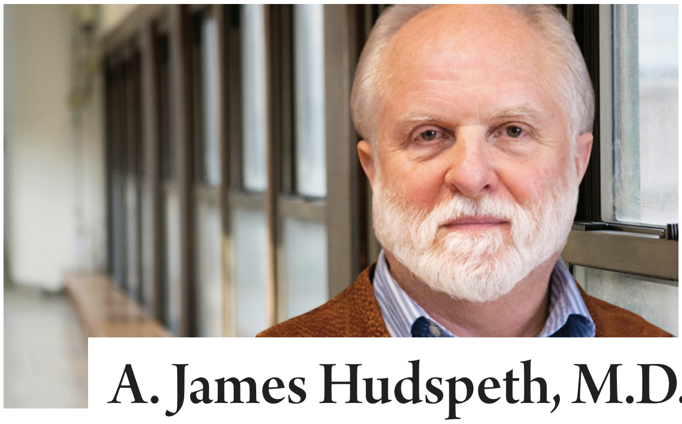

A. James Hudspeth, M.D., Ph.D.

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The majority of the hearing-impaired suffer from sensorineural hearing loss, which results from damage to the sensory hair cells of the inner ear. The human cochlea contains about 16,000 of these cells, which do not regenerate after damage. In an effort to prevent or reverse deafness, Hudspeth's group is working to better understand the normal hearing process, the causes of hearing deterioration, and possible means to regenerate hair cells.

Within the cochlea, mechanical signals representing sound are converted into vibrations along the basilar membrane, upon which stand some 16,000 hair cells. Each hair cell is endowed with a few hundred fine "feelers," or stereocilia, that constitute its hair bundle. Sound-induced vibrations set the hair bundle in motion, evoking electrical responses by opening mechanically sensitive ion channels. As a result of the direct connection between the hair bundle and ion channels, the transduction process of hair cells is remarkably rapid; we can consequently hear sounds at frequencies as great as 20 kHz. The direct nature of auditory transduction also makes the process highly sensitive.

The extraordinary sensitivity of our hearing results from cochlear amplification of its mechanical inputs. Researchers in Hudspeth's research group are exploring how human hearing benefits from a mechanical amplifier in each hair bundle. They have found that bundles are spontaneously active and that a small force synchronizes this motion with the stimulus. Measurement of the mechanical work performed in this situation confirms that a hair bundle can amplify and tune its mechanical inputs. Members of the research group are now extending these results to the mammalian ear. Identifying the active process in the human cochlea is especially important because hearing loss usually begins with deterioration of this amplifier.

In an effort to learn how hair cells develop, Hudspeth's group is conducting molecular-biological experiments on the larval zebrafish. In the lateral line of this species, new hair cells continually arise to replace those that die as a result of aging or chemical toxicity. The division of a precursor cell consistently produces a pair of hair cells, one of which responds to water movement toward the animal's anterior, whereas the other is sensitive to posterior flow. To establish which signaling pathways lead to the production of new hair cells, members of the group are isolating hair cells and their precursors and examining their gene expression. The investigators hope to identify pathways that might be activated in the human ear to foster the replacement of hair cells.

Finally, members of the lab are investigating the regeneration of hair cells in the inner ear of the mouse, a preparation that resembles the human inner ear. They have identified a potent and nontoxic chemical that inhibits a group of enzymes called Lats kinases and fosters the proliferation of supporting cells, an initial step toward hair cell regeneration. Related compounds have proven effective in eliciting the proliferation of neuronal precursors in the eye and even of cardiomyocytes in the heart.

Hudspeth's research has led to a deepened understanding of the receptor cells of the inner ear and how they contribute to hearing and hearing loss. He hopes that further investigation will indicate both the causes of and potential remedies for certain forms of human hearing impairment, an affliction that affects 10 percent of the American population.

EDUCATION

B.A. in biochemical sciences, 1967
Harvard College

M.A. in neurobiology, 1968
Ph.D. in neurobiology, 1973
Harvard University

M.D., 1974
Harvard Medical School

POSTDOC

Karolinska Institute, 1974

Harvard Medical School, 1975

POSITIONS

Assistant Professor, 1975–1978
Associate Professor, 1978–1982
Professor, 1982–1983
California Institute of Technology

Professor, 1983–1989
University of California, San Francisco, School of Medicine

Professor, 1989–1995
University of Texas Southwestern Medical Center

Professor, 1995–
Director, F.M. Kirby Center for Sensory Neuroscience, 1997–
The Rockefeller University

Investigator, 1993–
Howard Hughes Medical Institute

AWARDS

W. Alden Spencer Award, 1985

K.S. Cole Award, Biophysical Society, 1991

Charles A. Dana Award, 1994

Lewis S. Rosenstiel Award, 1997

Award of Merit, Association for Research in Otolaryngology, 2002

Ralph W. Gerard Prize, Society for Neuroscience, 2003

The Rockefeller University Distinguished Teaching Award, 2009

Guyot Prize, University of Groningen, 2010

Kavli Prize in Neuroscience, 2018

Passano Award, 2019

Louisa Gross Horwitz Prize, 2020

HONORARY SOCIETIES

National Academy of Sciences

American Academy of Arts and Sciences

American Philosophical Society

Norwegian Academy of Science and Letters

SELECTED PUBLICATIONS

Kastan, N. R. et al. Development of an improved inhibitor of Lats kinases to promote regeneration of mammalian organs. *Proc. Natl. Acad. Sci. U.S.A.* 119, e2206113119 (2022).

Martin, P. and Hudspeth, A. J. Mechanical frequency tuning by sensory hair cells, the receptors and amplifiers of the inner ear. *Annu. Rev. Condens. Matter Phys.* 12, 29–49 (2021).

Kastan, N. et al. Small-molecule inhibition of Lats kinases may promote Yap-dependent proliferation in postmitotic mammalian tissues. *Nat. Commun.* 12, 3100 (2021).

Alonso, R.G. et al. Fast recovery of disrupted tip links induced by mechanical displacement of hair bundles. *Proc. Natl. Acad. Sci. U.S.A.* 117, 30722–30727 (2020).

Erzberger, A. et al. Mechanochemical symmetry breaking during morphogenesis of lateral-line sensory organs. *Nat. Phys.* 16, 949–957 (2020).