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Lipid nanocapsule hydrogel: a glioblastoma-targeted, local and sustained drug delivery system

Marion Sicot1, Elia Bozzato2, Claire Gazaille1, Umer Farooq1, Adélie Mellinger1, Patrick Saunlier1, Joël Eyer1, Véronique Préat2, and Guillaume Bastiat1*

1 UNIV Angers, INSERM 1065, CNRS 6021, MINT, Angers, France. 2 Univ Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Brussels, Belgium
*guillaume.bastiat@univ-angers.fr

Introduction

The standard care for glioblastoma (GBM), a 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, 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 (LNC), without polymer matrix, was designed and allowed the gradual release of gemcitabine (Gem-C12)-loaded LNC. 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 785.40-63 (NFL) peptide, able to associate with LNC in suspension [3].

![LNC and NFL interaction and NFL-LNC hydrogel](image)

- Negative surface charge of LNC leads to total and instant adsorption of NFL
- Negative charges on LNC surface decrease the viscoelastic properties but NFL adsorption restores and strengthens them
- Negatively charged LNC release is more sustained when the NFL peptide is associated to the hydrogel

![NFL-LNC hydrogel and GBM (in vitro assays)](image)

- NFL-LNC from dissolved hydrogel preferentially targets GBM cells
- Decrease of cell viability after NFL-LNC treatment compared to the LNC one, both from dissolved hydrogels

![NFL-LNC hydrogel and GBM (in vivo assays)](image)

- Stronger accumulation and deeper penetration of LNC into the tumour tissue with NFL
- Targeting peptide combined with a local treatment increases the median survival

Conclusion

The LNC hydrogels were formulated with the NFL peptide: a GBM targeting 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 LNC in the presence of NFL 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 LNC.

References:

Acknowledgements: