	Invasive Candidiasis and Candidemia (n=56)	Mucocutaneous Candidiasis (not VVC) (n=32)	Vulvovaginal Candidiasis (n=14)	Invasive Pulmonary Aspergillosis (n=10)	Chronic Pulmonary Aspergillosis (n=1)
Complete, Partial Response, or Clinical Improvement	35 (62.5%)	17 (53.1%)	10 (71.4%)	4 (40%)	0
Stable Disease	13 (23.2%)	11 (34.3%)	1 (7.1%)	1 (10%)	1 (100%)
Clinical Improvement Criteria Not Met (VVC only)	-	-	2 (14.3%)	-	-
Progression of Disease	4 (7.1%)	3 (9.4%)	0	4 (40%)	0
Indeterminate	4 (7.1%)	0	1 (7.1%)	1 (10%)	0
Deaths	0	1 (3.1%)	0	0	0

P057

All- cause mortality in patients with invasive Candidiasis or candidemia from an interim analysis of a Phase 3 Open-label Study (FURI)

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Background: There are limited oral treatment options for patients with high-mortality fungal infections such as candidemia or invasive candidiasis who fail currently available antifungals or have an infection caused by resistant organisms. Ibrexafungerp is an investigational broad-spectrum glucan synthase inhibitor with activity against *Candida* species, including azole- and echinocandin-resistant strains. A Phase 3 open-label, single-arm study of ibrexafungerp (FURI; NCT03059992) is ongoing for the treatment of patients intolerant of, or with invasive fungal disease refractory to, standard antifungal therapy. We present an interim analysis of all-cause mortality within 30 days post-treatment from the FURI study by fungal disease type for patients with candidemia or invasive candidiasis, who completed therapy up until October 2021.

Methods: FURI patients are eligible for enrolment if they have proven or probable: severe mucocutaneous candidiasis or invasive candidiasis, or candidemia, with documented evidence of failure, intolerance, or toxicity related to a currently approved standard-of-care antifungal treatment; or patients who cannot receive approved oral antifungal options (eg, due to susceptibility), and continued IV antifungal therapy is clinically undesirable or unfeasible. Patients were followed through 30 days post-treatment for all-cause mortality.

Results: Out of the 113 patients who completed therapy in the FURI study through October 2021, 56 (50%) had invasive candidiasis or candidemia and were treated with ibrexafungerp. The most common infections in this group were candidemia (15/56, 26.8%), intra-abdominal infection (13/56, 23.2%), and bone infection (10/56, 17.9%).

Overall survival within 30 days post-treatment in this group of 56 patients was 94.6%. Of the 56 patients with candidemia or invasive candidiasis, three (5.3%) died within 30 days after completion of treatment with ibrexafungerp, a fourth died at 31 days, a fifth died at 50 days, and a sixth died at 56 days. The mean age of the expired patients was 56 years. All 4 patients had candidemia (3 with *C. parapsilosis* and 1 with *C. albicans*), and 2 had intra-abdominal candidiasis, (both with *C. glabrata*). The average time on therapy with ibrexafungerp was 15.7 days. The mean time to death post-treatment for these patients was 27 days (median, 21 days). In five cases, the deaths were due to causes other than the underlying fungal disease. For the other case, the cause of death was not disclosed.

Conclusions: Analysis of all-cause mortality in these patients from the FURI study indicates that oral ibrexafungerp provides a favorable therapeutic response in patients with challenging fungal diseases and limited treatment options.

P059

The overexpression of efflux pump gene cdr1B resulting in voriconazole- and isavuconazole- resistance in *Aspergillus fumigatus* recovered from a patient with chronic pulmonary aspergillosis in China

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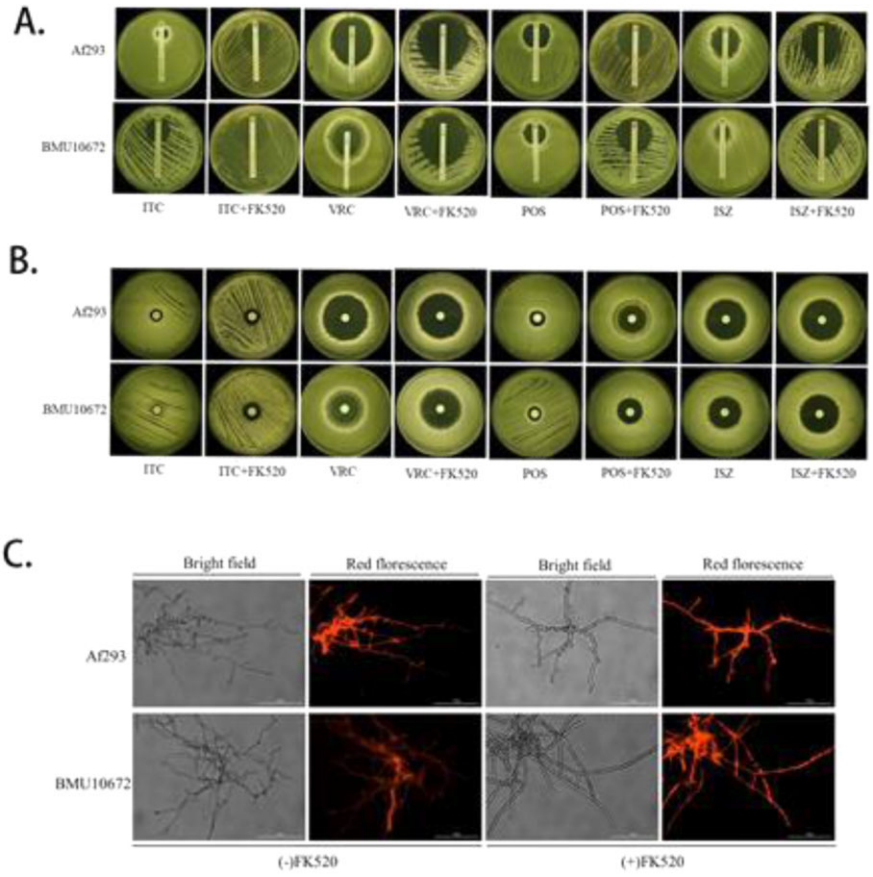
Objectives: Triazole resistance in the pathogenic *Aspergillus fumigatus* has been increasing worldwide, posing a growing therapeutic challenge. To date, triazole resistance in clinical isolates of *A. fumigatus* causing pulmonary aspergillosis has been mainly attributed to the mutations in the cyp51A gene or its promoter, followed by mutations in cyp51B and hmg1 gene encoding 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. From chronic pulmonary aspergillosis (CPA) patient, we isolated a strain of *A. fumigatus* (BMU10672) with resistance to voriconazole (VRC) and isavuconazole (ISZ), which was caused by overexpression of efflux pump Cdr1B.

Methods: Antifungal susceptibility testing of the isolate of *A. fumigatus* BMU10672 was performed using the broth microdilution method (CLSI M38-A3), E-test and disk diffusion method. The promoter region and open reading frame of the cyp51A, cyp51B, and hmg1 gene were amplified and sequenced. Then, the expression levels of cyp51A, cyp51B, and efflux pump gene cdr1B with or without being exposed to VRC or ISZ were quantified using real-time PCR, compared with triazole-susceptible *A. fumigatus* Af293. And the function of efflux pump Cdr1B was tested by efflux pump substrate (Nile red) accumulation assay and efflux pump inhibitor (FK520) assay.

Results: The minimum inhibitory concentration (MIC) of itraconazole (ITC), VRC, posaconazole (POS), ISZ and amphotericin B (AMB), and the minimal effective concentration (MEC) of caspofungin (CAS) against *A. fumigatus* BMU10672 was 1 μg/ml, 2 μg/mL, 0.5 μg/mL, 2 μg/mL, 1 μg/mL and 0.125 μg/mL, respectively. The results of E-test and disk diffusion assay were consistent with those of the broth microdilution method (Figs. 1a and b). Together, these results indicate that *A. fumigatus* BMU10672 is resistant to VRC and ISZ, while being susceptible to ITC, POS, AMB, and CAS. Sequencing of the cyp51A, cyp51B and hmg1 gene of *A. fumigatus* BMU10672 were all intact. The basal and VRC- or ISZ- induced expression levels of efflux pumps gene cdr1B in *A. fumigatus* BMU10672 were all higher (> 4-fold) than those in triazole-susceptible *A. fumigatus* Af293. However, no differences in basal and VRC- or ISZ- induced expression levels of cyp51A gene and cyp51B gene were observed between *A. fumigatus* BMU10672 and Af293. The efflux pump substrate Nile red accumulation assay showed the *A. fumigatus* BMU10672 accumulated less Nile red than Af293, confirming that Cdr1B was active at exporting Nile red, while efflux pumps inhibitor FK520 can increase the accumulation of the Nile red in *A. fumigatus* BMU10672 (Fig. 1c). Inhibition of efflux pumps activity by inhibitor FK520 resulted in a MIC reduction of 4-fold in VRC and ISZ MICs, and 2-fold in ITC and POS, against *A. fumigatus* BMU10672 (Figs. 1a and b).

Conclusion: Overexpression of efflux pumps gene cdr1B resulting in VRC- and ISZ- resistance in the clinical isolate of *A. fumigatus* BMU10672.



P060

A preliminary *in vitro* and *in vivo* evaluation of the effect and action mechanism of 17-AAG combined with azoles against azole-resistant *Candida* spp.

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Invasive candidiasis is the primary reason for the increasing cases of mortality in a medical environment. The resistance spectra of *Candida* species to antifungal drugs, among which *Candida auris* is the most prominent, have gradually expanded.

Objectives: Hsp90 plays a protective role in the stress response of fungi and facilitates their virulence. In contrast, Hsp90 inhibitors can improve the resistance of fungi to antifungal drugs by regulating the heat resistance of Hsp90 and thereby destroying the integrity of the fungal cell walls. Therefore, we used Hsp90 inhibitor in combination with different antifungal drugs to explore its antifungal effect and mechanism.

Methods: The drugs tested for the resistance included itraconazole, voriconazole, posaconazole, fluconazole, and 17-AAG. A total of 20 clinical strains of *Candida* were investigated. The broth microdilution checkerboard technique, as adapted from the CLSI M27-A4 method, was applied in this study. At the same time, the effect of 17-AAG combined with antifungal drugs on the formation of *Candida* biofilm was observed, and the animal experiment of *C. mellonella* was carried out *in vivo*. Moreover, we determined that with the use of rhodamine 6 G to detect drug efflux and that of dihydrorhodamine-123 to detect intracellular reactive oxygen species (ROS).

Results: We found that 17-AAG alone exerted limited antifungal activity against all tested strains. The MIC range of 17-AAG was 8 to >32 μg/ml. The synergy among 17-AAG and itraconazole, voriconazole, and posaconazole was observed against 10 (50%), 7 (35%), and 13 (65%) of all isolates, respectively. Moreover, the synergy between 17-AAG and fluconazole was observed against 5 (50%) stains of azole-resistant *Candida*. However, no antagonism was recorded. *In vivo* test, the combination group also significantly prolonged the infection event and improved the survival of larvae. Treatment with 17-AAG combined with azole drugs inhibited the efflux pump of fungi and promoted the accumulation of ROS in the fungal cells.

Conclusion: Our result adequately verifies the influence of 17-AAG on the formation of *Candida* spp. biofilm. The mechanism of 17-AAG combined with azoles could kill fungi by inhibiting drug efflux and increasing intracellular reactive oxygen species. These results thereby provide a new idea to further explore drugs against drug-resistant *Candida* spp.

P062

Identification of Octenidine (dihydrochloride) inhibiting fungal filamentation by the repurposing approach

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Objectives: Hyphal formation is an important virulence factor of opportunistic pathogenic fungi and plays a vital role in invasive fungal infections. Therefore, hyphae can act as a specific target against invasive fungal infections and it is a new attempt to focus on identification of compounds inhibiting hyphal growth. Amphotericin B has potent inhibitory effect on the growth of hyphae, but its high toxicity limits its clinical use. To address this question, we performed a high-throughput screen of an FDA-approved compound library (HY-L022, MCE®) to identify compounds with mycelial inhibitory function.

Methods: We performed a high-throughput screen of an FDA-approved compounds library to identify potentially novel compounds for inhibiting hyphal growth and used amphotericin B (1.56 μM) as a positive control drug. The screening schematic is shown in Figure 1a. Firstly, we investigated the mycelial inhibitory activity of each compound at 100 μM in RPMI 1640 medium with *Candida albicans* SN152 strain. Secondly, micro checkboard dilution method was applied to determine the minimum hyphae-inhibiting concentration of compounds. The compound being included in the next round could inhibit the hyphal formation when its concentration was $\leq$12.5 μM. Lastly, we expanded medium to YPD containing 10% FBS, YPD containing 5 mM N-acetylglucosamine (GlcNAc), and Spider medium. The final Candidate compound was determined due to its minimum hyphae-inhibiting concentration was $\leq$3.125 μM in four mediums.

Results: We screened a library of FDA-approved compound and identified 117 Candidate compounds that inhibit hyphal growth ($\leq$100 μM). We excluded 14 compounds with known antifungal activity, and finally 103 compounds were included in the next step of mycelial inhibitory activity screening (Fig. 1a). We further identified that 14 of 103 Candidate compounds (red square) could significantly inhibit the growth of mycelium at a concentration not higher than 12.5 μM in RPMI 1640 medium (Fig. 1b). We then expanded the types of media that induce mycelial growth (such as YPD medium with 10% FBS, YPD medium with 5 mM GlcNAc, and Spider medium) and used amphotericin B (1.56 μM) as a positive control drug and found that Octenidine (dihydrochloride) still has a significant inhibitory effect on mycelial growth in various mycelial induction media when it is as low as 3.125 μM (Figs. 2a and b).

Conclusion: Our study demonstrates that Octenidine (dihydrochloride) has a potent hyphal inhibitory activity and is helpful to open the way for the development of new antifungal therapeutics targeting filamentous formation.