INTERVIEW

Vector production in academia: obstacles and opportunities

DANIELA BISCHOF is an Assistant Professor of Clinical Medical and Molecular Genetics, and Director of Vector Production at the Indiana University School of Medicine. She has almost 20 years of experience in the field of gene therapy and has been involved in the production of clinical grade gene therapy lentiviral and retroviral products since 2007.

EMILY HOPEWELL is the Director of Cell and Gene Therapy Manufacturing and an Assistant Professor in Clinical Medical and Molecular Genetics at Indiana University, and is charged with implementing and building manufacturing for cell, gene, and immune therapy at Indiana University.

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Q What are your respective roles and activities at Indiana University (IU)?

EH: I joined IU in July 2018. I'm the Director of Cell and Gene Therapy Manufacturing, which comprises vector production, as well as our cell immunotherapy and transduction

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facility, and the bioprocess development lab. The cell immunotherapy facility and the bioprocess development lab were initiated in 2017–2018.

I spend a lot of time talking with investigators who are interested in initiating trials. But my main goal is to develop a robust Good Manufacturing Practice (GMP) team, centered around a common quality management system and facility operations team.

DB: I am the Director of Vector Production that is part of Cell and Gene Therapy Manufacturing. We have a clean-

room facility that contains four separate suites in which we manufacture GMP lentiviral (LVV) and retroviral (RVV) vectors for use in Phase 1/2 gene therapy clinical trials. To that end, we also generate certified cell banks that are used in the production of viral vectors.

My responsibilities include managing all the tasks associated with vector production, beginning with liaising with customers to determine their requirements so that we can manufacture customized products to meet their needs. I ensure that the facility, equipment, processes, raw materials, documentation, and so on are current and ready for use. I also manage financial facets of projects together with our accountant, and legal aspects jointly with the Indiana University legal office.

Q Can you tell us more about the cell and gene therapy manufacturing capabilities and capacities at IU?

DB: The Vector Production Facility was established by Dr Kenneth Cornetta in 1995. It started as a means of enabling scientists and physicians funded by the NIH in initiating Phase 1/2 gene therapy clinical trials. Less than 10 years later we started producing GMP lentiviral vectors. I joined the group towards the end of 2007, and at that time we were in an old facility that had been built into the existing building, which was not ideal as it presented space and design challenges. With the assistance of an NIH Construction Grant (NCRR C06-RR020128-01), a new GMP cleanroom was incorporated into the design of a new research building being developed for the Indiana University School of Medicine. The facility was released to us in 2009.

Initially, there were two staff members in the new facility. We produced 2–4 GMP LVVs and approximately 4 GMP RVVs per year – RVVs were the main product we manufactured at that time. We also generated about 1 GMP-comparable LVV a year. (By GMP-comparable, I mean that these products are generated in the same manner as GMP LVVs, but they’re not produced in a cleanroom setting; they are usually on a smaller scale, and the certification is abbreviated). We were also generating 1–3 cell banks per year.

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During this period our maximum scale was 20-liter productions but as we recruited more staff, we transitioned to 30-, 40- and 60-liter productions. We are now averaging about 6–10 GMP LVVs, 3–5 GMP RVVs, and 2–3 GMP-comparable LVVs a year – plus 2–5 cell banks. (I do need to stress these are all approximate numbers, as it varies from year to year).

There is currently a very high demand for vector products, and we are in the process of hiring and training more personnel. Depending on demand, we aim to eventually manufacture at maximum capacity, which is around 16 GMP LVVs, 10 GMP RVVs, 2–4 GMP-comparable LVVs, and 10–14 cell banks.

EH: On the cell side, we have a suite with two cleanrooms. We aren't actually manufacturing cells yet – we are still getting the facility up and running – but we have three projects at a similar preclinical level, and we plan to begin manufacturing in the second half of 2020.

Here at IU, cell manufacturing for INDs has not been done for some time. However, in 2016, Dr Anantha Shekhar, Executive Associate Dean for Research Affairs, received the first Grand Challenges Award from IU for a precision health initiative. The goal is to improve outcomes through precision medicine, and it's been operationalized by weaving areas of technical expertise with targeted disease states. One of the pillars of precision health is cell, gene and immune therapy, so there was a windfall of resources. This is part of the reason why they have decided to invest in vector and cell manufacturing. Around the same time, IU alum, Dr Don Brown, made a sizeable donation to IU to create the Brown Center for Immunotherapy. I'm very lucky to have come in at a time when we've got really good investment in resources and leadership.

Q What are your thoughts on academic facilities expanding and moving into commercial manufacture?

EH: I came from the Moffitt Cancer Center in Tampa, Florida, and last year Moffitt launched a CRO focused on immunotherapy. The trend is definitely there, although I am not sure if it will continue.

The goal of many academic facilities is to support their investigators, but there is no reason they shouldn't capitalize on their areas of expertise, too. This benefits the academic institution as well as the plethora of start-up companies that can't afford to build their own clean room facilities or are too early in development to want to invest. Academic institutions that are already manufacturing for Phase 1 and 2 clinical trials have the experience and are able to help reduce a massive bottleneck for manufacturing, especially in the early phases.

Q What are the key challenges faced in viral vector manufacturing in the academic setting today?

EH: *Staffing is one of our major hurdles.* It is very difficult for us to find and retain staff with such high demand in the industry for people who have manufacturing experience. We spent 6 to 8 months after I arrived working with HR to adjust compensation appropriately so that we would have a better ability to hire and keep good quality staff. We're also working on optimizing our training to get them up to speed more efficiently.

DB: *As Emily mentioned, hiring suitable technical personnel for manufacturing is definitely a challenge.* Academia simply cannot compete with commercial entities when it comes to salaries. A disadvantage of being a small group is that personnel have to perform multiple tasks, including procuring and qualifying raw materials, preparing them, maintaining the facility and equipment, qualifying processes, and manufacturing products. This entails a lot of work and numerous procedures that staff need to be trained on. It takes close to a year to train staff to be competent in all these tasks. Also, in a university setting, obtaining enough space to accommodate growing staff and supply needs tends to be a challenge.

Q What specific supply chain related challenges have you encountered, and what steps are you taking to address them?

DB: All of our processes were qualified using specific materials – again, as a small group we did not have the personnel to qualify processes using multiple sources of material. Additionally, at that time, specialized supplies were often available only from one vendor. As a result, we now face backorder issues that can affect our ability to complete projects in a timely fashion. Some of the material qualifications are also rather time-consuming. For example, qualification of our current tangential flow filtration (TFF) system took almost 2 years to optimize and get ready to incorporate into our GMP manufacturing processes.

As much as possible we have tried to find equivalent materials from alternate vendors

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for critical supplies. Additionally, we order supplies well in advance, but inadequate storage space means we cannot order materials for a year, or even 6 months, for example. There are also some materials that have a relatively short shelf life.

With gene therapy on the rise and more groups starting to manufacture vector products, we have experienced extended back-order issues with some supplies. We also order custom products from certain vendors, and we have had cases where agreed upon lead times by the vendor were suddenly extended, and we weren't notified. This has caused problems for us. We are now in the process of drafting quality agreements with these vendors in the hopes of alleviating this problem for critical materials.

Another issue is the plasmids we use to generate LVVs – it frequently takes 4–6 months to obtain plasmids. I recently read that some plasmid production companies have a backlog of up to 12 months. As this is obviously a problem, we have to plan well in advance to ensure the plasmids are available when needed.

EH: Procurement is certainly a major bottleneck and related to that is the quality of the plasmids and shortages for production of plasmids. It will be interesting to see what regulations the FDA will require in this regard, moving forward. Phase 1 has a bit more flexibility, but as trials progress you obviously need higher quality raw materials.

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Q Can you tell me about your work in terms of scaling up vector bioprocesses, and how that's evolving?

DB: Just under a year ago, the department hired a faculty member to lead a Bioprocessing Development Laboratory (BDL) for Cell and Gene Therapy Manufacturing. Prior to this time, we tried to perform optimization studies during short 'down' periods, but this is not an efficient manner to perform such studies – it was a challenge. In collaboration with Vector Production, BDL is tasked with scaling-up vector manufacturing utilizing a suspension cell system in a bioreactor setting. Alternative methods for transfection during vector production are also being explored – we're always looking to optimize processes, get better titers and increase the efficiency of processes.

EH: The skillset required for process improvement, optimization, scalability and so on is different to the skillset required to manufacture the vector. You need to have a knowledge of manufacturing requirements, but you also need to have a more robust scientific understanding and scientific process.

There was another faculty member brought on board, outside of our group, who is going to be implementing a preclinical vector core facility that will help investigators at IU who want to use viral vectors for research. In turn, this will assist us in understanding what the

investigators need much earlier on, to help streamline the process of moving from preclinical- to clinical-scale manufacturing.

Q What would be top of your respective wish lists in the way of new innovation from the enabling tool and device providers?

DB: As we are a small group with limited financial resources, I would like to collaborate with industry partners who have the kind of systems in place that we are looking to develop, such as bioreactors for scale-up, or continuous flow centrifuges for vector concentration – right now, the expense for such processes is prohibitive for us. Developing a collaboration with industry would definitely help us to improve and grow our processes.

Q What are your chief goals and priorities for the future?

DB: As discussed earlier, top of the list is hiring adequate personnel, so that technicians can become more specialized in a subset of tasks. This would permit us to maximize our production capacity. Right now, the wait period to have a GMP product made is approximately 2 to 2 and a half years. We would like to reduce that substantially, so customers can get their product sooner. This in turn will allow customers to move their gene therapy clinical trials forward at a quicker pace.

EH: One of my priorities is to make sure that we have a robust and sustainable program that we can use for manufacturing of both cell and vector products for use in clinical trials. And as Daniela said, so much of your success is down to building the right team.

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AUTHORSHIP & CONFLICT OF INTEREST

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