CELL & GENE THERAPY INSIGHTS

VECTOR CHANNEL: ADHERENT CULTURE SYSTEMS

PODCAST INTERVIEW with:
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Viral Vector Manufacturing and Transfection Efficiency in the iCELLis® Bioreactor System

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Q What platforms (suspension versus adherent) are best positioned today for the manufacture of viral vectors, and which one would you choose if you were to manufacture gene therapy vectors?

RL: Currently, the gold standard expression system used by the industry for adeno-associated viral vector (AAV) production is transient transfection in adherent cell culture.

As of today, the adherent platform is still in the best position. Others are growing in popularity, though – people are also using insect cells that are already in suspension, and adapting suspension cells from their adherent cell line. I forecast that as the market grows, this technology will be ready to move into packaging/stable cells, both in adherent and suspension platforms.

The criteria for choosing an adherent platform as the best pick for your current process will be to first consider your urgency to go into the market. If urgency is a high priority, we know that in most cases the data shows that HEK293 adherent cell culture processes demonstrate higher specific productivity than suspension cells.

Consider whether your process requires multiple manipulations – if you need to change media during the transient transfection process, utilize perfusion if using lentivirus, or lyse the cells at the end of the process, then you should choose an adherent platform.

The third criteria I would consider is when you scale up your upstream manufacturing process, does the appropriate technology exist and do you currently have a large-scale fixed-bed bioreactor? For example, the iCELLis® 500+ bioreactor size is a proven platform to scale up to enabling large viral vector production for global clinical trials.

If you plan to build your own manufacturing site, with internal process development, know-how, and scalability, then you can go with adherent. If your scale demands are no higher than $5x10^{17}$ viral genome per batch, calculated for a certain number of patients and number viral vectors per patient, than you can still use adherent cells. And of course, the existing regulatory approved drugs based on adherent platforms make this less risky moving forward with clinical trials.

If you find that the best platform for your current need is the adherent platform, the iCELLis® bioreactor is proven in bringing approved AAV drugs to market using a scale-out strategy. The iCELLis® 500 maximizes your manufacturing flexibility, enabling production of various molecules with different scale demands, from 66 m^2 to 500 m^2 surface growth area. This is equivalent to 37 HYPERStack®-36, to 278 HYPERSTACK-36, with the same bioreactor footprint.

> "...when you scale up your upstream manufacturing process, does the appropriate technology exist and do you currently have a large-scale fixed-bed bioreactor?"

However, if time to market is less critical, and you have time to develop high-performance suspension HEK293 cells with high specific productivity and high cell density, and the right media formulation preventing

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cell collapse, then you can move forward with a suspension stirred tank bioreactor (STR). Additionally, if you cannot build up your manufacturing site, and need to use an external CDMO, the majority of global CDMOs are already experienced with suspension bioreactors from monoclonal antibody production.

> "...we believe the combination of the iCELLis® bioreactor and PEIpro® transfection technologies offers a powerful platform for gene therapy manufacturing."

One last point in favor of suspension: some therapeutic indications require very large viral vector demands, larger than $5x10^{17}$ per batch, especially for therapeutic indications targeting a large number of patients. In these cases, I would move towards a suspension platform.

In summary, there is no right or wrong answer – there is only what is the best fit for your needs.

Q Today, most processes for viral vector manufacture rely on plasmid-based transient transfection. What are the advantages of chemical transient transfection over other techniques for large-scale manufacturing, and what are the specific challenges?

AN: To produce viral vectors in mammalian HEK293 cells you need to rely on high co-transfection efficiency of several plasmid DNA, which varies in numbers depending on the viral vector type you are producing, to address safety concerns and to avoid the toxicity of vector plasmid components when using producer cell lines.

For viral vector production, chemical transfection techniques you come across at small scale are mostly calcium phosphate, polyethylenimine (PEI), and more rarely, cationic lipids. Calcium phosphate can be seen as the cost-effective option, due to the cost of the calcium phosphate itself. But when you compare it to PEI, you can clearly identify the limitations it has.

Several viral developers and manufacturers we work with completely switched to PEIpro® transfection reagent after they tested both in parallel. You can reduce DNA amounts by up to tenfold, which is one of the bigger costs in viral vector production. You can improve your yields, and cherry on the cake PEIpro® is also suitable for suspension cell systems. This is not really the case with calcium phosphate, because in absence of serum, typically you will be using synthetic media when you culture suspension cells, and it simply does not work.

When Polyplus developed PEIpro®, we did this in close collaboration with viral vector producers. They told us they needed to be able to scale up production, they needed the transfection step to be scalable with no loss in titer yield compared to small scale, and they needed to be able maintain the reproducibility of yield between production batches. Last but not least, they required flexibility in use, i.e. the ability to use the transfection reagent in both adherent and suspension systems.

"...the issue with adherent-based cell systems such as flask or cell factories, is that they are generally difficult to scale up. You have an increased chance of mishandling risks..."

RL: Transient transfection methods using chemical transfection reagents are getting good results in small scale adherent or suspension cells. However, from the manufacturing process perspective, there are challenges when scaling up.

When looking at a transfection reagent, I consider how easy it is to transfer the transfection reagent from site to site, and operator to operator. I will choose a transient transfection with high performance, of course, and one for which no additional development expertise is required. I would like to have it in GMP grade, since the vendor must have it in large scale for GMP purposes for clinical trials.

When you are considering large scale, you also have to keep in mind that you have a very large volume of DNA and transfection reagent. You need to know how gently to mix them together. Calcium phosphate, for example, is not a good reagent for scalability. We have had a good experience with PEIpro®, and with gentle mixing we can maintain the integrity of the complex and get good transfection efficiency.

When you have large volume of complex – 2,000 liter or 500 m^2 for adherent – you have to deliver that in a gentle manner, so you are not damaging the complex of transfection reagent and DNA, but also very rapidly.

Finally, it is critical when you are choosing a transfection reagent that you consider scalability. Consistency is critical – every time you do a transfection process at the larger scale, you have to get the same outcome in terms of the yield.

Q Pall and Polyplus have teamed up to publish a general guidance for DNA transfection in the iCELLis® bioreactor. What was the rationale behind this collaboration between the two suppliers?

FC: Once you have developed a product, and completed the early development work, the next big challenge is industrialization. The selection of the technology and the elaboration of the strategy for process development and scaling up are key elements to consider, and can be the difference between success and failure.

This guidance was written to help our customers make the best decisions, and deploy the best strategies, to hit the market quickly and at low risk. Pall and Polyplus-transfection have teamed up because we believe the combination of the iCELLis® bioreactor and PEIpro® transfection technologies offers a powerful platform for gene therapy manufacturing.

We also know that the performance of technology alone is not sufficient – a strong and reliable supply chain from development to commercialization is a must-have. We are confident that Pall and Polyplus have proven records that establish that we can take on the supply chain challenge.

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Lastly, and this is a very important point, technical expertise is a key element. It is absolutely critical that you partner with suppliers who know and have mastered their technology, and who can answer your questions and guide you. I am confident that in this respect both Pall and Polyplus offer high quality technical and scientific assistance to their customers.

AN: What we observed before we started writing up the guide with Pall was that we were getting a lot of questions from iCELLis® users for guidance to optimize their transfection in the iCELLis® system, whether at small or large scale. And vice versa, from our customers looking to scale up their adherent cell platform.

We know the issue with adherent-based cell systems such as flask or cell factories, is that they are generally difficult to scale up. You have an increased chance of mishandling risks because you are manipulating a higher number of culture vessels. The iCELLis® bioreactor addressed these time and space concerns, and was fully compatible with the use of PEIpro®.

We tested the iCELLis® bioreactor in-house, and several viral vector manufacturers also used the combination of the iCELLis® bioreactor and PEIpro® and published their results. It was a perfect time to write a guide that was going to meet the existing demand of customers who need to scale up. The customers need us, as suppliers, to offer a roadmap on how to proceed with our respective technologies.

Q The general guidance for DNA transfection specifically focuses on iCELLis® technology. What advantages does this technology currently have as compared to stirred tank reactors?

FC: As Rachel pointed out, both technologies work very well for gene therapy – but the iCELLis® bioreactor does have some advantages.

Aside from the fact that today most cell lines used for gene therapy are still adherent cells, adherent processes tend to reach market faster than their suspension counterparts. Zolgensma®, for instance, is produced in the iCELLis® bioreactor. One of the reasons for this is that scale-up in the iCELLis® bioreactor is rather straightforward, from the iCELLis® Nano benchtop system up to the iCELLis® 500+ bioreactor.

By comparison, although it may be quite easy to scale up a suspension transfection process from lab scale to, for example, a 200 liter STR, scaling up above 200 liters requires more development and time. Adherent cell lines tend to be more productive than suspension cells, to the point that cost of goods between the iCELLis® bioreactor and the STR technology might be on par. Besides that, some practical aspects such as media management and harvest may be much simpler when using a fixed-bed bioreactor like the iCELLis® bioreactor.

That being said, suspension cell lines, like suspension HEK cells, can also be used in iCELLis® bioreactors. In this case you can combine the advantages of an easy seed train preparation, and the advantages of a fixed-bed bioreactor.

Q What are the key parameters that need to be optimized during development for viral vector manufacturing, and could you elaborate

on how you ensure your transfection process is proceeding optimally?

RL: I like the holistic approach; at a very early stage of the process you have to keep in mind the large scale conditions in your head. When you are doing all of the optimization of the process at an early stage, at the small scale bioreactor, or in flatware, you have to keep in mind the manufacturing target you need to move forward.

Firstly, I will consider on a very high level what optimizations are needed, and then I will zoom in to the transfection process. You have to keep in mind that everything you bring into the process is critical. The quality of the cells coming into the bioreactor is very important. They are not supposed to be clumping, they are supposed to have high viability, and the doubling time should be ok.

The cells inoculating the production bioreactor must be of high quality. Then you have to consider the cells' seeding density into the production bioreactor. This is very important to simplify and also adapt the cells into the bioreactor. Next you have to look at agitation, and what the best agitation for the media to flow through the cell is, or the agitation of the STR, depending on your process. You have to consider the glucose control – do you want to flood the cells with glucose, or let the glucose drop down by not adding it? Consider pH control, media exchange strategy, and growth media production – we can consider batch, fed batch, or profusion, depending on the viral vector in place. And of course, the virus harvest. When zooming in to the optimization of the transfection, remember the end point.

One of the parameters we consider for optimization is the DNA concentration for a certain number of cells, and then we have to adjust for the best ratio by mass for all the plasmid used. Some people use two plasmids for transient transfection, or three or even four. You have to optimize the ratio by mass for each plasmid. At the same time, you must study and optimize the plasmid to PEI ratio. If you are using PEIpro® as a transient transfection reagent, you have to make sure that you are trying, in small scale, different ratios of the plasmid DNA and the transfection reagent.

It is also important to study the time for complex formation. We know that each process has an optimized complex size. If it is too small it may not contain all the plasmid, and if it is too large it may not enter the cells. You have to optimize the size of the complex for the best transfection efficiency outcome, and consider the effect of the pump used on the complex size.

AN: I completely agree with Rachel that the first step to look at are key parameters at large scale. Once you can answer that question, you take that into account at small scale. Two things really impact transfection at large scale – volume constraints, and the fact that you are working with large transfection volumes that need to be added to the bioreactor. And second to that, time constraints. These are large volumes that need to be added to the bioreactor, and depending on if you are using a pump, or not, these all impact the size of complexes, which has a direct impact on the transfection efficiency.

There is another point to be addressed, which is of course the cell culture system. If you are using adherent or suspension that impacts the plasmid to PEIpro® ratio, and the DNA concentration per million cells. These are all parameters we go over in the guide.

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Q What are the specific pain points you might encounter when moving into commercial scale volumes for both adherent and suspension cells?

AN: As I discussed above, the specific pain points we may encounter are validating the manufacturing process, and the need to think about how you would manufacture at large scale first. Then, taking into account all of the parameters chosen for large scale, you can adapt and put them in place at small scale.

An important parameter for that is looking at your raw material supply. A raw material that is adapted for large scale manufacturing should be a raw material that you can obtain with no shortage of supply. It should also be raw material that could be used for commercialization, i.e. GMP compliant.

It is very important from the get-go to identify raw materials, including the transfection reagent, that are available at different quality grades so that the manufacturing process you validate during your process development does not need to be modified or changed when moving on to large scale clinical-grade manufacturing.

There is a second point worth addressing that we haven't mentioned, which is the type of viral vector produced. Depending on the viral vector you are producing, and the system that the viral manufacturer chooses, adherent or suspension, transfection will be impacted.

With our expertise in transfection reagents, we are focused on developing transfection reagents to obtain the highest yield in lentiviral or AAV vectors. We are aware that depending on the type of viral vector you are producing, a given transfection reagent might not be optimal.

Therefore PEIpro® is the first of a series of transfection reagents we are developing. PEIpro® is ideal for the production of various types of viral vector, in both adherent and suspension cells. But when compared to our recently launched FectoVIR®-AAV, which is a transfection reagent dedicated specifically to AAV vector production in suspension-based systems, PEIpro® is outperformed. FectoVIR®-AAV leads to two to three times higher yields in comparison.

You need to identify how you are planning to produce your viral vector, and from there identify the raw materials you are going to use at small scale to develop your process, and take

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into account the type of viral vector you are producing.

RL: Focusing on the adherent side, one of the pain points going into large scale manufacturing of any viral vector is the seed train, because we know that adherent cells are grown in a flatware adherent platform.

We don't want people to use multiple flatware culture vessels like roller bottles, and multilayer flasks, when going into production scale. You have to use multiple operators, multiple biosafety cabinets, and you are pooling everything. This brings a lot of risk to the process, so we want to resolve the seed train of adherent cells.

The other point, elaborating on what Alengo said, is rapid delivery of large volumes of shear sensitive DNA and PEIpro® complex into the large scale production bioreactor. You have to think about this challenge when you are transferring large volumes in a rapid manner and avoid using, for example, a peristatic pump – this can destroy your complex, as it is very sensitive.

The third point for adherent is large scale AAV production. Before we developed the iCELLis® 500, people could not manufacture more than 40 HYPERSTACK-36 per batch. They were not able to progress to a global, advanced scale of clinical trial. The iCELLis® 500 large-scale fixed-bed bioreactor has made it possible for people to get to this large scale, as long as they are still working with adherent cells.

I will touch on four elements I consider a challenge in suspension cell scalability. Firstly, the challenges of transferring large volumes in a fast manner is the same as in adherent. Secondly, with most of the processes we observe in the market, HEK293 cell performance is a challenge. The specific productivity is lower than in adherent in most cases, and the cell density is not as high as we would expect from suspension cells. With suspension cells, when you increase the density, they produce clumps unless you are using an optimized media and additives, or engineering key process parameters in the bioreactor to prevent that from happening.

The third issue is medium manipulation pre- and post-transfection. As Alengo said, the media is critical for transfection. With adherent you can change the media very easily because the cells are adhered to the fixed bed. But in suspension, media change is a bit of a challenge, so you have to bypass it by developing an optimized strategy.

The last point is the harvest cell culture feed to the downstream process. You have to consider two major impacts. Currently you have to lyse the cells at time of the harvest in order to release the AAV product, in most cases. You are also bringing in a very high turbidity feed stream, which must be overcome in the downstream clarification step.

Q What do you think is the most efficient process development and scale up strategy to overcome some of these pain points that

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are raised before ensuring consistency? In particular, could you elaborate on DNA transfection and the harvest step?

FC: In brief, I think we all agree that the most efficient process development strategy is not to scale up, but rather to scale down.

Our preferred option is to begin designing the process at the iCELLis® 500 bioreactor scale. Further development is then performed using the equivalent small-scale bioreactor, the iCELLis® Nano bioreactor.

This top-down strategy allows us to clearly identify the procedures that will impact the process at industrial scale, and will facilitate both process optimization and decision making.

I will provide some examples. The volume of transfection complexes is a critical parameter, in the sense that it may impact your productivity, but it will also impact the process operability. Addition of volumes larger than 40 liters in the iCELLis® 500 bioreactor becomes rather impractical; 15 liters is a much sweeter spot. But if you do not pay attention, you may develop a process at small scale and end up with unnecessarily huge transfection volumes at large scale.

The same applies to the harvest. On many occasions, a lysis buffer is used to recover the product, and it is preferable to keep the harvest volume in the lower range to facilitate the downstream process.

That being said, some process parameters are very specific to the iCELLis® fixed-bed technology, and may have a decisive impact on your productivity. I can list for instance the linear speeds, or media velocity throughout the fixed-beds, and also the media recirculation or perfusion rates. And lastly, because iCELLis® offers full control on the bioreactor environment, the pH and the dissolved oxygen.

All of these parameters must be optimized using the iCELLis® Nano bioreactor. However, keep in mind that the initial development work such as media selection, DNA to PEI ratio, DNA quantity optimization, the harvest strategy, and so on, is best performed using flatware, which has many advantages – including easy set-up, speed, and low cost.

AN: As François mentions, parameters need to be optimized using the iCELLis® Nano bioreactor, based on criteria already defined for the iCELLis® 500+ bioreactor. There is some initial work which needs to be done regarding which media can be used, the DNA/PEIpro® ratio, DNA quantity characterization, etcetera. Indeed, these are all critical parameters for transfection, and the DNA/PEIpro® ratio can be optimized down so that you can use the lowest amount of DNA.

On top of that, regarding the transfection, the fact you need to keep in mind is the volume of transfection that will be needed at large scale. It is harder to add 40 liters to an iCELLis® bioreactor, compared to adding 10 to 15 liters of transfection complexes. This is

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why with PEIpro® we have optimized the protocol for the iCELLis® bioreactor so that you prepare the transfection complexes down to 5% of the final cell culture volume. You can decrease the volume of transfection complexes that need to be added to the bioreactor, making it more practical and easier to handle at large scale.

This also allows the process to fit more with time constraints. Your DNA/PEIpro® complexes are stable, and need to be over a certain size for optimal transfection. This size will be maintained during a certain window as the stability of transfection complexes is limited, and you need to be able to add these transfection complexes in total amounts to your cells. These are time and volume constraints that we have worked around in the guide, to facilitate the implementation of transfection at large scale.

Q Can you tell us more about the regulation and quality of raw materials coming into the process that need to be addressed in the final drug product?

RL: Implementation of supply chain management is critical to ensure all raw materials coming into the viral vector production process are of high quality.

As I mentioned before (and I will never stop mentioning it!) what you put into the process impacts what you get out of the process. It is critical to ensure all of your raw material are fully characterized and validated from the vendor side, so that you maximize your final viral vector drug product quality and minimize process variability. Consistency is also very important for making sure the process will move into clinical production. All material received for a process should be very well characterized, including information on the stability and shelf life of each raw material, and the testing that the vendor is doing.

For example, you have to evaluate your complete growth and production media, and that can start from powder media. The powder media should be very well validated for supporting cell culture growth and production. If you start with liquid media, you have to make sure it is clean from all adventitious agents that can impact the process. Remember that the final vector product is a virus, so you don't want to have a lot of other virus contaminants in your drug product coming from the raw material.

I consider the HEK293 cell a raw material as well. The cell should be at high quality coming into the production scale, as I mentioned earlier. You have to make sure that they are sterile, endotoxin free, mycoplasma free, and human viruses free. Also, the market is moving on the regulatory side from HEK293 T, which has an antigen that has to be removed from a safety standpoint, to HEK293.

The plasmid is also a raw material for viral vector production. You have to make sure of the identity, integrity, stability, and purity. When I say purity, I include percent of supercoil form and residual genomic cell DNA, RNA, and protein level, that can have a negative impact on the safety of the final product. And of course, the concentration that you are putting in should be evaluated and accurate.

Regarding the transfection reagent, we have to measure the quality of the GMP grade we are getting. The anti-foam, the buffer during the downstream process: everything coming into

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the process is, as far as we are concerned, a raw material. It has to be of high quality. We have multiple strategies to ensure that, including aligning with the vendors.

AN: Quality of raw materials is definitely a pain point. Raw materials must be sourced from qualified suppliers in order to ensure that they have had rigorous testing, which in turn ensures reliable transfection efficiency, in order to achieve reproducible virus production.

To fulfil these quality requirements, associated here with the use of PEIpro® for the manufacturing of viral vectors, we supply higher quality grades of PEIpro® up to GMP compliant PEIpro®. We know each quality grade has its own market, from process development going through to clinical trials, and up to commercialization.

We also know that while regulatory agencies recommend that one starts as early as possible in the process with a GMP compliant raw material, we trust our customers to make their own risk assessment and select the quality level they need, while guaranteeing reproducible viral titer yields. This applies to whichever quality grade they decide to use: PEIpro®, PEIpro®-HQ, or PEIpro®-GMP.

There is one additional thing that is linked to the quality of raw material – guidelines regarding residual levels of raw materials that could potentially be present in the final drug product. It is becoming very important to determine the residual level present in this final drug product, if any, of certain key raw materials such as plasmid DNA and transfection reagent.

For this, you need a test in place. We recently developed a PEIpro® residual test to allow manufacturers to precisely and accurately detect PEIpro® with the lowest limits of detection and quantification, either throughout their manufacturing or in their final drug product. This is to meet the regulatory demands to be able to assess how much of each key raw material, if any, is in the final product, to ensure reproducible and safe administration to patients.

BIOS

Rachel Legmann

Dr Rachel Legmann is currently serving as the technical lead at Pall's gene therapy business unit. In her role she is supporting global customers and building high level networks, Rachel is supporting various internal cross-functional activities including due diligence and new product development. Rachel has more than 20 years of experience in the field of scalable manufacturing of therapeutic products, viral vector and proteins for gene therapy, oncolytic and biologics. She completed her PhD in Food Engineering and Biotechnology at the Technion-Israel Institute of Technology, Israel. Rachel joined Pall in 2014 as the senior lab manager established the US accelerator process development services lab and led the upstream, downstream, analytics and project manager teams for serving multiple customers bringing various viral vector products into the clinical. Prior to joining Pall, Rachel held several scientific and leadership roles at Microbiology & Molecular Genetics department at Harvard Medical School, SBH Sciences, Seahorse Biosciences, and Goodwin Biotechnology.

François Collard

François Collard, PhD, is supporting the Pall Accelerator Process Development Service, and R&D, as a Bio-Process Knowledge Manager. He holds a PhD in bio-chemistry from the de Duve Institute & University of Louvain (Belgium) and performed a post-doc at the Case Western Reserve University (Cleveland, OH) in the field of structural biology and enzyme catalysis. He started his career at Pall as a scientific lead of various process development projects, such as viral vaccines, gene therapy and exosomes.

Alengo Nyamay'Antu

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