

Advanced Materials for Implantable Neuroelectronics

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Guest Editors

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Abstract

Materials innovation has played arguably one of the most important roles in the development of implantable neuroelectronics. Such technologies explore biocompatible working systems for reading, triggering, and manipulating neural signals for neuroscience research and provide the additional potential to develop devices for medical diagnostics and/or treatment. The past decade has witnessed a golden era in neuroelectronic materials research. For example, research and development on soft material-based devices have exploded and taken center stage for many applications, including both central and peripheral nerve interfaces. Recent developments have also witnessed the emergence of biodegradable and multifunctional devices. In this article, we aim to overview recent advances in implantable neuroelectronics with an emphasis on chronic biocompatibility, biodegradability, and multifunctionality. In addition to highlighting fundamental materials innovations, we also discuss important challenges and future opportunities.

Introduction

The dynamics of the nervous system control our feelings and activities. Implantable neuroelectronics serve as one of the most important means for reading, triggering, and manipulating precise neural signals. Motivated by the possibility of understanding and intervening in the nervous system, myriad neuroelectronic implants have been developed. [1, 2] Compared to other electronic applications, neuroelectronics arguably enjoy the most diversity owing to the rich space in neurobiology. The presence of neuroelectronic diversity originates from each individual need and highlights their very significance.

Considering different anatomy, neuroelectronics can be divided into central nervous system (brain, spinal cord) and peripheral nervous system devices. Indeed, various brain probes, spinal cord stimulation electrodes, and nerve cuff electrodes have been developed for interfacing with the neurons and nerves close to tissue device interfaces. Depending on their position with respect to the interfacing organs, neuroelectronic implants usually fall into two categories: surface-type devices and penetration probes. Surface-type devices typically interface with superficial cells from the organ surface, whereas penetration probes are inserted into the organ and can deeply interact with cells. Based on the application purposes, neuroelectronics can also be divided into neuroscience tools and devices for medical diagnostics and/or treatment. Neuroscience tools such as the Neuropixels probes have been used to reveal neuronal circuit functions and relationships between signal dynamics and behaviors, and more generally, to answer basic neuroscience questions. Understanding the neurotransmission mechanisms also has paved the way for the development of diagnoses and treatments for brain-related diseases. For example, stereoelectroencephalography with depth electrodes has been used as a minimally invasive

approach for localizing seizures and guiding epilepsy surgeries. Deep brain stimulation with deep brain leads has been demonstrated as an effective method for treating Parkinson's disease and epilepsy.

In general, different neuroelectronic applications have specific requirements for their underlying materials; nevertheless, they share one common, basic property – being able to provide an appropriate host response in the specific application. This is commonly and loosely referred to as "biocompatibility." An ideal neuroelectronic implant must operate safely in vivo and (most essentially) be biocompatible. The construction materials in direct contact with the neural tissues should not have any toxic or injurious effects. Any mechanical mismatches between the implants and soft tissues can cause tissue irritation and damage. These aspects have motivated the development of various soft neuroelectronics, such as those using organic and carbon materials.[3] However, many challenges remain to long-term stable electrical performance and chronic biocompatibility. To date, true chronic biocompatibility enabling high-fidelity operation has not been achieved for neuroelectronics; it remains an active pursuit of current research. From a perspective of device functionality, neuroelectronics need electrical conductors to conduct bioelectricity and electrical insulators to support those conductors for the essential electronic functions. Traditional conductor materials include metals (gold, titanium, platinum) and silicon (Si). In recent years, conductive polymers and carbon-based materials have been extensively investigated owing to their flexibility and electrochemical stability. The insulators, as the diffusion barriers, should guarantee the stable and reliable working operation of the device under physiological conditions. The materials must simultaneously exhibit inertness, hermeticity, and compatibility with the manufacturing of neuroelectronic

devices. Common insulation materials include Si, Polyimide, Parylene C, and polydimethylsiloxane (PDMS); most of these are polymers.[4] Aside from the most basic electrical functions, additional materials are also often required from a bio-interfacing perspective, for example, for low impedance (for single-neuron recording), high charge capacities (for stimulation), electrochemical stability (for the chemical sensing of neurotransmitters), and resistance to biofouling.

Generally speaking, some of the most challenging aspects of neuroelectronic research lie in scaling up toward larger throughput and in device engineering toward chronic biocompatibility (**Figure 1**). Recent developments in neuroelectronics have also led to more advanced performance features, such as device biodegradability and multifunctionality.[5, 6] Correspondingly, different materials are being utilized and developed. Neural implants constructed with biodegradable materials are being developed for applications where only short-term functionality is necessary. Simultaneously, device multifunctionalities are being driven by the pull to integrate the advantages from different modalities (such as electrical recording, optogenetic stimulation, and chemical sensing), aiming to provide new insights into the functions of neural circuits and unprecedented interfacing capabilities.

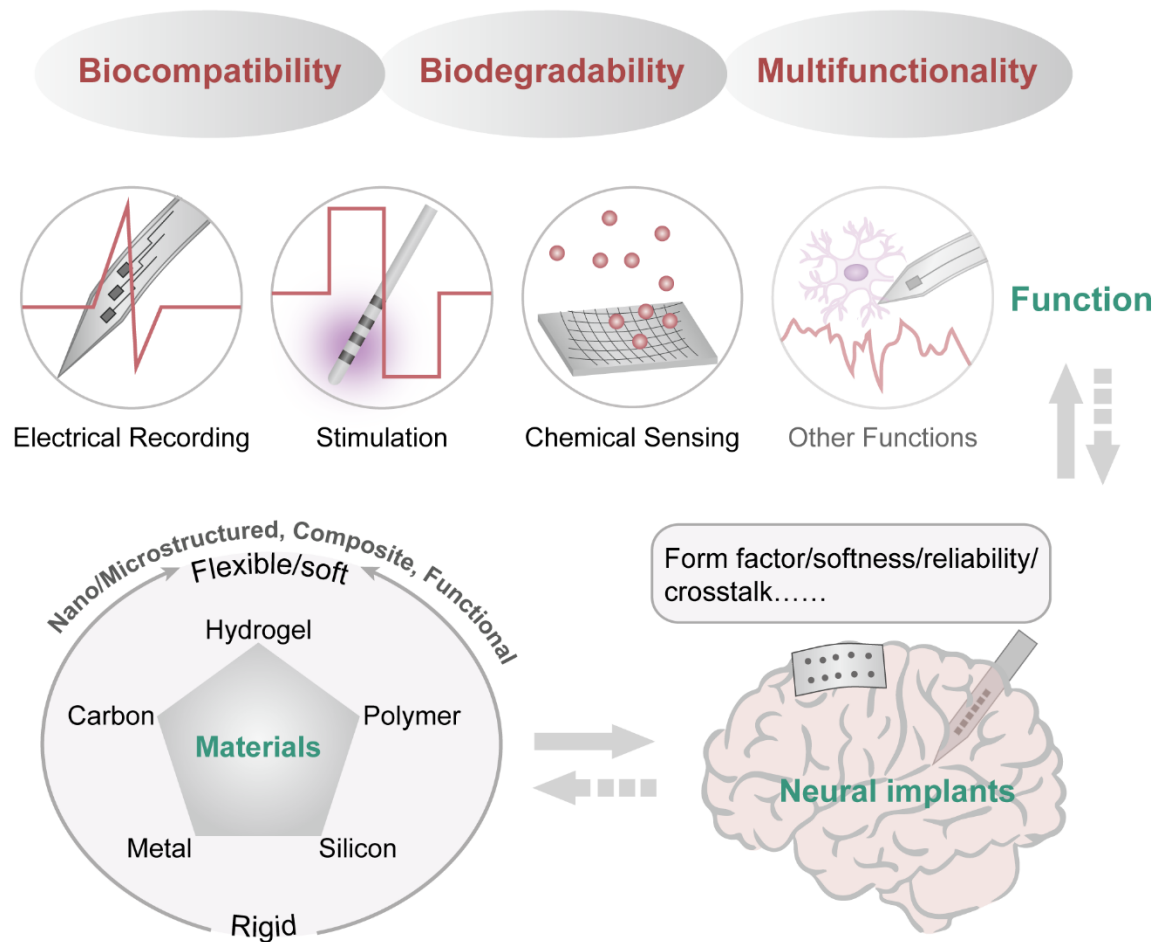


Figure 1. Interplay of materials, devices, and functions in emerging implantable neuroelectronics.

This issue of MRS Bulletin introduces recent development in advanced materials for implantable neuroelectronics and comprises five outstanding articles. The article by Ying Fang et al. is an overview of the development of implantable neural probe technologies as enabled by advanced materials and processing strategies. Neural probes allowing for large-scale and long-lasting neural activity recording are highlighted and probes combining electrophysiological recording with modulation functionalities are described. Lacour et al. highlights recent progress in hydrogel materials and the associated technologies for the design of implantable bioelectronics. Owing to their biomimetic properties related to

biological tissues, soft hydrogels have been developed to be integrated into (or to form) implantable neural interfaces and offer long-term bio-integrated neurotechnologies. This article comprises a brief review of the essential structural, mechanical, and electrical properties of hydrogels and composite hydrogels and presents the manufacturing methods suitable for these multi-scale materials. Meanwhile, to improve the information transfer between neural tissues and electronic devices, a comprehensive understanding of the biological activities around the neural electrode is critical. The article by Cui et al. provides an overview of in vivo fluorescence microscopy systems and imaging configurations for studying neural electronic interfaces. The recent findings in biological mechanisms learned from using these advanced optical imaging modalities are also described. Notably, devices inserted for diagnosis and treatment can become a source of infection or another risk factor for mechanical damage; this has driven the emergence of transient neuroelectronics. The development of biodegradable materials for transient neuroelectronics is introduced in the article from Koo et al. The hydrolysis mechanisms of the candidate electrode materials and their neuroelectronics properties are described. In addition, the article reviews the challenges to and strategies for improving the programmed stability of the electrodes and recent applications using biodegradable neuroelectronic devices. Ultimately, researchers will seek to apply the advances in implantable neuroelectronics to advance medicine. In this context, the article by Dayeh et al. summarizes the state-of-the-art electrode array systems in the context of translation for use in humans. The article discusses the effects of electrode scaling for recording and stimulation, recent efforts in the connectorization and packaging of high channel-count electrode arrays, and wireless monitoring systems. In this introductory article, we provide a brief overview of these articles and highlight the aspects

of chronic biocompatibility, biodegradability, and multifunctionality in emerging neuroelectronics.

Materials strategies toward chronic biocompatibility

A fundamental design objective for implantable neural interfaces is the maintenance of long-term functioning in vivo. The most prevalent of these obstacles can be collectively summarized as a sustained foreign body response (FBR) to the implant. An FBR degrades the efficacy of the interface over time. In addition, severe and/or prolonged FBR can also be harmful to the body. The FBR has motivated a vast body of research focused on developing electrodes and implant strategies to address specific elements of the FBR or limit its effects on device performance, with distinct approaches offering discrete improvements.

In the past decade, numerous studies have been undertaken to facilitate chronic use of neural interfaces. In this context, materials degradations such as metal corrosion can hamper signal delivery and potentially cause a toxic response. Tungsten microwires have been demonstrated to corrode in the brain with a corrosion rate of 100 $\mu\text{m}/\text{year}$, leading to a degradation in the signal quality.[7] Chemically stable transition metals such as gold, platinum, iridium, and various alloys are commonly adopted to enhance the corrosion resistance of implants. The implantation of neuroelectronics will also damage the tissue and induce acute and chronic FBR, causing the body to construct a glial scar around the neural interface. This will lead to signal attenuation and electrode failure owing to the degradation of the implant performance over time. In addition to the tissue damage upon implantation, a mechanical mismatch between the rigid device and soft tissue can also cause excessive glial scarring over time. The glial encapsulation surrounding the electrodes

blocks the charge transfer and becomes a communication barrier between the neural probe and adjacent neurons. Therefore, to ensure that the neural implant interface can communicate effectively with the neurons, the FBR response must be minimized. Correspondingly, efforts have gone toward the miniaturization of probes, developing organic flexible/soft neuroelectronics, and integrating polymer/hydrogel coatings and bioactive materials to enhance chronic biocompatibility.

The device form factor is an important issue for the chronic tissue response. It has been shown that reducing the device size can minimize the trauma of insertion and reduce the severity of the glial scar in chronic implants. In one study, Si-based neural probes at a cellular scale ($5\text{ }\mu\text{m} \times 10\text{ }\mu\text{m}$ cross-section) were inserted into superficial or deep brain structures and recorded large spikes in freely behaving rats for seven weeks.[8] Neuropixels probes with dense recording sites and a $70\text{ }\mu\text{m} \times 20\text{ }\mu\text{m}$ cross-section have been demonstrated to work for two months in rat brains without degradation of the spiking activity.[9] The small cross-sectional area facilitates minimizing the brain tissue damage. With a feature size smaller than $10\text{ }\mu\text{m}$, the implants often show diminished glial encapsulation.[10] Indeed carbon fiber electrodes (length of $10\text{ }\mu\text{m}$ and diameter of $6.8\text{ }\mu\text{m}$) can maintain high recording yields for over two months in vivo.[11] Overall, device miniaturization can provide benefits while avoiding substantial tissue damage and scar formation; thus, it enhances the operational stability.

In addition to reducing the size of the implants, soft implants have attracted increasing interest mainly as alternatives for overcoming the mechanical mismatches between rigid device materials and soft neural tissues. Traditional rigid neural implants made of metal and Si have moduli and bending stiffnesses orders of magnitude higher than those of soft

tissues. These can lead to tissue damage and loss of signal fidelity over the lifetime of the implant. Flexible neural implantable systems constructed on plastic substrates (e.g., Polyimide, Parylene C) can reduce chronic FBR and provide intimate interfaces with soft neural tissues, thereby enabling stable measurements of neural signals. As an example, recently developed flexible electrode arrays with a total device thickness of 1 μm have provided months-long stable electrophysiological recording (**Figure 2a,b**).^[12] Materials in even softer electrodes most commonly rely on polymers such as PDMS and hydrogels. The electronic dura matter developed by Lacour et al. ^[13] demonstrated long-term (6 weeks) biocompatibility in soft neural implants by employing PDMS as the substrate and encapsulation layer and a platinum-silicone composite as the soft electrodes (**Figure 2c,d**). Soft neural implants constructed using hydrogel-based conductors (ionically conductive alginate matrixes enhanced with carbon nanomaterials) and outer encapsulation layers can overcome the limitations in matching with soft biological tissues and intimately conform to the convoluted surface of the brain cortex (**Figure 2d,f**).^[14] Nevertheless, the device insertion of penetrating neuroelectronics becomes challenging when they are soft. Advanced insertion approaches are still being developed, with significant progress in strategies such as temporary stiffening (e.g., through soluble polymer coating) or leveraging shuttles (e.g., through a rigid microwire) to facilitate implantation.

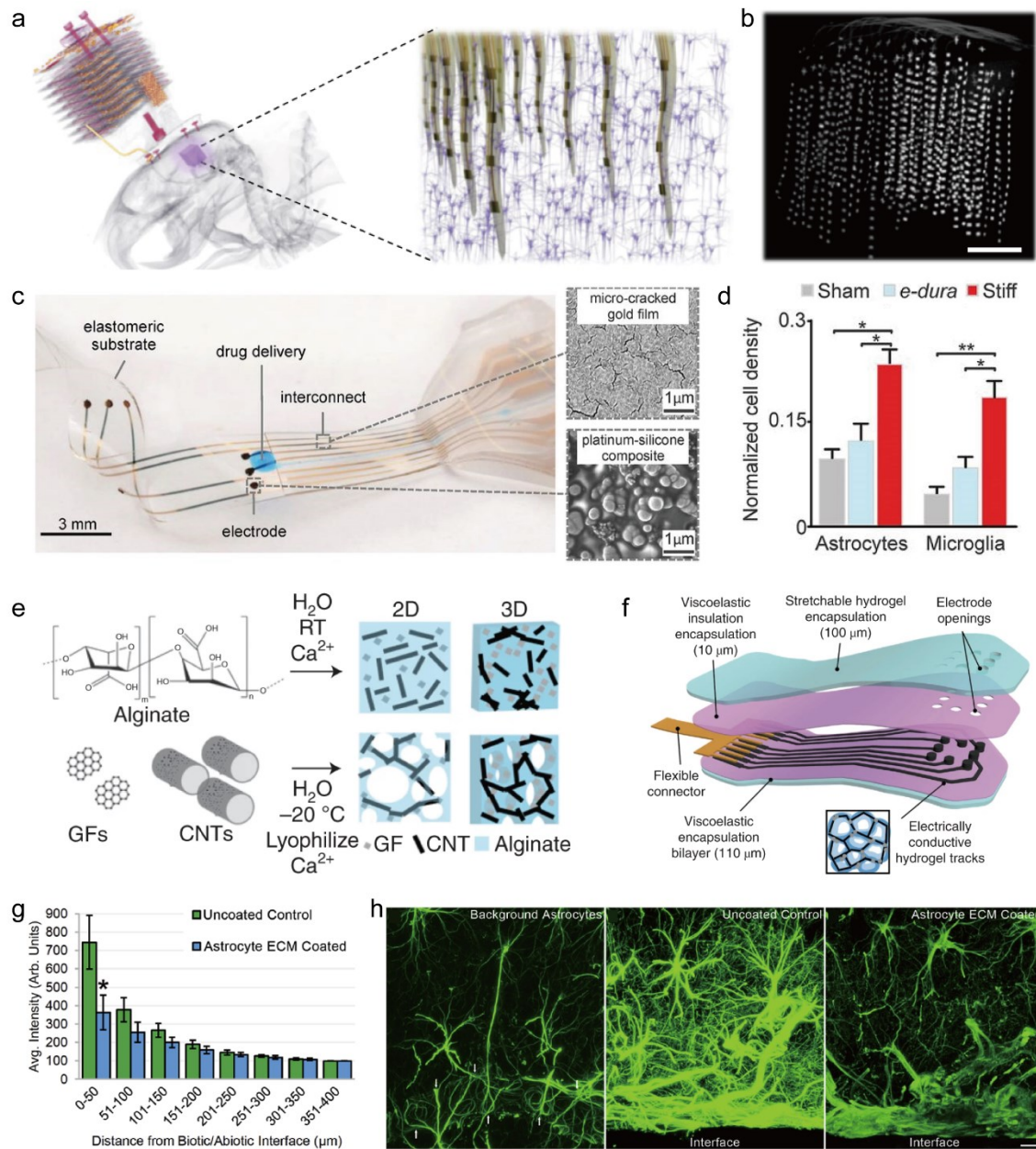


Figure 2. Materials strategies to improve biocompatibility. (a) Left: a micro-computed tomography (CT) scan of an implanted nanoelectronic thread (NET) array in a rat brain consisting of eight 128-channel modules (1,024 channels in total) at a high 3D density. The purple cube highlights the NET array. Right: schematics of the 3D NET array embedded in cortical tissues. (b) Micro-CT scan showing the volumetric distribution of an $8 \times 8 \times 16$ (1,024-channel) NET array in a mouse visual cortex. (a, b) adapted with permission from Reference [12]. (c) Optical image of an implant and scanning electron micrographs of the gold film and platinum-silicone composite. (d) Heat maps and bar plots showing normalized astrocyte and microglia density. (c, d) adapted with permission from Reference [13]. (e) Schematic showing the fabrication of nano-conductive gels (CGs) and microCGs. An alginate solution, graphite felts (GFs), and/or carbon nanotubes (CNTs) were mixed and immediately crosslinked to create the nanoCGs (top). When the mixed solution was

frozen and lyophilized before crosslinking, microCGs were formed with a higher density of carbon additives in the gel walls (bottom). RT, room temperature. (f) Schematic of the proposed device and its various components. (e, f) adapted with permission from Reference [14]. (g) Glial fibrillary acid protein (GFAP) immunofluorescence as a function of distance from the electrode/biotic interface compared to uncoated controls 8 weeks after implantation. (h) GFAP immunolabeling observed in normal rat cortical tissue at the same level as the implant site (left), At the uncoated microelectrode interface (middle) and at the microelectrode astrocyte-derived extracellular matrix (ECM)-coated interface (right) 8 weeks after implantation. Scale bar 10 μm . (g, h) adapted with permission from Reference [15].

Another approach to improving chronic biocompatibility is to increase the similarities between the host tissue and foreign implants, as this motivates the development of bioactive neural interfaces. These technologies usually use traditional materials (e.g., platinum, tungsten) as the base construct and common coatings such as silk, various hydrogels, or synthetic polymers. Bioactive materials, *e.g.*, bioactive molecules, living cells, or some combination of these, are included in the coatings to improve the biological compliance and promote chronic device-tissue integration. Microelectrodes primarily composed of extracellular matrix (ECM) proteins have been found to exhibit markedly diminished neuroinflammation and glial scarring in early chronic experiments in rats.[16] Compared to uncoated implants, a statistically significant decrease was observed in the spatial distribution and intensity of the glial fibrillary acid protein (GFAP) immunoreactivity surrounding astrocyte-derived ECM-coated microelectrode arrays after an 8-week implantation (**Figure 2g, h**). GFAP labels the cytoskeleton of astrocytes and has been used as an indicator of the tissue reactivity surrounding chronical implants. Although neural implants with bioactive material coatings provide improved biocompatibility, one ongoing challenges for these strategies concerns the limited duration of the effect as the

biomolecules diffuse away from the implant; this results in a poor translation of results from in vitro experiments to in vivo implants.

The emergence of novel materials and materials engineering techniques has promoted the development of various neural implants with features including miniaturization, flexible/soft mechanical properties, and bio-mimic surfaces. These strategies can, to some extent, enhance the biocompatibility. Nevertheless, true chronic biocompatibility has not been achieved and remains under the active pursuit of current research.

Biodegradable materials for implantable neuroelectronics

Biodegradable (or transient) neuroelectronics represent an emerging technology for applications requiring only finite operating lifetimes. Ideally, the devices disappear after they are no longer needed, thereby eliminating the risks, costs, and discomfort associated with a secondary surgical extraction. Potential applications of biodegradable devices include neurophysiologic monitoring and transient physiologic recording for neurotherapy and neuroregeneration.

Biodegradable neural implants should be able to completely degrade without releasing any toxic by-products. An increasing number of biodegradable materials have been studied to establish a material database for these implant systems. To date, biodegradable inorganic semiconductors and metals (including Si, Mg, Zn, Fe, and Mo) are commonly used as the essential functional materials. The biodegradable polymers extensively studied as biomedical implants, such as polylactic acid, poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), collagen, and silk, are employed as the substrates and encapsulation layers. In active electronics, the insulators are often formed using SiO₂, ZnO,

MgO, *etc.* The biodegradable behaviors and biosafety of these constituent materials have been examined by many researchers. In biofluids, the existing biodegradable materials mainly degrade through hydrolysis. For Si, the dissolution process is $\text{Si} + 4\text{H}_2\text{O} \leftrightarrow \text{Si}(\text{OH})_4 + 2\text{H}_2$, forming the silicic acid $\text{Si}(\text{OH})_4$ as a product. The metals are dissolved in a manner similar to their corrosion processes, whereas synthetic polymers can degrade through hydrolysis of the ester bonds. The degradation rates of the construction materials can be different in vitro and in vivo, as they are susceptible to environmental conditions such as the pH, concentrations of $\text{Ca}^{2+}/\text{Mg}^{2+}$, and protein. The end products of the currently used biodegradable materials become either essential nutrition in the human body or are metabolized and excreted out of the human body; this is a principle most researchers follow while exploring new biodegradable materials.

Based on different combinations of the above biodegradable materials, various neural implants have been demonstrated for transient monitoring, peripheral nerve stimulation, and other applications. In one study, bioresorbable Si electrodes insulated by SiO_2 and using a flexible PLGA sheet as the substrate were developed to record in vivo electrophysiological signals from a cortical surface (**Figure 3a**).^[17] A fully biodegradable electroactive device composed of thin-film metallic electrodes (made of Mg and FeMn) and embedded in a biodegradable nerve guidance conduit with a bilayer structure comprising PCL and poly(L-lactide)-poly(trimethylene carbonate) was used to provide electrical stimuli for promoting peripheral nerve regeneration (**Figure 3b**).^[18] A platform for wireless and programmable electrical peripheral nerve stimulation built with Mg and PLGA was used to enhance neuroregeneration and functional recovery after multiple episodes of electrical stimulation to injured nervous tissue in rodent models (**Figure 3c**).^[19]

These devices were shown to function in vivo for a few days. The relatively short work life resulted from the biofluids penetrating through the encapsulation layers and the fast dissolution of Mg.

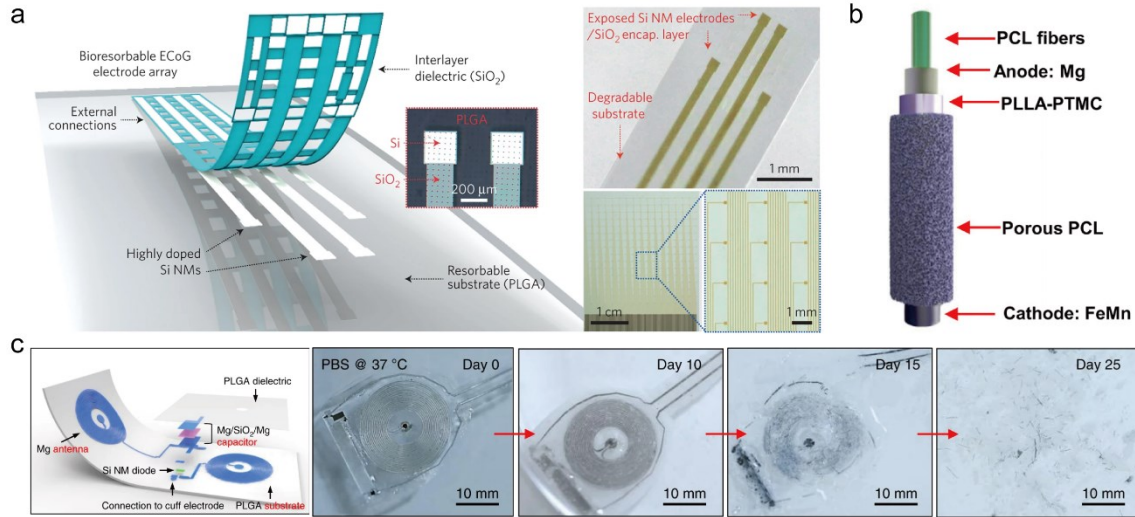


Figure 3. Implantable neuroelectronics constructed by biodegradable materials. (a) Right: schematic exploded-view illustration of the construction of a passive, bioresorbable neural electrode array for electrocorticography (ECoG) and subdermal electroencephalography (EEG) measurements. Left: photographs of bioresorbable neural electrode arrays with four channels (top) and 256 (16×16 configuration) channels (bottom). Adapted with permission from Reference [17]. (b) Schematic exploded illustration of a biodegradable, self-electrified, and miniaturized conduit device for sciatic nerve regeneration. Adapted with permission from Reference [18]. (c) Images of dissolution of a bioresorbable wireless stimulator associated with immersion in phosphate-buffered saline (PBS) (pH = 7.4) at 37 °C. Adapted with permission from Reference [19].

The most important property of transient electronics is to be able to operate stably for a certain period of time and then dissolve harmlessly after completing operations. Thus, the accurate control of the degradation kinetics of the working systems (e.g., to match the biological processes) is critically important. Currently available methods are passively protecting the device with biodegradable encapsulation or actively initiating the degradation reaction by triggering via on-demand control of transient devices. The work

lives of the active sites can be extended or programmed through control of the dissolution kinetics of a passivation layer. Si-based oxides/nitrides, Al_2O_3 , and biodegradable polymers have been used as barrier materials against water permeability. Compared to combinations of other strategies, using multiple encapsulation layers with different materials have been demonstrated as most efficient way to extend the lifetime of a transient Mg trace. However, as biodegradable materials usually have poor waterproof properties and the thickness of the passivation layers is only on the order of tens of microns, it remains a significant challenge to achieve extended and stable operation times for biodegradable devices.

Materials innovation to realize multifunctional neuroelectronics

Neurotransmission is multimodal in nature. Understanding brain function requires neural implants able to facilitate multimodal measurements to link the multi-scale spatiotemporal neuronal circuit processes with the patterns of global brain activity. Materials innovation brings new opportunities to develop multifunctional neuroelectronics that integrate the advantages of electrophysiological recording, optogenetic stimulation, optical imaging, neurochemical modulation *etc.*, thereby providing comprehensive perspectives on neuronal activity.

For example, one important multifunctional neuroelectronics approach integrates electrical recording and optogenetic stimulation. Optogenetics stimulation allows for cell-type-specific modulation in a diverse set of cells. The optical stimulation can be delivered either by optical waveguides or micro-light-emitting diodes (μLEDs). Integrating electrical

recording sites with optical stimulation platforms enables simultaneous monitoring of the neural responses to optogenetic stimulation, providing an attractive tool for revealing the causal relationships between specific neural circuits and their functions. Polina et al.[20] developed a device composed of an optical waveguide and six electrodes via fiber drawing (**Figure 4a**). The probes were solely fabricated using polymers and polymer composites and evoked a lower tissue response and blood-brain barrier relative to similarly sized steel microwires. These flexible probes achieved collocated neural recording and optical stimulation in mouse brains. In general, a precise analysis of neural activity requires a high spatial resolution for the electrical recording and optical stimulation; however, the high-density integration of light sources inevitably introduces stimulation artifacts. Yoon et al. demonstrated the mitigation of artifacts using a multi-metal-layer architecture and heavily boron-doped Si substrate.[21] Based on materials engineering innovations, optoelectronic probes integrating 256 recording sites and 128 μ LEDs on the surface of four 30- μ m thick Si shanks allowed recording and stimulation across a 0.9 mm \times 1.3 mm brain area in behaving mice (**Figure 4b**).[22]

Another type of multifunctional neuroelectronics allows for simultaneous optical imaging. Optical imaging, especially two-photon imaging, is an increasingly powerful and versatile technique in neuroscience. Two-photon imaging can observe the neural activity of hundreds of neurons at a subcellular spatial resolution. However, it typically has low temporal resolution and does not provide precise measurements of all spike activities. Electrical recordings can record neural activity directly with high temporal precision; thus, a hybrid system can maximize the advantages and complement the shortcomings of each method. The main challenges in the integration of optical imaging with electrical

recordings are in achieving optical access through the electrode arrays and light-induced artifacts. In this context, the emergence of transparent electrode arrays has opened up opportunities for avoiding blocking the field of view and minimizing the artifacts. Transparent electrode arrays can be obtained either by using intrinsic transparent materials (*e.g.*, graphene, carbon nanotube, conductive hydrogel, conductive polymers, indium tin oxide (ITO)) or by structural modification of opaque materials.[23] In one study, transparent electrodes fabricated with ITO were integrated with light-emitting diodes. The devices showed an average transmittance of ~94% over the visible wavelength range.[24] Forming mesh-like or porous nanostructures also makes it possible to obtain optical transparency from opaque materials and thin-film stacks while maintaining their functional properties. Bilayer-nanomesh microelectrode arrays engineered by template electroplating low-impedance coating poly(3,4-ethylene-dioxythiophene) polystyrene sulfonate (PEDOT:PSS) on a gold nanomesh have been demonstrated to provide more than one order of magnitude lower impedance than graphene and ITO microelectrodes, albeit with slightly less optical transparency. In one example, flexible 32 bilayer-nanomesh microelectrodes allowed for *in vivo* two-photon imaging of single neurons in layers 2/3 of the visual cortexes of awake mice, along with high-fidelity and simultaneous electrical recordings of visually evoked activity (**Figure 4c**).[25] Overall, the most important point of such a multifunctional device is that the electrical and optical signals must be accurately measured without interfering with each other. One important application might be in the source localization of electrocorticography signals from simultaneous epicortical recording and optical imaging.

Integrating electrical recording sites with a drug delivery platform enables the recording and modulating of electrical signals with various chemical stimuli present. To this end, neural probes microfabricated with embedded microfluidic channels have emerged. For instance, chemtrodes integrating microfluidic channels with seven recording sites have enabled the injection of as many as three different drugs alongside simultaneous electrophysiology (**Figure 4d**). [26, 27] Despite these efforts, delivering small molecules in vivo with a precision comparable to that of chemical neurotransmission remains a challenge. In general, neuropharmacology and optogenetic stimulation represent two highly informative and widely used approaches in neuroscience research. This has motivated the development of a series of optofluidic systems for integrating pharmacological and optogenetic functions within a single platform. In 2015, the Rogers group introduced optofluidic neural probes combining ultrathin and soft microfluidic drug delivery with cellular-scale inorganic light-emitting diode arrays orders of magnitude smaller than cannulas. This allowed for wireless and programmed spatiotemporal control of the fluid delivery and photostimulation in freely moving animals (**Figure 4e**). [28] Following this work, optofluidic systems with ultralow power operation and wireless, battery-free functionality were designed for deployment on either peripheral nerves [29] or for interaction with the brain (**Figure 4f**). [30] These devices are well-suited for investigations of the interactions between optogenetically activated circuits and the subsequent neurochemical signaling in the behavioral paradigm.

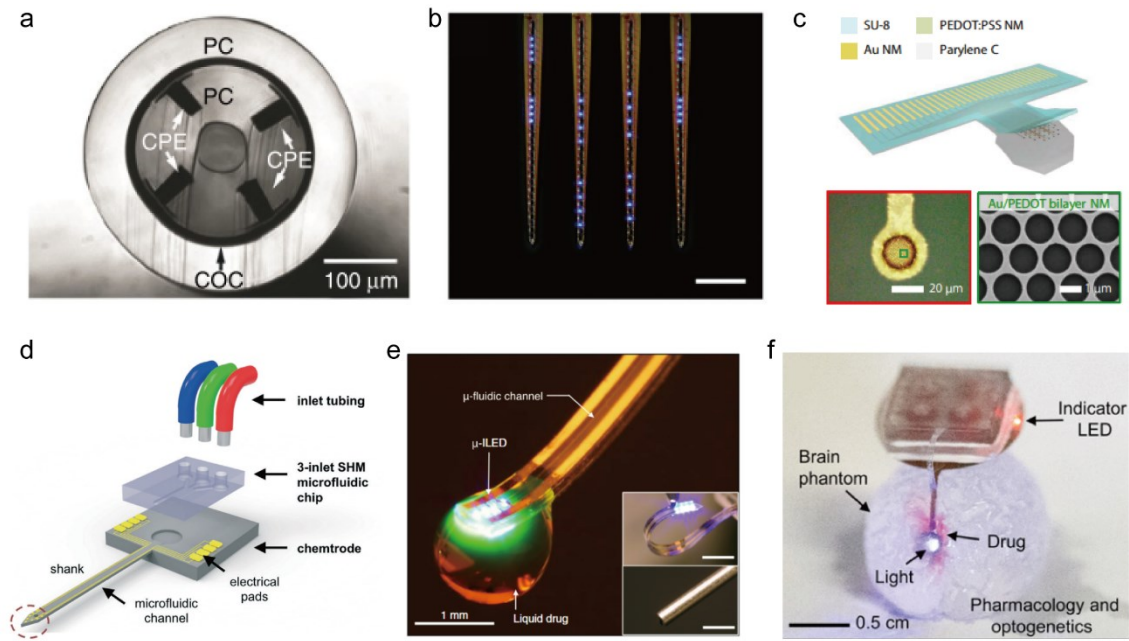


Figure 4. Images of different multimodal implantable neuroelectronics. (a) Cross-sectional optical images of the multimodality probe tips. Adapted with permission from Reference [31]. (b) Microphotographs of a fabricated hectoSTAR micro-light-emitting diode (μ LED) optoelectrode. Note blue light being generated from active μ LEDs, scale bar is 300 μ m. Adapted with permission from Reference [22]. (c) Device schematic of the 32-channel Au/poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) nanomesh microelectrode array (MEA), microscope image of a Au/PEDOT:PSS bilayer-nanomesh microelectrode and scanning electron microscope (SEM) image of a zoomed-in region of the microelectrode shown on the left. Adapted with permission from Reference [25]. (d) Conceptual diagram of each component (tubing, three-inlet staggered herringbone mixer (SHM) chip, and chemtrode) of the proposed neural probe system for multi-drug delivery before and after assembly. Adapted with permission from Reference [27]. (e) Optofluidic neural probe during simultaneous drug delivery and photostimulation. (Insets) Comparison of such a device (top) and a conventional metal cannula (bottom; outer and inner diameters of \sim 500 and 260 μ m, respectively). Scale bars, 1 mm. Adapted with permission from Reference [28]. (f) Demonstration of wireless fluid delivery and optical stimulation in a brain tissue phantom. Adapted with permission from Reference [30].

Driven by the progress in materials science and engineering, neuroelectronics integrating three or more functionalities have emerged in recent years. For instance, microelectromechanical system neural probes have achieved simultaneous optical

stimulation, drug delivery, and electrical signal recording through monolithically integrating an SU-8 optical waveguide, microfluidic channels, and iridium microelectrode arrays [32]. Multimodality all-polymer fiber probes have allowed for simultaneous optical stimulation, neural recording, and drug delivery in behaving mice.[31] An Si/PDMS hybrid chemtrode incorporated a Pt nanoparticle-modified IrOx reference electrode, microfluidic channel, and enzyme microstamping to detect glutamate and choline in rat brains.[33] The continuously increasing array of multifunctional neural implants provide new opportunities for neuroscience studies and neurotherapies.

Outlook

Advances in materials have facilitated the emergence of a broad range of neuroscience study platforms, offering many unique capabilities for neuroscience research and opening up potential opportunities for clinical applications. Various miniaturized and flexible/soft neural implants have been developed to overcome the mechanical mismatches between the stiff implanted devices and soft neural tissue, helping to reduce tissue damage and FBRs. The biodegradability of neural implants enables temporary functioning, thereby avoiding potential long-term tissue damage from foreign substances or a second surgery to remove the implanted device. Meanwhile, recently developed multifunctional neural implants are powerful tools for providing comprehensive perspectives on neural activity. Materials innovation become a significant engine for advancing neuroelectronic development.

Despite significant progress in materials and devices, many significant challenges must be overcome. The FBR is one of the most significant barriers to chronic neural implants. The

development of neural implants with miniaturization, flexible/soft mechanical properties, and bio-mimic surfaces represents the leading approach to reducing these effects, but in many cases, the reduction is at the expense of increased impedances and long-term stable operation. In addition, the implantation of soft electrodes into deeper tissues requires insertion aids. Insofar as biodegradable neural implants, one significant challenge concerns achieving a programmed biodegradation profile to match the biological process(es) and targeted lifetime of the device. Current encapsulation strategies can protect active electrodes for a few days in vivo, but further extending the work life of the implants usually requires a thicker insulation layer. In the context of multifunctionality, challenges remain in integrating the platforms without sacrificing the individual functions' performance. Innovative materials engineering approaches are required to accurately measure or deliver signals without interfering with each other and must work synergistically. In addition, minimizing the integration impact on the device footprint and system overhead is another challenge. Although the emergence of implantable neuroelectronics provides many appealing concepts, critical challenges remain in connecting these methods to real-world applications (where chronically stable biocompatibility and high-fidelity operation must be guaranteed). These challenges also bring new opportunities for researchers.

Numerous opportunities exist for further materials innovation for future neuroelectronics. One area is in tailoring materials for specific uses to achieve chronic biocompatibility and high-fidelity signal recording or delivering, where soft materials with good inertness and hermeticity working as insulators and low-impedance materials used in active parts are highly desirable. Additionally, advanced manufacturing techniques will allow for the emergence of various device architectures and the fabrication of high-density electrode

arrays, for instance, by combining high-resolution 3D printing and laser cutting with traditional top-down lithography and bottom-up self-assembly. Finally, close research collaboration and workforce training across many disciplines are also needed to tackle the aforementioned challenges in this exceptionally interdisciplinary field. Researchers in different fields, such as material science, electrical engineering, and neuroscience, should work together closely to develop next-generation implantable neuroelectronics with biocompatibility, biodegradability, and multifunctionalities and translate them to different users to maximize their impact. Now is really an exciting time for materials engineering and device innovation for implantable neuroelectronics.

Conflict of Interest statement

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

References

- [1] E.M. Song, J.H. Li, S.M. Won, W.B. Bai, J.A. Rogers, *Nat. Mater.* **19**, 590 (2020)
- [2] H. Li, J. Wang, Y. Fang, *Microsyst. Nanoeng.* **9**, 4 (2023)
- [3] G.T. Go, Y. Lee, D.G. Seo, T.W. Lee, *Adv. Mater.* **34**, e2201864 (2022)
- [4] M. Mariello, K. Kim, K. Wu, S.P. Lacour, Y. Leterrier, *Adv. Mater.* **34**, e2201129 (2022)
- [5] S.-K. Kang, L. Yin, C. Bettinger, *MRS Bull.* **45**, 87 (2020)
- [6] S.M. Won, E.M. Song, J.T. Reeder, J.A. Rogers, *Cell* **181**, 115 (2020)
- [7] E. Patrick, M.E. Orazem, J.C. Sanchez, T. Nishida, *J. Neurosci. Methods* **198**, 158 (2011)
- [8] D. Egert, J.R. Pettibone, S. Lemke, P.R. Patel, C.M. Caldwell, D. Cai, K. Ganguly, C.A. Chestek, J.D. Berke, *J. Neurophysiol.* **124**, 1578 (2020)
- [9] J.J. Jun, N.A. Steinmetz, J.H. Siegle, D.J. Denman, M. Bauza, B. Barbarits, A.K. Lee, C.A. Anastassiou, A. Andrei, C. Aydin, M. Barbic, T.J. Blanche, V. Bonin, J. Couto, B. Dutta, S.L. Gratiy, D.A. Gutnisky, M. Hausser, B. Karsh, P. Ledochowitsch, C.M. Lopez, C. Mitelut, S. Musa, M. Okun, M. Pachitariu, J. Putzeys, P.D. Rich, C. Rossant, W.L. Sun, K. Svoboda, M. Carandini, K.D. Harris, C. Koch, J. O'Keefe, T.D. Harris, *Nature* **551**, 232 (2017)
- [10] L. Karumbaiah, T. Saxena, D. Carlson, K. Patil, R. Patkar, E.A. Gaupp, M. Betancur, G.B. Stanley, L. Carin, R.V. Bellamkonda, *Biomaterials* **34**, 8061 (2013)
- [11] E.J. Welle, P.R. Patel, J.E. Woods, A. Petrossians, E. Della Valle, A. Vega-Medina, J.M. Richie, D. Cai, J.D. Weiland, C.A. Chestek, *J. Neural. Eng.* **17**, 026037 (2020)
- [12] Z. Zhao, H. Zhu, X. Li, L. Sun, F. He, J.E. Chung, D.F. Liu, L. Frank, L. Luan, C. Xie, *Nat. Biomed. Eng.* 10.1038/s41551-022-00941-y(2022)
- [13] I.R. Minev, P. Musienko, A. Hirsch, Q. Barraud, N. Wenger, E.M. Moraud, J. Gandar, M. Capogrosso, T. Milekovic, L. Asboth, R.F. Torres, N. Vachicouras, Q. Liu, N. Pavlova, S. Duis, A. Larmagnac, J. Vörös, S. Micera, Z. Suo, G. Courtine, S.P. Lacour, *Science* **347**, 159 (2015)
- [14] C.M. Tringides, N. Vachicouras, I. de Lazaro, H. Wang, A. Trouillet, B.R. Seo, A. Elosegui-Artola, F. Fallegger, Y. Shin, C. Casiraghi, K. Kostarelos, S.P. Lacour, D.J. Mooney, *Nat. Nanotechnol.* **16**, 1019 (2021)
- [15] R.S. Oakes, M.D. Polei, J.L. Skousen, P.A. Tresco, *Biomaterials* **154**, 1 (2018)
- [16] W. Shen, S. Das, F. Vitale, A. Richardson, A. Ananthakrishnan, L.A. Struzyna, D.P. Brown, N. Song, M. Ramkumar, T. Lucas, D.K. Cullen, B. Litt, M.G. Allen, *Microsyst. Nanoeng.* **4**, 30 (2018)
- [17] K.J. Yu, D. Kuzum, S.W. Hwang, B.H. Kim, H. Juul, N.H. Kim, S.M. Won, K. Chiang, M. Trumpis, A.G. Richardson, H. Cheng, H. Fang, M. Thomson, H. Bink, D. Talos, K.J. Seo, H.N. Lee, S.K. Kang, J.H. Kim, J.Y. Lee, Y. Huang, F.E. Jensen, M.A. Dichter, T.H. Lucas, J. Viventi, B. Litt, J.A. Rogers, *Nat. Mater.* **15**, 782 (2016)
- [18] L. Wang, C.F. Lu, S.H. Yang, P.C. Sun, Y. Wang, Y.J. Guan, S. Liu, D.L. Cheng, H.Y. Meng, Q. Wang, J.G. He, H.Q. Hou, H. Li, W. Lu, Y.X. Zhao, J. Wang, Y.Q. Zhu, Y.X.

- Li, D. Luo, T. Li, H. Chen, S.R. Wang, X. Sheng, W. Xiong, X.M. Wang, J. Peng, L. Yin, *Sci. Adv.* **6**, (2020)
- [19] J. Koo, M.R. MacEwan, S.K. Kang, S.M. Won, M. Stephen, P. Gamble, Z. Xie, Y. Yan, Y.Y. Chen, J. Shin, N. Birenbaum, S. Chung, S.B. Kim, J. Khalifeh, D.V. Harburg, K. Bean, M. Paskett, J. Kim, Z.S. Zohny, S.M. Lee, R. Zhang, K. Luo, B. Ji, A. Banks, H.M. Lee, Y. Huang, W.Z. Ray, J.A. Rogers, *Nat. Med.* **24**, 1830 (2018)
- [20] S. Park, Y. Guo, X. Jia, H.K. Choe, B. Grena, J. Kang, J. Park, C. Lu, A. Canales, R. Chen, Y.S. Yim, G.B. Choi, Y. Fink, P. Anikeeva, *Nat. Neurosci.* **20**, 612 (2017)
- [21] K. Kim, M. Voroslakos, J.P. Seymour, K.D. Wise, G. Buzsaki, E. Yoon, *Nat. Commun.* **11**, 2063 (2020)
- [22] M. Voroslakos, K. Kim, N. Slager, E. Ko, S. Oh, S.S. Parizi, B. Hendrix, J.P. Seymour, K.D. Wise, G. Buzsaki, A. Fernandez-Ruiz, E. Yoon, *Adv. Sci.* **9**, e2105414 (2022)
- [23] Y.U. Cho, S.L. Lim, J.-H. Hong, K.J. Yu, *npj Flex. Electron.* **6**, (2022)
- [24] B.S. Ki Yong Kwon, Wen Li, *IEEE BioCAS* **4** (2012)
- [25] Y. Qiang, P. Artoni, K.J. Seo, S. Culaclii, V. Hogan, X.Y. Zhao, Y.D. Zhong, X. Han, P.M. Wang, Y.K. Lo, Y.M. Li, H.A. Patel, Y.F. Huang, A. Sambangi, J.S.V. Chu, W.T. Liu, M. Fagiolini, H. Fang, *Sci. Adv.* **4**, (2018)
- [26] H.J. Lee, Y. Son, J. Kim, C.J. Lee, E.S. Yoon, I.J. Cho, *Lab Chip* **15**, 1590 (2015)
- [27] H. Shin, H.J. Lee, U. Chae, H. Kim, J. Kim, N. Choi, J. Woo, Y. Cho, C.J. Lee, E.S. Yoon, I.J. Cho, *Lab Chip* **15**, 3730 (2015)
- [28] J.W. Jeong, J.G. McCall, G. Shin, Y. Zhang, R. Al-Hasani, M. Kim, S. Li, J.Y. Sim, K.I. Jang, Y. Shi, D.Y. Hong, Y. Liu, G.P. Schmitz, L. Xia, Z. He, P. Gamble, W.Z. Ray, Y. Huang, M.R. Bruchas, J.A. Rogers, *Cell* **162**, 662 (2015)
- [29] Y. Zhang, A.D. Mickle, P. Gutruf, L.A. McIlvried, H.X. Guo, Y.X. Wu, J.P. Golden, Y.G. Xue, J.G.G. Ales-Reyes, X.J. Wang, S. Krishnan, Y.W. Xie, D.S. Peng, C.J. Su, F.R. Zhang, J.T. Reeder, S.K. Vogt, Y.G. Huang, J.A. Rogers, R.W. Gereau, *Sci. Adv.* **5**, (2019)
- [30] Y. Zhang, D.C. Castro, Y. Han, Y. Wu, H. Guo, Z. Weng, Y. Xue, J. Ausra, X. Wang, R. Li, G. Wu, A. Vazquez-Guardado, Y. Xie, Z. Xie, D. Ostojich, D. Peng, R. Sun, B. Wang, Y. Yu, J.P. Leshock, S. Qu, C.J. Su, W. Shen, T. Hang, A. Banks, Y. Huang, J. Radulovic, P. Gutruf, M.R. Bruchas, J.A. Rogers, *Proc. Natl. Acad. Sci.* **116**, 21427 (2019)
- [31] A. Canales, X. Jia, U.P. Froriep, R.A. Koppes, C.M. Tringides, J. Selvidge, C. Lu, C. Hou, L. Wei, Y. Fink, P. Anikeeva, *Nat Biotechnol* **33**, 277 (2015)
- [32] H. Shin, Y. Son, U. Chae, J. Kim, N. Choi, H.J. Lee, J. Woo, Y. Cho, S.H. Yang, C.J. Lee, I.J. Cho, *Nat. Commun.* **10**, 3777 (2019)
- [33] B. Wang, X.M. Wen, Y. Cao, S. Huang, H.A. Lam, T.Y. Liu, P.S. Chung, H.G. Monbouquette, P.Y. Chiou, N.T. Maidment, *Lab Chip* **20**, 1390 (2020)