The Smartest Materials: The Future of Nanoelectronics in Medicine

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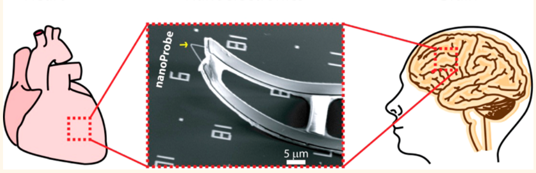
ABSTRACT



Electronics have become central to many aspects of biomedicine, ranging from fundamental biophysical studies of excitable tissues to medical monitoring and electronic implants to restore limb movement. The development of new materials and approaches is needed to enable enhanced tissue integration, interrogation, and stimulation and other functionalities. Nanoscale materials offer many avenues for progress in this respect. New classes of molecular-scale bioelectronic interfaces can be constructed using either one-dimensional nanostructures, such as nanowires and nanotubes, or two-dimensional nanostructures, such as graphene. Nanodevices can create ultrasensitive sensors and can be designed with spatial resolution as fine as the subcellular regime. Structures on the nanoscale can enable the development of engineered tissues within which sensing elements are integrated as closely as the nervous system within native tissues. In addition, the close integration of nanomaterials with cells and tissues will also allow the development of *in vitro* platforms for basic research or diagnostics. Such lab-on-a-chip systems could, for example, enable testing of the effects of candidate therapeutic molecules on intercellular, single-cell, and even intracellular physiology. Finally, advances in nanoelectronics can lead to extremely sophisticated smart materials with multifunctional capabilities, enabling the spectrum of biomedical possibilities from diagnostic studies to the creation of cyborgs.

Over the past several decades, electronics have become central to many aspects of biomedicine, ranging from fundamental biophysical studies of function in excitable tissues, such as the heart and brain, to medical monitoring and interventions. Implantable pacemakers and defibrillator devices have allowed the detection and treatment of cardiac arrhythmias,[1] and "grids-and-strips" devices have been used to map cerebral cortical activity in epilepsy.[2] Deep brain stimulation (DBS) has been delivered by implanted electrodes for the treatment of the disabling motor symptoms of Parkinson's disease, essential tremor, and dystonia.[3] Recently, there has been a growing interest in the development of electrical interfaces with tissues, and in electronic implants to restore limb movement directly or *via* a brain-to-machine interface to control a robotic arm.[4,5] An artificial retina has been developed that combines state-of-the-art microfabrication techniques to create photovoltaic elements that will supply the energy needed for stimulation of subretinal neurons in order to transfer an image to the visual cortex.[6] Such a fully integrated wireless implant is a step toward the restoration of vision to patients blinded by degenerative retinal diseases.

Nanomaterials and Nanoelectronics. The preceding examples show the enormous potential of implanted electronics in the human body. As in many other fields of science, the furtherance of such technological advances will necessitate the development of new materials and approaches, to enable enhanced tissue integration, interrogation, and stimulation of tissues and other functionalities. Nanoscience offers many avenues for progress in this respect. Recent years have seen the development of a wide range of nanoscale materials (Figure 1), including zero-dimensional nanoparticles,[7] one-dimensional wires and tubes,[8] two-dimensional layered materials,[9] and three-dimensional assemblies of the lower-order building blocks.[10] The wide range of purposes for such devices includes delivery of molecules of interest,[11] tissue engineering,[12,13] and nanogenerators for self-sustained biosystems.[14] One-dimensional nanostructures such as nanowires and nanotubes[15,16] serve as promising nanoelectronic building blocks for a variety of applications including sensing,[17,18] photonics,[19] energy conversion,[14,20] and electrical devices capable of forming complex logical functions.[21] A variety of materials can

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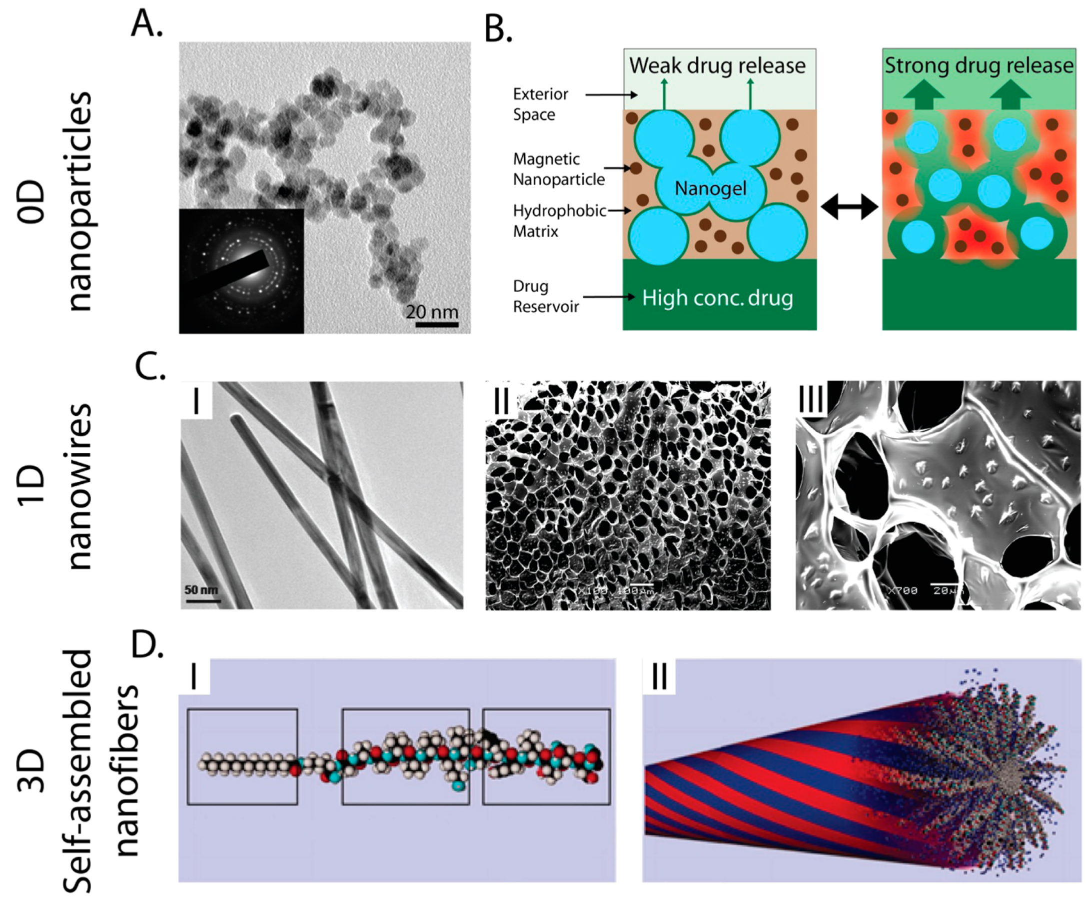

Figure 1. Nanomaterials in biomedicine. (A) Zero-dimensional (0D) nanoparticles for triggered release of drugs. Transmission electron micrograph (TEM) of superparamagnetic iron oxide nanoparticles. Inset: Diffraction pattern suggests an ensemble of randomly oriented crystalline particles. (B) Proposed schematic of a cross section of a nanocomposite membrane, showing nanogel particles (blue), iron oxide nanoparticles (dark brown), and an ethylcellulose matrix (light brown). Upon application of an oscillating magnetic field, the ferromagnetic iron oxide nanoparticles release heat (orange) and reversibly shrink the nanogels, enabling release of a drug (green) from a reservoir contained by the membrane. Adapted from ref 11. Copyright 2011 American Chemical Society. (C) One-dimensional (1D) nanowires in tissue engineering. (I) TEM of a typical distribution of gold nanowires, with an average length of ∼1 μm and average diameter of 30 nm. (II,III) SEM revealed that the nanowires (1 mg mL^{-1}) assembled within the pore walls of the scaffold into star-shaped structures with a total length scale of 5 μm. The assembled wires were distributed homogeneously within the matrix (II) at a distance of ∼5 μm from one another (III). Adapted with permission from ref 12. Copyright 2011 Nature Publishing Group. (D) Three-dimensional (3D) self-assembled nanostructures. (I) Peptide amphiphile monomer composed of three segmental domains: a sequence bearing a biological signal, a domain containing amino acids with a strong tendency to form β-sheets, and a hydrophobic alkyl tail. (II) Simulated structure that will form is a cylindrical aggregate in which twisted β-sheets (red) collapse through hydrophobic interactions among alkyl chains, thus displaying high densities of the biological signal. The blue regions represent water domains present in the interior of the supramolecular structure. Adapted with permission from ref 13. Copyright 2012 American Association for the Advancement of Science.

be used to achieve the aforementioned applications, including those from periodic table groups IV (Si–Ge), III–V (InAs–InP), II–VI (ZnO),[14–16] and carbon-based materials such as carbon nanotubes,[22] graphene,[9] and either conductive or coordination polymers.[23] Electrical signal recording with nanostructures, such as Si nanowires, has several advantages compared to conventional detection techniques with planar field-effect transistors (FETs) and multielectrode arrays (MEAs). Nanodevices, because of their high surface-to-volume ratios, exhibit high sensitivities with signal-to-noise ratios that outperform planar structures.[17,18] Therefore, they can be used as ultrasensitive sensors for various analytes including single virus particle detection,[24] protein sensing in the femtomolar range,[17,18] and DNA sequencing using nanowire-based sensors.[25] Nanostructures can also enhance cellular adhesion and activity,[26–28] perhaps because their dimensions are closer to those of the subcellular building blocks of biological entities, such as proteins within the cell membrane. For similar reasons, they can monitor biological events with subcellular resolution.

The spatial resolution of extant cell–electrical interfaces, as well the degree to which they are integrated with the surrounding tissue, is limited by their size scale, which is usually in the range of hundreds of micrometers to millimeters. They are typically a few cells in length, which hinders the spatial resolution of stimulation or monitoring of electrical activity that can be achieved. To address the need for even smaller devices—and spatial resolution as fine as the subcellular regime—a new class of molecular-scale bioelectronic interfaces can be constructed using either one-dimensional nanostructures, such as nanowires and nanotubes, or two-dimensional nanostructures, such as graphene. Nanowire-based devices have been used to record extracellular signals from cultured neurons,[29] cardiomyocytes,[30,33] brain slices,[31] and whole embryonic chicken hearts.[32,33] Recent developments in the synthesis of nanowires have enabled a free-standing nanowire-based three-dimensional nanoprobe (Figure 2A I),[34] which allows the recording of the intracellular electrical activity of cardiomyocytes (Figure 2A II). Various device geometries and synthetic approaches have been developed to internalize electrical devices within cells, using different device geometries and synthetic approaches, such as silicon-nanotube-based devices.[35−37] Such nanostructures can be assembled on flexible plastic substrates, as presented in Figure 2B I, II,[31,38−40] allowing them to conform to the shape of organs and tissues and enabling electrical monitoring and mapping of whole organs.[38−40]

The development of nanomaterials—including nanoelectronics—closely associated with tissues will have to address numerous issues other than the development of intricate circuitry. Biocompatibility (local and systemic toxicity) may be particularly important because many of the materials used in the fabrication of nanoelectronics (for conduction, insulation, and support) are neither closely related to commonly used biomaterials nor known to be biodegradable. There is a relative paucity of knowledge (and even fewer firm conclusions) about the biological side effects of many such materials, even with relatively commonly used ones, such as gold. Tissues or devices engineered to contain nanodevices would either be left with a permanent residue (with or without enduring functionality) or that residue would have to be designed so that it can degrade. As with all medical devices, it will be important to demonstrate that fouling does not readily impede function within the intended lifespan of the device. Mechanical properties of biomedical nanoelectronics will have to be commensurate with those of the target tissues. Biointegration—the interconnection between these nanodevices and the recipient tissue—will be important, as well. If inadequate, it can be enhanced by surface modification with biomolecules that enhance biointegration.[41]

The close integration of nanomaterials with cells and tissues will also allow the development of *in vitro* platforms for basic research or diagnostics.[42] Such lab-on-a-chip systems could, for example, enable testing of the effects of candidate therapeutic molecules on intercellular, single-cell, and even intracellular electrical activity. Furthermore, by the assembly and fabrication of multiple devices per chip, it is possible to investigate the effects of multiple analytes on cellular processes at a spatiotemporal resolution not easily achievable by other means.

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The small scale of nanomaterials could enable the development of engineered tissues within which nanostructured sensing elements are integrated as closely as the nervous system is within native tissue. Electronic nanostructures also have the potential to provide electrical stimulation to the tissues within which they are incorporated. That stimulation need not be purely electrical; an electrical impulse can initiate a secondary event, just as it does in the efferent limb of the nervous system. Thus, for example, electrical stimulation could trigger the release of bioactive molecules stored in nanoliter (or larger) quantities.[43] Sensing and stimulation could be linked, creating closed-loop feedback systems that would be analogous to reflex arcs in the autonomic nervous system. Interestingly, even if not integrated within circuitry, conductive nanomaterials can enhance the electrical performance of excitable tissues, for example, by enhancing wave propagation between isolated cell clusters within engineered scaffolds.[12] Nanodevices could further affect tissue development simply by virtue of their morphologies; nanotopography has been shown to have a profound impact on a wide range of cellular activities, including cell differentiation, proliferation, and gene expression.[27] Moreover, nanoelectronics, whether implanted as free-standing devices or integrated within an engineered tissue, could be assembled in a way that will introduce new functionalities to an engineered tissue or implantable devices. The nanostructures could not only incorporate sensing and stimulating capabilities but also potentially introduce computational capabilities and energy-generating elements (either photovoltaic or piezoelectric elements[14,20]); in this way, one could fabricate a truly independent system that senses and analyzes signals, initiates interventions, and is self-sustained. Future developments in this direction could, for example, lead to a synthetic nanoelectronic autonomic nervous system.

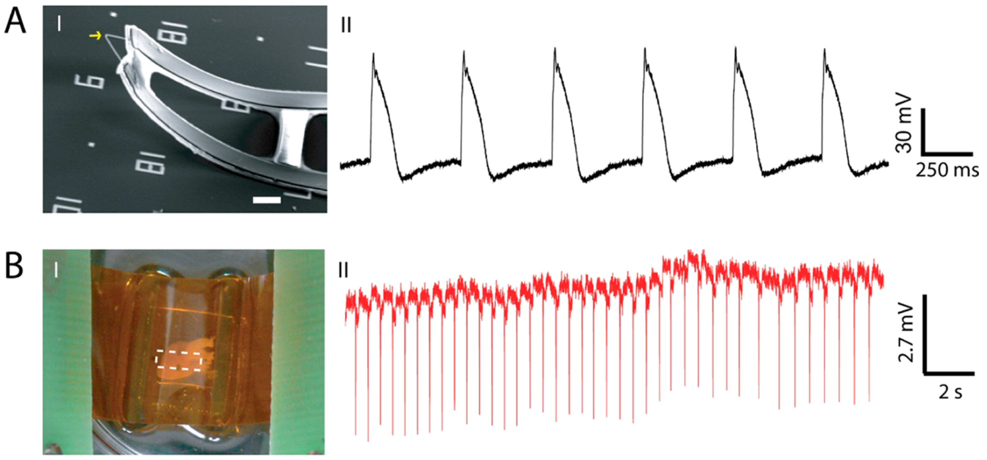

Figure 2. Bio–nano electrical interfaces from a single cell to a whole organ. (A) Single cell interfaced with a flexible free-standing three-dimensional (3D) silicon nanowire (SiNW) device. (I) SEM image of a 3D nanoprobe. The scale bar is 5 μm. (II) Recorded intracellular action potentials using a flexible 3D nanoprobe. Adapted with permission from ref 34. Copyright 2010 American Association for the Advancement of Science. (B) Assembled SiNW devices on a flexible substrate. (I) Top-down photograph of a flexible NW system, which enabled overall registration between heart and lithographically defined markers on the substrate. In this case, a 50 μm flexible substrate with assembled nanowire devices was interfaced with a spontaneously beating embryonic heart and monitored its electrical activity. The dashed white rectangle at the center of the chip highlights the location of a nanodevice array. (II) Recorded conductance data from a nanodevice in the configuration shown in panel A. Adapted from ref 32. Copyright 2009 American Chemical Society.

Nanoelectronics is a relatively young field with great potential in the biomedical sciences. As with many other areas of scientific endeavor in recent decades, continued progress will require the convergence of multiple disciplines, including chemistry, biology, electrical engineering, computer science, optics, material science, drug delivery, and numerous medical disciplines. Advances in this research could lead to extremely sophisticated smart materials with multifunctional capabilities that are built in—literally hard-wired. The impact of this research could cover the spectrum of biomedical possibilities from diagnostic studies to the creation of cyborgs.

Conflict of Interest: The authors declare no competing financial interest.

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