Title: Development of functionalized nanocarriers for drug targeting in tuberculosis

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Introduction: Tuberculosis (TB) is still a major public health problem globally. About one-quarter of the world's population is infected with this disease (1). TB is caused by *Mycobacterium tuberculosis* intracellular bacterium which can survive and persist in the host cell macrophages. Eliminating the bacteria inside the host cells is very challenging and improved methods are needed (2). Our approach is to target the macrophages and reach the intracellular bacteria as site of action with nanotechnology-based drug delivery (Fig. 1).

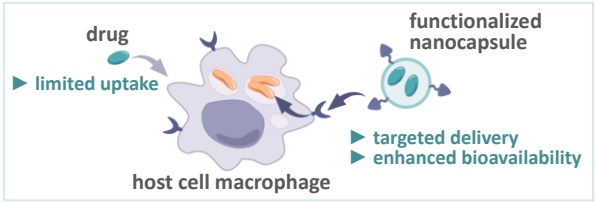

Fig. 1. Functionalized nanocapsule for macrophage targeting

Methods: The biocompatible and biodegradable chitosan polysaccharide was functionalized with macrophage targeting ligands, such as formyl peptide receptor and mannose receptor targeting ligands. Anti-TB drug (bedaquiline, BQ) loaded nanocapsules (NCs) based on the functionalized chitosan were prepared and characterized. The *in vitro* cytotoxicity and cellular internalization of the NCs was determined, as well as their efficiency to inhibit both extracellular and intracellular bacteria.

Results: The optimization process of the preparation of the functionalized NCs resulted in a simple method providing high yield, enhanced drug-loading and stability. The BQ loaded NCs showed outstanding activity on extracellular bacteria. Moreover, they were able to eliminate the intracellular bacteria at a very low concentration without cytotoxicity on the host cell macrophage model while the non-encapsulated BQ showed cytotoxicity. The functionalized NCs had higher internalization rate compared to the ungrafted NCs on the host cell model. This difference between the NCs was not observed in case of lung epithelial model cells. The internalized NCs mostly colocalized with lysosomes.

Conclusion: Applying functionalized NCs outstanding intracellular activity was achieved with improved selectivity towards the bacteria. These NCs are promising tools for targeting macrophages and eliminate intracellular bacteria in TB.

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References: (1) WHO Global tuberculosis report 2021, ISBN: 9789240037021. (2) Baranyai Z, Soria-Carrera H, Alleva M, Millán-Placer AC, Lucía A, Martín-Rapún R, Aínsa JA, Martínez de la Fuente J. Adv Therap. 2021, 4, 2000113.

Presenter biography: Zsuzsa Baranyai is a postdoctoral researcher at the Institute of Nanoscience and Materials of Aragon in Zaragoza, Spain. She received her Ph.D. at the Eötvös Loránd University (Budapest, Hungary). Her main research interests focus on drug-peptide conjugates and targeted drug delivery against infectious diseases and cancer.

Learning Objectives:
Chose the optimal method for nanoparticle functionalization

Understand the advantage of antitubercular agent encapsulation
Evaluate the differences in the biological activity between formulations

Keywords: intracellular, nanoparticle, *in vitro* models