

# CAR T-Cell Therapy:

## Advances in CAR T-cell Development for Cancer Therapy

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August 25-27, 2023

California Cancer Consortium Conference



**BUILDING HOPE**

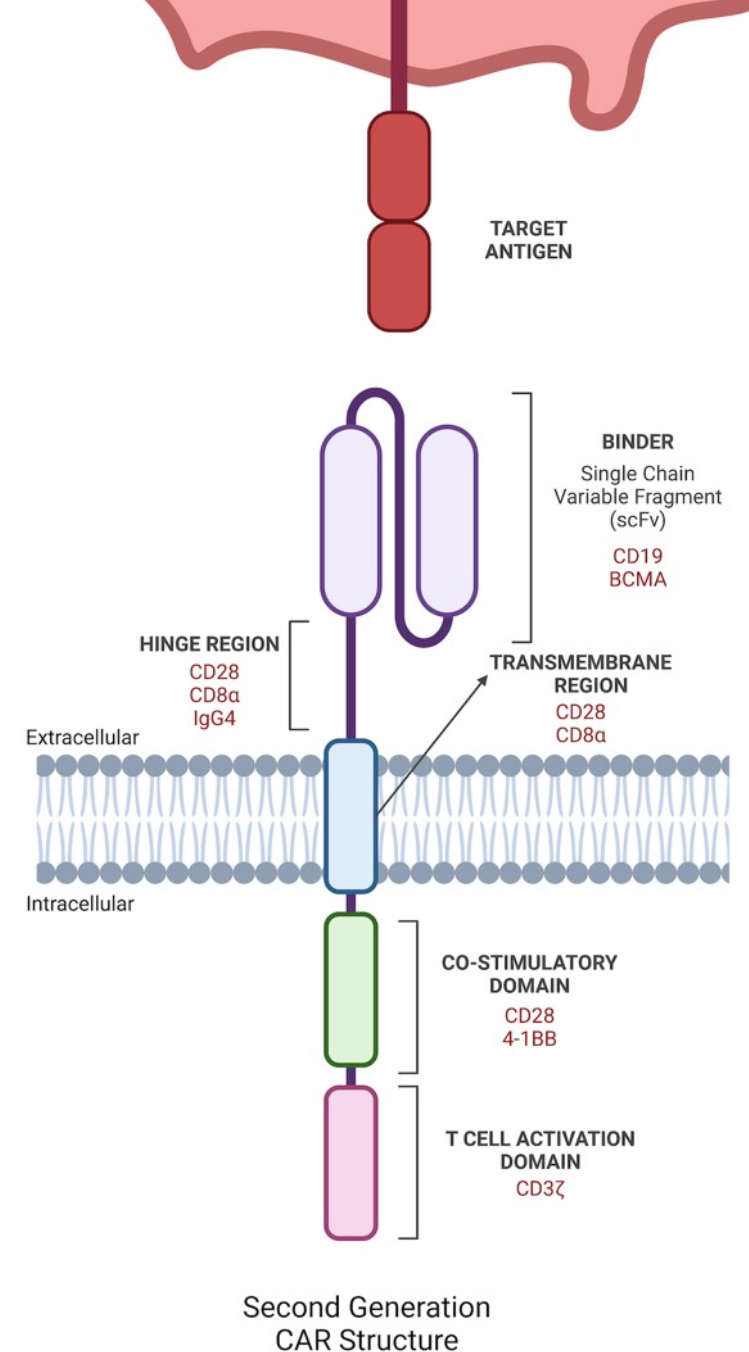
# Agenda

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- Introduction to CAR T cell therapy and its clinical applications in hematological malignancies
- Addressing key challenges in developing CAR T cell therapy:
  - Lengthy product development timelines
  - Complex manufacturing process and potential solutions

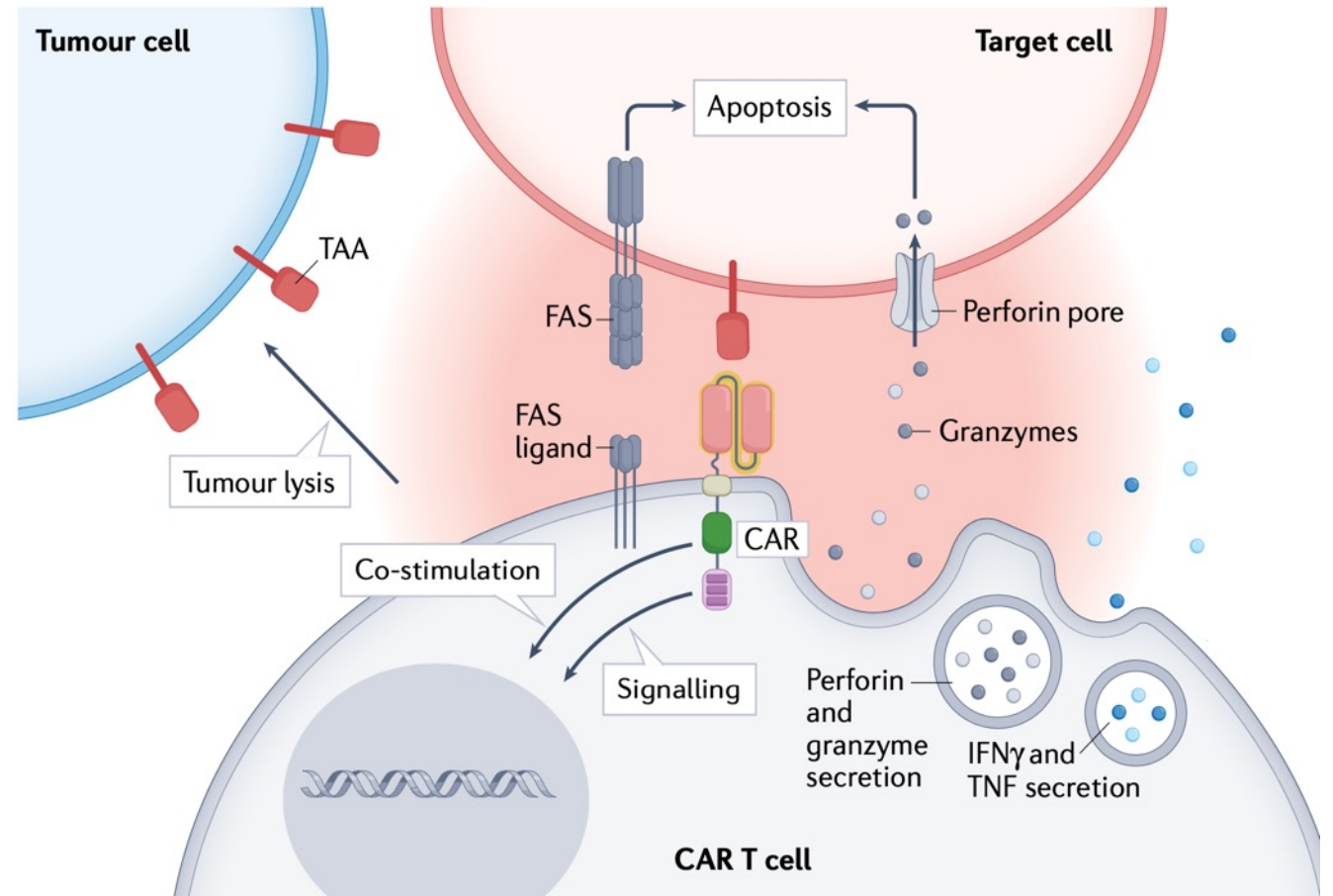
# Principles of CAR T cells

- **CAR T cells:** Personalized immunotherapy using patient's own T cells, genetically engineered to target specific tumor antigens for cancer treatment.
- **Chimeric Antigen Receptor (CAR) Structure:**
  - **Binder:** Ensures antigen recognition, specificity, and affinity
  - **Hinge region:** Provides flexibility and maintains optimal distance to the target
  - **Transmembrane Region:** Contributes to receptor stability and function
  - **Co-stimulatory Domain:** Augments T cell function, metabolism, and persistence
  - **T cell activation domain:** Facilitates downstream T cell activation and functional responses



# Principles of CAR T cells

- **CAR T Cell Killing Mechanism:**
  - Recognize Tumor-Associated Antigen (TAA)
  - Form Immune Synapse with Target Cell
  - Release Cytotoxic Granules
  - Induce Target Cell Apoptosis
  - Trigger Cytokine Release & Immune Activation
- **Main target: CD19**, specifically expressed on B-cells
- Remarkable success in hematological B-cell malignancies as a **third line** of treatment in **Lymphoma** and **Leukemia**
- Recently approved CAR T-cells targeting **BCMA** for **Multiple Myeloma**



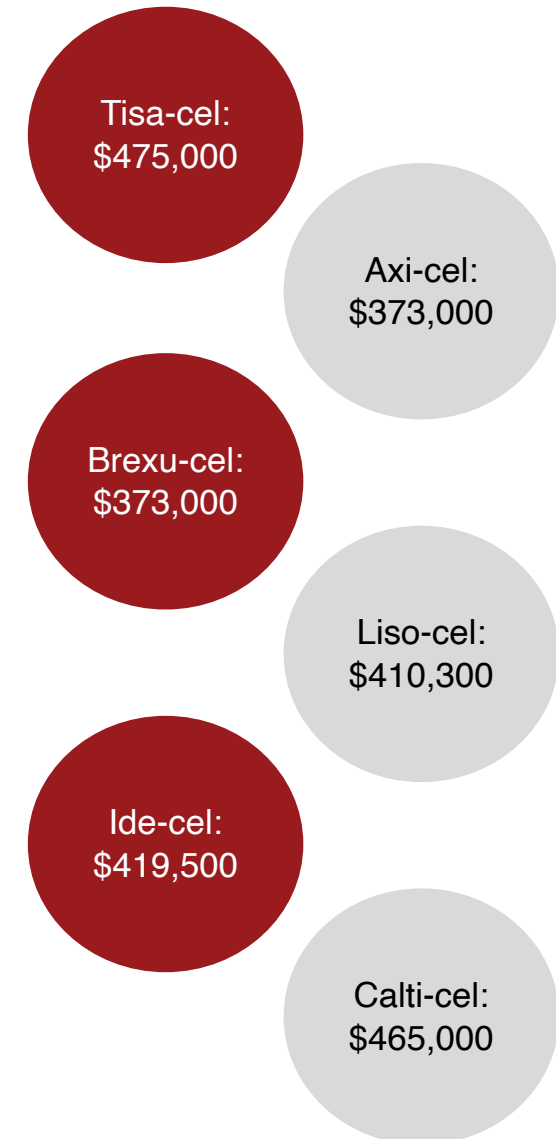
Flugel et al. Nat. Rev. Clin. Oncol. 2022

# FDA Approved CAR T cells

● 2017	<b>Tisa-cel</b>	→	Acute lymphoblastic leukemia (ALL) (B-cell precursor) Large B-cell lymphoma (LBCL) Follicular lymphoma (FL)
	<b>Axi-cel</b>	→	Large B-cell lymphoma (LBCL) Follicular lymphoma (FL)
● 2020	<b>Brexu-cel</b>	→	Mantle cell lymphoma Acute lymphoblastic leukemia (ALL) (B-cell precursor)
● 2021	<b>Liso-cel</b>	→	Large B-cell lymphoma (LBCL)
	<b>Ide-cel</b>	→	Multiple Myeloma (MM)
● 2022	<b>Cilta-cel</b>	→	Multiple Myeloma (MM)

# The Value of CAR T Cell Therapy

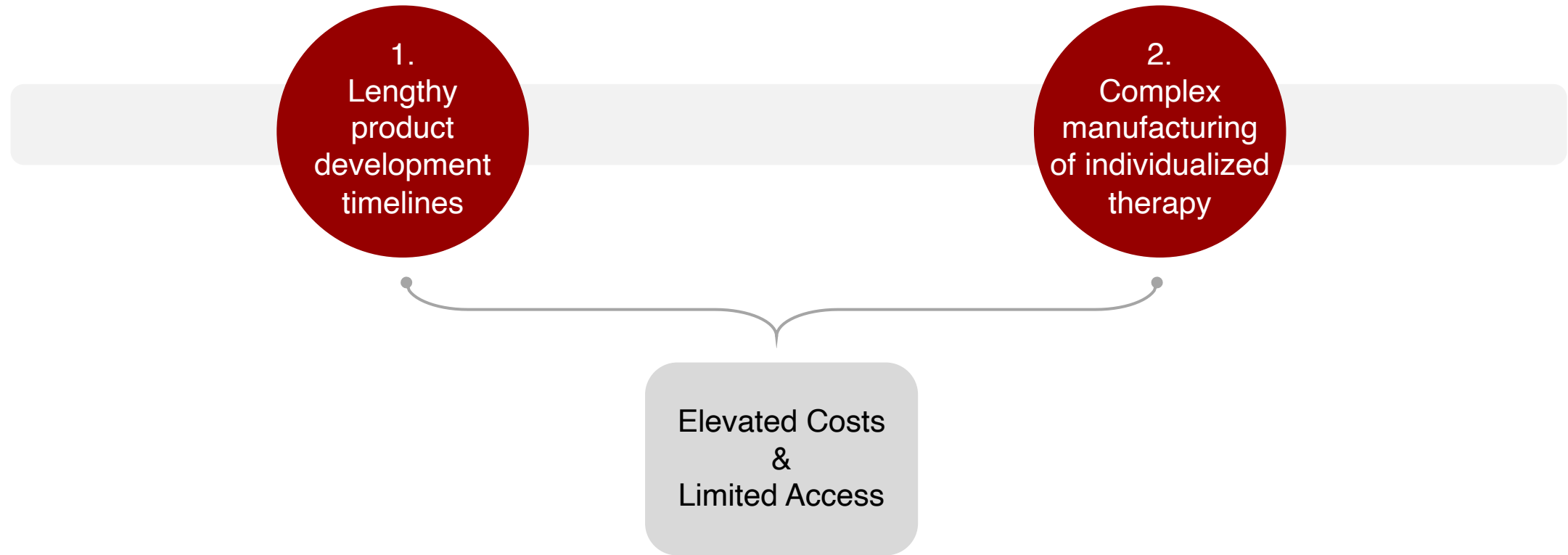
- Primary obstacle for first-line therapy adoption: **High cost of CAR T-cell therapy**
- **Price Range: \$373,000 to \$475,000** for a single dose
- **List price** does NOT cover hospitalization, pre- and post-treatment, or side effect management. Overall cost ranges from **\$500,000 to \$1 million**.
- **Medicare reimbursement** rate through MS-DRG 018 is insufficient to cover costs and related services
  - In-patient: Covers 65% of product cost
  - Out-patient: Covers full cost + 6% reimbursement to provider
  - Patient responsible for 20% cost-sharing





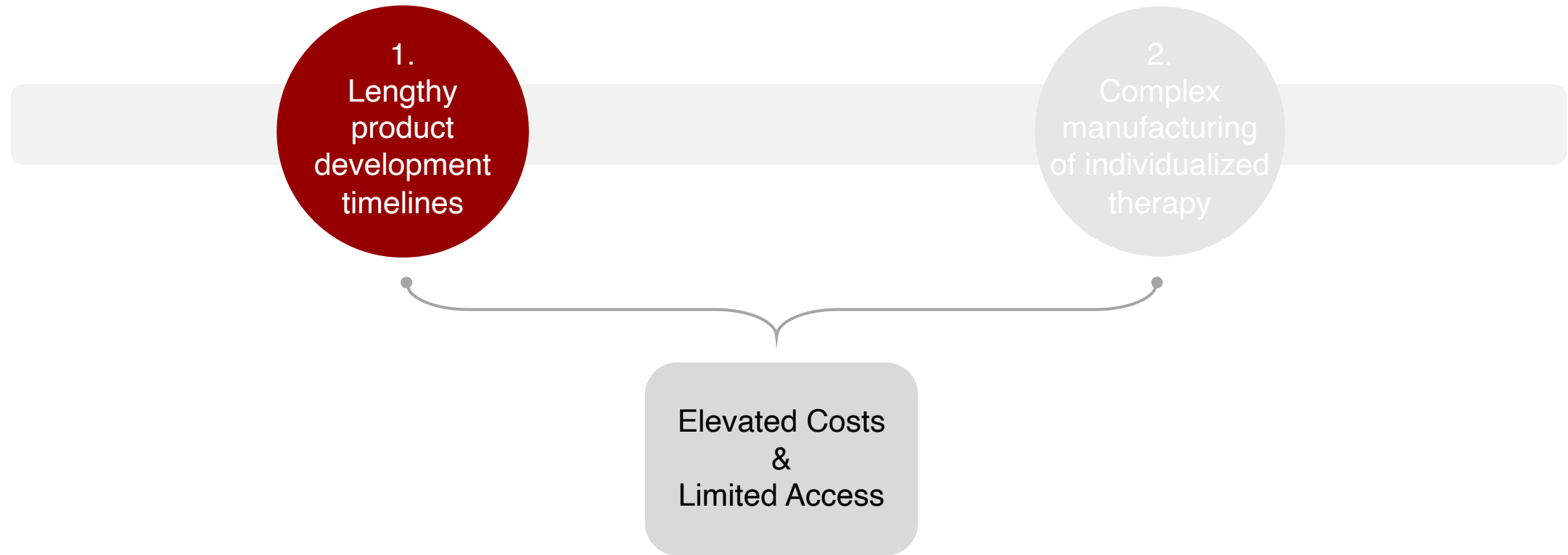
# Roadblocks to CAR T cell Therapy Adoption

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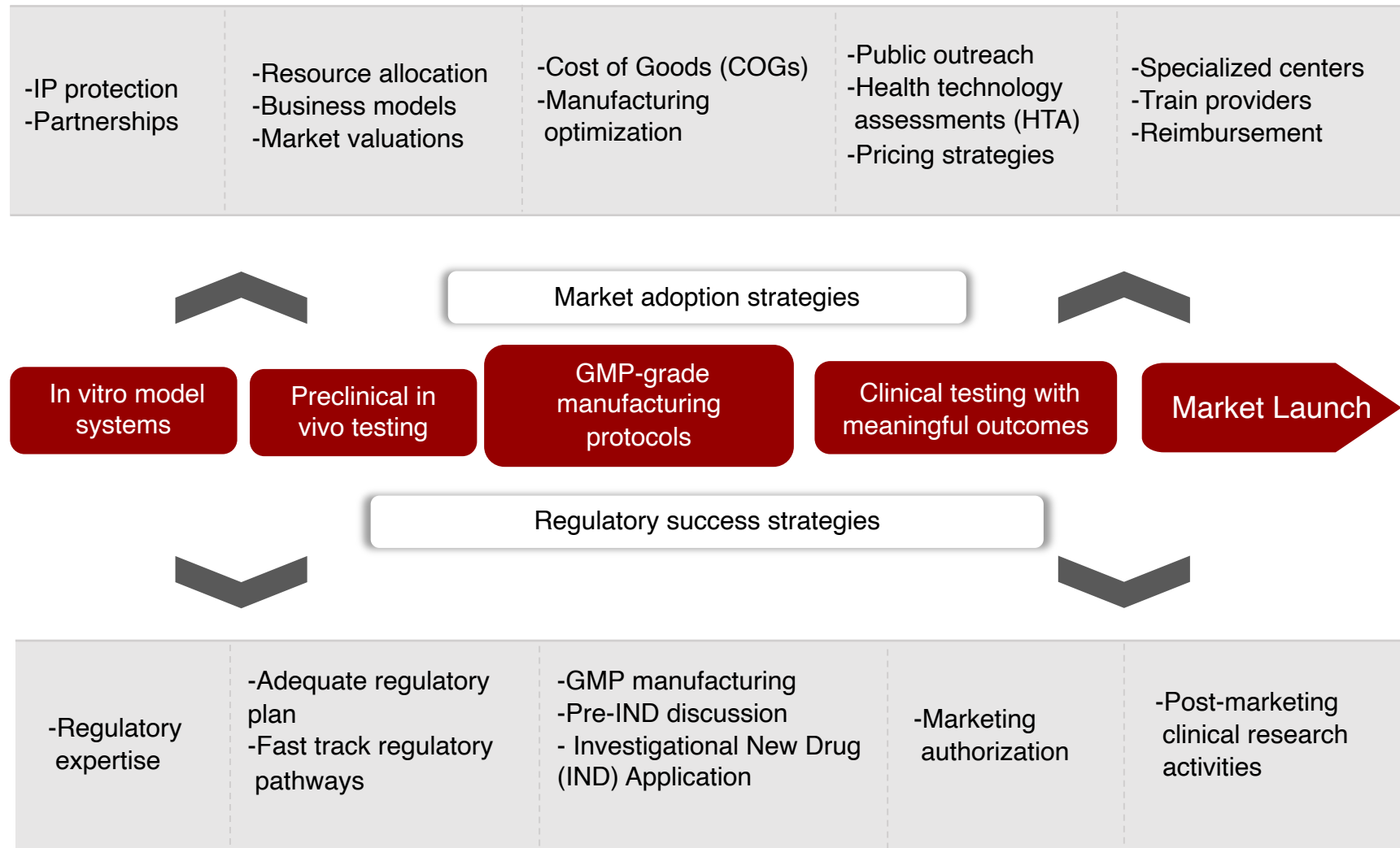
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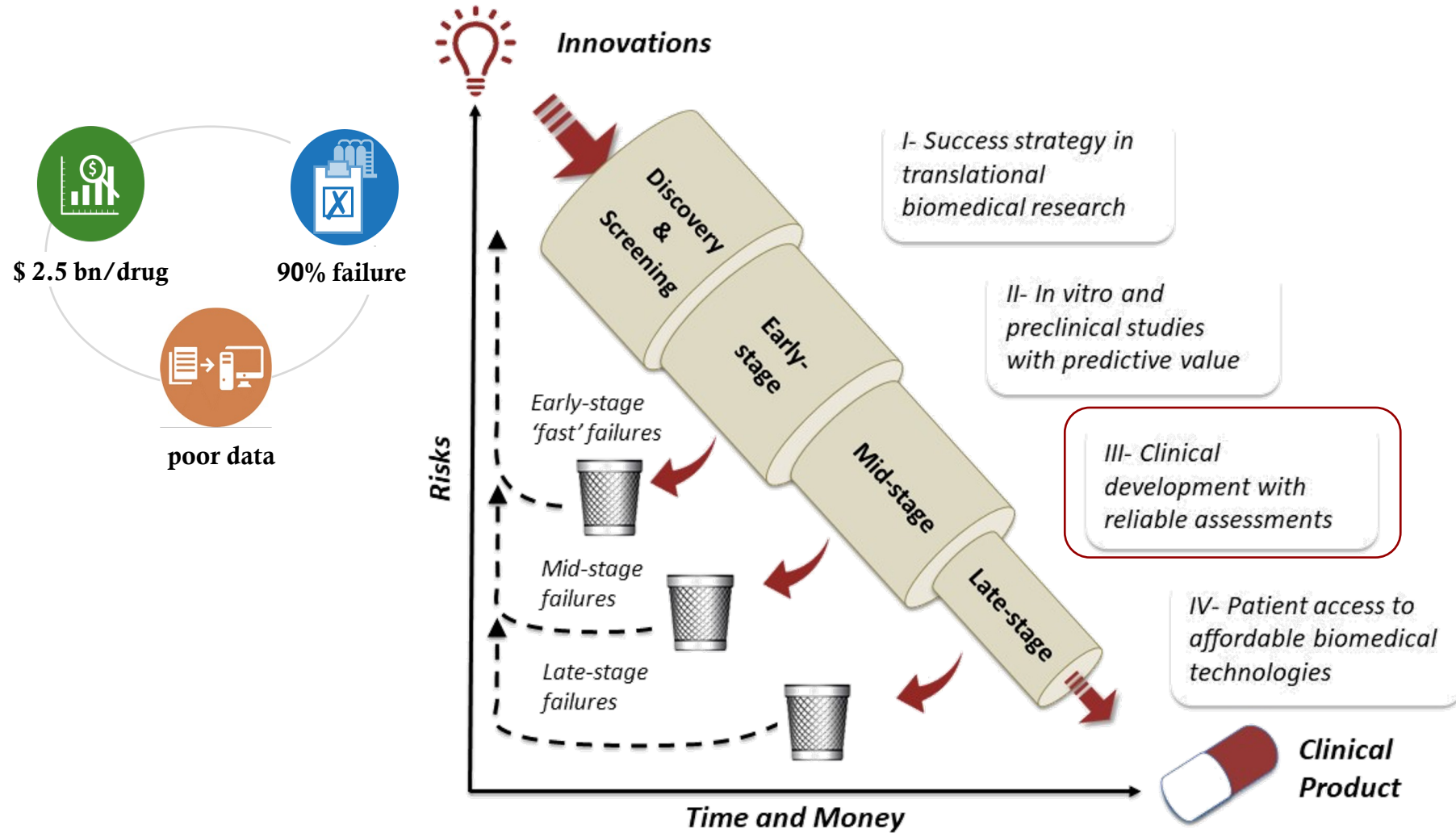




# Translating Cell Therapy Research

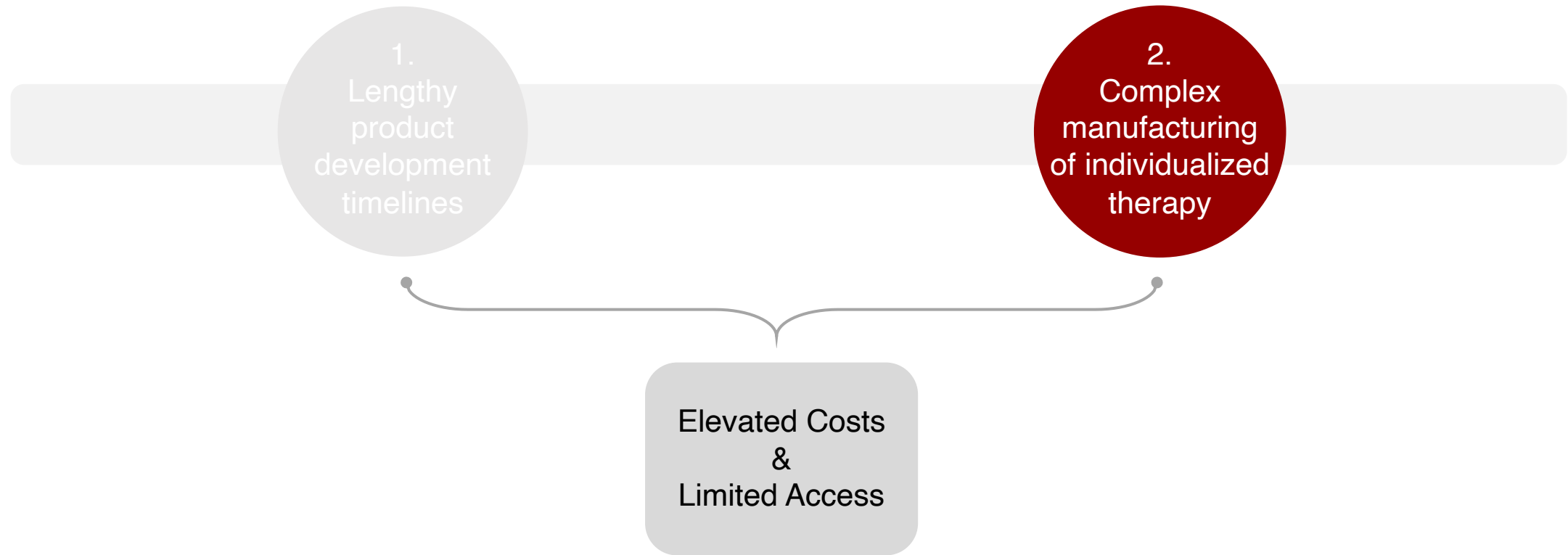


# Translating Cell Therapy Research

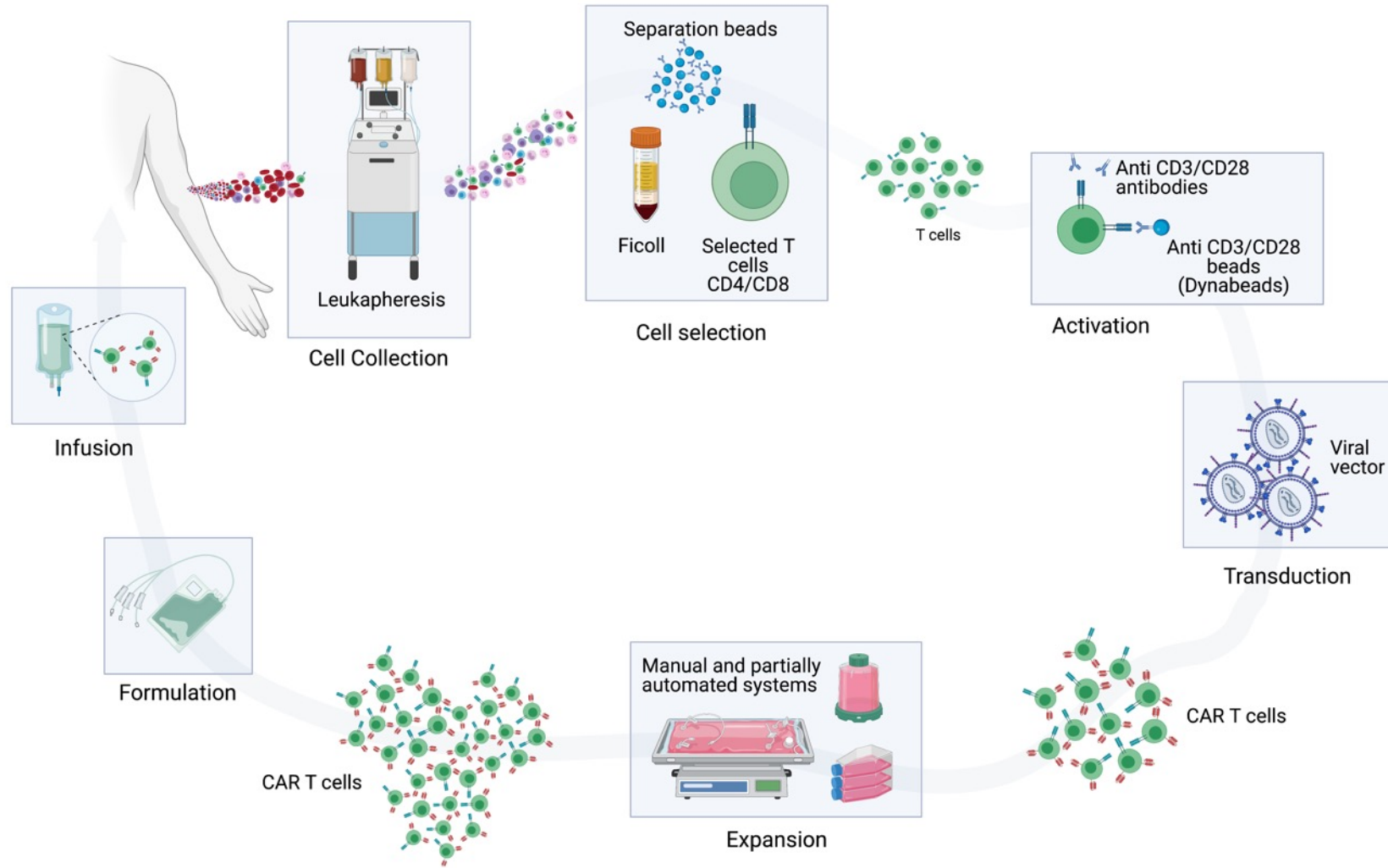


# Roadblocks to CAR T cell Therapy Adoption

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# CAR T Cell Manufacturing



# CAR T Cell Manufacturing

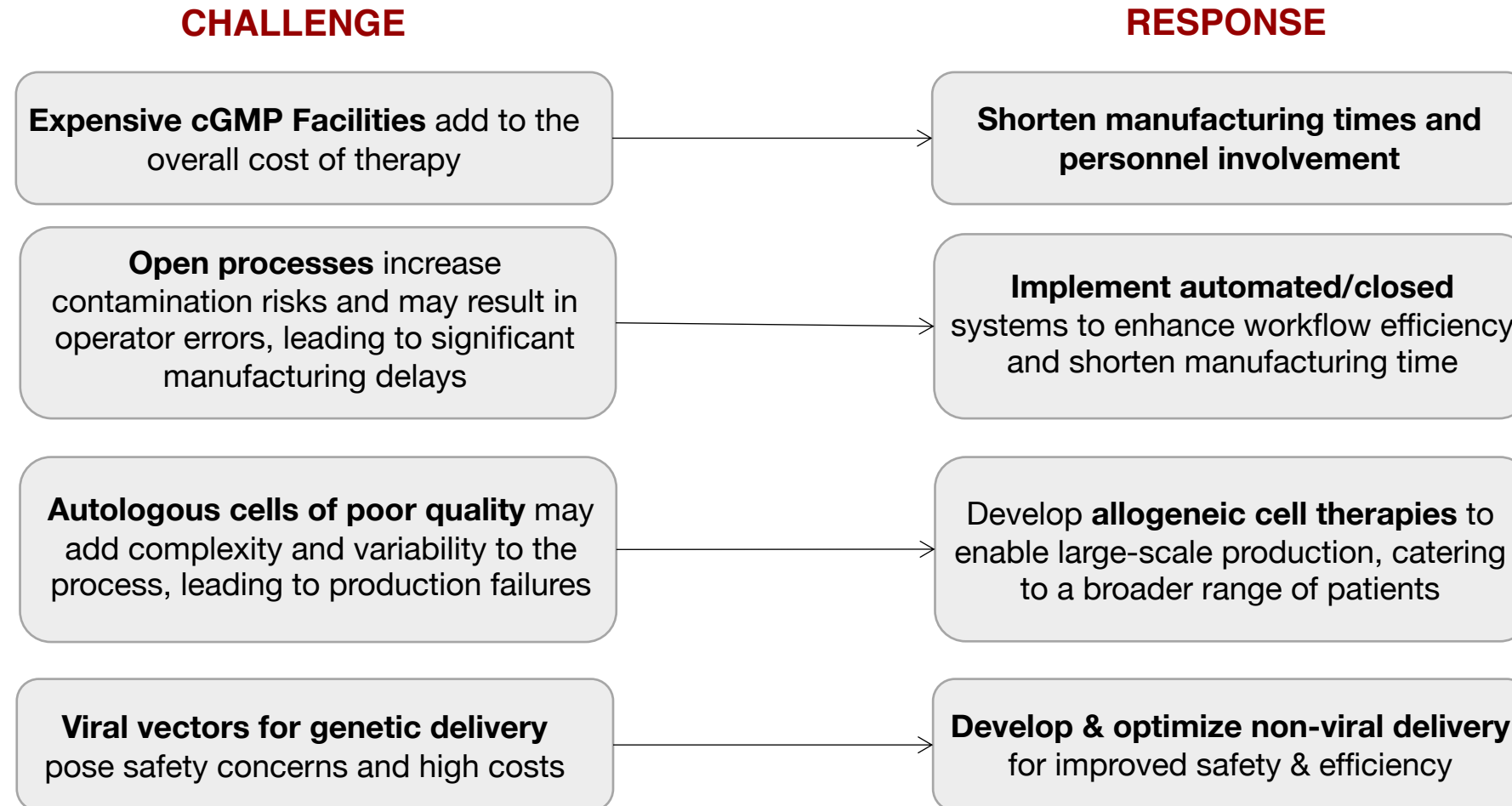
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## CAR T manufacturing process

- Lengthy  $\approx$  22 days for the entire process
- Largely manual and open processes
  - High variabilities among CAR T cell products
  - High risk of contamination
  - Relies on significant technical expertise
  - Difficult to scale
- Space and equipment are occupied during the production
- Currently, the cost remains prohibitive



# Cell Therapy Manufacturing: Overcoming Challenges



# 1-Cell Therapy Manufacturing: What is cGMP?



Highly controlled and clean environment



Periodic maintenance of premises & equipment



Specialized Personnel



Quality Management System



Identifying deviations, investigating causes, & taking actions



Operationally independent quality control (QC) system



Rigorous product testing under set acceptance criteria

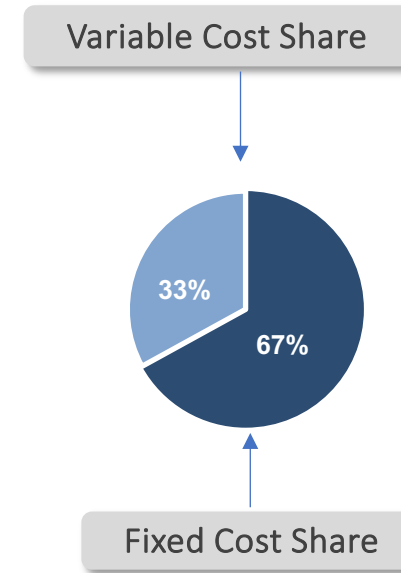
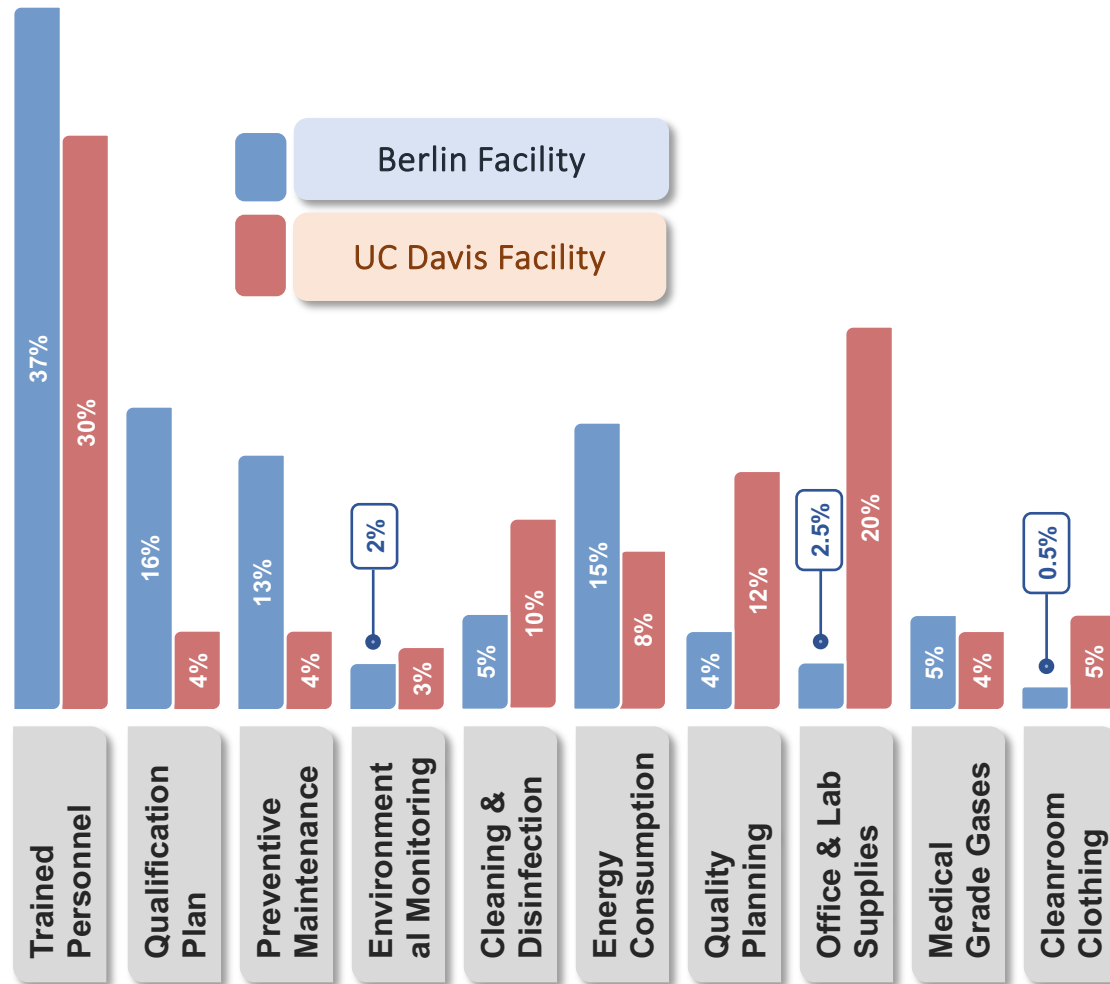


Traceability of starting materials, raw materials and final products



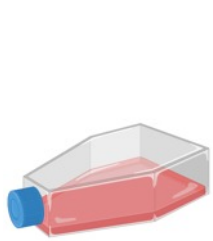


# 1-Cell Therapy Manufacturing: cGMP costs



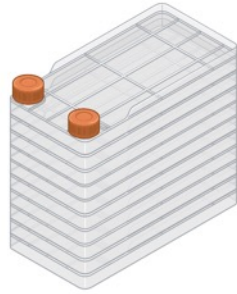
Abou-el-Enein *et al.*, Cytotherapy 2013

# 2-Cell Therapy Manufacturing: Closing the Process



**Flasks**

- Open systems
- Labor intensive (manual)
- Stringent cleanroom requirements



**Cell stacks**



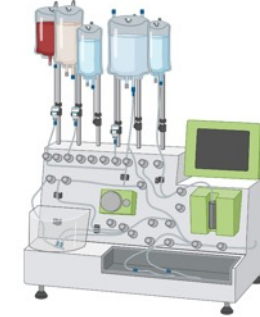
**G-Rex**

- Open & semi-closed
- High number of operator interventions
- Additional instruments required



**Bioreactors**

- Semi-closed
- Less operator interventions
- Additional instruments required



**CliniMACS Prodigy**

- Functionally closed/automated
- Minimal operator interventions
- Less stringent cleanroom requirement

**Open/Manual**

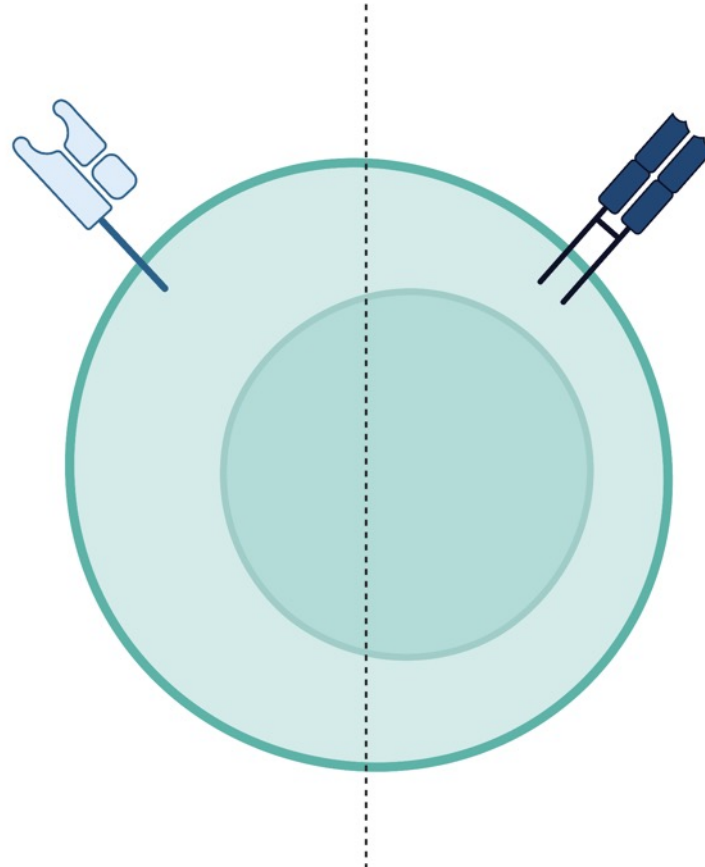


**Closed/automated**

# 3-Cell Therapy Manufacturing: Autologous to allogeneic

## AUTOLOGOUS CELLS

<b>Origin</b>	- Own Patient
<b>Variability</b>	- High
<b>Availability</b>	- Limited
<b>Quality of SM</b>	- Low
<b>Batch Size</b>	- Reduced
<b>Risks</b>	- Malignant cell transduction
<b>Benefits</b>	- Low immunogenicity

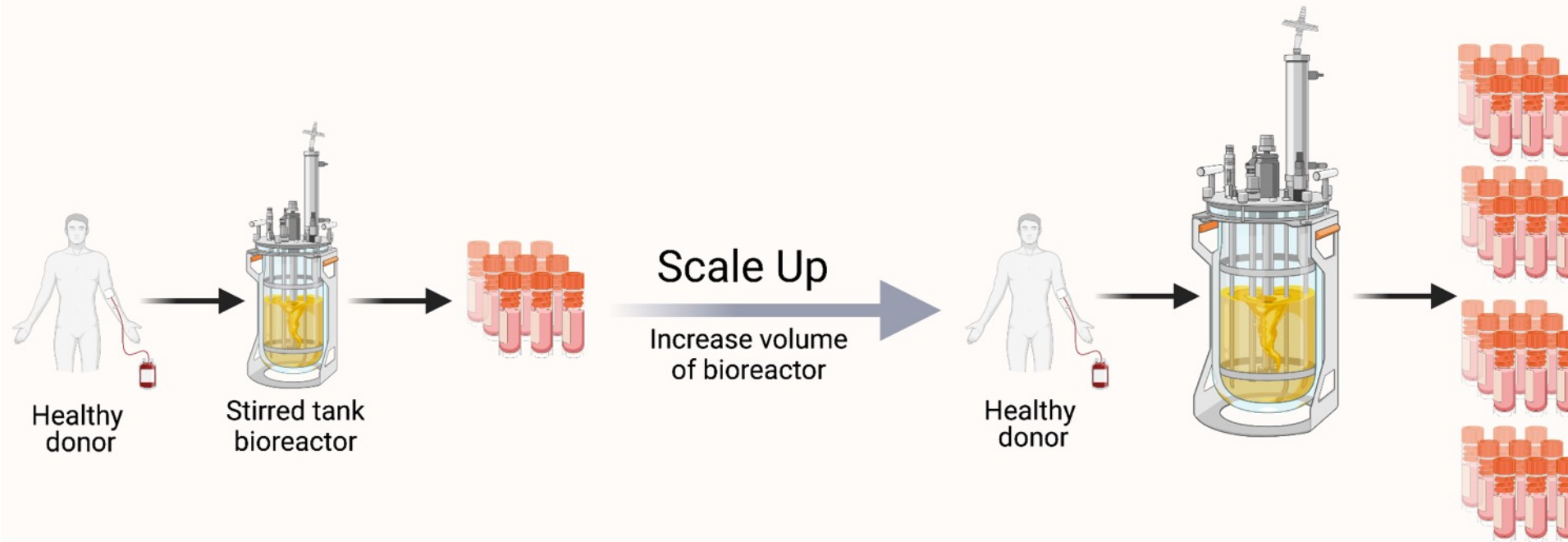


## ALLOGENEIC CELLS

- Healthy Donor
- Low
- On demand
- High
- Large scale
- Alloreactivity & GvHD
- Standardization & scaling

# 3-Cell Therapy Manufacturing: Autologous to allogeneic

## (B) Allogeneic CAR T cells



*Abou-el-Enein et. al. Blood Cancer Discov., 01 September 2021*

# 4-Cell Therapy Manufacturing: Viral to non-viral

## VIRAL VECTORS

### Advantages

- High transduction efficiency
- Specific delivery to target cells
- Widely used

### Disadvantages

- Pre-existing immunity
- High cost and complex production
- Limited scalability
- Low packaging capacity

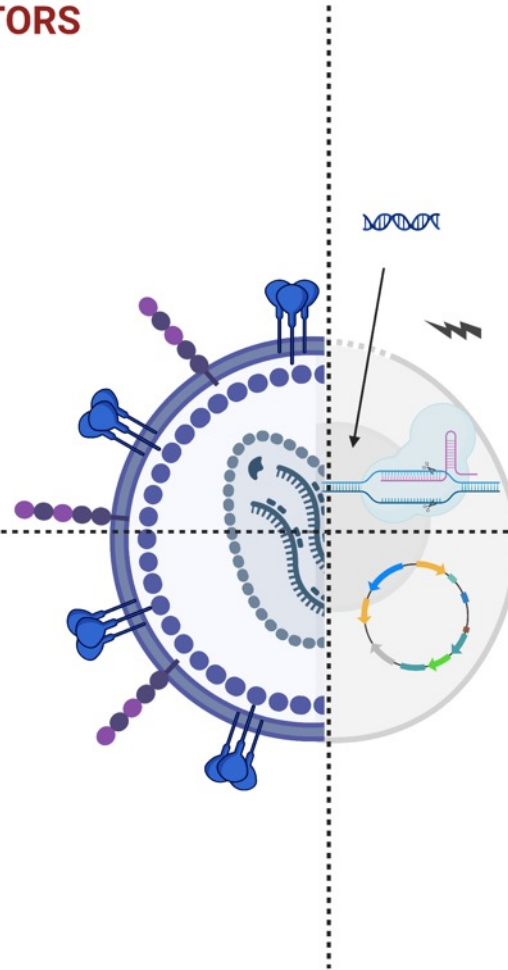
## NON-VIRAL VECTORS

### Advantages

- Low immunogenicity
- Low cost
- Scalable
- High packaging capacity
- Enable multiplex editing

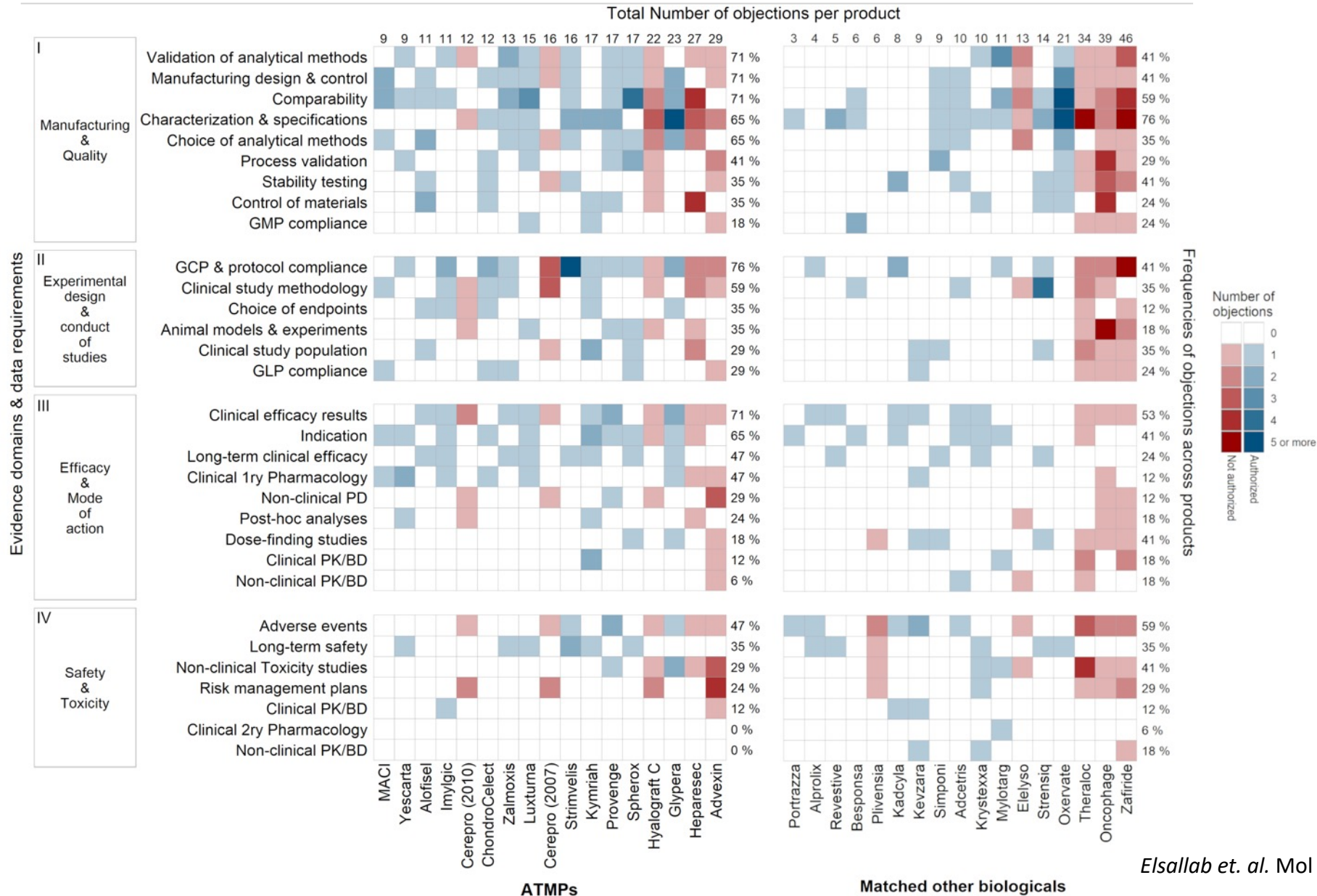
### Disadvantages

- Low transfection efficiency
- Low cell viability
- Need for cell sorting post-engineering
- Limited experience





# Cell Therapy Manufacturing: Is it really the barrier?



# Cell Therapy Manufacturing: Is it really the barrier?

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## **Clinical development programs are flawed**

- Adherence to the trial protocol
- Compliance to GCP
- Design and methodology of clinical studies
- Product efficacy (addressed by post marketing efficacy studies to collect more data about product efficacy)

## **Manufacturing issues comprise most of objections & concerns**

- Controlling and designing the manufacturing process
- Product comparability (investigational vs. final marketed product)
- Product characterization
- Validation of the used release assays



# Summary

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- CAR T-cell therapy has shown remarkable success in treating hematological B-cell malignancies and is moving towards earlier lines of treatment.
- High costs and reimbursement challenges limit the broad adoption of CAR T cell therapy.
- Addressing challenges such as lengthy product development timelines, and complex manufacturing can help reduce costs & improve accessibility.
- Automated and closed systems, allogeneic cell therapies, and non-viral gene delivery methods are being developed to overcome manufacturing challenges.
- Continued research and innovation are essential to optimize CAR T cell therapy and make it more accessible to a broader range of patients.

# Acknowledgment

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## USC/CHLA Cell Therapy Program

Alix Vaissie  
Amaia Cadinanos-Garai  
Xia Wu  
Victoria Olvera  
Vivian Quach  
Ivan Segovia

## Alpha Clinic

Thomas Buchanan  
Allan Wayne  
Juliane Glaeser  
Elia Plascencia  
Cort Brinkerhoff

## Norris Comprehensive Cancer Center

Caryn Lerman  
Steven Grossman  
Heinz-Josef Lenz  
Christopher Loertscher



Keck School of  
Medicine of **USC**



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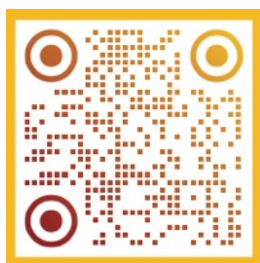


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**Thank you!**

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