A misfolded protein can be devastating. In diseases as broad ranging as Huntington’s, breast cancer, and cystic fibrosis, researchers are considering a new tactic: employing molecular chaperones.

RIGHT: Like firefighters called out to quench a raging blaze, molecular chaperones known as heat shock proteins (HSPs) respond to cellular stress. One type of HSP is trying to help the damaged cell shown three times here. The stress responding HSP (top) is found in exactly the same place in the cell as the abnormal clumps, or aggregates, of misshapen protein (middle), which are associated with disease. In the bottom image, the top and middle images are digitally overlaid, demonstrating the overlap of the HSP and the aggregates.
Ron Bailey wasn’t sure what was wrong. A few years earlier, he’d been laid off from his position as an account executive, where he’d earned, with bonuses, about $75,000 a year. Since then, he’d taken whatever work he could find, mostly odd jobs. He was in his mid-40s and the primary breadwinner of his family. His wife worked part-time; together, they supported two children. But eventually, Bailey found that he just couldn’t stay employed. Each new job might last a few months or a few days. He trained as a cashier at one store but could not ring up the merchandise fast enough. He worked in the collections department at another but was too slow on the computer.

Money was becoming tight. Two family cars were repossessed. Bailey and his wife couldn’t make the mortgage payments on the house they’d owned for more than a decade. Nor could they pay the back taxes they owed on the house. The sheriff made plans to sell the house in order to pay off the delinquent obligations. By filing for bankruptcy, Bailey saved the house.
Then, Bailey got a job working in a food warehouse, where he loaded trucks using a forklift and made deliveries.

The job was going well, though several times at the warehouse, Bailey lost his balance and fell. One day, after he had been at the warehouse for about six months, he was working on top of an enormous cooler and fell again. This time, he dropped 50 feet and hit his head on a cement floor. Amazingly, he didn't break any bones and wasn't injured by the fall. But once he got up off the floor, he went straight to his supervisor and quit. This was the worst fall he'd had. He felt it wasn't safe for him to work there anymore.

Family members convinced him to see a neurologist. They thought maybe he'd had a concussion or a stroke. The doctor asked Bailey to count down from 100 in increments of seven. Bailey got to 93 and couldn't continue. Then, the neurologist asked him to start with George W. Bush and go backward, naming the preceding U.S. presidents in order. Bailey had always been, he says, "a big freak" about the presidents—he could name them all. By then, he could name only the last four.

The neurologist had a devastating, though still tentative, diagnosis: He was fairly sure that Bailey had Huntington's disease, a fatal, progressive neurodegenerative disease. The neurologist sent Bailey's blood away for genetic testing. Bailey had to wait three months to find out that he had the disease.

During the months of waiting, Bailey had done some research—so he knew the destruction the disease wreaks. Huntington's patients develop involuntary, fleeting, jerking movements, which can affect the hands, feet, face, head, limbs, and trunk. Due to loss of motor control, people with the disease become less able to walk, speak, and swallow. As Huntington's progresses, short-term memory and the ability to concentrate become worse; the patient eventually develops dementia. Huntington's patients also experience emotional symptoms, such as uninhibited behavior. A person with Huntington's typically dies from the disease about 15 years after the onset of symptoms.

After the diagnosis, it took Bailey a couple of months before he was able to adopt a positive attitude. "There is going to come a time when I'm not going to be able to take care of myself," he says, "but I try not to think about it. I try to live each minute I can, do what I can, but it is tough."

Bailey's home was put up for sheriff's sale again. This time, because he knew that he had a disabling illness, he was able to get the mortgage payments reduced. His wife took a full-time job, and he started receiving a monthly Social Security disability check. But Bailey is not yet eligible for Medicare, and his wife's job provides no health insurance, so right now, the family is paying Bailey's medical expenses.

A year after his diagnosis, 48-year-old Bailey is doing everything he can to slow the progression of the disease. He takes vitamins his doctor recommended and minocycline, an antibiotic, which has been shown to protect the brain against Huntington's and other diseases resulting in dementia. Minocycline is believed to increase the life expectancy of Huntington's patients by a few years. Staying active can diminish the disease's impact, so every day, Bailey liftss 10-pound weights and walks three miles. He hates not working and gets bored during the days, while his wife is at work and his kids are at school, but he stays busy playing the drums, calling friends, doing laundry, washing dishes, mowing the lawn.

"I'm so excited every morning," he says. "I wake up and thank God that we kept the house, and I'm just trying to take good care of it now."

The toughest thing, he says, is not knowing "what's going to happen down the road, what type of nursing home I'm going to be in, how tough it's going to be on me and my wife." He worries about his kids; he knows each of his children have a 50 percent chance of ending up with the disease. He takes comfort in the fact that the disease progresses slowly. But late at night, he sometimes cries. "That's when my wife cries, too. [It's] the only time the kids aren't around," he says.

All the devastation caused by Bailey's disease results from a certain protein that is too long and has the wrong shape. Inside a cell, as a protein is made, it emerges as a long straight row of linked amino acids. The chain can be as short as a dozen amino acids or as long as several thousand. As soon as it's complete, the linear string then folds into a three-dimensional shape, with loops and curves and helices and crests and pockets. For each protein, there is only one correct way for it to fold, and it can only do the job it was created to do if it folds correctly.

But folding is no easy task. It's so problematic, that for some kinds of proteins, 60 to 80 percent of the protein that's produced folds incorrectly and has to be destroyed. Overall, perhaps a third of the proteins our bodies make don't fold correctly and are summarily done away with. It seems an awful waste of energy—to make all that protein only to destroy it. But to the cell, it's better than the alternative of leaving a misfolded protein in its midst.

If not destroyed, misfolded proteins tend to lump together into globs known as aggregates, which often are associated with disease.

These aggregates are a hallmark of Huntington's disease. In Huntington's, a genetic mutation causes the huntingtin protein to misform. (The protein is spelled differently than the disease.) Normally, in the midst of this protein's amino acid string, there is a point at which the amino acid glutamine is repeated up to 26 times (there is individual variability in the number of glutamine repeats). In people with the disease, however, there are one or more extra glutamines—so that instead of, say, 25 glutamines, there can be anywhere between 27 and 130 glutamines in a row. The extra glutamines cause the protein to misfold, and the misshapen protein lumps into aggregates.

In Huntington's, these clumps are found in cells in certain regions of the brain. But the cell has a natural quality-control mechanism to guard against the ill consequences of misfolded proteins. This is why a third of all proteins are destroyed almost as soon as they are made. "A cell has a choice—to exhibit caution and risk cell death or to shoot first and ask questions later," says Jeffrey Brodsky, associate professor of biological sciences. "We have a hyperactive protein quality-control system that shoots anyone it suspects of being a troublemaker."

One prime feature of the quality-control system: the proteins called molecular chaperones. The first thing seen by a newly made protein are chaperones, notes Brodsky: "They're the first helpers." The chaperone assists the protein in its efforts to fold and is likely to give the protein several chances to fold correctly—but if it doesn't, the chaperone is quick to step out of its nurturing role. It will become a stern judge, condemning the protein—which can't quite master the correct conformation of loops and curves and spirals—to destruction. (Some chaperones are either helpers or judges; others play both roles.) The chaperone looks out for the overall well-being of the cell.

But in Huntington's, the quality-control system somehow fails to rid the cell of all the misfolded huntingtin protein. Brodsky, along with Donald DeFranco, professor of pharmacology and neuroscience, wonders if chaperones might become part of a treatment strategy for the disease. If researchers could manipulate the
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cell so that it had more chaperones, would those extra sentinels be able to get rid of more of the mutated and misfolded protein, before it formed aggregates? Could chaperones someday be used to help people like Ron Bailey stave off the debilitating effects of Huntington’s?

DeFranco, a fast-talking, dark-haired PhD originally from New Haven, Conn., decided to test this idea. He contacted a group of scientists at Baylor College of Medicine and arranged a collaboration. The researchers chose to use spinocerebellar ataxia as a model for Huntington’s. Huntington’s is one of a family of polyglutamine diseases that are caused by excessive glutamine repeats. Like all the polyglutamine diseases, spinocerebellar ataxia is a fatal genetic neurodegenerative disease; it affects coordination and leads to unsteady walking and difficulties in swallowing. The collaborators chose spinocerebellar ataxia because, at the time, it was easier to study than Huntington’s—but the results would be generalizable to all polyglutamine diseases.

First, DeFranco inserted into human cells the mutated gene for ataxin-1, the protein that has excessive glutamines in spinocerebellar ataxia. Later, he looked into the microscope. Aggregates of the mutated ataxin-1 protein had formed in the cells. Next, he looked to see where in the cells the heat shock proteins (HSPs) were. (HSPs are one kind of molecular chaperone.) DeFranco’s team discovered that the HSPs, which are normally dispersed throughout the cell, had congregated at the site of the aggregates. DeFranco suspected the HSPs were doing something to try to fix what was going wrong.

As a further test, the researchers genetically manipulated the cells so that they would produce more (overexpress) HSP. The cells with more HSP had fewer aggregates.

DeFranco described these studies in an influential paper published in Nature Genetics in 1998; it was the first time anyone had linked molecular chaperones to polyglutamine diseases. “There’s very likely to be a protective effect against brain injury if we can somehow boost up heat shock proteins,” says DeFranco.

If you subject cells growing in culture to the stress of heat, the amount of heat shock protein increases—hence the name. Researchers discovered that HSP defends the cell against temperatures that are too high as well as other kinds of stress. HSP levels increase when the cell is under stress. HSP levels increase when the cell is under duress from, say, insufficient oxygen or an acute injury. It’s even been found that when mice are restrained in order to induce psychological stress, some of their cells start to produce more HSP.

Because HSP is part of the cell’s response to stress, researchers suspect that manipulating HSP levels could be useful in treating many different diseases. Scientists have shown that increasing HSP has a neuroprotective effect in a fly model of Parkinson’s disease. A clinical trial is currently under way to test an HSP-affected drug against breast cancer. In a cat model, DeFranco studies whether increasing HSP might be effective in reducing brain injury from stroke. HSP manipulation has also been considered as a way to treat Alzheimer’s disease and cystic fibrosis.

Since DeFranco’s pivotal paper linking HSPs to polyglutamine diseases, he and others have searched for a compound that might be used to treat these diseases. They have zeroed in on the compound geldanamycin and its variants. When administered to cells growing in a dish, geldanamycin increases HSP levels. But can it repair an injured brain? One group in Cincinnati injected the compound directly into the brains of rats modeling human stroke and observed some recovery. But in a similar study in rats modeling brain injury from cardiac arrest, DeFranco and Clifton Callaway, Pitt associate professor of emergency medicine, observed no recovery. The effectiveness of geldanamycin in animal models is spotty, and there are other hurdles to overcome. The geldanamycin compounds don’t cross the blood-brain barrier—so unless injected into the brain (not a practical treatment strategy for people), they never reach the brain cells where the aggregates form.

DeFranco is collaborating with a California company to test derivatives of geldanamycin to see if these new compounds will cross the blood-brain barrier. He injects the compounds into rats and then looks at their brains a few days later, checking to see if the compound reached the brain. So far, the answer has been no. The problem seems to be intractable.

“Since the mid-to-late ’90s, there have been compounds that people realized were effective agents to induce HSPs, but some eight years later, we still don’t have a compound that crosses the blood-brain barrier,” says DeFranco.

Even if the researchers can conquer the barrier problem, another issue remains. HSPs are found in every tissue in the body. If researchers find a compound that will increase HSP levels in the brain, to what extent will it affect other tissues in the body, having extensive and possibly deleterious results?

“Eight or 10 years ago, a number of companies gave up on these HSP-binding drugs, because they thought, ‘Every cell has heat shock proteins. There’s no way that we’re going to be able to develop drugs that are useful and that are not going to have side effects everywhere,’” says DeFranco.

But the pharmaceutical industry has perhaps been encouraged by its success in developing selective estrogen receptor modulators (SERMs). Estrogen acts on many tissues in the body; manipulating estrogen to achieve a desired effect in one tissue can lead to adverse effects in others. But with a SERM, a single drug has different effects in different tissues—enhancing the action of estrogen in some tissues, blocking estrogen action elsewhere. “There’s a new way of thinking in the pharmaceutical industry, as far as I can see, that we shouldn’t ignore these diffuse targets,” says DeFranco.

Asking DeFranco what the chances are that we’ll get an HSP-inducing drug that will help the brain, and he sighs. “You know, it seems like it really should happen,” he says. He cites two studies in which researchers genetically manipulated mice to overexpress HSP 70, a type of heat shock protein. “And I always thought that would be crazy, to try to overexpress HSP 70 all over, in all mouse tissues, and have the animal still survive and still function,” says DeFranco. But, in fact, the mice seemed able to tolerate the extra amounts of HSP 70—and the protein did help protect their brains against polyglutamine disease.

Still, the mice were followed for only a short time—whereas a chronic disease like Huntington’s would likely require long-term treatment. “How long [would you try to maintain hyperactivation of heat shock protein]?” wonders DeFranco. It might be more feasible to use HSP inducers in acute situations, like stroke.

“Managing chronic neurodegenerative diseases, that’s going to be a tough one,” he says, “but worth the effort.”

For privacy reasons, the patient’s name was changed in this story.