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of Candida spp. to Membrane-targeting Antifungals; Introduction; Azoles; Non-azole ergosterol biosynthesis inhibitors; Polyenes; Concluding remarks; 2: Point Mutations and Membrane-targeting Antifungal Resistance in Aspergillus fumigatus and Other Non-Candida Species; Introduction; Aspergillus fumigatus azole resistance in clinical settings; The molecular target of azoles, allylamines and polyenes: ergosterol and ergosterol biosynthesis pathway; Differences in

ergosterol pathway between Aspergillus spp. and yeasts Fungal 14-a sterol demethylases (SDMs): the main target

Fungal 14-a sterol demethylases (SDMs): the main target for azole antifungalsA. fumigatus azole susceptibility patterns and mechanisms of azole resistance linked with CYP51 point mutations; Azole resistance in non-fumigatus Aspergillus; Azole secondary resistance linked with point mutations in the 14- sterol demethylase enzyme in non-

Candida and non-Aspergillus species; Polyene resistance; Resistance to allylamines; General conclusion; 3: Echipocandins; Resistance

allylamines; General conclusion; 3: Echinocandins: Resistance

Mechanisms; Introduction; Structures; Echinocandin target: Fks1; Fks

gene family; Fks1 structure-function

Cell-free -1,3-glucan synthase systemsEchinocandin uptake and efflux; Acquired echinocandin resistance: Fks hot spots 1 and 2; Differential echinocandin resistance: discovery of hot spot 3; Impact of Fks heterozygosity and redundancy on acquired resistance; Fksindependent acquired echinocandin resistance; Intrinsic echinocandin resistance: hot spot 1 substitutions: Intrinsic echinocandin resistance: hot spot 3 substitutions; Intrinsic resistance: mechanism to be determined; Stage-specific intrinsic resistance; Conclusions and future prospects; 4: Biofilms and Antifungal Resistance Introduction to fungal biofilmsFungal biofilm infections of humans; Current standard of care for fungal biofilm infections; Mechanisms of fungal biofilm drug resistance; Challenges and strategies to developing therapeutics for fungal biofilm infections; 5: Drug Combinations as a Strategy to Potentiate Existing Antifungal Agents; Introduction; In vitro and in vivo combinations with known antifungal agents; In vitro and in vivo combinations of non-antifungals with known antifungal agents: Systematic drug combination screenings Chemogenetic approaches in the exploration of drug interaction mechanismsConclusions; 6: Approaches to Detect Alternative Mechanisms of Resistance to Systemic Antifungals; Introduction; 'Omics' approaches; Mutants collections screening; Comparison with others species; Concluding remarks; 7: New Antifungal Discovery from Existing Chemical Compound Collections: Introduction: A new career for acetylsalicylic acid as an antifungal; Other non-traditional antimicrobial agents; Conclusion and future perspectives; 8: Exploring New Insights into Fungal Biology as Novel Antifungal Drug Targets Introduction

Sommario/riassunto

Infections caused by pathogenic fungi are a significant global problem; a situation exacerbated by the limited availability of good antifungal options. Being eukaryotic organisms, these pathogens are phylogenetically much closer to the human host than bacterial pathogens. This sets serious limits to the range of exploitable fungal-specific drug targets. The advent of 'omics' and other high throughput technologies in recent years has revolutionized the field of antifungal research permitting researchers to quickly identify novel compounds and gain greater insights into drug resistance mechanism