



Future Prospected of Engineered Nanobiomaterials in Human Health Care

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Abstract

In recent years we have witnessed the beginning of the third medical revolution with the introduction of personalized treatments and the use of biotechnology to obtain antibodies and peptides with high selectivity for the therapeutic target. However, although this paradigm is still very recent, it is possible that we are simultaneously experiencing, even if still discreet, the fourth revolution of medicine. It is characterized by the development and miniaturization of devices. This allows remote and real-time monitoring of patient conditions, the introduction of smart dressings and implants, and the use of matrices made with organic and synthetic materials for varied purposes, such as serving as a biodegradable matrix for tissue growth or even as substituents for parts of the human body (cyborgs). These biotechnological products became possible because nanomaterials with greater flexibility, electrical conductivity, biocompatibility, resilience, and extremely sensitive were developed. In this chapter some of these materials and their practical applications are presented.

Keywords

Tattoo-Based wearable electrochemical devices · Smart dressing · Nanosensors · Cyborgs · Nano implant microchip devices

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14.1 Introduction

The association of nanotechnology with the treatment, medical diagnosis, monitoring, implants, tissue-engineered constructs, and even the design of cyborgs has brought a new concept in science, namely, nanomedicine. These devices have emerged to leverage the advances of the applications of nanobiomaterials in traditional medicine. In this interdisciplinary field of science, different areas of expertise, particularly pharmacists, chemists, engineers, physicians, and computer scientists, ought to work together.

Many advances in nanomaterial devices have recently been introduced or are currently seeking a development method and a further validation to be employed in clinical routine. The range of applicability of new products is huge due to the level of the scientific advancements. They have enabled devices to monitor the health status in real time, in a micronized way, integrated to the body to overcome some physiological limitations and even to generate superhuman responses as in the senses of hearing and sight.

In this chapter, we will highlight the recent progress in these emerging areas and briefly outline the possible future directions and advances. The most innovative topics within these fields, such as biomonitors (wearable or implants) and the development of cyborgs (implants and cyborganics), will be addressed. The monitoring of physiological parameters by the devices allows the patient's treatment to be faster, more precise, efficient, and at a lower cost. This characteristic was obtained after the introduction of nanomaterials such as coated carbon nanotubes, polyaniline (PANI), copper nanowires, and poly(N-isopropylacrylamide) (pNIPAM), which are reported during this chapter. They allow the measurement of temperature, pH, humidity, and even electrolytes or organic markers such as glycemia. The development and applicability of cyborgs are two of the most prominent areas within the field of nanobiomaterials. There is a clear need for biocompatible nanomaterials with high flexibility. We can highlight the silicon nanowire field-effect transistor (FET)-based nanoelectronic biomaterials and the use of 3D printer techniques using the raw material Ag nanoparticles and cartilage cells embedded within an alginate hydrogel matrix for cyborg implementation. Throughout the chapter, other nanomaterials will be reported.

14.2 Biomonitors

Many of the advances in bioelectronics occurred by the emergence of biocompatible materials, flexible, resilient, and smarter and less expensive that can be integrated with the dynamics of the human body. Nanobiomaterials are able to improve the detection systems and parameters such as reproducibility, precision, and reduced cost of experiments. That is possible due to their favorable properties such as high surface-to-volume ratio and sensibility, desired electrochemical properties and stabilities, and the demand for a very small amount of reagents and samples. Some nanomaterials exhibit conductivity and peculiar quantum effects that can be used to

amplify the signal stemming from the detection. However, the appropriate choice of nanomaterials is essential to successfully miniaturize the tests.

The desire to develop devices that can monitor real-time health status of a patient and evaluate the prognosis or therapeutic response of an intervention is directly dependent on technological advances and practical application of miniaturized sensors and the manufacture of “smart” materials. The development of flexible, efficient, and biocompatible materials allows commercial viability and great reliability of health monitors. Currently, the challenges are to be able to adapt and incorporate these materials into smart wearable systems (SWSs) (smart wound bandages, e-skin, and tattoo-based sensors), implantable diagnostic devices (IDDs), and miniaturized diagnostic devices (lab-on-a-chip and organ-on-a-chip) (Fig. 14.1).

Some of these new technologies enable us to perform personalized diagnosis, even in real time or a comprehensive outlook of a disease genetic makeup. Therefore, such information can guide decisions for patient-specific diagnosis and a smart therapy (pharmacogenetics, clinician-oriented or patient-oriented point of care [POC], and the best therapeutic regime). Possibly, one of the main advancements allowed by this association lies in the implementation of the POC. It will allow easier access from the primary care physician and the patient to clinical diagnostic testing. The perception of physiological changes allows the maintenance of homeostasis through feedback by the release of active substances. That can be considered

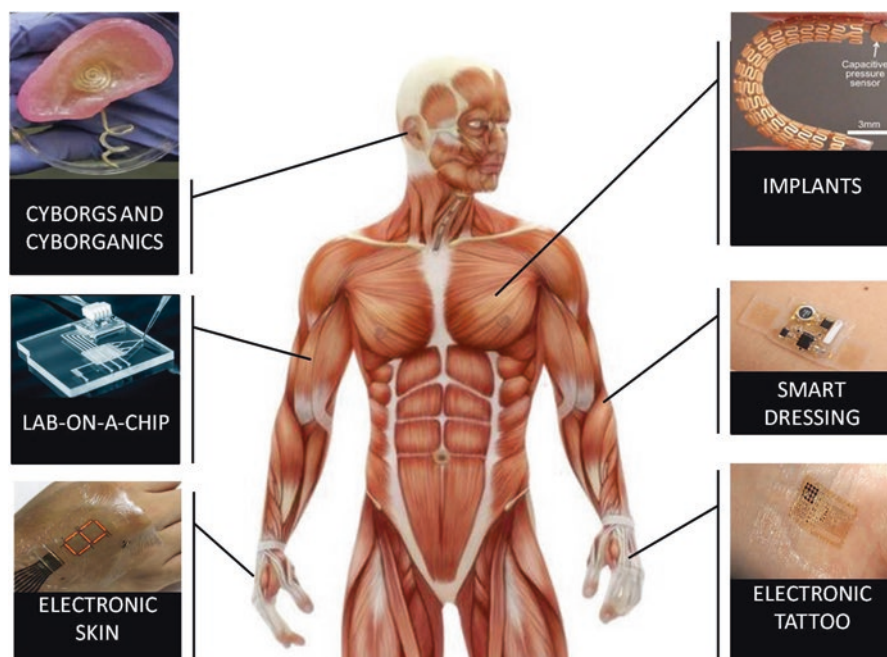


Fig. 14.1 The applicability of nanomaterials in medicine

as an autonomous and intelligent first-aid care with great utility in cancer, epilepsy, and cardiovascular diseases, among other clinical conditions.

The reduced size of these devices makes manipulation difficult by hand; therefore, they are automated or autonomous. Even though seductive, the miniaturization process of biosensors or cyborgs has a physical limitation because of three main reasons. The first is the size of blood cells, measured in micrometers. Therefore, the reduction below this diameter would prevent the flow of these cells by the device generating altered results or, in the case of cyborgs, nutritional deficiency and hypoxia. Another impediment is the volume of the aliquot, since the larger the device reduction, the smaller the sample volume. However, depending on what one wants to analyze, a larger volume of the aliquot is needed to find the analyte in the medium; for example, there is on average only one tumor cell per milliliter of blood; therefore, there is recommendation for the collection of at least 7 mL for a more reliable analysis. The third point is the increase in the sensitivity of excessive form, which generates false-positive results due to the contamination of substances present in the surface of the skin or in the ambient air, which can alter parameters like sanguine gases, pH, and even the presence of microorganisms.

In addition, another challenge to the large-scale introduction of these technologies is to obtain a high barrier property to avoid dimensional instability of the polymer material because of moisture and gas permeation. However, there are some materials that should not be completely impermeable such as smart bandages because gaseous exchange and moisture control are necessary. In these cases, semi-impermeable surfaces are desired. Therefore, the choice of nanomaterial is fundamental for the proper functioning of the devices. They must present flexibility, biocompatibility, and semi-conductivity as key characteristics needed in these applications. For instance, nanomaterials built with polyimide and parylene have been extensively used as components for bionanosensors as IDD and SWS (Mostafalu and Sonkusale 2014).

14.3 Wearable Devices

14.3.1 Smart Bandages

Wound healing is a dynamic and interactive biological process involving delivery of several inflammatory mediators, matrix molecules, and nutrients to the wound site. The wound healing stages are made up of three main phases, inflammatory, proliferative, and maturation, also known as remodeling. In normal healthy subjects, the healing process will occur properly. However, there is a possibility of errors occurring in numerous steps along this pathway, chiefly if the patient has certain pathological conditions (e.g., diabetes, infections, severe burns, and low nutrition content). In these cases, the prognosis worsens, and it can create chronic and honorable wounds with a high chance of becoming larger morbidities. Tissue healing in elderly patients is usually a slower and more costly process. Therefore, it is expected that chronic wounds stand out as one of the major global health challenges in the

coming years. Part of this clinical inefficiency is in the management of the wound site because it is neither monitored nor attended properly.

There is great difficulty in treating chronic wounds, which means that costs can exceed \$ 90 billion. These costs serve as an incentive for the development of new technologies. It is represented by a billionaire commercial industry divided into four main curative groups: passive, interactive, advance, and bioactive (Han and Ceilley 2017; Nussbaum et al. 2018). *Passive dressings* are considered as the elementary ones and include bandages and cloth gauze as basic physical barriers of protection. The adherence of these dressings to the wound bed is habitual, stable, and with difficult displacement. They are suitable for dry shallow wounds because they are not porous, nor do they retain local moisture (Han and Ceilley 2017).

On the other side, the introduction of polymeric films, hydrogels, and foams make interactive dressings permeable to gases and fluids. When the patient has exudate-producing wounds, for example, burns, deep wounds, and diabetic ulcers, the foam or sponge dressings can absorb this fluid better than gauze. The hydrogels present in this type of dressing exhibit several positive features, as they are able to reshape the wound site, maintain local humidity, and facilitate dressing removal, unlike what is observed with passive dressings (Fonder et al. 2008).

Advanced dressings maintain wound moisture within appropriate levels to improve the kinetics of tissue regeneration and avoid bacterial proliferation. They are usually made using alginate or hydrocolloids. Alginate is indicated when the wound contains heavy exudate levels because it can form a gel with the ion exchange between the sodium secreted from the wound and the calcium released from the alginate. Platelets are activated by the released calcium salts, which contributes to hemostasis.

Finally, the bioactive dressings are those that include biological scaffolds or drug delivery systems and stimulate healing through tissue regeneration, called tissue-engineered dressings, and stimulating angiogenesis (Brown et al. 2018). This type of dressing showed clinical efficacy in the tissue regeneration of patients with ulcers and burns, and, therefore, despite the higher cost, they reduce hospitalization time and shorten treatment duration. Some commercially available examples are Dermagraft, AlloDerm, Apligraf, and Biobrane.

The next generation of dressings has led us to think totally different about wound care, mainly because of the inclusion of wearable sensors. These sensors have been created in order to precisely identify real-time biomarkers, such as inflammatory markers, pH, and ionic concentration values and temperature at the wound site. The drug delivery system can be integrated with the sensors. With this, the kinetics of drug release will follow instantaneous responses and autonomously to varied situations, for example, to potential presence of pathogenic microorganisms, inflammation, or local allergy. These integrated systems are called multifactorial smart dressings because they allow therapeutic direction, responses to the clinical prognosis, reduction of health care costs, and availability of information on the patient's clinical situation. This information cannot be provided with traditional (not sensory) wound dressings. This information is obtained and transmitted, locally or remotely (Wi-Fi transmission), by sensors in the wound site coupled to the dressings.

The introduction of porous nanomaterials has increased the robustness of these devices, making them more resistant to mechanical changes and electroconductors. The most widely used nanomaterials are nanofibrous substrates (e.g., polyaniline [PANI]), poly(styrene-*b*-(ethylene-co-butylene)-*b*-styrene), and multiwall carbon nanotubes and their combination.

Sensors intended for use in wound care products should be able to measure potential biomarkers under abnormal conditions such as changes in pH, humidity, and ion concentrations, which occur, for example, during inflammatory or infectious processes. The sensors must also have the ability to adhere properly to the contours of the body without causing antigenic or toxic responses to the tissues. The pH of a wound can provide important information for interpreting what is occurring in a given tissue, for example, microorganism infection, angiogenic process, and protease activity. While an acidic environment enables healing to occur more quickly, extremely acidic pH values can also indicate bacterial infection. Various types of *pH sensors* have been manufactured for wound care applications, and all of them are flexible, biocompatible, and permeable enough to maintain conformal contact with curved surfaces and to yield smart wound bandages. Basically, they are divided into colorimetric and electrochemical. *While electrochemical pH sensors use, for example, potentiometric measurement and ion-selective field-effect transistors, the colorimetric pH sensors are simpler, because they work without the need for coupled electronic components* (Guinovart et al. 2014). The readings are generally performed by image processing. However, identification even to the naked eye can estimate pH at the wound site. Nevertheless, leakage of dye into the skin is still a recurring problem in the development of many colorimetric sensors. In order to solve this problem, the pH-responsive dyes can be incorporated into mesoporous silica particles and then encompassed by hydrogel fibers to prevent leakage into the skin during the analysis (Sridhar and Takahata 2009).

An example of the potentiometric approach is the thread-based pH sensor consisting of conductive threads and a microfluidic splitter with three channels for the delivery of a sample to the sensing chambers (Fig. 14.2a–d). In this method, the open circuit potential of a working electrode, carbon nanotubes (CNTs) coated with doped PANI, was measured. The dynamics of readout electronic circuitry starts with the detection of the parameters from the sensors, followed by wireless transmission of the results to an electronic device (smartphone or computer) near or in another location (Mostafalu et al. 2016).

A similar study also applied PANI as pH-sensitive nanomaterial in the development of a flexible smart bandage coupled to a Bluetooth module (Fig. 14.2e) (Punjiya et al. 2017). However, this device still needs to be tested *in vivo* to confirm the good sensitivity and real-time communication. It is noteworthy that the board, yet rigid, is small and inserted externally so as not to influence the performance of the sensor or to cause any discomfort to the prospective patient. In addition, it is possible to insert the electronic components onto the flexible printed circuit board on a polyimide substrate (Siegel et al. 2010).

Electrochemical and colorimetric *temperature sensors* are also usually employed in smart dressings. One of the strategies employed to reduce the cost of the devices

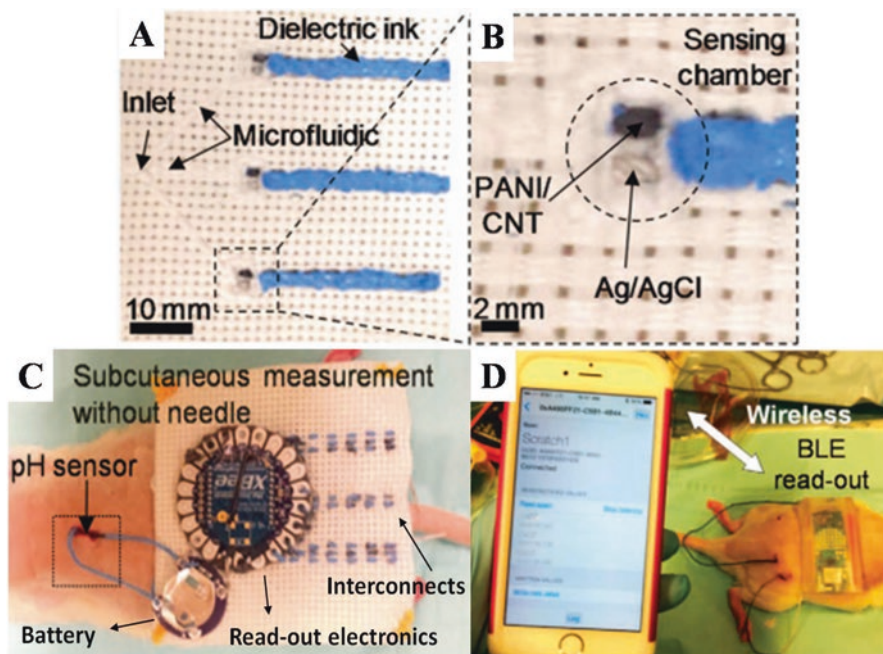


Fig. 14.2 Example of pH sensor. (a and b) Optical image of a multiplexed microfluidic pH sensor. (c) Implanted sensors connected to the patch. (d) Sensing system communicating with an external device. (Adapted from Mostafalu et al. 2016)

is the use of material-based inks. However, despite facilitating the flexibility of the final product, conductive paints suffer from the change in mechanical resistance induced by mechanical stresses and skin-shaped contact.

The introduction of the surgical suture made from silk with nanobioelectronic sensor was a great advance. It allows wound closure and monitoring of clinical response. This suture system makes it possible to obtain more than one information at a time, that is, temperature changes and temperature conductivity, which are related to the inflammation progress and the moisture content of the wound. The highest sensitivity in temperature variation (≈ 0.2 °C) was obtained with the incorporation of the silicon-based temperature sensor within this silk suture (Mehrali et al. 2018). This system consists of a polyimide substrate containing a sensor array that is connected with copper nanowires (CuNWs).

Other nanomaterials have enabled several utilities for suture. Nano-silver particles coated on the surface of conventional silk suture may improve inflammation process, promote wound healing, and have antibacterial action (Zakeri et al. 2016). There are studies demonstrating advantages in nano-coating the conductive materials. For example, CuNWs are highly conductive and fundamental for data transfer and heat conduction. Nevertheless, the degree of miniaturization is inversely proportional to electrical and thermal conductivity. The use of graphene to form graphene-encapsulated CuNWs increased electrical and thermal conductivity

compared to uncoated CuNWs, which allows a greater sensitivity in the detection of data even with miniaturization (Mehta et al. 2015).

During a tissue injury, there will be instantaneous damage of local blood vessels, edema, bleeding, and interruption of the nutritional oxygen supply to the cells previously nourished by these vessels. Local hypoxia activates angiogenic factors to restore vascularization and to avoid tissue necrosis. However, in certain situations, this process cannot occur correctly, impairing healing, and may even lead to possible amputations. Therefore, it is evident that monitoring the local tissue oxygenation allows us to evaluate the evolution of the healing process.

The great difficulty of introducing *oxygen sensors* in the intelligent dressings is to selectively analyze the oxygen concentration of the tissue without being influenced by the contact with atmospheric oxygen. There are available dressings with coatings impermeable to oxygen; however, as mentioned above, the ideal dressing should allow the passage of gases not to impair healing (Li et al. 2014). Actually, the gold standard test to quantify the tissue oxygen concentration is the needle-type Clark electrodes, an invasive procedure that can lead to painful, local injury, and changes in microcirculation. Due to these possible adverse effects of monitoring by needle-type Clark electrodes, many products have been developed to allow the detection of tissue oxygenation, e.g., laborious methods with hypoxia markers such as pimonidazole and those using radioactively labeled indicators. Another mechanism developed is a thin film with a flourishing feature dependent on the presence of oxygen, which is painted on the skin. It can be used to identify the oxygen concentration of the underlying skin tissue. The results of *in vivo* studies have been shown to be exciting and promising (Li et al. 2014).

During the healing process, there is the formation of inflammatory exudate. It is expelled by the wound and helps to maintain moisture. It is well documented and accepted that moisture balance is important in achieving optimum wound healing conditions. However, when the site is protected by some types of dressing, it prevents the maintenance of this moisture and may cause unbalance of this parameter. Excessive moisture wounds facilitate the proliferation of microorganisms, leading to an increased risk of infections (Farrow et al. 2012). Therefore, changing the bandage within the appropriate frequency is recommended. Nevertheless, clinicians have been unable to observe the moisture status of the dressing without disturbing it. Consequently, selecting the ideal time for this change has been a task with high failure rate. It is estimated that almost half of the changes occur before the ideal time, which results in increased patient costs and private or public health policies and unnecessary physical stress. Therefore, the development of *moisture sensors* is considered as a key tool in patient follow-up (McColl et al. 2007).

Many materials are used in moisture sensors and most of them can be classified based on organic and inorganic sensitive materials. Inorganic-based sensing materials, for example, Al₂O₃, In₂O₃, MnWO₄, SiO₂, SnO₂, TiO₂, WO₃, and ZrTiO₃, can detect the slightest variations of humidity in the wound environment and have limited utility in the microchip manufacturing. Manufacturing becomes more viable with products processed at low temperatures, such as hydrosoluble organic or

polymer-based sensing materials polyvinyl alcohol, poly(sodium 4-styrenesulfonate), poly(vinylpyrrolidone) (PVP), PANI, and its congeners. However, two disadvantages were noted: the high-water solubility of these materials in environments with high humidity and their relatively slow response time, which varies from 10 s until impractical 2 min. Therefore, these sensors are not considered adequate to integrate the sensorial devices, because they have low sensitivity and energy efficiency, in addition to an extended response time (Bruinink 2018).

Despite advances in the area of intelligent sensors, the limited and low number of wound care devices available in clinical practice is surprising. In 2013, WoundSense™ sensor came to the market. It can measure the moisture at the site of the wound and be adapted in any dressing (Fig. 14.3). It is based on two parallel electrodes with a defined distance measuring the impedance between them. This parameter is used to classify the local humidity into five rates: wet, wet to moist, moist, moist to dry, and dry (Milne et al. 2016).

Another promising approach is the use of graphene oxide (GO) to bind water molecules. This is due to the GO's ability to be an amphiphilic soft material. It allows excellent response time and recovery time of the humidity sensors (0.2/0.7 s, respectively) when comparing with other forms of graphene or nanomaterials, such as reduced GO (4 s/10 s), graphene quantum dots (10 s/20 s), carbon nanotube (6 s/120 s), or H-doped graphene (3 min/several hours).

The development of a wireless device to continuously and remotely monitor the wound healing process generates benefits to everyone involved, both patients and professionals. This remote communication allows the reduction of the physical inspection of the wounds so that one can know the ideal moment of some clinical intervention, reducing prolonged hospitalizations or repeated visits to clinics. Smart integrated wireless dressings follow a standard system in most devices (Fig. 14.4). The interesting thing to reduce the costs of the devices is always to try to reuse the part of the dressings represented by the sensors. The sensors to detect parameters on

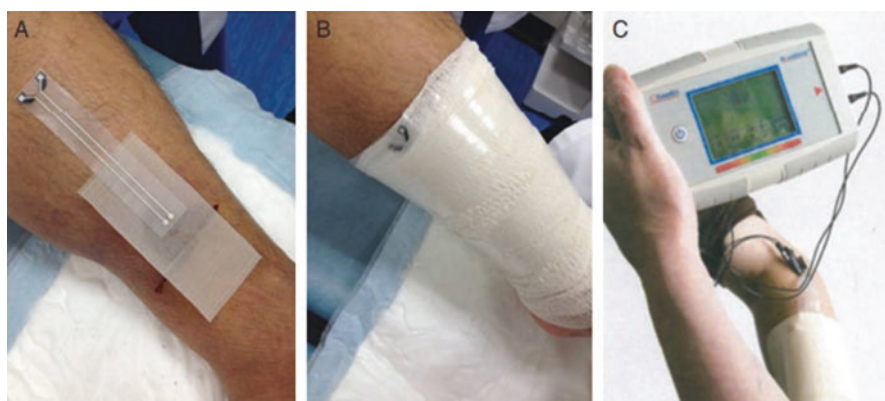


Fig. 14.3 (a) WoundSense™ sensor implanted at the wound site, (b) after dressing and (c) being measured by a mobile device (WoundSense™ meter) (Milne et al. 2016)

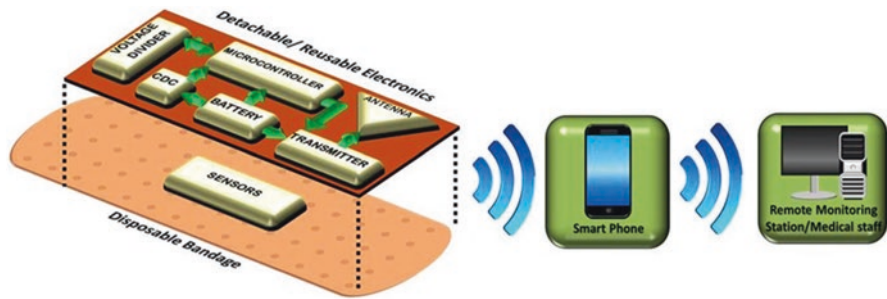


Fig. 14.4 Representation of the system design. Highlight of the two parts of the device, a disposable part and a reusable part, and its components (Farooqui and Shamim 2016)

the wound make up the disposable part, whereas the electronics are integrated and can be detached and reused multiple times. The values obtained by the sensors are processed by the electronics, and the information is sent wirelessly to a personal smartphone and remote monitoring station or medical staff (Farooqui and Shamim 2016).

14.3.1.1 Dressings with Active Delivery of Drugs

Monitoring the characteristics of a wound, as mentioned earlier in the text, is a fundamental part of modern rational treatment. Complementing this information with “smart” drug and healing factor delivery would put the dressings on a plateau above. Basically, we can divide the drug delivery system into two main processes: a passive one and an active one. The passive process is simpler than the active one because the drug embedded is released from dressings regardless of wound needs. However, the wound environment undergoes dynamic changes. Consequently, the need for drugs could be different at singular time points and curative stages, which requires adjustments in the release profiles in real time. On the other hand, active drug delivery systems allow greater control of release profile. These systems are usually designed to release only drugs in response to external stimulus sites such as temperature, pH, pressure, electrolyte, and mechanical concentration (Saghazadeh et al. 2018). Currently, researchers are seeking the ideal combination of local markers that signal the physiological changes of each clinical status, such as skin cancer, burn, psoriasis, and chronic wound. The definition of such desired markers enables the selection and arrangement of the sensors that will be incorporated into devices for active control of the release of drugs. Miniaturized pumps integrated with dressings are considered the most used strategy for delivering solutions containing drugs into the wound site. These pumps can be used integrated with microneedles to inject accurate concentration of drugs. Thermal stimulation is considered a safe, popular, and low-cost method, which can increase transdermal drug permeability and reduce healing time (Prausnitz et al. 2004).

An integrated multilayer bandage was developed in 2015. It features electrochemical pH sensors embedded in a hydrogel matrix composed also by thermoresponsive drug carriers cast on a flexible heater. When the sensor detects pH values

outside the previously determined range as acceptable, the heater is triggered to release antibiotics (Saghazadeh et al. 2018; Mostafalu et al. 2015).

Some thermally activated wound dressings use thermoresponsive particles of pNIPAM produced by means of a microfluidic system. Hydrogel-based dressing matrix structure with a flexible heater was used as thermoresponsive drug and growth factors carrier to the injured tissue. This device has the ability to store and release various chemical structures. An example of a complex consisting of different nanomaterials are the chitosan-based nanoparticles mixed with a polymeric solution. This flexible complex forms nanofibrous substrates composed of nanoparticles in its interior. Changes to local temperature stimulate the release of the drug (Huang et al. 2014). Numerous studies about the appropriate drug delivery to the wound site were recently discussed by Saghazadeh and collaborators (2018).

14.3.2 Electronic Skin (e-Skin)

Unlike dressings, e-skin was not designed to protect a wound or to serve as a platform for the release of active substances. Adequate functioning of the e-skin is dependent on many of the parameters also required for the performance of smart dressings, i.e., flexibility, sensitivity, and the ability to provide information on certain pathophysiological parameters. These devices can identify and signal changes in the most superficial layers of the skin even in the deep ones, e.g., invasive melanomas (Dagdeviren et al. 2015).

The viscoelastic changes of the skin are perceived by nanoelectronics and pressure sensors, which transform them into electrical signals for OLED processing into pixelated signals. These changes are detected by elastomeric pressure sensor built by the incorporation of carbon nanotubes (CNTs) with polydimethylsiloxane (PDMS) substrate and an electronic system that enables the conversion of the viscoelastic parameters into a pixelated format (Kim et al. 2015). New multifunctional circuits have been developed and promise to revolutionize the range of responses achieved by e-skin. Such multifunctional and mechanically robust platforms identify variations in thermic, moisture, and chemical components. Among the materials evaluated, CNT- and graphene-based nanoelectronics have been outstanding due to the excellent sensitivity towards temperature and humidity changes (Lu et al. 2019; Kim et al. 2015). However, when comparing some polymer nanocomposite-based strain sensors, it is concluded that 1D nanomaterials (CNTs and AgNWs) are preferable than other nanomaterials such as carbon blacks (CBs) and graphene and silver nanoparticles (AgNPs). This observation is confirmed by the values of gauge factor and stretchability and explained by the high-aspect ratios as well as the capability to sustain the percolation network at large strain presented by the 1D nanomaterials. A deficiency of conductive nanomaterials is that they do not support strain over 5%, so a designed conductive network is required that controls the transfer voltage to elastomeric matrix (Lu et al. 2019).

In order to obtain proper e-skin devices, there are still many obstacles to be overcome, such as materials that meet the practical needs (conductive nanomaterials,

high purity, adequate stretchability, and affordable price). Carbon black does not present good electrical conductivity and needs high loading to form the percolation network. Graphene-based strain sensors exhibit inadequate stretchability, which facilitates the appearance of irreversible cracks. Metal nanowires, for example, AgNWs and AuNWs, are expensive, which impede the widespread trade of devices. Low purity is highlighted as the main deficiency of CNTs. Therefore, it is clear that the science of nanomaterials needs to advance a little further before introducing this new technology on a large scale.

14.3.3 Tattoo-Based Electrochemical Sensors

Biosensors and electrochemical sensors have recently found extensive applications in medicine, mainly in diagnostic fields. These sensors are largely used in a number of analytical instruments in clinical laboratories and commercial point-of-care devices, e.g., pH electrodes and glucose biosensors. Electrochemical sensors work when they transform electrochemical information into an analytical signal. It is formed by two main components, a chemical recognition system and a physico-chemical transducer device that converts the chemical response into an electrical signal recognized by a working electrode. Otherwise, biosensors recognize biochemical markers when contacting their chemical sensors. The great challenge is building a sensor with high sensitivity, selectivity, accuracy, and low cost (Chandra 2016).

Screen printing, photolithography, and stamping methods are commonly used to introduce electrodes on planar substrates. This allowed the development of a simple manufacturing sensory device for low-cost monitoring, capable of performing non-invasive electrochemical analyzes of biomarkers present in body fluids, mainly body sweat. They are called functional sensing “tattoos,” also known as tattoo-based electrochemical or colorimetric sensors (TBECS) (Kabiri et al. 2017). One interesting feature of these wearable sensors is that they can evaluate parameters related to patient health in the form of varied artistic tattoo patterns. These parameters include quantification of electrolytes, lactate production, and even xenobiotics eliminated by sweating, such as heavy metals and drugs. In 2013, Jia et al. demonstrated the first example of a noninvasive enzymatic temporary-transfer tattoo electrochemical biosensor that provided a real-time analysis of sweat lactate during exercise (Fig. 14.5). This tattoo is composed of a surface of the electrodes imprinted with tetrathiafulvalene (TTF) and multiple wall carbon nanotubes (CNT), functionalized by the presence of the LOx enzyme adhered to the outer layer of chitosan. Screen techniques were used obeying the body contours for the synthesis of this sensor. Mixed with the printing ink, carbon fibers were added, which allowed greater resilience and robustness towards extreme mechanical stresses expected from physical activity. Unlike the traditional methods for measuring lactate, the tattoos allow to evaluate the results of anaerobic exercises, which produce lactate in the muscles by the consumption of glycogen stores, in a noninvasive and simpler way (Jia et al. 2013).

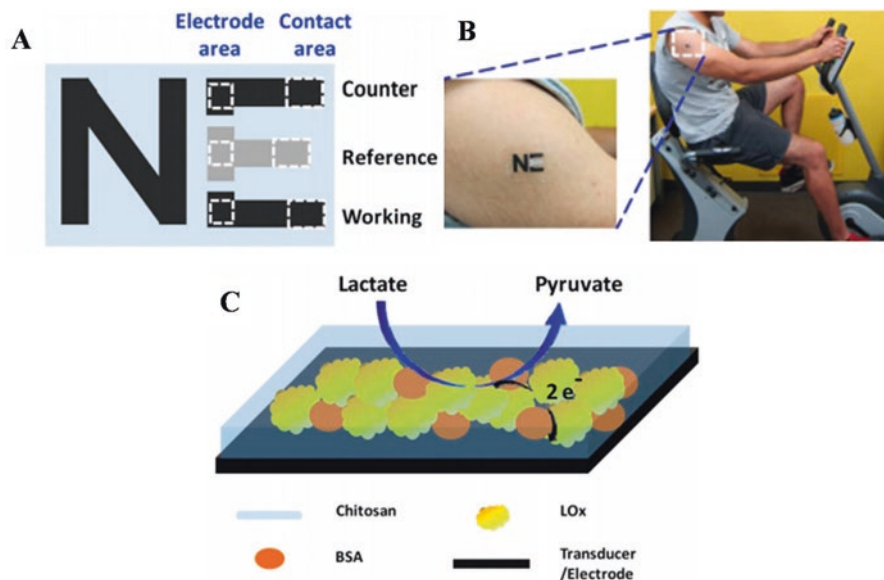


Fig. 14.5 (a) Schematic illustration of a three-electrode “NE” tattoo biosensor for electrochemical epidermal monitoring of lactate. (b) An “NE” lactate biosensor applied to a deltoid. (c) Constituents of the reagent layer of the working electrode that is coated by biocompatible polymer (chitosan). (Adapted from Jia et al. 2013)

14.4 Internal Healthcare Monitors (Implants)

As well as smart dressings, the growing number of breakthroughs in bioelectronics driven by the emergence of nanomaterials and micronization of devices allows real-time internal monitoring of health risk factors. Cardiovascular diseases are the leading causes of deaths and morbidities around the world. Therefore, monitoring the characteristics of blood pressure and cardiac function is vital for the treatment and prevention of these diseases. For this purpose, the electrocardiograms are used: a simple procedure, noninvasive, and capable of real-time monitoring of heart activity. However, it requires the patient to go to a hospital facility. Another questioning of the method is that the electrodes are not directly in contact with the myocardium, which may impair the precision of the stimulation and control of inotropic and chronotropic responses. Electrode implants should be flexible enough to adapt to the sinuous characteristics of organic tissues. Among the materials used, the 1D nanomaterials (silicon nanowires, silver nanowire, and CNT) are incorporated into biocompatible and flexible elastomers with good success rate. An *in vivo* study obtained signal-to-noise ratios and high spatial resolution from a silicon-based nanocircuit assembled onto a flexible polyimide (PI) substrate (Timko et al. 2009). A second study developed a device that consisted of an Au-based electrode network deposited onto a flexible PI substrate (25 μm). Due to its 288 electrical contact points, it was possible to record electrical signals with high sensitivity for signal-to-noise ratio

and temporal resolutions (≈ 34 decibels and < 2 ms, respectively) in the test in a porcine animal model (Viventi et al. 2010). Neural connections are complex, interdependent, multifunctional, and fundamental for the proper functioning of basic responses to the most complex ones, such as reasoning and memory. In order to understand and monitor the central nervous system, it would be innovative to apply the network of injectable, miniature wireless neural implants (Ferguson and Redish 2011). For example, identifying the exact location of the electrical trigger responsible for an epileptic seizure or previously excited regions prior to a panic syndrome allows researchers to better understand the diseases. A silicon nanomembrane device transistor into the electrode array is able to identify specific responses on the surface of visual cortex, for example, sleep spindles and single-trial visual evoked responses. The array was composed of 720 silicon nanomembrane transistors. Active electrode arrays were produced using a multilayer process, which can be divided into four layers: (i) doped silicon nano-ribbons (~ 260 nm, first layer); (ii) horizontal and vertical metal interconnect layers insulated using layers of PI; (iii) polymeric encapsulation layers (PI and epoxy); (iv) and platinum (~ 50 nm) deposited onto the surface electrodes (fourth layer). The device was either implanted on the cerebral surface or inserted interhemispheric fissure of the brain (Viventi et al. 2010).

14.5 Development of Cyborgs (Prosthetics and Cyborganics)

The idea of merging inanimate materials with living organisms, despite being innovative in several of its purposes, cannot be taken as recent. It derives largely from the cybernetic term, created in the early 1960s. At present, with the advancement of medicine, this term also encompasses technical healthcare monitors, implants, and prosthetic materials integrated to the body to overcome some physiological limitations and even create superhuman responses as in the senses of hearing and sight (Mehrali et al. 2018). With the development of these cybernetic products, another term emerged: cyborgs (short for “cybernetic organisms”). There are also lines of research that associate living tissues within intricate nanowire-based materials to create hybrid synthetic tissues, half-synthetic and half-organic. They are called cyborg organic constructs (cyborganics) (Dai et al. 2018).

Proper integration between the material to be introduced and the human body should ensure stability, durability, and quality of performance. Therefore, the material should have sufficient flexibility and biocompatibility to adapt to body characteristics without resorting to bodily movements (Simon et al. 2013; Zhou et al. 2017; Tamayol et al. 2016). The applications of cybernetic prosthetics become more numerous and rapidly expanding at the same speed as new nanomaterials and bio-electronic products are developed. Some examples of implants will be developed to treat still irreversible problems such as retinal implants that bridge the optic nerves with the brain region that interprets the signs, paraplegia (spinal cord implants), and deafness (ear implants that reestablish the auditory capacity). There is already a

product successfully developed in vivo that is characterized by the union of inanimate electronics with living tissues to create cyborganic transplants (Mehrali et al. 2018). In addition to allowing replacement parts for those physically disabled, the prostheses can also be used to enhance human capabilities beyond normality. It is hard to imagine the limit of this improvement in abilities that can range from an increase in hearing to even the creation of cyborganic muscle tissue with high efficiency and endurance.

Cyberorganics represent the evolution of science of materials, medicine, tissue engineering, and electronics. The breaking of a paradigm is evident when imagining the creation of hybrid tissues and hydrogel carriers made from a combination of inanimate and biological matter. These devices can be classified as permanent hybrid organs or biodegradable which may be of nanomaterials or hydrogel carriers embedded with biological matter (Mehrali et al. 2017). In short, the great difference between the two classes is that the permanent hybrid organs, as the name itself says, do not undergo purposive biodegradation of the nonorganic part. On the other hand, the biodegradable class uses hydrogel carriers and nanomaterials as a matrix of organic material until it reorganizes and assumes its function in the local tissue.

An example of the application of this technology can be observed in the study that carried out the maturation of stem cells inside a web of silicon nanowires (Tian et al. 2012). Silicon nanowire field-effect transistor (FET)-based nanoelectronic biomaterials have the capability of recording both extracellular and intracellular signals with subcellular resolution. The synthetic process can be described in three main steps: In the first, silicon nanowires were deposited randomly or in regular patterns for single nanowire FETs (Fig. 14.6 step A). Then, individual nanowire FET devices were lithographically patterned and integrated into free-standing macroporous scaffolds (Fig. 14.6 step B), the nanoelectronic scaffolds, nanoES, which simulate the extracellular matrices with high porosity and biocompatible flexibility. NanoES were then combined with synthetic or natural macroporous extracellular matrices providing (i) electrical sensory function and (ii) nanoES with biochemical environments suitable for tissue culture. Finally, cells were cultured within the nanoES (Fig. 14.6 step C) to yield 3D hybrid nanoelectronic tissue constructs. This technique was extended to the development of tissue embedded in nanoelectronic sensors, for example, human aortic smooth muscle cells (HASMCs) were cultured on 2D mesh vascular nanoES (Fig. 14.6D). The cells of hybrid nanoES/HASMC were able to produce the contractile protein in smooth muscles, α -actin.

The interest in creating/retrieving lost or damaged tissues has grown stronger through the advances of cyborganics (Fig. 14.7). Artificial ear was created, which was capable of auditory sensing in the radio-frequency range. This device was generated by a 3D printer using the raw material Ag nanoparticles and cartilage cells embedded within an alginate hydrogel matrix. The product of this mixture was deposited into a bioelectronic hybrid ear, where 3D structural matrix of the ear underwent biooxidation and the cartilage cells retained the ear-shaped morphology and developed with functionality (Mannoor et al. 2013).

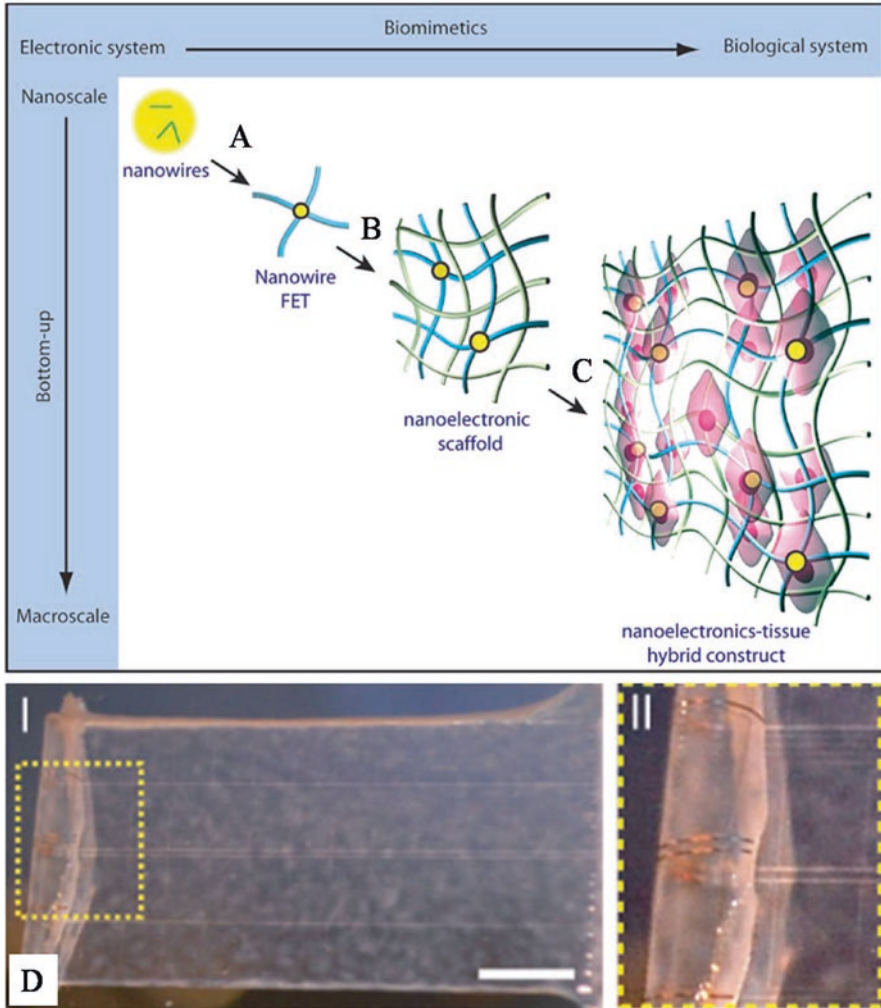


Fig. 14.6 Integrating nanoelectronics with cells and tissue. Three biomimetic and bottom-up steps have been designed: (A) patterning, metallization, and epoxy passivation for single nanowire FETs; (B) forming 3D nanowire FET matrices (nanoelectrical scaffolds); (C) incorporation of cells and growth of synthetic tissue via biological processes. (D) Synthetic vascular construct enabled for sensing. (I) Photograph of a single HASMC sheet cultured with sodium L-ascorbate on a nanoES. (II) Zoomed-in view of the dashed area in (I), showing metallic interconnections macroscopically integrated with cellular sheet. Note Fig. 14.6 A–C. Yellow dots, nanowire components; blue ribbons, metal and epoxy interconnects; green ribbons, traditional extracellular matrices; pink, cells. (Adapted from Tian et al. 2012)

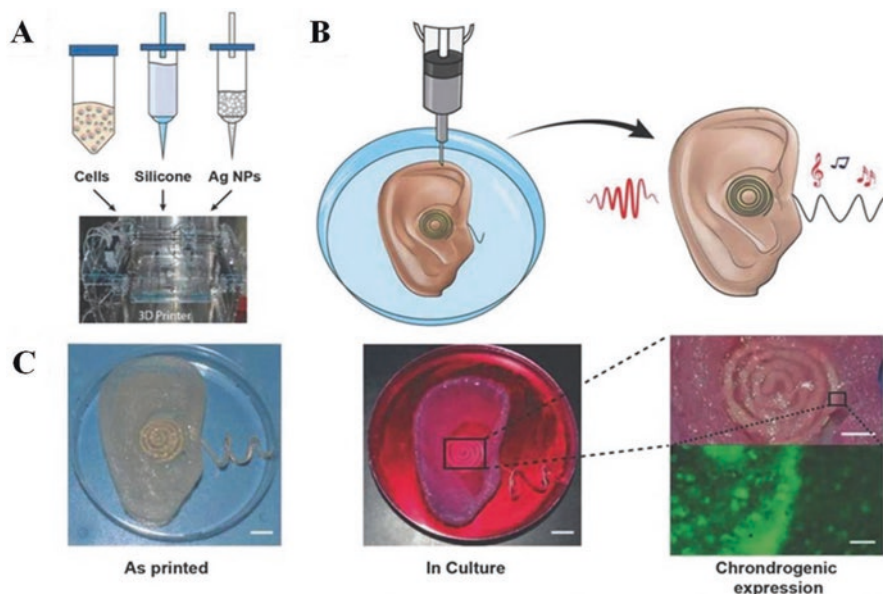


Fig. 14.7 Development of a cyborg ear. (a). Organic and synthetic constituents employed (b). Demonstration of the technique of 3D printing of the artificial ear (c). Images of the printed ear before and after culturing and highlighting the evaluation of chondrogenic cell viability (Mannoor et al. 2013)

14.6 What Are the Next Steps?

We can undoubtedly say that the field of nanomaterials has no limits and that predicting future events is bordered by a utopia. However, some predictions related to devices that are already produced are more feasible. Smart dressings are expected to integrate even more active markers and substances (drugs, growth factors, and even stem cells) into the same device. Measuring the concentration of a circulating drug in plasma or in a specific tissue in which it might accumulate would allow real-time monitoring of therapeutic regimens and toxic events. Sensors to identify the type of microorganism that colonizes a wound or diagnose cancers will be developed in the near future. However, it will be necessary to improve the nanomaterials and miniaturize the sensors so that the lab-on-a-chip devices perform the genetic sequencing. There is still a need to make nanoelectronic devices even smaller, to reduce production costs, and to conduct more clinical studies with surface dressings and implanted sensors. In this way, the products can be popularized and commercially viable. The tendency to universalize remote monitoring is a reality of modern medicine, which will reduce the medical costs of moving patients and mobile health services, face-to-face consultations, and variations in the patient's health status, which has difficulty receiving the adequate presential attendance of the medical team.

Cyborgs will revolutionize various areas of modern medicine, such as transplantation and implanting organs and tissues made from nanomaterials or using them as a matrix for stem cells. The cinematic idea of having a robotic member built of nanomaterials and coated with human tissues, with sensitivity to heat, pain, and touch, is ever closer. These “biotechnological tissues” will allow to reestablish lost functions as in blind individuals, in paraplegic, or in the queue of organ transplants, as well as to create tissues with superhuman responses. These super responses are fantastic: imagine seeing objects at great distances, performing facial identification of people through smart nanosensors placed in the eyes, or creating super athletes with high-resilience muscles. Let us imagine an individual with a family history of lung cancer with poor prognosis; he would clearly be a perfect candidate to replace this natural organ with a cyborg lung, 100% constructed with nanomaterials and with zero risk of tumor growth. Autoimmune diseases such as rheumatoid arthritis, Hashimoto’s disease, and type 1 diabetes would also be controlled without major problems by replacing the biological tissue (antibody antigen) with highly functionalized nanomaterials.

So, what are the next steps? Different answers can arise, but one thing is certain, we will certainly be surprised and experienced with this new industrial revolution!

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