Study paves way to design drugs aimed at multiple protein targets at once

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This is Brian L. Roth, M.D., Ph.D., Michael J. Hooker Distinguished Professor of Pharmacology in the UNC School of Medicine, professor in the Division of Chemical Biology and Medicinal Chemistry in the UNC Eshelman School of Pharmacy, and director of the National Institute of Mental Health Psychoactive Drug Screening Program. Credit: UNC School of Medicine

An international research collaboration led by scientists at the University of North Carolina School of Medicine and the University of Dundee, in the U.K., have developed a way to efficiently and effectively make designer drugs that hit multiple protein targets at once.

This accomplishment, described in the Dec. 13, 2012 issue of the journal *Nature*, may prove invaluable for developing drugs to treat many common human diseases such as diabetes, high blood pressure, obesity, cancer, schizophrenia, and bi-polar disorder.

These disorders are called complex diseases because each have a number of genetic and non-genetic influences that determine susceptibility, i.e., whether someone will get the disease or not.

"In terms of the genetics of schizophrenia we know there are likely hundreds of different genes that can influence the risk for disease and, because of that, there's likely no single gene and no one drug target that will be useful for treating it, like other common complex diseases," said study co-leader, Brian L. Roth, MD, PhD, Michael J. Hooker Distinguished Professor of Pharmacology in the UNC School of Medicine, professor in the Division of Chemical Biology and Medicinal Chemistry in the UNC Eshelman School of Pharmacy, and director of the National Institute of Mental Health Psychoactive Drug Screening Program.

In complex neuropsychiatric conditions, infectious diseases and cancer, Roth points out that for the past 20 years drug design has been selectively aimed at a single molecular target, but because these are complex diseases, the drugs are often ineffective and thus many never reach the market.

Moreover, a drug that acts on a single targeted protein may interact with many other proteins. These undesired interactions frequently cause toxicity and adverse effects.

"And so the realization has been that perhaps one way forward is to make drugs that hit collections of drug targets simultaneously. This paper provides a way to do that," Roth said.

The new way involves automated drug design by computer that takes advantage of large databases of drug-target interactions. The latter have been made public through Roth's lab at UNC and through other resources.

Basically, the researchers, also co-led by Andrew L. Hopkins, PhD in the Division of Biological Chemistry and Drug Discovery, College of Life Sciences, at the University of Dundee, in Scotland, used the power of computational chemistry to design drug compounds that were then synthesized by chemists, tested in experimental assays and validated in mouse models of human disease.

The study team experimentally tested 800 drug-target predictions of the computationally designed compounds; of these, 75 percent were confirmed in test-tube (in vitro) experiments.

Drug to target engagement also was confirmed in animal models of human disease. In a mouse model of attention deficit hyperactivity disorder (ADHD), mice missing a particular dopamine receptor engage in recurrent aberrant behaviors similar to what is seen in ADHD: distractibility and novelty seeking. "We created a compound that was predicted to prevent those recurrent behaviors and it worked quite well," Roth said.

The researchers then tested the compound in another mouse model where a particular enzyme for a brain neuropeptide is missing. Distractibility and novelty seeking also are behavioral features in these animals. And the drug had the same effect in those mice.

The new drug design process includes ensuring that compounds enter the brain by crossing the blood-brain barrier. These, too, were tested successfully in live animals.

According to Roth, pharmaceutical company chemists had suggested that the objective of a drug hitting multiple targets simultaneously is impossible and unlikely to succeed. "Here we show how to efficiently and effectively make designer drugs that can do that."

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