

# Implantable nanogenerators for medical research

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Nanogenerators are emerging as a transformative technology in implantable medical devices, offering new solutions to the challenge of powering these systems. This article delves into the different types of nanogenerators, each with unique mechanisms and designs tailored for compatibility with the human body. The selection of materials, from biodegradable to flexible options, is critical in ensuring biocompatibility and long-term functionality. Nanogenerators have demonstrated effectiveness across various human body systems and in treating different types of diseases, significantly enhancing treatment outcomes. Additionally, the article discusses the technical challenges related to material stability and power efficiency, while also considering the future potential of these devices in advancing medical research.

#### Introduction

Implantable medical devices have revolutionized health care by enabling continuous monitoring, targeted drug delivery, and therapeutic interventions directly within the human body.<sup>1–3</sup> However, one of the most critical challenges facing these devices is their reliance on a stable and long-lasting power source.<sup>4</sup> Traditional batteries, while effective in certain applications, present significant limitations when used in implantable devices.<sup>5,6</sup> These limitations include finite energy capacity, the need for periodic replacements or recharging, and the potential risks associated with invasive surgical procedures required for battery replacement.<sup>7,8</sup> Furthermore, the miniaturization of devices, combined with the demand for longer operational lifespans, exacerbates the power supply issue, creating a significant barrier to the advancement of implantable medical technologies.<sup>6,9,10</sup>

Nanogenerators represent a groundbreaking advancement in the field of energy harvesting, with particular relevance to implantable medical devices.<sup>6,11,12</sup> Over the past few decades, the intersection of nanotechnology and biomedical engineering has led to innovative solutions for powering medical implants, addressing the limitations of traditional power sources such as batteries.<sup>13</sup> The development of nanogenerators is a response to the growing demand for sustainable, efficient, and longlasting energy sources that can operate autonomously within the human body.<sup>14–16</sup> These devices harness energy from biomechanical movements, temperature gradients, or even biochemical processes, converting it into electrical energy to power various biomedical devices.<sup>17</sup> The concept of nanogenerators was first introduced by Z.L. Wang and his team in 2006, who demonstrated the feasibility of using the piezoelectric effect at the nanoscale to generate electricity.<sup>18–22</sup> This pioneering work laid the foundation for subsequent developments in the field, leading to the emergence of triboelectric nanogenerators (TENGs) and piezoelectric nanogenerators (PENGs).<sup>23,24</sup> Each type of nanogenerator exploits different physical principles, making them suitable for a range of biomedical applications.<sup>25–27</sup>

The significance of nanogenerators in the biomedical field cannot be overstated.<sup>28–30</sup> Traditional batteries, despite their widespread use, suffer from several limitations, including limited lifespan, potential toxicity, and the need for periodic replacement or recharging. In contrast, nanogenerators offer a sustainable alternative, capable of continuously harvesting energy from the body's own movements, temperature fluctuations, or biochemical reactions.<sup>31–33</sup> This self-sustaining

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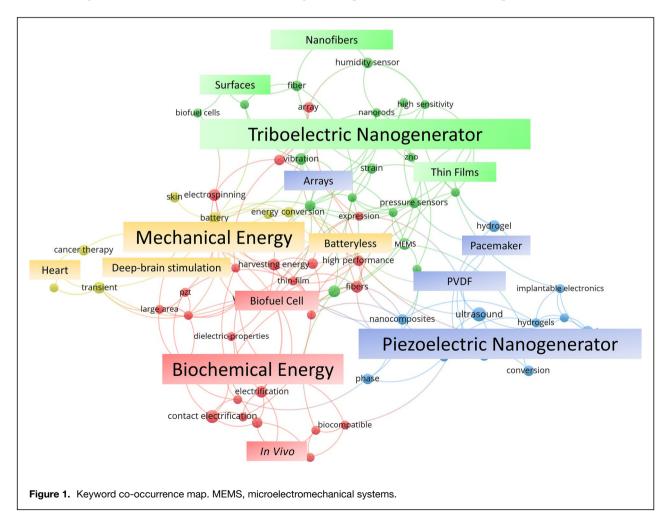
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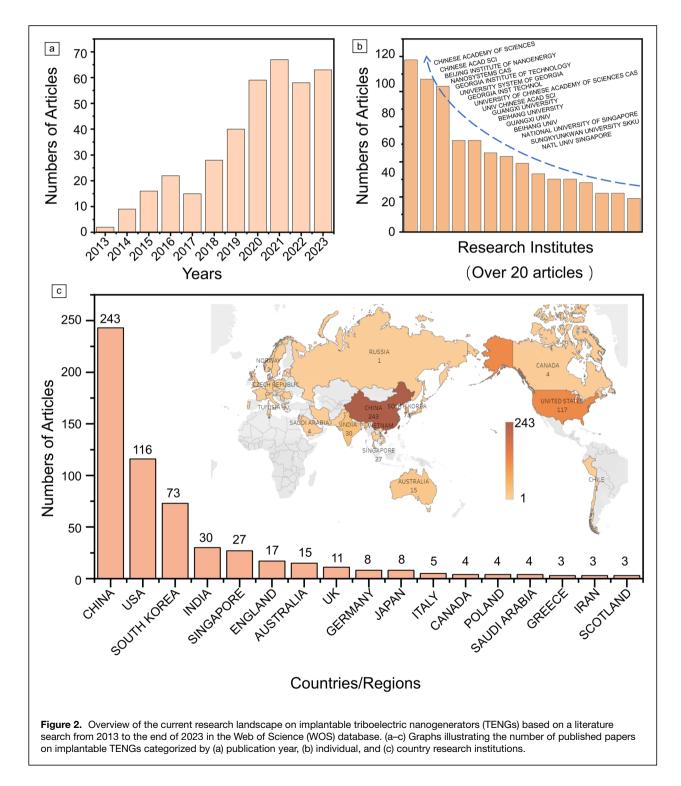
energy source is particularly advantageous for implantable devices, where replacing or recharging batteries can be invasive, costly, and risky for the patient. In addition to their energy-harvesting capabilities, nanogenerators also offer the potential for real-time health monitoring.<sup>34–36</sup> By integrating nanogenerators with sensors, it is possible to create systems that not only power themselves, but also monitor physiological parameters such as heart rate, blood pressure, or glucose levels.<sup>37–39</sup> This dual functionality positions nanogenerators as a key technology in the development of next-generation implantable medical devices.<sup>40–42</sup>

The primary objective of this article is to provide a comprehensive overview of the current state of nanogenerators in implantable medical science. One of the key areas of focus is the design and engineering of nanogenerators for specific biomedical applications.<sup>25,28,43</sup> The human body presents a unique set of challenges for any implantable device, including the need for biocompatibility, mechanical flexibility, and durability.<sup>44–47</sup> Nanogenerators must be carefully designed to meet these requirements while also delivering sufficient power to operate medical devices over extended periods. This article will explore the strategies used to optimize nanogenerator performance, including the selection of materials, structural design, and integration with existing biomedical technologies.<sup>48–52</sup> It also discusses the potential applications of nanogenerators in various medical fields. From powering pacemakers and neural stimulators to enabling real-time health monitoring, nanogenerators have the potential to impact a wide range of medical specialties.<sup>48,53</sup> Finally, we will address the challenges and future prospects of nanogenerators in implantable medical science, including issues related to material stability, power output, and long-term biocompatibility.<sup>54,55</sup> By identifying these challenges and discussing potential solutions, this review aims to provide a roadmap for future R&D in the field.<sup>19,56</sup>

VOSviewer was used to generate citation and keyword co-occurrence maps from the bibliographic data, as illustrated in **Figure 1**. The visualization reveals four distinct clusters, each represented by a different color, corresponding to various research themes. Prominent keywords such as "biochemical energy," "mechanical energy," "piezoelectric nanogenerator," and "triboelectric nanogenerator" emerge as the most significant topics. Key research areas for nanogenerators are centered around biomechanical and mechanical energy conversion. These high-frequency keywords not only spotlight the main areas of interest, but also indicate critical aspects that warrant further exploration.



The research progress and global influence of nanogenerators have been analyzed through publications and their geographical distribution. Building on similar statistical methods, the current advancements in implantable nanogenerators have been evaluated from the inception of nanogenerator technology in 2012 to the end of 2020 (**Figure 2**). Since 2013, the number of related publications has consistently increased each year (Figure 2a). Furthermore, the top four research institutions based on publication volume are the Chinese Academy of Sciences, Chinese ACAD SCI, Beijing Institute of Nanoenergy and Nanosystems CAS, and Georgia Institute of Technology (Figure 2b). Regionally, implantable nanogenerator research has expanded across major countries, with China, the United States, and South Korea leading the way (Figure 2c).



### **Materials**

The selection of materials for nanogenerators is a critical factor that determines their performance, biocompatibility, and overall suitability for implantable medical applications.<sup>57,58</sup> In the context of implantable nanogenerators, materials must meet stringent criteria, including biodegradability, flexibility, biocompatibility, and long-term stability.<sup>15,40,59–61</sup> This section will explore these materials in detail, focusing on the distinctions between biodegradable and nonbiodegradable materials, flexible and nonflexible materials, and the importance of biocompatibility in ensuring safe and effective interactions with biological systems.<sup>62–65</sup>

#### Biodegradable versus nonbiodegradable materials

Biodegradable and nonbiodegradable materials serve different purposes in the design of implantable nanogenerators. Biodegradable materials are designed to break down or dissolve within the body over time, reducing the need for surgical removal after their functional lifespan has ended. Nonbiodegradable materials, on the other hand, are intended for longterm applications where permanent implantation is required. The choice between these two types of materials depends on the specific application and the desired duration of the implant's functionality.<sup>66–68</sup>

# Advantages of biodegradable materials in biomedical applications

One of the most significant advantages of biodegradable materials is the reduction in risks associated with long-term implantation.<sup>62,69</sup> Because these materials naturally degrade within the body, they minimize the potential for chronic inflammation, immune responses, and other complications that can arise from prolonged exposure to foreign materials.<sup>70</sup> This is particularly important in scenarios where the nanogenerator is only needed for a temporary period, such as in postoperative monitoring or short-term therapeutic applications. Biodegradable materials can also promote tissue integration and regeneration, which is crucial for applications that involve interaction with biological tissues.<sup>62</sup> As the material degrades, it can be designed to release bioactive molecules that encourage cell growth and tissue repair, enhancing the healing process. This is particularly beneficial in regenerative medicine, where nanogenerators can be used to stimulate tissue growth while simultaneously providing power for monitoring or therapeutic functions.<sup>71</sup> Shown in Figure 3a-f, considerable research focuses on biodegradable materials.<sup>38,72–76</sup>

Poly(lactic acid) (PLA) is one of the most widely used biodegradable polymers in medical applications. It is derived from renewable resources such as corn starch and sugarcane, making it an environmentally friendly option. PLA degrades into lactic acid, a naturally occurring substance in the body, making it safe for use in implants. Xiao et al. introduces an ultrasound-driven, fully biodegradable, and injectable triboelectric nanogenerator (I-TENG) that uses PLA as the triboelectric layer to minimize infection and injury risks associated with implantable medical devices, while also enhancing cell migration and proliferation for improved healing.<sup>38</sup>

Polycaprolactone (PCL) is another biodegradable polymer commonly used in medical devices. It has a slower degradation rate compared to PLA, making it suitable for applications where longer-term functionality is required before the material degrades. Kang et al. explores the use of a naturederived chi-carrageenan-agar (chi C-Agar) composite as a high-performing triboelectric friction material in fully biodegradable TENGs.<sup>75</sup> The composite, optimized at 80 wt% chi C, exhibits significantly enhanced electron-donating properties and biocompatibility. It generates high output and shows minimal inflammation upon subdermal implantation, making it promising for self-powered transient electronics.

Magnesium is a biodegradable metal that has gained attention for its potential in implantable devices. It degrades into magnesium ions, which are naturally present in the body and can be safely absorbed. Therefore, magnesium, with its excellent biocompatibility and conductivity, is considered a highly promising material for electrodes. Imani et al. introduces an ultrasound-driven, biodegradable triboelectric nanogenerator with magnesium electrodes, which eliminates deep tissue microorganisms through electrical stimulation.<sup>51</sup> It effectively inactivates *Staphylococcus aureus* and *Escherichia coli* and can dissolve on demand, preventing surgical site infections without requiring surgical removal.

Poly(lactic-*co*-glycolic acid) (PLGA) is a promising material for nanogenerators due to its biodegradability. As it breaks down into lactic and glycolic acids, which are safely absorbed by the body, PLGA is ideal for use in biomedical devices where safe degradation is essential. Zheng et al. presents a biodegradable triboelectric nanogenerator utilizing PLGA for *in vivo* biomechanical energy harvesting.<sup>74</sup> The BD-TENG degrades and is resorbed by the body after use, generating tunable electrical output to power micrograting electrodes and facilitate nerve cell growth, showing promise as a power source for transient medical devices.

# Nonbiodegradable materials for long-term application in implantable nanogenerators

Although biodegradable materials offer several advantages, there are many applications where nonbiodegradable materials are more suitable.<sup>49</sup> For long-term implantable devices that require sustained functionality, nonbiodegradable materials provide the necessary stability and durability. These materials are designed to remain inert within the body, maintaining their structural integrity and performance over extended periods.<sup>77–79</sup> Common nonbiodegradable materials used in implantable nanogenerators include metals such as titanium and platinum, ceramics such as alumina, and polymers such as silicone. These materials are chosen for their excellent biocompatibility, mechanical strength, and resistance to corrosion. Their long-term stability ensures that

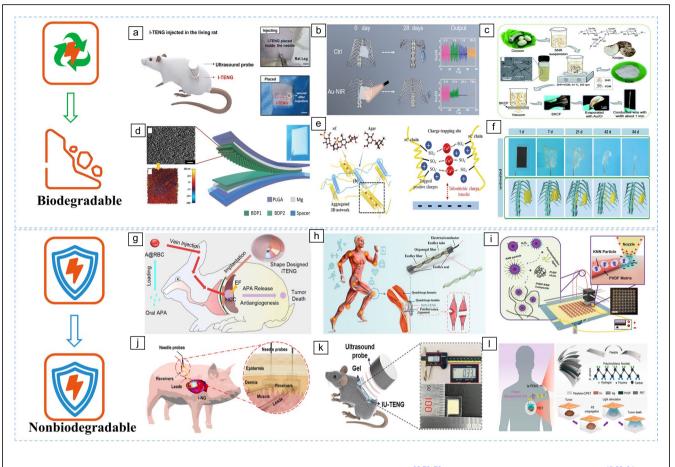


Figure 3. Biodegradable and nonbiodegradable materials. (a-f) Biodegradable materials.<sup>38,72-76</sup> (c, g-l) Nonbiodegradable materials.<sup>49,80-84</sup>

the nanogenerator can continue to function reliably without the need for frequent replacement or maintenance. Shown in Figure 3g-l, a significant amount of research focuses on nonbiodegradable materials.<sup>49,80-84</sup>

#### Flexible versus nonflexible materials

Flexibility is a crucial consideration in the design of implantable nanogenerators, especially when they are intended to conform to the dynamic environment of the human body.<sup>85</sup> Flexible materials allow the device to bend, stretch, and twist without compromising its functionality, making them ideal for applications where the nanogenerator needs to be integrated with soft tissues or organs. Nonflexible materials, although less adaptable, provide structural support and stability, which is essential in certain applications where rigidity is required.<sup>86</sup>

# Importance of flexible materials in implantable devices

The human body is a dynamic environment, characterized by continuous movement and deformation of tissues. Implantable devices that are rigid or inflexible can cause discomfort, restrict movement, or even lead to tissue damage over time. Flexible materials address these challenges by allowing the device to conform to the natural contours of the body, minimizing the risk of adverse reactions and enhancing patient comfort.<sup>87</sup> Flexible materials are particularly important in applications where the nanogenerator needs to be integrated with organs or tissues that undergo significant movement, such as the heart, lungs, or muscles. For example, a flexible PENG can be wrapped around the heart to harvest energy from its rhythmic contractions, whereas a flexible TENG can be implanted in the skin to capture energy from everyday movements. In these applications, the flexibility of the material ensures that the nanogenerator can move with the body, maintaining consistent energy output without causing irritation or damage to the surrounding tissues.

Silicone is a highly flexible polymer that is widely used in medical devices. Its excellent biocompatibility, flexibility, and durability make it ideal for use in implantable nanogenerators. Jiang et al. presents a compact, wearable self-charging power unit integrating a triboelectric nanogenerator with MXenebased microsupercapacitors, encased in a silicone rubber module.<sup>88</sup> The device harnesses and stores energy from human activities, with the microsupercapacitor achieving 23 mF/cm<sup>2</sup> capacitance and 95% retention after 10,000 cycles, while the nanogenerator delivers a maximum output of 7.8  $\mu$ W/cm<sup>2</sup>. The silicone rubber enhances the device's flexibility and integration with various electronic devices and sensors.

Poly(tetrafluoroethylene) (PTFE) is an excellent material for nanogenerators used in internal implants due to its high electronegativity. This property enhances its ability to generate electrical charges, making PTFE highly effective in converting mechanical energy into electrical energy. Its biocompatibility and stability further ensure reliable performance within the body. Liu et al. presents a bionic cochlear basilar membrane acoustic sensor integrated with a triboelectric nanogenerator.<sup>89</sup> The device features nine silver electrodes on poly(tetrafluoroethylene) membranes, achieving high frequency selectivity from 20 to 3000 Hz and self-powered operation by harnessing sound-induced vibrations. This design addresses the limitations of traditional cochlear implants and offers a novel approach to managing sensorineural hearing loss.

Hydrogels are networks of polymer chains that can hold large amounts of water, giving them a soft, gel-like consistency. They are highly flexible and can be engineered to mimic the mechanical properties of natural tissues, making them suitable for implantable nanogenerators. Zhang et al. introduces conductive, injectable hydrogels for self-powered, electrically responsive drug delivery.<sup>90</sup> These hydrogels, modified with an aniline tetramer and xanthan gum, exhibit high conductivity (23.27 mS/cm) and enable controlled drug release when a voltage is applied. Additionally, the hydrogels show potential as bioelectrodes and wearable drug carriers, while also serving as a triboelectric material in a nanogenerator, producing an output of 0.9–1.3 V for self-powered applications.

Although there are currently no standardized benchmarks specifically addressing the softness of materials for implantable flexible nanogenerators, researchers frequently draw upon established biocompatibility guidelines and the known mechanical properties of human tissues. By referencing such physiological parameters, researchers tailor materials properties to achieve a balance between flexibility, durability, and long-term functionality, ensuring that the materials can integrate seamlessly within the body without causing undue mechanical stress.

# Structural support and stability of nonflexible materials

Although flexibility is advantageous in many implantable applications, there are scenarios where nonflexible materials are necessary to provide structural support and stability.<sup>88</sup> For instance, in applications where the nanogenerator needs to be anchored to a specific location or where it is subjected to significant mechanical stress, nonflexible materials offer the required rigidity and strength. Nonflexible materials are often used in the core structure of the nanogenerator, providing a stable platform for the energy-harvesting elements. These materials can also be used to encapsulate the device, protecting the sensitive components from mechanical damage and ensuring that the nanogenerator maintains its performance over time.<sup>91</sup> In some cases, a combination of flexible and nonflexible materials is used, with the flexible materials providing adaptability and comfort, while the nonflexible materials ensure stability and durability.<sup>89</sup>

# Biocompatibility and interaction with biological systems

Biocompatibility refers to the ability of a material to perform its intended function without eliciting any undesirable effects in the body.<sup>49</sup> For implantable nanogenerators, this means that the materials used must not cause adverse reactions, such as inflammation, immune response, or toxicity, when in contact with tissues and bodily fluids. The biocompatibility of a material is crucial to the success of an implant, as it directly impacts the device's performance, patient safety, and the overall outcome of the medical treatment.

The interaction between the implantable nanogenerator and the surrounding tissues plays a critical role in determining the device's long-term performance. Materials that are not biocompatible can trigger an immune response, leading to inflammation, fibrosis, or even rejection of the implant. These reactions can compromise the device's functionality, shorten its lifespan, and cause discomfort or harm to the patient. Conversely, biocompatible materials can promote positive interactions with tissues, facilitating integration, minimizing inflammation, and ensuring stable performance over time.<sup>92</sup>

#### **Evaluation methods and standards**

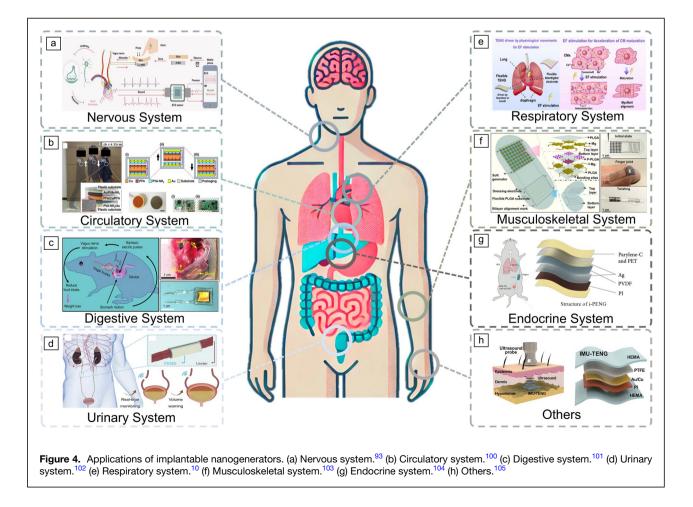
The biocompatibility of materials used in implantable nanogenerators is rigorously evaluated through a series of standardized tests and methods to ensure safety and effectiveness. These assessments are critical for identifying potential adverse effects and confirming that the materials meet the stringent requirements for medical implants. Among the common evaluation methods are cytotoxicity tests, which examine whether a material is toxic to cells by exposing it to cultured cells and monitoring for signs of damage or death, as cytotoxic materials can cause tissue damage when implanted. Sensitization tests are also conducted to determine if a material might trigger an allergic reaction, which is a significant concern for implantable devices due to the risk of chronic inflammation and immune responses that could compromise device performance. Irritation tests further assess whether contact with tissues might cause irritation, potentially leading to inflammation or discomfort, rendering the material unsuitable for long-term use. Hemocompatibility tests are essential for materials that interact with blood, as they evaluate the potential for causing clotting or hemolysis, both of which are critical factors for the safe use of vascular implants. Finally, long-term implantation studies involve placing the material in an animal model to monitor its performance over an extended period, allowing researchers to assess long-term biocompatibility, including tissue integration, immune response, and device stability.

#### Strategies for enhancing biocompatibility

To enhance the biocompatibility of materials used in implantable nanogenerators, researchers have developed various strategies aimed at minimizing adverse reactions and promoting positive interactions with tissues. Surface modifications are a key approach, where materials are altered to reduce inflammation and improve cell interaction. For instance, coatings with anti-inflammatory agents or proteins that promote cell adhesion can significantly lower the risk of inflammation and improve tissue integration.<sup>93–95</sup> Additionally, nanostructured surfaces that mimic the natural extracellular matrix have been shown to enhance biocompatibility by promoting cell growth and reducing immune responses.96-98 Bioactive coatings and functionalization techniques also play a crucial role; these coatings can be designed to release growth factors that stimulate tissue regeneration or antimicrobial agents that prevent infections. Functionalization can be further enhanced through the incorporation of bioactive molecules or drug-eluting coatings, which increase both biocompatibility and therapeutic efficacy. Moreover, incorporating biological molecules such as proteins, peptides, or polysaccharides into the material can improve its compatibility with surrounding tissues by promoting cell adhesion, reducing inflammation, and facilitating tissue integration. For example, incorporating collagen, a natural protein found in the extracellular matrix, can enhance the material's biocompatibility and support the healing process.

# Applications of nanogenerators for different physiology systems

Nanogenerators hold significant promise in a variety of biomedical applications, particularly in implantable medical devices. Their ability to harvest energy from the human body makes them a valuable tool for powering implants, sensors, and therapeutic devices.<sup>99</sup> This section will explore the diverse applications of nanogenerators in medicine, focusing on their potential to address different diseases and medical conditions. The discussion will be organized by organ systems and clinical presentations, highlighting how nanogenerators can be tailored to meet specific medical needs. Figure 4 illustrates the applications of implantable nanogenerators across various body parts, including the nervous system, circulatory system, digestive system, urinary system, respiratory system, musculoskeletal system, and endocrine system.<sup>10,93,100-105</sup> Each organ system presents unique challenges and opportunities for the use of implantable nanogenerators, depending on the specific characteristics of the tissues, the type of energy available for harvesting, and the medical requirements of the condition being treated.



#### Nervous system

Nanogenerators have the potential to revolutionize the treatment of neurological disorders by powering implantable devices that stimulate neural activity or monitor brain function.<sup>93</sup> For instance, TENGs can be used to power deep-brain stimulation (DBS) devices, which are commonly employed in the treatment of conditions such as Parkinson's disease, epilepsy, and chronic pain.<sup>106</sup> By integrating TENGs into these devices, it could be possible to harvest energy from the patient's movements or from the natural electrical activity of the brain, reducing the need for frequent battery replacements and improving the device's longterm performance.<sup>107</sup> Additionally, nanogenerators can power implantable sensors that monitor brain activity in real time, aiding in the early detection of neurological disorders and allowing for timely interventions.<sup>108</sup>

#### **Circulatory system**

Given the crucial role of the circulatory system in sustaining vital bodily functions, utilizing nanogenerators to harvest energy from the mechanical movements of the heart and blood vessels offers a promising solution to power implantable devices, while also advancing continuous monitoring of circulatory health.<sup>109–111</sup> Cardiovascular diseases are among the leading causes of death worldwide, and implantable devices such as pacemakers and defibrillators play a critical role in managing these conditions.<sup>100,112</sup> Nanogenerators, particularly PENGs, offer a promising solution for powering these devices by harvesting energy from the mechanical movements of the heart, such as the beating of the heart or the expansion and contraction of blood vessels.<sup>113,114</sup> This harvested energy can power cardiac devices, reducing the need for battery replacements and enhancing the patient's quality of life.<sup>112</sup> Furthermore, nanogenerators can be integrated into wearable devices that monitor cardiovascular health indicators such as blood pressure and heart rate, providing continuous monitoring without the need for external power sources.<sup>108</sup>

#### **Digestive system**

In the digestive system, nanogenerators can be employed in implantable devices that monitor gastrointestinal functions or treat specific conditions such as acid reflux or motility disorders.<sup>101</sup> These devices can harvest biomechanical energy from the peristaltic movements of the intestines or other digestive organs. The energy can be used to power sensors that provide real-time data on digestive processes, enabling better management of gastrointestinal diseases.<sup>115</sup>

#### Urinary system

Nanogenerators can also be applied to the urinary system, where they can power implantable sensors or therapeutic devices designed to monitor or treat conditions such as incontinence or kidney diseases.<sup>102</sup> For example, nanogenerators could harvest mechanical energy from the bladder's contractions, powering devices that monitor bladder function or assist in the management of urinary conditions.<sup>102</sup>

#### **Respiratory system**

Nanogenerators can be effectively utilized in the respiratory system, particularly for managing conditions such as chronic obstructive pulmonary disease (COPD) and asthma. These conditions often require continuous monitoring of lung function, which can be achieved through sensors powered by nanogenerators. By harvesting energy from the mechanical movements associated with breathing, nanogenerators can power these sensors, providing real-time data for better management of respiratory conditions. Additionally, nanogenerators can enhance drug delivery systems for respiratory diseases, enabling precise and responsive medication release based on the patient's lung function, thereby improving treatment efficacy and reducing side effects.<sup>10</sup>

#### Musculoskeletal system

In the field of orthopedics, nanogenerators can be used to power implants and sensors that monitor bone healing, joint function, and other musculoskeletal processes. Piezoelectric nanogenerators can be integrated into orthopedic implants to harvest energy from mechanical stress during movement. This energy can then be used to power sensors that monitor the progress of bone healing after fractures or surgeries, providing real-time data to clinicians without the need for external power sources. Additionally, nanogenerators can be used in wearable devices that monitor joint function in patients with conditions such as osteoarthritis or rheumatoid arthritis, harvesting energy from the patient's movements and allowing for continuous monitoring of joint health.<sup>103</sup>

#### Endocrine system

In the endocrine system, nanogenerators could be used in implantable devices that monitor hormone levels or deliver hormone therapies. For example, nanogenerators might power sensors that track glucose levels in real time, providing continuous data for diabetes management. This could improve the accuracy and convenience of monitoring without the need for frequent battery replacements.<sup>104</sup>

#### Others

Beyond the major systems, nanogenerators have the potential to treat a variety of chronic and acute diseases. Chronic diseases, such as diabetes, heart disease, and chronic pain, require long-term management and continuous monitoring.<sup>7,105,111</sup> Nanogenerators can play a crucial role in the development of implantable and wearable devices that provide ongoing care without the need for frequent battery replacements.<sup>116</sup> For example, nanogenerators can be used in implantable devices that deliver electrical stimulation to the nervous system, such as spinal-cord stimulators to treat chronic pain.<sup>117</sup> Acute diseases, such as infections, injuries, and acute organ failure, often require immediate and intensive treatment. Nanogenerators can be used in implantable devices that provide real-time monitoring and targeted interventions,

improving the precision and effectiveness of treatment.<sup>118</sup> For example, PENGs can be embedded in orthopedic implants to monitor bone healing, offering real-time data to healthcare providers and facilitating more effective interventions. In cases of acute organ failure, such as heart or respiratory failure, nanogenerators can be utilized in implantable devices that deliver critical interventions like cardiac pacing or respiratory assistance.<sup>119</sup>

### **Challenges and prospects**

#### **Material stability**

One of the most significant technical challenges in the development of implantable nanogenerators is ensuring that the materials used can remain stable in the complex and often harsh biological environment of the human body. Unlike external devices, implantable nanogenerators are continuously exposed to various physiological conditions, which can severely impact their performance and longevity. Addressing this issue is crucial to ensure reliable and safe operation in biomedical applications.

In the human body, implantable devices must endure constant exposure to body fluids such as blood, lymph, and interstitial fluid. These fluids contain a range of components, including salts, proteins, enzymes, and ions, which can interact with the materials used in nanogenerators. Over time, these interactions can lead to corrosion or a weakening of the material's structural integrity, negatively affecting the device's performance. Additionally, the pH levels within the body vary from one region to another, with certain areas, like the stomach, being highly acidic, while others maintain a more neutral pH. Such variations can accelerate material breakdown or trigger chemical reactions that degrade the nanogenerator's efficiency. Another major factor affecting material stability is the continuous mechanical stress to which implantable nanogenerators are subjected. The body is always in motion, and the devices experience compression, tension, bending, and twisting forces, especially in high-movement areas like joints. These mechanical stresses, if not accounted for in the design, can lead to material fatigue, fractures, or even device failure over time. The long-term degradation of materials used in nanogenerators is another critical concern. Constant exposure to the body's internal environment results in gradual degradation, reducing both structural integrity and the functionality of the materials. For example, piezoelectric materials such as lead zirconate titanate or triboelectric polymers often experience molecular changes due to prolonged mechanical stimulation and interaction with fluids. This leads to a gradual decrease in energy-conversion efficiency. Furthermore, the accumulation of microcracks or the delamination of layered materials can speed up degradation, ultimately causing the device to fail prematurely. Corrosion is a particular issue for the metallic components of nanogenerators, such as electrodes or connectors. These metals could undergo oxidation or electrochemical reactions when exposed to body fluids, leading to

corrosion that compromises the device's electrical pathways. This reduces the efficiency of the energy-harvesting process. Similarly, delamination can occur within composite or laminated structures, especially in triboelectric nanogenerators. When the layers that are essential for energy generation begin to separate due to mechanical stress or chemical reactions, the device's energy output can be drastically reduced.

To overcome these challenges, researchers are actively developing materials that are both corrosion-resistant and durable enough to function effectively within the body over extended periods. Biocompatible materials such as certain polymers, ceramics, and specially treated metals are being investigated for their ability to withstand the body's harsh internal environment while maintaining mechanical integrity and energy-conversion efficiency. These materials are key to improving the long-term reliability of implantable nanogenerators. Another promising approach to enhancing material stability is the use of protective coatings that act as barriers between the nanogenerator's materials and the surrounding biological environment. These coatings help prevent direct exposure to body fluids and reduce the risk of corrosion or delamination. Hydrophobic coatings, for instance, repel water and body fluids, limiting their contact with sensitive materials and reducing corrosion risks. Similarly, biocompatible polymers such as poly(dimethylsiloxane) or parylene are used to form thin, flexible layers that protect the device without interfering with its functionality. Advances in nanostructured surface modifications also offer solutions, with some surfaces designed to be superhydrophobic or anti-biofouling, preventing fluid absorption and biological contamination, and thereby extending the life of the nanogenerator. In addition, researchers are exploring the potential of self-healing materials, which have the ability to repair small cracks or restore their functionality after minor damage. Incorporating self-healing polymers or biomimetic materials into nanogenerators could lead to devices that are capable of maintaining performance even when subjected to continuous mechanical stress and chemical exposure. These innovations are key to ensuring the long-term stability and efficiency of implantable nanogenerators in biomedical applications.

#### Power output and efficiency

A key challenge for implantable nanogenerators lies in their relatively low power output and inefficient energy conversion compared to conventional energy sources such as batteries. Nanogenerators rely on converting mechanical, thermal, or biochemical energy from the body into electrical energy, but this process is often limited by the availability of energy within the body. Mechanical energy, such as movement from muscles or joints, is intermittent and varies in intensity depending on the individual's activity level. Similarly, thermal and biochemical energy sources, such as body heat or metabolic processes, provide only small amounts of energy. As a result, the total amount of electrical energy generated by nanogenerators is often insufficient for powering many types of implantable medical devices. Additionally, miniaturization—a necessity for implantable devices—presents another challenge. Reducing the size of nanogenerators limits the surface area available for energy harvesting, which directly impacts their ability to generate sufficient power, making it difficult to balance the need for smaller, implantable devices with the requirement for adequate energy output.

To address these limitations, researchers are exploring several potential solutions aimed at improving power output and conversion efficiency. One promising approach is the optimization of energy-conversion mechanisms. By improving the materials and structures used in nanogenerators, such as enhancing the piezoelectric or triboelectric properties, the devices can capture more energy from the body's natural movements and processes. Additionally, hybrid nanogenerators that combine multiple energy-harvesting mechanisms have emerged as a potential solution. These devices can simultaneously harvest mechanical, thermal, and biochemical energy, compensating for the limitations of any single energy source. For example, a hybrid nanogenerator might convert both the mechanical energy from body movements and the thermal energy from body heat into electrical power, resulting in a more reliable and consistent output. Moreover, advancements in energy-storage technologies are essential for managing the intermittent nature of energy harvesting. Improved supercapacitors and energy management systems can store the energy produced by nanogenerators and distribute it efficiently, ensuring that implantable devices receive a stable and continuous power supply. These strategies offer promising solutions to the current power and efficiency challenges faced by implantable nanogenerators, potentially paving the way for their wider adoption in biomedical applications.

#### Energy storage and management

A significant challenge for implantable nanogenerators is the intermittent energy supply they provide, which arises due to the body's varying physiological conditions. Unlike traditional batteries, which can offer a consistent and steady power output, nanogenerators depend on sporadic and variable energy sources such as body movements, thermal gradients, or biochemical processes. For example, mechanical energy generated by muscle contractions or joint movements is highly dependent on the individual's activity level. During periods of rest or reduced movement, the energy harvested by nanogenerators decreases significantly. Similarly, thermal energy from body heat could fluctuate depending on external temperature conditions or the metabolic state of the individual. This inconsistency in power generation creates a challenge for maintaining a reliable and continuous power supply to implantable medical devices, which often need a steady source of energy to function properly.

To overcome this variability, effective energy storage systems are crucial for managing the fluctuating power generated by nanogenerators. The intermittent nature of energy harvesting makes it necessary to store energy when it is available and release it as needed to ensure the smooth operation of medical devices. However, the small size of implantable systems imposes significant constraints on the design of these energy-storage systems. Traditional batteries are often too large or heavy for use in implantable devices, and they may not be compatible with long-term implantation due to safety concerns such as leakage or degradation over time. Therefore, the development of compact, efficient, and biocompatible energy storage solutions is a key focus of current research. Supercapacitors and micro-batteries, which can store energy efficiently in small volumes, are being explored as potential solutions. These storage devices need to have high energy density, long cycle life, and the ability to quickly charge and discharge to align with the unpredictable energy input from nanogenerators.

In addition to energy storage, power management systems play a vital role in ensuring that the energy harvested by nanogenerators is delivered in a controlled and efficient manner. These systems are responsible for regulating the flow of electricity to the medical device, ensuring that even when the energy input is intermittent, the device receives a stable and continuous supply of power. Advanced energy-management technologies are being developed to optimize the distribution of stored energy and to prevent energy wastage. Such systems can include energy-harvesting circuits that efficiently capture the maximum amount of energy from nanogenerators, as well as voltage regulation circuits that maintain the correct power levels for the device's operation. Furthermore, intelligent power management algorithms can adjust the energy usage of the medical device based on real-time monitoring of the energy supply, allowing for more efficient use of the harvested power.

#### **Biocompatibility and safety**

Biocompatibility and safety are essential considerations in the design of implantable nanogenerators, as these devices must function within the body without causing adverse health effects. One of the primary challenges is managing the risk of an immune response. The body's natural defense system may recognize the implanted device as a foreign object, triggering inflammation or rejection. Prolonged immune reactions, such as chronic inflammation, can lead to encapsulation of the device in fibrous tissue, which can impair its functionality or necessitate its removal. Therefore, ensuring that nanogenerators do not provoke such immune responses is critical for their long-term use. To address this, researchers focus on using biocompatible materials that do not cause adverse reactions. Materials such as biocompatible metals, polymers, and ceramics are commonly employed, and they are often coated with protective layers such as poly(dimethylsiloxane) (PDMS) or parylene to create a barrier between the device and surrounding tissue. These coatings not only shield the nanogenerator from biological degradation, but also help reduce the likelihood of immune responses.

A related issue is the potential release of degradation byproducts. Over time, nanogenerators could degrade within

the body, producing particles or chemicals that must be nontoxic and easily metabolized or eliminated. Harmful byproducts could cause tissue damage, systemic toxicity, or even organ failure, so developing materials that degrade safely and without causing harm is crucial. Addressing this, researchers are increasingly turning their attention to the development of biodegradable nanogenerators, which are designed to dissolve or break down into harmless substances after completing their function. This approach not only avoids the need for surgical removal, but also minimizes long-term risks associated with permanent implants. For example, biodegradable polymers and magnesium-based materials are being studied for their ability to generate power while gradually dissolving into nontoxic components. The use of such materials significantly reduces the risk of immune reactions and long-term complications, offering a safer and more practical solution for implantable medical devices.

#### **Durability and mechanical robustness**

Durability and mechanical robustness are crucial challenges for implantable nanogenerators, as these devices must endure continuous motion and mechanical stress within the body over long periods. Mechanical fatigue is a significant concern because the human body is constantly in motion. Nanogenerators implanted in areas subject to frequent movement, such as joints or muscles, are exposed to repetitive forces, including bending, stretching, and compression. Over time, this continuous mechanical stress can lead to fatigue, where the material's structural integrity weakens, reducing the device's efficiency in energy harvesting. In severe cases, mechanical fatigue can result in microcracks or fractures within the nanogenerator, ultimately leading to device failure.

In addition to mechanical fatigue, wear and tear from constant operation in a dynamic environment poses another long-term durability challenge. The harsh physiological environment, including exposure to body fluids and varying mechanical loads, can degrade materials, making it difficult for nanogenerators to maintain their functionality over time. The continuous exposure to such conditions can lead to issues such as erosion of the material surface, loss of flexibility, and degradation of energy-harvesting components. This degradation not only affects the performance of the nanogenerator but can also compromise its safety if materials break down and release harmful particles into the body.

To overcome these challenges, researchers are focusing on design innovations aimed at reinforcing the mechanical robustness of nanogenerators. One approach is the use of flexible and stretchable materials that can withstand repeated mechanical deformation without breaking or losing efficiency. These materials allow the nanogenerator to bend and stretch in sync with the body's movements, reducing the risk of fatiguerelated failures. Additionally, reinforced structures are being developed to improve the mechanical resilience of nanogenerators. These structures might include multilayer designs, where different layers provide both mechanical strength and energy-harvesting capability, or the incorporation of composite materials that combine flexibility with durability. By reinforcing the structural integrity of nanogenerators, researchers aim to extend their lifespan and ensure consistent performance, even in the dynamic conditions of the human body.

#### Conclusion

Implantable nanogenerators represent a promising frontier in the quest for sustainable and reliable power sources for medical devices. As the demand for advanced, long-lasting, and minimally invasive medical technologies continues to grow, nanogenerators offer a unique solution by harnessing the body's own energy to power these devices. This article has highlighted the various types and mechanisms of nanogenerators, including triboelectric and piezoelectric systems, each with its own set of advantages and challenges.

Currently, significant strides have been made in developing materials and designs that enhance the biocompatibility, efficiency, and stability of these nanogenerators. However, challenges remain, particularly in achieving sufficient power output and ensuring long-term material durability in the complex physiological environment. The integration of biodegradable and flexible materials, along with advanced surface modifications and bioactive coatings, shows great potential in overcoming these obstacles and enhancing the performance of nanogenerators in real-world applications.

Looking forward, the potential value of implantable nanogenerators is vast, with applications ranging from powering neuroprosthetics to supporting cardiac devices and biosensors. The continued development and refinement of these technologies could lead to a new era of self-sustaining medical implants, reducing the need for battery replacements and invasive procedures, thereby improving patient quality of life.

In conclusion, while implantable nanogenerators are still in the early stages of development, their future prospects are bright. With ongoing research and interdisciplinary collaboration, these devices could soon become a cornerstone of modern medical technology, offering innovative solutions to some of the most pressing challenges in healthcare today.

### Abbreviations

APA	Apatinib
BD-TENG	Biodegradable triboelectric
	nanogenerator
CM	Cardiomyocytes
ECG	Electrocardiogram
EF	Electric field
HCC	Hepatocellular carcinoma
HR	Heart rate
IMU-TENG	Implantable modulus-tunable ultrasound
	driven triboelectric nanogenerator
i-NG	Implantable nanogenerators

i-PENG	Implantable piezoelectric nanogenerator
iTENG	Implantable triboelectric nanogenerator
I-TENG	Injectable triboelectric nanogenerator
IU-TENG	Implantable ultrasound-driven TENG
LED	Light-emitting diode
LL-VNS	Low-level vagus nerve stimulation
OFS-TENG	Organogel/silicone fiber-helical sensor
	based on a triboelectric nanogenerator
RBC	Red blood cell
PDT	Photodynamic therapy
PS congregation	Photosensitizer congregation
SKCF	SNR-KGM Composite Film (SNR
	Silk nanoribbons, KGM Konjac
	glucomannan)
ts-PENG	Twinning structure piezoelectric
	nanogenerator

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The three co-first authors, Z.L., S.-W.K., and X.W., have made equal and essential contributions to all aspects of this review. Together, they identified the central theme, systematically reviewed and evaluated the literature, and collaboratively developed the key insights presented. Z.L., S.-W.K., and X.W. jointly led the overall structure of the manuscript and provided expert guidance in data analysis and figure preparation. Finally, all three authors contributed to the final editing and refinement of the text to ensure its rigor and originality.

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# **Data availability**

The data supporting the findings of this review are derived from previously published studies and are available from the cited sources.

# **Conflict of interest**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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