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A New Path for Antifungal Treatments

C. auris – a difficult to treat, emerging pathogen

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A New Path for Antifungal Treatments

Committed to positively impacting the lives of patients suffering from difficult-to-treat and often life-threatening infections

Objectives

- To provide a brief background on *C. auris*, an emerging multi-drug resistant organism that presents significant concerns as a pathogen.

- To introduce SCY-078, the first representative of a new class of glucan synthase inhibitors, and it's activity against *C. auris*.

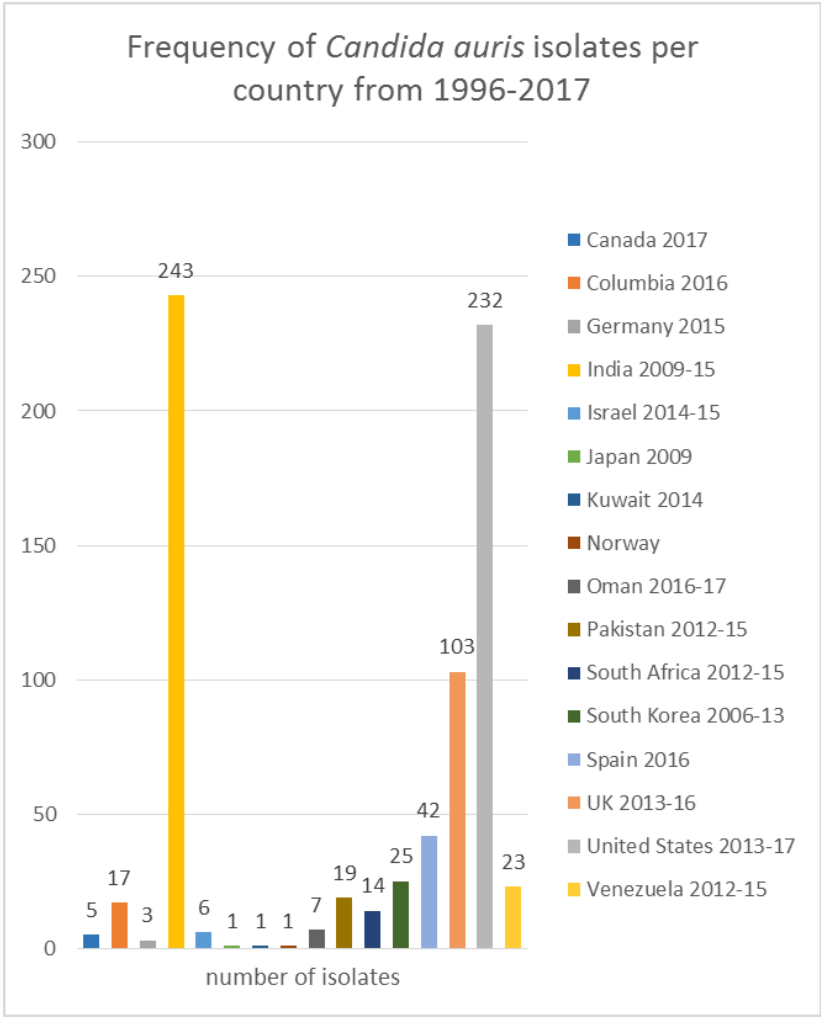
C. auris - Background

- *C. auris* is an emerging, multidrug-resistant yeast that can spread in healthcare settings.
- Initially isolated in 2009 in Japan from a patient's ear canal
  - Invasive infections due to *C. auris* have subsequently been reported in five continents
- Associated with nosocomial outbreaks in intensive care settings and high mortality rates
  - According to the US CDC, more than 1 in 3 patients with invasive *C. auris* infection will die

Tsay et.al., CID 2018 and Jeffrey-Smith et.al., Clin Micro Rev 2018, www.cdc.gov/fungal/diseases/candidiasis/pdf/Candida_auris_508.pdf

C. auris - Epidemiology

- Has been found on 5 continents and 16 countries
- Causes ear infections, blood stream infections, sepsis, invasive infections
- 4 main clades based on ribosomal DNA
  - Grouped by geographical origin



Sekyere JO, *Candida auris:* A systematic review and meta-analysis of current updates on an emerging multidrug-resistant pathogen, MicrobiologyOpen (2018), http://doi.org/10.1002/mbo3.578

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C. auris – Challenges for Treatment

- Often misidentified
  - Cannot use methods such as ChromAgar, BD Phoenix, Microscan
  - Identification requires:
    - MALDI-TOF
    - PCR/real-time PCR
    - Whole genome sequencing

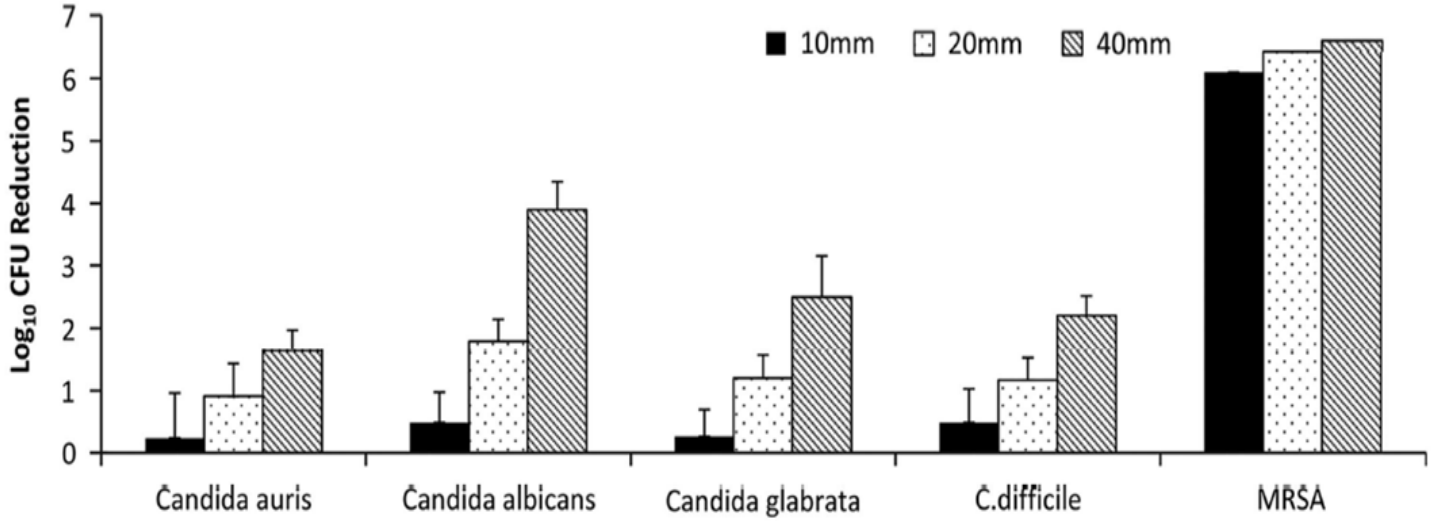
- Can be spread in health care setting
  - Difficult to disinfect; can persist in healthcare environment
  - Persists on skin
  - Transmission can occur between patients

Sekyere, j. Microbiology Open 2018, Tsay et.al., CID 2018

C. auris - UV Disinfection?

- Ultraviolet-C (UV-C) light room decontamination devices are often used in cleaning programs in healthcare facilities.

- *C. auris* is <u>less susceptible</u> to killing by UV-C exposure in comparison to other pathogens.



Cadnum JL, Shaikh AA, Piedrahita CT, *et al.*, Relative Resistance of the Emerging Fungal Pathogen *Candida auris* and Other *Candida* Species to Killing by Ultraviolet Light, Infect Control Hosp Epidemiol (2017), https://doi.org/10.1017/ice.2017.239

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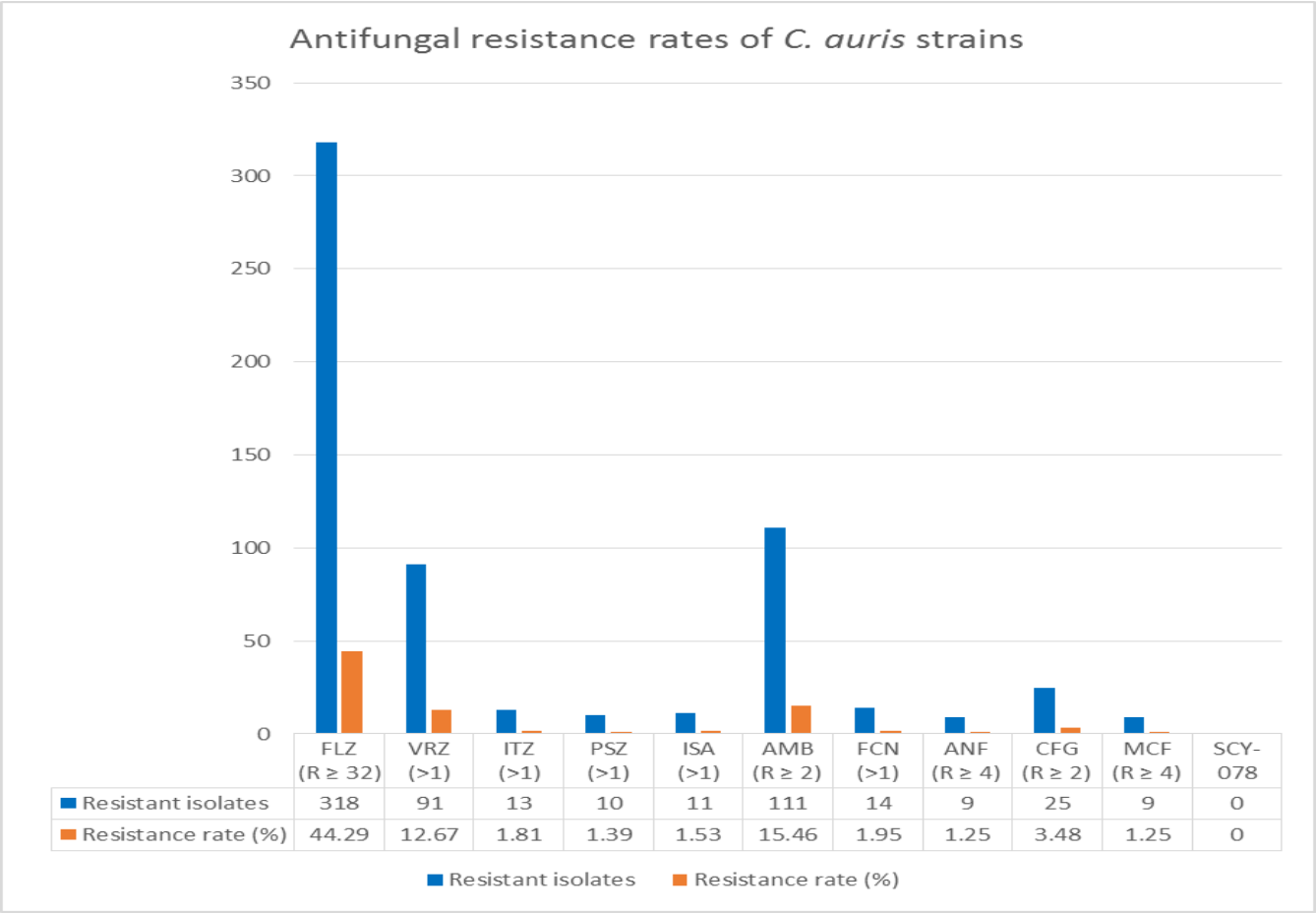
C. auris – Challenges for Treatment

- Isolates are often multi-drug resistant
  - In a meta-analysis of over 150 publications that identified 742 *C. auris* isolates, most were resistant to fluconazole and/or other azoles and to AMB
  - Resistance to all three classes of compounds (azoles, polyenes and echinocandins) have been reported

Sekyere, j. Microbiology Open 2018, Tsay et.al., CID 2018

C. auris – Challenges for Treatment



	FLZ (R ≥ 32)	VRZ (>1)	ITZ (>1)	PSZ (>1)	ISA (>1)	AMB (R ≥ 2)	FCN (>1)	ANF (R ≥ 4)	CFG (R ≥ 2)	MCF (R ≥ 4)	SCY-078
Resistant isolates	318	91	13	10	11	111	14	9	25	9	0
Resistance rate (%)	44.29	12.67	1.81	1.39	1.53	15.46	1.95	1.25	3.48	1.25	0

Sekyere JO, *Candida auris:* A systematic review and meta-analysis of current updates on an emerging multidrug-resistant pathogen, MicrobiologyOpen (2018), http://doi.org/10.1002/mbo3.578

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C. auris – Treatment Guidelines

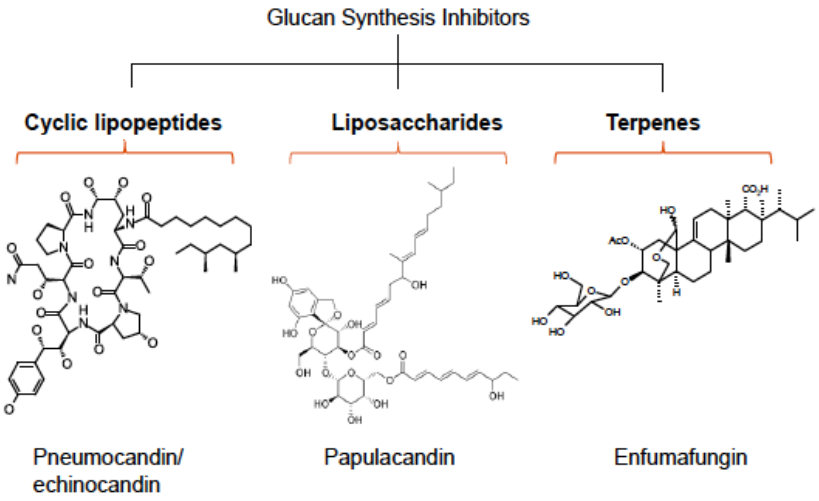
- Based on limited data available to date; the US CDC recommendations for treatment of adults consists of:
  - Initiation of therapy with an echinocandin
  - Due to the potential for rapid resistance development - patients should be carefully monitored for clinical improvement and follow-up cultures and repeat susceptibility testing should be conducted
  - Switching to a liposomal amphotericin B (5 mg/kg daily) could be considered if the patient is clinically unresponsive to echinocandin treatment or has persistent fungemia for >5 days.

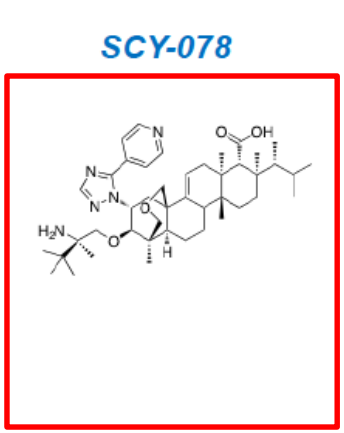
https://www.cdc.gov/fungal/diseases/candidiasis/c-auris-treatment.html

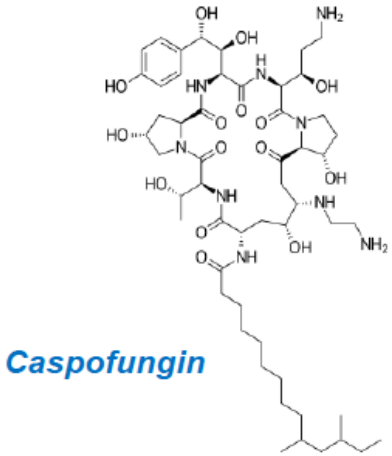
SCY-078 - Introduction

SCY-078 First-in-Class Triterpenoid Antifungal

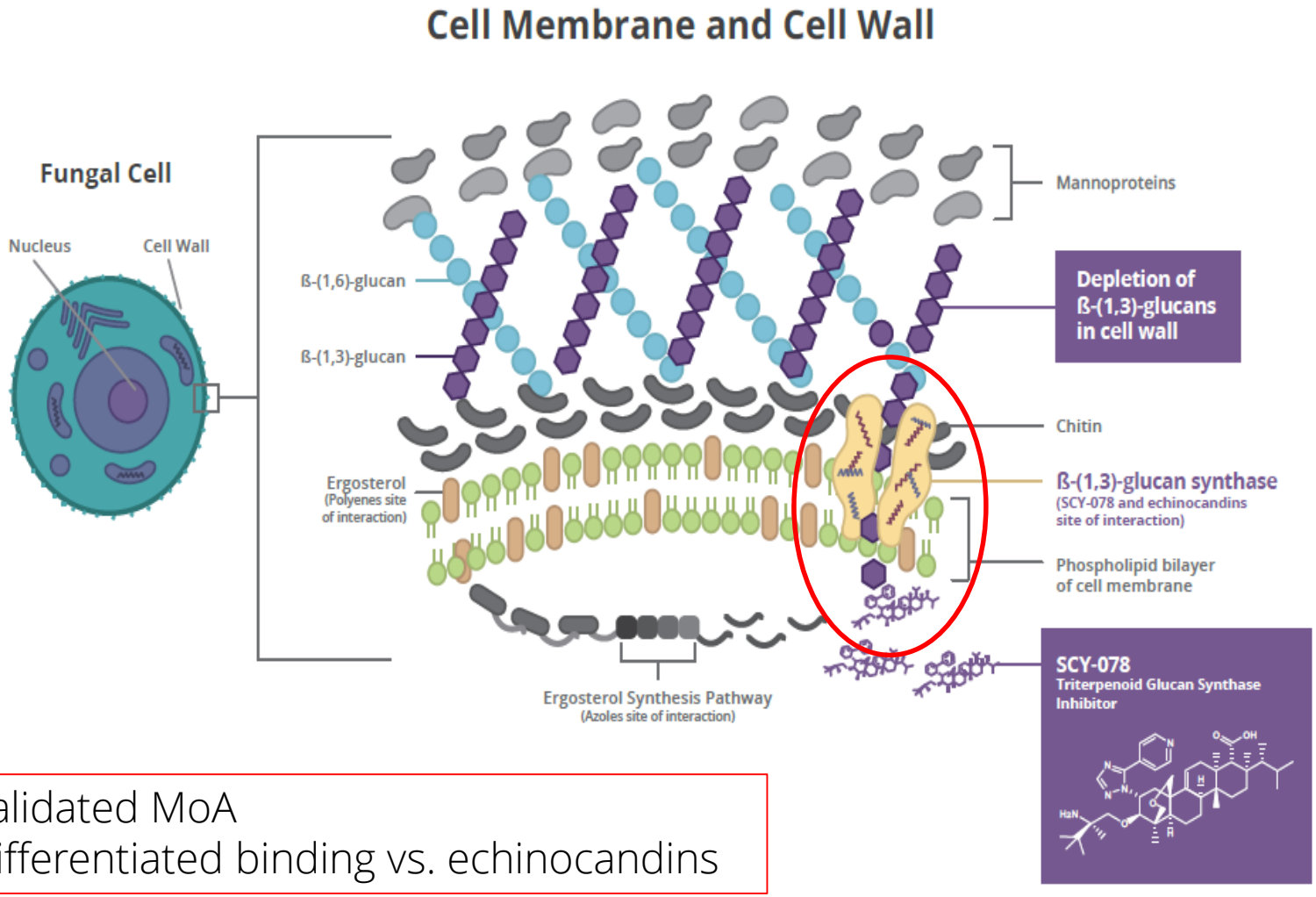
- SCY-078 has a distinct molecular structure
- Validated mechanism of action:
  - Inhibition of β-(1,3)-glucan synthase







SCY-078 MoA: Glucan Synthase Inhibitor



- Validated MoA
- Differentiated binding vs. echinocandins

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SCY-078 – *In vitro* activity vs *Candida* spp.

- SCY-078 has been evaluated for activity against >1500 clinical Candida isolates using CLSI and EUCAST methods
  - SCY-078 demonstrated *in vitro* activity against all of the *Candida* spp. isolates tested with MIC_{90} values ranging from 0.06 ug/mL to 4 ug/mL depending on the species tested
- Demonstrated similar activity against wild-type (WT) and azole-resistant Candida isolates
  - Overall, SCY-078 was effective against > 90% of the azole-resistant strains.
- Has been evaluated *in vitro* against ≈200 echinocandin-resistant clinical *Candida* spp. isolates with the majority of these isolates having mutations in the *fks* genes
  - Overall, the majority of the echinocandin-resistant strains tested in these studies remained susceptible to inhibition by SCY-078.
- SCY-078 has also demonstrated activity *in vitro* against bio-films

SCY-078 - In Vitro Activity vs *C. auris*

- The activity of SCY-078 against >110 clinical isolates of *C. auris* has been evaluated in two independent studies

	Berkow et.al. (N=100)	Larkin et.al. (N=16)
	SCY-078 MIC (μg/mL)	SCY-078 MIC (μg/mL)
Range	0.0625 – 2	0.5 – 2
Mode	1	1
MIC50	0.5	1
MIC90	1	1

SCY-078 showed activity against all clades of *C. auris* with very little variation in activity between the clades

Berkow et.al. AAC 2017, Larkin et.al., AAC 2017

SCY-078 - In Vitro Activity against ECH-R *C. auris*

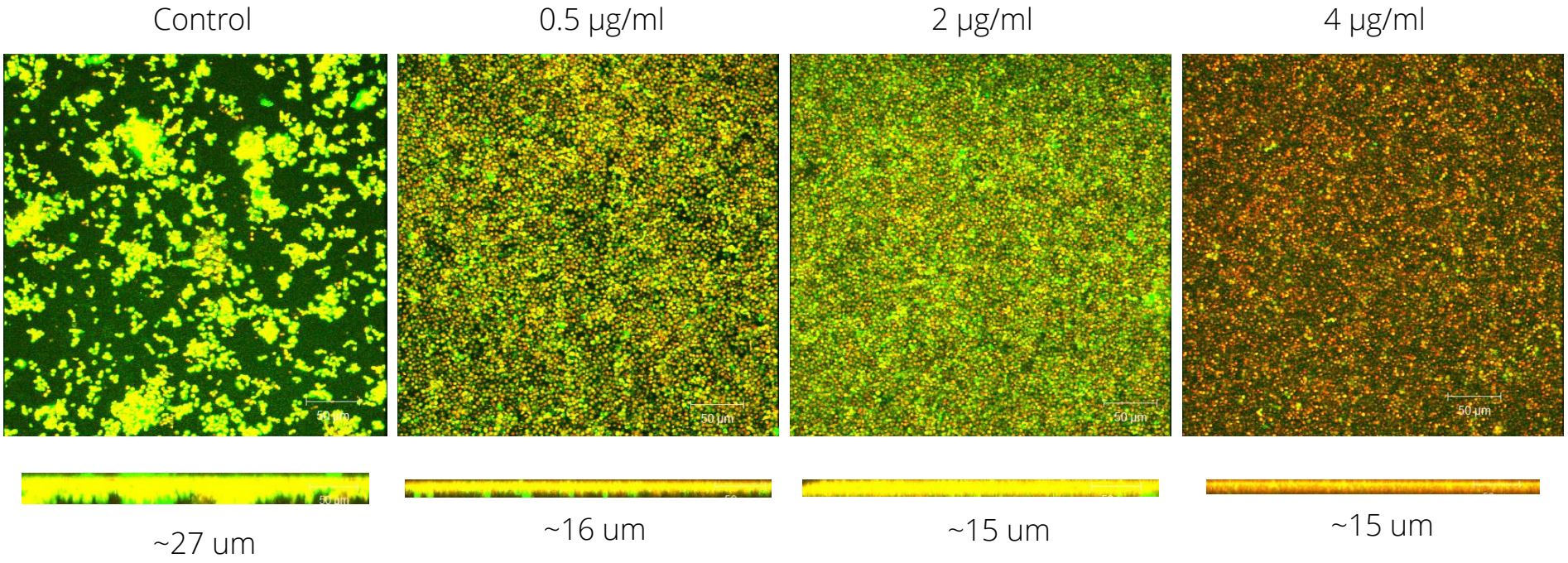
- SCY-078 was active against a panel of *C. auris* isolates with elevated ECH MICs

	Minimum Inhibitory Concentration (µg/ml)			
Isolate	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	.5	.5	0.5
6	>16	>16	>8	0.5
7	4	>16	1	1

Among seven isolates with elevated MICs to one or more echinocandins, the MIC range of SCY-078 was 0.5 to 1 ug/ml, similar to that observed against the panel of WT isolates

Berkow et.al. AAC 2017

SCY-078 - Activity vs *C. auris* Biofilms



Confocal analysis – A/E = no drug, B/F = SCY-078 0.5 mg/L, C/G= SCY-078 2 mg/L, D/H – SCY-078 4 mg/L
**P*-value compared to untreated control (P<0.05)

SCY-078 significantly inhibited *C. auris* biofilms at all concentrations tested.
(Reduction in green fluorescence resulting from concanavalin A [ConA] binding to polysaccharides)

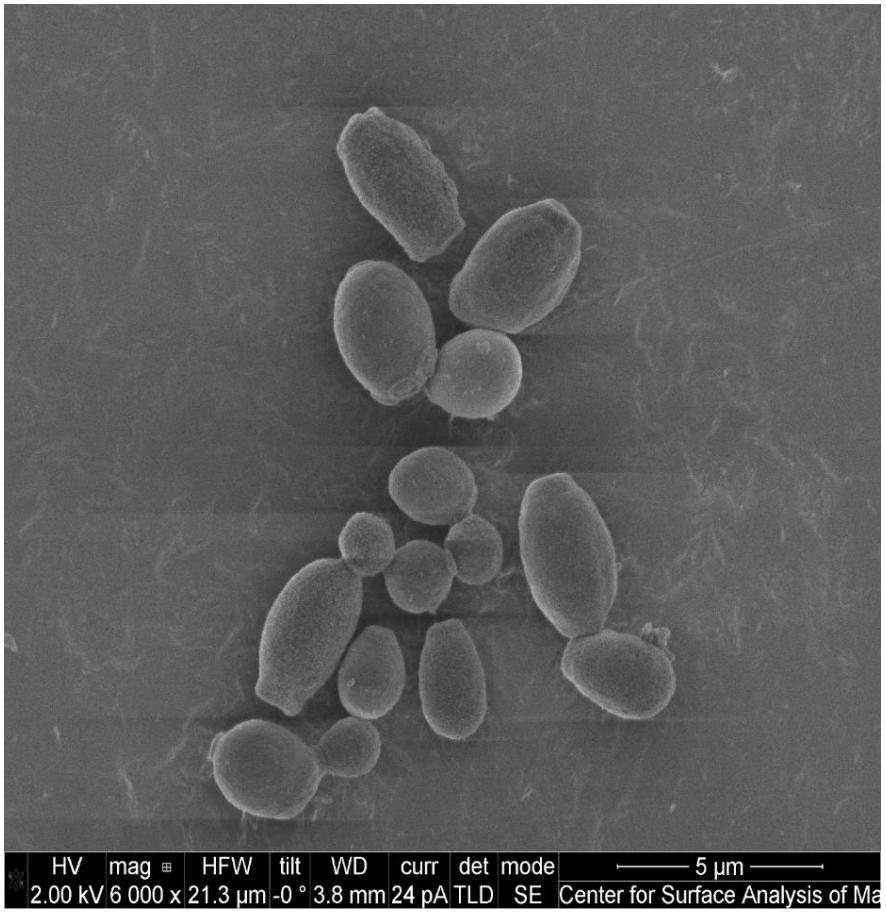
SCY-078 - Activity vs *C. auris* Biofilms

The thickness (I) and metabolic activity (J) of untreated (control) and SCY-078-treated biofilms.
* *P*-value compared to untreated control (P<0.05)

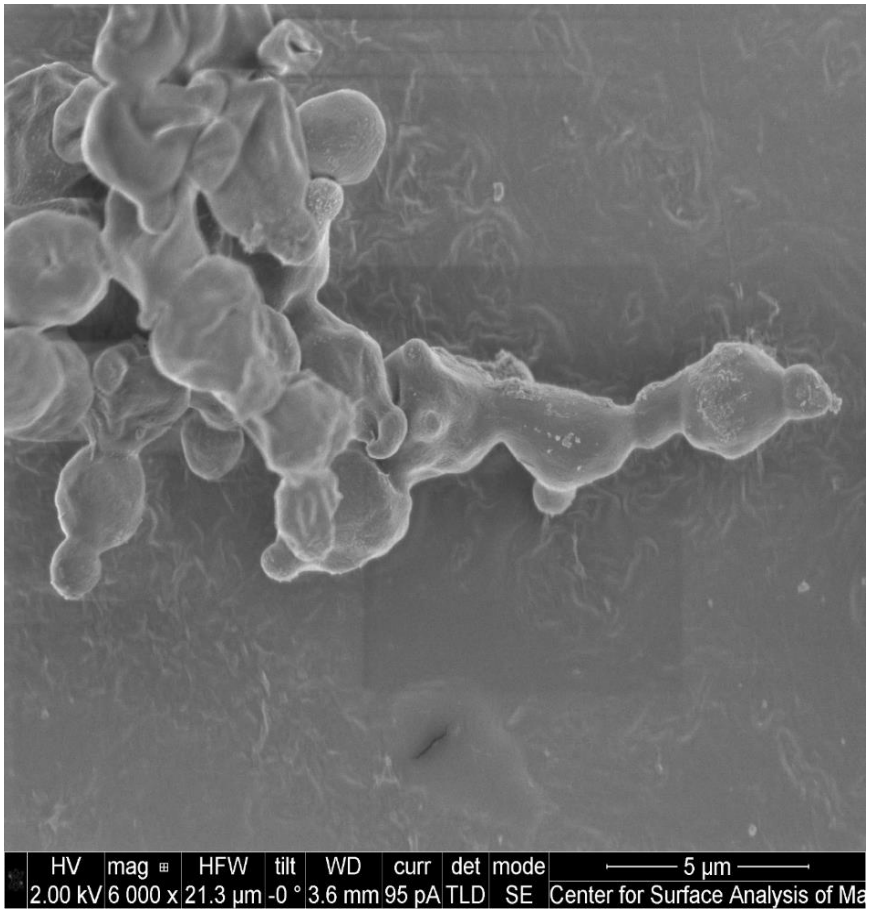
SCY-078 significantly reduced the metabolic activity and thickness of the *C. auris* biofilms at all concentrations tested

Activity of SCY-078 on *C. auris* (SEM)

C. auris before SCY-078



C. auris after SCY-078*



**C. auris* were exposed overnight to SCY-078 at 1X MIC (0.5 µg/mL) at 35^{0}C

SCY-078 interrupted *C. auris* cell division with the organism forming abnormal fused fungal cells

Larkin et.al. AAC 2017

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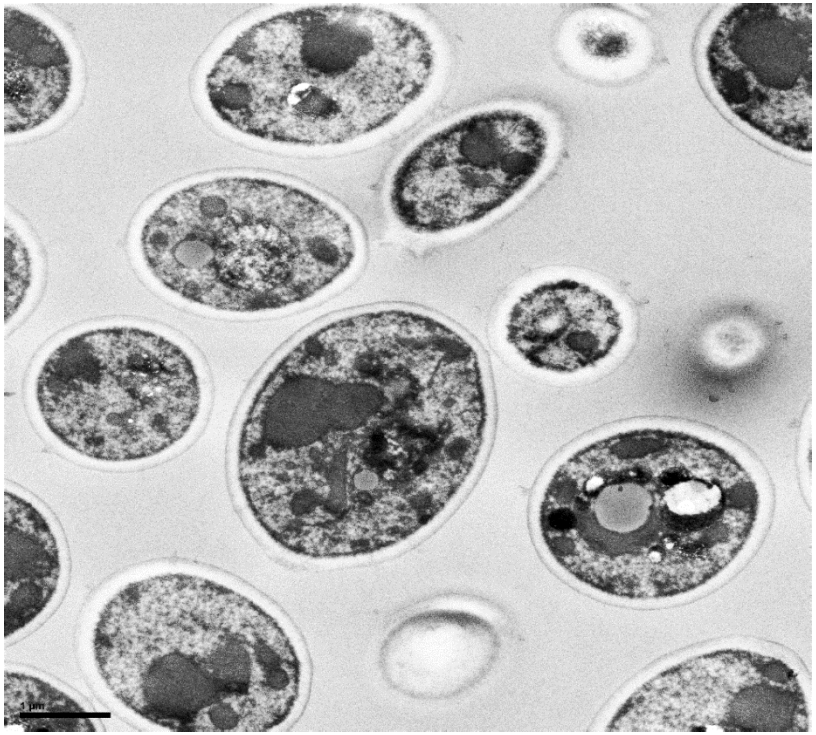
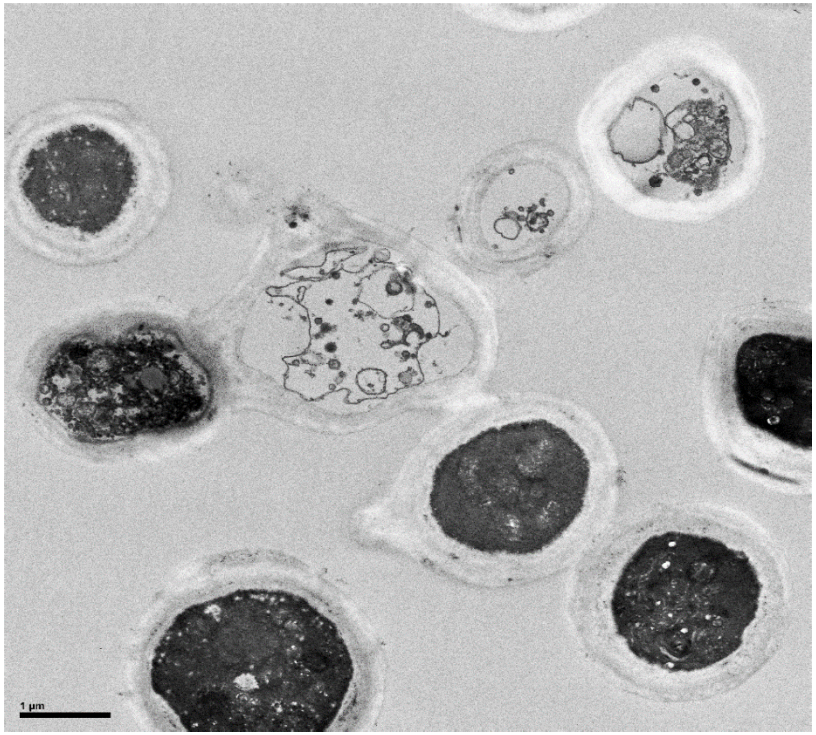
Activity of SCY-078 on *C. auris* (TEM)

C. auris before SCY-078



C. auris after SCY-078*



**C. auris* were exposed overnight to SCY-078 at 1X MIC (0.5 µg/mL) at 35^0C

- TEM analysis shows that SCY-078 treatment affected the ultrastructure of *C. auris* resulting in:
- Thickening of the outer cell envelop (thick cell wall and disappearance of cell membrane)
- Leakage of cytoplasmic material
- Destruction of the internal cytoplasmic structures where ghost cells were noted
- Abnormal fused fungal cells (confirming results from SEM)

(Dr. M. Ghanoum, personal communication, 2018)

SCY-078 – Ongoing efforts for *C. auris*

- *In vivo* PK/PD models in progress
  - Invasive infection model in mice
  - Cutaneous infection model in guinea pigs

- These *in vivo* models will further expand dose/exposure/response data for PK/PD modeling.

- Additional electron microscopy underway to compare morphological effects with other antifungal agents.

SCY-078 – Ongoing studies for patients with *C. auris*

- CARES
  - Open label study allowing inclusion of patients with any *C.auris* infection.
  - Currently open for enrollment in the US and soon in India and other territories.
- FURI
  - Open label study intended for patients with Candida infections (including *C. auris*) that are refractory to or intolerant of approved antifungal agents.
  - Centers open in US, Germany, Austria.
  - Centers in process of opening in UK, Netherlands, Spain and other territories.

Summary

- *C. auris* is a multi-drug resistant organism which presents a clear concern for human health.
- *C. auris* is difficult to identify, disinfect and treat.
- SCY-078 is the first representative of a new class of antifungal agents,
  - It has activity against *C. auris*, making it an important addition for antifungal treatment.

Backup Slides

In Vitro Activity of SCY-078 and Comparators Against Clinical Isolates of Predominant *Candida* spp.

	SCY-078[a]	CSP[a]	SCY-078[b]	CSP[b]	SCY-078[c]	MCF[c]	SCY-078[d]	MCF[d]	SCY-078[e]	MCF[e]	SCY-078[f]	CSP[f]
Candida spp.	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}	N MIC_{50} MIC_{90}
Albicans	29 0.125 1	29 0.125 2	69 0.125 0.25	69 0.03 0.25	33 0.06 0.125	33 ≤0.015 0.03	NA	NA	55 0.03 0.06	55 <0.007 0.007	30 0.125 0.125	30 0.03 0.06
Glabrata	29 0.5 2	29 0.125 16	67 0.5 4	67 0.06 2	23 0.25 1	23 ≤0.015 ≤0.015	137 0.5 1	137 0.03 0.03	33 0.125 0.5	33 <0.007 0.125	30 0.25 0.25	30 0.06 0.06
Parapsilosis	15 0.25 0.5	15 0.5 0.5	43 0.5 1	43 0.5 1	19 0.25 0.25	19 1 2	NA	NA	32 0.25 0.25	32 0.5 1	31 0.25 0.5	31 0.5 1
Tropicalis	21 0.25 1	21 0.06 1	31 0.25 0.5	31 0.03 0.03	12 0.125 0.25	12 ≤0.015 0.06	NA	NA	8 0.03 0.25	8 <0.007- 2	50 0.25 0.25	50 0.03 0.06
Krusei	19 0.5 2	19 0.125 1	34 1 2	34 0.125 0.25	6 0.5 - 4	6 0.03- 0.25	NA	NA	12 0.5 1	12 0.06 0.25	30 0.5 0.5	30 0.125 0.125

[a] Pfaller et.al., AAC 2013, [b] Pfaller et.al., AAC 2017; [c] Schell et.al., AAC 2017, [d] Borroto-Esoda et.al., ICAAC 2016, [e] Marcos-Zambrano et.al., JAC and [f] Personal communications, EUROFINS

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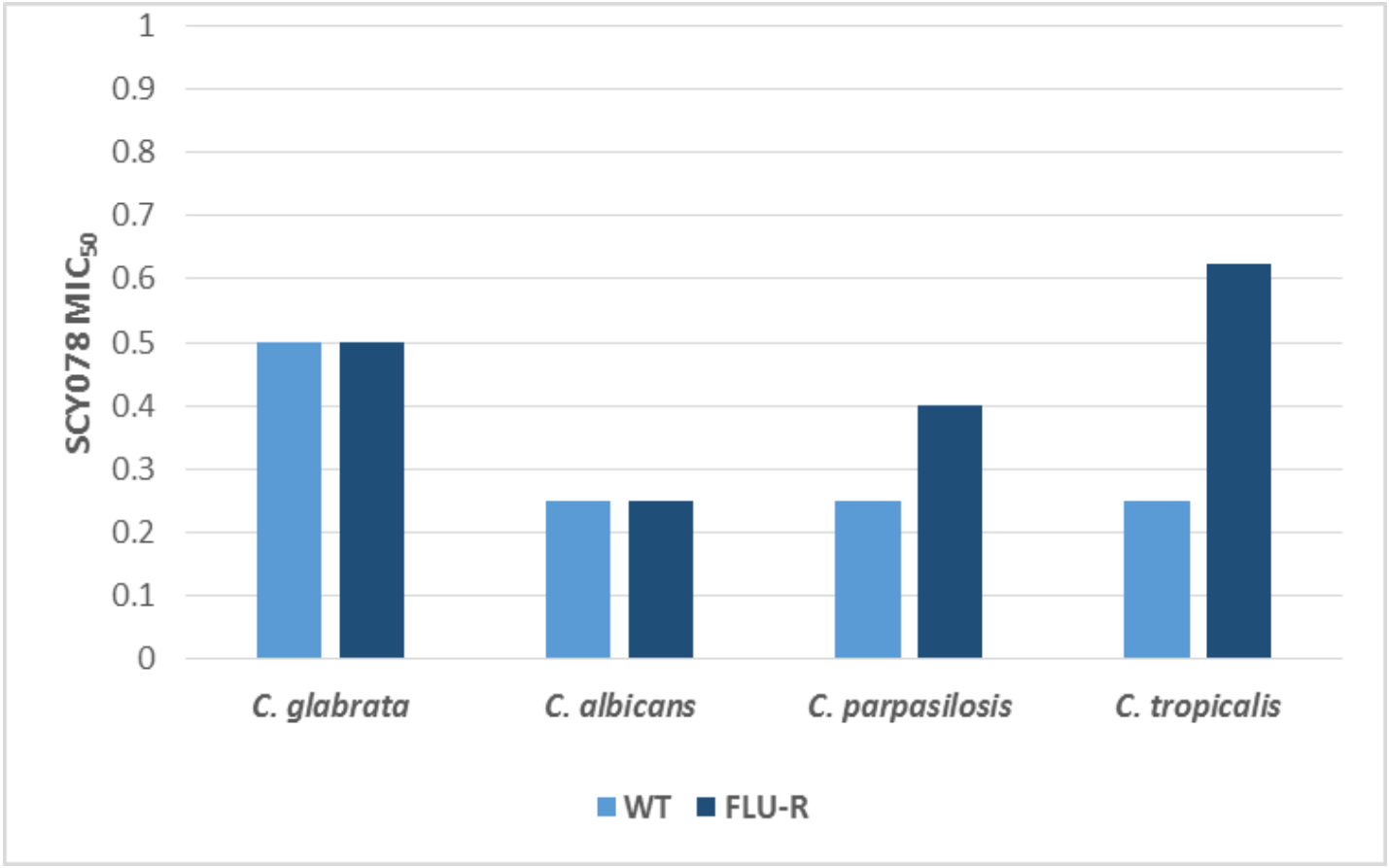
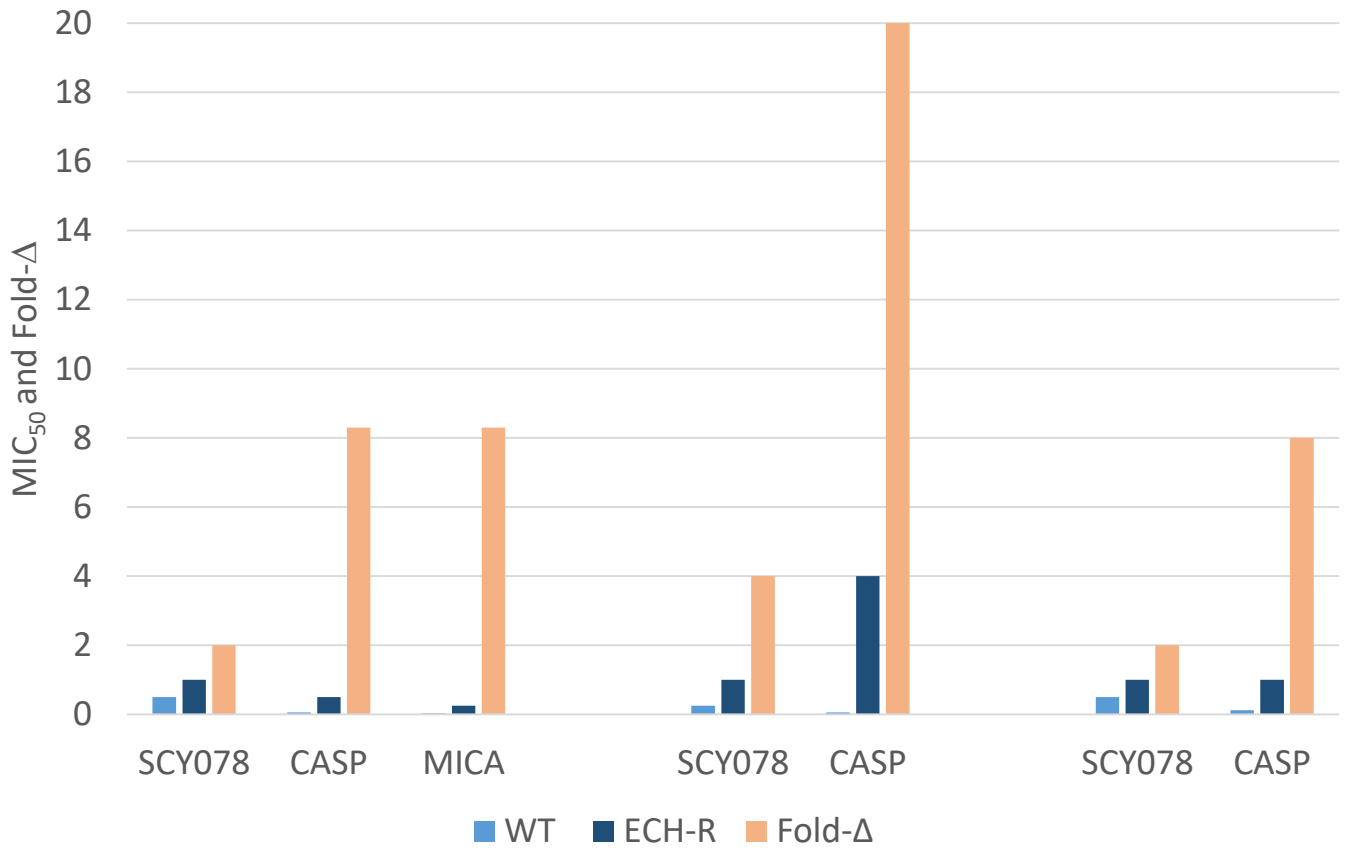
SCY-078 – In vitro Activity vs FLU-R *Candida* spp



SCY-078 demonstrated potent *in vitro* antifungal activity against 93% of the azole-resistant *Candida spp* tested

Borroto-Esoda et.al. ICCAC 2016, poster #44

SCY-078 – In vitro Activity vs ECH-R *Candida* spp



SCY-078 demonstrated superior *in vitro* activity as compared to CASP and MICA against *C. glabrata* isolates with *fks* mutations

Borroto-Esoda et.al. ICCAC 2016, poster #45

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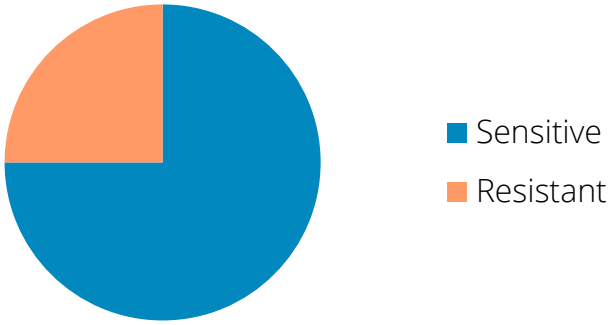
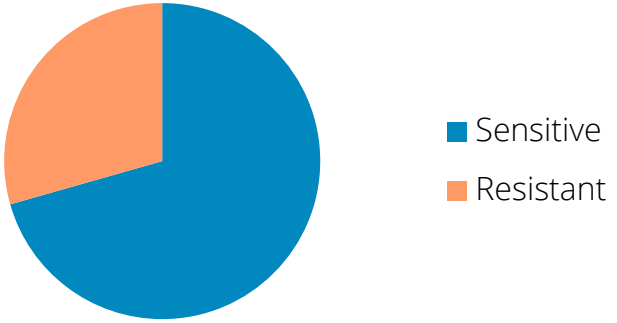
SCY-078 – In vitro Activity vs Multi-Drug Resistant (MDR) *Candida* spp

75% of MDR-*C. Albicans* Isolates Remain Sensitive to Inhibition by SCY-078



71% of MDR-*C. Glabrata* Isolates Remain Sensitive to Inhibition by SCY-078



The majority of MDR *C. albicans* and *C. glabrata* clinical isolates remained sensitive to inhibition by SCY-078 with MIC values ≤1 μg/mL

Borroto-Esoda et.al. ICCAC 2016, poster #46