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Development of a subcutaneous malaria whole-parasite vaccination

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Approaches in the development of a reliable malaria vaccine are numerous. Equally numerous are the remaining obstacles to overcome although feasibility is widely supported by evidence. So far, only whole sporozoite (SPZ) vaccination has achieved an adequate efficacy. One aspect among others that prevented the completion of such a chemoprophylaxis with sporozoites (CPS) vaccine is its unsuitability for subcutaneous applicability. In this project, research was performed on a rodent malaria model to increase protective efficacy following subcutaneous CPS immunisation.

Low protection after subcutaneous (SC) immunisation is associated with a low hepatic parasite load and a consequence of low SPZ infectivity. In order to increase liver infection, two substances have been selected based on the natural way of malaria transmission. Both, histamine and heparin mirror certain functions of mosquito saliva that were expected to play an important role for SPZ infectivity: Histamine, being a pro-inflammatory hormone that enhances perfusion and vessel permeability, may enable SPZ to migrate into blood vessels more effectively. Heparin, being an anti-clotting drug, can reduce physical barriers to SPZ migration.

Four experiments, all using the C57BL/6 *Plasmodium berghei* ANKA model, were designed to evaluate the significance of histamine and heparin supplementation on SPZ infectivity and CPS vaccine efficacy. In the first trial, the speed of symptom manifestation in mice was compared. Then, changes of liver burden were determined by *in vitro* quantification using real-time PCR in the second, and luciferase *in vivo* quantification in the third animal experiment. Ultimately, an immunisation trial in the rodent malaria model was conducted to assess whether previous findings are linked to an improved vaccine effectivity.

The results indicate a positive effect of histamine and heparin addition on SPZ infectivity. The maximal improvement of 10% liver load compared to the intravenous (IV) reference group was achieved by the addition of 100µg histamine and 5IU heparin. Moreover, increasing the SPZ count by 10 is accompanied by an additional 5-fold increase of liver load. Histamine was shown to increase liver burden dose dependent while heparin might be dispensable. Nonetheless, even the addition of 100µg histamine and 5IU heparin combined with SPZ multiplication by 10 did not result in a significantly higher protection of mice compared to the SC control group after a prime-two boost SC immunisation under chloroquine chemoprophylaxis.

In summary, histamine and heparin supplementation can contribute to future subcutaneous CSP vaccine development. Even though histamine and heparin addition failed to improve vaccine efficacy in immunisation experiments, the combination with other approaches might increase operational feasibility of future whole sporozoites vaccines.