Image-guided phase change nanodroplets for the treatment of brain tumours

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Background: High-Intensity Focused Ultrasound (HIFU) has attracted notable attention in the last years due to its ability to alter tissue characteristics and enhance the delivery of therapeutic molecules. In preclinical models (including non-human primates), HIFU has proved to intensify the permeability of macromolecules and nanoparticles through the Blood-Brain Tumor Barrier (BBTB). The BBTB acts as an inhibitory factor for the antineoplastic drugs, preventing most of them from entering the tumor and reducing their efficacy.

The phase-change nanodroplets (NDs) have a perfluorocarbon (PFC) core, that undergoes acoustic vaporisation and starts oscillating upon activation with HIFU energy. This event is called cavitation and potentially causes a reversible permeability of the BBTB for a short period. This study analyses the preparation of lipid-based NDs, labelled with fluorescent probes and drug-loaded to create a targeted drug delivery vehicle.

After the HIFU application, the gas-cored NDs will create a localised BBTB opening and selectively release the encapsulated drug molecules to the tumor site. Moreover, they can be adopted to be magnetic resonance imaging (MRI) traceable.

Methods: The lipid mixture is dried up until there is a thin lipid film. After the film hydration, the NDs are formulated with a series of ultrasound sonication cycles and the PFC addition. The ND stability is assessed by measuring their size over time. Moreover, the cavitation profile is measured with a high-speed camera and/or passive acoustic methods.

Results: The characterisation experiments proved that our formulated NDs start cavitating after ultrasound (US) exposure. There was also a clear correlation between the lipid and the gas ND composition to the cavitation effect. Furthermore, the NDs were labeled with a various of different near-infrared dyes. Moreover, the loss of encapsulated PFC was at ~15% after weekly storage.

The preliminary *in vitro* experiments in BBTB cell models showed an increase in cell membrane permeation after the combined application of US and NDs presence, comparing to the sole US application.

Conclusions: The physicochemical characterization data showed ND stability at 37ºC and for at least a week in fridge storage. Moreover, the cavitation results matched the ones of the approved microbubbles. The future experiments will prioritize the transition from the in vitro cell studies to the animal experiments.