

## REVIEW

## Near-infrared stimulation of the auditory nerve: A decade of progress toward an optical cochlear implant

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**Abstract**

**Objectives:** We provide an appraisal of recent research on stimulation of the auditory system with light. In particular, we discuss direct infrared stimulation and ongoing controversies regarding the feasibility of this modality. We also discuss advancements and barriers to the development of an optical cochlear implant.

**Methods:** This is a review article that covers relevant animal studies.

**Results:** The auditory system has been stimulated with infrared light, and in a much more spatially selective manner than with electrical stimulation. However, there are experiments from other labs that have not been able to reproduce these results. This has resulted in an ongoing controversy regarding the feasibility of infrared stimulation, and the reasons for these experimental differences still require explanation. The neural response characteristics also appear to be much different than with electrical stimulation. The electrical stimulation paradigms used for modern cochlear implants do not apply well to optical stimulation and new coding strategies are under development. Stimulation with infrared light brings the risk of heat accumulation in the tissue at high pulse repetition rates, so optimal pulse shapes and combined optical/electrical stimulation are being investigated to mitigate this. Optogenetics is another promising technique, which makes neurons more sensitive to light stimulation by inserting light sensitive ion channels via viral vectors. Challenges of optogenetics include the expression of light sensitive channels in sufficient density in the target neurons, and the risk of damaging neurons by the expression of a foreign protein.

**Conclusion:** Optical stimulation of the nervous system is a promising new field, and there has been progress toward the development of a cochlear implant that takes advantage of the benefits of optical stimulation. There are barriers, and controversies, but so far none that seem intractable.

**Level of evidence:** NA (animal studies and basic research).

**KEYWORDS**

cochlear implant, infrared stimulation, neural prostheses, optogenetics

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## 1 | INTRODUCTION

Cochlear implants (CIs) are one of the most successful neural prostheses, now with over 500 000 recipients across the world. However, the performance of individual users varies largely and noisy listening environments, music, and tonal languages challenge all listeners.<sup>1-3</sup> It has been argued that performance could be improved by reducing the interaction between neighboring CI electrode contacts, and subsequently creating more independent channels for stimulation.<sup>4-7</sup> Electrophysical barriers unfortunately limit the feasibility of this strategy and the number of electrodes in CIs has been static for decades.

More recently, it has been suggested that photons can be used to evoke neural responses,<sup>8-11</sup> especially since optical radiation can be delivered more selectively to groups of target neurons.<sup>12,13</sup> This has been investigated as far back as 2004, with much of this research carried out at our institution in the cochlea. It so far has been shown that infrared and near-infrared stimulation is spatially selective and feasible in mice, gerbils, guinea pigs, and cats.<sup>8,11-35</sup> It is anticipated that optical stimulation will enable neural prostheses with enhanced neural fidelity. Optical stimulation must be safe and must be able to accurately encode acoustic information for this technology to be feasible. We address these issues in the following review. In particular, we will summarize the parameters required to encode the acoustic signal via infrared neural stimulation (INS), and will compare this to the electrical stimulation paradigm. We will also make comparisons between direct stimulation with infrared light vs optogenetics (the expression of photosensitive ion channels to neurons unrelated to the perception of light), and describe progress toward an optical CI.

### 1.1 | INS—Neurons are activated by temporally and spatially confined heating

One of the first reports on laser irradiation as a method to stimulate neurons came from Fork's study on *Aplysia californica* (California sea hare) in 1971.<sup>36</sup> Irradiation of the tissue with blue light ( $\lambda = 488$  nm, spot size = 10  $\mu\text{m}$ ) evoked action potentials at stimulus levels above 12.5 mW.<sup>36</sup> More than three decades later, Wells and coworkers studied light-tissue interactions in great detail by using the tunable free-electron laser at Vanderbilt University, and thus determined the target wavelengths that could be used for neural stimulation. They identified several suitable wavelengths in the near-infrared and infrared,<sup>37</sup> and compact optical sources presently exist for stimulation in the 1840 to 2100 nm range. Water preferentially absorbs photons at these wavelengths,<sup>38</sup> and the heat generated then evokes an action potential. It also has been shown that temporally and spatially confined heating changes the membrane capacitance,<sup>30,39-41</sup> resulting in a depolarizing inward current. The change in capacitance might result from changes in membrane thickness<sup>42</sup> or from small-diameter nanopores.<sup>43</sup> Furthermore, we and others have shown that transient receptor potential cation channels of the vanilloid group (TRPV) are involved.<sup>31,44-47</sup> They are temperature sensitive and highly calcium selective.<sup>48-57</sup>

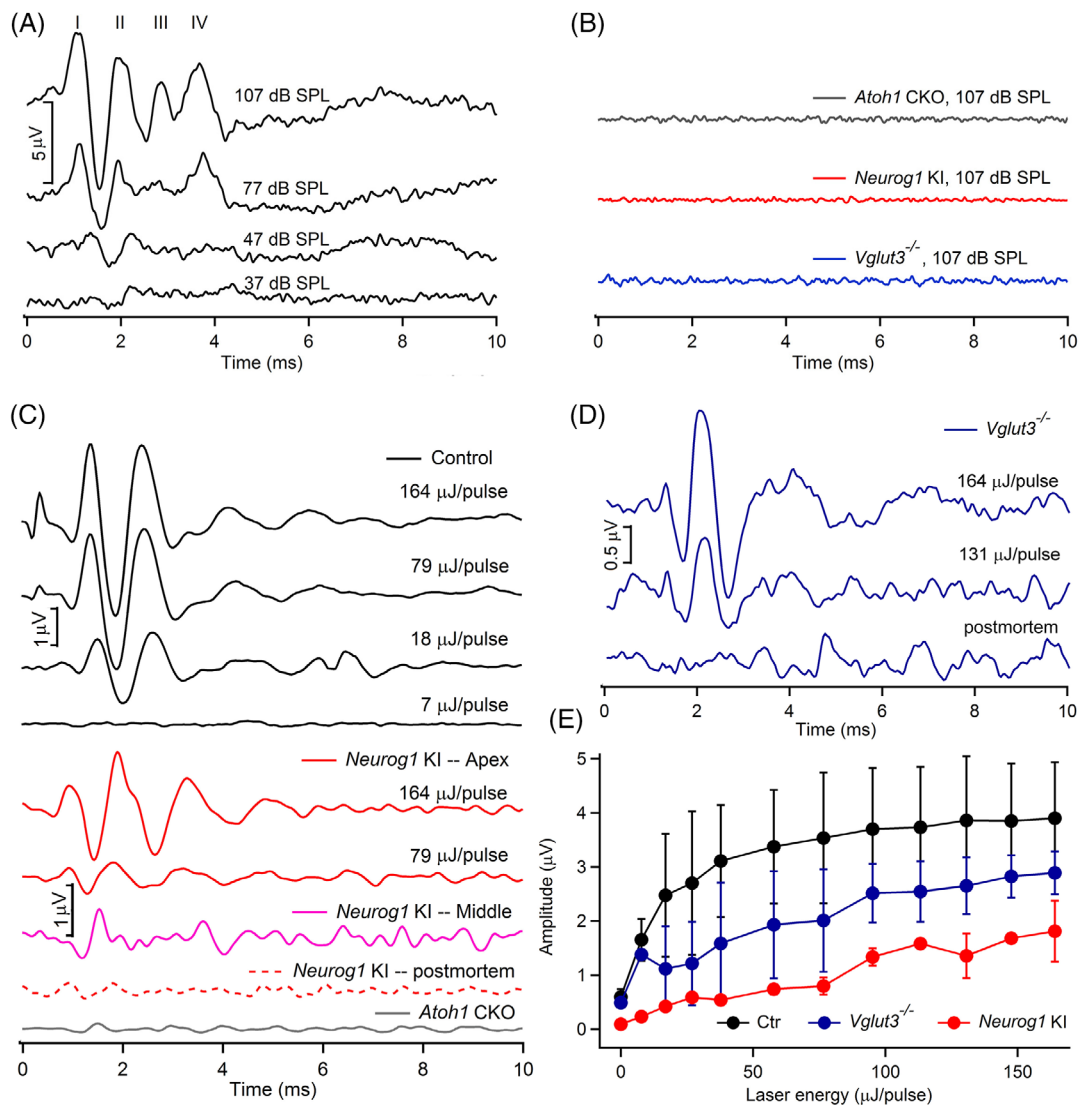
Published results and our data demonstrated that intracellular calcium homeostasis changes during INS.<sup>15,25,28,58,59</sup>

The spatially and temporally confined heating delivered by INS also causes stress relaxation waves,<sup>33</sup> and such optoacoustic phenomena must be considered whenever there is residual hearing. We have made direct pressure measurements in the cochlea during optical stimulation. The pressure in the cochlea at the threshold for INS is similar to the pressure generated by an acoustic stimulus of 50 dB SPL delivered to the outer ear canal.<sup>34</sup> The ongoing debate is if the resulting pressure is the dominating effect in cochlear INS. Results have been presented where cochlear INS did not evoke responses in deaf animals,<sup>60-64</sup> and yet results from experiments in genetically manipulated mice with missing or non-functional hair cells (Figure 1), and a study in deaf white cats argue for a direct stimulation of spiral ganglion neurons during INS.<sup>8,65,66</sup> The negative studies also differ from experiments where INS evokes auditory brainstem responses (ABRs) in congenitally deaf mice such as *Atoh1*<sup>f/k<sup>i</sup>Neurog1</sup> mice, which showed no ABR response to acoustical stimuli.<sup>65,67,68</sup> Another deaf mouse model (absent vesicular glutamate transporter-3) showed responses to INS, but not to acoustic stimuli, and these mice do not release glutamate at the inner hair cell afferent synapse.<sup>65,69-71</sup> A different argument that spiral ganglion neurons (SGNs) are the target for INS comes from the finding that responses from neurons in the central nucleus of the inferior colliculus (ICC) could only be recorded for a short segment along a track through the ICC, and required the SGNs to be in the beam path.<sup>32,72</sup>

The discrepancies in findings about the ability to evoke responses with INS after deafening have not been settled. The deafening protocols appear to be the most prominent differences with the studies that were unable to demonstrate INS. The animals in these studies were deafened with either neomycin or kanamycin and furosemide. These researchers were able to elicit a response to monopolar electrical stimulation, but not to optical stimulation.<sup>60-63</sup> The logical argument is that local heating creates a pressure wave, and that the hair cells are directly stimulated when this vibrates the basilar membrane.<sup>65</sup> However, this leaves several questions open and does not explain why stimulation is confined to the beam path,<sup>13,19,32,34</sup> or why only localized high frequency stimulation is possible in partially deaf animals.<sup>72</sup> It also does not explain why optical responses cannot be masked by acoustic stimuli when animals have increased auditory thresholds but still have remnant hearing.<sup>35,73</sup> This issue would ideally be studied using an animal model wherein there are no hair cells, but there are SGNs and a functioning nerve. Thus far, this has not been possible as the complete absence of hair cells always impairs neural function.<sup>74</sup> However, the aforementioned experiments on the three genetically modified deaf mouse models were done to address help these unsettled differences.

### 1.2 | INS is spatially selective

Spatial selectivity of stimulation along the beam path has been determined in previous experiments.<sup>8,12,13</sup> The target structures



**FIGURE 1** This figure is taken and modified from Tan et al.<sup>65</sup> A, Panel shows the ABRs of a normal hearing control mouse to acoustic clicks at different sound levels. Waves I to IV can be identified. B, No ABRs could be evoked acoustically at 107 dB SPL from either of the three genetically modified mice. C, Panel shows the ABR recordings of the same mice during INS. All mice but the *Atoh1* CKO mouse had responses to INS. (*Atoh1* CKO lack spiral ganglion neuron and thus the target for optical stimulation). Responses disappeared after euthanasia. D, Panel shows the ABR of another deaf mouse, *VGLUT3*<sup>-/-</sup>, which does not release transmitter at the synapse. INS was able to evoke responses in those deaf animals. E, Panel shows the population data (average ± SD). ABRs, auditory brainstem responses; INS, infrared neural stimulation

must be in the beam path to be stimulated with infrared light.<sup>12,13,19,32,34</sup> This has been shown in the guinea pig by using recordings of the auditory nerve CAP,<sup>34</sup> and by single unit responses in the ICC during cochlear INS.<sup>32</sup> Using post mortem X-ray imaging, the orientation of a side-firing fiber could be correlated to the neural responses, and the results confirmed that they were maximum when the SGNs were in the beam path. Remarkably, spatial tuning curves were narrower for INS than for acoustic stimulation. On average, the spread of activation evoked by optical stimuli was 357 μm, vs 383 μm for acoustic pure tone stimuli.<sup>12</sup> In contrast, it has been shown in the same animal model that the spread of monopolar electrical stimulation is several fold wider at 1500 μm.<sup>75</sup>

### 1.3 | Rate of optical pulses during INS from single auditory nerve fiber recordings

In contemporary cochlear implants, the envelope of the acoustical signal is used to modulate a carrier train of charge-balanced biphasic current pulses. The rate of the carrier is reported as the stimulation rate. Ample papers address the optimum rate for electrical stimulation, which appears to be at about 500 pps.<sup>76-83</sup> This pulse repetition rate is clearly higher than the maximum response rates typically found in recordings from single auditory nerve fibers in response to high level stimuli, ~300 action potentials per second. The rationale for the over-driven rates for electrical stimulation is to ideally map the acoustic frequency information, and to generate stochastic patterns of nerve

responses that increase the dynamic range of stimulation. In contrast to electrical stimulation, phase locking is not as prominent with optical stimulation, and therefore evokes a more stochastic firing pattern at the outset.

For acoustic stimuli, the absolute refractory period (time for which no action potential can be evoked) is slightly less than a millisecond, and it is even shorter for electrical stimulation at about 0.3 ms.<sup>84</sup> This is different than with laser stimulation, where the shortest latency is 2.5 ms. Although INS has evoked action potentials up to 1000 pps, phase locked responses to the stimulus are typically not more than 100 pps. Our average maximally sustained driven rate of action potentials with optical stimulation was  $97 \pm 52$  pps, while our average maximum *acoustically*-driven rate was  $158 \pm 82$  pps.<sup>85</sup> The maximum sustained electrically-driven rate was about 500 pps,<sup>86</sup> which is unquestionably higher than reported maximum sustained *acoustically*-driven rates.<sup>87</sup>

#### 1.4 | INS dynamic range

For INS, the radiant energy vs CAP amplitude contours show a sigmoid increase, which is similar to the increase in the discharge rate of single ANFs, and for activity recorded from single units of the ICC. Optical stimulation can saturate the responses for each of these. The dynamic range is about 6 dB, which is comparable to the increase in rate with electrical current, and is clearly less than the dynamic range for acoustic stimulation. However, a wider range over which the rate increases can be achieved with a novel coding strategy.<sup>88,89</sup>

#### 1.5 | Radiant energy for INS and safety considerations

The possibility of INS-induced cochlear damage has been tested in short-term experiments in small rodents. The selected optical parameters for INS were the pulse repetition rate (10-250 pps), and the radiant energy (0-127  $\mu\text{J}/\text{pulse}$ ), and we did not observe any changes in CAP amplitude for 250 pps and 20  $\mu\text{J}/\text{pulse}$  after up to 5 hours of continuous irradiation. The minimum radiant energy to evoke a response at  $\lambda = 1869$  nm and pulse duration of 100  $\mu\text{s}$  was typically below 4  $\mu\text{J}/\text{pulse}$  (units of the inferior colliculus) and 7  $\mu\text{J}/\text{pulse}$  for CAPs.<sup>17,32</sup> However, detrimental changes in CAP amplitude were not observed until radiant energies above 20  $\mu\text{J}/\text{pulse}$  at 250 pps, or faster repetition rates.<sup>8,16,21,23</sup> Corresponding cochlear histology from control animals and animals even exposed to 98 or 127  $\mu\text{J}/\text{pulse}$  at 250 pps did not show a loss of spiral ganglion cells, hair cells, or damage visible with light microscopy to other soft tissue structures of the organ of Corti. In addition to the acute experiments, we also examined cats chronically implanted with optical fibers. They were exposed to continuous optical stimulation at  $\lambda = 1850$  nm, 200 pps, and 12  $\mu\text{J}/\text{pulse}$ , 4 to 8 h/d for up to 30 days. Electrophysiological responses were stable despite long-term stimulation. Furthermore, SGN counts and post-implantation tissue

growth (which was localized at the fiber) were similar in chronically stimulated and sham implanted cochleae.<sup>21</sup>

#### 1.6 | INS vs optogenetics

The optogenetic approach starts with the delivery of genetic information with a viral vector to SGNs. This is to express light-gated ion channels, as first demonstrated for the auditory system by Hernandez et al in a mouse model in 2014.<sup>9,90</sup> The channels allow radiation in the visible range to control electrical excitability, intracellular acidity, and calcium influx. Crucial to the success of this method is the rate by which the ion channels are expressed. Low expression will require larger photon flux rates, and high expression may damage the cell. A recent paper on the optogenetic approach in the auditory system using deaf adult gerbils has shown that the success rate to evoke a response after an adeno-associated virus (AAV) transfer of a faster channelrhodopsin mutant (CatCh) was 46%.<sup>91</sup> Furthermore, the viral vector decreased the number of SGNs by about 25%.<sup>91</sup> Even with fast ion channels successfully expressed, the pulse repetition rate for which significant phase locking can be observed was not above 250 pps.<sup>91,92</sup> Figure 6b in the aforementioned publication<sup>92</sup> suggests that the rate limiting factor for the pulse repetition is the  $\sim 4$  ms delay for the response following the stimulus. In comparison, it is 0.3 ms with electrical stimulation and about 2.5 ms with INS. In gerbils, the radiant energy required to evoke ABRs through activation of light-gated channels in the optogenetic approach is 4  $\mu\text{J}/\text{pulse}$ ,<sup>91</sup> and 2  $\mu\text{J}$  to at the behavioral thresholds. These results show that radiant energies required to stimulate the auditory system are similar for direct INS and optogenetics, and that the most effective pulse rates are similar, although their upper limits are due to distinct mechanisms.<sup>32,72,85,93</sup>

As previously discussed, and in contrast to optogenetics, INS evokes action potentials via spatially and temporally confined heating of the SGNs. The temperature change is about 0.1°C per pulse ( $\lambda = 1860$  nm, fiber diameter 200  $\mu\text{m}$ ; pulse length 100  $\mu\text{s}$ ).<sup>94,95</sup> The challenge for INS is to heat the target structure(s) without thermal damage, so heat needs to dissipate quickly or be removed. At present, tissue heating limits the rate of stimulation to about 250 pps at a maximal radiant energy of 25  $\mu\text{J}/\text{pulse}$ ,<sup>16,94,96,97</sup> but lowering the radiant energy for INS would allow for faster repetition rates. We have demonstrated in our pilot studies that methods exist to reduce the radiant energy by about an order of magnitude.

#### 1.7 | Approaches to reduce the power requirements for INS

The photon absorption in water is similar at  $\lambda = 1550$  and 1860 nm. However, the technology for small optical sources is well-advanced for the 1370 to 1600 nm wavelengths used for communication networks, more so than what is available around 1860 nm. To explore the possibility of using 1550 nm for INS we have directly compared

evoked auditory responses at both 1550 and 1860 nm in the same animal, and stimulation with both wavelengths is comparable. Furthermore, we have tested sources at 1375 nm and found that INS is even more efficient at this wavelength, and about three times more efficient than sources for 1550 or 1860 nm.

A recent publication on the mechanism of INS has provided an elegant theoretical framework describing that the membrane of the neuron has two capacitive components (electrical and temperature dependent), and that their interactions must be considered during stimulation.<sup>41</sup> We have used those equations to predict the responses to pulses, with an energy profile that follows a square, ramp-up, ramp-down, or a triangle. Modeling predicted that the ramp-up waveform and the triangular waveform are more power efficient to increase the tissue temperature. Corresponding experiments using these pulse shapes in cats and guinea pigs confirmed that the ramp-up pulses are the most efficient.<sup>14</sup>

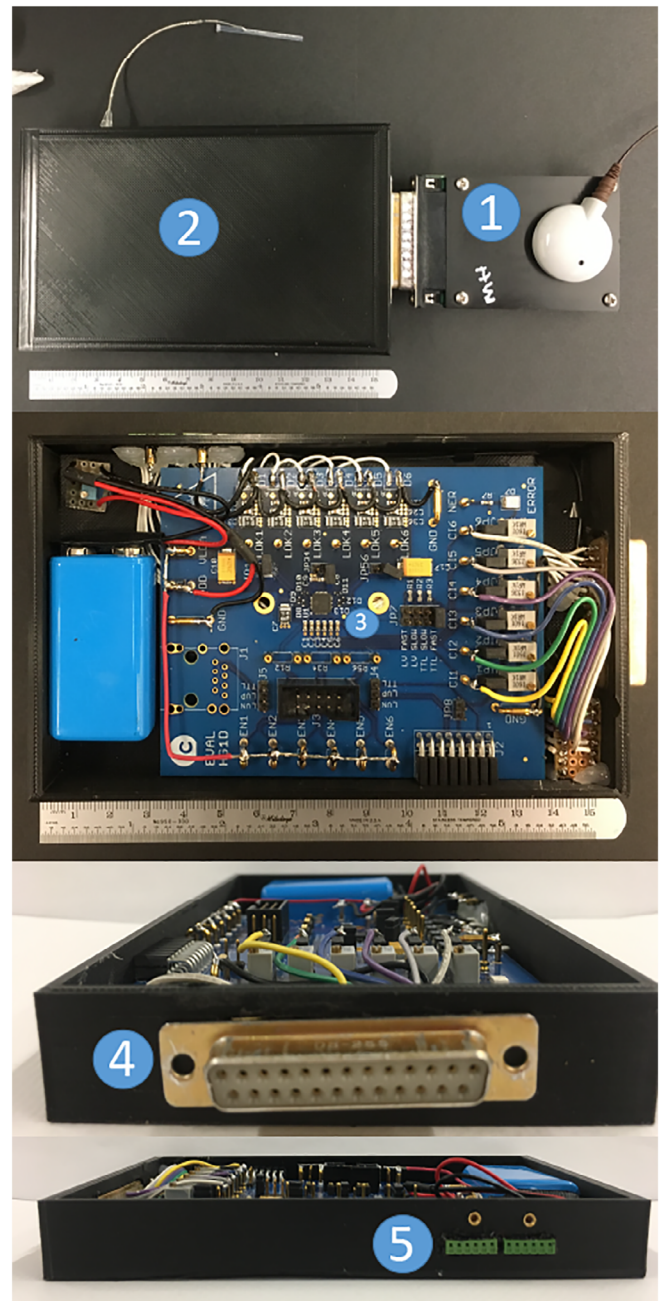
Combined optical and electrical stimulation reduces the radiant energy required for INS in peripheral nerves<sup>98-100</sup> and for auditory neurons in deaf white cats.<sup>66</sup> All cats were profoundly deaf with no response to acoustic stimuli up to 120 dB SPL. Histology showed severe degeneration of the cochleae with missing organs of Corti, complete loss of outer and inner hair cells, and a variably reduced number of SGNs. ABRs were recorded in response to electrical pulses of 0 to 1400  $\mu$ A, and in response to the laser pulses ( $\lambda = 1860$  nm, radiant energy = 0 to 164  $\mu$ J/pulse, pulse repetition rate = 10 Hz, and pulse width = 100  $\mu$ s). Responses to INS were only seen if the neuron counts were larger than 7% of those in normal hearing animals.<sup>66</sup> Further experiments are required to determine optimal timing of the electrical and optical pulses, but hybrid stimulation could also increase the safety, dynamic range, and maximum rate for INS.

## 1.8 | The optical/electrical cochlear implant

Any such device would still have the three-component design of all CIs: a speech processor, spike generator, and stimulation array. As with existing implants, the processor separates the acoustical signal into frequency bands, which are set to the number of intended sites of stimulation along the cochlea. However, the acoustic information for each frequency band is then translated into a series of both electrical and optical pulses. The timing and amplitude information for each modality is inherently different, so special attention must be given to the programming of the stimulator, as well as the design of the hybrid array. The pulse generator has two components, one generating biphasic electrical pulses and the other optical pulses. The electrode is a hybrid of electrical and optical sources. One of our first prototypes for an optical cochlear implant to be carried in a backpack of a large animal is shown in Figure 2.

## 1.9 | The light delivery system

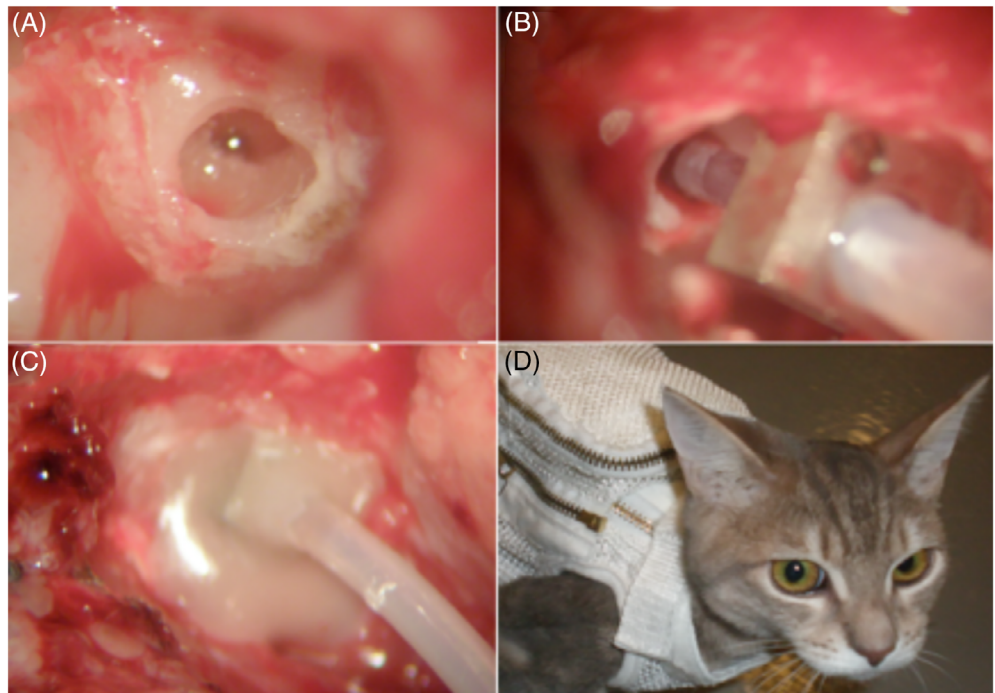
Light delivery systems (LDSs) can be made of small light sources or optical waveguides, but the technology understandably has to conform to the size of the cochlea. A detailed analysis based on micro-



**FIGURE 2** 1: A CI receiver is used to convert the signals into pulses of given length and amplitude. 2: Housing for a prototyping board shown in the next panel contains a microchip that then converts these pulses into outputs for the optical sources. 3: The microchip on the prototyping board. 4: The receiver can be replaced by direct computer input. 5: Outputs to the optical sources and electrode array. CI, cochlear implant

computed tomography studies of human temporal bones provides boundaries.<sup>101-103</sup> Conservative measurements show that the smallest diameter of a circular array that would fit into the scala tympani should be less than 0.97 mm at the base, and taper to 0.48 mm at the tip. Furthermore, it must be stiff enough to insert, yet flexible enough to do so without trauma. Initial proof of concept experiments for INS

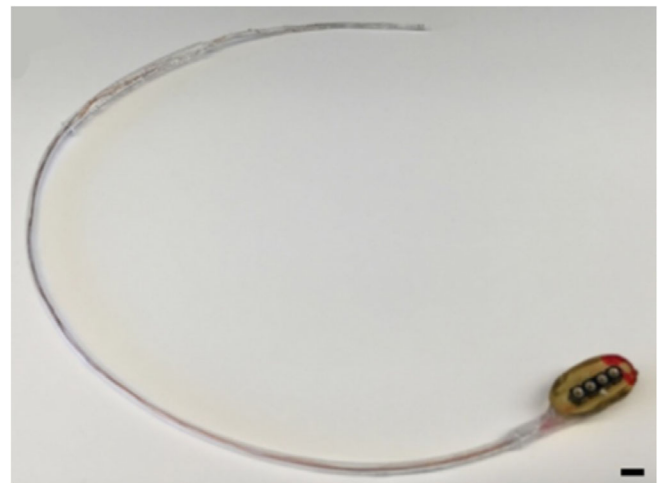
**FIGURE 3** The implantation of an optical fiber into a cat cochlea for chronic stimulation. A, The cochleostomy into the basal turn the left cochlea. B, The inserted fiber secured to the bulla with a metal bracket. C, The bulla is closed with dental acrylic. D, The backpack carrying the stimulator



used an open beam path of a free electron laser, or used flat polished optical fibers. The first chronic experiments were done in cats.<sup>21</sup> The animals carried a laser source in a backpack and extended periods of stimulation were possible (Figure 3).

The LDS was made with quartz glass optical fibers, but had limited a survival time in cats, demonstrating the limitations of this material. The two key failure points were at the anchor attached to the bulla and at the cutaneous feed through. Alternatively, an array can be built without fibers if small light sources can fit into the cochlea. Possible sources include vertical-cavity surface emitting lasers (VCSELs), edge emitting laser diodes, and micro light emitting diodes. VCSEL technology has significantly advanced over the last few years, but they have limited efficiency, and the radiant energy delivered to the tissue is too low for reliable stimulation with infrared light. For example, in the cochlea, the radiant energy is less than 6 dB above the energy required to evoke a measurable response. Alternatively, edge emitters are available for  $\lambda = 1850$  nm. The die is 300  $\mu\text{m}$  wide, 100  $\mu\text{m}$  thick, and can be 250, 350, or 450  $\mu\text{m}$  long. When operated in continuous wave mode the output power of the longest VCSEL was up to 50 mW average power. In pulsed mode operation, the output power could be increased by a factor of  $\sim 4.5$ . Meanwhile, high-efficiency microscale light emitting diodes ( $\mu\text{LEDs}$ ) are an option for optogenetic approaches.

To build optrodes using edge emitters, we have connected each of the light sources to a single 125  $\mu\text{m}$  diameter silver wire. The wire is the backbone of the array, and the silver also acts as a heat sink. The silver wire is connected to the cathode of the optical sources while the anode is a 25  $\mu\text{m}$  diameter platinum wire. After each wire has been connected with conductive epoxy to the light source, the array is placed into a mold that has the dimension of the final array to be inserted in the cochlea (Figure 4). This is then filled with silicone and cured.



**FIGURE 4** A fully assembled optrode, which has been implanted in cats. The scale bar is 1 mm

Waveguides (fibers) are another option, but glass waveguides are disadvantageous because they are stiff enough to damage the cochlea during insertion, and (as demonstrated with cats) fragile.<sup>104</sup> Polyimides are an alternative that are far more compliant than glass (20-40 times), and they transmit infrared light well. At the current state of technology, waveguides appear to us to be the best option for an optical CI, although our prototyping is in an extant phase.

### 1.10 | Flexible printed circuit board (FPCB)

We so far have discussed electrode array design, but optical stimulation using waveguides would also require a proximal source within the

receiver-stimulator casing. One novel option is to incorporate flexible printed circuit board (FPCB) technology. A single layer FPCB can be designed as the light source carrier, and this makes the fabrication process much easier. The substrate needs to be soft, flexible, and must have good biocompatibility. Polyimide polymers meet these criteria,<sup>105-109</sup> and we developed a prototype using polyimide for the support base and insulation cover layer, and copper was used as the conductor.

To fabricate the multichannel optrode carrier, 25  $\mu\text{m}$ -thick copper foil was laminated on the upper surface of the polyimide substrate. The foil was etched to create copper wires that were 80  $\mu\text{m}$  wide. To isolate the wires, a 25  $\mu\text{m}$ -thick polyimide film was then laminated over this surface. This insulating film was then etched off of the light source mounting areas and solder joints, which were further improved by electroplating a 25- $\mu\text{m}$ -thick gold layer on these contacts. We so far have only fabricated three channel optrodes, since our portable stimulator only has three light sources, but the number of contacts can easily be expanded. This carrier can also accommodate the red and infrared VCSELs,  $\mu\text{LEDs}$ , and edge emitting laser diodes. It also can incorporate metal contacts for electrical stimulation.

## 2 | CONCLUSION

Recent research on INS has demonstrated that the auditory system can be safely stimulated with infrared light, and in a much more spatially selective manner than with electric current. However, it also has been found the neural response characteristics are much different than with electrical stimulation, so existing CI stimulation paradigms will need to be modified for optical stimulation. Meanwhile, optogenetics renders neurons more sensitive to stimulation by inserting light sensitive ion channels via viral vectors. This so far has been complicated by a high rate of cell death, unlike direct INS, which has the advantage of relative simplicity. The rhodopsin channels also introduce a refractory delay that limits the rate for phase locking. Regardless, light stimulation of the nervous system is a promising new field, and there has been solid progress toward the development of an optical CI.

### CONFLICT OF INTEREST

Claus-Peter Richter is inventor on the following patents:

1. Cochlear implant including a modiolar return electrode. Inventors: Ho, S., Richter, C.-P. (2007) US Patent No. 7194314.
2. Optical stimulation of the auditory nerve, a novel concept for cochlear implants. Inventors: Walsh Jr., J., Izzo, A., Jansen, D., Richter, C.-P. (2010) US Patent No. 7833257.
3. System and Method for animal-human neural interface. LaFair, P., Richter, C.-P. (2016) US Patent 9327120.
4. Systems and Methods for neuromodulation device coding with transspecies libraries. Richter, C.-P., Heddon, C., LaFaire, P., Dougherty, B., (2019) US Patent No. 10300269.

5. Systems and methods for noise based coding in cochlear implants. Richter, C.-P., Roberts, R. (July 10, 2015) Application Number: 62191084.
6. Systems and Methods for Governing Information Encoding in the Nervous System Using Neurostimulation Devices Heddon, C., Roberts, R., Richter, C.-P. (Feb 23, 2016); Application Number: 62298992.
7. System and method for cochlear implant stimulation. Richter, C.-P., Albeck, D. (Aug 14, 2019) Application Number: US 62/718569.
8. Cochlear implant and method of generating stimulations for a cochlear implant. Richter, C.-P., Tan, X, Xu, Y, Albeck, D. (Feb 6, 2020) Application Number: US 62/801771.

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