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Activity of manogepix against *Aspergillus* spp. isolates with CYP51 alterations

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Introduction

- Fosmanogepix is the prodrug of manogepix, a novel antifungal agent targeting the Gwt1 enzyme.
 - This is a different target and mechanism of action relative to azoles, echinocandins, and amphotericin B.
- Fosmanogepix is currently in Phase 3 clinical trials for the treatment of invasive candidiasis and invasive mold infections.
- Given its novel mechanism of action, manogepix activity is not expected to be affected by typical resistance mechanisms that reduce susceptibility to other antifungal agents.
- Here, we look at the *in vitro* activity of manogepix against *Aspergillus* spp. isolates with identified CYP51 alterations leading to reduced azole susceptibility.

Methods

- Isolates were collected from the United States as a part of an antifungal surveillance program between 2017 and 2024.
 - There were 740 total isolates tested from all 9 Census regions and 18 states.
 - Isolates predominated from New England, Middle Atlantic, and East North Central with a smaller number from other regions (Figure 1).
- Only 1 isolate per patient episode was included.
- All isolates were identified by MALDI-TOF MS and/or DNA sequencing.
- Isolates were tested by CLSI reference broth microdilution method (M38) for manogepix, voriconazole, itraconazole, and amphotericin B.
 - Minimum effective concentration (MEC) was read for manogepix; minimum inhibitory concentration (MIC) was read for all comparators.
- CLSI breakpoints (M38M51S) or epidemiological cutoff values (ECVs, M57S) were applied for comparator agents as available; no breakpoints or epidemiological cutoff values are available for manogepix.
- Isolates that were non-wildtype (NWT) for ≥1 azole had CYP51A/B sequencing performed.

Results

- There were 16 *Aspergillus* spp. isolates with CYP51A or CYP51B alterations identified.
 - These were from 7 states and 6 Census regions (West South Central, East South Central, South Atlantic, Middle Atlantic, New England, and East North Central; Figure 2).
 - The most isolates were from Virginia (6) and Indiana (5) with 1 each from other states.
- The itraconazole MICs were 1 to >8 mg/L, voriconazole 0.5 to >8 mg/L, amphotericin B 0.25 to 4 mg/L (Table 1).
 - 15 of the isolates (93.8%) were NWT to itraconazole, 5 (31.3%) were NWT to voriconazole, and 1 (6.3%) was NWT to amphotericin B.
 - There were 3 isolates that were intermediate to voriconazole by breakpoint but WT by ECV.
- Isolates with CYP51 alterations were 12 *A. fumigatus*, one *A. brasiliensis*, one *A. niger*, one *A. welwitschiae*, and one *A. tubingensis*.
- All 16 isolates had CYP51A point alterations, but no promoter changes were observed. Only one *A. niger* isolate had a CYP51B point alteration.
- Manogepix MECs were 0.008 to 0.06 mg/L among the isolates with CYP51 changes.
 - The manogepix MECs were similar regardless of genetic background or MICs to antifungal comparator agents.
 - Overall manogepix MECs were similar at $MEC_{50/90}$ 0.015/0.03 mg/L (data not shown).

Conclusions

- Single amino acid changes in CYP51A predominated among *Aspergillus* spp. isolates that were NWT to azole antifungal agents collected in the United States.
- Isolates had elevated MICs to itraconazole and voriconazole, but maintained low MECs to manogepix.
- Fosmanogepix is a promising agent for future development in the treatment of invasive mold infections including infections caused by molds containing resistance mechanisms to current first-line therapies.

References

CLSI, *M38M51S Ed4. Performance standards for antifungal susceptibility testing of molds*. 2026, Clinical and Laboratory Standards Institute: Wayne, PA.

CLSI, *M57S Ed4. Epidemiological cutoff values for antifungal susceptibility testing*. 2022, Clinical and Laboratory Standards Institute: Wayne, PA.

CLSI, *M38 Ed3. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi*. 2017, Clinical and Laboratory Standards Institute: Wayne, PA.

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Table 1. MEC and MIC (mg/L) for manogepix (MGX), voriconazole (VRC), itraconazole (ITR), posaconazole (PSC), and amphotericin B (AmB) in *Aspergillus* spp. isolates with CYP51 alterations

Organism	CYP51A	CYP51B	MGX	ITR	VRC	AmB
Aspergillus brasiliensis	V6I, M53I, K246Q	wildtype	0.015	>8	8	0.25
Aspergillus fumigatus	I242V	wildtype	0.015	2	1	1
Aspergillus fumigatus	A9T	wildtype	0.03	2	0.5	2
Aspergillus fumigatus	I242V	wildtype	0.015	2	0.5	2
Aspergillus fumigatus	G448S	wildtype	0.015	>8	4	1
Aspergillus fumigatus	I242V	wildtype	0.015	2	0.5	4
Aspergillus fumigatus	F46Y, M172V, N248T, D255E, E427K	wildtype	0.015	2	0.5	2
Aspergillus fumigatus	I242V	wildtype	0.015	2	0.5	1
Aspergillus fumigatus	F46Y, M172V, N248T, D255E, E427K	wildtype	0.008	>8	2	1
Aspergillus fumigatus	I242V	wildtype	0.015	2	0.5	1
Aspergillus fumigatus	I242V	wildtype	0.03	4	1	1
Aspergillus fumigatus	I242V	wildtype	0.03	1	1	1
Aspergillus fumigatus	G448S	wildtype	0.06	>8	>8	0.25
Aspergillus welwitschiae	W221R, H382R, L383V	I285V	0.015	8	2	1
Aspergillus tubingensis	V17A	wildtype	0.06	>8	4	1
Aspergillus niger	T57A, S346R, I507S, M511L	wildtype	0.008	8	2	0.25

NWT (non-wildtype) values in green; blue shading reflects isolates intermediate but WT to voriconazole

Figure 1. Geography and source of all 740 collected isolates

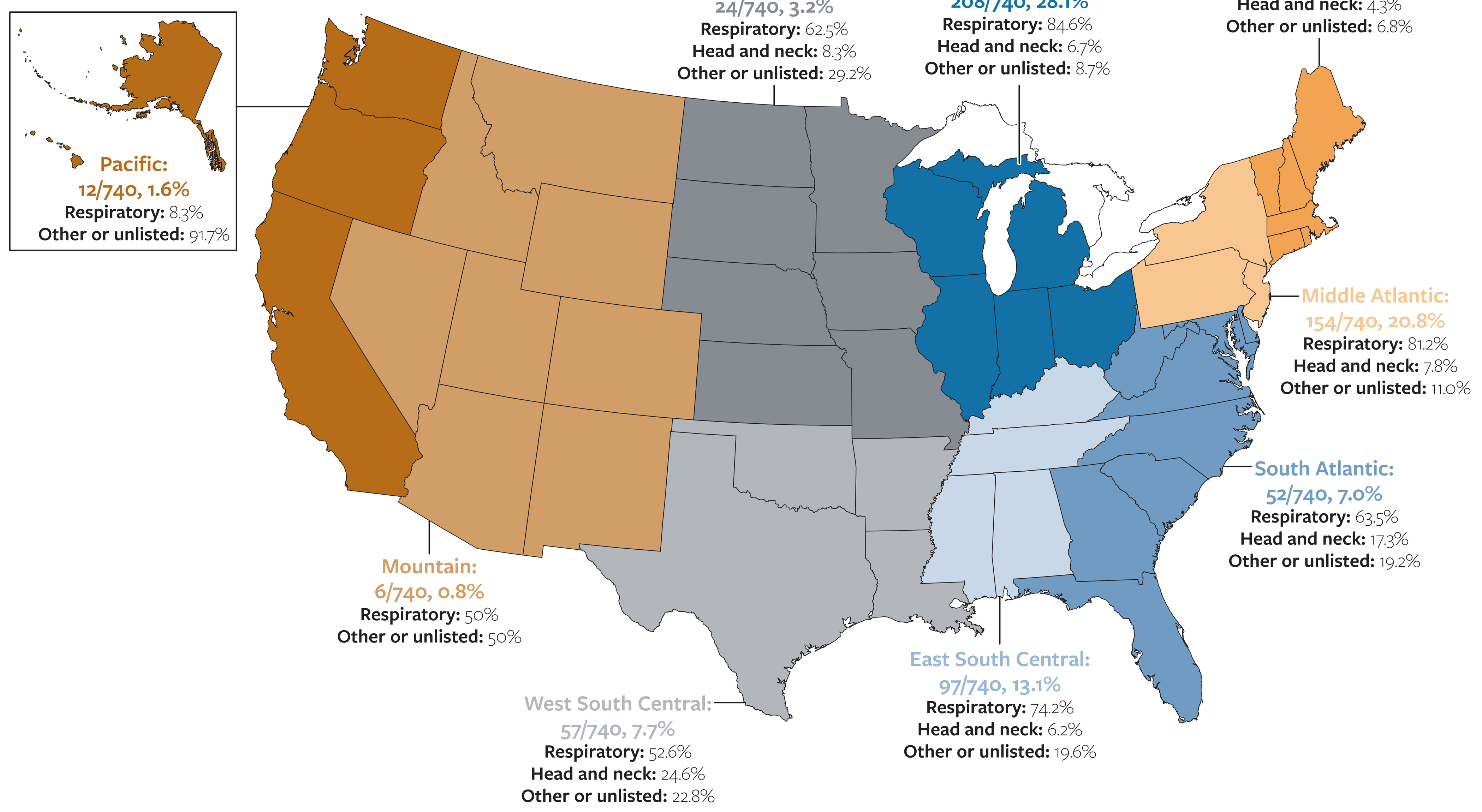
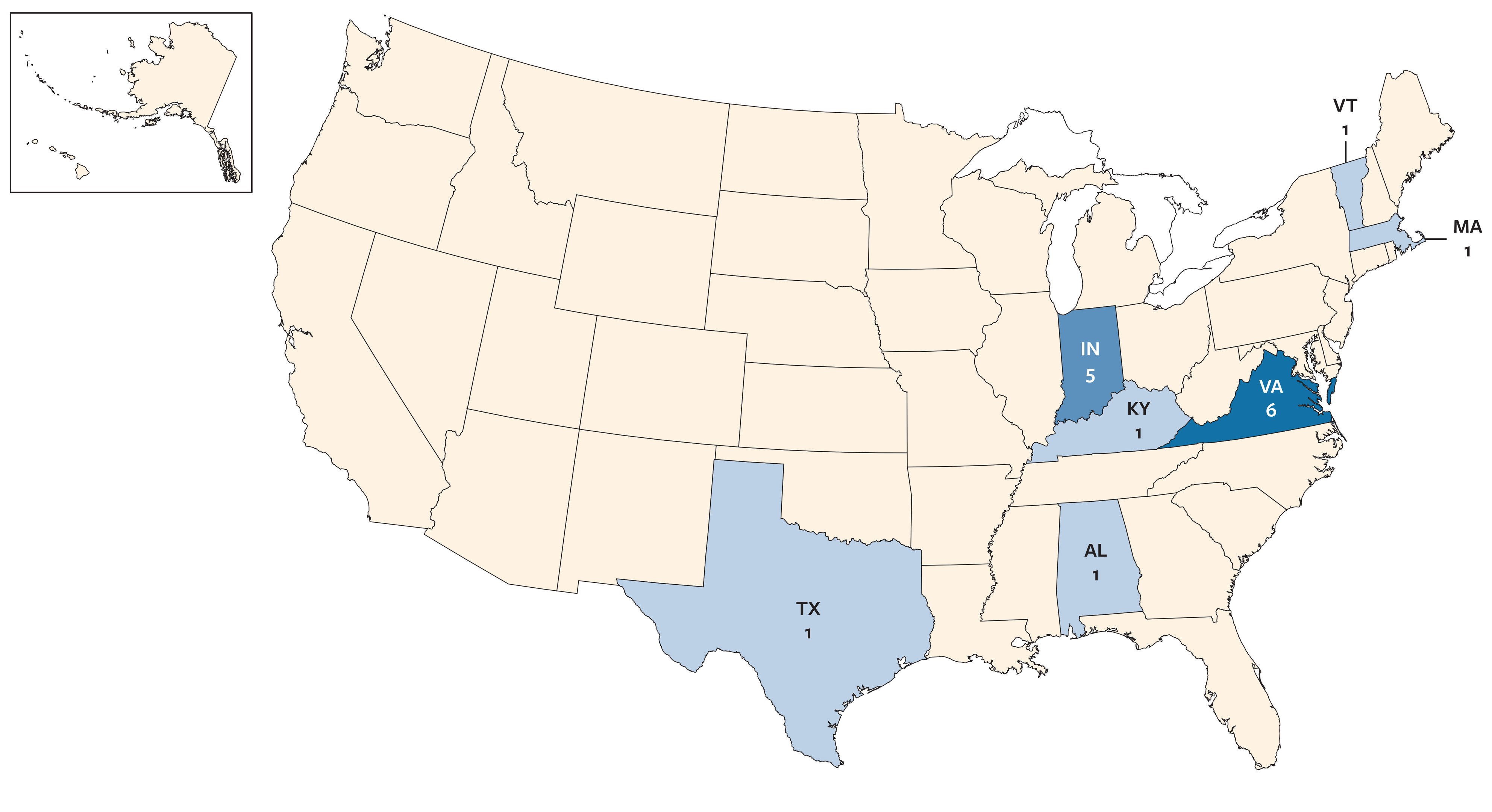

Pacific:
12/740, 1.6%
Respiratory: 8.3%
Other or unlisted: 91.7%
West North Central:
24/740, 3.2%
Respiratory: 62.5%
Head and neck: 8.3%
Other or unlisted: 29.2%
East North Central:
208/740, 28.1%
Respiratory: 84.6%
Head and neck: 6.7%
Other or unlisted: 8.7%
New England:
130/740, 17.6%
Respiratory: 90.0%
Head and neck: 4.3%
Other or unlisted: 6.8%
Middle Atlantic:
154/740, 20.8%
Respiratory: 81.2%
Head and neck: 7.8%
Other or unlisted: 11.0%
South Atlantic:
52/740, 7.0%
Respiratory: 63.5%
Head and neck: 17.3%
Other or unlisted: 19.2%
Mountain:
6/740, 0.8%
Respiratory: 50%
Other or unlisted: 50%
East South Central:
97/740, 13.1%
Respiratory: 74.2%
Head and neck: 6.2%
Other or unlisted: 19.6%
West South Central:
57/740, 7.7%
Respiratory: 52.6%
Head and neck: 24.6%
Other or unlisted: 22.8%

Figure 2. Geography of isolates with CYP alterations (states in blue) with shading reflective of number of isolates per state


VT
1
MA
1
IN
5
KY
1
VA
6
AL
1
TX
1

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