Profile of Christine Petit

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Over the last 20 years, geneticist and neurobiologist Christine Petit has written the canticle of the cochlea from scratch, revealing the long-shrouded machinery of the auditory system molecule by molecule. Along the way, she has identified more than 20 genes responsible for hearing impairments, with each of these cochlear deficits accounting for the observed sensory impairment, a succinct story that seemed to stop at the cochlea (1, 2). As Petit, a professor at the Collège de France and Institut Pasteur in Paris, explains, "the proteins encoded by these deafness genes were therefore implicitly considered as nonessential for the central auditory system." In her Inaugural Article (3), Petit, elected to the National Academy of Sciences in 2016, challenges this view by looking deep into the brain and demonstrating that two adhesion proteins at the heart of the mechanoelectrical transduction machinery of the auditory apparatus also play a role in the embryonic migration of neurons to the auditory cortex. This discovery suggests that treating or compensating for hearing impairment with cochlear interventions, like implants, stem cells, or gene therapy, may not be sufficient to restore optimal hearing.

Genetic Determination

Petit was born in 1948 in Laignes, in the Burgundy region of France. She grew up in a family with strong winemaking roots and with a father who, as an engineer, was "always talking about new scientific discoveries and technological advances," she recalls. "I grew up with a strong interest in science." In 1967, Petit entered the faculty of medicine of Paris VI University with the aim of becoming a medical doctor. However, medicine did not fully satisfy her interest in science. "I quickly realized that I wanted to get more deeply into the science than medicine would allow." She began taking biochemistry and genetics classes at the faculty of sciences of Paris XI University at Orsay to supplement her medical education, and graduated with a Master's degree in genetics and biochemistry in 1973. "During my medical training, I spent as much time as possible in laboratories," recounts Petit. After completing her medical doctorate, she entered a doctoral program in natural sciences and biochemistry at the Institut Pasteur in 1976.

A few years into her doctoral research, Petit moved from the laboratory of Nobel-winning biologist François Jacob, who would prove to be a mentor throughout her scientific career, to an immunochemistry laboratory, a move she felt would bring her closer to her interest in the genetic control of cell differentiation. "Genetics has always been my favorite experimental approach to basic biological mechanisms," she explains. After obtaining her doctorate in 1982 and completing a short postdoctorate at the Institute of Immunology in Basel, Switzerland, Petit moved to the CNRS in Gif-sur-Yvette and began mapping genes controlling the cell-specific expression of the albumin gene through the development of microcell hybrids (4). She returned to Institut Pasteur as a staff scientist in 1985.

Christine Petit. Image courtesy of Tina Merandon/Signatures.

Around this time, the development of a genetic linkage map of human chromosomes was starting to pave the way for the identification of disease-causing genes and thus the elucidation of their normal functions. Petit capitalized on this emerging advance, working with the geneticist Jean Weissenbach on sex determination in humans. By the late 1980s, Petit had established that maleness in XX individuals results from abnormal crossovers between the X and Y chromosomes during paternal meiosis, leading to the transfer of a major sex-determining gene to the X chromosome, an abnormal meiotic exchange that involves homologous DNA sequences on the X and Y chromosomes (5, 6).

Interest in Olfaction and Hearing

By 1993, Petit had established her own laboratory at the Institut Pasteur within the neuroscience department, which was then headed by Jean-Pierre Changeux. "Jean-Pierre was always ready to exchange views on new results or concepts," she says. Mirroring her family's oenological roots, Petit set out to identify molecules involved in olfaction and to decipher their functions. She first looked for

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genes underlying Kallman syndrome, a disorder characterized by anosmia, a lack of a sense of smell, and a failure to undergo puberty. Petit and her colleagues identified the first causal gene, *KAL1*, and showed that anosmin-1, the protein encoded by KAL1, is an extracellular adhesion protein that binds to cell surface heparan sulfate (7, 8). It was nearly a decade later, however, that Petit's research revealed that anosmin-1 promotes the necessary branching of the axons of the olfactory bulb neurons and facilitates the projection of these collaterals onto the brain's olfactory cortex (9).

Petit soon began to consider other sensory systems that could be deciphered with genetics. She quickly ruled out vision. With more than 100 million photoreceptors in the retina, she explains, biochemical approaches had already led to the identification and characterization of many key retinal proteins, particularly those involved in phototransduction. The auditory system was different. Petit recalls that in the late 1980s little was known about the molecules underlying hearing, the deficiency of which can be partly attributed to the small numbers of each type of cochlear cell. "There are no more than a few thousand auditory sensory cells in a cochlea, too few for the biochemical identification of their molecular components," Petit explains.

"On the contrary, the genetic approach was particularly promising, as its efficacy is independent of the number of cells and molecules involved in a given process. However, the tendency of deaf people in the developed world to intermarry precluded such a straightforward genetic approach," says Petit. She circumvented the problem through collaborations with scientists and clinicians from Tunisia, Lebanon, Jordan, and other Mediterranean countries to undertake studies of affected families living in geographically isolated regions. "Members of such families would be expected to carry the same mutated gene responsible for deafness," she explains. Her approach led to the mapping of the first two genes responsible for profound congenital deafness—the autosomal recessive forms of deafness, DFNB1 and DFNB2—to human chromosomes (10).

Interdisciplinary Approach

The genetic approach in humans had its limitations, however. "Right from the start, it was clear that the functions of the proteins encoded by deafness genes could not be deciphered in patients," says Petit. In her opinion, audiological examinations provide only rudimentary information, and direct observation of the cochlea is not possible. Petit and her coworkers set about developing mouse models of human deafness: at first, knockout models and, later, conditional knockout models. The strategy was to focus on syndromic deafness, which refers to forms of deafness associated with other clinical symptoms, to increase the likelihood of unraveling protein networks underlying cochlear functions. Usher syndrome, a genetic disorder that causes both deafness and progressive blindness as a result of retinitis pigmentosa, was the first target.

Petit studied the interactions between the proteins encoded by genes responsible for Usher syndrome. The first protein complex she deciphered consisted of cadherin-23, harmonin, and myosin VIIa, proteins encoded by three genes responsible for Usher syndrome type 1, and the strategy eventually revealed that the Usher-1 protein complex underlies major developmental and physiological functions in sensory hair cells (11). Petit has identified and characterized proteins encoded by various deafness genes, in turn elucidating molecular mechanisms that underlie the development and function of hair bundles and the sensitive membrane that strings along atop these clusters of stereocilia, as well as the process of hair-cell synaptic exocytosis (11–13).

Links between the hair-bundle stereocilia, as Petit has shown, are important for a variety of functions. The Usher-1 protein complex constitutes both the embryonic hair-bundle lateral links and the tip-links gating the mechanotransduction channel, and anchors them to actin filaments (11, 14). Ankle links, near the base of the stereocilia, have a role in functional polarity, and the top connectors participate in a function called cochlear suppressive masking, which is essential for speech intelligibility (15, 16). Recently, Petit examined another facet of hearing impairment, showing that peroxisomes play a key role in protecting the auditory system against damage from noise overexposure, which she says is a major environmental cause of hearing loss (17).

From Hair Cells To Auditory Cortex

In her Inaugural Article, Petit penetrates deep into the auditory system, focusing on the auditory cortex (3). She established an unexpected link between hair cells and auditory cortex neurons. Petit and her coworkers found that cadherin-23 and protocadherin-15, proteins that form tip-links that gate the mechanoelectrical transduction channel, are also expressed by the GABAergic interneuron precursors of paravalbumin interneurons of the auditory cortex. The researchers found that the two cadherins are essential for both the embryonic migration of these neuronal precursors and their survival in the auditory cortex. As Petit explains, the results suggest the existence of an early "adhesion code" that targets populations of newborn GABAergic interneuron precursors to functionally specific neocortical areas. According to Petit, the discovery of intrinsic auditory cortex deficits in forms of deafness that were previously thought to involve only cochlear deficits lays down a challenge for clinical practice: the development of adapted auditory rehabilitation methods and cortical therapies.

Translation into clinical practice is important to Petit, whose trove of basic research findings are mirrored by clinical work (18). She is involved in the molecular diagnosis of hereditary deafness and the development of gene therapy, particularly for Usher syndrome (17). Her work deciphering the pathogenic mechanisms of a spectrum of deafness guides therapeutic decisions by determining which patients are most likely to benefit from cochlear implants. However, Petit feels the translational work lags behind.

Despite a career that crosses scientific boundaries, Petit relishes every opportunity to expand her horizons.

Petit loves to dive into areas of research that she might not otherwise get to explore, such as auditory cognition or music perception. As professor at the Collège de France, "I have a unique opportunity to explore many facets of hearing," says Petit, an avid pianist, flautist, and concert-goer. As director of the Hearing Institute in Paris, an interdisciplinary research center associated with a clinical research center that is slated to open in 2018, Petit is bound to find opportunities to break out into new basic science and translational research.

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