

ROUND TABLE 11 - SUMMARY

EXPERIMENTAL MODELS IN PATHOLOGY AND IMMUNOLOGY

Chairman: William E. Collins*

Co-Chairman: Jurg Gysin*

W. Collins presented a review of the use of South American monkeys in the testing of anti-malarial vaccines. Different *Aotus* and *Saimiri* monkeys have been shown to be susceptible to infection with the human malarial *Plasmodium falciparum*, *P. vivax*, and *P. malariae*. Anti-sporozoite vaccine trials are being conducted in Bolivian *Saimiri*; *Aotus lemurinus griseimembra* from Colombia and *A. vociferans* from Peru are candidates for *P. falciparum* sporozoite vaccine trials. Blood-stage vaccines are being tested in *A. nancymai* from Peru, *A. lemurinus griseimembra* from Colombia, *A. lemurinus lemurinus* from Panama and *Saimiri* sp. from different geographic origins. Studies with these monkeys allow for the testing of immunogenicity and efficacy using different antigens and adjuvants to provide data not obtainable from other animal and human studies.

J. Gysin reported on the protective immunity against the asexual forms of *P. falciparum* in *Saimiri* monkeys. Passive transfer of intact IgG anti-*P. falciparum* antibodies isolated from protected monkeys protected naive non-immune monkeys against *P. falciparum* infection. Antibodies are species specific but not strain restricted and opsonize infected erythrocytes via the FcRIII receptors expressed on circulating monocytes. Non-protective anti-*P. falciparum* antibodies are not opsonizing and compete with the protective opsonizing antibody at the target level. Protection of the host depends not only on recognizing antigens exposed on the surface of infected erythrocytes but also on the balance between the two antibody populations. Opsonizing antibodies are capable of conferring protection to *P. falciparum* in non-immune and splenectomized *Saimiri* monkeys.

B. Enders described the protection of *Aotus* monkeys immunized with recombinant single

and combined antigens of *P. falciparum*. *Aotus* monkeys were immunized with *E. coli* derived fused proteins coding for partial sequence of the merozoite surface antigen (MSA-1), serine-stretch protein (SERP), and the histidine alanine rich protein II (HRPII), as well as a group of recombinant antigens obtained by antiserum raised against a protective 41 kD protein band. Intact monkeys were immunized three times and then splenectomized prior to challenge. HRPII, a combination of three different fusion proteins of the 41 kD group and a mixture of two sequences of SERP with AL(OH)₃ adjuvant conferred significant protection against challenge with *P. falciparum*. Two hybrid proteins expressed in *E. coli* administered in a new oil-based adjuvant protected monkeys from severe experimental *P. falciparum* infection.

S. Herrera assessed different *P. falciparum* vaccine candidates in *Aotus* monkeys in Colombia. Monkeys were immunized with the recombinant protein 190L, a fragment of the MSA-1 antigen, and a construct containing 190L and the T helper epitope C₃STH₃ of the CSP. Two out of five of the 190L group spontaneously cured the parasitemia and three out of four immunized with the construct were protected. Monkeys were immunized with the synthetic protein SPF (66)30 containing fragments of different blood stages and the NANP peptide from the *P. falciparum* CS protein. Monkeys received six immunizations with the peptide in Freund's adjuvant or alum. This protein failed to significantly protect the animals.

L. Monjour reported on the humoral and cellular responses to six different antigenic fractions prepared from the blood stages of *P. falciparum*. Homogenized parasitized erythrocytes were electrophoresed on SDS-polyacrylamide gels. Antigens were prepared by electroelution of six strips by referring to molecular markers run in parallel. Mice, rabbits

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and *Saimiri* monkeys were immunized three times at four week intervals using Freund's complete and incomplete adjuvants. All fractions led to the formation of antibodies reactive with the asexual blood stages or the surface membrane of parasitized erythrocytes as detected by IFA. As measured by Western blot analysis, each of the six fractions recognized only one or two major proteins. Maximal inhibition of parasite growth in *in vitro* cultures was obtained with antiserum induced by the 94 to 67 kDa band.

M. Aikawa presented *P. coatneyi*-infected rhesus monkeys as a model for human cerebral malaria. Studies were made of the brains of rhesus monkeys infected with *P. coatneyi*. Sequestration and cytoadherence of knobs of parasitized erythrocytes (PRCB) was demonstrated in the cerebral microvessels of these monkeys. Cerebral microvessels with sequestered PRCB

were shown by immunohistochemistry to possess CD36, thrombospondin and intracellular adhesion protein-1. These proteins were not evident in the cerebral microvessels of uninfected control monkeys.

R. Weller reported on the detection of impaired renal function in 16 *Aotus nancymai* monkeys 25 and 37 months following infection with *P. falciparum*. Impaired renal function was suggested by significant decreases in endogenous creatinine clearance, creatinin excretion, and urine volume, and increases in blood urea nitrogen, urine protein, and fractional excretion of phosphorus, potassium, and glucose. Serum concentrations of calcium and glucose were also significantly decreased. The results suggest a subclinical pathologic process, characterized by chronic progression, persisted in the kidneys of these monkeys following resolution of their parasitemias.