Researchers studying defective protein in search of cystic fibrosis treatment

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Ryerson researcher Russell Viirre is leading a research team that is examining the defective protein that causes cystic fibrosis in order to ultimately create stronger drugs for treating the disease.

(Medical Xpress) -- Cystic fibrosis is the most common fatal genetic disease affecting Canadian children and young adults, more than two children each and every week are diagnosed with cystic fibrosis (CF). New research at Ryerson University, in partnership with The Hospital for Sick Children, is examining the interaction between lab-tested drugs and the defective protein that causes CF to understand how and why the drugs work and to create stronger, more powerful second generation drugs to treat CF.

Cystic fibrosis is caused by a defective gene that would normally create a protein called cystic fibrosis transmembrane conductance regulator protein (CFTR), which is involved with regulating the content of salt and water in mucous. When the gene is defective, CF patients have thicker, stickier mucous that builds up in the lungs as well as other organs. Symptoms include lung infections, difficulty breathing and trouble with digestion. Ultimately, CF is fatal.

Russell Viirre is a synthetic organic chemist and a professor in Ryerson University's Department of Chemistry and Biology whose research focuses on synthesizing molecular probes to study the detective protein that causes CF with the hope of creating new drugs to treat it.

"We're looking at drugs that can interact with the defective protein, essentially restoring it to its native function," says Viirre. "In other words, helping the defective protein behave like it's supposed to."

According to Viirre, fixing the defective protein should eliminate the symptoms of CF. As part of their research, Viirre and his team are examining the structures of failed drugs that, in a previous lab setting fixed the defective protein but for a variety of reasons, never made it to patient trials. The team modifies the structure of the drug slightly and in such a way that biochemists can examine how each of the failed drugs interacts with the defective protein. Once modified, the drug is brought to SickKids Hospital where the research group of collaborator Christine Bear, Senior Scientist in SickKids' Molecular Structure & Function Program, conducts further testing. Experiments carried out there determine if the modified drug repairs the defective protein.

"We're making molecular probes to help pinpoint the position and the nature of the interaction between the drug and the protein" says Viirre. "The Bear group at SickKids uses these probes to try to find the site on the protein where a particular drug binds."

A recent paper published by the research team for the Journal of Medicinal Chemistry describes the first successful batch of these probes, based on one particular drug. The paper identifies what part of the drug molecule the team was able to change.

Viirre likens their work to that of finding out how a key fits in a lock.

“Once we know what the key hole looks like, we can make a key that fits that hole better,” says Viirre. “The idea is that the better the key fits, the more powerful and successful the CF drug treatment will be.”

Viirre and his collaborators have identified approximately a dozen previously tested drugs and the team will study each of them. Within the next five years, they will start to get answers about the protein and how it interacts with these drugs, which will ultimately give them the information needed for the creation of stronger, more effective drugs for the treatment of CF.

Synthesis and Properties of Molecular Probes for the Rescue Site on Mutant Cystic Fibrosis Transmembrane Conductance Regulator was published in the December 22, 2011 issue of the *Journal of Medicinal Chemistry* and was funded by the Canadian Institutes of Health Research and Cystic Fibrosis Canada. The article can be downloaded free of charge at pubs.acs.org/doi/abs/10.1021/jm201335c

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