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Designing Tuftsin Conjugate for Directing Antimicrobial Ionophores to Macrophages

College of Sciences and Health Professions

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Abstract

For all microorganisms, acquisition of metal ions is essential for survival in the environment or their infected host. Metal ions are required in many biological processes as cofactors for proteins or structural elements for enzymes. These ions play a role in chemotaxis, phosphorylation, transport of sugars and proteins, and initiation of DNA replication, among other things. It is critical for bacteria to ensure that metal uptake and availability meet its physiological needs; too little can impede these important biological processes, while too much can be toxic leading to radical formation which can cause damage to proteins and cell structures (Porcheron, Gaëlle. et al. 2013). Host defense strategies against infection consist of metal starvation by sequestration using chelators or metal overload with concentrated amounts of metals using ionophores (Norris, V et al. 1996). Ionophores are lipid-soluble molecules that transport ions across a cell membrane. Pyrithione, an ionophore, is a well-known antimicrobial used to control the symptoms of dandruff and dermatitis. It inhibits fungal and bacterial cell division and is active against different bacterial systems such as *E. coli* and *C. neoformans*; it has also been found to be toxic to mammalian cells (Helsel, M et al. 2012). The aim of this research project is to target pyrithione to the site of infection - in macrophages. Tuftsin (Thr-Lys-Pro-Arg) is known to be responsible for activation of macrophage cell lines. It is internalized through a receptor-mediated mechanism by macrophages and conjugates can be made without affecting this recognition (Feng, J et al. 2010). Attaching pyrithione to tuftsin would target the ionophore to macrophages, allowing for specificity to pathogens.

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