

## Remodelling of tumour vasculature by targeted nanoparticle delivery in a xenograft model of glioblastoma multiforme

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Glioblastoma multiforme (GBM) is a grade IV type of glioma, one of the worst and most aggressive types of brain cancer affecting the central nervous system and with extremely poor prognoses. Patients with GBM have a very low rate of survival, with average prognosis of 14 months after standard treatment involving surgical resection followed by combined chemotherapy and radiotherapy.<sup>1</sup> One of the greatest challenges in achieving a long-term survival is poor drug delivery to the tumour. In fact, accessing the entire population of the diseased cells with chemotherapeutic and radiotherapeutic drugs is proving extremely challenging, due to the presence of a structurally abnormal and dysfunctional vascular network, preventing homogeneous delivery of chemotherapeutics to tumour cells, and of the brain blood-brain-barrier (BBB), which is largely impenetrable to nanoparticle drug carriers.<sup>2,3</sup> “Tumour remodeling” is a promising strategy aiming to assist access to cells by drug carriers by enhancing diffusion across the membranes of blood vessels. Currently the most widely used approach to remodel the tumour vasculature to improve drug delivery is by antiangiogenic therapy, which restores a functional vascular network around the tumour.<sup>4</sup> However, this approach still fails to improve patient overall survival due to tumour recurrence driven by extensive hypoxia development in tumour regions not reached by the first line of chemotherapy.<sup>5</sup> Thus, our work involves investigating the use of novel nanoparticles (NPs) to exploit the enhanced permeability and retention (EPR) effect as an alternative strategy to improve drug delivery to the tumour. This strategy relies on targeting tumour-associated platelets as a mean to render the tumour vasculature more ‘leaky’, hence enhancing extravasation and accumulation of the drug-carrier NPs into the tumour tissue.<sup>6</sup> In particular, we intend to study the effects of the novel NPs on the tumour vasculature morphology in a human xenograft model of GBM in mice, and to compare these with currently clinically used antiangiogenic treatment. We assess tumour vasculature morphology changes *via* measurements of microvascular density, BBB integrity and levels of hypoxia, both with *in vivo* MRI/PET and optical imaging, and with *ex vivo* immunohistochemistry. Our ultimate goal is to establish correlations between *in vivo* imaging data and molecular biomarkers expression that will enable us to better understand at the molecular level the phenomena of tumour angiogenesis, BBB disruption and cellular necrosis.

### References

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Research interests: Investigating the effects of targeted nanoparticles on tumour vasculature remodelling in models of glioma by use of multimodal imaging techniques, including PET/MRI and optical imaging.

