

# Biointegrated flexible inorganic light emitting diodes

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**Abstract:** The use of light-emitting diodes (LEDs) as therapeutic tools has been actively studied over the past few decades due to their advantages of high safety, low cost, excellent portability, and wide bandwidth. In addition, their application in biomedical fields has been expanded to such areas as nerve stimulation, photodynamic therapy, and LED-based biosensors, and LED lights are thus receiving attention as alternatives to conventional biomedical light sources such as lasers. Recently, several developments in the area of flexible inorganic LEDs along with advanced nanoelectronic technologies have pointed toward the possibility of new innovative biotechnologies in the near future. In this paper, we review the salient features of high-performance biointegrated LED applications, together with future challenges for the realization of implantable, flexible biointegrated electronic devices.

**Keywords:** flexible, inorganic, biointegrated, light-emitting diodes, nerve stimulation, photodynamic therapy, biosensor

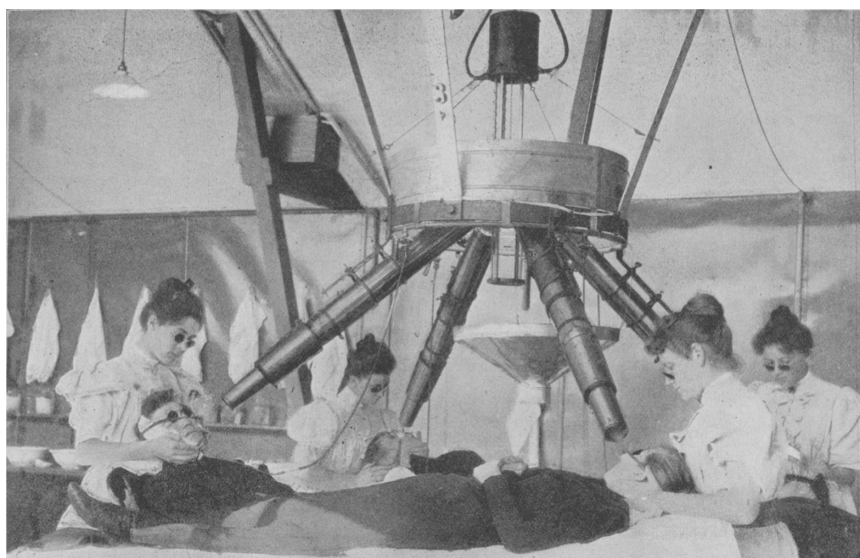
## Introduction

Population aging in recent decades has led to expanded interest in efficient health care systems that allow pain-free diagnoses and treatments. In particular, compatible, remote, and portable systems based on nanoelectronics to replace conventional cumbersome devices are candidates to help realize ubiquitous health care networks.

Soft and flexible devices engineered from nanotechnology have advantages of absence of pressure from weight, even in a body-embedded condition, and conformal contact on dynamically sloping surfaces.<sup>1,2</sup> Many researchers have reported flexible components, such as sensing electrodes,<sup>3</sup> memories,<sup>4</sup> and radiofrequency identification antennae<sup>5</sup> for in vivo and in situ systems. Most notably, the recent development of flexible inorganic light emitting diodes (LEDs)<sup>6,7</sup> could be a crucial breakthrough for a new avenue of biomedical applications.

Light has been employed as a therapeutic and diagnostic tool for thousands of years, with some of the earliest applications being sunlight therapy for skin diseases in ancient Egypt, India, and China. The rediscovery of solar therapy (Figure 1) by Niels Ryberg Finsen, who won the Nobel Prize in Physiology or Medicine in 1903, has motivated many researchers to study light healing and sensing applications of various medical diseases.<sup>8</sup> In this paper, we briefly review the salient features of biointegrated LED applications and describe the future challenges of flexible biodevices based on nanotechnology.

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**Figure 1** Finsen's phototherapy.<sup>8</sup> Finsen's artificial carbon arc lighting has contributed to the treatment of various dermal diseases, such as lupus vulgaris. Reprinted from Bie V. Remarks on Finsen's phototherapy. *BMJ*. 1899;2:825.

## Biomedical applications of light

Most light applications in the biomedical field involve phototherapy, ie, photo wound healing, classified as photothermal treatment (acute wound closure<sup>9</sup> and debridement<sup>10</sup>), and nonthermal photobiomodulation (chronic wound healing acceleration<sup>11,12</sup> and nerve regeneration<sup>13</sup>). Light therapy, from daylight to specific wavelength light, including lasers, LEDs, and fluorescent lamps, has been actively employed since the first demonstration of photobiostimulation effects, ie, photobiomodulation for animal hair growth with a low-level laser (694 nm) in the late 1960s by Endre Mester, a Hungarian physician.<sup>14</sup>

In recent decades, LEDs have garnered interest as an effective alternative to other irradiation sources due to their high efficiency, high safety, low cost, and excellent portability. LEDs provide wide bandwidth light over ultraviolet, visible, and near infrared wavelength (247–1300 nm) ranges. In addition, the power of the light can be better controlled so as not to damage surrounding tissues as compared with lasers. In addition, because LEDs do not require optical focusing, unlike lasers, they are suitable for moving targets in daily life. A range of biomedical applications can therefore be covered by LED light sources, regardless of time and space restrictions. The properties and applications of both visible lights are compared in Table 1.

Although LED applications based on nonthermal light source properties have been studied mainly in relation to dermatology therapies, such as wound healing acceleration,<sup>11</sup> inflammation reduction,<sup>15</sup> photorejuvenation,<sup>16</sup> and scar prevention,<sup>17</sup> they have been widely expanded to include nerve stimulation, photodynamic therapy, and optical biosensing.

However, the mechanism of LED light action is not yet clear. Studies in dermatology therapy have shown that free radicals such as nitric oxide hinder cell respiration. In this context, LED light can prevent nitric oxide from binding to cytochrome *c* oxidase, which is present in the mitochondrial inner membrane as a respiratory chain component.<sup>18</sup> Recently, Ishiguro et al<sup>13</sup> demonstrated nerve regeneration using red LED (660 nm). In support of previous studies, they proposed that an antioxidation effect induced by LED light promoted regeneration of bilateral transected sciatic nerves.

## Nerve stimulation

Since the first demonstration of neuron stimulation in *Aplysia* ganglia using high power blue (488 nm) laser light in 1971 by Richard L Fork<sup>19</sup> at Bell Laboratories, laser light has been widely used for studying the coordinated activities

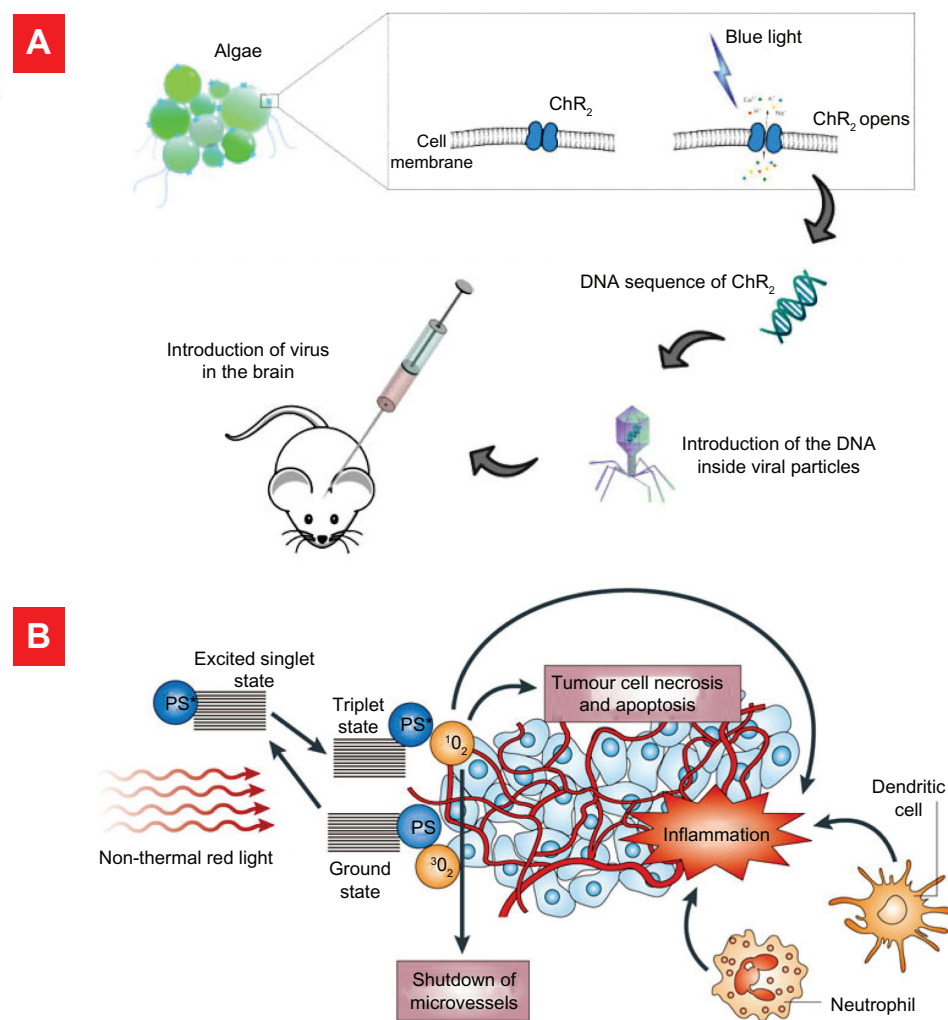
**Table 1** Comparison of representative inorganic visible light emitting diode lights<sup>29,30,45,46,67–70,74</sup>

	Blue	Red
Peak wavelength (nm)	450–470	630–700
Materials	ZnSe, InGaN, GaN	GaAs, GaP:Zn-O, GaAlAs
Skin penetration depth (μm)	Approximately 200	Approximately 10,000
Applications	Wound healing, <sup>67</sup> dental composite polymerization, <sup>68</sup> optogenetics <sup>29,30</sup>	Wound healing, <sup>69,74</sup> low-level light therapy, <sup>70</sup> photodynamic therapy <sup>45,46</sup>

**Abbreviations:** ZnSe, zinc selenide; InGaN, indium gallium nitride; GaN, gallium nitride; GaAs, gallium arsenide; GaP:Zn-O, zinc oxide doped gallium phosphide; GaAlAs, aluminium gallium arsenide.

of neuron cells. The research of neural stimulation has expanded recently to combine genetics and optics, a field known as “optogenetics”<sup>20</sup> (see Figure 2A). Using this method, visible light-sensitive proteins, called opsins, such as Channelrhodopsin 2 (ChR2) and Halorhodopsin, are genetically encoded in certain cells, and can be activated by visible light of approximately 470 nm and 580 nm wavelength, respectively.<sup>21–23</sup> The use of a light source for effectively illuminating large volumes of the brain has also received considerable attention. Cardin et al<sup>24</sup> investigated excitatory neurons of the macaque frontal cortex, and Kravitz et al<sup>25</sup> stimulated basal ganglia circuitry in vivo for controlling parkinsonian motor behaviors using a laser-coupled optical fiber (473 nm). Although optogenetics using optical fibers combined with a laser has been intensively studied, this approach is not suitable for use in multimicroarray stimulation

over a large area because of the possibility of tissue damage and the design limitations of optical fibers. Alternatively, the conventional light can be replaced by LEDs, which are thin enough to mount above the brain, relatively cheaper than lasers, and operate at a lower power.<sup>26</sup> In addition, III–V LEDs (GaN, GaAs) for photostimulation can provide a broad wavelength range of visible light, including blue, green, and red.<sup>27,28</sup> In optogenetics, the use of LEDs as a light source is gradually increasing. Huber et al<sup>29</sup> mounted a blue miniature LED (470 nm) above an implanted window for optical stimulation in the barrel cortex of freely moving mice. A micro-LED array (64 × 64 arrays, diameter 20 μm microemitters) reported by Grossman et al<sup>30</sup> provided two-dimensional neuron stimulation with sufficient irradiation power. Bruegmann et al<sup>31</sup> reported optogenetic control ability of the heart muscle in vitro and in vivo by ChR2 with



**Figure 2** Mechanisms of (A) optogenetics<sup>20</sup> (courtesy of Champalimaud Foundation) and (B) photodynamic therapy (Reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Cancer*,<sup>35</sup> copyright 2006). (Optogenetics: ChR2 is expressed in the plasma membranes of neurons and optical stimulation allows depolarizing and activating of the neurons. Photodynamic therapy: after photosensitizer is injected to target tissue in the presence of oxygen, light illumination by photosensitizer drugs can produce reactive oxygen species and then destroy cells.)

**Abbreviations:** ChR2, Channelrhodopsin.

blue light (475 nm), which could surpass the limitations of electrical stimulation and induce alteration of pacemakers.

## Photodynamic therapy

Photodynamic therapy, which involves local treatment of tissues using photosensitive drugs, a light source, and oxygen, has been successfully used for numerous carcinomas of the skin, lung, larynx, pancreas, and prostate, as well as noncancerous diseases, such as acne vulgaris, age-related macular degeneration, and endometriosis.<sup>32,33</sup> The mechanism of photodynamic therapy is that the photosensitizer is activated by light and then interacts with molecular oxygen to generate cytotoxic oxygen species and free radicals, which can selectively destroy tumor cells with minimal side effects for patients, as illustrated in Figure 2B.<sup>34,35</sup> In this method, the photosensitizers are directly incorporated into the cell membrane, targeting specific tissue. Various photosensitizers have been studied over the past several decades. Photofrin<sup>®</sup>, first reported for prostate cancer therapy by Windahl et al<sup>36</sup> in 1990, has been widely used as a photosensitizer. It absorbs light at a 630 nm wavelength, releasing cytotoxic oxygen to break down cancer cells. Kuhara et al<sup>37</sup> investigated the effect of aminolevulinic acid-induced photodynamic therapy on human oral squamous cell carcinoma. In addition, four photosensitizers, ie, porfimer sodium (Photofrin), verteporfin (Visudyne<sup>®</sup>), aminolevulinic acid (Levulan Derastick<sup>®</sup>), and methyl aminolevulinic acid (Metvixia Cream<sup>®</sup>), have been approved by the US Food and Drug Administration.<sup>38</sup>

Once an adequate amount of photosensitizer is injected into the target tissue, light should be delivered to the desired tissue in order to activate photosensitizers, which offer increased specificity and efficiency.<sup>39–41</sup> Conventional photodynamic therapy light sources are generally pulsed dye lasers and intense pulsed lasers. Currently, LEDs show huge potential as a photodynamic therapy light source owing to numerous advantages, such as a suitable light spectrum, high efficacy, safety, low price, convenience, and light weight.<sup>42–44</sup> LED-based photodynamic therapy systems (630 nm) have been used clinically by Haas et al<sup>45</sup> for the treatment of nonmelanoma skin cancer (aminolevulinic acid-photodynamic therapy). Schmidt et al<sup>46</sup> also used the same photodynamic therapy systems for the treatment of brain tumors (Photofrin-photodynamic therapy).

## Biosensors

A biosensor is an analytical device consisting of a biological element and a signal transducer. The physiological and chemical changes of biological elements such as enzymes, antibodies, organelles, nucleic acids (DNA and RNA), and

synthetic ligands enabling a reversible interaction with a target analyte are transformed into measurable data, such as electrical or optical signals through transducer processing. Starting from Bergveld's invention<sup>47</sup> of an electrochemical sensor in 1970, diverse types of biosensors have been actively pursued by many researchers, using thermometric,<sup>48</sup> piezoelectric,<sup>49</sup> magnetic,<sup>50</sup> and optical<sup>51</sup> transducer approaches. Surface plasmon resonance optical sensors interposing a metal film between two different reflective index media have attracted interest as sensitive labels or label-free detectors. Especially, laser-based surface plasmon resonance optical sensors interposing a metal film between two different reflective index media have attracted interest as sensitive labels or label-free detectors. However, they have the drawbacks of interference artifacts and speckles as well as high instrumental costs caused by a laser light source.<sup>52</sup>

In the context of addressing these problems, the LED-based optical biosensor is regarded as a promising future real-time biomedical sensor due to the advantages of low temperature drift, low power consumption, low cost, visible radiation application, nondestructive operation, and fast signal generation and reading. LED biosensors using light adsorption or fluorescence of biological elements and photodiode detection have been reported in several studies. Ciortea et al<sup>53</sup> described a 570 nm yellow light device for monitoring human blood sedimentation and for determination of the erythrocyte sedimentation rate in testing for inflammatory diseases and dysglobulinemia. In addition, noninvasive hemoglobin measurement using a five-wavelength LED array was demonstrated by Jeon et al.<sup>54</sup> In light propagation through the fingertip below 1000 nm wavelength, two of the five irradiation lights interact with the arterial vessels and three others encounter only soft tissue for compensation.

## Flexible electronics: transplanting light in the human body

Low molecular weight analyte detection with a much faster and convenient testing procedure than that currently used is necessary for portable clinical monitoring such as hand-held point-of-care testing devices. Additionally, miniaturization and conformal contact on a curvilinear surface could facilitate the realization of implantable micro-sized surgical robots and in vivo real-time health care systems.

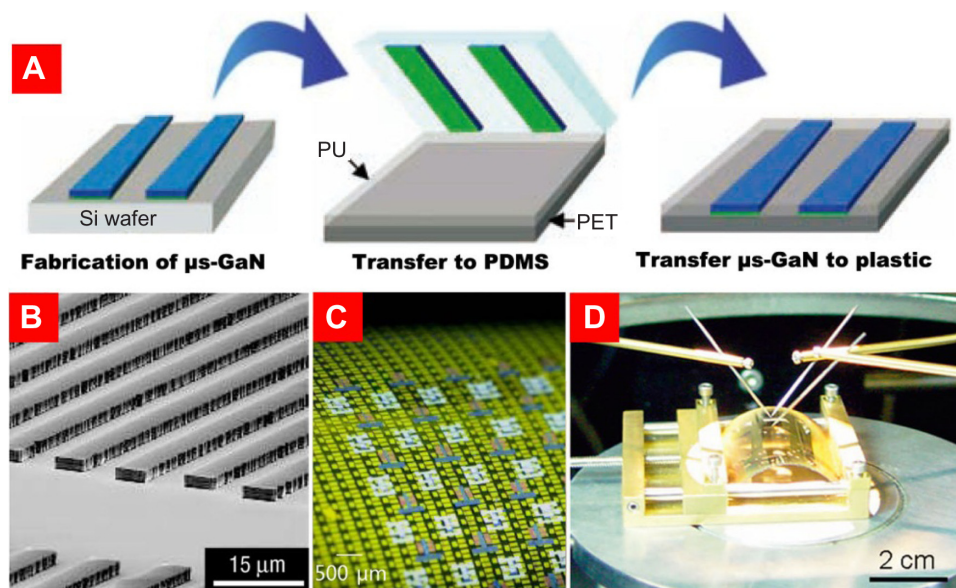
Many researchers have actively demonstrated flexible and implantable biomedical devices, such as in vivo sensing electrodes via nanofabrication technologies, including micro-electromechanical systems and dry-transfer printing methods. Recent compliant flexible and stretchable electrodes, which

consist of a polymer substrate and metal pads, have been widely applied for *in vitro* and *in vivo* neural stimulation and recoding.<sup>3,55–58</sup> Conventional rigid microelectrode arrays<sup>59</sup> have disadvantages of short-term and unstable interfaces with nerves and critical cell damage caused by the sharp probe tips; soft and flexible electrodes, on the other hand, can decrease interface impedance and tissue damage due to conformal contact.

Since the first demonstration of flexible inorganic GaN materials in 2005 by Lee et al,<sup>60</sup> many III–V semiconductor compound devices have successfully been assimilated onto flexural surfaces and have shown promise as high-performance flexible electronics. The “top-down” dry-transfer method of microstructured semiconductors ( $\mu$ S-c), as depicted in Figure 3A, provides an attractive alternative approach that compensates for the relatively low fill factor of “bottom-up” synthesized materials, such as nanotubes or nanowires; one-dimensional nanostructured materials in active spaces can cause low device performance and poor uniformity. Additionally, the ultrathin ribbon microstructures lead to highly enhanced flexibility of brittle inorganic materials with mechanical durability. The basic concept stems from the fact that even a rigid and bulky active material can be flexible if the material is extremely thin. In the case of a 100 nm thick silicon ribbon with approximately 0.7% critical tensile strain,

cracking of the silicon nanoribbons will occur only when the bending radius falls below approximately 7  $\mu$ m.<sup>61</sup>

This process starts with the growth of a thin GaN film on a silicon wafer. After micropatterning of the active GaN material via conventional photolithography and an etching process, the underlying sacrificial silicon layer is removed by wet anisotropic etching in an alkaline solution. The free-standing  $\mu$ S-GaN ribbons are conformably contacted to a polydimethylsiloxane transfer element. Strong van der Waals forces between the  $\mu$ S-GaN and the polydimethylsiloxane enable the  $\mu$ S-GaN materials to be lifted off from the underlying silicon substrate when the polydimethylsiloxane is peeled away. Finally, the  $\mu$ S-GaN elements are transferred from the polydimethylsiloxane on a plastic substrate coated with an adhesive layer. Figure 3B shows an image of flexible GaN ribbons transferred onto another solid silicon wafer using the dry-transfer process.<sup>62</sup> In addition, stamp-based printing has allowed inorganic materials to be integrated with disparate substrates and to be stacked vertically one upon another, thus forming three-dimensional configurations. Ahn et al<sup>63</sup> demonstrated stacked heterogeneous structures of various inorganic elements including single-crystal GaN, GaAs, and silicon materials on flexible substrates. Figure 3C shows an example of three-dimensional heterogeneously integrated



**Figure 3** Flexible inorganic semiconductors transferred onto plastic substrates. (A) Fabrication procedure for flexible inorganic devices.<sup>60</sup> (B) GaN ribbons transferred onto another solid silicon wafer.<sup>62</sup> (C) Three-dimensional heterogeneously integrated electronic devices including a three-layer stack of GaN nanoribbon HEMTs, silicon nanoribbon MOSFETs, and SWNT network TFTs.<sup>63</sup> (D) Bending test for flexible III–V semiconductors.<sup>64</sup>

**Abbreviations:** HEMTs, high electron mobility transistors; MOSFETs, metal oxide semiconductor field-effect transistors; SWNT, single-walled carbon nanotube; TFTs, thin-film transistors.

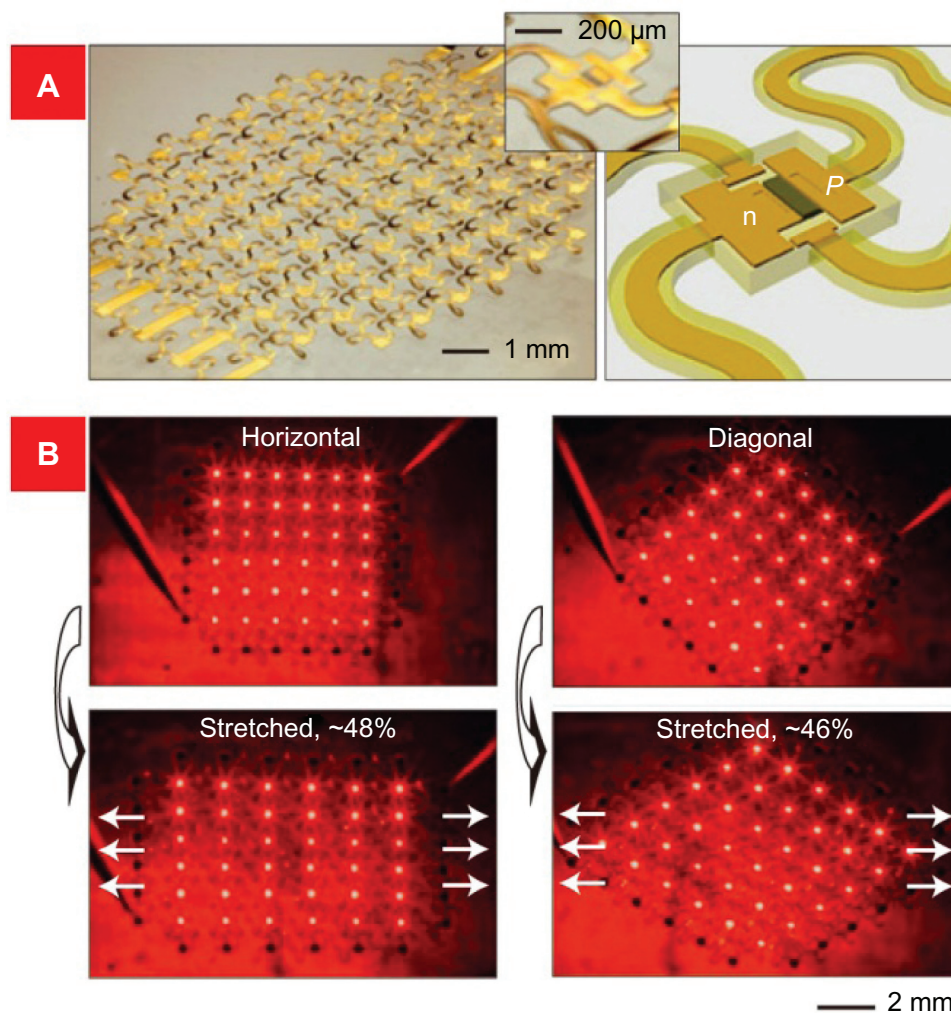
**Notes:** (A) Reproduced with permission of the publishers of Lee KJ, Lee J, Hwang H, et al. A printable form of single-crystalline gallium nitride for flexible optoelectronic systems. *Small*. 2005;1:1164–1168. (B) Reproduced with permission of the publishers of Meitl MA, Zhu ZT, Kumar V, et al. Transfer printing by kinetic control of adhesion to an elastomeric stamp. *Nat Mater*. 2006;5:33–38. (C) From Ahn Jh, Kim HS, Lee KJ, et al. Heterogeneous three-dimensional electronics by use of printed semiconductor nanomaterials. *Science*. 2006;314:1754–1757. Reprinted with permission from AAAS. (D) Reprinted with permission of the publishers of Lee KJ, Meitl Ma, Ahn JH, et al. Bendable GaN high electron mobility transistors on plastic substrates. *J Appl Phys*. 2006;100:124507. Copyright 2006, American Institute of Physics.

electronic devices including a three-layer stack of GaN nanoribbon high electron mobility transistors (HEMTs), Si nanoribbon metal oxide semiconductor field-effect transistors (MOSFETs), and single-walled carbon nanotube (SWNT) network thin-film transistors (TFTs). Consistent properties of inorganic materials after their transfer onto plastic substrates are important for application to higher performance flexible devices. The flexible inorganic semiconductor properties were measured, as shown in Figure 3D.<sup>64</sup> Although the results describing their electrical and physical properties are not presented in this paper, the authors did investigate their consistency of  $\mu\text{s-GaN}$  high electron mobility transistors fabricated by a similar dry-transfer protocol as a function of the bending radius, and obtained very stable characteristics.

In recent years, many impressive results for flexible inorganic LEDs based on III–V compound semiconductors

have led to interest in developing versatile flexible electronics, such as biointegrated LED devices. Kim et al<sup>6</sup> reported the enhanced flexibility of a GaAs-based  $\mu\text{s-LED}$  relative to previously reported devices using noncoplanar serpentine bridges, as shown in Figure 4A. Their flexible GaAs red LEDs can cover large array size areas and various surfaces with higher flexibility (see Figure 4B), as well as accommodate the needs of integrated biosystems. Furthermore, the authors demonstrated glucose concentration detection based on the variation of transmitted light intensities with a photodiode. However, the GaAs LED emits only infrared and red light due to its narrow wavelength range, thus ultimately limiting its possible applications.

The recent development of flexible  $\mu\text{s-GaN LEDs}$ <sup>65</sup> enables the extension of LEDs to a wider clinical scale as well as consumer electronic applications, owing to superb

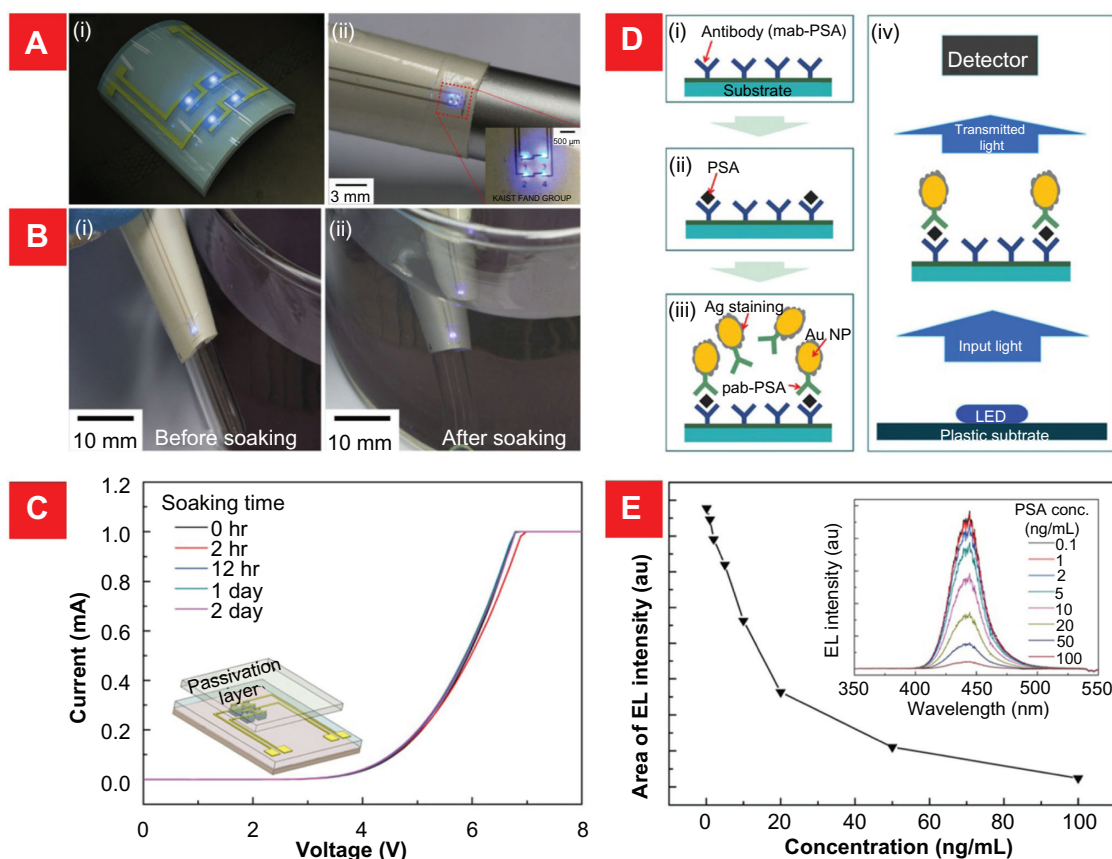


**Figure 4 (A)** Optical image of a flexible GaAs-based light emitting diode array with non-coplanar serpentine bridges (left). Schematic illustration (right) and corresponding image (inset) of a flexible light emitting diode with epoxy encapsulation. **(B)** Photograph of flexible inorganic light emitting diode showing uniform emission under different uniaxial applied strains.

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material properties with a relatively wide band gap (GaN: 3.4 eV, GaAs: 1.43 eV) and high efficiency. Lee et al<sup>7</sup> fabricated the first water-resistant flexible  $\mu$ s-GaN LED on a liquid crystal polymer substrate for implantable biomedical applications using dry-transfer technology. High temperature annealing at 600°C between gold and n-/p-GaN contacts prior to transfer onto plastics enables the formation of an ohmic contact for low electrical resistance, thus contributing to the realization of a high-performance inorganic LED light source. Thereafter, LED layers are transferred onto a liquid crystal polymer substrate by means of conventional microfabrication and soft lithographic techniques. A schematic illustration in Figure 5A (i) and a photographic image of rolling up a cylindrical aluminum rod, shown in Figure 5A (ii) of flexible  $2 \times 2$  GaN LED arrays on a liquid crystal polymer substrate are shown. The water resistance of the GaN LED was evaluated, as shown in Figure 5B and C. A soaking test was conducted in phosphate-buffered saline (PBS; pH 7.4) solution mixed with black ink. The curves shown in Figure 5C indicate that the electrical properties remain stable

during the phosphate-buffered saline soaking condition. The prostate-specific antigen (PSA) sensing mechanism in the LED biochip is illustrated in Figure 5D. PSA antigen (Fitzgerald) solution ( $1 \times$  phosphate-buffered saline) are added to the monoclonal-PSA coated substrate, causing a specific binding reaction (Figure 5D). Polyclonal anti-(pab)-PSA-Au nanoparticle conjugates are captured using a sandwich-type immunogold assay. To increase the light blocking effects from nanoparticles immobilized on the surface, silver staining is performed on the gold nanoparticles, as shown in Figure 5D (iii). Figure 5D (iv) shows the measurement module which consists of three parts, ie, a flexible GaN LED for the optical input, an electroluminescence detector, and a reaction chip. Figure 5E shows the integrated electroluminescence intensity of the flexible LED as a function of PSA concentration. As the PSA concentration is increased, less transmitted light passing from the flexible LED through the reaction chip is detected. The inset of Figure 5E shows the electroluminescence spectra as a function of PSA concentration. From this data, we verify that the limit of detection of the PSA used in their experiment



**Figure 5** (A) Flexible GaN-based light emitting diode array: (i) schematic illustration and (ii) photograph and magnified image of GaN light emitting diode rolling up a cylindrical aluminum rod. (B) Optical images of flexible GaN light emitting diodes (i) before and (ii) after soaking in phosphate-buffered saline. (C) I-V curve results of soaking test, (D) prostate-specific antigen sensing mechanism in light emitting diode biochip, and (E) prostate-specific antigen concentration detecting results from electroluminescence intensity.<sup>7</sup> **Abbreviation:** PSA, prostate-specific antigen; EL, electroluminescence.

is approximately 1 ng/mL, which is promising for prostate cancer screening between a healthy person and a patient at a concentration of 4 ng/mL PSA.

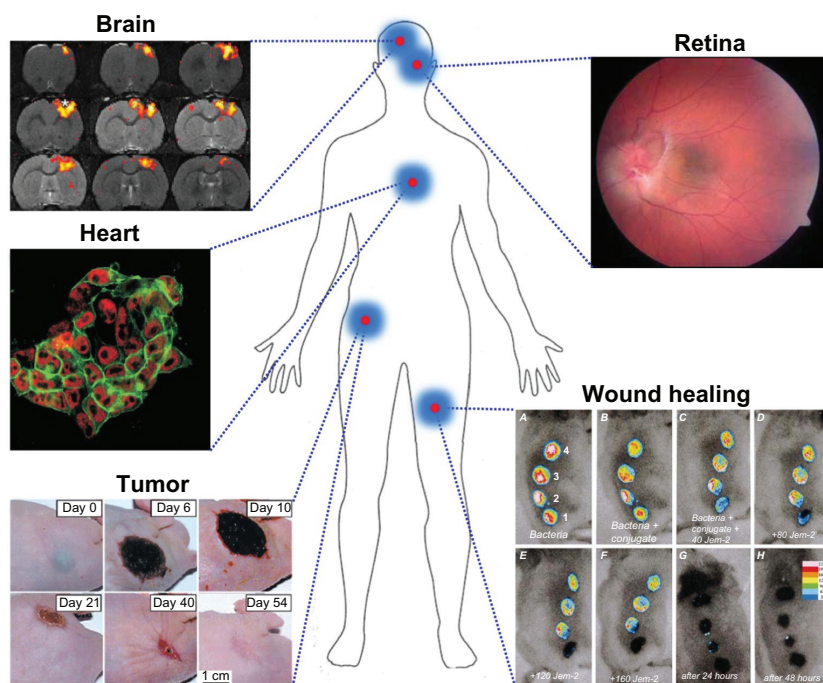
## Implantable flexible biomedical systems

Numerous researchers have demonstrated the effectiveness of LED-based therapeutic and diagnostic systems in biomedical areas such as wound healing, optogenetics, photodynamic therapy, and biosensors. Furthermore, the development of nanofabrication technology makes it possible to surpass the mechanical limits of brittle inorganic-based devices and realize innovative applications of flexible and stretchable electronics.

Many organisms do not have stationary forms, such as angular, rigid, or flat morphologies, but rather tend to be soft, round, and curved. In this context, flexible inorganic LEDs have potential to provide an effective light dose to target regions such as the heart, corrugated brain, and vertebra. In addition, when a damaged site is located within the living body, light cannot penetrate very far into the tissues, and thus an internal light delivery system is needed in order to

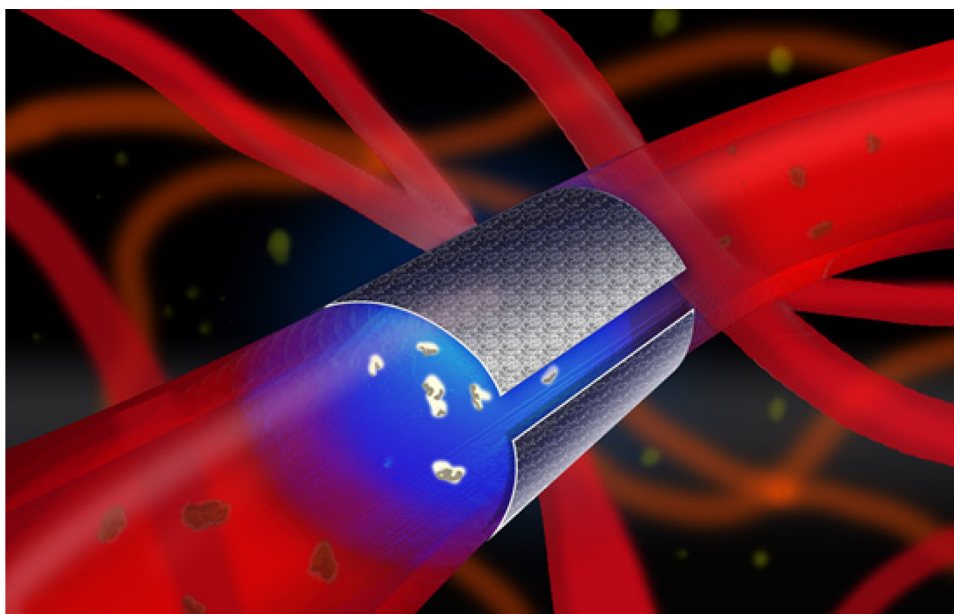
accomplish this goal. Both lasers with optical fibers and LEDs are available as light sources. Unlike optic fibers, which can be focused on very narrow and stationary sites, along with tissue damage, the flexible inorganic LED, composed of multimicro LED arrays, can illuminate a two-dimensional surface, providing the desired pattern of light and avoiding the side effects of penetration into the tissue. More interestingly, the flexible inorganic LED, which is thin enough to be inserted into extremely narrow and small locations in the body, may lead to expansion of the field of light-based therapies targeting the skin, brain, heart, retina, and even deeply located tissue with tumors for healing and sensing purposes, as shown in Figure 6.

This type of flexible LED system can be used for diagnosing and treating diverse cancers and in vivo continuous monitoring of glucose, cholesterol, and hemoglobin. Figure 7 is a conceptual schematic of rolling up a blood vessel with a flexible LED for in vivo biosensing or treatment. A label-free biomolecular detection method with flexible LEDs and photodiodes would provide a promising implantable biosensor. For example, based on the correlation between serum absorption spectrum and



**Figure 6** Expansion of flexible inorganic light emitting diode applications: brain (reprinted by permission from Macmillan Publishers Ltd: *Nature*,<sup>71</sup> copyright 2010), heart (reprinted by permission from Macmillan Publishers Ltd: *Nature Methods*,<sup>31</sup> copyright 2010), tumor (reprinted by permission from Macmillan Publishers Ltd: *Nature Medicine*,<sup>72</sup> copyright 2003), retina (reproduced with permission of the publishers of Sachdeva R, Dadgostar H, Kaiser PK, Sears JE, Singh AD. Verteporfin photodynamic therapy of six eyes with retinal capillary haemangioma. *Acta Ophthalmol.* 2010;88(8):e334–e340)<sup>73</sup>, and wound healing (reproduced with permission of the publishers of Hamblin MR, O'Donnell DA, Murthy N, Contag CH, Hasan T. Rapid control of wound infections by targeted photodynamic therapy monitored by in vivo bioluminescence imaging. *Photochem Photobiol.* 2002;75(1):51–57.<sup>74</sup> (Brain: a photograph indicates the reaction analyses of brain stimulation with ChR2 opsin and a 473 nm blue light laser including an optical fiber. Heart: heart muscles are activated by ChR2 opsin and 479 nm blue light emitting diodes coupled via optical fibers. Tumor: skin cancer is treated by methyl aminolevulinate and 635 nm red light. Retina: photodynamic therapy is performed using verteporfin and a 689 nm ocular photoactivation diode laser for treatment of choroidal neovascularization. Wound healing: light exposure using a 470 nm blue light emitting diode on a wound area accelerates wound repair process).





**Figure 7** Conceptual schematic of wrapping a blood vessel with implantable flexible inorganic light emitting diodes for label-free disease diagnosis without any other pretreatment, such as antibody immobilization, and clinical pain-free treatment.

cholesterol concentration in a wave band of 450 to 470 nm,<sup>66</sup> cholesterol detection is possible by use of a flexible GaN LED and photodiode without any other pretreatment, such as antibody immobilization.

## Conclusion

Offering advantages of safety, nonthermal behavior, and nontoxicity, LEDs have been actively studied as therapeutic and diagnostic tools. In addition, the possibility of noninvasive medical treatment using LEDs has intrigued researchers in relation to new methodologies of innovative therapy and disease detection in biomedical fields. Notably, the progress of flexible nanotechnology over the last few years has led to the development of implantable, flexible inorganic devices such as high-performance flexible inorganic LEDs. Hence, although the study of flexible inorganic electronics is at an early stage and reported by only a few research groups at present, a fully flexible inorganic electronic system could be utilized in the human body for an implantable ubiquitous biomedical system. To achieve this goal and expand the applications of LEDs, future research should focus on better understanding of the light activation mechanism as well as innovative device fabrication.

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## Disclosure

The authors report no conflicts of interest in this work.

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