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REVIEW ARTICLE (INVITED)

Hope on the Horizon: Novel Fungal Treatments in Development

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The treatment of invasive fungal infections remains challenging due to limitations in currently available antifungal therapies including toxicity, interactions, restricted routes of administration, and drug resistance. This review focuses on novel therapies in clinical development, including drugs and a device. These drugs have novel mechanisms of action to overcome resistance, and some offer new formulations providing distinct advantages over current therapies to improve safety profiles and reduce interactions. Among agents that target the cell wall, 2 glucan synthesis inhibitors are discussed (rezafungin and ibrexafungerp), as well as fosmanogepix and nikkomycin Z. Agents that target the cell membrane include 3 fourth-generation azoles, oral encochleated amphotericin B, and aureobasidin A. Among agents with intracellular targets, we will review olorofim, VL-2397, T-2307, AR-12, and MGCD290. In addition, we will describe neurapheresis, a device used as adjunctive therapy for cryptococcosis. With a field full of novel treatments for fungal infections, the future looks promising.

Keywords. antifungal drugs; invasive fungal infections; novel treatment; review.

Fungal infections are among the most difficult diseases to manage in humans, with approximately 1.7 billion individuals suffering from these infections worldwide [1, 2]. Invasive fungal infections (IFIs) refer to systemic fungal infections, in which fungi have infiltrated and established themselves in the deep tissues, resulting in life-threatening illness [3]. Although IFIs have a lower incidence compared with superficial fungal infections, they carry substantial human morbidity, mortality, and economic burden [1, 2, 4]. The overall mortality in patients with IFIs is as high as 45% [5]. These mortality rates remain high, and they often exceed deaths due to tuberculosis [6, 7] and malaria, despite the availability of several effective antifungal drugs [1, 2, 4].

More than 90% of all reported fungal-related deaths result from *Cryptococcus*, *Candida*, *Aspergillus*, *Histoplasma*, and *Pneumocystis* [2, 7]. Other emerging opportunistic fungal pathogens, including molds such as *Fusarium* spp, *Scedosporium* spp, *Penicillium* spp, *Lomentospora* spp, and the *Mucorales*, are becoming significantly more prevalent due to selective pressure from use of antifungals in agriculture, prophylaxis, and empirical therapy [8–10]. There has recently been a rise in resistant species and isolates, such as *Candida auris*, azole-resistant *Aspergillus* spp, and *Lomentospora* (previously *Scedosporium*) *prolificans*, some of which are resistant to all currently available antifungals [11–13].

Great strides were made in the 1990s after the introduction of second-generation azoles, echinocandins, and lipid formulations of amphotericin B (AmB), but drug development has largely stalled since then [1]. Currently, 3 main classes of antifungals are approved for the treatment of IFIs: polyenes, azoles, and echinocandins [14]. These agents target ergosterol in the cell membrane, lanosterol 14α-demethylase, and 1,3-β-glucan synthase, respectively [14]. The newest class of antifungal drugs, the echinocandins, was discovered in the 1970s and took almost 30 years to be approved. The first echinocandin, caspofungin, gained approval in 2001, representing the only novel class of antifungals to be approved in the 21st century [15]. Only 1 antifungal drug (isavuconazole) has been approved and marketed over the last decade [16]. Compared with the development of new antibacterials, antifungal drug development is hampered because fungal pathogens are very closely related to humans, using the same eukaryotic machinery, and therefore offer few pathogen-specific targets [5, 17]. New antifungal therapies that act through novel mechanisms are needed to reduce the high mortality of invasive fungal disease and combat the emergence of resistance to existing therapies. However, with several promising drugs in development, the future looks bright. This review focuses on novel therapies in the pipeline at various phases of clinical development.

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THE NOVEL THERAPEUTICS

AGENTS TARGETING CELL WALL INTEGRITY

Rezafungin (CD101)

Mechanism of action and potential role.

Rezafungin (formerly SP3025 and CD101; developed by Cidara Therapeutics, San Diego, CA) is a novel echinocandin, currently in phase 3 development for treatment of candidemia and invasive candidiasis, with pharmacokinetic and safety qualities that distinguish it as a next-generation echinocandin [18–21]. Studies have also shown potential use for prevention of infections caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp in bone marrow transplant patients, with a prophylaxis trial in planning [22, 23]. The US Food and Drug Administration (FDA) has designated intravenous (IV) rezafungin as a Qualified Infectious Disease Product (QIDP) with fast track status for its development program.

Rezafungin is a structural analog of anidulafungin with a modified choline moiety at the cyclic echinocandin core for greater chemical and metabolic stability and solubility. This might prevent hepatotoxicity by decreasing secondary metabolites [18] while retaining the antifungal activity of an echinocandin by inhibition of β-1,3-glucan synthesis [22] (Figure 1 and Table 1).

Pharmacokinetics/Pharmacodynamics

Pharmacologically, rezafungin has a much longer half-life (approximately 80 hours after the first dose and 150 hours after the second or third dose) than any currently available echinocandin, allowing for extended-interval IV dosing, such as weekly regimens [21]. Theoretically, this would increase pathogen killing and reduce spontaneous mutations by maximizing the drug effect early in the course of therapy when the burden of the pathogen is greatest [21, 25].

Evidence supports the use of weekly dosing for the treatment of patients with candidemia and invasive candidiasis, and higher doses might be able to overcome FKS mutant *Candida* isolates [26]. To evaluate the potential for resistance to rezafungin in *Candida* spp, spontaneous mutations to the drug were compared with caspofungin and anidulafungin, and results indicated an overall low potential for resistance development. Rezafungin has the additional advantage of higher plasma drug exposure due to the front-loaded dosing regimen, which further lowers the risk of resistance development [27]. However, the risk of development of resistance in the long "tail" of the pharmacokinetics (PK) has yet to be fully evaluated.

Activity

Rezafungin exhibits a broad in vitro potency against fungal pathogens comparable to that of other echinocandins [20, 25, 28, 29] (Figure 2). Rezafungin has concentration-dependent fungicidal activity and is highly bound to plasma proteins with extensive tissue distribution and minimal urinary excretion [21, 22, 30]. Rezafungin is being developed as a subcutaneous and IV medication [18, 31]. Previous in vivo pharmacodynamics studies demonstrated robust efficacy against *Candida* spp, including multidrug-resistant isolates such as *C auris* [32–34] and *Aspergillus* spp [35]. By both Clinical and Laboratory Standards Institute (CLSI) and EUCAST broth microdilution methods, the minimum inhibitory concentrations (MICs) for rezafungin were determined to range between ≤0.008 and 2 mg/L against *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida dubliniensis*, and *Candida krusei* and between 0.5 and 2 mg/L against *Candida parapsilosis* [20]. Activity against *Aspergillus* spp, including *Aspergillus fumigatus*, *Aspergillus terreus*, *Aspergillus flavus*, and *Aspergillus niger* isolates, was comparable to other echinocandins with minimal effective concentrations (MECs) that ranged from ≤0.008 to 0.03 mg/L in one study [20] and ≤0.015–2 mg/L for all *Aspergillus* isolates, including azole-resistant isolates in another study [29].

Stage of Development and Ongoing Clinical Studies

A phase 1 study showed low toxicity and a favorable safety profile in humans with no serious or severe adverse events (AEs) or withdrawals from the study due to an AE, with the majority of AEs being mild and all with complete resolution [21]. Studies showed no biotransformation in liver microsomes or hepatocytes, reducing the risk of hepatotoxicity, and minimal inhibition of cytochrome P450 (CYP450) enzymes [21, 22]. Rezafungin, compared with conventional echinocandins, displays improved drug penetration for intra-abdominal candidiasis (IAC) [36].

In a phase 2 multicenter, randomized, double-blinded trial (STRIVE trial, NCT02734862), patients with candidemia and/or invasive candidiasis receiving rezafungin were compared with patients receiving a regimen of daily caspofungin with fluconazole stepdown once clinically stable. Rezafungin was well tolerated and provided clearance of blood cultures and other sterile sites, meeting all primary safety and efficacy end points [37]. Currently, patients are being recruited for a phase 3 study (ReSTORE study, NCT03667690) to determine the noninferiority of rezafungin compared with caspofungin in treatment of candidemia and/or invasive candidiasis, with the primary outcome being all-cause mortality at day 30. Future plans include a second phase 3 trial (ReSPECT study) using rezafungin in a 90-day prophylactic regimen for *Candida*, *Aspergillus*, and *Pneumocystis* infections in allogeneic bone marrow transplant patients, with results expected in 2020 (Figure 3). Unfavorable results from a phase 2 trial (RADIANT study, NCT02733432) investigating topical rezafungin (gel and ointment) resulted in the withdrawal of the topical formulation for the potential treatment of vulvovaginal candidiasis (VVC) [38, 39].

Ibrexafungerp (SCY-078)

Mechanism of Action and Potential Role

Ibrexafungerp (previously MK-3118 and SCY-078; developed by Scynexis, Jersey City, NJ) is a first-in-class oral glucan synthase

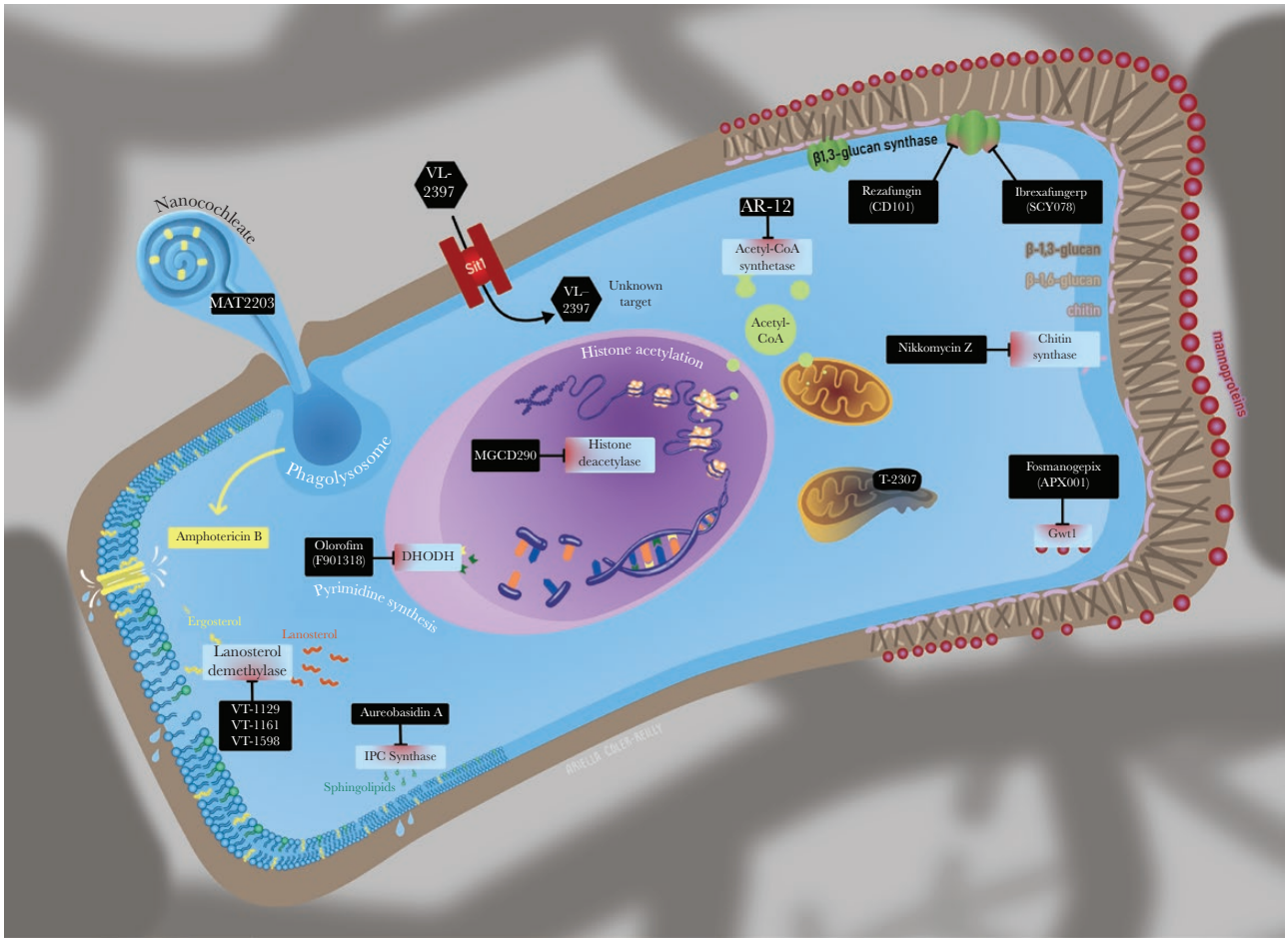


Figure 1. Mechanism of action and target sites of the novel antifungals. The antifungal compounds currently in development have several novel mechanisms of action or new formulations to (1) improve efficacy or reduce toxicity and (2) target different sites in the cell wall, cell membrane, and also intracellular targets. DHODH, dihydroorotate dehydrogenase; IPC, inositol phosphorylceramide.

inhibitor, semisynthetic derivative of enfumafungin and represents the first compound of the triterpenoid antifungals to reach clinical development for the treatment of invasive candidiasis [40]. Although structurally different from echinocandins, it has the same fungal target through inhibition of β-1,3-glucan synthase [41] (Figure 1 and Table 1). Ibrexafungerp has been designated as a QIDP for oral and IV use by the FDA, for the indications of invasive candidiasis and invasive aspergillosis.

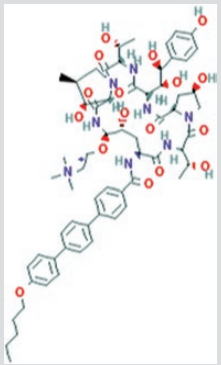
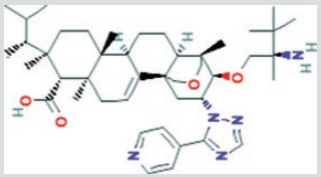
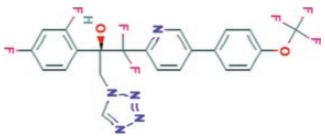
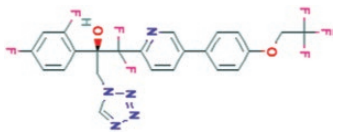
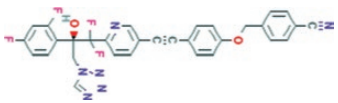
Pharmacokinetics/Pharmacodynamics

Ibrexafungerp is being developed for both oral and IV dosing, but only the oral dosing is currently in clinical trials [41]. It is characterized by high-volume distribution and extensive tissue penetration. It met efficacy end points across multiple murine models of invasive candidiasis at concentrations that have been safely achieved after oral administration in humans, but it does not achieve central nervous system (CNS) penetration [16, 40]. Despite binding to plasma proteins, the affinity may be weak, thereby allowing distribution to tissues [40]. An in vitro study showed robust drug penetration at the site of infection for IAC. Drug concentrations within the necrotic center of liver abscesses are almost 100-fold higher than the serum concentrations at corresponding time points [42]. Ibrexafungerp exhibits pH-dependent solubility, achieving the highest concentrations in acidic media consistent with simulated gastric and intestinal fluids, which may increase its efficacy in vaginal tissues as well as in abscesses [40]. Orally administered ibrexafungerp accumulates in the acidic environment of vaginal tissue in mice [43]. In vitro studies indicate that ibrexafungerp is a modest inhibitor of CYP450 (CYP2C8) with markedly lower effect over other CYP450 isozymes; however, substrates were not affected to a clinically meaningful extent in the presence of therapeutically relevant ibrexafungerp concentrations, suggesting low risk for significant CYP450 drug-drug interactions [44, 45].

Activity

In vitro and in vivo studies have demonstrated potency against the most common *Candida* spp, as well as resistant isolates [41, 46–51]. In addition, it demonstrates excellent in vitro activity against wild-type and azole-resistant strains of *Aspergillus* spp,

Table 1. Novel Antifungals With Chemical Structure, Mechanism of Action, Spectrum of Activity, Expected Benefits

Class	Novel Therapy	Chemical Structure	Mechanism of Action	Spectrum of Activity	Expected Benefits
Glucan synthesis inhibitors	Rezafungin (CD101)		Inhibition of β-1,3-glucan synthesis	*Candida* spp (including *Candida auris*), *Aspergillus* spp, and *Pneumocystis* spp	• Not hepatotoxic • Longer half-life (weekly dosing) • Better penetration (IAC) • Less risk of resistance • Active against resistant strains • SQ and IV formulation • Better adherence, less hospital costs
	Ibrexafungerp (SCY078)			*Candida* spp (including *C auris*), *Aspergillus* spp *Paecilomyces variotii*, *Lomentospora prolificans*, *Pneumocystis* spp Lacks activity: *Mucor* and *Fusarium* spp	• Oral and IV formulation • Active against resistant strains • Better penetration (IAC) • Minimal drug-drug interactions
Azoles	VT-1129		Inhibition of lanosterol 14α-demethylase (CYP51)	*Cryptococcus neoformans/C gatti*, *Candida* spp	• Minimal DDI (selective for fungal CYP51 enzyme) • Oral formulation
	VT-1161 (Oteseconazole)			*Candida* spp, *Coccidioides immitis/C posadasii*, *Trichophyton* spp, *Rhizopus arrhizus var. arrhizus*	• Minimal DDI (selective for fungal CYP51 enzyme)
	VT-1598			*Candida* spp (including *C auris*), *Aspergillus* spp, *Coccidioides*, *Blastomyces*, *Histoplasma*, *R arrhizus*	• Minimal DDI (selective for fungal CYP51 enzyme) • Broad spectrum • Longer half-life

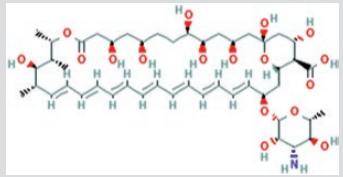
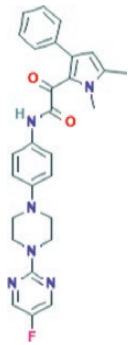
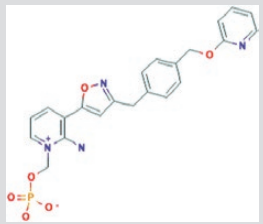
Class	Novel Therapy	Chemical Structure	Mechanism of Action	Spectrum of Activity	Expected Benefits
Polyenes	MAT2203 (CAmB)		Ergosterol binding, pore formation in the fungal membrane	*Candida* spp, *Aspergillus* spp, *Cryptococcus* spp	• Oral formulation • Less toxicity • Minimal DDI
Orotomides	Olorofim (F901318)		Inhibition of fungal DHODH, pyrimidine synthesis	*Aspergillus* spp, *Histoplasma, Blastomyces, C immitis, Taloromyces marneffei, Fusarium* spp, *L prolificans, Scopulariopsis brumptii* Lacks activity: *Candida* spp, *Cryptococcus* spp and *Mucorales*	• Oral formulation • Active against pan-resistant fungi • Less toxicity (fungal specific target)
Glycosylphosphatidylinositol (GPI) inhibitors	Fosmanogepix (APX001)		Inhibition of Gwt1, GPI-anchor protein synthesis	*Candida* spp (including *C auris*), *C neoformans, C immitis, Aspergillus* spp, *Fusarium, Mucorales, Lomentospora* Lacks activity: *Candida krusei*	• Less toxicity (fungal specific target) • Broad spectrum, active against resistant isolate

Table 1. Continued

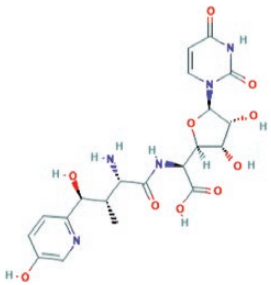
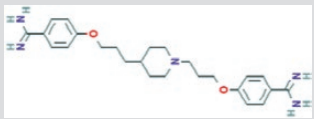
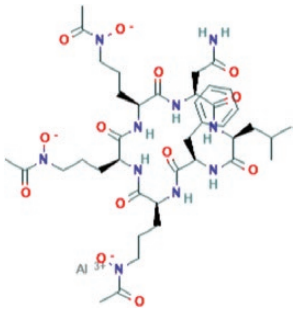
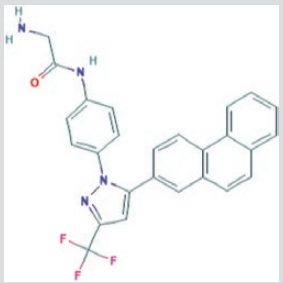
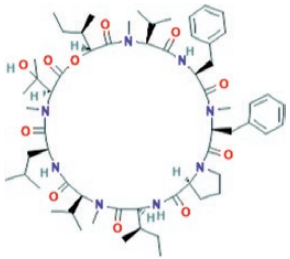
Class	Novel Therapy	Chemical Structure	Mechanism of Action	Spectrum of Activity	Expected Benefits
Chitin synthases inhibitors	Nikkomycin Z		Inhibition of chitin synthases	*C immitis, Histoplasma capsulatum, Blastomyces dermatitidis* Adding echinocandins: *Candida* spp, *Aspergillus* spp Lacks activity: *Aspergillus* spp	• Synergistic effect with echinocandins • Orphan drug for coccidioidomycosis
Arylamidine	T-2307		Unknown, possible mitochondrial collapse	*Candida* spp, *C neoformans/C gattii, Malassezia furfur*, *Aspergillus* spp and *Fusarium solani*	• Clinically safer than pentamidine • Preferential uptake by fungal cells
Siderophore	VL-2397 (ASP2397)		Unknown intracellular target, uptake via specific siderophore iron transporter (Sit1)	*Aspergillus* spp, *C glabrata, Candida kefyr, C neoformans*, and *Trichosporon asahii* Lacks activity: *Aspergillus niger,* other *Candida* spp, *Mucorales, Scedosporium apiospermum*, and *Fonsecaea pedrosoi*	• Selective fungal target • Activity against azole-resistant isolates
Anticancer protein kinase inhibitor	AR-12		Inhibition of fungal acetyl-CoA synthetase	*Candida* spp, *C neoformans, Blastomyces, Histoplasma, Coccidioides, Fusarium, Mucor, Lomenstospora, Trichophyton rubrum*	• Repurposed antifungal agent

Table 1. Continued

Class	Novel Therapy	Chemical Structure	Mechanism of Action	Spectrum of Activity	Expected Benefits
Glycolipid inhibitors	Aureobasidin A		Inhibition of inositol phosphorylceramide (IPC) synthase, sphingolipid syntheses	*Saccharomyces cerevisiae, Candida* spp, *Cryptococcus* spp, *Schizosaccharomyces pombe*	• Less toxicity • Broad spectrum
Histone deacetylase inhibitors	MGCD290	Structure not disclosed [24]	Inhibition of fungal histone deacetylase (Hos2) and nonhistone proteins (Hsp90)	*Candida* spp, *Aspergillus* spp, *Mucor* and *Fusarium* (in combination with azole/echinocandin)	• Synergistic effect with azoles and echinocandins • Decreases MICs in resistant isolates
Device	Neurapheresis	N/A	Extracts contaminated CSF through filtration system	Cryptococcal meningitis	• Adjunctive therapy for CM • Decrease risk of hydrocephalus • Allows to modulate high ICP • Minimize repeat LP and shunt placement

Abbreviations: CAmB, encochleated amphotericin B; CM, cryptococcal meningitis; CSF, cerebrospinal fluid; DDI, drug-drug interactions; IAC, intra-abdominal candidiasis; ICP, intracranial pressure; IV, intravenous; LP, lumbar puncture; MIC, minimum inhibitory concentration; N/A, not applicable; SQ, subcutaneous.

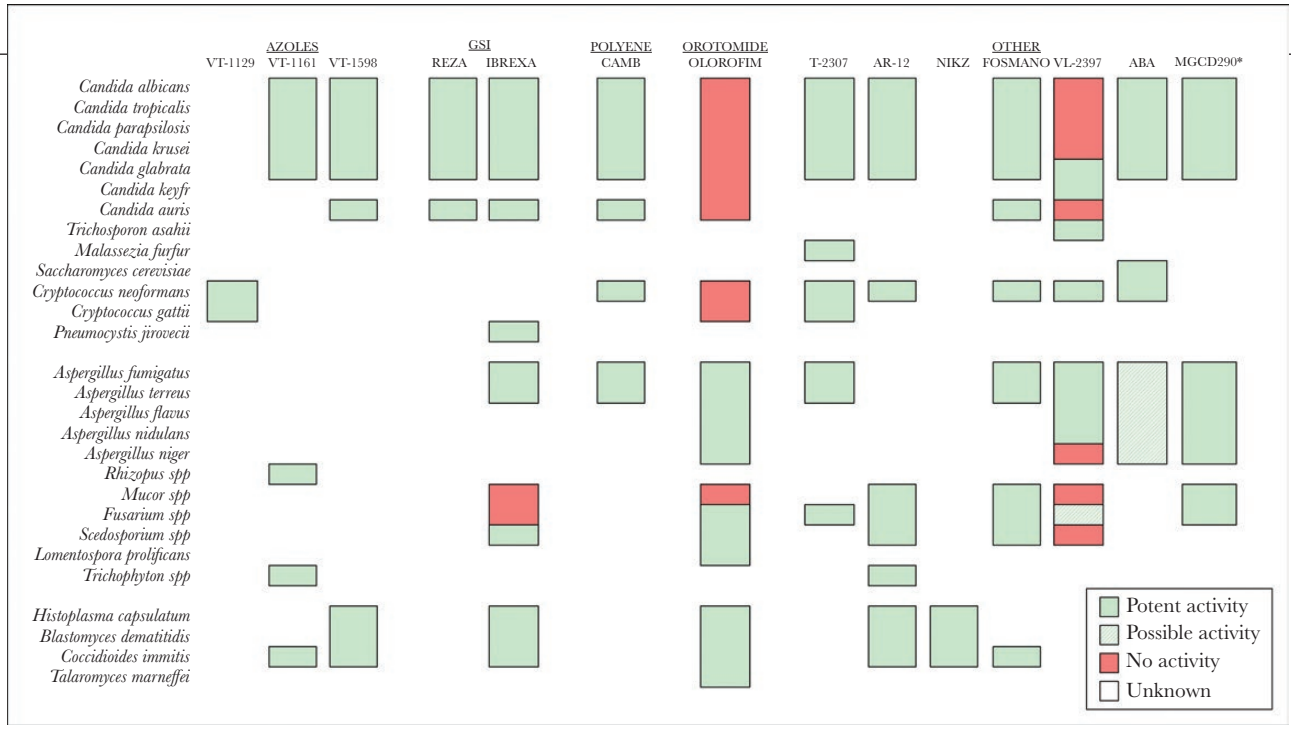


Figure 2. Novel antifungals with spectrum of activity. New antifungal compounds show extensive spectrum of activity to overcome resistant fungi; however, several gaps still remain. *MGCD290: Potent activity in combination with azoles and/or echinocandins. ABA, aureobasidin A; CAMB, encochleated amphotericin B; FOSMANO, fosmanogepix; GSI, glucan synthase inhibitor; IBREXA, ibrexafungerp; NIKZ, nikkomycin Z; REZA, rezafungin.

Paecilomyces variotii, and some activity against *L prolificans*, but poor activity was observed against *Mucor* and *Fusarium* spp [47, 52]. It retains activity against *Candida* FKS1 or FKS2 mutants [53], including echinocandin-resistant isolates of *C glabrata* and *C auris* [41, 46–51]. Due to differential binding sites, the FKS mutations associated with echinocandin resistance are distinctly different from those reducing susceptibility to the enfumafungin derivatives including ibrexafungerp, limiting cross-resistance [47]. By both CLSI and EUCAST broth microdilution methodologies, MICs were determined to be 0.06–2 mg/L against *C albicans* and *C tropicalis*, 0.25–1 mg/L against *C parapsilosis*, and 0.5–2 mg/L against *C glabrata* and *C krusei* [46]. Against *Aspergillus* spp, MEC values reported were 0.03–1 mg/L and 0.015–0.25 mg/L when tested by CLSI and EUCAST methods, respectively [47]. Studies also show that oral ibrexafungerp could be a viable option for managing *Pneumocystis* in immunocompromised patients, because it has shown significant activity in a murine therapy and prophylaxis model [54, 55] (Figure 2).

Stage of Development and Ongoing Clinical Studies

Ibrexafungerp met primary end points in 2 phase 2 clinical trials (NCT02679456, NCT02244606) in VVC and invasive candidiasis, respectively. In VVC, oral ibrexafungerp was superior compared with oral fluconazole (78% vs 65%), and at the end of a 4-month follow-up period (88% vs 65%) with a lower recurrence rate (4% vs 15%) [56]. For invasive candidiasis, ibrexafungerp, as an oral step-down treatment after 3–10 days of echinocandin therapy, compared with fluconazole, achieved the predetermined target exposure in most subjects [57]. Mild-to-moderate gastrointestinal events such as diarrhea, nausea, vomiting, abdominal pain or discomfort were seen with ibrexafungerp, but no discontinuations due to AEs or serious AEs were observed. No mycological failure was reported in the study drug arm [57]. A recently completed phase 2 trial, the DOVE study (NCT03253094), explored 5 dosing regimens of oral ibrexafungerp versus fluconazole in patients with acute VVC to identify an optimal dose for a phase 3 trial. Results have not been published.

Currently, there are multiple ongoing phase 3 trials [58] (Figure 3). The CARES study (NCT03363841), open for enrollment in the United States and India, is assessing ibrexafungerp for the treatment of *C auris* infections. Initial evidence of efficacy and safety in 2 subjects was presented with promising results [59]. The FURI study (NCT03059992) is evaluating the efficacy and safety in patients with an invasive and/or severe fungal disease that are refractory or intolerant to standard-of-care antifungal treatment. Initial results of 20 patients who completed therapy were favorable [60]. The Data Review Committee adjudicated 55% of patients as achieving complete or partial response, 30%

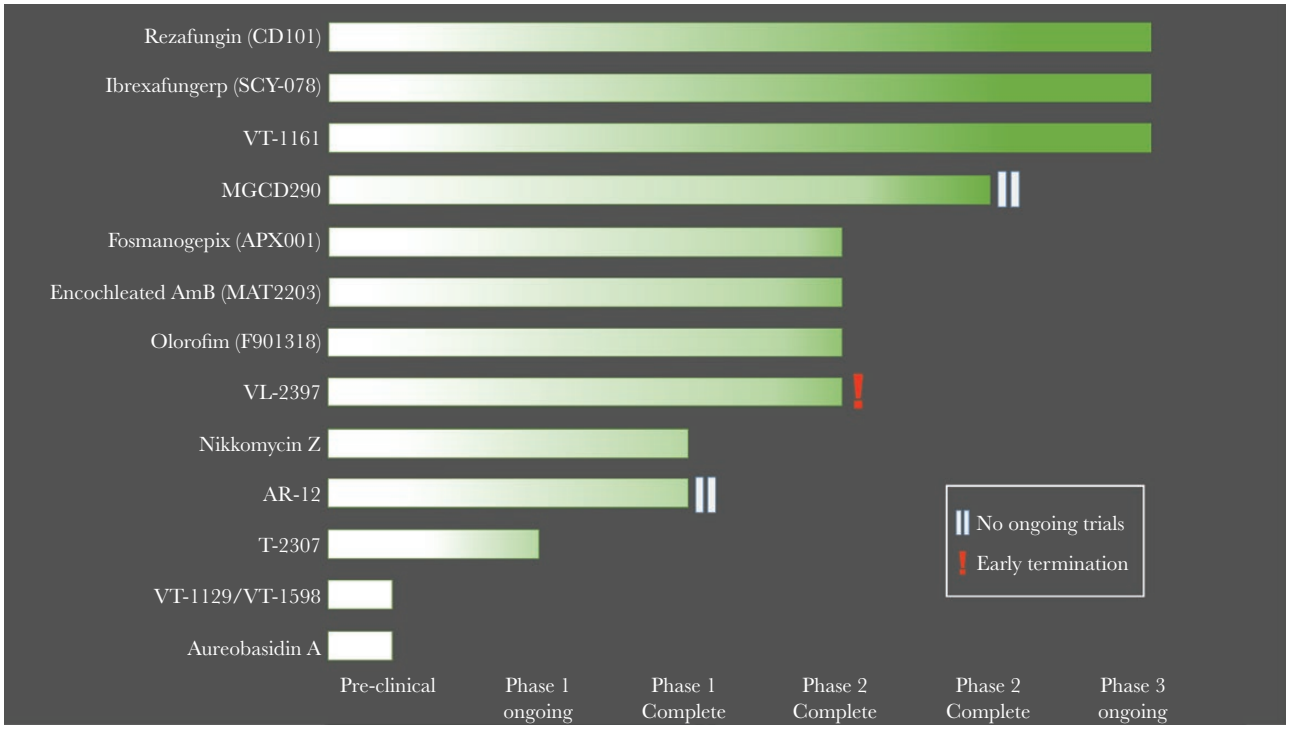


Figure 3. Stage of clinical development of the novel antifungals. New antifungal compounds are currently in several stages of development. Most have advanced to phase 2 or 3, but a few still remain in phase 1 or preclinical development. VL-2397 had early termination of phase 2 trial, and there are currently no ongoing trials. AR-12 and MGCD290 have no ongoing trials.

maintaining stable disease, 10% with progression of disease, and 1 case was considered as indeterminate [60]. Outcomes for 2 cases of *C albicans and C tropicalis* spondylodiscitis have shown clinical data for its use in bone infections [61]. Upcoming studies will evaluate oral ibrexafungerp in patients with acute VVC (VANISH306 study, NCT03987620) and as combination therapy with voriconazole in patients with invasive pulmonary aspergillosis (SCYNERGIA study, NCT03672292).

Fosmanogepix (APX001)

Mechanism of Action and Potential Role

Fosmanogepix (also known as APX001) (synthetized by Amplyx Pharmaceuticals, San Diego, CA), a first-in-class antifungal, is a prodrug of Manogepix (E1210), and it displays highly selective antifungal activity by inhibiting fungal enzyme Gwt1 and subsequently inactivating posttranslational modification of glycosylphosphatidylinositol (GPI) anchor proteins, also known as mannoproteins [62]. The GPI-anchored proteins become covalently linked to β-1,3-glucan, helping maintain the integrity of the fungal cell wall and play a role in adherence and invasion of host tissues. After GPI-anchor synthesis is disrupted, β-1,3-glucan can be exposed, increasing recognition of the fungus by immune cells [63]. The action of fosmanogepix appears to be specific to fungi, because it does not inhibit human inositol acylation, resulting in a wide therapeutic index [63] (Figure 1 and Table 1). Fosmanogepix received QIDP and fast track designations as well as orphan drug status for 4 indications: invasive candidiasis, invasive aspergillosis, coccidioidomycosis, and rare molds, including *Scedosporium* and *Fusarium*.

Activity

Fosmanogepix has in vitro activity against a broad spectrum of fungi, including yeast such as *Candida* spp [62–64], *Cryptococcus neoformans* [65], *Coccidioides immitis* [66], and *C auris* [67, 68], but it lacks activity against *C krusei* [62, 69], and it also has activity against many molds, including *Aspergillus* (even non-*A fumigatus* spp), *Fusarium*, *Mucorales*, and *Scedosporium* spp (including *L prolificans*) [62, 70, 71] (Figure 2). This drug has also shown efficacy in animal models of IFIs, including candidiasis caused by azole and echinocandin-resistant isolates, aspergillosis, and fusariosis [72–75]. Animal models in both rats and monkeys indicate that fosmanogepix is extensively distributed to major tissues relevant to IFIs (including liver, lung, brain, and eye) and cleared primarily by biliary and fecal excretion [76].

Stage of Development and Ongoing Clinical Studies

Phase 1 clinical studies have demonstrated >90% bioavailability for fosmanogepix, in both oral and IV formulations. These trials (NCT02957929, NCT02956499, NCT03333005) have determined the safety, tolerability, and PK of fosmanogepix in healthy volunteers and patients with acute myelogenous leukemia, who are at increased risk of IFIs. The clinical pharmacological profile, including drug-drug interactions and drug distribution, was also studied [77, 78]. Currently, phase 2 proof-of-concept

studies are being conducted in patients with invasive candidiasis/candidemia and invasive aspergillosis [79] (Figure 3).

Nikkomycin Z

Mechanism of Action and Potential Role

Nikkomycin Z ([NikZ] developed by Valley Fever Solutions, Inc., Tucson, AZ) is a first-in-class antifungal derived from *Streptomyces tendae*, with a novel mechanism of action through inhibition of chitin synthases, an essential component of the fungal cell wall [80] (Figure 1 and Table 1). The target enzyme is absent in mammalian hosts, making NikZ selective to fungal cells with little to no toxicity in humans [80]. This agent was first described in the 1970s, but it was not until the early 2000s that NikZ gained interest for the treatment of endemic mycoses, particularly coccidioidomycosis [80]. This agent is under development as an orphan product for the treatment of coccidioidomycosis, and in 2014 it gained the QIDP designation.

Activity

Nikkomycin Z has potent in vitro and in vivo activity against dimorphic fungi with high quantities of chitin, including *C immitis* and *Blastomyces dermatitidis*. This agent has demonstrated activity in murine models of coccidioidomycosis, blastomycosis, and histoplasmosis [81–84]. Its fungicidal effect exceeded that of azoles and AmB, by sterilizing the lungs of most mice in murine models of pulmonary coccidioidomycosis and blastomycosis; however, moderate efficacy was seen for histoplasmosis [83, 85]. As monotherapy, it has limited activity against some yeasts, such as *C albicans*, and no activity against filamentous fungi, such as *Aspergillus* [83]. Despite its narrow spectrum, it has the potential to enhance other antifungal treatments when combined with other drugs. For example, NikZ in combination with echinocandins produced a synergistic effect against *A fumigatus* [86, 87], and it has also been productive in combination with fluconazole and itraconazole for different *Candida* and *Aspergillus* species [88] (Figure 2).

Pharmacokinetics/Pharmacodynamics

Pharmacologic studies in mice showed that NikZ administered through IV infusion was rapidly eliminated; however, oral administration resulted in slow absorption, allowing inhibitory levels to persist for hours [83]. Experimental murine studies suggest that twice-daily dosing of 250–500 mg could achieve optimal plasma concentrations in humans [89].

Stage of Development and Clinical Studies

Nikkomycin Z has completed phase 1 clinical development (NCT00834184) and showed excellent safety in healthy humans, without AEs observed [90]. A phase 2 trial (NCT00614666) to determine a safe dose in patients with pulmonary coccidioidomycosis was terminated early due to recruitment challenges and lack of funding [91, 92], but a phase 2a trial is planned for 2020 (Figure 3).

AGENTS TARGETING CELL MEMBRANE

VT-1129, VT-1161, and VT-1598

Mechanism of Action and Potential Role

One of the main limitations of the azole class of antifungals is the clinically significant drug-drug interactions experienced due to inhibition of off-target CYP450 [93]. VT-1129, VT-1161 (or Oteseconazole), and VT-1598 (developed by Viamet Pharmaceuticals, Durham, NC) are next-generation azoles, termed tetrazoles, attempting to remedy this limitation through improved binding discrimination between fungal and mammalian CYP450 enzymes. By replacing the triazole metal-binding group with a tetrazole, this group achieves greater selectivity for fungal lanosterol 14α demethylase (CYP51) [94, 95], which will hopefully result in fewer safety issues and lower MICs (Figure 1 and Table 1). The inhibition of this enzyme prevents conversion of lanosterol to ergosterol, an essential component of the fungal membrane. The FDA has granted QIDP, fast track, and orphan drug designation to VT-1598 for the treatment of coccidioidomycosis, and VT-1161 received QIDP and fast track status for recurrent VVC.

Activity

Each of these agents has potent activity against various yeast isolates, including *C albicans* and non-*C albicans* species, and *Cryptococcus* spp, as well as significant mold activity, including the *Mucorales* (Figure 2).

Potent in vitro activity has been reported for VT-1161 against *Candida* spp (MIC range, ≤0.03–0.25 mg/L), including wild-type isolates and some azole- and echinocandin-resistant strains, *C immitis*/Coccidioides *posadasii* (1–4 mg/L), *Trichophyton* spp (≤0.03–0.06 mg/L) [96–99], and against molds such as *Rhizopus arrhizus var. arrhizus* [100]. In vitro activity against *Candida* species has translated into in vivo efficacy in various animal models, including those of VVC and invasive candidiasis secondary to wild-type, azole- and echinocandin-resistant *C albicans* [101]. In murine models of coccidioidomycosis, VT-1161 provided prolonged suppression of fungal burden, improved survival, and prevented dissemination of infection from the original inoculation site to a greater extent than fluconazole [96]. This suggests that VT-1161 might have the ability to cure the "uncurable" syndromes such as meningitis. Efficacy has also been demonstrated in a guinea pig model of onychomycosis with either once-daily or weekly administration [102]. VT-1161 could be a potential treatment for mucormycosis because it has in vitro activity against *Rhizopus arrhizus var. arrhizus*. This has translated into in vivo efficacy in a mouse pulmonary infection model, but the in vitro potency of this agent appears to be reduced against *R arrhizus var. delemar* [100].

VT-1129, which is structurally very similar to VT-1161, was mainly designed to treat cryptococcal meningitis (CM). It has potent in vitro activity against resistant *Candida* spp [99], and activity is maintained against *C neoformans/C gatti* genotypes

with reduced susceptibility to fluconazole [103, 104]. Studies have shown MIC_{50} that range between 0.05 and 0.25 μg/mL for dose-dependent and -resistant *Cryptococcus* isolates, respectively [103, 104]. In a murine model, oral administration of this agent resulted in improved survival and reduced tissue fungal burden. Due to the long half-life of this agent (more than 6 days in mice), elevated concentrations were detected in the brain long after dosing was stopped [105]. A loading dose-maintenance dose strategy has been shown to quickly reach highly efficacious concentrations [106]. No antagonism was observed when VT-1129 was combined with AmB [105].

Of these 3 investigational agents, VT-1598 has the broadest spectrum and most potent activity against molds, including various *Aspergillus* spp and *R arrhizus*, as well as endemic fungi, including *Coccidioides* with elevated fluconazole MICs, *Blastomyces* and *Histoplasma* isolates [105, 107]. A murine model of CNS coccidioidomycosis also showed the efficacy of VL-1598 [108]. This agent demonstrates potent in vitro and in vivo activity against *Candida* species [109], including resistant isolates such as *C auris* (MIC range, 0.03–8 mg/L). An in vivo study of neutropenic mice with invasive *C auris* infection treated with VT-1598 resulted in significant dose-dependent improvements in survival and reductions in kidney and brain fungal burden compared with the control [110].

Stage of Development and Ongoing Clinical Studies

Preclinical results of VT-1129, VT-1161, and VT-1598 have been reported in the literature, and VT-1161 is currently in clinical development (Figure 3). Phase 2 clinical trials have evaluated the efficacy and safety of VT-1161 for the treatment of tinea pedis, onychomycosis, and acute and recurrent VVC (NCT02267382, NCT02267356, NCT01891331, NCT01891305) [111]. Two phase 3 trials in recruitment (NCT03561701 and NCT03840616) will evaluate the effectiveness and safety of VT-1161 versus fluconazole and a placebo for the treatment of VVC.

Encochleated Amphotericin B (MAT2203)

Mechanism of Action and Potential Role

MAT2203 (developed by Matinas BioPharma, Bedminster, NJ) is a novel encochleated amphotericin B (CAmB) formulation for oral administration [4]. Encochleated AmB, like all forms of amphotericin, binds with sterols, leading to increased cell membrane permeability to ions [112, 113] (Figure 1 and Table 1). Despite the highly favorable antifungal activity of AmB, the successful treatment of IFIs remains difficult due to toxicity in critical mammalian organ systems caused by its lack of selectivity between fungal and animal sterols [112, 113]. Recent investigations have shown the safety and efficacy of the lipid-based cochleates formulation as a delivery system for AmB for use in *Candida* infections [114]. The cochleates consist of solid phospholipid bilayer vehicles, designed for hydrophobic drug delivery, that are arranged in rolled-up sheets composed of divalent cation precipitates, specifically phosphatidylserine and calcium. This structure protects the AmB encapsulated in the cochleates molecules from degradation in the gastrointestinal tract [114]. Cochleates result in a stable, nontoxic, highly efficacious AmB lipid particle, enabling its potential oral formulation [112]. The drug is released upon interaction of the cochleate with the target cells in the presence of the low intracellular calcium concentrations [4, 16]. There is direct interaction between CAmB and the fungus cell membrane, but the precise mechanism by which cochleates fuse with cell membranes is not yet fully understood [113]. Presumably, the drug is delivered to the target cell cytoplasm after phagocytosis by macrophages, and the fungal cells make contact with the lysosome and deliver the drug content after fusion with the lysosome [4]. Its potential for oral delivery and reduction in toxicity are the main advantages of this drug. Encochleated AmB received QIDP designation as well as fast track status from the FDA in 2015 for the treatment of invasive candidiasis, aspergillosis, and the prevention of IFIs in patients on immunosuppressive therapy. It recently received QIDP, fast track status, and orphan drug designation for treatment of CM.

Pharmacokinetics/Pharmacodynamics

The high efficiency in vitro and in vivo can be explained by increased uptake of the drug by fungus, which is mediated by a direct interaction and fusion between CAmB and the fungus cell membrane [113]. Animal models have shown extensive tissue distribution and penetration of CAmB into target organs after administration of a single dose. The liver acts as a reservoir, releasing AmB slowly, increasing its potential for the treatment of IFIs [115]. In vivo, orally administered CAmB resulted in adequate amounts of AmB reaching target organs, including the liver, spleen, and kidneys, early in treatment. Mice treated with CAmB had 100% survival and comparable efficacy with that of deoxycholate AmB (DAmB), resulting in substantial colony-forming unit count reduction in the kidneys and lungs [116]. Targeted therapy was demonstrated after the higher AmB concentrations were seen in infected mice, whereas no such accumulation occurred in the organs of healthy animals [116]. Further work will be required to assess whether immune cells are required for efficacy and concentration, because a significant portion of fungal infections occur in neutropenic patients.

Further investigations have also shown the in vivo efficacy of oral CAmB in a murine model of disseminated aspergillosis [117] and activity in visceral leishmaniasis [114, 118]. Oral CAmB has potential for treatment for CNS fungal infections, in combination with flucytosine (5FC) in a murine model of CM proving as effective as parenteral DAmB plus 5FC, and superior to oral fluconazole without inconvenient toxicity after a 28-day treatment schedule [119].

In vivo safety studies in murine models have shown 100% survival after 30 days when administering escalating daily doses of intraperitoneal CAmB, and equivalent safety of high oral CAmB doses, suggesting that CAmB could be administered in more aggressive doses (as high as 25 mg/kg) than currently available formulas [112, 113]. Encochleated AmB produced no hemolysis at concentrations as high as 500 μg/mL AmB, whereas DAmB was highly hemolytic at 10 μg/mL, possibly due to a low interaction of CAmB with red blood cells, in contrast to DAmB [113].

Stage of Development and Ongoing Clinical Studies

Preliminary results from a phase 1 study demonstrated that single doses of 200 and 400 mg were well tolerated without serious AEs, opening the way for phase 2 trials (NCT02971007) [120]. MAT2203 was well tolerated, with AEs mostly related to mild gastrointestinal symptoms, and showed a favorable safety profile without the renal and hepatic toxicities seen with IV AmB [121].

Enrollment is currently underway for a phase 2a clinical trial assessing orally administered MAT2203 (200–800 mg) in refractory mucocutaneous candidiasis (NCT02629419). Preliminary results are promising, with MAT2203 being well tolerated and effective [121]. A phase 1/2 trial is planned to start recruitment in Uganda in October 2019 to evaluate CAmB for CM (EnACT trial, NCT04031833). A phase 2 study was being planned to investigate MAT2203 for the prevention of IFIs, but the trial was recently withdrawn due to protocol redundancy (NCT03187691). Matinas plans to conduct a phase 2 trial to get MAT2203 approved for IFI prophylaxis in patients with acute lymphoblastic leukemia [121] (Figure 3).

Aureobasidin A

Aureobasidin A ([AbA] developed by Takara Bio, Shiga, Japan) is a cyclic depsipeptide antibiotic isolated from the filamentous fungus *Aureobasidium pullulans* R106 [122, 123]. Aureobasidin A was initially discovered in 1989, although its license patent was granted in 2007 to AureoGen Biosciences/Merck & Co. for further development [124].

Mechanism of Action and Potential Role

Aureobasidin A exhibits antifungal activity through inhibition of inositol phosphorylceramide synthase, an important enzyme expressed from the AUR1 gene involved in sphingolipid synthesis, exclusively found in the fungal cell membrane [125–127] (Figure 1 and Table 1). The absence of this enzyme in mammalian cells decreases the risk of toxicity. Resistance to AbA can be seen due to mutation of the AUR1 gene in fungi [127].

Activity

In vitro studies have shown activity against *Saccharomyces cerevisiae*, *Candida* spp, *Cryptococcus* spp, *Schizosaccharomyces pombe*, and some *Aspergillus* spp [122] (Figure 2). An in vivo murine model of candidiasis showed fungicidal activity of AbA with low toxicity and prolonged survival [123].

Stage of Development and Clinical Studies

This drug remains in the preclinical developmental, but it has a favorable profile to advance for clinical use (Figure 3).

AGENTS WITH INTRACELLULAR TARGETS

Olorofim (F901318)

Mechanism of Action and Potential Role

Olorofim (developed by F2G, Inc., Manchester, UK) is a novel antifungal drug in a novel class of orotomides. Its mechanism of action involves the inhibition of fungal dihydroorotate dehydrogenase (DHODH), an important enzyme in pyrimidine biosynthesis essential for deoxyribonucleic acid synthesis [128] (Figure 1 and Table 1). Olorofim has no activity against human DHODH and therefore selectively arrests fungal pyrimidine biosynthesis, resulting in limited toxicity and a favorable safety profile [128]. There are several other appealing characteristics of this drug including oral bioavailability and potent activity against triazole-resistant isolates and other pan-resistant fungal pathogens [129]. The European Medicines Agency Committee for Orphan Medicinal Products has recently granted orphan drug status to olorofim for the treatment of invasive aspergillosis and rare mold infections caused by *Lomentospora* spp.

Pharmacokinetics/Pharmacodynamics

Olorofim is relatively insoluble in water and highly protein bound [129], but it has good distribution to tissues, including kidney, liver, lung, and, although at lower levels, has been detected in the brain [128]. Olorofim demonstrates time-dependent killing effect [129, 130] and shows a typical pharmacokinetic profile when dosed by IV and oral routes (bioavailability >45%) [131]. Olorofim is cleared by multiple CYP450 enzymes; however, it does not induce CYP450 enzymes itself. It is a weak CYP3A4 inhibitor [132], making it prone to drug-drug interactions [16]. Olorofim has a delayed fungicidal effect if the exposure is prolonged [130].

Activity

In vitro studies have shown broad-spectrum activity against filamentous and dimorphic fungi including *Aspergillus* spp, *Histoplasma capsulatum*, *B dermatitidis*, *C immitis*, *Talaromyces* (formerly *Penicillium*) *marneffei*, and *Fusarium* spp [128], as well as organisms pan-resistant to clinically available antifungal agents such as *Scedosporium apiospermum*, *L prolificans and Scopulariopsis* spp (including *Scopulariopsis brumptii*) [133–135]. It is highly active against all pathogenic *Aspergillus* spp including wild-type and azole-resistant CYP51A mutant strains, with an MIC of <0.1 μg/mL. It is active against cryptic species of *Aspergillus* that can be hard to treat with current antifungal therapies,

such as *Aspergillus nidulans*, *Aspergillus tubingensis*, *Aspergillus lentulus*, and *Aspergillus calidoustus*, with lower MICs than AmB, voriconazole, and posaconazole [129, 136, 137]. This agent displays potent in vitro activity against most molds with a limited variation in EUCAST susceptibility testing [138]. Organisms that remain susceptible to olorofim are grouped together under the same DHODH phylogenetic tree, whereas the lack of activity seen against *Candida* spp, *C neoformans*, and *Mucorales* is due to a distantly related DHODH [128]. Resistance to olorofim, as assessed by serial passage and drug gradients, does not appear to be easily induced, at least with *A fumigatus* [128]. Lack of cross-resistance was also demonstrated with azole-resistant *Aspergillus* spp mutant strains [139] (Figure 2).

Olorofim demonstrated in vivo efficacy in murine models of invasive aspergillosis caused by wild-type and azole-resistant strains [128, 129, 140]. Olorofim was also highly efficacious in prolonging survival of mice with disseminated aspergillosis [128, 129, 140]. In vivo efficacy with up to 88% survival of intraperitoneal olorofim dosing (15 mg/kg 3 times daily) was recently reported against infection with *A fumigatus*, *A nidulans*, and *Aspergillus tanneri* in both neutropenic and chronic granulomatous disease mouse models of invasive aspergillosis [141]. Olorofim therapy demonstrated robust antifungal activity, leading to prolonged survival and a concentration-dependent decline in circulating galactomannan levels in an immunosuppressed murine model of acute sinopulmonary infection caused by 4 clinical *A flavus* isolates (MIC ranged from 0.015 to 0.06 mg/L), which correlated with histological clearance of lung tissue [142].

Stage of Development and Ongoing Clinical Studies

Both oral and IV formulations are being developed, but the exact dosing regimen for both formulations is still being studied. An oral immediate release tablet evaluated in a phase 1 study (NCT03340597) showed that olorofim was well tolerated and effective [143]. The IV formulation was studied during clinical development (NCT02342574 and NCT02142153) and achieved the target steady-state plasma concentrations predicted for efficacy. Two phase 2 trials (NCT02856178 and NCT03036046) for use as fungal prophylaxis were recently withdrawn, because they were no longer required, and the drug is now in phase 2b clinical development with a global open-label study (FORMULA-OLS, NCT03583164) to evaluate olorofim for difficult-to-treat IFIs, including azole-resistant aspergillosis, scedosporiosis, lomentosporiosis, and other rare molds, in patients lacking suitable alternative treatment options [144] (Figure 3).

VL-2397

Mechanism of Action and Potential Role

VL-2397 (formerly ASP2397, developed by Vical Pharmaceuticals) potentially represents a new class of antifungal agents. It is a cyclic hexapeptide isolated from the fermentation broth of *Acremonium persicinum* [145]. VL-2397 is structurally related to the siderophore ferrichrome, a low molecular weight siderophore with high specificity for iron. This agent is able to chelate aluminum ions instead of iron; however, its exact mechanism of action is not fully understood, because the aluminum compound does not inhibit fungal growth [146]. Activity results from its effect on an unknown intracellular target (Figure 1 and Table 1). However, it is known that it triggers a potent and rapid antifungal effect after transport into fungal cells, specifically *A fumigatus*, via siderophore iron transporter 1 (Sit1), which is absent in mammalian cells. Live cell imaging suggests that VL-2397 causes arrest of hyphal elongation [147]. The FDA has granted QIDP, Orphan Drug, and fast track designations to VL-2397 for the treatment of invasive aspergillosis.

Activity

VL-2397 is active against different fungi (Figure 2). It demonstrates rapid onset of inhibition (within the first 2 to 4 hours) and potent in vitro fungicidal activity against hyphal elongation compared with existing drugs [147, 148]. It has proven activity against *Aspergillus* spp (including wild-type as well as azole-resistant strains), some *Candida* spp (only *C glabrata* and *C kefyr*), *C neoformans*, and *Trichosporon asahii*. The agent appears to have limited activity against *Fusarium solani*, and it is not active against *A niger*, *Mucorales*, *Scedosporium apiospermum*, and *Fonsecaea pedrosoi* [148]. This has translated into in vivo efficacy in a silkworm model and neutropenic murine models of invasive pulmonary aspergillosis, where VL-2397 caused dose-dependent prolongation of survival and reduction in fungal burden in the lung [145]. There is evidence of in vivo efficacy in a neutropenic murine model of invasive candidiasis caused by both wild-type and azole- and echinocandin-resistant *C glabrata* isolates [149].

Stage of Development and Ongoing Clinical Studies

A phase 1 study showed that this agent was well tolerated in healthy volunteers who received escalating single and multiple IV doses per day [150]. It was well tolerated up to 1200 mg, and no accumulation was observed for 21 days [150, 151]. There were no reported serious AEs related to the drug [150, 151]. VL-2397 demonstrated nonlinear saturable binding kinetics, most likely due to protein binding [148]. A phase 2 trial (NCT03327727) for the treatment of invasive aspergillosis in acute leukemia patients and recipients of bone marrow transplants was underway, but this was terminated early due to a business decision [152]. It is unfortunate that there are no ongoing trials at this time (Figure 3).

T-2307

Mechanism of Action and Potential Role

T-2307 (synthesized at Toyama Chemical Co., Llt., Tokyo, Japan) is an investigational arylamidine, structurally similar to a class of aromatic diamidines that includes pentamidine [153].

Its mechanism of action remains unknown; however, it appears to cause the collapse of fungal mitochondrial membrane potential in yeasts [154] (Figure 1 and Table 1). T-2307 is preferentially taken up by fungal cells via high-affinity spermine and spermidine transport systems with evidence of little effect on rat liver mitochondrial function [153, 155]. This transporter-mediated uptake contributes to its activity against *Candida* and makes it clinically safer than pentamidine. T-2307 inhibits the respiratory chain complexes in whole yeast cells and isolated yeast mitochondria, which is key for selective disruption of yeast mitochondrial function and antifungal activity [156].

Activity

T-2307 has potent in vitro and in vivo activity against *Candida* species, including azole- and echinocandin-resistant *Candida* spp, *C neoformans*, *C gattii*, *Malassezia furfur*, and *F solani* [157–161]. The in vitro activity of T-2307 was far superior to the activities of fluconazole, voriconazole, micafungin, and AmB. T-2307 was active against *Aspergillus* spp, and in vitro activity against these species was shown to be comparable to the activities of micafungin and voriconazole [157] (Figure 2).

Stage of Development and Ongoing Clinical Studies

For this potential antifungal drug, phase 1 studies are still ongoing, and no clinical efficacy data are available (Figure 3).

AR-12

Mechanism of Action

AR-12 (developed by Arno Therapeutics Inc., Flemington, NJ) is a novel molecule, antitumor celecoxib-derivative that has progressed to clinical development as an anticancer agent and has activity against a number of infectious agents including fungi, bacteria, and viruses [162]. With the goal of repurposing, a set of anticancer protein kinase inhibitors were screened for molecules with fungicidal activity towards *C neoformans* and *C albicans*, and AR-12 was found to have good antifungal activity against both species [163]. This agent acts by 2 different mechanisms of action, first by inhibiting the activity of fungal acetyl-CoA synthetase [164], and by downregulating host chaperone proteins, increasing the host immune response [16, 17] (Figure 1 and Table 1). It is interesting to note that AR-12 has also shown activity against bacteria, including *Salmonella* and *Francisella*, and hemorrhagic fever viruses [162]. The European Commission has designated AR-12 as an orphan drug for use in combination with other drugs for treatment of cryptococcosis and tularemia.

Activity

AR-12 has broad-spectrum antifungal activity against yeasts, molds, and dimorphic fungi (Figure 2). This includes *Candida* spp, including *C glabrata* and *C krusei*, and isolates of *C neoformans* with elevated fluconazole MICs [164]. It has also shown activity against dimorphic fungi including *Blastomyces*, *Histoplasma*, and *Coccidioides* [164]. In a murine model of cryptococcosis, AR-12 was synergistic with fluconazole [165]. However, the most promising feature of AR-12 is its in vitro activity against difficult-to-treat molds, including *Fusarium*, *Mucor*, and *Scedosporium* [164]. In a recent study, AR-12 was found to be highly active against *Trichophyton rubrum*, one of the organisms predominantly responsible for onychomycosis [166].

Stage of Development and Ongoing Clinical Studies

Target serum concentrations providing antifungal activity were safely achieved during phase 1 clinical trials as an anticancer agent (NCT00978523), indicating that AR-12 is promising candidate for repurposing as an antifungal agent [162]. However, Arno Therapeutics declared bankruptcy in 2017 leaving the future of the medication in limbo (Figure 3).

MGCD290

Mechanism of Action and Potential Role

MGCD290 (developed by MethylGene, Inc., Montreal, Canada) is a novel antifungal that inhibits fungal histone deacetylase 2 [16, 17]. Histone deacetylase is an enzyme that removes lysine residues of core histones, which control gene transcription and expression (Figure 1 and Table 1). They also control nonhistone proteins, including Hsp90, a molecular chaperone that regulates cellular stress response. In fungal cells, Hsp90 has been shown to be responsible for morphogenetic changes, stress adaptation, virulence, and antifungal resistance [167]. MGCD290 has shown a synergistic effect with other antifungals such as azoles or echinocandins [17, 167]. In cases of mutant-resistant isolates, MGCD290 produces a favorable influence on the MICs, restoring sensitivity [168].

Activity

MGCD290 only has modest activity against *Candida* spp [168]. However, it has demonstrated in vitro synergy with azoles and echinocandins against many azole- and echinocandin-resistant isolates including *Candida* spp, *Aspergillus* spp, *Mucor*, and *Fusarium* [168, 169] (Figure 2).

Stage of Development and Clinical Studies

This drug is currently in clinical development, and a phase 2 trial (NCT01497223) was completed that evaluated the cure rate with combination treatment of MGCD290 and fluconazole compared with fluconazole alone for patients with moderate to severe VVC [170] (Figure 3). This yielded poor results with no statistically significant benefit of combination therapy [171].

DEVICE

Neurapheresis

Mechanism of Action and Potential Role

The neurapheresis therapy system (developed by Minnetronix, Inc., St. Paul, MN) is a closed-loop system designed to filter

fungal pathogens from human cerebrospinal fluid (CSF) (Table 1). It operates by extracting CSF from the subarachnoid space, removing pathogens through a filtration system, and then redepositing the CSF through the same catheter [172]. It is currently considered as a potential novel adjunctive therapy for CM.

Stage of Development and Ongoing Clinical Studies

Smilnak et al [172] demonstrated the effects both in vitro and in vivo. Filtration of *C neoformans* in vitro accomplished a 5-log reduction in yeasts over 24 hours, compared with AmB plus 5FC, which achieved 0.42-log clearance of colony-forming units of yeast/mL per day from CSF [173]. Another in vivo rabbit model demonstrated a large decrease (97%) in yeast concentration after 4–6 hours of filtration. Concentrations of cryptococcal antigen decreased substantially (≥90%) postfiltration. Removal of cryptococcal antigen, which is responsible for occluding arachnoid villi, as well as rapid clearing of both single and clumping yeasts from the CSF, may reverse outflow obstruction in CM patients and alleviate resulting headaches and hydrocephaly. The neurapheresis system is expected to (1) allow physicians to modulate the high ICP typical of CM patients more directly and (2) also serve as a favorable alternative to other drainage procedures, minimizing the need for repeated lumbar punctures and/or placement of shunts [172]. The system was first used in a patient with subarachnoid hemorrhage, for which she underwent lumbar catheter placement and completed 9 hours of CSF filtration without complications. Repeat imaging demonstrated interval reduction of subarachnoid hemorrhage immediately after filtration [174]. In addition, it was piloted as treatment for other conditions such as bacterial meningitis and leptomeningeal disease [175, 176]. The ability of neurapheresis to reduce *C neoformans* and cryptococcal antigen demonstrates its potential to efficiently treat CM as an adjunctive therapy to systemic antifungals. Given its utility and the ability to directly remove the pathogen and secondary virulence factors, this platform is an appealing choice for adjunctive treatment of other fungal meningitis, such as the coccidioidal meningitis [172].

Ongoing studies include a clinical trial (PILLAR trial, NCT02872636) evaluating the safety and feasibility of this system in patients with subarachnoid hemorrhages. Another study testing the potential of neurapheresis therapy to reduce fungal burden in human patients with CM is currently being planned. Upcoming studies will explore the ability of the neurapheresis system to (1) filter smaller mediators such as cytokines and chemokines to control the neuroinflammatory response seen in CM and (2) avoid dangerous levels of inflammation or even immune reconstitution inflammatory syndrome (IRIS) within the CNS [172].

DISCUSSION

Despite a large number of patients suffering, the global burden of IFIs remains relatively underappreciated and underfunded. We face many challenges in the treatment of these diseases due to increasing resistance to currently available antifungals, demanding the need for development of new treatment options. This review focused on several novel antifungal therapies at various clinical stages in the development pipeline, including a first device used as adjunctive therapy.

These new antifungals have many potential roles and advantages over current drugs. New drugs, including olorofim, fosmanogepix, and ibrexafungerp, are now available options for the treatment of previously pan-resistant organisms. This is incredibly important because these drugs offer options for physicians where there were previously no treatment avenues available. In the case of olorofim, physicians now have another course of action in tackling triazole-resistant *Aspergillus* isolates [129] and other pan-resistant fungal pathogens including *Lomentospora* spp [133]. Still, chemical classes for IFI treatment are so few that emergence of resistance to even 1 drug class tragically limits therapy options.

Many of the described therapies have improved safety profiles with reduced toxicity and fewer adverse effects and drug-drug interactions while preserving efficacy. A majority of IFI cases are seen in patients with other comorbid conditions [177], and a variety of treatments and procedures for other conditions are well recognized risk factors for developing IFIs, such as abdominal surgery, chemotherapy, and use central venous catheters. With these patients being treated for multiple reasons concurrently, drug-drug interactions and compound toxicities are significant concerns for physicians. A patient's ability to tolerate the effects of treatment can limit a clinician when prescribing a course of treatment, especially in critically ill patients. For example, CAmB minimizes the toxicity seen with AmB by using cochleates as a drug delivery system to target the fungal cell membrane. Likewise, olorofim and fosmanogepix have lower risk of toxicity due to fungal-specific targets, and they also possess novel mechanisms of action by inhibition of fungal DHODH for pyrimidine synthesis and Gwt1 for GPI-anchor protein synthesis, respectively. The caveat of olorofim is related to possible drug-drug interactions given its weak inhibition of CYP3A4. Drug-drug interactions are minimized while using CamB and also with tetrazoles because they selectively target the fungal CYP51 enzyme.

The burden of administration requirements is reduced with the oral formulation of ibrexafungerp, olorofim, and CAmB decreasing barriers of IV administration, and rezafungin has a longer half-life allowing weekly dosing. Complex dosing schedules and IV administration requirements are known to negatively impact medication adherence [178, 179], and, for patients receiving antifungal treatment for extended periods, these oral formulations and reduced dosing intervals have the potential to

decrease hospital and clinic visits and ultimately increase patient adherence during treatment.

CONCLUSIONS

These promising features begin to address the urgent need for improvement in available therapies, but there is work still to be done. It is unfortunate that the potential toxicities and disadvantages of these therapies have not been fully evaluated, because most of them have not reached advanced clinical development in stage 3 or 4 studies. Even with all of the drugs in development, not every compound with antifungal activity will result in an approved drug for the market. Translating the results of early studies into clinical candidates can be difficult due to efficacy and financial reasons, and only approximately 20% of the potential antifungal targets published in the literature were further developed [16]. However, given the number of new promising compounds in development, the future is brighter than it has ever been.

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