Therapeutic landscape

Traditional therapies, such as small molecules and monoclonal antibodies, regulate disease pathology by modulating protein targets that are products of the disease-causing gene.[10,11] They are systemically distributed, increasing the potential for off-target effects that can result in toxicities.[12,13]

Small-molecule drugs may be inhibitors or antagonists of disease-causing proteins, yet only 10% to 14% of proteins have active binding sites that offer "druggable" targets.[14]

Biologics, such as monoclonal antibodies, modulate signaling pathways, recruit cells or proteins, deliver cytotoxins, or neutralize or modulate circulating factors.[15] Moreover, monoclonal antibodies may have challenges with immunogenicity.[16]

DNA-targeted therapies, such as gene editing, precisely alter a specific section of the DNA at the genetic level to correct a disease-causing mutation by inserting, deleting, or replacing specific DNA sequences within the gene target. This directly modifies the target gene, causing potentially irreversible alterations to the patient's genome.[8,14]

RTTs: AN INNOVATIVE APPROACH

RTTs differ from other drug modalities, leveraging an innovative approach designed to address known challenges, including offering the potential to impact previously "undruggable" targets, enable rapid and efficient development, and alter the mRNA construct to optimize treatment.[7,14]

RNA-targeted therapies:

- **Act at the RNA level** to reduce protein production, offering an alternative approach for diseases with genetic components[10]
- **Reversibly alter gene expression** at the RNA level to reduce protein production without altering a patient's genome[8]

IONIS

Over 35 years of leadership in RNA-targeted therapies[17,18]

- We're driven by a **deep understanding of the genetic foundations of diseases** and a commitment to advancing next-generation technology
- **We have pioneered important firsts for 3 decades, including groundbreaking approaches in spinal muscular atrophy and amyotrophic lateral sclerosis**
- Today, we celebrate the development of 6 commercialized RTTs and **continue to commit to ongoing innovation, with dozens of RTTs in development**
- As we look to the future, our work is far from done. We plan to advance and expand our chemistry platform, aiming not only to identify the appropriate medicines for specific diseases but also to **maximize their impact and effectiveness, delivering transformational medicines to people living with serious diseases**

Additional questions?
Email us at **Info@ionis.com**

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INNOVATION SPOTLIGHT

RNA-targeted therapies: an innovative approach to treating disease[1]

RNA-targeted therapies (RTTs) are an established platform and class of medicines aimed at regulating disease-causing genes and their variants at the RNA level.[1]

There are many RTTs approved by the FDA to treat a variety of conditions — including kidney, liver, cardiovascular, neurological, neuromuscular, eye, infectious, and rare diseases — many serve as first-line therapies for their respective diseases.[2-5]

Ionis is currently developing a novel investigational medicine that explores the potential of RTT for hereditary angioedema (HAE).[6]

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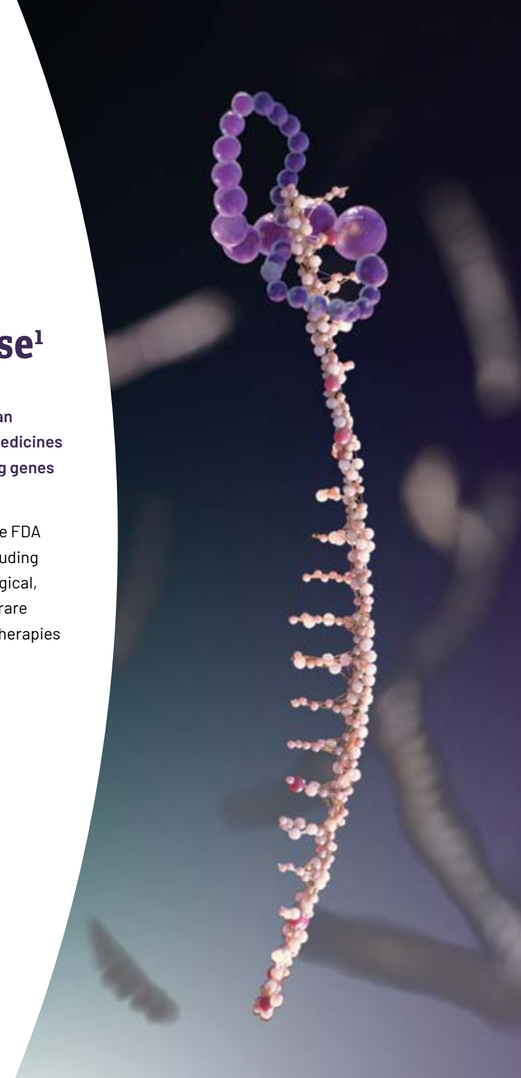

The science behind RNA-targeted therapies

RTTs use RNA-based molecules to modulate gene expression by targeting mRNA upstream of protein production.[7] They selectively target a single gene product and are thus designed to alter gene expression at the level of translation without altering a patient's genome.[1,8]

RNA-targeted therapies contain several chemical modifications and features that enhance their therapeutic potential[9]:

- A **phosphorothioate** modification that **increases stability**
- A **sugar** modification that enhances **pharmacokinetic and pharmacodynamic properties**
- **Sequence-specific** base pairing to **target mRNA**

RNA-targeted therapies can leverage ligand-conjugated antisense (LICA) technology (eg, GalNAc), which adds specific chemical structures or molecules to allow for receptor-mediated delivery of the RNA-targeted therapy to a particular organ or tissue, for instance hepatic parenchymal cells.

A rich history of more than 45 years[7,8]

1978 Concept of ASOs as therapeutic agents proposed

1980

1990 Concept of mRNA-encoded drugs conceived

1990 Discovery of aptamer

1990

1993 Discovery of miRNA

1998 Discovery of RNAi

2000

1998 First ASO drug approved

2006 First aptamer drug approved

2010

2018 First siRNA drug approved

2020 First 2 mRNA vaccines approved

2020

ASO=antisense oligonucleotide; mRNA=messenger RNA; miRNA=microRNA; RNAi=RNA interference; siRNA=small interfering RNA.

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