

A novel transient cell line to enable high yield and scalable rAAV production with low encapsidated host cell DNA

The landscape of recombinant adeno-associated virus (rAAV) manufacturing is witnessing a transformative shift, where stable producer cell lines are emerging as the cell factories of the future. However, the move towards producer cell lines is a nuanced journey, requiring the use of transient transfection cell lines where flexibility and speed are of essence. To address these needs, we developed a novel human embryonic

kidney (HEK) 293 suspension cell line, the ELEVECTA™ transient cell line designed to seamlessly integrate into various research workflows or large-scale GMP production. Here we demonstrate its capability for efficient and scalable production of rAAVs across multiple serotypes with low levels of encapsidated host cell DNA (hcDNA).

Introduction

The newly developed ELEVECTA transient cell line offers a simple solution for scalable AAV production. It's a HEK293 derived suspension cell line that harnesses the power of transient transfection to deliver high titers across multiple rAAV serotypes. The cell line is robust to scale with proven performance between 15 mL microbioreactors and the Xcellerex™ XDR-10 L bioreactor. Together with the cell line, we developed an optimized good manufacturing practice (GMP) compatible HyClone™ prime expression medium that supports high cell density and efficient transfection processes. In this work, by combining the ELEVECTA transient cell line and HyClone prime expression medium, we demonstrated average rAAV titers of 4.9×10^{11} viral genomes (vg) per mL ($\pm 5.6 \times 10^{10}$ vg per mL) with an average of 52% full capsids ($\pm 6.5\%$) in XDR-10 L bioreactors.

In addition to achieving high cell densities with low cell aggregation and relevant rAAV titers, the ELEVECTA transient cell line showcases a significant reduction of encapsidated hcDNA in the final rAAV product. The reduction of encapsidated hcDNA is the result of *DFFB* gene (DNA fragmentation factor subunit beta) inactivation, which reduces DNA fragmentation upon cell death. Encapsidated hcDNA is a process-related impurity that “may have adverse effects on product quality and safety” according to FDA guidance (1). With the ELEVECTA transient cell line we demonstrate ≤ 12.4 nanograms (ng) hcDNA per 10^{14} vg in the 10 L scaled up process, a 100-fold reduction over another commercially available cell line.

Detailed materials and methods are found at the end of this article.

Results

Significant reduction in host cell DNA with the ELEVECTA transient cell line

To understand ELEVECTA transient cell line performance, hcDNA levels were quantified and compared to a reference FreeStyle 293-F control cell line. Bioreactor rAAV production was performed at the 3 L and 10 L scale, followed by subsequent purification via affinity chromatography and anion exchange (AEX) chromatography enrichment of full capsids. The ELEVECTA transient cell line hcDNA concentrations (including encapsidated) ranged between 6.4 and 12.4 ng/ 10^{14} vg, which was approximately a two-log reduction in hcDNA compared to the 293-F samples that yielded between 922 and 1130 ng/ 10^{14} vg. Importantly, hcDNA levels remained consistent after enrichment of full particles via AEX for both cell lines, which indicates that the majority of the hcDNA impurities after capture are encapsidated (Fig 1). Regulatory guidance recommends reducing any non-vector DNA contamination in the final product, and there's a regulatory expectation to control residual DNA to ≤ 10 ng per administered dose (1, 2, 3). Residual DNA includes both DNA outside of viral capsids and encapsidated DNA impurities (such as plasmid DNA or hcDNA) (1, 4). Up until now, however, the residual DNA guidelines have been difficult to meet for rAAV therapies due to large quantities of encapsidated DNA impurities. This level of impurity often comes with recommended mitigations such as quality data, risk assessments, and control strategies (1). Reducing the total hcDNA to levels that could fall below the overall residual DNA guideline limits may substantially simplify these risk mitigation strategies.

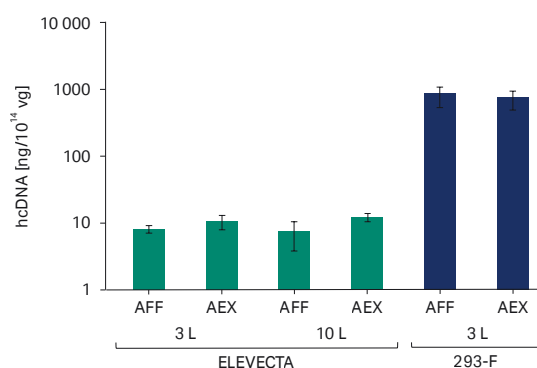


Fig 1. Host cell DNA (including encapsidated) for 3 L (n=3) and 10 L (n=3) bioreactor scales for the ELEVECTA transient cell line and 3 L scale for the 293-F cell line (n=3). Samples were taken from the affinity (AFF) pool and the peak containing full capsids following AEX enrichment (AEX), respectively. Error bars represent one standard deviation. Statistical analysis was performed using Welch's t-test, confirming a statistically significant difference for hcDNA as a proportion of viral genome DNA between ELEVECTA and 293-F in all possible comparisons and combinations ($p < 0.05$).

Evaluation of the ELEVECTA transient cell line for AAV production of various serotypes

To evaluate the performance of the ELEVECTA transient cell line for vector production across serotypes rAAV2, rAAV5, rAAV8, and rAAV9, a series of 15 mL microbioreactor runs were conducted. A power input of 120 W/m³ was utilized for microbioreactor and 3 L scale to enable improved gas transfer dynamics and reduced cell clustering behavior, where it has been demonstrated that an increase in power input for HEK cells can be beneficial to cell cultivation (5). The target power input for 10L scale was 120 W/m³, but due to an updated characterization of the system, the power number (Np) was decreased which resulted in an actual power input of 37 W/m³. No adverse effects were observed.

As shown in Figure 2, comparable growth and viability independent of the rAAV serotype was observed. Alongside the serotype assessment, the RevIT AAV Enhancer from Mirus Bio was used after transfection to further boost rAAV production. Cells demonstrated fast growth kinetics with population doubling times (PDT) around 19 h and high viability (> 95%) prior to the transfection step (Fig 2, black dotted line). Within the production phase from day 3 to 6, a notable difference in growth was observed regarding the presence or absence of the RevIT Enhancer. In bioreactors without RevIT, cells continued to grow to cell densities of up to 6×10^6 cells/mL, whereas with the RevIT supplemented cultures there was slight decrease of viable cell density (VCD) (Fig 2). A decrease in VCD and viability post-transfection is expected with a highly efficient transfection process and is an overall positive indication of a successful process.

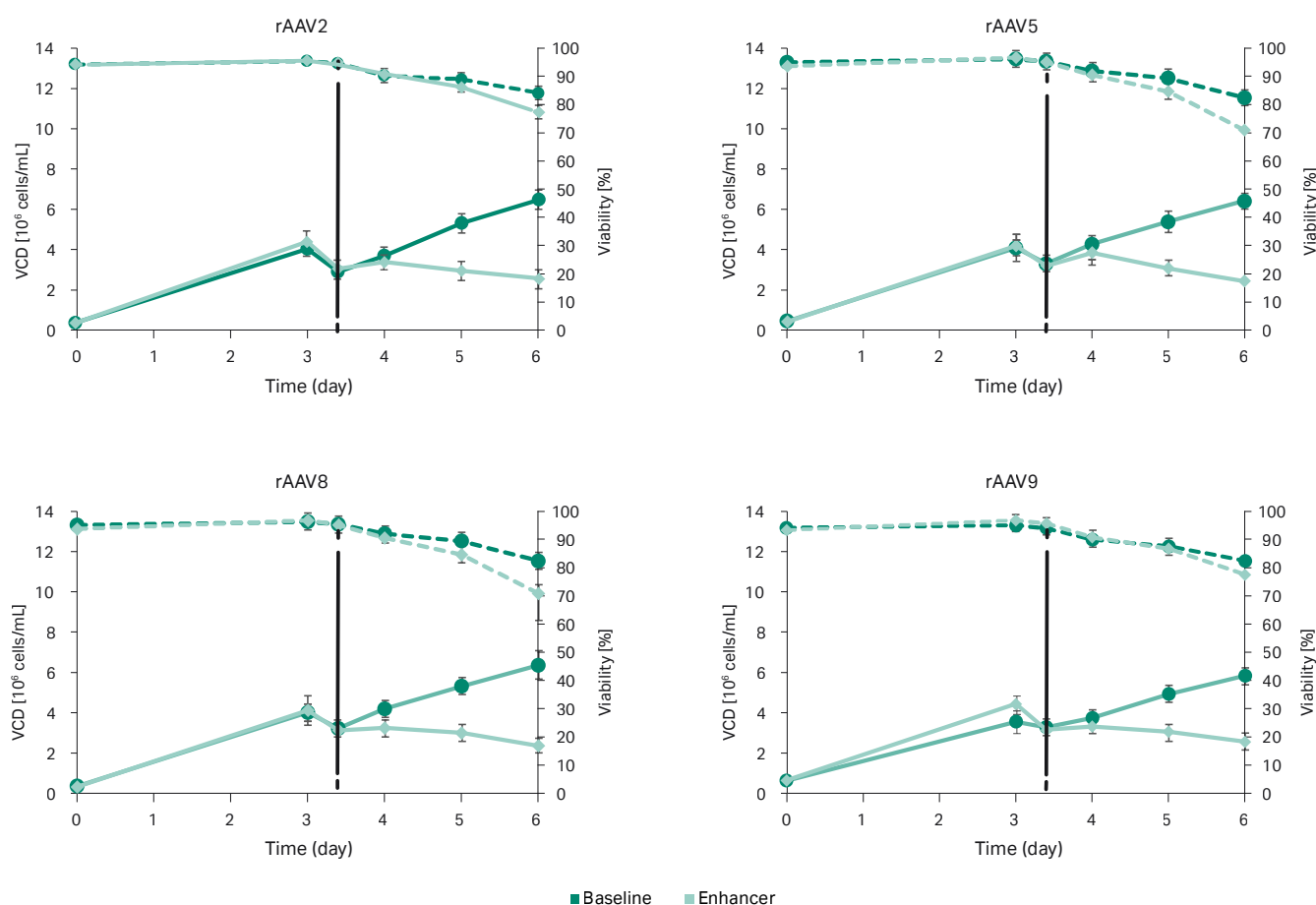


Fig 2. Viable cell density (solid lines) and viability (dashed lines) of the ELEVECTA transient cell line. Average data and standard deviations from three independent microbioreactor runs in duplicate (n=6) are shown. Black dotted lines represent the transfection timepoint in which cell density was adjusted to reach the desired transfection VCD. Cultivation continued either without RevIT supplementation (baseline) or with addition of RevIT Enhancer (enhancer).

Three days post-transfection, vessels were harvested for analysis of genomic and capsid titers via qPCR and ELISA. Lysis was performed with Triton X-100 (versus Tween 20 solution in bench top bioreactors), however similar titers were attained between the two lysis methods (data not shown). As shown in Figure 3, in the non-supplemented baseline process, cells produced robust genomic titers ranging from 4.8×10^{10} vg/mL for rAAV2 and up to 2.4×10^{11} vg/mL for rAAV5. Titers were further improved with the supplementation of RevIT Enhancer in a serotype-dependent manner by a factor of 1.8 to 3.0 for rAAV2 to rAAV9, respectively. The addition of RevIT resulted in average volumetric titers of 8.3×10^{10} vg/mL (rAAV2), 4.9×10^{11}

vg/mL (rAAV5), 4.0×10^{11} vg/mL (rAAV8) and 2.7×10^{11} vg/mL (rAAV9). A similar enhancer-dependent pattern increase was observed for capsid titers, which in turn yielded a calculated qPCR/ELISA ratio of 25% to 70% full AAV capsids (Fig 3).

Overall, data from the 15 mL microbioreactor experiments demonstrated that the ELEVECTA transient cell line can provide high titer productivity for various serotypes. To demonstrate the scalability of the process, we scaled up a representative process (serotype rAAV8 with RevIT Enhancer) in the following steps.

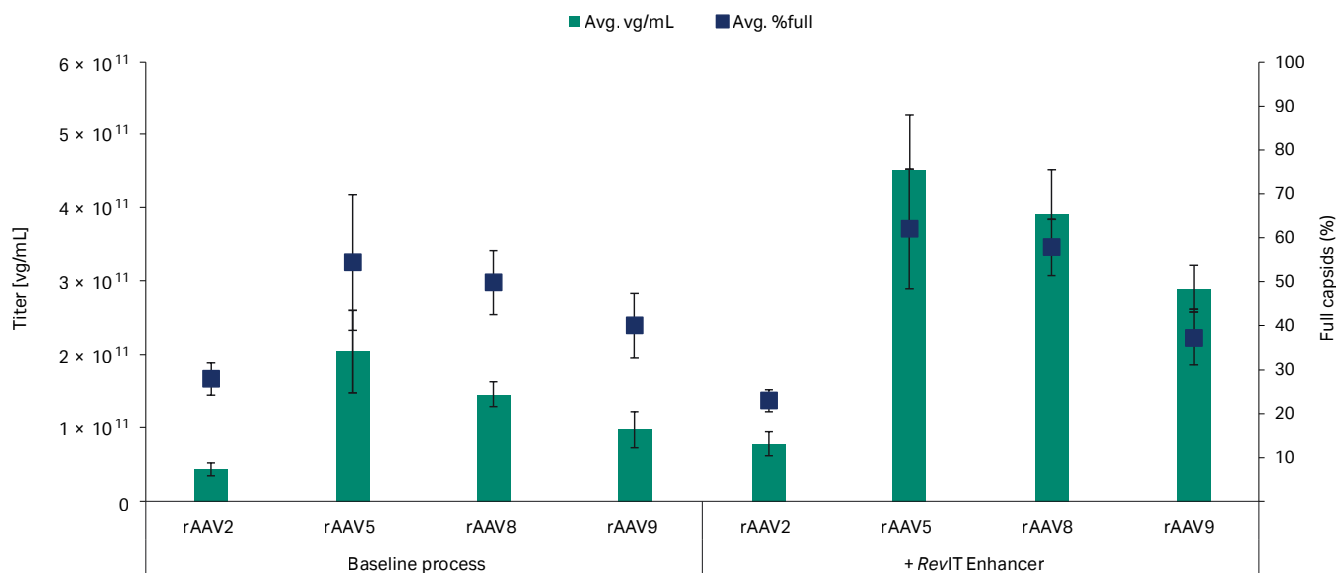


Fig 3. Productivity data of the ELEVECTA transient cell line for various serotypes in microbioreactors. Extensive optimization was not required to obtain these results. Average genome and capsid titers as well as fullness based on qPCR/ELISA data from three independent runs in duplicate (n=6) are shown. Percent full capsids is calculated by dividing vg/mL by virus particles (vp)/mL. Error bars correspond to standard deviation of biological replicates. Baseline process corresponds to the non-supplemented process (left), whereas RevIT Enhancer was added to the supplemented process (+ RevIT Enhancer, right).

Process scalability assessment

To evaluate scalability, the rAAV8 production process was performed in 3 L (Applikon) and 10 L (XDR-10) bioreactors. The results in Figure 4 are from three production batches at each scale. We saw comparable cell growth and viability during scale-up with PDT around 19 h and high viability (> 95%) until the transfection step at day three (Fig 4). Within the production phase, from day 3 to 6, there was a slight decrease of VCD and cell viability over time, similar to the RevIT Enhancer supplemented microbioreactor trends in previous studies (Fig 2).

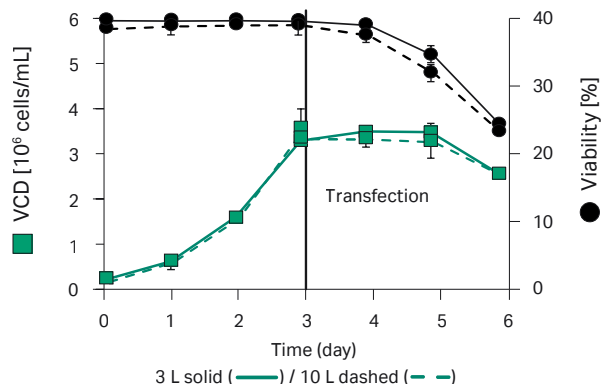


Fig 4. Viable cell density (VCD) (solid lines) and viability data (dashed lines) for 3 L (n=3) and 10 L (n=3) bioreactor scales for the ELEVECTA transient cell line (n=3). All bioreactor runs were done with addition of the RevIT Enhancer. Day two samples were only taken for one 3 L and one 10 L bioreactor, thus there is no standard deviation for day two cell growth or viability. Transfection performed on day three. Error bars correspond to standard deviation of biological replicates.

Bioreactors were harvested after a three day production phase, in which cells were lysed and analyzed for genomic and capsid titers via ddPCR and ELISA, respectively. As shown in Figure 5, average genomic titers of 5.4×10^{11} vg/mL at 48% full capsids were achieved at the 3 L scale, and 4.9×10^{11} vg/mL at 52% full capsids were measured at the 10 L scale in an XDR-10 bioreactor. Overall, these results were highly comparable to the average titer observed at the 15 mL microbioreactor scale (3.9×10^{11} vg/mL at 58% full capsids, Fig 3), suggesting successful scale-up and process robustness in the benchtop bioreactor format.

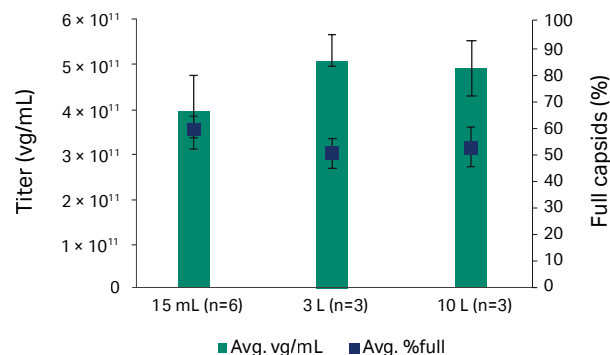


Fig 5. rAAV8 titer comparison of 15 mL (n=6), 3 L (n=3), and 10 L (n=3) bioreactor scales for the ELEVECTA transient cell line. Error bars correspond to standard deviation of biological replicates. Viral genomes were quantified with qPCR for 15 mL scale and ddPCR for 3 L and 10 L scale. Data shown includes use of RevIT Enhancer.

Additionally, to better understand the ELEVECTA transient cell line titers during scale-up without the RevIT enhancer, the process was performed at the 10 L scale for rAAV8 with no supplementation (one replicate, data not shown). The resulting titer was 2.7×10^{11} vg/mL (42% full capsids) compared to 1.5×10^{11} vg/mL (49% full capsids) in 15 mL microbioreactors (Fig 3). These results suggest that the process is scalable and with relevant rAAV titers with or without use of a titer enhancer.

Conclusions

The ELEVECTA transient cell line is a robust, fast-growing cell line delivering high titers and high percent full capsids that is suited for research and development as well as clinical and commercial stages. The cell line enables the production of AAV with very low amounts of encapsidated hcDNA that is consistent throughout the downstream purification steps and at various scales ($\leq 12.4 \text{ ng}/10^{14} \text{ vg}$ for rAAV8). This may substantially simplify product risk assessments relating to residual DNA impurity levels. Additionally, scalability was demonstrated across microbioreactors to 10 L bioreactors with consistent titers and full capsids greater than or equal to 3.9×10^{11} rAAV8 vg/mL and 48% full capsids, respectively. Having a high portion of full capsids may help ease the downstream purification challenges. Overall, the use of the ELEVECTA transient cell line in combination with HyClone prime expression medium and RevIT Enhancer results in a scalable, robust process that yields high titer rAAVs of multiple serotypes.

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Thank you to Mirus Bio for helpful discussions around using the RevIT AAV Enhancer during bioreactor process development.

Amendments

This document is an updated version (previous version dated from 19Dec2024). The scale up process utilized in the original iteration of this application note from the microbioreactor and 3 L bioreactors used a power input number (P/V) of $120 \text{ W}/\text{m}^3$ and therefore was used for scaling up into the XDR10. However, updated modelling and characterization of the XDR10 power number (Np) and subsequent updates to the Bioreactor Scaler Tool have shown that the Np for the XDR10 is significantly lower than previously measured. As a result, the agitation used in this application note for the XDR10 to achieve a P/V of $120 \text{ W}/\text{m}^3$ is in fact $37 \text{ W}/\text{m}^3$. The purpose of this amendment is to explain the difference in the P/V used in the scale up process described in this application note. For any further questions, please reach out to Cytiva.

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A cell line designed with speed, simple, and scalable in mind: Learn more about ELEVECTA transient cell line.

Materials and methods

Table 1. Plasmids

Description	Supplier	Product code	Size (kb)
pALD-AAV2	Aldevron	5057-10	6.080
pALD-AAV5	Aldevron	5058-10	6.021
pALD-AAV8	Aldevron	Custom product	6.083
pALD-AAV9	Aldevron	Custom product	6.083
pALD-HELP	Aldevron	5082-10	11.584
pAAV-LUC-GFP	Aldevron	Custom product	8.502

Table 2. Reagents

Description	Supplier	Product code
ELEVECTA transient cell line	Cytiva	ETCL-RUO
HyClone prime expression medium, liquid (1 L)	Cytiva	SH31199.02
RevIT AAV Enhancer	Mirus Bio	MIR8006
PEI MAX	Polysciences	#24765-1
FreeStyle 293-F Cells	Thermo Fisher	R79007
Expi293 Expression Medium	Thermo Fisher	A1435102
Sodium Bicarbonate (NaHCO ₃)	Sigma-Aldrich	S6014-2.5KG

Microbioreactor testing

The ambr 15 microbioreactor system (Sartorius) was used. Three independent experimental runs with luciferase:green fluorescent protein (LUC-GFP) as transgene were performed with duplicates for individual conditions per run (total n=6 per condition). The ELEVECTA transient cells were seeded at 4.0×10^5 viable cells per mL in HyClone prime expression medium without centrifugation in 13.7 mL. 293-F cells were seeded at 7.0×10^5 cells per mL in Expi293 medium. Three days after seeding, the cultures were diluted to obtain 3.3×10^6 viable cells in 12.9 mL, and transfection mixture was added to obtain a final cell density of 3×10^6 viable cells in 14 mL production volume. The RevIT enhancer (Mirus Bio) was added directly to specific cultures immediately after complex addition in a 1:1000 ratio. Bioreactors were harvested 72 h post-transfection. Microbioreactor parameters and transfection conditions are listed in Table 3.

Table 3. Microbioreactor setpoints and parameters

Parameter	Value
Production volume	14 mL
pH range	7.3 ± 0.1 (post-transfection), PID control
DO (%)	40 (PID control, O ₂ on demand)
Temperature (°C)	37
Sparger airflow (VVM)	0.013
Maximum gas flow rates	CO ₂ max: 1.24 mL/min, O ₂ max: 0.91 mL/min
Agitation (W/m ³)	120
Growth and production medium	HyClone prime expression medium
Base	1 M sodium bicarbonate

Table 3, continued

Transfection	
Plasmids	pALD-HELP; pAAV-LUC-GFP; pALD-AAV2,5,8,9
Plasmid ratio	1:1:1 molar ratio
Transfection reagent	PEI MAX
Complexation volume (%)	10%
Target transfection cell density (viable cells/mL)	3.0×10^6
Plasmid DNA/cell	0.67 µg DNA/10 ⁶ cells
Plasmid DNA to transfection reagent ratio	1:4
Complexation medium	HyClone prime expression medium
Complexation time (min)	15 to 20
Day of transfection	3
Production phase/harvest	Harvest at 3 days post-transfection
Lysis buffer	10X: D-PBS with 10% Triton X-100
Endonuclease	C-Lecta Denerase®, 60 U/mL
Time, temperature	30 min, 37°C

DO is dissolved oxygen. VVM is volumetric gas flow per minute.

Bioreactor scale-up

The Applikon bioreactor (Getinge) and Xcellerex™ XDR-10 bioreactor (Cytiva) were used for scalability studies. The ELEVECTA transient cell line cells, expanded in shake flask cultures, were inoculated at a cell density of approximately 2.5×10^5 cells/mL, reaching a starting volume of 2.1 L for the 3 L Applikon Bio bioreactor and 8.3 L for the 10 L Xcellerex XDR-10 bioreactor. 293-F cells were seeded at 6.0×10^5 cells per mL in Expi293 medium. After 3 days, the cultures were diluted as required to a target transfection density of 3.3×10^6 cells/mL. RevIT enhancer was added to the diluted DNA prior to complexation in a 1:1000 ratio. The transfection complex solution was added to the bioreactors with a final approximate bioreactor volume of 2.3 L for the 3 L bioreactor and 9.2 L for the 10 L bioreactor, reaching target transfection final cell density of 3×10^6 cells/mL. Harvest was performed 72 hours post-transfection after the addition of endonuclease and 10x lysis buffer (Table 4).

Table 4. Bioreactor (3 L and 10 L) setpoints and parameters

Parameter	Value
pH range	7.3 ± 0.1 (PID control)
DO %	40 (PID control, O ₂ on demand)
Temperature (°C)	37
Sparger airflow (VVM)	0.02
Maximum gas flow rates	3 L: CO ₂ max: 500 mL/min, O ₂ max: 500 mL/min 10 L: CO ₂ max: 400 mL/min, O ₂ max: 1000 mL/min
Agitation (W/m ³)	120 (3 L); 37 (10 L)
Growth and production medium	HyClone prime expression medium
Base	1M sodium bicarbonate

Table 4, continued

Transfection	
Plasmids	pALD-HELP; pAAV-LUC-GFP; pALD-AAV8
Plasmid ratio	1:1:1 molar ratio
Transfection reagent	PEI MAX
Complexation (%)	10% of total volume post-transfection
Target transfection cell density (viable cells/mL)	3.0×10^6
Plasmid DNA/cell	0.67 μ g DNA/ 10^6 cells
Plasmid DNA to transfection reagent ratio	1:2
Complexation medium	HyClone prime expression medium
Complexation time (min)	15 to 20
Day of transfection	3
Production phase/harvest	Harvest at 3 days post-transfection
Lysis buffer	10 \times buffer formulation: 20 mM $MgCl_2$, 10% Tween 20, 10 mM Tris, pH 8.0
Endonuclease	C-Lecta Denarase®, 25 U/mL
Lysis + endonuclease time, temperature, and agitation	1 h, 37°C, 120 W/m ³ (3 L); 37 W/m ³ (10 L)

Purification

Lysate pools from the 3 L and 10 L bioreactors producing rAAV8 were clarified using a three-stage filtration process made up of PDP8 and Bio10 depth filters followed by Supor™ EKV sterilizing-grade filters (Cytiva) run in series. Clarified pools coming from 10 L bioreactors were concentrated to a target 10-fold volumetric concentration factor using either hollow fiber TFF modules (300 kDa, Polysulfone, 0.5 mm inner diameter, 60 cm length; Cytiva) or T-series flat sheet TFF cassettes with Omega membrane (100 kDa, PES; Cytiva).

Affinity chromatography

Affinity chromatography was performed on an ÄKTA avant™ 150 chromatography system (Cytiva). The clarified lysate was loaded to a POROS GoPure AAVX (Thermo Fisher) prepacked 5 mL column. The column was equilibrated over 10 column volumes (CV) with 50 mM Tris, 0.5 M NaCl, pH 8.0. Prior to loading, the feed was spiked with EDTA to a final concentration of 10 mM. After the sample was loaded the column was washed with 10 CV of 50 mM Tris, 0.5 M NaCl, pH 8.0, followed by 10 CV of 50 mM Tris, pH 8.0. Elution was performed with 100 mM glycine pH 2.5, over 5 CV. The eluate was neutralized with Bis-Tris Propane (BTP), pH 9 at a ratio of 1:5 (neutralizing buffer:eluate).

Anion exchange chromatography

Anion exchange chromatography was performed using a Capto™ Q HiTrap™ 1 mL column (Cytiva) on an ÄKTA avant 25 system (Cytiva). A two-step elution method was utilized during all AEX experiments. The AEX load was diluted by

a factor of 20 with 25 mM BTP, pH 9.0, 2 mM $MgCl_2$, 5% glycerol. This upfront dilution was done to ensure the feed was properly equilibrated to binding conditions. After the sample was loaded the column was washed with 25 mM BTP, pH 9.0, 2 mM $MgCl_2$, 5% glycerol over 5 CV. The first elution step was performed over 20 CV with 25 mM BTP, pH 9.0, 2 mM $MgCl_2$, 5% glycerol adjusted to a conductivity of 5.5 mS/cm with sodium acetate. The second elution step was performed over 15 CV with 25 mM BTP, pH 9.0, 2 mM $MgCl_2$, 5% glycerol adjusted to a conductivity of 9.0 mS/cm with sodium acetate. A strip step was then performed with 25 mM BTP, 1 M NaCl, pH 9.0 for 10 CV. All steps were performed at a flow rate of 2 CV per minute.

Analytical methods

Viral genome titer measurements

The viral genome titer was measured by either droplet digital polymerase chain reaction (ddPCR) or quantitative PCR (qPCR). The ddPCR assay used the Bio-Rad QX200 AutoDG Droplet Digital PCR System and qPCR was done in a Roche LightCycler 480. In both cases, samples were pretreated by DNase digestion then Proteinase K digestion, before additional dilution. The viral genome was quantified using PCR primer/probe combination from IDT targeting an SV40 amplicon of rAAV due to the presence of SV40 Poly A tail.

Capsid titer measurement

The PROGEN Quantitative ELISA kit corresponding to the analyzed serotype (CAT PRAAV2R, PRAAV5, PRAAV8XP, PRAAV9) was used according to the manufacturer's instructions to perform a sandwich ELISA for the intact capsid titer determination of rAAV particles.

hcDNA analysis

Host cell DNA (hcDNA), including encapsidated hcDNA, was quantified using the qPCR-based resDNASEQ Quantitative HEK293 DNA Kit (Applied Biosystems, #A46014). Samples were prepared using the HighPure Nucleic Acid Kit (Roche, #11858874001), which includes a Proteinase K treatment to release encapsidated hcDNA, but no prior nuclease treatment to remove non-encapsidated DNA was used. Both kits were used according to the manufacturer's instructions.

For microbioreactor work (Cytiva Cologne), lab notebook reference VVP24-17, VVP24-18, and VVP24-21. Experimental work was done through November 2023 – March 2024 and data is held within Cytiva Westborough and Cytiva Cologne.



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