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Flexible Electronics

Nanomaterial-Based Soft Electronics for Healthcare Applications

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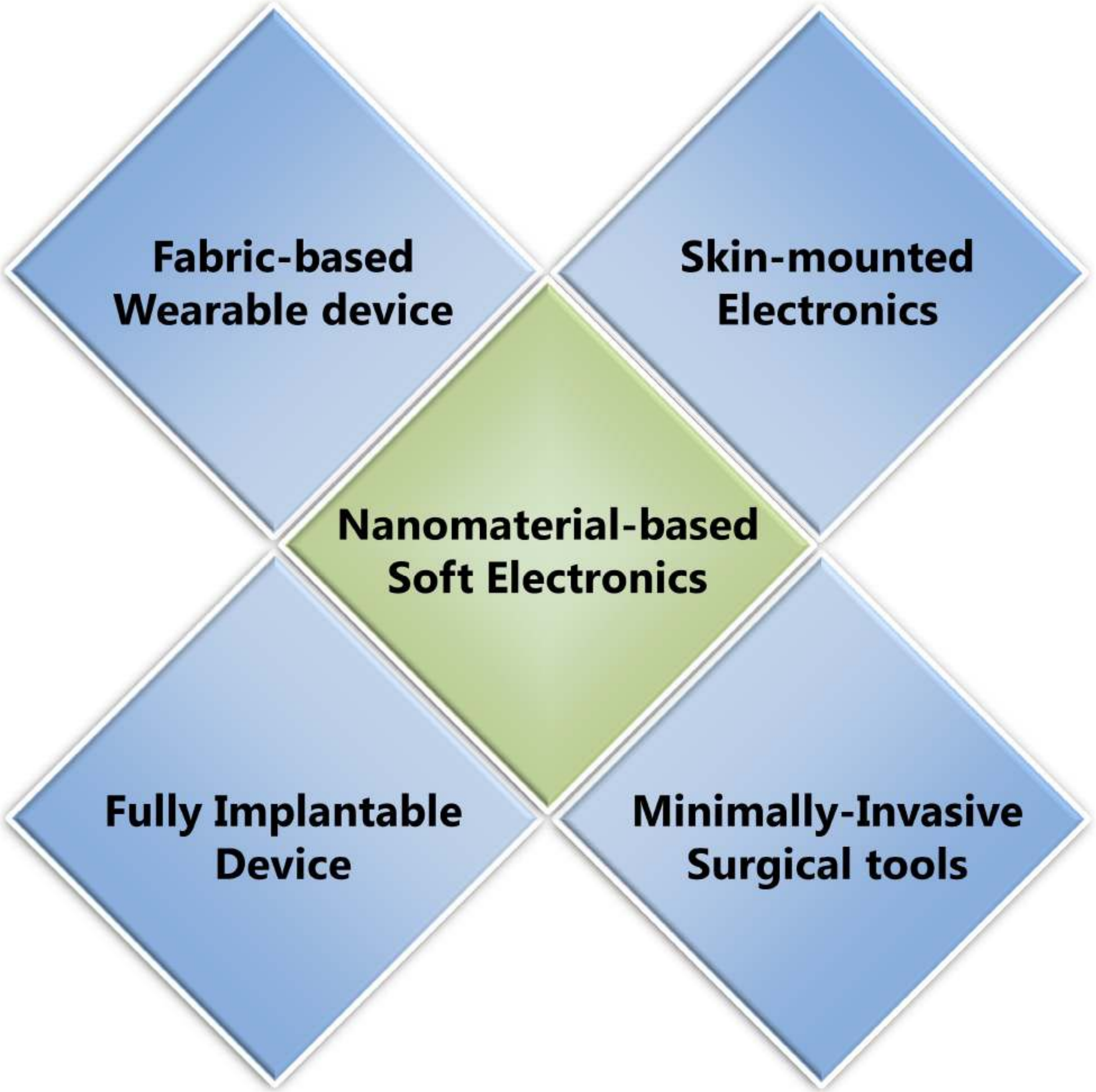

Abstract: Soft electronic devices, particularly for healthcare applications, have been intensively studied over the past decade owing to their unique advantages over conventional rigid electronics. These advantages include conformal contacts on target tissues such as the skin, heart, and brain along with a high deformability that minimizes unwanted inflammatory responses. To achieve mechanically soft but multifunctional high performance electronics for wearable and implantable biomedical devices, several strategies have been employed including designed assembly of high quality nanomaterials, the combination of unconventional manufacturing processes with existing microprocessing technologies, new device designs with deformable structures, and disease-specific system-level integration of diverse soft electronics. In this Focus Review, we summarize recent advances in soft electronic devices for healthcare applications. More specifically, we describe assembly methods for various nanomaterials, new device designs and integration strategies, their applications to textile-based and skin-attached wearable electronics, and their incorporation in fully and/or minimally invasive medical devices. Finally, this review concludes with a brief description on the future direction of healthcare applications using nanomaterial-based soft bioelectronics.

1. Introduction

Since the development of the field effect transistor in 1920s, the electronics industry has focused on high speed and large capacity devices such as microprocessors and random access memories. However, the recent emergence of personalized and mobile electronics has diversified the research efforts from performance-oriented research to human-friendly topics.[1] Therefore, flexible and stretchable electronics whose mechanical properties are similar to those of human tissues but whose performances are on par with conventional electronics have been highlighted.[2] Meanwhile, the increase in the life expectancy has significantly enlarged the market size of healthcare devices, and the need for innovative medical devices to bring about significant improvements in conventional clinical protocols has become substantial.[3] Recently, nanomaterial-based soft bioelectronics have attracted great attention for healthcare applications because of their unique features including medical multifunctionality, mechanical deformability, and outstanding performances.[4] In achieving these unique advantages, nanomaterials have played a crucial role. For example, the large surface area of mesoporous-silica nanoparticles enables an efficient drug delivery,[1c] the unique deformability of carbon nanotubes allows a stretchable electrode,[4c] and the unusual chemical structure of graphene accomplishes the high mobility in soft electronics.[4d]

These biomedical devices based on soft-electronics have been developed in wearable[5] and/or implantable[6] forms. More specifically, they can be categorized into four different groups: 1) fabric-based wearable devices, 2) skin-mounted electronics, 3) fully implantable devices, and 4) minimally invasive surgical tools. The synthesized (bottom-up) and processed (top-down) nanomaterials are seamlessly integrated for multifunctionality and/or enhanced performances of the soft electronic devices.[7] Special device designs and the monolithic assemblies of various devices lead to optimized systems for particular organs and specific disease models.[8] In this Focus Review, we will focus on recent advances, particularly those within last three years, in the nanomaterials and their assemblies, deformable device designs, and the integration of various soft electronics for wearable and implantable biomedical devices. Additional detailed information about nanomaterials and their integration for bio-electronic devices in a past decade can be found in another recent review paper.[4a] A brief prospect for future researches and the importance of soft bioelectronics are presented in the conclusion.

2. Assembly of nanomaterials, deformable designs, and integration with soft-electronics

Various nanomaterials, ranging from 0D nanocrystals to 1D nanowires, and to 2D nanomembranes, have been used in soft bio-electronics for improving device performances as well as achieving mechanical deformability and multifunctionality (Figure 1 a).[9] Nanomaterials have distinctive physical/chemical/electrical characteristics, superior to those of bulk counterparts, such as quantum confinement effect of 0D quantum dots,[10] superparamagnetism of magnetic nanocrystals (Figure 1 a; top-left),[11] unidirectional carrier transport of 1D nanowires (Figure 1 a; top-right),[7b] distinctive transparency and conductance of 2D graphene (Figure 1 a; bottom-left),[12] and mechanical flexibility and high mobility of 2D silicon nanomembranes (Figure 1 a; bottom-right).[13] Therefore the monolithic integration of nanomaterials in electronics and/or optoelectronics is very important.

To achieve the nanomaterial-based device array, their uniform and large-scale assembly is essential. Several assembly techniques such as spin casting, Langmuir Blodgett (LB) method, mechanical molding, dry transfer printing, and lithography have been used to integrate the nanomaterials into soft-electronics (Figure 1 b).[14] The LB method is an easy process for

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manufacturing large-area, self-assembled monolayers of nanocrystals (Figure 1 b; top-left).[14a] Molding the composites of polymers and nanomaterial fillers by applying external heat/photon/pressure enables the fabrication of uniform and high aspect ratio micro-/nano-structures (Figure 1 b; top-right).[14b] The transfer printing technique is another powerful tool for assembling nanomaterials in a 2D plane of micro-/nano-configurations at the desired locations. Additive transfer printing with a structured stamp is widely used for transferring 2D semiconductor nanomembranes (Figure 1 b; bottom-left).[14c,d] Meanwhile, the intaglio transfer printing can be utilized for transferring the assembled colloidal nanocrystal layer with significantly higher resolution patterns (Figure 1 b; bottom-right).[14e]

Along with the intrinsic flexibility of the nanomaterials, advanced design strategies have been applied to increase deformability of the device (Figure 1 c).[4b,15] Decreasing the thickness of electronics is important for enhancing the flexibility as well as for reducing the induced strain on the devices, since the strain is proportional to the system thickness and inversely proportional to the bending radius (Figure 1 c; top-left).[4b] Buckled structures can provide bendability and 1D stretchability following the wrinkled direction (Figure 1 c; top-right),[15a] and serpentine-structured interconnections composed of ultrathin metal film can afford 2D large-scale deformations (Figure 1 c; bottom-left).[15b] In addition, the percolated structure of carbon nanotubes helps the composition of the stretchable electronic sheet to have uniform electrical and mechanical properties over the large area even under mechanical deformations (Figure 1 c; bottom-right).[4c]

The integration of individual soft-electronics (i.e., sensors, actuators, memory, and displays) is important for performing multifunctional tasks in the diagnosis and therapy against a specific disease. For instance, graphene/Au mesh-based biosensors (i.e., glucose, pH, humidity, and tremor sensor) and drug-loaded microneedles were monolithically assembled on a thin elastomer film for monitoring and treating diabetes (Figure 1 d; top-left).[16] A conductive elastomeric composite of Ag nanowires and styrene-butadiene-styrene (SBS) rubber was used for performing articular thermotherapy (Figure 1 d; top-right).[7b] Ultrathin Si nanomembrane strain gauges and Au nanoparticle (NP)-based memory devices were integrated on an epidermal electronic patch for obtaining quantitative data of the tremor frequency in motion-related neurological disorders, for storing recorded bio-signals to form big data, and for delivering drugs transdermally based on the data analysis (Figure 1 d; bottom-left).[1c] Moreover, ultrathin epidermal quantum dot (top) or polymer (bottom) light emitting diodes (LEDs) were integrated with wearable electronics to serve as a visual display of healthcare-related data and as an user interface to medical devices (Figure 1 d; bottom- right).[14e,17]

3. Fabric-based wearable devices

The demand for fabric-based wearable electronics in healthcare, particularly in mobile and military medical applications, is continuously increasing owing to their various advantages; they are easily attached on and/or detached from clothes,[18] are highly portable and easy to wear,[19] offer minimal discomfort to the patients and users,[20] and are capable of continuously monitoring bio-signs with a high signal-to-noise ratio.[21] Relatively thick and bulky energy storage modules including batteries can also be easily mounted on the fabric. To integrate soft electronics on the surface of or within the fabric and/or fibers, electronic textiles (e-textiles) such as fiber-based devices

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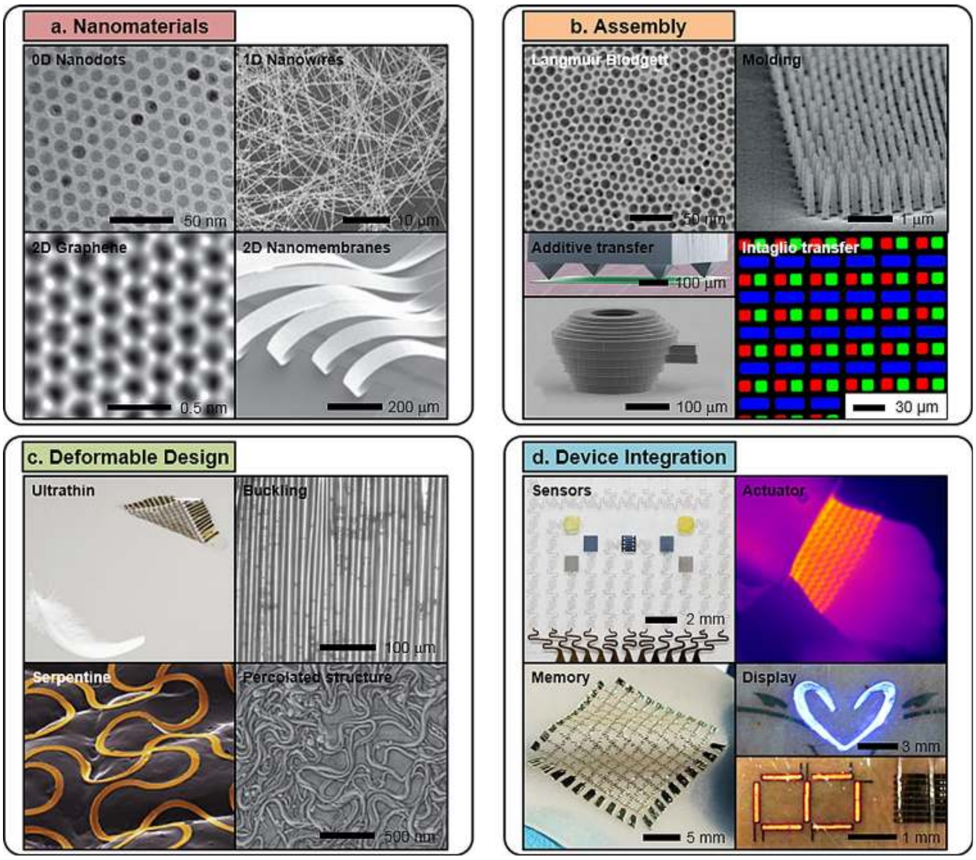

Figure 1. Nanomaterials, their assembly, deformable device design, and system integration for wearable and implantable soft electronics. a) Fe_3O_4 nanoparticles (0D, left-top), Ag nanowires (1D, right-top), graphene (2D, left-bottom), and Si nanomembranes (2D, right-bottom). b) Diverse assembly methods: Langmuir-Blodgett assembly of the nanoparticles (left-top), molding of nanocomposites based on the photo-curable polymer (right-top), additive transfer printing of Si nanomembranes (left-bottom), and intaglio transfer printing of quantum dots (right-bottom). c) Deformable designs for flexible and stretchable soft-electronics: Ultrathin thickness of organic transistor array (left-top), buckling of graphene (right-top), serpentine-shaped interconnection composed of ultrathin metal film (left-bottom), and percolated structure of carbon nanotubes (right-bottom) improve the system-level deformability. d) System-level device integration: Sensors (pH, glucose, humidity, and tremor sensor; left-top), actuator (heater, right-top), memory (left-bottom), and display (quantum dot and polymer LED; top and bottom, respectively in the right-bottom frame). Reprinted from Ref. [11, 7b, 12, 13, 14a, b, c, d, e, 4b, 15a, b, 4c, 16, 1c, 17] with permission. Copyright 2004, 2011, 2012, 2013, 2014, 2015, 2016 Nature Publishing Group, 2015 American Chemical Society, 2012 Materials Research Society, 2016 American Association for the Advancement of Science, 2012, 2013 Wiley-VCH, 2016 IOP science.

or ultrathin fabric-based electronics have been intensively studied.

In particular, fabric-based energy harvesting and storage devices that supply power to the soft bio-electronics have gathered great attention.[22] Nanomaterial-based triboelectronic nanogenerators (TENGs) that convert the mechanical energy generated by human motions to electricity are one of the promising options for wearable energy-harvesting devices. For example, a foldable nanopatterned TENG composed of an Ag-coated textile and ZnO nanorods integrated on a nanopatterned polydimethylsiloxane (PDMS) film was recently reported (Figure 2 a).[23] This foldable TENG shows a high output voltage and current up to 120 V and 65 µA, respectively, under a 10 kgf compressive force. The right-bottom inset in Figure 2 a shows the scanning electron microscope (SEM) image of the textile device with nanopatterned PDMS. Diverse nanomaterials have been employed to improve performances of TENGs. Al nanocrystals are imbedded to the fabric-based TENG (left of Figure 2 b), and the TENG can be easily integrated with commercial cloth (right of Figure 2 b) for the wearable energy source during daily lives.[24] A nanostructured fiber-based TENG using Al microwires and PDMS microtubes is also shown in Figure 2 c (top).[25] This TENG woven into the fabric is highly robust and reliable even after 25 % stretching (bottom of Figure 2 c).[25]

By integrating the deformable TENGs with other wearable sensors and energy storage modules, various wearable electronic systems with new features have been developed. Conductive carbon fabric-based TENGs, combined with supercapacitors and pressure sensors for monitoring daily activity/motion, for example, were reported. As shown in Figure 2 d, TENGs located in the armpit region produce electricity by the friction induced from swing motions, and the supercapacitor positioned in the chest stores the electricity, which is supplied to sensors.[19] A wearable fall detection system was also developed by combining TENGs, stretchable lithium ion battery, electronics (i.e., accelerometers/microcontrollers), and Bluetooth modules (Figure 2 e).[21] Furthermore, a hybridized elec-

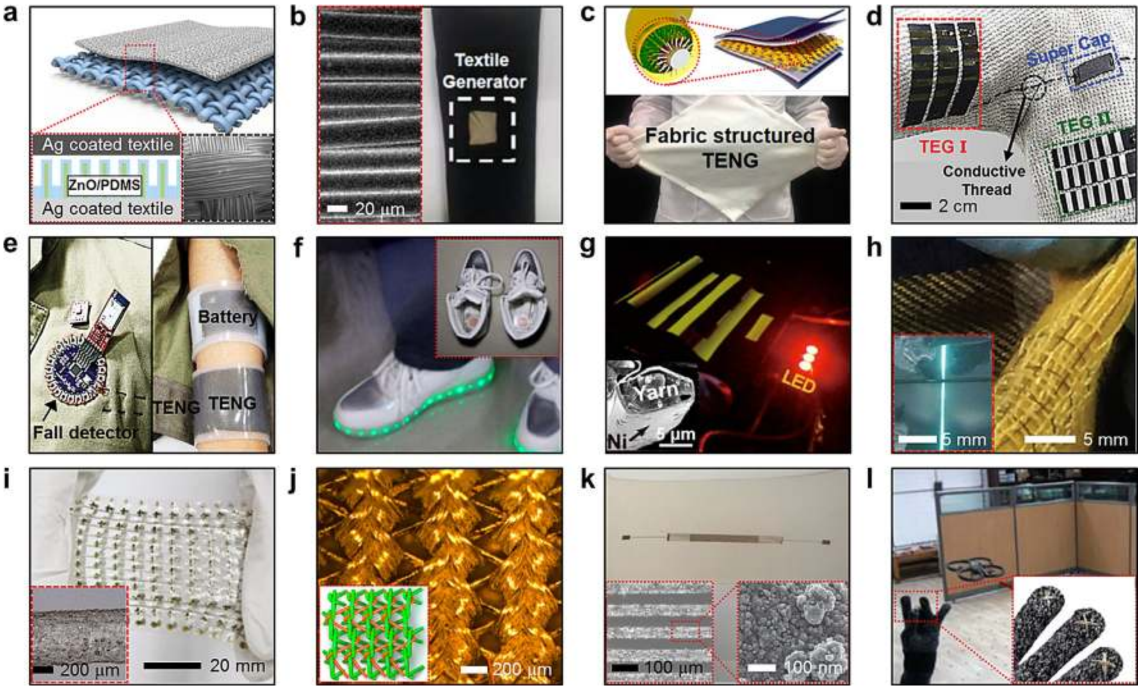

Figure 2. Fabric-based wearable electronics. a–c) Triboelectronic nanogenerators (TENGs): Various nanomaterials, such as a) ZnO nanorods, b) Al nanocrystals, and c) Al microwires, are employed for enhancing the performance of TENGs. d) Integrated energy devices including carbon fabric-based TENGs and supercapacitors. e) Wearable fall-detecting system composed of TENGs, a stretchable Li-ion battery, sensors, and electronics. f) Hybridized electromagnetic TENG for energy-harvesting shoes. g) Yarn-shaped battery electrode with multiple strands coated with Ni and battery active materials. h) Weavable polymer-based electrochemical LEDs. i) Ag flake-based highly stretchable elastic conductors. j) 3D weaving design to enhance the durability and deformability. k) SBS/Ag nanoparticle-based stretchable conductors. Inset shows magnified SEM image of conductors. l) SBS/Ag nanoparticle-based ultrasensitive pressure sensors. Reprinted from Ref. [23, 24, 25, 19, 21, 26, 27, 28, 29, 30, 31, 32] with permission. Copyright 2013, 2015 American Chemical Society, 2015 Elsevier, 2014, 2015 Wiley-VCH, 2012, 2015 Nature Publishing Group.

tromagnetic TENG, which can be used as flashing shoes, was recently employed for harvesting energy more efficiently during walking (Figure 2 f).[26]

Wearable optoelectronic devices can be integrated on the fabric for energy harvester or information display. A wearable textile-based solar rechargeable lithium ion battery, for examples, was recently demonstrated. The inset of Figure 2 g shows a SEM image of yarn-shaped battery electrode consisting of multiple strands coated with the composite of Ni and battery active materials.[27] The textile battery can be charged using a flexible polymer solar cell and discharged to light LED bulbs (Figure 2 g).[27] Inorganic LED chips can be replaced with fiber-shaped LEDs to create a fully soft smart fabrics. Peng et al. reported ultralight weavable polymer-based electrochemical LEDs that provided various tunable colors (Figure 2 h).[28]

To interconnect individual textile-type electronics, highly stretchable conductors were used. Someya et al. proposed printable and stretchable elastic conductors (216 % stretchability) based on Ag flakes (inset of Figure 2 i) for fabricating stretchable active matrix organic transistors and wearable electromyogram sensors (Figure 2 i).[29] Woven design of textiles can be employed to enhance the durability and deformability of the system. For instance, the 3D woven fabric design improved omnidirectional deformability compared with conventional design (Figure 2 j).[30] Spray coated micropatterned SBS fiber/Ag nanoparticle composites were applied to stretchable conductors which showed 200 % stretchability without resistance changes (Figure 2 k).[31] Ultrasensitive pressure sensors were also demonstrated using SBS/Ag NP-composited Kevlar fibers (inset of Figure 2 l), which successfully detected hand motions and triggered signals to control the moving direction of a drone (Figure 2 l).[32]

4. Skin-mounted electronics

Among various body parts, skin is a preferred position to mount medical devices for monitoring bio-signals, detecting diseases, and delivering therapies, because it is easily accessible and conformal contacts with devices can be well made.[21, 33] Therefore, many researchers have developed various skin-based biomedical electronics for clinical applications.[34] A variety of nanomaterials and flexible/stretchable device designs have been applied for skin-attached devices to achieve a high electronic performance and mechanical deformability.[35] Figure 3 a and 3 b depict the 'epidermal electronics', an integrated system composed of high performance sensors that collect clinically useful information[2a] and a co-integrated nanocrystal-based flash memory for storage of recorded data.[14a] Someya et al. reported an organic semiconductor-based imperceptible system with ultrathin and ultralight device designs, ideal for the electronic skin (Figure 3 c, 3 d).[36] These strategies for deformable structures, which include ser-

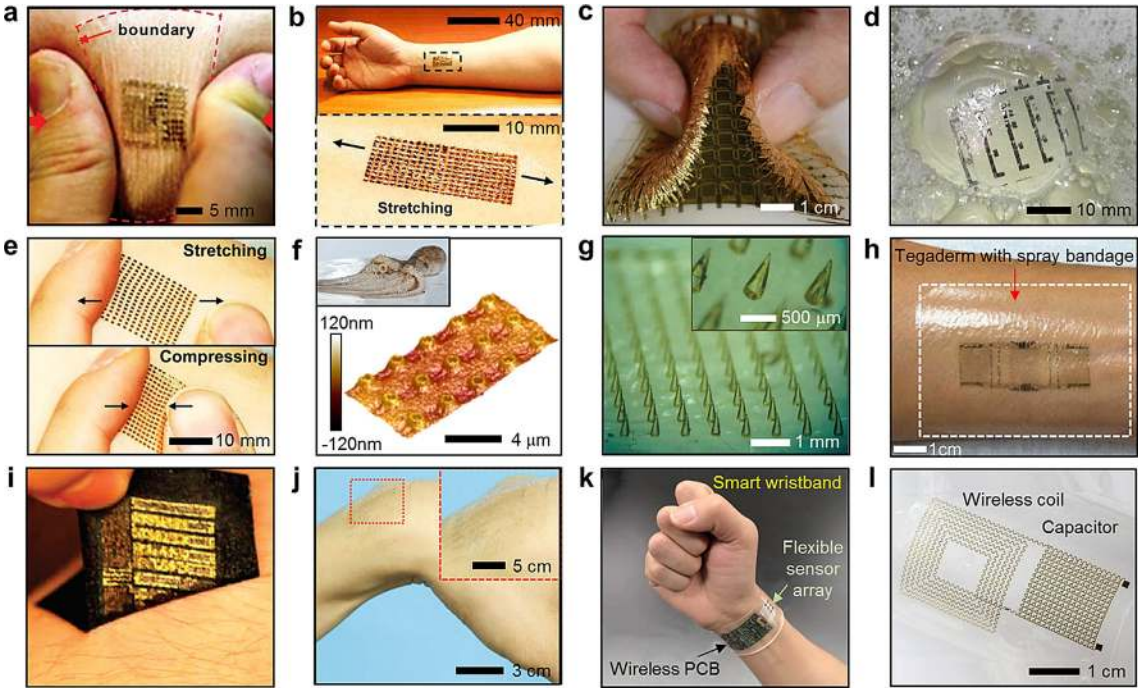

Figure 3. Skin-mounted electronics. a, b) Representative images of skin-based electronics integrated with various sensors and electronics. c, d) Ultrathin and ultralight imperceptible system. e–h) Various methods for achieving robust adhesion using e) Van der Waals force through conformal contacts, f) negative pressure through bio-inspired suction cups, g) mechanical interlocking through swellable microneedles, and h) chemical bonding through a spray-type chemical adhesive. i) Reusable electronic patch. j) Transparent electronic system made of patterned graphene sensors and actuators. k) Wireless data transmission using a smart wristband. l) Wireless power supply through an inductively coupled coil. Reprinted from Ref. [2a, 14a, 36a, b, 37, 20, 38, 15b, 39, 40, 1b, 42] with permission. Copyright 2011, 2016 American Association for the Advancement of Science, 2013, 2014, 2015, 2016 Nature Publishing Group, 2015 American Chemical Society, 2013, 2015, 2016 Wiley-VCH.

pentine designs and an ultrathin thickness, enable mechanical and electrical reliability of devices on the skin under stretching and/or compressing.

In addition to high electrical performances and strain-releasing designs, a tight and conformal adhesion of the devices on the dynamically contorting skin is important for the long-term monitoring of subtle physiological and electrophysiological signals. To achieve strong adhesion, various strategies have been employed such as controlling the modulus of the elastomeric substrate, employing interfacial micro-/nano-structures, and applying chemical adhesives. Substrate made of ultrasoft elastomers, whose moduli are similar to that of the epidermis (~100 kPa), permit conformal contact of the system that maximize the Van der Waals force (Figure 3 e).[37] Bio-inspired microstructures facilitate further robust bonding to the skin. An elastomeric patch with microscale suction cup structures, for example, shows a three-fold higher adhesion compared to a plain elastomeric patch (Figure 3 f).[20] Another bio-mimetic adhesive, known as swellable microneedles, achieved a 3.5 times greater adhesion than that of a conventional staple fixation (Figure 3 g).[38] Sprayed chemical adhesives that are significantly thinner than the film-type adhesives, keep the device mounted for as long as two weeks under touching, washing, and deforming (Figure 3 h).[15b] Furthermore, a re-attachable electronic system is essential for reducing long-term costs. As shown in Figure 3 i, a reusable and washable system was developed by integrating the electronics on a special adhesive rubber.[39]

Meanwhile, devices whose colors are distinct from the skin color seem unnatural and might give rise to user discomfort. Accordingly, transparent motion sensing and transdermal drug delivery systems utilizing invisible materials such as graphene and silver nanowire networks were developed for considering aesthetic aspects and user privacy (Figure 3 j).[40] In addition, wireless linkages between the skin-mounted electronics and exterior smart devices are crucial issues in data transmission and power supply while maintaining a good mobility.[41] A Bluetooth-equipped smart-band can wirelessly transfer data from the wearable bio-sensors to a mobile handset (Figure 3 k).[1b] A remote recharging system using an inductive coil also solves the power supply issues by wirelessly charging the battery (Figure 3 l).[42] These enable ubiquitous healthcare connected through the wireless network.

Skin-based electronics can continuously and non-invasively record important medical information from human body and accumulate them to generate big data.[43] Big data analysis of the continuously monitored vital signs (i.e., activity, electroencephalogram, electrocardiogram, pulse, and body temperature), for example, predicts and/or prevents many diseases including cardiac and lifestyle illness. Figure 4 a depicts self-powered strain gauges employing piezoelectric materials for quantifying human activities.[44] Skin-mounted soft electronics have also successfully measured the electroencephalogram with an accuracy similar to that of the commercial devices (Figure 4 b).[45] Bao et al. demonstrated cardiac monitoring from the carotid-femoral arteries by measuring the pulse waves and

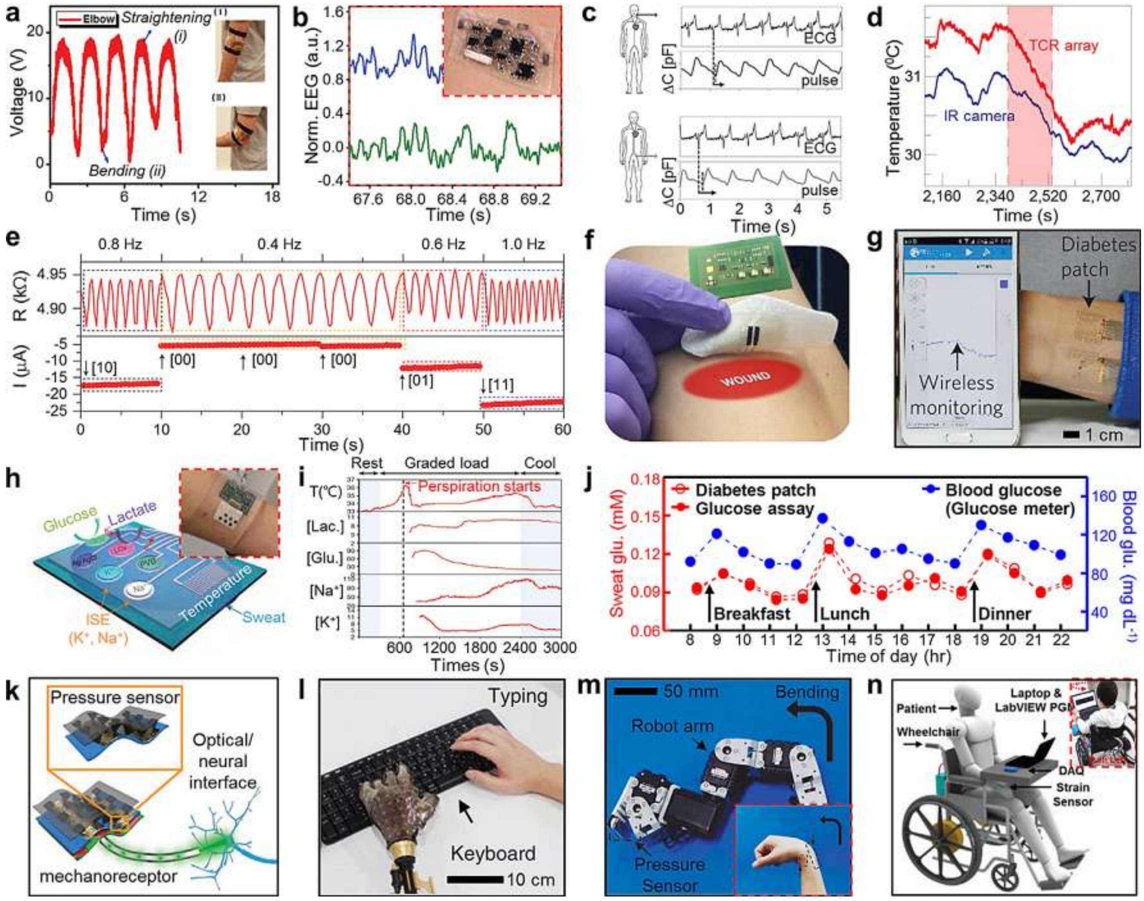

Figure 4. Biomedical applications of skin-laminated systems. a–d) Monitoring of diverse vital signs such as a) body movements, b) electroencephalogram, c) cardiac signals based on electrocardiogram and pulse, and d) body temperature. e) Detection of tremors, a typical symptom of Parkinson's disease and epilepsy. f–h) Wireless biochemical sensors for f) wound healing monitoring and g, h) in situ perspiration analysis. i) Monitoring of biomarkers in sweat including glucose, lactate, Na^+, and K^+. j) Sweat-based glucose monitoring with a wearable diabetes patch. k–n) Patient-assistant tools: prosthetic skin including k) optical pulsation and l) electrical pulses. m) Remote robot controller and n) wheelchair controller. Reprinted from Ref. [44, 45, 46, 1a, c, 49, 16, 1b, 51, 33, 53, 54] with permission. Copyright 2015 Wiley-VCH, 2014, 2015 American Association for the Advancement of Science, 2013, 2014, 2016 Nature Publishing Group, 2015 Elsevier.

electrocardiograms (Figure 4 c).[46] The carotid-femoral pulse wave velocity, a criteria for determining the stiffness of blood vessel, was estimated from the monitored data and employed for identifying hypertensive patients. The body temperature was monitored in real-time through an silicon nanomembrane temperature sensor (Figure 4 d).[1a] The blood flow can be calculated by mapping the anisotropic thermal transport in the blood vessel.[47] These real-time monitoring of vital signs offer great opportunities for identifying the early signs of various diseases and treating them in the early stage. For instance, a patient suffering from Parkinson's syndrome or epilepsy might show abnormal tremors. Motion sensors mounted on the electronic patch are capable of detecting early cues of these movement disorders (Figure 4 e).[1c] Furthermore, a feedback therapy through the transdermal drug release can be performed to relieve these symptoms.

Sensing biomolecules that are key indicators of many physiological conditions plays a crucial role in many diagnostics and therapeutics. However, conventional in vitro biomarker sensors require blood collection that causes pain and stress. Wearable biosensors that detect biochemical molecules in bodily secretions serve as an alternative platform for non-invasive and painless biomarker monitoring.[48] Wang et al. developed a wound care patch by monitoring the uric acid levels, a key indicator of the wound healing (Figure 4 f).[49] In addition, several groups measured targeted biochemicals through in situ perspiration analyses and remotely transferred the data to external devices (Figure 4 g, 4 h).[1b, 16] Sweat-based electrochemical sensors can detect variations in the concentration of biomarkers such as glucose, lactate, K^+, and Na^+ during exercise (Figure 4 i).[1b] These non-invasive and continuous glucose monitoring systems are extremely helpful for diabetic patients, who need to check their glucose levels periodically. Using sweat-based sensing systems, daily changes in the glucose levels were successfully monitored (Figure 4 j).[16]

Skin electronics are utilized not only for diagnosis and therapy but also as prosthetic devices and patient-assistant systems.[50] For instance, artificial skin that translates external applied pressures into frequency-modulated optical pulsations can be used for a skin prosthesis connected to human nervous system (Figure 4 k).[51] Another type of prosthetic skin, which operates in response to perceiving sensations including pressure, strain, temperature, and humidity, transforms the data into electrical pulses and injects them into the peripheral nerves through a stretchable neural interface (Figure 4 l).[33] Together with the robot arm, prosthetics whose functions are almost same as real human limbs can be achieved. In addition, body motion can be detected using skin-mounted sensors[52] and can be used to control a robot arm[53] and a wheel chair[54] (Figure 4 m, 4 n). These aiding tools are helpful for performing remote robot surgeries and assisting paralyzed patients, respectively.

5. Fully implantable devices

Although skin-based electronics are quite useful in medical applications, electrophysiological and physiological signals oftentimes need to be measured directly from the target tissues in inner organs for better signal quality. A direct measurement from the target organ minimizes noise and enables a high spatio-temporal resolution mapping.[55] Furthermore, detecting, diagnosing, and treating atypical tissues with high precision through electrical stimulation and/or chemical therapies are possible using implanted devices.[8b] In spite of these advantages, inferior contacts of devices on wet organ surfaces compared to a dry skin surface may hamper precise local measurements and therapies.[8b, 56] The use of a biocompatible hydrogel is one strategy for improving the contact (Figure 5 a).[2c] The gel strongly adheres and fixes an electrode array to a rat's heart surface with negligible slippage. An elastomeric sock, a cardiac integumentary membrane that completely envelopes the epicardium, is also presented for local electrocardiogram and pH mapping without the gliding of the measuring point (Figure 5 b).[57] A full wrapping on the epicardium with a highly conductive rubber mesh using a silver nanowire composite is another approach for synchronized ventricular pacing and electrocardiogram recording without increasing end-diastolic pressure (Figure 5 c).[58] This cardiac mesh successfully improves heart activity in post-myocardial-infarction model and treats heart failures.

Similar with the cardiac devices, a more complicated and miniaturized design can be used for neural interfacing devices. An arrayed implantable device was administered for monitoring the brain without damaging the neural synapses. Malliaras et al. developed an organic semiconductor-based ultrathin multi-electrode array that can be attached on the cortex surface of an epilepsy patient.[59] Without penetration of the electrodes into the brain tissue, multichannel electrodes record the action potentials with a high signal to noise ratio during the surgery (Figure 5 d).[60] The flexible nature of the organic electronics enables highly amplified neural mapping from the cortex surface. Elastomer-based soft electronics were also utilized for developing a biocompatible neural interface to the spiral cord, called the 'electronic dura mater' (Figure 5 e).[3a, 61] It not only measures the electrospinogram and stimulates the spinal neurons but also injects drugs through microfluidic channels. These long-term neuroprostheses can provide new opportunities for high quality brain-machine interfaces.

Meanwhile, one of the significant issues in implantable devices is the second surgery required for removing the implanted device after initially planned monitoring and treatment.[62] The device elements remaining in the body can potentially cause an immune response and side effects. Therefore, applying bioresorbable electronics that operate for a certain period of time and then dissolve in the bio-fluids and blood stream can solve these issues. Bioresorbable pressure sensors utilizing dissolvable materials (i.e., silicon, Mo, and poly(lactic-co-glycolic acid)) were recently reported for continuously monitoring the intracranial pressure (Figure 5 f).[63] A bioresorbable Mg-based stent integrated with multifunctional sensors, data storage modules, and drug delivery therapeutic devices was also deployed to the artery for monitoring the blood flow and preventing restenosis after angioplasty (Figure 5 g).[64]

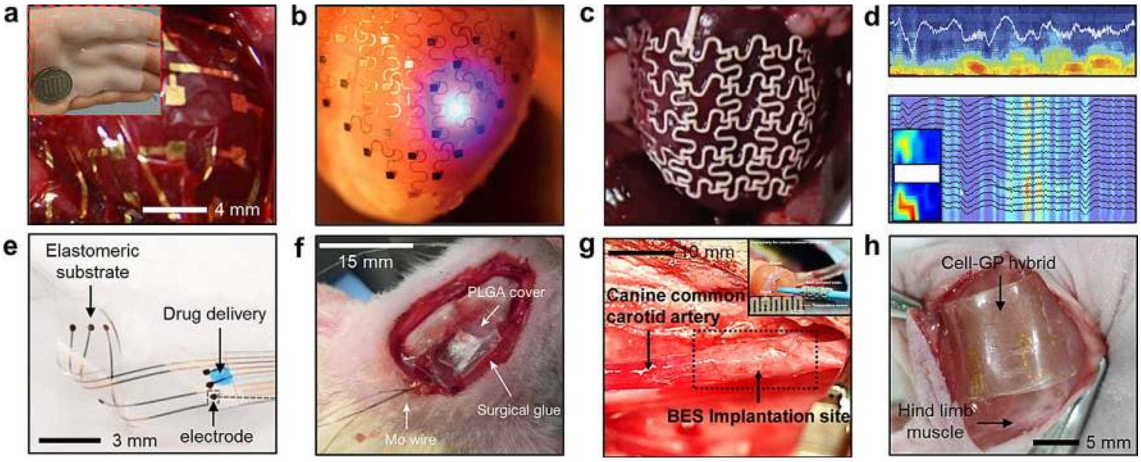

Figure 5. Fully implantable devices. a–c) Diverse methods for improving organ-interfacial adhesion using a) bonding through adhesive hydrogel and mechanical wrapping through b) elastomeric socks and c) silver nanowire composite based cardiac mesh. d) Recorded electrocorticogram from multichannel electrode array laminated on the cortex. e) Soft neural prosthesis, called 'Electronic dura mater'. f) Biodegradable electronics implanted into the skull. g) Multifunctional biodegradable electronic stent. h) Cell sheet transplantation to a scarred hind limb muscle. Reprinted from Ref. [2c, 57, 58, 60, 61, 63, 64, 66] with permission. Copyright 2014, 2015, 2016 Nature Publishing Group, 2015, 2016 American Association for the Advancement of Science, 2015 American Chemical Society, 2016 Wiley-VCH.

Enabling appropriate treatments in response to the diagnosis is another benefit of implantable devices.[65] Drug delivery, electroceuticals, and cell therapies are actively being incorporated with soft bioelectronics. For example, treatments through cell sheet transplantation and electrical stimulation using soft electrodes have been reported (Figure 5 h).[15a,66] Cell sheets cultured in vitro can be integrated on soft bioelectronics and then implanted on a target wounded site for tissue regeneration. The soft electrodes can apply pulsed electrical currents to help the regeneration. The cell sheet on soft multi-electrodes also improves neural interfaces and suppresses immune responses that have been significant issues in long-term implantation of devices.

6. Minimally invasive surgical tools

Owing to the high risks in surgery and long convalescent periods of fully implantable devices, the significance of minimally invasive surgery has increased. When minimally invasive surgical tools are inserted through a narrow incision, however, the visual field is limited, and indirect observations of the target surgery sites through X-ray or endoscopic camera are often utilized. However, limited visual observation in comparison with laparotomy may cause accidents; for instance, non-contacted radio frequency ablation using balloon catheters may lead to blood clot formation and occlusion of the blood vessels. A multifunctional balloon catheter that includes various sensors can compensate for the limited visual field and prevent such accidents. The balloon catheter with the tactile and pressure sensor perceives an exact touch between the electrode array and epicardium, and the atypical tissues are electrically detected and ablated (Figure 6 a, 6 b).[67]

Endoscopes have been widely utilized to acquire vision in minimally invasive surgery, but conventional endoscopes have limited functions, i.e., visual observation with restricted field of view and a guide of surgical scissors. A multifunctional endoscope-based interventional system, including transparent diagnostic/therapeutic electronics on its camera and theragnostic nanoparticles injected through intravenous routes, was recently reported for simultaneously detecting and treating colorectal cancer (Figure 6 c).[68] Transparent sensors and actuators are integrated onto the endoscopic camera without obstructing the surgeon's view and complement the camera in detecting colon cancers (Figure 6 d).[68] The multifunctional system facilitates high density bio-sensing and feedback therapy for the selected regions within the limited space in the colon. Theranostic nanoparticles also enhance the imaging quality as well as completely remove residual tumor tissues through combined therapies (i.e., photothermal-, photodynamic-, and chemotherapy).

Reducing the incision area and minimizing damages are key issues in designing minimally invasive surgical tools. For the brain, in particular, a device used for sensing and treatment may cause permanent damage to the neural tissues adjacent to the device. Thus, soft neural probes have been researched to solve this issue. To deliver soft-electronics into the small brain cavity with minimal tissue damages, Lieber et al. reported a syringe-injectable electronic system (Figure 6 e).[69] The syringe-type electrode array enables the mapping of the local field potential in the somatosensory cortex with minimal brain damage (Figure 6 f).[70] A needle-shaped injectable optogenetic device was also demonstrated for the optical stimuli of a specific targeted neuron tissue (Figure 6 g).[71] A co-integrated strip-type microfluidic device was employed for the controlled drug delivery into the nervous system (Figure 6 h).[71b]

7. Conclusion and outlook

In this Focus Review, we have discussed recent advances in soft bioelectronics that utilize assembled nanomaterials, strain

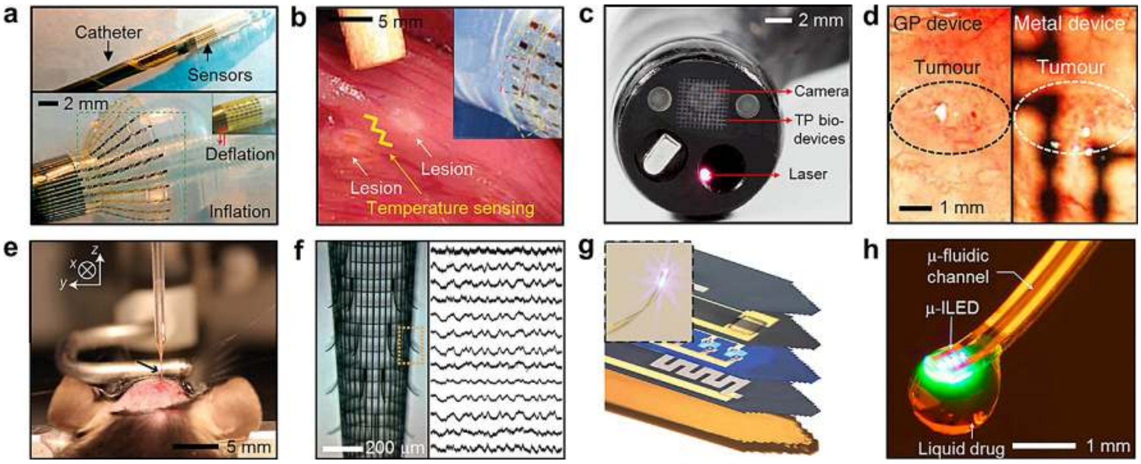

Figure 6. Minimally invasive surgical tools. a) Multifunctional balloon catheter in the inflated/deflated state. b) Ablation of arrhythmogenic foci using a thermal actuator on the balloon catheter. c) Multifunctional surgical endoscope integrated with transparent graphene sensors/actuators and therapeutic nanoparticles. d) Tumor image taken through a transparent graphene device (left) and an opaque metal device (right). e, f) Syringe injectable brain probe for measuring the cerebral potential. g) Needle-shaped injectable electronics for electrophysiological measurements and optoelectronic stimulations. h) Needle-shaped injectable electronics with strip-type microfluidic channel for a controlled drug delivery to the brain. Reprinted from Ref. [67, 68, 69, 70, 71a, b]] with permission. Copyright 2011, 2015 Nature Publishing Group, 2013 American Association for the Advancement of Science, 2015 Elsevier.

relief designs, and various integrated electronics for wearable and implantable biomedical applications. Because of several advantages such as conformal contacts, high deformability, and a biocompatible interface, the significance of soft electronics in medicine is kept increasing. The soft electronics has been widely applied in diverse fields including 1) textile-based electronics, 2) skin-originated devices, 3) implantable instruments, and 4) minimally invasive surgical tools. Integration of various nanomaterials enables unconventional functions in clinical procedures. The multifunctional systems based on integrated soft electronics, whose design is optimized for specific disease model, increase the efficiency and effectiveness of medical sensing, diagnosis, and therapy. In spite of considerable technical progresses, various issues continue to exist and should be studied further. Toxicity issues in semiconducting nanocrystals (e.g., CdS, CdSe, and PbSe) and silver nanowires should be resolved in order to apply those nanomaterials to the biomedical devices. Heavy-metal-free nanocrystals (e.g., CISe and InP) and gold nanowires are appropriate alternatives. Additionally, improvements in uniform and reproducible synthesis of nanomaterials in a large scale are required for the mass-production and commercialization. The interface between the devices and tissues needs to be improved. Long-term biocompatibility of nanomaterials particularly in implantable devices is an important issue to study further. Robust interfacial adhesion and strain relief designs can enhance the measurement quality, allow long-term attachment, and suppress immune responses. Not just small animal evaluations but also large animal experiments and human applications are necessary steps to commercialize soft bioelectronics. Medical systems integrated with versatile sensors, memory devices, wireless modules, energy-harvesting devices, and therapeutic actuators can innovate previously existing clinical procedures and protocols for the management of various diseases. Continuous, stable, and long-lasting power supply to implanted electronics is another overarching goal of the device research. Soft bioelectronics would pave the way for ubiquitous healthcare and smart surgeries.

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Keywords: flexible electronics · implantable devices · minimally invasive surgical tools · nanomaterials · wearable electronics

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