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Overcoming drug-resistant yeast infections

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New approaches to the treatment of candidiasis are in development as levels of drug resistance among *Candida* sp. continue to climb. One approach is a new drug that, say its developers, possesses a unique dual mechanism of action to overcome strains resistant to standard imidazole and triazole therapies. PLD118 was originally synthesized by scientists at Bayer (Leverkusen, Germany), but is undergoing further development by the Pliva Pharmaceutical Company (Zagreb, Croatia).

Candidiasis

Candidiasis, especially that caused by *Candida albicans*, is extremely common; however, it is unclear why these usually harmless commensal organisms become pathogenic. Candidiasis can occur in most parts of the body although oral and vaginal candidiasis (thrush) are the most common. Infection is particularly common in young children and elderly people following antibiotic treatment. People with diabetes and suppressed immune systems are also vulnerable to candidiasis.

Most infections are little more than troublesome local infections, but for immunosuppressed patients they can become systemic and life-threatening, especially if they are infected with a drug-resistant strain.

A new mechanism of action

PLD118 is a derivative of cispentacin, a cyclic β-amino acid originally isolated from *Bacillus cereus* and subsequently found to be active against *Candida* sp. [1]. It is actively accumulated by sensitive fungi and inhibits intracellular isoleucyl tRNA-synthetase, a vital enzyme in protein synthesis and cell growth (Fig. 1) [2,3].

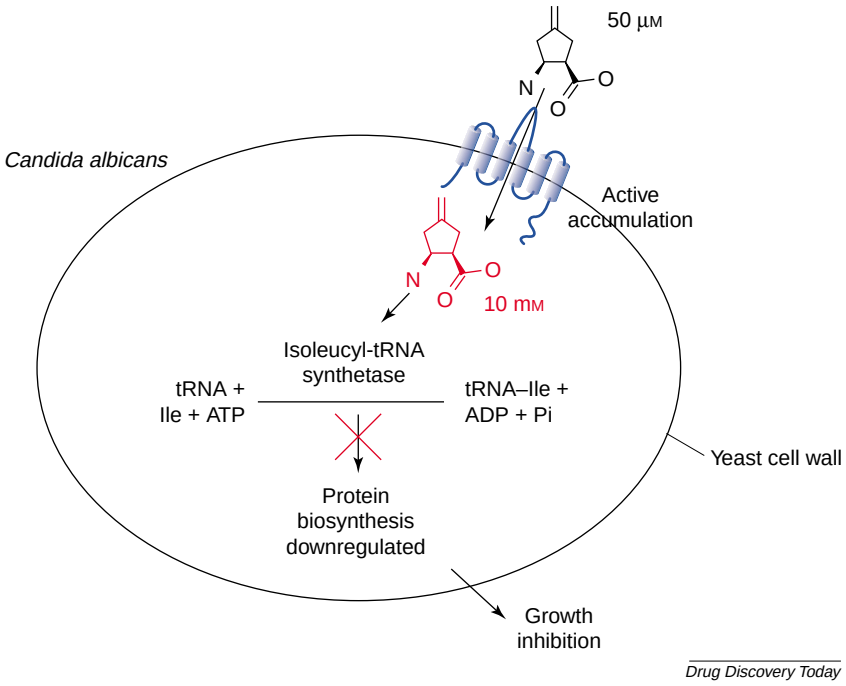

Figure 1. Mechanism of action of PLD118 [(–)-(1*R*,2*S*)-2-amino-4-methylene-cyclopentane carboxylic acid]. PLD118 is actively accumulated by sensitive fungi and inhibits intracellular isoleucyl tRNA-synthetase, a crucial enzyme for protein synthesis. Figure kindly provided by Pliva Pharmaceutical Company (Zagreb, Croatia).

The uptake of PLD118 is mediated by an H^+-coupled amino acid transporter with specificity for the branched-chain amino acids isoleucine, leucine and valine [2]. The transporter concentrates PLD118 within *C. albicans* 200-fold when the yeast is grown in nitrogen-rich media. Researchers have shown that PLD118 is accumulated in all *Candida* species investigated and *Streptomyces cerevisiae*, but not in *Aspergillus fumigatus*. The accumulation of PLD118, therefore, appears to be yeast specific [2,4].

One of the mechanisms by which *Candida* sp. become resistant to azole antifungals is to increase drug efflux by altering the expression of efflux pumps. However, because PLD118 simply diffuses out of yeast cells after having its toxic effect [2], this type of resistance will probably not reduce the effectiveness of the drug, although data on efflux-related resistance are limited. Moreover, because the mechanism of action of PLD118 differs from that of currently available antifungal agents, the drug could avoid the problem of cross-resistance.

Clinical development

PLD118 has a minimum inhibitory concentration (MIC_{90}) for *C. albicans* of 4–32 mg ml^{-1} *in vitro*, although activity varies depending on the medium used to grow the yeast [5]. Animal studies suggest promising pharmacokinetics with high bioavailability, low binding to plasma proteins and no active metabolites [3]. Moreover, according to scientists

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at Pliva, PLD118 does not appear to be metabolized via the cytochrome P450 (CYP450) enzyme system and, therefore, unlike the azole antifungals, could carry a low risk of interactions with other drugs. This could be an important advantage in the treatment of patients taking multiple drugs.

An oral formulation of PLD118 is now undergoing Phase I clinical evaluation. Scientists at Pliva believe that patients with *Candida* infections, including non-albicans strains and azole-resistant strains, could benefit from treatment with PLD118, and these patients will be studied in ongoing and future clinical trials.

Other new antifungal compounds

A variety of antifungal agents are currently under investigation as treatments for candidiasis. Some are variations on the triazole theme, such as voriconazole, posaconazole and ravuconazole, but others, such as PLD118, offer completely new approaches to treating the infection.

The triazole antifungal drugs inhibit fungal CYP450-dependent lanosterol 14-α-demethylase, which is essential for the conversion of lanosterol to ergosterol in fungal cell membranes. Inhibition of this enzyme causes an accumulation of toxic ergosterol precursors in membranes and thus inhibits cell growth. The newer triazole drugs have a broader spectrum of activity than the older drugs that includes *Aspergillus* sp. and possibly other fungi as well as *Candida* sp. [6].

New classes of antifungal drugs – echinocandins, pneumocandins, sordarin derivatives, and the nikkomycins – take different approaches [6]. The echinocandins (caspofungin, anidulafungin, mycofungin) kill fungal cells by destabilizing their cell walls. This is achieved by inhibiting the 1,3-β-D-glucan synthase complex that is responsible for incorporating glucan fibrils into cell walls. Because glucan fibrils are not present in human cells, this is a promising fungi-specific drug target. So far, the echinocandins show promise against a variety of fungi and triazole-resistant *Candida* sp. [6].

The sordarin derivatives show most promise against *Candida* infections. These drugs block fungal protein synthesis by inhibiting elongation factor-2, which promotes the movement of the ribosome along mRNA. Finally, the nikkomycins are another new class of antifungal agents that competitively inhibits chitin synthase and blocks the formation of chitin, a component of the fungal cell wall. Although the nikkomycins have shown activity against some fungi, they have not, to date, shown significant activity against yeasts such as *Candida* sp. [6].

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Viral Trojan horse for combating tuberculosis

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The emergence of pathogenic bacteria resistant to one or more antibiotics has outpaced the development of new drugs. Using bacteriophage, Raul Barletta (Dept of Veterinary and Biomedical Sciences, University of Nebraska, Lincoln, NE, USA) and colleagues at the California Pacific Medical Center (San Francisco, CA, USA) have devised a promising new approach to killing the intracellular pathogens *Mycobacterium avium*, which commonly afflicts AIDS patients, and *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Their findings were presented at the *41st Interscience Conference on Antimicrobial Agents and Chemotherapy* hosted by the American Society for Microbiology in Chicago, IL, USA [1].

Why bacteriophage?

Bacteriophage (phage) are viruses that infect their specific bacterial host, but do not infect other bacterial species or