Exploring the potential of synthetic sulphonated polymers as candidates for adjunct therapies for malaria

[1,2]Rebecca Mobley, [2]Haneen AL-Zharani, [3]Vito Ferro, [2]Mark Skidmore, [1,2]Paul Horrocks

[1]School of Medicine and [2]School of Life Sciences, Keele University, [3]Australian Infectious Diseases Research Centre, Queensland University

Malaria continues to cause health and economic concerns despite control efforts, highlighting the urgent need for new therapeutics. Previously, heparin was evaluated as an adjunct treatment for malaria but was discontinued due to the health risks associated with its anticoagulant activity. The antiplasmodial activity of heparin has been attributed to the negatively charged sulphate groups within its structure, although how these directly affect *Plasmodium* and the host erythrocytes is not well understood.

To tackle the anticoagulant risk of heparin, a library of synthetic sulphonated polymers were evaluated as alternatives. Their antiplasmodial activity and rate of kill (RoK) was determined using luciferase bioluminescence assays. Potent antiplasmodial activity was found within this library and was demonstrated in two distinct strains of *Plasmodium falciparum* ($NF54^{luc}$ and $Dd2^{luc}$), with some having more potent antiplasmodial activity than heparin. Microscopy investigations and RoK investigations suggest the blocking of erythrocyte invasion and/or egress, with fast action. These stages are a unique target and offer promise for the development of drugs with low resistance potential. The anticoagulant properties of lead compounds was assessed using Prothrombin time (PT) and activated partial thromboplastin time (aPTT) assays. These compounds demonstrated no anticoagulant activity in the PT assay and some levels of anticoagulant activity was observed in the aPTT assay, lower than that of heparin. This study explores the benefits and risk of utilizing synthetic sulphonated compounds as an adjunct therapy in combination with current treatments of malaria.