during manufacture and immunization, and its immunogenicity could be enhanced by strategic targeting of immune cells. Another viral disease for which mRNA vaccines may be especially useful is dengue. Efforts to develop an effective dengue vaccine have been hampered by the observation that some dengue-specific antibodies generated during a primary dengue infection actually enhance disease severity during a secondary dengue infection[9]. A customized mRNA vaccine that encodes low-risk epitopes from all four dengue virus serotypes but omits epitopes that enhance secondary infection might address this issue.

The development of alternative influenza vaccine approaches that could be rapidly deployed in the event of a pandemic should be a public-health objective of high priority. Thanks to their speed and ease of production, nucleic acid–based vaccines, such as the one described by Petsch *et al.*[1], may be more likely to meet this objective than are traditional protein vaccines. As mRNA vaccines can theoretically encode any antigen, they may also facilitate novel antigen-targeting approaches, such as cross-reactive HA epitopes that elicit antibodies that neutralize multiple influenza subtypes[10,11]. These epitopes, when delivered by an immunogenic, flexible and scalable method such as mRNA, could provide an effective universal influenza vaccine.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Lothar, S. *et al. Nat. Biotechnol.* **30**, 1210–1216 (2012).
2. Fiore, A.E., Bridges, C.B. & Cox, N.J. *Curr. Top. Microbiol. Immunol.* **333**, 43–82 (2009).
3. Ulmer, J.B., Mason, P.W., Geall, A. & Mandl, C.W. *Vaccine* **30**, 4414–4418 (2012).
4. Hoerr, I., Obst, R., Rammensee, H.G. & Jung, G. *Eur. J. Immunol.* **30**, 1–7 (2000).
5. Shinya, K. *et al. Nature* **440**, 435–436 (2006).
6. Pearce, M.B., Belser, J.A., Houser, K.V., Katz, J.M. & Tumpey, T.M. *Vaccine* **29**, 2887–2894 (2011).
7. Louz, D., Bergmans, H.E., Loos, B.P. & Hoeben, R.C. *Crit. Rev. Microbiol.* (2012).
8. Richardson, J.S., Dekker, J.D., Croyle, M.A. & Kobinger, G.P. *Hum. Vaccin.* **6**, 439–449 (2010).
9. Dejnirattisai, W. *et al. Science* **328**, 745–748 (2010).
10. Corti, D. *et al. Science* **333**, 850–856 (2011).
11. Ekiert, D.C. *et al. Nature* **489**, 526–532 (2012).

Extracting energy from the inner ear

Kenneth Shepard, Taku Ito & Andrew J Griffith

The endocochlear potential in a guinea pig's ear is captured and used to run a low-power radio.

Small, measurable electrical potentials exist in living systems. In recent work, the energy in trees[1] and invertebrates[2] has been harvested to power electronic chips; now, a similar feat has been achieved in a mammal. In this issue, Mercier *et al.*[3] report that a radio chip can be powered by tapping the endocochlear potential in the inner ear of a guinea pig, opening the way to potential clinical and basic scientific applications in the auditory and vestibular organs, as well as other systems.

Medical implant devices—including pacemakers, cochlear implants, deep brain stimulators for Parkinson's disease and spinal cord stimulators for pain management—are rapidly becoming commonplace. These devices must be low power, and they generally make use of batteries or radio-frequency inductive power transfer, the latter either to directly power the device or, more often, to charge a battery or ultracapacitor. Power levels are generally in the regime of tens of microwatts to milliwatts.

For some applications, and by exploiting the scaling of integrated circuit technology, it may be possible to drive down the power consumption of implant devices to the point that they can rely solely on energy from the environment[4]. Environmental sources of energy include chemical energy (e.g., generated by an enzymatic fuel cell), mechanical energy (in vibrations), thermal energy (in systems with a temperature gradient) and radio-frequency electromagnetic energy. The power levels of such devices are much lower than those for inductive power transfer—generally in the microwatt range or below. **Figure 1** shows the relative power consumption of some representative devices and the power available with various energy-extraction approaches.

To harvest energy from a mammal, Mercier *et al.*[3] exploit the inner ear, which is embedded deep within the temporal bone, the densest bone in the human body. The cochlea is the snail-like, coiled part of the inner ear that mediates our sense of hearing. Between the endolymph fluid filling the cochlear duct and adjacent cells and tissues, there is a large, positive electrochemical potential of approximately 70–100 mV (ref. 5; **Fig. 1**).

The endocochlear potential derives largely from a high concentration of potassium ions, which are pumped into the endolymph from the lateral wall of the cochlea[6]. It is required for normal transduction of mechanical energy into electrical energy in sensory hair cells and is critical for hearing. Because the endocochlear potential is easily diminished or lost with interventions that violate the integrity of the endolymph or its tight-junction barriers, the notion of harvesting sustainable energy from the cochlea, which involves inserting an electrode into the endolymph, has seemed unthinkable. With the work of Mercier *et al.*[3], this novel energy source now appears to be within reach, owing to a combination of clever engineering and meticulous surgical technique.

The available power of the endocochlear potential is in the nanowatt regime. Harvesting this power requires an integrated circuit that carefully buffers energy, allowing the chip to be active only 0.0001% of the time. Mercier *et al.*[3] designed a complementary metal-oxide-semiconductor (CMOS) integrated circuit (2.4×2.4 mm^2) mounted on a printed circuit board 11 mm × 9 mm, which includes a 200-nF capacitor for energy storage and a 3 mm × 4 mm loop antenna. To test the device, they inserted glass capillaries into the endolymph of guinea pigs under general anesthesia, with the printed circuit board located outside of the animal's body. Data were collected for up to 5 h using the endocochlear potential as the only source of energy into the system. The authors showed excellent results of steady energy extraction with only slight fluctuations, and used the energy to power a radio transmitter that allowed measurement of the endocochlear potential itself.

To determine whether the device damaged the animal's hearing, they measured compound action potential thresholds of the auditory nerve before and after electrode insertion and before and after current draw. A small effect on compound action potential thresholds was seen, and this was attributed to the large size of the electrodes. Overall, the results were encouraging for the feasibility of this approach, at least for the duration of the experiment. Both the power dissipated by the device (in the few-nanowatt regime) and the energy extracted from the endocochlear potential (perhaps up to tens of nanowatts) are noted in **Figure 1** for comparison.

Among the potential applications of this technology, an especially compelling one is

Kenneth Shepard is in the Department of Electrical Engineering and Biomedical Engineering, Columbia University, New York, New York, USA, and Taku Ito and Andrew J. Griffith are in the Otolaryngology Branch, National Institute on Deafness and Other Communication Disorders, US National Institutes of Health, Rockville, Maryland, USA.
e-mail: shepard@ee.columbia.edu or griffita@nidcd.nih.gov

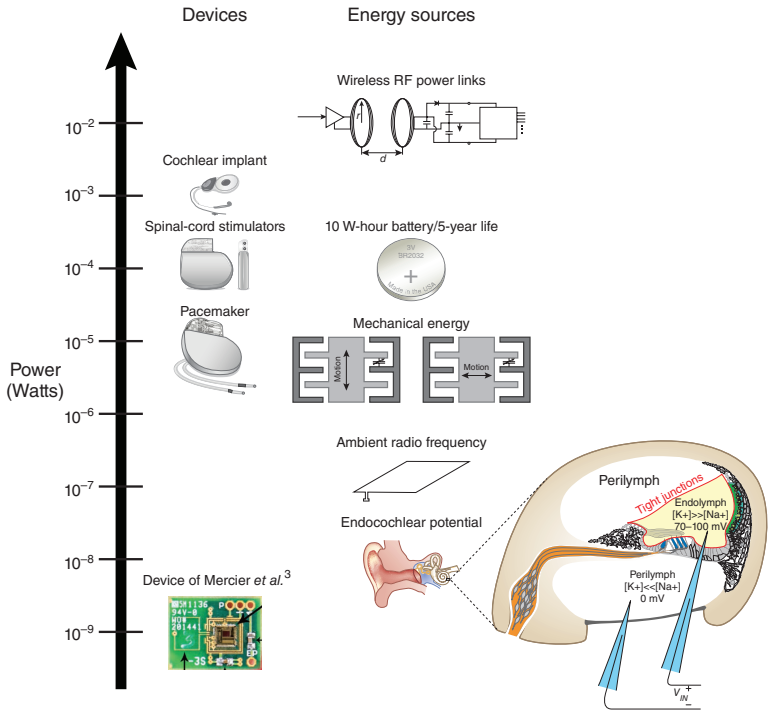

Figure 1 Commonly used biomedical devices with their power requirements (in Watts) and energy sources. The device described in Mercier *et al.*[3] is shown along with its energy source, the cochlear duct. Potassium ion secretion from the lateral wall of the cochlear duct generates a 70–100 mV electrochemical potential.

the study of hearing loss in humans and animals. Hearing and balance are compromised in hundreds of different human disorders[7]. Some of the most challenging to treat or rehabilitate are those in which hearing or balance function fluctuates. Ménière's disease, for example, is characterized by sudden and debilitating episodes of hearing loss, severe spinning dizziness, and fullness and ringing in the ear[8]. It has long been speculated that disorders such as Ménière's disease are caused directly or indirectly by fluctuations in endocochlear potential. This has never been proven, however, because the inner ear has been essentially a black box, particularly in live humans, where access is possible only by surgery that involves drilling through the temporal bone. The work of Mercier *et al.*[3] paves the way to direct understanding of the physiology of fluctuating hearing loss and balance in live, awake humans, and, we hope, to therapeutic interventions.

Several hurdles remain to be surmounted before the device of Mercier *et al.*[3] becomes a practical tool. The study highlights some of the challenges of the bioelectronic interface. First, the potentials involved are small, similar to the thermal voltage (kT/q) that determines the voltage scale for the modulation of current under the control of the gate in transistors. As a result, it is very difficult for CMOS integrated circuits to start up at low voltages. The authors rely on an alternate energy source—radio-frequency harvesting—for this startup. Second, electrophysiological energy sources rely on ions to carry charge, whereas integrated circuits rely on electrons. To convert ions to electrons requires an electrochemical interface that often (but not always, as in the case of redox intermediaries) consumes a chemical reagent when dc current is required, ultimately limiting the lifetime of the electrodes. The electrodes are also susceptible to other degradation mechanisms that limit their stability. Stability may become a bigger issue with awake and moving recipient animals, although the high density and stability of the temporal bone may be beneficial in this respect. It will also be useful to adapt the device for use in mice, a common animal-model in auditory and vestibular research.

In considering the future potential of the work of Mercier *et al.*[3], it is worth recalling the history of the cochlear implant[9], a revolutionary neural prosthesis that has restored auditory perception, speech and language in >200,000 people worldwide. When the concept of the cochlear implant was first introduced, very few believed that it would work[10]. Mercier *et al.*[3] have given us a reason to believe that the future is bright for harnessing the body's own energy to monitor, heal and hear.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Himes, C., Carlson, E., Ricchiuti, R.J., Otis, B.P. & Parviz, B.A. *IEEE Trans. Nanotechnol.* **9**, 2–5 (2010).
2. Halamkova, L. *et al.* Implanted biofuel cell operating in a living snail. *J. Am. Chem. Soc.* **134**, 5040–5043 (2012).
3. Mercier, P.P., Lysaght, A.C., Bandyopadhyay, S., Chandrakasan, A.P. & Stankovic, K.M. *Nat. Biotechnol.* **30**, 1240–1243 (2012).
4. Sarpeshkar, R. *Ultra Low Power Bioelectronics: Fundamentals, Biomedical Applications, and Bio-inspired Systems* (Cambridge University Press, Cambridge, UK; 2010).
5. Von Bekesy, G. *Nature* **169**, 241–242 (1952).
6. Wangemann, P. *J. Physiol. (Lond.)* **576**, 11–21 (2006).
7. Schuknecht, H.F., Merchant, S.N. & Nadol, J.B. *Schuknecht's Pathology of the Ear*, 3rd edn. (People's Medical Publishing House; 2010).
8. Ménière, P. *Gaz. Med. de Paris* **16**, 88–89 (1861).
9. Moore, D.R. & Shannon, R.V. *Nat. Neurosci.* **12**, 686–691 (2009).
10. Eisen, M.D. *Otol. Neurotol.* **24**, 500–506 (2003).

Research Highlights

Papers from the literature selected by the Nature Biotechnology editors (follow us on Twitter, @NatureBiotech #nbtHighlight)

Maintenance of hematopoietic stem cells through regulation of Wnt and mTOR pathways
Huang, J. *et al. Nat. Med.* doi:10.1038/nm.2984 (11 November 2012)

A physical, genetic and functional sequence assembly of the barley genome
The International Barley Genome Sequencing Consortium. *Nature* doi:10.1038/nature11543 (17 October 2012)

Efficient TALEN-mediated gene knockout in livestock
Carlson, D.F. *et al. PNAS* **109**, 17382–17387 (2012)

Maturation-dependent HIV-1 surface protein redistribution revealed by fluorescence nanoscopy
Chojnacki, J. *et al. Science* **338**, 524–528 (2012)

DNA template strand sequencing of single-cells maps genomic rearrangements at high resolution
Falconer, E. *et al. Nat. Methods* **9**, 1107–1112 (2012)