Table S1. Devices development for Glioblastoma application

Device	Matrix composition	Proposed mechanism	Study model (In vitro, in vivo, ex vivo)	Major Findings	Reference
Hydrogel system	HA-functionalized Methacrylate gelatin/poly(ethylene glycol) (PEG)4A	Mimic the microenvironment matrix for GBM cells	2-3D cultures, patient-derived GBM cells	HA-dose-dependent alterations in GBM malignancy-associated markers. HA can lead to a specific interaction in EGFR+ cells via CD44.	[Pedron et al., 2013] 10.1016/j.biomaterials.2013.06.024
Composite hydrogel	Collagen-Hyaluronan	Mimic the microenvironment matrix for GBM cells	3D culture, patient-derived GBM cells	Cell morphology, spreading and migration were influenced by collagen type and HA concentration.	[Rao et al., 2013] 10.1021/am402097j
Hydrogels	HA-Gelatin thiol-reactive PEG diacrylate (PEGDA)/PEG divinyl sulfone (PEGDVS) crosslinked	Mimic the microenvironment matrix for GBM cells and develop a better analytical analysis *in vitro*	Single-cells, 3D culture, U118, U87R cell lines	Potential to identify differences in the invasive behaviour of the cell and analyse the cellular response to biophysical signals in the extracellular environment.	[Heffernan et al., 2014] 10.1007/s10439-014-1223-1
Composite scaffold	Chitosan-HA scaffold	Mimic the microenvironment matrix for GBM cells	Single-cells, 2D culture, GSC GBM6 cell lines	Better cellular morphology, growth patterns, and malignant behaviour than adherent monolayers.	[Wang et al., 2016] 10.1002/adhm.201600684
Micelles	HA-Modified Micelles lauroyl-gemcitabine (Gem-C12) and honokiol (HNK) encapsulated	Nanocarriers for targeting drug delivery of combined chemotherapeutics	Single-cells, 3D culture, U87 cell line Subcutaneous glioma-bearing mice; orthotopic xenograft GBM	Deep penetration into spheroids, endocytosis mediated by the CD44 receptor, and increased cytotoxicity of the combined treatment. Enhanced animal survival rate.	[Liu et al., 2018] 10.1021/acs.molpharmaceut.7b01035

Thermosensitive hydrogel	Doxorubicin/paclitaxel embedded Pluronic F127/HA hydrogel system (freeze-dried micelles)	Intratumoral administration of combined chemotherapy	Degradation rate, drug release Injection force determination, Chicken meat model	Controlled release of both chemotherapeutics and great stability. The formulation also showed easy injectability.	[Rezazadeh et al., 2018] 10.4103/1735-5362.228918
Hydrogel	HA/ poly(ethylene glycol) (PEG)	Mimic the microenvironment matrix for GBM cells	3D culture, patient-derived GBM cells	Cell viability and proliferation rates are as good as or better than standard glioma spheres culture. Compatible results for use in molecular and cellular analyses.	[Xiao et al., 2018] 10.3791/58176
Aerogel sponge	Stromal cell derived factor-1α loaded in Silk fibroin-HA-Heparin	Chemoattractant loaded scaffold trap for brain tumor cells	Single-cells, NIH3T3 cell line	Cytocompatible material with adequate mean pore diameter (60 μm) and connectivity for welcoming cells. Texture similar to brain tissue (6–13 kPa Young's Modulus), slower biodegradation and 93% retention of SDF-1α.	[Najberg et al., 2019] 10.1016/j.carbpol.2020.116107
Nanofibers scaffold	Polycaprolactone (PCL) /gelatin (Gel) / hyaluronic acid (HA)	Mimic GBM extracellular matrix	Single-cells, U251 cell line	The topography and surface chemistry (hydrophilic) played an important role in the biomechanical, proliferative, and morphological properties of the cells.	[Unal et al., 2020] 10.3390/ma13112661
Drug loaded Hydrogel	Crosslinked-HA-adipic acid dihydrazide (ADH) loaded with human urotensin (hUII) peptide and doxorubicin (DOX) or temozolomide (TMZ)	Chemoattractant matrix to trap and eradicate GBM cells	Single-cells, U87MG cell line	Cell migration and invasion into the hydrogel in response to the hUII. Significant cytotoxicity of DOX-loaded hydrogels for U87MG cells.	[Kasapidou et al., 2021] 10.1039/d1sm01003d
Drug-loaded hydrogel	Peptide functionalized HA (HACF) cross-linked by	Drug delivery reservoir for resection cavity	Single-cells, patient-derived GBM cells	Biocompatible, adaptable, and adjustable to local tissue stiffness. 45% improvement in patient survival.	[Parkins et al., 2021] 10.1016/j.biomaterials.2021.120919

	cucurbit[8]uril (CB[8])		Patient-derived xenograft (PDX) rats		
Hydrogel	Methacryloyl-modified HA (HAMA)	Tissue engineering application	-	Suitable structure, porosity, and stiffness for tissue engineering purposes. Also, it showed to be resistant to collagenase biodegradation.	[Velasco-Rodriguez et al., 2021] 10.3390/ijms22136758
Composite scaffold	HA/gelatin (Gel) modified bacterial cellulose (BC)	Mimic GBM extracellular matrix	3D culture, U251 cell line	Good cell vitality, forming multi-layers and cell clusters in the scaffolds.	[Unal et al., 2021] 10.1007/s10570-020-03528-5
Drug loaded Nanogel	Lactoferrin (Lf)/phenylboronic acid (PBA)-functionalized HA nanogels crosslinked with disulfide-bond and doxorubicin hydrochloride (DOX)-loaded	Drug delivery and dual-targeting GBM	Single-cells and coculture, G422, bEnd.3 cell lines SD rats - pharmacokinetics, ICR mice - biodistribution	Controlled release of the drug, effective BBB penetration, and precise glioma dual-targeting (PBA and HA), presenting strong cytotoxicity against G422 cells.	[Zhang et al., 2021] 10.1016/j.cjche.2021.08.029
Polymer-drug conjugate	HA-Hydrazone-DOX	GBM local treatment	2-3D culture GL261, U87MG, B16F10 cell lines GL261-bearing mice	Increased tumor cell mortality and inhibition of the tumor growth. Bio-responsive linker was crucial for the observed bioperformance.	[Malfanti et al., 2022] 10.3390/pharmaceutics14010124

Table S2. Systems developed for CNS injuries application

Device	Matrix composition	Proposed mechanism	Porosity connectivity diameter	Mechanical properties	Study model (In vitro, in vivo, ex vivo)	Major Findings	Reference
Hydrogel	HA –PDL hydrogel	Scaffold material for the repair of defects brain tissue	Good connectivity and adherence	-	• Human DRG cell line and NSCs • 3 months old Sprague Dawley rats	After implantation, the polymer hydrogel rightly bridged the tissue defect, establishing a permissive interface with the host tissue to aid cell ingrowth and angiogenesis.	[Tian et al.2005] 10.1089/ten.2005.11.513
Hydrogel	HA-arginine-glycine-aspartic acid (RGD)	Tissue engineering for brain regeneration	-	-	• Sprague-Dawley rats, cortex implantation	HA-RGD hydrogel provided a structural, 3D continuity across the cortex and favoured reorganisation of local wound-repair cells, angiogenesis, and axonal growth.	[Cui et al., 2006] 10.1007/s10856-006-0615-7
Hydrogel	HA- Poly-D-lysine (PLL)/ nogo-66 receptor antibody (antiNgR)	Tissue engineering for nerve regeneration	10 to 100 μm interconnected network	-	• Sprague-Dawley rats, lateral hemisection of spinal cord	Inhibited the glial scar formation, support angiogenesis, and promote axonal extension.	[Wei et al., 2007] 10.1002/jbm.b.31689

Sponge-like scaffold	Collagen type I and II/HA	Neurogenic induction of cells seeded into a construct for brain regeneration	80-200μm pore size(75% to 91%)	1-6.3kPa Young modulus	• 2-3D, primary cell culture	The scaffolds favour the differentiation of neural stem cells (NSCs) to neuronal cells in vitro.	[Wang et al., 2009] 10.1016/j.actbio.2009.03.033
Gel	HA	Matrix to reduce the marginal glial scarring	120 to 182 μm porosity	Tensile strength: 4.1-6.3 N/mm2	• Sprague-Dawley rats	Inhibited the glial scar formation by decreasing the thickness of gliosis and by reducing the number of the glial cells.	[Lin et al., 2009] 10.1016/j.wneu.2009.09.004
Hydrogel-microspheres composite	HA hydrogel / recombinant human brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF)-poly(lactic-co-glycolic acid) microspheres loaded	Delivery system for NSCs	-	-	• 2-3D, primary and single-cells cultures (Sprague-Dawley embryos forebrain cells)	Stable releasing of the biofactors, promoting cells survival and growth. The soft property was suitable for CNS tissue. Biocompatible material, with great adhesion and cell proliferation.	[Wang et al., 2011] 10.1007/s11095-011-0452-3
Hydrogel	HA-Modified methylcellulose	NSPCs cells delivery vehicle	-	-	• Rat NSPCs cells	Increased oligodendrocytes differentiation.	[Tam et al.,2012] 10.1039/c2jm33680d

Electrospun nanofiber scaffold	HA-laminin-coated polycaprolactone (PCL) nanofibers	Neural tissue engineering for restore damaged tissue	Fiber diameters: 600–1200 nm	-	• 2-3D cell culture, eGFP neuronal SH-SY5Y cell line	The aligned nanofibers permitted the guidance of neurite outgrowth.	[McMurtrey, 2014] 10.1088/1741-2560/11/6/066009
Hydrogel	HA-laminin/SDF-1α loaded	Matrix to enhance neural transplant retention and migration delivery system	-	-	• 3D, primary cell culture; NPSCs • C57BL/6 mice, brain injection	SDF-1α signalling critically mediates NPSC transplant chemotactic migration, and the matrix increases NPSCs transplant retention.	[Addington et al., 2017] 10.1016/j.matbio.2016.09.007
Microporous annealed particle hydrogel	HA/K-peptide/Q-peptide/RGD	Matrix to promote brain tissue repair after stroke	-	-	• C57BL/6, stroke-induced	Reduced inflammatory response following stroke and increased peri-infarct vascularization.	[Nih et al., 2017] 10.1002/adma.201606471
Drug delivery scaffold	SA and HA loaded device	Microenvironnement to embed stem cells in traumatic brain injury	200 µm to tens of µm	0.1 kPa to 1 kPa Young Modulus	• HUC-MSCs • SD rats	NSCs embedded in HA collagen biomaterials may promote reinnervation of damaged facial nerves, and artificial conduction of NSCs may provide	[Zhang et al., 2008] 10.1039/C7TB03213G

						a potential treatment for peripheral nerve injury.	
Hydrogel	Glycidyl methacrylate-HA and Methacrylic anhydride-HA/Collagen I and laminin functionalized	Engineered scaffold for tissue regeneration	1 μm pore size	2-6kPa Young modulus	• Schwann Cells and dorsal root ganglia (DRGs) cell lines • Rat isolated tissue (sciatic nerve, brain and spinal cord)	The material can be tuned to numerous soft tissues, and supported 3D axonal elongation of DRGs cultures.	[Spearman et al., 2020] 10.1002/jbm.a.36814.
Hydrogel	HA-galactose oxidase (GalOx)-horseradish peroxidase (HRP)/ bone mesenchymal stem cells (BMSC) and nerve growth factors (NGF) encapsulated	Implant or cell/drug delivery vehicle for tissue repair	<100um pore size loose and porous structure	Low elastic modulus <0.1kPa	• 3D and single-cells models; BMSC cells • Traumatic Brain Injury (TBI) model, C57BL/6 mice	Good biocompatibility, stability, and biodegradability. Suitable for cell survival and proliferation, accelerated brain repair process.	[Wang et al., 2022] 10.1016/j.mtbio.2021.100201
Hydrogel	HA-poly(N-isopropylacrylamide)	Hybrid interpenetrating polymer network as cell carrier for	-	0.1kPa-8kPa Elastic modulus	• Primary culture, NP cells • Cartilage and intervertebral	The matrix supported the cell viability and the phenotype expression of the encapsulated cells.	[Guo et al., 2022] 10.1016/j.carbpol.2021.118828

		nucleus pulposus (NP) repair			disc (IVD) organ culture		
Nanogel	Iron oxide (Fe3O4)-HA	Theranostic material for Alzheimer's disease	–	-	• Single-cells culture, C8-D1A cell line	Non-cytotoxic matrix. Efficient generation of negative contrast in MRI.	[Chen et al., 2022] 10.1016/j.arabjc.2022.103748

Table S3. Systems developed for PNS injuries application

Device	**Matrix composition**	**Proposed mechanism**	**Porosity and connectivity**	**Mechanical properties**	**Study model (In vitro, in vivo, ex vivo)**	**Major Findings**	**Reference**
Composite Conduit	HA / collagen	Tissue engineering for nerve regeneration	Diameter 1.2 mm Porosity 50 μm	-	• Rat SCs and neurospheres • NSCs from neural cortex of SD rat embryos	Cultured rat Schwann cells and neurospheres grow *in vitro* on new artificial HA-based nerve conduits. After 3 weeks of culture, conduits stayed circular with a round lumen, and cell-conduits conserved their original structure.	[Sakai et al., 2007] PMID: 17502696
Composite conduit	HA / collagen	Tissue engineering for nerve regeneration	7 mm in length	-	• Normal adult New Zealand rabbits	NSC-embedded NT-3 HA-collagen composite scaffold, has shown that a number of nerve fibers were still unmyelinated. Degeneration and swelling of myelin lamellae were also visible.	[Zhang et al., 2008] 10.1186/1479-5876-6-67

Composite Conduit	HA-Silk Fibroin composite device	Tissue engineering for nerve regeneration	79% of porosity	G'/G': 6 to 7 viscoelasticity	• Rat Schwann cells (rSCs) • Male CD-1 mice	Both HA and HA-SF scaffolds were received by the host with no residual immune response at 8 weeks. The results show that SF incorporation improves the mechanical properties of the material and leads to promising biocompatible conduits for tubing strategies.	[Gisbert et al., 2020] 10.1016/j.ijbiomac.2020.01.149
Composite Conduit	PDLLA/β-TCP/HA/CHS/NGF	Polymer based scaffold for controlled release of NGF	Semi-permeable, pore size less than 10 μm	13-60 kPa Elastic modulus	• PDLLA/β-TCP nerve conduits • Sciatic nerve defect in SD rat	Substantial enhancements in nerve regeneration were noticed after using the PDLLA/β-TCP/HA/CHS/NGF NGCs based on the different assessments. In vivo studies show that the PDLLA/ β-TCP/ HA/ CHS/NGF sustained-release NGCs can significantly stimulate peripheral nerve regeneration, and the effect is comparable to that of autograft.	[Yan et al., 2021] 10.1007/s11595-021-2450-6
Scaffold	PEDOT-doped HA NPs/ CS / Gel matrix	Tissue engineering for nerve regeneration	200– 300 μm pore size 83-92% porosity	13-60 kPa Elastic modulus	• PC12 cell line	8% PEDOT-HA/Cs/Gel scaffold had a higher cell adhesive efficiency and cell viability in comparison to the other conductive scaffolds. It also has shown a higher expression of synapse growth genes of GAP43 and SYP compared	[Wang et al., 2017] 10.1016/j.msec.2016.10.029

						with the Cs/Gel control group.	
Hydrogel	HA-CS composite system	Hydrogels for nerve growth factor(NGF) sustained release and nerve regeneration	Porosity: 20 to 100μm	2 to 4 kPa Elastic modulus	• RSC96 rat SCs and PC12 cell lines • Healthy adult Sprague-Dawley (SD) rats	• The good mechanical, porous, and swelling properties play a synergistic role in enhancing nerve regeneration. The CS-HA/NGF hydrogels through a sustained release are favorable for promoting cell adhesion, spreading, and differentiation • Chitosan and HA inhibited extraneural scarring, promoted nerve regeneration, raised the nerve conduction velocity and amended the recovery of nerve function.	[Xu et al., 2016] 10.1177/0883911516662068 [Li et al., 2018] 10.3892/mmr.2018.8388

						Combined together they enhance neural regeneration and repair.	
Hydrogel	HA-CS/NGF hydrogel	Injectable hydrogels aimed to sustained release of nerve growth factor (NGF)	Pore size 53-73μm Porosity(82-87%)	2.3-4.5kPa Elastic modulus	• BMMSCs, RSC96 rat SCs cells and PC12 cell line	PDLLA/β-TCP nerve conduits formulated with CS-HA/NGF hydrogels improved the axon regeneration and myelination, contrasted to the PDLLA/β-TCP hollow nerve conduits and the autograft group. These findings imply that the CS-HA/NGF injectable hydrogel can successfully upgrade nerve regeneration, hence, it is a good candidate in the field of neural tissue engineering.	[Xu et al., 2022] 10.1016/j.compositesb.2021.109509