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LTX-109 - A Rapidly Fungicidal Antimicrobial Drug

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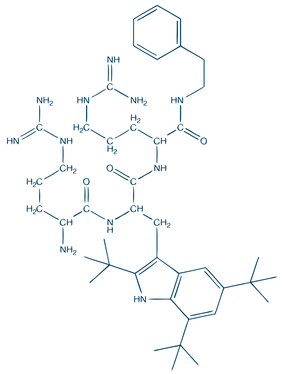
Lytix Biopharma

LTX-109

- **A synthetic protein fragment – a peptidomimetic**
- **High stability against degradation**
- **Produced in large scale**
- **Low cost of synthesis**



(LTX-109 strukturbilde)

Introduction

Candida species are the most common cause of fungal infections ranging from superficial infections to invasive diseases. In particular, *Candida* affects high-risk patients who are either immunocompromised or critically ill.

LTX-109 is a novel antimicrobial agent initially being developed as a topical agent for impetigo, nasal decolonisation and biofilm infections. The drug is a mimetic of a membrane-active host defence peptide having a membrane lysing mode of action causing rapid membrane disruption. LTX-109 shows a broad efficacy against a range of pathogens including Gram+ and Gram÷ bacteria, yeasts and fungi.

The compound is equally effective against antibiotic-resistant species such as methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant *Enterococci* (VRE) and multi-resistant *Pseudomonas isolates*. LTX-109 shows a low propensity for resistance development and no in vitro cross-resistance with other classes of antibiotics.

Objective

There is a medical need for new and fast-acting antifungals to treat various fungal diseases. The present study demonstrates the potential fungicidal effect of LTX-109 by using minimal fungicidal concentration (MFC) and time-kill kinetics experiments.

Methods

MFCs for LTX-109 were determined in broth (MOPS-buffered RPMI 1640 without sodium bicarbonate but containing phenol red and glutamine) according to CLSI criteria with a doubling dilution concentration range (0.25 – 256 mg/L) for 15 different fungal strains and species and compared to that of amphotericin B (0.015 – 16 mg/L). *Candida parapsilosis* (ATCC 22019) was included as an extra control reference strain for amphotericin B.

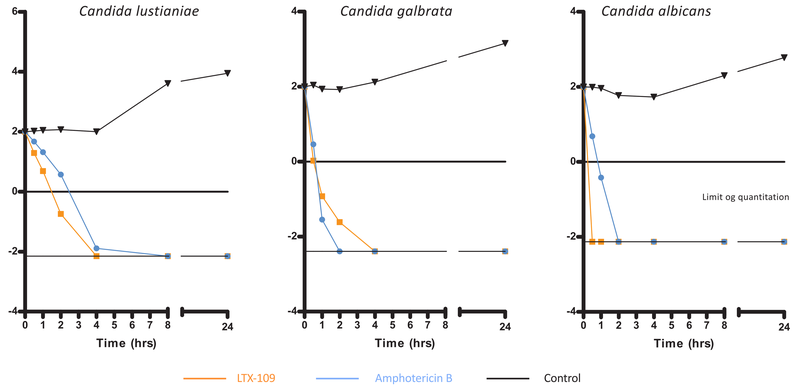
Time-kill experiments were performed in RPMI 1640 broth on three test Candida species, C. albicans, C. glabrata and C. lusitaniae, at four concentrations (1, 2, 4 and 8xMIC). Viable counts (Log10 percentage survival) were determined between 0 and 24h after inoculation.

Results

LTX-109 is overall fungicidal

Species	Strain ref	Amphotericin B		LTX-109	
		MIC (mg/L)	MFC (mg/L)	MIC (mg/L)	MFC (mg/L)
Alternaria alternata	NCPF 7147	1	2	4	4
Candida albicans	ATCC 90028	1	2	16	32
Candida glabrata	NCPF 3309	2	2	8	16
Candida lusitaniae	NCPF 3516	2	2	4	16
Epidermophyton floccosum	NCPF 5011	0.25	0.25	4	8
Microsporum audounii	NCPF 436	1	1	8	16
Microsporum canis	NCPF 177	0.5	0.5	8	32
Microsporum ferrugineum	NCPF 988	0.12	0.25	8	8
Mucor circinelloides	NCPF 2743	1	1	8	8
Sporothrix schenckii	NCPF 7075	1	1	8	8
Trichophyton interdigitale	NCPF 175	1	1	8	8
Trichophyton mentagrophytes	NCPF 224	1	1	8	8
Trichophyton rubrum	NCPF 118	0.5	0.5	8	16
Trichosporon cutaneum	NCPF 3853	0.25	0.25	2	2
Candida parapsilosis	ATCC 22019	1	1	8	8

LTX-109 is as fungicidal as amphotericin B



LTX-109 at 8xMIC (shown in figs.) was as fungicidal as amphotericin B, demonstrating a 3-log reduction within 4 hours in time-kill kinetics experiments.

Candida lusitaniae:
- LTX-109 and amphotericin B were non-fungicidal at 1 and 2xMIC, but fungicidal at 4 and 8xMIC with LTX-109 being slightly more active

Candida glabrata:
- LTX-109 was fungicidal at 2xMIC and above. Both compounds were more rapidly fungicidal against *C. glabrata* than to *C. lusitaniae*

Candida albicans:
- LTX-109 and amphotericin B were fungicidal at 1xMIC and above. Both agents demonstrated better activity against this *Candida* species compared to the two others

Conclusions

- LTX-109 is a fungicidal antimicrobial drug
- LTX-109 is as fungicidal as amphotericin B in time-kill experiments
- These data suggest a potential application for LTX-109 in treatment of fungal infections
- Further studies to document the antifungal efficacy in humans are envisaged

LTX-109

- Novel mechanism of action and broad spectrum of activity
- Low propensity for resistance development and active against drug-resistant strains
- Effective against fungal and bacterial biofilms
- Superior efficacy compared to market leaders (Bactroban®, Fucidin®, Altabax®/Altargo®)
- In Phase I and two Phase I/IIa trials LTX-109 has demonstrated good tolerance and minimal systemic bioavailability
- LTX-109 has demonstrated Proof-of-Concept in decolonisation of nasal MRSA/MSSA.
- Currently a Phase II Proof-of-Concept study in a large population with impetigo is ongoing, where results are expected in first half of 2014

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