Communication and Marketing Department
Isebe loThungelwano neNtengiso
Kommunikasie en Bemarkingsdepartement

Private Bag X3, Rondebosch 7701, South Africa
Welgelegen House, Chapel Road Extension, Rosebank, Cape Town
Tel: +27 (0) 21 650 5427/5428/5674 Fax: +27 (0) 21 650 5628

www.uct.ac.za

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New research brings hope of winning the TB battle

Scientists at the University of Cape Town are engaged in new research in the battle against tuberculosis (TB), which has overtaken HIV/AIDS as the leading cause of death from infectious disease. According to the World Health Organisation (WHO), TB kills about 4 000 people a day.

Professor Valerie Mizrahi's team, based in the Institute of Infectious Disease and Molecular Medicine (IDM), has collaborated with international researchers in publishing four new papers on TB drug discovery that have generated considerable attention in the field.

"These papers illustrate what South African scientists are doing in this area of TB research," says Professor Mizrahi, director of the IDM. Mizrahi and her research team are internationally recognised for their work on studying aspects of the physiology and metabolism of *Mycobacterium tuberculosis* (Mtb) relevant to TB drug discovery, as well as drug resistance.

In one of the recently-published studies, done under the auspices of the More Medicines for Tuberculosis (MM4TB) consortium funded by the European Commission, Mizrahi's group worked with collaborators in Switzerland, Italy, Hungary and the United Kingdom (UK) to identify and validate the enzyme GuaB2 as a new TB drug target. This study, led by UCT postdoctoral fellow Vinayak Singh, exemplifies the 'phenotypic' approach to TB drug discovery; which starts with finding a molecule that can inhibit the growth of the TB bacterium, and then figuring out how it works.

In this case, MM4TB researchers – led by Stewart Cole from the École Polytechnique Fédérale de Lausanne, in Switzerland – identified a molecule (VCC234718) which could kill the Mtb TB bacterium, but showed limited toxicity against mammalian cells.

"One of the ways to work out the mechanism of action of such a molecule is to see if we can isolate any natural variants or 'mutants' of Mtb that can resist its killing effects. By analysing the genome sequence of VCC234718-resistant mutants of Mtb, the researchers could pinpoint GuaB2 as the probable target of this drug," explains Mizrahi.

In Mtb, GuaB2 plays an essential role in synthesizing a class of metabolites known as purines, which are used for many purposes, including production of the building blocks of DNA and RNA. Crippling purine biosynthesis by treatment with a GuaB2 inhibitor is lethal to the TB bacterium.

In a related study, Joanna Evans (another postdoc in Mizrahi's group) validated a component of Mtb's enzymatic machinery for producing the ubiquitous cofactor 'coenzyme A' as another new TB drug target. As in the GuaB2 study, this project, which was carried out under the TB Drug Accelerator programme funded by the Bill & Melinda Gates Foundation, involved international collaboration – this time with world-leading scientists from Weill Cornell Medical College and the National Institutes of Health (NIH), in the USA.

Collaborative work has paid off, with research groupings within the IDM drawing on one another's experience and expertise, says Mizrahi. These include the MRC/NHLS/UCT Molecular Mycobacteriology Research Unit, which Mizrahi leads together with her colleague Associate Professor Digby Warner; and others, such as UCT's H3D Centre for Drug Discovery and Development, led by Professor Kelly Chibale.

The IDM is constantly extending its reach by working with top researchers across the globe.

"I am particularly proud of our work in leading – from South Africa – collaborative research on problems such as TB, which are so important here and in the rest of Africa. Not only can we do this type of research in Africa, but we must," says Mizrahi.

An urgent need for new drugs

Beyond helping to put South Africa and UCT on the map, research of this type is potentially lifesaving. The World Health Organisation has estimated that in 2015, 10.4 million people developed TB and 1.8 million people died from the disease (including 40 000 people with HIV). Of particular concern is the rising incidence of multi drug-resistant (MDR) and extensively drug-resistant (XDR) TB, which further underscores the urgent need for new drugs.

Noting the profound impact that the availability of antiretroviral (ARV) drugs has had on the control of HIV/AIDS, Mizrahi lauds the role that scientists have played in developing the drugs that are taken by millions of South Africans through the national ARV roll-out programme.

"The pivotal role of world-class science in delivering tools for the management of HIV/AIDS must never be forgotten. ARVs are lifesavers. While there are important lessons here for TB, there are major scientific challenges in TB-drug discovery and development which make this a particularly tough undertaking."

For example, the TB bacterium is enveloped in a lipid-rich cell wall that presents a formidable permeation barrier for drugs. This very slow-growing organism, which is hard to work with in the laboratory, is also capable of defending itself against drugs through detoxification and efflux mechanisms.

But despite the challenges, Mizrahi is hopeful.

"I am convinced that applying cutting-edge science to address these and other challenges will enable us to develop new therapies for this disease."

Mizrahi's team is particularly interested in going after drugs with novel mechanisms of action that are active against strains of Mtb that are resistant to existing TB drugs, and responsible for causing MDR and XDR-TB – forms of the disease that are much more difficult and costly to treat.

Breakthroughs come from collaboration

The IDM director is very grateful for the long-term support she has received from the government, through the South African Medical Research Council (SAMRC) and the National Research Foundation (NRF). This funding has provided a solid foundation that has helped her group and others in the IDM to secure international grants for its work on TB.

Coordinating consortium projects is daunting. But it has a rewarding ripple effect, says Mizrahi: "The benefits have been tremendous in terms of growing our networks and getting to know people. Our students and postdocs have also benefited tremendously from being in constant contact with top international groups."

Mizrahi believes that breakthroughs these days are more likely to come from international and interdisciplinary collaborations between researchers who can tackle a problem from many different angles.

"When I first started, my career research was largely 'me' driven. It was all about you as the first or last author on papers, and as the originator of the ideas. This culture still prevails, as reflected in the criteria used for promotion in academia. I don't see nearly enough attention paid to 'us' – the teams that work together."

She sees immense value in collaborative work, and perceives it as the future for the next generation of scientists. She credits UCT for making a big push in this area through the creation of a number of new interdisciplinary research institutes.

"The challenges we are confronting can't be tackled in a piecemeal way. We need to get together as chemists, biochemists, pharmacologists, microbiologists, cell biologists and clinicians, to tackle TB drug discovery in a comprehensive way."

It's not just hard science that Professor Mizrahi is consumed by. She says it's untenable that so many people – particularly the poor – still have to suffer and die from TB.

"Why should the most sophisticated tools of biomedical science not be used to tackle this ancient disease? Why should we live with diagnostic methods that are 130 years old? Why should we not develop better drugs to treat this disease, as well as an effective vaccine? Absolutely, we must! Researchers in South Africa have a very important role to play in these efforts."

But Professor Mizrahi recognizes that new drugs, vaccines and diagnostics are not the panacea. She says that far more needs to be done to drive down the poverty, inequality and poor living conditions that have led to a "tsunami of TB" in South Africa and other countries.

"It is humbling. There is work we can and we must do. We need a multi-pronged attack on this disease."

Despite the challenges, Mizrahi sees great promise in new developments.

"I would love nothing more than to see us contributing in a meaningful way to developing a new TB drug regimen that works on drug-resistant and drug-sensitive TB, and is shown to have a public health impact on people in Africa."

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Issued by: UCT Communication and Marketing Department

Thami Nkwanyane
Media Liaison and Monitoring Officer
Communication and Marketing Department
University of Cape Town
Rondebosch
Tel: (021) 650 5672
Fax: (021) 650 3780
Cell: (072) 563 9500
Email: thami.nkwanyane@uct.ac.za
Website: www.uct.ac.za