

The Echinocandin Rezafungin (CD101)  
Demonstrates Potent In vitro Activity against  
*Aspergillus fumigatus*, including Azole-  
Resistant Isolates

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# Disclosures

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- F2G
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- Viamet

## Speakers Bureaus

- Gilead

# Aspergillosis

- Acute invasive aspergillosis

- Estimated ~200,000 cases/year
- Leading cause of invasive mould infections
  - SOT recipients (TRANSNET)
  - Lung transplant recipients (TRANSNET)
  - HSCT recipients (TRANSNET & PATH Alliance)
    - Leading cause IFI in HSCT recipients

- Chronic pulmonary aspergillosis

- Estimated >3 million people infected worldwide
- Common with underlying lung disease
  - Tuberculosis, sarcoidosis

- Azole Resistance

- Point mutations in *CYP51A* (gene encoding for 14 $\alpha$ -demethylase – azole target) observed in *A. fumigatus* clinical and laboratory isolates with azole
- Position of point mutation determines azole resistance
  - Some cause pan-resistance, others specific for voriconazole/isavuconazole or posaconazole/itraconazole

- Historically observed with chronic azole exposure

Denning et al. *Bull World Health Organ* 2011;89:864-872.

Denning et al. *Eur Respir J* 2013;41:621-626.

Denning et al. *Med Mycol* 2013;51:361-370.

Seyedmousavi et al. *Drug Resist Updat* 2014;17:37-50.

# Environmental Exposure to Azoles

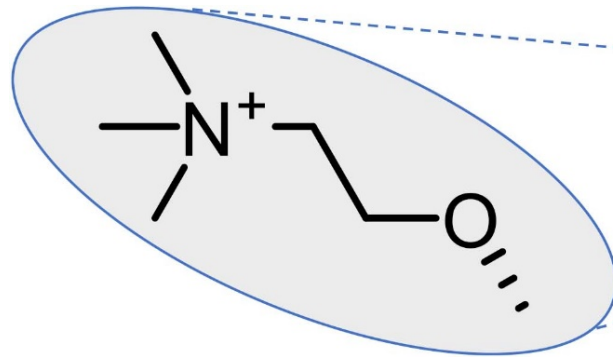
- Azole-resistant IA identified in patients without prior azole exposure in parts of Europe
  - Indoor environment in hospitals & direct proximity to medical centers
  - Fields where azole fungicides used
    - Used in agriculture to combat crop failure & other products to prevent rotting
- Mechanisms of azole resistance in environmental isolates & azole-naïve patients
  - TR<sub>34</sub>/L98H
  - TR<sub>46</sub>/Y121F/T289A

Snelders et al. *Appl Environ Microbiol* 2009;75:4053-3057. Chowdhary et al. *PLoS One* 2012;7:e52871.

van der Linder et al. *Clin Infect Dis* 2013;57:513-520. Chowdhary et al. *J Antimicrob Chemother* 2014;69:555-557.

Chowdhary et al. *J Antimicrob Chemother* 2014;69:2979-2983.

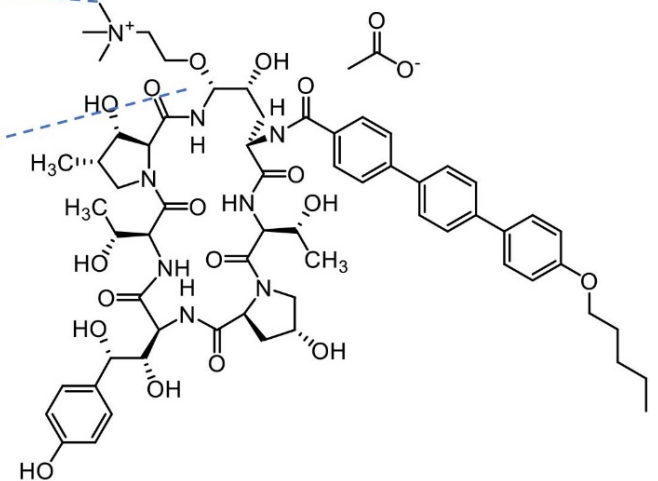
# Rezafungin (CD101)



Structural modification yields chemical stability & enhanced biological properties

Permanent charge and highly stable ring structure...

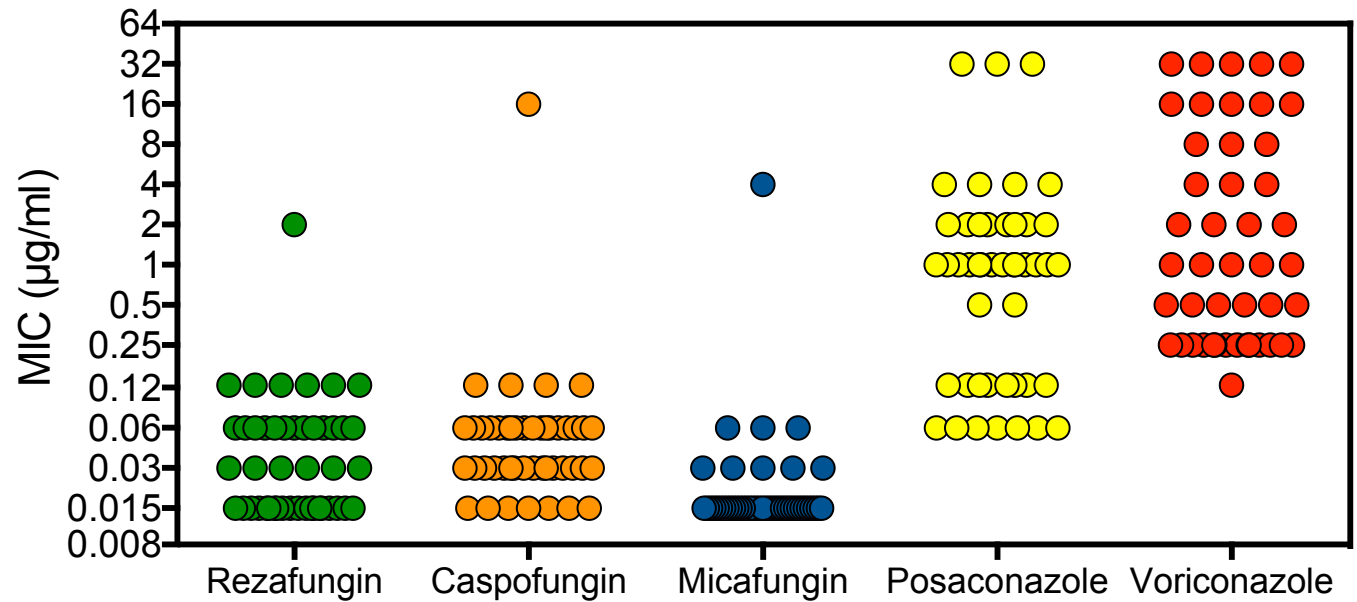
- Prolongs PK ( $t_{1/2}$  130 hrs)
- Allows high exposures: treats less susceptible pathogens
- Enables multiple formulations: intravenous and subcutaneous



# Methods

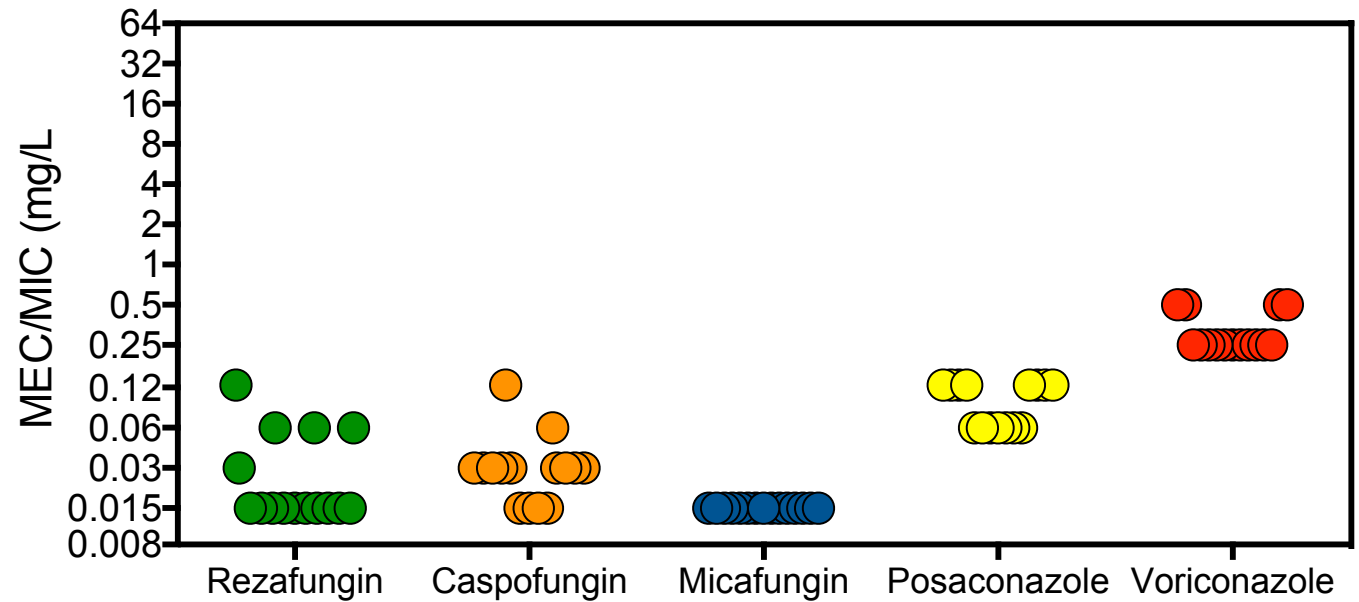
- Wild-type and azole-resistant clinical *A. fumigatus* isolates from U.S. institutions
  - Isolates confirmed to the species level by DNA sequence analysis
    - $\beta$ -tubulin & calmodulin genes and
    - morphologic/phenotypic characteristics (growth at 50°C)
- Susceptibility testing performed by CLSI M38-A2 broth microdilution methods
  - Rezafungin, caspofungin, & micafungin MECs read at 24 hours
  - Posaconazole & voriconazole MICs read at 48 hours
    - 100% inhibition of growth

# Results: All Isolates



Parameter	Rezafungin	Caspofungin	Micafungin	Posaconazole	Voriconazole
All <i>A. fumigatus</i> isolates (n = 46)					
MEC/MIC Range	≤0.015-2	≤0.015->8	≤0.015-4	0.06->16	0.125->16
MEC/MIC <sub>50</sub>	0.03	0.03	≤0.015	1	1
MEC/MIC <sub>90</sub>	0.12	0.06	0.03	4	>16
GM MEC/MIC	0.036	0.046	0.020	0.703	1.502

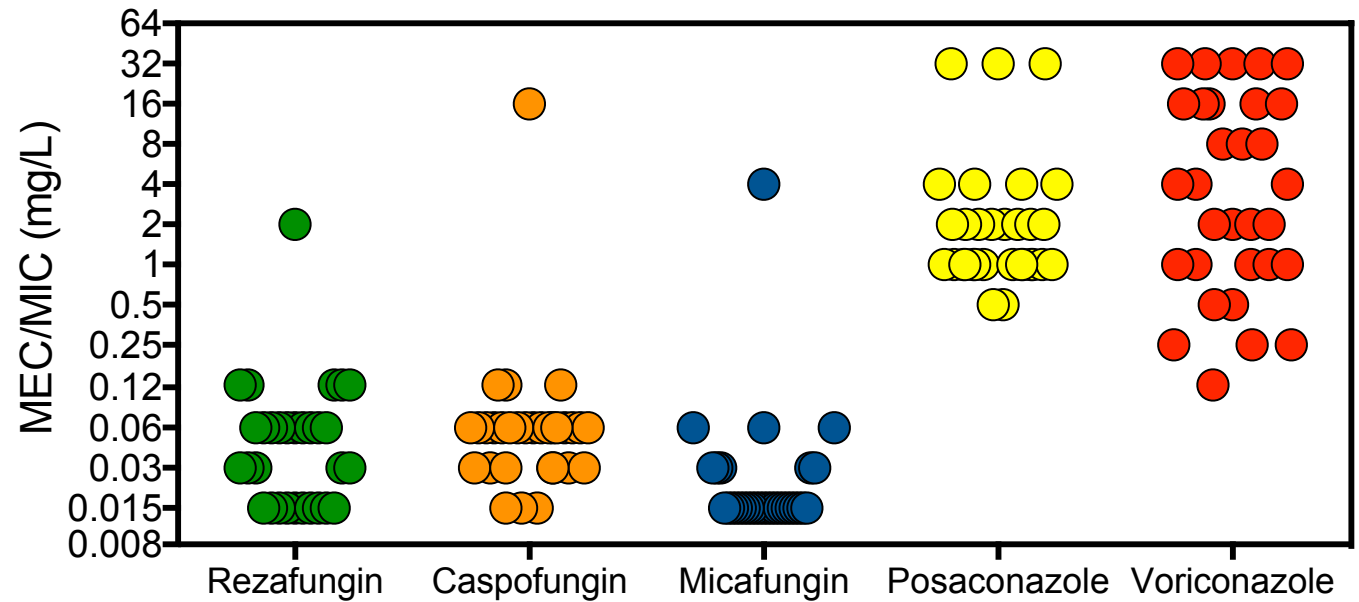
# Results: Wild-Type



Parameter	Rezafungin	Caspofungin	Micafungin	Posaconazole	Voriconazole
Wild-Type <i>A. fumigatus</i> isolates (n = 15)					
MEC/MIC Range	≤0.015-0.12	≤0.015-0.06	≤ 0.015	0.06-0.12	0.25-0.5
MEC/MIC <sub>50</sub>	≤0.015	0.03	≤0.015	0.12	0.25
MEC/MIC <sub>90</sub>	0.06	0.03	≤0.015	0.12	0.5
GM MEC/MIC	0.024	0.029	≤0.015	0.089	0.301



# Results: Azole- Resistant



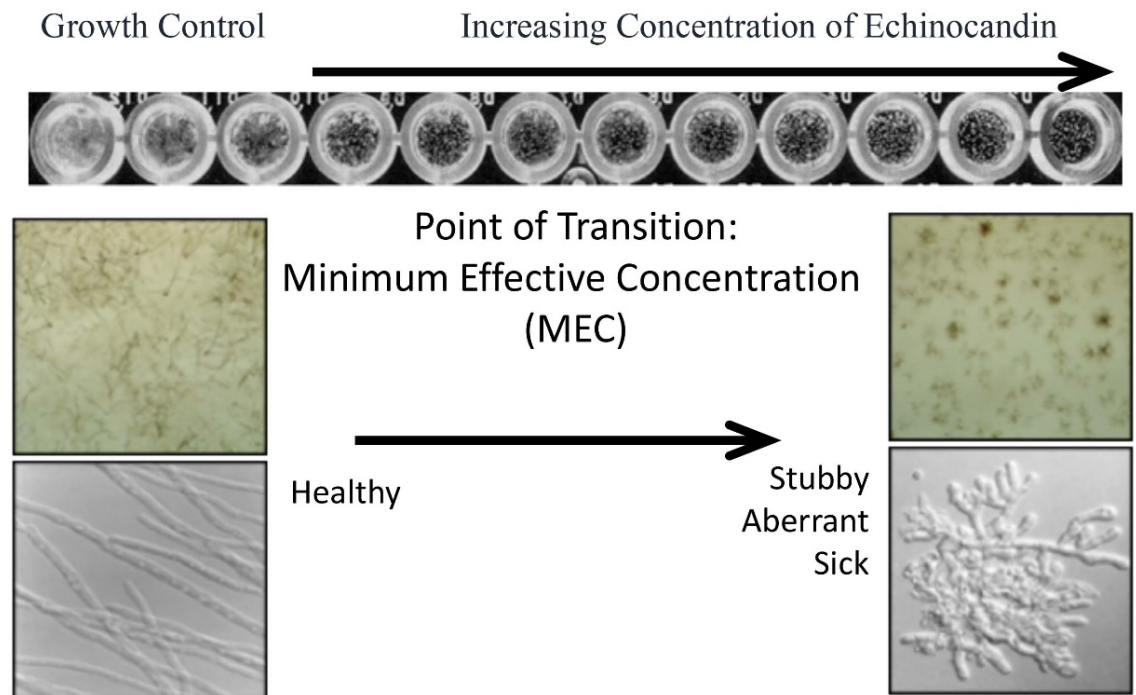
Parameter	Rezafungin	Caspofungin	Micafungin	Posaconazole	Voriconazole
Azole-Resistant <i>A. fumigatus</i> isolates (n = 31)					
MEC/MIC Range	≤0.015-2	≤0.015->8	≤0.015-4	0.5->16	0.12->16
MEC/MIC <sub>50</sub>	0.06	0.06	≤0.015	1	4
MEC/MIC <sub>90</sub>	0.12	0.06	0.06	4	>16
GM MEC/MIC	0.043	0.058	0.023	1.91	3.27

# Azole-Resistant Isolates

Azole Resistance Genotype (CYP51A)	No.	Rezafungin	Caspofungin	Micafungin
<i>CYP51A</i> only	13	≤ 0.015-0.125	≤ 0.015-0.25	≤ 0.015-0.03
TR <sub>34</sub> /L98H	2	0.06-0.125	0.06	≤ 0.015
TR <sub>46</sub> /Y121F/T289A	2	≤ 0.015-0.06	0.06	≤ 0.015
Resistant – no <i>CYP51A</i> mutations	6	≤ 0.015-2	0.03->8	≤ 0.015-4
Resistant - <i>CYP51A</i> status unknown	8	≤ 0.015-0.125	≤ 0.015-0.06	≤ 0.015-0.06

# Limitations & Next Steps

- Echinocandin MEC endpoint based on changes in morphology
- Relationship to clinical outcome unknown
- In vivo efficacy data needed
  - *CYP51A* mutations only
  - TR<sub>34</sub>L98H
  - TR<sub>46</sub>/Y121F/T289A
  - Unknown mechanisms of resistance



# Summary

- Rezafungin demonstrated potent in vitro activity against *Aspergillus fumigatus*
  - Activity similar to that of caspofungin and micafungin
- Activity maintained against azole-resistant isolates
  - *CYP51A* mutations
  - TR<sub>34</sub>/L98H & TR<sub>46</sub>/Y121F/T289A isolates
  - Unknown mechanisms of resistance
- Further work needed to determine in vivo efficacy and potential clinical utility

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