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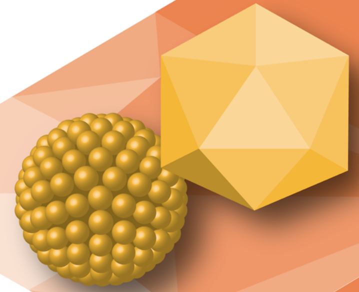

DOWNSTREAM PROCESSING

INNOVATOR INSIGHT

AAV downstream challenges: expert insights

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Q What are some of the recent advancements or innovations in AAV manufacturing that you have found particularly promising?

MR: Firstly, on the upstream side, there has been a push to understand what is happening inside the cell during vector production. Multiple publications have focused on

investigating both the proteome and transcriptome while AAV is being produced. Additionally, researchers are comparing high- and low-producing conditions to identify which genes and proteins are abundantly expressed in high-producing scenarios. The findings from these studies are exciting, as they could help us identify producer genes to be modified chemically or through gene editing, potentially leading to much higher yields or potency.

I have also noticed an increase in offerings from vendors in the AAV space. Compared to 5 years ago, there has been a huge influx of new reagents and products focused on increasing yield, particularly upstream products like transfection enhancers. A great aspect of this is that companies are now providing data upfront, allowing users to compare it with their own results. This is relatively new. These are two developments that I am really excited about.

WK: One of the most significant challenges in downstream processing (DSP) is the separation (removal) of empty capsids, and there has been a lot of great progress in this area. Removing empty capsids is crucial for increasing potency. We are now reaching the point where we can separate not only empty from full capsids, but also begin separating partially packaged capsids as well.

I want to highlight some work presented at the American Society of Gene and Cell Therapy (ASGCT) annual meeting this year by a leading gene therapy biotech company. They developed an anion exchange chromatography method using a combination of resin chemistry optimization, column overloading, and fine-tuning of elution salts and cosolvents, which allowed them to remove over 95% of empty capsids and 40% of partially packaged capsids, all while achieving a respectable yield of 80%. This is a significant step forward, particularly if this approach can be applied to other serotypes.

Looking beyond manufacturing, I am excited about combining modalities, such as conjugating antibodies to AAV. Another industry leader presented on this at ASGCT, demonstrating how they were able to fine-tune the tropism of an AAV capsid to cross the blood–brain barrier while de-targeting the liver. This has great potential for improving safety and efficacy but also brings new challenges as we take an already complex modality like AAV, and make it even more complex by coupling an antibody to it. I am eager to work on these kinds of challenges in the future.

NL: In recent years, we have generally seen an increase in production efficiency. Optimized plasmid design has enhanced production systems, leading to higher yields and more consistent AAV output, which is crucial. From an upstream processing (USP) standpoint, we have also seen the release of optimized media for cell culture. While this isn't entirely new, there has been a systematic shift towards suspension culture and away from adherent culture, and a greater focus on suspension cells over systems like insect cells.

From a purification perspective, the introduction of immunoaffinity for capture has been a major advancement in large-scale vector production from an industrial standpoint. In my opinion, this was a key development and a barrier-breaker. New technologies for separating full and empty capsids have already been mentioned, which remains one of the major challenges we face. Additionally, we have seen the introduction of new analytical methods and equipment

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in recent years, such as mass photometry, which provides a quick and accurate understanding of what is happening during production. This has definitely supported further development.

NC: I am most excited by the emphasis on optimizing upstream conditions. There are many new reagents, cell lines, helper plasmid designs, and Rep/Cap plasmid designs that are being developed and evaluated. The key here is not just increasing the vector genome yield, which for the past 20 years has been the primary goal, as we were focusing on 'the more the better', but other critical quality attributes. We are now prioritizing better quality as well.

As my colleagues have mentioned, there are significant efforts to increase the yield of full capsids while reducing the number of empty capsids and decreasing the amount of plasmid co-packaged in the empties, which ties back to the plasmid design. This also involves reducing other impurities or residuals in the harvest process. The focus on optimizing not just quantity but also quality right from the start is something that truly excites me.

In addition, in an effort to optimize constructs and manufacturing conditions, AI is now here to help us design the next generation of AAV vectors from multiple angles, whether it is the vector genome, the helper plasmid, or the cell line. With over 40 years of accumulated data, including many production successes and failures, there is now an opportunity to use machine learning platforms to analyze this vast body of information and determine the best approaches. Although I have not yet witnessed the direct impact of these new 'AI-engineered' constructs on AAV manufacturing, I am eager to see what will come next.

Q What for you are the key current challenges in the downstream purification of AAV vectors, and what strategies or techniques have you found most effective in overcoming them?

NL: I will divide my answer into three parts: the capture step, polishing, and analytics. Each plays a key role in DSP.

Firstly, on capture: currently, immunoaffinity is the standard for 99% of AAV producers. One major challenge with using this resin is processing time - this step can take hours or even days. The issue lies in the discrepancy between the extremely high capacity of immunoaffinity resins and the relatively low titers of the feedstock. Despite recent increases in titers, this means loading times remain very long, which poses risks for manufacturing. The extended timeframe increases the risk of equipment failure, leakage, or other problems, requiring personnel to constantly monitor the process. There is also a risk to the product itself—stability can decrease

> "For polishing, the main challenge remains the separation of full and empty capsids."

over time, and prolonged processing increases the chance of contamination. Addressing this challenge requires changes such as optimizing the geometry of the column, implementing single-pass tangential flow filtration (TFF) ahead of the column, using multi-column chromatography or rapid cycling, and exploring other technologies. We are also hoping for systems like membranes that could enable rapid capture, although such options are not available on the market yet.

For polishing, the main challenge remains the separation of full and empty capsids. As my co-panelist mentioned, there are numerous initiatives, trials, and application notes addressing this, but we still lack a universal method to separate full from empty capsids. Each new serotype, construction, and even lot or batch, requires redevelopment of separation steps, which is a significant bottleneck. This is an area where progress is urgently needed in the coming years.

Lastly, on analytics: one of the long-standing challenges in this field is the lack of accuracy and high variability in analytical methods. These methods are time-consuming, costly, and resource-intensive, with variability often reaching 20–25%. This makes development challenging, as multiple assays and analytics are needed to determine the correct direction. Addressing this bottleneck requires the development of new tools to improve speed and accuracy from an analytical standpoint, which I believe is crucial for advancing the field.

MR: Nicolas did a great job covering the empty-full—a longstanding issue in the field. We are definitely not at the point where separation can be fully standardized, but hopefully, we will get there. Right now, people have found suitable strategies for individual capsids, but having a more broadly applicable solution, which would also shorten the development timeline, would be ideal.

Beyond that, our focus has been on studying post-translational modifications (PTMs) to better understand the product at each stage of the process. We have been conducting process hold and degradation studies to identify the conditions that drive PTMs, such as deamidation. Additionally, we are correlating these modifications with *in vitro* and *in vivo* potency to determine what could potentially lead to a drop in efficacy. Together, these efforts have allowed us to identify critical parameters for maintaining potency throughout the process, even for steps that might have been overlooked in the past.

WK: As we move towards a more mature modality, cost will increasingly become a key challenge. One major focus is identifying the biggest cost drivers in DSPs and finding ways to reduce them. Benzonase™ or other nucleases used to clear host cell DNA, while highly effective, are also quite expensive. Alternatives like flocculation, using either low pH or quaternary ammoniums, have shown promise in reducing the cost of DNA clearance before harvest.

Another significant cost driver, as Nicolas mentioned, is affinity chromatography, which is a major advancement but comes with high costs. Affinity resins are among the most expensive components in DSP. To address this, improving the number of times an affinity resin can be cycled, through effective clean-in-place procedures, is crucial.

NC: One of the key bottlenecks we all agree on is the separation of full and empty capsids, but I would like to frame this in a broader context. Each AAV product is unique and finding universal approaches for upstream or downstream will remain challenging unless we standardize the vector design itself. The complexity arises not only from the capsid but also from what is inside the capsid, which makes downstream particularly difficult. Even if you do not necessarily need to reinvent the wheel for each construct, it does often require making adjustments to the platformed processes, which can be time-consuming and costly for every drug product.

In terms of separating full and empty capsids, it has become clear that it is not simply about separating fulls from empties, or even from partially packaged capsids. These are not discrete species; rather, there is a continuum between full and empty capsids, with all sorts of intermediates. Current techniques are not designed to specifically target and bind to fully packaged capsids, and whoever solves that, will make a major breakthrough in the field.

Cost is also an important factor, but a significant challenge is the overall recovery, especially in downstream steps. While tremendous progress has been made upstream, with yields multiplied by a factor of 10 or even 100, downstream remains a bottleneck. At best, a 30% final recovery in the vialed drug product is considered good, which makes me think, 'What can we do better?' One approach could be to simplify DSP processes. We know that every additional step taken to make the product cleaner and purer, results in the loss of full capsids. Therefore, I believe we should focus on reducing the number of steps or developing more powerful but fewer steps to improve efficiency and recovery.

Q What are the most important upstream process (USP) techniques, tools, or strategies to focus on with the goal of helping DSP?

NC: Optimizing upstream with downstream in mind is so important. It is often overlooked that we need to develop a platform where both USP and DSP work together to optimize not only the yields but also the product quality. I am a strong believer that quality starts upstream. With that in mind, it is crucial to develop upstream conditions that optimize several critical quality attributes, such as improving vector genome titers, reducing empties, and minimizing contaminating residual plasmids, host cell DNA and host cell proteins.

One impurity that has been overlooked for quite some time, but is now getting more attention, is residual host cell DNA and plasmid DNA; I have heard many times how excessive DNA in the harvest can significantly impact DSP. DNA is viscous, which can affect the filtration and/or binding steps. DNA can even bind to capsids and cause aggregation in unpredictable

ways. Therefore, improving upstream by minimizing DNA from the harvest is crucial, and there are several platforms and solutions to explore in this area.

Regarding cell lysis, one key aspect for downstream is receiving a homogenous and consistent product from the beginning. If upstream can consistently provide the same type and quality of material, downstream will not have to reinvent the wheel for every batch. They will be able to predict outcomes more accurately based on titers and capsid counts, for example.

Consistency in production—whether by transfection or infection, depending on the platform—and homogeneity of the clarified material is critical. Whether it is through Benzonase digestion or other methods to ensure complete cell lysis and AAV release, these considerations will also support downstream steps like TFF or filtration. In summary, providing downstream with material that is both homogenous and of consistent quality will greatly simplify the process.

NL: We have seen cases where, even with the same serotype, affinity can vary depending on the specific construct being used, and this affects steps like chromatography. The polishing step in particular is highly influenced by these variations.

Regarding nuclease use, this is a crucial point. I see many customers adding large amounts of endonucleases or nucleases to their feedstock without checking if the enzyme is actually effective, or if they still have nucleic acids at the end. Often, they spend a lot of money on nuclease but still end up with high residual DNA levels, because they do not consider that most of these enzymes are inhibited by salt or other conditions common in cell culture. This renders the enzyme inefficient. Fortunately, we now have enzymes on the market that are salt-tolerant, and my recommendation would be to switch to one of these, but always pay attention to your nuclease treatment.

I also want to emphasize clarification. It is key in a DSP process, and it is an area where we need to put the most effort. It may seem obvious, but the cleaner and clearer the feedstock you load onto capture chromatography, the better the resin's performance in terms of yield, consistency, and step reproducibility. Clarification also impacts the reusability of the resin. If the feedstock is cleaner, the resin is easier to clean and can be reused more times. Investing time in optimizing USP will ultimately make DSP easier and save considerable time, money, and resources.

MR: I completely agree with both sets of comments. In past years, the primary focus has been on yield, but there is now a definite shift towards prioritizing percent full, capsid even early on in USP. We have found that while our purification processes are capable of substantial enrichment, the lower the starting percent full, the more challenging it is to achieve a higher percent full at the end of purification. For example, if you are aiming for a two- to three-fold enrichment, starting at 5% full is going to be much more difficult for the DSP—ideally, we want at least 20% full from the outset.

When conducting Design of Experiments (DoE) studies or screening experiments in upstream, we still prioritize yield, but we also set a threshold for percent full. On the bright side, as USP continues to improve, we are seeing more conditions with higher percent full

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> "On the bright side, as upstream processing continues to improve, we are seeing more conditions with higher percent full becoming more common."

becoming more common. Another strategic point is ensuring that impurities are properly considered. It may sound obvious, but sometimes in the excitement of increasing yield by two- or three-fold, people overlook impurities, leading to downstream issues—particularly with residual host cell DNA.

During process intensification, if you are increasing viable cell density significantly, you could be in a situation where yield has gone up two- or three-fold, but cell density has increased five-fold, making downstream purification (especially at the anion exchange step) much harder due to the extra residual host cell DNA. Therefore, our focus has been on cell-specific productivity rather than just viral genome titer or capsid titer alone.

WK: As a downstream scientist, I completely understand the excitement when yield goes up two- or three-fold! But my first question is always: what has happened to the total capsid level and percent full capsids? These factors can significantly impact the DSP. One key element affecting the percent full ratio in upstream is the transfection process—specifically, the cell health at transfection and the scalability of the mixing and delivery of the transfection cocktail.

Upstream teams might do a great job developing a process at a 2 L or 10 L scale, but when scaling up to 500 L or 2,000 L, delivering a consistent transfection cocktail with the same type of mixing becomes very challenging. This is something I always watch for during scale-up, as changes to the feed stream and percent full capsids can impact what we see downstream. It is not an easy task and often requires significant effort because you cannot simply do process development at scale. Utilizing modeling or thoughtful experiments can be a way to address these challenges without heavy investments of time and plasmid. I realize I have pointed out a problem for upstream to solve here, without providing a solution—a typical downstream perspective!

Q What approaches or techniques do you use to determine the optimal purification tools for a given AAV process?

WK: Focusing on chromatography, I prefer conducting early-stage development in a high-throughput or semi-high-throughput manner. This approach does not necessarily require an expensive robotic liquid handler—it can be done with well-plates and resin, using a multichannel pipette for sample handling and collection. This setup allows for much more data generation compared to using individual columns connected to a traditional chromatography system.

Once you generate all this data, you may face a bottleneck at the analytics stage. To address this, high-throughput, directional analytical tools can be used. While they may not provide precise values like droplet digital PCR (ddPCR), they do give useful directional insights. Several analytical instruments are very efficient for this purpose, providing data on dynamic light scattering, capsid titer, empty/full ratio, and aggregation. You can also use absorbance-based readings from well plates, which are common in analytical labs. This approach gives quick readouts for A_{260} and A_{280}, providing a preliminary empty/full ratio. After screening conditions with these tools, you can proceed to more detailed analytics like ddPCR and, eventually, analytical ultracentrifugation for deeper characterization.

This high-throughput approach can be adapted to study affinity chromatography by evaluating binding, washes, and elution in a loose resin format. For anion exchange (AEX), high-throughput studies can be conducted on dilution/load preparation, and binding steps. However, when you get to developing gradient elution over AEX, it is best to transition from loose resin to small columns that can provide smooth gradient formation. Thermo Scientific™ MiniChrom™ columns of 200–500 µL, pre-packed and connected to a downstream chromatography system with low flow capabilities, work well here. This setup allows for efficient screening of elution salts or cosolvents, which is particularly impactful for empty/full separation over AEX. This is my go-to approach to chromatography in a semi-high-throughput fashion.

NC: I want to emphasize how crucial it is to have strong analytics at these steps. I completely agree with what Nicolas mentioned earlier—you will be making decisions by comparing many different conditions, whether it is binding buffers, wash, or elution buffers, and submitting these samples to various assays, including ddPCR. What often gets overlooked is the impact of the matrix on these analytics.

Fortunately, with ddPCR, the impact of the matrix is reduced, but it is still not negligible. You will be comparing samples that vary significantly in pH, salt concentration, and titer, from very diluted to highly concentrated, depending on the steps being evaluated. It is essential to trust your analytics and ensure they are capable of making accurate comparisons.

To achieve this, it is important to have a set of assays specifically designed for evaluating the various conditions during screening. Additionally, multiple critical quality attributes should be assessed when selecting optimal conditions. Vector genome titer and total capsid titers are key attributes, but do not overlook potency or infectivity—these can be evaluated in a relatively simple, high-throughput manner. As mentioned previously, residual DNA is another critical factor. It is crucial to screen for multiple quality attributes rather than focusing solely on one, such as vector genome, as was often the case in the past.

NL: Working for a supplier of chromatography resins, my choice is quite straightforward. I, of course, recommend using Thermo Scientific™ POROS™ and Thermo Scientific™ CaptureSelect™ resins for both capture and polishing. As William mentioned earlier, high-throughput is important, and it is worth noting that these resins come in various formats, ranging from Thermo Scientific™ RoboColumns™ to 96-well screening plates, pre-packed

columns, and even magnetic beads for quick evaluation of AAV purification or determining if a method will work effectively. It can be beneficial to utilize these different formats.

Additionally, I encourage people to contact their local suppliers and application specialists for support in developing their purification steps. This can save a significant amount of time and effort. I may be advertising myself here, but I strongly recommend reaching out to your local application support for assistance.

Q How do you navigate the complexities of AAV purification to ensure both high purity and yield in your downstream process?

MR: This can be a challenge, particularly for the empty/full separation. I think of it as a balancing act, trying to achieve a high degree of purity while maintaining yield. Fortunately, affinity chromatography has been extremely helpful in reaching high purity levels early in the DSP. Our main strategy is to identify options and levers within the process, particularly in the post-affinity chromatography steps, that we can adjust to change purity or yield if needed. This approach allows us to maintain good process understanding, which is hopefully applicable across multiple products.

One example of this is increasing the salt concentration of a wash during anion exchange to remove more empty capsids if we are starting with a lower percent full capsids for that particular construct. It might also involve changing the salt concentration in the load or the buffer you are diluting with, or using TFF to exchange into a different solution. My advice here is to ensure that you are not only focused on empty/full capsids but also giving appropriate attention to residuals. Especially when developing a pooling strategy for AEX, it is important to observe how residual levels change across pools. Ideally, conduct a study where you are fractionating individually to analyze residual host cell DNA or plasmid DNA at different points of your peak (start, middle, and end), which provides valuable insights into these levels.

NC: This is a challenging question, and it is something we have all encountered at some point when developing drug products for clinical use. We have discussed recovery: if achieving the highest purity means a 99% loss, making it impossible to reach the clinic because there is not enough product, that becomes a significant challenge. While purity is paramount and we should strive for it, safety must also guide the development of a platform that meets your needs for clinical trials. Always remember that you are also evaluating product safety during your IND-enabling toxicology studies, which play a crucial role in assessing how well your processes are performing in terms of ensuring production of a safe product.

WK: When preparing to file, the focus should be on SISPQ: strength, identity, safety, purity, and quality. Yield is not part of an IND filing requirement, meaning purity, potency, and safety are prioritized over yield. Ensuring that safety and potency come first is crucial. One factor that can impact potency is the rate of deamination—an impactful post-translational

> "To effectively approach scale-up, it is essential to begin addressing scalability early in development."

modification on the capsid surface that can reduce potency. Finding ways to improve stability during in-process holds to maintain potency is an important aspect of development.

To echo what Matt said, most yield loss occurs during AEX. Understanding the balance between yield and purity by analyzing different fractions across AEX—not just focusing on empty and full capsids but also considering other post-translational modifications, deamination, and residual host cell proteins or DNA—provides a clearer understanding of what needs to be compromised to achieve a particular yield. Having these kinds of insights is critical for making good decisions.

Q How do you ensure the scalability and reproducibility of your AAV purification process in large-scale manufacturing?

WK: This is particularly important as gene therapy moves toward larger scales and doses, especially for applications beyond rare disease indications. For instance, Nathalie works at Siren, which focuses on treating cancer, indicating the need for substantial vector quantities. To effectively approach scale-up, it is essential to begin addressing scalability early in development.

If you receive a process from an academic partner that involves non-scalable unit operations, such as freeze-thaw cycles or ultracentrifugation for separating empty from full capsids, it is crucial to *immediately* start developing scalable alternatives, like detergent lysis or AEX for that separation. It is important to manage expectations regarding initial performance, as investing in scalable unit operations early will pay off later during scale-up.

In terms of chromatographic scale-up for AAV, a key strategy is to size your chromatography columns by fixing the load challenge across scales. This involves knowing the dynamic binding capacity of your affinity column and ideally, matching the column bed height when moving from small- to large-scale, by increasing the column diameter. This bed height matching is particularly vital for AEX, as it requires high-resolution separation, while affinity chromatography can tolerate some variation without significant impact.

It is also essential to maintain consistent residence times and match gradient slopes and lengths between small and large scales. A crucial *watch out* during AEX scale-up is ensuring proper gradient formation in larger-scale chromatography systems. Working at the lower range of pump capabilities can lead to instability and result in nonlinear gradients. This can adversely affect separation quality. Additionally, variations in the upstream empty-full ratio can occur during scale-up; therefore, early-stage process development should include testing the robustness of the AEX process against different percent full capsid levels.

Lastly, while somewhat tangential, having scientists present in the GMP suite during tech transfers is crucial. Observing chromatography and filtration steps firsthand provides insights that are far more valuable than hearing about them later. These tips are key for ensuring reproducibility and setting the stage for successful large-scale operations.

NC: My approach begins with selecting scalable methods right from the start of the process development phase and Phase 1 clinical studies. It is essential not to adopt a mindset of 'we'll figure it out later', as this can lead to significant complications in Phase 2 and at the BLA submission stage. Understanding the concept of scaling out is critical: to produce sufficient product, you will need to multiply the number of bioreactors or centrifuges.

If you have the opportunity, choose methods that are inherently scalable, enabling a smooth transition to subsequent clinical trials and BLA submissions. For example, although cesium chloride gradient purification method may have historical significance, they are not scalable, so it is best to avoid them when possible. Focusing on USPs in suspension culture instead is also a more effective strategy for achieving scale-up or scale-out.

MR: The key to our success has been thoroughly understanding each part of the process, including the smallest details, as we transition to large-scale manufacturing. In the past, process development teams often assumed factors like process hold times would not significantly impact outcomes, especially in early-stage processes, and underestimated their importance. While AAV can appear to be robust, we now recognize the necessity of delving deeper into these aspects as our product candidates mature.

Moreover, when working with a CDMO, it is essential to cultivate a collaborative and positive environment. This fosters effective process transfers and ensures scalability and reproducibility. Establishing clear lines of communication and making collaboration as seamless as possible is critical to achieving our goals.

NL: As Nathalie emphasized, it is crucial to think about large-scale processes right from the beginning of development. Connecting with experts who understand the constraints of running chromatography and DSP techniques at scale is vital. This collaboration allows you to develop a process that is both scalable and robust enough for successful transfer.

When considering chromatography, selecting the right format and media is essential. Not all materials have the same properties, and managing back pressure becomes a key concern when scaling up. Non-compressible materials, for example, make scaling easier since their back pressure is influenced solely by flow and bed height, not diameter.

Additionally, as William pointed out, accuracy in gradients should be a priority. Whenever possible, I recommend minimizing the use of gradients, as they can complicate the robustness of your process. If a gradient is necessary, ensure that initial separations do not occur at the beginning of the gradient, as pump inaccuracies can significantly alter results. By focusing on these elements and collaborating with large-scale manufacturing experts, you can develop processes that are well-suited to successful scale-up.

BIOGRAPHIES

NATHALIE CLEMENT has over 25 years of experience in the field of gene therapy with industry-leading expertise in AAV vector manufacturing. Since January 2022, Nathalie has held the role of Vice President of Vector Development for Translational Gene Therapies at Siren Biotechnology, San Francisco, CA, USA a startup focused on delivering a cure to cancer using AAV-mediated gene transfer.

WILLIAM KISH is a Purification Scientist with over a decade of experience across industry and academia. As a Principal Scientist at Taysha Gene Therapies, Durham, NC, USA he leads their downstream CMC activities, including process development, characterization, tech transfer, CDMO oversight, and the authoring of regulatory documents. He holds PhD and Master's degrees in Chemical Engineering from North Carolina State University, Raleigh, NC, USA.

NICOLAS LAROUDIE is a Senior Field Application Scientist at Thermo Fisher Scientific, Strasbourg, France supporting the technical implementation of POROS™ and CaptureSelect™ chromatography products in southwestern Europe. A biochemist by education, he has over 20 years of experience in downstream processing purification, from lab-scale R&D to commercial manufacturing.

MATTHEW ROACH is the Director of AAV production at BridgeBio, Cary, NC, USA where he is focused on designing and implementing new strategies for the production and purification of AAV. Matt completed his Bachelor's degree in Biological Sciences at North Carolina State University, Raleigh, NC, USA and his Master's degree in Microbiology and Cell Science at the University of Florida, Gainesville, FL, USA.

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AUTHORSHIP & CONFLICT OF INTEREST

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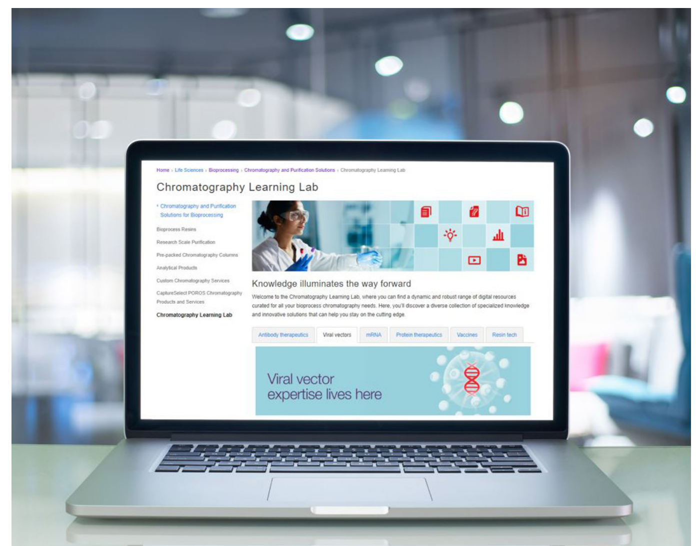

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