

Drug designer: New tool reveals mutations that cause HIV-drug resistance

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Protease inhibitor drugs are one of the major weapons in the fight against HIV, the virus that causes AIDS, but their effectiveness is limited as the virus mutates and develops resistance to the drugs over time. Now a new tool has been developed to help predict the location of the mutations that lead to drug resistance.

First discovered in 1995, protease inhibitor drugs have dramatically reduced the number of AIDS deaths. Taken in combination with two other anti-HIV drugs, protease inhibitors work by halting the action of the protease enzyme, a protein produced by HIV that is necessary for replication of the virus. However, almost half of <u>HIV patients</u> who initially respond to treatment with protease inhibitors develop <u>drug-resistance</u> strains and stop responding to treatment within eight to 10 months.

Currently there are nine FDA approved protease inhibitors, and 21 most common drug-resistant mutations.

The main reason for the short-term effectiveness of the drug has to do with the evolution of the drug within the body, said the study's author, Yi Mao, a postdoctoral fellow at the National Institute for Mathematical and <u>Biological Synthesis</u>.

In the new study, published today in the journal *BMC Structural Biology*, Mao used a mathematical modeling technique called elastic network modeling to examine the physical properties and interactions of the



proteins. The model reveals where mutations are occurring during the evolution of the <u>HIV-virus</u> proteins and how these mutations help the virus survive.

"With this kind of knowledge, better strategies for designing anti-HIV drugs could be developed," Mao said.

HIV kills the body's <u>immune system cells</u>, called CD4 cells. Once the number of CD4 cells dips below 200, an HIV patient enters the last stage of his or her disease: Acquired Immune Deficiency Syndrome, or AIDS. The first cases of AIDS were reported thirty years ago. Since then, more than 60 million people have been infected with HIV, and more than 30 million people have died from AIDS. Today an estimated 34 million people worldwide are living with HIV – 1.2 million in the U.S.

More information: Mao Y. 2011. Dynamical Basis for Drug Resistance of HIV-1 Protease. *BMC Structural Biology*. Published online 8 July 2011. 11:31. <u>doi:10.1186/1472-6807-11-31</u>

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