The sensitive journey of the cell

This is a really exciting time for the research community working on cell-based therapies. “The fact that there are some therapies making it through to clinic gives us all hope that we can get there,” says Dr Karen Coopman from Loughborough University. She has been testing whether GrowDex can enhance stability of mesenchymal stem cells, enabling them to be stored under different conditions.

A lot is happening in the field of cell-based therapies. There are hundreds if not thousands of clinical trials going on at the moment, and varied types of cell-based therapies are being explored. “The scale goes all the way from stem cells such as mesenchymal stem cells through to T cell therapies, for example. Last year, Kymriah cell therapy for blood cancers received FDA approval and made big headlines. So it’s a really exciting time. There are still challenges but we are now starting to see the fruits of that labour as we see particular therapies making it to clinic. It is what we always wanted,” says Dr **Karen Coopman** from Loughborough University.

Coopman leads the Cell Technologies Research Group that is based at the Centre for Biological Engineering at Loughborough University. The overarching theme of the group’s research is the manufacture of cellular therapies. Work is being done with industrial partners. “In our field, collaboration between industry and academia is incredibly important. We need it to understand what kinds of bottlenecks and challenges for manufacturing still exist and what kinds of novel technologies or applications should be developed.”

Potency, purity and safety

Coopman’s current research focus is in developing scalable systems for stem cell growth and improving methods of cell preservation. “The key challenge for us is cost. We recognise that these are expensive products to develop and manufacture. We also have a real challenge with variability. Whenever we work with patient or donor material, we have that inherent biological variability: my cells will be different from yours.”

Coopman notes that in such instances, the sector as a whole does not really have a good understanding of what a particular cell type or the critical quality parameters or characteristics really are – what makes a particular cell type and what makes it effective therapeutically. “But the fact that there are some therapies making it through to clinic gives us all hope that we can get there. There’s just a lot of research that has to be done.”

Growing mesenchymal stem cells

Coopman’s research group, together with Prof Hewitt (Aston University), Prof Nienow (University of Birmingham) and Dr Rafiq (UCL), has focused on growing adherent cells, particularly mesenchymal stem cells in stirred-tank reactors. They have reached cell densities of about a million cells per mL.

“We’ve faced some challenges along the way, and one of them is harvesting the cells from the microcarriers. We had to recreate the T-flask ‘tap’ to get the grown cells out of the system. We got that to work without harming the cells, which was a good achievement,” Coopman says.

The team did some work in 5-litre reactors. They were one of the first academic groups to go up to those sorts of scales and have cells grow successfully. “But it gets expensive. And in product or process development, that sort of scale is not needed. It might even be that for some autologous therapies where we need to make relatively small batches for one single patient, you don’t need to go to particularly large scale.”

The team also published a paper on their work in ambr, a small scale automated bioreactor system with a maximum volume of 15 mL. “With ambr, you can do multiple reactors in a single system. The nice thing is that you can trial different media compositions or different microcarriers or feeding strategies within this much smaller system.”

Life after extremely low temperatures

Some of the group’s studies that are now under review deal with how well cells perform post-cryopreservation. There have been some interesting findings.

Firstly, the medium in which cells are grown makes a difference to how the cells perform after cryopreservation. Secondly, certain cells survived cryopreservation much better than others although they didn’t grow so well to start with. This is why Coopman suggests that we should not ignore some cell types or donors just because the cells do not seem to grow well.

“If the slow growers are actually the cells that survive the whole process the best, is there any point in growing lots of cells in order to lose some of them later on down the process? Maybe we are better off growing cells more slowly to retain them the whole way through. This is an instinct thought that the community really needs to pay attention to, because a lot of people are looking at individual operations in isolation. They are focusing on improving just the growth medium, the harvesting process or the cryopreservation, when they should be looking at all of them together.”

Can cells be preserved and stored in GrowDex?

When Karen was first introduced to GrowDex, she thought about what her team could use it for, something new and different. **“**We know that people are looking at GrowDex as a potential of growing cells in a 3D environment, but I’m looking at its potential for the preservation and storage of cells. For me, the best attributes of GrowDex are biocompatibility and flexibility.”

Coopman is looking at cell therapy manufacture as a whole. She thinks that we need to pay attention to how the cell progresses throughout its journey, starting with taking cells from a patient and getting all the way to how it is stored for a clinician to use it either in a few days’ or a few months’ time. “I’m starting to recognise that cells are sometimes quite sensitive to changes that we make at one part of the process, in terms of how they behave in a different part of the process. I think the ability to tie all those bits together in the future, giving patients cells that have been grown and stored in GrowDex, is really quite exciting.”

Coopman’s research group has been testing GrowDex to enhance stability of mesenchymal stem cells to be stored. Before trying GrowDex, the group had tried matrix-free hypothermic storage, storing the cells in a medium. They noticed that the cells tended to clump together and disassociating them was hard. “This is why I thought a biomaterial might help. But the challenge

there is that once you introduce the biomaterial, you have to have some kind of release mechanism as well."

With GrowDex, there is the release mechanism available. Removing the matrix by enzymatic degradation is possible with GrowDase, a purified and optimized mixture of enzymes that specifically degrades cellulose to soluble glucose without affecting the cells. But Coopman notes that there is still work to be done.

Exciting future applications with GrowDex

One of the challenges of cell therapies is that millions of cells need to be stored for just a single dose. Coopman and her research group are now looking at how they could use GrowDex in large volumes and still retain a stable structure in the matrix. "We are investigating of new ways of using GrowDex as a storage and a delivery vehicle whereby we can control and adjust the cell dose based on encapsulation. I think it's also exciting for researchers who are using GrowDex as a culture substrate to imagine what else you can embed within GrowDex that would actually help the cells survive or grow better."

Feedback, development and collaboration highly appreciated

Coopman has been working with UPM for around 12 months, she appreciates the fact that UPM listens to feedback and develops products on the basis of what researchers are saying, for example with the launch of the new user-friendly syringe packaging for GrowDex. "What I really like is that UPM is also open to early career researchers. I think we should give them a chance to get involved in these projects, to start to work with industrial partners and to come up with innovative solutions."

Coopman notes that by doing small projects initially, both parties get to see how the other works and they can develop the cooperation for mutual benefit and understanding from this solid starting point. "With UPM, it's not so formal and focused on track records and things like that. I think it is really good for early career researchers and I would encourage the company to keep doing this."