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Don't Shoot the Messenger... Silence it!

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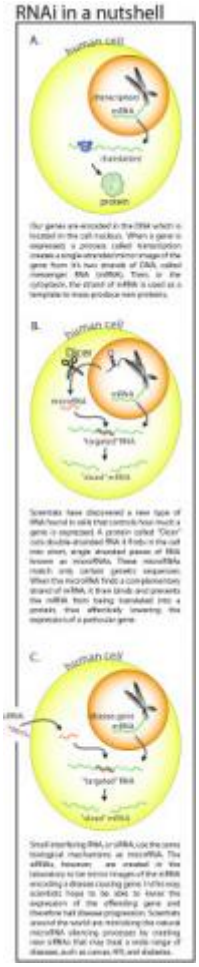

A new tool that gives researchers the ability to block disease-causing genes is the next wave in biotechnology. If successful, ?RNA interference? (known as RNAi) could provide new cures for everything from cancer to HIV to diabetes. Dr. Michael McManus, a world leader in RNAi, recently moved his MIT laboratory to the Diabetes Center at UCSF to focus his groundbreaking research on the problem of diabetes.

In the era of the human genome, it is clear that our genes play a vital role in determining our health. Mutations in specific genes, either inherited or caused by environmental damage, are responsible for a wide array of human disease. Subverting these mutated genes and the damage they cause would address disease at its source, providing long-lasting or permanent cures.

But exactly how do you stop a bad gene? There are several ways. For one, you could target the DNA that encodes the bad gene. Known as gene therapy, this technique has met with only limited success. On the other hand, you could target the proteins that precipitate the ill-effects of the bad genes. While this has proven more practical, in many cases, one bad gene can affect the function of many different proteins and so therapies targeted at proteins are

often only partially effective.

RNA, the lesser-known cousin of DNA offers a third technique. RNA is an intermediary in the creation of proteins from genes. Single-stranded RNA molecules, known as messenger RNA act as templates for constructing new proteins encoded by the gene. Therefore, shutting down the RNA of a specific gene should do the trick. To date, attempts at targeting RNA with ?antisense? pieces of artificial single-stranded RNA that bind and disable the messenger RNA have not been overly successful.

However, in 1998 a new form of RNA was discovered known as ?small interfering RNA? or siRNA. These short, single stranded molecules are part of an ancient mechanism for regulating genes that is found in both plants and in animals as diverse as yeast and humans. Each piece of siRNA is specific for a given gene and is capable of stopping its expression, halting the effects of the mutation or overexpression that is causing a disease.

According to Dr. McManus, ?siRNA acts like a one-way volume dial on a radio -- quickly turning down the amount of a specific gene that is expressed. We call the process ?gene silencing?."

Over 300 hundred of these small RNA volume knobs have been discovered. Now called microRNAs, scientists are only beginning to determine which specific genes that each acts upon. According to McManus, however, one microRNA known as miR-375 was recently found to regulate insulin secretion.

?We certainly expect that we will uncover additional control RNAs that relate to both type 1 and type 2 diabetes,? says McManus. ?In the meantime, we are working to learn more about how siRNA functions and how we can harness this discovery to develop new therapies.?

Dr. McManus is currently investigating a gene called ?Dicer,? which was originally discovered through the Human Genome Project. Dicer is a naturally occurring protein that acts like a pair of scissors to cut double stranded RNA into the siRNAs that regulate gene expression. Without it, gene silencing doesn?t work. So determining exactly how Dicer functions and the pathways that microRNAs use to silence specific genes may lead to new treatments for diseases where gene silencing has broken down. His studies may also offer ways to enhance the "tailored siRNAs" that could be used to treat diseases like diabetes.

Researchers have already tailor-made siRNA that target the gene Phosphatase-1B (PTP-1B), which is involved in insulin resistance.

While this treatment gives the appearance of a "magic bullet", McManus says the biggest challenge so far is finding ways to deliver siRNAs to the cells.

?In organisms such as plants and worms, siRNAs are easily taken up by cells. In mammals, siRNAs need help from chemical carriers,? he says. Many pharmaceutical companies are working day and night to develop chemical treatments intended to deliver the siRNA to the intended target. "RNAi has transformed the way scientists are performing gene function studies and has consumed the biotech industry like wildfire. It was recently given the title of 'Breakthrough of the Year' by Science magazine, and Fortune magazine has heralded it as 'Biotech's Billion-Dollar Breakthrough'." McManus says, "I believe it will revolutionize the way we look at medicine".

?In addition to his work with Dicer, McManus is collaborating with other Diabetes Center scientists like Mike German and Matthias Hebrok. Among other things, they are looking to determine the role of microRNAs in beta cell development.

?There is much research to be done? he says. ?I came here because of the fantastic forward-thinking attitude in research and medicine. Look around you, UCSF is a place of tremendous growth and accomplishments. The UCSF Diabetes Center is at the forefront -- it is a place where my research can contribute to the major advances being made in both basic science and the curing of diseases such as diabetes.?
