Journal of Bioanalysis & Biomedicine

Anderson, J Bioanal Biomed 2018, 10:4
DOI: 10.4172/1948-593X.1000212

Short Communication Open Access

GAG Nanoparticles for Brain Repair and Beyond: A Commentary on Nih et al., Nature Materials 2018

Sean M. Anderson*

Founder, Aqua Regenerative Therapies, San Diego, California, USA

Short Communication

In the May 21, 2018 issue of Nature Materials, Nih et al. artfully revealed how heparin nanoparticles can be employed to regrow brain tissue after damage from stroke [1]. This landmark finding revolutionizes the way we think of stroke and recovery, and also demonstrates the unrivaled power of tissue engineering. Further, if heparin nanoparticles can down-regulate the natural inflammatory response and stimulate morphological repair of complex tissue structures in the brain, strong hope exists that the heparin nanoparticles can also repair damaged heart tissue, diabetes-induced necrotic tissue, chronic wounds, and spinal cord injuries.

I am a graduate of the Segura lab from when it was located at the University of California, Los Angeles (UCLA) and I know these heparin nanoparticles very well as I originally developed the particles for my thesis project. Initially tasked with studying the cell signaling of bound growth factors on engineered surfaces [2], I had to pause the project when a key antibody required to study our signaling network went on backorder. To fill the time, I conceptualized the idea of the heparin nanoparticles and approached Dr. Segura about it. To my disappointment, she quickly rejected the idea, claiming it would not work, but I worked on it anyway.

After a few months of developing the technology on my own, I showed Dr. Segura the data, and she finally supported it. We published the work in Biomaterials [3] and then worked with the UCLA Office of Intellectual Property to patent the heparin nanoparticles. However, UCLA decided that the invention was not worth pursuing, and they abandoned the patent application.

At this time, I obtained my own equipment and lab facilities with the aim of improving the material and processing. This work culminated in an independent patent application that is pending. Part of the novelty of the improved material is its sourcing, which matters significantly in the regulatory environment within which our therapies are developed. Another novel aspect is the flexibility in the design of the material, and its consequent application beyond brain repair.

Heparin is commercially sourced from the intestine of pigs [4]. While animal-sourced material is not ideal, this does not prevent heparin from being a worldwide blockbuster drug. However, significant risks are involved with animal-sourced material, especially in the case of heparin. Supply shortages, like what happened in 2008 with Baxter's Chinese heparin supplier [4], are a substantial risk. The cost of goods is also affected, as heparin is 70% more expensive than other glycosaminoglycans (GAGs) like hyaluronic acid, according to prices from research scale supplier Alfa Aesar. There are also regulatory concerns such as transmission of animal viruses or other inflammatory material through the supply chain. From my own experience in the biotechnology field, I have witnessed a push from my regulatory colleagues for animal-free material, such as chemically defined media, in place of animal-sourced serum, for cell culture. There are certainly challenges for the therapy, as outlined in Nih et al., to make it to the market [1]. Whether the therapy would pass the rigorous standards of worldwide regulatory agencies is unknown, and even if it does, there are business risks in the supply chain and cost of goods.

Thankfully, there are non-animal sources of GAGs that can be engineered to perform in the same manner as heparin from the growth factor-binding perspective [5]. The anti-coagulation activity of heparin is much more difficult to mimic [6], but as Nih et al. point out, the heparin in nanoparticle form has diminished anti-coagulation activity, and anti-coagulation is not ideal in this tissue regeneration application anyway [1].

Developing a non-animal sourced version of the heparin nanoparticles is neither trivial nor obvious. The sulfation pattern is critical, as evidenced by the Baxter heparin crisis in 2008 [4]. The design of an animal-free version of the heparin nanoparticles requires careful consideration of the degree of sulfation. At my company Aqua Regenerative Therapies, I have successfully developed a non-animal sourced version of the heparin nanoparticles, and it is called nanoScyl. We currently have collaborations for nanoScyl use in implantable brain biosensors and skin care/wound healing. Internally, we are working on its use as a diabetes treatment. We are currently looking for partners to apply the material in the brain, heart, and spinal cord.

The key to this class of material, as Nih et al. described, is its ability to sequester pro-inflammatory cytokines and allow developmental-like tissue generation to occur [1]. I would hypothesize that the mechanism of action lies in the material's stabilizing effect on these cytokines. When the cytokines interact with the nanoparticle, the sulfate groups on heparin guide the lysine and arginine side chains of the so-called "heparin-binding domain" of the cytokines into a preferred orientation that is ideal for presentation to cell surface receptors. Due to the electrostatic strength of this matrix-bound state, the physics of the interaction between the cytokine and cell surface receptor is altered, igniting alternative signaling patterns within the cell [7]. The authors of Nih et al. found that brain levels of stroke-induced pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α) decreased because of binding to the heparin nanoparticles [1]. Indeed, TNF-α has a heparin binding domain [8]; however, the authors seem to suggest that because of the binding to the heparin nanoparticles, TNF-α no longer plays a signaling role in the regenerative environment [1]. Alternatively, I would propose that TNF-α still interacts with the cells, but in a matrix-bound state, which then facilitates pro-repair behavior.

***Corresponding author:** Sean M. Anderson, Founder of Aqua Regenerative Therapies, San Diego, California, USA, E-mail: sean@aquabiomaterials.com

Received June 30, 2018; **Accepted** July 17, 2018; **Published** July 24, 2018

Citation: Anderson SM (2018) GAG Nanoparticles for Brain Repair and Beyond: A Commentary on Nih et al., Nature Materials 2018. J Bioanal Biomed 10: 91-92. doi:10.4172/1948-593X.1000212

The potential for GAG nanoparticles to improve tissue engineering and regenerative medicine cannot be overstated. Heparin nanoparticles can regrow brain tissue, which is something that was not possible before. Furthermore, well-designed GAG nanoparticles, such as nanoScyl, have potential in applications that go far beyond brain repair. Sequestration and altered presentation of cytokines in the tissue microenvironment flips the switch from pro-inflammation to anti-scarring, as demonstrated in Nih et al [1]. Wound healing, heart repair, incorporation of implantable biosensors, and much more could benefit from this technology, and bringing these therapies to market is our goal at Aqua Regenerative Therapies.

References

1. Nih LR, Gojgini S, Carmichael ST, Segura T (2018) Dual function injectable angiogenic biomaterial for the repair of brain tissue following stroke. Nat Mater 17: 642-651.
2. Anderson SM, Chen TT, Iruela-Arispe ML, Segura T (2009) The phosphorylation of vascular endothelial growth factor receptor-2 (VEGFR-2) by engineered surfaces with electrostatically or covalently immobilized VEGF. Biomaterials 30: 4618-4628.
3. Anderson SM, Siegman SN, Segura T (2011) The effect of vascular endothelial growth factor (VEGF) presentation within fibrin matrices on endothelial cell branching. Biomaterials 32: 7432-7443.
4. Harris G (2008) Chinese factory linked to drug under inquiry in U.S. New York Times.
5. Purcell DP, Kim IL, Chuo V, Guinen T, Dorsey SM, et al. (2014) Incorporation of sulfated hyaluronic acid macromers into degradable hydrogel scaffolds for sustained molecule delivery. Biomater Sci 2: 693-702.
6. Vaidyanathan D, Williams A, Dordick JS, Koffas MAG, Linhardt RJ (2017) Engineered heparins as new anticoagulant drugs. Bioeng Transl Med 2: 17-30.
7. Anderson SM, Shergill B, Barry ZT, Manousiouthakis E, Chen TT, et al. (2011) VEGF internalization is not required for VEGFR-2 phosphorylation in bioengineered surfaces with covalently linked VEGF. Integr Biol 3: 887-896.
8. Kenig M, Gaberc-Porekar V, Fonda I, Menart V (2008) Identification of the heparin-binding domain of TNF-alpha and its use for efficient TNF-alpha purification by heparin-sepharose affinity chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 867: 119-125.