Sterol Biosynthesis Mutations in Azole Resistant Fungal Pathogens

Steven Kelly, Institute of Life Science and School of Medicine, Swansea University, Swansea, Wales, UK.

Azole antifungals have been used extensively in medicine and agriculture and their mode of action involves inhibition of 14-demethylation of sterol during the production of ergosterol, the main fungal sterol. This step is undertaken by a cytochrome P450 (CYP51) that is the only activity in the superfamily found also in other eukaryote Kingdoms and some bacteria. Azole resistance has emerged as a problem correlated with increased infection rates and the more extensive use of azole drugs in patients suffering HIV infection, chemotherapy, organ transplant patients and in intensive care. The mechanisms identified include altered target site, increased efflux of drug and second site sterol biosynthesis mutation in sterol 5-desaturase that changes the main 14-methylated sterol accumulated under treatment from a 3,6-diol to 14-methylfecosterol that can support growth.

The frequency of the different resistant mechanisms remains unclear and the presentation will include data from a study in intensive care unit with Professor David Denning (Manchester) that found four CYP51 mutants among 30 also showing increased efflux. Also presented will some results from an EU wide study EURESFUN with Dr O. Bader and Professor Uwe Gross at Gottiningen supported by FP6. Resistant strains of both *Candida albicans* and *Candida glabrata* were investigated yielding novel CYP51 mutations and new strains defective in sterol 5-desaturase. Also among the strains were mutants of other sterol biosynthetic steps including for 22-desaturation and 8-isomerisation and the characteristics of the strains will be described.