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Novo goes early to leapfrog haemophilia gene therapies

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Novo Nordisk took an early step towards genome editing with yesterday's Bluebird tie-up, and isn't ruling out a move into conventional gene therapies.

Novo Nordisk claims to be a leader in haemophilia, but looks to have missed the boat with the first wave of gene therapies for the disorder.

The group acknowledged this yesterday when it struck a deal with Bluebird Bio covering *in vivo* genome editing, which it hopes will become the next big thing. But, like many Novo collaborations, the project is extremely early, and the haemophilia space could look very different in several years' time.

In haemophilia A, the initial focus of the Novo-Bluebird project, several gene therapies are approaching the market. The most advanced, Biomarin's valoctocogene roxaparvovec (valrox), is set to be filed by the end of this year, and is expected to become the third-biggest seller in the disease by 2024, according to *EvaluatePharma* sellside consensus.

Meanwhile, Novo's next haemophilia hope, the tissue factor pathway inhibitor concizumab, is forecast to bring in just $47m that year. That asset is due to begin phase III development this year.

Top five haemophilia A therapies in 2024					
				Annual sales ($m)	
Product	**Company**	**Description**	**Status**	**2018**	**2024e**
Hemlibra	Roche/Chugai	Anti-factor IXa/X bispecific MAb	Marketed	230	3,979
Eloctate	Sanofi/Swedish Orphan Biovitrum	Factor VIII	Marketed	1,239	1,234
Valoctocogene roxaparvovec (valrox)	Biomarin	AAV-factor VIII gene therapy	Filing imminent	-	1,212
Advate/Adynovate	Takeda	Factor VIII	Marketed	2,860	1,173
NovoSeven	Novo Nordisk	Factor VII	Marketed	1,033	595
Source: EvaluatePharma.					

Valrox and other conventional gene therapies are based around a viral vector that delivers the gene for a missing clotting factor to patients' livers – factor VIII in the case of haemophilia A.

Meanwhile, Novo and Bluebird hope to elicit a genetic change directly in patients using the latter's megaTAL editing technology.

Daniel Timmerman, vice-president of Novo's biopharm transformational research unit, admitted that were the company to start developing a traditional haemophilia gene therapy now, its chances of being competitive would be "relatively slim".

However, he stopped short of ruling out such a move. "Classic gene therapies are still attractive for Novo. We're interested in new opportunities close to where we're already working," he told *Vantage*, citing rare genetic diseases as an area of interest for Novo and also a sector that "lends itself well to gene therapies".

Given Novo's reputation as a builder rather than a buyer, this seems unlikely to translate into a big acquisition. But perhaps this possibility should not be completely dismissed given the Danish group's strategy shift last year, not long after it tried and failed to buy Ablynx (*Novo casts its net wider but shrinks in the process, September 19, 2018*).

MegaTALented?

Various methods are currently being explored for *in vivo* genome editing. Bluebird's megaTAL platform essentially combines aspects of two better-known technologies: Talens and meganucleases.

The TAL motif is responsible for DNA binding, while the meganuclease part provides the DNA strandbreak, Mr Timmerman explained. He highlighted megaTALs' specificity and the possibility of limiting off-target effects.

When asked why Novo had chosen not to work with traditional Talens – a space dominated by the French Car-T player Cellectis – Mr Timmerman said intellectual property had been a consideration, but that the main attraction was Bluebird's technology.

He added that, while other genome editing modalities, including Talens, required two proteins to carry out DNA cleavage, megaTALs only needed a single molecule. This simplicity could turn out to be an advantage in a sector where caution around safety is high, he said, but conceded that this needed to be proven.

It will be a while before it becomes clear whether Novo has made a good move. The groups hope to have a candidate to take into preclinical testing by the end of the three-year collaboration.

No financial details of the deal were given, and Bluebird will continue to develop megaTALs for other applications.

Rivals include Casebia Therapeutics, a joint venture between Bayer and Crispr Therapeutics that is investigating Crispr/Cas9 in haemophilia, among other diseases. Sangamo Therapeutics has an *in vivo* editing candidate for haemophilia B based on its zinc finger technology, as well as its conventional AAV-vector based haemophilia A gene therapy.

Mr Timmerman noted that genome editing held the promise of a truly lifelong correction of a faulty gene, which might not be the case with gene therapies. He conceded, however, that the approach could also raise the risk of a lifelong genetic error being inadvertently introduced. No wonder Novo is taking it slowly.