Computer-designed molecules point to new therapy for cystic fibrosis

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By developing software that uses 3-D models of proteins involved in cystic fibrosis, a team of scientists at Duke University has identified several new molecules that may ease the symptoms of the disease.

Computer algorithms created by the team predict how well a given molecular structure will block a basic protein-protein interaction known to occur in cystic fibrosis. To test the predictions, the scientists synthesized the molecules and measured how well they attached to one of the proteins in that interaction. The team then placed the best molecule into human cells with the cystic fibrosis mutation in a laboratory dish and found that their new drug blocked the protein-protein interaction and increased the cells' ability to balance salt and water levels.

The results, which appear in the April 19 Public Library of Science Computational Biology, suggest that computers could make drug design for cystic fibrosis faster.

"We have known the genetic cause of cystic fibrosis since 1985. Now, by understanding its biology and chemistry, we can design and create targeted drugs to correct for the genetic flaw," said Bruce Donald, a Duke computer scientist and biochemist who led the study.

Cystic fibrosis, or CF, is a childhood disease causing the lungs and pancreas to fill with mucus, making it hard to breathe and absorb nutrients from food. The mucus builds in the organs as the levels of salt

and water in the cells become unbalanced because of a defective protein.

That protein, called CFTR, the cystic fibrosis transmembrane conductance regulator, regulates salt and water in the cell. In CF, it is defective because the genes that generate it are mutated. CFTRs are routinely rounded up for recycling in the cell by a protein called CAL that binds to CFTR and hauls it away. But defective CFTR proteins in cystic fibrosis patients send a signal that they are faulty, making their recycling rate much higher.

Currently, no treatments exist to target the genetic mutations that cause cystic fibrosis. Scientists have discovered molecules that target CFTRs' defects, such as incorrect folding and fast recycling, and there are a few molecules that help correct how CFTR folds or slow down the CAL recycling truck. These molecules help keep copies of CFTR functioning in the cell membrane to maintain some balance between salt and water levels.

Donald and his graduate student Kyle Roberts thought that computer algorithms based on the structure of CAL and similar proteins could quickly generate several dozen more molecules for slowing recycling by CAL and increase the pool of potential cystic fibrosis treatments.

"Research shows that you only need a fraction of normal CFTR activity to alleviate cystic fibrosis symptoms, so keeping CFTR in the membrane by using our inhibitors could have a significant therapeutic effect," said Roberts, first author of the new study.

Donald and Roberts' algorithms searched several thousand potential inhibitors and ranked them based on how strongly it predicted each would bind with CAL. In collaboration with researchers at Dartmouth and in Germany, the scientists synthesized 11 of the highest-ranked sequences and used fluorescent light to measure each molecule's

attachment to CAL.

The results show that many of the algorithm-generated molecules attach more strongly to CAL than the connection between CAL and CFTR in nature. The best computer-generated molecules also bind more efficiently to CAL than any previously reported inhibitor.

In a culture of human cells with the cystic fibrosis mutation, the best algorithm-generated inhibitor increased CFTR activity by 12 percent. Donald said the new molecule could be used in combination with another molecule, which corrects how CFTR proteins fold and raises CFTR's activity by 15 percent. The two molecules should work together and could increase CFTR's activity by about 27 percent, he said.

He cautioned that it could be several years before patients with the disease could use the new molecular combination as treatment because the molecules have not yet been tested in patients with the disease. The team has made its software freely available, Donald said, so the computer-design approach could quicken the pace at which molecules and resulting cystic fibrosis therapies are developed.

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