CATAPULT
Cell and Gene Therapy

Targeting the tumour vasculature with CAR T-cells for treatment of solid tumours

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About us

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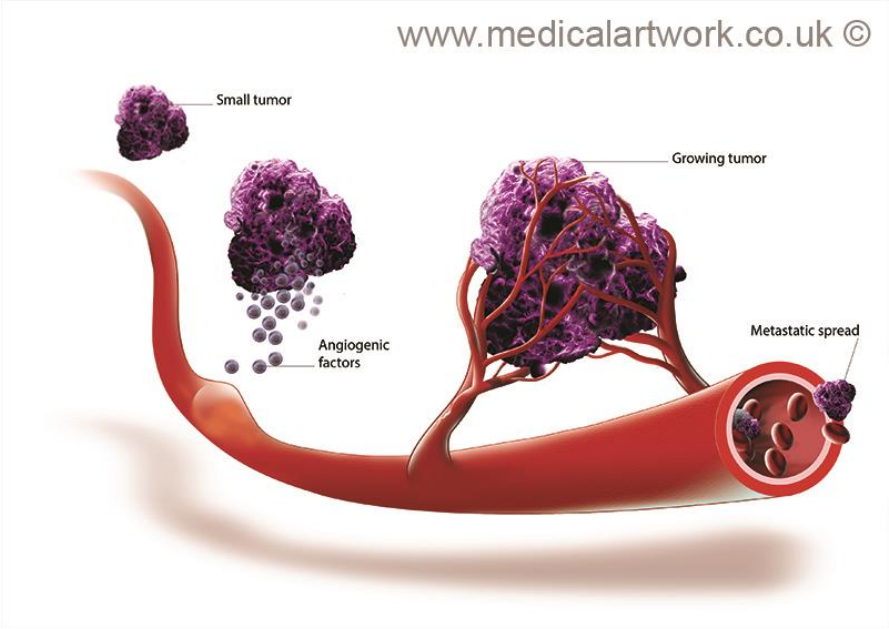
Bridge the gap between businesses and academic research

Were established by Innovate UK as a **not-for profit,** independent centre

CARs and Cancer

CARs targeting CD19 in leukaemia and lymphoma can be highly effective

YESCARTA™
(axicabtagene ciloleucel) Suspension for IV infusion



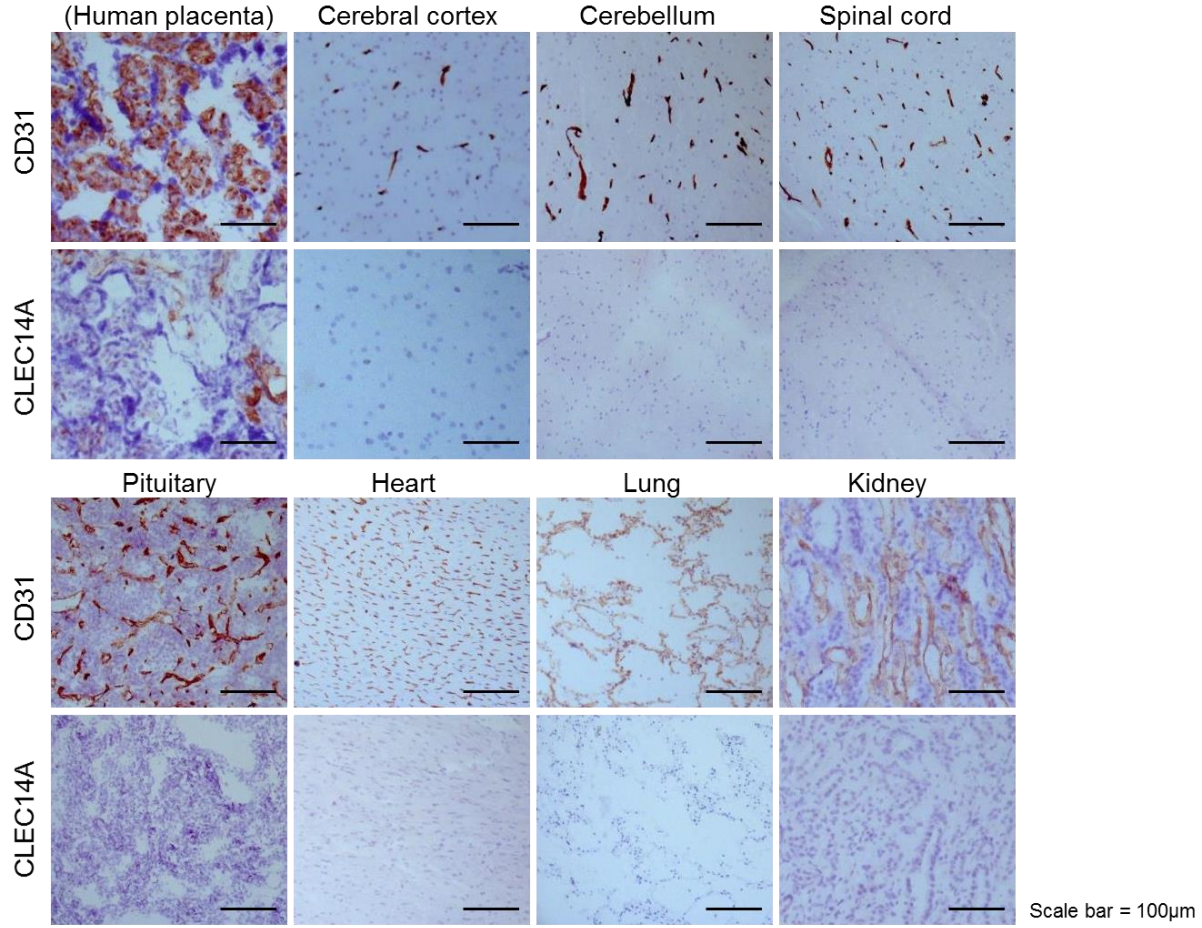
Targeting solid tumours is likely to be more challenging:

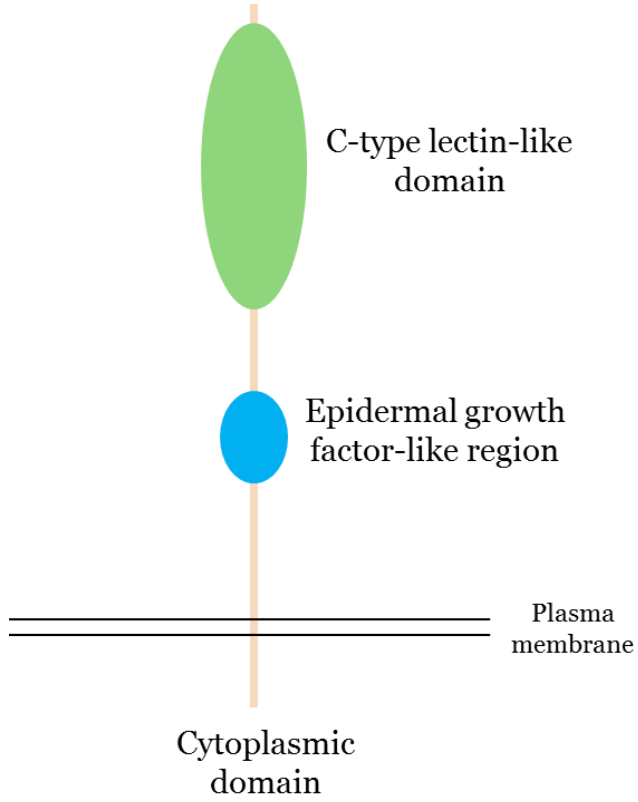
- Access to the tumour tissue
- Identification of specific target antigens
- Immunosuppressive tumour microenvironment

Target the tumour stroma?
- Angiogenesis is essential for tumor growth and metastasis
- Damage at one point in a vessel that leads to a blood clot will affect not only tumour cells in the immediate vicinity but all tumour tissue downstream of this blood supply.

CLEC14A - C-type lectin domain containing 14A

Plays a role in angiogenesis through mediating filipodia formation, endothelial migration and tube formation

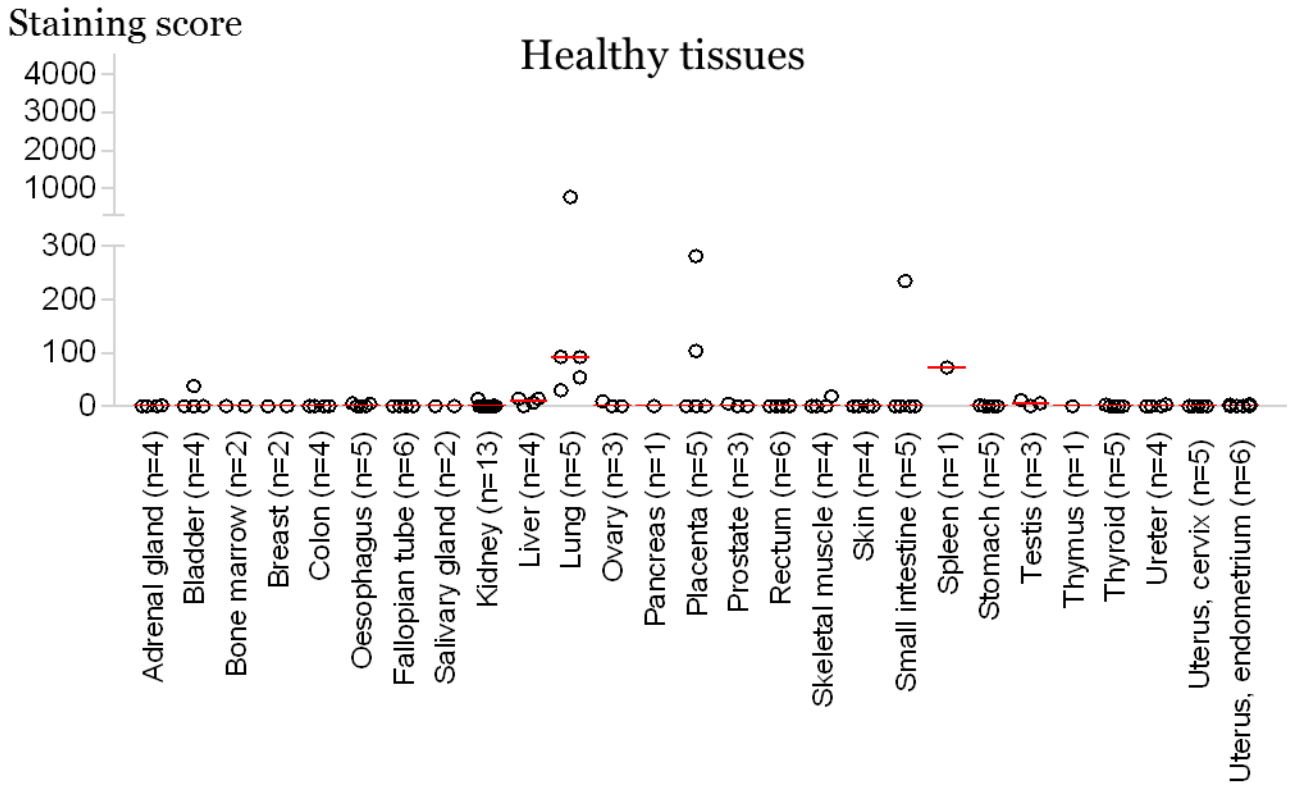




Mura et al. Oncogene 31:293 (2012); Zanivan et al. Mol Cell Proteomics 12:3599-3611(2013); Noy PJ et al. Oncogene (2015); Bocci et al. Angiogenesis (2018)

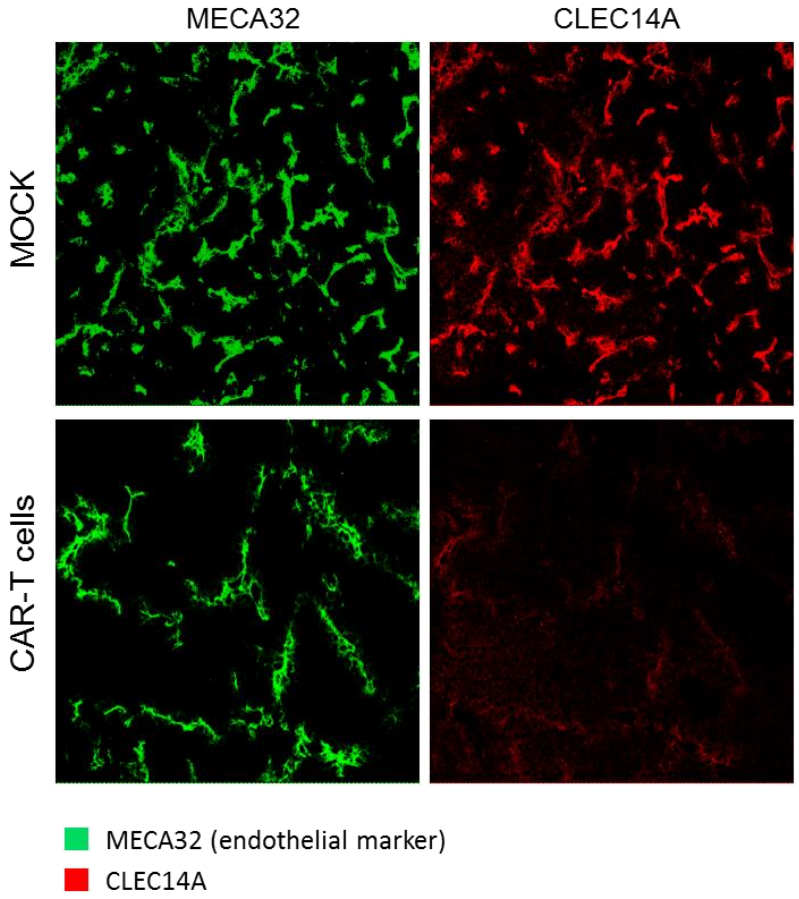
Clec14A expression in human tissue

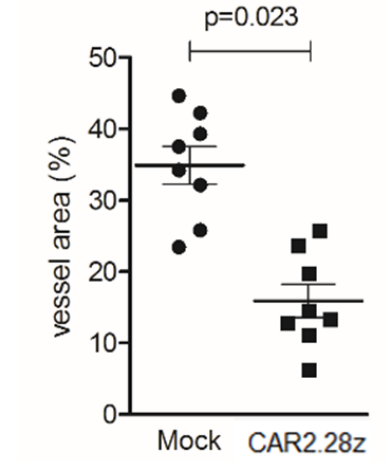
Tissue microarrays (Pantomics, Richmond CA., USA). Surgical samples fixed within 30 mins of removal.

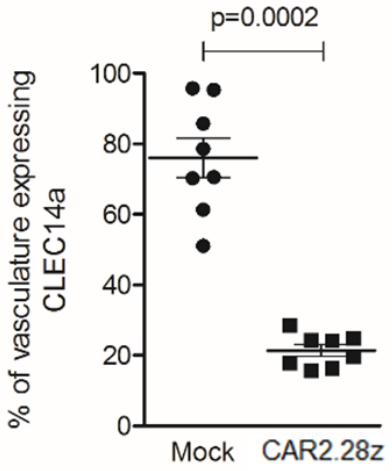


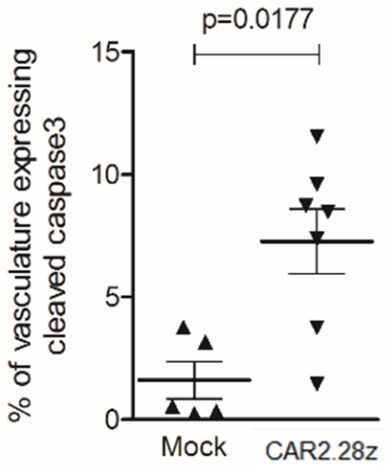
Staining score = staining intensity (0-4) x % vasculature that is stained
x % tissue that is vasculature

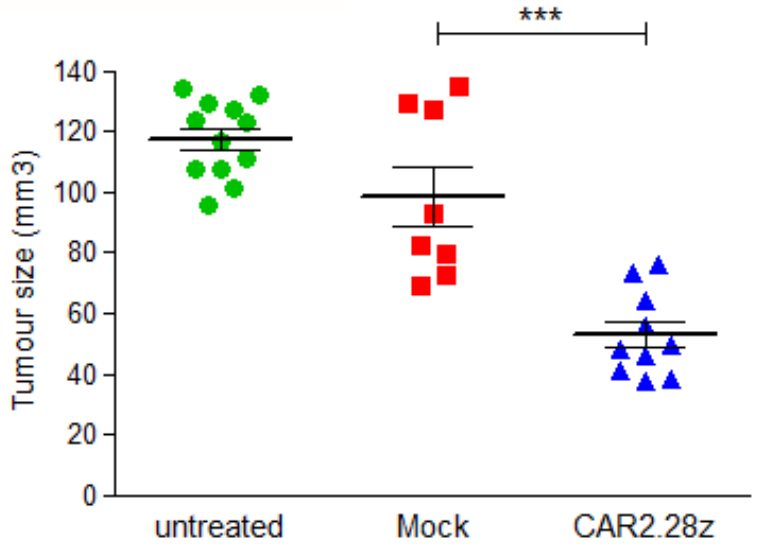
RipTag2 (F. Maione, E. Giraudo, Turin)





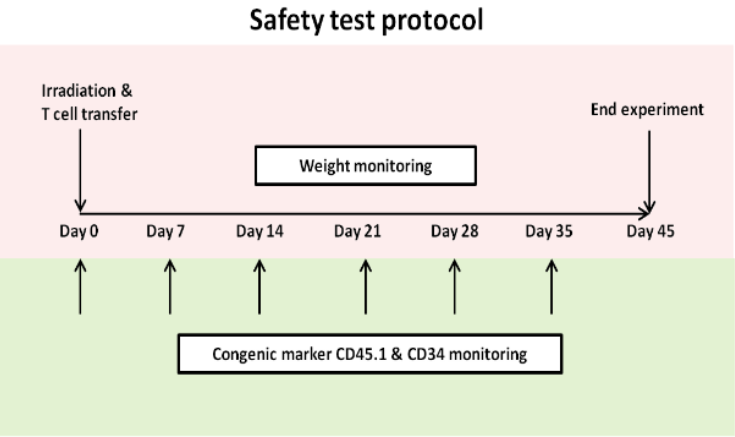




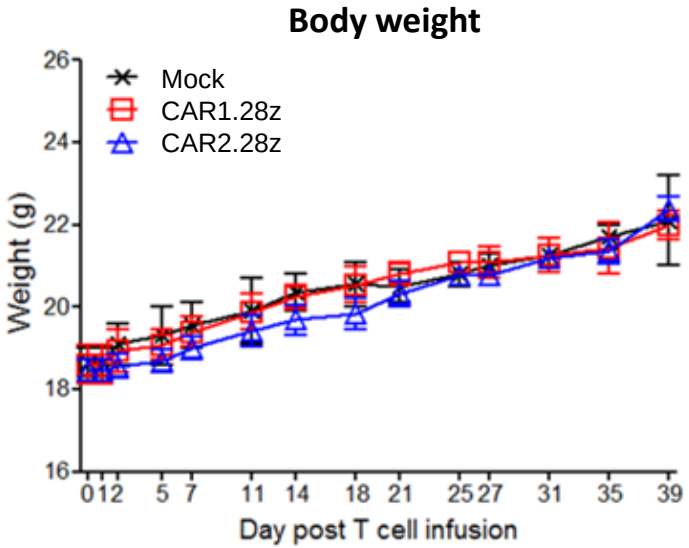


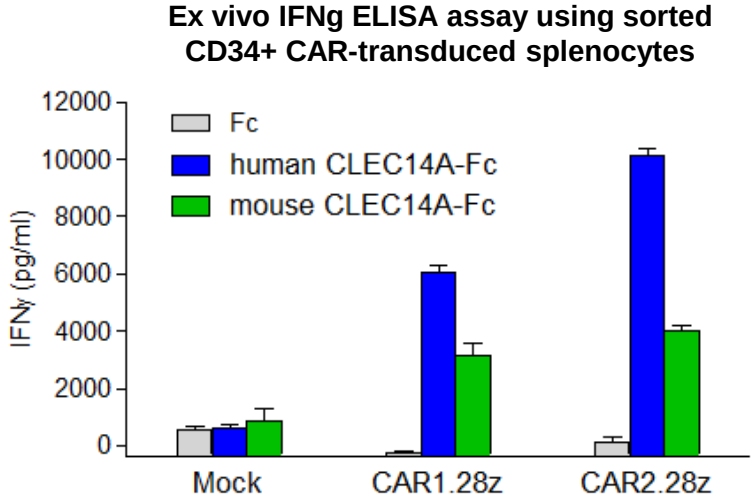
Mock-treated mice were analysed at 14 weeks of age (4/12 mice died before this time point)
CAR-treated mice were analysed at 16 weeks of age (2/12 mice died between 14-16 weeks)

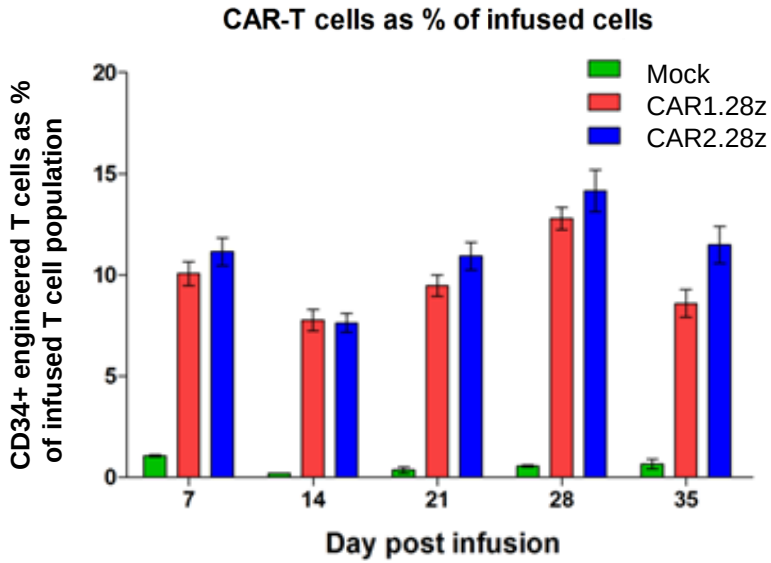
In vivo tox



- Histological analysis (brain, heart, lung, liver, colon and kidney) **indicated no signs of toxicity**
- Additional studies including 220 mice (49 treated with 15 million CAR-T cells) have shown **no sign of toxicity and gained weight as expected**



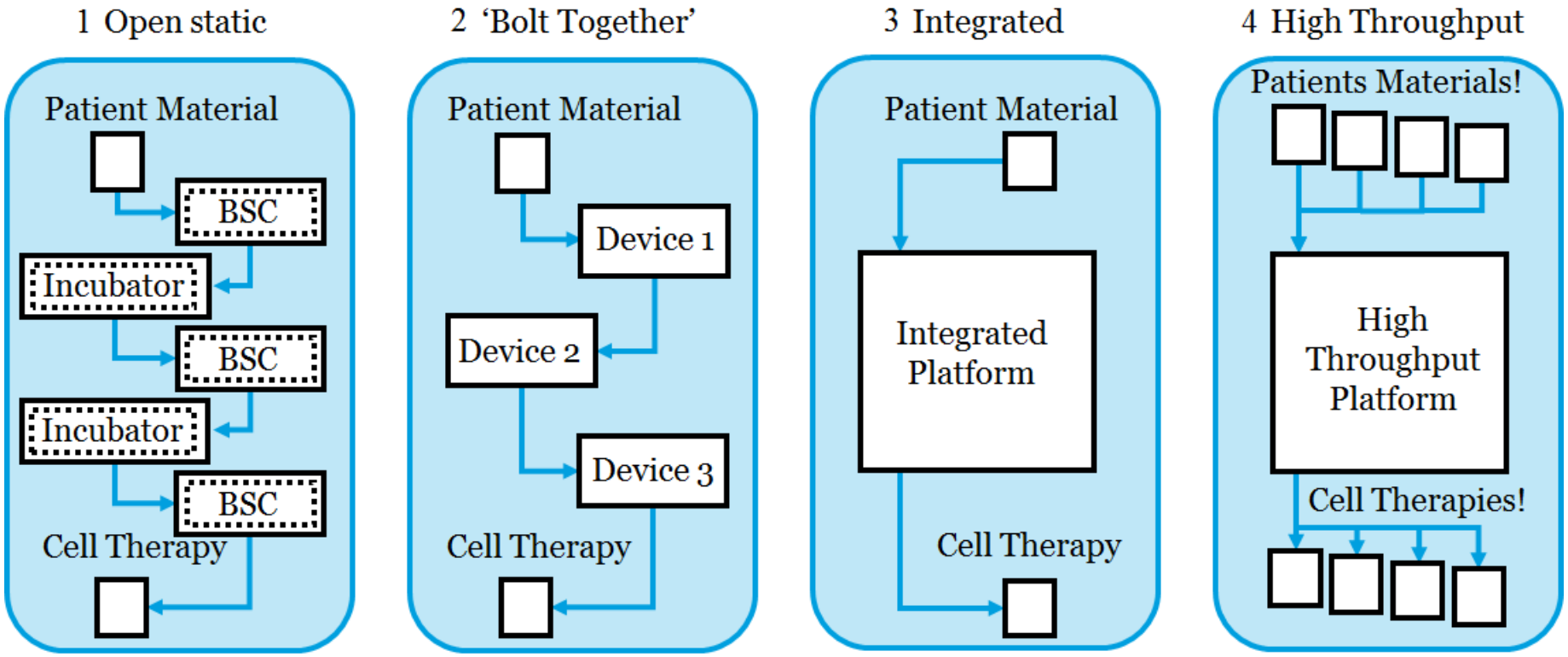




Summary

- Targeting tumour stroma represents an attractive approach for treatment of solid tumours
- ~50% reduction in tumour burden achieved using CAR-T cells targeted to CLEC14A
- No signs of toxicity in mouse model

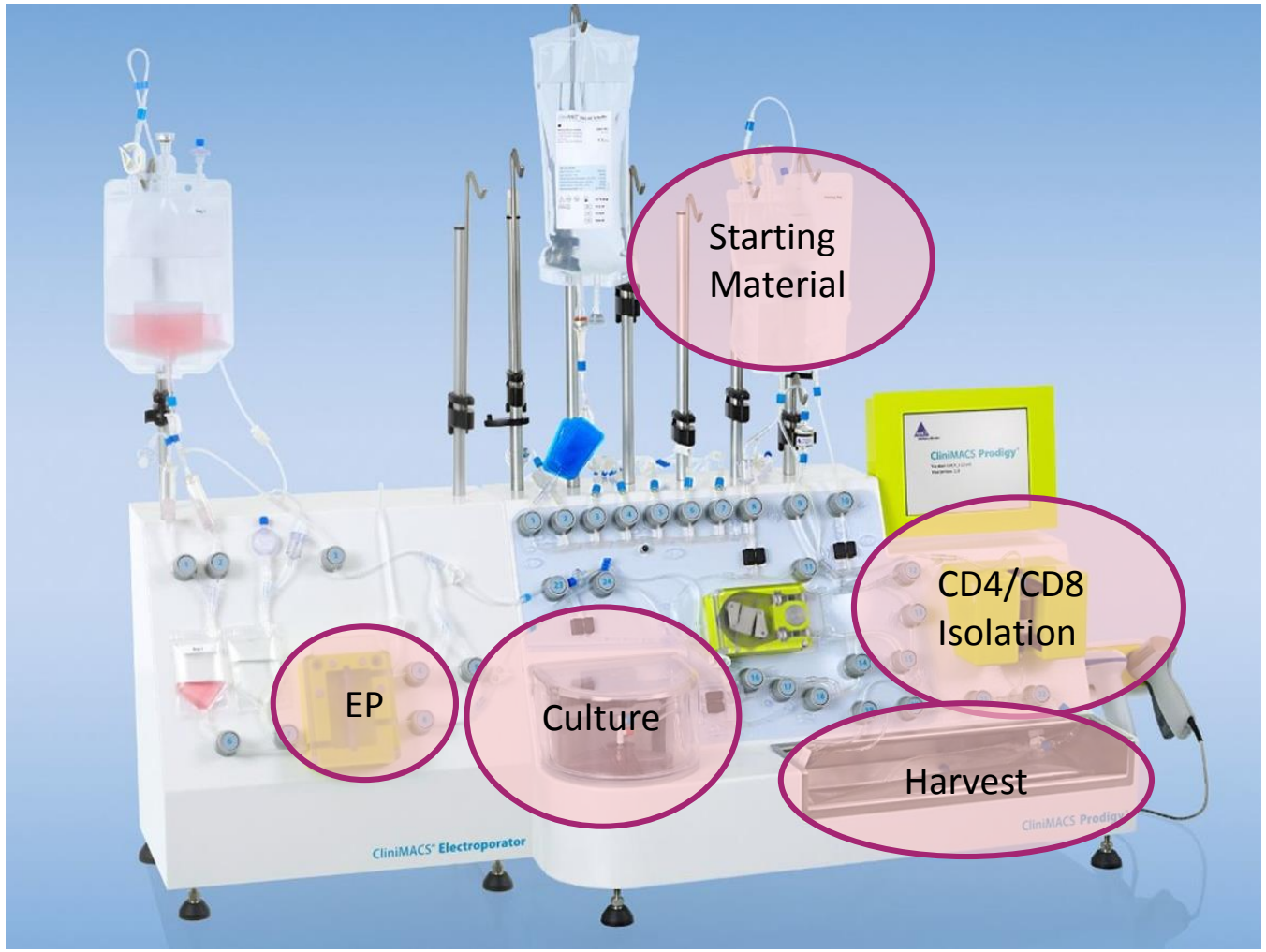
Automation Strategies for Autologous Therapies



Increasing integration + automation –> increased facility throughput

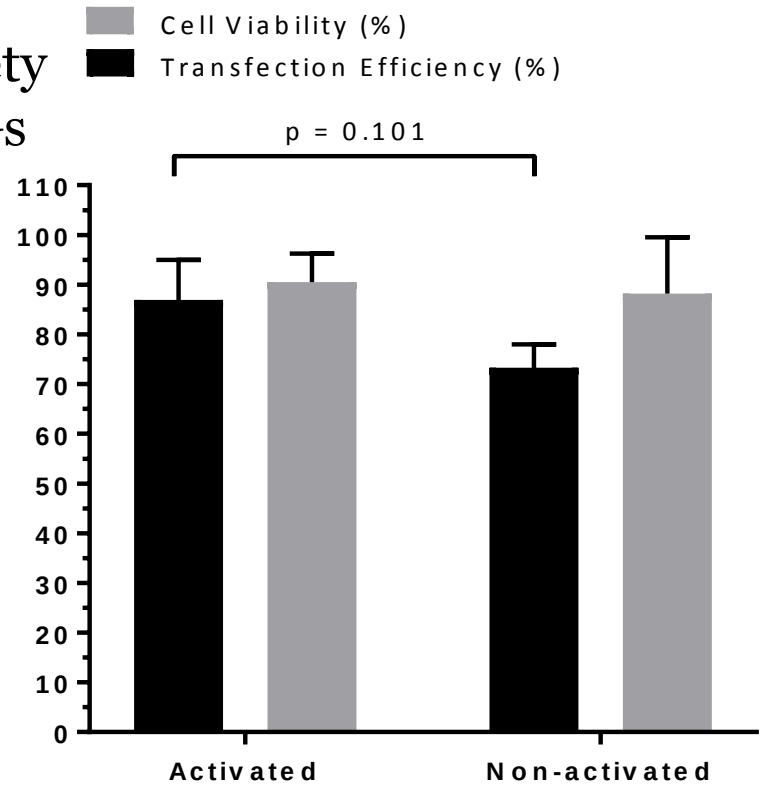
Increasing integration + automation –> decreasing cost of goods

mRNA CAR-T cells

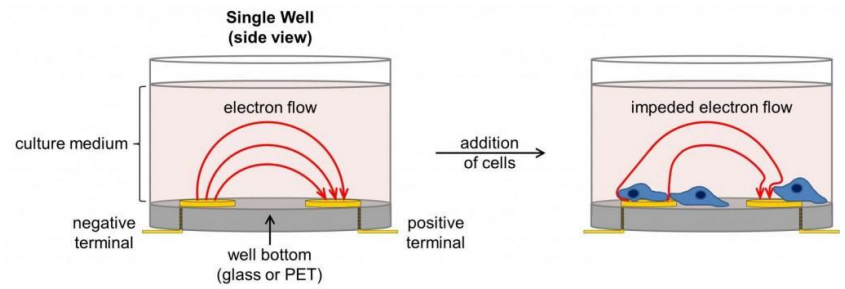


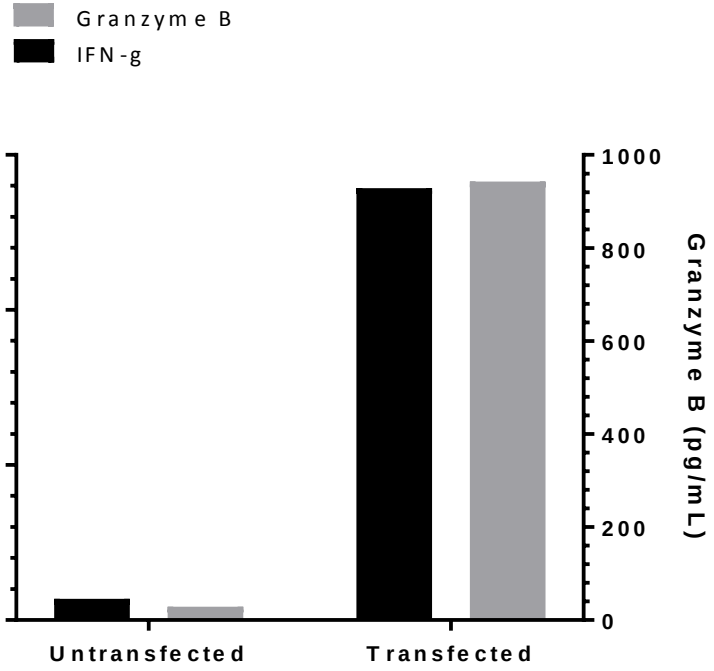
Why mRNA CAR?

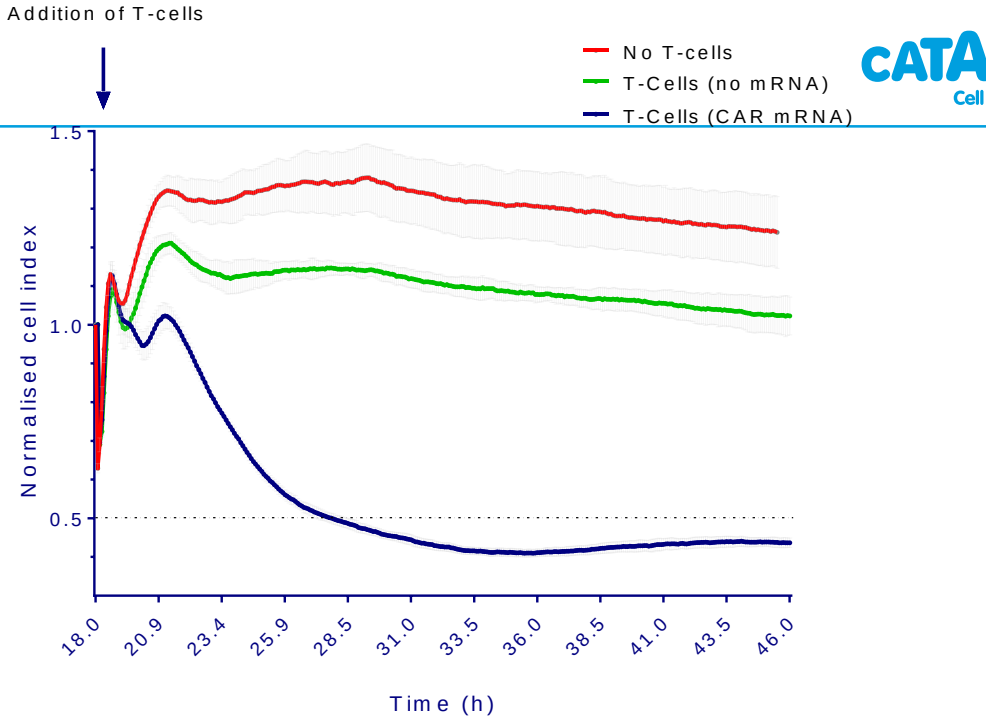
- Safety
- CoGs

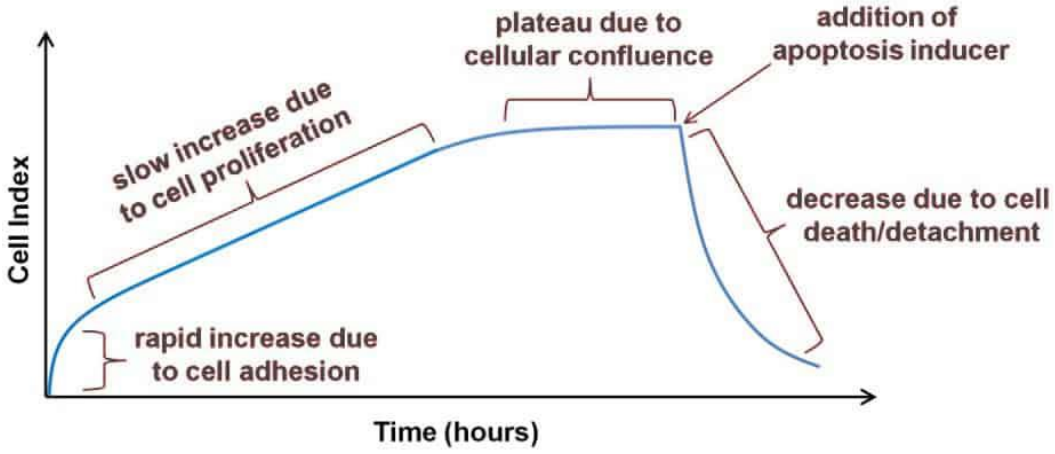


In vitro potency









Summary

- We have optimised an integrated platform for generated mRNA based CAR-T cell therapies at high efficiency, viability and low cost

- mRNA based CAR-T cells capable of reproducibly killing target cells

Further work:

- Assess mRNA CAR-T cells in animal models (multi-dose studies)

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We work with Innovate UK

RipTag2 (F. Maione, E. Giraudo, Turin)

Rat insulin promoter (RIP) directs expression of the SV40 Large T antigen transgene (TAg) to beta cells of the pancreatic islets

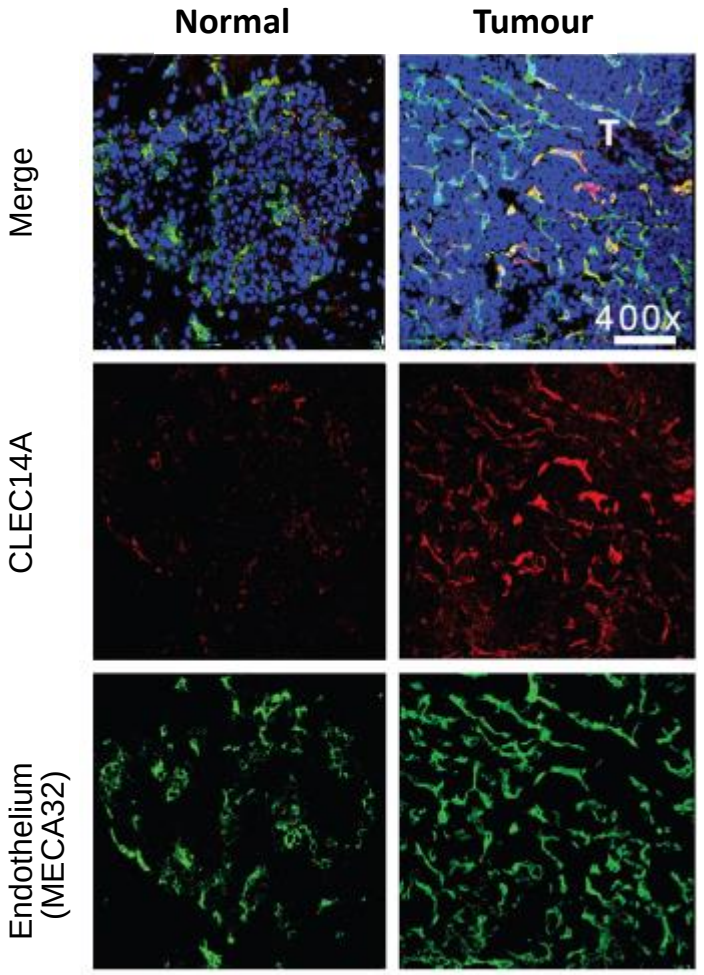
Birth

3-4 weeks old: Hyperplastic islets appear

10 weeks old: Small encapsulated adenomas emerge

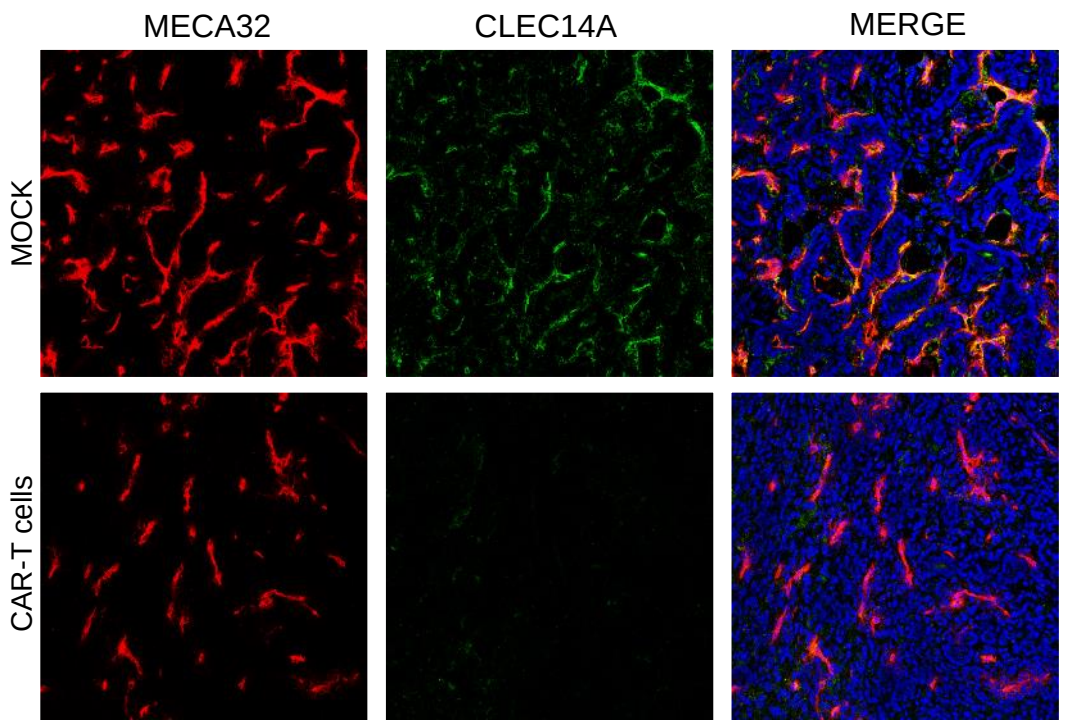
12-13 weeks old: Large adenomas

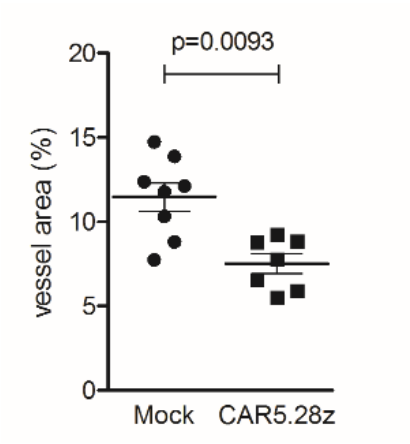
14 weeks old: Death

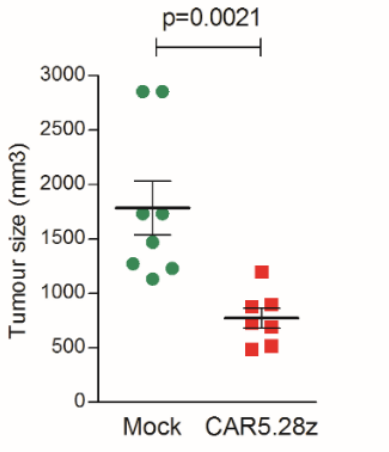


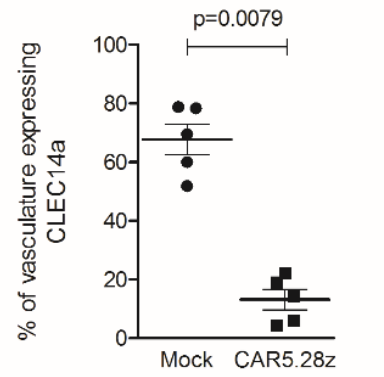
Zanivan et al. Mol Cell Proteomics 12:3599-3611(2013)

Pancreatic Ductal Adenocarcinoma (PDAC)









Lewis lung carcinoma model