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INSIGHT: FDA Approves First-Ever RNAi-based Therapy

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On Aug. 10, 2018, the Food and Drug Administration approved a first-of-its-kind gene therapy product that turns off the expression of an undesired protein using a ''small interfering RNA'' (siRNA). The approval marks a significant milestone in the story of a Nobel Prize-winning technique, RNA interference (RNAi), and clears the way for a new type of biologic, siRNA.

Alnylam, a company focused on RNAi therapeutics, secured approval and Orphan Drug Designation for its siRNA product Onpattro (patisiran), a therapy for peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR). The disease is a rare and debilitating genetic condition caused by mutations in a protein called ''transthyretin.'' Abnormal forms of the transthyretin protein build up in nerves, the heart, and other organs causing nerve damage, neuropathic pain, and loss of sensation in the hands and feet. In Alnylam's Phase III clinical trial, Onpattro reversed polyneuropathy and improved multiple clinical manifestations of the disease, demonstrating safe and effective administration of an siRNA product. Onpattro is the first FDA-approved treatment for this disease.

RNAi-based therapy: ups and downs

The approval of Onpattro comes after over a decade of pursuing RNAi for human therapy. The initial discovery of RNAi was hailed as a major scientific breakthrough. *Science* declared it 2002's Breakthrough of the Year. In 2006, the Nobel Prize for Physiology and Medicine was awarded to Craig Mello and Andrew Fire in recognition of their discovery of RNAi and its potential importance to medicine. In contrast to other therapies, such as small molecules and antibodies, siRNAs can be designed to turn off the expression of any human gene, opening up new possibilities for treating diseases.

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Many companies, like Alnylam, began developing RNAi-based drug candidates. These companies included Allergan, Sirna Therapeutics, Quark Pharmaceuticals, Silence Therapeutics, and RXi Pharmaceuticals, among others. Researchers of RNAi-based therapies targeted a range of conditions including cancers, asthma, macular degeneration, ocular disorders, and rare hereditary diseases.

But a series of pharma exits from the RNAi space suggested that the technical hurdles associated with bringing an RNAi-based therapy to market were too great. In 2011, Pfizer announced it was exiting therapeutic RNAi research and development as part of a global cost-saving restructuring plan. In 2014, Merck sold the technology and intellectual property it acquired for $1.1 billion in purchasing Sirna Therapeutics in 2006 to Alnylam for $175 million. In 2015, Novartis sold its decade-old RNAi business to Arrowhead for $35 million in cash and stock.

A significant hurdle for RNAi-based therapy has been getting the siRNA to the right location in the body. To turn off gene expression, the siRNA must be inside the cell of interest. This means the siRNA must be transported to the tissue in the body where the target cells reside and then it must cross through the cell's membrane. These requirements are generally referred to as ''delivery'' of the siRNA to the desired location.

What are RNAi and siRNA and why is siRNA delivery so difficult?

RNAi is a natural process that occurs in cells to stop a gene from being expressed (producing a particular protein). siRNA is the molecule that carries out the process of RNAi. Administering siRNA as a therapeutic is a way of using the cell's natural RNAi process to turn off the expression of a gene of interest.

siRNA works by interfering with the production of a protein at an intermediate stage, before the protein is made. Proteins are made in carefully prescribed steps: first the DNA sequence of a gene is transcribed into a molecule called a messenger RNA (mRNA); next the mRNA sequence (carrying over the gene's sequence) is translated into the corresponding amino acid sequence or protein. siRNA stops the production (and therefore activity) of a protein by interfering with the mRNA and preventing it from being translated into protein. Once an mRNA sequence of interest is known, an siRNA can be designed with a complementary sequence that is

able to bind to the mRNA and cause its destruction. Without the mRNA, protein synthesis is effectively stopped.

A key feature of siRNA is that a single siRNA can degrade many mRNAs, making it a powerful way of turning off unwanted protein production. In the case of Onpattro, the therapeutic siRNA interferes with the production of the protein that causes transthyretin-mediated amyloidosis.

RNAi falls under the umbrella of gene therapy. It differs from other gene editing technologies, like CRISPR, in that siRNAs target the intermediate mRNA molecule, whereas gene editing techniques like CRISPR target the DNA sequence of the gene of interest. siRNA is also distinct from other types of biologics, such as therapeutic antibodies, which bind to proteins in the body and impact their function.

Despite the promise of siRNA as a therapeutic and pharma's investment, delivering siRNA to the desired location in the body proved difficult. Delivery is challenging because siRNAs are relatively large, negatively charged molecules that do not naturally travel through a cell's outer membrane into the cell. siRNAs are also rapidly excreted from the blood stream when introduced into the body. Further, siRNAs were found to trigger innate immune molecules to initiate inflammation, raising concerns about how to safely and selectively transport siRNA to target tissues in the body and avoid unwanted inflammation.

Overcoming delivery to bring forward a new class of therapeutics

Alnylam developed siRNA therapeutic candidates that employ two different delivery approaches. The first approach is to deliver the siRNA molecule in a lipid nanoparticle. Lipid nanoparticles naturally accumulate in the liver and are able to pass through the membrane of a cell. This delivery method is therefore well-suited for protein targets that are found in the liver. It is used for Onpattro to treat hATTR because the transthyretin protein is produced predominantly in the liver.

Alnylam's other late-stage siRNA therapeutic candidates utilize a different delivery approach in which the siRNA is attached to another molecule that guides the siRNA to the target location. Because this approach is not limited to targeting the liver, it opens up the possibility of treating a wider range of human diseases. In the case of Alnylam's late-stage products (Givosiran for acute hepatic porphyrias, Fitusiran for hemophilia, and Inclisiran for hypercholesterolemia), the siRNA is attached to a sugar molecule for target-specific delivery.

Patient access

On the same day as Onpattro's approval, Alnylam announced that it agreed on the structure and key terms of value-based agreements (VBA) with leading health insurers, paving the way for patient access. VBA agreements effectively provide a money-back guarantee if Onpattro does not deliver outcomes to patients that are similar to those in the clinical trials resulting in approval. The financial terms are therefore linked to the product's performance.

Patent perspective and regulatory exclusivity

With the first siRNA therapy now a reality and new products on the horizon, patent disputes involving siRNA are likely as well. For example, Alnylam recently filed a declaratory judgment action against Silence Therapeutics in the District of Massachusetts for non-infringement of patents directed to modified nucleic acid molecules. The suit follows ongoing litigation in the U.K. between the companies also involving Silence Therapeutics' patents. In addition, Alnylam filed *post-grant* reviews (PGRs) before the U.S. Patent and Trademark Office challenging Silence Therapeutics' patents directed to siRNA molecules as unpatentable. Alnylam argues the patents lack written description and enablement for failing to disclose a single example of an siRNA molecule while claiming a large number of structurally diverse siRNA molecules.

In addition to any patent exclusivity, regulatory exclusivity also is undoubtedly important to new siRNA products. Under the Biologics Price Competition and Innovation Act of 2009 (BPCIA), new biologics are granted 12 years of non-patent market exclusivity. Therefore, what falls under the category of a ''biologic'' is important to recouping investment in R&D. Last month, the FDA issued draft guidance for the industry on regulation of human gene therapies for rare diseases. In that guidance it stated that gene therapy products meet the definition of ''biological product'' under the Public Health Service (PHS) Act ''when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings.'' Some companies, however, may challenge the FDA's interpretation of ''biological product'' because gene therapy is not expressly included in the definition of ''biological product.'' On the other hand, biosimilar makers may embrace regulating gene therapies as biologics because they then have an abbreviated regulatory pathway to gain approval of a siRNA.