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Biosensing Technologies for Medical Applications, Manufacturing, and Regenerative Medicine

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Abstract

Purpose of Review The review covers biosensing technologies, their impact on healthcare, and future applications.

Recent Findings Advancements in biosensing technologies that can detect a wide range of bioanalytes at reduced costs are described.

Summary Biosensing technologies are becoming essential for advancing human healthcare. A biosensor detects a specific biological analyte and monitors its function within a biological milieu; this technology has gained the attention of many researchers worldwide owing to its importance in medical applications. Noninvasive, cost-effective, high-resolution, and portable biosensors can be extensively utilized; however, there remain numerous challenges to overcome, including real-time, in vivo monitoring of organ functionality in high-risk patients. Herein, we review biosensors, their fabrication, and their various uses. Additionally, we provide an overview of their role in medical applications such as cardiovascular disease, diabetes, wound healing, cancer diagnosis, and prosthesis fabrication. Furthermore, the applications of biosensing technologies in regenerative medicine such as biomanufacturing procedures, organ-on-a-chip technologies, and indicators of therapeutic efficacy are discussed. Finally, an overall perspective of the field and its potential future directions are considered.

Keywords Biosensor · Regenerative medicine · Noninvasive · Biomanufacturing · Biomonitoring · Therapeutic efficacy

Introduction

The use of biosensors for medical technologies has increased exponentially [1•]. Biosensors can detect specific biological analytes and monitor their functions within a biological milieu. Despite the tremendous improvements in biosensor technologies, there remain challenges to overcome as more ambitious medical goals necessitate noninvasive, small-sized, portable, and cost-effective sensors. Many researchers worldwide are working to devise improved, highly sensitive, and rapid-response biosensors for medical applications.

Regenerative medicine is a unique approach to managing disease owing to its interdisciplinary nature that comprises tissue engineering [2, 3], cell therapies [4], biomaterial sciences, and biofabrication [5•]. Biosensing can play a role in regenerative medicine through multiple aspects including biomanufacturing/product release criteria, organ-on-a-chip technologies, and indicators of therapeutic efficacy. Noninvasive, cost-effective, high-resolution, and portable biosensors may be utilized for in vivo monitoring of organ functionality in high-risk patients.

Herein, we review the concept of biosensing as well as biosensor mechanisms and characteristics. The applications of biosensors in various fields such as cancer diagnosis, cardiovascular disease, and wound healing are discussed. Furthermore, we review the important role of biosensors and their applications in manufacturing as well as regenerative medicine. We provide a broad perspective of the biosensing field based on the current state of the art technologies, real-life medical applications, and potential future applications.

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Biosensing

Beside an electronic system, the two essential biosensor components are the bioreceptor and transducer. A variety of techniques and approaches are applied to enhance the functionality of these components to boost biosensing ability and sensitivity. Figure 1a depicts different biosensor architectures including different bioreceptors and transducers.

Bioreceptors

The bioreceptor typically comprises a layer of macromolecules that specifically recognize a biological analyte. In that sense, bioreceptors can generally be divided into two overarching categories: catalytic-based (that usually rely on enzymes) and affinity-based (that largely use proteins, nucleotides, and antibodies) [6•]. Such interactions produce a measurable change in electrical charge or in a visually observed

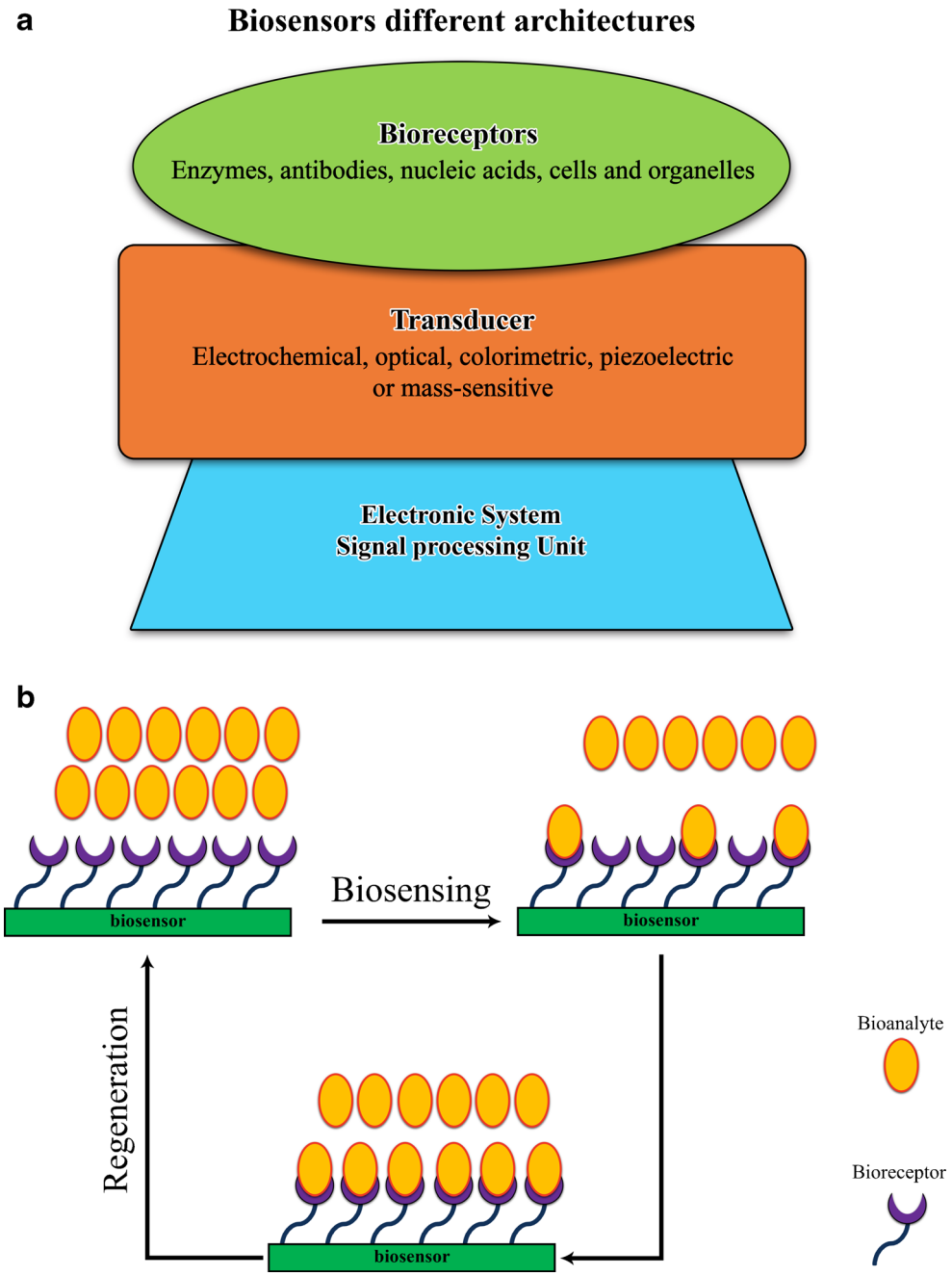

Fig. 1 **a** Biosensors include three critical components: the bioreceptor, the transducer, and the signal processing unit. Designing a biosensor requires the selection of an appropriate and relevant bioreceptor and transducer. The bioreceptor typically comprises a layer of macromolecules such as enzymes, antibodies, or nucleic acids that have specific affinities to the biological analytes of interest. The transducer converts biosensing events into measurable parameters, i.e., the sensory signal. Biosensor can have different types of transducers including optical, electrochemical/electrical, piezoelectric, and colorimetric. The signals are monitored using a signal processing unit. **b** Biosensors function via bioreceptors that are immobilized, generally, through appropriate linker molecules. Regeneration techniques, such as enthalpic interactions, entropic interactions, as well as chemical, thermal, and electrochemical regenerations, are being devised to prolong the usage time of biosensors. This ensures the continued high performance and sensitivity of the biosensor over a long period of operation

colorimetric endpoint at the sensor-transducer interface [1•]. This characteristic provides a bioreceptor with both the specificity to interact with a particular biomolecule of interest as well as the flexibility to act as an artificial, multifaceted sensor of biological signals that are not readily detected or bound using chemical or other nonbiological-based receptors.

A critical unmet need in regenerative medicine is the ability to measure intratissue biological activity that sustains the engineered tissue's viability, such as cell signaling and angiogenesis, without damaging the construct in the process [7]. In that respect, bioreceptors must be designed to bind factors related to cellular growth, maintenance, and adhesion, as well as microenvironmental components that include minerals and vital gases (namely oxygen). Moreover, they must also be able to detect markers of adverse cellular events such as oxidative stress. Lastly, they must be free of contamination with unrelated reactants yet be able to sustain long-term monitoring while tissue construction/biofabrication is underway [7].

Enzymes are used as bioreceptors because of their specificities for target molecules of interest combined with their ability to amplify the detection signal owing to the reaction that ensues upon binding [8]. The enzymes themselves are conventionally immobilized by cross-linking, covalent binding, or entrapment in gels or membranes, although these methods do not necessarily produce reliable bonds (particularly for tissue engineering applications) [9, 10]. Alternatively, biomolecule immobilization on electropolymerized films to entrap enzymes in specific polymers offers a more durable method, particularly for tissue-engineered constructs where such enzyme-binding techniques may be applied to hydrogels [10].

Antibodies are used in bioreceptors in their capacity as immunosensors (in contrast to other nonengineering-related uses such as pathogen detection). They are sometimes preferred owing to their relatively strong binding capabilities as well as their specificities elicited by exact antibody-antigen matching [11]. Antibodies are usually linked to the surface of transducers through covalent bonds such as amide, ester, or thiol bonds. However, because their interactions are irreversible and relatively strong, they are not best suited for tissue engineering applications that require a long-term and reversible sensor; moreover, changing pH and temperatures within constructs can render antibody-based bioreceptors highly variable in terms of their binding affinities [9].

Nucleic acid detection using biosensors is also a growing need for purposes of genetic screening and mutation detection in patients with certain diseases. While there have been important advances in devising bioreceptors using DNA to bind to other nucleic acids of interest, the applicability of these types of bioreceptors for tissue engineering purposes appears to be minimal to date. However, the development of nucleic acid-based receptors that can detect non-DNA/RNA molecules (known as *aptamers*) may introduce exciting opportunities for tissue engineering as they are improved and made capable of binding molecules such as metal ions and microenvironmental components while simultaneously enhancing their detection via fluorescence-based or electrochemical modalities [12•].

Cells and organelles are also used as bioreceptors for tissue engineering purposes. Similar to antibodies, using living cells for sensing and binding environmental factors provides much-desired selectivity, specificity, and prompt bioresponse. However, the fact that cells, by their very nature, comprise a complete set of surface receptors, in addition to the fact that specific cell types can be selected based on the desired engineered tissue of interest, makes cell-based bioreceptors uniquely versatile for regenerative medicine studies. They can be used to detect or interact with single- or multicell structures as well as constructed tissues [13]. As cells comprising bioreceptors have distinct uses from those in standard cell cultures, they are usually immobilized using extracellular methods that include either uniform or integrated chemical coating with the surface topology; these vary depending on the nature of the substrate and the type of transducer [14].

Emerging technologies have contributed to devising novel biosensing methods, including so-called biomimetic receptors exemplified by the *molecular imprinting* technique to create artificial interacting surfaces [8, 15]. Such technologies will herald more sensitive and relevant methods to further improve the quality and reliability of bioreceptors going forward.

Each type of bioanalyte can be detected using a variety of bioreceptors, and there are no guidelines by which to optimize the sensitivity and performance of such receptors before their fabrication. Therefore, researchers apply numerous biosensor architectures (bioreceptor and transducer) to detect bioanalytes. In each specific system, the composition of each bioreceptor must be determined appropriately. For example, in most enzymatic glucose biosensors, glucose oxidase is used. Assuming that each unit of this enzyme can oxidize 1.0 μmol of β-D-glucose, a simple calculation shows that 1 million units of the enzyme can oxidize 1 mol of glucose. It is worth noting that the normal blood sugar level for a healthy human is 0.4–0.78 mmol/dL; this implies that biosensors are prone to reduced performance and sensitivity over time. To maintain high-quality performance, the relevant biosensor components must be replaced regularly. However, this may increase the cost of biosensing to a point where it is unaffordable. Therefore, biosensor regeneration is critical for both maintaining the device's sensitivity for long-term usage and lowering costs. Many different regeneration techniques such as enthalpic and, entropic interactions as well as chemical, thermal, and electrochemical regenerations have been used for various biosensors [6•]. Figure 1b shows the process of detection and the effect of regeneration on biosensing.

Transducers

The role of the transducer is to convert biosensing events into measurable parameters, i.e., the sensory signal. Various types of transducers have been applied for biorecognition; many are based on optical, electrochemical/electrical, piezoelectric, and calorimetric measurements.

An electrochemical transducer measures the current produced from oxidation and reduction reactions as a result of the interaction of the sensory analyte with the biosensor [1•, 16]. This interaction can alter the electrical resistance and, hence, the conductivity of the film [1•, 17–22]. Electrochemical biosensors are divided into four subcategories based on the nature of the electrochemical changes: amperometric, potentiometric, impedance, and conductometric [1•, 17–24]. The current generated by the sensor can be correlated with the concentration of the bioanalyte or its rate of production and consumption. These sensors have shown high sensitivity, low cost, and simplicity of measurement [22, 24].

Optical biosensing is one of the most commonly used analytical schemes and has diverse applications in the field of medical diagnostics. A variety of optical contrasts (e.g., absorption, fluorescence, surface-enhanced Raman scattering, and refraction) are used to detect optical changes produced by the interaction between the target of interest and the biological recognition element [25–30].

Fluorescence is the most frequently used optical contrast method in biosensing [25, 26]. The spectral shift of the emission, the decay time of a specific emission signal [28], and the change in the emission amplitude can all be used to gain information about molecular interactions, since these processes depend upon the excited state of the molecules and their local molecular environments [25–27]. Furthermore, monitoring the electromagnetic radiation energy often identifies any changes in the local environment surrounding the analyte, its intramolecular atomic vibrations, or its new energy level formations (i.e., Raman, infrared, or terahertz absorption spectroscopies) [28, 29].

Other optical transducers may rely on a change in the polarization or phase of emitted or reflected light from the molecules. The surface plasmon resonance of materials can also be quantified for biosensing. A plasmon is described as the collective vibrations of the electron cloud in conductive materials such as gold or silver nanostructures; irradiation frequency that is matched to these vibrations is referred to as *surface plasmon resonance*. Metal and gold nanoparticles show surface plasmon resonance in the visible part of the electromagnetic spectrum. The incident angle of the surface plasmon resonance depends on the refractive index of the medium defined by local mass density on the metal surface and is used as a sensory transducer [30].

Colorimetric detection involves measuring the color products that result from the interaction between the biological recognition element and the sensory analyte of interest; these techniques are considered label-free approaches. The color change is then observed by the naked eye or measured using an optical sensing instrument [31].

Piezoelectric transducer biosensors or mass-sensitive sensors use piezoelectric crystals such as quartz crystals for detection [32]. Piezoelectric materials produce an electric signal in response to mechanical forces. The crystals are made to vibrate at a specific frequency (depending on the crystal's type) by an applied electric signal. Biomolecules that exhibit specific binding properties are anchored on crystals; upon the interaction of the biomolecules with the sensory analyte, the vibrational frequency shift of the crystal is detected.

Characterization

Biosensors are evaluated using certain critical parameters as follows: (1) measurement range, i.e., the maximum and minimum limits that a sensor is able to detect; (2) sensitivity, which is the ratio of the output change resulting from a given input change (another way to define sensitivity is via the slope of the calibration curve that is derived by plotting the output values against a range of input values); (3) response time, defined as the time required for the sensor to attain a certain steady-state output value in response to a fluctuating input; (4) accuracy, which is defined as the difference between the detected value and the actual amount and is classically determined as a ratio and provided as a percentage of the full-scale reading; (5) precision, which refers to the reproducibility of the measurement under similar conditions; (6) resolution, which refers to the smallest input change that is detectable by the sensor; (7) reproducibility, defined as the proximity of the output values when the same amount of input is provided to the sensor under similar conditions; (8) limit of detection (LOD), an important parameter representing the minimum amount of an analyte detectable by the biosensor; and (9) hysteresis, which refers to the situation when in some sensors, the input-output behavior follows a different nonlinear trend depending on whether the input is increasing or decreasing.

Biosensors for Medical Applications

Biosensors for Cardiovascular Applications

Cardiovascular diseases are the primary cause of death worldwide, and their timely detection may save large number of lives annually. Biosensors are being used for currently known cardiac markers such as cardiac troponin (both T and I), C-reactive protein (CRP), creatine kinase (CK), myoglobin, and others. Cardiac troponin is one of the most important biomarkers for diagnosing myocardial infarction [33]. Cardiac

troponin I (cTnI) was detected using silicon nanowire field-effect transistors [34••], in which the electrical performance and sensing area of the device were enhanced by silicon nanowires. Antibodies were immobilized on the nanowires, and the device produced an LOD of 5 pg/mL. Nonspecific binding tests confirmed the high specificity of the system for cTnI. A double-layer AlGaN/GaN transistor was used to detect cTnI [35]. The system was able to detect target proteins in physiological solutions; the biosensor showed a wide range of detection (from 6 pg/mL to 148 ng/mL with a response time of 5 min) in purified protein solutions and clinical serum samples. Cardiac troponin T (cTnT) was also detected using a zinc oxide (ZnO) electrode, a flexible and disposable electrochemical sensor [36]. The system included porous flexible polyimide substrate and ZnO sensing electrodes and employed the electrochemical impedance spectroscopy (EIS) for detection. The pores allowed the biosensor to detect a low volume of fluid, and the biosensor had an LOD of 1 pg/mL. CK is an enzyme that catalyzes the transfer of high-energy phosphate from creatine phosphate to adenosine triphosphate and is rapidly released upon muscle damage [33]. Among the three CK isoenzymes, CK-myocardial band (CK-MB) is primarily produced by the myocardium and is highly specific to cardiac injury. A bi-enzyme biosensor that detects glucose oxidase and hexokinase was devised to detect CK and glucose; the system was designed to measure the rate of ATP production by CK.

Printing technologies provide promising opportunities for electronic devices [37, 38] and have been employed in biosensor technologies. For example, CK-MB was detected using a biosensor that used quantifying enzymes [39]. The phosphorylated form of creatine (Pcrea) was immobilized on a screen-printed gold electrode; at low potentials, the Pcrea acts as an electroactive species where its interaction with the enzyme produces a change resulting in CK-MB detection based on the redox properties of Pcrea. This sensor also required characterization by EIS and cyclic voltammetry (CV) to measure the redox potentials.

In coronary artery disease, major arteries responsible for blood supply to the heart are hardened and narrowed. Elevated CRP levels due to acute inflammation are considered an additional risk factor in individuals at risk of developing coronary artery disease. A carbon nanofiber-based biosensor was previously used to detect CRP; these nanofibers were grown using plasma-enhanced chemical vapor deposition. The biosensor showed a detection limit in a clinically relevant range of 11 ng/mL [40]; however, the detection mechanism of the biosensor was based on the CV and EIS. The reduction in redox current in CV and the charge transfer resistance in EIS were changed upon CRP detection. Another CRP biosensor using DNA aptamer-conjugated peripheral blood mononuclear cells was fabricated with an LOD of 8.4 ng/mL [41]. Moreover, an electrochemical immunosensor for CRP was reported using gold-based working electrodes. Anti-human CRP antibodies were immobilized on the working electrode and labeled with horseradish peroxidase [42], and the system was used in conjunction with ELISA. This sensor had an LOD of 2.2 ng/mL in serum samples.

Biosensors for Diabetes

Diabetes is a major chronic metabolic disorder with more than 400 million individuals afflicted worldwide. Uncontrolled chronic hyperglycemia leads to the damage and failure of multiple organs, causing severe morbidity and mortality [43]. Tight control of blood glucose levels can decrease the frequency and severity of these complications [44, 45]. In 1962, Clark and Lyons introduced the first biosensor for measuring glucose levels by placing the glucose oxidase enzyme on an oxygen electrode [46]. With the production of the first self-monitoring blood glucose (SMBG) device using glucose dehydrogenase enzyme in 1987 [47], the management of diabetic patients was revolutionized. Nowadays, SMBG plays a key role in the management of diabetes, especially type I [48, 49]. Most of these devices use either a ferricyanide or ferrocene mediator [50]. Multiple fingertip pricks for SMBG and the injection of a pre-calculated dosage of insulin is the current method for management of type I diabetes. As this can be painful and inconvenient for patients, alternative minimally invasive and noninvasive methods are being widely investigated. The most common noninvasive approaches are optical or transdermal methods using tears or saliva as the glucose measurement source [51, 52].

Continuous glucose monitoring is a major achievement in diabetes management and was first introduced by needle-type enzyme electrode glucose biosensors for subcutaneous implantation [53]. These devices measure the interstitial fluid glucose level using an enzyme-coated wire inserted into the subcutaneous tissue. Readings are later calibrated with capillary glucose measurements. These devices showed improved and efficient glycemic control in diabetic patients, providing timely notifications regarding high or low blood glucose levels [54]. Today's advances in biosensors open the possibility for an artificial pancreas as well as closed-loop control of blood glucose in diabetes, including a continuous glucose monitor, control algorithm, and insulin infusion device; these are considered ultimate goals of diabetes treatment. There have been many efforts in this field during the past three decades [55], and while systems have been evaluated thoroughly in hospital settings [56], a wearable artificial pancreas for outpatient management is not yet commercially available. Recent studies have shown the effectiveness and safety of these portable platforms in reducing periods of hypo- and hyperglycemia in diabetic patients, although challenges remain to be overcome [57].

Biosensors for Wound Healing

Wound healing is a complex process that requires the cooperation of many different tissues and biological pathways [58]. Failure of these processes to occur in a timely and orderly fashion leads to chronic wounds, potentially placing a heavy financial burden on healthcare systems [59]. Such failures involve many factors, such as uncontrolled inflammatory processes, bacterial infections, and disruptions in the acidic pH of the skin, oxygen levels, and matrix metalloproteinases (MMPs) [59, 60]. Since regular assessment is critical in chronic wound management [59], biosensors are being actively investigated to allow clinicians to closely monitor the healing process. A wearable pH sensor was produced by integrating screen-printing electrodes with Ag/AgCl-conductive ink [61]. The reference and working electrodes were electropolymerized with polyvinyl butyral polymer and polyaniline, respectively, and the sensor monitored the pH within a range of 4.35–8.00. Mesoporous polyester particles containing pH-sensitive dyes were incorporated into alginate-based microfibers to create a pH-sensitive wound dressing [62]. Flexible fibers were attached to a transparent medical tape, and using a smartphone, photographs were acquired for colorimetric measurements. The biocompatibility of these alginate-glycerol fibers was also shown by co-culturing them with human-derived keratinocytes. A wireless optical sensor for pH was fabricated by immobilizing a pH indicator dye on a commercial dressing and then integrating the pH-sensing layers with an optoelectronic probe [63]. This wireless sensor detected pH changes in the range of 6–9, and by using radiofrequency identification (RFID), was able to transfer the measurements to a computer or smartphone for close monitoring of the wound. A smart bandage incorporated with an oxygen sensor and wireless capability was designed and 3D printed [64•]. Notably, using thermo-responsive microparticles carrying drugs and embedded in hydrogel, a smart bandage was created with a wireless drug delivery system [65]. An elastomer material was used for printing the bandage, and an electrochemical galvanic oxygen sensor was constructed with silver and electroplated zinc as electrodes on parylene C. Gold and chromium were used to create a flexible microfabricated heater that shrinks the microparticles, thereby releasing the drug.

Biosensors for Cancer Applications

The application of biosensors in cancer diagnosis holds great potential. Cancer is the second leading cause of death in the USA [66], and considering that the concentration of biomarkers in the early stages of tumor development is very low, the sensitivities of the biosensors or their LODs would be important for early diagnosis [67]. The early detection of cancerous cells before they metastasize generally produces better treatment results and saves lives. Therefore, there is a great demand for specific, accurate, and rapid-response biosensors in oncology.

Breast cancer diagnosis has improved tremendously with recent biosensor advances [68]. Breast cancer is the most common malignancy among women in the USA after skin cancer and is the second deadliest after lung cancer [69]. Traditional methods to diagnose breast cancer including mammography, magnetic resonance imaging, and enzyme-linked immunosorbent assays (ELISAs) have shown remarkable results in breast cancer diagnosis; however, many false negative or positive outcomes continue to occur, and the adverse effects of some invasive techniques necessitate new highly sensitive, reliable, and noninvasive methods for detection and assessing prognosis [68]. Several important biomarkers such as human epidermal growth factor receptor 2 (HER2), *BRCA1*, carbohydrate antigen 15-3 (CA15-3), and miR-155 have been targeted for detection by biosensors. HER2 is one of the most common tumor markers, and molecular electronics (namely, DNA-based) have been devised to detect this protein [70••]. Chemical detection of HER2 is conducted using a DNA-generated redox current. The electrochemical current is generated by the reaction of DNA phosphate with molybdate. Previously, this current was proportional to the HER2 concentration in its clinically relevant range (0.01–5 ng/mL with an LOD of 5 pg/mL); the detection range was later enhanced to 1–100 pg/mL with an LOD of 0.047 pg/mL [71].

A label-free electrochemical DNA biosensor was also constructed to detect *BRCA1* [72]. The sensor was based on a zwitterionic low-fouling peptide in a self-assembled monolayer and relied on electrochemical impedance spectroscopy. The system produced a linear detection range between 1.0 fM and 10.0 pM, with an LOD of 0.3 fM. CA15-3 was also successfully detected using a surface plasmon resonance sensor. Gold/zinc oxide films were used to enhance the sensor's performance, and a range of concentrations between 0.0125 and 160 U/mL was detected, with an LOD of 0.025 U/mL [73]. Biomolecule-based biomarkers such as microRNAs also have been detected using biosensing technologies. An electrochemical biosensor for miRNA-155 was devised that exhibited a sensitivity of 10 aM to 1.0 nM, with an LOD of 5.7 aM, in human serum samples [74]. Biosensors that detect biomarkers in other types of cancer have also been successfully fabricated, such as for carbohydrate antigen 19-9 (CA19-9), a biomarker for pancreatic, colon, and lung cancers [75]. A thin-film sensor was produced using gold electrodes, polyethyleneimine, and carbon nanotubes [76]. After absorbing the target analyte (i.e., CA19-9) with a supporting layer of chemicals using impedance spectroscopy, the sensor detected CA19-9 with high selectivity and an LOD of 0.35 U/mL. Other analytes such as glucose, ascorbic acid, and p53 were also detected. Moreover, antibody-quantum dot conjugates were used to amplifying the

signal in surface plasmon resonance to detect α-fetoprotein, carcinoembryonic antigen, and cytokeratin fragment 21-1 in clinical samples [67]. This system showed an LOD of 0.1 ng/mL for target concentrations ranging from 10^{-1} to 10^{3} ng/mL.

Artificial Limbs (Prostheses)

The ability of prostheses to restore the sensory capabilities of human skin would provide artificial limb users a more natural feel [77]. For instance, application of a pressure sensor on an artificial hand may adjust the amount of force applied by the fingers while holding objects. This may prevent the object from falling, owing to an underestimated applied force, or from breaking because of an overestimated force. A device comprising sensors for electromyography, temperature, and strain integrated into stimulation electrodes was fabricated [78], and its successful application was reported for prosthetic control with sensory feedback as well as for electrical muscle stimulation [79]. A myoelectric sensor using electromyography was fabricated and implanted into an amputee's residual muscles. Sensors placed at the source of muscle contraction demonstrated the ability to control 2 degrees of freedom in a hand and wrist prosthesis. Sensors were fabricated that mimic the tactile sensing properties of natural skin pressure [80]. These flexible, capacitive pressure sensors had a fast response time (< 1 s) and used an organic field-effect transistor and microstructured dielectric rubber that changes its electric properties upon sensing pressure pulses. These sensing devices are aptly referred to as "electronic skin."

Biosensing for Regenerative Medicine

Biosensors provide a controlling platform for other technologies to enable real-time monitoring of the behavior of the system for enhanced efficiency. There are various applications of biosensing technologies in regenerative medicine, including biomanufacturing (such as for product release criteria), organ-on-a-chip technologies, and indicators of therapeutic efficacy.

Regenerative Medicine Biomanufacturing

Biomanufacturing is a relatively new industrial approach of utilizing biological systems to produce commercially relevant biological products such as human tissues. Additive manufacturing such as 3D printing and other biofabrication strategies are used to manufacture industrial-scale bioproducts. Moreover, biomanufacturing facilities may use engineered cells to produce chemical or molecular production or may mass culture cells for organ fabrication. Such applications render biomanufacturing useful for various fields including healthcare, food production, and even agriculture. Controlling the quality and condition of the biological structure is critical for obtaining reliable products; this can be achieved using biosensing technologies. For example, electrochemical enzyme-based biosensors were used for the real-time measurement of metabolites in cell culture media [81]. Different metabolic analytes that reflect cell viability and density were monitored during U937 lymphoma cell incubation for over 88 h. Such sensors can enhance the biomanufacturing process, improve quality assurance, and reduce processing costs by determining the optimal time to replenish media during mass cell culturing. Furthermore, the engineered cells can help to produce metabolic products [82•]. However, this process is time-consuming and consists of laborious methods. Recently, genetically encoded biosensors were derived from small molecule-responsive transcription factors to provide a fluorescent readout that reflects the intracellular amount of a target metabolite. This illustrates the potential for high-throughput techniques to evaluate the quality of genetic variants or product conditions.

Organ-on-a-Chip Technologies

Organ-on-a-chip technologies have introduced a new biomedical research avenue by utilizing microfluidic equipment and organoids. Organoids are small cell clusters of a particular tissue type that may more closely replicate the behavior of normal tissues and organs. Organ-on-a-chip technologies are used for different applications and for assessing the response of organoids to drugs and other external stimuli [83]. The technology has advanced vastly by using biosensors for real-time monitoring of the behavior of microtissues and organoids. A novel microfluidic aptamer-based electrochemical biosensor was used to monitor damage to cardiac organoids [84]. The CK-MB biosensor was added to the microfluidic device, and the amount of secreted CK-MB was detected upon damage to the cardiac tissue that was constructed using embryonic stem cell-derived cardiomyocytes upon exposure to doxorubicin, a cardiotoxic drug, and the selectivity and sensitivity of the biosensors were tested. The biosensor showed an LOD of 2.4 pg/mL with a range of 0.01–100 ng/mL. The system did not show any change by adding albumin and glutathione S-transferase alpha, confirming the selectivity of the aptamer-based biosensor for CK-MB. Inkjet printing of transparent conductive electrodes for electronic applications, such as biosensors, has been achieved [85, 86]. Moreover, printing technologies eliminate the tedious requirement for multistep lithographic processes to build biosensors on microfluidic devices [87]. A cardiac microphysiological device was fabricated using 3D printers, and sensors were integrated into the microfluidic device using high-conductance, piezoresistive, and biocompatible materials. Contractile stresses inside cell incubator settings as well as

drug tests were monitored. Moreover, the printed electronics enabled researchers to use biocompatible materials to fabricate electronic devices (such as biosensors) instead of toxic materials [88, 89]. In another study, multiple organoid models were integrated into a multisensor system [90]. A physical, biochemical, and optical sensing platform was used for automated in situ monitoring of biophysical and biochemical parameters of organoids throughout the experiment. However, like many other biosensors, the system still requires CV and EIS, rendering it far from a portable technology.

Indicators of Therapeutic Efficacy in Regenerative Medicine

Biosensors for determining the efficacy of regenerative medicine-related therapies remain relatively unexplored, given that most outcomes are observed visually (e.g., a regenerated tissue or a healed wound) or functionally (i.e., improved sensory ability). However, there are therapeutic evaluation approaches in which biosensors may play an increasingly important role in the future. One such avenue involves therapies that indirectly alter the host's cellular/extracellular environment to elicit desired regenerative pathways. For example, the administration of cord blood-derived CD34-positive cells in mice that have been subjected to a stroke has been shown to promote neovascularization in the affected area in a manner that increased neuroblast migration [91]. Similar techniques have been used to replenish hematopoietic and immunological cells that were destroyed following myeloablative chemotherapy [92]. As with glucose sensors, one can envision the use of biosensors by patients who receive such therapies to self-monitor the presence of required growth factors in their bloodstream after undergoing treatment.

Nanotechnology can also be incorporated into biosensors that monitor stem cell differentiation status prior to their transplantation for therapeutic purposes [93]. For example, the technology allows for measuring small cellular surface proteins and secreted neurotransmitters to confirm the differentiation of stem cells into dopamine-producing neural cells prior to their implantation into patients with Parkinson's disease [94].

Such examples provide a glimpse into the future uses of biosensing in the application and monitoring of regenerative medicine therapies in patients, including biosynthesized tissue

Table 1 Different applications of biosensors, popular bioreceptors, and transducers as well as current or future impact of biosensors

Application	Bioanalyte examples	Common bioreceptors	Common transducers	Current or future impact of biosensing technologies
Cardiovascular	cTnT/I, CRP, CK-MB, myoglobin	mAb for cTnT/I, anti-human CRP antibodies, hexokinase	Electrochemical, optical	Early detection of cardiomyocyte ischemia and infarction—decreased morbidity and mortality in cardiovascular diseases
Diabetes	Glucose	Glucose oxidase	Electrochemical	Real-time monitoring of glucose levels in diabetics
Wound healing	pH, O_2, MMPs, cytokines, TNF-α	pH-sensitive dyes, CRP antibodies, mAb to TNF-α	Electrochemical, optical	Monitoring healing, preventing septic shock
Cancer	HER2, *BRCA1*, CA15-3, miR-155	Peptides, oligonucleotides	Electrochemical, optical	Early detection of cancer for high-risk patients and early detection of related or unrelated recurrence in cancer survivors reduce mortality and decrease the cost for mental and physical healthcare
Artificial limbs	Pressure and temperature	Piezoelectric crystal, pressure-sensitive rubber	Piezoelectric, calorimetric	Enabling patients with artificial limbs to have increased sensation capabilities, such as tactile texture or temperature
Biomanufacturing	Metabolism in cell culture media	Related to the manufacturing procedure	Electrochemical, optical	Automation of biomanufacturing that reduces the cost of human resources and optimizes performance
Organ-on-a-chip technologies	Related to the tissue on the chip	Related to the biomarker	Electrochemical, optical	Real-time monitoring of tissues/cells
Indicators of therapeutic efficacy in regenerative medicine	Related to the therapeutic procedure	Related to the therapeutic procedure	Electrochemical, optical, colorimetric	Real-time monitoring of therapeutics efficacy

cTnT/I cardiac troponins T and I, *CRP* C-reactive protein, *CK-MB* creatine kinase-myocardial band, *mAb* monoclonal antibody, *MMPs* matrix metalloproteinases, *TNF-α* tumor necrosis factor-α

preparation and self-monitoring post treatment. The advent of improved technologies and stem cell-related applications will provide for novel applications of biosensors by physicians and patients alike. In addition to biosensing technologies, bioprinted drug delivery arrangements have advanced dramatically [95]. This can facilitate fabrication of comprehensive monitoring/controlling systems using bioprinted drug delivery units attached to the biosensors. Table 1 summarizes the applications of biosensing technologies, common biosensor architectures (bioreceptors and transducers), as well as their current or future impacts.

Conclusion, Future Directions, and Perspectives

Advances in fabrication technologies such as 3D printing, as well as the integration of other electronic devices with biosensors, have opened new horizons in biosensing technologies. Nanomaterials such as carbon nanotubes and other nanoparticles that enhance selectivity and sensitivity are also being incorporated into different types of biosensors. Taken together, tremendous efforts are being exerted globally for the use of biosensing in numerous medical applications, including regenerative medicine. Nevertheless, additional research is required to develop reliable, noninvasive, cost-effective, and portable devices. Portability is critical for more sophisticated applications such as real-time monitoring of transplanted human organs or cardiovascular system functionality in a patient with high risk of cardiovascular disease. Notably, biosensors must provide a platform to detect essential biomarkers individually or collectively in an accurate and noninvasive manner. Therefore, we envision the field shifting towards the development of comprehensive personalized monitoring/controlling systems that are portable, affordable, and noninvasive for patients with specific needs. Smart controlling/monitoring systems integrated with a drug release part and biosensing capabilities will likely become more available with the advancement of portable biosensors and smart drug delivery systems. These developments may help personalize medicine in the future by enabling tailored and specific treatments for each individual. Furthermore, biosensing technologies enable the early detection of many biomarkers of numerous diseases. They can also reduce the costs of healthcare by avoiding expensive invasive procedures. For example, early detection of breast cancer biomarkers can save lives by preventing metastasis. Moreover, breast cancer survivors can use implantable biosensors for early detection of related or unrelated recurrences. Ultimately, prevention is always much less expensive than treatment. Therefore, biosensing technologies may also be used as a foundation of preventative medicine, thus having the potential to alter care pathways and decrease costs.

Compliance with Ethical Standards

Conflict of Interest Ashkan Shafiee, Elham Ghadiri, Jareer Kassis, Nima Pourhabibi Zarandi, and Anthony Atala declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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