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Bioresorbable Electronic Implants: History, Materials, Fabrication, Devices, and Clinical Applications

*Gi Doo Cha, Dayoung Kang, Jongha Lee, and Dae-Hyeong Kim**

Medical implants, either passive implants for structural support or implantable devices with active electronics, have been widely used for the diagnosis and treatment of various diseases and clinical issues. These implants offer various functions, including mechanical support of biological structures in orthopedic and dental applications, continuous electrophysiological monitoring and feedback of electrical stimulation in neuronal and cardiac applications, and controlled drug delivery while maintaining arterial structure in drug-eluting stents. Although these implants exhibit long-term biocompatibility, surgery for their retrieval is often required, which imposes physical, biological, and economical burdens on the patients. Therefore, as an alternative to such secondary surgeries, bioresorbable implants that disappear after a certain period of time inside the body, including bioresorbable active electronics, have been highlighted recently. This review first discusses the historical background of medical implants and briefly define related terminology. Representative examples of non-degradable medical implants for passive structural support and/or for diagnosis and therapy with active electronics are also provided. Then, recent progress in bioresorbable active implants composed of biosignal sensors, actuators for therapeutics, wireless power supply components, and their integrated systems are reviewed. Finally, clinical applications of these bioresorbable electronic implants are exemplified with brief conclusion and future outlook.

1. Introduction

Concurrent with increased human lifespan and technological advances in materials, devices, and fabrication methods, various types of biomedical devices[1–3] optimized for specific diseases have been developed. In particular, research on medical implants, including those with active electronics, has been highlighted in recent years, as these implantable devices provide effective solutions for critical clinical challenges. As an example, passive physical supports are widely used for the maintenance of orthopedic,[4,5] dental,[6] and facial structures.[7] More advanced forms of medical implants with integrated electronics enable closed-loop health monitoring and advanced feedback therapy such as in situ active programmed stimulation in brain,[8] cochlear[9,10] or retinal prostheses,[11,12] and nerve or cardiac stimulators.[13–17] Advanced therapeutic functions such as targeted drug delivery are also achievable, for example, in drug-eluting stents[18–20] and insulin pumps.[21,22]

These medical implants are located inside the human body to offer the designated functions to the target organs. Proximity of implants to the target organs dramatically improves the bio-sensing accuracy and the therapeutic efficacy compared with non-invasive approaches[23] such as wearable medical devices,[24] imaging tools, and orally administered drugs.[25–27] However, long-term exposure to abiotic components implanted near organs can cause short- and/or long-term negative immune responses.[28] Therefore, after the desired use, surgical extraction of chronic implants is often required, but this additional secondary surgery imposes both physical and economic burdens on patients.

As an alternative to implanted devices that may require additional secondary surgeries, bioresorbable implants that can dissolve inside the body and be absorbed by the body have attracted great attention. Passive bioresorbable implants such as suture thread[29,30] and bioadhesive glue[31] are widely used in clinical fields. However, medical implants integrated with active electronics that perform advanced functions and are composed of bioresorbable materials/components are not yet commercially available. Research on various types of bioresorbable device components (e.g., substrates, active components, and encapsulation layers) has been reported in recent publications.[32–37] Several groups have also reported the clinical potential of bioresorbable medical devices, as demonstrated in vivo using animal models.[8,38–40]

In this article, we review materials, devices, and fabrication technologies for bioresorbable electronic implants. We first review the historical background of medical implants, including bioresorbable ones. Then, we specify different categories of

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medical implants and explain the related terminology. After introducing conventional bioinert and bioresorbable passive implants that are in clinical use, we discuss material design and fabrication techniques for bioresorbable active implants. Subsequently, recent progress in bioresorbable active medical implant technologies is described, from individual device components, such as energy devices, sensors, and actuators, to fully integrated systems, including demonstrations of their potential applications in vivo. Finally, we conclude this review with a brief assessment of the future outlook of bioresorbable electronic implants.

2. History of Medical Implants and Recent Demand for Bioresorbable Electronic Implants

Among therapeutic approaches, medical implants have often been proposed as the most viable solution for many clinical issues because their proximity to the target organ offers high efficiency and accuracy in disease diagnosis and therapy. Despite these obvious benefits, the exceptionally unusual environment inside the human body and the necessary but burdensome surgeries for device implantation impose many constraints on materials and device design options for implantable devices. **Figure 1** shows schematic illustrations of representative types of medical implants. Among them, active electronics made of bioresorbable materials, an emerging type of next-generation medical implant, are the particular focus of this review.

Medical implants have been applied for various parts of the human body (Figure 1a) such as bones, eyes, ears, neurons, blood vessels, and even deeply located key organs (e.g., heart and brain).[1,41] A device can be implanted at the target site after surgical incision (Figure 1b). Most widely commercialized implants are made of non-degradable bioinert materials (Figure 1c), and the constituent materials permanently remain in the body rarely inducing a severe negative host response in the host biosystem.[42,43]

However, in some cases, bioinert implants require removal from the body after a certain period of time, and this secondary surgery places physical and economical burdens on the patients. Bioresorbable implants that dissolve into harmless substances without any severe biological reactions, therefore, have been suggested for these cases. Such implants function for a desired period of time and then disappear by degradation inside the body, eliminating additional burdens on patients and reducing the rare but possible side effects associated with the chronic presence of bioinert materials in the body. The concept of bioresorbable implants was initially applied to replace simple, passive implants (Figure 1d) used for physical support (e.g., sutures and absorbents).[44,45]

However, the demand for advanced functions such as sensing and feedback therapy has increased, leading to the development of electronic medical implants made of bioresorbable materials. Hence, new types of bioresorbable active electronic components for medical implants (e.g., sensors, batteries, and memory modules)[38,39,46] have been developed recently. These bioresorbable "active implants" (Figure 1e) meet the functional requirements of conventional bioinert active implants, such as various signal sensing and feedback stimulation therapy capabilities including controlled drug delivery functions,[47,48] and feature the ability to completely dissolve inside the human body after the desired period of use.

Material selection for bioresorbable active implants has been a critical issue because the condition of bioresorbability severely limits the choice of electronic materials.[37,49,50] Furthermore, special fabrication techniques are required for bioresorbable electronics in order to design sophisticated device microstructures while preventing hydrolytic disintegration of the materials during device fabrication.[51,52] Significant efforts from several research groups have afforded suitable bioresorbable materials for each layer in an electronic device (e.g., conductor, semiconductor, insulator, and substrate)[53] and fabrication techniques[54] appropriate to such bioresorbable materials. Based on these results, researchers have also developed bioresorbable active components that exhibit levels of function comparable to those of conventional non-degradable bioinert devices, such as physical/electrophysiological sensors, energy devices, and actuators (Figure 1f, bottom). The integration of such device components provides controllable feedback-loop systems, including monitoring and therapy in conjunction with an external host controller (Figure 1f, top). This closed-loop process typically begins with an implanted bioresorbable sensor that sends sensing signals (e.g., temperature, pressure, pH, electrocardiogram (ECG) signals, or electroencephalography (EEG) signals) to the host controller (Figure 1f, right). Then, the central processing unit processes the signals and

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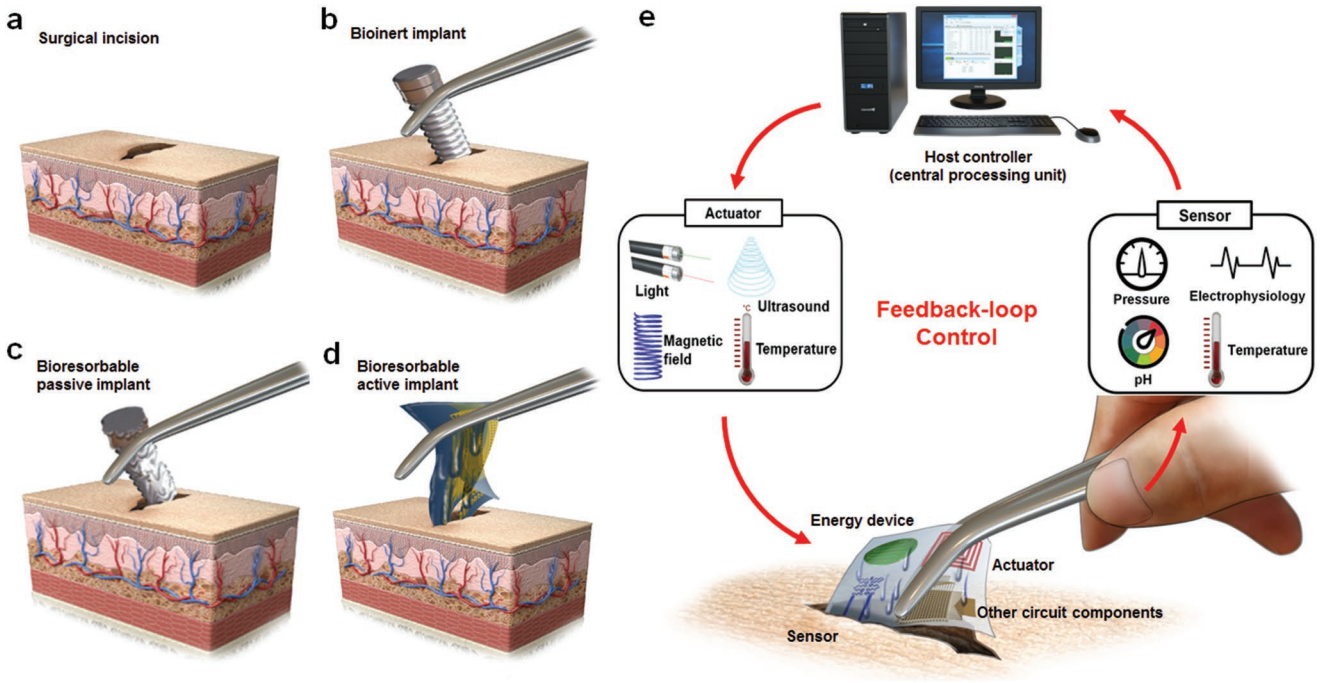

Figure 1. History of medical implant and recent demand for bioresorbable electronic implants. Schematic illustration of a) surgical incision and the implantation of b) bioinert implant, c) bioresorbable passive implant, and d) bioresorbable active implant. e) Schematic illustration of operation process of bioresorbable active implant that provides closed-loop control of the functions with external host controller and sensing/actuating tools.

triggers the actuators to apply feedback outputs that penetrate into the target tissue (e.g., ultrasound, magnetic field, light, or temperature) when necessary (Figure 1f, left). The required power for the system can be supplied by bioresorbable energy devices. By integrating bioresorbable electronic device components and optimizing them for specific disease requirements, bioresorbable and implantable integrated electronic systems can be fabricated, which have enormous potential for solving unmet clinical challenges.

3. Definitions of Biocompatibility, Biodegradability, and Bioresorbability

Before discussing medical implants in detail, some related terminology that will be used throughout this review article should be clarified. The terms "biocompatible", "biodegradable", and "bioresorbable" are widely used to classify biomaterials and biomedical devices based on their bioreactive responses to the external environment.

According to the International Union of Pure and Applied Chemistry (IUPAC), biocompatibility is defined as the ability to be in contact with a living system without causing any adverse biological effects,[43] which is an important prerequisite for medical implants (**Figure 2**a). To select appropriate materials for medical implants, diverse factors, including chemical compositions, biological material responses, and even mechanical properties, should be considered to achieve biocompatibility and mitigate negative immune responses.[55]

Biocompatible materials do not need to be degradable (i.e., such materials can be bioinert). However, biodegradable materials should be decomposed by living organisms in the environment such as fungi and bacteria (Figure 2b) with an appropriate biodegradation rate. For example, to be classified as a biodegradable material, more than 90% dissolution of the substance within 6 months is required.[56]

Meanwhile, bioresorbability, a synonym of bioabsorbability, requires more demanding conditions than biodegradability. Substances that degrade without any abnormal responses in the human body can be defined as bioresorbable materials.[53] These materials are disintegrated through a series of metabolic and hydrolytic reactions, and the resulting products are absorbed into the body or discharged from the body without any biological problems (Figure 2c). Therefore, the composition of the material is an important factor for bioresorbability. Furthermore, the dissolution rate should be carefully set to prevent high local concentrations of the dissolved components. Over a certain threshold, the dissolved components may cause toxicity, although they are safe at lower concentrations.[57,58] By contrast, if dissolution is too slow, the benefits of the bioresorbable implants may be eliminated. To meet these specifications, bioresorbable materials require comprehensive verification through a series of biological assays and tests, such as in vitro assays, in vivo tissue responses, and in vivo degradation tests.[59]

4. Bioinert Non-degradable Medical Implants

Conventional medical implants are typically composed of non-degradable bioinert materials. However, bioresorbable materials have been used when dissolution of an implant after a desired period of time is recommended. In such cases, the

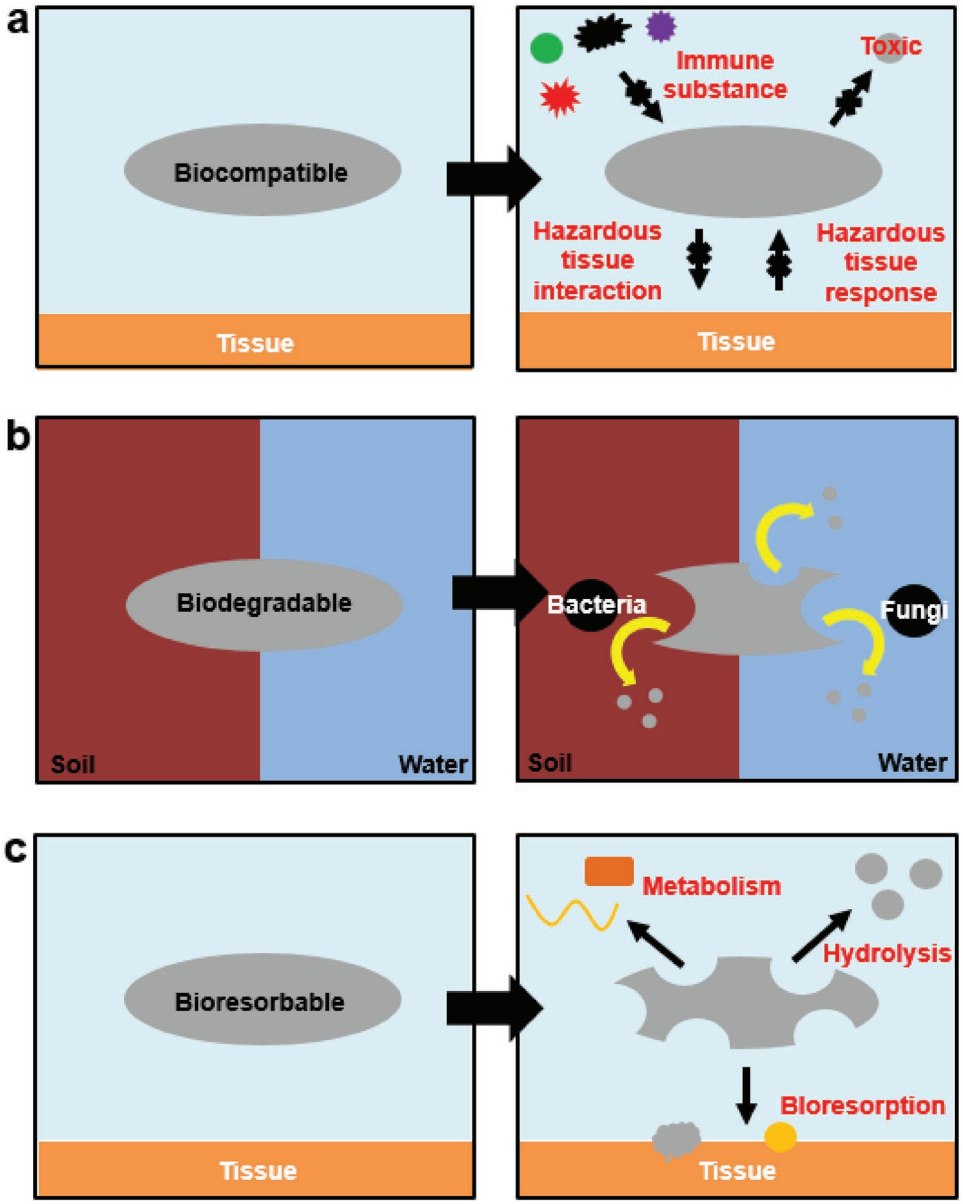

Figure 2. Schematic illustrations of the concept of bioreactivity-related terminology. Reaction of a) biocompatible materials in the human body, b) biodegradable materials in the external environment, and c) bioresorbable materials in the human body.

bioresorbable implant should provide the same functions as the original bioinert implant. We will first briefly introduce several representative examples of nondegradable bioinert medical implants before reviewing the details of bioresorbable medical implants to provide insights into their roles and functions.

4.1. Conventional Bioinert Passive Implants

Early medical implants were primarily used as mechanical substitutes for irreversibly lost body parts. Such implants are composed of bioinert materials for permanently implantable structural support. The most representative example is an orthopedic implant[60] to supplement a broken bone or an abraded joint, which mainly results from accidental injury or aging (**Figure 3**a). These implants, which serve as skeletons with controlled sizes and shapes, are typically made of stainless steel or titanium alloys for high mechanical strength. Physical supports are also required for reconstructive surgeries[7] on many human body parts, including the nose, jaw, and chest (Figure 3b). These implants permanently support the desired body part, so the materials should be fully biocompatible and bioinert.

Another type of passive medical implant is mesh-shaped devices. Such devices are often implanted to mechanically fix an organ in a desired shape and location. A surgical mesh, for example, wraps the target organ after surgery to fix it at the designated location (Figure 3c).[61] Early versions

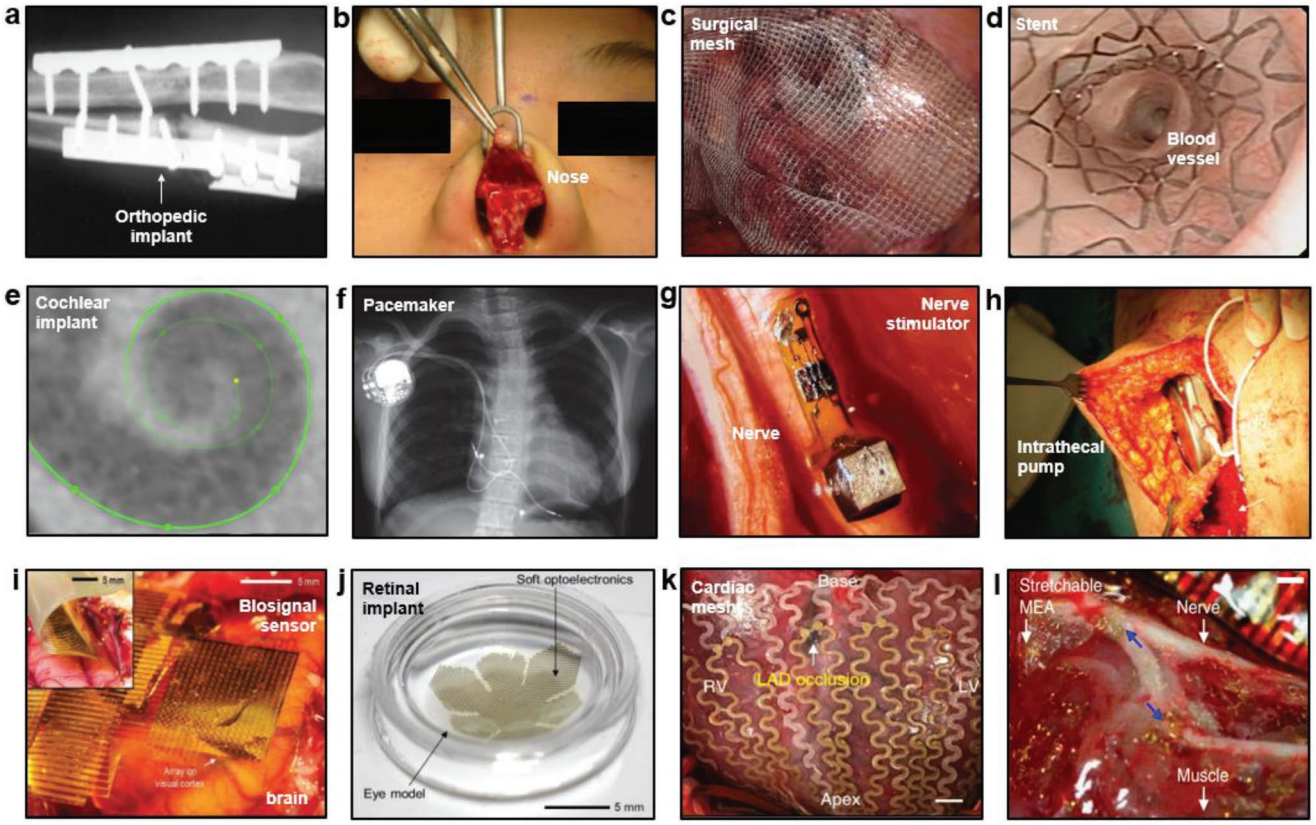

Figure 3. Bioinert implants. a) X-ray image of orthopedic implant for ulna. Reproduced with permission.[60] Copyright 2014, ACT. b) Optical image of reconstructive surgery for nose. Reproduced with permission.[7] Copyright 2017, The Korean Society of Plastic and Reconstructive Surgeons. c) Optical image of a surgical mesh implant for tissue fixation. Reproduced with permission.[61] Copyright 2015, Frontiers Media SA. d) Optical image of implantation of stent in blood vessels. Reproduced with permission.[63] Copyright 2018, PLOS. e) CT image of cochlear implant. Reproduced with permission.[64] Copyright 2018, PLOS. f) X-ray image of pacemaker implanted in the chest. Reproduced with permission.[65] Copyright 2014, The Japenese Association of Rural Medicine. g) Optical image of implanted nerve stimulator. Reproduced with permission.[66] Copyright 2016, AAAS. h) Optical image of implanted intrathecal pump. Reproduced with permission.[68] Copyright 2008, Dove Medical Press. i) Optical image of flexible electrophysiological sensor on brain cortex. Reproduced with permission.[71] Copyright 2011, Nature Publishing Group. j) An optical image of flexible optoelectronics on curved surface. Reproduced with permission.[72] Copyright 2017, Nature Publishing Group. k) Optical image of stretchable nanocomposite that wraps the heart. Reproduced with permission.[74] Copyright 2018, Nature Publishing Group. l) Optical image of flexible multi-electrode array on nerve. Reproduced with permission.[75] Copyright 2014, Nature Publishing Group.

of mesh were made of rigid components, but to solve issues associated with mechanical mismatch between the mesh and the target organ, soft surgical meshes have been developed using flexible materials such as polypropylene and polyvinylidene fluoride (PVDF).[62] As another type of medical implant with a mesh structure, a stent maintains a blood vessel in the open state to prevent vascular stenosis (Figure 3d).[63] Stents, which are implanted inside blood vessels through a minimally invasive procedure, called angioplasty, have been fabricated using various materials from polymers to self-expandable metallic materials, depending on the clinical situation.

4.2. Conventional Bioinert Implants with Active Electronics

Bioinert passive devices do not have active functions, such as sensing or stimulating functions, but these functions are often important. For example, the cochlear implant, which restores hearing capability for patients with auditory disorders (Figure 3e),[64] senses external sound and converts it into electrical stimulation signals that are transmitted to the auditory nerves through implanted electrodes. Another important electronic implant is the cardiac pacemaker for heart diseases, such as arrhythmia or myocardial infarction (Figure 3f).[1,65] An advanced pacemaker analyzes cardiac signals as well as related health signals (e.g., blood gas concentration, body temperature, and hormone levels), and self-feedback therapy is achieved via cardiac electrical stimulations based on the sensing results. A similar electrical stimulating device can also be implanted on the central nervous system (Figure 3g).[66] Most nerve stimulators apply electrical stimulation pulses to adjacent nerves for pain relief. Currently, electrical stimulation research is being performed for diverse diseases (e.g., obesity and neurological disorders). Furthermore, deep brain stimulation can be used for diverse neurodiseases such as Parkinson's disease or depression. Another popular application of active implants is drug delivery pumps such as the insulin pump[67] or the intrathecal

pump[68] (Figure 3h). These devices are usually a substitute for oral drug administration to enhance drug delivery and therapeutic efficiency. As drugs are injected directly into the target site through a catheter, an internal barrier and digestion do not interfere with drug delivery.

4.3. Flexible and Stretchable Bioinert Implants

Most commercialized non-degradable bioinert active implants are encapsulated in a rigid metallic container. However, the development of soft active implants confers various clinical advantages, including higher biocompatibility owing to the mechanical compatibility between tissues and soft devices as well as accurate sensing and efficient feedback stimulation derived from the conformal contact between the curved surface of the organ and the flexible device.[69,70] For example, soft electronics can be applied as multiplexed electrophysiological sensors for the brain (Figure 3i)[71] and as prosthetic image sensors and neural stimulation electrode arrays for blind eyes (Figure 3j).[72] Hundreds of Si-based arrays on a thin polyimide (PI) substrate can record various electrocorticography (ECoG) signals, such as sleep spindles and visually evoked responses, with high spatial resolution in vivo (Figure 3i).[71] Soft optoelectronics based on a truncated strain-releasing design and intrinsically soft and ultrathin materials (e.g., MoS_2, graphene, and PI), which allow high-resolution optical imaging and soft mechanical properties close to the human eye, are suitable for retinal implants (Figure 3j).[72]

Furthermore, soft implantable electrode arrays can be applied to the curved surfaces of various organs.[73] Choi et al. introduced a highly conductive and stretchable nanocomposite with excellent biocompatibility for application as a mesh-like cardiac stimulator that can wrap the heart for electrical signal recording and feedback stimulation (Figure 3k).[74] Ag-Au core-shell nanowires mixed with an elastomer exhibit highly stretchable properties while maintaining high conductivity. Further, the Au sheath that wraps around the Ag core provides high biocompatibility. A stretchable multi-electrode array can also be used for stimulating peripheral nerves based on sensing signals from artificial skin (Figure 3l).[75] An electrode array decorated with ultrathin platinum nanowires coated with ceria nanoparticles achieved low impedance and minimal neurotoxicity. Successful neuro-stimulation of the peripheral nerves was confirmed through corresponding EEG signals measured on the brain.

5. Bioresorbable Passive Implants

In some cases, medical implants are no longer needed after a certain period of time because the body recovers to the original state after a period of treatment using an implant. In these cases, a permanent implant can cause unexpected side effects and/or can place an unnecessary load on patients. Hence, surgery to retrieve the implant is often required. To make secondary surgery unnecessary, the fabrication of medical implants with bioresorbable materials has been investigated. These attempts first focused on conventional passive implants, in which the original mechanical functionality was unchanged but the constituent materials of the implant were modified into bioresorbable ones.

5.1. Bioresorbable Implants for Physical Supports

Suture thread is one of the earliest medical implants to have been fabricated using a bioresorbable material (**Figure 4**a).[30] It has a relatively simple structure/function and thus can easily be replaced with bioresorbable materials. Bioresorbable suture thread is typically composed of natural/synthetic polymers and degraded through hydrolysis and proteolytic enzymatic reactions within 6 months, which is longer than the time required for typical wound regeneration.[76] Surgical mesh (Figure 4b)[77] can also be fabricated with absorbable synthetic polymers. Similarly, as a structural support, bioresorbable orthopedic implants whose mechanical rigidity is comparable to that of conventional bioinert implants have been developed (Figure 4c).[29,78] Such implants are based on several degradable metals (e.g., manganese, iron, and zinc), and their alloys have been used to tune the biodegradation behavior and improve the mechanical properties. These materials have also been used to fabricate bioresorbable stents (Figure 4d).[79] As these devices are designed to dissolve naturally at the implant location, long-term side effects, such as stent thrombosis and restenosis in the case of stents, can be prevented.[80,81] Polymer-based (e.g., polylactic acid (PLA), polycarbonate, and salicylic acid) bioresorbable stents have also been developed, as they exhibit reduced toxicity and an extended degradation period in comparison with absorbable metal stents.[82] Absorbable polymer-based tissue scaffolds (Figure 4e)[83] have been devised as temporary templates for tissue engineering. There are various options for component materials, from hydroxyapatite to collagen, which determine the strength of the cell culture scaffold and affect cellular processes such as proliferation and differentiation.

5.2. Bioresorbable Drug Delivery Devices

In addition to passive implants for structural support, bioresorbable materials can be used as drug reservoirs in drug delivery devices. Implantable drug delivery systems usually exhibit superior delivery efficiency compared with other drug delivery approaches such as oral drug intake or transdermal drug delivery because the drugs are directly injected into the target site. This approach enables short-term burst release as well as long-term controlled release of drugs. Certain bioresorbable polymers, such as those specially tuned for slower degradation, can be used for sustained drug release. Bioresorbable nanoparticles,[84] for example, can retain drug molecules for an extended period of time (Figure 4f). Drugs are released gradually as the polymer shell degrades inside the body. For example, ocular drug delivery using a bioresorbable polymer reservoir (Figure 4g)[85] is particularly useful for prolonged drug release inside the eye. Without such a system, the dynamic movement of the ocular fluids typically removes the drugs rapidly. This

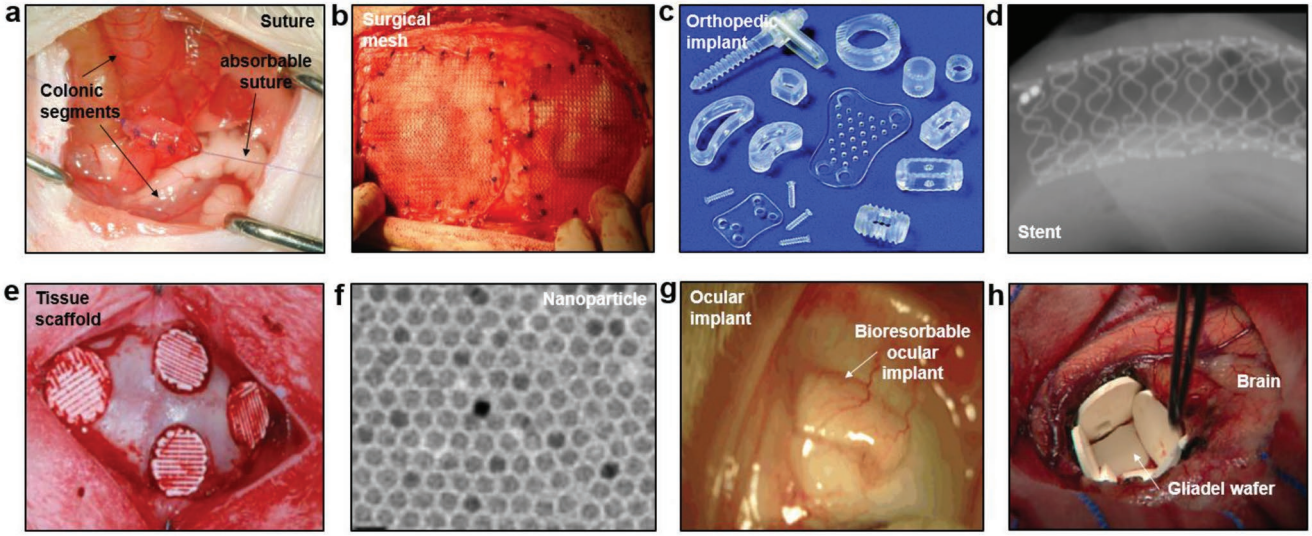

Figure 4. Bioresorbable passive implants. a) Optical image of bioresorbable suture for anastomosis. Reproduced with permission.[30] Copyright 2018, PLOS. b) Optical image of bioresorbable surgical mesh in abdominal defects. Reproduced with permission.[77] Copyright 2011, Springer. c) Optical image of bioresorbable orthopedic implant for fixation and repair. Reproduced with permission.[78] Copyright 2015, Dove Medical Press. d) X-ray image of bioresorbable stent implanted in blood vessel. Reproduced with permission.[79] Copyright 2013, MDPI. e) Optical image of bioresorbable tissue scaffold for rabbit skull defect. Reproduced with permission.[83] Copyright 2016, Nature Publishing Group. f) Transmission electron microscope (TEM) image of bioresorbable nanoparticles. Reproduced with permission.[84] Copyright 2005, Wiley-VCH. g) Slit-lamp optical image of ocular implant in eye. Reproduced with permission.[85] Copyright 2011, PLOS. h) Optical image of Gliadel wafers in a glioblastoma resection cavity. Reproduced with permission.[86] Copyright 2016, Kleinberg.

ocular drug delivery implant is made of a soft bioresorbable film that is suitable for the soft, sensitive, and curved structure of the eye. Furthermore, sustained drug delivery is necessary for organs with limited accessibility. For example, hydrogel/patch-type devices have been developed for intracranial sustained drug release. Patch-type bioresorbable drug reservoirs (e.g., Gliadel wafer; Figure 4h)[86] can be applied to the treatment of brain tumors. In brain tumors, drug delivery via the conventional routes is difficult owing to the blood-brain-barrier. Therefore, intracranial implantation of a drug-releasing bioresorbable patch after primary surgical tumor removal is effective for preventing tumor recurrence. In addition, the bioresorption of intracranial implants is helpful to prevent seizures and/or epilepsy.

The above bioresorbable passive implants satisfy the requirement that the implant lasts only for a fixed period of time in vivo. However, it is difficult to cope with the continuously changing in vivo conditions with such bioresorbable passive implants. Therefore, bioresorbable active electronics have been suggested to address such issues. In the following sections, we will review materials, fabrication techniques, and individual device components for bioresorbable electronics, as well as some examples of integrated bioresorbable active implants, including in vivo demonstrations.

6. Materials for Bioresorbable Electronics

To develop bioresorbable electronic implants, electronic materials (e.g., insulators, semiconductors, and conductors) that can be degraded inside the body without any abnormal responses are required. **Table 1** shows representative examples of such bioresorbable electronic materials.

6.1. Bioresorbable Conductors

Bioresorbable conductors include alkaline metals, such as Mg and Ca, transition metals, such as Mo, Zn, and Fe, and alloys of these metals (Table 1). These materials can be disintegrated into metal cations via hydrolysis and resorbed by the body near the implant site. As each metal exhibits different dissolution kinetics and distinctive advantages, bioresorbable conductors need to be chosen by considering the specific application, the desired operation time of the device in the body, and the physiologically allowed local concentration threshold.

Alkaline metals, especially Mg, show high biocompatibility and are also compatible with conventional microfabrication techniques. Therefore, they have been widely used as bioresorbable conducting units, such as electrodes, resistors, and capacitors, in bioresorbable devices.[40] However, without encapsulation, such materials may break down rapidly and non-uniformly in vivo. Therefore, they are typically accompanied by surface encapsulation. By contrast, transition metals, which exhibit much slower dissolution rates than alkaline metals in biological environments, can be exposed to biofluids for some period of time even without encapsulation.[87] This property is useful for sensing electrodes for electrophysiological applications. For example, bioresorbable brain-signal-sensing electrodes[38,71] fabricated using Mo showed stable operation over 24 h.

Table 1. Classification of bioresorbable materials according to their usage in bioresorbable electronics.

	Type		Materials	Ref.
Conductor	Alkaline metal		Mg, Ca	[40]
	Transition metal		Fe, Zn, Mo, W	[38,71]
	Alloy		Mg Alloy	[39]
	Metallic glass		Mg-Zn-Ca	[90]
Semiconductor	Inorganic		Si nanomembrane, ZnO	[34,94]
	Natural Organic		Indigo, Melanin	[95,96]
	Artificial Organic		Polypyrrole, PDPP-PD	[97]
Insulator/encapsulation	Metal nitride		Si_3N_4	[50]
	Metal oxide		SiO_2, MgO	[8,39,98]
	Natural polymer	Polysaccharide	glucose, cellulose, alginic acid, chitin, levan	[52,102,103]
		Polypeptide	silk, collagen, biotin, keratin	[100,104,105]
		Lipids	phospholipid, triglycerides	[48]
	Artificial polymer	Polyester	PLA, PLGA, PCL, PHB	[8,38]
		Polyanhydride	PSA, PCPP:SA	[101]
			copolymers	[108]

The local concentration threshold is also important for the selection of bioresorbable conductors, as the degradation products of biocompatible metals may cause negative immune responses when released in large amounts locally over a short period of time. Compared with microelectromechanical systems (MEMS), which usually require less than 1 mg of metals, a much greater amount of metal is required for electrode arrays and/or mechanical supports in medical implants (e.g., electronic stents).[39,88] In this regard, Mg alloys are preferred for implants operated over an extended time period because they exhibit slower and more controlled degradation than pure Mg.[89] Notably, amorphous metallic glasses composed of Mg, Zn, and Ca[90] show long-term mechanical/electrical stability, and thus have the potential to be used for long-term implantable electrode array applications.

6.2. Bioresorbable Semiconductors

Compared with bioresorbable metals and insulators, which have been widely investigated as materials for passive implants, bioresorbable semiconducting materials have only been investigated very recently owing to the increasing demand for bioresorbable electronics. Si, an obviously indispensable semiconducting material, was first examined as a bioresorbable semiconductor through structural modification. Bulk Si is generally considered to be non-degradable, partly owing to the formation of native oxides on its surface. However, when its dimensions are decreased to the nanoscale, complete dissolution can occur in biofluids.[91] For example, a single-crystalline Si nanomembrane (Si NM) exhibits a dissolution rate of ≈2–4 nm per day[34] in phosphate buffered saline (PBS). The dissolution rate is also affected by dopants. Furthermore, the Si NM and its biodegradation products were confirmed to be biocompatible, even in the presence of small amounts of dopants.[92] Therefore, lightly doped Si NMs can be used for bioresorbable electronics, as they undergo complete hydrolysis to form innocuous degradation products inside the body within reasonable timescales.[93]

Bioresorbable metal oxides with controlled concentrations of oxygen vacancies (e.g., ZnO_x and MgO_x; $x < 1$) can also be used as semiconductors in bioresorbable devices such as energy generators[94] and memory devices.[19] As such inorganic semiconductors are compatible with conventional photolithography, they have high potential for use in high-resolution/performance bioresorbable active implants.

Organic semiconductors have also been proposed as promising candidates for bioresorbable devices, mainly owing to their soft/flexible mechanical properties and potential for large-scale synthesis. Indigo[95] and melanin[96] are representative natural semiconducting materials that have been applied to transistors and batteries. Such natural semiconducting polymers show high biocompatibility, but there are issues with performance and uniformity. Compared with natural polymers, synthetic semiconducting polymers have advantages in terms of property control and structural diversity. Up to now, polypyrrole-based polymers[97] have been studied as artificial bioresorbable semiconducting polymers that show high biodegradability, thermal stability, and reasonable electrical performance.

6.3. Bioresorbable Insulators and Encapsulation

Bioresorbable insulating materials (e.g., metal oxides, metal nitrides, and polymers) can be used either as the dielectric layer or as an encapsulant in bioresorbable electronics. Inorganic materials such as the oxides/nitrides of Si and Mg have been widely used for bioresorbable insulators because they show bioresorbability when deposited as thin films.[8,39,50,98] Further, the compatibility of these materials with vacuum deposition processes and photolithography is an advantage for achieving high-performance and high-resolution bioresorbable electronics.[35,38,99]

Both natural[52,100] and artificial[38,101] polymers, which have been broadly studied for bioresorbable passive implants, can be applied to bioresorbable insulating and/or encapsulating layers. For example, plant-based polysaccharides[52,102,103] and animal-based polypeptides,[100,104,105] which are now commonly used for bioresorbable surgical sutures and absorbents, have been investigated for insulation/encapsulation applications in bioresorbable electronics. Typically, reproducible and finely-tunable synthetic polymers are preferred to natural polymers. For example, different molecular ratios of PLA and polyglycolic acid (PGA) in poly(lactic-glycolic acid) (PLGA) can result in different dissolution rates, which determine the degree of encapsulation and the lifespan of bioresorbable active implants.[106,107] In addition, the solution processability and well-proven bioabsorbability of synthetic polymers[8,38] are also advantageous. However, bulk erosion inside the body limits their use in moisture- and acid-sensitive applications. As an alternative, polyanhydrides have been highlighted as promising materials for insulating/encapsulating layers, as they show slow surface erosion and uniform dissolution rates, which extends the lifetime of bioresorbable encapsulation.[101] Recently, the operation time of bioresorbable encapsulation was successfully extended to the month scale. However, further research should be conducted on polymeric materials (e.g., copolymers of the natural and artificial polymers mentioned above[108]) to optimize the degradation rate, mechanical properties, low water and oxygen permeabilities, and biocompatibility.

7. Fabrication Technologies for Bioresorbable Electronics

To realize bioresorbable active electronics with various patterns and/or functions,[109] conventional MEMS fabrication technologies, such as photolithography and the shadow-masking technique, have been applied. However, many conventional techniques cannot be directly applied owing to the intrinsic dissolvability of bioresorbable materials. As bioresorbable materials dissolve when exposed to water, fabrication processes that involve direct contact with water should be minimized. In addition, most bioresorbable polymers exhibit morphological transitions at temperatures of >50 °C, but high-temperature processes are often required in conventional device fabrication processes.[53] Therefore, MEMS fabrication technologies should be modified to be compatible with bioresorbable materials.[58]

Depending on the type of material, it can be fabricated based on either solution- or vacuum-deposition processes. Solution processes, which tend to be low cost and performed at relatively low temperatures, can be applied to organic materials owing to their high solubility. In contrast, vacuum-deposition processes are frequently used for inorganic materials because of difficulties in preparing their solutions. In general, higher quality thin films can be obtained via vacuum-deposition processes.[110,111] The Bao group suggested the fabrication of biodegradable electronics composed of organic semiconductors using a series of solution/vacuum processes (**Figure 5**a).[112] In this work, a solution of a synthesized organic semiconductor was spin-coated on a bioresorbable substrate. A dielectric oxide and metal interconnections were subsequently fabricated through vacuum deposition processes to build a logic gate. In another study, multi-layered bioresorbable polymers were combined with bioabsorbable metal electrodes (Figure 5b, left) to fabricate bioresorbable pressure/strain sensors (Figure 5b, right) that work inside the body.[40]

The fabrication of bioresorbable devices based on single-crystal Si NMs, one of the highest quality semiconducting materials for bioresorbable electronics, is mainly conducted on the handling wafer. After fabrication, the device is transfer-printed onto bioresorbable substrates (Figure 5c).[54] Transfer-printing is an attractive strategy for bioresorbable electronics because the exposure of the bioresorbable substrate to water can be minimized during the fabrication process. In this process, all layers except for the substrate are deposited on the wafer (Figure 5c, top left) with a sacrificial layer (poly(methyl methacrylate) (PMMA)) and a protecting layer (diluted PI). The sacrificial layer aids in detaching the device from the handling wafer, and the protecting layer prevents direct exposure of the device to water. After all the layers are fabricated, the device is dipped into a solvent (acetone) that selectively dissolves the sacrificial layer (PMMA) (Figure 5c, top middle). The released device is picked up using a stamp (Figure 5c, right; polydimethylsiloxane (PDMS)), and subsequently transferred onto the bioresorbable substrate (Figure 5c, bottom middle). Finally, the protecting layer is removed (Figure 5c, bottom left).[54] Transfer-printing techniques can also be applied to different materials (Figure 5d).[50] Using Si_3N_4 and SiO_2 as passivation layers and dextran as a sacrificial layer, the Rogers group established nanoscale foundry-based biodegradable electronics (Figure 5e).[50]

Although the transfer-printing process is well developed for the fabrication of bioresorbable electronics, it still has disadvantages such as high costs and a long fabrication time. Hence, the fabrication of bioresorbable electronics has also been attempted using other technologies. For example, Zn nanoparticles were directly printed onto a bioresorbable substrate using inkjet printing (Figure 5f)[51] to fabricate a bioresorbable device with a conducting layer of Zn nanoparticles. In addition, many unconventional technologies (e.g., laser cutting,[48] vapor condensation evaporation,[113] and screen printing[52]) have also been applied.

Despite the limited amount of fabrication technologies for bioresorbable electronics, many studies have successfully demonstrated bioresorbable devices with comparable performances to conventional electronic devices (Figure 5g).[49] However, improved fabrication techniques for bioresorbable electronics should be developed to enable the integration of more diverse materials[114,115] and device components toward fully integrated bioresorbable electronic systems.

8. Device Components for Bioresorbable Electronics

Bioresorbable electronic materials, unique device designs, and novel fabrication strategies enable the fabrication of various individual bioresorbable electronic device components from energy generators to sensors and actuators. These components can be integrated to form implantable medical systems. Prior to describing the system-level integration and in vivo applications, we first review the individual device components in this section.

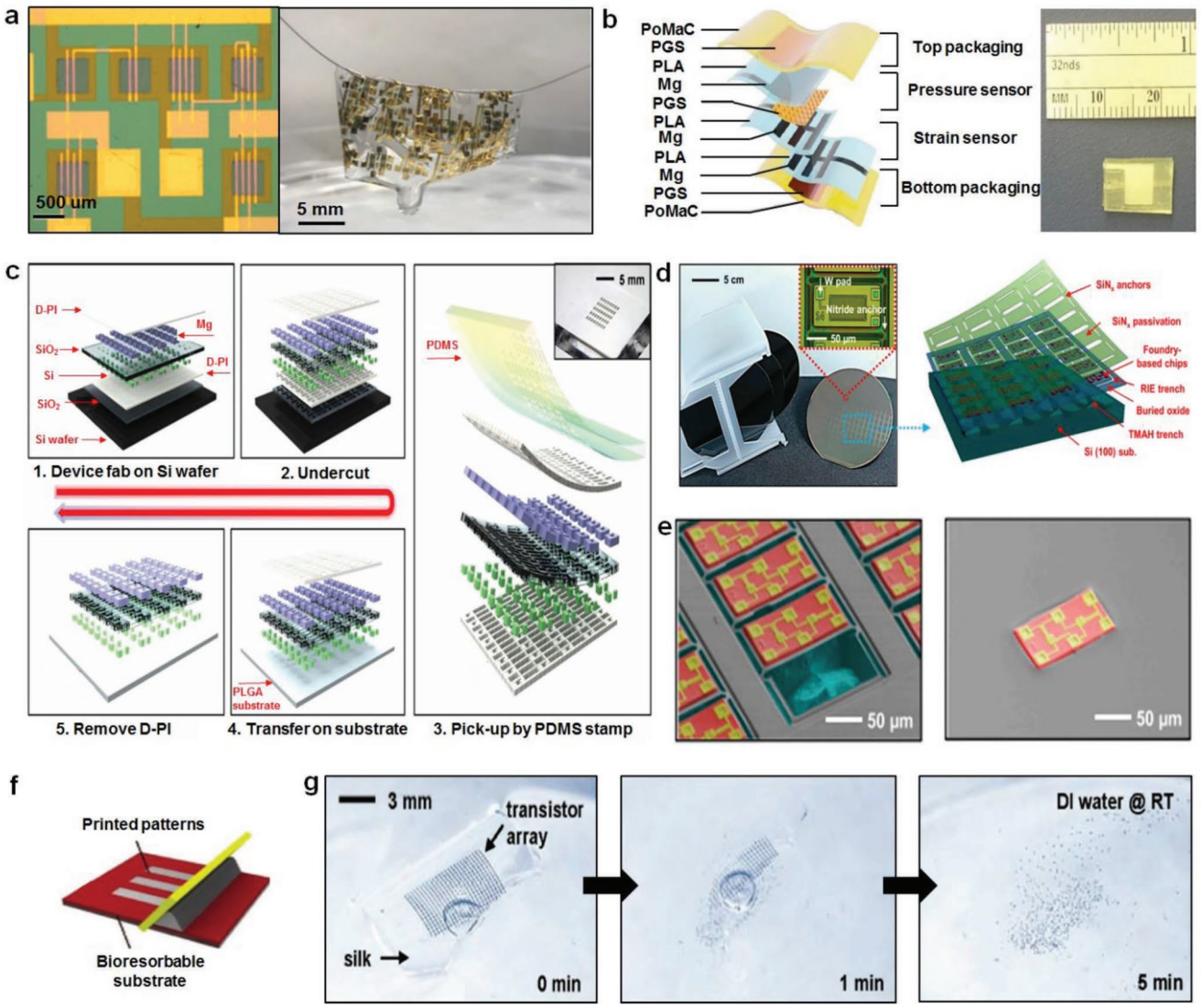

Figure 5. Fabrication techniques of bioresorbable electronics. a) Optical microscopic image of biodegradable organic electronics (left) and the device picked up by a human hair (right). Reproduced with permission.[112] Copyright 2017, National Academy of Sciences. b) Schematic exploded view of bioresorbable electronics composed of multi-organic layers (left) and optical image of assmebled sensor (right). Reproduced with permission.[40] Copyright 2018, Nature Publishing Group. c) Schematic exploded view of the fabrication process of bioresorbable electronics using transfer-printing technique. Reproduced with permission.[54] Copyright 2014, Wiley-VCH. d) Optical image of foundry-based biodegradable electronics on wafer (left) and schematic exploded view of electronics (right). Reproduced with permission.[50] Copyright 2017, National Academy of Sciences. e) Scanning electron microscope (SEM) image of biodegradable electronics after undercut (left) and transferred on substrate (right). Reproduced with permission.[50] Copyright 2017, National Academy of Sciences. f) Schematic illustration of patterning bioresorbable materials via inkjet printing. Reproduced with permission.[51] Copyright 2017, Wiley-VCH. g) Optical images of degradation of bioresorbable electronics versus time. Reproduced with permission.[49] Copyright 2013, Wiley-VCH.

8.1. Bioresorbable Energy Devices

8.1.1. Batteries

Bioresorbable energy storage devices are indispensable components for bioresorbable electronic implants, as they eliminate the necessity for external power supply wires. **Figure 6** reviews bioresorbable energy devices, from batteries and microsupercapacitors to energy harvesters. For example, a bioresorbable primary battery using galvanostatic pairs of bioresorbable metal foils (Mg and Mo served as the anode and cathode, respectively), a PBS electrolyte, and a polyanhydride package has been reported (Figure 6a)[46] with a reasonable theoretical energy density and excellent biocompatibility. The performance of the single cell battery exhibited a constant discharge current density (0.1 mA/cm^2) and an operating voltage of ≈0.45 V for 24 h (Figure 6b). A bioresorbable primary battery with molybdenum trioxide (MoO_3)[116] as the cathode has also been reported to exhibit a stable output voltage of up to 1.6 V with a lifetime of ≈13 days.

Redox biomolecules and their derivatives have been used as electrode materials in rechargeable energy-storage devices. Kim et al. reported the use of melanin pigments as anode

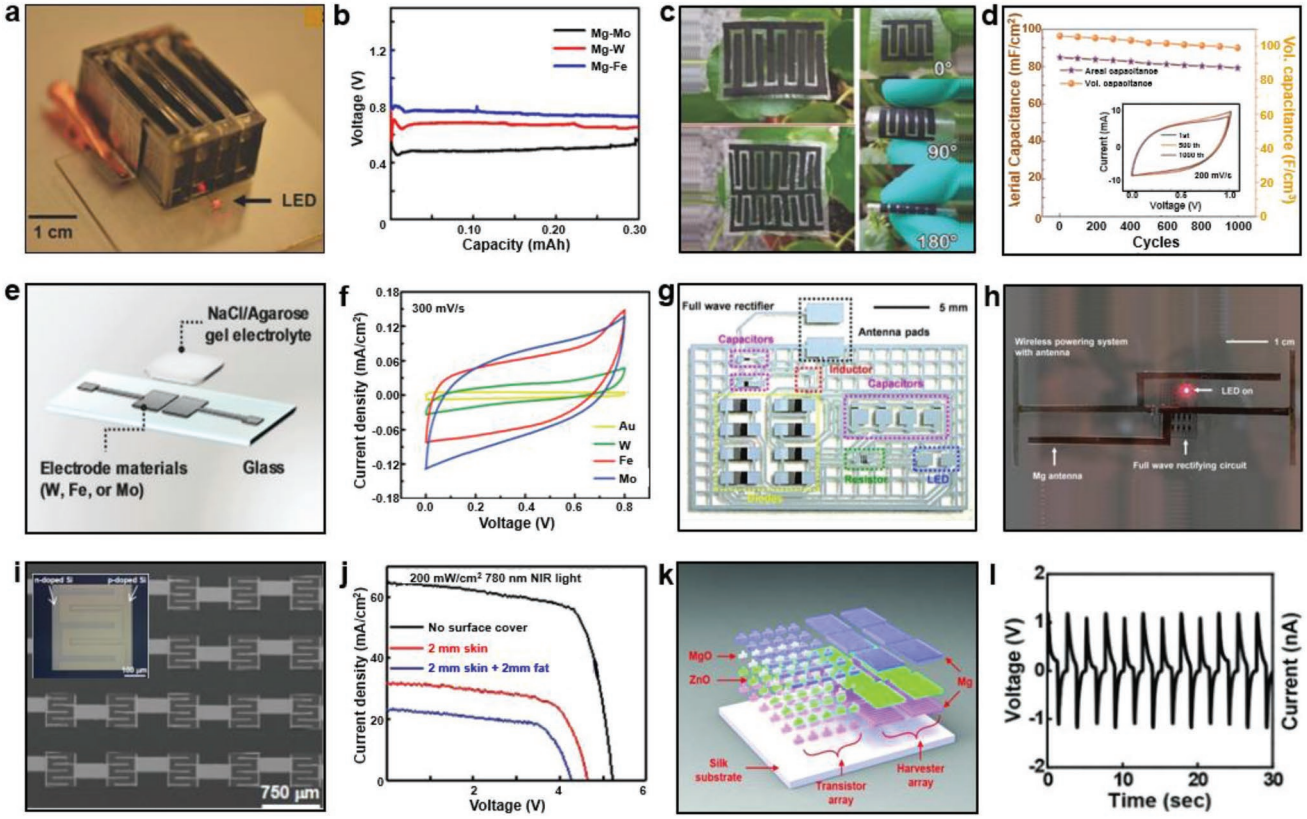

Figure 6. Bioresorbable energy sources: batteries, supercapacitors, and energy harvesters. a) Optical image of Mg-Mo bioresorbable primary battery powering a red LED. Reproduced with permission.[46] Copyright 2014, Wiley-VCH. b) Discharging behavior of Mg-X primary battery with constant current. Reproduced with permission.[46] Copyright 2014, Wiley-VCH. c) Optical image of bioresorbable microsupercapacitors with different configuration patterns (left) and in bent states (right). Reproduced with permission.[119] Copyright 2017, Wiley-VCH. d) Cycling performance of the bioresorbable microsupercapacitors. Reproduced with permission.[119] Copyright 2017, Wiley-VCH. e) Schematic exploded view of bioresorbable pseudocapacitor. Reproduced with permission.[101] Copyright 2017, Wiley-VCH. f) Cyclic voltammetry of the bioresorbable psudocapacitor. Reproduced with permission.[101] Copyright 2017, Wiley-VCH. g) Schematic illustration of bioresorbable full-wave rectifying circuit. Reproduced with permission.[35] Copyright 2013, Wiley-VCH. h) Optical image of the full-wave rectifying circuits wirelessly powered with RF transmitter. Reproduced with permission.[35] Copyright 2013, Wiley-VCH. i) SEM image of bioresorbable photovoltaic array and optical image of single microcell (inset). Reproduced with permission.[120] Copyright 2018, Wiley-VCH. j) *I–V* curve of the photovoltaic with different materials on its surface. Reproduced with permission.[120] Copyright 2018, Wiley-VCH. k) Schematic exploded view of bioresorbable thin film transistors and piezoelectric energy harvester/strain gauges. Reproduced with permission.[94] Copyright 2013, Wiley-VCH. l) Graph of output voltage versus time during bending cycles. Reproduced with permission.[94] Copyright 2013, Wiley-VCH.

materials in aqueous Na-ion batteries.[96] Na^+-loaded melanin anodes exhibited a high specific capacity of ≈30.5 mAh/g, and a full cell paired with a λ-MnO_2 cathode showed an initial operating voltage of 1.0 V and a specific capacity of ≈16 mAh/g. The Guo group demonstrated that humic acid and emodin (6-methyl-1,3,8-trihydroxyanthraquinone) with redox-active quinone groups could be used as anodic and cathodic materials, respectively, for rechargeable batteries.[117] The as-fabricated full cell exhibited a specific capacity of ≈60 mAh/g and succeeded in powering portable devices.

8.1.2. Microsupercapacitors

Charge storage in microsupercapacitors is based on the accumulation of ions in the electrolyte on the electrode surface to form electrical double layers. Because the electrical double layer is formed by the physical movement of ions, there is no chemical reaction involved.[118] Therefore, bioresorbable microsupercapacitors fabricated with activated carbon electrodes (Figure 6c) exhibit superior endurance during charge-discharge cycling, even under mechanical deformation (Figure 6d).[119]

Other microsupercapacitors that exploit pseudocapacitance for energy storage are based on Faradaic electron charge transfer between the electrode and the electrolyte. As Faradaic energy storage occurs via redox reactions in the pseudocapacitor, microsupercapacitors show faster charging/discharging rates than batteries.[118] Lee et al. demonstrated a bioresorbable pseudocapacitor built using water-soluble metal electrodes (W, Fe, and Mo) and ion salts (Na^+ and Cl^-) in a biopolymer hydrogel electrolyte (agarose gel) (Figure 6e).[101] The operation exploited pseudocapacitance originating from the metal-oxide layer generated by electrochemical corrosion at the interface between the water-soluble metal electrode and the hydrogel electrolyte. A complete set of bioresorbable microsupercapacitors with Mo interdigitated electrodes offered

an areal capacitance of 1.6 mF/cm^2 and a power density of 1.0 mW/cm^2 (Figure 6f).

8.1.3. Energy Transfer Devices and Energy Harvesters

Bioresorbable systems implanted in the body can receive power from external sources. One option is to use radio frequency (RF) energy transfer. Hwang et al. reported a bioresorbable RF power transfer system with a Mg antenna designed to operate at 2.4 GHz and 950 MHz (Figure 6g).[35] This system wirelessly received energy from an external RF transmitter (distance ≈2 m), whose transferred power was high enough to turn on a red LED (Figure 6h). Luyao et al. demonstrated an ultrathin photovoltaic array based on monocrystalline Si microcells devised to operate between red and near-infrared (NIR) wavelengths, which exhibit long penetration depths in biological tissues, so that external illumination could provide power to photovoltaic devices implanted under the skin (Figure 6i).[120] This array generated an output power of 64 μW and an open circuit voltage (V_{oc}) of 4.25 V under NIR illumination through a 4 mm thick porcine skin (Figure 6j). Harvesting energy from mechanical motion is also possible. A piezoelectric energy harvester based on Mg electrodes, ZnO active materials, and a silk substrate/encapsulant was introduced (Figure 6k).[94] The voltage and current outputs from the piezoelectric device were maximized under large bending deformations, with a peak output power density of ≈10 nW/cm^2 (Figure 6l).

8.2. Bioresorbable Sensors

Bioresorbable sensors are usually developed to measure diverse health signals, including prognosis monitoring near the target organ after treatment. Recently reported examples include bioresorbable thermoresistive temperature sensors, chemical/mechanical sensors (e.g., pH sensors, piezoresistive strain gauges, and pressure sensors), and electrophysiological signal sensors.

8.2.1. Temperature Sensors

The real-time detection of local temperature changes in tissues or organs is of great interest, as these changes are highly related to inflammation and/or deviations in homeostasis.[121,122] Resistance-based temperature detectors (RTDs) are widely used in bioresorbable devices owing to their merits of high accuracy, fast response, and simplicity of fabrication.[123] **Figure 7**a depicts the geometry and constituent materials of a representative RTD.[124] The sensor is composed of three main parts: the sensing element, interconnections, and pads for external wiring (Figure 7a, left). The sensing element consists of thin 10 μm Mg traces so that its electrical resistance is much larger (≈130 times) than that of the interconnections (Figure 7a, middle and right). Thus, the resistances of the wiring and interconnections are negligible in comparison with that of the sensing element, resulting in the sensing element showing accurate and dynamic temperature responses. A Peano fractal design was adopted for the interconnections[125] to confer stretchability to the entire structure and thus to conform to the curved surface of an organ (Figure 7a, middle and right). The sensor consisting of a Mg active layer, a Si_3N_4 dielectric layer, and a SiO_2 encapsulation layer (Figure 7a, left) successfully exhibited a linear response to temperature changes over a large range without any hysteresis (Figure 7b). This measurement range and sensitivity can be easily tuned by varying the thickness of the sensor element or substituting the active layer with another bioresorbable material.[38,39,126]

8.2.2. Pressure Sensors

Measuring vital physiological pressures (e.g., diaphragmatic contraction pressure, intraarticular pressure, intraocular pressure, and intracranial pressure) is important for monitoring health status, preventing potential damage to specific organs induced by accumulated internal forces,[127] and monitoring and controlling novel mechanical stimulation approaches.[128,129] On the basis of their sensing mechanisms, bioresorbable pressure sensors can be classified into three types, i.e., piezoresistive, capacitive, and piezoelectric pressure sensors.[130]

One of the most widely used bioresorbable pressure sensors is the piezoresistive pressure sensor, which measures piezoresistive changes to detect pressure changes.[38] The diaphragm deforms in response to an external pressure change and the piezoresistive sensor on the diaphragm detects the dimensional change of the diaphragm. Using this principle, Kang et al. proposed a piezoresistive pressure sensor based on a Si NM on a flexible PLGA membrane,[38] which forms the top seal of an underlying Si cavity (Figure 7c, left). The associated air cavity allowed the membrane to be deformed in response to pressure changes in the surroundings (Figure 7c, right). A larger pressure caused greater deformation of the PLGA membrane, which in turn led to a larger resistance change. The device showed stable measurements of pressure in vivo and dissolved completely into biocompatible products after a fixed time period.

Despite its simplicity, the piezoresistive pressure sensor has some disadvantages, including temperature-related variations in sensitivity.[131] These problems can be solved in capacitive pressure sensors. Generally, such sensors consist of two parallel conductive electrode plates (e.g., Fe-Mg) separated by a dielectric elastomer (e.g., poly(glycerol sebacate) (PGS)) (Figure 7d).[132] When an external pressure is applied to one of the conductive plates, the volume of the dielectric material enclosed between the two parallel conductive plates is reduced, and the capacitance between the electrodes changes. The sensor exhibited high pressure sensitivity, even in the low pressure regime (<10 kPa) (Figure 7d, inset). The sensitivity and sensing range can be adjusted by tuning the thickness and modulus of the PGS film.[133]

Finally, the piezoelectric pressure sensor utilizes piezoelectric materials, such as ceramics[134] (e.g., PZT ceramics) or single-crystal materials[135,136] (e.g., gallium phosphate, quartz, and tourmaline), which convert mechanical deformation into electricity and vice versa.[137] Although bioresorbable piezoelectric pressure sensors have been rarely explored, mainly owing to challenges in finding appropriate bioresorbable piezoelectric materials, PLA has recently been found to exhibit shear piezoelectricity when the crystallinity and the orientation degree of

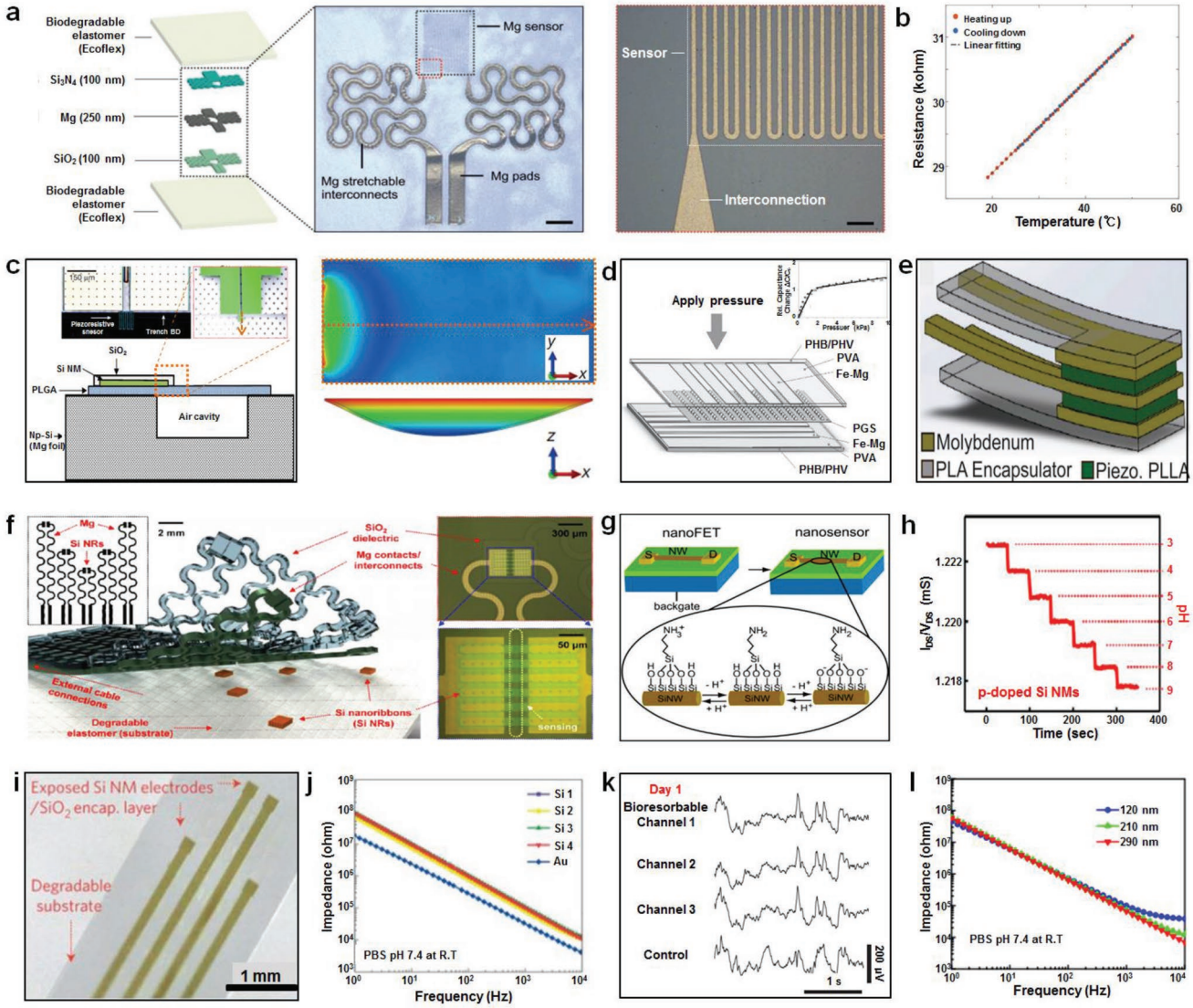

Figure 7. Bioresorbable sensors for temperature, pressure, pH and electrophysiology. a) Schematic exploded view of bioresorbable resistive temeprature detectors (RTDs) (left). Schematic illustration of the Mg active layer (middle) and the magnified view of the junction area between the sensor and the interconnector (right). Reproduced with permission.[124] Copyright 2017, Wiley-VCH. b) *I–V* curve of the RTDs with linear response over a wide temperature range without any significant hysteresis. Reproduced with permission.[124] Copyright 2017, Wiley-VCH. c) Schematic illustration of cross-sectional side view of the bioresorbable pressure sensor (left bottom) and optical image of the sensing region (left top). Distribution of the principal strains across the PLGA layer, determined from finite element analysis method (FEM) for an external pressure (right top) and the corresponding displacement profile evaluated along the red dotted line (right bottom). Reproduced with permission.[38] Copyright 2016, Nature Publishing Group. d) Schematic illustration of bioresorbable and flexible piezoresistive pressure sensor and its pressure response curve in inset. Reproduced with permission.[132] Copyright 2015, Wiley-VCH. e) Schematic illustration of bioresorbable piezoelectric PLA pressure sensor. Reproduced with permission.[141] Copyright 2018, Nature Publishing Group. f) Schematic illustration of bioresorbable and stretchable pH sensors (left) and its top view (inset). Optical image of the sensor (right top) and its magnified view (right bottom). Reproduced with permission.[108] Copyright 2015, American Chemical Society. g) Schematic illustration of the changes in the surface charge in response to pH. Reproduced with permission.[143] Copyright 2001, AAAS. h) The conductance change of the device at various pH stages (from 3 to 10). Reproduced with permission.[108] Copyright 2015, American Chemical Society. i) Optical image of a bioresorbable electrophysiology sensor with 4 channels. Reproduced with permission.[8] Copyright 2016, Nature Publishing Group. j) Graph of electrochemical impedance magnitude, measured at four different recording sites. Reproduced with permission.[8] Copyright 2016, Nature Publishing Group. k) Representative ECoG signals recorded by the bioresorbable electrophysiology sensor with three different electrodes and the control electrode. Reproduced with permission.[8] Copyright 2016, Nature Publishing Group. l) Impedance spectra of differnt thicknesses of the Si NM electrodes. Reproduced with permission.[8] Copyright 2016, Nature Publishing Group.

the polymer chains are optimized.[138,139] Such piezoelectrical properties are due to the electrical polarity of the carbon-oxygen double bonds (C=O) branching out from the polymer backbone.[140] Curry et al. developed a bioresorbable piezoelectric pressure sensor by alternately sandwiching three Mo electrodes and two piezoelectric PLA films (Figure 7e).[141] The sensitivity can be further adjusted by changing the number of PLA layers.

8.2.3. pH Sensors

Monitoring pH is also important because several hormones, enzymes, and even the immune system are affected by pH changes.[142] Hence, bioresorbable pH sensors have been suggested. Figure 7f left shows a schematic illustration of the pH sensor based on an amine-/oxide-functionalized Si nanoribbon (Si NR) field-effect transistor (FET).[100] The sensor is composed of Si NRs as the sensing blocks, whereas SiO_2 and Mg serve as insulation/encapsulation and electrode/interconnection components, respectively (Figure 7f, right). 3-Aminopropyltriethoxysilane (APTES) was used to functionalize the surface of the Si NR with $-NH_2$ and -SiOH groups (Figure 7g).[143] At low pH, $-NH_2$ is protonated to form $-NH_3^+$, whereas at high pH, −SiOH is deprotonated to form $-SiO^-$. The resulting changes in the surface charge chemically gated the Si NR. As a result, the conductance of the Si NR changed stepwise with discrete changes in pH (from 3 to 10) (Figure 7h). The pH sensitivity can be adjusted by varying the doping concentration and geometry (e.g., surface-to-volume ratio) of the Si NR FET.

8.2.4. Electrophysiological Sensors

The human body generates a wide range of electrophysiological signals (i.e., electrical potentials changes, including EEG, ECG, and electromyography (EMG) signals). These electrical potential changes can be detected in various body parts and can be used for clinical diagnosis. For example, neurophysiological monitoring[144–146] is commonly used for diagnosing and treating neurological disorders such as epilepsy,[147] Parkinson's disease,[148] depression,[149] and chronic pain.[150] These electrophysiological signals are also commonly monitored in intensive care units.[151] Flexible ultrathin highly doped Si NM electrodes on a PLGA substrate can be used for electrophysiological monitoring (Figure 7i). A SiO_2 layer insulates the connection traces to isolate the electrodes from biofluids and adjacent tissues, whereas the terminal pads are exposed to the target tissue for accurate electrophysiological measurements. As the quality of the measurement depends on the interface impedance between the electrode and the target tissue surface,[152,153] electrochemical impedance spectroscopy (EIS) fitting can be helpful. For example, if the electrodes at four different recording sites show similar impedance values, it can be concluded that the electrode fabrication, installation, and fitting processes have been successful (Figure 7j). Si NM electrodes were successfully applied to monitor neural signals in rats (Figure 7k). The dopant concentration of the Si NM (phosphorus) and the thickness of the Si NM electrodes had little effect on the impedance, suggesting that continuous and reliable measurements were obtained, even during dissolution of the Si NM (Figure 7l).

8.3. Bioresorbable Actuators

Bioresorbable actuators stimulate target tissues or actuate drug delivery devices in response to dynamically changing internal physical conditions monitored by bioresorbable sensors. Inductive coils combined with serpentine resistors are widely used as remotely controllable thermal actuators to suppress surgical site infections by stimulating drug delivery. Energy from an alternating current (AC) source is transferred from the external primary coil to the receiver coil in the bioresorbable circuit (**Figure 8**a), thereby driving the corresponding resistor to generate heatm which can induce drug delivery (Figure 8b).[47] The resonant frequency can be tuned by modifying the coil's turn number, turn width, and turn spacing. Hence, integration of inductive coils of different resonance frequencies enables selective actuation of the desired region (Figure 8c). Such a device can be constructed on a degradable polymer substrate (e.g., silk or starch) that contains drugs (e.g., pTH(1-34), dextran, or doxorubicin) for on-demand, localized drug delivery (Figure 8d). For example, a thermal actuator mounted on a phospholipid film, whose stacking orientation is sensitive to the transition temperature, can control drug release by selectively inducing phase changes in the lipid membranes (Figure 8e).[48]

The inductive coil can be integrated with electrodes to deliver pulses of electricity to the target tissue. Koo et al. designed a bioresorbable implantable wireless electrical actuator that combines an RF power harvester and stimulation electrodes (Figure 8f).[99] A bioresorbable metal strip was embedded in a PLGA encapsulation layer to prevent electrical leakage, whereas the tip of the electrode was exposed to deliver electrical stimuli to the target tissue. The flexible soft terminal pad made conformal contacts between the electrodes and the tissue (Figure 8g). Through modulation of the power delivered to the antenna receiver, a controlled periodic pattern of electrical stimulation pulses can be introduced. Such electrotherapy has various applications including treatment of neurological disorders, nerve regeneration, wound healing, and cell proliferation.[99] A particular challenge for actuators is the development of methods for external control of such deeply implanted devices and the elaborate correlation of this wireless control with electrical stimulations to realize therapeutic efficacy.

9. Bioresorbable Integrated Electronic Systems

By integrating suitable bioresorbable device components (introduced in section 8), bioresorbable integrated electronic systems could be fabricated as promising solutions for various clinical challenges.[154–156] One particular application of interest is postoperative monitoring, which could be applied to critical but commonly performed surgeries and procedures such as those on the central nervous system (e.g., brain and spinal cord),[8] circulatory system (e.g., heart and blood vessels),[38,39] and motor control system (e.g., bones, joints, and tendons).[40] Yu et al. developed a bioresorbable EEG/ECoG sensor array composed of a highly doped Si NM (**Figure 9**a).[8] Such a device can be mounted on the surface of the brain to record spatiotemporal ECoG signals up to 33 days after surgery (Figure 9b) without any negative neuronal responses. It also successfully measured EEG signals when implanted on the periosteum.[8] In another case, Hwang et al. reported a wireless bioresorbable intracranial sensor that monitors important physiological signals (e.g., temperature, pressure, pH, and thermal conductivity/diffusivity; Figure 9c,d).[38] The

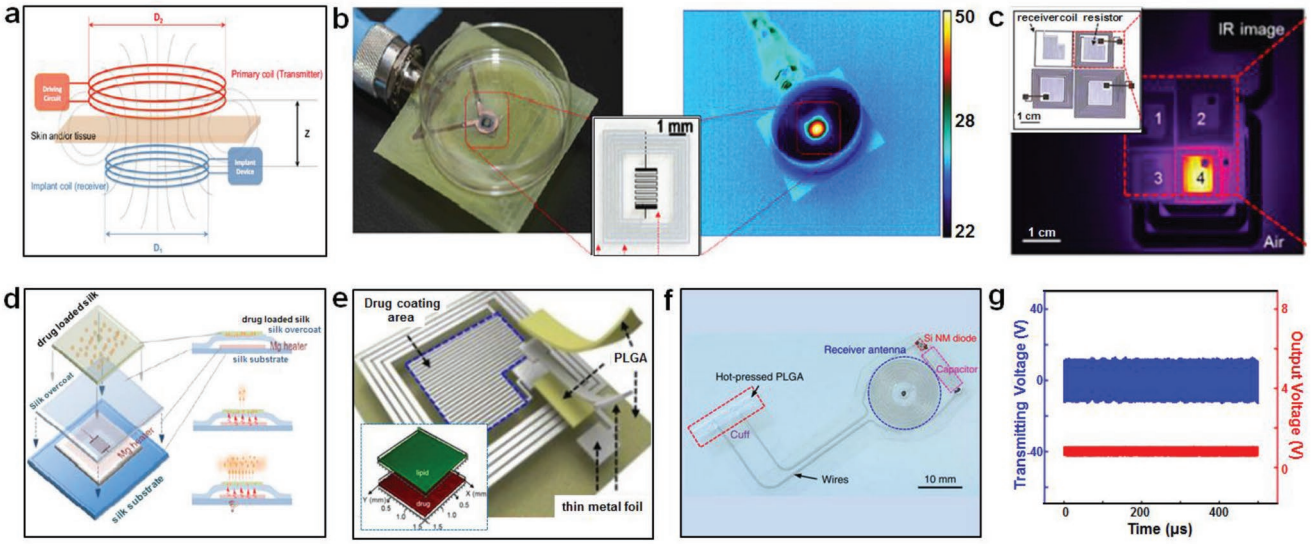

Figure 8. Bioresorbable actuators: heat/electrostimulation. a) Schematic illustration of induction coupling between the primary coil and the receiver coil. Reproduced with permission.[47] Copyright 2014, National Academy of Sciences. b) Optical image (left) and infrared (IR) image (right) of the thermal acuator, wirelessly powered by an external RF transmitter, with magnified view of the active region of the thermal actuator (middle). Reproduced with permission.[47] Copyright 2014, National Academy of Sciences. c) IR image collected during operation of representative device with corresponding optical image (inset) showing spatially controlled heating. Reproduced with permission.[48] Copyright 2015, Nature Publishing Group. d) Schematic illustration of the thermal actuator integrated with antibiotics-doped silk film for wirelessly activated drug release. Reproduced with permission.[47] Copyright 2014, National Academy of Sciences. e) Schematic illustration of the thermal actuator integrated with a lipid membrane substrate loaded with drug (inset). Reproduced with permission.[48] Copyright 2015, Nature Publishing Group. f) Optical image of bioresorbable electrostimulator. Reproduced with permission.[99] Copyright 2018, Nature Publishing Group. g) Graph of output waveform voltage (stimulator, red) wirelessly generated by an alternating current applied to the transmission coil (transmitter, blue). Reproduced with permission.[99] Copyright 2018, Nature Publishing Group.

bioresorbable sensor exhibited comparable performance to conventional devices, implying that it has clinical potential for post-operative brain monitoring.

Bioresorbable sensors for motor function monitoring have also been reported recently. Boutry et al. reported a stretchable bioresorbable strain/pressure sensor (Figure 9e)[40] to monitor the forces applied to tendons during regeneration and recovery (Figure 9f, left). The device was implanted subcutaneously on the back of a rat, and by acting as a bioresorbable capacitance sensor, the strain/pressure changes were successfully monitored for up to 3.5 weeks without any significant immune responses (Figure 9f, right). Even very small changes in strain and pressure, such as 0.4% and 12 Pa, respectively,[40] could be detected at the implant site.

An important surgical procedure on the circulatory system is angioplasty, after which a stent is typically implanted to prevent re-narrowing of the artery. However, the most common symptom related to angioplasty and following stent implantation is the re-accumulation of lipids/plaques around or inside the stent (in-stent restenosis).[157,158] As a potential solution to in-stent restenosis, bioresorbable stents have been developed. Recently, Son et al. proposed a multi-functional bioresorbable electronic stent (Figure 9g),[39] which provides post-operative monitoring and treatment functions in addition to the original functions of a conventional bioresorbable stent. The proposed bioresorbable electronic stent was equipped with a bioresorbable flow sensor for blood flow monitoring and a bioresorbable heater and temperature sensor for controlled post-operative drug delivery (Figure 9h,i).[39] The entire system was composed of bioresorbable materials, and thereby complete biodegradation of the stent reduced the possibility of restenosis. Future research directions for bioresorbable electric stents include integration of the flow sensor, temperature sensor, memory,[159] and even therapeutic nanoparticles.[160]

Bioresorbable electronics have been highlighted as next-generation medical implants by demonstrating the successful operation of individual device components. However, in contrast to the many integrated bioinert electronic systems demonstrated for various implantable diagnosis and therapy applications,[161,162] only a few studies have introduced fully integrated bioresorbable electronic systems. Therefore, further research is required toward fully integrated bioresorbable systems, and each system needs to be carefully optimized for the conditions and requirements of the targeted diseases.

10. Conclusion and Future Perspectives

Up to now, bioinert materials have typically been used for medical implants such as permanent physical supports. However, in some cases, surgery for the retrieval of implants is required, which can impose physical and economical burdens. In this regard, medical implants with active electronics composed of bioresorbable materials are being investigated for sensing of key biological signals and feedback stimulation therapy in vivo. Thanks to innovative materials chemistry research and novel device fabrication techniques, the development of various types of bioresorbable medical implants as efficient solutions for the diagnosis and therapy of highly challenging clinical issues is being accelerated. For example, various bioresorbable electronic

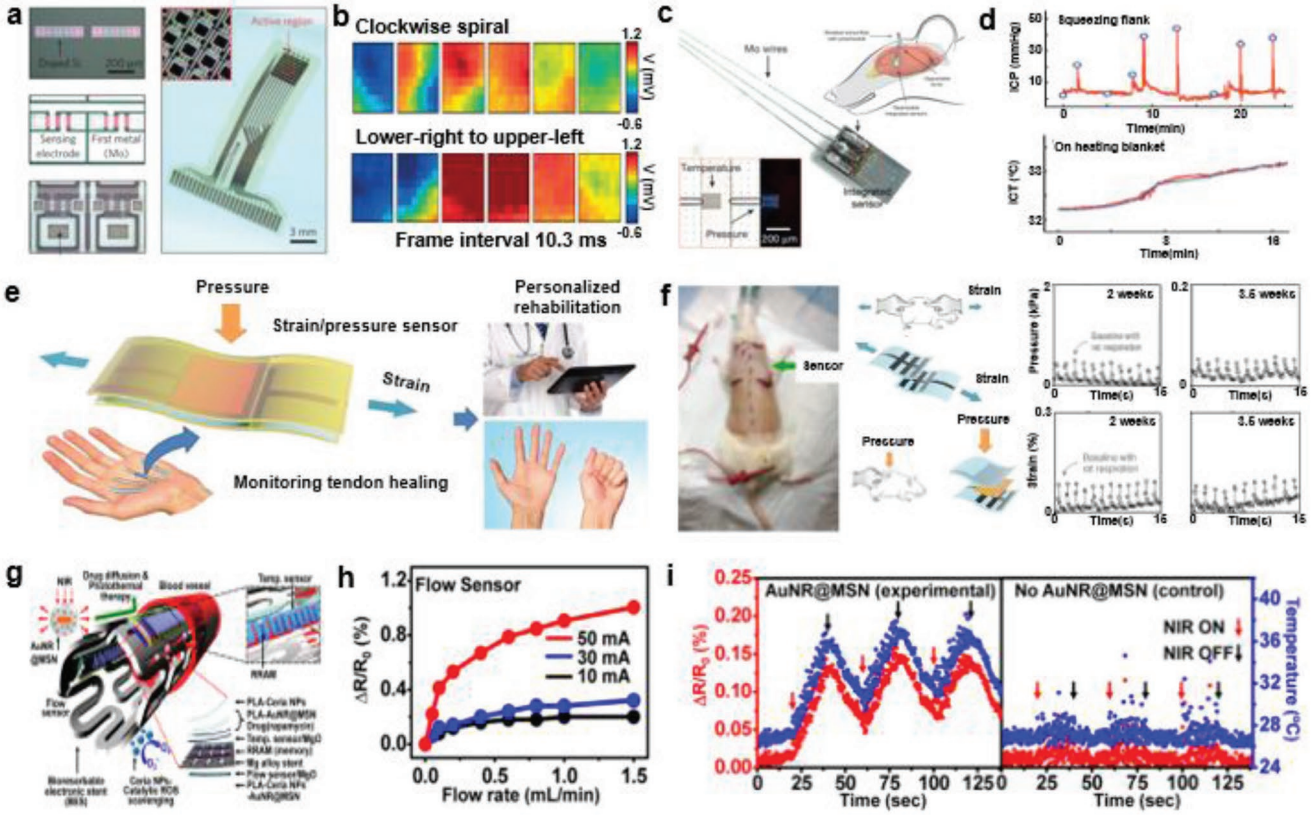

Figure 9. Bioresorbable integrated electronic systems. a) Optical microscopic image of unit cells in each fabrication stage (left) and complete bioresorbable electrophysiological sensor (right). Reproduced with permission.[8] Copyright 2016, Nature Publishing Group. b) Movie frames of spatiotemporal EcoG voltage patterns by 64 electrodes corresponding to each spike patterns. Reproduced with permission.[8] Copyright 2016, Nature Publishing Group. c) Optical images of integrated bioresorbable sensors (middle) and schematic diagram of bioresorbable sensor implanted to the mouse brain (right). The inset shows the optical microscopic image of sensing regions. Reproduced with permission.[38] Copyright 2016, Nature Publishing Group. d) Wireless measurement of intracranial pressure (top) and temperature (bottom) with bioresorbable sensor compared to commercial sensor. Reproduced with permission.[38] Copyright 2016, Nature Publishing Group. e) Schematic illustration of post-operative personalized rehabilitation program with bioresorbable sensor for monitoring the tendon. Reproduced with permission.[40] Copyright 2018, Nature Publishing Group. f) Optical image of bioresorbable sensor implanted to back on the mouse (left) and schematic illustration of procedure of applying pressure/strain in vivo (middle) and its recorded signal (right). Reproduced with permission.[40] Copyright 2018, Nature Publishing Group. g) Schematic illustration of bioresorbable stent (left) with top view (top right) and layer information (bottom right). Reproduced with permission.[39] Copyright 2015, American Chemical Society. h) Resistive change of flow sensor versus the flow rates. Reproduced with permission.[39] Copyright 2015, American Chemical Society. i) Resistive change of temperature sensor (red line) with (left) and without (right) hyperthermic nanorod compared to the real temperature (blue line) versus the time. Reproduced with permission.[39] Copyright 2015, American Chemical Society.

device components have already been proposed, exhibiting similar electrical performances to conventional bioinert electronic devices. Ultimately, the integration of suitable individual device components to realize optimized bioresorbable systems is suggested as a solution for unmet clinical issues in targeted disease models. However, integrated bioresorbable electronic implants that meet all the requirements of a target organ/disease have rarely been reported. Future research efforts, therefore, should be aimed at the integration and optimization of bioresorbable electronic systems to provide key solutions for clinical challenges.

Even though fully integrated bioresorbable active electronics have been successfully demonstrated, there are many remaining challenges for commercialization. For example, although the bioresorption of bioresorbable electronics has been demonstrated in vivo, systematic and long-term biocompatibility tests should be conducted. The successful operation of bioresorbable electronics in large animal models should be also studied further, as large-scale systematic experiments using large animal models can reveal many unexpected biological hurdles and clinical issues. Finally, such biocompatibility assays and device operation studies in large animals should be compatible for extension to human applications, and eventually should be corroborated in human models. There is a high chance that the devices will require modification to optimize parameters such as the degradation behavior and time or device size and performance for use in human models. Despite these challenges and the need for systematic clinical studies, the research and development of bioresorbable materials and devices, as well as corresponding fabrication and integration technologies for bioresorbable electronic systems, will present many new opportunities for next-generation medical implants and provide potential diagnostic and therapeutic solutions for currently unmet clinical issues.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

bioresorbable electronics, bioresorbable materials, implantable devices, medical implants, transient electronics

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