Infection diseases pose a serious global health threat. Currently used antibiotics to treat common infections are becoming ineffective due to bacteria becoming resistant to antimicrobial drugs. *Staphylococcus aureus* is an important human pathogen causing a range of diseases including life-threatening endocarditis, osteomyelitis and sepsis. This pathogen is not only becoming more antibiotic-resistant but also researchers have not been able to deliver an effective vaccine to protect us from staphylococci. Therefore, we urgently need to provide alternative therapies to combat this deadly pathogen. One of the novel strategies is to develop drugs that will boost our immune system to clear bacteria more effectively, rather than directly target bacteria using antibiotics.

Our immune system consist of multiple specialized cell including professional phagocytes (macrophages and neutrophils) which primary objective is to capture invading microbes by ingesting them and subsequently killing them within. To this end, phagocytes generate hostile environment to internalized microbes such as acidic pH or production of reactive oxygen species (ROS). Additionally, in concert with acidification and ROS generation, to inactivate intracellular pathogens, phagocytes utilize an ancient cellular survival response, called autophagy. However, my previous research and work of others have shown that internalized staphylococci could exploit autophagic response to their benefit and able to hide within infected phagocytes. To make things worse, phagocyte which are mobile cells may serve as vehicles for the dissemination of staphylococci and subsequently cause disease in distant tissues. This demonstrates that the interaction between staphylococci and our immune system is more complex and in order to develop new therapeutics we need to understand disease progression by further investigating the process of infection.

Therefore in this work, I plan to study mechanisms underlying the autophagic response to staphylococci, generation of free oxygen radicals and acidification and their relations to each other. I will also determine the exact role of each of these processes in professional phagocytes infected with staphylococci. Using the acquired knowledge during this project, I will subsequently aim to modulate the immune response especially autophagy to boosting microbial killing and improve disease outcomes.

In order to achieve the goals of this project I will use a range of models of infection, phagocytic cells isolated from healthy volunteers and animals - mice and zebrafish which recapitulate the complex process of infection occurring in humans. The larval zebrafish model which I developed previously, provides a possibility of non-invasive visualization of the immune response in living body due to their optical transparency. In addition, zebrafish offer an affordable system allowing us to study the role of multiple genes, using genetically modified fish lines. The results obtained in zebrafish will be confirmed in mammalian model of infection, even more closely resembling humans.

I believe that this project will help us to understand the complexities of how *Staphylococcus aureus* causes disease. I am convinced that a more detailed understanding of disease progression and the action of the immune system will help us to develop new therapeutic strategies to combat bacterial disease and antibiotic resistance with important consequences for patient well-being.