



*Process development for GMP
production of LV genetically
modified primary cells*

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Cell Process Development Manager*

GENE AND CELL THERAPY

June 23th, 2020

Leading the way in Cell & Gene therapy



Disclaimer

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Agenda

1. *Company Overview*
2. *How to achieve efficient transduction of HSCs*
3. *Process development and large-scale production of autologous LV CAR-T cells*



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MolMed is a pure player in the Cell&Gene arena



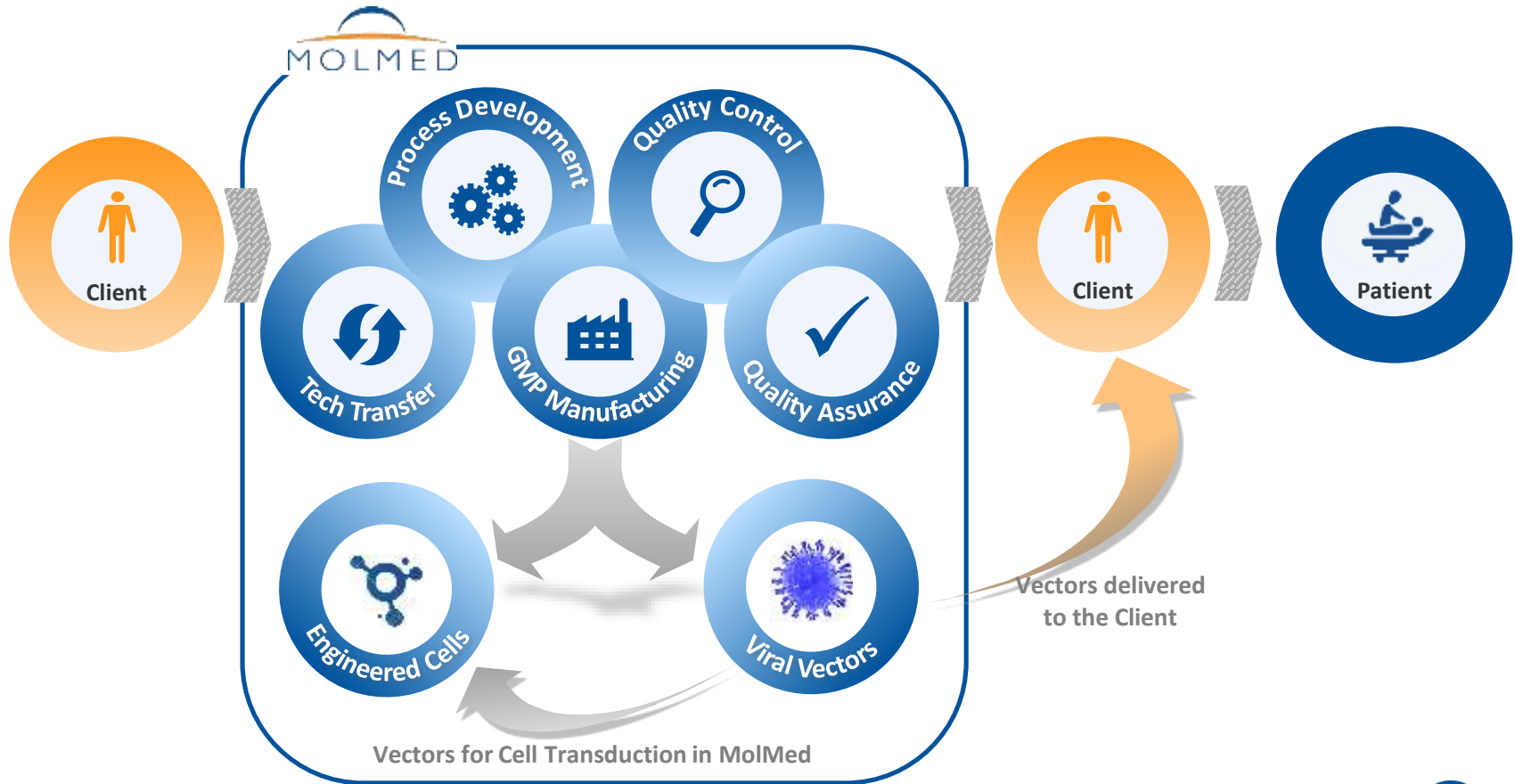
Focusing on **innovative cell and gene therapies** that can meet the therapeutic needs in the treatment of **tumors and rare diseases**, with a clear and solid industrial project based on **research, development** and **production excellence**



CDMO Business, with 35+ Programs developed with our Partners

R&D Business on our Autologous Product CAR-T CD44v6

CDMO business experience in manufacturing of vector and modified cells



Current manufacturing platforms

Viral Vector Manufacturing

Development/Feasibility

Tech transfer/Engineering

GMP manufacturing

LV/RV 48L Cell Factories – adhesion

LV/RV 200L bioreactor - adhesion

Cell Engineering

Development/Feasibility

Tech transfer/Engineering

GMP manufacturing

LV/RV T-Cell Transduction

LV CD34+ Cell Transduction

Excellent GMP capacity with more than 230 scientists and support staff

Milan Site (San Raffaele)

- **1,500 SQM** (16,000 SQF) and **6 grade B/C suites**
- **2003:** Authorized GMP manufacturing facility for **Clinical programs**
- **2015:** Authorized GMP manufacturing facility for **Commercial products**

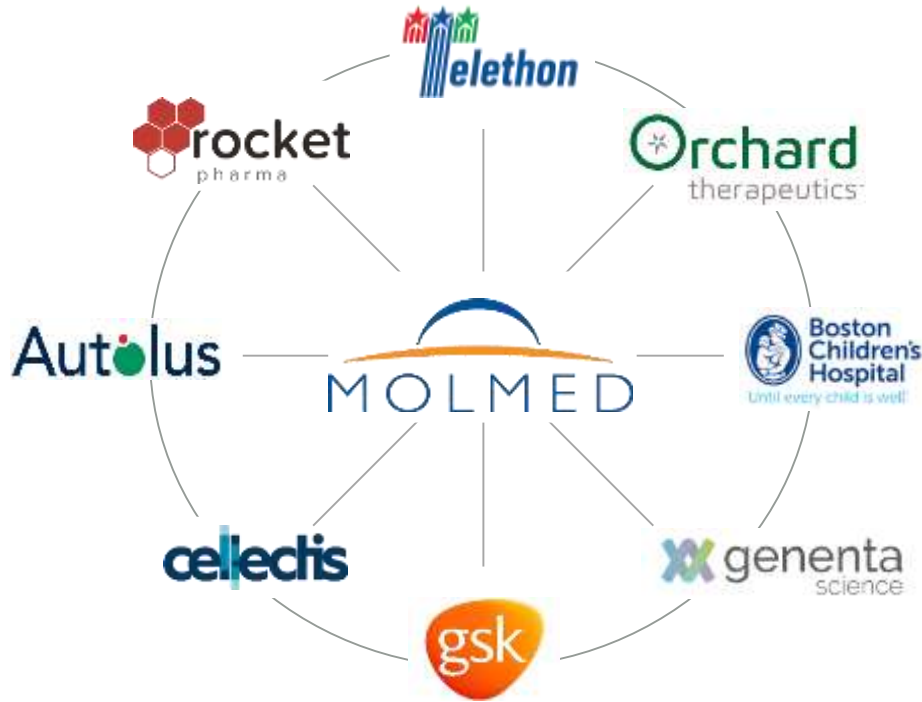


Bresso Site



- **3,300 SQM** (36,000 SQF) and **>20 Grade B/C suites**
- Authorized for **GMP manufacturing** and **QC** for the production of **clinical** and **commercial** products
- **Recently authorized Stream#2**, for further services and new collaborations

Development and manufacturing partners in EU and US geographies



35+ Programs currently in Development and GMP

2 Commercial Cell-Engineered Products in EU

2 Commercial Viral Vectors in EU

15+ Cell-Engineering programs for EU&US

20+ Viral Vectors programs for EU&US

Track Record

300+ Treated Patients (autologous)

220+ Manufactured GMP Vectors

30+ C&G Clinical Trials Supplied in EU&US

8+ International Service Partners

Strenghts of MolMed CDMO

High **GMP manufacturing Capacity** thanks to new facility in Milan area

25yrs **Experience** in proprietary projects now available for CDMO collaborations

Recognized **Flexibility** in accommodating Partners' requests



160 QC tests
internalized, ensuring
reduction in time and cost

Ready **Proprietary Processes** for vectors
and cells engineering

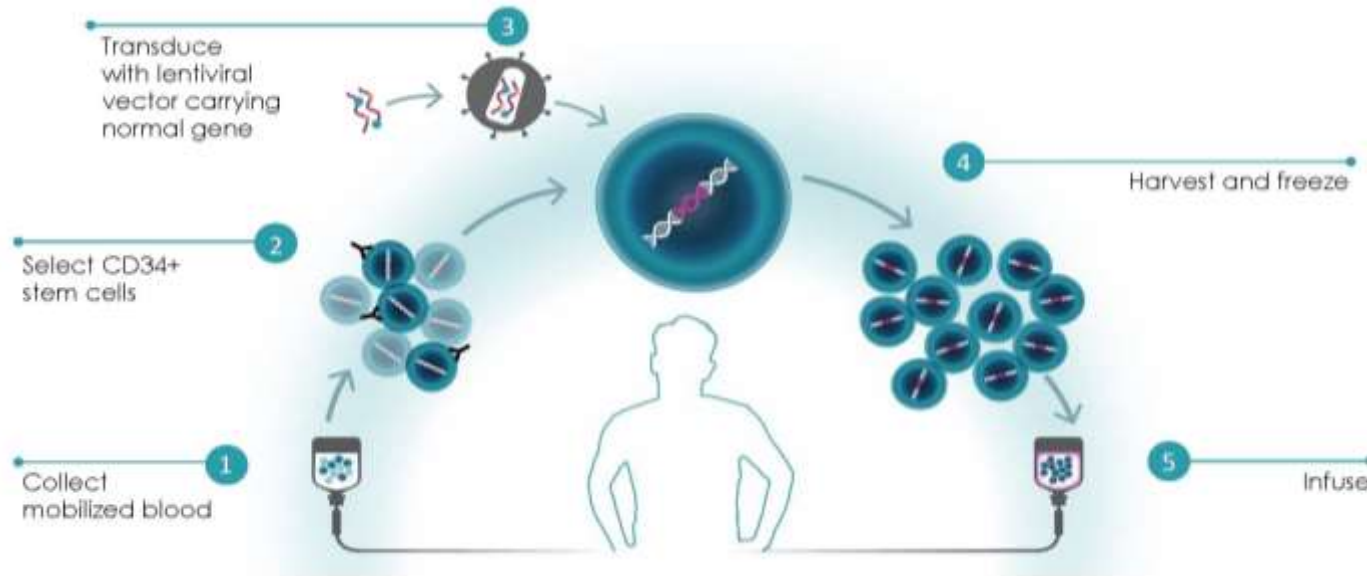
1st Approved Facility for
C&G therapies

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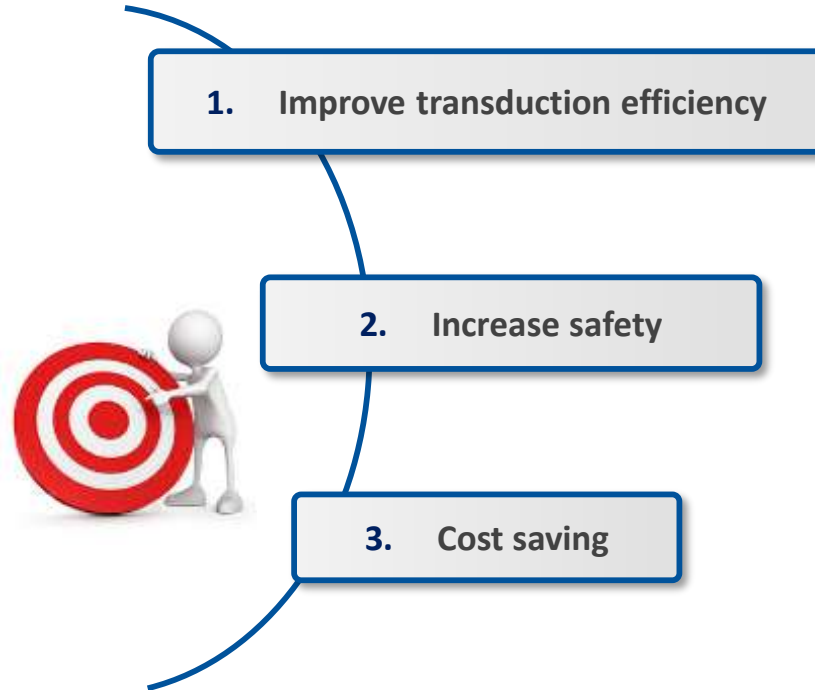
How to achieve efficient transduction of HSCs



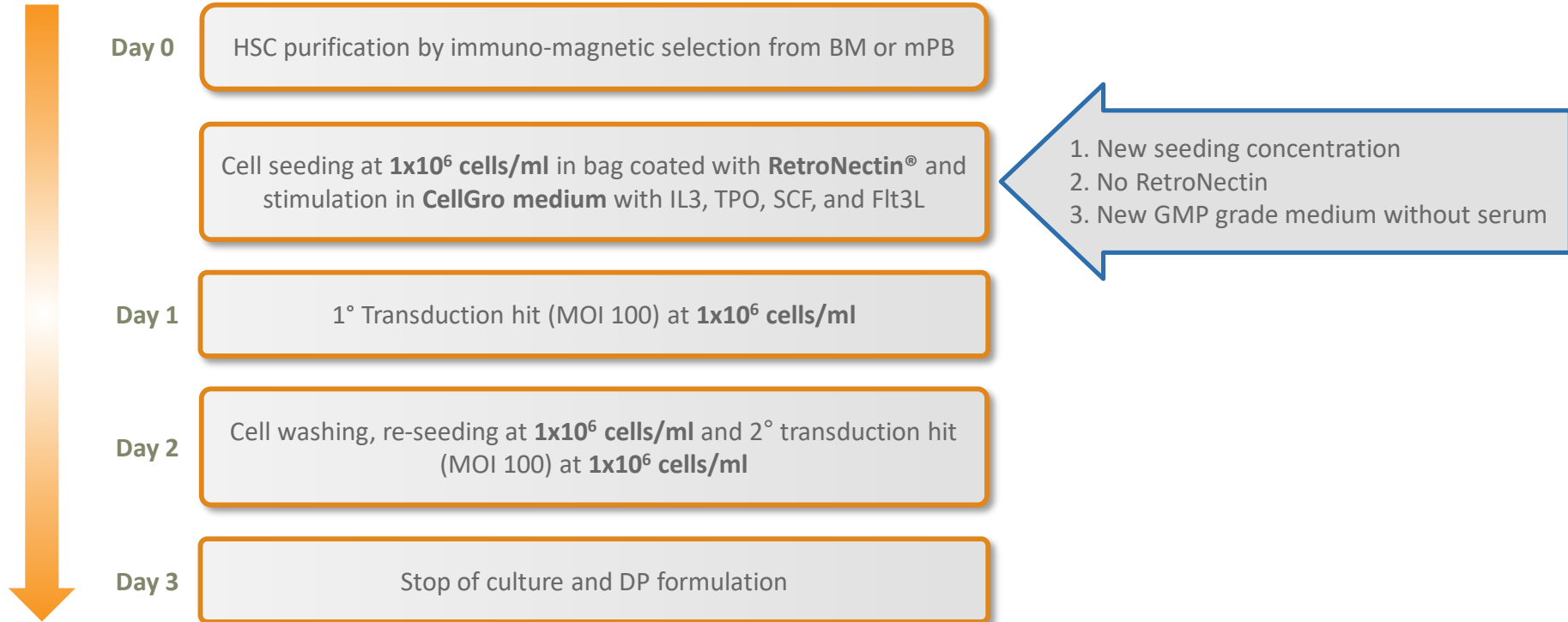
High-efficiency transduction with minimal manipulation of HSCs remains a crucial point to improve

Optimize manufacturing process

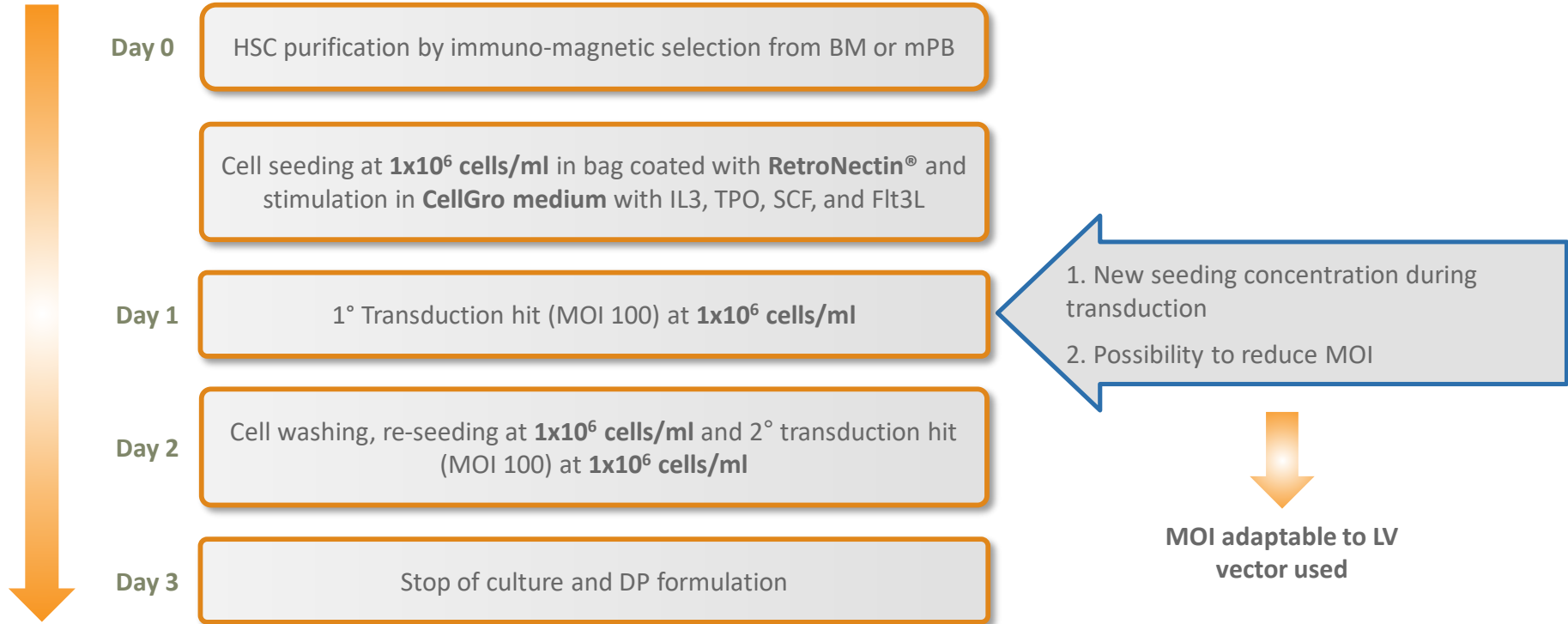
Which are our goals
for industrial process
development?



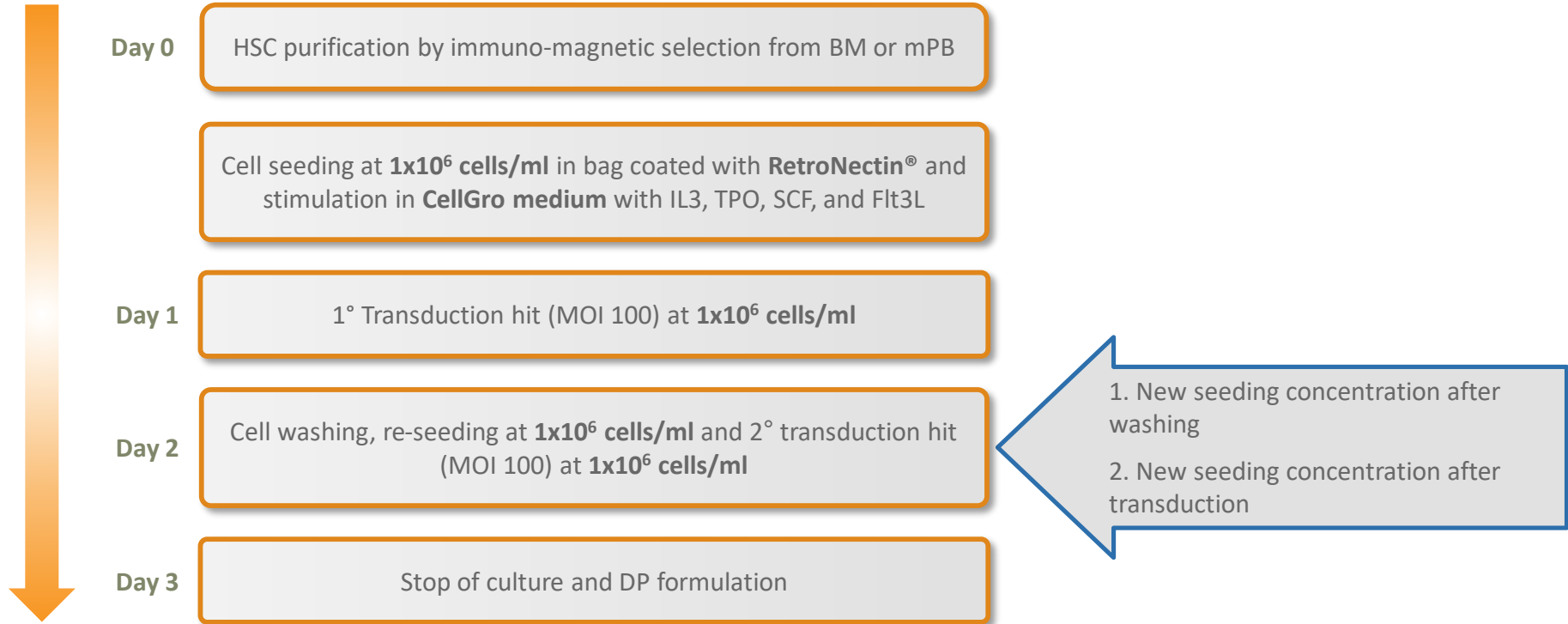
LV CD34+ transduction process



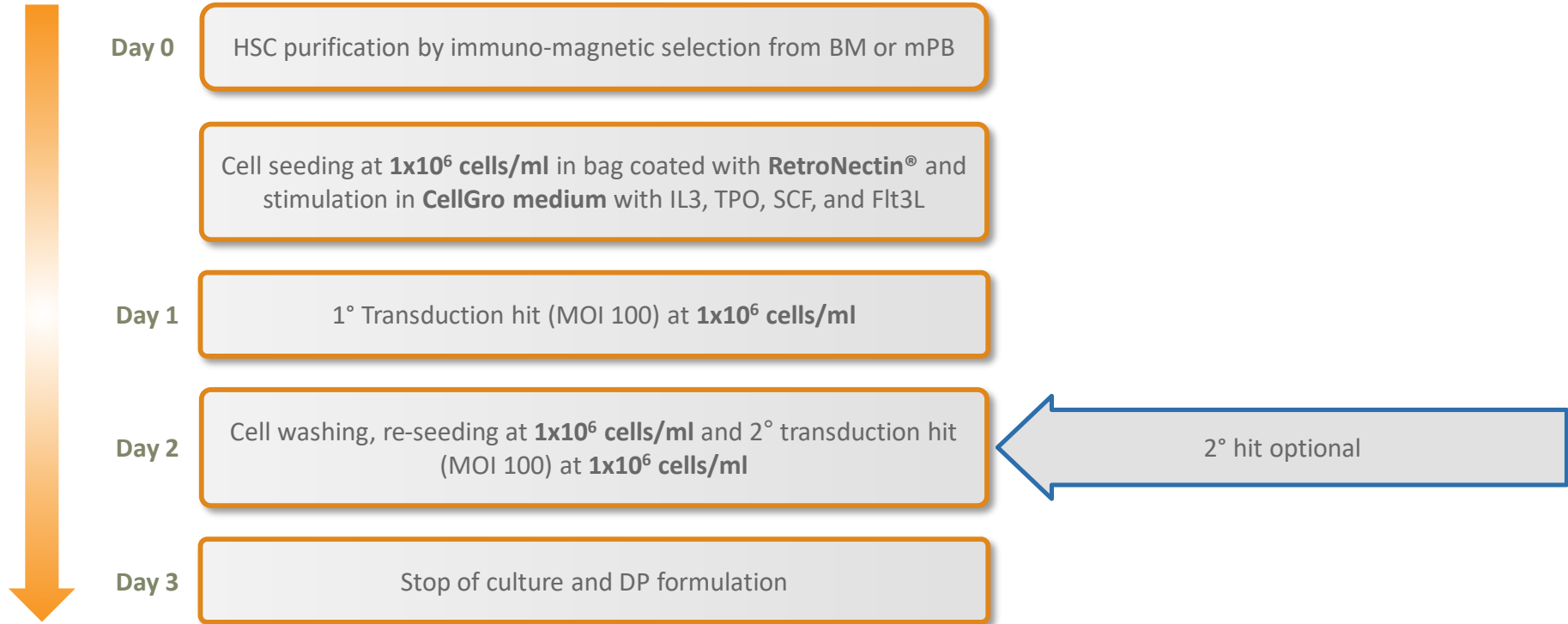
LV CD34+ transduction process



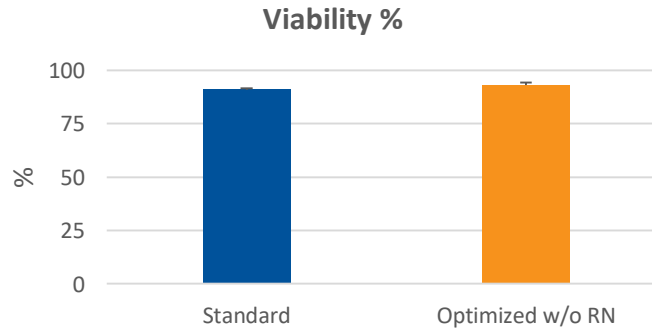
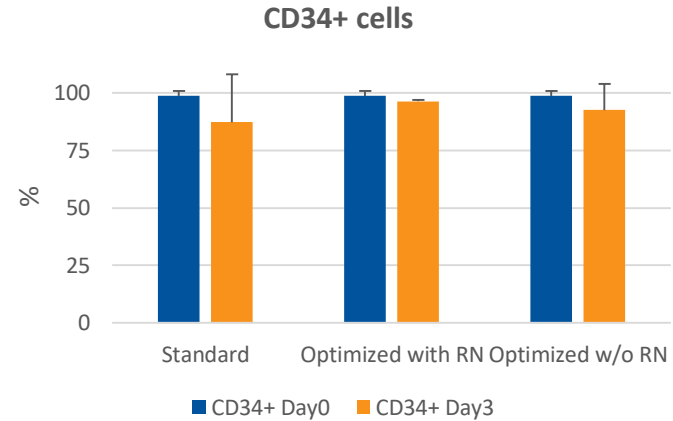
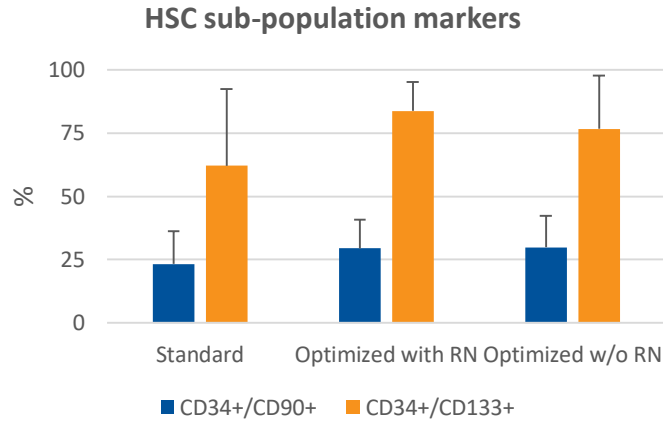
LV CD34+ transduction process



LV CD34+ transduction process

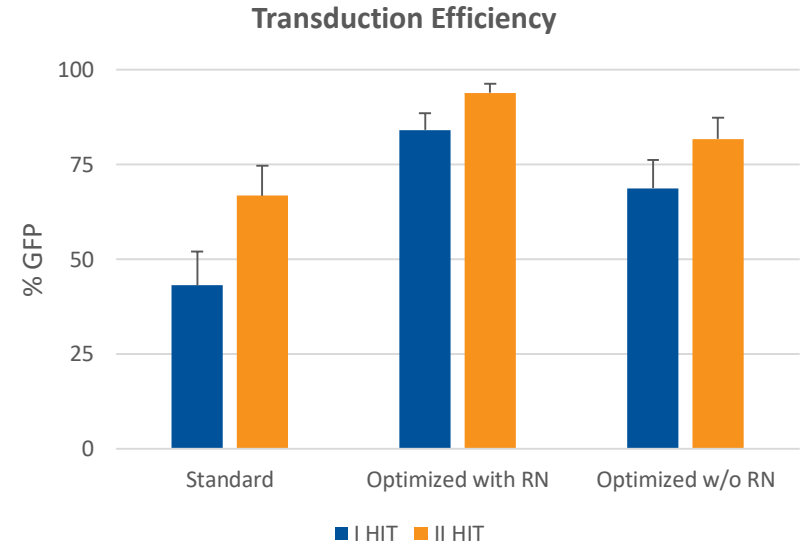
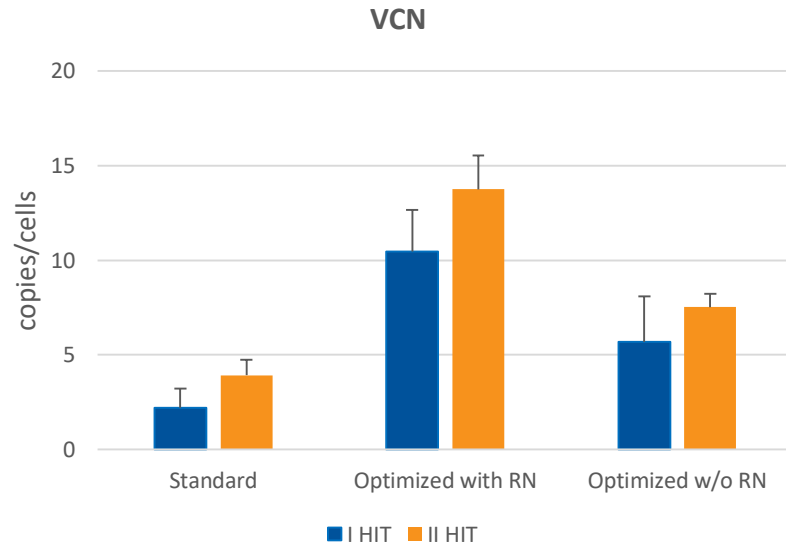


Optimized LV CD34+ transduction process: Results



Mean of 4 large scale experiments (3 starting from mPB and 1 from BM)

Optimized LV CD34+ transduction process: Results



Mean of 4 large scale experiments (3 starting from mPB and 1 from BM)

Optimized LV CD34+ transduction process: Conclusions

Process features

- ❖ Adaptable MOI and 2nd hit of transduction optional
- ❖ Improved culture conditions
- ❖ Avoid the use of transduction enhancers
- ❖ New chemically defined medium and No animal derived components

Benefits

- ✓ **Cost reduction**
- ✓ **Increased maintenance of stem potential**
- ✓ **High-efficiency transduction**
- ✓ **No IP restrictions**
- ✓ **Cost reduction**
- ✓ **Increased Safety**
- ✓ **Increased maintenance of stem potential**

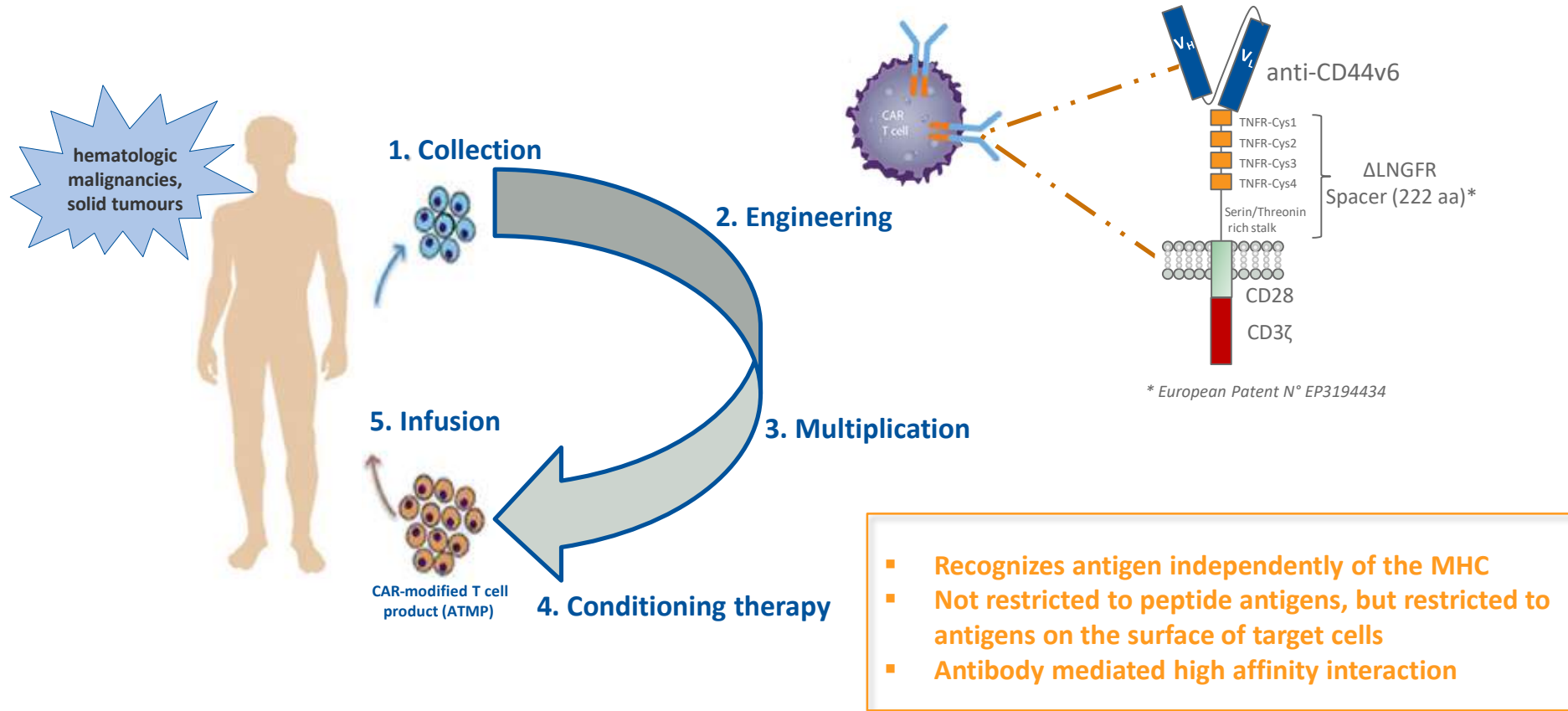


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CAR-T Cell Therapy: How does it work?



CAR-T Cell Therapy: Optimization and Scale-up?

Which are our goals for industrial process development?



1. Obtain significantly higher cell transduction efficiency

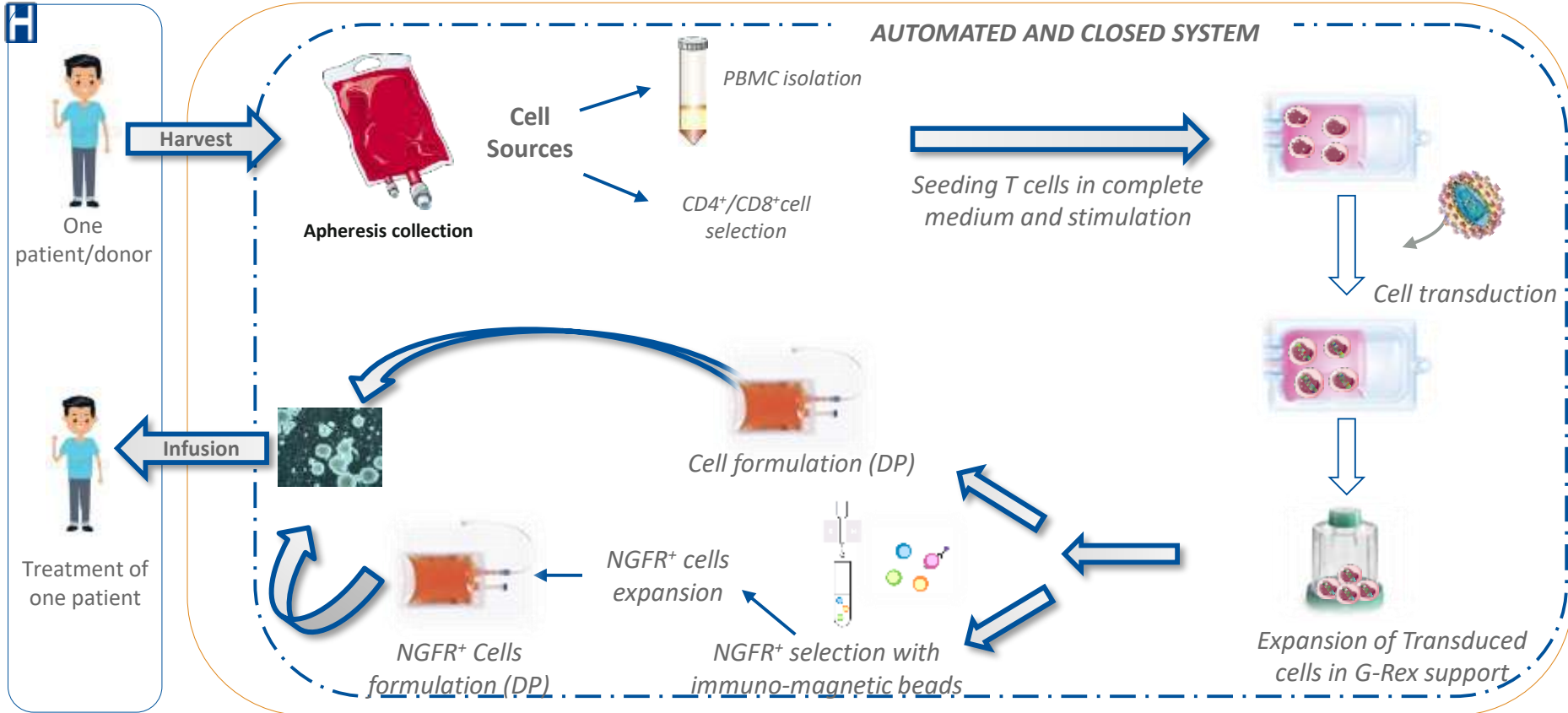
2. Improve the flexibility and safety

3. Improve the process yield

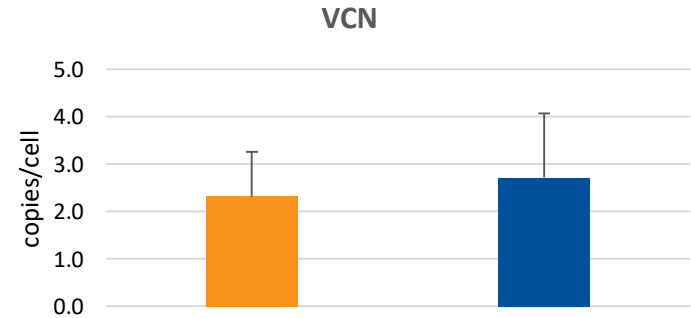
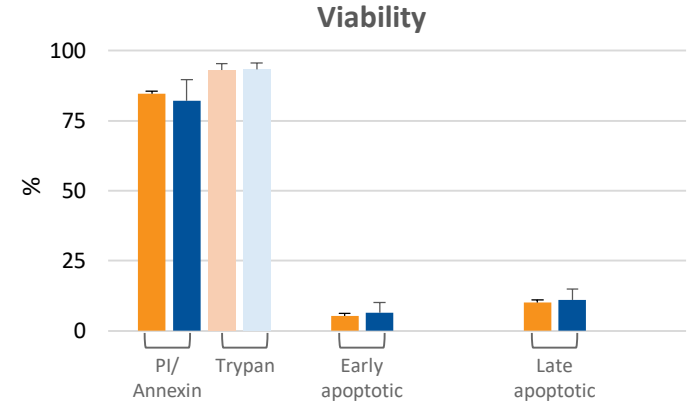
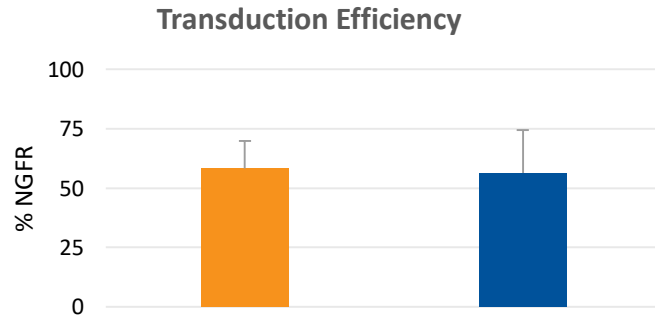
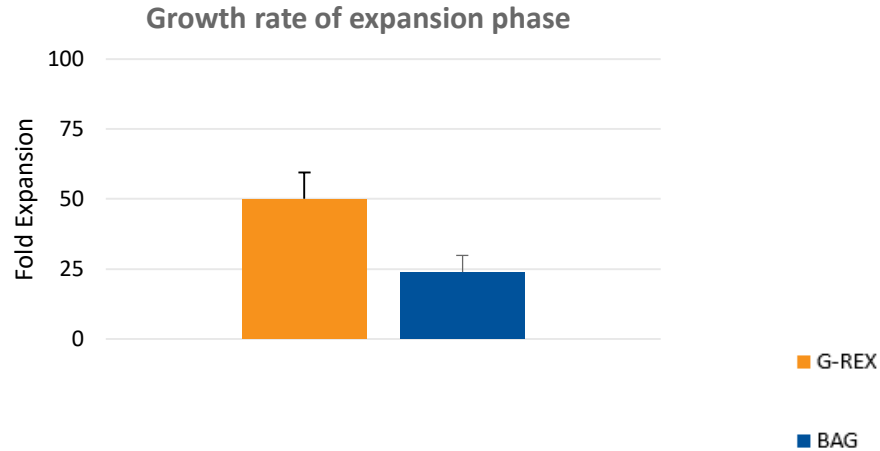
4. Cost reduction

LV CAR-T Cell Process: Overview

Autologous/ Compatible Donor Therapy

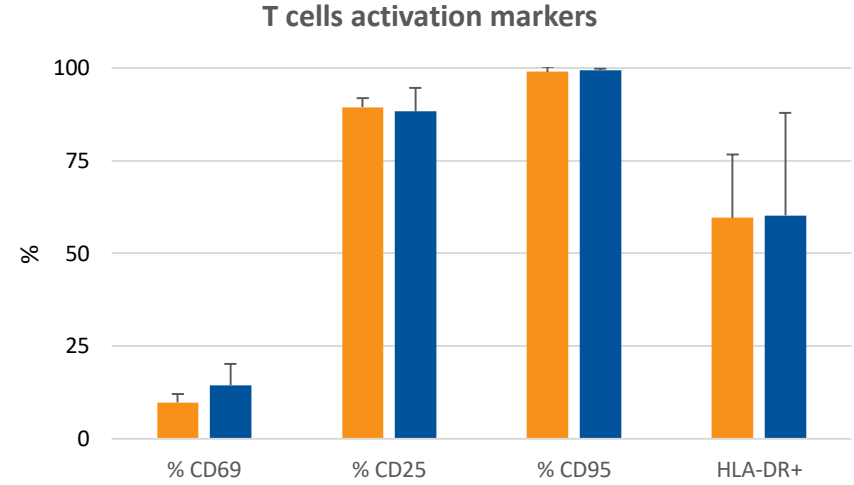
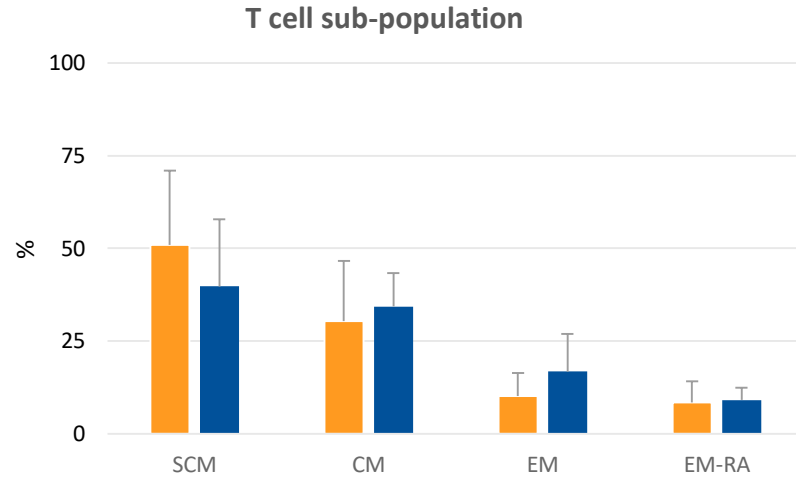


LV CAR-T Cell Process: Results



Mean of 5 large scale experiments from healthy donors PBMC transduced with CD44v6.CAR LV

LV CAR-T Cell Process: Results



■ G-REX

■ BAG

Mean of 5 large scale experiments from healthy donors PBMC transduced with CD44v6.CAR LV

LV CAR-T Cell Process: Conclusions

✓ Cost saving

- ❖ Reduced consumption of reagents
- ❖ No use of adjuvants

✓ Short window of expansion

- ❖ Increased fold expansion
- ❖ Maintenance of naïve T cells



✓ Flexibility

- ❖ Different sources of starting material
- ❖ Different process steps options
 - ❖ Open or closed system

✓ Safe

- ❖ Suitable for closed and semi automated systems (e.g. CliniMacs Prodigy and LOVO instruments)
 - ❖ No animal-derived components
 - ❖ Reduced manipulation volumes



Thank you for your attention!

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MolMed S.p.A.