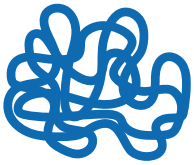
siRNA: A New Treatment Approach

The role of proteins in disease

Proteins are needed for the structure, function, and regulation of the body's tissues and organs[1].

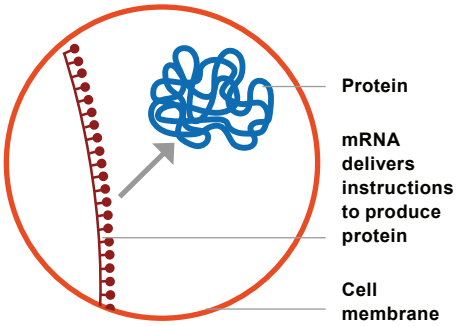
Over- or under-production of specific proteins can play an important role in the development of diseases[2].



Protein production, messenger RNA and the RNAi process

Messenger ribonucleic acid (RNA) carries the instructions to produce proteins within the cells.

RNA interference (RNAi) is a naturally occurring process within our cells that targets messenger RNA (mRNA) to prevent the production of specific proteins[3,4].



siRNA harnesses RNAi to regulate protein production

Small interfering RNAs (siRNAs) are molecules operating in the RNAi process.

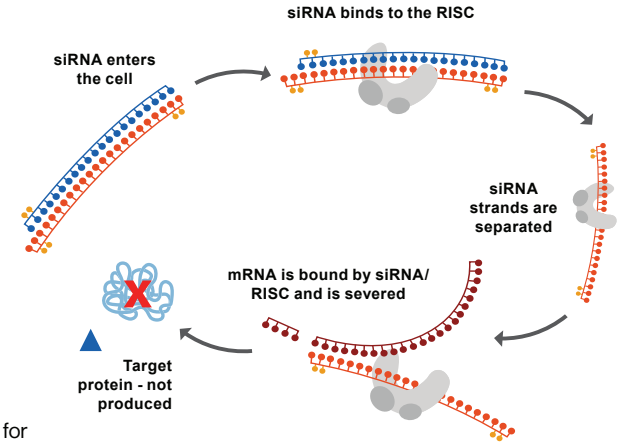
siRNAs bind to the RNA-induced silencing complex (RISC), resulting in a single-stranded siRNA/RISC that matches very specifically to the mRNA encoding the target protein[2,3].

siRNAs used for treatment

siRNAs are now being used as a new treatment approach because they have a durable, or long-lasting, therapeutic effect and are very specific to their target mRNA[3,5].

siRNAs have been approved for rare diseases including: givosiran for acute hepatic porphyria, patisiran for transthyretin-mediated amyloidosis in adult patients and lumasiran for primary hyperoxalura type 1[6-8].

Leqvio® (inclisiran) has been FDA approved as the first and only siRNA therapy in certain patients to lower low-density lipoprotein cholesterol (LDL-C). Leqvio injection is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with clinical atherosclerotic cardiovascular disease (ASCVD) or heterozygous familial hypercholesterolemia (HeFH) who require additional lowering of LDL-C. The effect of Leqvio on cardiovascular morbidity and mortality has not been determined[9].



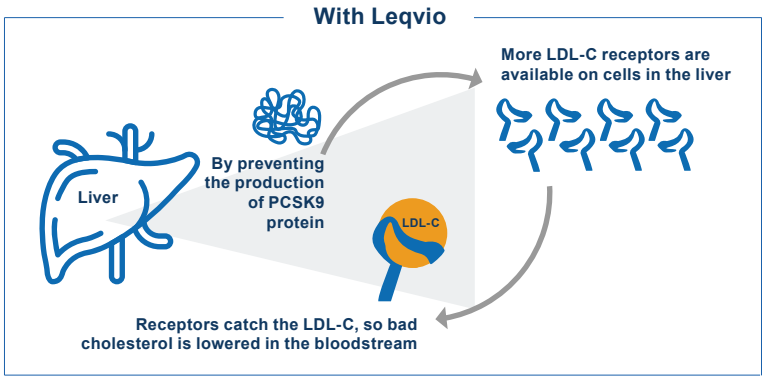
Approved new treatment in siRNA class to reduce "bad" cholesterol (LDL-C)

The regulation of LDL-C levels in the bloodstream takes place in the liver.

Leqvio has been shown to harness RNAi to increase the liver's natural ability to clear LDL-C from the bloodstream[5].

With 2 doses a year, after an initial dose and another at 3 months, Leqvio is the first siRNA that is proven to provide effective and sustained reduction of LDL-C over each 6-month dosing interval[10,11]. Because it's a new therapy within the siRNA class, Leqvio works differently from other currently approved lipid-lowering therapies[5].

In clinical trials, the most common side effects of Leqvio were: injection site reaction (including pain, redness and rash), arthralgia (joint pain), urinary tract infection, diarrhea, bronchitis, pain in legs or arms and dyspnea (shortness of breath)[9].



REFERENCES

1. US National Library of Medicine: Genetics Home Reference. What are proteins and what do they do? Accessed September 29, 2021. https://ghr.nlm.nih.gov/primer/howgeneswork/protein. **2.** Tatiparti K, et al. siRNA delivery strategies: a comprehensive review of recent developments. *Nanomaterials (Basel).* 2017;7(4):77. **3.** Castanotto D, et al. The promises and pitfalls of RNA-interference-based therapeutics. *Nature.* 2009;457(7228):426-433. **4.** US National Library of Medicine: Genetics Home Reference. How do genes direct the production of proteins? Accessed September 29, 2021. https://ghr.nlm.nih.gov/primer/howgeneswork/makingprotein **5.** Stoekenbroek RM, et al. Inclisiran for the treatment of cardiovascular disease: the ORION clinical development program. *Future Cardiol.* 2018;14(6):433-442. **6.** GIVLAARI (givosiran) product fact sheet. Alnylam Pharmaceuticals. 2020. **7.** ONPATTRO (patisiran) product fact sheet. Alnylam Pharmaceuticals. 2019. **8.** OXLUMO (lumasiran) product fact sheet. Alnylam Pharmaceuticals. 2020. **9.** LEQVIO prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021. **10.** Ray KK, et al. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med.* 2020;382(16):1507-1519. **11.** Raal FJ, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med.* 2020;382(16):1520-1530.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

12/21 156792