From Centralised Manufacturing to Bedside Production: Advancing CAR T-Cell Therapies Through Collaborative Innovation

***Desmet Thomas*[1,2]**, *Simoens Steven*[1], *Van Dyck Walter*[2], *Huys Isabelle*[1]

[1]Clinical Pharmacology and Pharmacotherapy, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven (Belgium);
[2]Healthcare Management Centre, Vlerick Business School, Ghent (Belgium)

Background

With scientific progress in chimeric antigen receptor T-cell (CAR T) therapy, there will likely be a rapid increase in demand for these types of therapies, requiring the design of robust and scalable manufacturing and distribution models to ensure timely and cost-effective delivery of the therapy to the patient.

Challenge: High cost of complex supply chain (represents 30% of total cost of care (TCOC)) of existing industry-driven centralised production of CAR T-cell therapies, limiting flexibility and patient access in developed and developing countries

To achieve the long-term potential of these therapies we must debottleneck key elements of the current supply chain model (e.g. need for cryopreservation and cross-border logistics, etc.)

Research questions:

- What supply chain structures can reliably and cost-efficiently deliver autologous CAR T cell therapies?
- Is it feasible to manufacture CAR T-cell therapies for low and middle-income countries (LMICs) using a fully automated closed system?

Hypothesis: Decentralised or **point-of-care** manufacturing has the potential to overcome some challenges such as the need for cryopreservation, complex and expensive logistics, reduce the vein-to-vein time, and duration of bridging therapy.

Objective

To find the similarities, strengths and limitations of the existing industry-based manufacturing pathways versus decentralised platform-based manufacturing (closed automated systems)

Methods

A comprehensive review of current manufacturing practices and logistics for CAR T-cell therapies in **literature** (PubMed, EMBASE, grey literature), focusing on centralised versus decentralised models.

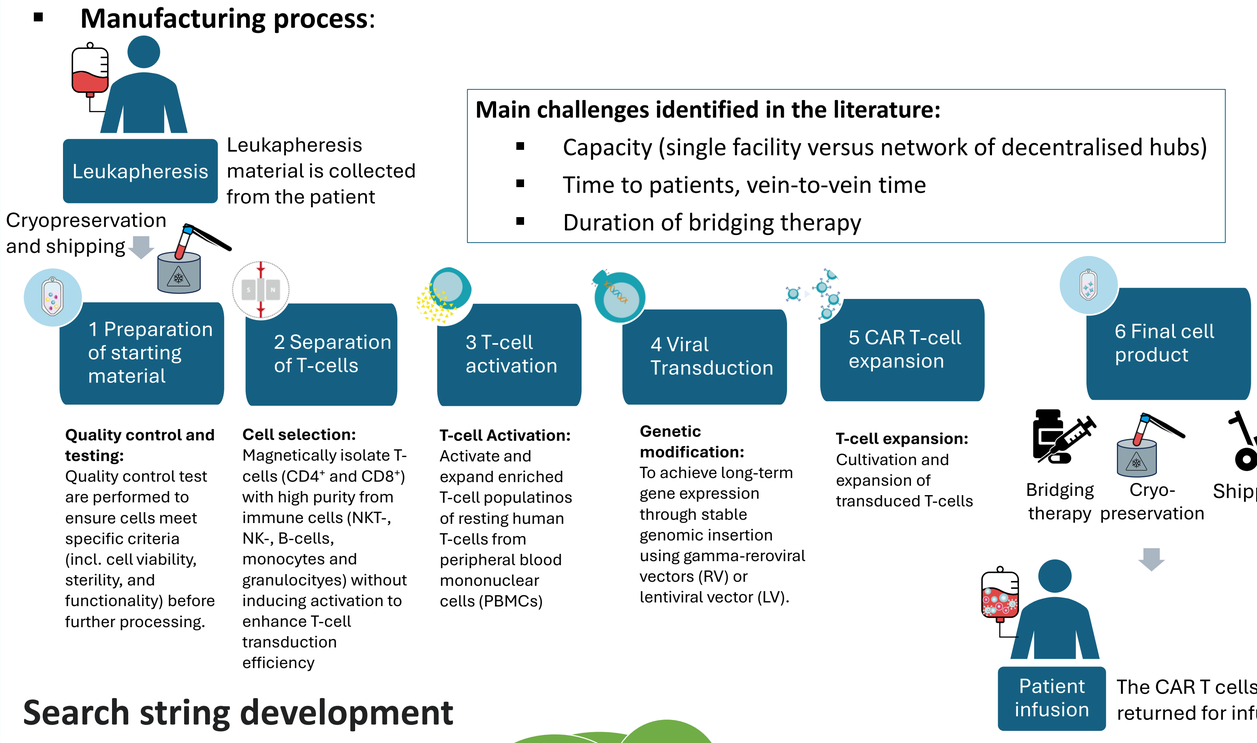
Interviews with industry experts and stakeholders to identify bottlenecks and potential solutions for streamlining the manufacturing and distribution processes.

Preliminary results from the literature

- 6 autologous CAR T-cell therapies approved in Europe:

Kymriah® (tisagenlecleucel)
Yescarta® (axicabtagene ciloleucel)
Tecartus® (brexucabtagene autoleucel)
Abecma™ (idecabtagene vicleucel)
Breyanzi™ (lisocabtagene maraleucel)
Carvykti® (ciltacabtagene autoleucel)

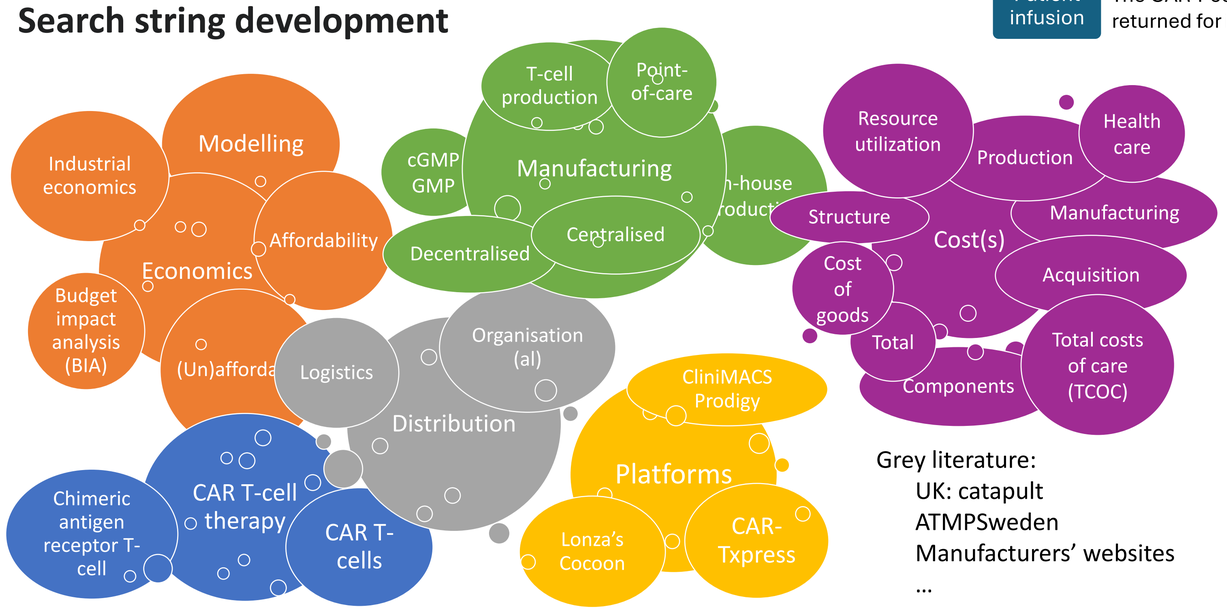
- **Total cost of treatment is dependent of:**
  - Treatment acquisition costs
  - Supply chain costs: cryopreservation, transport and logistical risks
  - Treatment administration costs at the point of care
    - Intensive Care Unit (ICU) stays associated with CAR T infusion, cost of leukapheresis, bridging chemotherapy, lymphodepletion therapy
    - Adverse event (AEs) management: Cytokine release syndrome (CRS) events, neurologic events, neutropenia and anaemia
  - Indirect costs, e.g., lost income during time of treatment, recovery and follow-up for patient and/or family members
- **Manufacturing process**:



Main challenges identified in the literature:

- Capacity (single facility versus network of decentralised hubs)
- Time to patients, vein-to-vein time
- Duration of bridging therapy

Search string development



Grey literature:
UK: catapult
ATMPSweden
Manufacturers' websites
…

Decentralised or Point-of-Care CAR-T manufacturing solutions

Functionally closed, automated manufacturing platforms: composed of a cultivation chamber, a cell separation column, quality control sampling pouches, filling bags, etc.

- No need fro cryopreservation of CAR T-cells
- Scalability and flexibility
- Protected environment of single-use cultivation and tubing sets
- Reduced cleanroom requirements
- **GMP conditions**: highly skilled and knowledgeable personnel: head of production, qualified person, head of quality control, trained technicians
- External labs for sterile control and specimen tests

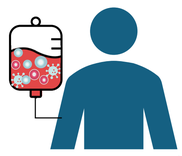
Fully automated closed systems

Clean room | Lonza's Cocoon® | Miltenyi CliniMACS Prodigy®

How to address the current challenges to ensure sustianable CAR T-cell therapies in the fast-pace healthcare system?

Current centralised model

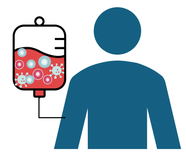
- Leukapheresis
- Bridging therapy
- Patient infusion



- Cross-border shipping of living cells
- Cryopreservation needed

Future decentralised model

Production hub at the treatment facility (hospital site)



- One stop shop for the patient
  - Leukapheresis
  - Bridging therapy
  - Patient infusion

Potential advantages:

- Cut down on logistics
- Reduce vein-to-vein time
- Reduce duration of bridging therapy

List of abbreviations

AEs= Adverse events
CAR = Chimeric antigen receptor
CRS = Cytokine release syndrome
GMP = Good manufacturing principles
ICU = Intensive Care Unit
LMIC = Low and middle income
TCOC = Total costs of care

Acknowledgements

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Conclusions

- Balancing cooperation and competition between biopharmaceutical companies, research institutions, and healthcare providers is essential to meet the growing demand for CAR T-cell therapies. Decentralised manufacturing, supported by automated and closed-system technologies, can enhance scalability and maintain product quality, ultimately facilitating broader patient access.