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Bioengineering applications for hearing restoration: emerging biologically inspired and biointegrated designs

Jason A Brant[1,2], Dayo O Adewole[1,2,3,4,7], Flavia Vitale[2,3,5,6,7] and Daniel K Cullen[2,3,4,7]

Cochlear implantation has become the standard of care for hearing loss not amenable to amplification by bypassing the structures of the cochlea and stimulating the spiral ganglion neurons directly. Since the first single channel electrodes were implanted, significant advancements have been made: multi-channel arrays are now standard, they are softer to avoid damage to the cochlea and pre-curved to better position the electrode array adjacent to the nerve, and surgical and stimulation techniques have helped to conform to the anatomy and physiology of the cochlea. However, even with these advances the experience does not approach that of normal hearing. In order to make significant advances in performance, the next generation of implants will require novel interface technology. Advances in regenerative techniques, optogenetics, piezoelectric materials, and bioengineered living scaffolds hold the promise for the next generation of implantable hearing devices, and hope for the restoration of natural hearing.

Addresses
[1] Department of Otorhinolaryngology, Perelman School of Medicine, University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104, USA

[2] Center for Brain Injury & Repair, Department of Neurosurgery, University of Pennsylvania, 240 S. 33rd St., 301 Hayden Hall, Philadelphia, PA 19104, USA
[3] Department of Bioengineering, School of Engineering and Applied, Science, University of Pennsylvania, 220 S 33rd St., Philadelphia, PA 19104, USA
[4] Center for Brain Injury & Repair, Department of Neurosurgery, University of Pennsylvania, 3320 Smith Walk, 105 Hayden Hall, Philadelphia, PA 19104, USA
[5] Department of Neurology, Perelman School of Medicine, University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104, USA
[6] Department of Physical Medicine & Rehabilitation, Perelman School of Medicine, University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104, USA
[7] Center for Neuroengineering & Therapeutics, University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104, USA

Corresponding author:
Cullen, Daniel K (dkacy@pennmedicine.upenn.edu)

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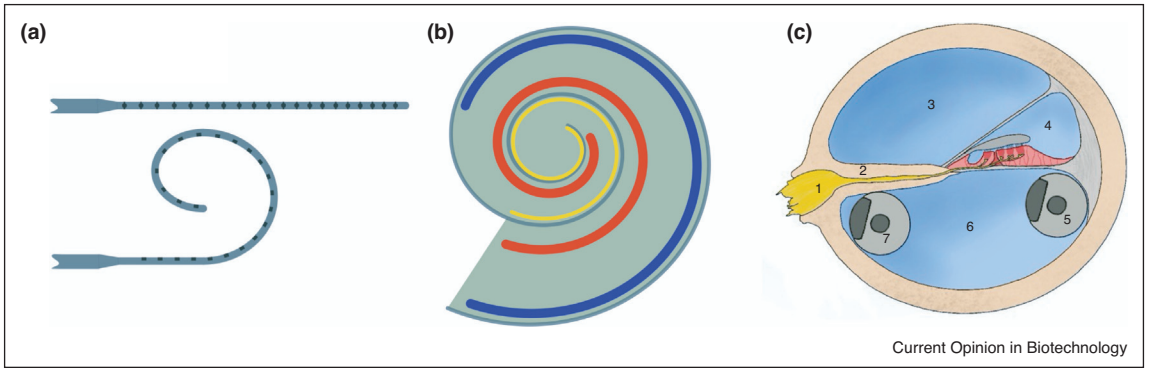
Introduction

It is estimated that 15% of the world's population have some degree of hearing loss and that over 5% suffer from disabling deafness [1]. The majority of adult hearing loss is secondary to cochlear hair cell loss, with fewer pathologies affecting the spiral ganglion neurons. When hearing loss has progressed to the point that amplification is no longer sufficient, cochlear implantation has become the standard of care. Cochlear implants (CI) stimulate the auditory nerve directly, bypassing damaged portions of the cochlea. The impact of cochlear implantation cannot be overstated and a majority of implantees obtain significant benefit from their devices [2]. However, despite their clear success, cochlear implants do not restore natural hearing, outcomes can be varied [3•] and even high performers can have difficulty with speech in noisy settings, talking on the telephone, and appreciating complex sounds such as music.

The fundamentals of CI electrode array design have remained essentially unchanged since the first implants were developed in the 1960's — a linear array with a variable number of channels that is inserted along the length of the cochlea from its base. Advancements in electrode design have included multichannel arrays that exploit the tonotopic organization of the cochlea, precurved designs to mimic the shape of the cochlear duct and position electrode array closer to the spiral ganglion, and decreased stiffness to reduce damage on insertion and ensure placement in the appropriate scala (Figure 1) [4••,5]. Despite these advancements, current spread and cross-stimulation

Figure 1



Cochlear implant electrode arrays and placement.
(a) Modern multichannel straight (lateral wall), and pre-curved (peri-modiolar) electrode arrays. The portion shown is inserted into the cochlea from the round window or a cochleostomy close to the round window in the basal turn of the cochlea. The leads from the electrode extend to attach to a processor device implanted under the skin of the scalp. Pre-curved electrode arrays are straightened with a stylette or sheath that is removed during insertion to allow the electrode to curl within the cochlea. **(b)** Cartoon of placement within the cochlea of straight (blue) and pre-curved (red) electrode arrays within the cochlear duct along with proximity to the spiral ganglion (yellow) located along the modiolus (central axis) of the cochlea. **(c)** Cross section of the cochlear duct showing location of the pre-curved and lateral wall electrode arrays and their proximity to the spiral ganglion. 1) Spiral ganglion, 2) Osseus spiral lamina with axons of spiral ganglion cells, 3) scala vestibuli, 4) scala media with organ of Corti, 5) placement of straight (lateral wall) electrode array, 6) scala tympani, 7) placement of pre-curved (peri-modiolar) electrode array.

limit the number of independent channels available. It is estimated that 30–50 independent channels are required to approximate normal hearing, while fewer than 10 are often achieved with current technologies [6].

Several strategies have been developed to compensate for these limitations. Pre-operative imaging is being used to more precisely choose electrode sizes for individual patients [7], post-operative image-guided programming techniques can inform selective deactivation of interfering electrodes and provide initial frequency programming estimates [8], and intraoperative electrocochleography can monitor insertion trauma in real-time [9]. Stimulation and encoding strategies have also been developed to more precisely guide current flow and stimulation sites within the cochlea and to mimic biological signal patterns [10].

There is a single central nervous system implant approved in the United States for patients with neurofibromatosis type 2. The Auditory Brainstem Implant (ABI) has a flat array of electrodes intended to be placed against the surface of the cochlear nucleus (CN) [11]. In contrast to the success of cochlear implants, just over 1000 have been placed and the performance has not approached cochlear implants. A modification of the ABI including both surface and penetrating electrodes attempted to exploit the tonotopic arrangement of the CN; however, no improvement in outcomes was achieved [12]. An alternative central implant, the auditory midbrain implant (AMI) with 20 ring electrodes along a single shank was intended to be implanted into the inferior colliculus (IC). While pre-clinical data was promising, in a small clinical trial outcome goals were not achieved, and the device remains investigational [13].

Here we present a brief review of emerging bioengineering solutions intended to overcome the obstacles detailed above and deliver the next generation of auditory implants (Table 1).

Alterations to the cochlea

Several methods have been developed to alter the cochlear environment to improve the performance of existing electrode array technology. Many of these are based on the induction of neuronal growth between the electrode array and remaining spiral ganglion cells. Reducing this distance will allow for decreased stimulation intensity and thus reduced activation of adjacent neurons. *In vitro* studies have found several factors that can promote neurite extension in spiral ganglion cells including growth hormone, brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, ciliary neurotrophic factor, and erythropoietin [14,15]. Alternatively, coatings of the device itself have been evaluated. Laminin coated electrode arrays [16•], BDNF gene transfer [17••], and chronic intrascalar growth factor were shown to induce neuronal outgrowth into the scala tympani potentially allowing for direct contact with implanted electrodes.

Preservation of residual hearing following implantation allows for both acoustic and electric stimulation which has

Table 1

Summary of emerging technologies for auditory rehabilitation

Technology	Techniques	Potential benefits	Challenges	References
Electrode/ stimulation evolution	Decreased stiffness of electrodes to limit insertion damage.		Effect on residual hearing/cochlear architecture from insertion damage and immediate and delayed inflammatory response.	
	Pre-curved electrodes to decrease distance to spiral ganglion.	Utilization of existing technology with significant clinical experience.		[4••,5–10]
	Stimulation strategies to more closely mimic natural neuronal patterns and current steering to prevent spread.		Limitation of number of independent channels due to current spread.	
Alterations to cochlea	Induction of neuronal outgrowth from spiral ganglion to electrode.	Utilization of existing electrode technologies.	Difficult access for introduction of agents and monitoring of effects.	[14,15,16•,17••,18–20]
	Suppression of inflammatory response after implantation.		Possible requirement of long-term delivery of anti-inflammatory agents.	
Regenerative	Stem cell.		Difficult access for introduction and monitoring of agents/cells and control of expression.	
	Induction of hair cell and/or spiral ganglion regeneration	Possible restoration of natural anatomy and physiology of the cochlea.	Requirement of complex three-dimensional anatomy of the cochlea to be effective.	[21]
Optical Stimulation	Optogenetic transformation of native spiral ganglion neurons for optic stimulation.	Lack of current spread.	Difficult access for introduction of agents and control/monitoring of expression.	
	Several techniques for stimulation that avoid genetic transformation.	Frequency and intensity resolution compatible with stimulation of complex auditory signals.	Need for long-term biosafety confirmation. Possible similar immediate and prolonged cochlear inflammatory concerns as traditional electrodes.	[22•,23••,24,25,26•,27,28]
Piezoelectric	Inherent property of transformation between mechanical and electrical energy.	Potential for completely implantable devices.	Biosafety and ototoxicity concerns.	
		Adaptable form factors of materials.	Piezoelectricity levels for more biocompatible organic piezoelectric materials.	[29–31,32••]
Living Electrodes		Biocompatible scaffolds for long-term implantation and limited insertion trauma.	Utilization of harvested/transplanted neuronal tissue.	
	Customizable bioengineered scaffold with living neuronal tissue designed for specific applications of interest.	Neuronal populations specific to application of interest.	Need for long-term monitoring of biologic integration/growth behavior.	[33–36,37•,38••,39,43, 44•,45,46]
		Functionalization with optogenetics.		
		Synapse-specific stimulation.		
		In vitro genetic transformation.		

superior outcomes as compared to electric-only stimulation. Hearing can be lost either by direct trauma at the time of surgery or delayed due to inflammation which has driven interest in methods to reduce any cochlear inflammatory response. Coating electrodes with hydrophilic and protein-repellent polymers, silicone fibers, and conductive hydrogels helped to prevent fibroblast growth [18] and potentially mitigate the inflammatory response [19]. Multiple techniques have also been proposed for the sustained release of anti-inflammatory agents within the cochlea following implantation [20].

Regenerative techniques

Damage to cochlear hair cells that leads to sensorineural hearing loss is generally irreversible and can lead to downstream loss of spiral ganglion cells. The need for auditory implants would be obviated by the ability to restore the natural function of the cochlea. Gene therapies have been proposed for the preservation or regeneration of cochlear hair cells, and for treatment of specific genetic forms of hearing loss [21]. These techniques require the ability to introduce therapeutic agents into the inner ear without causing additional damage and

several nanotechnology delivery platforms are being developed to address this constraint. Stem cell-based therapies, including induced pluripotent stem cells, have also shown promise for both hair cell and auditory nerve cell regeneration [21]. These technologies face challenges such as control of genetic changes, establishment of functional synapses, and anatomically correct placement within the complex structure of the cochlea, and accessibility of the inner ear *in vivo*. Given the location of deficits in hearing loss, regenerative techniques have fewer central applications.

Optical stimulation

Optical stimulation has been proposed as an alternative to traditional electrical stimulation as it may overcome the specificity issues arising from current spread and may be finely tuned to the frequency and intensity resolution required to simulate complex sounds [22•]. Virally based optogenetic transfection of spiral ganglion cells and linear multichannel micro-LED arrays have been shown to be able to stimulate the auditory system in animal models [23••,24], and techniques for optical stimulation that do not require transfection are also being investigated [25]. While there are several important technical challenges to overcome such as viral delivery, variable expression along the length of the cochlea, optimal opsin selection, and biosafety [26•] before such technology can be applied in the clinical setting, the advantages of optical stimulation for both cochlear and central auditory applications remain appealing [27,28].

Piezoelectric

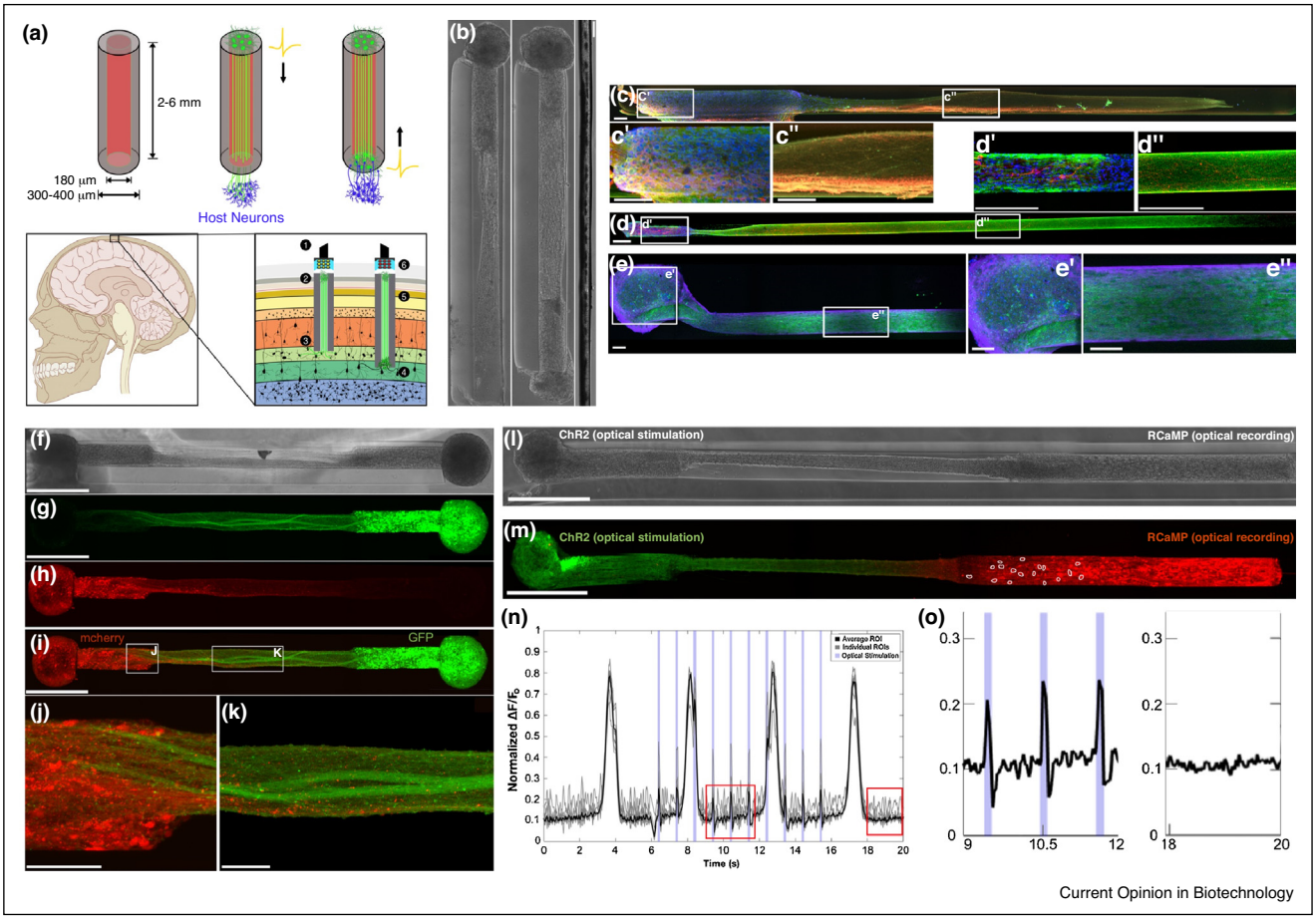
Piezoelectric materials have the ability to convert between electrical and mechanical energy — a property that naturally lends itself to peripheral auditory applications. Such materials have been investigated for auditory applications as thin films, electrospun fibers [29], and nanoparticles [30]. Piezoelectric materials have also been proposed as key for the development of fully implantable hearing systems [31]. Similar to optogenetic technologies, while the potential for piezoelectric materials to form the foundation of next generation auditory implants is great, there remain significant technological hurdles to overcome. Specifically, there have been recent advances in the development of organic piezoelectric materials that aim to alleviate biocompatibility, flexibility and processibility concerns of traditional options, however these organic versions often suffer from weak piezoelectricity [32••].

Future directions: living electrodes

There have recently been significant advances in the development of transplantable micro-tissue engineered neural networks (micro-TENNs) for reconstruction of brain pathways [33–36], spinal cord regeneration [37•], and modulation of brain networks [33–36,38••]. Micro-TENN constructs are generated *in vitro* by seeding neuronal populations within customizable soft hydrogel scaffolds [39]. The neurons contained in these scaffolds extend neurites along pre-formed channels while the cell bodies remain in a defined location. Axons projecting from each of the micro-TENN neurons may synapse directly onto the cell body (or dendrites) of neurons in the target tissue, thus eliminating the potential for current spread. The construct can be placed so that the axons are directed to a location of interest while the cell bodies remain accessible. Any non-organic components of a neural interface, including traditional electrodes or optrodes for stimulation of transplanted neuronal cells, remain external to the brain parenchyma or cochlea. Implantation of micro-TENNs induces minimal acute trauma [36], and is less likely to cause chronic inflammation than traditional electrodes [40]. An accessible neuronal aggregate with directed axonal projections creates an interface for stimulation or recording of neuronal tissue combined with synapse-specific stimulation — an anatomically inspired 'living electrode'. The neurons utilized in the construct can be stimulated with traditional electrical techniques or genetically modified with light-sensitive proteins and selectively controlled via optical stimulation [38••].

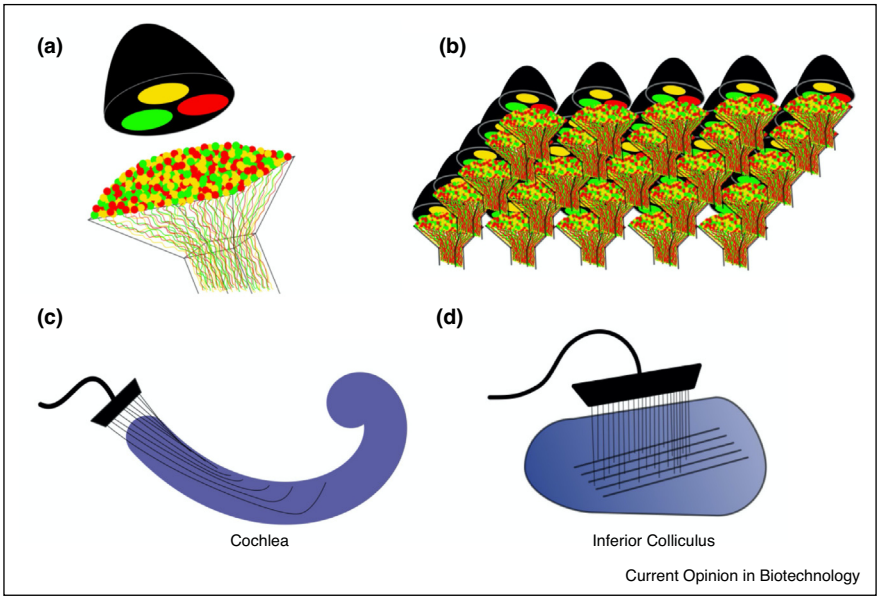
Future application of the micro-TENNs technology to the auditory system has several potential advantages over existing solutions. The scaffolds can be designed for the complex anatomy of the IC or CN [41]. Both the IC and CN have a basic tonotopic structure, but complex sounds such as speech may not obey this simplified model [42]. It is likely that to recreate these complex sounds, stimulation throughout the nuclei will be required. The biocompatibility of living electrodes may allow for a greater volume of auditory nuclei to be accessible while avoiding issues of chronic inflammation. Previous work has shown that axons can be grown to several centimeters in length [37•,43,44•] sufficient for cochlear applications utilizing established implantation techniques. The cell bodies of the implanted neurons can remain in the mastoid where they are stimulated while their axons are positioned to terminate at variable sites along the length of the cochlea. Unpublished work by our group has confirmed the ability of living electrode constructs to physiologically interact with spiral ganglion neuronal populations and such interactions *in vivo* will benefit from the native spiral ganglion neuronal outgrowth strategies described above [45]. Further benefits of this approach emerge when combined with optogenetics. Unlike current methods, the neuronal tissue utilized for living electrodes is cultured *in vitro*, thus eliminating the risks of *in vivo* delivery and allowing for verification of range and extent of expression before implantation. Finally, specific optical stimulation channels can be assigned as specific frequency channels post-implant based on the precise location of axo-somatic synaptic integration and thus can be customized based on monitoring and feedback. A summary of the existing

Figure 2



Microtissue engineered neural networks (micro-TENN) as 'living electrodes'.
(a) Current range of biomaterial dimensions for implantable living electrodes (top left). Living electrodes may relay external inputs to target brain areas (unidirectional, top middle) or relay host activity as represented in the dorsal aggregate (bidirectional, top right) following synapse formation with host neurons (purple) and (bottom) a cartoon showing implantation orientation, here in the cortex of optogenetically active living electrodes as transplantable input/output channels. Inputs: An LED array (1) photostimulates a unidirectional, channelrhodopsin-positive living electrode (2) to activate layer IV neurons (3). Outputs: Layer V neurons (4) synapse a bidirectional living electrode (5); representative neuronal activity is detected by a photodiode array on the brain surface (6). Adapted from Ref. [38••]. **(b)** Phase contrast images of unidirectional (left) and bidirectional (middle) living electrodes built using cerebral cortical neurons, each at five days *in vitro* (DIV), next to a single human hair (right). Scale bar: 100 μm. **(c)** Confocal reconstruction of an excitatory living electrode built using primarily glutamatergic cerebral cortical neurons, immunolabeled at 28 DIV for axons (β-tubulin-III; red) and neuronal somata/dendrites (MAP-2; green), with nuclear counterstain (Hoechst; blue). Insets of the aggregate (c′) and axonal (c″) regions are outlined and shown underneath. Scale bars: 100 μm. **(d)** Confocal reconstruction of a dopaminergic living electrode built using neurons isolated from the ventral mesencephalon, immunolabeled at 28 DIV for axons (β-tubulin-III; green) and tyrosine hydroxylase (dopaminergic neurons/axons; red), with nuclear counterstain (Hoechst; blue). Insets of the aggregate (d′) and axonal (d″) regions are outlined and shown to the right. Scale bars: 250 μm. **(e)** Confocal reconstruction of an inhibitory living electrode built using neurons isolated from the medial ganglionic eminence (source of GABAergic neurons), immunolabeled at 14 DIV for axons (β-tubulin-III; purple) and GABA (inhibitory neurons/axons; green), with nuclear counterstain (Hoechst; blue). Insets of the aggregate (e′) and axonal (e″) regions are outlined and shown to the right. Scale bars: 100 μm. Adapted from [46]. **(f)** Phase image of a bidirectional, GFP/mCherry-labeled living electrode at 5 DIV. **(g)–(i)** Confocal reconstruction at 7 DIV, with insets in (i) showing axons from each aggregate making contact with the opposing population **(j)** and growing along each other **(k)** in the microcolumn lumen. Scale bars: 500 μm (f, g, i), 100 μm (j, k). Phase image **(l)** and confocal reconstruction **(m)** of a living electrode at 10 DIV *in vitro*, virally transduced such that the left aggregate expresses ChR2 (optical actuator) and the right aggregate expresses the calcium reporter RCaMP, enabling simultaneous control and monitoring with light. **(n)** Normalized pixel intensity of ROIs within the output (RCaMP+) aggregate from (l-m) during stimulation of the input (ChR2+) aggregate. Gray lines indicate representative, user-defined ROIs randomly selected for analysis, which were averaged to obtain a mean ROI of the aggregate (solid black line). Blue bands along the abscissa represent photostimulation pulses (465 nm, 1-Hz, 100-ms). The changes in activity within the output aggregate due to stimulation of the input aggregate can be seen as sharp spikes occurring within the endogenous, large-amplitude slow-wave activity. **(o)** Zoom-ins of the red insets from (n) showing living electrode activity during (left) stimulation and after (right) optical stimulation [38••].

Figure 3



Cartoon of future living electrode design.
(a) Single optrode with micro-LEDs emitting three distinct wavelengths and neuronal cell body aggregate with populations of neurons optogenetically transduced to respond to the three wavelengths emitted by the optrode. Individual neurons and their axon projections are shown as red, green, or yellow based on the light wavelength they would be programmed to respond to. **(b)** Two-dimensional array of optrodes and cell body pairs. This portion of the construct will remain in the auditory bulla or outside of brain-stem parenchyma for cochlear or brainstem implantation, respectively. **(c)** Cartoon of cochlear construct showing optrodes and neuronal aggregate located external to the cochlear duct. Black lines represent axonal tracts terminating at various positions along the cochlea. This implementation relies on successful synaptic formation between the implanted living electrode axons and the native spiral ganglion cells. **(d)** Cartoon of inferior colliculus construct showing optrodes and neuronal aggregate located outside of the brainstem parenchyma with axonal tracts terminating in various locations within the volume of the inferior colliculus — the parallel lines within the inferior colliculus represent the tonotopic layers accessible by the individual channels of the construct. The array in (b) as well as all non-organic components of the living electrode system are represented external to the cochlea in (c) and inferior colliculus in (d).

living electrode constructs and optogenetic functionalization is provided in Figure 2, and cartoons of potential cochlear and brainstem applications of multi-channel, multi-wavelength living electrode implants are show in Figure 3. Future applications include both central and peripheral placement with relatively minor alterations.

There remain important technological hurdles to overcome before clinical applications. The current implementations rely on harvested neuronal tissue and human applications will require of induction of pluripotent stem cells into the neuronal subtype(s) of interest. The long-term synaptic, axonal ingrowth, and stimulation parameters will also require characterization for each implant site, neuronal population, and construct morphology. Further, adaptation for the cochlea will require direct interaction between the implanted axons with native spiral ganglion neurons which will rely on promotion of neuronal outgrown into the scala tympani as described above for cochlear adaptation to existing electrode technology. Finally, stimulation techniques and parameters will likely differ significantly from those developed over decades for traditional electrodes, and thus significant efforts will be required to optimize the induced audiologic experience following transplantation.

Conclusions and perspectives

Auditory implants are the only widely available method for restoration of a human sense. Significant advancements have been made in the decades since the first single-channel cochlear implant was shown to provide reliable auditory sensations and these have generally been inspired by the natural structure and function of the cochlea — gravitating towards more anatomically and physiologically friendly designs. However, to date these designs have remained constrained within the confines of traditional electrode technology. While the results have been life-changing for hundreds of thousands of patients suffering from hearing loss, a fundamental rethinking of the prosthetic interface will be required to advance the outcomes to those approaching natural hearing. As the methods for optimization of traditional electrode technology continue to advance, including electrode properties, drug elusion, surface coating, and cochlear adaptation, outcomes will continue to be improved for individual patients. Moving forward, multiple additional

lines of investigation including optogenetics, piezoelectric materials, nanotechnology, and living electrodes hold promise to form the basis for entirely novel methods for the restoration of hearing.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

D.K.C. is a co-founder of two University of Pennsylvania spin-out companies concentrating in applications of neuroregenerative medicine: INNERVACE, Inc. and Axonova Medical, LLC. There are four patent applications related to the methods, composition, and use of microtissue engineered neural networks, including U.S. Patent App. 15/032,677 titled 'Neuronal replacement and reestablishment of axonal connections' (D.K.C.) US Patent App. 16/093,036 titled 'Implantable living electrodes and methods for use thereof' (D.K.C.), U.S. Provisional Patent App. 62/758,203 titled "Engineering of innervated tissue and modulation of peripheral organ activity (D.K.C), and US Provisional Patent App. 63/153,321 titled 'Preformed Neural Tissue to Restore or Augment Auditory Inputs to the Brain' (D.K.C., J.A.B., D.O.A.).

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