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Vertex goes small with Mammoth deal

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Vertex strikes yet another gene editing deal, this time with the “ultra-small” Crispr specialist Mammoth.

Vertex Pharmaceuticals was already an enthusiastic backer of very early gene editing projects, with deals in place with the likes of Crispr Therapeutics and Arbor Biotechnologies. The group spread its bets even further today, signing up another Crispr player, Mammoth Biosciences, for $41m up front.

The agreement involves in vivo gene editing but other details are thin on the ground – the companies will not even say which diseases they are looking at. Still, Mammoth’s co-founder and chief scientific officer, Lucas Harrington, tells *Evaluate Vantage* that, in general, the group is focused on potential one-time cures rather than redoseable therapies, which could give some clues.

The smaller the better?

Privately-held Mammoth’s unique selling point is that it has created “ultra-small” Crispr systems based around enzymes such as Cas14 and Casϕ, both of which the group licensed from the lab of another co-founder, the Crispr pioneer Jennifer Doudna.

By contrast, the large size of SpCas9, the most widely used Crispr enzyme, can make it tricky to package up for delivery alongside a guide RNA. This is particularly relevant for AAV viral vectors, which have a limit on the size of the cargo they can carry.

“SpCas9 is about 1,370 amino acids. Some of the systems we’ve discovered are less than 500 – some of them around 400,” says Mr Harrington. “You don’t have the same payload restrictions as with SpCas9.”

Of course, there are other ways to deliver gene editing machinery and, as well as viral vectors, Mammoth is working on non-viral methods such as lipid nanoparticles (LNPs).

Although LNPs do not have the same size restrictions as AAVs, there are still advantages to using small cargoes with the former, for example durability and consistency, according to Mr Harrington. “Also, if your cargo is a quarter or a third of the size, you can now fit three times the number of molecules in there, so you can get dosing efficiencies as well.”

Mammoth and Vertex are not saying which delivery method or methods the partnership covers.

High fidelity

Another advantage Mammoth claims is the high accuracy of its systems, which could minimise off-target effects, although Mr Harrington will not give more details about how the company has achieved this.

Neither will he say when the Vertex-partnered projects might go into the clinic.

On intellectual property, however, he is more forthcoming. Mr Harrington believes that Mammoth can sidestep the legal battle that has ensnared the original Crispr/Cas9 players. "We've worked very hard on making sure our systems are much cleaner in terms of IP than the original Cas9."

There is clearly excitement around Mammoth: the group raised a $150m series D in September, giving it unicorn status. And today's deal with Vertex provides further validation.

But the group now has to make sure it doesn't get lost among Vertex's growing roster of gene editing partners. On this point, Mr Harrington says: "There are a lot of diseases out there, and it's not one size fits all. Many diseases require specialised Crispr systems, and that's what Mammoth brings."

Vertex's advanced therapy collaborations

Company	Technology	Setting	Terms	Deal date
Mammoth Biosciences	Ultra-small Crispr systems for in vivo gene editing	Two undisclosed rare diseases	$41m up front (includes a convertible note), $650m milestones	Oct 2021
Arbor Biotechnologies	Crispr-edited ex vivo cell therapies	T1DM, SCD & beta-thal	Up to $1.2bn	Aug 2021
	Gene editing	CF & "four other diseases"	Not disclosed	Jan 2019
Crispr Therapeutics	Crispr/Cas9-edited ex vivo cell therapy (CTX001)	SCD & beta-thal	$900m up front, $200m milestones	Apr 2021
	Crispr/Cas9-based therapies	DMD & DM1	$175m up front	Jun 2019
	Crispr/Cas9-edited ex vivo cell therapy (CTX001)	SCD & beta-thal	Any new terms undisclosed	Dec 2017
	Crispr/Cas9-based therapies	CF, SCD & other diseases	$105m up front, $420m milestones on any project licensed in	Oct 2015
Moderna	Gene editing via mRNA	CF	$75m up front, $380m milestones	Sep 2020
	mRNA therapeutics	CF	$40m up front, $275m milestones	Jul 2016
Affinia Therapeutics	AAV vectors for gene therapy	DMD, DM1 & CF	Up to $1.6bn	Apr 2020

CF=cystic fibrosis; DM1=myotonic dystrophy type 1; DMD: Duchenne muscular dystrophy; SCD=sickle cell disease; T1DM=type 1 diabetes. Source: Evaluate Pharma & company releases.

The table in this story has been updated to clarify the terms of the Mammoth/Vertex deal.

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