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World Symposium – Orchard leads the crop of Hurler syndrome hopefuls

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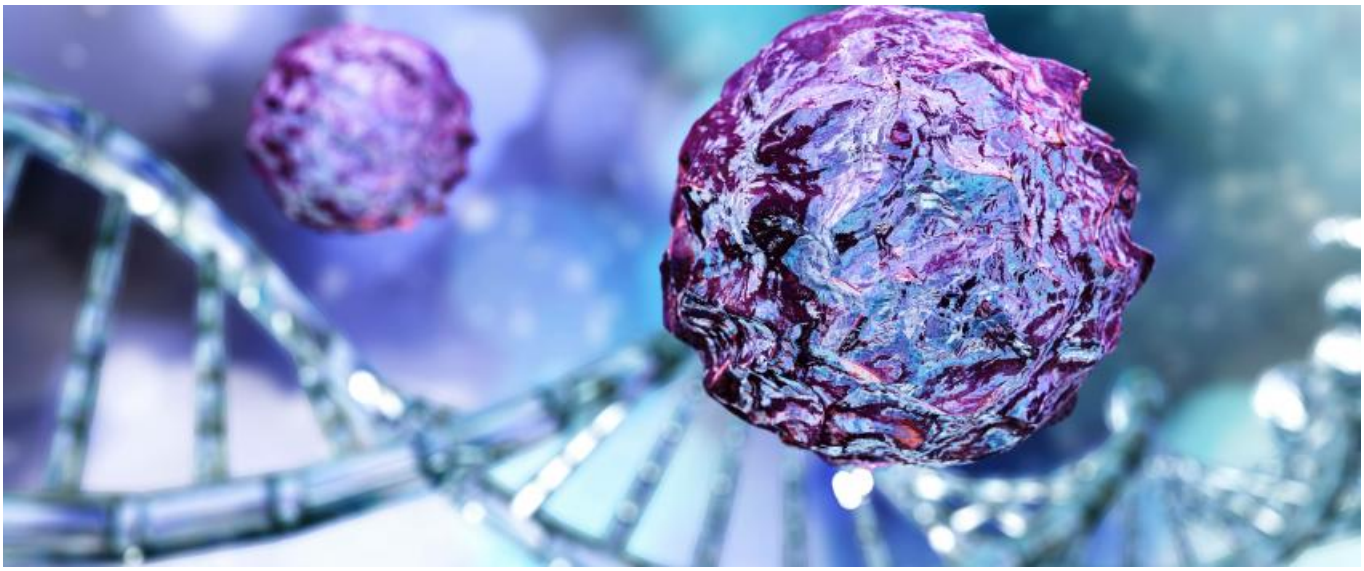

Promising early data with the group's gene therapy put it ahead of Regenxbio for now.

Gene therapy companies have been under pressure lately, but Orchard Therapeutics got a lift yesterday from promising early data with its mucopolysaccharidosis type I candidate OTL-203.

The company is seeking to supersede the current standard of care, enzyme-replacement therapy or bone marrow transplant. But other gene therapy contenders are not too far behind, notably Regenxbio, which in December started a proof-of-concept study of its rival project, RGX-111.

Good IDUA

Both projects seek to deliver the *α-l-iduronidase* (*IDUA*) gene, which is mutated in MPS-I, leading to a deficiency of the IDUA enzyme. This enzyme usually breaks down glycosaminoglycans (GAGs), so in MPS-I patients these build up, causing tissue and organ damage. Symptoms of MSP-I, also known as Hurler syndrome, include cognitive impairment and skeletal deformity; if left untreated, patients rarely survive beyond the age of 10.

And both OTL-203 and RGX-111 are designed as one-time therapies, whereas the current enzyme replacement, Biomarin/Sanofi's Aldurazyme, is given intravenously once a week.

However, the gene therapy candidates go about restoring IDUA enzyme activity in different ways. OTL-203 uses hematopoietic stem cells taken from the patient, then genetically modified using a lentiviral vector to express the IDUA gene, before being reinfused.

RGX-111, meanwhile, uses an adeno-associated viral vector to deliver the gene directly to the brain, getting around a central problem with Aldurazyme, which cannot cross the blood-brain barrier.

Selected projects in development for mucopolysaccharidosis type I				
Project	**Company**	**Description**	**Status**	**Trial details**
OTL-203	Orchard Therapeutics	Modified autologous haematopoietic stem cells	Ph1/2 data reported	NCT03488394*
JR-171	JCR Pharmaceuticals	BBB-penetrating enzyme	Ph1/2	NCT04227600, ends Sep 2021
RGX-111	Regenxbio	AAV9 vector gene therapy, direct to CNS	Ph1/2	NCT03580083, ends Nov 2021
ISP-001	Immusoft	Autologous programmed B cells	Preclinical; IND H1 2021	-
SIG-005	Sigilon Therapeutics	Off-the-shelf "shielded living therapeutic"	Preclinical	-
TXB4-LS1	Ossianix	BBB-penetrating enzyme	Preclinical	-

**Sponsored by San Raffaele Telethon Institute for Gene Therapy. Source: EvaluatePharma & clinicaltrials.gov.*

Getting into the brain should not be a problem for OTL-203 either, Orchard's head of medical affairs, Leslie Meltzer, told *Evaluate Vantage*. She explained that hematopoietic stem cells naturally cross the blood-brain barrier and, once in the CNS, differentiate into a microglial-like cell.

This claim appears to be supported by the latest data, which admittedly come in just a handful of subjects. The eight-patient phase I/II trial, presented at the World Symposium yesterday, found increases in the IDUA enzyme in patients' blood and cerebrospinal fluid. There was also a decrease in GAGs in the CSF and urine.

Encouragingly, this activity appears to have translated into a clinical benefit: all eight patients showed stable cognitive scores and stable motor function versus baseline, as well as growth in the normal range for patients' age.

"It's a progressive disease, so you'd expect these things to worsen over time, but the fact they continued to be stable is very promising," Ms Meltzer said. She admitted that the data were early, with only around a year of follow-up on most of the clinical endpoints.

Orchard plans to start a registrational study by the end of this year. Ms Meltzer would not give any details on design, saying this would be finalised after feedback from regulators.

Regenxbio's proof-of-concept study of RGX-111 is due to complete in November, putting the project about a year behind OTL-203.

One candidate that will go no further is Sangamo's SB-318. The company reported disappointing data with the *in vivo* zinc finger nuclease genome-editing project two years ago, and has since said it would focus on second-generation zinc finger projects.

Still, even two gene therapies might be too many for an ultra-rare disease like MPS-I, which affects just one in 100,000 people. Asked whether this market could support more than one gene therapy, Ms Meltzer said newborn screening recently implemented in countries including the US could lead to a revision of that estimate.

But, as in other rare disorders that have attracted several gene therapy players, a battle over a limited patient pool could be shaping up.