



Oligonucleotide treatments

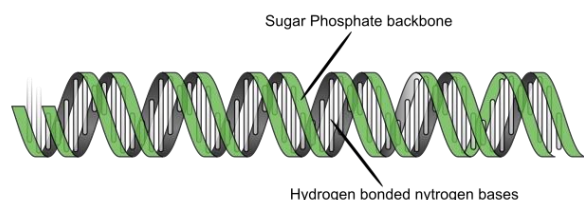
How are companies using oligonucleotides to develop novel treatments for diseases?



What are nucleotides?

Nucleotides are the building blocks of DNA and RNA, made up of a five-carbon sugar, phosphate group and nitrogenous base. The

sugar and the phosphate group together form the backbone of the DNA or RNA. The nitrogenous bases form hydrogen bonds to other bases, constructing the double helix in the case of DNA and other structures in the case of RNA.



Short strands of nucleotides, called oligonucleotides (oligos), exist within the body and can be created synthetically in a lab for various purposes.

These oligonucleotides sometimes control the expression of genes in the cell and this function is used by oligonucleotide drugs to affect protein expression levels.

As a result, they can be used to prevent the expression of mutated proteins associated with genetic disease or to reduce endogenous proteins for other therapeutic effects.

How do nucleotide drugs target mRNA?

When a gene is read, the information held in DNA is transferred to messenger RNA (mRNA) via a process of transcription. This mRNA strand is subsequently translated into proteins.

The first type of nucleotide-based drug developed was antisense technology, which uses a single-stranded oligonucleotide to bind to an mRNA and prevent it from being

translated into protein. Antisense drugs do this by binding so tightly to the mRNA that they constrict it, preventing it from physically interacting with the mRNA translation machinery (the ribosome).

Antisense drugs also achieve gene suppression by triggering RNase, an enzyme that cleaves the connection between mRNA and DNA. RNase H-mediated degradation has been shown to reduce mRNA protein expression by [more than 80%](#).

The single-stranded nature of antisense technology increases its molecular instability, requiring antisense therapeutics to go through extensive modification to improve their chemical properties.

What is the siRNA pathway?

Small interfering RNAs (siRNAs) are a different oligonucleotide technology that uses short, double-stranded RNA hairpins to trigger the degradation of targeted mRNA molecules. These siRNAs bind to an mRNA and recruit argonaute proteins that degrade the complex.

The advantage of this approach is that the double-stranded nature of the drugs means they require less chemical alteration compared to antisense technology.

However, this comes at the cost of cell penetration, requiring delivery systems, including viral vectors or liposomes.

For example, the siRNA nucleotide drug Onpattro is encapsulated in a lipid nanoparticle.

Have there been any recent movement in the clinical space?

In addition to currently approved oligonucleotide drugs (see table below), there has been a good deal of recent activity in the clinic for oligonucleotide treatments.

Recently, the FDA accepted a new drug application from NS Pharma for Duchenne muscular dystrophy for viltolarsen, while Dynacure has dosed the first patients in its

Edison Insight

‘Silence’s technology and know-how in the nucleotide space is central to its investment case. It is one of the original pioneers in nucleotide-based drug design and this legacy has been recognised by other drug developers.’

Edison Investment Research, [Solving disease by targeting genes with siRNA](#)

Phase I/II study on DYN101 for centronuclear and myotubular myopathies.

In January, Akcea released positive top-line results for its drug AKCEA-ANGPTL3-LRx in Phase II trials, which is currently targeting hypertriglyceridemia, Type 2 diabetes and non-alcoholic fatty liver disease.

Nucleotide silencing drugs

Product	Drug	Company	Approval	Indication	Technology
Kynamro	Mipomersen	Kastle	2013	Homozygous familial hypercholesterolemia (HoFH)	Antisense
Exondys 51	Eteplirsen	Sarepta Therapeutics	2016	Duchenne muscular dystrophy	Antisense
Spinraza	Nusinersen	Biogen	2016	Spinal-muscular atrophy	Antisense
Onpattro	Patisiran	Alnylam	2018	hATTR amyloidosis	siRNA
Tegsedi	Inotersen	Akcea Therapeutics	2018	hATTR amyloidosis	Antisense
Waylivra	Volanesorsen	Akcea Therapeutics	2019	Familial chylomicronemia syndrome	Antisense
Givlaari	Givosiran	Alnylam	2019	Acute hepatic porphyria (AHP)	siRNA
Vyondys 53	Golodirsen	Sarepta Therapeutics	2019	Duchenne muscular dystrophy	Antisense

Around the same time, Ionis Pharmaceuticals (which owns a majority share of Akcea) announced that its treatment for Alexander disease, ION373, received orphan drug designation from the European Medicines Agency (EMA). Alexander disease is a genetic illness that produces abnormal protein deposits.

Silence Therapeutics expects its siRNA, SLN124, for iron overload, as a consequence of beta-thalassemia and myelodysplastic syndrome, to enter clinical trials in Q120.

This is alongside its preclinical siRNA candidate SLN360 for cardiovascular disease and its collaboration with Mallinckrodt Pharmaceuticals for preclinical asset SLN500.