Nanotechnology: Why Should We Care?

Scott R. Nodzo, MD, Donald W. Hohman, MD, and Krishnan Chakravarthy, MD, PhD

The orthopedic community is increasingly deluged with advancements in the basic sciences. With each step, we must evaluate the necessity of new information and the relevance of these topics for clinical practice. Since the late 1990s, the promise of nanotechnology to effect significant changes in the medical field has been heralded. However, in this coming decade, we as a profession will see unprecedented advances in the movement of this technology "from the bench to the bedside." Not unlike many other basic science advancements in our field, nanotechnology is poorly understood among clinicians and residents. As the use of biologics and drug delivery systems expands in orthopedics, nanoparticle-based devices will become more prevalent and have a momentous impact on the way we treat and diagnose orthopedic patients.

A nanoparticle is generally defined as a particle in which at least 1 dimension is between 1 to 100 nanometers and has material properties consistent with quantum mechanics.[1] Nanomaterials can be composed of organic and inorganic chemical elements that enable basic chemical processes to create more complex systems. Individual nanoparticle units can be synthesized to form nanostructures, including nanotubes, nanoscaffolds, nanofibers, and even nanodiamonds.[2-4] Nanoparticles at this scale display unique optical, chemical, and physical properties that can be manipulated to create specific end-use applications. Such uses may include glass fabrication, optical probes, television screens, drug delivery, gene delivery, and multiplex diagnostic assays.[5-7] By crossing disciplines of physics, engineering, and medical sciences, we can create novel technology that includes nanomanufacturing, targeted drug delivery, nanorobotics in conjunction with artificial intelligence, and point-of-care diagnostics.[7-9]

The field of orthopedics has benefited from nanotechnologic advances, such as new therapeutics and implant-related technology. Nanotubes are hollow nanosized cylinders that are commonly created from titania, silica, or carbon-based substrates. They have garnered significant interest for their high tensile and shear strength, favorable microstructure for bony ingrowth, and their capacity to hold antibiotics or growth factors, such as bone morphogenic proteins (BMPs).[10] The current local delivery limitations of BMPs via a collagen sponge have the potential to be maximized and better controlled with a nanotechnology-based approach. The size, internal structure, and shape of the nanoparticle can be manipulated to control the release of these growth factors, and certain nanoparticles can be dual-layered, allowing for release of multiple growth factors at once or in succession.[11,12] A more powerful and targeted delivery system of these types of growth factors may result in improved or more robust outcomes, and further research is warranted.

It is possible that carbon-based nanotubes can be categorized as a biomedical implant secondary to their mechanical properties.[13] Their strength and ability to be augmented with osteogenic materials has made them an attractive area of research as alternative implant surfaces and stand-alone implants. Nanotubes are capable of acting as a scaffold for antibiotic-loaded, carbon-based nanodiamonds for localized treatment of periprosthetic infection, and research has been directed toward controlled release of the nanodiamond-antibiotic construct from these scaffolds or hydrogels.[4,14] Technologies like this may allow the clinician to treat periprosthetic infections locally and minimize the use of systemic antibiotics. The perfection of this type of delivery system may augment the role of antibiotic-laden cement and improve our treatment success rates, even in traditionally hard-to-treat organisms.

Nanoscaffolds and nanofibers are created from nanosized polymers and rendered into a 3-dimensional structure that can be loaded with biologic particles or acting as a scaffold/template for tissue or bone ingrowth. Nanofibers created using biodegradable substrates such as poly(lactic-co-glycolic acid) (PLGA) and chitosan have been extensively studied for their delayed-release properties and biocompatibility.[15] These scaffolds are often soaked or loaded with chondrogenic, osteogenic, or antibacterial agents, and have been evaluated in both in vitro and in vivo studies with promising results.[15,16] They have been an exciting area of research in tissue engineering, and have been accepted as an adjunct in tendon-repair treatments and local bone regeneration.[3,17] As this technology is perfected, the potential to treat more effectively massive rotator cuff tears or tears with poor tissue integrity will dramatically improve and expand the indications for rotator cuff repair.

Dr. Nodzo is Resident, Department of Orthopaedic Surgery, State University of New York at Buffalo, Buffalo, New York. Dr. Hohman is Adult Reconstructive Orthopaedic Surgeon, Greater Dallas Orthopaedics, Dallas, Texas. Dr. Chakravarthy is Resident, Department of Anesthesiology, Johns Hopkins University, Baltimore, Maryland.

Authors' Disclosure Statement: The authors report no actual or potential conflict of interest in relation to this article.

Am J Orthop. 2015;44(3):E87-E88.

Augmentation of implant surfaces with nanomaterials that improve osseointegration, or that act as antimicrobial agents have also been a focus of research in hopes of decreasing the rates of aseptic failure and periprosthetic infection in arthroplasty procedures. Nanocrystalline surfaces made of hydroxyapatite and cobalt chromium have been evaluated for their enhanced osteoconductive properties, and may replace standard surfaces.[18-20] Recent work evaluating nanoparticle-antibiotic constructs that have been covalently bound to implant surfaces for delayed release of antibiotics during the perioperative period has shown promise, and may allow a more targeted and localized treatment strategy for periprosthetic infection.[21,22]

Major limitations regarding successful clinical implementation of nanotechnology include both cost and regulatory processes. Currently, pharmaceutical companies estimate that, on average, successful clinical trials from phase 1 to completion for new drugs can cost hundreds of millions of dollars.[23] Such high costs result partially from the laborious and capital-intensive process of conducting clinical trials that meet US Food and Drug Administration (FDA) requirements. These regulations would apply to both surface-coated implants and nanoparticle-based drug delivery systems. These types of implants would not be expedited into the market secondary to their drug delivery component and would likely require lengthy clinical studies. Implant companies may be reluctant to invest millions of dollars in multiple FDA trials when they have lucrative implants on the market.

Other limitations include the particles' complex 3-dimensional structure, which can present challenges for mass production. Producing large quantities of nanoparticles at a consistent quality may be a major limitation to the more unique and target-based nanotherapies. Recent concerns with the toxicity profile of nanotechnology-based medicines have resulted in more intense scrutiny of the nanotechnology safety profile.[24,25] Currently, nanoparticle technology is evaluated case by case with each technology requiring its own toxicology and safety profile testing if it is intended for human use. These tests can be cost-prohibitive and require extensive private and government capital for successful market entry. Despite these limitations, nanotechnology will impact the next generation of orthopedic surgeons. Current estimates project the nanomedicine market to be worth $177.6 billion by 2019.[26]

Advances in nanobased orthopedic technologies have expanded dramatically in the past decade, and we, as the treating physicians, must make educated decisions on how and when to use nanoparticle-based therapies and treatment options. Nanotechnology's basic science is confusing and often burdensome, but contemporary review articles may be helpful in keeping the orthopedic resident and clinician current with advancements.[10,27,28] The more we educate ourselves about evolving nanotechnologies, the less reluctance we will have when evaluating new diagnostic and therapeutic treatment modalities.

References

1. Hewakuruppu YL, Dombrovsky LA, Chen C, et al. Plasmonic "pump-probe" method to study semi-transparent nanofluids. *Appl Opt*. 2013;52(24):6041-6050.
2. Balasundaram G, Webster TJ. An overview of nano-polymers for orthopedic applications. *Macromol Biosci*. 2007;7(5):635-642.
3. Zhang Z, Hu J, Ma PX. Nanofiber-based delivery of bioactive agents and stem cells to bone sites. *Adv Drug Deliv Rev*. 2012;64(12):1129-1141.
4. Mochalin VN, Shenderova O, Ho D, Gogotsi Y. The properties and applications of nanodiamonds. *Nat Nanotechnol*. 2012;7(1):11-23.
5. Kneipp J, Kneipp H, Rice WL, Kneipp K. Optical probes for biological applications based on surface-enhanced Raman scattering from indocyanine green on gold nanoparticles. *Anal Chem*. 2005;77(8):2381-2385.
6. Wang L, O'Donoghue MB, Tan W. Nanoparticles for multiplex diagnostics and imaging. *Nanomedicine (Lond)*. 2006;1(4):413-426.
7. Krebs MD, Salter E, Chen E, Sutter KA, Alsberg E. Calcium phosphate-DNA nanoparticle gene delivery from alginate hydrogels induces in vivo osteogenesis. *J Biomed Mater Res A*. 2010;92(3):1131-1138.
8. Myers FB, Lee LP. Innovations in optical microfluidic technologies for point-of-care diagnostics. *Lab Chip*. 2008;8(12):2015-2031.
9. Sacha GM, Varona P. Artificial intelligence in nanotechnology. *Nanotechnology*. 2013;24(45):452002.
10. Ganguly DY, Shahbazian R, Shokuhfar T. Recent advances in nanotubes for orthopedic implants. *J Nanotech Smart Mater*. 2014;1:1-10.
11. Srivastava S, Kotov NA. Composite Layer-by-Layer (LBL) assembly with inorganic nanoparticles and nanowires. *Acc Chem Res*. 2008;41(12):1831-1841.
12. Panda HS, Srivastava R, Bahadur D. Shape and size control of nano dispersed Mg/Al layered double hydroxide. *J Nanosci Nanotechnol*. 2008;8(8):4218-4223.
13. Wang X, Li Q, Xie J, et al. Fabrication of ultralong and electrically uniform single-walled carbon nanotubes on clean substrates. *Nano Lett*. 2009;9(9):3137-3141.
14. Zhu Y, Li J, Li W, et al. The biocompatibility of nanodiamonds and their application in drug delivery systems. *Theranostics*. 2012;2(3):302-312.
15. Wu L, Ding J. In vitro degradation of three-dimensional porous poly(D,L-lactide-co-glycolide) scaffolds for tissue engineering. *Biomaterials*. 2004;25(2):5821-5830.
16. Wu X, Rabkin-Aikawa E, Guleserian KJ, et al. Tissue-engineered microvessels on three-dimensional biodegradable scaffolds using human endothelial progenitor cells. *Am J Physiol Heart Circ Physiol*. 2004;287(2):H480-H487.
17. Xia W, Liu W, Cui L, et al. Tissue engineering of cartilage with the use of chitosan-gelatin complex scaffolds. *J Biomed Mater Res B Appl Biomater*. 2004;71(2):373-380.
18. Laurencin CT, Kumbar SG, Nukavarapu SP. Nanotechnology and orthopedics: a personal perspective. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2009;1(1):6-10.
19. Webster TJ, Ejiofor JU. Increased osteoblast adhesion on nanophase metals: Ti, Ti6Al4V, and CoCrMo. *Biomaterials*. 2004;25(19):4731-4739.
20. Webster TJ, Ergun C, Doremus RH, Siegel RW, Bizios R. Enhanced functions of osteoblasts on nanophase ceramics. *Biomaterials*. 2000;21(17):1803-1810.
21. Stewart S, Barr S, Engiles J, et al. Vancomycin-modified implant surface inhibits biofilm formation and supports bone-healing in an infected osteotomy model in sheep: a proof-of-concept study. *J Bone Joint Surg Am*. 2012;94(15):1406-1415.
22. Hickok NJ, Shapiro IM. Immobilized antibiotics to prevent orthopaedic implant infections. *Adv Drug Deliv Rev*. 2012;64(12):1165-1176.
23. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ*. 2003;22(2):151-185.
24. Vines T, Faunce T. Assessing the safety and cost-effectiveness of early nanodrugs. *J Law Med*. 2009;16(5):822-845.
25. Nel A, Xia T, Mädler L, Li N. Toxic potential of materials at the nanolevel. *Science*. 2006;311(5761):622-627.
26. *Nanomedicine Market (Neurology, Cardiovascular, Anti-Inflammatory, Anti-Infective, and Oncology Applications): Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013-2019*. Transparency Market Research website. http://www.transparencymarketresearch.com/nanomedicine-market.html. Published August 1, 2014. Accessed January 20, 2015.
27. Sullivan MP, McHale KJ, Parvizi J, Mehta S. Nanotechnology: current concepts in orthopaedic surgery and future directions. *Bone Joint J*. 2014;96-B(5):569-573.
28. Pleshko N, Grande DA, Myers KR. Nanotechnology in orthopaedics. *J Am Acad Orthop Surg*. 2012;20(1):60-62.