When pathologists examine the brain of people who had Parkinson’s disease, they find small “spots” inside nerve cells, called Lewy Bodies, after neurologist Friedrich Heinrich Lewy who discovered them in 1912. It took 85 years before scientists realized that the main component of Lewy bodies was a protein called alpha-synuclein – a relatively small protein whose function still is not well understood. What we do know is that in Parkinson’s disease, alpha-synuclein molecules clump together to form the Lewy bodies. If the clumping of alpha-synuclein into Lewy bodies is what causes the disease, then blocking the clumping may lead to therapy for Parkinson’s that will not only treat the symptoms, but also the cause of the disease.

The last two decades of research have provided multiple evidence supporting the idea that alpha-synuclein clumping can cause Parkinson’s. Genetic evidence shows that mutations in the alpha-synuclein gene cause familial Parkinson’s. Even without a mutation, just an increase in the amount of protein due to abnormal duplication or triplication of the alpha-synuclein gene causes familial Parkinson’s. In addition, many experiments showed that alpha-synuclein on its own is not toxic to nerve cells, but when its molecules clump together, the clumps are toxic. However, increasing evidence shows that the final clumps, those that are found in Lewy bodies, which contain thousands of molecules or even more, probably are not what causes Parkinson’s disease. Rather, small, elusive aggregates called “oligomers” that contain only a few molecules, and form on the way to the final clumps, are the most toxic structures. The oligomers shut down nerve cells, including those that produce dopamine, and eventually kill them.

If so, the strategy should be changed from trying to prevent formation of the final clumps in the Lewy bodies, to preventing formation of the oligomers. Or maybe the strategy simply should be defined as anything that blocks the toxicity of alpha-synuclein?
This is exactly the line of thought that has guided Dr. Gal Bitan, Associate Professor of Neurology at UCLA, in his search for a potential drug. Dr. Bitan discovered compounds called “molecular tweezers,” which were prepared by his collaborators, Drs. Thomas Schrader and Frank-Gerrit Klärner, at the University of Duisburg-Essen in Germany, and realized that they could block the formation of toxic protein clumps, not only for alpha-synuclein, but for many other proteins that cause related diseases, such as Alzheimer's, Huntington's, ALS (Lou Gehrig's disease) and more. This is because the molecular tweezers block not a particular protein, but the process of formation of the toxic clumps, which is common to all of these diseases. They do that by preventing the molecular interactions that lead to formation of the toxic oligomers, taking advantage of the fact that the oligomers are very unstable. They are held together by weak forces, unlike normal proteins, which have a stable structure held by strong forces that have been optimized through millions of years of evolution. Therefore, they do not interfere with normal protein function and are not expected to have side effects.

Dr. Bitan's team put these molecules to the test, in collaboration with several research groups at UCLA, including Dr. Jeff Bronstein and Dr. Marie-Françoise Chesselet, and with chemists and physicists including Dr. Joe Loo at UCLA and Dr. Lisa Lapidus at Michigan State University.

Simple test-tube experiments showed that their lead molecular tweezer, called CLR01, stopped the formation of alpha-synuclein clumps and dissociated pre-existing clumps. The researchers then tested whether CLR01 could prevent the toxicity of alpha-synuclein oligomers in cell culture experiments and found that indeed the compound was effective as a toxicity inhibitor. In collaboration with Dr. Bronstein, they then examined the effect of CLR01 in a zebrafish embryo model that expresses the human form of alpha-synuclein. CLR01 prevented formation of toxic oligomers and clumps, allowed the fish, which otherwise would suffer deformation, to develop normally, and extended their lives significantly. Importantly, there were no observable side effects to the treatment.

One of Dr. Bronstein’s main interests is the effect of pesticides as risk factors for developing Parkinson's. He has examined many pesticides used by farmers and household plant growers and found that most of them increased the risk for Parkinson’s. Among these pesticides, ziram causes a higher risk of developing Parkinson’s. But why ziram is toxic and confers a higher risk for Parkinson's is not known. Could it be because it induces alpha-synuclein to form toxic oligomers and clumps? If so, CLR01 could prevent the toxicity of ziram and protect...
against the increased risk of Parkinson’s. Using a zebrafish embryo again, this is exactly what was found. CLR01 prevented the toxicity of ziram because it did not allow the zebrafish synuclein (which is an analogue of the human alpha-synuclein) to form toxic oligomers and clumps.

In a parallel set of experiments, Dr. Chesselet examined the effect of CLR01 in a mouse model that has the human form of alpha-synuclein in the brain. As a result, the mice show motor deficits already at 2-3 months of age and later develop a loss of dopamine. The mice were given CLR01 by a special injection device that maintains a constant slow release of the compound into the blood stream or directly into the brain. The treatment lasted for a month and the mice receiving the compound performed significantly better than those receiving placebo in tests of motor deficits. Again, the mice showed no side effects.

In fact, Dr. Bitan has tested CLR01 in normal mice, which were similar to those that participated in the experiments described above, but do not have the human form of alpha-synuclein in their brain, at much higher doses than those that led to the improvement and found that the compound has a high safety window. All of these results suggest that molecular tweezers are promising compounds for treatment of Parkinson’s disease. The team currently is trying to raise the funds needed to perform the tests required by the FDA before clinical trials can begin.

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