Halting Heart Damage
Small targeted RNA turns off mutant genes that impair heart muscles.

There are more than 1,000 ways in which genes can be mutated to cause hypertrophic cardiomyopathy (HCM). But any one of the mutations has the same result: the heart thickens, it has trouble pumping blood, and eventually up to 1 in 500 people with the condition dies. There is no cure, but HHMI Investigator Christine Seidman, at Brigham and Women’s Hospital, has figured out how to prevent HCM symptoms from worsening in mice by shutting off some of the mutant genes that cause the disease.

Many of the mutations linked to HCM can be found in the genes that encode the heart muscle protein myosin. To develop new treatment strategies, Seidman focused on mutations in the mouse gene Myh6 that encodes myosin; HCM myosin mutations alter the heart’s ability to contract and relax. Her team designed small pieces of RNA, called RNAi (for RNA interference), that prevent the mutant gene from producing proteins. They used a virus that homes in on heart cells to deliver the RNAi to the correct location in the mice.

The experiment worked. For five months, mice with an HCM mutation in Myh6 showed no thickening or other changes in their hearts, according to her team’s report in Science on October 4, 2013. Although HCM could be prevented, existing damage wasn’t reversed; but it didn’t get worse, which is a benefit.

Unfortunately, each RNAi targets only a single mutation. “There are nearly 1,000 human HCM mutations,” acknowledges Seidman, “and it would be an extraordinary effort to make an RNAi that was specific for each one.” As an alternative, her team also created an RNAi that targets common genetic variants that are tightly linked to a broad spectrum of mutations. Like the mutation-specific RNAi, this one worked for five months, making it a very promising method for targeting HCM mutations.

Next, Seidman wants to figure out why the RNAi becomes ineffective after five months. She suspects it’s getting used up and that a booster of inhibitor could extend its effectiveness. — Nicole Kresge

Mutations in the heart protein myosin (red molecules) can cause hypertrophic cardiomyopathy.

Survival, specifically in bone.

Massagué and his colleagues previously discovered that breast cancer cells expressing a set of genes called the Src response signature (SRS) were more likely to metastasize to the bone. Cells that expressed those genes were more sensitive to cell growth-promoting molecules—called cytokines—that are expressed by bone cells, the researchers reported August 29, 2013, in Cell.

“For any cancer cell, it’s dreadfully rough to survive in the body after leaving a tumor,” says Massagué. “These cells selected for being more responsive to cytokines might just have this tiny extra chance of surviving in bone. But when you’re talking about tens of thousands of cancer cells circulating in the body per day, that tiny extra chance is enough to change the odds of a metastatic tumor forming.”

Massagué is now testing drugs that affect the SRS pathway to see if they can block cancers from spreading to the bone.

Creating False Memories
Many a science fiction movie is based on the idea of “brainwashing” into remembering something that never occurred. But is it really possible to create a false memory?

For mice, the answer is yes. HHMI Investigator Susumu Tonegawa made rodents, after being placed in a certain location, recall receiving a mild shock there when, in reality, the event happened in a completely different place.

Memories cause lasting physical and chemical changes in brain cells. A few years ago, Tonegawa and his colleagues used these changes to pin point which nerve cells were activated in response to different situations. As a follow-up, they decided to see if they could use this information to create a false fear association in mice.

First, Tonegawa and colleagues at the Massachusetts Institute of Technology identified the nerve cells triggered in mice while they were exploring a new cage. Next, they put the mice in a different cage and applied a mild shock to their paws while stimulating the cells that contained memories of the previous cage. Finally, the mice were placed in the first cage again. They froze in place.

“We got the animal to be scared of an environment where, technically, nothing bad had ever happened to it,” explains Steve Ramirez, a graduate student in the Tonegawa lab. The results were published July 26, 2013, in Science.

Next, the team would like to see if they can introduce pleasurable memories in mice, or memories of objects and other mice.

A Calcium Super Sensor
When a nerve cell receives a message from a neighboring neuron, a wave of calcium ions rushes into the cell to keep the signal moving. Scientists at Janelia Farm Research Campus have created a new molecular sensor that glows each time it detects one of these calcium waves. By following the flashes of light, researchers can watch as a message gets passed from neuron to neuron throughout the brain.

Calcium sensors for brain activity have been around for about two decades, but earlier versions were less accurate or more cumbersome to use. “You can think of the brain as an orchestra with each different neuron type playing a different part,” says Janelia Lab Head Karel Svoboda. “Previous methods only let us hear a tiny fraction of the melodies. Now we can hear more of the symphony at once.”

Svoboda, along with Janelia Lab Heads Loren Looger, Vivek Jayaraman,