

Finding the Off-Switch

BLOCKING A COMMON GENETIC VARIATION IN HUNTINGTON'S PATIENTS MIGHT DIMINISH THE DISEASE'S EFFECTS.

Although the gene mutation that causes Huntington's disease—a neurodegenerative disorder that causes jerky, random movements—was discovered in 1993, a genetic cure has been elusive. Huntington's patients have one abnormal version of the *Huntingtin* gene and one healthy version that allows for limited motor function. Researchers have been unable to find a drug target that exists only



Gathering the sequences of Huntington's genes let researchers zoom in on an ideal drug target.

on the diseased copy of the gene. Now, HHMI investigator Phillip Zamore has spotted a key difference.

Huntingtin contains a region with a repetitive sequence of DNA—it reads “C-A-G” between 6 and 28 times in the normal gene. The abnormal gene contains this repetition many more times—over a hundred in some cases. More repeats means more severe disease and an earlier age of onset.

Zamore, at the University of Massachusetts Medical School, studies small molecules called small interfering RNA (siRNA) that can bind to a given mRNA sequence and prevent it from functioning. It was hard to imagine how an siRNA could bind just the abnormal *Huntingtin* if the only difference from the healthy copy was a greater number of repeats.

“The problem is that even the normal gene has too many C-A-G repeats for an siRNA to tell the difference between it and the disease version,” says Zamore. But it occurred to him that if he looked more closely at the disease version, there might be small, but common, variations—called polymorphisms—that don't affect the way a gene works but could be exploited to block it.

Zamore and his collaborators sequenced the genes of more than a hundred patients. They uncovered a polymorphism that, in 48 percent of the patients, appeared only in the disease-causing version of *Huntingtin*. It was far rarer in healthy copies of the gene—either in patients or in control subjects. The results appear in the May 12, 2009, issue of *Current Biology*.

Zamore is working to develop an siRNA that targets the polymorphism; it would block only the diseased *Huntingtin* gene, allowing the normal version to keep doing its job. ■ —SARAH C.P. WILLIAMS

IN BRIEF

in the April 17, 2009, issue of *Cell*. In healthy cells, the two proteins accumulate on opposite sides of a cell. *Smurf* genes create this necessary imbalance, they found, by destroying one of the proteins on one side of the cell.

PLUG AND PLAY SYNTHETIC BIOLOGY

Creating novel biological systems in the laboratory, for study purposes, is a time-consuming, difficult task. But it's one that gets easier as scientists understand more about how parts of cells—genes, proteins, and signaling pathways—work together. To save some time in the process of putting parts together into new systems, HHMI investigator James J. Collins, at Boston University, has developed a strategy to generate “plug and play” parts.

The difficult part of putting together a new biological network is predicting how different parts will interact. Collins and his colleagues set out to create and test one set of parts—gene promoters, which tell genes when to turn on and off—to create guidelines for how to use these parts together. They created libraries of two types of promoters, with 20 in each set.

They then matched up promoters from each set with one another to see which would win out. The genes, Collins explains, play tug-of-war, with each wanting to turn others off. By developing a quantitative model of the constructed network, Collins can predict how future combinations of the promoters will work. The results were published in the May 2009 issue of *Nature Biotechnology*.

To test whether the components could be assembled into a useful network, Collins' team used the promoters, and a predictive mathematical model, to create a cellular network that successfully controlled the timing of steps within yeast sedimentation, a precise chain of events used in industrial beer, wine, and bioethanol fermentation.

SPERM INSTRUCTION MANUAL

Some paternal genes aren't needed until an embryo is well into development; others are important soon after a sperm and egg fuse to form a zygote. New research by HHMI investigator Bradley R. Cairns has revealed that the genes needed early on are packaged in a distinctive manner for easy access.

Cairns, of the University of Utah, found that a sperm passes along information to the zygote in the form of histones—proteins that form spools for DNA. DNA that's more loosely wound around the histones is easier for a cell to access.

Previously, researchers had noticed that in mature sperm, rather than wrapping around histones, DNA primarily winds around a different protein, protamine, which compacts the DNA even tighter. This finding hinted that mature sperm don't pass along much information about when to express various genes.

To test whether histones still played a role in passing along developmental information, Cairns used sperm from human donors and analyzed which DNA was bound to histone proteins and which was bound to protamine proteins. He found that a number of genes needed in embryonic development are bound to histones in sperm. Depending on when the genes are needed in development, the histones carry different tags, likely telling the cell when to unwrap them. These tags ensure that genes are expressed only when needed. The results were published online, on June 14, 2009, in *Nature*.