

# POINT-OF-CARE CAR-T MANUFACTURING

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The Ottawa  
Hospital | L'Hôpital  
d'Ottawa



# DECLARATION/COI

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Honoraria/ad board: Novartis, Kite/Gilead, BMS

# OBJECTIVES

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- How do we define point-of-care manufacturing
- How can point-of-care manufacturing be rolled out to new sites
- Advantages and disadvantages of point-of-care manufacturing
- Cost of point-of-care manufacturing
- Pathways for use of point-of-care manufacturing: worldwide examples

# POC MANUFACTURING - DEFINITION



**Proximity to Patients**

**Closed, automated systems**



**Customization**

MANUFACTURE CAR-T OR OTHER CELLULAR  
VIA AN AUTOMATED, CLOSED-SYSTEM AT  
ADJACENT SITES

ORDING NEW MANUFACTURING SITES WITH RIGOROUS  
AND COMPREHENSIVE PROCESSES TO ENSURE A  
STANDARDIZED, COMPARABLE PRODUCT AT ALL SITES

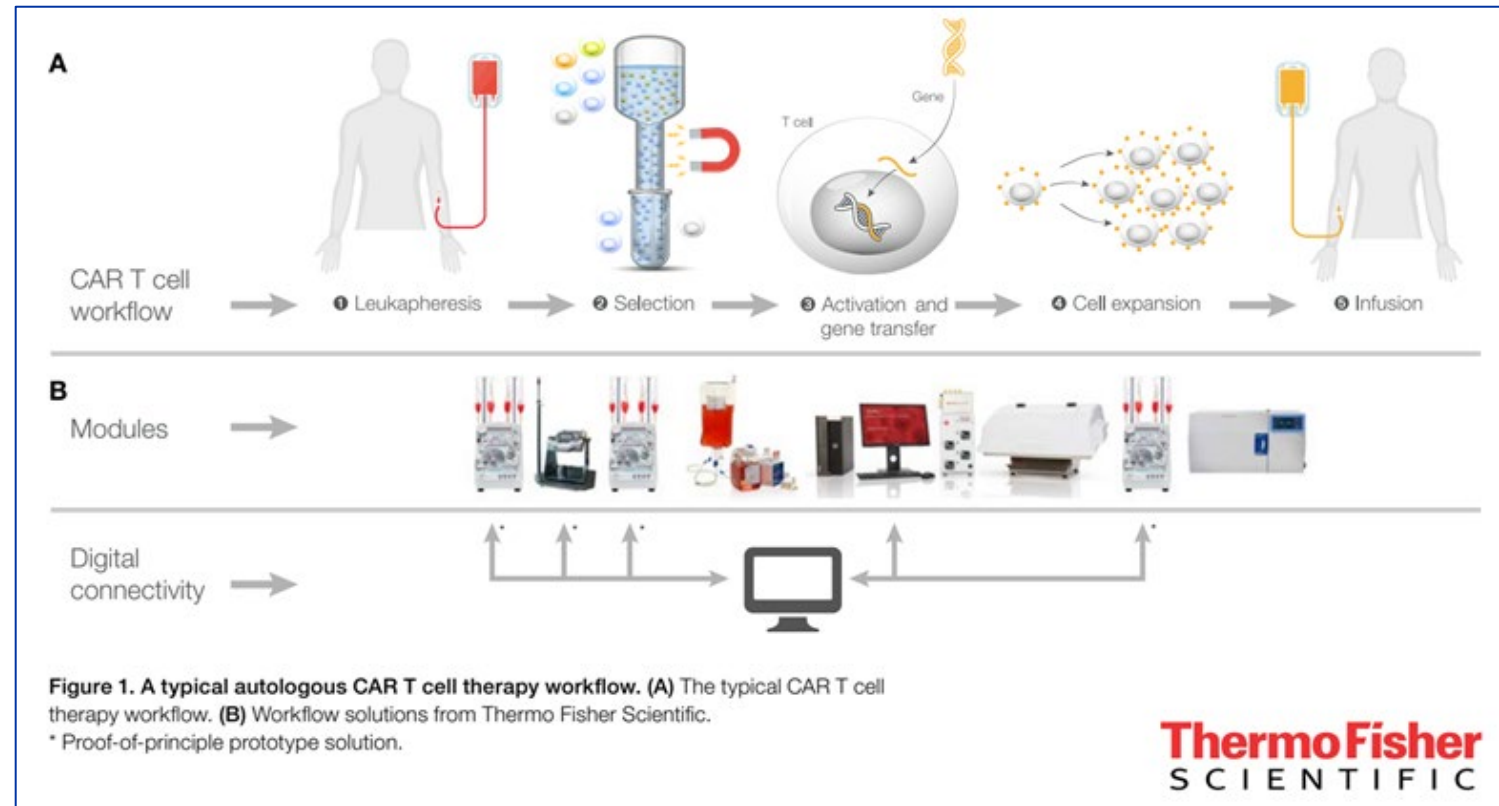
# FULLY AUTOMATED SYSTEMS

- Fully automated process which eliminates any handling of the product during manufacturing
  - One product on one machine at a time
  - Handles cell separation, activation, and transduction
- 1) Miltenyi Biotec's CliniMACS Prodigy
  - 2) Lonza's Cocoon



# PARTIALLY AUTOMATED SYSTEMS

- Modular platforms where some steps can be automated
- Different processing devices for individual manufacturing steps
- Less product handling than manual systems
- Other examples include:
  - Celyad's CYAD-01 System
  - CellGenix's CellXpert System



# ONBOARDING NEW SITES

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Knowledge translation to new sites:

- (1)Gap Assessment:** performed by first manufacturing centre to assess level of equivalence/appropriateness of site-specific technology and potential regulatory gaps.
- (2)Technology Transfer Package:** provide the blueprint for how to implement the technology developed already to the recipient POC site.
- (3)Audit:** Quality and Manufacturing personnel from chosen site perform an onsite audit of the recipient POC site.

# ONBOARDING NEW SITES

*How do we ensure that we are making a standard or consistent quality product across multiple sites?*

- Split batch runs
- Site by site comparability studies
- All products need to meet basic benchmark of CofA



# CENTRALIZED VERSUS DECENTRALIZED

## Centralized Manufacturing

- Increased timelines due to transport, chain of custody
- Complex manufacture and delivery process
- Single manufacturing site: risk and vulnerability
- Products need to cross U.S. border

## POC/Decentralized Manufacturing

- Often shorter manufacturing and vein-to-vein times
- Less risk of human error with automated processes
- Multiple sites: less risk and vulnerability
- Products made close to hospital

# CENTRALIZED VERSUS DECENTRALIZED

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## Centralized Manufacturing

- High capacity for manufacturing
- Quality control of multiple facilities not needed
- Highly trained staff can train and work in one facility, avoiding duplication of labour

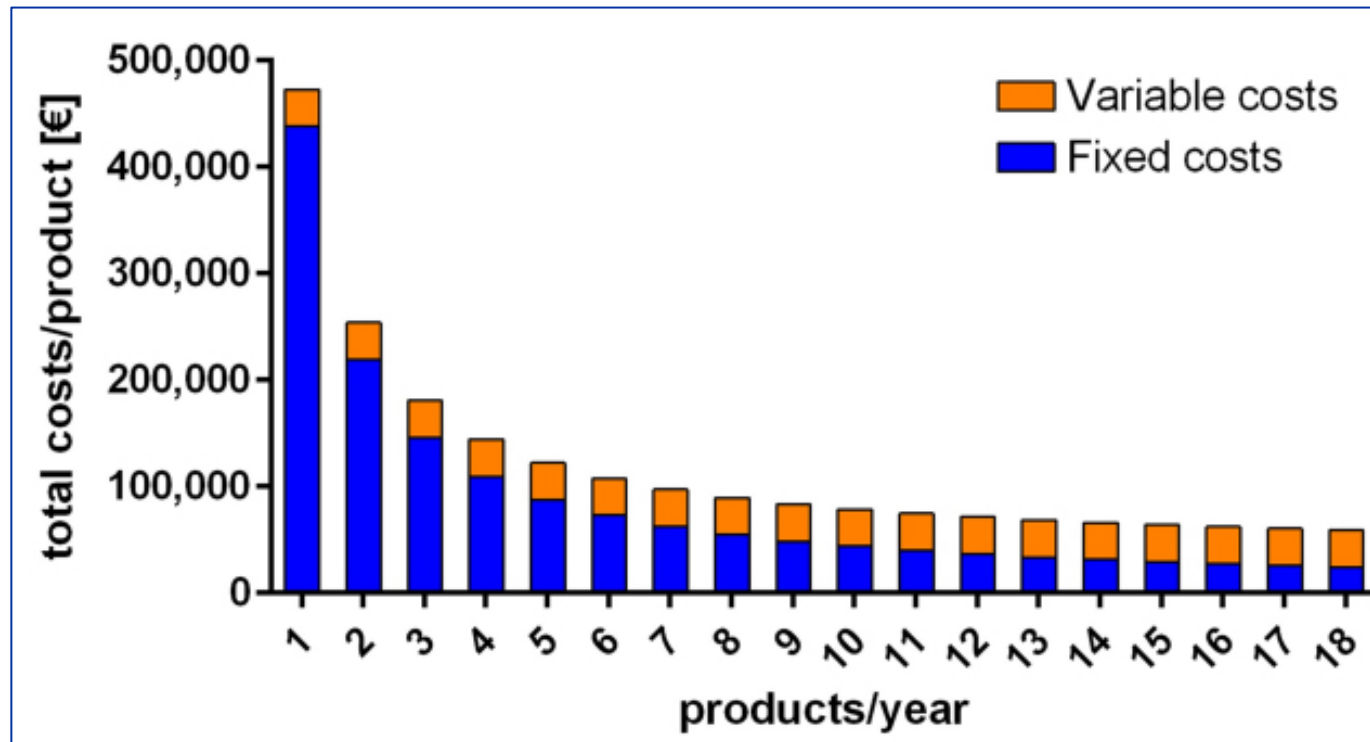
## POC/Decentralized Manufacturing

- Limited to one product on one machine at a time, infrastructure to build capacity more limited
- Multiple facilities means multiple audits and quality teams
- Duplication of manufacturing and QA/QC members

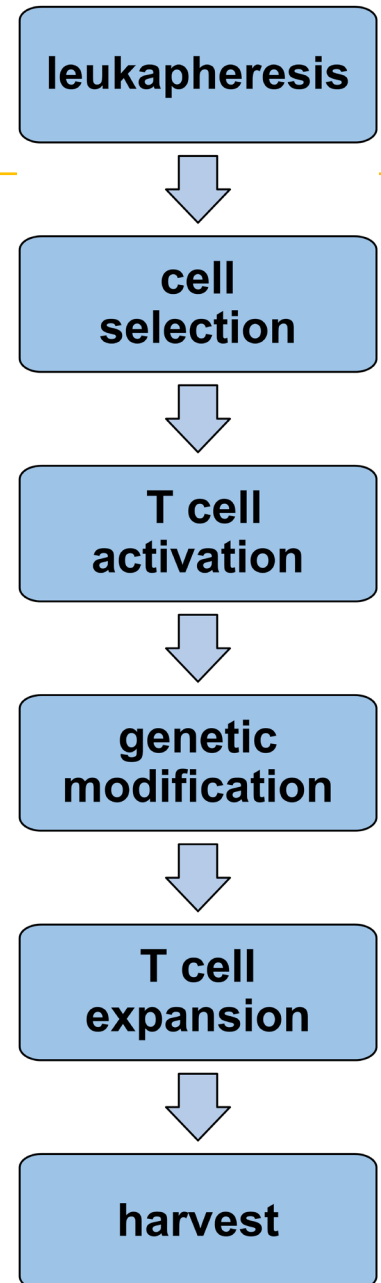
# WHAT ABOUT COST?

Costing model from German Cancer Research Center in Heidelberg, Germany in 2018

Cost per product: \$60,000 if 18 manufactured versus \$605,000 if 1 manufactured



Tao Ran and Stefan B. Eichmüller et al, Cancer Therapy and Prevention, 2020



# WHAT ABOUT COST?

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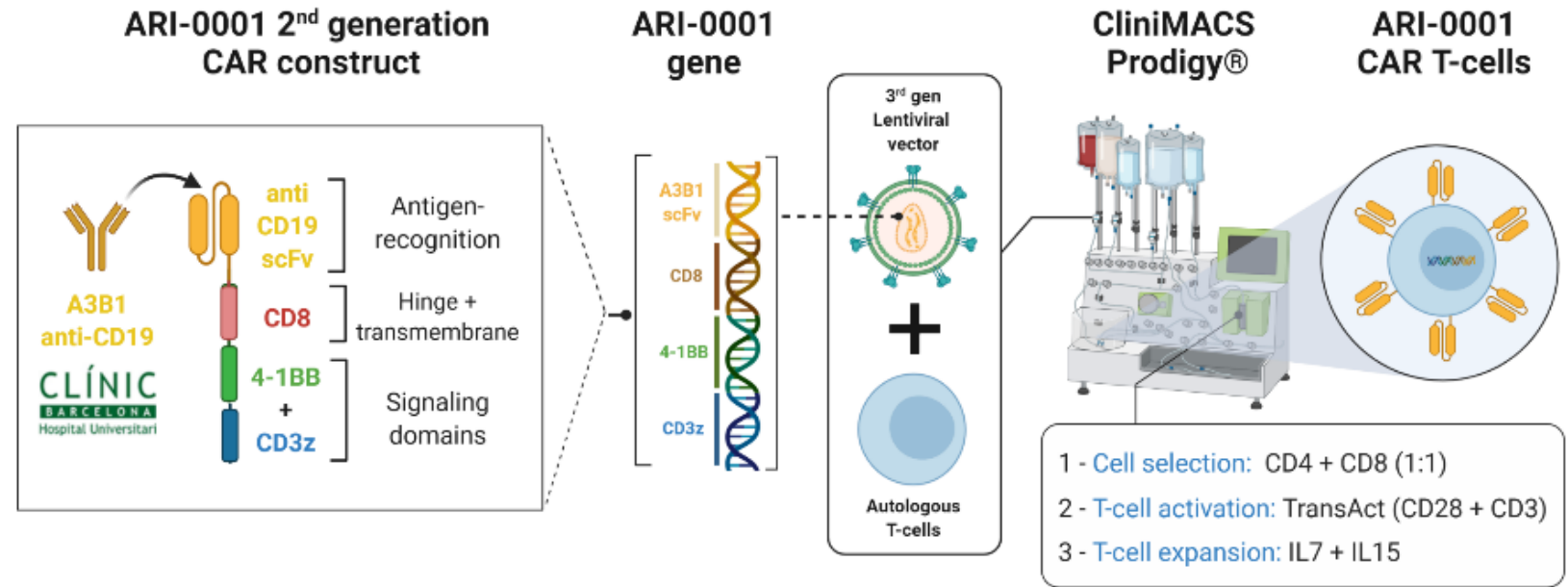
Critics would argue that manufacturing costs are just one piece of the puzzle, other factors to consider:

- Quality oversight and regulatory affairs, especially if multiple manufacturing sites
- Intellectual property management
- Sponsor oversight and liability
- Fixed and variable costs are jurisdictional, not generalizable
- Costs go down with scaling up manufacturing, but to what end



# SUCCESS 1: SPANISH ACCESS AND AFFORDABILITY

- Hospital Exemption (allowing Spain to regulate the product for Spain while EMA application ongoing), dossier submitted to the Spanish agency in Feb 2020
- ARI-0001 cells (var-cel) approved for patients older than 25 years of age with R/R ALL (Feb 2021)
- Compassionate use program approved for patients outside currently approved indications
- Price & reimbursement agreed with Ministry of Health in June 2021 → €89,270 (97K USD)
- Phase 2 trial in 12 Spanish centres, specifically intended for adult patients with R/R ALL → finished recruitment in August 2023
- Applying for conditional EMA approval



Picture courtesy of Dr. Julio Delgado, ARI-0001 PI

# SUCCESS 1: SPANISH ACCESS AND AFFORDABILITY



Spain has proven that an academic not-for-profit network could provide affordable access to CAR-T outside of clinical trial



For academic networks to build and sustain an affordable and accessible CAR-T platform:

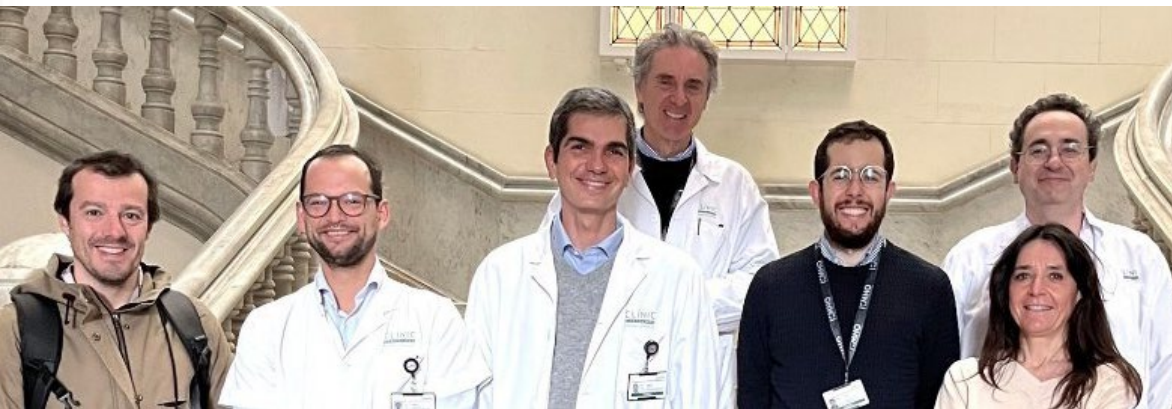
Upfront \$\$\$ (usually government)

Sustainable quality oversight

Agreement for reimbursement



FDA/Health Canada both in consultations now to understand how academic POC platforms can facilitate innovation, foster access and affordability and understand the hurdles associated with regulating and overseeing these platforms



# SUCCESS 2: ACCESS AND AFFORDABILITY

## Decentralized Manufacturing (CLIC Point- of-Care Platform)

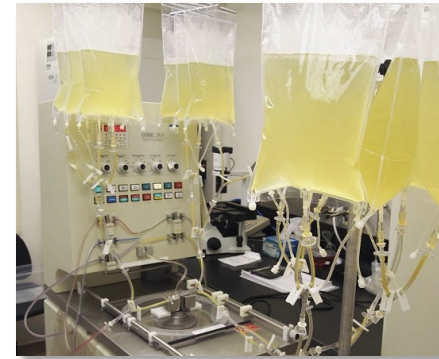
-  Therapeutics are 100% made-in-Canada
-  Lower costs: all processes completed within the same institution
-  Decreased timelines and faster patient delivery
-  Treatment at the point of care; standardized protocols across sites



Victoria, BC



Ottawa, ON



Toronto, ON

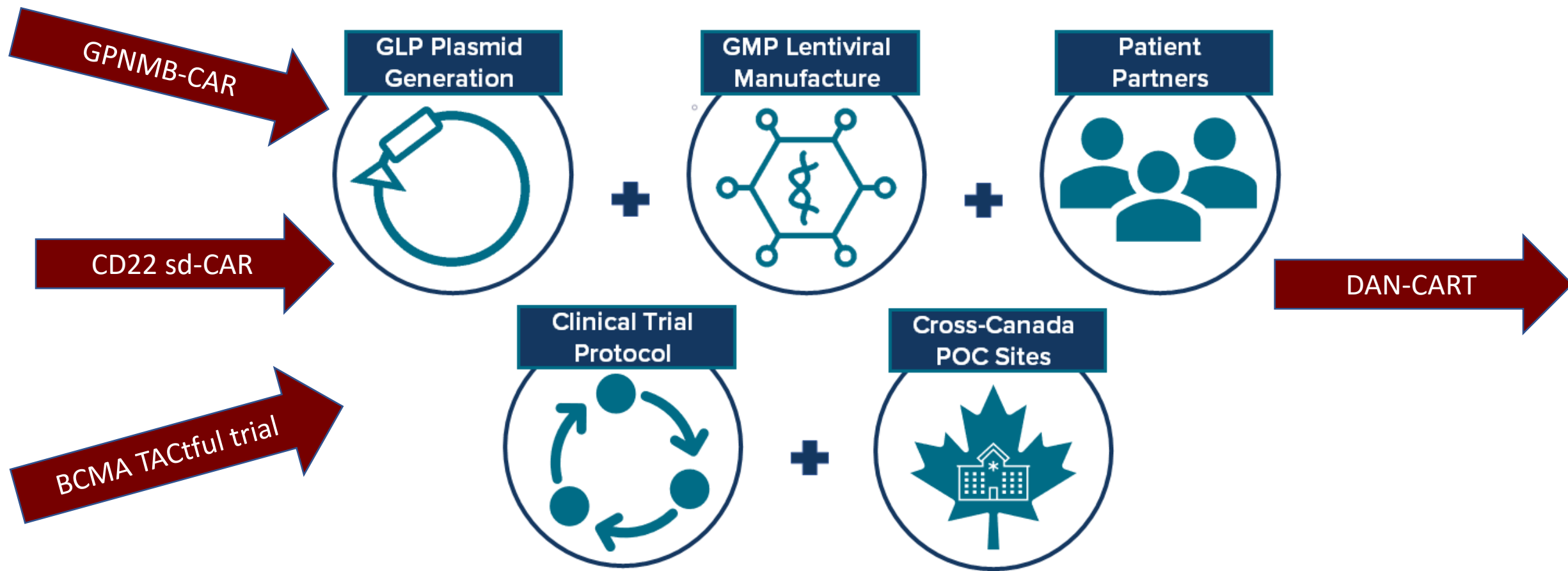


Winnipeg, MB

**Rapid Deployment of Made-in-Canada Clinical Trials**

## SUCCESS 2: ACCESS AND AFFORDABILITY

In addition to access/affordability, this allowed us to build a pipeline for Canadian innovation to reach trial



**Rapid Deployment of Made-in-Canada Clinical Trials**

# SUCCESS 3: FACILITATING COMMERCIAL TRIALS

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- Zamtocabtagene autoleucel, a *first-in-class* anti-CD19/anti-CD20 bispecific CAR was first tested in clinical trial at the Medical College of Wisconsin (MCW) under a Phase 1 investigator-initiated study
- This identified both a safe dose for future trials and defined the manufacturing process for this product, using the CliniMACS Prodigy fresh out-fresh in procedure
- This informed the development of two ongoing clinical trials in Europe and the United States with Miltenyi Biomedicine



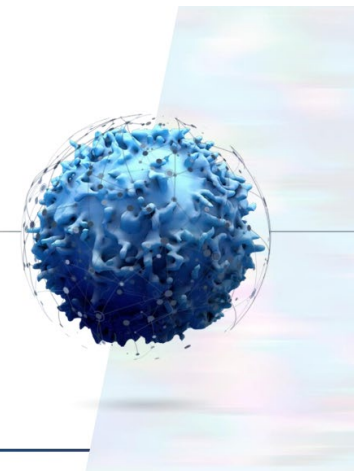
# SUCCESS 4: FACILITATING COMMERCIAL TRIALS

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- Stanford developed an anti-CD22 CAR construct for patients with relapsed DLBCL after CD19 CAR-T exposure
- This utilized the CliniMACS Prodigy for manufacturing as part of a Phase 1 IIS and identified a safe dose with promising efficacy
- Now translated to a now multi-center Phase II study led by CARGO Therapeutics
- Academic data advised the design, safety, and dose to utilize in the Phase II and should allow this product to reach market authorization.



**CARGO**  
THERAPEUTICS



# SUCCESS 4: FACILITATING COMMERCIAL TRIALS

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Academic centers are free to test novel concepts and can often initiate trials quickly generating early data to help support larger trials



Results of this work can then direct pharma companies allowing them to focus on high value assets for multicenter/registrational trials

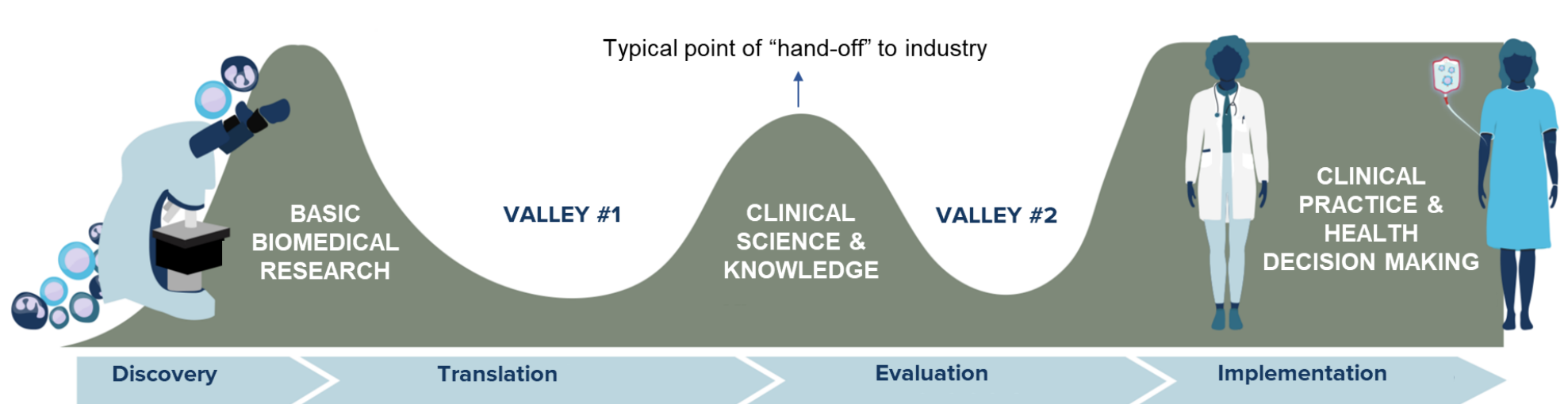
# CONCLUSIONS

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- CAR-T therapy remains restricted in access in all parts of the world, including the USA
- USA has shown patients residing farther from treatment centers are less likely to receive CAR-T
- USA also showed increased mortality in patients with larger distances to treatment centres
- Point-of-care manufacturing can improve access and affordability
- Point-of-care can allow for feasible and fast first-in-human phase I/II trials

# CONCLUSIONS

Point-of-care manufacturing can facilitate the peaks and valleys from discovery to implementation of CAR-T therapies



## 1) Decentralized biomanufacturing



## 2) Creating innovative health system adoption pathways



**Requires regulatory & policy strategies**

# PROJECT TEAM AND ACKNOWLEDGEMENTS

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