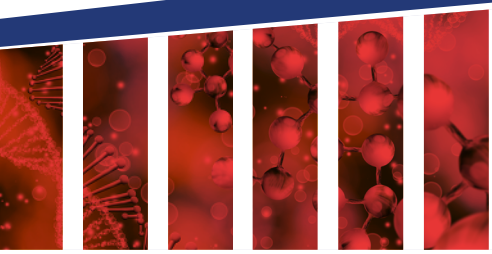


SYNERGISTIC DRUG COMBINATION FOR TREATING DRUG-RESISTANT TUBERCULOSIS BY INHALATION

KEYWORDS

- Mycobacterial infections treatment
- MDR and XDR-Tuberculosis
- Dry powder formulation for inhalation treatment

Collaboration type
Collaborative R&D (preclinical, early clinical)
Licensing

IP Status
EA 034983 B1 granted 14/04/2020, EP3237011 A1 (BE, CH, DE, FR, GB, IE, NL) granted 10/11/2021

WO2020/136276 pending AU, BR, CA, CN, EP, HK, IL, IN, JP, KR MX, RU, SG, US, ZA

The inventors
Prof. Véronique FONTAINE
Prof. Nathalie WAUTHOZ

CONTACT

KNOWLEDGE TRANSFER OFFICE

Knowledge Transfer Office
ULB Research Department

Frédéric Pierard
IP Manager
+32 (0)2 650 32 26
frederic.pierard@ulb.be

www.ulbkto.be

THE TECHNOLOGY IN A NUTSHELL

New synergistic drug combination of Vancomycin and Orlistat formulated as dry powder for inhalation treatment of *Mycobacterium tuberculosis* including multi-drug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis.

STATE OF THE ART

Tuberculosis (TB) is a highly contagious disease condition caused by inhalation of aerosolized roplets of *Mycobacterium tuberculosis* (Mtb). According to the World Health Organization (WHO), more than 2 billion people worldwide are infected with Mtb. In 2014, 9.6 million people fell ill with TB and 1.5 million died from the disease. Unfortunately, Mtb has a high intrinsic resistance to the majority of clinically used antibiotics, which severely limits treatment options. This intrinsic resistance has been attributed, in part, to its impermeable, hydrophobic cell envelope that acts as a barrier to entry of certain antibiotics. Moreover, MDR and XDR strains have emerged with limited therapeutic option. Therefore, there is an urgent and unmet need to develop new treatments for TB and its resistant strains.

THE INVENTION

New specific combinations between a lipase inhibitor, Orlistat, and a glycopeptide, Vancomycin, display synergistic mycobacteriostatic and/or mycobactericidal properties, thanks to the action of Orlistat on PDIM of the cell envelope enabling the diffusion of Vancomycin to inhibit the peptidoglycan synthesis of this cell envelope. The specific combination of Vancomycin and Orlistat also displays significant efficiency against drug susceptibility, multidrug-resistant and extensively drug-resistant mycobacterial strains providing a new array of combination treatments to be used as alternative or adjuvant to established therapies.

In order to overcome the poor oral permeability of those drugs, an innovative formulation of the drug combination was developed and paves the way to treatment of TB by inhalation. The corresponding dry powder formulation is based on high drug dosage and a triglyceride excipient already approved for human use in inhalation and is well tolerated *in vivo* in mouse lungs. It also enables to formulate combinations including additional drug compounds used in first line treatment such as rifampicin and shows significant *in vivo* efficiency in preclinical murine models.

KEY ADVANTAGES OF THE TECHNOLOGY

- New combination treatment against all mycobacteria including MDR and XDR-TB.
- *in vitro* and *in vivo* tolerance and efficacy demonstrated in pre-clinical studies.
- Dry powder formulation enabling inhalation treatment of TB.

Cofinancé par l'Union européenne
Wallonie

TECHNOLOGY READINESS LEVEL: 1 2 **3** 4 5 6 7 8 9

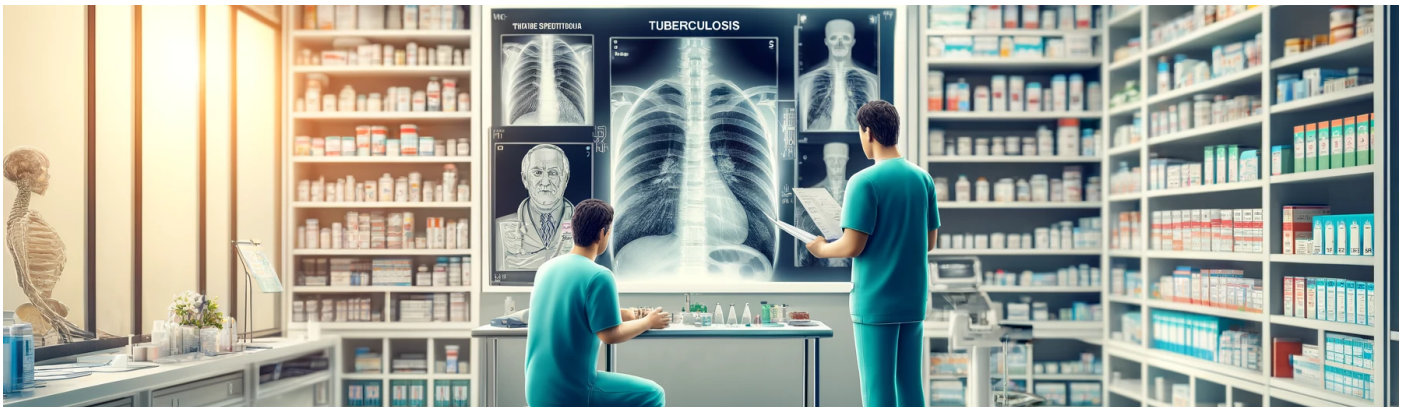
LABORATORIES:

PHARMACEUTICAL MICROBIOLOGY AND HYGIENE LAB – PROF. V. FONTAINE

The research activities of this unit are related to the study of microorganisms and antimicrobial defenses, among others on the study of microbial invasion and the development of new therapeutics against bacteria, viruses or cancers induced by microorganisms. In virology, our studies are mainly focusing on human papillomaviruses (HPV). On the opposite, in bacteriology, we are focusing our research on mycobacteria.

UNIT OF PHARMACEUTICS AND BIOPHARMACEUTICS – PROF. N. WAUTHOZ

The research activities of this unit are related to the development of innovative dry powders for inhalation, using well tolerated excipients, and scalable particle engineering techniques. The aim is to overcome the limitations of the actual therapies by optimizing the factors affecting the adherence of the patient to the inhaled treatment. Depending on the requirements of the disease: high-drug dosage, high-drug stability, cell targeting, controlled release are properties that can be applied to the design of the microparticles to optimize the frequence, the efficacy and reduce the side effects of the medications.



RELEVANT PUBLICATIONS

> Increased Vancomycin Susceptibility in Mycobacteria: a New Approach To Identify Synergistic Activity against Multidrug-Resistant Mycobacteria. Soetaert K., Rens C., Wang X. M., De Bruyn, J., Laneelle, M. A., Laval, F., Lemassu, A., Daffe, M., Bifani, P., Fontaine, V., & Lefèvre, P. (2015). Antimicrob Agents Chemother. 2015;59(8):5057-5060.

> Effects of Lipid-Lowering Drugs on Vancomycin Susceptibility of Mycobacteria. Rens C., Laval F., Daffé M., Denis O., Frita R., Baulard A., Wattiez R., Lefèvre P., & Fontaine V. (2016). Antimicrobial agents and chemotherapy, 60(10), 6193–6199.

> *In vitro* and *in vivo* local tolerability of a synergistic antituberculosis drug combination intended for pulmonary delivery. Faustine Ravon,Elena Menchi,Coralie Lambot, Sahar Al Kattar, Selma Chraibi, Myriam Remmelink, Véronique Fontaine, Nathalie Wauthoz. J Appl Toxicol. 2023 Feb;43(2):298-311

> Efficient and Innovative Dry Powders for Inhalation of a Synergistic Combination to Combat Mycobacterium tuberculosis in infected Macrophages and Mice. Faustine Ravon, Emilie Berns, Isaline Lambert, Céline Rensx, Pierre-Yves Adnet, Mehdi Kiass, Véronique Megalizzi, Cédric Delporte, Vanessa Mathys, Samira Boarbi, Cédric Delporte, Nathalie Wauthoz, Véronique Fontaine.

ULB KTO
KNOWLEDGE TRANSFER OFFICE
www.ULBKTO.be