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DEVELOPMENT OF A SYNTHETIC VACCINE AGAINST MALARIA SPOROZOITES

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Protetive immunity against rodent, simian and human malaria sporozoites is acquired by immunization with irradiated sporozoites (1). Passive transfer of antibodies specific for the repeat domain of the immunodominant surface protein of sporozoite, the curcumsporozoite (CS) protein, confers protection against challenge with viable sporozoite (2). Furthermore, active immunization of mice with synthetic peptides representing the repeated B-cell epitope induces a high degree of protective immunity (3).

To obtain antibody mediated protection high antibody titers are needed. This has been achieved by coupling B-cell epitopes to foreign protein carriers such as tetanus toxoid (3). However, this procedure has serious limitations. First, large quantities of conjugates are required for immunization, which limits its use in man due to carrier toxicity, and second, individuals previously immunized with the carrier protein could have an impaired antibody response to the conjugated B-cell epitope (epitope supression).

A synthetic subunit vaccine would be more efficient if it contained parasite-derived B and T epitopes. This vaccine would prime sporozoite-specific T-helper cells, which would induce a secondary antibody response upon exposure to sporozoites injected by the bite of infected mosquitoes. It would also boost pre-existing anti-sporozoite immunity in individuals living in malaria endemic areas and hopefully also induce cell-mediated mechanisms of protection.

To achieve these goals, it is essential to identify functional T helper epitopes which occur either within the CS protein or in a closely related sporozoite antigen.

By using synthetic peptides representing the CS protein of **P. berghei**, we have identified several T helper epitopes. They are located in the amino terminal as well as carboxi-terminal end. The repeat domain though recognized by antibodies, is not recognized by T cells. Immunization with the synthetic peptide which contains both a T- and a B-cell epitopes, induces antibodies against the repeat sequence. The T epitope sequence is therefore capable of priming T-helper cells, overcoming the unresponsiveness to the repeat sequence.

Finally, we observed that sporozoite immunization primes specific helper T-cells which proliferate *in vitro* with the synthetic peptides representing these T epitopes. This immunization protocol mimics the conditions which will be encountered when applying a vaccine in a malaria-endemic area. Most of individuals to be vaccinated in

such an area would have been primed by the bite of sporozoite infected mosquitoes. The vaccine would, therefore, be expected to induce a secondary, anamnestic response, as we observed in mice.

The **P. berghei** model is uniquely suited for the comparison of the efficacy of different constructs and to determine the best chemical linkage, the optimal type of association of T- and B-cell epitopes and the most favorable molar ratio between these epitopes within the synthetic polymers. In view of the considerable structural and functional similarities of the CS protein of the malaria parasites of rodent and human malaria, the assay of candidate vaccine in the rodent model should provide valuable clues for the preparation of malaria vaccines for human use.

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