PUBLISHABLE EXECUTIVE SUMMARY

Infectious diseases remain one of the largest causes of death in the world. Among infectious diseases, tuberculosis is responsible for the greatest number of deaths. Each year, 54 million people are infected with Mycobacterium tuberculosis, 6.8 million develop clinical disease and 2.4 million people die of tuberculosis. Tuberculosis is responsible for 5% of all deaths worldwide.

Vaccines against tuberculosis are urgently needed. CD4 T cell responses play a major role in the generation of acquired immunity against *M. tuberculosis*. There is mounting evidence from animal studies that CD8 T cells are involved in the control of latent *M. tuberculosis* infection and it is increasingly recognised that CD8 cytotoxic T cells (CTL) also contribute to optimal host defense against mycobacteria. Relatively little has, however, been published on the functional role of mycobacteria-specific CD8 T cells in humans, nor on the actual mycobacterial antigens and epitopes targeted by these killer cells, and only a few CTL responses against TB have been identified. The object of this proposal is to perform a complete antigen- and epitope- discovery of relevance for human immune CTL responses against *M. tuberculosis*.

Thus, we have so far discovered 129 new epitopes of which 71 are HLA-A2-, 17 HLA-A3- and 41 HLA-B7 -restricted peptides. These peptides were found to be capable of inducing CD8 T cell proliferation. Interestingly, 44 of the 71 HLA-A2- binding Mtb peptides were recognized by more than one donor. Furthermore, 499 peptides selected by our prediction algorithms have been tested for binding to HLA class I molecules and 435 of these have been shown to bind with an affinity of better than 500nM, which is the generally accepted threshold for a peptide to be antigenic. Moreover, we have generated a high quality shotgun-expression library representing the whole genome of the MTB-strain H37Rv and used it to screen blood samples. Using this method, 37 different antigens could be identified and characterized. In the last year of the project, we have performed in vivo immunization studies in HLA-A2 transgenic mice, investigating immune recognition of the most promising HLA-A2- binding Mtb peptides. The results obtained in this project provide new target epitopes for the development of vaccines against TB.

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