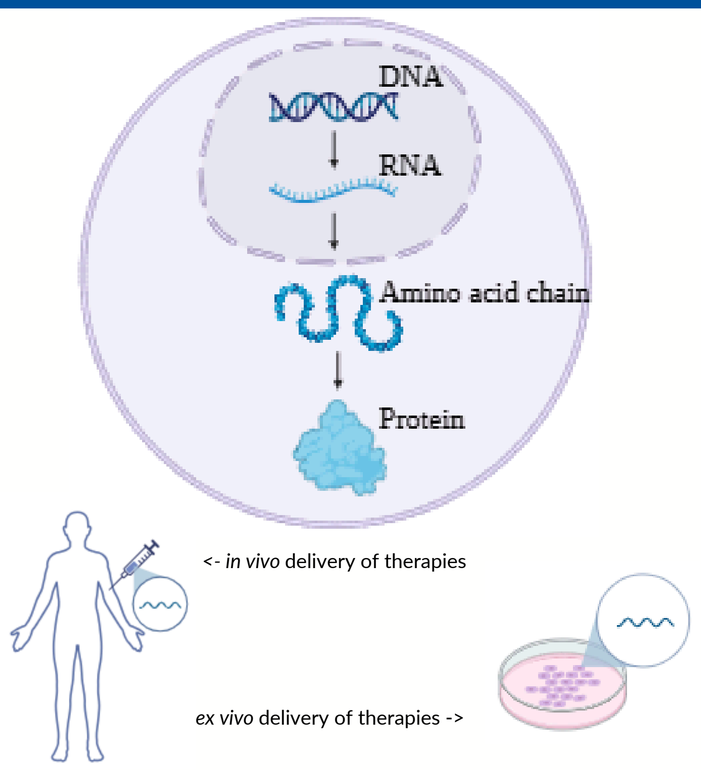
What is Genetically Targeted Technology?

DNA --> RNA --> Protein



<u>Genetically Targeted Technology (GTT)</u> is a class of small molecule therapies that target genetic material (either DNA or RNA).

Deoxyribonucleic acid (DNA) is the genetic code that determines what proteins are made and how cells function. Proteins do the principal work of cells.

DNA is first transcribed to ribonucleic acid (**RNA**) in the cell's nucleus.

Messenger RNA then leaves the nucleus and provides the assembly instructions to make functional proteins.

DNA- and RNA-based therapies can be used to treat diseases caused by an identified genetic variation, also called a mutation. These mutations produce nonfunctional protein, too much of a given protein, or not enough of a necessary protein – all of which can cause disease in patients.

DNA- and RNA-based therapies can be delivered *in vivo*, meaning directly to the patient, or *ex vivo*, meaning to patient-derived cells, usually stem cells collected from the patient's blood. Treating a small number of cells, rather than the whole person, allows for precise targeting of specific cell types.

<u>Antisense Oligonucleotides</u>

Antisense oligonucleotides (ASOs) are single-stranded RNA molecules which bind to messenger RNA (mRNA) and prevent mRNA from being translated into protein.

ASOs can prevent protein production by splitting mRNA, blocking the interaction of mRNA with molecules that initiate RNA splitting or protein assembly, or recruiting the RNA interference pathway.

<u>ASOs and RNAi</u> are typically delivered *in vivo* through injection, infusion or inhalation.

<u>The RNA Interference Pathway</u>

RNA Interference (RNAi) uses double-stranded RNA molecules that recruit the RNA-inducing silencing complex (RISC) to break down RNA or prevent its translation to protein depending on the type of RNA molecule delivered.

The use of small interfering RNA (siRNA) results in splitting of mRNA while the use of microRNA (miRNA) results in miRNA binding to mRNA and blocking further translation to protein.

<u>The CRISPR/Cas9 Complex</u>

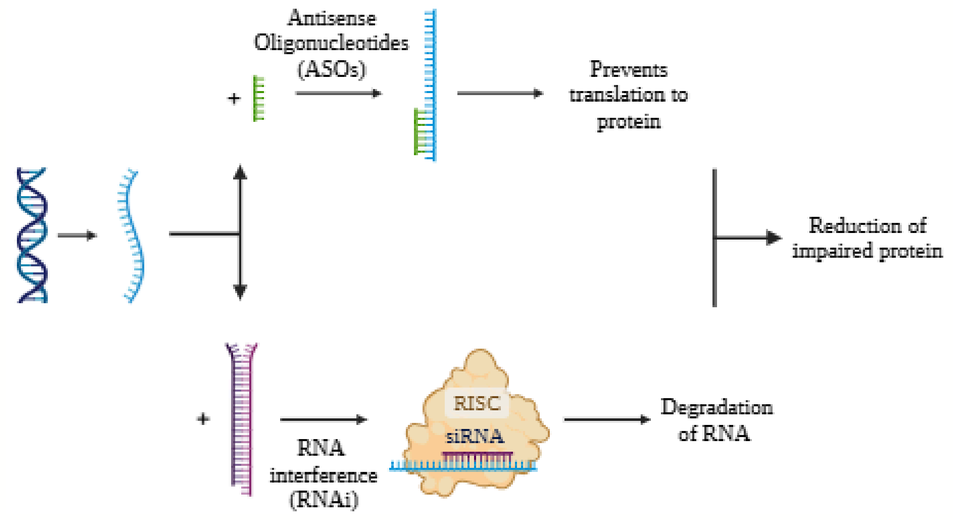
Clustered Regularly Interspersed Short Palindromic Repeats/CRISPR-associated protein 9 (CRISPR/Cas9) is a guide RNA and protein complex that allows for precise gene editing.

CRISPR/Cas9 interacts with DNA to add in repaired DNA sequences or cut out disease-causing mutations.

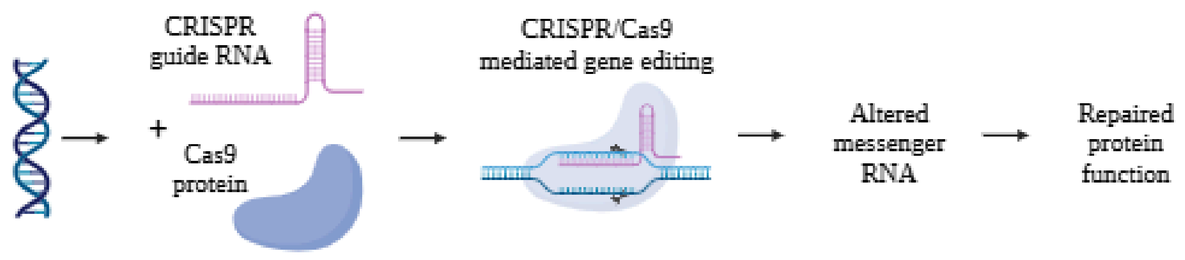
<u>CRISPR-Cas9</u> is delivered *in vivo* or *ex vivo* via injection or electroporation, an electricity-mediated delivery across cell membranes.

How does genetically targeted technology alter cell function?

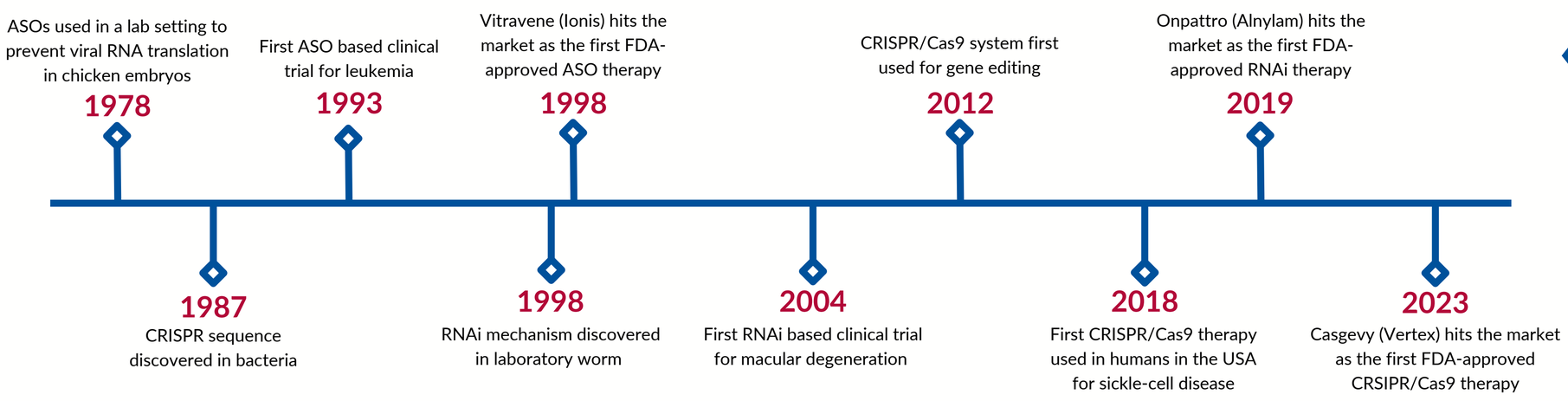
<u>ASOs and RNAi target RNA to prevent protein production</u>



<u>CRISPR/Cas9 targets DNA to repair the effects of mutations.</u>



A Brief History of Genetical Targeted Technology

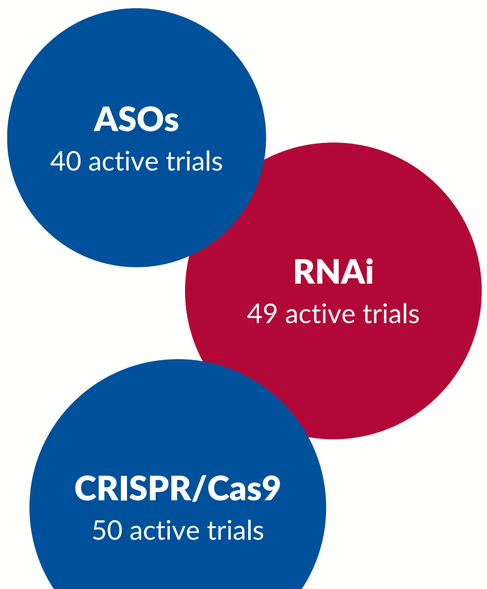


<u>DID YOU KNOW?</u>

The actions of GTT are derived from naturally occurring cellular mechanisms discovered previously in plant or animal tissue.

What are some current uses of GTT?

<u>Current GTT Clinical Trials*</u>



<u>Examples of Disease Indications for GTT</u>

Neurological Diseases
Alzheimer's
Huntington's
ALS

Rare Diseases
Muscular Dystrophy
Cystic Fibrosis
Alport Syndrome

Cancer
Leukemia
Lung Cancer
Prostate Cancer

Cardiovascular and Blood Diseases
Sickle Cell Disease
Elevated Lipoprotein
Cardiomyopathy

<u>FDA Guidances</u>

A <u>June 2024 FDA guidance</u> on the development of oligonucleotide therapies (ASOs, RNAi, and others) recommends specific clinical evaluations to assess:

- Changes to heart rate or other cardiac effects
- Immune system activation after treatment delivery
- Drug-to-Drug interactions
- Impairment of liver and kidney function

A <u>January 2024 FDA guidance</u> on the development of gene therapies using gene editing (CRSIPR/Cas9 and others) recommends specific clinical evaluations to assess:

- Characterization of on- and off-target editing events and their biological consequences
- Changes to genome integrity and cancer risk
- Immune system activation after treatment delivery

*Source: Clinicaltrials.gov. Trials selected with a not yet recruiting, recruiting, or active, not recruiting status

Biological images generated with Biorender.com

Research!America's "Exploring the Capability and Potential of Genetically Targeted Technology" briefing was supported in part by Alnylam Pharmaceuticals, the American Brain Coalition, Eli Lilly and Company, the EveryLife Foundation for Rare Diseases, Ionis Pharmaceuticals, Novartis, and the Society for Women's Health Research.