Researchers can watch drug activity in a molecule (w/ Video)

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(PhysOrg.com) -- Weill Cornell's Scott Blanchard has developed technology that can observe drug activity in a solitary molecule while in motion. The development may lead to newer, safer drug therapies.

That means that, for first time, researchers can see how molecular movements are affected by antibiotic binding. The findings, which are published in the March issue of Nature Chemical Biology (6:3), may lead to the development of new drug therapies.

"Understanding molecular movements is important because enzyme function hinges on motion," said Scott Blanchard, senior author and associate professor of physiology and biophysics at WCMC. "To observe the molecule, we are decorating it with fluorescent markers, called fluorophores, that make it glow."

The fluorophores are attached to the biomolecule and are designed to exchange energy with each other in a way that accurately reports on the distance between them, like a molecular global positioning system. This process is called fluorescence resonance energy transfer. When applied to the study of single-molecules, one can actually use this technique to monitor changes in the structure of individual enzymes as they function.

Traditionally, to understand how drugs affect enzymes, researchers have measured changes in the rate at which an enzyme generates product, which often requires a great deal of starting material. The new single-molecule approach provides the ability to observe enzyme function from

the perspective of motion, and how such motions are influenced by the presence of substrates or drug compounds.

In the current study, Blanchard and his team investigated whether the binding of aminoglycoside-class antibiotics -- an important family of clinically useful small-molecule compounds -- affects how the ribosome moves. The ribosome, one of the largest and most essential molecular machines in the cell, is the target of almost half of all known antibiotics currently in use.

The aminoglycosides, while highly effective, tend to be toxic. Blanchard's goal was to explore the relationship between aminoglycoside activities and ribosome movements and to search for compounds with more potent activities but that have fewer side effects.

While the approach has many advantages, one of the most valuable is that it is "green," said Blanchard. As implied by its name, single-molecule methods are characterized by a greatly reduced demand for biological material. Consequently, less human and capital costs go into large-scale sample preparations. In principle, the researchers believe the single-molecule technique may one day be engineered to require a million times less starting material than is required by traditional drug screening methods.

"In addition to this material advantage, the information content of the single-molecule approach is greater, increasing the cost effectiveness of each experiment," said Blanchard. "Our challenge now is to understand whether the approach is generalizable to other enzyme systems where an understanding of its regulation and the mechanism of drug action are lacking."

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