

Glycoengineered 3D Bioprinted Glioblastoma Models: from *in silico* design to personalized medicine application

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Glioblastoma multiforme (GBM) is an aggressive brain tumour characterized by extensive extracellular matrix (ECM) remodeling and poor response to therapy, highlighting the need for clinically relevant *in vitro* models[1]. *In silico* analysis from GBM patient datasets has been employed to prioritize key ECM glycosignatures, providing a rational framework for the design of biomimetic bioinks incorporating hyaluronic acid (HA), gelatin (Gel), chondroitin sulfate (CS) and α -NeuNAc-(2 $\rightarrow$ 3)- β -D-Gal- [2,3]. These bioinks were used to generate 3D bioprinted model employing patient-derived GBM cells, where four different formulations, with differential glycosignature, were employed to evaluate the impact of glycosignatures on drug response. The resulting models were characterized through multiplex immunofluorescence (IF) and synchrotron nano-computed tomography (nanoCT). Drug treatment revealed matrix-dependent adaptive responses, with different glycosignatures driving distinct mechanisms of cellular plasticity and therapy resistance through ECM remodeling and activation of alternative survival pathways. Overall, our integrated *in silico*–*in vitro* platform shows how glycoengineered extracellular matrices can improve the predictive value of bioprinted GBM models, supporting the development of patient-relevant systems for preclinical drug screening and future clinical translation.

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