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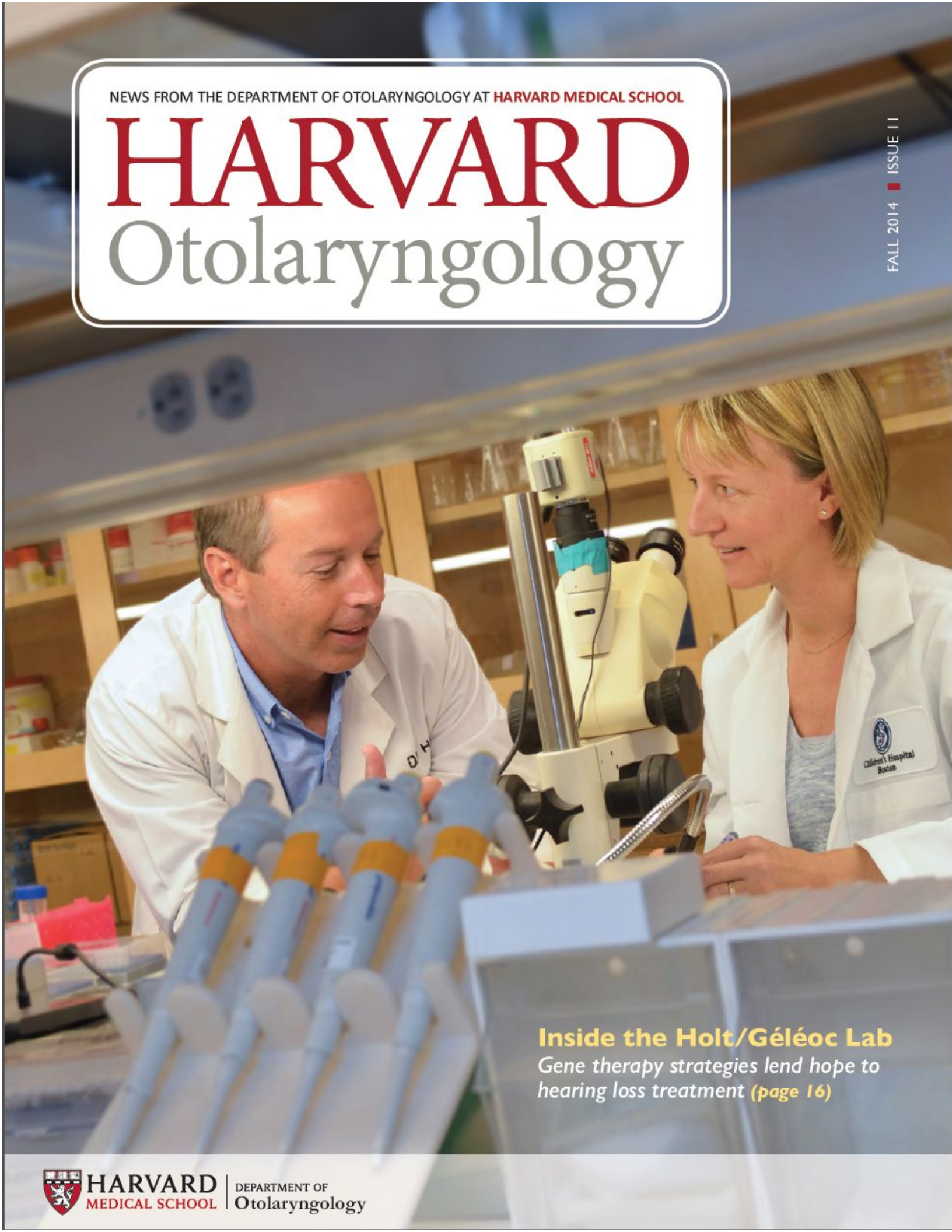

Inside the Holt/Géléoc Lab

Gene therapy strategies lend hope to hearing loss treatment **(page 16)**

HARVARD MEDICAL SCHOOL | DEPARTMENT OF Otolaryngology

INSIDE THE Holt/Géléoc Lab

Gene therapy strategies lend hope to hearing loss treatment

When Jeffrey Holt, Ph.D., and his wife Gwenaelle Géléoc, Ph.D., were offered faculty positions in the Harvard Medical School Department of Otolaryngology four years ago, they made the difficult decision to move their research efforts—and their lives together—from Charlottesville, Va., to Boston.

At the time, they were excited about a possible hearing research breakthrough, in which they believed they had found two genes and proteins responsible for hair cell transduction in the inner ear. The two scientists, who met as postdocs at Mass General, had served ten years on the faculty at the University of Virginia, where they had grown a highly productive research program in inner ear physiology.

"We really struggled with the decision to move, because we loved Charlottesville and weren't looking for a change," Dr. Holt said. "But we recognized that this was an important discovery, and we were excited about the opportunity for collaboration in Boston, a city where the science is just phenomenal."

Drs. Holt and Géléoc have since made substantial contributions in the area of gene therapy for hearing loss. In their lab at Boston Children's Hospital, they have identified TMC1 and TMC2 as components of the hair cell transduction channel, key molecules required for auditory processing, and have designed a gene therapy trial using viral vectors to correct mutations in TMC1. They are also developing similar gene therapy strategies for Usher syndrome, a genetic condition that affects hearing and vision.

"We're developing vectors to target the hair cells of the inner ear and also the photoreceptors of the retina, which are also affected by Usher syndrome," Dr. Géléoc

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"It's an exciting time. There are a lot of labs involved in this research right now, and I think we're moving faster now than we were 10 years ago."

Dr. Gwen Géléoc

said. "We're working to find ways to counteract the progression of deafness and retinal degeneration."

As researchers in genetic hearing loss, they now play a role in an international movement to develop biological treatment strategies for human deafness. Otolaryngology researchers around the world are working concurrently to develop stem cell therapies, drug therapies and gene therapy approaches in the hopes that multiple successful strategies will cover the broad, varying types hearing loss. Drs. Holt and Géléoc reviewed exciting progress in the field in a 2014 issue of *Science*.

"It's really a multifactorial problem, because deafness can arise from many different sources," Dr. Holt said.

"Unfortunately, every gene, every mutation affected may require a different approach and demand a very personalized treatment," Dr. Géléoc said. "So I think having all these different approaches tested concurrently will give us the best chance."

Genetic inner ear research has accelerated in the ten years since the Human Genome Project was declared complete, with more than 20,000 genes identified in human beings. Scientists have taken on the challenge of identifying what those genes are doing and where they are expressed in the body.

In 2013, Drs. Holt and Géléoc published a paper in *Neuron* that demonstrated that TMC1 and TMC2 are part of the hair cell transduction channel in the inner ear, opening the door for a gene therapy trial to correct mutations of TMC genes that cause hearing loss.

Since that paper was published, they have identified viral vectors to introduce TMC genes into the sensory cells of the inner ear. Preliminary data demonstrate successful restoration of cellular function in a dish and partial restoration of auditory function in deaf mice up to one month old. The team will continue to measure responses to optimize the treatment and to see if it can be extended throughout the two-year lifetime of a mouse.

"It was one of those eureka moments, the first time we did this and it actually worked," Dr. Holt said. "To be able to restore the mechanical sensitivity of the cells to a responsive state was just phenomenal."

In a separate set of experiments, they have tested this approach on live human inner ear tissue extracted during surgical removal of brain tumors. They developed techniques to keep the inner ear tissue alive in a dish and have had success with the viral vectors in this situation. This intermediate step provides further support for the technique eventually translating to humans.

"We want to carry this through to the maximum in the mouse model before we begin adapting to humans," Dr. Holt said. "But I think if the successes continue at the rate they have been, we should be there in a reasonable timeframe—perhaps within a few years."

Their work in developing viral vectors to treat mutations of TMC1 has informed a similar project on developing gene therapy strategies for Usher syndrome.

"Really, most of what we're learning from the TMC project can be used for the Usher project, and vice versa," Dr. Géléoc said.

Studying a mouse model of the Usher 1c gene mutation, Dr. Géléoc is working to understand the development of hearing deficits associated with Usher syndrome. Her research has shown that, in the mouse model for Usher syndrome, the ear develops normally.

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Dr. Jeffrey Holt

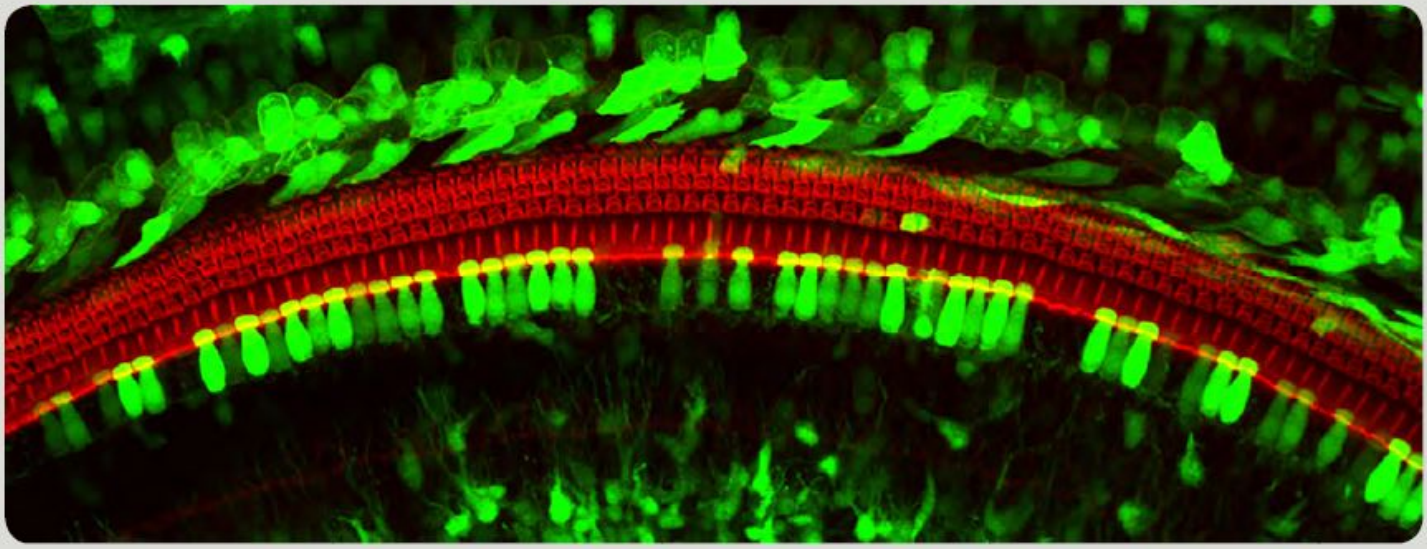

Photo by Charles Askew.

A portion of the mouse cochlea stained in red to illuminate the sensory hair cells. Cells that were infected with the gene therapy vectors appear green.

"Our work is demonstrating that the ear is really developing quite well in the beginning, which gives us a window of opportunity for therapy," she said. "The fact that the sensory epithelium develops normally means that we could potentially reinsert the missing gene and allow the sensory epithelium to survive."

The gene therapy work in the Holt/Géléoc lab has attracted the attention of philanthropist Ernesto Bertarelli. The Bertarelli Foundation funded a preliminary project headed by the Holt/Géléoc team in collaboration with Patrick Aebischer of the École Polytechnique Fédérale de Lausanne in Switzerland. Based on their initial studies and their proof-of-concept successes, the Bertarelli Foundation has just pledged an additional $720,000 to support continued development of gene therapy for TMC1 mutations and Usher Syndrome 1c.

There is some hesitation in the medical community related to gene therapy, especially the fear that the viral vectors will get into the vasculature and then throughout the body, causing side effects elsewhere. However, inner ear researchers are fortunate that a regulatory process prohibits the therapeutics from going systemic.

"The ear is actually a good model for gene therapy, because the fluid-filled spaces of the inner ear are protected by the blood-labyrinthine barrier," Dr. Holt said. "We've found that the viral vectors will stay there after injection."

As they continue this remarkable progress in their research toward developing gene therapy strategies for hereditary hearing loss, Drs. Holt and Géléoc feel very fortunate for their partnership in the lab and in life, which has allowed them unique opportunities for achieving professional goals and work-life balance.

"When we were both ready to start a lab, we said, 'why don't we start a lab together and see how that goes?' And that test drive carried off into a lifetime experience," Dr. Géléoc said. "I feel that we can really bounce ideas off one another and get things moving much faster this way."

Dr. Géléoc also feels that their partnership allows her to enjoy more hands-on time in the lab, something she may not be able to do as the sole principal investigator.

"With the Usher project especially, I'm fully involved in the tissue prep, recordings, the confocal microscope work…" she said. "And I believe in the data because I've seen it first-hand."

It's a system that's working well for them in a field that's moving forward at a fast pace and with a bright future.

"I think it's an exciting time," Dr. Géléoc said. "There are a lot of labs involved in this research right now, and I think we're moving faster now than we were 10 years ago. Only a short time ago, it was just a dream, but now, scientists are really thinking that biological treatments for deafness could be a reality in the not too distant future."