

# Just because you can, doesn't mean you should: Why higher upstream titer may not be best for your AAV process

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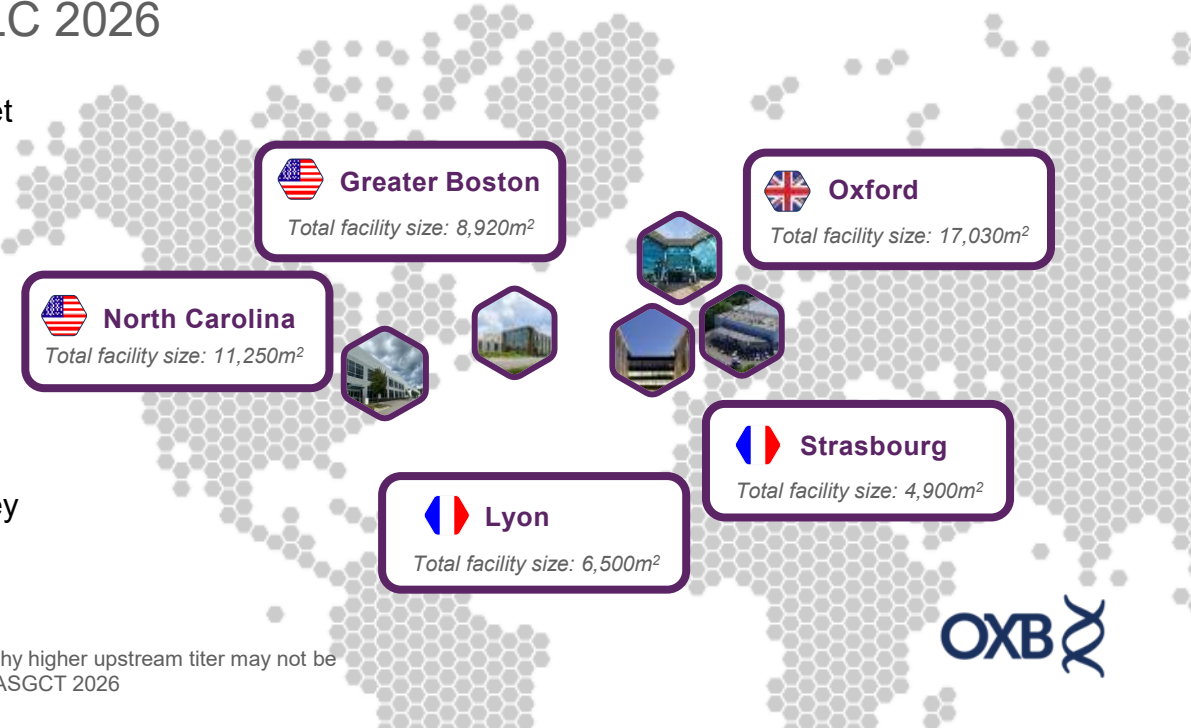


## Unique competitive positioning

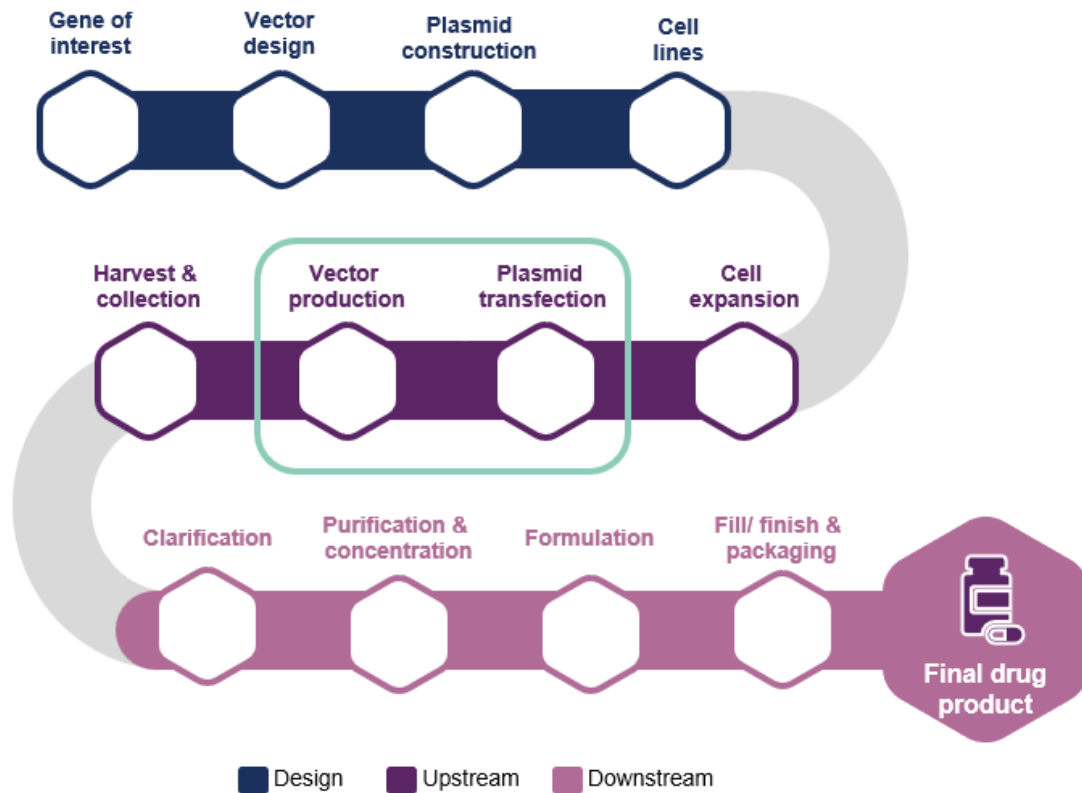
- ✓ **Best-in-class capabilities** across AAV, lentivirus & other vector types
- ✓ **Trusted by global industry leaders** – successful collaborations with big pharma, established biotech and emerging biotech
- ✓ **State-of-the-art facilities & scalable production capabilities** designed to meet the growing demand for C&GTs
- ✓ **Deep scientific know-how** – a team of world-leading specialists in viral vector optimisation
- ✓ **Cutting-edge technology** – leveraging 30 years of insights to enhance speed, efficacy, quality and safety in new therapies
- ✓ **Global reach & strategic positioning** with manufacturing facilities located in key biotech hubs

30+	~1,000	40+	45+	100+
Years of manufacturing experience	Successful GMP batches since 2014	Current client programmes	Regulatory submissions	Successful audits

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# Historical focus on highest upstream VG titers

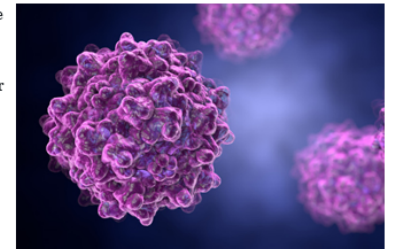


## Achieving rAAV Bioreactor Titer Of >1E15 vg/L With Novel Plasmid Transient Transfection Platform

Source: [Oxford Biomedica](#)

By Jin Yin, Oxford Biomedica Solutions

Recombinant adeno-associated virus (rAAV) vectors have become a popular gene therapy delivery platform due to their high safety profile, low immunogenicity, and capacity for transduction into different cell and tissue types. Furthermore, rAAV can be delivered through either intravenous injection (systemic delivery) or direct injection into the affected tissue (targeted delivery).



Transient transfection of plasmids into suspension HEK293 cells is the most common platform for producing rAAV, owing to its flexibility and speed in moving drug candidates into clinical trials. Despite this, its utility has been limited by its perceived low productivity and poor scalability when compared to other platforms (e.g., Baculovirus expression systems with insect sf9 cells, adenovirus-infected producer cell line systems, and Herpes simplex virus helper systems) [1]. Based on data from 136 ongoing clinical trials, 77% of systemically delivered rAAVs are dosed at  $1E14 - 1E16$  vector genomes (vg) or higher, whereas 59% of targeted delivered are dosed at  $1E12 - 1E14$  vg or higher [2]. The high level of rAAV dosage poses a major supply and cost challenge for manufacturers and gene therapy companies – in some cases of systemic delivery, one 200L bioreactor batch is insufficient to dose one patient.

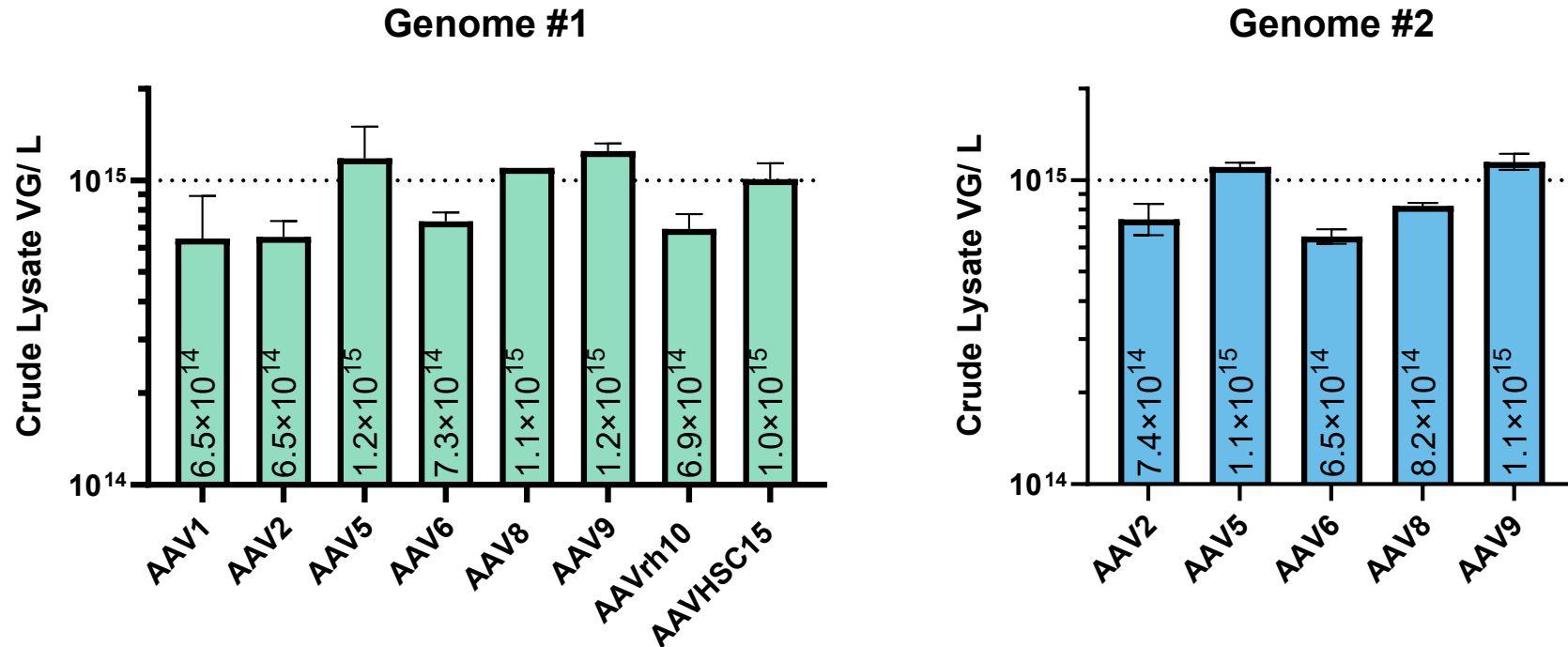


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# Historical upstream process yields >1E15 VG/ L

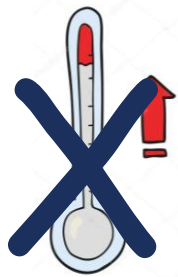
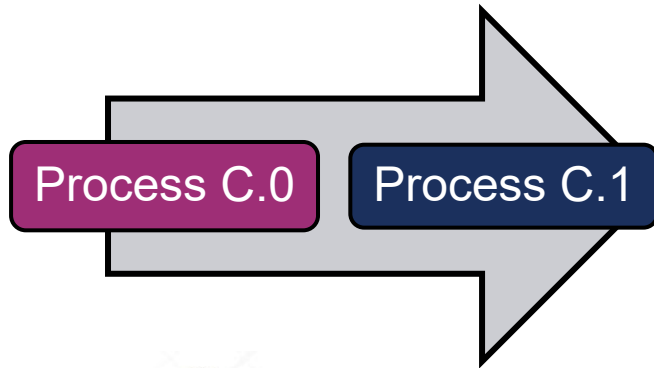
Process C.0 upstream crude lysate VG titers



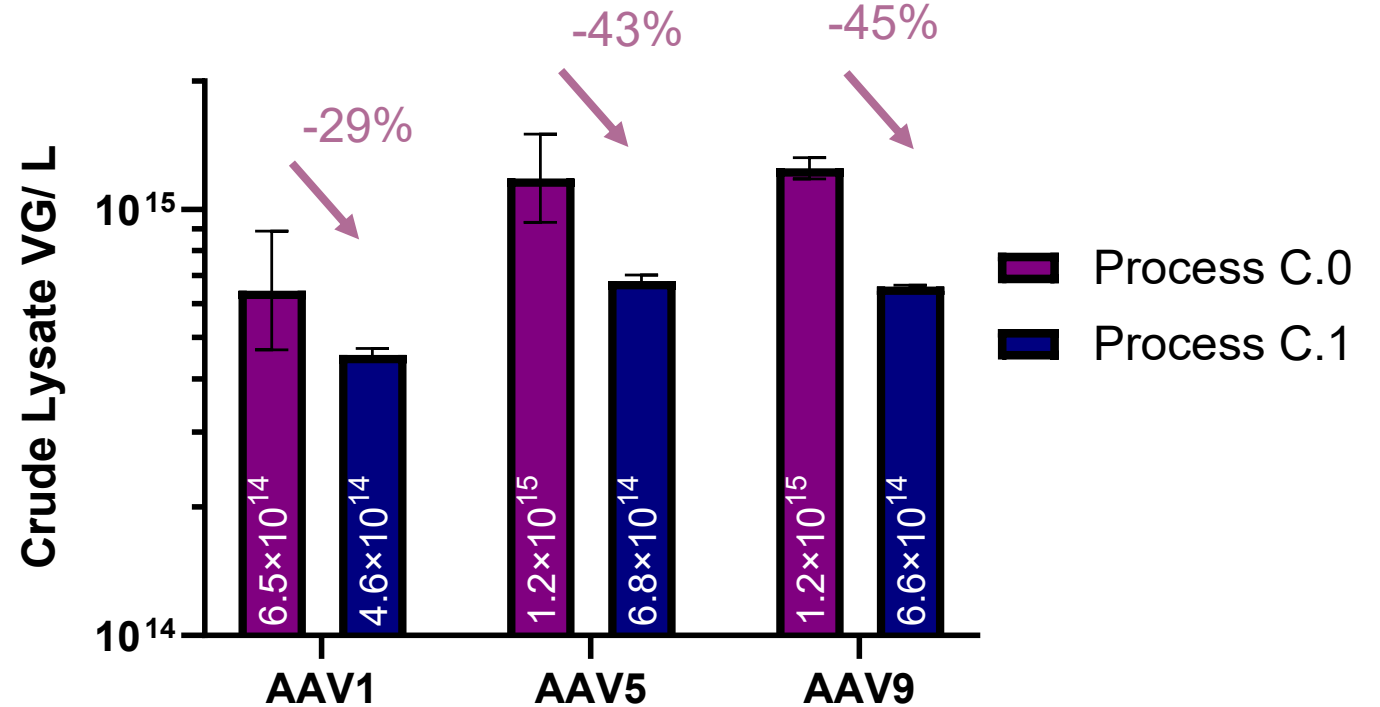
Our previous upstream process produced VG titers above 1E15 VG/L for AAV5 and AAV9 (clade F) capsids packaging two different recombinant genomes

# Upstream process changes reduces crude lysate titers

Why would this upstream loss be desirable?



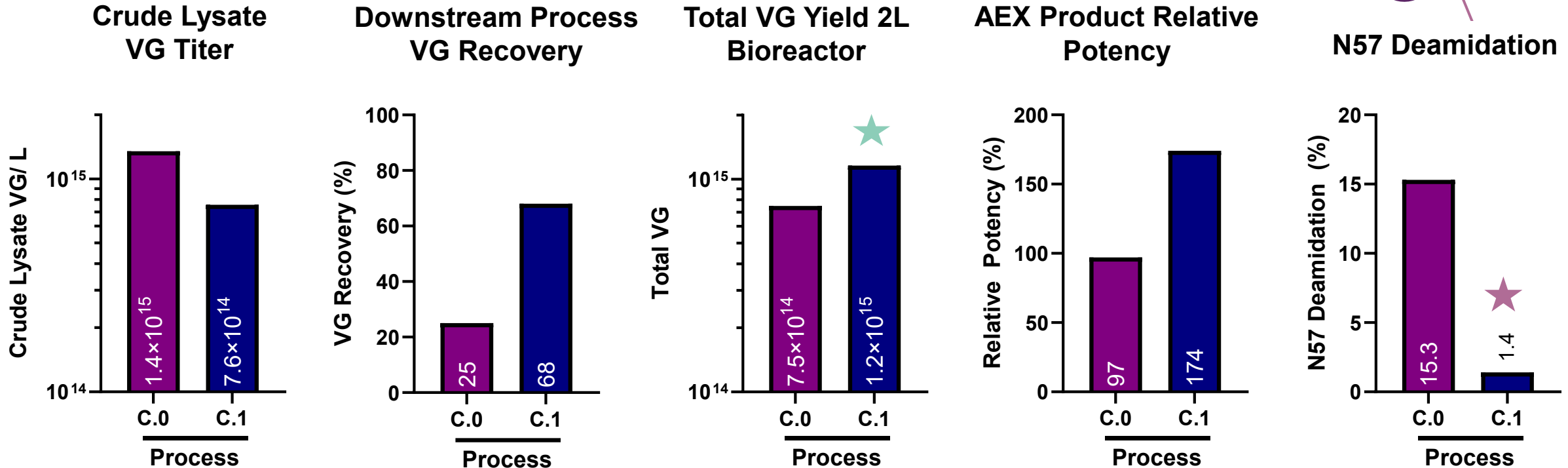
Eliminated a post-transfection temperature shift and shortened the production time between transfection and harvest



Transition from process C.0 to process C.1 resulted in ~40% reduction in crude lysate VG yields across serotypes

# Downstream recovery & product quality improves

Example: AAV9



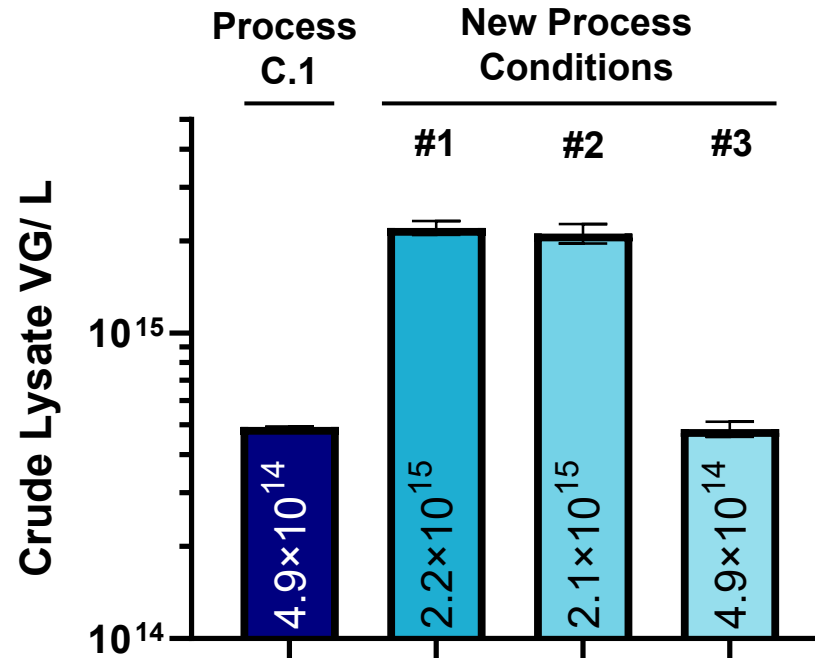
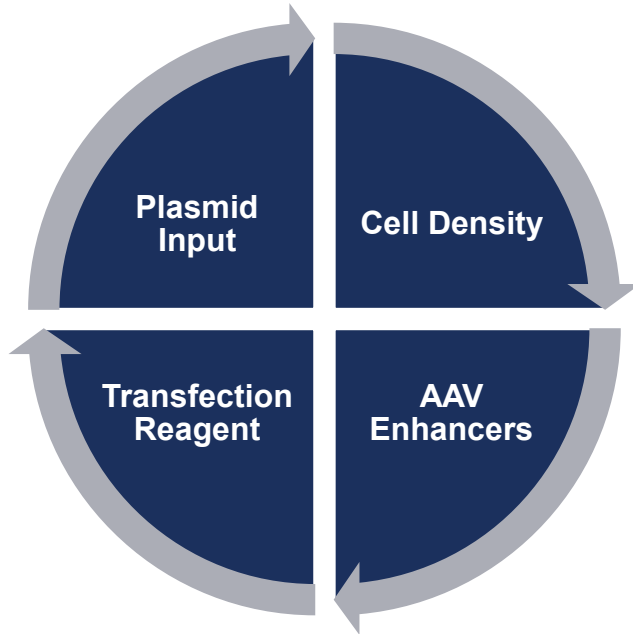
★ In process C.1, upstream VG titer produces >40% loss but downstream recovery greatly improves and total VG recovery from a 2L bioreactor almost doubles compared to process C.0

★ Vector produced with process C.1 is more potent and contains less deamidated capsids, which is correlated with improved downstream recovery

# Decreasing process costs by reducing plasmid usage

Updating critical upstream process parameters can improve VG titer >4X

## Critical Upstream Process Parameters



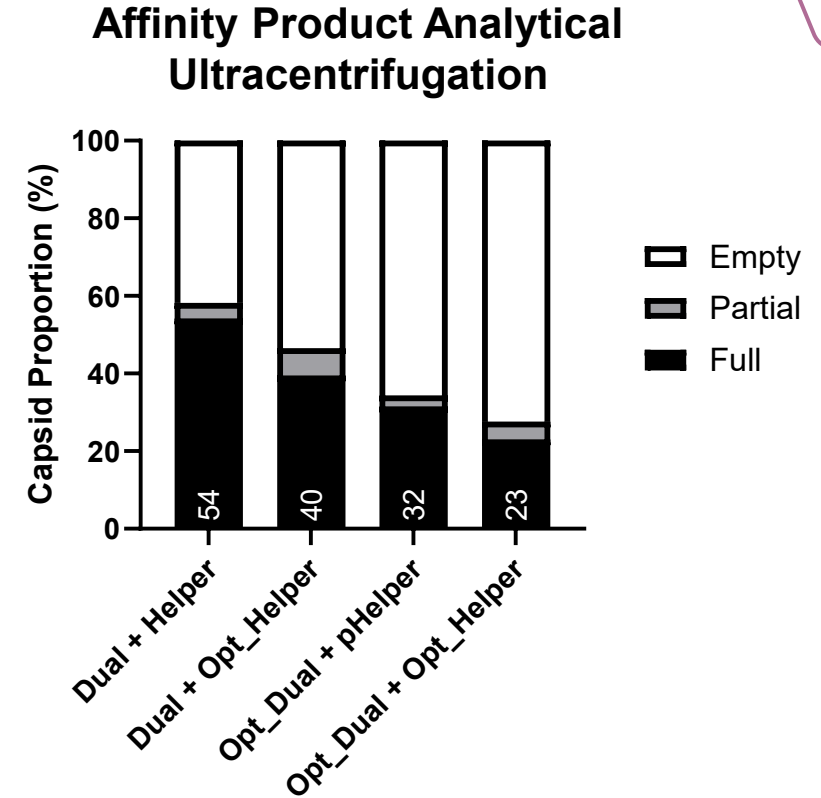
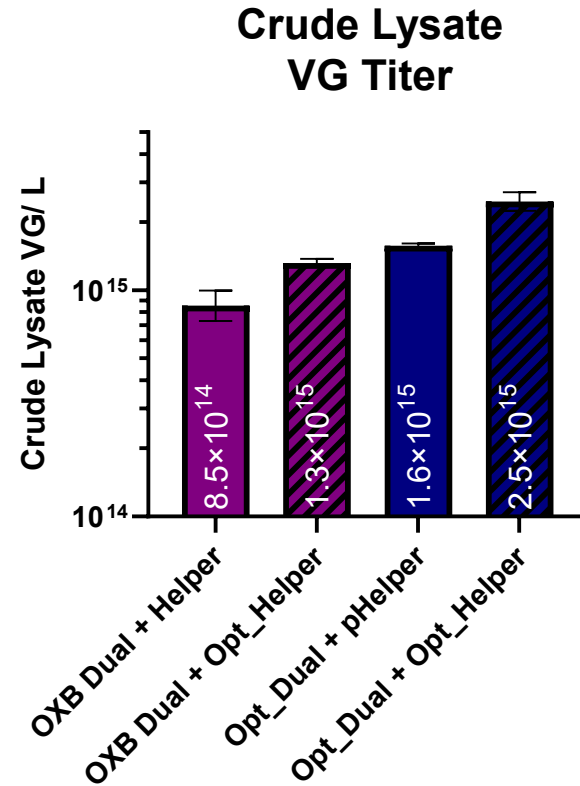
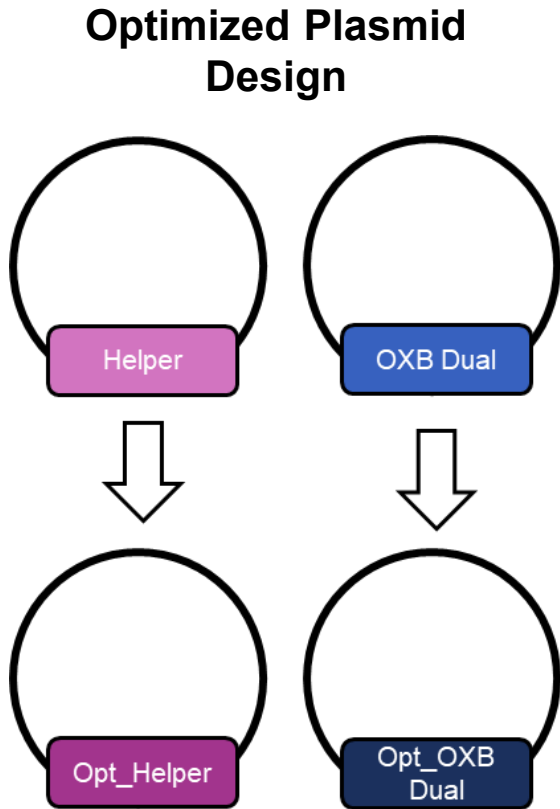
Similar upstream process performance can be achieved using 2/3 less plasmid DNA, driving upstream costs down relative to process C.1

Alternatively, 4X VG titer increases can be achieved for relatively similar costs to process C.1 through changes in critical upstream process parameters

Normalized Plasmid Input (%)	100	66.6	66.6	33.3
Normalized PD Upstream Process Cost (%)	100	107	96	74

# Plasmid design is a major driver of upstream titer

Balance upstream VG productivity with the quality of packaged vectors

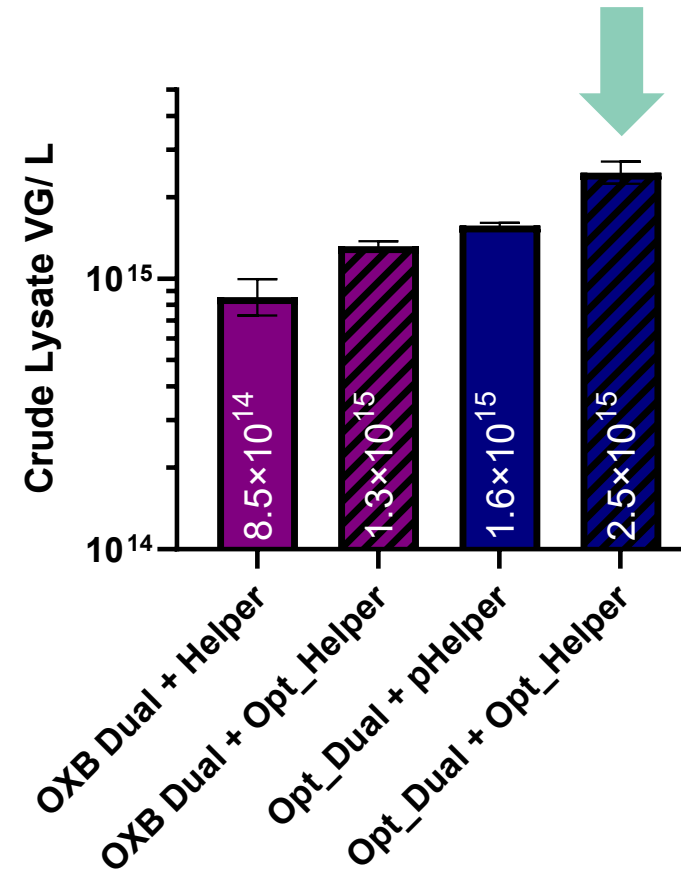
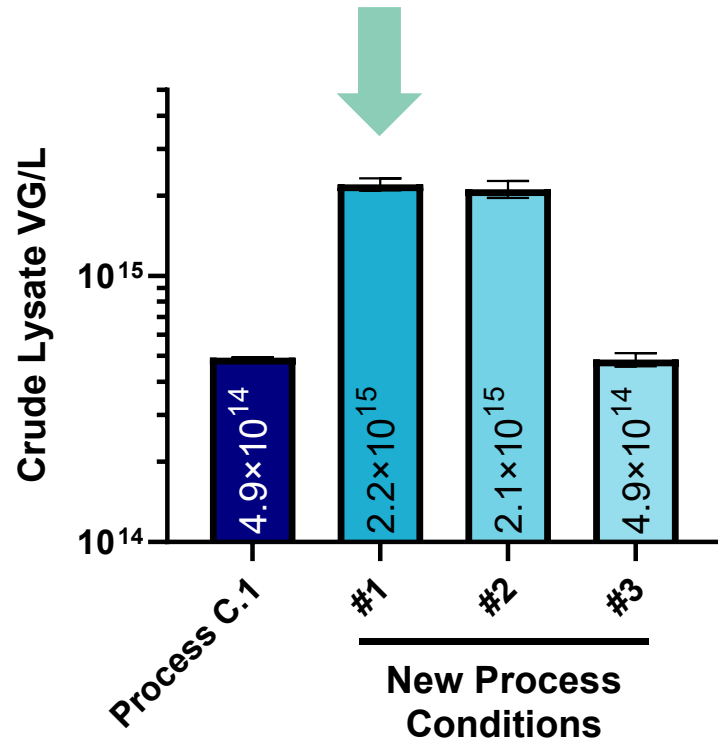


Optimized plasmids increase crude lysate VG titer almost 3X

Increased upstream crude lysate titer is correlated with declining full capsids present post affinity chromatography purification

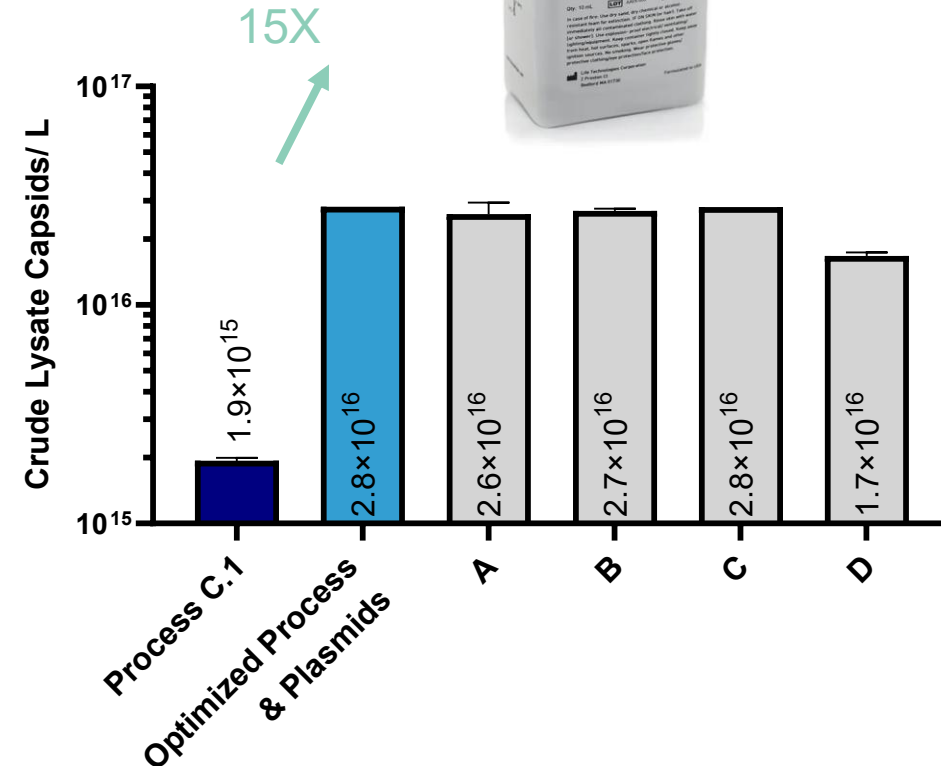
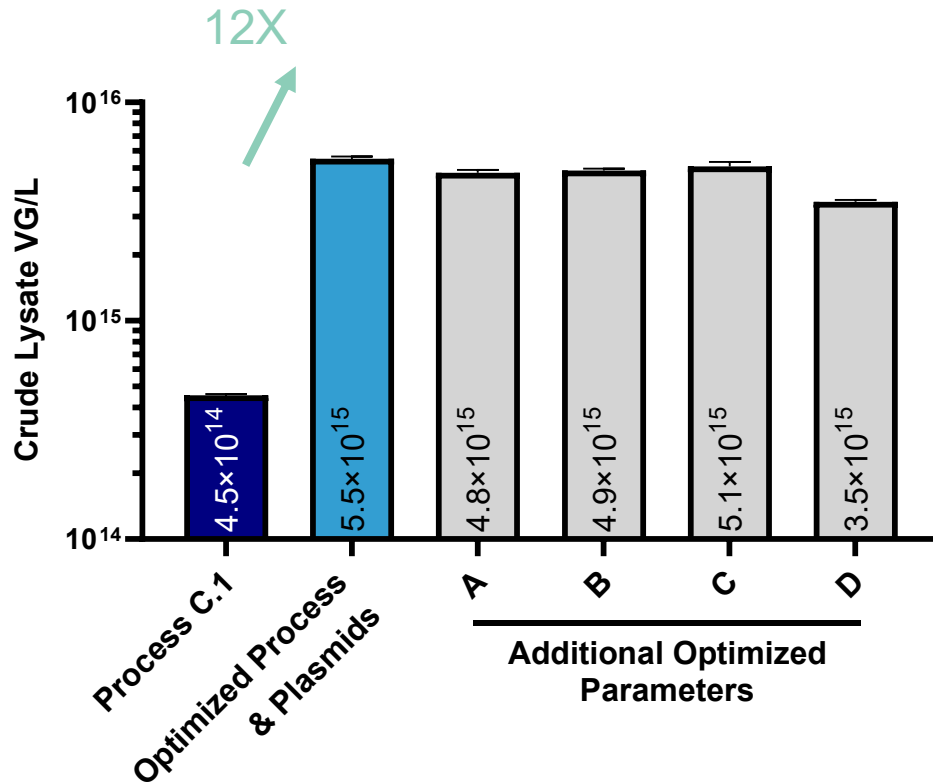
# Combining updated upstream process parameters with optimized plasmid designs

Are these upstream improvements both additive?



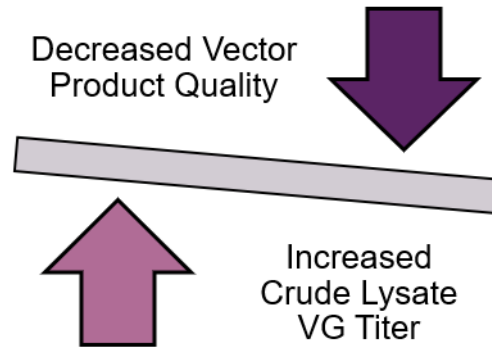
# New upstream process parameters & optimized plasmids combined yields >5E15 VG/L

Capsid burden for affinity purification also increases



Crude lysate titers 12X higher than process C.1 are achievable however capsid production also increases significantly, increasing the downstream purification costs overall

# Summary



**At OXB, we have learned that chasing the highest upstream titers is not always what is optimal for the overall AAV process**

- We aim to strike a balance between maximizing vector yield while prioritizing the highest product quality all while keeping cost in mind to ensure we provide the best overall process to our clients and their patients

# Acknowledgement

Thank you

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