

# Local companies delve deep into cell origami

## Researchers seek drugs that can cure diseases by refolding or ousting errant proteins

By Carolyn Y. Johnson, Globe Staff | April 13, 2009

A devastating disease that robs the elderly of their memories seems a world away from rare genetic diseases that set children on a path of pain, deformity, and even early death. But scientists are focusing on a common thread: an intricate origami gone awry in cells.

Normally, cells make proteins that are folded into various three-dimensional shapes and ferried to different areas of the cell to do their work. Those jobs, ranging from fighting infections to helping orchestrate cell processes, are essential to the life of the cell. But sometimes, because of genetic mutations or reasons scientists still don't fully understand, key proteins crumple into the wrong shape.

That simple mistake can result in anything from emphysema to cancer to mad cow disease. In some diseases, such as cystic fibrosis, misfolded proteins aren't transported to the part of the cell where they are critically needed. In others, misfolded proteins clump into toxic tangles like the ones found in the brains of Alzheimer's patients.

Now, a growing slate of Cambridge companies have joined the search for drugs that could correct, clear away, or stabilize misfolded proteins and reverse the damage they cause.

"For a long time, people felt it was impossible; people had a preconceived notion that it was unlikely a small molecule could actually fix a broken protein. . . . But it turns out that may not be the case," said Paul Negulescu, vice president of research at [Vertex Pharmaceuticals Inc.](#) Vertex is targeting errant, misfolded proteins in cystic fibrosis and Huntington's, and has just begun a trial of the effectiveness of its cystic fibrosis drug.

"The whole protein-folding pathway has become an area of increased interest," Negulescu said. "It's kind of an exploding area."

Last year, Proteostasis Therapeutics Inc. raised \$45 million for its work, which focuses on the entire cellular machinery that folds the proteins, transports them to the right part of the cell, and degrades misfolded proteins.

Link Medicine Corp., a start-up that is focusing on ways to clear errant proteins like the ones that form toxic clumps in Alzheimer's and Parkinson's diseases, said in September that it had raised \$40 million.

Satori Pharmaceuticals Inc., which raised \$22 million in January, is searching for ways to block the formation of misfolded proteins in neurodegenerative diseases.

And FoldRx is expecting results this summer from a trial of a drug designed to stop a mutated protein from misfolding and accumulating in a rare genetic disease.

"Protein-folding therapeutics gets at the fact that there's a basic biological balance in the cell. Proteins have to fold into these complicated shapes, and getting folded when you're being jostled by your neighbors is not an easy thing to do," said Susan Lindquist, a cofounder of FoldRx and a member of the MIT-affiliated Whitehead Institute for Biomedical Research, in Cambridge. "All living organisms have the same problem, and in human beings it's an extreme problem; it plays a major role in the axis of health versus disease."

Lindquist has been studying heat-shock proteins, which play a critical role in helping proteins fold correctly under stress. She has found that some cancers exploit this stress response to help them survive, suggesting that the special proteins may provide clues for new cancer treatments.

Those proteins even seem to play a role in infections, she said.

A fungal spore heats up quickly when it enters a body - a stressful situation in which the heat-shock proteins perform a protective function, allowing proteins to fold correctly and function even under duress. That gives researchers a potential new drug target for fighting infections.

The diseases pharmaceutical companies are attacking by targeting misfolded proteins fall into two general classes: those that occur when proteins are not trafficked to the right area, and those resulting when proteins clump together.

One approach is to find a drug that binds to misfolded proteins, helping them fold and get to the correct part of the cell. That's the approach of Amicus Therapeutics, a New Jersey company working on creating drug chaperones that could be treatments for lysosomal storage diseases, in which waste accumulates in cells, causing a variety of problems - including deformity, neurological problems, even early death.

FoldRx is working on a therapy for transthyretin amyloidosis a rare genetic disease in which clumps of proteins form and build up in the heart and nerve tissues. Their drug, now in trials, stabilizes the proteins and prevents them from clumping.

Another approach is to tune up the processing and transporting of proteins in the cell. That includes blocking production of errant proteins, or making sure misfolded proteins are broken down.

If you think of the cell as a hotel room, said Peter Lansbury, chief scientific officer of Link Medicine, "what you want to do is to keep that hotel room clean - reduce production of garbage and/or increase the housekeeping."

Chris Mirabelli, chairman of the board of Proteostasis, said his company is looking for ways to exploit "the natural biology, the natural network normally controlling protein function."

P. Michael Conn, professor of pharmacology at Oregon Health and Science University, suggested that one day diseases that involve misfolded proteins, such as Alzheimer's and cataracts, could be treated by lifestyle medicines taken before symptoms even appear.

"By opening this new class of drugs," he said, "we're targeting a series of diseases, [and] have the ability to help people who could not have previously been helped."