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Rising malaria resistance a growing threat - warns UCT professor in his inaugural lecture

Professor Gregory Smith Photo: Lerato Maduna/UCT

Although malaria mortality rates have decreased over the years, the problem still lies with rising resistance, according to Professor Gregory Smith, a professor of inorganic chemistry in the Department of Chemistry at the University of Cape Town (UCT). He recently delivered his inaugural lecture to mark his promotion to full professorship, the highest academic rank.

Professor Smith's lecture was titled "The Marriage of Organometallic Chemistry – Something Old, Something New, Something Borrowed, Something Blue". He is the leader of the UCT Organometallic Chemistry Research Group in the Faculty of Science.

Organometallic chemistry is where the worlds of inorganic and organic chemistry unite, giving rise to compounds that are the backbone of innovation in catalysis, materials science,

medicinal chemistry, and organic synthesis. Professor Smith's research approach aims to solve realistic problems within the pharmaceutical, petrochemical, and mineral industries. A pressing issue South Africa has been wrestling with for decades is the beneficiation of metals mined in the country – especially platinum group metals.

Professor Smith emphasised the crucial role of metals in combating the growing resistance, citing the example of ferroquine, a compound with significant potential. "Ferroquine contains an organometallic entity in the lateral side chain. It features an iron-containing compound sandwiched between two cyclopentadienyl rings, a unique characteristic present in the lateral side chain of the chloroquine clinical drug," he said.

Ferroquine first entered clinical trials in 1997 and completed the programme in 2011. Professor Smith said that after a brief hiatus, it re-entered clinical trials in 2015 and is currently in an advanced stage of patient exploratory trials as part of a combination therapy to treat malarial infections. Professor Smith and his colleagues then jumped on the bandwagon. They decided to try to make a variety of compounds based on various types of metals to try and target malarial infections.

Professor Smith said there's been quite a paradigm shift in the approach to treating malaria, moving from monotherapies to a multi-targeted approach, targeting multiple effects within the parasites.

His former student Diana Melis prepared quinoline triazole compounds and attached the extrinsic fluorophore. Professor Smith said this was quite a serendipitous discovery because they aimed to target the digestive vacuole, an important target for antimalarial drug discovery.

"But what we found is that our compounds were certainly not targeting the digestive vacuole at all but rather targeting other membranes, which seems to us, as we understood it at the time, to mean that the compounds were certainly starving the parasite of vital nutrients that it needed, and in that way, they were killing off the parasites," said Professor Smith.

However, with the toolbox of chemical biology tools available, Professor Smith and his colleagues could now structure compounds to target specific organelles within the parasite. "We could build up compounds targeting different organelles within the malaria parasite. We could also use it to determine where our metals are going because of these fluorescent molecules. So, using live cell screening, we could find out where our compounds were localising within the parasite cells," he added.

Professor Smith mentioned that several compounds have been known to treat malarial infections. Many of these compounds, discovered through phenotypic screening, have a quinoline base. Some of the clinical compounds used are quinine, amodiaquine, and chloroquine. Nobel laureate Tu Youyou discovered some non-quinoline-based treatments such as lumefantrine, amodiaquine and piperaquine. She found that they are more effective when used in combination with another drug, now known as artemisinin-based combination therapy. The combination of these two drugs shows enhanced efficacy.

"Quinine has been used to treat severe malarial infections over the years," said Professor Smith. Quinine was originally discovered in the bark of a cinchona tree in South America. Explorers to South America would often use quinine to treat the effects of malaria or the symptoms of a malaria infection. Due to its bitter taste, they would often mix it with water.

Speaking at the lecture, UCT Vice-Chancellor Professor Mosa Moshabela said: "By increasing our understanding of Professor Smith's research in inorganic chemistry, we also build our understanding of the important role metals can play in biological systems: for instance, in

delivering drugs to specific sites in the body for treatment of diseases such as cancer; or as contrast agents in imaging techniques such as MRI scans – to mention just two common applications. As these examples illustrate, the study of bioorganometallic chemistry can combine an understanding of biology, chemistry, and medicine to solve complex problems."

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