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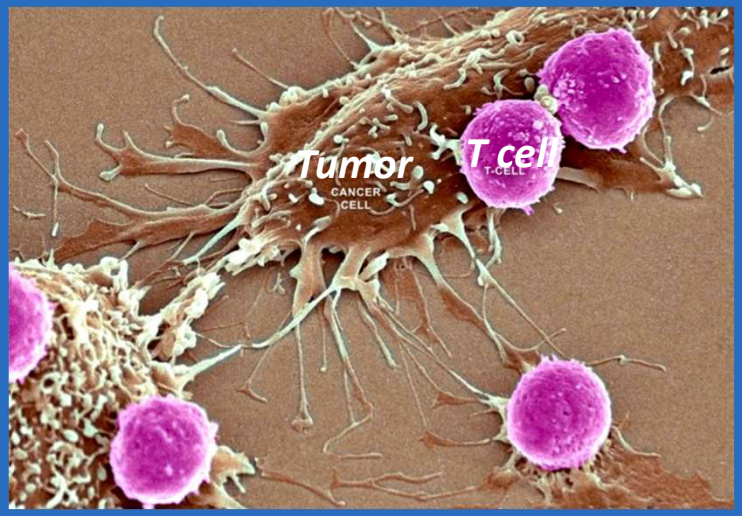
CAR T Therapy for AML



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DISCLOSURES

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Advisory board/Consultancy: Roche/Genentech Inc, Gilead Inc.

Objectives

- To overview the current landscape and limitations of CAR T therapy for AML
- To consider potential ways to improve the efficacy and safety of using CAR T cells for AML

CAR T Cell Development for AML Is Still at the Starting Line

FDA APPROVED

B cell Lymphoma → CD19CAR (2018)

Multiple Myeloma → BCMACAR

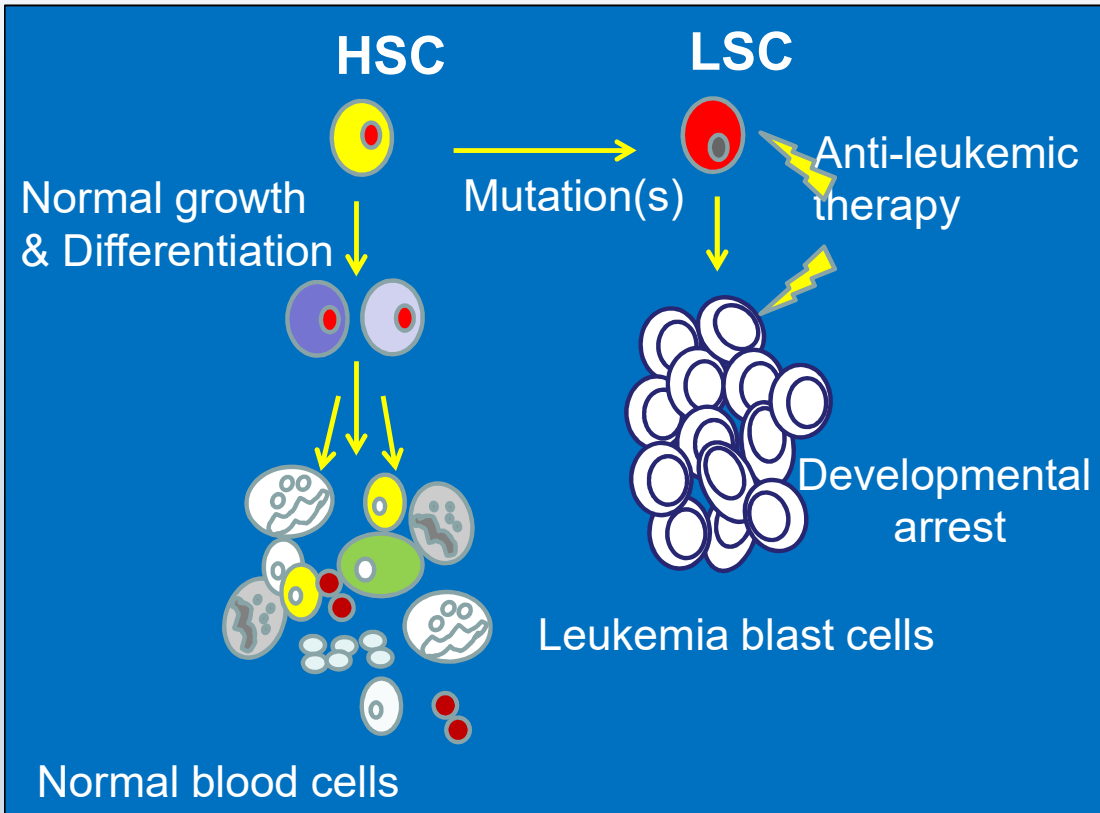
ALL → CD19CAR (2017)

New cases in 2020: 6150

AML →

New cases in 2020: 19,940

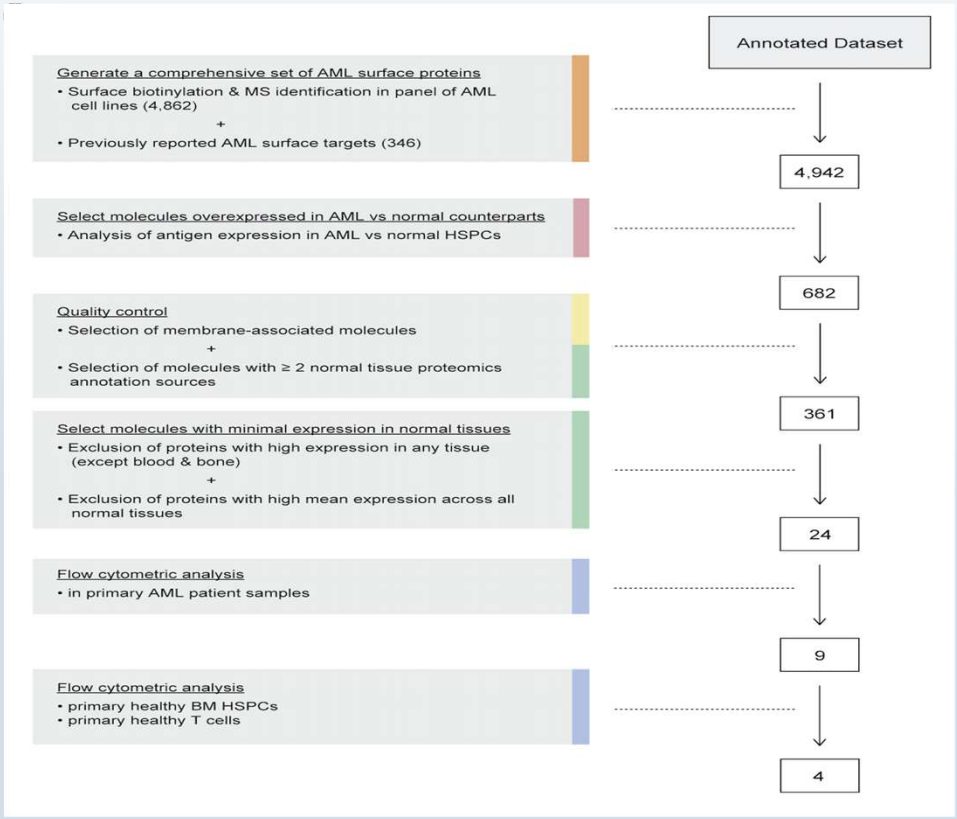
Major Challenge in Acute Myeloid Leukemia



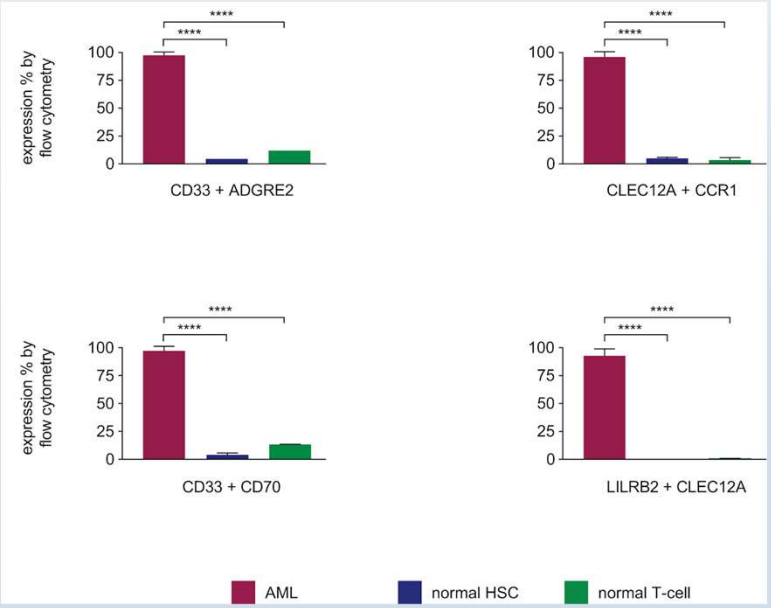
Ideal cell based antigen target:

- only on leukemic cells
- Shared by most if not all AML patients
- Not on any normal tissue/cell

AML Surface Antigens for CAR-based Cell Therapy ?



No single good candidate identified
4 potential pairs for combinatorial targets:



Perna et al., Cancer Cell (2017)

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Major Challenge in Acute Myeloid Leukemia

Ideal cell therapy target:
yet to be identified

- Clonal heterogeneity of LSCs.
- Similarity of LSCs with normal stem cells.
- Lack of antigens with lineage specific expression.

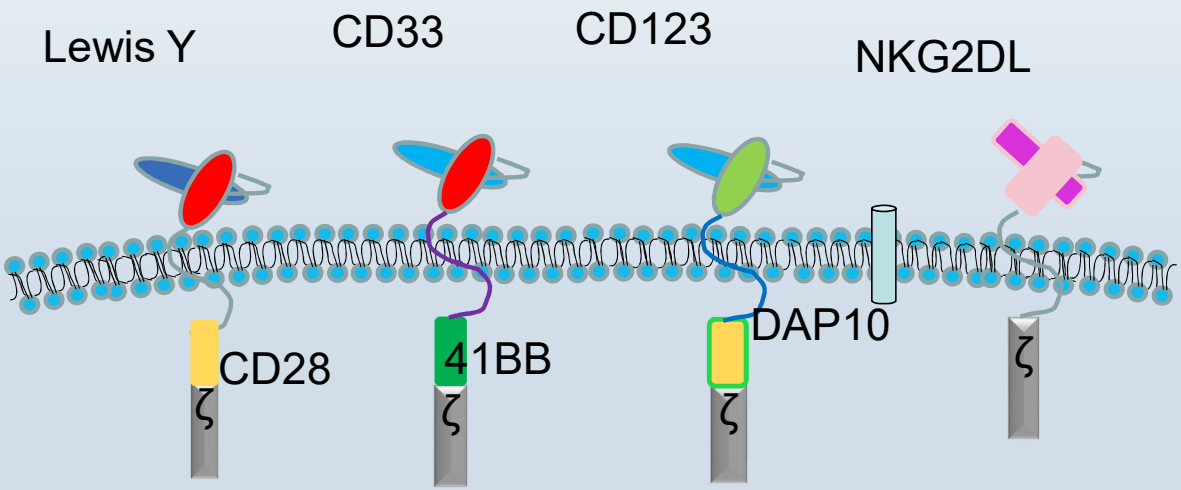
High risk for on-target, off leukemic effects

CAR T Based Cellular Therapy Targets for AML

TARGETS (preclinical)

CD7, CD25, CD32, CD33, CD38, CD44v6, CD47, CD117, CD123, FLT-3, TIM3, IL-1RAP, Lewis Y, CLL-1, Folate R-b, MUC-1, NKG2D, WT-1, and more

TARGETS in the clinic



- CD44v6, CLL-1, Dual/multi-Ag targeting (CD33xCLL1, CD123 x CD33, etc)

CAR T Cell Trials for R/R AML (an Incomplete List)

Targets	Ref.	CAR	T cell source	Pt. Age	Lympho depletion	CAR T dose	Activities and relevant AEs
Lewis Y	NCT01716364	Retrovirus CD28	auto	≥ 18 y.o.	Flu/Cytarabine	1.48 to $9.2x10^8$	1 pt achieved cytogenetic CR N=4
NKG2DL	NCT02203825	Retrovirus DAP10	auto	≥ 18 y.o.	no	$7.38x10^5$ to $2.45 x10^7$	No DLT; no responders N=7
	NCT03018405	Retrovirus DAP10	auto	≥ 18 y.o.	no	$3x10^8$ to 3 $x10^9$(up to 6 doses)	No DLT; 1CRh, 2CRi N=10
CD33	NCT01864902	Lentivirus 4-1BB	Auto or allo	5-90 y.o	No	$4.25x\ 10^8$	Transient Blast reduction >50% to <6% at 2 weeks N=1
CD33	NCT03971799	Lentivirus 4-1BB	auto	1-35 y.o	Flu/Cy	$3x10^5$/kg	n/a

Ritchie et al. Mol Ther 2013; Wang et al. Mol Ther 2013; Wang et al. Mol Ther 2015; Baumeister et al. Cancer Immuno Res 2019; Sallman et al. ASH 2018; Liu et al. ASH 2018;

CD123CAR T Trials for R/R AML in North America

	costim	Gene delivery	T cell source	dose	Status
NCT02159495 COH	CD28	lentivirus	allo or auto	50-500M	active
NCT02623582 Penn	4-1BB	mRNA electroporation	auto	$4x10^6$/kg x 4 $4x10^6$/kg x 6	Terminated 10.2017
NCT03190278 Cellectis	4-1BB	lentivirus	universal donor (UCART)	6.25x 10^4/kg to 6.25 $x10^6$/kg	Terminated reopened
NCT03766126 Penn	4-1BB	lentivirus	auto	$2x10^6$/kg 10%/30%/60%	Opened 2.2019

. Several trials opened in China

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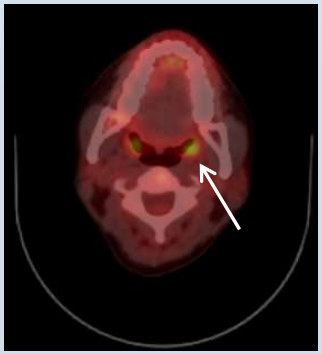
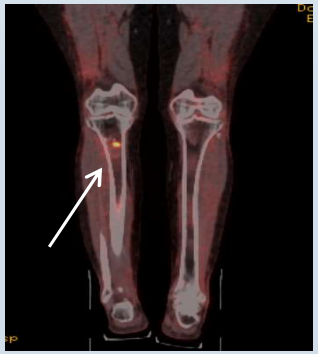
Case #2: UPN263

36 y.o F with refractory AML

- 10 prior lines of therapies
- 2 prior allogeneic transplant.

- Relapse 3 months post 2nd alloHCT
- BM 27% blasts, Cyto: 45,XX, inv(3)(q21q26.2), -7, t(9;22)(q34;q11.2)
- + right tibia, hard palate





D0 — 200M T cells

D14 — BM: 5-10% cellularity
NED

Fever (D13 &14)
septicemia
Multifocal PNA

D23 — BM: < 5% cellularity
NED

MLFS

D57 — BM:20% cellularity;NED
Cyto: 46, XY; Chimerism:100% donor

D60 — PET scan: NED

CRi

D84 — **ANC 2.2 k/ul;**
Hgb 11.4 g/dl
PLT >102 k/ul

CR, MRD-

Limitations of the current CAR T for AML

1. Rel/Ref AML patients represent a challenging population to manage.

Product# 87%	CAR Infusion 47% (7/15)	Reason for no CAR T infusion
UPN128	No	Infection/disease progression, deceased
UPN136	Yes	-
UPN138	Yes	-
UPN139	No	Disease progression, deceased
UPN154	No	Disease progression, deceased
UPN162	No	MRD-ve
UPN167	Yes	-
UPN175	No	Sepsis, deceased
UPN178	Yes	-
UPN190	No	Sepsis, deceased
UPN195	Yes	-
UPN200	Yes	-
UPN203	Yes	-
UPN212	No	Failed leuk product & CNS progression
UPN236	No	Failed leuk product & CNS progression

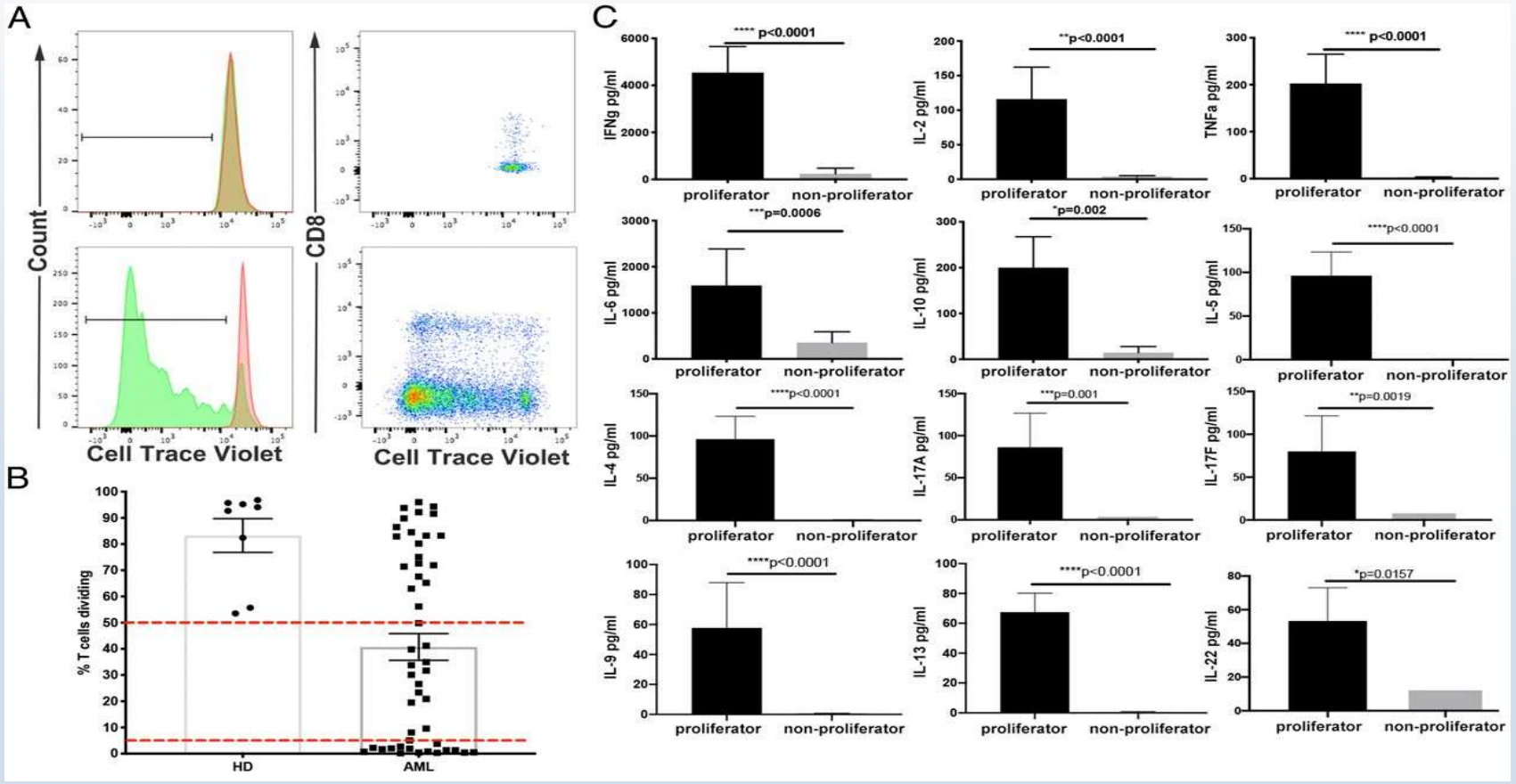
Budde, unpublished

Limitations of the current CAR T for AML

1. Rel/Ref AML patients represent a challenging population to manage.

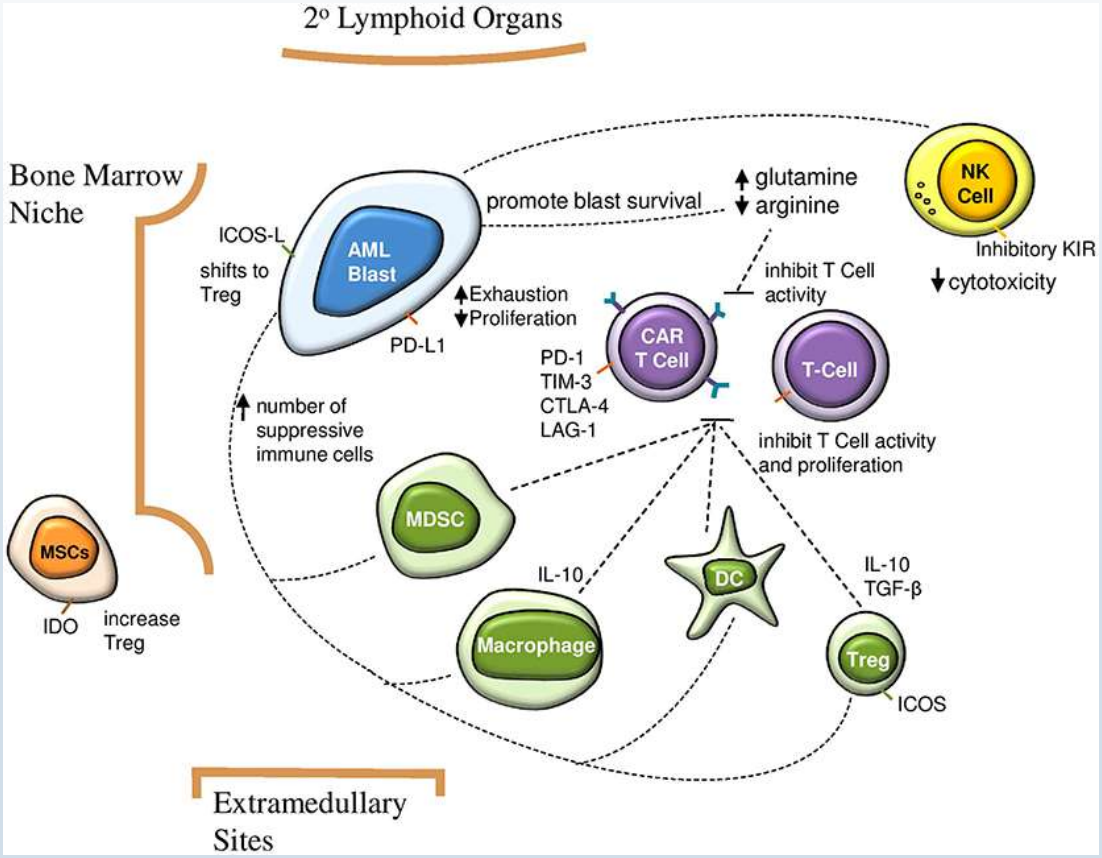
2. Suppressive immune system in patients with active AML
   - Unfit T cells
   - TME

Impaired T cell proliferation and cytokine production in response to TCR stimulation in a subset of patients with AML.



Adam J. Lamble et al. PNAS 2020;117:25:14331-14341

AML: Suppressive Microenvironment



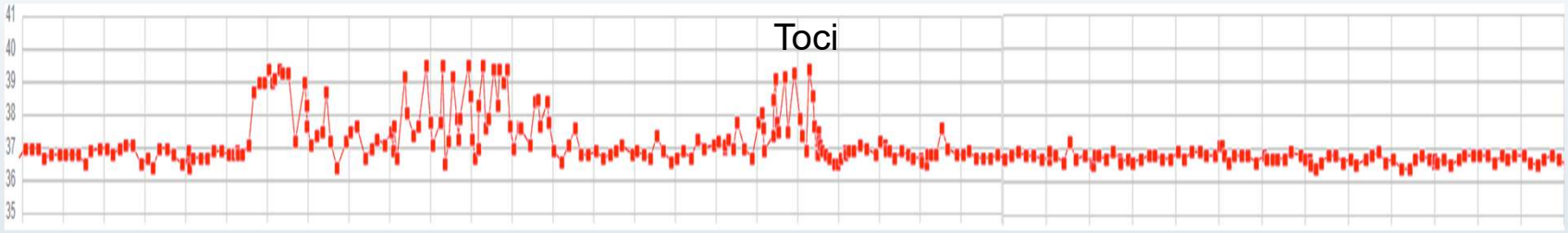
Epperly R , Gottschalk S and Velasquez. Front Oncol., 2020

Limitations of the current CAR T for AML

1. Rel/Ref AML patients represent a challenging population to manage.
2. Suppressive immune system in patients with active AML
3. Clonal evolution of AML blasts

UPN297

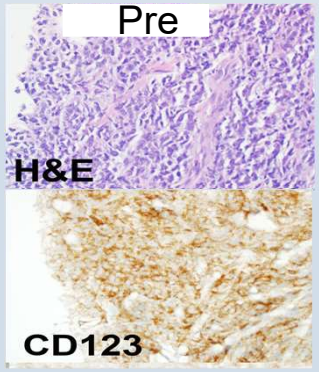
Fever curve

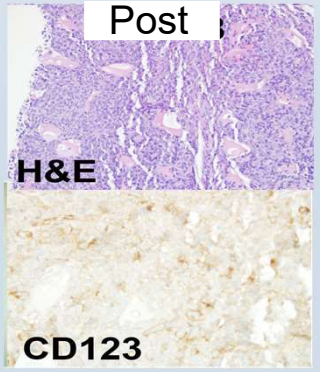


D-5 D0 D7 D9 D14 D18

D9 Chloroma resolved

D18 Nodules Left elbow and hand biopsy day 22

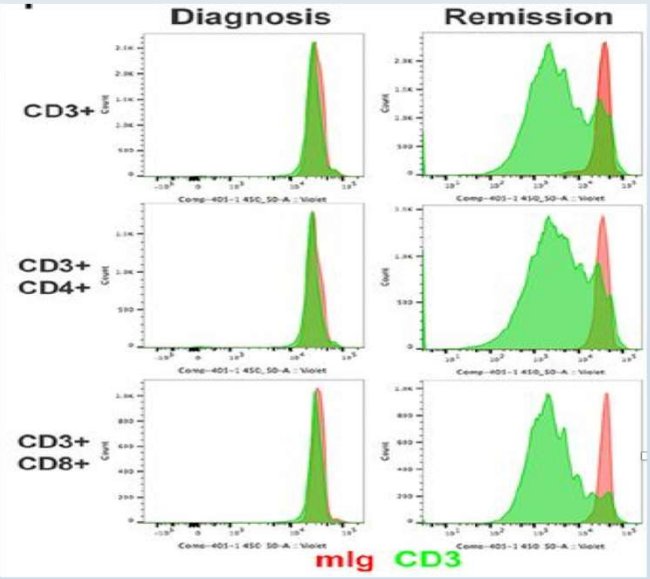




Ways to Improve CAR T Therapy for AML

- Patient selection

  Collect immune cells from high risk AML patients in remission



- Treat when AML progression occurs
- Maintenance therapy

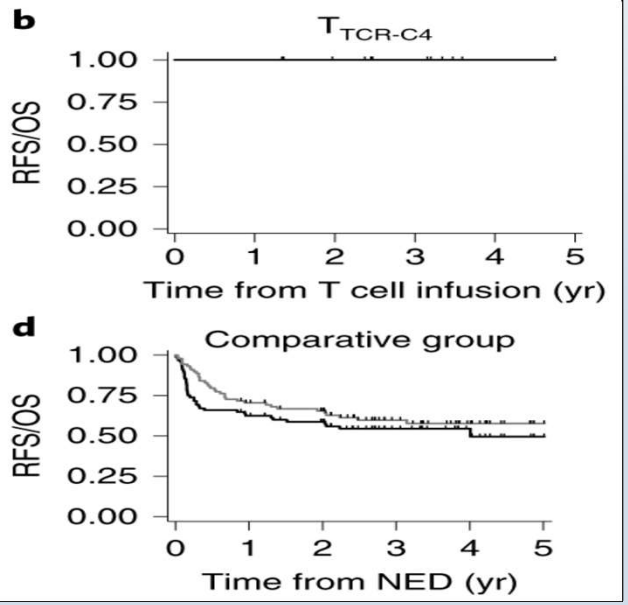
TCR Based Cell Therapy

NCT01640301 (FHCRC)
Patients: AML, poor risk, post HCT with NED
HLA-A*0201^{+} donor derived EBV-specific WT-1 T ($T_{TCR\text{-}C4}$) cells

median f/u of 44 months

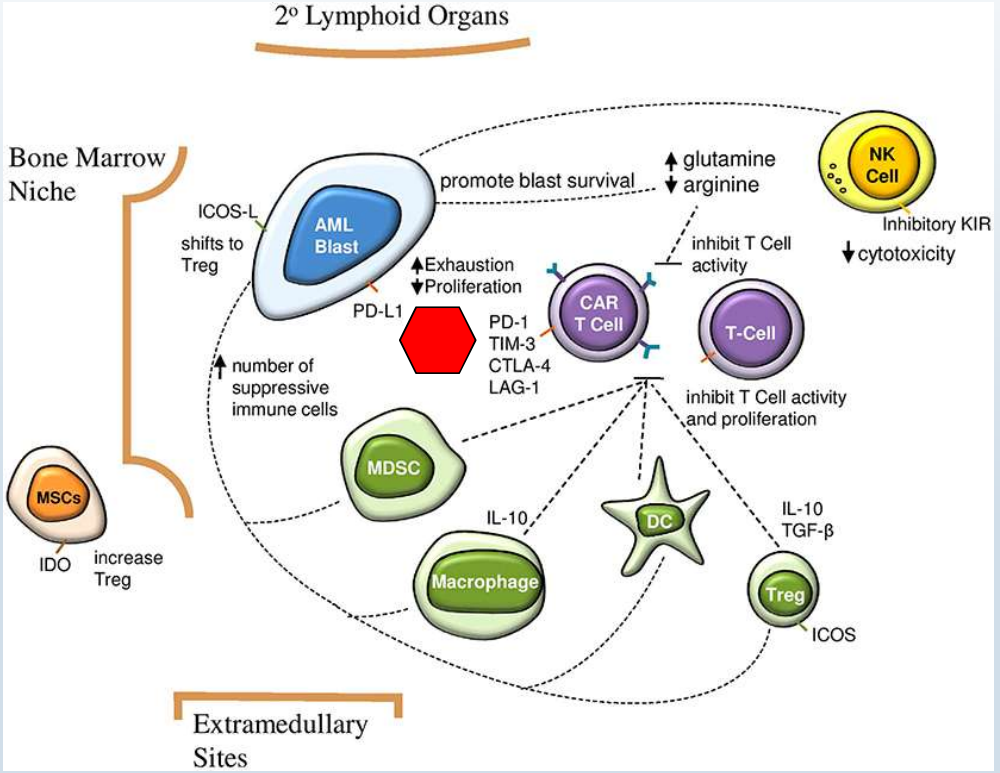
100%,
N=12

54%,
matched control
N =88



Ways to Improve CAR T Therapy for AML: Increase Potency

- Combinational therapy
  - CAR + CPI blockade
  - CAR + Cytokines (i.e. IL15/IL2/IL21)
  - Dual targeting
    - CAR1+ CAR2 (2 better than 1?)

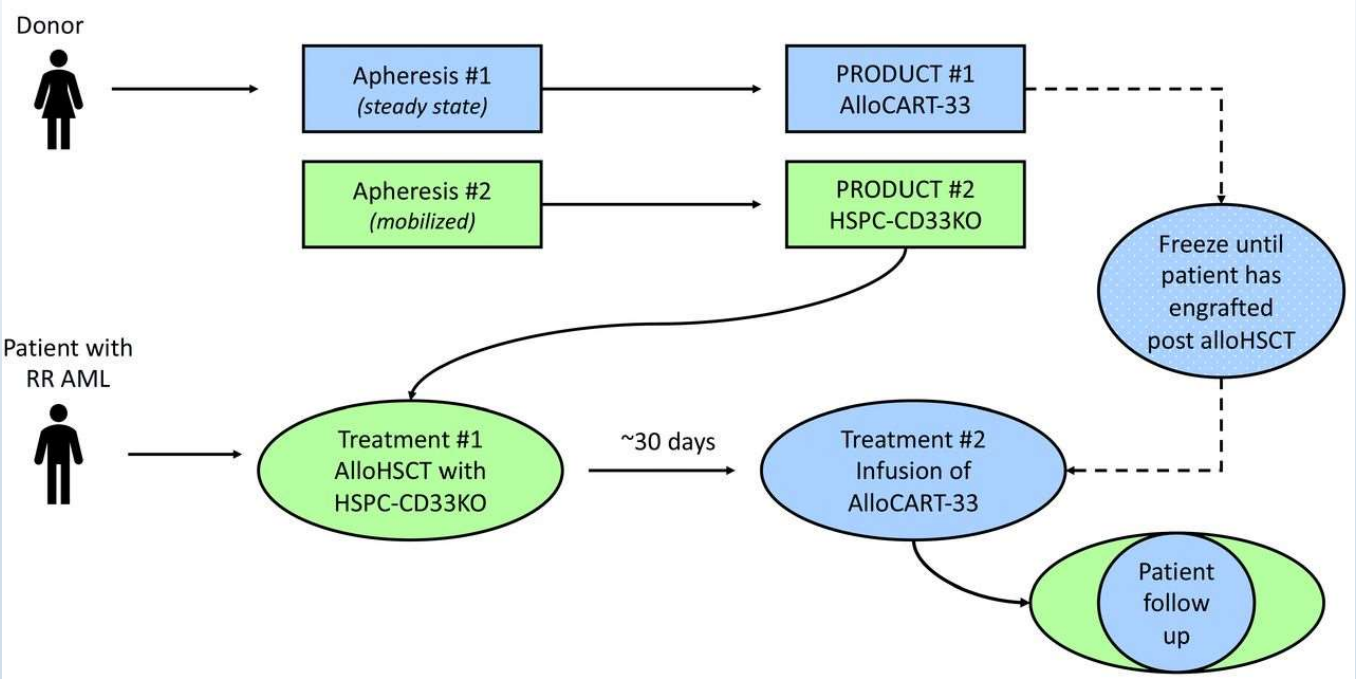


Adam J. Lamble et al. PNAS 2020;117:25:14331-14341

Ways to Improve CAR T Therapy for AML: Toxicity Mitigation

- How to overcome potential myeloablation
  - build in conditional switch ?
  - *generate CAR T resistant HSCs (Penn)*

A novel therapeutic platform: combining HSPC-CD33KO with CD33CART therapy.

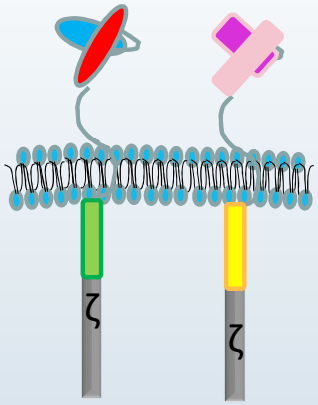


Katherine D. Cummins, and Saar Gill Haematologica 2019;104:1302-1308

Ways to Improve CAR T Therapy for AML

- How to overcome potential myeloablation
  - build in conditional switch (icaspase, EGFRt, CD20…)
  - *generate CAR T resistant HSCs*
  - *use CAR T as a bridge and conditioning regimen*

Compound CARs targeting CLL-1 and CD33



CLL-1scFv-CD28

P2A

CD33scFv-41BB

Study design

Cell product: Autologous CLLCAR/CD33CAR

3 dose levels: $1x10^6$/kg, $3x10^6$/kg, $9x10^6$/kg

6 yo F with AML

Day 19 empty marrow → Day 21 NMA conditioning → Day 29 Haplo HSCT → CR

23 yo AP-CML

Day 20 empty marrow → Day 24 NMA conditioning → Day 32 Haplo HSCT → CR

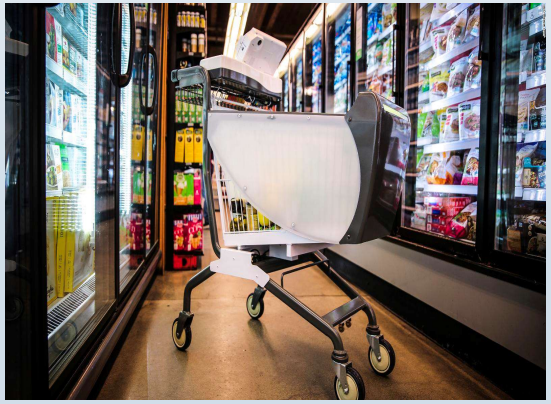
Liu et al. ASH 2018; EHA 2020

Ways to Improve CAR T Therapy for AML: Increase Feasibility and Affordability

allogeneic off the shelf product

Allo-CAR T (UCAR, PBCAR), iPSC-CAR NK/T, NK-CAR,,…

- *low cost, massive production, immediate availability*
- *Need to demonstrate efficacy and durability*



Conclusion and Future Directions

- Engineered cell therapy for AML is still at very early stage.
- CD123CAR, NKG2D CAR T and WT1 TCR T cell therapy for AML demonstrated the feasibility, safety and encouraging activity.
- An effective engineered cell therapy for AML requires understanding the mechanism of action, cell product optimization (design & manufacturing platform), smart combinations, and answering the needs of patients.

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