CAR T cell Therapy for Hematologic Malignancies

Nabil Ahmed, MD, MPH

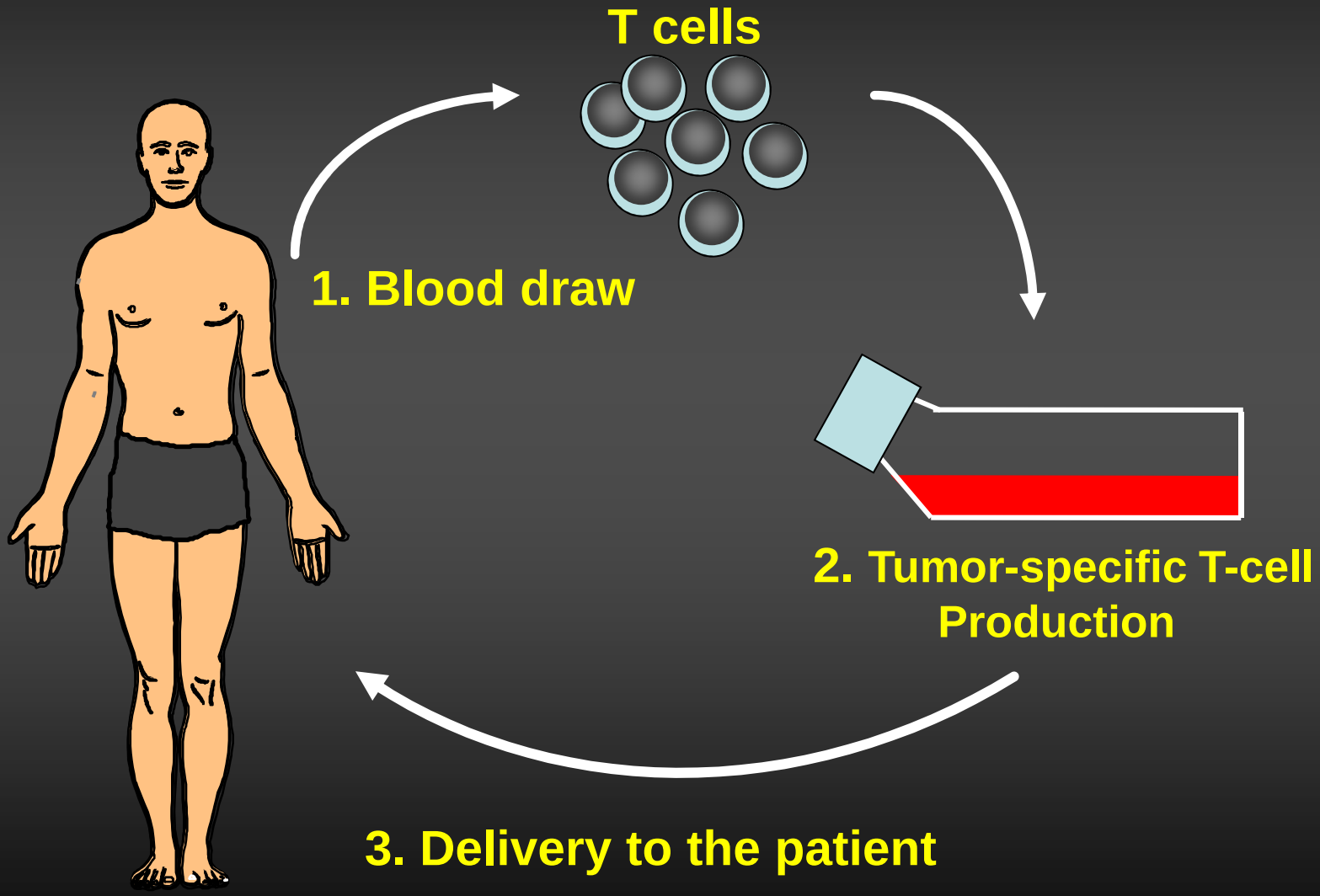
Carlos A. Ramos, MD, *et al.*

Associate Professor, Baylor College of Medicine, Houston, Texas

Outline

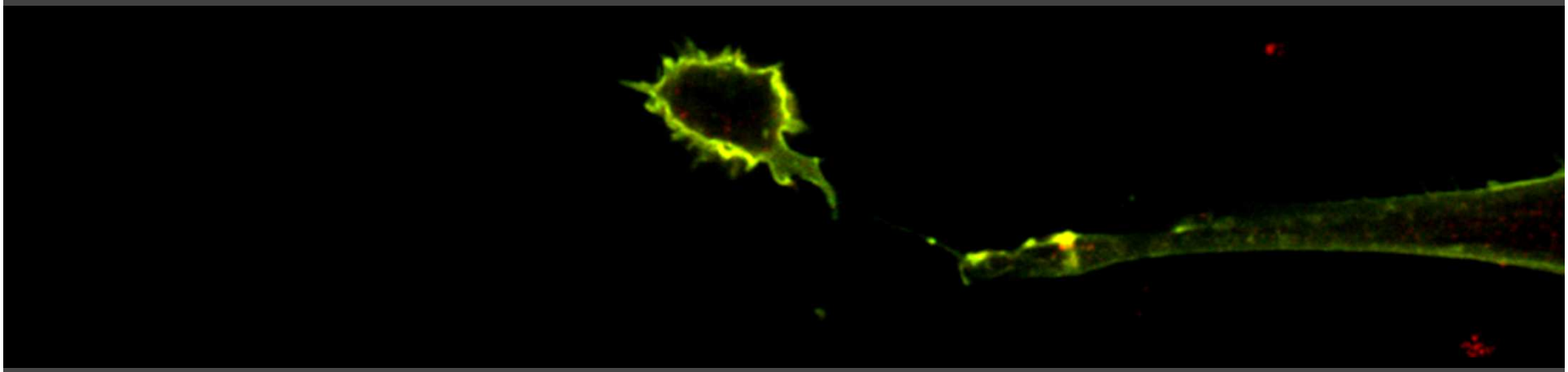
- **Adoptive T cell Transfer**
- **Chimeric Antigen Receptor T cells**
- **CD19 CAR T cells in the Clinic**
- **Non-CD19 CAR Trials**
- **Complications of CAR T cell Therapies**

T cell Therapy



T cell Therapy: *advantages*

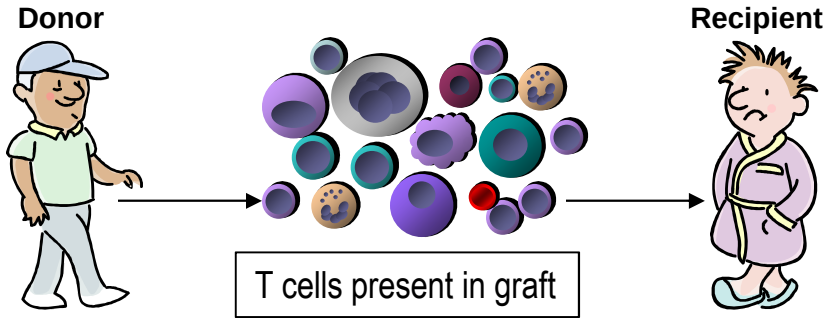
- **Δ killing mechanisms …** *conventional Rx*



- **Migrate; extravasate; expand …** *vs. MAb*
- **↑ frequency; ↓ anergy …** *vs. DC vaccines*
- **↓ autoimmunity …** *vs. tumor cell vaccines*

Bollard et al. *Blood* 2004. Plautz et al. *Clin Can Res* 2000; Marras et al. *Curr Opin Onc* 2003

Earliest examples of T cell therapy for hematological malignancies



- Allogeneic BMT GVL (co-infused T cells)
  - Initially unappreciated

*Donor Lymphocyte Infusion
**Post Transplant Lymphoproliferative Disorder

Treatment and prevention of PTLD with EBV-CTLs

Reference	Source	Intent	Efficacy
Heslop 2009	BMT donor	Prophylactic	99% success
Heslop 2009*	BMT donor	Therapeutic	85% ORR
Doubrovina 2012	BMT donor	Therapeutic	68% ORR
Leen 2013 Tzannou 2015	3rd party	Therapeutic	73% ORR
Prockop 2015	3rd party	Therapeutic	63% ORR

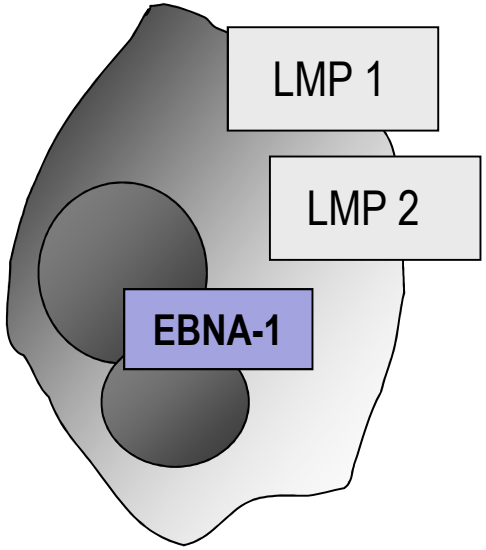
*and unpublished data

(ORR: overall response rate)

EBV-CTLs work in other malignancies

- Hodgkin lymphoma (Bollard *et al.*, JEM 2004)
- DLBCL (Bollard *et al.*, Blood 2007)
- NPC (Straathof *et al.*, Blood 2005)

- Optimization has included:
  - Overexpression **of weakly immunogenic proteins**
  - Introduction of **resistance to the effects of TGF-β**

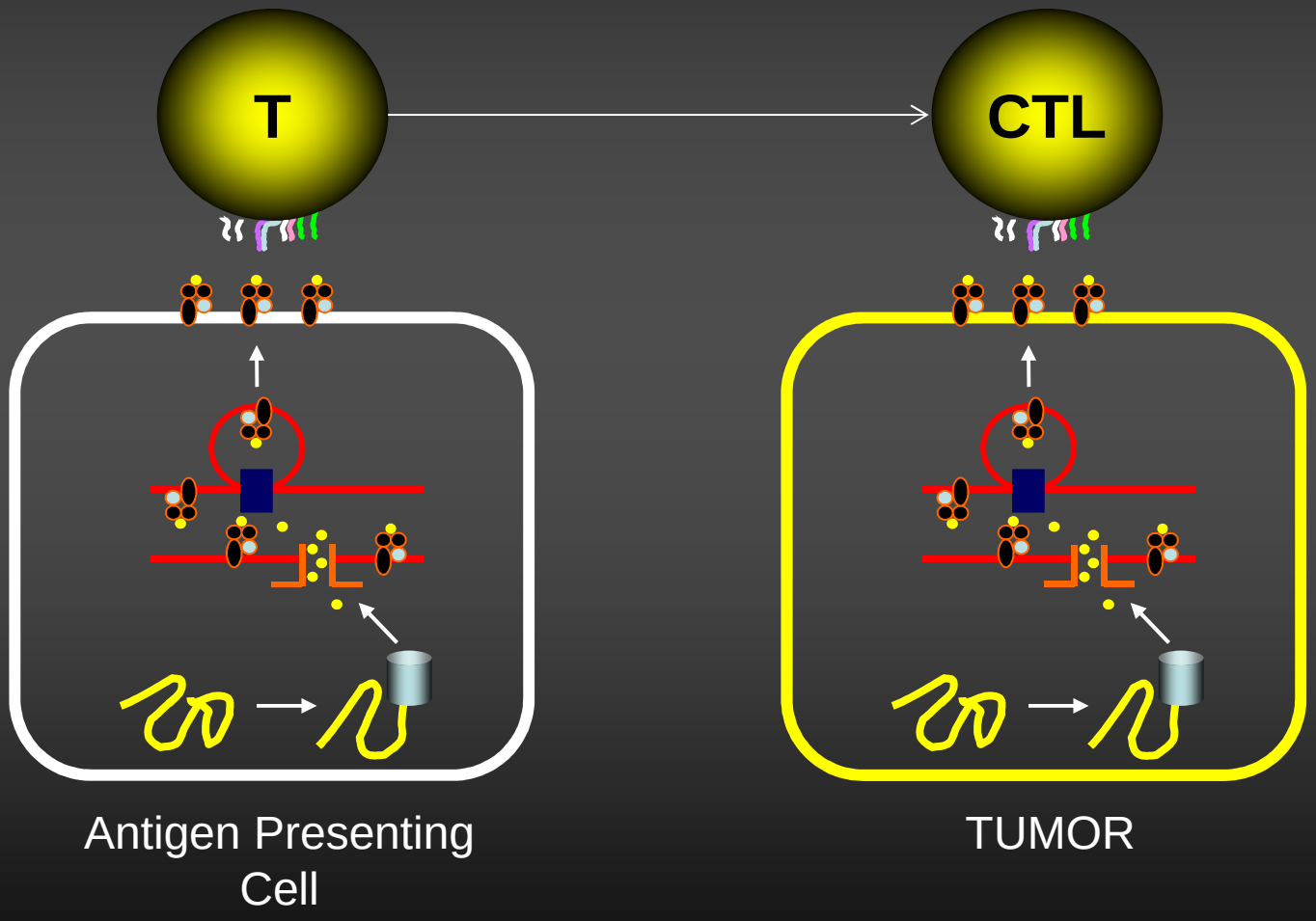


Type 2 Latency
Hodgkin's disease/NHL
Nasopharyngeal carcinoma

Making T-cell therapy more broadly applicable…

- Most tumors do not contain exogenous, viral antigens
- Can we consistently manufacture T cells that recognize weak, tumor associated antigens?
  - One approach: **genetically engineer T cells** to introduce new T-cell receptors
    - αβ (native T-cell receptors)
    - Chimeric Antigen Receptors (CAR)

MHC Restricted Operation

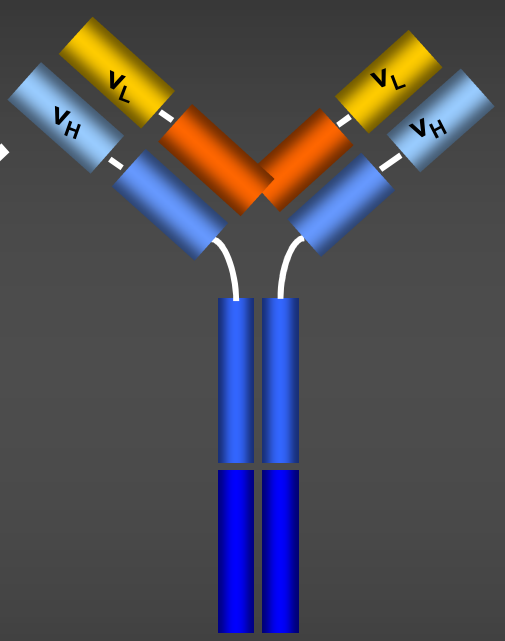


Pule et al. *Cytotherapy* 2004.

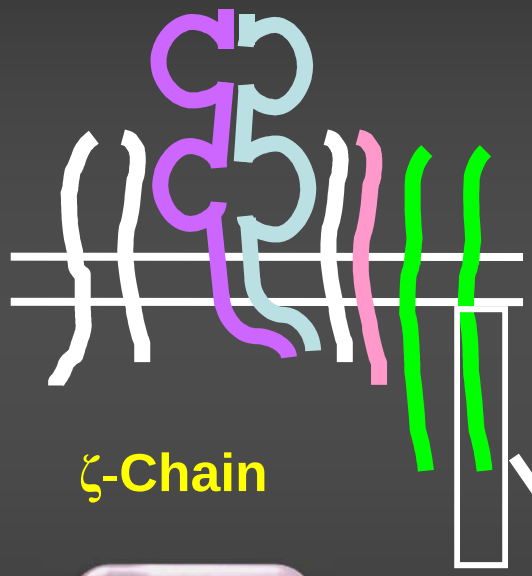
Chimeric Antigen Receptors

T cell Receptor

Variable Domain

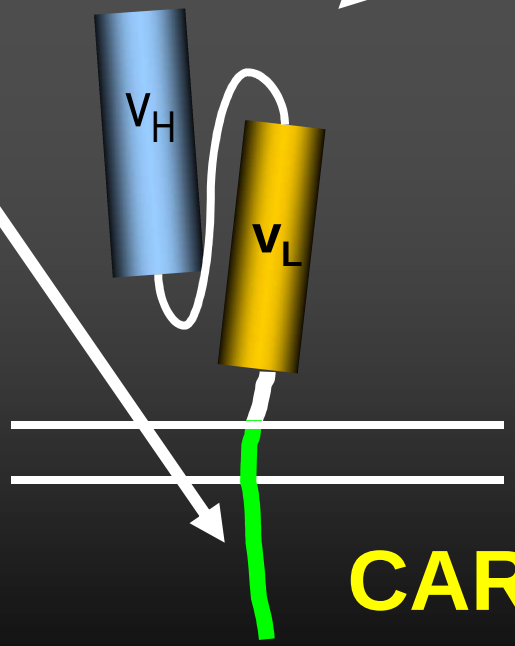


Antibody



ζ-Chain

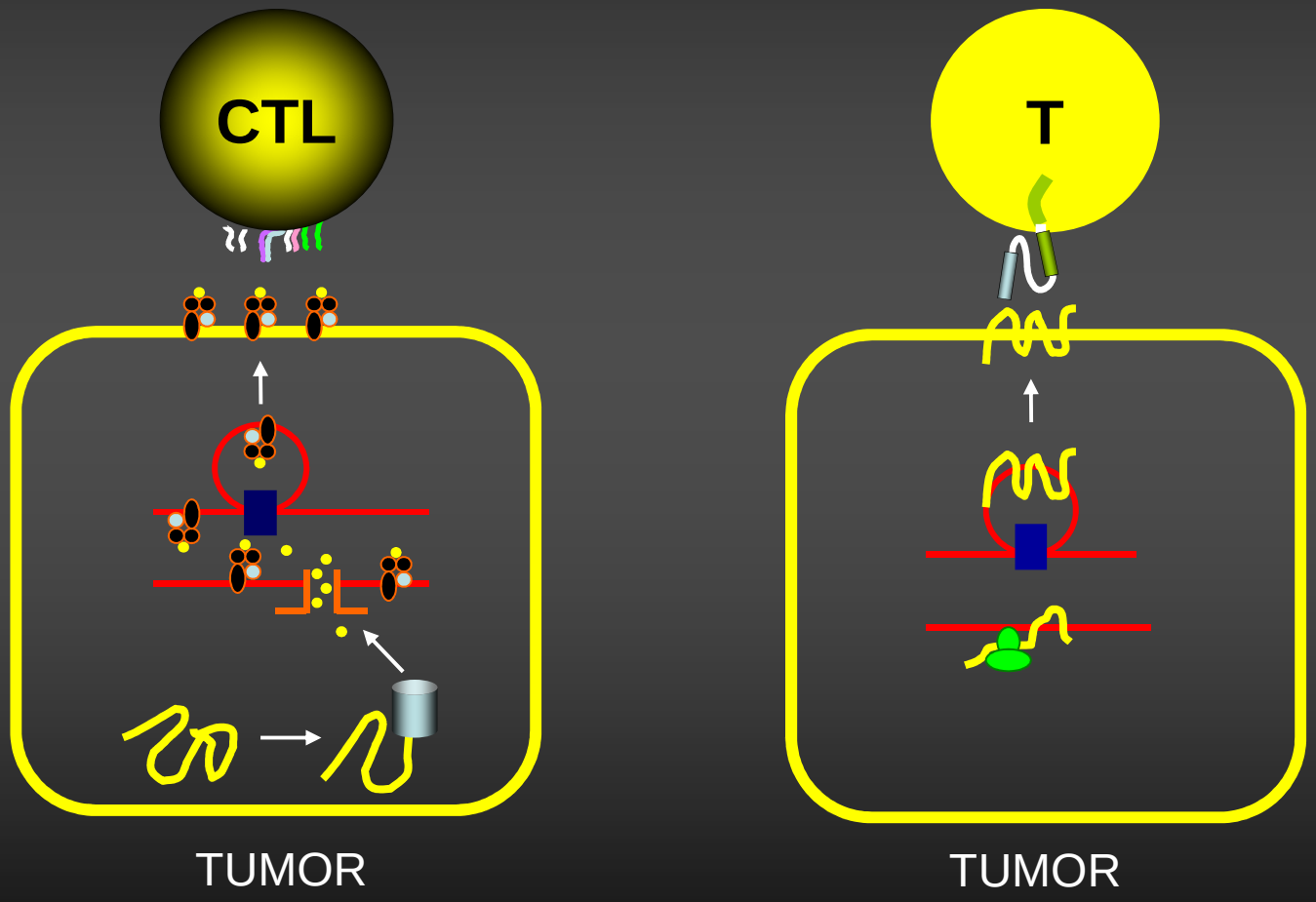
Zelig Eshhar



CAR

Eshhar et al. *PNAS* 1993

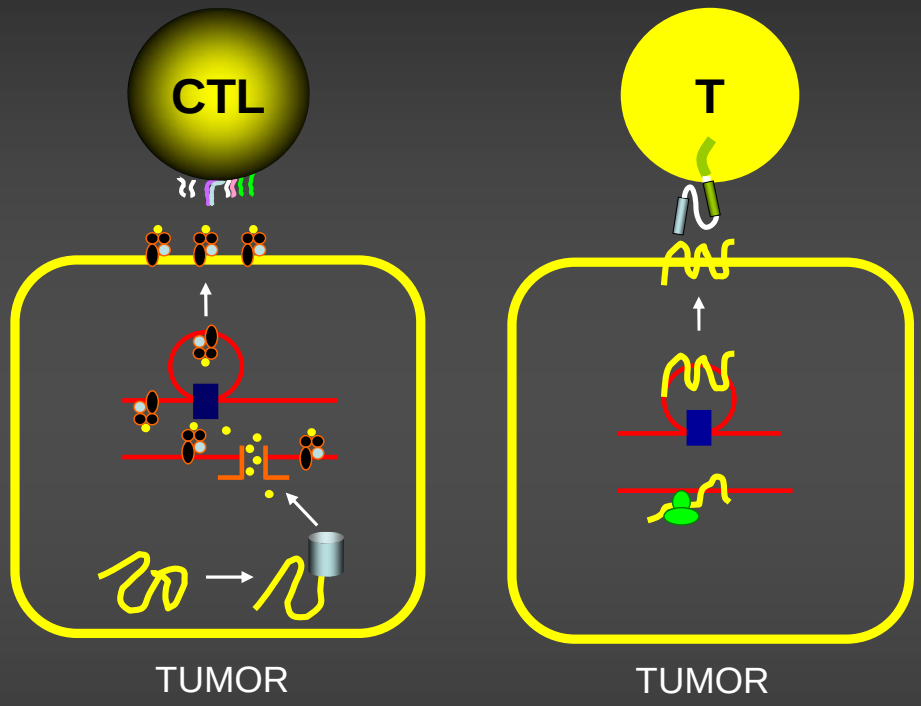
MHC UN-Restricted



Pule et al. *Cytotherapy* 2004.

T cell Therapy: *advantages*

- **MHC-unrestricted**

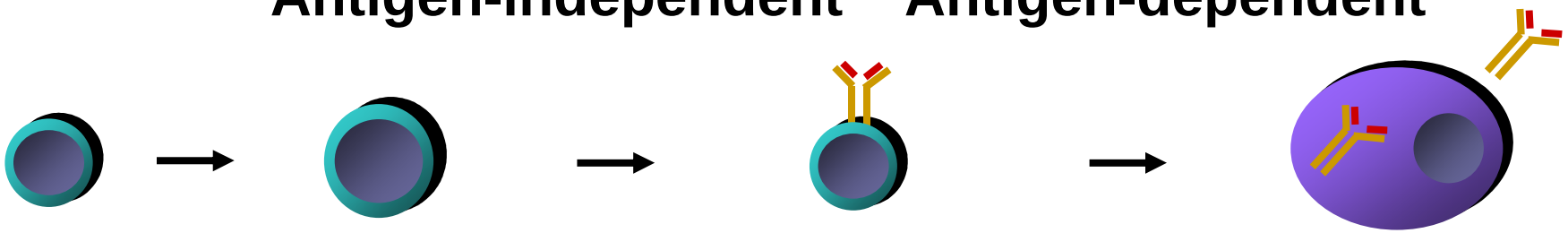


- **Customizable**
- **Reliable & timely manufacturing**
- **Third Party Product “blood bank model”**

Pule et al. *Cytotherapy* 2004.

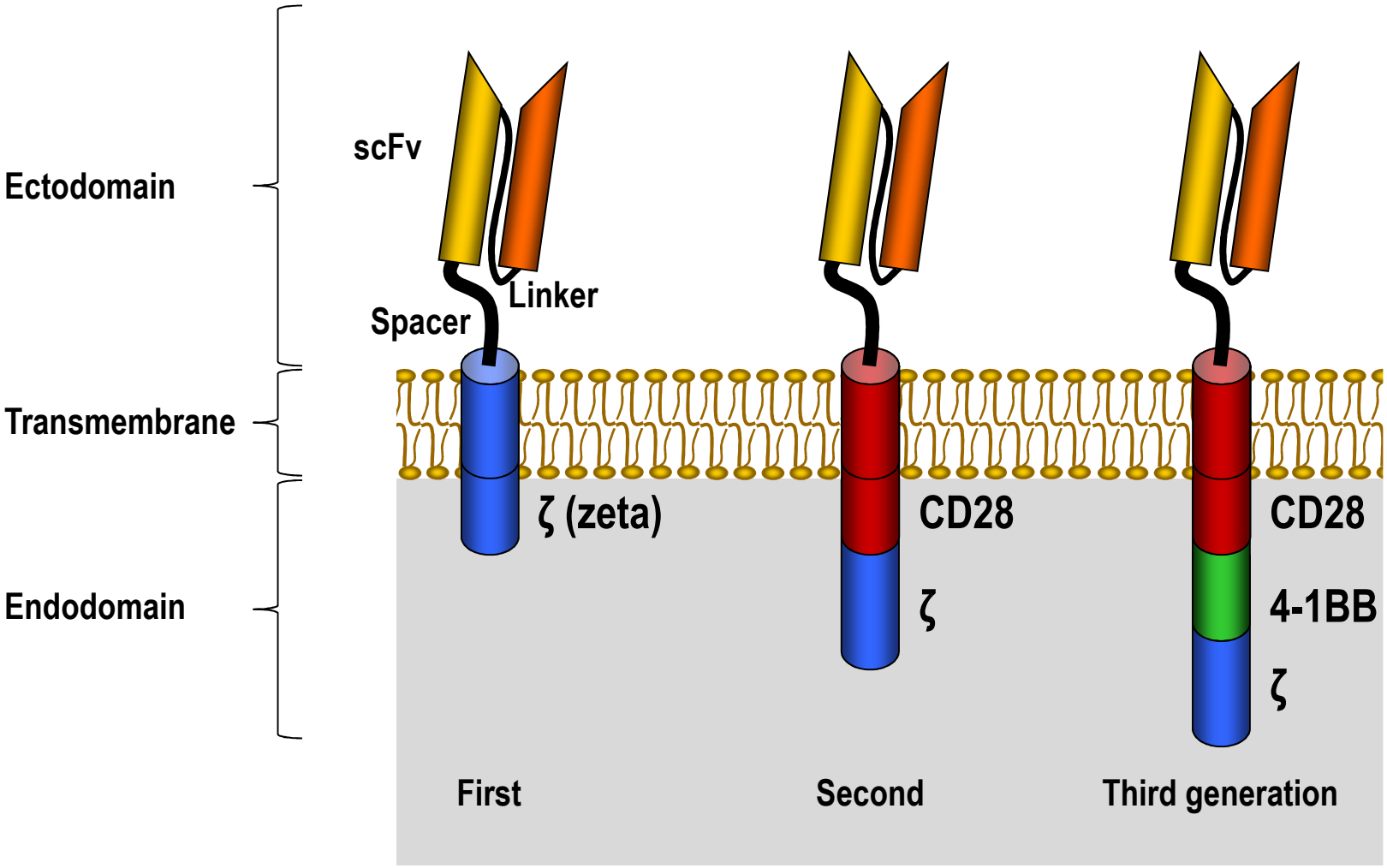
Selecting B-cell lymphoma antigens

Antigen-independent **Antigen-dependent**



	HSC	B lymphocyte precursor	Naïve mature B lymphocyte	Plasma cell
CD19	+	+	-/+
CD20	-	+	-/+
CD38	+	+	+++
CD138	-	-	+++
sIg (κ/λ)	-	+ (IgM,IgD)	-/+

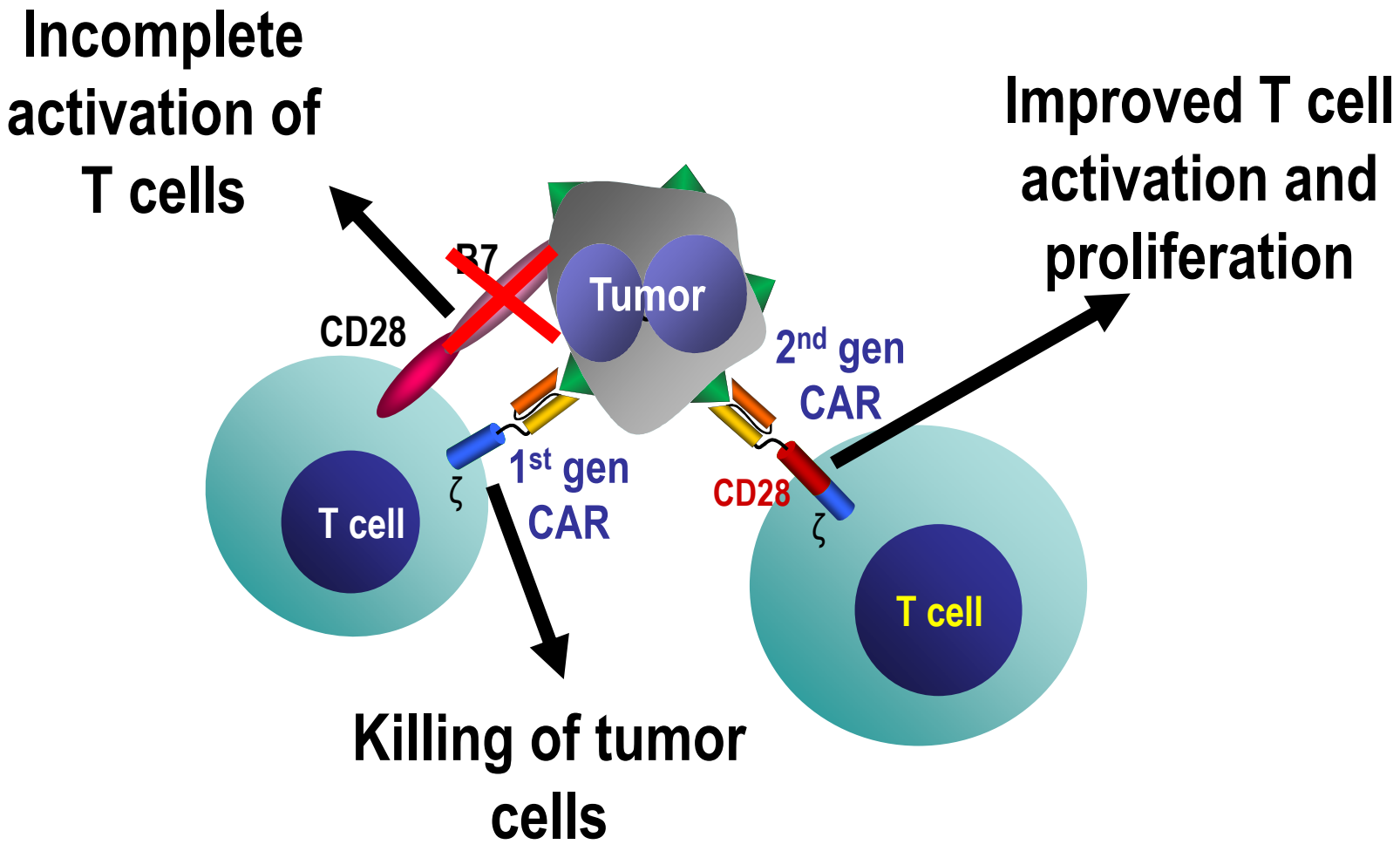
First vs. later generation CARs



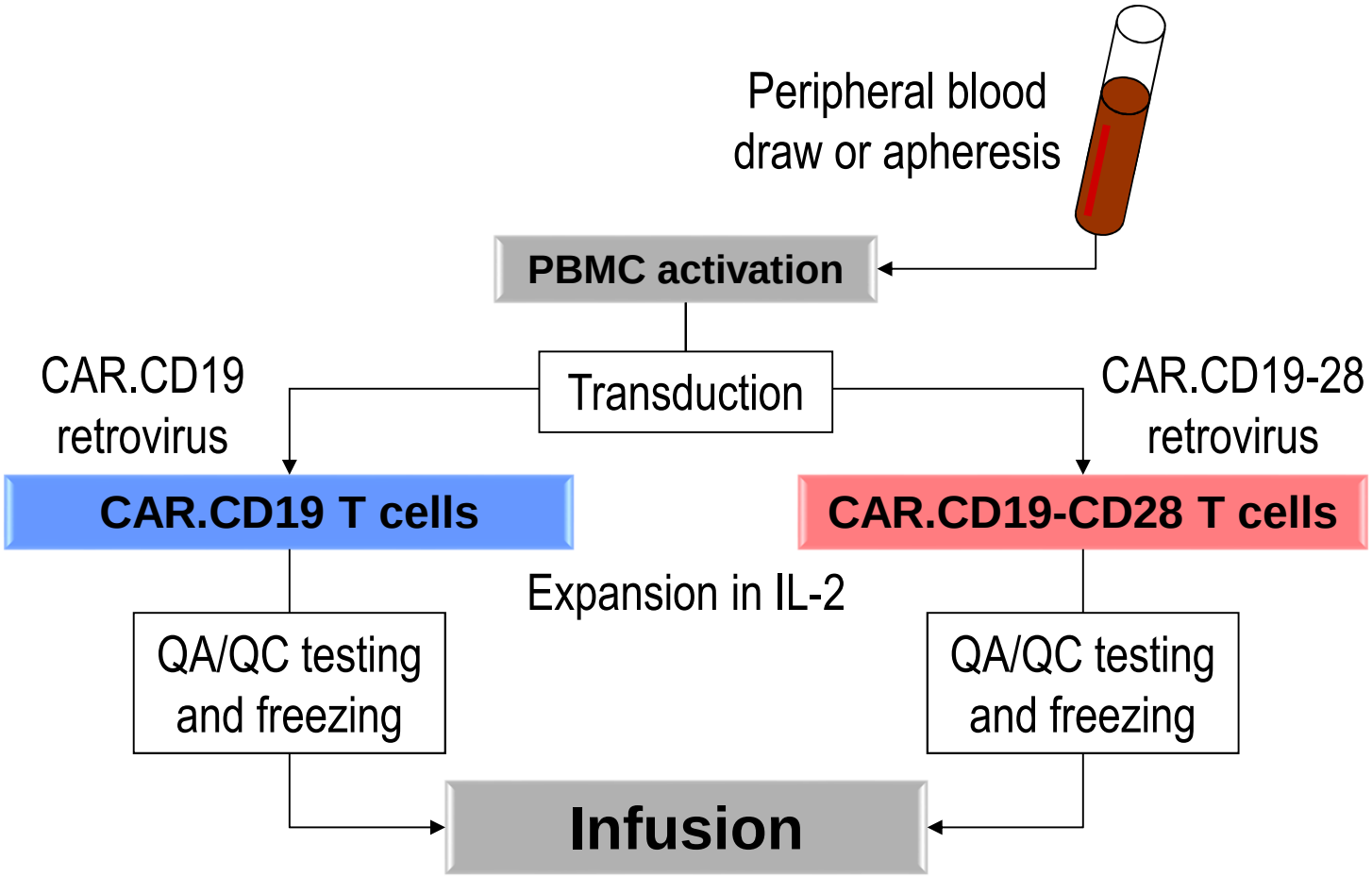
Clinical trials using 1st generation CD19.CAR-T cells

- Feasibility of the approach was established
- Lack of significant anti-tumor effects
- Limited persistence of CAR-modified T cells

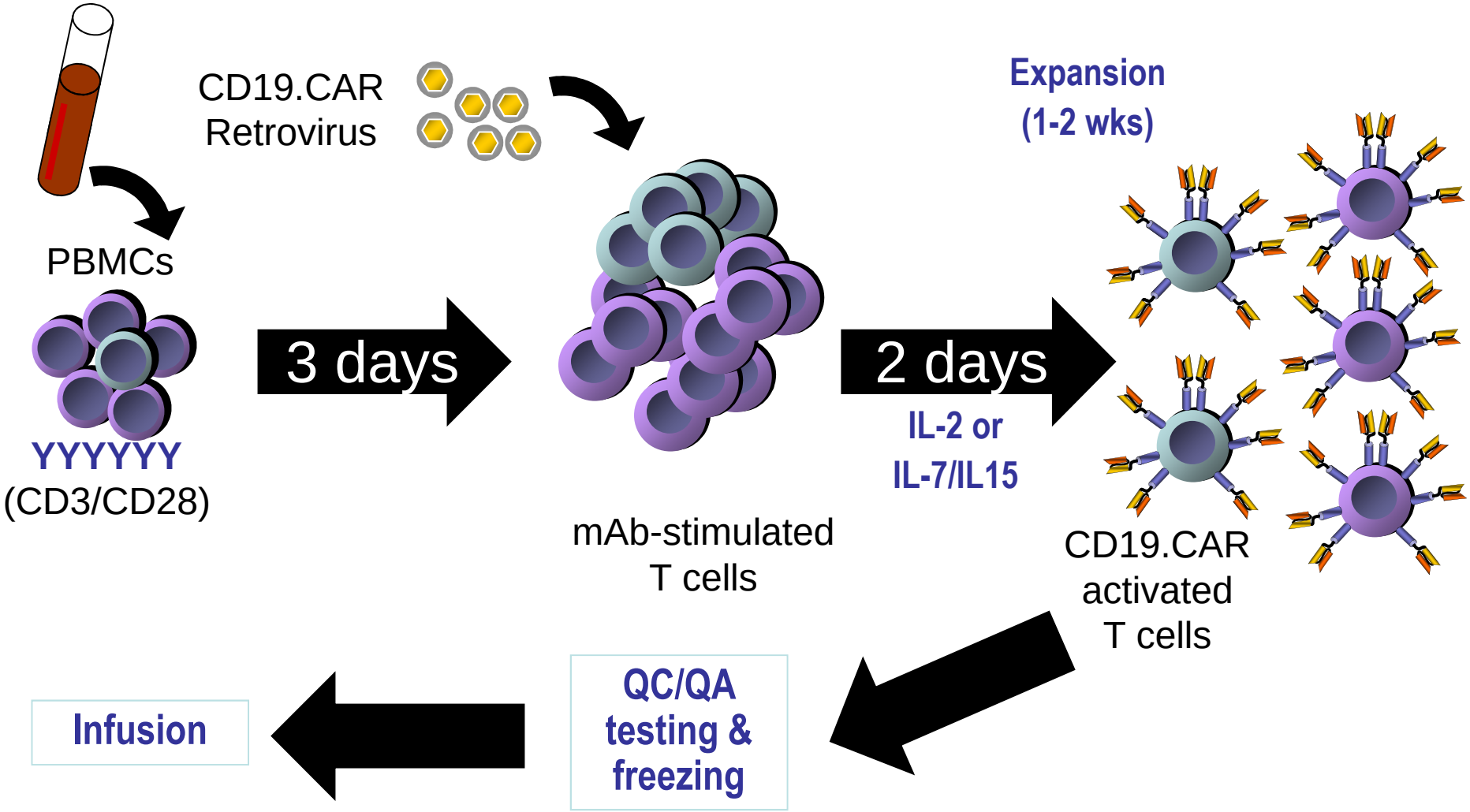
Incomplete activation of 1st generation CAR-directed T cells



Are 2nd gen CAR-T cells superior to 1st gen CAR T cells? (CRETI study)



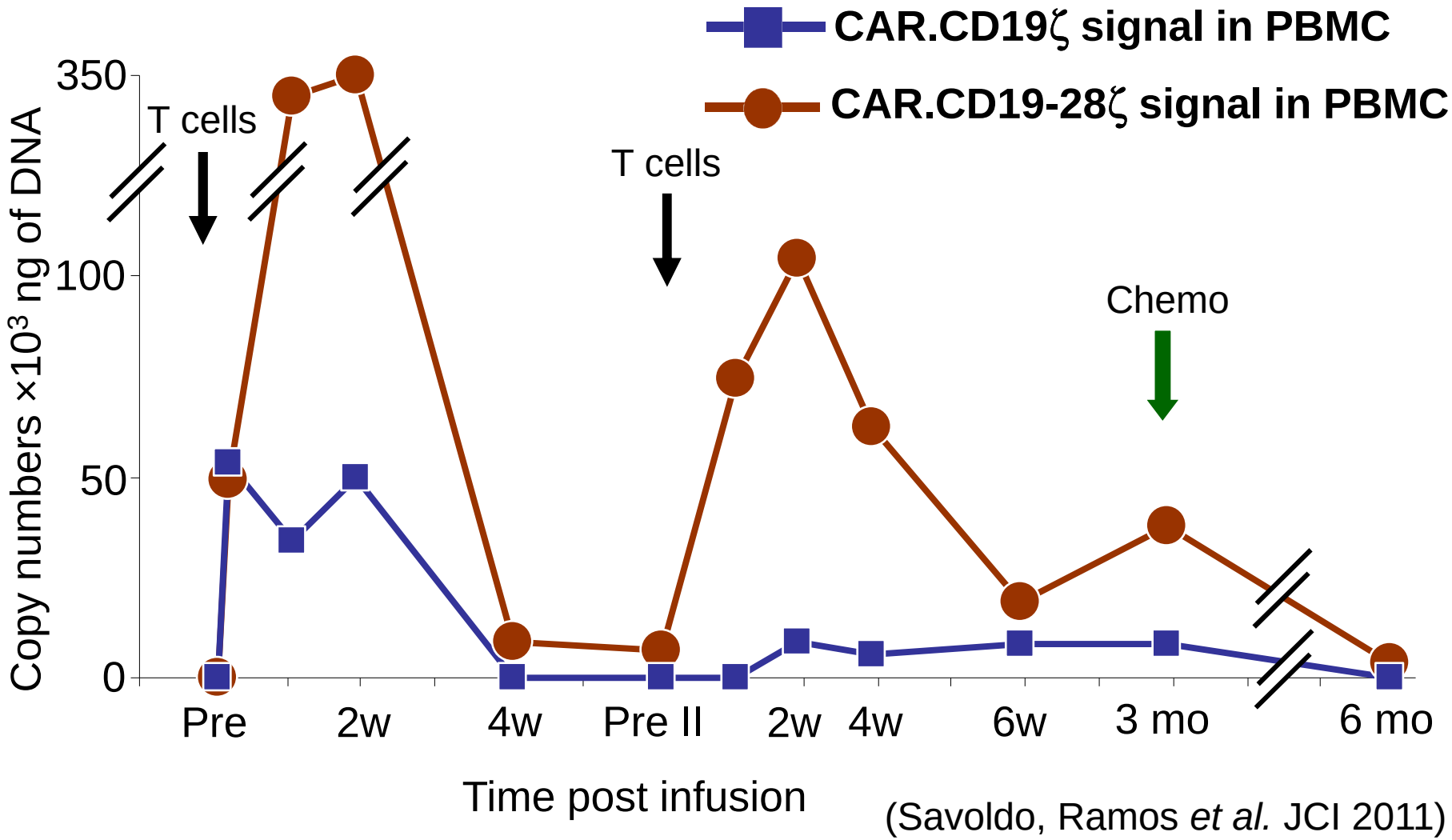
CAR-T cell manufacture



Patient details

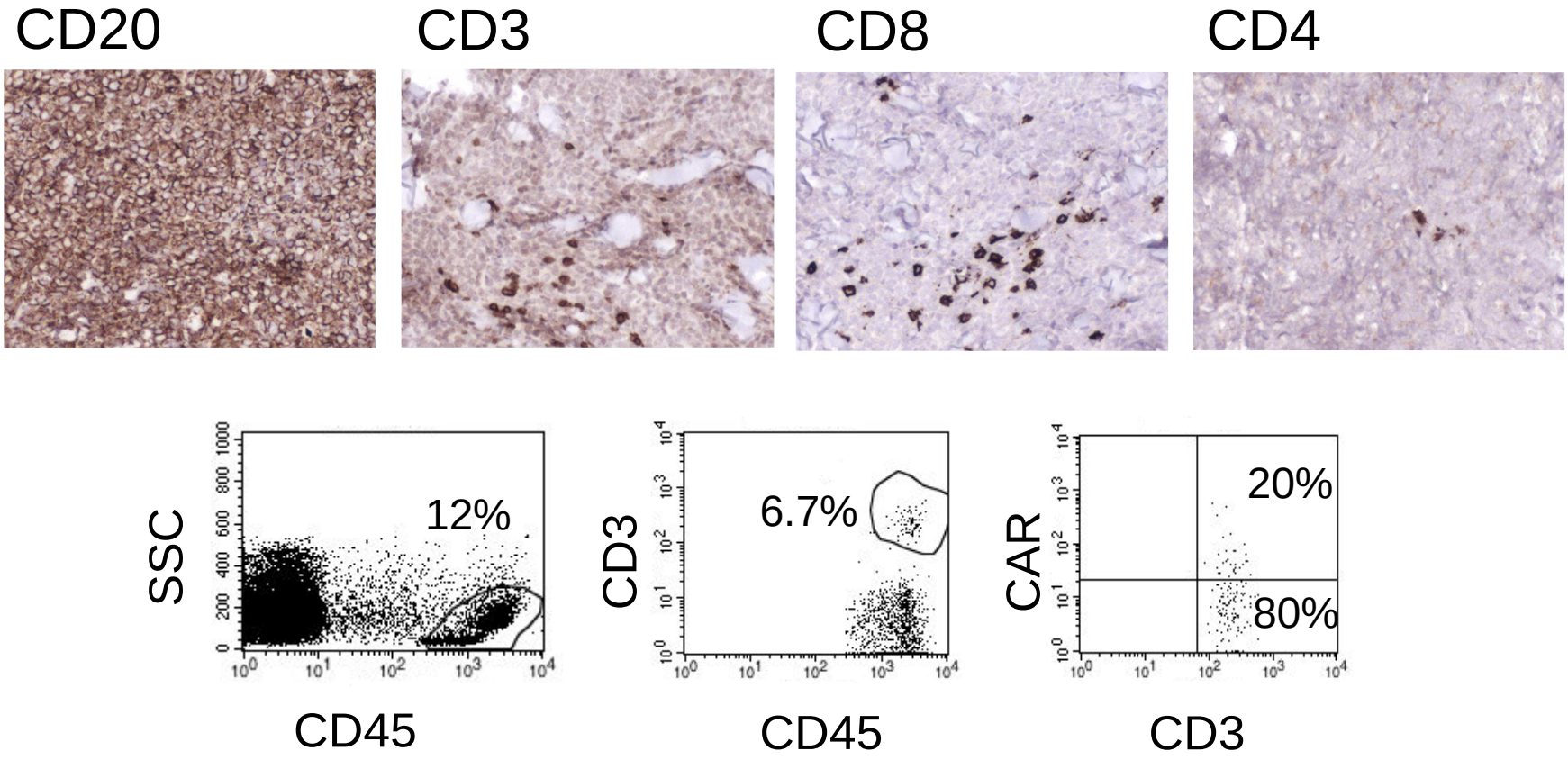
Age	Diagnosis	Previous therapy	Disease status
M/53	B-CLL	FCR, FC	Cervical, axillary, RP, inguinal LAD
M/56	FL→ DLBCL	R-CHOP×8, XRT, FCR×6, R-ICE×2, CDDP/Ara-C, TTR×2	Cervical LAD
M/46	DLBCL	R-CHOP×6, R-ESHAP×4, R-ICE×2, R-IGEV, TTR, R, HyperCVAD×2	Retroperitoneal (RP) lymphadenopathy (LAD)
M/57	DLBCL	R-CHOP×4,R-ESHAP×2, R-BEAM/ASCT, XRT	Cervical, RP LAD
F/59	FL→ DBLCL	R-CHOP×8, R-ESHAP×3, R-BEAM/ASCT, XRT, R	Muscle and skin
M/49	DLBCL CNS & systemic	MTX×4, ESHAP, temozol., R-ICE×6, R-HyperCVAD×2, R-BEAM/ASCT, XRT×2	Brain & RP LAD

2nd gen CAR-T cells have greater in vivo expansion and persistence



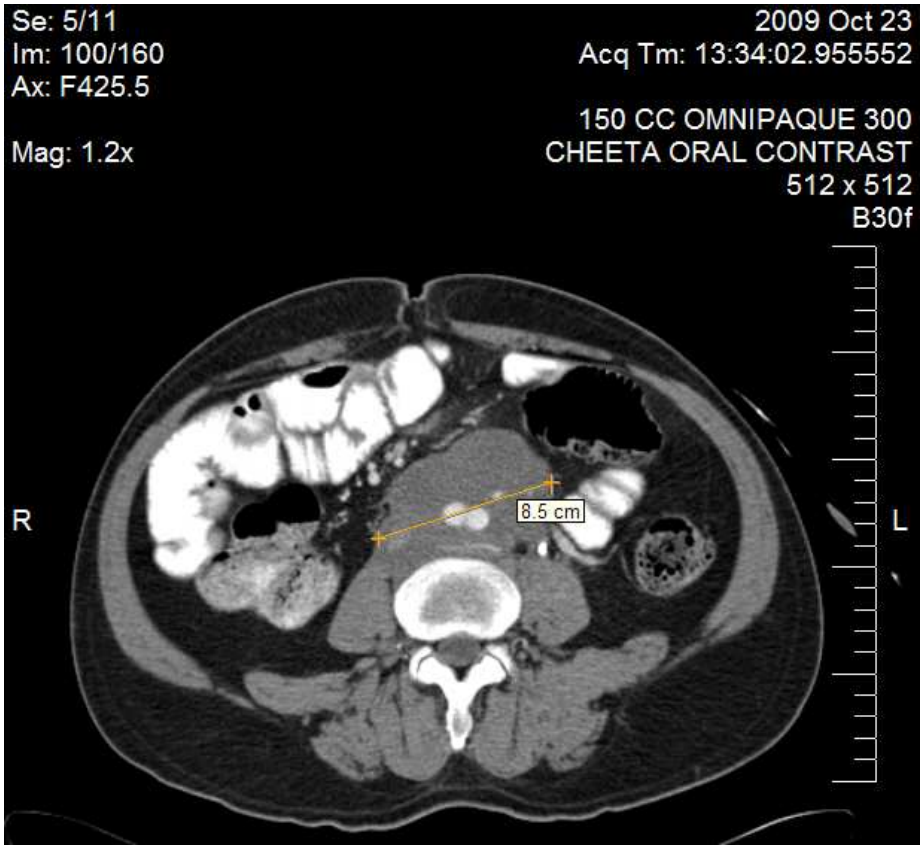
(Savoldo, Ramos *et al.* JCI 2011)

2nd gen CAR-T cells are detected at tumor sites

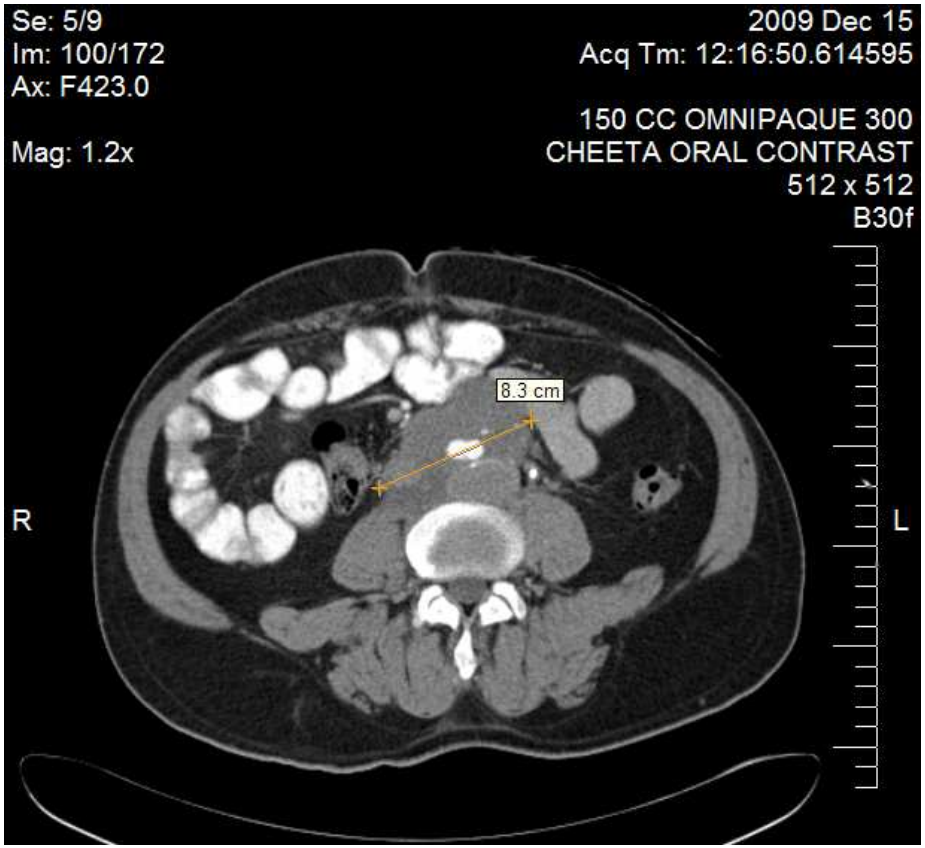


(Savoldo, Ramos *et al.* JCI 2011)

Anti-tumor activity: stable disease



Pre-infusion CT scan



Six-week post-infusion CT scan

Pt #3, dose level 2

CD19.CAR-T cell therapy can be highly effective…

Non-Hodgkin Lymphoma/Chronic Lymphocytic Leukemia

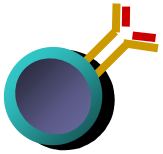
Reference	Center	N	Efficacy
Kochenderfer, JCO 2015	NCI	30 (adult/peds)	53% CR 27% PR
Porter, Blood (ASH) 2014	UPenn	15 (adult)	29% CR 29% PR
Savoldo, JCI 2011	BCM/HMH	6 (adult)	33% SD

Acute Lymphoblastic Leukemia

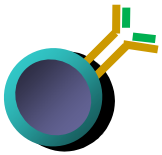
Reference	Center	N	Efficacy
Maude, NEJM 2014	UPenn	30 (adult/peds)	90% CR
Davila, SciTM 2014	MSKCC	15 (adult)	88% CR
Lee, Lancet 2015	NCI	21 (peds/AYA)	67% CR (ITT)

… but B-cell aplasia occurs after major responses

- CD19 is a universal B marker
- More restricted antigens may leave B-cell subpopulations intact
  - κ and λ light chains are mutually exclusive
  - Malignancies are monoclonal, i.e., κ^+ or λ^+
  - Targeting one should spare reciprocal population

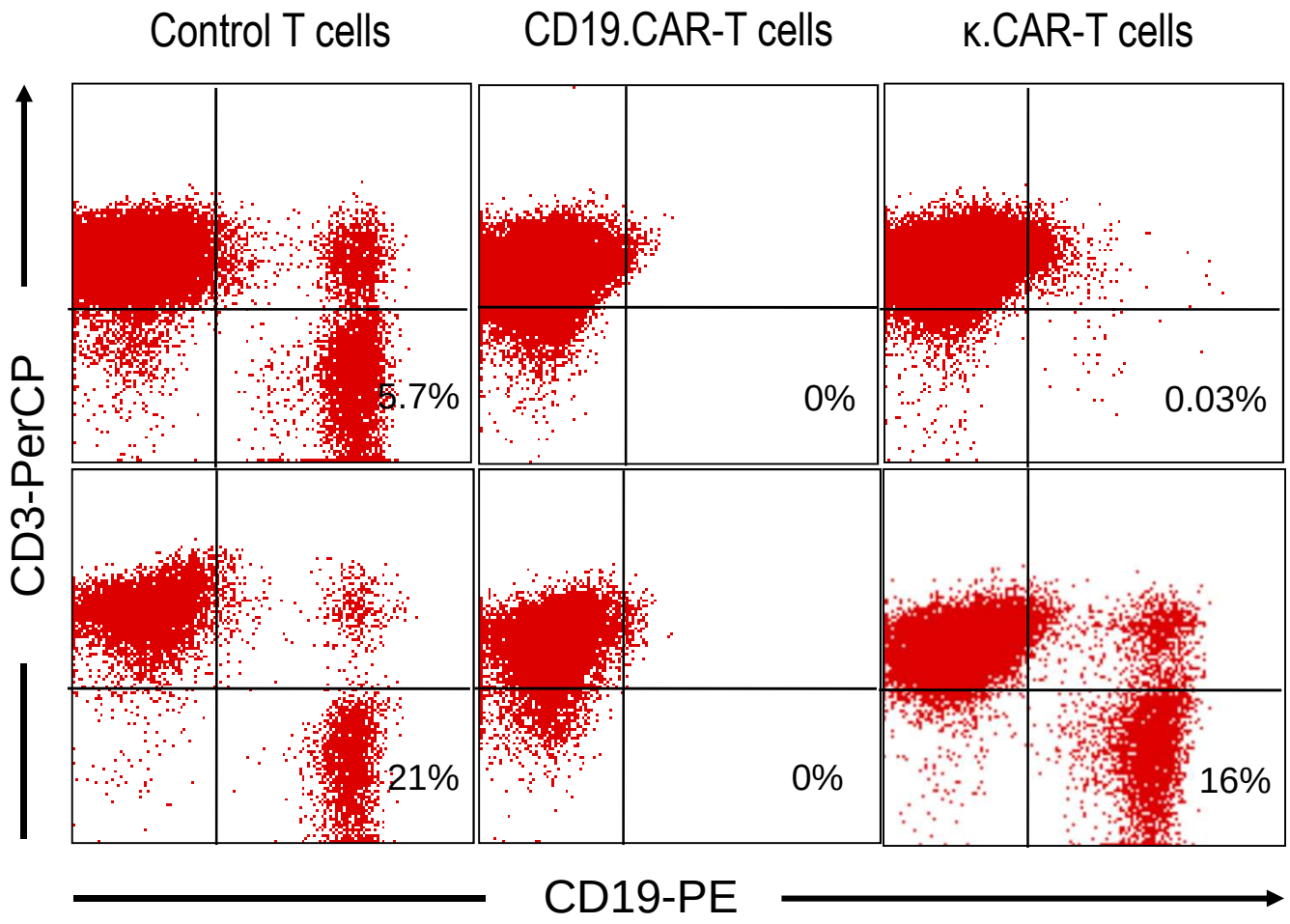


κ light chain surface Ig



λ light chain surface Ig

κ.CAR-T cells selectively eliminate κ+ CLL cells



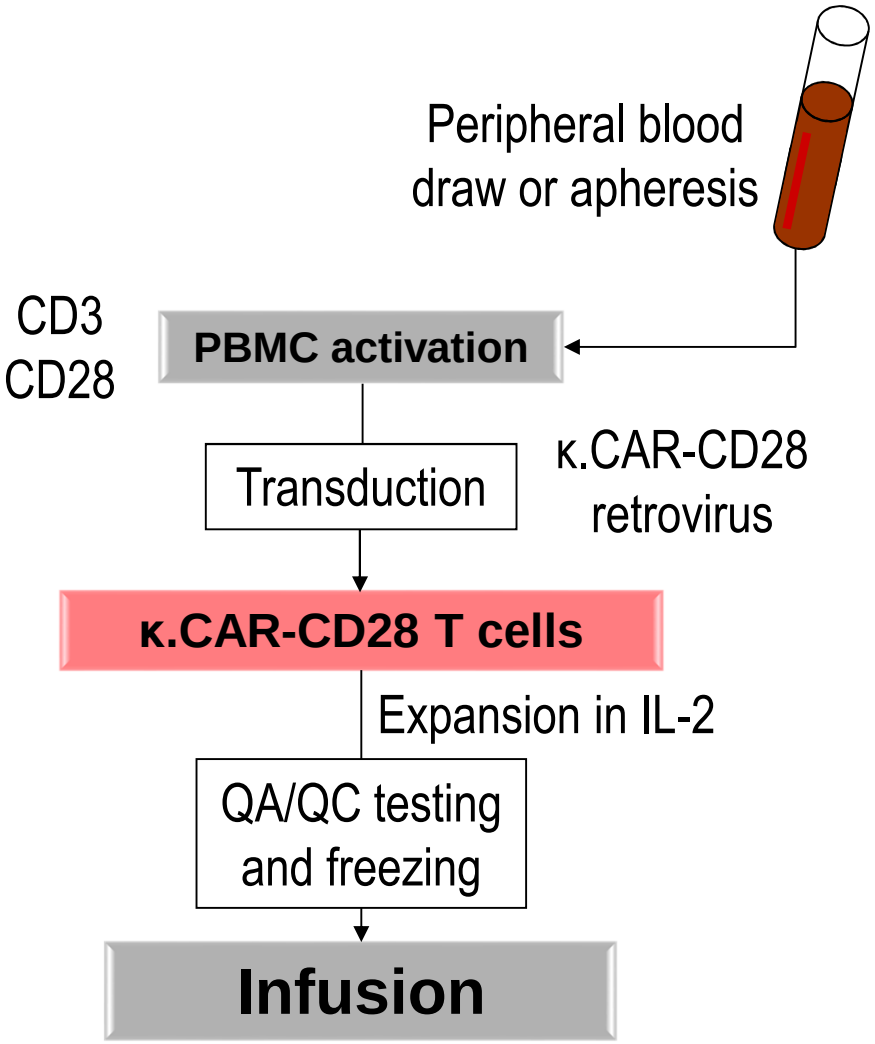
κ+ CLL

λ+ CLL

T cells co-cultured (5:1 ratio) with CLL cells for 3 days

(Vera *et al.*, Blood 2006)

CHARKALL trial



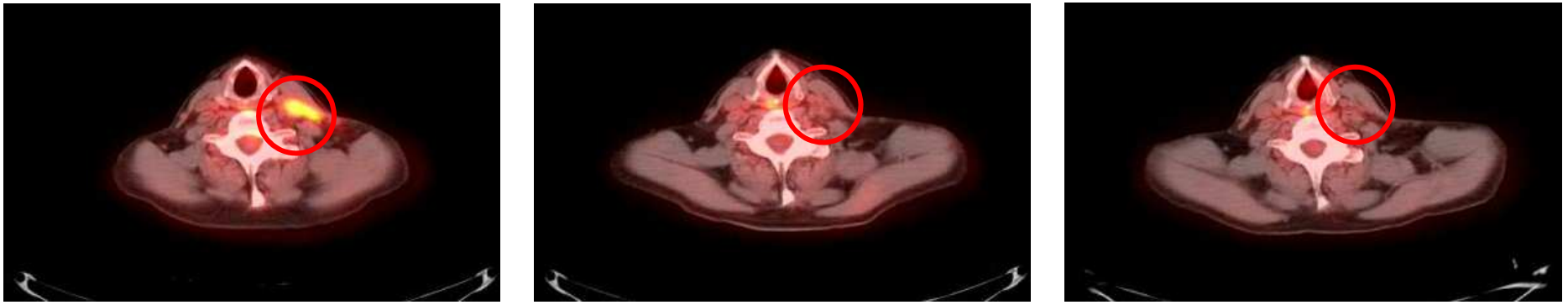
Patient characteristics: NHL

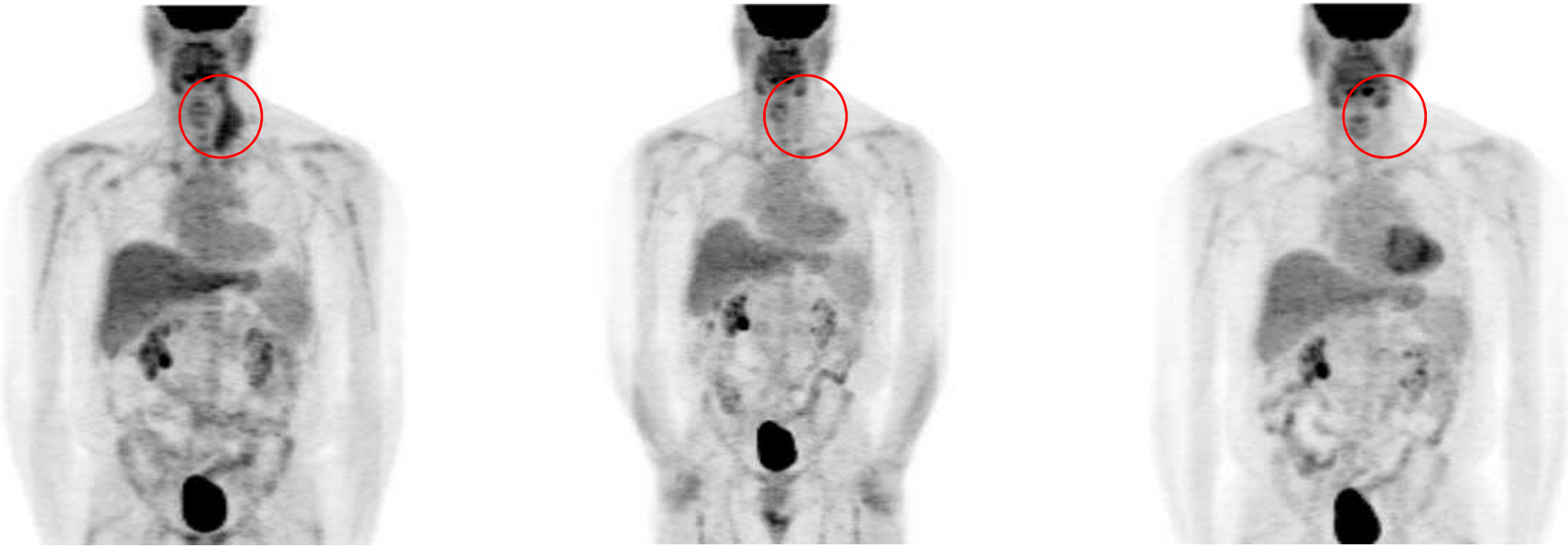
#	Age/ Sex	Diagnosis	Previous therapies
1	53/F	Relapsed lymphoplasmacytic lymphoma	R-CHOP, 2CDA, R-BEAM/ASCT
2	60/M	Relapsed follicular lymphoma transformed to DLBCL	R-CHOP/XRT, FCR, R-ICE, TTR, CD19.CAR-T cells, R-bendamustine,
3	71/M	Relapsed DLBCL, leg-type	R-CHOP, ASCT, bortezomib
5	73/M	Relapsed CLL/SLL	R-bendamustine
6	59/M	Relapsed lymphoplasmacytic lymphoma	R-CVP, CHOP, bortezomib
9	55/M	Relapsed follicular lymphoma	R-CHOP, R-IE, R-BEAM/ASCT
10	69/F	Relapsed CLL/SLL	R-fludarabine, R-bendamustine
13	74/M	Relapsed MCL	R-hCVAD, bortezomib, carfilzomib/lenalidomide, R-bendamustine
16	69/M	Relapsed DLBCL	R-CHOP, R-BEAM/ASCT, BVR, R-ibrutinib, R-ESHAP

κ.CAR activated T cells (Pt #2)

Follicular lymphoma → DLBCL

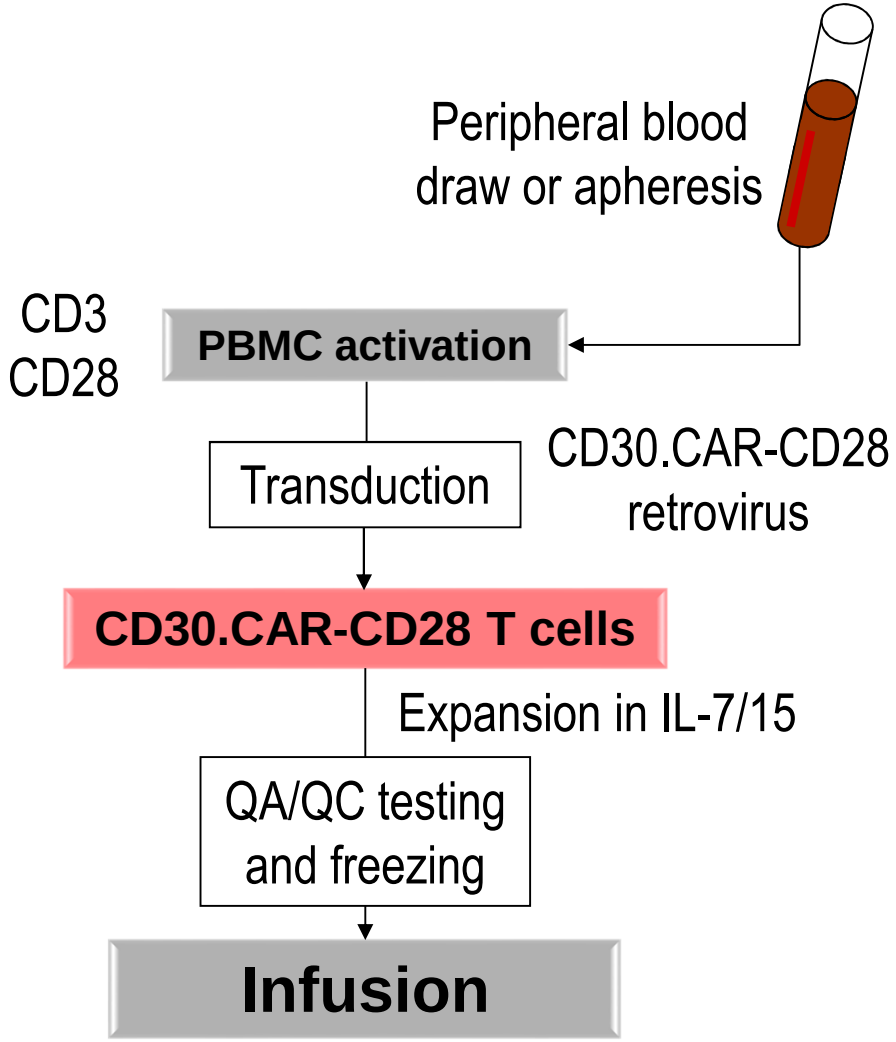
Pre-infusion **6 wks post-inf. #1** **6 wks post-inf. #2**





Can we target non-B cell malignancies? (CART CD30)

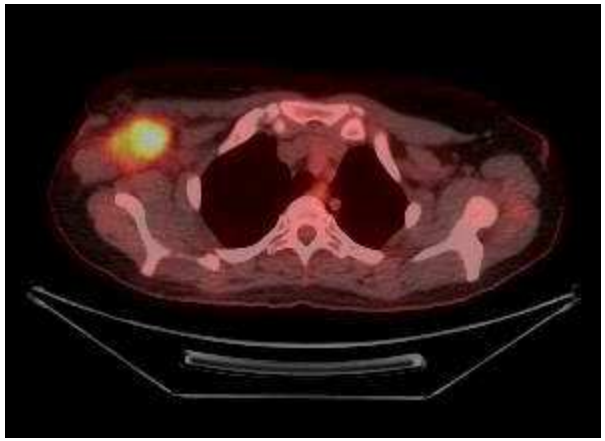
- Hodgkin lymphoma
- Some non-Hodgkin lymphomas:
  - Anaplastic large T-cell lymphoma
  - CD30^{+} diffuse large B-cell lymphoma

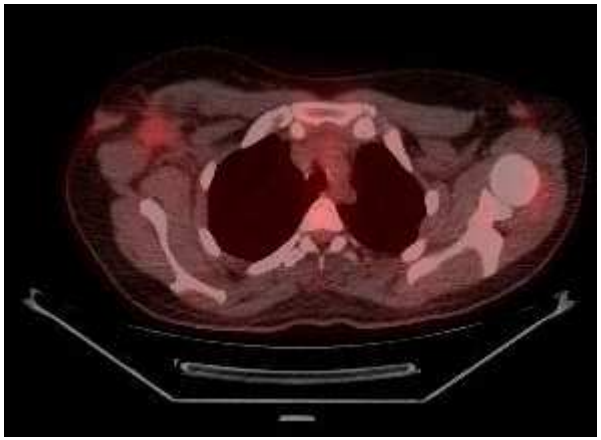


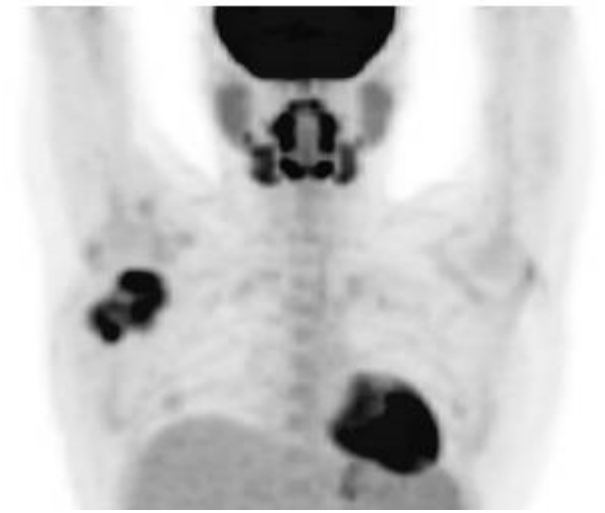
2nd generation CD30.CAR T-cells can also be effective

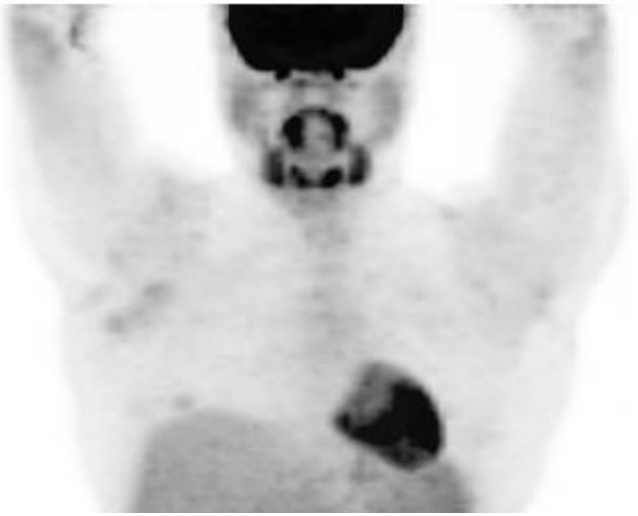
Pre-infusion

6 wks post-infusion





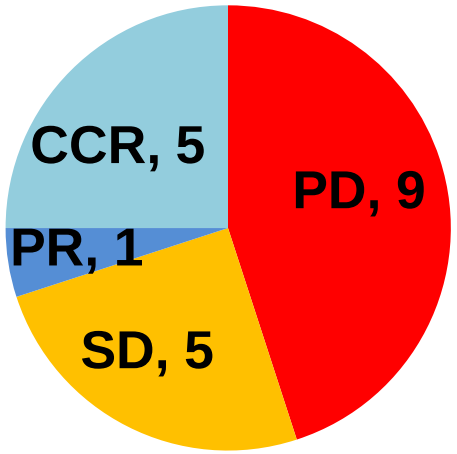




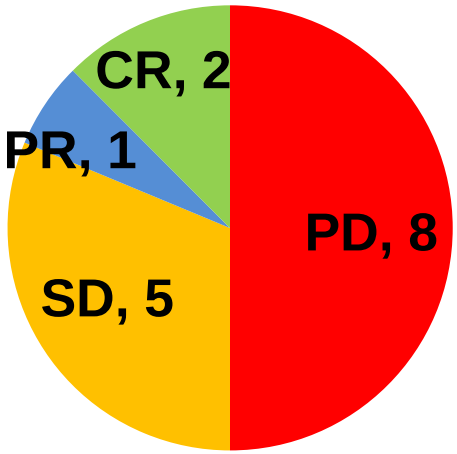
ALCL

2nd generation CAR-T cell protocols at CAGT/HMH

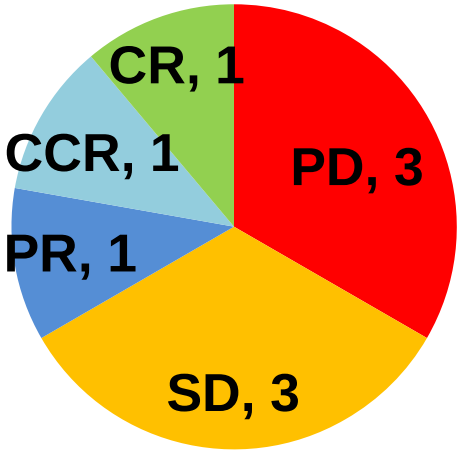
CD19.CAR



κ.CAR



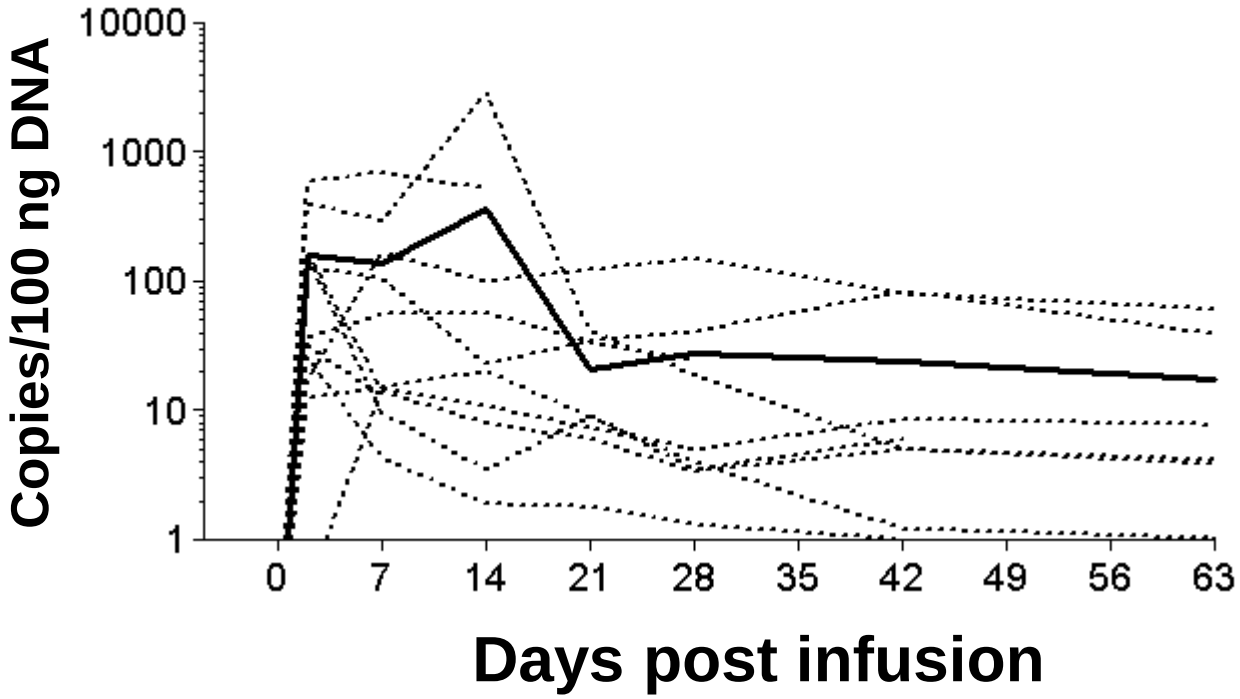
CD30.CAR



- Encouraging but far from perfect…

κ.CAR-T cells still have limited persistence…

(as CD19/30.CAR-T cells also do have)



Critical issues emerging from clinical trials

- Adequate host **lymphodepletion** may be necessary
  - Cytokine Release Syndrom
- CAR may need to be expressed in **specific T cell subsets**
  - Naïve vs. experienced cells
- Different **co-stimulatory domains** may not be equivalent
  - CD28 vs. others

Critical issues emerging from clinical trials

- Adequate host **lymphodepletion** may be necessary
  - **Cytokine Release Syndrome**
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  - Naïve vs. experienced cells
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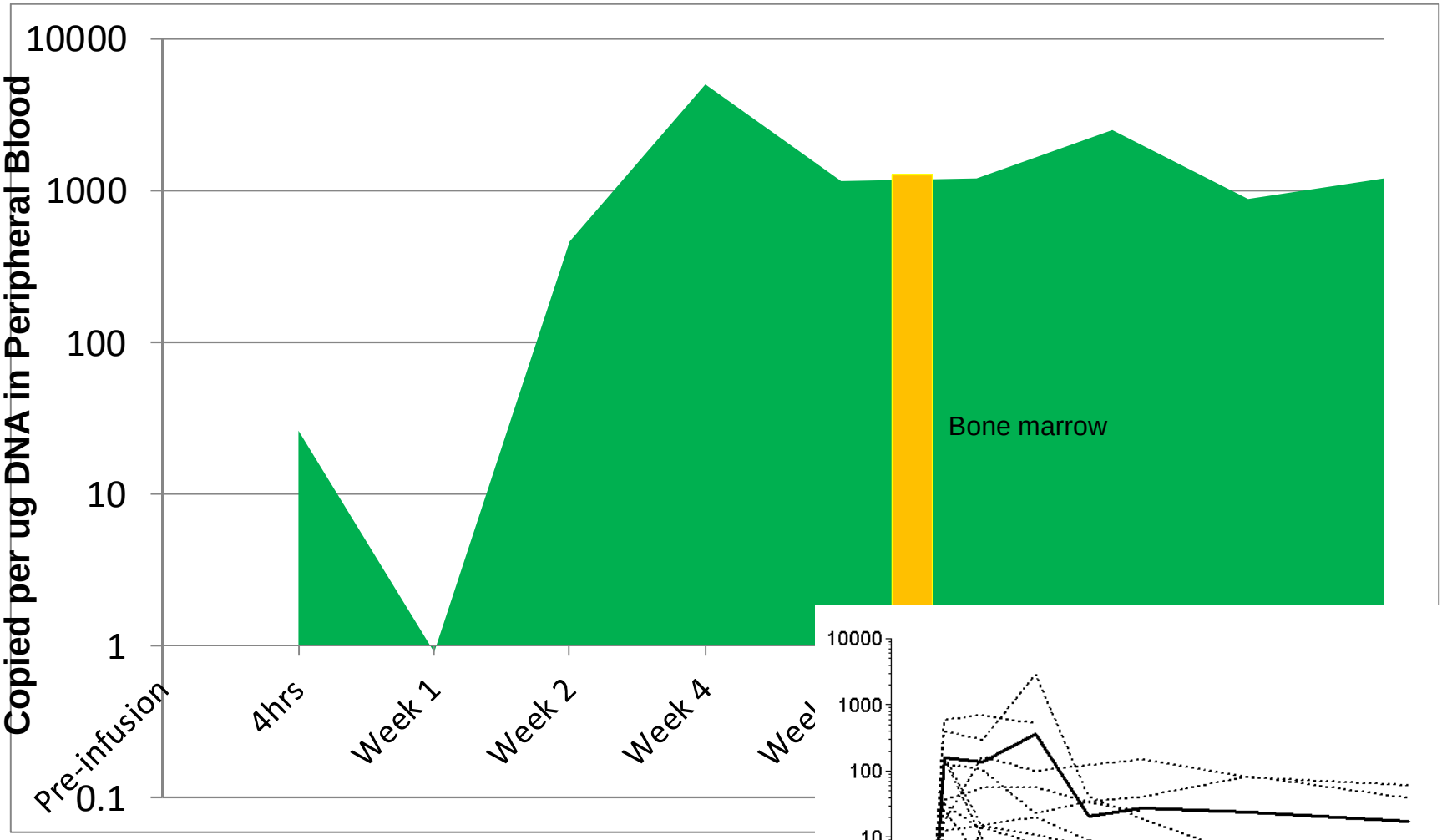
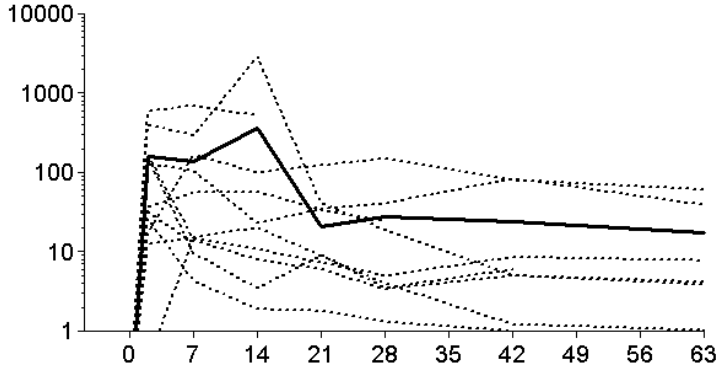
Lymphodepletion: *α persistence*





PACT
Production Assistance for Cellular Therapies
National Heart Lung and Blood Program

Children's Mercy Hospitals & Clinics'
Children's Mercy Cancer Center
(CMCC)

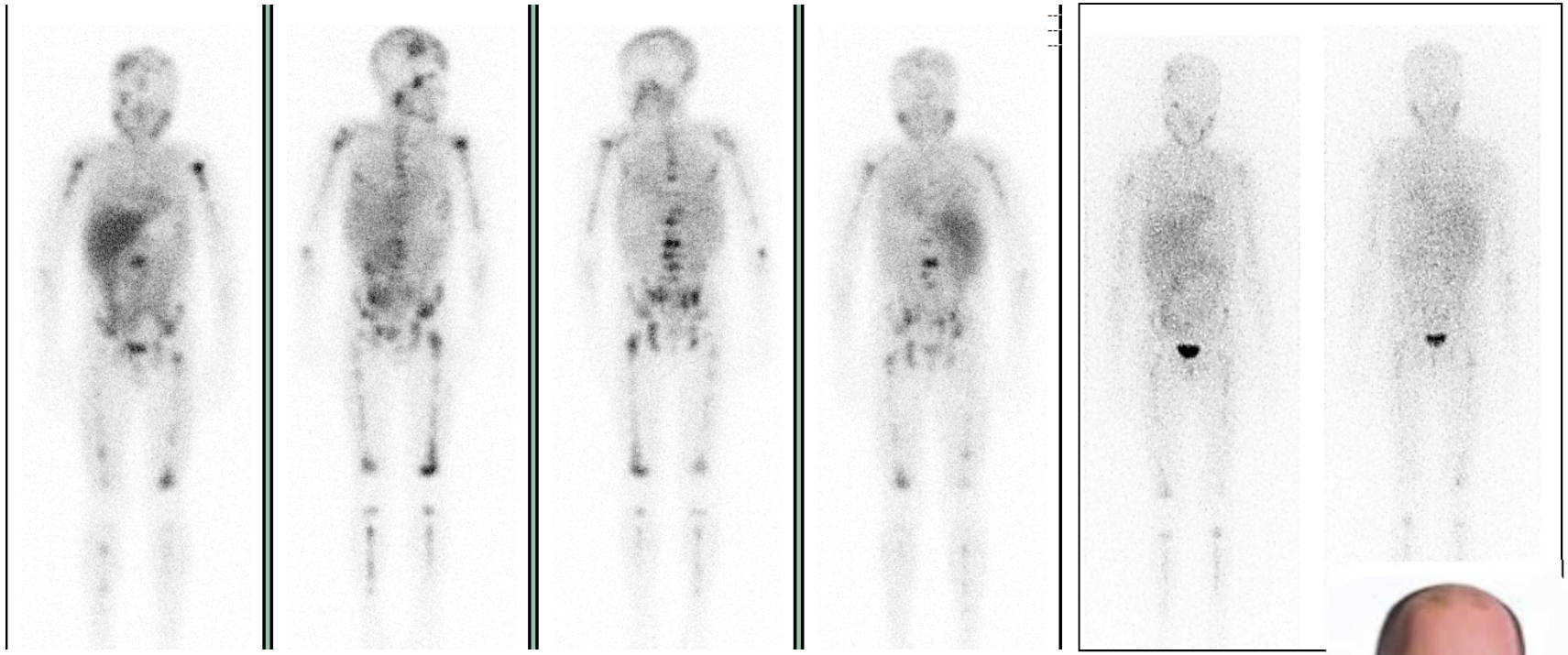
Center for CAGT Cell and Gene Therapy

Allo-SCT & GD2.CAR CTL^{EBV}

pre-transplant

15 weeks post HSCT

9 weeks post CTL



Doug Myers

PACT
Production Assistance for Cellular Therapies
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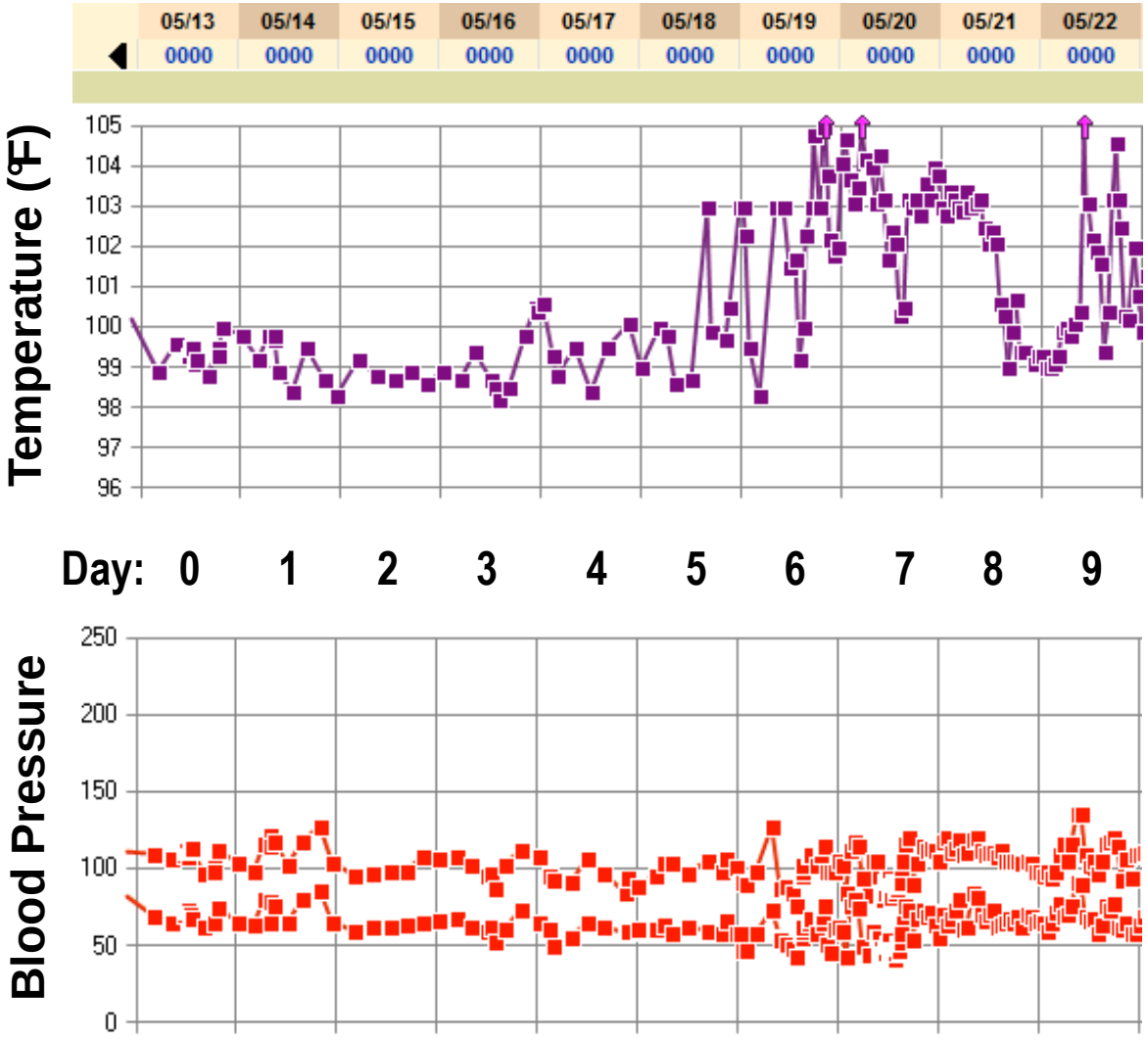
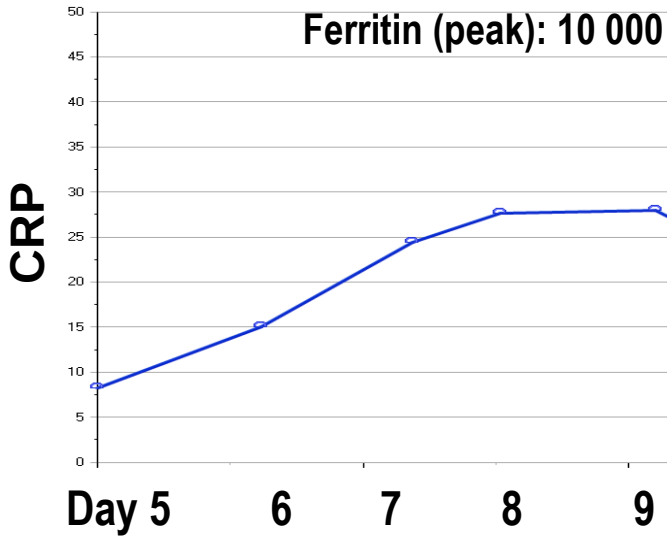
Children's Mercy Hospitals & Clinics'
Children's Mercy Cancer Center
(CMCC)

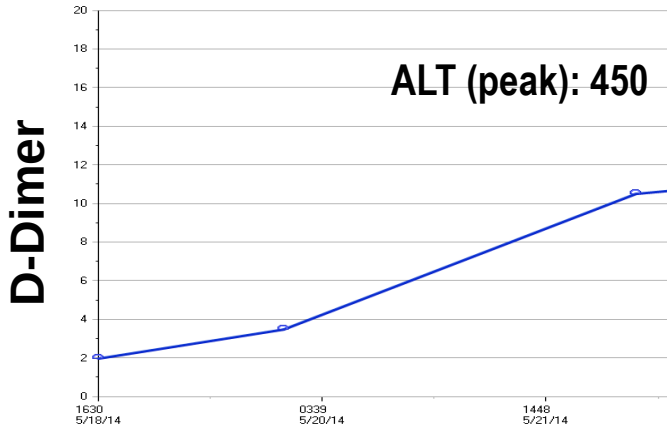
Children's Mercy Cancer Center

Center for CAGT Cell and Gene Therapy

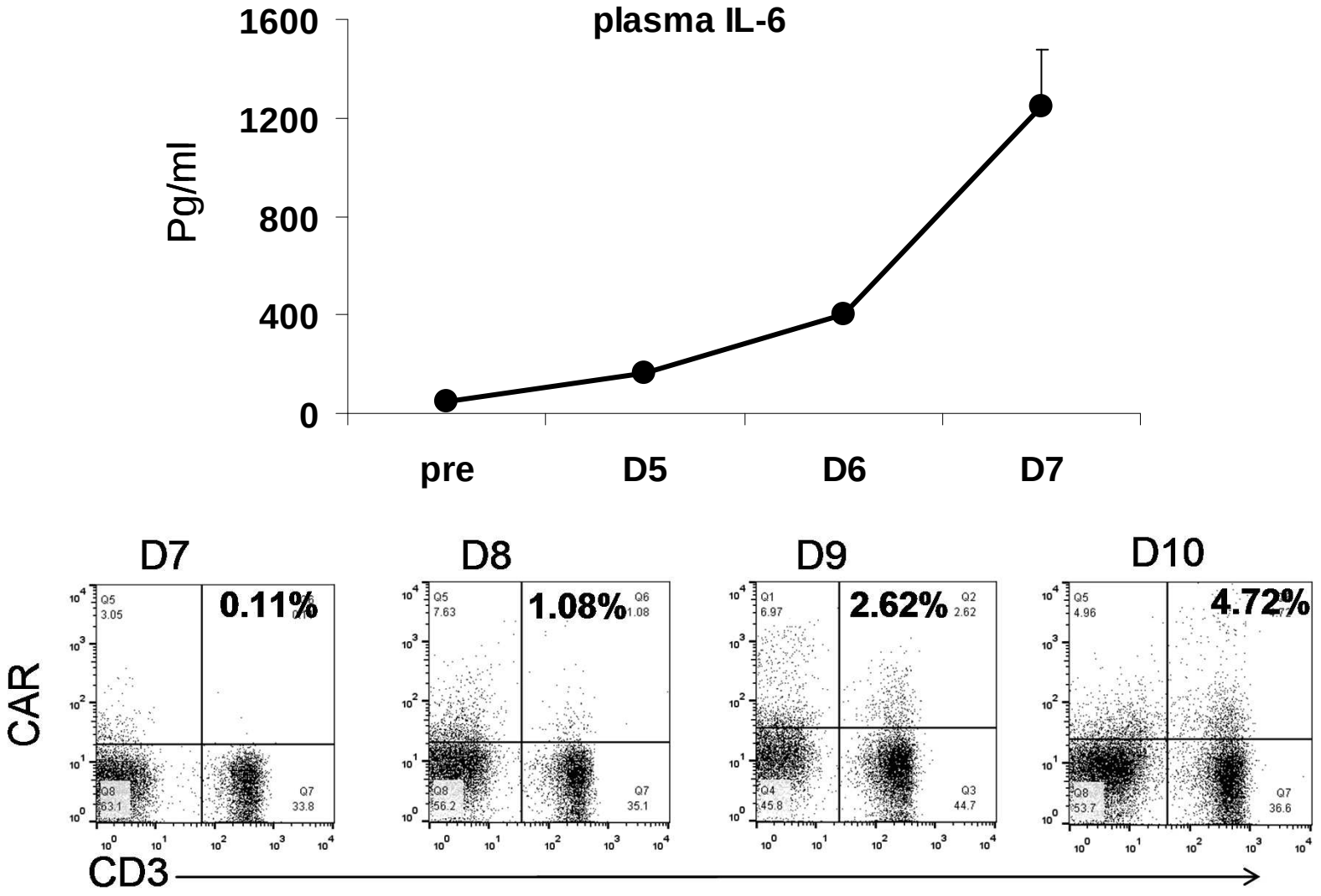
CD19.CAR-T cells in a lymphodepleted patient



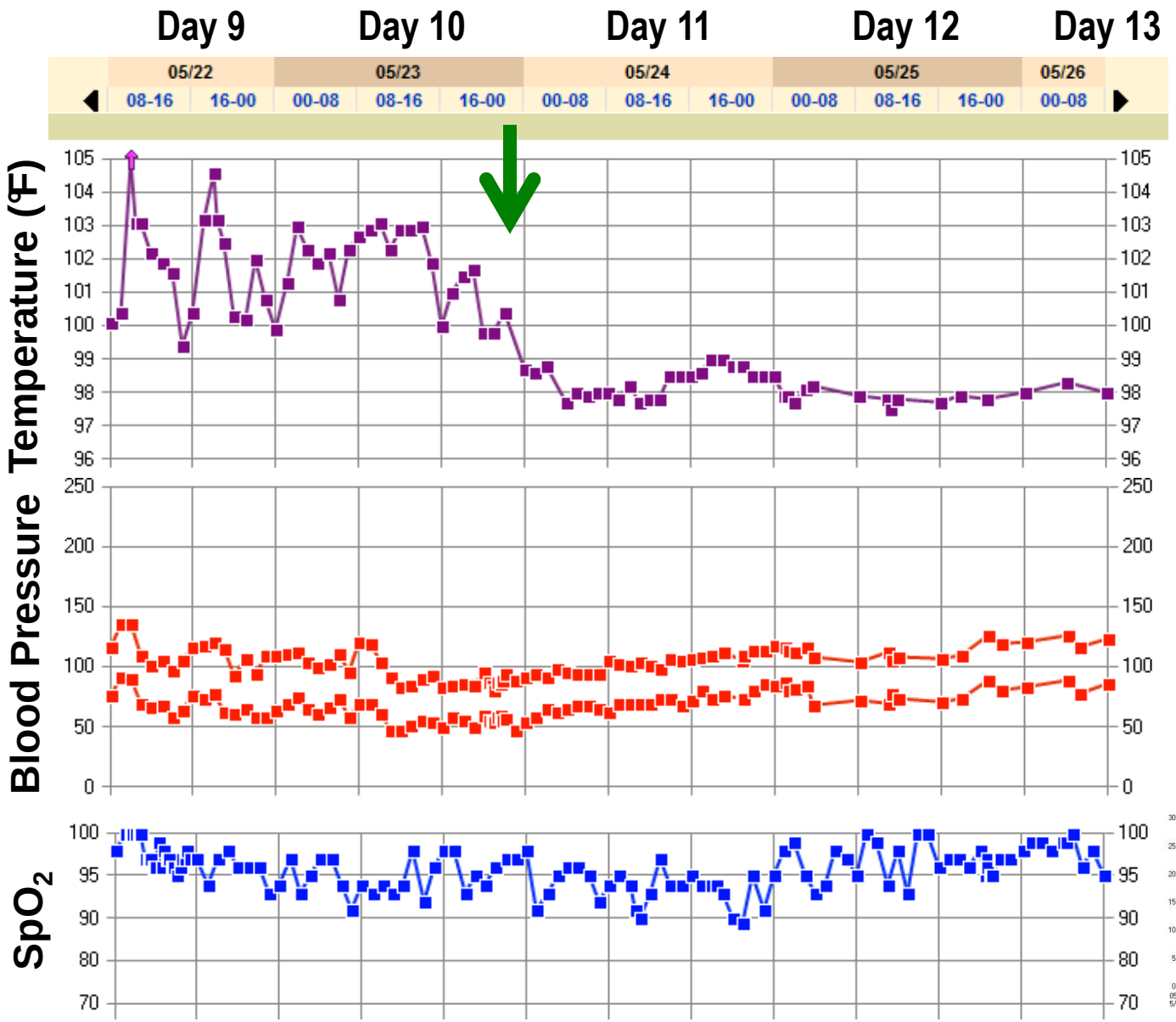




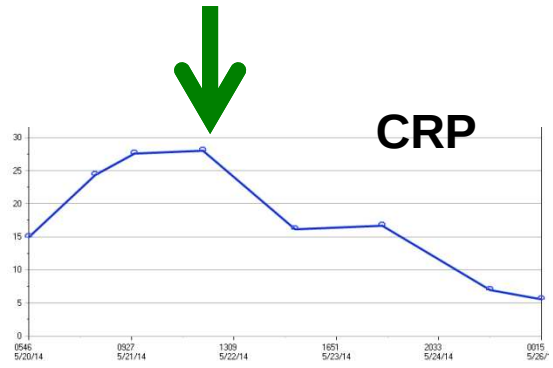
Cytokine release syndrome and CAR-T cell expansion



Resolution with IL-6R mAb



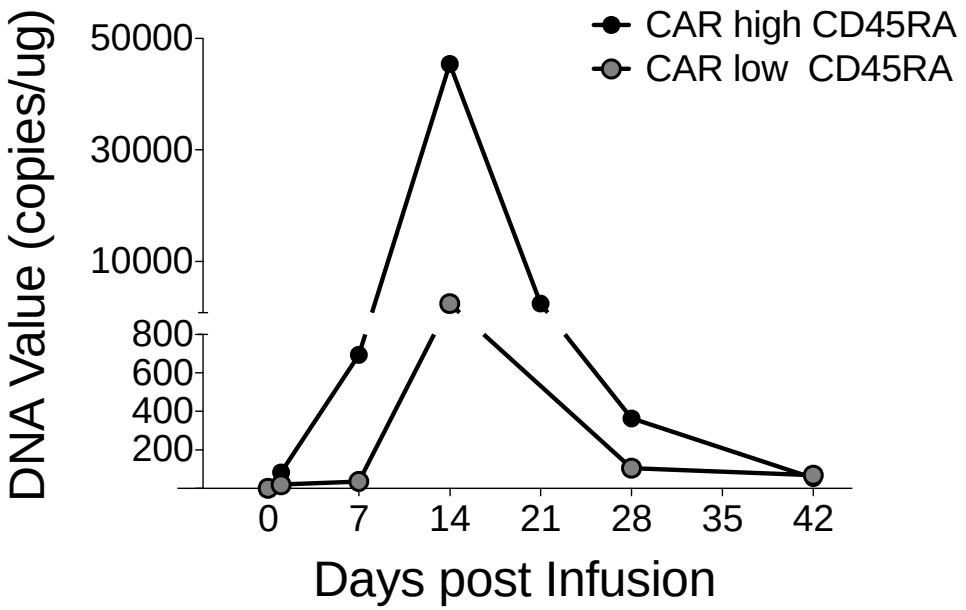
= tocilizumab
4 mg/kg IV×1

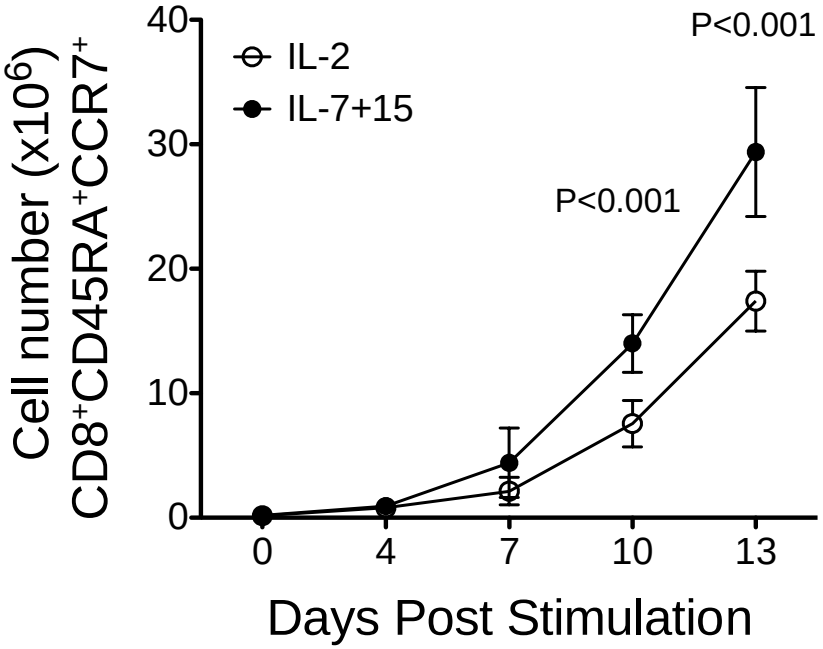


Critical issues emerging from clinical trials

- Adequate host lymphodepletion may be necessary
  - Lymphocyte homeostasis; Treg removal
- CAR may need to be expressed in **specific T cell subsets**
  - Naïve vs. experienced cells
- Different co-stimulatory domains may not be equivalent
  - CD28 vs. others

Naïve T cell subset expands better in vivo: IL-7/IL-15 preserve better the naïve subset





(Xu *et al.* Blood 2014)

Critical issues emerging from clinical trials

- Adequate host lymphodepletion may be necessary
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- CAR may need to be expressed in specific T cell subsets
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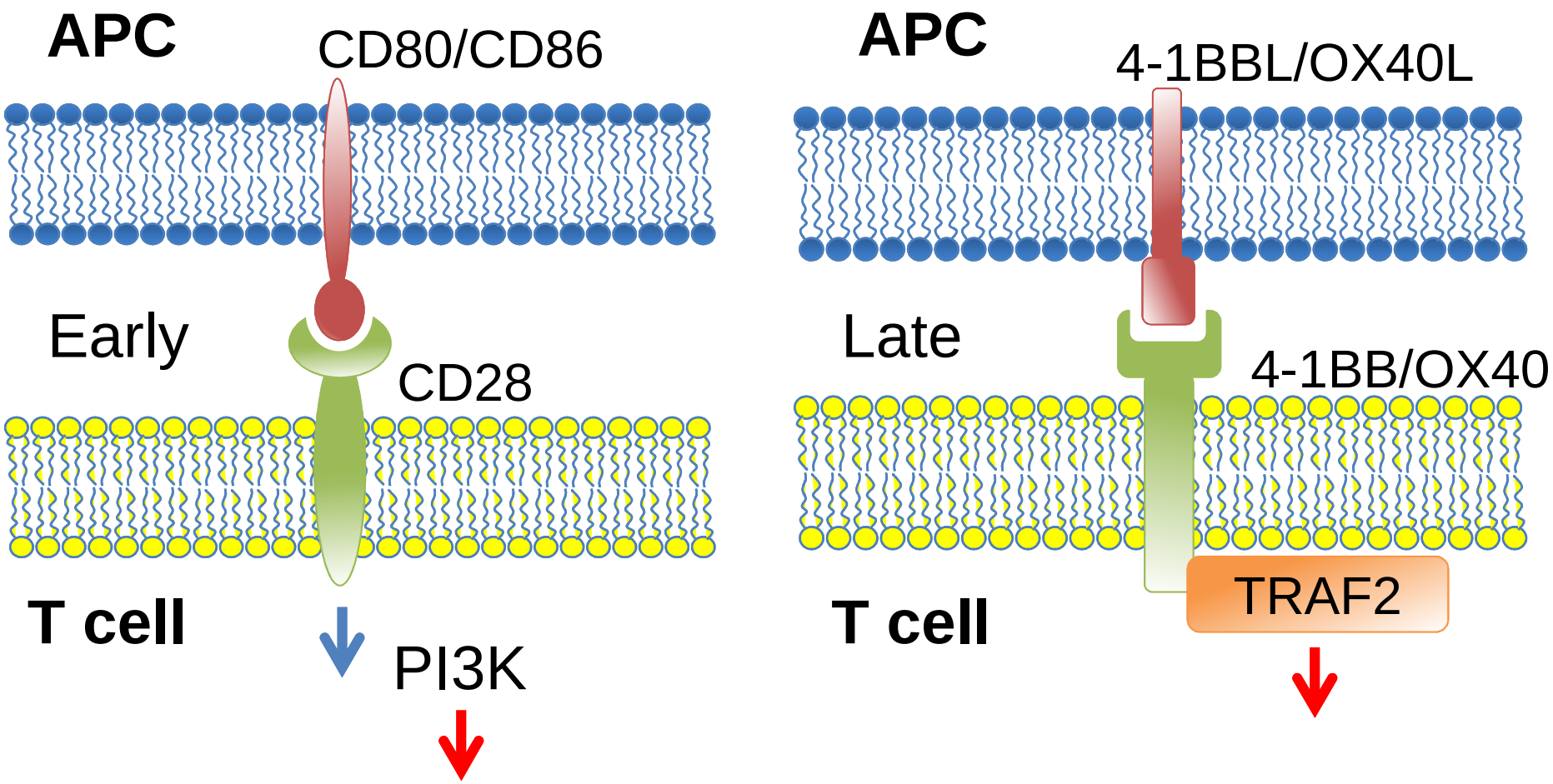
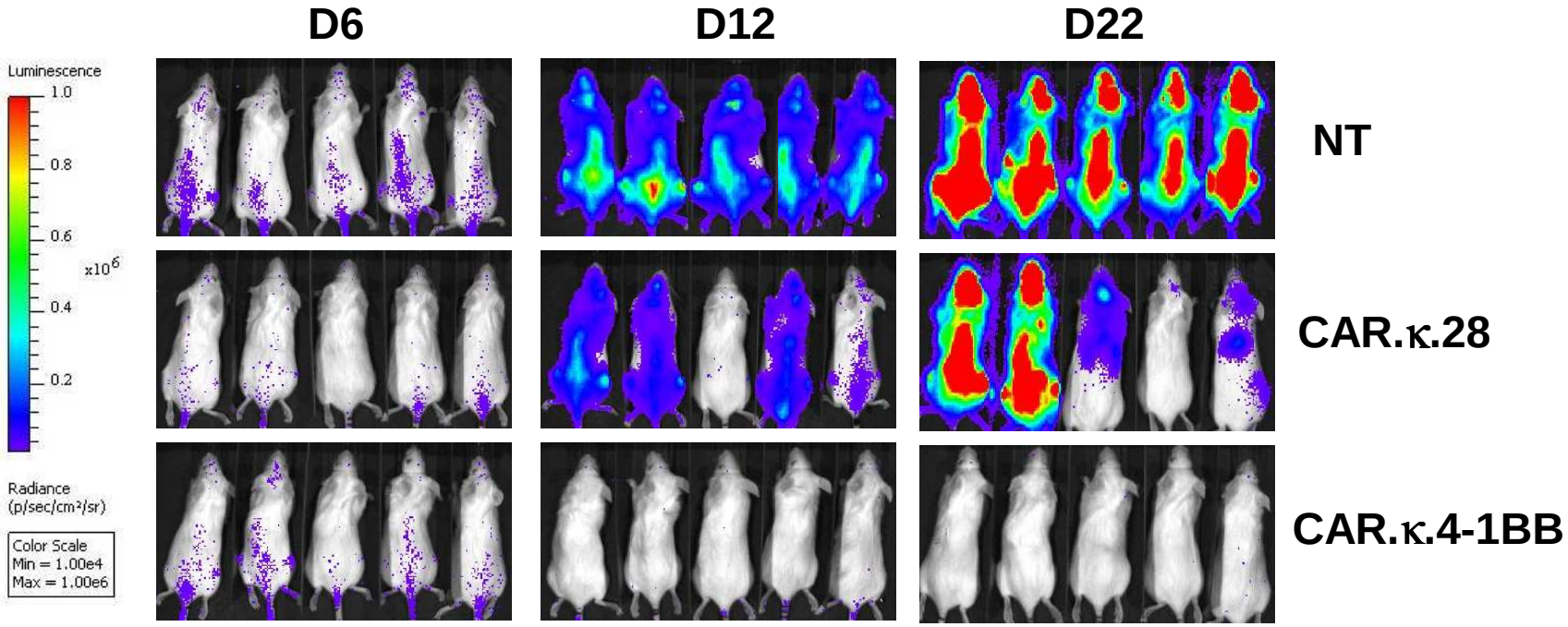
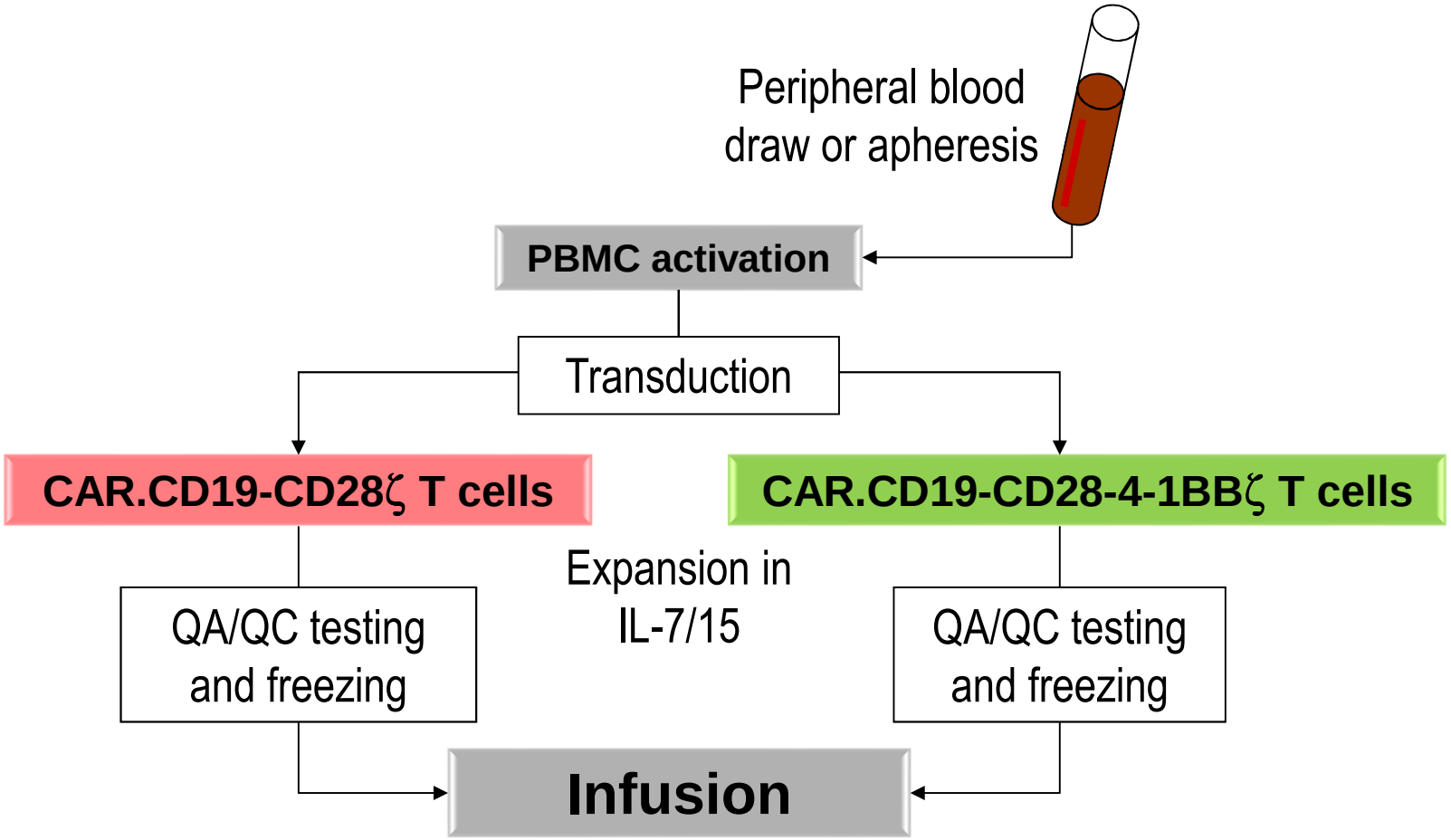
Rationale for exploring alternative costimulatory endodomains



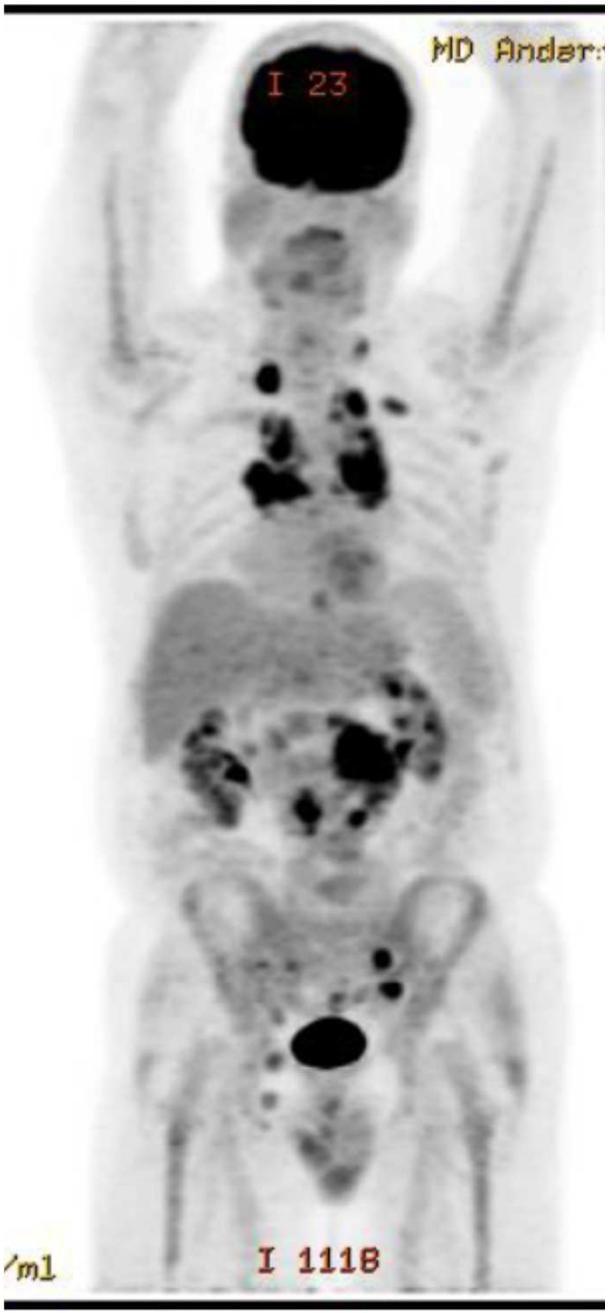
Antitumor activity of κ.CAR.4-1BB T cells



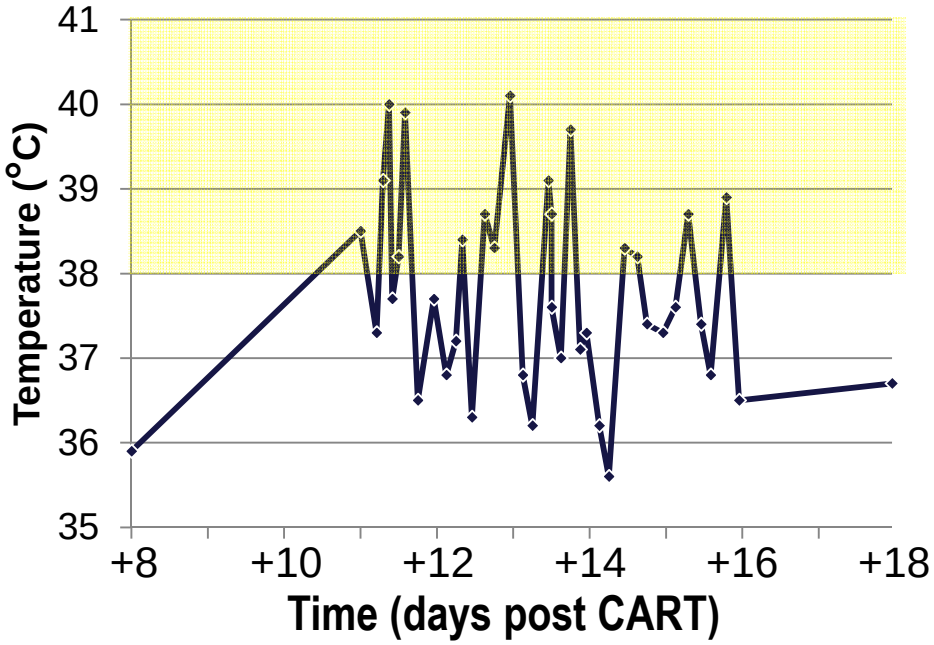
2nd (CD28) vs. 3rd (CD28-4-1BB) generation CAR-T cells



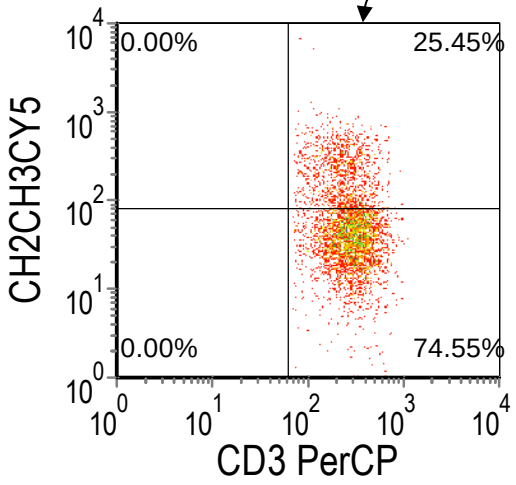
Pre: 08/20/15

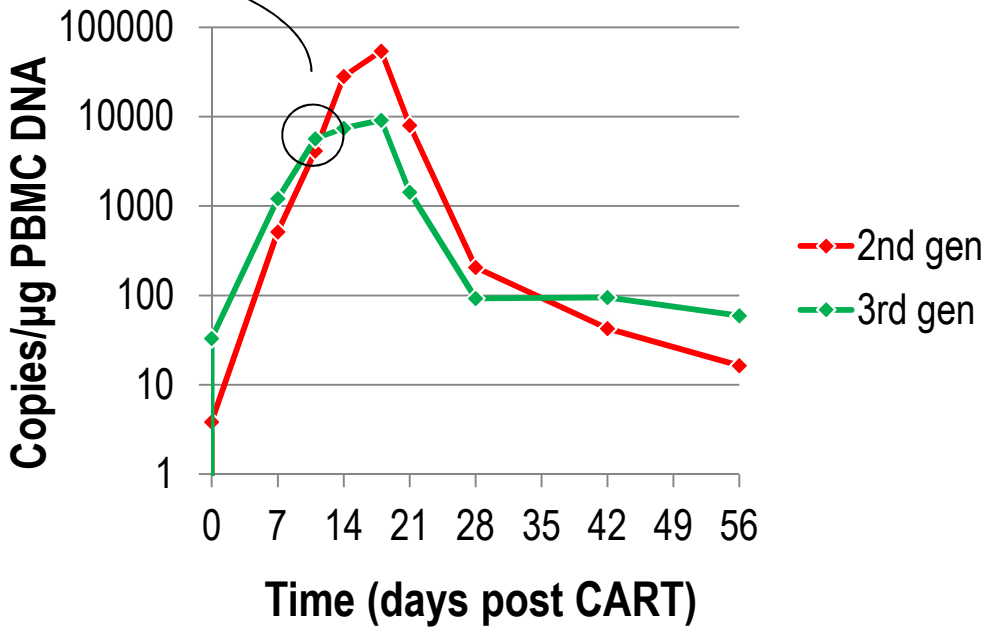


- 67 yo M, stage IVA **follicular lymphoma with transformation to DLBCL**
  - R-CHOP: response then progression
  - Lenalidomide/rituximab: no response
  - R-ICE: response then progression
  - Unable to proceed to transplant
- Cytoxan/fludarabine, then CAR-T cells



CRP: 12.2 (d +12) → 6.2 (d +16)





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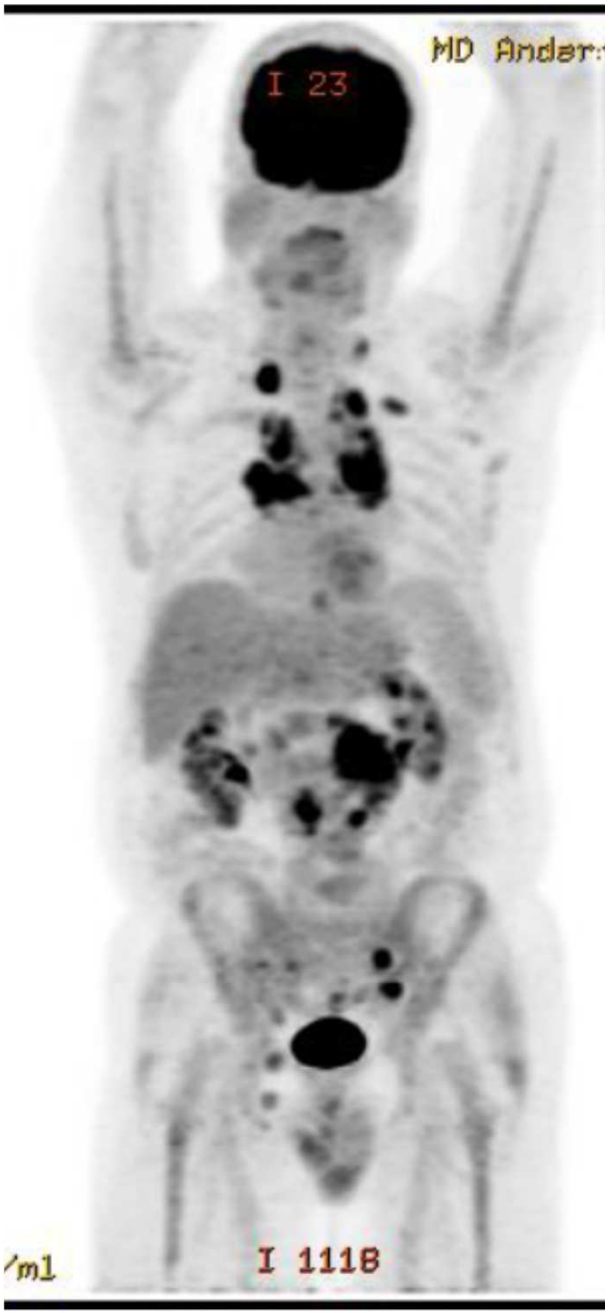
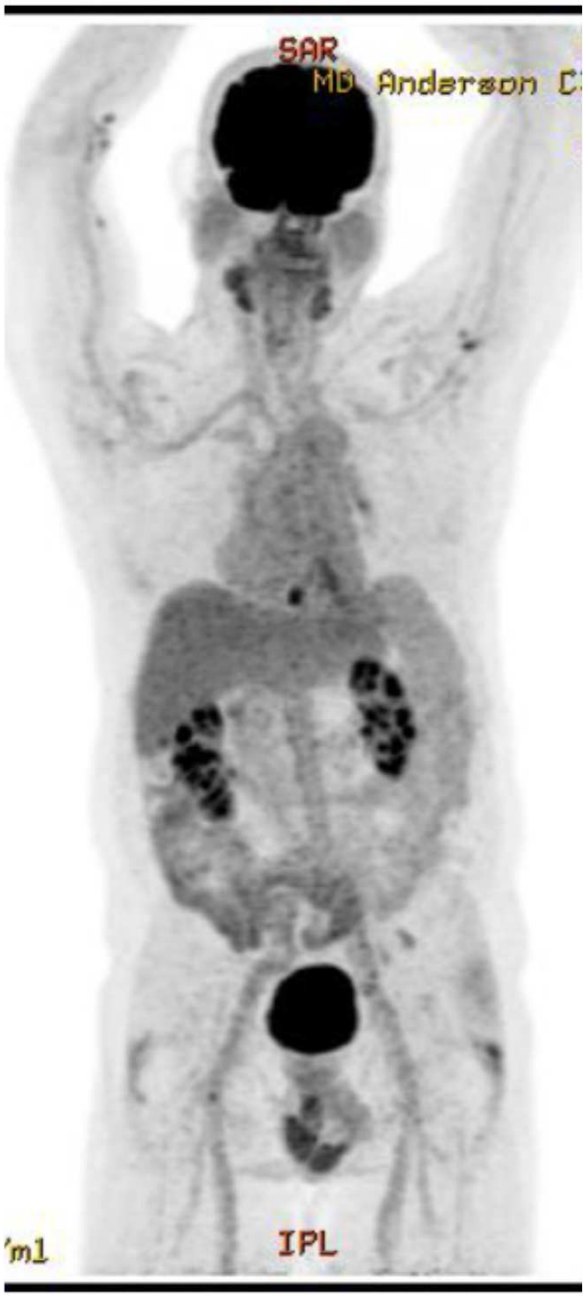


6 wk post: 10/12/15



Conclusions

- **Later generation** CAR-T cells can have remarkable activity against B-cell malignancies
  - Especially ALL and CLL, even relapsed/refractory
- Severe **cytokine release syndrome** occurs with major tumor responses
  - Manageable so far with IL-6R antibodies
- CARs can successfully travel **beyond CD19**
  - e.g. κ (and beyond B cells, e.g. CD30)
- **Antigen Escape**
- **Numerous trials** are ongoing…
  - CARs to be incorporated in standard therapy?
    - As consolidation? Bridge to BMT? BMT replacement?

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