

Advancing Spinal Cord Regeneration Through Targeted Nanoparticle Delivery Systems

⁺Akhil Ramasani, Rajagopal Appavu⁺⁺

⁺Adlai E.Stevenson High School - 1 Stevenson Dr, Lincolnshire, IL 60069
akhilramasani@gmail.com

⁺⁺School of Research Rising Stars, Tampa, Florida 33647
drraj@researchrisingstars.com

1. Abstract

This study aims at how spinal cord injuries lead to significant loss of motor, sensory, and autonomic functions, presenting major challenges in neural regeneration [1] resulting in the permanent loss of nerve function below the injury level, leaving the patient paralyzed and wheelchair-bound for the remainder of his/her life. Achieving effective therapeutic concentrations at injury sites has been a slow process, partly due to the difficulty of delivering drugs effectively [3]. Nanomaterials have opened new avenues for SCI treatment. Among them, performance-based nanomaterials derived from a variety of materials (i.e metallic) that facilitate improvements in the microenvironment of traumatic injury and, in some cases, promote neuron regeneration. Nanoparticulate drug delivery systems enable the optimization of drug effects and drug bioavailability, thus contributing to the development of novel treatments [2].

2. Introduction

Spinal cord injuries (SCIs) are caused through trauma (like car accidents, falls, or sports injuries), often leading to severe and potentially permanent loss of sensory and motor functions below the injury site. The spinal cord's complex structure is crucial for transmitting signals between the brain and body [4], making repair efforts intricate. Traditional treatments—such as surgery, drug therapy, Traction, Splints, braces, halos

or other support devices [5] and rehabilitation—primarily focus on stabilizing the spine, managing symptoms, and maximizing functional recovery. However, these methods often do not address the underlying cellular and molecular damage caused by SCIs. The recent advancements depict that nanoparticles like hydrogels or biopolymers can play a vital role in promoting repair and regeneration of the spinal cord [9] with greater effectiveness and efficiency. This study will explore the potential of these nanoparticles as viable therapeutic strategies for SCI treatment, examining their mechanisms of action, therapeutic benefits, and the challenges in their application of SCI injuries.

3. Spinal Cord Structure:

The spinal cord is an essential part of the central nervous system, the body's command center. It is a tubular bundle of tissue that extends from the brainstem to the lower back. In other words, the spinal cord runs through the center of the spine that sends out electrical signals from the brain to other parts of the body and back. These signals help you feel sensations, move your body and keep breathing. Any damage to your spinal cord can affect your movement or function. The spinal cord is structured in organized layers, containing three protective membranes that encompass it: the Dura mater [19] (The outer layer that protects your spinal cord from injury), the middle arachnoid layer, and the fragile pia mater [19] (The deepest inner

layer). The interior of the spinal cord contains two main types of tissues: Gray matter (which has a butterfly shape that is located in the center of the cord and contains neurons that process sensory and motor information) and white matter (that surrounds the gray matter and forms pathways that carry signals up and down the cord [20]. The cord, itself, is divided into five different segments: the cervical vertebrae, thoracic vertebrae, lumbar vertebrae, sacral, and coccygeal [19]. The cervical vertebrae, which contains eight nerve pairs, is located in the neck and is crucial for breathing and permits head turning and tilting [21]. The thoracic vertebrae, which constraints twelve nerve pairs, helps with breathing and posture; it holds the rib cage which protects the heart and lungs. The lumbar vertebrae [21], which contains five nerve pairs, controls different lower body functions such as hip movements. The sacral, which contains five nerve pairs, is located in the lower spine which are fused together with the hip bones; they form a ring called the pelvic girdle [21] and have different functions such as controlling the bowel, bladder, etc. Lastly, the coccygeal, which has only one pair of nerves, is located in the tailbone region and Its main function is to provide attachment for ligaments and muscles of the pelvic floor [21]. Thus, the structure of the spinal cord contains many parts/ functions and are organized into intricate layers.

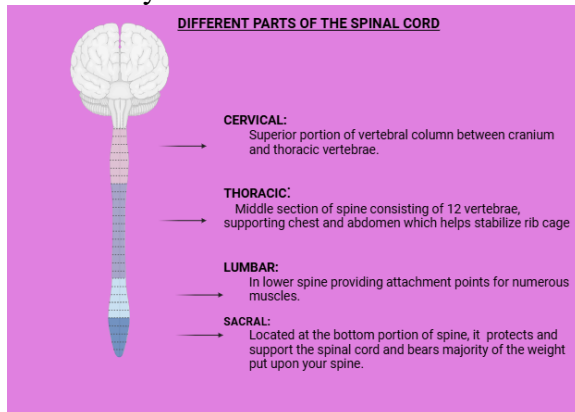


Figure 1: The above image gives a brief overview on the structure of the spinal cord and how its organized

into sections called *vertebrates*. These sections are better known as the *cervical vertebrae*, *thoracic vertebrae*, *lumbar vertebrae*, and the *sacral vertebrae*, going from the top of the spinal cord to the bottom.

4. Beneficence (Minimizing Harm):

The principle of beneficence emphasizes the importance of minimizing harm and maximizing potential benefits. In animal research, this means researchers should take every possible step to ensure that experiments are as non-invasive as possible and that any suffering is minimized. Reports of rushed experiments leading to animal deaths suggest that this principle may not have been fully adhered to in Neuralink's testing. A balance must be struck between the urgency of technological advancement and the ethical responsibility to minimize suffering in animals.

5. Spinal Cord Injury and Effects:

Immediately after a spinal cord injury, one might experience spinal shock which can cause loss of motor function, sensation, and autonomic control[8], resulting in total or partial paralysis depending on the location and severity of the damage [22]. The pathologic mechanisms causing SCIs are classified as either primary or secondary. Primary injury, often irreversible, arises from direct spinal cord damage. Secondary injury occurs as a consequence of the changes induced by a primary injury, such as inflammation. Nerve axon disruption produces motor and sensory function loss below the level of injury [23]. Psychological effect is also significant with depression, anxiety, and adjustment disorders being the rule rather than the exception for patients as they adapt to their new abilities and status. The primary stage of the injury occurs immediately after the event and describes the consequences of the initial impact of the

injury. Depending upon the circumstances, haemorrhaging, laceration and compression of the bones of the spine can be seen at the site of injury. A common injury is fractures and dislocations [23], which are caused by sudden trauma, like a fall or car crash and can limit range and motion in arms, legs, etc. Furthermore, the secondary injury is a cascade of biochemical events that occur in the hours and days following the trauma [23] such as inflammation, cell death, and apoptosis-causing more neural damage. One secondary injury that is common, but significant, and results from spinal cord wounds is a pressure ulcer (better known as pressure sore) [23] that occurs through ongoing pressure onto somebody as a result of sitting or lying in an unfavorable position for too long. The resulting effect of this prolonged pressure can reduce mobility, and more importantly be life-threatening if left untreated. Thus, spinal cord injuries can occur in two phases and if left untreated, they create a significantly negative impact on the quality of life.

6. Economic/Social Impact:

Spinal cord injury (SCI) affects not only the victim but the society as well. In cases of traumatic spinal cord injuries the patients often seek medical care consisting of both surgical stabilization and vertebral decompression [18]. The medical care is economically strenuous, beginning with acute intensive care and followed by long-term rehabilitation, home modification, and ongoing medical care. The lifetime cost for a single patient can range from hundreds of thousands to millions of dollars, depending on the nature and severity of injury. This presents significant challenges to health systems, insurers, and families [18]. Most of the patients who suffer traumatic injuries will also have an impact on mental health like depression and suicide. It will require

prolonged work absence or never resume pre-injury work, with resultant lost productivity and additional economic cost. More recent therapies, however, provide an optimistic outlook.

7. Current Treatment Options:

Presently, the main treatments for SCI involve surgical decompression and pharmacotherapy (Li et al., 2023) [8]. Studies indicate that performing decompression surgery

within the first 24 hours post-injury leads to better sensorimotor recovery compared with delayed interventions (Du et al., 2019; Badhiwala et al., 2021). The drug treatment predominantly adopted in clinics can foster functional recovery albeit with limited long-term benefits (Fehlings et al., 2017). Nonetheless, the usage of drugs is contentious due to severe side effects, such as infections and gastrointestinal bleeding (Bowers et al., 2016) [8]. Thus, efficient drug delivery mechanisms are vital for successful treatment. Nanoparticles, as a drug delivery system, stand out for their potential to enhance drug safety, efficacy, and bioavailability in SCI therapy, marking a significant advancement in the field [8].

Nanoparticles are exceptionally biocompatible, efficient in drug loading, and capable of penetrating the BSCB, making them highly promising for SCI treatment [14]. These particles, which range in size from 1 nm to 1000 nm, can either have therapeutic effects themselves or act as carriers for drugs. Nanoparticles smaller than 5 nm are quickly cleared by the kidneys [8], while those larger than 100 nm tend to accumulate in the liver or spleen [16]. Appropriately sized nanoparticles can significantly extend the half-life of drugs in the body (Dolai et al., 2021) [13]. Traditional small molecules and peptide/protein drugs often struggle to reach

effective concentrations in the spinal cord due to barriers such as the BSCB, cellular efflux mechanisms, and enzymatic degradation (Lu et al., 2023). Nanoparticles, however, can overcome these challenges, showing increased accumulation in the injured spinal cord following systemic administration (Chen et al., 2020). A previous study has shown that nanoparticles are more easily taken up by the central nervous system, thanks to their ability to be endocytosed by vascular endothelial cells and escape lysosomes (Kong et al., 2012). For example, polymer-based nanoparticles efficiently penetrate the BSCB without excessive buildup in the liver and kidney (Shen et al., 2021), and intravenously injected nanoparticles remain in the body for days without quick elimination (Jiang et al., 2022). Beyond merely transporting drugs, some nanoparticles have inherent therapeutic properties. Additionally, nanoparticles are excellent drug carriers; their surface charge and large specific surface area enable them to adsorb and encapsulate large quantities of drugs [8]. Mesoporous silica nanoparticles use their porous surface to adsorb numerous drug molecules (Zhang et al., 2021) [8], while albumin nanoparticles encapsulate drugs within their structure, further enabling drug loading (Lin et al., 2019) [8]. Various nanoparticles, including polyethylene glycol, liposomes, and poly (lactic-co-glycolic acid) nanoparticles, have been shown to enhance drug stability, solubility, and transmembrane transport (Son et al., 2023), thereby improving drug bioavailability. The trend towards in situ implantation of biomaterials for optimized drug delivery further underscores the synergy between nanoparticles and biomaterials (Li et al., 2016; Suzuki et al., 2023). For example, liposomes can be incorporated into hydrogel and collagen scaffolds for localized implantable drug delivery (Li et al., 2018; Wang et al., 2018) [8]. In essence,

nanoparticles offer unique advantages over traditional small molecule and peptide/protein drugs due to these properties.

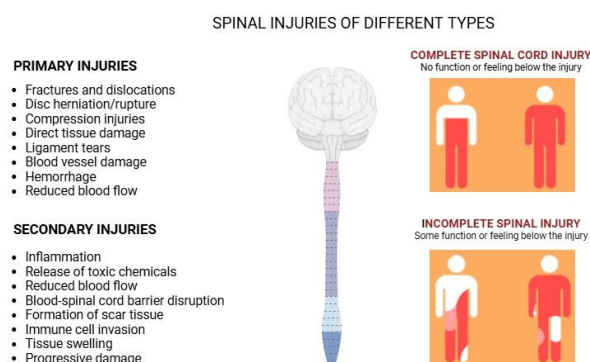


Figure 2: The above image displays the various injuries that result from damage to the spinal cord. Spinal cord injuries can be organized into two categories known as the primary injury (more direct damage) and the secondary injury (secondhand injury resulting from the primary injury).

8. Types of nanoparticles:

Nanoparticles can be classified into different types based on their structural configuration and composition, as outlined below:
Inorganic Nanoparticles:

Inorganic nanoparticles are known to be microscopic in nature. These nanoparticles are known for their stability and hydrophilic nature due to their hydraulic nature they love to mix with water. Commonly used materials in their construction include carbon and silica, as well as precious metals like gold, silver, and iron oxide. The metal-based structure of these nanoparticles enhances their reactivity and efficiency, offering remarkable properties compared to their bulk metal counterparts. These nanoparticles are frequently used in diagnostic and imaging applications.

9. Organic Nanoparticles:

Organic nanoparticles are biodegradable and non-toxic in nature. Organic nanoparticles

are typically composed of lipids or natural or synthetic polymers. Unlike inorganic nanoparticles, organic nanoparticles can be metabolized by the body's own mechanisms, significantly minimizing long-term tissue accumulation issues. Organic nanoparticles are thermally or electromagnetically sensitive, such as to heat and light. Their ability to encapsulate hydrophobic and hydrophilic drugs has rendered them effective drug delivery vehicles. Moreover, organic nanoparticles can be metabolized by the body's own processes, thus eliminating concern for long-term tissue accumulation by a great degree. They can also be engineered with unique surface modifications to enhance their circulation time in the blood and facilitate targeting of the diseased tissue.

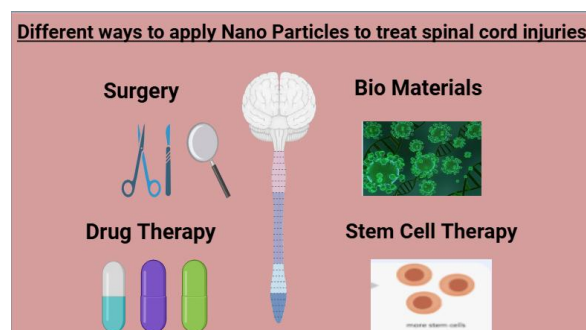


Figure 3: The above image displays the different methods scientists utilize to deliver the necessary nanoparticles to the spinal cord for treatment. These methods include surgery, drug therapy, bio material utilization, and stem cell therapy.

10. Hydrogel Nanoparticles:

Hydrogel nanoparticles can be considered a hybrid material that is both inorganic and organic. Hydrogels are three-dimensional cross-linked polymer networks capable of absorbing substantial quantities of water when immersed in aqueous solutions. Their inherent properties—softness, flexibility, elasticity, and natural wetness—closely resemble biological tissues, making them exceptionally valuable for biomedical and pharmaceutical applications [11].

Additionally, hydrogels such as peptide hydrogels (formed from peptides, which are short chains of amino acids) and biopolymer hydrogels (formed from natural polymers such as proteins or polysaccharides) derived from proteins and glucose can modulate the inflammatory response, provide structural support for cell growth, and facilitate targeted drug delivery [11].

11. Mechanisms of spinal cord regeneration:

The spinal cord is an integral part of the central nervous system and maintains most communications between the brain and the rest of the body. Injury to the spinal cord results in disruption of this communication and is associated with very serious, even lifetime consequences. Thus, it is of prime importance to develop effective and versatile treatments for SCI. With the help of nanomaterials, it is possible to identify a very promising method for the treatment of SCI. In general, two main functions are possible for nanoparticles: as drug carriers, delivering active components directly to the place of injury, and/or influencing the immune system by guiding immune cells throughout the body. Such immune cells reprogram to enhance the immune response to spinal cord damage in order to enhance tissue regeneration.

This is proven by research, where it shows that nanoparticles alter the behavior of immune cells, influencing cell spread, gene activation, and general functionality [24]. Upon the introduction of nanoparticles, more immune cells with nanoparticles aggregate at the site of injury. It reduces some inflammation-producing immune cells and increases gene activity that fights inflammation and ensures healing [24]. Due to this, nanoparticles can change the surroundings around the cells into a better shape that may improve cellular function and

hence makes more therapeutic compounds available at the site of injury. This is also used to provide an ideal environment for nerve regeneration through injectable hydrogels among other scaffolds, which helps repair the damaged part of the nerve tissue[11].

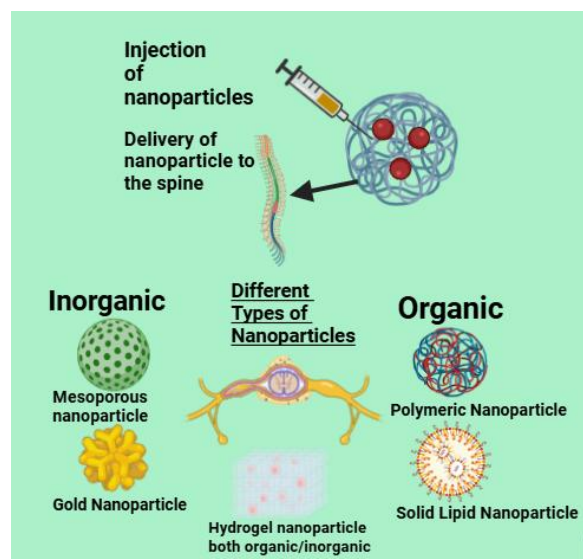


Figure 4: The above image displays the different types of nanoparticles and its delivery into the spinal cord for treatment. Additionally, the various nanoparticles, such as the few displayed in the image, can be organized into two categories: organic and inorganic nanoparticles.

12. Stem Cell Validation: (Timeline for regen of SC)

Most impressively, it is the mending and regenerative capability manifested through the activity of the human body in which healthy stem cells, by transplantation, replace the damaged or diseased ones and start the restorative journey[25]. First 2 to 3 Weeks: The initial signs of recovery appear as white blood cells, especially neutrophils, have a gradual increasing trend. This rise enhances the resisting power of the body against infection. By the end of the first month, platelets begin to increase. Increased platelets help the blood to clot and prevent excessive bleeding; this, in turn, helps with wound healing. Over the Next Few Months: The

number of red blood cells increases, thus increasing oxygen carriage to all parts of the body, thereby restoring vitality and a feeling of well-being. Meanwhile, some more specialized immune cells undertake the slower process of rebuilding their more intricate networks, which protects them against infection. Up to a year or more: This is a very complex process of cellular regeneration and involves the relearning of the protective functions by the immune system, along with reestablishment. The body needs this period for regaining its full strength and vitality. Thus, the healing process after stem cell transplantation is an indication of how the human body can adeptly repair themselves, starting with simple and basic immune cells and gradually reconstructing itself to develop more complex systems. Although the healing journey can take a significant amount of time, it can ultimately end up restoring the body's strength and ability to protect itself from other illnesses.

Materials/Methods: (practical approach of handling nanoparticles/buffers in sterile environment throughout clinical process)

When working with nanoparticles/buffers in a sterile environment throughout the clinical process, it is important to use proper methods and materials to remain safe. For instance, arm/sleeve protectors are required because high levels of exposure or splashes of solutions containing nano particles may harm your skin. Additionally, activities that are likely to release nanoparticles (such as the opening and emptying of reactors) shall not be performed on the open bench because contaminants of the nanoparticles may go airborne, causing biological implications to those around the nanoparticles, who either inhale the nanoparticle or the nanoparticles enter their skin. As a result of the potential dangers of nanoparticles that come into contact with someone, it is essential that

these activities be performed in a fume hood (or other vented enclosure), biological safety cabinet, glove box or a vented filtered enclosure to contain the nanoparticle contaminates. In addition, while working with nanoparticles, having adequate protection like wearing gloves will mitigate the potential risk of skin exposure. Also, respirators may be required for activities that cannot be controlled using ventilation. Thus, given the potential dangers and consequences of nanoparticles being exposed, it is vital to take the necessary precautions and methods in order to help prevent any significant danger[17].

Conclusion:

In conclusion, given the challenges the landscape of spinal cord injury treatment continues to evolve through remarkable scientific innovation. Scientists are finding innovative ways to deal with the issue of spinal cord injury. The use of stem cell therapy combined with nanotechnology is a new and emerging field in SCI treatment. Researchers are developing sophisticated biomaterials and nanomaterials with precise targeting capabilities to deliver therapeutic agents directly to injured sites, effectively modulate inflammatory responses within the microenvironment, and stimulate neural tissue regeneration. Mesenchymal stem cells have emerged as especially valuable in this context, demonstrating significant efficacy in regulating inflammation and enhancing functional recovery. When combined with established rehabilitation protocols, these advanced therapeutic approaches offer a comprehensive treatment paradigm that not only addresses the physiological damage but potentially reduces the substantial personal and societal burden associated with spinal cord injuries. As these technologies mature, they hold the promise of transforming SCI from a permanently debilitating condition to

one with meaningful paths toward recovery and improved quality of life.

References:

1. Yang Q, Lu D, Wu J, Liang F, Wang H, Yang J, Zhang G, Wang C, Yang Y, Zhu L, Sun X. Nanoparticles for the treatment of spinal cord injury. *Neural Regen Res*. 2025 Jun 1;20(6):1665-1680. doi: 10.4103/NRR.NRR-D-23-01848. Epub 2024 May 13. PMID: 39104097; PMCID: PMC11688544.
2. Gong W, Zhang T, Che M, Wang Y, He C, Liu L, Lv Z, Xiao C, Wang H, Zhang S. Recent advances in nanomaterials for the treatment of spinal cord injury. *Mater Today Bio*. 2022 Dec 17;18:100524. doi: 10.1016/j.mtbio.2022.100524. PMID: 36619202; PMCID: PMC9813796.
3. Surgery, 1Department of Orthopedic. (n.d.). Nanoparticles for the treatment of Spinal Cord Injury: Neural Regeneration Research. LWW. https://journals.lww.com/nrronline/fulltext/2025/06000/nanoparticles_for_the_treatment_of_spinal_cord.10.aspx
4. Gong W, Zhang T, Che M, Wang Y, He C, Liu L, Lv Z, Xiao C, Wang H, Zhang S. Recent advances in nanomaterials for the treatment of spinal cord injury. *Mater Today Bio*. 2022 Dec 17;18:100524. doi: 10.1016/j.mtbio.2022.100524. PMID: 36619202; PMCID: PMC9813796.
5. Surgery, 1Department of Orthopedic. (n.d.). Nanoparticles for the treatment of Spinal Cord Injury: Neural Regeneration Research. LWW. https://journals.lww.com/nrronline/fulltext/2025/06000/nanoparticles_for_the_treatment_of_spinal_cord.10.aspx
6. Nógrádi, A. (1970, January 1). Anatomy and physiology of the Spinal Cord. *Madame Curie Bioscience Database* [Internet].

<https://www.ncbi.nlm.nih.gov/books/NBK6229/>

7. Anatomy and physiology I. The Vertebral Column | Anatomy and Physiology I. (n.d.). <https://courses.lumenlearning.com/suny-ap1/chapter/the-vertebral-column/>

8. Yang, Qiwei, et al. "Nanoparticles for the Treatment of Spinal Cord Injury." Neural Regeneration Research, U.S. National Library of Medicine, 1 June 2025, [pmc.ncbi.nlm.nih.gov/articles/PMC11688544/](https://pubmed.ncbi.nlm.nih.gov/articles/PMC11688544/).

9. U.S. Department of Health and Human Services. (n.d.-a). Nanoparticles promote functional healing following spinal cord injury. National Institute of Biomedical Imaging and Bioengineering. <https://www.nibib.nih.gov/news-events/newsroom/nanoparticles-promote-functional-healing-following-spinal-cord-injury>

10. PNAS. (n.d.). <https://www.pnas.org/doi/10.1073/pnas.2304819120>

11. Author links open overlay panel Yao Jiang, Abstract The incorporation of nanoparticles into hydrogels yields novel superstructures that have become increasingly popular in biomedical research. Each component of these nanoparticle–hydrogel superstructures can be easily modified, Farokhzad, O. C., Amreddy, N., Calo, E., Zhang, R. X., Chen, Z. G., Rizvi, S. A. A., Singh, R., Golombek, S. K., Dacoba, T. G., Fang, R. H., Angsantikul, P., Jiang, Y., Li, C., Hoffman, A. S., Klouda, L., Kopecek, J., Zhu, J., ... Conde, J. (2020, May 26). Nanoparticle–Hydrogel Superstructures for Biomedical Applications. Journal of Controlled Release. <https://www.sciencedirect.com/science/article/abs/pii/S0168365920303187>

12. Ray, U. (2023, June 13). What are the different types of nanoparticles?. AZoNano. <https://www.azonano.com/article.aspx?ArticleID=4938>

13. Jayanta Dolai, Kuheli Mandal, and Nikhil R. Jana
ACS Applied Nano Materials 2021 4 (7), 6471-6496
DOI: 10.1021/acsanm.1c009871.

14. Lu D, Wu JP, Yang QW, Wang HY, Yang JJ, Zhang GG, Wang C, Yang YL, Zhu L, Sun XZ. Recent advances in lipid nanovesicles for targeted treatment of spinal cord injury. Front Bioeng Biotechnol. 2023 Aug 16;11:1261288. doi: 10.3389/fbioe.2023.1261288. PMID: 37691909; PMCID: PMC10486273.

15. Choi HS, Liu W, Misra P, Tanaka E, Zimmer JP, Ipe B, Bawendi MG, Frangioni JV. Renal clearance of quantum dots. Nat Biotechnol. 2007 Oct;25(10):1165-70. doi: 10.1038/nbt1340. Epub 2007 Sep 23. PMID: 17891134; PMCID: PMC2702539.

16. Singh S, Sharma A, Robertson GP. Realizing the clinical potential of cancer nanotechnology by minimizing toxicologic and targeted delivery concerns. Cancer Res. 2012 Nov 15;72(22):5663-8. doi: 10.1158/0008-5472.CAN-12-1527. Epub 2012 Nov 8. PMID: 23139207; PMCID: PMC3616627.

17. Chrome-Extension://EFAIDNBMMNNIBPCAJPCLCLEFINDMKAJ/<https://www.nejm.org/doi/pdf/10.1056/nejmoa1905795?articletools=true>. Share your feedback on Acrobat DC. (n.d.). <https://acrobat.uservoice.com/forums/931921-adobe-acrobat-in-browsers/suggestions/47606612-chrome-extension-efaidnbmnnnibpcajpclclefindmka>

18. Chrome-Extension://EFAIDNBMMNNIBPCAJPCLCLEFINDMKAJ/https://www.nejm.org/doi/pdf/10.1056/nejmoa1905795?articletools=true. Share your feedback on Acrobat DC. (n.d.).

<https://acrobat.uservoice.com/forums/931921-adobe-acrobat-in-browsers/suggestions/47606612-chrome-extension-efaidnbmnnnibpcajpclclefindmka>

Reviewer 1: ☒ Approved

Reviewer 2: ☒ Approved

Reviewer 3: ☒ Approved

19. professional, C. C. medical. (2024, December 19). What are the three main parts of the spinal cord?. Cleveland Clinic. <https://my.clevelandclinic.org/health/body/21946-spinal-cord>

20. Nair, R. (2019, November 12). A Guide to the spinal cord: Anatomy and injuries. MedicalNewsToday. <https://www.medicalnewstoday.com/articles/326984>

21. (BCCA), B. C. A. (2020, May 21). What are the 5 sections of the spine? Spinal Column Anatomy. <https://www.bcchiro.com/what-are-the-5-sections-of-the-spine-spinal-column-anatomy/>

22. U.S. Department of Health and Human Services. (n.d.). Spinal Cord Injury. National Institute of Neurological Disorders and Stroke. <https://www.ninds.nih.gov/health-information/disorders/spinal-cord-injury>

23. Bennett, J. (2024, December 13). Spinal Cord Injuries. StatPearls [Internet]. <https://www.ncbi.nlm.nih.gov/books/NBK560721/>