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Scalable Upstream Process Development for the Suspension-Based Production of Lentiviral Vectors for CAR-T Cell Therapies with Multiparallel and Benchtop Bioreactor Systems and Design of Experiment Methodology

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Introduction

Cell and gene-based therapies present a new treatment paradigm that has the potential to address clinical needs that are unmet by current small molecule and biotherapeutic approaches [1].

Viral vectors such as adenoviruses, adeno-associated viruses and retroviruses are effective delivery systems for genetic material used in cell and gene therapies and vaccines. Lentiviruses in particular are used, for example, for the transfer of genetic information for novel cellular immunotherapies (gene modified cell therapies), like CAR-T cell therapy [2]. These innovative approaches will be a substantial part of next-generation therapies to cure devastating diseases.

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The number of clinical candidates is growing vastly and their manufacture at commercial scale is becoming a reality. The processes to produce viral vectors require a high level of operator expertise and application of GMP guidelines however, they are currently based solely on an R&D approach. There are two main strategies that viral vector manufacturers use to produce viral vectors. HEK293T cells are commonly used as a workhorse cell line for lentiviral vector (LVV) production for cell and gene therapy applications. Adherent production processes with these cells utilize static flask cultures, such as T-flasks, cell factories or cell stacks. These adherent processing methods are quite easy to develop and perform, however, they significantly lack the capacity for automation and scaling.

Typical bioreactors using either a rocking motion, or stirred tank agitation could provide these features. Therefore, in order to produce viral vectors at commercial scale, the 2D adherent processing methods must be shifted to 3D suspension cultures, representing a significant challenge for the cell and gene therapy industry.

The transition from adherent 2D cultures to a 3D cultivation can be made with the use of a suspension adapted cell line. The Ambr® 15 microbioreator system can help to facilitate the transition and enable fast process optimization, by screening many process parameters in parallel in small volumes of 10-15 mL [4].

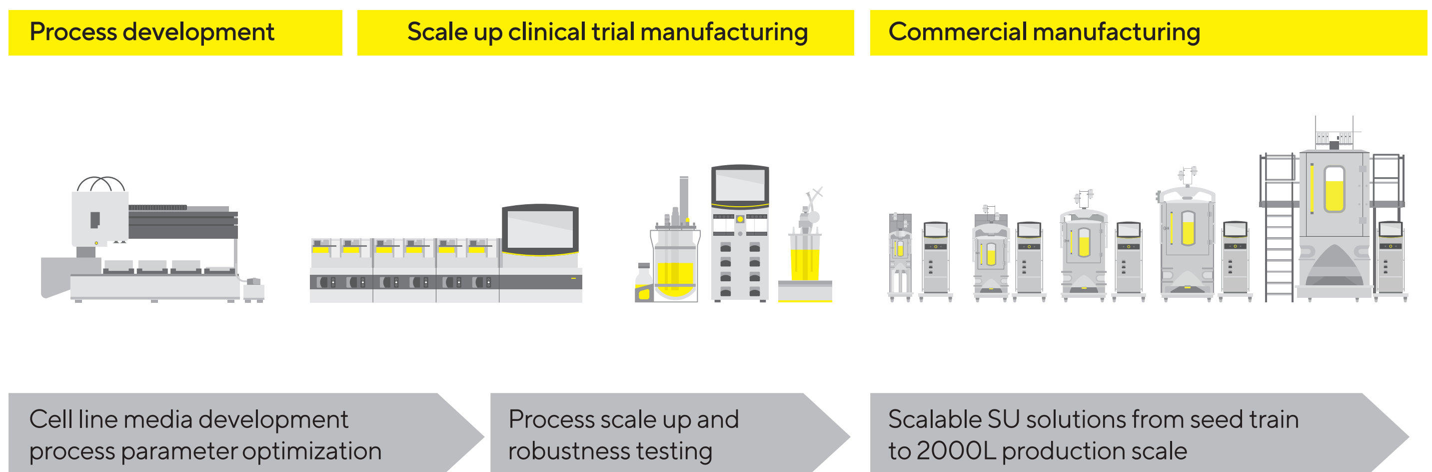
Ambr® 15 is an automated micro-scale bioreactor system that enables process control (including pH, DO, temperature and stirring rate) similar to that of larger scale bioreactors. However the system's small volumes and easy set-up, reduce the associated costs of reagent used, time and labor. Process parameters can be screened in a way that results in financial savings which are important for CDMOs and start-up companies. The parallel processing, automation and good consistency provided by the Ambr® 15 system [6], enable rapid, high throughput process optimization, including design of experiments (DOE) studies [4; 5]. Time spent in data analysis, is also released, thanks to its integration to the DOE software MODDE®.

Furthermore, the "big brother" of Ambr® 15, the Ambr® 250 Modular, a bioreactor system with working volumes of 100-250 mL, provides a scale-down model for larger stirred bioreactor systems. The Ambr® 250 Modular also facilitates upstream process development with reduced effort due to its parallel cultivation capacity and capacity for "hands-off" workflow automation.

The Ambr® 15 and Ambr® 250 have been shown to be valuable scale-down model systems [6; 7]. Although some effort is needed to characterize them and also novel scale-down model criteria might need to be established (reviewed by [8]), due to the high throughput screening capabilities of both instruments, this characterization can be performed efficiently.

Figure 1

Sartorius Stirred Bioreactor Portfolio for Different Stages of Biotherapeutic Manufacturing.



The Univessel® 2L single-use (SU) benchtop bioreactor together with the Biostat® B control unit is an ideal tool for pilot production runs, robustness studies and initial DSP material generation for small scale DSP studies. It also allows scientists to confirm the scale up strategy, for shifting to the larger stirred tank bioreactors (STRs) that are suitable for GMP manufacturing. Sartorius also supports scale-up strategies with well characterized and optimized systems based on extensive studies on kLa, PPV and mixing time [9].

Figure 1 highlights the beforementioned capabilities of the Ambr® bioreactor systems. Due to their scalability to larger stirred bioreactor systems [11], they are the ideal tools for process development.

Objective

The aim of our study was to establish a working protocol for the cultivation of suspension adapted HEK293T cells and the production of CD19-CAR lentivirus in small and benchtop scale stirred bioreactors as a proof of concept.

First, we aimed to optimize culture conditions, focusing on stirring speed and culture pH. The Ambr® 15 microbioreactor system was used to screen for improved viable cell count, viability and lentivirus productivity. The factors have mainly been selected based on previous findings. Some factors, e.g. the cell line, the seeding cell density and percentage of DO have been optimized prior to the study presented here. In a second experiment we aimed to optimize the transient transfection step in order to obtain the highest possible and most robust lentivirus titer. We optimized the viral production medium, DNA amount, ratio of DNA / transfection reagent (PEIpro® from Polyplus Transfection) and ratio of plasmids.

In order to get meaningful results with the least number of samples, we performed a DOE study to identify optimal culture and transfection conditions by using the MODDE® software for experimental planning and analysis of results.

In a next step, we wanted to confirm our findings on Ambr® 15 by scaling up the optimal conditions for lentivirus production to larger volumes in the Ambr® 250 Modular and the single-use benchtop bioreactor Univessel® SU 2L. Furthermore, we used the parallel processing capabilities of the Ambr® 250 Modular to optimize the gas flow rate.

Methods

Lentivirus production
Third generation lentivirus was produced by transient transfection of suspension HEK293T/17 SF cells (ATCC #ACS-4500) in a stirred bioreactor (either Ambr® 15, Ambr® 250 Modular or Univessel® SU 2L from Sartorius). The cells were passaged at least twice before starting the lentivirus production.

Freestyle 293 media (Thermo Fisher Scientific) was used to fill the respective bioreactors on day 0 and process parameter control was initiated. Later, on day 0, the cells were seeded into the bioreactor at a final VCD of $1x10^6$ cells/mL. An equivalent lentivirus culture was prepared and cultured in a 125 mL shake flask (positive control). After 24 h, transfection of a CD19-CAR encoding transfer plasmid and three lentiviral helper plasmids (Aldevron) was performed using PEIpro® DNA transfection reagent (Polyplus Transfection). A defined amount of DNA (sum of all four plasmids) per $1x10^6$ cells was diluted in Freestyle 293 medium at a certain plasmid ratio (the volume was 1:20 of the final culture volume). In a separate reaction tube a defined volume of PEIpro® per $1x10^6$ cells was diluted in Freestyle 293 medium (the volume was 1:20 of the final culture volume). Diluted PEIpro® was added to the diluted DNA, gently mixed and incubated for 15 min at room temperature. The mixture was added dropwise to the cells. A negative control without using a transfection reagent was prepared and treated equally (cells were cultured in a 125 mL shake flask).

On the next day, i.e. 18 h after transfection, anti-clumping reagent (1:500 (v/v), Thermo Fisher Scientific) and 10 mM sodium butyrate (Sigma) were added.

Lentivirus was harvested 72 h post transfection. Before harvesting, the virus suspension was treated with 10 U/mL DENARASE® (c-Lecta) for 1 h for digestion of nucleic acids.

Lentivirus quality control and analysis
As a primary readout on virus concentration, we performed a p24-ELISA, that measures lentivirus-associated p24 protein, to determine the total viral particle titer. The assay was performed according to the manufacturer´s protocol (Cell Biolabs). The assay's accuracy was determined to be below 8 % CV.

Due to the nature of typical infectious titer assays, being very laborious and giving low sample throughput, we decided to primarily run a particle titration assay (p24-ELISA) and only determine the infectious titer of selected samples based on the viral particle titer results. Still, viral particle titers allow us to observe overall effects of factors on the lentivirus production process.

A flow cytometry-based assay was performed to determine the infectious lentiviral titer by transducing adherent HEK293T cells with the lentiviral supernatants [5; 6]. The HEK293T/17 SF density and viability were measured with a Cedex HiRes instrument (Roche).

Results & Discussions

Optimization of culture conditions for lentivirus production with Ambr® 15

In the first experiment we sought to identify optimal culture conditions to produce lentiviral vector with the Ambr® 15 system and a DOE approach. Two factors were analyzed regarding their contribution to the lentivirus titer: stirring speed and culture pH. Both factors were analyzed in a range shown in Table 1.

Table 1

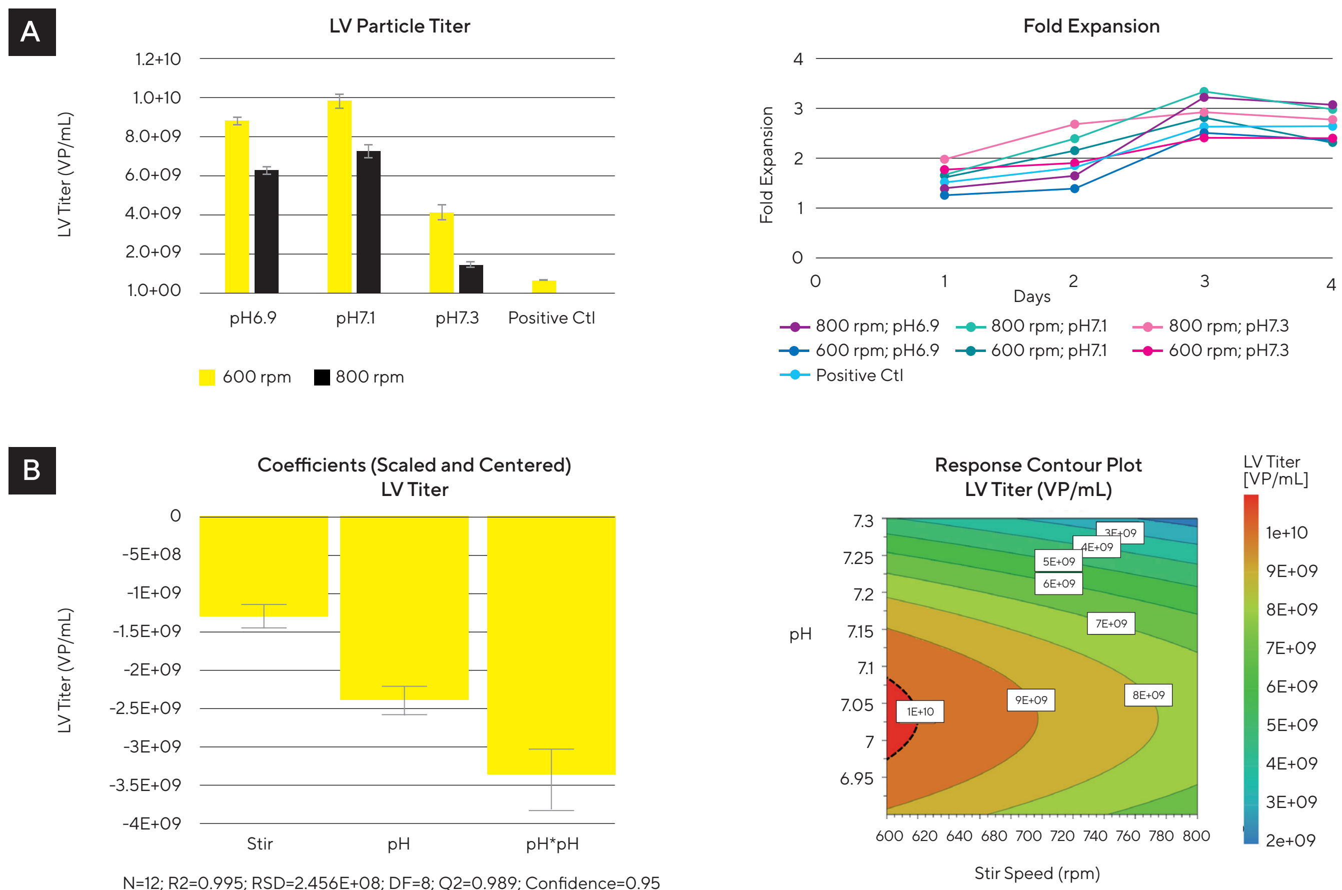
Cultivation and Transfection Conditions of Experiment 1 (Ambr® 15)

Process Parameters	Set points
Stir speed (rpm)	600, 800
pH	6.9; 7.1; 7.3
Constant parameters	30% DO; 15 mL fill volume; 37°C cultivation temperature;
Transfection conditions	1 µg DNA + 2 µL PEIpro® /10^6 cells; plasmid ratio: 5:2.5:1.5:1 (GOI:gag-pol:VSV-G:rev)

All conditions were analyzed in duplicates. The experimental design (full factorial design with two replicates of each condition) was created with MODDE® software.

The cultivation and lentiviral particle titer results, as well as the DOE model analysis are shown in Figure 2.

Figure 2



Note. (A) Lentiviral particle titer and HEK293T/17 SF cells fold expansion during the optimization of the culture conditions in the Ambr® 15. Shown are mean values of duplicate vessels with standard deviation. Positive control = standard shake flask culture

(B) Results graphs from the analysis of the DOE model with MODDE®. Model coefficient factors on the left (stir speed and pH) and their impact on the process readout lentivirus particle titer. In the right, a response contour plot with LV particle titer profile.

According to Figure 2 A, the cells generally grew better in the Ambr® 15 than in the control shake flask culture. However, large differences in the fold expansion can also be observed, depending on the different conditions tested in the Ambr® 15. The viability of the cells cultured at pH 7.3 dropped significantly at day 2 (not shown) which explains the reduced lentivirus titer at this pH. Overall, we didn't observe any toxic effects of PEIpro® on the cells.

Generally, it was observed that higher pH values and stirring speeds yielded improved cell growth, but these factors negatively correlate to LV particle titer as seen in the DOE model (Figure 2 B). This could imply that a 2-step approach needs to be implemented, including a shift of the main process parameters, when transitioning from the growth phase to the production phase at the time of the plasmid transfection.

We also identified, that the LV particle titer is higher in the Ambr® 15 vessels than in the positive control shake flask. According to Figure 2 A, we could clearly identify optimal culture conditions for lentivirus production in the Ambr® 15 microbioreactor. A stirring speed of 600 rpm and a pH between 6.9 and 7.1 yielded the highest lentivirus titer (8.8×10^9–9.8×10^9 VP/mL). This trend could be confirmed with the DOE model. According to the response contour plot a clear trend could be observed, of an increasing lentiviral particle titer with decreasing stirring speed and a peak lentiviral titer was observed at pH culture values between 7.0 and 7.1. It can be concluded that the culture pH and the stirring speed are critical process parameters that have a significant effect on the viral vector production.

Optimization of transfection with PEIpro® for lentivirus production in Ambr® 15

In a following experiment, we aimed to optimize the transient transfection process by using the Ambr® 15 microbioreactor system.

We optimized four parameters that could have an impact on the success of the transient transfection and virus production proceses: viral production medium, DNA amount, ratio of DNA / transfection reagent and ratio of plasmids. Using a DOE approach we were able to screen all these parameters in one cultivation run. In Table 2 the actual ranges of the parameters tested are listed. The selection of the parameters ranges or set points was based on previous experience and manufacturer protocols. A D-optimal design with triplicate center points was chosen, leading to the analysis of 23 different conditions / vessels.

Table 2

Cultivation and Transfection Conditions of Experiment 2 in Ambr® 15

Process Parameters	Set points/Ranges
Constant parameters	600 rpm; pH limits 6.9- 7.1; 30% DO; 15 mL fill volume; 37°C culture temperature
Viral production medium	Freestyle293; SFM4Transfx-293
DNA amount	0.5 – 4 µg DNA/10^6 cells (at transfection)
Ratio PEIpro®:DNA	1:1 – 4:1
Plasmid ratio: GOI:gag-pol:VSV-G:rev	5:2.5:1:1; 5:1:2.5:1; 5:1:1:2.5

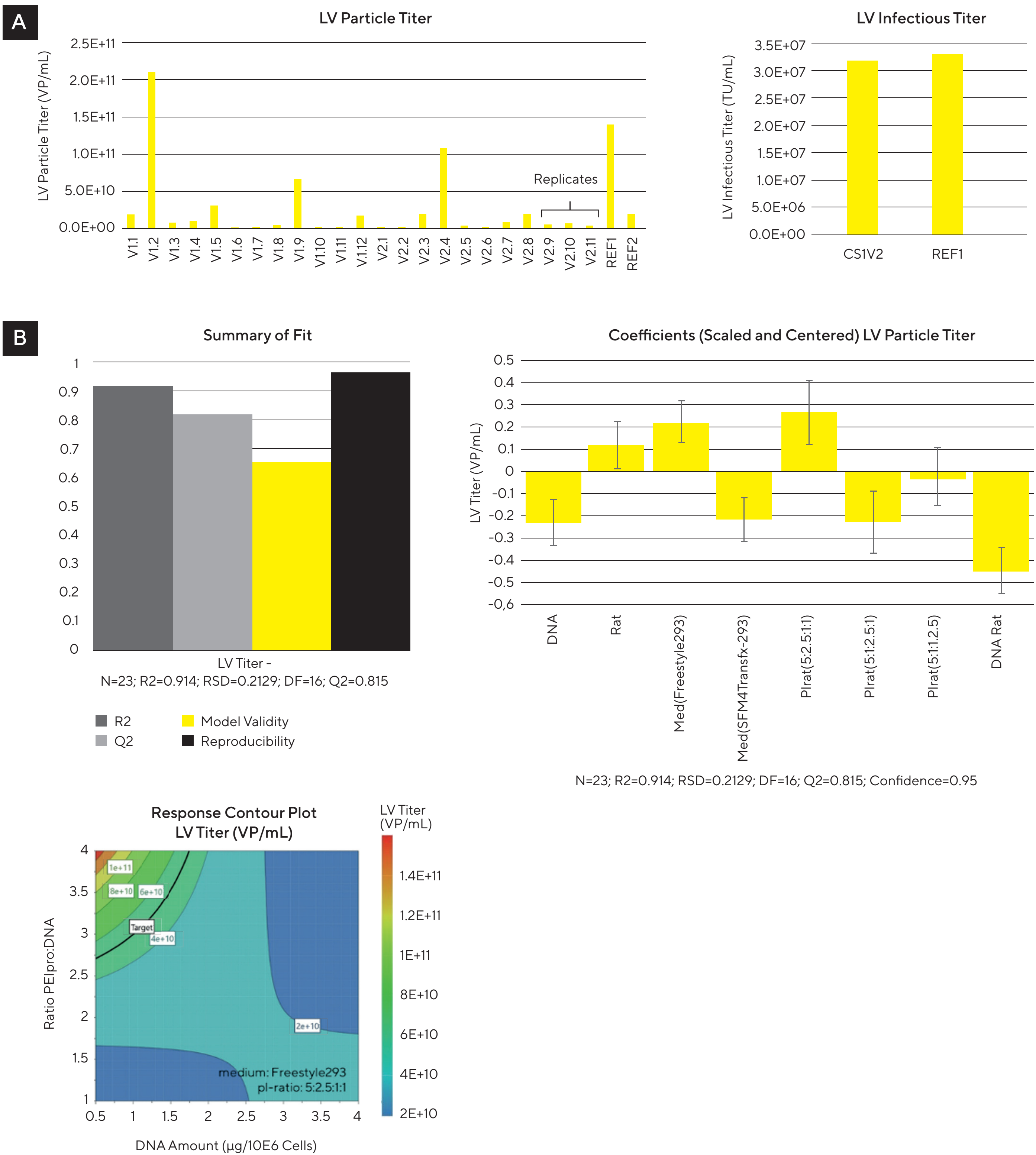
According to Figure 3 A the LV particle titer is higher in some of the Ambr® 15 vessels than in the shake flask positive control. Depending on the conditions used for transfection, extreme differences in titers are observed between the culture vessels, indicating that the factors analyzed do have a significant effect on the lentiviral productivity.

At optimal conditions, a viral titer of 2.1×10^{11} VP/mL and a specific productivity, meaning the particle titer per cells at the time of transfection, of 1.3×10^5 VP/cell was obtained which was higher than the titer obtained in the reference shake flask (1.4×10^{11} VP/mL and 5.9×10^4 VP/cell).

The infectious viral titer produced under the best conditions in the Ambr® 15, seems to be equal to the one in the positive control shake flask. However, when comparing the specific productivity of the lentivirus, meaning the infectious titer per cells at the time of transfection, this value is significantly higher for the Ambr® 15 vessel (20.13 for the Ambr® 15 vs. 13.66 TU/cell for the reference shake flask).

Furthermore, when comparing the highest viral particle titer obtained in this lentivirus production run with the highest one from the first experiment, we see another twentyfold increase in viral particles, gained through this optimization.

Figure 3



Note. (A) Lentiviral particle and infectious titer obtained in a screening experiment to optimize the transfection process with the Ambr® 15. (REF1/2=shake flask control with each of the tested media; each bioreactor vessel represents a different transfection condition as defined by the DOE layout) (B) Analysis of the DOE model of the transfection conditions screening experiment.

After obtaining the LV particle titer for all culture vessels, we analyzed the DOE model of this screening experiment with the MODDE® software. Our results lead to a good modeling of the DOE for the optimization process. Furthermore, when we plotted the results in a response contour plot, we could clearly see an optimal spot of the lentivirus particle titer when the ratio of PEIpro® to DNA was high and the DNA amount per 10^6 cells was low. We were able to identify several factors that have a significant effect on the lentivirus titer during the transfection process. For example, the ratio of the amount of PEIpro® to DNA, the usage of Freestyle 293 medium and the plasmid ratio of 5:2.5:1:1 positively correlate to LV particle titer. However, the amount of DNA, the usage of SFM4Transfx 293 medium and a plasmid ratio of 5:1:2.5:1 negatively correlate to the lentivirus titer. The plasmid encoding the gene of interest (GOI) was always present in excess due to the large size of the plasmid and the GOI in order to not limit the virus particle production capacity. Reducing the VSV-g amounts while increasing gag-pol amounts provides a good balance between the proteins needed for virus replication and the proteins involved in the LV enveloped particles formation.

Therefore, with only one cultivation run we were able to identify factors that have a strong impact on the lentivirus titer and an optimal set point which yielded in a twentyfold increase in LVV titer compared to the standard protocol used in experiment 1.

According to the optimizer function of the DOE software MODDE® our new optimal conditions for the transfection step during LVV production are: DNA amount: 0.5 µg/10^6 cells; ratio PEIpro®:DNA: 4:1; viral production medium: Freestyle 293; plasmid ratio: 5:2.5:1:1 (GOI:gag-pol:VSV-G:rev)

Upscaling lentivirus production process to Ambr® 250 Modular

After having optimized the transient transfection process step and the cultivation parameters for lentivirus production, we tested the feasibility of upscaling the optimized process to the Ambr® 250 Modular. Furthermore, we aimed to optimize the gas flow rate and stir direction which is enabled in this bioreactor system with automated processing. These parameters could potentially have a significant impact in the viral titer due to its sensitivity to externally applied forces (ie.: shear forces) and the dependence of the viral titer on the cell viability.

The culture parameter set points and transfection conditions are listed in table 3. Due to the limited scalability of the Ambr® 15 system, the optimal stirring speed for the production process in the Ambr® 250 Modular was identified by running a separate experiment which included testing of four different stir speeds in the Ambr® 250 Modular.

Table 3

Cultivation and Transfection Conditions of Experiment 2 in Ambr® 15.

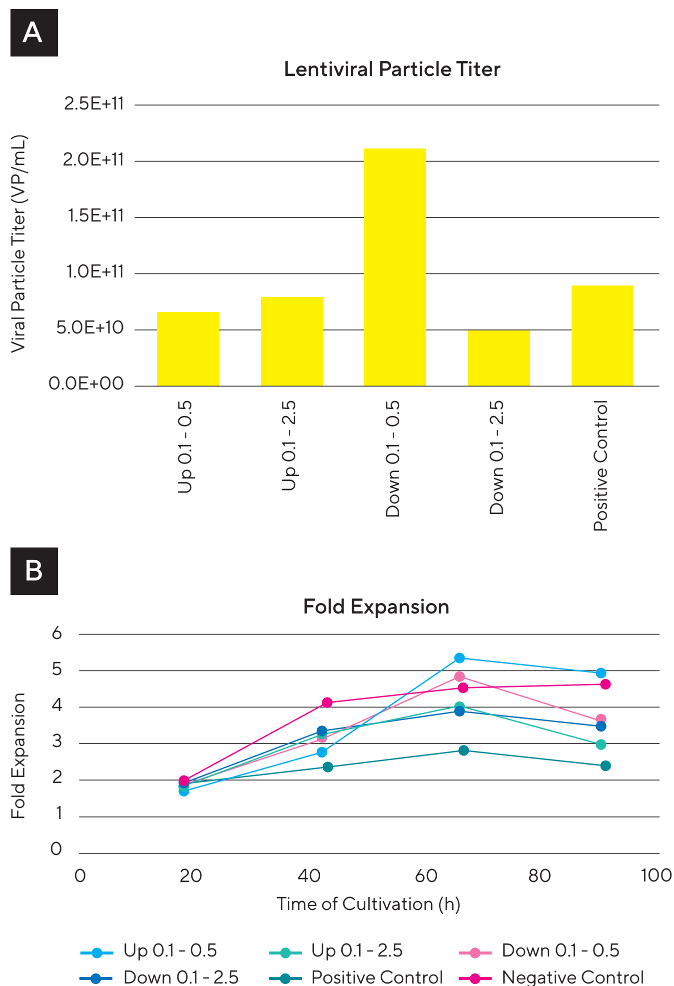
Process Parameters	Set points
Constant parameters	400 rpm; pH 7.1; 30% DO; 250 mL fill volume; 37°C culture temperature
Transfection conditions	0.5 µg DNA + 2 µl PEIpro® /10^6 cells; plasmid ratio: 5:2.5:1:1 (GOI:gag-pol:VSV-G:rev)

Vessel | Condition	Gas flow rates (air/mix) (mL/min)	Stir direction
1	0.1-0.5	Up
2	0.1-2.5	Up
3	0.1-0.5	Down
4	0.1-2.5	Down
All:	CO_2 and O_2 added flow: 0-5	

According to the results shown in Figure 4, the lentiviral particle titer was significantly higher in vessel/ condition 3 of the bioreactor system which corresponds to a maximum gas flow rate of 0.5 mL/min and a down stirring direction of the impellers.

In this vessel, a viral titer of 2.1 x 10^{11} VP/mL and a specific productivity of 1.3 x 10^{5} VP/cell was obtained which was higher than the titer obtained in the reference shake flask (8.9 x 10^{10} VP/mL and 3.7 x 10^{4} VP/cell).

Figure 4



Note. lentiviral particle titer (A) and fold expansions (B) of the HEK293T/17 SF cells obtained in an upscaling experiment to optimize the gas flow rate and stir direction with the Ambr® 250 Modular.

The highest viral titer was obtained with the lowest gas flow rate and we could prove that the gas flow rate and the stir direction have a significant effect on the lentiviral particle titer, indicating a negative effect of high gas flow rates on the lentiviral titer.

The differences caused by the varying flow rates and stir directions can also be seen in the differences between the fold expansions of the cells in the course of the lentivirus production. Even though the viral particle titer was very high in vessel 3, we also observed a good growth rate of the cells in this bioreactor. In general, the cells cultured in vessel 1 and 3 showed a better growth profile than vessels 2 and 4, indicating that the gas flow rate has a major impact on cell growth and viability.

In this experiment we were able to show not only that the optimized lentiviral vector production protocol is scalable to larger bioreactor volumes, but also that the gas flow rate has a significant effect on the lentiviral titer. With the most optimal condition, we were able to obtain a lentiviral particle titer of 2.1 x 10^{11} VP/mL and a specific productivity of 1.3 x 10^{5} VP/cell in Ambr® 250 Modular which was consistent with the optimized LV production in Ambr® 15 (2.1 x 10^{11} VP/mL and 1.3 x 10^{5} VP/cell).

These results show that the production of lentiviral vectors can be directly scalable from the Ambr® 15 microbioreactor system to a larger stirred bioreactor system without loss in yield.

Upscaling lentivirus production process to the bench-scale bioreactor Univessel® SU 2L

We aimed to prove that further upscaling of lentivirus production to larger volume stirred bioreactor systems is feasible. To this end, we scaled up the previously established lentivirus production process to the single-use Univessel® benchtop bioreactor with a volume of 2 L as this system can be used for process robustness testing and material generation for DSP studies.

The culture parameter set points used for this experiment are listed in Table 4 and transfection conditions were the same as in the previous experiment. The scaling of the stir speed was calculated based on a constant optimal tip speed identified with the Ambr® 250 Modular, according to a method described by Ruhl et al. [9].

Table 4

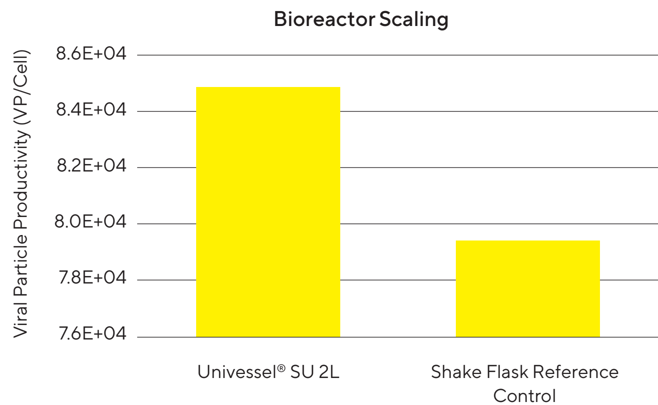
Conditions Used for LVV Production with Univessel® SU 2L

Parameter	Set point
Stir speed (rpm)	190
pH	7.1
DO (%)	30
Temperature (°C)	37

Through this experiment, we showed that the lentivirus productivity of the bioreactor culture was higher than the shake flask culture (8.5×10^4 vs. 7.9×10^4 VP/cell, Figure 5).

Figure 5

Lentiviral Particle Specific Productivity of the HEK293T/17 SF Cells Obtained in an Upscaling Experiment with the Univessel® SU 2L



When comparing the lentiviral particle titer of the lentivirus production in the Univessel® SU 2L (1.2×10^{11} VP/mL) with the particle titer obtained in the other bioreactors used in this study (2.1×10^{11} VP/mL), it can be observed that the yield in the Univessel® was lower than in Ambr® bioreactors, however, virus productivity was higher in all used bioreactors compared to the respective standard shake flask. This indicates the advantages of process control for viral vector production. Further optimization can be performed at a 2 L scale as only one culture run was evaluated here.

Conclusion

This study demonstrates that the Ambr® 15 microbioreactor system in combination with the DOE software MODDE® enables a systematic investigation of critical process parameters and rapid, high throughput process optimization in reduced time.

We could show that not only the optimization of cultivation parameters but also of the transfection process itself led to a significant improvement in lentiviral titer.

The outcome of such a study will help manufacturers to gain important knowledge on which parameters need to be controlled in order to set up a robust and predictable lentivirus production process. It is important to note that the type of cell line, and especially the quality of the plasmids have a significant effect on the viral yield. For the study presented here, the source of the cell line and plasmids had been evaluated beforehand.

The results prove that the transition from shake flask to a scalable stirred bioreactor system can be accomplished very fast, yielding superior lentiviral titers.

The main benefits from transitioning from a shake flask to the Ambr® 15 system are:

- the system is scalable, and has the ability to screen many conditions in, facilitating especially DOE studies
- process parameters including pH, DO and CO_2 are controlled

Furthermore, upscaling was proven to be efficient and simple using the Ambr® 250 Modular, which also allows for rapid optimization of process parameters. Results in the Ambr® 15 correlated well with those obtained in he Ambr® 250 Modular and provided a good basis for further scale-up to 2 L. The results presented provide a good basis for the scaling of the process for manufacturing scales up to 2000 L [8].

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Abbreviations

CAR	Chimeric Antigen Receptor
CPP	Critical Process Parameter
DO	Dissolved Oxygen
DOE	Design of Experiment
DSP	Downstream Processing
GMP	Good Manufacturing Practice
GOI	Gene of Interest
RPM	Revolutions Per Minute
STR	Stirred Tank Reactor
SU	Single-Use
TU	Transducing Units
VCC	Viable Cell Count
VP	Viral Particles

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