Alnylam®

SUMMARY OF RNAi

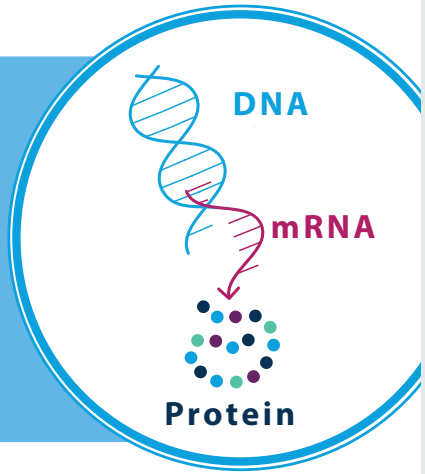
AN OVERVIEW OF RNAi DISCOVERY, HOW RNAi WORKS, AND THE POTENTIAL OF RNAi THERAPEUTICS

This summary is based on published scientific literature on RNA interference (RNAi).

Developed and funded by Alnylam Pharmaceuticals.
For US healthcare professionals and patient advocacy group leaders only.

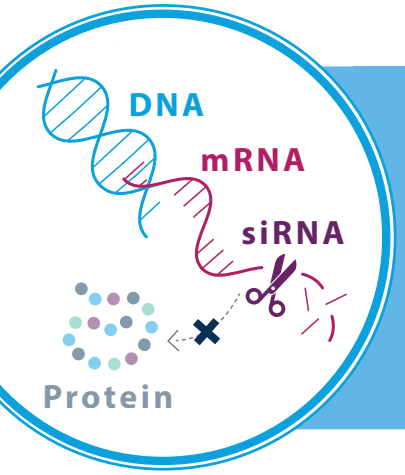
WHAT IS RNA?[1]

- RNA is a molecule that carries genetic instructions, like the code for a protein, from DNA
- A type of RNA called messenger RNA (mRNA) delivers these instructions to the part of the cell that builds proteins, guiding the production of one specific type of protein
- Certain proteins may cause or contribute to disease[2]



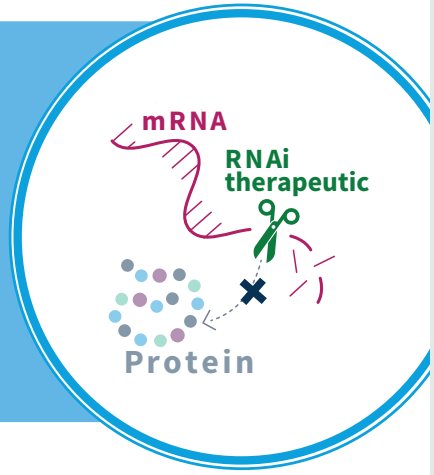
WHAT IS RNAi?[3-6]

- RNA interference (RNAi) is a process that uses small RNAs called small interfering RNAs (siRNAs) to break down matching mRNA
- This reduces how much of a specific protein the cell makes

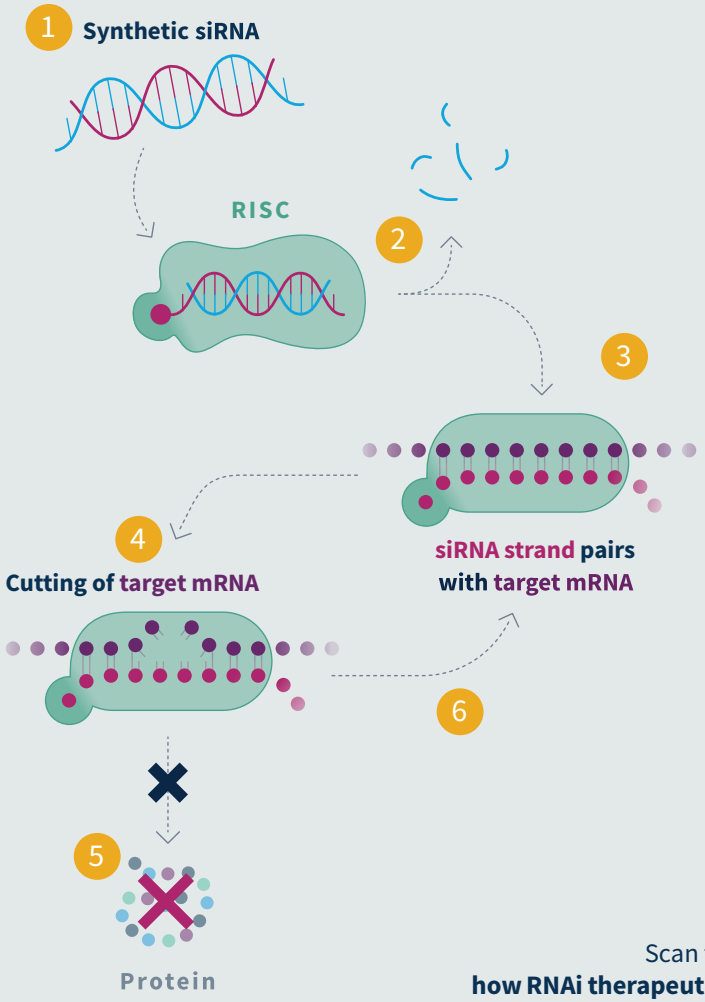


WHAT ARE RNAi THERAPEUTICS?[7-9]

- RNAi therapeutics are synthetic double-stranded siRNA molecules made to match a single target mRNA sequence
- They are designed to reduce the production of a specific protein to help treat a disease of interest



HOW DO RNAi THERAPEUTICS WORK?[3-6]



1. siRNAs contain 2 strands; 1 **strand** matches and pairs with the **target mRNA**
2. The 2 siRNA strands are separated by a group of proteins called **RISC**
3. The **strand** that remains in **RISC** is the one that matches the code on the **target mRNA**
4. **RISC** cuts the **target mRNA** and causes it to break down
5. Breaking down the **target mRNA** causes **the production of a specific protein to be decreased**
6. The same siRNA-loaded **RISC** can be used repeatedly to break down multiple copies of the **target mRNA**

Scan to watch **how RNAi therapeutics work** at RNAiScience

For US healthcare professionals only.

RNAi therapeutics use the natural process of RNAi to **reduce** the production of a specific **protein** associated with a disease[9]

FEATURES OF RNAi THERAPEUTICS

RNAi therapeutics:

- Are different from traditional medicines[10,11]
  - Traditional therapies (such as small molecules or antibodies) usually bind to a target protein to stop it from working, or block a receptor
  - RNAi therapeutics work by targeting mRNA to reduce the production of specific proteins that cause or affect the development of a disease
- Control protein production without making any changes to the DNA—their effects on mRNA and protein production are fully reversible[8]
- Are selective for the target mRNA[3,12]
- Can work over extended periods because chemical modifications help them stay stable in the body[8,12]
- Have the potential to treat different diseases throughout the body[13-16]

Scan to learn more about **Alnylam's pipeline of investigational therapies** at RNAiScience

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HOW ARE RNAi THERAPEUTICS DELIVERED?

RNAi therapeutics can be delivered through different methods.

Currently, delivery mechanisms include:[3,12,17]

Intravenous infusion
Infusion into a vein (e.g., every 3 weeks)

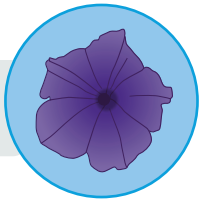
Subcutaneous injection
Injection under the skin (e.g., monthly to twice yearly)

Intrathecal injection
Injection into the space surrounding the spinal cord (being studied)

THE HISTORY OF RNAi AND ALNYLAM

1990-2001

1990 Effect of RNAi first seen in nature in petunias[18]



1998 Scientists discovered how RNAi works[19]

2002

2002 Alnylam founded

RNAi TECHNOLOGY

2004 RNAi first used to reduce protein production from a natural gene using synthetic siRNA[20]

2006 Nobel Prize awarded for RNAi discovery[21]

2018+

2018 The first RNAi therapeutic, developed by Alnylam, approved for use[22]

2018-2025 Since then, 5 additional Alnylam-discovered RNAi therapeutics have been approved for use[23-27]

ALNYLAM HAS A STRONG RECORD OF ADVANCING DEVELOPMENT OF RNAi THERAPEUTICS[28-36]

To date, RNAi therapeutics have been tested in over **2700 patients** across **12 major clinical trials**[27-36]

Several Alnylam-discovered RNAi therapeutics are approved and available to patients worldwide to treat rare and common diseases[22-27,37]

Many more RNAi therapeutics are being studied for use across a variety of diseases[10,11]

GLOSSARY

DNA Deoxyribonucleic acid	The molecule that stores genetic instructions
mRNA Messenger ribonucleic acid	A specific type of RNA that carries instructions from DNA to the part of the cell that makes proteins
RISC Ribonucleic acid–induced silencing complex	A group of proteins that uses siRNA to find and break down matching mRNA
RNA Ribonucleic acid	A molecule present in all living cells that carries genetic information
RNAi Ribonucleic acid interference	A process that reduces protein production by breaking down specific mRNA
siRNA Small interfering ribonucleic acid	A type of RNA that can match and break down specific mRNA, helping to lower the amount of a certain protein

KEY TAKEAWAYS: RNAi THERAPEUTICS

Use a **natural process to reduce the production of a specific protein** associated with a disease[9]

Can be **made to match 1 specific target mRNA** to avoid effects on other proteins[7,8]

Remain active in RISC and **can be used repeatedly** to lower protein levels[3,8,12,38,39]

May allow for **infrequent dosing**[8,12,38]

Have the **potential to treat many different diseases**[13-16]

REFERENCES

1. National Human Genome Research Institute. Fact sheet—Ribonucleic acid (RNA). Updated May 24, 2024. Accessed July 2, 2025. https://www.genome.gov/about-genomics/educational-resources/fact-sheets/ribonucleic-acid-fact-sheet; 2. Valastyan JS, Lindquist S. *Dis Model Mech.* 2014;7:9-14; 3. Friedrich M, Aigner A. *BioDrugs.* 2022;36:549-571; 4. Cuccato G, et al. *BMC Syst Biol.* 2011;5:19; 5. Martinez NJ, Gregory RI. *RNA.* 2013;19:605-612; 6. Varley AJ, Desaulniers JP. *RSC Adv.* 2021;11:2415-2426; 7. Lam JKW, et al. *Mol Ther Nucleic Acids.* 2015;4:e252; 8. Ranasinghe P, et al. *Br J Pharmacol.* 2023;180:2697-2720; 9. Traber GM, Yu AM. *Mol Pharmacol.* 2024;106:13-20; 10. Jay PY, et al. *Int J Cardiovasc Sci.* 2022;35:665-675; 11. Zhang MM, et al. *Biochem Pharmacol.* 2021;189:114432; 12. Hu B, et al. *Signal Transduct Target Ther.* 2020;5:101; 13. Chen X, et al. *Cancer Metastasis Rev.* 2018;37:107-124; 14. Forbes TA, et al. *Br J Clin Pharmacol.* 2022;88:2525-2538; 15. Seyhan AA. *Hum Genet.* 2011;130:583-605; 16. Ardiana M, et al. *Noncoding RNA Res.* 2023;8:487-506; 17. Brown KM, et al. *Nat Biotechnol.* 2022;40:1500-1508; 18. Napoli C, et al. *Plant Cell.* 1990;2:279-289; 19. Fire A, et al. *Nature.* 1998;391:806-811; 20. Soutschek J, et al. *Nature.* 2004;432:173-178; 21. Nobel Prize. The Nobel Prize in Physiology or Medicine 2006—Advanced information. Accessed July 2, 2025. https://www.nobelprize.org/prizes/medicine/2006/advanced-information/; 22. ONPATTRO® (patisiran) Summary of Product Characteristics; 23. GIVLAARI® (givosiran) Summary of Product Characteristics; 24. OXLUMO® (lumasiran) Summary of Product Characteristics; 25. LEQVIO® (inclisiran) Summary of Product Characteristics; 26. AMVUTTRA® (vutrisiran) Summary of Product Characteristics; 27. QFITLIA® (fitusiran) US Prescribing Information; 28. Adams D, et al. *N Engl J Med.* 2018;379:11-21; 29. Adams D, et al. *JAMA Neurol.* 2025;82:228-236; 30. Balwani M, et al. *N Engl J Med.* 2020;382:2289-2301; 31. Garrelfs SF, et al. *N Engl J Med.* 2021;384:1216-1226; 32. Raal FJ, et al. *N Engl J Med.* 2020;382:1520-1530; 33. Ray KK, et al. *N Engl J Med.* 2020;382:1507-1519; 34. Fontana M, et al. *N Engl J Med.* 2025;392:33-44; 35. Hayes W, et al. *Pediatr Nephrol.* 2023;38:1075-1086; 36. Michael M, et al. *Am J Kidney Dis.* 2023;81:145-155; 37. Jadhav V, et al. *Nat Biotechnol.* 2024;42:394-405; 38. Brown CR, et al. *Nucleic Acids Res.* 2020;48:11827-11844; 39. Li Z, Rana TM. *Acc Chem Res.* 2012;45:1122-1131.

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