Infographic: Gene therapy drugs that silence the effects of faulty genes could help tackle Huntington’s and other neurodegenerative diseases

Huntington’s disease (HD) is an inherited condition that causes widespread deterioration in the brain and disrupts thinking, behaviour, emotion and movement. The disease usually begins in midlife, with subtle changes such as mood swings and difficulty in staying focused. As it progresses, people develop dementia and an inability to speak or move.

There are no treatments available to stop or slow the progression of Huntington’s, even though its genetic cause has been clear since 1993. Most other neurodegenerative diseases also lack effective therapies and, although their genetic roots are less clear-cut than for Huntington’s, many of the genes associated with conditions such as motor neuron disease (amyotrophic lateral sclerosis, or ALS), Alzheimer’s and Parkinson’s have been known for decades.

Now, the tide might be turning for treating these kinds of diseases. Many researchers are hopeful about drugs known as antisense oligonucleotides (ASOs). These are short strings of DNA or RNA letters that are designed to cling to particular sequences of RNA made by faulty genes, and to rebalance the levels of proteins they produce — boosting missing proteins or quashing faulty ones.

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The US Food and Drug Administration (FDA) approved the first ASO for a neurological disease in 2016, and there has since been an explosion of activity in this area.
TOGGING PROBLEM PROTEINS

An emerging class of drug called antisense oligonucleotides (ASOs) uses tiny pieces of DNA or messenger RNA matched to disease-causing proteins to suppress or correct them.

**Silencing**

Diseases such as Huntington’s and motor neuron disease (amyotrophic lateral sclerosis) are caused by a build-up of mutant proteins. ASOs in development aim to quell their production.

**Boosting**

ASOs can replace missing proteins. The ASO nusinersen treats spinal muscular atrophy (SMA), in which the body lacks a protein called SMN. There are two SMN genes: in healthy people, SMN1 makes a stable protein and SMN2 an unstable version. In people with SMA, SMN1 is disrupted. Nusinersen makes up for this by acting on SMN2 to stabilize its normally inactive protein.

![Diagram of gene expression and drug treatment](image)

**Healthy individual**

- **SMN1**
  - Transcription
  - Splicing
  - Translation
  - Active protein

- **SMN2**
  - Transcription
  - Splicing
  - Translation
  - Unstable protein

**Drug treatment**

- **SMN1 gene**
  - Block transcription
  - ASO tagged for degradation

- **SMN2**
  - ASO stabilizes mutated mRNA
  - Drug treatment fixes mutation in SMN2

- **Drug treatment fixes mutation in SMN2**
  - mRNA degraded

**SMA disrupts SMN1 gene**

- **SMN1**
  - Transcription
  - Splicing
  - Translation
  - Disease-causing protein

- **SMN2**
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  - Splicing
  - Translation
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