

# RNA Interference (RNAi) and the Future of Drug Development

## The History of RNAi

- Alnylam is leading the translation of RNA interference (RNAi) as a potential new class of innovative medicines. The science of RNAi is widely considered one of the most promising and rapidly-advancing frontiers in biology and drug development today.<sup>1</sup>
- 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.<sup>1</sup>
- A specific class of RNA, called small-interfering RNA (siRNA), appeared to exert cellular control resulting in gene silencing. This mechanism of interference might work not only in worms, but has been also shown to occur in plants, invertebrates, and mammals.<sup>2</sup>
- In 2001, researchers confirmed that siRNA-mediated gene silencing did, indeed, occur in human cells.<sup>3</sup> 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.<sup>4</sup> Today, after years of research, investigational therapies based on this discovery are in late-stage clinical development.

## A Potential New Approach to Human Therapeutics

- 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 a complementary match 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.<sup>5</sup>
- Drugs based upon RNAi are a potential 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 can be 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.<sup>5</sup> 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 this promising approach for a number of human diseases.
- Alnylam is leading the translation of RNAi into a whole new class of innovative medicines based on Nobel Prize-winning science, which has 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.

### 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 February 2018, the company has seven clinical programs evaluating RNAi compounds in diseases with high unmet medical need that fall under 3 Strategic Therapeutic Areas (STArS): genetic medicines, cardio-metabolic diseases, and hepatic infectious diseases.
- Of Alnylam’s seven clinical programs, one – patisiran – has completed Phase 3 clinical trials. In the APOLLO study, patisiran was evaluated for the treatment of hereditary ATTR (hATTR) amyloidosis, an inherited, rapidly progressive life-threatening disease. Patisiran is currently under review by US and EU regulatory health agencies. The remaining six Alnylam compounds are either in early- or late-stage clinical development.

For more information, please contact [media@alnylam.com](mailto:media@alnylam.com) or visit [alnylam.com](http://alnylam.com).

*Patisiran has not been approved by the U.S. Food and Drug Administration, European Medicines Agency, or any other regulatory authority and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.*

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<sup>1</sup> Couzin J. Small RNAs make a big splash. *Science*. 2002;298:2296-7.

<sup>2</sup> Fire A, Xu S, Montgomery MK, et al. *Nature*. 1998;391:806-11.

<sup>3</sup> Elbashir SM, Harborth J, Lendeckel W. *Nature*. 2001;411:494-8.

<sup>4</sup> The Nobel Assembly at Karolinska Institutet. The 2006 Nobel Prize in Physiology or Medicine. Nobel Media AB 2014.

<sup>5</sup> de Fougères A, Vornlocher H-P, Maraganore J, et al. *Nat Rev Drug Discov*. 2007;6:443-53.