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Boehringer takes a different approach in cystic fibrosis gene therapy

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Deals this week with a UK consortium and Oxford Biomedica see the group bet on lentiviral vectors.

Boehringer Ingelheim is not a cystic fibrosis player, but it hopes to change that. The group yesterday made a bet on a preclinical inhalable cystic fibrosis gene therapy, licensing rights from the UK Cystic Fibrosis Gene Therapy Consortium.

The company is taking a different approach to most other cystic fibrosis gene therapy hopefuls in that it has plumped for a lentiviral vector to deliver a healthy *CFTR* gene into lung cells. There are plenty of other cystic fibrosis gene therapies in early development, the table below shows, but most employ adeno-associated virus (AAV) vectors, which might have some drawbacks in this disease.

“We feel that lentiviral vectors are the best route,” Matthew Thomas, Boehringer’s head of immunology and respiratory research, tells *Evaluate Vantage*. “And we feel we’re differentiated in that regard.”

The German group is not in fact completely unique here: a potential rival, Spirovant Sciences, is developing AAV and lentiviral projects alike, and claims to be the only player doing so.

Boehringer is gaining lentivirus knowhow via Oxford Biomedica, to which it also paid £3.5m yesterday. The companies have been working together since 2018, along with the UK consortium.

The missing 10%

Cystic fibrosis is caused by mutations in the *CFTR* gene, which leads to a defective and/or missing CFTR protein. Current therapies include CFTR modulators, such as Vertex’s market-leading drug Trikafta, but even this can only treat 90% of the patient population. There is thus great interest in gene therapies, which offer a potential cure regardless of a patient’s mutation status.

Initially, Boehringer hopes that its candidate, BI 3720931, could be used in the 10% of patients who have no other options, but Mr Thomas says those who do not respond well to Trikafta could be potential candidates. And if all goes well, gene therapy could have an even broader reach, to include currently treated patients who wish for a more convenient option.

However, progress in this area has been slow. One problem has been delivering the large *CFTR* gene via AAV vectors, which have a limit on the size of the gene they can carry. Lentiviral vectors, meanwhile, can deliver a

full-length *CFTR* gene.

The other advantage of lentiviral vectors, according to Mr Thomas, is that "the immunogenicity challenges of a lentivirus are far, far less compared to other systems". This should allow redosing, something Boehringer is planning for BI 3720931.

For now, though, Mr Thomas will not say how often the project would ideally be administered.

Safety questions

One potential downside is that there have been toxicity concerns with lentiviral vector-based gene therapy projects, most recently with Bluebird Bio's Lentiglobin in sickle cell disease and Lenti-D in cerebral adrenoleukodystrophy. Bluebird recently concluded that a case of myelodysplastic syndrome was related to the latter; a clinical hold on Lentiglobin has been lifted, but questions still hang over this approach.

Mr Thomas says Boehringer is "mindful" of the worries around gene therapy, but that it will monitor safety carefully. He adds: "There's nothing that relates to our programme that causes any major concerns right now."

Still, BI 3720931 is at a very early stage, and Mr Thomas will not be pinned down on when it might enter the clinic. The focus right now is formulation. As Mr Thomas puts it: "How will we get this to the right regions of the lung to make the best impact on patient biology that we can?"

He believes that the group is "ahead of the game" in the cystic fibrosis gene therapy race, although 4D Molecular Therapeutics, which plans to go into the clinic by the end of the year, might have something to say about that.

And it might be unwise to bet against Vertex on its home turf, despite the group's recent woes in other disorders. The company is collaborating with Affinia Therapeutics on gene therapy projects in diseases including cystic fibrosis, and also has gene editing deals with Crispr Therapeutics and Arbor Biotechnologies.

In addition, Vertex has an agreement with Moderna covering inhaled mRNA for cystic fibrosis, but this approach took a blow earlier this year with the failure of a project from Translate Bio.

Selected gene therapy approaches in cystic fibrosis

Project	Company/ies	Description
4D-710	4D Molecular Therapeutics	Inhaled gene therapy (AAV vector)
ABO-401	Abeona Life Sciences	Inhaled gene therapy (AAV vector)
BI 3720931	Boehringer Ingelheim/Oxford Biomedica	Inhaled, redoseable gene therapy (lentiviral vector)
KB407	Krystal Biotech	Inhaled, redoseable gene therapy (herpes simplex viral vector)
SP-101	Spirovant Sciences	Inhaled, single-dose gene therapy (AAV vector)
SP-102	Spirovant Sciences	Inhaled, single-dose gene therapy (lentiviral vector)
Unnamed	Vertex/Affinia Therapeutics	Gene therapy (AAV vector)

Note: all preclinical. Source: Evaluate Pharma, clinicaltrials.gov & SEC filings.