Evaluate Vantage

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Vantage View – Behind the hype, Crispr is a story of slow progress and acrimony

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Some people reading this morning's mainstream press headlines about a Nature paper describing the correction of a germline mutation using Crispr might be excused for thinking that we are entering a Gattaca-like world of designer babies.

The truth, as is often the case, is more prosaic. So far an acrimonious patent case over Crispr has progressed further than have attempts to get this research tool into US human clinical trials. But this is not to say that the Nature study will necessarily harm market valuations of the three listed Crispr-focused biotechs.

And this, perhaps, is the point. As long as Crispr continues to capture the imagination of the general public – getting into a taxi outside a scientific congress and being engaged by the driver in conversation about Crispr is already reality – these groups will have no trouble raising cash, however little real progress they might be making.

Where is that study?

It is roughly a year after the much-publicised Nasdaq flotations of three US Crispr-focused companies: Editas Medicine, Intellia and Crispr Therapeutics. True, R&D pipelines of sorts have emerged, and Crispr Therapeutics claims still to be on track to file a US IND for a clinical trial late this year.

But Intellia has yet to start IND-enabling studies, while Editas delayed its first IND filing to mid-2018, citing a manufacturing setback. And the sector has been embroiled in a patent dispute that attests to the breadth of Crispr use by academics before this gene-editing technology was spun into commercial enterprises (*Patent twists and turns make Crispr no easier to value, February 16, 2017*).

Selected Crispr-edited gene therapy projects		
Project	**Crispr mechanism used**	**Timeline**
Crispr Therapeutics ($670m mkt cap, +19% since IPO)		
Beta-thalassaemia	Knock Out (KO) (ex vivo)	IND filing late 2017; partnered with Vertex
Sickle cell	KO (ex vivo)	Partnered with Vertex
MPS-1 & SCID	KO, insertion (ex vivo)	
Glycogen storage disease & haemophilia	KO, insertion	
Duchenne muscular dystrophy & cystic fibrosis	KO	
Editas Medicine ($650m mkt cap, -10% since IPO)		
Leber congenital amaurosis	KO, repair	IND delayed from 2017 to mid-2018
Usher syndrome etc	KO, repair	
Beta-thalassaemia, sickle cell	KO, repair (ex vivo)	
Duchenne muscular dystrophy	KO, repair	
Cystic fibrosis & alpha-1 antitrypsin deficiency	KO, repair	
Intellia Therapeutics ($550m mkt cap, -31% since IPO)		
Transthyretin amyloidosis	KO	IND-enabling trials H1 2018; partnered with Regeneron
Hepatitis B	KO	Hoping to start animal model trials 2017
Alpha-1 antitrypsin deficiency	KO, repair	
Primary hyperoxaluria	KO, repair, insertion	
Source: company filings.		

Another apparent delay concerns the use of Crispr in knocking out endogenous T-cell receptors in a cell therapy trial run at University of Pennsylvania and likely belonging to Dr Carl June's group Tmunity Therapeutics.

This got clearance from the NIH's recombinant DNA advisory committee a year ago, and a clinical safety trial was expected in the first quarter; several months on, there is apparently not even an IND approved, let alone a clinical study.

Strictly this does not involve gene therapy, because its purpose is to modify T cells for reinfusion into a patient to stimulate an immune response, rather than replacing a defective gene with the direct aim of curing a disease. If even this approach has made slow progress, what hurdles are faced by true somatic gene therapy, let alone the type of germline gene therapy approach described in Nature?

There is an important point here: several countries, including Australia, Canada and Germany, expressly prohibit modifying germ cells on the grounds that any such changes would be inherited. Germline gene therapy is not prohibited in the US, but it cannot be considered by the FDA in any clinical setting.

Thus, while not breaking the law, the US researchers appear to have gone against the spirit of local guidelines. This is not to deny that the Nature trial suggests some degree of progress, and shows that germline mutation correction is feasible, at least in theory.

But Clinicaltrials.gov reveals nine clinical trials involving Crispr, all in China – which is probably the way things will remain for a while. Designer babies are still science fiction; far simpler hurdles must be crossed before this

becomes even a vague possibility.

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