New hope exists in treating inherited disease by suppressing DNA mutations

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Genetic mutation can disrupt the way human cells make proteins, which in turn leads to inherited disease. David Bedwell, a professor in the University of Alabama at Birmingham (UAB) Department of Microbiology, says scientists are closer than ever to producing drugs that fix this disrupted-protein pathway and drastically improving treatment of genetic disease.

Bedwell is a renowned researcher on a select group of genetic alterations called nonsense mutations - DNA alterations that can lead to nonfunctional or missing proteins. He will present a lecture today at the Experimental Biology 2010 conference.

His talk, "Pharmacological suppression of nonsense mutations to treat genetic diseases," examines the promise of Bedwell's groundbreaking research on the experimental drug ataluren (formerly called PTC124) that may help to treat some cystic fibrosis patients. Ataluren also holds promise in treating more than 2,400 different genetic disorders caused by nonsense mutations.

"When treating a genetic disease with suppression therapy, the key consideration is the fraction of the missing protein that must be restored to yield a therapeutic benefit," Bedwell says. "It comes down to the threshold of protein rescue needed. For some diseases, it might be one percent of the normal amount of protein that must be restored, and for other diseases, you may need 50 percent of protein restored."

In Bedwell's most well-known study, ataluren restored up to 29 percent of normal protein function in mice with cystic fibrosis. Another researcher not affiliated with UAB has reported ataluren restored up to 25 percent of the missing or abnormal protein function in mice with Duchenne muscular dystrophy.

An estimated one-third of gene defects responsible for human disease are thought to come from nonsense mutations. In the case of cystic fibrosis, the absence of a certain protein leads to an imbalance of salt and water in the linings of the lungs and other membranes. The UAB study showed that ataluren allowed the protein to be made in mouse cells where it was previously absent, and it helped the body's regulatory system to restore salt and water balance in the membrane.

Bedwell says the true promise of drugs that suppress nonsense mutations is their selectiveness, meaning the drugs work well to suppress disease-causing mutations while generally sparing healthy genes.

Ataluren is now being tested in humans for its effectiveness in treating Duchenne/Becker muscular dystrophy, cystic fibrosis, hemophilia A, hemophilia B and other conditions. The agent works in an oral form.

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