Laudatio

held by Prof. Kai Simons

Max-Planck-Institute of Molecular Cell Biology and Genetics, Dresden, Germany

at the prize ceremony in Heidelberg on May 25, 2011

for Assistant Professor Suzan Rooijakkers, PhD

University Medical Center Utrecht, Department of Medical Microbiology

Winner of the Eppendorf Award for Young Investigators 2011

We are constantly under attack by pathogenic bacteria that try to invade our body. These invasion attempts are most of the time successfully halted by a complex battery of defence mechanisms. However, during evolution of pathogenic bacteria these have evolved means to escape from these counter measures. There is a continuous battle going on that we usually win. And when the bacteria are on the winning streak, we have antibiotics at our disposal that can be used to clear the body of the invaders. One emerging problem in modern medicine is the development of resistance. Bacterial resistance is a menace in today's clinical practice. Unfortunately, we are running out of antibiotics that can overcome this problem.

Therefore, it is important to understand the mechanisms by which bacteria fool our defences. This is the area in which our Eppendorf Award winner has been active. Suzan Rooijakkers has been studying Staphylococcus aureus, an important pathogen that causes community- and hospital-derived infections that complicate wound healing, lead to food poisoning and cause serious disease such as blood sepsis or endocarditis. The emergence of strains resistant to antibiotics such as methicillin makes this bacterial pathogen a widely acknowledged threat to public health. In her PhD work she studied proteins that Staphylococcus aureus secretes. The bacterium has evolved a bacteriophage-encoded pathogenicity gene cluster that encodes for human-specific violence proteins. She found out that one of these proteins, named SCIN has a strong anti-phagocytic effect. This protein is secreted from the bacterium and blocks phagocytosis by human neutrophils and does so by acting on the complement factor C3 convertase. Complement is one

of the key components of the innate immune defence against pathogens. The activation of complement by e.g. microbe-bound antibodies initiates a cascade of protein-protein interactions and proteolytic cleavages, which result in covering of the bacterium by complement factors that then bind to receptors on neutrophils or macrophages that phagocytose the bacteria and kill them. When SCIN interacts with C3 convertase and inhibits this crucial enzyme in the complement cascade, phagocytosis of the bacteria cannot occur efficiently. Thus, Staphylococcus aureus evades this important host defence mechanism by inactivating the complement cascade. Suzan Rooijakkers has continued this pioneering work by determining the atomic structure of SCIN in collaboration with Piet Gros. Binding of SCIN induced dimerization of the C3 convertase and this dimeric complex is inactivated so that it cannot mediate the cascade.

Further work by the research group of Suzan Rooijakkers has identified a second gene cluster in Staphylococcus aureus that encodes for immune modulators. She found four novel convertase inhibitors that in concert with additional complement modulators block the complement cascade. The redundancy of this system shows how well equipped the bacteria are to carry out their detrimental work when invading our body. These new modulators are promising drug targets for the development of antibiotic drugs that could prevent Staphylococcus aureus infections. One of the novel modulators, Ecb, also showed strong anti-inflammatory properties and could potentially have therapeutic potential in severe acute inflammatory diseases.

The pioneering work of Suzan Rooijakkers and her co-workers has been based on an intelligent mix of different technologies to unravel the clever tricks that bacteria have developed to get ahead in life. The aim of the research group is now to explore similar strategies in other bacteria and also in fungi to find out how they manage to overcome host defences. They will also engage in smart vaccine development to impair these evasion mechanisms in order to boost our own defences against infection.

Suzan Rooijakkers obtained her PhD from the Department of Microbiology, University Medical Center Utrecht under the supervision of Professor J.A. Y. van Strijp. She continued as a postdoc in Utrecht and then as an EMBO postdoctoral fellow she did a second post-doc in the laboratory of Professor Victor Nizet at the Department of Pharmacology and Drug Discovery, University of San Diego. In 2009 she returned to Utrecht where she is the head of bacterial complement evasion group at the Department of Medical Microbiology. She recently received a large VIDI grant from The Netherlands Organisation for Scientific Research (NOW).