ACRONYM: **ABIMMUNE**

Title: **Repurposing disused antibiotics with immune modulators as antimicrobial strategy for respiratory tract infections**

Keywords: **immune-modulators; vulnerable patients; innate immunity; phagocyte activation; autophagy; toll-like receptor**

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Abstract:

Bacterial respiratory infections represent a real threat to public health worldwide, especially in hospital-acquired situations where patients frequently present several co-morbidity factors. Although antibiotics are recognized as the most effective therapy, treatments are often associated with failure due to bacteria that are resistant to multiple first-line antibiotics, and patients who are immune compromised.

The proposal ABIMMUNE aims to enhance the therapeutic arsenal against respiratory infections. The idea is to combine Neglected and Disused AntiBiotics (ND-AB) with registered immune modulators that impact host innate immunity. ABIMMUNE will select (i) ND-AB that are not used as first-line antibiotics in standalone treatment of respiratory infections, and (ii) marketed immunostimulatory drugs that target distinct immune pathways including macrophage activation, neutrophil potentiation, immuno-metabolism, or pattern-recognition receptors.

There are several advantages to this approach: first, antibacterial activity of innate immunity is independent of antibiotic-resistance. Second, it is difficult for the pathogen to develop resistance to innate immunity since this latter involves multiple killer cells and antibacterial molecules, and bacteria would have to develop an entirely new suite of interactions with the host. Third, targeting host innate immunity may reinstate some immune defense in vulnerable patients. Fourth, innate immunity and ND-AB may synergize to kill bacteria thereby allowing for dose reduction of ND-AB and potentially reducing side effects. Fifth, using ND-AB may globally dampen the proportion of bacteria resistant to first-line antibiotics, allowing their maintenance in clinics.

These combination therapies will be tested in clinically relevant models of respiratory infections with the leading Gram-positive and Gram-negative bacteria causing community- and hospital-acquired pneumonia. ABIMMUNE will validate in vitro the proof-of-concept of additive or synergistic activity of ND-AB and immunostimulatory drugs with appropriate host target cells and collection of bacterial isolates. The impact on emergence and maintenance of resistance to first-line antibiotics and ND-AB will also be evaluated. Experiments will be accompanied by translational PK/PD modeling analyses to quantify the joint ND-AB/immune modulators interaction for selection of the most promising regimens for pneumonia in the context of immune vulnerability.