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'Rational drug design' identifies fragments of FDA-approved drugs relevant to emerging viruses

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A massive, data-crunching computer search program that matches fragments of potential drug molecules to the known shapes of viral surface proteins has identified several FDA-approved drugs that could be the basis for new medicines -- if emerging viruses such as the H5N1(avian flu) or H1N1/09 (swine flu) develop resistance to current antiviral therapies -- according to a presentation at the American Society for Cell Biology 49th Annual Meeting, Dec. 5-9, 2009 in San Diego.

The compounds were identified through a "rational drug design" project in the laboratory of Andrew McCammon, Ph.D., HHMI investigator at the University of California at San Diego.

The McCammon lab honed the search algorithms that helped identify the second generation of anti-HIV drugs.

Like fitting a key to a lock, computer search algorithms take the known shapes of drugs and match them, one after another, to the known shapes of disease-related proteins.

In the study presented at the ASCB conference, Daniel B. Dadon, a member of the McCammon lab, will explain how the search targeted the neuraminidase proteins, one of the two major sets of glycoproteins on the outer surface of influenza viruses.

Because biomolecules don't sit still -- they're moving targets -- scientists must consider how the protein can slightly shift position or shape. Dadon said, "A single picture of a sleeping cheetah, for example, might suggest that the animal is always lethargic. In reality, a cheetah is dynamic, spending much of its time sitting, running, climbing, attacking, and walking."

The successful capture of cheetahs or influenza viruses requires an understanding of their motions over time.

A search algorithm that accounts for the flexibility of the molecular docking sites is at the core of the McCammon group's relaxed complex scheme (RCS).

After studying neuraminidase flexibility, the researchers created a virtual library of drug-like molecules by mixing and matching parts of various FDA-approved drugs.

The information gained from the RCS simulations was used to identify molecules in this new library that would best inhibit neuraminidase function.

Six compounds were predicted to inhibit neuraminidase better than FDA-approved drugs such as oseltamivir, peramivir and zanamivir.

The computer data also suggests that some of these compounds may target other parts of the neuraminidase protein. The ability to target these additional parts of the neuraminidase protein could prove useful if the new viruses develop resistance to current therapies.

Source: American Society for Cell Biology