Malaria remains the most prevalent parasitic disease for which a vaccine is still not available. So far, whole-sporozoite (Wsp) vaccines have shown most success among current candidates. The applicant's lab has defined and established the proof-of-concept of a novel approach to Wsp malaria vaccination, based on the use of non-pathogenic rodent malaria parasites, genetically engineered to express antigens of their human-infective counterparts. *Pb*Vac, a *Plasmodium berghei* (*Pb*) parasite that expresses the *P. falciparum* (*Pf*) circumsporozoite protein is the first member of this new class of vaccine candidates. *Pb*Vac has demonstrated high safety profile and significant immunizing efficacy in recent phase I/IIa clinical trials. Stemming from these encouraging results, we now propose to generate and evaluate a new transgenic *Pb* parasite with enhanced immunogenicity and efficacy against *Pf* infection. To this end, we will engineer a *Pb* parasite line that expresses multiple antigens of the human-infective *Pf* parasite, we will characterize the expression of the inserted transgenes, and we will define its infectivity both in the mosquito vector and in the mammalian host. In order to ensure the safety and regulatory compliance of the newly generated *Pb*-based immunization agent, we will make use of GSK-DDW's blood-humanized (BH) mouse model to pre-clinically assess lack of infection of human (Hu) red blood cells (RBC) by these parasites. This is a pivotal step in the definition of the parasite's safety profile and a crucial requirement for the regulatory approval of its clinical use.