CAR T-cells: Life in the fast lane

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Leucid

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Disclosures

- Shareholder in Autolus Therapeutics (NASDAQ)
- Currently funded by Leucid Bio
- Hold patents related to CAR T-cell technology

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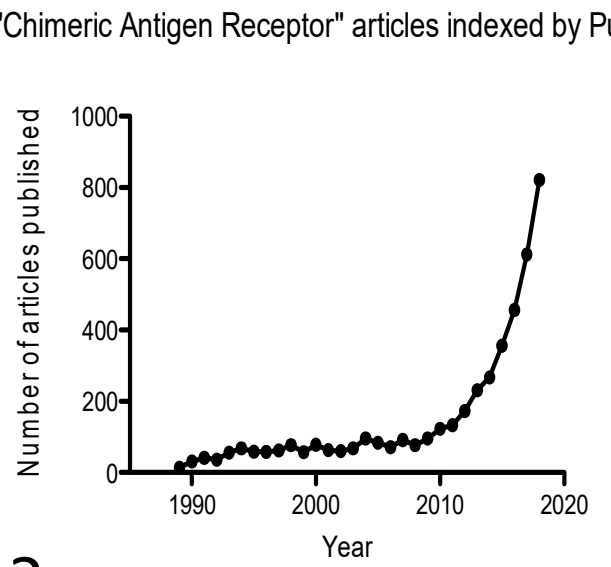
Introduction

- Interest in CARs has dramatically increased in the last decade
- How did CARs come to be?
- How successful are CARs?
- What is the future for CARs?



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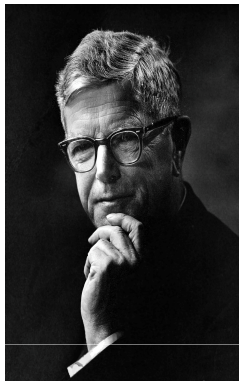
Brief History: Immunotherapy



1891
W.B Coley observed tumour regression after bacterial infection in patients

1955
Adoptive transfer of lymph nodes in mice showed anti-tumour activity

1957
Thomas and Burnet's theory of immunosurveillance

1976
Treatment of bladder cancer patients with bacteria prevents relapse

1978
Characterisation and cloning of IL2 allows *ex vivo* culture of lymphocytes

1991
A Tumour specific antigen was administered and successfully elicited an immune response

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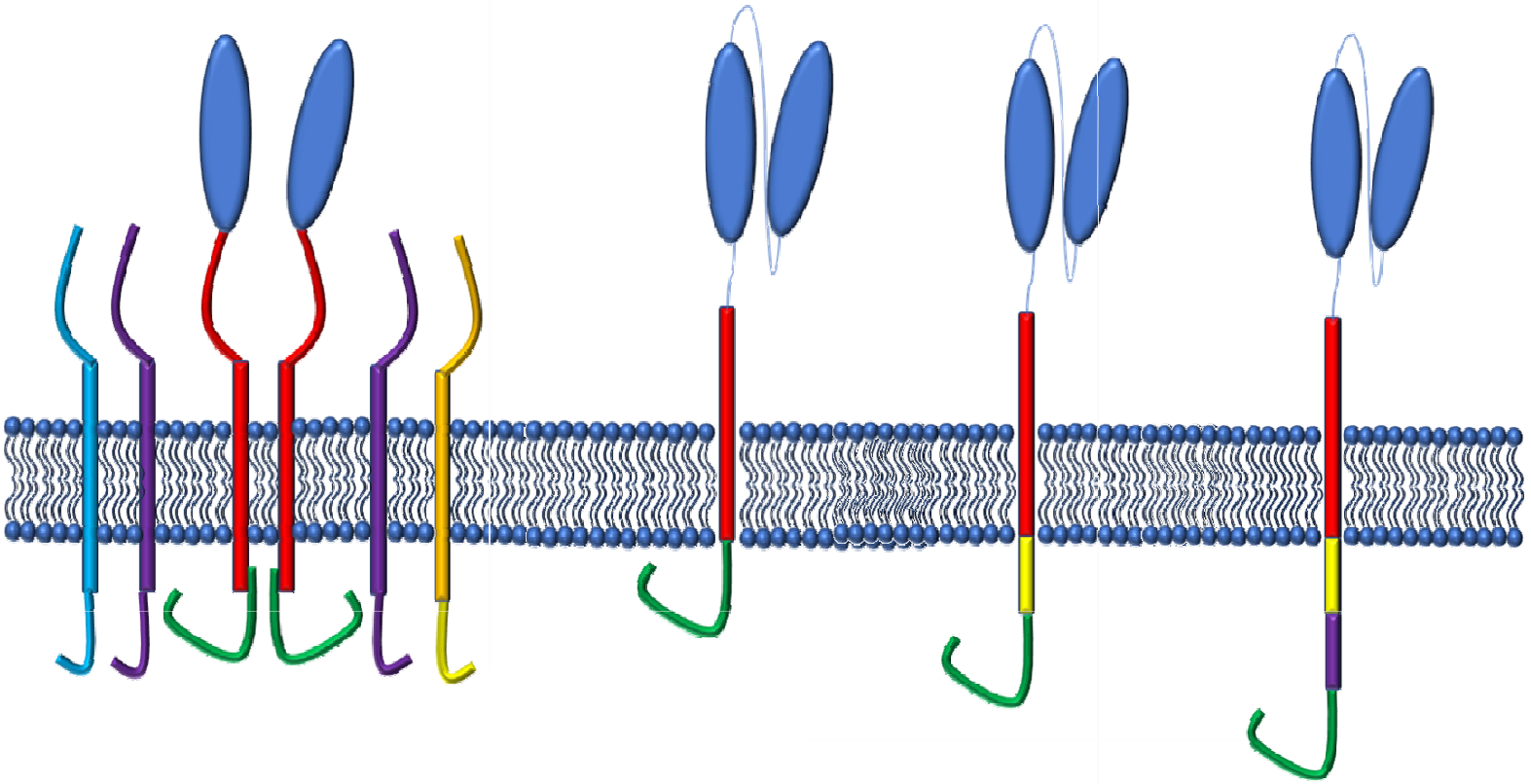

Binding moiety (ScFv/ligand)

Extracellular Spacer (Stalk/Hinge)

Transmembrane

CD28/4-1BB

4-1BB/OX40

CD3ζ

1987 T-body
Antibody variable regions fused onto constant region of the TCR

1991 1G
The first recognizable CAR. A ScFv on a spacer with CD3ζ signaling domain

1998 2G
Addition of costimulation (CD28/ICOS) greatly improved the T-cell activity

2008 3G
Multiple costimulatory molecules added (CD28-OX40 or CD28-41BB). Not proven better than 2G

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Early CAR Trials

- 2006: First clinical trial with a 1st Generation CAR targeting folate receptor in ovarian cancer
  - Limited efficacy
  - T-cells undetectable in all of patients 10 days post-infusion
- 2007: Results from a 1st generation CAR targeting CD171 in neuroblastoma showed similar results
- 2011: Results from a 2nd Generation CAR targeting CD19 in a CLL patient resulted in a complete response with CAR+ T-cells detectable at least 6 months post-infusion

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CARs in Haematological Malignancies

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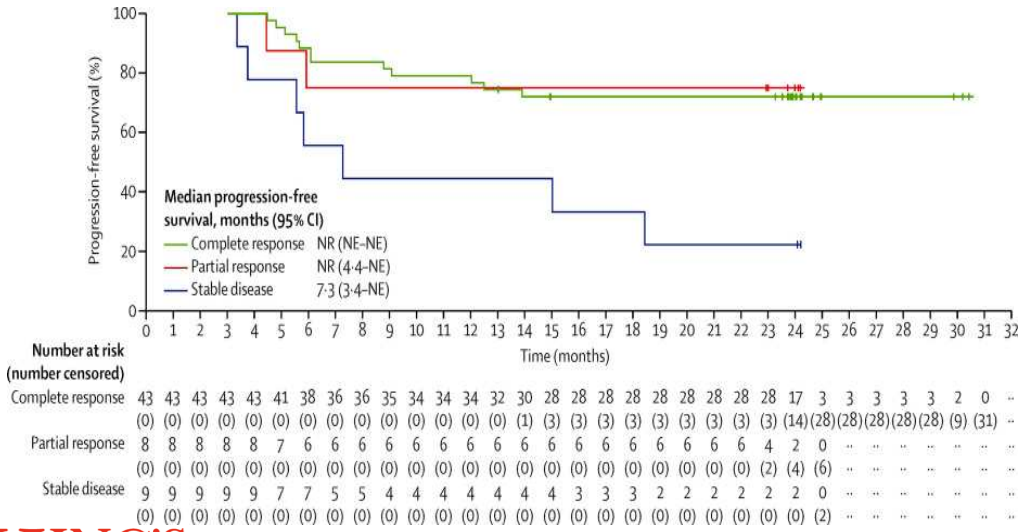
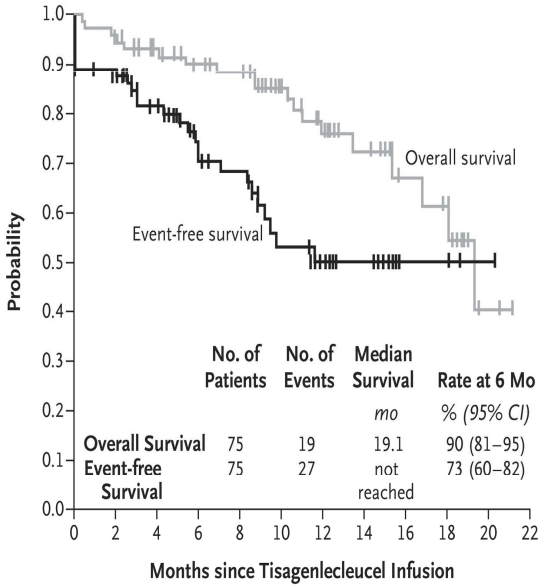
CD19 CAR Success

- CD19 targeted CARs have been approved by the FDA, EMA and MHRA for ALL and DLBCL

Yescarta (DLBCL)



Kymriah (ALL)



	No. of Patients	No. of Events	Median Survival (mo)	Rate at 6 Mo (% (95% CI))
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

No. at Risk												
Overall survival	75	72	64	58	55	40	30	20	12	8	2	0
Event-free survival	75	64	51	37	33	19	13	8	3	3	1	0

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CD19 CAR Toxicity

Adverse Events	Any	Grade 1/2	Grade 3	Grade 4	Grade 5
Any	108 (100%)	0	28 (26%)	69 (64%)	9 (8%)
Treatment-related	107 (99%)	36 (33%)	53 (49%)	16 (15%)	2 (2%)
SAE	60 (56%)	8 (7%)	34 (31%)	9 (8%)	9 (8%)
Neurological Event	72 (67%)	37 (34%)	32 (30%)	3 (3%)	0
Cytokine Release Syndrome	100 (93%)	88 (81%)	7 (6%)	4 (4%)	1 (1%)

5 Grade 5 due to relapse

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CD19 CAR Toxicity

- Cytokine Release Syndrome (CRS) or Tumour Lysis Syndrome results from a “cytokine storm” due to a vast number of T-cells becoming activated.
- IL6 is implicated
- Treatment with tocilizumab (anti-IL6)
- Can lead to death in severe cases

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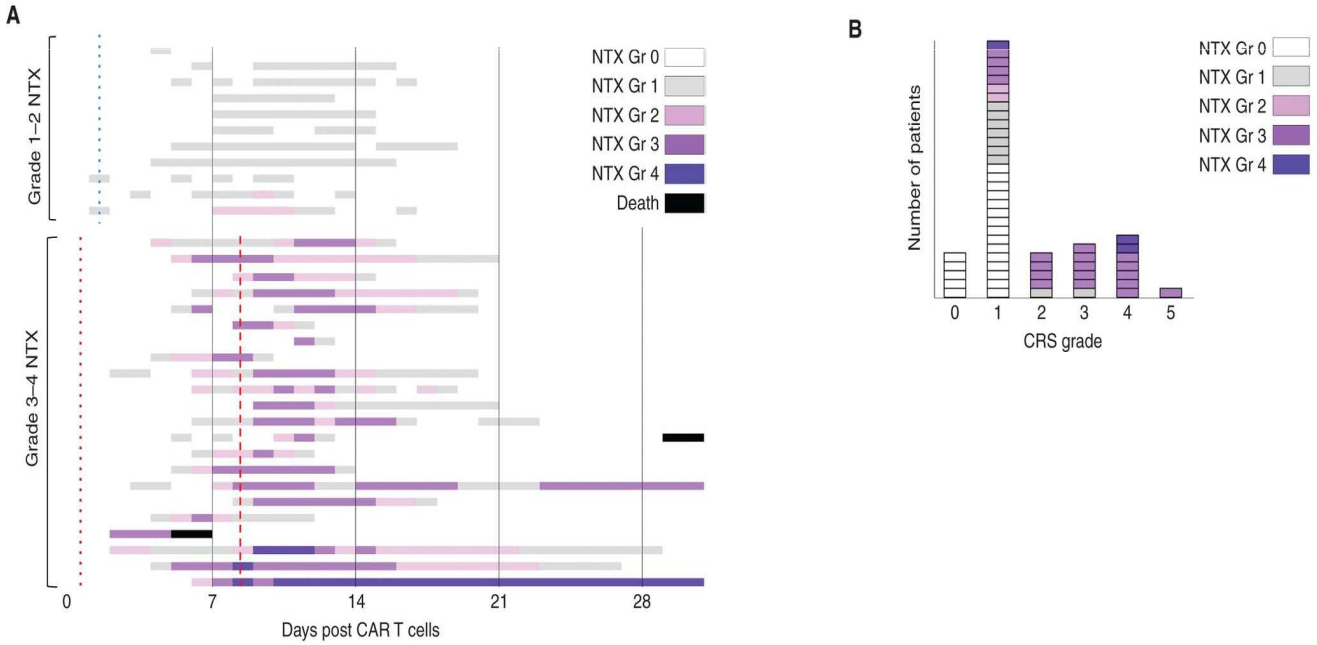
CD19 CAR Toxicity

- CRS is a serious side-effect of CAR-T therapy which can lead to neurotoxicity.



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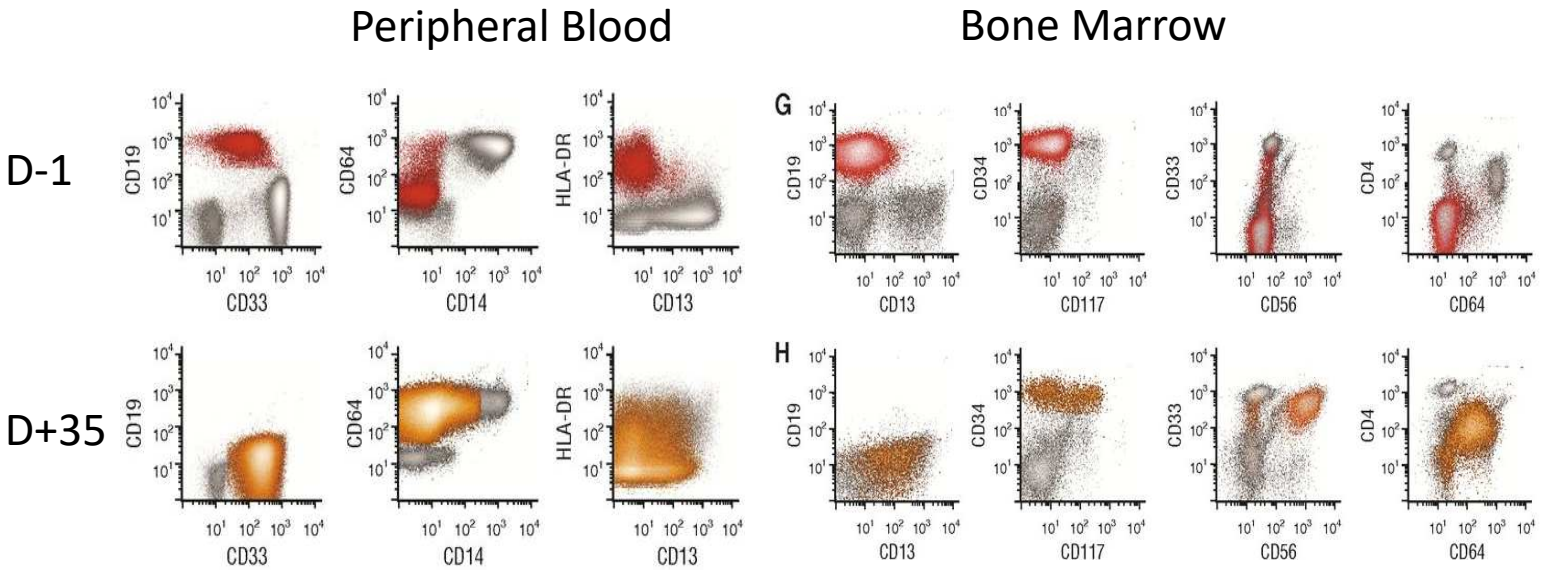
CD19 CAR Relapse

- A majority of relapses occur with CD19- or CD19 variants



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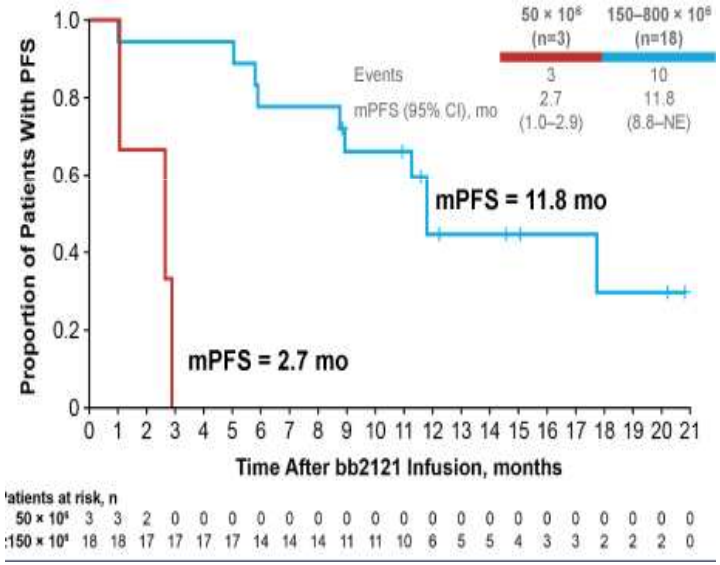
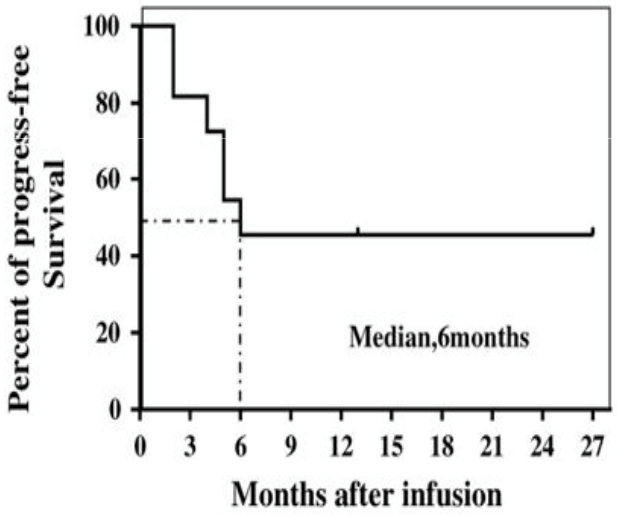
Gardner *et al.*, Blood (2

Other targets

BCMA CAR (phase II; Myeloma)



CD20 CAR (phase II; Advanced NHL)



- CD22 (ALL)
- TRBC2 (T-ALL)
- TRBC1 (T-ALL)
- CD33 (CML)
- CD44v6 (AML)
- …

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Haematological Malignancies - Summary

- Success in CD19+ ALL and DLBCL has lead to two CD19 targeted CARs approved for use in patients
- Early phase trial results from other targets and diseases are promising
- Antigen loss can be solved by targeting multiple antigens
- Toxicity can be managed

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CARs in Solid Malignancies

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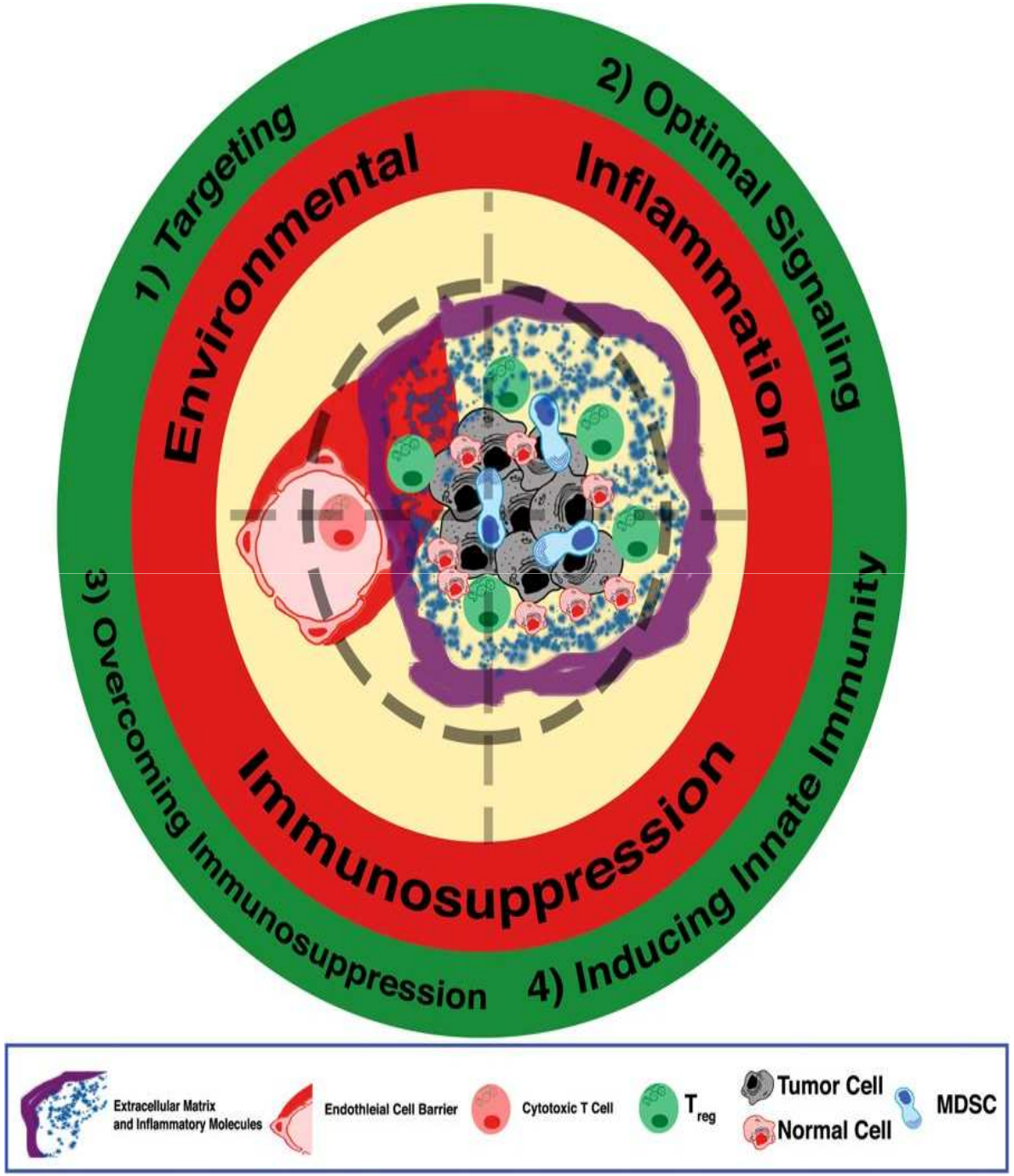

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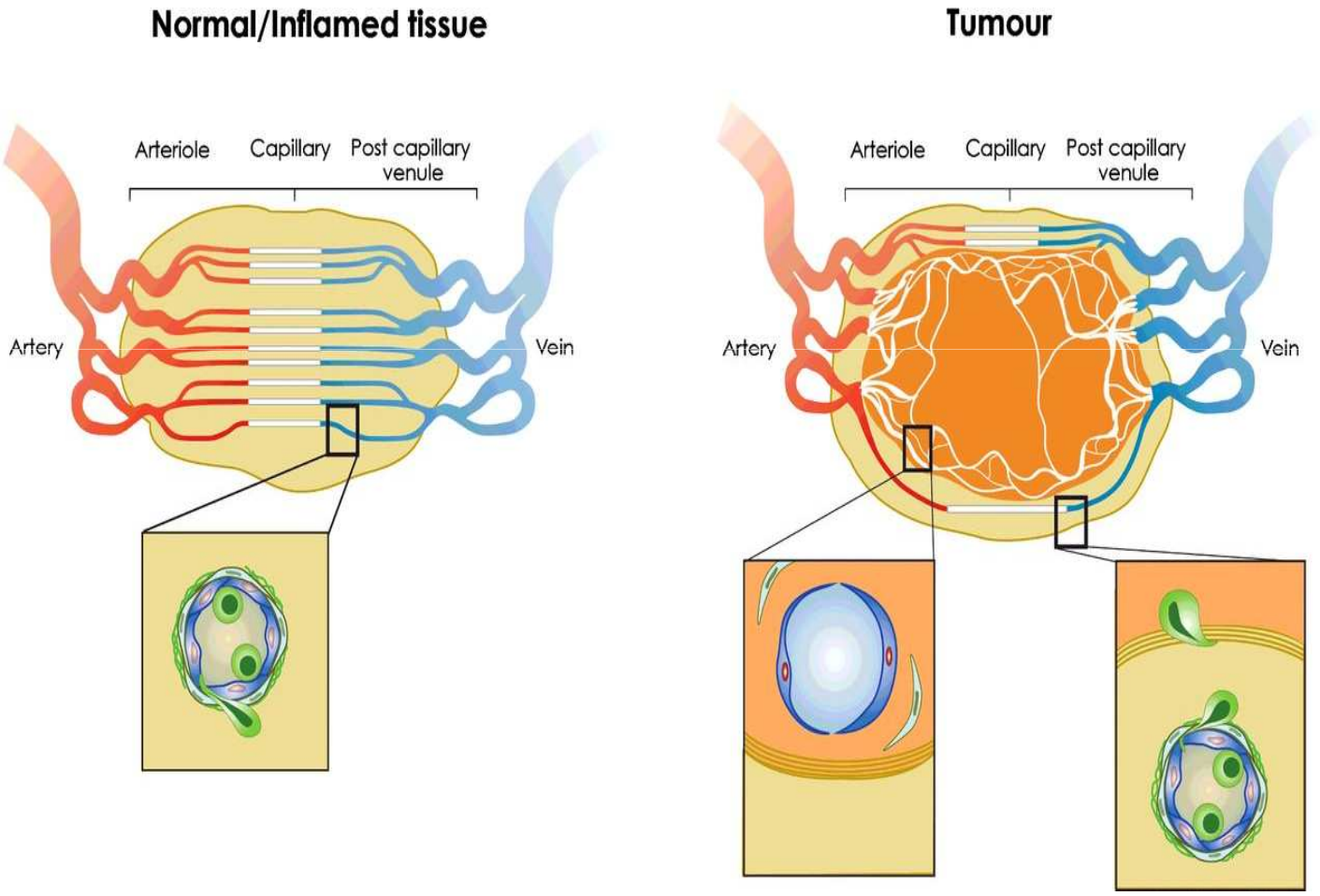
Castellarin et al. (20

Solid Tumour Access



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Ager *et al*. Biochemical Society Transactior

Solid Tumour Microenvironment

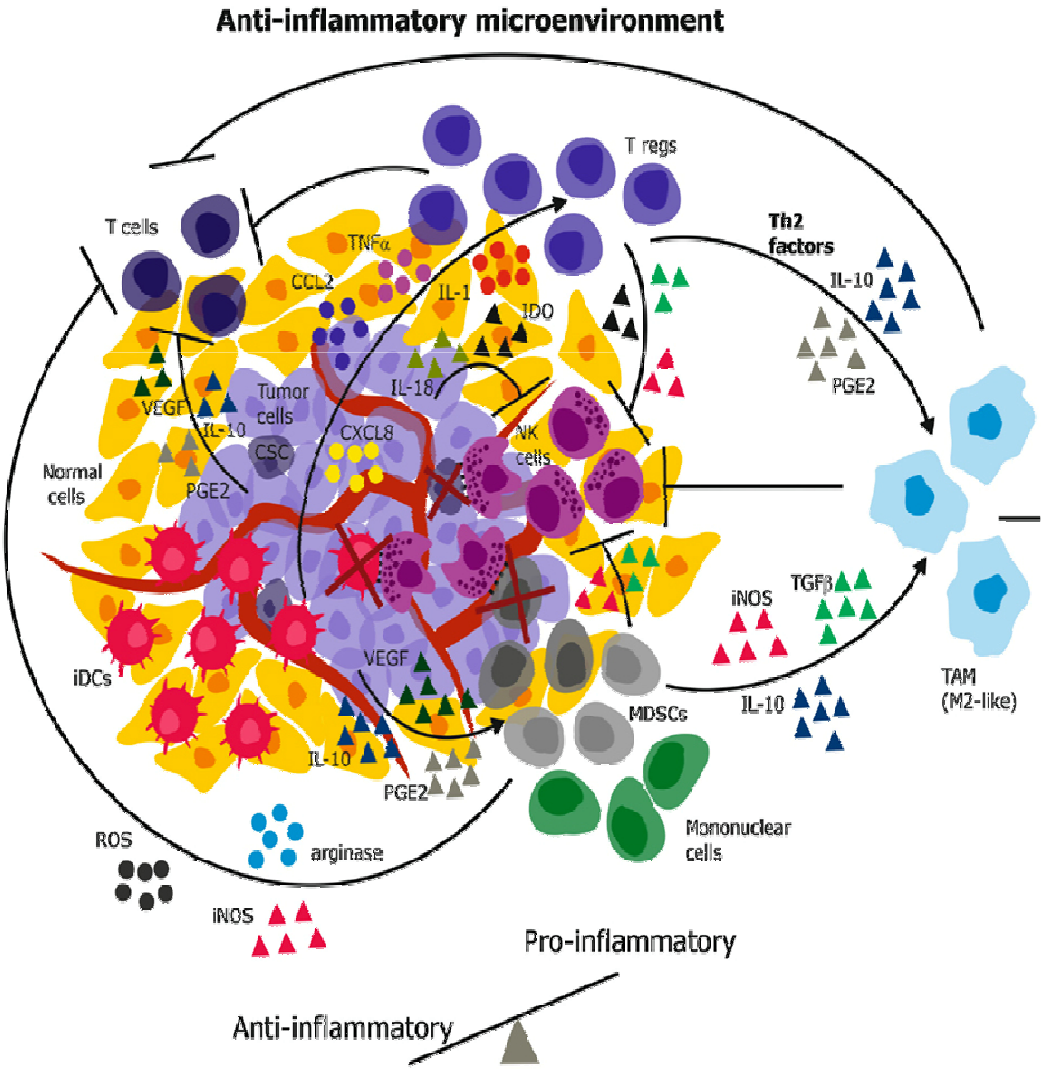
Expressing immunosuppressive molecules

- PDL1, PDL2, Adenosine

Attracting anti-inflammatory cells

- MDSCs, Tregs

Polarising macrophages to M2



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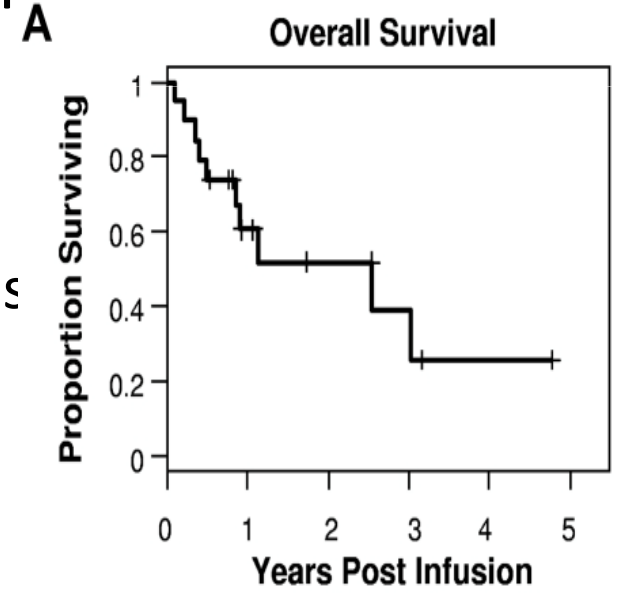
Solid Tumours – Clinical Trials

- Despite these problems, some trials are still going ahead
- In general results show CARs are well tolerated



- 100+ Phase I
  - Safety results in a number of indications
  - Few efficacy
- 42 Phase II
  - No results published

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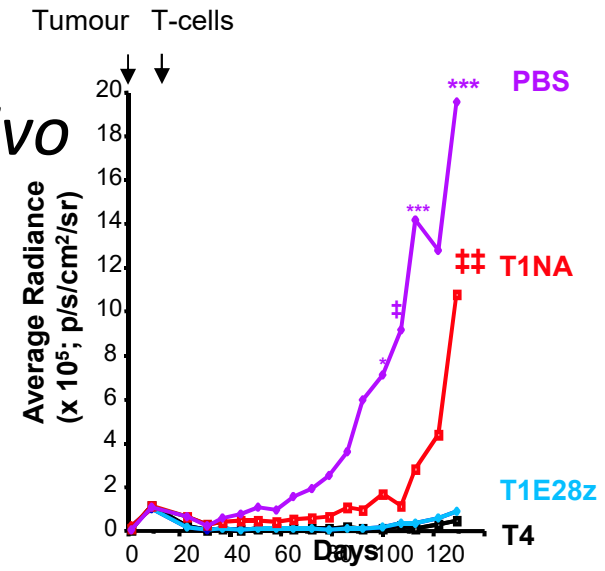
Solid Tumours – T4 Trial

- Pan-ErbB targeted second generation CAR (T1E) for treating HNSCC
- Promising preclinical data *in vivo*
- Led to phase I trial



N=5-7 mice per group

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Solid Tumours – T4 Trial

- Single centre
- 3 + 3 dose-escalation
- Single dose intratumoural injection of CAR T-cells

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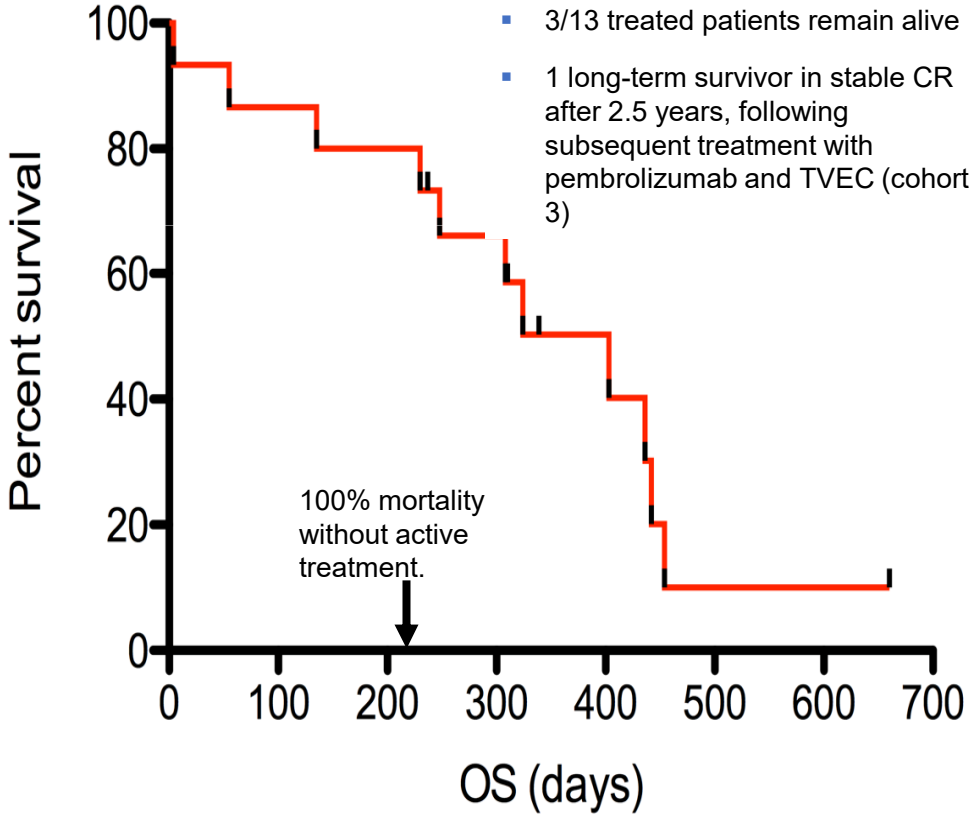
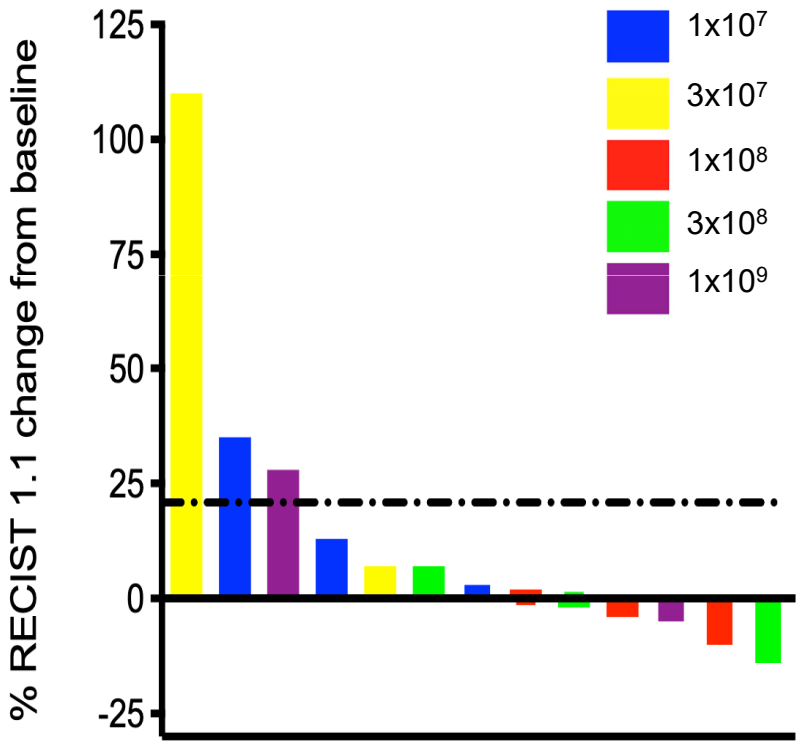
Solid Tumours – T4 Trial

- 1 patient died prior to treatment
- 3/13 treated patients remain alive
- 1 long-term survivor in stable CR after 2.5 years, following subsequent treatment with pembrolizumab and TVEC (cohort 3)





Solid Tumours – T4 Trial

Patient	Cohort	Serious Adverse Event/ Reaction	CTCAE grade	Related to T4 immunotherapy
1	1	Abnormal liver function tests, due to prescription of nortriptylene	3	No
6	2	Intra-tumoural pain due to disease progression	4	No
10	3	Oral haemorrhage due to tumour biopsy prior to T4 immunotherapy	2	No
15	5	Prolongation of hospitalisation – discharged at 48h	1	Yes
17	5	Prolongation of hospitalisation – discharged at 48h	1	Yes

Adverse Events

Cohort	Dose	Possibly related	Likely related	Definitely related
Cohort 1	1 x 10^7	4		
Cohort 2	3 x 10^7	1		
Cohort 3	1 x 10^8	3	9	
Cohort	3 x 10^8	2	1	25
				7

- No dose-limiting toxicities in any patient.
- 145 non-serious adverse events in 15 treated patients.
- No SUSARs.
- 5 serious adverse events, two of which was related to T4 immunotherapy (SAR).
- No cytokine release syndrome or neurotoxicity.

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Solid Tumours - Summary

- Efficacy seen in haematological malignancies is not replicated in a solid tumour setting
- Many obstacles to overcome for potential successful treatment
- Some trials showing some efficacy
- A long way to go yet

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The Future of CARs

- Further engineering

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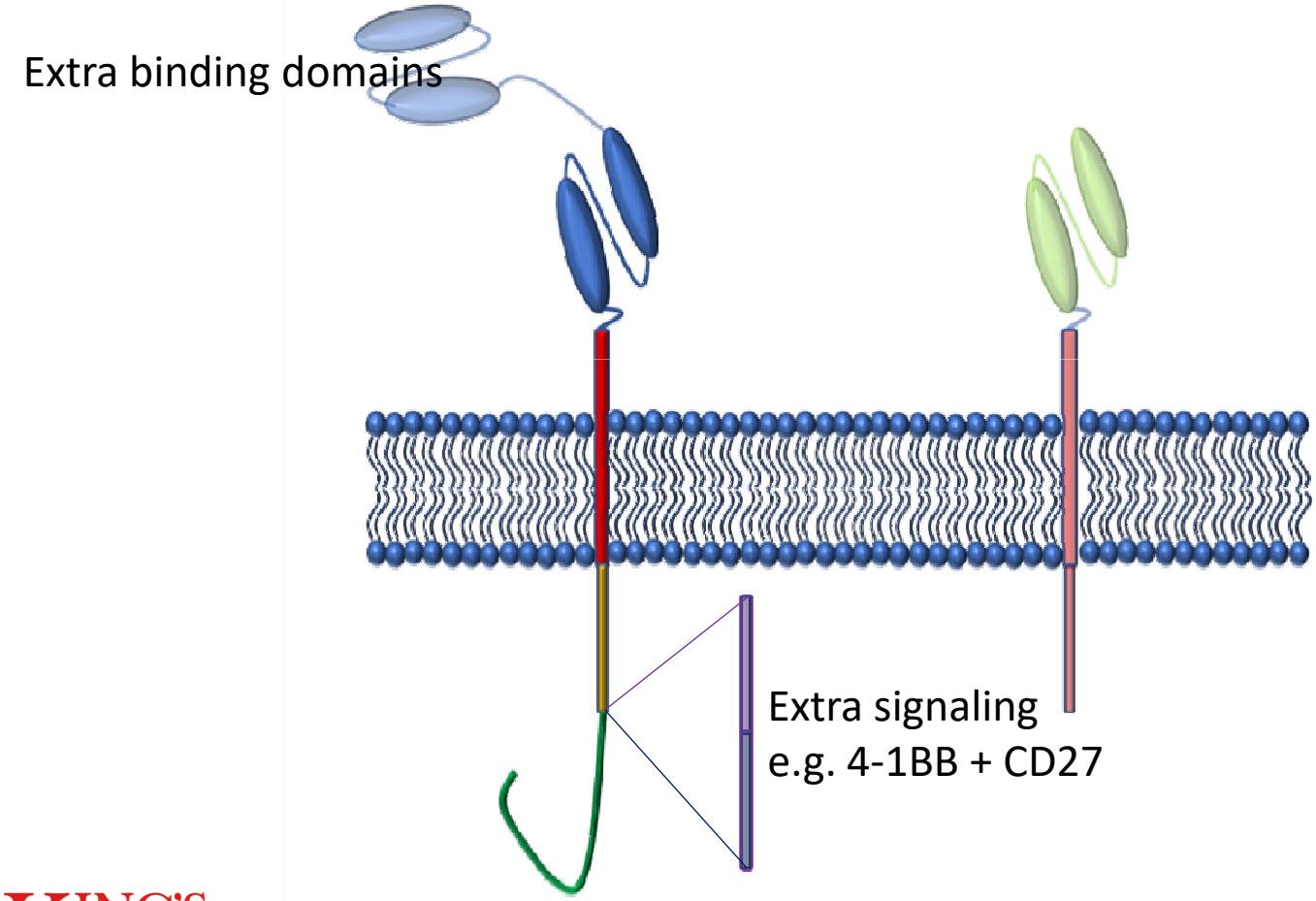
“4th Generation” CARs



Extra molecules
e.g.

- Costimulation
- Growth
- Checkpoint evasion
- Secretory factors
- Logic gate
- Extra CARs

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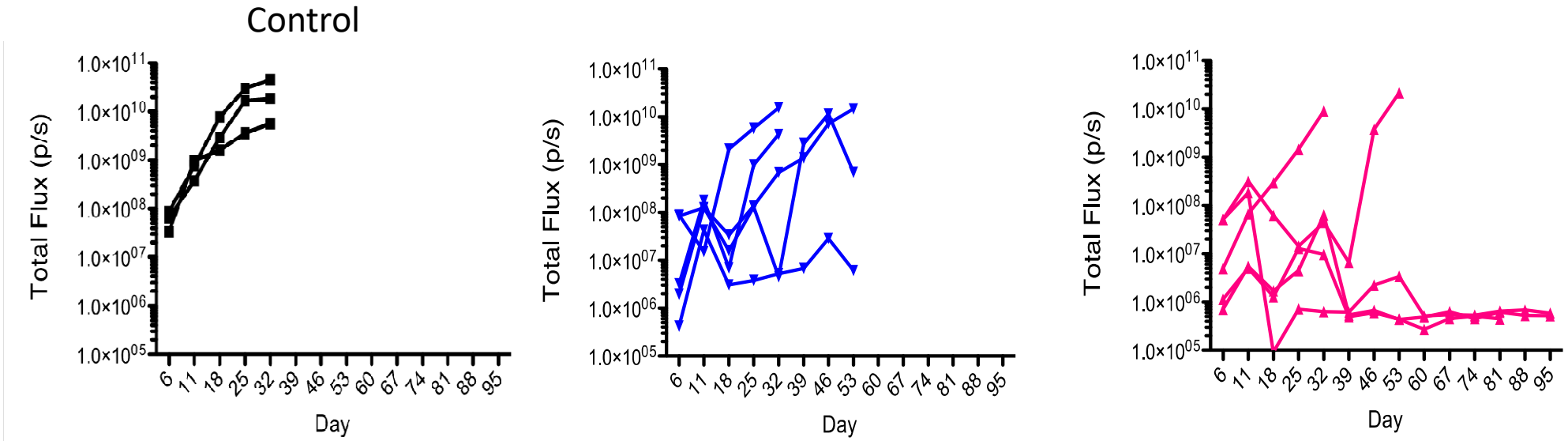
“4th Generation” CARs

- Success *in vitro* and *in vivo*, more testing required before testing in trials



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The Future of CARs

- Further engineering

- Combination therapy

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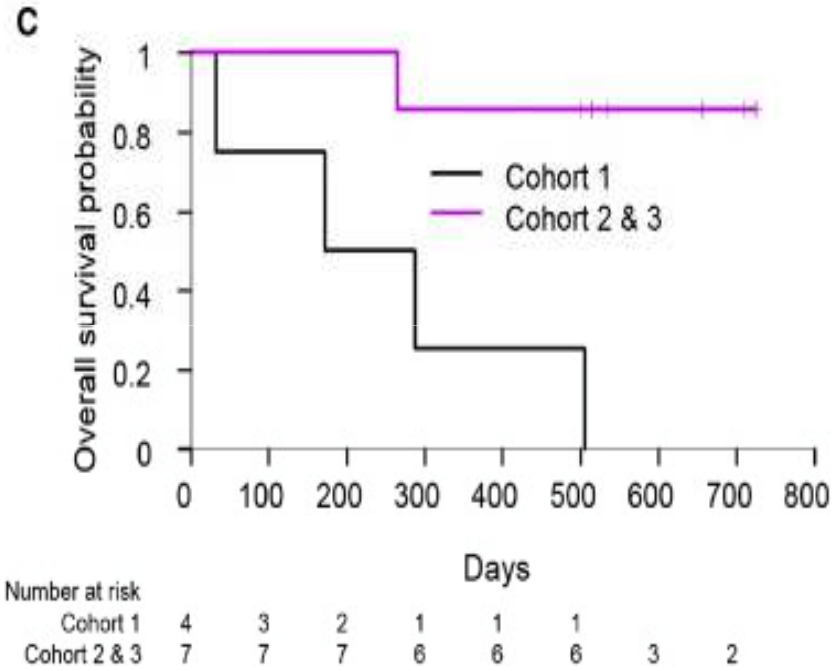
Combination therapy

- Checkpoint Inhibitors
- Oncolytic viruses?
- Supportive therapy?



CAR alone

CAR + Cy/Flu
+/- Anti-PD1

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Heczey et al., Molecular Therapy

The Future of CARs

- Further Engineering
- Combination Therapy
- “Under the hood”

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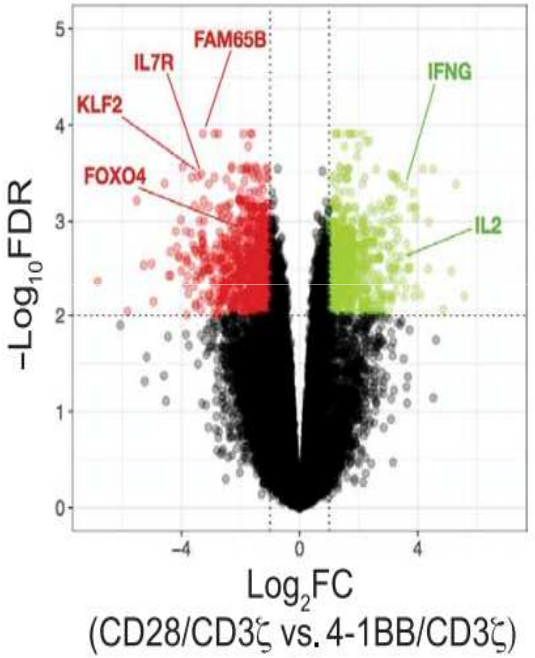
Under the Hood of CARs

- Metabolism
- 'Omics
  - Phosphoproteomics
  - Transcriptomics
  - Genomics
- Beyond CD4:CD8
  - Maintain memory phenotype?
- Immune Synapse
  - Different to TCR
- Make CARs more TCR-like?
  - More ITAMs?
  - Fewer ITAMs?



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Salter et al, Science Signalling (2

The Future of CARs

- Further Engineering
- Combination Therapy
- “Under the hood”

All together will result in a better understanding of tumour immunology leading to better therapeutics

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CAR Commercialisation

- Success of CD19 targeted CARs greatly increased their value
- Cracking solid tumours will probably be even more lucrative
- $Billions invested in CAR companies across the world

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Summary

- CAR T-cells have shown success in haematological malignancies
- This success has not been replicated in a solid tumour setting
- More research and better understanding is required before solid tumour treatment will be effective
- Commercialisation is a double-edged sword
  - More money but less collaboration and more emphasis on

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References

Reviews

- Mata & Gottschalk, Drugs (2019)
- Feins et al., American Journal of Haematology (2019)

Research

- Salter et al., Science Signalling (2018) [Proteomics]
- Locke et al., Lancet Oncology (2018) [Yescarta update]
- Davies et al., Molecular Medicine (2012) [T4 preclinical]
- Helson et al., Nature Communications (2018) [CAR Engineering]

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Acknowledgements

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