BACKGROUND: Paediatric brain tumours pose a formidable challenge in oncology, necessitating innovative approaches to bridge the gap between molecular understanding and therapeutic efficacy. Current preclinical models lack fidelity in capturing the dynamic interplay between tumour cells and their microenvironment, hindering translation of research findings into clinical practice. METHODS: We are developing advanced three-dimensional (3D) models of paediatric brain tumours, integrating crucial components of the tumour microenvironment. Leveraging self-assembling peptide amphiphiles (PAs), we are constructing subgroup-specific PA-ECM-Immuno models mimicking brain stiffness, ECM composition, immune cell interactions, and oxygen levels. Spatial transcriptomics and multiplex immunohistochemistry are being employed to elucidate tumour-microenvironment interactions. RESULTS: Building upon our successes in modelling brain tumour growth and behaviour, as well as other types of tumours (the Mata lab has previously successfully established PA-ECM models of prostate and ovarian cancer), our approach demonstrates feasibility in incorporating immune cells and subgroup-specific ECM components into PA-ECM matrices. These models provide insight into dynamic interactions driving tumour progression, facilitating identification of key pathways and potential therapeutic targets. CONCLUSIONS: Our approach represents a novel paradigm in paediatric neuro-oncology research, aiming to establish clinically relevant 3D models faithfully recapitulating intricate tumour-microenvironment interactions. By elucidating mechanisms of tumour progression and employing spatial transcriptomics and multiplex immunohistochemistry, our tailored models will enable the identification of precision therapies with enhanced efficacy and reduced off-target effects. Collaborative efforts through our multidisciplinary approach are poised to advance the field towards personalised treatments and improved outcomes for paediatric brain tumour patients.