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Implantable microfluidics: methods and applications

Tao Luo, *[a,b] Lican Zheng,[c] Dongyang Chen,[a] Chen Zhang,[a] Sirui Liu,[a] Chongjie Jiang,[a] Yu Xie,[a] Dan Du[d] and Wei Zhou[a]

Implantable microfluidics involves integrating microfluidic functionalities into implantable devices, such as medical implants or bioelectronic devices, revolutionizing healthcare by enabling personalized and precise diagnostics, targeted drug delivery, and regeneration of targeted tissues or organs. The impact of implantable microfluidics depends heavily on advancements in both methods and applications. Despite significant progress in the past two decades, continuous advancements are still required in fluidic control and manipulation, device miniaturization and integration, biosafety considerations, as well as the development of various application scenarios to address a wide range of healthcare issues. In this review, we discuss advancements in implantable microfluidics, focusing on methods and applications. Regarding methods, we discuss progress made in fluid manipulation, device fabrication, and biosafety considerations in implantable microfluidics. In terms of applications, we review advancements in using implantable microfluidics for drug delivery, diagnostics, tissue engineering, and energy harvesting. The purpose of this review is to expand research ideas for the development of novel implantable microfluidic devices for various healthcare applications.

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1. Introduction

Implantable devices are devices that can be surgically implanted into the body, either temporarily or permanently, to revolutionize the diagnosis, monitoring, and treatment of certain medical conditions.[1] For instance, widely used implantable cardioverter-defibrillators and pacemakers help manage heart rhythm disorders.[2] These devices continuously monitor the heart's electrical activity and provide electrical impulses or shocks when necessary to regulate the heart rate and prevent life-threatening arrhythmias. Implantable neurostimulation devices, such as deep brain stimulators and spinal cord stimulators, are utilized to manage conditions like Parkinson's disease by delivering electrical signals to neurons in specific regions.[3] Implantable devices also facilitate real-time *in vivo* monitoring and on-demand drug delivery. For example, implantable continuous glucose monitoring systems offer a

[a]*Pen-Tung Sah Institute of Micro-Nano Science and Technology, Xiamen University, Xiamen, 361102, China. E-mail: luotao@xmu.edu.cn*
[b]*The State Key Laboratory of Fluid Power & Mechatronic Systems, Zhejiang University, Hangzhou 310027, China*
[c]*School of Aerospace Engineering, Xiamen University, Xiamen, 361102, China*
[d]*School of Medicine, Xiamen University, Xiamen, 361102, China*

Tao Luo

Tao Luo received his Ph.D. from City University of Hong Kong in 2018. From 2019 to 2020, he worked at the Department of Biological and Environmental Engineering, Cornell University, as a postdoctoral associate, and then he moved to Xiamen University in Nov. 2020 as an assistant professor. His current research focuses on microfluidics, microrobotics and flexible electronics for biomedical applications.

Lican Zheng

Lican Zheng joined Xiamen University as a bachelor's degree candidate in Mechanical Design Manufacturing and Automation in 2021. His current research interest is microfluidic technology for implantable medical devices

more convenient and accurate way to monitor blood sugar levels in people with diabetes.[4–6] Additionally, implantable insulin pumps can adjust insulin delivery based on glucose levels, ensuring improved diabetes management.[7,8] Furthermore, implantable devices can delivery medications directly to specific areas of the body, enhancing drug efficacy while minimizing systemic side effects.[9,10]

The manipulation and control of small volumes of fluids within microscale channels and chambers, known as microfluidic functionalities, play a vital role in the development of various implantable devices.[11–13] For instance, microfluidic systems enable precise control over drug release and dosage within these devices. By utilizing microfluidic channels and valves, the flow rate and timing of drug delivery can be finely adjusted.[14] Microfluidic functionalities can also be integrated into implantable devices for the collection and analysis of biological samples.[15,16] Within the device, miniaturized microfluidic sensors can analyze analytes such as glucose,[17] electrolytes,[18] proteins,[19] or hormones[20,21] in bodily fluids. This allows for real-time monitoring of health conditions and early detection of abnormalities, facilitating timely interventions. Moreover, precise fluid management and circulation may be necessary for implantable devices. This is especially relevant in devices like artificial organs, where controlled fluid dynamics are crucial.[22–24] In summary, implantable microfluidic functionalities enhance the capabilities of implantable devices by enabling precise drug delivery, real-time monitoring, on-site diagnostics, and artificial tissues/organs. Consequently, the integration of microfluidic systems or components within implantable medical devices to manipulate and control small volumes of fluids within the body, known as implantable microfluidics, has gained significant attention over the past two decades.[25–27]

Despite notable progress, several challenges need to be addressed for the widespread implementation and adoption of implantable microfluidic devices. These challenges include biocompatibility,[28] long-term stability,[29] power supply,[30] and miniaturized integration with existing healthcare systems.[31] Ensuring biocompatibility is crucial to minimize the risk of adverse reactions or immune responses. This necessitates the use of non-toxic and non-inflammatory materials in the microfluidic components.[32,33] Additionally, for many applications, implantable microfluidic devices must exhibit long-term stability and reliability to ensure continuous and accurate performance over extended periods of time. Preventing biofouling or clogging of microfluidic channels during long-term implantation presents another challenge.[34–36] Furthermore, implantable microfluidic devices often require a power source to operate components such as pumps, valves, or sensors for extended durations. Providing a reliable and long-lasting power supply within the limited space of the implantable device poses a significant challenge.[37] Exploring battery technologies, energy harvesting methods, or wireless power transfer techniques is essential to address this challenge effectively.[38] Last but not least, achieving miniaturization is crucial for implantable microfluidic devices to fit within the limited space available inside the body. However, accomplishing the desired level of miniaturization while maintaining the functionality and reliability of the microfluidic system presents technical challenges that complicate the design and fabrication process.[39]

Undoubtedly, addressing these challenges necessitates interdisciplinary collaborations to drive continuous advancements in both methods and applications of implantable microfluidics. This review provides a comprehensive summary of the progress in implantable microfluidics, considering both methods and applications (Fig. 1). Regarding methods, we delve into the techniques employed for fluid manipulation, device fabrication, and biosafety measures. For instance, we discuss the utilization of external pressure-driven pumps, electric fields, magnetic fields, and ultrasound for fluid manipulation and control in implantable microfluidic devices. In terms of applications, we review the diverse uses of implantable microfluidics, including drug delivery, diagnostics, tissue

Dongyang Chen

Dongyang Chen received the B.S. degree in Mechanical Design Manufacturing and Automation from Wuhan University of Technology, and entered Xiamen University in 2022 as a master's degree candidate. His current research focuses on implantable microfluidic devices for biomedical applications.

Wei Zhou

Wei Zhou received his Ph.D. degrees in mechanical engineering from South China University of Technology, Guangzhou, China, in 2010. From 2010 to 2012, he was a postdoc researcher at Sun Yat-sen University. He was appointed as an associate professor in mechanical & electrical engineering of Xiamen University from December 2012–July 2016. Now he is a full professor at Xiamen University. His current research interests focus on design and fabrication of microstructures for biomedical devices.

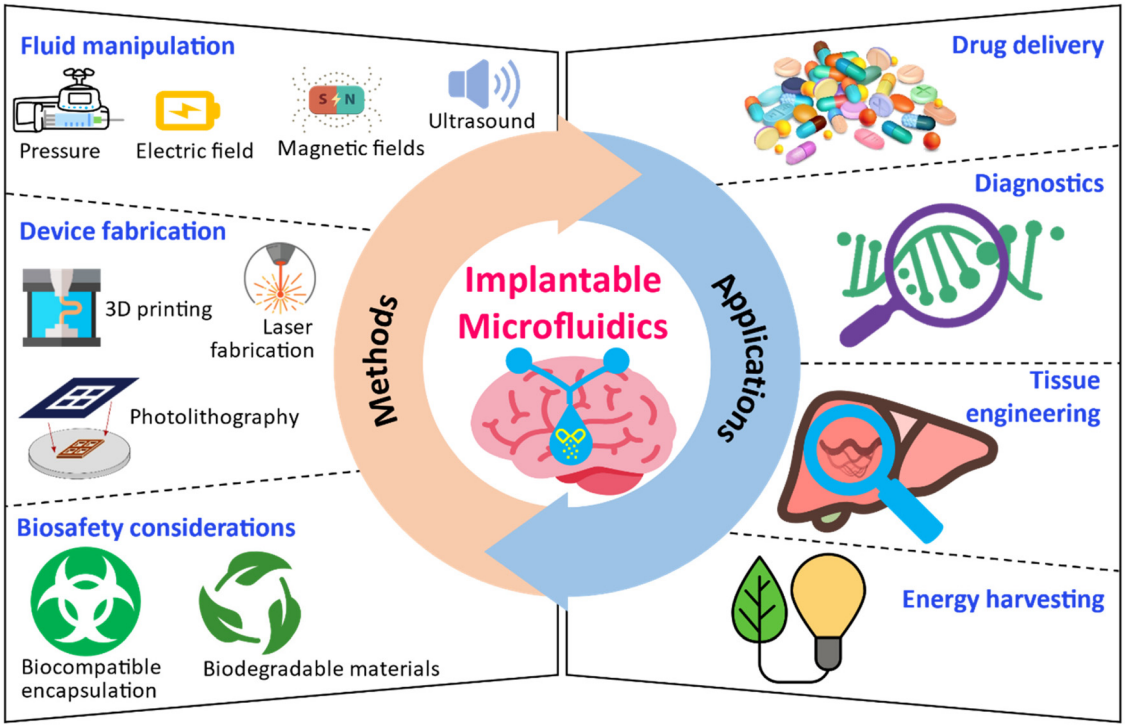

Fig. 1 Overview of methods and applications of implantable microfluidics.

engineering, and energy harvesting. We highlight the potential benefits and advancements in each area. Lastly, this review identifies the challenges that implantable microfluidics still faces and outlines future directions for development. It calls for ongoing research and development in this field to uncover new applications and further expand the capabilities of implantable microfluidics.

2. Methods

2.1 Fluid manipulation

Fluid manipulation serves as the foundation of implantable microfluidics, facilitating the accurate control and manipulation of fluids inside the human body. This capability is essential for attaining the intended therapeutic and diagnostic results in a minimally invasive and targeted manner. Numerous techniques exist for microscale fluid manipulation in implantable microfluidic devices. For instance, in semi-implantable microfluidic devices, precise and controllable fluid manipulation can be effortlessly achieved by employing external pressure pumps, such as syringe pumps or peristaltic pumps.[40–44] The external pump connects to the implanted section of the device through tubing, enabling controlled fluid delivery and regulation of flow. As depicted in Fig. 2a, Meng *et al.* developed a parylene-based cuff electrode with integrated microfluidic channels for recording, stimulating, and delivering drugs to peripheral nerves.[45] The liquid drug was infused through the use of an external syringe pump, which allowed for precise flow rates below 1 μL min^{-1}. The fluid manipulation approach relying on external pumps offers a balance between implantable and external control systems, offering enhanced flexibility, convenience, and adaptability. It harnesses the strengths of both implantable and external technologies to enable fluid manipulation and control within the body.

Electrokinetic methods, which utilize electric fields to manipulate fluids, are important techniques for fluid manipulation in implantable microfluidic devices. This approach involves applying a voltage across the microfluidic channels, resulting in the generation of an electro-osmotic flow.[46–48] Erickson *et al.* introduced an implantable microfluidic device that integrates an electroactive microwell structure for efficient, low-power drug delivery in autonomous microsystems. This innovative system harnesses localized electrokinetic effects to regulate the timing and rate of chemical release from individual well compartments, as illustrated in Fig. 2b.[49] By utilizing this method, the administration time of doses is significantly reduced from hours to seconds, surpassing the slower diffusion-based approaches. Moreover, this achievement is accomplished with minimal energy expenditure, requiring as little as 20 mJ per dose. The electrokinetic technique allows for precise fluid control and manipulation at the microscale within the limited spaces of the devices. This capability is particularly valuable in implantable microfluidic devices.

Microscale thermal expansion can serve as a method for fluid manipulation in implantable microfluidic devices. This

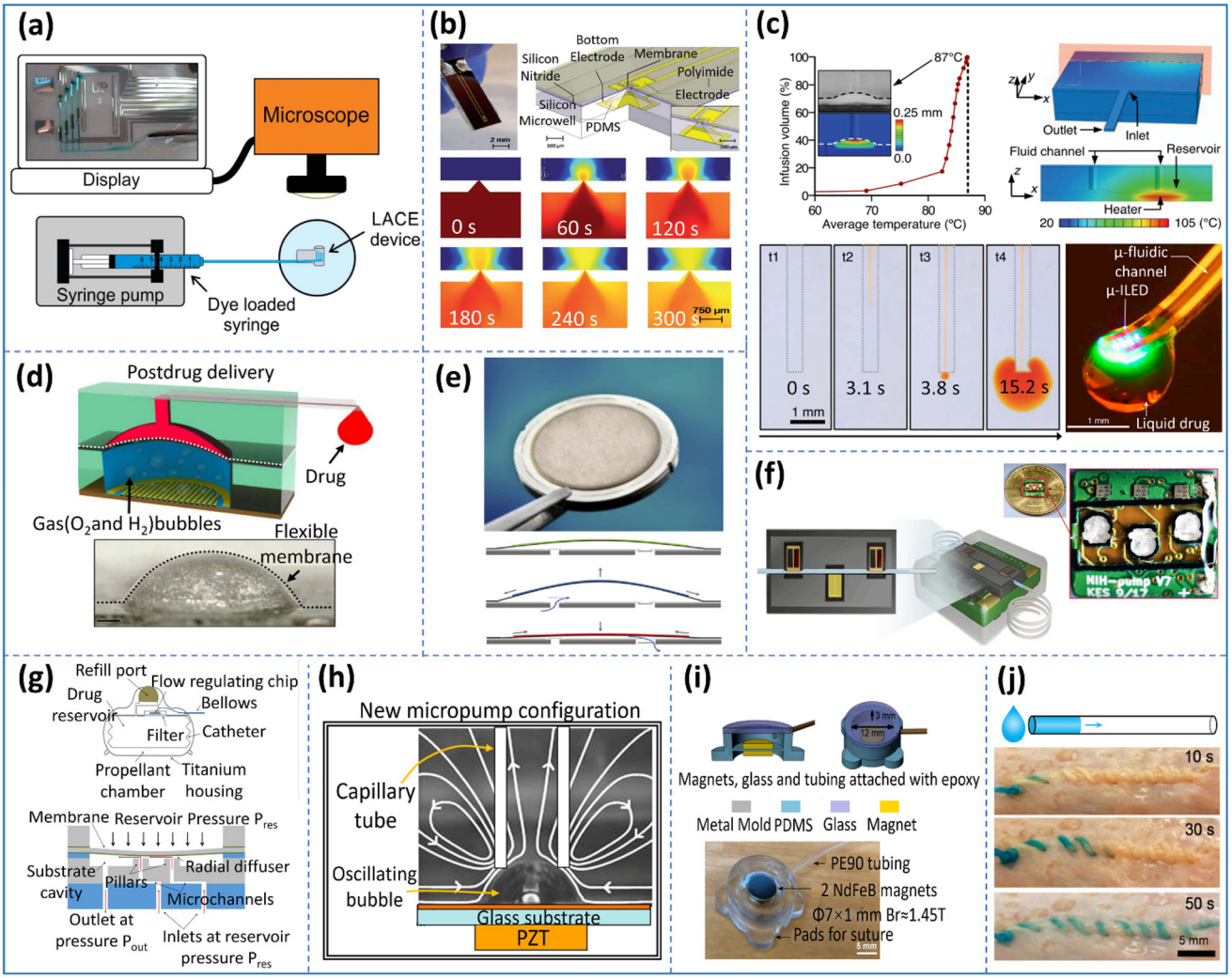

Fig. 2 Various fluid manipulation methods for implantable microfluidic devices. (a) Precise flow control with an external syringe pump. Reproduced from ref. 45 with permission from IEEE, copyright 2019. (b) The release of chemicals stored in a microchamber are controlled through localized electrokinetic effects. Reproduced from ref. 49 with permission from The Royal Society of Chemistry, copyright 2008. (c) A device utilizes a microfluidic channel with a Joule heating element, initiating the expansion of an active layer to pump the drug through the corresponding microfluidic channel for controlled fluid delivery. Reproduced from ref. 52 with permission from Elsevier, copyright 2015. (d) A microfluidic system incorporates an electrochemical pumping chamber for the controlled release of liquid drugs. Reproduced from ref. 56 with permission from AAAS, copyright 2019. (e) A piezoelectric titanium micropump employs an alternating high voltage to cause oscillating movement of a diaphragm, achieving fluid movement through two passive spring valves. Reproduced from ref. 59 with permission from Elsevier, copyright 2021. (f) Directional flow is induced using a miniaturized peristaltic micropump that sequentially compresses the microtubing *via* expansion and contraction of a thermal phase-change material located in three integrated chambers. Reproduced from ref. 60 with permission from Elsevier, copyright 2019. (g) Implantable infusion pumps employ 3-stack MEMS-based passive flow regulators, utilizing the non-linear deflection of a Si membrane in direct communication with a pressurized reservoir. Reproduced from ref. 62 with permission from IEEE, copyright 2020. (h) Vertical fluid pumping is achieved through acoustically excited oscillating microbubbles. Reproduced from ref. 63 with permission from SAGE, copyright 2010. (i) A compact microfluidic pump, wirelessly actuated by an external magnet, can modulate fluid flow in the intramedullary cavity. Reproduced from ref. 66 with permission from MDPI, copyright 2020. (j) Capillary action causes the flow of a blue dye in a cotton thread patterned on chicken skin. Reproduced from ref. 68 with permission from Springer Nature, copyright 2016.

technique exploits the phenomenon of volume or dimensional changes in materials at the microscale in response to temperature fluctuations.[50,51] By selectively heating specific regions of the microfluidic device, it is possible to induce localized thermal expansion. This expansion can generate pressure gradients or flow within the microchannels, enabling precise control over fluid movement by manipulating temperature and timing. A semi-implantable wireless optofluidic system for programmable *in vivo* pharmacology, as illustrated in Fig. 2c, employed microscale Joule heating and a thermally expandable polymer to initiate pumping of fluid from the reservoirs.[52] Using the thermal actuation method, a maximum flow rate of 5 μL min^{-1} was achieved. By adjusting the geometries of the reservoirs and the dimensions of the channels, the flow rate

can be modulated to suit various applications. However, it is crucial to emphasize that thermal expansion-based methods necessitate precise temperature control and meticulous design considerations to guarantee reliable and consistent fluid manipulation.

The electrochemical pumping mechanism is an ultralow-power and miniaturized approach utilized in fully implantable microsystems. This method employs water electrolysis to generate gas bubbles, which in turn induce microscale expansion.[53–55] The electrolysis process commonly involves the utilization of electrodes, typically composed of materials like platinum or gold, along with an electrolyte solution. When a voltage is applied across the electrodes, an electrochemical reaction takes place at one of the electrodes, leading to the generation of gas bubbles. These bubbles accumulate and grow on the electrode surface, and their expansion creates a pressure differential that propels the surrounding fluid through the microfluidic channels. The rate of fluid flow can be controlled by adjusting parameters such as the applied voltage, electrode geometry, and electrolyte composition. By modulating these factors, it becomes possible to precisely manipulate fluid flow within the implantable microfluidic device. As depicted in Fig. 2d, a fully implantable optofluidic cuff was developed for wireless optogenetic and pharmacological neuromodulation of peripheral nerves. This device incorporated electrolysis-based electrochemical micropumps with Au/Cu interdigitated electrodes, which initiated the electrolysis process in an aqueous solution of potassium hydroxide (KOH; 50 mM), leading to the generation of hydrogen and oxygen gases.[56] The gases generated from the electrolysis mechanically deform the flexible membrane, facilitating the movement of the drug from the reservoir, through the microfluidic channel, and ultimately out of the corresponding outlet at the cuff. The reported maximum flow rates achieved by this method are approximately 1.5 μL min^{-1}. This gas bubble-driven pumping approach operates without the requirement for external power sources or moving parts, rendering it well-suited for miniaturized and implantable systems.

Miniaturized piezoelectric and peristaltic pumps have been extensively investigated and are frequently employed in implantable microfluidic devices.[57,58] Miniaturized piezoelectric micropumps employ the piezoelectric effect, wherein the application of an electric field causes mechanical deformation in piezoelectric materials, resulting in the generation of fluid flow. A titanium micropump, as illustrated in Fig. 2e, measuring 20 mm in diameter and 1.5 mm in height, was demonstrated to be able to pump water with a flow rate of up to 14.2 ± 2.5 mL min^{-1}.[59] Piezoelectric micropumps demonstrate rapid response times, enabling swift adjustments to flow rates. This responsiveness is particularly advantageous for applications that necessitate dynamic control or the ability to promptly adapt to changing physiological conditions. Pumping resolution is a crucial parameter for achieving long-term drug delivery with minimized dosing. A nanoliter-resolution implantable micropump was developed for drug delivery to the murine inner ear, as depicted in Fig. 2f.[60] This micropump uses cyclic phase-change actuation of three chambers to compress sub-millimeter catheter microtubing and drive peristalsis. Controlled by resistive heaters, the phase change material (paraffin wax) undergoes sequential melting and solidification, enabling controlled expansion and shrinking for sequential compression of the deformable microtubing at three locations to induce directional flow. This peristaltic micropump achieves a resolution of 2.39 nL min^{-1}, with flow rates ranging from 10–100 nL min^{-1}.

Pressure variations can present challenges to the flow accuracy of micropumps, including miniaturized ones. Ensuring a controllable, consistent, and reliable flow rate is critical for numerous *in vivo* applications of micropumps. Passive flow regulators can help mitigate the impact of pressure variations on the flow accuracy of pressure-driven fluidic systems.[61] An implantable and ambulatory infusion pump with a 3-stack MEMS-based passive flow regulator was designed for stable infusion, as illustrated in Fig. 2g. This triple-stack structure, composed of silicon and borosilicate, incorporates valves arranged in parallel.[62] Flow regulation is achieved through the deflection of a silicon membrane that gradually obstructs the valves as the reservoir pressure rises. The pressure range of 200–1000 mbar allows for flow regulation, with an overall flow rate variability of ±10%. By integrating this flow regulating chip with an implantable pump system, consisting of a titanium housing and a propellant-pressurized drug reservoir, a constant water flow rate of 1 ml h^{-1} and 1 ml day^{-1}, respectively, was attained within the pressure range of 500 ± 300 mbar.

Micropumps usually necessitate an electrical power source, often relying on batteries, to provide relatively high voltages. The integration and management of the power supply can introduce complexity to the overall system design and maintenance. A method of micropumping utilizing acoustically excited oscillating microbubbles eliminates the need for on-board powering, as depicted in Fig. 2h.[63] This pumping method utilizes the cavitational microstreaming flow generated by oscillating bubbles, enabling a flow rate of approximately 36 μL min^{-1}. This pumping principle eliminates the need for mechanically moving parts or intricate wiring for signal and power inputs. To initiate pumping, acoustic waves from an external acoustic transducer (including widely used ultrasonic transducers for ultrasound imaging) can be wirelessly applied to the desired *in vivo* locations. Magnetic micropumps are another common type of microfluidic pumping device that can be activated wirelessly using an external magnetic field.[64,65] An implantable magnetic microfluidic pump was developed for *in vivo* bone remodeling, as depicted in Fig. 2i.[66] The microfluidic pump, measuring 22 mm in diameter and 5 mm in thickness, incorporates NdFeB magnets, enabling wireless remote operation and pressurization of the pump chamber with approximately 102 mmHg static pressure elevation. In addition to this pump, capillary action, also known as capillary wicking, can be effectively employed to passively direct fluid flow within implantable microfluidic devices, utilizing the inherent tendency of fluids to flow in

narrow channels or porous materials.[67] Thread-based capillary microfluidics can be embedded into tissue for *in vivo* diagnostics, as illustrated in Fig. 2j.[68] The wicking property of conductive cotton threads infused with nanomaterials was utilized to passively transport fluid at a flow rate of approximately 10.6 μL min^{-1}. Leveraging capillary action for fluid manipulation in implantable microfluidics offers several advantages, including low power consumption and miniaturization.

2.2 Device fabrication

Implantable microfluidic devices are commonly fabricated using specialized techniques that provide meticulous control over the device's structure, dimensions, and materials. Soft lithography, for instance, is frequently employed to achieve high-resolution definition of microfluidic channel patterns.[69] A customized Polydimethylsiloxane (PDMS) thin-film transfer process based on soft lithography facilitates the integration of microfluidic channels onto silicon microprobes, as illustrated in Fig. 3a.[70] The process involves two steps of time-controlled deep reactive-ion etching to create a silicon mould with two different depths. This mould enables the transfer of free-standing ultra-thin PDMS channels in a single step. A layer of PDMS thin-film, containing channels, is cured against the silicon mold with varying depths. It is then directly transferred to the SiO_2 surface on the back side of the probe through oxygen plasma bonding, resulting in an enclosed channel. The silicon probe serves as the channel's bottom surface, while the PDMS acts as the cover. The fabricated ultra-thin PDMS channels, with a depth of 10 μm, allow for precise local injection of chemical solutions at the nanoliter scale.

Soft lithography alone is not suitable for fabricating microfluidic channels on curved surfaces because achieving high-resolution microscale structures on the curved surface of a mold presents a significant challenge. To address this challenge, as depicted in Fig. 3b, Wu *et al.* utilized a combination of soft lithography and thermoforming techniques. This hybrid approach enabled the fabrication of microfluidic contact lens sensors for continuous monitoring of intraocular pressure.[71] The process employed by Wu *et al.* can be summarized in five steps: soft lithography, substrate silanization, plasma-treated bonding, thermoforming, and liquid injection. Soft lithography is utilized to create the microfluidic channel pattern on a PDMS film, while thermoforming enables the formation of the contact lens's spherical shape. Injection molding is also an effective method for fabricating microfluidic devices with intricate three-dimensional (3D) structures.[72] As depicted in Fig. 3c, the fabrication of the implantable magnetic microfluidic pump involved injection molding of PDMS using a series of stainless-steel molds.[66] 3D microfluidic channels can be fabricated by stacking and bonding multiple layers. As depicted in Fig. 3d, a bio-functionalized microfluidic system based on silk protein hydrogel elastomeric materials was developed with a straightforward multilayer fabrication technique.[73] This approach employed gelatin sacrificial molding and layer-by-layer assembly to construct interconnected 3D microchannel networks within silk hydrogels, achieving a minimum feature resolution of 100 μm. These microfluidic systems based on silk hydrogels open up new possibilities for engineering active diagnostic devices, as well as tissues and organs that can be implanted *in vivo*.

Threads, commonly utilized in the apparel industry, have emerged as promising candidates for the development of 3D microfluidic circuits due to their inherent wicking property and flexibility.[74] Fabricating functional threads for implantable microfluidics involves a distinct process compared to conventional methods such as photolithography, screen-printing, and molding used for PDMS-based microfluidics. Fig. 3e illustrates the fabrication process proposed by Sonkusale *et al.*, which entails sequentially coating the thread with functional inks.[68] The fabrication process involved passing the core cotton threads through a series of wells containing conductive inks in a sequential manner. To solidify the coating layer, a dryer was employed as necessary. This technique enabled the creation of strain and pH sensors that could be embedded into tissue for *in vivo* diagnostics.

The technique of 3D stacking/bonding is commonly employed to achieve highly integrated microfluidic functionalities in fabrication processes.[75,76] As shown in Fig. 3f, a fully implantable optofluidic cuff system is fabricated by alignment assembly of multiple functional layers. Adhesives are used for forming a reliable bonding between adjacent layers.[56] The microfluidic probe of this optofluidic cuff was fabricated by standardized soft lithography and plasma bonding.

2.3 Biosafety considerations and measures

Implantable microfluidic devices necessitate careful attention to biosafety to ensure patient safety and minimize adverse effects. Several strategies have been developed to enhance the biocompatibility and biodegradability of these devices. An essential aspect for achieving optimal biosafety lies in the careful selection of materials used in device fabrication.[77,78] The materials chosen for implantable microfluidic devices should possess non-toxic properties, be non-immunogenic, and exhibit compatibility with the surrounding tissues and bodily fluids. To prevent direct contact between the device and surrounding tissues, the use of encapsulation or barrier layers is recommended. Additionally, thorough biocompatibility testing should be conducted to evaluate the device's impact on host tissues and the immune system. This testing may involve *in vitro* studies using cell cultures as well as *in vivo* studies using appropriate animal models. In the case of the peristaltic micropump shown in Fig. 4a, it was encapsulated with a parylene-C layer approximately 2 μm thick. This encapsulation not only provides a biocompatible moisture barrier but also serves as electrical insulation for the electronics.[60] The biocompatibility of the micropump with the parylene-C coating was confirmed through cell viability assays and subcutaneous implantation in a mouse model.

Implantable microfluidic devices can utilize biodegradable materials, which gradually degrade and are absorbed by the body. The degradation kinetics should be carefully controlled to align with the device lifespan and the healing process.

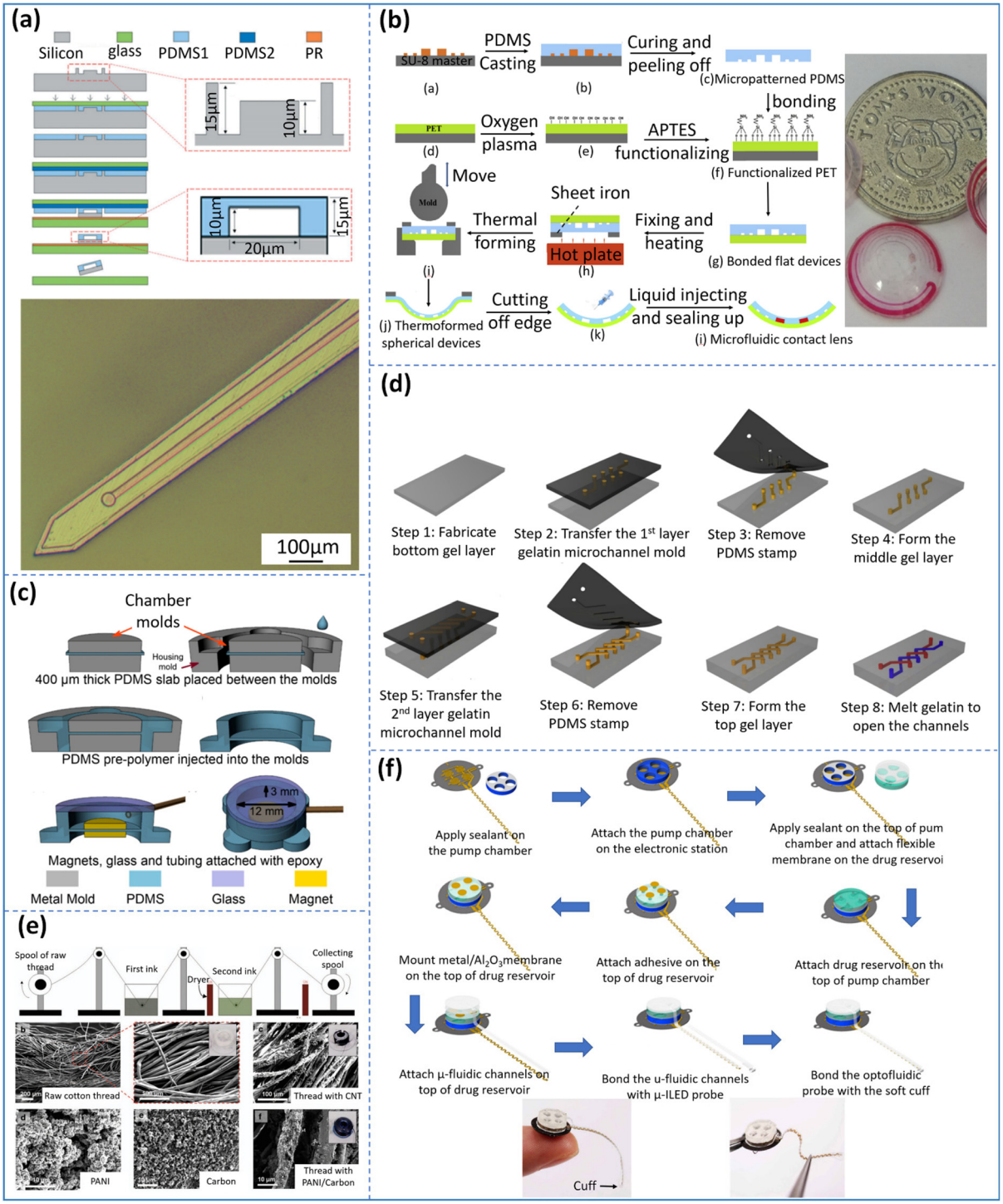

Fig. 3 Various fabrication methods for implantable microfluidic devices. (a) A photolithography-based thin-film transfer process is utilized for microfluidic channel fabrication on an implantable multifunctional neural microprobe. Reproduced from ref. 70 with permission from The Royal Society of Chemistry, copyright 2020. (b) Microfluidic contact lenses for intraocular pressure monitoring are fabricated by combining soft lithography and thermoforming techniques. Reproduced from ref. 71 with permission from Elsevier, copyright 2019. (c) A magnetic microfluidic pump is fabricated using the injection moulding of PDMS. Reproduced from ref. 66 with permission from MDPI, copyright 2020. (d) A two-layer silk hydrogel microfluidics is fabricated through a process involving gelatin moulding and layer-by-layer stacking methods. Reproduced from ref. 73 with permission from Elsevier, copyright 2016. (e) Conductive and hydrophilic functional threads are fabricated using a multi-step coating process. Reproduced from ref. 68 with permission from Springer Nature, copyright 2016. (f) The assembly process of a fully implantable optofluidic cuff system involves the alignment bonding of multiple layers based on a double-sided pressure-sensitive adhesive. Reproduced from ref. 56 with permission from AAAS, copyright 2019.

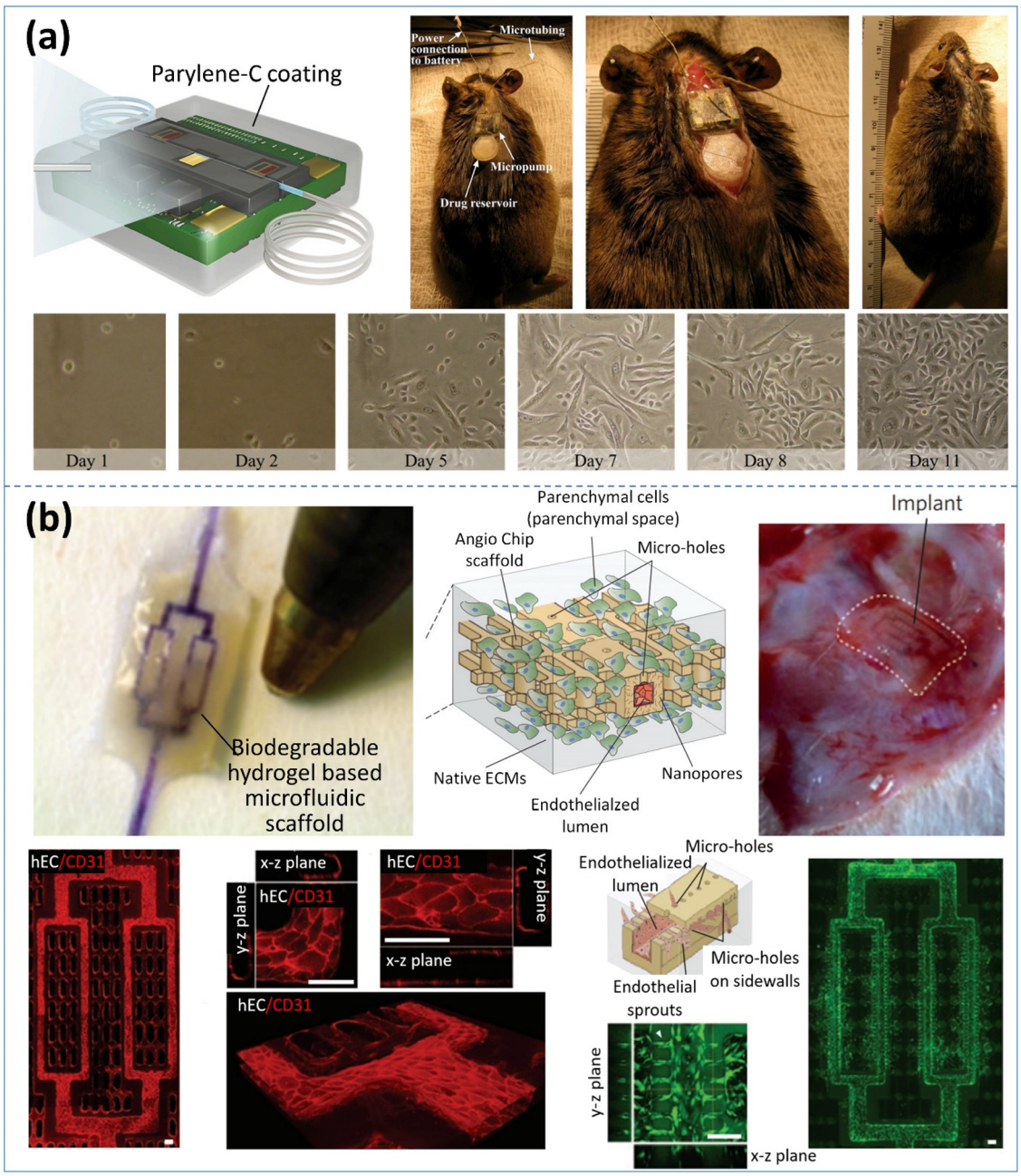

Fig. 4 Strategies for addressing biosafety and compatibility issues of implanted microfluidic devices. (a) A 2 μm-thick layer of parylene-C was coated on the surface of an implantable peristaltic micropump, providing a biocompatible moisture barrier. The biocompatibility was verified through cell viability assays and one month of subcutaneous implantation in a mouse. Reproduced from ref. 60 with permission from Elsevier, copyright 2019. (b) A biodegradable elastomer, poly(octamethylene maleate(anhydride)citrate), was used to construct microfluidic scaffolds for the surgical anastomosis of cardiac tissue. Reproduced from ref. 80 with permission from Springer Nature, copyright 2016.

Biodegradable devices eliminate the need for device removal surgeries, reducing potential complications.[79] As depicted in Fig. 4b, Radisic *et al.* introduced a biodegradable scaffold called AngioChip for organ-on-a-chip engineering and direct surgical anastomosis.[80] The AngioChip scaffolds were fabricated using a biodegradable elastomer called poly(octamethylene maleate(anhydride)citrate) (POMaC). POMaC is UV-polymerizable and undergoes hydrolytic biodegradation, enabling easy assembly under mild conditions. Studies on biodegradation and biocompatibility demonstrated that POMaC polymer discs remained intact *in vivo* for a minimum of 5 weeks.

Except for considering biosafety from the perspective of biocompatibility and biodegradability, immune response and mechanical compatibility should also be assessed.[81] Implantable microfluidic devices can elicit immune reactions

that may affect device performance and patient well-being. Immunological evaluations, such as cytokine profiling and histological analysis, can provide insights into the device's immunomodulatory properties and aid in optimization.[82] Implantable microfluidic devices need to be mechanically compatible with surrounding tissues to minimize damage, irritation, and disruption.[83] Mechanical properties, including flexibility, rigidity, and elasticity, should be carefully considered during device design and material selection to ensure optimal integration and long-term stability.

3. Applications

3.1 Drug delivery

Implantable microfluidic devices offer great potential for targeted drug delivery applications. By utilizing these devices, drug delivery can be localized, reducing systemic exposure and increasing drug concentration at the intended site, resulting in enhanced therapeutic effectiveness.[84] In addition, implantable microfluidic devices enable precise control over drug dosing, allowing for on-demand release and localized delivery. This level of control enhances treatment outcomes and minimizes potential side effects. Various mechanisms can be incorporated for controlled release, including passive diffusion,[85] osmotic pumps,[86] electrokinetic pumps,[87] electrochemical triggers,[53] or stimuli-responsive materials.[88] Implantable microfluidic devices enable sustained drug release over extended periods and on-demand release in response to specific biological cues. This level of control opens up opportunities for personalized medicine, as drug delivery strategies can be tailored to individual patient needs and conditions.[89] Implantable microfluidic devices can be customized to accommodate individual patient needs, including drug dosage, release profiles, and treatment schedules. This personalized approach maximizes therapeutic outcomes by tailoring the device to the specific requirements of the patient. Furthermore, these devices enable combination therapy by delivering multiple drugs or therapeutics simultaneously or in a sequential manner. This capability enhances treatment effectiveness and expands the possibilities for targeted and synergistic therapies.[90] Integrating various drug reservoirs or channels within implantable microfluidic devices enables synergistic effects and the targeting of multiple pathways, leading to enhanced therapeutic efficacy. This approach ensures continuous and reliable drug delivery, especially for long-term treatment regimens.

In recent years, there has been extensive research focused on microfluidics-based implantable drug delivery, particularly within animal models. A wireless optofluidic system, as shown in Fig. 5a, was developed for precise spatiotemporal control of fluid delivery and photostimulation in the deep brain tissue. This system allows for programmable manipulation of fluids and light, enabling targeted effects to be achieved.[52] The effectiveness of these devices in freely moving mice by delivering peptide ligands and antagonist drugs to manipulate mesoaccumbens reward-related behaviour was tested. They discovered that delivering mu-opioids into the ventral tegmental area resulted in stereotypical, repeated rotation behavior. Implantable microfluidic devices have the potential to provide targeted and localized therapy by delivering therapeutic agents directly to specific nerves, allowing for nerve regeneration and neuromodulation. As shown in Fig. 5b, a parylene-cased cuff electrode with integrated microfluidic channels was used for targeted drug delivery to the rat sciatic nerve fascicles.[45]

Microneedles are tiny, needle-like structures that can painlessly penetrate into the tissue. By incorporating microfluidic channels into the microneedles, a continuous flow of drugs or therapeutic agents can be delivered directly to specific locations, such as subcutaneous tissue or blood vessels, bypassing the need for traditional injections. Kang *et al.* developed a microneedle-based flexible 3D neural interface with microfluidic interconnection for direct intracerebral drug injection (Fig. 5c).[91] Their experiments on *in vivo* rat brains showed an increase in neural spikes after injecting a 10 mM KCl solution. Hollow microneedles can be designed to deliver drugs to specific regions or target sites. Fatouros *et al.* fabricated 6 × 6 hollow microneedles with 3D printing for delivery of insulin across human skin.[93] Their study shows that syringe-like hollow microneedles are more suitable for macromolecular drug delivery. These works highlight the potential of microneedle-based implantable microfluidic devices for targeted drug delivery to specific regions. Drug delivery using implantable microfluidic devices not only enables therapy but also offers the possibility of behavior control in insects or animals using specific agents or chemicals. A hybrid implantable microfluidic and electronic system was developed to manipulate insect flight (Fig. 5d), which demonstrates the potential of implantable microfluidics for controlling insect behavior.[92] The microfluidic device was implanted in the dorsal thorax of a Manduca sexta to deliver L-glutamic acid neurotransmitters for flight control. The rapid onset of paralysis, occurring within 5 seconds, demonstrated the fast response of the system. However, it was noted that an overdose of the neurotransmitters led to a temporary 50% reduction in mean flight speed, which was recoverable.

3.2 Diagnostics

Implantable microfluidics has become a crucial technology with profound implications for diagnostics, providing healthcare professionals with valuable information and empowering patients to actively manage their health. By incorporating miniature fluidic systems inside the body, it enables continuous monitoring and analysis of diverse biomarkers and physiological parameters in real time.[94] One notable example is the development of implantable biosensors that continuously monitor glucose levels in individuals with diabetes.[95,96] These devices eliminate the need for frequent blood sampling, providing real-time data on glucose fluctuations and alerting patients to potential hypoglycemic or hyperglycemic episodes. Implantable microfluidic devices also show promise in the

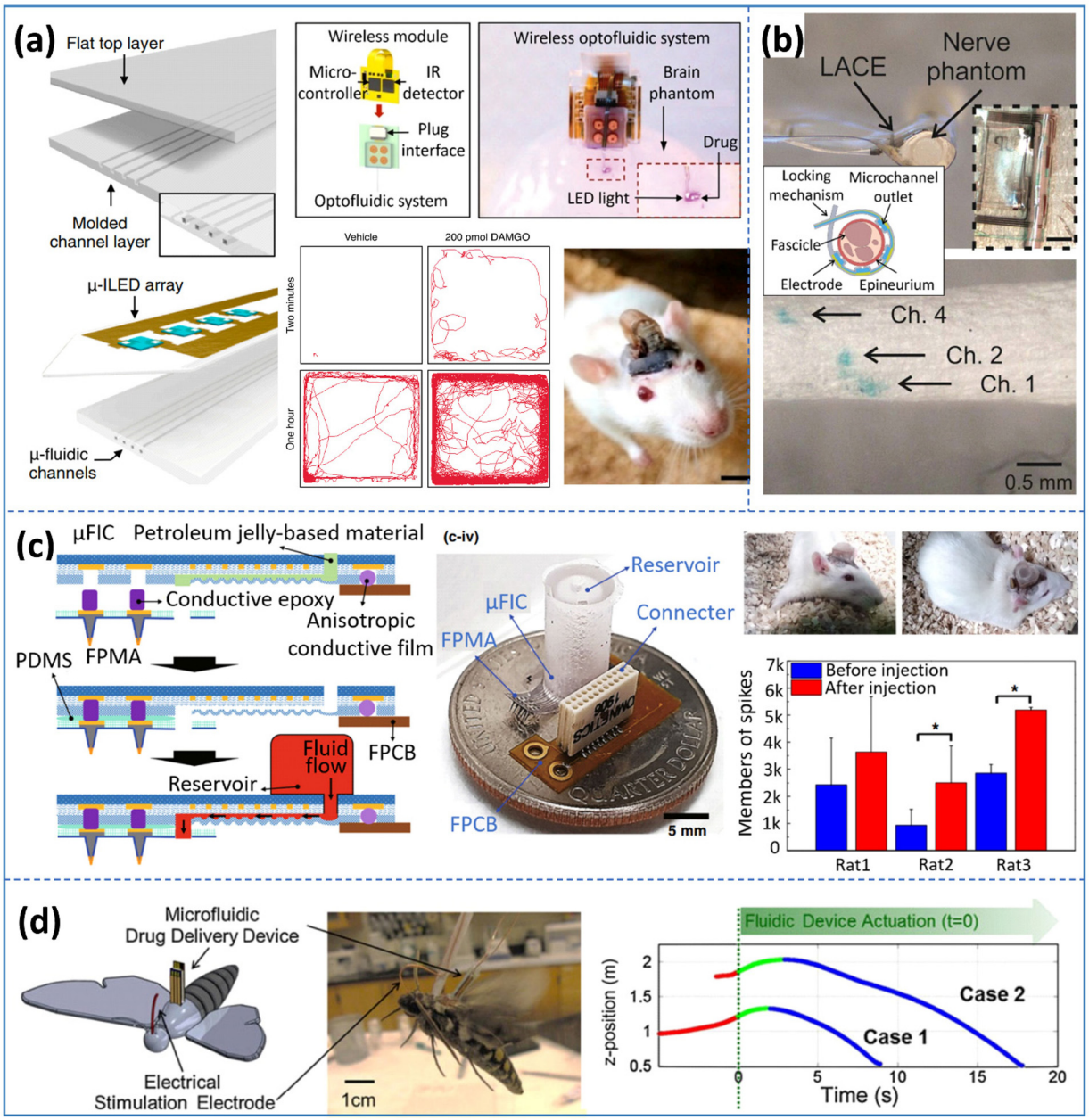

Fig. 5 Application of various implantable microfluidic devices for drug delivery. (a) Wireless optofluidic neural probes with ultrathin and soft microfluidic channels was employed for programmed spatiotemporal control of fluid delivery to discreetly targeted regions of the deep brain for neuroscience research. Reproduced from ref. 52 with permission from Elsevier, copyright 2015. (b) Implantable microfluidic channels integrated with the parylene-based cuff electrode allow for targeted delivery of chemical agents to stimulate specific nerve fascicles. Reproduced from ref. 45 with permission from IEEE, copyright 2019. (c) A microfluidic interconnection cable (μFIC) was integrated with a flexible penetrating microelectrode array to deliver chemicals to the electrodes for combining chemical delivery with electrical recording, as demonstrated by implantation in a rat. Reproduced from ref. 91 with permission from Springer Nature., copyright 2021. (d) A microfluidic chip was utilized to modulate the flight activity of Manduca by combining chemical injection and electrical stimulation. Reproduced from ref. 92 with permission from Springer Verlag, copyright 2012.

early detection of cancer. They can detect circulating tumor cells and specific biomarkers associated with different types of cancer, enabling early diagnosis and timely intervention.[97] Additionally, the integration of microfluidics within the body enables *in vivo* analysis of cellular information and drug metabolism.[98] Implantable microfluidics have the potential to transform diagnostics, allowing continuous monitoring of vital signs, detection of infections, and measurement of drug levels, thereby revolutionizing healthcare.[99]

Monitoring intraocular pressure plays a crucial role in the diagnosis, management, and treatment of various eye conditions, particularly those related to glaucoma. As shown in

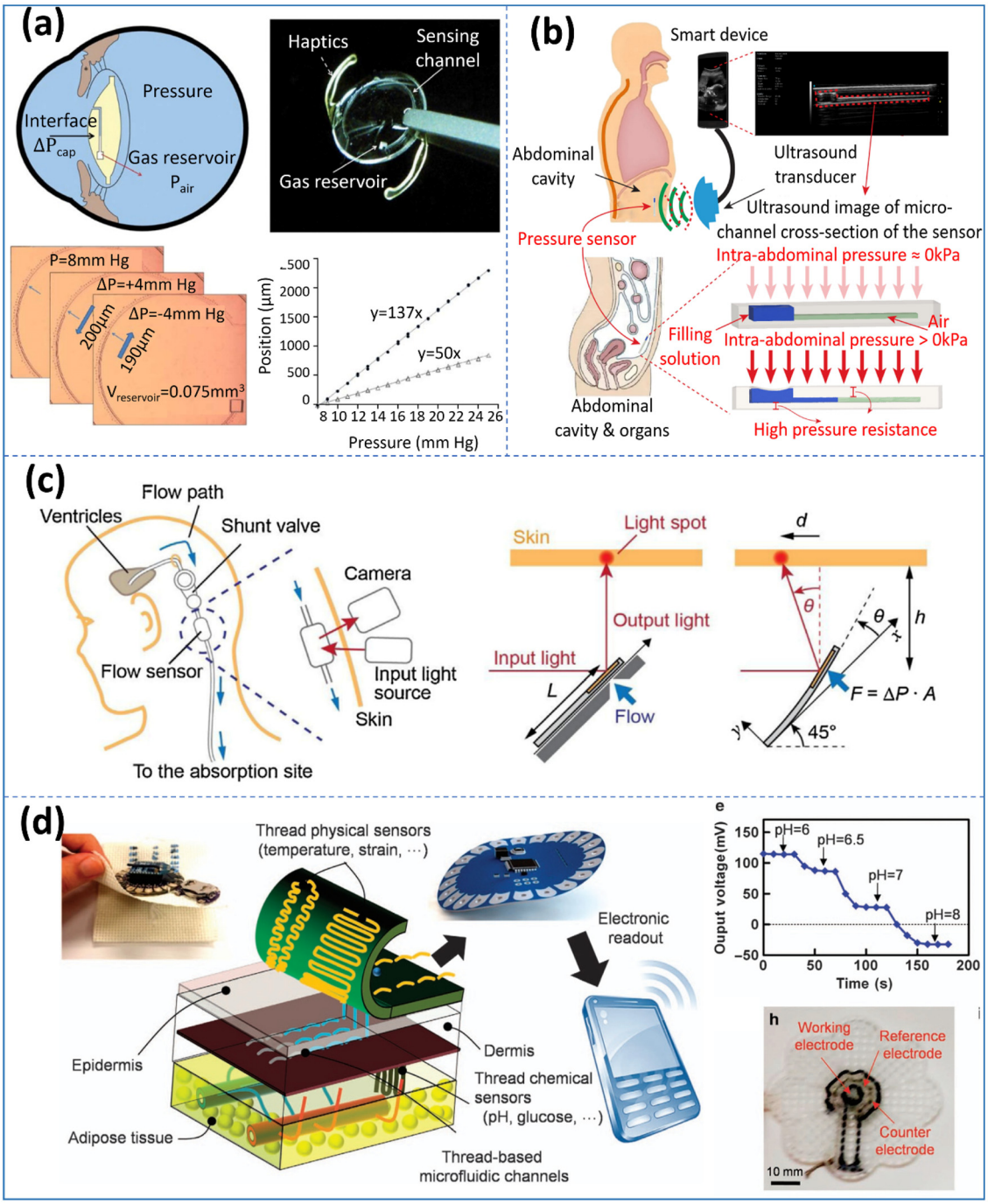

Fig. 6 Application of various implantable microfluidic devices for *in vivo* diagnostics. (a) An implantable microfluidic sensor for measuring intraocular pressure, which provides accurate images of intraocular pressure fluctuations of glaucoma patients over time based on the liquid length in the microchannel. Reproduced from ref. 100 with permission from Springer Nature, copyright 2014. (b) An implantable microfluidic device based wireless passive intra-abdominal pressure sensing *via* ultrasonic imaging. Reproduced from ref. 101 with permission from IEEE, copyright 2021. (c) An implantable cerebrospinal fluid flow sensor enables non-invasive measure of the flow rate and pressure in a cerebrospinal fluid shunt for the diagnosis of blockage in the shunt. Reproduced from ref. 102 with permission from Elsevier, copyright 2021. (d) Thread-based implantable microfluidic channels for sampling with capillary action to measure physiological and chemical parameters such as strain, gastric and subcutaneous pH values, and the data can be transmitted in real-time for analysis through wireless modules. Reproduced from ref. 68 with permission from Springer Nature, copyright 2016.

Fig. 6a, Mandel *et al.* reported an implantable microfluidic device for self-monitoring of intraocular pressure with a detection limit of 1 mm Hg, high sensitivity and excellent reproducibility.[100] The pressure sensing is based on the principle of microfluidic physics, which use a smartphone camera equipped with an optical adaptor and image analysis software

to detect the aqueous–air interface position for intraocular pressure measurement. This implantable microfluidic sensor was tested in pig eyes during conventional cataract extraction surgery. However, it is a great challenge to readout the pressure in deep tissue by a camera. To overcome this issue, Rahimi *et al.* developed an implantable microfluidic pressure sensor, which can be implanted into the abdominal cavity, for wireless passive intra-abdominal pressure sensing *via* ultrasonic imaging. As shown in Fig. 6b, the novel pressure sensing microfluidic system consists of sub-mm scale reservoir connected to micro-channel, where the reservoir is filled with water and covered by a thin and pressure sensitive PDMS membrane.[101] Increase in external pressure leads to deflection of the pressure sensitive membrane and pushes the water from the reservoir into the microchannel, and the fluid displacement in the microchannel can be quantified using simple ultrasound imaging. The sensor presented a highly linear slope of 42 kPa mm^{-1} and a spatial resolution of 1.2 kPa per 30 μm in the physiological range of abdominal compartment syndrome. Flow sensing allows continuous monitoring of the cerebral spinal fluid flow within the shunt. This monitoring is essential to ensure the shunt is functioning properly, preventing complications due to overdrainage or underdrainage. Hoshino *et al.* developed an implantable microfluidic flow sensor that can be implanted into the brain ventricle to assess flows in a cerebral spinal fluid shunt. As shown in Fig. 6c, the sensing device is designed to be implanted in the flow path of the cerebral spinal fluid shunt, directly below the valve.[102] A light is input onto the patient's skin directly above the implanted optical system which is several millimeters below the surface of the skin. The position of the reflected light spot on the surface of the skin corresponds to the flow rate over the sensor, which is monitored by an external camera. It is a great advantage for an implantable device to be monitored passively without the need to implant additional active electrical components.

Except for implantable microfluidic physical sensors, implantable microfluidic biochemical sensing is also crucial for many *in vivo* diagnosis. As shown in Fig. 6d, thread-based microfluidics was used for engineering chemical sensors that can be embedded into the tissue beneath the skin.[68] Hydrophilic threads were embroidered onto a highly hydrophobic woven fabric to serve as microfluidic channels for the controlled delivery of bodily fluids to the sensing zones. Conductive threads infused with functional nanomaterials were used as electrodes for the *in vivo* measurement of glucose and pH. Their sensors showed a rapid response time (~30 s) for pH measurement. Hollow microneedles with microfluidic channels have the potential to be utilized in glucose measurement and monitoring for individuals with diabetes. These microneedles enable the extraction of interstitial fluid with glucose from the epidermis into the sensor chamber of continuous glucose monitoring systems.[103] Compared to porous microneedles, hollow microneedles allow for sufficient extraction of interstitial fluid or blood without limitations posed by diffusion.[104]

3.3 Tissue engineering

Implantable microfluidics plays a vital role in tissue engineering and regenerative medicine, revolutionizing the field and offering promising solutions for tissue repair and regeneration.[105,106] These microscale devices provide precise control over the delivery of nutrients, growth factors, and cells, creating optimal microenvironments for tissue development. For instance, researchers have successfully utilized implantable microfluidic scaffolds to guide the growth of vascular networks within engineered tissues, facilitating their survival and integration upon transplantation.[107] Additionally, microfluidic systems have been employed to mimic the complex physiological conditions of tissues, enabling the study of cell behavior and tissue response to various stimuli.[108] This technology also allows for the on-demand release of therapeutic agents, such as stem cells or growth factors, to promote tissue healing and regeneration.[109] By harnessing the power of implantable microfluidics, tissue engineering and regenerative medicine are advancing toward the creation of functional, transplantable tissues and organs, holding tremendous potential for the treatment of injuries, diseases, and organ failure.

The 3D vasculature is of paramount importance in tissue engineering due to its critical role in supporting the development, functionality, and viability of engineered tissues. Cho *et al.* developed an implantable microfluidic device for the formation of 3D vasculature by human endothelial progenitor cells. As shown in Fig. 7a, the microfluidic device was made of biodegradable poly(lactic-*co*-glycolic acid) (PLGA) using a microchannel patterned silicon wafer made by soft lithography.[110] The device totally has nine microchannels with dimensions of 10 mm length, 1 mm width, and 150 μm height. Four channels with small injection ports were prepared for human endothelial progenitor cells (hEPCs) culture using Col I hydrogel and five channels with large injection ports were prepared for the medium supplement. The microfluidic device provides 3D microenvironments for endothelial differentiation of hEPCs and spatial control of vascular network formation, which was tested by the implantation in the subcutaneous space of mice.

Implantable microfluidics can also promote vascularization and tissue repair. As shown in Fig. 7b, Shen *et al.* presented a novel MXene-incorporated hollow fibrous scaffold with dynamically responsive microfluidic channels for promoting vascularization and skin flap regeneration by using a microfluidic-assisted 3D printing strategy.[111] The photothermal conversion capacity of the MXene nanosheets and temperature-responsive ability of poly(NIPAM) hydrogels in the scaffolds enable near-infrared (NIR)-responsive shrinkage/swelling behavior of the scaffolds, which not only facilitates the cell penetration into the scaffold channels from the surrounding environment, but also allows for controllable delivery of vascular endothelial growth factor to promoted proliferation, migration, and proangiogenic effects of endothelial cells. *In vivo* tests based on the implantation of the scaffold into the flap skin of mice show that their hollow scaffolds with microchannels can effectively

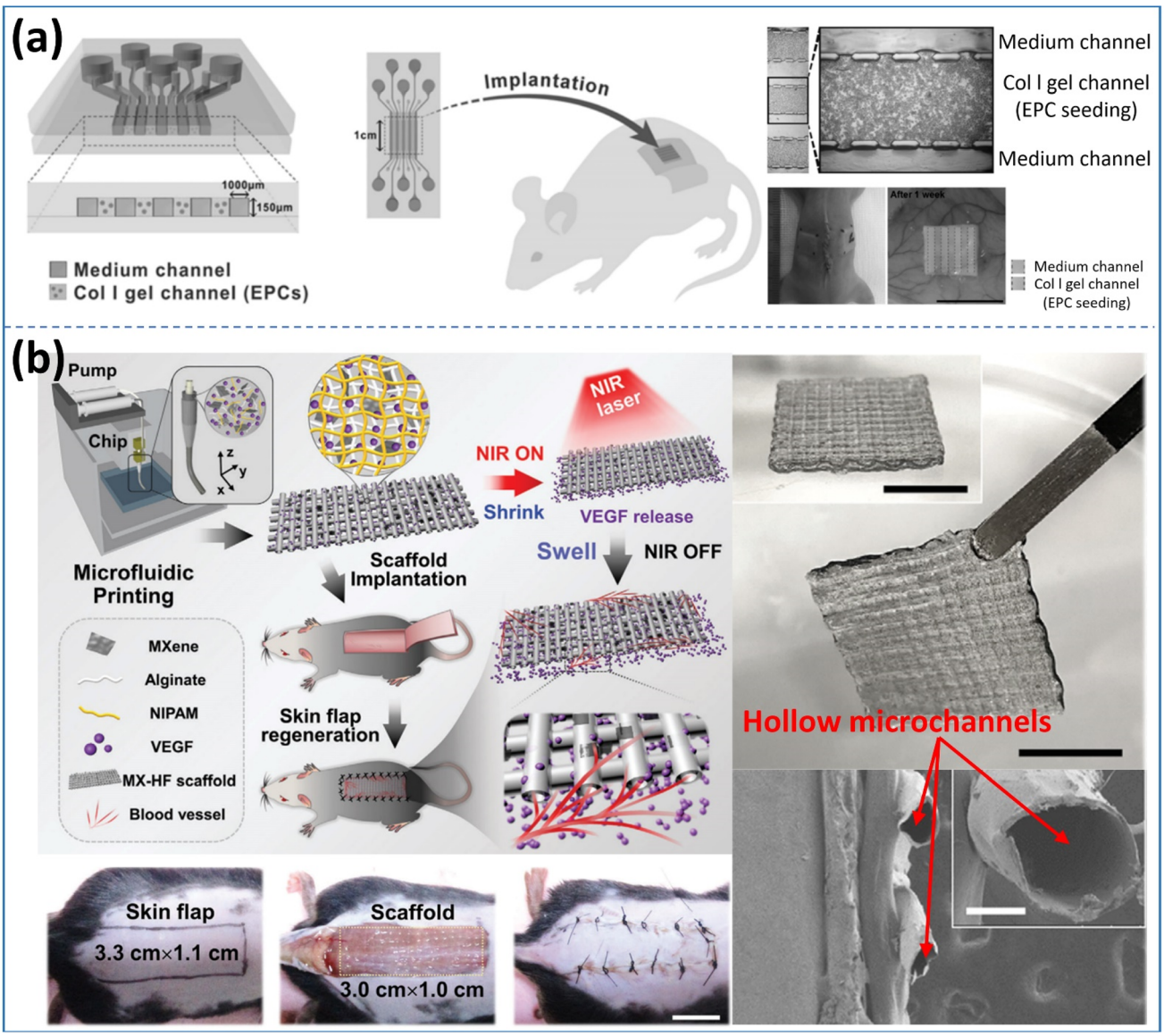

Fig. 7 Application of implantable microfluidic devices in regenerative medicine or tissue engineering. (a) An implantable microfluidic device for serving as a biologically functional scaffold to enhance vasculogenesis mediated by stem or progenitor cells. The device is made of biodegradable PLGA. Reproduced from ref. 110 with permission from Springer Nature, copyright 2014. (b) A dynamically responsive scaffold with hollow microchannels for skin flap regeneration, which can promote vascularization and tissue repair in skin flap regeneration. Reproduced from ref. 111 with permission from Wiley-VCH, copyright 2022.

improve skin flap survival by promoting angiogenesis, decreasing inflammation, and attenuating apoptosis in skin flap.

3.4 Energy harvesting

Implantable microfluidics has emerged as a significant technology for energy harvesting and as a power source in various applications.[112] These microscale devices have the potential to harness and convert energy from biological or environmental sources, providing sustainable power for implantable medical devices. For instance, implantable microfluidic systems can harvest energy from biological fluids such as blood flow or cerebrospinal fluid, converting the mechanical or chemical energy into electrical energy to power implanted sensors or therapeutic devices.[113,114] The ability to harvest energy and serve as a power source within the human body or in surrounding environments offers great potential for the development of long-lasting and autonomous implantable devices, reducing the need for frequent battery replacements or external power sources.[115]

While implantable microfluidic devices as energy harvesters or power sources are not yet widely implemented, there is immense potential for their future integration. Ongoing research and technological advancements are paving the way for the development of implantable microfluidic systems

capable of harvesting energy from biological or ambient sources within the body. As shown in Fig. 8a, Krupenkin and Taylor presented a high-power energy harvesting approach based on reverse electrowetting.[116] Electrical energy generation is achieved through the interaction of arrays of moving microscopic liquid droplets with nanometer-thick multilayer dielectric films, which has high power densities up to 10^3 W m^{-2}. This approach uniquely suited for high-power energy harvesting within the body to power implantable electrical stimulators or sensors. Except for harvesting mechanical energy, microfluidics can also be engineered as a chemical power source. As shown in Fig. 8b, Liu *et al.* presented a membraneless micro-

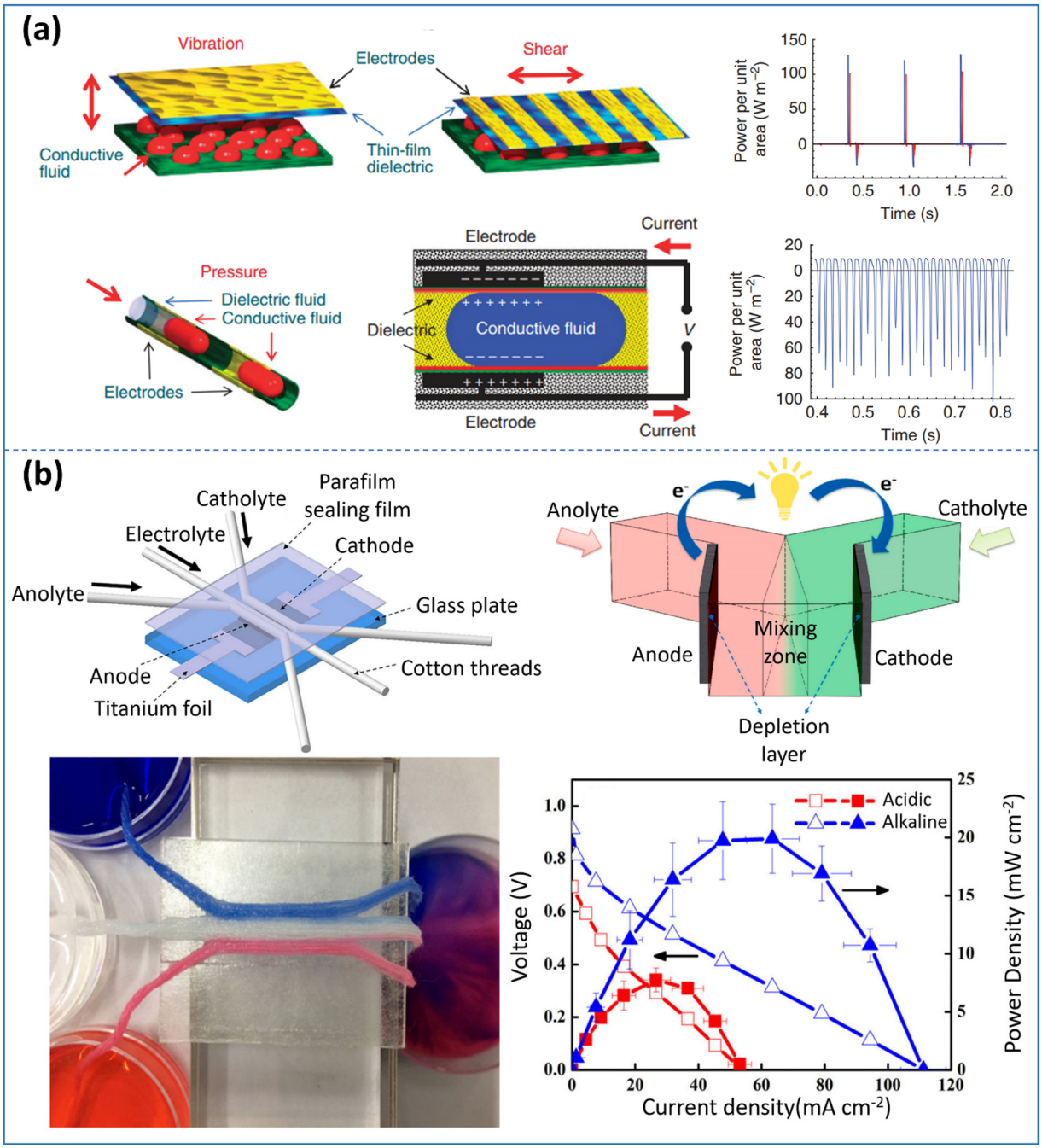

Fig. 8 Microfluidics based energy conversion or harvesting. (a) A "mechanical-to-electrical energy conversion technology" utilizes the microfluidic phenomenon of "reverse electrowetting" between microscopic liquid droplets and multilayer thin films to generate electricity. Reproduced from ref. 117 with permission from Springer Nature, copyright 2011. (b) A membraneless microfluidic fuel cell with continuous multistream flow through cotton threads. This microfluidic fuel cell achieved a peak power density of 19.9 mW cm^{-2} and a limiting current density of 111.2 mA cm^{-2}. Reproduced from ref. 117 with permission from Elsevier, copyright 2021 and reproduced from ref. 118 with permission from Wiley-VCH, copyright 2019.

fluidic fuel cell based on cotton threads. The anolyte and catholyte of the microfluidic fuel cell are driven by capillary action of cotton threads without any external pumps.[117,118] The results show that the middle stream could separate other two streams effectively to prevent the diffusive mixing of anolyte and catholyte. A peak power density of 19.9 mW cm^{-2} and a limiting current density of 111.2 mA cm^{-2} are delivered, which provides a new direction for miniature power sources for potential implantable applications.

As these technologies described above continue to evolve, we can anticipate exciting possibilities for self-sustaining implantable devices, reducing the reliance on external power supplies and enhancing their long-term functionality. With further advancements and exploration, implantable microfluidic devices as energy harvesters or power sources hold great promise for the future of medical implants and other applications.

4. Conclusions and perspective

Implantable microfluidics has emerged as a promising field that integrates microfluidic functionalities into implantable devices, enabling personalized and precise diagnostics, targeted drug delivery, and tissue or organ regeneration. Significant progress has been made in both the methods and applications of implantable microfluidics. Advancements in fluid manipulation techniques, such as external pressure-driven pumps, electrokinetics, thermal expansion, electrochemical pumping, and miniaturized pumps, have enabled precise control and manipulation of fluids within implantable devices. Fabrication techniques, such as soft lithography, thermoforming, and injection molding, allow for the production of more integrated and miniaturized microfluidic devices. When it comes to biosafety, careful material selection is required for implantable microfluidic devices to achieve biocompatibility and biodegradability. Encapsulation or barrier layers can be employed to prevent direct contact between hazardous device components and surrounding tissues.

In terms of applications, implantable microfluidics has proven instrumental in drug delivery, diagnostics, tissue engineering, and energy harvesting. By incorporating microfluidic systems or components into implantable devices, precise control of drug release and dosage has been achieved, resulting in reduced systemic side effects and improved therapeutic outcomes. The use of miniaturized microfluidic sensors enables real-time monitoring of health conditions, facilitating early detection of abnormalities and enabling timely interventions. Moreover, implantable microfluidics plays a vital role in tissue engineering and the development of artificial organs, where controlled fluid dynamics are critical for device functionality.

It is desirable for implantable microfluidic devices to be small, biocompatible, and capable of reliable long-term functionality within the body without complications. In spite of extensive research endeavours pushing the advancement of diverse implantable microfluidic devices toward clinical application, biocompatibility, long-term reliability, power supply, and miniaturization persist as substantial challenges necessitating continual and innovative technological inputs. Hence, there have been very few commercially available products of implantable microfluidic devices, with only a handful of implantable micropumps for drug delivery currently existing in the market. Commercial implantable micropumps include the ALZET Pumps and iPRECIO pumps from ALZET Osmotic Pumps (Cupertino, CA, USA), Synchro Med II from Medtronic (Minneapolis, MN, USA), Prometra® II from Flowonix (Mount Olive, NJ, USA), IP 2000 V from Tricumed (Kiel, Germany), and MIP 2007 from Medtronic MiniMed Inc. (Northridge, CA, USA). ALZET pumps are small and single-use implantable micropumps that work based on the passive osmotic pressure, allowing for precise and predictable drug delivery with a duration up to 6 weeks. Other large-size micropumps with integrated battery are capable of drug delivery with wireless programmable dosing protocols and durations up to several years. The limited availability of implantable microfluidic devices in the market is not only due to the complex nature of their development but also due to the stringent regulatory requirements in the medical field. The regulatory approval process for implantable medical devices involves rigorous testing and evaluation to ensure safety and efficacy. Manufacturers must adhere to strict standards set by health authorities, such as the Food and Drug Administration in the United States or the European Medicines Agency in Europe. Complying with these regulations requires extensive research, clinical trials, and data analysis, which further results in the limited number of available products.

Looking ahead, ongoing interdisciplinary research and development efforts are necessary to overcome these challenges and fully unlock the potential of implantable microfluidics. Regarding biocompatibility, beyond the passive utilization of biocompatible materials to avert adverse reactions or immune responses, it is imperative to explore materials capable of actively releasing drugs to ameliorate inflammation and promote tissue healing. Fabricating implantable microfluidic devices using biocompatible soft materials to minimize the modulus of elasticity mismatch between the devices and soft living tissue is crucial in suppressing inflammation. Additionally, the implementation of antifouling measures on the surfaces of implantable microfluidic devices holds promise for enhancing their long-term reliability by mitigating the accumulation of biological substances or biofilms, thereby preserving functionality and minimizing the risk of microfluidic channel clogging. Moreover, the realization of prolonged power supply and further miniaturization for implantable microfluidic devices could be achieved through the integration of wearable electronics with these devices. Wireless energy transmission from the wearable electronics to the implantable device *via* biocompatible waves facilitates on-demand activation or control of the implantable device, enabling diverse applications such as diagnostics and drug delivery. Advancements in materials and technology, along with colla-

borative efforts between researchers, clinicians, and regulatory authorities, are essential to overcome numerous barriers and bring these transformative devices closer to clinical use. We firmly believe that an increasing number of implantable microfluidic devices, particularly those for continuous *in vivo* monitoring and localized drug delivery, will thrive in the market over the next two decades.

Author contributions

T. L., L. Z., D. C., C. Z., S. L., C. J., Y. X., D. D. and W. Z. jointly wrote this review article.

Conflicts of interest

There are no conflicts to declare.

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