TARGETING POLYMERIC CONJUGATES WITH BIOLOGIC-RESPONSIVE PROPERTIES TO MANUFACTURE DOCETAXEL-LOADED NANOPARTICLES FOR GLIOBLASTOMA CHEMOTHERAPY

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Background: Glioblastoma is the most lethal brain cancer, with a median survival time of only 15 months. Docetaxel is one of the most effective chemotherapeutics against glioblastoma, although it presents pharmacokinetic constraints mainly due to its low solubility and poor blood-brain barrier (BBB) permeation. This project proposes a targeted, biologic-responsive nanomedicine to circumvent these inadequacies based on docetaxel-loaded nanoparticles for glioblastoma treatment. The developed nanomedicine comprises a poly(lactic-co-glycolic) acid (PLGA) core and a polyethylene glycol (PEG) shielding of long- and short-length. The long-length PEG possesses an Angiopep-2 moiety for BBB targeting (binding to the low-density lipoprotein receptor) and is able to dissociate in the acidic pH of BBB endosomes, hence sterically de-protecting the short-length PEG coupled with L-histidine for further glioblastoma targeting (binding to the L-type amino acid transporter 1) upon brain arrival.

Methods: Chemical strategies based on carbodiimide, hydrazone formation via Schiff base reaction and Thiol-Michael addition were employed to synthesize the **PLGA-acid-cleavable, long-length PEG-Angiopep-2** and **PLGA-short-length PEG-L-Histidine** polymeric conjugates that will constitute the nanoparticle matrix. These polymeric conjugates were further characterized by different techniques such as nuclear magnetic resonance (NMR), Fourier-transform infrared spectroscopy (FTIR) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). Preliminary work has focused the production of docetaxel-loaded nanoparticles post-polymer synthesis through a scale-up microfluidic manufacturing technique.

Results: The chemical synthesis achieved a total conjugation efficiency value of around 70% and 90% for the **PLGA-acid-cleavable, long-length PEG-Angiopep-2** and **PLGA-short-length PEG-L-Histidine** polymeric conjugates, respectively, as demonstrated by NMR calculations. FTIR confirmed the successful reactions by elucidating the formation of intermediary bonds between the constituents of the polymeric conjugates, and MALDI-TOF confirmed the different ionization behaviors and proved the presence of PLGA and PEG monomers in the structure of the polymeric conjugates. The physicochemical characterization of docetaxel-loaded nanoparticles manufactured through the microfluidic technique demonstrated around 100 nm average size, 0.1 polydispersity index and 10% drug loading.

Conclusions: Overall, this work has allowed, so far, the synthesis of targeted, biologic-responsive polymeric conjugates with high conjugation efficiency (>70%) and suitable to manufacture low size, monodisperse and highly loaded docetaxel nanoparticles in a microfluidic technique with potential to scale-up the batch size. Future work will be dedicated to test the efficacy of the developed targeted, biologic-responsive nanomedicine in vitro and in vivo. The current need to accelerate drug delivery to glioblastoma, bypassing the BBB and targeting tumor tissue of brain, places this system in a privileged position in the field of translational nanomedicines. This work also lays foundation for future targeted, biologic-responsive delivery of other therapeutics to a range of pathologies.