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Daleke, M.H.

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SCOPE OF THE THESIS

The aim of the research described in this thesis was to investigate how proteins secreted by the mycobacterial type VII secretion systems are recognized and targeted for secretion, with main focus on the enigmatic PE and PPE proteins that are secreted via the ESX-5 system.

In **chapter 2** the *M. tuberculosis* PE protein LipY and its *M. marinum* homologue, which contains an N-terminal PPE domain, are shown to be exported to the surface of *M. marinum* by the ESX-5 secretion system. These two proteins are subsequently used as model substrates to investigate the role of the N-terminal PE and PPE domains in ESX-5 secretion. The role of the PE domain in secretion is further investigated in **chapter 3**, using the newly identified ESX-5 substrate PE_PGR33 as model.

Chapter 4 describes a detailed search for specific sequences that are required for ESX-5 secretion. In this study, secretion of the previously identified ESX-5 substrate PPE41 (83), and its partner PE25 is investigated. These two proteins form a complex for which the structure has been elucidated (127), and inspection of this structure allowed us to select flexible or exposed residues that might be involved in protein-protein interaction and secretion. The role of these residues and regions were examined by deletion and mutation analysis.

The study described in **chapter 4** resulted in the identification of a motif that is required for secretion via ESX-5, but which is not sufficient to direct the substrates to this system. This means that an additional signal must be present that targets the substrates to the correct secretion machinery. Proteins destined for export across the inner membrane or out of the bacterial cell are often delivered to their cognate secretion system by cytosolic chaperones (131-133). In **chapter 5**, we characterize the function of the cytosolic ESX-5 system component $EspG_5$, and investigate if this protein interacts with substrates of ESX-5.

Finally, the results obtained in this thesis are summarized and discussed in **chapter 6**.