

What's new in the anti-fungal pipeline ?

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What's the plan



Tackling Emerging Threat of Antifungal resistance

General observations

Difference Between Bacterial and fungal resistance



What do we need ?

What are our present and futures problem pathogen in France

Worldwide



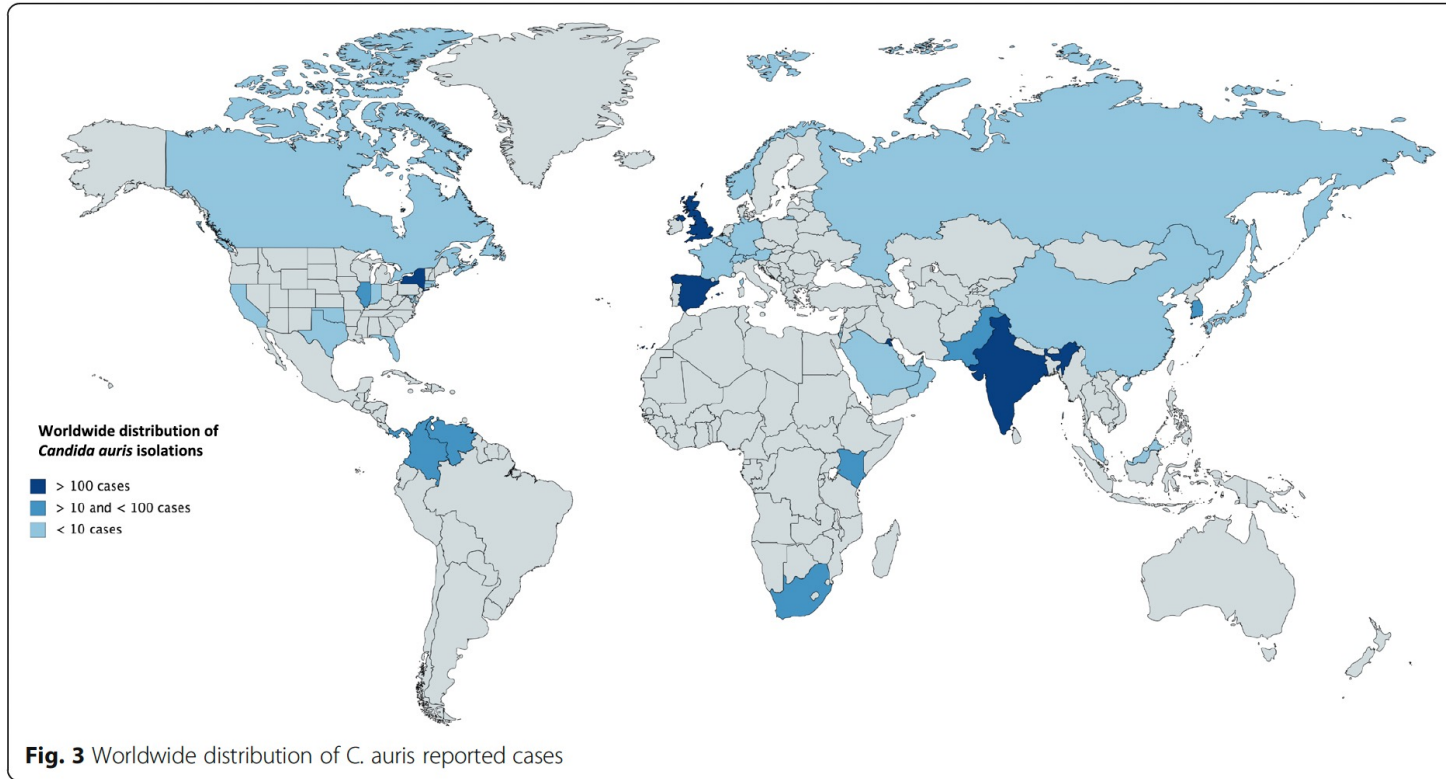
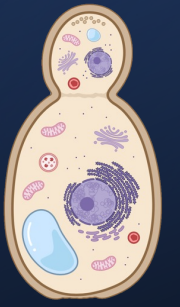
New Drugs in the pipeline

Mechanisms of Action

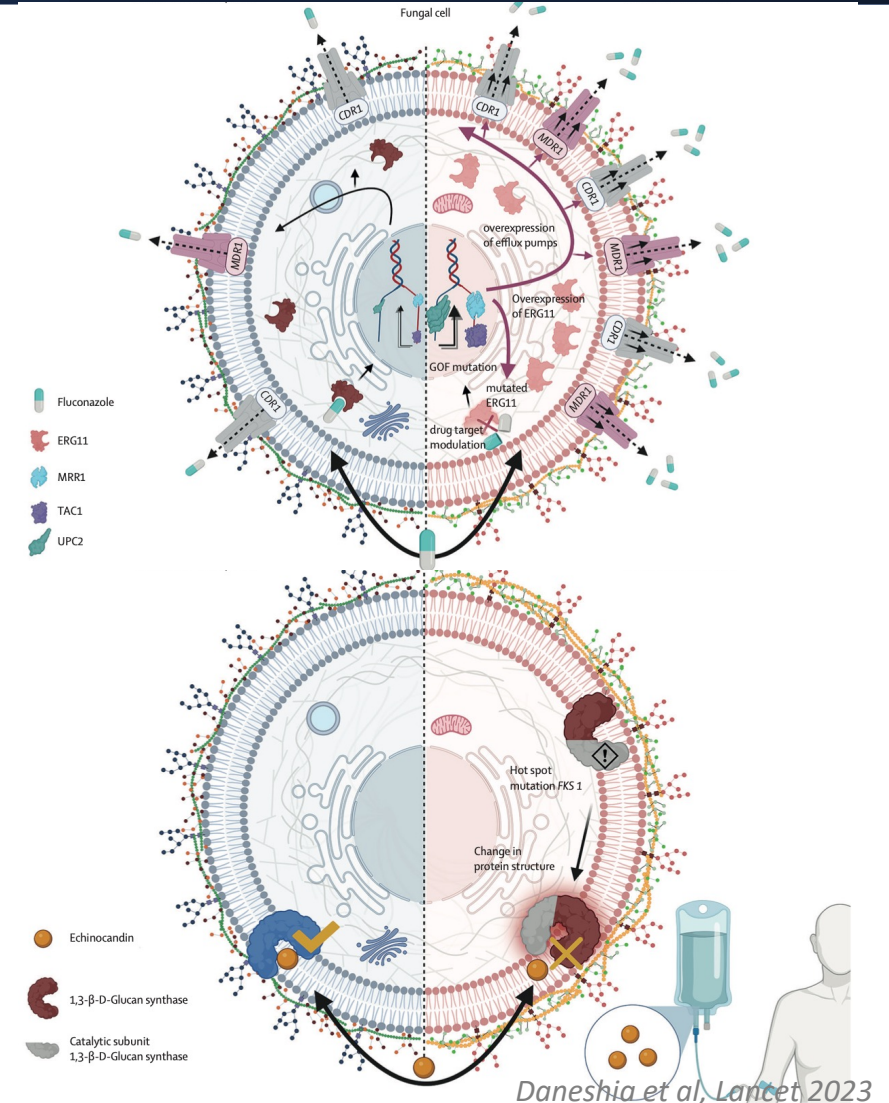
Spectrum of activity

I/ Tackling Emerging Threat of ATF resistance

Resistance is spreading: Yeast

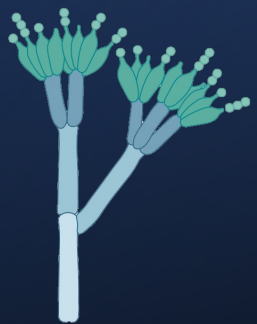


Cortegiani et al, Lancet 2022



I/ Tackling Emerging Threat of ATF resistance


One-Health resistance: Mould




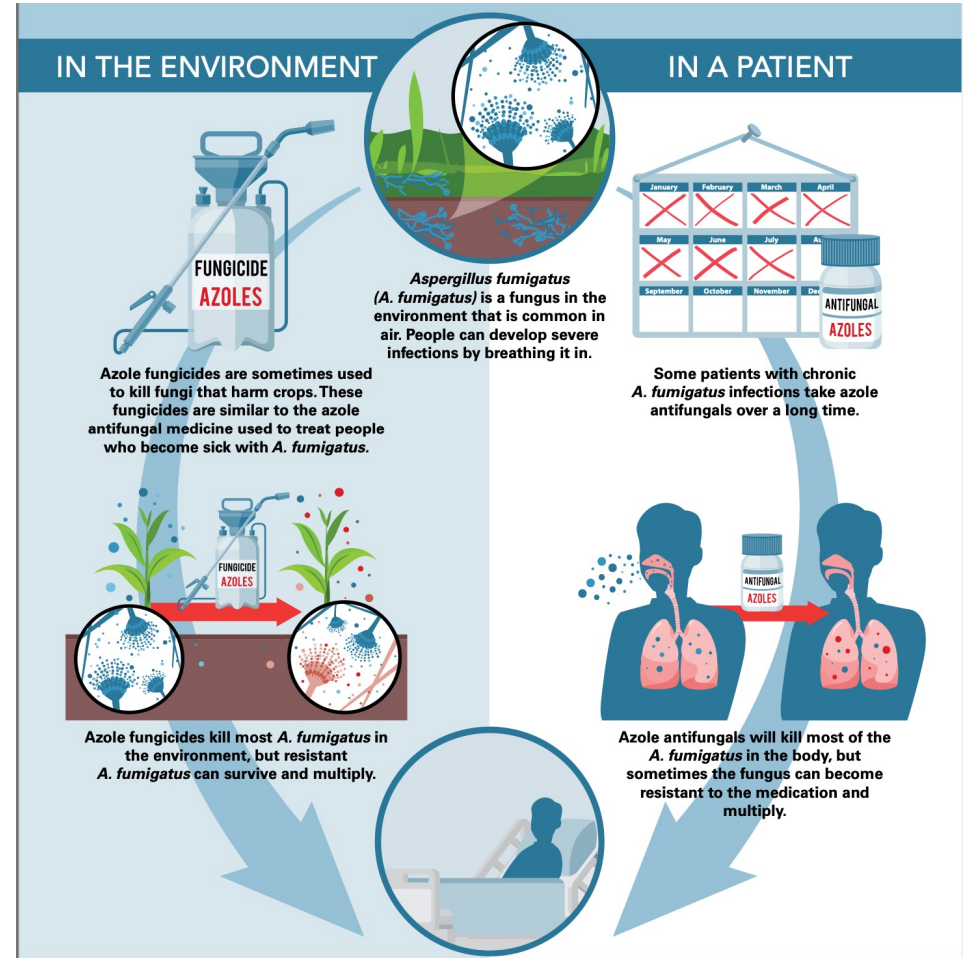
10 to 31% Voriconazole-Resistance *A. fumigatus* in Netherlands

Parameter		Center 1 (60 Cases)	Center 2 (59 Cases)	Center 3 (77 Cases)	Total (196 Cases)
Invasive aspergillosis	Putative	15 (25%)	14 (24%)	7 (9%)	36 (18%)
	Probable	24 (40%)	39 (66%)	54 (70%)	117 (60%)
	Proven	21 (35%)	6 (10%)	16 (21%)	43 (22%)
	Voriconazole susceptible	54 (90%)	41 (69%)	64 (83%)	159 (81%)
	Voriconazole resistant	6 (10%)	18 (31%)	13 (17%)	37 (19%)
ICU	Voriconazole susceptible	18 (90%)	17 (74%)	10 (63%)	45 (76%)
	Voriconazole resistant	2 (10%)	6 (26%)	6 (37%)	14 (24%)
Non-ICU	Voriconazole susceptible	36 (90%)	24 (67%)	54 (89%)	114 (83%)
	Voriconazole resistant	4 (10%)	12 (33%)	7 (11%)	23 (17%)

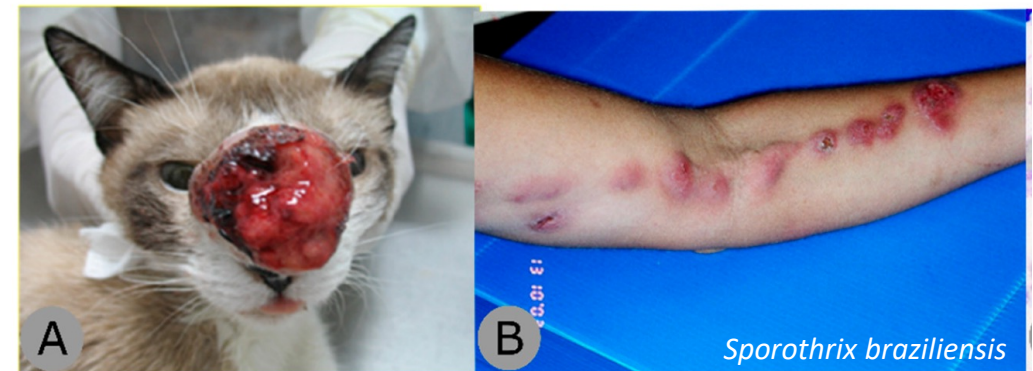
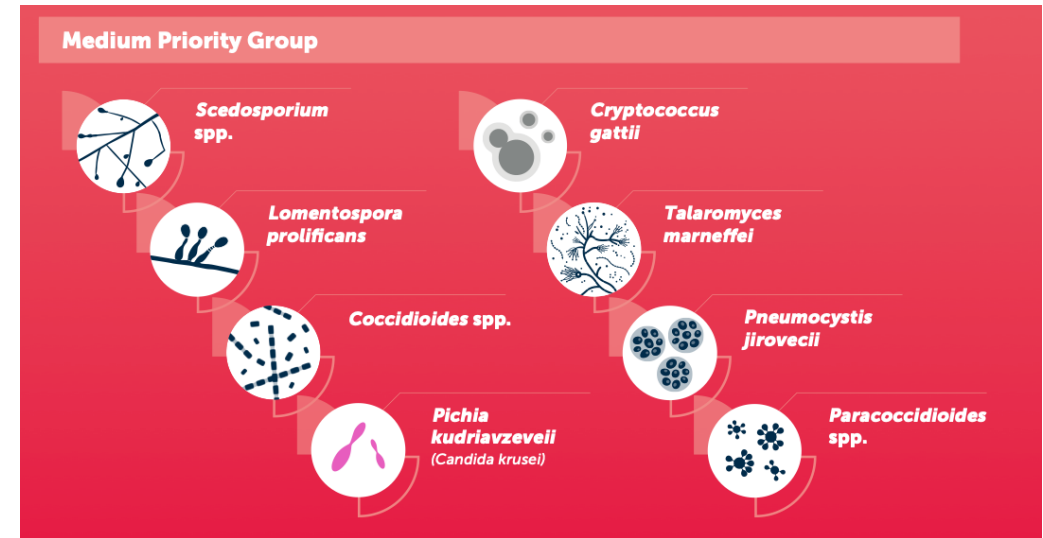
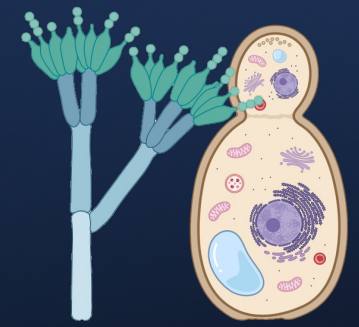
Lestrade et al, 2019

 Environnemental effect

 ICU effect




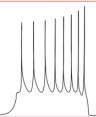



I/ Tackling Emerging Threat of ATF resistance ~~ESKAPE~~: The WHO Priority fungal problem pathogen



I/ Tackling Emerging Threat of ATF resistance

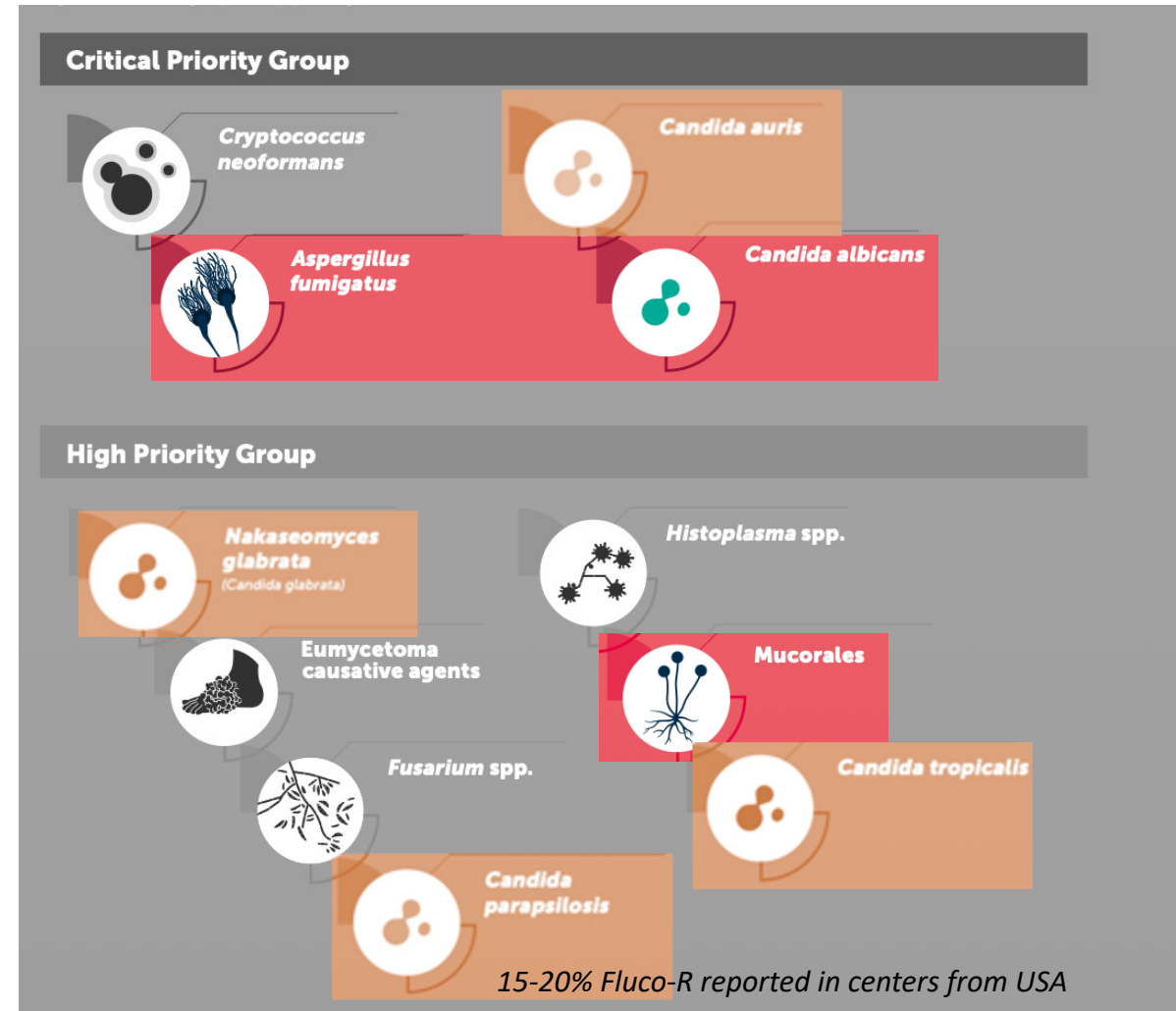
Difference Between Bacterial and fungal resistance

Bacterial AMR	Fungal AMR
<p>Bacterial Resistome</p> <ul style="list-style-type: none"> No Genetic Frontiers between species Severe Mobile Genetic elements bacteriophages, plasmids, cassettes 	<p>No Fungal Resistome</p> <ul style="list-style-type: none"> Genetic Frontiers No Horizontal Gene Transfer between species Rare endonucleases 
<p>Commensal Resistance Reservoir</p> <ul style="list-style-type: none"> Environmental/commensal = reservoir Transfer Genes available to pathogenic species Rarely De Novo 	<p>No Reservoir / De Novo Resistance</p> <ul style="list-style-type: none"> Environmental and commensal fungal = disease Resistance is constrained within the specie but De novo « species–drug combination » 
<p>Animal Reservoir of Resistance</p> <ul style="list-style-type: none"> Zoonotic transmission Zoonotic Reservoir 	<p>Unknow Animal Reservoir</p> <ul style="list-style-type: none"> Zoonotic transmission possible (Sporotrichosis, Dermatophytis, etc) 
<p>Lots of Data and Surveillance Program</p> <ul style="list-style-type: none"> International program for 40 years Systematic surveillance, sampling 	<p>Lack of Surveillance</p> <ul style="list-style-type: none"> SENTRY for <i>Candida spp</i> Paucity of Reference Labs 
<p>Antibacterial drugs available</p>	<p>Paucity of available drugs</p> 

II/ What to we need ?


Current (and futures) problem fungal pathogen in France

1. Echinocandin and Azole-Resistant *Candida spp* (*C. parapsilosis*, *C. auris*, *C. tropicalis*)
2. Azole-Resistant *Aspergillus spp*
3. Emerging & rare Moulds:
 - Mucorales
 - Dematiaceous moulds (*Penicillium*, *Talaromyces*, ..)
 - *Fusarium*, *Scedosporium*, *Lomentospora*




II/ What to we need ?

Azole-Resistant *Aspergillus spp* ?





Antifungal agents	Fosmanogepix	Ibrexafungerp	Olorofim
Pathogens			
 <i>Aspergillus calidoustus</i>			
<i>Aspergillus fumigatus</i>			
<i>Azole-resistant 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>			

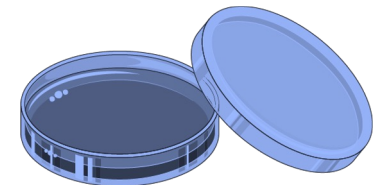
II/ What to we need ?

Echinocandin / Azole-Resistant / Ampho-B resistant *Candida spp* ?

Antifungal agents	Fosmanogepix	Ibrexafungerp	Rezafungin
 <i>Candida albicans</i>			
<i>Candida auris</i>			
<i>Candida dubliniensis</i>			
<i>Candida glabrata</i>			
<i>Candida krusei</i>			
<i>Candida lusitanae</i>			
<i>Candida parapsilosis</i>			
<i>Candida tropicalis</i>			

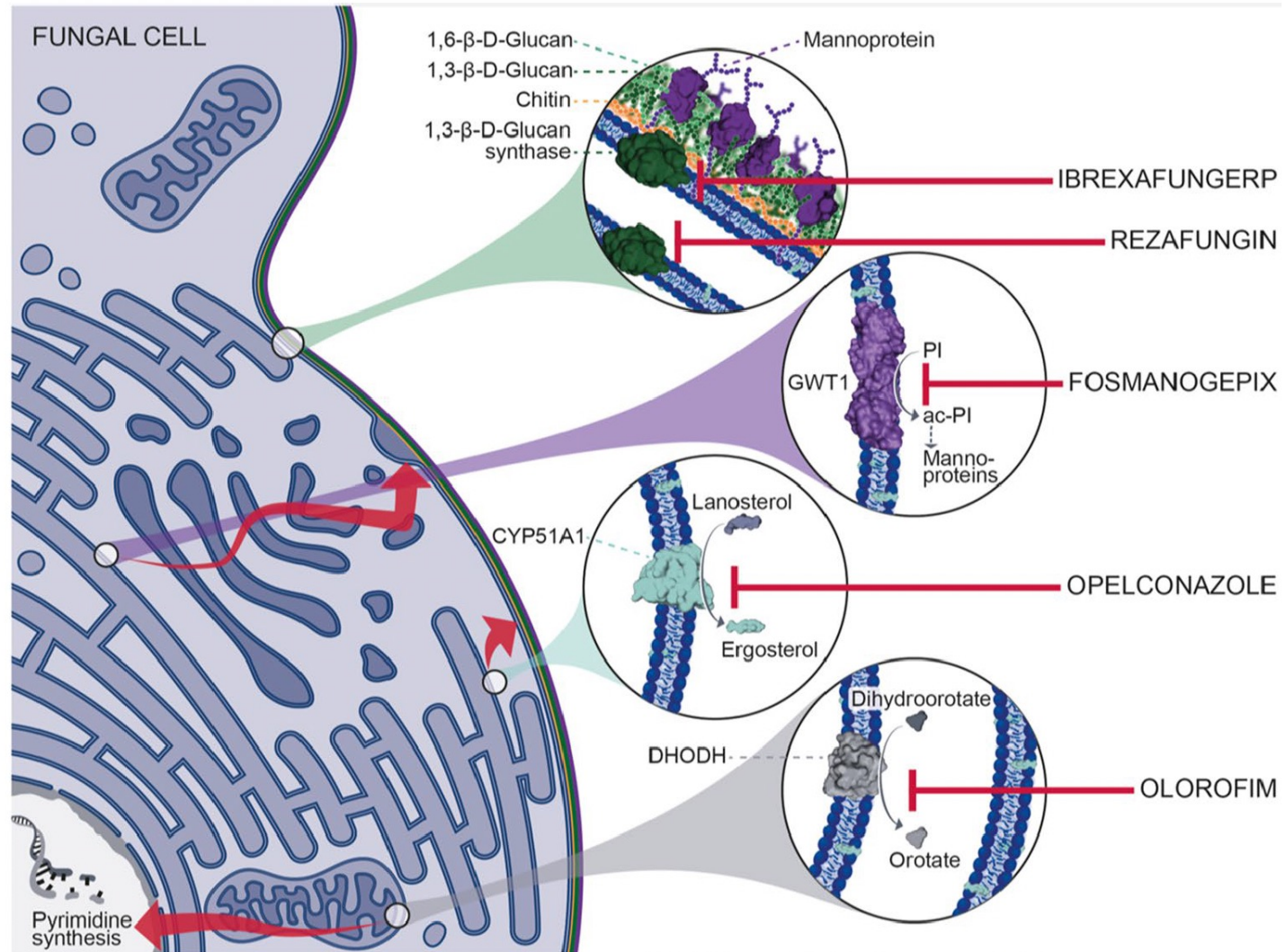
II/ What to we need ? Emerging and Rare molds ?

Antifungal agents	Fosmanogepix	Ibrexafungerp	Olorofim
Pathogens			
 <i>Fusarium spp.</i>	Green	Red	Orange
 <i>Alternaria alternata</i>	Orange	Green	Red
<i>Cladosporium spp.</i>	Green	Green	
<i>Paecilomyces variotii</i>	Green	Orange	Green
<i>Purpureocillium lilacinum</i>	Green	Red	Orange
<i>Scopulariopsis spp.</i>	Green	Red	Green
<i>Rasamsonia spp.</i>	Green		Green
 <i>Scedosporium spp.</i>	Green	Orange	Green
<i>Lomentospora prolificans</i>	Green	Orange	Green
 <i>Cunninghamella</i>	Orange	Red	Red
<i>Lichtheimia</i>	Orange	Red	Red
<i>Mucor</i>	Orange	Red	Red
<i>Rhizopus</i>	Orange	Red	Red



III/New Drugs in the pipeline

Mechanisms of action



III/New Drugs in the pipeline

Ibrexafungerp – « Enhanced oral Echinocandin »

Keypoints

- Oral drug
- Family : triterpenoid antifungal
- biosynthesis of 1,3-beta-D-glucan
- Different Binding site from others Candins
- Low Cross-Resistance (FKS mutations)

C. glabrata Distribution of ibrexafungerp by echinocandin MIC value

Drug	No. of isolates (isolates/isolates with <i>FKS</i> mutation) at MIC ($\mu\text{g/ml}$) of ^a :										
	<0.03	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16
Ibrexafungerp	1	0	2	19	28	27	11	0	1	0	0
Caspofungin	0	3/0	3/1	6/4	7/3	11/5	5/4	10/9	9/9	13/12	22/21
Anidulafungin	0	7/1	4/2	4/1	4/2	12/8	16/15	29/27	13/12	0	0
Micafungin	1/0	1/0	1/0	6/4	16/12	9/5	21/16	21/18	12/12	0	1/1

FKS mutants with the F641S, F649del, F658del, F659del have reduced susceptibility to ibrexafungerp

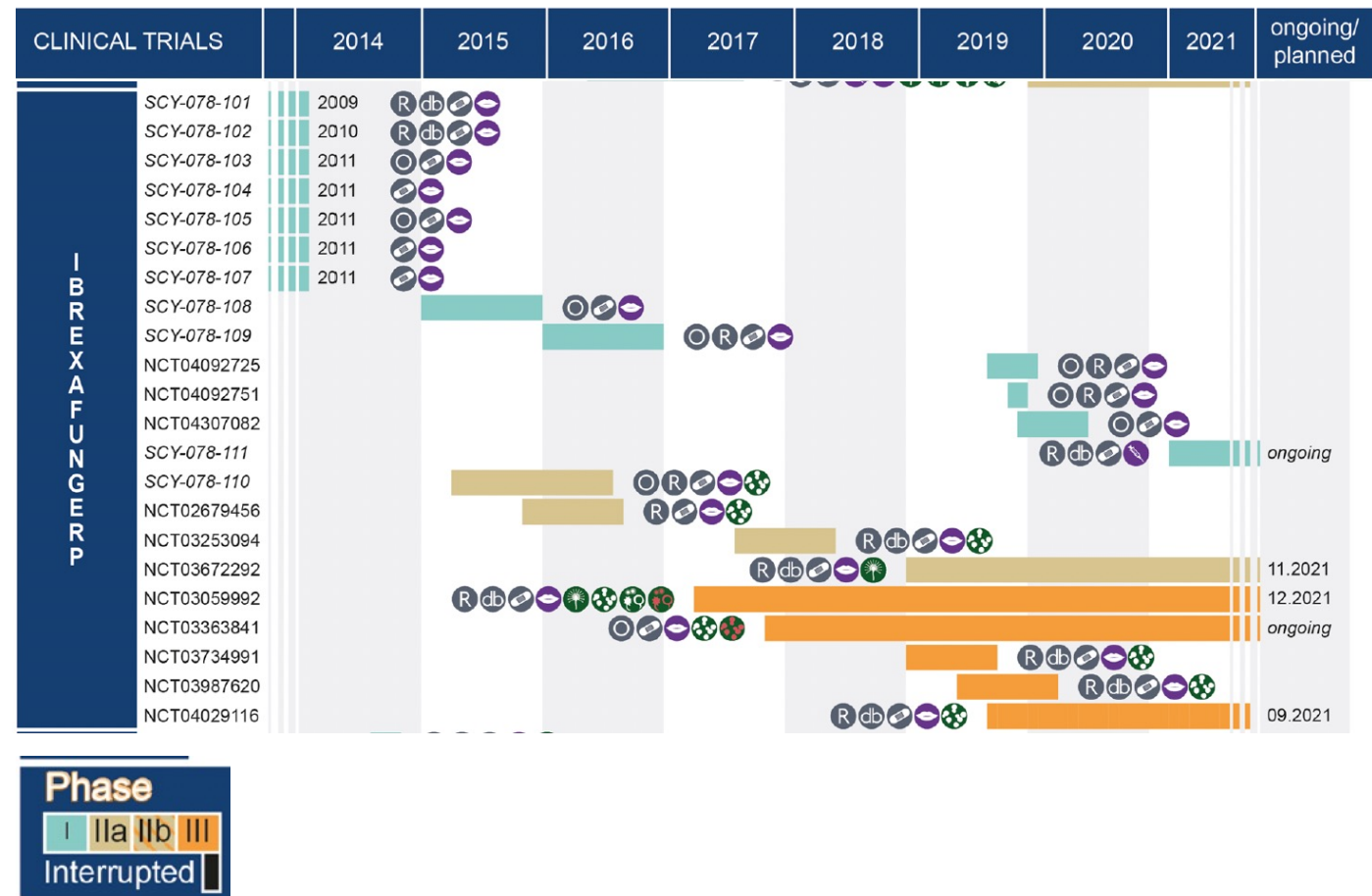
Shell et al, AAC, 2017
Nunally et al, AAC, 2019
Arendrup et al, AAC, 2020

III/New Drugs in the pipeline

Ibrexafungerp – « Enhanced oral Echinocandin »

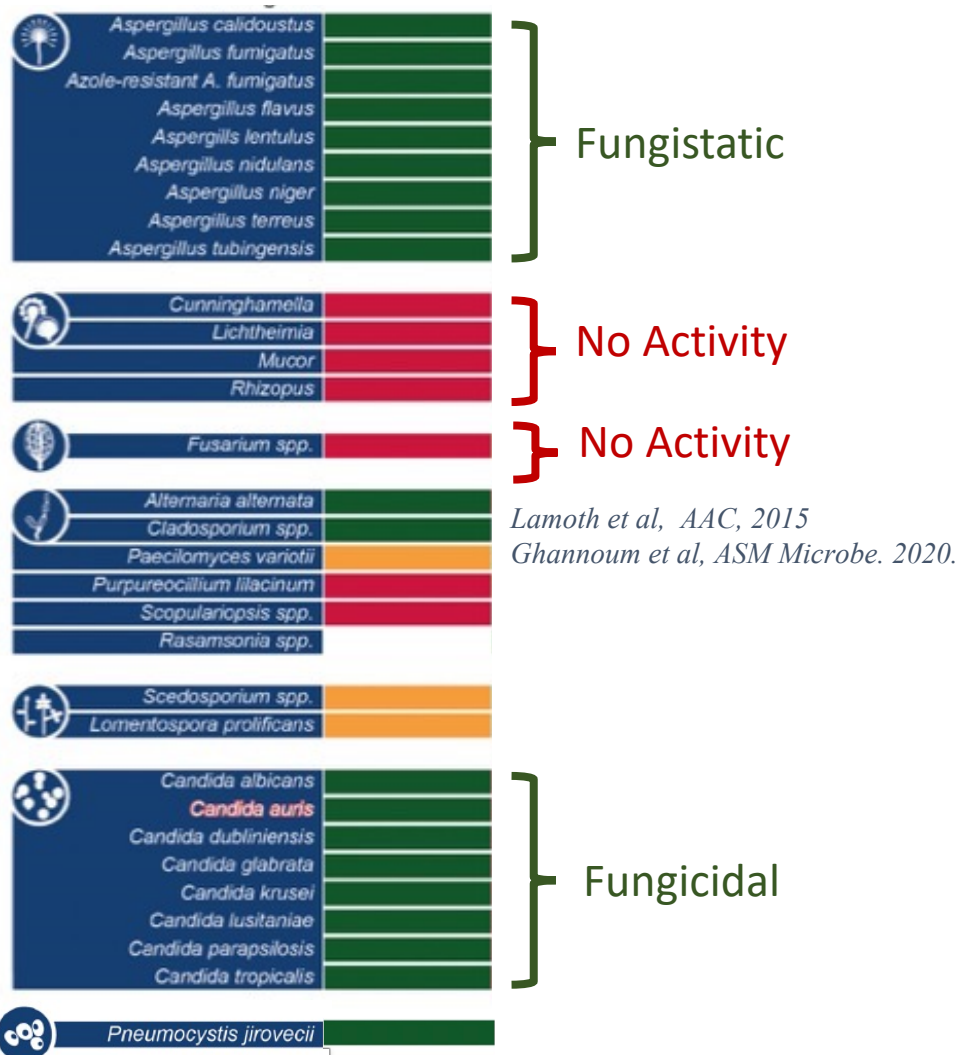
Keypoints

- ORAL drug
- Invasive fungal infection :
 - LD 750 mg x 2 / 2 days – 750mg/day
- Superficial fungal infection:
 - LD 300 mg x 2 / 2 days – 300mg/day
- ½ life. = 30 hours
- Low Interaction. (CYP3A4. substrate)
- Low Distribution in CNS



III/New Drugs in the pipeline

Ibrexafungerp – « Spectrum of activity and Trials »



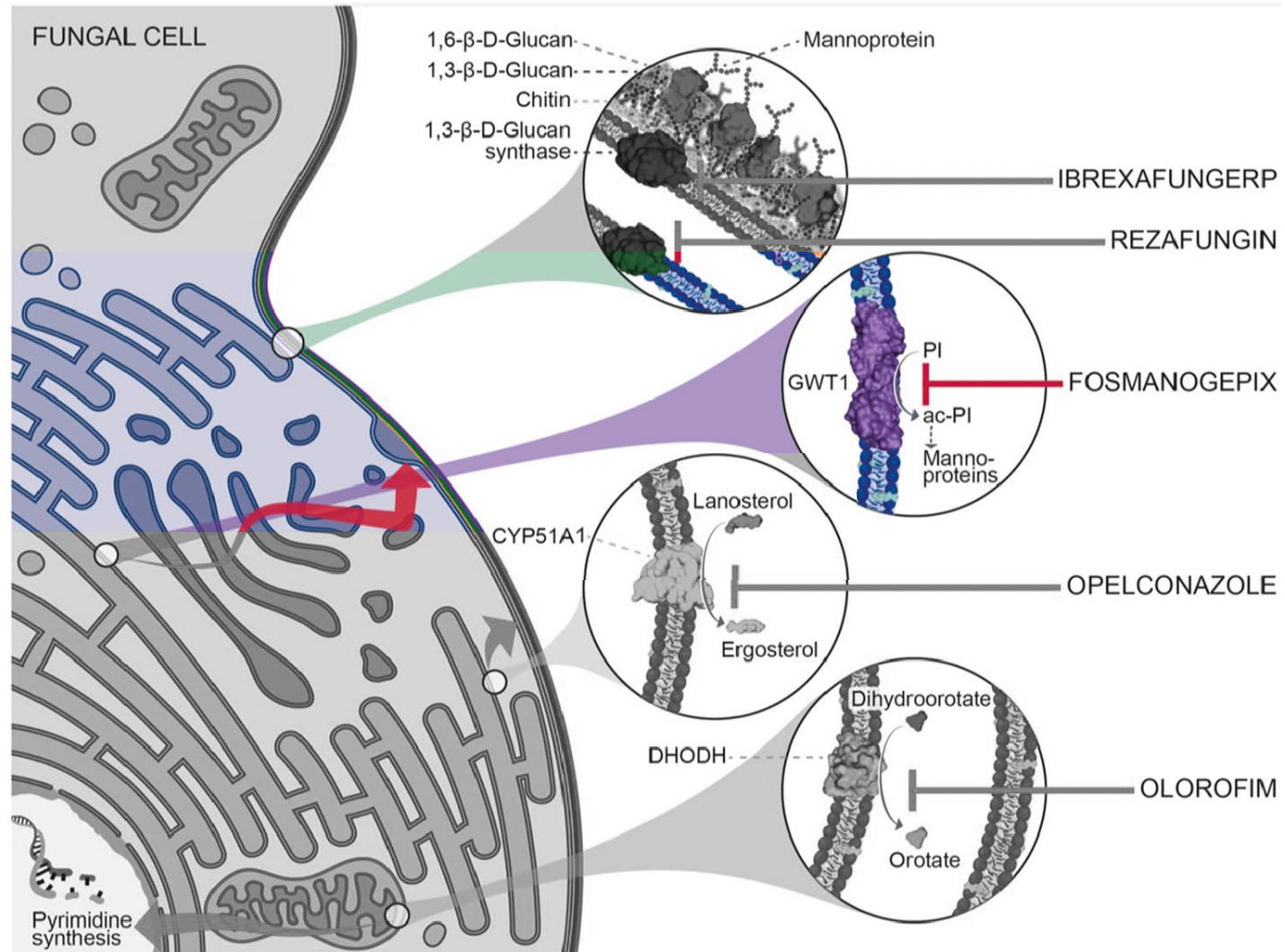
Study	Comparator	Main Result
Phase 2 Invasive Candidiasis NCT02244606	Mica followed by Fluconazole or Ibrexa	Open-Labeled, Randomized 86% Ibrexafungerp 71% fluconazole
Phase 3 Invasive Candidiasis <i>C. auris</i> NCT03363841	No comparator	CARES- 30 patients <i>80% success on first 8/10</i>
Phase 3 Invasive candidiasis NCT05178862	Vs Oral Fluconazole	After echinocandin IV Begin 08/2022 - MARIO
Phase 3 Invasive Respiratory Aspergillosis	Ibrex + isavuco Vs Isavuco	SCYNERGIA <i>In progress</i>
Phase 3 Prophylaxis Pneumocystis	Cotrimoxazole	

Azie NJ, CARES study, 31st ECCMID, 2021.
Helou et al, . Am J Obstet, 2017
Schwebke et al, Am J Obstet Gynecol. 2020

Nunally et al, AAC, 2019
Hoeninglet al, 2022

III/New Drugs in the pipeline

Fosmanogepix : New mechanism of Action

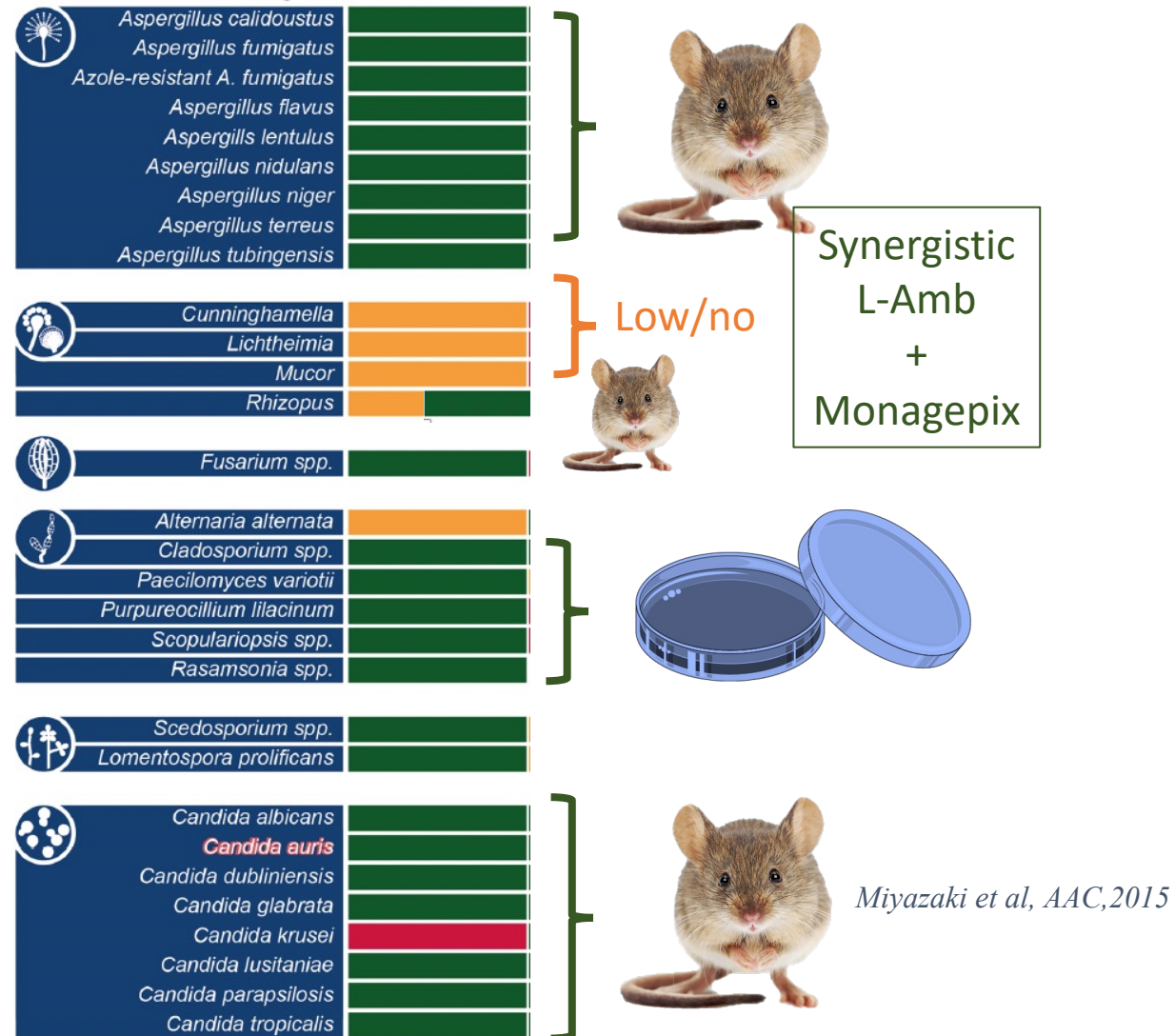


III/New Drugs in the pipeline

Fosmanogepix/Manogepix: Promising Broad-spectrum activity

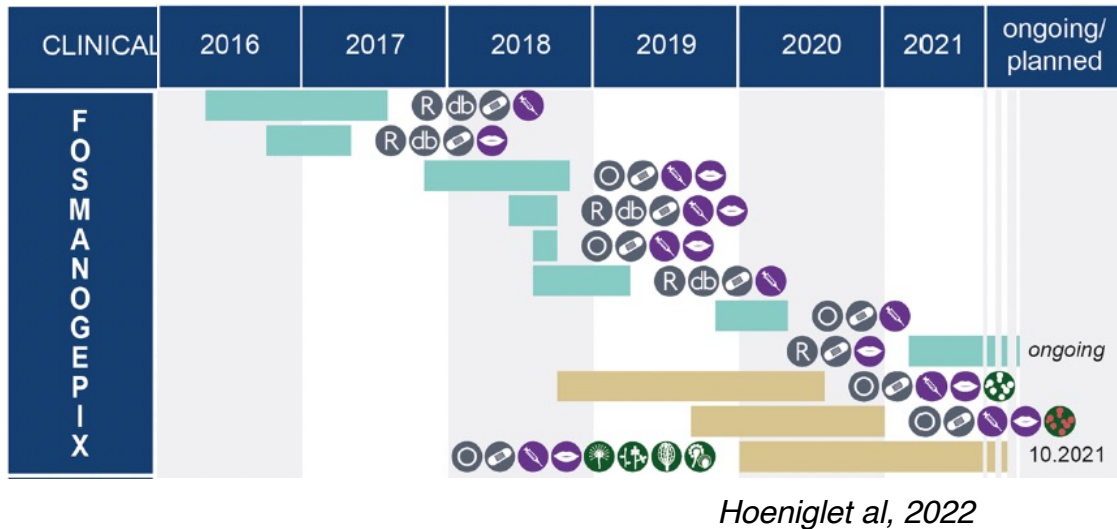
Keypoints

- Oral and IV drug
- Pro-Drug : Phosphatase metabolism to Manogepix
- Target GPI Anchored Protein maturation by inhibition Gwt1
- Gwt1 is essential for trafficking and anchoring of mannoprotein to cell wall
- No Activity on PIGW (human enzyme)
- AUC/CMI : PK/PD activity



III/New Drugs in the pipeline

Fosmanogepix/Manogepix: Trials

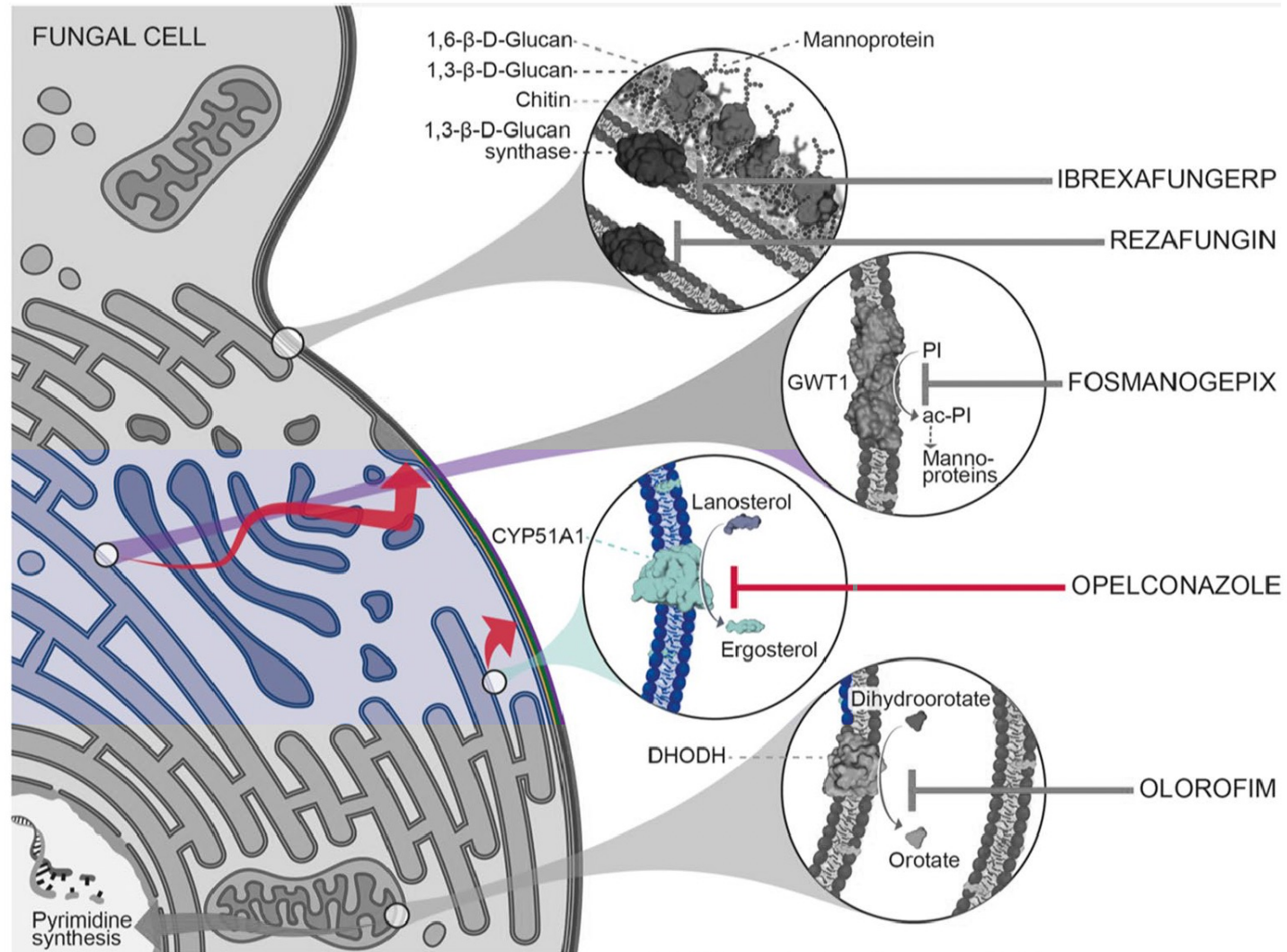


LD 1000 mg x 2 during 1 day –
600 mg x 1 IV (or 700 mg orally)

Study	Comparator	Main Result
Phase 2 Non Neutropenic Candidemia NCT03604705 <i>Pappas et al, JAC, 2023</i>	Single arm No comparator	85% Success Day 28 Day to negative Blood Culture = 2,4 days Including L-Amb-R or Caspo-R
Phase 2 NCT04240886 - AEGIS	« Limited or no treatment options or a lack of clinical response to SOC »	<i>Aspergillus</i> <i>Scedosporium</i> <i>Fusarium</i> Rare mould ...
Phase 3 NCT05421858 Invasive Candidiasis <i>Pappas et al, JAC, 2023</i> <i>Lamoth et al, IDR, 2023</i>	casprofungin	Randomized Trial Begin 2024

III/New Drugs in the pipeline

Opelconazole




III/New Drugs in the pipeline

Opelconazole – Nebulized Triazole

Keypoints

- **Nebulized Azole**
- Target: CYP51A1
- Lipophilic:
 - Low Diffusion from the lungs
 - Low plasma concentration
 - ✓ = No TDM
 - ✓ = Low Toxicity and drug interaction
 - Prolonged lung retention
- Prophylaxis or Treatment of Invasive Aspergillosis

Antifungal agents	Pathogens
	Opelconazole
	<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>

Hoeninglet al, 2022

III/New Drugs in the pipeline

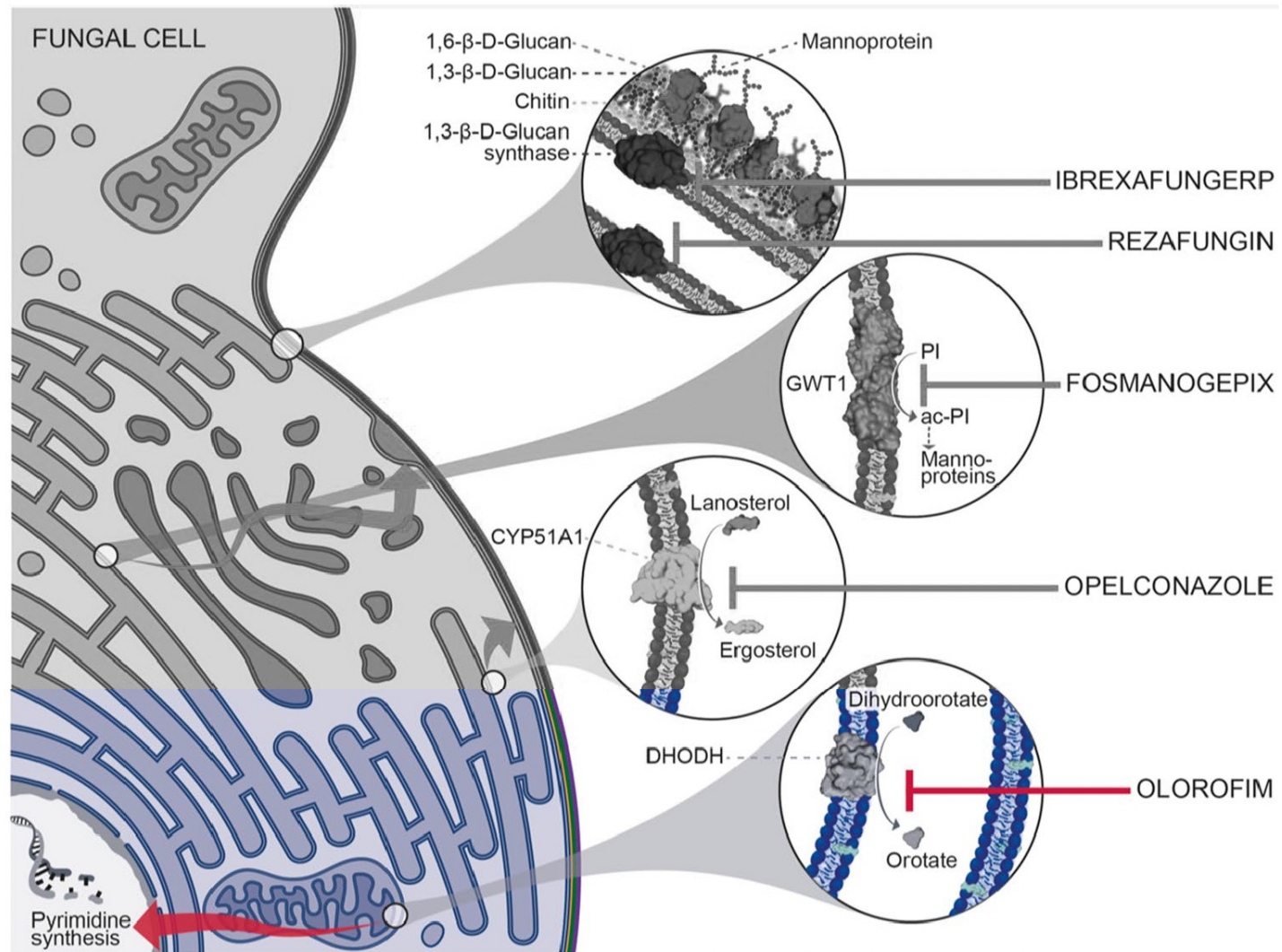
Opelconazole – Nebulized Triazole

5 mg/Day over 15-30 minutes

Study	Comparator	Main Result
Compassionate Use : No response with usual ATF	None	8/9 patients with improvement
Phase 2b	Prophylaxis and Preemptive of Invasive aspergillosis in Lung Transplant recipient	NCT05037851
Phase 3	A double-blind, randomized, placebo- controlled treatment of refractory invasive pulmonary aspergillosis (+ SOC)	2021-004554-32

III/New Drugs in the pipeline

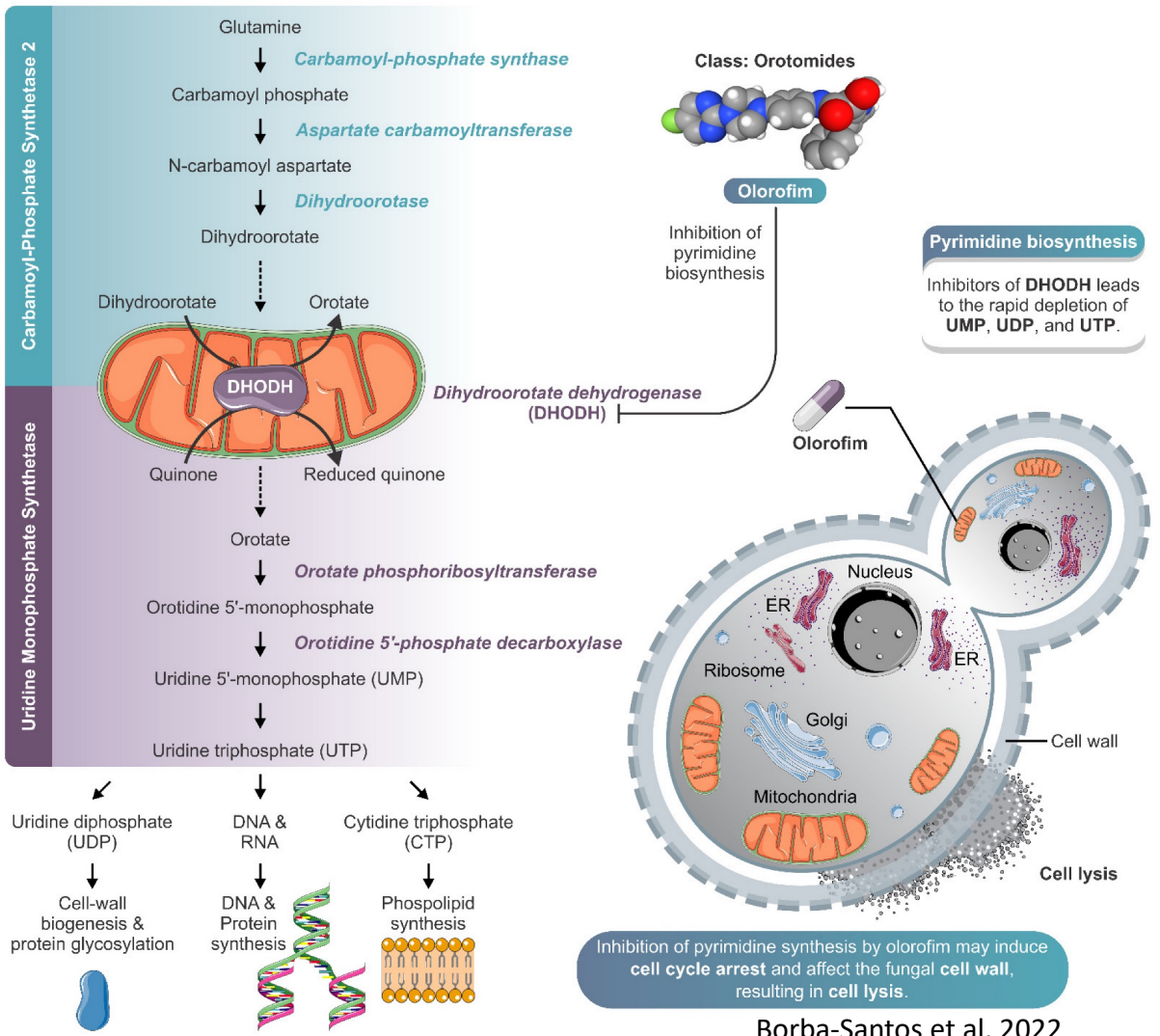
Olorofim : Promising against Azole-R and emergent/rare mould infection



III/New Drugs in the pipeline

Olorofim : Mechanism and Spectrum of activity

No activity against : yeast & Mucorales



	<i>Aspergillus calidoustus</i>	Active
	<i>Aspergillus fumigatus</i>	Active
	Azole-resistant <i>A. fumigatus</i>	Active
	<i>Aspergillus flavus</i>	Active
	<i>Aspergillus lentulus</i>	Active
	<i>Aspergillus nidulans</i>	Active
	<i>Aspergillus niger</i>	Active
	<i>Aspergillus terreus</i>	Active
	<i>Aspergillus tubingensis</i>	Active

	<i>Cunninghamella</i>	Inactive
	<i>Lichtheimia</i>	Inactive
	<i>Mucor</i>	Inactive
	<i>Rhizopus</i>	Inactive

	<i>Fusarium spp.</i>	Active
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	<i>Blastomyces dermatitidis</i>	Active
	<i>Coccidioides immitis</i>	Active

	<i>Paecilomyces variotii</i>	Active
	<i>Purpureocillium lilacinum</i>	Active
	<i>Scopulariopsis spp.</i>	Active
	<i>Rasamsonia spp.</i>	Active

	<i>Scedosporium spp.</i>	Active
	<i>Lomentospora prolificans</i>	Active

Species Specific

← CNS

III/New Drugs in the pipeline

Keypoints & Trials

- Oral LD 150 mg x 2 Day 1 and 90 mg x 2
- No adverse event, well tolerated
 - No discontinuation
 - Elevation of Liver enzymes (<3N)
- Drug interactions : Yes, Olorofim is a weak inhibitor of CYP3A4
 - Adaptation of tacrolimus and everolimus dose regimen

Wiederhold et al, JoF, 2020
Faure et al, EID, 2023

Study	Comparator	Main Result
Phase 3 NCT03583164 Invasive infection with rare/resistant mold <i>L. prolificans</i> , <i>Scedosporium spp.</i> , <i>Aspergillus spp</i>	No alternative treatment	50-60% success M3 8% Elevated Liver Enz. <i>Maertens et al</i> , OFID 2022 (100/200 patients)
Phase 3 : OASIS NCT05101187 Azole-Resistant Aspergillosis	L-Amb	Resistant invasive pulmonary aspergillosis

III/New Drugs in the pipeline

Few Reports on rare molds : *Microascus* / *Scopulariopsis*

No current guidelines for *Microascus* / *Scopulariopsis* treatment

Species name (no. of strains tested)	MIC/MEC parameter	MIC ^a (μg/ml)								MEC ^a (μg/ml)
		AMB	CPX	TRB	5FC	FLC	ITC	POS	VRC	CFG
<i>Microascus albonigrescens</i> (2)	Individual values	8 ^b	>16	0.5	>64	>64	>16	>16	8, >16	0.5, 8
<i>M. caviariformis</i> (1)	Individual value	1	>16	2	>64	>64	>16	>16	16	0.25
<i>Microascus cinereus</i> (3)	Range	>16	16->16	1-2	>64	>64	>16	>16	16->16	1-8
<i>M. cirrosus</i> (3)	Range	16->16	8->16	1 ^b	>64	>64	>16	>16 ^b	2-16	1 ^b
<i>M. longirostris</i> (3)	Range	2->16	4->16 ^b	1-0.5 ^b	>64	>64	>16	>16	8->16	0.5-1
<i>M. manginii</i> (4)	Range	16->16 ^b	>16	0.25-4	>64	>64	>16	>16	16->16	0.5-16
<i>M. nidicola</i> (1)	Individual value	4	1	1	>64	>64	8	>16	4	ND
<i>M. pyramidus</i> (1)	Individual value	ND	>16	8	>64	>64	>16	>16	4	1
<i>M. senegalensis</i> (2)	Individual values	16, >16	>16	1, >16	>64	>64	>16	0.5, >16	8, >16	8
<i>M. trigonosporus</i> (3)	Range	2->16 ^b	16->16	1-2	>64	>64	>16	>16	>16	0.5-2

AmB-R
5FC-R
Azole-R
Lower MIC To Micafungin

III/New Drugs in the pipeline

Few Reports on rare molds : *Microascus* / *Scopulariopsis*

No current guidelines for *Microascus* / *Scopulariopsis* treatment

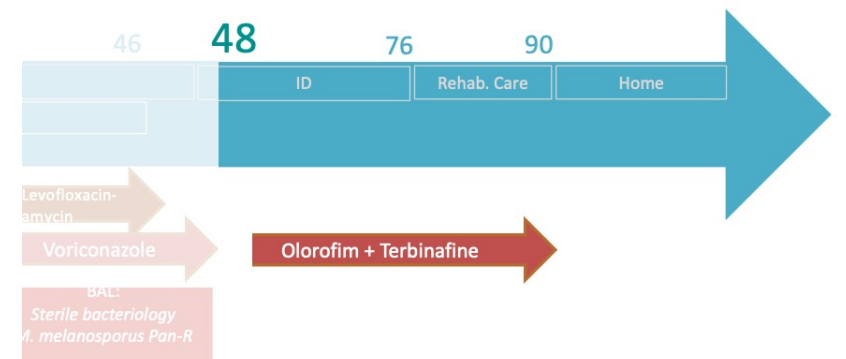
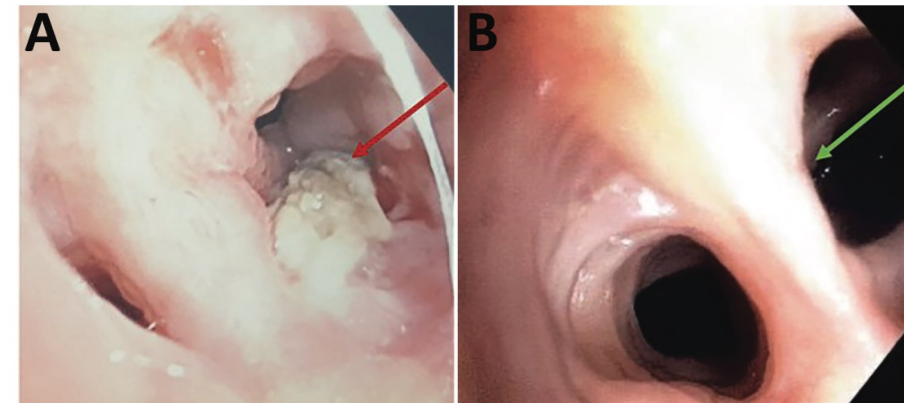
	Patients	Site	Mortality		Treatment
Miossec <i>et al</i> 2019	1/9 : No underlying disease 3/9 : SOT 5/9 : HCST	Lung Lung Lung	0/1 3/3 5/5	85% 100% IC	L-Amb VCZ / PSZ TRB
Liu <i>et al</i> 2021	1/1 : Bronchiectasis	Lung	0/1		L-Amb (IV+inh) +VCZ
Schoeppler <i>et al</i> , 2015	1/1 : Lung Transplant	Lung	1/1		L-Amb (IV+inh) + PSZ
Ustun <i>et al</i> , 2006	1/1 : HCST	Lung	1/1		D-AmB + ITR + TRB
Baddley <i>et al</i> , 2000	1/1 : HCST	Lung Brain	1/1		D-AmB - ITR

III/New Drugs in the pipeline

Olorofim : Case Reports on *Microascus spp*

Table. Medical history and keypoints of 3 case-patients with refractory microascus bronchopulmonary infection, France*

Characteristic	Case 1	Case 2	Case 3
Age, y	17	61	65
Immunocompromised status	No	Lung transplant	Lung transplant
Years since transplantation	NA	4	6
Chronic lung allograft dysfunction	NA	Y (for 2 y)	Y (for 5 y)
Intensification of immunosuppressive drug regimen in medical history	NA	Antithymocyte globulin, steroids, rituximab, alemtuzumab, extracorporeal photophoresis	Steroids, rituximab, bortezomib
Maintenance therapy on the onset of <i>Microascus</i> infection	NA	Tacrolimus (C ₀ 4-6 ng/mL), everolimus (C ₀ 4-6 ng/mL), prednisone (5 mg/d)	Tacrolimus (C ₀ 4-6 ng/mL), Everolimus (C ₀ 4-6 ng/mL), prednisone (5 mg/d)
Recent antifungal exposition <3 mo	None	Isavuconazole	Isavuconazole
Tolerance			
Clinical	No SSE	NA	No SSE
Biologic	No ELE	Drug interaction with tacrolimus and everolimus	No ELE



New Drugs in the pipeline

Olorofim : Cordyceps Included

- Era of
- Global Warming & Climate Change
- Pandemic Threat
- Outbreak of Fungal infection



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How I may use the new drugs from the Pipeline ? (Personal Point of view)

	Echinocandin & Azole Resistant <i>Candida spp</i>	Azole-Resistant <i>Aspergillus spp</i>			Emergent & rare moulds	Cordyceps-hijacked zombie
		Curative	Salvage	Prophylaxis		
Ibrexafungerp			bithery			
Manogepix					+ L-Amb for Mucorales	
Opelconazole		Respiratory	bithery			
Olorofim						

Thanks for
your
attention

