CORA Cork Open Research Archive
Cartlann Taighde Oscailte Chorcaí

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.
Publication date	2018
Original Citation	Kornev, V.A., Grebenik, E.A., Solovieva, A.B., Dmitriev, R.I. and Timashev, P.S., 2018. Hydrogel-assisted neuroregeneration approaches towards brain injury therapy: A state-of-the-art review. Computational and structural biotechnology journal. 16, 488-502 DOI:10.1016/j.csbj.2018.10.011
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://www.sciencedirect.com/science/article/pii/S2001037018300977?via%3Dihub - 10.1016/j.csbj.2018.10.011
Rights	© 2018 The Author(s). Published by Elsevier B.V. on behalf of Research Network of Computational and Structural Biotechnology. - https://creativecommons.org/licenses/by/4.0/
Download date	2026-11-06 02:26:10
Item downloaded from	https://hdl.handle.net/10468/8287

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

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
• 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 *in vitro* [32,41,42,49] • stimulates neurite outgrowth of HNPCs *in vitro* [40] • promotes neuronal differentiation of hiPS-NPCs *in vivo* [14,47] • holds antigliosis and anti-inflammatory effects *in vivo* [45,46] • supports survival and proliferation of C17.2 and ReNcell *in vivo* [65] • shields transplanted cells from host immune response *in vivo* [14,65] • HA-PLGA co-gel provides functional improvement *in vivo* [46] • does not influence gel stiffness in co-gels [55] • superior to Matrigel in terms of neurite outgrowth in SH-SY5Y cell line *in vitro* [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]	• poor adhesiveness [32,34,36,49] • does not interact with integrins [23,35] • does not support hiPS-NPCs viability *in vivo* [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
• biocompatible [48,62–64] • non-toxic[64] • biodegradable [48] • non-immunogenic [21,63–65] (though negated by Itosaka *et al.* [113]) • self-healing *in situ* [64] • reduces micro- and astrogliosis *in vivo* [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]	• 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 *in vitro* and *in vivo* [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 *in vitro* [107] • inferior to Matrigel in terms of NSCs viability, differentiation, and migration *in vitro* [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
• 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]	• 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 *in vivo* [78]

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

Positive findings	Negative findings
• 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]	• 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
• 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 *in vivo* [102]	• 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
• 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 *in vivo* [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 *in vitro* [107] • growth factor reduced form is superior to RADA16-I in terms of viability, migration, and maturation of ES-NPCs *in vitro* [109] • superior to collagen I in terms of NSCs viability, neuronal differentiation, and migration *in vitro* [61] • supports viability and maturation of spiral ganglion neurons *in vitro* [111] • applicable for modification of porous PEG scaffold to promote rat neurons' neurite outgrowth [156]	• 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 *in vitro* [106] • inferior to RADA16-I in terms of NSCs survival and neuronal differentiation *in vitro* [108] • inferior to RADA16-I hydrogel in terms of NSCs viability *in vitro* [61] • inferior to HA in terms of neurite outgrowth in SH-SY5Y cell line *in vitro* [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
• 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 *in vitro* [120] • supports viability and promotes neuronal differentiation and migration of BMSCs *in vivo* [113] • salmon fibrin is superior to Matrigel in terms of stimulating neurite growth of cortical and spinal neurons *in vitro* [106] • Tisseel fibrin gel is superior to PEG in terms of NPC neuronal differentiation *in vitro* [159]	• pro-inflammatory [114,115] • requires modifications for proper neuron-glial differentiation of ES-NPCs *in vitro* [118] • inferior to collagen type I in terms of DRG neurite outgrowth stimulation *in vitro* [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
• non-toxic [16,129] • resistant to acid stress [16] • injectable [124,126] • *in situ* gelling [124] • porous [127,129]	• promotes oligodendrocytal differentiation of NS/PCs *in vitro* [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
• 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 *in vitro* [108] • Keratin-based hydrogels support NS/PC survival *in vitro* [136] • RADA16-I is an advantageous and easy-tunable drug-delivery system *in vitro* [137,138] • RADA16-I supports NSC viability *in vitro* [143] and *in vivo* [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 *in vivo* [130] • RADA16-I readily integrates with host tissue and reduces micro- and astrogliosis *in vivo* [104,148] • RADA16-I is superior to Matrigel in terms of NSC survival and differentiation *in vitro* [108] (though neglected by [109]) • RADA16-I is superior to Matrigel in terms of NSC viability *in vitro* [61] • elastin-like proteins support DRG viability *in vitro* [146] • human keratin promotes neurite growth and vascularization of peripheral nerves *in vivo* [147] • RADA16-I promotes neurite outgrowth and supports survival of iPS-NPCs *in vivo* [104]	• 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 *in vitro* [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
• highly hydrophilic [158] • supports neurite extension at low concentrations (PC12 and DRG cells) *in vitro* [157,160] • 4-arm PEG-cross-linked PLL hydrogels are biodegradable and promote viability, proliferation, and neuronal differentiation of NPCs and NSCs *in vitro* [153,154] • PEG-RADA16-I composite supports DRG neurite outgrowth *in vitro* [161] • IGF-1 gradient in PEG-PLGA system directs axonal growth *in vitro* [163] • PLA-b-PEG-b-PLA-based hydrogels attenuate glial response *in vivo* [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]	• 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 *in vitro* [159] • requires modifications to support cell viability and proliferation [152,158] • PEG-Si increases glial response *in vivo* [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
• pHPMA is highly porous [167] • pHEMA can be modified to tune drug release kinetics *in vitro* [168] • sialic acid-modified pHPMA is highly biocompatible, stimulates vascularization, host cell migration, their neuronal differentiation, TH-positive fiber growth, and prevents gliosis *in vivo* [167] • pHEMA integrates with host spinal cord, stimulates neurofilament growth and attenuates glial response *in vivo* [171] • pHPMA-RGD stimulates axonal growth and neuronal migration *in vivo* [172,174] • pHEMA attenuates astrogliotic response and inhibits the synthesis of neuroinhibitory CSPG *in vivo* [175] • PLA-b-pHEMA is non-toxic to spinal motoneurons and allows neurite outgrowth *in vitro* [170] • PLA-b-pHEMA stimulates axonal growth and prevents glial scar formation *in vivo* [170]	• 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 *in vivo* [172] • pHPMA and pHEMA induce microglial infiltration *in vivo* [174,175] • PLA-b-pHEMA induces microglial and macrophageal response *in vivo* [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)