NEW ANTIFUNGALS IN DEVELOPMENT

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Outline

- Fungal infection scope
- Currently approved antifungals
- Antifungal needs
- Antifungal innovations
  - In clinical development
    - Existing target improvement
    - Novel target
  - In preclinical development

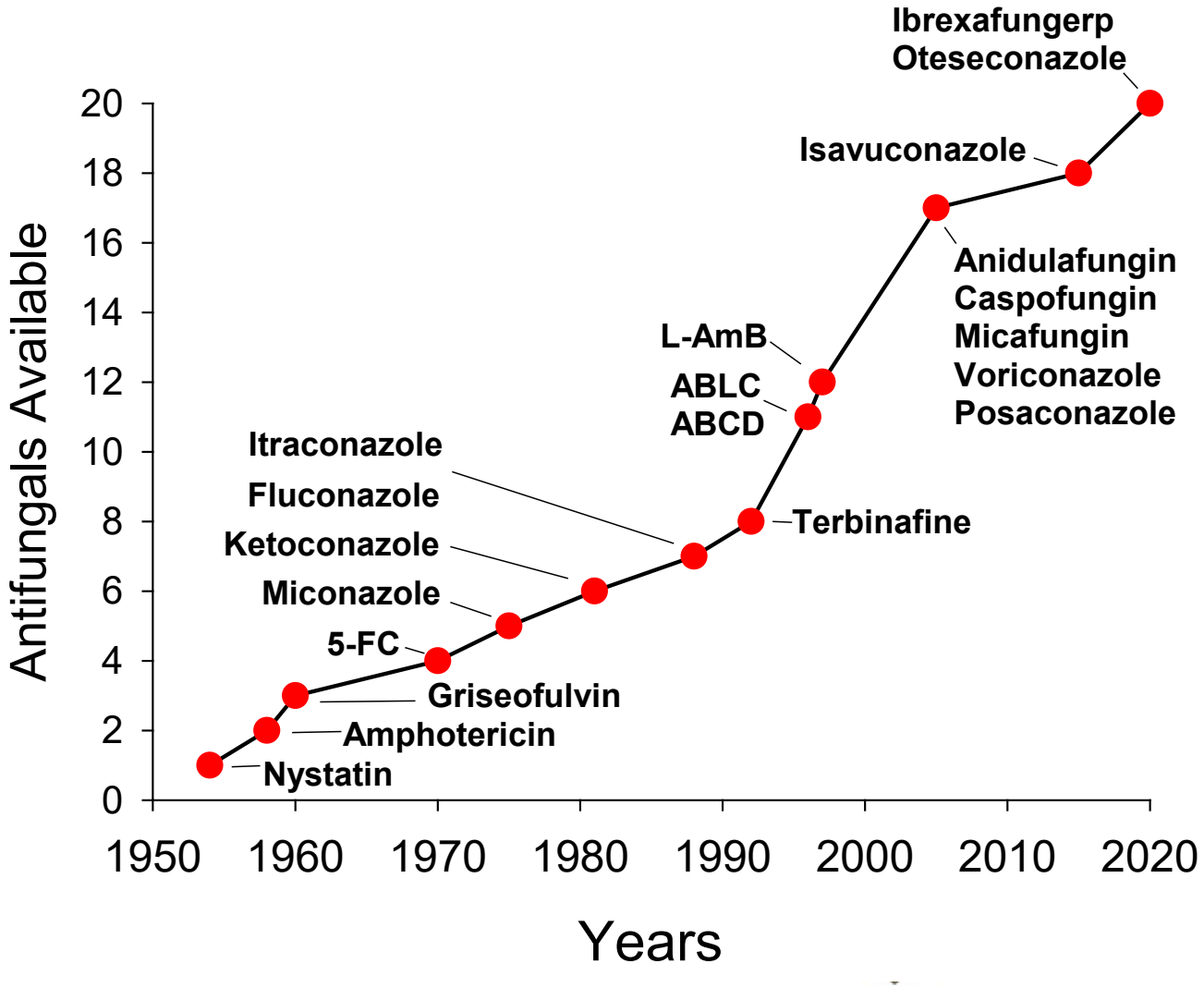
Worldwide Fungal Infections

>1 billion infections annually, 1.6 million deaths

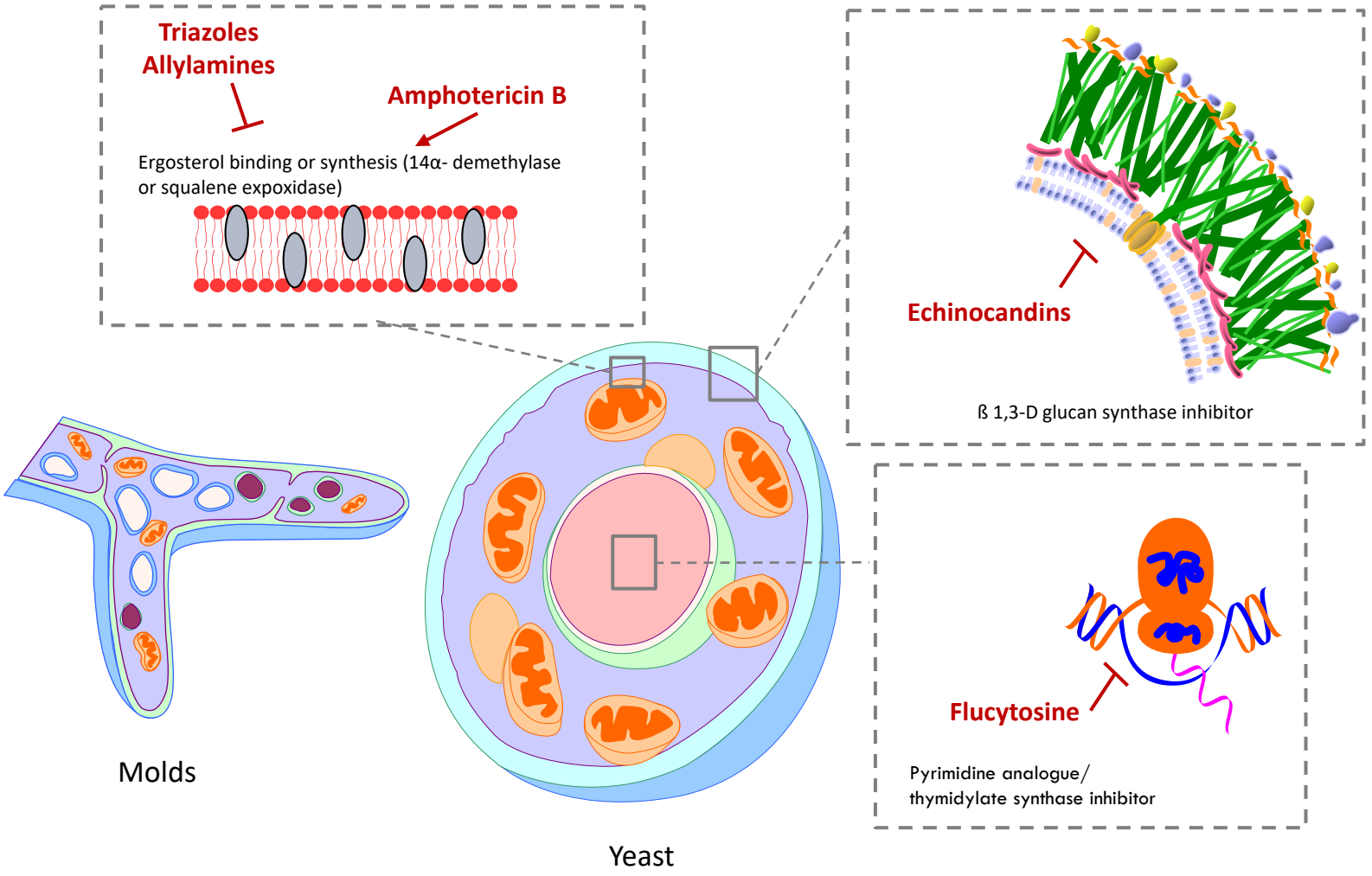
Fungal disease	Estimated cases per year	Estimated mortality
Cryptococcosis	>1,000,000	20%–70%
Candidiasis	>400,000	10%–75%
Aspergillosis	>200,000	30%–95%
Mucormycosis	>11,000	30%–90%
Blastomycosis	~3000	<2%–68%
Coccidioidomycosis	~20,000	<1%–70%
Histoplasmosis	~25,000	28%–50%
Paracoccidioidomycosis	~4000	5%–27%
Penicilliosis	>8000	2%–75%
Pneumocystis	>400,000	20%–80%

Adapted from Pianalto and Alspaugh, J of Fungi 2016

The Current Armamentarium



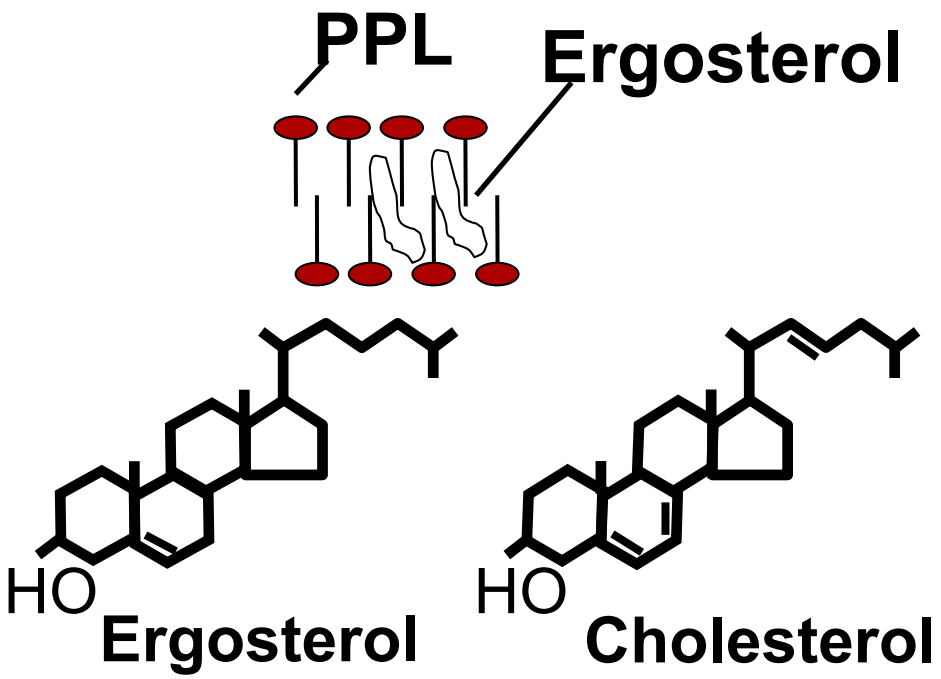
Current Antifungal Targets



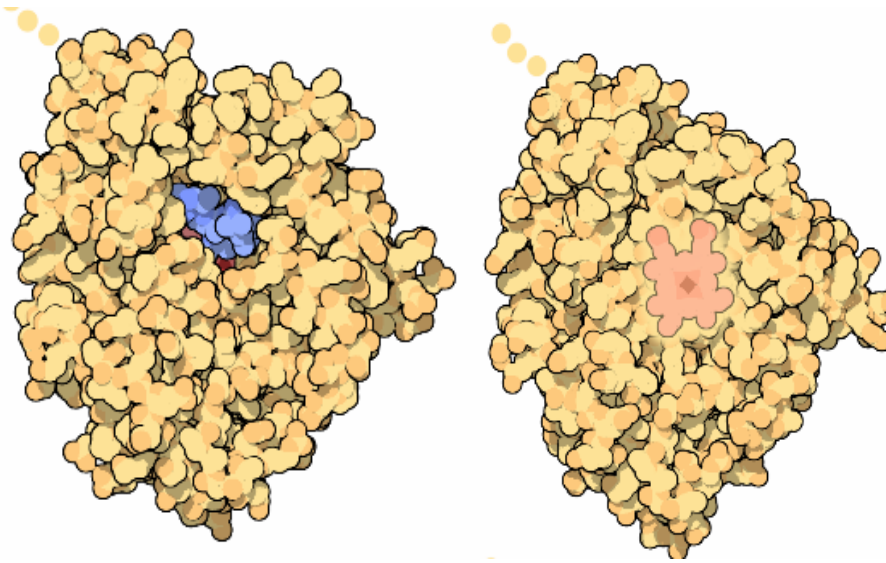
Challenging Efficacy vs Toxicity Bar

Eukaryotic conservation of cellular and metabolic biology limits exploitable fungal-specific drug targets

Cellular



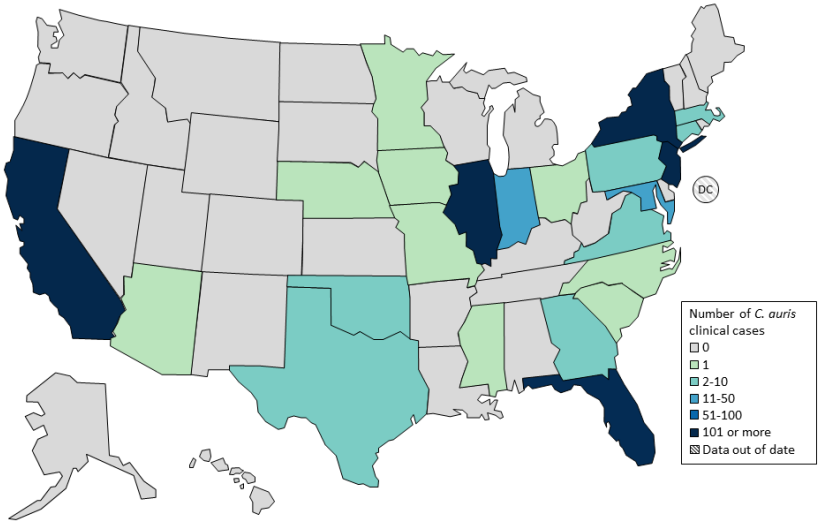
Metabolic



Homology of fungal and mammalian targets (e.g., P450 enzymes)

Emerging Resistance

- C auris
  - 80% azole-R, 30% MDR
  - >60% mortality



- C glabrata
  - Echinocandin-R 2-15%
- A fumigatus
  - Triazole-R 5-50% worldwide, US 5%
- Emerging mold pathogens with intrinsic resistance

CDC.gov
Toda MMWR Surveill Summ 2019
Alexander et al CID 2013
Wiederhold Curr Opin Infect Dis 2020

Drug Interactions and Toxicity

Interactions

- Triazole drug interactions
  - >80% hospitalizations
  - 20-60% contraindicated

Toxicities

- AmB
  - Renal insufficiency
    - >60%, reversible, reduces survival
- Triazole
  - Teratogenicity
  - Hepatitis 1-15%
  - Heart block - QTc prolongation
  - Voriconazole
    - Visual 30%, Skin, CNS, Bone

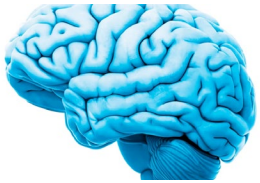
Andes et al AAC 2016

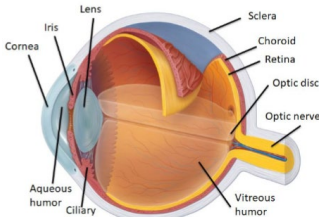
Pharmacokinetic Liabilities

- **CNS/Eye are common sites of fungal dissemination**
- **CNS/Eye are pharmacokinetic sanctuaries**

CNS/Eye Accumulation

- Fluconazole 80%
- Flucytosine 75%
- Voriconazole 60%
- **Everything else<1%**





Nett IDCNA 2016

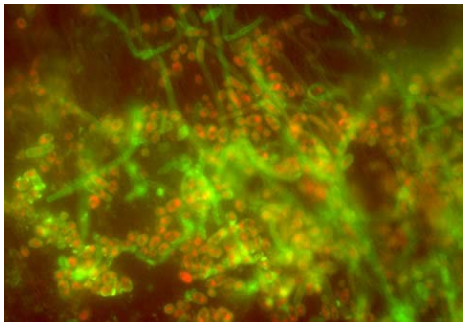
Antifungal Gaps

Intravenous Only

- Candins/AmB

Toxicity

- AmB>Azoles



Limited PK Distribution

- CNS/Eye

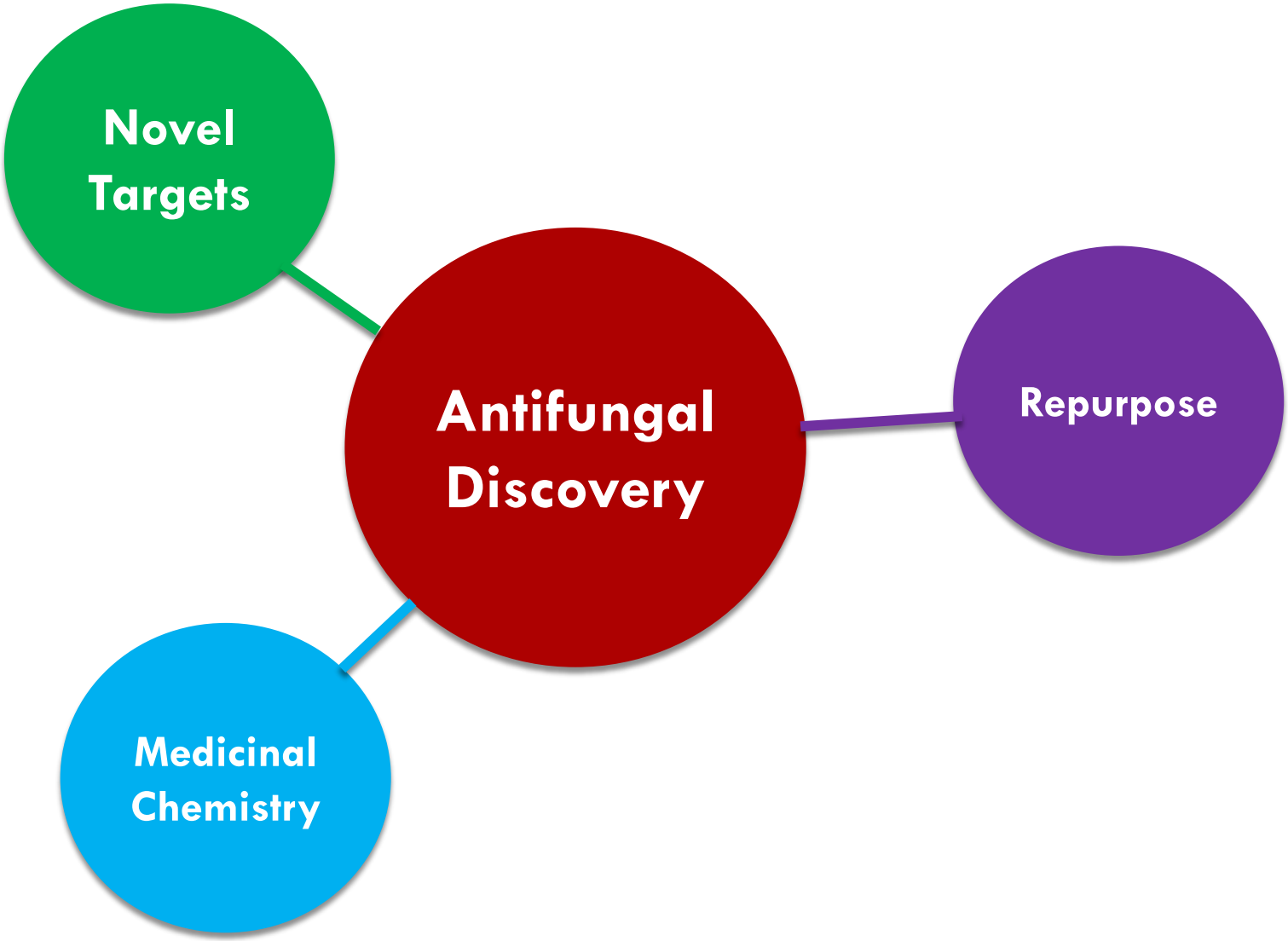
Drug Interactions

-Azoles

Emerging Resistance and Pathogens

- MDR C auris
- Candin-R C glabrata
- Azole-R Aspergillus
- Fusarium/Scedosporium/Zygomycetes

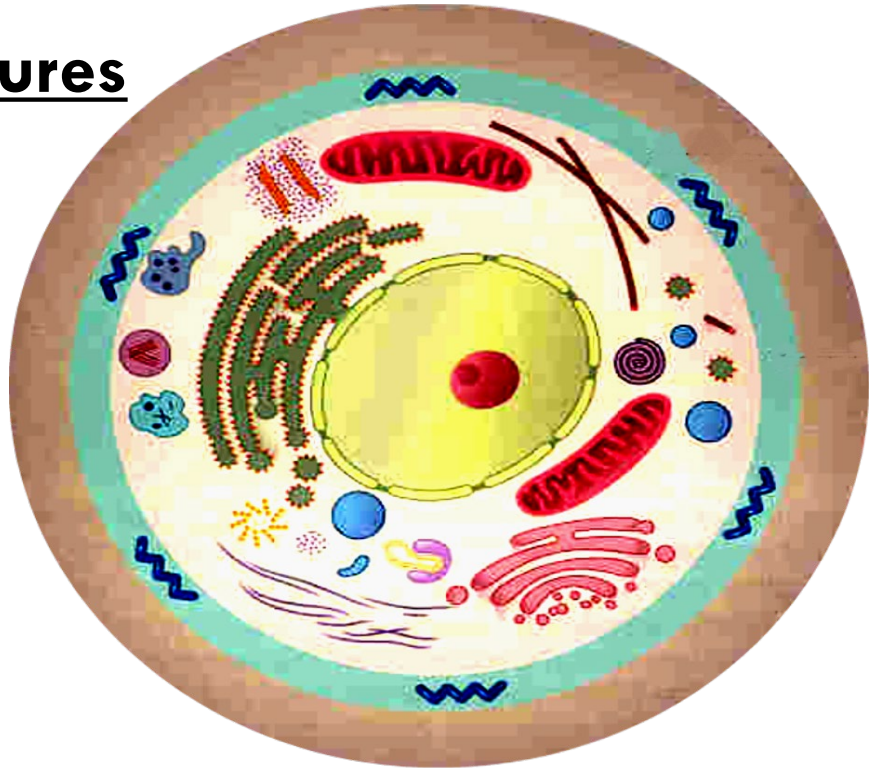
Antifungal Innovations



Antifungal Discovery Approaches

Similar Target
Improved Features

- Rezafungin
- Tolsura
- VT-1161
- MAT2203



Novel Target

- Ibrexafungerp
- Fosmanogepix
- Olorofim
- Nikkomycin
- T-2307
- MGCD290
- VL-2397
- Aureobasidin
- BHBM
- Turbinmicin

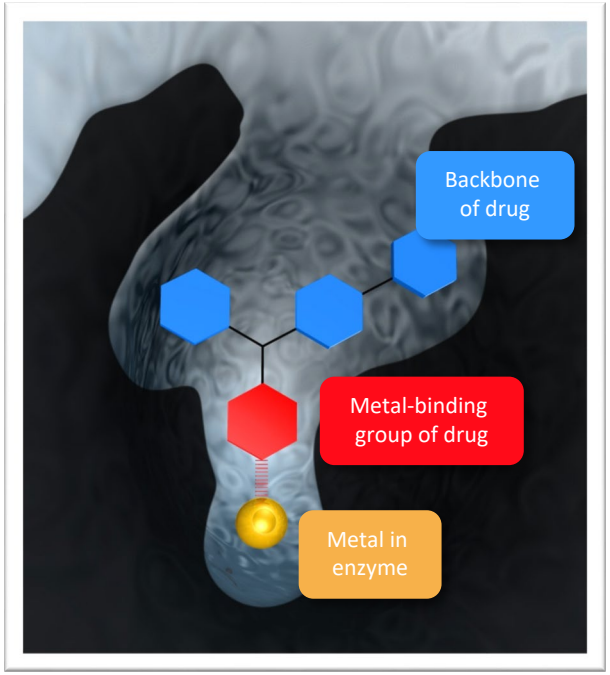
Repurposing

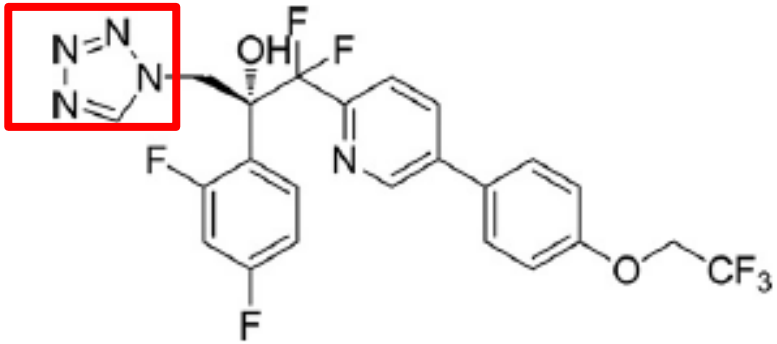
- AR-12
- Tamoxifen
- Sertraline

Pianalto and Alspaugh, J of Fungi 2016

Similar Target – Improved Features

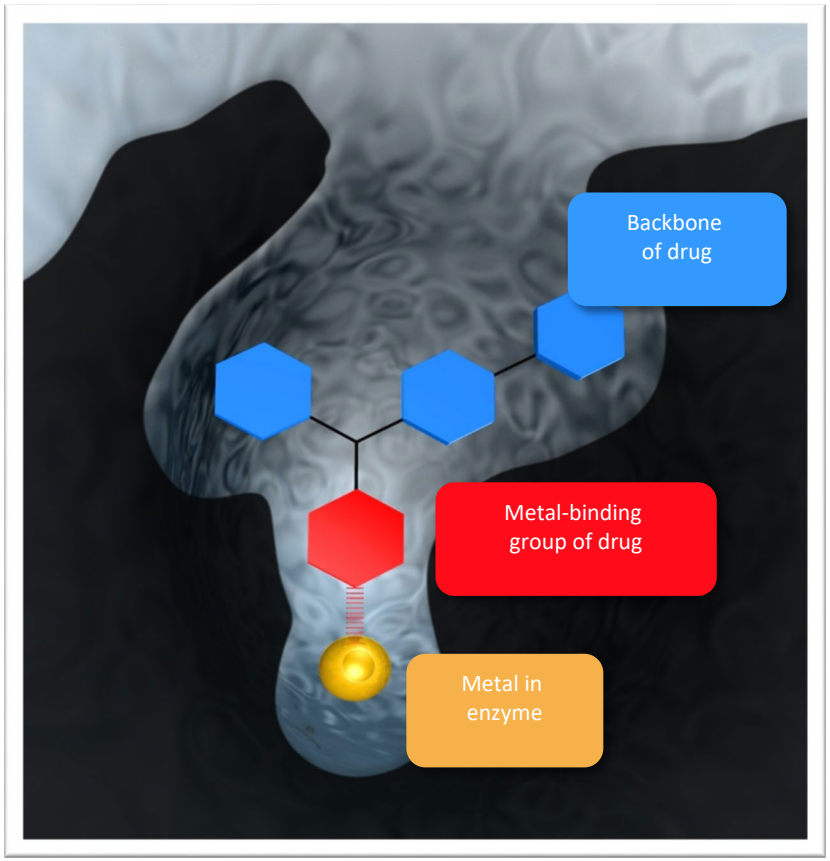
- **VT-1161(Oteseconazole)**
  - Tetrazole (next generation azole)
  - Designed for improved fungal CYP51 (lanosterol 14α demethylase) specificity
  - Spectrum Candida, dermatophytes, endemics
  - Improved pharmacokinetics
    - Half-life >48h
    - CNS penetration
    - Oral bioavailable (73%)
  - Fewer off-target effects
    - Minimal drug interactions
    - Predictable drug levels





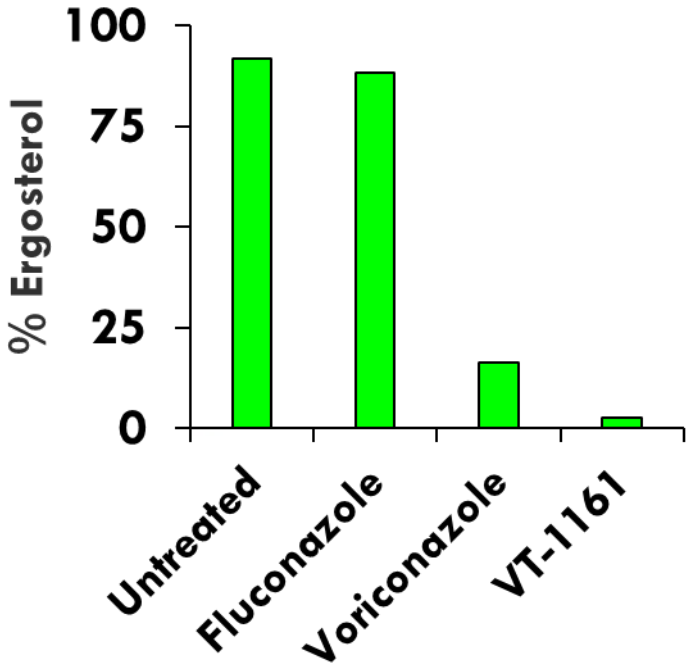
Warrilow et al. 2014 AAC

VT-1161(Oteseconazole) Mechanism of Action



CYP51 K_d *Candida*/human

Clotrimazole	2.1
Fluconazole	543
Itraconazole	4.8
Voriconazole	229
VT-1161	>2000



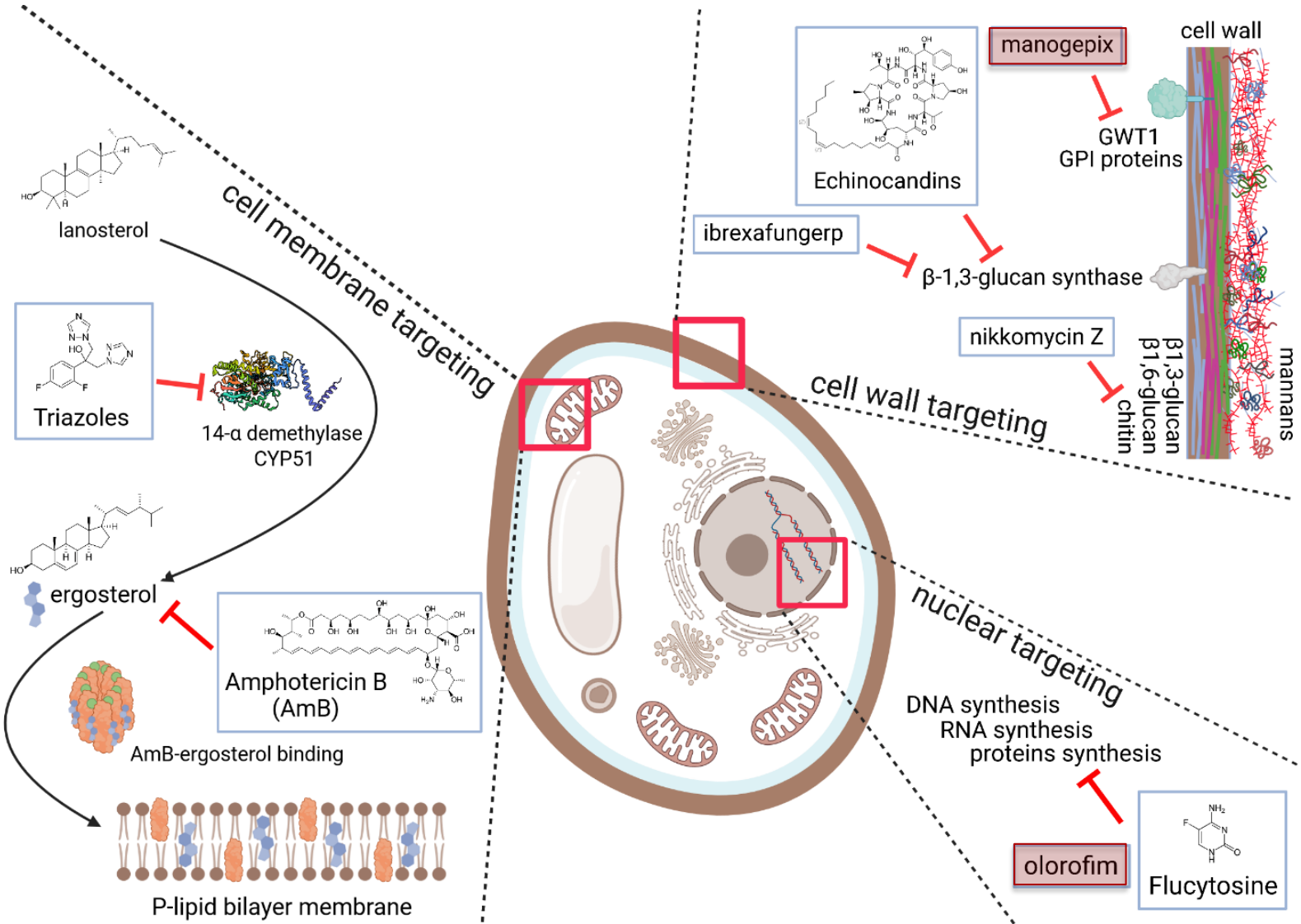
www.viamet.com/technology/overview.php, Warrilow et al. 2014 AAC

Oteseconazole (VT-1161)

7 trials listed in clinicaltrials.gov

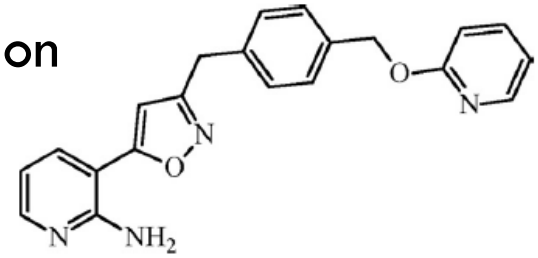
Indication	Preclinical	Phase 1	Phase 2	Phase 3	Comment
Vulvovaginal Candidiasis (acute/recurrent)				Phase 3 (VIOLET NCT03561701, ultra-VIOLET NCT03840616)	- Long half-life (superior to SOC for VVC) - Fewer DDI and toxicities
Onychomycosis Tinea pedis			Phase 2 (NCT02267356, NCT01891305)		

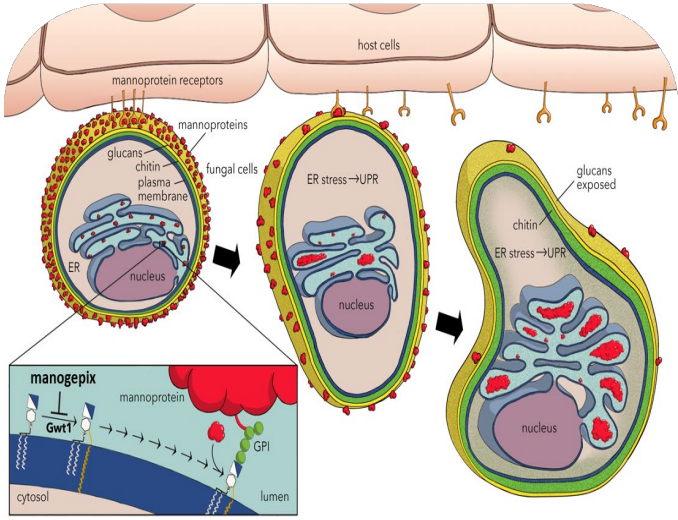
Novel Targets in Clinical Development



Novel Target

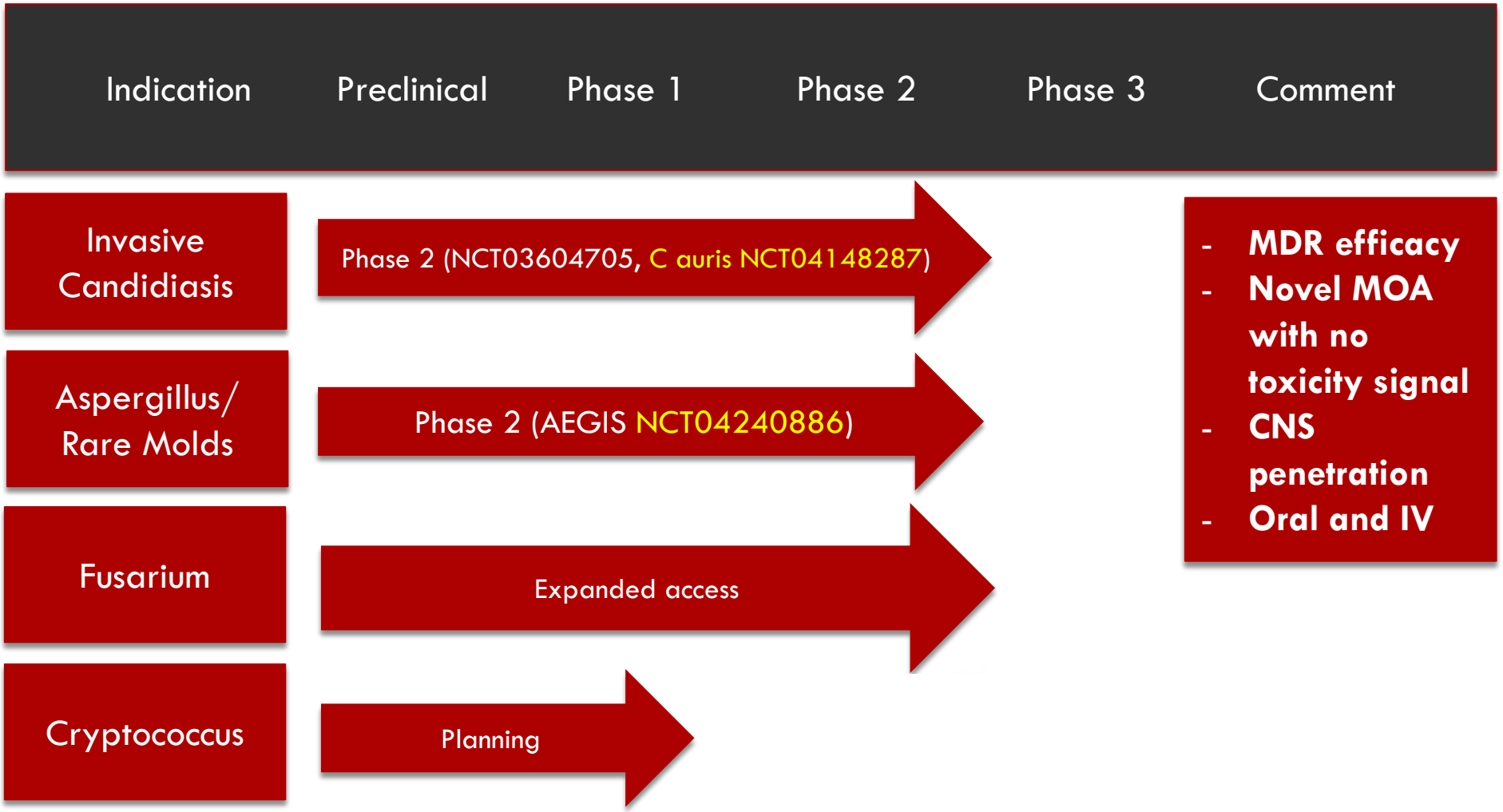
- **Fosmanogepix (APX-001)**
  - GPI inhibitor (Gwt1= GPI-anchored wall protein transfer protein 1 = inositol acyltransferase)
    No activity vs human ortholog Pig-W
  - Disrupts mannoproteins - cell wall integrity
  - Broad spectrum (Candida [except C. krusei] Aspergillus, Fusarium, Scedosporium, Zygomycetes, Endemics)
  - Oral (>90% bioavailable) and IV
  - >2d half-life
  - CNS/eye penetration





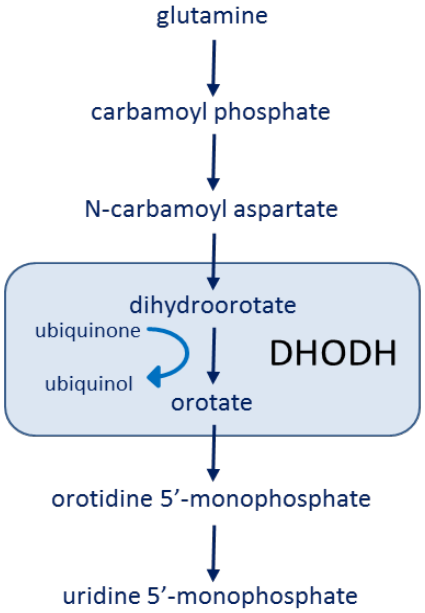
Fosmanogepix (APX-001)

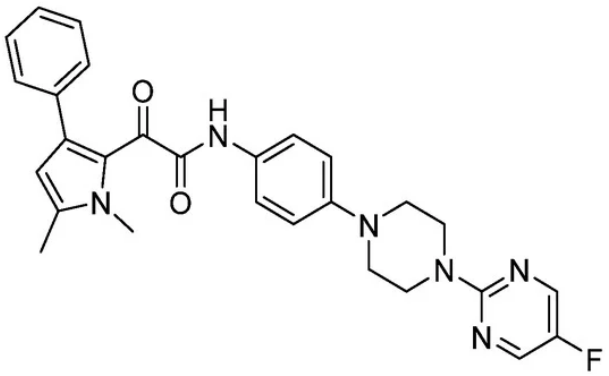
9 trials listed in clinicaltrials.gov



Novel Target

- **Olorofim (*F901318*)**
  - Orotamide class
  - DHODH (Dihydroorotate dehydrogenase) inhibitor - pyrimidine biosynthesis (DNA/RNA) 2000X less activity against human DHODH
  - Aspergillus, Scedosporium, Endemics, +/- Fusarium (Not *Candida/Zygomycetes/Cryptococcus*)
  - Oral (45-82% bioavailable) and IV
  - CNS penetration
  - CYP3A4 substrate (DDI risk)

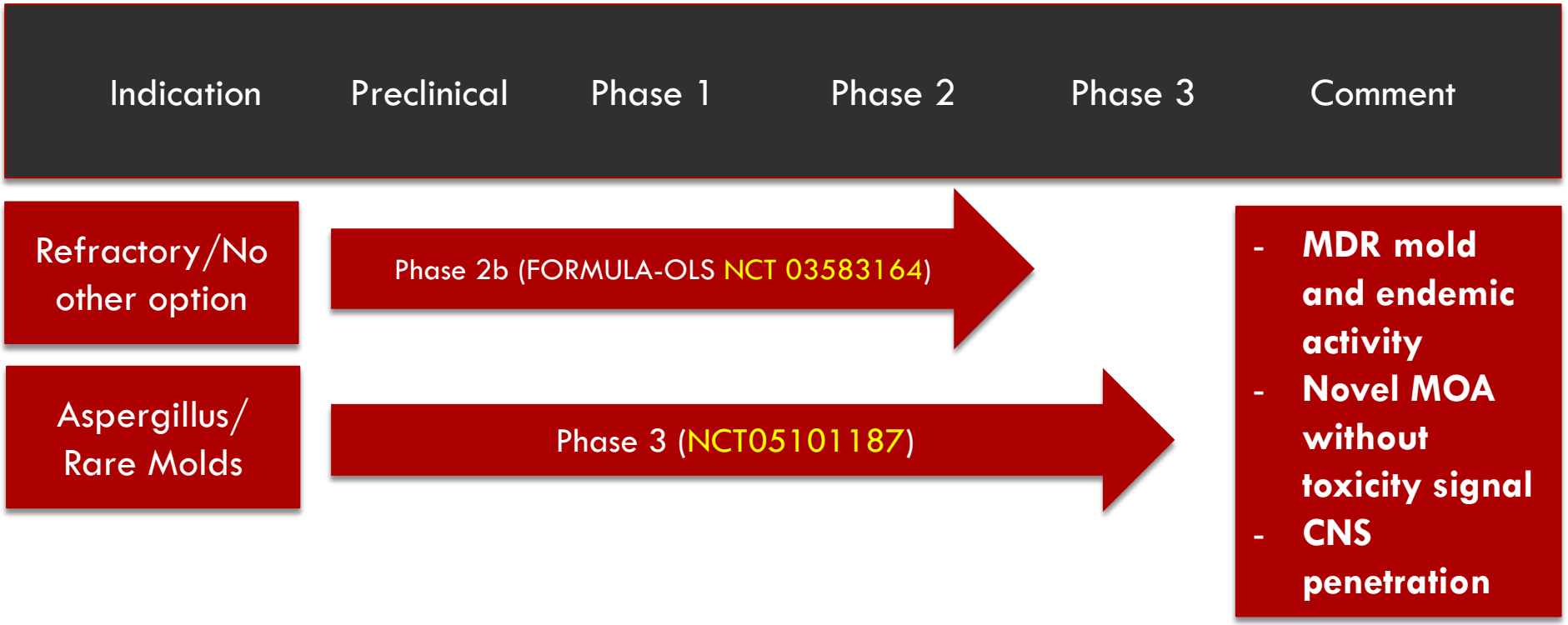




Oliver et al. PNAS 113:12809-14, 2016.
Beckmann et al. ICAAC 2015; Fothergill et al. ICAAC 2015; Buil et al.JAC 2017; Rivero-Menéndez et al ECCMID 2017; Oliver et al PNAS 2016; Jorgensen et al. TIMM 2017

Olorofim (F901318)

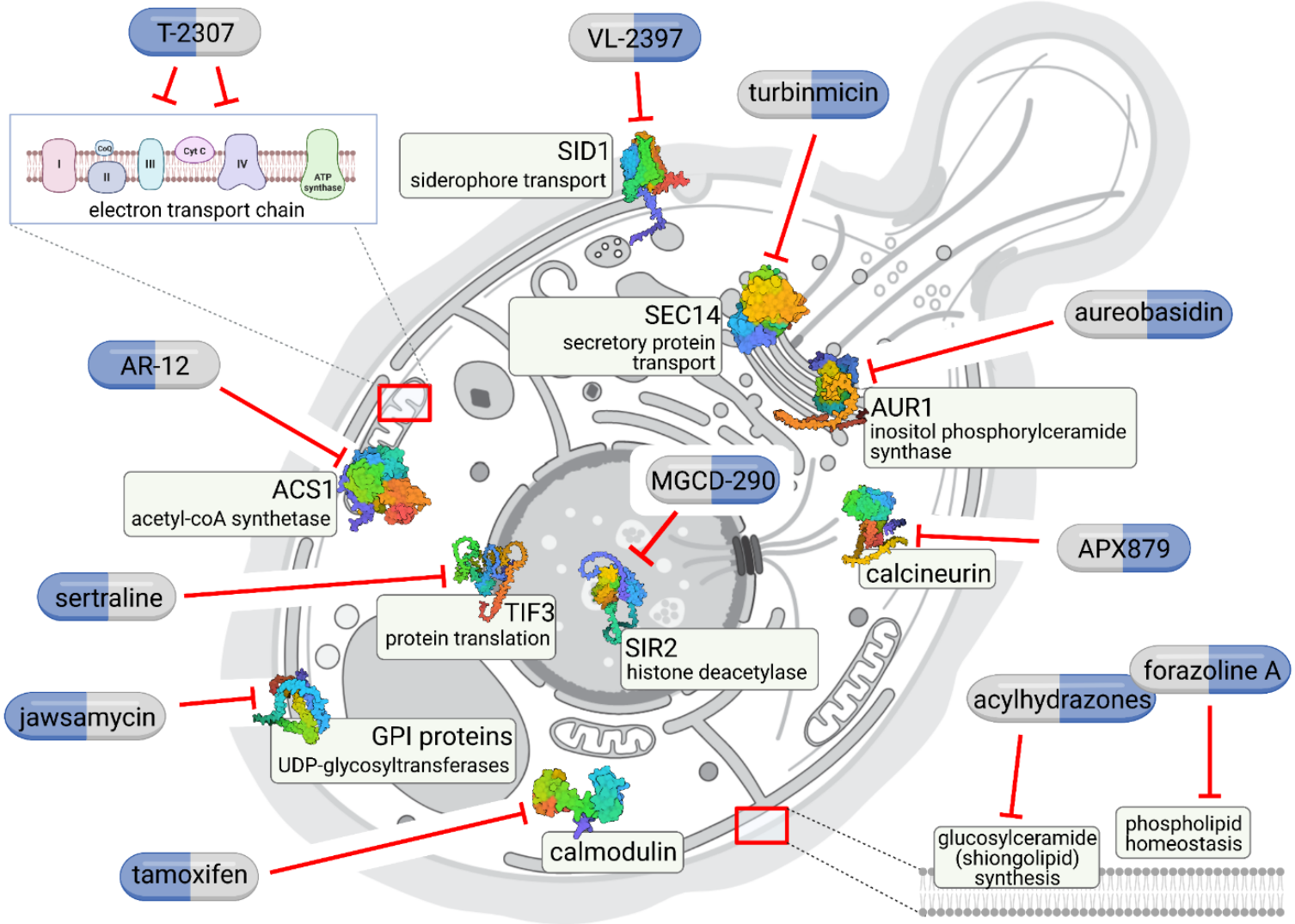
20 trials listed in clinicaltrials.gov



‘Near’ Antifungal Gap Checklist

	MDR Activity				Pharmacokinietcs				Toxicity
	Novel MOA	MDR Candida	A fumigatus	Other Molds	Oral	CNS/Eye	Urine	Interactions	Safety
Rezafungin	-	-	-	-	-	-	-	+	+
Ibrexafungerp	-	+/-	-	-	+	-	-	?	+
VT-1161	-	-	-	-	+		-	+	+
Fosmanogepix	+	+	+	+	+	+	-	?	+
Olorofim	+	-	+	+	+	+	-	?	+

New Antifungal Targets



Early Clinical Novel Target

Drug	Novel MOA	Spectrum	Study Phase
Nikkomycin	Chitin synthase inhibitor	Coccidioides	P2 stalled
T-2307	Mitochondrial membrane potential	Candida, Cryptococcus, Aspergillus	P1
MGCD-290	Histone deacetylase inhibitor	Candida, Aspergillus, Molds	P2 failed
AR12	Acetyl CoA synthetase inhibitor	Candida, Molds, Endemics	P1
VL-2397	SIT1 uptake (siderophore)	Candida, Aspergillus, Cryptococcus	P2 stalled

Preclinical Novel Target

Drug	MOA	Spectrum	Study Phase
Aureobasidin	Sphingolipid synthesis	Candida, Aspergillus, Cryptococcus	Preclinical
Turbinmicin	Vesicle transport	Candida, Aspergillus, Fusarium, Scedosporium	Preclinical
Forazoline A	Phospholipid homeostasis	Candida, Aspergillus	Preclinical
Jawsamycin	GPI inhibitor (UDP-glycosyltransferase)	Candida, Aspergillus, Mucor	Preclinical
APX879	Calcineurin inhibition	Cryptococcus	Preclinical
Acylhydrazones	GlcCer synthase inhibitor (sphingolipid)	Candida, Aspergillus, Cryptococcus	Preclinical
Australifungin	Sphingosine-N-acyltransferase inhibitor (sphingolipid)	Candida, Aspergillus, Cryptococcus	Preclinical

Summary

- Antifungal gaps
  - Emerging resistance
  - Challenging target (host toxicity and PK liabilities)
- Discovery innovation
  - Novel targets
  - Med chemistry
  - Repurposing
- Meaningful clinical development progress
- Fate of most ‘promising’ compounds unknown
- One-Health stewardship important for management of new antifungal options

Thank you!
Questions?

Thoughtful Reviews:

Rauseo et al. Open Forum Infect Dis 2019
Donlan and Meyers. Drug Discovery Today 2022
Mota Fernandes et al. Antimicrob Agents Chemother 2021
Heard et al. Curr Opin Biotech 2021