RNA Interference (RNAi) and the Future of Drug Development

The History of RNAi

- Alnylam is leading the translation of RNA interference (RNAi) into innovative medicines. The science of RNAi is widely considered one of the most promising and rapidly advancing frontiers in biology and drug development today.[1]
- Historically, RNA was only thought to be involved in protein synthesis. However, in recent years, RNAs have been identified to also play significant roles in regulatory functions within the cell.[1]
- A specific class of RNA, called small-interfering RNA (siRNA), appeared to exert cellular control resulting in gene silencing.[2]
- In 2001, researchers confirmed that siRNA-mediated gene silencing did, indeed, occur in human cells.[3] This form of gene silencing has since become widely known as RNA interference, or RNAi for short. In 2006, Andrew Z. Fire, Ph.D., and Craig C. Mello, Ph.D., were awarded the Nobel Prize in Medicine, honoring their discovery of a fundamental RNA-based mechanism controlling the flow of genetic information.[4]
- In 2018, after years of research, ONPATTRO® (patisiran) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults, marking the arrival of an entirely new class of medicines. Using the same RNAi technology, GIVLAARI® (givosiran) was approved in 2019 for the treatment of adults with acute hepatic porphyria (AHP), OXLUMO® (lumasiran) was approved in 2020 for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients, Leqvio® (inclisiran)* approved in 2021 for the treatment of hypercholesterolemia and AMVUTTRA® (vutrisiran) was approved in 2022 for the subcutaneons treatment of polyneuropathy of hATTR amyloidosis in adults.

RNAi: A Revolution in Biology

- At the heart of the RNAi mechanism is a protein complex known as RISC (the RNA-induced silencing complex), a key component of the RNAi pathway. Researchers have found that RISC can bind to siRNAs that have been designed to be complementary for strands of the target mRNA. Once bound to the siRNA, RISC prowls the cell, searching for a lock-and-key match to the siRNA strand it carries. When it finds a matching mRNA, it degrades it. This cleavage disrupts synthesis of the protein.[5]
- Drugs based upon RNAi have represented a new class of human therapeutics. Traditionally, drugs have been developed to stop the activity of disease-causing proteins directly, but do not get to the root cause. RNAi therapeutics are designed to address the underlying mechanism of a disease by blocking production of disease-causing proteins, acting upstream of traditional therapies that work at later steps in disease pathogenesis.
- Because siRNAs can be designed to target essentially any protein-coding mRNA, this opens up possibilities for addressing a variety of genetically validated targets.[5] siRNAs can also be designed to exhibit great specificity and can enter into the cell to silence the expression of intracellular proteins. Clinical trials are currently being conducted to evaluate the safety and efficacy of using this promising approach for a number of human diseases.
- Based on Nobel Prize winning science, RNAi therapeutics represent a powerful approach for the treatment of a wide range of severe and debilitating diseases, affording us the potential to transform the lives of patients who have limited treatment options.
- Alnylam is advancing its proprietary RNAi delivery technology known as the Enhanced Stabilization Chemistry (ESC)-GalNAc-conjugate delivery platform to enable subcutaneous administration.

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RNAi Fast Facts

- Alnylam was founded in 2002 to explore therapeutic applications of RNAi and has committed itself to developing a deep pipeline of products with the potential to treat a wide range of human diseases.
- The RNAi mechanism was discovered, in part, by the scientific founders of Alnylam.
- Andrew Z. Fire, Ph.D., and Craig C. Mello, Ph.D., were awarded the Nobel Prize for Medicine in 2006 for their groundbreaking work that revealed a novel RNA-based mechanism for gene-silencing RNAi.
- siRNAs activate RISC, then silence gene expression by targeting specific messenger RNAs (mRNA) and inhibiting synthesis of the targeted protein.
- As of January 2022, Alnylam has eleven clinical programs evaluating RNAi compounds in diseases with high unmet medical need that fall under four Strategic Therapeutic Areas (STArs): genetic medicines, cardio-metabolic diseases, infectious diseases and CNS diseases.

For more information, please contact media@alnylam.com or visit alnylam.com.

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