Nanotechnologies in Surgery: The New Paradigm

4

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Introduction

> …it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and "looks" around. …It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately-functioning organs.
>
> Feynman RP (attributed to AR Hibbs) [1]

> What I want to talk about is the problem of manipulating and controlling things on a small scale. … It is a staggeringly small world that is below. In the year 2000, when they look back at this age, they will wonder why it was not until the year 1960 that anybody began seriously to move in this direction.
>
> Feynman RP [1]

The twentieth century saw the surgeon become a master at precision excision and minimally invasive tissue manipulation and repair. About the time of Feynman's famous lecture at CalTech quoted above, 1960, the operating microscope began to revolutionize operations for neurosurgeons, otolaryngologists, ophthalmologists, and other surgeons. Over the following decades, techniques such as endoscopy and laparoscopy made minimally invasive surgery a reality—the length of both incisions and postoperative hospital stays decreased dramatically. Sophisticated microendovascular techniques have come close to realizing Feynman's "mechanical surgeon inside the blood vessel" not only for cardiac disease but also for more peripheral arterial disease and various vascular malformations such as cerebral aneurysms.

Feynman's mechanical endovascular surgeon was not a true "nanosurgeon" but rather a miniaturized twentieth century endovascular surgeon separated from the catheter controlled by the "full-size" human surgeon. The twenty-first century "nanosurgeon" was envisaged four decades later in 1999 by Richard Smalley, the Nobel Prize-winning chemist who discovered the C^{60} buckyball:

> Twenty years ago, without even this crude chemotherapy, I would already be dead. But 20 years from now, nanoscale missiles will target cancer cells in the human body and leave everything else blissfully alone. I may not live to see it. But I am confident it will happen.
>
> Smalley R [2]

Although Smalley died 6 years later, in 2005, of non-Hodgkin's lymphoma, his prediction regarding "nanoscale missiles" for targeting cancer cells is very much "on target." Numerous other nanotechniques for surgery are being developed, many of them much more subtle than nanoscale missiles or endovascular micro- or nano-robotic surgeons.

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It would be remiss to look toward the future of nanotechniques in surgery without acknowledging the past. The Damascus blade of medieval Muslim blacksmiths was never replicated by Western blacksmiths—much to the chagrin (and likely loss of life) of the Crusaders. The extraordinary mechanical properties and sharpness of the Damascus blade have recently been attributed to carbon nanotube "impurities" in the blade [3]. It appears that ores from India used in the forging process were responsible for the formation of carbon nanotubes—resulting in the unique characteristics of the Damascus blade. The loss of supply of these ores during the eighteenth century led to the demise of this chemical skill amongst the blacksmiths of Damascus, relieving the world of an instrument capable of atrocities with surgical precision.

A single chapter can only provide an overview of nanotechniques being developed for surgery. Recent books on nanosurgery and related topics have appeared [4, 5]. The US National Nanotechnology Initiative web site is an extensive resource (www.nano.gov).

The Nanorealm and Nanomaterials

One nanometer is 10^{-9} m (Fig. 4.1) [6], *nanos* being Greek for dwarf. The nanorealm is typically considered to be particles, devices, or techniques less than 100 nm in size, although practically speaking less than 1 μm (1,000 nm) is more appropriate. One micron is roughly 1/10 the diameter of a red blood cell, or 1/100 the diameter of a human hair.

Equally important to small size for nanotechnology is the concept of constructing or manipulating materials atom-by-atom or molecule-by-molecule. This concept was expressed—and the term "nanotechnology" coined—by Norio Taniguchi in 1974. Two quite different techniques for nanofabrication include (1) "top-down" methods such as nanolithography (Greek "small writing on rocks") and (2) "bottom-up" methods such as self-assembly (of atoms, molecules, proteins, etc) and chemical vapor deposition (e.g., to produce carbon nanotubes—Fig. 4.2a, b) [7].

Three types of nanomaterials important for nanomedicine and nanosurgery include nanoparticles (NPs), nanoscaffolds (NSs), and nanotubes/nanofibers. Several types of nanoparticles and nanotechniques for tumor targeting are depicted in Fig. 4.3a–j [8]. Another important nanoparticle is the quantum dot (QD) [9, 10]. QDs (Fig. 4.4a–c) have the unusual property that they fluoresce with a different color depending on their size. QDs are therefore extremely useful for multiple tagging—drugs, tumor cells, receptors, etc.—to follow the various tagged moieties over time and space [11].

NSs are typically self-assembling arrays such as the peptide NS illustrated in Fig. 4.5a–c [12]. Peptides composed of charged amino acids self-assemble into scaffolds in the presence of physiological salt solutions and body fluids

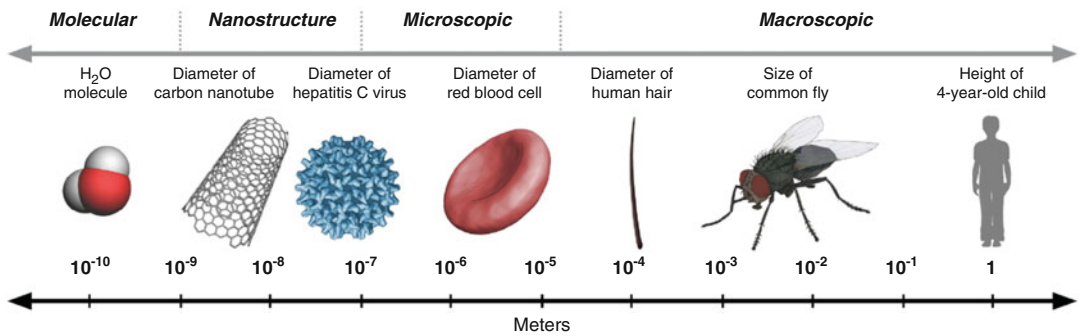

Fig. 4.1 Comparison of size of objects from 10^{-10} to 1 m. (Used with permission from Kateb B, Chiu K, Black KL, et al. Nanoplatforms for constructing new approaches to cancer treatment, imaging, and drug delivery: what should be the policy? Neuroimage 2011;54:S106–S124)

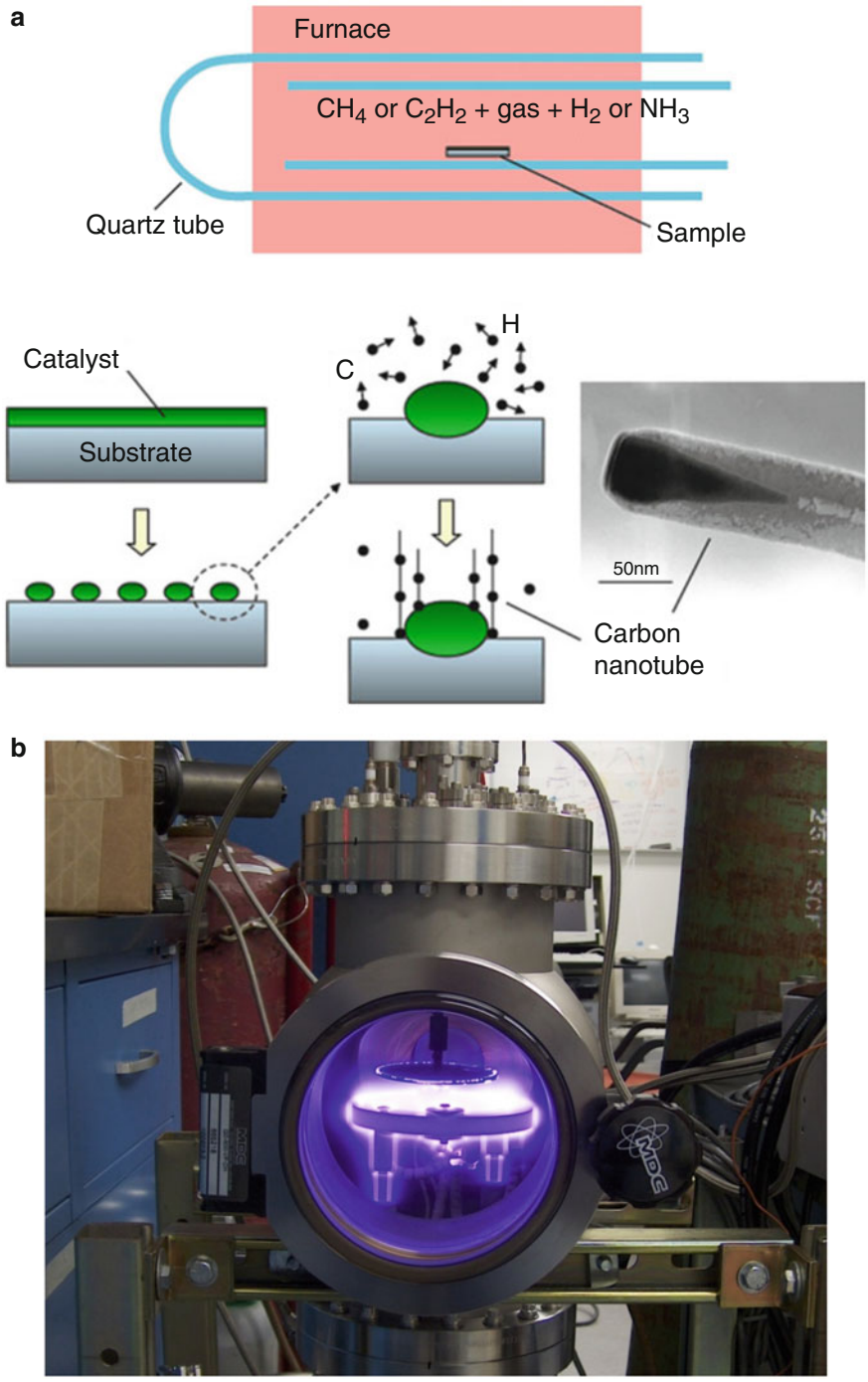

Fig. 4.2 (**a**, **b**) (**a**) Schematics of a chemical vapor deposition reactor (*top*) and the basic sequence of carbon nanotube growth (*bottom*). (**a**: Used with permission from Daraio C, Jin S. Synthesis and patterning methods for nanostructures useful for biological applications. In: Silva GA, Parpura V, editors. Nanotechnology for Biology and Medicine. New York: Springer Science + Business Media; 2012). (**b**) Photograph of a custom built plasma enhanced chemical vapor deposition reactor. (**b**: Courtesy of NASA Ames Center for Nanotechnology)

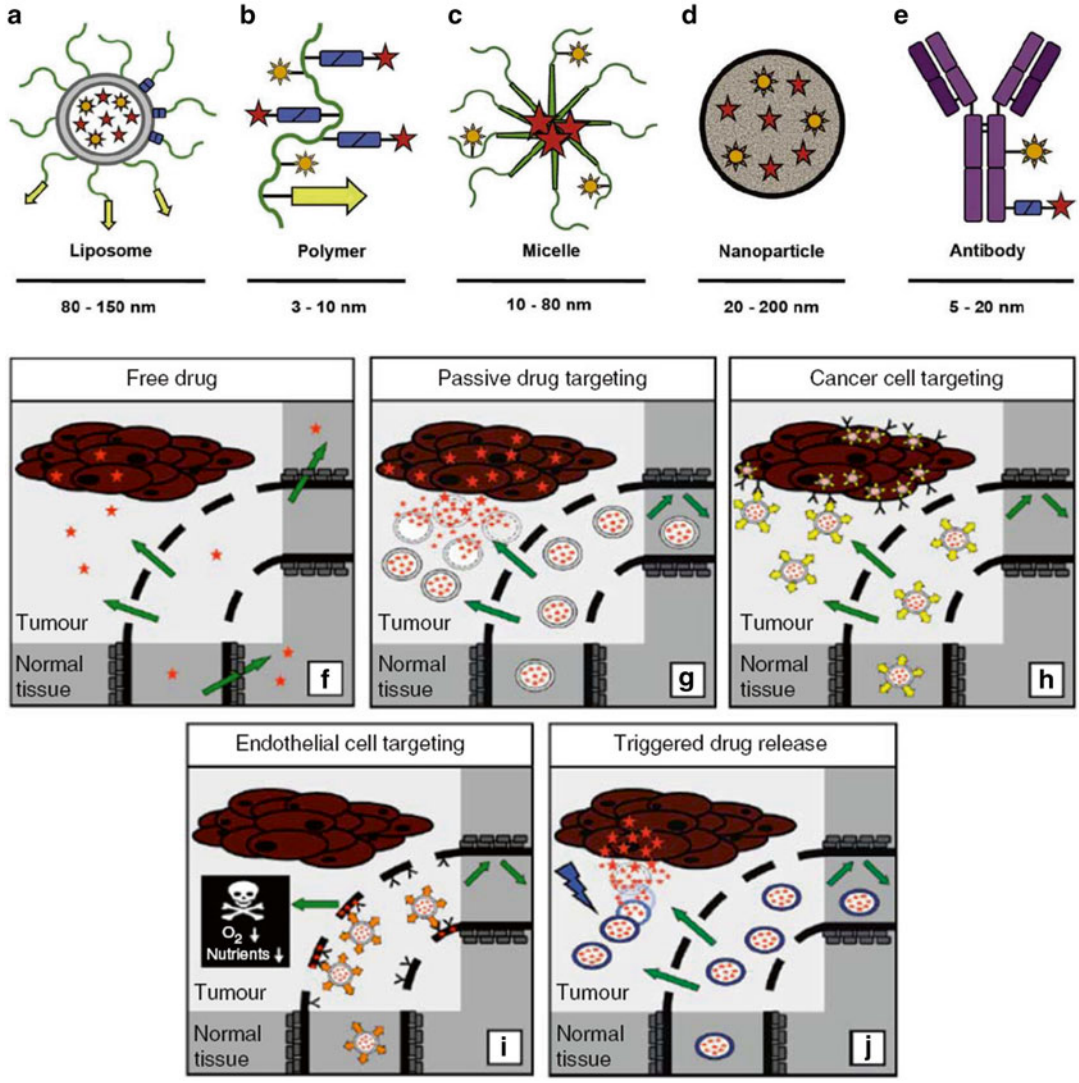

Fig. 4.3 (**a**–**j**) (**a**–**e**) Examples of nanomaterials, nanotechniques, and nanoparticles: liposomes and liposomal bilayers—*gray*; polymers and polymer coatings—*green*; linkers for drug release and "stealth" coatings—*blue*; targeting ligands—*yellow*; imaging agents—*orange*; conjugated or entrapped (chemo-) therapeutic agents—*red*. (**f**–**j**) Drug targeting strategies for tumors. Passive drug targeting with NPs (**g**) offers some benefit over free drug administration (**f**) (intravenous) but even more advantageous is active drug targeting of tumor cell surface receptors (**h**), local endothelial cell receptors (**i**), and triggered drug release (**j**) (by stimuli such as hyperthermia, pH change, or ultrasound). (**a**–**j**: Used with permission from Rizzo LY, Theek B, Storm G, Kiessling F, Lammers T. Recent progress in nanomedicine: therapeutic, diagnostic and theranostic applications. Curr Opin Biotechnol 2013;24(6):1–13; Lammers T, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. J Control Release. 2012 Jul 20;161(2):175–87; Lammers T, Aime S, Hennink WE, Storm G, Kiessling F. Theranostic nanomedicine. Acc Chem Res. 2011 Oct 18;44(10):1029–38)

(e.g., blood, cerebrospinal fluid). The impressive properties of NSs for both hemostasis and tissue repair are discussed below.

Carbon nanotubes (CNTs) and the closely related carbon nanofibers (CNFs)—see Figs. 4.2a, b and 4.6—have properties that allow novel interactions with tissues, from acting as carriers for antitumor drugs (Smalley's "nanoscale missiles") to tissue monitors and modulators with sensitivity orders of magnitude higher than non-nano techniques.

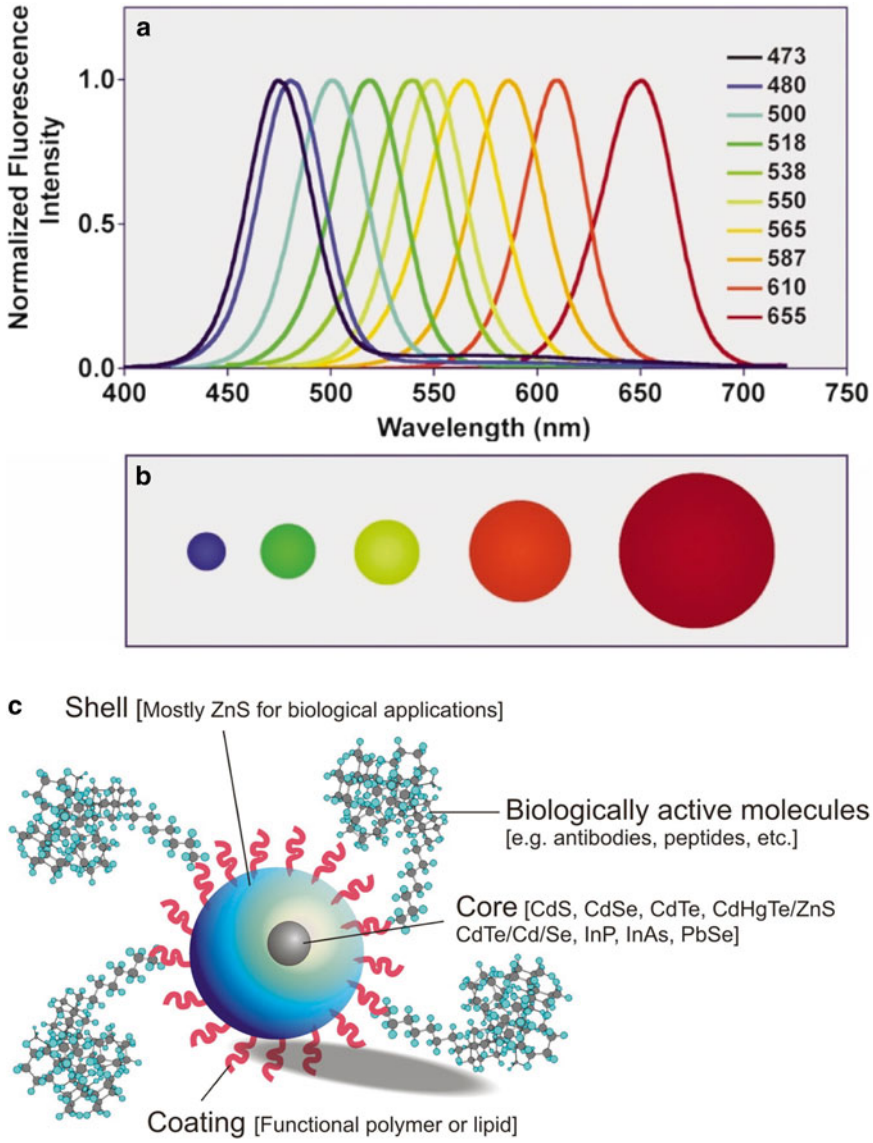

Fig. 4.4 (**a**–**c**) (**a**, **b**) Graph (**a**—*top*) showing that the wavelength of the light emitted by QDs varies with the diameter of the QD (**b**—*bottom*). (**a**, **b**: Used with permission from Smith AM, Nie S. Chemical analysis and cellular imaging with quantum dots. Analyst 2004;129:672–677.) (**c**) Structure of a semiconductor QD. The heavy metal core is responsible for the fluorescence properties of the QD. The shell stabilizes the core, while the coating provides anchor sites for organic and biological ligands such as antibodies, and peptides. (**c**: Used with permission from Pathak S, Cao E, Davidson MC, Jin S, Silva GA. Quantum dot applications to neuroscience: new tools for probing neurons and glia. J Neurosci 2006;26(7)1893–1895)

Figure 4.7 details some of the advantages of nanoelectrode arrays as biosensors based on size alone; other advantages—particularly important for recording and stimulating nervous system tissues (e.g., neuromodulation and deep brain stimulation)—include greatly reduced impedance and greatly increased capacitance with nanoarrays in comparison with traditional electrodes.

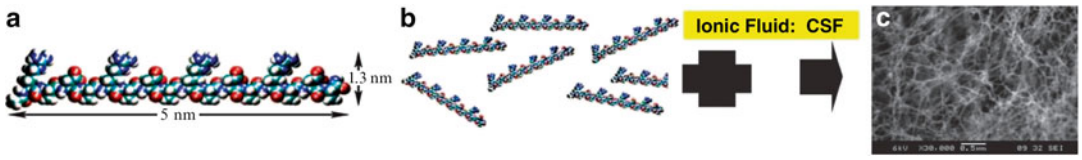

Fig. 4.5 (**a**–**c**) Self-assembling peptide nanofiber scaffold (SAPNS). (**a**) Model of the arginine-alanine-aspartate-alanine (RADA) 16-I molecular building block. (**b**) Model of numerous RADA 16-I molecules which undergo self-assembly to form well-ordered nanofibers with the hydrophobic alanine sandwich inside and the hydrophilic residues outside. (**c**) SEM of SAPNS (scale bar: 500 nm). (**a**–**c**: Used with permission from Ellis-Behnke RG, Liang YX, You SW, et al. Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision. PNAS 2006;103(13):5054–5059)

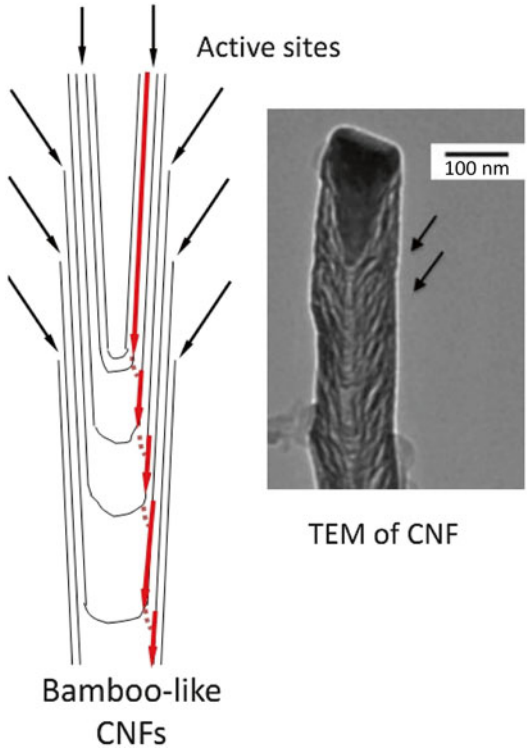

Fig. 4.6 Schematic of a carbon nanofiber showing the bamboo-like (or stacked dixie cup-like) structure of the multiple active sites (*left*) and TEM of a CNF (*right*). The multiple active sites result in very high electron transfer and very high capacitance. (Courtesy of NASA Ames Center for Nanotechnology)

Nanotechniques for Imaging, Targeting, and Healing

Superparamagnetic iron oxide NPs are being developed as improved MRI contrast agents for assessing the cerebral vasculature and malignant brain tumors [13]. Figure 4.8a presents MRI scans (7 T) of the human brain: (1) without contrast, (2) with gadoteridol (0.1 mmol/kg), and (3) with ferumoxytol (510 mg), a superparamagnetic iron oxide NP. Because ferumoxytol particles are much larger than gadoteridol particles (30 nm vs. 1 nm), they tend to leak out of the blood vessels into tumors more slowly (Fig. 4.8b). Gadoteridol enhancement peaks less than 30 min following injection; ferumoxytol enhancement peaks at about 24 h. This offers significant advantages: one can obtain an MRI of the brain immediately after ferumoxytol contrast injection and visualize the cerebral vasculature feeding the tumor, and repeated scans can be obtained over hours following contrast injection without repeating the contrast, especially important for intraoperative MRI scanning where several scans may be required during surgery.

Imaging of tumors with either gadoteridol or ferumoxytol relies on passive targeting, i.e., the tumor imaging or targeting depends on the tumor blood vessels being "leakier" than normal blood vessels. The leaky vessels adjacent to the tumor result in slow clearance of the contrast agent or QD-PEG (polyethylene glycol) NPs, causing an accumulation of NPs in the extracellular environment of the tumor. More effective imaging/targeting of tumors occurs with active techniques [8, 9, 14], Active targeting utilizes an antibody against the tumor cells conjugated to the QDs, by which the NPs accumulate on the tumor cell membrane and are incorporated within the tumor cells.

More sophisticated, multimodality NP techniques for tumor imaging and treatment are being developed, as illustrated in Figs. 4.3a–j and 4.9.

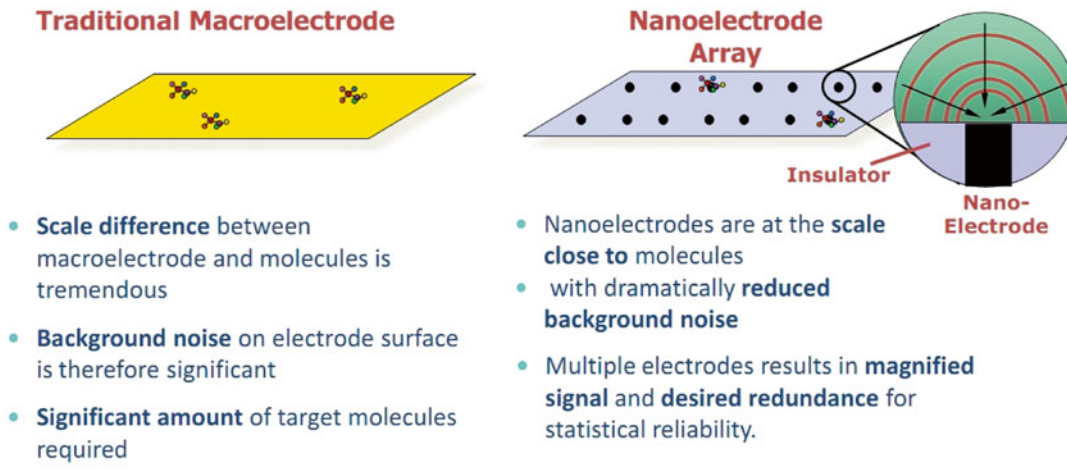

Fig. 4.7 Nanoscale electrodes offer dramatic improvement over traditional macro- or microelectrodes for detecting and quantifying small analytes in low concentrations. (Courtesy of NASA Ames Center for Nanotechnology)

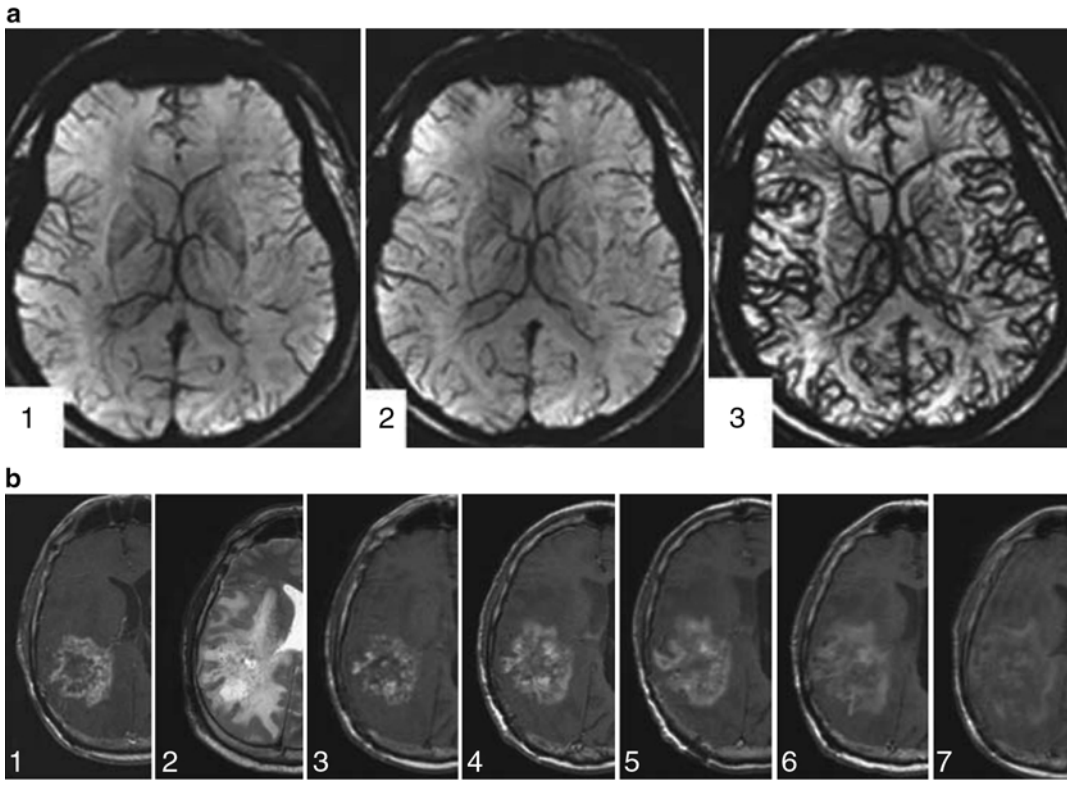

Fig. 4.8 (**a**, **b**) (**a**) Cerebral vasculature with 7T MRI. (1) Without contrast agent. (2) With gadoteridol 0.1 mmol/kg i.v. (3) With ferumoxytol 510 mg i.v. (**b**) Time course of ferumoxytol enhancement (1.5T MRI) in a patient with recurrent glioblastoma multiforme. (1) T1—gadoteridol. (2) T2. 3–7: T1—at the following five time points (hours post-injection of ferumoxytol): (3) 4–6 h; (4) 6–20 h; (5) 24–28 h; (6) 48–52 h; (7) ~72 h. Peak enhancement with ferumoxytol is at 24–28 h, much later than the ~30 min peak enhancement with gadoteridol. (**a**, **b**: Used with permission from Weinstein JS, Varallyay CG, Dosa E, et al. Superparamagnetic iron oxide nanoparticles: diagnostic magnetic resonance imaging and potential therapeutic applications in neurooncology and central nervous system inflammatory pathologies, a review. J Cereb Blood Flow Metab 2010;30:15–35)

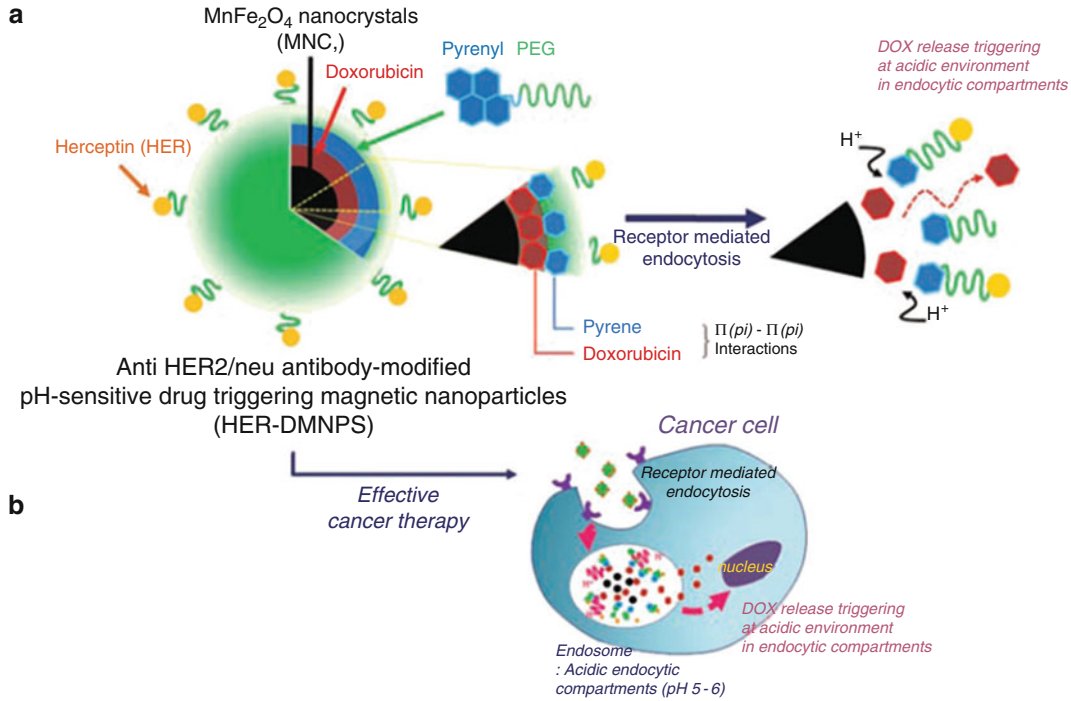

Fig. 4.9 Schematic illustration of anti-HER2/neu antibody-modified pH-sensitive drug-releasing magnetic NPs (HER-DMNPs) for cancer therapy followed by MRI. *DOX* doxorubicin, *HER* herceptin, *PEG* polyethylene glycol. (Used with permission from Wang LS, Chuang MC, Ho JA. Nanotheranostics—a review of recent publications. Int J Nanomed 2012;7:4679–4695)

In Fig. 4.9, a nanocrystal coated with polyethylene glycol (PEG) uses an antibody to target, pH sensitivity to release the chemotherapeutic agent, and magnetic properties for MRI detection [14]. Another technique by which NPs can improve cancer treatment is by thermotherapy (e.g., heating tumors using an MRI scanner once the tumor has been targeted with magnetic NPs) [15]. NPs can also enhance the efficacy of standard external beam radiation therapy for tumors. The radiation interacts with hafnium oxide NPs to generate a much larger number of electrons than radiation therapy alone, resulting in greatly increased treatment effect [16].

NPs are also being developed to reduce inflammation and improve healing in conditions ranging from arthritis to infection to endovascular stenting. The use of NPs incorporated into drug-eluting stents (to promote endothelial healing and minimize restenosis) for interventional cardiology has been reviewed [17]. NPs containing aspirin-triggered Resolvin D1 (a hexaenoic acid) have recently been shown to decrease inflammation in several conditions [18]. Examples of this nano-pro-resolving medicine (AT-RvD1 NPRM) are given in Fig. 4.10a, b, where a mouse model of (1) peritonitis (produced by intraperitoneal injection of zymosan) and (2) temporomandibular joint (TMJ) inflammation (produced by local injection of T Freund's adjuvant) were treated pre-insult by intravenous injection of AT-RvD1 NPRM. Figure 4.10a graphs the decrease in acute inflammation with the peritonitis model when AT-RvD1 NPRM was administered; Fig. 4.10b graphs the decrease in myeloperoxidase activity (MPO) by ELISA 12 h following injection of the TMJ.

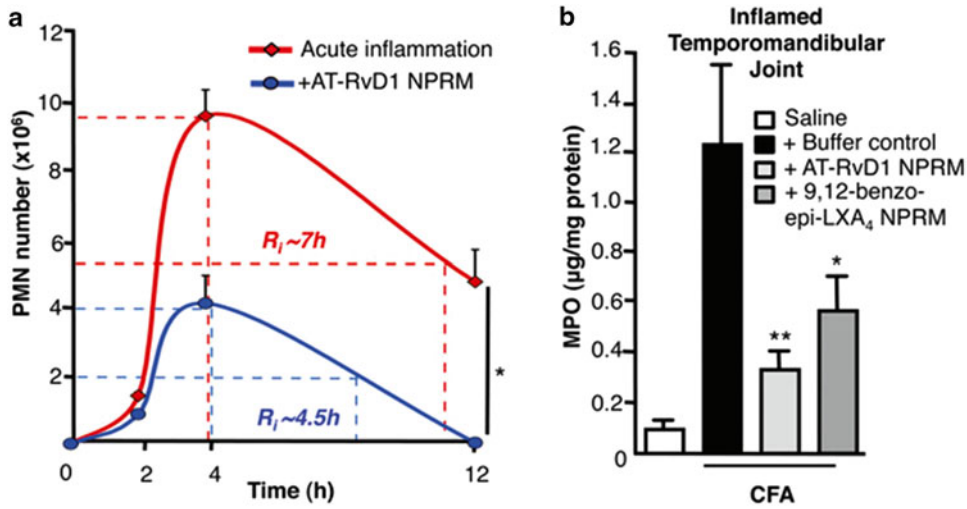

Fig. 4.10 (**a**, **b**) (**a**) Reduction in acute inflammation (PMN count) when AT-RvD1 NPRM was given i.v. prior to administration of inflammation-inciting zymosan i.p. in mice. PMN—polymorphonuclear cell. (**b**) Reduction in mouse temporomandibular joint (TMJ) inflammation (myeloperoxidase—MPO) induced by complete Freund's adjuvant (CFA) followed by i.v. NPRM (either AT-RvD1 or LXA_4). (**a**, **b**: Used with permission from Norling LV, Spite M, Yang R, Flower RJ, Perretti M, Serhan CN. Humanized nano-pro-resolving medicines mimic inflammation resolution and enhance wound healing. J Immunol 2011;186(10):5543–5547)

Nanotechniques for Hemostasis and Tissue Regeneration: Nanoscaffolds

Nanoscaffolds, being peptides composed of amino acids that self-assemble into nanofibers, are not recognized by the immune system as foreign, and thus do not incite an immune response. Moreover, peptidases remove the NS over time, an ideal intervention that performs its role and then disappears by natural means. The remarkable hemostatic properties of NSs—arresting bleeding even from small arteries within seconds—are well documented [19]. As illustrated in Fig. 4.11a–f, NPs form a clear gel through which one can operate in standard surgical fashion. NPs should be of significant utility in various surgical subspecialties, e.g., general, cardiovascular, cerebrovascular, urological.

NPs also possess remarkable properties to facilitate tissue regeneration. One example of central nervous system regeneration is documented in Fig. 4.12a–f [12]. Juvenile hamsters underwent superior colliculus (SC) sharp transection, as shown in Fig. 4.12a, b. Injecting 10 µl of a 1 % solution of the NP illustrated in Fig. 4.5a–c (arginine, alanine, aspartate, alanine—named RADA-1) into the region of SC transection, in contrast to 10 µl of saline control, resulted in the dark-field histological sections as shown: c and e are from 24 h and 30 days saline control animals, d and f are from 24 h and 30 days experimental (NP) animals. Impressively, 75 % of animals receiving NP treatment regained useful functional vision; recovery of vision was correlated with axonal reinnervation (up to 80 % of normal innervation), with no reinnervation (or visual return) being seen in the control animals.

Nanotechniques for the Tissue-Device Interface: Carbon Nanotubes and Nanofibers

Implanted medical devices such as cardiac pacemakers and deep brain stimulators depend on the electrical interaction of the device with tissues—

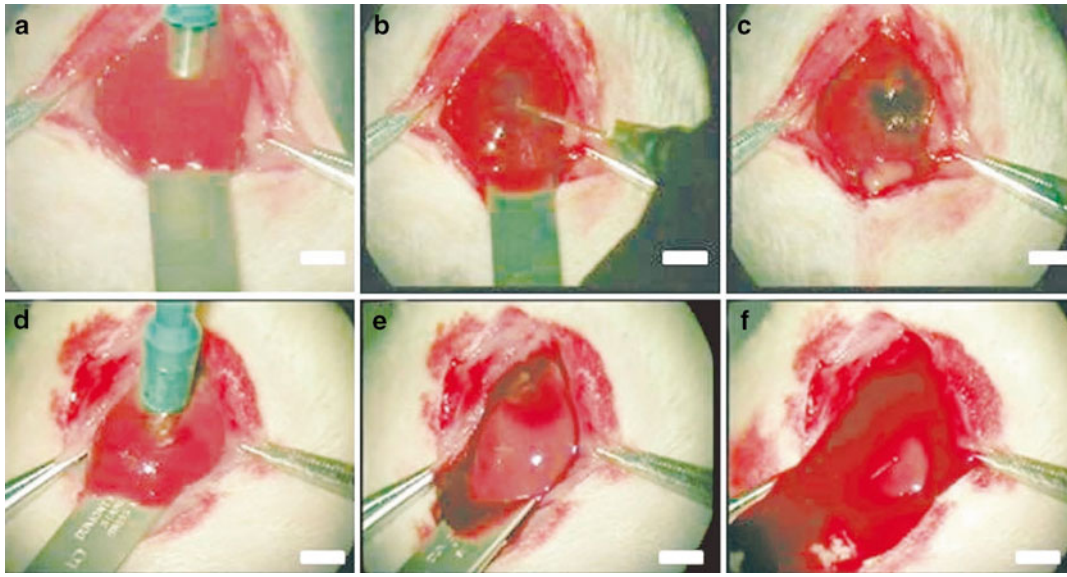

Fig. 4.11 (**a**–**f**) Rat liver punch biopsy (4 mm dia). (**a**–**c**) Topical treatment with a 3 % solution of the RADA SAPNS illustrated in Fig. 4.5. (**d**–**f**) Topical treatment with saline. (**a**, **d**) Time of punch biopsy, with profuse bleeding. (**b**) Treatment with RADA SAPNS, with complete hemostasis in approximately 10 s. (**e**) Treatment with iced saline and cautery, with continued bleeding. (**c**, **g**) 30 s after the punch biopsy—no bleeding with RADA SAPNS, continued bleeding with saline and cautery. (**a**–**f**: Used with permission from Ellis-Behnke R. At the nanoscale: nanohemostat, a new class of hemostatic agent. WIREs Nanomed Nanobiotechnol 2011;3:70–78)

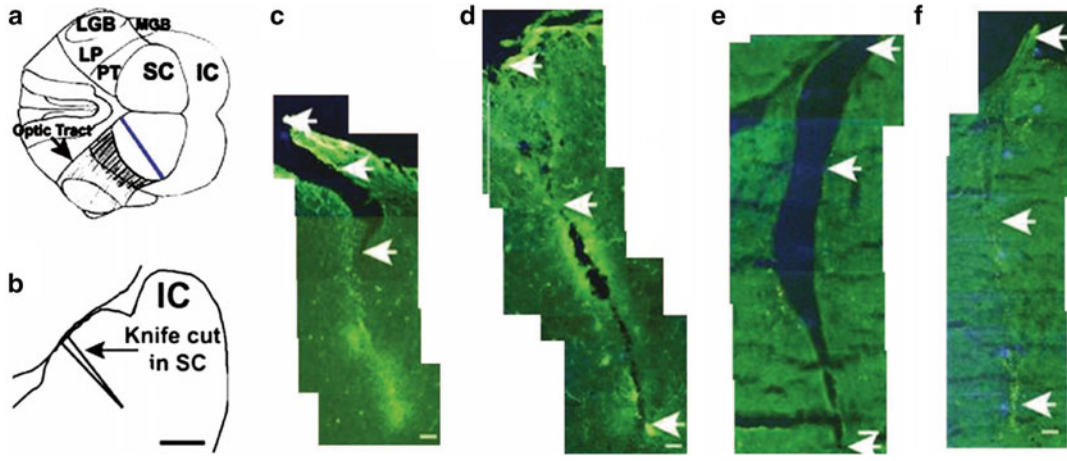

Fig. 4.12 (**a**–**f**) SAPNS for axonal regeneration in the hamster optic tract. Animals received saline 10 µl injection of 1 % SAPNS into the cut; controls received 10 µl saline injection. (**a**) Dorsal view of hamster brain with cortex removed; rostral to *left*, caudal to *right* in all figures. *Blue line*—optic tract transection at P2 in the SC of the midbrain. *IC* inferior colliculus, *LGB* lateral geniculate body, *LP* lateral posterior nucleus, *MGB* medial geniculate body, *PT* pretectal area, *SC* superior colliculus. (**b**) Parasagittal section of the hamster midbrain, indicating the optic tract transection in the SC. (**c**–**f**) Dark-field composite photos of parasagittal sections. (**c**, **d**) Animals sacrificed at 24 h after lesion and treatment, control (**c**) and treatment (**d**). (**e**, **f**) Animals sacrificed at 30 days after lesion and treatment, control (**e**) and treatment (**f**). Note the large gap in (**e**), not present in (**f**). (Used with permission from Ellis-Behnke RG, Liang YX, You SW, et al. Nano neuro knitting: peptide nanofiber scaffold for brain repair and axon regeneration with functional return of vision. PNAS 2006;103(13):5054–5059)

heart and brain, respectively. Improving the electrical charge transfer between the device and the tissue (by decreasing the impedance and/or increasing the capacitance) can markedly enhance clinical efficacy and battery life. CNTs and CNFs have been shown to improve charge transfer by orders of magnitude over electrodes not employing these nanotechniques. A simple but elegant example is the mere coating of standard electrodes for recording and stimulating the brain with CNTs; this provided a 20-fold decrease in impedance and a 40-fold increase in capacitance over uncoated electrodes [20]. By coating nanoarrays with conducting polymers, even more dramatic improvements in electrical charge transfer have been achieved [21].

Although the tissue-device interface has concentrated on electrical activity recording and stimulating, chemical activity (such as that of neurotransmitters in the brain) is clearly essential to understanding and correcting disorders of tissue function throughout the body. For example, Parkinson's disease (PD) occurs when there is a deficiency of dopamine in certain regions of the striatum of the brain. Drug treatment consists of replacing the dopamine deficiency with pills (orally); side effects such as dyskinesias often occur, which may—at least in part—be due to the replacement dopamine going to regions other than those deficient in dopamine (resulting in a relative excess). The most effective nondrug treatment for PD is deep brain stimulation of the subthalamic nucleus, which it is hypothesized tends to restore the electrical firing patterns in the brain to a more normal state. However, in a swine model, it has been shown that stimulation of the subthalamic nucleus (with parameters similar to those used in humans with PD) results in release of dopamine in the striatum [22]. The same group also showed that electrical stimulation (again similar to deep brain stimulation clinically) of astrocyte cell cultures results in release of another neurotransmitter, glutamate [23].

These data strongly suggest that monitoring neurotransmitters as well as electrical activity will greatly increase our understanding of many brain disorders and likely facilitate our treatment of those disorders. To that end, nanotechniques have been applied to our ability to monitor chemical activity in real time, in the brain (and potentially in other tissues such as the myocardium). Differential pulse voltammetry (DPV) is a well-established technique to monitor single neurotransmitters in the brain in near real time. However, DPV is unable to distinguish neurotransmitters such as dopamine and serotonin under in vivo conditions (e.g., when ascorbic acid is present) since dopamine and serotonin have oxidation potentials differing only by about 150 mV. It has recently been shown that CNF electrodes, unlike standard glassy carbon electrodes, can distinguish dopamine and serotonin in the presence of ascorbic acid (Fig. 4.13) [24].

Equally promising is the application of carbon nanotube techniques to myocardial disorders. Biomimetic extracellular matrices or scaffolds are a major thrust in myocardial tissue engineering. Problems with biocompatible scaffolds (polymers/gels) to date have included (1) mechanical weakness in comparison with myocardial tissues, (2) inability to match the conductive properties of myocardium, and (3) lack of submicron architectures that mimic myocardial tissues (architectures which are important in regulating cellular behavior) [25]. A recent publication demonstrates that gelatin methacrylate (GelMA) hydrogel (which has potential as a cardiac patch) demonstrates properties desirable in a cardiac patch when NT networks are embedded in the GelMA hydrogel [25]. The structure of the CNT-GelMA hydrogel is illustrated in Fig. 4.14a–d, the effect of various concentrations of CNTs on spontaneous beating and excitation threshold in Fig. 4.15, and proposed mechanisms for the cardioprotective effects of CNT-GelMA hydrogel against the reversible cardio-inhibitor heptanol and the cytotoxic agent doxorubicin in Fig. 4.16. CNT-GelMA hydrogel represents a significant advance in the search for a truly biomimetic cardiac patch, and the characteristics that CNTs (and other nanomaterials) add to tissue scaffolds are likely to prove effective for many tissue engineering challenges.

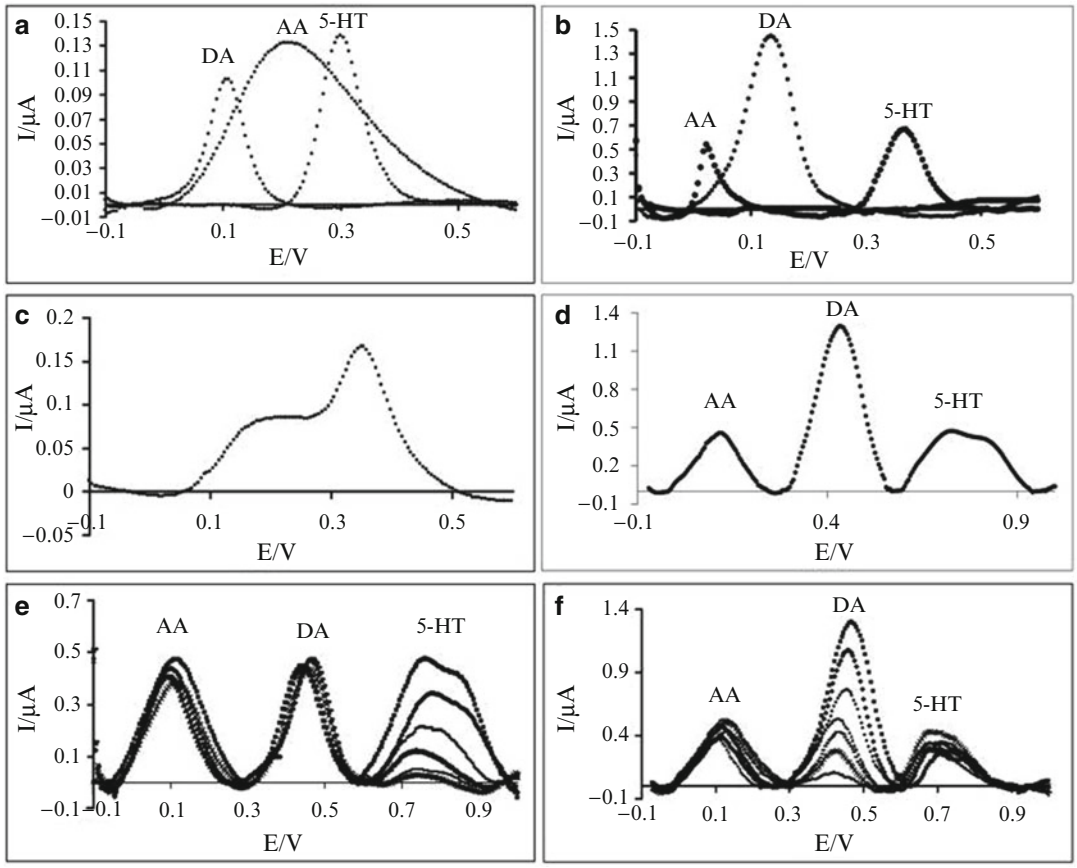

Fig. 4.13 Simultaneous detection of dopamine and serotonin in the presence of ascorbic acid. DPV plots of individual detection of 1 mM AA, 10 μM DA, 10 μM 5-HT (*left*), and a ternary mixture of 1 mM AA, 10 μM DA, 10 μM 5-HT (*right*) (glassy carbon electrode top row, carbon nanofiber electrode *middle row*). *Bottom row* (carbon nanofiber electrode): DPV plots of a ternary mixture of 1 mM AA, 10 μM DA, 5-HT (10, 5, 2.5, 1, 0.5, and 0.25 μM) (*left*), and a ternary mixture of 1 mM AA, DA (10, 5, 2.5, 1, 0.5, and 0.25 μM), 10 μM 5-HT (*right*). (Used with permission from Rand E, Eriyakaruppan A, Tanaka Z, et al. A carbon nanofiber based biosensor for simultaneous detection of dopamine and serotonin in the presence of ascorbic acid. Biosens Bioelectron 2013;42:434–438)

Conclusions

Richard Feynman did not address how the "swallowed surgeon" would get from the gastrointestinal tract to the blood vessels in order to operate on the faulty heart valve. Fortunately our endovascular colleagues have become adept at threading increasingly small catheters into increasingly small blood vessels. Indeed, the vascular "highway system"—from the aortic "interstate" to the capillary "alley"—can be employed to access all tissues in the body down to the cellular level. It has been demonstrated that electrical recordings and stimulations of the nervous system can be performed by an electrode in the blood vessel as effectively as by an electrode inserted into the brain parenchyma [26]. Furthermore, as suggested by Kendall Lee (personal communication, 2011), monitoring of chemicals in tissues (such as neurotransmitters in the brain) can be achieved by poking the electrode through the capillary wall. A nanoelectrode can be several hundred nanometers (or less) in diameter—only 1/10 the diameter of a red blood cell—so bleeding would not be a problem.

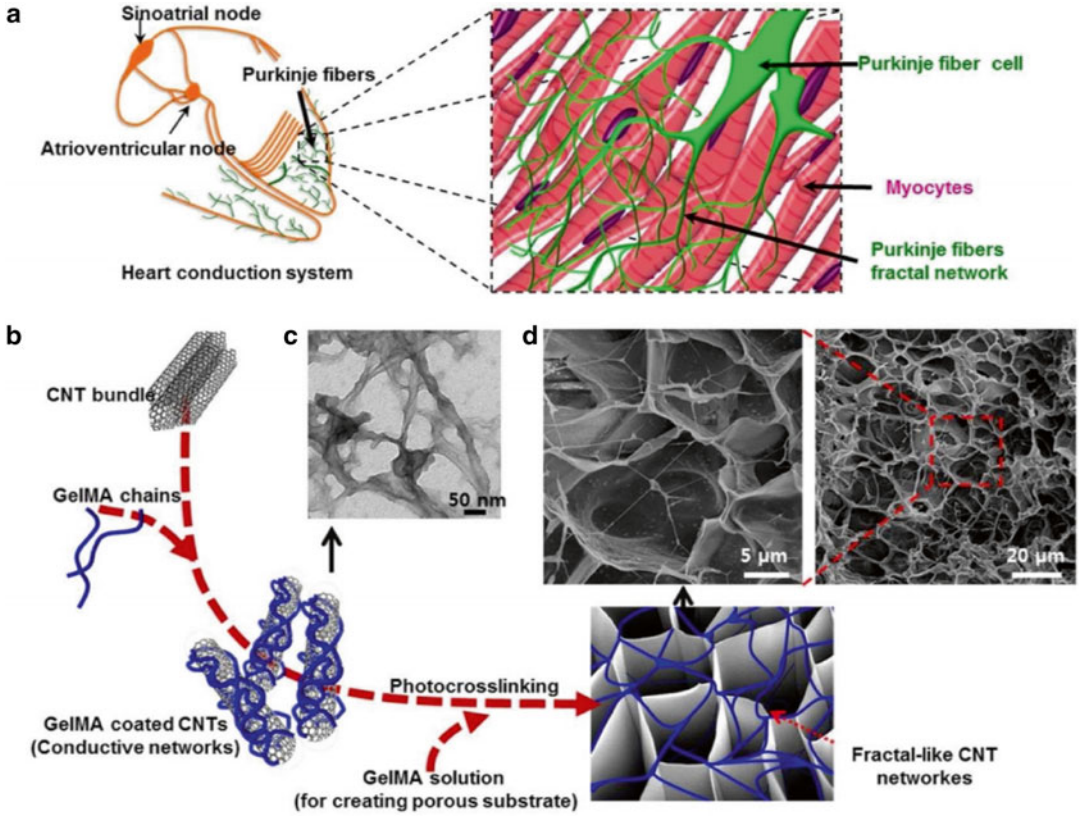

Fig. 4.14 (**a**–**d**) (**a**) Schematic of the isolated heart conducting systems. (**b**) Preparation procedure of fractal-like CNT networks embedded in GelMA hydrogel. (**c**) TEM of GelMA coated CNTs. (**d**) SEM of porous surfaces of 1 mg/ml CNT-GelMA thin film. Magnified image shows nanofibrous networks across and inside a porous structure. (**a**–**d**: Used with permission from Shin SR, Jung SM, Zalabany M, et al. Carbon-nanotube-embedded hydrogel sheets for engineering cardiac constructs and bioactuators. ACS Nano 2013;7(3):2369–2380)

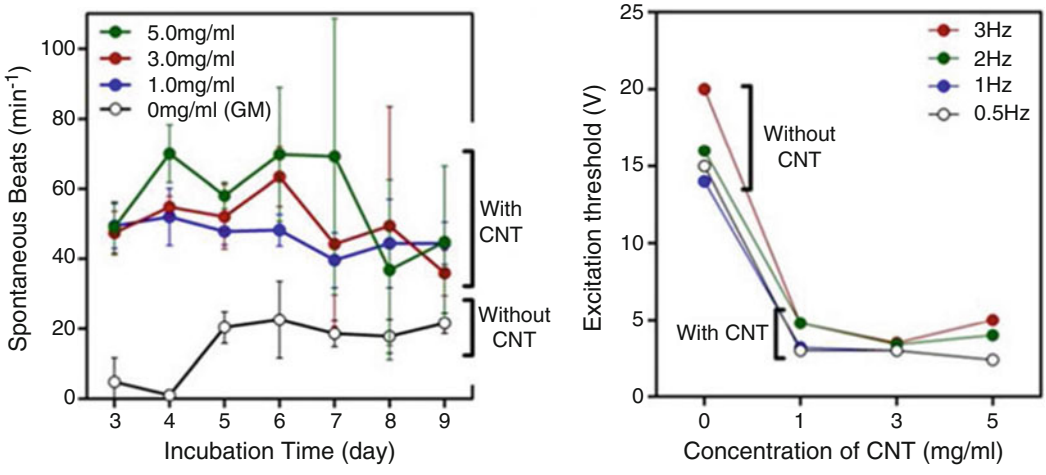

Fig. 4.15 *Left*. Spontaneous beating rates of cardiac tissues recorded from days 3 to 9. *Right*. Excitation threshold of cardiac tissues on CNT-GelMA was 85 % lower than on pristine GelMA. (Used with permission from Shin SR, Jung SM, Zalabany M, et al. Carbon-nanotube-embedded hydrogel sheets for engineering cardiac constructs and bioactuators. ACS Nano 2013;7(3):2369–2380)

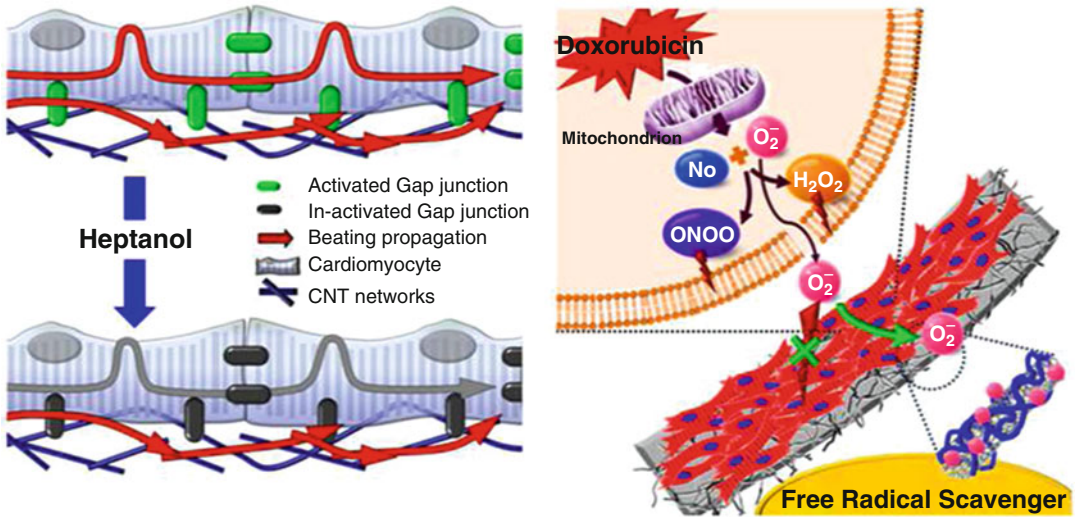

Fig. 4.16 *Left*. Schematic of alternative electric signal propagation through CNT networks after inhibition of direct intercellular gap junctions by heptanol. *Right*. Proposed mechanisms for CNTs to protect cardiac cells from oxygen free radical damage. (Used with permission from Shin SR, Jung SM, Zalabany M, et al. Carbon-nanotube-embedded hydrogel sheets for engineering cardiac constructs and bioactuators. ACS Nano 2013;7(3):2369–2380)

Feynman's vision is becoming a reality. In the present era of surgical technology, one must think small to make big advances!

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