Methotrexate is the first line of treatment of rheumatoid arthritis. Since many patients become unresponsive to methotrexate treatment, only very expensive biological therapies are effective and increased methotrexate tolerance strategies need to be identified. In a previous European project NANOFOL, we performed the encapsulation of methotrexate in a new liposomal formulation using a hydrophobic fragment of surfactant protein conjugated to a linker and folate to enhance their tolerance and efficacy. We evaluate the efficiency of this system to treat rheumatoid arthritis, by targeting folate receptor β present at the surface of activated macrophages, key effector cells in this pathology. The specificity of our liposomal formulation to target folate receptor β 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. A new project, called FOLSMART, will perform the preclinical development and the phase I clinical trials of this new liposomal formulation.