Neues in der Antimykotika-Pipeline

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Disclosures

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- AMGEN

PERSPECTIVES

INFECTIOUS DISEASE

How to bolster the antifungal pipeline

Few drugs are coming to market, but opportunities for drug development exist

By **David W. Denning**[1,2] and **Michael J. Bromley**[1,3]

About 1.2 billion people worldwide are estimated to suffer from a fungal disease (*1*, *2*). Most are infections of the skin or mucosa, which respond readily to therapy, but a substantial minority is invasive or chronic and difficult to diagnose and treat. An estimated 1.5 to 2 million people die of a fungal infection each year, surpassing those killed by either malaria or tuberculosis (*3*). Most of this mortality is caused by species belonging to four genera of fungi: *Aspergillus*, *Candida*, *Cryptococcus*, and *Pneumocystis*. Although great strides were made in the 1990s, drug development has largely stalled since then. Opportunities exist for accelerating development, particularly in fungal asthma, and to treat chronic and invasive aspergillosis.

INFECTIOUS DISEASE SERIES

Antifungal therapy has become progressively more effective since second-generation azoles, echinocandins, and lipid formulations of amphotericin B were introduced from the 1990s onward (*3*). These compounds act by inhibiting ergosterol and β-D-1,3 glucan synthesis and perturbing the cell membrane (see the figure). Voriconazole is now the agent of choice for invasive aspergillosis, allowing patients to survive leukemia and transplantation who would otherwise have died (*4*, *5*).

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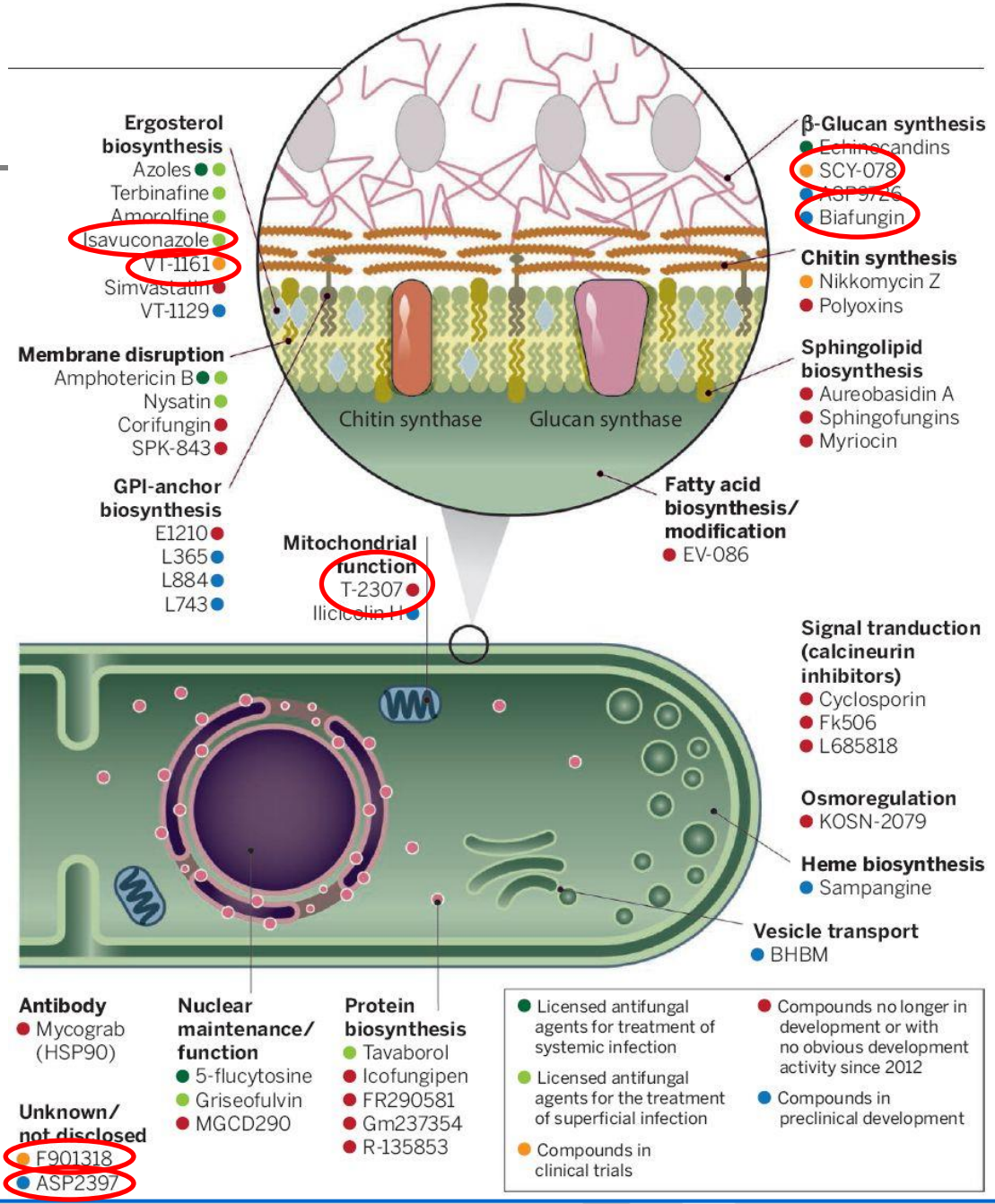
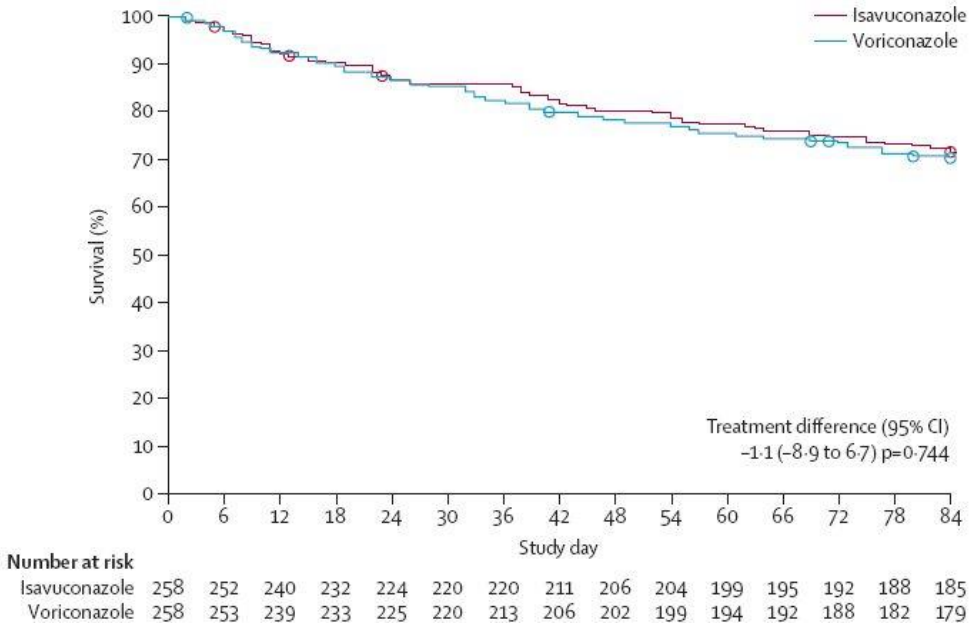
Photomicrograph of *Aspergillus fumigatus*. This fungus causes life-threatening invasive and chronic aspergillosis as well as driving severe asthma. Although drug treatments exist, mortality remains high.



Isavuconazol Secure Studie

Phase 3, randomisiert, doppel-blind, multizentrische Studie
(Invasive Aspergillose, Fadenpilzinfektion VRC sensitiv)
Isavuconazol (263) versus Voriconazol (264) -> ITT (258/258), mITT (143/129)
prim. Endpunkt: Unterschied Mortalität ITT Tag 42 ≤10%



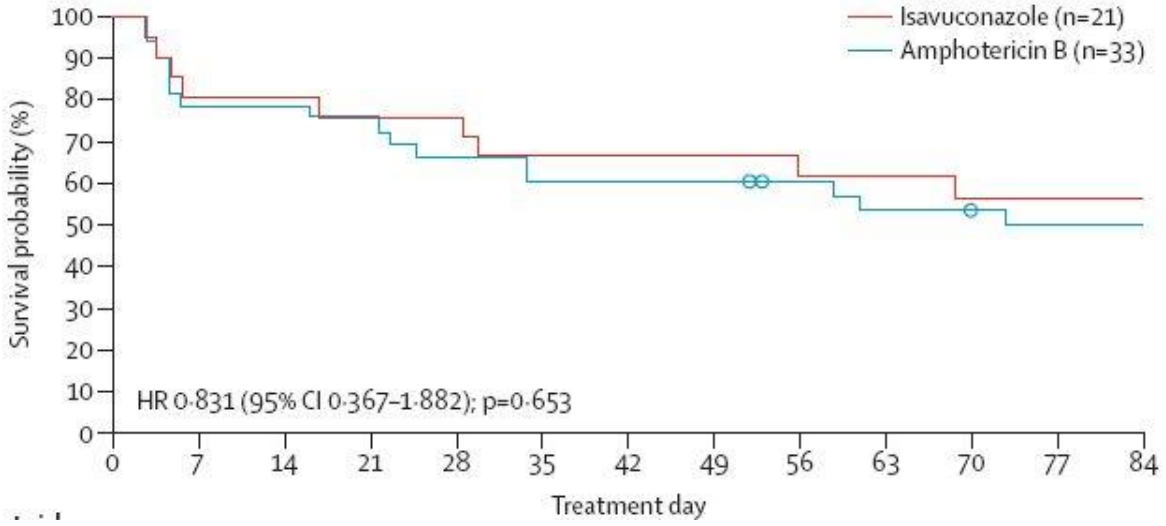
	Isavuconazole	Voriconazole
Non-*Aspergillus* spp only	5 (3%)	6 (5%)
Rhizopus spp¶	1 (1%)	0
Mucor spp¶	0	1 (1%)
Fusarium solani	2 (1%)	0
Fusarium spp¶	1 (1%)	3 (2%)
Exserohilum rostratum	0	1 (1%)
Talaromyces marnefei	0	1 (1%)
Talaromyces spp¶	0	1 (1%)
Trichosporon inkin	1 (1%)	0

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0·122
Gastrointestinal disorders	174 (68%)	180 (69%)	0·705
Infections and infestations	152 (59%)	158 (61%)	0·719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0·658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0·859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0·289
Nervous system disorders	95 (37%)	89 (34%)	0·582
Skin and subcutaneous tissue disorders*	86 (33%)	110 (42%)	0·037¶
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0·357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0·703
Psychiatric disorders†	70 (27%)	86 (33%)	0·151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0·495
Vascular disorders	67 (26%)	77 (30%)	0·378
Renal and urinary disorders	55 (21%)	58 (22%)	0·832
Cardiac disorders	43 (17%)	57 (22%)	0·148
Eye disorders‡	39 (15%)	69 (27%)	0·002¶
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0·526
Hepatobiliary disorders§	23 (9%)	42 (16%)	0·016¶

Maertens JA, et al. *Lancet* 2016; 387:760-9

Isavuconazol Vital Studie

Offene, multizentrische Studie
(Seltene Pilzinfektionen, Invasive Aspergillose + Niereninsuffizienz)
Auswertung zu 37 Patienten mit Mucormykose
(32 proven, 5 probable; 21 primary, 11 refractory, 5 intolerant)
<u>Fallkontrollauswertung:</u>
gematcht -> CNS or diss., haem. malignancy, surgery ≤ 7 days
21 primary ISAV <-> 33 Pat. aus FungiScope Register (7 cAmB, 26 L-AmB)



	Isavuconazole	Amphotericin B
Pathogen		
Actinomucor spp	1 (5%)	0
Lichtheimia spp	2 (10%)	6 (18%)
Mucor spp	6 (29%)	5 (15%)
Mucorales moulds	6 (29%)	7 (21%)
Rhizomucor spp	2 (10%)	2 (6%)
Rhizopus spp	4 (19%)	13 (39%)
Matching covariate†		
Haematological malignancy	11 (52%)	18 (55%)
Severe disease‡	12 (57%)	13 (39%)
Surgical treatment§	9 (43%)	13 (39%)

Marty FM, et al. *Lancet Infect Dis* 2016; Mar 8 Epub

Isavuconazol Active Trial

Phase 3, randomisiert, doppel-blind, multizentrische Studie
Proven Candidiasis oder Candidämie
Isavuconazol versus Caspofungin
-> Tag +10 -> ISAV/VRC p.o. mgl.
mITT: 199 ISAV – 201 CASPO

<u>prim. Endpunkt:</u>
Successful response
am Ende der i.v.-Therapie i.d. mITT

<u>successful overall response at EOIV:</u>
ISAV 120/199 (60%)
versus
CASPO 143/201 (71%)

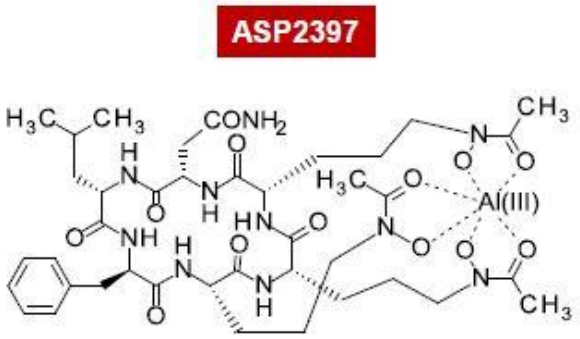
Adjusted difference (95%CI):
-10.8 (-19.9, -1.8)

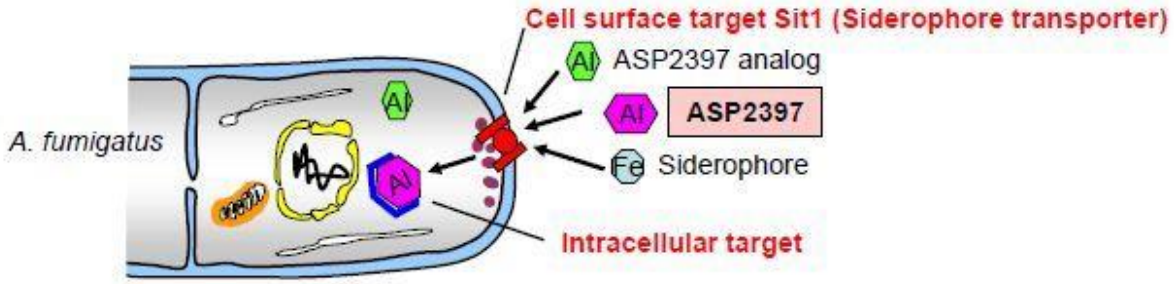
Parameter **mITT**	**Isavuconazole (n=199)**	**Caspofungin (n=201)**
Mean APACHE II score	14	14
Baseline neutropenia, n (%)	24 (12.1)	24 (11.9%)
Infecting pathogen, n (%)		
C. albicans	84 (42.2)	74 (36.8)
C. tropicalis	41 (20.6)	38 (18.9)
C. parapsilosis	26 (13.1)	27 (13.4)
C. glabrata	22 (11.1)	21 (10.4)
IV duration [days], mean (SD)	12.8 (7.6)	14 (8.7)
Successful overall response, n (%)		
FU1	109 (54.8)	115 (57.2)
All-cause mortality, n (%)		
Day 14	29 (14.6)	25 (12.4)
Day 56	61 (30.7)	60 (29.9)

Kullberg BJ, et al. ECCMID 2016; Abstract 1239 (O423)

ASP2397

Isoliert aus *Acremonium sp.* MF-347833





Auch bei Azolresistenz wirksam

Fig.5. ASP2397 completely halts the hyphal elongation from germinated conidia revealed by live cell imaging

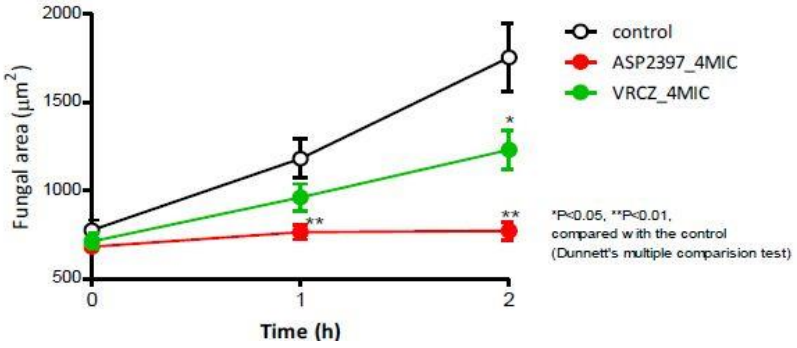
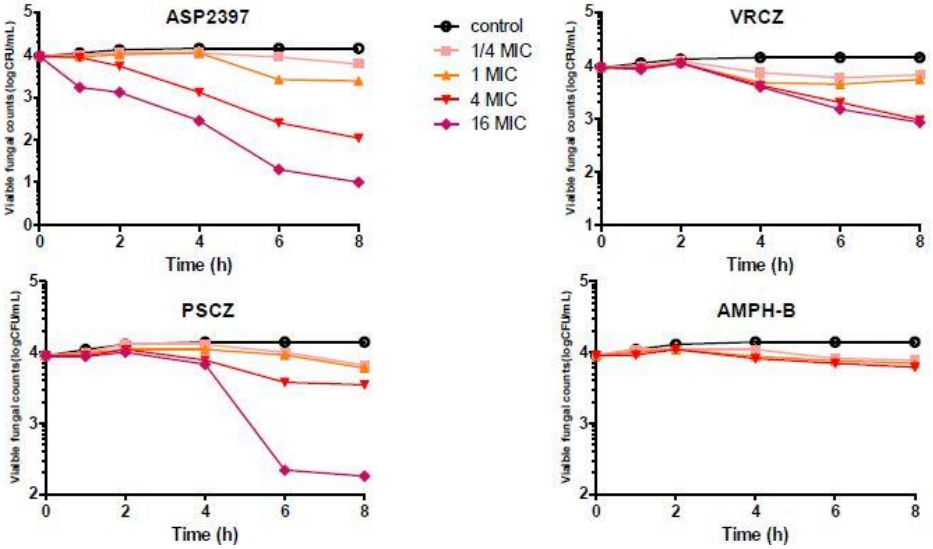


Fig.6. ASP2397 showed a rapid and potent fungicidal activity against *A. fumigatus*



Nakamura I, et al. ICAAC 2014; F-1590
Arendrup MC, et al. Antimicrob Agents Chemother 2016; 60: 532-6

ASP2397

neutropenic mouse model (cyclophosphamide)
Therapies on day 1 post infection

Fig.3. Survival efficacy against azole-refractory IPA mice model of *A. fumigatus*

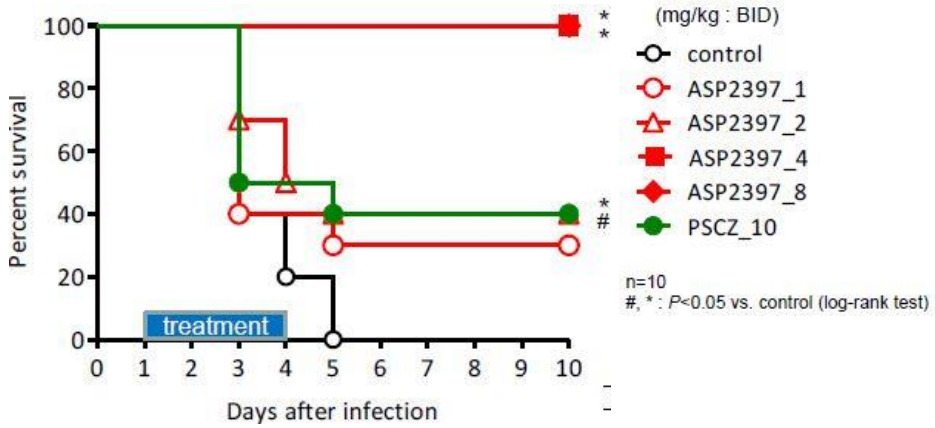
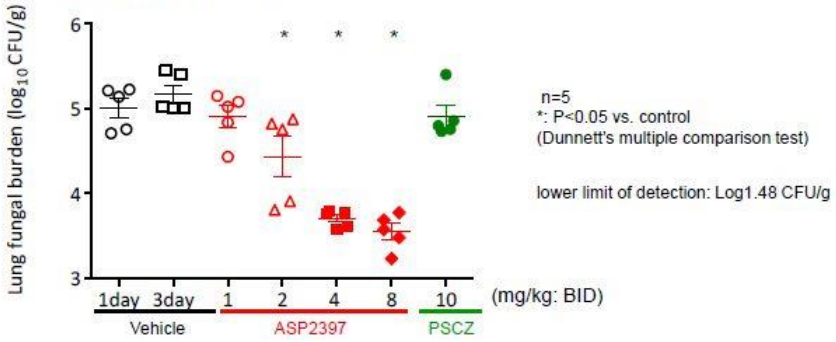


Fig.4. Fungicidal effect against lung fungal burden in azole-refractory IPA mice model of *A. fumigatus* 20030



<u>PK/PD-Studie</u>

neutropenic mouse model -> intratracheal infection with *A. fumigatus* (D 0)
ASP2397 doses of 1, 2, 4, 8, and 16 mg/kg s.c. (QD, BID, and QID)
post-infection Days 1, 2, and 3
-> ↓ CFU/g lung tissue (D 4) correlated with daily dose of ASP2397

Nakamura I, et al. ICAAC 2014; F-1591
Nakamura I, et al. ICAAC/ICC 2015; F-746

T-2307

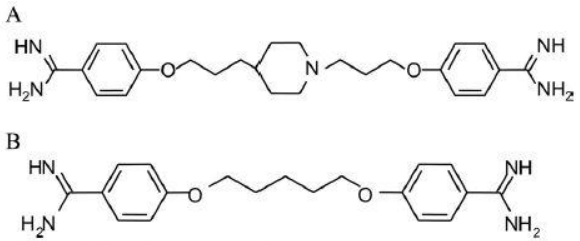


FIG 1 Chemical structure of T-2307 (A) or pentamidine (B).

T-2307 (Arylamidin)

4-{3-[1-(3-{4-[amino(imino)-methyl]phenoxy}propyl)piperidin-4-yl]propoxy}benzamidine

Pentamidin

Mitochondrieninhibierung

>>500-fache höhere Hemmung Pilz- versus Rattenmitochondrien

Aktivitätsspektrum: *Aspergillus sp., Candida sp., C. neoformans*

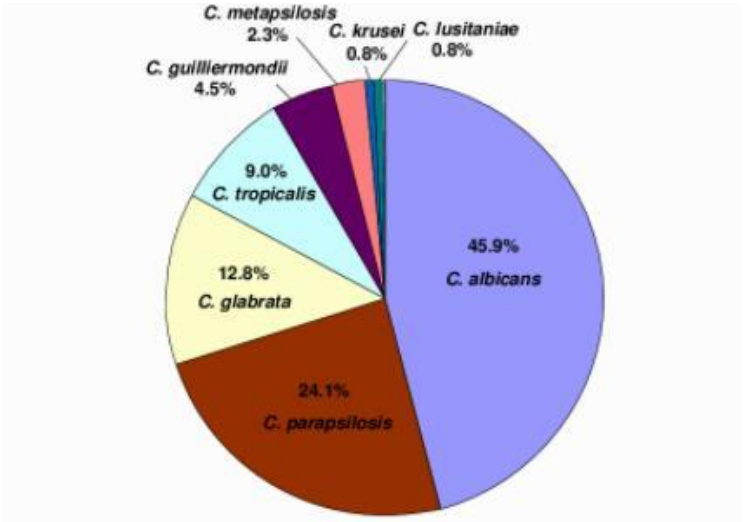


Figure 2. Species distribution of the 133 CBI collected between 2008 and 2013.

Table 1. MICs of T-2307 and other antifungal agents against CBI

Organism (No. of strains)	Agent	MIC (μg/ml) Range	MIC$_{50}$	MIC$_{90}$
All *Candida* spp. (133)	**T-2307**	**0.0000625 — 0.0313**	**0.0005**	**0.0039**
	FLC	0.0625 — >64	0.25	4
	ITC	0.0313 — >4	0.125	0.5
	VRC	0.001 — 4	0.0078	0.125
	AMB	0.5 — 4	2	2
	CAS	0.002 — 1	0.125	0.5
	MFG	0.0156 — 2	0.0625	1

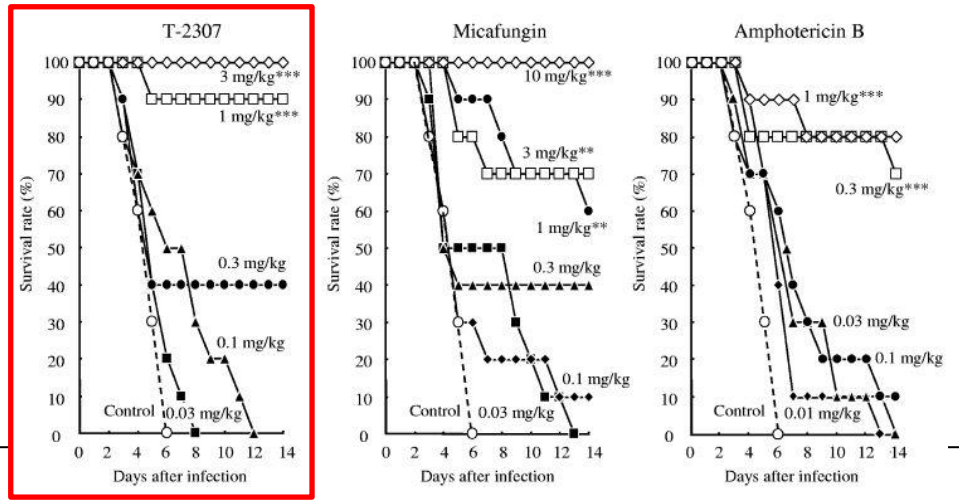
Table 2. MICs of T-2307 and other antifungal agents against azole- or candin-resistant strains

Organism	Strain No.	MIC (μg/ml) T-2307	FLC	ITC	VRC	AMB	CAS	MFG
C. glabrata	FC-710	0.0078	8	0.5	0.125	2	0.125	0.5
C. glabrata	FC-725	0.0039	64	>4	2	2	0.125	0.0625

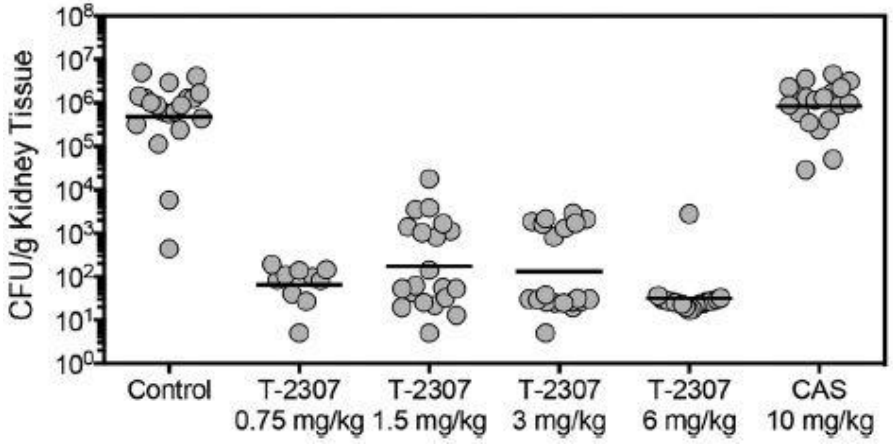
Sakagami T, et al. ICAAC/ICC 2015; M-847
Shibata T, et al. *Antimicrob Agents Chemother* 2012; 56: 5892-7

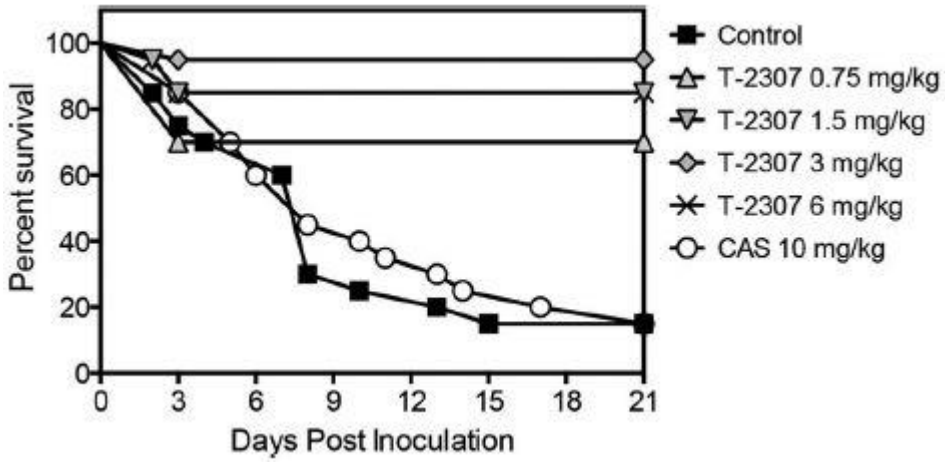
T-2307

Mausmodell (Neutropenie)
-> 8,4x10^4 CFU *A. fumigatus* i.v.
-> 0,03-3mg/kg T-2307 oder
0,03-10mg/kg MICA oder
0,01-1mg/kg AmB



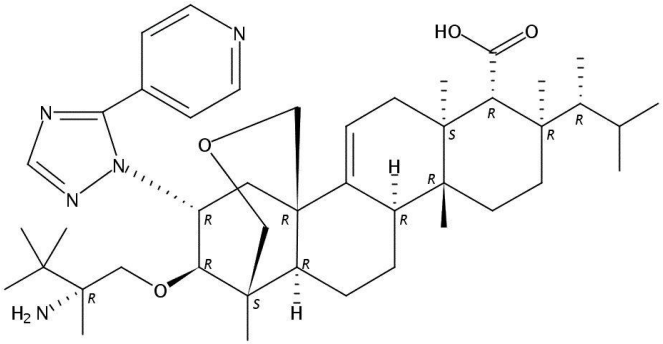
Immunkompetentes Mausmodell
-> D0 i.v. Injektion 1x10^6 *C. albicans* (Echinocandin-resistent)
0,75-6mg/kg T-2307 s.c. oder 10mg/kg CASPO i.p. (d1-7)





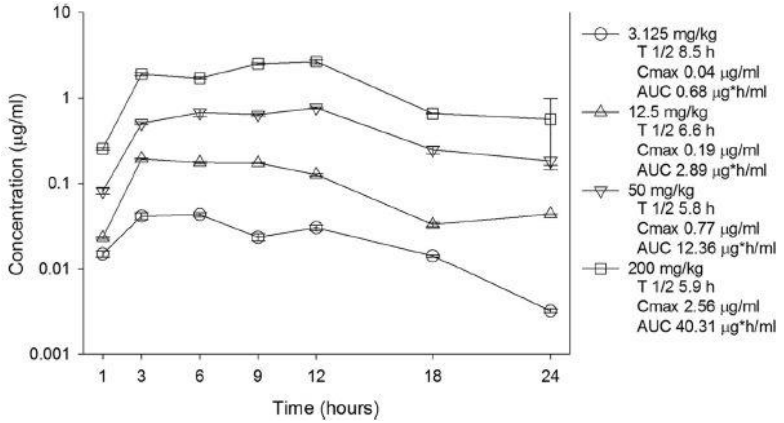
Mitsuyama J, et al. *Antimicrob Agents Chemother* 2008; 52: 1318-24
Wiederhold NP, et al. *Antimicrob Agents Chemother* 2015; 59: 1341-3

SCY-078 = MK-3118



halbsynthetisches Derivat von Enfumafungin
Glucansyntheseinhibitor
-> orale Therapie möglich (Bioverfügbarkeit?)

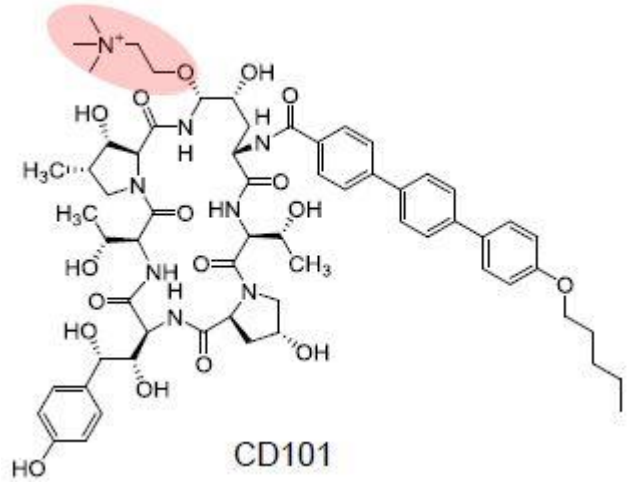
CD-1 mice (Neutropenie)
Einzeldosis SCY-078 3,125 - 200 mg/kg



CD-1 mice:
oral SCY-078 3 - 100 mg/kg bid for 7 days
Day 7: Plasma and BAL samples collected
-> median ELF:plasma ratio 5.2 (2.7-16.9)
C_{max} plasma: 2h sample; C_{max} ELF 12 h

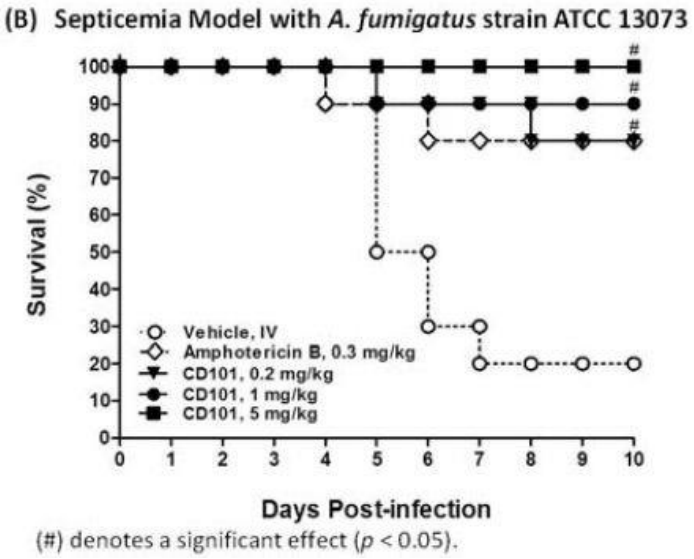
Lepak AJ, et al. Antimicrob Agents Chemother 2015; 59: 1265-72
Wring S, et al. ICAAC/ICC 2015; A-468c

Biafungin = CD101



Derivat von Anidulafungin
Lange HWZ
-> Dosierung 1x wöchentlich

Mausmodell (Neutropenie)
10^4 *A. fumigatus* CFU/mouse i.v.
->2 Std. 0,2 – 5mg/kg CD101 bid 5 Tage

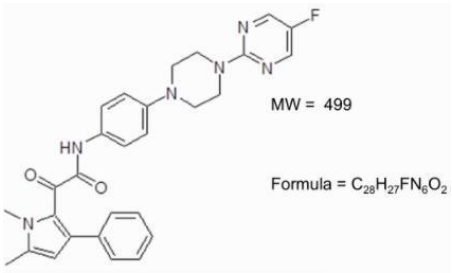


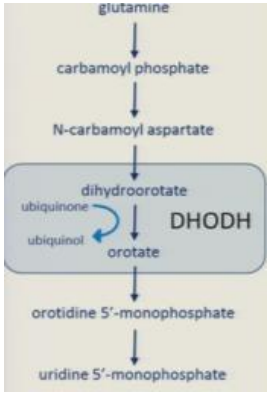
<u>Phase I Studie (ECCMID 2016)</u>
32 Probanden: 50, 100, 200, 400 mg Einzeldosis (1 Std.) CD101
C_{max} (dosisabhängig) 2.76 - 22.7 µg/mL, $t_{1/2}$ >80 h, Urinrecovery <1%
Keine SAEs

Miesel L, et al. ICAAC/ICC 2015, Session 197
Helou S, et al. ECCMID 2016, O425

F901318

Orotomid -> Pyrimidinsyntheseinhibitor

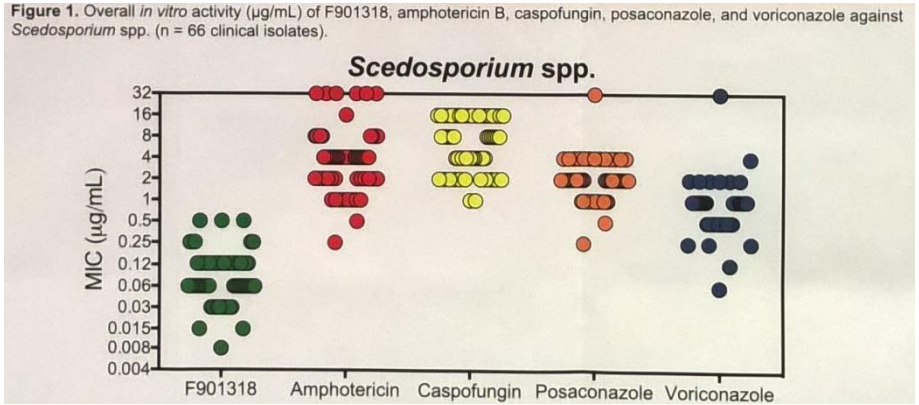


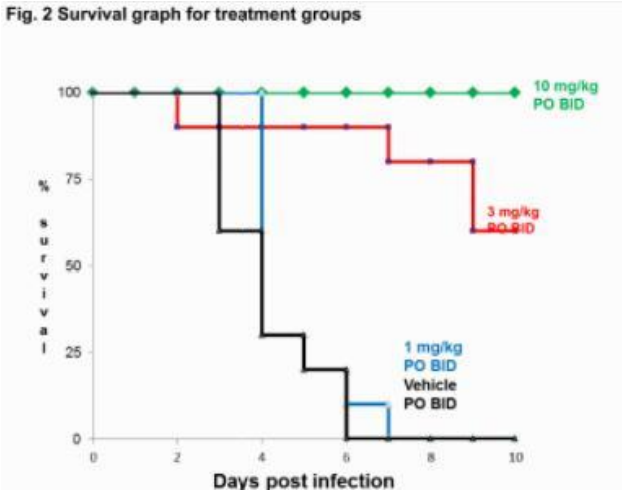


2200-fache höhere Hemmung
A. fumigatus DHODH
versus
humane DHODH

In vitro Aktivität
Fadenpilze: v.a. *Aspergillus sp.*
In vitro Test. (CLSI) *Scedosporium sp.*

Mausmodell (Neutropenie)
-> 1,35x10^5 CFU *A. fumigatus* i.v.
-> 24 Std.: 1-10mg/kg F901318 oral

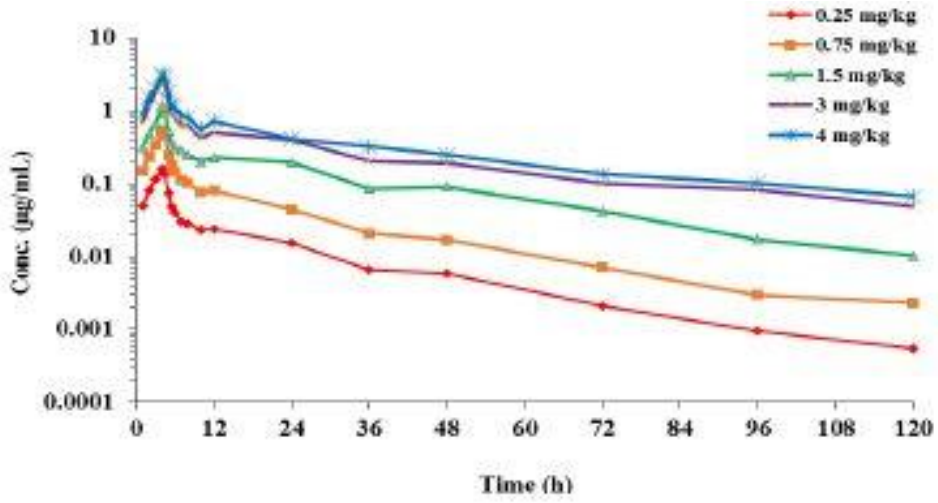




Law D, et al. ICAAC/ICC 2015; F-759
Fothergill AW, et al. ECCMID 2016; P-1575

F901318

Phase I Studie
6 Probanden pro Dosisstufe
-> 0.25, 0.75, 1.5, 3 und 4 mg/kg F901318 über 4 Std. i.v.

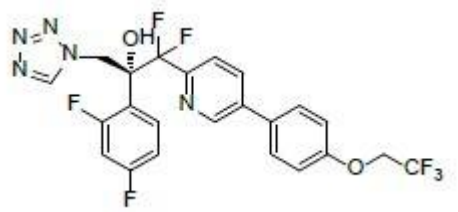


Dose (mg/kg)	C_{max} (µg/mL)	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	$t_{1/2}$ (h)	CL (mL/h)/kg	V_z (mL)/kg
0.25	0.172 (36.5)*	1.30 (58.6)	1.31 (58.6)	15.2 (23.5)	235.9 (42.5)	3002 (19.3)
0.75	0.550 (18.2)	4.02 (17.9)	4.09 (18.0)	21.9 (42.5)	188.1 (16.9)	3494 (41.5)
1.5	1.171 (25.1)	12.68 (27.4)	13.07 (26.9)	25.1 (21.9)	121.0 (23.9)	3342 (23.1)
3.0	2.74 (19.0)	29.92 (25.7)	28.78 (22.7)	23.9 (37.8)	108.7 (22.7)	2893 (32.0)
4.0	3.26 (24.6)	38.04 (30.3)	40.94 (34.0)	30.2 (33.1)	110.5 (43.1)	3198 (12.2)

C_{max}: 0,172 - 3,26 µg/ml
$t_{1/2}$: 15,2 – 20,3 Std.
<0,2% Urinrecovery von F901318
„well tolerated…no adverse events observed“

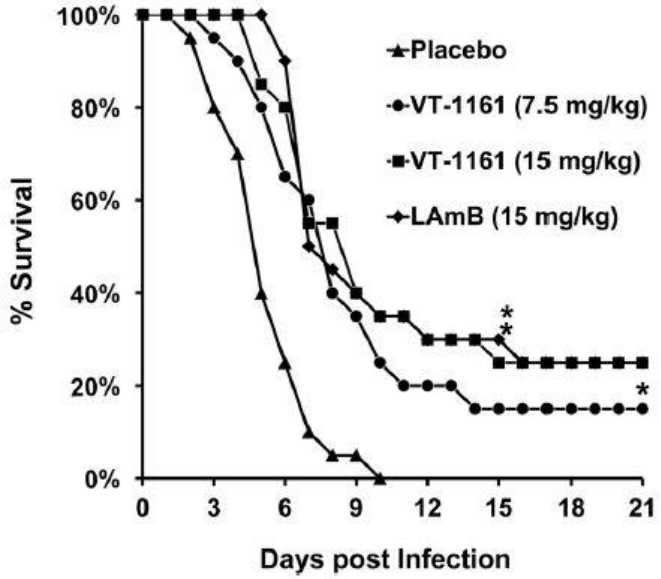
Kennedy A, et al. ICAAC/ICC 2015; F-751

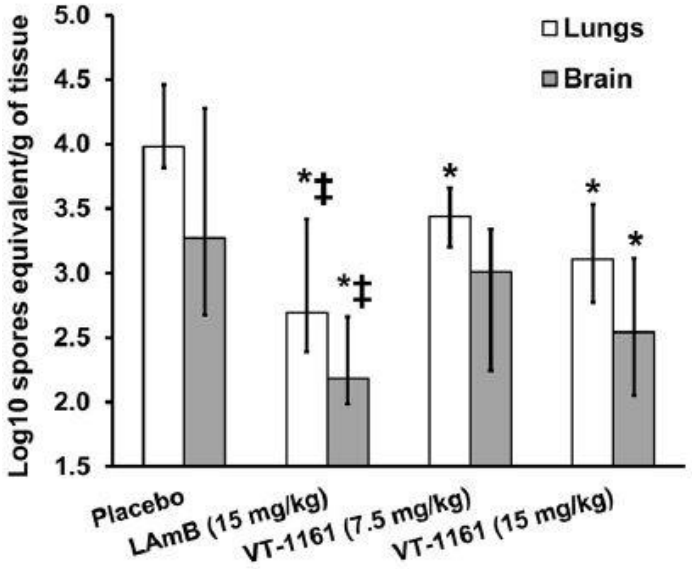
VT-1161



14-Lanosterol Demethylase (CYP51) Inhibitor

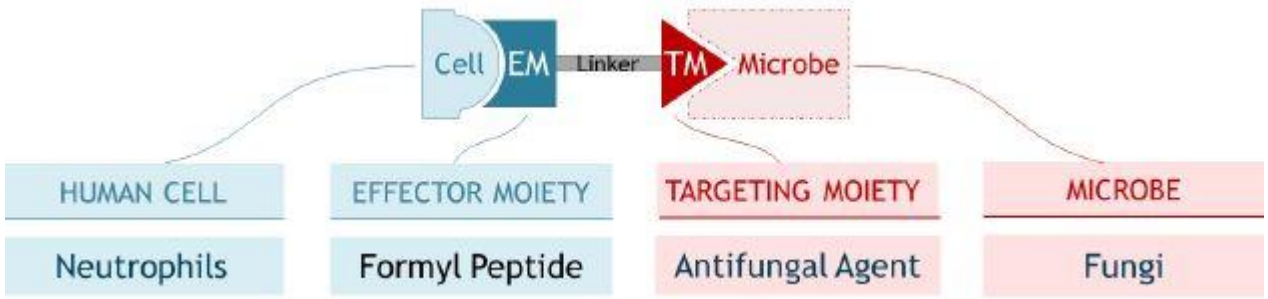
<u>Mausmodell (Neutropenie)</u>
-> 2.5 x 10^5 Sporen *Rhizopus arrhizus var. arrh.* intratracheal
-> nach 16 Std. 7.5/15 mg/kg VT-1161 oral bis Tag 7
-> nach 16 Std. 15 mg/kg LAmB i.v. bis Tag 4



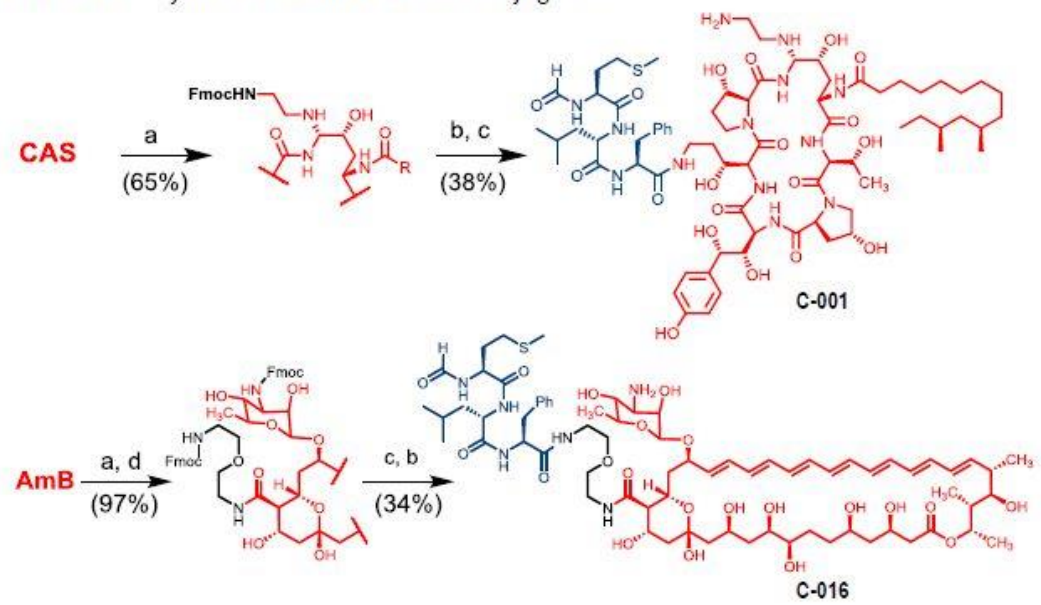


Gebremariam T, et al. Antimicrob Agents Chemother 2015, 59: 7815-17
Gebremariam T, et al. ICAAC/ICC 2015

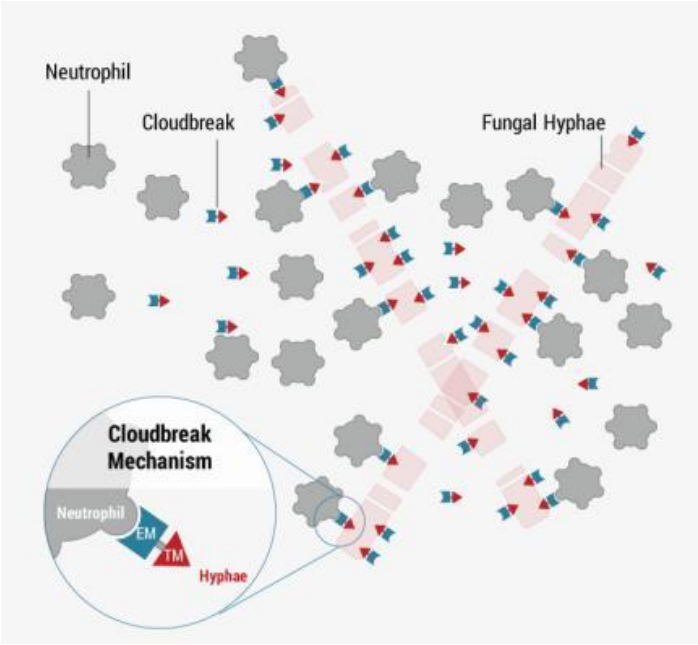
Chemotactic agents



Scheme 1. Synthesis of Bifunctional Conjugates

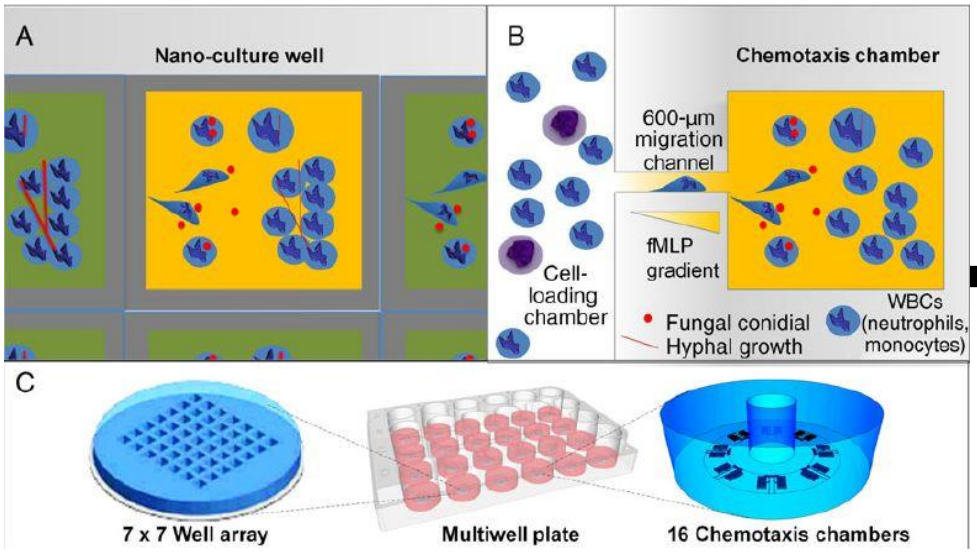


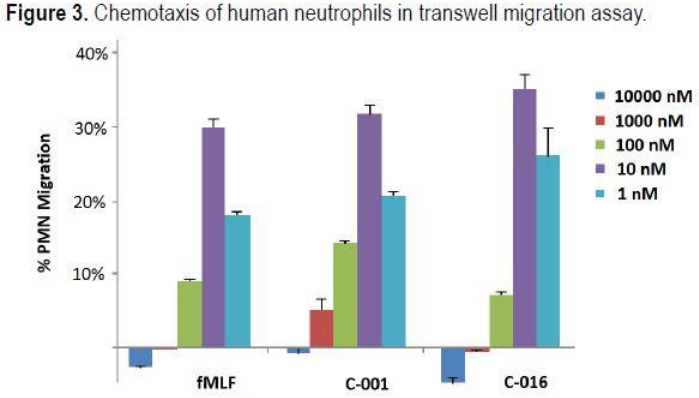
a) Fmoc-OSu b) fMet-Leu-Phe-OSu c) piperidine d) Fmoc-NH-$(CH_2)_2$-O-$(CH_2)_2$-NH_2, COMU, DIPEA

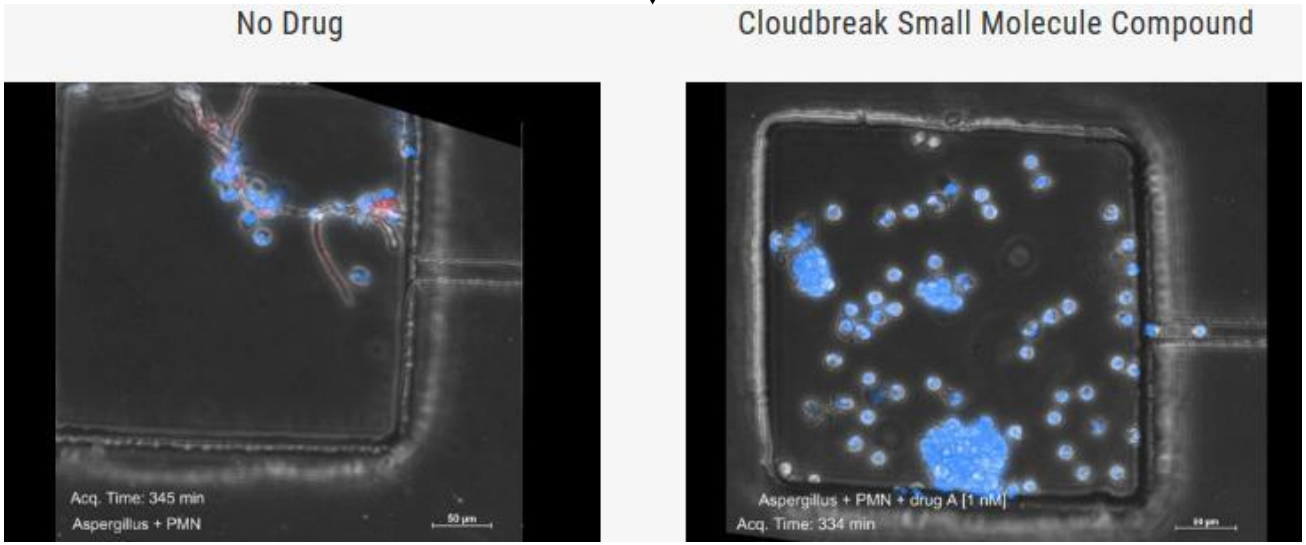


http://www.cidara.com/cloudbreak/
Jones C, et al. ICAAC/ICC 2015, F-762

Chemotactic agents



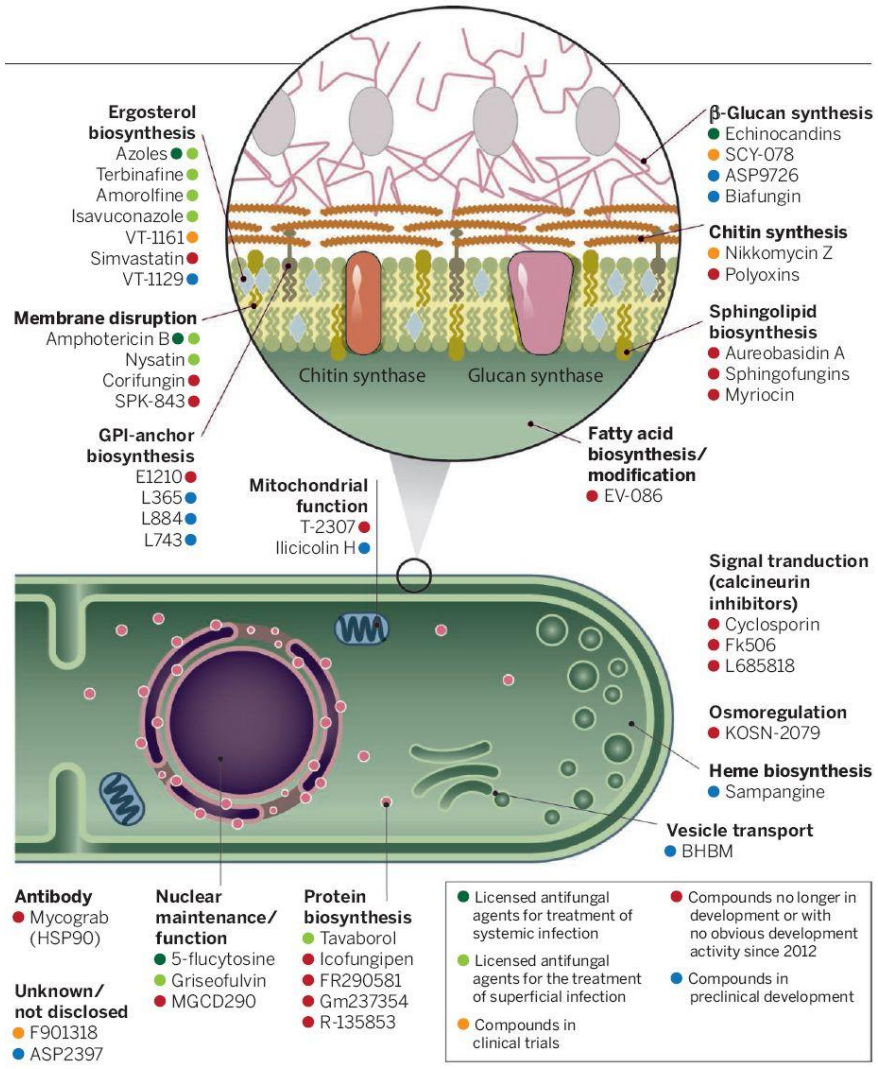




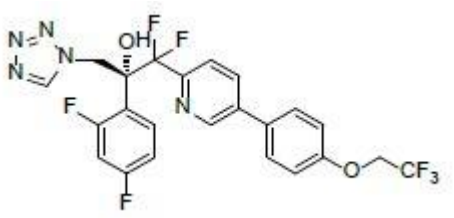
http://www.cidara.com/cloudbreak/

Jones C, et al. J Infect Dis 2016, 213: 465-75

Pipeline ...


Ergosterol biosynthesis
Azoles
Terbinafine
Amorolfine
Isavuconazole
VT-1161
Simvastatin
VT-1129
Membrane disruption
Amphotericin B
Nysatin
Corifungin
SPK-843
GPI-anchor biosynthesis
E1210
L365
L884
L743
Chitin synthase
Glucan synthase
β-Glucan synthesis
Echinocandins
SCY-078
ASP9726
Biafungin
Chitin synthesis
Nikkomycin Z
Polyoxins
Sphingolipid biosynthesis
Aureobasidin A
Sphingofungins
Myriocin
Fatty acid biosynthesis/ modification
EV-086
Mitochondrial function
T-2307
Ilicicolin H
Signal tranduction (calcineurin inhibitors)
Cyclosporin
Fk506
L685818
Osmoregulation
KOSN-2079
Heme biosynthesis
Sampangine
Vesicle transport
BHBM
Antibody
Mycograb (HSP90)
Unknown/ not disclosed
F901318
ASP2397
Nuclear maintenance/ function
5-flucytosine
Griseofulvin
MGCD290
Protein biosynthesis
Tavaborol
Icofungipen
FR290581
Gm237354
R-135853
Licensed antifungal agents for treatment of systemic infection
Licensed antifungal agents for the treatment of superficial infection
Compounds in clinical trials
Compounds no longer in development or with no obvious development activity since 2012
Compounds in preclinical development

VT-1161



14-Lanosterol Demethylase (CYP51) Inhibitor

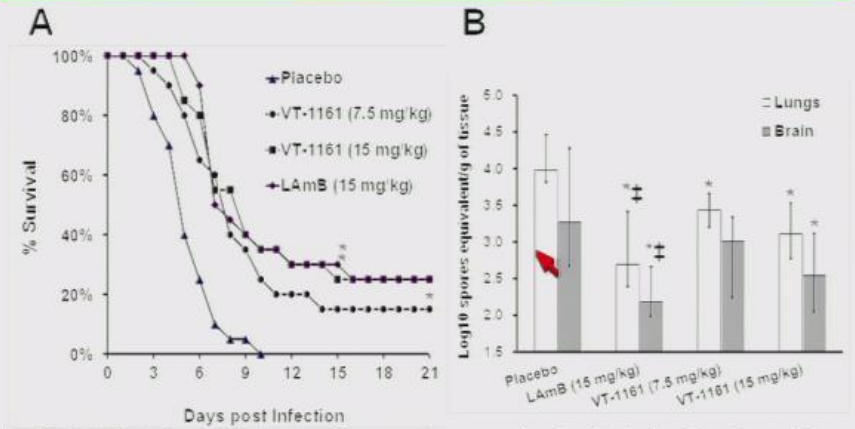
Prophylactic Treatment of Pulmonary Mucormycosis with VT-1161 Using Immunosuppressed Mice

Teclegiorgis Gebremariam,[1] Nathan P. Wiederhold,[2] Annette W. Fothergill,[2] Edward P. Garvey,[3] William J. Hoekstra,[3] Robert J. Schotzinger,[3] Thomas F. Patterson,[2,4] Scott G. Filler,[1,5] Ashraf S. Ibrahim[1,5*]

[1]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center; [2]University of Texas Health Science Center at San Antonio; [3]Viamet Pharmaceuticals

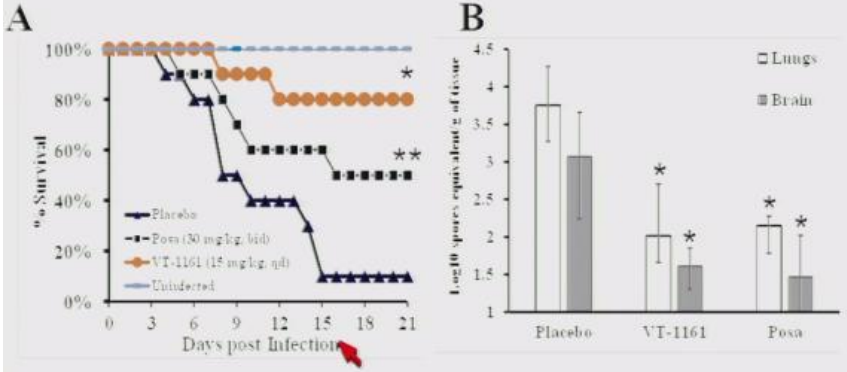
Research support
- NIAID HHSN272201000038I (Task Order A13)
- VT-1161 was provided by Viamet Pharmaceuticals

VT-1161 is as effective as high dose LAmB in improving survival and reducing fungal burden (Delayed Therapy)



(A) *$P < 0.001$ of all treated mice (n=20 per arm) compared to placebo by Log Rank test; (B) Mouse lungs and brains (n=20 per arm) were harvested on day −4 post infection. *$P < 0.002$ compared to placebo while ‡$P < 0.02$ versus VT-1161 at 7.5 mg/kg by Wilcoxon Rank Sum test.

VT-1161 and Posaconazole Protects Immunosuppressed Mice from Mucormycosis (Continuous Therapy)



(A) *$P < 0.002$; **$P < 0.06$ of all treated mice (n=10 per arm) compared to placebo by Log Rank test; (B) Mouse lungs and brains (n=10 per arm) were harvested on day −4 post infection. *$P < 0.05$ compared to placebo by Wilcoxon Rank Sum test.

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Gebremariam T, et al. ICAAC/ICC 2015