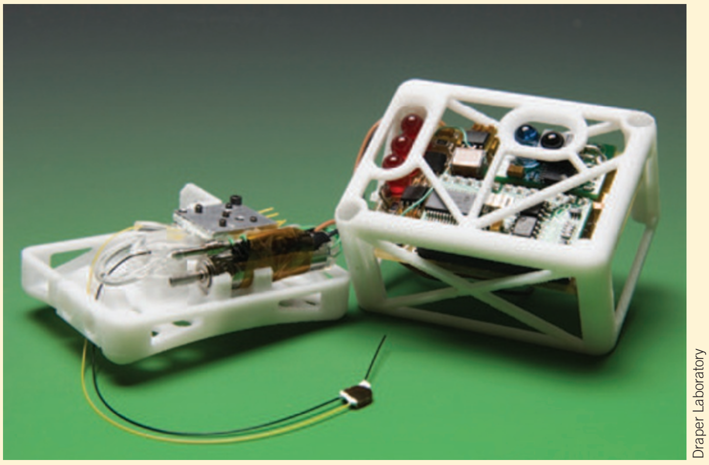
Innermost desires


Draper Laboratory

The inner ear is called the 'bony labyrinth'—and for good reason. This essential part of our hearing organ consists of a maze of skeletal cavities, including the snail-shell–shaped cochlea, the target of most agents designed to combat hearing loss. Unfortunately, getting drugs into the cochlea has proven a complex puzzle.

Many compounds in pills don't cross the blood-cochlear barrier and come with off-target effects, whereas drugs injected into the space behind the ear drum don't always permeate from the middle ear into the organ's inner recesses. Thus, for deeper drug penetration, some researchers have been working on implantable devices that can directly deliver compounds into the inner cochlear fluid.

The most advanced such model is being developed by Jeffrey Borenstein and his colleagues at the Charles Stark Draper Laboratory in Cambridge, Massachusetts. By combining a microfluidic pump, a drug reservoir, an electronic control system and tiny tubing, Borenstein's team has devised an apparatus that could one day be implanted in the temporal bone just behind the human ear to provide long-term drug delivery in a controlled and timed manner.

"Bringing it to clinical fruition is really what we're aiming to do," says Borenstein, whose group is working to miniaturize the device, with plans to build a prototype suitable for human clinical trials in 2015. "You can take out quite a bit of that [bone] and not do anything structurally that would cause any problems. That's what the surgeons tell me."

In collaboration with auditory scientists at the nearby Massachusetts Eye and Ear Infirmary in Boston, Borenstein's team is first testing a prototype on guinea pigs: a contraption about the size of a ring box, with all the components connected to a thin tube surgically implanted in the cochlea. The researchers had tried strapping the device (pictured) to the rodents' backs, but that didn't work. "We started referring to them as 'Little Houdinis' because they literally managed to get out of every jacket or backpack we designed for them," says Erin Pararas, a Draper scientist. The group eventually found a workaround by fastening the pods surgically to the top of the guinea pigs' heads.

Currently, the researchers are using the device to infuse a chemical called 6,7-dinitroquinoxaline-2,3-dione (DNQX), which temporarily blocks signals between sensory hair cells and nerve fibers leading to the brainstem by blocking glutamate receptors. Thanks to the fact that hair cells close to the entrance of the cochlea pick up higher-frequency sounds than cells further down the length of the coiled tube do, the researchers can track where the drug has traveled using a series of hearing tests. In the future, they plan to switch over to agents that protect or even help regenerate, rather than hinder, the ear's most delicate structure.

"Implantable-type devices are all in the fairly early stages," says David Borkholder, a biomedical engineer at the Rochester Institute of Technology in upstate New York who is working on an intracochlear drug delivery system in mice. "But I view them as an essential tool that will enable advanced deafness therapy research and development beyond what people do today." *—ED*

to market. Based on intellectual property developed by Richard Kopke, a former ear surgeon at the Naval Medical Center in San Diego, the drug contained an antioxidant called *N*-acetylcysteine (NAC), which is used as a prescription drug to counteract

acetaminophen overdose and as a nutraceutical for its liver- and lung-protective functions.

In extensive preclinical testing, Kopke and many others showed that NAC protected against various forms of hearing loss, including loud noise, by scavenging the free radicals that form during and after the metabolic stress and contribute to acquired deafness. But the results from human testing were more lackluster. A 2003 Navy trial, the largest conducted to date, enlisted 566 Marine recruits undergoing two weeks of weapons training with M-16 rifles. Subjects in the still-unpublished study were randomized to receive 900 milligrams of NAC or placebo three times a day with each meal for the duration of the boot camp.

According to Kopke, who helped run the trial, less than a third of the recruits, all of whom wore ear plugs for protection, experienced any hearing loss, and, for those people who did, the NAC treatment only reduced the occurrence of significant hearing loss by about 25%. However, a similar follow-up study in another population of recruits-in-training that tested a higher dose of NAC and controlled for smoking and painkiller use found no such effect.

"There may be some suggestion of benefit, but there are some statistical measures that don't support this," says Michael Hoffer, a Naval Medical Center neurotologist who was not involved in the two trials but who has worked with the study authors testing NAC in other settings, including in soldiers fighting in Iraq.

Beta testing

"The Hearing Pill was really a beta test for the concept, and the concept was, 'Will people buy an orally dosed nutraceutical to address