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Glioblastoma-targeted, local and sustained drug delivery system based on an unconventional lipid nanocapsule hydrogel

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Abstract

Introduction: The standard of care of glioblastoma (GBM), malignant brain tumors, consists in a tumor resection, followed by the Stupp protocol (chemotherapy and/or radiotherapy) 4 to 6 weeks later. This non-specific and non-curative protocol allowed a slight increase in the median survival, but without preventing tumor recurrences due to incomplete GBM resection, leading to the death of the patients. One of the factors associated with the recurrences is the gap between surgery and Stupp protocol, but necessary for good tissue healing and recovery of the patient. The objective of this project is to develop an implantable therapeutic hydrogel which will bridge this gap to ensure continuity in treatment for the patients. A hydrogel of self-associated lipid nanocapsules (LNCs), without polymer matrix, was already designed to allow the gradual release of gemcitabine-loaded LNCs (Figure 1A). Promising results have shown the therapeutic efficacy *in vivo* of this implant in murine GBM resection models [1-2]. However, the released LNCs were not specific to GBM cells. One of the opportunities to improve the targeting is the use of NFL-TBS.40-63 (NFL) peptide, able to associate with LNCs in suspension [3].

Method: A large range of methods was used for this purpose: chemistry (synthesis of lauroyl-modified gemcitabine GemC12), formulation process (LNC design using phase inversion method), LNC-based hydrogel characterizations (viscoelastic properties, LNC size distributions, drug payloads, and release profiles), GBM cell cultures and GBM resection murine models for the LNC hydrogel evaluation.

Results: The LNC-based hydrogels were formulated with the NFL peptide. It was totally and instantaneously adsorbed at the LNC surface, without modifying the hydrogel mechanical properties, and remained totally adsorbed after the hydrogel dissolution. In addition, *in vitro* studies on GBM cell lines showed a faster internalization of the LNCs in the presence of NFL (Figure 1B) and a better cytotoxicity. Finally, *in vivo* studies in the murine GBM resection model proved the better specificity with the implants in which the NFL is adsorbed at the surface of the LNCs.

Conclusions: This LNC-based hydrogel therefore proves to be a promising clinical strategy to target and treat GBM during the therapeutic hiatus, concomitant to Stupp protocol. The gemcitabine-loaded LNCs with adsorbed NFL could target the non-resected GBM cells and significantly delay or even inhibit the apparition of recurrences.

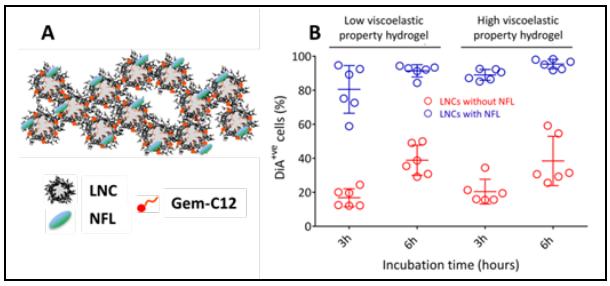

Figure 1. A) Design of the glioblastoma-targeted lipid nanocapsule (LNC) hydrogel, exclusively based on the LNC association using Gem-C12 as crosslinking agent and NFL for targeting. B) Influence of NFL on the internalization of LNC in U-87 MG cell line, quantified using flow cytometry (incubation of 3 or 6h at 37°C), after hydrogel (with or without NFL) dissolution (n = 6 ; mean ± SD).

[1] C. Bastiancich, K. Vanvarenberg, B. Ucakar, M. Pitorre, G. Bastiat, F. Lagarce, V. Préat, F. Danhier, *J.Control. Release*, (2016)

[2] C. Bastiancich, J. Bianco, K. Vanvarenberg, B. Ucakar, N. Joudiou, B. Gallez, G. Bastiat, F. Lagarce, V. Préat, F. Danhier,*J. Control. Release*, (2017)

[3] J. Balzeau, M. Pinier, R. Berges, P. Saulnier, J-P. Benoit, J. Eyer, *Biomaterials*, (2013)