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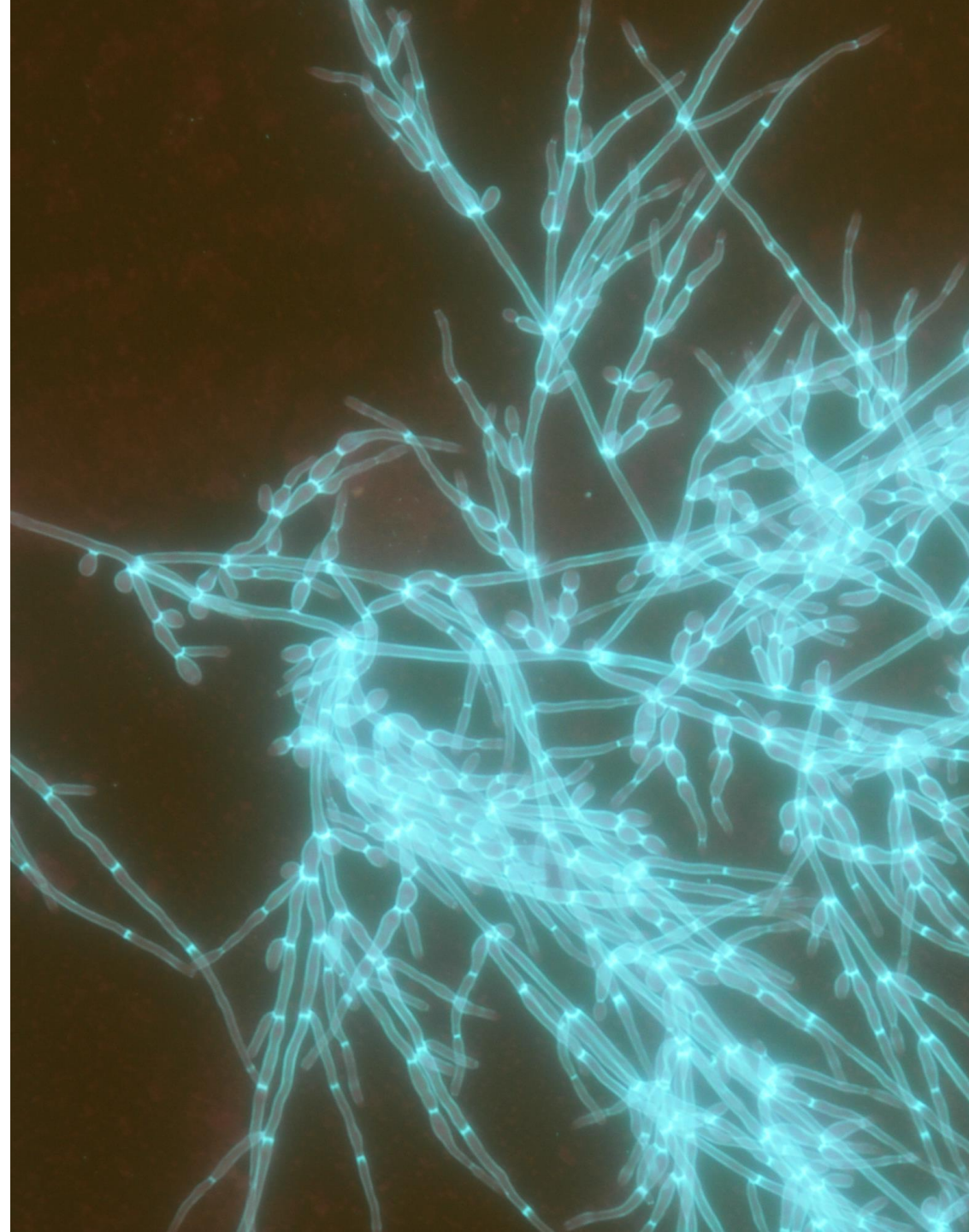
WHAT'S NEW IN ANTIFUNGAL TREATMENT

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LEARNING OBJECTIVES

- Review the mechanism of action and spectrum of activity of novel antifungals
- Explore cases to highlight the role of novel antifungal agents

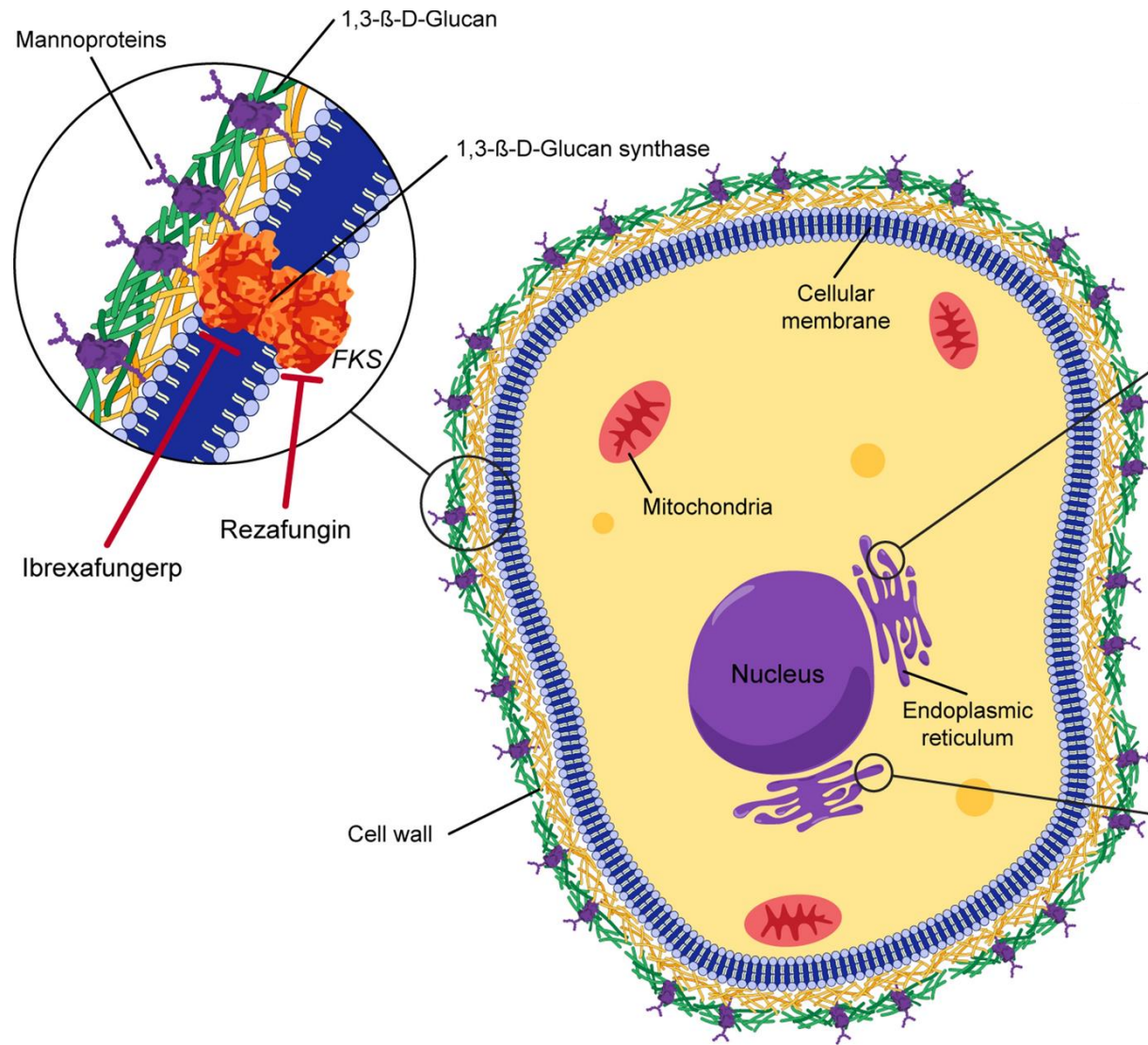
WHAT HAS CHANGED OVER THE LAST DECADE?

- Geographic distribution of endemic mycoses
- Emergence of resistance (*Candida auris*, azole-resistant *Aspergillus fumigatus*)
- COVID-associated aspergillosis, mucormycosis
- Advances in diagnostics (identification of rare mold, cryptic species of *Aspergillus*, microbial cell-free DNA next generation sequencing)
- Precision medicine small molecules, biologic therapy
- Novel antineoplastic agents and drug-drug interactions with antifungals (midostaurin for *FLT3*-mutated AML)
- New broad-spectrum triazole antifungals (posaconazole, isavuconazole)



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CANDIDEMIA AND INVASIVE CANDIDIASIS



REZAFUNGIN VS CASPOFUNGIN

- **ReSTORE Trial:** Multicenter, double-blind, double-dummy, randomised phase 3 trial
- Systemic signs and mycological confirmation of candidemia or invasive candidiasis
- Randomly assigned (1:1) to weekly **rezafungin** (400 mg in week 1, followed by 200 mg weekly) or **casposfungin** (70 mg loading dose on day 1, followed by 50 mg daily) up to 4 weeks
- 100 [50%] rezafungin, 99 [50%] casposfungin
- 22/93 (24%) in **rezafungin** group and 20/94 (21%) in **casposfungin** group died at day 30 (treatment difference 2.4% [95% CI -9.7 to 14.4])
- 55/93 (59%) in **rezafungin** group and 57/94 (61%) in **casposfungin** group had a global cure at day 14 (treatment difference -1.1% [95% CI -14.9 to 12.7])

Thompson GR et al. Lancet. 2023 Jan 7;401(10370):49-59

REZAFUNGIN

- Prolonged half-life (133 hours)
- Administered once weekly
- Front-loaded exposure
- Better tissue penetration compared to other echinocandins
- *Candida* endocarditis
- Primary *Candida* peritonitis, necrotizing pancreatitis, hepatosplenic candidiasis
- *Candida* pleural empyema
- Prosthetic joint infection
- *Candida auris* infection
- Risk of emergence of resistance
- Antifungal prophylaxis (**ReSPECT**)

Ordaya DA, Clement J, Vergidis P. *Mycopathologia* 2023 Jul 20

IBREXAFUNGERP

- Structurally distinct from the echinocandins
- Oral bioavailability 35-50%
- Excellent tissue penetration overall
- Poor penetration into the CNS
- Extensive hepatic metabolism, <2% unchanged in urine

- Activity against *Candida*, *Aspergillus*, *Histoplasma*
- No activity against *Mucor*, *Rhizopus*, *Fusarium*

MARIO TRIAL

- A Phase 3, multicenter, prospective, randomized, double-blind study of two treatment regimens for candidemia and/or invasive candidiasis
- Non-inferiority trial
- NCT05178862
- Initial treatment with IV echinocandin
- **Isolate susceptible to fluconazole:** Double-blinded treatment ibrexafungerp or fluconazole
- **Isolate non-susceptible to fluconazole:** Open-label ibrexafungerp or best available therapy (echinocandin, high-dose fluconazole, voriconazole)

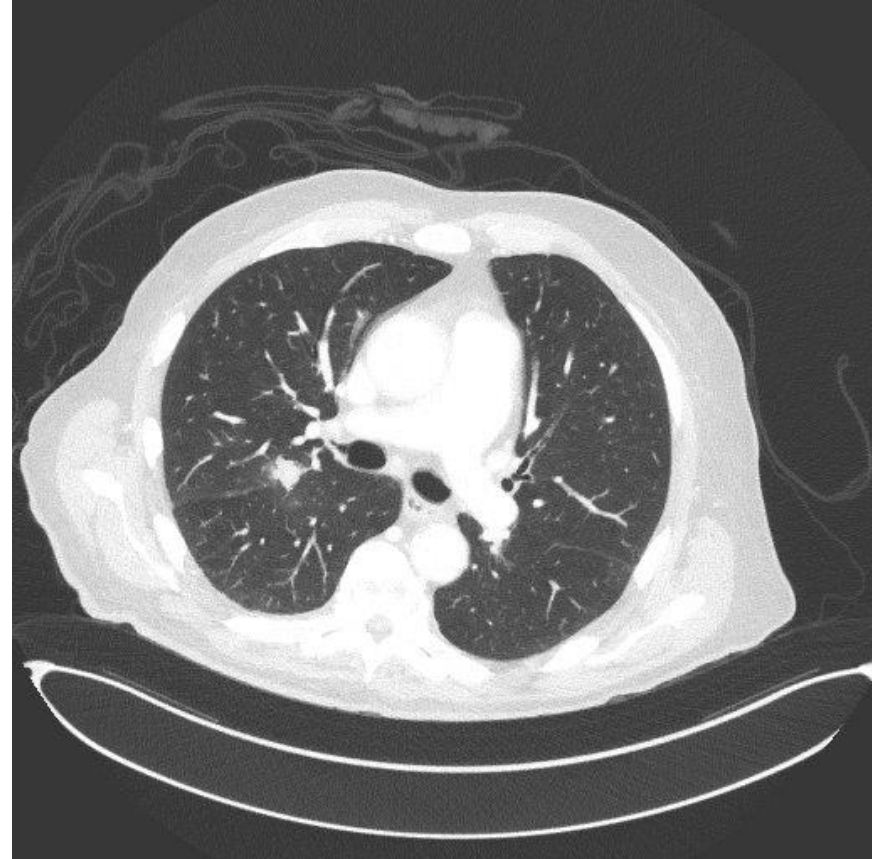


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INVASIVE MOLD INFECTIONS

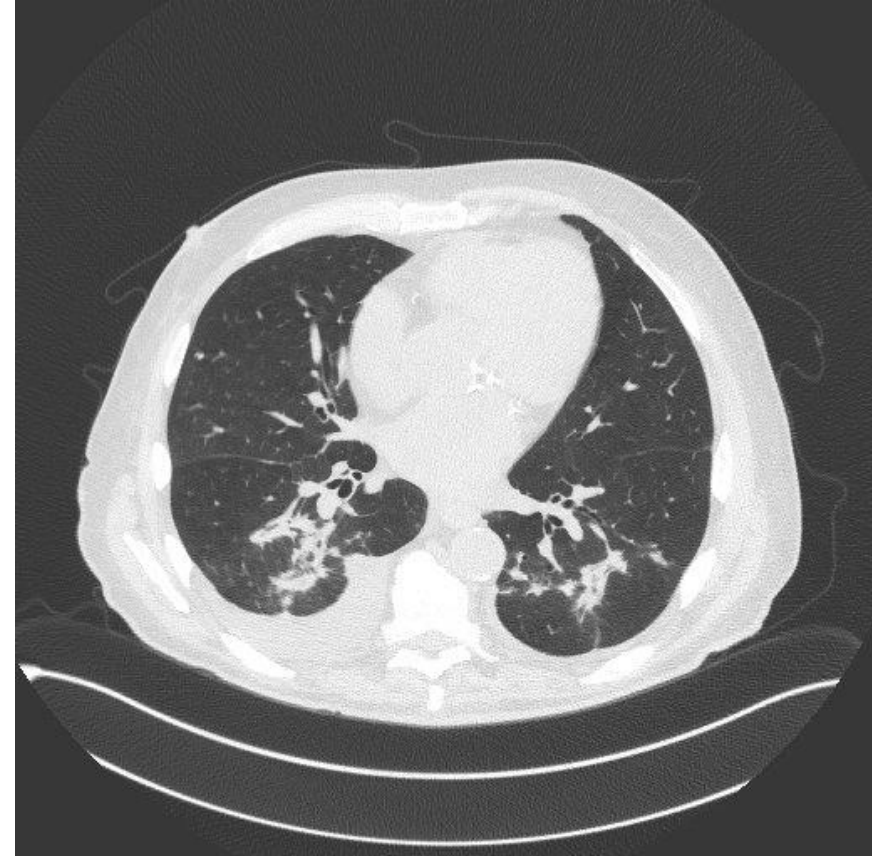
CASE 1

- 78 yo man with myelodysplastic syndrome that progressed to AML
- Hyperplastic bone marrow with 19% blasts
- Mutant isocitrate dehydrogenase-1 (*IDH1*) enzyme
- Treated with ivosidenib
- Neutropenic fever. Dry cough



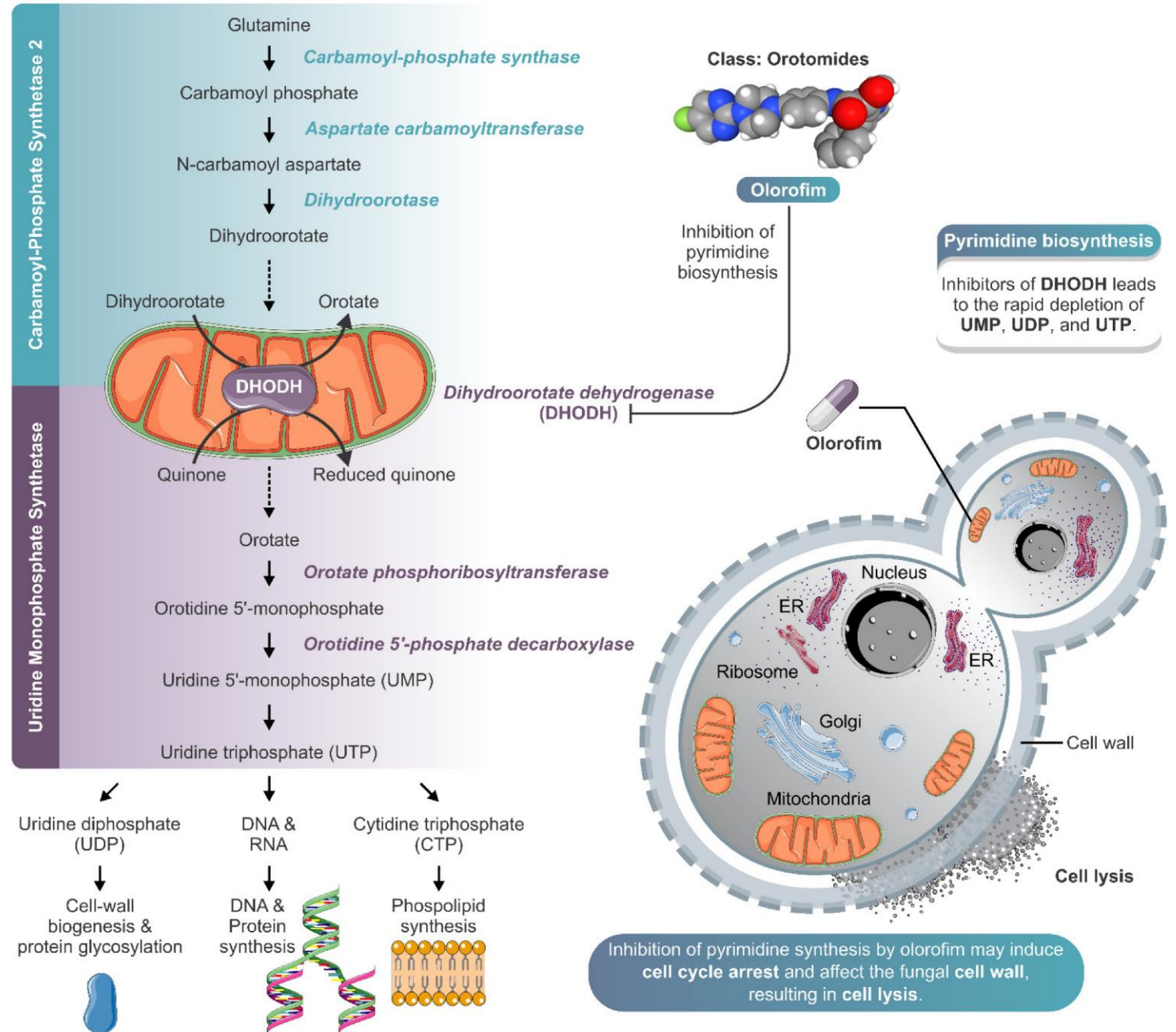
CASE 1

- 78 yo man with myelodysplastic syndrome that progressed to AML
- Neutropenic fever, pulmonary nodules, positive BAL *Aspergillus* galactomannan
- Treated with posaconazole → transaminitis
- Switched to isavuconazole



OLOROFIM

- Orotomide



Borba-Santos LP et al.
J Fungi 2022 Sep;8(10):1004

OLOROFIM

- No activity against yeast
- Active against *Aspergillus* and *Scedosporium* spp
- Good activity against *Fusarium* with some isolates demonstrating higher MICs
- No activity against *Mucorales*

OLOROFIM

- Olorofim *Aspergillus* Infection Study (**OASIS**), NCT05101187
- A Phase III randomized study to evaluate the efficacy and safety of treatment with olorofim versus AmBisome® followed by standard of care in proven or probable **invasive aspergillosis**
- Patients requiring therapy with an antifungal agent other than a mold-active azole on the basis of invasive aspergillosis
 - Refractory to mold-active azole therapy
 - Proven resistance to the mold active azoles
 - Breakthrough infection on mold-active triazole prophylaxis
 - Azole drug-drug interactions
- Primary endpoint: All-cause mortality at day 42

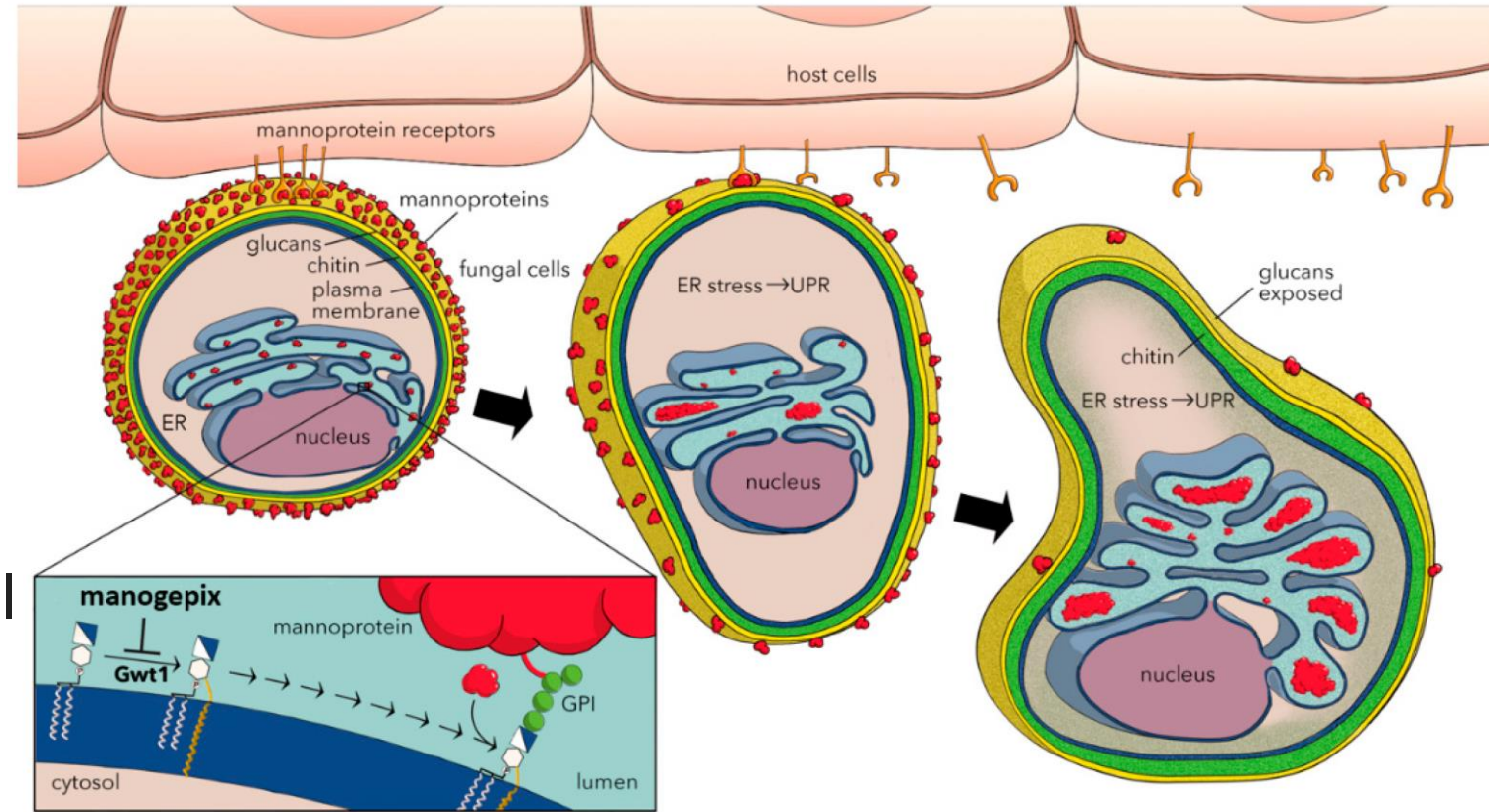
CASE 2

- 53 yo woman with history of high-grade B cell lymphoma s/p haploidentical peripheral HSCT
- *Fusarium verticilloides*
 - Amphotericin B 2 mcg/mL
 - Voriconazole 16 mcg/mL
 - Posaconazole 16 mcg/mL
 - Isavuconazole 16 mcg/mL



FOSMANOGEPIX

- Systemic phosphatases convert fosmanogepix to manogepix
- Glycosylphosphatidylinositol (GPI)-anchored mannoproteins








Shaw KJ et al. J Fungi 2020 Oct;6(4):239

FOSMANOGEPIX

- Active against *Candida*, *Aspergillus*, *Fusarium*, *Scedosporium* spp
- Lack of activity against *C. krusei*
- Variable activity against *Mucorales*

SUMMARY

Antifungal agents	Fosmanogepix	Ibrexafungerp	Olorofim	Opelconazole	Rezafungin
Pathogens					
 <ul style="list-style-type: none"> <i>Aspergillus calidoustus</i> <i>Aspergillus fumigatus</i> Azole-resistant <i>A. fumigatus</i> <i>Aspergillus flavus</i> <i>Aspergillus lentulus</i> <i>Aspergillus nidulans</i> <i>Aspergillus niger</i> <i>Aspergillus terreus</i> <i>Aspergillus tubingensis</i> 	Green	Green	Green	Green	Green
	Green	Green	Green	Green	Green
	Green	Green	Green	Red	Green
	Green	Green	Green	Green	Green
	Green	Green	Green	Green	Green
	Green	Green	Green	Green	Green
	Green	Green	Green	Red	Green
	Green	Green	Green	Green	Green
	Green	Green	Green	Green	Green
 <ul style="list-style-type: none"> <i>Fusarium spp.</i> 	Green	Red	Orange		
 <ul style="list-style-type: none"> <i>Scedosporium spp.</i> <i>Lomentospora prolificans</i> 	Green	Orange	Green		
	Green	Orange	Green		
 <ul style="list-style-type: none"> <i>Pneumocystis jirovecii</i> 		Green	Red		Green
 <ul style="list-style-type: none"> <i>Blastomyces dermatitidis</i> <i>Coccidioides immitis</i> <i>Histoplasma capsulatum</i> 	Green	Green	Green		
	Green	Green	Green		
	Green	Green	Green		

Hoeningl M et al. *Drugs*. 2021 Oct;81(15):1703-1729

2ND ATLAS / FDLC COURSE IN CLINICAL FUNGI

Mayo Clinic Rochester, Minnesota

23-28 September 2024



Course Directors

- Sybren De Hoog
- Paschalis Vergidis
- Nancy Wengenack
- Sean Zhang

