Targeting of *Plasmodium* transmission stages with polymers-FITC for future antimalarial delivery strategies

Joana Marques[1], Michael Delves[2], Ursula Straschil[2], Elisabet Martí[1], Elisabetta Ranucci[3], Paolo Ferruti[3], Robert Sinden[2], Xavier Fernàndez-Busquets[1]

1. Institute for Bioengineering of Catalonia, Barcelona Centre for International Health Research, Centre Esther Koplowitz planta 1, Rosselló 149-153, E08036 Barcelona, Spain
2. Sinden Lab, Imperial College, 6th Floor SAF Building, South Kensington, London, SW7 2AZ, UK
3. Department of Chemistry, Università degli Studi di Milano, Via Golgi 19, IT-20133 Milano, Italy

joana.a.marques@gmail.com

With malaria elimination now firmly on the global research agenda, but resistance to the currently available drugs on the rise, there is an urgent need to invest in the research and development of new antimalarial strategies(1). Drugs can potentially target a suite of parasite life stages inside two different hosts: the human and the mosquito vector.

Asexual blood stages are responsible for all symptoms and pathologies of malaria, and therefore resident parasites inside *Plasmodium*-infected RBCs (pRBCs) are the main target for current chemotherapeutic approaches(2). As there can be several hundred billion pRBCs in the bloodstream of a malarious person it is nearly impossible to clear infections with single-dose administrations. Multiple doses are required instead and this continuous exposure to drugs increases the likelihood for resistance to develop, which will rapidly decrease treatment efficacy. This is prompting research oriented to target bottlenecks in the parasite life cycle, i.e. the pathogen population consisting of a few individuals in certain transmission stages from the human host to the insect and vice versa(3,4,5), which will reduce the probability of resistance emergence(6).

Although the innate immune system of mosquitoes is capable of completely clearing a malaria infection(7), it is far from the sophisticated arsenal providing long-term protection in mammalian adaptive immunity. This might result in parasite stages with reduced defenses because they only need to survive for a few weeks inside the insect facing an immune surveillance not as demanding as in the human host. Drugs targeting early *Anopheles* stages must kill only ca. 5×10^3 parasites to free a mosquito from *Plasmodium* infection(8), and the absolute low corresponds to oocysts, of which there are only 2-5 in a single insect(5) and which are around for over a week.

Previous results obtained by our group indicated that certain polymers can have a dual role as antimalarial drugs and as targeting elements towards pRBCs(9,10). Thus, we explored if these polymers could also be targeting agents against the *Plasmodium* mosquito stages (gametocytes, sporozoites, ookinetes, and oocysts).

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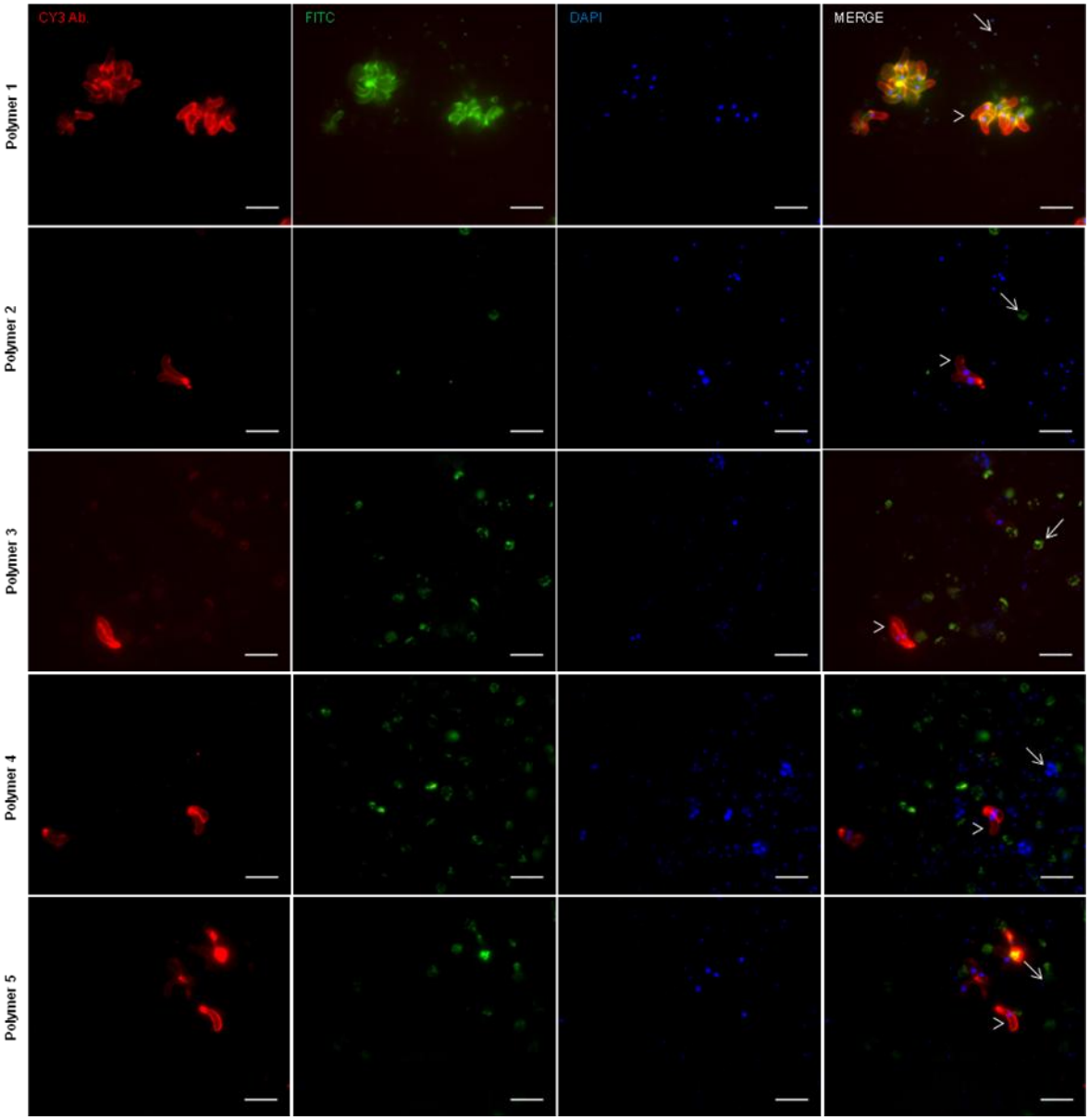

Figure 1. Targeting assay of the 5 polymers in study to *Plasmodium berghei* ookinetes. Polymers labelled with FITC were added to living cultures of *P. berghei* ookinetes and incubated for 90 minutes before sample preparation for microscopic analysis. Each series shows ookinetes (arrowheads) and pRBCs (arrows) as control of the specificity of the targeting. Scale bars correspond to 10 µm.