

# [The role of biomaterials as angiogenic modulators of spinal cord injury: mimetics...](https://assignbuster.com/the-role-of-biomaterials-as-angiogenic-modulators-of-spinal-cord-injury-mimetics-of-the-spinal-cord-cell-and-angiogenic-factor-delivery-agents/)

[Health & Medicine](https://assignbuster.com/essay-subjects/health-n-medicine/)

## Introduction

Vascular disruption following SCI plays a critical role in triggering some of the secondary events associated with this injury such as uncontrolled infiltration of inflammatory cells and ischemia. The extension of intraparenchymal hemorrhage that appears as a consequence of SCI has been correlated with the area occupied by the cystic cavity ( [Noble and Wrathall, 1989a](#B50) , [b](#B51) ). Two days following the incidence of SCI, the density of blood vessels decreases and only residual levels are observed at the injury site ( [Ng et al., 2011](#B48) ). Angiogenesis (the growth of blood vessels from preexisting ones) initiates 3 to 4 days after injury and is seen up to 1 week after SCI ( [Casella et al., 2002](#B14) ; [Dray et al., 2009](#B22) ). Although different studies showed revascularization similar to pre-lesion levels or even fivefold higher, these new vessels are not associated with astrocytes, pericytes, or neurons. Moreover, no restoration of Glut-1 transporters (essential for the continuous supply of glucose to metabolically unbalanced neurons) was seen until 2 weeks following SCI ( [Ng et al., 2011](#B48) ). This demonstrates that endothelial cells (ECs) within newly formed vessels are not in the desired phenotype, and hence, do not guarantee satisfactory recovery from the initial disruption. Different therapeutic approaches have correlated improvements in functional recovery with augmented densities of blood vessels in spinal cord tissue ( [Glaser et al., 2006](#B25) ; [Kaneko et al., 2007](#B36) ). This is further sustained by the elevated metabolic need of neurons, making these cells more susceptible to damage during prolonged ischemia ( [Attwell and Laughlin, 2001](#B6) ). Moreover, the proper restoration of the blood-spinal cord barrier (BSCB) may help control the influx of inflammatory cells into the damaged spinal cord and direct the inflammatory response toward a regenerative path.

The angiogenic response following SCI appears to be modulated by a complex interplay between different proteins ( [Kundi et al., 2013](#B40) ). Among these, vascular endothelial growth factor (VEGF) is thought to possess an ambiguous role in SCI angiogenesis, since some studies show that it has no impact ( [Benton et al., 2009](#B10) ) or increases the lesion volume ( [Benton and Whittemore, 2003](#B11) ). Others correlate the administration of VEGF with higher densities of blood vessels, tissue sparing and improved motor outcomes ( [Widenfalk et al., 2003](#B70) ; [Kim et al., 2009](#B38) ). This might be due to the roles that different VEGF isoforms have on SCI angiogenesis and pathophysiology, the route of administration, dose and short circulatory half-life ( [Crafts et al., 2015](#B17) ). The synergistic action between VEGF and angiopoietin-1 (ANG-1) in the context of SCI was explored by administering these GFs into the lesion immediately after injury. This therapeutic approach promoted vascular stabilization, reduced the lesion volume and functionally translated into improved locomotor behavior in the chronic phase ( [Herrera et al., 2010](#B33) ). ANG-1 limits vascular permeability, helping to maintain the integrity of the BSCB by reducing the number and size of the gap junctions between ECs ( [Baffert et al., 2006](#B7) ). Additionally, ANG-1 contributes to the stabilization and maturation of blood vessels during the final phases of angiogenesis ( [Wong et al., 1997](#B71) ). During an SCI event, mRNA expression and protein levels of ANG-1 are diminished, contributing to decreased integrity of the BSCB ( [Durham-Lee et al., 2012](#B24) ). Delivery of ANG-1 into an SCI animal model resulted in the preservation of blood vessels at the injury site whilst improving locomotor function and permanently rescuing white matter, features that correlated with increased perfused blood vessels ( [Han et al., 2010](#B30) ). Matrix metalloproteinases (MMPs) have also been implicated in the vascular events following SCI ( [Verslegers et al., 2013](#B67) ). This class of enzymes are capable of cleaving all the extracellular matrix (ECM) components and are key to cell migration ( [Nagase et al., 2006](#B46) ). Depletion of MMP-2 in a contusion SCI animal model led to a decrease in EC division during the first 2 weeks following SCI and to significant vascular decline 21 days post-injury ( [Trivedi et al., 2016](#B64) ). On the other hand, up-regulation of MMP-11 during the acute phase of SCI seemed to be involved in disrupting the BSCB and increasing its permeability. The expression of MMP-11 reaches a maximum at 24 h after injury, followed by a dramatic reduction at 72 h and then undetectable at 7 days ( [Noble et al., 2002](#B49) ). These results open the possibility of using modulation of the expression of MMPs as a target for improved vascularization and functional outcomes in SCI.

Biomaterials can aid modulation of the vascular response following SCI via two distinct mechanisms, namely acting as vehicles for the delivery of pro-angiogenic molecules ( [Yu et al., 2016](#B72) ) or as ECM-mimetic platforms that support cell growth and proliferation ( [Rauch et al., 2009](#B55) ). The capacity that biomaterials have for protecting cells and therapeutic agents from the harsh conditions found in SCI lesion sites puts them in a privileged position for the development of targeted regenerative therapies. Furthermore, this is complemented by the possibility of tailoring their mechanical properties to match native ECM and to their biocompatible and biodegradable characteristics ( [Haggerty et al., 2017](#B29) ). Biocompatibility reduces the risk of triggering toxic or immunological responses within the CNS, a feature that if not fulfilled could induce chronic inflammation at the biomaterial interface resulting in the restrain of the scaffold by an avascular glial scar ( [Orive et al., 2009](#B52) ; [Slaughter et al., 2009](#B63) ; [Sensharma et al., 2017](#B61) ). The natural degradation processes of biomaterials under physiological conditions, without originating toxic metabolites, represents another advantage in SCI as it eliminates the need of follow-up surgical procedures for their subsequent removal. Tuning the degradation of these materials allows control of the rate of release of angiogenic factors thereby enabling the optimization of bioavailability and therapeutic concentration ( [Sensharma et al., 2017](#B61) ). Therefore, the present mini-review intends to give an overview of the potential of biomaterials as modulators of vascularization in SCI lesion sites. Emphasis will be given to their capacity to deliver neurovascular agents in a localized manner and to their suitability to act as ECM-like structures that aim to restore vascularization and BSCB following SCI.

## Biomaterials as Tools for the Modulation of Angiogenesis and Vascularization

### ECM-Like Platforms to Support Angiogenesis and Vascularization

In their native environment, cells are embedded in a three-dimensional ECM responsible for providing adequate mechanical and physical cues that provide instructions to engage in specific behaviors ( [Guvendiren and Burdick, 2013](#B28) ). Additionally, the ECM confers to cells mechanical support and protection from the external environment ( [Slaughter et al., 2009](#B63) ). This structure interacts with angiogenic GFs, to coordinate their bioavailability, concentration, and signaling ( [Martino et al., 2015](#B44) ). For instance, VEGF disseminates across the interstitial space and binds both to the ECM and receptors on the surface of cells creating a concentration gradient that attracts endothelial sprouts in the direction of hypoxic regions ( [Vempati et al., 2011](#B66) ). Cell-derived proteases regulate the availability of functional GFs linked to the matrix through their capacity to degrade ECM constituents or by cleaving these molecules into isoforms with reduced bioactivity that are incapable of binding to the ECM ( [Briquez et al., 2016](#B12) ).

Given the importance of the ECM during angiogenesis, developing precise analogs of this structure to therapies that aim to restore vascular perfusion seems particularly promising. On this front, biomaterials seem a perfect fit due to their ability to mimick the mechanical properties of the ECM and to provide specific molecular cues ( [Devolder and Kong, 2012](#B21) ). Commonly, these biomaterials can be of natural origin (ECM-derived or otherwise) or synthetic. Hydrogels from ECM-derived proteins like fibrin, collagen or gelatin are normally used and can be modified regarding their mechanical properties, degradability, cell adhesion, and GF-bearing capacity to a limited extent ( [Browne and Pandit, 2017](#B13) ). Natural non-protein biomaterials, including alginate ( [Dalheim et al., 2016](#B18) ), pectin ( [Neves et al., 2015](#B47) ), dextran ( [Riahi et al., 2017](#B56) ) and gellan gum ( [Gomes et al., 2016](#B26) ), are bioinert and require functionalization with appropriate adhesion motifs to acquire biological activity. Additionally, mechanical properties and degradation profiles are adjustable by varying the degree and nature of crosslinking or by including cell degradable peptides, respectively ( [Lau and Wang, 2013](#B41) ). On the other hand, synthetic biomaterials such as polyethylene glycol (PEG), poly(ε-caprolactone) (PCL) and poly(lactic-co-glycolide) (PLGA) are excellent alternatives to natural polymers due to the possibility to modulate their properties to a greater extent. Moreover, they can be obtained in a reproducible manner, which enables control over molecular weight, mechanical strength, degradation, crosslinking degree, and cell adhesive behavior ( [Zhu and Marchant, 2011](#B74) ). Therefore, incorporating cell adhesion motifs together with protease-sensitive sites represents a common strategy to induce angiogenesis and vascularization of natural and synthetic materials and the biomaterial-tissue interface ( [Hanjaya-Putra et al., 2012](#B32) ; [Tsurkan et al., 2013](#B65) ; [Chwalek et al., 2015](#B16) ; [Jha et al., 2016](#B35) ). Interestingly, by controlling the spatial distribution and density of these molecular cues it is possible to modulate not only the maturation and formation of newborn blood vessels but also the rate at which they degrade the engineered ECM and infiltrate into host tissue or vice versa ( [Hanjaya-Putra et al., 2011](#B31) , [2012](#B32) ). Thus, these types of materials can be considered blank canvasses to create tunable platforms that can modulate the angiogenic response in a specific way unlike ECM-derived materials.

### Enhancers of the Delivery of Angiogenic GFs

Delivery of angiogenic GFs has been acknowledged as a promising tool to stimulate angiogenesis and restore vascular perfusion. Nevertheless, clinical translation has proven difficult as these molecules have short *in vivo* half-lives, dosages are sub-optimal and poor retention kinetics ( [Browne and Pandit, 2017](#B13) ).

Biomaterials provide a route to circumvent some of these problems as they can protect GFs from degradation and can be tuned to release them in a controllable way ( [Abdeen and Saha, 2017](#B1) ). Consequently, biomaterials can be designed to create a chemical gradient during the release of GFs, mimicking *in vivo* angiogenesis, and affecting the rate of EC invasion, its direction, structure and network formation ( [Guo et al., 2012](#B27) ; [Akar et al., 2015](#B2) ). Biomaterials can be functionalized with more than one type of GFs and further replicate native angiogenesis, a process that depends on distinct concentration gradients and bioavailability of these molecules ( [Richardson et al., 2001](#B57) ; [Shin et al., 2011](#B62) ; [Assal et al., 2013](#B5) ; [Rufaihah et al., 2017](#B60) ). Indeed, both synthetic and natural biomaterials have been used either by physically entrapping the GFs or by establishing chemical bonds with the matrix ( [Wang et al., 2009](#B68) ; [Anderson et al., 2011](#B4) ; [Des Rieux et al., 2014](#B20) ; [Mittermayr et al., 2016](#B45) ). Perhaps the best approach to enhance the angiogenic response would be to combine the delivery of GFs with molecules capable of inducing their expression, such as sonic hedgehog (Shh). Consequently, Shh induces the expression of VEGF, Ang-1 and Ang-2, increasing their concentration and leading to the formation of more functional and stable vessels *in vivo* ( [Pola et al., 2001](#B53) ; [Rivron et al., 2012](#B58) ). This methodology enables cells to regulate the secretion of GFs, whilst helping the formation of microgradients and granting the possibility of expressing different GFs simultaneously ( [Baiguera and Ribatti, 2013](#B8) ).

### Integration of Biomaterials in SCI Angiogenic Therapies

Reestablishing the BSCB and potentiating the recovery of adequate blood supply in SCI would appear a fundamental requirement for efficacious therapies. [Han et al. (2010)](#B30) administered intravenous injections of Ang-1 and C16 (an angiogenic peptide) in a thoracic SCI mouse model and observed neuroprotective action of this treatment materialized by sparing epicenter blood vessels and white matter, increased angiogenesis and reduction of harmful inflammation. Most importantly, these histological findings correlated with significant motor recovery of the animals. Ang-1 reduced vascular permeability, monocyte transmigration as well as microglia/macrophages activation and infiltration (important players in white matter damage). Adding to its effect on preserving blood vessels at injury site, C16 showed pro-angiogenic activity and, noteworthy, also anti-inflammatory properties as it decreased monocyte transmigration across an EC layer *in vitro* ( [Han et al., 2010](#B30) ). This study clearly demonstrates the potential of developing strategies aiming to restore vascularization following SCI. As depicted in the previous sections, biomaterials can provide interesting platforms to enhance these particular therapies and in fact have shown the capacity to modulate angiogenesis and vascularization following SCI ( [Bakshi et al., 2004](#B9) ; [Rauch et al., 2009](#B55) ; [King et al., 2010](#B39) ; [Hurtado et al., 2011](#B34) ; [Zeng et al., 2011](#B73) ; [López-Dolado et al., 2016](#B43) ; [Chedly et al., 2017](#B15) ). Accordingly, [Duan et al. (2015)](#B23) utilized neurothrophin-3 (NT-3) loaded chitosan tubes to fill the void left by the transection of rat spinal cords and found that this material promoted nerve growth, neurogenesis and functional recovery of the animals. Thus, this study found an upregulation on genes related to vascular development, angiogenesis and hypoxia response in the NT-3 treatment group, when compared to uninjured and untreated animals ( [Duan et al., 2015](#B23) ). Differently, [Rauch et al. (2009)](#B55) created a co-culture system consisting of ECs and neural progenitor cells (NPCs) in a biodegradable PLGA scaffold and tested its ability to form functional vessels in an SCI hemisection model. After implantation, this system created a suitable environment for vessel inosculation and angiogenesis in the experimental group, contributing to a 3. 5-(PLGA implantation without cells group) and 5-fold (lesioned animals group) increase in number of functional vessels at injury epicenter at 8 weeks. The crosstalk between ECs and NPCs was fundamental due to the secretion of NO by NPCs, which induces the production of VEGF and brain-derived neurotrophic factor on ECs and contribute to further enhance NO production, promoting vessel formation and stabilization. Notably, the co-culture platform seemed to promote the re-establishment of BSCB since half of the vessels in the experimental group were positive to endothelial barrier antigen (a major marker for BSCB). In contrast, all the other cohorts (untreated, PLGA implantation, PLGA and ECs implantation and PLGA harboring NPCs group) had no expression of this marker ( [Rauch et al., 2009](#B55) ). Even though the authors did not assess BSCB functionality and observed limited regeneration, this work underlines the potential of integrating biomaterial-based ECs transplantation into SCI experimental treatments due to their capacity of reestablishing perfusion and BSCB, helping to modulate a regenerative phenotype. In an interesting approach, [López-Dolado et al. (2016)](#B43) evaluated the regenerative capacity of graphene oxide scaffolds in a hemisection rat model due to its capacity of inducing neuronal and astrocytic growth and neurogenesis. Upon implantation, these scaffolds promoted angiogenesis inside their structure, showing abundant and functional new vessels in their proximity in comparison to lesioned animals without scaffold implantation. Additionally, the scaffolds also seemed to have immunomodulatory capacity due to an increased presence of pro-regenerative macrophages on its interface. On the other hand, infiltration of neurons into the scaffolds was very low and no measurements on functional outcomes were assessed ( [López-Dolado et al., 2016](#B43) ). Nevertheless, this study presents some encouraging results and it is worth underlining the outstanding conductible properties of graphene, a feature that can play a pivotal role in therapies that apply electric stimulation to induce neural growth ( [Li et al., 2013](#B42) ; [Akhavan et al., 2016](#B3) ). [Ropper et al. (2017)](#B59) implanted a PLGA scaffold encapsulating human mesenchymal stem cells (hMSCs) in a thoracic hemisection rat model to study the potential of this system in SCI recovery. This treatment induced significant moto-sensory improvements regarding untreated animals or the groups where either scaffold insertion or hMSCs transplantation occurred. Additionally, treatment with hMSCs encapsulated in PLGA lead to significant decreases in lesion volume and improvements in neuropathic pain in comparison to controls. Furthermore, histological analysis of spinal cord sections showed an increased angiogenesis around the epicenter (observable by a significant increase in laminin concentration on the treatment group) which together with neurotrophic, anti-inflammatory and neurogenic mechanisms helps explaining the obtained moto-sensory improvements of this experimental approach. Nevertheless, therapeutic differences between the direct application of hMSCs and their prior encapsulation in PLGA may reside in the protective action of the polymer toward the inhospitable environment found on SCI, which was transduced in augmented hMSCs survival upon implantation for that group ( [Ropper et al., 2017](#B59) ). The positive impact of MSCs on the angiogenesis and vascularization of SCI was probably driven by the secretome of these cells which is extremely rich in pro-angiogenic GFs ( [Ranganath et al., 2012](#B54) ). Accordingly, several researchers have taken advantage of the aforementioned features of biomaterials to explore delivery of angiogenic GFs in SCI animal models and assess their impact on recovery following injury ( [De Laporte et al., 2011](#B19) ; [Kang et al., 2012](#B37) ; [Des Rieux et al., 2014](#B20) ; [Wen et al., 2016](#B69) ; [Yu et al., 2016](#B72) ). Combinatorial approaches utilizing different angiogenic GFs perhaps represent the best way of attaining better functional outcomes following SCI. Consequently, [Yu et al. (2016)](#B72) delivered PLGA microspheres containing VEGF, ANG-1 and basic fibroblast growth factor into the injury site of a contusion rat model and observed increased axonal growth on the treated animals in comparison to animals that received the empty microspheres. The authors associated these results with increased density of functional vessels and neural precursors recruitment to the injury site. Moreover, these cells closely associated with blood vessels opening the possibility of the microvascular network having a role on axonal guidance and growth across the lesion cavity. This study also found increased expression levels of miR-210 in treated animals, an inducer of VEGF expression, and suppression of ephrin-A3 (negative modulator of neurogenesis), a finding that demonstrates that increased neurogenesis found on the treated group was probably directly due to the GFs administration, broadening their spectrum of action ( [Yu et al., 2016](#B72) ).

## Conclusion

The application of biomaterials to influence angiogenesis/vascularization in SCI has shown interesting results. Biomaterials can deliver angiogenic GFs efficiently, enhancing their action and replicating some of the features found in native angiogenesis. Moreover, biomaterials protect cells from the harsh environment found in SCI, allowing their proliferation and exertion of biological effects, and a route (in some cases) to bridge the cavity that forms following SCI, allowing neuronal recovery. Addressing SCI vascularization using biomaterials certainly has potential and their incorporation in future therapies may be essential. Indeed due to the complex nature of SCI, unidimensional approaches are unlikely to be the best strategy or succeed. Therefore, integrating revascularization approaches in therapies that provide a means for neuronal growth and to modulate the environment into regenerative pathways is probably the best option moving forward. Due to their versatility, biomaterials can provide excellent platforms to be integrated into the development of more effective therapies.

## Author Contributions

LR drafted the manuscript. RS and DL helped to draft the manuscript and revised it critically. AS conceived the analysis, participated in its design and coordination, helped to draft the manuscript and gave the final approval of the version to be published. All authors read and approved the final manuscript.

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Acknowledgments

The authors acknowledge the financial support by Prémios Santa Casa Neurociências – Prize Melo e Castro for Spinal Cord Injury Research; Portuguese Foundation for Science and Technology [Doctoral fellowship (PD/BDE/127835/2016) to LR; IF Development Grant IF/00111/2013 to AS; by National Funds through Grant TUBITAK/0007/2014]. This article has been developed under the scope of the projects NORTE-01-0145-FEDER-000013, supported by the Northern Portugal Regional Operational Programme (NORTE 2020), under the Portugal 2020 Partnership Agreement, through the European Regional Development Fund (FEDER). This work has been funded by FEDER funds, through the Competitiveness Factors Operational Programme (COMPETE), and by National funds, through the Foundation for Science and Technology (FCT), under the scope of the project POCI-01-0145-FEDER-007038.

## References

Abdeen, A. A., and Saha, K. (2017). Manufacturing cell therapies using engineered biomaterials. *Trends Biotechnol.* 35, 971–982. doi: 10. 1016/j. tibtech. 2017. 06. 008

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28711155) | [CrossRef Full Text](https://doi.org/10.1016/j.tibtech.2017.06.008) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Manufacturing+cell+therapies+using+engineered+biomaterials.&journal=Trends+Biotechnol.&author=Abdeen+A.++A.&author=and+Saha+K.&publication_year=2017&volume=35&pages=971-982)

Akar, B., Jiang, B., Somo, S. I., Appel, A. A., Larson, J. C., Tichauer, K. M., et al. (2015). Biomaterials with persistent growth factor gradients in vivo accelerate vascularized tissue formation. *Biomaterials* 72, 61–73. doi: 10. 1016/j. biomaterials. 2015. 08. 049

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26344364) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2015.08.049) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Biomaterials+with+persistent+growth+factor+gradients+in+vivo+accelerate+vascularized+tissue+formation.&journal=Biomaterials&author=Akar+B.&author=Jiang+B.&author=Somo+S.++I.&author=Appel+A.++A.&author=Larson+J.++C.&author=Tichauer+K.++M.&publication_year=2015&volume=72&pages=61-73)

Akhavan, O., Ghaderi, E., Shirazian, S. A., and Rahighi, R. (2016). Rolled graphene oxide foams as three-dimensional scaffolds for growth of neural fibers using electrical stimulation of stem cells. *Carbon* 97, 71–77. doi: 10. 1016/j. carbon. 2015. 06. 079

[CrossRef Full Text](https://doi.org/10.1016/j.carbon.2015.06.079) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Rolled+graphene+oxide+foams+as+three-dimensional+scaffolds+for+growth+of+neural+fibers+using+electrical+stimulation+of+stem+cells.&journal=Carbon&author=Akhavan+O.&author=Ghaderi+E.&author=Shirazian+S.+A.&author=and+Rahighi+R.&publication_year=2016&volume=97&pages=71-77)

Anderson, S. M., Siegman, S. N., and Segura, T. (2011). The effect of vascular endothelial growth factor (VEGF) presentation within fibrin matrices on endothelial cell branching. *Biomaterials* 32, 7432–7443. doi: 10. 1016/j. biomaterials. 2011. 06. 027

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21783250) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2011.06.027) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=The+effect+of+vascular+endothelial+growth+factor+(VEGF)+presentation+within+fibrin+matrices+on+endothelial+cell+branching.&journal=Biomaterials&author=Anderson+S.++M.&author=Siegman+S.++N.&author=and+Segura+T.&publication_year=2011&volume=32&pages=7432-7443)

Assal, Y., Mie, M., and Kobatake, E. (2013). The promotion of angiogenesis by growth factors integrated with ECM proteins through coiled-coil structures. *Biomaterials* 34, 3315–3323. doi: 10. 1016/j. biomaterials. 2013. 01. 067

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23388150) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2013.01.067) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=The+promotion+of+angiogenesis+by+growth+factors+integrated+with+ECM+proteins+through+coiled-coil+structures.&journal=Biomaterials&author=Assal+Y.&author=Mie+M.&author=and+Kobatake+E.&publication_year=2013&volume=34&pages=3315-3323)

Attwell, D., and Laughlin, S. B. (2001). An energy budget for signaling in the grey matter of the brain. *J. Cereb. Blood Flow Metab.* 21, 1133–1145. doi: 10. 1097/00004647-200110000-00001

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11598490) | [CrossRef Full Text](https://doi.org/10.1097/00004647-200110000-00001) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=An+energy+budget+for+signaling+in+the+grey+matter+of+the+brain.&journal=J.+Cereb.+Blood+Flow+Metab.&author=Attwell+D.&author=and+Laughlin+S.+B.&publication_year=2001&volume=21&pages=1133-1145)

Baffert, F., Le, T., Thurston, G., and McDonald, D. M. (2006). Angiopoietin-1 decreases plasma leakage by reducing number and size of endothelial gaps in venules. *Am. J. Physiol. Heart Circ. Physiol.* 290, H107–H118. doi: 10. 1152/ajpheart. 00542. 2005

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16126815) | [CrossRef Full Text](https://doi.org/10.1152/ajpheart.00542.2005) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Angiopoietin-1+decreases+plasma+leakage+by+reducing+number+and+size+of+endothelial+gaps+in+venules.&journal=Am.++J.++Physiol.++Heart+Circ.++Physiol.&author=Baffert+F.&author=Le+T.&author=Thurston+G.&author=and+McDonald+D.+M.&publication_year=2006&volume=290&pages=H107-H118)

Baiguera, S., and Ribatti, D. (2013). Endothelialization approaches for viable engineered tissues. *Angiogenesis* 16, 1–14. doi: 10. 1007/s10456-012-9307-8

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23010872) | [CrossRef Full Text](https://doi.org/10.1007/s10456-012-9307-8) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Endothelialization+approaches+for+viable+engineered+tissues.&journal=Angiogenesis&author=Baiguera+S.&author=and+Ribatti+D.&publication_year=2013&volume=16&pages=1-14)

Bakshi, A., Fisher, O., Dagci, T., Himes, B. T., Fischer, I., and Lowman, A. (2004). Mechanically engineered hydrogel scaffolds for axonal growth and angiogenesis after transplantation in spinal cord injury. *J. Neurosurg. Spine* 1, 322–329. doi: 10. 3171/spi. 2004. 1. 3. 0322

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15478371) | [CrossRef Full Text](https://doi.org/10.3171/spi.2004.1.3.0322) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Mechanically+engineered+hydrogel+scaffolds+for+axonal+growth+and+angiogenesis+after+transplantation+in+spinal+cord+injury.&journal=J.+Neurosurg.+Spine&author=Bakshi+A.&author=Fisher+O.&author=Dagci+T.&author=Himes+B.+T.&author=Fischer+I.&author=and+Lowman+A.&publication_year=2004&volume=1&pages=322-329)

Benton, R. L., Maddie, M. A., Gruenthal, M. J., Hagg, T., and Whittemore, S. R. (2009). Neutralizing endogenous VEGF following traumatic spinal cord injury modulates microvascular plasticity but not tissue sparing or functional recovery. *Curr. Neurovasc. Res.* 6, 124–131. doi: 10. 2174/156720209788185678

[CrossRef Full Text](https://doi.org/10.2174/156720209788185678) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Neutralizing+endogenous+VEGF+following+traumatic+spinal+cord+injury+modulates+microvascular+plasticity+but+not+tissue+sparing+or+functional+recovery.&journal=Curr.+Neurovasc.+Res.&author=Benton+R.+L.&author=Maddie+M.+A.&author=Gruenthal+M.+J.&author=Hagg+T.&author=and+Whittemore+S.+R.&publication_year=2009&volume=6&pages=124-131)

Benton, R. L., and Whittemore, S. R. (2003). VEGF165 therapy exacerbates secondary damage following spinal cord injury. *Neurochem. Res.* 28, 1693–1703. doi: 10. 1023/A: 1026013106016

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14584823) | [CrossRef Full Text](https://doi.org/10.1023/A%3A%201026013106016) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=VEGF165+therapy+exacerbates+secondary+damage+following+spinal+cord+injury.&journal=Neurochem.+Res.&author=Benton+R.+L.&author=and+Whittemore+S.+R.&publication_year=2003&volume=28&pages=1693-1703)

Briquez, P. S., Clegg, L. E., Martino, M. M., Gabhann, F. M., and Hubbell, J. A. (2016). Design principles for therapeutic angiogenic materials. *Nat. Rev. Mater.* 1: 15006. doi: 10. 1038/natrevmats. 2015. 6

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21926148) | [CrossRef Full Text](https://doi.org/10.1038/natrevmats.2015.6) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Design+principles+for+therapeutic+angiogenic+materials.&journal=Nat.+Rev.++Mater.&author=Briquez+P.+S.&author=Clegg+L.+E.&author=Martino+M.+M.&author=Gabhann+F.+M.&author=and+Hubbell+J.+A.&publication_year=2016)

Browne, S., and Pandit, A. (2017). Engineered systems for therapeutic angiogenesis. *Curr. Opin. Pharmacol.* 36, 34–43. doi: 10. 1016/j. coph. 2017. 07. 002

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28806581) | [CrossRef Full Text](https://doi.org/10.1016/j.coph.2017.07.002) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Engineered+systems+for+therapeutic+angiogenesis.&journal=Curr.+Opin.+Pharmacol.&author=Browne+S.&author=and+Pandit+A.&publication_year=2017&volume=36&pages=34-43)

Casella, G. T. B., Marcillo, A., Bunge, M. B., and Wood, P. M. (2002). New vascular tissue rapidly replaces neural parenchyma and vessels destroyed by a contusion injury to the rat spinal cord. *Exp. Neurol.* 173, 63–76. doi: 10. 1006/exnr. 2001. 7827

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11771939) | [CrossRef Full Text](https://doi.org/10.1006/exnr.2001.7827) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=New+vascular+tissue+rapidly+replaces+neural+parenchyma+and+vessels+destroyed+by+a+contusion+injury+to+the+rat+spinal+cord.&journal=Exp.+Neurol.&author=Casella+G.+T.+B.&author=Marcillo+A.&author=Bunge+M.+B.&author=and+Wood+P.+M.&publication_year=2002&volume=173&pages=63-76)

Chedly, J., Soares, S., Montembault, A., von Boxberg, Y., Veron-Ravaille, M., Mouffle, C., et al. (2017). Physical chitosan microhydrogels as scaffolds for spinal cord injury restoration and axon regeneration. *Biomaterials* 138, 91–107. doi: 10. 1016/j. biomaterials. 2017. 05. 024

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28554011) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2017.05.024) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Physical+chitosan+microhydrogels+as+scaffolds+for+spinal+cord+injury+restoration+and+axon+regeneration.&journal=Biomaterials&author=Chedly+J.&author=Soares+S.&author=Montembault+A.&author=von+Boxberg+Y.&author=Veron-Ravaille+M.&author=Mouffle+C.&publication_year=2017&volume=138&pages=91-107)

Chwalek, K., Tsurkan, M. V., Freudenberg, U., and Werner, C. (2015). Glycosaminoglycan-based hydrogels to modulate heterocellular communication in in vitro angiogenesis models. *Sci. Rep.* 4: 4414. doi: 10. 1038/srep04414

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24643064) | [CrossRef Full Text](https://doi.org/10.1038/srep04414) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Glycosaminoglycan-based+hydrogels+to+modulate+heterocellular+communication+in+in+vitro+angiogenesis+models.&journal=Sci.+Rep.&author=Chwalek+K.&author=Tsurkan+M.++V.&author=Freudenberg+U.&author=and+Werner+C.&publication_year=2015)

Crafts, T. D., Jensen, A. R., Blocher-Smith, E. C., and Markel, T. A. (2015). Vascular endothelial growth factor: therapeutic possibilities and challenges for the treatment of ischemia. *Cytokine* 71, 385–393. doi: 10. 1016/j. cyto. 2014. 08. 005

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25240960) | [CrossRef Full Text](https://doi.org/10.1016/j.cyto.2014.08.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Vascular+endothelial+growth+factor%3A+therapeutic+possibilities+and+challenges+for+the+treatment+of+ischemia.&journal=Cytokine&author=Crafts+T.++D.&author=Jensen+A.++R.&author=Blocher-Smith+E.++C.&author=and+Markel+T.++A.&publication_year=2015&volume=71&pages=385-393)

Dalheim, M. Ø., Vanacker, J., Najmi, M. A., Aachmann, F. L., Strand, B. L., and Christensen, B. E. (2016). Efficient functionalization of alginate biomaterials. *Biomaterials* 80, 146–156. doi: 10. 1016/j. biomaterials. 2015. 11. 043

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26708091) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2015.11.043) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Efficient+functionalization+of+alginate+biomaterials.&journal=Biomaterials&author=Dalheim+M.&author=Ø.+Vanacker&author=J.+Najmi&author=M.+A.+Aachmann&author=F.+L.+Strand&author=B.+L.+and+Christensen&publication_year=2016&volume=80&pages=146-156)

De Laporte, L., Des Rieux, A., Tuinstra, H. M., Zelivyanskaya, M. L., De Clerck, N. M., Postnov, A. A., et al. (2011). Vascular endothelial growth factor and fibroblast growth factor 2 delivery from spinal cord bridges to enhance angiogenesis following injury. *J. Biomed. Mater. Res. A* 98, 372–382. doi: 10. 1002/jbm. a. 33112

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21630429) | [CrossRef Full Text](https://doi.org/10.1002/jbm.a.33112) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Vascular+endothelial+growth+factor+and+fibroblast+growth+factor+2+delivery+from+spinal+cord+bridges+to+enhance+angiogenesis+following+injury.&journal=J.++Biomed.++Mater.++Res.++A&author=De+Laporte+L.&author=Des+Rieux+A.&author=Tuinstra+H.+M.&author=Zelivyanskaya+M.+L.&author=De+Clerck+N.+M.&author=Postnov+A.+A.&publication_year=2011&volume=98&pages=372-382)

Des Rieux, A., De Berdt, P., Ansorena, E., Ucakar, B., Damien, J., Schakman, O., et al. (2014). Vascular endothelial growth factor-loaded injectable hydrogel enhances plasticity in the injured spinal cord. *J. Biomed. Mater. Res. A* 102, 2345–2355. doi: 10. 1002/jbm. a. 34915

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23946111) | [CrossRef Full Text](https://doi.org/10.1002/jbm.a.34915) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Vascular+endothelial+growth+factor-loaded+injectable+hydrogel+enhances+plasticity+in+the+injured+spinal+cord.&journal=J.+Biomed.+Mater.+Res.+A&author=Des+Rieux+A.&author=De+Berdt+P.&author=Ansorena+E.&author=Ucakar+B.&author=Damien+J.&author=Schakman+O.&publication_year=2014&volume=102&pages=2345-2355)

Devolder, R., and Kong, H. J. (2012). Hydrogels for in vivo-like three-dimensional cellular studies. *Wiley Interdiscip. Rev. Syst. Biol. Med.* 4, 351–365. doi: 10. 1002/wsbm. 1174

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22615143) | [CrossRef Full Text](https://doi.org/10.1002/wsbm.1174) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Hydrogels+for+in+vivo-like+three-dimensional+cellular+studies.&journal=Wiley+Interdiscip.+Rev.+Syst.+Biol.+Med.&author=Devolder+R.&author=and+Kong+H.++J.&publication_year=2012&volume=4&pages=351-365)

Dray, C., Rougon, G., and Debarbieux, F. (2009). Quantitative analysis by in vivo imaging of the dynamics of vascular and axonal networks in injured mouse spinal cord. *Proc. Natl. Acad. Sci. U. S. A.* 106, 9459–9464. doi: 10. 1073/pnas. 0900222106

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19470644) | [CrossRef Full Text](https://doi.org/10.1073/pnas.0900222106) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Quantitative+analysis+by+in+vivo+imaging+of+the+dynamics+of+vascular+and+axonal+networks+in+injured+mouse+spinal+cord.&journal=Proc.+Natl.+Acad.+Sci.+U.S.A.&author=Dray+C.&author=Rougon+G.&author=and+Debarbieux+F.&publication_year=2009&volume=106&pages=9459-9464)

Duan, H., Ge, W., Zhang, A., Xi, Y., Chen, Z., Luo, D., et al. (2015). Transcriptome analyses reveal molecular mechanisms underlying functional recovery after spinal cord injury. *Proc. Natl. Acad. Sci. U. S. A.* 112, 13360–13365. doi: 10. 1073/pnas. 1510176112

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26460053) | [CrossRef Full Text](https://doi.org/10.1073/pnas.1510176112) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Transcriptome+analyses+reveal+molecular+mechanisms+underlying+functional+recovery+after+spinal+cord+injury.&journal=Proc.++Natl.++Acad.++Sci.++U.S.A.&author=Duan+H.&author=Ge+W.&author=Zhang+A.&author=Xi+Y.&author=Chen+Z.&author=Luo+D.&publication_year=2015&volume=112&pages=13360-13365)

Durham-Lee, J. C., Wu, Y., Mokkapati, V. U. L., Paulucci-Holthauzen, A. A., and Nesic, O. (2012). Induction of angiopoietin-2 after spinal cord injury. *Neuroscience* 202, 454–464. doi: 10. 1016/j. neuroscience. 2011. 09. 058

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22020092) | [CrossRef Full Text](https://doi.org/10.1016/j.neuroscience.2011.09.058) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Induction+of+angiopoietin-2+after+spinal+cord+injury.&journal=Neuroscience&author=Durham-Lee+J.+C.&author=Wu+Y.&author=Mokkapati+V.+U.+L.&author=Paulucci-Holthauzen+A.++A.&author=and+Nesic+O.&publication_year=2012&volume=202&pages=454-464)

Glaser, J., Gonzalez, R., Sadr, E., and Keirstead, H. S. (2006). Neutralization of the chemokine CXCL10 reduces apoptosis and increases axon sprouting after spinal cord injury. *J. Neurosci. Res.* 84, 724–734. doi: 10. 1002/jnr. 20982

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16862543) | [CrossRef Full Text](https://doi.org/10.1002/jnr.20982) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Neutralization+of+the+chemokine+CXCL10+reduces+apoptosis+and+increases+axon+sprouting+after+spinal+cord+injury.&journal=J.+Neurosci.+Res.&author=Glaser+J.&author=Gonzalez+R.&author=Sadr+E.&author=and+Keirstead+H.+S.&publication_year=2006&volume=84&pages=724-734)

Gomes, E. D., Mendes, S. S., Leite-Almeida, H., Gimble, J. M., Tam, R. Y., Shoichet, M. S., et al. (2016). Combination of a peptide-modified gellan gum hydrogel with cell therapy in a lumbar spinal cord injury animal model. *Biomaterials* 105, 38–51. doi: 10. 1016/j. biomaterials. 2016. 07. 019

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27505621) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2016.07.019) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Combination+of+a+peptide-modified+gellan+gum+hydrogel+with+cell+therapy+in+a+lumbar+spinal+cord+injury+animal+model.&journal=Biomaterials&author=Gomes+E.+D.&author=Mendes+S.+S.&author=Leite-Almeida+H.&author=Gimble+J.+M.&author=Tam+R.++Y.&author=Shoichet+M.+S.&publication_year=2016&volume=105&pages=38-51)

Guo, X., Elliott, C. G., Li, Z., Xu, Y., Hamilton, D. W., and Guan, J. (2012). Creating 3D angiogenic growth factor gradients in fibrous constructs to guide fast angiogenesis. *Biomacromolecules* 13, 3262–3271. doi: 10. 1021/bm301029a

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22924876) | [CrossRef Full Text](https://doi.org/10.1021/bm301029a) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Creating+3D+angiogenic+growth+factor+gradients+in+fibrous+constructs+to+guide+fast+angiogenesis.&journal=Biomacromolecules&author=Guo+X.&author=Elliott+C.+G.&author=Li+Z.&author=Xu+Y.&author=Hamilton+D.+W.&author=and+Guan+J.&publication_year=2012&volume=13&pages=3262-3271)

Guvendiren, M., and Burdick, J. A. (2013). Engineering synthetic hydrogel microenvironments to instruct stem cells. *Curr. Opin. Biotechnol.* 24, 841–846. doi: 10. 1016/j. copbio. 2013. 03. 009

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23545441) | [CrossRef Full Text](https://doi.org/10.1016/j.copbio.2013.03.009) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Engineering+synthetic+hydrogel+microenvironments+to+instruct+stem+cells.&journal=Curr.+Opin.+Biotechnol.&author=Guvendiren+M.&author=and+Burdick+J.+A.&publication_year=2013&volume=24&pages=841-846)

Haggerty, A. E., Marlow, M. M., and Oudega, M. (2017). Extracellular matrix components as therapeutics for spinal cord injury. *Neurosci. Lett.* 652, 50–55. doi: 10. 1016/j. neulet. 2016. 09. 053

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27702629) | [CrossRef Full Text](https://doi.org/10.1016/j.neulet.2016.09.053) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Extracellular+matrix+components+as+therapeutics+for+spinal+cord+injury.&journal=Neurosci.+Lett.&author=Haggerty+A.+E.&author=Marlow+M.+M.&author=and+Oudega+M.&publication_year=2017&volume=652&pages=50-55)

Han, S., Arnold, S. A., Sithu, S. D., Mahoney, E. T., Geralds, J. T., Tran, P., et al. (2010). Rescuing vasculature with intravenous angiopoietin-1 and αvβ3 integrin peptide is protective after spinal cord injury. *Brain* 133, 1026–1042. doi: 10. 1093/brain/awq034

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20375135) | [CrossRef Full Text](https://doi.org/10.1093/brain/awq034) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Rescuing+vasculature+with+intravenous+angiopoietin-1+and+αvβ3+integrin+peptide+is+protective+after+spinal+cord+injury.&journal=Brain&author=Han+S.&author=Arnold+S.+A.&author=Sithu+S.+D.&author=Mahoney+E.+T.&author=Geralds+J.+T.&author=Tran+P.&publication_year=2010&volume=133&pages=1026-1042)

Hanjaya-Putra, D., Bose, V., Shen, Y.-I., Yee, J., Khetan, S., Fox-Talbot, K., et al. (2011). Controlled activation of morphogenesis to generate a functional human microvasculature in a synthetic matrix. *Blood* 118, 804–815. doi: 10. 1182/blood-2010-12-327338

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21527523) | [CrossRef Full Text](https://doi.org/10.1182/blood-2010-12-327338) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Controlled+activation+of+morphogenesis+to+generate+a+functional+human+microvasculature+in+a+synthetic+matrix.&journal=Blood&author=Hanjaya-Putra+D.&author=Bose+V.&author=Shen+Y.-I.&author=Yee+J.&author=Khetan+S.&author=Fox-Talbot+K.&publication_year=2011&volume=118&pages=804-815)

Hanjaya-Putra, D., Wong, K. T., Hirotsu, K., Khetan, S., Burdick, J. A., and Gerecht, S. (2012). Spatial control of cell-mediated degradation to regulate vasculogenesis and angiogenesis in hyaluronan hydrogels. *Biomaterials* 33, 6123–6131. doi: 10. 1016/j. biomaterials. 2012. 05. 027

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22672833) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2012.05.027) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Spatial+control+of+cell-mediated+degradation+to+regulate+vasculogenesis+and+angiogenesis+in+hyaluronan+hydrogels.&journal=Biomaterials&author=Hanjaya-Putra+D.&author=Wong+K.+T.&author=Hirotsu+K.&author=Khetan+S.&author=Burdick+J.+A.&author=and+Gerecht+S.&publication_year=2012&volume=33&pages=6123-6131)

Herrera, J. J., Sundberg, L. M., Zentilin, L., Giacca, M., and Narayana, P. A. (2010). Sustained expression of vascular endothelial growth factor and angiopoietin-1 improves blood-spinal cord barrier integrity and functional recovery after spinal cord injury. *J. Neurotrauma* 27, 2067–2076. doi: 10. 1089/neu. 2010. 1403

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20799882) | [CrossRef Full Text](https://doi.org/10.1089/neu.2010.1403) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Sustained+expression+of+vascular+endothelial+growth+factor+and+angiopoietin-1+improves+blood-spinal+cord+barrier+integrity+and+functional+recovery+after+spinal+cord+injury.&journal=J.++Neurotrauma&author=Herrera+J.+J.&author=Sundberg+L.+M.&author=Zentilin+L.&author=Giacca+M.&author=and+Narayana+P.+A.&publication_year=2010&volume=27&pages=2067-2076)

Hurtado, A., Cregg, J. M., Wang, H. B., Wendell, D. F., Oudega, M., Gilbert, R. J., et al. (2011). Robust CNS regeneration after complete spinal cord transection using aligned poly-l-lactic acid microfibers. *Biomaterials* 32, 6068–6079. doi: 10. 1016/j. biomaterials. 2011. 05. 006

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21636129) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2011.05.006) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Robust+CNS+regeneration+after+complete+spinal+cord+transection+using+aligned+poly-l-lactic+acid+microfibers.&journal=Biomaterials&author=Hurtado+A.&author=Cregg+J.++M.&author=Wang+H.++B.&author=Wendell+D.++F.&author=Oudega+M.&author=Gilbert+R.+J.&publication_year=2011&volume=32&pages=6068-6079)

Jha, A. K., Tharp, K. M., Browne, S., Ye, J., Stahl, A., Yeghiazarians, Y., et al. (2016). Matrix metalloproteinase-13 mediated degradation of hyaluronic acid-based matrices orchestrates stem cell engraftment through vascular integration. *Biomaterials* 89, 136–147. doi: 10. 1016/j. biomaterials. 2016. 02. 023

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26967648) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2016.02.023) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Matrix+metalloproteinase-13+mediated+degradation+of+hyaluronic+acid-based+matrices+orchestrates+stem+cell+engraftment+through+vascular+integration.&journal=Biomaterials&author=Jha+A.+K.&author=Tharp+K.+M.&author=Browne+S.&author=Ye+J.&author=Stahl+A.&author=Yeghiazarians+Y.&publication_year=2016&volume=89&pages=136-147)

Kaneko, S., Iwanami, A., Nakamura, M., Kishino, A., Kikuchi, K., Shibata, S., et al. (2007). A selective Sema3A inhibitor enhances regenerative responses and functional recovery of the injured spinal cord. *Nat. Med.* 12, 1380–1389. doi: 10. 1038/nm1505

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17099709) | [CrossRef Full Text](https://doi.org/10.1038/nm1505) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=A+selective+Sema3A+inhibitor+enhances+regenerative+responses+and+functional+recovery+of+the+injured+spinal+cord.&journal=Nat.+Med.&author=Kaneko+S.&author=Iwanami+A.&author=Nakamura+M.&author=Kishino+A.&author=Kikuchi+K.&author=Shibata+S.&publication_year=2007&volume=12&pages=1380-1389)

Kang, C. E., Baumann, M. D., Tator, C. H., and Shoichet, M. S. (2012). Localized and sustained delivery of fibroblast growth factor-2 from a nanoparticle-hydrogel composite for treatment of spinal cord injury. *Cells Tissues Organs* 197, 55–63. doi: 10. 1159/000339589

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22796886) | [CrossRef Full Text](https://doi.org/10.1159/000339589) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Localized+and+sustained+delivery+of+fibroblast+growth+factor-2+from+a+nanoparticle-hydrogel+composite+for+treatment+of+spinal+cord+injury.&journal=Cells+Tissues+Organs&author=Kang+C.++E.&author=Baumann+M.++D.&author=Tator+C.++H.&author=and+Shoichet+M.++S.&publication_year=2012&volume=197&pages=55-63)

Kim, H. M., Hwang, D. H., Lee, J. E., Kim, S. U., and Kim, B. G. (2009). Ex vivo VEGF delivery by neural stem cells enhances proliferation of glial progenitors, angiogenesis, and tissue sparing after spinal cord injury. *PLoS One* 4: e4987. doi: 10. 1371/journal. pone. 0004987

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19319198) | [CrossRef Full Text](https://doi.org/10.1371/journal.pone.0004987) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Ex+vivo+VEGF+delivery+by+neural+stem+cells+enhances+proliferation+of+glial+progenitors%2C+angiogenesis%2C+and+tissue+sparing+after+spinal+cord+injury.&journal=PLoS+One&author=Kim+H.+M.&author=Hwang+D.+H.&author=Lee+J.+E.&author=Kim+S.+U.&author=and+Kim+B.+G.&publication_year=2009)

King, V. R., Alovskaya, A., Wei, D. Y. T., Brown, R. A., and Priestley, J. V. (2010). The use of injectable forms of fibrin and fibronectin to support axonal ingrowth after spinal cord injury. *Biomaterials* 31, 4447–4456. doi: 10. 1016/j. biomaterials. 2010. 02. 018

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20206381) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2010.02.018) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=The+use+of+injectable+forms+of+fibrin+and+fibronectin+to+support+axonal+ingrowth+after+spinal+cord+injury.&journal=Biomaterials&author=King+V.+R.&author=Alovskaya+A.&author=Wei+D.+Y.+T.&author=Brown+R.+A.&author=and+Priestley+J.+V.&publication_year=2010&volume=31&pages=4447-4456)

Kundi, S., Bicknell, R., and Ahmed, Z. (2013). The role of angiogenic and wound-healing factors after spinal cord injury in mammals. *Neurosci. Res.* 76, 1–9. doi: 10. 1016/j. neures. 2013. 03. 013

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23562792) | [CrossRef Full Text](https://doi.org/10.1016/j.neures.2013.03.013) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=The+role+of+angiogenic+and+wound-healing+factors+after+spinal+cord+injury+in+mammals.&journal=Neurosci.+Res.&author=Kundi+S.&author=Bicknell+R.&author=and+Ahmed+Z.&publication_year=2013&volume=76&pages=1-9)

Lau, T. T., and Wang, D.-A. (2013). Bioresponsive hydrogel scaffolding systems for 3D constructions in tissue engineering and regenerative medicine. *Nanomedicine* 8, 655–668. doi: 10. 2217/nnm. 13. 32

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23560414) | [CrossRef Full Text](https://doi.org/10.2217/nnm.13.32) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Bioresponsive+hydrogel+scaffolding+systems+for+3D+constructions+in+tissue+engineering+and+regenerative+medicine.&journal=Nanomedicine&author=Lau+T.++T.&author=and+Wang+D.-A.&publication_year=2013&volume=8&pages=655-668)

Li, N., Zhang, Q., Gao, S., Song, Q., Huang, R., Wang, L., et al. (2013). Three-dimensional graphene foam as a biocompatible and conductive scaffold for neural stem cells. *Sci. Rep.* 3: 1604. doi: 10. 1038/srep01604

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23549373) | [CrossRef Full Text](https://doi.org/10.1038/srep01604) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Three-dimensional+graphene+foam+as+a+biocompatible+and+conductive+scaffold+for+neural+stem+cells.&journal=Sci.+Rep.&author=Li+N.&author=Zhang+Q.&author=Gao+S.&author=Song+Q.&author=Huang+R.&author=Wang+L.&publication_year=2013)

López-Dolado, E., González-Mayorga, A., Gutiérrez, M. C., and Serrano, M. C. (2016). Immunomodulatory and angiogenic responses induced by graphene oxide scaffolds in chronic spinal hemisected rats. *Biomaterials* 99, 72–81. doi: 10. 1016/j. biomaterials. 2016. 05. 012

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27214651) | [CrossRef Full Text](https://doi.org/10.1016/j.biomaterials.2016.05.012) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Immunomodulatory+and+angiogenic+responses+induced+by+graphene+oxide+scaffolds+in+chronic+spinal+hemisected+rats.&journal=Biomaterials&author=López-Dolado+E.&author=González-Mayorga+A.&author=Gutiérrez+M.+C.&author=and+Serrano+M.++C.&publication_year=2016&volume=99&pages=72-81)

Martino, M. M., Brkic, S., Bovo, E., Burger, M., Schaefer, D. J., Wolff, T., et al. (2015). Extracellular matrix and growth factor engineering for controlled angiogenesis in regenerative medicine. *Front. Bioeng. Biotechnol.* 3: 45. doi: 10. 3389/fbioe. 2015. 00045

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=25883933) | [CrossRef Full Text](https://doi.org/10.3389/fbioe.2015.00045) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Extracellular+matrix+and+growth+factor+engineering+for+controlled+angiogenesis+in+regenerative+medicine.&journal=Front.+Bioeng.+Biotechnol.&author=Martino+M.+M.&author=Brkic+S.&author=Bovo+E.&author=Burger+M.&author=Schaefer+D.+J.&author=Wolff+T.&publication_year=2015)

Mittermayr, R., Slezak, P., Haffner, N., Smolen, D., Hartinger, J., Hofmann, A., et al. (2016). Controlled release of fibrin matrix-conjugated platelet derived growth factor improves ischemic tissue regeneration by functional angiogenesis. *Acta Biomater.* 29, 11–20. doi: 10. 1016/j. actbio. 2015. 10. 028

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26497625) | [CrossRef Full Text](https://doi.org/10.1016/j.actbio.2015.10.028) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Controlled+release+of+fibrin+matrix-conjugated+platelet+derived+growth+factor+improves+ischemic+tissue+regeneration+by+functional+angiogenesis.&journal=Acta+Biomater.&author=Mittermayr+R.&author=Slezak+P.&author=Haffner+N.&author=Smolen+D.&author=Hartinger+J.&author=Hofmann+A.&publication_year=2016&volume=29&pages=11-20)

Nagase, H., Visse, R., and Murphy, G. (2006). Structure and function of matrix metalloproteinases and TIMPs. *Cardiovasc. Res.* 69, 562–573. doi: 10. 1016/j. cardiores. 2005. 12. 002

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16405877) | [CrossRef Full Text](https://doi.org/10.1016/j.cardiores.2005.12.002) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Structure+and+function+of+matrix+metalloproteinases+and+TIMPs.&journal=Cardiovasc.++Res.&author=Nagase+H.&author=Visse+R.&author=and+Murphy+G.&publication_year=2006&volume=69&pages=562-573)

Neves, S. C., Gomes, D. B., Sousa, A., Bidarra, S. J., Petrini, P., Moroni, L., et al. (2015). Biofunctionalized pectin hydrogels as 3D cellular microenvironments. *J. Mater. Chem. B* 3, 2096–2108. doi: 10. 1039/C4TB00885E

[CrossRef Full Text](https://doi.org/10.1039/C4TB00885E) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Biofunctionalized+pectin+hydrogels+as+3D+cellular+microenvironments.&journal=J.++Mater.++Chem.++B&author=Neves+S.++C.&author=Gomes+D.++B.&author=Sousa+A.&author=Bidarra+S.++J.&author=Petrini+P.&author=Moroni+L.&publication_year=2015&volume=3&pages=2096-2108)

Ng, M. T. L., Stammers, A. T., and Kwon, B. K. (2011). Vascular disruption and the role of angiogenic proteins after spinal cord injury. *Transl. Stroke Res.* 2, 474–491. doi: 10. 1007/s12975-011-0109-x

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22448202) | [CrossRef Full Text](https://doi.org/10.1007/s12975-011-0109-x) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Vascular+disruption+and+the+role+of+angiogenic+proteins+after+spinal+cord+injury.&journal=Transl.+Stroke+Res.&author=Ng+M.+T.+L.&author=Stammers+A.+T.&author=and+Kwon+B.+K.&publication_year=2011&volume=2&pages=474-491)

Noble, L. J., Donovan, F., Igarashi, T., Goussev, S., and Werb, Z. (2002). Matrix metalloproteinases limit functional recovery after spinal cord injury by modulation of early vascular events. *J. Neurosci.* 22, 7526–7535.

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12196576) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Matrix+metalloproteinases+limit+functional+recovery+after+spinal+cord+injury+by+modulation+of+early+vascular+events.&journal=J.+Neurosci.&author=Noble+L.+J.&author=Donovan+F.&author=Igarashi+T.&author=Goussev+S.&author=and+Werb+Z.&publication_year=2002&volume=22&pages=7526-7535)

Noble, L. J., and Wrathall, J. R. (1989a). Correlative analyses of lesion development and functional status after graded spinal cord contusive injuries in the rat. *Exp. Neurol.* 103, 34–40. doi: 10. 1016/0014-4886(89)90182-9

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=2912748) | [CrossRef Full Text](https://doi.org/10.1016/0014-4886%2889%2990182-9) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Correlative+analyses+of+lesion+development+and+functional+status+after+graded+spinal+cord+contusive+injuries+in+the+rat.&journal=Exp.+Neurol.&author=Noble+L.++J.&author=and+Wrathall+J.++R.&publication_year=1989a&volume=103&pages=34-40)

Noble, L. J., and Wrathall, J. R. (1989b). Distribution and time course of protein extravasation in the rat spinal cord after contusive injury. *Brain Res.* 482, 57–66. doi: 10. 1016/0006-8993(89)90542-8

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=2706482) | [CrossRef Full Text](https://doi.org/10.1016/0006-8993%2889%2990542-8) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Distribution+and+time+course+of+protein+extravasation+in+the+rat+spinal+cord+after+contusive+injury.&journal=Brain+Res.&author=Noble+L.+J.&author=and+Wrathall+J.+R.&publication_year=1989b&volume=482&pages=57-66)

Orive, G., Anitua, E., Pedraz, J. L., and Emerich, D. F. (2009). Biomaterials for promoting brain protection, repair and regeneration. *Nat. Rev. Neurosci.* 10, 682–692. doi: 10. 1038/nrn2685

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19654582) | [CrossRef Full Text](https://doi.org/10.1038/nrn2685) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Biomaterials+for+promoting+brain+protection%2C+repair+and+regeneration.&journal=Nat.+Rev.+Neurosci.&author=Orive+G.&author=Anitua+E.&author=Pedraz+J.+L.&author=and+Emerich+D.+F.&publication_year=2009&volume=10&pages=682-692)

Pola, R., Ling, L. E., Silver, M., Corbley, M. J., Kearney, M., Blake Pepinsky, R., et al. (2001). The morphogen Sonic hedgehog is an indirect angiogenic agent upregulating two families of angiogenic growth factors. *Nat. Med.* 7, 706–711. doi: 10. 1038/89083

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11385508) | [CrossRef Full Text](https://doi.org/10.1038/89083) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=The+morphogen+Sonic+hedgehog+is+an+indirect+angiogenic+agent+upregulating+two+families+of+angiogenic+growth+factors.&journal=Nat.+Med.&author=Pola+R.&author=Ling+L.+E.&author=Silver+M.&author=Corbley+M.+J.&author=Kearney+M.&author=Blake+Pepinsky+R.&publication_year=2001&volume=7&pages=706-711)

Ranganath, S. H., Levy, O., Inamdar, M. S., and Karp, J. M. (2012). Harnessing the mesenchymal stem cell secretome for the treatment of cardiovascular disease. *Cell Stem Cell* 10, 244–258. doi: 10. 1016/j. stem. 2012. 02. 005

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22385653) | [CrossRef Full Text](https://doi.org/10.1016/j.stem.2012.02.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Harnessing+the+mesenchymal+stem+cell+secretome+for+the+treatment+of+cardiovascular+disease.&journal=Cell+Stem+Cell&author=Ranganath+S.++H.&author=Levy+O.&author=Inamdar+M.++S.&author=and+Karp+J.++M.&publication_year=2012&volume=10&pages=244-258)

Rauch, M. F., Hynes, S. R., Bertram, J., Redmond, A., Robinson, R., Williams, C., et al. (2009). Engineering angiogenesis following spinal cord injury: a coculture of neural progenitor and endothelial cells in a degradable polymer implant leads to an increase in vessel density and formation of the blood-spinal cord barrier. *Eur. J. Neurosci.* 29, 132–145. doi: 10. 1111/j. 1460-9568. 2008. 06567. x

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19120441) | [CrossRef Full Text](https://doi.org/10.1111/j.1460-9568.2008.06567.x) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Engineering+angiogenesis+following+spinal+cord+injury%3A+a+coculture+of+neural+progenitor+and+endothelial+cells+in+a+degradable+polymer+implant+leads+to+an+increase+in+vessel+density+and+formation+of+the+blood-spinal+cord+barrier.&journal=Eur.+J.+Neurosci.&author=Rauch+M.++F.&author=Hynes+S.++R.&author=Bertram+J.&author=Redmond+A.&author=Robinson+R.&author=Williams+C.&publication_year=2009&volume=29&pages=132-145)

Riahi, N., Liberelle, B., Henry, O., and De Crescenzo, G. (2017). Impact of RGD amount in dextran-based hydrogels for cell delivery. *Carbohydr. Polym.* 161, 219–227. doi: 10. 1016/j. carbpol. 2017. 01. 002

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28189232) | [CrossRef Full Text](https://doi.org/10.1016/j.carbpol.2017.01.002) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Impact+of+RGD+amount+in+dextran-based+hydrogels+for+cell+delivery.&journal=Carbohydr.+Polym.&author=Riahi+N.&author=Liberelle+B.&author=Henry+O.&author=and+De+Crescenzo+G.&publication_year=2017&volume=161&pages=219-227)

Richardson, T. P., Peters, M. C., Ennett, A. B., and Mooney, D. J. (2001). Polymeric system for dual growth factor delivery. *Nat. Biotechnol.* 19, 1029–1034. doi: 10. 1038/nbt1101-1029

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11689847) | [CrossRef Full Text](https://doi.org/10.1038/nbt1101-1029) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Polymeric+system+for+dual+growth+factor+delivery.&journal=Nat.+Biotechnol.&author=Richardson+T.++P.&author=Peters+M.++C.&author=Ennett+A.++B.&author=and+Mooney+D.++J.&publication_year=2001&volume=19&pages=1029-1034)

Rivron, N. C., Raiss, C. C., Liu, J., Nandakumar, A., Sticht, C., Gretz, N., et al. (2012). Sonic Hedgehog-activated engineered blood vessels enhance bone tissue formation. *Proc. Natl. Acad. Sci. U. S. A.* 109, 4413–4418. doi: 10. 1073/pnas. 1117627109

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22388744) | [CrossRef Full Text](https://doi.org/10.1073/pnas.1117627109) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Sonic+Hedgehog-activated+engineered+blood+vessels+enhance+bone+tissue+formation.&journal=Proc.+Natl.+Acad.+Sci.+U.S.A.&author=Rivron+N.+C.&author=Raiss+C.+C.&author=Liu+J.&author=Nandakumar+A.&author=Sticht+C.&author=Gretz+N.&publication_year=2012&volume=109&pages=4413-4418)

Ropper, A. E., Thakor, D. K., Han, I., Yu, D., Zeng, X., Anderson, J. E., et al. (2017). Defining recovery neurobiology of injured spinal cord by synthetic matrix-assisted hMSC implantation. *Proc. Natl. Acad. Sci. U. S. A.* 114, E820–E829. doi: 10. 1073/pnas. 1616340114

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28096400) | [CrossRef Full Text](https://doi.org/10.1073/pnas.1616340114) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Defining+recovery+neurobiology+of+injured+spinal+cord+by+synthetic+matrix-assisted+hMSC+implantation.&journal=Proc.+Natl.+Acad.+Sci.+U.S.A.&author=Ropper+A.++E.&author=Thakor+D.++K.&author=Han+I.&author=Yu+D.&author=Zeng+X.&author=Anderson+J.++E.&publication_year=2017&volume=114&pages=E820-E829)

Rufaihah, A. J., Johari, N. A., Vaibavi, S. R., Plotkin, M., Di Thien, D. T., Kofidis, T., et al. (2017). Dual delivery of VEGF and ANG-1 in ischemic hearts using an injectable hydrogel. *Acta Biomater.* 48, 58–67. doi: 10. 1016/j. actbio. 2016. 10. 013

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27756647) | [CrossRef Full Text](https://doi.org/10.1016/j.actbio.2016.10.013) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Dual+delivery+of+VEGF+and+ANG-1+in+ischemic+hearts+using+an+injectable+hydrogel.&journal=Acta+Biomater.&author=Rufaihah+A.++J.&author=Johari+N.++A.&author=Vaibavi+S.++R.&author=Plotkin+M.&author=Di+Thien+D.++T.&author=Kofidis+T.&publication_year=2017&volume=48&pages=58-67)

Sensharma, P., Madhumathi, G., Jayant, R. D., and Jaiswal, A. K. (2017). Biomaterials and cells for neural tissue engineering: current choices. *Mater. Sci. Eng. C* 77, 1302–1315. doi: 10. 1016/j. msec. 2017. 03. 264

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=28532008) | [CrossRef Full Text](https://doi.org/10.1016/j.msec.2017.03.264) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Biomaterials+and+cells+for+neural+tissue+engineering%3A+current+choices.&journal=Mater.++Sci.+Eng.+C&author=Sensharma+P.&author=Madhumathi+G.&author=Jayant+R.+D.&author=and+Jaiswal+A.+K.&publication_year=2017&volume=77&pages=1302-1315)

Shin, Y., Jeon, J. S., Han, S., Jung, G.-S., Shin, S., Lee, S.-H., et al. (2011). In vitro 3D collective sprouting angiogenesis under orchestrated ANG-1 and VEGF gradients. *Lab Chip* 11, 2175–2181. doi: 10. 1039/c1lc20039a

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21617793) | [CrossRef Full Text](https://doi.org/10.1039/c1lc20039a) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=In+vitro+3D+collective+sprouting+angiogenesis+under+orchestrated+ANG-1+and+VEGF+gradients.&journal=Lab+Chip&author=Shin+Y.&author=Jeon+J.+S.&author=Han+S.&author=Jung+G.-S.&author=Shin+S.&author=Lee+S.-H.&publication_year=2011&volume=11&pages=2175-2181)

Slaughter, B. V., Khurshid, S. S., Fisher, O. Z., Khademhosseini, A., and Peppas, N. A. (2009). Hydrogels in regenerative medicine. *Adv. Mater.* 21, 3307–3329. doi: 10. 1002/adma. 200802106

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20882499) | [CrossRef Full Text](https://doi.org/10.1002/adma.200802106) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Hydrogels+in+regenerative+medicine.&journal=Adv.+Mater.&author=Slaughter+B.+V.&author=Khurshid+S.+S.&author=Fisher+O.+Z.&author=Khademhosseini+A.&author=and+Peppas+N.+A.&publication_year=2009&volume=21&pages=3307-3329)

Trivedi, A., Zhang, H., Ekeledo, A., Lee, S., Werb, Z., Plant, G. W., et al. (2016). Deficiency in matrix metalloproteinase-2 results in long-term vascular instability and regression in the injured mouse spinal cord. *Exp. Neurol.* 284, 50–62. doi: 10. 1016/j. expneurol. 2016. 07. 018

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27468657) | [CrossRef Full Text](https://doi.org/10.1016/j.expneurol.2016.07.018) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Deficiency+in+matrix+metalloproteinase-2+results+in+long-term+vascular+instability+and+regression+in+the+injured+mouse+spinal+cord.&journal=Exp.+Neurol.&author=Trivedi+A.&author=Zhang+H.&author=Ekeledo+A.&author=Lee+S.&author=Werb+Z.&author=Plant+G.+W.&publication_year=2016&volume=284&pages=50-62)

Tsurkan, M. V., Chwalek, K., Prokoph, S., Zieris, A., Levental, K. R., Freudenberg, U., et al. (2013). Defined polymer-peptide conjugates to form cell-instructive starPEG-heparin matrices in situ. *Adv. Mater.* 25, 2606–2610. doi: 10. 1002/adma. 201300691

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23576312) | [CrossRef Full Text](https://doi.org/10.1002/adma.201300691) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Defined+polymer-peptide+conjugates+to+form+cell-instructive+starPEG-heparin+matrices+in+situ.&journal=Adv.+Mater.&author=Tsurkan+M.++V.&author=Chwalek+K.&author=Prokoph+S.&author=Zieris+A.&author=Levental+K.++R.&author=Freudenberg+U.&publication_year=2013&volume=25&pages=2606-2610)

Vempati, P., Popel, A. S., and Mac Gabhann, F. (2011). Formation of VEGF isoform-specific spatial distributions governing angiogenesis: computational analysis. *BMC Syst. Biol.* 5: 59. doi: 10. 1186/1752-0509-5-59

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21535871) | [CrossRef Full Text](https://doi.org/10.1186/1752-0509-5-59) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Formation+of+VEGF+isoform-specific+spatial+distributions+governing+angiogenesis%3A+computational+analysis.&journal=BMC+Syst.+Biol.&author=Vempati+P.&author=Popel+A.+S.&author=and+Mac+Gabhann+F.&publication_year=2011)

Verslegers, M., Lemmens, K., Van Hove, I., and Moons, L. (2013). Matrix metalloproteinase-2 and -9 as promising benefactors in development, plasticity and repair of the nervous system. *Prog. Neurobiol.* 105, 60–78. doi: 10. 1016/j. pneurobio. 2013. 03. 004

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23567503) | [CrossRef Full Text](https://doi.org/10.1016/j.pneurobio.2013.03.004) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Matrix+metalloproteinase-2+and+-9+as+promising+benefactors+in+development%2C+plasticity+and+repair+of+the+nervous+system.&journal=Prog.+Neurobiol.&author=Verslegers+M.&author=Lemmens+K.&author=Van+Hove+I.&author=and+Moons+L.&publication_year=2013&volume=105&pages=60-78)

Wang, Y., Liu, X.-C., Zhao, J., Kong, X.-R., Shi, R.-F., Zhao, X.-B., et al. (2009). Degradable PLGA scaffolds with basic fibroblast growth factor: experimental studies in myocardial revascularization. *Texas Hear. Inst. J.* 36, 89–97.

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19436800) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Degradable+PLGA+scaffolds+with+basic+fibroblast+growth+factor%3A+experimental+studies+in+myocardial+revascularization.&journal=Texas+Hear.+Inst.+J.&author=Wang+Y.&author=Liu+X.-C.&author=Zhao+J.&author=Kong+X.-R.&author=Shi+R.-F.&author=Zhao+X.-B.&publication_year=2009&volume=36&pages=89-97)

Wen, Y., Yu, S., Wu, Y., Ju, R., Wang, H., Liu, Y., et al. (2016). Spinal cord injury repair by implantation of structured hyaluronic acid scaffold with PLGA microspheres in the rat. *Cell Tissue Res.* 364, 17–28. doi: 10. 1007/s00441-015-2298-1

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=26463048) | [CrossRef Full Text](https://doi.org/10.1007/s00441-015-2298-1) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Spinal+cord+injury+repair+by+implantation+of+structured+hyaluronic+acid+scaffold+with+PLGA+microspheres+in+the+rat.&journal=Cell+Tissue+Res.&author=Wen+Y.&author=Yu+S.&author=Wu+Y.&author=Ju+R.&author=Wang+H.&author=Liu+Y.&publication_year=2016&volume=364&pages=17-28)

Widenfalk, J., Lipson, A., Jubran, M., Hofstetter, C., Ebendal, T., Cao, Y., et al. (2003). Vascular endothelial growth factor improves functional outcome and decreases secondary degeneration in experimental spinal cord contusion injury. *Neuroscience* 120, 951–960. doi: 10. 1016/S0306-4522(03)00399-3

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12927201) | [CrossRef Full Text](https://doi.org/10.1016/S0306-4522%2803%2900399-3) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Vascular+endothelial+growth+factor+improves+functional+outcome+and+decreases+secondary+degeneration+in+experimental+spinal+cord+contusion+injury.&journal=Neuroscience&author=Widenfalk+J.&author=Lipson+A.&author=Jubran+M.&author=Hofstetter+C.&author=Ebendal+T.&author=Cao+Y.&publication_year=2003&volume=120&pages=951-960)

Wong, A. L., Haroon, Z. A., Werner, S., Dewhirst, M. W., Greenberg, C. S., and Peters, K. G. (1997). Tie2 expression and phosphorylation in angiogenic and quiescent adult tissues. *Circ. Res.* 81, 567–574. doi: 10. 1161/01. RES. 81. 4. 567

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=9314838) | [CrossRef Full Text](https://doi.org/10.1161/01.RES.81.4.567) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Tie2+expression+and+phosphorylation+in+angiogenic+and+quiescent+adult+tissues.&journal=Circ.++Res.&author=Wong+A.++L.&author=Haroon+Z.++A.&author=Werner+S.&author=Dewhirst+M.++W.&author=Greenberg+C.++S.&author=and+Peters+K.++G.&publication_year=1997&volume=81&pages=567-574)

Yu, S., Yao, S., Wen, Y., Wang, Y., Wang, H., and Xu, Q. (2016). Angiogenic microspheres promote neural regeneration and motor function recovery after spinal cord injury in rats. *Sci. Rep.* 6: 33428. doi: 10. 1038/srep33428

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=27641997) | [CrossRef Full Text](https://doi.org/10.1038/srep33428) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Angiogenic+microspheres+promote+neural+regeneration+and+motor+function+recovery+after+spinal+cord+injury+in+rats.&journal=Sci.+Rep.&author=Yu+S.&author=Yao+S.&author=Wen+Y.&author=Wang+Y.&author=Wang+H.&author=and+Xu+Q.&publication_year=2016)

Zeng, X., Zeng, Y. S., Ma, Y. H., Lu, L. Y., Du, B. L., Zhang, W., et al. (2011). Bone marrow mesenchymal stem cells in a three-dimensional gelatin sponge scaffold attenuate inflammation, promote angiogenesis, and reduce cavity formation in experimental spinal cord injury. *Cell Transplant.* 20, 1881–1899. doi: 10. 3727/096368911X566181

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21396163) | [CrossRef Full Text](https://doi.org/10.3727/096368911X566181) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Bone+marrow+mesenchymal+stem+cells+in+a+three-dimensional+gelatin+sponge+scaffold+attenuate+inflammation%2C+promote+angiogenesis%2C+and+reduce+cavity+formation+in+experimental+spinal+cord+injury.&journal=Cell+Transplant.&author=Zeng+X.&author=Zeng+Y.++S.&author=Ma+Y.++H.&author=Lu+L.++Y.&author=Du+B.++L.&author=Zhang+W.&publication_year=2011&volume=20&pages=1881-1899)

Zhu, J., and Marchant, R. E. (2011). Design properties of hydrogel tissue-engineering scaffolds. *Expert Rev. Med. Devices* 8, 607–626. doi: 10. 1586/erd. 11. 27

[PubMed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22026626) | [CrossRef Full Text](https://doi.org/10.1586/erd.11.27) | [Google Scholar](http://scholar.google.com/scholar_lookup?&title=Design+properties+of+hydrogel+tissue-engineering+scaffolds.&journal=Expert+Rev.++Med.++Devices&author=Zhu+J.&author=and+Marchant+R.++E.&publication_year=2011&volume=8&pages=607-626)