BIZCOMMUNITY

We are using computer models to fight drug resistance

By Ozlem Tastan Bishop

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The infectious disease burden in Africa is very high, particularly for tuberculosis (TB), malaria and HIV/Aids. In 2018, nearly a quarter (24%) of TB cases in the world were in Africa. The region accounted for 93% of malaria cases. The continent also bears the brunt of the HIV epidemic: 20.6 million of the 37.9 million people living with HIV are in eastern and southern Africa.

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To solve the disease problems, scientists in Africa need to push boundaries and think outside the box. And I believe that we can do so.

My research is based on using computers to understand biological problems at the protein level. This is part of bioinformatics, a young but broad discipline. Its applications are wide and range from understanding the genome sequence of any organism to drug discovery.

My research goal is to understand the mechanisms, at a molecular level, of diseases relevant to Africa – and to find solutions. Under a grant from Grand Challenges Africa: Drug Discovery Programme we would like to tackle two separate but interlinked biological problems. These are: to understand drug resistance mechanisms; and to find alternative drug targeting sites to design novel drugs.

Our research is outside the box of conventional drug discovery as it asks the following question: what are the drug resistance mechanisms – at a molecular level – behind TB and malarial drugs?

In previous research we made a novel and significant finding. We were able to identify the resistance mechanism in an HIV drug target protein. We did this by observing a change of behaviour in the protein against eight currently used drugs.

The findings are the first step to designing better drugs against HIV because they gave us novel drug targeting sites in the protein. Now we would like to apply our approaches to understand TB and malarial drug resistance. From there we hope to identify alternative drug targeting sites.

The problem

Let's look at the problem from the perspective of infectious diseases. Many drugs target the functional site of a protein of a pathogen (the microorganism that causes disease). We call them active site drugs. They aim to block the function of the protein, hence the pathogen's life cycle. These drugs have been successfully used in therapies, for instance to reduce viral loads in HIV patients to undetectable levels.

Unfortunately, these drugs compete with natural substances which are required for the function of the protein, and may introduce selective evolutionary pressure to the pathogen. This leads to drug resistant mutations. Pathogens mutate to survive. This is why these drugs become less effective over time.

Continuously emerging strains of pathogens that are resistant to current drugs present a huge challenge for the eradication of infectious diseases. To design more effective drugs, we first need to understand the drug resistant mutation effects.

To answer the questions about resistance, my group developed computational approaches. We modelled the 3D structure of proteins with mutations, and simulated the behaviour of proteins with different mutations in a cell-like environment.

We then compared the behavioural change between proteins with no mutation and proteins with drug resistant mutations. Proteins consist of residues. These residues make networks and communicate with each other. Some residues are more popular than others. Popular residues are functionally more important.

We also looked at how the popularity of these residues changed with mutations. This is called dynamic residue network analysis. Residue network analysis was used in static protein structures.

We went on to develop this approach by applying the dynamic proteins in a cell-like environment. And we developed a tool for others to use.

Way forward

Both TB and malaria remain a public health challenge with high global prevalence and death rates. Fighting against these infectious diseases is an ongoing battle as pathogens continuously develop resistance to the drugs used against them.

For instance, recently we again witnessed a malarial parasite gaining resistance to the first-line artemisinin-based combination therapies in Southeast Asia. The main concern now is whether the resistant parasite strains will spread to Africa, where most malaria cases are located.

Next in our research we would like to see if there is a common pattern in these resistance mechanisms. This will help us design new compounds for drug development against TB and malaria. This is a long journey and we are only at the very beginning of it.

ABOUT THE AUTHOR

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