RNAi Gene Therapy: Gene Silencing Drug 'Speaks Up' Following FDA Approval

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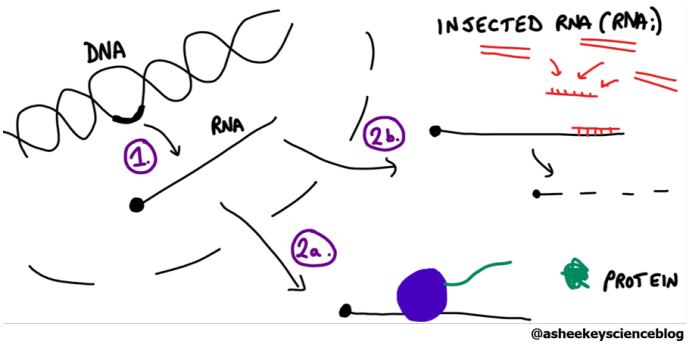
Twenty years after the molecular mechanism of gene silencing was unraveled, researchers are making critical steps forward following the US Food and Drug Administration (FDA) approval of a new gene silencing therapeutic. The drug, Onpattro (Patisiran), licensed by Alnylam Therapeutics, is designed to treat patients with hereditary transthyretin-mediated (hATTR) amyloidosis, a rare but life-threatening disease that causes damage to the peripheral nerves. The drug works by targeting RNA before it has a chance to be translated into a disease-causing protein. Now that this drug approval barrier has been overcome, have doctors and researchers entered a new era of treating genetic diseases?

WHAT IS GENE SILENCING THERAPY?

Many pharmaceutical therapies work to inhibit harmful protein activities. Conventional pharmaceutical drugs act by directly binding and blocking the actions of proteins. Alternatively, therapies can indirectly prevent the action of a dangerous protein by stopping that protein from being manufactured in the first place. Gene silencing, one such natural cellular phenomenon, achieves this blockage by causing degradation of the intermediate RNA form of a gene before the RNA code can be translated to make the protein. Also known as RNA interference (RNAi), gene silencing involves recognition of the single-stranded RNA intermediate (mRNA) by another single-stranded RNA molecule that comes from a double-stranded RNA precursor. Once the RNA molecules interact, a whole suite of decay factors are recruited to degrade the targeted mRNA (Figure 1).This RNA-on-RNA interaction can serve as a therapeutic model: researchers are able to introduce double-stranded RNA that is designed to target an RNA coding for a protein of interest. There are numerous benefits to using RNAi over conventional drugs – it is highly specific to target genes, works at low doses, and can potentially be adapted to target any gene.

WHAT TOOK THEM SO LONG?

While FDA-approval is an astonishing achievement for the field of RNAi drugs, you might be wondering why it took so long to occur. The mechanism of RNAi has been understood for decades when it was first unraveled in the nematode worm by Andrew Fire and Craig Mello2, culminating in the receipt of the Nobel Prize in Physiology or Medicine in 2006. However, researchers had to overcome several challenges in order to take the RNAi theory to therapy 4. Firstly, they needed mechanism of administration to ensure the RNA was delivered to the correct cells at the right time. Secondly, there was also concern that – despite the specificity of



RNA binding – there could be unwanted side effects of RNAi. For example, back in 2008, RNAi to treat age-related macular degeneration was thought to cause further degeneration in some patients (5). While the impact of side effects is likely to vary for different RNAi drugs, caution must be taken in clinical trials to minimize them.

HOW DOES ONPATTRO WORK?

Onpattro prevents the symptoms of peripheral nerve disease (polyneuropathy) in patients with hereditary transthyretin-mediated (hATTR) amyloidosis by targeting the mRNA transcript for transthyretin (TTR). Patients with hATTR have mutations in the TTR gene, which has deleterious consequences if the protein is expressed. Consequences include damage to body organs, particularly the heart and peripheral neurons, resulting in muscular weakness and autonomic dysfunction. RNA molecules to target and reduce the transcript levels of TTR are the basis of Onpattro. Lipid nanoparticles encase the small RNA molecules which are then injected intravenously into the patients and taken up by the liver cells where TTR is predominantly synthesized. Destruction of TTR RNA by Onpattro reduces the amount of TTR protein present in the liver. The efficacy was confirmed in a Phase 3 clinical trial, where patients treated with Onpattro showed improved walking speed 3.

CAN WE EXPECT MORE RNAI DRUGS?

While RNAi has the flexibility to be designed to target many different genes with high specificity, there are still issues with administration and efficacy. Lipid nanoparticles are by no means the only mechanism currently being investigated. Other methods involve tagging injected RNA so that it is recognized by specific cell types. Furthermore, Alnylam Therapeutics is not the only company with

other RNAi drugs in the pipeline. Arrowhead Pharmaceuticals is designing an RNAi treatment for cystic fibrosis. Many of these drugs are at late stages of clinical trials. At a price of $450,000 per patient, Onpattro is not a cheap treatment, but with encouraging results from the clinical trial and a "money back guarantee" if ineffective (6), it seems likely that the medical profession will hear more from gene-silencing therapies in the coming years.

SOURCES

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