Ultrasound responsive piezomagnetic carbon nanoneedles for non-invasive blood brain barrier penetration and anticancer drug delivery system for glioblastoma treatment

Arathyram Ramachandra Kurup Sasikala[1], Dean Kavanagh[2], Hanene Ali-Boucetta[1]

[1]School of Pharmacy, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, [2]Institute of Cardiovascular Sciences, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

Background: Blood Brain Barrier (BBB) protects the brain from unwanted chemicals and provides a precisely regulated microenvironment to function normally. However, this defense barrier presents a challenge in shuttling therapeutic cargoes into the brain for the treatment of brain tumours and neurodegenerative diseases. Therefore, an ideal drug delivery system (DDS) for transporting drugs across the BBB is the objective of intensive research in recent times. Here we report the development of an ideal DDS called PiezoMagnetic Carbon Nanoneedles (PMCNNs) to penetrate the BBB and deliver anticancer drug for the treatment of glioblastoma (GBM).

Methods: To prepare PMCNNs, PiezoMagnetic Nanoparticles and functionalised carbon nanotubes (f-CNT) were separately synthesized and covalently functionalized as a single nano construct. For that firstly, a highly dispersive polyvinylpyrrolidone (PVP) assisted tetragonal barium titanate nanoparticles (BTNPs) were fabricated through a modified hydrothermal method. Secondly, Superparamagnetic Iron Oxide Nanoparticles were seeded onto the BTNPs by an in situ co-precipitation method to prepare PMNPs. Thirdly, pristine CNTs were carboxylated by sonicating them in a mixture of sulfuric and nitric acids to obtain f-CNT. To fabricate the PMCNNs, the obtained PMNPs were attached onto COOH-functionalised CNTs through electrostatic and covalent functionalization. PMCNNs were characterised through TEM, DLS, XRD and FTIR. The piezoelectric characterisation of PMCNNs were evaluated by measuring the US driven voltage generation by using an oscilloscope. The BBB penetration capability of PMNPs was evaluated in the self assembled multicellular BBB spheroid model that mimic the complex arrangement of individual cell types in the BBB structure. The penetrated PMNPs were tracked using the inherent Second Harmonic Generation Imaging property of the unique PMCNNs. Anticancer drug cisplatin (CDDP) was covalently functionalised to PMCNNs to assess the therapeutic effects of PMCNNs-CDDP for GBM treatment in 3D glioblastoma tumour spheroid prepared by the Liquid Overlay Method

Results: US responsive PMCNNs were synthesised and characterised for excellent biocompatibility and piezoelectric properties. Multicellular BBB spheroids were prepared and found that the human primary astrocyte formed as BBB spheroid core and brain endothelial cells and pericytes cover the surface of the BBB spheroids mimicking the exact cellular organization of BBB. The BBB spheroid also displayed excellent expression of tight junction markers such as Claudin, Occludin and zonula Occludin. As expected, the PMCNNs exhibited effective penetration of BBB spheroid when stimulated with US in comparison with no US treated controls when noninvasively tracked by the inherent Second Harmonic Generation (SHG) imaging property of PMCNNs. The PMCNNs-CDDP exhibited superior anticancer effects in 3D GBM models due to the synergistic effect of enhanced cellular penetration and anticancer therapeutic (CDDP) delivery which is proved by the size reduction of 3D GBM spheroids over-time by optical microscopy, Live/dead imaging and different cytotoxicity assays including Cell Titer-Glow 3D

Conclusions: Ultrasound responsive self-powered PMCNNs were successfully developed for the effective translocation into BBB spheroids. The PMCNNs acted as an ideal DDS and exhibited superior anticancer effects in 3D GBM models due to the combinatorial and synergistic effect of enhanced cellular penetration and anticancer therapeutic cisplatin delivery with inherent second harmonic imaging capabilities