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Autolus takes its first baby steps into the clinic

Jacob Plieth

The private UK company Autolus has been very reluctant to reveal what it is up to since emerging as a stealth player in cell therapy almost three years ago, but slowly information has dribbled out.

Today it went public with news that its first two CAR-T assets have entered the clinic in haematological malignancies. Close followers of scientific meetings will of course already be familiar with the projects in question, as well as with the fact that these represent just the tip of the iceberg of what Autolus and UCL's Martin Pule, the scientific brains behind the group, has planned.

At first sight the projects might not seem all that revolutionary; one hits BCMA – by now a hot antigen in cell therapy work targeting multiple myeloma – and the other the well-established targets CD19 and CD22, in leukaemia and lymphoma.

New twist

But the multiple myeloma asset, which Autolus now calls Auto2, takes a new twist on BCMA, using the April protein to bind both BCMA and the related antigen Taci. BCMA tends to be present on plasma cells – the cells whose proliferation is responsible for multiple myeloma – while Taci is involved in plasma cell differentiation.

Autolus claims that Auto2 is the first dual-targeting CAR-T therapy in the clinic for multiple myeloma. This appears not to be correct – at Asco the Chinese group Nanjing Legend Biotech presented promising multiple myeloma data with a bispecific CAR against BCMA and CD38 (*Asco – Mystery Chinese group gives Bluebird a run for its money, June 5, 2017*).

Of course, Autolus's construct is not bispecific; it is just that its binder happens to hit two antigens, as detailed in a preclinical presentation at Ash 2016. This could open up the possibility of toxicity – it might recognise additional proteins, or one or both of these antigens could be present on non-cancer cells.

A bispecific of sorts is what Autolus is working on with its next CAR, which comprises two constructs targeting the B-cell proteins CD19 and CD22, expressed using a single vector. The idea is not novel: some patients with B-cell malignancies relapse by loss of CD19, and one strategy is to treat them with an anti-CD22 CAR, which is the thinking behind Juno's JCAR018, for instance.

The theory is that using a bispecific CAR can delay relapse, as either one or other antigen can trigger its activity. The NCI is working on a true anti-CD19/CD22 bispecific – a single construct with two binding domains – but this has yet to enter the clinic, and at its last presentation researchers said this project still needed refinement.

A poster at this year's International Conference on Malignant Lymphoma revealed that the Autolus CAR, named Auto3, is slightly more advanced. It uses humanised binding domains, which might help increase persistence, and either an Ox40 or (the more common) 4-1BB co-stimulatory domain.

Clinical work

Auto2 has completed dosing in an undisclosed first cohort of an 80-subject study, while Auto3 has entered safety trials in acute lymphoblastic leukaemia and diffuse large B-cell lymphoma.

If these still seem like relatively basic ideas, according to Mr Pule's scientific presentations Autolus is working on far more advanced concepts. These include CARs against the T-cell receptor, and logic-gated bispecific CARs whose activation might depend on both antigens being present, or on one but not the other.

After an initial period in stealth mode Autolus last year named Christian Itin, the former head of Micromet, chief executive, and raised £40m ($54m) in a series B round that included Woodford Investment Management. The company is now one of the more important holdings in the ailing Woodford portfolio.

Its private backers can rest assured that there is plenty more to come.

Autolus CAR-T projects in the clinic				
Project	**Antigens targeted**	**Study**	**Design**	**Eudra CT ID**
Auto2	BCMA & Taci (via April)	April	80 multiple myeloma pts	2016-003893-42
Auto3	CD19 & CD22 bispecific	Amelia	50 ALL pts	2016-004680-39
Auto3	CD19 & CD22 bispecific	Alexander	120 DLBCL pts	2016-004682-11

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobPlieth on Twitter