A novel hierarchical *in silico* approach for the prediction of drug and vaccine targets against *Chlamydophila pneumoniae*

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Chlamydophila pneumoniae is one of the most important and well-studied gram-negative bacterial pathogens. This obligate intracellular bacterium is a major cause of pneumonia and is associated with the development of other respiratory diseases in humans, including Chronic Obstructive Pulmonary Disease (COPD), chronic asthma, pharyngitis and bronchitis. According to the World Health Organization, COPD is predicted to become the third leading cause of death by the year 2030. Although much is known about the biology of *C. pneumoniae*, particular attention should be given to the development of strategies to contain infection by this bacterium. The era of Next Generation Sequencing (NGS) is pushing forward genome-based studies for the prediction of therapeutic targets against a variety of diseases caused by pathogenic microorganisms. To date, 13 complete genome sequences of *C. pneumoniae* were made available on NCBI, allowing us to conduct the search for candidate therapeutic targets against this bacterium. For this, we performed a comparative genomic analysis using a novel hierarchical approach. In Phase I, four different sets of proteins were mined through analysis of chokepoint, pathways, virulence factors, resistance genes and protein networks. In Phase II, selected protein sets were filtered through subtractive channel analysis to find out targets that are likely to be essential for the survival of the pathogen and non-similar to proteins present in the human intestinal microbiome. Finally, in Phase III, the candidate targets were qualitatively characterized by analyzing cellular localization, broad spectrum, interactome involvement, functionality, and druggability. A total of 595 non-human homologous proteins was identified and submitted to reverse vaccinology, evaluating antigenic properties of vaccine candidates. These proteins also went through subtractive and modelomics approaches for drug target identification. Based on these analyses, we classified 36 gene products as secreted proteins, putative surface-exposed proteins or membrane proteins. By using modelomics, a total of 8 cytoplasmic proteins constituting distinct quality model were selected as putative drug targets. These proteins were subjected to virtual screening using twoa different compound libraries extracted from the ZINC database and plant-derived natural compounds. The proposed drug molecules exhibit favorable interactions, lowered energy values and high complementarity with the predicted protein targets. The outcome of this study constitutes a preliminary step for the development of novel strategies to combat human infections caused by *C. pneumoniae*.