> prime editing … could in theory correct up to ~89% of known human pathogenic mutations

in the heteroduplex with the additonal use of sgRNAs matching only the edited sequence. In this way, the non-edited strand is also nicked, but only upon flap-resolution of the edited strand, to minimize concurrent nicking of both strands and thus DSB formation.

In human cells, prime editing corrected a transversion causing sickle cell disease, and the 4 bp insertion that causes Tay–Sachs disease. The system functioned also in terminally differentiated mouse neurons, and can edit all types of local mutation with high efficiency and low off-targeting levels.

Based on the targeting scope and range of insertions and deletions supported by prime editing, it could in theory correct up to ~89% of known human pathogenic mutations.

Eytan Zlotorynski

ORIGINAL ARTICLE Anzalone, A. V. et al. Search-and-replace genome editing without double-strand breaks or donor DNA. *Nature* https://doi.org/10.1038/s41586-019-1711-4 (2019)
RELATED ARTICLE Pickar-Oliver, A. & Gersbach, C. A. The next generation of CRISPR–Cas technologies and applications. *Nat. Rev. Mol. Cell Biol.* **20**, 490–507 (2019)

by intracerebroventricular or intraperitoneal injections. Fly lifespan was increased and disease-relevant behavioural phenotypes were attenuated in mice. Moreover, mHTT toxicity was diminished in neurons derived from iPSCs from patients with HD. Interestingly, the compounds recognized expanded polyQ and thus also lowered the levels of mutant ATXN3 (another expanded polyQ-containing protein) in fibroblasts from a patient with spinocerebellar ataxia type 3.

Additional studies are required to establish the suitability of the compounds for therapy, but this study indicates that, in principle, targeting disease-causing polyQ proteins to autophagosomes is a valid approach for treatment.

Kim Baumann

ORIGINAL ARTICLE Li, Z. et al. Allele-selective lowering of mutant HTT protein by HTT–LC3 linker compounds. *Nature* https://doi.org/10.1038/s41586-019-1722-1 (2019)
RELATED ARTICLES Iadanza, M. G. et al. A new era for understanding amyloid structures and disease. *Nat. Rev. Mol. Cell Biol.* **19**, 755–773 (2018) | Dikic, I. & Elazar, Z. Mechanism and medical implications of mammalian autophagy. *Nat. Rev. Mol. Cell Biol.* **19**, 349–364 (2018)

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TRANSLATING THE RIGHT WAY

As a graduate student at Harvard University in the mid-1970s, one of my first courses, taught by Walter Gilbert, turned out to be among the most important experiences of my life. Gilbert would assign papers to read, with emphasis on those with ground-breaking but incorrect claims. Our task was to find what critical errors occurred, and how the correct conclusions could be otherwise reached. The course taught me to read papers sceptically, even those written by famous scientists.

> …what at first appeared to be ingeniously designed studies suffered from substantial flaws

I particularly remember the papers from the Rich and Schweet labs, which were published independently in 1965. At the time, the direction of mRNA translation was controversial, and the erroneous conclusion of each of these papers was that ribosomes translate mRNAs from the 3′-end towards the 5′-end. The mistake was based on experiments in rabbit reticulocytes, which consisted of translating the globin mRNA from polysomes treated with exonucleases degrading RNA either in the 5′-to-3′ or 3′-to-5′ direction, followed by comparing the levels of radioactively labelled globin peptides. Digesting mRNAs from different directions was expected to have considerably different effects on the relative expression of amino-terminal or carboxy-terminal peptides, but instead, digestion using the 3′-to-5′ exonuclease led to modestly more reduction in the expression of the amino-terminal peptide than of the carboxy-terminal peptide, leading the authors to conclude that translation initiates at or near the 3′-end of the mRNA.

The studies suffered from several shortcomings. First, the data were marginal and complete mRNA degradation was never achieved. Second, the exonucleases were present throughout the translation process, possibly degrading also tRNAs and rRNAs. Third, the 5′-to-3′ enzyme is sensitive to 5′-triphosphates and 5′-cap structures, and the authors never extracted and analysed the RNAs after digestion. Finally, little true translation initiation from polysomes occurred. Thus, what at first appeared to be ingeniously designed studies suffered from substantial flaws.

The lesson was further driven home when Gilbert next asked us to read the paper by Terzaghi et al. (1966), which provided a simple and elegant proof that mRNAs are in fact translated in the 5′-to-3′ direction. The authors compared the protein sequences of wild-type and mutant phage T4 lysozymes. The mutant enzyme had a +1 frameshift mutation followed not far downstream by a −1 frameshift mutation. The amino acid sequences of the wild-type and mutant proteins between the mutations were compared and aligned to possible nucleotide triplets from the genetic code. The analysis unequivocally showed that protein synthesis can occur only in the 5′-to-3′ direction.

The lesson I learned from this was that sometimes approaching questions from a completely different direction can yield unexpected and satisfying answers. Throughout my career I have been grateful for lessons like this, which have made me a better and hopefully a more innovative scientist.

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