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UCT researchers uncover molecular “switch” that fuels cancer progression



Dr Lateef Nashed and Professor Kevin J Naidoo.

Photo: SCRU

Researchers from the University of Cape Town’s (UCT) [Scientific Computing Research Unit \(SCRU\)](#) have uncovered a critical molecular “switch” that drives the formation of cancer-associated antigens. The [study](#), published in *Nature Communications*, details how the spatial relocation of enzymes within a cell’s internal machinery leads to the aberrant “sugar coating” of proteins, a hallmark of cancer progression.

The research – led by SCRU Director Professor Kevin J Naidoo, working with senior postdoctoral fellow in the SCRU Glycobiomedical laboratory Dr Lateef Nashed, SCRU computational scientists Dr Tharindu Senapathi and doctoral student Kyllen Dilsook – focused on Mucin 1 (MUC1), a protein that behaves very differently in healthy and cancerous cells due to changes in glycosylation, the process by which sugar molecules attach to proteins. Using a novel “one-pot” synthetic biology method, combined with advanced computer-based

reaction simulations, the team recreated the complex conditions found inside the cell's Endoplasmic Reticulum (ER) and Golgi apparatus.

A key discovery of the study is that in cancer cells, initiation enzymes known as GALNTs relocate from the Golgi to the ER. This spatial shift extends reaction times and prevents inhibition by other enzymes, resulting in complete "Tn antigen" occupancy of the MUC1 protein. Furthermore, the study identified that the enzyme ST6GALNAC1 has a strict preference for a specific location on the protein, the T13 site, which drives the high-density synthesis of the tumour-associated sialyl-Tn (sTn) antigen.

"Our systems modelling approach allows us to decode the enzyme localisation and substrate specificities that are fundamental to tumorigenesis," said principal investigator Professor Naidoo. "By understanding exactly how these cancer-associated antigens are built, we open new doors for the development of precision vaccines and targeted drug discovery."

The study, titled *"An in vitro approach for simulating divergent Golgi O-glycosylation of tumour-associated MUC1 from normal MUC1,"* represents a significant leap in glycobiology, moving beyond simple gene expression to a mechanistic understanding of how metabolic networks are rewired in disease.

By developing a "one-pot" synthetic biology assembly line and using advanced computer simulations, the research team has decoded how the relocation of glycoenzymes in cancer cells leads to the high-density synthesis of tumour-associated antigens. Specifically, the team has identified the T13 site as the primary target for sialylation. This is a finding with significant implications for cancer vaccine and drug development.

Issued by: UCT Communication and Marketing Department

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