

ANTIFÚNGICOS

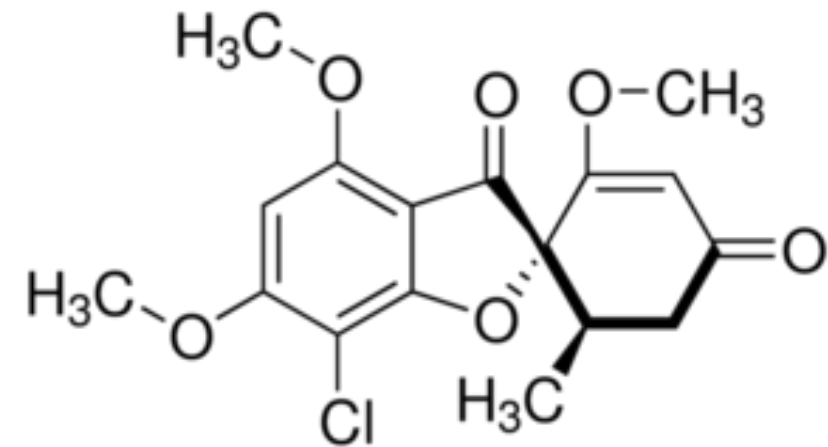
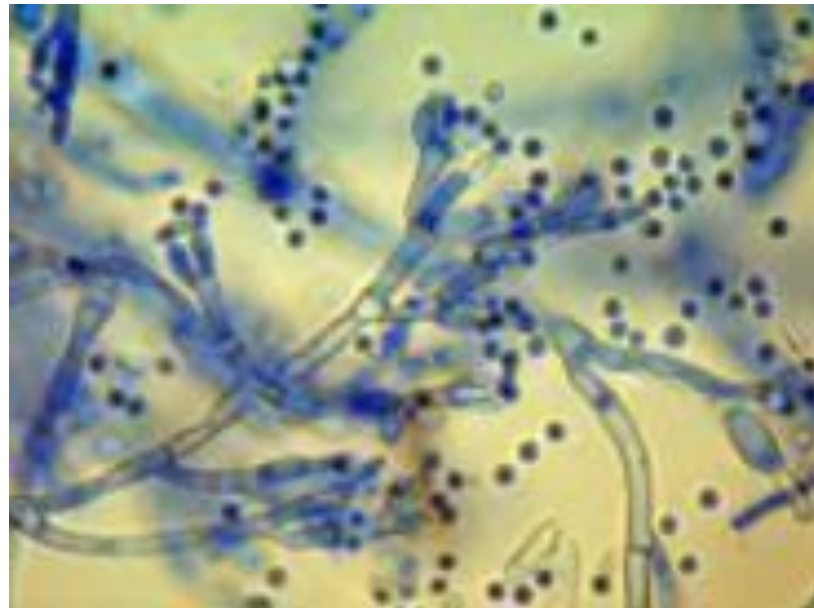
Danilo Yamamoto Thomaz

Faculdade de Medicina da Universidade de São Paulo

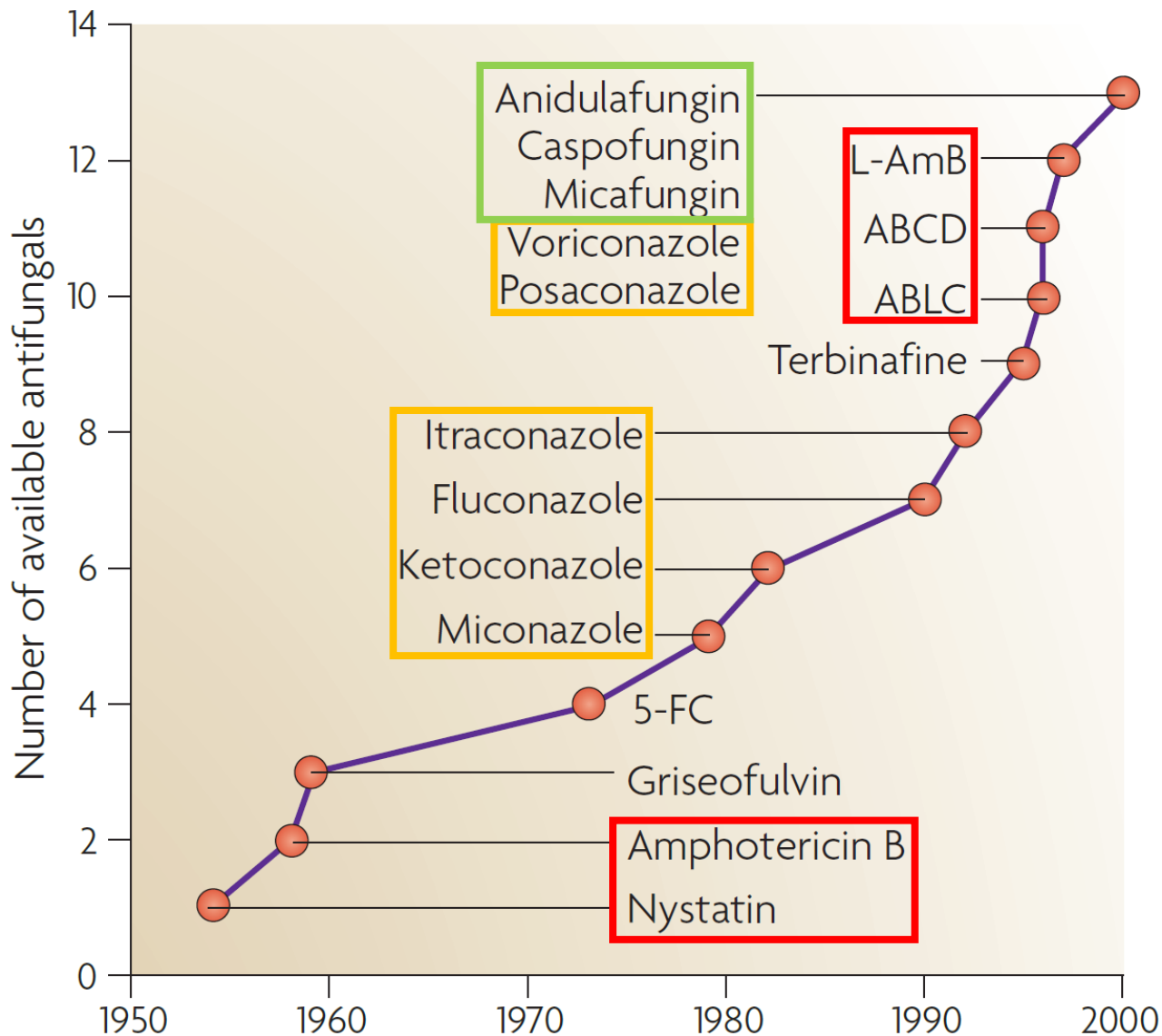
São Paulo, 2021

Griseofulvina (1939)

- 1ª molécula com atividade inibitória seletiva contra fungos;
- *Penicillium griseofulvum*.



Antifúngicos sistêmicos (1950s)



EQUINOCANDINAS

- Restrito espectro de ação;
- Bom perfil de segurança.

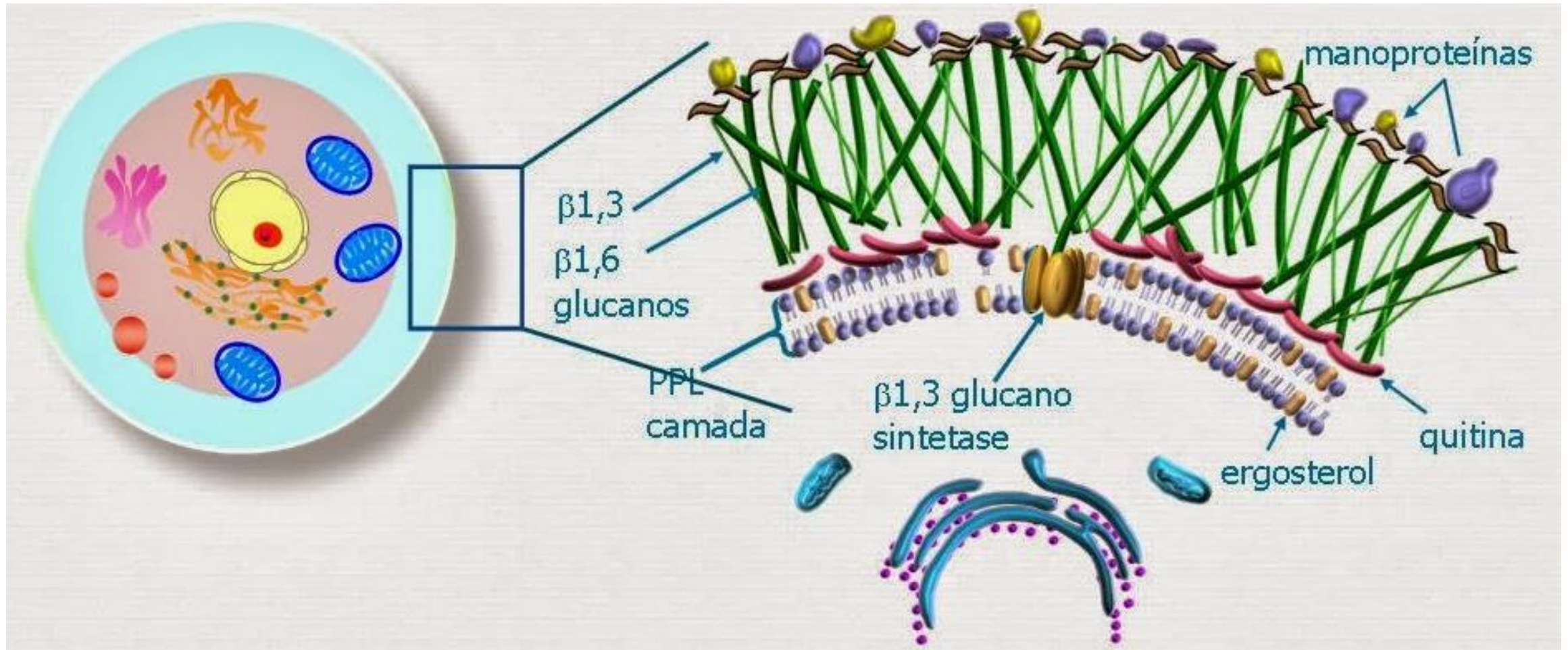
AZÓIS

- Interações medicamentosas;
- Moderada hepatotoxicidade.

POLIENOS

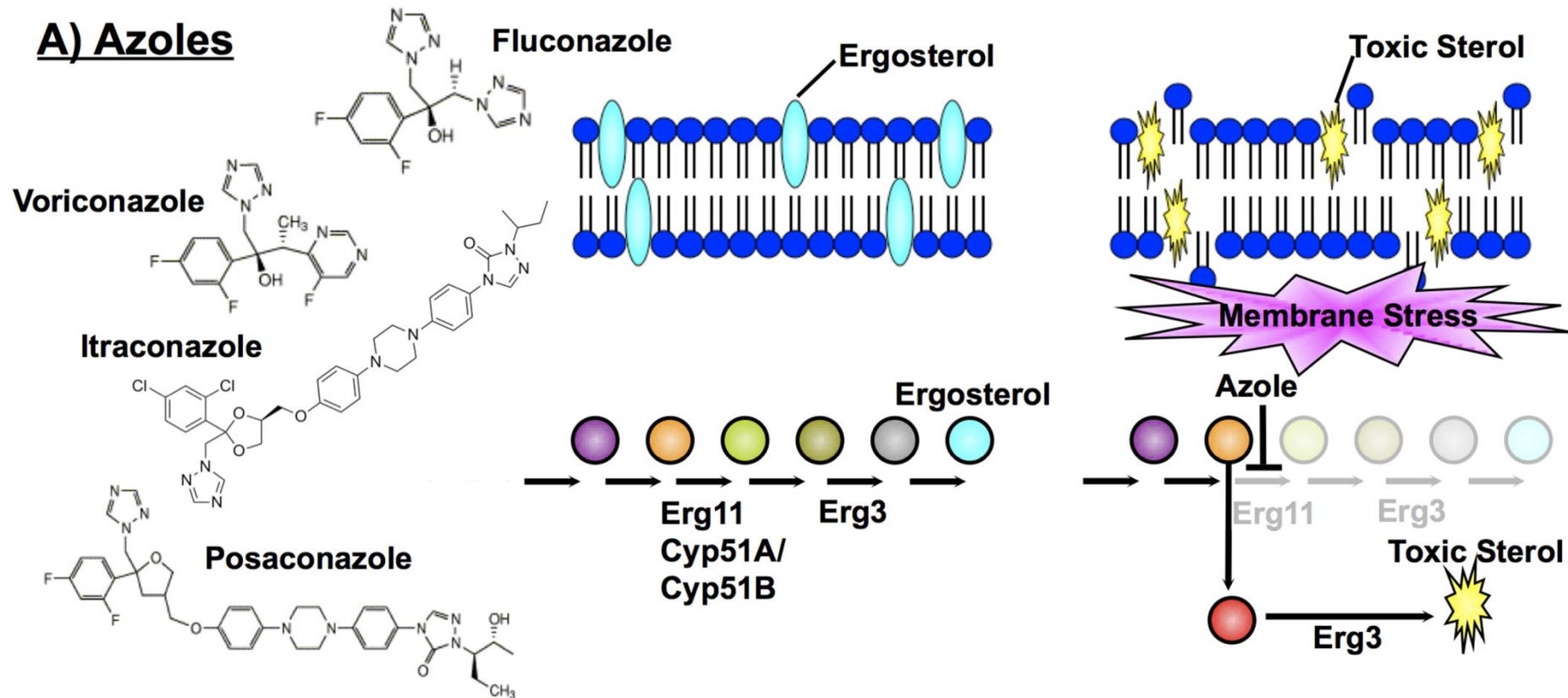
- Amplo espectro de ação;
- Elevada nefrotoxicidade.

Célula fúngica

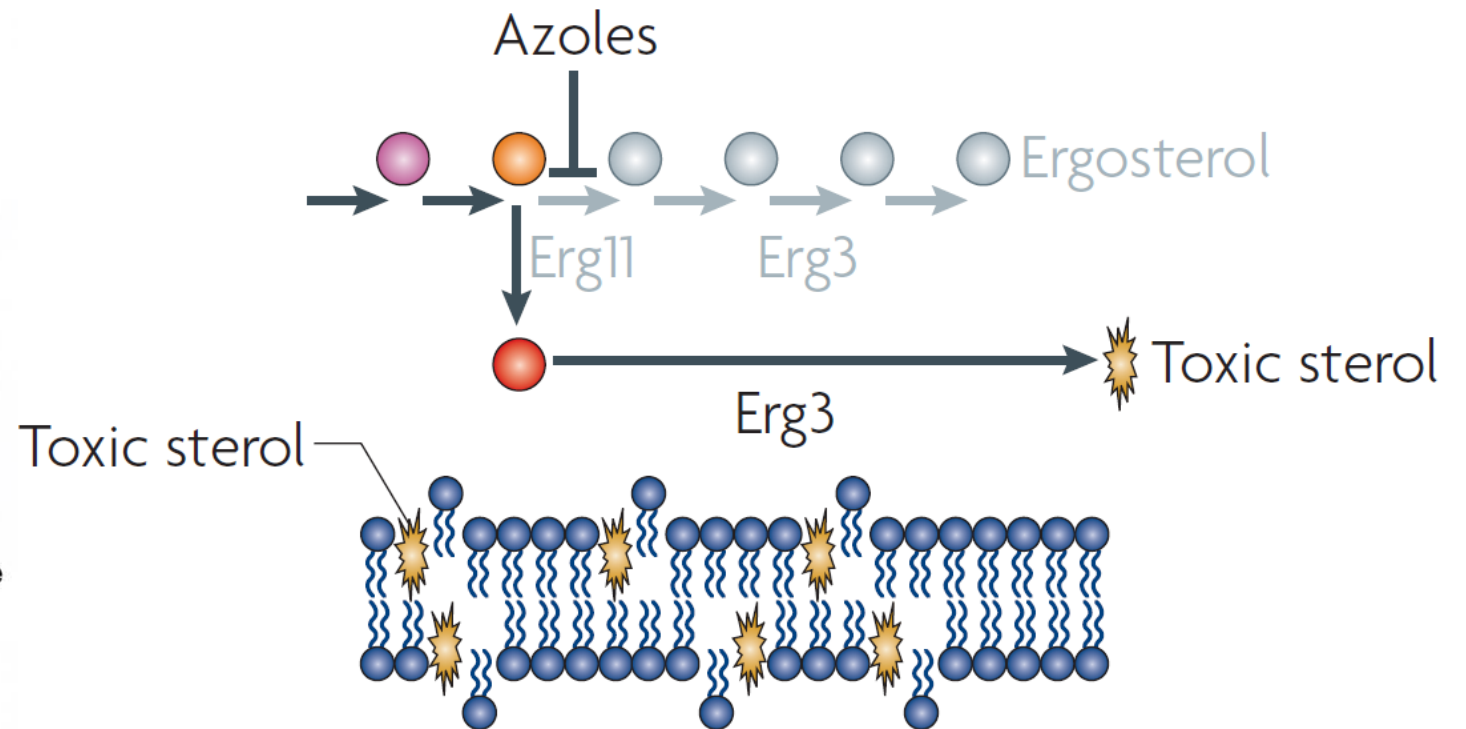
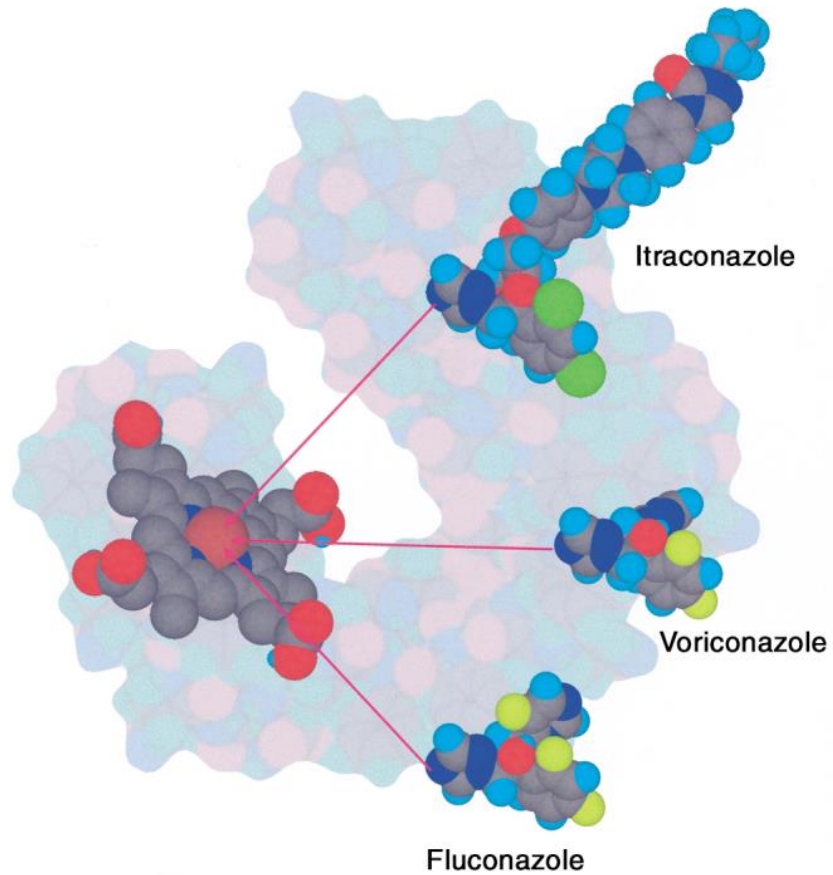


Azóis – mecanismo de ação

- Alteram a permeabilidade da membrana celular do fungo;
- Inibição da síntese de ergosterol (fungistático).



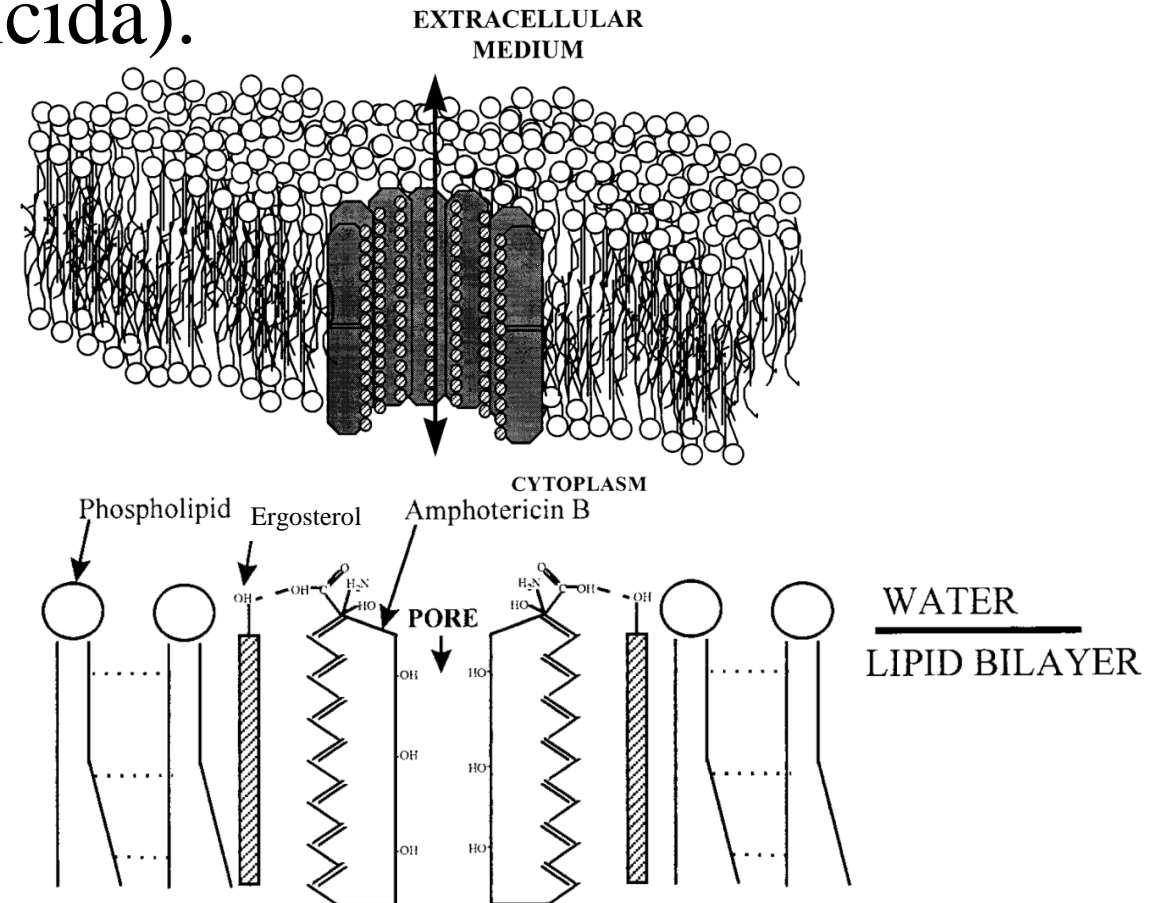
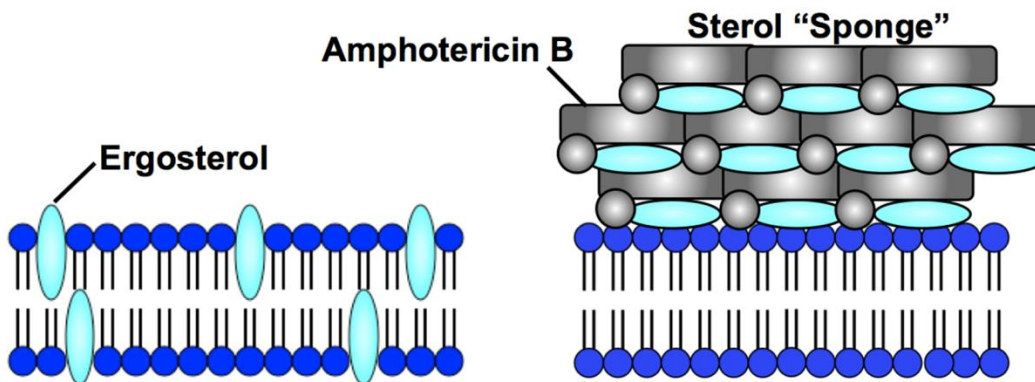
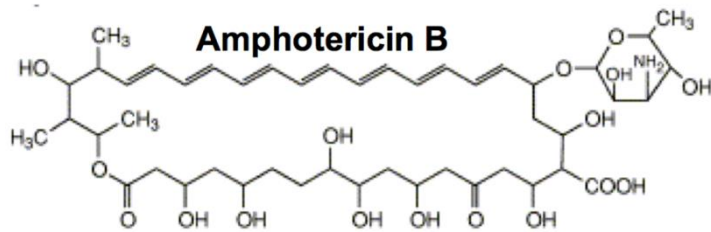
Azóis – mecanismo de ação



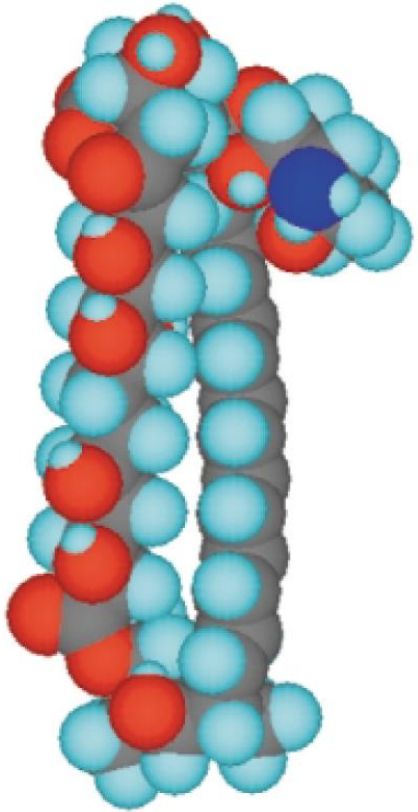
Polienos – mecanismo de ação

- Desestabilizam a membrana celular do fungo;
- Ligação direta ao ergosterol (fungicida).

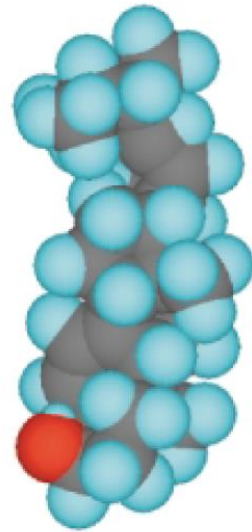
B) Polyenes



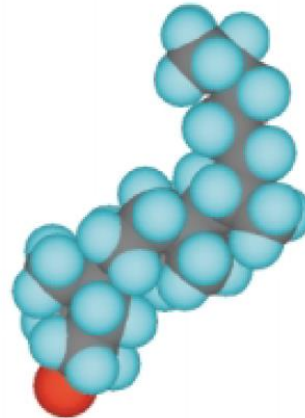
Polienos – mecanismo de ação



Amphotericin B

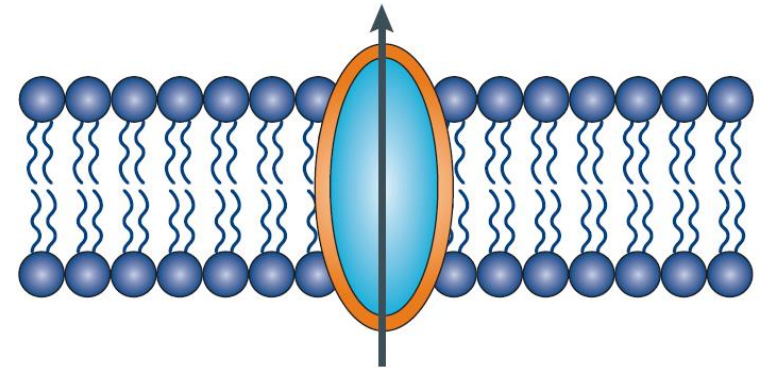


Ergosterol



Cholesterol

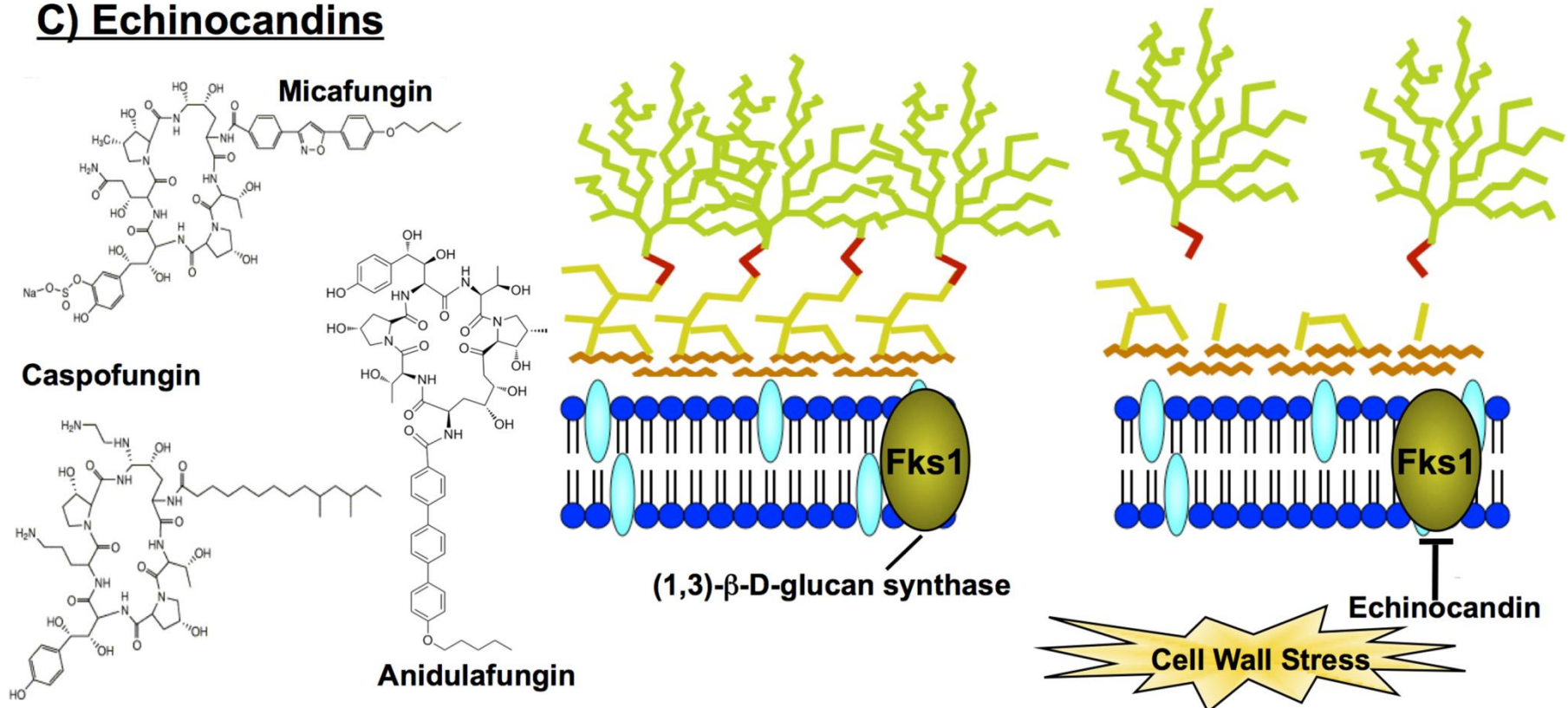
- Nefrotoxicidade.



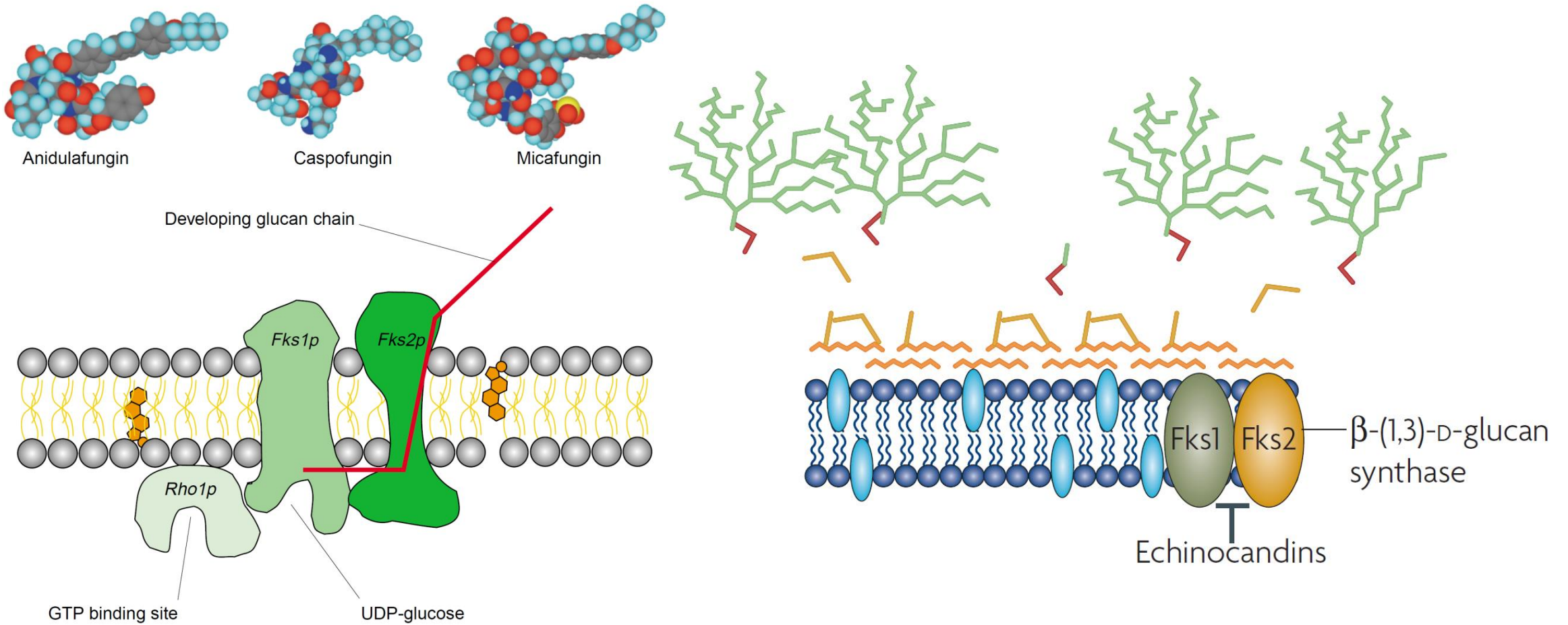
Equinocandinas – mecanismo de ação

- Alteram a integridade da parede celular do fungo;
- Inibição da síntese de β -1,3-glucana (fungistático ou fungicida).

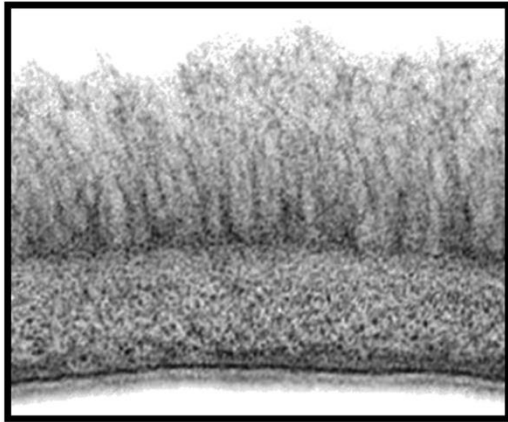
C) Echinocandins



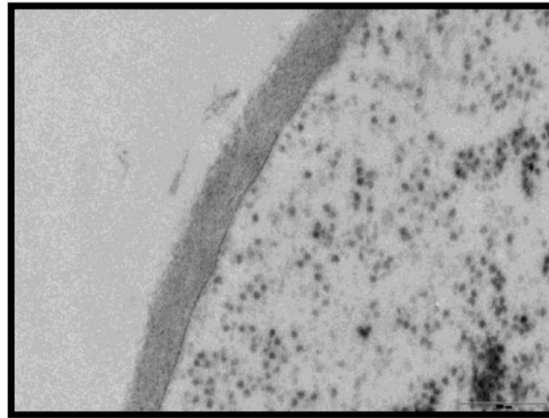
Equinocandinas – mecanismo de ação



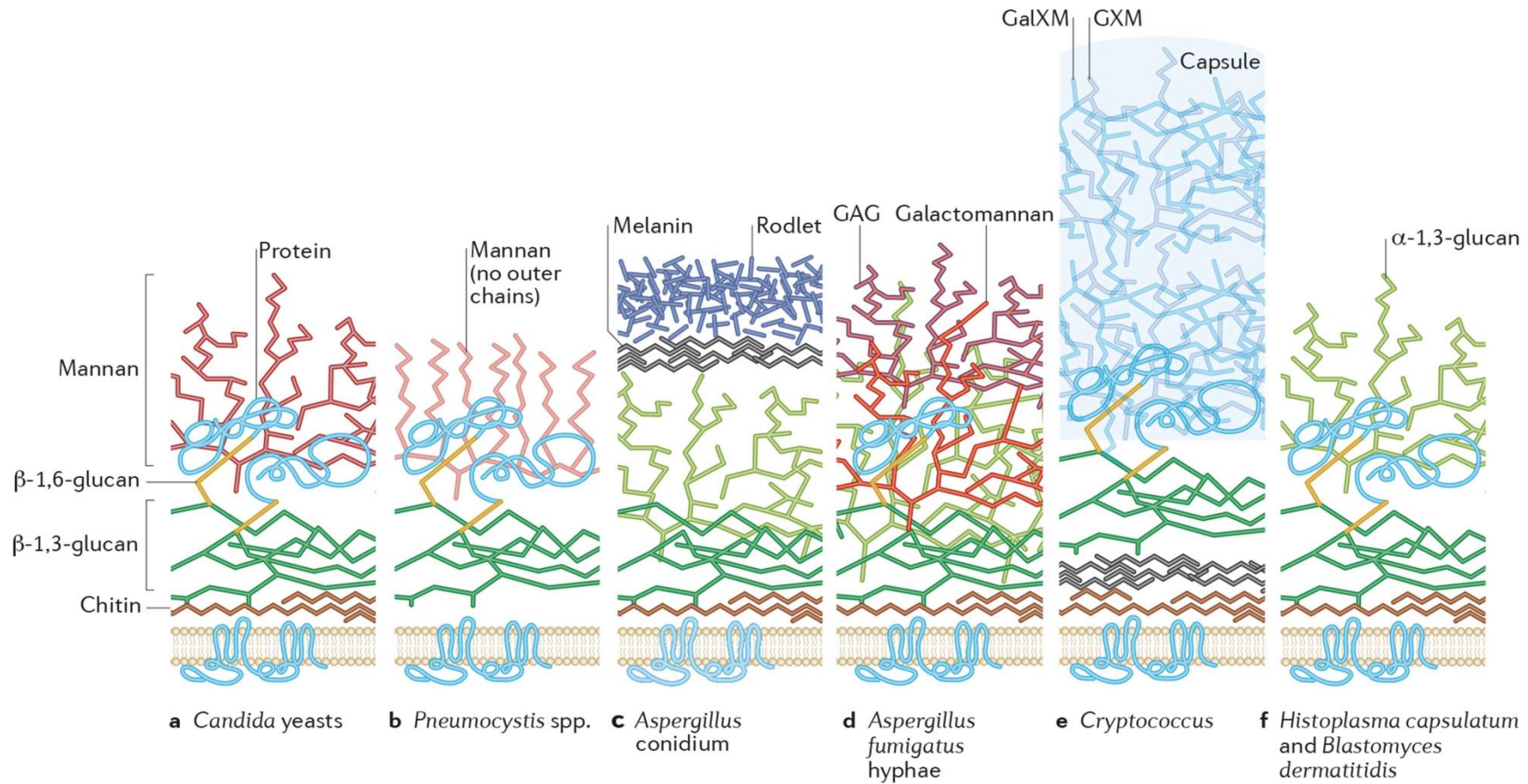
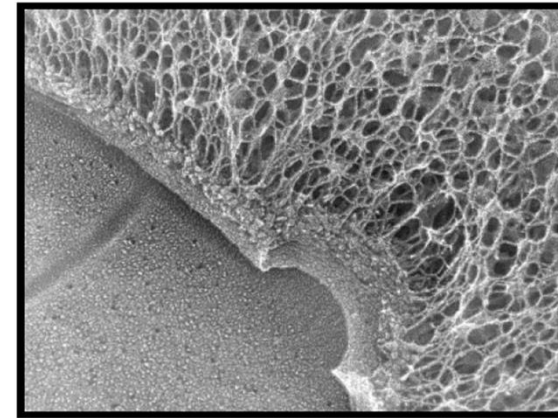
Candida albicans



Aspergillus fumigatus



Cryptococcus neoformans



Espectro de ação dos antifúngicos

	AMB	FLU	ITR	VOR	POS	ISA	CAS	MIC	ANI
<i>Candida</i> spp.									
<i>C. albicans</i>	++	++	++	++	++	++	++	++	++
<i>C. glabrata</i>	++	-	+	++	++	++	+	+	+
<i>C. parapsilosis</i>	++	++	++	++	++	++	++	+	++
<i>C. tropicalis</i>	++	++	++	++	++	++	++	++	++
<i>C. krusei</i>	++	-	+	++	++	++	++	++	++
<i>C. lusitaniae</i>	-	++	++	++	++	++	++	++	++
<i>Cryptococcus</i> spp.									
<i>C. neoformans</i>	++	++	++	++	++	++	-	-	-
<i>C. gattii</i>	++	++	++	++	++	++	-	-	-
<i>Aspergillus</i> spp.									
<i>A. fumigatus</i>	++	-	++	++	++	++	+	+	+
<i>A. flavus</i>	+	-	++	++	++	++	+	+	+
<i>A. terreus</i>	-	-	++	++	++	++	+	+	+
<i>A. niger</i>	++	-	+	+	++	++	+	+	+
Mucorales									
<i>Rhizopus</i> spp.	++	-	-	-	++	++	-	-	-
<i>Mucor</i> spp.	++	-	-	-	++	++	-	-	-
<i>Lichtheimia</i> spp.	++	-	-	-	++	++	-	-	-
<i>Fusarium</i> spp.	+	-	+	+	+	+	-	-	-
<i>Scedosporium</i> spp.	+	-	+	+	+	+	-	-	-
<i>Histoplasma capsulatum</i>	++	+	++	++	++	++	-	-	-
<i>Blastomyces dermatitidis</i>	++	+	++	++	++	++	-	-	-
<i>Coccidioides immitis</i>	++	++	++	++	++	++	-	-	-

EQUINOCANDINAS

- *Candida* spp;
- *Aspergillus* spp.

AZÓIS

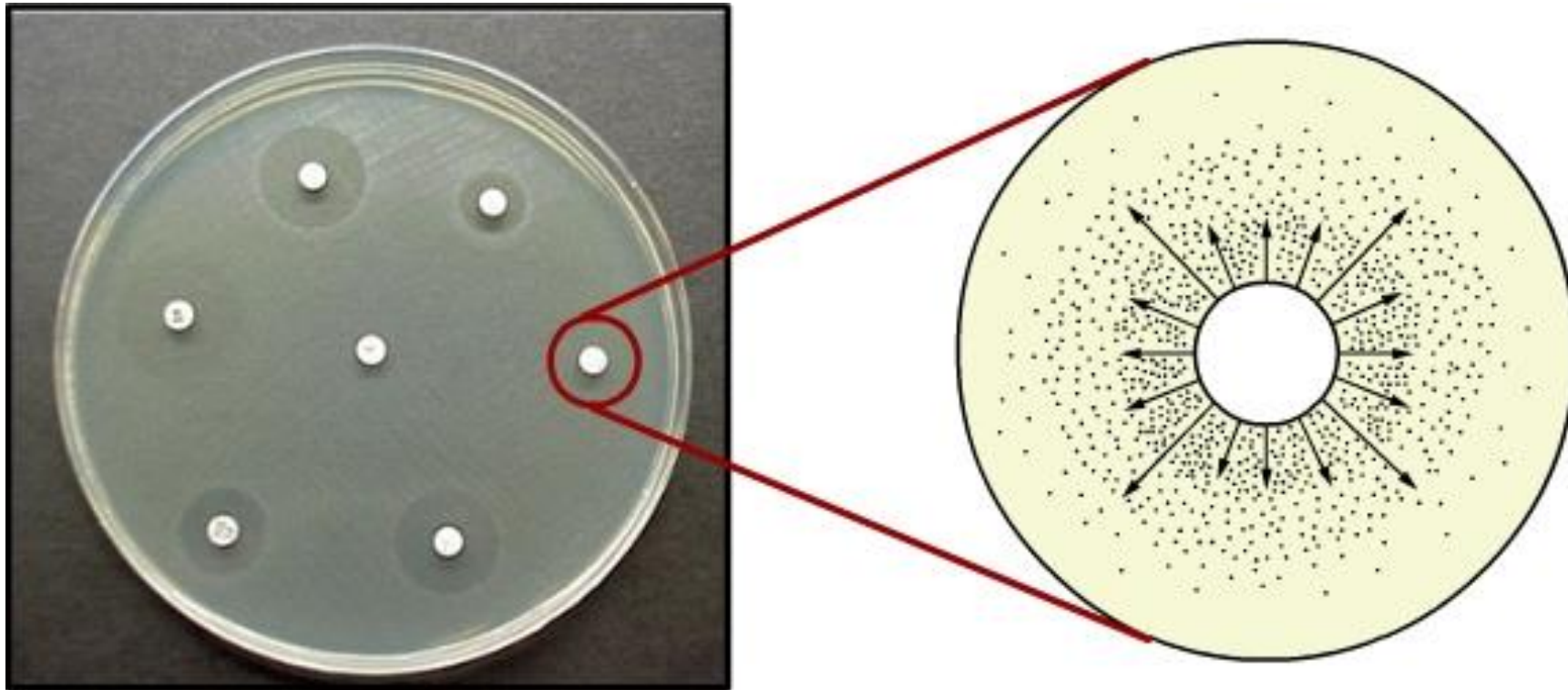
- Fluconazol X Bolores

POLIENOS

- Amplo espectro de ação.

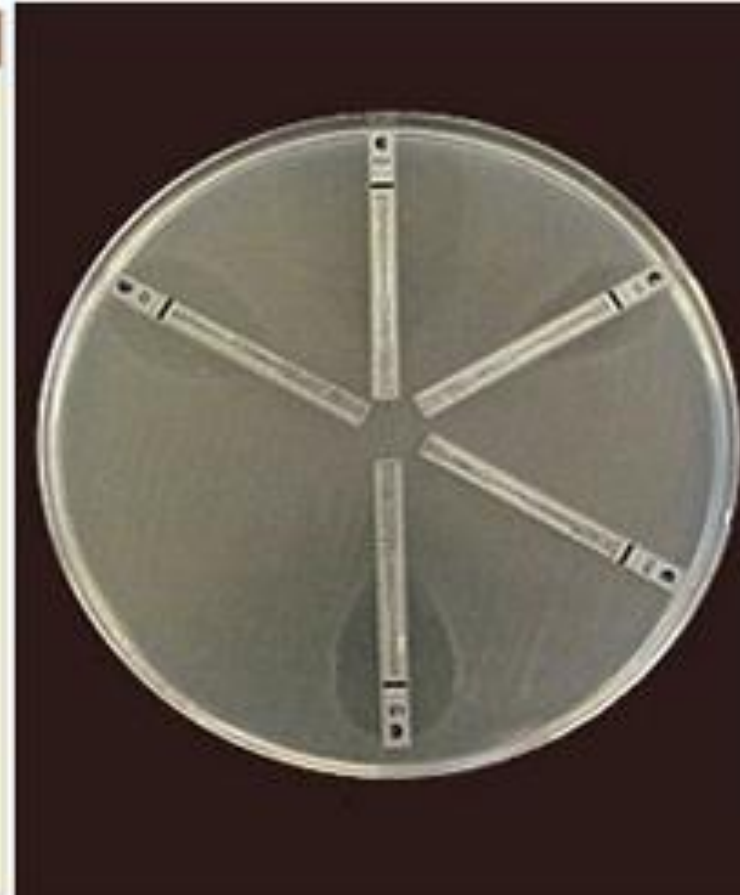
Teste de suscetibilidade aos antifúngicos

- Teste de disco-difusão em ágar.



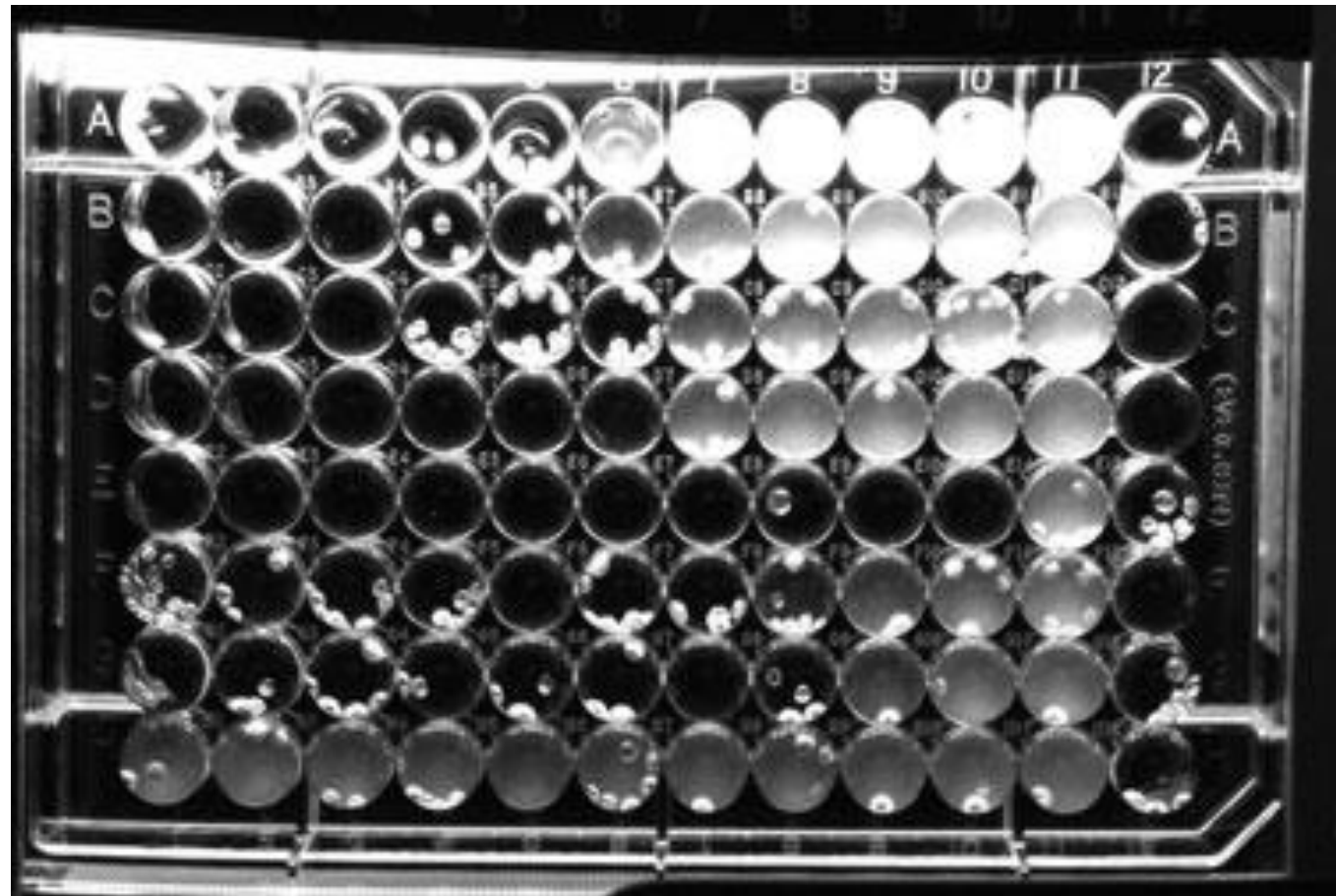
Teste de suscetibilidade aos antifúngicos

- Teste de difusão de gradiente antimicrobiano em ágar.



Teste de suscetibilidade aos antifúngicos

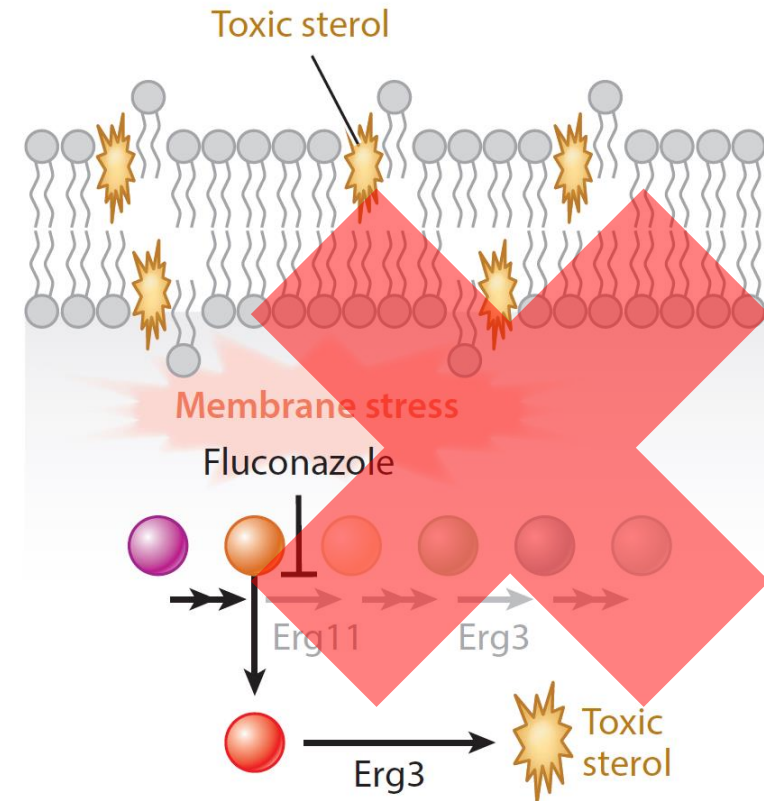
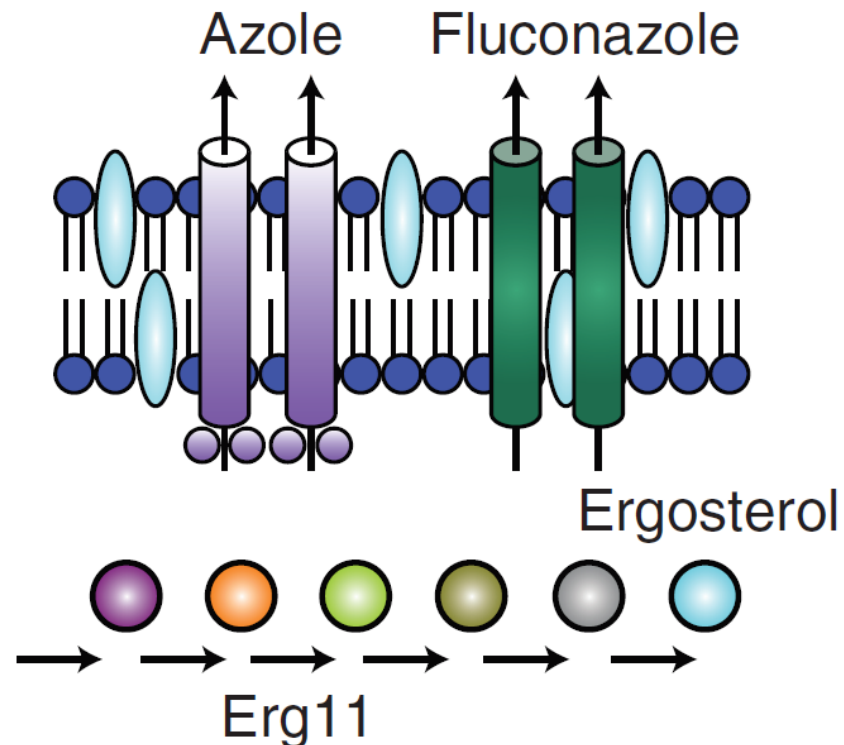
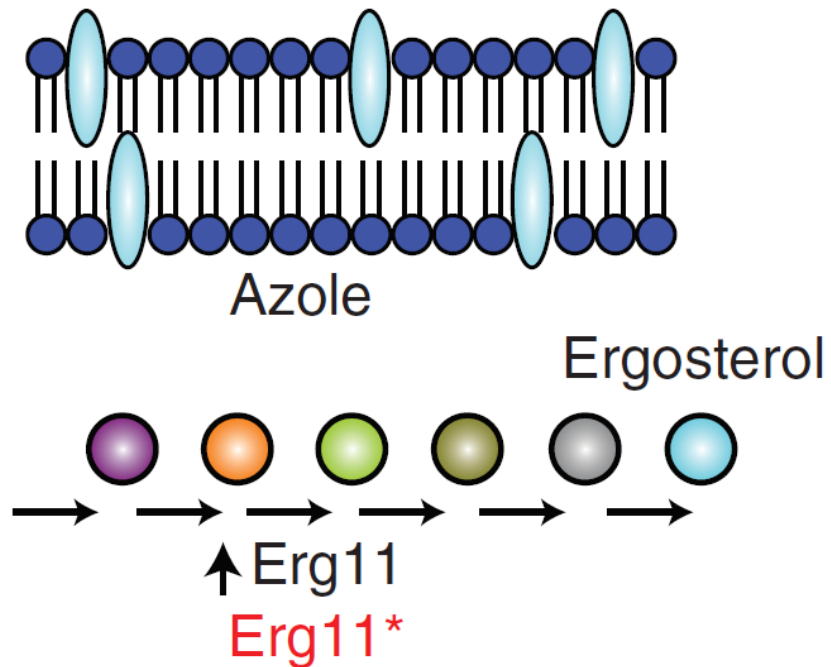
- Microdiluição em caldo.



Azóis – mecanismo de resistência

- Mutação e superexpressão do gene *ERG11*;
- Superexpressão de bombas de efluxo.

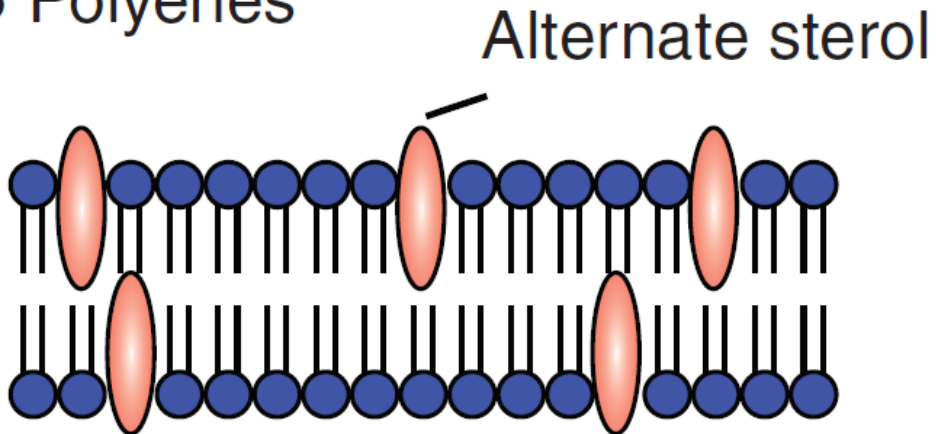
A Azoles



Polienos – mecanismo de resistência

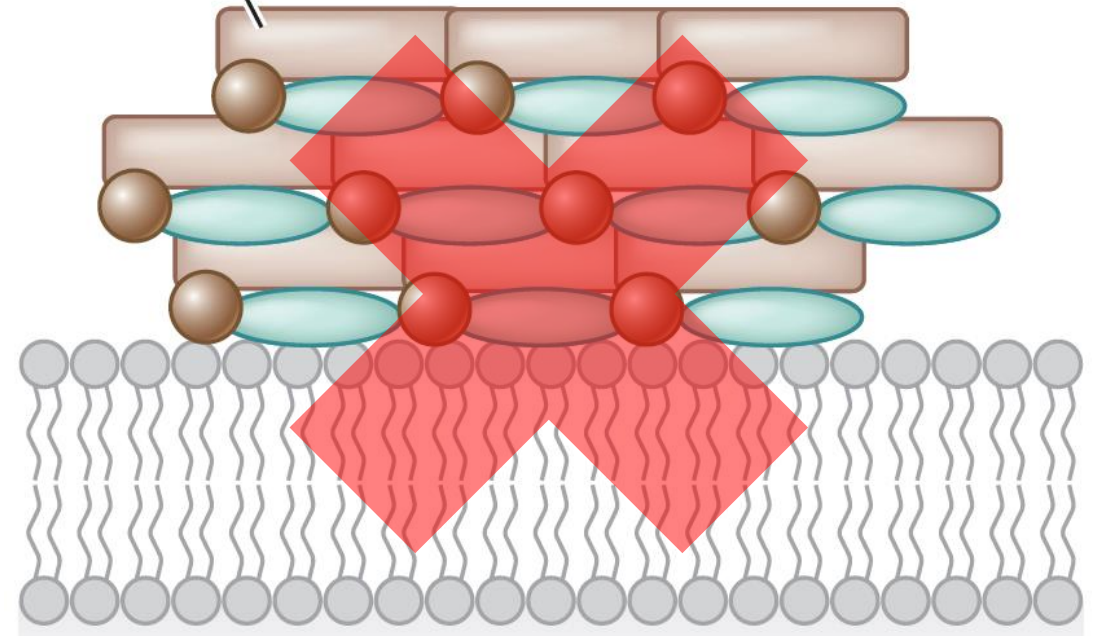
- Mutação em genes envolvidos na biossíntese do ergosterol;
- Substituição do ergosterol por um **esterol alternativo**.

B Polyenes



Amphotericin B

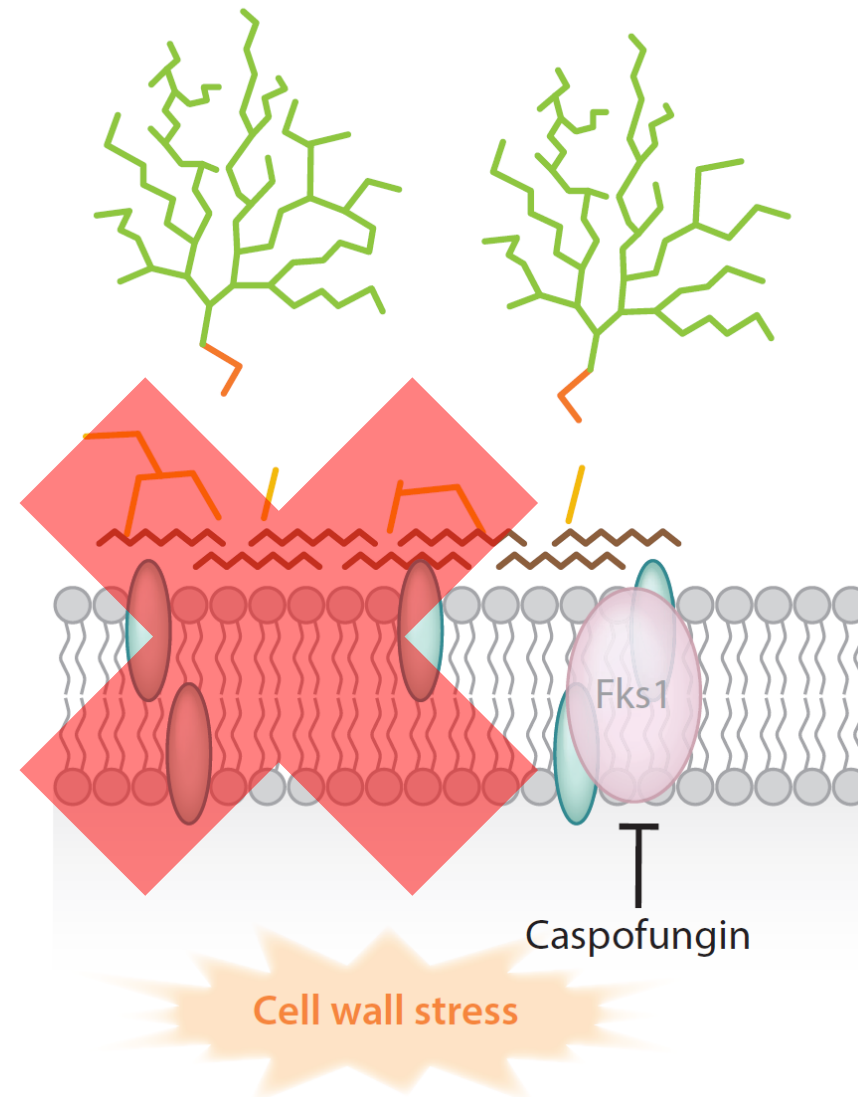
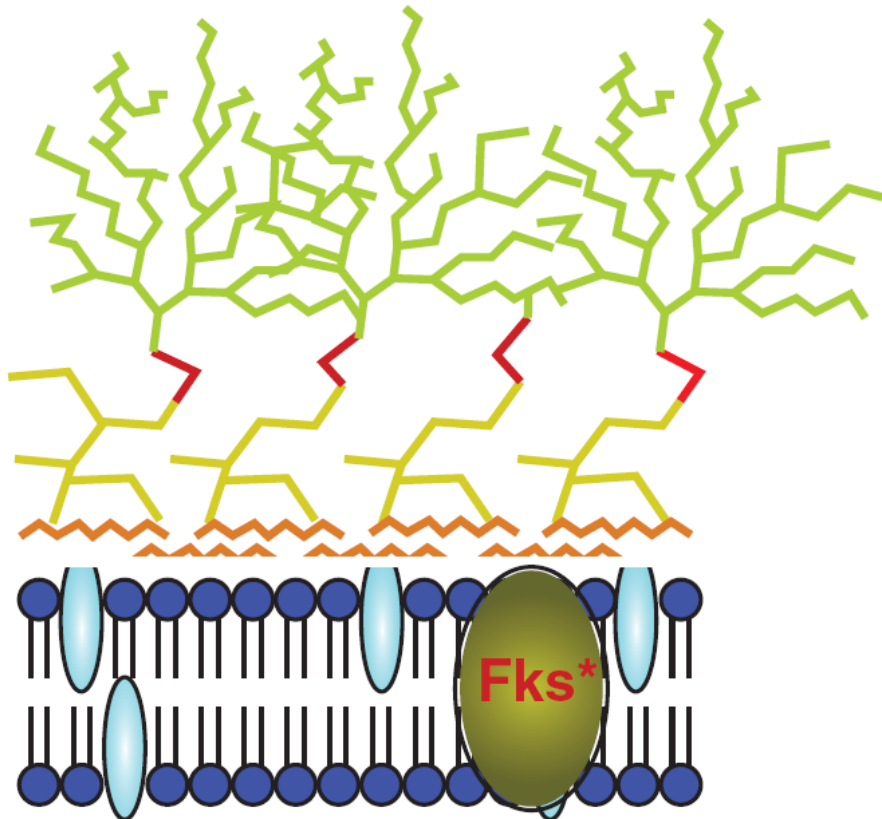
Sterol "sponge"



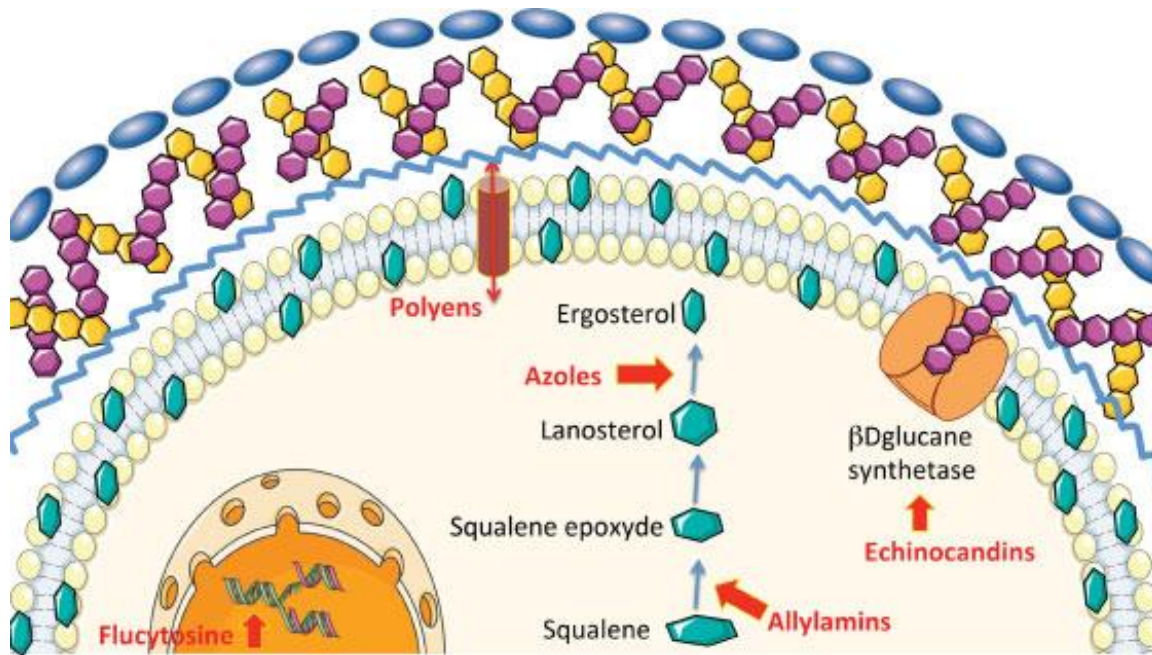
Equinocandinas – mecanismo de resistência

- Mutação no gene *FKS*.

C Echinocandins



Mecanismos de ação e de resistência



Antifungals	Mode of action	Mechanism of action	Mechanism of resistance
Polyenes Amphotericin B Nystatin	Fungicidal	Binding to sterols in cell membrane forming aqueous pores	Reduction of ergosterol concentration ablating drug-target binding Alteration in POL gene family
Azoles Fluconazole Itraconazole Ketaconazole Posaconazole Voriconazole Miconazole	Fungistatic	Affects ergosterol biosynthesis by blocking the key enzyme, lanosterol 14 α -demethylase (Erg11p)	Efflux of drug by multi-drug transporters; ABC gene family Amino acid substitution to Erg11p affecting drug-target binding Over-expression of Erg11p minimizing effect of drug Change in toxic-sterol concentration due to mutation in Erg3 alleles
Echinocandins Caspofungin Micafungin Anidulafungin	Fungistatic or Fungicidal	Binding to β -(1, 3)-D-glucan synthase and inhibition of β -(1, 3)-D-glucan, a cell-wall component.	Mutation in Fks1 and Fks2 binding units

Dermatofitoses (Tineas) – tratamento

Review

Therapy of Skin, Hair and Nail Fungal Infections

	First line
Tinea pedis (dry type)	Terbinafine 250 mg/day for 2 weeks Itraconazole 200–400 mg/day for 1 week
Tinea corporis (extensive)	Terbinafine 250 mg/day for 1 week Itraconazole 200 mg/day for 1 week
Onychomycosis due to dermatophytes *	Terbinafine 250 mg/day for 12 weeks (toe nails) or 6 weeks (fingernails) Itraconazole 200 mg bid for 1 week/month for 3 months (toe nails) or 2 months (finger nails)
Tinea capitis (children)	Terbinafine 125 mg (<25 kg), 187.5 mg (25–35 kg) or 250 mg (>35 kg) daily for 3–4 weeks Mainly <i>Trichophyton</i> infections Griseofulvin 10–15 mg/kg/day for 6–8 weeks Mainly <i>Microsporum</i> infections

- Fluconazol (alternativa).

J. Fungi **2018**, *4*, 99; doi:10.3390/jof4030099



Candidíases – tratamento

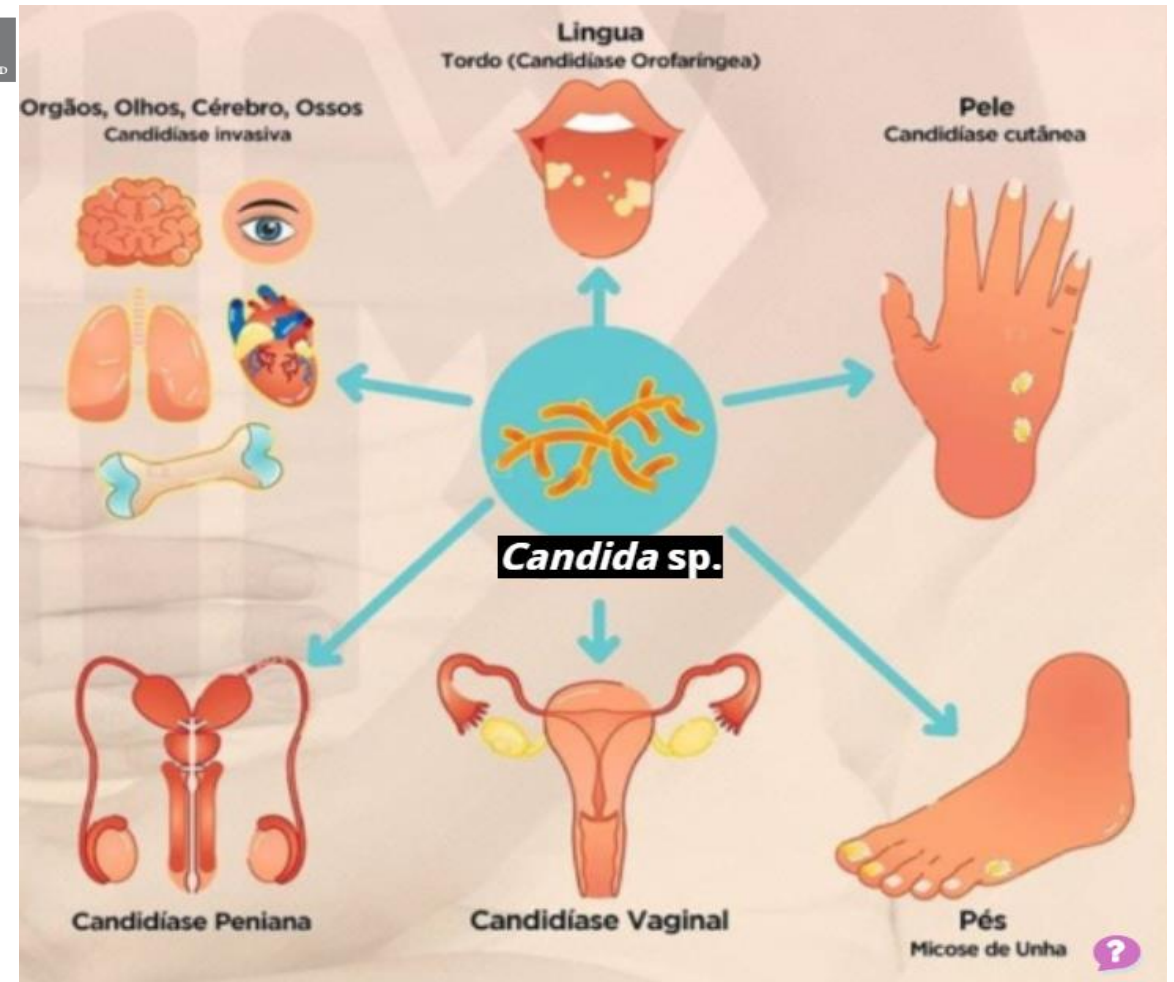
Clinical Infectious Diseases

IDSA GUIDELINE



Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

- **Candidemia:**
 - Equinocandina;
 - Fluconazol (alternativa).
- **Candidíase CNS:**
 - Anfotericina B lipossomal;
 - Fluconazol (em seguida).
- **Cistite por *Candida sp.*:**
 - Fluconazol (S-FLC);
 - AMB desoxicolato (R-FLC).
- **Candidíase vulvovaginal:**
 - Fluconazol;
 - Nistatina (alternativa).



Referências Bibliográficas

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