CELL & GENE THERAPY INSIGHTS

INNOVATOR INSIGHT

Optimizing vector production and purification to enhance scalable AAV manufacturing

Jonathan Zmuda, Chantelle Gaskin, James Molinari, Jenny England

The constant growth in the number of clinical trials in the gene therapy space highlights the need for a reliable and scalable viral vector manufacturing solution. This article describes scaling up AAV production using the Gibco™ AAV MAX helper-free AAV production system and presents a purification wash and elution optimization study using the POROS™ CaptureSelect™ AAVX chromatography resin.

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CTS AAV-MAX PRODUCTION SYSTEM

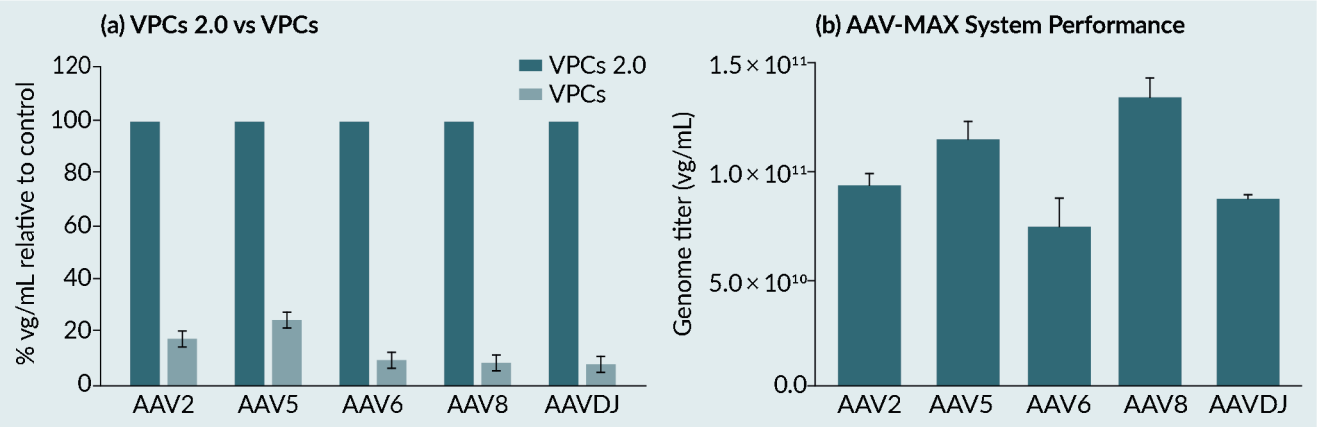
Thermo Fisher Gibco Cell Therapy Systems (CTS) products are designed to enable clinical and commercial cell and gene therapy manufacturing. All CTS reagents are manufactured under cGMP, with cell and gene therapy-specific intended use statements, extensive safety testing, and proactive regulatory documentation provided to ensure quality materials, help minimize risk, ease the burden on quality systems, and support regulatory submissions. Within the CTS portfolio, the CTS AAV-MAX production system is a fully integrated and optimized system for scalable high-titer production of adeno-associated virus (AAV).

The AAV-MAX system comprises several core components, starting with the viral production cell (VPC) line 2.0, viral production medium, AAV-MAX transfection reagent and booster, Viral-Plex™ complexation buffer (used to complex plasmid DNA with the AAV-MAX transfection reagent and booster), and AAV-MAX enhancer (to drive high titers of viral vector production). Finally, the AAV-MAX lysis buffer is a polysorbate 20-based

FIGURE 1

AAV-MAX system performance.

(a) AAV titers generated with VPC 2.0 cell lines versus original VPC cell line. (b) Viral titers achieved with VPC 2.0 in different AAV serotypes.



lysis buffer for liberating AAV prior to downstream purification.

The heart of the AAV-MAX system is Thermo Fisher Scientific's VPC 2.0 – a clonal, 293F-derived suspension cell line for superior AAV production. These cells have no associated SV40 large T antigen and allow for high-titer viral vector production, as the cells grow to a very high density in suspension culture. In a typical shake flask, these cells will obtain 12 million cells per ml or greater and benefit from a non-clumping phenotype with robust scalability. To date, we have grown these cells up to 3000 L scale in single-use bioreactors with excellent comparability to shake flask dynamics. The cell line has a fast recovery post-thaw so that cells can be rapidly scaled up in the seed train for transfection and rapid growth rates for 293 cell lines, with less than a 24 h doubling time. The VPC 2.0 cell line will be available cGMP banked later in 2022.

Figure 1 compares the new VPC 2.0 cell line with the original VPC cell line and demonstrates the high viral titers (ranging from 5×10^{10} to above 1×10^{11}) viral titers achieved across multiple different serotypes.

The CTS AAV-MAX production system allows for excellent flexibility from discovery through preclinical testing, clinical manufacturing, and ultimately commercial-grade production of AAV for gene therapy.

OPTIMIZING POROS CAPTURESELECT RESINS FOR AAV AFFINITY CAPTURE

Downstream process scientists are presented with some unique purification challenges in the AAV workflow, including:

- Increased impurity burden due to cell lysis, including host cell protein (HCP) and host cell DNA (HCD) removal
- Recovery – Cumulative yield losses with each unit operation
- Removal of empty capsids
- Removal of adventitious viruses
- Scalability
- Large variety of AAV serotypes

POROS CaptureSelect AAV affinity resins are designed to address key challenges using a single chromatography step.

POROS CaptureSelect AAVX resin is a pan-serotype affinity resin that binds both wild-type and novel or engineered capsids. Since the AAVX ligand is coupled to the POROS backbone, the resin delivers good pressure-flow properties. This resin is manufactured to quality standards and has the proper documentation for its use in GMP processes.

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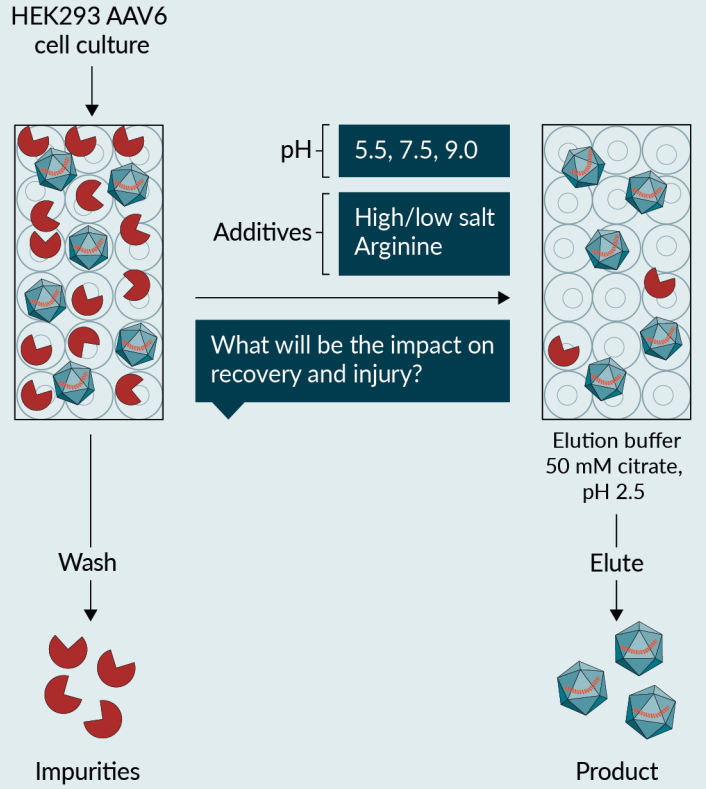
FIGURE 2

Design of AAVX wash optimization study.



Run	Wash buffer
1	50 mM Tris pH 7.5
2	50 mM Tris pH 7.5, 0.1 M NaCl
3	50 mM Tris pH 7.5, 0.1 M NaCl (D)
4	50 mM Tris pH 7.5, 1.5 M NaCl
5	50 mM Tris pH 7.5, 0.250 M arginine
6	50 mM Tris pH 9.0
7	50 mM Tris pH 9.0, 1.5 M NaCl
8	50 mM Tris pH 9.0, 0.250 M arginine
9	50 mM citrate pH 5.5
10	50 mM citrate pH 5.5, 1.5 M NaCl
11	50 mM citrate pH 5.5, 0.250 M arginine

*All buffers in study contain 0.01% PF-68

The growing use of AAV viral vectors in the gene therapy field has emphasized the need to optimize the downstream purification process, with demand for higher purity and recovery.

AAVX WASH BUFFER OPTIMIZATION

The purity and recovery of AAV6 capsids produced in HEK293 cells were assessed after treatment with 11 different wash buffers, with varying pH and compositions (Figure 2).

The samples were clarified by adding diatomaceous earth and then filtered with a 0.22 µm polyethersulfone (PES) vacuum filter before loaded onto POROSTM GoPureTM AAVX Pre-packed 1mL columns. A summary of the method is shown in Table 1. All buffers in the study contain 0.01% Pluronic F-68 (PF-68).

Intermediate wash buffers containing Tris at pH 7.5 resulted in similar elution peak profiles and similar peak areas for all buffers tested. Notably, a marked decrease in the strip peak area was observed with the addition of high salt and arginine in the wash buffer compared to the lower conductivity wash buffers.

The Tris pH 9 wash buffers resulted in a similar increase in elution peak areas with both the high salt and arginine wash buffers. However, an increase in the elution pool volume was observed when arginine was added to the wash buffer, accompanied by a decrease in the strip and clean-in-place (CIP) peak areas.

Lastly, the pH 5.5 group of wash buffers resulted in the lowest elution peak area with the citrate-only wash, but the addition of arginine in the citrate wash buffer increased the elution peak area. The addition of high salt both increased the elution peak area and decreased the strip peak area.

Figure 3 gives a snapshot of the total capsid recovery for each wash buffer tested, using total capsid ELISA for titer determination. In general, the Tris-based wash buffers containing salt generated the highest recoveries regardless of pH, and the highest recovery was with the 50 mM Tris, plus the 1.5 M sodium chloride at pH 9 as a wash buffer. The

TABLE 1

Experimental summary for AAVX wash optimization study.

Step	Buffer	Column volumes	Residence time (min)	Flow direction
Equilibration	50 mM Tris pH 7.5 + 100 mM NaCl	5	1	Downflow
Load	Clarified lysate	100	1	Downflow
Wash	Variable	5	1	Upflow
Elution	50 mM citrate pH 2.5	5	1	Upflow
Regeneration	100 mM phosphoric acid	5	3	Upflow
Cleaning	6 M guanidine HCl	5	3	Upflow
Storage	20% ethanol	5	1	Downflow

FIGURE 3

Total capsid recovery with a range of wash buffers.

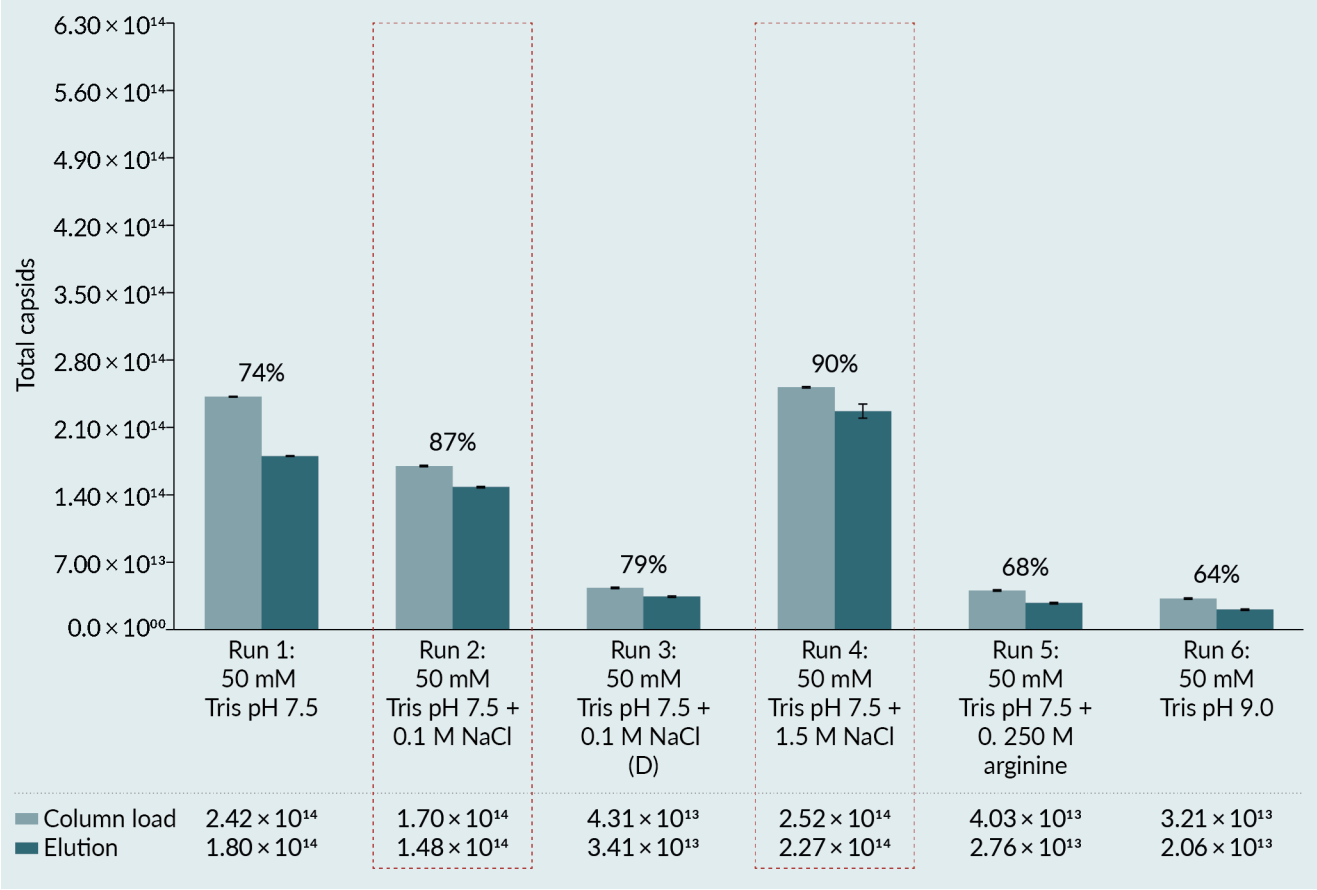


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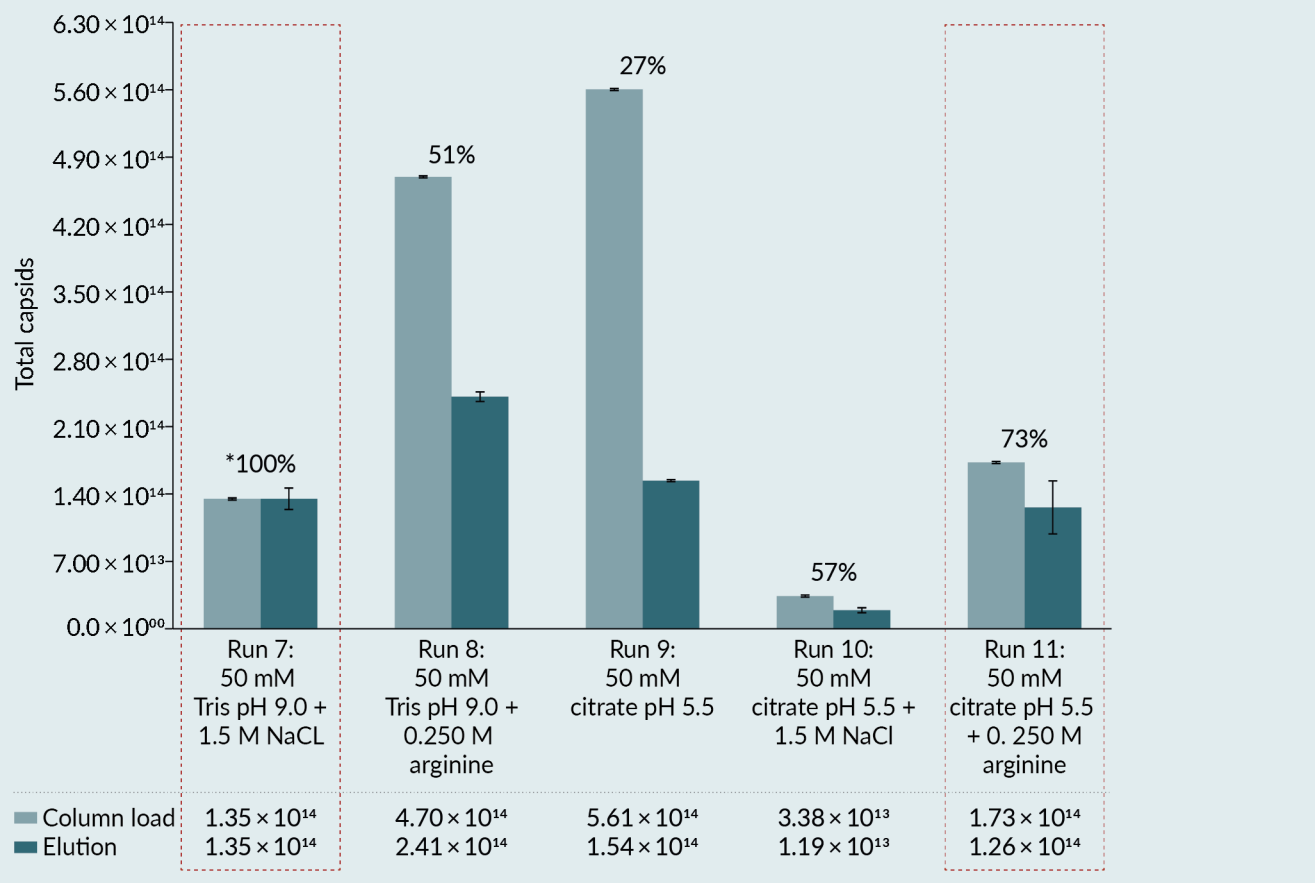
FIGURE 3 (cont.)

Total capsid recovery with a range of wash buffers.



citrate-based wash buffers generally yielded the lowest recoveries, but the addition of arginine to the citrate buffer increased the recovery to 73%.

All wash buffers provided greater than 4 log reduction values (LRV) of HCP with an average LRV of 4.5 across the board, and an average LRV of 3.2 for HCD.

In conclusion, the wash buffers that yielded the best recoveries (over 85%) were Tris buffers at pH 7.5 and 9, with the addition of sodium chloride 1.5 M. These buffers were therefore selected for the next set of experiments.

TABLE 2

Design of combination wash study.

Combo run	Wash buffer
1	50 mM Tris pH 7.5, 0.100 M NaCl
	50 mM Tris pH 9.0, 1.5 M NaCl
	50 mM Tris, pH 7.5
	50 mM pH 7.5, 0.100 M NaCl
2	50 mM Tris pH 7.5, 0.100 M NaCl
	50 mM Tris pH 9.0, 1.5 M NaCl
	50 mM Citrate pH 5.5, 0.250 M arginine
	50 mM pH 7.5, 0.100 M NaCl
3	50 mM Tris pH 7.5, 0.100 M NaCl
	50 mM Tris pH 9.0, 1.5 M NaCl
	50 mM Tris pH 9.0
	50 mM pH 7.5, 0.100 M NaCl

Combination wash study

In the combination wash study, each run contained three Tris-based washes, as well as a third variable wash buffer (summarized in Table 2).

As before, samples were clarified with diatomaceous earth and filtered with a 0.22 µm PES vacuum filter before being loaded onto

TABLE 3

Experimental summary for combination wash study.

Step	Buffer	Column volumes	Residence time (min)	Flow direction
Equilibration	50 mM Tris pH 7.5 + 0.100 M NaCl	5	1	Downflow
Load	Clarified lysate	100	1	Downflow
EQ wash 1	50 mM Tris pH 7.5 + 0.100 M NaCl	10	1	Upflow
Wash 2	50 mM Tris pH 9.0 + 1.5 M NaCl	5	1	Upflow
Wash 3	Variable	5	1	Upflow
EQ wash 4	50 mM Tris pH 7.5 + 0.100 M NaCl	10	1	Upflow
Elution	50 mM citrate pH 2.5	5	1	Upflow
Regeneration	100 mM phosphoric acid	5	3	Upflow
Cleaning	6 M guanidine HCl	5	3	Upflow
Storage	20% ethanol	5	1	Downflow

a POROS GoPure AAVX Pre-packed 1 mL column. The protocol is described in Table 3.

All combination runs in this set of experiments featured a sharp peak presenting with an elution pool volume of 1 column volume.

The elution recovery was similar for all combination wash runs, with over 80% recovery (Figure 4) but there was a relatively lower HCP LRV with the citrate combination wash run. HCD removal followed a similar trend to

FIGURE 4

Recovery and host cell protein removal for combination runs.

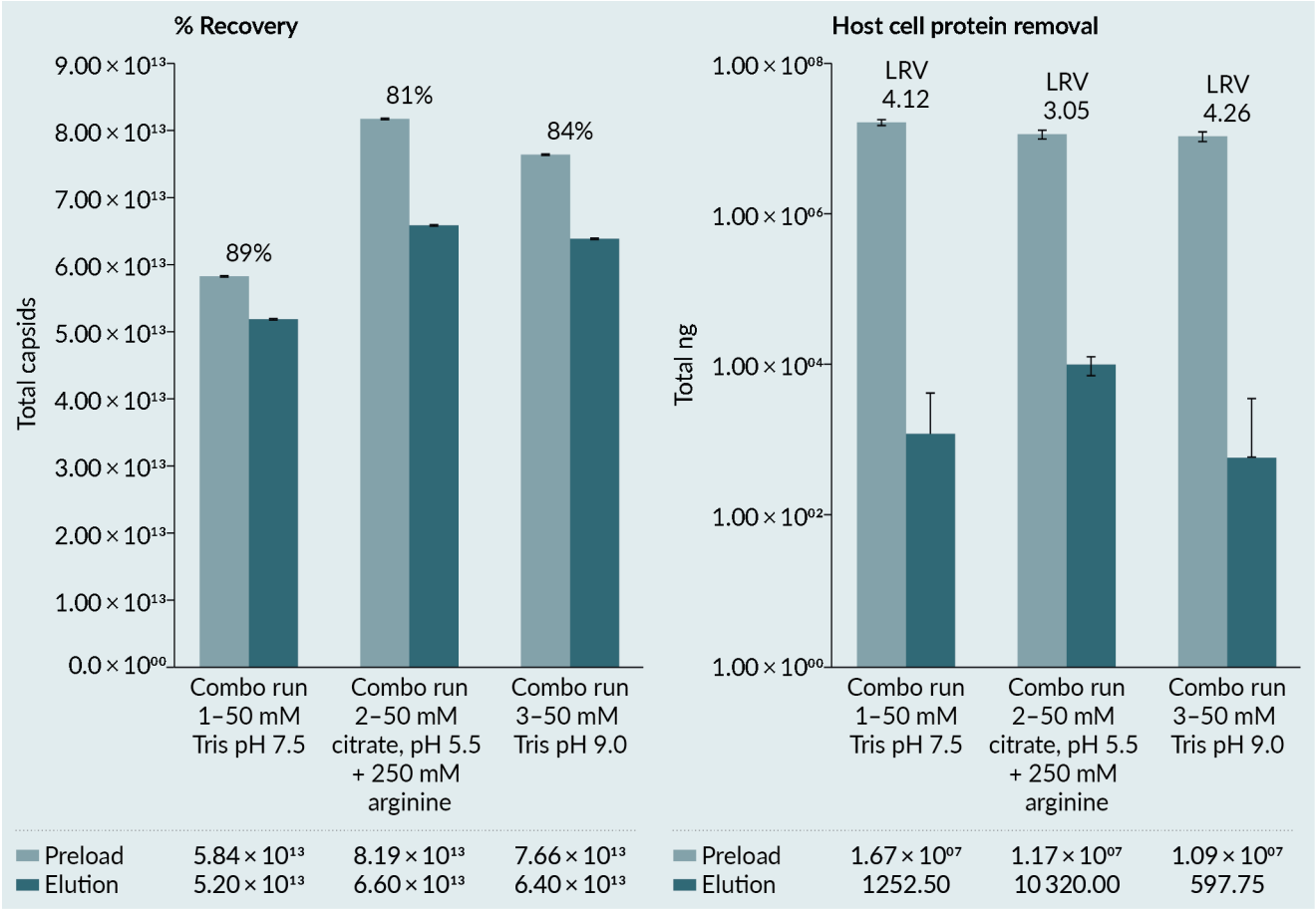


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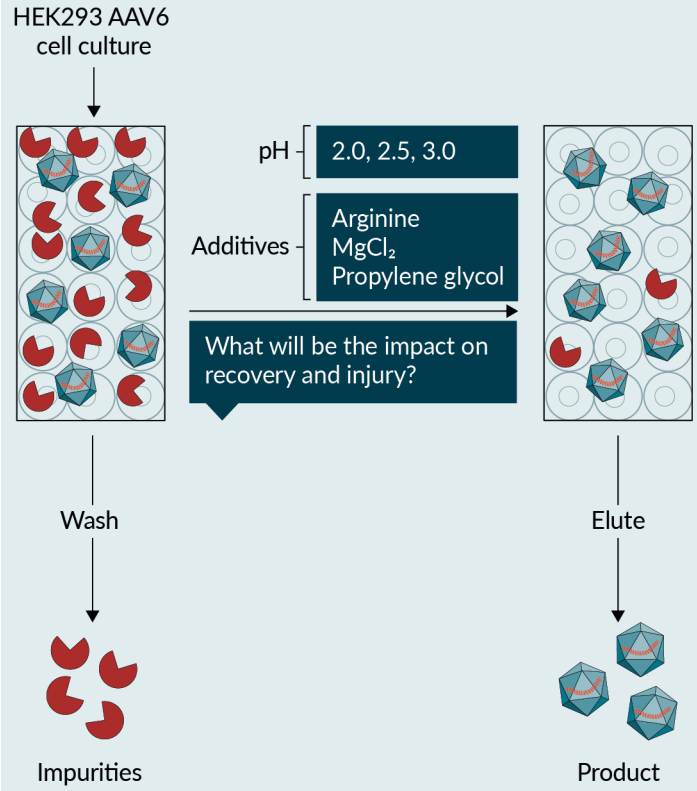
FIGURE 5

Design of AAVX elution optimization study.



Run	Elution buffer
1	100 mM glycine pH 2.0
2	100 mM glycine pH 2.5
3	100 mM glycine pH 3.0
4	100 mM glycine pH 3.0, 0.5 M arginine
5	100 mM Glycine pH 3.0, 0.5 M $MgCl_2$
6	100 mM glycine pH 3.0, 40% propylene glycol
7	100 mM glycine pH 3.0, 0.5 M arginine, 0.5 M $MgCL_2$
8	100 mM glycine pH 3.0, 0.5 M arginine, 40% propylene glycol

*All buffers in study contain 0.01% PF-68

TABLE 4

Experimental summary for elution buffer HTS study.

Experimental summary		
Resin volume	20 µLs	
Column load density	1 mg AAV6/mL of resin	
Equilibration buffer	50 mM tris, 150 mM NaCl, 0.01% PF-68 pH 7.5	
High salt buffer	50 mM tris, 1.5 M NaCl, 0.01% PF-68 pH 7.5	
Elution buffer	Variable	
Strip	100 mM phosphoric acid, 0.01% PF-68	
	pH	**Excipients**
100 mM Glycine	2.0	**Arginine:** 0.1 M, 0.25 M, 0.5 M
	2.5	**$MgCl_2$:** 0.1 M, 0.25 M, 0.5 M
	3.0	**Propylene glycol:** 20%, 30%, 40%

the single wash step runs, with an average LRV of 3.6 across the different combination runs.

In conclusion, Tris pH 7.5 or pH 9 buffers with 1.5 M sodium chloride followed by a low-salt wash resulted in the greatest recovery of AAV capsids from the AAVX resin in this set of experiments. Citrate alone as a wash buffer resulted in a poor yield but the addition of arginine improved recovery by 25 to 50%.

While HCP and HCD removal were similar for all combination wash runs, the

TABLE 5

Summary of HTS results.

pH	Arginine	$MgCl_2$	Propylene glycol
2.0	▸ Greatest impact on recovery ▸ Additive effect as a function of concentration with 0.5 M with the greatest recovery	No impact as a function of concentration	No impact as a function of concentration
2.5			
3.0		▸ Negative impact on recovery ▸ 0.5 M MgCl2 with poorest recovery	

TABLE 6

AAVX RoboColumn experimental method.

Step	Buffer	CVs	Res time (min)
Equilibration	50 mM tris pH 7.5 + 0.100 M NaCl	5	1
Load	Purified AAV6	2.5	1
Wash 2	50 mM tris pH 9.0 + 1 M NaCl	5	1
EQ wash 4	50 mM tris pH 7.5 + 0.100 M NaCl	10	1
Elution	Variable	5	1
Strip	100 mM phosphoric acid	5	3
CIP	6 M guanidine HCl	5	3
Storage	20% ethanol	5	1

TABLE 7

AAVX RoboColumn elution conditions.

	pH	Excipients
100 mM Glycine	2.0 2.5 3.0	0.5 M Arginine
		0.5 M Arginine, 0.5 M $MgCl_2$
		0.5 M Arginine, 40% Propylene Glycol
		0.5 M Arginine, 0.5 M $MgCl_2$, 40% Propylene Glycol

TABLE 8

RoboColumn screening results summary (with % recovery).

Excipient	2.0	2.5		3.0		
None	59		69		68	
0.5 M arginine	89	(++)	85	(++)	91	(++)
0.5 M arginine 0.5 M $MgCl_2$	46	(-)	62	(=)	28	(--)
0.5 M arginine 40% propylene glycol	74	(+)	49	(-)	72	(+)
0.5 M arginine 0.5 M $MgCl_2$ 40% propylene glycol	57	(=)	67	(=)	28	(--)

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TABLE 9

Experimental summary for column elution buffer study.

Step	Buffer	Column volumes	Residence time (min)	Flow direction
Equilibration	50 mM tris pH 7.5 + 0.100 M NaCl	5	1	downflow
Load	Clarified lysate	100	1	downflow
EQ wash 1	50 mM tris pH 7.5 + 0.100 M NaCl	10	1	upflow
Wash 2	50 mM tris pH 9.0 + 1.5 M NaCl	5	1	upflow
Wash 3	50 mM tris pH 7.5	5	1	upflow
EQ wash 4	50 mM Tris pH 7.5 + 0.100 M NaCl	10	1	upflow
Elution	Variable	5	1	upflow
Strip	100 mM phosphoric acid	5	3	upflow
CIP	6 M guanidine HCl	5	3	upflow
Storage	20% ethanol	5	1	downflow

Tris-based buffers outperformed the citrate-based wash buffers.

ELUTION BUFFER OPTIMIZATION

To optimize the elution buffer for purity and recovery, eight different buffer compositions were compared (Figure 5).

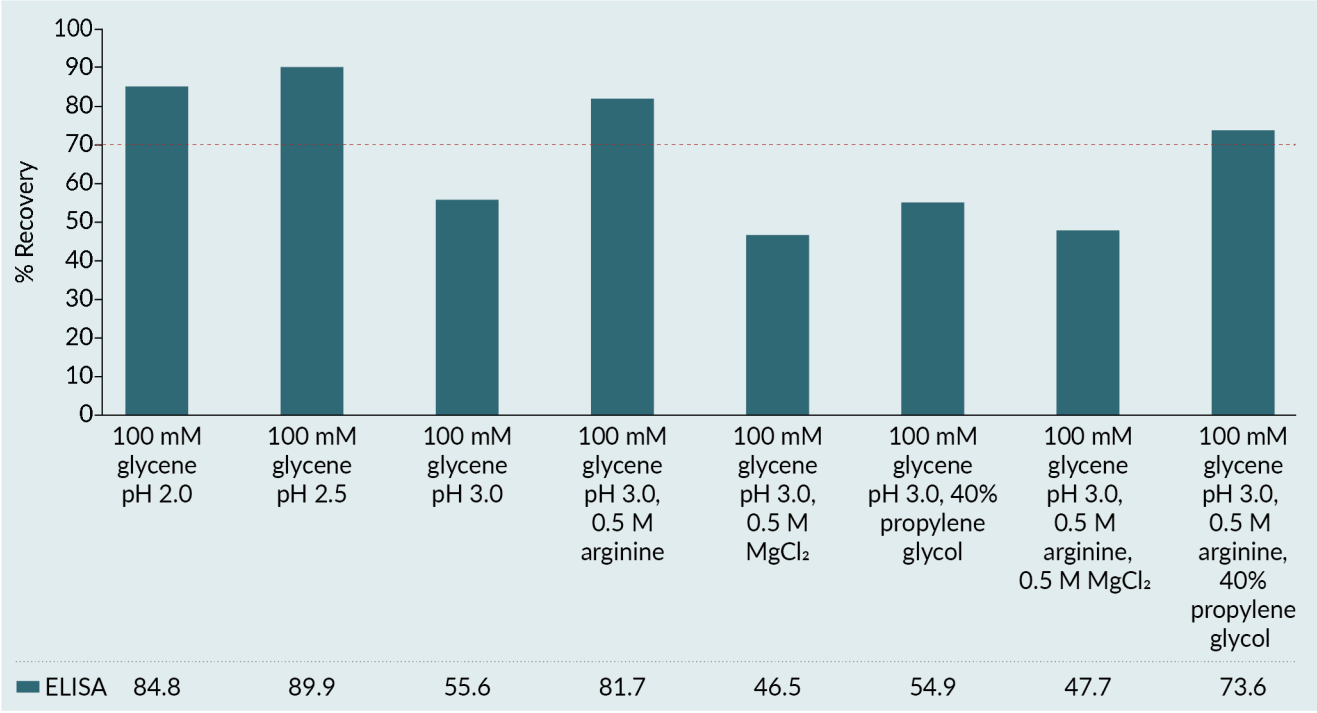
A set of high-throughput screening (HTS) experiments was carried out using a 96-well format protocol and purified AAV6 capsids as the load material (Table 4).

After a 1 h incubation while shaking at room temperature, the eluates were collected and absorbance at 280 (A280) was measured as a surrogate for concentration.

The addition of arginine had the greatest positive effect on recovery independent of pH (Table 5). Magnesium chloride had either no effect or a negative effect on recovery, depending

FIGURE 6

Comparison of excipient effect on AAV6 recovery.



on the pH, with the addition of 0.5 M magnesium chloride at pH 3 having the poorest recovery of all the tested buffer conditions. Finally, propylene glycol had no impact on recovery regardless of pH or concentration.

Next, selected experiments were repeated on a ten-fold larger scale using 0.2 mL POROS™ AAVX RoboColumns (Table 6).

Purified AAV6 capsids were loaded onto the columns and a two-step Tris-based wash buffer followed by various elution buffers were applied (Table 7). In this case, UV absorbance at 280 nm was also used to quantify the eluted sample.

The results (Table 8) show the addition of arginine had an overall positive effect on recovery regardless of pH. The addition of propylene glycol had a slightly positive effect on recovery at pH 2 and pH 3, but a negative effect at pH 2.5. The addition of magnesium chloride had an overall equal or negative effect on recovery. These results support the findings from the HTS experiments.

Next, selected experiments were verified on a 1 mL pre-packed column. Clarified lysate containing AAV6 capsids was loaded, and four wash buffer combination runs using only Tris-based buffers were applied, with varying elution buffers (Table 9).

Figure 6 provides a snapshot of the recovery as a function of the elution buffer compositions tested. The greatest recoveries (over 70%) were achieved with glycine pH 2 and 2.5 alone.

In summary, the elution buffer experiments showed that the best recoveries were generated with the lowest pH elution buffers at pH 2 and pH 2.5, but equal recovery can be obtained at a slightly higher pH of pH 3 if arginine or arginine and propylene glycol are added.

ASK THE AUTHORS

(Left) **Jonathan Zmuda, Director, Cell Biology R&D, ThermoFisher Scientific** and (Right) **Chantelle Gaskin, Field Application Scientist, ThermoFisher Scientific** answer your questions

Q Is the VPC 2.0 cell line available to buy?

JZ: The VPC 2.0 cell line is available as a research-use-only cell line currently as part of the AAV-MAX system. The GMP-banked version of those cells should be available later this year.

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Q I'm using the POROS™ AAV9 resin in my process. Do you recommend the same wash and elution conditions for that resin?

CG: We are currently planning experiments with the POROS AAV9 resin for wash and elution optimization. But we do recommend that you try these optimized buffer conditions in your AAV9 process.

One thing to note is that the AAV9 ligand has a slightly higher affinity for AAV9 capsids than AAVX so I would suggest using the combination wash steps shown above, followed by the glycine elution buffer with arginine at pH 2.5.

Q Can you comment on the scalability of the AAV-MAX system in the bioreactor setting?

JZ: These systems are intended to be used for both research and optimization of your AAV production conditions, but also to scale up to larger scale clinical and eventually commercial manufacturing.

We have looked at the scalability of the AAV-MAX system from multi-well plates through to shake flask cultures up to the 5 L scale, Wave bags, and up to 50 L single use bioreactor runs in HyPerforma or DynaDrive bioreactors.

We are aware of AAV-MAX users that have gone to hundreds of liters, and we plan to generate in-house data at these larger scale in the coming months.

We have taken the VPC 2.0 cell line up to full volume in a 3,000 L single-use bioreactor, a DynaDrive bioreactor for growth studies, and the data indicated that the cells behaved almost identically to the cells in shake flasks.

With any optimization of scalability, the first step is ensuring that the cells can get to that scale and be healthy for the time of transfection. We had excellent results for cell growth with the VPC 2.0 cell line so we expect later this year to be able to demonstrate actual transfection and production at these very large scales.

Q For large-scale production, what are the typical yield rates for the AAV9 POROS CaptureSelect chromatography process step? Would you suggest repeated capture and wash cycles in a smaller column to save resin costs, or use a larger column?

CG: These experiments were for AAVX, but for AAV9 CaptureSelect we typically see elution recoveries around 75 to 90%. I would suggest adding a TFF step before the AAVX or AAV9 capture step to produce a higher titer column load and prevent the need for repeat load cycles.

Q What are the key protocol "watch-outs" to ensure maximal AAV titers from the AAV MAX system?

JZ: First, with any production system, the cells are the foundation, and cell health is critical to ensuring good transfection and eventually good production of your viral vector.

Therefore, we provide very detailed information in terms of the growth characteristics of the VPC 2.0 cell line. Those cells should be maintaining a doubling time of roughly 23 h during all stages of their growth and ensuring that you are adhering to best practices in cell culture is absolutely critical.

Second, as with any of these systems, the complexation reaction of plasmid DNA and transfection reagent is also critical. In the case of the AAV-MAX system, we make this process very simple – the plasmid DNA is pumped into a bag of cold Viral-Plex media. Viral-Plex is a complexation media that is fully chemically defined and protein-free, with no insulin, transferon, or other components that are present in a lot of complexation media. The plasmid DNA can be pumped into that cold bag and will remain very stable for long periods. When you are ready to transfect, you simply add your neat AAV-MAX transfection reagent into the bag and allow the mixture to come together based on the various charges of the components.

One thing you have to be careful of is not to over-mix, as this can prevent complexes from forming correctly, or cause them to over-complex. Be gentle during the complexation step – there is no additional input or force needed. The complexes will form on their own and will be easily pumpable into your final bioreactor setting.

Q Did you characterize the impurities you removed in the wash study?

CG: No, we limited the analytics for this study to just residual HCP and HCD. Many of our customers do perform analytics like mass spectrometry on a different fraction to get an idea of their impurity profile.

However, in my experience, the bulk of the impurities will be HCP, HCD, and – in the case of the AAV-MAX system – residual plasmid.

If you are looking at a co-infection process – for example, if you are using HSV or baculovirus to make DNA with a different process – you might expect to see some residual viral DNA in protein as well.

Q Which component of the system is primarily responsible for the high AAV titers observed?

JZ: We develop our systems to work synergistically with one another. For example, the VPC 2.0 cell line media was developed to work synergistically with the AAV-MAX Viral Production Mediu and the transfection reagent.

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What sets the AAV-MAX system apart is the optimization of the components working together, which allows very high titers across many different serotypes.

The VPC 2.0 cell line typically achieves 5–20-fold higher titers than the parental VPC cell line so a lot of the performance of the system begins with the foundational aspect of the cells themselves. Then the componentry is built around that high-producing, robust cell line to provide the highest titers across as many serotypes as possible.

Q Has there been similar work using AAVX resin carried out with other serotypes and were the results similar?

CG: With these experiments, we only used the AAV6 constructs. But the AAVX is a pan-serotype-specific resin so we would expect to see similar results for other serotypes, and of course, our customers use a variety of serotypes with their AAVX process. However, we always recommend doing small-scale screening experiments.

The difference is going to be in the binding affinity for each serotype, which could affect the wash and elution results. However, from what we have seen, a bigger factor is the nature of the feed stream. Anything that impacts binding to the resin will also impact optimization of the wash and elution steps.

Therefore, we always recommend optimizing your clarification steps and your TFF steps upstream from the capture chromatography, to put you in the best position for optimizing your wash and elution steps, regardless of the serotype.

Q Do you regulate the pH into your bioreactor with the VP 2.0 cell line?

JZ: For AAV we have not implemented pH regulation during the bioreactor process thus far. We do have an application note online for 3 L stir tank protocols, as well as 50 L upstream protocols in our HyPerforma and DynaDrive reactors. Almost everything in there is being regulated just by the gassing and natural pH fluctuation of the cells during the growth and productivity phases.

To date, the VPC 2.0 cell lines in the AAV-MAX system have very readily moved from the shake flask into the stirred tank reactor environment, at multiple scales, without any significant modulation of those parameters.

However, for certain constructs, a fully optimized process could generate higher titers with further optimization of the upstream parameters and that is something you would want to do with every AAV construct that you are expressing.

Q I was told that for optimal binding with AAVX, the sample concentration plays an important role and the higher the better. Is 1×10^{11} total particles (TP) per mL high enough to ensure good binding?

CG: I would agree that higher load titers tend to yield the best results, and the required sample concentration will be dependent on your process. If you have optimized your clarification step prior to the load of the capture column and any filtration TFF in front of that, you should be in a good position with 1×10^{11} TP per ml as the titer going onto the column.

The main thing to keep in mind is the binding capacity of the column. We would typically recommend you start at around 5×10^{13} to 1×10^{14} TP per ml of resin for loading.

BIOGRAPHIES

JONATHAN ZMUDA, PhD is a Director of Cell Biology R&D within the Biosciences Division of Thermo Fisher Scientific located in Frederick, MD (USA). Within Cell Biology, Jon leads various teams that focus on developing new technologies for protein expression, viral vector produtions, transfection and classical cell culture. Dr Zmuda received his PhD. in Cell Biology from the University of Maryland, College Park and his undergraduate degree from Dickinson College in Carlisle, PA.

CHANTELLE GASKIN is a Field Applications Scientist, specializing in protein and viral vector purification and downstream process development. She held leadership positions at Applied Genetic Technology Corporation and Brammer Bio, prior to joining the Thermo Fisher Scientific Bioproduction Division in 2020. With over 10 years of experience in gene therapy, Chantelle has accumulated comprehensive knowledge of standard industry practices and regulatory standards, applying this knowledge to advance development of therapies for a variety of indications including ocular, CNS and systemic disease. Chantelle holds a Master's degree in Chemistry from University of Florida and a Bachelor's in Chemistry from Smith College.

JAMES MOLINARI NEED BIO

JENNY ENGLAND is a Staff Scientist in the Applications and Innovation group in Purification and Pharma Analytics at Thermo Fisher Scientific. Jenny is a biophysicist by training and earned her PhD from Georgetown University. After graduate school, she did a post doc at the National Cancer Institute that focused on structure-based drug design for protein kinase complexes. Jenny currently leads the application group for process development of the POROS resin products for antibody, mRNA, plasmid, and viral vector purification. Additionally, Jenny evaluates new and emerging technologies that can be applied to solve unmet customer needs in the bioproduction workflow.

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AUTHORSHIP & CONFLICT OF INTEREST

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