

Title	Hydrogel-assisted neuroregeneration approaches towards brain injury therapy: A state-of-the-art review
Authors	Kornev, Vladimir A.; Grebenik, Ekaterina A.; Solovieva, Anna B.; Dmitriev, Ruslan I.; Timashev, Peter S.
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Appendix A. Supplementary data

Table S1. Inherent characteristics of hyaluronic acid (HA) as a candidate for hydrogel-based brain tissue regeneration.

Positive findings	Negative findings
<ul style="list-style-type: none"> • natural component of the CNS (biocompatible) [23,25,41,44,46] • immunoneutral [32,65] • biodegradable [32] • highly porous [34,44] • stimulates neuronal viability and differentiation of NS/PCs, NPCs, and iPS-NPCs <i>in vitro</i> [32,41,42,49] • stimulates neurite outgrowth of HNPCs <i>in vitro</i> [40] • promotes neuronal differentiation of hiPS-NPCs <i>in vivo</i> [14,47] • holds antigliosis and anti-inflammatory effects <i>in vivo</i> [45,46] • supports survival and proliferation of C17.2 and ReNcell <i>in vivo</i> [65] • shields transplanted cells from host immune response <i>in vivo</i> [14,65] • HA-PLGA co-gel provides functional improvement <i>in vivo</i> [46] • does not influence gel stiffness in co-gels [55] • superior to Matrigel in terms of neurite outgrowth in SH-SY5Y cell line <i>in vitro</i> [38] • HA-modified alginate supports greater cell viability and neuronal differentiation of ESCs and NSCs and neurite extension when compared to unmodified alginate [78] • HA is a shear-thinning agent in co-gels [96] 	<ul style="list-style-type: none"> • poor adhesiveness [32,34,36,49] • does not interact with integrins [23,35] • does not support hiPS-NPCs viability <i>in vivo</i> [14] • requires modifications to reduce the biodegradation rate [23,34,35,49] • requires another component (e.g. collagen) for stabilization [49] • swelling [93]

NS/PCs – neural stem/progenitor cells – a heterogeneous cell population; NPCs – neural progenitor cells; iPS-NPCs – induced pluripotent stem cell-derived neural progenitor cells; hiPS-NPCs – human induced pluripotent stem cell-derived neural progenitor cells; C17.2 – a mouse immortalized NSC line; ReNcell – human immortalized NPC line; PLGA – poly(lactic-co-glycolic acid); SH-SY5Y – human neuroblastoma cell line; ESCs – embryonic stem cells; NSCs – neural stem cells

Table S2. Inherent characteristics of collagen type I as a candidate for hydrogel-based brain tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none"> • biocompatible [48,62–64] • non-toxic[64] • biodegradable [48] • non-immunogenic [21,63–65] (though negated by Itosaka <i>et al.</i> [113]) • self-healing <i>in situ</i> [64] • reduces micro- and astrogliosis <i>in vivo</i> [64,66] • gels under physiological conditions [49] • supports differentiation of BMSCs towards neuronal lineage [59] • retains and stabilizes HA [49,63] • supports viability, proliferation, and differentiation of embryonic, postnatal, and adult NS/PCs when mixed with HA [49,63] • supports neurite outgrowth [53,58,60,157] 	<ul style="list-style-type: none"> • does not naturally occur in mammalian brain tissue, except subventricular zone [49,61] • has no measurable effect on NSC's viability [57,152] • decreases in volume post gelation both <i>in vitro</i> and <i>in vivo</i> [64] • increases stiffness in co-gels [55,59] • inferior to Matrigel and self-assembling peptides in terms of NSCs survival and differentiation [61] • inferior to Matrigel in terms of neural differentiation and neurite growth in hESCs experiments <i>in vitro</i> [107] • inferior to Matrigel in terms of NSCs viability, differentiation, and migration <i>in vitro</i> [61]

BMSCs – bone marrow-derived stem cells; *hESCs* – human embryonic stem cells

Table S3. Inherent characteristics of alginate as a candidate for hydrogel-based brain tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none">• non-toxic [68,71–73,78,91]• biocompatible [78]• non-inflammatory [78]• shields NSCs from host immune response [78]• neuro-protective [73,75]• stimulates structural and functional maturation of NSCs, glial cells [74,75]• supports NSCs viability and proliferation [71,74,78]• promotes self-healing when used as a cross-linker for the chitosan-based hydrogel [91]• chitosan-alginate co-gel supports viability and neuronal differentiation of NSCs [91]• alginate-poly(γ-glutamic acid) ICC scaffolds are highly porous, non-cytotoxic to iPS-NPCs and promote their neuronal differentiation [76]	<ul style="list-style-type: none">• does not naturally occur in mammalian brain tissue [67,68]• poorly recovers after shear stress [77]• hardly injectable [77]• non-degradable [68]• degradation products decrease NPCs proliferation [68]• insufficient porosity [68,74]• requires modifications to provide cell attachment and survival [74,78]• supports worse NSCs spheroids proliferation and differentiation when compared to chitosan-based hydrogel [77]• requires cross-linking to prevent diffusion <i>in vivo</i> [78]

Table S4. Inherent characteristics of chitosan as a candidate for hydrogel-based brain tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none">• thermally cross-linkable [84]• highly porous [85,86,90]• biodegradable [85]• non-immunogenic [83]• non-toxic to NSCs [77,91]• cell-adhesive for cervical ganglion neurons and embryonic cortical neurons [82,85]• decreases stiffness in chitosan-agarose co-gel [82]• suits for drug delivery systems [89]• favors NSC spheroids' proliferation and differentiation [77]• improves functional recovery in zebrafish embryos when injected with neurosphere NSCs [77]• chitosan-alginate co-gel supports viability and neuronal differentiation of NSCs [91]	<ul style="list-style-type: none">• long gelling time [84,89]• can induce cationic cytotoxicity [90]• requires modifications to support cell viability and neurite outgrowth [84,85]• requires modifications for self-healing [77,89,91]

Table S5. Inherent characteristics of methylcellulose- and HAMC- as candidates for hydrogel-based tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none"> • gelling at physiological temperatures [15] • injectable [15,93,94,97,101,103] • biodegradable [103] • exhibit anti-inflammatory [93,97–100,103] and anti-astrogliosis effects [98–100,103] • non-toxic [97,103] • applicable to drug delivery systems [92,93,95–100] • support viability of NS/PCs [94] • improve the solubility of sparingly soluble drugs [92] • methylcellulose reduces swelling in co-gels [93,94,103] • methylcellulose is self-healing [96,103] • HAMC prevents cell sedimentation and aggregation [94,102] • HAMC promotes NSC viability and penetration into host brain <i>in vivo</i> [102] 	<ul style="list-style-type: none"> • methylcellulose exhibits low hydrophilicity unless blended with HA or modified [92] • barely functionalizable backbone [96]

Table S6. Inherent characteristics of Matrigel as a candidate for hydrogel-based brain tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none"> contains growth factors and adhesive proteins [15,20,22,26,104] injectable [15] porous [180] physiological stiffness [106] growth factor-reduced form exhibits an anti-inflammatory effect, supports ES-NPCs viability and neuronal differentiation, and promotes host cell proliferation <i>in vivo</i> [109] promotes NS/PCs maturation and functionality in MCAO model [112] superior to collagen I in terms of neuronal differentiation and neurite growth in hESCs experiments <i>in vitro</i> [107] growth factor reduced form is superior to RADA16-I in terms of viability, migration, and maturation of ES-NPCs <i>in vitro</i> [109] superior to collagen I in terms of NSCs viability, neuronal differentiation, and migration <i>in vitro</i> [61] supports viability and maturation of spiral ganglion neurons <i>in vitro</i> [111] applicable for modification of porous PEG scaffold to promote rat neurons' neurite outgrowth [156] 	<ul style="list-style-type: none"> unstandardized composition [15,66,105,109] immunogenic [15] solidifies at room temperature [108] inferior to salmon fibrin in terms of stimulating neurite growth of cortical and spinal neurons <i>in vitro</i> [106] inferior to RADA16-I in terms of NSCs survival and neuronal differentiation <i>in vitro</i> [108] inferior to RADA16-I hydrogel in terms of NSCs viability <i>in vitro</i> [61] inferior to HA in terms of neurite outgrowth in SH-SY5Y cell line <i>in vitro</i> [38] increases stiffness in co-gels [110]

ES-NPCs – embryonic stem cell-derived neural progenitor cells; MCAO – middle cerebral artery occlusion; RADA16-I – a 16-mer peptide consisting of four RADA (arginine, alanine, aspartate, alanine) tetramers, also known as PuraMatrix; PEG – poly(ethylene glycol)

Additional citation:

[180] Balachandran NTL and HL and NMS and K. Fabrication of a matrigel–collagen semi-interpenetrating scaffold for use in dynamic valve interstitial cell culture. *Biomed Mater* 2017;12:45013.

Table S7. Inherent characteristics of fibrin as a candidate for hydrogel-based brain tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none"> • easily tunable mechanical properties [113,116,120,121] • porous [121] • biodegradable [15,119,121] • injectable [15,113,122] • bioactive (contains RGD peptide) [119,121] • non-toxic [120] • can be produced from patient's own blood (non-immunogenic) [113] • advantageous drug delivery platform [116–118,122] • promotes neuronal differentiation and maturation rather than glial differentiation of NSCs <i>in vitro</i> [120] • supports viability and promotes neuronal differentiation and migration of BMSCs <i>in vivo</i> [113] • salmon fibrin is superior to Matrigel in terms of stimulating neurite growth of cortical and spinal neurons <i>in vitro</i> [106] • Tisseel fibrin gel is superior to PEG in terms of NPC neuronal differentiation <i>in vitro</i> [159] 	<ul style="list-style-type: none"> • pro-inflammatory [114,115] • requires modifications for proper neuron-glial differentiation of ES-NPCs <i>in vitro</i> [118] • inferior to collagen type I in terms of DRG neurite outgrowth stimulation <i>in vitro</i> [53]

RGD – a cell-adhesive tripeptide (arginine-glycine-aspartate); DRG – dorsal root ganglion

Table S8. Inherent characteristics of gellan gum as a candidate for hydrogel-based brain tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none">• non-toxic [16,129]• resistant to acid stress [16]• injectable [124,126]• <i>in situ</i> gelling [124]• porous [127,129]	<ul style="list-style-type: none">• promotes oligodendrocytal differentiation of NS/PCs <i>in vitro</i> [126]• aggregates NS/PCs [126]• requires purification from divalent cations prior to injection [127,128]• requires modifications to support cell viability, differentiation and neurite outgrowth [127–129]

Table S9. Inherent characteristics of self-assembling peptides and proteins as candidates for hydrogel-based brain tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none"> • biocompatible at working concentration [61,137,143] • biodegradable [130,149] • non-immunogenic [61] • RADA16-I is porous [137,139,143] • RADA16-I is injectable and self-healing [104,148,149] • RADA16-I supports NSC migration and differentiation into neurons and astrocytes <i>in vitro</i> [108] • Keratin-based hydrogels support NS/PC survival <i>in vitro</i> [136] • RADA16-I is an advantageous and easy-tunable drug-delivery system <i>in vitro</i> [137,138] • RADA16-I supports NSC viability <i>in vitro</i> [143] and <i>in vivo</i> [149] • RADA16-I is mechanically tunable [143] • RADA16-I improves viability, differentiation, morphological and functional maturation of ES-NPCs [129] • keratin-based hydrogels are highly porous [147] • keratins contain internal RGD motifs [147] • K_xL_y, R_xL_y and E_xL_y are easily injectable, porous, cause minimal gliosis and inflammation, exhibit no evident toxicity to neurons and induce vascularization <i>in vivo</i> [130] • RADA16-I readily integrates with host tissue and reduces micro- and astrogliosis <i>in vivo</i> [104,148] • RADA16-I is superior to Matrigel in terms of NSC survival and differentiation <i>in vitro</i> [108] (though neglected by [109]) • RADA16-I is superior to Matrigel in terms of NSC viability <i>in vitro</i> [61] • elastin-like proteins support DRG viability <i>in vitro</i> [146] • human keratin promotes neurite growth and vascularization of peripheral nerves <i>in vivo</i> [147] • RADA16-I promotes neurite outgrowth and supports survival of iPS-NPCs <i>in vivo</i> [104] 	<ul style="list-style-type: none"> • RADA16-I is toxic to human NSCs at concentrations above 1% [108] • keratins are slowly degradable [147] • K_xL_y, R_xL_y and E_xL_y support limited ingrowth of nerve fibers and neuron-supportive astroglia [130] • RADA16-I does not promote migration of neurons and oligodendrocytes and does not prevent host cells from apoptosis [148] • RADA16-I is inferior to growth factor-reduced Matrigel in terms of viability, migration, and maturation of ES-NPCs <i>in vitro</i> [109]

K_xL_y, R_xL_y, and E_xL_y – diblock copolypeptide hydrogels including combinations of lysine and leucine (K_xL_y), arginine and leucine (R_xL_y), and glutamate and leucine (E_xL_y)

Table S10. Inherent characteristics of PEG as a candidate for hydrogel-based brain tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none"> • highly hydrophilic [158] • supports neurite extension at low concentrations (PC12 and DRG cells) <i>in vitro</i> [157,160] • 4-arm PEG-cross-linked PLL hydrogels are biodegradable and promote viability, proliferation, and neuronal differentiation of NPCs and NSCs <i>in vitro</i> [153,154] • PEG-RADA16-I composite supports DRG neurite outgrowth <i>in vitro</i> [161] • IGF-1 gradient in PEG-PLGA system directs axonal growth <i>in vitro</i> [163] • PLA-b-PEG-b-PLA-based hydrogels attenuate glial response <i>in vivo</i> [165,166] • PEG-Si is thixotropic (shear-thinning and self-healing) [162] • a PLA-b-PEG-b-PLA triblock-derived hydrogel is biocompatible and minimally-swelling [166] 	<ul style="list-style-type: none"> • poorly porous [156,159] • non-degradable [152,157–159,162,164,165] • bioinert [160] • photo-encapsulation of primary neurons induces apoptosis [120] • poorly supports neuronal differentiation of NPCs <i>in vitro</i> [159] • requires modifications to support cell viability and proliferation [152,158] • PEG-Si increases glial response <i>in vivo</i> [162]

PC12 – rat pheochromocytoma cells; PLL – poly-L-lysine; IGF-1 – insulin-like growth factor 1; PLA-b-PEG-b-PLA – triblock polymer built of poly(lactic acid) and poly(ethylene glycol); PEG-Si – a thixotropic PEG-based hydrogel with dispersed silica nanoparticles

Table S11. Inherent characteristics of MA- and MAA-based polymers as candidates for hydrogel-based tissue regeneration

Positive findings	Negative findings
<ul style="list-style-type: none"> • pHPMA is highly porous [167] • pHEMA can be modified to tune drug release kinetics <i>in vitro</i> [168] • sialic acid-modified pHPMA is highly biocompatible, stimulates vascularization, host cell migration, their neuronal differentiation, TH-positive fiber growth, and prevents gliosis <i>in vivo</i> [167] • pHEMA integrates with host spinal cord, stimulates neurofilament growth and attenuates glial response <i>in vivo</i> [171] • pHPMA-RGD stimulates axonal growth and neuronal migration <i>in vivo</i> [172,174] • pHEMA attenuates astrogliotic response and inhibits the synthesis of neuroinhibitory CSPG <i>in vivo</i> [175] • PLA-b-pHEMA is non-toxic to spinal motoneurons and allows neurite outgrowth <i>in vitro</i> [170] • PLA-b-pHEMA stimulates axonal growth and prevents glial scar formation <i>in vivo</i> [170] 	<ul style="list-style-type: none"> • pHEMA and pHPMA are non-degradable [12,16,167,170,175] • pHEMA is stiff [168] • pHPMA is swelling [167] • pHPMA does not prevent glial scarring <i>in vivo</i> [172] • pHPMA and pHEMA induce microglial infiltration <i>in vivo</i> [174,175] • PLA-b-pHEMA induces microglial and macrophageal response <i>in vivo</i> [170]

pHPMA – poly(*N*-[2-hydroxypropyl] methacrylamide); *pHEMA* – poly(2-hydroxyethyl methacrylate); *PLA-b-pHEMA* – a block copolymer hydrogel built of poly(lactic acid) and poly(2-hydroxyethyl methacrylate); *TH* – tyrosine hydroxylase (the key dopamine synthesis enzyme)