Glioblastoma-targeting peptide adsorbed on lipid nanocapsule surface: optimization of the process and targeting efficacy

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	The current standard of care of glioblastoma (GBM): the highest grade brain tumor is not a curative treatment and does not prevent high patient mortality (median survival of 14 months, and 5-year survival rate lower than 10% (Stupp R et al., N. Engl. J. Med, 2005; Stupp R et al., Lancet Oncol., 2009)). The scientific community must address solutions to these unmet medical and patient needs and opportunities can be found to develop innovative and complementary treatment to the standard therapeutic scheme. The GLIOGEL project (ERA-NET Cofund EuroNanoMed III) focuses on a hydrogel of GBM-targeting, drug-loaded lipid nanocapsules (LNCs). This new drug delivey system will be implantable directly after GBM resection, and will close the treatment gap until Stupp protocol (radiotherapy and/or adjuvant chemotherapy, 4 to 6 weeks after resection). The sustained LNCs release will specifically target the residual infiltrating GBM cells at resection border, main cause of tumor recurrences. The proof of concept of adsorption of a targeting peptide: the NFL-TBS.40-63 (NFL) at LNC surface was already done, with the specific targeting property for GBM cells (Berges R et al., Mol. Ther., 2012 ; Balzeau J. et al., Biomaterials, 2013). So the first part of the project was to confirm and optimize the association NFL-LNCs, and to show correlations regarding NFL and LNC physicochemical properties.
Résumé en anglais	LNCs in suspension with different sizes (from 30 to 100nm), surface charges (positive, neutral and negative) and Span® 80 composition (from 0 to 15% w/wLNCs) have been performed according to a phase inversion process (Heurtault et al., WO2001 / 064328, 2001). Different LNC concentrations (0.001 to 275mg/mL) were incubated at room temperature for 12h with fixed NFL concentrations (50 to 200µg/mL). Free NFL proportions were quantified in the free NFL and NFL-adsorbed LNC mixtures without prior separation, i.e. directly after incubation, to avoid all the bias that can be observed using physical separations such as filtration by centrifugation and dialysis. A Steric Exclusion Chromatography method was developed for this purpose. Due to NFL properties (slightly positively charged and capacity to form H-bond), we showed that the NFL adsorption at LNC surface was enhanced with negatively charged LNCs, and when Span® 80 proportion at LNC surface increase. These results were confirmed using two other methods without prior separation: NMR diffusometry using the diffusion coefficients for both free and adsorbed NFLs, and Fluorescence Correlation Spectroscopy using FITC-labeled NFL. Other protein or peptide-adsorbed nanoparticles could be characterized using these three methods, and the absence of physical separation before the quantification is a real benefit for the accuracy and veracity of data. Finally, the best LNC candidates with total NFL adsorption were tested on a large library of GBM cell lines, with different incubation times in order to verify the targeting efficacy. The LNCs internalization is faster when the NFL is present at their surface. Nevertheless, we observed that the efficiency depends on different parameters: the amount of NFLs at LNC surface and also the cellular models.
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