

Antifungal therapy: what comes out of the pipeline in the near future?

Professor William Hope

Centre for Antimicrobial Pharmacodynamics

University of Liverpool

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Disclosures

- William Hope holds or has recently held research grants with F2G, AiCuris, Astellas Pharma, Spero Therapeutics, Matinas Biosciences, Antabio, Amplyx, Allecra, Bugworks, NAEJA-RGM, AMR Centre, and Pfizer. He holds awards from the Medical Research Council, National Institute of Health Research, FDA and the European Commission. William Hope has received personal fees in his capacity as a consultant for F2G, Amplyx, Ausperix, Spero Therapeutics and BLC/TAZ.

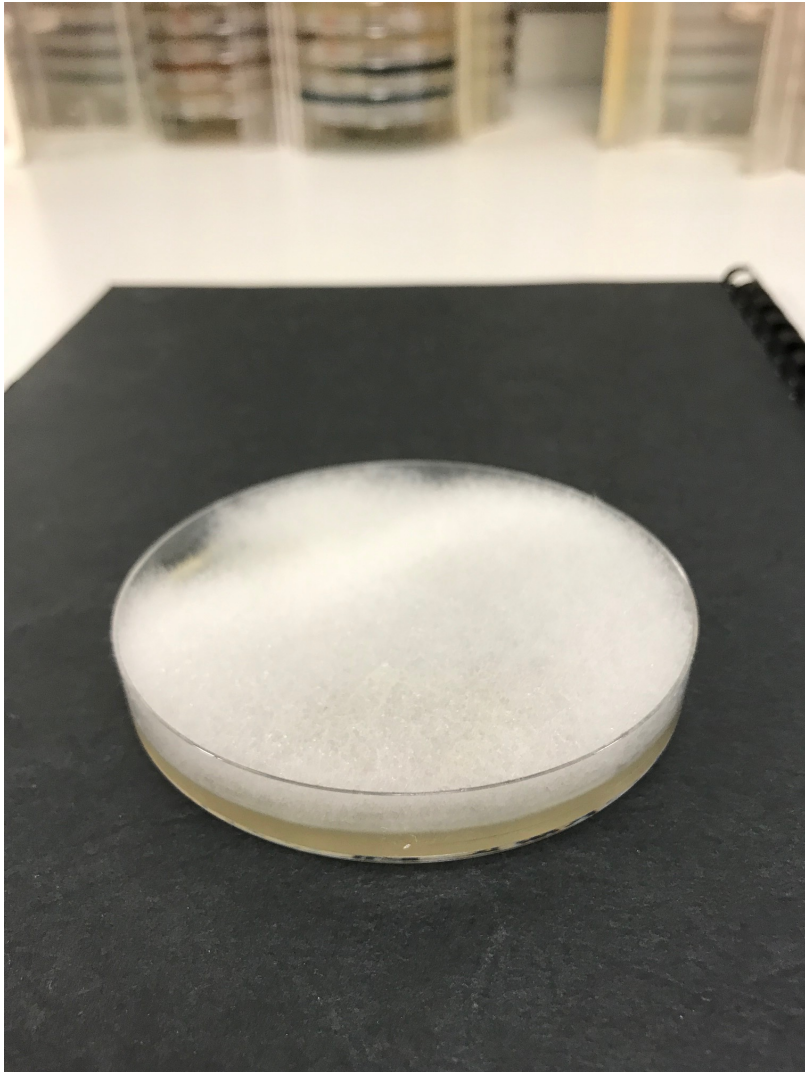
Firstly, a case from Liverpool (courtesy Dr Dav Taylor)

- 45 year old man with CML transforming to ALL
- BCR-ABL (Philadelphia chromosome) 7.1%. Treated with imatinib
- Induction with Flag-IDA. Cycle #1 uncomplicated
- Imatinib changed to ponatinib after 1st cycle (BCR-ABL 10.9%)
- 2nd cycle associated with *C. perfringens* bacteremia with hemolysis, multiorgan failure. Dialysis dependent.
 - eGFR approx. 40 with recovery
- On isavuconazole (empirically)
- Develops fever, raised CRP, pulmonary infiltrate

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Lichtheimia corymbifera



Overt hemolysis from clostridial sepsis

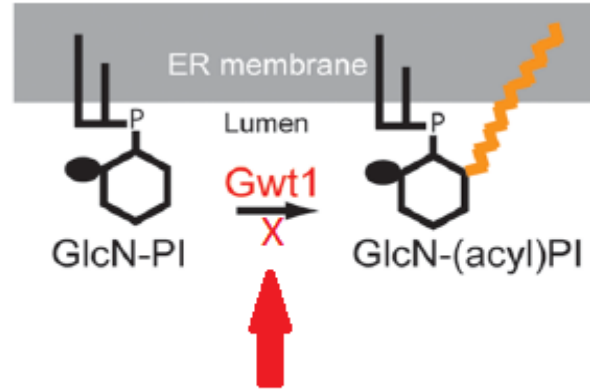
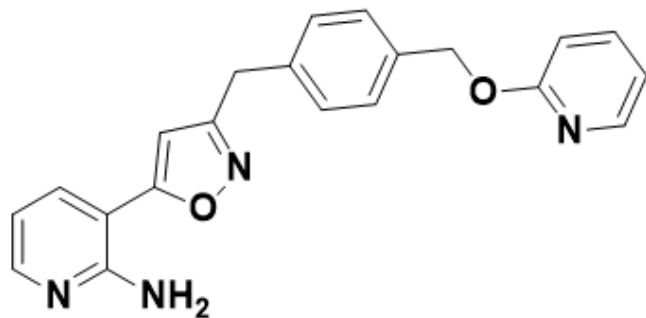
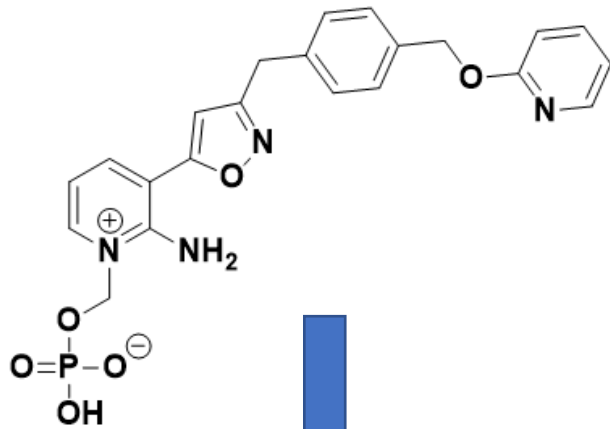


The case highlights current treatment challenges

- Antifungal resistance
 - Inherent resistance: e.g. Mucorales, *Lemontospora*
 - Acquired resistance : e.g. *Candida*, *Aspergillus*
- Antifungal drug toxicity
 - Polyenes (whether to risk liposomal amphotericin B)
- Drug-Drug interactions
 - e.g. triazoles and TKIs
- Too few agents for some common fungal diseases
 - (Mucorales)
 - Cryptococcal meningitis
 - *Candida* vaginitis

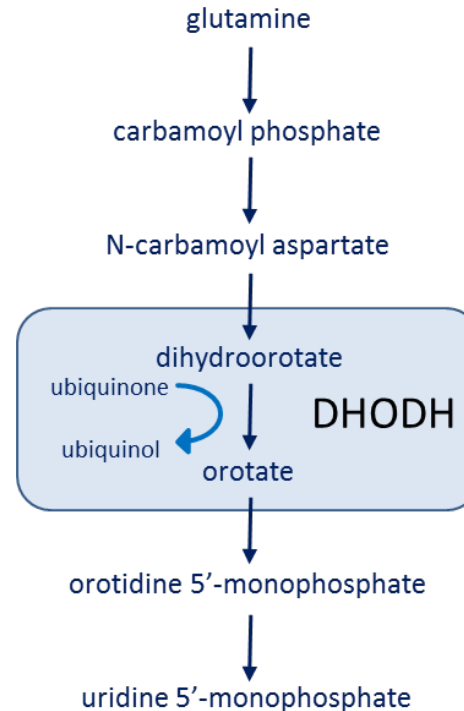
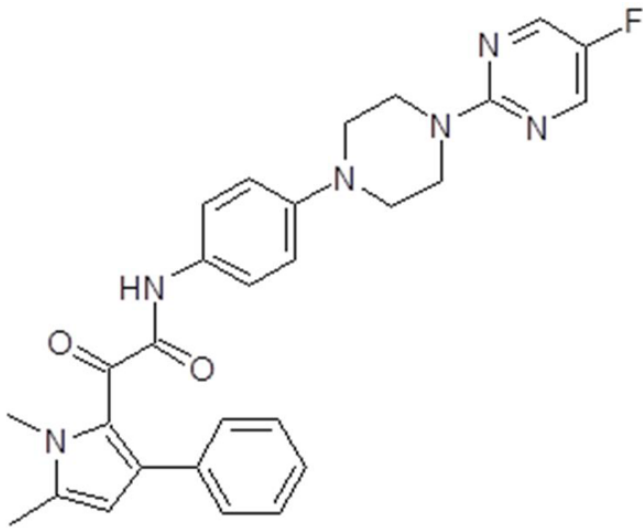
What agents are currently in development?

APX001 (Amplyx Pharmaceuticals)



- Oral and i.v. preparations
- Broad spectrum antifungal activity (yeasts & moulds)
- Concentration-dependent pharmacodynamics
- Oxidative metabolism
- Phase 2 studies
 - Invasive candidiasis/ candidemia

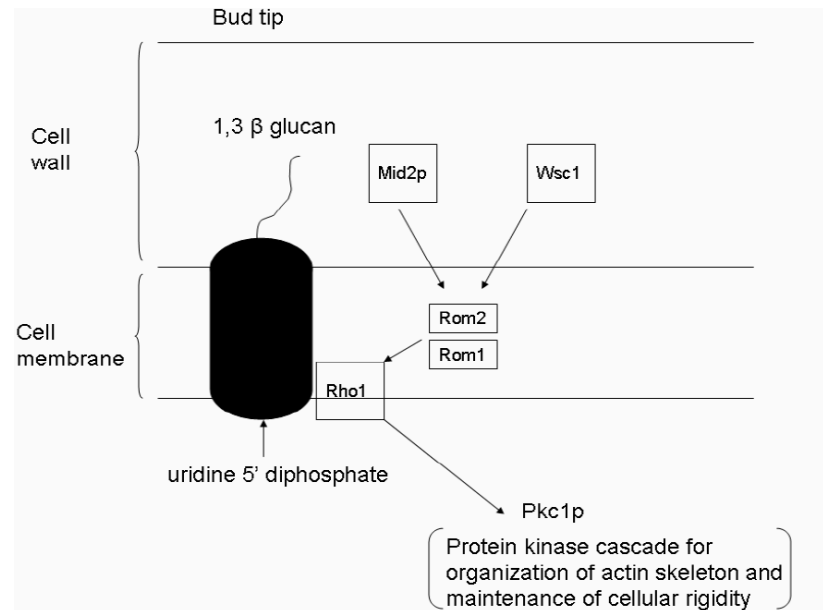
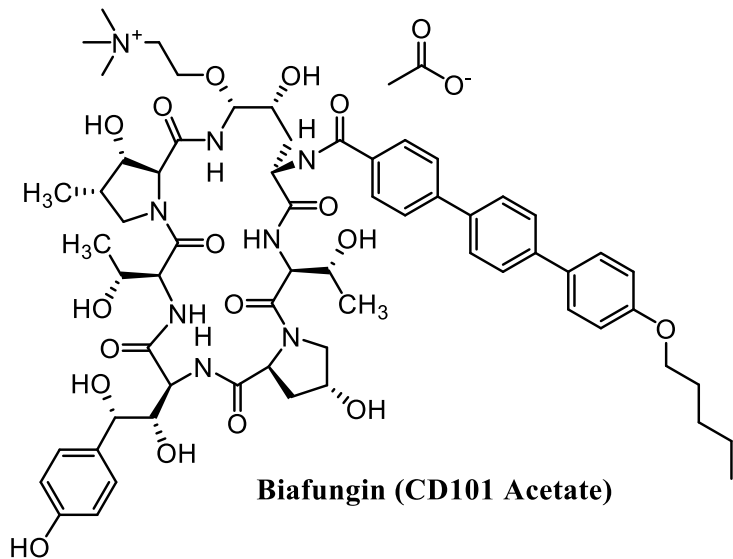
Olorofim (F2G Ltd.)



- Oral with i.v. in preparation
- Antifungal activity limited to moulds
- Time-dependent PD
- Oxidative metabolism via CYP3A4
- Phase IIb study enrolling

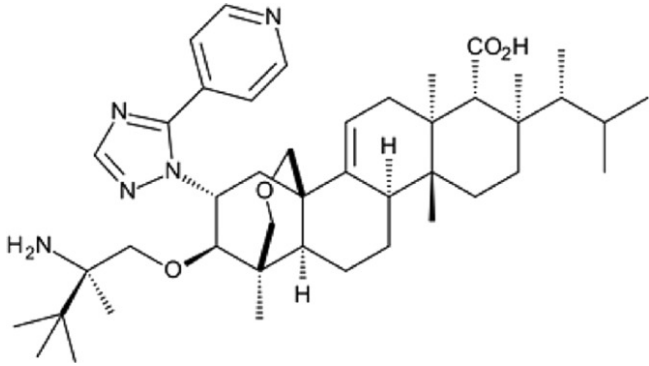
Oliver et al PNAS 2016 and Hope et al mBio 2017

Rezafungin (Cidara)

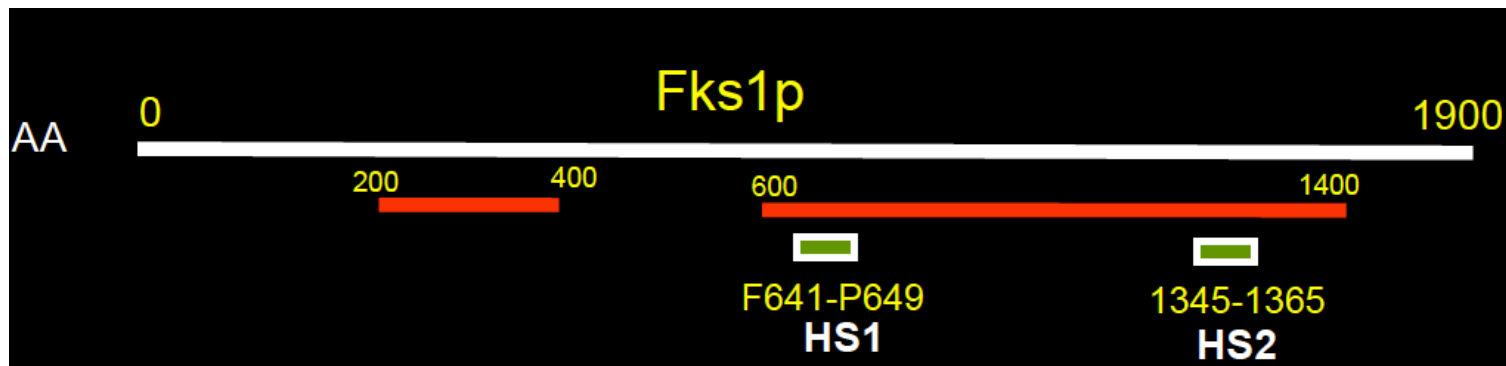


- i.v. only
- Activity against *Candida*, *Aspergillus* (and PJP)
- Concentration-dependent pharmacodynamics
- Phase 3
 - Invasive candidiasis

SCY-0870 (Scynexis)

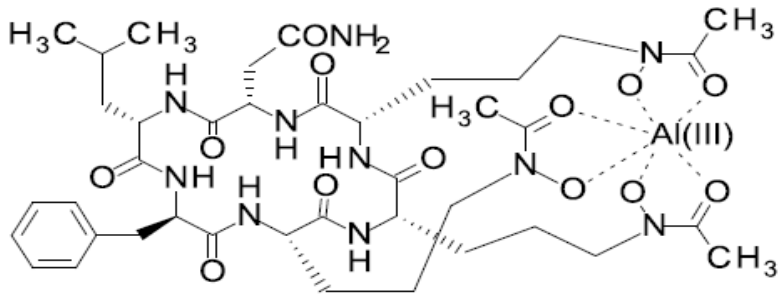


Glucan synthase binding site away from echinocandins

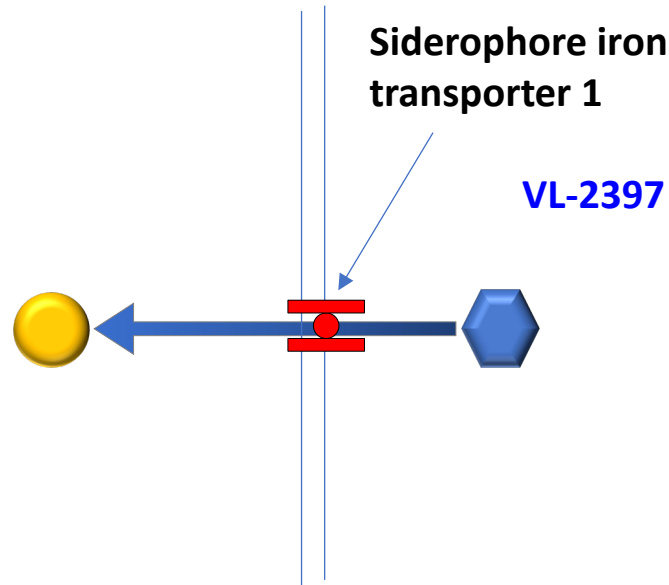


- Oral and i.v.
- Activity against *Candida* spp., *Aspergillus* spp. and PJP
- Oxidative metabolism via CYP3A4
- Clinical studies
 - Phase 2a Invasive candidiasis
 - Phase 3 vulvovaginal candidiasis
 - Phase 2 combination invasive aspergillosis
 - Open label refractory IFIs (FURI)
 - Open label *C. auris* (CARES)

VL-2397 (Vical); Note: development halted



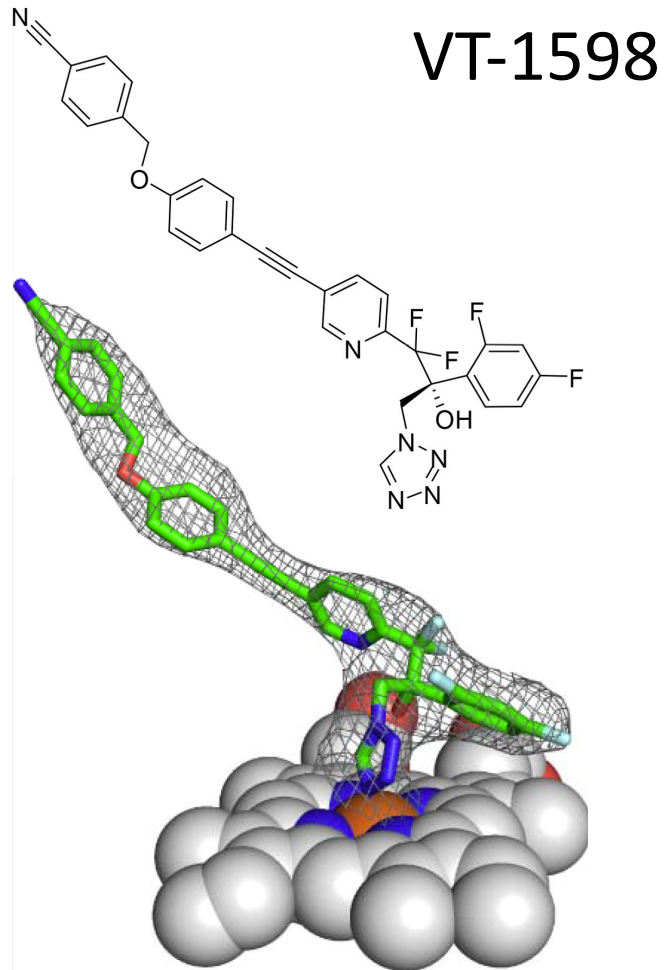
From *Acremonium persicinum*



- i.v. only
- Antifungal activity against *Aspergillus* spp., *C. glabrata*, *C. neoformans* and *Trichosporon asahii*
- Concentration-dependent PD
- Phase IIb study recently terminated

Rubino et al Open Forum Infectious Diseases 2017 4(Suppl 1) S473
and Kovanda et al AAC submitted

VT-1598 and VT-1161 (Mycovia Pharmaceuticals)



Hargrove et al AAC 2017 61(7)

In vitro and in some cases in vivo activity against

- *Cryptococcus neoformans*
- *Coccidioides* spp.
- *Candida auris*
- Triazole resistant *Candida albicans*
- *Aspergillus fumigatus*
- *Rhizopus arrhizus*

Wiederhold et al AAC 2018 62(4)

Wiederhold et al JAC 2018 73(2)

Wiederhold et al AAC 2019 63(3)

Nishimoto et al AAC Mar 25

Addressing current
treatment challenges ...

DDI and Toxicity

- For toxicity and DDIs studies/data remain incomplete for all compounds
- Will be an important determinant how these drugs are ultimately deployed

New agents for triazole-
resistant *Aspergillus* spp.

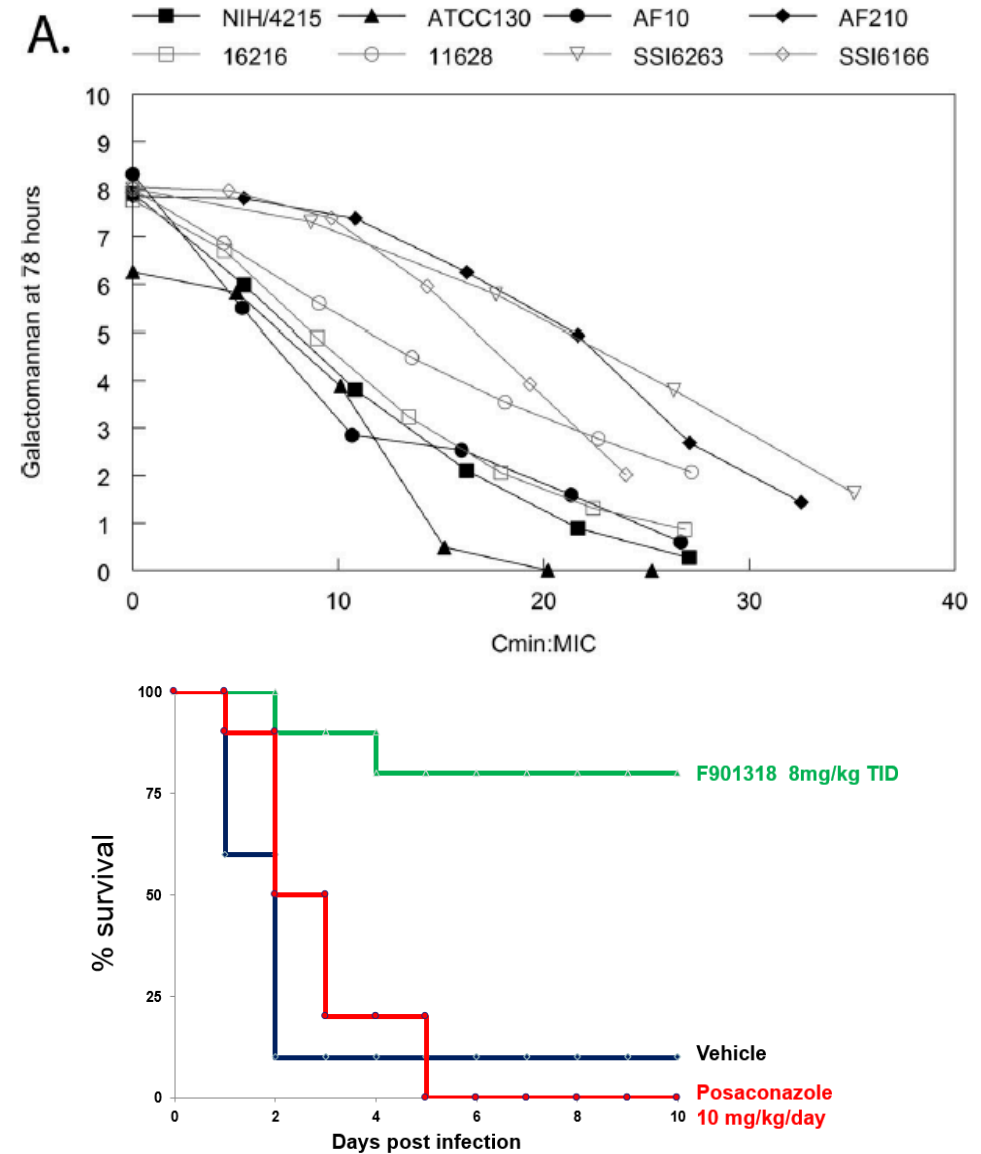
Antifungal drug resistance in *Aspergillus* spp.

- (Proven triazole resistance difficult to define and prospectively enroll)
- Suspected triazole resistance is easy and common...
- That is, a patient with
 - Triazole *prophylaxis* (posaconazole, voriconazole)
 - “Breakthrough” (fever and CT abnormality, GM negative (or positive), BAL is not done or not possible)
 - Reluctance to use a triazole for *treatment* (because of possible cross resistance)

Olorofim (Clinical Study enrolling; ClinicalTrials.gov Identifier: NCT03583164)

Isolate	cyp51A amino acid substitutions	F901318			
		Itraconazole	Posaconazole	Voriconazole	F901318
F6919	M220K	>8	>8	1	0.08
F7075	G54E	>8	>8	0.5	0.08
F11628	G138C	>8	2	8	0.04
F12219	G54R	>8	2	0.12	0.08
F12636	G54E	>8	2	0.25	0.04
F12776	Y431C	>8	2	2	0.08
F13619	H147Y G448S	8	1	>8	0.04
F13747	G434C	>8	1	2	0.08
F14403	G54R	>8	2	0.12	0.08
F16134	M220K	>8	>8	2	0.04
F16157	G54V	>8	2	0.5	0.04
F16216	L98H+TR	>8	1	4	0.04
F17294	L98H+TR	>8	1	4	0.04

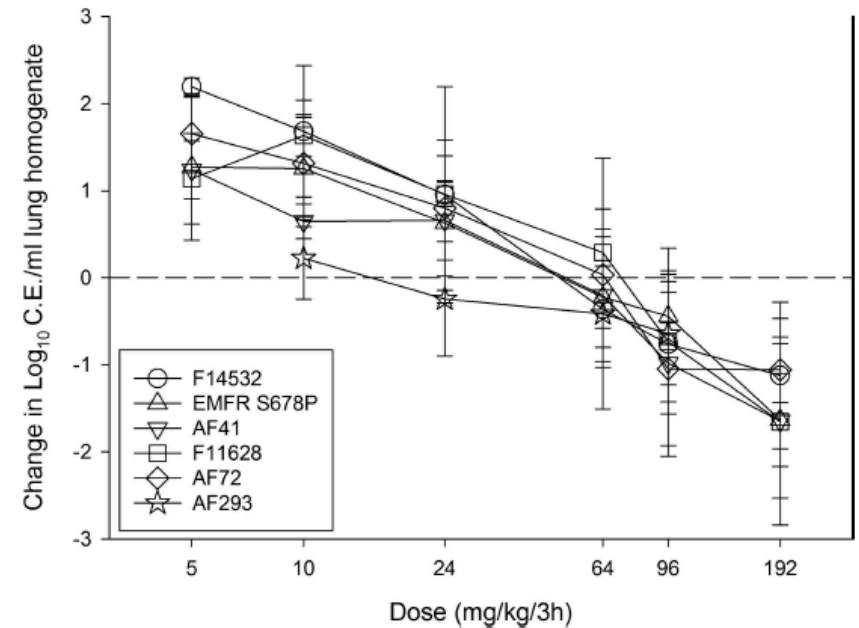
Hope at al mBio 2017 and Oliver et al PNAS 2016



APX001 (Clinical study in startup)

Species	Isolate no.	MIC/MEC ($\mu\text{g/ml}$) for ^a :						
		ITR	PSC	VRC	AMB	ANF	CSF	E1210
<i>A. fumigatus</i> SC	8686	>8	1	2	1	0.015	0.12	0.12
	8687	>8	1	2	1	0.015	0.12	0.06
	8688	>8	1	1	1	0.008	0.12	0.03
	8689	>8	1	2	1	0.015	0.12	0.06
	8690	>8	2	8	1	0.008	0.12	0.06
	8737	4	1	2	1	0.015	0.12	0.03
	8737	>8	1	0.25	1	0.008	0.12	0.03
<i>A. niger</i> SC	8698	4	1	2	1	0.008	0.12	0.008
	301	4	1	2	0.5	0.008	0.12	0.008
<i>A. terreus</i> SC	8731	4	2	>8	2	0.008	0.12	0.015

Pfaller et al AAC 2011 55(11)



Strains are triazole WT and Cyp mutants with higher triazole MICs

Zhao et al AAC 2019 63(4)

VL-2397 (clinical study terminated for invasive aspergillosis: “business decision”)

FierceBiotech

BIOTECH RESEARCH CRO MEDTECH

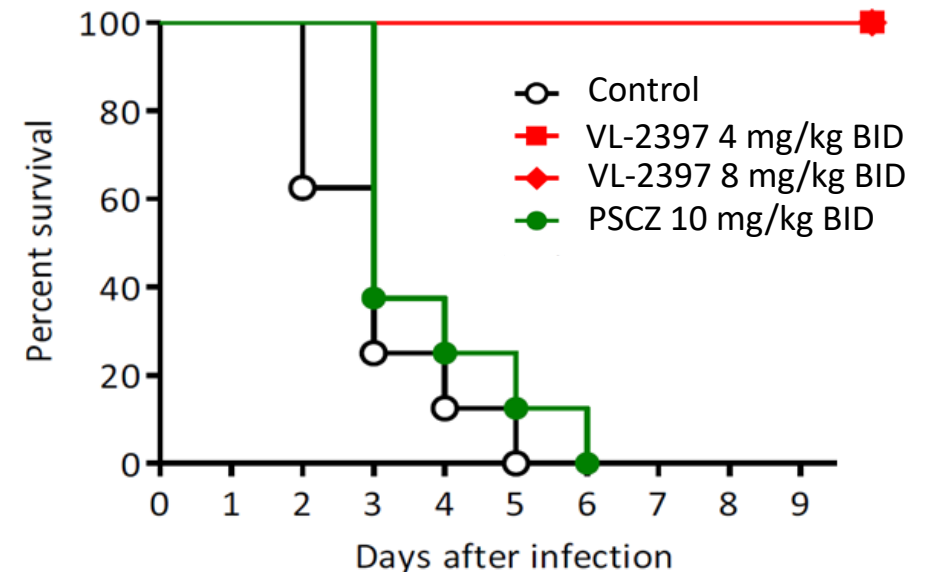
Biotech

Vical stops antifungal trial, lays off staff to eke out cash

by Nick Paul Taylor | Feb 20, 2019 9:24am

Organism	No. of isolates	Drug	MIC in human serum: µg/ml				MIC in RPMI: µg/ml			
			Range	90%	Range	90%				
<i>A. fumigatus</i>	49	ASP2397	1	4	2	0.06	0.5	0.5		
		VRCZ	0.12	1	0.5	0.12	1	0.5		
		ITCZ	0.5	8	4	0.12	0.5	0.5		
		PSCZ	0.06	0.5	0.25	0.03	0.25	0.12		
		AMPH-B	0.5	2	2	0.25	1	0.5		
Azole-resistant <i>A. fumigatus</i>	4	ASP2397	1	2	0.06	1				
		VRCZ	0.12	8	0.25	4				
		ITCZ		>8		>8				
		PSCZ	1	8	1	>8				
		AMPH-B	0.5	2	0.25	1				

Triazole resistant strain



Nakamura et al ICAAC 2014 Poster F-1590

New agents for *Candida auris*

Unmet need is too few active agents

SCY-0870 and *Candida auris*

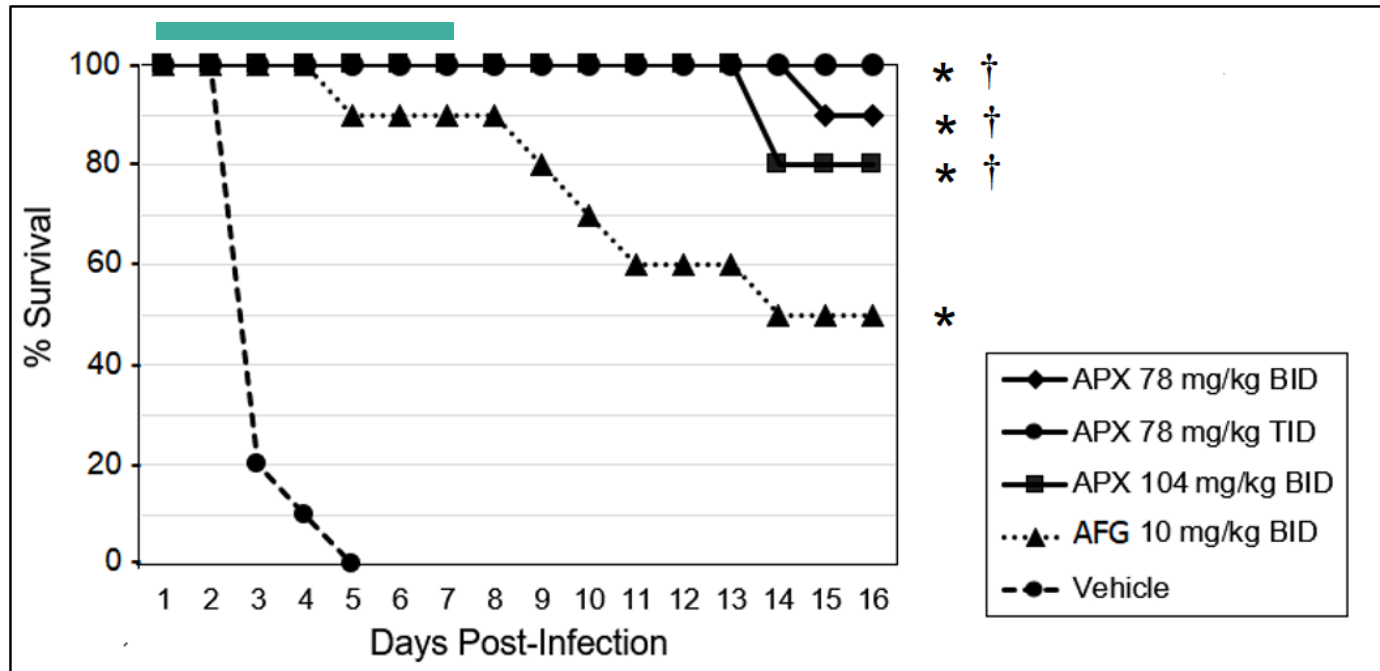
- In vitro activity of SCY-0870 demonstrated against *C. auris*¹

Isolate	MIC (μ g/ml) of drug:			
	Anidulafungin	Caspofungin	Micafungin	SCY-078
1	8	1	4	1
2	16	1	4	1
3	1	16	1	1
4	2	16	2	1
5	4	0.5	0.5	0.5
6	>16	>16	>8	0.5
7	4	>16	1	1

- CARES
 - Open label non comparative trial for invasive candidiasis (including candidemia) caused by *C. auris*
- ClinicalTrials.gov Identifier: NCT03363841

¹Berkow et al AAC 2017 61(7)

APX001 and *Candida auris*

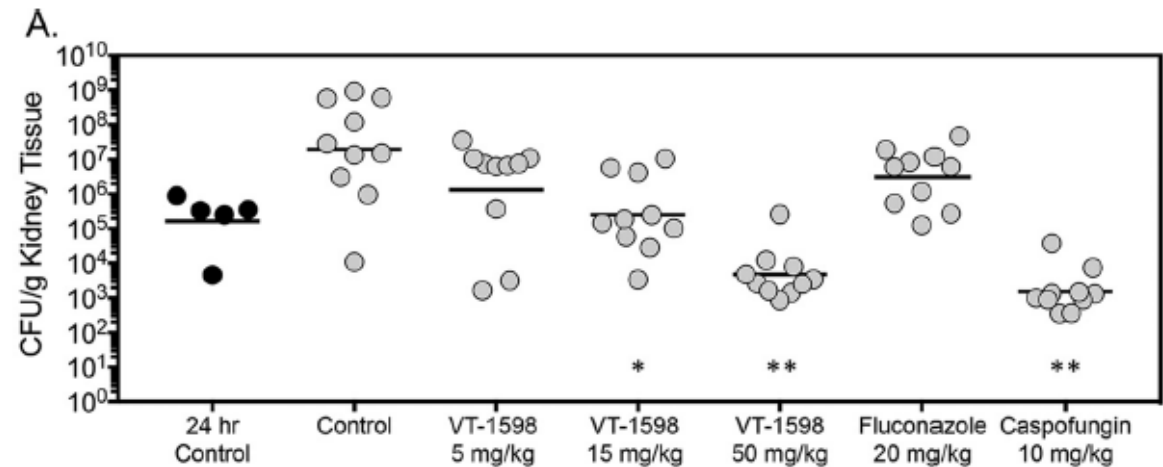
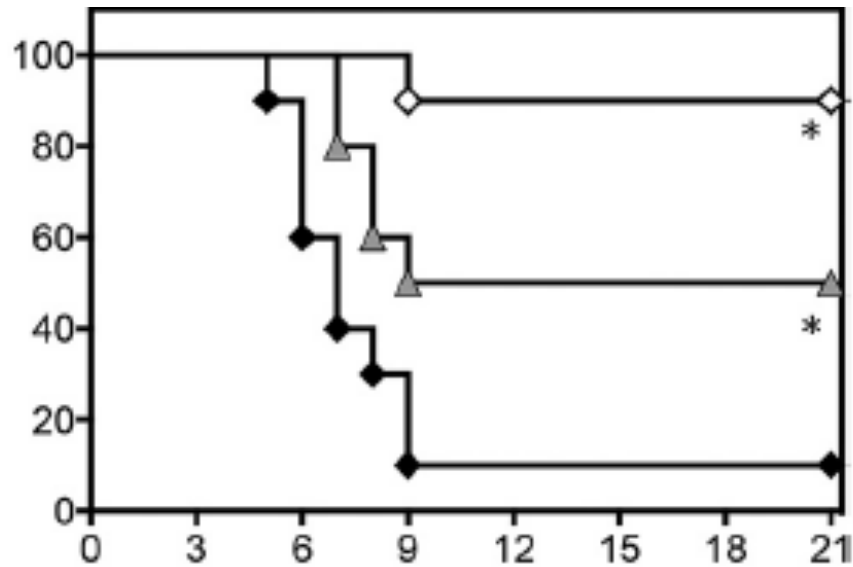


ClinicalTrials.gov Identifier: NCT03604705

Clinical study in
antifungal resistant
candidemia currently
recruiting

Hager 2018 AAC 2018 62(3)

VT-1598 and *Candida auris*



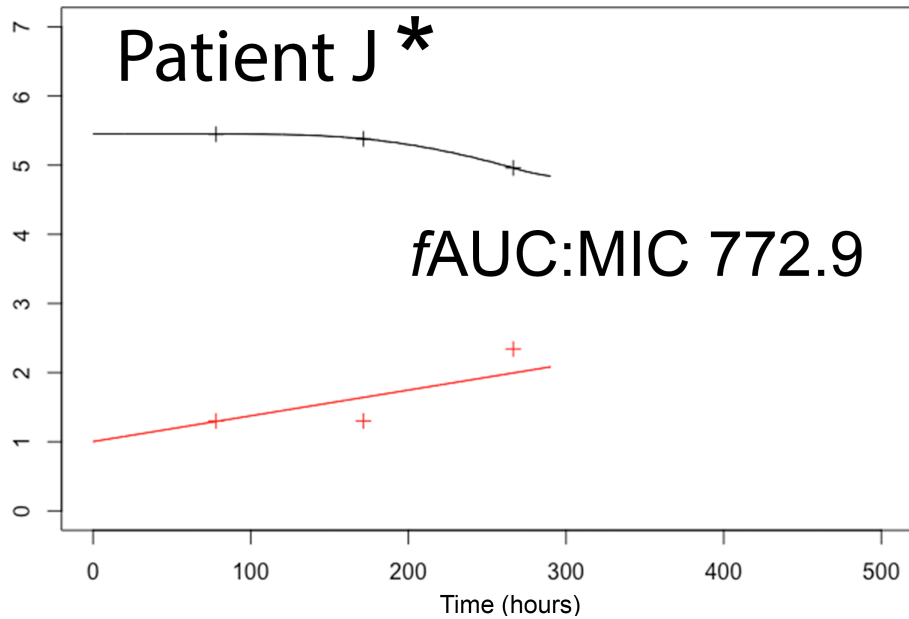
No clinical studies enrolling or imminent

Wiederhold et al AAC 2019 63(3)

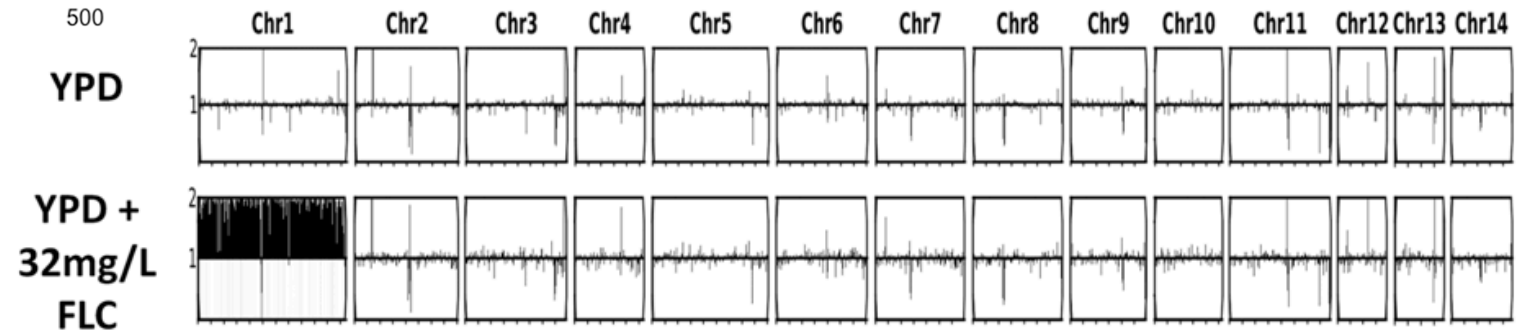
New agents for cryptococcal meningitis

The unmet medical need is safe orally bioavailable agents that are fungicidal in the CSF/ CNS

Fluconazole monotherapy 1200 mg/d

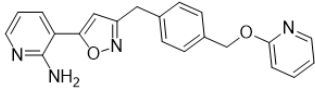
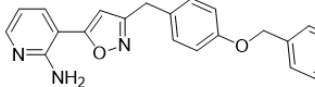
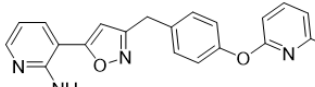


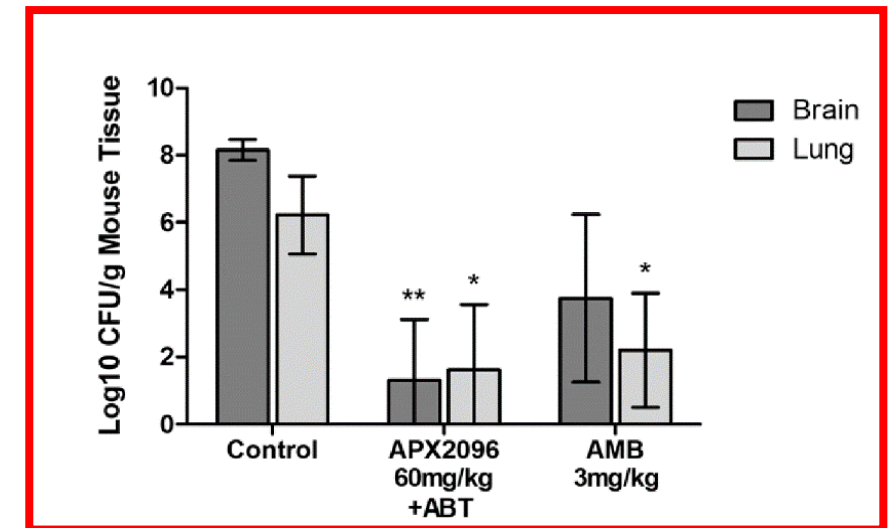
Chromosomal Map



Efficacy of APX compounds in a murine model of cryptococcal meningitis

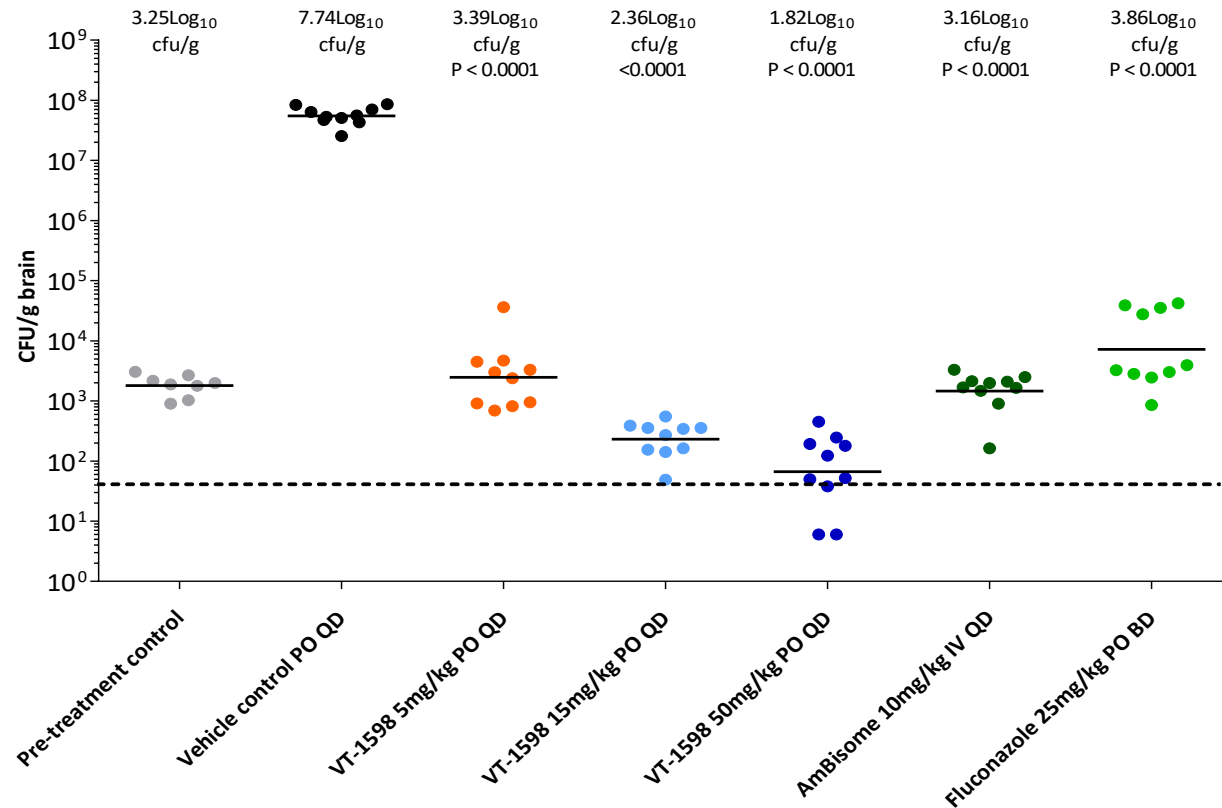
- Administration of APX2096 results in striking reductions in both brain and lung CFU vs APX001 and APX2097
Sterilization of lung tissue/near sterilization of brain

Compound	Structure	Prodrug	MIC ($\mu\text{g/mL}$)			MEC ($\mu\text{g/mL}$)
			<i>C. neoformans</i> H99	<i>C. gattii</i> WM276	<i>C. albicans</i> 90028	<i>A. fumigatus</i> MYA3626
APX001A		APX001	0.25	0.125	0.008	0.008
APX2020		APX2097	0.031	0.031	0.016	0.016
APX2039		APX2096	0.008	0.004	0.031	0.063



Slide modified from JR Perfect; ASM-ESCMID, Lisbon, 2018

VT-1598 and cryptococcal meningitis



Clinical plans for VT-1598 are in development (courtesy Dr Ed Garvey)

Garvey et al JAC 2018 73(10)

New agents for vulvovaginal candidiasis (VVC)

The unmet need is recurrent fluconazole resistant disease

Scynexis and VVC

Efficacy Evaluation at Day 24 (culture-confirmed VVC)					
N Rate %	SCY-078 1250mg (D1), 750mg (D2-3) (n= 24)	SCY-078 1250mg (D1), 750mg (D2-5) (n= 26)	SCY-078 (Combined) (n= 50)	Fluconazole 150mg (D1) (n= 20)	% Δ SCY-078 (combined) vs. Fluconazole
Clinical Cure	19 79.2%	19 73.1%	38 76%	13 65%	+11%
Efficacy Evaluation at Month 4					
Recurrences Requiring Antifungal Therapy	1 4.2%	1 3.8%	2 4%	3 15%	-11%

Phase 3 placebo controlled trial currently enrolling
 ClinicalTrials.gov Identifier: NCT03734991

VT-1161 (Mycovia Pharmaceuticals)

A phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of orally administered VT-1161 in the treatment of recurrent vulvovaginal candidiasis



Stephen R. Brand, PhD; Thorsten P. Degenhardt, PhD; Karen Person, MSc; Jack D. Sobel, MD; Paul Nyirjesy, MD; Robert J. Schotzinger, MD, PhD; Amir Tavakkol, PhD, DipBact

Phase 3 placebo controlled trial currently enrolling
ClinicalTrials.gov Identifier: NCT03562156

Do these new drugs address treatment challenges?

- For inherent antifungal resistance: yes, in part
- For acquired antifungal resistance in *Aspergillus* spp. and *Candida* spp.: yes
- To improve safety and DDI: maybe, let's see
- New treatment options for common fungal diseases: yes

Last slide

- Thank you
- We are at www.liverpool.ac.uk/apt
- @APTlivuni

