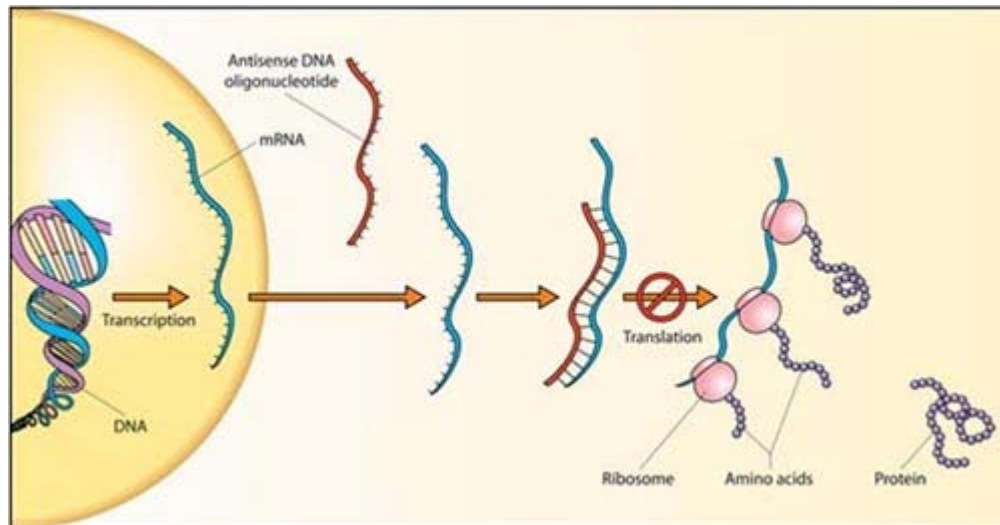


RNA THERAPY

[Sub topic of Therapies for ALS]



*Antisense DNA or RNA binds to a specific mRNA and prevents it from being translated into protein.
Robinson R (2004) RNAi Therapeutics: How Likely, How Soon? PLoS Biol 2(1): e28*

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<http://www.alsa.org/research/article.cfm?id=613>

Overview Summary

Scientists are not sure exactly what is toxic about the mutant SOD1 protein in ALS. Nevertheless, with antisense and other RNA targeting technologies, researchers hope to block the production of the protein, and perhaps stop the disease in its tracks.

RNA targeting is a very precise strategy to halt production of a specific protein. In the case of ALS, lowering the amount of SOD1 protein should not harm the body. Scientists have already demonstrated that mice lacking normal amounts of SOD1 do not show any obvious ill effects.

What is RNA?

RNA, the abbreviation for ribonucleic acid, serves as the intermediary between genes and the proteins that they code for.

What is antisense technology?

Antisense refers to opposing the normal order ("sense") of the code in DNA. The DNA (deoxyribonucleic acid) in genes directs cells to assemble the proteins which comprise living creatures. The order of bases in DNA corresponds to the ordering of amino acids to form the proteins.

To produce protein, the DNA of the genes in cells is first transcribed into a very similar molecule called RNA. RNA can move out of the cell's nucleus, where the genes have to stay. In the surrounding cytoplasm, proteins are put together according to the RNA's sequence of bases, matching the DNA instructions.

Antisense molecules prevent the protein assembly machinery from seeing the genetic instructions on how to order the amino acids. If scientists make a molecule that complements the sequence of bases in the RNA, it will stick to the RNA. The antisense molecule, bound to RNA, will prevent the RNA from making protein. Just as two



RESEARCH DEPARTMENT GLOSSARY OF ALS RESEARCH TOPIC AREAS

Reviews written by Roberta Friedman, Ph.D., ALSA Research Department Information Coordinator

Edited by Lucie Bruijn, Ph. D., Science Director and Vice President, The ALS Association

complementary pieces of Velcro stick together, hiding their loops, the antisense molecules bind to RNA and hide its instructions.

Thus, antisense stops the synthesis of the protein coded for by the targeted RNA. In effect antisense has turned off the specific gene, or DNA, that was coding for that protein.

What is RNA silencing (RNA inhibition, or RNAi)?

A newer method that also prevents a particular gene from making protein is called RNA inhibition (RNAi). Again, the aim is to silence the gene by targeting RNA, which carries the genetic message to the protein assembly plant in the cytoplasm.

By accident, scientists working in the 1990s to enhance the purple color in petunias discovered that a short piece of double-stranded RNA will cause destruction of a corresponding gene. This process is probably part of a cell's defenses against viruses, as many viruses are paired strands of RNA. Mammalian cells usually have only single stranded RNA.

Researchers now seek to design short RNAs (called short interfering RNAs, or siRNAs) that will prompt a cell to destroy matching RNA, preventing the production of a protein from a particular gene.

Challenges

RNAi plays into an existing pathway in cells that is designed to get rid of certain RNA. But it is a strategy that depends on getting RNA molecules into cells, no easy feat. Cells are designed to prevent RNA from entering, as that normally means a virus is trying to invade.

Therapeutic molecules targeting RNA must get into cells, and they must stay around long enough to work. The RNA targeting molecules must not produce an immune response or interfere with other proteins. Researchers purposely alter antisense molecules to resist destructive enzymes. Changing the backbone of the molecules slightly retains the action in binding to RNA, but resists breakdown (see also gene therapy).

Scientists are meanwhile using the approaches designed for gene therapy(link), to introduce RNAs into cells. They use disarmed viruses, called vectors, to carry the therapeutic RNAs across the cell membranes to reach the gene of interest.