Discovery aids in fight against antifungal drug resistance

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A University of Otago, New Zealand, research breakthrough from the Sir John Walsh Research Institute is helping pave the way for novel antifungal drugs designed to overcome the world-wide problem of growing resistance to current treatments.

Fungal infections by organisms such *Candida*, *Aspergillus* and *Cryptococcus* play an increasingly significant role in disease. Infections such as thrush affect premature babies, the elderly, females of reproductive age, individuals with dry mouth and terminal cancer patients. They can be fatal; 1.4 million people die annually due to fungal infections made worse by co-infections with tuberculosis and AIDS or by medically-induced immune deficiency.

To date, efforts to expand the array of antifungal treatments available have been hindered by the lack of molecular-level understanding of potential drug targets and mechanisms causing drug resistance.

Now, Otago researchers led by Dr Brian Monk, and working with colleagues at the University of California San Francisco, have determined the complex structure of a key cell membrane protein involved in sterol metabolism and resistance in a yeast model. Their findings appear in the latest online early edition of the prestigious US journal *Proceedings of the National Academy of Sciences* (*PNAS*).

Dr Monk says the research team's feat will provide new insights into mechanisms underlying fungal resistance to triazole drugs and aid in

efforts to develop new broad-spectrum drugs with minimal side-effects.

"Membrane proteins in general are important molecules in cells and they also represent around 70 per cent of all drug targets. However, they are notoriously tricky for scientists to extract from cells and successfully study, so we are delighted that we have been able to do so."

The researchers' X-ray crystallography images of the structure reveal new features likely to be held in common with up to half of all membrane proteins, including closely related proteins that modify the action of most commonly prescribed drugs.

"They tell us how the fungal enzyme and its relatives interact with the membrane and provide important clues about relationships with substrates, inhibitors and products that have broad implications for biology, drug design and personalised medicine."

Dr Monk notes that their success in solving the membrane protein structure parallels a similar recent achievement by Professor Greg Cook's team in Otago's Department of Microbiology and Immunology.

Last month, Professor Cook and colleagues published the structure of a membrane protein essential for bacteria to generate energy, a finding which opens the way to developing new classes of antimicrobial drugs. Less than 0.5% of the protein structures so far determined worldwide are for membrane proteins.

It is particularly impressive for two groups at Otago to have published such structures in 2014, which is the United Nations-sanctioned International Year of Crystallography in honour of a century of multidisciplinary contributions to humanity, Dr Monk says.

The next steps for Dr Monk and colleagues are further study of the

membrane protein in several important fungal pathogens and use state-of-the-art screening technology to identify new broad-spectrum drugs that target this protein.

More information: Architecture of a single membrane spanning cytochrome P450 suggests constraints that orient the catalytic domain relative to a bilayer, Brian C. Monk, Thomas M. Tomasiak, Mikhail V. Keniya, Franziska U. Huschmann, Joel D.A. Tyndall, Joseph D. O'Connell III, Richard D. Cannon, Jeffrey G. McDonald, Andrew Rodriguez, Janet S. Finer-Moore, and Robert M. Stroud, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1324245111

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