A Novel Treatment for Candida glabrata Infection

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Candida glabrata is a fungus that causes life threatening infection in humans. Recently, some strains have become resistant to current antifungal drugs such as caspofungin, and new drugs are urgently needed. Last year, I discovered that the transcriptional regulator Ada2 is required for C. glabrata to resist antimicrobial peptides and caspofungin, and is necessary for virulence in Galleria mellonella (wax moth) larvae. My hypothesis is that a compound that inhibits Ada2 can potentially be used to treat C. glabrata infection. My objective was to discover a new drug to treat C. glabrata infection. Computer-assisted modelling, docking, and screening were used to identify potential Ada2 inhibitors. Ten of these compounds were selected based on structural diversity and availability and were purchased from a commercial source. To test for toxicity, each compound was injected into G. mellonella, and survival was monitored over a seven day period. Each non-toxic compound was tested for its capacity to protect G. mellonella from lethal C. glabrata infection using survival as the endpoint. Computer modelling generated a list of 400 potential Ada2 inhibitors. Of the 10 compounds that were selected and tested, only three were non-toxic. Of these three, the compound 6-methyl-2-oxo-N-(2-pyridylmethyl)-1H-pyridine-3-carboxamide significantly improved survival of infected G. mellonella in two separate experiments (p=0.011 as compared to control by the log-rank test). Therefore, the compound 6-methyl-2-oxo-N-(2-pyridylmethyl)-1H-pyridine-3-carboxamide is a promising antifungal drug for treating C. glabrata infection.

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