Phase I study using T cells expressing a CD123-specific chimeric antigen receptor and truncated EGFR for patients with relapsed or refractory acute myeloid leukemia

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Acute Myeloid Leukemia

- The most common acute leukemia in adults and has the highest mortality rate
- Cure rate for primary AML is 35% and decreases with age
- 5-year OS for AML patients post-1st relapse: ~10%
- AlloSCT is the preferred treatment route following a 2nd CR
- However less than half of patients are able to proceed to transplant due to treatment resistance

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AML – second CR

- Ideally, AlloSCT candidates should be in remission, to improve post-transplant outcomes
- 2nd CR is not easily achieved
  - < 20% in patients with early relapse (<1yr in remission)
  - ~40% in patients with late relapse (≥1yr in remission)
- We need new treatments for relapsed AML as a potential bridge to transplant.

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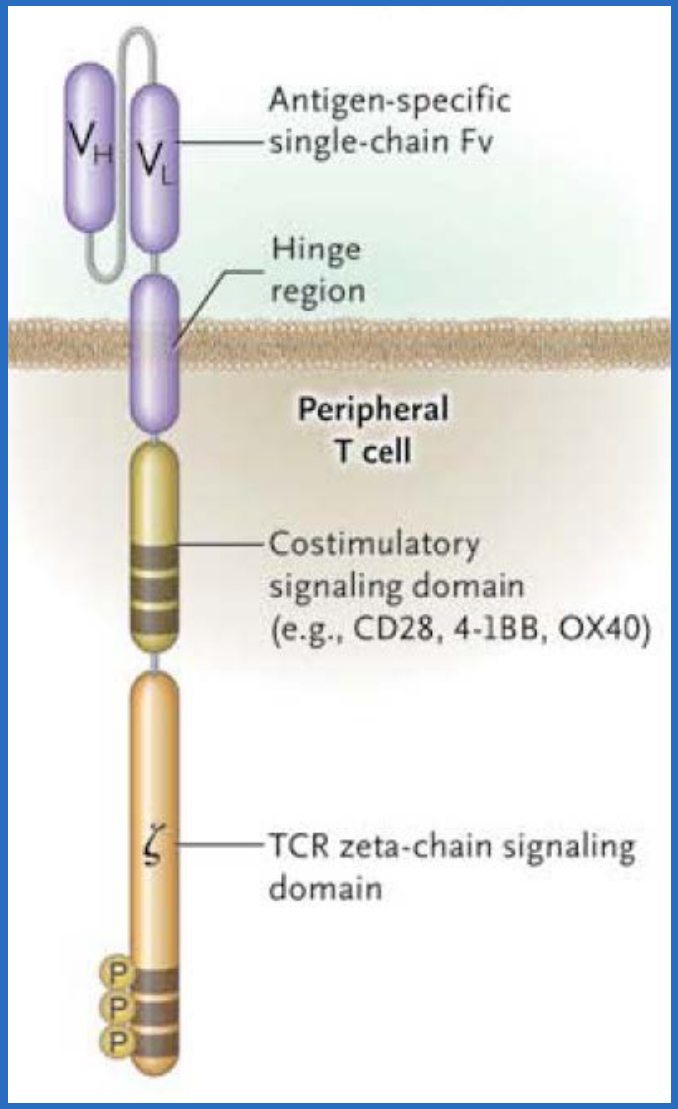
Chimeric Antigen Receptors (CARs)



Urba WJ *N Engl J Med* 2011

- Redirect T cell specificity in an MHC-independent manner
- Target cell surface antigens only
- Impressive remission rates are seen with CD19CAR T cells for treatment of ALL (CR rate as high as 88%)
- Allows many patients to proceed to transplant in remission

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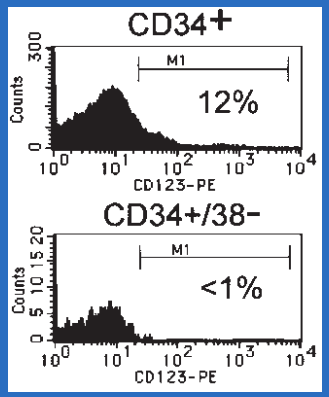
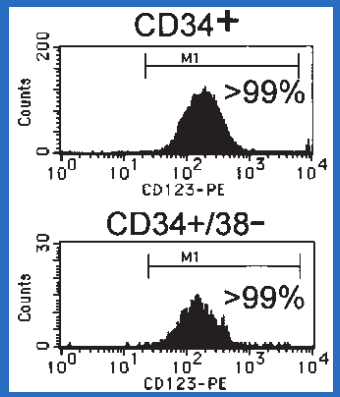
CD123-AML associated Antigen

- Over-expressed on AML cells compared to normal adult hematopoietic stem/progenitor cells

Normal BM



AML



(Jordan CT *et al. Leukemia* 2000)

- Expressed at highest levels on plasmacytoid dendritic cells; at lower levels on basophils, monocytes, eosinophils, and myeloid dendritic cells

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CD123 expression on AML patients

AML Sample ID	Age/Sex	Cytogenetics	Clinical status	Sample Type	CD123 (RFI)	CD34+ selected %CD123+
179	74/M	Intermediate-risk t(1;7), t(14;15)	Relapsed	PB	428.32	99.22
373	47/M	Poor-risk, Complex abnormalities in 3 cell lines	Relapsed	PB	1052.83	99.66
493	46/F	Intermediate-risk Trisomy 8	Relapsed	PB	23.98	76.80
519	44/F	del(17p), dic (11;7), clonal loss of TP53/17p13.1	Relapsed	PB	63.18	97.40
545	58/M	Intermediate-risk t(3;6), del(7)	Induction failure	PB	52.73	99.32
559	59/M	Complex abnormalities, Massive hyperdiploidy	Relapsed	Apheresis	9.30	45.0
605	55/M	Normal	Persistent	PB	58.48	99.91
722	22/M	Intermediate risk t(14;21), del(9q)	Untreated	PB	33.53	92.74
813	48/F	Complex abnormalities, Trisomy 8, Trisomy 21, add(17)	Untreated	PB	37.19	90.93

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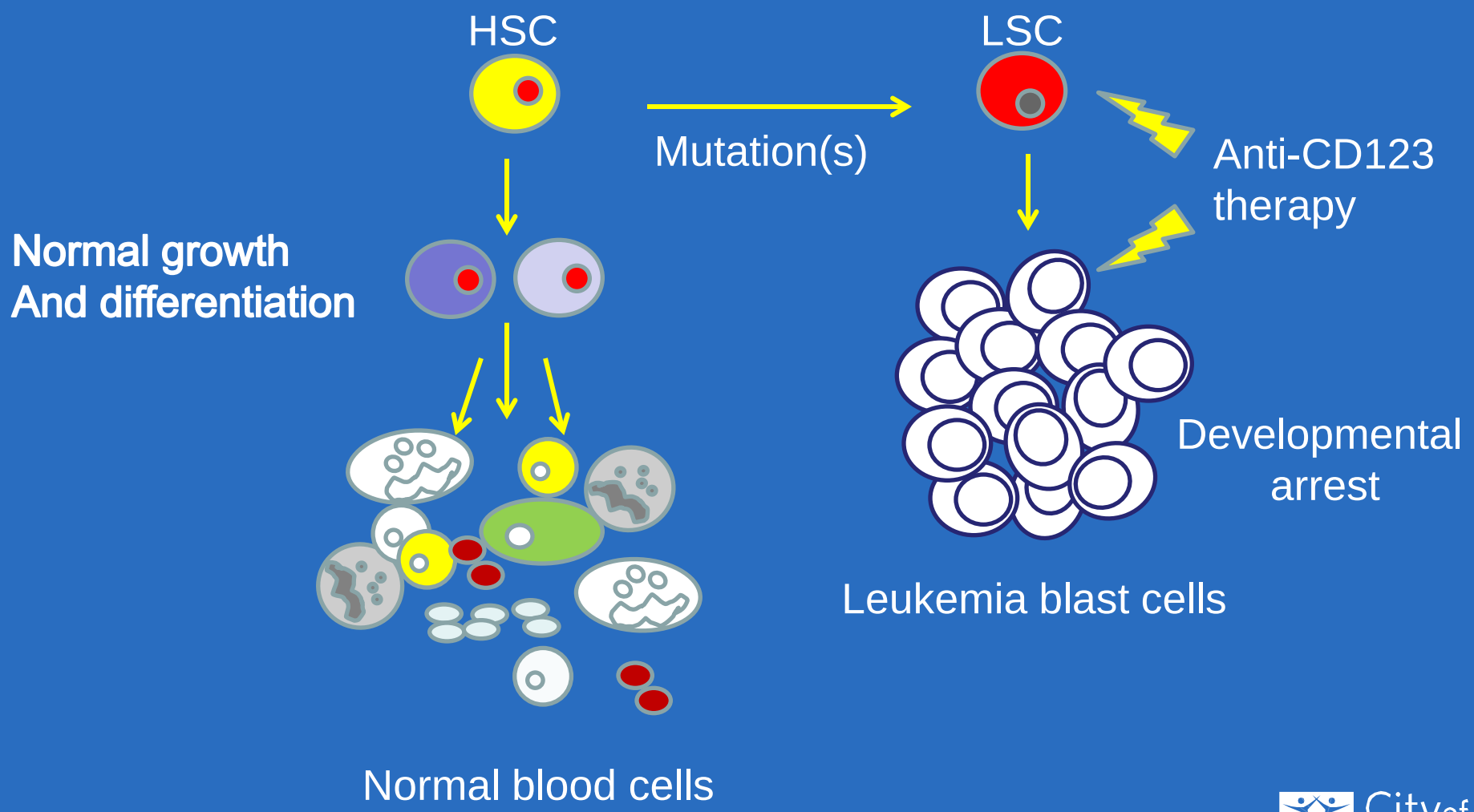
Therapeutic concept



CD123 Clinical Experience

- Two phase I trials (CSL360 and SL-401) have been completed (NCT00401739 and NCT00397579)

Trial	Treatment	#	SAE	Response
CSL360 Roberts et al. (ASH, 2008)	7G3mAb weekly x 12	23	1- fungal infection 2-infusion rxn	1 CR
SL-401 Frankel et al. (2010)	DT-IL3 q.o.d. x 6	45	8 - grade 3 AST/ALT	1 CR 2 PR

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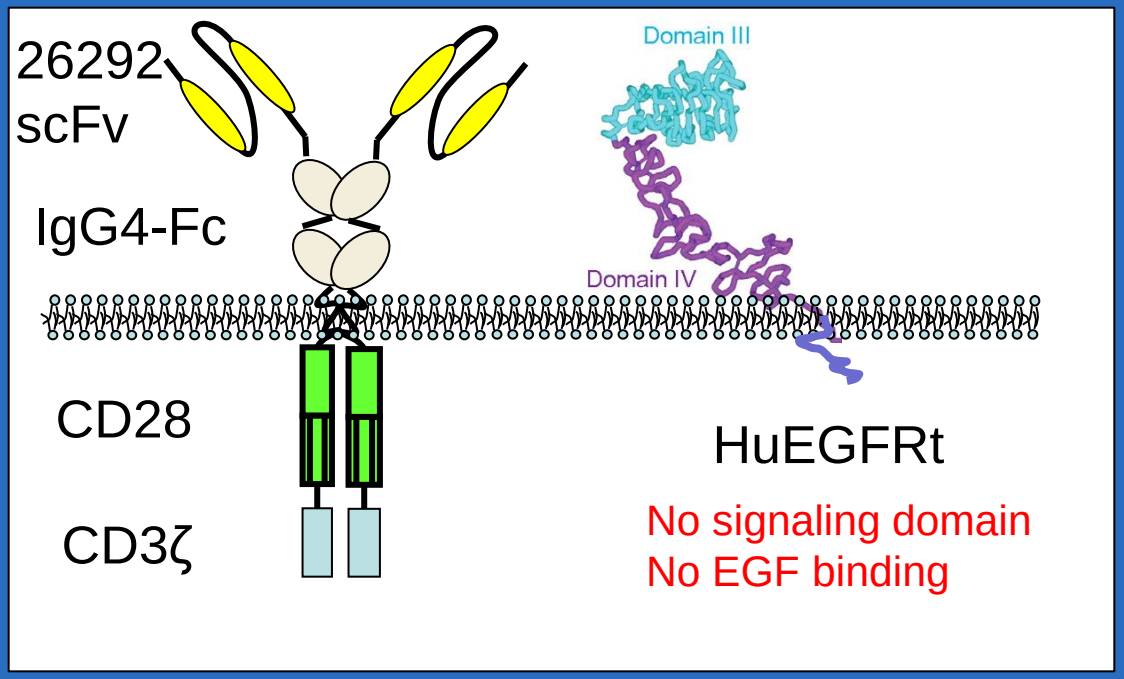
CD123 CAR T cells



- Ag-specific activation
- Ag-driven proliferation
- Effective killing of autologous AML blasts

Wang et al. (Forman lab) 2011 Blood
Mardiros et al. (Forman lab) 2013 Blood

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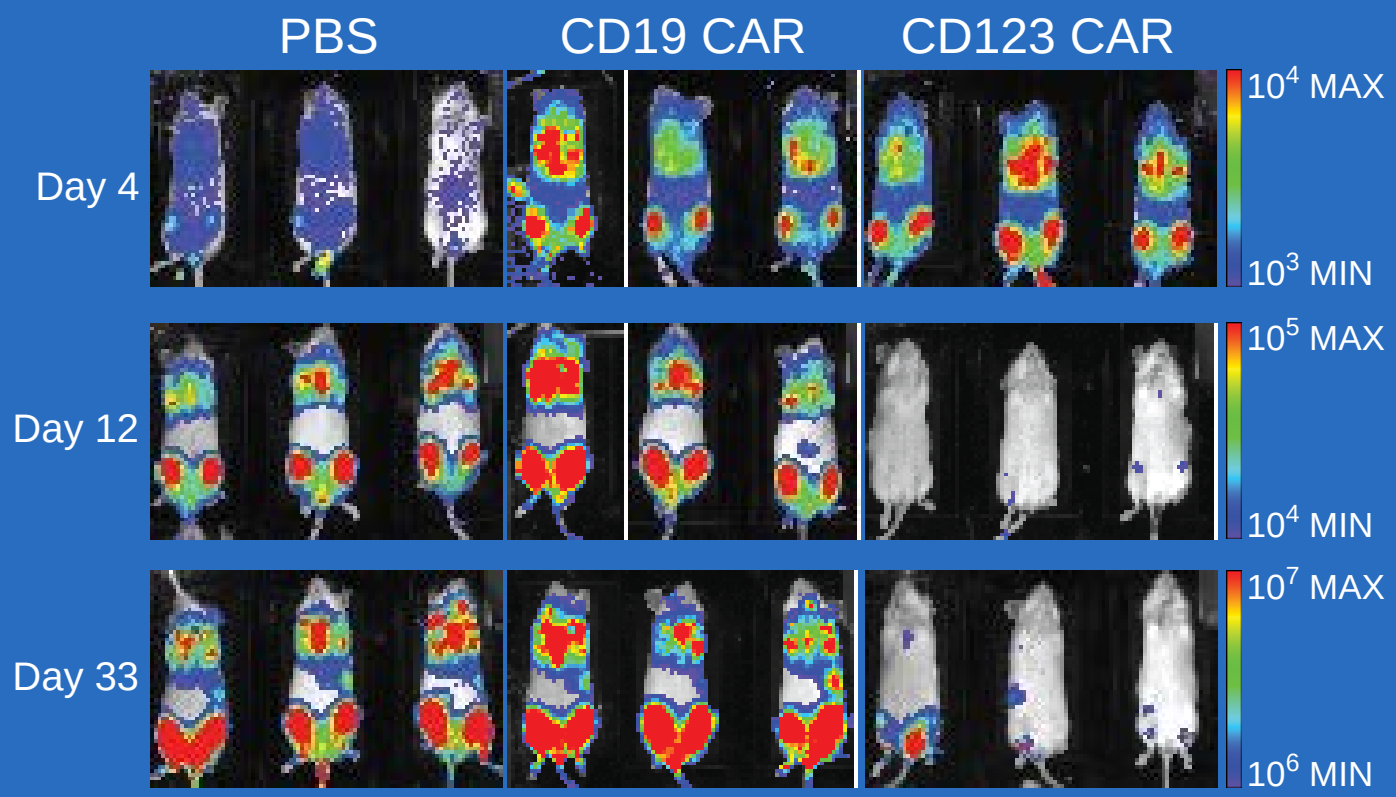
CD123 CAR T cell exhibit anti-AML activity in a xenogeneic model of AML

Day 0 Infusion – 0.5×10^6 KG1a-GFPffluc (IV)
Day 5 Infusion – 5.0×10^6 CAR^+ T cells (IV)



Mardiros et al. 2013 Blood

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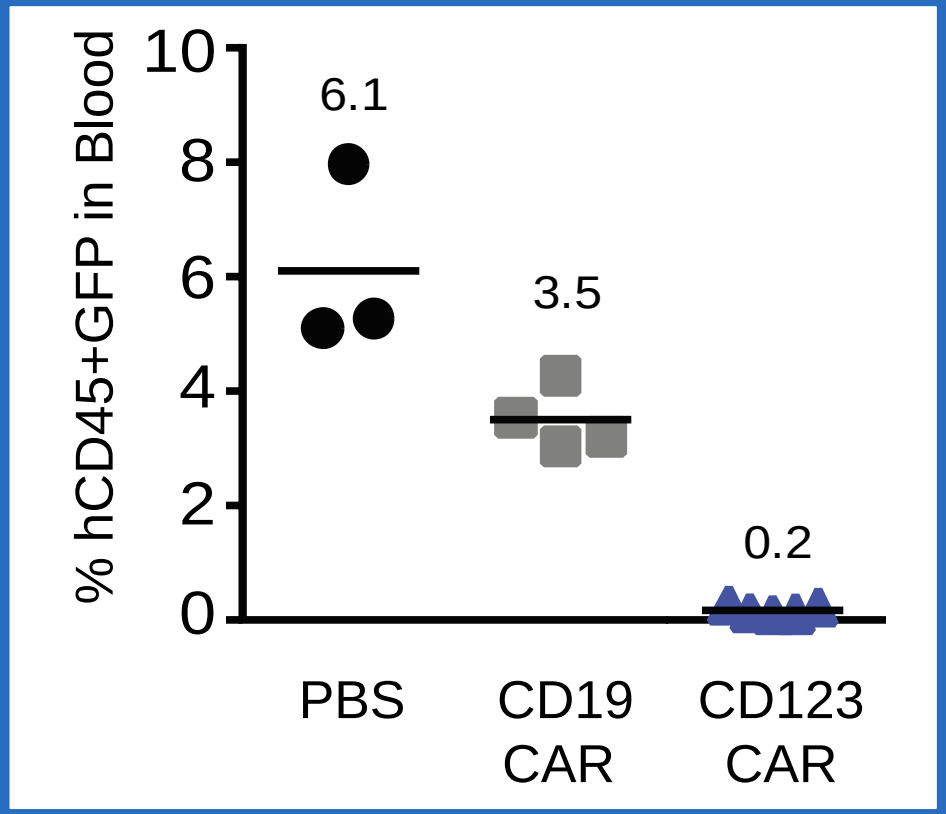
CD123 CAR T cells exhibit anti-leukemic activity in a xenogeneic model of AML



Decreased leukemic burden in peripheral blood at day 32

PBS vs CD19 CAR	$p = 0.0270$
PBS vs CD 123 CAR	$p < 0.0001$
CD19 CAR vs CD123 CAR	$p < 0.0001$

Mardiros et al. 2013 Blood

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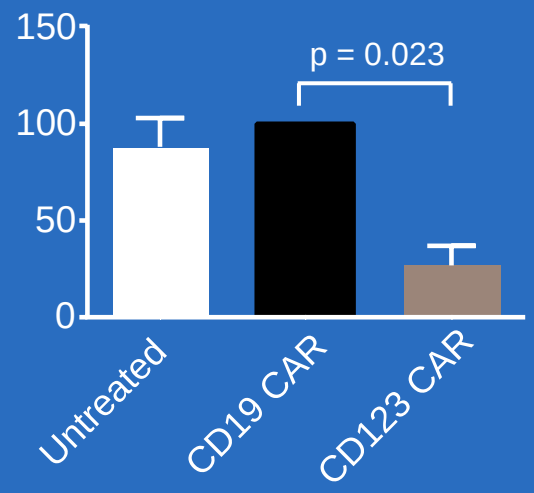
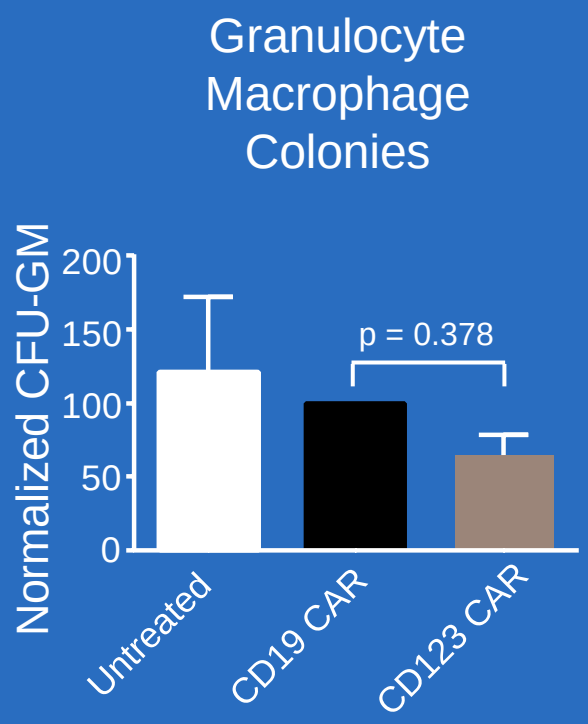
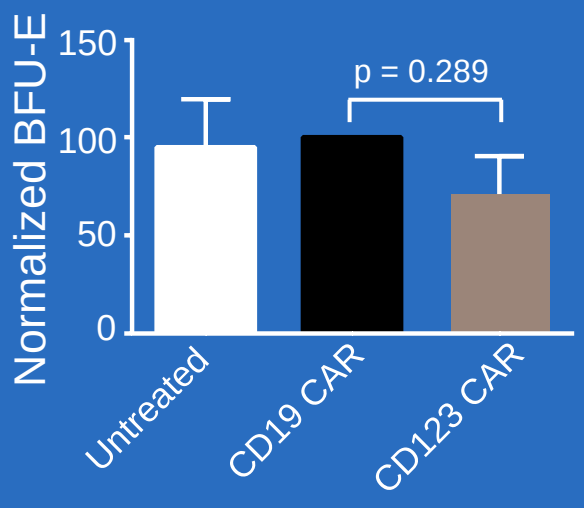
Effect of CAR T cells on normal and leukemic progenitors







Mardiros et al. 2013 Blood

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CD123 and HSPC

CD123 is expressed on a limited subset of CD34+CD38- hematopoietic stem/progenitor cells (HSPC).

- Limited killing of HSPC by CD123 CAR CIK T cells (Pizzitola Leukemia 2014).
- Reduced hematopoiesis by 30% when CD34+CD38- HSPCs treated with 7G3 Ab (Jin Stem Cell 2009).
- When fetal liver-derived CD34 cells are used there is a greater impact on HSPC (Gill Blood 2014) compared to adult or cord blood progenitors (Mardiros Blood 2013; Gill Blood 2014).

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Hypothesis

CD123 CAR T cells will recognize leukemia cells leading to remission in patients with relapsed or refractory AML. This investigational product will serve as a bridge to potentially curative alloSCT.

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Primary Objectives

- Assess the safety of administering autologous CD123R(EQ)28ζ/EGFRt+ T cells
- Determine the recommended Phase II cell dose

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Secondary Objectives

- Assess anti-leukemic activity of the investigational product based on disease response
- Assess T cell persistence within 28 days of infusion
- Immunogenicity of investigational product

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Exploratory Objectives

- Impact on hematopoiesis
- CD123 expression levels on leukemic cells
- Effects of cetuximab on EGFRt-mediated CAR T cell depletion in selected patients

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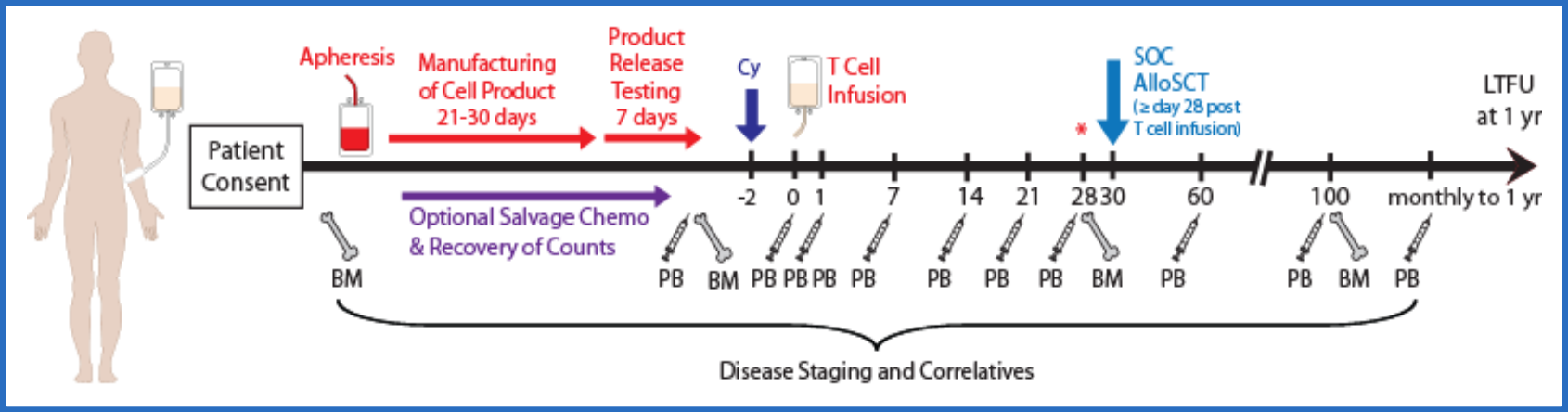
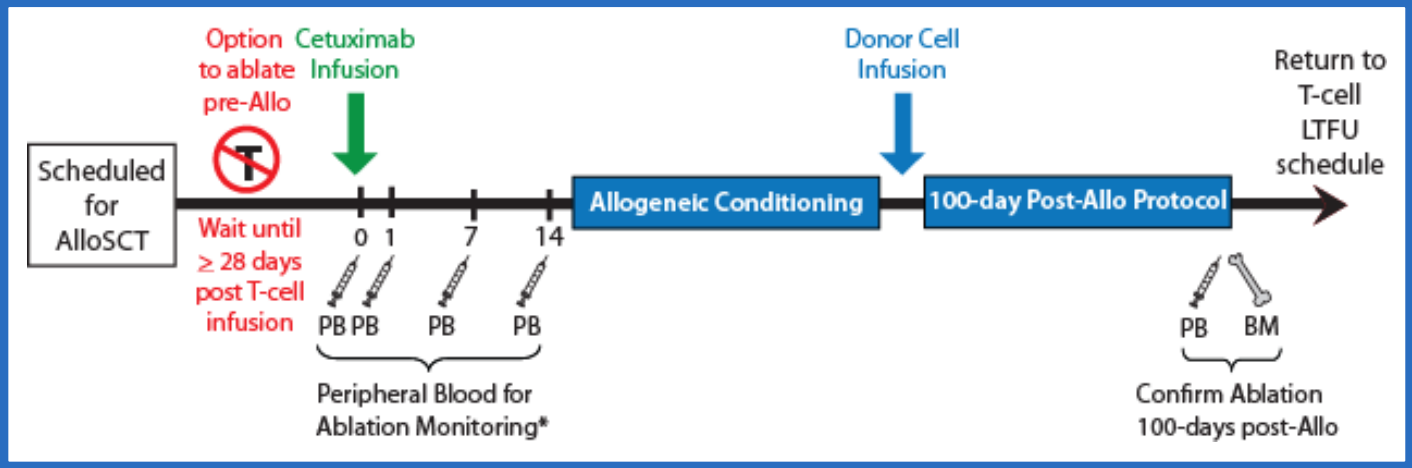
Trial Design

T Cell Product Manufacturing and Administration Schema



*Optional second T cell infusion

T Cell Product Ablation Schema (Elective)



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Key Inclusion Criteria

- Relapsed or refractory AML
- ≥ 18 years old
- Karnofsky score ≥ 70
- Adequate organ function
- Identified donor for AlloSCT

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Key Exclusion Criteria

- APL and variants
- Known CNS involvement
- Use of systemic steroids, or immunosuppressants
- HIV seropositivity, active hepatitis B or C infection
- History of AlloSCT

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Statistical Design

- Adaptive design based on targeted toxicity range
- Patients accrued in cohorts of 3, similar to 3+3
- Sample size: 18 (min 6, max 24)
- Dosing:

Dose -1	Starting Dose Dose 0	Dose 1
$5x10^6$ CAR+ cells	**$50x10^6$ CAR+ cells**	**$\leq 500x10^6$ CAR+ cells**

- DLT definition: any grade 3 or above non-hematologic or immunological AEs ≥7 days, grade 4 immunological AEs ≥ 7 days related to the T cell infusion occurring within 28 days of T-cell infusion

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Feasibility

# Rel/Ref AML	2009	2010	2011	2012	2013
AlloSCT	36	41	21	29	37
MRD/URD	9/27	16/25	7/14	14/15	17/20

- Over 600 transplants performed in 2013 (350 Allo)
- On-campus cGMP facility
- Extensive experience in CAR T cell production
- We have held 8 INDs for CAR T cell products

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Management of Potential Toxicity

- Tumor Lysis Syndrome
  - management per standard care
- Cytokine Release Syndrome
  - supportive care
  - tocilizumab
  - high dose steroids

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Impact on Leukemia and Hematopoiesis

Assessment

- Serial CBC with differential
- Bone marrow flow and morphologic study (lineage markers,CD34,CD38 staining)
- Cytogenetics
- Presence of CD123 CAR T cells in blood and marrow

Responders with incomplete blood count recovery will proceed to AlloSCT.

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In Conclusion

- For safety reasons, we are defining the toxicity of this product in the setting of bridge to AlloSCT
- We expect to see anti-leukemic activity with manageable toxicity
- We will characterize recovery of hematopoiesis
- Possible future expansion to non-transplant treatment of AML and to other CD123-positive diseases

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