One hundred years after the discovery of antimicrobials and antibiotics, intracellular bacterial pathogens remain a major cause of global morbidity and mortality. This is due to the complex and intricate ability of these pathogens to undergo intracellular replication while evading host cell immune defense. Bacterial agents such as *Legionella pneumophila*, *Francisella tularensis*, and *Mycobacterium tuberculosis*, as the causative agents of Legionnaires' disease, pulmonary tularemia, and tuberculosis (TB), respectively, contribute to this burden. Moreover, these agents are weaponizable pathogens due to their aerosolizability.

TB represents a global health problem, although a potentially curative therapy has been available for approximately 50 years; this intracellular disease affects approximately 1 in 3 people worldwide, with over 10 million new cases per year and one death every three minutes. TB can usually be treated with a 6- to 9-month course of combined therapy. The necessity of using a cocktail of anti-TB drugs and the long-term treatment schedules required for conventional therapy, however, result in poor patient compliance; therefore, the risk of treatment failure and relapses is higher. Hence, improved drug delivery strategies for the existing drugs can be exploited to shorten the duration of TB treatment and avoid the selection of drug-resistant mutants.

In this context, nanoparticle (NP) technology has emerged as one of the most promising approaches for overcoming the above-listed shortcomings associated with intracellular infection therapies, because of the unique physicochemical properties of NPs. Fabrication of nanocarriers for drug delivery into the lungs, the primary site of TB infection, offers an elegant technique for therapy. Nanobead-based structures follow the route of particulate matter, including intracellular pathogens, and they are preferentially taken up by phagocytes, which further enhances their intracellular targeting. Similarly, the development of effective and safe nanobead-based interventions can be particularly relevant to increasing antibacterial concentrations within the infected site and reducing doses in the systemic circulation, thereby avoiding off-target toxic effects.

Thus, this work utilizes graft and block amphiphilic copolymers to explore self-assembled drug delivery systems for the treatment of intracellular infections. The aim of this thesis was to develop and comprehensively analyze both graft and block copolymer-based assemblies capable of targeting macrophages; nanoarchitecture studies, cytotoxicity analyses and biological system interactions were the main pillars.

By way of a comprehensive analysis based on several complementary instrumental techniques, it was demonstrated that the graft and block polymeric matrices were capable of self-association while providing interesting colloidal behavior, passive macrophage targeting, and low cytotoxicity. Rifampicin-loaded NPs were found to be well tolerated in zebrafish and mice while providing improved anti-TB efficiency. We show that these results are due to improved pharmacokinetic and pharmacodynamic parameters.