Integration of Biology and Engineering to Enable Industrialization of Complex Biotherapeutics

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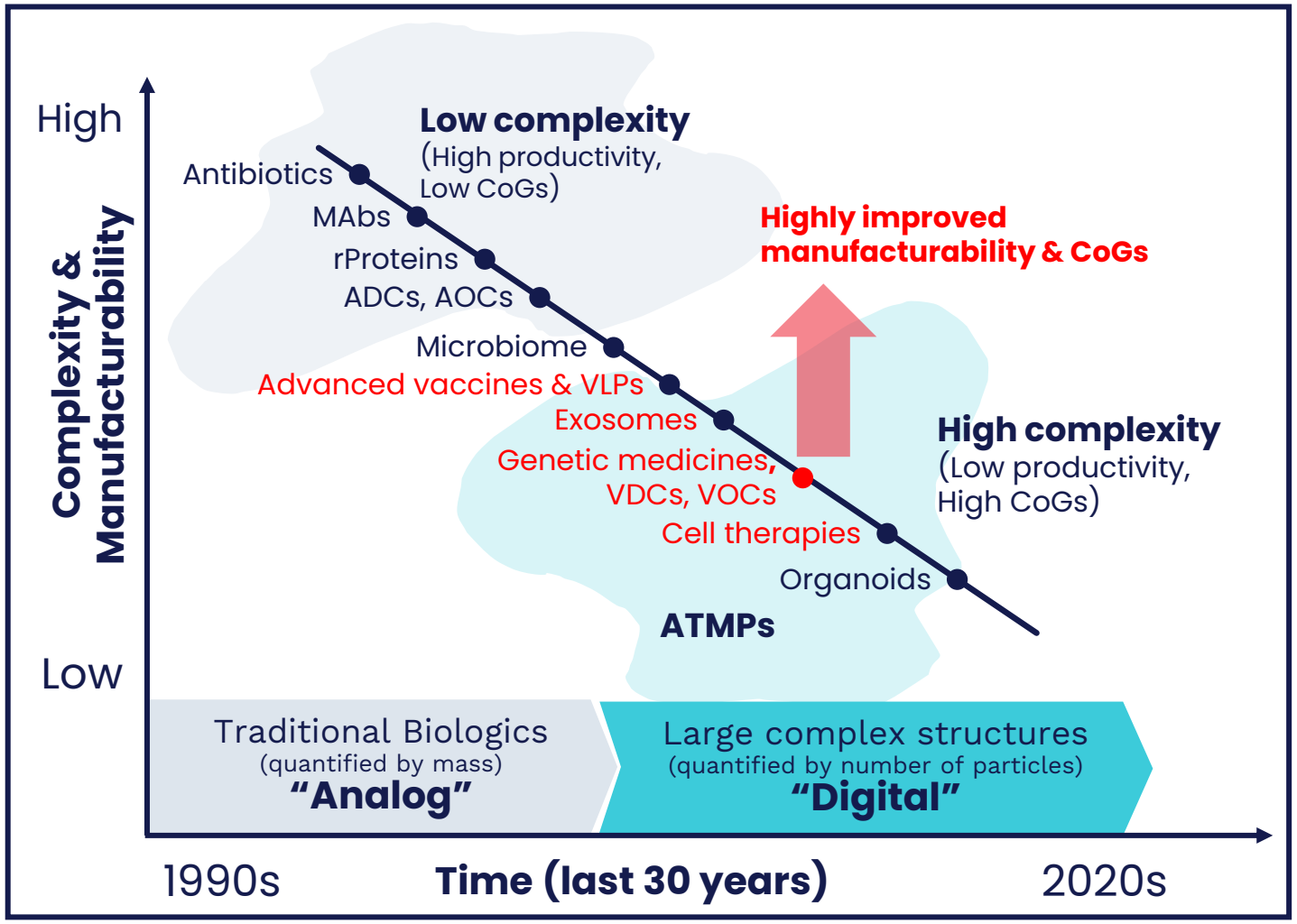
Agenda

- **Complex modalities (bio-nanoparticles) have tremendous clinical potential but are sharply constrained by poor manufacturability**
- **Creative new solutions are required**
  - Case 1: Targeted protein cages carrying different payloads
  - Case 2: Continuous large-scale manufacturing of exosomes

Key messages

1. Product design is a key enabler of industrialization
2. Modular product structure + downstream assembly = high manufacturability
3. DSP is evolving from "purification only" to "assembly line + purification"
4. Continuous manufacturing can play a major role in producing complex modalities
5. Continuous manufacturing requires a high maturity level across process elements

Growing Complexity of New Modalities Reduces Manufacturability: Low Productivity & High CoGs



What do we need?

- Significantly reduced product/process complexity (to the level of traditional biologics)
- Dramatically improved manufacturability, productivity, low CoGs (≥100X)
- Low risk for commercial failure after BLA clinical approval

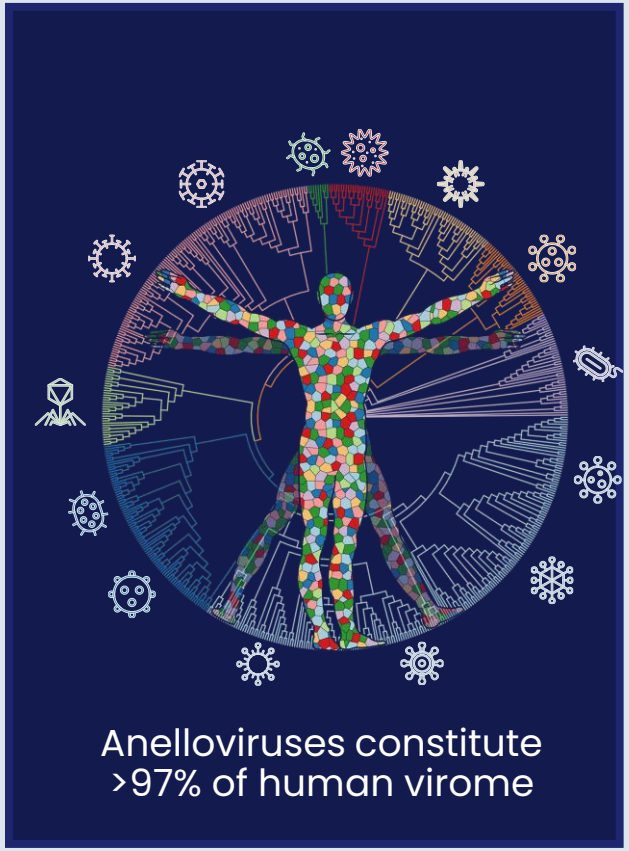
Product structure/characteristics are key enabler to efficient large-scale manufacturing

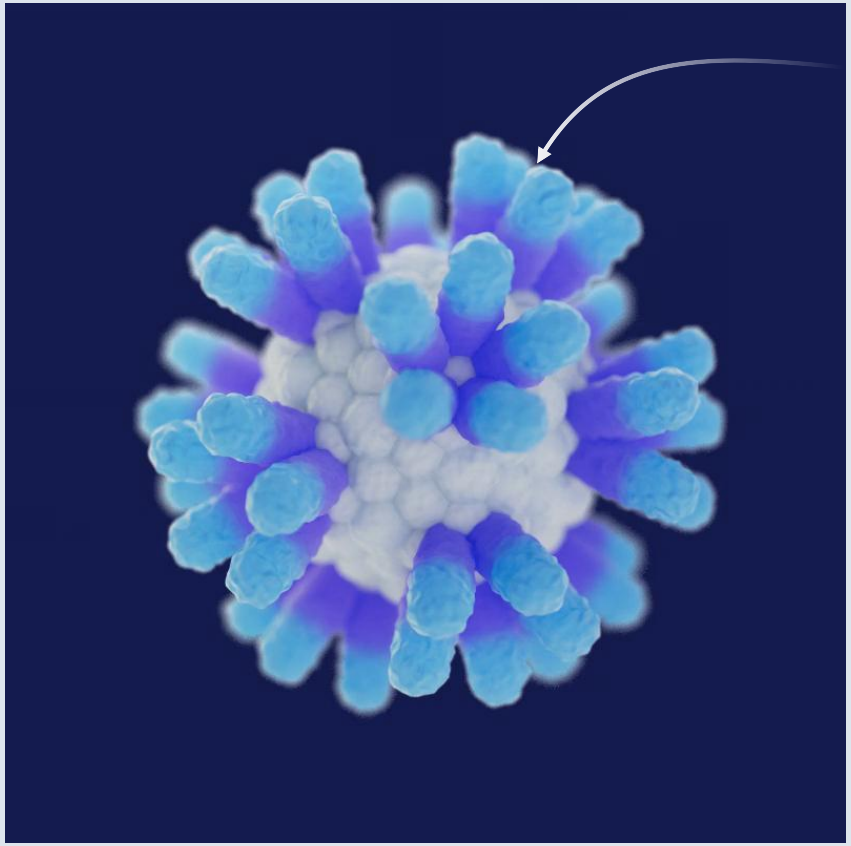
Case 1: High-productivity manufacturing of nanotherapeutics based on modular product design and DSP assembly

WHAT IF...

Is the Ideal Vector Already Inside Us?

Creating the first & only new class of viral vector in 50 years





AnelloVector

Unprecedented diversity, ubiquitous biodistribution, natural immune evasion

- **Broad tissue and cellular tropism**
  Natural tropism can be augmented by capsid protein engineering
- **Potential for redosability**
  Other non-integrating viral vectors are not redosable
- **Programmable payload versatility**
  Oligos, small molecules, cssDNA. Other viral vectors limited to native cargo
- **Naturally non-pathogenic**
  Innate human virus

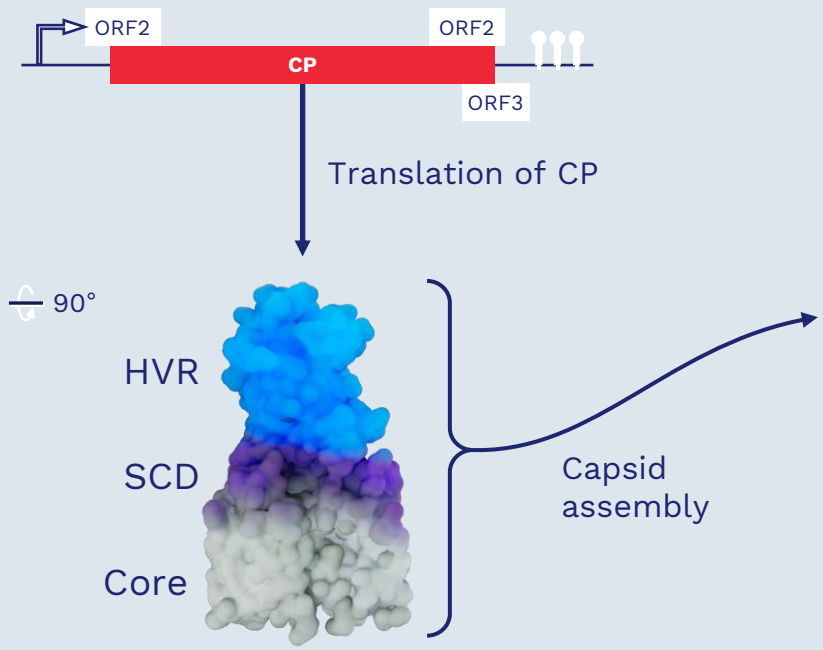
Mfg process: ***Modular assembly technology*** enables high productivity & novel payloads

Capsid Protein (CP) Engineering and Expression Enable High Productivity At Scale

AnelloBricks: Ring's new high-productivity manufacturing platform

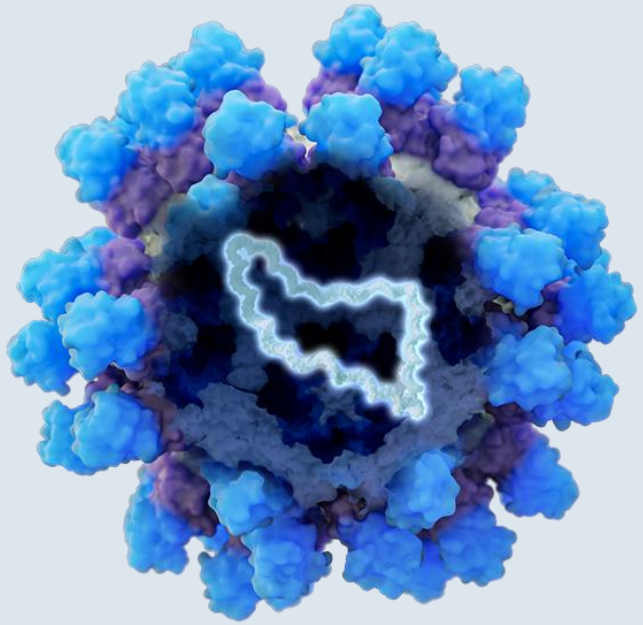
Capsid defines key properties

Simple structure - single CP



In vitro assembly platform enabling payload versatility

>5,000 CP sequence library available for assembly



AnelloVectors

- Can control whether particles are empty or not
- Potential to package different payloads

Treatments for patients

- Potential for redosability
- Tissue and cellular tropism
- Payload versatility
- Potency

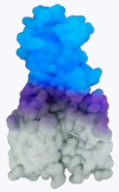
Abbreviations: HVR - hypervariable region; SCD - semi-conserved domain

Modularity Enables Unprecedented Platform Versatility

Assembled structures can target a broad variety of clinical indications

Three modules define the structure & functionality of the Drug Product

Capsid proteins (in a pentamer form)



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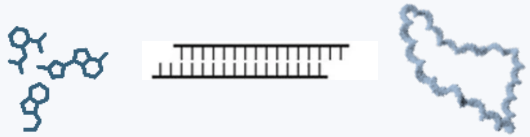
Payloads (single or multi)



Small molecules | Oligos (siRNA, ASO) | cssDNA (native)

+

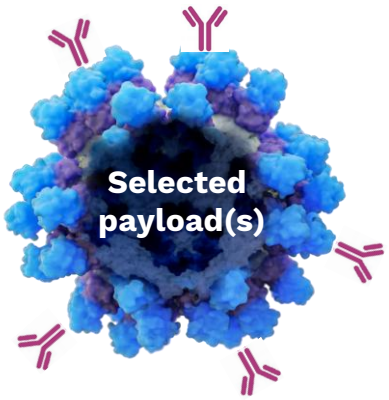
Affinity ligands (targeting)

Mabs

Others (+/- integrated)

Selected modular components from three libraries

High DAR compared to ADC and AOC



Drug Product

- **Vector Drug Conjugates (VDCs)**
- **Vector Oligo Conjugates (VOCs)**
- **Gene Therapy**
- **Combination payloads**

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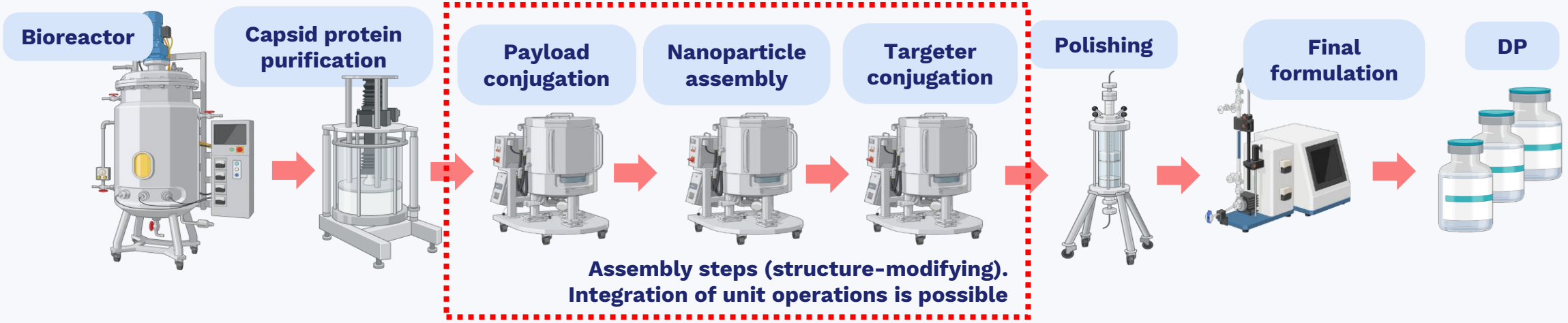
Modular Product Structure Enables High-Performance Manufacturing

The complex problem is solved by breaking it down into simpler, manageable parts

Streamlined process flow



Downstream processing (DSP) new role: from *DSP = Purification* to *DSP = Assembly line + Purification*

- Given the favorable stoichiometry (1g CP = 1.4e17 capsids), a single large-scale campaign (500-2kL) has the potential of producing an unparalleled amount of loaded particles
- Standard off-the-shelf equipment and scalable unit operations
- Clear path to intensification and industrialization

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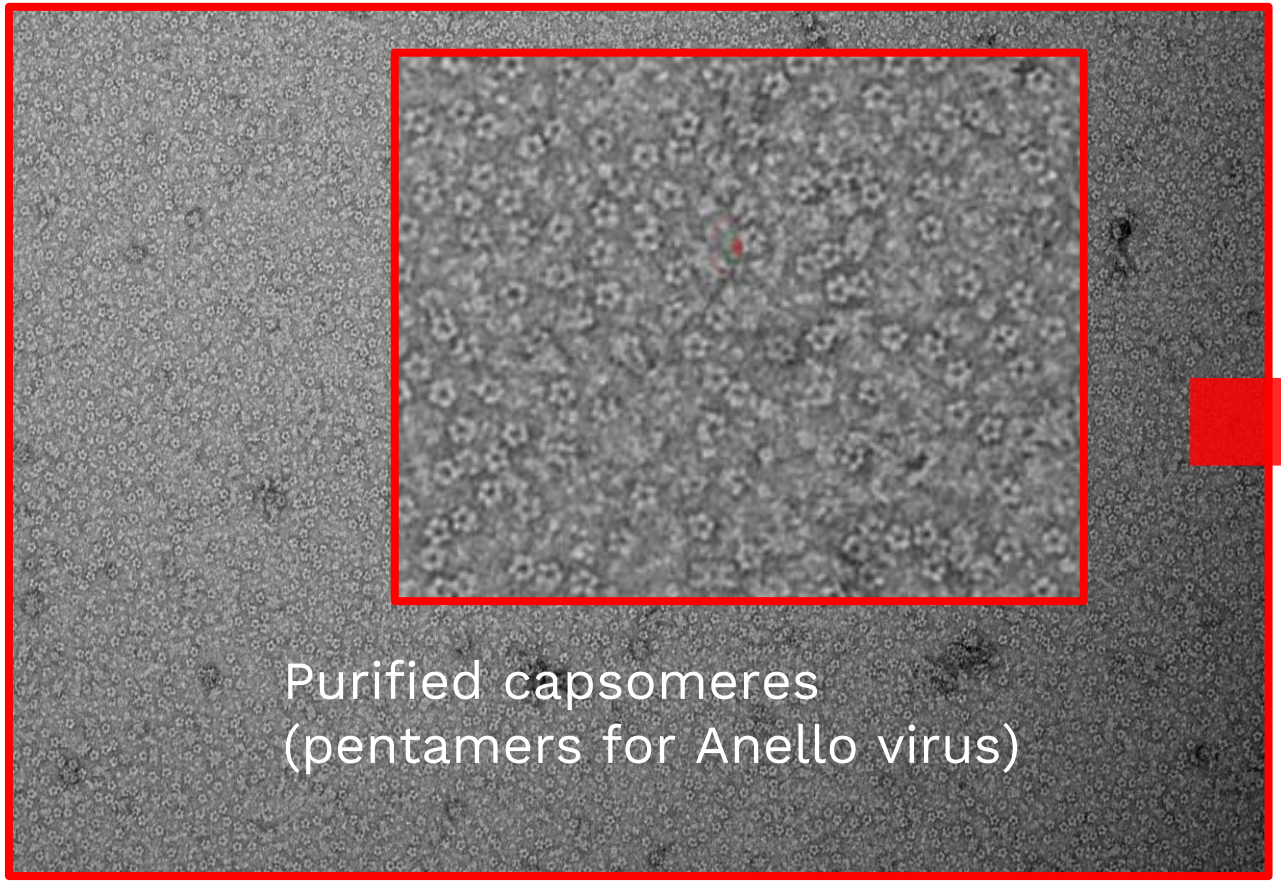
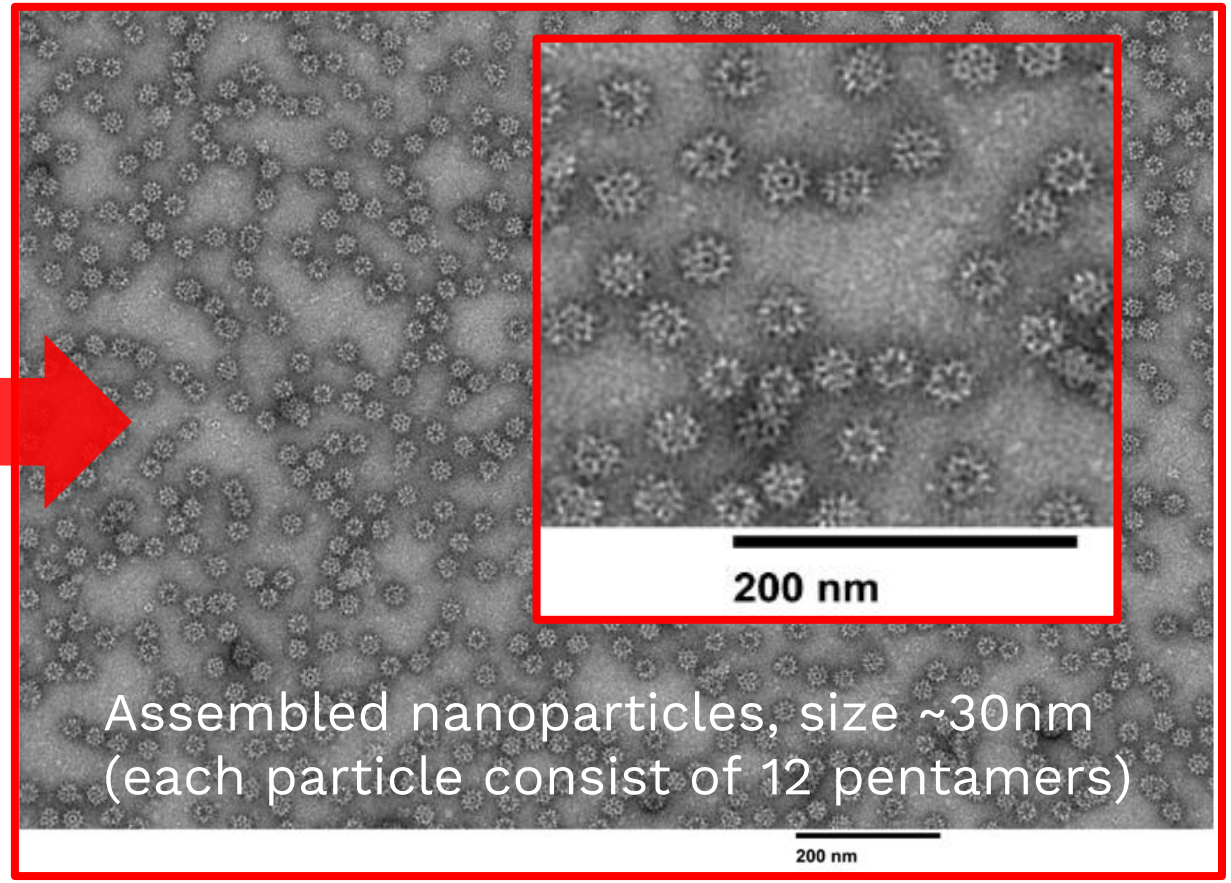
Electron Microscope Images of Process Intermediates Before and After the Nanoparticle Assembly Step





Assembly quality and yield was dramatically improved through Capsid Protein engineering and process optimization

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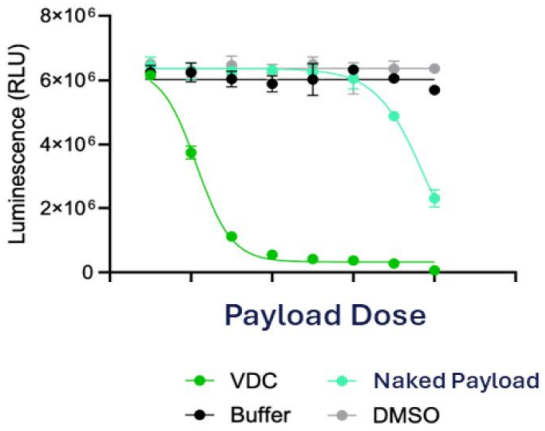
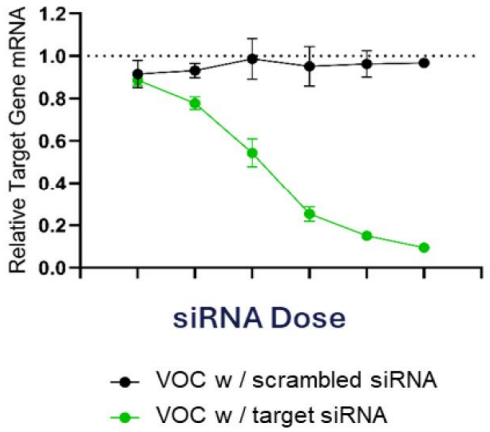
Ring's Vectors Deliver Diverse Payloads

Examples with small molecules, oligos, DNA

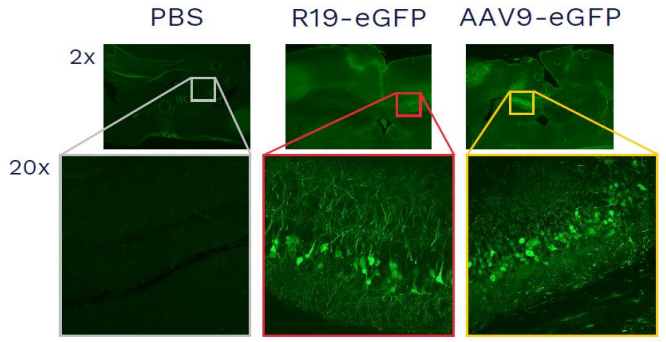
VDCs
(Small Molecules)



VOCs
(siRNA)

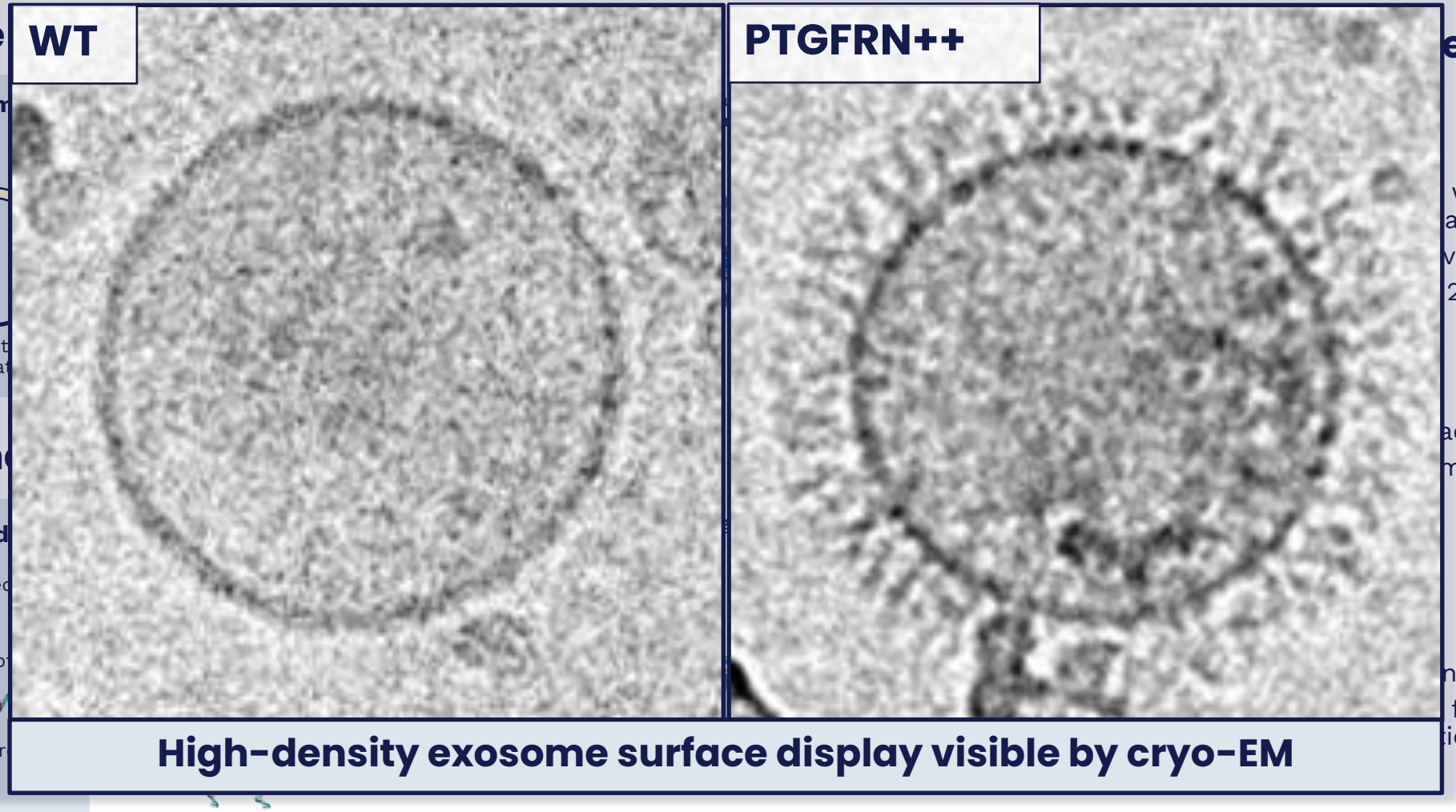


Gene Therapy
(DNA)

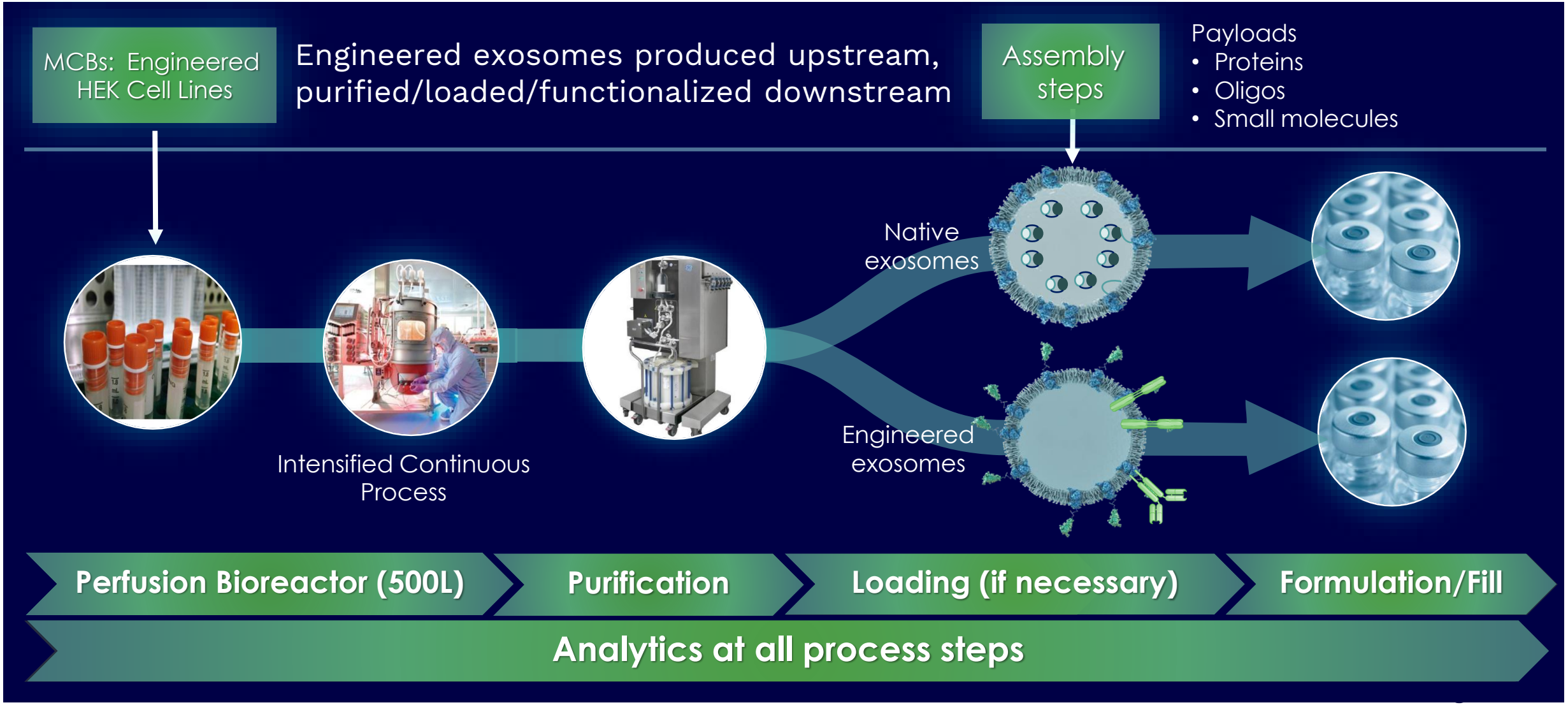


Case 2:

Advanced Product Engineering for Large-scale Continuous Manufacturing of Exosome-based Therapeutics

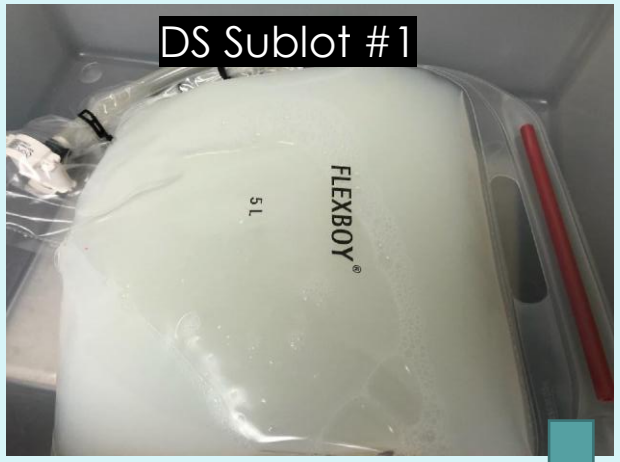


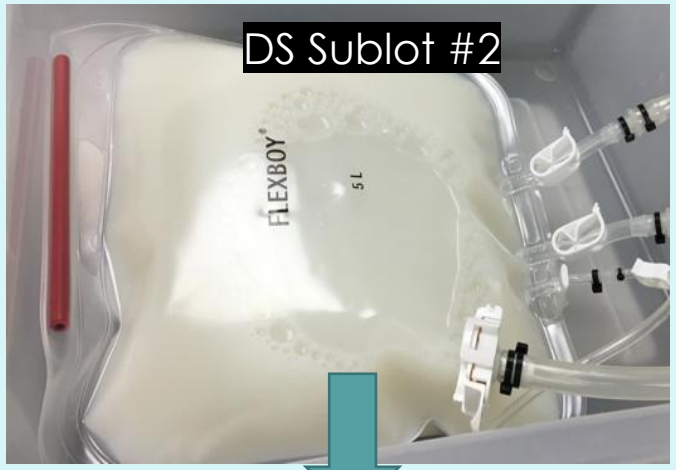
Well-Designed Product Structure Enabled Advanced Large-Scale Continuous Manufacturing of Exosome Therapeutics

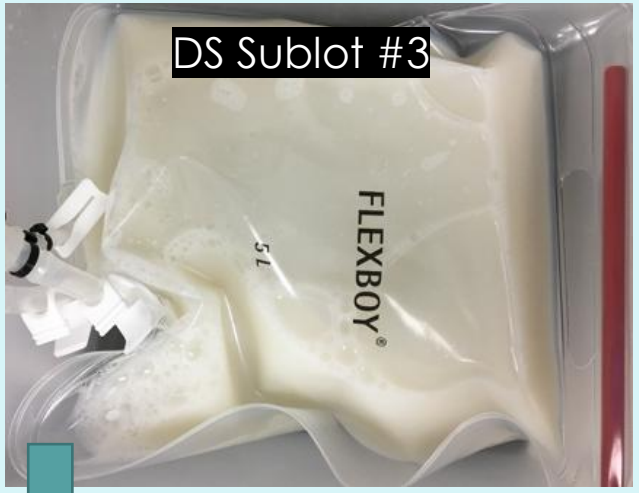


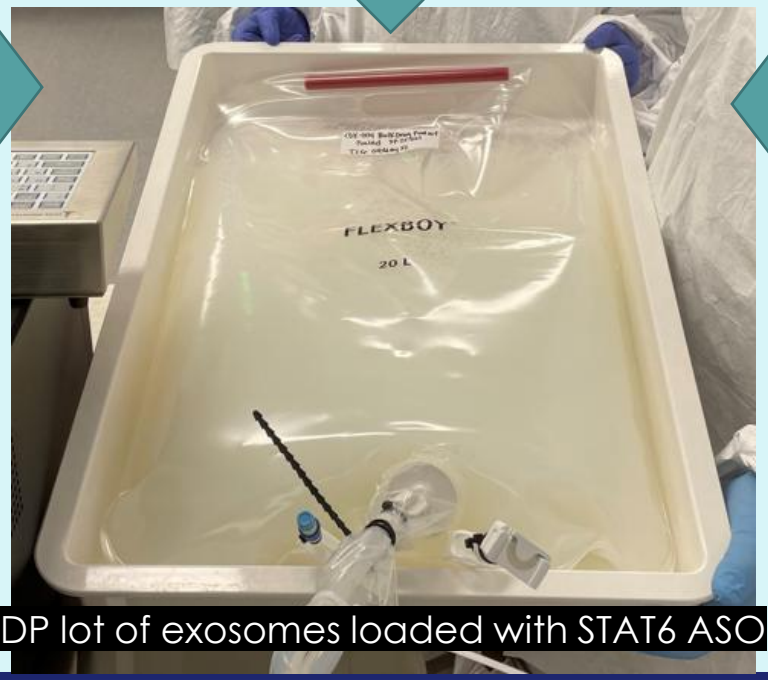
Exosomes: Large Scale (500L) GMP Manufacturing

DS & DP sublots of engineered exosomes from a single perfusion run









DP lot of exosomes loaded with STAT6 ASO

- **Three DS sublots in 5L sterile Flexboy bags**
- **DP lot in a 20L sterile Flexboy bag**

- **Run yielded e17–18 highly purified exosomes**
- **Significant upward potential**

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