Voyager's CNS gene therapy

A deal focused on gene therapies to treat severe neurodegenerative conditions saw Neurocrine Biosciences pay Voyager Therapeutics $165 million up front for their adeno-associated virus (AAV) vector platform. In the collaboration Neurocrine will fund the clinical development of four of Voyager's neurology gene therapy programs: VY-AADC for Parkinson's disease, VY-FXN01 for Friedreich's ataxia, and two further programs to be determined. The deal, announced on January 29, could be worth up to $1.7 billion for Voyager in potential milestone payments.

Voyager's vector is VY-AADC, an AAV-2 vector carrying a therapeutic gene under the control of a cytomegalovirus promoter. In the case of Parkinson's disease, the therapeutic gene encodes the aromatic L-amino acid decarboxylase (AADC), the enzyme that converts L-DOPA to dopamine. Standard treatment with oral levodopa aims to correct neurotransmitter levels to control parkinsonian symptoms, but its beneficial effects wane over time because the death of AADC-expressing neurons in the substantia nigra reduces the amount of dopamine.

The platform designed by Voyager could correct AADC levels by delivering the *AADC* gene directly into the putamen by intracranial injection. On the basis of phase 1 data demonstrating safety and improvements in motor function over two years following treatment, VY-AADC was granted Regenerative Medicine Advanced Therapy status by the US Food and Drug Administration in June 2018, and the phase 2 RESTORE-1 trial was initiated in December 2018.

Friedreich's ataxia is a rare genetic disease caused by a mutation in the frataxin gene *FXN* that results in decreased expression of the FXN protein, causing progressive muscle weakness, sensory loss and cardiomyopathy. In a preclinical model, Voyager's VY-FXN0, an AAV-based vector carrying the *FXN* gene, prevented disease progression for up to a year after one intravenous administration.

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CRISPR target prediction remains blunt tool for clinical applications

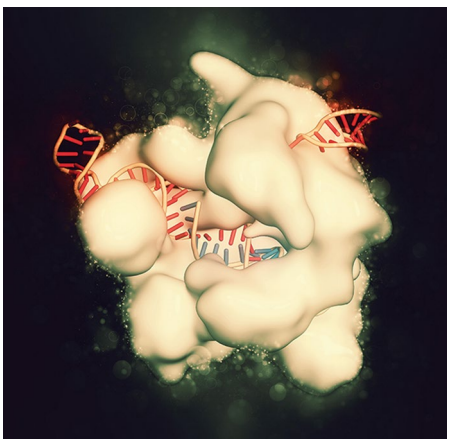
Computational approaches to predict gene editing repair by CRISPR endonucleases remain a work in progress.

Applying gene-editing endonuclease systems to correct disease genes in patients requires much greater efficiency, fidelity and quality control than editing genes in the laboratory. Although the combination of wet-lab and machine learning algorithms promises more accurate prediction of CRISPR–Cas9 editing outcomes, two recent large-scale studies illustrate the scope of the challenge before such tools are truly ready for CRISPR clinical programs.

The two projects—one at the Wellcome Sanger Institute at Hinxton in the UK (*Nat. Biotechnol.* **37**, 64–72, 2018) the other from researchers at Harvard University, MIT and Massachusetts General Hospital (*Nature* **563**, 646–650, 2018)—involved computer scientists working with wet-lab biologists. Both produced online tools (inDelphi and FORECasT) to predict the range of on-target repair outcomes from CRISPR–Cas9 experiments, extending work first published in 2016 by Andy May, then CSO at Caribou Biosciences and now at Sana Biotechnology.

The intrinsic downside of CRISPR–Cas9, however, is that it depends on prevailing cellular repair mechanisms to restore DNA cleavage sites, and these mechanisms vary with cell type and other factors. Richard Sherwood, assistant professor at Brigham and Women's Hospital, Harvard Medical School and one of the principal investigators of the Cambridge, Massachusetts group, notes that repair mechanisms for Cas9-induced breaks are less random than was once thought.

First to note that the repairs were not random was Kosuke Yusa's group at Wellcome Sanger (*Nat. Biotechnol.* **32**, 267–273, 2014). Two years later, in 2016, Caribou scientists demonstrated that the guide RNA sequence defined the spectrum of repair outcomes; there were some rules. But while Caribou's early findings described genomic repair profiles at 223 genomic sites resulting from 96 different guide-RNA sequences, the recently published work reports an order-of-magnitude scale-up in the experimental samples.



In the CRISPR-CAS9 gene editing complex, the Cas9 nuclease cuts are not random, as was once thought; the repairs in the cell follow certain patterns. Credit: molekuul.be / Alamy Stock Photo

The Cambridge, Massachusetts group used a library of 2,000 Cas9 guide RNAs to train a machine learning model, inDelphi, to predict the type and frequency of insertions and deletions. A bigger data set still, covering 40,000 guide RNAs and more than a billion mutational outcomes, was generated by the Wellcome Sanger researchers to develop the FORECasT tool. Both groups, to achieve scale, used synthetic cassettes containing both the guide RNA and the target sequences.

"The main application [of FORECasT] is in designing gene knockout experiments" says Felicity Allen, co-lead author and one of the computer scientists from the Wellcome Sanger group. "The aim is to avoid three-nucleotide deletions since these might still be expressed as altered but functional products."

For the US group, better knockout design is important, but the results could also have implications for the clinic. If, as their findings suggest, the prevailing repair for Cas9-induced breaks is microhomology-mediated end joining rather than random, nonhomologous end joining as previously thought, Cas9 gene