REVIEW



Recent advances of triboelectric nanogenerator based applications in biomedical systems

Xin Xia¹ Qing Liu² | Yuyan Zhu² | Yunlong Zi¹

Correspondence

Yuyan Zhu, Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University, Kowloon, Hong Kong. Email: yuyan.zhu@polyu.edu.hk

Yunlong Zi, Department of Mechanical and Automation Engineering, The Chinese University of Hong Kong, New Territories, Hong Kong. Email: ylzi@cuhk.edu.hk

Funding information

Chinese University of Hong Kong, Grant/ Award Number: 4055086; Hong Kong Polytechnic University, Grant/Award Number: P0030234; Research Grants Council, University Grants Committee, Grant/Award Number: 24206919

Abstract

Triboelectric nanogenerators (TENGs) are a promising power and sensing solution for biomedical applications attributed to the high electrical output and sensitivity with low-cost and widely available materials. Here, the recent developments in TENG-based biomedical applications with various structures and functionalities are discussed and summarized. Wearable TENGs perform well in motion and respiratory monitoring with excellent flexibility and low bio-risks. Implantable TENGs enable interactions with the cardio-cerebral vascular system and nervous system to monitor and treat different diseases with good biodegradability. Furthermore, explorations of TENGs in in vitro systems, including drug delivery, cellular proliferation and differentiation, are reviewed. Perspectives on the biomedical applications of TENGs are proposed based on investigation in this area in the past two decades. With continuous efforts in miniaturization and optimization of robustness, the TENG-based self-powered biomedical systems will definitely play an important role in the healthcare market in the future.

KEYWORDS

biomedical systems, in vitro systems, in vivo applications, triboelectric nanogenerators

1 INTRODUCTION

Disease prevention, diagnosis, and therapy are attractive research topics since they are essential to human health. Accordingly, precise signal monitoring of health-related physiological parameters, which can reflect the health conditions of patients in real time, is of paramount importance.1-4 Current instruments for clinical diagnosis, such as electrocardiograph (ECG) monitor, electroencephalograph

Xin Xia and Qing Liu contribute equally to this work.

(EEG), gastroscope, and enteroscope, are usually bulky, and it is hard to upgrade them into wearable devices to realize in vivo real-time monitoring.⁵ Additionally, clinical instruments for therapeutic purposes such as using the pulse generator to stimulate brain are usually expensive, which hinders their wider applications and more frequent use on patients. Low-cost portable, wearable, and implantable devices are urgently required to meet the demands of in vivo health monitoring and disease treatment.^{6,7}

Rapid development in flexible materials and technologies has given rise to the emergence of wearable

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2020 The Authors. EcoMat published by The Hong Kong Polytechnic University and John Wiley & Sons Australia, Ltd.

wileyonlinelibrary.com/journal/eom2 EcoMat. 2020;2:e12049.

¹Department of Mechanical and Automation Engineering, The Chinese University of Hong Kong, New Territories, Hong Kong

²Department of Applied Biology and Chemical Technology, Hong Kong Polytechnic University, Kowloon, Hong Kong

electronics in recent years. Products such as smart watches, sports bracelets, and wearable micro devices with characteristics of miniaturization and flexibility have been produced.8 However, these traditional products are hampered by short battery life-span, and thus frequent charging or battery replacement is required.9 A possible solution is to convert the energy extracted from the surrounding environment into electricity, especially the mechanical energy generated by human motions in daily activities that is dissipated into the environment via heat, which can be realized through nanogenerators. The triboelectric nanogenerator (TENG), a promising new energy harvesting technology proposed in 2012, presents a huge potential for applications in biomedical systems attributed to its high electrical output and sensitivity. 10,11 Zhang et al developed a multifunctional TENG based on textile, which was used as a water energy collector and self-powered body motion sensor.¹² And their group also reported a wearable self-charging power system (SPS) consisted of a H-TENG and several supercapacitors, which could transfer the energy stored in the raindrop into stable output.¹³ Compared with piezoelectric nanogenerator for biomedical systems, which shows narrow material selections, 14 TENG has been proven to be a reliable and sustainable energy harvester with a wide selection of materials for fabrication and low manufacturing cost.15-17 It can convert various forms of mechanical energy around us into electrical energy on the basis of the coupling effects of triboelectric effect and electrostatic induction for further applications as a power source.¹⁸ Moreover, TENG on its own can serve as a highly sensitive sensor for detection of physical signals, ¹⁹ providing a method for achieving self-powered biomedical systems for disease diagnosis and treatment.

Previous review articles have summarized some wearable and implantable nanogenerators with applications as sensors and power sources for biomedical systems. For example, Li et al discussed implantable nanogenerators as energy harvesters from the aspect of materials in 2017¹⁴ and Prof. Lang's group reviewed biomedical systems with the nanogenerator as the power source in 2018.20 In 2019, Zhao et al summarized different TENGbased medical sensors.²¹ In 2019, Liu et al summarized different wearable and implantable TENGs (iTENGs) serving as power sources or self-powered sensors, 22 where the iTENGs were reviewed in terms of biodegradability. In 2019, Zhang et al described recent research on TENG-based green hybrid power system.²³ However, these review articles only focused on a certain type or a certain aspect of TENG-based biomedical systems, and some state-of-art applications of TENG in biomedical systems are not yet well discussed, such as drug delivery. Therefore, a systematic review for TENG applied in biomedical systems comprehensively covering recent developments is still required.

This review summarizes the recent development of various types of TENG-based biomedical applications. TENG can either serve as a sensor for detecting biological signals or act as a power source for powering commercial medical sensors, implying a huge potential in selfpowered biomedical systems for monitoring health and regulating physiological functions, such as sensors for heart rate, blood pressure, respiratory rhythm, motion, power sources for drug delivery, tissue repairing, nerve stimulation, and so on. In this article, recent advances in TENG-based biomedical systems are divided into three main parts. The first part focuses on the in vivo applications of TENGs that are implantable via the encapsulation by biocompatible materials for both health monitoring and disease treatment. The second part mainly discusses wearable TENGs that collect physical signals from the human body. The last part summarizes other TENG-based explorations such as cell proliferation and differentiation, and drug delivery. Wearble TENGs exhibit huge advantages on its flexibility and biosafety, while in vivo and in vitro systems provide more direct ways to treat different diseases and monitor human health status in real time. Challenges and perspectives of employing TENG in biomedical systems based on its current development are discussed at the end of this review.

2 | TENG-BASED APPLICATIONS IN IN-VIVO BIOMEDICAL SYSTEMS

TENG, based on Maxwell's displacement current, ^{24,25} presents high sensitivity for detecting mechanical stimuli with outstanding electrical output, and the pulse output can be easily recorded and recognized. ²⁶ Thus it can be actuated by weak mechanical motions such as inspiratory movement, ^{27,28} systole of the heart and blood flow, a feature that is desirable for in-vivo biomedical monitoring. ^{19,29,30}

2.1 | TENG for cardiac monitoring and treatment

iTENGs, which are encapsulated with bio-compatible or bio-degradable materials, are usually employed for two functions, serving as self-powered biosensors for endocardial pressure heart rate monitoring or electrical power source for stimulation applications such as cardiac pacemaker, ^{29,31} for interactions with the nervous system, ^{32,33} and for administration of regenerative medicines such as wound healings. ^{34,35} Liu et al reported a miniaturized TENG-based self-powered endocardial

pressure sensor (SEPS) with excellent flexibility and sensitivity that can also detect cardiac arrhythmias such as ventricular fibrillation and ventricular premature contraction (Figure 1A). 10 The TENG presented a multilayer structure, where a spacer was sandwiched by an inductively coupled plasma-treated Polytetrafluoroethylene (PTFE) film with gold electrode deposited on the back surface and an aluminum (Al) layer, and the total structure was encapsulated by a Polydimethylsiloxane (PDMS) layer with a size of 1 cm \times 1.5 cm \times 0.1 cm. Integrated with a heparin-coated polyvinyl chloride (PVC) stretchable catheter, minimally invasive implantation of the

SEPS was achieved in a male adult Yorkshire pig, where working signals of ECG, femoral arterial pressure (FAP), and SEPS were documented and a sensitivity of 1.195 mV mmHg⁻¹ was obtained.

Figure 1B shows an implantable wireless cardiac sensor based on TENG that was proposed by Zheng et al.³⁶ The iTENG had a similar multilayer structure, with a PTFE film and a gold layer working as the triboelectric surface pair, while its deformation-recovery ability was realized through a highly resilient titanium strip that worked as the keel structure. in vivo evaluations for 72 hours of this iTENG were successfully demonstrated.

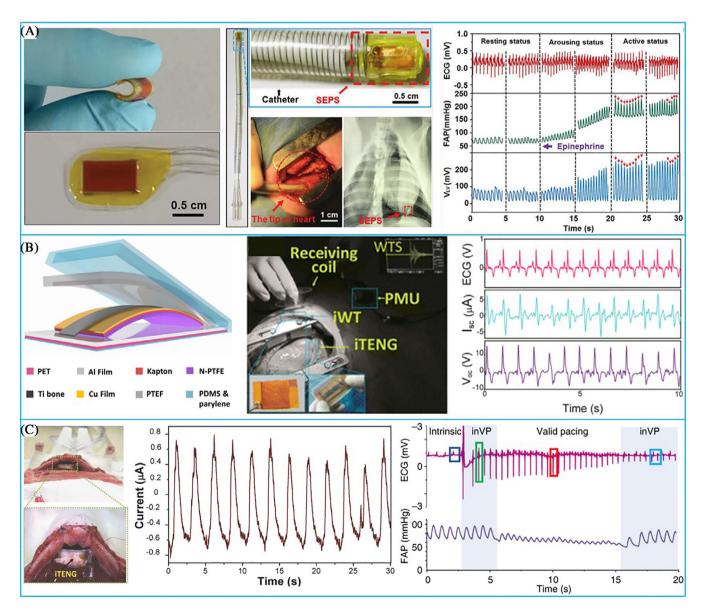


FIGURE 1 Cardiac pacemaker & Blood Pressure. A, Structures and setup of the transcatheter endocardial pressure sensor based on an implantable TENG. 10 Reproduced with permission. Copyright 2019, John Wiley & Sons. B, Structure, setup, and the output characteristics of the TENG attached on the heart of the swine for wireless cardiac signals detection. Reproduced with permission. Copyright 2017, John Wiley & Sons. 36 C, TENG for cardiac pacemaking. Reproduced with permission. Copyright 2014, John Wiley & Sons. 27 Copyright 2019, Springer Nature Group³¹

and the $V_{\rm OC}$ of $\sim \! 10$ V and $I_{\rm SC}$ of $\sim \! 5$ $\mu \rm A$ were obtained as driven by the heartbeat of the adult swine, which are consistent with the signal waves recorded by ECG. Additionally, the authors proposed a self-powered wireless transmission system for real-time wireless cardiac monitoring, with the electrical output successfully recorded.

Besides cardiac monitoring, TENG was implanted in vivo for powering cardiac pacemaker (Figure 1C). In 2014, Prof. Li's group proposed an iTENG with the Al-Kapton pair with a spacer enclosed in the structure to power a prototype pacemaker driven by the heartbeat of a living rat²⁷; a power density of up to 8.44 mWm⁻² was achieved by normal breathing of the rat and the pacemaker was successfully powered in vivo with the assistance of an external capacitor for energy storage. In a subsequent study, they demonstrated the use of an iTENG-based symbiotic cardiac pacemaker in a large animal model for regulating and preventing the deterioration of sinus arrhythmia.31 The performance of the iTENG was improved by introducing a memory alloy keel, where energy of 0.496 µJ was obtained from each cardiac motion cycle, which exceeded the required endocardial pacing threshold energy of 0.377 µJ.

2.2 | TENG interacted with nervous systems

As an invasive therapeutic method, neuromodulation has been widely used to regulate body functions via introducing artificial neurophysiological signals to the nerve system. Recently, TENG has been demonstrated to realize variable therapeutic purposes by generating electrical stimulation for neuromodulation (Figure 2). In 2018, Yao et al reported a battery-free vagus nerve stimulation (VNS) system based on TENG for effective weight control, whose flexibility and compatibility were ensured by encapsulating the entire device with a polyimide, PDMS and ecoflex composite. (Figure 2A)³⁷ The device was attached on the surface of the stomach of rat models, and it generated biphasic voltage signals when contact and separation processes were continuously driven by the peristalsis of the stomach at a frequency of 0.05 Hz as recorded. A bilateral VNS, for both the anterior vagus nerves (AVNs) and posterior vagus nerves (PVNs) that could be observed by staining images, was employed by wrapping the two gold leads nearby the gastro-esophageal junction. As directly connected to the vagus nerve, the voltage output generated by the TENG successfully suppressed food intake and thus reduced fat mass; an average body weight reduction of 350 g was achieved within 100 days (38% less than the control groups).

A series of studies in direct muscle stimulation for rehabilitative treatment toward muscle function loss were conducted by Prof. Lee's group in 2019. 32,38,39 Figure 2B shows a stacked-layer TENG proposed to successfully power muscle stimulation at a short-circuit current of 35 µA. The current pulse generated by the TENG was introduced to the skeletal muscle tissue via the multiple-channel intramuscular electrodes, which were implanted and sutured in the tibias anterior (TA) muscle tissue with fixation by a knot. The 6-electrode sites on each side of the intramuscular electrodes were separated by insulating the substrate of polyimide to prevent current flow between two sides, and thus multiple channels were formed to transfer current output, allowing motoneuron mapping of stimulation efficiency optimization with the assistance of the stimulation efficiency matrix. The diode-amplified TENG was also developed by them to overcome the current threshold for direct muscle stimulation, which significantly enhanced the stimulation efficiency.³⁸ Furthermore, Prof. Lee's group investigated the factors of electrode configurations and stimulation stability that hindered the TENG muscle stimulation, and provided a guidance to achieve stable stimulations as well, validating the possibility of TENG powering muscle stimulation.³² A water/air-hybrid TENG for peripheral nerve stimulation was reported by Lee et al in 2018 (Figure 2C).33 A sponge and a suspended dielectric thin film were applied to enhance the output of the device as well as its robustness regarding multiple phases of water droplet. Connected with the neural electrode, the water/ air-hybrid TENG performed efficient nerve stimulation and in vivo monitoring of rats.

Figure 2D shows a self-powered control system that was composed of a TENG as the sensor and a bistable micro-actuator for control purpose. It was proposed by Hassani et al in 2018 for the therapeutic purpose of underactive bladder control.40 The TENG sensor was structured by a wet sponge enclosed between the PDMS and copper surfaces to allow charge transfer by the motion of water through the sponge. The sensor was placed between the bladder surface and the flexible bottom PVC sheet and the voltage output was connected to a spring-based actuator, which was fabricated by the shape memory alloy NiTi with an external voltage of 4 V applied for the restoration phase. When enough water was squeezed out of the sponge due to the force by the liquid filling the bladder, the actuator started to compress the bladder to void as the voltage output of the TENG was larger than 4 V, which in turn weakened the voltage output of TENG, then the actuator turned to the restoration phase again. This self-powered control system was reported to realize a voiding percentage of up to 78% of the bladder volume in a rat-model in vivo experiment, a

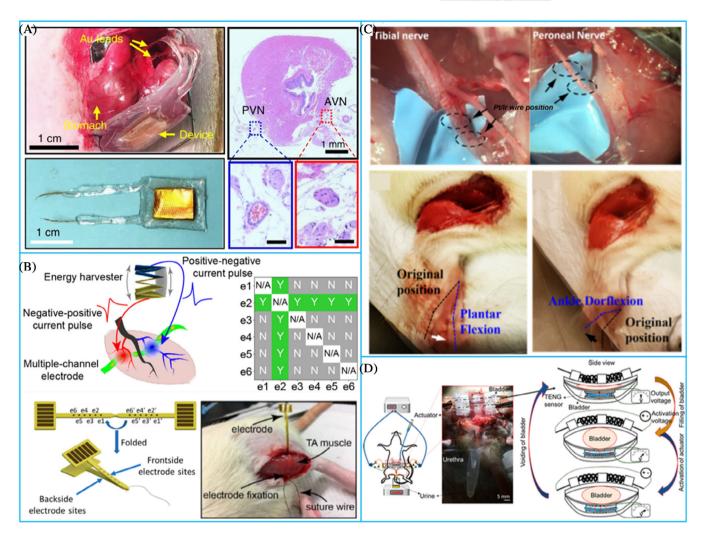


FIGURE 2 The application of TENG on interactions with nervous systems. A, Effective weight control realized by electrical stimulating on the stomach of rats via Au electrodes from the TENG.³⁷ Reproduced with permission. Copyright 2019, Springer Nature Group. B, Direct muscle stimulation via TENG.³⁹ Reproduced with permission. Copyright 2019, Elsevier Publishing Group. C, Images of the nerve of muscles involved modulated by force based on TENG.³³ Reproduced with permission. Copyright 2018, Elsevier Publishing Group. D, Setups and working mechanism of the self-control bladder system applied in rats.⁴⁰ Reproduced with permission. Copyright 2018, American Chemical Society

performance that was comparable to that of the common catheterization method.

2.3 | TENG for regenerative medicine

When external energy strategies, such as voltage output stimulation, laser therapy, near-infrared treatment, are applied on fibroblast cells, cell migration across the scratch wound is accelerated, which is beneficial to the scratch-wound healing process. Thus, TENGs are also employed in the field of regenerative medicine in short-term treatment in combination with biodegradable materials, especially for in vivo self-powered cure system for wounds. In 2015 Tang et al reported an

in vivo low-level laser cure system powered by TENG for osteogenesis of a mouse model. (Figure 3A)⁴⁴ A vertical contact-separation (CS) mode TENG with pyramidarray patterned PDMS and TiO₂ pair was applied to power a capacitor for driving the infrared laser through a rectifier. It was demonstrated that a larger obvious mineralized area in the TENG-based infrared irradiation groups of murine calvarial preosteoblasts was obtained compared with the reference group without laser treatment, a result that was similar to the results of the battery-lasered irradiation group. In order to meet the demands for biodegradable implantable electronics after realizing the therapeutic purpose, Zheng et al in 2016 proposed a biodegradable TENG (BD-TENG) to harvest biomechanical energy for short-term

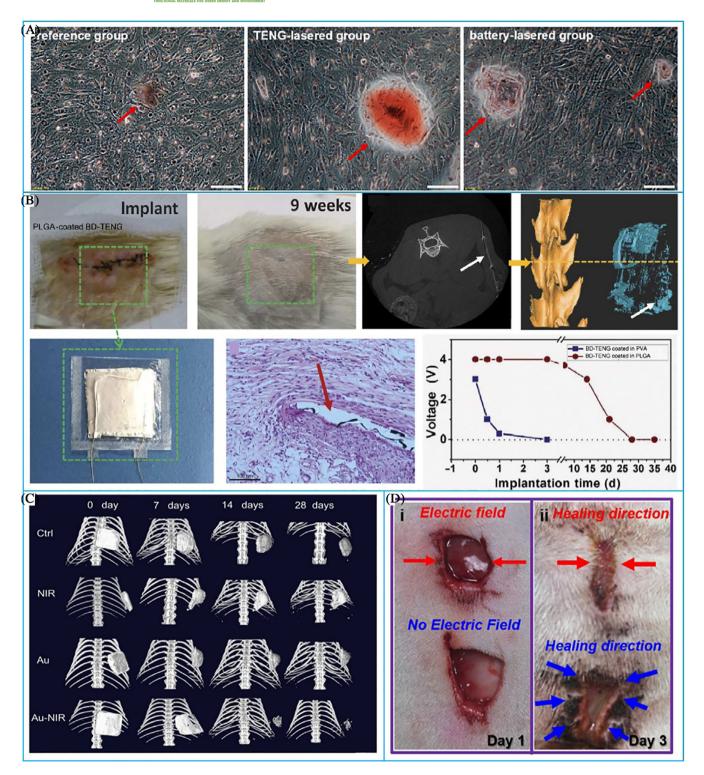


FIGURE 3 Regenerative medicine. A, Laser from implantable TENG induced bone formation with battery-lasered group. 44 Reproduced with permission. Copyright 2015, American Chemical Society. B, Effective wound healing with well biodegradation realized by a PLGA/PVA-coated TENG implanted in SD rats. 79 Reproduced with permission. Copyright 2016, American Association for the Advancement of Science. C, TENG with photothermally tunable biodegradability. 35 Reproduced with permission. Copyright 2018, Elsevier Publishing Group. D, Wearable TENG for effectively wound repairing. 4 Reproduced with permission. Copyright 2018, American Chemical Society

applications.⁷⁹ (Figure 3B) The BD-TENG had a multilayer structure with a space enclosed inside and was entirely encapsulated by bio-degradable polymers with excellent biodegradability and biocompatibility. Two sterilized BD-TENGs coated with poly(L-lactide-co-glycolide; PLGA) and PVA were implanted in the sub-

dermal region of Sprague Dawley (SD) rats in vivo, and the wounds were cured well after 9 weeks without any obvious infection or significant inflammatory reactions. Besides, the output voltage of BD-TENGs driven by the respiratory motion decayed a lot with time, which could be attributed to the fibrous encapsulations by the foreign body response. Additionally, the growth of neuron cells was demonstrated to be orientated successfully by the DC-pulse electric field generated between two electrodes with comb structures by the powering of the BD-TENG. An iTENG with tunable biodegradation was proposed by Li et al in 2018³⁵; the contact-separation process of the device was ensured by the hemisphere array structure of Au. The Au nanorods were doped in a PLGA film (the bottom biodegradable dielectric layer) to respond to NIR treatment. The encapsulation layer and the triboelectric surface (the top dielectric layer) employed biodegradable materials as well. To evaluate the in vivo controllable degradation against time, the PLGA-iTENG was implanted into the subdermal region of SD rats after sterilization. (Figure 3C) Computedtomography (CT) images showed that faster degradation could be obtained when Au-Nano-Rods (AuNRs) doping and NIR treatment were used in combination, compared with other groups that had undergone only one or no treatment at all, demonstrating the feasibility of using tunable biodegradation in healthcare applications. Further experiments on tissue repair were conducted by the authors, and the results showed the migration process of fibroblast cells was significantly accelerated by the output of the TENG. In 2018, Long et al reported an electrical bandage on the basis of TENG for skin wound healing.34 The TENG, with a polyethylene terephthalate (PET)-Cu foil-PTFE multilayer structure, generated electricity from the skin movement to induce an alternative electric field between the two dressing electrodes that were located near the wound. Rapid closure of rectangular skin wound along the electric field was demonstrated within 3 days by applying the electrical bandage with skin wounds, as shown in Figure 3D, while 12 days were required for normal healing process with multiple closure directions.

3 | WEARABLE TENGS FOR HEALTH MONITORING

Compared with iTENGs, wearable TENGs enable more flexible applications with less concern on biosafety and biocompatibility. In this section, wearable TENGs that work as self-powered monitor are reviewed in three categories according to different functionalities.

3.1 | Wearable self-powered heart rate sensors

More and more people are living in a sedentary lifestyle, which has obvious health risks such as the increased risked of heart diseases. This has made the development of latent disease monitoring devices an increasingly interesting research topic for scientists.⁴⁵ It has been reported that 90% of cardiovascular diseases are preventable.² Heart rate has been widely used to evaluate the health status of individuals; it is also an important index to reflect the stability of the cardiovascular system. 46 A series of technologies have been extensively applied to measure heartbeating pulses, such as photoplethysmography (PPG) and piezoelectric pulse transducer (PPT). However, these technologies have disadvantages, such as difficulty in data recognition and analysis, low density of devices and high cost that limit their development. To address these issues. TENG is employed as a promising and user-friendly self-powered active sensor to monitor these medical signals.

In 2014, Peng et al demonstrated the use of a membrane-based triboelectric sensor (M-TES) as a selfpowered method to monitor air pressure variation for personal healthcare and security surveillance. 47A piece of acrylic sheet served as the substrate of M-TES, and two copper films were deposited at both sides of substrate as electrode. Fluorinated ethylene propylene (FEP) film was pasted over the electrode and packaged by a latex membrane. There was an air conducting aisle in the middle of the equipment, which formed an air cavity when air pressure changed. M-TES could detect changes in chest pressure caused by heartbeat rhythm, and generate voltage signals accordingly. The voltage output was able to trigger the security alarm through the processing unit (Figure 4A). Therefore, the periodical air pressure change resulted in output voltage signals to reflect the heart rate in real time. The simple and low-cost M-TES was demonstrated to be able to respond effectively to changes in air pressure caused by footsteps, heartbeats and respirations without the help of any external energy supplies.

In 2019, Chen et al proposed a TENG-based flexible self-powered detector installed on the thumbnail for calculating oxyhemoglobin saturation and pulse rate by detecting stable photoplethysmography (PPG) signals. Driven by a stretchable TENG that was fabricated with a crumpled gold (Au) electrode and a PDMS triboelectric layer, the LED was able to emit light that contained hemoglobin information. Then, the reflected light was detected by the photodetector (PD) to acquire blood oxygen information. (Figure 4B). The output performance of TENG could be significantly improved by the rough nanostructures on the electrode and PDMS.

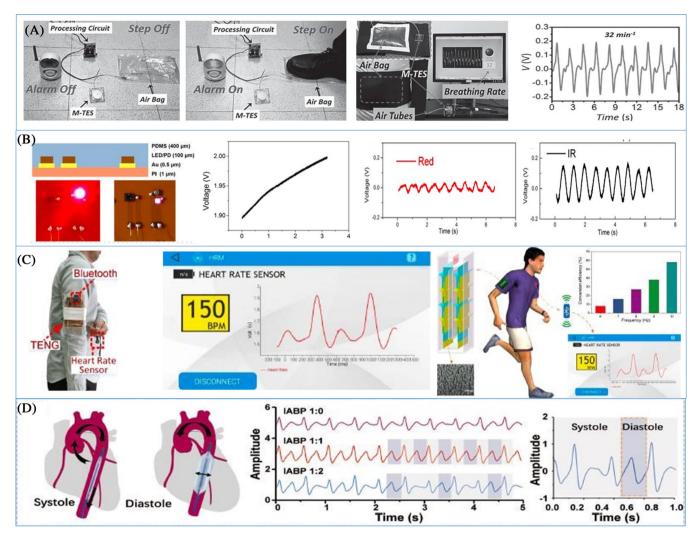


FIGURE 4 Heart rate and pulse monitor, A, Setup of a wireless security system and demonstration of respiratory detection by utilizing the M-TES. ⁴⁷ Reproduced with permission. Copyright 2014, John Wiley & Sons. B, The principle of TENG-based sensor in blood oxygen detection. ⁴⁸ Reproduced with permission. Copyright 2019, MDPI. C, Demonstrations of the TENG attached with the arm and the electronic signal detected by heart rate sensor. ¹⁹ Reproduced with permission. Copyright 2017, American Chemical Society. D, The systole and diastole of heart schematically illustrating the working principle of IABP. ⁴⁹ Reproduced with permission. Copyright 2017, John Wiley & Sons

The advanced technologies in personal disease diagnosis and health monitoring system highly depend on the development of body sensor network (BSN). Conventional devices are powered by traditional batteries that have the shortcomings of limited lifespan and harmful to the environment.⁷ TENG has been recently developed as a promising method to detect indication of body functions and give data on the health status of individuals in the form of wearable self-powered sensors. In 2017, Lin et al reported a wireless BSN system driven by downy-structure-based TENG (D-TENG) for noninvasive real-time human heartrate monitoring (Figure 4C).¹⁹ The system was composed of a power management circuit, a heart-rate sensor, a bluetooth module for wireless data transmission and a signal processing part. The D-TENG consisted of two basic functional units, the polytetrafluoroethylene (PTFE) thin

films and an acrylic sheet. The highly integrated BSN system was motivated by the energy collected from human walking through the D-TENG. In order to make the BSN work as a real-time heart monitor, heart rate signals were first obtained by a signal process circuit, then transmitted by Bluetooth wireless technology for display in a smartphone.

In 2017, Ouyang et al demonstrated a self-powered ultrasensitive pulse sensor (SUPS) to convert human pulse biomechanical signal into electric signal. ⁴⁹ The SUPS exhibited perfect performance when it was pressed on the radial artery. An output voltage of 1.52 V, response time of 50 μ s and signal-noise ratio of 45 dB were realized to obtain pulse signals that could be easily processed. Besides, the performance of the SUPS was tested by an implanted intraaortic balloon pump (IABP),

where the cardiovascular system was regulated through systole and diastole of the balloon pump (Figure 4D). Additionally, the SUPS was integrated with a bluetooth chip to support real-time monitoring of the cardiovascular system on a smartphone.

Motion sensors that work by monitoring body/muscle motions from eye-balls, body gestures, and finger poses have been widely used in e-skin and health-care systems. 50-54 Chiu et al proposed a self-powered gesture sensor to be installed on the back of hand to discern finger motions (Figure 5A).⁵⁰ Two hands could form 64 gesture combination, a number that was sufficient to represent 26 English letters. Chitosan/glycerol films were applied to make the triboelectric surfaces to ensure its performance in harsh conditions such as high humidity. This system was also integrated into gloves to boost its availability and practicability. In 2019, Partha et al established a TENG-based pressure sensor (TEPS) for usage in selfpowered human gesture detection.⁵² It performed well with high sensitivity even under tiny pressure changes with fast response time (<9.9 ms). Different signal profiles were created by utilizing the TEPS sensor to differentiate multiple gestures from the human elbows, knees, and fingers.

In 2018, Wang et al proposed an extendible and selfpowered TENG motion sensor based on kinesio tapes (KT-TENG) (Figure 5B).⁵¹ The KT-TENG comprised two triboelectric layers (PET and Kapton films), with two kinesio tapes and electrode layers on the back side, and electric signals output produced by tiny motions. The bending angles and slight movements showed linear relationship with the $Q_{\rm SC}$ as well as $V_{\rm OC}$, enabling its good performance on real-time human motion monitor. Fang et al reported a new type of sensor system that was made assembling stretchable-rubber-based (SR-based) TENG devices to detect moving directions, and thus could overcome the limitations of rigid substrates.⁵³ This system consisted of an elastic rubber layer and an Al film. The SR-based TENG exploited the length expansion through introducing an in-plane charge separation, resulting in the potential difference between the Al electrode and the ground, and an alternating output current was generated by periodically released. Serving as a multifunctional sensor, the SR-based TENG was also able to detect breathing and joint motion.

For body motion detection, TENG can distinguish different gesture types produced by different electric signals, demonstrating the possibility of using TENG to detect abrupt motions such as people falling and other hazard signals. In 2019, Ahmed et al developed a multifunctional self-powered alerting sensor enabled by the smart ferrofluid-based triboelectric nanogenerator (FO-TENG) as an efficient platform for real-time hazard

monitoring.⁵⁴ As shown in Figure 5C, the output voltage amplitude of the sensor increased with increasing swimming speed, and different swimming techniques produced distinct signal profiles. The FO-TENG signal was higher than normal when the swimmer was drowning, due to the struggling and random motions with giant amplitude from the swimmer. The waterproof FO-TENG was composed of a silicone rubber tube, a patterned copper wire electrode with ferrofluid as the triboelectric layer. It was also integrated with the human body in different arrangements and worked as a multifunctional self-powered sensor with extraordinary confirmability. Guo et al presented an all-fiber hybrid piezoelectricenhanced TENG (TPNG) on conductive fabrics manufactured by electrospinning silk fibroin and polyvinylidene fluoride (PVDF) nanofibers.55 Compared with other textile-based nanogenerators, TPNGs showed higher power levels of voltage (500 V), short-circuit current (12 μ A) and power density (0.31 mWcm⁻²). It could be customized to be embedded in clothes in any sizes and shapes to identify multiple types of body motions, a feature that made it very promising in real-time health monitoring.

Gait monitoring is critical in clinical biomotion analysis, sports training and medical diagnosis. Monitoring human motion enables identity recognition since each person has his/her own gait characteristics. Han et al reported a TENG-based band for detecting muscle activity and recognizing identity through identifying gait patterns (Figure 5D).56 The soft, stretchable and low-cost band was fabricated with a rubber tube wrapper with physiological saline as the electrode. The band could detect walking information, including six types of human motions (swallowing, jumping, squatting, breathing, calf raising, and bicep curling). In 2018, Lin et al proposed a smart insole for real-time gait monitoring based on TENG.⁵⁷ The TENG-based sensors, which were fabricated by rubbers and copper layers, were distributed at the front and rear sides of the insole. The TENGs relied on contact-separation motions of two triboelectric layers to generate electrical output, with excellent stability and mechanical durability. Furthermore, the various gait patterns such as jump, and run was exactly presented by the time difference between two feet contact with ground. Jao et al developed a chitosan-based TENG (C-TENG) to harvest biomechanical energy through human motions for self-power healthcare sensing such as sweat and gait detection.⁵⁸ Compared with traditional TENGs, the output features of the C-TENG remained unchanged as the relative humidity inside shoes varies from 20% to 80%. A biocompatible chitosan-glycerol film was combined with a textile to exert its multifunctional capability in this work.

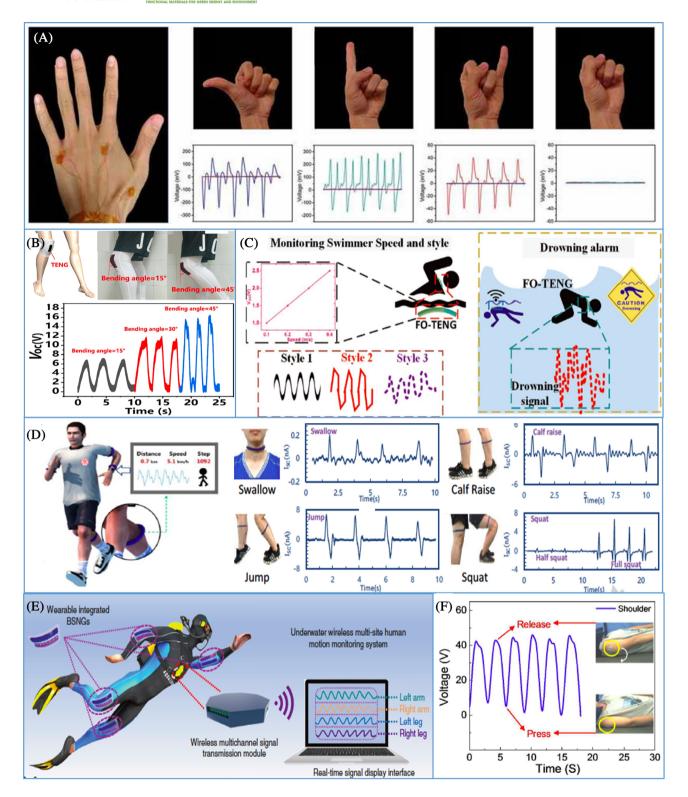


FIGURE 5 The application of TENG in motion sensor. A, Photos of gesture sensors on the back of the hand and the relative voltage outputs by various gestures. ⁵⁰ Reproduced with permission. Copyright 2019, Informa UK Limited. B, The KT-TENG band for joint motion monitor in real-time and the measurement of VCO₂ with bending angle. ⁵¹ Reproduced with permission. Copyright 2018, MDPI. C, FO-TENG monitor the swimmer's speed and style in the right panel, and its application in the drowning detection. ⁵⁵ Reproduced with permission. Copyright 2019, John Wiley&Sons. D, TENG band for quantitative motion information monitoring. ⁵⁶ Reproduced with permission. Copyright 2019, Elsevier Publishing Group. E, Schematic of BSNG-based human motion detect sensor for underwater application. ⁵⁹ Reproduced with permission. Copyright 2019, Springer Nature Group. F, TES binding with shoulder and its corresponding voltage changes during sleep. ⁶⁰ Reproduced with permission. Copyright 2016, American Chemical Society

Wearable electronics that can function well underwater is attracting increasing attentions. Such devices need to be waterproof and contain a sustainable power source. Zou et al, inspired by the electric eel (*Electrophorus electricus*) that could generate thousands of volts of electricity under water, proposed a bionic stretchable nanogenerator (BSNG) combined with TENG for energy harvesting and underwater sensing (Figure 5E).⁵⁹. Through utilizing the unmatched stress effect caused by polydimethylsiloxane (PDMS) and silicone, a mechanically controlled tunnel was produced by imitating ion channels in the electrocyte membrane. The BSNG is a promising power source for wearable electronics in mute-position motion monitoring and underwater rescuing.

Sensors for detecting specific sleep postures and conducting physiological analysis in real time have been reported recently to diagnose sleep deprivation through detecting the airflow from breathing and body movements of patients. Song et al. reported an APLE (Alplastic laminated film)-based TENG device to monitor sleep behavior and body movements (Figure 5F).⁶⁰ A fold APLE and a 2 mm cantilever spring leaf inside the fold APLE constituted the sandwiched structure of TENG, thus electrostatic charges were created on both parts. The TENG sensitivity was highly enhanced due to the high open-circuit voltage of 55 V. Changes in pressure attributed to body motions during sleeping were sensitively detected by TENG in real time. Lin et al developed a textile TENG array as a bedsheet for real-time sleep behavior monitoring.61 The textile TENG was a sandwiched structure with conductive fibers laminated onto the top and bottom fabrics, and wavy-structured polyethylene terephthalate (PET) films in the middle. The smart textile exhibited short response time of less than 80 ms and excellent sensitivity of 0.77 V Pa⁻¹. The electrical signals obtained through the textile TENG-based smart mattress would provide real-time information on the sleep quality and health status of the sleeper. This represented a smooth and noninvasive method to monitor sleep behavior with excellent washability and sensitivity, which fits well to the integrated signal processing system.

The e-skin is becoming popular in both commercial and academic communities due to its unique properties and excellent performance. In 2018, Dong et al exhibited a skin-inspired triboelectric nanogenerator (SI-TENG) as a multifunctional e-skin. 62 SI-TENG demonstrated favorable stretchability, excellent sensitivity, and accuracy attributed to the three-ply-twisted silver-coated nylon yarn. A $V_{\rm OC}$ of 160 V and an instantaneous average power density of 230 mW m $^{-2}$ were generated by this SI-TENG. Its high sensitivity to pressure and fast response can lead to potential applications in wrist pulse detection, voice recognition, and biomedical prostheses.

In 2018, a whirligig-inspired portable TENG (Wi-TENG) equipped with high-frequency rotations and sustainable power was reported by Tang et al 63 The Wi-TENG worked in noncontract freestanding mode with radial-array electrodes to minimize resistance for achieving high-speed rotation. A rotor speed of 11 250 rpm, the maximum $I_{SC},\ V_{OC},$ and instantaneous output power of $\sim\!317~\mu\text{A}, \sim\!153~\text{V},$ and $\sim\!40.18~\text{mW}$ was achieved by the Wi-TENG. Being portable and sustainable, the Wi-TENG has been successfully applied in blood glucose test and worked as temperature-humidity detector.

Respiration rate is one of the most vital and reliable indices that directly reflects human physiological health status, and provides pivotal information for diagnosis of potential respiratory diseases and personal health management. In 2018, Cao et al reported a nanofiber-based triboelectric sensor (SNTS) to monitor health conditions through the respiratory rate (Figure 6A).⁶⁴ A screenprinted Ag nanoparticle (AgNP) electrode and an electrospun PVDF nanomembrane constituted the SNTS with an arch structure. The air permeability of A4 paper was 1.4 mm/s, while that of this SNTS was up to 6.16 mm/s, which was much higher than traditional cast films. It also exhibited remarkable softness when it was folded, bent, or even twisted, and thus the skin-friendly characteristics ensured its splendid electronic performance. Moreover, SNTS was regarded as a finger motion tracer and activity trailer due to its outstanding performance. In 2018, Wang et al showed a self-powered TENG-based respiratory monitoring driven by air flow, which transformed human respiratory mechanical energy into electric signals to realize real-time monitoring.65 The TENG comprised a flexible PTEE thin film, which generated vibrations under laminar flow. When the PTFE film was installed in a mask, it responded effectively and provided a real-time display of breathing patterns through different air flow rates, as reflected by the charge transfer. Thus, the TENG-based system provided a direct way to measure human breath patterns. In 2019, Zhang et al developed an integrated wireless respiratory monitoring system that was located in the waist through detecting breathing signals by a smart strap (Figure 6B). The cyclical variations perceived by TENG were used to collect respiratory information. The sensor could be activated even by a minimum amplitude of the slide shift (2.5 mm) with efficient wireless transmission as demonstrated by a mechanical test. Xia et al designed an easyto-fold and portable hybrid triboelectric-electromagnetic generator (TEMG) with high sensitivity to detect airflow. It was used to harvest mechanical energy and had practical application for respiratory rate calculation as well.⁶⁶

The textile triboelectric nanogenerators (t-TENGs) have exhibited distinguished superiority in self-powered

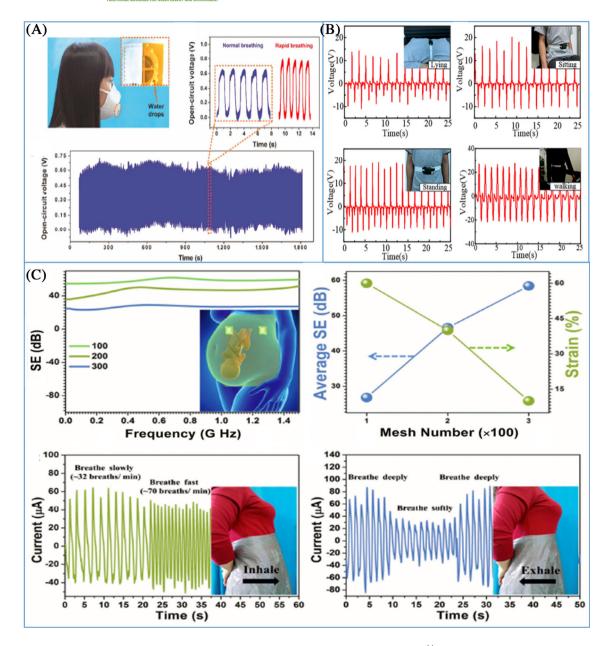


FIGURE 6 Respiration monitor. A, Schematic of SNTS application in respiratory monitor. ⁶⁴ Reproduced with permission. Copyright 2018, Elsevier Publishing Group. B, The TENG sensor fastened on the waist in various daily activities for respiration monitoring. ⁸⁰ Reproduced with permission. Copyright 2019, Springer Nature Group. C, Photograph of ES-HNG as a respiration sensor and health monitor to protect a pregnant woman. ⁶⁸ Reproduced with permission. Copyright 2017, John Wiley&Sons

sensing and energy harvesting. In 2016, Zhao et al demonstrated a machine-washable and fabrication-scalable t-TENGs as a wearable respiratory monitor to record human respiratory depth and rate.⁶⁷ The new t-TENG consisted of Cu-coated polyethylene terephthalate (Cu-PET) warp yarns and polyamide (PI)-coated Cu-PET (PI-Cu-PET) yarns. The triboelectric charges were effectively generated by very subtle deformation such as tapping or bending, and a maximum short-circuit current density of 15.50 mA m⁻² was achieved. Thus, the new t-TENG was able to respond quickly to subtle changes in human

motions and work as a wearable respiratory detector to monitor human health.

In 2017, Qian et al reported a stretchable electromagnetic shielding hybrid nanogenerator (ES-HNG), which scavenged mechanical and thermal energy as well as monitored human health by attachment to the on human abdomen (Figure 6C).⁶⁸ The ES-HNG was composed of a stretchable TENG and some PPENGs forming an island structure, and was able to transform mechanical and thermal energy into electricity. As a computer keyboard cover, ES-HNG could generate energy through charging

13 of 20

a capacitor to 3 V by typing, which was sufficient to drive the portable devices. Moreover, more than 99% of radiation from the computer or other facilities was shielded by ES-HNG.

4 | TENG-BASED APPLICATIONS IN IN-VITRO BIOMEDICAL SYSTEMS

Applications of TENG in biomedical systems are not limited within in vivo or wearable functionalities. With the advantages of novel materials and design, the use of TENGs with micro-structured patterns and high sensitivity has been explored in several in-vitro applications such as drug delivery, ⁶⁹⁻⁷¹ cell proliferation, ⁷² sterilization, and functional sensors. ⁷³

4.1 | TENG for drug delivery

To treat various diseases with little harm to the body, precise therapeutic drug delivery at the targeted location and controlled drug release is required, and thus a number of noninvasive technologies for drug delivery are established. Among those technologies, TENG is a promising method for drug delivery with no external power source assisted. Zhao et al reported a drug delivery system (DDS) that was controlled by TENG for cancer therapy.⁷⁴ The triboelectric surfaces of the TENG were Ti and PTFE with Cu deposited, and a small magnet was

attached on the back of each friction layer to maintain the output performance of the device for long-term applications. The entire device was encapsulated with PTFE and PDMS layers to prevent damages in harsh environment. When red blood cells (RBCs) were successfully loaded with doxorubicin(DOX, an anti-tumor drug) by the hypotonic dialysis method in a suspension and were placed on a simulation device with an electrodedeposited substrate, the electric field of 4 kV cm⁻¹ generated by the TENG was applied to the device to release DOX. (Figure 7A) After withdrawing the EF, the DOX drug was loaded in RBCs again for the next release process. Sixty HeLa-tumor-bearing BALB/c-nu mice were treated with phosphate buffer saline (PBS) (the control group), electric field (EF), DOX, DOX + EF, DOX loaded RBCs (D@RBCs), and D@RBC + EF with a dosage of DOX equal to 5 mg kg⁻¹to investigate the antitumor efficacy of the DDS in vivo. D@RBC + EF DDS performed the best therapeutic effect in inhibiting tumor growth, with mice in this group showing the minimum tumor cell proliferation and only 2 of the 5 mice died on the 54th day, while all the mice in the other five groups died within 46 days.

In 2017, Song et al reported an implantable pumping drug delivery system that was driven by a TENG for ocular diseases therapy. The rotating TENG was fabricated with a PTFE film sandwiched between two Cu electrodes with radial grating structures on the electrode surfaces. The pump system, which was comprised a PDMS ocular drug reservoir, a PDMS microtube and a pair of Au electrodes on the silicon substrate, was driven by the TENG

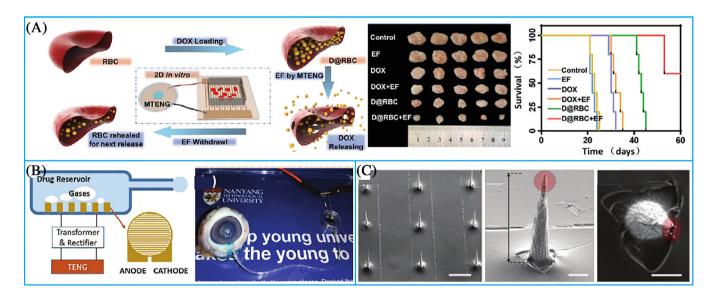


FIGURE 7 Drug delivery. A, TENG for cancer therapy.⁷⁴ Reproduced with permission. Copyright 2019, John Wiley & Sons. B, Implantable TENG for ocular drug delivery⁷⁰ Reproduced with permission. Copyright 2017, John Wiley & Sons. C, Patterns and structures of the microneedles employed on the back side of the electrode of TENG for delivering drug.⁷¹ Reproduced with permission. Copyright 2018, Royal Society of Chemistry

through a transformer with pumping flow rates from 5.3 to 40 μL min⁻¹. (Figure 7B) This system was applied into the anterior chamber of porcine eyes through incision and successfully delivered ocular drugs driven by the biokinetic energies of human hands. TENG integrated with microneedle patterns was also preferred for noninvasive drug delivery. In 2018, Bok et al proposed a drug delivery system composed of deoxyribonucleic acid (SDNA)-based dissolving microneedles device for drug insertion and a CS mode TENG for electric field induction.⁷¹ With a density of 80 microneedles per array (Figure 7C), this system was successfully employed in porcine cadaver skin for drug intercalation, demonstrating its potential for in-vivo drug delivery. A similar electrode structure with silicon nanoneedles to realize noninvasive drug delivery was reported by Liu et al in 2019, in both in vitro and in vivo conditions.⁶⁹ Driven by the TENG through simple finger friction or hand slapping, significant enhancement in efficiency of the transdermal biomolecule delivery was realized by the sufficient high local electrical field located at the nanoneedle-cell interface.

4.2 | Other applications of TENG in in-vitro biomedical systems

Apart from drug delivery system, TENG was also demonstrated in cell differentiation, proliferation and migration with high efficiency. Figure 8A shows a system reported by Jin et al in 2016 for the nonviral direct conversion of primary mouse embryonic fibroblasts (PMEFs) to induced neuronal (iN) cells, with TENG serving as the triboelectric stimulator (TES).⁷⁵ Here, the CS mode TENG was structured with an Al film as the top electrode, a PDMS-pillar patterned Kapton film, and a Cu film on the backside of the Kapton as the bottom electrode, where an electric output of $V_{\rm OC} \approx 30 \, \text{V}$ and $I_{\rm SC} \approx 270 \; \rm nA$ was obtained. The output was connected to the cell culture substrate fabricated with highly conductive Ti-deposited Si, which successfully enhanced the PMEF differentiation, as demonstrated both in the cell culture template and skin tissues of mice. Additionally, in 2019 Tian reported a stimulator that was composed of a spring-CS mode TENG with the triboelectric pair of Al/PTFE and a flexible interdigitated electrode for bone formation. (Figure 8B)76 They demonstrated that the electric field generated by TENG was effective for promoting the attachment, differentiation and proliferation of the murine calvarial preosteoblasts, MC3T3-EI, where 72.76% in adhesion, 23.82% in proliferation rate, and 28.2% in differentiation rate were enhanced by continuous stimulation, respectively.

Similar functionalities of cell proliferation and migration based on a disc-shaped rotating TENG were reported by Hu et al in 2019.⁷²

In 2019, Yao et al proposed an omnidirectional TENG to promote hair regeneration in SD rats by using the generated alternating electric field.⁷⁷ This system comprised a TENG connected with a pair of comb-shaped electrodes, and the device was placed on the back of rats with the top layer of the electrodes in contact with the skin. (Figure 8C) When the TENG was driven by random motions, spatially distributed electric field was applied on the skin of the SD rats by the comb electrodes, where hair regeneration with higher density of hair follicles and longer hair shaft was successfully manifested. Furthermore, the secretion of vascular endothelial growth factor and keratinocyte growth factor were also enhanced by the system and finally hair regeneration of the defective nude mice was achieved. The TENG-based sterilization system. which was reported by Tian el al in 2017, was another example of the successful application of TENG in biomedical system.⁷³ Here, the wave-driven TENG was enclosed in a PS shell, and the electrical output of TENG was connected with two Ag/ZnO nano-brush electrodes, where two cambered Al layers were deposited on the inner surface of the shell separately and a rubber ball was employed to slide on the inner surface. This sterilization system was employed to treat Escherichia coli (E coli), Staphylococcus aureus (S aureus) and natural river water, with significant reduction in colony forming units (CFUs) in both instant and sustainable sterilization, as a result of the synergetic work of the electroporation generated during electric field treatment by TENG and sterilization by the sustained intracellular reactive oxygen (ROS) while withdrawing electric species (Figure 8D).

The use of biosensors based on TENG for special signal monitoring was realized as well. Zhao et al reported a TENG for detecting neurotransmitters and neural electric signals between neuron synapses, (Figure 8E) as the Schottky barrier height could be tuned by the TENG output.78 The multifunctional detection of the Schottky to Ohmic reversible (SOR) biosensor was attributed to the reversible conversion between Schottky and Ohmic contacts by the treatment of the high-voltage pulse from TENG, where the Schottky-contact SOR biosensor was highly sensitive to low concentration of neurotransmitters, and the Ohmiccontact SOR biosensor was able to detect bioelectrical signals. In-vitro detection of dopamine monitoring for neural electric signals of the bullfrog sciatic nerve trunk before and after conversion was both realized by the demonstrating SOR biosensor, ability multifunctional detection.

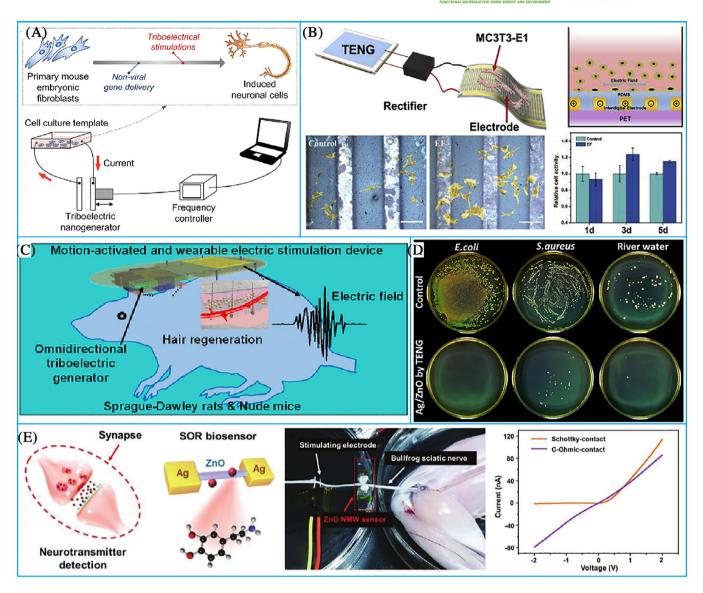


FIGURE 8 Other applications of TENG in in-vitro biomedical systems. A, TENG for accelerating the nonviral direct conversion. Reproduced with permission. Copyright 2016, John Wiley & Sons. B, Implantable TENG for promoting proliferation and differentiation of osteoblasts. Reproduced with permission. Copyright 2018, American Chemical Society. C, Wearable TENG for effective hair regeneration. Reproduced with permission. Copyright 2019, American Chemical Society. D, TENG with anti-bacterial ability applied in sterilization system. Reproduced with permission. Copyright 2017, Elsevier Publishing Group. E, TENG as a sensor for neurotransmitter detection. Reproduced with permission. Copyright 2019, John Wiley & Sons

5 | SUMMARY AND PERSPECTIVE

In summary, this review presents various types of TENG-based biomedical applications during their rapid development in recent years with different structures and functions. The self-powered TENG can collect biological information and act as power sources for commercial medical sensors, enabling the applications in health monitoring and the regulation of physiological functions, such as sensors for heart rate, blood pressure, respiratory rhythm, motion, power source for drug delivery, nerve stimulation, and others. This review discusses the in vivo applications

of TENGs that are implantable via the encapsulation with biocompatible materials for both health monitoring and disease treatment, and the applications of wearable TENGs with various structures for collecting information of physical characteristics. Other explorations based on TENGs such as cell proliferation and differentiation, and drug delivery are also reviewed. The output performance of reviewed TENGs as reflected by the $V_{\rm OC}$ and the output power are summarized in Table 1, where the function and size of each TENG are listed as well.

TENG can be implanted into the body, mounted onto the skin or clothes, or woven into fabrics as smart

TABLE 1 Performance summary of TENGs in the reviewed articles

Туре	NO.	Functions	$V_{ m OC}$	Power	Size
In Vivo	10	Endocardial pressure sensor	Up to 6.2 V	N/A	$1 \text{ cm} \times 0.5 \text{ cm} \times 0.1 \text{ cm}$
	27	Power cardiac pacemaker	\sim 12 V	$107~\mathrm{mWm}^{-2}$	$1.2 \text{ cm} \times 1.2 \text{ cm}$
	31	Power cardiac pacemaker	Up to 65.2 V	8.44 mWm^{-2}	39 mm × 61 mm × 0.99 mn
	33	Peripheral nerve stimulation	\sim 30 V	0.496 μJ/cycle	$2 \text{ cm} \times 2 \text{ cm}$
	34	Skin wound healing	0.2-2.2 V	40 μW	$10 \text{ cm} \times 1.2 \text{ cm}$
	35	TENG with tunable biodegradation	~2 V	95 μW	$1.2 \text{ cm} \times 1.2 \text{ cm} \times 0.65 \text{ mm}$
	36	Wireless cardiac sensor	\sim 14 V	0.9 μW	25 mm \times 10 mm \times 1.5 mm
	37	Weight control	50-120 mV	N/A	16 mm × 12 mm × 2.5 mm
	39	Muscle stimulation	∼47 V	N/A	$10 \text{ cm} \times 10 \text{ cm}$
	40	Sensor for underactive bladder control	$35.6\sim114\;\text{mV}$	32.6 mWm ⁻²	1.4 cm × 2.2 cm
	44	Power the infrared laser	∼0.2 V	N/A	$1.5 \text{ cm} \times 1.0 \text{ cm}$
	79	Harvest biomechanical energy	~40 V	N/A	$2.0 \times 3.0 \text{ cm}$
Wearable	47	Pressure sensor	0.2-20.4 V	N/A	$3.7 \text{ cm} \times 3.7 \text{ cm} \times 0.2 \text{ cm}$
	48	Blood oxygen monitor system	∼75.3 V	0.2 mWcm^{-2}	$1 \text{ cm} \times 1 \text{ cm}$
	49	Ultrasensitive pulse sensor	∼1.52 V	N/A	20 mm \times 10 mm \times 0.1 mm
	50	Gesture-sensing system	Up to 250 mV	N/A	$2 \text{ cm} \times 3 \text{ cm}$
	51	Human motion sensor	Up to 24.1 V	N/A	$1.5 \text{ cm} \times 4 \text{ cm}$
	52	Human gesture detector	Average 50 nA	N/A	$3 \text{ cm} \times 3 \text{ cm}$
	53	Movement sensor in different directions.	∼65 V	76.27 μWm ⁻²	30 mm × 88 mm
	54	Hazard stimulus sensing	Up to 14 V	N/A	N/A
	55	Falling-down detection and timely remote alarm	~500 V	3.1 Wm ⁻²	$2 \text{ cm} \times 4 \text{ cm}$
	56	Identity recognition through gait pattern	Up to 89.4 V	0.33 mWm ⁻²	15 cm \times 200 μ m (thick), d = 1 cm
	57	Insole for real-time gait monitor	Up to 35 V	N/A	Diameter = 20 mm
	58	Healthcare sensor	Up to 130 V	N/A	$5 \text{ cm} \times 3 \text{ cm}$
	59	Underwater applications	Up to 600 V	N/A	$10 \text{ cm} \times 6 \text{ cm} \times 8 \text{ mm}$
	60	Sleep monitor	∼55 V	N/A	Diameter = 2 cm
	61	Sleeping monitor	Up to 3 V	N/A	$2 \text{ m} \times 1.5 \text{ m}$
	62	Biomechanical energy harvest and versatile pressure sensing	∼160 V	230 mW m ⁻²	80 mm × 40 mm
	63	Personal health monitor	Up to 153 V	40.18 mW	70 mm × 100 mm
	64	Respiratory monitor	10-25 V	N/A	1 cm × 2 cm
	65	Real-time respiratory monitor	~2.4 V	1.3 mW	N/A
	66	Breath detector	~500 V	2 mW for the TEG and 15.8 μW for the EMG	$5 \text{ cm} \times 5 \text{ cm} \times 2 \text{ mm}$
	67	Respiratory monitor	\sim 5 V	23.86 mWm ⁻²	N/A
	68	Health monitor	~3 V	N/A	12 cm × 3 cm
			-	1	



TABLE 1 (Continued)

Type	NO.	Functions	$V_{ m oc}$	Power	Size
In Vitro	69	Transdermal biomolecule delivery	∼20 V	N/A	4 × 5.5 cm
	70	Drug delivery system for ocular diseases therapy	∼115 V	N/A	N/A
	71	Dissolving microneedles device for drug insertion	∼95 V	N/A	$2 \text{ cm} \times 3 \text{ cm}$
	72	Cell proliferation and migration	∼160 V	N/A	N/A
	73	Sterilization system	∼50 V	N/A	Shell $d = 8$ cm, rubber ball, $d = 4$ cm
	74	Drug delivery system for cancer therapy	∼70 V	N/A	Diameter = 4 cm
	75	Nonviral direct conversion	\sim 30 V	N/A	N/A
	76	Bone formation	${\sim}100~\mathrm{V}$	N/A	$3 \text{ cm} \times 3 \text{ cm}$
	77	Promote hair regeneration	${\sim}430~\text{mV}$	N/A	$2 \text{ cm} \times 2 \text{ cm}$
	78	Neurotransmitters and neural electric signals detecting	350-500 V	N/A	8 cm × 8 cm

textiles. It shows great potential in the healthcare market, but there are still challenges to be addressed before its industrialization and commercialization, which are summarized as follows:

- 1. To enhance the robustness, durability, compatibility, etc. of TENGs in various biomedical situations, further optimizations in the size, biocompatibility, and flexibility of TENG-based systems toward being implanted in specific parts of human body such as muscles are still required.
- 2. Current applications are limited by the critical clinical challenges toward wider applications and industrialization, especially the issue of foreign body response effect by the immune system. Such a foreign body response will encapsulate the implanted devices with fibroblasts, inhibiting TENG from receiving bio-mechanical motion stimuli toward long-term applications.
- For wearable TENG, improving its sensitivity and stability are two important factors apart from optimizing the device structure and enhancing anti-interference ability.
- 4. The output performance of TENG and power management units need to be optimized, such as packaging and miniaturizing of the whole system.
- 5. TENG is applied as an external power source to provide an electric field assisted by other electrodes management circuits to regulate cell development and drug delivery in vitro, and thus, the interaction between TENG and cells is weak. Future work should simplify biomedical systems with functional TENG

structures to directly realize the strong interaction between TENG and cells. Additionally, further studies on the TENG-based devices to regulate cell adhesions and apoptosis are greatly helpful for the development of anti-cancer strategies.

Despite these challenges, considering the following advantages of TENG, various available materials with low-cost for fabrication, simple fabrication process, extraordinary high sensitivity and output in response to slight stimuli. As the current trend of electronic equipment toward wearable and portable electronics, the prospect of TENG-based wearable health monitor systems will surely have an brilliant future in the healthcare market.

ACKNOWLEDGMENT

This work was funded by HKSAR The Research Grants Council Early Career Scheme (Grant no. 24206919), The Chinese University of Hong Kong Direct Grant (Grant no. 4055086), and The Hong Kong Polytechnic University (PolyU Project ID. P0030234).

ORCID

Yunlong Zi https://orcid.org/0000-0002-5133-4057

REFERENCES

- Adami H-ODN, Trichopoulos D, Willett W. Primary and secondary prevention in the reduction of cancer morbidity and mortality. Eur J Cancer. 2001;37(suppl S8:118-127.
- 2. McGill HC Jr, McMahan CA, Gidding SS. Preventing heart disease in the 21st century: implications of the Pathobiological

- determinants of atherosclerosis in youth (PDAY) study. Circulation. 2008;117(9):1216-1227.
- Perez-Pozuelo I, Zhai B, Palotti J, et al. The future of sleep health: a data-driven revolution in sleep science and medicine. NPJ Digit Med. 2020;3:42.
- 4. Park SY, Kim Y, Kim T, Eom TH, Kim SY, Jang HW. Chemoresistive materials for electronic nose: Progress, perspectives, and challenges. *InfoMat*. 2019;1(3):289-316.
- Marin-Neto JA. Challenges and opportunities for primary, secondary, and tertiary prevention of Chagas' disease. *Heart.* 2009; 95(7):524-534.
- DMM-P S. Wearable wireless health monitoring: current developments, challenges, and future trends. *IEEE Microwave Magazine*. 2015;16(4):55-70.
- Khan Y, Ostfeld AE, Lochner CM, Pierre A, Arias AC. Monitoring of vital signs with flexible and wearable medical devices. *Adv Mater*. 2016;28(22):4373-4395.
- Yao S, Swetha P, Zhu Y. Nanomaterial-enabled wearable sensors for healthcare. Adv Healthc Mater. 2018;7(1):1700889.
- 9. Zheng Q, Shi B, Li Z, Wang ZL. Recent progress on piezoelectric and triboelectric energy harvesters in biomedical systems. *Adv Sci (Weinh)*. 2017;4(7):1700029.
- Liu Z, Ma Y, Ouyang H, et al. Transcatheter self-powered ultrasensitive endocardial pressure sensor. Adv Funct Mater. 2019;29(3):1807560.
- 11. Wang J, Wu C, Dai Y, et al. Achieving ultrahigh triboelectric charge density for efficient energy harvesting. *Nat Commun*. 2017;8(1):88.
- Zhang Q, Liang Q, Liao Q, et al. Service Behavior of Multifunctional Triboelectric Nanogenerators. Adv Mater. 2017; 29(17):1606703
- 13. Zhang Q, Liang Q, et al. An amphiphobic hydraulic triboelectric nanogenerator for a self-cleaning and self-charging power system. *Adv Funct Mater.* 2018;28(35):1803117.
- Li J, Wang X. Research update: materials design of implantable nanogenerators for biomechanical energy harvesting. APL Mater. 2017;5(7):073801.
- Liu X, Zhao K, Wang ZL, Yang Y. Unity convoluted design of solid li-ion battery and triboelectric nanogenerator for selfpowered wearable electronics. Adv Energy Mater. 2017;7: 1701629.
- Cheng G, Lin ZH, Lin L, Du ZL, Wang ZL. Pulsed Nanogenerator with huge instantaneous output power density. ACS Nano. 2013;7(8):7383-7391.
- Lin L, Wang S, Xie Y, et al. Segmentally structured disk triboelectric nanogenerator for harvesting rotational mechanical energy. *Nano Lett.* 2013;13(6):2916-2923.
- Niu S, Wang ZL. Theoretical systems of triboelectric nanogenerators. Nano Energy. 2015;14:161-192.
- 19. Lin Z, Chen J, Li X, et al. Triboelectric Nanogenerator enabled body sensor network for self-powered human heart-rate monitoring. *ACS Nano*. 2017;11(9):8830-8837.
- Parvez Mahmud MA, Huda N, Farjana SH, Asadnia M, Lang C. Recent advances in nanogenerator-driven self-powered implantable biomedical devices. *Adv Energy Mater*. 2018;8(2):1701210.
- 21. Zhao L, Li H, Meng J, Li Z. The recent advances in self-powered medical information sensors. *InfoMat.* 2019;2(1): 212-234.

- 22. Liu Z, Li H, Shi B, Fan Y, Wang ZL, Li Z. Wearable and implantable triboelectric nanogenerators. *Adv Funct Mater*. 2019;29:20.
- 23. Zhang Q, Zhang Z, Liang Q, et al. Green hybrid power system based on triboelectric nanogenerator for wearable/portable electronics. *Nano Energy*. 2019;55:151-163.
- Wang ZL. On Maxwell's displacement current for energy and sensors: the origin of nanogenerators. *Mater Today*. 2017;20(2): 74-82.
- Wang ZL. On the first principle theory of nanogenerators from Maxwell's equations. *Nano Energy*. 2020;68:104272.
- Wang X, Yin Y, Yi F, et al. Bioinspired stretchable triboelectric nanogenerator as energy-harvesting skin for self-powered electronics. *Nano Energy*. 2017;39:429-436.
- 27. Zheng Q, Shi B, Fan F, et al. In vivo powering of pacemaker by breathing-driven implanted triboelectric nanogenerator. *Adv Mater.* 2014;26(33):5851-5856.
- Li J, Kang L, Long Y, et al. Implanted battery-free directcurrent micro-power supply from in vivo breath energy harvesting. ACS Appl Mater Interfaces. 2018;10(49):42030-42038.
- Li N, Yi Z, Ma Y, et al. Direct powering a real cardiac pacemaker by natural energy of a heartbeat. ACS Nano. 2019;13(3): 2822-2830.
- 30. Ma Y, Zheng Q, Liu Y, et al. Self-powered, one-stop, and multifunctional implantable triboelectric active sensor for real-time biomedical monitoring. *Nano Lett.* 2016;16(10):6042-6051.
- 31. Ouyang H, Liu Z, Li N, et al. Symbiotic cardiac pacemaker. *Nat Commun*. 2019;10(1):1821.
- 32. Wang J, Wang H, He T, He B, Thakor NV, Lee C. Investigation of low-current direct stimulation for rehabilitation treatment related to muscle function loss using self-powered TENG system. *Adv Sci (Weinh)*. 2019;6(14):1900149.
- 33. Lee S, Wang H, Wang J, et al. Battery-free neuromodulator for peripheral nerve direct stimulation. *Nano Energy*. 2018;50:148-158.
- Long Y, Wei H, Li J, et al. Effective wound healing enabled by discrete alternative electric fields from wearable Nanogenerators. ACS Nano. 2018;12(12):12533-12540.
- Li Z, Feng H, Zheng Q, et al. Photothermally tunable biodegradation of implantable triboelectric nanogenerators for tissue repairing. *Nano Energy*. 2018;54:390-399.
- 36. Zheng Q, Zhang H, Shi B, et al. In vivo self-powered wireless cardiac monitoring via implantable triboelectric Nanogenerator. *ACS Nano*. 2016;10(7):6510-6518.
- 37. Yao G, Kang L, Li J, et al. Effective weight control via an implanted self-powered vagus nerve stimulation device. *Nat Commun*. 2018;9(1):5349.
- Wang H, Wang J, He T, Li Z, Lee C. Direct muscle stimulation using diode-amplified triboelectric nanogenerators (TENGs). *Nano Energy*. 2019;63:103844.
- Wang J, Wang H, Thakor NV, Lee C. Self-powered direct muscle stimulation using a triboelectric Nanogenerator (TENG) integrated with a flexible Multiple-Channel intramuscular electrode. ACS Nano. 2019;13(3):3589-3599.
- Arab Hassani F, Mogan RP, Gammad GGL, et al. Toward selfcontrol Systems for Neurogenic Underactive Bladder: a triboelectric Nanogenerator sensor integrated with a Bistable microactuator. ACS Nano. 2018;12(4):3487-3501.

- 41. Love MR, Palee S, Chattipakorn SC, Chattipakorn N. Effects of electrical stimulation on cell proliferation and apoptosis. *J Cell Physiol.* 2018;233(3):1860-1876.
- Love MR, Sripetchwandee J, Palee S, Chattipakorn SC, Mower MM, Chattipakorn N. Effects of biphasic and monophasic electrical stimulation on mitochondrial dynamics, cell apoptosis, and cell proliferation. *J Cell Physiol*. 2019;234(1): 816-824.
- Ross CL. The use of electric, magnetic, and electromagnetic field for directed cell migration and adhesion in regenerative medicine. *Biotechnol Prog.* 2017;33(1):5-16.
- Tang W, Tian J, Zheng Q, et al. Implantable self-powered low-level laser cure system for mouse embryonic osteoblasts' proliferation and differentiation. ACS Nano. 2015;9(8):7867-7873.
- Niu S, Wang X, Yi F, Zhou YS, Wang ZL. A universal selfcharging system driven by random biomechanical energy for sustainable operation of mobile electronics. *Nat Commun*. 2015;6:8975.
- 46. Yang J, Chen J, Su Y, et al. Eardrum-inspired active sensors for self-powered cardiovascular system characterization and throat-attached anti-interference voice recognition. *Adv Mater*. 2015;27(8):1316-1326.
- 47. Bai P, Zhu G, Jing Q, et al. Membrane-based self-powered triboelectric sensors for pressure change detection and its uses in security surveillance and healthcare monitoring. *Adv Funct Mater.* 2014;24(37):5807-5813.
- 48. Chen H, Xu Y, Zhang J, Wu W, Song G. Self-powered flexible blood oxygen monitoring system based on a triboelectric Nanogenerator. *Nanomaterials (Basel)*. 2019;9(5):778.
- Ouyang H, Tian J, Sun G, et al. Self-powered pulse sensor for Antidiastole of cardiovascular disease. *Adv Mater*. 2017;29(40): 1703456.
- Chiu CM, Chen SW, Pao YP, Huang MZ, Chan SW, Lin ZH. A smart glove with integrated triboelectric nanogenerator for self-powered gesture recognition and language expression. *Sci Technol Adv Mater.* 2019;20(1):964-971.
- 51. Wang S, He M, Weng B, et al. Stretchable and wearable triboelectric Nanogenerator based on Kinesio tape for self-powered human motion sensing. *Nanomaterials (Basel)*. 2018;8(9):657.
- 52. Das PS, Chhetry A, Maharjan P, Rasel MS, Park JY. A laser ablated graphene-based flexible self-powered pressure sensor for human gestures and finger pulse monitoring. *Nano Res.* 2019;12(8):1789-1795.
- 53. Yi F, Lin L, Niu S, et al. Stretchable-rubber-based triboelectric Nanogenerator and its application as self-powered body motion sensors. *Adv Funct Mater*. 2015;25(24):3688-3696.
- 54. Ahmed A, Hassan I, Mosa IM, et al. An ultra-shapeable, smart sensing platform based on a multimodal Ferrofluid-infused surface. *Adv Mater*. 2019;31(11):e1807201.
- 55. Guo Y, Zhang X-S, Wang Y, et al. All-fiber hybrid piezoelectricenhanced triboelectric nanogenerator for wearable gesture monitoring. *Nano Energy*. 2018;48:152-160.
- Han Y, Yi F, Jiang C, et al. Self-powered gait pattern-based identity recognition by a soft and stretchable triboelectric band. *Nano Energy*. 2019;56:516-523.
- 57. Lin Z, Wu Z, Zhang B, et al. A triboelectric nanogenerator-based smart insole for multifunctional gait monitoring. *Adv Mater Technol.* 2019;4(2):1800360.

- 58. Jao Y-T, Yang P-K, Chiu C-M, et al. A textile-based triboelectric nanogenerator with humidity-resistant output characteristic and its applications in self-powered healthcare sensors. *Nano Energy*. 2018;50:513-520.
- Zou Y, Tan P, Shi B, et al. A bionic stretchable nanogenerator for underwater sensing and energy harvesting. *Nat Commun*. 2019;10(1):2695.
- Song W, Gan B, Jiang T, et al. Nanopillar arrayed triboelectric Nanogenerator as a self-powered sensitive sensor for a sleep monitoring system. ACS Nano. 2016;10(8):8097-8103.
- 61. Lin Z, Yang J, Li X, et al. Large-scale and washable smart textiles based on triboelectric nanogenerator arrays for self-powered sleeping monitoring. *Adv Funct Mater*. 2018;28(1):1704112.
- 62. Dong K, Wu Z, Deng J, et al. A stretchable yarn embedded triboelectric Nanogenerator as electronic skin for biomechanical energy harvesting and multifunctional pressure sensing. *Adv Mater.* 2018;30(43):e1804944.
- 63. Tang Q, Yeh M-H, Liu G, et al. Whirligig-inspired triboelectric nanogenerator with ultrahigh specific output as reliable portable instant power supply for personal health monitoring devices. *Nano Energy*. 2018;47:74-80.
- 64. Cao R, Wang J, Zhao S, et al. Self-powered nanofiber-based screen-print triboelectric sensors for respiratory monitoring. *Nano Res.* 2018;11(7):3771-3779.
- 65. Wang M, Zhang J, Tang Y, et al. Air-flow-driven triboelectric Nanogenerators for self-powered real-time respiratory monitoring. *ACS Nano*. 2018;12(6):6156-6162.
- 66. Xia X, Liu G, Chen L, et al. Foldable and portable triboelectricelectromagnetic generator for scavenging motion energy and as a sensitive gas flow sensor for detecting breath personality. *Nanotechnology*. 2015;26(47):475402.
- Zhao Z, Yan C, Liu Z, et al. Machine-washable textile triboelectric Nanogenerators for effective human respiratory monitoring through loom weaving of metallic yarns. *Adv Mater*. 2016;28 (46):10267-10274.
- Zhang Q, Liang Q, Zhang Z, et al. Electromagnetic shielding hybrid Nanogenerator for health monitoring and protection. *Adv Funct Mater*. 2018;28(1):1703801.
- Liu Z, Nie J, Miao B, et al. Self-powered intracellular drug delivery by a biomechanical energy-driven triboelectric Nanogenerator. Adv Mater. 2019;31(12):e1807795.
- 70. Song P, Kuang S, Panwar N, et al. A self-powered implantable drug-delivery system using biokinetic energy. *Adv Mater.* 2017; 29(11):1605668.
- Bok M, Lee Y, Park D, et al. Microneedles integrated with a triboelectric nanogenerator: an electrically active drug delivery system. *Nanoscale*. 2018;10(28):13502-13510.
- 72. Hu W, Wei X, Zhu L, et al. Enhancing proliferation and migration of fibroblast cells by electric stimulation based on triboelectric nanogenerator. *Nano Energy*. 2019;57:600-607.
- 73. Tian J, Feng H, Yan L, et al. A self-powered sterilization system with both instant and sustainable anti-bacterial ability. *Nano Energy*. 2017;36:241-249.
- 74. Zhao C, Feng H, Zhang L, et al. Highly efficient in vivo cancer therapy by an implantable magnet triboelectric nanogenerator. *Adv Funct Mater.* 2019;29(41):1970285.
- Jin Y, Seo J, Lee JS, et al. Triboelectric Nanogenerator accelerates highly efficient nonviral direct conversion and in vivo reprogramming of fibroblasts to functional neuronal cells. Adv. Mater. 2016;28(34):7365-7374.

- 76. Tian J, Shi R, Liu Z, et al. Self-powered implantable electrical stimulator for osteoblasts' proliferation and differentiation. *Nano Energy*. 2019;59:705-714.
- 77. Yao G, Jiang D, Li J, et al. Self-activated electrical stimulation for effective hair regeneration via a wearable omnidirectional pulse generator. *ACS Nano*. 2019;13(11):12345-12356.
- Zhao L, Li H, Meng J, et al. Reversible conversion between Schottky and Ohmic contacts for highly sensitive multifunctional biosensors. Adv Funct Mater. 2019;30(5):1907999.
- 79. Zheng Q, Zou Y, Zhang Y, et al. Biodegradable triboelectric nanogenerator as a life-time designed implantable power source. *Sci Adv.* 2016;2(3):e1501478.
- 80. Zhang Z, Zhang J, Zhang H, et al. A portable triboelectric Nanogenerator for real-time respiration monitoring. *Nanoscale Res Lett.* 2019;14(1):354.

AUTHOR BIOGRAPHIES



XIA Xin received her BS degree from Xi'an Jiaotong University in 2018. She has joined the Chinese University of Hong Kong as a PhD student since August 2018, as a member of the Nano Energy and Smart System laboratory. Her current research interests include

mechanism of contact electrification and discharge, mechanical energy harvesting, high-voltage applications of triboelectric nanogenerators, self-powered system, and novel energy harvesting technologies.



LIU Qing is a PhD student in Applied biology and Chemical technology of The Hong Kong Polytechnic University. Her research interests focus on molecular nutrition and adipose tissue function, cell biology, and lipid metabolism.



Yuyan Zhu received her Bachelor's degree from the School of Animal Science at Zhejiang University in 2009. After graduation, she went to Purdue University for the PhD training, and received her PhD degree from the Department of Food Science

in 2016. Under Dr. Kee-Hong Kim's supervision, she got sufficient training in adipose biology, and mainly investigated dietary supplemental interventions for obesity prevention and pharmaceutical approaches for obesity treatment, especially adipocyte generation and function regulation. Afterward, she worked as a Postdoctoral Fellow in the Department of Biology at Georgia Institute of Technology under Dr. Liang

Han's supervision. She got rich experiences in using dynamic transgenic mouse models to study neural responses. Dr. Zhu joined the Department of Applied Biology and Chemical Technology at Hong Kong Polytechnic University as an Assistant Professor in July 2019. She published article in journals including *J Lipid Research*, *J Func Food Nature Neurosci*, and so on. She teaches physiology related courses to undergraduates majored in biomedical engineering, nursing, and radiology at HKPolyU. She won several awards including "Young Investigator Award" by 20th diabetes and cardiovascular risk factors—East Meets West Symposium (2018) and Bilsland Fellowship by Purdue University (2015).



ZI Yunlong is an Assistant Professor in Department of Mechanical and Automation Engineering at the Chinese University of Hong Kong since 2017. Dr. Zi received his PhD in Physics from Purdue University in 2014; his Bachelor of Engineering in

Materials Science and Engineering from Tsinghua University in 2009. Before joining CUHK, he worked as a Postdoctoral Fellow at Georgia Institute of Technology during 2014 to 2017. His current research interests mainly focus on high-efficiency mechanical energy harvesting through triboelectric nanogenerators (TENG), triboelectric effect, discharge, TENG triggered high-voltage applications, and selfpowered systems. As the first and corresponding authors, his research studies have been published in top-notch journals, including Nature Nanotechnology, Nature Communications, Advanced Materials, Nano Letters, ACS Nano, Nano Energy, and etc. He was honored as the winner of MRS Postdoctoral Award by Materials Research Society in 2017, as the first recipient from Georgia Tech; the Emerging Investigators by Journal of Materials Chemistry C in 2018; MINE Young Investigator Finalist in 2018; and one of "5 students who are transformation makers" as highlighted in Purdue homepage in 2013.

How to cite this article: Xia X, Liu Q, Zhu Y, Zi Y. Recent advances of triboelectric nanogenerator based applications in biomedical systems. *EcoMat.* 2020;2:e12049. https://doi.org/10.1002/eom2.12049