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Invasive candidiasis: Investigational drugs in the clinical development pipeline and mechanisms of action

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Abstract

Introduction—The epidemiology of invasive *Candida* infections is evolving. Infections caused by non-*albicans Candida* spp. are increasing; however, the antifungal pipeline is more promising than ever and is enriched with repurposed drugs and agents that have new mechanisms of action. Despite progress, unmet needs in the treatment of invasive candidiasis remain and there are still too few antifungals that can be administered orally or that have CNS penetration.

Areas covered—The authors shed light on those antifungal agents active against *Candida* that are in late-stage clinical development. Mechanisms of action and key pharmacokinetic and pharmacodynamic properties are discussed. Insights are offered on the potential future roles of the investigational agents MAT-2203, oteseconazole, ATI-2307, VL-2397, NP-339, and the repurposed drug miltefosine.

Expert opinion—Ibrexafungerp and fosmanogepix have novel mechanisms of action and will provide effective options for the treatment of *Candida* infections (including those caused by multiresistant *Candida* spp). Rezafungin, an echinocandin with an extended half-life allowing for once weekly administration, will be particularly valuable for outpatient treatment and prophylaxis. Despite this, there is an urgent need to garner clinical data on investigational drugs, especially in the current rise of azole-resistant and multi-drug resistant *Candida* spp,

Keywords

Antimycotic; antiinfective; resistance; activity; trials; APX001; CD101; SCY-078; manogepix; fosmanogepix; ibrexafungerp; rezafungin; MAT2203; oteseconazole; VT-1161; ATI-2307; VL-2397; NP-339; miltefosine

1. Introduction

Candida spp. are the most common causes of invasive fungal infections in humans and are associated with high mortality rates[1]. As a result of the universal use of antifungals in prophylaxis and treatment, novel immunosuppressive therapies, central venous lines

and other invasive procedure, the population of patients at risk for invasive candidiasis is growing. In parallel, the epidemiology of invasive *Candida* infections continues to change, with increasing proportions of infections caused by non-albicans *Candida* spp., including multidrug resistant *Candida glabrata* as well as emerging multidrug resistant *Candida auris* [2].

Until very recently, the antifungal armamentarium was extremely limited, with just four classes of antifungals (polyenes, azoles, echinocandins, and flucytosine), each with limitations including toxicities, route of administration, and increasing resistance. The pace of antifungal drug development until approval stage has been lagging due to fundamental scientific, economic, and regulatory challenges ranging from the identification of target structures that are non-toxic in humans to obstacles in the design of clinical trials and the demands of approval agencies. In recent years, however, significant improvements have been made through novel ways of screening for compounds and by facilitating regulatory processes. In response to the global increase of antifungal resistance in *Candida* spp., new or repurposed treatments, including with new mechanisms of action, are required.

In this review, we discuss extensively the most promising drugs including new antifungal classes in late-stage clinical development with fosmanogepix (a novel Gwt1 enzyme inhibitor), ibrexafungerp (a first-in-class triterpenoid) and rezafungin (an echinocandin designed to be dosed once-weekly), and several auspicious antifungal agents in their early stage of development including drugs with novel areas of application (miltefosine), improved pharmacokinetic/pharmacodynamic (PK/PD) properties (MAT2203, oteseconazole) or novel mechanisms of action (ATI-2307, NP339, VL-2397) (Fig 1). Literature search was performed in February 2022 and included: PubMed search for each compound name (old and new names) separately, searching the reference lists for additional studies, as well as search through abstracts presented at major scientific meetings in the field during the last 10 years.

2. Antifungal resistance to licensed drug classes for systemic use

Drug resistance refers to a genetic variant (inherent or acquired) that is passed on to the next generation, which allows the fungus to grow in the high concentrations of antifungal drugs. Of note, antifungal resistance is a complicated phenomenon involving multiple factors and the outlines provided here only represent a simplified picture.

Azoles target 14-α lanosterol demethylase, encoded by *ERG11*, and disrupt the ergosterol biosynthetic pathway and once occupied by azoles, the accumulation of toxic intermediates hypothetically result in growth inhibition[3]. Therefore, drug target mutations modulating the azole binding are known to be one of the most widely known mechanisms underlying azole resistance. Mutations in catalytic site (Y132, P405), extended fungus-specific external loop (D446, G448, F449, and G450), proximal surface (F145), and residues between proximal surface to heme region (K143 and G464) are the most known ones proved to elevate fluconazole minimum inhibitory concentrations (MIC) ≥4 in *Candida* spp [4-6].

Studying a large collection of clinically-derived fluconazole resistant *C. albicans* isolates identified concomitant overexpression of *ERG11* and efflux pumps, especially *CDR1*,

in conjunction with notable *ERG11* mutations associated with azole resistance [4]. Efflux pumps known to be involved in azole resistance are categorized into two groups, namely ATP-binding cassettes (ABC) transporters, such as *CDR1*, and major facilitator superfamily (MFS), such as *MDR1*[3]. Gain-of-function (GOF) mutations occurring in transcription factors regulating the expression of *CDR1* and *MDR1*, namely *TAC1* (*PDR1* in *C. glabrata*) and *MRR1*, respectively, render them hyperactive and thereby result in the overexpression of these efflux pumps followed by effective evacuation of azoles [7]. Moreover, the GOF mutations occurring in *UPC2* can result in overexpression of *ERG11* as a compensation for the occupied drug target and to maintain the cellular homeostasis [7]. Nonetheless, the role of such GOF mutations in other prevalent species, namely *C. parapsilosis* and *C. tropicalis*, are yet to be defined. Understanding the extent of involvement of efflux pumps in major *Candida* species are of paramount importance, as evidenced by the discovery that a Cdr1 inhibitor, azoffluxin, showed promising in-vitro and in-vivo activities [8].

A lower level of drug uptake in laboratory-derived azole resistant *C. auris* isolates has been reported [8], which remained to be investigated in the context of clinical isolates. Although rare, mitochondrial dysfunction resulting small and slow growing cells with inability to use non-fermentable carbon sources, known as *petite*, has been proposed as another mechanisms involved in azole resistance [9]. *Petites* may also confer to a higher tolerance to echinocandins and resistance to macrophage killing up to 24 hours after phagocytosis by macrophages compared to wild-type parental strains [10].

Unlike mechanisms underlying azole resistance, echinocandin resistance (ECR) mechanism is more straightforward, which mainly involves the acquisition of mutations in the catalytic subunit of β-glucan synthase, encoded by *FKS* gene. These mutations mainly include those mapping to two short stretches of *FKS* gene, known as hotspot 1 (HS1) and HS2 [3]. In *C. auris* and *Candida* species within the CTG-clade, the most clinically relevant mutations accountable for ECR are mapped to HS1 and HS2 of *FKS1*, while mutations occurring in HSs of *FKS1* and *FKS2* are associated with ECR in *C. glabrata* [3]. Of note, mutations outside but in close proximity to HS region has been shown to cause ECR and echinocandin therapeutic failure *in vivo* [11]. HS mutations without in-vitro phenotype were found to be linked to echinocandin therapeutic failure in real-life [12]. Historically, *C. parapsilosis* isolates are known to confer high MICs against echinocandins, which is due to an inherently occurring polymorphism, P660A, in HS1 of *FKS1* [13]. Nonetheless, identification of R658G in HS1-Fks1 of clinical *C. parapsilosis* isolates proved that inherent high MICs *per se* may not confer full protection [14].

Amphotericin B (AMB) exert its potent antifungal activity through binding to ergosterol on the cell membrane, followed by formation of pores, leakage of the cellular contents, and thereby disturbing the cellular homeostasis. Moreover, accumulation of intracellular reactive oxygen species (ROS) once stressed with AMB further challenge the viability of the cells [15]. Unlike increasing prevalence of ECR and FLZR in clinical isolates of *Candida* species, AMB resistance has rarely been reported and this rarity has been associated with severe fitness cost applied to the resistant colonies. Nonetheless, researchers have taken the advantage of studying species with inherent high MIC values against AMB to gain insight into mechanisms underpinning AMB resistance. Recently, a study found the

absence of ergosterol in the membrane of *C. haemulonii* species complex, potent membrane integrity once challenged with AMB, resistance to ROS, and changing respiratory status to fermentative pathway. Therefore, species within the *C. haemulonii* complex had poor growth on media containing non-fermentable carbon sources and minimally used oxygen [16]. On the other hand, recent studies focusing on acquired AMB resistance in *C. auris* identified the involvement of *ERG6* as a rare mediator of this phenotype and importantly a detailed genome-wide analysis of *C. auris* isolates identified multiple candidate genes potentially involved in AMB resistance [6]. Moreover, non-synonymous mutations occurring in *ERG3* and *ERG4* also have been found to be associated with AMB resistance in *C. lusitaniae* [17].

Although the current paradigm has largely focused on coding genes, which encompass only a minority of the genome, a growing body of evidence have identified the involvement of non-coding part of genome regulating important responses to both host-related stressors and antifungal drugs. Recently, a long non-coding RNA, named *DINOR*, was shown to regulate global responses to membrane-assaulting, DNA-alkylating agents, hydrogen peroxide, and antifungal drugs. Interestingly, mutants lacking *DINOR* showed an attenuated virulence while tested in vivo [18]. Moreover, a recent comprehensive bioinformatic study identified numerous non-coding RNAs in major *Candida* species potentially involved in host-pathogen interaction, which could be served as a valuable resource for future studies [19]. Therefore, these studies unveil that drug resistance mechanisms are much broader and complicated that we have envisioned and that such targets may represent promising hits for effective drug discovery in the future.

Of note, antifungal tolerance, a transient and reversible resistance caused by drug target copy number variation driven by chromosomal aneuploidy[20], has also been recently reported that potentially could result in therapeutic failure. Details regarding this concept has been provided elsewhere[21]. Moreover, it has been suggested that specific SNP occurrence in the mismatch repair gene, *MSH2*, has been linked with a higher propensity of acquirement of drug resistance in *C. glabrata*[22,23] and reported for other fungal pathogens[24], but the direct involvement of such polymorphisms in drug resistance remains elusive and epidemiological studies have related such SNPs with sequence type prediction rather than a facilitator to development of drug resistance[25,26].

3. Antifungal Drugs in Clinical Development

3.1. Fosmanogepix/Manogepix

3.1.1. Mechanism of action, PK PD, and *Candida*> resistance—Manogepix (APX001A, Amplyx Pharmaceuticals, Inc., San Diego, CA; formerly E1210, Eisai Co., Ltd., Tokyo, Japan), is the active moiety of the N-phosphonooxymethyl prodrug fosmanogepix (APX001, formerly E1211) [27,28]. The drug targets glycosylphosphatidylinositol (GPI)-anchored protein maturation by inhibiting the fungal inositol acyltransferase enzyme Gwt1, which is essential for trafficking and anchoring mannoproteins to the fungal cell wall and membrane [29,30]. Broad-spectrum *in vitro* activity has been demonstrated against *Candida* spp., with potent activity also against azole and echinocandin-resistant strains of *C. albicans, C. glabrata*, and *C. auris* [31-35]. Pan-resistant *C. auris* isolates (exhibiting resistance to triazoles, echinocandins, and amphotericin B) also exhibited low manogepix MICs [36] (Table

1). However, it lacks activity against certain species, including *C. krusei* and *C. inconspicua*, and to a lesser extent *C. kefyr* [32,34]. Point mutations within Gwt1 (V162A in *C. albicans* and V163A in *C. glabrata*) following *in vitro* exposure can lead to significant increases in manogepix MICs, but not fluconazole resistance [37]. However, clinical isolates with elevated manogepix MICs without Gwt1 mutations are universally resistant to fluconazole [32]. This cross-resistance between manogepix and fluconazole has been attributed to efflux pumps, [38] as point mutations within Gwt1 that confer reduced manogepix susceptibility do not affect fluconazole, and point mutations within lanosterol 14α-demethylase that lead to fluconazole resistance do not affect manogepix. However, these data are currently limited, and changes in both manogepix and fluconazole MICs were minimal despite marked increases in transcription levels of genes encoding efflux pumps in *C. albicans* (*CDR11, SNQ2*, and *MDR1*) and *C. parapsilosis* (*MDR1*)[38].

The potent *in vitro* activity of manogepix has also translated into *in vivo* efficacy in experimental models of candidiasis caused by different *Candida* species, [35,39,40] with the effectiveness being maintained against infections were caused by strains resistant to clinically available antifungals. The PK/PD parameter most closely associated with efficacy is the AUC/MIC, followed by Cmax/MIC. In one murine model of invasive candidiasis caused by *C. albicans*, the total AUC/MIC ratios associated with fungal burden stasis ranged from 675.5 to 11,270, corresponding to free fraction AUC/MIC ratios of 1.35 to 22.54 due to extensive protein binding of manogepix (99.8%)[40]. Robust penetration of manogepix into liver abscess and clearance of *C. albicans* from the liver has also been reported in a murine model of intra-abdominal candidiasis [41]. Pharmacokinetics of fosmanogepix/manogepix are summarized in Table 2.

3.1.2. Clinical Studies—Fosmanogepix has been reported to be safe and well tolerated in several phase I clinical trials. In each, all adverse effects were mild and transient, with headache being the most frequently reported, and no clinically significant adverse effects were observed [42,43]. Fosmanogepix was also well-tolerated with no treatment-related serious adverse effects or discontinuations in the MITT group (n = 20) of a phase II multicenter, open-label, non-comparative, single-arm study in non-neutropenic patients with invasive candidiasis (Supplemental Table 1) [44]. In this study, a successful outcome, defined as clearance of *Candida* spp., was observed in 80% in the MITT population, and overall survival at day 30 was 85% with no deaths considered to be related to fosmanogepix. Negative blood cultures occurred a mean of 2.4 days following fosmanogepix initiation, while 15% of patients who failed therapy had persistently positive cultures. No worsening of renal function, evidence of drug-related nephrotoxicity, or required dosage adjustments were reported in this study in which the majority of patients (66%) had renal insufficiency, suggesting that fosmanogepix may be safe in the setting of impaired renal function [44,45]. A multicenter, open-label, non-comparative study to evaluate the efficacy and safety of fosmanogepix against invasive candidiasis caused by *C. auris* was terminated early due to the impact of COVID-19 on trial related activities (NCT04148287). A phase III study comparing fosmanogepix to echinocandin therapy for the treatment of invasive candidiasis is currently in the planning stages.

3.1.3. Future Role in treating *Candida* infections—The U.S. Food and Drug Administration (FDA) has granted fast-track status to fosmanogepix for the treatment of invasive candidiasis. Its broad spectrum *in vitro* and *in vivo* activity against most *Candida* spp., including *C. auris*, is encouraging, and clinical trials will further define the role of fosmanogepix for the treatment of invasive candidiasis/candidemia, including infections caused by strains resistant to other antifungals (Table 3).

3.2. Ibrexafungerp

Ibrexafungerp represents a first-in class triterpenoid antifungal, a new class of antifungals also called the"-fungerps".

3.2.1. Mechanism of action, PK PD and *Candida* Resistance—While the binding site is different, the mode of action is similar to that of the echinocandins. By non-competitively inhibition of the 1,3-beta-D-glucan synthase enzyme, ibrexafungerp impairs the synthesis of a major *Candida* cell wall component, 1,3-beta-D-glucan. Ibrexafungerp is fungicidal against *Candida* spp.[28,46,47]. Whilst for most *Candida* spp., ibrexafungerp reveals good *in vitro* activity, including azole-resistant *Candida* strains [48], *in vitro* activity against echinocandin resistant *FKS*-mutants turned is variable [49,50]. In detail, specific *FKS*-mutations have been associated with an increase in MIC compared to wild-type strains [49] including F641S, F649del, F658del and F659del mutations [51-54]. However, in general, activity of ibrexafungerp against *FKS*-mutants is higher compared to that of echinocandins, with approximately 70 to 85% of *FKS*-mutants being susceptible to ibrexafungerp but only 17 to 50% are susceptible to echinocandins [55]. Importantly, also difficult to treat *Candida* spp. like echinocandin resistant *C. glabrata* [50] and *C. auris* [56] are usually susceptible to ibrexafungerp (Table 1).

Ibrexafungerp may either be administered orally or intravenously, while most of the currently available studies have investigated the oral formulation. This is based on the good bioavailability of 30 to 50% after oral intake [57,58]. For invasive fungal diseases, ibrexafungerp is usually administered with a loading dose for two days, followed by a maintenance dose. A peak plasma concentration is usually reached after 4 to 6 hours with a median half-life time of approximately 20 to 30 hours, allowing for once daily dosing [59]. Even though ibrexafungerp is highly protein bound (99%), tissue distribution is high, maybe as a consequence of low protein binding affinity. In a murine model, high tissue to bloodstream area under the curve ratios after oral administration have been observed within bone marrow (25-fold), kidney cortex (21-fold), liver (50-fold), lung (31-fold), skin (12 to 18-fold) and spleen (54-fold), whilst there was insufficient distribution into brain tissues and the eye lens (0 and 0.08, respectively). The route of ibrexafungerp elimination is mainly via feces and it is only marginally recovered from urine [60]. Most relevant pharmacokinetic data of Ibrexafungerp are displayed in Table 2.

3.2.2. Clinical studies—Ibrexafungerp is already approved by the U.S. Food and Drug Administration for treatment vulvovaginal candidiasis (VVC) with a recommended dose of 300 mg twice daily for one day [61]. This recommendation was based on two phase 3 trials, VANISH-303 and VANISH-306 [62,63]. In these randomized control trials, ibrexafungerp

demonstrated superiority over placebo for the primary endpoint, which was clinical cure at day 11 (±2) in the modified intention-to-treat analyses [RR (95% CI) 1.70 (1.2 – 2.5) for the VANISH-303 trial and RR (95% CI) 1.35 (1.06 – 1.73) for the VANISH-306 trial.

Several studies investigating the efficacy and safety of ibrexafungerp in invasive candidiasis are currently ongoing. Ibrexafungerp has already been investigated as an oral step-down strategy in patients with invasive candidiasis including candidemia who initially were treated with intravenous echinocandins in comparison to fluconazole, and non-inferiority was demonstrated in terms of a favorable global response [64]. In addition, six out of eight patients in this study who were suffering from *C. glabrata* or *C. krusei* infection had a favorable outcome when treated with ibrexafungerp in contrast to fluconazole [64]. In the currently ongoing open-label, single arm FURI trial (NCT03059992; Supplemental Table 2) patients with invasive candidiasis that are intolerant to standard-of-care treatment or have refractory invasive candidiasis may be treated with oral ibrexafungerp. Final study results are not yet available, however, an interims analysis ibrexafungerp demonstrated good efficacy in these patients [65]. The majority of patients included had *C. albicans* or *C. glabrata* infections and 70% turned had clinical improvement, complete or partial remission, whilst no patient had disease progression during ibrexafungerp treatment [65]. In addition, interims analysis of the phase 3 CARES trial (NCT03363841), highlighted that 80% of patients with invasive candidiasis due to *C. auris* had a complete response with ibrexafungerp treatment [66].

3.2.3.1. Future Role: Due to the broad use of azoles and echinocandins, resistances against the main antifungal agents used to treat invasive candidiasis are complicating the management of these patients in clinical routine. Ibrexafungerp, as a new first-in-class antifungal, may overcome some of echinocandin resistance mechanisms and thus extend the treatment options. Currently ibrexafungerp is only FDA approved for the treatment of VVC as final results from several phase 2/3 trials are still pending. Depending on the final results, further indications like the treatment of multi-resistant *Candida* strains, treatment of refractory *Candida* infections or oral step-down treatment after initial intravenous treatment may granted in the near future (Table 3).

3.3. Rezafungin

3.3.1. Mechanism of action, PK/PD and *Candida* Resistance—Rezafungin (formerly SP3025 and CD101; Cidara Therapeutics, San Diego, CA) is a second-generation echinocandin with a novel pharmacokinetic profile[28]. As with other echinocandins, the antifungal activity results from inhibition of the enzyme complex β-1,3-D-glucan synthase responsible for fungal cell wall biosynthesis[28]. A structural modification at the cyclic hexapeptide core differentiates rezafungin from its chemical analogue anidulafungin [67]. This modification increases chemical stability to host degradation pathways and results in a considerably longer half-life while maintaining the antifungal activity and safety profile of the echinocandins [67,68].

Two phase I dose-escalation studies (NCT02516904 and NCT02551549, Supplemental Table 1) have demonstrated the novel PK properties with a prolonged half-life of more than

80h [69]. This allows for once-weekly administration of rezafungin. Mean plasma C_{max} *and* AUC increase in proportion to dose [69]. In a murine model of intra-abdominal candidiasis, rezafungin had better penetration into abdominal abscesses than micafungin [70]. Lack of reactive intermediates and stability in liver microsomes reduces the risk of liver toxicity [68]. Renal clearance has a minor role in rezafungin excretion [69]. Pharmacokinetics of Rezafungin is summarized in Table 2.

In vitro activity of rezafungin against *Candida* spp. is comparable to those of other echinocandins [28]. The majority of *C: albicans* isolates were inhibited at MIC values ≤0.125μg/ml using both CLSI and EUCAST methods [71,72]. Wild type *C. dubliniensis*, *C. fabianii, C. glabrata*, *C. inconspicua*, *C. kefyr*, *C. krusei*, *C. lipolytica, C. pulcherrima, C. sojae* and *C. tropicalis* were also inhibited by MICs ≤0.125μg/ml [72,73]. *C. lusitaniae* and *C. auris* MIC values were 0.25μg/ml [73]. *C. metapsilosis*, *C. orthopsilosis* and *C. guilliermondii* were less susceptible with MIC values between 0.5μg/ml and 1μg/ml [73]. *C. parapsilosis* was the least susceptible isolate with MICs up to 4μg/ml [72]. *C. albicans*, *C. dubliniensis*, *C. glabrata*, *C. krusei* and *C. tropicalis* isolates harboring *FKS* hot spot mutations were overall similarly *in vitro* susceptible to rezafungin as to other echinocandins [71,74]. Rezafungin was active against azole-resistant strains of *C. albicans, C. glabrata* and *C. tropicalis* [73,75]. In summary, rezafungin has *in vitro* activity against most wild-type and azole-resistant *Candida* spp., including *C. auris*. Cross-resistance with other echinocandins to *FKS* mutations has been observed [74].

In vivo efficacy for the treatment has been demonstrated in immunocompromised murine models of disseminated candidiasis by *C. albicans, C. auris, C. glabrata*, and *C. parapsilosis* [76,77].

3.3.2. Clinical Studies—Both phase I dose escalation studies (Supplemental Table 3) have shown a favorable safety profile for once-weekly intravenous doses of 400mg rezafungin with the majority of adverse effects (AEs) reported being mild [69]. In addition, a randomized, double-blind, phase I study evaluating cardiac effects of supratherapeutic doses detected no adverse effects on QT interval or echocardiogram [78].

The Phase II STRIVE trial (NCT02734862) was a randomized controlled trial that evaluated rezafungin IV compared to caspofungin followed by oral fluconazole for the treatment of invasive candidiasis [79]. In terms of safety, the most reported AEs were mild to moderate diarrhea, fever, hypokalemia, and vomiting [28]. For efficacy, 200 mg rezafungin once weekly with 400 mg loading dose showed the highest cure rates and lowest all-cause mortality at day 30 [79]. Of note, certain forms of invasive candidiasis such as endophthalmitis and osteomyelitis were excluded.

Currently, two phase III trials are further determining rezafungin efficacy. The randomized, double-blind ReSTORE trial (NCT03667690) evaluates rezafungin against caspofungin with optional fluconazole step-down for the treatment of invasive candidiasis. In preliminary results, rezafungin demonstrated non-inferiority, reaching a global cure rate of 59.1% at day 14 compared to caspofungin with 60.6% [80]. ICU stay was shorter for patients receiving rezafungin than caspofungin with 5 and 14.5 days in average, respectively. The randomized,

double-blind ReSPECT trial (NCT04368559) examines rezafungin for the prevention of IFD including *Candida* spp. in allogenic BMT patients. Fungal-free day 90 survival will be evaluated as primary outcome.

Rezafungin was also investigated for topical treatment of non-invasive acute vulvovaginal candidiasis (RADIANT, NCT02733432). Standard-of-care with fluconazole maintained the highest cure rate and the development of topical rezafungin formulations for VVC was discontinued [81].

3.3.3. Future Role in treating *Candida* infections—Rezafungin was designed with a novel PK profile that allows for once-weekly dosing while maintaining the advantages of the echinocandin class with low potential for renal or hepatic toxicity or serious drug-drug interactions [28]. This may enable earlier hospital discharge and use in outpatient setting if prolonged treatment is demanded in invasive candidiasis. Sufficient penetration into intra-abdominal *Candida* abscesses was demonstrated in a mouse model, which is encouraging for the treatment of deep-seated infections [70]. More data are needed on tissue distribution and efficacy in certain forms of invasive candidiasis such as endophthalmitis and osteomyelitis (Table 3).

Rezafungin use for preventing IFD including *Candida* infections in immunocompromised patients could overcome standard multidrug regimens as prophylactic agent. This includes prophylaxis in the setting of HSCT or during the early phase after SOT. Ongoing Phase III trials will provide valuable data on the safety and clinical efficacy of rezafungin both as treatment and prophylaxis for invasive candidiasis (Supplemental Table 1).

3.4. MAT2203

MAT2203 is a novel nanoparticle-based encochleated formulation that protects and delivers its antifungal cargo, AMB, from the gastrointestinal tract into the systemic circulation. This formulation attempts to deliver the potent broad-spectrum antifungal activity into the host to treat mucosal and systemic invasive fungal infections with reduced host toxicity. Preliminary *in vitro* and *in vivo* studies support this therapeutic platform [82].

3.4.1. Mechanism of action, PK PD and *Candida* Resistance—Cochleates are composed of negatively charged lipids along with divalent cations. Within the multilayer lipid matrix AMB can be carried so that in its encochleated state AMB is protected from harsh environments such as gastrointestinal tract but able to be released in blood, lymphatics and/or macrophages. In a murine model of systemic candidiasis MAT2203 appears to have potent anticandidal activity in kidney and central nervous system orally and compares favorably to treatment with AMB deoxycholate parenterally. MAT2203 appears to have a dose-dependent anticandidal activity in several important organ sites [83].

The animal models supported this creative delivery of one of the most potent and broad-spectrum antifungal agents we have against *Candida* species. It also appeared to have reduced organ toxicity and could be tolerated by humans orally. *Candida* resistance is low by the nature of its fungicidal pay load but MAT2203 resistance will best be judged in the

hosts where its creative formulation must consistently meet its necessary tissue antifungal activities. Table 2 summarizes pharmacokinetics of MAT2203.

3.4.2. Clinical Studies—Phase l studies were performed to observe for toxicities in which most common side effects were gastrointestinal such as nausea but importantly renal function was preserved. The single doses of 200 mg and 400 mg of MAT2203 were judged to be well tolerated and these doses were taken into phase 2 studies on candidiasis. There are two clinical trials reported in candidiasis and both studies were under very challenging conditions and patient populations. First, a phase 2a study of MAT2203 in the treatment of chronic mucocutaneous candidiasis in patients refractory or intolerant to standard non-intravenous therapy. All four patients achieved 50% clinical improvement as an endpoint with measurable serum AMB levels and no toxicity noted in the 400mg or 800mg/day dosing [84]. The second study (NCT02971007) was a multi-center randomized study to evaluate the safety, tolerability and efficacy of 200 mg MAT2203 and 400 mg MAT2203 for 5 days in the treatment of moderate to severe VVC. The CAMB composites of clinical cure 52%; mycological eradication 36%; overall success 16% were observed. The comparator was one dose of 150 mg of fluconazole [85] .The 200 mg dose of MAT2203for 5 days (25pts) showed: clinical cure (52%); mycological eradication (36%); overall success (16%). The 400 mg dose of MAT2203for 5 days (22pts) showed: clinical cure (55%); mycological eradication (32%); overall success (14%). The comparator of one dose of 150 mg fluconazole (32pts) reported: clinical cure (75%); mycological eradication (84%); overall success (69%). There were no serious adverse side effects with any regimens and all reported side effects were between 22-27% for CAMB and 9% for fluconazole. From these studies it is clear that MAT2203 orally can deliver safely AMB levels into tissue that possess anti-*Candida* activity in humans. However, it is also true in the unique environment of vaginal candidiasis the delivery of AMB to the candida through an encochleated formulation does not yet approach the efficacy of fluconazole.

3.4.3. Future Role in treating *Candida* infections—It is clear from both animal studies and early human trials that the founding principle of MAT2203 is true. This encochleated product of AMB can provide systemic antifungal exposure of this polyene to the host through oral administration safely. However, at present for mucocutaneous candidiasis it remains suboptimal compared to standard antifungal regimens. Further studies are encouraged: (1) to optimize its dosage; (2) to understand how it could be used in step-down therapy for candidemia; (3) to utilize as a prophylactic agent in high-risk patients for invasive candidiasis; and (4) to perform in combination treatment with other oral antifungals for *Candida* treatments. MAT2203, if approved, will likely find a niche in the management of candidiasis (Table 3).

3.5. Oteseconazole (VT-1161)

3.5.1. Mechanism of action, PK PD and *Candida* Resistance—Oteseconazole is one of several novel tetrazole agents which are characterized by a much greater affinity for fungal CYP51 compared to human cytochrome P450 enzymes[86]. This compound has greater selectivity and potentially fewer side effects and drug-drug interactions along with possible improved efficacy compared to currently available azole antifungals. Some studies

have suggested that the affinity for fungal CYP51 is at least 2000-fold greater compared to the human enzyme counterpart [87,88]. As such, fewer drug-drug interactions and less direct toxicity are anticipated with this agent and this class of azoles. The target enzyme of oteseconazole (14-α demethylase) is the same as for other azoles as well as the mechanism of action (inhibition of ergosterol synthesis) (Fig 1).

Oteseconazole demonstrates broad activity against most *Candida* spp. *In vitro* studies suggest that the compound is active against fluconazole-resistant *Candida* strains such as *Candida krusei* and *Candida glabrata,* including selected echinocandin-resistant strains [89,90]. The agent is also active against a broad array of dermatophytes, endemic fungi, and selected Mucorales species. Available data on oteseconazole pharmacokinetics is shown in Table 2.

3.5.2. Clinical Studies—Orally administered oteseconazole has been examined among women for different stages of VVC and among subjects with onychomycosis. In a randomized, placebo- controlled, double-blind dose-ranging study in women with recurrent VVC, oteseconazole was well-tolerated, when administered on a weekly basis at doses ranging from 150 to 300 mg. In terms of efficacy, a significant reduction in recurrent VVC compared to placebo was observed among women receiving any of 4 regimens of oteseconazole [91]. In a second phase 2 trial involving women with acute VVC, patients received 3 different regimens of oteseconazole compared to standard-of-care treatment with single dose fluconazole 150 mg. Therapeutic cure was observed among almost 80% of women receiving oteseconazole compared to 62.5% in the fluconazole group. Recurrence of VVC at 3- and 6-months following completion of therapy was observed in 28% and 46% in the fluconazole group, while it was extremely rare in the oteseconazole groups [92]. To date over 850 women have participated in clinical trials involving oteseconazole for VVC.

Oteseconazole has also been studied for treatment of onychomycosis due to *Candida* spp. and various dermatophytes. In a randomized, double-blind trial involving 269 subjects with onychomycosis, 1 of 4 regimens of oteseconazole were compared to placebo [93]. Oteseconazole dosing regimens were 300 mg to 600m g daily for 2 weeks, followed by once weekly dosing for 10 or 22 weeks. Efficacy in the placebo arm was 0% compared to 32% and 42% in the oteseconazole treatment arms.

3.5.3. Future Role in treating *Candida* infections—The potential role of oteseconazole in the treatment of *Candida* infections is probably limited to those involving mucosal surfaces and nail structures. The agent is currently being considered as a treatment for recurrent vulvovaginal candidiasis [94] and onychomycosis. Oteseconazole is only available orally, and at present there are no plans to develop it into a therapeutic option for invasive candidiasis (Table 3).

3.6. ATI-2307

3.6.1. Mechanism of action, PK PD and *Candida* Resistance—ATI-2307 is an aromatic diamidine, like pentamidine and furamidine, that acts by disrupting the mitochondrial membrane potential (Fig 1) [95,96]. Available data suggests that ATI-2307 disrupts mitochondrial membrane potential through inhibition of respiratory chain complexes III and IV in *Saccharomyces cerevisiae* and *C. albicans*, resulting in decreased

intracellular adenosine triphosphate (ATP) [97]. In isolated *S. cerevisiae* mitochondria, membrane potential collapsed at 8.8 μg/mL, while nonfermentive growth in yeast cells was inhibited at concentrations of 0.001 to 0.002 μg/mL [98]. This difference may be due to ATI-2307's ability to concentrate in yeast cells. *In vitro* studies have demonstrated that ATI-2307 concentrates 3200 to 5100 times the extracellular concentrations in *C. albicans* cells, but only 35 times in rat hepatocyte cells [99]. Animal models have indicated that ATI-2307 exhibits more than 500-fold higher selectivity for fungal than mammalian mitochondria [98]. Uptake of ATI-2307 appears to occur by high-affinity spermine and spermidine transport system regulated by Agp2 [100]. In Table 2, most relevant pharmacokinetic parameters of ATI-2307 are listed.

ATI-2307 inhibits growth of *Candida* (MICs 0.00025 to 0.0078 μg/ml) and *Cryptococcus* spp. (MICs 0.0039 to 0.0625 μg/ml for *Cryptococcus neoformans*), filamentous fungi, including isolates that are resistant to clinically approved azoles and *Malassezia furfur* [101]. Furthermore, ATI-2307 shows activity against echinocandin-resistant strains of *C. albicans* and *C. glabrata* as well as fluconazole-resistant strains of C. *auris*. ATI-2307 did not exhibit activity against *Saccharomyces cerevisiae* and *Trichosporon asahii* [101,102].

3.6.2. Clinical Studies—To this date, there are no publications relating to clinical studies. According to the sponsor (Appili Therapeutics, Inc.) three Phase 1 studies have been completed [103,104]. In those studies, 80 healthy volunteers received at least 1 dose of ATI-2307. Single doses from 0.125 through 20 mg and multiple doses from 2.5 QD to 20 mg BID up to a duration of 21 days were explored. ATI-2307 was found to be well tolerated at the maximum doses administered. There were no drug-related serious AEs. There were two infusion site reactions leading to withdrawal and one subject withdrew after experiencing mild to moderate paresthesias, dysphagia, dyspnea, and chest discomfort. The most frequently reported adverse events were mild to moderate tachycardia, oral hypoaesthesia, chills, headache, dysgeusia, hypoaesthesia, and paraesthesia. ATI-2307's rate and extent of absorption increased more than proportionally with dose. The PK profile exhibited multi-compartment kinetics, with a terminal half-life of 17h at 20 mg. Plasma protein binding in humans was 54% and the Vd was 96L at 20mg[105]. Phase 2 development in cryptococcal meningitis and invasive candidiasis is being planned [104].

3.6.3. Future Role in treating *Candida* infections—Future role of ATI-2307 could be treatment of invasive candidiasis among other fungal diseases, such as cryptococcal meningitis. The drug exhibits a novel mechanism of action inhibiting mitochondrial membrane potential and is very potent as exhibited by low MICs in *Candida* and *Cryptococcus* species. ATI-2307 may play a role in treating invasive candidiasis caused by azole- and echinocandin-resistant strains, an emerging area of unmet need (Table 3).

3.7. VL-2397 (now GR-2397)

3.7.1. Mechanism of action, PK PD and *Candida* Resistance—VL-2397 (formerly ASP2397) is a cyclic hexapeptide with a structure similar to the siderophore ferrichrome [106], that is now further developed by Gravitas Therapeutics as GR-2397. It was originally isolated from an *Acremonium persicinum* mould isolate found in a tropical forest

as part of a research program searching for new agents for pulmonary aspergillosis [106]. The intracellular drug target is unknown, but the antifungal activity is dependent on uptake via a specific siderophore iron transporter SIT1 (Fig 1) [107]. Consequently, the antifungal activity is limited to species in which SIT1 is present [107,108]. For candidiasis, the spectrum is limited to SIT1 positive strains, including *C. glabrata* and *C. kefyr* (current name *Kluyveromyces marxianus*) but include echinocandin and azole resistant *C. glabrata* [107,109,110].

In vivo efficacy in a neutropenic murine model of invasive candidiasis caused by wild-type and azole- and echinocandin-resistant *C. glabrata* isolates was presented at the ASM microbe in 2017 [110]. PK/PD data has not been published for *Candida*, whereas for *A. fumigatus*, fAUC/MIC was the PK/PD parameter best associated with efficacy in a murine model of invasive pulmonary aspergillosis [111]. Table 2 lists pharmacokinetic information on VL-2397. There are no data on acquired resistance in *Candida*.

3.7.2. Clinical Studies—A phase 1 study showed that VL-2397 was well tolerated up to 1200 mg in healthy volunteers who received escalating single and multiple IV doses per day with no reported serious AEs related to the drug [112]. Following single infusions of VL-2397, the overall and maximum exposures rose less than proportionally with increasing doses from 3 mg to 1,200 mg as indicated by AUC and C_{max} [112]. The major serum binding protein for VL-2397 is zinc-α2-glycoprotein (Zinc-alpha-glycoprotein, ZAG), which was proposed as the likely primary source of nonlinearity [113]. Body surface area was the only covariate with a significant relationship to clearance [113]. Mean AUC_{24}, C_{max} and $t_{½}$ after 300/600/1200 mg dosing were 47/91/165 ng*h/mL, 15/25/33 ng/ml and 72/84/86 h with no signs of VL-2397 accumulation. Renal elimination increased with increasing dose (7%-47% for doses 3-1200 mg) and played a major role in total body clearance at doses above 10 mg [112].

VL-2397 had early termination of phase 2 trial against aspergillosis due to a business decision, and there are currently no ongoing trials registered at www.clinicaltrials.gov website (viewed January 04, 2022).

3.7.3. Future Role in treating *Candida* infections—Given the narrow spectrum for *Candida*, the future role for VL-2397 in *Candida* infections will be targeted therapy of *C. glabrata* and *C. kefyr* (*Kluyveromyces marxianus*) infections. *C. glabrata* is the second most common *Candida* spp. causing invasive candidiasis in most countries in the northern hemisphere and Asia Pacific [2,114]. It is intrinsically less susceptible to azoles and it is the *Candida* spp. that most frequently acquires antifungal drug resistance to echinocandins and azoles [115]. Consequently, new agents with new molecular targets against *C. glabrata* will have a future role. *C. kefyr* (*Kluyveromyces marxianus*) is an uncommon species, most frequently encountered in patients with underlying hematologic disease. It is normally susceptible to the available antifungal agents, but acquired resistance to echinocandins have been described in which case VL-2397 would be a potential alternative [116]. Finally, due to its renal excretion, it may have a specific role for *C. glabrata* infections involving the urinary tract (Table 3).

3.8. NP339

3.8.1. Mechanism of action, PK PD and *Candida* Resistance—NP339 is a 2-kDa polyarginine polypeptide with antifungal activity [117]. Synthetic polyarginine peptides have been developed as cell-penetrating peptides to deliver various cargoes (drugs or dyes) to the mammalian cell [118,119]. However, Duncan et al. were the first to test their antifungal potential and to develop the novel polypeptide NP-339.

NP339 was designed based on endogenous cationic human defense peptides, which are important constituents of the immune defense against pathogenic microbes. NP-339 specifically targets the fungal cell membrane through a charge-charge-initiated membrane interaction and does not penetrate the mammalian cell (Fig 1). As a consequence, it possesses a differentiated safety and toxicity profile in comparison to presently known antifungal agents. It is active against genera of *Candida, Cryptococcus, Aspergillus*, and *Exophiala*. Duncan et al. also mention efficacy against other fungi without further specification. It is fungicidal against both planktonic cells and biofilms. Furthermore, NP339 has not only be proven to effective against fungi in tissue cultures but also in human whole blood and saliva.

Its fungicidal effect is achieved rapidly *in vitro*. In addition, it does not elicit development of resistance or cross-resistance to well-known and frequently used antifungals such as azoles or echinocandins. In murine models of candidiasis, a significant improvement in the vaginal candidiasis model as well as in the oropharyngeal candidiasis model could be achieved, whereas for disseminated candidiasis a trend, but not a significant effect on the fungal burden was observed. However, there is a need for further data generated in optimized *in vivo* models of infection.

NP339 is not cytotoxic or hemolytic *in vitro*. In addition, it does not cause a nonspecific immune response. The observations described by Duncan et al. indicate a unique safety and toxicity profile. Exogenous peptides are not processed in the liver, which minimizes the risk of the involvement of NP339 in adverse drug-drug interactions [120,121]. Pharmacokinetic data of NP339 is not yet available.

3.8.2. Clinical Studies—As NP339 has only recently been developed clinical studies have not been performed so far. At present, it is not possible to predict the actual NP339 efficacy and performance for clinical application. As its further development for application against specific fungal diseases is actively pursued future studies will show its efficacy in the treatment of candidiasis.

3.8.3. Future Role in treating *Candida* infections—The future role of NP339 could be the treatment of invasive candidiasis among other fungal diseases. The drug exhibits a novel mechanism of action by targeting the fungal cell membrane and does not penetrate the mammalian cell. The risk of the involvement in adverse drug-drug interactions is therefore small. This anticipates its applicability for the treatment of candidiasis in high-risk patients, e.g. patients undergoing chemotherapy, transplant recipients and otherwise immunocompromised and seriously ill individuals already subject to poly-pharmaceutical interventions (Table 3).

3.9. Miltefosine

3.9.1. Mechanism of action, PK PD and *Candida* Resistance—Miltefosine is an alkyl phosphocholine analog first developed as an anti-cancer drug that has found use in the treatment of leishmania [122]. It has broad antifungal activity *in vitro* against a wide spectrum of fungi, including yeasts [123]. Miltefosine has been shown to be active against planktonic cells and biofilms of *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis*, *C. krusei,* and *C. auris* [124,125]. In addition, miltefosine and amphotericin B were synergistic against *C. auris* [126]. The mechanism of action has not been fully elucidated, but in *C. krusei*, miltefosine antifungal activity may be carried out by interaction with ergosterol, leading to apoptosis (Fig 1) [127]. Resistance to miltefosine is reported and has been linked to lipid asymmetry across the plasma membrane [128].

Miltefosine has good bioavailability and is administered orally. In children, pharmacokinetics are non-linear, and an allometric weight-based dosing schedule achieves better exposure (and clinical response in visceral leishmaniasis). Gastrointestinal toxicity is common. High doses may result in hemolytic anemia. Teratogenicity precludes use in pregnancy [122]. Published pharmacokinetic data on miltefosine is sparse (Table 2).

3.9.2. Clinical Studies—Nanocarrier formulations may offer drug delivery with lower toxicity. Alginate nanoparticles (AN) miltefosine did not cause hemolysis or other toxicity in *Galleria mellonella* larvae with candidiasis [129]. In addition, miltefosine-containing nanocarriers were effective in the topical treatment of vaginal candidiasis caused by *C. albicans* in a murine model [130]. Human clinical studies evaluating miltefosine in candidiasis are lacking.

3.9.3. Future Role in treating *Candida* infections—Miltefosine was granted orphan drug designation by the FDA on November 1, 2021 for the treatment of invasive candidiasis [131] (Table 3).

4. Conclusion

Several promising antifungal agents are currently in late-stage clinical development that will add to the armamentarium against antifungal resistant Candida spp. Many of these antifungals offer novel mechanisms of action, some allowing for less frequent or oral dosing, having the potential to significantly advance care for Candida infections.

5. Expert Opinion

Several of the drugs discussed in this review have novel mechanisms of action. While preclinical data and also clinical trials often focus on the treatment of refractory, resistant, or breakthrough infections [132], some drugs that show advantages in pharmacokinetics (e.g. allowing for oral or less frequent dosing) may soon have additional indications allowing broader clinical use. Importantly, even for those agents that are already in advanced clinical development, there are still some gaps of knowledge regarding their pharmacokinetics and pharmacodynamics and whether therapeutic drug monitoring may be required. Only once these drugs are broadly used in real-world scenarios, we will find out how prone these new

drugs are to the evolution of novel drug resistance mechanisms. Also, some of the new drugs in development have a much narrower spectrum of activity compared to some of the currently available broad-spectrum agents and may therefore be less promising for empirical therapy, which is frequent for *Candida* infections. Some of these drugs may therefore only be used in cases where the causative fungal pathogen has been identified on a species level.

Three of the drugs discussed in this review are in late-stage clinical development. Fosmanogepix has a novel mechanism of action and can be dosed orally or intravenously. While the drug has a broad spectrum of activity against most *Candida* spp. (including *C. auris* and multiresistant *C. glabrata*), it lacks activity against *C. krusei*. Ibrexafungerp has also a novel mechanism of action and is currently available only in the oral formulation. In 2021, ibrexafungerp has been approved by the FDA for the treatment of vulvovaginal candidiasis. The drug is currently being evaluated in a number of studies for treatment of a variety of infections caused by *Candida* spp. Given its oral formulation, ibrexafungerp will likely be a good primary and stepdown option for infections from *Candida* spp., and it will have a role in the treatment of azole-resistant *Candida* spp., and possibly against echinocandin resistant *C. auris* and *C. glabrata* isolates[28]. Rezafungin is a once-weekly intravenous echinocandin with favorable activity against *Candida* spp., including azole-resistant *Candida* spp. Rezafungin may serve as a promising option for prolonged treatment for complicated cases of invasive candidiasis and allow for earlier hospital discharge in some cases with candidemia where step down to fluconazole is not an option. Moreover, its broad-spectrum activity against *Candida* spp., but also *Aspergillus* spp., and *Pneumocystis jirovecii* will make it a candidate in post-transplant prophylaxis[28].

Other investigational antifungals that have activity against *Candida* spp. are currently in preclinical development or in the very early phase of clinical evaluation. This includes MAT2203, ATI-2307, and VL-2397. These drugs have the potential to play a significant role in managing invasive candidiasis.

MAT2203 is an encochleated formulation of amphotericin B and is an exciting antifungal as it may provide an oral option of polyene therapy, but currently, further studies are needed to evaluate the proper dose and efficacy. ATI-2307 exerts its activity by disrupting mitochondrial membrane potential and has activity against yeast and filamentous fungi, including azole-resistant *Candida* spp.; however, clinical data are lacking. VL-2397 depends on siderophore iron transporter SIT1 for its activity. While VL-2397 is a promising therapeutic agent against invasive aspergillosis, its anti-*Candida* spp. activity is limited to *C. glabrata* and *C. kefyr* (*Kluyveromyces marxianus*). However, pending more clinical data, VL-2397 will provide an option against azole-resistant *C. glabrata* and *C. kefyr* (*Kluyveromyces marxianus*), especially for urinary infections as it is mainly excreted in the urine. Oteseconazole binds with greater affinity to fungal CYP51 than currently licensed azoles, possibly leading to fewer side effects. It is orally available and has been proven effective in vulvovaginal candidiasis and onychomycosis. The polyarginine cationic NP339 interacts charge-charge-initiated with the fungal membrane and is well tolerated in *in vivo* models. It has a broad spectrum of antifungal activity but evaluation in clinical trials is pending. Miltefosine already has a place in the treatment of leishmaniasis, whereby pharmacokinetics and side effects are known. Due to its antifungal activity that is carried out

by a largely unexplored mechanism it was recently granted orphan drug designation for the treatment of invasive candidiasis.

Despite the promise of newly approved and investigational antifungal drugs, unmet needs in the treatment of invasive candidiasis still exist. Even with these new and emerging options, there are still too few antifungals that can be given orally or have CNS penetration. There is an urgent need to garner clinical data on investigational drugs, especially in the current trend of the rise of azole-resistant and multi-drug resistant *Candida* spp, such as *C. auris*, *C. glabrata,* and *C. parapsilosis*. Thus, despite the promise that these new antifungal options hold, continued research and development into new options including drugs from novel antifungal classes will help replenish the current antifungal armamentarium.

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*Availability of data and material Data available upon request.

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Article Highlights:

- For the first time in two decades, the antifungal pipeline is loaded and includes several repurposed drugs and drugs with new mechanisms of action.
- Ibrexafungerp, a first-in class triterpenoid antifungal, has recently been FDA approved for treatment of vulvovaginal candidiasis and may provide an option for treatment of multi-resistant refractory *Candida* infections or oral step-down treatment.
- Rezafungin is an echinocandin with a novel PK profile that allows for once-weekly dosing, which may be of benefit particularly for outpatient treatment or *Candida* prophylaxis.
- Fosmanogepix has a novel mechanism of action with broad spectrum activity and has been granted FDA fast-track for the treatment of invasive candidiasis.
- MAT2203 is an encochleated product of amphotericin B, providing systemic exposure after oral administration, and may find a niche in the management of candidiasis

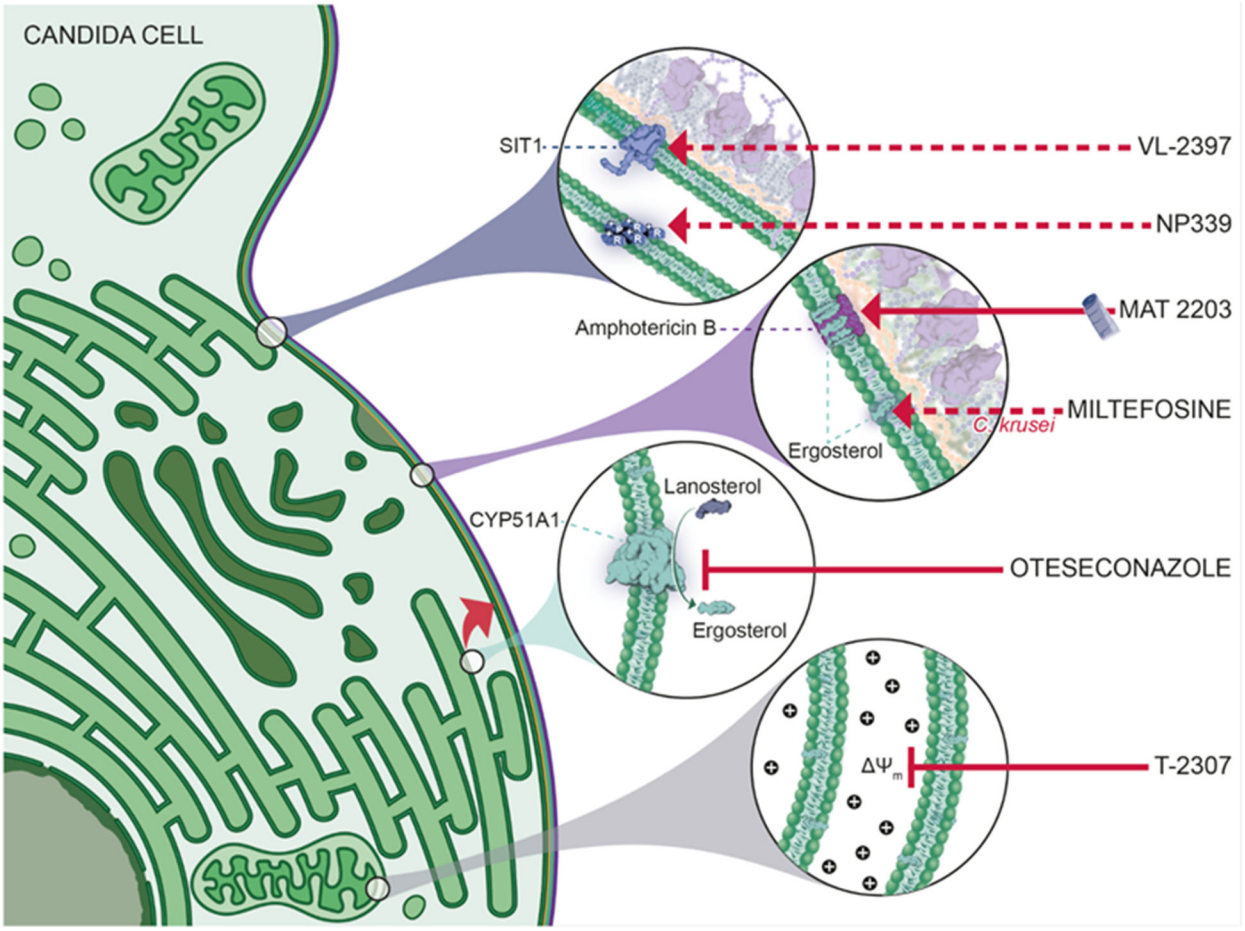

Figure 1:

Mechanism of action of the novel antifungals MAT2203, miltefosine, NP339, oteseconazole, ATI-2307 (=T-2307) and VL-2397. For ibrexafungerp, fosmanogepix and rezafungin a corresponding figure has been published before [28]. Dotted lines indicate that the exact mechanism of action is still under investigation. Depicted mechanism for miltefosine is based on Wu et al., 2020 [127]; NP339 is based on Duncan et al., 2021 [117]; VL-2397 on Dietl et al., 2019 [107] Abbreviations: CYP, cytochrome P; SIT1, siderophore iron transporter 1.

Table 1.

Activity and strengths of new antifungals against *Candida auris*.

Drug	New mechanism	Formulation	Activity against *Candida auris*			Comments
			In vitro	Animal model	Clinical trials	
Rezafungin	−	IV	+ CLSI MIC_{90} 0.25 mg/L[73]	+[77]	+	in ReSTORE trial NCT03667690
Fosmanogepix/ Manogepix	+	PO, IV	+ CLSI MIC_{50} 0.004 mg/L MIC_{90} 0.031 mg/L[39]	+[35]	unk	APEX trial NCT04148287 terminated due to COVID-19
Ibrexafungerp	(+)	PO, (IV)	+ CLSI MIC_{50} 0.12–1 mg/L[56] CLSI MIC_{90} 1 mg/L[133]	+[39]	+	in CARES trial NCT03363841 interim analysis
VL-2397	+/unk	IV	unk	unk	unk	
NP339	+	unk	unk	unk	unk	
MAT2203	−	PO	unk	unk	unk	
Oteseconazole	−	PO, IV	unk	unk	unk	
ATI-2307	+	unk	+ CLSI MIC_{50} ≤0.008-0.015 mg/L[102]	+[102]	unk	
Miltefosine	+/unk	PO	+ CLSI MIC_{50} 2-4 mg/L[126]	+[125]	unk	Synergistic effect with amphotericin B *in vitro*

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Table 2.

Pharmacokinetics of new antifungals

Drug	Dose (in current studies)	Route of administration	Half-life	Volume of distribution	Protein binding %	Metabolism	(Anticipated) drug-drug interactions	Elimination route	Tissue distribution	Relevant PK/PD target parameter
Fosmanogepix/ Manogepix	50-600	P.O., I.V.	60 h	n.d.	99.8	Manogepix is active	n.d.	Biliary	Wide tissue distribution	AUC/MIC
Ibrexafungerp	300 mg b.i.d. for 1 day	P.O., I.V. F=30-50%	20-30 h	600 L	99	Hydroxylation by CYP3A4	CYP3A4 substrate	Biliary excretion	High cnc. in liver, lung, skin, spleen, bone marrow, low in brain and eye	n.d.
Rezafungin	200 mg once weekly, LD 400 mg	I.V.	340 h	89 L	97.4	Hydroxylation	n.d.	70% feces, 30% urine	High cnc. in abdominal abscess	n.d.
MAT2203	1-2 g in 4-6 doses	P.O.	48 h (t ½ β)	n.d.	>90	n.d.	no	Uptake by macrophages	n.d.	n.d.
Oteseconazole	300 mg q.d. −600 mg b.i.d for 3 days	P.O. F=40-70%	76-160 h	n.d.	99.5	n.d.	n.d.	Feces	Tissue > blood	n.d.
ATI-2307	Up to 20 mg	I.V.	1.1 h (0.9 - 1.3; t ½ β) 16.6 h (5.4 - 34.4; t ½ γ)	96L (54 - 621)	~50	No relevant metabolism	No relevant DDIs identified	Urine (15-30%), feces (35-45%)	High cnc. In liver, kidney, lower in pancreas, spleen, thyroid, low in eyeball, heart, lung, stomach, intestines, and CNS	Not yet known, Cmax? AUC?
VL-2397	300-1,200 mg q.d.	I.V.	71-88 h (t ½ γ)	270-500 L	Saturable, low at high cnc.	Minor role	Minor role	Renal	n.d.	AUC/MIC
NP339	n.d.	I.V.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Miltefosine	2.5 mg/kg/d	P.O.	5-7 d (t ½ β) 31 d (t ½ γ)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

N.d. no data available

Table 3

Future roles for new antifungals once approved in routine clinical use.

Antifungals	Substance class	Novel aspects	Future areas of use	Special clinical settings	Advantages	Limitations/ Disadvantages	Standard dosage from clinical trials	Regulatory approval status
Rezafungin	Echinocandin	Echinocandin with prolonged half-life	IC	Outpatient setting Prophylaxis in HSCT and SOT	Favorable side effect profile Limited drug-drug interactions Once weekly IV application	Subcutaneous administration failed in clinical trials Unfavorable results of topical formulations in vulvovaginal candidiasis	Treatment and prophylaxis of invasive infection: 400mg IV in week 1, then 200mg IV once weekly	Expected FDA approval Q1 2023; expected EMA approval Q3 2023
Fosmanogepix/ Manogepix	N-phosphono-oxymethyl (pro)drug	Novel MOA - Inhibition of Gwt1, targets GPI-anchored protein maturation	IC for all *Candida* spp. except *C. krusei*	Difficult-to-treat infections	Activity against fungi with limited treatment options Favorable side effect profile Synergism with AMB	Lack of activity against *C. krusei*	Treatment of invasive infection: 1000mg IV bid for 1 day, then 600mg IV qd for at least 2 days, followed by either 600mg IV qd or 700mg PO qd	FDA granted fast track status for treatment of IC
Ibrexafungerp	Triterpenoid	Novel MOA - Glucan synthase inhibitor with alternative binding site	IC including *C. auris* and *C. glabrata* VVC	Oral step-down therapy Outpatient setting	Favorable side effect profile Limited drug-drug interactions High tissue penetration Oral application Synergism with AMB	IV formulation still in early stage of clinical testing	Treatment of invasive infection: 750mg PO bid for 2 days, then 750mg PO qd In combination with azoles: 500mg PO bid for 2 days, the 500mg PO qd Treatment of VVC: 300mg PO bid for 1 day	FDA approved for VVC 07/2021
VL-2397	Cyclic hexapeptide with structure similarity to ferrichrome	Novel/unknown MOA – Uptake via siderophore iron transporter (=SIT 1)	Targeted therapy of *C. glabrata* and *C. kefyr**	*C. glabrata* infections of the urinary tract	Activity against azole/echinocandin resistant *C. glabrata*	Intracellular drug target unknown Spectrum limited to SIT1 exhibiting species (*C. glabrata* and *C. kefyr**)	Well tolerated up to 1200mg IV qd in a phase I study	-
NP339	Synthetic polyarginine polypeptide	Novel MOA – cell-penetrating polypeptide specifically targeting fungal cell membrane	CMC	High-risk patients subject to poly-pharmaceutical interventions	Absence of eliciting development of resistance Unique safety and toxicity profile due to MOA No processing in the liver	No significant effect on fungal burden in first murine models with disseminated candidiasis	No published data so far	-
MAT2203	Polyene (AMB)	Nanoparticle-based enchochleated formulation Oral option of polyene therapy	Combination treatment in IC VVC/CMC	Oral step-down therapy Prophylaxis in high-risk patients Combination treatment	Potent activity in kidney/CNS in murine models Reduced host/organ toxicity Oral availability	Suboptimal in CMC compared to SOC	Treatment of CMC: 400mg or 800mg qd Treatment of VVC: 200mg or 400mg qd for 5 days	-

Antifungals	Substance class	Novel aspects	Future areas of use	Special clinical settings	Advantages	Limitations/ Disadvantages	Standard dosage from clinical trials	Regulatory approval status
Oteseconazole	Tetrazole	Greater affinity for fungal CYP51	VVC/ Onychomycosis	Outpatient setting Resistant strains (fluconazole-resistant *C. krusei*, *C. glabrata* and selected echinocandin-resistant strains)	Higher selectivity – favorable side effect profile, improved efficacy, limited drug-drug interactions	No intentions to develop as therapeutic option for IC	Treatment of VVC: 150mg - 300mg once weekly Treatment of onychomycosis: 300mg - 600mg qd for two weeks followed by once weekly dosing for 10 – 22 weeks	-
ATI-2307	Aromatic diamidine	Novel MOA – disruption of fungal mitochondrial membrane potential	Treatment of IC caused by azole-echinocandin-resistant strains	Yet uncertain	Activity against fluconazole-resistant *C. auris* and echinocandin resistant *C. albicans/C. glabrata*	Yet uncertain	No published data so far	-
Miltefosine	Alkyl phosphocholine analogue	Yet uncertain	Orphan drug designation by the FDA (11/2021) for treatment of IC	Yet uncertain	Broad antifungal activity Biofilm activity Synergistic effects with AMB against *C. auris*	Exact MOA unknown	No published data for candidiasis so far	FDA Orphan Drug designation for IC 11/2021

Abbreviations: AMB – amphotericin B; bid, twice daily; COVID-19, coronavirus disease 2019; CMC – chronic mucocutaneous candidiasis; FDA = Food and Drug Administration; GPI, glycosylphosphatidylinositol; Gwt1, GPI-anchored wall transfer protein 1; HSCT, hematopoietic stem cell transplant; IC = invasive candidiasis; ICU, intensive care unit; IV = intravenous; MOA – mechanism of actions; PO = per os; qd, once daily; SOC = standard of care; SOT, solid organ transplant; VVC – vulvovaginal candidiasis

* Kluyveromyces marxianus