
Synthetic lipopeptides to fight against multiresistant fungal infections

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Résumé

As invasive fungal infections (IFI) are increasingly common in the nosocomial setting (> 1.6 million patients die annually of IFI(1)), the WHO published in 2022 a fungal priority pathogen list, counting as a first step to prioritize fungal pathogens and promote a research that until then was somehow left behind.

Echinocandins (ECs), as part of the more recent antifungals, are cyclic lipopeptides (LPs) which non-competitively inhibit the β -(1,3)-D-glucan synthase (GS)(2) (found exclusively in fungi), leading to the loss of the fungal cell wall integrity(3). Their specificity gives them the advantage of being well-tolerated, but despite their evident potential only 4 ECs are currently on the market and some examples of resistant strains have already been identified(4).

The aim of the project Fungipep is to identify new drug candidates inhibiting the GS with the objective of skirting emerging resistance encountered with currently available ECs. Another important aspect of this project is to elucidate the inhibition mechanisms used by these original lipopeptides as the recognition site of ECs on the FKS1 catalytic unit of GS has never been totally confirmed.

To reach these high goals, a first part of the project was focused on the development of a SPPS methodology (sometimes associated to click-like bioconjugate chemistry), to access unprecedented EC analogues. For now, around 40 original LPs were generated and all of them were tested on various strains of fungi, making it possible to quickly evaluate their bioactivity and adjust their structure accordingly.

The synthetic routes developed during this project were also exploited to synthesize innovative molecular tools like LPs carrying a fluorophore. These will later be used in fluorescence microscopy to try to confirm the binding site of ECs by FRET experiments (in association with a GS fusion protein that we have designed and are currently bioproducing).

(1) Odds et al. Lancet. Infect. Dis. 2002, 2, 73

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(2) Yu et al. *Nature*, 2023, 616, 190; Zhao et al. *Sci. Adv.* 2023, 9, eadh7820

(3) M. Feuilhade et al. *Médecine et Maladies Infectieuses*, 2003, 33, 183

(4) Cowen et al. *Chem. Rev.* 2021, 121, 3390

Mots-Clés: lipopeptides, invasive fungal infections, antifungals, β , (1, 3), D, glucan synthase