antisense molecules designed to knock down expression of the mutant *HTT* gene while preserving expression of the wild-type gene. Its approach exploits the presence of a number of single nucleotide polymorphisms (SNPs) in different mutant *HTT* alleles that are not present in wild-type alleles. Its first two drug candidates address the needs of about 70% of the patient population. Recent interim data from an early-stage trial with one candidate, WVE-120102, prompted a negative reaction from company shareholders because of its perceived lack of potency compared with that of RG6042 in the earlier Roche/Ionis trial. The molecule achieved a 12% reduction in mHTT protein in the cerebrospinal fluid, whereas the Roche/Ionis drug attained a reduction of total HTT protein production of about 40% in the two high-dose groups. This weaker effect may be because it is easier to design a potent antisense oligonucleotide to address any part of the *HTT* gene than to be restricted to a region harboring a specific SNP sequence. Wave officials remain sanguine, however. "We have target engagement — we are dose-escalating," says CEO Paul Bolno. Wave reported a reduction in mutant HTT protein WVE-120102 with all doses from 2 to 16 milligrams, whereas RG6042 doses of 90 and 120 milligrams were required to achieve potent HTT reduction.

Wave is now initiating 32-milligram dose cohorts in its two ongoing trials, although that is unlikely to be the maximum dose it will employ. "We're in the process of assessing what that dose level will be," says Wave's chief medical officer, Michael Panzara. The long-term consequences of reducing healthy HTT protein production in adults with Huntington's disease are as yet unclear. "There is definitely a risk given the fact that the wild-type protein may be important for maintenance of neuronal circuits or synaptic homeostasis," says Frédéric Saudou of the Grenoble Institute of Neurosciences at the University of Grenoble, France, who is a consultant to Wave. HTT protein has a key role in embryonic and early postnatal development. Genetic knockout in mice is embryonically lethal; conditional knockdown causes neurological deficits and acute pancreatitis in infant animals. The importance of huntingtin protein in the adult brain is less well understood. "There are more and more functions that are being discovered," Saudou says. For that reason, Wave maintains that their company is best positioned to treat presymptomatic patients and those with juvenile-onset disease. "It's pretty clear that's a patient population in which you want to spare the wild-type protein as much as possible," Panzara says. Roche's phase 3 data should provide important insights into this and into many other aspects of this inexorably grim disease and at the same time help other firms hone their development strategies. ❐

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PODCAST

First Rounders: Bassil Dahiyat

Bassil Dahiyat is cofounder, president and CEO of Xencor. His conversation with *Nature Biotechnology* covers his parents immigrating from Jordan, how Xencor has survived (and changed) over the past 22 years, and when it's necessary for a CEO to speak out.
https://www.nature.com/nbt/podcast

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FDA dictates on gene therapy sameness

The US Food and Drug Administration (FDA) issued a draft guidance to help companies developing gene therapies determine whether their therapy is the same as another product when aiming to apply for orphan drug designation and orphan drug exclusivity. The agency states that when a gene therapy shares the same "principal molecular structural features" as another gene therapy with orphan drug status, it cannot be approved by the FDA for the same condition (albeit with certain exceptions, such as when a second product is clinically superior). The "molecular structural features" refer to the transgene and vector of a gene therapy, and thus the FDA will consider two gene therapies different if they express different transgenes and/or use different vectors, such as a retrovirus vector or an adeno-associated virus (AAV). If vectors from the same viral class are used (such as different AAV subtypes), then the FDA will determine on a case-by-case basis whether the gene therapies are the same. The FDA notes that additional features, such as regulatory elements or the cell type transduced, might be taken into account when determining sameness. As a consequence, even when two gene therapies share the same transgene and vector, they might not be considered the same. But questions remain before the guidelines can be put into practice. "Would a gene editing tool be considered a principal molecular structure in a manner analogous to a vector?" says Emily Marden, counsel at Sidley Austin, Palo Alto, California. Nevertheless, having the FDA's views in guideline format is useful. "By explaining some of FDA's thinking, the guidance helps companies better formulate questions for discussion with the agency," says Philip Katz, partner at Hogan Lovells, Washington, DC. The draft guidelines are open for comments until 29 April.

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