Lentivirus production

Production and clarification of lentiviral vectors at the 50 L scale

Keywords
Lentivirus, LV-MAX, DynaDrive S.U.B., HyPerforma 5:1 S.U.B., LV production, LV scale-up, gene therapy

Introduction

With the tremendous growth of viral vector–based applications for vaccine and gene therapy production, researchers must decide how to scale their manufacturing processes to deliver products that fulfill clinical and commercial needs. Here we provide data on the production and clarification of a lentivirus (LV) encoding anti-CD19 chimeric antigen receptor (LV-αCD19CAR) using the Gibco™ CTS™ LV-MAX Production System in the Thermo Scientific™ DynaDrive™ and HyPerforma™ 5:1 Single-Use Bioreactors (S.U.B.s) at the 50 L scale, alongside shake flask controls, to demonstrate scalability of the process. We also provide guidance on two different scalable clarification processes for use with the 50 L LV-αCD19CAR harvest material. One of these processes uses depth filters, and the other utilizes the Thermo Scientific™ DynaSpin™ Single-Use Centrifuge instead of the primary depth filters.

Materials and methods

Culture of CTS Viral Production Cells

In all steps of the process, Gibco™ CTS™ Viral Production Cells (VPCs) were maintained in Gibco™ CTS™ LV-MAX Production Medium (Table 1). The cells were thawed and maintained in shake flasks as recommended in the CTS LV-MAX system **user guide**, before inoculating each bioreactor at a low turndown ratio to further expand the cells prior to each production run.

Table 1. Materials and reagents.

Component	Description
Cell line	CTS Viral Production Cells
Cell culture and production medium	CTS LV-MAX Production Medium
CTS LV-MAX Transfection Kit	• CTS LV-MAX Transfection Reagent • CTS LV-MAX Supplement • CTS LV-MAX Enhancer
Transfection buffer	Gibco™ CTS™ Opti-MEM™ I Medium
Plasmid DNA	2.5 mg plasmid DNA per liter of culture to be transfected (1.5 mg LV-MAX™ Lentiviral Packaging Mix + 1 mg transfer plasmid)
Antifoaming agent	Gibco™ FoamAway™ Irradiated AOF (animal origin–free) Antifoaming Agent
Nuclease	Thermo Scientific™ Pierce™ Universal Nuclease for Cell Lysis (250,000 U/mL)
Magnesium chloride	Invitrogen™ $MgCl_2$ (1 M)
Single-use bioreactors (S.U.B. hardware)	• DynaDrive S.U.B. • HyPerforma 5:1 S.U.B.
Bioprocess containers (BPCs)	• 50 L Thermo Scientific™ DynaDrive™ BioProcess Container (BPC) with Thermo Scientific™ Aegis™ 5-14 film • 50 L Thermo Scientific™ HyPerforma™ 5:1 BPC with Aegis5-14 film • 2D 5 L Thermo Scientific™ Labtainer™ BioProcess Container with Aegis5-14 film • 2D 50 L Labtainer BioProcess Container with Aegis5-14 film • 3D 100 L Thermo Scientific™ Productainer™ BioProcess Container with Aegis5-14 film with outer support drum and plastic dolly
Bottle transfer assemblies	Standard single-use bottle assembly system, 1 L size
Clarification	Thermo Scientific™ DynaSpin™ Single-Use Centrifuge Thermo Scientific™ DynaSpin™ Single-Use Rotor Masterflex™ L/S™ pump Millistak+™ CE50 filters Sartopure™ PP3 3.0 µm filters Sartopure™ PP3 0.45 µm filters

Bioreactor setup and seed train expansion

The DynaDrive and HyPerforma 5:1 S.U.B.s were set up following their respective product user guides. A Thermo Scientific™ HyPerforma™ G3Pro™ Bioprocess Controller was used to control each bioreactor. The operating parameters for the seed expansions and production runs on the DynaDrive and HyPerforma S.U.B.s are listed in Tables 2 and 3, respectively. CTS VPCs were expanded from vented, non-baffled shake flasks into each bioreactor at a working volume of 10 L and a density of 0.5 x 10^6 viable cells per mL (VC/mL). After culturing the cells for 3 days, the bioreactors were brought up to a working volume of 25–26 L and a viable cell density of 0.8 x 10^6 VC/mL to 1.0 x 10^6 VC/mL as an N-1 reactor. After 3 days, the cells were diluted to a volume of 40 L and a cell density of 4.0 x 10^6 VC/mL. The pH set point was shifted to 6.8 to prepare for transfection of the culture. Control cultures were grown in vented, non-baffled 125 mL shake flasks throughout scale-up and production. Growth kinetics, metabolic profiles, and viral genome titers were measured and compared to the corresponding bioreactor data.

Table 2. DynaDrive S.U.B. operating parameters.

Parameter	N-2 expansion	N-1 expansion	Production run
Final working volume	10 L	26 L	48 L
Temperature	37°C		
pH	7.2	7.2	6.8
pH control	0 to 1 slpm CO_2 through the drilled-hole sparger (DHS) at a pH controller output of 0 to –100		
Agitation	90 rpm, P/V: 17.3 W/m^3, tip speed 0.51 m/s	95 rpm, P/V: 18.4 W/m^3, tip speed 0.54 m/s	95 rpm, P/V: 16.2 W/m^3, tip speed 0.54 m/s
Dissolved oxygen (DO)	40%		
DO cascade	0–0.25 slpm air at a DO controller output of 0–25 and 0–1 slpm oxygen at a controller output of 24–100, both through the DHS		
Headspace aeration	1.0 slpm	1.5 slpm	1.5 slpm
Target inoculation cell density	0.5 x 10^6 VC/mL	1.0 x 10^6 VC/mL	4.0 x 10^6 VC/mL

Table 3. HyPerforma 5:1 S.U.B. operating parameters.

Parameter	N-2 expansion	N-1 expansion	Production run
Final working volume	10 L	25 L	48 L
Temperature	37°C		
pH	7.2	7.2	6.8
pH control	0 to 1 slpm CO_2 through the drilled-hole sparger (DHS) at a pH controller output of 0 to –100		
Agitation	97 rpm, P/V: 15.0 W/m^3, tip speed 0.56 m/s	132 rpm, P/V: 15.1 W/m^3, tip speed 0.77 m/s	166 rpm, P/V: 15.7 W/m^3, tip speed 0.97 m/s
Dissolved oxygen (DO)	40%		
DO cascade	0–1 slpm oxygen through the DHS at a controller output of 0–100		
Headspace aeration	1.0 slpm	1.5 slpm	1.5 slpm
Target inoculation cell density	0.5 x 10^6 VC/mL	1.0 x 10^6 VC/mL	4.0 x 10^6 VC/mL

Transfection of bioreactor cultures

Reagent volumes for transfecting a 40 L culture in a 50 L bioreactor are shown in Table 4. All reagents were maintained at 4–8°C prior to complexation of the transfection reagent and plasmid DNA. The combined mixture of the LV packaging mix plasmid DNA and αCD19CAR transfer plasmid DNA was placed in a 1 L PETG bottle. The plasmid mixture was then transferred to a Labtainer BPC containing CTS Opti-MEM I Medium at 4–8°C by replacing the lid of the bottle with the 2-port cap of a Thermo Scientific™ Standard Single-Use Bottle Assembly System and sterile-welding the tubing onto the BPC before gravity-draining into it. The CTS LV-MAX Transfection Reagent was transferred to another BPC containing CTS Opti-MEM I Medium in a similar manner, utilizing a single-use bottle assembly system cap and welding it to the Labtainer BPC. The two BPCs were then sterile-welded together, and the contents were combined by adding the diluted plasmid DNA into the BPC containing the diluted transfection reagent. The BPC was gently mixed by wave motion for 5–10 seconds and then incubated at room temperature without agitation for 10 minutes. During this time, the BPC was sterile-welded to one of the 50 L bioreactors. Once incubation was complete, a peristaltic pump was used to transfer the complexation solution into the bioreactor at a rate of 1.8 L/min, which allowed for addition within 10 minutes. This process was repeated for each bioreactor. Four hours post-transfection, BPCs containing CTS LV-MAX Enhancer and CTS LV-MAX Supplement were sterile-welded to each bioreactor, and their contents were transferred into the cultures using a peristaltic pump set to 1.8 L/min.

Culture monitoring

Samples were collected daily to assess the growth rate and health of the cells. Approximately 15 mL was pulled from each bioreactor and discarded to flush the sampling lines. Fresh 20 mL samples were then collected to measure pH, pO_2, pCO_2, nutrient, and metabolite levels using a BioProfile™ FLEX2 Automated Cell Culture Analyzer (Nova Biomedical). A Vi-CELL™ XR Cell Viability Analyzer (Beckman Coulter) was used to evaluate the concentration and viability of the cells. The remaining volumes were then dispensed into 1 mL vials and frozen at –80°C for titer analysis. FoamAway antifoaming agent was added to the bioreactor cultures as needed to minimize foaming. No FoamAway agent was added to the DynaDrive S.U.B., and a total of 7.45 g of FoamAway agent was added to the 5:1 S.U.B. over the course of the seed expansion and production run.

Harvest and clarification

On the day of harvest, approximately 48 hours post-transfection, 1 M $MgCl_2$ and Pierce Universal Nuclease for Cell Lysis were added to the bioreactors to final concentrations of 2 mM and 90 U/mL, respectively, to digest any unencapsidated nucleic acid. The bioreactors were then agitated and incubated at 37°C for 2 hours.

Two different scalable clarification processes were utilized for clarification of the LV-αCD19CAR harvest material. The first method of clarification utilized a Millistak+ CE50 filter as a primary filter and a Sartopure PP3 3.0 µm filter as a secondary filter, with a Sartopure PP3 0.45 µm filter as a final filter. The second method of clarification eliminated the primary filter by utilizing the DynaSpin Single-Use Centrifuge for initial clarification, followed by the same secondary and final filters that were utilized in the first method.

Table 4. Reagent volumes for a 50 L production run (40 L transfection volume).

Reagent	Volume required per liter of culture to transfect	Volume added for 40 L transfection volume
Total plasmid DNA	2.5 mg	100 mL*
Opti-MEM I Medium required to dilute plasmid DNA	50 mL	2 L
Opti-MEM I Medium required to dilute transfection reagent	50 mL	2 L
LV-MAX Transfection Reagent	6 mL	240 mL
LV-MAX Supplement	50 mL	2.0 L
LV-MAX Enhancer	40 mL	1.6 mL
Final culture volume	1.2 L	48 L

* Assuming stock plasmid DNA concentration of 1 mg/mL.

For the first method of clarification, two 50 L 5:1 S.U.B.s were utilized for 100 L of culture material. To prepare the depth filter train for clarification, the depth filters were flushed with deionized (DI) water as instructed in their respective user guides and until all air was purged from the filters. The primary filter was flushed with a minimum of 100 L/m^2 of filter area (154 L) at a flow rate of 600 L/m^2 per hour (15.4 lpm). The outlet of the primary filter was then connected to the inlet of the secondary filter and then also flushed with a minimum of 100 L/m^2 of filter area (270 L) at a flow rate of 100 L/m^2 per hour (4.5 lpm). This process was then repeated by connecting the final filter and flushing that with a minimum of 100 L/m^2 of filter area (160 L) at a flow rate of 100 L/m^2 per hour (2.67 lpm). Once the filters were flushed and purged of air, the entire filter train was equilibrated with clarification buffer at a volume of 1.5x the total hold-up of the filter train (39.4 L) at a flow rate of 150 L/m^2 per hour (3.85 lpm). The nuclease-treated culture from one of the S.U.B.s was then pumped through the filter train at a flow rate of 75 L/m^2 per hour (1.93 lpm), followed by the second culture. There was an initial discard volume of 50% of the total holdup volume (13.1 L), after which all of the material was collected for further downstream processing. Clarification buffer (1.5x the depth filter hold-up volume) was then pumped through the filter train to ensure all harvest material was recovered.

For the second method of clarification, one 50 L DynaDrive S.U.B. was utilized. The DynaSpin centrifuge was prepared by loading the single-use rotor into the hardware and loading the linesets into their respective pumps along the side of the hardware and attaching the inlet lineset to the bioreactor, and the centrate and concentrate linesets to Labtainer BPCs. The depth filter train was prepared similarly to method 1, with the same minimum flush requirements for each filter of 100 L/m^2/ hour (135 L total for the secondary filter and 80 L total for the final filter). Once the filters were flushed and purged of air, the filter train was equilibrated with 1.5x the total filter hold-up volume (8.9 L) of clarification buffer at a flow rate of 3.85 lpm to match the flow rates of method 1.

The nuclease-treated culture was harvested through the DynaSpin centrifuge at an inlet flow rate of 3.5 lpm, with the outlet centrate pump set to 3.35 lpm and the outlet concentrate pump set to 0.15 lpm. These pump flow rates were set based on the calculated packed cell volume of the culture, to minimize loss of the centrate as the cells are separated out in the concentrate line. The centrate material was collected into a 50 L Labtainer BPC so samples could be collected for analysis, then was pumped through the secondary and final depth filters at a flow rate of 1.93 lpm to match method 1. Clarification buffer (1.5x the total filter hold-up volume) was then pumped through the filter train to ensure all harvest material was recovered.

Pressure sensors were added to each filter train during processing, one sensor before each filter. Pressure readings were recorded at least every 5 minutes during processing. For the first clarification method, the delta pressure between the first and second pressure sensors was used to determine the primary filter's pressure. The delta pressure between the second and third pressure sensors was used to determine the secondary filter's pressure. The pressure reading from the third sensor was used to determine the final filter's pressure; pressures above 10 psi indicate clogging of the filter. The second method's pressures were similarly calculated, using the delta pressure between the first and second pressure sensors to determine the initial (secondary) filter's pressure and the pressure reading from the second sensor to determine the final filter's pressure.

Quantitation of infectivity titers

Samples were collected and frozen at –80°C for titer determination. Viral infectivity titers were determined by flow cytometry. Briefly, frozen samples were thawed on ice and serial dilutions were prepared in DMEM supplemented with 10% FBS and 8 µg/mL polybrene. HT1080 cells were spinfected in a 96-well plate at 900 x *g* for 30 min and incubated at 37°C. 72 hours post-transduction, cells were stained with an anti-V5 PE antibody. Titers in transduction units per mL (TU/mL) were calculated based on the percentage of V5-positive cells.

For reporting of titers during downstream clarification, the titer in TU/mL was multiplied by the total volume in mL at each process step to determine total TU. Total TU was then divided by the total liters of cell culture that were processed at each step, to determine the titer in TU/L of cell culture. These calculations allow for the loss in titer between process steps to be determined without being skewed by loss of volume from sampling at each process step. The change in titer in TU/L of cell culture was used to determine the step yield at each process step.

Turbidity measurements

Turbidity measurements during the harvest and clarification steps were taken using 40 mL samples of the material on a Hach™ TL2360 turbidity meter.

Results

Production of LV-αCD19CAR at 50 L scale in S.U.B.s

Cell density and viability in the DynaDrive and HyPerforma 5:1 S.U.B.s were highly comparable to those in control shake flasks throughout in-vessel expansions and during the LV-αCD19CAR production runs (Figure 1). Glucose usage and lactate and ammonium production in the bioreactors and control flasks were also comparable (Figures 2–4), indicating that the scale-up of the process from shake flasks to the bioreactors was robust.

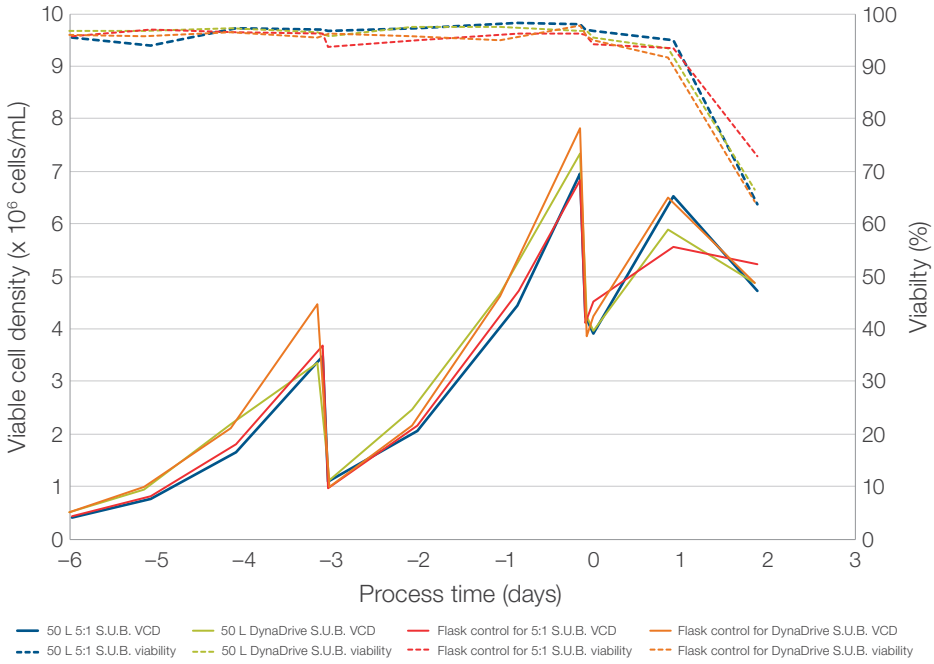

Figure 1. Growth profiles of CTS Viral Production Cells during in-vessel scaling and LV-αCD19CAR production in 50 L DynaDrive and HyPerforma 5:1 S.U.B.s alongside 125 mL shake flask controls. The solid lines represent viable cell density (VCD), and the dotted lines represent percentage of viable cells.

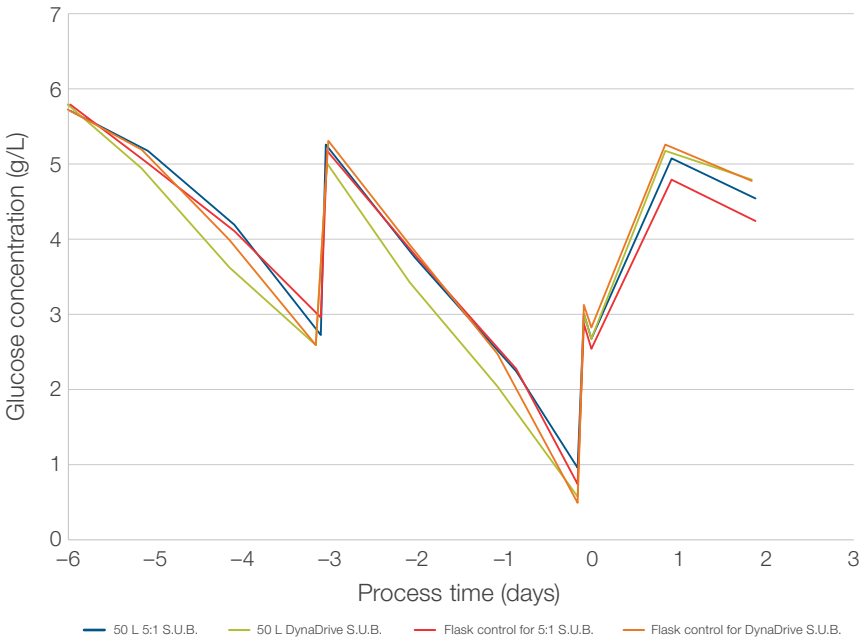

Figure 2. Glucose profiles of CTS Viral Production Cells during in-vessel scaling and LV-αCD19CAR production in 50 L DynaDrive and HyPerforma 5:1 S.U.B.s alongside 125 mL shake flask controls.

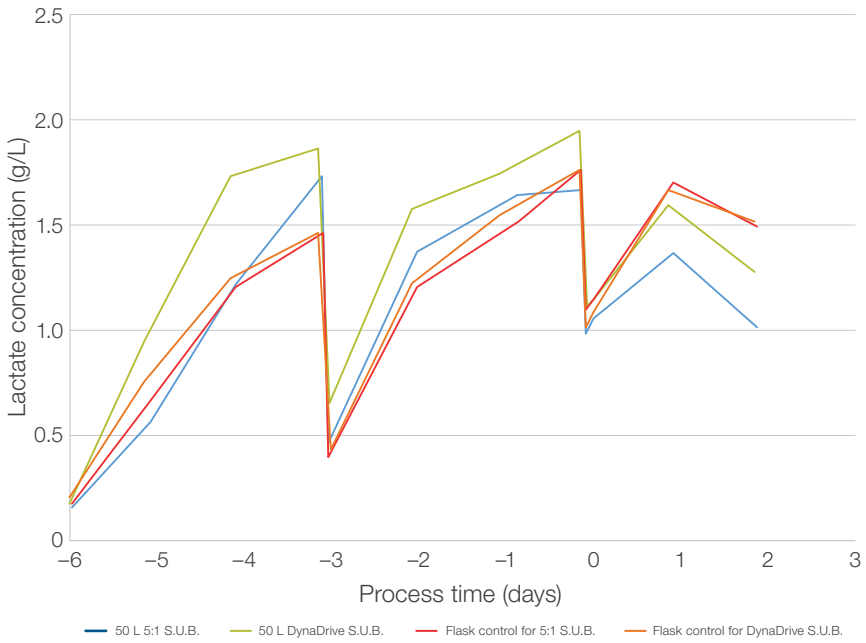

Figure 3. Lactate profiles of CTS Viral Production Cells during in-vessel scaling and LV-αCD19CAR production in 50 L DynaDrive and HyPerforma 5:1 S.U.B.s alongside 125 mL shake flask controls.

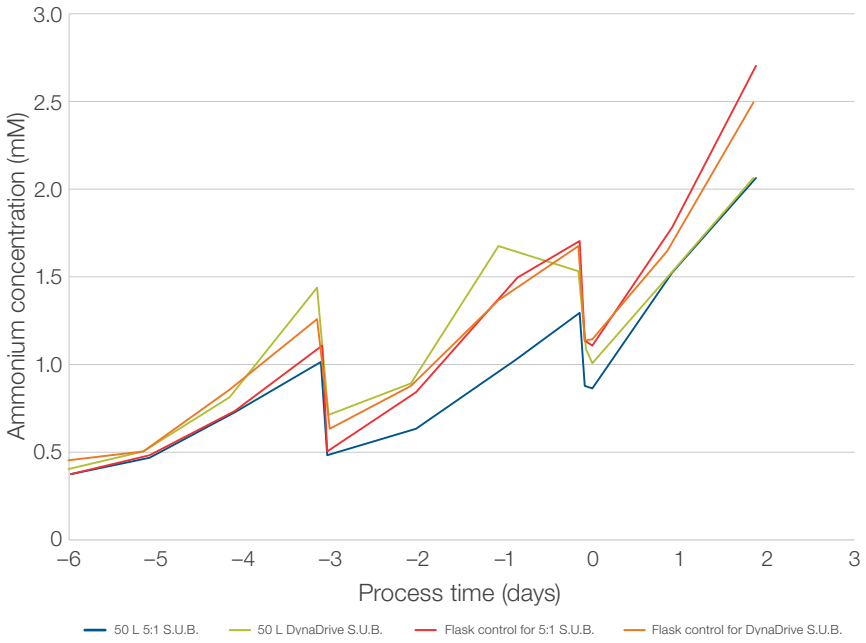

Figure 4. Ammonium profiles of CTS Viral Production Cells during in-vessel scaling and LV-αCD19CAR production in 50 L DynaDrive and HyPerforma 5:1 S.U.B.s alongside 125 mL shake flask controls.

Figure 5 shows the pH trends for both the DynaDrive S.U.B. and the HyPerforma 5:1 S.U.B. alongside the averaged trends for the control shake flasks, as well as the pCO_2 levels.

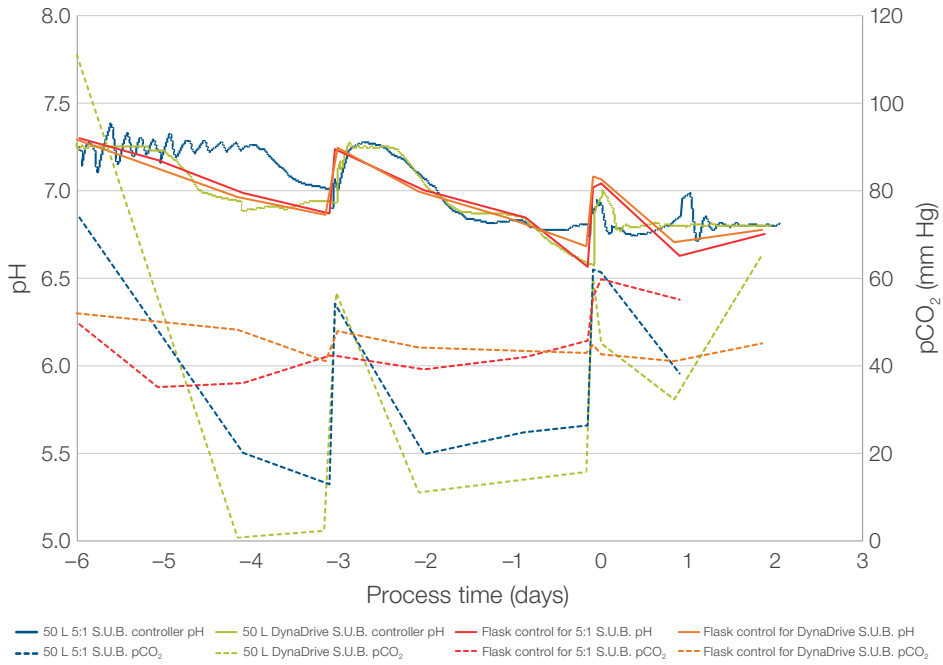

Figure 5. pH and pCO_2 profiles of CTS Viral Production Cells during in-vessel scaling and LV-αCD19CAR production in 50 L DynaDrive and HyPerforma 5:1 S.U.B.s alongside 125 mL shake flask controls. The solid lines represent pH, and the dotted lines represent pCO_2.

The dissolved oxygen (DO) levels were well maintained for both reactor systems (Figures 6–7). Minimal gassing of approximately 0.009 VVM total gassing on average was required through the drilled-hole sparger (DHS) for both systems to maintain the DO set point.

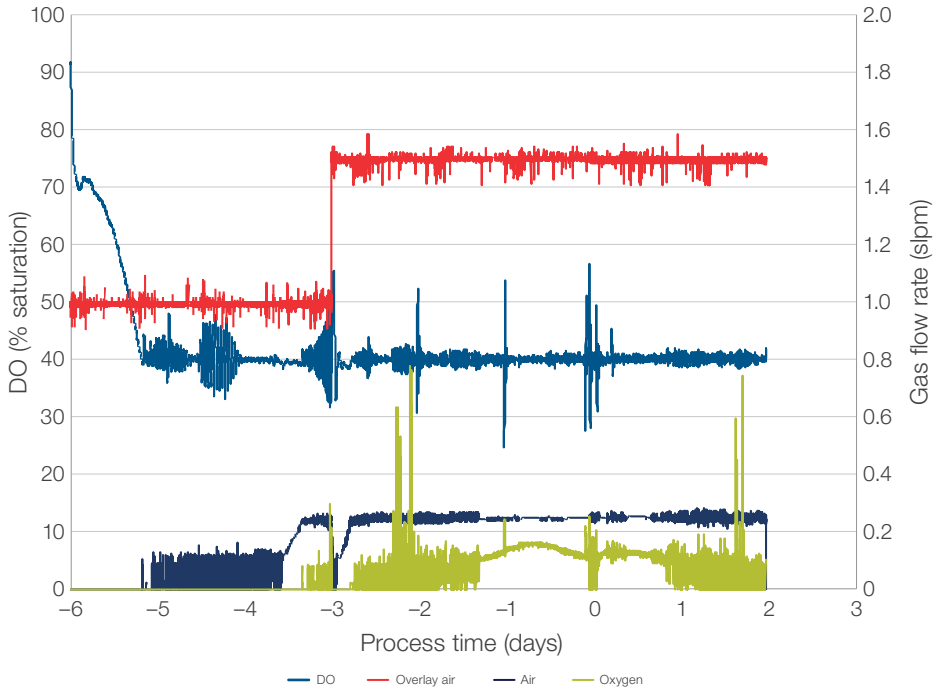

Figure 6. Dissolved oxygen (DO) and sparged gas controller profiles of CTS Viral Production Cells during in-vessel scaling and LV-αCD19CAR production in the 50 L DynaDrive S.U.B.

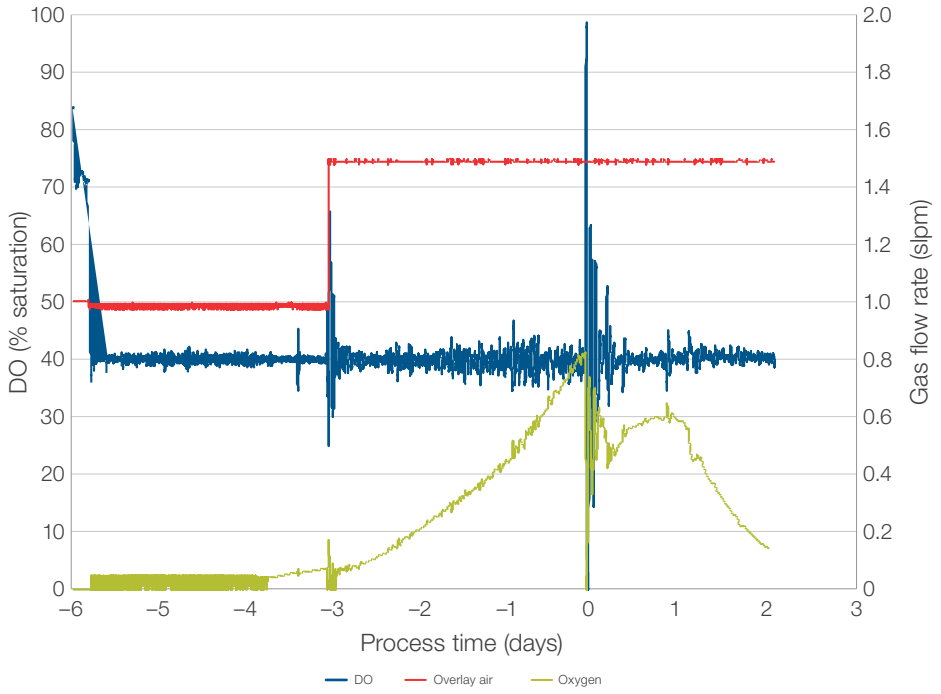

Figure 7. DO and sparged gas controller profiles of CTS Viral Production Cells during in-vessel scaling and LV-αCD19CAR production in the 50 L HyPerforma 5:1 S.U.B.

Figure 8 shows the infectious titers prior to clarification of each of the bioreactors, compared to their respective control flasks. Each bioreactor was within 10% of its respective shake flask control.

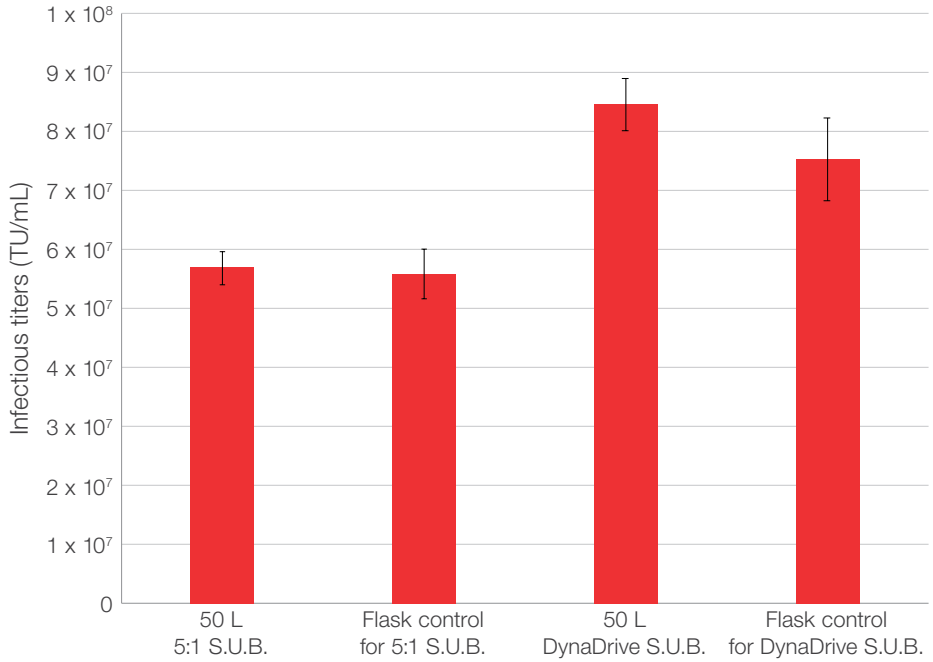

Figure 8. Infectious titers of CTS Viral Production Cells of LV-αCD19CAR prior to harvest in the 50 L DynaDrive and HyPerforma 5:1 S.U.B.s, compared to 125 mL shake flask controls.

Clarification of LV-αCD19CAR at 50 L scale

As stated in the materials and methods section, two different methods were used to clarify the LV-αCD19CAR. With the first method of utilizing depth filtration for clarification, the nuclease-treated LV-αCD19CAR bulk from two 50 L 5:1 S.U.B.s had a starting turbidity of 488.5 NTU (Figure 9) and a titer of 4.87 x 10^{10} TU/L of cell culture (Figure 10). Clarification through the filter train took a total of 73 minutes. The maximum pressure on the primary filter reached 4.05 psi, the maximum pressure on the secondary filter reached 0.07 psi, and the maximum pressure on the final filter reached 2.66 psi (Figure 11). This method of clarification reduced turbidity to 34.1 NTU (Figure 9) and had a step yield of 97.87% with a titer of 4.76 x 10^{10} TU/L of cell culture (Figure 10).

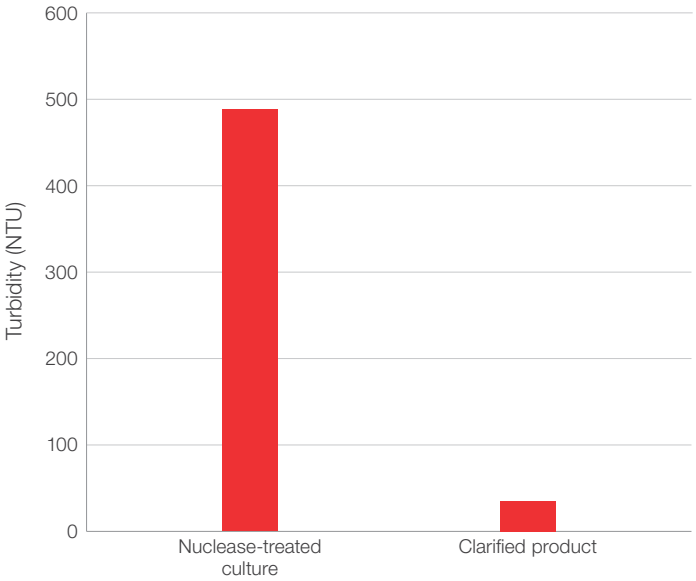

Figure 9. Turbidity during clarification using the first method of clarification using only depth filtration.

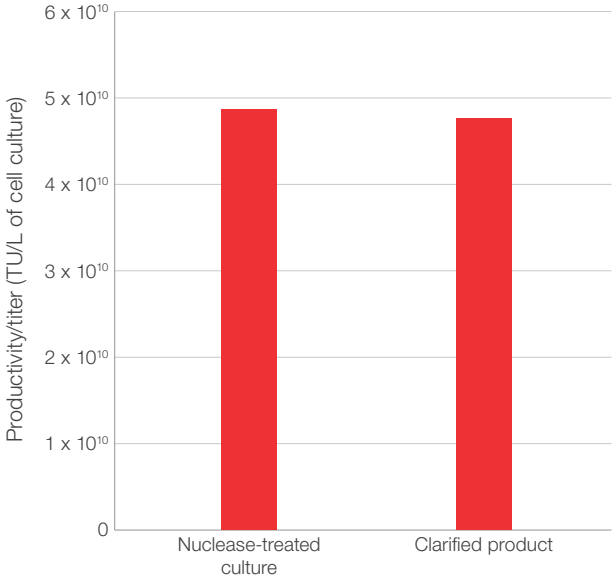

Figure 10. Productivity (in transduction units per liter of cell culture processed) at each process step for clarification using the first method of clarification using only depth filtration.

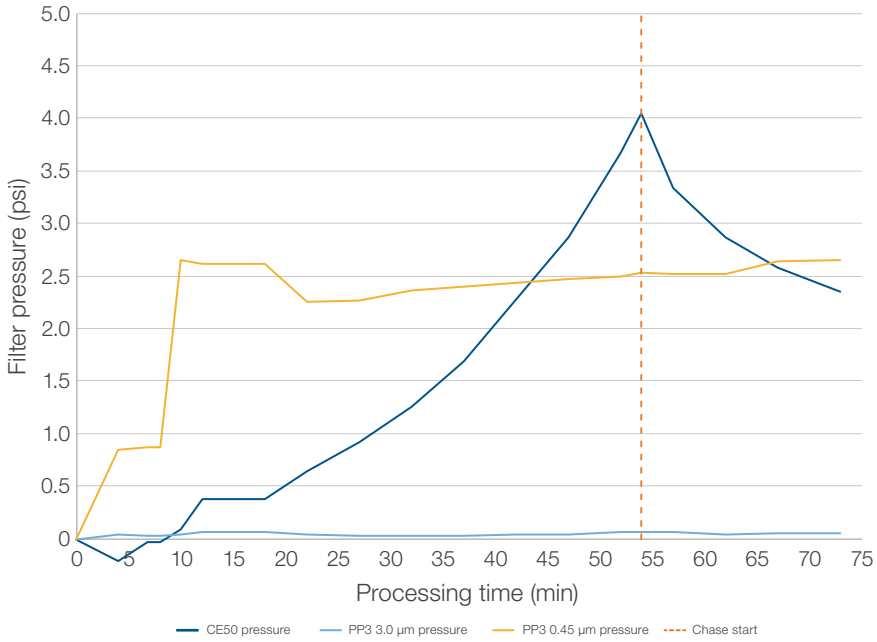

Figure 11. Clarification filter pressure vs. processing time using the first method of clarification using only depth filtration.

With the second method of clarification utilizing the DynaSpin centrifuge in place of the primary depth filter, the nuclease-treated LV-αCD19CAR bulk had a starting turbidity of 395 NTU (Figure 12) and a titer of 5.9 x 10^{10} TU/L of cell culture (Figure 13). Clarification through the DynaSpin centrifuge took a total of 15 minutes, with the following secondary clarification through the depth filters taking a total of 24 minutes. The maximum pressure on the secondary filter reached 0.2 psi, and the maximum pressure on the final filter reached 3.5 psi (Figure 14). This method of clarification reduced turbidity to 93.4 NTU after the DynaSpin centrifuge step and 38 NTU after clarification (Figure 12) and had a step yield of 107% after the DynaSpin centrifuge step and 82.9% after the remaining clarification steps with corresponding titers of 6.33 x 10^{10} TU/L cell culture and 5.24 x 10^{10} TU/L cell culture (Figure 13).

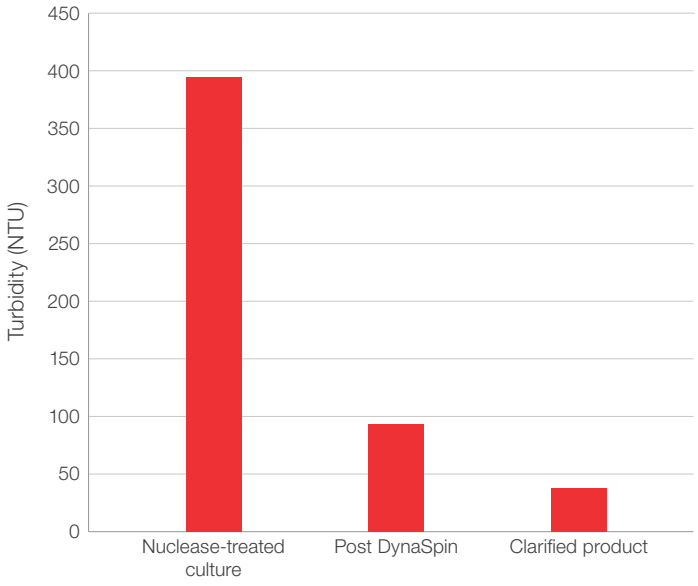

Figure 12. Turbidity during clarification using the second method of clarification using the DynaSpin centrifuge in conjunction with depth filtration.

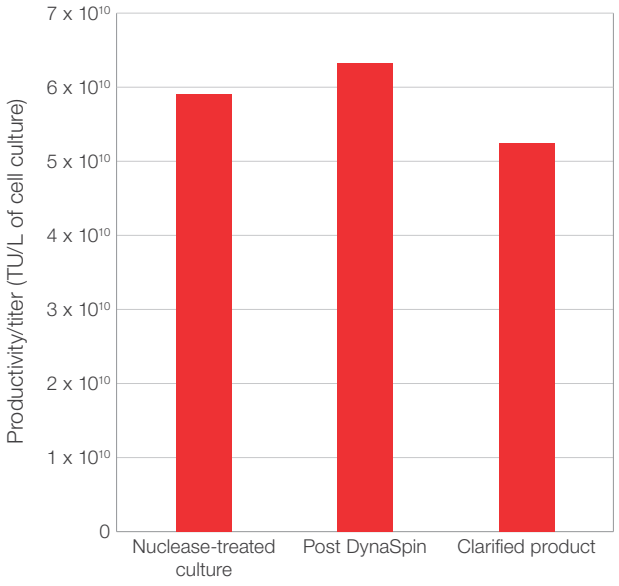

Figure 13. Productivity (in transduction units per liter of cell culture processed) at each process step for clarification using the second method of clarification using the DynaSpin centrifuge in conjunction with depth filtration.

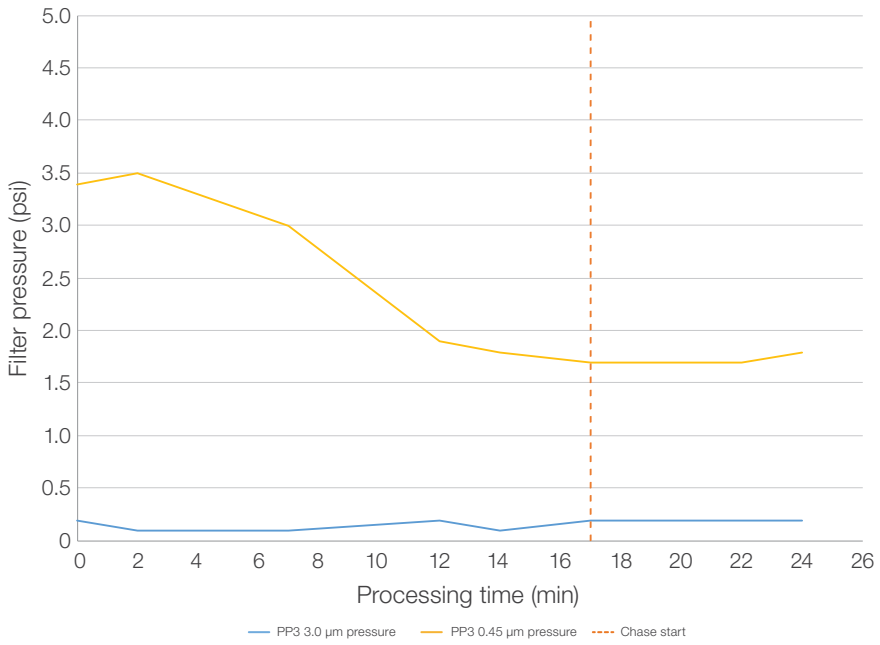

Figure 14. Clarification filter pressure vs. processing time of filters used during the second method of clarification using the DynaSpin centrifuge in conjunction with depth filtration.

Conclusions

In this study, we have demonstrated the ability of the CTS LV-MAX Production System to scale up to 50 L in both the DynaDrive and HyPerforma 5:1 S.U.B.s producing LV-αCD19CAR. Robust scalability of the CTS LV-MAX system allows for streamlined use of the system from R&D through clinical and commercial manufacturing. The capability to scale up LV production can enable gene therapy researchers to utilize one system throughout their entire development process with consistent performance. Additionally, the HyPerforma and DynaDrive families of S.U.B.s allow for production volumes up to 2,000 L and 5,000 L, respectively, well suited for commercial production of LV.

Lastly, we have demonstrated two scalable clarification strategies for harvesting biologically active LV-αCD19CAR. The first is a traditional depth filtration method, while the second utilizes the DynaSpin Single-Use Centrifuge to eliminate the primary depth filter and potentially decrease the surface area required for the secondary filter. The advantage of the DynaSpin centrifuge is that it is not limited by volumetric throughput. As the process is scaled in either volume or process intensity, the cost of consumables for the single-use centrifuge remains fixed, whereas an increasing number of depth filters are required for standard depth filtration processes. As shown above, the secondary filters were kept the same between the two methods. But when examining the filter pressure during processing, the secondary filter may not have been necessary and could have been eliminated, providing further cost savings.

Taken together, these results highlight the robustness and scalability of the CTS LV-MAX Production System and the HyPerforma and DynaDrive S.U.B.s to meet current and future demands of gene therapy developers in producing lentiviral vectors for clinical and commercial use. We have also shown possible scalable methods for clarification of those vectors, including with the DynaSpin Single-Use Centrifuge.

Authors

Paula Decaria, Arjen Van den Berg, Nils Williston, Nicole Orr, and Chris Leary, Thermo Fisher Scientific

Ordering information

Description	Quantity	Cat. No.
Gibco LV-MAX products		
LV-MAX Lentiviral Production System	1	A35684
LV-MAX Production Medium	1 L	A3583401
	6 x 1 L	A3583402
Viral Production Cells	1 vial	A35347
	6 vials	A35827
LV-MAX Transfection Kit • LV-MAX Transfection Reagent • LV-MAX Supplement • LV-MAX Enhancer	For 1 L culture	A35348
Opti-MEM I Reduced Serum Medium	100 mL	31985062
Gibco CTS LV-MAX products		
CTS LV-MAX Production Medium	1 L	A4124001
	6 x 1 L	A4124004
	10 L	A4124002
	20 L	A4124003
CTS Viral Production Cells	1 vial	A53956
CTS LV-MAX Transfection Kit • CTS LV-MAX Transfection Reagent	For 1 L culture	A4132601
• CTS LV-MAX Supplement • CTS LV-MAX Enhancer	For 10 L culture	A4132602
CTS Opti-MEM I Medium	100 mL	A4124801
	500 mL	A4124802
Additional upstream LV production products		
FoamAway Irradiated AOF (animal origin–free) Antifoaming Agent	0.5 L in a 1 L bag	A1036902
Pierce Universal Nuclease for Cell Lysis	100 kU	88702
1 M $MgCl_2$	100 mL	2682707
Thermo Scientific bioprocess equipment and BPCs		
DynaDrive S.U.B. 120 V—50 L	1 each	DDB0050.1011
DynaDrive BioProcess Container—50 L	1 each	SH31192.01
HyPerforma 5:1 S.U.B., jacketed, AC motor—50 L	1 each	SUB0050.8100
HyPerforma 5:1 BioProcess Container, Aegis5-14 film—50 L	1 each	SH31073.01
HyPerforma G3Pro Bioprocess Controller	1 each	F100-2961-001
2D Labtainer BioProcess Container	5 L	SH30712.01
	50 L	SH30723.04
3D Productainer BioProcess Container, 2 Top Ports and 1 Bottom Port	100 L	SH30967.02
Conical LLDPE drum, 1 port, size 10.2 cm, with clamps	100 L	SV50517.05
Plastic drum dolly	For 50 L, 100 L, and 200 L drums	SV50102.02
Standard Single-Use Bottle Assembly System	1 L, 2-port	SB00004-I
Thermo Scientific clarification products		
DynaSpin Single-Use Centrifuge hardware unit	1 each	DSPIN.9000
DynaSpin Single-Use Rotor	1 each	SUT00056

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