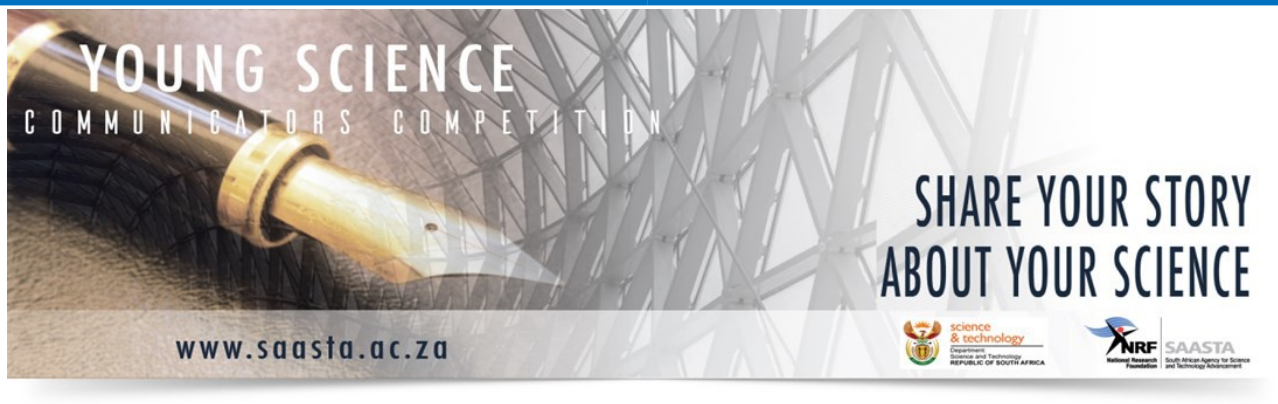

YOUNG SCIENCE COMMUNICATORS COMPETITION 2016/2017
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Understanding Molecular Machines To Fight TB

By Angela Kirykowicz

I saw my first molecular machine while at school; the textbook showed a brightly coloured picture of the components of ATPase, an enzyme which fuels your body with chemical energy, busily churning out ATP, the molecule of life. My god, I thought, it looks just like a generator. I would not have thought back then that my own research would be directed towards finding out the structures of these molecular machines, which runs all living things, much like the intricate circuits of a computer. Specifically, we need to know about the large machines directing the growth and survival of *Mycobacterium tuberculosis*, the organism which causes tuberculosis (TB).

TB is a deadly problem in South Africa. Not only does it cost us tens of thousands of lives every year, according to the World Health Organisation, it is also an enormous economic burden. In one study, drug-resistant TB consumes almost a third of the national TB budget despite comprising only around 2% of TB cases. The rise of drug-resistant TB is particularly alarming: another study finds that in the Eastern Cape alone, the cases of drug-resistant TB doubled in only a three year period.

We cannot fight what we do not know. *M tuberculosis* is a particularly difficult pathogen to treat, resulting in months worth of chemotherapy for TB patients. And that is if the patient is only infected with drug-susceptible TB. Drug-resistant TB can cause treatment to stretch on for years. Basic research, the type I complete, is therefore critical in finding new drug targets to combat the pathogen.

Like all living things, *M tuberculosis* relies on a web of interconnected proteins, the workhorse of life, in order not only to survive but also to thrive in the human host. Many are familiar with the idea of genes, the inheritance molecule, directing the production of proteins. However, how the proteins carry out their functions is a fascinating field of study. What we are particularly interested in is what those proteins look like. It would be unfathomable to build a house without knowing the blueprints. Likewise, we cannot design smart drugs, those with fewer side effects, without understanding the architecture, or structure, of the target.

A crucial question you may ask is: how do we know what to target? We know little about the web of interconnected proteins in the TB pathogen, let alone what they look like. We suspect that large protein machines exist and drive the pathogen; much like ATPase churns out energy for our body to use, other proteins machines must carry out specific life-giving functions which can be targeted. So we have to go on a hunt.

Mycobacterium smegmatis is a harmless soil-dwelling bacterium which is related to the disease-causing *M tuberculosis*. It is a good place to start. Most researchers would start with a specific target and spend months or years figuring out its architecture and function. The most popular technique, known as X-ray crystallography, for discovering protein architecture has a low success rate. It is also not as suitable for finding out the structure of large protein machines. There is, however, an alternative technique, called transmission electron microscopy (TEM), which is more suitable for use on large molecular machines.

By growing the bacteria, breaking them up, sifting out the molecular machines, and imaging them using TEM we can begin to build up a picture. Thus, the architecture of sifted out molecular machines is reconstructed, giving an important start into gaining deep insights into how it functions in the cell.

It has been quite a ride. We have several structures of interesting machines which are currently being identified. Evidently, it will take a long time to figure out the architecture of the interconnected web of proteins and how this contributes to the survival of the TB pathogen within the human host. If we can begin to understand the system in greater detail, then we will be well on our way to curing TB not just in some undefined future but also for generations to come.

About the Young Science Communicators Competition

The South African Agency for Science and Technology Advancement (SAASTA's) Young Science Communicators competition is an initiative that aims to encourage young scientists to communicate their world to the public, beyond their academic peer community.

It is one of a number of initiatives at SAASTA aimed at developing science communication skills in scientists and researchers.

The competition awards four categories, namely: popular article; video clip; audio clip; and an open category. Participants are encouraged to explore their creativity in communicating their work.

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