VT-1129 and VT-1161 have *in vitro* activity against *Candida* isolates from patients with chronic mucocutaneous candidiasis

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Background

Patients with inherited syndromes of chronic mucocutaneous candidiasis (CMC) frequently develop azole resistance, which makes treatment of their fungal infections challenging. VT-1129 and VT-1161 belong to a new class of antifungals that specifically target fungal cytochrome CYP51. These drugs are effective *in vitro* against azole-susceptible and -resistant fungal strains and *in vivo* in animal models of fungal disease. VT-1161 is currently in Phase 2b studies of recurrent vulvovaginal candidiasis (RVVC) and onychomycosis, having successfully met proof-of-concept goals in Phase 2a studies of acute VVC and tinea pedis. The drugs' long half-lifes, efficacy even when dosed once weekly, and decreased drug-drug interaction potential makes them attractive for patients with CMC who require long-term, often lifelong, antifungal prophylaxis.

Methods

1. ***In vitro* susceptibility analysis:** The *in vitro* susceptibility of VT-1129, VT-1161, azoles, echinocandins, 5-FC and amphotericin was tested against 31 mucosal Candida strains obtained from patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy by the CLSI broth microdilution (M27-A3). The 24-hour minimum inhibitory concentration (MIC) at which 50% of strains were inhibited (MIC_{50}) was determined.
2. **Drug levels:** *Act1*$^{-/-}$ mice (deficient in IL-17 signaling) were used to determine the levels of VT-1129 or VT-1161 in serum and mucosal tissue. The drugs were administered via oral gavage at 20 mg/kg on 4 consecutive days, and organs were harvested 1 day following the last administration. The concentration of each drug was determined using LC-MS/MS with electrospray ionization.
3. ***In vivo* efficacy analysis:** An oral *Candida* strain (Y72) that was found to be susceptible to both VT-1161 and fluconazole was chosen to determine the efficacy of VT-1161 in the clearance of *Candida* from the oral mucosa of *Act1*$^{-/-}$ mice *in vivo*. Mice were sublingually infected with Y72. Eighteen hours post-infection and once a day thereafter for 4 total administrations, mice were given vehicle (0.5% carboxymethycellulose), fluconazole (25mg/kg), or VT-1161 (20mg/kg). One day following the last administration of the drugs (day 5 post-infection), tongues were harvested, and the number of *Candida* colony forming units (CFUs) was quantified.

Results

Table 1: VT-1129 and VT-1169 are active *in vitro* against azole-susceptible and azole-resistant *Candida* isolates from patients with chronic mucocutaneous candidiasis

		Drug compounds, MIC values (µg/mL)										
Isolate	**Species**	**VT1161**	**VT1129**	**Fluconazole**	**Itraconazole**	**Voriconazole**	**Posaconazole**	**Caspofungin**	**Micafungin**	**Anidulafungin**	**Amphotericin**	**Flucytosine**
Y31	*C. albicans*	0.13	0.13	32	0.5	0.5	0.5	0.06	0.03	0.015	0.5	0.12
Y37	*C. albicans*	0.03	0.06	64	0.12	0.12	0.06	0.03	<=0.008	<=0.015	0.5	0.25
Y42	*C. albicans*	0.03	0.03	<=0.12	0.03	<=0.008	<=0.008	0.015	<=0.008	0.015	0.5	0.12
Y43	*C. albicans*	0.03	0.03	0.25	0.06	<=0.008	0.015	0.015	<=0.008	0.015	0.5	0.12
Y46	*C. glabrata*	0.06	0.13	8	0.5	0.25	1	0.12	0.015	0.015	0.5	>0.06
Y47	*C. albicans*	0.03	0.03	0.25	<=0.015	<=0.008	<=0.008	0.03	<=0.008	<=0.015	1	<=0.06
Y48	*C. albicans*	0.03	0.03	0.5	0.06	<=0.008	0.015	0.06	<=0.008	<=0.015	0.5	0.5
Y49	*C. glabrata*	2.00	2.00	128	>16	2	>8	0.12	0.015	<=0.015	0.5	<=0.06
Y51	*C. albicans*	0.03	0.03	4	0.12	0.06	0.12	0.3	<0.008	<0.15	0.5	1
Y52	*C. glabrata*	1.00	2.00	256	>16	2	>8	0.06	0.015	0.03	1	<=0.06
Y54	*C. glabrata*	0.50	1.00	128	16	2	8	0.12	0.015	0.03	0.5	0.06
Y55	*C. albicans*	0.50	1.00	16	0.12	0.25	0.12	0.03	0.008	0.015	0.5	4
Y57	*C. albicans*	>16	>16	4	0.06	0.015	0.06	0.03	<= 0.008	<= 0.015	0.5	N/A
Y72	*C. albicans*	0.031	0.031	0.5	0.06	0.015	0.03	0.03	<=0.008	0.06	0.5	0.5
Y73	*C. nivariensis*	0.063	0.125	16	0.5	0.25	1	0.12	0.015	0.03	0.5	0.12
Y75	*C. albicans*	0.031	0.031	1	0.06	<=0.008	0.06	0.03	<=0.008	<=0.015	0.5	<=0.06
Y79	*C. albicans*	0.031	0.031	0.5	0.06	0.015	0.03	0.015	<=0.008	<=0.015	0.5	0.25
Y82	*C. utilis*	0.063	0.250	4	0.25	0.12	0.25	0.03	0.015	<= 0.015	0.25	<= 0.06
Y83	*C. albicans*	0.03125	>16	2	0.12	0.06	0.06	0.06	0.015	0.06	0.5	<= 0.06
Y84	*C. albicans*	0.031	0.031	0.5	0.06	0.015	0.015	0.12	0.015	0.03	0.25	0.12
Y87	*C. glabrata*	0.031	0.063	8	0.25	0.25	0.5	0.06	0.015	0.03	5	<= 0.06
Y88	*C. albicans*	0.03125	0.03125	0.5	0.03	<=0.008	0.015	0.06	<=0.008	<=0.015	0.5	<=0.06
Y92	*C. dubliniensis*	0.03	0.03	0.25	0.06	<= 0.008	0.06	0.06	0.03	0.06	0.5	0.12
Y93	*C. albicans*	0.031	0.031	0.5	0.06	0.008	0.03	0.015	<= 0.008	<= 0.015	0.5	0.25
Y107	*C. albicans*	0.0625	>16	0.5	0.06	0.015	0.015	0.06	0.008	0.015	0.5	0.12
Y111	*C. albicans*	0.03125	>16	0.5	0.03	0.008	0.015	0.03	0.015	0.03	0.5	0.06
Y121	*C. glabrata*	0.13	0.25	16	0.5	0.5	1	0.12	0.015	0.03	1	0.12
Y125	*C. krusei*	0.13	0.25	16	0.12	0.12	0.12	0.25	0.12	0.06	0.5	16
Y126	*C. parapsilosis*	0.031	0.031	0.25	0.06	<=0.008	0.03	0.25	2	2	0.5	0.12
Y152	*C. albicans*	0.03125	0.03125	<=0.12	<=0.015	<=0.008	<=0.008	0.03	<=0.008	<=0.015	0.25	<=0.06
Y160	*C. albicans*	0.031	0.031	1	0.03	0.03	0.015	0.03	<=0.008	<=0.015	0.25	<=0.06

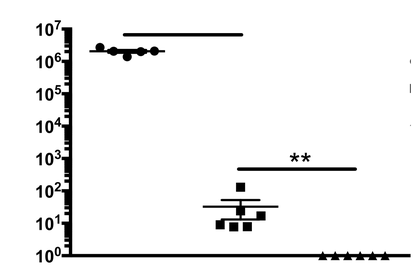
Table 2: MIC_{50} for VT-1129 and VT-1161 against *Candida* isolates

***Candida* Spp.**	**MIC_{50} (µg/mL)**		
	VT-1161	**VT-1129**	**Fluconazole**
Candida albicans	0.03	0.03	0.5
Candida glabrata	0.125	0.25	16
non-*albicans*/non-*glabrata* *Candida* strains	0.06	0.125	4
all tested strains	0.03	0.06	4
Fluconazole-resistant strains	0.125	0.25	16

Table 3: Drug levels of VT-1129 and VT-1161 in *Act1*$^{-/-}$ mice

Tissue Type	**Concentration (SEM)**		**Units**
	VT-1161	**VT-1129**	
Tongue	42 (6)	14 (2)	µg VT-1161/g sample
Serum	10 (1)	4.0 (0.6)	µg VT-1161/mL
Stool	38 (4)	11 (2)	µg VT-1161/g sample

Figure 1: VT-1161 clears *Candida* from the oral mucosa of *Act1*$^{-/-}$ mice



Act1$^{-/-}$ mice were sublingually infected with *C. albicans* strain Y72 and given vehicle, fluconazole, or VT-1161 via oral gavage 18 hours post-infection and every day thereafter for 4 total doses. At day 5 post-infection, the total number of *Candida* in the tongues of these mice was determined. The data were analyzed using Mann-Whitney test (** $p < 0.01$). 5-6 mice were used per group.

Summary and Future Directions

- VT-1161 and VT-1129 have strong *in vitro* activity against susceptible and resistant isolates from CMC patients.
- Both compounds have plasma and tissue levels well above their MIC values after oral administration in mice.
- A clinically relevant oral dose of VT-1161 led to eradication of viable fungi in a mouse model of oral candidiasis.
- Future studies will examine the dose-dependency of this finding, as well as test *in vivo* activity against fluconazole-resistant *Candida*.

References

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