JN 25es Journées Nationales d'Infectiologie
DEAUVILLE et la région Normandie
du mercredi 12 au vendredi 14 juin 2024

Les antifongiques systémiques: le nouvel arsenal thérapeutique

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Centre National de Référence Mycoses invasives et Antifongiques / Laboratoire associé sur les Aspergilloses chroniques LA AspC

Déclaration d'intérêt de 2014 à 2023

- Intérêts financiers : non
- Liens durables ou permanents : non
- Interventions ponctuelles : Gilead, MSD, MundiPharma, Pfizer, Shionogi
- Intérêts indirects : non

Les cibles d'action des antifongiques (infections invasives)

4 classes d'antifongiques

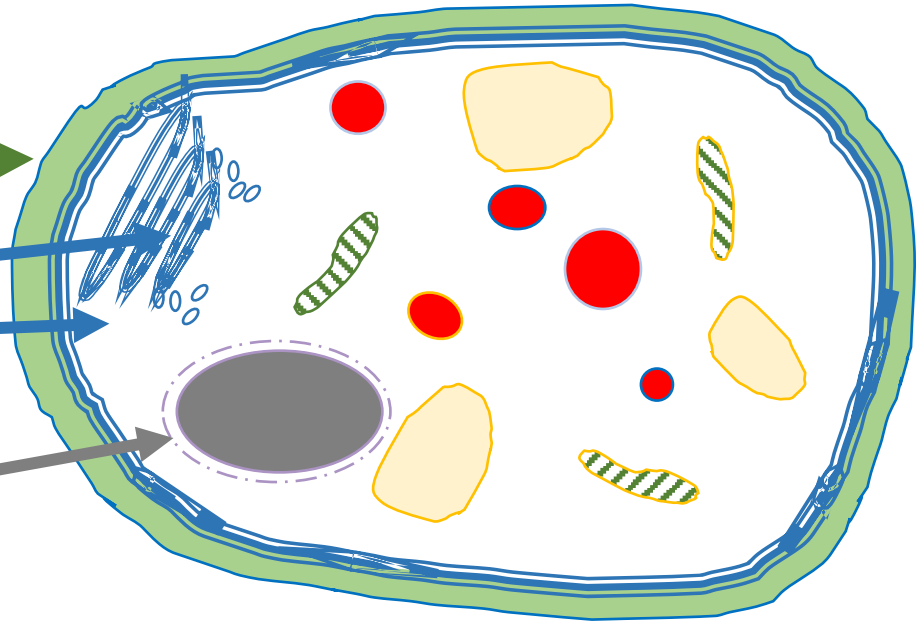
1. Echinocandines

2. Azolés

3. Polyènes

4. Analogue de pyrimidine /Flucytosine

(Allylamines)



Paroi fongique
(β-1-3 glucane synthase)

Synthèse de l'ergostérol
(C14α déméthylase)

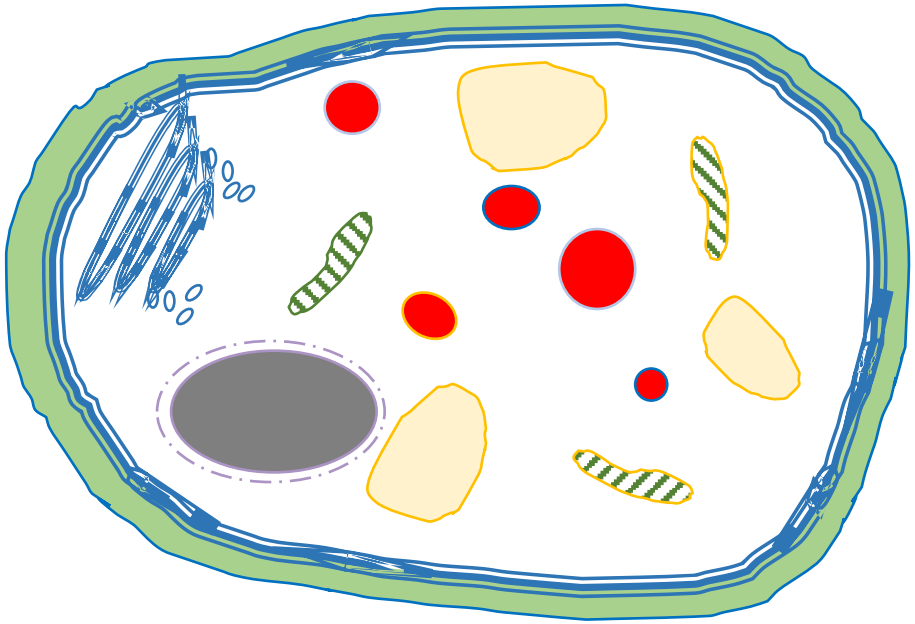
Fixation à l'ergostérol

Biosynthèse des acides nucléiques

6 classes d'antibiotiques

9 classes d'antiviraux

Les cibles d'action des antifongiques (infections invasives)



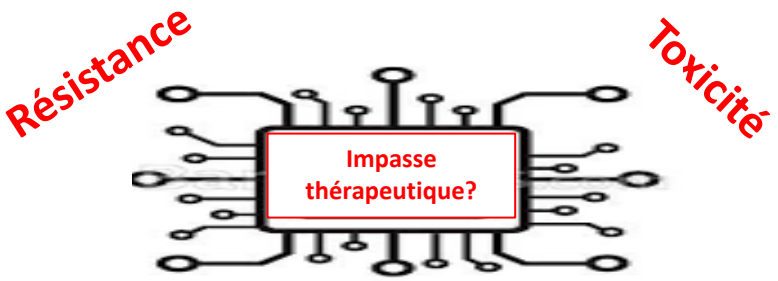
Paroi fongique
(β-1-3 glucane synthase)

Synthèse de l'ergostérol
(C14α déméthylase)

Fixation à l'ergostérol

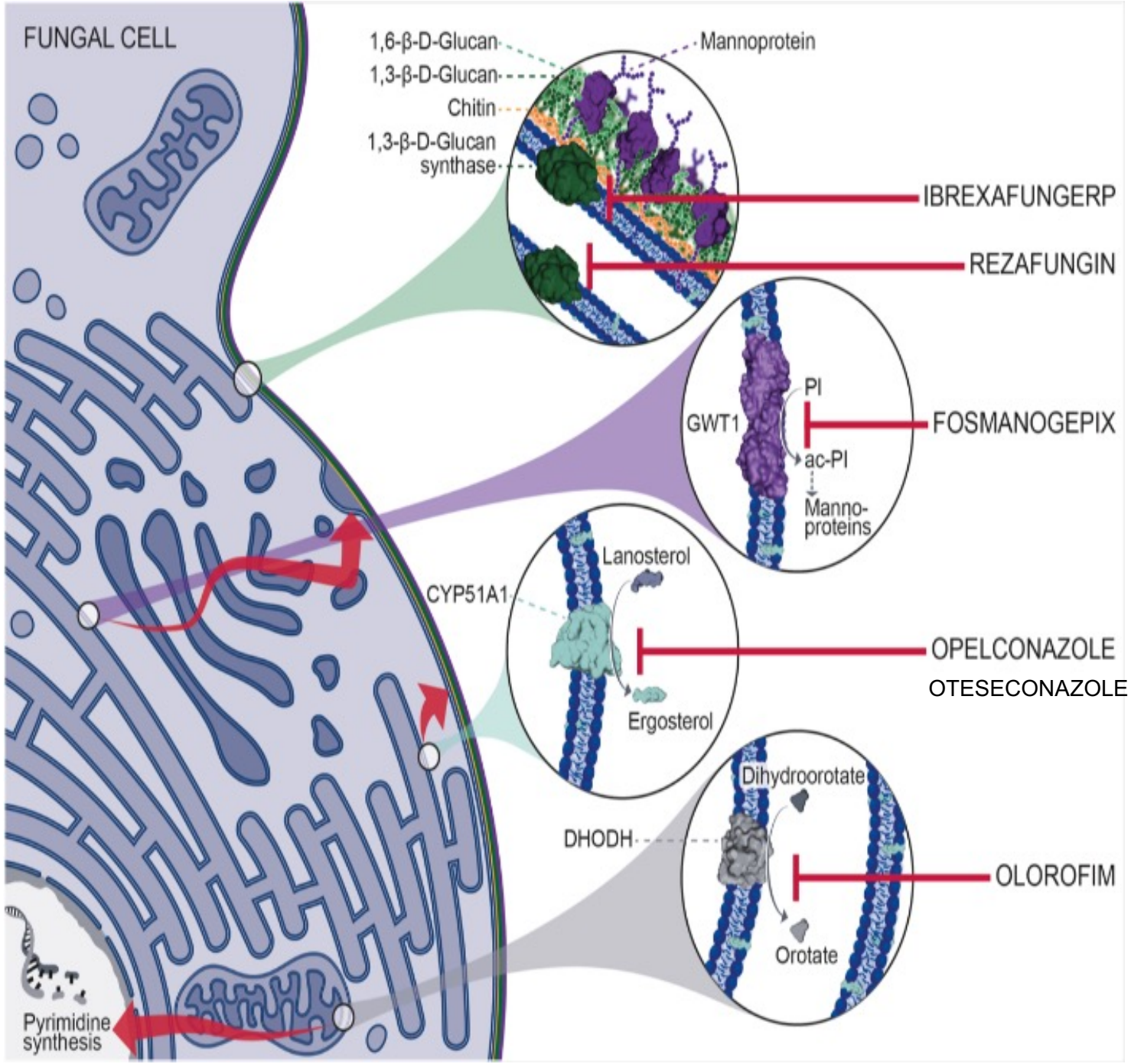
Biosynthèse des acides nucléiques

Résistance	Toxicité
FKS1, FKS2, FKS3	**hépatique**
CYP51A / ERG11	**hépatique**
+/- *(ERG11, ERG6, ERG3, ERG2)*	**rénale**
FCA1, FUR1, FCY21, and FCY22	**hématologique**



Interactions médicamenteuses

Nouveaux antifongiques



Triterpenoïde = inhibition de la βDGlucane synthase: levures++

Rezafungine = nouvelle échinocandine

Gepix = inhibition synthèse des mannoprotéines de la paroi: filamenteux, levures et mycoses endémiques

Opelconazole: Aspergillose
Oteseconazole: Candidose

Orotomide = inhibiteur de la dihydroorotate deshydrogénase: filamenteux

Adapté de Hoenigl et al., Drugs 2021

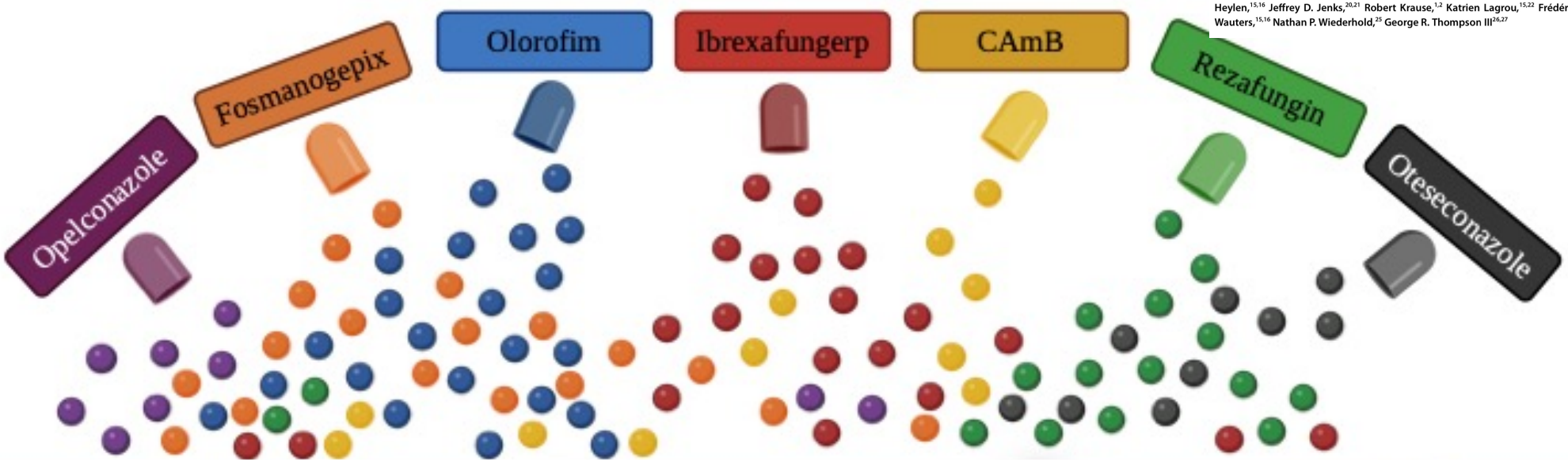
Nouveaux antifongiques

AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews 2024

Mycology | Invited Review

Novel antifungals and treatment approaches to tackle resistance and improve outcomes of invasive fungal disease

Martin Hoenigl,[1,2] Amir Arastehfar,[3,4] Maiken Cavling Arendrup,[5,6,7] Roger Brüggemann,[8,9] Agostinho Carvalho,[10,11] Tom Chiller,[12] Sharon Chen,[13,14] Matthias Egger,[1] Simon Feys,[15,16] Jean-Pierre Gangneux,[17,18] Jeremy A. W. Gold,[12] Andreas H. Groll,[19] Jannes Heylen,[15,16] Jeffrey D. Jenks,[20,21] Robert Krause,[1,2] Katrien Lagrou,[15,22] Frédéric Lamoth,[23,24] Juergen Prattes,[1,2] Sarah Sedik,[1] Joost Wauters,[15,16] Nathan P. Wiederhold,[25] George R. Thompson III[26,27]



Nouveaux antifongiques

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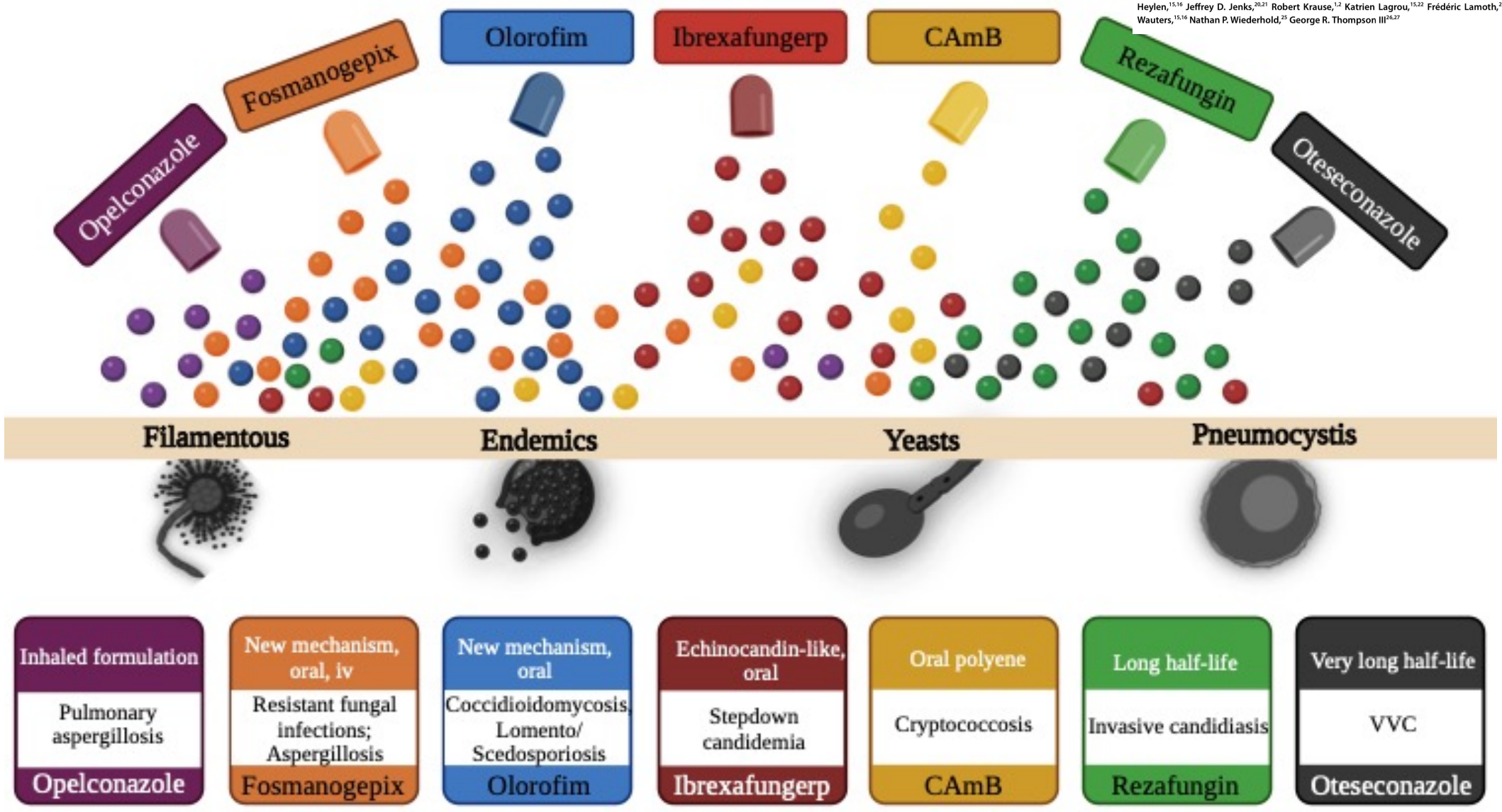
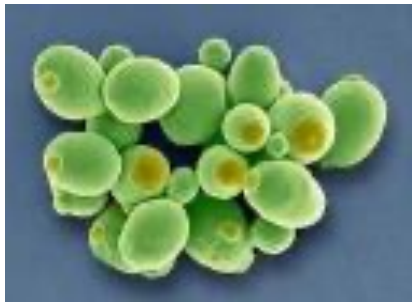


Nouveaux antifongiques



Candidoses

Autres germes sensibles

Ibrexafungerp

- ✓ *Candida dont C. auris*
- ✓ *C.* FKS R

Alternaria, Cladosporium, Pneumocystis,
Mycoses endémiques

Rezafungine

- ✓ *Candida dont C. auris*

Pneumocystis

Fosmanogepix

- ✓ *Candida dont C. auris*
- ✓ *C.* FKS R
- ~~*C. krusei*~~

Fusarium, Scedo-Lomentospora
Rasamsonia, Cladosporium, Paecilomyces
Scopulariopsis, Cryptococcus, Trichosporon
Exophiala, Malassezia,
Mycoses endémiques

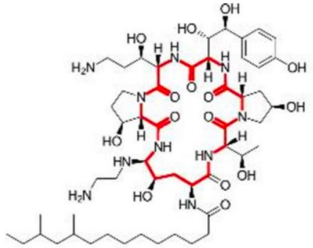
ARAf : Azole-Resistant *Aspergillus fumigatus*

Nouveaux antifongiques

Ibrexafungerp

Voie orale
IV

Caspofungine



Ibrexafungerp

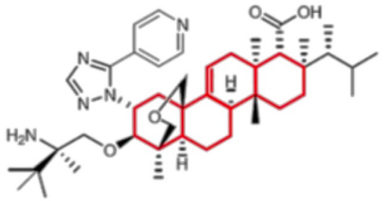
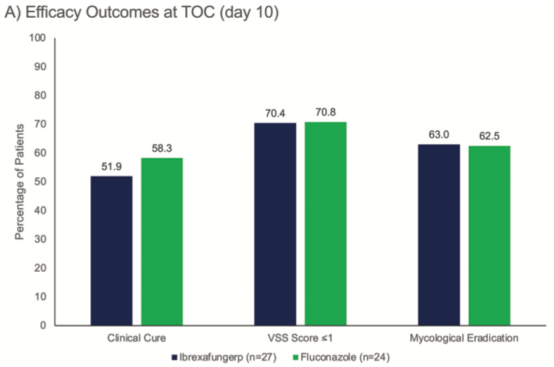
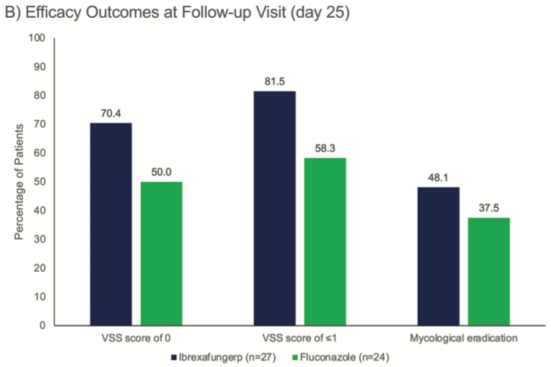
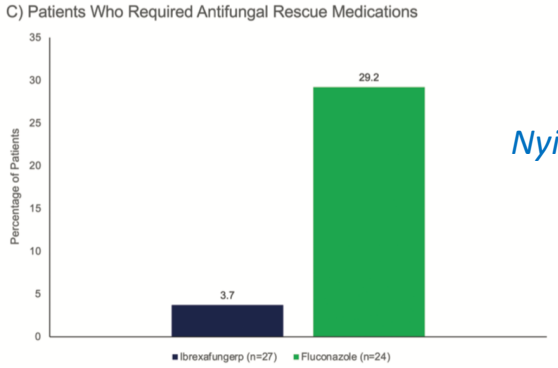


Figure 2. Molecular structures of caspofungin (**left**) and ibrexafungerp (**right**). Red structures indicate core structural components.

- ✓ 1er d'une nouvelle classe : les triterpenoïdes qui inhibent la synthèse de la βDGlucane synthase
- ✓ Indication dans la candidose vulvo-vaginale aigue et/ou récidivante en 1 prise (FDA USA, 2021)







Nyirjesy et al., CID 2022

- ✓ Phase III CARES : candidoses invasives à *C. auris*
- ✓ Phase II SCYNERGIA : IBX + Vori versus Vori dans l'aspergillose invasive
- ✓ Phase II FURY : IFI réfractaire aux autres ATF

Angulo et al., JoF 2022

Nouveaux antifongiques

Rezafungine

- ✓ Echinocandine de longue demi-vie (env. 150h après 2 injections)
- ✓ Phase III RESTORE : Candidoses invasives confirmées de l'adulte

Longue demi-vie
1 dose IV/semaine

Rezafungin versus caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial

Lancet 2023; 401: 49–59

George R Thompson III, Alex Soriano, Oliver A Cornely, Bart Jan Kullberg, Marin Kollef, Jose Vazquez, Patrick M Honore, Matteo Bassetti, John Pullman, Methee Chayakulkeeree, Ivan Poromanski, Cecilia Dignani, Anita F Das, Taylor Sandison, Peter G Pappas, on behalf of the ReSTORE trial investigators

Rezafungine (n=93)

Caspofungine (n=94)

1 IV – 400mg, semaine 1
Puis IV – 200 mg hebdomadaire

1 IV – 70mg, Jour 1
Puis IV – 50 mg quotidienne
Désescalade optionnelle fluconazole oral

Traitement: 14 à 28 jours

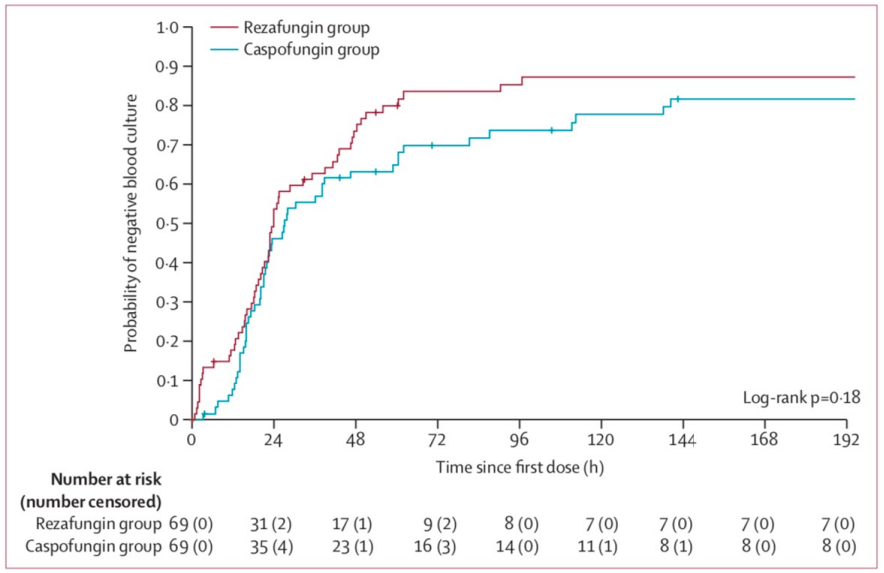


Figure 2: Time to negative blood culture after treatment with rezafungin versus caspofungin in the modified intention-to-treat population

	Rezafungin group (n=93)	Caspofungin group (n=94)	Treatment difference (95% CI)*
Patients with negative blood culture†			
24 h	36/67 (54%)	30/65 (46%)	..
48 h	49/66 (74%)	41/64 (64%)	..
Outcomes at the day 14 visit			
Global cure as assessed by DRC§	55 (59%)	57 (61%)	−1·1 (−14·9 to 12·7)¶
Mycological eradication	63 (68%)	62 (66%)	1·8 (−11·7 to 15·2)
Patients with candidaemia only	46/64 (72%)	47/67 (70%)	1·7 (−13·9 to 17·2)
Investigator assessment of clinical cure	62 (67%)	63 (67%)	−0·4 (−13·8 to 13·1)

- ✓ Phase III RESPECT : prophylaxie des IFI chez transplantés de cellules souches

Nouveaux antifongiques

Fosmanogepix

Voie orale
IV

✓ 1er d'une nouvelle classe : inhibiteurs de la synthèse des mannoprotéines (Gwt1 inhibitor)

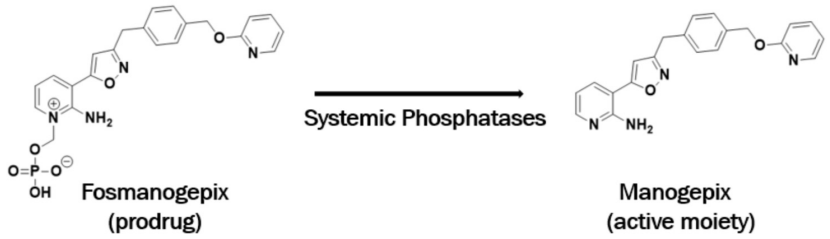
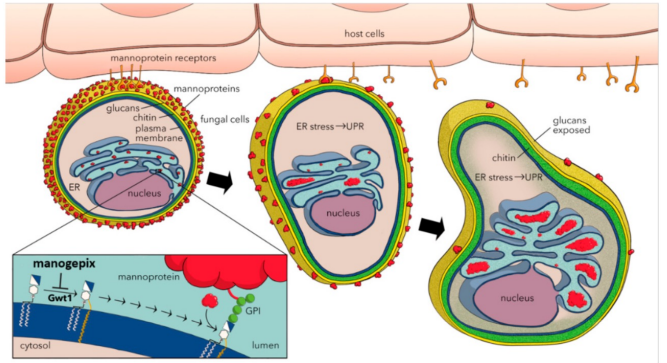


Figure 1. The structures of fosmanogepix and manogepix.



✓ Phase II: Candidose invasive
✓ Phase II: Candidose invasive à *C. auris*

Seiler & Ostrosky-Zeichner, Curr Fung Infect Rep 2022

Clinical Efficacy and Safety of a Novel Antifungal, Fosmanogepix, in Patients with Candidemia Caused by *Candida auris:* Results from a Phase 2 Trial

Jose A. Vazquez,[a] Peter G. Pappas,[b] Kenneth Boffard,[c] Fathima Paruk,[d] Paul A. Bien,[e] Margaret Tawadrous,[f] Eric Ople,[e] Pamela Wedel,[e] Iwona Oborska,[e] Michael R. Hodges[e]

AAC 2023

Mycological outcome	Total (*N* = 9)	no. of Participants by Treatment Outcome	DRC assessed treatment outcome
EOST			
Eradication	6	6	Treatment Success
Indeterminate	2	1: no EOST culture taken	Treatment Success
		1: death on Day 11	Treatment Failure
Recurrence	1[a]	1[a]	EOST Treatment Success, followed by early relapse
Follow-up period (2 and 4 wks after EOST combined)			
Eradication	7	1[a]	Recurrence at EOST, subsequently eradication (early relapse)
		6	Treatment Success sustained
Indeterminate	2	1 death on Day 11	Treatment Failure at EOST
		1 death on Day 36	Treatment Success at EOST, not sustained through follow-up
Recurrence	0		

[a]Patient with investigator-assessed mycological recurrence at EOST visit was assessed as treatment success followed by early relapse by DRC, because the single *C. auris* in blood culture was sampled 2 days after stopping study drug, *de facto* in the early follow-up period. All subsequent blood cultures were negative and assessed as eradication by the investigator. EOST, end of study treatment.

✓ Phase II: IFI à moisissures

Nouveaux antifongiques

Aspergilloses

Opelconazole

✓ ***Aspergillus* sp.**

~~***ARAf***~~

Olorofim

✓ **AR*Af***

Fosmanogepix

✓ **AR*Af***

Rezafungine

✓ **AR*Af***

ARAf : Azole-Resistant *Aspergillus fumigatus*

Nouveaux antifongiques

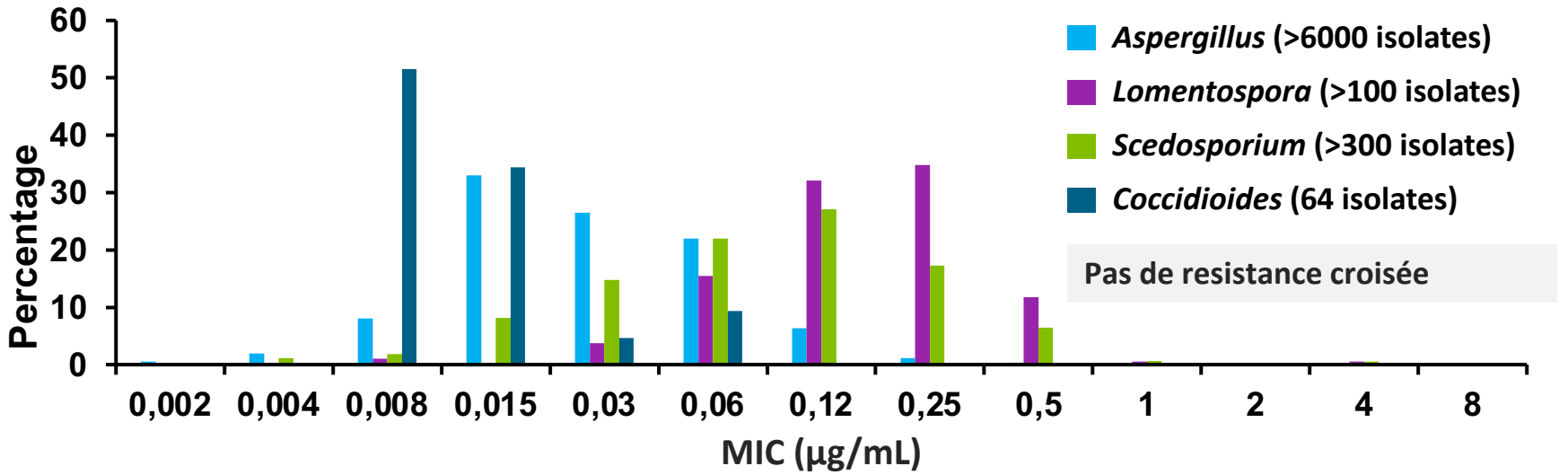
Aspergilloses et autres filamenteux

Opelconazole

- ✓ **Nébulisation**
- ✓ **Essai en cours en association avec ATF systémique dans l'aspergillose invasive**

Olorofim

- ✓ **Nouvelle classe des orotomides : inhibiteur de la dihydroorotate deshydrogénase**
- ✓ **Voie orale**
- ✓ **Phase III en cours : Olorofim versus AmB liposomale dans les IFI réfractaires**
- ✓ **Phase IIb en cours: sauvetage d'IFIF**



Fosmanogepix

- ✓ **Phase II: IFI à moisissures**

Hoenigl et al., Drugs 2021
Wiederhold, JoF 2020
Ribeiro-Menendez et al, JAC 2019

Approuvés. vs en essai

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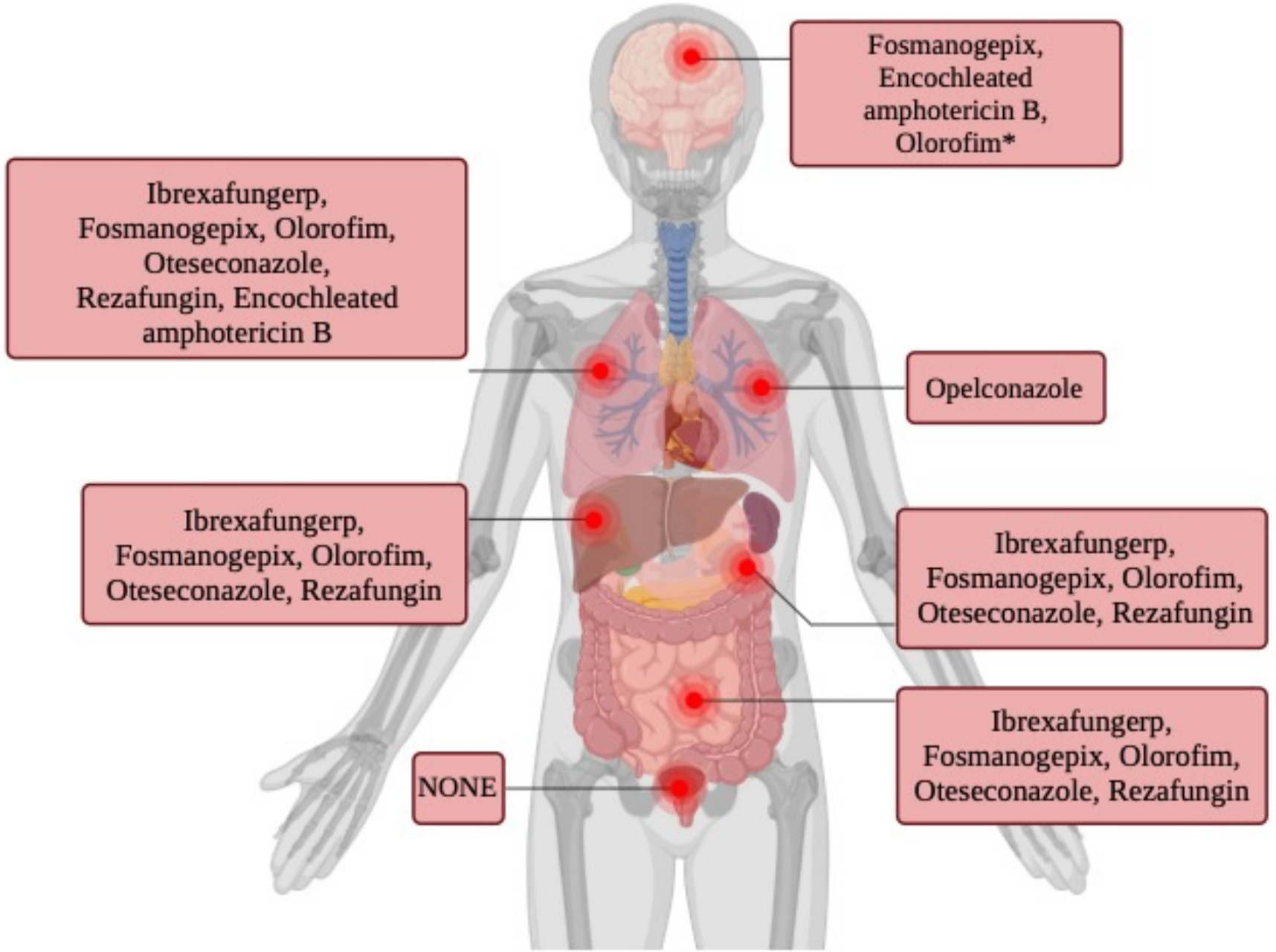
Substance	Latest study phase	FDA approval	EMA approval
Rezafungin	III Primary Tx for IC	✓ For Invasive Candidiasis	✓ For Invasive Candidiasis
Ibrexafungerp	III Stepdown Tx Candidemia	✓ For VVC	✗ Pending
CAmB	II	✗ Pending	✗ Pending
Oteseconazole	III Refractory VVC	✓ For VVC	✗ Pending
Olorofim	III (Salvage) Tx IA (OASIS)	✗ Pending	✗ Pending
Fosmanogepix	II	✗ Pending	✗ Pending
Inhaled formulations			
Opelconazole	III Refractory IPA	✗ Pending	✗ Pending
TFF Voriconazole	II	✗ Pending	✗ Pending
Substance	Latest study phase	FDA approval	EMA approval

Clinical trials timeline and approval status for novel antifungals.

Diffusion tissulaire



CMR 2024

Encore en développement…

Tétrazoles

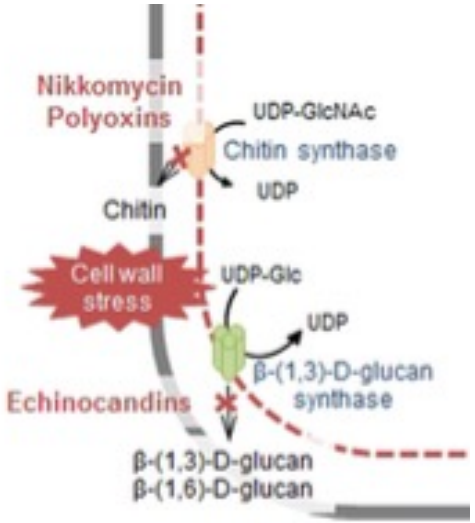
- ✓ **Otéséconazole : candidose vulvovaginale, dermatophytose**
- ✓ **Quilséconazole : cryptococcose neuroméningée**

Amphotéricine B encochlée

- ✓ **Voie orale**
- ✓ **Nanocristaux lipidiques => phagocytés par les macrophages**
- ✓ **Large spectre mais évaluée surtout dans les candidoses et cryptococcoses**
- ✓ **Faible toxicité rénale**

Nikkomycin Z

- ✓ **Premier d'une nouvelle classe d'inhibiteurs de la chitine synthétase**
- ✓ **Activité pré-clinique sur *Candida*, *Coccidioides* sp. et autres mycoses endémiques**



Gintjee et al., JoF 2020
Campoy & Adrio, Biochem Pharmacol 2017

Encore en développement…

Arylamidine

- ✓ **Inhibition des fonctions mitochondriales**
- ✓ ***Candida, Aspergillus*** **et autres moisissures**
- ✓ **Proche de la pentamidine**

HDAC Inhibitor

- ✓ **Inhibition de la « Fungal histone deacetylase » (HDAC)**
- ✓ **En combinaison avec un autre ATF**
- ✓ ***Candida*** **et** ***Aspergillus***

Gintjee et al., JoF 2020
Campoy & Adrio, Biochem Pharmacol 2017

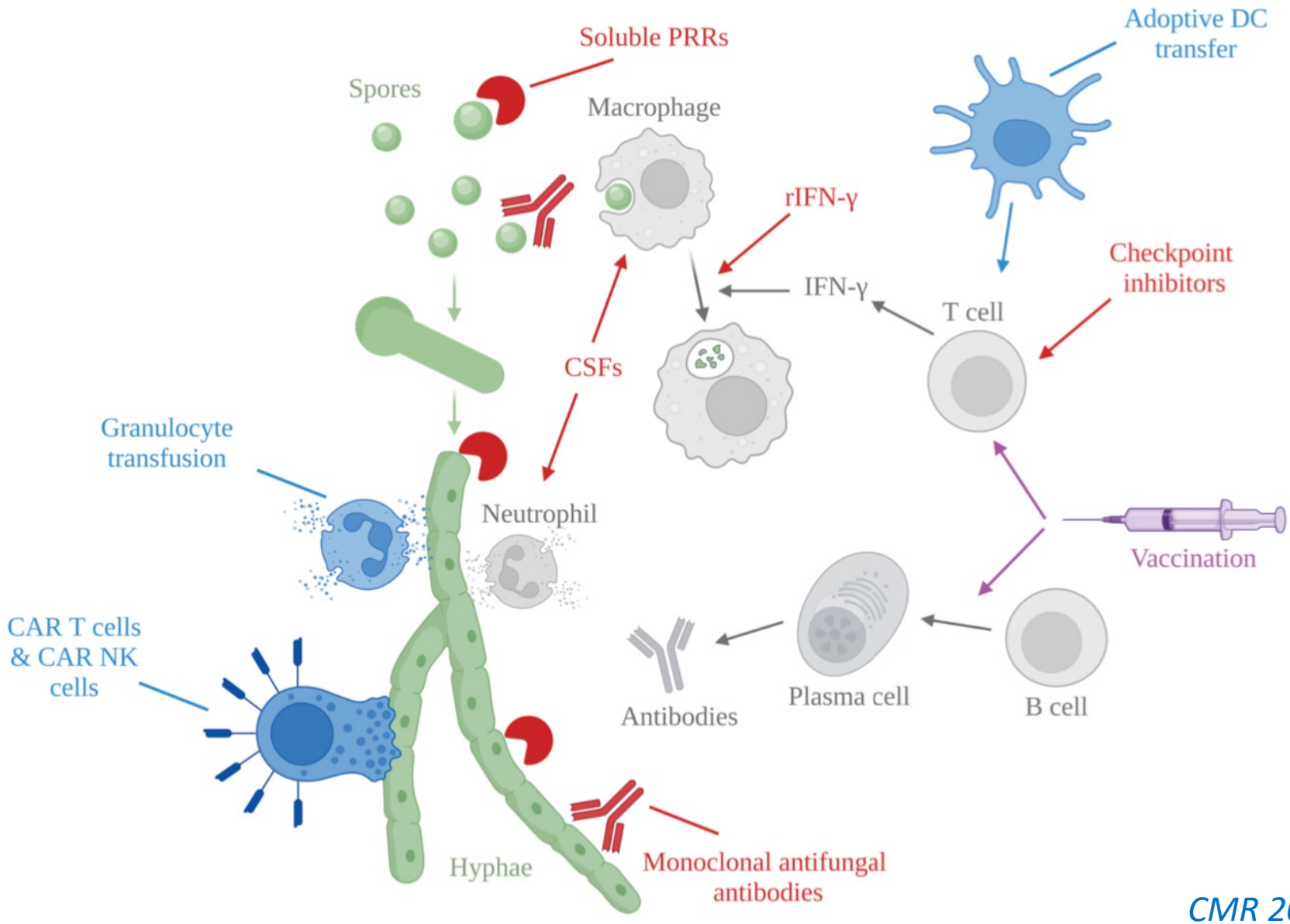
Autres pistes ?

Immunothérapie

Cellular immunotherapy

Molecule-based immunotherapy

Vaccination



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CHU Rennes

Centre d'Excellence Européen en Mycologie Médicale

European Confederation of Medical Mycology ECMM

Centre National de Référence Mycoses invasives et Antifongiques
Laboratoire associé sur les Aspergilloses chroniques LA AspC

Santé publique France