Introduction: Glioblastoma (GBM) is the most lethal and frequent cancer originating from central nervous system. Median survival of GBM remained in 12-15 months, as GBM constantly develops resistance to treatments. Many novel therapeutic strategies showing promising results in pre-clinical models have failed in clinical trials, partially due to lack of a translational model platform that recapitulates actual microenvironment surrounding the tumor. Aberrant expression and deposition of hyaluronic acid (HA), the major glycosaminoglycan in brain, and other cell-adhesive, extracellular matrix (ECM) proteins have been frequently observed in GBM. The influence of the HA and other ECM and the mechanisms dictating therapeutic responses remain largely uncharacterized, in part because of a lack of physiological translatable experimental models in which to study GBM. We have developed three-dimensional (3D) microenvironments as ex vivo culture systems that mimic the native brain microenvironment and maintain the physiology of patient-derived, primary GBM cells (Fig. 1A). These platforms can provide researchers with a controlled experimental space, in which microenvironmental cues can be modularly varied and their influence in GBM explored.

Results and Discussion: To date, we have compared our culture model with traditional gliomasphere (GS) system through whole RNA sequencing and whole exosome sequencing. The expression patterns of patient-derived GBM cells cultured in our hydrogel platform showed significant differences compared to cells cultured in GS system (Fig. 1B). In the aspect of translational oncology research, we explored feasibilities of using our hydrogel system to screen therapeutic response, study influences of matrix microenvironment on drug response, and molecular mechanisms dictating matrix mediated drug resistance (Fig. 1C, D). Our culture platform can serve as powerful tool for development of personalized medicine and investigation of mechanisms of GBM oncology.