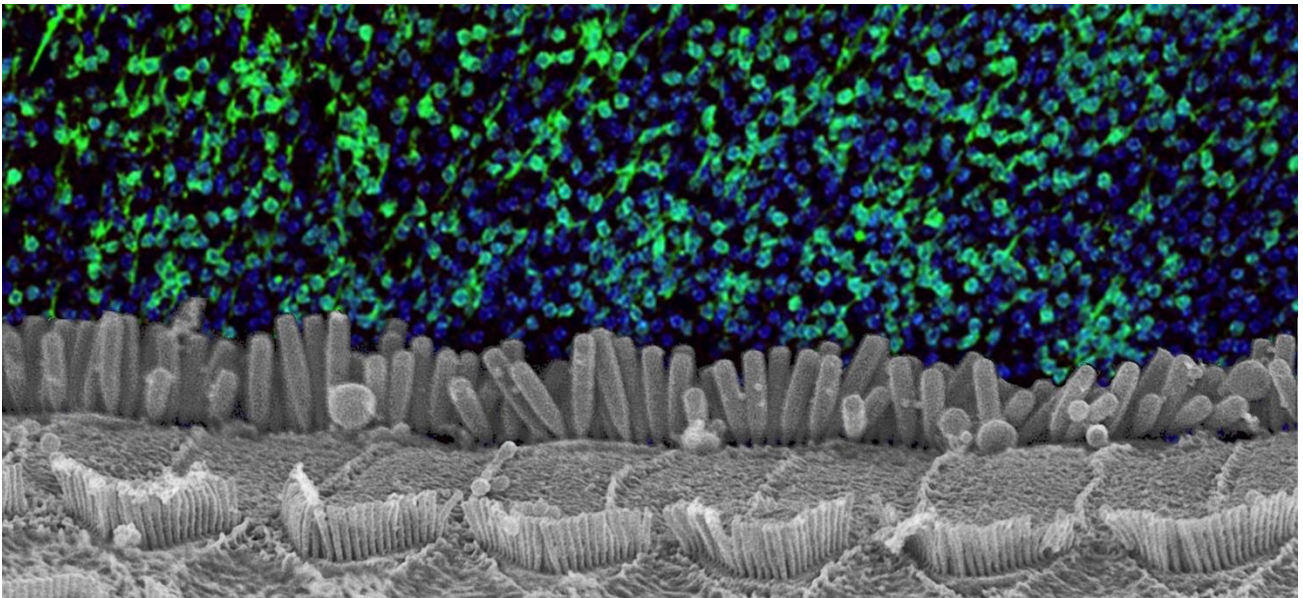




International inaugural congress

The Hearing Institute

September 16 and 17, 2019 at *Collège de France*



press kit



COLLÈGE
DE FRANCE
—1530—

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To mark the occasion of the creation of the Hearing Institute, an Institut Pasteur center dedicated to research into auditory neuroscience, Professor Christine Petit is organizing an inaugural scientific congress at the *Collège de France* on September 16 and 17, 2019, in partnership with the *Fondation pour l'Audition* and Inserm. This international scientific meeting will mark the birth of the Hearing Institute, which aims to promote an integrative approach to auditory neurosciences and to develop diagnostic tools and innovative curative treatments for individuals suffering from hearing loss.

Hearing loss is a decrease in auditory acuity. It may occur at any age and at many different degrees of severity. It is the most frequent sensory defect.

By depriving those affected of the social interactions intimately linked to the understanding of speech, hearing defects cause social isolation, which may be a source of major psychological suffering and is often associated with a depressive state. They also deprive the individual of an ability to appreciate and derive pleasure from music. We now know that hearing loss in adults is the most important risk factor for dementia. The elimination of such hearing loss could potentially lead to a decrease of about 10% in the number of people with dementia.

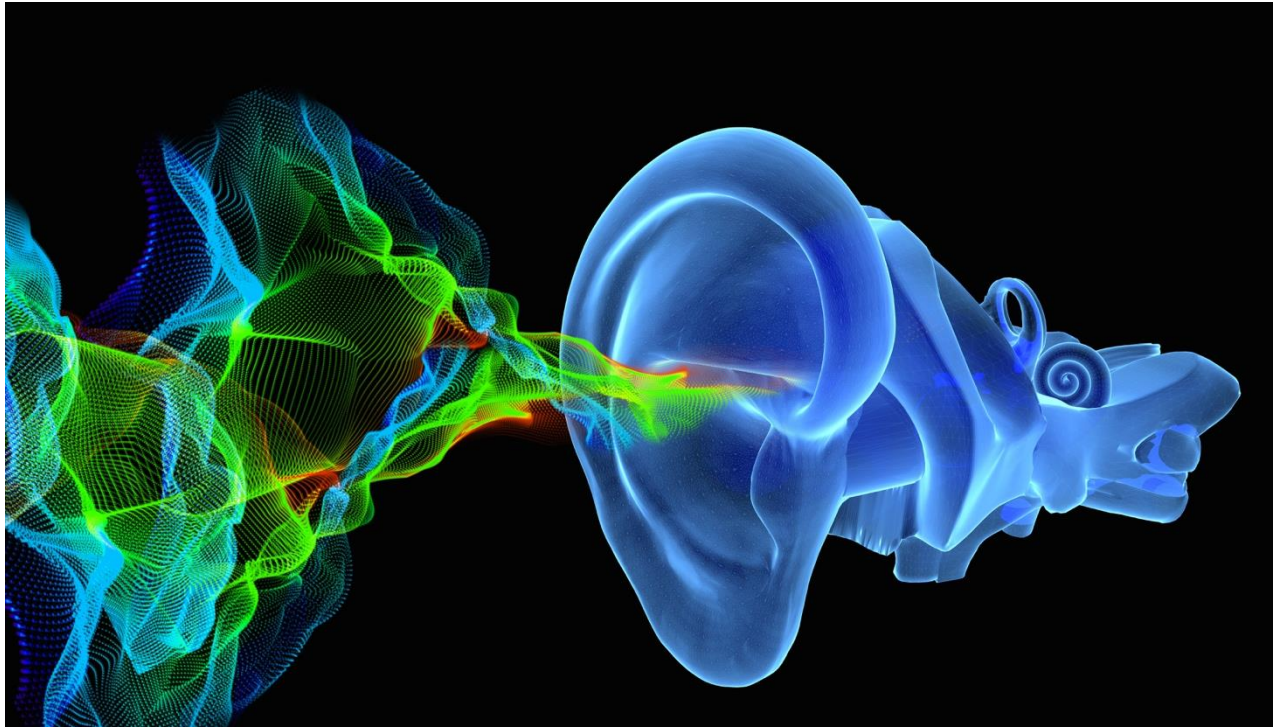


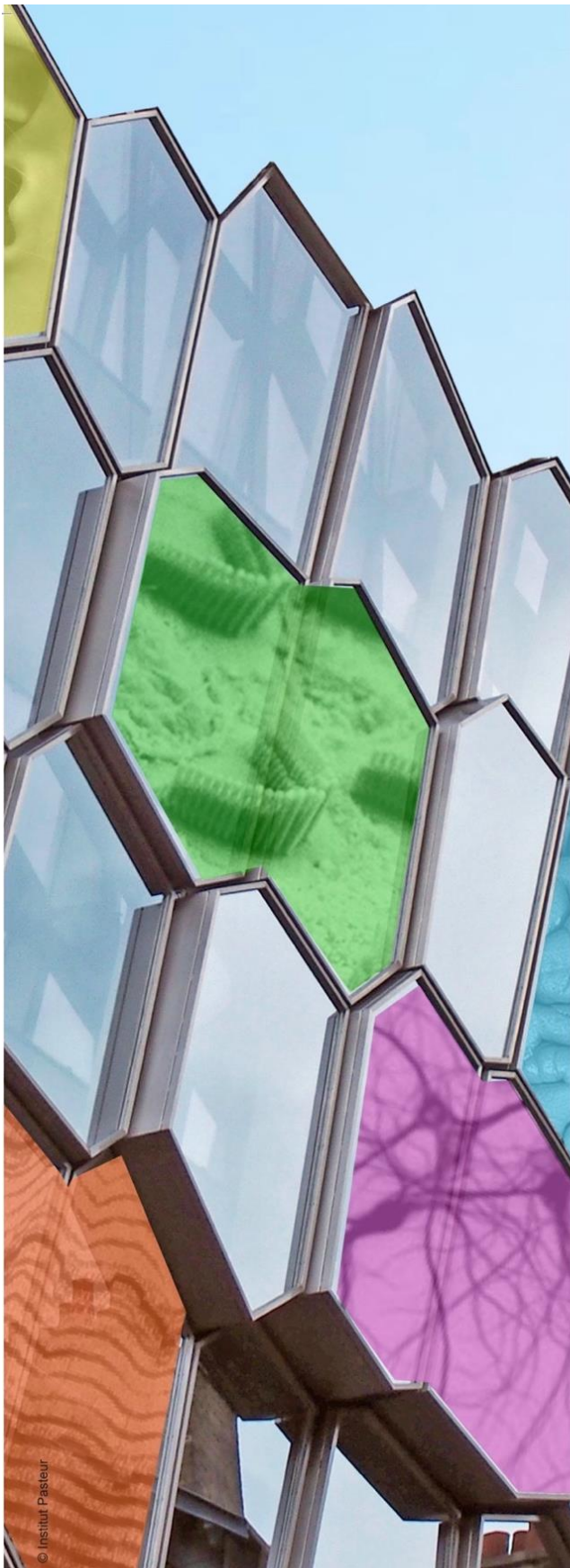
Hopes have been raised by recent major advances, at the Genetics and Physiology of Hearing laboratory at Institut Pasteur in particular. These advances have driven the creation of an institute dedicated to hearing — the Hearing Institute — a new research center of the Institut Pasteur created at the initiative of the *Fondation pour l'Audition* and Institut Pasteur.

“It’s very satisfying to be able to bring together the best scientific experts in the domain of hearing at the occasion of the inauguration of the Hearing Institute, and, what’s more, in a format that breaks down the persistent divisions between research on the peripheral auditory system (the cochlea, the auditory sensory organ and its innervation) and research on brain auditory centers. It will also be an opportunity for exchanges with our colleagues studying other sensory systems, a necessity if we are to understand the properties common to different sensory systems (particularly their mechanisms of plasticity) and how different types of sensory information are integrated to deliver a unique perception. It will also allow us to highlight the pertinence of continuous interactions between basic and medical research, and of continually comparing the findings of research on humans and animals. These exchanges are essential for the development of authentic diagnostic and therapeutic innovation for hearing defects. This inaugural congress thus reflects the active interdisciplinarity at the heart of the Hearing Institute project. Finally, a source of great pleasure, this congress has made it possible to bring our friends together; the creation of the Hearing Institute owes

much to their enthusiastic support.” explains Professor Christine Petit, Director of the Genetics and Physiology of Hearing mixed research unit of the Institut Pasteur and Inserm, member of the French and American Academies of Science, Professor at *Collège de France* and the first Director of the Hearing Institute.

This information file goes over the creation of this center of excellence in research and the latest advances in hearing research at the Institut Pasteur.





INTERNATIONAL INAUGURATION MEETING

Hearing Institute-Paris

16-17th September 2019

Collège de France

This meeting marks the opening of the Hearing Institute*, a new Institut Pasteur center with the objective of promoting integrative approaches to auditory neuroscience and developing innovative diagnostic tools and curative treatments for hearing disabilities.

SPEAKERS:

May-Britt Moser (NTNU, Norway) – *opening lecture*

Jean-Julien Aucouturier (IRCAM, Paris)

Karen Avraham (Tel Aviv Univ., Israël)

Volker Bormuth (Sorbonne Univ., Paris)

Steve Brown (MRC Harwell, United Kingdom)

David DiGregorio (Institut Pasteur, Paris)

Robert Fettiplace (Univ. of Wisconsin, USA)

Paul Fuchs (Johns Hopkins, USA)

Stefan Heller (Stanford Univ., USA)

Ingeborg Hochmair (MED-EL, Austria)

James Hudspeth (Rockefeller Univ., USA)

Andrew King (Oxford Univ., United Kingdom)

Charles Liberman (Harvard Univ, USA)

Brigitte Malgrange (Liège Univ., Belgium)

Pascal Martin (Institut Curie, Paris)

Tobias Moser (Uni-Goettingen, Germany)

Israel Nelken (Hebrew Univ. of Jerusalem, Israël)

Nicolas Renier (ICM, Paris)

Botond Roska (IOB, Switzerland)

Shihab Shamma (ENS, Paris)

Carla Shatz (Stanford Univ., USA)

Christoph Schmidt-Hieber (Institut Pasteur, Paris)

Robert Zatorre (McGill Univ., Canada)

Fan-Gang Zeng (Univ. of California Irvine, USA)

Christine Petit (Institut Pasteur, Hearing Institute)

Luc Arnal (Institut Pasteur, Hearing Institute)

Brice Bathellier (Institut Pasteur, Hearing Institute)

Aziz El Amraoui (Institut Pasteur, Hearing Institute)

Yann Nguyen (Institut Pasteur, Hearing Institute)

Said Safieddine (Institut Pasteur, Hearing Institute)

Hung Thai-Van (Institut Pasteur, Hearing Institute)

ORGANIZATION:

Christine Petit, Paul Avan, Brice Bathellier, Nicolas Michalski

* **The Hearing Institute**, a Center of the Institut Pasteur, created on the initiative of Fondation Pour l'Audition and Institut Pasteur, is an interdisciplinary fundamental and medical research center with the objective of promoting integrative approaches to auditory neuroscience and developing innovative diagnostic tools and curative treatments for hearing disabilities.

The Institut Pasteur, a non-profit foundation with recognized charitable status set up by Louis Pasteur in 1887, is today an internationally renowned center for biomedical research with a network of 32 institutes worldwide. In the pursuit of its mission to prevent and control diseases in France and throughout the world, the Institut Pasteur operates in four main areas: research, public health, education and training, valorisation and technology transfer.

The Fondation Pour l'Audition, created by Françoise Bettencourt Meyers, Jean-Pierre Meyers, and the Fondation Bettencourt Schueller, and recognized as a public-interest organization since 2015, aims to unite talents to promote breakthroughs in hearing health and help improve the everyday lives of people with hearing loss.

INFORMATION AND REGISTRATION ON:
<https://ida2019.sciencesconf.org/>



THE HEARING INSTITUTE

The Hearing Institute is center of the Institut Pasteur. The objective of this basic and medical research center is to promote an integrative approach to hearing neurosciences and to develop innovative methods for the diagnosis and preventive and curative treatment of hearing loss.

It was created at the initiative of, and with the support of the *Fondation Pour L'Audition*. This foundation, created by Françoise Bettencourt Meyers, Jean-Pierre Meyers and the *Fondation Bettencourt Schueller*, was recognized as a public-interest organization in 2015. It aims to bring together the most talented researchers in the field, to support research and innovation, and to improve the everyday lives of deaf and hearing-impaired individuals.

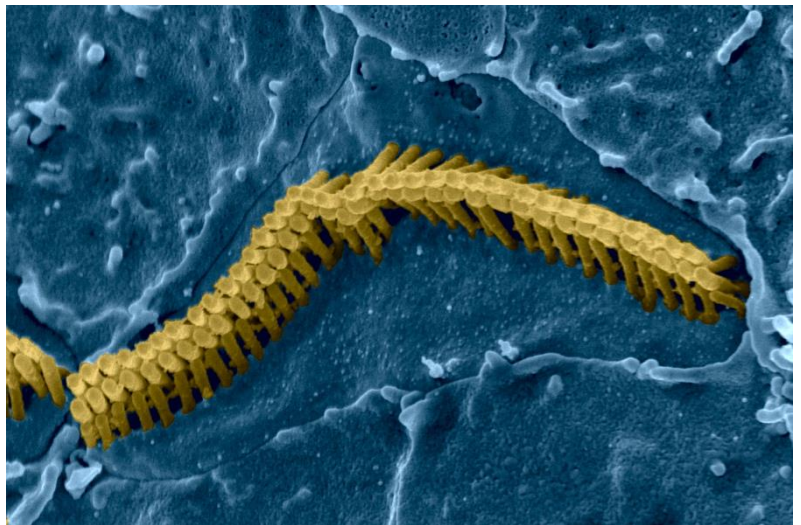
The creation of the Hearing Institute satisfies three priority objectives:

1. To perform excellent basic research aiming to elucidate the principles and mechanisms underlying:

- The development, functioning and plasticity of the auditory system;
- Auditory perception and cognition;
- Communication through sound;
- Multisensory integration;
- Interactions between the genome and the sound environment;

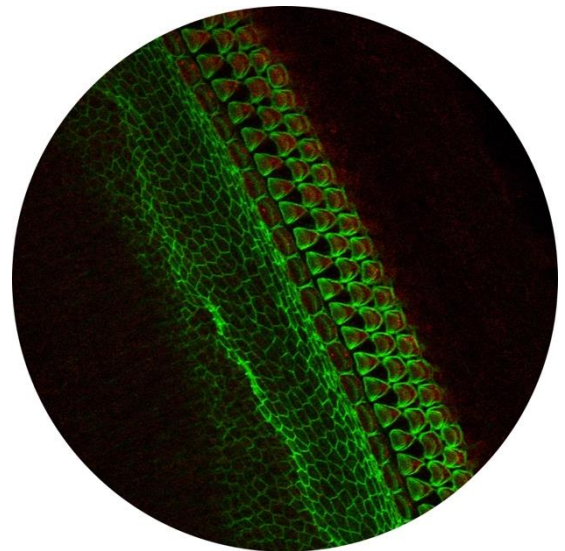
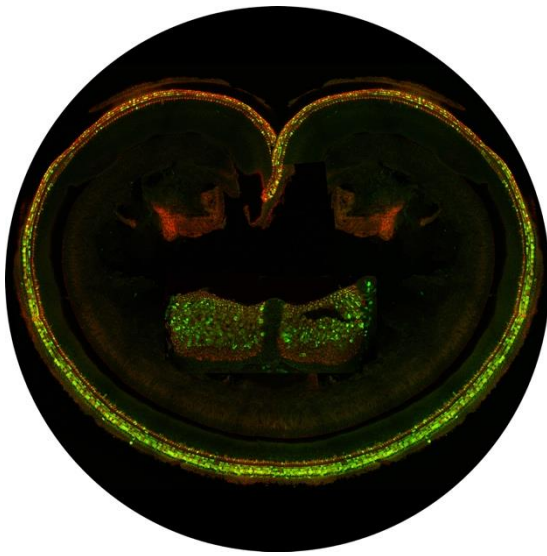
2. To develop translational approaches for:

- Understanding the pathogenesis of neurosensory hearing loss or general diseases, including isolated or syndromic deafness and neurodegenerative diseases in particular;
- Developing multiparametric tools for the diagnosis of peripheral and/or central hearing loss, with a view to developing precision medicine;
- Developing innovative treatments (gene therapy, pharmacological treatments and, in the near future, cell therapy) in children, young and aging adults.



- These approaches will extend to balance problems (the sensory organ for balance, the vestibule, forms the inner ear together with the cochlea, which it closely resembles);
- Developing auditory rehabilitation based on advances in basic scientific knowledge, including, in particular, an understanding of the mechanisms underlying the plasticity of the auditory cortex.

3. Communicating the knowledge generated within the institute to the wider international medical, paramedical and scientific community, and the consequences of these discoveries to the hearing-impaired. Raising the awareness of the general public concerning the problems associated with being “hard-of-hearing”.



An original project based on interdisciplinarity and knowledge transfer

This project has a number of original features:

- The interdisciplinarity of its research, extending from biophysics to computational neuroscience;
- The study of the auditory system, from the sensory organ to the brain, i.e. from sound reception to the recognition of its meaning, triggering appropriate behavior;
- Continual exchanges between human and animal studies;
- A continuum between basic and medical research, to optimize interactions between research and industry, so as to contribute to the emergence of a national industrial sector in the domain of hearing and to contribute to European industrial efforts;

- The communication of knowledge within the scientific community, among healthcare professionals (doctors, speech therapists and hearing aid specialists, for example), and with associations for the hearing impaired and the general public.

This is a pioneering project resolutely turned towards the future, which will bring together researchers, engineers, doctors and other actors in innovation, industry, associations and patients, to work together to improve the acoustic environment, quality of life and management of the hearing-impaired throughout their lives.

An “external” Institut Pasteur campus, to bring together a unique collection of teams

At term, the Institute will house 10 research teams, corresponding to about 110 to 130 people, in a building in the heart of Paris, close to the Vision Institute, thereby favoring advances in the domains of multisensory integration and conditions

affecting both sight and vision, such as Usher syndrome.



The Hearing Institute is an Institut Pasteur/INSERM mixed research unit housing scientific teams from Institut Pasteur, INSERM and the CNRS. These research teams from several different public research bodies will be affiliated to the Neurosciences Department of Institut Pasteur.

The city of Paris is also a partner in this project. The city authority bought the building and contributed to its renovation and rehabilitation for this purpose. The research teams will move into the facilities at the end of 2019 and the start of 2020. The Ile-de-France regional authority has also announced its support for the project.

The Hearing Institute will include the *Centre de Recherche et d'Innovation en Audiologie Humaine* (CERIAH; the Center for Research and Innovation in Human Audiology) directed by Prof. Paul Avan (Clermont-Ferrand University Hospital), who will build on his previous work and inventions to

develop innovative diagnostic methods. The Hearing Institute will pursue its collaborations with geneticists and ENT specialists in France and elsewhere, with a view to strengthening the international network essential for determining the causes of deafness, particularly those of genetic origin. This network has already provided the first hope for curative treatments for deafness. Through the links it has created with many countries in North Africa and the Middle East, prolonged by

projects with Necker-Enfants Malades Hospital in Paris and with regional university hospitals (e.g. Clermont-Ferrand, Bordeaux, Lille, Lyon), this network will continue to reach out to additional university hospitals, and auditory health professionals, including hearing aid specialists and speech therapists in particular, and will extend to other countries and other clinical practices.

A tripartite convention has been signed between the *Fondation pour l'Audition*, Institut Pasteur and the Parisian public hospital network (AP-HP), bearing witness to the strong desire of these organizations to develop common research programs. This desire has already led to a university hospital research (RHU) program at Necker Hospital, Institut Pasteur and Sensorion for the development of gene therapy to treat a hereditary form of deafness. In the context of this convention, the Hearing Institute will collaborate with centers for clinical research in audiology (CeRCAs, *Centres d'études et de Recherche Clinique en Audiologie*), currently those of Necker-Enfants Malades Hospital and Pitié-Salpêtrière Hospital (both part of the AP-HP network), but also those at other university hospitals in the future.

Public-private partnerships with actors from the biotech sector have already been established, notably between the Institut Pasteur laboratory and Sensorion. These partnerships should intensify and expand in the future, thereby dynamizing the industrial sector in these domains.



SCIENTIFIC PROGRAM FOR THE INAUGURAL CONGRESS

Monday, September 16, 2019

09:00 – 09:45	INTRODUCTION Thomas Römer, Stewart Cole, Gilles Bloch, Jean-Pierre Meyers, Christine Petit
09:45 – 10:50	Neuronal circuits Botond Roska, Shihab Shamma, May-Britt Moser, Christoph Schmidt-Hieber
10:50 – 11:10	Coffee break
11:10 – 13:00	Physiologie and development of the cochlea Paul Avan, Andrei Kozlov, James Hudspeth, Pascal Martin, Robert Fettiplace, Brigitte Malgrange
13:00 – 14:30	Lunch and poster session
14:30 – 16:20	Central auditory function Luc Arnal, Boris Gourévitch, Andrew King, David Digregorio, Brice Bathellier, Israel Nelken
16:20 – 16:50	Coffee break
17:00 – 18:00	Cochlear implants Charles Liberman, Adrien Eshragi, Ingeborg Hochmair, Yann Nguyen, Fang-Gang Zeng, Tobias Moser

Tuesday September 17, 2019

09:00 – 10:50	The cochlea: development and disease Paul Fuchs, Raphaël Etourney, Karen Avraham, Stefan Heller, Aziz El Amraoui, Steve Brown
10:50 – 11:20	Coffee break
11:20 – 13:00	Sensory circuits and multifaceted plasticity David Digregorio, Nicolas Michalski, Carla Shatz, Volker Bormuth, Nicolas Renier, Botond Roska
13:00 – 14:30	Lunch and poster session
14:30 – 16:10	Hearing in humans: from salient sounds to music Andrew King, Israel Nelken, Luc Arnal, Robert Zatorre, Jean-Julien Aucouturier, Shihab Shamma
16:10 – 16:40	Coffee break
16:40 – 18:20	Auditory deficits and rehabilitation Fan-Gang Zen, Frank R. Lin, Charles Liberman, Hung Thai-Van, Said Safieddine, Paul Fuchs
18:20 – 18:35	CONCLUSION

All presentations will be given in English. A book of abstracts will be made available on the day of the conference.

DEAFNESS

Hearing impairment is the most frequent sensory problem in humans and is characterized by a total or partial loss of the ability to hear. Since the 1990s, progress in molecular biology and genetic analysis has made it possible to decipher the molecular mechanisms involved in the development, differentiation and function of the cochlea, the auditory sensory organ. Genetic studies of human deafness have led to the identification of many genes underlying human deafness and have shown that most severe or profound forms of deafness are hereditary.

These discoveries have paved the way for improvements in the management of patients with hearing problems, thanks, in particular to targeted molecular diagnosis and more appropriate treatments.

Deafness: some figures

500 million people worldwide have hearing impairment

6 million people in France have hearing impairment

7th leading cause of everyday disability worldwide by 2030

Source: WHO

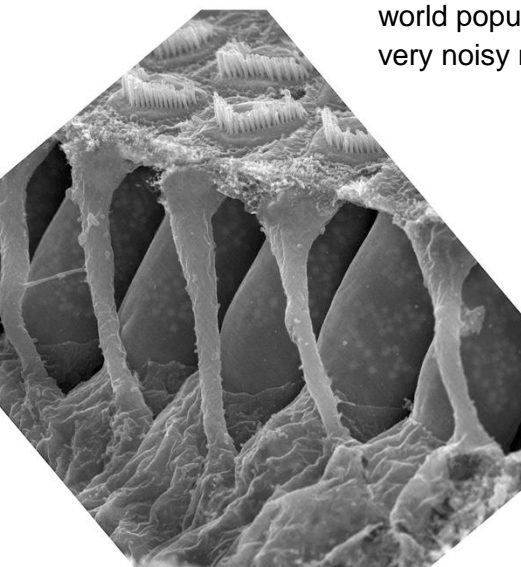
Epidemiology

Selon l'Organisation mondiale de la santé (OMS), on estime à près de **500 millions** le nombre des malentendants à travers le monde ; en France, leur nombre est évalué à **6 millions**. Par leur ampleur et leurs conséquences, les atteintes de l'audition constitueront, d'ici 2030, la **7ème cause la plus importante d'invalidité au quotidien**, selon l'OMS. A l'horizon de l'année 2050, toujours selon l'OMS, **900 millions de personnes** seront malentendantes, – soit une personne sur 10 souffriront de déficience auditive incapacitante.

The auditory system is also the sensory system most vulnerable to environmental changes linked to urbanization. Its principal aggressor, worldwide and in individuals of all ages, is overexposure to noise. According to the WHO, 1.1 billion young people are currently at risk of hearing loss, principally because they listen to loud music for long periods (particularly through headphones and on their mobile phones).

Noise levels are continually increasing in the urban zones in which 56% of the world population is concentrated (this figure will rise to 68% by 2050, mostly in very noisy megapolises, particularly in developing countries).

The number of people with presbycusis (age-related sensorineural deafness) is continually growing, due to the aging of the population and overexposure to noise linked to the continual increase in population density in towns.



Deafness, a public health concern

Les atteintes de l'audition surviennent à tout âge et revêtent tous les degrés de sévérité.

En privant les malentendants de l'interaction sociale que sous-tend la perception de la parole, elles engendrent une souffrance liée à l'isolement, parfois accompagnée d'un syndrome dépressif.

Les atteintes auditives liées à la surexposition à des bruits continus ou l'exposition à des bruits impulsifs constituent le premier poste de dépenses de santé des armées aux États-Unis et le second en France.

Causes

Deafness has multiple and diverse causes, which can be classified according to the severity of hearing loss in the patient, and the site of the primary defect.

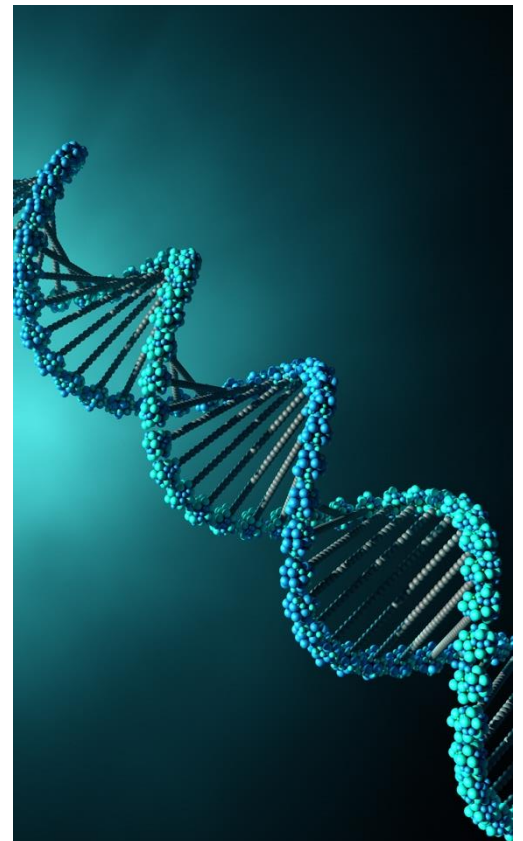
Deafness can thus be described as mild, moderate, severe or profound, according to the magnitude of the disability caused.

We can also distinguish between several different types of deafness:

- Conductive hearing loss, linked to an outer or middle ear defect,
- And perceptive or sensorineural hearing loss, linked to a defect somewhere between the inner ear and the cerebral auditory cortex.

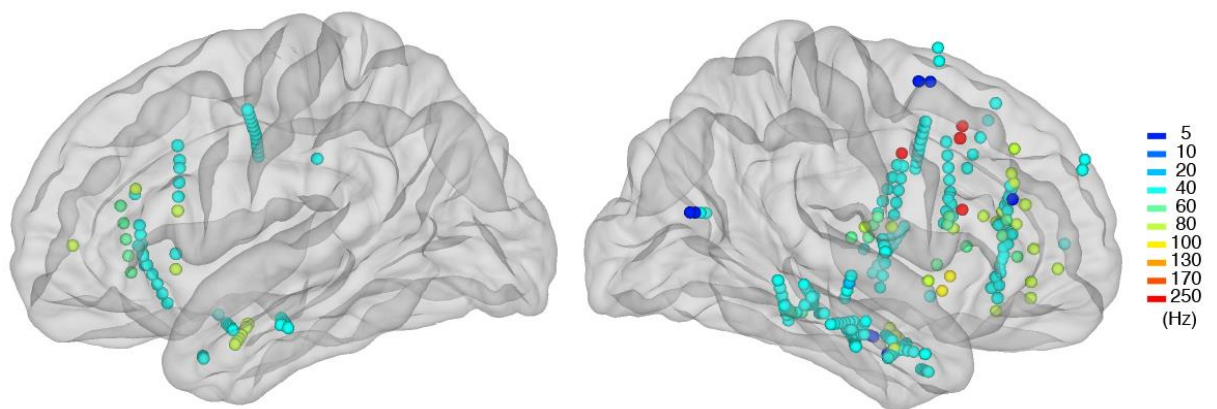
In the absence of clear environmental risk factors, significant hearing loss may be considered to result from a hereditary form of deafness. Thanks to the identification of the genes responsible and the proteins involved, researchers have been able to develop molecular diagnosis for some forms of deafness, favoring improvements in the management of hearing-impaired patients.

Conductive hearing loss, which often occurs after an ear infection, is generally mild or moderate. Conductive hearing loss may be caused by ear malformations (such as aplasia) associated with a hereditary condition. Late-onset forms are known, such as otosclerosis (which causes tinnitus, and sometimes dizziness), which is caused by a problem with the stapes, an ossicle in the middle ear. Most forms of conductive hearing loss can be “cured” surgically.



Perceptive and sensorineural forms of deafness have a high prevalence and often result from inner ear defects. The degree of hearing loss is variable. These forms of deafness are generally severe or profound and are caused by genetic factors.

In France, they affect one in 700 children at birth, and one young adult in 500 at the age of 20 years. Deficits of this type cause major difficulties in the acquisition of speech and in academic learning. Affected children are managed by educative approaches, speech therapy and the fitting of prostheses (conventional hearing aids or cochlear implants).



Presbycusis, or age-related sensorineural hearing loss, accounts for more than 80% of all cases of hearing loss. It can be attributed to both genetic and environmental causes, primarily overexposure to noise. According to current estimates, presbycusis affects one third of people over the age of 65. Its progression can disrupt social links and lead to isolation and considerable psychological suffering, or even a depressive state.

Usher syndrome is a genetic disease characterized by congenital deafness associated with a progressive loss of vision due to retinitis pigmentosa. The discovery of the genes responsible for the most severe form by the Institut Pasteur researchers, and the understanding of the corresponding hearing loss developed have made it possible for children suffering from this syndrome to benefit from cochlear implants. Children with this condition are now managed increasingly early.

Diagnosis

The molecular diagnosis of a form of deafness makes it possible to establish the genetic origin of the form of deafness concerned and to inform the parents of the risk of deafness in any subsequent children or the patient (depending on the age of the patient concerned). It is based on the identification of pathogenic mutations in so-called “deafness” genes. Such diagnosis is possible for early-onset forms of deafness with simple patterns of heredity (Mendelian) facilitating the identification of the gene responsible. It is currently available at several centers in France and in several developing countries.

By contrast, late-onset forms of hearing loss often have a complex heredity, with a number of genetic factors contributing to different extents to hearing loss, associated with other risk factors (for cardiovascular disease and diabetes for example) and environmental factors, the most important of which is overexposure to noise.



New methods of DNA sequencing are accelerating molecular diagnosis through the parallel exploration of several hundreds of genes implicated in isolated or syndromic deafness.

Treatments

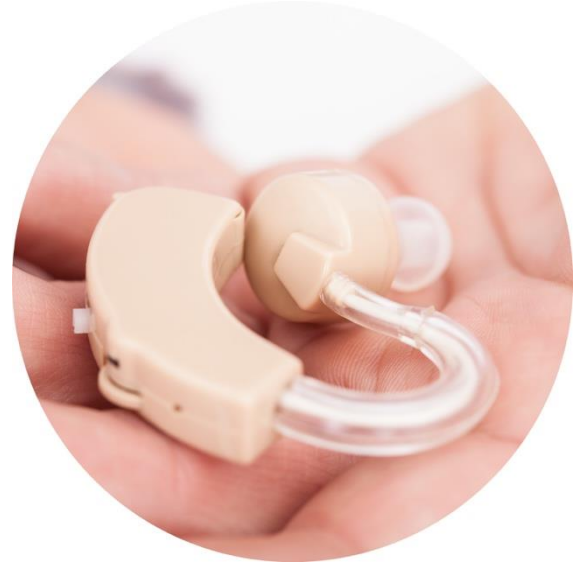
Numerous genes cause hereditary deafness, with diverse consequences for hearing loss. It is therefore essential to adapt treatment and follow-up according to the precise form of deafness. Thus, for deafness due to a major cochlear dysfunction, the fitting of a cochlear implant can be proposed, whereas such implants are not suitable for other forms of deafness due, for example, to auditory neuron defects.

Identification of the causal genes and an understanding of the associated pathophysiological mechanisms based on animal models of deafness can greatly improve indications for auditory prostheses and the adaptation of their settings. In addition, as described below, authentic curative treatments are now being developed.

Hearing aids

All individuals with progressive hearing loss are at risk of isolation. It is, therefore, necessary to manage patients as promptly as possible, particularly as delaying the fitting of a hearing aid leads to a desensitization of the brain to noise. When the brain does not receive signals corresponding to certain sounds, or receives them poorly, it loses the habit of decoding these signals and must, therefore, readapt to noise once the hearing aid is fitted. The wearing of a hearing aid is one possible solution when hearing loss becomes a problem.

Progress in science and technology has made it possible to improve hearing aids considerably. Modern hearing aids are much more effective and smaller than their predecessors. Intra-auricular models, invisible to the eye and with no need for daily manipulation, are now available. Hearing aids are particularly effective for presbycusis (late-onset deafness due to aging).



Cochlear implants

Cochlear implants are currently the only available means for improving hearing in cases of profound deafness. Most cases of profound deafness can be corrected by the surgical fitting of a cochlear implant, an electroacoustic system driven by an emitter hidden behind the ear.

This emitter replaces the dysfunctional sensory organ and converts the sound message into an electrical signal, which is then delivered directly to the auditory neurons by electrodes. Finally, these neurons transmit the signal, via the central auditory pathways, to the brain.

The success of cochlear implants depends largely on the presence of intact, functional auditory neurons, facilitating the optimal transmission of the electrical impulses generated by the implant to the auditory centers.

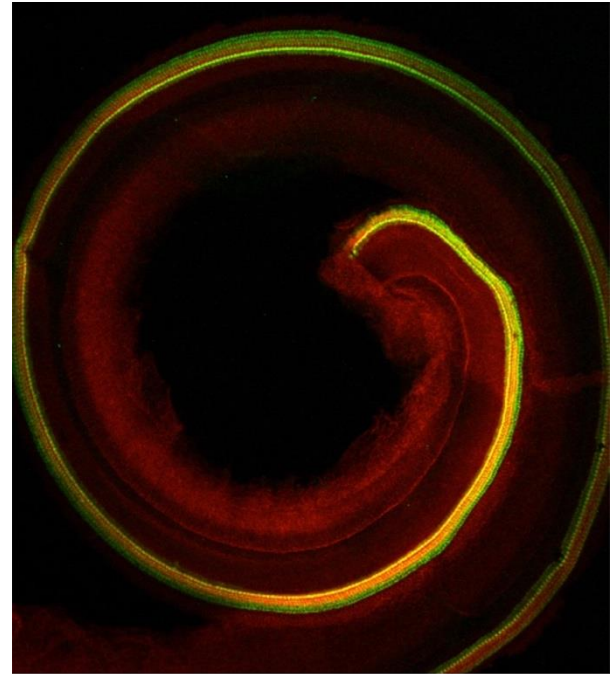
For this reason, cochlear implants are not always effective.

- For example, in one particular form of deafness, the auditory neuropathy DFNB59, hearing loss results from damage to the neurons of the afferent pathway (the pathway followed by nerve impulses to reach the central nervous system). In this case, the gene encoding the pejkakin protein is affected, disrupting communication between the ear and the brain. In this form of deafness, the sensory cells of the cochlea function normally, whereas the auditory neurons do not, delaying and desynchronizing the transmission of signals to the central nervous system. These signals, the translation of the sound message, are profoundly altered. For this reason, children with this form of deafness do not benefit from the fitting of cochlear implants.

- Another example is provided by DFNB9, a form of deafness in which hearing loss results from defects of the inner hair cells in the cochlea. The otoferlin protein is defective in this form of deafness, which is impossible to distinguish clinically from forms of deafness due to auditory nerve or central auditory pathway defects. However, it is important to know whether or not the cochlea is affected in these patients, as cochlear implants are effective only if the auditory nerve can be stimulated by the electrodes of the implant and if the auditory pathways are functional. The surgical fitting of a cochlear implant is therefore possible in children with a demonstrated defect of the gene encoding otoferlin, but this intervention must occur early.

Gene therapy

Building on the considerable progress that has been made towards understanding the mechanisms underlying the various forms of deafness, researchers are now developing alternative or complementary therapies for preventing and/or treating hearing loss



See the examples on the following pages



ADVANCES IN DEAFNESS RESEARCH AT INSTITUT PASTEUR

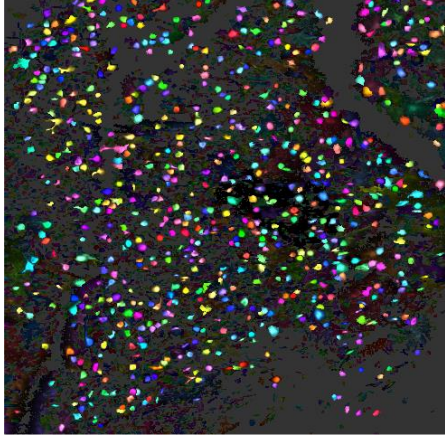
Since the 1960s, Institut Pasteur has hosted a number of neuroscience research teams internationally recognized for their discoveries, some working extensively in the domain of hearing. Over the last 25 years, the Institut Pasteur teams working specifically on hearing have been directed by Professor Christine Petit, the Director of the Genetics and Physiology of Hearing Unit and Professor at the *Collège de France*.

The cochlea contains only a very small number of cells. This is a major obstacle to the use of the biochemical and molecular biology approaches classically used to decipher the molecular basis of the development and function of tissues and organs.

The Genetics and Physiology of Hearing Unit of Institut Pasteur overcame this difficulty by developing the genetic dissection of molecular and cellular mechanisms of hearing. The decision was taken to work on humans, to ensure a rapid transfer to patients of any applications derived from this work. This unit determined the experimental conditions for studies aiming to identify the causal genes for deafness in humans.



Working in close collaboration with geneticists and ENT specialists in several countries, principally in North Africa and the Middle East, this research unit mapped the first gene for isolated deafness onto human chromosomes. This approach proved particularly fruitful, leading to the discovery of the genes responsible for about 20 forms of deafness, mostly congenital severe or profound forms of sensorineural deafness, including some of the most frequent.

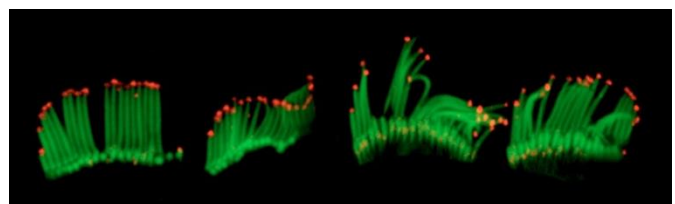


Through interdisciplinary studies of mouse models of human deafness, Christine Petit's team then assembled the proteins encoded by these genes into complexes or molecular networks and investigated their roles in the development and physiology of the cochlea. In this way, the researchers of the laboratory were able to decipher several molecular mechanisms underlying essential functions of the cochlear cells, including the auditory sensory cells in particular. These mechanisms included those involved in the development and sound-processing function of the hair bundle, the structure responsible for sound reception.

This Institut Pasteur laboratory has made major advances in studies of auditory mechanoelectrical transduction (the conversion of sound stimuli into electrical signals) and synaptic exocytosis. The researchers also revealed the hitherto unsuspected essential role of various fibrous links connecting the stereocilia of the hair bundle (except for the tip-links, the role of which in the auditory mechanoelectrical transduction machinery had long been established). It was, thus, genetics that brought hearing into the molecular era.

In addition to improving our understanding of the molecular mechanisms of hearing, this laboratory elucidated the pathophysiological mechanisms of many hereditary cochlear defects. The researchers also revealed a new mechanism involving peroxisomes that protects sensory cells and auditory neurons against noise-induced damage (noise being the principal environmental factor associated with hearing loss). The demonstration that the same genes can be responsible for both peripheral and central hearing loss raised the possibility of extending the genetic approaches used for deciphering the mechanisms involved in hearing to the development and functioning of the auditory cortex.

Finally, the knowledge of the molecular pathophysiology of various types of hearing loss established by this laboratory laid the foundations for current efforts to develop curative treatments for deafness.

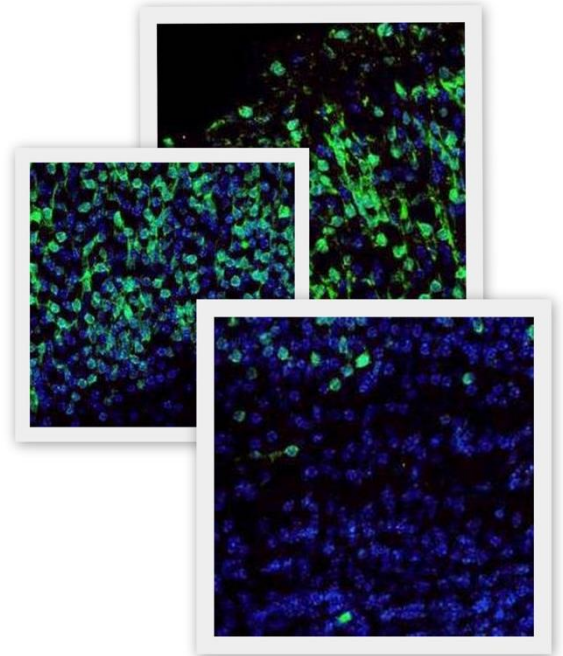


Hereditary deafness: when both the ear and the auditory cortex are affected

Researchers from the Institut Pasteur, Inserm, *Collège de France* and Pierre and Marie Curie University have shown that mutations of three genes responsible for Usher syndrome (a hereditary syndrome combining deafness and blindness) affect not only the functioning of the ear, or, more precisely, the sensory cells of the cochlea, but also the development of the auditory cortex. This discovery could explain why, even after the fitting of a cochlear implant, an electroacoustic device bypassing the defective cochlea, certain patients continue to find it difficult to understand speech. This work is the subject of a publication in *Proceedings of the National Academy of Sciences of the USA*.

13.07.2017 – Link to the press release:

<https://www.pasteur.fr/fr/espace-presse/documents-presse/surdites-hereditaires-quand-oreille-cerveau-auditif-sont-tous-deux-touchez>



Discovery of the genetic cause and mechanisms of noise-related deafness

Researchers from the Institut Pasteur, Inserm, *Collège de France* and Pierre and Marie Curie University, working closely with researchers from the University of Auvergne, have discovered the function of pejkakin, an essential molecule for the auditory system. Its absence leads to noise-related deafness, one of the most frequent types of hearing loss. This scientific discovery, published in *Cell*, opens up new perspectives for patient management.

05.11.2015 – Link to press release:

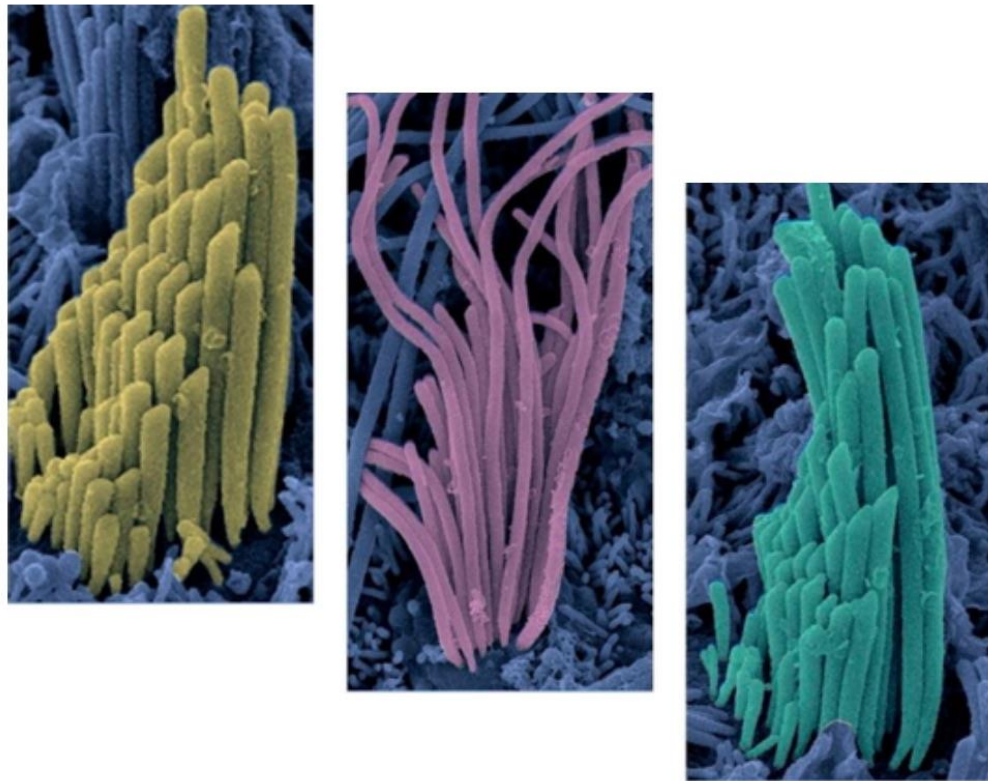
<https://www.pasteur.fr/fr/decouverte-cause-genetique-du-mecanisme-surdites-liees-au-bruit>

Usher syndrome: the restoration of hearing and balance by gene therapy

Researchers from the Institut Pasteur, Inserm, CNRS, *Collège de France*, Pierre and Marie Curie University and the University of Clermont-Auvergne have managed to restore, for the first time, hearing and balance in a mouse model of Usher syndrome type IG (USH1G). Thanks to a local injection of the USH1G gene, which is essential for the formation and maintenance of the mechanoelectrical transduction machinery in the sensory cells of the inner ear, the researchers were able to restore the functioning of this structure, leading to the restoration of both hearing and balance in a mouse model of this syndrome. These results, published in *PNAS*, pave the way for the development of gene therapy for certain genetic forms of deafness.

19.09.2017 – Link to press release:

<https://www.pasteur.fr/fr/espace-presse/documents-presse/syndrome-usher-restauration-audition-equilibre-grace-therapie-genique>



Gene therapy durably restores hearing in mice with congenital deafness

Researchers from the Institut Pasteur, Inserm, CNRS, *Collège de France*, Sorbonne University and the University of Clermont-Auvergne, in collaboration with the universities of Miami, Columbia (New York) and San Francisco, managed to restore hearing in adult mice with DFNB9, one of the most frequent types of congenital deafness of genetic origin. Individuals with DFNB9 are profoundly deaf, as they have genetic defects leading to a lack of the otoferlin protein, which is essential for the transmission of sound information at the synapses of auditory sensory cells. By injecting the otoferlin gene into the cochleas of model mice with this form of deafness, the researchers were able to restore the functioning of the auditory synapse and the auditory thresholds of the mice to near-normal levels. These results, published in *PNAS*, pave the way for future gene therapy trials in patients with DFNB9.

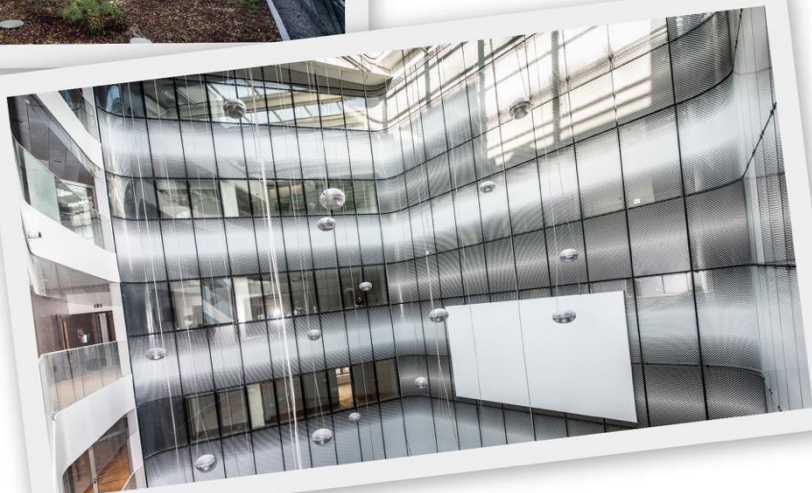
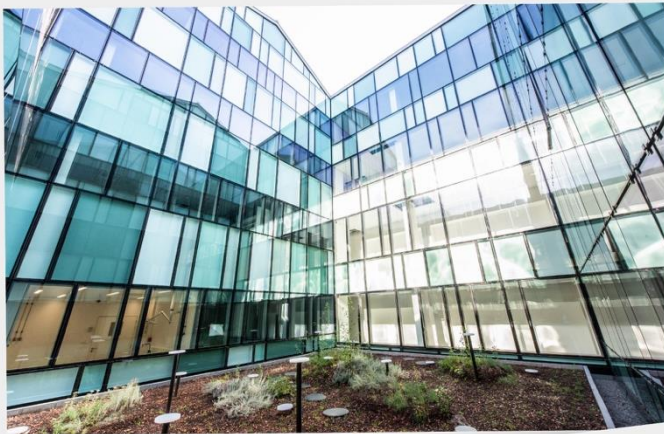
18.02.2019 – Link to the press release:

<https://www.pasteur.fr/fr/espace-presse/documents-presse/therapie-genique-inverse-durablement-surdite-congenitale-souris>

A promising context for the creation of the Hearing Institute

It is, thus, in a very promising scientific context that the Hearing Institute will open its doors. It will benefit from a number of important advantages:

- Breakthroughs made, in particular, in the Genetics and Physiology of Hearing laboratory, which have established the basic knowledge required for the development of novel diagnostic methods and curative treatments for defects of the cochlea and its innervating neurons;
- A critical mass of experts in the domain, extending from biophysics to cognitive neurosciences, creating ideal conditions for major discoveries relating to our understanding of the development and functioning of the auditory system as a whole, over multiple scales, from the molecule to behavior.
- Translational research (bench-to-bedside), with the support of a network of national and international collaborations with public and private institutions, the CERIAH and the CeRCA network.



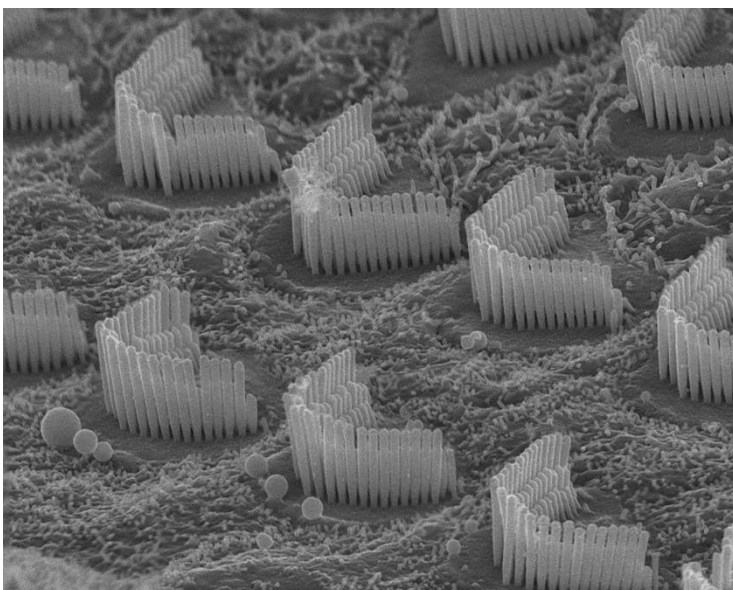
PROFESSOR CHRISTINE PETIT

Christine Petit, eminent researcher and holder of both a medical and a scientific doctorate, is the Director of the Genetics and Physiology of Hearing mixed research unit at the Institut Pasteur (Inserm), a member of the French National Academy of Science and Professor at the *Collège de France*. She is also a member of the French National Academy of Medicine, the American National Academy of Sciences and the Norwegian Academy of Science and Letters.

Most of Christine Petit's research has been devoted to the biology of hearing. By proposing and implementing an approach based on the genetic dissection of the molecular and cellular mechanisms of hearing based on the identification of deafness genes in humans, Christine Petit provided neurosciences with a knowledge of the auditory system at the molecular scale. Her discovery of the genes responsible for Usher syndrome (deafness and blindness, with or without balance problems) or isolated forms of deafness, and the construction of multidisciplinary teams opened up exciting new possibilities. The genes identified provided a new way to access the molecular machineries enabling the sensory cells to act as ultrasensitive sound receptors, tuned to particular frequencies and encoding sounds with extreme temporal precision, and emitting distortion products.



These studies led to the development of molecular diagnosis for hereditary deafness by Christine Petit and her team, together with colleagues in several developing countries. Through studies performed with Prof. Paul Avan (Clermont-Ferrand University Hospital), these results also improved our understanding of the meaning of certain audiological tests used in clinical practice, paving the way for a scientific approach to the indications for cochlear implants and auditory rehabilitation.



Today, Christine Petit is committed to new objectives: understanding the cellular and molecular mechanisms underlying presbycusis and the vulnerability of the auditory system to noise in humans, with a therapeutic objective in mind; developing precision medicine for hearing loss, based on methodological innovation and multifactorial diagnosis; and discovering curative treatments for hearing loss (gene therapy and pharmacological treatments), regardless of the age at which hearing loss occurs.....now a realistic hope.

Christine Petit's discoveries have been recognized in the form of many international scientific prizes, including the L'Oreal-UNESCO "For Women in Science" Award - Europe (2004), the Bristol-Myers-Squibb "Freedom to Discover" Award in Neuroscience - USA (2005), the Louis-Jeantet Prize for Medicine (2006), the INSERM Grand Prix for Medical Research - France (2007), The Brain Prize - Grete Lundbeck Foundation - International (2012), and the ARO (Association for Research in Otolaryngology) Award of Merit - USA (2018).

More recently, on September 4, 2018, the Norwegian Academy of Science and Letters awarded her the prestigious Kavli Prize, an international prize in the field of neurosciences, for her pioneering work on the molecular and neuronal mechanisms of hearing.

FOR MORE INFORMATION

Presentation of the Hearing Institute

<https://www.pasteur.fr/en/our-missions/research/hearing-institute>

Institut Pasteur

<https://www.pasteur.fr/en>

La Fondation pour l'Audition

<https://www.fondationpourlaudition.org/en>

Information about deafness (in French)

<https://www.pasteur.fr/en/medical-center/disease-sheets/hearing-loss>

Credits and pictures captions

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Cover: Photomontage displaying hair bundles of cochlear sensory cells in the foreground and auditory cortex neurons stained in green in the background.

Page 6: Image of the hair bundle, the sound reception antenna of cochlear sensory cells.

Page 7, left: Photomontage based on pictures of the auditory and vestibular sensory organs.

Page 7, right: Image of the auditory sensory organ, the organ of Corti.

Page 8: Facade of the Hearing Institute.

Page 9, left: Facade of the Hearing Institute.

Page 9, right: View of the atrium in the Hearing Institute.

Page 11: Image showing a row of auditory sensory cells.

Page 14: Photo showing audiometric tests performed on a newborn child.

Page 15: Photo of a hearing aid.

Page 16: Image of the auditory sensory organ in which sensory cells are stained in green.

Page 17: Photos showing an electrophysiology set-up and researchers of the Hearing Institute.

Page 18, top: Layer delineating the position of neurons on a slice of the auditory cortex.

Page 18, bottom: Image of hair bundles (the sound reception antenna of cochlear sensory cells) stained in green.

Page 19: Images showing a subpopulation of neurons specific of the auditory cortex and stained in green.

Page 20: Images showing hair bundles of vestibular sensory cells in normal (yellow) and pathological (pink and green) conditions.

Page 21, bottom: Photos of the new Hearing Institute building.

Page 22, bottom: Photos of hair bundles, the sound reception antenna of cochlear sensory cells.