# Polyacrylamides mimicking antifungal peptides kill *Candida albicans* and synergistically prevent infection

*Sebastian Schaefer*[1,2,3,4]*, Sascha Brunke[4], Nathaniel Corrigan[1,2], Megan Lenardon[3] and Cyrille Boyer[1,2]

[1] School of Chemical Engineering, UNSW Sydney, Australia
[2] Australian Centre for Nanomedicine, UNSW Sydney, Australia
[3] School of Biotechnology and Biomolecular Sciences, UNSW Sydney, Australia
[4] Department of Microbial Pathogenicity Mechanisms, Hans Knoell Institute Jena, Germany
*s.schaefer@unsw.edu.au*

Fungal infections represent a serious burden on human health with *Candida albicans* being the most common fungal pathogen in human.[1] Increasing numbers of susceptible hosts, a limited set of approved antifungal drugs which frequently trigger undesired side effects, and the emergence of resistant strains highlight the urgent demand for novel antifungal drug formulations. However, the biological similarity of human and fungal cells hampers the development of new antifungal drugs which do not also harm humans. In nature, organisms in almost all domains of life produce antimicrobial peptides to combat microbial pathogens. Those peptides share certain characteristics, such as being short, amphiphilic molecules with a positive net charge and can be harnessed to combat fungal infections.[2] We designed a library of synthetic, ternary polyacrylamides which mimic the properties of naturally occurring antifungal peptides, varying in degree of polymerization (DP) and hydrophobicity. The positively charged, amphiphilic polymers are advantageous over peptides because of their easy synthesis and stability against proteases. Initial structure-activity-relationship studies revealed an optimal degree of hydrophobicity and DP to ensure activity against *C. albicans* and simultaneous biocompatibility with host cells.[3] In terms of their therapeutic index, certain compositions outperformed the broad-spectrum antifungal amphotericin B (AmpB).[3] The four most promising compositions were even effective against other fungal species and killed *C. albicans* faster than AmpB.[3] Hence, these polymer compositions were selected for further investigation on their mode-of-action. Clinical, drug-resistant *C. albicans* isolates were not affected in their susceptibility to the polymers indicating a novel drug target. The transcriptome of *C. albicans* cells treated with subinhibitory concentrations of the polymers and electron microscopy studies indicated damage to mannoproteins, a class of structural glycoproteins in the cell wall of yeasts. Membrane damage was also observed utilising a *C. albicans* strain expressing the fluorescent protein GFP intracellularly. The *in vitro* therapeutic potential of the best polymer composition was tested in a human epithelial cell (HEC) model simulating *C. albicans* infection. The combination of polymer with the antifungal drugs caspofungin or fluconazole showed very strong synergistic effects at otherwise non-inhibitory concentrations of the individual antifungals, successfully stopping fungal infection *in vitro* without damaging the HECs. These results underline the potential of synthetic polymers as an alternative treatment for fungal infections with low toxicity to human cells and a novel mode-of-action.

**References:**

[1] Brown, G.; Denning, D.; Gow, N.; Levitz, S.; Netea, M.; White, T. *Sci Transl Med* **2012**, *4*, 165rv13
[2] Ullivarri, M.; Arbulu, S.; Garcia-Gutierrez, E.; Cotter, P. *Front Cell Infect Microbiol* **2020**, *10*, 00105
[3] Schaefer, S.; Pham, T.; Brunke, S.; Hube, B.; Jung, K.; Lenardon, M.; Boyer, C. *ACS Appl Mater Interfaces* **2021**, *13*, 27430-27444