ALGINATE-AMPHOTERICIN B BIFUNCTIONAL CONJUGATES FOR RESISTANT AND RECURRENT FUNGAL INFECTIONS

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Antimicrobial resistance (AMR) is among the top threats to global human health [1]. The progressive increase in AMR supersedes the rate of development of new antibiotics [2]. Moreover, fungal biofilm infections are up to 1000-fold more tolerant to antifungal agents than fungal cells in planktonic growth [3]. This intrinsic resistance illustrates the need to develop improved anti-fungal drugs with greater efficacy against biofilm growth, while also reducing the potential for drug toxicity, resistance and tolerance. Amphotericin B (AmpB) is a polyene macrolide antibiotic with broad specificity and has been the gold standard for antifungal treatment since the 1950s for the most severe fungal infections. Unfortunately, AmpB has poor solubility and is limited by infusion-related reactions and nephrotoxicity [4]. Although new formulations such as liposomal AmpB have shown significant reductions in nephrotoxicity [5], there is still considerable scope for improvement for less toxic formulations.

Alginates are a family of anionic and linear polysaccharides produced by brown algae and some bacteria and consist of 1→4 linked β-D-mannuronic acid (M), and its C5-epimer α-L-guluronic acid (G) (Fig. 1). Research has shown that low molecular weight alginate oligosaccharides possess biofilm disruption properties [6], which combined with their high solubility and low toxicity represent ideal candidates for creating novel bifunctional anti-fungal compounds. Using click chemistry, we have developed a novel conjugation at the reducing end that retains the intrinsic biofilm disruption properties of the low molecular weight alginate oligosaccharides while also maintaining the fungal cell-wall disrupting role of the AmpB component. Preliminary data shows the conjugates have reduced toxicity and improved solubility characteristics, while maintaining the AmpB anti-fungal properties.

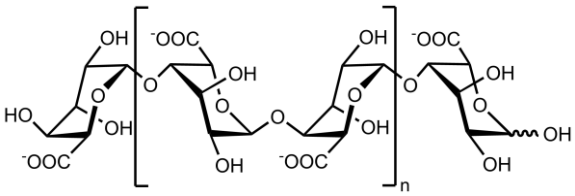

Figure 1. The structure of alginate consisting of α-L-guluronic acid (G) residues.

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