Cellexus

# User Interview:

## Using the CellMaker to manufacture bacteriophage: Interview with Manuel Garrido from TechnoPhage as featured in Capsid & Tail

Jessica Sacher from the Phage Directory, and publisher of Capsid and Tail, interviewed Dr. Manuel Garrido from TechnoPhage, about how they have scaled up their phage manufacturing with the help of the Cellexus CellMaker. Phage manufacturing is a bottleneck for the global phage field, so it was exciting to chat about this topic with Dr. Garrido, Production Specialist at the Portugese biotech company. They discussed his experience with phage production, how he's worked to overcome its associated challenges, and his experience using the Cellexus CellMaker.

### Jessica: Can you start by telling me about your background, and how you came to work at TechnoPhage?

Manuel: I have a degree in biochemistry, and I worked for some time in neuroscience research, doing a PhD in neuroscience in Germany. After that, I joined a biopharmaceutical company in Portugal, a contract manufacturing organization (CMO), and I worked there for around nine years. I had the opportunity to work directly in the manufacturing of various biological products for clinical trials, therapeutic products and vaccines. In the last few years, I kept direct contact with manufacturing, and developed side work as a project manager.

And then TechnoPhage was starting a manufacturing facility. The company is not only devoted to phage therapy, as the company name may indicate — the idea is to produce other biomolecules too. But essentially, it's a company with a history of phage work and phage product development. And because of their plans to start clinical trials, and a lack of companies that would be open to working with phages, they got the opportunity to get some space to build a manufacturing facility. And so they advertised a position online and I applied and joined them.

Now I work as a production specialist, but in a small team, so it's a bit like being a production manager. So I have approximately 10 years of biomolecules manufacturing experience, and now around 1.5 years working with phages. I've helped the team with product development, and we're manufacturing phages now in our GMP manufacturing facility.

### Have phages turned out to be challenging to manufacture? How do they compare with other biomolecules you've manufactured?

Manuel: All of them have their own specificities. I've worked with viruses in the past, but on viruses from mammalian and insect cells, which also have their specificities. But the way that somebody from manufacturing looks at them is kind of the same. I mean, they're viruses, they infect, and they need the right conditions to infect, replicate and to be released from the cells. But the reality with bacteria is that everything happens more quickly, so you can run a process from start to finish within a week. With mammalian cells, it can take you a month to amplify, infect, and get the product done.

## For your phage production, do you do a lot of tweaking and optimizing processes in a flask first, and then take things into a bioreactor? And do you typically see issues with that transition, with scaling up?

Manuel: We need to find out and fine tune the best conditions in flasks. We cannot have, for instance, five or six bioreactors in parallel, and try several different conditions. So you need to optimize the multiplicity of infection, the medium that works best, and the point that you infect at, whether you infect at a higher density, or at a lower density — that balance, you need to find in flasks. Getting into a bioreactor, and getting into a bioreactor which uses airlift technology, which is the case for the Cellexus CellMaker, can require extra components, such as antifoam. The antifoam itself is something that, in principle, is of no harm to anything. But eventually if you add too much, you may run into troubles. In my experience, if it works in flasks, it will work in the bioreactor. A “good” phage in a flask will be good in the bioreactor, as well as a “bad” phage in a flask in principle will be a bad phage in the bioreactor. Biology does not change.

## Let’s talk about the Cellexus machine and how you brought it into your workflow. What was the issue beforehand, and why did you decide to bring that in?

Manuel: When I joined, the bioreactor was already selected. And my impression was that it was the most cost-effective option on the market for a single-use option with temperature control. It also had the potential to control pH and pO2 levels. I can guarantee to you that in terms of price, it is one of the least expensive I have heard about, and this goes for the bioreactor bags as well. I’ve worked with other companies who sold disposable bags, where I needed to spend 3 to 4 times more for the same volume of bioreactor bag.

The TechnoPhage team uses the Cellexus CellMaker for its phage production. Source: TechnoPhage.

## How has the CellMaker system helped you, and helped TechnoPhage as a company?

Manuel: The system has allowed us to grow in scale and also allowed us to achieve higher productivity, which is the amount of phage that you can get from each liter of culture. Instead of scaling “out”, by using several flasks, we can combine it all in one bag inside the bioreactor. And therefore, from the small version of the bioreactor, we can easily get between three and eight liters of phage lysate, and in the larger version, somewhere between 10 and 50 liters, just in one go, and with higher phage concentration per unit of volume.

## Wow. So how often would you say you run one of these batches in a given week? How much phage are you producing on a regular basis?

Manuel: We're currently producing phages for a phase one clinical trial, so we've produced one batch of each phage that goes into the cocktail. Roughly, we did something like one week per phage fermentation cycle throughout several weeks to produce all phages in the cocktail. But in theory, if you have a team to work on it, and if there are no other constraints related to good manufacturing practice, or batch changeover, room cleaning and so on, in theory, you could run one fermentation after the other. With this system, you could run a fermentation each day with a different phage. You could just swap in a different bag, connect the lines in and lines out, and if you have your media ready to go, you could just go straight for it.

## Do you find that some phages or phage-host combinations work really well in the bags and some don't? Are some easier or harder to produce?

Manuel: So far I have not observed a phage that works well in the shaker flask and fails in the bioreactor. But if you have a bad phage in the flask, you will have a bad phage in the bioreactor.

## So if someone new were to order one of these Cellexus CellMakers and get it set up in their lab, could they be up and running with it pretty quickly?

Manuel: This depends a little bit on the background of the people in the lab. If you have people that are used to scaling things up, and they are used to working with hoses and pumps to pump in and pump out, and they are used to using filters, then it's pretty straightforward. If you're not, then it becomes problematic — not because it's difficult to work with the system, but because people will not know exactly how to manage it. After a few insights and resolving some small issues, I think it would become easier. But if you asked me, if Cellexus comes and mounts a bioreactor in your lab, would you be ready and would it be easy to get going? I don't think so. It's not because it's difficult to work with the Cellexus bioreactor. I'm also sure that the Cellexus team will support you. Any bioreactors that arrive in a traditional research lab will have the same problems, or even worse, to be solved. It's a question of people's training and background.

One of the advantages of the Cellexus system is the fact that it "lives by itself". It only needs electricity. From electricity you can get air supply, because the CellMaker itself has a pumping system to generate the air. It cools, it heats, it measures the gas. It's a standalone system that only needs a plug. The majority of bioreactors need a plug, a separate cooler or heater, and a supply of air, so normally they bring quite a few more needs.

## That's really useful to know. Do you have any tips for phage biotechs that are considering this? Would you tell them to go ahead, that this is a good option?

Manuel: Yes, when you balance the cost-benefit, this is a good option for the phage biotechs. It fits and is adequate for the purpose. As we all know, there are other options on the market in case money is no issue that would also fit the purpose.

## I heard that airflow is one of the CellMaker's selling points. Have you been happy with that aspect?

Manuel: With this system, there is very good aeration; the air provides mixing and provides oxygen. So any microorganism that needs oxygen will be very happy in this system. Some other fermenters are pretty limited in this, because it's a problem of single-use bags; with single-use bags, you cannot work with pressure (or the bag will blow up). So if you need to have really good oxygen transfer. Cellexus' system is a good system, as it was constructed to increase oxygen transfer by the bubble size in the bubble generator tube.

I have no experience working in anaerobes in this system, but my impression is that we could easily do it just by injecting a gas, such as N2, instead of compressed air.

## So with regards to TechnoPhage, what are you excited about lately?

Manuel: TechnoPhage has a product for phase one clinical trials with an IND submitted, and we expect that this year, the phase one trial will start. And we have some other products with phages and also with antibodies in the pipeline and in the development phase.

What I want to mention here is that we can also do manufacturing for others. We're starting to have clients that know they will take advantage of our phage expertise for their production culture media screening, optimization, and process development (in shaker flasks), and their transition to a small scale bioreactor, and then to a 50-L bioreactor. Our capacity also includes the purification of biological molecules. We have the capacity to clarify the product, to perform tangential flow filtration, or cross flow filtration, and to do chromatography to reduce impurities, such as DNA, host cell proteins and endotoxins. So we're setting that up for our own products, and now we're set up to do this for clients. We are working on our products and open to do work for other companies.

## Would you produce phages for anyone, for any reason?

Manuel: We would prefer to produce phages for human application. For trials, we've had inspections, we are GMP-certified for biological medicinal products.

## I know TechnoPhage has been really responsive and helpful when we send out phage alerts for compassionate use cases. Would you prepare phages for a compassionate use case if asked?

Manuel: This level of decision is not mine, but the feeling I have is that we're open to help, and if what we have in stock is of value for somebody, then there will be a way to share it, to help and contribute.

## This is all great to hear, because there's definitely a shortage of facilities with GMP manufacturing capacity that work with phages.

Manuel: And I think that was one of the reasons why TechnoPhage decided we needed to do it ourselves. We'd invested so much in phages, but who could produce it for us, and at what cost? There is a shortage of companies that are available to manufacture, and when they exist, they are expensive. And normally their schedule is not very accommodating, they'll say 'we can do it in two years' or 'we can do it in the second half of next year'. That is not compatible with our needs. So we are aware that there are not many companies with capacity to respond to phage GMP manufacturing needs and in an acceptable time frame.

## Last question — as someone who's worked both outside and inside the phage field, do you see phage therapy being taken more seriously in the biotech/pharma space in general, or is it still on the fringes?

Manuel: You need to show that it works. Once you show it, then there will be demand, and people will understand that they need to invest in it. It's like gene therapy — for many, many years, it was no more than promises. We know that it works. But then a gene therapy-associated death happened in the late 90s, and everything slowed down. So for phages, there is evidence especially from Georgia that they work in humans, but the thing is, you need to show people in Western Europe that they really work, with results in humans in this area. And you need to advertise those results. Once you get there, the interest will further grow, and there will be more products being developed and more interest in phages.

Dr. Manuel Garrido is a Production Specialist at TechnoPhage SA, an innovative biopharmaceutical company committed to the R&D of new molecules — chemical and biological — in diverse therapeutic areas, such as infection, neuroscience, and ophthalmology.

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