

RAC 1004-1034

**Protocol: Phase I Study of the Administration
of EBV CTLs Expressing CD30 Chimeric
Receptors (CAR.CD30) for Relapsed
CD30+ Hodgkin Lymphoma and
CD30+ Non-Hodgkin Lymphoma**

Carlos Ramos MD: Clinical Investigator

**Barbara Savoldo MD PhD: Preclinical
development and murine models**

Gianpietro Dotti MD PhD: Retroviral vectors

CTLs Targeting EBV Antigens for Hodgkin's Disease and NHL

- Studies of EBV and LMP-specific CTLs have enrolled over 50 subjects
- No severe adverse events attributable to study agent
- Accumulation of LMP-CTL at disease sites
- Anti-tumor effects (>70% response rate)

BUT

- Many lymphomas EBV negative

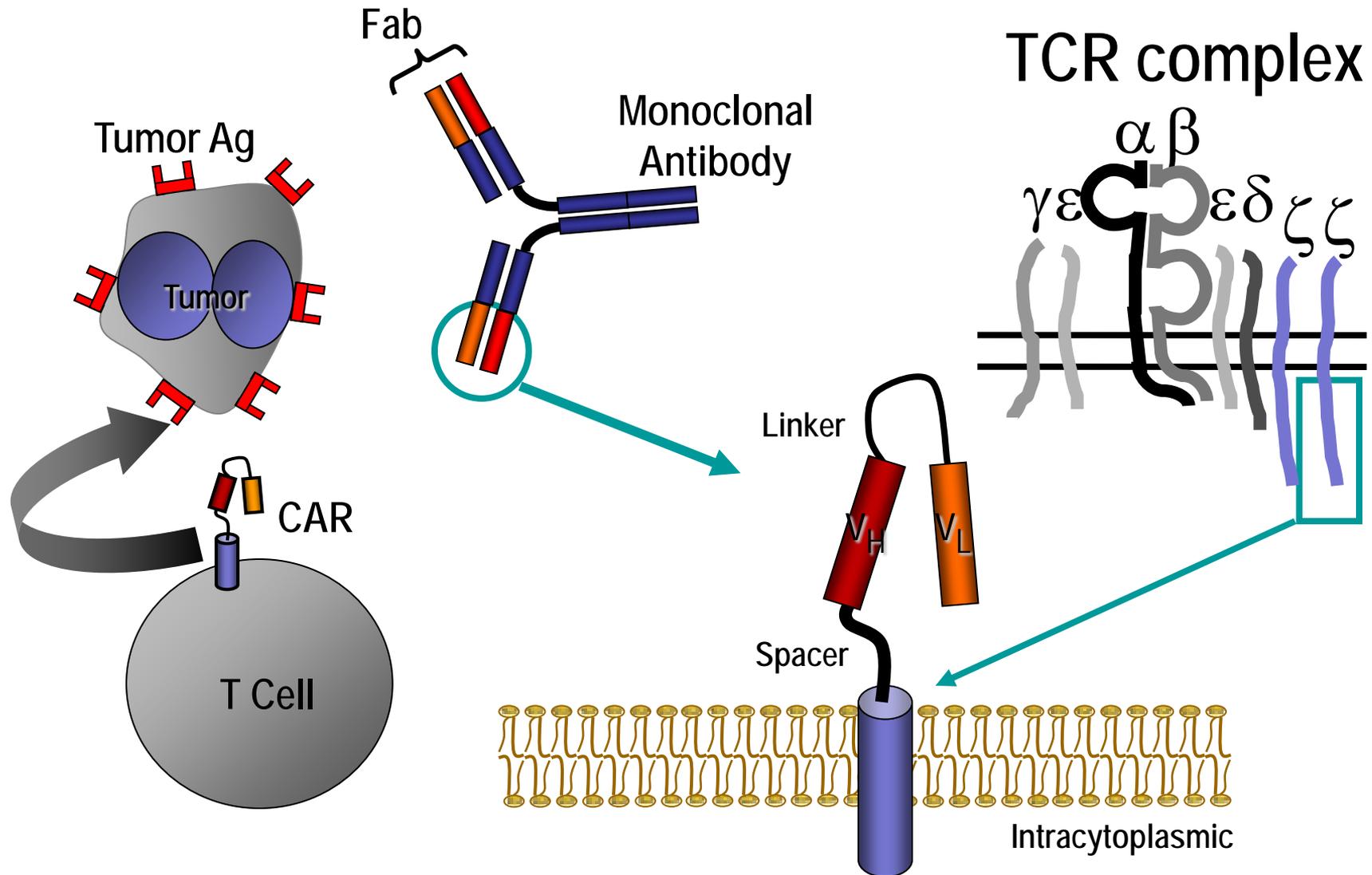
Extending Applicability

- Graft CTLs with chimeric antigen receptor targeting cell surface antigen
- CD19 CAR studies for B-NHL
 - enrolled 6 subjects
- CD30 CAR
 - Hodgkin's disease
 - Some NHL subtypes

CD30 as a Target

- Expressed on RS cells
- Phase I and II clinical trials with anti-CD30-immunotoxin
 - Unmodified (Falini et al, Br J Haemat. 1992)
 - Ber-H2-saporin toxin (Falini et al, Lancet 1992)
 - Ki-1-ricin A (Schnell et al, Leuk Lymph. 2001)
 - SGN-30 (Ansell et al, ASH 2004; Leonard et al, ASH 2004; Forero-Torres et al, Br J Haem 2009, 146:171; Duvic et al, Clin Cancer Res, 2009, 15:6217)
- Anti-CD30 chimeric antigen receptor (Hombach et al, Cancer Res. 1998)

Chimeric T-cell receptors (CARs)



(Eshhar *et al.*, PNAS 1993)

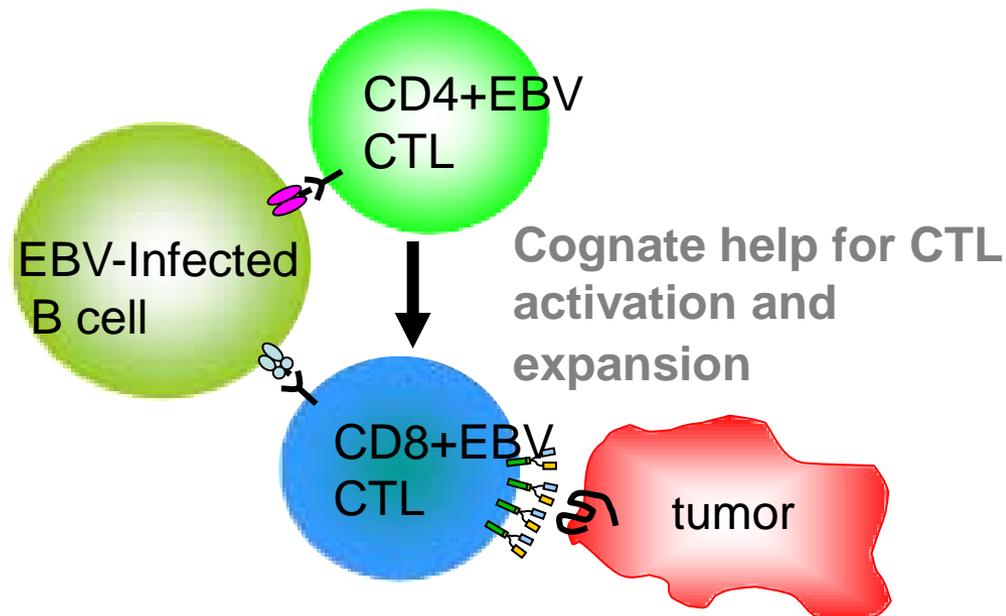
Overcoming Limitations of CARs

- Incorporate more signaling domains

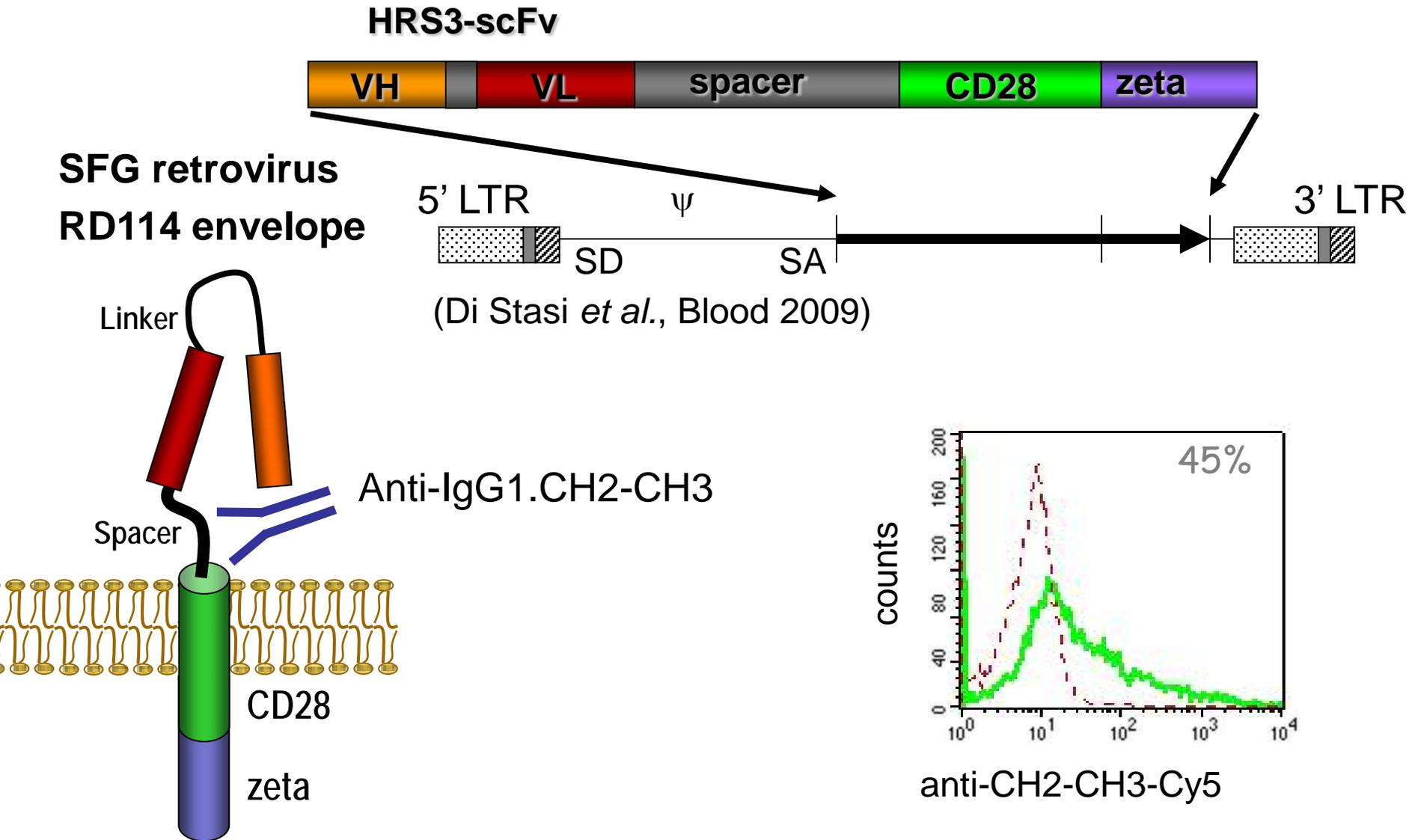
(Maher et al, Nat Biotech 2002; Finney et al, J Immunol 2004; Pule et al. Molecular Therapy, 2005)

- Dual-specific T cells

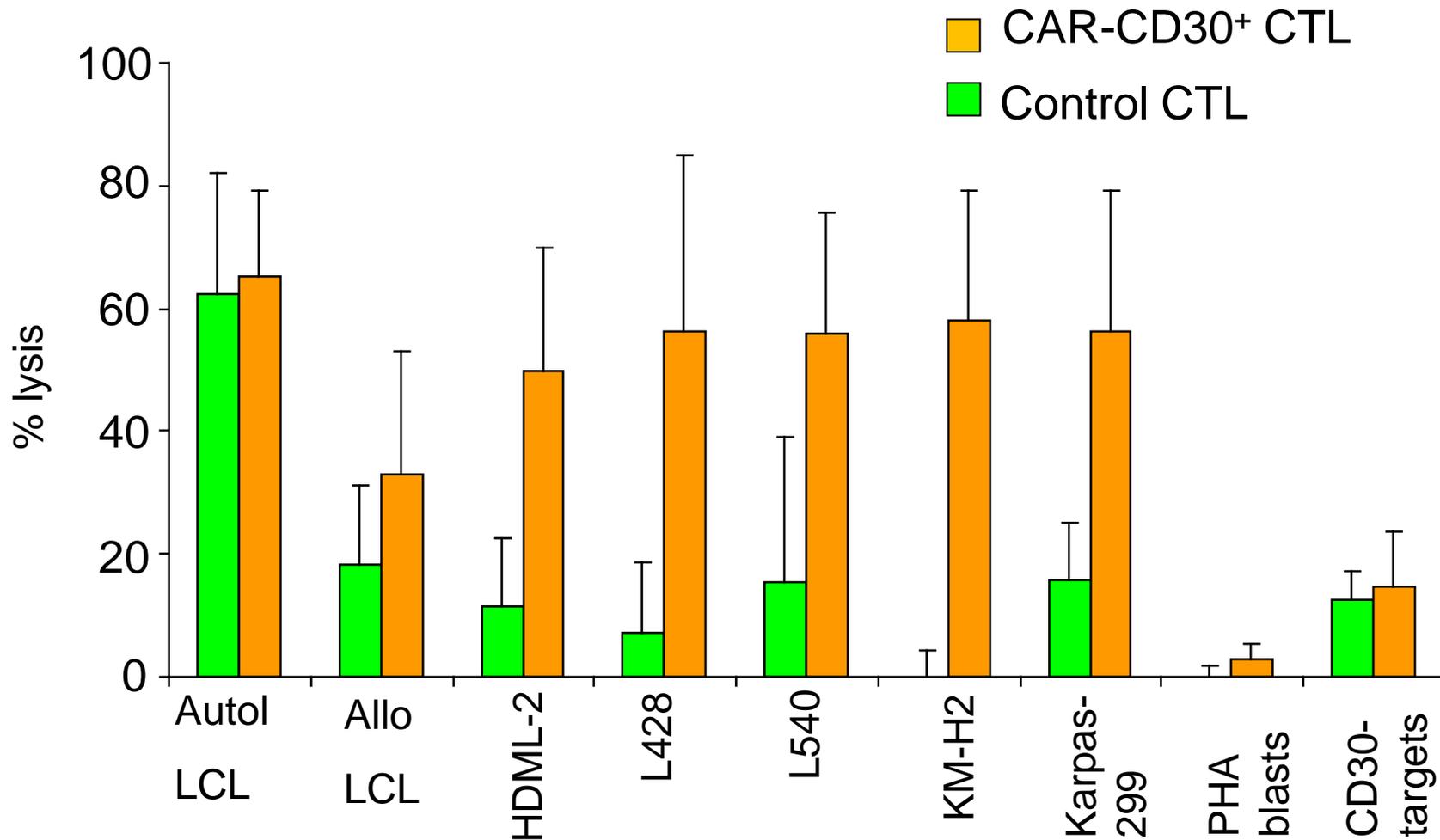
(Rossig et al, Blood 2002; Kershaw et al, Nat Biotech 2002; Cooper et al, Blood 2004; Savoldo et al, Blood 2007; Pule et al, Nat Med 2008)



Expression of CAR-CD30 in EBV-CTL



CAR-CD30+ EBV-CTLs Efficiently Kill CD30+ Tumor Cells



CD30 Expression: Potential Concerns

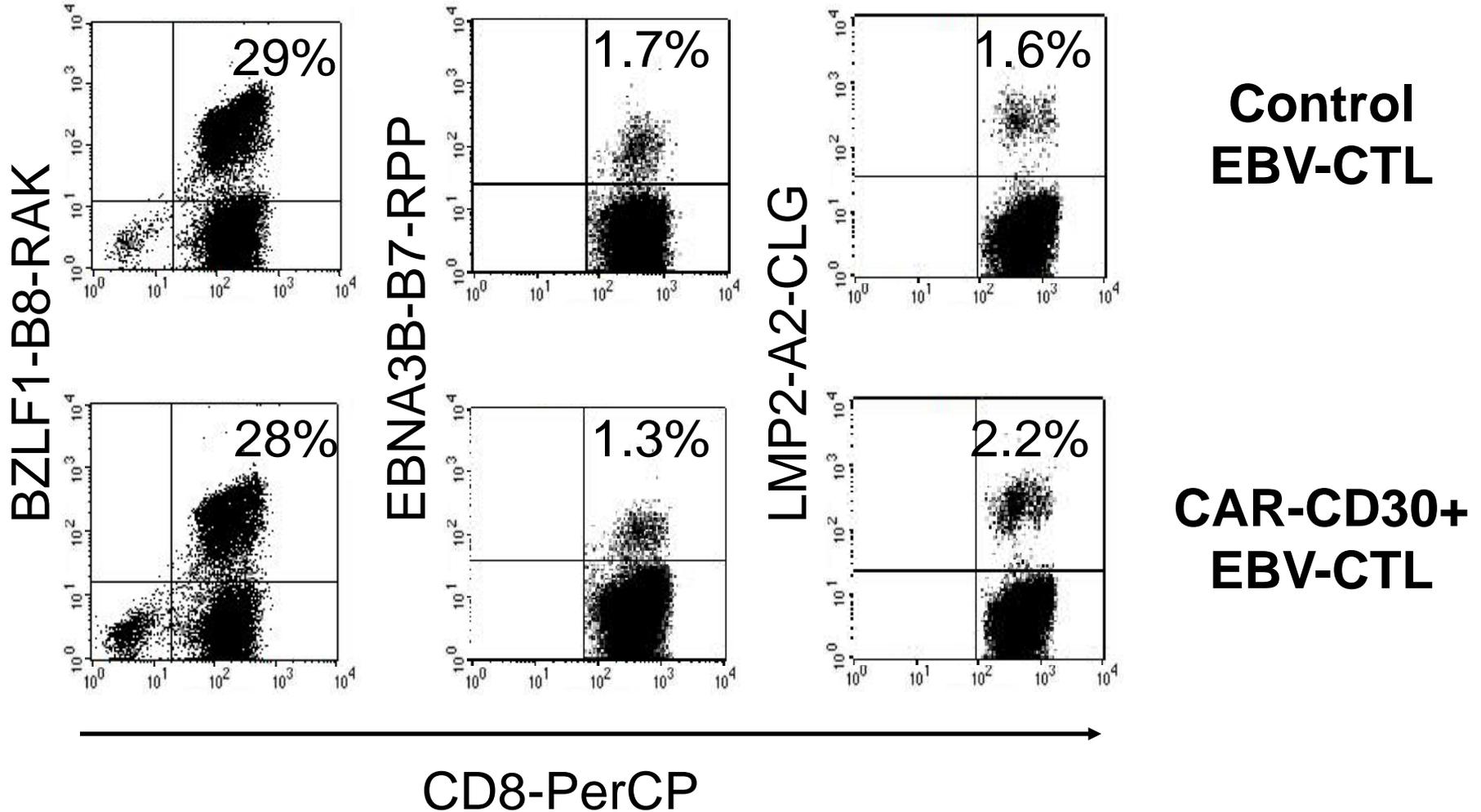
Transient expression on T cells in culture after mitogen activation or antigen receptor crosslinking

Preferentially and/or constitutively expressed by Th2 or Tc2 cells

Constitutively expressed after viral infection

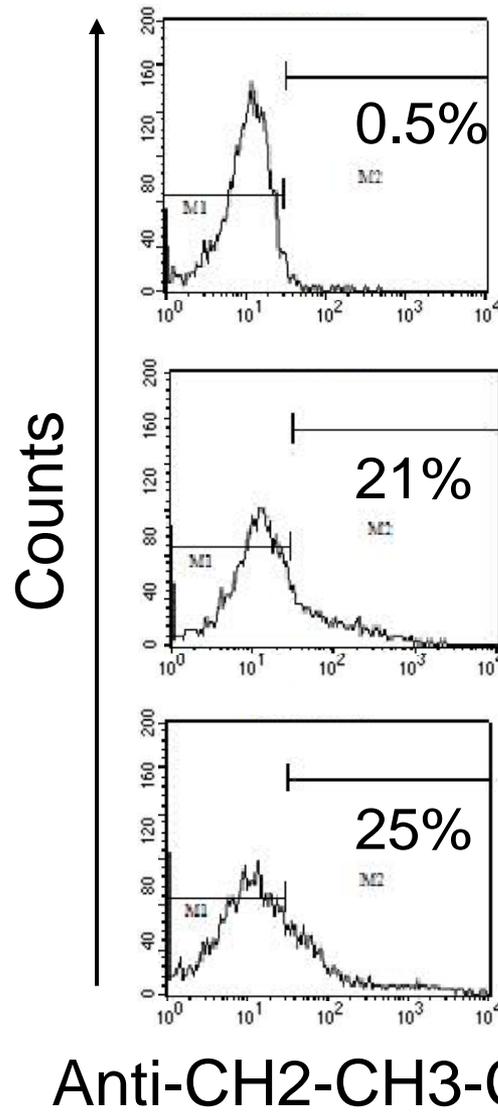
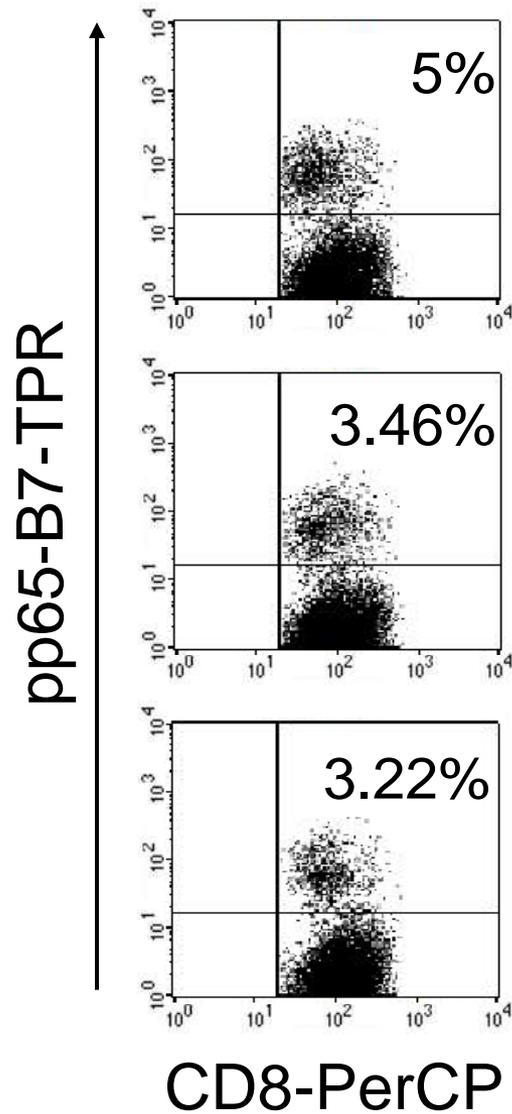
Do CD30 chimeric receptor
transduced EBV-CTL kill
themselves?

CAR-CD30 transduced CTLs retain their EBV-specific frequency



Will CD30 chimeric receptor transduced EBV-CTL kill other T cells as they respond to viral infections?

Co-culture experiments: CMV-CTL



+EBV-CTL

**+CAR-G_{D2}+
EBV-CTL**

**+CAR-CD30+
EBV-CTL**

Conclusions

EBV-CTL can be redirected to kill CD30+ HD cell lines while retaining their specificity and antigen repertoire

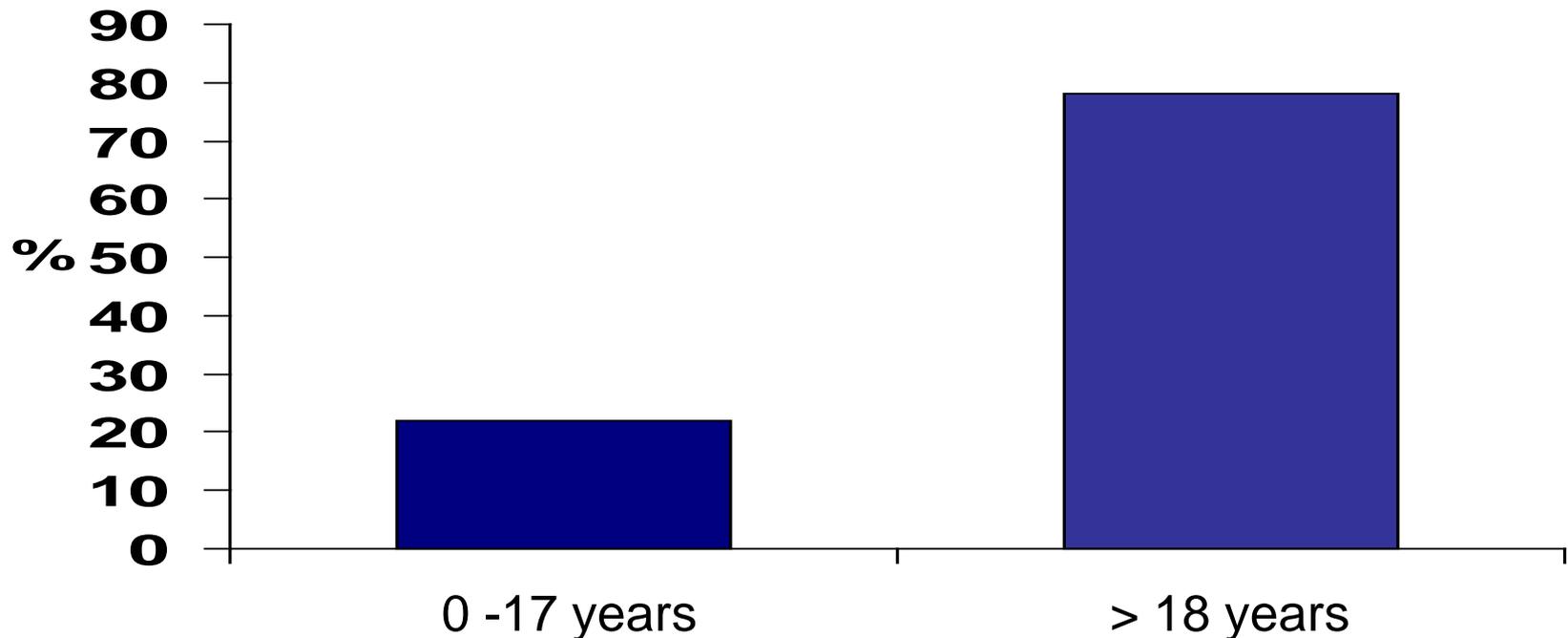
These data support the feasibility of using EBV-CTL bearing a chimeric receptor for CD30 to treat EBV negative Hodgkin's Disease.

Study Eligibility

- Relapsed Hodgkin Disease or NHL
- CD30+ve Lymphoma cells
- Tumor need not be EBV+ve
- Patient HIV and HTLV1 negative

Clinical Trial Eligibility

- Pediatric patients included for equitable access to clinical research
- Most subjects will be adults from experience in screening for current lymphoma study



Previous Experience with CAR Studies in Children

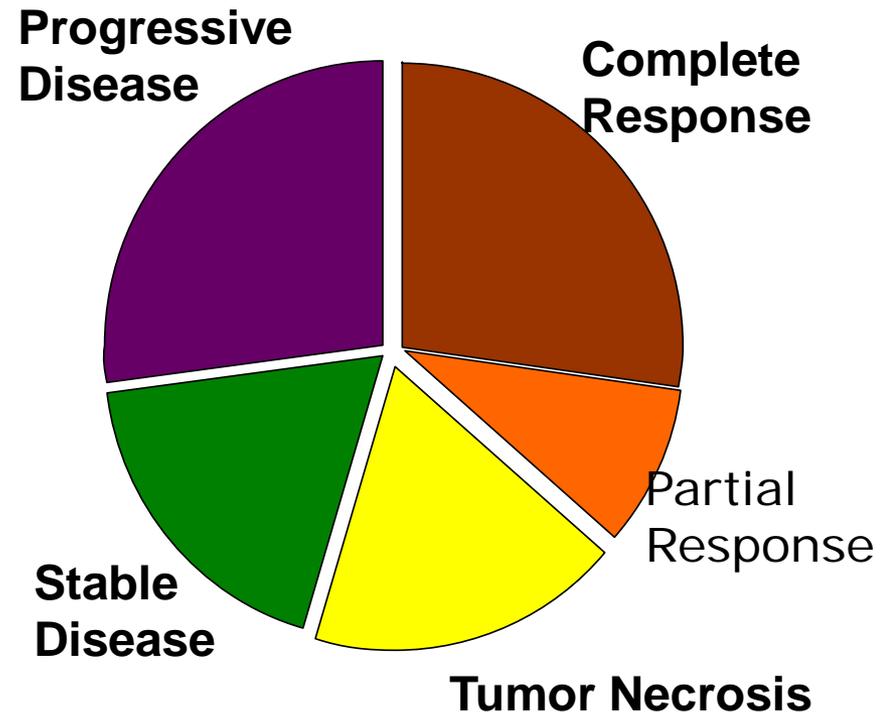
- 19 children with neuroblastoma enrolled on study of GD2-CARs
- Child life specialist involved in consent discussion with younger subjects
- Children received infusions in pediatric GCRC at Texas Children's Hospital

GD2-CAR Study

- 19 patients have been treated each with two products
 - EBV CTLs and activated T cells transduced with distinguishable GD2 CAR
- Median age of 7 years (range 2-20)
- No SAEs attributable to study agent

Best Response: Patients with Active Disease at the Time of GD2 T cell Infusion (N=11)

- 3 CR (27%)
 - Bone marrow resolution
 - Resolution of spinal lesion
 - MIBG lesion of skull from + to –
- 1 PR (9%)
- 2 tumor necrosis (18%)
 - Scapular lesion
 - Liver lesion
- 2 SD (18%)



Study Process

- Referred subjects initially consent to procurement blood to manufacture cell lines
 - 1 to 2 collections depending on count
 - Pheresis if needed
- Also receive infusion consent so have time to read with families
- Updates and discussion with clinical research staff during manufacture

Clinical Trial

- After line release by QA, subjects eligible for infusion component
- Timing will depend on disease and other therapies and studies
- Infusion consent rediscussed

CTL Product

- Dose escalation based on previous studies:
 - Level 1: $2 \times 10^7/\text{m}^2$
 - Level 2: $5 \times 10^8/\text{m}^2$
 - Level 3: $1 \times 10^8/\text{m}^2$
- CRM monitored by study statistician, Dr Hao Liu

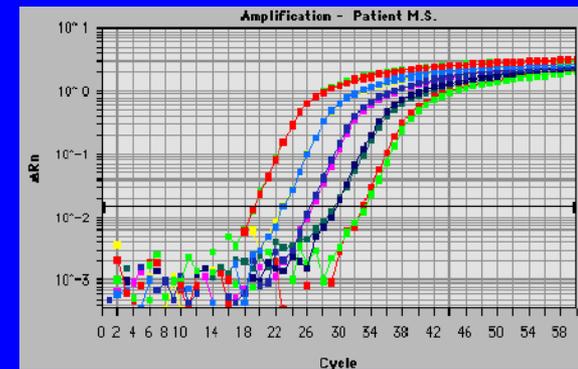
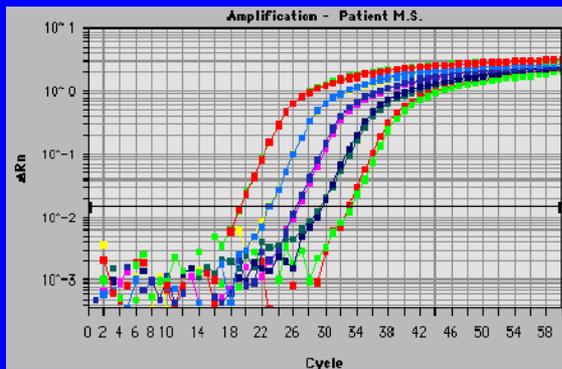
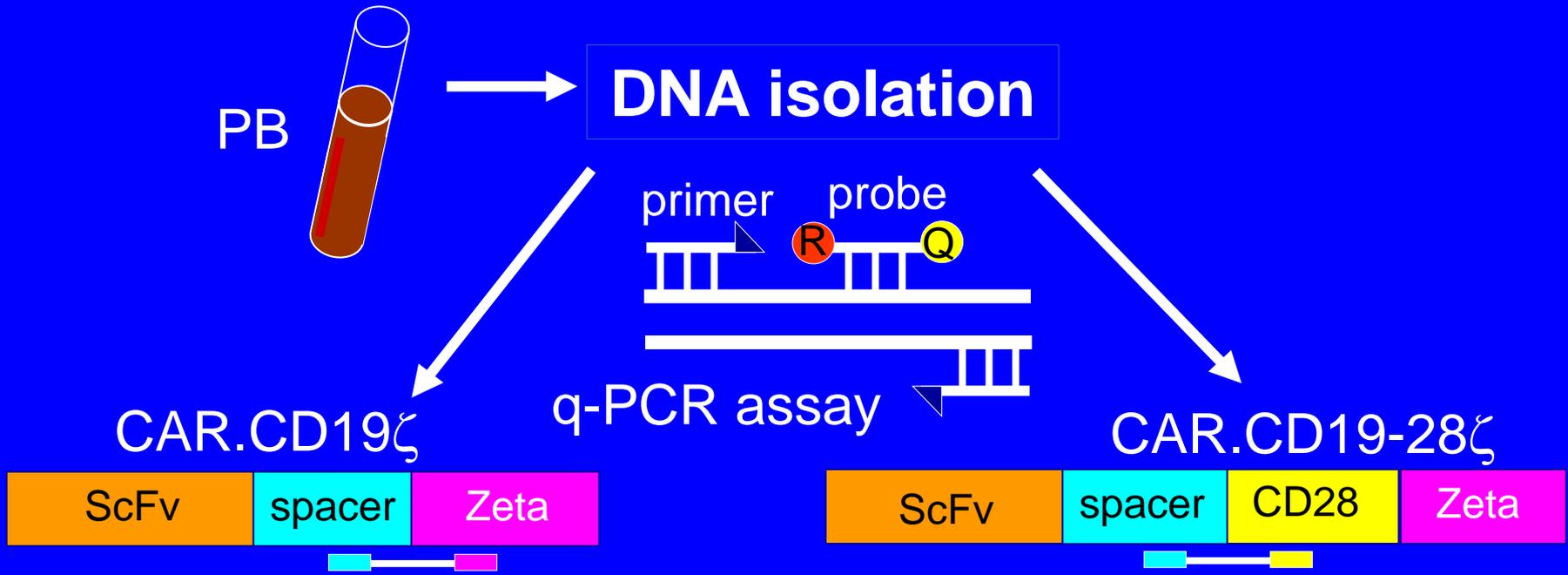
Monitoring

- Clinical evaluation for AEs
- Persistence monitored by qPCR
- Clonality studies per FDA guidelines if transgene detection $>0.5\%$
- Anti-tumor effects

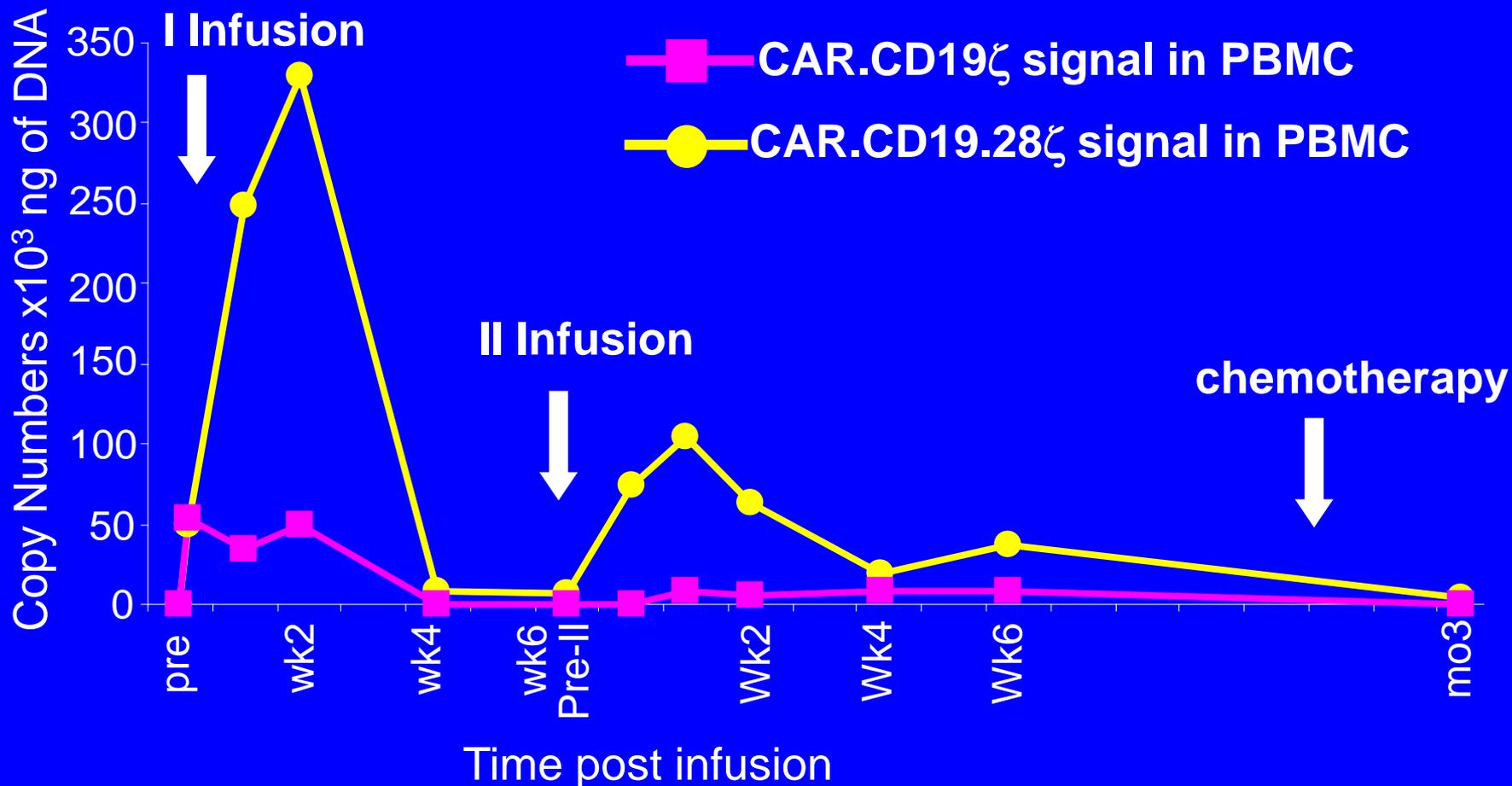
Risk of Cytokine Storm

- No lymphodepletion immediately prior to T cell infusion
- Starting T cell dose 3 logs lower
- CAR targeting a different antigen
- CAR incorporates CD28 and zeta but not 41BB
- Risk addressed in consent

Monitoring expansion and persistence of each product

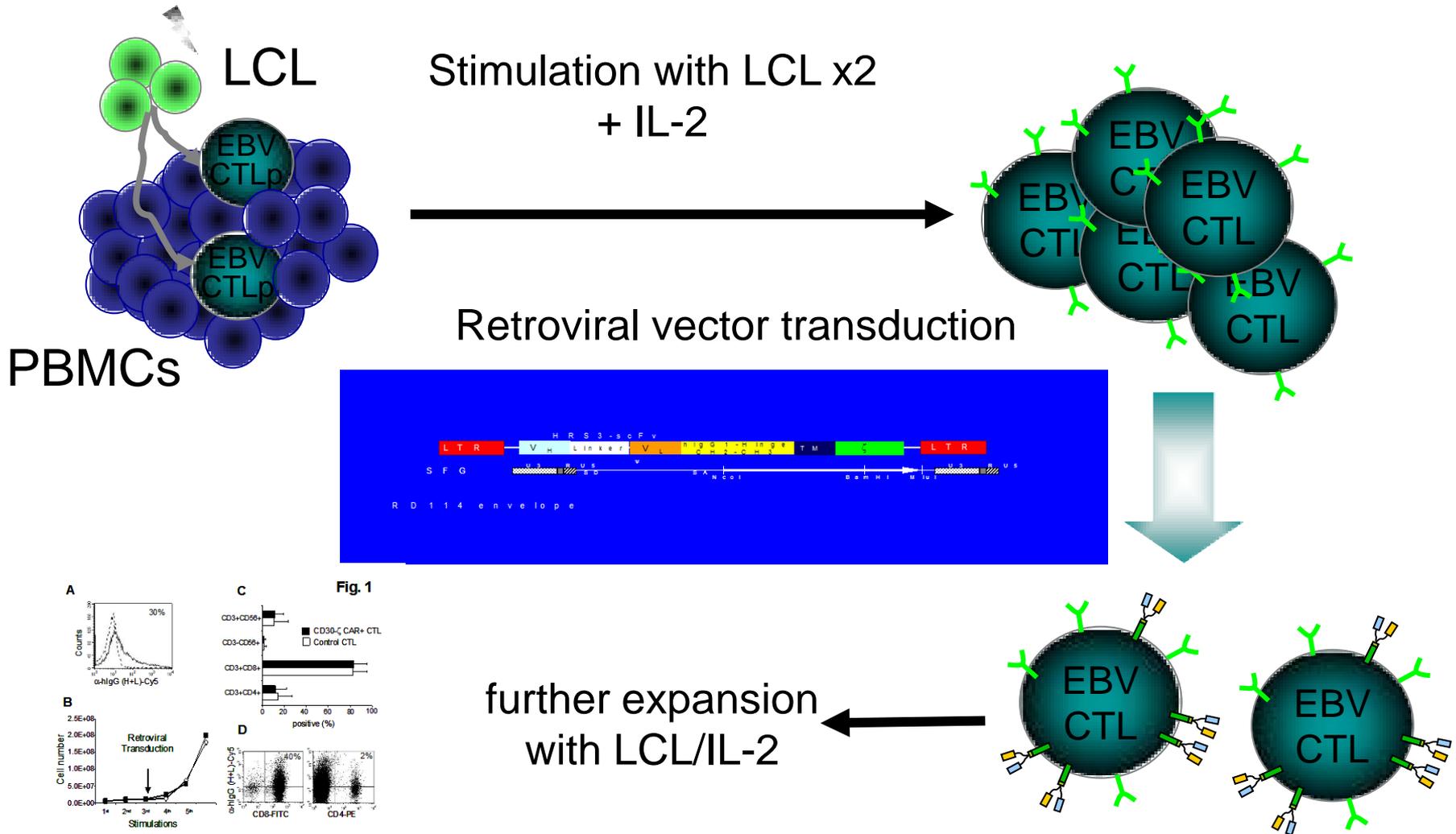


CAR.CD19-28⁺ T cells have greater *in vivo* expansion and persistence

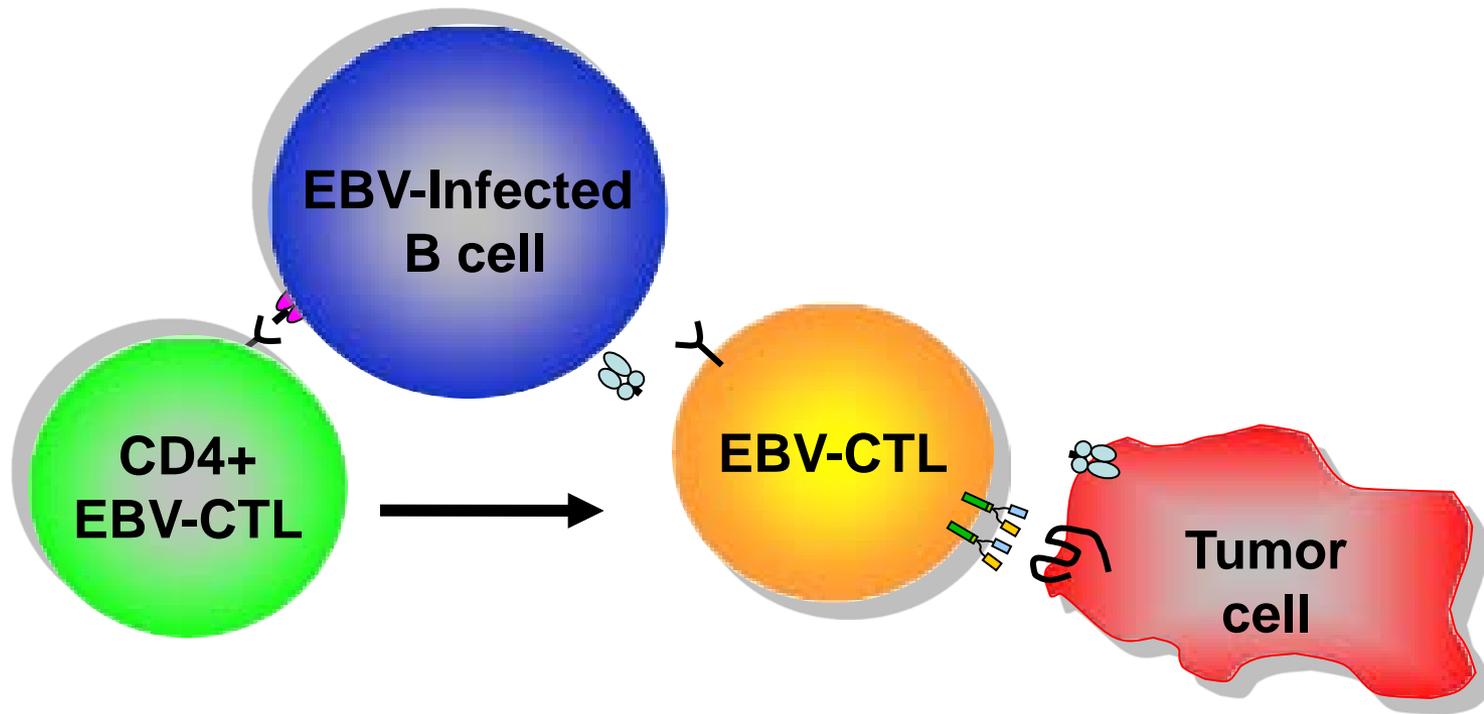


Pt #3, dose level 2

Generation of CD30- ζ CAR transduced EBV-CTL



Benefits of Transferring CAR to EBV CTLs



Cognate help for CTL activation and expansion
even if tumor EBV-ve

Rossig et al, Blood 2002

Savoldo et al, Blood 2007

Pule et al, Nature Medicine 2008