Enhancing the fungicidal activity of antibiotics: are magnetic nanoparticles the key?

“Unique physicochemical and biological features of nanomaterials make them the interesting tools for developing modern antifungal methods.”

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Within the last 40 years, the number of fungal infections is continuously growing. More than 70% of reported cases are caused by *Candida spp.*, especially in the population of patients with immune disorders and/or those hospitalized with serious underlying diseases [1]. *Candida* are the most common fungal pathogens, causing diseases ranging from superficial (oral and vaginal) to systemic such as peritonitis and meningitis candidiasis [2]. Despite a high number and diverse group of currently available antibacterial drugs, the number of active substances for treatment of pathogenic fungi is limited. Recent reports show that a growing number of *Candida*-mediated infections are resistant to the currently used classes of antifungal agents, particularly the azoles (where resistance has climbed most prominently) [3]. This implies the need to search for new therapeutic methods and the development of novel antifungal strategies. The increased resistance of fungi pathogens and the lack of effective treatment options for affected patients are considered to be one of the bigger challenges in current medicine. Different therapeutic approaches, including combined drug therapy, chemical structure modifications and the use of drug transporters, are employed to overcome pathogenic strain resistances [4–6]. Unique physicochemical and biological features of nanomaterials make them the interesting tools for developing modern antifungal

methods [7,8]. Several reports indicate that nanoparticles possess the ability to inhibit the function of efflux drug transporters, promote apoptosis of fungal cells and reduce the formation of biofilm [9]. The above properties were already successfully employed during the development of novel molecules against resistant bacterial strains, where increasing activity of vancomycin-loaded nanoparticles, as compared with drug in free form against VRE-resistant enterococci, has been observed [10]. Interestingly, an analogous approach has been explored to provide new tumor-suppressing drugs against multidrug-resistant cancer cells. Indeed, the downregulation of *mdr1* genes and the decrease of P-glycoprotein expressions were observed upon the administration of magnetic nanoparticles (MNPs) [11]. It should be emphasized that a majority of studies show that nanotechnology-based approaches might provide a method to reverse the mechanism of *Candida* resistance to classic antibiotics as well as expand their antimicrobial spectrum [12,13]. Our recently published results indicate that iron-oxide-based nanosystems provide a new strategy to overcome fungal resistance through the inactivation of catalase Cat-1. Importantly, and in agreement with other studies, we observed that a low dose of the tested nanosystems were effective to display antibiofilm activity (prevention and therapeutic efficiency), whereas

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a five- or ten-times higher concentration of drug in free form was required to obtain similar effects [5]. It is worth emphasizing that nanotechnology-based strategies might provide a surprising outcome, as reported by Hussein-Al-Ali, who observed that a well-known antibiotic, ampicillin, when immobilized on chitosan-coated MNPs, showed activity against *Candida albicans*. Even if this phenomena might be partially explained by the antimicrobial properties of chitosan and MNPs (which were the components of the tested nanocomposite) [14], it should be kept in mind that a lot of the nondescript yet antifungal activities might be hidden behind the nanotechnology gate.

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While the immobilization of classical antibiotics on a nanoparticle's surface is not a new idea, the above works describe a new direction in this important area of nanomedicine, which is the development of new approaches for the treatment of fungal diseases. In addition, the use of MNPs as a magnetic fluid hyperthermia inductor to restrict the formation of biofilm and decrease bacteria-cell adhesion might also be used in cases of fungal-derived infections [15]. Apart from the usefulness of magnetic nanostructures in magnetic fluid hyperthermia-mediated eradication of pathogenic biofilm, there are data about the development of novel therapeutic solutions in which metallic nanoparticles are employed as enhancers of photosensitizers for antifungal photodynamic therapy [16].

An important aspect during nanoparticle creation is understanding the interactions between nanomaterials and the biological system. This will guide the

approaches for the safe uses of nanomaterials in the biomedical field. It is established that a nanoparticle's surface interacts with macromolecules like lipopolysaccharides, lipoteichoic acid and other proteins which are expressed on pathogen cells via hydrophobic/electrostatic/chemical adsorption [17–21]. On the other hand, this interaction also takes place with eukaryotic cells; however, recent reports have found that the difference of surface charge can help in moderating surface cytotoxic and/or antimicrobial propensities of nanoparticles. Additionally, it has recently been reported that one restriction during a nanoparticle's systemic administration is the problem associated with an affinity of blood proteins to the particle surface and the formation of a cloud (i.e. the protein corona) around it [22]. This might lead to the covering of the homing ligands that are presented on the nanoparticle's surface. Based on this observation, we suggest that the potential way to limit the 'protein cloud effect' of nanomedicine application in fungal-caused infections will be the direct administration of nanoparticles into infected area. Accordingly, more efforts should be directed to understand the toxic aspect of nanomaterials and their pharmacological properties.

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