CAR NK cells + anti-CD20

vs.

bispecific T/B cell engagers

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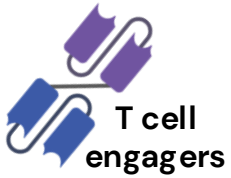
Conflict of interest statement

Company name	Honoraria; expenses	Consulting; advisory board	Funded research
Amgen; AstraZeneca; Aurinia; GSK; Lilly; Otsuka; Roche	x	x	x
Biogen; Gilead; Janssen; Novartis; UCB	x	x	
BMS		x	x

Beyond mAbs to deplete B cells

Multiple approvals in NHL
32-50% CR in aggressive NHL (Breyanzi/BMS, Kymriah/Novartis, Yescarta/Gilead), proven activity in autoimmune diseases
High CRS rates, high tocilizumab usage[1], ICANS[2] (Müller NEJM 2024, Cabaletta Bio and Kyverna Tx corp. updates)

Evidence of activity in NHL
Limited data in autoimmune disease
CRS: Caribou's CB-010 44%[5]; Allogene's 501/501A 33%[6]



Multiple approvals in NHL
38-42% CR (Epkinly, Lunsumio), activity in autoimmune diseases ($Teclistamab_{BCMAxCD3}$, $iTab_{CD19xCD19}$[4], $Blinatumomab_{CD19xCD3}$[4])
CRS: $Epcoritamab_{CD20xCD3}$ 51%, $Glofitamab_{CD20xCD3}$ 70%, $Mosunetuzumab_{CD20xCD3}$ 39%, $Teclistamab_{BCMAxCD3}$ 70%[3]
High Tocilizumab usage; 8/10 patients with Teclistamab with CRS[4]

Evidence of activity in NHL
Limited data in autoimmune diseases
No evidence of CRS or ICANs

(1) USPIs: Breyanzi, Kymriah, Yescarta; (2) Müller et. Al., NEJM 2024, CABA and KYTX; CABA and KYTX corporate updates; (3) USPIs: Epkinly, Lunsumio; (4) ACR 2024; (5) ANTLER study update, ASCO 2024; (6) Allogene, ASCO 2024

CAR T vs. CAR NK

ÖREBRO UNIVERSITY

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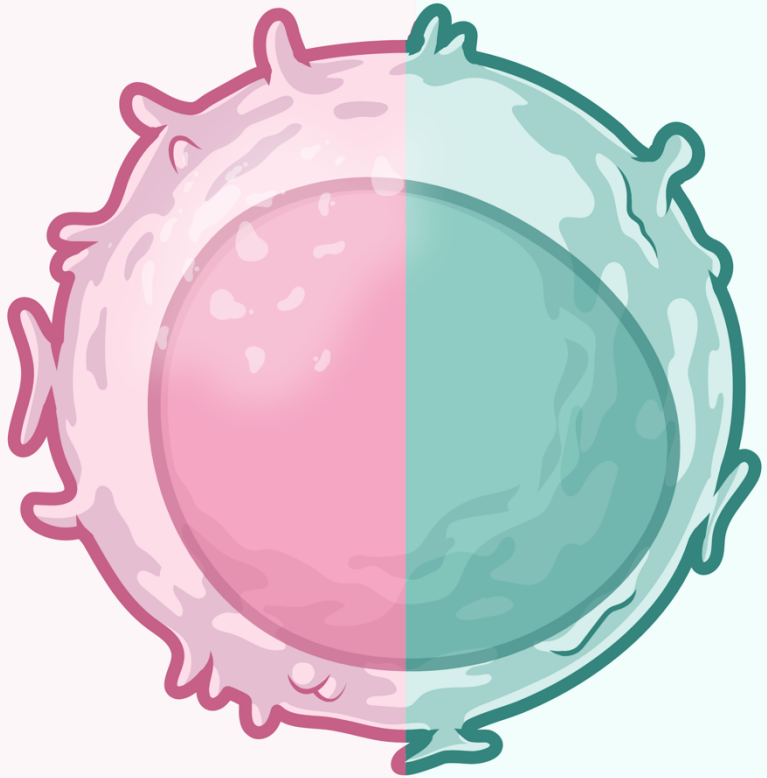
CAR-T

- Source: autologous cells
- GvHD, CRS neurotoxicity risk
- CAR-restricted cytotoxicity
- High transduction efficiency
- Good *in vivo* persistence
- High cost of production
- Longer production time



CAR-NK

- Source: allogeneic cells
- Low risk for GvHD, CRS, neurotox
- Multiple mechanisms of cytotoxicity, including ADCC
- Low transduction efficiency
- Limited *in vivo* persistence
- Low cost of production
- Off-the-shelf manufacturing

Combined advantages with CAR NK

Monoclonal antibody

Advantages

Manageable

Off-shelf

Safe

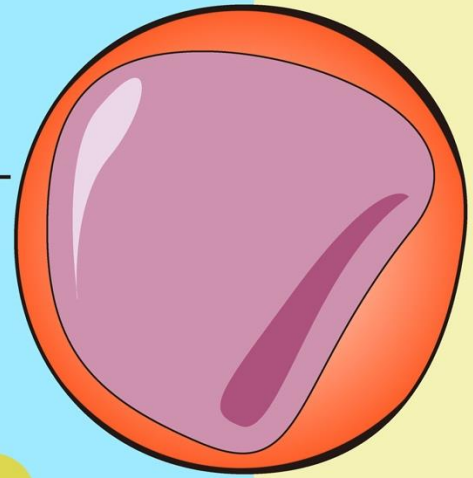
Disadvantages

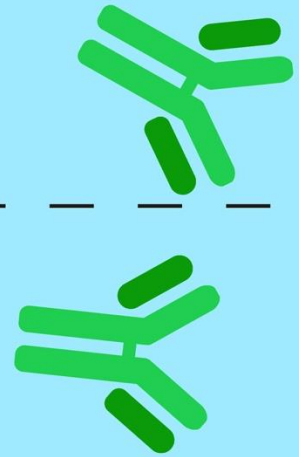
Multiple administration

Short half-life

Specificity

B cell

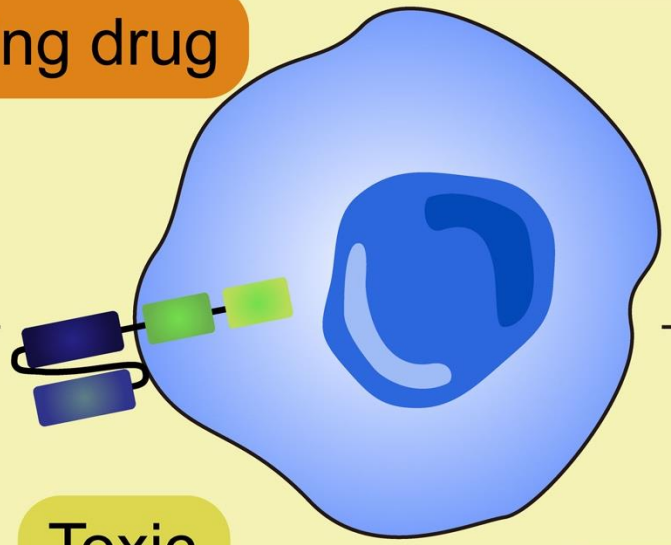




Personalized

High efficacy

Living drug



CAR T cell

Toxic

Costly

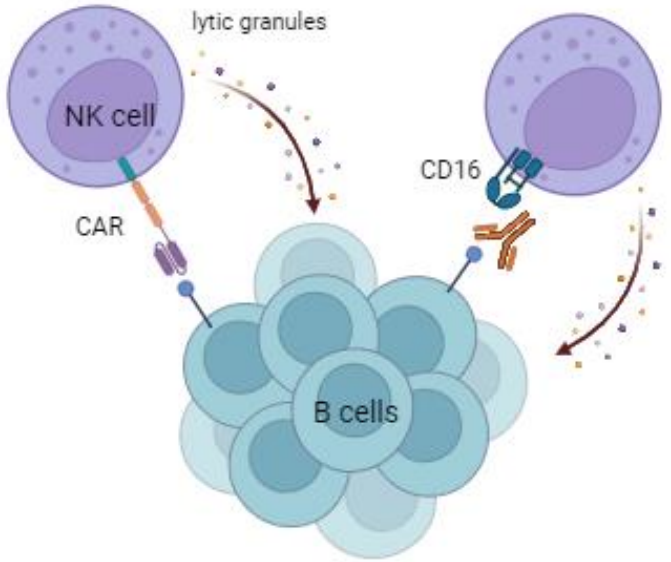
Precondition

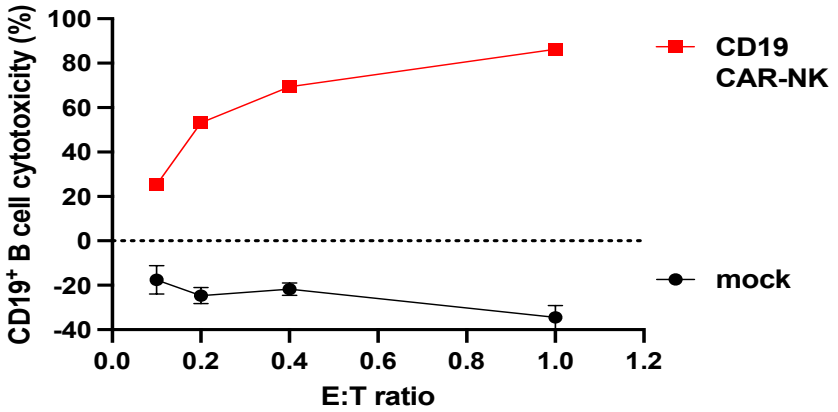
Heterogeneous stablity

Advantages with CAR NK cell therapy

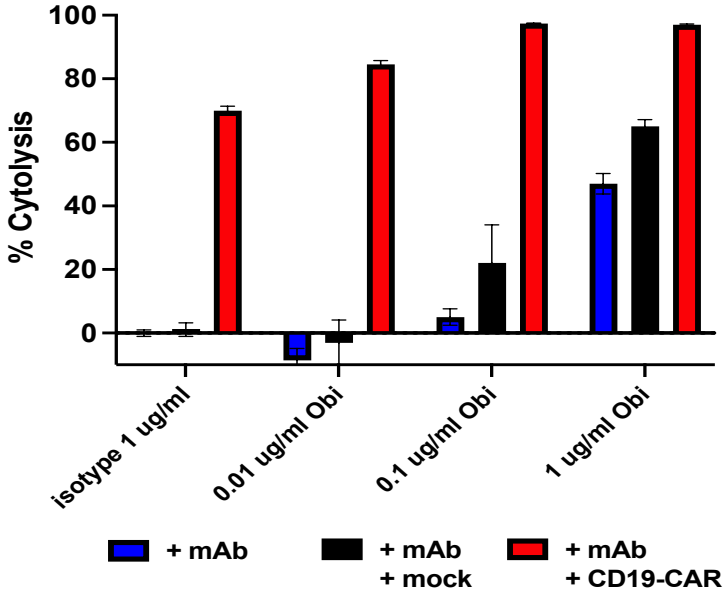
Feature	CAR NK + anti-CD20	Bispecific T/B cell engagers
Mechanism	Engineered NK cells target tumour cells (e.g., CD19), anti-CD20 antibody provides additional B-cell depletion	Redirect T or B cells to kill via dual engagement (e.g., CD20xCD3, CD19xCD3)
Clinical activity in NHL	Early trials show responses (e.g., Fate Therapeutics, MDACC studies)	Approved agents (Epkinly, Lunsumio, Glofitamab); 38–42% CR
Data in autoimmunity	Very limited, preclinical only	Emerging: Teclistamab, iTab CD19xCD19, Blinatumomab
Toxicity profile	No CRS or ICANS reported	High CRS rates (up to 70%); frequent tocilizumab usage
Persistence	Limited — NK cells may require repeated dosing or cytokine support	Short half-life but repeatable; off-target effects possible
Scalability	Allogeneic, off-the-shelf potential	Off-the-shelf; ready-to-use antibodies
Immune escape	Dual targeting (e.g., CD19 + CD20) may reduce escape	Monospecific or dual-specific; escape possible via antigen loss

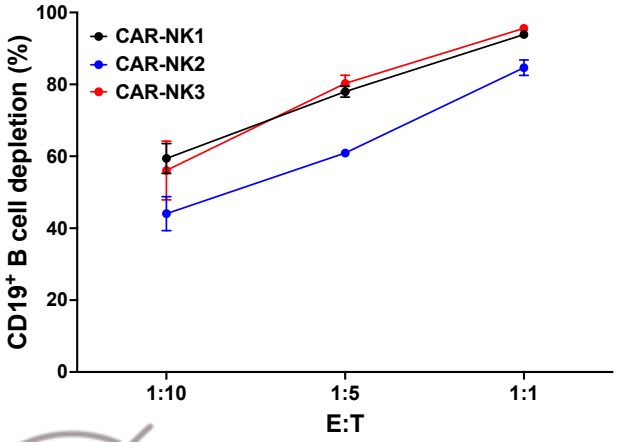
Early *in vitro* feasibility

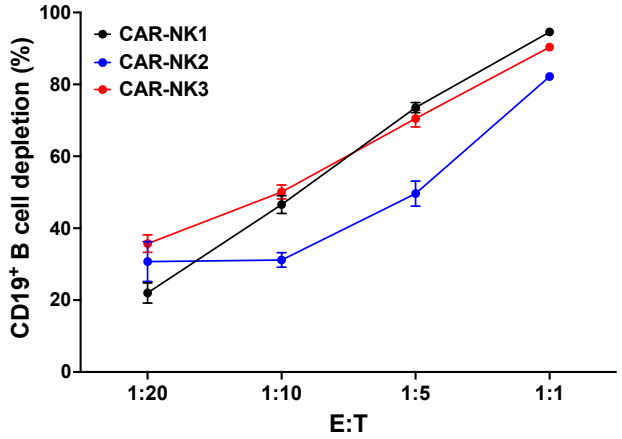




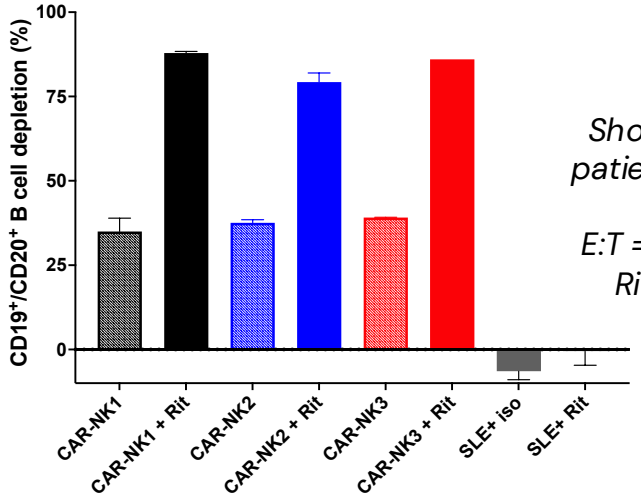
Glycostem CD19-CAR-NK data
Short-term assay (4h), targeting healthy B cells





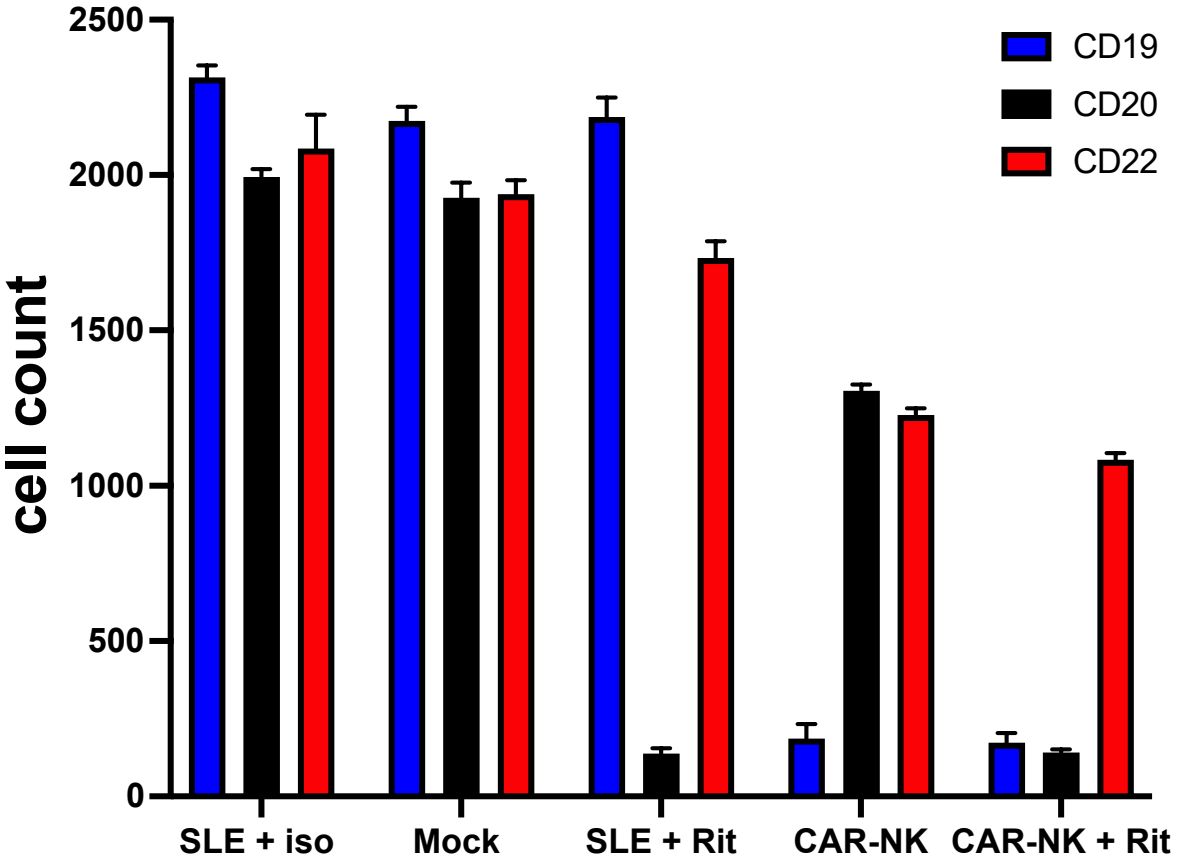


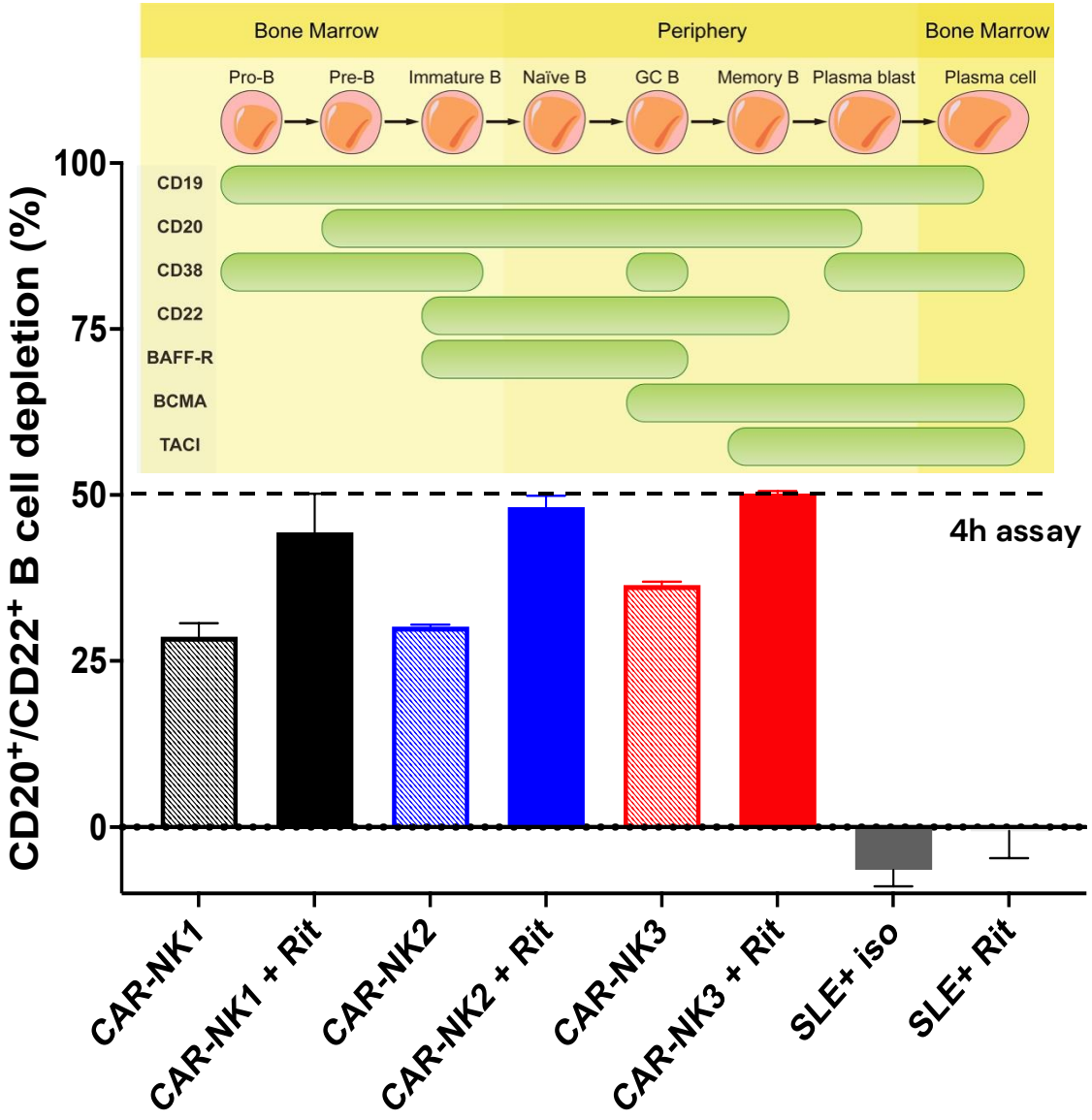
Short term co-culture of SLE patients' PBMCs and CD19-CAR-NK cells (4h)
E:T CD19-CAR-NK:PBMC



Short term co-culture of SLE patient #2's PBMCs and CD19-CAR-NK cells (4h)
E:T = 1:1 (CD19-CAR-NK:PBMC)
Rit: Rituximab (0.1 µg/mL)

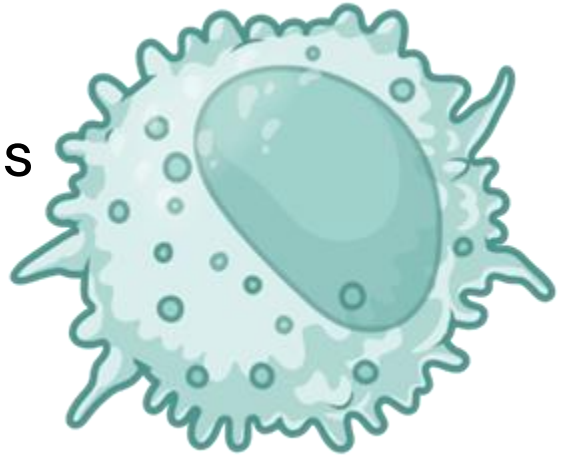
Avoid overestimation of depletion





Advantages with CAR NK cell therapy

- Preclinical *in vitro* and *in vivo* efficacy against CD19+ and CD20+ B cell malignancies encouraged evaluation of CAR NK in SLE
- Early *in vitro* feasibility in SLE demonstrates **efficient dual B cell depletion by CD19-CAR NK cells and ADCC**
- **Low(er)-cost** manufacturing, **off-the-shelf** availability, **universal donor** applicability, excellent **safety** profile, option to repeat infusion
- NK cell homing to bone marrow and other lymphoid organs facilitates efficient **targeting of tissue-resident autoreactive B cells**
- Reliable assessment of safety and extent of B cell depletion is key to determining true efficacy



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Debate 3: CAR NK cells+anti-CD20 vs Bispecific T/B engagers

Ioannis Parodis (NK)

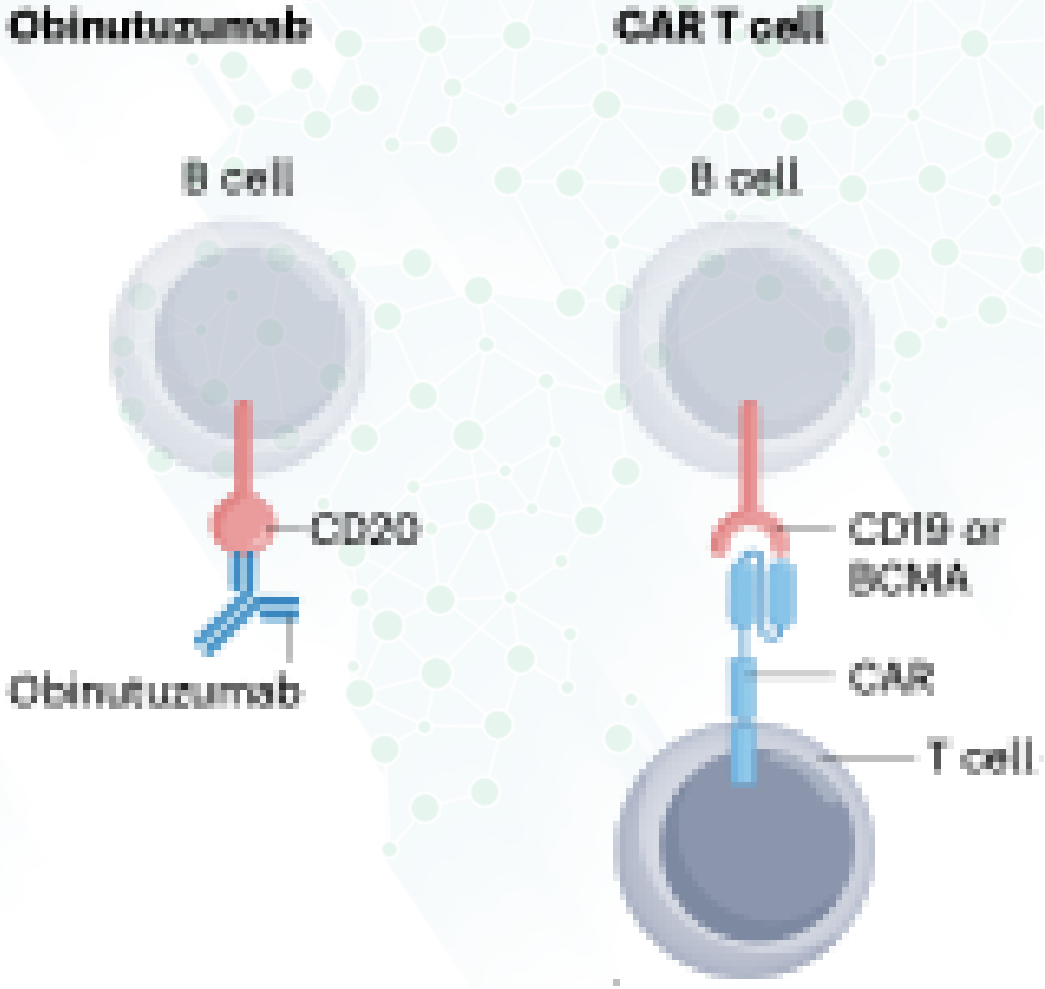
Shaun Jackson (bispecific)

DISCLOSURES

	I do not have a relationship with a for-profit and/or a not-for-profit organization to disclose
X	I have a relationship with a for-profit and/or a not-for-profit organization to disclose:

Company Name	*Direct financial payments/honoraria*	*Membership on advisory boards or speakers' bureaus*	*Funded grants or clinical trials*	*Patents on a drug, product or device*	*All other investments or relationships*
Sail Biomedicines	X	X			
IgM Biosciences	X				
Bristoll-Myers Squibb	X	X			
Merck	X	X			

Bispecific T cell Engagers



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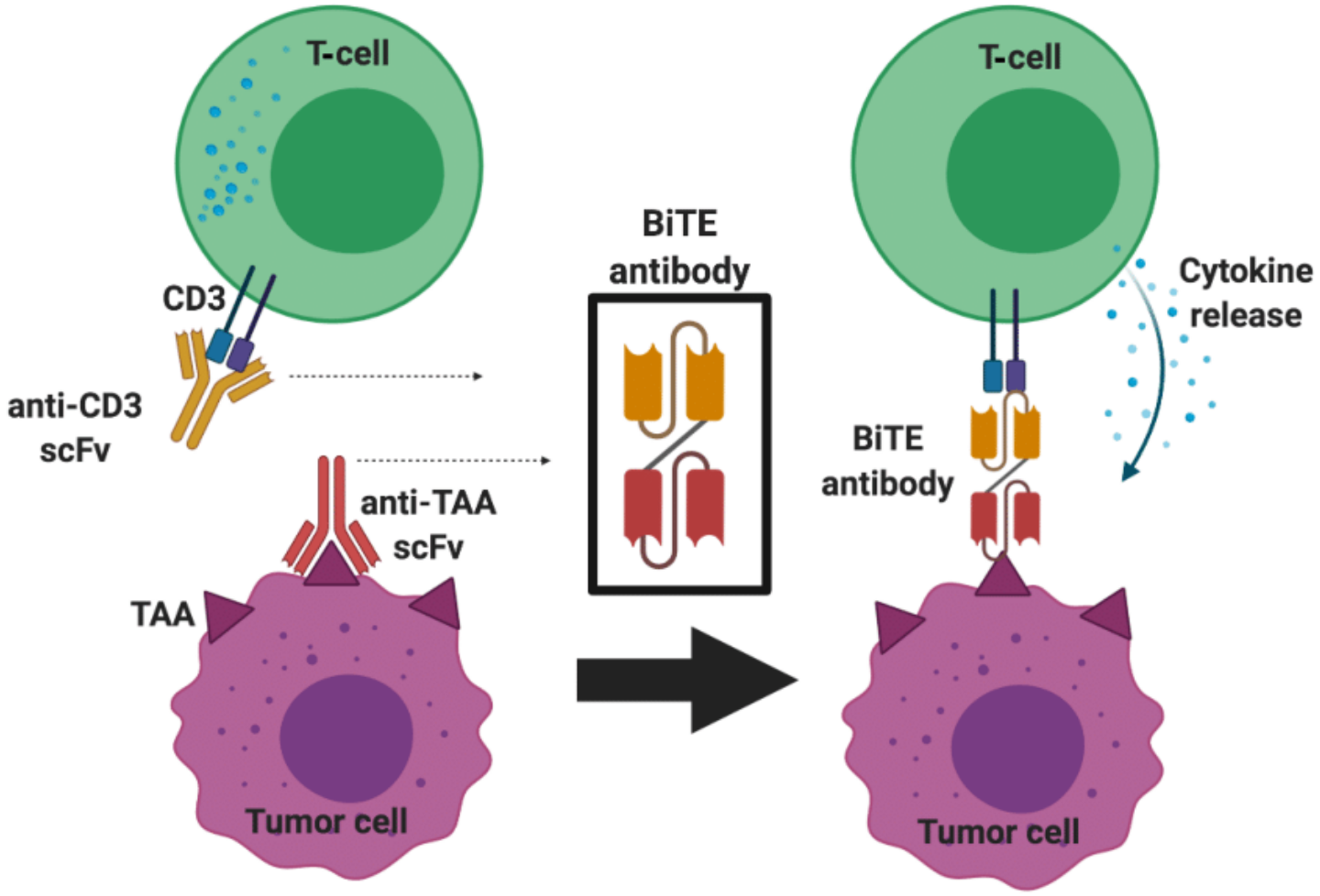
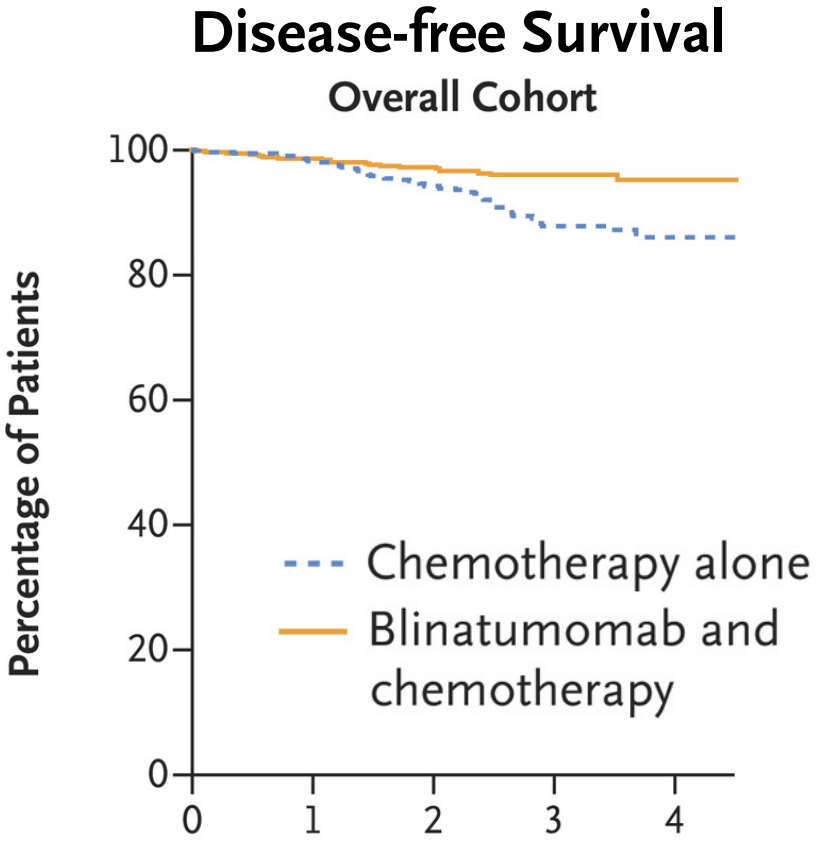
BISPECIFIC T CELL ENGAGERS – MECHANISM OF ACTION





Blinatumomab in Standard-Risk B-Cell Acute Lymphoblastic Leukemia in Children

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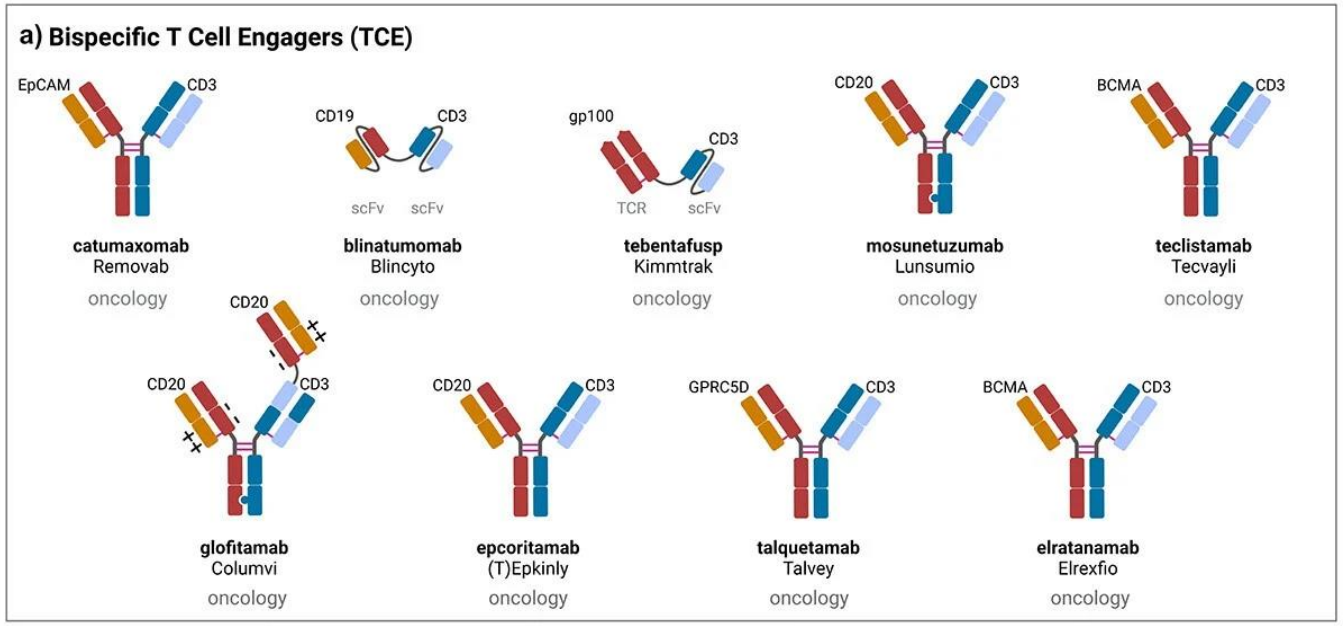
BISPECIFIC T CELL ENGAGERS – MECHANISM OF ACTION

Advantages:
- Off-the-shelf (i.e. cheaper)
- No need for lymphodepleting chemotherapy
- Theoretical potential for CAR T cell-like degree of B cell depletion.

Disadvantages:
- Risk for cytokine release syndrome (CRS) / ICANS
- Short-half life of BiTE format (Fc-based molecules are in development)
- Immunogenicity



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Open question:
Do BiTE's achieve "CAR T cell-like" B cell depletion?