Graphene oxide nanoscale platforms for deep tissue translocation within the tissue microenvironment of glioblastoma

Maria Stylianou[1], Thomas Kisby[1], Kostas Kostarelos[1,2]

[1]Nanomedicine Lab, Faculty of Biology, Medicine & Health, The University of Manchester, Manchester, U.K.

[2]Catalan Institute of Nanoscience & Nanotechnology (ICN2), CSIC and BIST, Campus UAB, Bellaterra, 08193 Barcelona, Spain

kostas.kostarelos@manchester.ac.uk

The anatomical localization, blood brain barrier, highly tissue heterogeneity, drug-resistant tumor cell population and a “cold” immune microenvironment with a predominantly immunosuppressive myeloid compartment, together lead to a serious compromises in glioblastoma (GBM) treatment efficacy. Nanoscale transport systems, including thin, 2-dimensional graphene oxide (GO) sheets, may circumvent some of these challenges, by-passing biological barriers and having the additional capacity to deliver multiple therapeutic cargoes. This can potentially impact several pathways simultaneously, including the tumor immune component.

The interactions between different cellular GBM components with graphene oxide (GO) nanoscale sheets in two orthotopic glioblastoma models (U87 and GL261) were investigated here. A single intracranial administration of GO sheets showed extensive distribution throughout the tumour mass and demonstrated no significant impact on tumor growth and progression. The spatial distribution of GO nanosheets was determined to be spread extensively throughout the tumor volume overtime, without traversing tumor borders. Internalization within tumor cells was also scarce, with the majority of sheets preferentially taken up by activated IBA1+ microglia/macrophages.

These results indicated that GO sheets could potentially offer a nanoscale tool that homogenously distributes throughout the tumor volume, with the capacity to preferentially be internalized by their myeloid compartment to ameliorate their immunosuppressive character. Further studies are currently undertaken in our laboratory to elucidate the mechanisms of GO sheet transport within the tumor mass and their capacity to deliver biomolecules that could help unlock the efficacy of clinically established immunotherapies for GBM.

Overall, we have developed a toolkit of graphene-based flat nanotechnology designs, each transforming a unique set of nanomaterial characteristics into a value and solution proposition for specific clinical challenges in brain disease. This talk will illustrate how this transformation from a 2D nanomaterial to a platform for cellular modulation and reprogramming has been achieved in the context of brain malignancies.

References

de Lázaro, I. et al (2021). Deep tissue translocation of graphene oxide sheets in human glioblastoma 3D spheroids and an orthotopic xenograft model. *Advanced Therapeutics*, 4: 2000109.

Sharp, P., Stylianou, M. et al. (2022) Graphene oxide nanoscale platform enhances the anti-cancer properties of bortezomib in glioblastoma models. *Advanced Healthcare Materials*, 2201968

Figure

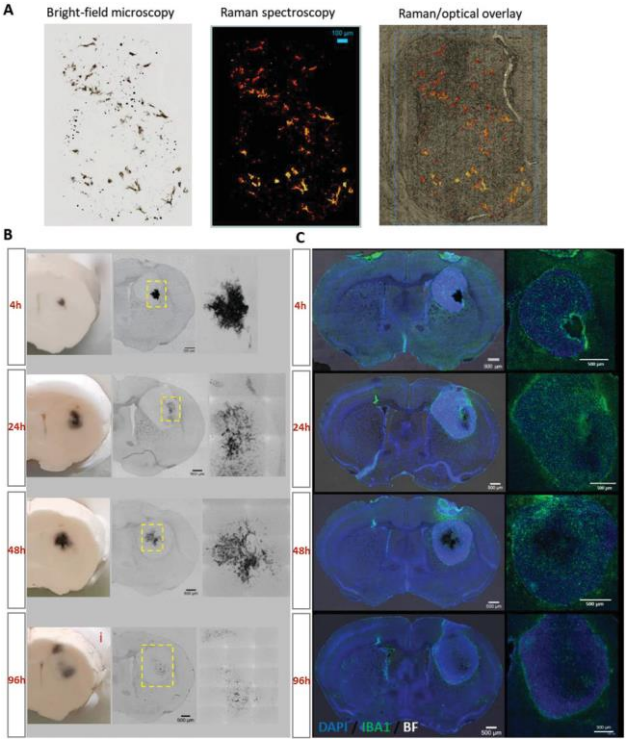

Figure 1. Time-course of graphene oxide nanosheet distribution in orthotopic U87 gliomas. 1 µg of GO was delivered intratumorally at 12 days post inoculation (n=12) and brains were harvested at 4, 24, 48, and 96 h post GO delivery (n=3 per group). **A)** Co-localization of the GO Raman signal and black matter observed under bright-field imaging in brain sections. **B)** Representative images of the whole brain and corresponding 20 µm sections showing the redistribution of intratumoral GO over time (scale bar 500 µm). **C)** Representative epifluorescence images of the whole brain and tumor region showing the distribution of intratumoral GO in relation to DAPI staining and IBA1+ macrophage/microglia cells. Scale bar = 500 µm.