AIDS Research, at Home

Here’s an easy (and free) way to help researchers develop HIV drugs: Simply donate your personal computer’s unused processing power—in other words, let it crunch some data for scientists when you’re not using it. Researchers from FightAIDS@Home explain how logging on to this program may lead to newer drugs, faster.

February 16, 2010 By Tim Horn and David Evans

AIDSmeds and POZ.com have a secret: Our offices double as HIV drug development laboratories. Our scientific work— evaluating mutations and prospective candidates for HIV drug discovery—continues around the clock, without a single lab tech or test tube in sight. Best of all, you too can contribute reams of data to the relentless pursuit of better antiretrovirals and, quite possibly, a cure.

It’s not as clandestine as it sounds. All that’s required from us is that we donate our unused personal computer processing time to FightAIDS@Home, a program of IBM’s World Community Grid and the Olson Lab at The Scripps Research Institute in La Jolla, California. It’s nothing more than a glorified screensaver that doubles as a software program capable of downloading and analyzing small chunks of data from the World Community Grid. After the software performs the necessary calculations—all taking place while you’re computer is idle—the results are passed along to Scripps, where researchers are standing by to sift the processed data for mutations associated with HIV drug resistance and for evidence of small molecules that can bind to, and effectively block, HIV.

FightAIDS@Home began in 2000 and now boasts a network of labs tucked away inside more than a million personal computers around the word. Even more exciting is the fact that grid computing—the joining together of many individual computers to create a large system with computational power that surpasses that of a handful of supercomputers—is yielding results.

According to a paper published in the March issue of *Chemical Biology & Drug Design*, researchers at Scripps identified two compounds that bind to unique sites of HIV’s protease enzyme and may prove useful in preventing and treating drug-resistant virus. They embarked on this work thanks to theories about drug resistance and molecule design that were shaped by processed data from the FightAIDS@Home network.

To learn more about this network and its awesome potential, AIDSmeds checked in with Arthur Olson, PhD, head of the Olson Lab at Scripps and the founder of FightAIDS@Home, and David Stout, PhD, head of the Stout Lab at Scripps and the lead author of the March *Chemical Biology* paper.

Did FightAIDS@Home originate in your lab?

Arthur Olson: Yes, that’s correct. At that time, it wasn’t part of the World Community Grid [Scripps partnered with the World Community Grid in November 2005]. It was an independent effort that started with a small start-up company called Entropia that was interested in the idea of Internet-shared computing. They wanted a pilot project to demonstrate its utility and approached me, since I have a [National Institutes of Health]-funded program to better understand HIV drug resistance.

This was around the time that SETI@Home started gaining popularity. [SETI@Home, which began in 1999 and is run by the University of California at Berkeley, involves software that downloads and analyzes radio telescope data for evidence of extraterrestrial technology.] FightAIDS@Home, as far as I know, is the first biomedically relevant Internet-based computing project.

Is the work you do possible without FightAIDS@Home?

Olson: It’s possible, but on a different scale. The kinds of computations we’re doing involve millions upon millions of what we might call individual experiments, where we’re computationally docking a drug against its target biological molecule. You can do one of those calculations on your laptop or home computer, but to do millions of them would essentially be impossible or take a very, very long time. We’ve been using the World Community Grid for about five years now. In this time, we’ve performed calculations that would have taken a single computer 100,000 years to complete. Without FightAIDS@Home we wouldn’t have gotten very far at all.

You focus primarily on HIV drug resistance, specifically involving HIV’s protease enzyme and “spanning mutants.” Can you explain this?

Olson: The concept of “spanning mutants” is new. Basically HIV mutates continuously, and those mutations that allow HIV to survive in the presence of a therapeutic drug are drug resistant. The number of possible mutations for any given drug target, such as the HIV protease, is enormous—billions or more.

Our FightAIDS@Home computations try to predict how large libraries of different chemicals—potential drug molecules—interact with all potential mutations. To do this exhaustively is too great a computation for even the largest network of computers. What we have found is that a much smaller subset of these mutants can represent the larger class of possible drug resistant mutants—and thus can “span” the range of possible resistant mutants in terms of how they respond to the large chemical libraries.

We have identified a set of “spanning mutants”—about 10 or so—that we can use as a proxy for the large number of possible mutants when computationally testing interactions of these chemical libraries. This, in turn, allows us to use the computational power of the FightAIDS@Home network to create a better—dynamic—model of these spanning mutants in our calculations.

Dr. Stout, can you tell us a little about your paper published in *Chemical Biology & Drug Design*?

David Stout: Our experiments validate the theoretical prediction that there are other sites on protease that no one has ever targeted before with all the FDA-approved drugs. All the FDA-approved drugs target the enzyme’s active site [responsible for snipping HIV’s genetic material into segments so that it can be reassembled as infectious virus]. We’re focused on parts of the enzyme outside the active site. That’s a powerful strategy for drug development because we can target a second drug against the same molecule.

The concept is that we could develop a class of drugs that would bind outside the active site, meaning that we’re going to hit the protease twice, and the hypothesis is that it would help suppress resistance and provide a new family of therapeutics. The compounds we discovered are allosteric inhibitors—they target the sites on protease that affect how the enzyme works, not the enzyme’s active sites.

How did FightAIDS@Home help?

Stout: I could have done the experiment on my own, but the fact that Arthur Olson’s lab [with the help of Alex Perryman, a postdoctoral fellow in the lab] has done all these calculations—including FightAIDS@Home computing—helped us greatly. They didn’t predict the exact hits, but the concept involves using FightAIDS@Home. In the future, we’re excited about what I see as a real challenge for this research to make a more rigorous connection between the theory and the experiment.

Now we’ve got this experimental result and want to do more experiments where we can demonstrate other molecules binding in the same place. We have enough examples so that the FightAIDS@Home programmers can tweak the program, allowing us to teach the theory how to be more accurate. We can then screen an enormous number of small molecules.

Are you focusing on enzymes other than the protease?

Olson: We recently published a paper about our first foray into a new target, which is HIV integrase. We’ve developed a model that will allow us to generate hypotheses regarding how two drug-resistant mutants have circumvented the effect of the integrase inhibitor raltegravir (Isentress). It’s a start—not a completed project by any means. We’re just about to start some World Community Grid FightAIDS@Home computations on the model, and we believe it is probably the best model out there for starting to understand the nature of integrase inhibition and the evolution of integrase drug-resistance. This is going to become increasingly important as more and more people are treated with integrase inhibitors.

So the hope is that you might be able to use the information that you get from doing these sophisticated computations and build a compound from the ground up that might overcome some of these resistance problems?

Olson: Right. That's essentially what we've been doing with protease and now integrase. It's like a chess game—the virus can only move in certain directions, because if it mutates in some other direction it can no longer function. It has its own constraints it must avoid to remain viable. So the idea is to use a combination of drugs to box in the virus. If we know which direction a mutating virus takes, we can figure out how to block all directions so it has nowhere to go.

So that's the driving hypothesis in a sense—that we can box [the virus] in in a number of ways, and one of them is to find new binding sites that might be synergistic with active binding sites of the protease for instance. And the other one is to start to understand the mechanisms of this new target, HIV integrase. So it's complex game because even though a virus isn't intelligent, it certainly acts intelligent. Drug resistance is part of natural selection in essence, from the virus's point of view.

Our readers sometimes feel that HIV/AIDS research is this very abstract thing that happens very far away from them and that they can't contribute other than by donating money to certain organizations or participating in clinical trials. It sounds like FightAIDS@Home—allowing people to donate their computer's unused processing abilities—can help you do your work more quickly. Is that right?

Olson: Very much so. I mean, it's an amazing resource. Certain types of experiments, before we started this type of computing, needed to be limited because of the amount of computing time it would take to complete a project. In some cases, it might take a thousand years to get results—I don't think I'm going to live that long. FightAIDS@Home allows us to think in much broader terms, as it allows us to get more information out of these larger computations. It's something we're extremely grateful for. The people who are essentially loaning us their computer power are enabling this research that would otherwise not be feasible.

To learn more about FightAIDS@Home and to download the software needed to contribute to the work of the Olson Lab at Scripps, click here.
