Does Sabouraud Dextrose Broth, Compared to RPMI, Differentiate Susceptibility Between Resistant and Susceptible *C. glabrata* and *C. albicans* Isolates to SCY-078, a Novel β-D-glucan Synthase Inhibitor, and Caspofungin?

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BACKGROUND

SCY-078 is a first-in-class triterpenoid antifungal, orally-bioavailable glucan synthase inhibitor, with broad *in vitro* and *in vivo* activity against different species of *Candida* and *Aspergillus*, including echinocandin-resistant (ER) strains (mostly with FKS1 and/or FKS2 mutations). SCY-078 is orally bioavailable, which could potentially lead to better patient compliance and tolerability. Determining the antifungal susceptibility of *Candida* to echinocandins, particularly caspofungin using the CLSI M27-A3 methodology that employs RPMI as a medium is challenging. Here we compared the ability of RPMI and Sabouraud dextrose broth (SDB) to differentiate between susceptible (S) and ER *Candida* isolates.

METHODS

- Two types of clinical *Candida* species [*C. glabrata* (22 ER and 11 S) and *C. albicans* (11 ER and 12 S)] were tested. All resistant isolates with the exception of 1 *C. albicans*, were FKS1 and/or FKS2 mutants.
- Susceptibility testing was performed according to CLSI M27-A3 microdilution assay and minimum inhibitory concentration (MIC) values were determined.
- Two growth media were utilized: RPMI-1640 (drug concentrations of 0.016 – 8 µg/ml) and SDB (drug concentrations of 0.002 – 1 µg/ml).
- The isolates were tested against SCY-078, caspofungin, and micafungin.
- Isolates were tested in parallel at the Center for Medical Mycology, Cleveland, Ohio, and the Fungus Testing Laboratory, San Antonio, Texas, to verify reproducibility.

RESULTS

- MIC values for SCY-078 and caspofungin in SDB were lower than those obtained in RPMI (Table 1).
- Overall, MIC values for micafungin in SDB and RPMI remained consistent (Table 1).
- For both SCY-078 and caspofungin, wider separation of MIC values between ER and S *Candida* isolates were obtained in SDB, compared to RPMI, potentially indicating that SDB may be able to better differentiate resistant strains than RPMI (Table 2).
- For caspofungin, the separation difference in MIC values between the two media was substantially large (up to 4 dilutions wider in SDB).
- In contrast, the MIC separation difference for SCY-078 was small (up to 1 dilution wider in SDB).
- Inability to separate MIC for SCY-078 in either media of the ER *Candida* strains may indicate that isolates resistant to caspofungin and micafungin may be susceptible to SCY-078.

Table 1: MIC ranges for compounds against two *Candida* species in two different medias. (µg/mL)

C. Glabrata	**RPMI**		**SDB**	
	S N=11	ER N=22	S N=11	ER N=22
SCY-078	0.5 - 2	0.25 - 4	0.016 - 0.125	0.008 - >1
CASPOFUNGIN	0.5 - 1	0.25 - >8	0.001 - 0.06	0.016 - >1
MICAFUNGIN	<0.016 - 0.125	<0.016 - 2	0.008 - 0.06	0.008 - >1
C. Albicans	RPMI		SDB	
	S N=12	ER N=11	S N=12	ER N=11
SCY-078	0.06 - 1	0.5 - 4	0.004 - 0.125	0.016 - 0.5
CASPOFUNGIN	0.06 - 0.25	0.25 - 4	<0.001 - 0.03	0.016 - >1
MICAFUNGIN	<0.016 - 0.03	0.25 - 2	0.016 - 0.06	0.03 - >1

Table 2: MIC_{50} and MIC_{90} for compounds against two *Candida* species in two different medias. (µg/mL)

C. glabrata	**RPMI**						**SDB**					
	MIC_{50}		D	MIC_{90}		D	MIC_{50}		D	MIC_{90}		D
	S N=11	ER N=22		S N=11	ER N=22		S N=11	ER N=22		S N=11	ER N=22	
SCY-078	1	1	0	1	4	2	0.06	0.125	1	0.125	0.5	2
CASPOFUNGIN	0.25	1	2	0.5	2	2	0.004	0.25	6	0.03	1	5
MICAFUNGIN	<0.016	0.5	6	0.06	2	5	0.03	0.25	3	0.03	1	5
C. albicans	RPMI						SDB					
	MIC_{50}		D	MIC_{90}		D	MIC_{50}		D	MIC_{90}		D
	S N=12	ER N=11		S N=12	ER N=11		S N=12	ER N=11		S N=12	ER N=11	
SCY-078	0.25	2	3	1	4	2	0.016	0.125	3	0.03	0.25	3
CASPOFUNGIN	0.125	2	4	0.25	4	4	0.004	0.25	6	0.03	>0.5	5
MICAFUNGIN	<0.016	0.5	6	0.03	2	6	0.03	0.5	4	0.06	>0.5	4

Abbreviations: D = Number of dilutions difference between the S and ER isolates, MIC_{50} = minimum inhibitory concentration for 50% of tested isolates, MIC_{90} = minimum inhibitory concentration for 90% of tested isolates

CONCLUSIONS

This data indicates that MIC testing of caspofungin and SCY-078 in SDB may allow for improved differentiation of resistant strains; however, further testing is warranted.

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