Activity of a novel 1,3-beta-D-glucan inhibitor, Ibrexafungerp (formerly SCY-078), against *Candida glabrata*

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BACKGROUND

Emergence of echinocandin resistance in invasive candidiasis has become an area of clinical concern. Ibrexafungerp (IBX , formerly SCY-078**)** is a novel glucan synthase inhibitor with oral availability that has activity against *Candida*, *Aspergillus* and *Pneumocystis*, including echinocandin-resistant species. In this study, IBX was evaluated for activity against *C. glabrata, in vitro* and *in vivo*.

METHODS

- *In vitro* activity of IBX against 33 *C. glabrata* clinical isolates (*n*=11 wild type, 22 echinocandin-resistant) was tested according to CLSI M27-A4 methodology and in a time-kill assay.
- In the time-kill assay, *Candida* cells were adjusted to 1x10^5 cells/mL and added to tubes with different concentrations of IBX.
- Tubes were then incubated for 1, 4, 8, 24, or 48 h at 37°C.
- 100µL of sample was taken from each time point, plated on agar plates, and incubated at 37°C to determine colony forming units (CFU).
- *In vivo* activity of IBX given orally was evaluated in a murine model using echinocandin-susceptible and -resistant *C. glabrata* strains.
- Female 6-8 week old CD-1 mice were immunosuppressed with cyclophosphamide (200 mg/kg) 3 days prior to infection and 150 mg/kg 1 day post-infection.
- Mice were inoculated with either 1x10^7 cells/mL of the resistant strain or 1x10^8 cells/mL of the wild-type strain via the lateral tail vein.
- Treatments were administered 2 hours post-infection for 7 days BID for a total of 14 doses.
- Mice were sacrificed 12 hours after the last dose, their kidneys removed, homogenized, and plated to determine CFU.

RESULTS

The IBX MIC range against 33 *C. glabrata* clinical isolates was 0.5-4.0 µg/mL, with an MIC90 of 2.0 µg/mL (Table. 1). Time-kill studies showed that IBX, at concentrations of 0.25 to 1 µg/mL, produced a 4 to 6 log reduction in growth of the susceptible strain at 24- and 48-hour time points (Fig. 1). Similarly, at concentrations of 0.25 to 4 µg/mL, growth of the resistant strain was reduced by more than 5 log. IBX concentrations >4 µg/mL led to complete inhibition of growth in both strains beginning at 8 hours. Mice infected with *C. glabrata* and treated with IBX doses ≤ 30 mg/kg showed significant reductions in kidney CFU for both a susceptible strain ($P \leq 0.01$) and a resistant strain ($P \leq 0.03$) (Figs. 2 and 3, respectively).

	CAS	MICA	IBX
Range	0.25-2.0	<0.016-2.0	0.5-4.0
MIC_{50}	1.0	0.06	1.0
MIC_{90}	2.0	1.0	2.0

Table 1. MIC values (µg/mL)

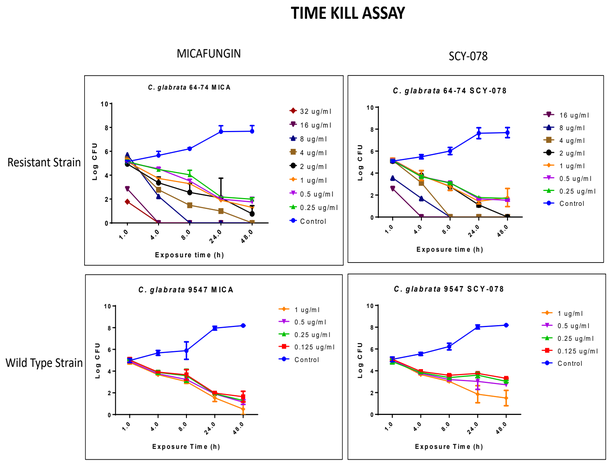

Figure 1.

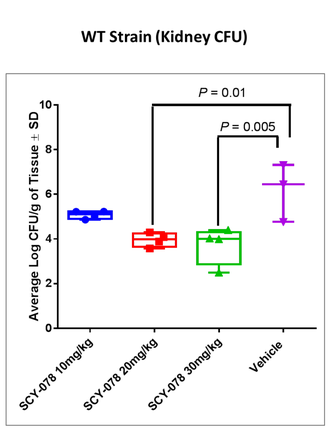

Figure 2.

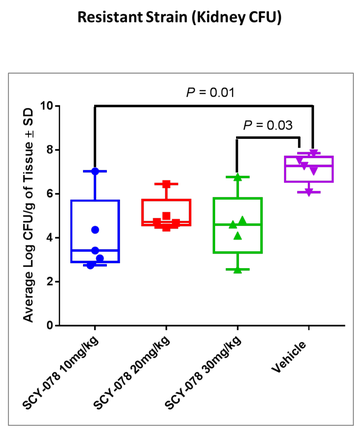

Figure 3.

CONCLUSIONS

In vivo and *in vitro* assays suggest that IBX has promise for the treatment of invasive candidiasis caused by wild-type and echinocandin-resistant *C. glabrata.*

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