Evaluate Vantage

July 17, 2023

Sanofi goes back to Scribe

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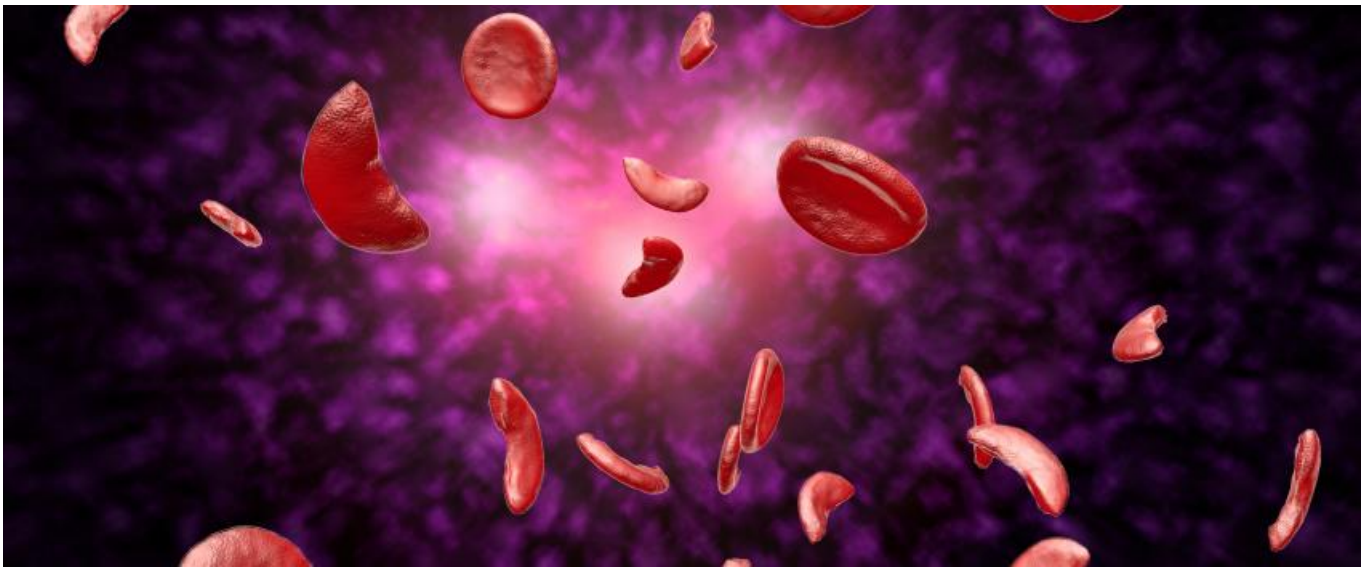

The latest deal focuses on in vivo Crispr editing for sickle cell disease, and follows last year's cancer collaboration.

18 months ago Sanofi canned a collaboration with Sangamo over an ex vivo gene-edited project for sickle cell disease. Now the French group has returned to the sickle cell field, partnering with the Crispr editing player Scribe Therapeutics in a deal worth $40m up front.

The latest move does not signal a change of heart from Sanofi, however. When it cancelled the Sangamo deal the group said it wanted to focus on allogeneic genomic medicine approaches rather than autologous personalised cell therapies. And the new Scribe deal involves in vivo editing – which many believe is the future of gene medicine.

This is also the second agreement between Sanofi and Scribe within a year, and the fourth Scribe has signed with a big pharma since 2020.

In vivo vs ex vivo

The most advanced gene edited candidate for sickle cell disease is Crispr Therapeutics and Vertex's exa-cel, which is due an FDA decision on approval by 8 December. This is an ex vivo project that involves haematopoietic stem cells being taken from the patient, edited and reinfused, following chemotherapy conditioning to deplete the patient's remaining stem cells.

These harsh conditioning regimens will likely mean that such autologous therapies are reserved for the most severely affected. There are also questions about the practicalities of this approach, particularly in developing nations – an important consideration in sickle cell disease, which disproportionately affects people of African descent.

It is hoped that in vivo approaches could broaden access to gene editing, as they do not require such conditioning and are also simpler to administer. However, current in vivo candidates are limited to liver-mediated diseases as the key delivery vehicle for in vivo editing, lipid nanoparticles, tend to accumulate in that organ.

In sickle cell disease, a major problem will be delivering the gene editing machinery to haematopoietic stem cells. This is something Sanofi is working on with its targeted LNPs.

Scribe's chief executive Benjamin Oakes has been sceptical about efforts to target LNPs, previously telling *Evaluate Vantage*: "Anyone who says they're confident of being able to deliver LNPs anywhere but the liver is

either brave or something else."

Now, speaking to *Vantage* about the latest deal, Oakes says: "While delivery outside the liver is incredibly difficult, and you do have to be brave to attempt [it], I do know and believe it's possible. But I think it requires the technologies like Sanofi has started to develop. And that's why we're working with them."

Smaller is better?

These targeted LNPs will be combined with Scribe's Crispr X editing, based around the CasX enzyme – making it distinct from other Crispr-based approaches, which most commonly use Crispr/Cas9.

Scribe, which was co-founded by the Crispr pioneer and Nobel Prize winner Jennifer Doudna, has described X editing as "honed for greater activity and specificity" versus other Crispr systems.

Oakes also points to the small size of the CasX enzyme as a potential advantage, even with LNP delivery – although this is not as important as with another common delivery vehicle, adeno-associated viruses, which have a "hard limit" on the size of the cargo they can carry.

Using a different enzyme could also help the group sidestep the legal wrangling that has enveloped Cas9.

Sanofi has already worked with Scribe and clearly liked what it saw. The companies began a collaboration last year around ex vivo NK cell therapies for cancer.

The French group is not the only one to see promise in privately held Scribe, which has also signed deals with Lilly and Biogen. Although its work is early, increasing big pharma buy-in looks like a good sign.

But pharma is putting many small bets on gene editing at present, with Life Edit and Verve recently scoring deals with Novo Nordisk and Lilly respectively. There is clearly a lot of interest here, but it would be premature to try and pick a winner.

For a deeper discussion on ex vivo versus in vivo gene editing, and novel delivery approaches, download Evaluate Vantage's recent report on the sector.

Scribe's big pharma collaborations			
Partner	**Financials**	**Details**	**Date**
Sanofi	$40m up front; $1.2bn milestones	In vivo gene medicines for sickle cell & "other genomic diseases"	Jul 2023
Lilly (Prevail subsidiary)	$75m (incl undisclosed equity) up front; $1.5bn milestones	In vivo therapies for neurological & neuromuscular diseases	May 2023
Sanofi	$25m up front; $1bn milestones	Ex vivo genetically modified NK cell therapies for cancer	Sep 2022
Biogen	$15m up front; $400m milestones	Crispr-based therapies for neurological diseases incl ALS (expanded to include 2nd target in May 2022)	Oct 2020
Source: company announcements.			