to understand that they need to consider their preservation method as an integral part of their process design, rather than leaving it as an after thought.

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It's perhaps less of a challenge for autologous therapies because scale will never be a challenge as you'll always be scaling out and doing multiple patients rather than creating big batches. But it becomes quite important for allogeneic therapy. We can quite easily freeze 5 or 10 vials of cells, but even if you're using a vialing system, it can take an hour to prepare 400 vials if it's going off to a cell bank for creating an allogeneic therapy. Can your cells sit in their formulation for an hour and what is the impact of formulation on the cells? You might have shown that cells can be frozen, but you don't know how the cells are going to be affected with all those holding steps over those time scales. That could make a big difference.

For autologous therapy, donor variability is the main challenge. You have patients who are not well, and how those particular patient cells deal with whether it's hypothermic storage or cryopreservation might be different. You will need to determine the 'safe' process parameters that give you a consistent product output even with input variability. That may be quite challenging but incredibly important because you won't ever want to face a case where you suddenly find yourself apologising to a patient that their cells didn't make it.

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Q With so many variables in the cell and gene therapy supply chain, how can the risk of delays and temperature excursions be mitigated?

KC: You must work with logistics companies which understand what your product can and cannot undergo, and you must develop close relationships with those companies. Even on just a small scale, if I think about cells I have shipped worldwide as part of collaborations, there were certain couriers I would trust more than others. Because they understand the impact and take necessary measures like having extra dry ice in case they get stuck at customs.

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We also need to develop robust processes. We need to test how the products actually respond to factors like temperature excursions so as to establish a base limit. For instance, would the cells be fine if a 5-minute period of a freezer not working, or is it 2 hours when it becomes a problem? Those sorts of things really need to be understood. Many companies are probably doing this as part of their regulatory portfolio they have put forward, but it's not something that gets reported in literature necessarily.

It goes without saying that we need data loggers and other technologies to record and track data. A lot of those systems exist in other areas such as the food industry, we must be able to take advantage of these technologies from the other industries.

Q How do you see the field emerging in the next 3-5 years? Do you think a fully integrated, end-to-end supply chain would be a reality in the near future?

KC: Efforts for integrating the supply chain is already underway. In terms of logistics, its promising to see that processes such as controlled thawing are gaining attention and we will have a better understanding of it in the coming years.

As an industry, not just necessarily in logistics, it's about those bedside point of care or closed systems that are going to have the most impact. They won't necessarily work for modalities like CAR-Ts because there's so much additional processing needed, but I think those are a good step forwards to try and simplify and take away some of the manual processes within cell therapy manufacturing.

We need systems that make traceability, particularly for autologous products, as easy as possible. That's where the relevance of cell orchestration platforms come into picture. These platforms enable the easy integration of the delivery path from needle to needle. It will give stakeholders on-demand visibility and chain-of-custody data for immediate traceability and validation. By traceability, I meant not just about where the sample was and was there consent but creating a temperature map of these cells from one point to another. This will be very important to develop end-to-end process control.

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