Published in final edited form as:

J Plast Reconstr Aesthet Surg. 2016 January ; 69(1): 1–13. doi:10.1016/j.bjps.2015.08.028.

Nanotechnology and regenerative therapeutics in plastic surgery: The next frontier

Aaron Tan^{a,d,*}, Reema Chawla^b, G Natasha^a, Sara Mahdibeiraghdar^{c,j}, Rebecca Jeyaraj^a, Jayakumar Rajadas^d, Michael R. Hamblin^{e,f,g}, and Alexander M. Seifalian^{h,i}

^aUCL Medical School, University College London (UCL), London, England, UK

^bDepartment of Plastic & Reconstructive Surgery, John Radcliffe Hospital, Oxford University Hospitals, NHS Trust, Oxford, England, UK

^cUCL Institute of Child Health, University College London (UCL), Great Ormond Street Hospital for Children NHS Foundation Trust, London, England, UK

^dBiomaterials & Advanced Drug Delivery Laboratory (BioADD), Stanford University School of Medicine, Stanford University, Stanford, CA, USA

^eWellman Centre for Photomedicine, Massachusetts General Hospital, Boston, MA, USA

^fDepartment of Dermatology, Harvard Medical School, Boston, MA, USA

^gHarvard-MIT Division of Health Sciences & Technology, Cambridge, MA, USA

^hCentre for Nanotechnology & Regenerative Medicine, UCL Division of Surgery & Interventional, Science, University College London (UCL), London, England, UK

ⁱNanoRegMed Ltd, London, England, UK

^jSchool of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, Northern, Ireland, UK

Summary

The rapid ascent of nanotechnology and regenerative therapeutics as applied to medicine and surgery has seen an exponential rise in the scale of research generated in this field. This is evidenced not only by the sheer volume of papers dedicated to nanotechnology but also in a large number of new journals dedicated to nanotechnology and regenerative therapeutics specifically to medicine and surgery. Aspects of nanotechnology that have already brought benefits to these areas include advanced drug delivery platforms, molecular imaging and materials engineering for surgical implants. Particular areas of interest include nerve regeneration, burns and wound care,

*Corresponding author. UCL Medical School, University College London (UCL), London WC1E 6BT, UK. aaron.tan@ucl.ac.uk (A. Tan).

Ethical approval

N/A.

Funding

None.

Conflict of interest

None.

artificial skin with nanoelectronic sensors and head and neck surgery. This study presents a review of nanotechnology and regenerative therapeutics, with focus on its applications and implications in plastic surgery.

Keywords

Nanotechnology; Plastic surgery; Cyborg tissue; Nanoelectronics; Nanoengineering; Theranostics

Introduction to nanotechnology: getting smaller and smarter

In 1959, the world-renowned physicist and Nobel laureate Richard Feynman delivered a lecture entitled *There's Plenty of Room at the Bottom* at the California Institute of Technology (Caltech), describing various thought-provoking experiments and the infinite possibilities afforded by miniaturization.¹

'Why cannot we write the entire 24 volumes of the Encyclopaedia Britannica on the head of a pin?'

Although the term nanotechnology was not coined until 1974 by Norio Taniguchi,² Feynman's monumental address can be said to be the impetus behind the ideas and concepts of nanoscience and nanotechnology. The prefix *nano*-is of Greek origin, meaning dwarf. However, the size of this industry has grown beyond measure, and nanotechnology has even been hailed as the 'next Industrial Revolution', with significant advances such as the invention of the scanning tunnelling microscope in 1981,³ the discovery of fullerenes in 1985⁴ and graphene in 2004.⁵ Interestingly, the electronics industry was the front runner in shaping the field of nanotechnology, within which there was a constant rat race to innovate smaller, faster and more complex microprocessors and integrated circuits. In the early 1970s, International Business Machines Corporation (IBM) developed electron beam lithography technology, which was later adopted to engineer devices and nanostructures between 40 and 70 nm.⁶

The UK government saw the potential this field offered in a plethora of applications revolutionizing numerous industries, ranging from electronics to medicine. In 2003, the Royal Society and the Royal Academy of Engineering were commissioned to conduct an independent study on nano-technology and nanoscience to appraise its current status, future challenges and its potential impact upon society.⁷ The Royal Society's report defines *nanoscience* as the study and manipulation of matter at the atomic, molecular and macromolecular scales, while *nanotechnology* relates more to the application of this system to a wide range of industries. *Nanomedicine* is a term used to describe the medical application of nanotechnology. One billionth of a metre (i.e. 10^{-9} m) is equivalent to 1 nm. To put this into perspective, the width of a strand of human hair is about 80,000 nm, and the diameter of a single red blood cell is approximately 7000 nm⁸ (Figure 1).

The unique feature of nanotechnology is that the material properties at a nanoscale may differ from that at a macro level, which can be attributed to two reasons: Firstly, nanomaterials have a large surface area-to-volume ratio, causing them to be highly reactive. This consequently affects their mechanical and electrical properties. Secondly, in the

nanoscale, quantum effects dominate the material's behaviour, causing interesting observations in their electromagnetic and optical properties.⁹ Nanomedicine covers a range of applications, including nanomaterials, nanoelectronic biosensors and molecular nanotechnology. Regenerative medicine involves the use of biological systems and material science to repair, replace or regenerate whole tissues and organs. Nanotechnology and regenerative medicine often go hand in hand. For instance, the use of nano-biomaterials, stem cells and nanoscale drug delivery systems is of great importance in the field of regenerative medicine. Indeed, there are several nanotechnology-based therapeutics that are already approved by the US Food and Drug Administration (FDA) for clinical use (Table 1). Research in these aspects warrants the need for a multidisciplinary team comprising scientists, engineers, physicians and surgeons and is an emerging field in plastic surgery.⁸

The future of tissue engineering: nanocomposite polymer platforms for breast implants

The recent health scare in Europe involving Poly Implant Prosthèse (PIP) breast implants¹⁰ that were prone to rupture and leakage has highlighted the impetus for research into new composite materials that are both biocompatible and mechanically robust. One such family of materials that our laboratory is actively researching on is nanocomposite polymers, which can be specifically engineered to be functional organ constructs.

Nanocomposite polymers can be made up of two or more constituent entities that when combined exhibit a synergistic effect, often enhancing overall biomechanical properties. The term nanocomposite is used when one or more of the constituent materials are in the nanoscale sizes. A typical composite material comprises two main elements: a matrix and a filler material (or reinforcement). The latter can come in many forms, including layered (e.g. clay), spherical (e.g. metals) and fibrous (e.g. carbon nanotubes) forms. Apart from the material used and the relative composition, the manufacturing process can greatly affect the final biophysical properties exhibited by the composite material. For instance, the high-performance composite material, carbon fibre, is a common choice for numerous advanced applications, ranging from structural supports in civil engineering to the monocoque of supercars in the automobile industry. This is due to its robust mechanical properties and lightweight characteristics.¹¹ Remarkably, and less well known, composite materials can also be found in the natural world. For instance, the dactyl clubs of the aggressive marine stomatopod, *Odontodactylus scyllarus* (peacock mantis shrimp), are made up of a complex hypermineralized structure capable of fracturing crab exoskeletons including the glass of an aquarium tank.¹²

Nanomaterials that our group has developed, such as polyhedral oligomeric silsesquioxane poly(carbonate-urea) urethane (POSS-PCU), have a myriad of applications in medicine, such as drug delivery, imaging, treatment of disease and, potentially, in the realm of plastic surgery.¹³ For example, nanotopography has been found to significantly affect fibroblasts that are crucial in the long-term biointegration of breast implants.¹⁴ In addition, antimicrobial agents could be integrated into the coating of breast implants to minimize capsular contracture and the risk of infection. Perhaps, in the future, breast implants could also function as a tool for cancer surveillance; through embedding of

microelectromechanical system devices within breast cancer tissue, enabling the detection of neoplasms and alerting oncologists of recurrences.¹⁵

In another example, Chun and Webster showed that nanostructured polytetrafluoroethylene (PTFE) is non-immunogenic in vivo owing to low macrophage adhesion and low protein absorption.¹⁶ Nanomaterials have also been shown to reduce the ability of microorganisms to form biofilms. The capability of reducing an immunogenic response may lead to the development of implants with immunologically inert nanostructured surfaces that can resist infection and lower the body's inflammatory response. Nanotechnology will undoubtedly lead to advancements in the art and science of plastic surgery. The future is exciting, although much research is, however, needed to fine-tune and perfect these materials to tailor them to clinical needs.

Regenerative therapeutics: bio-inspired nanoengineering nerve conduits

One of the most exciting areas of surgical nanotechnology is that of nerve repair, with significant development in this field, and its intrinsic relevance to plastic surgery. Reconnecting nerves can be extremely difficult; primary repair of severed axons has not been successful traditionally due to the practical difficulties of operating on a subcellular level. Recently, axon repair has gained attention with focus on the ones significant enough to regain nervous function. Nanomaterials are able to mimic cellular characteristics and can serve as temporary scaffolds to guide organization and formation of new tissues. As nanotechnology has the potential to organize nerve cells on a nanoscale, it can be used to present an ideal environment to regulate the regeneration of axons in the form of biologically inspired engineering.

The realm of biologically inspired engineering is one that has taken centre stage in recent times. Incorporating elements of the natural world, engineering techniques like these have been intensely studied, particularly in medical science and surgical applications. Drawing inspiration from biology, bio-inspired nanoengineering is exemplified by the field of nerve regeneration using nanomaterials based on self-assembly.¹⁷ The development of artificial nerve conduits for peripheral nerve injury is a prime example of how bio-inspired nanoengineering can influence design and construction.¹⁸ Recent evidence suggests that peptide amphiphiles (PA) can be used as building blocks for the construction of bioartificial nerve conduits.¹⁹ PAs are peptides that possess the ability to self-assemble, and are able to form nanofibres.²⁰ The ability of PAs to self-assemble can be largely attributed to its balance of attractive and repulsive forces within its nano-architectural three-dimensional (3D) configuration²¹ (Figure 2).

The biodegradability, non-immunogenicity and biocompatibility of PAs make them an attractive candidate for nerve conduit engineering. The products of degradation are amino acids and sugars, and are therefore non-toxic and do not elicit an appreciable immunological response.²² Due to the fact that PAs can be considered 'polymers' of amino acids with charged groups, its nano-architecture can be modulated by changes in pH. Experimental evidence has shown that the nanofibre self-assembly architectural framework promotes the proliferation of neural cells, thereby aiding in nerve regeneration.²³ Bioactive epitopes

include integrin, isoleucine–lysine–valine–alanine–valine (IKVAV), Arginylglycylaspartic acid (RGD) and sonic hedgehog homologue within the PA architecture have been shown to increase nerve regeneration (Figure 3). Indeed, the use of bio-inspired nanoengineering could form the basis of manufacturing nerve conduits for use in plastic surgery.

Nanotechnology in burns and wound care: less is more?

Nanotechnology has the potential to revolutionize the treatment of wounds and skin infections through therapeutically active wound dressings. This can be achieved by a technique known as electrospinning, which creates long nanofibres with anaesthetics, antimicrobial compounds and anti-inflammatories embedded within them.²⁴ Heunis and Dicks demonstrated the use of nanofibres to create materials with huge densities of growth factors, bacteriocins and antibiotics embedded within the structure.²⁵

Tian et al. reported that wound healing was hastened by using silver nanoparticles (11 days vs. 26.5 days) in rat models of thermal injury as opposed to using pure silver sulfadiazine.²⁶ Furthermore, it was observed that there was less hypertrophic scarring observed in models treated with silver nanoparticles.

Cybernetic organism (cyborg) tissue for functional auricular reconstruction

The successful integration of the engineered tissue into the host biological system is the holy grail of tissue engineering. Indeed, the next breakthrough in tissue-engineered constructs could well be artificial organs that are not only biologically compatible but also possess the functionalities of the organs they replace. This is often termed cybernetic organism (cyborg) tissue.

Mannoor et al.²⁷ worked on the concept of cyborg tissue illustrated, whereby a bionic ear made of conductive polymer was created using 3D printing technology. In that study, biological cells were interfaced with nanoparticle-based electronic elements using additive manufacturing. The 3D printing technology was used to generate an alginate hydrogel matrix that was seeded with chondrocytes. In addition, electrically conductive silver nanoparticles were infused into the composite to form the inductive coil antenna connected to cochlea-shaped electrodes that was structurally supported by silicone. In vitro cell culture revealed that chondrocytes were able to proliferate on the cyborg ear construct, indicative of its biocompatibility. The cyborg construct was also able to respond to radio frequencies, indicating its capacity for being an electrically functional organ (Figure 4).

Research pertaining to cyborg technology is mainly concerned with the integration of nanoelectronics in biological cells for regenerative therapeutics. In order to manufacture high-performance cyborg tissue, extracellular matrices should be made of synthetic 3D macroporous biomaterials.²⁸ This is because biofunctionalized 3D nano-materials would enable the study of effects concerning spatiotemporal biochemical stimulants during cell and tissue development.²⁹ It allowed for the study of pharmacological response of the cells in 3D as well. This would facilitate a more robust correlation to in vivo relevance compared to 2D cultures.

Stretchable and flexible planar arrays that are adaptable to tissue surfaces^{30–36} and implantable microfabricated probes³⁷ form the core of research efforts aiming to combine live tissue with electronics. These techniques have been used to interrogate electrical activities near the surfaces of organs such as the brain,³⁵ heart³³ and skin.³⁶ Due to the comparatively large size of electronic sensors as opposed to the cells and their extracellular matrix, it is a technical challenge to combine tissues with electronics whilst minimizing tissue disruption. Studies involving nanoscale field effect transistors (nanoFETs) have revealed that electronic devices with nanoscale features are able to measure extra- and intracellular potentials from single cells; however, these findings were largely limited to the surface of the tissues/organs, and high-fidelity integration between electronics and tissues remain an unresolved issue.^{31,32} In a pioneering study, the Lieber group³⁸ proposed several solutions: macroporous electronic structures to allow 3D penetration with the biomaterial, electronic networks should be in the nanometre scale, 3D inter-connectivity should be present in the electronic network and it should have similar mechanical properties to the biomaterial.

Efforts have been made to incorporate nanoelectronics into 3D tissues. This comprises the integration of biological or biomimetic scaffolds into nanoelectronic networks in the nanoscale.³⁹ This initially involves using silicon nanowires, which are registered and electrically connected to form FETs for nanoelectronic sensor elements. Individual nano-FETs are then configured into the desired tissue scaffolds, collectively termed nanoelectronic scaffolds. These nano-electronic scaffolds are designed to be in the nanoscale, possessing high porosity, flexibility and biocompatibility. In addition, biodegradable extracellular matrix (ECM) can be incorporated into the nanoelectronic scaffold to create specific microenvironments in tissue culture. Cells can then be cultured on the nanoelectronic scaffolds to generate 3D nanoelectronic structures.

Multiplexed electrical signals can also be recorded from the extracellular field potentials of the nanoelectronic-innervated tissue, and data can be obtained, for example, about the effect of drugs on the tissue. Thus, it is entirely feasible to monitor electrical signals continuously from 3D cyborg tissues for both diagnostic and therapeutic purposes.³⁹

Integrating nanogenerators and implantable electronics in human organs: touching the future?

A recent groundbreaking report in *Nature Materials* featured ultra-thin films that were capable of mapping the mechanical properties of human skin to a high level of fidelity.⁴⁰ These thin films were made of conformational piezoelectric transducers and could potentially be used to monitor the spatiotemporal release kinetics of drugs applied to the skin; they were also used to see how well the wound was responding to drug treatments. Indeed, in addition, it is postulated that the wound healing process can be tracked in real time, thereby tailoring drug and surgical treatments in a more precise and controlled manner. Wirelessly controlled drug-delivery microchips⁴¹ could also potentially be implanted in a surgical site that could be programmed to deliver specific doses of drugs at preset times, thereby minimizing the effect of non-compliance in patients or missed doses.

Thus, it can be seen that the advancement of semiconductor science is not only relevant to the technology sector but also has spillover effects on the medical industry. The ever-increasing miniaturization of microprocessors in tandem with the augmentation in computing power is testament to the significance of electronics engineering. Indeed, research has focused on electronic devices that are constructed from nanostructures where they can be configured in the nanoscale.⁴² Nanomaterials that are increasingly being used include graphene,⁴³ colloidal nanoparticles⁴⁴ and semiconductor nanowires.⁴⁵ Properties such as composition tunability, morphology and characteristics at different length scales are seen as vital prerequisites for nanomaterials to function as viable platforms. Therefore, semiconductor nanowires have become one of the more successful platforms in this respect.

In recent years, it has been possible to synthesize nanowires *de novo*, with varying degrees of complexities and modulations in defect,⁴⁶ doping,⁴⁷ composition⁴⁸ and topography.^{49,50} Such high degrees of tunability and control enable the synthesis of building blocks with predictable physical properties, thereby functioning as test limits for the measurement of performance.^{51,52} Thus, nanowires have tremendous potential in the field of nanoscience specifically tailored for medical and surgical applications.

The multidisciplinary nature of nanotechnology engenders new breakthroughs that can potentially revolutionize the treatment of diseases.^{53,54} Exploring the multifaceted applications of semiconductor nanowires and its interactions with biological systems at a cellular level could in principle result in important discoveries pertaining to nanogenerators and implantable electronics for plastic surgery. Indeed, the application of such interactions can be used to obtain information from biological systems, while simultaneously delivering small molecules in a controlled manner to minimize side effects.

Basic nanowires have well-defined physical and chemical properties, and have wide array of applications, including integrated circuits and energy-scavenging systems. In terms of functioning as basic platforms for plastic surgery applications, vertical nanowire arrays⁵⁵ and planar nanowire FETs⁵⁶ can be used in cell/tissue imaging,⁵⁷ controlled drug delivery,⁵⁸ extracellular recording and biomolecular sensing. Advanced nanowires exist to solve more complex issues in plastic surgical applications, which include intra-cellular FET probes,⁵⁹ and bioartificial tissues interfaced with nanoelectronic systems.

Nanowires can be made into nanoelectronic components and interfaced with biological tissues to form the basis of implantable electronics (Figure 5). These implantable electronics are conductive in nature, and they can respond to various biological stimuli (Figure 6). Indeed, whole-organ monitoring could be achieved, with an example demonstrated by Timko et al.,³¹ whereby action potential from chicken hearts integrated with nanowires were recorded (Figure 7). The concept of creating a nanogenerator that could produce electricity was reported by Zhu et al.⁶⁰ In that study, a self-powered triboelectric sensor was developed, which relied on contact electrification. This enabled the implantable electronic device to generate voltage signals in response to physical contacts without the need of an external power supply (Figure 8). This breakthrough could have ramifications for plastic surgery applications, as artificial skin could be developed that could sense changes in the environment such as contact pressure.

Multifunctional theranostic nanoparticles for head and neck cancer

Due to the proximity of numerous important and delicate structures, reconstructive surgery for head and neck cancer presents a technical challenge to plastic surgeons. This creates a difficult situation where residual tumour may continue to proliferate. This necessitates the use of other treatment modalities, namely a combination between radiosurgery, radiotherapy and chemotherapy. Nanotechnology is set to revolutionize the diagnosis and management of head and neck cancers via a rapidly advancing field called theranostics.

Theranostics is a burgeoning field in biomedicine, which involves uniting therapeutic and diagnostic modalities onto a single system.⁶¹ This field is driven by the trend towards personalized and precision medicine, in which therapy is tailored to be patient-specific.⁶² The unique properties of nanoparticles can be exploited to achieve site-specific drug delivery and function as a tracking beacon that identifies biomarkers as well.⁶³ Examples of such therapeutic agents include anticancer drugs and small interfering RNA that can be conjugated to gold nanoparticles,⁶⁴ while quantum dots (QDs) are examples of diagnostic agents that can be used for in vivo imaging in head and neck cancer⁶⁵ (Figure 9).

By combining molecular imaging and molecular therapy, this field has a wide range of applications, including disease detection, staging, therapy selection, planning of treatment and monitoring the course of treatment.⁶⁶ For instance, the ultimate personalized medicine theranostic cancer system could first diagnose the cancer subtype, enabling tailored treatment, and also monitor the efficacy of the treatment regime. Furthermore, using nanotechnology offers numerous advantages in diagnostics and treatment. For example, nanosensors have the ability to measure a wide range of biomarkers from a relatively small sample volume,^{67–69} while nanomedicine allows the delivery of drugs at high doses while minimizing the side effects through receptor-mediated active targeting.⁷⁰ Although their potential value to medicine is undeniable, theranostic systems require further research before inception into the clinical context.

Conclusion and future directions

The field of nanotechnology as applied to medicine and surgery is moving at a rapid pace. It is therefore likely that further advances in nano-inspired breakthroughs in plastic surgery would be seen in the foreseeable future. Perhaps the most exciting aspects of nanotechnology, as applied to plastic surgery, would be advances in bio-inspired nanomaterials for nerve regeneration as well as safer and more robust surgical implants. The integration of nanoelectronics to create functional cyborg tissue can be seen as the next revolution in tissue engineering strategies, especially in replacing or reconstructing organs such as ears. Equally inspiring in the field of plastic surgery would be the advent of nano-theranostics, which would enable simultaneous diagnostics and therapeutics to be delivered on a single streamlined platform, which would aid in complex surgical procedures, especially in the surgical reconstruction of head and neck cancers. Therefore, it can be reasonably concluded that nanotechnology would be the next frontier poised for breakthroughs in plastic surgery.

References

1. Feynman RP. There's plenty of room at the bottom. *Eng Sci.* 1960; 23:22–36.
2. Taniguchi N. *Proc. Intl. Conf. Prod. Eng. Tokyo, Part II, Japan Society of Precision Engineering.* : 18–23.
3. Binnig G, Rohrer H. Scanning tunneling microscopy—from birth to adolescence. *Rev Mod Phys.* 1987; 59:615–625.
4. Smalley RE. Discovering the fullerenes. *Rev Mod Phys.* 1997; 69:723–730.
5. Novoselov KS, Geim AK, Morozov SV, et al. Electric field effect in atomically thin carbon films. *science.* 2004; 306:666–669. [PubMed: 15499015]
6. Pease R. Electron beam lithography. *Contemp Phys.* 1981; 22:265–290.
7. Dowling, A.; Clift, R.; Grobert, N., et al. Nanoscience and nano-technologies: opportunities and uncertainties. London: The Royal Society & The Royal Academy of Engineering Report; 2004. p. 61-64.
8. Kim BY, Rutka JT, Chan WC. Nanomedicine. *N Engl J Med.* 2010; 363:2434–2443. [PubMed: 21158659]
9. Roduner E. Size matters: why nanomaterials are different. *Chem Soc Rev.* 2006; 35:583–592. [PubMed: 16791330]
10. Berry M, Stanek JJ. The PIP mammary prosthesis: a product recall study. *J Plast Reconstr Aesth Surg.* 2012; 65:697–704.
11. Meier U. Strengthening of structures using carbon fibre/epoxy composites. *Constr Build Mater.* 1995; 9:341–351.
12. Weaver JC, Milliron GW, Miserez A, et al. The stomatopod dactyl club: a formidable damage-tolerant biological hammer. *Science.* 2012; 336:1275–1280. [PubMed: 22679090]
13. Tan A, Farhatnia Y, Seifalian AM. Polyhedral oligomeric silses-quioxane poly (Carbonate-Urea) urethane (POSS-PCU): applications in nanotechnology and regenerative medicine. *Crit Reviews™ Biomed Eng.* 2013:41.
14. Barr S, Hill E, Bayat A. Current implant surface technology: an examination of their nanostructure and their influence on fibroblast alignment and biocompatibility. *Eplasty.* 2009:9.
15. Nasir AR, Brenner SA. Think small: nanotechnology for plastic surgeons. *Ann Plast Surg.* 2012; 69:580–587. [PubMed: 22395049]
16. Chun YW, Webster TJ. The role of nanomedicine in growing tissues. *Ann Biomed Eng.* 2009; 37:2034–2047. [PubMed: 19499340]
17. Niece KL, Hartgerink JD, Donners JJ, Stupp SI. Self-assembly combining two bioactive peptide-amphiphile molecules into nanofibers by electrostatic attraction. *J Am Chem Soc.* 2003; 125:7146–7147. [PubMed: 12797766]
18. Chalfoun C, Wirth G, Evans G. Tissue engineered nerve constructs: where do we stand? *J Cell Mol Med.* 2006; 10:309–317. [PubMed: 16796801]
19. Cui H, Webber MJ, Stupp SI. Self-assembly of peptide amphi-philes: from molecules to nanostructures to biomaterials. *Peptide Sci.* 2010; 94:1–18.
20. Tysseling-Mattiace VM, Sahni V, Niece KL, et al. Self-assembling nanofibers inhibit glial scar formation and promote axon elongation after spinal cord injury. *J Neurosci.* 2008; 28:3814–3823. [PubMed: 18385339]
21. Hartgerink JD, Beniash E, Stupp SI. Peptide-amphiphile nano-fibers: a versatile scaffold for the preparation of self-assembling materials. *Proc Natl g Sci.* 2002; 99:5133–5138.
22. Angeloni NL, Bond CW, Tang Y, et al. Regeneration of the cavernous nerve by sonic hedgehog using aligned peptide amphiphile nanofibers. *Biomaterials.* 2011; 32:1091–1101. [PubMed: 20971506]
23. Sur S, Pashuck ET, Guler MO, Ito M, Stupp SI, Launey T. A hybrid nanofiber matrix to control the survival and maturation of brain neurons. *Biomaterials.* 2012; 33:545–555. [PubMed: 22018390]
24. Ibrahim AM, Theodore G, Rabie AN, et al. Nanotechnology in plastic surgery. *Plast Reconstr Surg.* 2012; 130:879e–887e.

25. Heunis T, Dicks L. Nanofibers offer alternative ways to the treatment of skin infections. *BioMed Res Int*. 2010;2010.
26. Tian J, Wong KKY, Ho CM, et al. Topical delivery of silver nanoparticles promotes wound healing. *ChemMedChem*. 2007; 2:129–136. [PubMed: 17075952]
27. Mannoor MS, Jiang Z, James T, et al. 3D printed bionic ears. *Nano Lett*. 2013; 13:2634–2639. [PubMed: 23635097]
28. Wylie RG, Ahsan S, Aizawa Y, Maxwell KL, Morshead CM, Shoichet MS. Spatially controlled simultaneous patterning of multiple growth factors in three-dimensional hydrogels. *Nat Mater*. 2011; 10:799–806. [PubMed: 21874004]
29. Kloxin AM, Kasko AM, Salinas CN, Anseth KS. Photodegradable hydrogels for dynamic tuning of physical and chemical properties. *Science*. 2009; 324:59–63. [PubMed: 19342581]
30. Rogers J, Lagally M, Nuzzo R. Synthesis, assembly and applications of semiconductor nanomembranes. *Nature*. 2011; 477:45–53. [PubMed: 21886156]
31. Timko BP, Cohen-Karni T, Yu G, Qing Q, Tian B, Lieber CM. Electrical recording from hearts with flexible nanowire device arrays. *Nano Lett*. 2009; 9:914–918. [PubMed: 19170614]
32. Timko BP, Cohen-Karni T, Qing Q, Tian B, Lieber CM. Design and implementation of functional nanoelectronic interfaces with biomolecules, cells, and tissue using nanowire device arrays. *Nanotechnol IEEE Trans*. 2010; 9:269–280.
33. Kim D-H, Lu N, Ghaffari R, et al. Materials for multifunctional balloon catheters with capabilities in cardiac electrophysio-logical mapping and ablation therapy. *Nat Mater*. 2011; 10:316–323. [PubMed: 21378969]
34. Viventi J, Kim DH, Moss JD, et al. A conformal, bio-interfaced class of silicon electronics for mapping cardiac electrophysiology. *Sci Transl Med*. 2010; 2 24ra22–24ra22.
35. Viventi J, Kim DH, Vigeland L, et al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in vivo. *Nat Neurosci*. 2011; 14:1599–1605. [PubMed: 22081157]
36. Kim D-H, Viventi J, Amsden JJ, et al. Dissolvable films of silk fibroin for ultrathin conformal bio-integrated electronics. *Nat Mater*. 2010; 9:511–517. [PubMed: 20400953]
37. Prohaska OJ, Olcaytug F, Pfundner P, Dragaun H. Thin-film multiple electrode probes: possibilities and limitations. *Bio-med Eng IEEE Trans*. 1986:223–229.
38. Tian B, Lieber CM. Synthetic nanoelectronic probes for biological cells and tissue. *Annu Rev Anal Chem (Palo Alto, Calif.)*. 2013; 6:31. [PubMed: 23451719]
39. Tian B, Liu J, Dvir T, et al. Macroporous nanowire nano-electronic scaffolds for synthetic tissues. *Nat Mater*. 2012; 11:986–994. [PubMed: 22922448]
40. Dagdeviren C, Shi Y, Joe P, et al. Conformal piezoelectric systems for clinical and experimental characterization of soft tissue biomechanics. *Nat Mater*. 2015; 14:728–736. [PubMed: 25985458]
41. Farra R, Sheppard NF Jr, McCabe L, et al. First-in-human testing of a wirelessly controlled drug delivery microchip. *Sci Transl Med*. 2012; 4 122ra121–122ra121.
42. Jeong M, Doris B, Kedzierski J, Rim K, Yang M. Silicon device scaling to the sub-10-nm regime. *Science*. 2004; 306:2057–2060. [PubMed: 15604400]
43. Geim AK. Graphene: status and prospects. *science*. 2009; 324:1530–1534. [PubMed: 19541989]
44. Yin Y, Alivisatos AP. Colloidal nanocrystal synthesis and the organic-inorganic interface. *Nature*. 2005; 437:664–670. [PubMed: 16193041]
45. Lieber CM. Semiconductor nanowires: a platform for nano-science and nanotechnology. *MRS Bull*. 2011; 36:1052–1063. [PubMed: 22707850]
46. Tian B, Zheng X, Kempa TJ, et al. Coaxial silicon nanowires as solar cells and nanoelectronic power sources. *Nature*. 2007; 449:885–889.
47. Yang C, Zhong Z, Lieber CM. Encoding electronic properties by synthesis of axial modulation-doped silicon nanowires. *Science*. 2005; 310:1304–1307. [PubMed: 16311329]
48. Duan X, Huang Y, Cui Y, Wang J, Lieber CM. Indium phosphide nanowires as building blocks for nanoscale electronic and optoelectronic devices. *Nature*. 2001; 409:66–69. [PubMed: 11343112]

49. Tian B, Cohen-Karni T, Qing Quan, Duan X, Xie P, Lieber CM. Three-dimensional, flexible nanoscale field-effect transistors as localized bioprobes. *Science*. 2010; 329:830–834. [PubMed: 20705858]
50. Tian B, Xie P, Kempa TJ, Bell DC, Lieber CM. Single-crystalline kinked semiconductor nanowire superstructures. *Nat Nano-technol*. 2009; 4:824–829.
51. Lu W, Lieber CM. Nanoelectronics from the bottom up. *Nat Mater*. 2007; 6:841–850. [PubMed: 17972939]
52. Li Y, Qian F, Xiang J, Lieber CM. Nanowire electronic and optoelectronic devices. *Mater Today*. 2006; 9:18–27.
53. Mukherji S, van Oudenaarden A. Synthetic biology: understanding biological design from synthetic circuits. *Nat Rev Genet*. 2009; 10:859–871. [PubMed: 19898500]
54. Patolsky F, Timko BP, Zheng G, Lieber CM. Nanowire-based nanoelectronic devices in the life sciences. *MRS Bull*. 2007; 32:142–149.
55. Wang ZL, Song J. Piezoelectric nanogenerators based on zinc oxide nanowire arrays. *Science*. 2006; 312:242–246. [PubMed: 16614215]
56. Whang D, Jin S, Wu Y, Lieber CM. Large-scale hierarchical organization of nanowire arrays for integrated nanosystems. *Nano Lett*. 2003; 3:1255–1259.
57. Xie C, Hanson L, Cui Y, Cui B. Vertical nanopillars for highly localized fluorescence imaging. *Proc Natl Acad Sci*. 2011; 108:3894–3899. [PubMed: 21368157]
58. Shalek AK, Robinson JT, Karp ES, et al. Vertical silicon nano-wires as a universal platform for delivering biomolecules into living cells. *Proc Natl Acad Sci*. 2010; 107:1870–1875. [PubMed: 20080678]
59. Duan X, Gao R, Xie P, et al. Intracellular recordings of action potentials by an extracellular nanoscale field-effect transistor. *Nat Nanotechnol*. 2012; 7:174–179. [PubMed: 22179566]
60. Zhu G, Yang WQ, Zhang T, et al. Self-powered, ultrasensitive, flexible tactile sensors based on contact electrification. *Nano Lett*. 2014; 14:3208–3213. [PubMed: 24839864]
61. Kelkar SS, Reineke TM. Theranostics: combining imaging and therapy. *Bioconjug Chem*. 2011; 22:1879–1903. [PubMed: 21830812]
62. Ma X, Zhao Y, Liang X-J. Theranostic nanoparticles engineered for clinic and pharmaceuticals. *Acc Chem Res*. 2011; 44:1114–1122. [PubMed: 21732606]
63. Liu J, Huang Y, Kumar A, et al. pH-Sensitive nano-systems for drug delivery in cancer therapy. *Biotechnol Adv*. 2014; 32:693–710. [PubMed: 24309541]
64. Huo S, Jin S, Ma X, et al. Ultrasmall gold nanoparticles as carriers for nucleus-based gene therapy due to size-dependent nuclear entry. *ACS Nano*. 2014; 8:5852–5862. [PubMed: 24824865]
65. Kobayashi H, Hama Y, Koyama Y, et al. Simultaneous multicolor imaging of five different lymphatic basins using quantum dots. *Nano Lett*. 2007; 7:1711–1716. [PubMed: 17530812]
66. Hamburg MA, Collins FS. The path to personalized medicine. *N Engl J Med*. 2010; 363:301–304. [PubMed: 20551152]
67. Chikkaveeraiah BV, Bhirde AA, Morgan NY, Eden HS, Chen X. Electrochemical immunosensors for detection of cancer protein biomarkers. *ACS Nano*. 2012; 6:6546–6561. [PubMed: 22835068]
68. Shao H, Min C, Issadore D, et al. Magnetic nanoparticles and microNMR for diagnostic applications. *Theranostics*. 2012; 2:55. [PubMed: 22272219]
69. Swierczewska M, Liu G, Lee S, Chen X. High-sensitivity nano-sensors for biomarker detection. *Chem Soc Rev*. 2012; 41:2641–2655. [PubMed: 22187721]
70. Farokhzad OC, Langer R. Nanomedicine: developing smarter therapeutic and diagnostic modalities. *Adv Drug Deliv Rev*. 2006; 58:1456–1459. [PubMed: 17070960]

Figure 1.

Nanotechnology and plastic surgery. Nanomaterials that have been approved by FDA include liposomes and protein-based nanoparticles for treatment of cancer and gold nanoparticles and superparamagnetic iron oxide for diagnostic purposes. The concept of integrating therapy and diagnostics in a single platform is increasingly being studied upon for plastic surgery applications such as breast cancer. Figure reproduced with permission from Kim et al., 2010. Copyright© 2010 Massachusetts Medical Society.

Figure 2.

Self-assembled peptide amphiphiles. (A) Peptide amphiphiles are made up of four regions: hydrophobic tail, beta-sheet-forming agent, charged groups and a bioactive epitope. (B) The three-dimensional architecture of peptide amphiphiles. (C) Scanning electron microscopy of a network of peptide amphiphiles. (D) Transmission electron microscopy of peptide amphiphiles. (E) A computer-generated graphics rendering of how nerve conduits can be self-assembled using peptide amphiphiles. Panels A, B, C and D reproduced with permission from Cui et al., 2010. Copyright© 2010 John Wiley & Sons, Inc. Panel E reproduced with permission from Tysseling-Mattiace et al., 2008. Copyright© 2008 Elsevier.

Figure 3.

Nerve regeneration using bio-inspired nanoengineering. (A) Simulated fluorescence process images of neural regeneration on nerve conduits manufactured from peptide amphiphiles. Green depicts calbindin, red depicts neurons. (B) The effects of increasing concentration of the IKVAV bioactive epitope on nerve regeneration. (C) Graphics rendering of an ideal nerve conduit supporting nerve regeneration. Panels A and B reproduced with permission from Sur et al., 2012. Copyright© 2012 Elsevier. Panel C reproduced with permission from Chalfoun et al., 2006. Copyright© 2006 John Wiley & Sons, Inc.

Figure 4.

3D printed electrically functional cyborg ear. A cyborg ear can be manufactured using 3D printing that integrates electronics and biological components. The functionality of this is demonstrated by the ability of the cyborg ear to recognize and receive radio and audio frequencies. Figure reproduced with permission from Mannoor et al., 2013. Copyright© 2013 American Chemical Society.

Figure 5. Interfacing nanoelectronics with biological tissues. (a) Bottom-up approach from the nanoscale to the macro-scale. (b) Building blocks for implantable electronic. (c) The interactions between nanoelectronic scaffolds, cells and traditional cellular scaffolds. Figure reproduced with permission from Tian et al., 2013. Copyright© 2013 Annual Reviews.

Figure 6.

Nanoelectronic scaffolds with synthetic tissues. (a) A 3D confocal fluorescence image of reticular nanoelectronic scaffold. (b) Scanning electron microscopy of single-linked nanowire in a reticular scaffold. (c–d) Reconstructed 3D confocal images of neurons after culturing on nanoelectronic scaffolds. (e) Confocal image of synthetic cardiac patch. (f) Epifluorescence of the cardiac patch. (g) Conductance against time of a single-nanowire field effect transistor before and after the administration of epinephrine. (h) Multiplex electrical recording from different types of nanowire field effect transistor. Figure

reproduced with permission from Tian et al., 2012. Copyright© 2013 Nature Publishing Group.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 7.

Action potential recording from whole organ. (a–b) A silicon nanowire field effect transistor interfaced with cardiac tissue. (c) A flexible silicon nanowire field effect transistor chip interfaced with a chicken heart. (d) Recorded conductance from silicon nanowire field effect transistor. Copyright© 2009 American Chemical Society.

Figure 8.

A self-powered triboelectric sensor. (a) Schematics of a triboelectric sensor. (b) Scanning electron microscopy of individual pillars of nanowires created by plasma dry etching. (c) Photograph of a flexible thin-film triboelectric sensor. Figure reproduced with permission from Zhu et al. Copyright© 2014 American Chemical Society.

Figure 9.

Nano-theranostics for plastic surgery. (A) Nanocarriers can be used to deliver therapeutic drugs and even genes into cells with high efficacy. (B) Quantum dots can be used to image lymph nodes in head and neck cancer. (C) Nanoparticles can contain drugs for therapeutic purposes and contrast and imaging agents for diagnostic purposes. (D) Theranostic nanoparticles combine therapeutics and diagnostics into a single platform for multifunctional applications. Panel A reproduced with permission from Huo et al. Copyright© 2014 American Chemical Society. Panel B reproduced with permission from Kobayashi et al. Copyright© 2007 American Chemical Society. Panel C reproduced with permission from Ma et al. Copyright© 2011 American Chemical Society. Panel D reproduced with permission from Liu et al. Copyright© 2014 Elsevier.

Table 1

List of FDA-approved nanomedicine.

Nanomaterial	Trade Name	Application	Target	Adverse Effects	Manufacturer	Current Status
Iron oxide	Feridex	MRI contrast	Liver	Back pain, vasodilation	Bayer Schering	FDA approved
Iron oxide	Resovist	MRI contrast	Liver	None reported	Bayer Schering	FDA approved
Gold	Verigene	In vitro Diagnostics	Genetic	N/A	Nanosphere	FDA approved
Protein	Abraxane	Cancer therapy	Breast	Cytopenia	Celgene	FDA approved
Liposome	Doxil	Cancer therapy	Various	Hand-foot syndrome, stomatitis	Janssen Products	FDA\approved