Transforming ARV treatment

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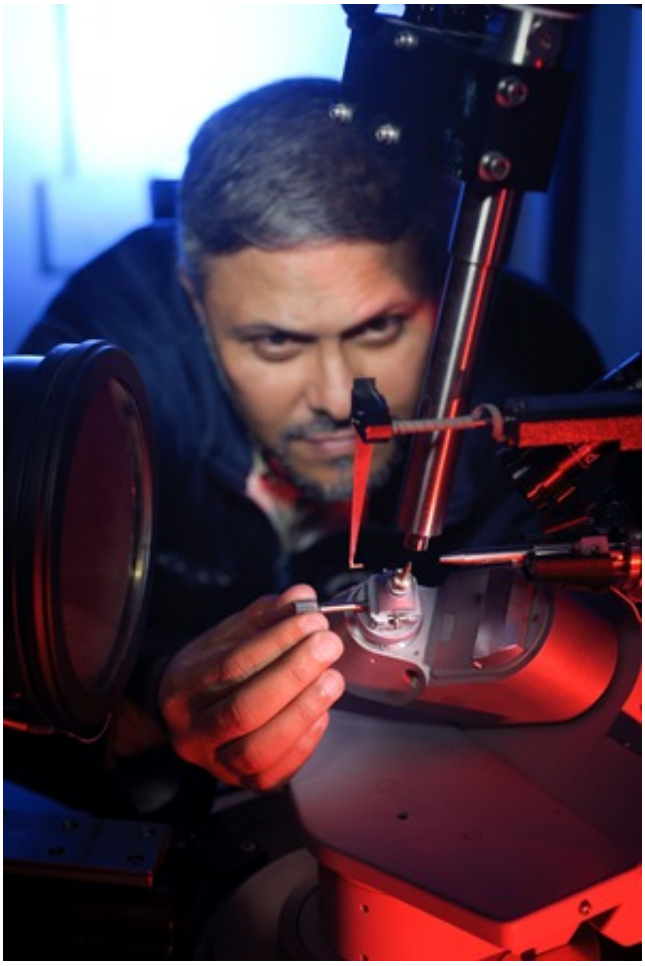

Professor Yasien Sayed, research leader of the HIV Proteins Research Thrust, Protein Structure-Function Research Unit in the School of Molecular and Cell Biology, has led his group to international acclaim by

solving the three-dimensional X-ray crystal structure of the South African HIV-1 subtype C protease.

To appreciate the importance of this research in the context of antiretroviral (ARV) treatment in sub-Saharan Africa, we need to understand the international focus of HIV treatment to date. The vast majority of HIV-infected individuals worldwide are located in sub-Saharan Africa. Thus far, the major target of ARV drugs has been the HIV protease molecule (one of three proteins/enzymes in the virus) through the use of drugs known as protease inhibitors. 'The problem is that all the drugs currently available to treat HIV worldwide have been designed to target the subtype B virus of HIV – the major cause of infection in North America and Europe,' says Sayed.

This has significant implications for Africa, India and China where the subtype A and C viruses account for the majority of infections. In South Africa, subtype C viruses account for more than 95% of HIV infections. Enter Sayed's group, which was the first in the world to solve the three-dimensional X-ray crystal structure of the HIV-1 South African subtype C protease. This serves as the foundation to improve the design of protease inhibitors specifically for the South African protease, which, if successful, will have an extremely positive impact on ARV treatment in sub-Saharan Africa.

'Our group set out to understand whether the drugs designed to target subtype B viruses were as effective on subtype C viruses because there are several amino acids changes in the protease enzyme between these subtypes. We therefore began to study drug binding to the South African HIV-1 subtype C protease.'

'Based on our crystal structure of the South African HIV-1 subtype C protease, we discovered subtle differences between the subtype B and subtype C proteases.' This research was undertaken by Previn Naicker,

Sayed's PhD student, who completed the research as part of his MSc. A research article by Sayed, co-authored by Naicker and six other researchers from South Africa, was published online in 2012 in the *Journal of Biomolecular Structure and Dynamics*. The implications of minor structural changes between proteases of different subtypes are enormous and support the research efforts of Sayed's group for the past 10 years, which clearly demonstrate that HIV drugs need to be designed to target specific proteases from specific viral subtypes. 'If you do not use the best drug to target a specific protease variant, you are allowing the virus to become more virally fit,' he states.

Sayed and co-workers produced the first paper on the efficacy of ARVs towards the South African HIV-1 subtype C protease 10 years ago, when they showed that although the current clinical protease inhibitors are reasonably effective, they do not bind as well to the South African HIV-1 subtype C protease as to the subtype B protease. 'When drugs do not bind tightly to the target molecule, it provides the virus with an escape route whereby it generates additional mutations in order to lower the usefulness of the drugs,' he explains. 'Therefore, we are ultimately contributing toward viral fitness and increased viral resistance which spells bad news for the HIVpositive patient.'

Virologists have determined that in a patient with HIV, a single virus in a 24-hour period can produce up to 100 million new copies of itself. Each virus also has the potential of introducing a large number and variety of mutations, all of which reduce the effectiveness of the drug. The research of Dr Salerwe Mosebi, one of Sayed's PhD students in 2008, examined the role of protease mutations in drug-treated individuals infected with the South African HIV-1 subtype C virus. The results demonstrated that mutations in the protease enzyme reduced the efficacy of ARV drug binding. Similar research is being conducted by Sayed's current MSc students: Lungile Ndlovu, Alison Williams and Jake Zondagh. 'The protease is essential to the HI virus' survival. Without the

protease, the virus cannot function 99 Wits Research Report 2012 Faculty of Science and mature, rendering the virus non-infective. Hence, if the function of the subtype specific protease is arrested then viral maturation cannot occur. '

'The plight of HIV-infected patients is aggravated when considering the role of pharmaceutical companies investigating ARV design because it is not in their financial interests to design subtype specific drugs. In my opinion, big pharmaceutical companies are not interested in South Africa or sub-Saharan Africa because we are not a viable economic market,' says Sayed. 'I therefore decided to initiate collaborative research work with local scientists with experience in organic/medicinal chemistry with a view to designing possible lead compounds that are more effective against our South African HIV-1 subtype C protease.'

This led to highly successful collaborations with two groups:

1. Organic chemists from the University of KwaZulu-Natal; notably, Professor Thavendran Govender and Professor Gert Kruger. In the past three years, the collaboration published several papers and synthesised several compounds. Some compounds have shown promise and may be used as potential lead compounds for the development of protease inhibitors against the South African HIV-1 subtype C protease.

2. Professor Emeritus Perry Kaye of the Department of Chemistry, Rhodes University, who has been instrumental in designing a bi-functional drug capable of binding the protease and another enzyme in the virus known as reverse transcriptase. Two papers have been published on this work.

'The area of HIV research in South Africa by South African scientists is wide open because South Africa displays the fastest rate of HIV infection in the world. Approximately six million people in South Africa

are HIV positive and about 1.5 million are on ARV treatment,' continues Sayed, who says he could not have achieved any of his research successes without the input and partnership of Wits researcher Professor Lynn Morris who heads HIV research at the National Institute for Communicable Diseases (NICD) and is a staff member in the Wits School of Pathology.

'Lynn is an outstanding scientist. I am thankful to her for kindly sharing information on HIV protease mutations in HIV-infected individuals. We are partnering on groundbreaking research concerning novel mutations and insertions occurring in the protease sequence of newborn babies in southern Africa. The babies are therefore not only born HIV-positive but the viruses contain novel mutations and insertions in the protease enzyme. The babies are drug-naïve and we do not know whether they will respond positively to current HIV-treatment regimens, or whether they will respond at all.'

This is one of many reasons why it is essential to develop drug compounds for the treatment of patients with the South African HIV-1 subtype C virus. 'We are presently optimising the drug compounds that were developed earlier. However, all our work was performed in test tube conditions,' says Sayed. 'The next step is to begin cell culture assay experiments where the drug compounds are tested against the South African HIV-1 subtype C virus. I will be performing this aspect of the research at the NICD laboratory with Professor Morris.

'My postgraduate students will continue furthering our research efforts to understand the molecular basis of HIV. I am very fortunate to have fantastic students working with me. This research would not have succeeded without their hard work, commitment, discipline and passion for protein biochemistry. It is not unusual to see my students working after hours and over weekends. They are doing a phenomenal job.'

Provided by Wits University