Integration of work flows for the generation of gene-modified cell products

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Chief Science Officer and General Manager
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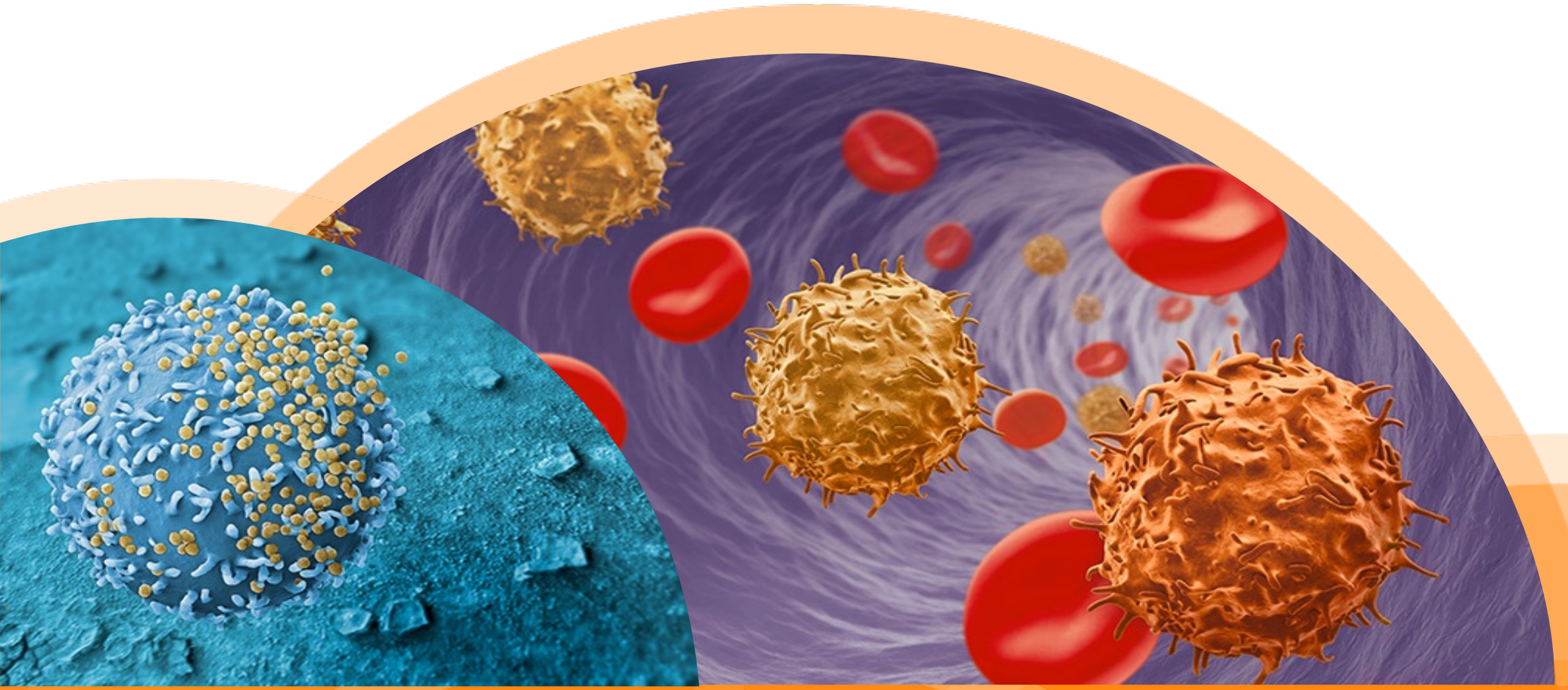

Miltenyi Biotec: Enabling Clinical Centers and Industry

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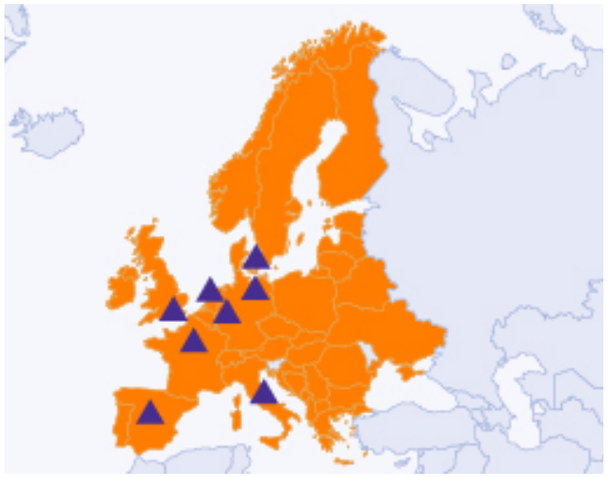

- Miltenyi Biotec is a 1800 person company with global operations
- Employs over 600 people in R&D and engineering
- Headquarters near Cologne, Germany
- Committed to supporting investigators with solutions that enable the clinical translation and practice of novel cell and gene therapies
- Lentigen was purchased in August 2014 by Miltenyi Biotec GmbH
- Integration of LV manufacturing competency with MB work flow solutions for the manufacture of gene-modified cell therapy products

Generation of CAR-T cell products using manual processes are complex and difficult to integrate

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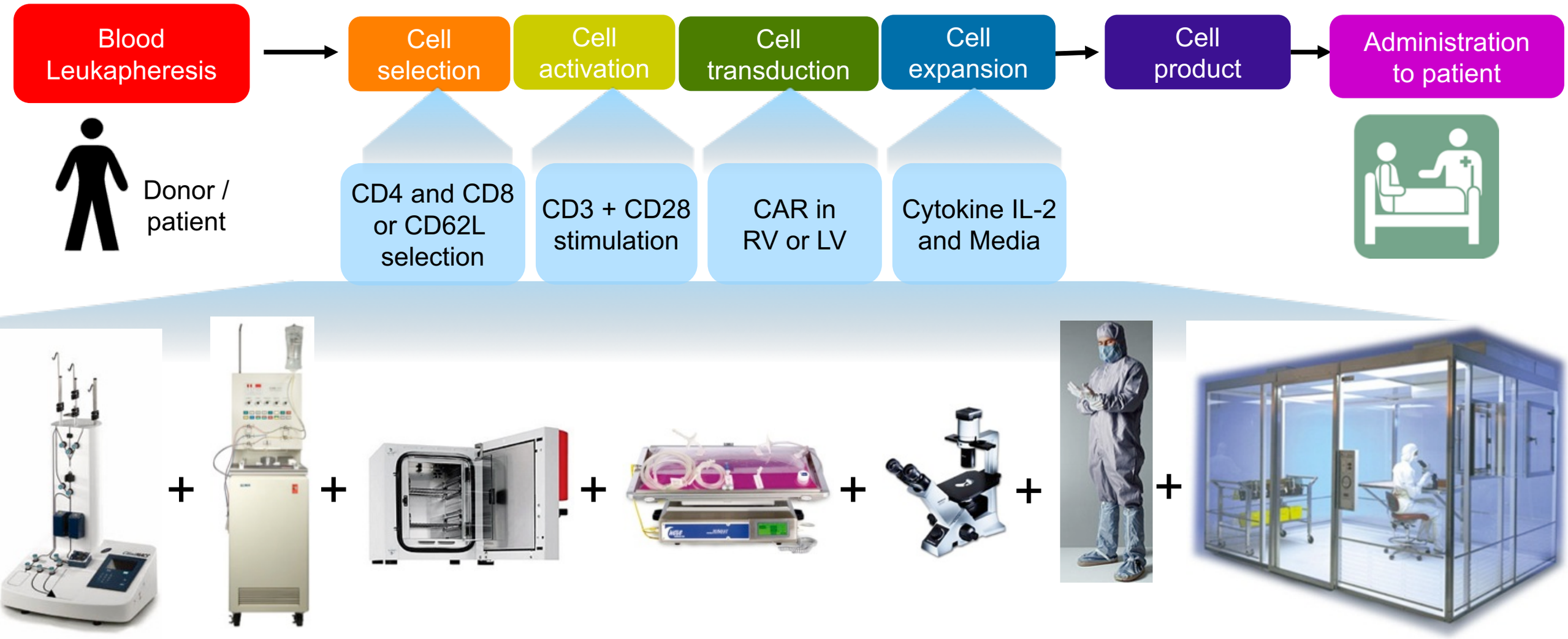

Integration of unit operations into a single device: Automation of cell processing

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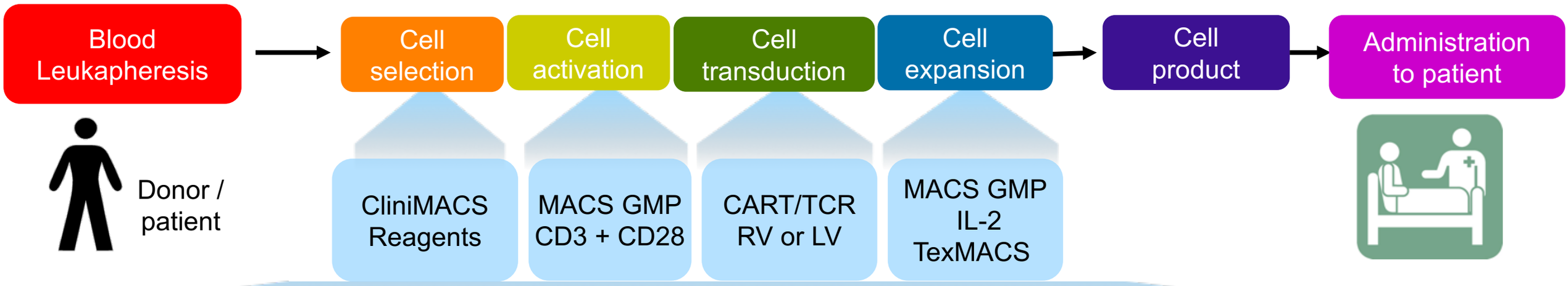

The CliniMACS Prodigy

- **Integrated cell processing from starting material to final cellular product:**
  - Sample preparation
  - Cell washing & density gradient separation
  - MACS cell separation
  - Cell activation
  - Genetic modification (LV)
  - Cell culture & expansion
  - Final product formulation

Automated cell processing provides options for the manufacture of patient specific cell therapies

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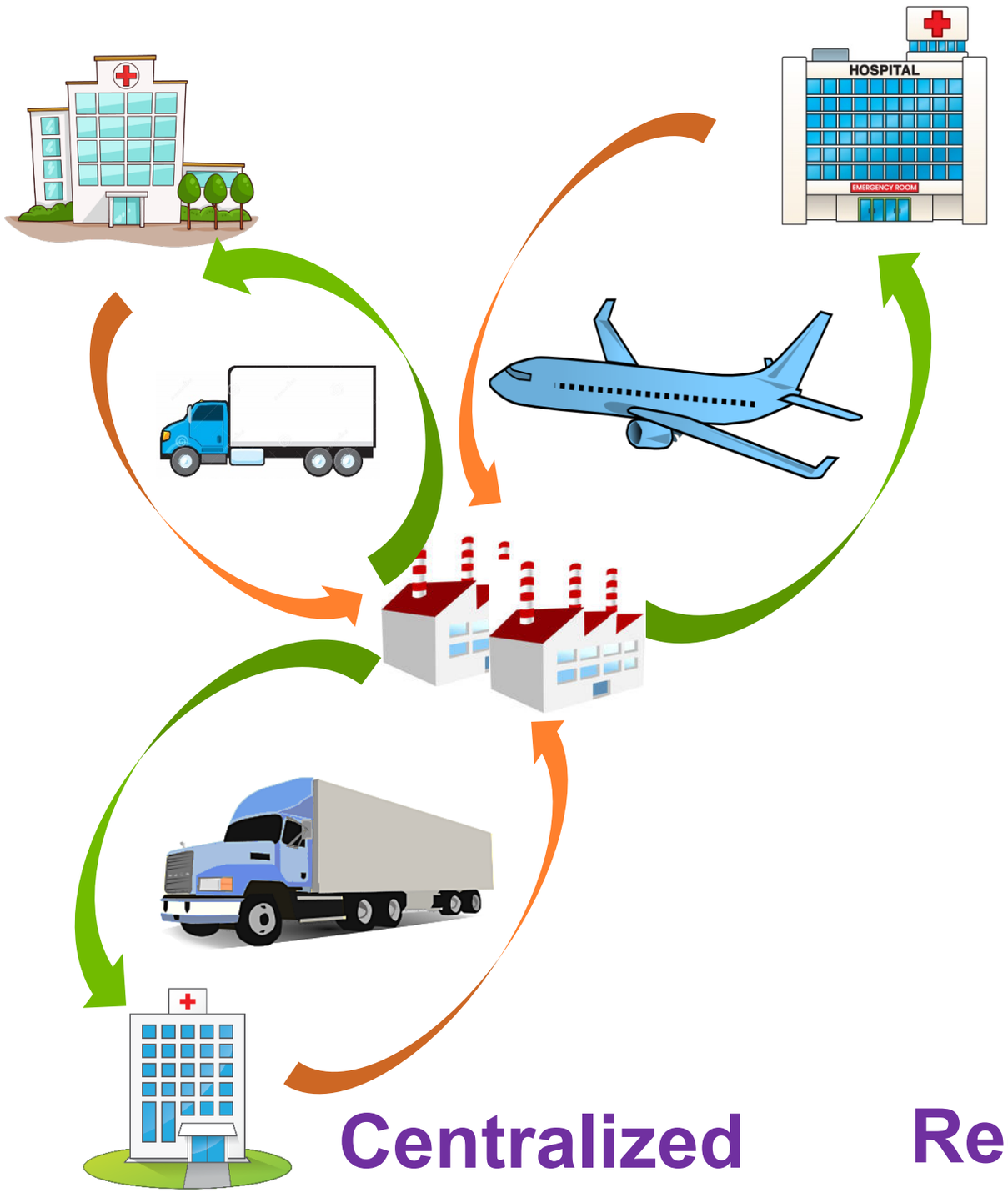
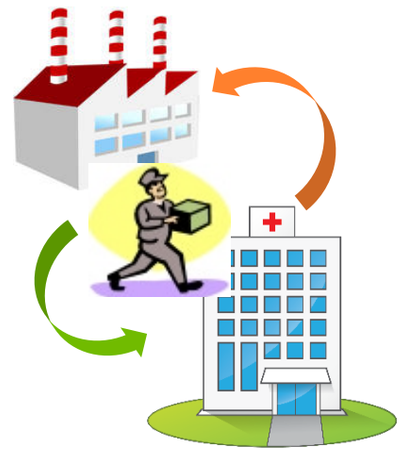
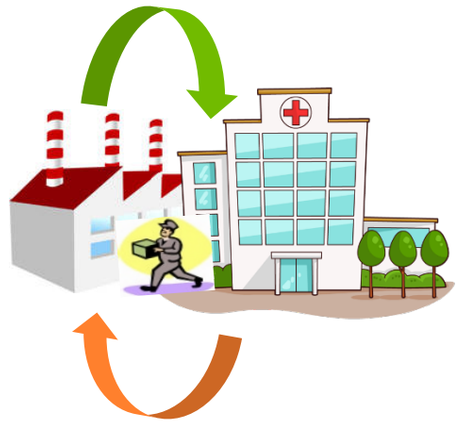
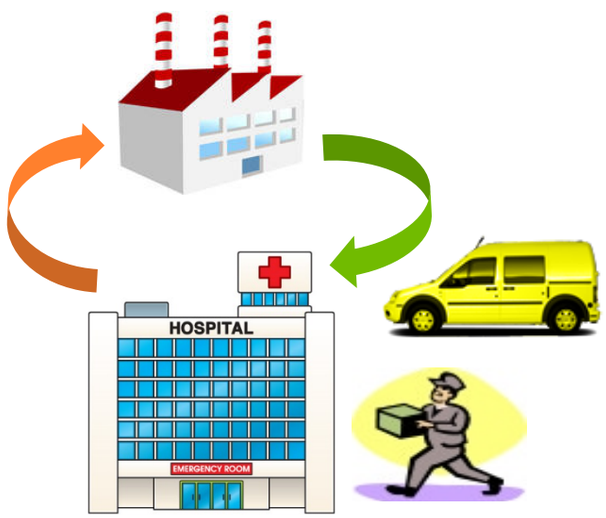






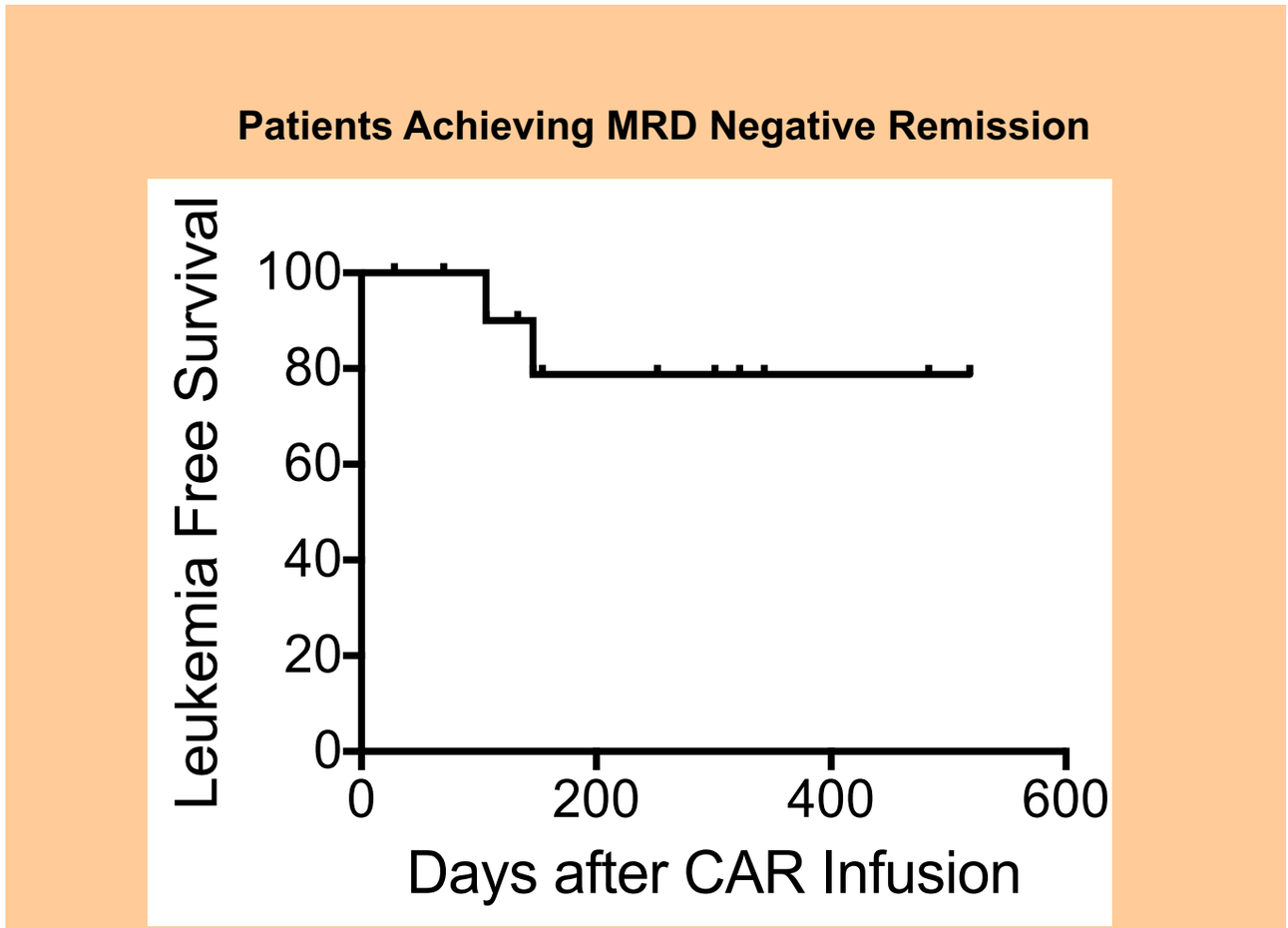


Centralized

Regional

Point-of-care

Clinical success of CD19 CAR T cells in Phase I Trials



Group	CR Rate
NCI, Ped. Onc. Branch	85%
UPenn, CHOP	90%
MSKCC	88%

CD19 Negative Relapse in 10-50% of CAR-T 19 treated patients

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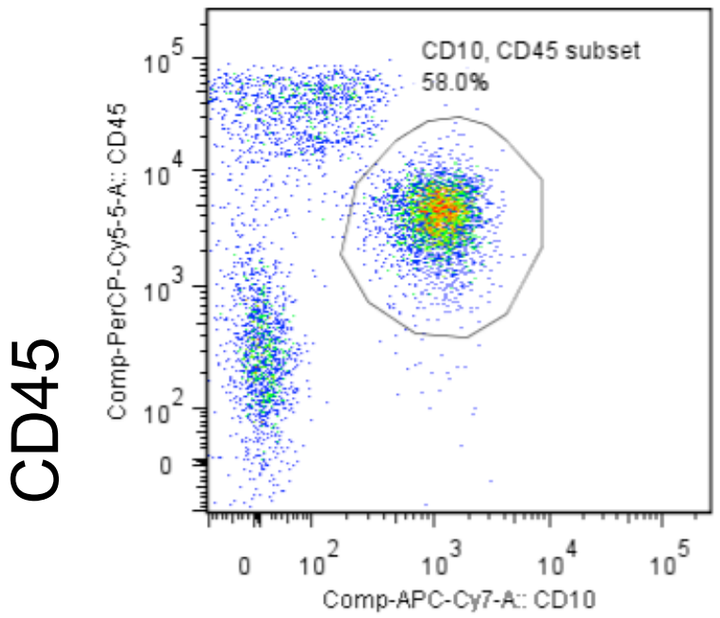
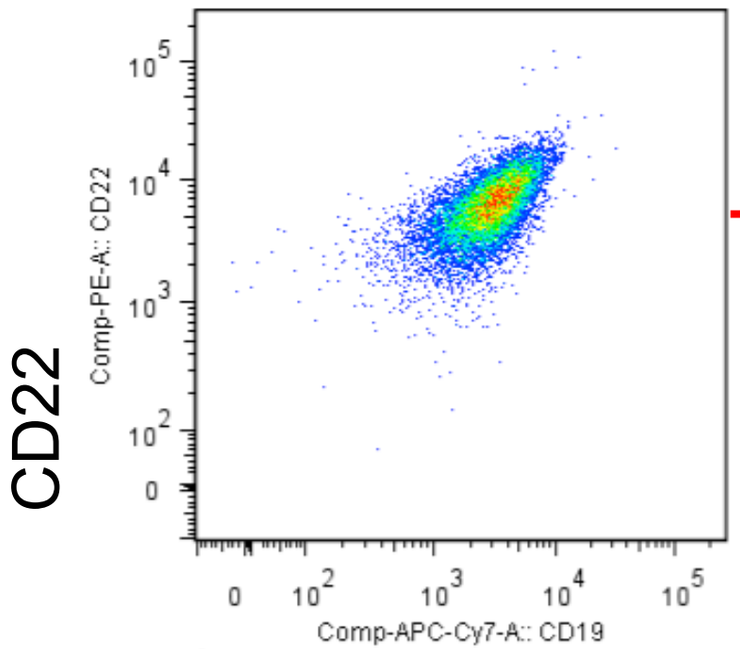
Pre-CD19 CAR Therapy



CD45

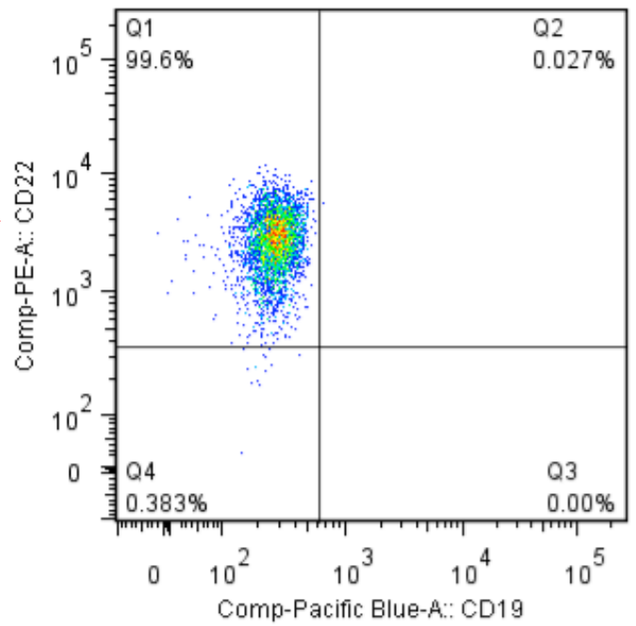
CD10



CD22

CD19

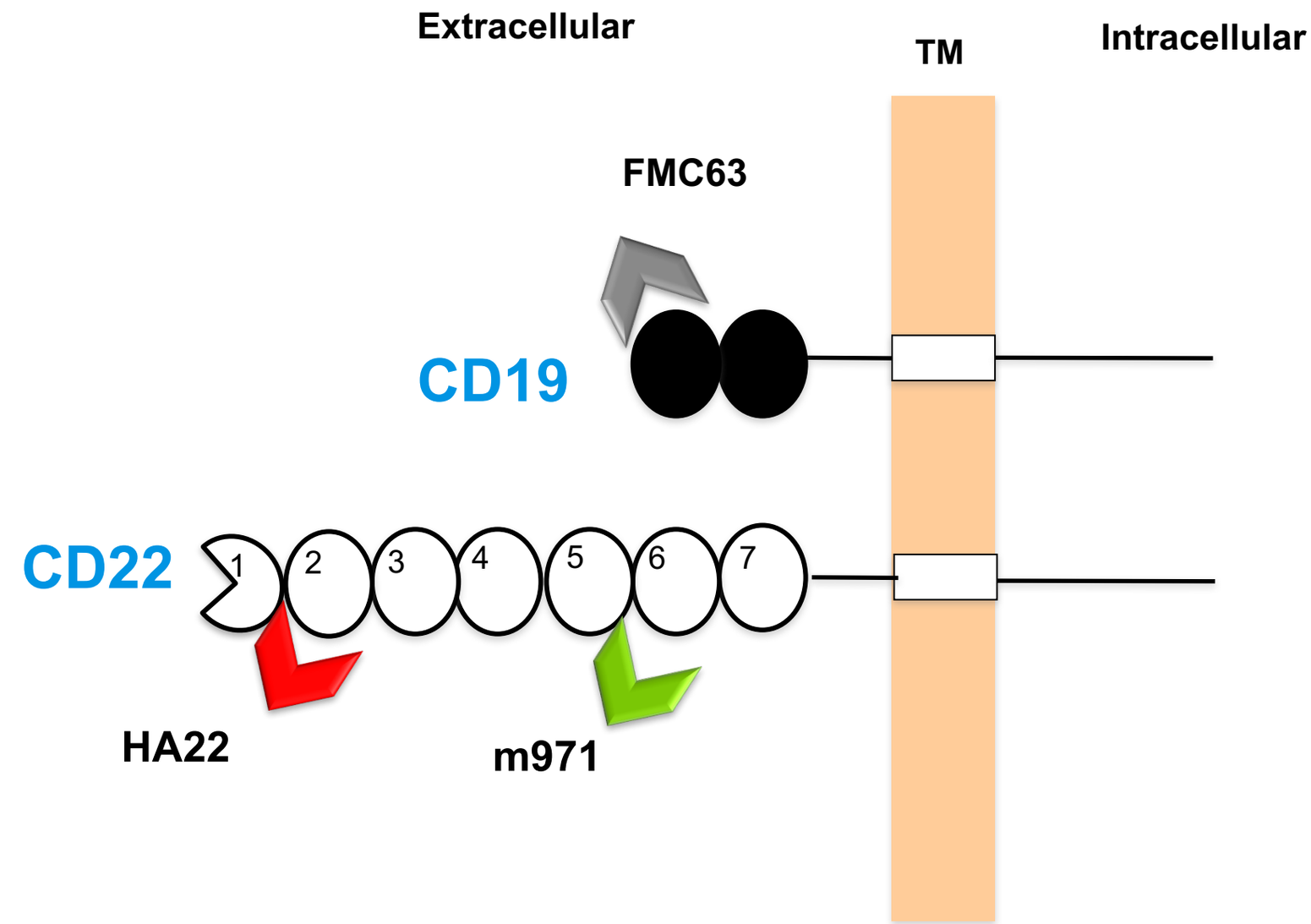
Relapse



CD22

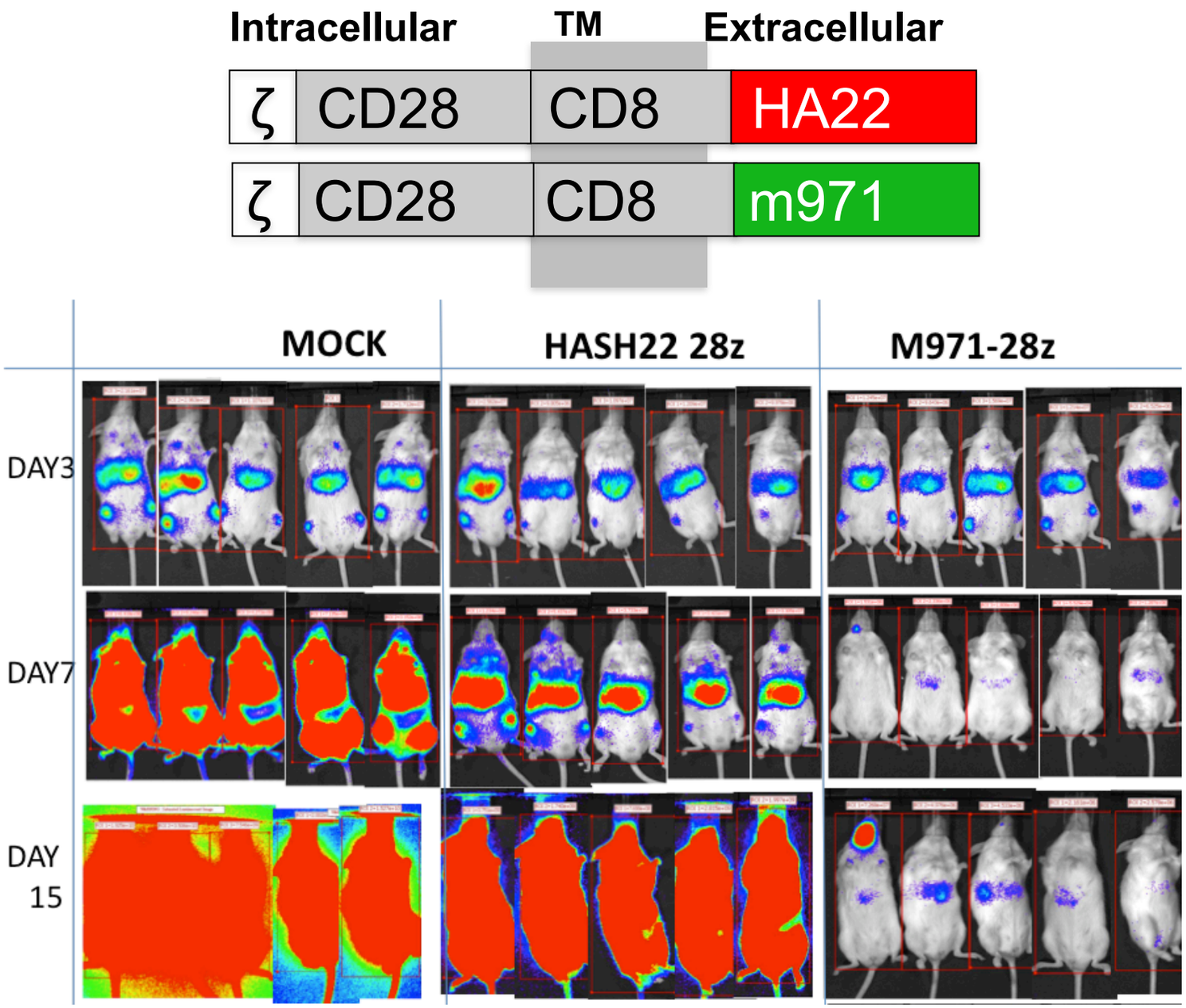
CD19

Improving CAR-T function: geometry of binding



Rimas Orentas
Waleed Haso
Terry Fry
Crystal MacKall

Site of binding matters for CAR potency



4-1BB costimulation is important for T cell persistence

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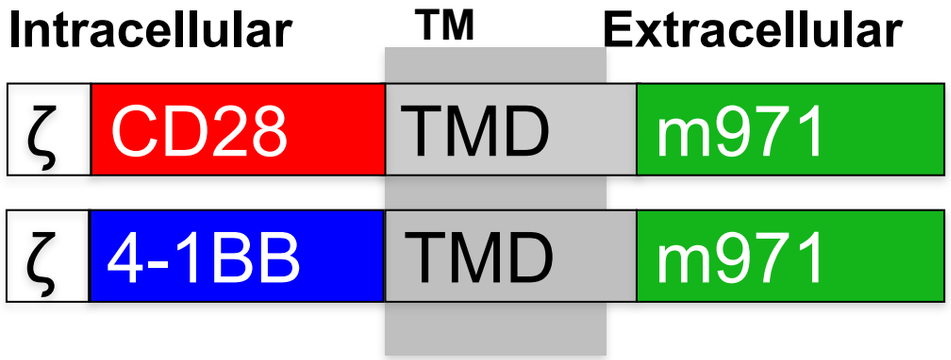
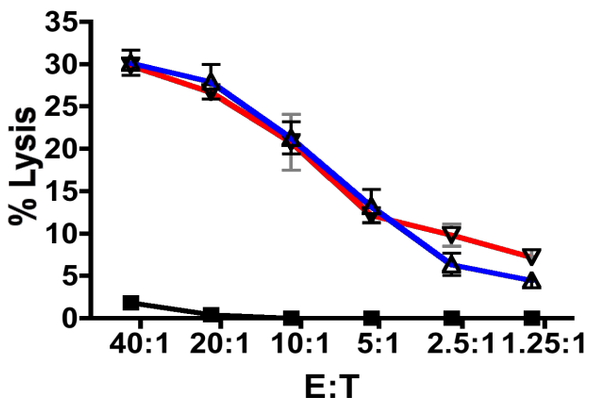
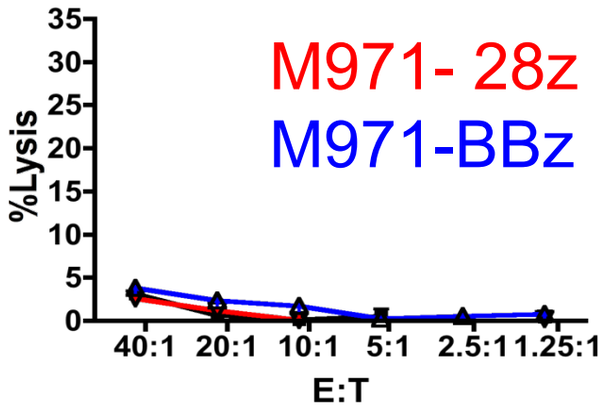
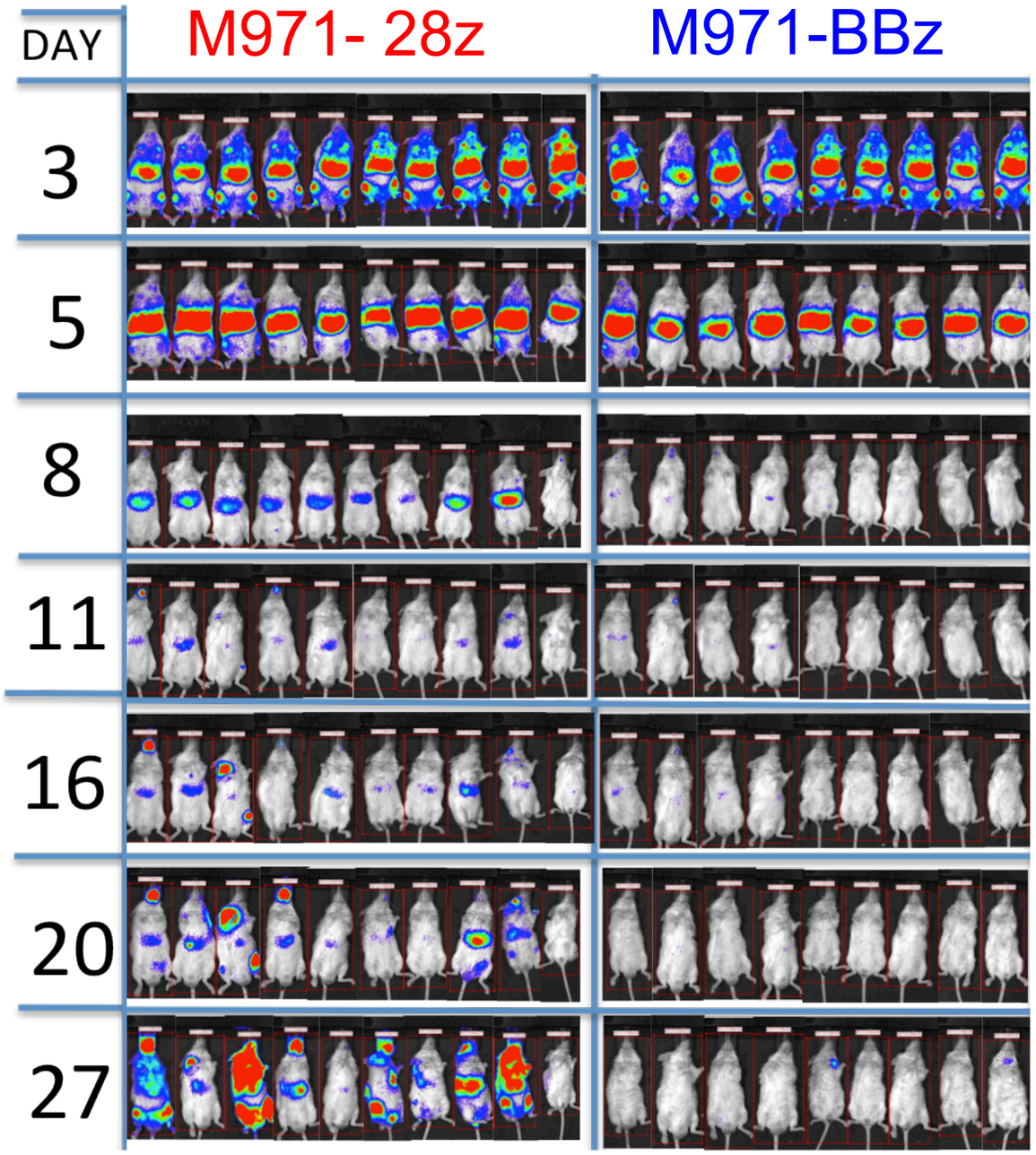


NALM6-GL



K562





Development of Tandem bispecific CD19-CD20 targeting CAR T cells for Adult Leukemia

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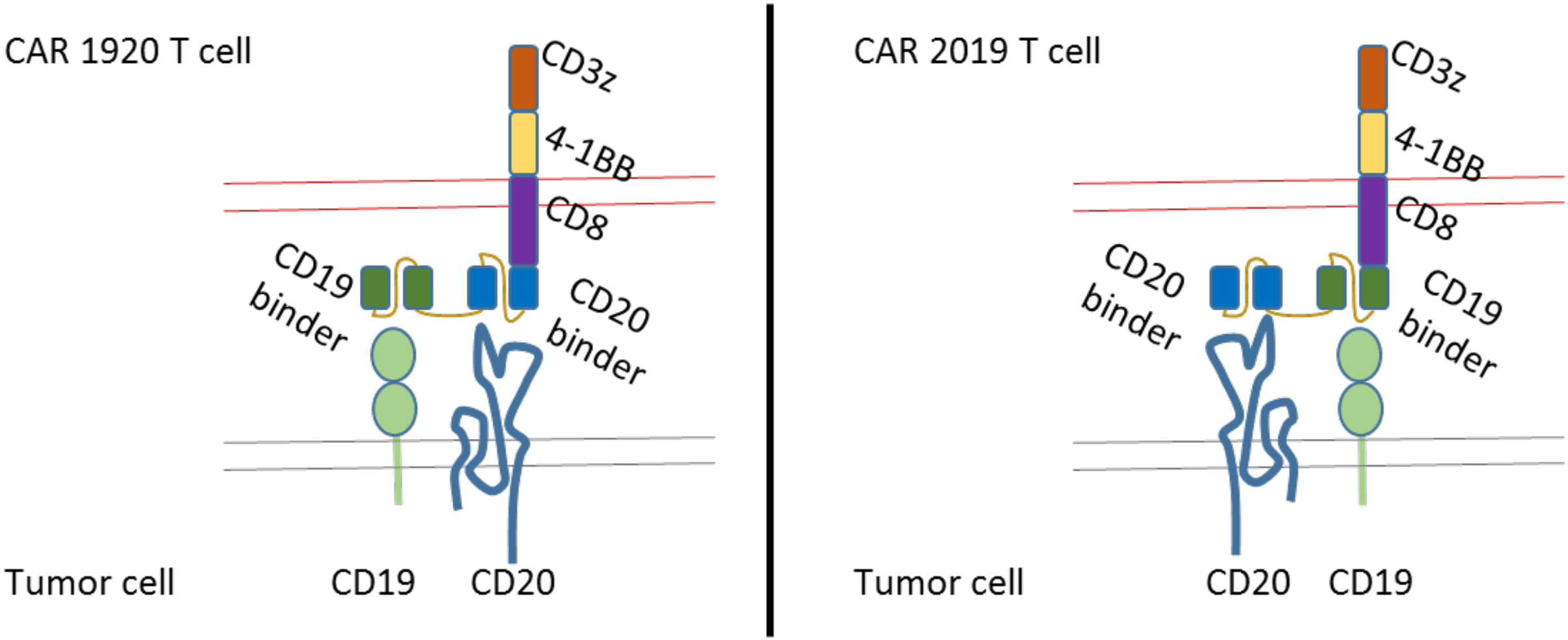
CAR T cells targeting two B cell tumor antigens at once are postulated to be more efficient, and to prevent tumor antigen escape



Specific detection of surface expression of tandem and single CD19/20 CAR in primary human T cells

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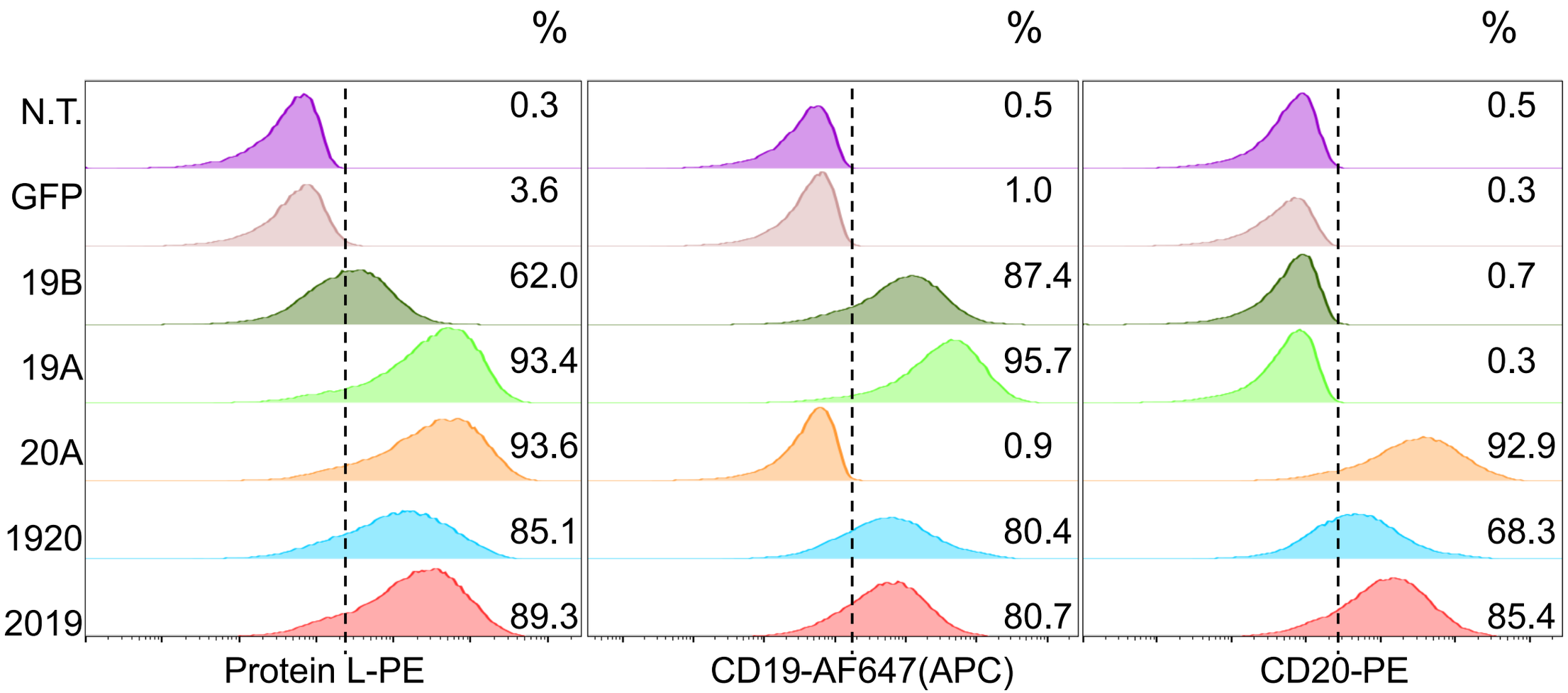
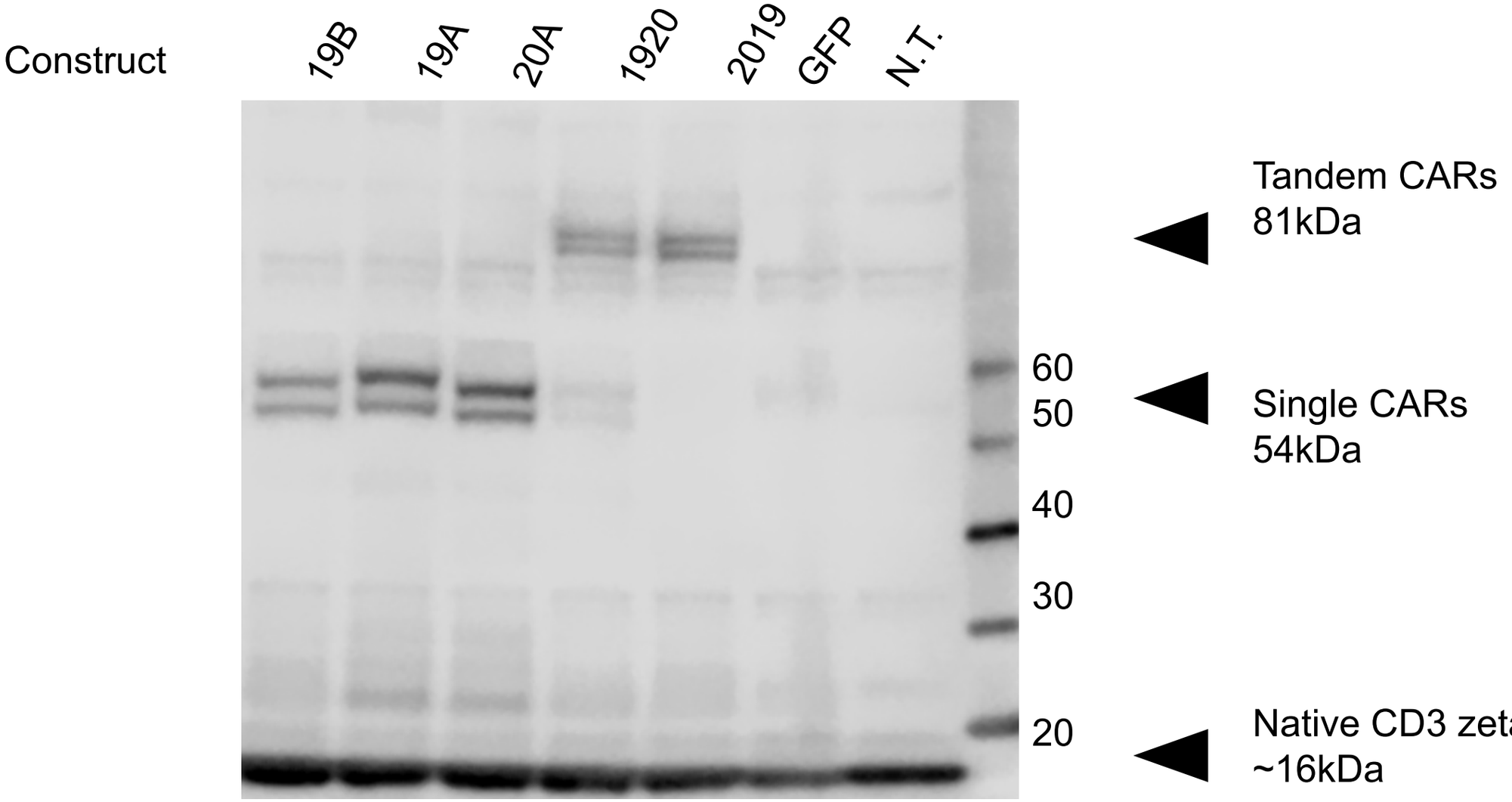
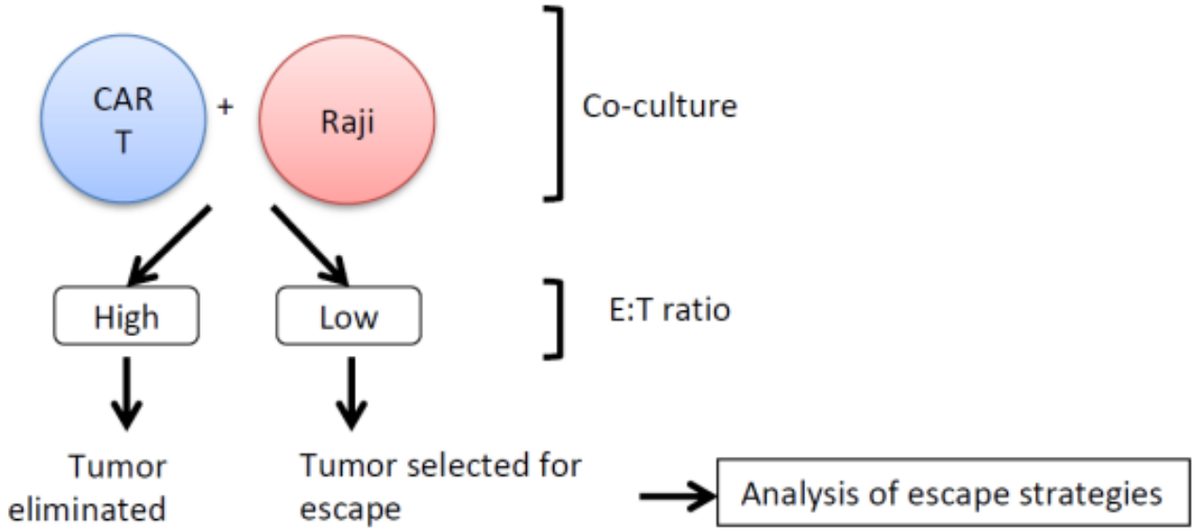


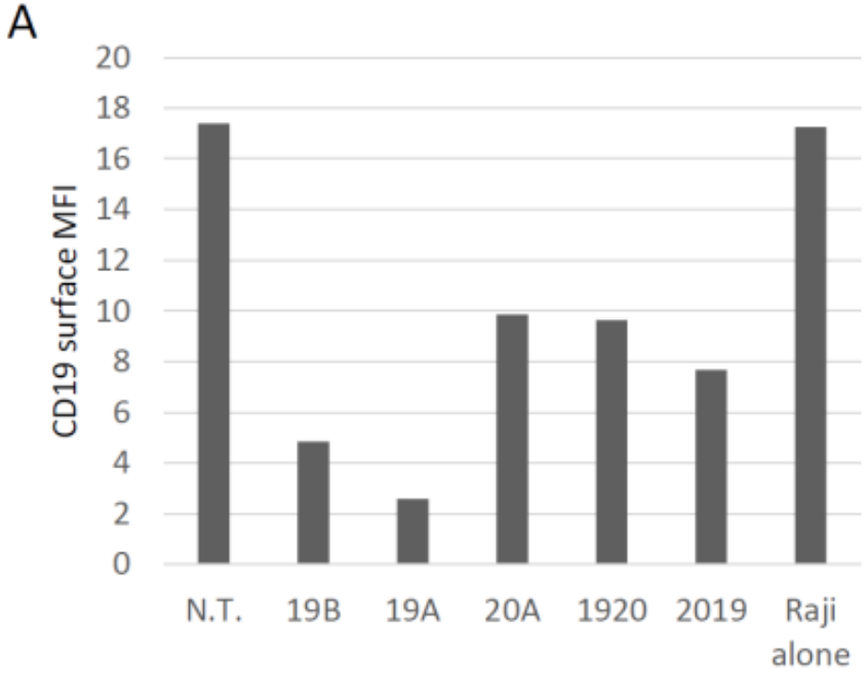
CAR T protein expression in primary human T cells as detected by Western Blotting

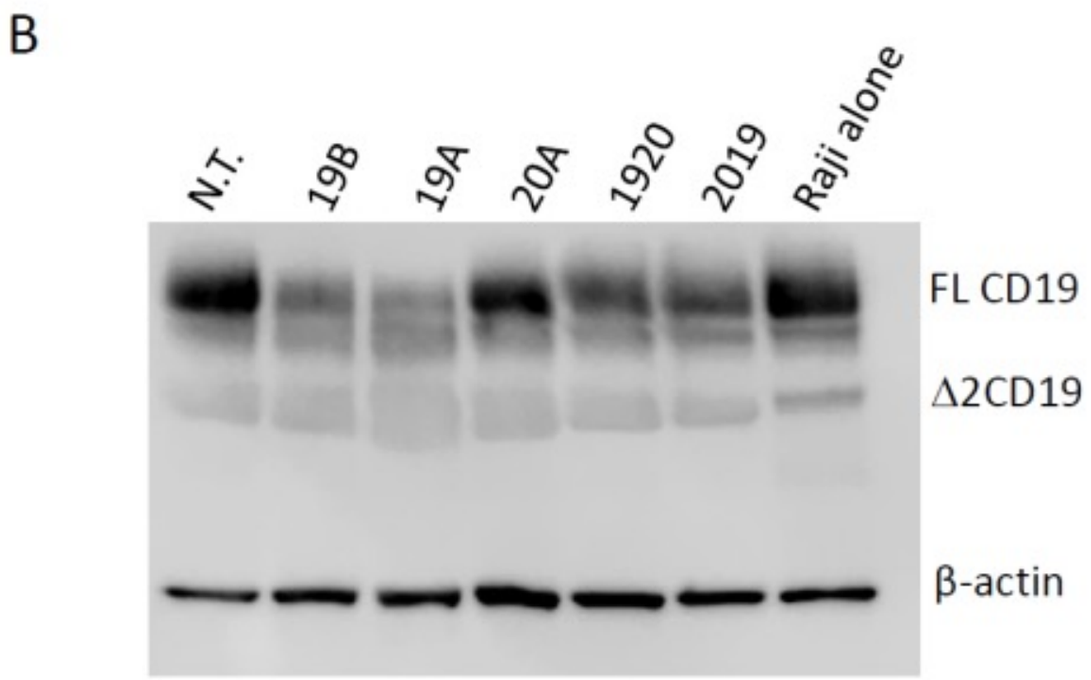


N.T. – non-transduced T cell control

Reduction of CD19 downregulation by Tandem CARs







Planned Phase I clinical trial at Medical College of Wisconsin, Milwaukee, WI, USA

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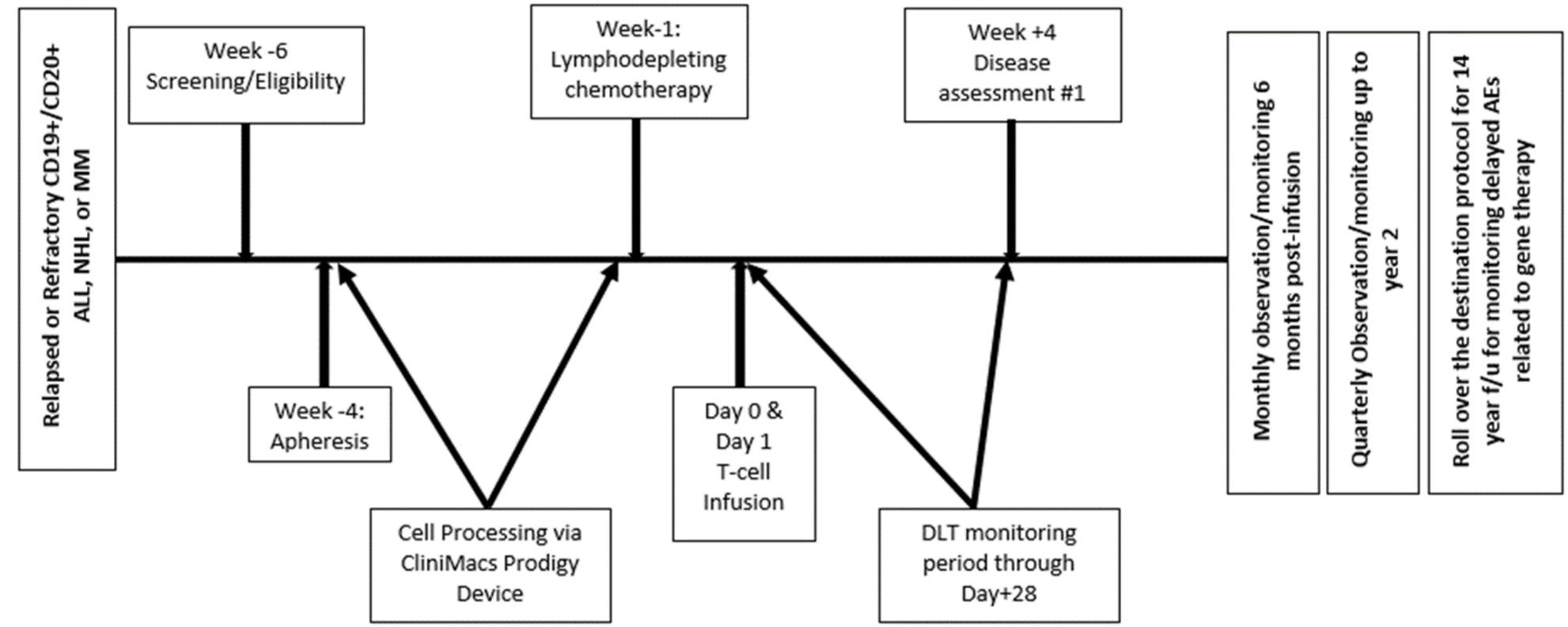
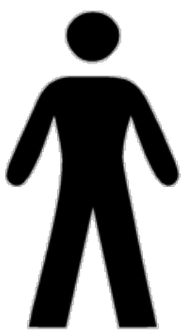
CART-20/19-T Cells
scFv CD20/CD19:CD3ζ-41BB





Shah, Taylor, MCW

Point-of-care cell processing facility blueprint

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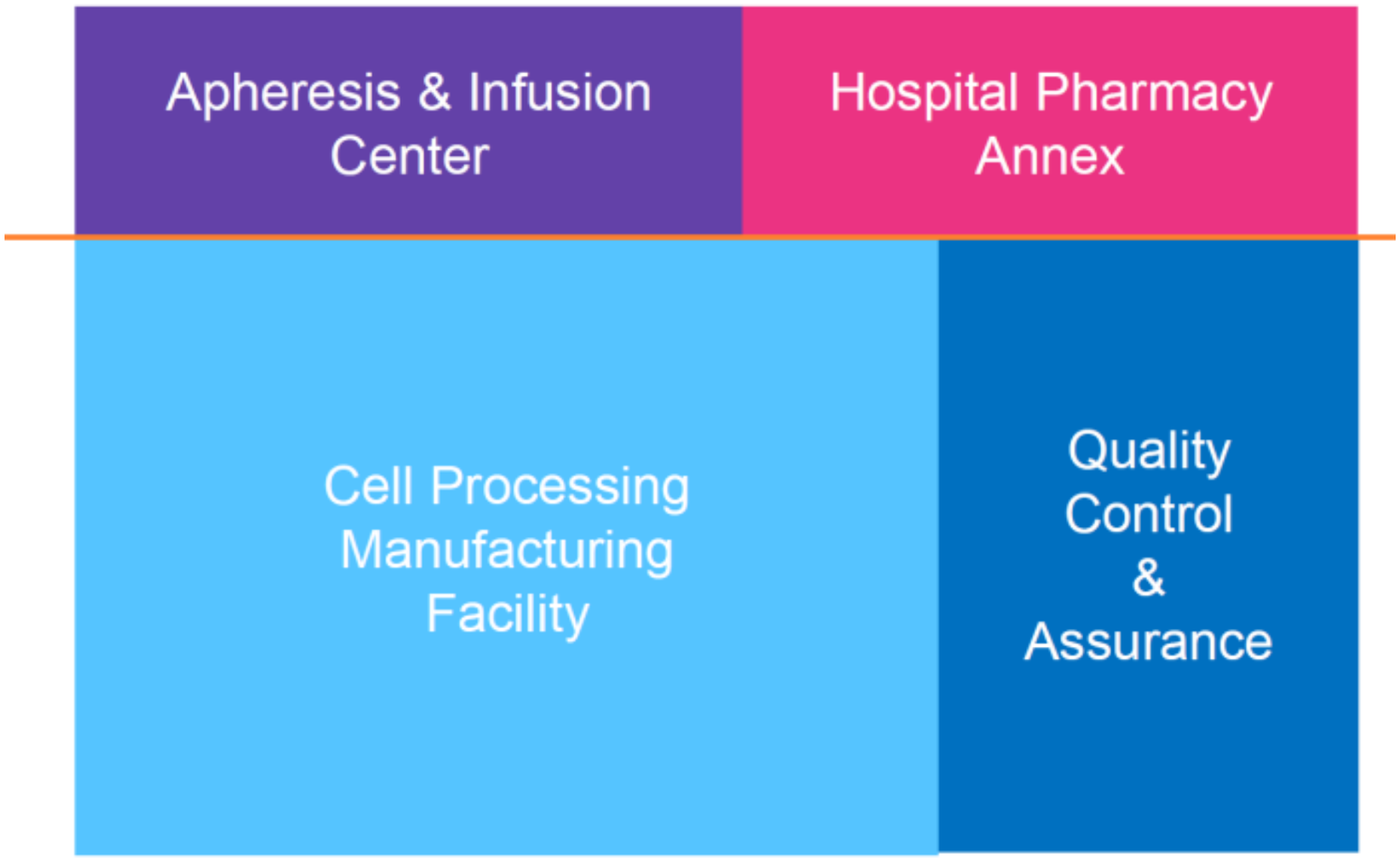

- Hospitals could be leveraged to decrease overall cost of manufacture
- Patients would benefit by local manufacture their patients' cell products - better control, no transportation, no cryopreservation → safer product
- If given a choice, hospitals would prefer a point-of-care model

Robust work-flows requires seamless integration of work-flow components and analytics

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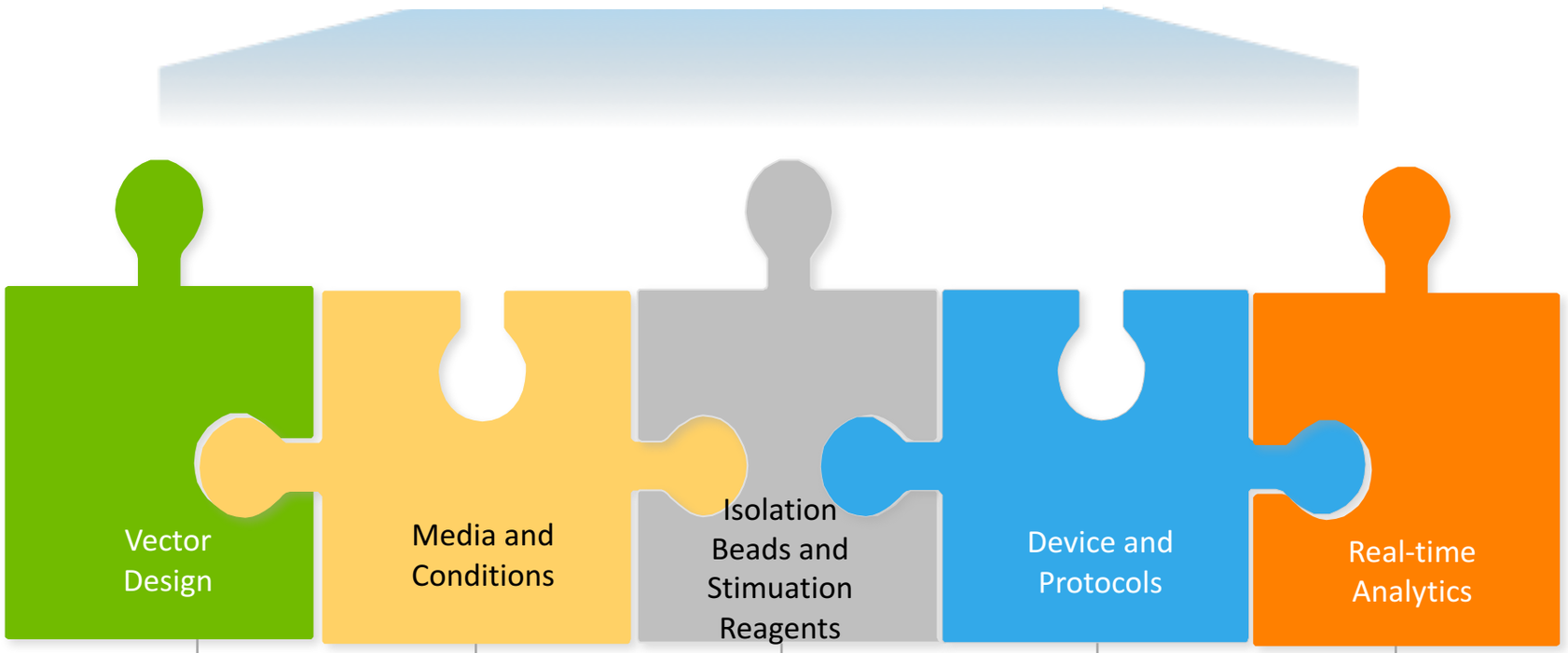
Blood Leukapheresis → Cell selection → Cell activation → Cell transduction → Cell expansion → Cell product → Administration to patient

Donor / patient



Single-source supply avoids costly qualification and validation of outsourced materials

Summary

- **Miltenyi Biotec is an enabler for gene and cell therapy**
  - Enable companies with custom LVs, automated work-flows, reagents, regulatory support
  - Enable clinical centers with automated work-flows, reagents, “generic” products – CAR19 LV
- **Miltenyi’s vision for commercializing gene-modified cell therapy**
  - Automation improves economics and robustness of cell processing work-flows
  - Automation provides options for manufacturing: Point-of-Care models now possible
- **Development of “generic” & novel LV GMP CARs for clinical testing**
- **Manufacture of patient CAR-T cells in Prodigy device is robust**
  - Programs for Hematopoietic Stem Cells and other cell types: available or in development
- **New products – Prodigy electroporation unit and Tyto flow-though microchip sorting of specific cell types**
- **Committed to helping investigators to turn their innovations into clinical and commercial realities**

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