PERSPECTIVE

Eclipsed by CRISPR

As a source of potential treatments, gene editing gets all the attention. It's time for scientists to shout about RNA therapies, says **Lorna Harries**.

The merits and risks of gene editing and gene-manipulation technologies such as CRISPR–Cas9 have been hot topics for debate ever since such techniques were developed. Ask anyone on the street about gene editing and the chances are that most will have heard of it. There might be controversy over the benefits of using gene editing to tackle conditions and the ethical challenges it poses, but the public will probably be aware of the field's existence and potential. Ask the same people about RNA therapies (or even just RNA) and you will probably be greeted with a blank stare.

Why is this the case? Several RNA therapies have already been licensed for use in the clinic, yet the development of CRISPR–Cas9 in a clinical context is still in its infancy. The discovery of RNA was concomitant with that of DNA, but it has yet to appear on the public radar, despite the opportunities that it offers as a therapeutic tool.

One reason that RNA-based approaches are the lesser-known and seldom-seen sibling of DNA therapies might be the evident complexity of RNA biology, and the perceived difficulties in talking about it to a non-scientific audience.

As a scientist and educator, I am consistently met with the perception that RNA biology is too difficult to understand, and is therefore best left alone. It is true that it is a complex area, but so are genetics and epigenetics. Yet both are represented in and discussed by the media in a way that RNA biology is not. It is down to scientists and communicators to make the subject accessible and easy to understand. It's not impossible — we just need to engage with the task and to give it priority. I find that the public is actually very receptive to information on the topic, and that with understanding often comes a willingness to embrace things.

The idea that you can change a DNA sequence by using a one-stop therapy to repair a genetic mutation is extremely attractive. But such interventions are difficult to revert, and have the potential to be transmitted to future generations. This area is one in which RNA therapies might have the upper hand, representing a more digestible solution to correcting genetic conditions for clinicians and the public. Unlike gene editing, RNA therapies do not alter the actual sequence of a mutated gene, but instead alter its output. Those changes are temporary, not permanent. As much as 50% of diseases in people might arise from changes in RNA transcription, processing or turnover. Increasingly, we are realizing that the risk of developing many common long-term conditions is also influenced by changes in the expression of genes, rather than in the structures of the proteins that they encode.

RNA therapies might be relatively new, but already several such drugs have made it to the clinic. These include: patisiran for hereditary transthyretin amyloidosis, a build-up of the protein amyloid in nerves and organs; eteplirsen for certain types of Duchenne muscular dystrophy, an inherited form of progressive muscle degeneration; and nusinersen for spinal muscular atrophy, a rare genetic neuromuscular condition. Before the advent of these drugs, all three conditions were life threatening, or potentially so.

Such drugs work by changing how RNA-encoded messages sent from mutated genes are produced, processed or degraded. This can restore the number of messages that are produced, or alter the nature of those messages so that they more closely resemble those from genes without mutations.

In many ways, RNA therapies are not so different from other existing medications. They are prescribed and taken regularly (but perhaps less often than are conventional drugs), and their effects do not last indefinitely.

As well as the challenges imposed by RNA therapies in terms of their delivery, targeting and efficacy, there are some less tangible barriers to their use.

First, there might be psychological barriers to their uptake. Any new treatment can seem frightening to patients and their families. Even medical professionals sometimes prefer to stick with less effective, but more familiar, approaches to managing conditions. There is work to be done in making RNA therapies less alien and more akin to conventional medications, but this is best done by communicating the vast health benefits that they might bring. The first applications of such drugs have been in rare genetic diseases. Parents of children with these conditions have often run out of conventional treatment options. They might also be better connected to medical professionals and therefore be more willing to try fresh approaches.

WITH SAFE AND EFFECTIVE TREATMENTS, GENETIC DISEASES THAT ARE INCURABLE NEED NOT BE A LIFE SENTENCE.

Second, RNA therapies are more expensive than many drugs that are already on the market. The UK National Institute for Health and Care Excellence, which approves treatments for use by the UK National Health Service on the basis of cost-effectiveness, currently quotes a cost of £450,000 (US$553,000) for the first year of treating spinal muscular atrophy with nusinersen, and then £225,000 for each subsequent year. Advances on the scale of RNA therapies do not come cheap, and we should not underestimate the value of an effective therapy to the family of a child with spinal muscular atrophy.

Finally, by and large, these medications are best for tackling conditions with a common genetic aetiology. In an era of personalized medicine, it might not be cost-effective to design a specific intervention for individual mutations. However, many inherited diseases do share specific types of mutation, and these are ripe for the development of RNA therapies.

This fresh approach to tackling genetic diseases has the potential to create a sea change in how we think about treating people with inherited conditions. With safe and effective treatments that really work, genetic diseases that are incurable at present need not be a life sentence in the future. The barriers that remain are not insurmountable. We still have work to do, but the future is bright for RNA therapies. ■

Lorna Harries *is professor of molecular genetics at the University of Exeter, UK.*
e-mail: l.w.harries@exeter.ac.uk