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Breakthrough with mutant gene that causes familial form of Lou Gehrig's disease

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that eventually destroys most motor neurons, causing muscle weakness and atrophy throughout the body. There is no cure and the current treatment has only a moderate effect on the march of the disease, which typically kills within three to five years. This week in *PNAS*, a team of Brandeis scientists reports an innovative approach to treating the most common form of familial ALS, commonly known as Lou Gehrig's disease.

In the study, researchers studied mutations in the gene that makes a particular protein, known as SOD1, responsible for causing much of the familial form of ALS, said Brandeis University chemist and study author Jeff Agar. Genetic mutations make the SOD1 protein unstable, causing it to fall apart into two identical pieces called monomers that are sticky and prone to clumping up inside the axon, the long projection of the motor neuron that conducts electrical impulses. Motor neurons are a meter long; when the axon inside the neuron gets clogged, it eventually dies.

"Picture a tennis ball stuck to a small piece of double sided tape. Now picture another. Turn the balls until both pieces of tape come into contact and that's what scientists call a dimer, and it's stable," explained Agar. "It won't stick to anything else. That's what normal SOD1 looks like, and there are billions of SOD1 dimers in every motor neuron.

Now pull the tennis balls apart, turn one 180 degrees, stick them back together and there's a sticky end. That's what ALS-associated SOD1

mutants do. You could stick millions of these balls together if you had them, and a neuron has billions of them. "What we're trying to do is prevent this from happening," said Agar.

Agar, along with post-doctoral fellow Jared Auclair, and biochemists Greg Petsko and Dagmar Ringe, developed an ingenious "chemical rope" to tie the two monomers together, creating a stable dimer. This strategy potentially solves the instability problem, especially since the protein proved able to withstand 40 degrees of heating above body temperature before falling apart again. SOD1 is one of the body's hardest working antioxidants, and its job is to turn a dangerous free radical called superoxide into water. Some ALS mutations stop SOD1 from doing its job, a process called inactivation, and the chemical ropes were even able to reactivate these SOD1 mutants and get them working again.

Next, the scientists had to create a version of their proof-of-concept "chemical rope" that was potentially amenable to development into a therapeutic, because the first one was toxic. Here they adopted a less toxic type of chemistry known as a thiol-disulfide exchange.

"This is only the beginning," said Agar. "It's one thing to do what we've done using purified proteins, but it is orders of magnitude more difficult to accomplish the same thing inside a complex organism. We have a lot more work to do before this could benefit ALS patients."

While the familial form of ALS, known as fALS, affects only about two percent of all ALS cases, there is growing evidence that changes in the same protein can cause some cases of sporadic (non inherited) ALS, and the researchers believe that perhaps 30 to 40 percent of cases where there is no genetic cause could potentially also benefit from the same treatment. The next step is to study SOD1 in cell cultures and in a mouse model to develop a pre-clinical candidate drug using this strategy.