Virtual screening leads to real progress in drug design

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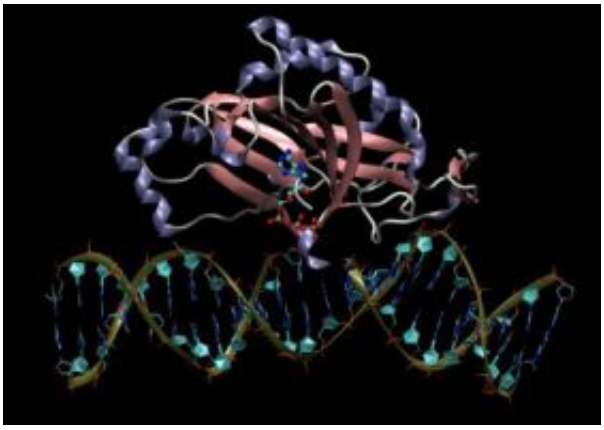

Model of the REL1 enzyme (in pink and purple ribbon) interacting with an RNA substrate (gold ribbon). An ATP molecule, which is necessary for the enzyme's activity, is bound to REL1. Credit: Rommie Amaro and J. Andrew McCammon

Around 150,000 people per year get African sleeping sickness, a disease spread by the biting tsetse fly and caused by the parasite Trypanosoma brucei. Unless treated, the illness is invariably fatal. And the only available medicines are either difficult to administer, expensive, or toxic. The widely used drug melarsoprol, for example, is essentially arsenic dissolved in antifreeze.

Only one new drug to treat African sleeping sickness has appeared in the past 50 years. "The biomedical significance of new drugs to treat trypanosomal diseases, which occur mainly in developing countries,

would be huge," says Peter Preusch, of the National Institute of General Medical Sciences (NIGMS).

A team led by computational biologist J. Andrew McCammon of the University of California, San Diego, may offer a solution. The researchers used a unique computational approach to identify five compounds that could lead to new drugs to combat the disease. The compounds block the activity of the trypanosomal REL1 enzyme, which the parasite needs to survive.

REL1 has a unique role in the trypanosome's mitochondria, the organelles that provide the parasite with energy. The enzyme joins mitochondrial messenger RNA fragments, making them whole and functional. These messages are the blueprints for making the proteins that power the mitochondria. Without REL1, some of these mitochondrial proteins are missing, which slows energy production and kills the parasite.

The results appear online this week in the *Proceedings of the National Academy of Sciences.*

The approach developed by McCammon's group uses a combination of several computational tools. It starts with a detailed model of the biological target—REL1 in this case—derived from X-ray crystallography. It then uses biophysical principles to find all the ways in which the protein can twist, turn, and wiggle.

"We know that proteins aren't static," said Rommie Amaro, Ph.D., the lead author of the study. "They're dynamic moving machines. The unique thing about this approach is that it allows full protein flexibility."

But predicting the countless shapes that a large, complex molecule like a protein can adopt requires enormous computer power. A REL1 analysis

done on a regular desktop could take years while those on supercomputers take a few days. The computers used in this study, explains Amaro, are among the most powerful in the country.

Once they know the dynamics, the researchers carry out a virtual screen of hundreds of compounds, testing their ability to stick to a key part of REL1. Compounds that stick tightly have a good chance of inhibiting the enzyme's activity and killing the parasite.

"It's rather like a child's puzzle where one must put the cow-shaped piece into the cow shaped hole in the barnyard scene," explains Preusch, who oversees computational biology grants at NIGMS, which partially funded the work. But like real cows, he added, molecules are in constant motion. "McCammon has developed methods that take these motions into account, as well as the changes in a protein's shape that can occur upon binding."

The virtual screen predicted that about a dozen compounds would bind tightly to REL1's hot spot. Knowing that a slightly different version of one of these might stick even more tightly, the researchers searched a large database of existing compounds for structurally similar molecules.

When they tested their best candidates experimentally, five inhibited REL1. These five molecules, which block the activity of a crucial trypanosomal enzyme, can now serve as the basis for future drug design and discovery efforts.

McCammon's computational method has already proven its utility for designing other important drugs. His group used it to develop a model for a new class of drugs to treat AIDS that led to raltegravir, which the Food and Drug Administration approved in 2007. McCammon's team also used the method to identify promising drug candidates for treating H5N1 avian flu.

McCammon's team is now focusing on designing even better inhibitors of trypanosomal REL1. The goal is to tweak the inhibitors' structures, making them bind even more tightly to REL1 and less tightly to related human enzymes. Binding to human enzymes makes an inhibitor less attractive as a drug candidate because the interactions could cause undesired side effects.

This work, says McCammon, "tells a story that may be of wide interest." The computational approach not only could lead to improved drugs for treating African sleeping sickness, but it could be used to develop compounds for use against other illnesses for which we need better medications.

Source: NIH/National Institute of General Medical Sciences