Evaluate Vantage

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Crispr: nice valuation, but where's the clinical trial?

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It will have escaped few people's attention that the combined valuation of the three listed Crispr companies more than tripled over the past year, and now stands at nearly $6bn. And yet, despite the promises, none has even a clinical trial to show for it.

The latest disappointment came yesterday, when Crispr Therapeutics – which claims to be the leader by timeline – said the US FDA had slapped a clinical hold on its Vertex-partnered lead. Even after opening down 8% today this company is still worth $3bn; there is just one enrolling western trial of a Crispr-based therapy, and ironically it does not feature any of the three listed players (see table below).

This study is being run by the private group Tmunity Therapeutics, and strictly speaking does not involve a Crispr-based gene therapy. Rather, it tests the *ex vivo* modification of autologous NY-ESO-1-directed T cells to edit out PD-1 and their endogenous T-cell receptors; these cells are then reinfused into a patient to stimulate an anti-tumour response.

Even that was a long time coming. The NIH's recombinant advisory committee had given Tmunity the go-ahead in mid-2016, but it took a year before an IND was filed; according to Clinicaltrials.gov the trial only started enrolling patients this month, and it is not clear whether any have yet been treated.

Late

Crispr Therapeutics managed to file its own US IND last month, but according to yesterday's statement this has been set back by the FDA raising "certain questions". Investors will note that it is only months since a scientific paper suggested that most people might be immune to Crispr Cas9 (*JP Morgan interview – Crispr hopes its CAR will overtake Cellectis, January 12, 2018*).

Editas, at whose JP Morgan presentation this issue was raised, still maintains that the IND for its first project, against a form of inherited blindness, will be filed in mid-2018; if this happens it will come six months later than originally planned.

Meanwhile Intellia, the last of the listed Crispr trio, has yet to undertake IND-enabling activities. It had earlier planned to begin these in mid-2018, but its last presentation simply stated 2018 as the timeframe.

Selected US-focused Crispr players				
Project	**Sponsor**	**Status**	**Detail**	**Trial ID**
NY-ESO-1 eTCR	Tmunity	Recruiting	TCR-deleted, PD-1-deleted T cells, various cancers	NCT03399448
CISH-inactivated TILs	NCI	Not yet recruiting	Gastrointestinal cancers	NCT03538613
CTX001	Crispr Therapeutics/Vertex	IND on clinical hold	Sickle cell disease (EU β-thalassaemia study to start H2 2018)	(none)
EDIT-101	Editas	IND filing mid-2018	Leber congenital amaurosis	(none)
CTX101	Crispr Therapeutics	IND filing end 2018	Anti-CD19 CAR-T	(none)
ATTR programme	Intellia/Regeneron	IND-enabling trials 2018	Transthyretin amyloidosis	(none)
P-BCMA-ALLO1	Poseida/J&J	Preclinical	Allogeneic CAR-T, using Cas-Clover	(none)
Not yet defined	Beam Therapeutics	Preclinical	Claims to be able to make single-base corrections	(none)
Source: Clinicaltrials.gov & company materials.				

With the US timeline slipping so badly it might come as a surprise that the only other near-term Crispr trial has nothing to do with industry.

This is to be run by Dr Steve Rosenberg's surgery branch at the NCI, and involves autologous tumour-infiltrating lymphocytes with the gene coding for CISH, the cytokine-inducible SH2-containing protein, edited out. A Clinicaltrials.gov entry that appeared just this week says this study should start in June.

Clinicaltrials.gov also lists six Crispr trials actively enrolling patients in China. There are likely many more that have not been filed with the US registry, and thanks to a favourable regulator and relatively low chances of litigation China might lead western markets in Crispr for some time.

Then there is a broader problem, namely a long-running Cas9 patent dispute between the Broad Institute and the University of California, Berkeley. Judging by the slow pace of development, however, intellectual property is not the first thing Crispr-focused investors have to worry about.

Disclosed clinical trials involving Crispr in China				
Project	**Sponsor**	**Status**	**Detail**	**Trial ID**
CCR5-modified CD34+ cells	Peking University	Recruiting	HIV-infected subjects with haematological malignances	NCT03164135
CD19 CAR-T	Chinese PLA General Hospital	Recruiting	Allogeneic, CD19+ve leukaemia & lymphoma	NCT03166878
Dual-specificity CD19/CD20/CD22 CAR-T	Chinese PLA General Hospital	Recruiting	Allogeneic, leukaemia & lymphoma	NCT03398967
PD-1-knockout T cells	Anhui Kedgene Biotechnology	Recruiting	Oesophageal cancer	NCT03081715
PD-1-knockout T cells	Chengdu Medgencell	Recruiting	NSCLC	NCT02793856
PD-1-knockout EBV-CTLs	Nanjing Uni Medical School	Recruiting	EBV-associated malignancies	NCT03044743
PD-1-knockout T cells	Cell Biotech	Not yet recruiting	Muscle-invasive bladder cancer	NCT02863913
PD-1-knockout T cells	Cell Biotech	Not yet recruiting	Castration-resistant prostate cancer	NCT02867345
PD-1-knockout T cells	Cell Biotech	Not yet recruiting	Renal cell carcinoma	NCT02867332
Source: Clinicaltrials.gov.				