Development and Characterization of a Sterol Selective Non-Toxic Amphotericin B Derivative

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Amphotericin B (AmB) is a clinically essential antifungal drug with dose-limiting toxicities that fails to eradicate infections. Our previous efforts established that AmB's primary mechanism of action is binding and sequestration of ergosterol in yeast and may be toxic to human cells by binding and extracting cholesterol. Therefore, a derivative that selectively binds ergosterol over cholesterol would enable a high-dose treatment with improved clinical efficacy. Towards this goal, we have utilized the site-selective acylation methodology developed in our lab to efficiently synthesize a new derivative C2'epiAmB, which only differs from AmB in the stereochemistry at a single atom. This derivative showed reasonable potency against fungi but is non-toxic to human cells up to the highest dose in related assays. We also confirmed C2'epiAmB has a similar fungi killing mechanism compared to AmB. Further safety evaluation showed this new derivative is significantly less toxic than the commercially available drug AmBisome® in mice. We envision this derivative would enable a new high-dose treatment paradigm for invasive fungal infections.

In Vivo Ratiometric Photoacoustic Imaging of Copper(I)

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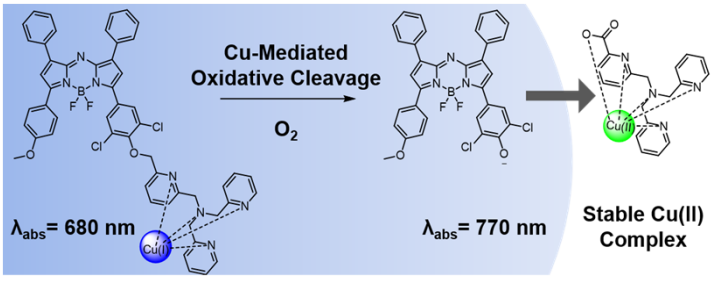
Copper is an essential element for the survival of living organisms. It is known to act as a cofactor in a variety of enzymes (e.g., superoxide dismutase). Unsurprisingly, dysregulation of copper can cause oxidative stress resulting in various disease states. Our aim is to study the role of copper in various diseases. Recently, we have developed a reaction-based probe for selective ratiometric photoacoustic imaging of Cu(I). In this design, the reactive trigger binds to Cu(I) and leverages the redox activity of copper to trigger an oxidative cleavage, producing a stable Cu(II) complex. In turn, the initial signal is lost, while generating a red-shifted signal. Furthermore, we can tune the binding affinity of the Cu(II) complex and thus render copper unavailable. Here, we evaluate its performance in vitro and in vivo using BALB/c mice. Future plans include assessing its performance in disease models, such as Wilson's disease, and for copper chelation therapy.



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