How complement molecules kill bacteria

Summary of the context and overall objectives of the project

Problem/issue
Antibiotic-resistant bacteria form a serious threat for public health and novel treatment strategies are needed urgently. One way to achieve this is to improve the activity of our immune system via therapeutic antibodies or vaccination. However, such developments are severely hampered by the lack of mechanistic insights into anti-bacterial immune mechanisms.

Overall objective
This grant aims to unravel the molecular mechanisms underlying bacterial killing by the human immune system. In particular, we investigate the molecular functioning of the complement system, a large protein network in plasma that plays an essential role in the immune response against all invading bacteria. Complement rapidly labels bacteria for phagocytosis by immune cells and directly kills Gram-negative bacteria via pore formation (Membrane Attack Complex (MAC)). Within the ERC project, we aim to provide insight on how Gram-negative bacteria are directly killed by complement. We have recently established novel methods to study the Membrane Attack Complex (MAC) allowing us to provide insight...
into MAC-dependent killing of bacteria.

Importance for society
A better understanding of complement will improve desired complement activation by therapeutic antibodies and vaccination strategies in infectious diseases. Furthermore, our studies will create new avenues for blocking the undesired complement activation during systemic bacterial infections and sepsis.

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

So far we gained crucial insights into how complement kills bacteria. We find that C5 convertases are crucial for insertion of pores into bacterial membranes. Structural studies are ongoing to elucidate the molecular mechanism. Studying the collaboration with antibiotics revealed that MAC can allow antibiotics considered specific for Gram-positives can be potentiated for killing of Gram-negative bacteria. Furthermore, the project has resulted in development of novel methodologies for functional characterisation of convertase enzymes and permeabilization of bacterial membranes.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the project so far)

So far we have managed to develop novel methodologies to functionally characterize C5 convertase enzymes and study permeabilization of bacterial membranes at a cell population level. We have already obtained new insights into how complement and antibiotics can work together to kill bacteria. By the end of this project we expect to have obtained unique biochemical insights into C5 convertases and understanding of how the Membrane Attack Complex kills bacterial cells.