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 its efficacy.

The phase-change nanodroplets (NDs) have a perfluorocarbon core that starts oscillating upon activation with HIFU energy 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 due to the cavitation effect, while they will selectively release the encapsulated drug molecules to the tumor site. Moreover, they can be adopted to be MRI (magnetic resonance imaging) traceable.

Methods: The lipid mixture is dried up until there is a thin lipid film. After the hydration of the film and a series of sonications and the addition of the perfluorocarbon the NDs are formulated. The ND stability was assessed measuring their size over time and their their ability to cavitate was measured with high-speed camera and/or passive acoustic methods.

Results: The primary characterisation experiments proved that our formulated blank and drug-loaded NDs start cavitating after the HIFU exposure, while there was a clear correlation of lipid and gas composition to the cavitation effect. Furthermore, the encapsulation efficiency of the SN-38 (a topoisomerase I inhibitor) reached ~100% without disturbing the stability of the NDs.

After further investigation, successful preparation and physicochemical characterisation of the drug-loaded NDs, the preliminary *in vitro* experiments in BBTB cell models showed an increase in membrane penetration after the application of FUS and NDs.

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. However, further studies need to be conducted before we move into animal studies.