Folate-targeted liposomes for rheumatoid arthritis therapy

Eugénia Nogueira* and Artur Cavaco Paulo

CEB — Centre of Biological Engineering, University of Minho, Campus of Gualtar, Braga, Portugal

*e-mail: enogueira@ceb.uminho.pt

Rheumatoid arthritis is the most common inflammatory rheumatic disease, affecting almost 1% of the world population [1]. Although the cause of rheumatoid arthritis remains unknown, the complex interaction between immune mediators (cytokines and effector cells) is responsible for the joint damage that begins at the synovial membrane [2]. Activated macrophages are critical in the pathogenesis of rheumatoid arthritis [3] and showed specifically express a receptor for the vitamin folic acid, folate receptor β [4]. This particular receptor allows internalization of folate-coupled cargo [5]. Here we propose the encapsulation of methotrexate in a new liposomal formulation using a hydrophobic fragment of surfactant protein conjugated to a linker and folic acid to enhance their tolerance and efficacy [6]. In this study we aim to evaluate the efficiency of this system to treat rheumatoid arthritis, by targeting folate receptor β present at the surface of activated macrophages. The specificity of our liposomal formulation was investigated both in vitro as in vivo using a mouse model of arthritis (collagen-induced arthritis in DBA/1J mice strain).

In both systems, the liposomal constructs were shown to be highly specific and efficient in targeting folate receptor β. These liposomal formulations also significantly increase the clinical benefit of the encapsulated methotrexate in vivo in arthritic mice (Figure 1) [7]. In conclusion, our formulation might be a promising cost-effective way to treat rheumatoid arthritis and delay or reduce methotrexate intolerance.

Figure 1. In vivo specific targeting and prophylactic efficiency of folate receptor-targeted liposomes in arthritic mice. (A) In vivo uptake specificity of fluorescently labeled liposomes (30 min). (B) Clinical effects of liposomes encapsulating methotrexate on arthritis. Treatment started 14 days after immunization. The mean clinical score in each group over time is shown [8].

Acknowledgments: Eugénia Nogueira thanks for a scholarship (SFRH/BD/81269/2011) from Fundação para a Ciência e a Tecnologia (FCT). This work has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement NMP4-LA-2009-228827 NANOFOL. This work was supported by FEDER through POFC – COMPETE and by Portuguese funds from FCT through the project PEst-OE/BIA/UI4050/2014. The authors also thank the FCT Strategic Project of UID/BIO/04469/2013 unit, COMPETE 2020 (POCI-01-0145-FEDER-006684), BioTecNorte operation (NORTE-01-0145-FEDER-000004) funded by European Regional Development Fund under the scope of Norte2020 - Programa Operacional Regional do Norte and the European Union Horizon 2020 research and innovation programme under grant agreement NMP-06-2015- 683356 FOLSMART.