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CAR-T meeting – To hit solid tumours use a superCAR

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However remarkable initial response rates to CAR-T therapy continue to be in certain leukaemias it is a different story in solid tumours, which for several reasons remain an extremely tough nut to crack.

But not for want of trying, as the inaugural Clinical Applications of CAR-T Cells meeting at Memorial Sloan Kettering Cancer Center (MSKCC) in New York heard last week. It seems clear that a standard CAR-T approach will not cut it, and groups associated with Juno and Novartis are leading the way in constructs that either have a novel design or that incorporate extra elements to boost activity.

Dr Steven Albelda of the University of Pennsylvania – Novartis's partner – outlined the problem: CAR-T cells are inefficiently trafficked to solid tumours, he said, and an immunosuppressive tumour microenvironment, where multiple inhibitory factors are present, damps down T-cell function.

One of his ideas is a chimaeric switch receptor that could boost the efficacy of CAR-T cells in solid tumours by converting a negative PD-1 signal into a positive one.

He also presented a CAR designed additionally to express the protein RIAD. This construct, he said, could make the T cells resistant to the immunosuppressive effects of adenosine and PGE2 – the two most powerful factors in the tumour microenvironment.

In a keynote address Dr Michel Sadelain, whose work at the MSKCC is linked with Juno, spoke about the need to improve on the current second-generation CAR constructs.

Interestingly, he said he had "reservations" about third-generation constructs, which incorporate two co-stimulatory domains instead of one, and an example of which is in clinical development at Sweden's Uppsala University.

Instead, he is putting his faith in a fourth-generation construct, in which a 4-1BB ligand is expressed on the T cell – separately from the CAR construct. His aim is now to take this into the clinic.

Dr Sadelain suggested that solid tumour CAR-T therapy was only the first stage of progressing beyond CD19 antigen-based cancers. He sees future potential in infectious and autoimmune diseases – for instance using T regulatory cells – and further still CAR therapy has potential in regenerative medicine.

The antigen problem

That said, none of this solves a separate issue – that solid cancers generally lack tumour-specific cell-surface antigens that can be targeted with CAR-T therapy.

Two studies show the problem: a patient on an NCI trial of a Her2 CAR died – likely because this antigen is also expressed on lung endothelium – causing a suspension of Her2-directed CAR-T studies; and a trial of Novartis's CART-meso produced underwhelming efficacy (*AACR – Solid tumour CAR-T foray lives up to its low-key billing, April 20, 2015*).

But this has not stopped work on either antigen. Aurora Biopharma is still targeting Her2 with Baylor College, though when studies restarted after the patient death it was at what Baylor's Dr Stephen Gottschalk called a "homeopathic dose".

A related approach – targeting ErbB dimers – is being pursued by Leucid Bio, and early data in four patients has shown promising hints. One key here seems to be intratumoural delivery, which results in the T cells remaining fairly localised and thus avoiding adverse events in the lung (*Interview – Leucid Bio swings for the fences in CAR-T, December 15, 2016*).

Selected solid tumour CAR-T studies					
Antigen	**Indication**	**Group**	**Trial ID**	**Note**	**Data**
EGFRvIII	Glioblastoma	NCI*	NCT01454596		
EGFRvIII	Glioblastoma	Penn/Novartis	NCT02209376		8 pts treated; signs of antigen elimination, no responses
IL13Rα2	Glioblastoma	City of Hope	NCT02208362	Ligand CAR, not using ScFv	No grade >3 tox, no cytokine release syndrome or neurotox
Her2	Glioblastoma and sarcoma	Baylor/Aurora	NCT02442297		19 sarcoma pts: 4 SDs, 13 PDs; 17 glioblastoma pts: 1 PR, 7 SDs, 9 PDs
ErbB dimers	Head & neck cancer	King's/Leucid Bio	NCT01818323	Ligand CAR (T1E), not using ScFv	4 pts treated; transient tumour regression/symptomatic improvement, safety
Mesothelin	Mesothelioma	Penn/Novartis	NCT02159716		4 SDs in first 6 pts treated
Mesothelin	Mesothelioma, lung, breast cancers	MSKCC	NCT02414269	Includes Bellicum's caspase-9 suicide switch	40 pts screened, 4 enrolled, 2 treated
Mesothelin	Mesothelioma	Penn/Novartis	NCT01355965	mRNA CAR	
Mesothelin	Pancreatic cancer	Penn/Novartis	NCT01897415	mRNA CAR	10 pts enrolled, 6 treated; 2 SDs, 4 PDs
Muc16	Ovarian cancer	MSKCC/Juno	NCT02498912	IL12-secreting "armored" CAR	3 pts screened, none recruited yet
L1-Cam	Neuroblastoma	Seattle Children's/Juno	NCT02311621		
cMet	Breast cancer	Penn/Novartis	NCT01837602	mRNA CAR	
*Notes: *CRADA with Kite Pharma; SD=stable disease; PD=progressive disease; PR=partial response.*					

Others want to make the most of the few remaining amenable targets. Juno's study with a CAR against Muc16, for instance, is the group's first attempt at taking an "armored" CAR into the clinic.

In this case the T cells are additionally made to express the cytokine IL12, which it is hoped will induce T-cell response, enhance expansion and perhaps even overcome inhibition mediated by T regulatory cells.

MSKCC's Dr Renier Brentjens, a scientific founder of Juno, picked up Dr Albelda's theme of jazzing up CARs to overcome the shortcomings, proposing two further "armored" CARs: CAR-T cells that additionally express CD40 ligand, and those that deliver checkpoint blockade.

But Dr Roisin O'Cearbhaill, the primary investigator of the anti-Muc16 trial, cautioned that inducing IL12 release could have toxic effects on the lung, liver and intestine, possibly causing death. This is one reason why MSKCC has designed into this CAR a "suicide gene", based on the expression of a truncated EGFR that could be triggered by Erbitux.

But is in any way a realistic safety switch? Doctors have so far not dared use it in the clinic, fearing the inflammatory effects of Erbitux in very sick patients. The Fred Hutchinson Cancer Center's Dr Cameron Turtle put it bluntly: "It's a nice idea," he told the meeting, "But I'm nervous about [infusing] Erbitux."

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