Exploration of glycosaminoglycans as antimalarials and as targeting molecules for nanovector-mediated drug delivery to *Plasmodium*-infected red blood cells.

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Abstract

Antimalarial drug delivery currently relies mainly on the administration of compounds with little or no specificity for the main target cell, the *Plasmodium*-infected red blood cell (pRBC), and thus delivery approaches for most antimalarials require high doses. Targeted nanovectors can fulfill the objective of achieving the intake of total doses sufficiently low to be innocuous for the patient but locally high enough to be lethal for the parasite.

We have quantified the *in vitro* antimalarial activity of heparin (Figure 1) and have studied heparin for its pRBC targeting specificity, hemolysis, unspecific cytotoxicity, and anticoagulant activity *in vivo* (mice assays). We will present the use of heparin-lipidic nanoparticle conjugates for the delivery of antimalarial drugs in the treatment of malaria. The design of the heparin-nanoparticle conjugate should be within a narrow balance between the amount of positive charge in the lipidic nanoparticle and the amount of conjugated heparin (which is negatively charged) in order to provide the intended therapeutic and targeting effect. In a situation of heparin excess, there would be a high risk of significant heparin release prior to contact with pRBCs, increasing undesired haemorrhagic effects. On the other hand, an excess of positive charge on the liposome surface, besides providing unspecific toxicity for the organism, might bind heparin with too much strength for it to manifest targeting or antimalarial activity.

Because heparin is eventually found in the blood, *Plasmodium* must have been exposed to it during its long coevolutionary history with humans and yet parasite resistance has not been described so far. Whether the reason for this resides in a not sufficiently long exposure of *Plasmodium* or pRBCs to heparin or in an antimalarial activity mechanism the parasite is having trouble to deal with, this family of glycoconjugates should not be wasted in badly-designed treatments that could induce the appearance of resistant strains. Heparin might be the spearhead of a new generation of GAG-related molecules exhibiting a synergistic activity as antimalarials and as targeting molecules for the localized delivery of drugs to *Plasmodium*-infected cells.

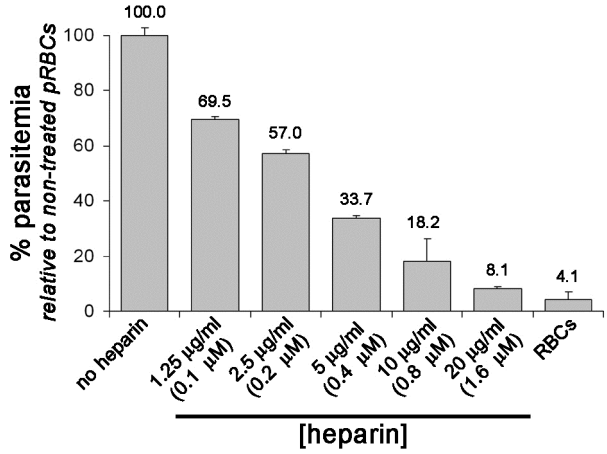

Figure 1. Antimalarial activity of heparin according to *P. falciparum* growth inhibition assays.