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Interview – Leucid Bio swings for the fences in CAR-T

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It is one thing for an academic institution to launch a company focusing on the complex field of CAR-T therapy, but for this group to begin a clinical trial with nothing more than grant funding seems particularly impressive. Yet this is what Leucid Bio, a spin-out of the UK's King's College, managed when in June it put its CAR-T therapy into the first patient in a study at Guy's Hospital.

More amazing still is that the group has no truck with the low-hanging fruit of leukaemia or the CD19 antigen. "The angle that we have taken has very much focused on solid tumours," Leucid Bio's chief scientific officer, Dr John Maher, tells *EP Vantage*. "That's where 90% of the cancer is, and 95% of the unmet need."

Over the past two years CAR-T therapy has scored numerous successes, leading to the formations of billion-dollar biotechs like Juno and Kite Pharma. But these have primarily focused on targeting CD19, which by virtue of being expressed on B cells allows treatment of B-cell malignancies like acute lymphoblastic leukaemia (ALL).

Huge leap

Extending CAR-T therapy beyond leukaemia is tough, largely because of the immunosuppressive microenvironment that surrounds many tumours, and a lack of available targets. Dr Maher makes no secret of the difficulty, calling solid cancers "a huge leap".

The Leucid Bio study, of which he is principal investigator, aims to recruit 21 head and neck cancer patients, and enrolled its fourth participant a week ago. So far there have been no dose-limiting toxicities in this dose-escalation trial, with "some hints of biological activity", says Dr Maher.

His CAR-T project, T1E28z, is unusual in that it targets not one antigen but several – namely eight of nine homo and heterodimers formed by the ErbB family. "It's pretty difficult to find a solid tumour that you cannot target with this CAR, at least *in vitro*," says Dr Maher.

"But the obvious elephant in the room is how you can ever conceive of doing this safely." He cites an NCI study of an ErbB2 CAR that produced serious adverse events, though he reckons he has a chance of avoiding this. For one thing he is not lymphodepleting his patients, hoping this way to avoid toxicity through uncontrolled expansion and sustained engraftment of CAR-T cells.

Perhaps most important is the intratumoural delivery he uses, based on his finding in mice that this route avoided toxicity – in contrast to putting CAR-T cells into the peritoneal cavity, which induced cytokine storm. "That led us to propose potential for eking out a therapeutic window," he states. "The hope [is] that the cells would remain in the tumour where the target is expressed."

Apart from the targeting moiety the second-generation construct is the same as that used in Juno's JCAR015, a CAR Dr Maher helped design when working in Dr Michel Sadelain's lab at Memorial Sloan Kettering Cancer Centre.

Clever

There is another clever aspect to Leucid Bio's rationale that differentiates T1E28z from others: the addition to the CAR-T cells of a receptor that renders them responsive to the cytokine IL-4.

This means that only the genetically engineered cells will grow during the manufacturing process on exposure to IL-4, enabling Dr Maher's team to obtain good transduction rates even in lymphopenic patients – those with extremely low T-cell counts.

Low cell counts is a known problem in very young ALL patients, leading to production failures in a recent Novartis study of CTL019. While Leucid Bio is dealing with the opposite end of the spectrum – elderly people – the issue is the same.

Of course, Leucid Bio is not the first group to go after solid tumours with CAR-T: the NCI's GS2 CAR-T and

Novartis's CART-meso disappointed in neuroblastoma and mesothelioma respectively. Juno is running a neuroblastoma trial with JCAR023, targeting L1-CAM, the NCI has an EGFRvIII CAR-T in glioma, while Bellicum plans to go into pancreatic cancer with BPX-601, a CAR-T against PCSA.

"It's very, very difficult to identify safe targets," says Dr Maher. "We need to be thinking about developing strategies to identify therapeutic windows, treading a fine line between a target that's upregulated on a tumour but expressed at lower levels on healthy tissue."

A separate question is why Dr Maher is not looking at engineered T-cell receptors (TCRs), which groups like Adaptimmune and Kite have opted for in solid tumours. But he points to limited TCR applicability owing to HLA restriction, as well as the low affinity of many natural TCRs and the risk of unexpected cross-reactivity.

No money

As far as attracting venture finance goes Leucid Bio is still talking to investors, with "no money in the company yet". And it faces a major obstacle: "Unfortunately when we developed a number of the molecules like the ErbB CAR and the IL-4 expansion system there was no interest in protecting them," says Dr Maher.

"There isn't IP surrounding the [head and neck cancer] trial, which makes commercialisation not impossible but a little more difficult. But there is a pipeline that is being properly protected, so hopefully in the future we will have things we can commercialise through Leucid Bio."

Funding for the study came from the Wellcome Trust and the JP Moulton Charitable Foundation. Thus Leucid Bio became the second UK CAR-T player to emerge from stealth mode this year, after the UCL spin-out Autolus, though this seems not yet to have entered the clinic (*Interview – UK CAR-T player enters in stealth mode, January 23, 2015*).

Dr Maher stresses that he was first: "We were doing CARs before UCL here at King's in 2004. Of course at that time nobody had any interest in CAR-T cells."

Project	Study	Trial ID
T1E28z CAR	21 pts with squamous head & neck cancer not suitable for conventional active therapy	NCT01818323

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