QIMR Berghofer
Medical Research Institute

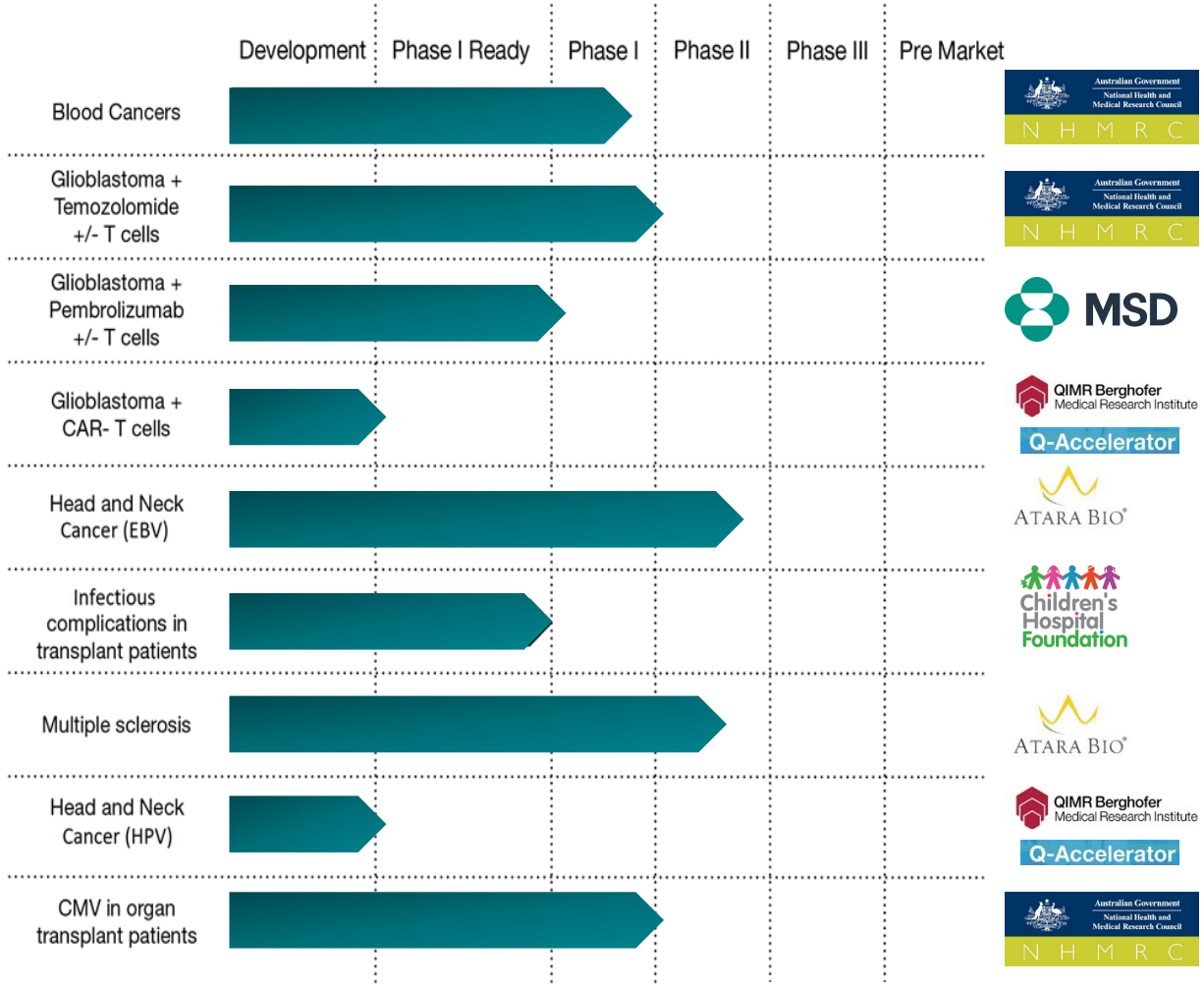
‘Off-the-shelf’ CMV EphA3 CAR T cell therapy for solid tumours

Partnering Opportunity - 2022

Non-confidential

QIMR has 25 years of experience in translating adoptive T cell therapies from bench to bedside

- 25 years of excellence in T cell therapy manufacturing and clinical trials
- ~250 patients treated with adoptive T-cell therapy
- Investigator initiated phase I/II clinical trials
  - 6 completed
  - 2 in progress
  - 2 planned
  - 40+ patients under Special Access Scheme
- Industry sponsored phase I/II clinical trials
  - 1 in progress
  - Multiple planned



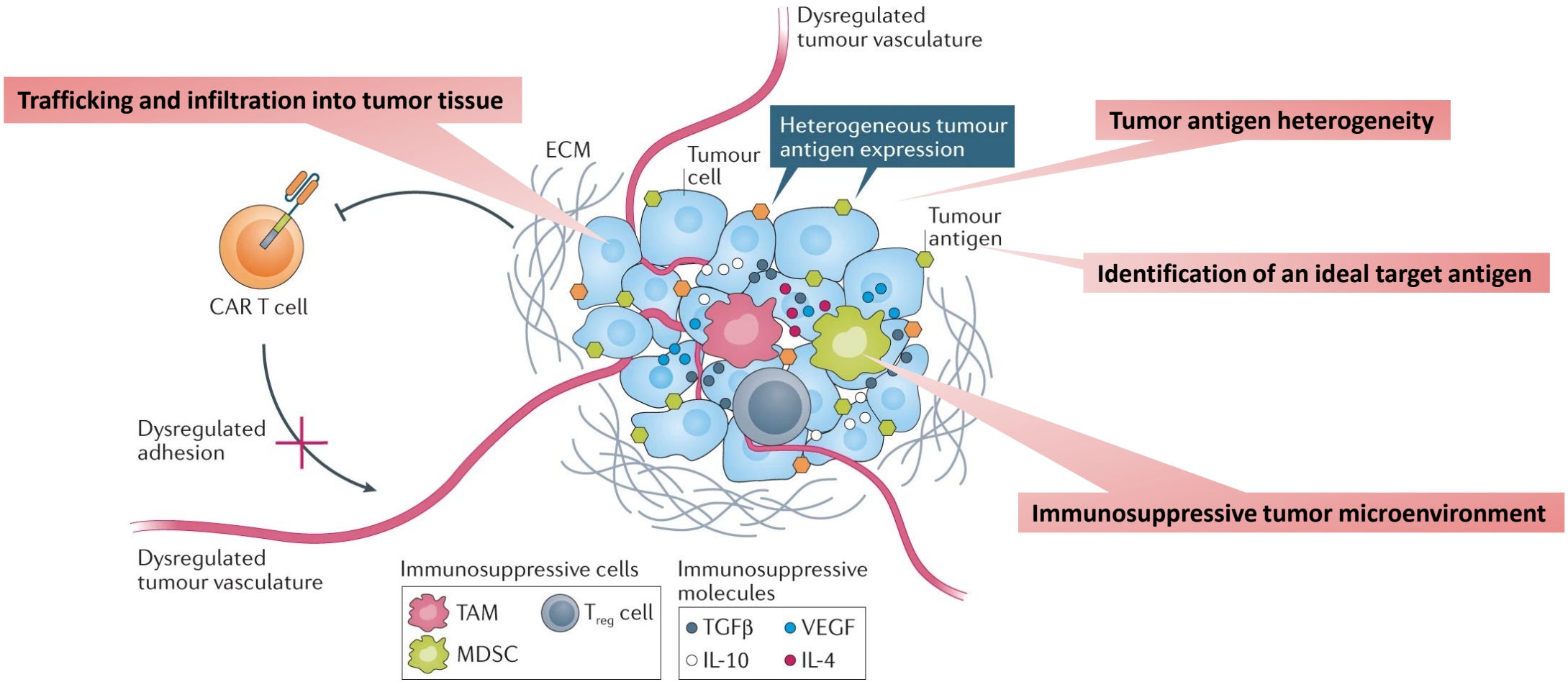
QIMR has a dedicated TGA-accredited cGMP cell therapy manufacturing facility, QGen Cell Therapeutics

Principal Investigator Professor Rajiv Khanna has extensive experience in commercialisation

Professor Rajiv Khanna

- Coordinator of QIMR Berghofer Centre for Immunotherapy and Vaccine Development
- Multiple cell therapy products and vaccine licensed to Atara Biotherapeutics with an ongoing R&D partnership, ATA-188 (EBV CTL) entering phase 2
- BK/JCV CTL licensed to Cellevolve Bio, preparing for phase 2
- CMV diagnostic product successfully entered market
- Multiple cell therapy products in clinical trials
- Consultant to Atara Biotherapeutics, Cellevolve, CSL, Cellestis Inc. and Oxford Immunotech

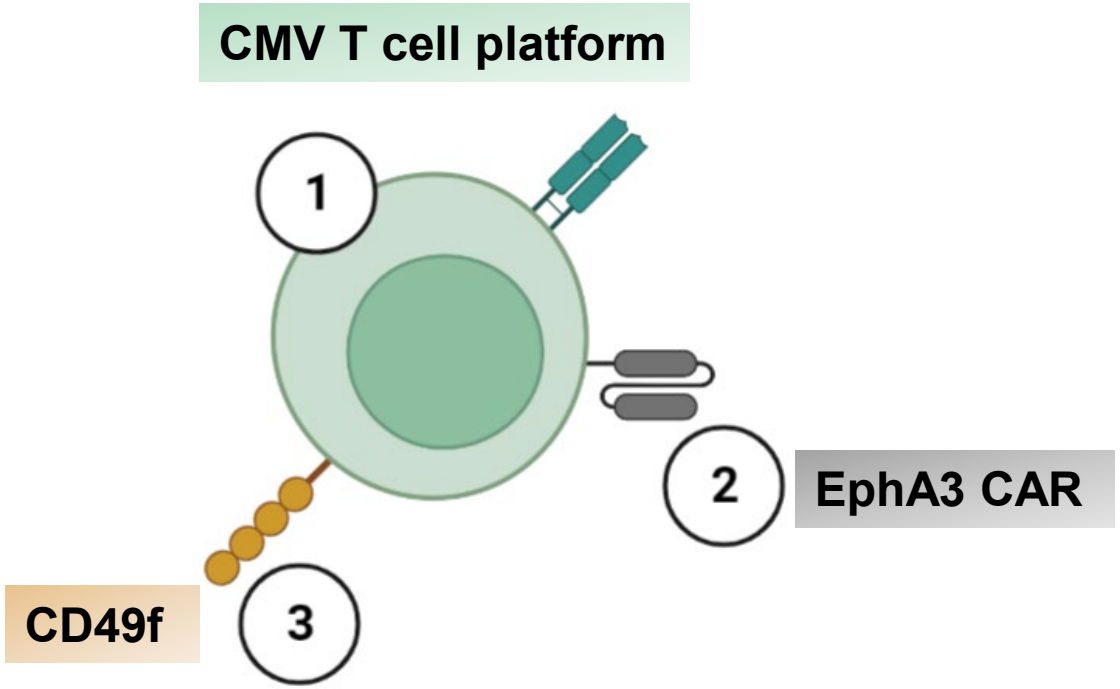
Adoptive T cell therapy is a promising treatment option for solid tumours but faces numerous obstacles

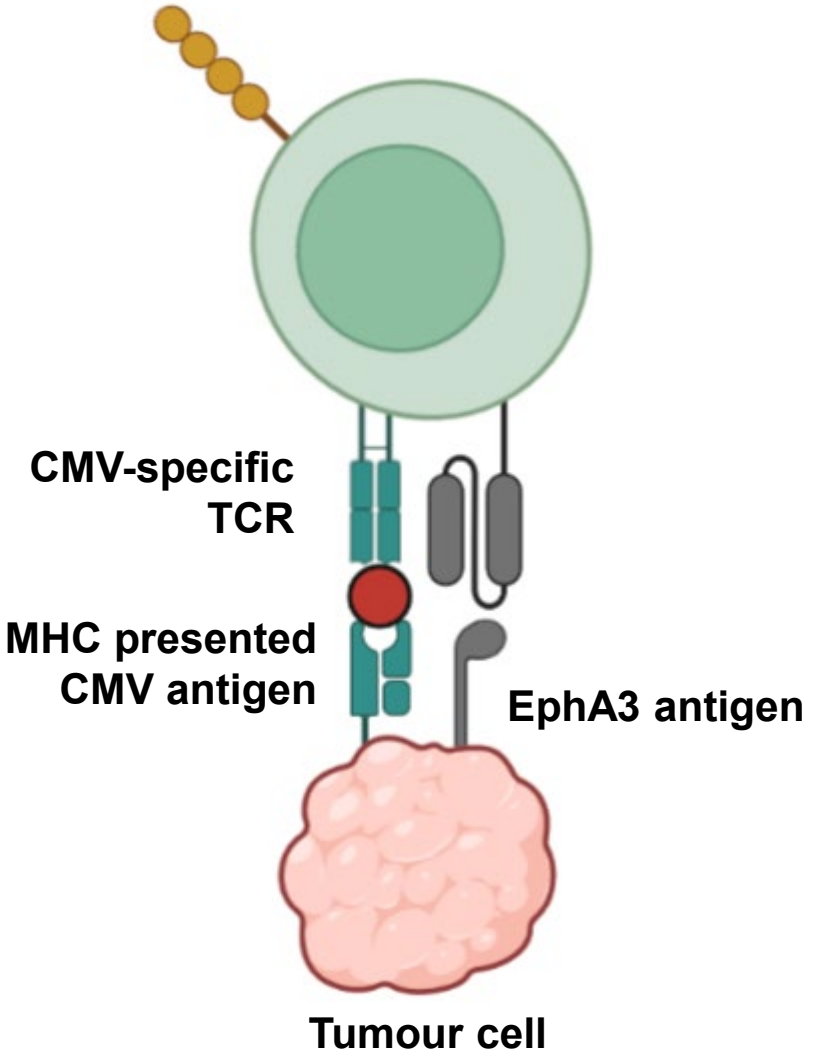


Nature Reviews Drug Discovery volume 20, pages 531–550 (2021)

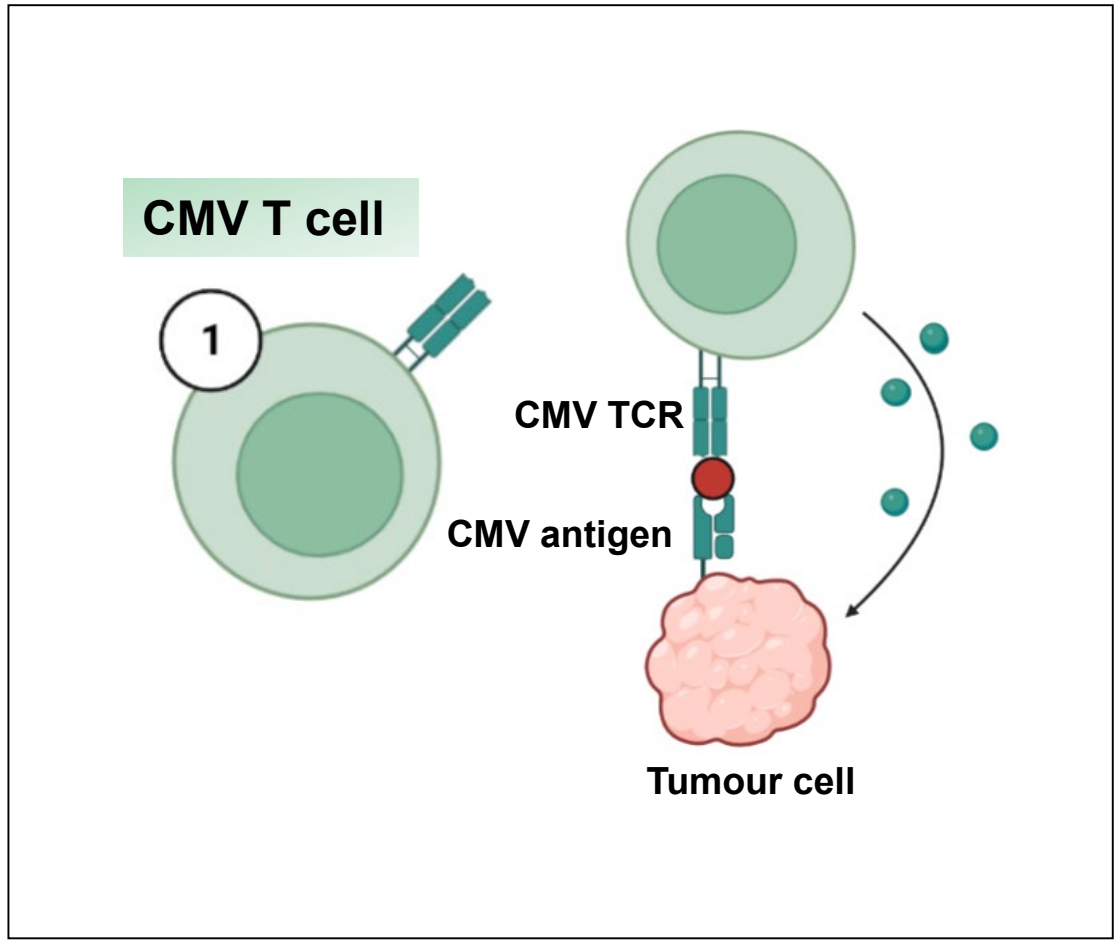
QIMR has developed a T cell therapy which can overcomes these hurdles

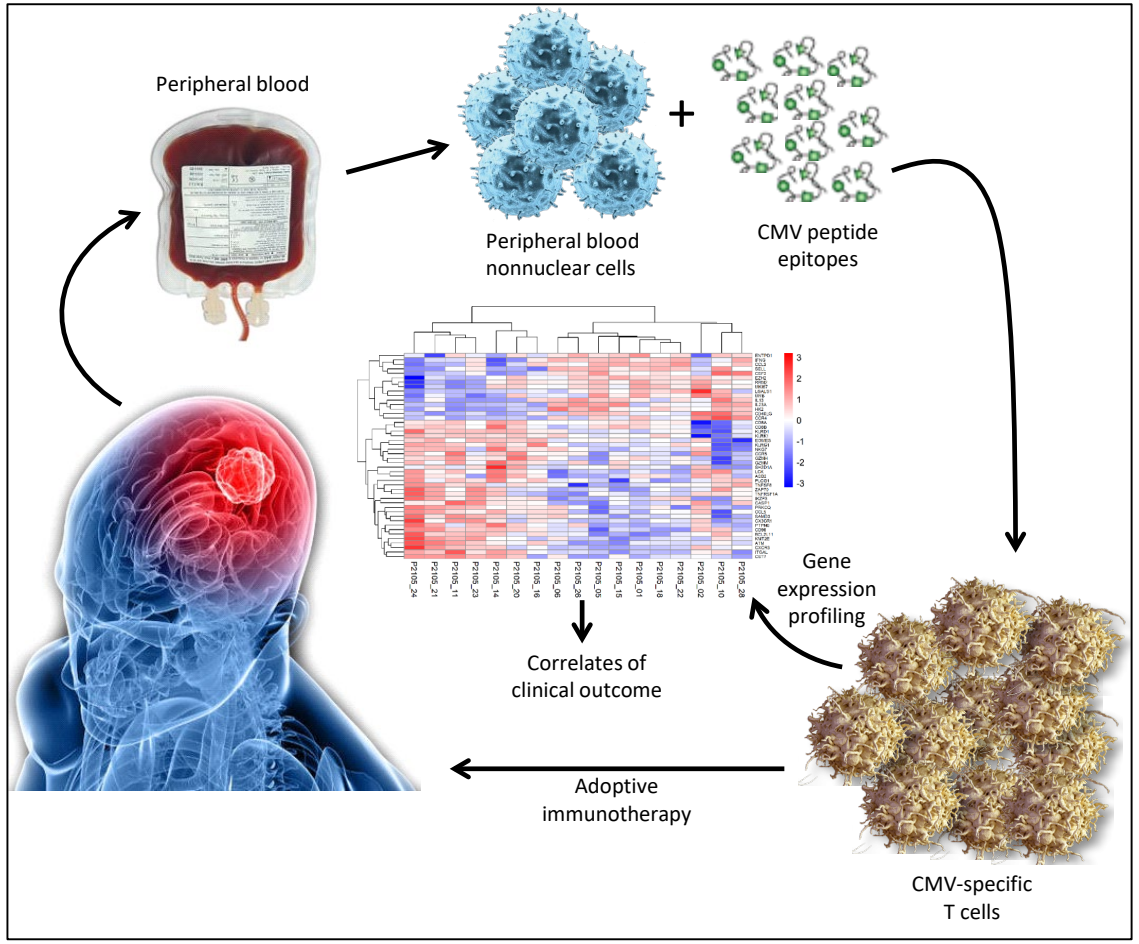
There are 3 components to QIMR's novel T cell therapy





QIMR developed a CMV-specific T-cell therapy for the treatment of solid tumours and transplant indications





Ref: Clin Transl Immunology. (2015);4(3):e35***Cancer Res***. (2014);74(13):3466-76

QIMR completed 3 clinical trials using CMV immunotherapy in GBM and transplant patients with promising results

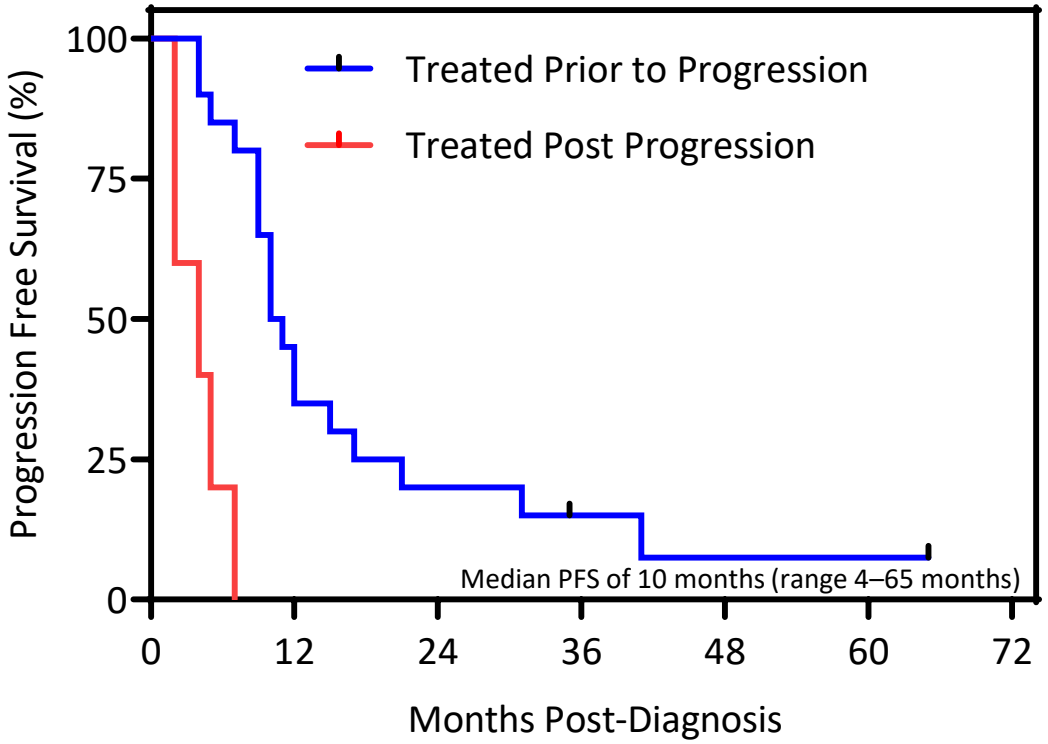
Phase I – Autologous CMV-specific T cells

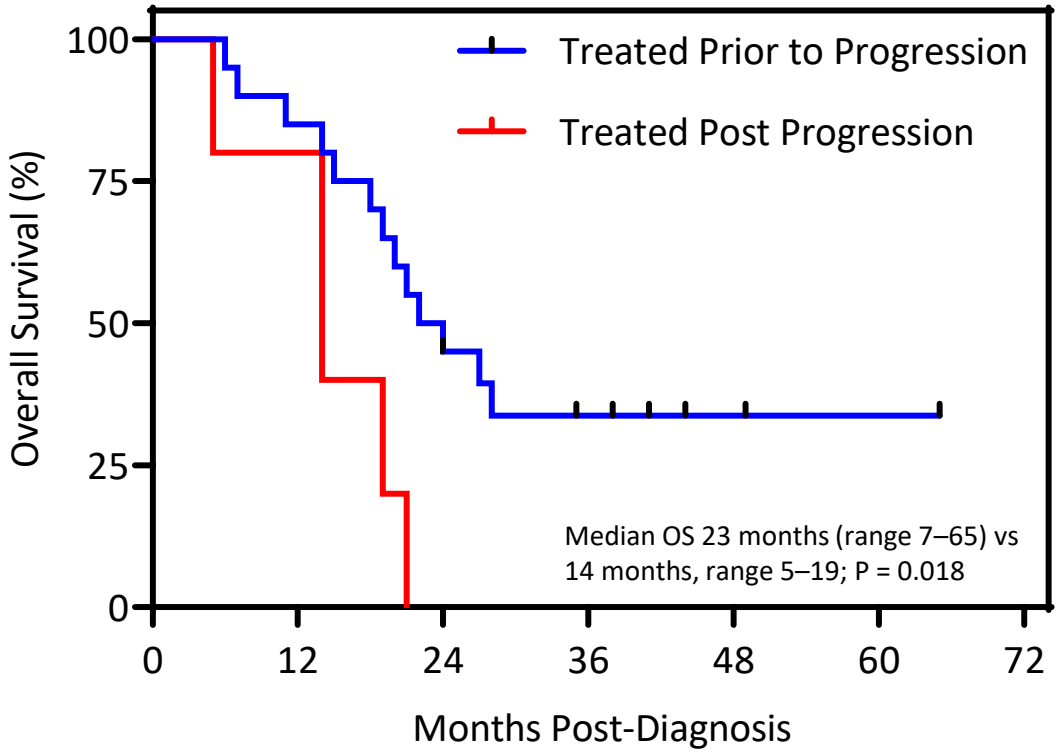
	Drug-resistant CMV Solid Organ Transplant	Recurrent Glioblastoma	Primary Glioblastoma
Patient number	• 22 patients recruited (13 treated)	• 19 patients recruited (11 treated)	• 28 patients recruited (25 treated)
Adverse events	• Grade 1 or 2 AEs in 2 patients • No AEs were definitely related to T cell therapy	• One SAE recorded unlikely associated with T cell therapy	• No AEs associated with CMV T cell therapy
Clinical Response	• 11/13 patients (84%) showed clinical improvement	• Overall survival ranged from 133 to 2,428 days (median 403 days) • 4 out of 11 patients showed progression free survival	• Patients treated before recurrence showed significantly improved overall survival

QIMR's CMV T cell therapy was safe with preliminary efficacy signals

Ref: J Clin Invest. (2020);130(11):6041-6053, ***Clin Infect Dis***. (2019);68(4):632-640, ***J Clin Invest***. (2019);129(11):5020-5032, ***Clin Transl Immunology***. (2015);4(3):e35, ***Cancer Res***. (2014);74(13):3466-76

The CMV T cell therapy improved survival in primary GBM patients treated prior to progression





Ref: J Clin Invest. (2020);130(11):6041-6053

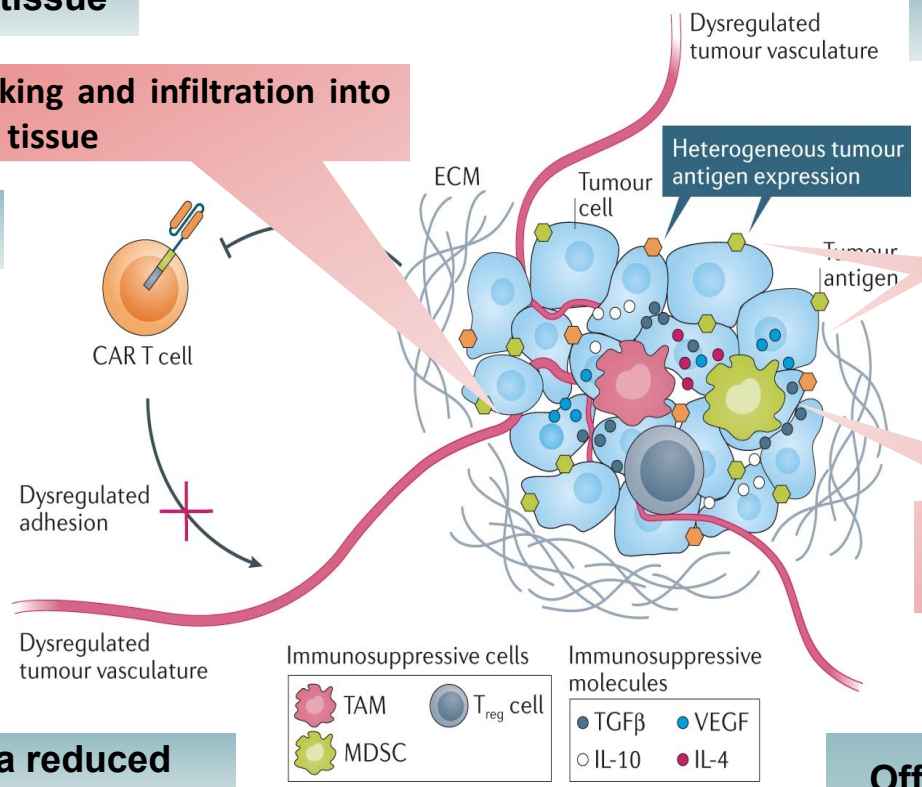
The CMV T cells can be used as a safe and effective delivery platform for adoptive immunotherapy

Penetrates solid tumour tissue

Traffics to brain

Improves cell persistence

Trafficking and infiltration into tumor tissue



Allows dual targeting

Tumor antigen heterogeneity

Identification of an ideal target antigen

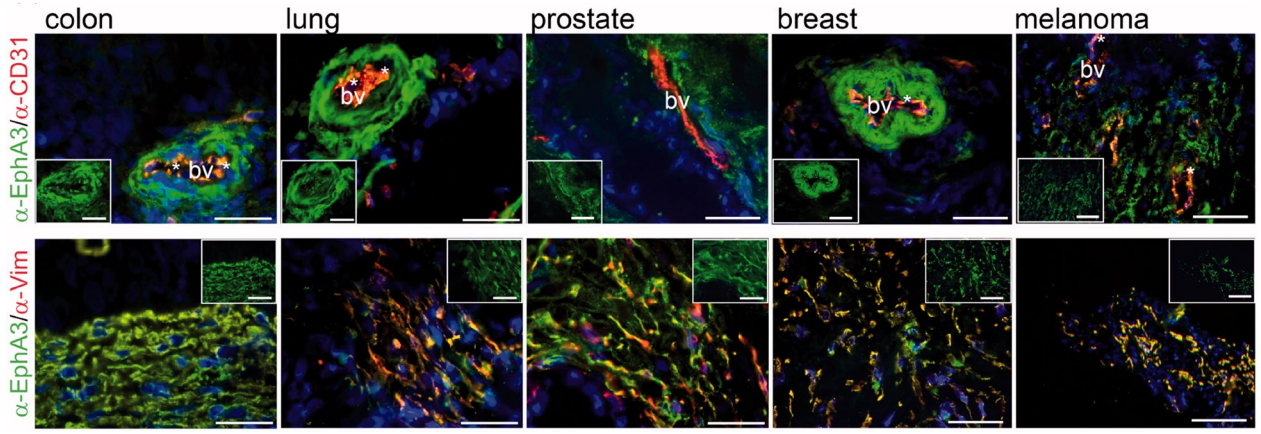
Immunosuppressive tumor microenvironment

Improved safety via reduced alloreactivity

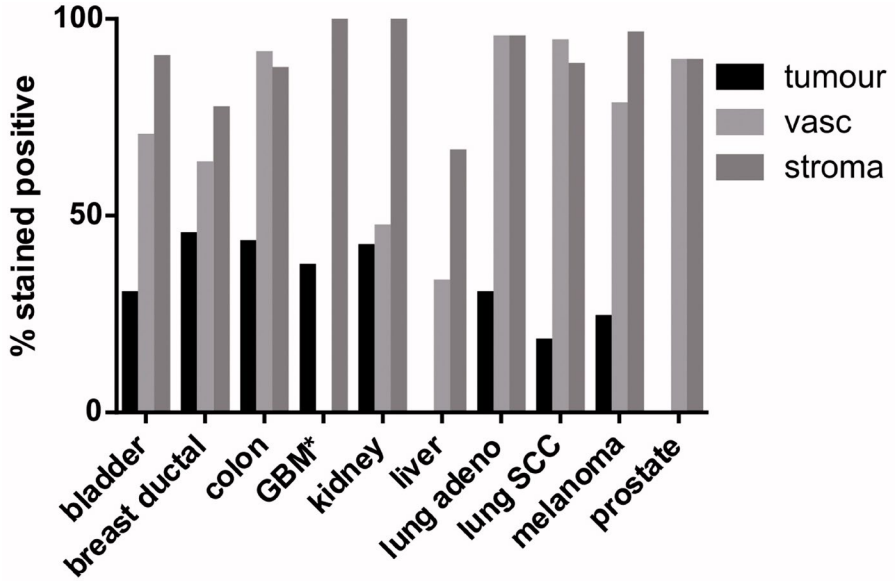
Off-the-shelf product
- Reduced cost
- Treatment without delay
- Defined cell population
- Broader coverage

EphA3 is a potentially safe, solid-tumour target for the CMV CAR T cell platform

- EphA3 promotes cancer stem cell self-renewal
- EphA3 is highly expressed on multiple cancer types, including GBM, NSCLC, colorectal prostate, renal and leukemia
- EphA3 is expressed in stromal and vascular tissues of human tumors but virtually undetectable expression in normal adult tissues and organs
- Targeting of EphA3 inhibits tumor growth by disruption of the architecture and function of the vascularised tumour microenvironment

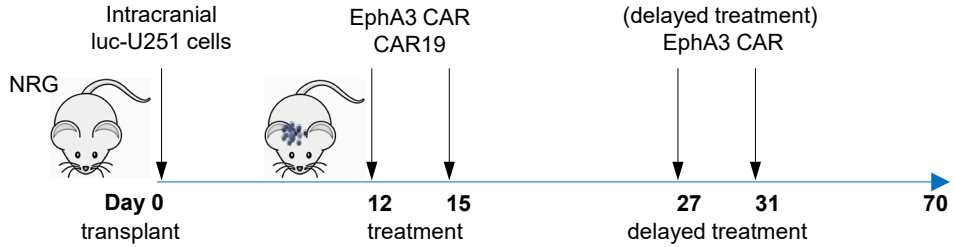


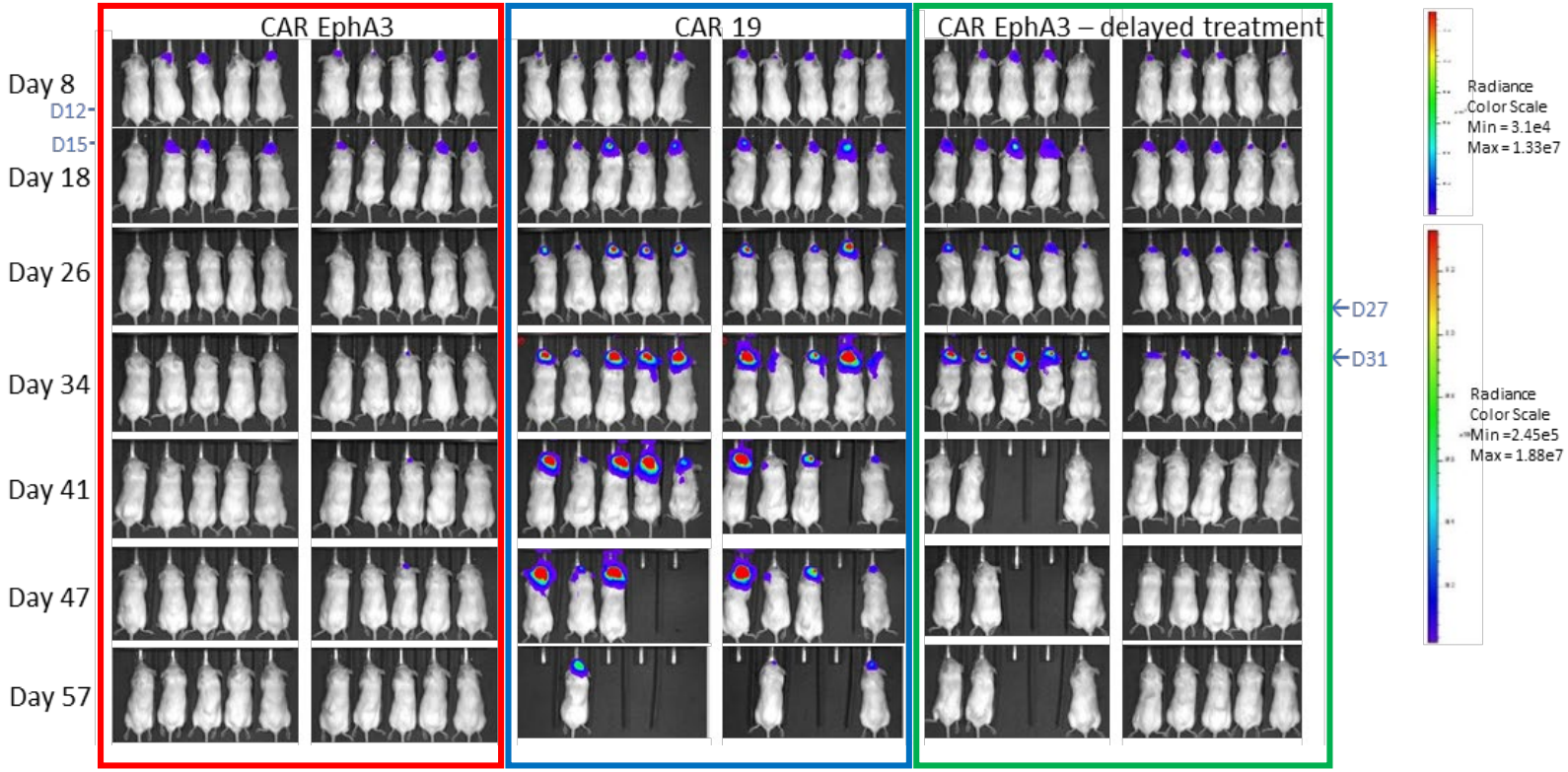
Cancer Res (2014) 74 (16): 4470–4481.

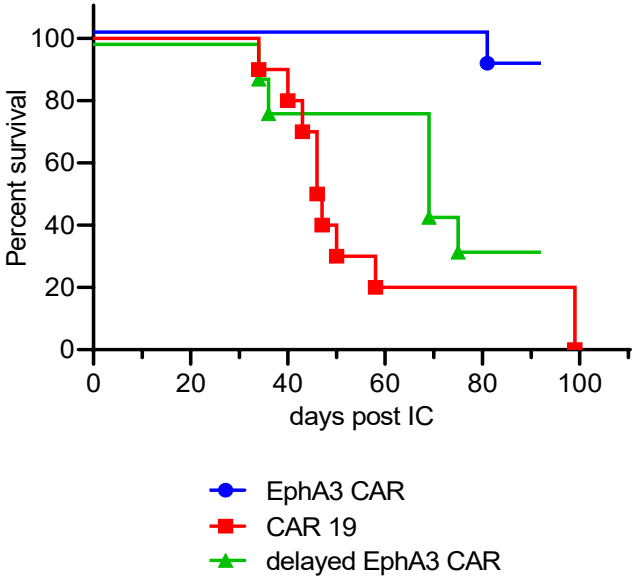


We have designed a novel EphA3 targeting CAR

Adoptive immunotherapy with EphA3 CAR T cells leads to complete tumour regression in an orthotopic GBM model

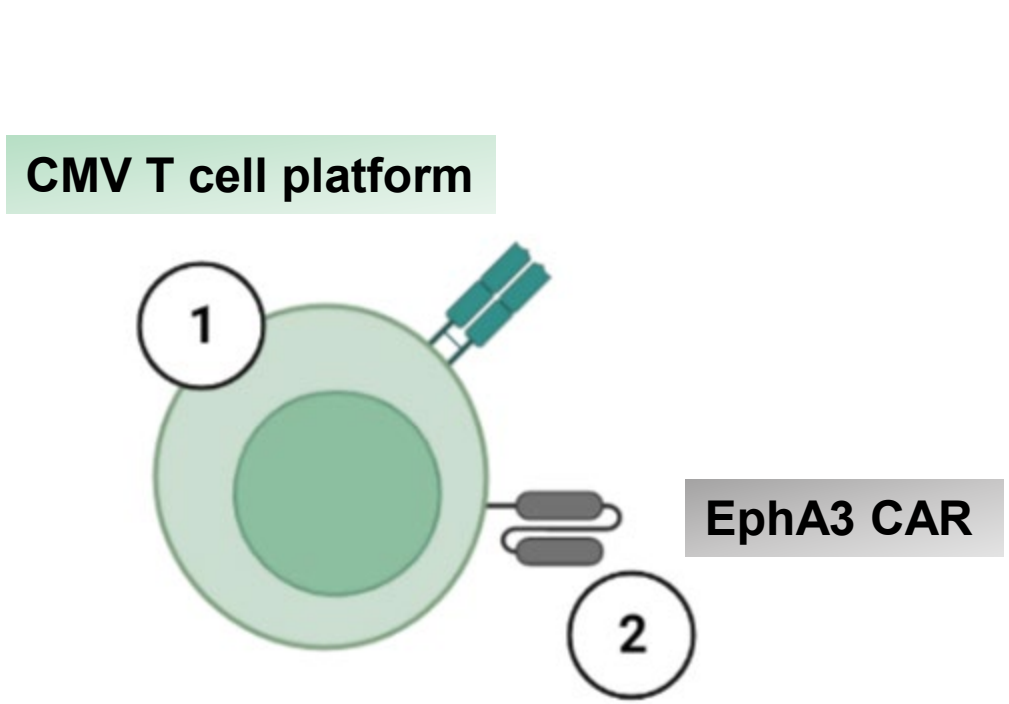




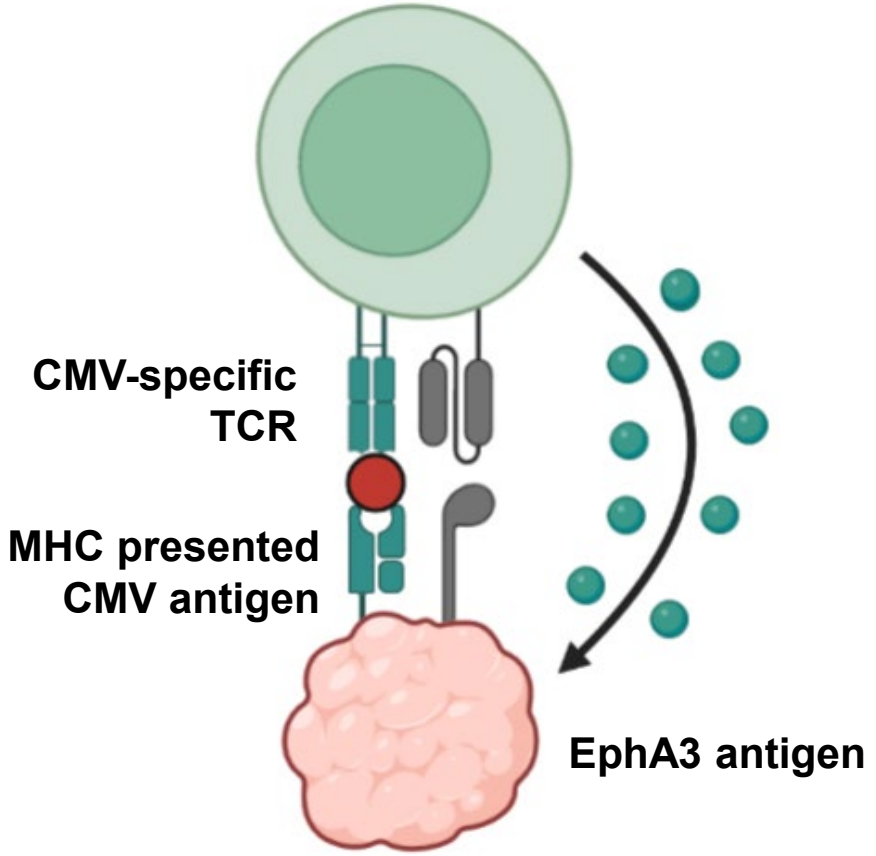


Next Step: The safety and efficacy of EphA3-CAR T cells are being studied in a PDX model of GBM

Cellular immunotherapy combining EphA3-CAR and CMV-specific targeting will augment tumour-specific immunity and prevent immune escape

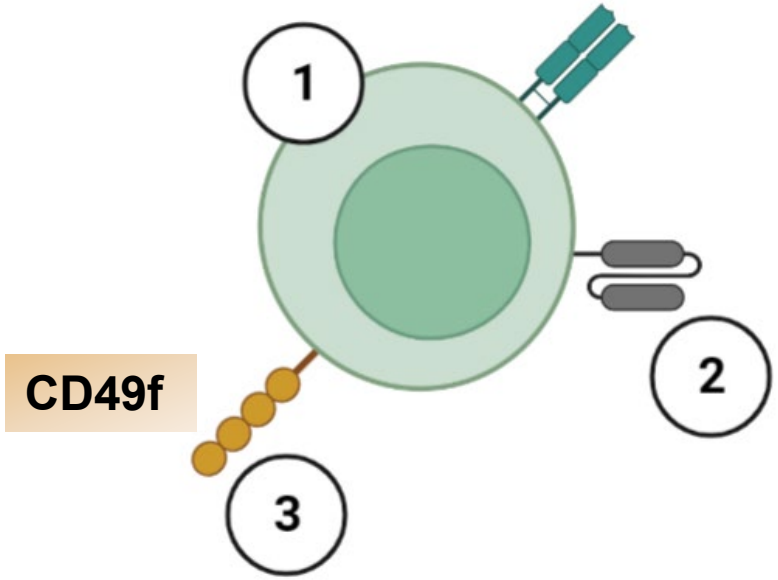


EphA3 CMV-specific CAR T cell

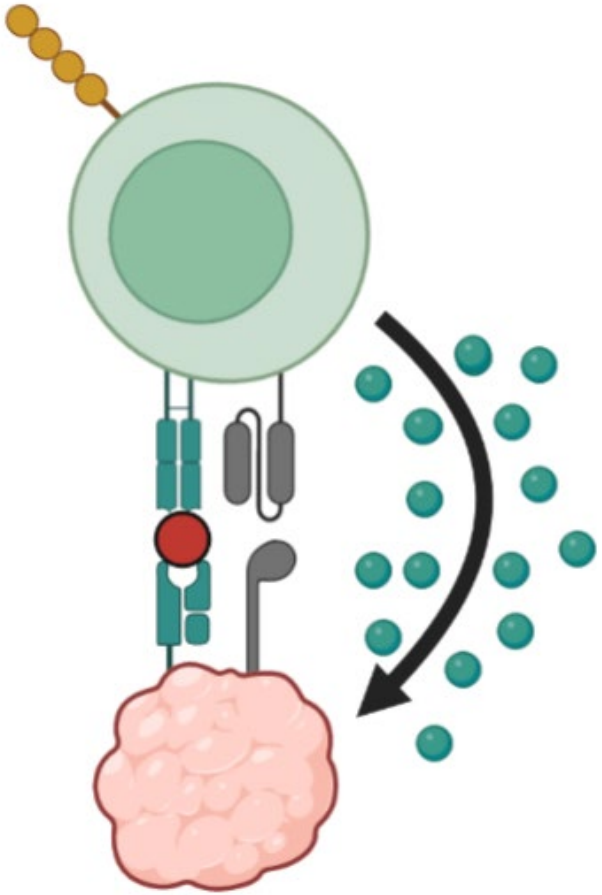


Tumour cell

Enrichment using the novel stemness marker CD49f will further enhance the efficacy of CMV-EphA3 CAR T cells



CD49f+ CMV EphA3 CAR T cell

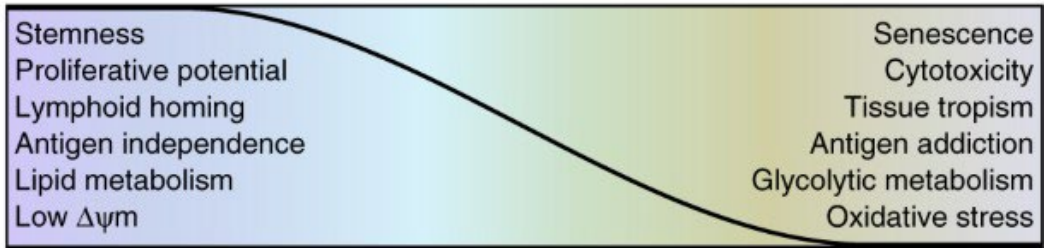


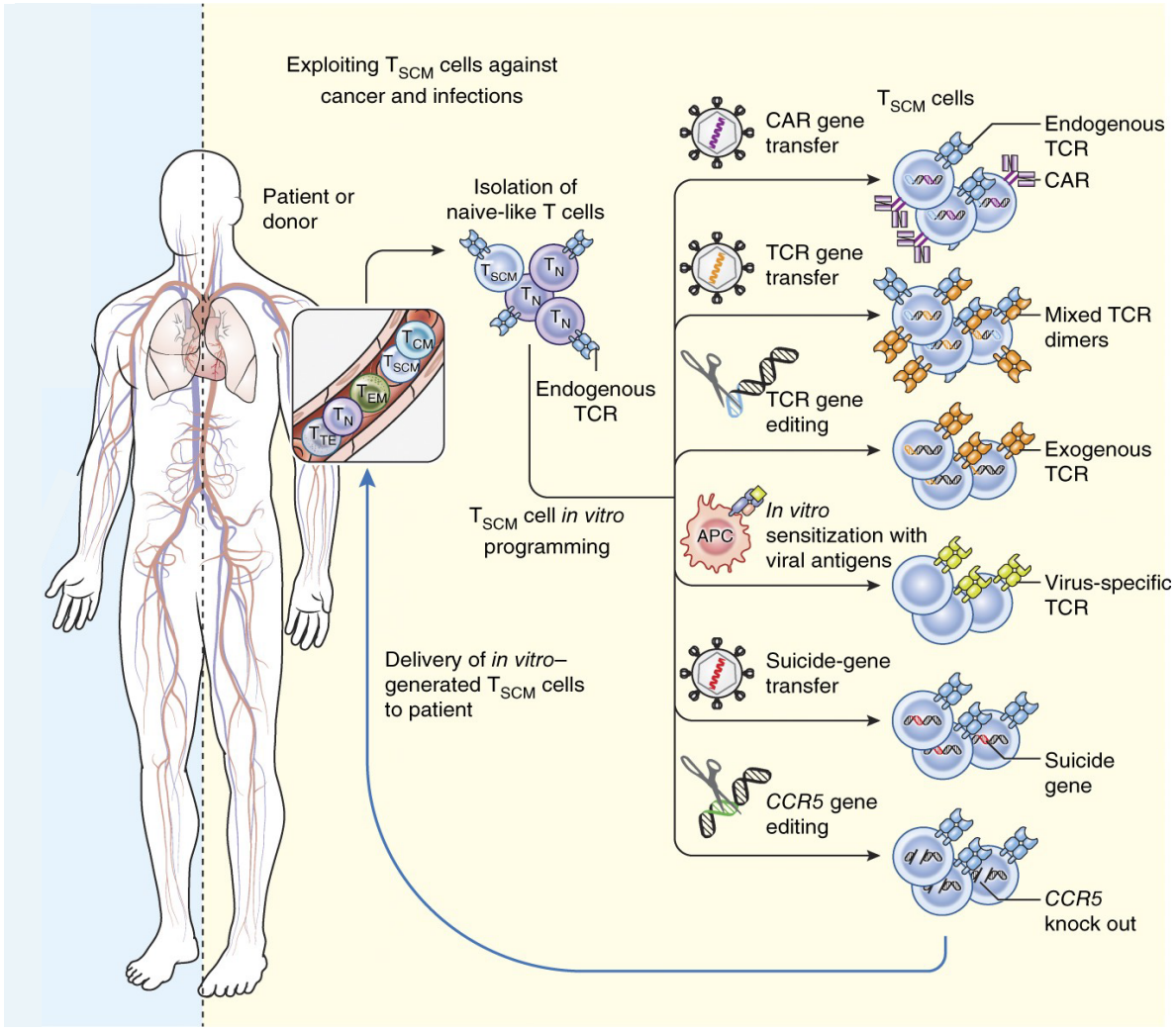
Tumour cell

CD49f is uniquely expressed on T memory stem cells

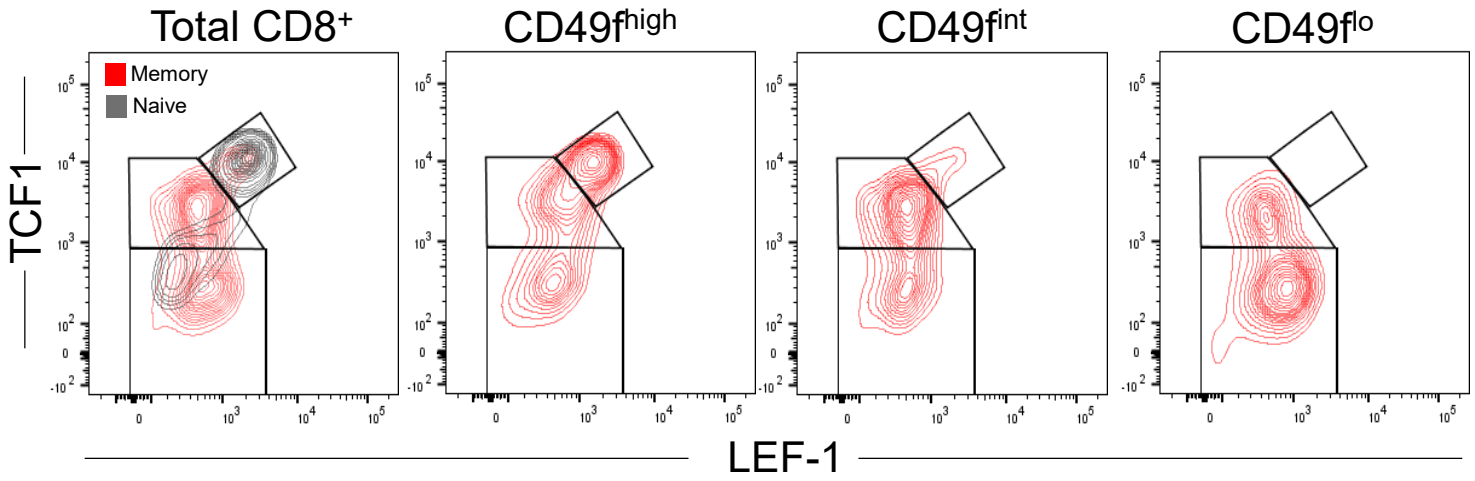
T memory stem cells (T_{scm}) have emerged as a powerful tool for improving CAR T cell therapy efficacy and safety

	T_N	T_{SCM}	T_{CM}	T_{EM}	T_{TE}
CD45RA	+	+	–	–	+
CD45RO	–	–	+	+	–
CCR7	+	+	+	–	–
CD62L	+	+	+	–	–
CD28	+	+	+	+/–	–
CD27	+	+	+	+/–	–
IL-7Rα	+	+	+	+/–	–
CXCR3	–	+	+	–	–
CD95	–	+	+	+	+
CD11a	–	+	+	+	+
IL-2Rβ	–	+	+	+	+
CD58	–	+	+	+	+
CD57	–	–	–	+/–	+

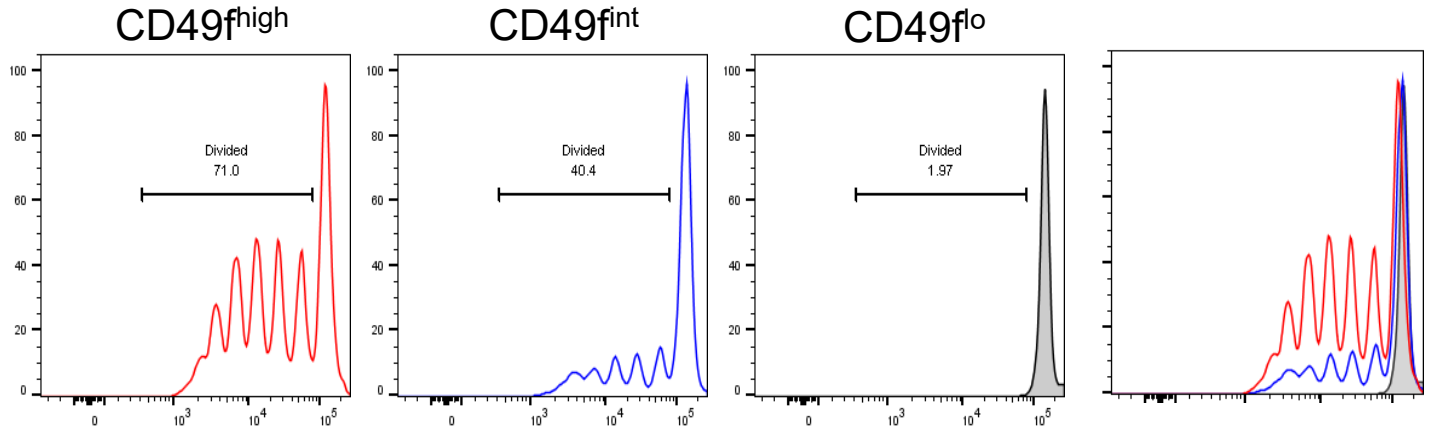




We identified CD49f as a marker for T_{scm}, and cells are more proliferative *in vitro*



anti-CD3/28



T_{scm} proliferation is known to drive long-term persistence

The CMV platform, EphA3 targeting and CD49f enrichment will combine to overcome hurdles in treating solid tumours with immunotherapy

Penetrates solid tumour tissue

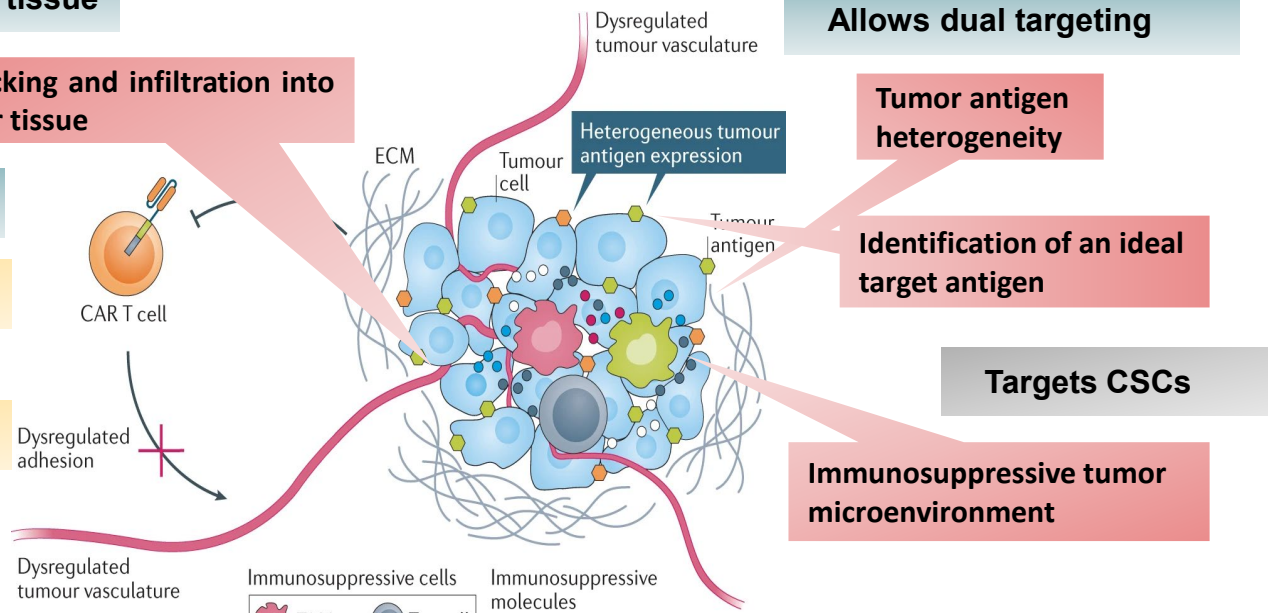
Traffics to brain

Trafficking and infiltration into tumor tissue

Improves cell persistence

Improves cell persistence

Increases proliferation



Allows dual targeting

Tumor antigen heterogeneity

Identification of an ideal target antigen

Targets CSCs

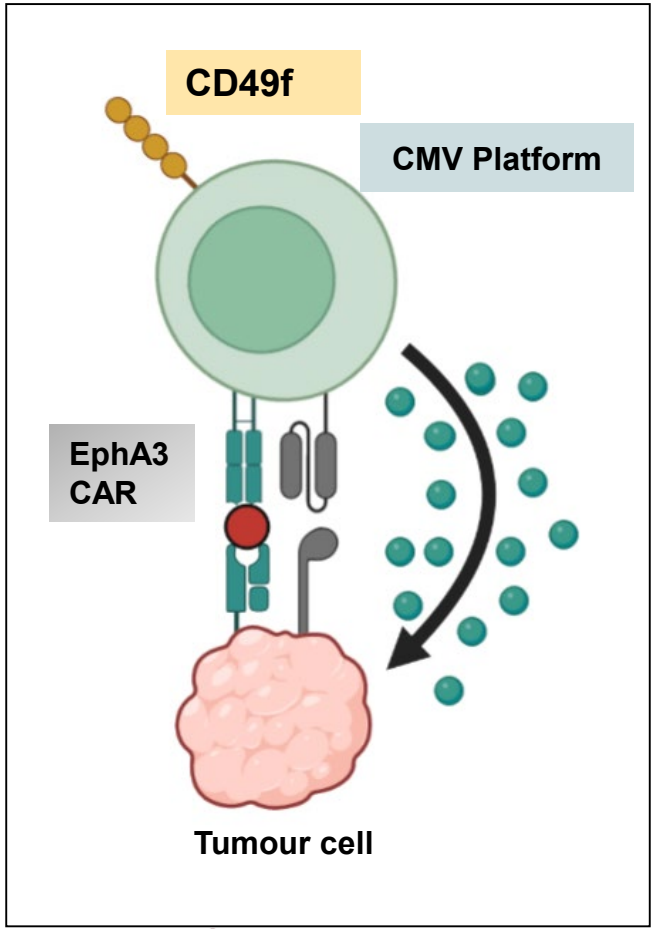
Immunosuppressive tumor microenvironment

Improved safety via reduced alloreactivity

Improves safety

Targets solid tumours

Off-the-shelf product
- Treatment without delay
- Defined cell population
- Broader coverage



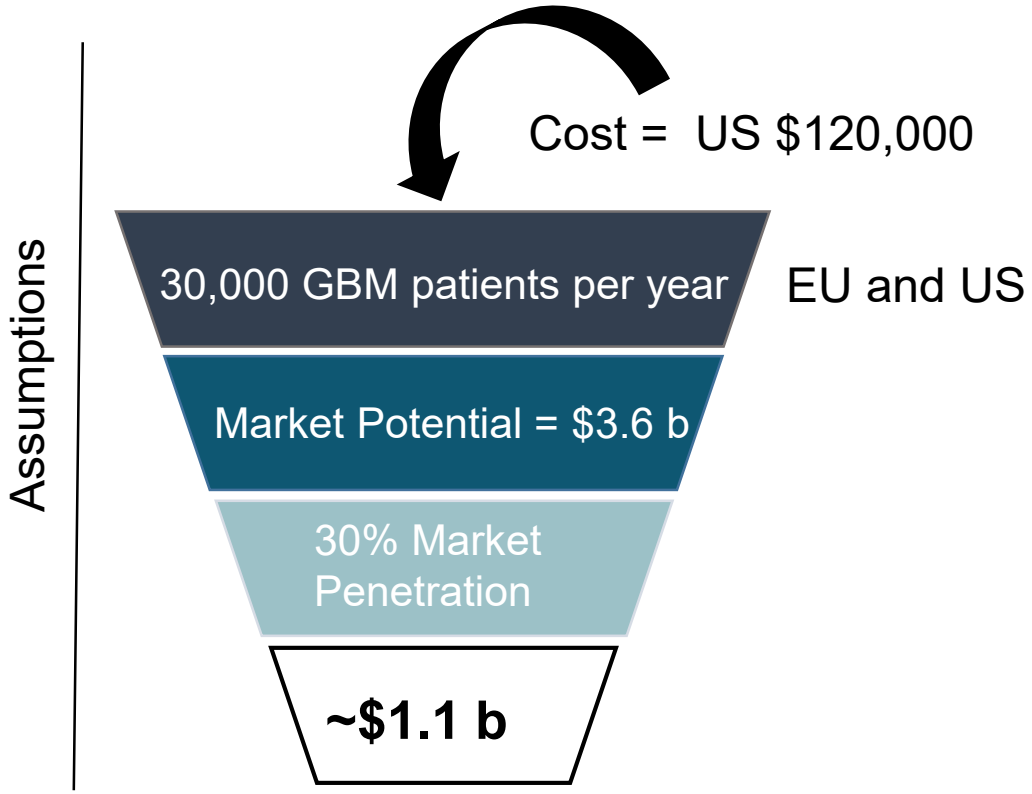
CMV EphA3 CAR T CD49f+ offers multiple advantages over competitors

		Allogeneic Platforms	
	Autologous CAR T for GBM	**Virus-specific T cell platforms**	**Non-T cell platforms**

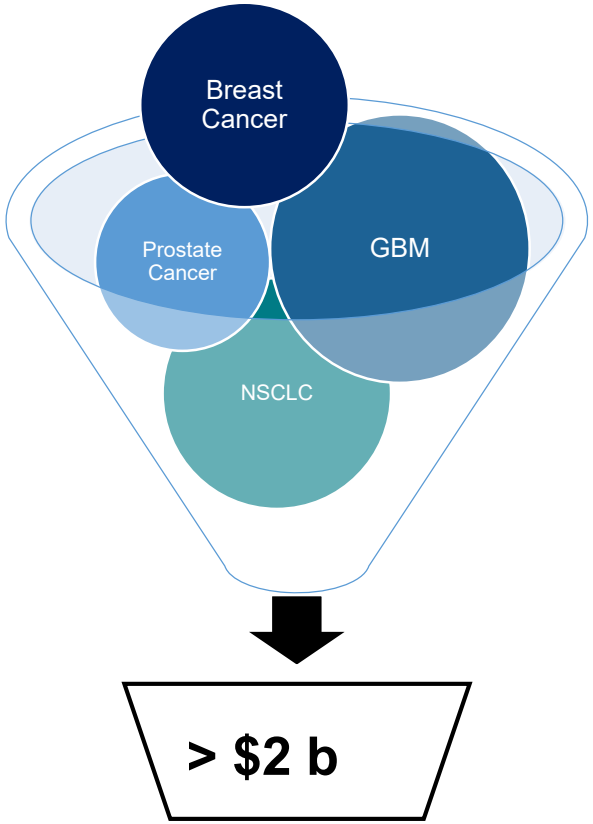
Competitor	Phase I clinical trials
	• 15 CAR T therapies (CD70, B7H3, EGFRIII, CD147)
	
	Phase II clinical trials (6)
	• HER2
	• EGFRIII
		Allogeneic EBV T cell platforms
		• Atara Biotherapeutics
		  • EBV CD19 CAR T, B cell malignancies (pre-clinical)
		• Tessa Therapeutics
		  • EBV CD30 CAR T for Hodgkin's Lymphoma (phase I)
			NK cells - NKarta
			
			IPSCs - Fate Therapeutics
			
			Gamma delta - Adicet Bio
			
			Macrophages

Advantage	**Off-the-shelf product** • **Reduced cost** • **Treatment without delay** • **Defined cell population** • **Broader coverage** • **Improved cell persistence** • **Targets CSC** • **Dual targeting**	• **CMV differentiated from competitors** • **CMV platform clinically validated in solid tumours** • **Disease indication distinct**	• **T cell modality is commercially validated** • **Platforms initially targeting hematological malignancies** • **More complex manufacturing**

There is an untapped market for an effective GBM therapy and potential to expand to multiple indications



GBM market for CMV EphA3 CAR T



Market expansion

GBM market expected to grow to USD 3.7 billion by 2028 at a CAGR of 8.8%

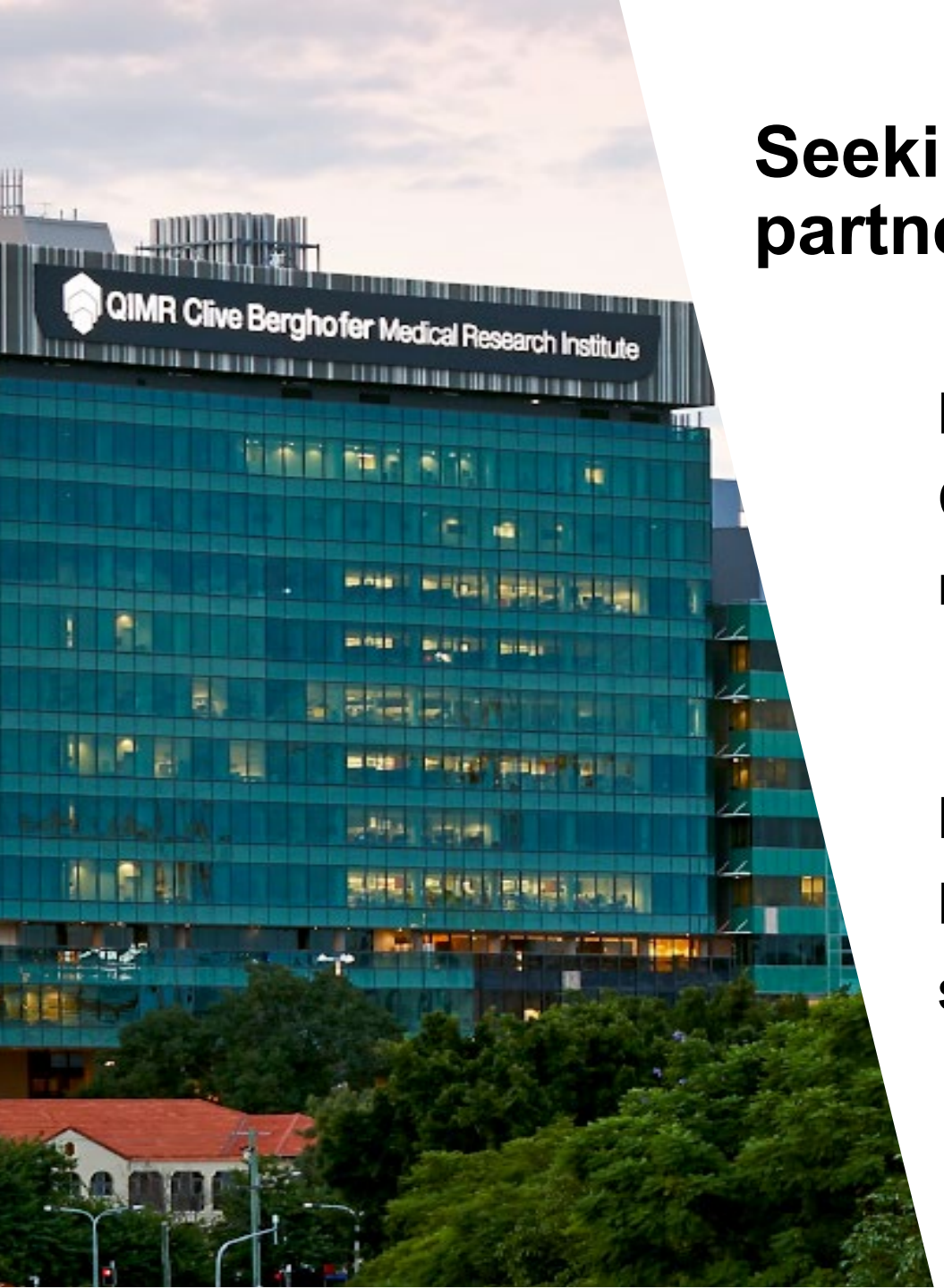
This project combines IP for the three components of the cell therapy; CMV CTLs, EphA3 targeting and CD49f cell enrichment

	Patent Title	PCT number	Priority Date	Status
CMV CTL	Adoptive T-Cell Therapy For CMV Infection and CMV-Associated Diseases	PCT/US2019/032688	25-08-2018	National Phase EU, US, AU, CN, JP, HK, CA
	CMV Epitopes	PCT/IB2017/000849	23-05-2016	National Phase US, CA, AU, CN, JP, CA
EphA3	Targeting EphA3 and uses thereof	PCT/AU2020/051090	09-10-2019	National Phase EU, US, AU, CN, JP, HK, CA, ZA, SG, KT, IL, IN
CD49f	Immune cells with Enhanced Function	PCT/AU2021/050374	17-04-2020	PCT

QIMR has also developed a product selection algorithm, to match off-the-shelf products to patients

Exclusivity Strategy

- Orphan drug exclusivity
  - 7 years in US, 10 years in EU
- New biologics exclusivity
  - 12 years in US, 10 years in EU
- Paediatric Exclusivity
  - 6 months added to any existing exclusivity



Seeking a licensing and development partner to progress the program

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