A CHEMICAL-BIOLOGY TOOL-BOX FOR DECIFERING THE ACTIVITIES OF ANTIFUNGAL AGENTS

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Research from our group in the past several years has demonstrated that targeting of an antifungal drug to a particular organelle can significantly improve its therapeutic properties. Azole and echinocandin antifungals are amongst the very few classes of antifungal drugs used as the first line of antifungal infection therapy. We developed inherently fluorescent antifungal azole probes that localize either to the fungal cell mitochondria or to the endoplasmic reticulum (ER). The ER harbors the target of the azoles, lanosterol 14α-demethylase (also known as CYP51). The antifungal activity of ER-localized azoles against a panel of fungal pathogens was up to two orders of magnitude more potent than that of the mitochondria-localized azoles. More recently, we developed fluorescent probes of drugs of the echinocandin class that non-competitively inhibiting β-(1→3)-glucan synthase, the membrane-bound protein complex that catalyzes the formation of an essential component of the fungal cell wall. We developed a rapid and simple assay that measures the intracellular uptake of the fluorescently labeled drug caspofungin that enabled the prediction of echinocandin resistance. Live-cell imaging of the different fluorescent echinocandin drugs revealed a correlation between antifungal potency and the localization on the cell surface that harbors the target glucan synthase complex. The results of our work suggest that modifications that ensure delivery of drugs to the organelle where their target resides can markedly improve the potency of antifungals.

References

[1] Benhamou, Raphael I.; Bibi, Maayan; Steinbuch, Kfir B.; Hamutal, Engel; Levin, Maayan; Roichman, Yael; Berman, Judith; **Fridman**, **Micha**. *ACS Chemical Biology*, **2017**, 12, 1769−1777.

[2] Benhamou, Raphael I.; Bibi, Maayan; Berman, Judith; **Fridman**, **Micha**. *Angewandte Chemie International Edition*, **2018**, 57, 6230-6235.

[3] Benhamou, Raphael I.; Jaber, Qais Z. Herzog, Ido M. **Fridman**, **Micha**. *ACS Chemical Biology*, **2018**, 13, 3325-3332.

[4] Louzoun Zada, Sivan; Jaber, Qais Z.; **Fridman**, **Micha**. *Angewandte Chemie International Edition,* **2019**, 58, 2-13.

[5] Jaber, Qais. Z; Bibi, Maayan.; Ksiezopolska, Ewa.; Gabaldon, Toni.; Berman, Judith. **Fridman**, **Micha**. *ACS Central Science,* **2020**, 6, 1698-1712.