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PERSPECTIVE

# Wearable and Implantable Electronics: Moving toward Precision Therapy

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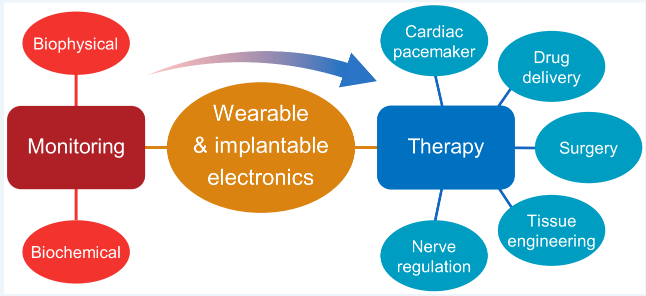
**ABSTRACT:** **Soft wearable and implantable electronic systems have attracted tremendous attention due to their flexibility, conformability, and biocompatibility. Such favorable features are critical for reliably monitoring key biomedical and physiological information (including both biophysical and biochemical signals) and effective treatment and management of specific chronic diseases. Miniaturized, fully integrated self-powered bioelectronic devices that can harvest energy from the human body represent promising and emerging solutions for long-term, intimate, and personalized therapies. In this Perspective, we offer a brief overview of recent advances in wearable/implantable soft electronic devices and their therapeutic applications ranging from drug delivery to tissue regeneration. We also discuss the key opportunities, challenges, and future directions in this important area needed to fulfill the vision of personalized medicine.**




The emerging field of personalized healthcare has received tremendous attention in modern society as it can enhance therapeutic efficacy, reduce costs, and lead to improved quality of life. Advances in wearable and implantable electronics have opened up a spectrum of applications in personalized health monitoring and precision therapies.[1] Compared with the rigid and planar characteristics of conventional electronics, flexible and malleable forms of bioelectronics enable conformal and compliant integration onto the soft, curvilinear, and dynamically deforming human tissue.[2] By incorporating advanced materials and novel fabrication procedures, efficient and low-cost biosensors have been embedded into small areas with high sensitivity.[3−5] These features add various capabilities to wearable and implantable devices such as continuous monitoring of both biophysical and biochemical information.[6−8]

Current trends are propelling the development of health monitoring systems that are biocompatible with and applicable for domestic diagnosis and therapies.[9] Meanwhile, considering the fact that health monitoring through wearable or implantable bioelectronics is the first step toward personalized healthcare, precision therapies based upon health data and diagnostic feedback can be realized through therapeutic and surgical mechanisms incorporated in soft bioelectronic systems.[10] Wearable and implantable electronics have shown great promise in various therapeutic applications ranging from closed-loop drug delivery to electrical-stimulation-assisted tissue regeneration, as exemplified by Yao *et al.* in this issue of *ACS Nano*.[11] Researchers have also designed battery-free self-powered bioelectronic devices to harvest biomechanical energy to power biomedical devices for chronic disease management.[12] In this Perspective, we highlight recent advances in wearable and implantable electronic devices, moving from health monitoring to therapeutic applications. We also discuss the opportunities and challenges that lie ahead in this emerging field. We anticipate that soft bioelectronic devices for healthcare monitoring and precision therapy will have numerous practical applications.

**Wearable/Implantable Electronics-Enabled Continuous Health Monitoring.** Owing to recent advances in flexible electronics, powering strategies, and safe adhesive interfaces, wearable and implantable electronic devices show remarkable prospects in real-time, continuous monitoring of a number of physiological parameters including vital signs,[13] electrophysiological signals,[14] and biochemical analytes.[15]

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Wearable soft electronic systems have been explored to monitor electrophysiological processes related to the activity of the brain (*i.e.*, electroencephalograms, EEGs),[16] the heart (*i.e.*, electrocardiograms, ECGs),[17] and muscle tissue (*i.e.*, electromyograms, EMGs).[18] Figure 1a shows a transparent epidermal tattoo-like electronic patch with multifunctional measuring

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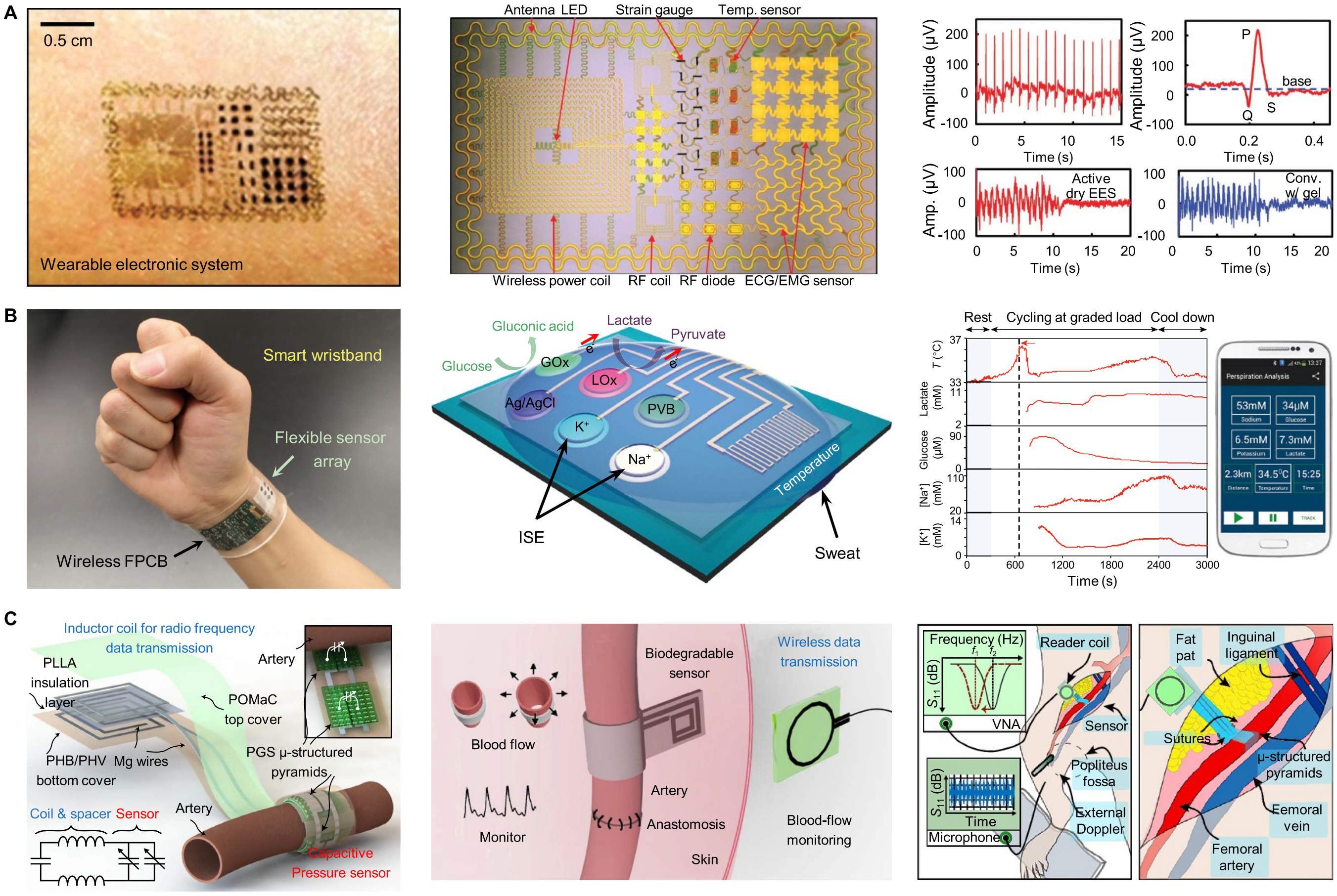


**Figure 1. Wearable/implantable, electronics-enabled, real-time, continuous health monitoring. (A) Ultrathin, soft epidermal tattoo-like electronic system for electrophysiology monitoring. Reproduced with permission from ref 19. Copyright 2011 American Academy for the Advancement of Science. (B) Fully integrated wearable platform for multiplexed monitoring of analytes in human sweat. Reproduced with permission from ref 28. Copyright 2016 Springer Nature. (C) Biodegradable and implantable soft electronic system for passive arterial-pulse monitoring. Reproduced with permission from ref 33. Copyright 2019 Springer Nature.**

capabilities that attaches onto the skin and performs simultaneous monitoring of ECG/EMG, temperature, and strains.[19] In another example, Chung *et al.* developed a wireless binodal wearable patch capable of measuring ECG and photoplethysmogram (PPG) for vulnerable neonates; water enables easy adherence of the sensor to the skin, and the small size and lack of cables minimize discomfort for the neonate and caregivers.[20] In addition to electrophysiology, soft, wearable electronic devices also offer various advantages in sound sensing,[21] motion recognition,[22] thermal management,[23] and blood pressure monitoring[24] owing to their conformal and compliant attachment to skin.

Although the majority of wearable sensors are focused on monitoring biophysical information, there is an increasing trend to develop flexible electronics that can perform biochemical sensing because body fluids contain a number of biomarkers that could reflect health status.[25,26] Wearable and implantable glucose sensors have the potential to monitor blood glucose levels in real-time noninvasively or minimally invasively through analyzing interstitial fluids from the skin.[27] Sweat, a key body fluid naturally excreted by the human body, is a promising candidate for noninvasive molecular monitoring by wearable bioelectronics. Figure 1b shows a fully integrated wearable patch capable of continuous, multiplexed quantitative analysis of various sweat metabolites (*e.g.*, glucose, lactate) and electrolytes (*e.g.*, $Na^+$, $K^+$) during prolonged physical activities.[28] Recent advances in wearable sweat sensors have shown great promise in a number of applications including hydration/dehydration monitoring,[28,29] cystic fibrosis diagnosis,[30] drug monitoring,[31] and noninvasive glucose monitoring.[32]

Soft electronics have not only greatly improved the capabilities of skin-interfaced wearable devices but also enabled advanced *in vivo* health monitoring inside the body through implantable devices. To meet the requirements of various surgical operations, wireless and battery-free systems based on biocompatible materials and malleable structures have been developed to monitor crucial physiological parameters. For instance, Boutry *et al.* developed an implantable, biodegradable, conductive-polymer-based pressure sensor to monitor arterial blood flow continuously and wirelessly after microvascular reconstruction surgery (Figure 1c);[33] three-dimensional, multifunctional elastic integumentary membranes were developed that could provide spatiotemporal cardiac physiological mapping across the entire epicardium;[34] an *in vivo* voltage map of the anterior and posterior of the heart could be monitored with a highly conductive and stretchable metallic nanowire-based implantable cardiac mesh.[35] Moreover, implantable soft electronic devices are also capable of monitoring real-time blood pressure for hypertension patients[36] and monitoring mechanical forces on tendons for patients during the healing process after surgery.[37]


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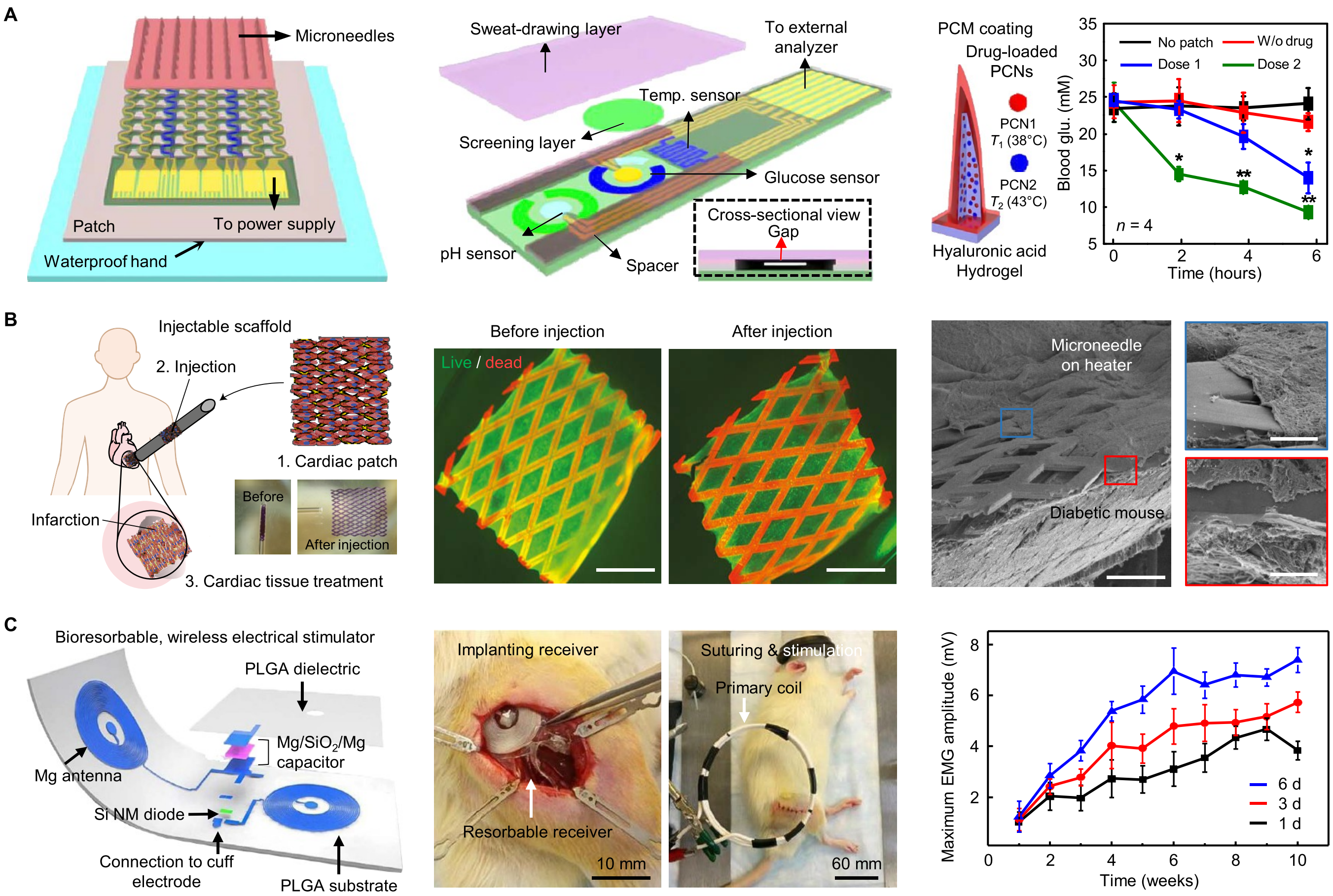


**Figure 2. Wearable/implantable, electronics-enabled therapeutic applications. (A) Wearable, microneedle-based, transdermal drug-delivery system for controlled diabetes management. The drug-loaded thermoresponsive microneedles for point-of-care therapy can be activated according to the data obtained from the flexible glucose sensor. Reproduced with permission from ref 42. Copyright 2017 American Academy for the Advancement of Science. (B) Flexible shape-memory scaffold for *in vivo* tissue regeneration. Reproduced with permission from ref 45. Copyright 2017 Springer Nature. (C) Bioresorbable, wireless electrical stimulator for electronic neuroregenerative medical therapy. Reproduced with permission from ref 46. Copyright 2018 Springer Nature.**

**Wearable/Implantable Electronics-Enabled Therapeutic Applications.** Wearable electronics have enabled real-time monitoring of physiological signals, introducing the feasibility of controlled on-demand therapy. Aiding the early diagnosis of diseases, wearable therapeutic systems can reduce patients' health risks and long-term medical costs. To achieve sustained, noninvasive, and precise drug delivery, mechanoresponsive,[38] electrically activated,[39] light-triggered,[40] and bioresponsive therapeutic approaches[41] can be implemented on wearable therapeutic systems. Multifunctional wearable devices that integrate biosensors and transdermal drug-delivery modules in a soft, skin-conformal, and multicomponent packaging layout are particularly desirable to achieve closed-loop transdermal drug administration. As illustrated in Figure 2a, a disposable wearable patch was shown to be capable of multiplexed monitoring in conjunction with a feedback transdermal drug-delivery module.[42] In response to the measured sweat glucose level, thermal-responsive microneedles can be controlled by multichannel thermal actuators with multistage and spatially patterned transdermal drug release modules. Such soft bioelectronics-based closed-loop therapeutic systems would be advantageous for personalized and continuous disease diagnosis and control, such as glycemic control in diabetes mellitus.

Soft wearable/implantable systems have shown great promise in clinical surgery. For example, Hwang *et al.* used a flexible transient silicon electronic device to provide transient thermal therapy to control surgical site infections.[43] To increase the viability of transplanted cells in heart transplantation for ischemic heart diseases and heart failure treatments, Zhang *et al.* developed a soft scaffold made by a biodegradable elastomer to connect arteries to arteries and veins *in vivo* through surgical anastomosis to avoid coronary artery blockage.[44] Considering that the transplantation of scaffolds still requires an invasive surgical procedure, that is, opening the chest, Montgomery *et al.* developed a minimally invasive delivery method in which cells cultured on a shape-memory biodegradable polymeric scaffold were directly injected into the infarcted heart through an orifice as small as 1 mm (Figure 2b).[45] The viability and functionality of engineered tissues on the scaffold were not influenced before or after the injection and showed ideal fixation onto the porcine left ventricle.

Another important therapeutic application for wearable/implantable electronics is nerve regeneration. Peripheral nerves, which spread extensively in the human body, can be damaged in injuries resulting from sports, road accidents, or occupational hazards, and the affected individuals may require physical therapy or surgical intervention to regenerate


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peripheral nerves. To accelerate peripheral nerve injury recovery, Koo *et al.* introduced a wireless, programmable electrical peripheral nerve stimulation platform (Figure 2c).[46] Daily electrical stimulation therapy on rats using the implanted bioresorbable nerve stimulators wrapped around the sciatic nerve validated the effectiveness of electrical stimulation for nerve regeneration in the early stages of postsurgical recovery. The cell regeneration capacity of electrotherapy appeals to a wide range of clinical applications, including nerve regeneration,[47] wound healing,[48] and cell proliferation.[49]

**Self-Powered Wearable/Implantable Therapeutic Electronics.** With the synergistic development of advanced materials and manufacturing techniques, wearable/implantable bioelectronics is becoming increasingly attractive for therapeutic applications for chronic disease management. However, to maintain functionality, most current systems require on-board power sources such as batteries, which can be toxic, bulky, and burdensome to replace, particularly during implantable use. In this regard, it is critical to realize self-powered systems to provide long-term, continuous health supervision through efficient energy harvesters, such as biofuel cells,[50] solar cells,[51] and nanogenerators.[52]

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Among various energy conversion methods, triboelectric nanogenerators (TENGs) offer several important advantages in extreme robustness and energy accessibility.[53] They are capable of harvesting biomechanical energy and can function as a long-term energy provider for wearable/implantable devices to enable self-powered precision therapy.[54] For example, powered by an implantable TENG, a symbiotic pacemaker (SPM) enabled cardiac pacing and sinus arrhythmia correction in a large animal model (Figure 3a).[55] Ouyang *et al.* developed a wearable TENG-based, transdermal drug-delivery system that can scavenge energy from biomechanical motions and stabilize the electricity for drug release actions (Figure 3b).[56] Such self-powered, on-demand drug-delivery systems provide patients with easy therapy to achieve customized rates and dosages of drug release.

In addition to harvesting energy, TENGs can exert alternating currents as an electrical stimulation source for neuromodulation, a nondestructive and reversible therapy for manipulating physiological functions. For example, Yao *et al.* developed a TENG-enabled implantable vagus nerve stimulation system to respond spontaneously to stomach movement.[57] It stimulates the vagus nerves to reduce food intake and to realize effective weight control (Figure 3c). In addition, Jiang *et al.* developed a fully biodegradable implantable TENG with natural materials for tissue engineering.[58] Consisting of a TENG and interdigital electrodes, this integrated self-powered simulation system could be utilized to accelerate the beating rates of dysfunctional cardiomyocyte clusters (Figure 3d).

In this issue of *ACS Nano*, Yao *et al.* present a universal motion-activated and wearable electric-stimulation device (*m*-ESD) that can effectively treat alopecia, otherwise known as patchy hair loss (Figure 3e).[11] The majority of people suffering from hair loss are treated with topical treatments, oral medicine, or hair transplantation, which are high in cost and can potentially lead to discomfort and sexual dysfunction. Electrical stimulation is an alternative therapeutic strategy that can promote hair regeneration without any known adverse side effects. The *m*-ESD consists of two modules: an omnidirectional triboelectric generator acting as the electric pulse generator and a pair of interdigitated dressing electrodes providing spatially distributed electrical fields (Figure 3e). A study comparing the efficacy of the *m*-ESD to that of conventional medicine showed that the hairs in the *m*-ESD applied regions were significantly longer and denser in both rats and nude mice. Such wearable TENG-activated electrical stimulation could serve as an effective hair regeneration strategy and is expected to quickly evolve into a practical and facile solution to address hair loss in millions of people worldwide.

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## SUMMARY AND PROSPECTS

Wearable and implantable electronic devices are expected to revolutionize personalized healthcare monitoring and precision therapy. They have the potential to become the crux of many biomedical applications due to their diverse advantages, including, but not limited to, multifunctional characteristics, conformal contacts, flexible and stretchable properties, and biocompatible interfaces. Progress in electrode designs, materials, and structures of bioelectronics devices has enabled the real-time monitoring of minute changes in physiological signals such as biochemical analytes, biophysical signals, and blood flow detection. In terms of precision therapy, bioelectronic platforms with novel surgical procedures, multifunctional materials, and specific targets have been developed, including systems capable of closed-loop drug delivery, active tissue engineering, and electrotherapy nerve recovery. To achieve long-term continuous therapy, self-powered bioelectronic systems are being developed to enhance traditional biomedical therapies of chronic diseases.

Many bottlenecks need to be addressed prior to the implementation of these bioelectronic systems in practical applications. For multiplexed signal monitoring, the main challenges are device accuracy and long-term stability. It is often difficult to distinguish the targeted physiological signals from background noise or other interfering signals. In the future, efficient extraction and calibration of important physiological signals should be improved by either isolating body movement and environmental conditions or detecting multiple signals assisted by comprehensive signal processing and machine-learning algorithms. For implantable bioelectronics, material selection is critical for biocompatibility, bioresorbability, and long-term biosafety. Efficient fixation between implantable devices and biological tissue is expected to enhance long-term stability and to reduce the difficulty of anchoring operations. Constructive research in surface



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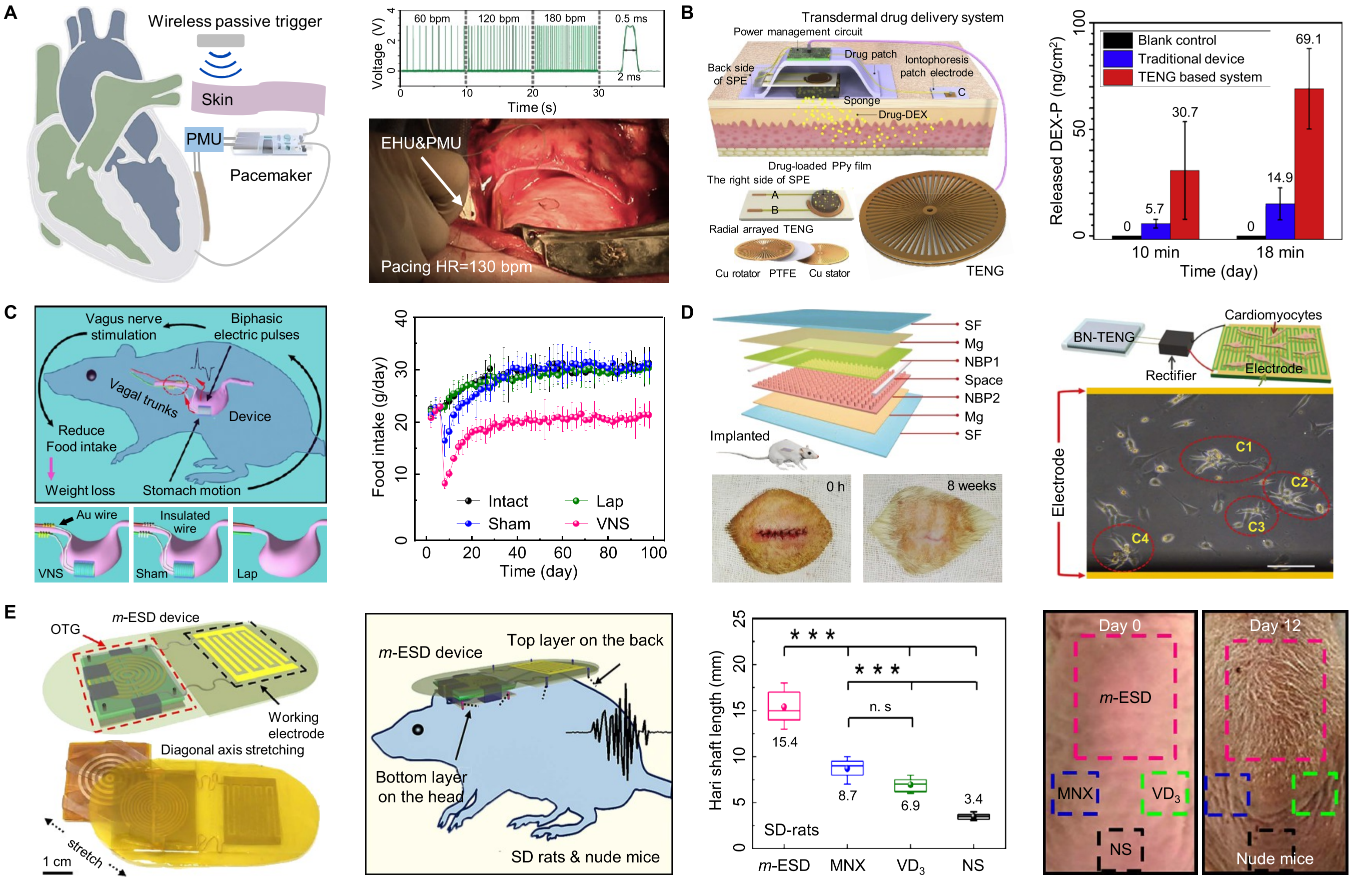


**Figure 3. Self-powered, wearable/implantable therapeutic electronics. (A) Self-powered symbiotic cardiac pacemaker system that can be turned on *in vivo* by a wireless passive trigger. Reproduced with permission from ref 55. Copyright 2019 Springer Nature. (B) Self-powered, on-demand, transdermal drug-delivery system consisting of transdermal patches, a triboelectric nanogenerator (TENG), and power management circuit. Reproduced with permission from ref 56. Copyright 2019 Elsevier. (C) Battery-free implantable vagus nerve stimulation (VNS) system for effective diet therapy. Reproduced with permission from ref 57. Copyright 2018 Springer Nature. (D) Bioresorbable, natural-material-based TENG that enables self-powered stimulation for tissue engineering. Reproduced with permission from ref 58. Copyright 2018 Wiley-VCH. (E) Universal motion-activated, wearable electric-stimulation device (*m*-ESD) that can effectively promote hair regeneration *via* random body activities. Reproduced from ref 11. Copyright 2019 American Chemical Society.**

modification will improve fixation capability and stability. In addition, minimally invasive surgery can reduce the incidence of infections, which is vital in the clinical field. Strategies to implant biomedical devices deserve to be studied in depth. These challenges will provide great perspective in the further development of bioelectronics for practical applications. With the ultimate goals of enabling personalized and predictive monitoring of physiological signals as well as realizing precision therapy, soft bioelectronics devices shed light on advanced, smart healthcare and wellness.

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### Notes

The authors declare no competing financial interest.

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