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Science AMA Series: We are 3 scientists who are collaborating on an open science project to find treatments for Zika. Ask Us Anything!

OPEN_ZIKA R/SCIENCE

Hi reddit!

The Zika virus outbreak in the Americas has caused global concern. To help advance the fight against this debilitating virus, we launched OpenZika. OpenZika is a project running on World Community Grid, an IBM philanthropic initiative which provides scientists with free, massive computing resources, donated by volunteers worldwide. Specifically, we're enlisting the help of World Community Grid volunteers to run docking experiments against crystal structures and homology models of Zika proteins (and other related flavivirus targets that are structurally similar) on their computers and Android devices. We are harnessing World Community Grid's massive computational power to search through thousands of current drugs (to see if they can be re-purposed against Zika) and millions of drug-like compounds (to lay the foundation for subsequent drug development against Zika). After we have selected and our collaborators have tested compounds that could be effective in killing the Zika virus, we will publish our data and results and share them with the public. As soon as we have proven that some of the candidate compounds can actually either (a) prevent the replication of the Zika virus in cell-based tests or (b) prevent the virus from infecting cells, we and other labs can then modify and evolve these molecules to increase their potency against the virus, improve their other properties (such as solubility, permeability, and metabolic stability), and reduce their toxic side effects, to advance and accelerate the discovery and development of new antiviral drugs against the Zika virus.

Carolina Horta Andrade – I am Adjunct Professor at Faculty of Pharmacy of Federal University of Goias, Brazil, and head of LabMol – Laboratory for Molecular Modeling and Drug Design.

My research focuses on Computer-Aided Drug Design (CADD) for Neglected Tropical Diseases and Cancer, using an integration of computational and experimental approaches in order to identify new hit and lead compounds for malaria, tuberculosis, leishmaniosis, schistosomiasis, dengue, Chagas disease, as well as for cancer. My group is also focused on the development of in silico tools to predict ADME and toxicity properties of chemical compounds, and development of web platforms as alternatives for animal testing. My laboratory is working in collaboration with many researchers in the US and Europe, as well as in Brazil, integrating computational and experimental approaches to drug design and discovery. We believe that drug discovery is an interdisciplinary process and we need to collaborate to advance science.

Alexander L. Perryman - I am a senior researcher in Joel Freundlich's lab at the Rutgers University, New Jersey Medical School. I have been studying protein structures and how they interact with other molecules for 2 decades. For the past 18 years, I have been developing and applying computational approaches to help advance drug discovery and development research, with a focus on discerning mechanisms of multi-drug resistance and figuring out how to defeat them. I devoted a couple years to cancer research at MU, followed by a dozen years working on HIV at UCSD and TSRI (including running the day-to-day operations of FightAIDS@Home on World Community Grid for 6 years). I also designed and ran the GO Fight Against Malaria (GO FAM) project on World Community Grid, which is when I began working on malaria and tuberculosis. In the Freundlich lab, I am the computational core that helps guide our research on tuberculosis and the drug-resistant ESKAPE pathogens (such as MRSA).

Sean Ekins- I am CEO of Collaborations Pharmaceuticals, Inc. I have spent 20 years working on using computers to help drug discovery. Over the last 8 years I have worked on neglected diseases like tuberculosis, Chagas disease, Ebola and Zika.

We will be back at 4 pm ET to answer your questions, ask us anything!

READ REVIEWS

WRITE A REVIEW

CORRESPONDENCE:

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People constantly focus and worry about microcephaly, but what about individuals who don't or won't have children? Should they be worried?

vestinel

Yes - some suggestion virus affects memory - Lots more work needed here (Sean)

People constantly focus and worry about microcephaly, but what about individuals who don't or won't have children? Should they be worried?

vestinel

Yes, everyone should be worried, because we really don't know all the consequences in long term that the Zika virus causes. Thanks, CHA.

Do you think targeting the virus is a better route of attack versus combating the mosquitoes? Has there been any work done on sequencing the viral genome? What class of drugs do you think have the best chance at preventing the spread of the virus and/or mitigating the effects of the virus?

t3hasiangod

Thank you - good question - targeting mosquito gets at route, but what about those with the virus, targeting mosquito is not going to help them. One could consider blocking entry of virus into cells, inhibiting machinery of virus, increase the immune response etc.. all equally valid perhaps. We know all the protein components of the virus, we have crystal structures for some of them so OpenZika really just tackles the 'inhibiting proteins that are part of Zika' (sean).

Do you think targeting the virus is a better route of attack versus combating the mosquitoes? Has there been any work done on sequencing the viral genome? What class of drugs do you think have the best chance at preventing the spread of the virus and/or mitigating the effects of the virus?

t3hasiangod

We have to combat both, virus and mosquitoes. However, it's impossible to exterminate all the mosquitoes in the world. So, we need to have weapons, e.g. drugs and vaccines, to tackle the virus. The Zika viral genome has been already sequenced. In the OpenZika project, we are using all the 15 proteins encoded in the Zika virus genome to search for a potential drug, using massive computational virtual screens. We are screening all classes of FDA-approved drugs and NIH-clinical collection, in a strategy called drug repurposing. In this case, we can have an anti-Zika drug in at least half of the time spent to develop a totally new drug. Thanks, CHA.

What sort of computation time is expected for the search to identify potential anti-Zika candidate compounds? If distributed computing weren't available, would there be any realistic alternative for such an exhaustive search?

How much faster could a re-purposed drug be created, tested, and approved compared to conventional drug discovery?

shiruken

Thank you - a repurposed compound could technically skip some of the preclinical studies if its used at

the same clinically approved dose. This could really speed up the process.

The only alternative approach to exhaustive docking is exhaustive HTS of millions of compounds - so far we have only seen a few compounds screened by labs and then they do not cover all approved drugs Just some from USA (Sean)

redditWinnower

thank you !!!

Hi there, can anyone participate or do you have to have a specific kind of expertise? Is this similar/dissimilar to the protein folding games that were so successful? If anyone can help, are there links to your project that you can share with us?

p1percub

Anyone can participate in the World community grid - just need a computer or android phone https://secure.worldcommunitygrid.org/research/zika/overview.do

(sean)

[removed]

[deleted]

Thanks - we have zero funding - thats why we started OpenZika - thats why we started a a Zazzle shop to raise awareness and a few dollars to buy compounds..http://www.zazzle.com/openzika+gifts (sean)

How does a docking study work? Don't you need to know the potential binding sites for the specific drug candidate ahead of time (eg from X-Ray crystallography) to judge how strongly the ligand will bind? Or does one simply try a large number of positions/orientations of the ligand and pick the ones with lowest total energy as test binding sites?

zetadin

This is a good point. A docking study works with binding sites, experimentally determined or predicted. In the case of Zika virus, for those proteins that we don't have the crystal structure, we can use the template target (from experiments) to determine the potential binding site of the protein target in question. CHA

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zetadin

There are other types of programs that we can use to try to predict the location of a binding site (such as AutoLigand, from the Olson lab, where I used to work). For the targets we have used on OpenZika thus far, it has been pretty easy to figure out where the binding sites are, just by looking at the structure, especially when the Zika target protein is superimposed onto the crystal structures of related proteins from other viruses (West Nile Virus, Dengue Virus, Yellow Fever Virus, Japanese Encephalitis Virus), many of which have some substrate, cofactor, or small molecule inhibitor bound to them.

Docking calculations explore a large number of different positions, orientations, and conformations of each compound that we dock. The lowest energy binding mode, out of the 8 or 9 different modes produced for each compound in each "docking job" is one criteria. I then generally apply different types of interaction based filters (for example, a minimum number of predicted hydrogen bonds to the target) and sometimes ligand efficiency filters (the docking score divided by the number of heavy atoms (non-hydrogen atoms)). Those other docking filters help me select with of the best-scoring compounds I then visually inspect.

For some additional details, I just copied and pasted this from the page I wrote for my previous GO FAM project: (just replace malaria target with Zika target, and you'll get the general idea)

http://gofightagainstmalaria.scripps.edu/index.php/project-details

General description of the "docking" calculations we are performing

We computationally predict how potent these candidate compounds might be at disabling key target molecules from the malaria parasite by performing “docking” calculations. Docking is a way of trying to figure out how well a small chemical compound can bind to and block the activity of a target protein. These calculations predict how potent the small chemical compound might be at blocking the activity of the target molecule, the location where it binds on the protein target, and the detailed binding mode it uses to potentially disable that target. It's like trying to find the right key to open a particular lock. However, both the lock and the keys are flexible—they can change shape, or transform their conformation, as they wiggle, jiggle, dance, expand, and contract in the warm watery environment in which they reside. In addition, some locks have multiple different types of keyholes, and only one or two of them might be useful at disabling the parasite's molecular machinery. When, by chance, the lock's internal structure happens to change a bit, the potential for evolutionary improvement occurs. If that change in the lock's guts happens to help the parasite escape the effects of a key/drug, then that new lock becomes a “drug-resistant mutant”. To make it even trickier, the total number of potential keys that could exist in the universe (the size of “chemical space”) is estimated to be about 10 to the 60th power (that is, 1 with 60 zeros after it). We obviously can't computationally evaluate flexible models of that many different keys, so we'll focus these experiments on the types of keys that are somewhat similar to the types of molecules that have already become approved drugs. In the GO Fight Against Malaria project, we will computationally evaluate millions of chemical compounds (potential keys) against models of at least 15 different drug targets from the malaria parasite. Compounds that can bind tightly to the right regions of particular proteins from Plasmodium falciparum have the potential to “gum up” the parasite's machinery and, thus, help advance the discovery of new types of drugs to cure superbugs of malaria.

See also: http://openzika.ufg.br/help-to-fight-zika/

Cheers, ALP

What are you thoughts on using biological controls like Wolbachia to fight against Zika spread in mosquitoes? Is it another approach that can be complementary to your work?

pensivebadger

Thanks - I think its interesting - definitely outside my ethical comfort zone - potentially wiping out a species because it spreads viruses that infect humans..(Sean)

Have you evaluated evidence of association of zika infection with microcephaly? Is this evidence conclusive?

xbk1

Thank you - So far yes based on the published peer reviewed science. The effect on mouse brain even in newborn mice exposed to the virus has been known for 40 years so microcephaly is really not surprising really. (sean)

What's the story on the Avian flu, swine flu, SARS? Use them as an example as the world lives on after imminent threat of them.. depends on the year medication against then was marketed

beatvox

Thank you - so lets wipe away any discussion of conspiracy theory - reality is we are a truly global world, many people travel - they go to once exotic places - they pick up viruses and move on - they spread, the viruses change / mutate.. our immune systems try to fight them and viruses are tough. We do not have vaccines or drugs for every virus.. we are seeing what is effectively an ongoing warfare - human vs virus, you are seeing evolution in real time every flu season, Zika is just another example (sean)

The Rockefeller foundation patented the zika virus in 1947, a brief search will show the details. Is not their archives the place to start looking for a cure, rather than pleading for help that may simply be redoing research from long ago?

sgtpinback

Thank you, that may be so but do you see them coming up with drugs or a vaccine. No. So yes the virus has been known of for decades. But its only really since it hit Brazil that we have become more widely aware of its impact and the need for a vaccine or treatment of some description. We might only find dust in the Rockefeller archives, unless you know something the rest of the world does not :) (Sean)

Hello, didn't Pittsburgh just find a vaccine that is in phase 1 trials?

kavakavaroo

Yes, but still we need drugs to cure those people who are already infected with the Zika virus, mainly pregnant woman. Vaccines are very useful to prevent the infection, and drugs are necessary to cure those who are already infected. Thanks, CHA.

What should women do if they wish to postpone pregnancy because they are worried about microcephaly?

CowsAreTopkek

This question is best answered by an M.D., not by a Ph.D. like me. But I will try to be helpful, even though it can be a touchy political subject. Condoms should help prevent both pregnancy and the sexual transmission of the Zika virus. Other forms of birth control, such as IUD's (implanted devices that release birth control drugs), the birth control pill, etc., can help prevent / postpone pregnancy, but they will NOT prevent the sexual transmission of the Zika virus (or other STD's, such as HIV, herpes, etc.). I haven't studied it in detail, but some of the IUD's have much higher efficacy rates / lower failure rates than the birth control pill, but that is definitely something to talk to your medical doctor about. That is not really my area of expertise. Some would suggest abstinence, but that is not very practical, and abstinence-only advice tends to not work at all, on a social policy level.

Best wishes, ALP

Hi,

I've read some REALLY bad Zika papers published in high profile journals. However, this is one of the best ones out there that I've seen (http://biorxiv.org/content/early/2016/07/06/061671). It has actual *a priori* rationale for the investigation, multiple MOIs, real controls, and the data are fairly convincing.

Compared to some of the, in my opinion, more poorly done work (don't want to link and be a hater but it's out there), what are your thoughts?

ennervated_scientist

Thanks - no actually I think you should call out some of the poor work - so that others are aware.. I have read so many papers that seemed rushed, poorly thought out studies. (Sean)

Hi,

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ennervated_scientist

I have to agree with you and with Sean. "Hot topics" sometimes enable sloppy science to get published. Very well-established labs can also sometimes get sloppy work published quickly in very high profile journals (especially if they are on the editorial board of that journal or a similar journal that is part of the same publishing company). It's sad but true.

When I help teach the critical reading in the chemical biology of pathogens class, I try to emphasize that everyone should read each paper as though they were a peer reviewer. One has to be critical and see whether the data actually supports the conclusions (and whether the experiments were done properly). Don't believe everything you read. But the great thing about science is that eventually the well-done experiments bubble up to the top, and the truth wins out.

Cheers, ALP

PS--Derek Lowe's Pipeline blog has many great posts about the sloppy science and the well-done, inspiring studies. He also lays bare some harsh truths about the nature of drug discovery.

What do you you think will be the effects of this virus in future medical research? What can we learn from the current research being done? And what is your opinion on the measures being placed by the United States government, as well as the international community to counter the spread of the virus? What can or should we do to better understand and by doing so, learn to deal with this virus in particular? Thank you so much for your time. And sorry for the long questions.

AlphaMW3

Thank you - again this virus shows how desperately slow we were to respond to it and our knowledge was thin. Look at the evidence - Brazil has had it for most of last year and the USA just woke up to it in Jan. Hello.. in January there were 150 papers on Zika in PubMed..now 1586 today. There were no crystal structures - now we have a handful but it took months and months. So response time needs to be faster. We need antivirals that are safe against these and related viruses. Lets face it - we have nothing for many viruses - time to change that. (Sean)

I see that Drs. Andrade and Perryman both work/have worked in cancer drug discovery as well and I'm interested to hear a little about the overlap between drug discovery for infectious diseases and chronic disease like cancer. Is it common in your line of work to tackle many diseases at a time?

divvyflax

Some of the same tools and strategies can be used to help advance drug discovery research against many different types of diseases. A lot of the same principles apply (in terms of the biochemistry and biophysics that governs how drug-like compounds and protein targets interact with each other, as well as the medicinal chemistry principles and strategies that help one develop a compound that could actually work as a drug in a person). Similar trends can occur regarding how different bacteria, viruses, and even some cancer targets evolve resistance against the drugs, which is a constant battle. There are more similarities between bacteria and viruses than there are with cancer, since the hallmark of cancer is genomic instability (that is, the number of chromosomes actually changes, as well as the organization of large clusters of genes on those chromosomes), which makes cancers a more diverse and trickier target, in my opinion.

In the computational field, many of us will work on different diseases from time to time. Sometimes that just depends on which collaborators we meet, and which projects they need our help with. And, of course, another aspect is controlled by which projects we can get grant funding to advance. We have to spend most of our time on the projects that are funded by grants, with nights and weekends devoted to some of the side projects…….which is what I generally have to do with Zika research, since I have no actual funding for this project (my work on this project is all pro bono, during what little free time I have). I mostly work on tuberculosis and the ESKAPE pathogens (such as MRSA). But I enjoy the opportunity to work on many different projects that can impact different diseases. It keeps life interesting and fulfilling.

Best wishes, ALP

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divvyflax

Yes, like Dr. Perryman said, in our field, is common to apply the same approaches and tools to advance drug discovery research in many different types of diseases. In my case, I have funded projects on infectious diseases, such as leishmaniasis, schistosomiasis, tuberculosis, as well as in cancer. So, we apply the computational approaches to accelerate the discovery of active compounds against the disease, and then our collaborators from wet labs test those compounds to validate our computational approach and to move forward towards the discovery of new drug candidates. Thanks, CHA.

Mr. Parryman, I would like to thank you for your efforts on the FightAIDS@home project on the World Community Grid.

Can you comment on the impact volunteer computing has had on the biomedical field over the last several years? If there were more volunteers on the World Community Grid, would that speed up the discovery of potential cures for viruses like HIV and Zika?

TechWizardry

You are most welcome.

It would take a very long time to really answer that question. Specific impacts on different projects are described in the Project Updates and News Stories on the World Community Grid site, as well as Newsletters, updates, and webinars that can be found on project specific sites (such as the FightAIDS@Home.scripps.edu , the GOFightAgainstMalaria.scripps.edu site, or the OpenZika.ufg.br site). I am not up to speed on the FAAH project any more, since I left that lab about 3 years ago. But they are still analyzing the HIV data. I am still working on some of the malaria data and TB data from GO FAM, but those are side projects. For Zika, we have only recently started identifying "candidate" compounds from the docking experiments. They have not yet been tested in "wet lab" experiments (cell-based assays to see if they block Zika replication or Zika infection). But those assays should begin soon.

In general, it has enabled me and many other scientists to greatly accelerate and expand the scope and scale of our computational research, by several orders of magnitude. Having these huge resources also inspires us to come up with new tools and new strategies for dealing with these massive mountains of data, which helps both our research and can potentially help many other drug discovery scientists who work on other diseases.

The more people who volunteer to donate their dormant CPU power to World Community Grid, the quicker we can perform each experiment. It helps us get more computational work done quicker, and it helps the other projects on WCG, which work on other important areas of research that benefit humanity, as well.

Best wishes, ALP

Is there any known time frame a woman could wait and no longer have to worry if she got pregnant?

MrControll

I am not sure. I don't think the answer to that question is known for sure at this point. I advise checking the CDC's Zika webpages for the most current information about that.

Best wishes, ALP

Even if you cure it, the brain is left devastated already. An adult that is cured just won't have as good of a memory anymore. Zika eats away at the progenitor cells in your brain.

redeclipze

That is a good point. The most severe damage is done during the developmental stages. In addition, at least one new study indicates that adults who get infected with Zika might suffer long-term effects on their memory.

Best wishes, ALP