Efficacy of an 8-hydroxyquinoline-containing polymeric micelle system therapy for visceral leishmaniasis in the murine model of infection with *Leishmania infantum*

Carolina Kei Miyazaki[1], Letícia Martins dos Reis Lage[1], Daniela Pagliara Lage[2], Marcella Rezende Rodrigues[2], Lucas Magno Oliveira Santos[1], Érica da Silva Oliveira[1], Ana Maria Ravena Severino Carvalho[2], Bruno Mendes Roatt[1], Daniel Menezes-Souza[1,2], Carlos Alberto Pereira Tavares[3], Ricardo José Alves[4], José Mário Barichello[5,6], Eduardo Antonio Ferraz Coelho[1,2], Mariana Costa Duarte[1,2]

[1]Departamento de Patologia Clínica, COLTEC, Universidade Federal de Minas Gerais; [2]Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical, Faculdade de Medicina, Universidade Federal de Minas Gerais; [3]Departamento de Bioquímica e Imunologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais; [4]Departamento de Produtos Farmacêuticos, Faculdade de Farmácia, Universidade Federal de Minas Gerais; [5]Departamento de Farmácia, Escola de Farmácia, Universidade Federal de Ouro Preto; [6]Laboratório de Tecnologia Farmacêutica, Centro de Ciências Químicas, Farmacêuticas e de Alimentos, Universidade Federal de Pelotas

New therapeutics are urgently needed to treat visceral leishmaniasis (VL). Due to the fact that drug discovery is a long and expensive process, the development of delivery systems to carry old and toxic drugs could be considered, as well as the evaluation of new molecules that have already shown to present biological activity. In this context, the present study evaluated the *in vitro* and *in vivo* antileishmanial activity of an 8-hydroxyquinoline (8-HQN)-containing polymeric micelle (8-HQN/M) system against *Leishmania infantum*, the main causative agent of VL in the Americas. The experimental strategy used was based on the evaluation of the parasite load by a limiting-dilution technique in the spleen, liver, bone marrow and draining lymph nodes of the infected and treated animals, as well as by a quantitative PCR (*q*PCR) technique to also assess the splenic parasite load. The immune response developed was evaluated by the production of IFN-γ, IL-4, IL-10, IL-12 and GM-CSF cytokines, as well as by antileishmanial nitrite dosage and antibodies production. Hepatic and renal enzymes were also investigated to verify cellular injury as a result of treatments toxicity. In the results, 8-HQN/M-treated mice, when compared to the other groups: saline, free amphotericin B (AmpB, as a drug control), 8-HQN and B-8-HQN/M (as a micelle control) showed more significant reductions in their parasite burden in all evaluated organs. These animals also showed an antileishmanial Th1 immunity, which was represented by high levels of IFN-γ, IL-12, GM-CSF and nitrite, associated with a low production of IL-4 and IL-10

and *anti-Leishmania* IgG1 isotype antibodies. In addition, any hepatic or renal damage was found in these treated animals. In conclusion, 8-HQN/M was effective in treating *L*. *infantum*-infected BALB/c mice, and can be considered alone, or combined with other drugs, as an alternative treatment for VL