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Zelluna joins the adoptive cell therapy chase

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As the tiny Norwegian biotech gears up to put its first asset into the clinic, investors could use an ongoing trial to handicap its chances of success.

Engineered T-cell receptors have spent years overshadowed by CAR-T therapy, but they are bidding to capture investors' imaginations again. One of the newest entrants, Norway's Zelluna, will test the market's appetite when it goes out to raise cash next year before starting its first clinical trial.

The study will be a key test of Zelluna's approach, based on exclusive rights to Oslo University Hospital's biobank of cancer vaccine "super responders" for development as engineered T-cell receptor (TCR) therapeutics. A prototype is already in the clinic in the university's own trial, and data generated could be used to gauge the chances of the company's autologous therapy.

The university's trial started this year, and is testing an engineered TCR against the TGFβRII antigen in colorectal cancer. The TCR in question was isolated from the biobank, and has the same target as the project that Zelluna will aim to put into the clinic in early 2020.

The private company's chief executive, Miguel Forte, urges caution with readacross, telling *Vantage* that there are key differences between an academic study and one using an industrial manufacturing process, as Zelluna aims to do via a tie-up with Masthercell. But the university's "clinical data will give valuable information", he states.

The biobank, established 10-15 years ago, comprises clinical material from patients with advanced solid cancers who had been treated with vaccines against KRAS, hTert and TGFβRII.

Across the population no particular benefit was evident, but some of these patients – "super responders" – showed unexpectedly long survival. Mr Forte characterises them as having experienced a "very good, long-term sustained immune response with a memory component plus a corresponding long-term clinical benefit.

"Cells isolated form those patients were cloned and expanded. The TCR from the cells that recognised peptides used in the vaccines are now being used through gene modification via a lentiviral vector to provide an adoptive cell therapy."

TCR entrants

Zelluna is thus the latest of several groups to step up TCR activity. Last month Regeneron took a $100m equity stake in Bluebird Bio under a tie-up focusing on six undisclosed TCR targets, and Medigene, a more established player, signed up Structured Immunity to improve an in-house TCR's specificity and recognition properties.

If this is a sign of renewed interest after the stunning successes of CAR-T therapy in haematology then investors must bear in mind the complexity. One problem is that, unlike CARs, TCRs only recognise antigens presented on a target cell’s major histocompatibility complex; in humans many different haplotypes of this complex exist, and so each product must be matched appropriately.

Another is finding TCRs with just the right level of target affinity. In contrast to Adaptimmune, which aims to enhance the affinity of its TCRs, Zelluna reckons some cell clones in the Oslo biobank are already evolved into memory cells with affinities in the desired range.

“We are in a serendipitous position,” says the chief exec. A further twist is that a large number of the TCRs in the biobank have turned out to be class II restricted, meaning that they can be engineered onto patients' CD4+ T cells.

Zelluna believes that this is vital to hit solid tumours because of the broad immune system stimulation elicited by CD4+ cells, sometimes called T helper cells.

Meanwhile, most engineered TCR work has focused on class I constructs and CD8+ (cytotoxic) T cells. At present the only clinical-stage engineered TCR asset focusing on CD4+ T cells seems to be the NCI’s TCR against Mage-A3.

Selected engineered TCR projects				
Company/group	**Project**	**Target**	**Status**	**Trial ID**
Adaptimmune	MAGE-A10 TCR	MAGE A10	Phase I	NCT02592577
	MAGE-A4 TCR	MAGE A4	Phase I	NCT03132922
	AFP TCR	Alpha-fetoprotein	Phase I	NCT03132792
Gilead	KITE-718	MAGE A3/A6	Phase I	NCT03139370
	KITE-439	HPV-16 E7	Phase I	NCT02858310
	KRAS TCR	G12V variant of mutated RAS	Phase I	NCT03190941
	SSX2 TCR	SSX2	Preclinical	NA
NCI (NIH)	HPV-16 E6 TCR	HPV-16 E6	Phase I	NCT03197025
	MAGE A3 TCR	MAGE A3	Phase I	NCT02153905
Glaxosmithkline	GSK3377794	NY-ESO-1	Phase I	NCT02992743
	PRAME TCR	PRAME	Preclinical	NA
Celgene	JTCR016	WT-1	Phase I	NCT02408016
Bellicum	BPX-701	PRAME (rimiducid-activated suicide switch)	Phase I	NCT02743611
Cell Medica	CMD-602	WT-1	Phase I	NCT02550535
	CMD-601	Survivin	Preclinical	NA
Tmunity	NYCE T cells	NY-ESO-1 (Crispr-edited, TCR-deleted, PD-1-deleted)	Phase I	NCT03399448
Immatics	IMA201	Undisclosed	Phase I	NCT03247309
	IMA202	Undisclosed	Phase I	NCT03441100
Medigene	MDG1011	PRAME	Phase I	NCT03503968
	TCR-IIT	MAGE A1	Preclinical	NA
Medigene/Bluebird	None	Six undisclosed targets	Preclinical	NA
Regeneron/Adicet Bio	None	Undisclosed targets for allogeneic use	Preclinical	NA
Regeneron/Bluebird	None	Six undisclosed targets	Preclinical	NA
Zelluna	TCR-CRC-001	TGFβII	Preclinical	NCT03431311
Source: company filings & clinicaltrials.gov.				

If autologous TCR-based adoptive cell therapy were not enough Zelluna has two other tricks up its sleeve. “A platform around off-the-shelf products, using NK cells as a vehicle for our TCRs, is integral to our strategy,” says its chief scientific officer, Namir Hassan. “The third arm is a soluble TCR approach.”

Despite a surge in interest three years ago NK therapeutics have made barely any progress, however, as problems handling the cells in manufacturing became apparent. As Mr Hassan was until recently a vice-president of Immunocore, soluble TCRs might be expected to play a more prominent role at Zelluna, though he cautions that the initial focus is adoptive cell therapy.

Zelluna might also want to distance itself from the problems at Immunocore, which has seen five senior

executives exit since February (*Amid Immunocore's C-suite bloodletting Glaxo provides solace, August 20, 2018*). There is no suggestion that the technology is flawed, but sources close to Immunocore have told *Vantage* of ideological differences while the company burned through most of its record $320m raise in just three years.

For Zelluna, which so far has attracted just $8m of start-up funding, raising too much cash would be a nice problem to have.