



Investigational Agents for the Treatment of Resistant Yeasts and Molds

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Accepted: 3 May 2021 / Published online: 28 May 2021

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Abstract

Purpose of Review This review summarizes the investigational antifungals in clinical development with the potential to address rising drug resistance patterns. The relevant pharmacodynamics, spectrum of activity, preclinical studies, and latest clinical trial data are described.

Recent Findings Agricultural and medicinal antifungal use has been selected for inherently drug-resistant fungi and acquired resistance mechanisms. The rates of fungal infections and immunocompromised populations continue to grow as few new antifungals have hit the market. Several agents with the potential to address the emergence of multidrug-resistant (MDR) molds and yeasts are in clinical development.

Summary Evolved formulations of echinocandins, polyenes, and triazoles offer less toxicity, convenient dosing, and greater potency, potentially expanding these classes' indications. Ibrexafungerp, olorofim, oteseconazole, and fosmanogepix possess novel mechanisms of actions with potent activity against MDR fungi. Successful clinical development is neither easy nor guaranteed; thus, perpetual efforts to discover new antifungals are needed.

Keywords Antifungal drugs · Antifungal resistance · Invasive fungal infections · *Candida auris* · Novel therapies · Review

Introduction

Only five antifungal classes exist on the market. The polyenes, which destabilize the cell membrane via ergosterol binding, are limited by significant toxicities and intravenous (IV) only formulations for now. Azoles block ergosterol production by inhibiting lanosterol-14 α -demethylase (LDM) but often create drug–drug interactions and toxicities by cross-inhibition of mammalian cytochrome P (CYP) enzymes. Echinocandins prevent the biosynthesis of (1,3) β -d-glucan and are relatively safe but only exist in IV formulations and lack central nervous system (CNS)

penetration, and their fungicidal spectrum is limited mostly to *Candida* species. The pyrimidine analog, flucytosine, is indicated only as a combination therapy [1, 2]. Finally, the allylamines are only used in dermatophyte infections often requiring months of use at the cost of many side effects [2].

Nearly 20 years have passed since the introduction of the newest antifungal class to the market. The incidence of invasive fungal infections (IFI) has since increased along with the immunocompromised population carrying significant mortality rates and costs to healthcare systems [3, 4]. The estimated annual costs of fungal infections in the USA have reached \$7.2 billion [5]. With the emergence of multidrug-resistant (MDR) and pan-resistant fungi, there is a critical need for novel antifungals to overcome therapeutic barriers and resistance. In this article, we review fungal resistance patterns and the investigational drugs in clinical development which may rise to meet these challenges.

This article is part of the Topical Collection on *Current Management of Fungal Infections*

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Epidemiology and Mechanisms of Antifungal Resistance

The evolution of antifungal resistance is a multifactorial, global phenomenon. Antifungal pesticides in agricultural systems

and widespread healthcare use have fueled acquired resistance as well as shifted fungal prevalence toward species with inherent antifungal resistance [6]. Climate change and animal reservoirs are also theorized to play an important role, namely, with the global outbreak of *C. auris* [7]. In this section we will describe the known resistance mechanisms of yeast, mold, and dimorphic fungi.

Yeast

Historically, candidiasis was most often caused by *C. albicans* and was typically sensitive to most azole agents. Widespread fluconazole use has promoted acquired resistance amongst all *Candida* species and shifted the epidemiology of invasive candidiasis (IC). While *C. albicans* remains the most common cause of IC, non-albicans species are on the rise (*C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei*) [8]. *C. krusei* is intrinsically resistant to fluconazole, and *C. glabrata* carries a very high rate of resistance. Resistance in *Candida* species is mediated by the amplification of zinc cluster transcription factors such as UPC2, TAC1, MRR1, or CgPdr1 (particularly in *C. glabrata*). UPC2 upregulation causes the overexpression of the LDM gene *ERG11*, while mutations in *TAC1*, *MRR1*, and *CgPdr1* overexpress drug efflux transporters. Additionally, resistance can occur via altered LDM structure from point mutations in *ERG11* [8, 9].

Due to azole resistance, and better clinical outcomes, echinocandins are now the initial drug of choice for IC. Intrinsically elevated minimum inhibitory concentrations (MICs) are present in certain species (*C. guilliermondii* and *C. parapsilosis*), yet consistent treatment failures have yet to be demonstrated. On the other hand, mutations in glucan synthase subunits, *FKS1* and *FKS2*, have demonstrated clinically significant echinocandin resistant and MDR isolates [8]. These mutations are more likely to develop with repeated and prolonged drug exposures, especially in those with GI tract biofilm reservoirs [8]. *C. auris* has burst onto the scene as a major cause of MDR, healthcare-associated candidiasis with mortality rates ranging from 30 to 45% [10, 11]. Various studies have reported fluconazole resistance 90–93%, amphotericin B (AmB) resistance 15–30%, and echinocandin resistance 2–10% [11].

Polyene resistance amongst yeast is uncommon and typically involves depletion of ergosterol from the cell membrane. It has been seen in *Trichosporon* species, amongst *Candida* species (notably *C. lusitanae* and *C. auris*), and some reports of *C. neoformans* with high MICs [8].

Molds

The most common mold-related IFI is invasive aspergillosis (IA). Triazoles are the first-line therapy and prophylaxis. While resistance rates remain generally favorable amongst

common *Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. versicolor*, etc.), pan-azole-resistant *A. fumigatus* is increasingly reported in Europe and the USA, and intrinsic triazole resistance is higher amongst cryptic species [12]. The most prevalent azole resistance mechanisms are the overexpression and alteration of the target enzyme gene, *Cyp51A*, and its promoter region (*TR*₄₆/*Tyr121Phe/Thr289Ala*; *TR*₃₄/*Leu98His*) [8]. Other mechanisms include biofilm formation, drug efflux, and mutations in transcription factor, HapE [8, 13]. Polyene resistance amongst *Aspergillus* species typically involves selection for inherently resistant species including *A. terreus*, *A. flavus*, and *A. nidulans* [8].

Scedosporium and *Lomentospora* species are rare opportunistic molds demonstrating broad and even pan-resistant tendencies with mortality rates breaching 80%. Voriconazole and surgical debridement remain first-line therapies [14]. Similarly, *Fusarium* species offer a broad spectrum of inherent drug resistances to polyenes, azoles, and echinocandins with variable MICs to triazoles. The mechanisms of this are unclear but theorized to be related to multiple LDM paralogues: *CYP51A*, *B*, and *C* [15].

Mucorales species possess baseline resistance to echinocandins, itraconazole, and voriconazole via alterations in LDM. AmB, posaconazole, and isavuconazole remain the first-line agents, and there is limited data supporting combination therapies [16].

Thermally Dimorphic Fungi

Endemic fungal diseases such as histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis are either increasing or are underreported [17, 18]. They generally carry primary resistance to echinocandins, and fluconazole resistance is noted amongst histoplasmosis isolates. Thus, polyenes and azoles remain the preferred agents. While drug resistance remains uncommon, these diseases remain difficult to cure due to the lack of oral polyenes, drug toxicities, and tissue penetration [19].

Investigational Agents

Agents in Phase III Clinical Trials

Ibrexafungerp (SCY-078)

Ibrexafungerp (IBX) is a semi-synthetic derivative of enfumafungin. Similar to echinocandins, IBX inhibits (1,3)- β -d-glucan synthase but via alternative binding sites rendering it unaffected by *FKS* mutations. It is anticipated to advance the treatment of highly resistant *Candida* infections; however, its spectrum of activity also includes *Cryptococcus* species, *Aspergillus* species, and endemic fungi (Fig. 1) [20].

It is soluble at lower pH, enhancing its penetration into acidic environments such as abscesses or vaginal tissue [21]. Although it is a CYP2C8 inhibitor, this effect is unlikely to be clinically significant [22]. Additionally, IBX did not show evidence of reproductive harm in animal models [23].

IBX maintains in vitro activity against fluconazole and echinocandin-resistant *Candida* species including pan-resistant *C. auris* [24•, 25, 26•]. It maintained an average MIC₅₀ of 0.5 µg/mL and MIC₉₀ of 1 µg/mL against 100 *C. auris* isolates and demonstrated increased survival and decreased fungal tissue burden in mouse and guinea pig models of *C. auris* infections [25]. Amongst 195 *C. auris* isolates from an outbreak in New York City, 194 were susceptible to IBX with a mean MIC of 0.407µg/mL, including five pan-resistant isolates [26•].

Advancing to human clinical trials, IBX has been studied in IC, invasive pulmonary aspergillosis (IPA), and vulvovaginal candidiasis (VVC) (Table 1). In a phase II study of IC in non-neutropenic patients, oral IBX demonstrated similar safety and efficacy compared to fluconazole as step-down therapy following echinocandin treatment [27••]. Following a phase IIb trial demonstrating efficacy and safety IBX 300 mg BID for 1 day versus fluconazole for acute VVC, this dose was carried over to phase III VANISH 303 and 306 trials which established efficacy over placebo with a 50–65% cure rate determined by test-of-cure cultures [28, 29••]. CANDLE is a phase III trial studying IBX in recurrent VVC (NCT04029116).

Oral IBX is currently involved in several active phase III trials. The CARES study is a single-arm, open label study of IBX for invasive *C. auris* infections

(NCT03363841). SCYNERGIA is investigating the combination of IBX and voriconazole versus voriconazole monotherapy in IPA (NCT03672292). Finally, FURI studies the drug for various fungal infections refractory to other therapies (NCT03059992). Positive preliminary data has been released from this study reporting clinical improvement in 17 of 20 patients with esophageal or oropharyngeal candidiasis and intra-abdominal abscesses with the predominant pathogens being *C. glabrata* and *C. krusei* [30••].

Rezafungin (CD101)

Rezafungin (RZF), developed by Cidara Therapeutics, is the latest echinocandin. Structural modifications have enhanced its chemical stability and solubility granting a long half-life enabling once-weekly IV dosing [31]. This is its greatest novelty as it shares the tissue distribution, favorable safety and drug–drug interaction profiles, and spectrum of activity as other echinocandins (Fig. 1).

Like other echinocandins, RZF demonstrates potent in vitro activity against wild-type and azole-resistant *Candida* species [32, 33]. *FKS1* mutations raise its MIC, although to a lesser degree compared to anidulafungin and micafungin [34]. In mice with invasive *FKS* mutant *C. auris*, RZF improved survival and reduced fungal tissue burden compared to micafungin and AmB [35]. Translating RZF to humans with IC has demonstrated safety and efficacy as seen in the phase II STRIVE trial in which the weekly dosing regimen of 400 mg IV for the first week, followed by 200 mg thereafter demonstrated equal, if not slightly better

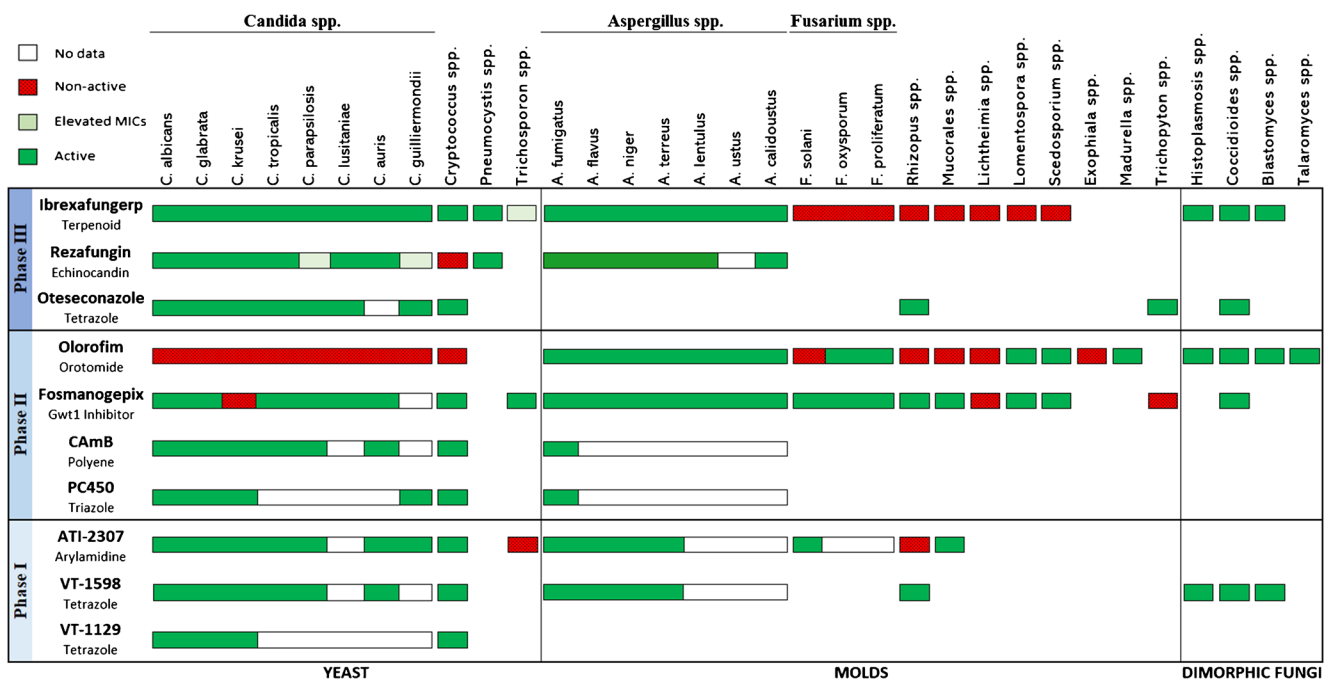


Fig. 1 Spectrum of activity of investigational antifungals organized by their respective phase of clinical development

Table 1 Investigational antifungals currently involved with active preparations for clinical trials

| Agent | Class | Mechanism of action | Formulation | Spectrum of activity including resistant fungi | FDA designations | Phase II and III clinical trials |
|--------------------------------|----------------|--|---------------------|--|-----------------------------------|---|
| Ibrexafungerp | Terpenoid | Inhibition of (1,3) β -d-glucan synthase | Oral Intravenous | MDR <i>Candida</i> spp. MDR <i>Aspergillus</i> spp. | QIDP | Oral step-down in IC Acute and Recurrent VVC Invasive <i>C. auris</i> infections IPA in combination with voriconazole IFI refractory to standard therapies |
| Rezafungin | Echinocandins | Inhibition of (1,3) β -d-glucan synthase | Intravenous | Like other echinocandins | QIDP Fast track | IC Prophylaxis of IFI in stem-cell transplants |
| Oteseconazole (VT-1161) | Tetrazole | Lanosterol 14 α -demethylase inhibitor | Oral Intravenous | Echinocandin-resistant <i>C. glabrata</i> <i>Rhizopus</i> spp. <i>Trichophyton</i> spp. <i>Coccidioides</i> spp. | QIDP Fast track | Acute and recurrent VVC Moderate-to-severe onychomycosis |
| VT-1129 | Tetrazole | Lanosterol 14 α -demethylase Inhibitor | Oral | <i>Cryptococcus</i> spp. | Orphan drug QIDP | Cryptococcosis |
| VT-1598 | Tetrazole | Lanosterol 14 α -demethylase Inhibitor | Intravenous | <i>C. glabrata</i> , <i>C. krusei</i> | Orphan drug QIDP | Phase I trials targeting trials for <i>C. auris</i> , <i>Cryptococcus</i> , and <i>Coccidioides</i> infections |
| Fosmanogepix | Gwt1 inhibitor | Inhibits the formation of mannoproteins in cell wall and exposing (1,3) β -d-glucan to the host immune system. | Oral Intravenous | Resistant <i>Candida</i> spp., <i>C. auris</i> <i>Cryptococcus</i> spp. Endemic fungi MDR <i>Candida</i> spp. <i>C. auris</i> <i>Scedosporium</i> spp., <i>Fusarium</i> spp., <i>Mucorales</i> spp. | Fast track QIDP Fast track | IC in non-neutropenic patients Invasive <i>C. auris</i> infections IFI due to <i>Aspergillus</i> or rare molds |
| Olorofim | Orotomide | Inhibits dihydroorotate dehydrogenase blocking pyrimidine biosynthesis | Oral Intravenous | MDR <i>Aspergillus</i> spp. <i>Lomentospora</i> spp., <i>Scedosporium</i> spp. Endemic fungi | Orphan drug | Refractory of resistant IFIs |
| ATI-2307 | Arylamidine | Inhibits fungal mitochondrial synthesis | Oral | MDR <i>Candida</i> spp., <i>C. auris</i> , <i>Cryptococcus</i> spp. | | Phase I trials targeting future trials for cryptococcosis and MDR IC |
| CAmB | Polyene | Spiraled lipid bilayer encasing amphotericin B | Oral | Like amphotericin B | Orphan drug QIDP Fast track | Refractory mucocutaneous candidiasis Moderate-to-severe VVC Cryptococcal meningitis IPA in lung transplants and chronic lung disease In combination with triazole for IPA |
| PC945 | Triazole | Lanosterol 14 α -demethylase Inhibitor | Inhalation | Triazole-resistant <i>A. fumigatus</i> , <i>C. auris</i> | | |

Abbreviations: Encochleated amphotericin B (CAmB), central nervous system (CNS), invasive candidiasis (IC), invasive fungal infection (IFI), invasive pulmonary aspergillosis (IPA), multidrug-resistant (MDR), vulvovaginal candidiasis (VVC)

efficacy compared to caspofungin (71% vs 63%). Species included *C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* [36•]. Now RZF has advanced to phase III trials (Table 1). ReSTORE is a multicenter, double blinded, randomized control trial actively recruiting patients with IC to compare weekly IV RZF versus IV caspofungin and step-down oral fluconazole (NCT03667690).

RZF has been studied in the treatment of other yeasts and molds. Like other echinocandins, it lacks adequate activity against *C. neoformans* [33]. Echinocandins are not used to treat pneumocystis infections due to inactivity against trophic forms [37]. However, RZF has shown activity against *Pneumocystis*, reducing biofilm mass and inhibiting its production as well as preventing pneumocystis pneumonia (PJP) in immunocompromised mice [38•].

Against *Aspergillus* species, RZF has not only exhibited in vitro activity against *A. fumigatus* and cryptic species, but also azole-resistant species recovered from the lungs of lung transplant recipients who were taking triazole agents for prophylaxis [39, 40•]. Moreover, extended interval dosing of RZF increased survival in a mouse model of azole-resistant disseminated IA [41]. Although these results are encouraging, further phase II and phase III trials are needed to determine its efficacy and safety in human subjects for the prevention and treatment of IA. A phase III trial, ReSPECT, is actively recruiting patient to study RZF's efficacy in the prevention of IFI in allogeneic blood and bone marrow transplant recipients (NCT04368559).

Oteseconazole

Oteseconazole (VT-1161), developed by Mycovia Pharmaceuticals, belongs to the tetrazole class, a new generation of oral lanosterol 14 α -demethylase inhibitors which boast higher specificity for fungal CYP51 and therefore theoretically less cross-inhibition of mammalian CYP enzymes leading to fewer drug–drug interactions and adverse effects [42].

Preclinical studies show VT-1161 possess a wide spectrum of activity including *Candida* species, *Rhizopus* species, *Trichophyton* species, and coccidioidomycosis (Fig. 1) [43–46, 47•, 48•]. It exhibited potent in vitro activity against most fluconazole-resistant *C. albicans* and *C. krusei* isolates (mean MIC \leq 0.15 μ g/mL) as well as echinocandin-resistant *C. glabrata* [44, 49]. This effect was demonstrated in a mouse model of VVC which included fluconazole-resistant *Candida* species [50]. Additionally, VT-1161 has demonstrated in vivo efficacy as prophylaxis against *Rhizopus arrhizus* infections and coccidioidomycosis treatment [45, 46]. There is early evidence of possible cross-resistance between triazoles and tetrazoles mediated by target enzyme modification or overexpression, as well as *PDR1*-mediated drug efflux transporters [44, 49].

While VT-1161 is currently in early clinical phases for the treatment of IFIs, it has advanced to phase II and III trials for recurrent VVC and onychomycosis (Table 1). Current treatment options for onychomycosis carry a low success rate. Oral terbinafine or itraconazole offer better efficacy than topical antifungal but at the cost of added toxicities. In a phase II randomized, blinded, placebo-controlled trial of adults with moderate-to-severe onychomycosis, treatment with VT-1161 saw a 42% cure rate without hepatotoxicity or cardiac toxicity [47•]. The agent's safety and efficacy were also demonstrated in a phase IIb trial for recurrent VVC [48•]. Three phase III clinical trials of VT-1161 for recurrent VVC are underway (NCT03561701, NCT02267382, NCT03562156).

Agents in Phase II Clinical Trials

Fosmanogepix

Fosmanogepix, a prodrug of manogepix, is a first-in-class Gwt1 inhibitor developed by Amlyx Pharmaceuticals. Gwt1 is an inositol acyltransferase which catalyzes post-translational modification of glycosylphosphatidylinositol (GPI), creating mannoproteins which are anchored into the fungal cell wall, covalently linked to β -1,3-glucan [51]. These mannoproteins maintain cell wall integrity while facilitating mucosal surface adhesion, biofilm formation, and host invasion. When GPI anchoring is disrupted, β -1,3-glucan is exposed to the host immune system. It has no activity against the closest mammalian Gwt1 ortholog, GIPW, implying fungal specificity [52]. It has acquired QIDP, orphan drug, and fast track designations for invasive candidiasis, aspergillosis, scedosporiosis, fusariosis, mucormycosis, cryptococcosis, and coccidioidomycosis (Table 1).

Fosmanogepix possesses broad in vitro activity against many genera of fungi: *Candida* (excluding *C. krusei*), *Trichosporon*, *Coccidioides*, *Cryptococcus*, *Aspergillus* (*A. fumigatus*, *A. flavus*, *A. niger*), as well as AmB-resistant strains of *Fusarium* and *Scedosporium* (Fig. 1) [51, 53–55]. Amongst *Candida* species, it maintains activity against echinocandin-resistant *FKS* mutants; however, elevated MICs were seen with some fluconazole-resistant isolates implicating potential efflux transporter-mediated cross-resistance [56]. Against *C. auris*, fosmanogepix possesses potent in vitro and in vivo activity [54, 57•]. In neutropenic mice with disseminated *C. auris*, this agent increased survivability and lowered fungal tissue burdens compared to echinocandins [54, 58•]. This agent also demonstrates effectiveness against highly resistant mold species. In mouse models of pulmonary scedosporiosis, disseminated fusariosis, and pulmonary mucormycosis, it extended median survival time and decreased fungal burden in lung and brain tissue [59•, 60•].

Safety, pharmacodynamics, and drug–drug interactions were studied in phase I trials both in healthy individuals and

patients with acute myelogenous leukemia (NCT02957929, NCT03333005, NCT02956499, and NCT04166669). Fosmanogepix has a higher barrier to acquired resistance, and Gwt1 enzyme mutations do not seem to cause cross-resistance amongst other classes [61].

Data from a phase II clinical trial of fosmanogepix for the treatment of invasive candidiasis in non-neutropenic patients reported an 80% treatment success rate without serious side effects. Additionally, the drug exhibited in vitro activity against all *Candida* isolates recovered in the study [62•]. Additional phase II trials are currently underway, studying efficacy for IC caused by *C. auris* (NCT04148287) and IFIs caused by *Aspergillus* species and other rare molds (NCT04240886).

Olorofim (F901318)

Olorofim, developed by F2G, is a first-in-class orotomide which affects pyrimidine synthesis via reversible inhibition of dihydroorotate dehydrogenase (DHODH) [63]. This agent has been developed in IV and oral formulations. It possesses time-dependent fungicidal activity and exhibits wide tissue distribution (including the CNS), with enterohepatic recirculation. Many molds and endemic fungi are within its spectrum of activity, but it lacks reliable activity against yeast (Fig. 1) [64]. It has been granted QIDP and orphan drug status for the treatment of coccidioidomycosis, invasive *Aspergillus*, *Scedosporium*, and *Lomentospora* species infections (Table 1).

Olorofim shows great promise for the treatment of resistant mold infections. It possesses activity against highly resistant and cryptic *Aspergillus* species including *A. lentulus*, *A. fumigatiaffinis*, and *A. calidoustus* [65•]. In vitro activity has been demonstrated against triazole-resistant *A. fumigatus* (MIC \leq 0.008–0.03 mg/L), *L. prolificans* (MIC 0.03–0.5 mg/L), *Scedosporium* species (MIC 0.03–0.5 mg/L), *Rasamsonia argillacea* (MIC \leq 0.008–0.03 mg/L), and certain *Fusarium* species (*F. oxysporum* complex but not *F. solani*) [66•, 67]. Against *Lomentospora prolificans* biofilms, this agent demonstrates greater penetration than AmB and micafungin [68•]. In vivo studies of olorofim in neutropenic mouse models of IPA (wild-type and triazole-resistant mutants), sinopulmonary *A. flavus*, and chronic granulomatous disease-related IPA (included resistant cryptic species *A. nidulans* and *A. tanneri*) demonstrated efficacy with reductions in galactomannan and mortality which were predicted by C_{\min} /MIC values [68•, 69, 70]. It is important to note this drug lacks activity against *Mucorales* species or *Exophiala dermatitidis* due to phylogenetically different DHODH target enzymes [63, 65].

Regarding endemic fungal diseases, olorofim exhibits low MICs for *Histoplasma capsulatum*, *Blastomyces* species, *Coccidioides* species, and *Talaromyces marneffeii* [71]. In a murine model, olorofim demonstrated increased survival of

mice with CNS coccidioidomycosis, a clinical entity notoriously difficult to completely cure [72, 73].

Nine phase I clinical trials of olorofim have been completed. Tolerability, safety, and pharmacodynamics have been assessed for single and multiple ascending doses of oral and IV formulations (NCT02142153, NCT02394448, NCT02342574, NCT02737371, NCT02808741). Olorofim exerts a mild inhibitory effect on CYP3A4 (NCT02680808, NCT04171739).

A phase IIb trial is currently underway enrolling patients with invasive fungal infections which are refractory or resistant to standard therapy (NCT03583164; FORMULA-OLS).

Enochleated Amphotericin B

Enochleated amphotericin B (CAmB), developed by Matinas Biopharma, is a novel oral polyene formulation in which AmB and calcium are encased within a cochleate (spiraled, negatively charged lipid bilayer). The cochleate stabilizes, protects, and delivers the drug into reticuloendothelial cells. Thus, low levels of active drug circulate in plasma mitigating the adverse effects commonly seen in AmB toxicities. As the compound is phagocytosed, calcium gradients facilitate the release of AmB into phagocytes and the extracellular space. This agent demonstrates broad tissue penetration including the brain, kidney, lung, and bone with a spectrum of activity akin to AmB (Fig. 1) [74].

The safety and efficacy of CAmB have been demonstrated in murine models of IA, IC, and cryptococcal meningitis [75–77]. One hundred percent of mice with IC treated with CAmB at doses ranging from 0.5 to 5 mg/kg/day survived with a dose-dependent decrease in kidney and lung fungal tissue burden [76]. CAmB was found to be equally efficacious as AmB with superiority over oral fluconazole in cryptococcal meningoencephalitis [77].

In a recent phase I study, HIV patients with prior history of cryptococcosis were administered different dosing regimens of CAmB: single administrations of ascending daily doses (1.0 g, 1.5 g, or 2.0 g) split into 4–6 divided doses and recurrent doses of 1.5 g daily split into 4–6 divided doses over 7 days. Excellent tolerability (98–100%) and improved safety compared to AmB were demonstrated. No nephrotoxicity was reported [78•].

Preliminary results of a phase IIa trial investigating CAmB in refractory mucocutaneous candidiasis demonstrated tolerability and improvement in symptoms without drug-related toxicities outside of nausea or dizziness [79]. Another phase II trial compared safety and efficacy of single doses of CAmB 200 mg, CAmB 400 mg, and fluconazole 150 mg for moderate-to-severe VVC. There were no serious adverse events reported, but clinical cure rates favored fluconazole over CAmB 200 mg and CAmB 400 mg (75%, 52%, and 54%, respectively) [80]. An additional phase II clinical trial studying CAmB in cryptococcal meningitis is underway (NCT04031833).

PC945

PC945 is the first topical, inhaled triazole. Developed by Pulmocide, this drug is designed primarily for the treatment of IPA, boasting prolonged lung tissue retention without significant systemic absorption. Its antifungal spectrum is analogous to systemic triazoles but with significantly greater potency maintaining activity against posaconazole and pan-azole-resistant *A. fumigatus*, as well as *C. auris* (Fig. 1) [81, 82]. Synergy with systemic triazoles was demonstrated in murine IPA models [83]. Following successful phase I clinical trials, phase II trials for IPA in patients with cystic fibrosis, chronic lung disease, and lung transplants have been terminated early due to the COVID-19 pandemic. A phase III trial with PC945 in combination with systemic antifungals for patients with IPA and no other treatment options planned (Table 1) [84].

Antifungals in Phase I and Preclinical Development

ATI-2307

ATI-2307 was originally developed by the FUJIFILM Toyama Chemical Co. under the name T-2307 until November 2019 when Appili Therapeutics Inc. acquired the development rights and renamed it. It is a first-in-class arylamidine with a novel antifungal mechanism: the disruption of yeast cellular respiration via inhibition of mitochondrial respiratory chain complexes III and IV. This is speculated to be a fungal-specific effect [85]. Preclinical studies have demonstrated potent, fungicidal in vitro and in vivo activity against azole and echinocandin-resistant *C. glabrata*, *C. auris*, *C. neoformans*, *C. gattii*, and *A. fumigatus* (Fig. 1) [86–90, 91]. Its application to human subjects has been targeted at cryptococcosis and invasive MDR candidiasis. Phase I clinical trials to determine safety, efficacy, and optimal human doses are currently underway with preliminary reports from a trial with cryptococcal meningitis indicating superior potency and acceptable safety compared to standard-of-care therapies (Table 1). Phase II clinical trials are anticipated to begin in 2022 [91].

Quilseconazole (VT-1129)

VT-1129 is an oral tetrazole being studied for the treatment of cryptococcal meningitis. The FDA has granted it orphan drug status and QIDP designation for this purpose. Preclinical studies have demonstrated robust in vitro and in vivo efficacy against *C. neoformans* and *C. gattii*, notably maintaining activity (mean MIC 0.027 µg/mL) against fluconazole-resistant or dose-dependent *C. neoformans* isolates (Fig. 1) [92–94]. In mice treated with doses ≥ 3 mg/kg daily, there was virtually no evidence of fungal burden in CNS tissues at the day of medication cessation or 20 days later, a finding not seen in

fluconazole-treated mice [94]. Additionally, in vitro studies denote activity against *Candida* species isolated from patients with chronic mucocutaneous candidiasis as well as *C. glabrata* and *C. krusei* isolates resistant to azoles and echinocandins [44, 95].

VT-1598

VT-1598, another oral tetrazole, boasts a wide antifungal spectrum including yeast, molds, and dimorphic fungi. It has been granted FDA fast track status for the treatment of coccidioidomycosis (Table 1). It is currently in phase I trials for potential use in *C. auris* infections, cryptococcosis, and coccidioidomycosis (NCT04208321).

In preclinical studies, VT1598 effectively inhibited *Candida* species (*C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. auris*, and azole-resistant *C. albicans*), *Cryptococcus* species, *Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. niger*, and *A. terreus*), *Rhizopus arrhizus* (except *R. arrhizus* var. *delemar* strains), *Coccidioides* species, *B. dermatitis*, and *H. capsulatum* (Fig. 1) [49, 96–98]. Like VT-1161, it is impacted by *UPC2*- and *PDR1*-mediated resistance mechanisms seen in triazole cross-resistant *C. glabrata* [97]. Efficacy and safety were seen in mouse models studying VT-1598 for invasive *C. auris* infections, cryptococcal meningitis, and CNS coccidioidomycosis [98–100].

Miscellaneous Agents Not in Active Clinical Trials

Nikkomyacin Z

Nikkomyacin Z is a first-in-class chitin-synthase inhibitor developed by Valley Fever Solutions as a targeted approach against endemic fungi, including *Coccidioides* species [101]. Additionally, it found a synergistic role in treating resistant *Candida* species. Preclinical studies showed efficacy in canine pulmonary coccidioidomycosis and murine echinocandin-resistant *FKS* mutant invasive candidiasis [102, 103]. While the initial phase I trial exhibited adequate safety, additional phase I and phase II trials were unable to recruit patients and lacked sufficient funding to continue [104]. With renewed interest and support, this agent could recrudescence into clinical development again.

MGCD290

MGCD290 is an inhibitor of fungal histone deacetylase. It showed early promise in preclinical trials as a synergistic agent restoring triazole susceptibility in *Candida*, *Fusarium*, and *Zygomycetes* species as well as echinocandin susceptibility in resistant *Candida* species [105, 106]. However, a phase II study of MGCD290 plus fluconazole in VVC did not show superiority compared to fluconazole alone (NCT01497223). Presently, there are no active clinical trials.

Conclusions

This arsenal of agents offers hope for the future. The rise of MDR and pan-resistant *Candida* species has been met with advanced stage investigational agents such as IBX, VT-1161, and RZF. IBX introduces a novel mechanism, potent broad spectrum of activity and a safe oral formulation, while VT-1161 is poised to treat recurrent VVC and onychomycosis with potential to garner other indications as clinical development progress. RZF offers convenient, once-weekly dosing for echinocandin for the treatment or prophylaxis in immunocompromised patients.

Perhaps the brightest future for the future of invasive mold infections lie in stage II and I agents fosmanogepix and olorofim, both first agents in their respective classes. Fosmanogepix has displayed efficacy in IC and is currently involved in trials for invasive *C. auris* and mold infections. Fosmanogepix and olorofim also possess activity against notoriously MDR pan-resistant mold genera, *Lomentospora* and *Scedosporium*. Currently, infections by these organisms have few, if any, reliable therapeutic options.

The reformulation of existing classes into new delivery systems will change the treatment of IFIs. CAmB offers safe oral administration of AmB, and PC945 is a potent inhaled topical triazole with minimal systemic absorption.

From conceptualization to proof of efficacy in humans, antifungal development is an expensive and protracted challenge. Many promising antifungals never reach the market due to poor recruitment, lack of funding, or trial failures. While these agents are a great start, with the rising immunocompromised population and perpetual evolution of antifungal resistance, it is essential that continual efforts are made toward the discovery of new therapies.

Declaration

Conflict of interest GTS does not have any conflict of interest to report. LO has received speaking, consulting, and/or research funds from Pfizer, Astellas, F2G, Amplyx, Cidara, Scynexis, and Gilead.

Human & Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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