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REVIEW

Emerging Implantable Energy Harvesters and Self-Powered Implantable Medical Electronics

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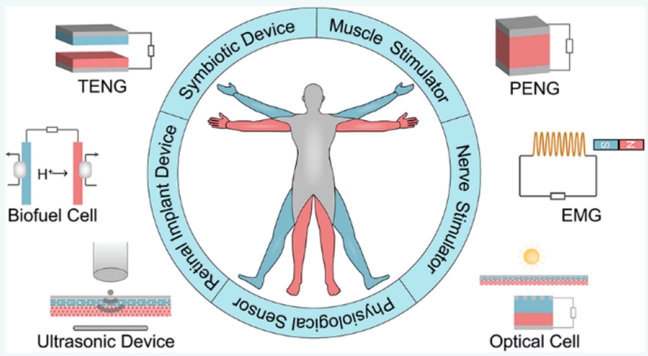
ABSTRACT: **Implantable energy harvesters (IEHs) are the crucial component for self-powered devices. By harvesting energy from organisms such as heartbeat, respiration, and chemical energy from the redox reaction of glucose, IEHs are utilized as the power source of implantable medical electronics. In this review, we summarize the IEHs and self-powered implantable medical electronics (SIMEs). The typical IEHs are nanogenerators, biofuel cells, electromagnetic generators, and transcutaneous energy harvesting devices that are based on ultrasonic or optical energy. A benefit from these technologies of energy harvesting *in vivo*, SIMEs emerged, including cardiac pacemakers, nerve/muscle stimulators, and physiological sensors. We provide perspectives on the challenges and potential solutions associated with IEHs and SIMEs. Beyond the energy issue, we highlight the implanted devices that show the therapeutic function *in vivo*.**



KEYWORDS: *implantable, energy harvesting, self-powered, medical devices, long-term, pacemaker, nerve stimulation, physiological sensor, biodegradable, bioelectronics*

Implantable medical electronics (IMEs) are utilized to diagnose, prevent, and cure diseases *in vivo*, such as cardiac pacemakers, spinal cord stimulators, and deep brain stimulators. To prolong the lifetime of the IMEs, researchers have invested enormous enthusiasm and energy to develop the power sources for them.[1−4] There are two primary strategies: one is enhancing the capacity of the power source used in IMEs, and another is harvesting power from organisms or the surrounding environment. Up to now, the limited capacity of power source has impeded the service life and performance of IMEs. Fortunately, abundantly available energy lies in our body during heartbeat, respiration, blood flow, and redox reaction of glucose. Then a variety of implantable energy harvesters (IEHs) that can obtain these energies have been proposed.[5−9] Mechanical types of IEHs, such as nanogenerators and electromagnetic generators, are fabricated to harvest energy from mechanical motions *in vivo*. Moreover, the optical and acoustic energies transferred from *in vitro* to *in vivo* by a transcutaneous approach are also be demonstrated, which is another promising method to solve the power limitations of IMEs. Chemical types of IEHs are enzymatic biofuel cells and ingestible galvanic cells, which can extract energy from the redox reaction of glucose and electrolytes in the gastrointestinal tract.

This review focuses on the research works that have realized animal tests. The attempt to put an IEH into a living animal can be traced back as early as 1963. Parsonnet *et al.* reported a piezoelectric device wrapped around the aorta of a dog, to harvest energy from the deformation of the aorta for powering a cardiac pacemaker.[10] After more than half a century of development, there are a lot of splendid achievements of IEHs and self-powered implantable medical electronics (SIMEs). In 2010, the biofuel cell was used to harvest energy from the glucose of rats.[11] In 2014, the triboelectric nanogenerator based on several polymer and metal films was used to obtain energy from the respiration of rat.[12] Then, various implantable medical electronics (IMEs) are becoming self-powered and operating *in vivo* for the long-term with the help of IEHs, including cardiac pacemaker, nerve/muscle stimulator, and physiological sensors (Figure 1).[13−15]

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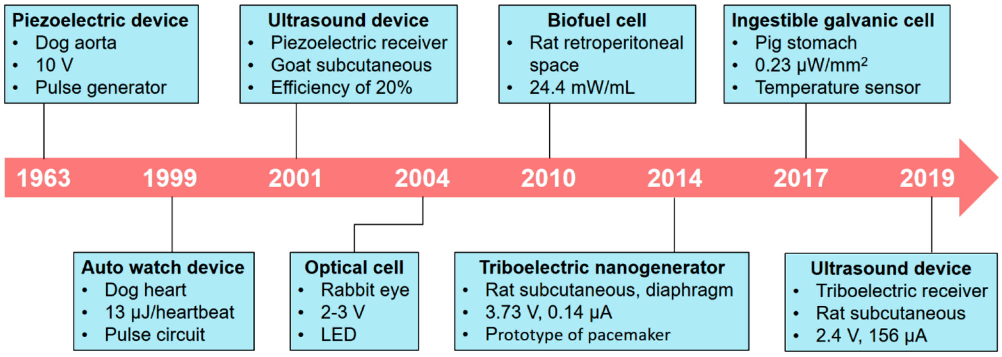

Figure 1. Milestones of IEHs and SIMEs which have realized animal tests. References: 1963,[10] 1999,[19] 2001,[20] 2004,[21] 2010,[11] 2014,[12] 2017,[22] and 2019.[23]

In recent decades, IEHs and SIMEs have experienced a period of rapid development. Some studies have reviewed them from different perspectives.[14,16,17] The main characteristics and research status of various IEHs have been summarized by them. For example, Shi *et al.* summarized six types of implantable energy harvesters that have been implanted into live models, particularly plants, insects, mollusks, crustaceans, and mammals.[9] Cosnier *et al.* have analyzed and summarized the evolution trends and research characteristics of biofuel cells implanted in the human body for powering artificial organs.[18]

In this review, we list the milestones of IEHs and SIMEs, and we summarize the research status of implantable energy harvesting technologies, from the aspects of mechanisms, output properties, application scenarios, and long-term *in vivo* performances. Furthermore, the different prototypes of SIMEs are classified and discussed. We label the various SIMEs in the organ or human diagrams and highlight them, which show the therapeutic function *in vivo*. Finally, we also discuss the challenges and provide the outlook for future IEH and SIME research focus and trends.

IMPLANTABLE ENERGY HARVESTERS

Nanogenerators. Nanogenerators (NGs) that can convert mechanical energy into electricity mainly include piezoelectric nanogenerators (PENGs) and triboelectric nanogenerators (TENGs).[24−29] Recently, the various NGs have been implanted in organisms for energy harvesting, sensing, and stimulating nerves and muscles.

Piezoelectric materials, such as zinc oxide (ZnO), lead zirconate titanate (PZT), and polyvinylidene fluoride (PVDF), will appear potentially different when deformed by an external force.[30−32] When an external force is applied to the piezoelectric material, an electric dipole moment will be produced due to the mutual displacement of anions and cations in the crystal. As a result, there is an internal piezoelectric potential difference in the direction of external force. PENG is based on the piezoelectric effect. Thus, a continuous alternative pulse current could be generated in the external circuit as the dynamic external force acting on the PENG (Figure 2).

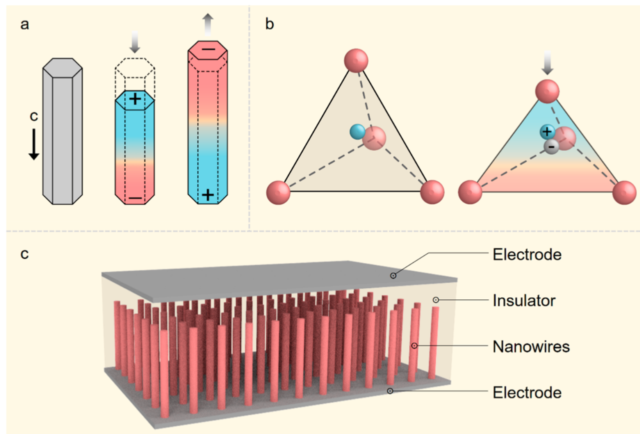

Figure 2. Schematic diagram of structures and mechanisms of PENG.

In 2006, Wang and his co-workers demonstrated a PENG based on ZnO nanowires to harvest tiny vibrational energy. The efficiency of the PENG is estimated to be from 17% to 30%.[33] In 2010, Li *et al.* realized an implantable PENG based on a single ZnO nanowire with a diameter of 100−800 nm and a length of 100−500 mm. This device was attached to the diaphragm and heart of a living rat, to harvest energy from breath and heart beating. The outputs are typically <50 mV and 500 pA.[34] In 2014, Dagdeviren *et al.* reported a kind of flake-like PENG based on PZT array to harvest energy from motions of the heart, lungs, and diaphragm *in vivo* and operation with the efficiency of ∼2%. The peak voltage is ∼4 V during the *in vivo* tests.[35] In 2016, Cheng *et al.* used a piezoelectric thin film based on PVDF to wrap around the ascending aorta of a pig, which can obtain an output power of 40 nW by harvesting the mechanical energy of the expansion and retraction process of the aorta *in vivo*.[36] In 2017, Jeong *et al.* realized a thin-film lead-free piezoelectric energy harvester driven by the heartbeat of a pig, which could generate power of 5 V and 700 nA.[37] In 2018, Wang *et al.* used poly(vinylidene fluoride-trifluoroethylene) nanofibers fabricated by the electrospun technique, which was implanted subcutaneous in the thigh region of a rat, and obtained the output of 6 mV and 6 nA.[38] Zhang *et al.* reported a kind of flake-like PENG that coupled implantable ZnO nanowire arrays with glucose oxidase. The thin device is 0.4 × 1.3 cm^2 in size and has a distinct interdigitated electrode structure.[39] Kondapalli *et al.* demonstrated a small PENG placed on valvular regions of the heart, to harvest energy from cardiac valvular perturbations and power a wireless sonomicrometry sensor.[40] In 2019, Han *et al.* reported a three-dimensional piezoelectric microsystem based on PVDF film, which can be used to harvest *in vivo* mechanical energy.[41]

Biocompatibility is one of the most pressing challenges of for PENG implantation. For example, PZT is a widely used

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piezoelectric material, but it is toxic. Thus, some biocompatible encapsulation materials such as polyimide or SU-8 passivation epoxy must be introduced.[35,42] ZnO and PVDF have excellent biocompatibility. However, the outputs of the implanted devices based on them are lower than PZT devices, which are at a magnitude of millivolt and nanoampere.

The triboelectrification effect appears at the interface between two different contacted dielectrics, which is quite common in our daily life. TENG relies on the coupling effects of triboelectrification and electrostatic induction.[43−45] When the two friction layers are brought into contact, triboelectric charges are transferred to the surfaces of the two due to the triboelectrification effect. Once the contact of the friction layers is finished, they could carry the same number of opposite signs of triboelectric charges. When the two friction layers are separated, there is an electrostatic field built by the triboelectric charges, which could drive the electrons to flow through the external circuit. According to the characteristics of the structure, the working modes of TENGs were classified into four fundamental categories, including vertical contact-separation mode, lateral sliding mode, single electrode mode, and freestanding triboelectric-layer mode (Figure 3a−d).

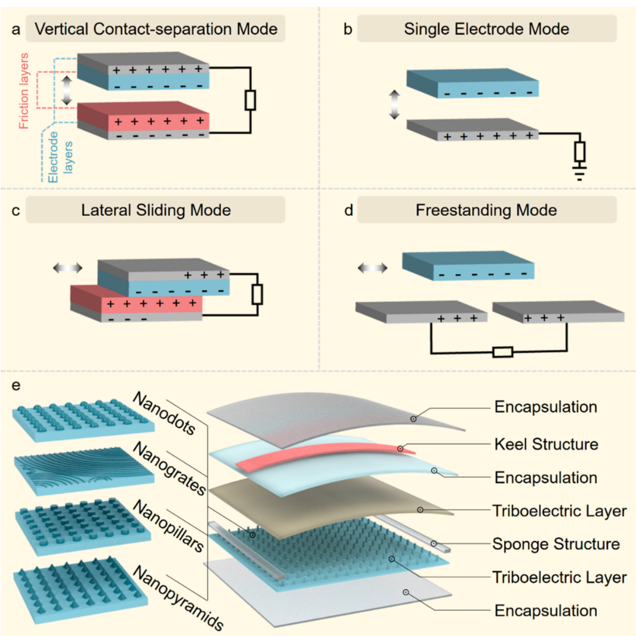

Figure 3. (a−d) Schematic diagram of structures and mechanisms of TENG. (e) Schematic diagram of multilayered TENG with keel and sponge structures and modified surface of triboelectric layer.

In 2012, Wang and his co-workers presented that TENG can convert ambient mechanical energy into electricity and act as a power supply for electronic equipment.[46] To this day, Wang has demonstrated a series of theories based on Maxwell's equations for a deeper understanding of the mechanism of the nanogenerators, including PENGs and TENGs.[43,47] In 2014, Zheng *et al.* reported a flake-like TENG to harvest energy from reparation, which was implanted under the left chest skin and placed between the diaphragm and the liver of the rat.[12] The triboelectric layers of the device were PDMS film and aluminum (Al) foil. A spacer-like spring or shim is commonly used in TENG to ensure a contact-separation process.[48−50] However, the structure of spring and shim is unstable *in vivo* and may cause difficulties in encapsulation. Then, a keel structure made by a highly resilient titanium strip and elastic sponge structure was introduced to replace the traditional spacers, which enhanced the outputs of the TENG as well as ensured the stability of the implantable device.[51]

To further improve the output performances of TENG, various approaches such as sandpaper polishing, inductively coupled plasma (ICP) etching, and corona discharge methods are used to modify the surface of the triboelectric layer of TENG.[52] In 2016, Zhao *et al.* used sandpaper to process the surface of Al foil and polymer film of TENG to make various microgrooves on the surface, which enhanced the output voltage by a factor of 3.[53] ICP etching is used to treat the polymer surface, resulting in some micro/nanostructures such as pillars, which are also useful in improving the outputs of the TENG. Zheng *et al.* demonstrated a TENG with surface modification by ICP etching and "keel structures" to improve the outputs significantly, which was implanted and fixed to the pericardium of a pig.[54] Corona discharge method is another practical surface modification approach for TENG. In 2019, Ouyang *et al.* fabricated a TENG modified by the Corona discharge method, which has a significant output enhancement when harvesting energy from heart motion.[51] Besides, Shi *et al.* demonstrated a convenient approach to harvest mechanical energy from body movements.[55] Just a piece of an implanted electrode can be used for energy harvesting, which will simplify the structure and reduce the design complexity of the energy harvesters.

It is noteworthy that IEHs with biodegradability are also attractive and develop rapidly, which can avoid a second operation for explanting the devices. In 2016, Zheng *et al.* realized a biodegradable TENG that can be degraded and resorbed *in vivo* after accomplishing its mission.[56] The biodegradable device is composed of the biodegradable polymers and resorbable metals. The outputs can reach up to ~40 V and ~1 μA. It can generate a DC-pulsed electric field (1 Hz, 10 V/mm) owing to the micrograting electrodes structure. In 2018, Curry *et al.* reported a biodegradable piezoelectric polymer device, which could be implanted into the abdominal cavity of a mouse to convert the mechanical energy of diaphragmatic motion into electricity.[57] It was fabricated by a piezoelectric poly-L-lactide (PLLA) polymer. In a wide range of 0−18 kPa, the device can precisely measure the pressures and has the potential to replace the biodegradable electronic devices. Jiang *et al.* demonstrated a bioabsorbable natural material-based TENG implanted in the dorsal subcutaneous region of rats.[58] The maximum voltage, current, and power density reach up to 55 V, 0.6 μA, and 21.6 mW m^{-2}, respectively. Li *et al.* fabricated a serious of biodegradable TENG modified by gold nanorods, which were implanted in the subdermal site on the back of the rats.[59] Due to the optical response of the gold nanorods, the *in vivo* degradation of the TENGs can be photothermally tuned. The achievements of NGs have attracted full attention. Higher outputs with smaller sizes will make the implantable NGs play a more significant role in IEHs and SIMEs. Even so, there are still some tricky issues that must be solved, including current improvement, minimization, long-term testing, and power management to make the pulsed outputs to a steady direct-current output.

Auto Wristwatch and Electromagnetic Generators. An auto wristwatch is a long-lasting device, which can harvest energy from wrist movements during daily use. The main parts of the auto wristwatch are a mechanical transmission system

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and an electromagnetic generator (EMG). An eccentric oscillating weight in the mechanical transmission system can convert object motion into rotation, and a winding spring accumulates mechanical energy. When a threshold of the mechanical energy is reached, the spring will drive the EMG to produce electrical pulses (Figure 4). In 1999, Goto *et al.* used a modified automatic quartz watch to convert heartbeat energy into electricity, which was placed on the right ventricular wall of a dog.[19] The harvested energy was stored in a capacitor to drive a pulse generator circuit to pace the heart of a dog.

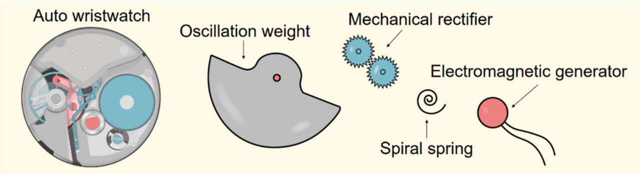

Figure 4. Structures and energy harvesting mechanism of auto wristwatch-based IEH.

In 2013, Zurbuchen *et al.* demonstrated an auto wristwatch type of IEH to convert heartbeat mechanical energy into electricity, which was sewn onto a sheep's heart. The output of the device was 16.7 μW.[60] In 2017, researchers remade auto wristwatches to be a series of energy harvesters implanted on the heart of living animals.[61,62] The weights of these devices range from 7.2 to 16.7 g, which have outputs ranging from ~10 μW to 90 μW.

The weight and flexibility might be challenging to the auto wristwatch type of IEHs. The components of the auto wristwatch are rigid, and the hard casing of the device is attached to soft biological tissue. It is difficult to fix the device on the heart firmly without affecting the functions of the heart after chest closing. How to reduce the size and weight without sacrificing the output power is one of the research focuses of the auto wristwatch device.

Furthermore, blood flow also contains energy. An electromagnetic generator based on permanent magnets and metal coils can be used to harvest the energy from blood flow. In 2018, Zurbuchen *et al.* presented an energy harvester consisting of copper coils surrounding a permanent magnet stack that was suspended between two spiral springs.[63] When an external acceleration forced the device, the permanent magnet stack would oscillate to generate electrical energy based on the electromagnetic induction. The device was implanted in the right ventricular cavity of a pig through the Seldinger technique and fixed on the endocardium, which can generate a power of 0.78 μW. In 2019, Haeberlin *et al.* reported an EMG containing intracardiac turbines to harvest energy from blood flow, which can be implanted into the heart chamber through the catheter.[64] The weight of the device is nearly 1.3 g. The output power of the device can reach 10.2 ± 4.8 μW in the pig heart (Figure 5).

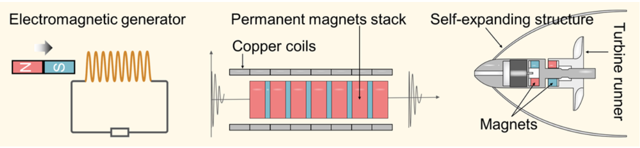

Figure 5. Electromagnetic generators implanted in a heart chamber for harvesting energy from blood flow.

For electromagnetic generators, the miniaturization is an enormous challenge. The size of the permanent magnet and the turns of the coil will directly influence the output of the device. Progress of MEMS and nanotechnologies may provide some potential solutions for the miniaturization of the electromagnetic generators. However, there are a few specific researches that have been realized *in vivo* recently.

Transcutaneous Energy Transferring Devices. Unlike the IEHs harvesting *in vivo* energy, the implantable ultrasonic devices and photovoltaic cells can harvest energy from external body power sources through a transcutaneous transmission approach (Figure 6).[65] For example, Hinchet *et al.* demonstrated a TENG placed underneath the skin of a living rat and inside the porcine tissue, which can be vibrated by the ultrasonic source *in vitro*.[23] The *in vivo* output voltage and current can reach 6.24 V and 200 μA, respectively. The PENGs are also suitable for transcutaneous energy transfer. Kawanabe *et al.* implanted a piezoelectric oscillator under the skin of the goat to receive energy and information released by the ultrasonic source outside the body.[20] Alam *et al.* used PZT and $BaTiO_3$ to fabricate a PENG for harvesting ultrasound energy.[66] The energy harvesting part of the device was implanted under the skin of a rat. Moreover, Kim *et al.* reported a small ultrasonic receiver based on PZT to light surface-mount LEDs *in vivo*.[67] Kang *et al.* assessed the long-term performance of implantable PZT devices powered by an ultrasonic source.[68]

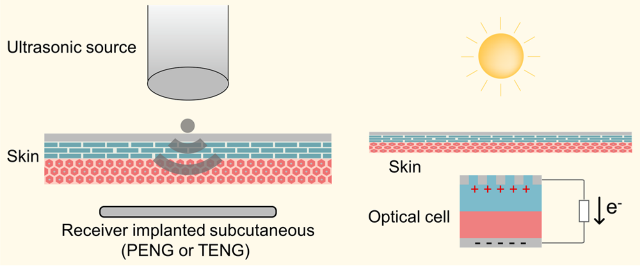

Figure 6. Transcutaneous energy transferring devices based on ultrasonic transmission and optical cells.

Compared to the commonly used wireless energy transmission based on electromagnetic induction, the essential advantage of ultrasonic energy transfer is causing little harm to the human body and no electromagnetic interference. At the same time, adjustable output power and longer transmission distance also make the ultrasonic technique an attractive and practical approach for powering IMEs.

Meanwhile, photovoltaic devices are another choice to transfer the external energy toward the inside body. The mechanism of the optical cell is based on the photovoltaic effect of the *p*−*n* junction. When sunlight falls into the *p*−*n* junction, the electrons will absorb the energy of photons by the photovoltaic effect. As a result, it could jump across the energy gap barrier from the valence to the conduction band and flow through the external circuit. In 2004, Laube *et al.* implanted an array of photovoltaic cells and a light-emitting diode into the eye of a rabbit, realizing an explanted energy harvesting system driven by light.[21] The service life of the systems ranged from 14 days to 7 months, which was determined by the defects of the photovoltaic cells or the defective contacts between photovoltaic cells and light-emitting diodes. Utilizing photovoltaic cells in fabricating subretinal prostheses is also a

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meaningful application of IEHs. In 2015, Haeberlin *et al.* implanted a solar cell in the subcutaneous site of a pig to harvest optical energy percutaneously.[69] In 2016, Song *et al.* reported an ultrathin photovoltaic device implanted under the skin of a hairless mouse that generated an output power of 647 μW.[70] In 2018, Wu *et al.* designed an implantable chip integrated with photovoltaic cells as the 256-pixel subretinal prostheses that were placed in the posterior pole of the eyeball of a pig.[71]

The significant challenges of transcutaneous energy transferring devices are how to improve energy efficiency and avoid damage to human tissue such as the cavitation effect caused by the ultrasonic transducer, which will affect skin cells by both ultrasonic and optical devices. For implantable optical cells, the light will be scattered and absorbed by biological tissues, which will reduce the optical energy efficiency. The piezoelectric device as a receiver will lose efficiency when converting ultrasonic energy into vibrational energy. What is more, keeping the ultrasonic source and implanted receiver focused also needs attention because any offset between them can cause a decrease in energy efficiency.

Enzymatic Biofuel Cells and Ingestible Galvanic Cells. Enzymatic biofuel cells (EBFCs) are an interesting electrochemical approach to harvest energy *in vivo*. The redox reaction of glucose in the body contains abundantly available energy. EBFCs can convert chemical energy inside the body into electricity for powering electric devices. Two enzymatic electrodes inserted in an organism can realize the energy harvesting from the redox reaction of glucose (Figure 7).

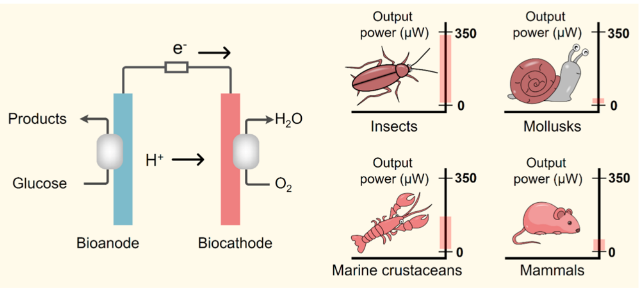

Figure 7. Schematic diagram of EBFC and typical value ranges of EBFC implanted in insects, mollusks, marine crustaceans, and mammals.

Recently, the EBFCs have been implanted in insects, mollusks, marine crustaceans and mammals, and human serum. In 2010, Cinquin *et al.* demonstrated a glucose biofuel cell based on enzymes and redox mediators that were implanted into a rat.[11] In 2011, Miyake *et al.* inserted a needle anode into a blood vessel of a rabbit ear to harvest energy.[72] In 2012, Rasmussen *et al.* realized energy harvesting from disaccharide trehalose in the hemolymph of a live cockroach.[73] In 2015, El Ichi *et al.* demonstrated an EBFC with a three-dimensional nanofibrous network, which was implanted in rat for 167 days.[74] In 2016, Shoji *et al.* investigated an EBFC backpacked by cockroaches, which can generate an output power of 333 μW and can drive a wireless sensor.[75]

Katz's group has reported various biofuel cells implanted in animals, including snail, clam, lobster, slug, and rat. The power densities range from 2 μW to 97 μW. In 2012, a snail could generate electricity through biocatalytic electrodes during feeding and relaxing.[76] Energy generated from clam-based EBFCs connected in serial and parallel was stored in a capacitor to drive an electrical motor.[77] In 2013, enzymatic electrodes implanted in living lobsters could drive a digital watch.[78] Buckypaper-based biocatalytic electrodes were placed onto an exposed rat cremaster tissue, which realized a current density of 5 μA/cm^2.[79] In 2019, modified biocatalytic buckypaper electrodes were inserted into the hemolymph of a slug to extract power from the glucose, which generated an output power of 2−10 μW and could drive a microelectronic sensor.[80] It is noted that researchers tried to obtain energy from human serum by utilizing EBFCs and realized outputs of 0.47 V and 5 mA. Meanwhile, researchers used endocochlear potential (EP) in the inner ear to harvest energy. The EP is a type of electrochemical gradient whose main driving force is different from biofuel. In 2012, Mercier *et al.* reported an EP device inserted into a guinea pig to power a wireless sensor for 5 h.[81]

The significant challenges and critical research contents of EBFCs are output improvement and long duration of function *in vivo*. The output voltage of the EBFCs is limited by oxidation−reduction potential (lower than 1 V), leading to a problem that the EBFCs cannot drive electronics with required voltage directly. The main voltage enhancement methods for EBFCs include a DC-DC converter and connection of multiple devices in series electrically. It is a pity that some other problems may happen when using these methods to improve the output voltage of the EBFCs. For example, the DC-DC converter will consume current as well the voltage will increase. Moreover, the series connection of multiple organisms or enzymatic electrodes is difficult when used in practical applications. At the same time, some byproducts generated, such as hydrogen peroxide, may affect the stability of anodic and cathodic enzymes and cause harm to the body, which will cause problems of long-term use *in vivo*.

Also, ingestible galvanic cells that can harvest energy from the gastrointestinal tract to drive wireless sensors have attracted extensive attention. In 2017, Nadeau *et al.* presented a self-powered ingestible device based on a primary cell battery.[22] Zinc-copper electrodes and gastric fluid acted as the electrolyte and formed the energy harvesting part of the device, which can drive a wireless temperature sensor in a large animal model for 6.1 days. Even though physiological sensing is a potential application to the IEHs, especially for detecting the dynamic mechanical factors of the organs, how to transfer the detected signals to the external body receiver is another problem that needs to be considered. Wireless transmission may be one of the suitable solutions, such as using an electromagnetic induction coil or far-field wireless transmitters.

The materials, configuration, and output of the representative IEHs are summarized in Table 1. The practical applications of IEHs are determined by these essential properties. Biocompatibility is also vital to the IEHs. For the long-term implanted IEHs, such as PENGs, EMGs, and photovoltaic cells, various biocompatible polymer materials can be used to encapsulate the IEHs flexibly to ensure the biocompatibility. For the transient IEHs, they are composed of biodegradable polymers, natural biodegradable materials, or resorbable metals, such as biodegradable TENGs and ingestible galvanic cells. These materials have excellent biocompatibility inherently.

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Table 1. Summarization of IEHs

types	electrical output	structures	materials	animal experiments
nanogenerator	0.03 V,[34] 4 V,[35] 40 nW,[36] 5 V,[37] 0.06 V,[38] 3.73 V,[12] 14 V,[54] 65.2 V,[51] 40 V,[56] 55 V[58]	single nanowire, multilayer, double contacting layers	ZnO nanowires, PZT, PTFE, Kapton/PET, Kapton/Al,	rat, bovine, ovine, pig
auto wristwatch and electromagnetic generator	16.7 μW,[60] 10−90 μW,[61,62] 0.78 μW,[63] 10.2 μW[64]	bulk, turbine	commercial automatic wristwatch, coils/permanent magnets	dog, sheep, pig
transcutaneous energy transferring devices	6.24 V,[23] 647 μW[70]	bulk, thin film	nanogenerators, P^+/N^- well diode arrays, Si PIN photodiodes, GaInP/GaAs, KXOB22-04X3, IXYS	rabbit, pig, rat
enzymatic biofuel cells and ingestible galvanic cells	333 μW,[75] 2−97 μW,[76,77] 2−10 μW[80]	needles	enzyme/electrodes, electrolyte/electrodes	rat, rabbit, lobster, mollusc, insect, pig

SELF-POWERED IMPLANTABLE MEDICAL ELECTRONICS

Implantable energy harvesters are basic to self-powered IMEs. As mentioned above, implantable energy harvesters have been rapidly developed during the last decades. The essential performance of IEHs can meet the power requirements of most IMEs already. More and more IMEs are evolving into self-powered with the support of the IEHs to solve the limitation of the service life of batteries. Numerous research has been devoted to making SIMEs a reality, which is of great significance in developing IEHs. Then, we classify and discuss the different prototypes of SIMEs.

Symbiotic Cardiac Pacemakers. The cardiac pacemaker has become a critical IME for heart disease patients since it was fully implanted in the human body in 1958. Symbiotic cardiac pacemakers are powered by the IHEs, which can break the limitation of the service life of the commercial pacemaker. In the future, the cardiac pacemaker will be batteryless and self-powered, which is able to harvest energy *in vivo* to power itself.[82,83] Human heart beating energy is about 1.4 W, and the power consumption of a commercial cardiac pacemaker is in the several microwatts range.[84] A cardiac pacemaker implanted for life will become a reality if the heartbeat energy can be efficiently used. In 1963, Parsonnet *et al.* made the earliest attempt to harvest *in vivo* mechanical energy from the pulsatile expansion of the aorta by an implanted piezoelectric device, which was used to power a prototype of a cardiac pacemaker.[10]

Flake-like IEHs, such as PENGs and TENGs, are suitable to be placed on the surface of the heart or implanted into the pericardium. Researchers have presented various types of these devices that harvest energy from the heartbeat of animals to power a prototype or commercial pacemaker.[12,35,51] The presentation of the symbiotic cardiac pacemaker is based on the TENG, which is inspired by the biological symbiosis phenomenon that involves the interaction between different organisms living in a close physical association, such as nitrogen-fixing bacteria with leguminous plants. The TENG of the symbiotic cardiac pacemaker implanted into the pericardium of a pig can harvest heartbeat energy for powering the cardiac pacemaker to release electrical pulses for correcting arrhythmia.[51] The emergence of a symbiotic cardiac pacemaker is a solid step toward the practical clinical applications of IEHs and SIMEs (Figure 8).

Meanwhile, transcutaneous energy transferring devices, including optical devices and EBFCs, have also been used to power cardiac pacemakers. For example, researchers presented a solar-powered cardiac pacemaker based on integrated solar cells and pulse circuit, which is a flexible pacemaker based on an implanted photovoltaic device.[69] The EBFCs, based on lobsters and human serum, have also been certificated to be feasible in powering a cardiac pacemaker.[78,85]

Can the IEHs with pulse-like electric outputs act as a pacemaker to stimulate the heart directly? Hwang *et al.* tried it in 2014. They used a PMN-PT piezoelectric energy harvester to stimulate the heart directly through two metal wires.[86] The output voltage and current can reach 8.2 V and 145 μA, respectively. The generated peak energy of the device was 2.7 μJ during one operation cycle, which was higher than the threshold energy to trigger the action potential of a heart contracting (1.1 μJ). However, the piezoelectric device was not implanted in an organism.

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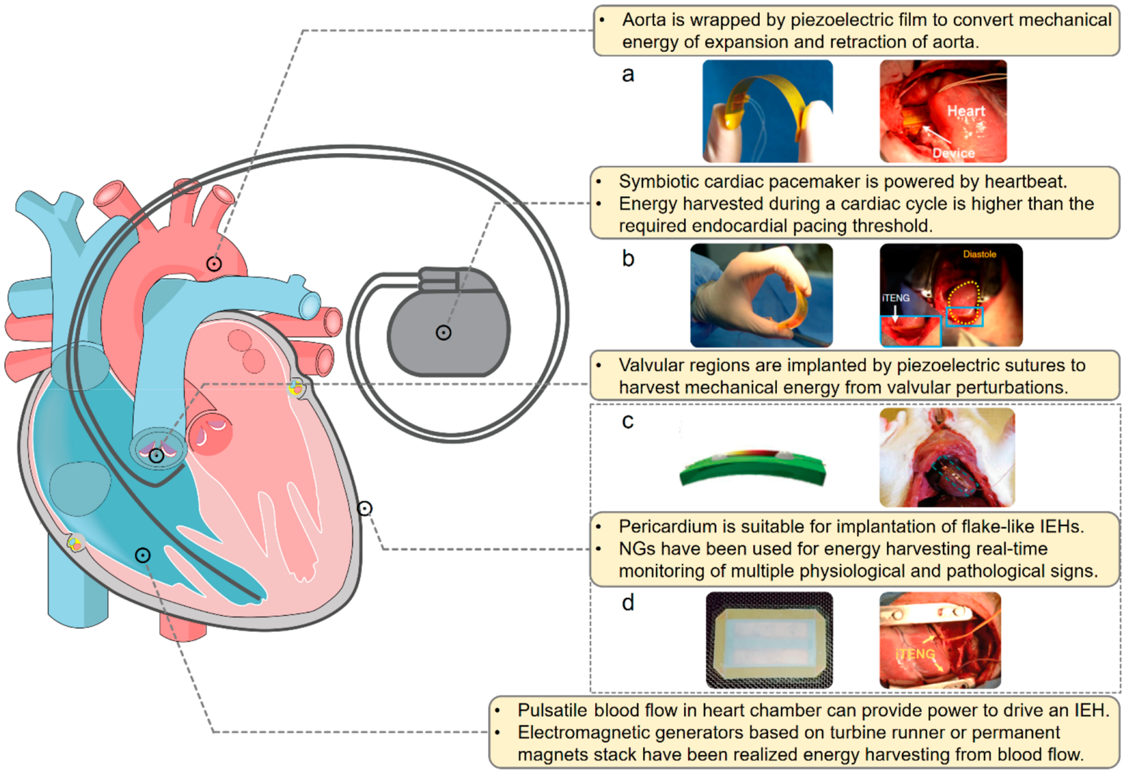

Figure 8. IEHs and SIMEs used in cardiovascular system. (a) Reproduced with permission from ref 36. Copyright 2016 Elsevier. (b) Reproduced with permission from ref 51. Copyright 2019 Springer Nature. (c) Reproduced with permission from ref 34. Copyright 2010 Wiley-VCH. (d) Reproduced with permission from ref 54. Copyright 2016 American Chemical Society.

To eliminate the complications caused by the lead, such as inflammation and thrombosis, a type of leadless cardiac pacemaker has been demonstrated.[83] A typical one is the MICRA transcatheter pacing system (TPS, Medtronic) with a size of 0.8 cm^3, which can be fixed on the ventricular wall through a dedicated catheter delivery system. The main challenge of the TPS type of pacemaker is the difficulty to explant the device after the battery is used up. To prolong the lifetime of that leadless cardiac pacemakers, researchers designed a microgenerator based on a flexible turbine runner and magnetic coupling implanted in the right ventricular outflow tract, which can be driven by the intracardiac blood flow, and had a volume of 0.34 cm^3 and a weight of 1.3 g.[64]

Devices for Stimulating Nerves and Muscles Directly. Self-powered nerves and muscles stimulator devices are powered by the IEHs, which can be used for healthcare monitoring and rehabilitation purposes. The electrical stimulations to nerves and muscles are useful in clinic applications, such as deep brain stimulation for relieving Parkinson's disease, spinal cord stimulation for reduced chronic pain symptoms, and muscle stimulation for treating muscle function loss. Pulsed outputs of NGs can be used to stimulate nerves directly. A PENG based on vertically aligned ZnO nanowires arrays was utilized to stimulate a sciatic nerve of a frog, which can induce innervation of the nerve of a frog.[87] Hwang *et al.* reported flexible indium-modified piezoelectric thin film to stimulate the motor cortex of a rat, which could induce forearm movements.[88] Zhang *et al.* demonstrated a TENG stimulation on the sciatic nerve of a frog.[89] Lee *et al.* utilized a water/air-hybrid TENG for a peripheral nerve stimulation to achieve a modulation of leg muscles in rats.[90] The above-reported examples have proved the feasibility and validity of the direct stimulations on nerves through NGs, yet these devices have not achieved implantation. In 2018, Yao *et al.* realized a fully implanted TENG for stimulating the nerve, which was attached on the surface of the stomach and generated electric pulse during stomach motion.[91] The TENG was packaged by composites polyimide, PDMS, and Ecoflex. Two gold (Au) leads of the device were wrapped around the vagus nerve near the gastroesophageal junction of a rat. After 100 days of *in vivo* tests, the weight of rats can be controlled significantly.

Muscles are another principal object of stimulation. Self-powered muscle stimulator devices could be utilized for functional rehabilitation of muscle function loss caused by neurological disorders and nerve injuries. In 2019, Lee *et al.* reported a stacked-layer TENG driven by hand tapping *in vitro* for direct muscle stimulation on the tibias anterior muscle of a rat.[92,93] Besides the TENGs forced by mechanical motions of organisms, the IEHs driven by the transcutaneous energy transmission system for nerve stimulations were also studied. Alam *et al.* reported an acoustic energy transferring system based on piezoelectric discs to stimulate directly the muscles of a spinal cord injured rat. The device at an 8 mm depth under the skin can generate a 5.95 mW output power when the acoustic intensity was 379.92 mW/cm^2.[66]

Although many NGs have been demonstrated to stimulate the nerve and muscles directly, just a few of them realized actual implantation. The issues of complicated implantation surgeries to place the IEHs at an optimal site *in vivo* and the stimulating electrodes into the target nerves or muscles correctly are challenging missions. Meanwhile, the muscle stimulation requires a higher output performance than that of nerve, which is also a significant challenge (Figure 9).

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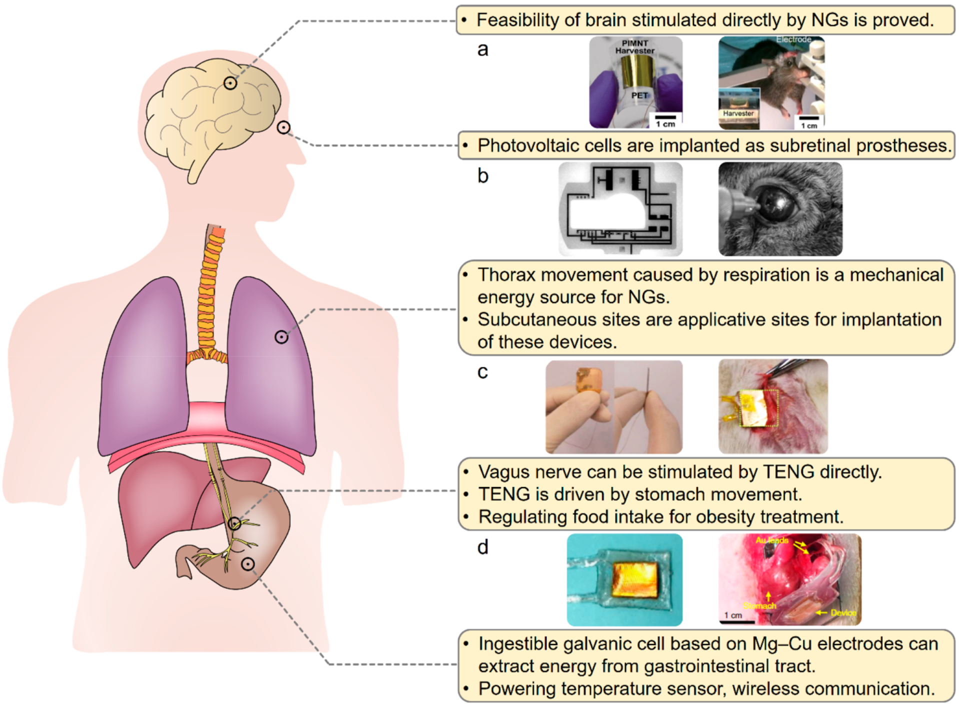

Figure 9. IEHs and SIMEs used for *in vivo* energy harvesting and stimulation except for cardiovascular system. (a) Reproduced with permission from ref 88. Copyright 2015 The Royal Society of Chemistry. (b) Reproduced with permission from ref 21. Copyright 2004 Springer Nature. (c) Reproduced with permission from ref 12. Copyright 2014 Wiley. (d) Reproduced with permission from ref 91. Copyright 2018 Springer Nature.

Physiological Sensors. Self-powered physiological sensors based on the IEHs can reflect the physiological information without a battery. Because the pulsed outputs of the NGs have an obvious correlation with organ motions like a heartbeat, respiration, and sphygmus, the NGs can be used as physiological sensors to reflect the dynamic specifications of the organs in real-time. Blood pressure is an important physiological parameter. Liu *et al.* demonstrated an endocardial pressure sensor based on TENG, which was implanted in the left ventricle through minimally invasive surgery.[94] Ma *et al.* used an implanted TENG to detect the motion of the heart and estimate the blood pressure.[95] At the time, the velocity of blood flow can also be calculated from the data detected by the implantable TENG. Besides the cardiovascular system, the bladder and diaphragmatic motion can also be detected by NGs. In 2018, Hassani *et al.* used a flexible TENG sensor to detect the fullness of the bladder of a rat.[96] Curry *et al.* demonstrated a biodegradable piezoelectric force sensor placed on the diaphragm in rats to detect the pressure of breathing movements.[57]

CHALLENGES AND OPPORTUNITIES

IEHs and SIMEs have been rapidly developed in recent decades due to their various functions in medical applications. Although most of IEHs and SIMEs have their own characteristics and advantages, considering that it is an emerging field, there are still some common challenges for them in the future.

Output Improvement. The NGs have a high voltage but low current with a level of several microamperes. On the contrary, the EBFCs have an milliampere current but low voltage lower than 1 V, which cannot match the voltage requests of several volts for most medical electronics. Various methods of device fabrication and design have been demonstrated to improve the output performance. For the mechanical types of IEHs, such as NGs and EMGs, the improvements of outputs are considered more in terms of materials modification, structure design, and power management techniques. Piezoelectric materials with a high piezoelectric coefficient can obtain more polarization charges under the same mechanical conditions. Triboelectric layer surface modification is often used in TENG for output enhancement. The material type and surface structure of the triboelectric layer can significantly influence the output properties of the TENG. For the chemical type of EBFCs and ingestible primary cell battery, the outputs are closely related to glucose or electrolyte concentration, enzyme activity, and electrode surface structure.

Miniaturization. The large size of the device often means that major surgery is needed for implantation. Therefore, the miniaturization is one of the emphases for research of IEHs and SIMEs. For example, the IEHs placed in the pericardium should be implanted through a thoracotomy, which is a complicated surgical operation for surgeons and recipients. To avoid disturbance to cardiac contraction, the weight and size of the devices implanted into pericardium must be controlled in a range of 3−6 g and <16 × 16 mm^2.[84] Transcatheter delivery is a minimally invasive surgery for device implantation, which is commonly used in cardiac surgery such as stent implantation. Some scientists have embarked on research in the area of catheter-based IEHs, which may be a more appropriate and practical research direction for the devices harvesting mechanical energy from a heartbeat.

Long-Term Operation *In Vivo*. The final goal of the IEHs and SIMEs is to realize the implant for life. Recently, most of these devices have been tested *in vivo* for less than one year, which is far from the long-term operation *in vivo*. The critical

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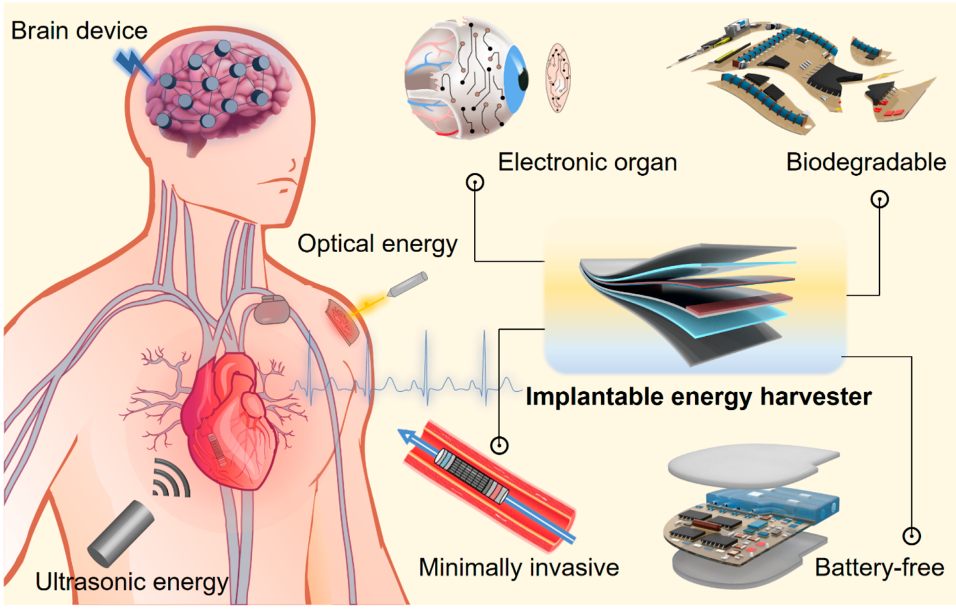

Figure 10. Prospects of future SIMEs based on implantable energy harvesters.

issue is how to keep a stable performance of the device and ensure excellent biocompatibility during the dynamic long-term *in vivo* conditions. Nanomaterial and nanotechnology can provide some solutions for the long-term challenge. For example, a nanomaterial-modified electrode with a three-dimensional structure can significantly improve the stability of the immobilization of enzymes. It can improve the stability of the output performance of the EBFCs *in vivo*. The encapsulation can directly influence the *in vivo* long-term properties of the devices. Various polymer materials, such as PDMS, PI, and parylene C, are biocompatible and can be used for flexible encapsulation of IEHs.

The fixation/adhesion of the device is another critical factor for *in vivo* operation. Stable adhesion to the target tissues is critical to achieving a stable output. However, instant adhesion is difficult on wet surfaces such as body tissues. Because the water between the two surfaces of devices and the target site will prevent the intermolecular forces. The latest advances in the field of materials science may provide us with fresh ideas.[97] By encapsulating IEHs and SIMEs with biopolymer materials, the adhesion performance of the device could be improved. It is also difficult to implant the device in an appropriate site to verify stability and reliable energy harvesting output or stimulation pulses for nerves and muscles. A suture is needed to implant TENGs and auto wristwatch devices on the surface of the heart. However, whether the suture approach would cause side effects like adverse physiological reactions or mechanical mismatches is still unknown. Finally, related clinical criteria of the devices must be established to guide the development of them.

On the other hand, challenge breeds opportunity. With the developments in material sciences, micro/nanofabrication technologies, and ultralow-power electronics, the IMEs will evolve into implanting for life. Predictably, implantable electronics will become self-powered, highly integrated, miniaturized, and ultraflexible. Furthermore, the self-powered approaches are hybrid ones that combine different modalities, including mechanical, chemical, or optical. Meanwhile, progress in sensor technology and computer science may help IEHs and SIMEs become smart and automatically adapt to the environment, which will stay with people all their life and act as a partner who knows them best (Figure 10).

CONCLUSION

Collecting the energy from organisms and the surrounding environment for powering IMEs has extensive practical significance. Various kinds of technologies are proposed to harvest these energies, such as nanogenerators, biofuel and solar cells, and auto wristwatches. In the developments of implantable energy harvesting technologies, SIMEs with different functions have been realized, such as symbiotic cardiac pacemakers, self-powered nerve stimulators, and self-powered physiological sensors. The widespread applications of IEHs and SIMEs can significantly influence our daily life in the future, from intelligent electronics to health supervision.

This review summarizes the development of implantable energy harvesters, from the aspects of mechanisms, output properties, application scenarios, and long-term *in vivo* performances. According to the different working characteristics, IEHs can be divided into three broad classes: Mechanical types of IEHs are fabricated to harvest energy from mechanical motions *in vivo*, such as nanogenerators and electromagnetic generators. Transcutaneous types of IEHs can harvest the optical and acoustic energy transferred from *in vitro* to *in vivo*. Chemical types of IEHs can obtain energy from the electrolyte in the gastrointestinal tract and redox reaction of glucose, such as enzymatic biofuel cells and ingestible galvanic cells. Furthermore, we classify and discuss the different prototypes of SIMEs based on IEHs by estimating the *in vivo* therapeutic function. The potential challenges and prospects of the IEHs and SIMEs have also been presented.

The development of implantable energy harvesting technology expedites the emergence of the SIMEs. The human body contains abundantly available energy such as heartbeat, respiration, blood flow, and redox reaction of glucose. To harvest these energies, many ingenious devices and methods have been presented, including nanogenerators, electromagnetic generators, biofuel cells, and transcutaneous energy

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transfer devices. After over 50 years of development and evolution, these devices and methods have been produced from concept to reality. Although it is full of challenges and needs more research and exploration, the future of IEHs and SIMEs is promising and achievable.

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The authors declare no competing financial interest.

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VOCABULARY

redox reaction, a chemical process that involves a transfer of electrons between two different materials; **piezoelectric effect**, an ability of certain materials that can generate an electric potential in response to the applied external force; **biocompatibility**, a property of the materials that are compatible with living tissue; **electrostatic induction**, a process in which static electricity is generated in a material when an electrically charged object is placed nearby; **minimally invasive surgery**, a surgical strategy that makes tiny cuts on the organ or tissue, instead of the large cuts usually needed in traditional surgery

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