

# Antifungal resistance: current trends and future strategies to combat

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**Abstract:** Antifungal resistance represents a major clinical challenge to clinicians responsible for treating invasive fungal infections due to the limited arsenal of systemically available antifungal agents. In addition current drugs may be limited by drug–drug interactions and serious adverse effects/toxicities that prevent their prolonged use or dosage escalation. Fluconazole resistance is of particular concern in non-*Candida albicans* species due to the increased incidence of infections caused by these species in different geographic locations worldwide and the elevated prevalence of resistance to this commonly used azole in many institutions. *C. glabrata* resistance to the echinocandins has also been documented to be rising in several US institutions, and a higher percentage of these isolates may also be azole resistant. Azole resistance in *Aspergillus fumigatus* due to clinical and environmental exposure to this class of agents has also been found worldwide, and these isolates can cause invasive infections with high mortality rates. In addition, several species of *Aspergillus*, and other molds, including *Scedosporium* and *Fusarium* species, have reduced susceptibility or pan-resistance to clinically available antifungals. Various investigational antifungals are currently in preclinical or clinical development, including several of them that have the potential to overcome resistance observed against the azoles and the echinocandins. These include agents that also target ergosterol and  $\beta$ -glucan biosynthesis, as well as compounds with novel mechanisms of action that may also overcome the limitations of currently available antifungal classes, including both resistance and adverse effects/toxicity. **Keywords:** azoles, echinocandins, *Aspergillus*, *Candida albicans*, investigational antifungals, non-*albicans Candida* species, acquired resistance, intrinsic resistance, *Candida auris*

## Introduction

Antifungal resistance is becoming a significant concern to clinicians who are charged with caring for patients at high risk for invasive mycoses. Resistance to currently available antifungal agents can develop secondary to acquired mechanisms following exposure to these drugs. Recent trends in acquired antifungal resistance include increased azole resistance among non-*Candida albicans* isolates, azoles resistance in *Aspergillus fumigatus*, and echinocandin resistance in *C. glabrata*.<sup>1–3</sup> In contrast, some fungal species are intrinsically resistant to certain drugs (e.g., *C. krusei* and fluconazole, or *C. lusitaniae* and amphotericin B), while others demonstrate microbiologic resistance to all clinically available antifungals (e.g., *Lomentospora* [formerly *Scedosporium*] *prolificans* and *Fusarium solani*).<sup>4–6</sup> New species are also emerging that may demonstrate resistance to multiple class of available agents (e.g., *C. auris*).<sup>7</sup> Although the prevalence of antifungal resistance is not at the levels observed for some bacteria against different

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antibiotics, treatment options for invasive fungal infections are limited, and patients at highest risk often have multiple comorbidities, including immunosuppression, which may limit the effectiveness of therapy even in the absence of drug resistance. Clearly, new treatment strategies are needed to address this issue, in addition to overcoming the toxicities/adverse effects and drug interactions that are associated with currently available antifungals, which themselves can limit the effectiveness of therapy. Several new antifungals are currently under preclinical and clinical evaluation that may help to address the problem of antifungal resistance. The purpose of this review is to discuss the current trends in antifungal resistance and new antifungals currently under preclinical development and in clinical trials that may improve outcomes in patients with invasive fungal infections. In addition, numerous extracts from different plants have also been shown to have activity against various fungi, including isolates resistant to currently available antifungal agents. However, a detailed discussion of medicinal plants and their extracts is beyond the scope of this review.

## Resistance in non-*C. albicans*

### Azole resistance

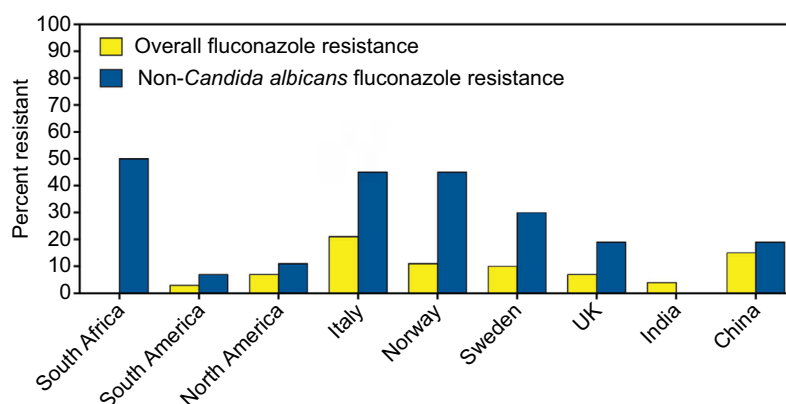
Although *C. albicans* is the most common *Candida* species cultured from patients with candidiasis, infections caused by other species within this genus are becoming more important in various regions around the world, including *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*, and the species can vary between different geographic regions. This is of importance, as resistance has been shown to be increasing in many of the non-*C. albicans* species in different institutions and geographic regions.<sup>8–10</sup> As reported by the World Health Organization, fluconazole resistance is indeed more common in non-*C. albicans* species (Figure 1).<sup>11</sup> This is of concern, since fluconazole is a relatively inexpensive and well-tolerated

medication that is easily administered orally. Furthermore, resistance to fluconazole may also mean resistance to other azoles, since mechanisms that reduce fluconazole susceptibility, such as point mutations within the *ERG11* gene that encodes lanosterol 14 $\alpha$ -demethylase, the target of the azoles (e.g., itraconazole, voriconazole, posaconazole, and isavuconazole), increase transcription of this gene, leading to increased amounts of the enzyme, or the efflux pumps, such as Cdr1 and Cdr2, also affect this class of antifungals.<sup>12,13</sup>

As previously noted, the predominant non-*C. albicans* species causing infections may vary between different geographic regions, and the rates of azole resistance may also differ between institutions. This may be influenced by the prescribing patterns of clinicians for both the treatment of and prophylaxis against invasive candidiasis.<sup>14</sup> In the USA, *C. glabrata* is the second most common cause of invasive candidiasis, and fluconazole resistance has been reported as high as 12%–18% in some institutions.<sup>15,16</sup> In contrast, in some health care institutions in India, *C. tropicalis* is the predominant species, and rates of fluconazole resistance may vary significantly.<sup>17,18</sup> The prevalence of *C. parapsilosis* approaches that of *C. albicans* in some Chinese hospitals in terms of the number of isolates cultured from patients with invasive infections.<sup>19–22</sup> Fluconazole susceptibility is also highly variable between institutions, with some reporting no azole resistance while others have reported that fluconazole-susceptible, dose-dependent plus resistant isolates may be as high as 50% in intensive care units.<sup>20,22</sup>

### Echinocandin resistance

The echinocandins are recommended as the first line of therapy against invasive candidiasis in immunocompromised patients and in those who have had prior azole exposure due to the fear of resistance.<sup>23</sup> Because the mechanism of action is different from that of the azoles, the echinocandins,



**Figure 1** Fluconazole resistance overall and in non-*Candida albicans* isolates as per the World Health Organization.

**Note:** Reprinted from World Health Organization. Antimicrobial Resistance: Global Report on Surveillance. Available from: <http://www.who.int/drugresistance/documents/surveillancereport/en/>. Copyright 2014.<sup>11</sup>

including anidulafungin, caspofungin, and micafungin, have been shown to maintain potent *in vitro* activity against many *Candida* isolates that have developed resistance to fluconazole and the other triazoles.<sup>24</sup> However, resistance to the echinocandins can develop with exposure to the members of this class, and this occurs via point mutations within highly conserved regions (i.e., hot spots 1 and 2) of the *FKS1* and *FKS2* genes, which encode subunits of the glucan synthase enzyme.<sup>25</sup> These hot spot regions are conserved across different *Candida* species, and their detection has been reported in multiple species collected from patients who have experience both microbiologic and clinical failure.<sup>26–28</sup>

Although the overall rate of echinocandin resistance remains low, some institutions in the USA have reported increasing rates of infections caused by *C. glabrata*, which often occur in patients with multiple comorbidities.<sup>29</sup> As with azole resistance, echinocandin resistance can develop with exposure to the members of this class. It has been suggested that echinocandin *in vitro* susceptibility results should be taken in context with a patient's history of exposure to these antifungals. In one study, the clinical failure rate approached 90% in patients who had prior echinocandin exposure and from whom a resistant *C. glabrata* isolate was isolated.<sup>30,31</sup> In those whose infections were caused by echinocandin-susceptible isolates but with prior echinocandin exposure, clinical responses were still only ~50%. In addition to a patient's history of echinocandin exposure, the type of *FKS* mutation may also play an important role in response to therapy and the likelihood of failing treatment with an echinocandin. *In vitro* studies have demonstrated that point mutations resulting in amino acid changes of serine to proline at codon 629 within Fks1p or codon 663 in Fks2p, as well as phenylalanine to serine at codon 659 in Fks2p in *C. glabrata* lead to reduced activity of the glucan synthase enzyme,<sup>32</sup> which have translated into reduced *in vivo* efficacy of echinocandin therapy in an animal model of invasive candidiasis.<sup>33</sup> Results from single-center, retrospective studies also suggest that this may have clinical consequences, as the majority of patients with infections caused by isolates harboring S663F or S663P amino acid changes failed therapy, while many of those with infections caused by other point mutations responded to treatment with an echinocandin.<sup>15,16</sup> Although the clinical data are limited and more robust studies are needed, there is the possibility that the identification of the specific point mutations causing microbiologic resistance along with a patient's history of echinocandin exposure may be used to predict the likelihood of response to echinocandin therapy.

## Multidrug-resistant *Candida* isolates

Resistance to multiple classes of drugs is also a concern in some non-*C. albicans* species. In one publication from the SENTRY study, 11% of fluconazole-resistant bloodstream infections were also resistant to an echinocandin.<sup>34</sup> More recently, in a large surveillance study conducted in four large metropolitan areas in the USA, an increase in echinocandin nonsusceptible *C. glabrata* isolates (e.g., isolates classified as intermediate or resistant) was reported.<sup>1</sup> While these results are consistent with those from single-center studies, in this multicenter surveillance study, which included over 1300 isolates, a third of the isolates that were nonsusceptible to an echinocandin were also resistant to fluconazole, compared to only 8.1% of the isolates that were echinocandin susceptible. Because of the differences in the mechanisms of action and known mechanisms of resistance, the exact cause of azole and echinocandin coresistance in some *C. glabrata* isolates is unknown. As many patients with invasive candidiasis due to *C. glabrata* have multiple comorbidities, previous exposure to these antifungal classes may also play a role. In addition, a hypermutable phenotype has been reported in isolates with a disrupted *MSH2* mismatch repair gene, which may be more likely to produce multidrug-resistant mutants.<sup>35</sup>

Recently, attention has focused on the emerging pathogen *C. auris*. First described in 2009 for an isolate collected from the external ear canal of a patient, *C. auris* has quickly spread to multiple countries in several continents and has become a significant clinical problem. In a recent retrospective review of the clinical history of 54 patients, most had multiple risk factors for invasive disease and candidemia was observed in 61%.<sup>7</sup> Strikingly, the mortality rate in this series of patients was 59%. Unfortunately, antifungal therapy may be limited, as up to 90% of the isolates may be resistant to fluconazole, and 50% have elevated voriconazole minimum inhibitory concentrations (MICs), which is secondary to point mutations in *ERG11* and *ERG3*.<sup>7,36</sup> Interestingly, posaconazole and isavuconazole appear to maintain some *in vitro* potency, although the clinical significance of this remains unknown. Currently, the echinocandins are recommended for the treatment of *C. auris* infections. However, elevated MICs secondary to *FKS* mutations have been found in some isolates.<sup>36–38</sup> Unfortunately, this species is often misidentified by commercially available, automated systems that use biochemical means for species identification.<sup>36,37</sup>

## Resistance in *Aspergillus* species

Recent attention has also begun to focus on azole-resistant *Aspergillus* species, with particular interest in resistant

*A. fumigatus* isolates. As in *Candida* species, resistance to the mold active triazoles, itraconazole, posaconazole, voriconazole, and isavuconazole can develop with prolonged clinical exposure. This has been well documented in the literature and can occur in patients with chronic pulmonary aspergillosis, where azole therapy is often administered to patients for years.<sup>39,40</sup> This acquired resistance in *A. fumigatus* is caused by point mutations in the *CYP51A* gene, which encodes the Cyp51 enzyme responsible for the conversion of lanosterol to ergosterol. Different mutations can differentially affect the azoles, with some causing resistance to voriconazole and isavuconazole, some causing resistance to posaconazole and itraconazole, and others causing pan-azole resistance.<sup>40–42</sup> In addition, it is now known that environmental exposure to the azoles, which are used in a variety of means, including agriculture to protect plants and crops, can also lead to the development of azole resistance. In these isolates, tandem base pair repeats (abbreviated TR) have been found within the promoter region of this gene in azole-resistant *A. fumigatus* isolates collected from the environment, in addition to the point mutations within the *CYP51A* gene. These include the TR<sub>34</sub>/L98H, which causes pan-azole resistance, and TR<sub>46</sub>/Y121F/T289A, which causes reduced posaconazole potency and high-level resistance to voriconazole and posaconazole.<sup>43,44</sup> Both of these mutations have been documented in isolates collected from patients with invasive aspergillosis without a history of prior azole exposure<sup>39,40,45</sup> and in the environment where azoles or similar demethylase inhibitors are used as fungicides.<sup>2,41,46</sup> Isolates harboring these mutations have also been documented in numerous countries around the world.<sup>2,3</sup> In addition to azole resistance in *A. fumigatus*, several cryptic or sibling species within *Aspergillus* section *Fumigati* (e.g., *Aspergillus lentulus*, *Aspergillus felis*, *Aspergillus parafelis*, *Aspergillus pseudofelis*, *Aspergillus pseudoviridinutans*, *Aspergillus udagawae*), as well as other *Aspergillus* species in different sections (e.g., *Aspergillus calidoustus*, *Aspergillus flavus*, *Aspergillus sydowii*, *Aspergillus terreus*, *Aspergillus versicolor*) may have reduced or variable susceptibility to the azoles as well as other antifungals.<sup>47–50</sup> Although *A. fumigatus* is the most frequently isolated species at many institutions, studies have reported that the prevalence of cryptic species may be as high as 11%–14.5%.<sup>51,52</sup> Thus, proper species identification in addition to antifungal susceptibility testing may help to guide therapy. However, cryptic species are difficult to differentiate based solely on phenotypic and morphologic characteristics.<sup>53</sup>

The emergence of azole resistance in *A. fumigatus* is problematic due to the limited treatment options against

infections caused by these fungi. Although both amphotericin B and the echinocandins can be used to treat patients with invasive aspergillosis, each has its limitations. Amphotericin B deoxycholate is associated with clinically significant nephrotoxicity that may limit its use, and although nephrotoxicity may be reduced with the lipid formulations of this polyene, it can still occur, especially with higher doses or prolonged administration.<sup>54</sup> Although the echinocandins avoid the toxicities observed with amphotericin B formulations, these agents are not recommended as monotherapy for invasive aspergillosis.<sup>55</sup> In addition, both amphotericin B formulations and the echinocandins must be administered intravenously, which can be problematic when prolonged therapy is required.

### Other molds with reduced susceptibility or intrinsic resistance to antifungals

Several other molds have reduced susceptibility or are intrinsically resistant to clinically available antifungal agents. Those that are often reported in epidemiologic studies to cause disease in immunocompromised hosts include *Scedosporium* species, *Lomentospora* (formerly *Scedosporium*) *prolificans*, and *Fusarium* species. Scedosporiosis is an invasive infection that can occur in persistently neutropenic patients, those with lymphopenia, and in lung transplant recipients.<sup>56–60</sup> The primary route of infection is via the lungs, but dissemination, including to the central nervous system, can occur. Several different *Scedosporium* species can cause this invasive mycosis, including *Scedosporium apiospermum*, *Scedosporium boydii* (formerly *Pseudallescheria boydii*), *Scedosporium aurantiacum*, *Scedosporium dehoogii*, *Scedosporium minutispora*, and *Scedosporium desertorum*.<sup>4,61</sup> Variable antifungal activity has been reported against these species for different antifungal agents, including the azoles, amphotericin B, and the echinocandins,<sup>4,62,63</sup> while *L. prolificans* is resistant to all clinically available agents.<sup>61,63</sup> Although some case reports have documented successful treatment with combination therapy that includes the antiparasitic agent miltefosine,<sup>64,65</sup> this strategy has not been evaluated in clinical studies to confirm efficacy.

Fusariosis is a significant cause of morbidity and mortality in immunocompromised hosts. Infections in highly immunocompromised patients, including neutropenic patients with leukemia or those receiving high-dose corticosteroids for graft-versus-host disease, are usually invasive and may disseminate through the bloodstream.<sup>59,66,67</sup> Although numerous *Fusarium* species are capable of causing disease in both plants and animals, the majority of infections in humans

are caused by those within the *F. solani* and *Fusarium oxysporum* species complexes.<sup>68</sup> The prognosis in patients with invasive fusariosis is poor, but may be improving due to the availability of newer antifungals and formulations, including voriconazole and lipid amphotericin B.<sup>67</sup> However, several *Fusarium* species have reduced in vitro susceptibility to various antifungal classes, while others, including *F. solani*, may be pan-antifungal resistant.

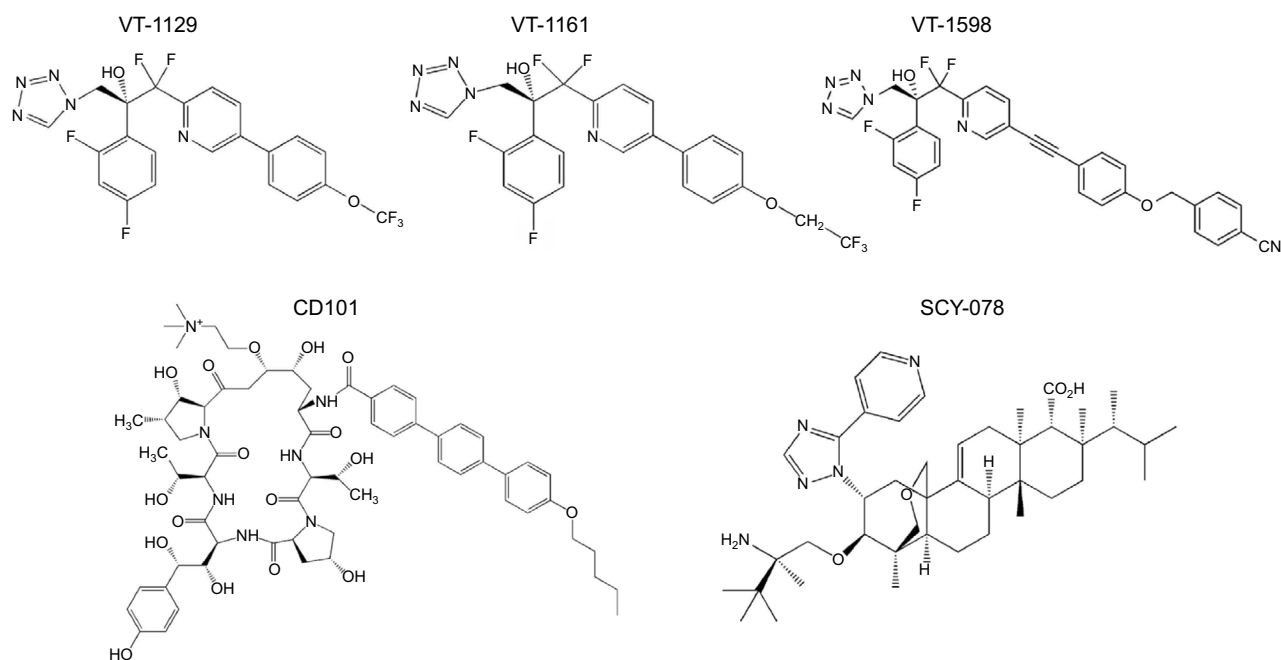
## New antifungals for the treatment of resistant fungi

Several investigational antifungals are currently under pre-clinical and clinical evaluation. These include agents that are similar to clinically available antifungal classes in terms of their mechanisms of action, but may offer distinct advantages to these drugs. Several of these agents have moved from pre-clinical development to clinical trials in healthy volunteers and patients. Some of these agents may soon be available for clinical use. In addition, several new compounds with novel mechanisms of action that may overcome both the limitations of resistance to and adverse effects of clinically available antifungals are also under development.

### VT-1129, VT-1161, and VT-1598 – fungal specific inhibitors of Cyp51

One of the main limitations of the azole class of antifungals is the clinically significant drug–drug interactions that occur

with the members of this class. In addition to inhibition of the fungal lanosterol 14 $\alpha$ -demethylase (aka Cyp51), the azoles can also inhibit cytochrome P450 (CYP 450) enzymes that are responsible for the metabolism of various substances, including numerous other drugs. In addition, some of the azoles (e.g., fluconazole, voriconazole, itraconazole, and isavuconazole) are also substrates of the CYP 450 enzymes, and therefore, drugs that inhibit or induce the activity of these enzymes can also lead to clinically significant changes in azole concentrations. To overcome the problem of drug–drug interactions associated with the azoles, Viamet Pharmaceuticals, Inc. (Durham, NC, USA) has replaced the triazole metal-binding group with a tetrazole that binds less avidly to the active site of the Cyp51 enzyme and mammalian CYP 450 enzymes, while also modifying the portion of the compound that is recognized by amino acids of the substrate-binding site within this enzyme. These modifications have resulted in compounds with more specific inhibition of fungal Cyp 51 compared to mammalian CYP 450 enzymes, and thus the potential for drug–drug interactions.<sup>69–71</sup> Preclinical results of three agents with these modifications have been reported in the literature (VT-1129, VT-1161, and VT-1598; Figure 2), and one agent is currently in clinical studies (VT-1129). Each of these agents has potent activity against various yeast isolates, including *C. albicans* and non-*C. albicans* species, and *Cryptococcus* species.<sup>72–75</sup> The potent in vitro activity observed with VT-1161 was also maintained against some



**Figure 2** Investigational antifungal agents with mechanisms of action similar to that of the azoles via inhibition of ergosterol biosynthesis (VT-1129, VT-1161, VT-1598), or echinocandins via inhibition of 1,3- $\beta$ -D-glucan synthesis (CD101, SCY-078).

fluconazole-resistant and echinocandin-resistant isolates, which has translated into in vivo efficacy in animal models of vulvovaginal and invasive candidiasis.<sup>72–78</sup> Similar to VT-1161, VT-1129 also has potent in vitro activity against *Candida* and *Cryptococcus* species, and the activity of this investigational agent is also maintained against *Cryptococcus gattii* genotypes with reduced susceptibility to fluconazole.<sup>75</sup> Of these three investigational agents, VT-1598 has the most potent activity against molds, including various *Aspergillus* species and *Rhizopus arrhizus*, as well as endemic fungi, including *Coccidioides* isolates, with elevated fluconazole MICs.<sup>79,80</sup> This agent also demonstrates potent in vitro activity against other *Candida* species, including *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*, although the potency was reduced against some *C. albicans* and *C. glabrata* isolates with elevated fluconazole MIC.<sup>81</sup> Similarly, reduced in vitro potency has also been observed against some azole-resistant *A. fumigatus* isolates. However, the degree to which different mechanisms that cause azole resistance, including point mutations in *ERG11/CYP51A* or upregulation of efflux pumps, affect the in vitro activity or in vivo efficacy of VT-1598, VT-1161, or VT-1129 is not yet understood. This agent also maintains in vitro activity against some *C. auris* isolates.<sup>82</sup>

## CD101 and SCY-078 – inhibition of glucan synthase

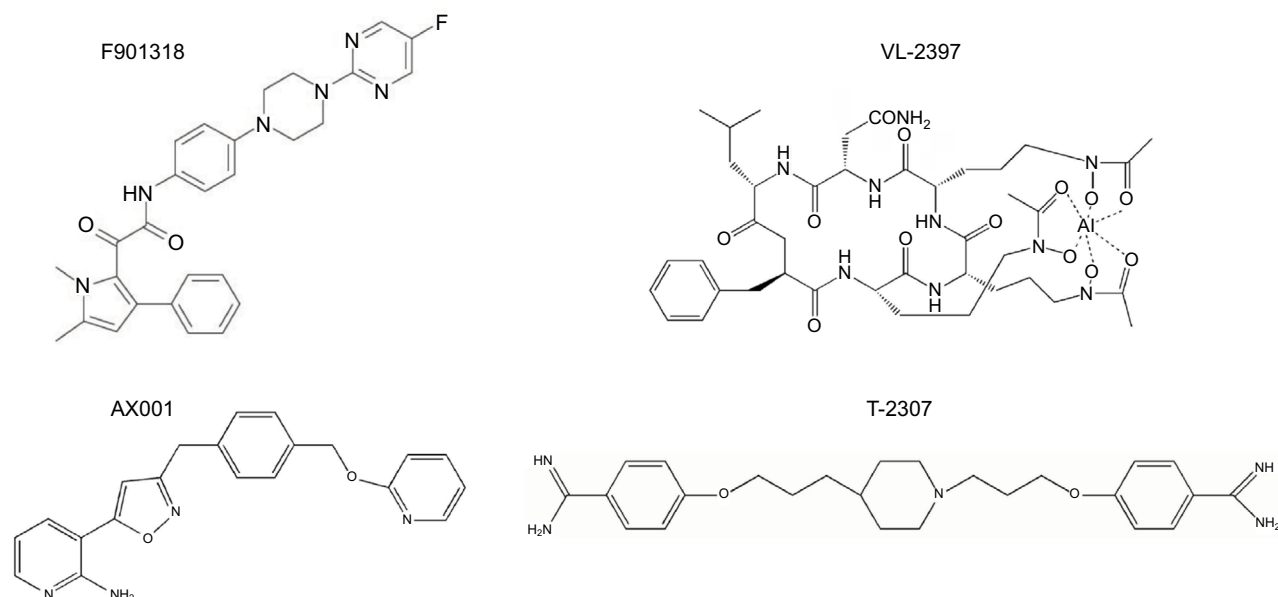
The echinocandins have the advantage of avoiding the drug–drug interactions associated with the azoles and the adverse effects/toxicities observed with amphotericin B formulations due to their inhibition of the fungal specific glucan synthase enzyme. However, as previously noted, *C. glabrata* resistance is increasingly being reported in some institutions. In addition, the echinocandins must be administered intravenously on a daily basis, thus prolonged use as treatment may pose logistic challenges. CD101 (biafungin, previously SP3025; Cidara Therapeutics, San Diego, CA, USA; Figure 2) is an investigational echinocandin currently under development that has been structurally modified to confer a long half-life (>80 hours),<sup>83,84</sup> which may allow for less-frequent intravenous administration (e.g., once weekly). This agent has also been shown to be safe without serious adverse effects or withdraws due to adverse effects in healthy volunteers.<sup>84</sup> In vitro studies have reported potent activity against *Candida* and *Aspergillus* species, with a similar low frequency for the development of mutations in hot spot regions of *FKS1* and *FKS2* as observed with anidulafungin and caspofungin.<sup>85,86</sup> This in vitro potency has also translated into in vivo efficacy

in murine models of invasive candidiasis caused by echinocandin-susceptible and echinocandin-resistant isolates, the later which may be due to the enhanced exposure conferred by the long half-life of this agent.<sup>87,88</sup> In vitro activity has also been reported for CD101 against *C. auris* in a small study that included 16 isolates (MIC<sub>50</sub> 0.125 mg/L, MIC<sub>90</sub> 0.25 mg/L), with a potency similar to that of anidulafungin but greater than that of caspofungin and micafungin.<sup>89</sup>

Another glucan synthase inhibitor that is currently being developed for both oral and intravenous administration is SCY-078 (Scynexis, Inc., Jersey City, NJ, USA; Figure 2). Although the mechanism of action of SCY-078 is the same as that of the echinocandins and CD101, this agent is structurally different from the echinocandins and allows for oral administration due to absorption from the gastrointestinal tract.<sup>90</sup> Similar to the echinocandins, SCY-078 demonstrates potent in vitro activity against various *Candida* species, including some isolates with known mutations in the *FKS1* and *FKS2* genes, as well as fluconazole-resistant isolates.<sup>90</sup> Efficacy has also been demonstrated against infections caused by different *Candida* species, including *C. albicans*, *C. glabrata*, and *C. tropicalis*, in an established murine model.<sup>91</sup> Two recent studies have also reported potent in vitro activity of SCY-078 against *C. auris* isolates, including inhibition of biofilm formation.<sup>92,93</sup> Thus, this orally available glucan synthase inhibitor may hold promise against this emerging pathogen. However, as with CD101, in vivo efficacy data against infections caused by *C. auris* are currently lacking. SCY-078 also lacks activity against the Mucorales and *Fusarium* species, while variable activity has been observed against other molds, including *Scedosporium* species.<sup>94</sup>

## F901318 – inhibition of fungal pyrimidine biosynthesis

The investigational agent F901318 (F2G, Inc., Manchester, UK; Figure 3) inhibits the oxidoreductase enzyme dihydroorotate dehydrogenase, which is important for pyrimidine biosynthesis.<sup>95</sup> The activity of F901318, a member of the orotomide class of compounds, is fungal specific, as its activity against *A. fumigatus* dihydroorotate dehydrogenase is significantly more potent compared to that of the human enzyme (IC<sub>50</sub> 44 nM versus >100 µM, respectively).<sup>95</sup> F901318 has potent in vitro activity against various molds, including *Scedosporium* species and *L. prolificans*, as well as endemic fungi (*Blastomyces dermatitidis*, *Coccidioides* species, *Histoplasma capsulatum*).<sup>96,97</sup> Potent in vitro activity has also been observed against *Aspergillus* species, including azole-resistant *A. fumigatus* that harbors the TR<sub>34</sub>/L98H



**Figure 3** Investigational antifungal agents with novel mechanisms of action, including prevention of fungal pyrimidine via inhibition of dihydroorotate dehydrogenase (F901318), prevention of GPI-anchored protein maturation via inhibition of fungal inositol acetyltransferase (AX001), collapse of fungal mitochondrial membrane potential (T-2307), and an unknown mechanism of action following transport into fungal cells by the Sit1 (VL-2397).

**Abbreviations:** GPI, glycosylphosphatidylinositol; Sit1, siderophore iron transporter 1.

mutation and cryptic *Aspergillus* species.<sup>95,98</sup> However, there are significant holes in the spectrum of activity of F901318, as this compound lacks activity against yeast and the members of the order Mucorales.<sup>95,96</sup> Both oral and intravenous preparations for administration are being developed, and Phase I studies in healthy volunteers have been completed.

### AX001 – inhibition of fungal glycosylphosphatidylinositol biosynthesis

Glycosylphosphatidylinositol (GPI)-anchored proteins serve as adhesions allowing microorganisms to adhere to host mucosal and epithelial surfaces.<sup>99</sup> Thus, GPI-anchored proteins are needed for the establishment of colonization and infection by fungi. AX001 (formerly E1210; Amplyx Pharmaceuticals, San Diego, CA, USA; Figure 3) is an investigational agent that inhibits inositol acyltransferase, thus preventing the maturation of GPI-anchored proteins.<sup>100</sup> Potent in vitro activity has been reported for AX001 against a broad-spectrum of fungi, including yeast (i.e., *Candida* species) and molds (i.e., *Aspergillus*, *Fusarium*, and *Scedosporium* species).<sup>100–103</sup> This in vitro activity has also translated into efficacy in animal models of invasive fungal infections, including invasive candidiasis caused by azole- and echinocandin-resistant isolates, aspergillosis, and fusariosis.<sup>104,105</sup> Interestingly, AX001 appears to lack in vitro activity against *C. krusei* and the Mucorales, although the in vivo significance of this is not yet known, given its

novel mechanism of action in preventing fungal adherence to host surfaces.

### T-2307 – collapse of fungal mitochondrial membrane

T-2307 (Toyama Chemical Co., Toyama, Japan; Figure 3) is an investigational arylamide that is structurally similar to aromatic diamidines.<sup>106</sup> Exposure to T-2307 causes collapse of fungal mitochondrial membrane potential, and this agent is preferentially taken up by fungal cells compared to mammalian cells by transporter-mediated systems.<sup>107,108</sup> Thus, T-2307 may offer significant safety advantages over other aromatic diamidines, including pentamidine. Potent in vitro activity has been reported against *Candida* species, including azole- and echinocandin-resistant isolates of *C. albicans* and *C. glabrata*,<sup>109,110</sup> and in vivo efficacy has also been demonstrated in the in vivo models of infections caused by resistant isolates.<sup>106,109,110</sup> In vitro activity and in vivo efficacy have also been reported against *Cryptococcus* and *Aspergillus* species.<sup>106</sup>

### VL-2397 – unknown mechanism of action

VL-2397 (formerly ASP2397; Vical Pharmaceuticals, San Diego, CA, USA; Figure 3) is a cyclic metallohexapeptide currently under preclinical development that is structurally related to the siderophore ferrichrome.<sup>111</sup> Although this agent, which was isolated from an *Acremonium* species, is able to

chelate aluminum ions instead of iron, its exact mechanism of action is not fully understood and appears to be independent of aluminum chelation.<sup>112</sup> However, it is known that it triggers a potent and rapid antifungal effect following transport into fungal cells via siderophore iron transporter 1, which is absent in mammalian cells.<sup>111</sup> VL-2397 is active against different fungi, including azole-resistant *Aspergillus* isolates, which has translated into in vivo efficacy in both silkworm and neutropenic murine models of invasive aspergillosis.<sup>113,114</sup> A recent study also reported the in vivo efficacy in a neutropenic murine model of invasive candidiasis caused by both wild-type and azole- and echinocandin-resistant *C. glabrata* isolates.<sup>115</sup> VL-2397 was also well tolerated with sustained levels, but without accumulation in healthy volunteers who received multiple doses per day.<sup>116</sup>

## Conclusion

Clinicians are currently facing several emerging challenges in antifungal resistance. These include increased rates of resistance to azole and echinocandins in several non-*C. albicans* species and azole resistance in *A. fumigatus* that may occur due to clinical or environmental exposure to these agents. In addition, there are several species of pathogenic fungi that have reduced susceptibility or frank resistance to many available antifungal agents. Several new antifungals are currently in development that may be more advantageous than the current drugs, both in terms of overcoming antifungal resistance and avoiding adverse effects and drug interactions associated with currently available agents. Continued preclinical evaluation and clinical studies are needed to determine if these agents will be successful in overcoming microbiologic and clinical failure in the setting of antifungal resistance.

## Disclosure

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