Chemists Rationally Design Inhibitors Against an RNA Molecule that Causes Myotonic Muscular Dystrophy

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UB chemist Matthew Disney's research shows that rational drug design can greatly expedite the discovery of new drugs that could be effective against RNA-mediated diseases, such as myotonic dystrophy.

(PhysOrg.com) -- Chemists at the University at Buffalo have used rational drug design to synthesize small, cell-permeable molecules that are effective in vitro against two common types of myotonic muscular dystrophy, a result that has implications for potentially curing muscular

dystrophy, as well as other diseases.

The UB research was reported in two papers published in the May and July issues of *ACS* Chemical Biology and Journal of the American Chemical Society, respectively.

Together, the papers demonstrate that rational drug design -- where information about a target's molecular structure is used to "custom-design" potential drugs -- can greatly expedite the drug discovery process in the fight against RNA-mediated diseases, including myotonic dystrophy type 1 and type 2. There is currently no cure for these diseases, which attack muscle tissue.

Sickle cell disease, fragile X syndrome, Huntington's disease and certain forms of breast cancer are other RNA-mediated diseases.

The work is a major step forward in a multi-year effort by Matthew Disney, Ph.D., UB assistant professor of chemistry, to develop a chemical code that would enable rational design of binders to any RNA structure.

"These results demonstrate that we can build a database containing RNA structures that bind to small molecules, and use that information to potentially target any 'toxic RNA structure,' that is, any RNA structure involved in disease," says Disney, lead author on the research.

He explained that muscular dystrophy belongs to a class of diseases called triplet repeat disorders in which the genetic code has an abnormal repetition of three letters of DNA.

"The DNA with the abnormal triplet repeats is made into a defective RNA that forms an unnatural structure that binds to a protein important in muscle function," says Disney. "It is this RNA-protein interaction that

causes the disease."

The UB group has developed a method of precisely designing ligands with higher affinity and specificity for the RNA structure than natural protein.

"If it has a choice of which to bind, the RNA will bind to our rationally designed small molecule, potentially interrupting the interactions that lead to muscular dystrophy," says Disney.

The UB group's next step is to begin working to develop the small molecule into a viable pharmaceutical product by testing its efficacy in cell culture and a mouse model of the disease.

In addition to the promise the research holds for myotonic dystrophy, the development of the RNA-small molecule database marks the start of a new approach to developing cures for other RNA-mediated diseases.

"RNA structures in general are unexplored as drug targets in part because they are much more complex than DNA," says Disney. "We are using our database of RNA structures that bind small molecules to compare to all toxic RNAs. Once an RNA sequence is found that causes disease, we can input that sequence into our database and search for structures in the disease-causing RNA that bind one of our small molecules. If we find one, we then have identified a lead molecule for exploring as a potential pharmaceutical compound."

Disney also is developing computational tools to mine the human genome against the RNA database in order to identify new RNA targets to which this approach can be applied. In this work, he is collaborating with computational scientists at the Center for Computational Research (CCR) in UB's New York State Center of Excellence in Bioinformatics and Life Sciences.

He notes: "It would be hard to envision doing this work without the support of CCR."

Provided by University at Buffalo (news : web)