7 scientists from 5 countries share USD $1 million prizes in fields of astrophysics, nanoscience and neuroscience

May 31, 2018 (OSLO) — The Norwegian Academy of Science and Letters today announced the winners of the 2018 Kavli Prizes. Given in the fields of astrophysics, nanoscience and neuroscience, this year’s prizes honor scientists who studied molecules in space and illuminated the life cycle of stars and planets, developed a tool to precisely edit DNA, and unlocked the neuroscience underlying human hearing.

This year’s winners are:

- **Kavli Prize in Astrophysics**: Ewine van Dishoeck (the Netherlands)
- **Kavli Prize in Nanoscience**: Emmanuelle Charpentier (France), Jennifer A. Doudna (USA), and Virginijus Šikšnys (Lithuania)
- **Kavli Prize in Neuroscience**: A. James Hudspeth (USA), Robert Fettiplace (UK), and Christine Petit (France)

“These Laureates represent truly pioneering science, the kind of science which will benefit humanity in a profound way. They will inspire both current and future generations to continue searching for answers to some of the most difficult questions of our time. Through their hard work, dedication and innovation, they have strengthened our understanding of existence,” says Ole M. Sejersted, President of the Norwegian Academy of Science and Letters.

The Prize consists of a gold medal and a cash prize of USD $1 million for each field. The Norwegian Academy of Science and Letters selected the Laureates, based on nominations by committees whose members are recommended by six of the world’s most renowned science societies and academies. The announcement of the 2018 Laureates was made in Oslo and streamed live to the World Science Festival in New York City.

The 2018 Kavli Laureates

**Astro: Shedding light on the Origins of Stars, Planets and Life**

The Kavli Prize in Astrophysics is given to Ewine van Dishoeck for her seminal work on revealing the chemical and physical processes in interstellar clouds, where stars and planets form. Her work has contributed to a breakthrough of astrochemistry, demonstrating how molecules form and evolve during the transformation of a cloud into stellar systems like our own.

Through observational studies using telescopes on Earth and in space, van Dishoeck unveiled the “water trail,” measuring water vapor from dense clouds to young stars. This helps us understand the formation mechanisms of molecules crucial for life as we know it. She also discovered important structures within the rings of dust and gas surrounding young stars, the birthplace of planets and comets.

Van Dishoeck is professor of molecular astrophysics at the University of Leiden and has played a leading role in advancing the field of astrophysics. This includes serving on the board of the internationally-supported Atacama Large
Millimeter/submillimeter Array (ALMA) in Chile—a collection of 66 dishes that can be connected to function as one telescope with a diameter of 10 km (6.2 miles). With this exceptional instrument, van Dishoeck and colleagues have studied the formation of solar-type stellar systems within our galaxy.

"Professor Van Dishoeck's research on the chemistry of the universe has transformed virtually every aspect of the subject. She has advanced a subject that was once regarded as a small activity on the fringes of mainstream astrophysics, and brought it to the forefront of astronomy as a whole,” says Robert Kennicutt, member of the astrophysics prize committee.

More details available at the Kavli Prize website.

**Nano: Inventing a Scalpel for the Code of Life**

The Kavli Prize in Nanoscience is awarded to three scientists who invented CRISPR-Cas9, the revolutionary nanotool for editing DNA, and opening a new chapter in biology, agriculture and medicine. The USD $1 million prize will be shared by Emmanuelle Charpentier of the Max Planck Society, Jennifer A. Doudna of the University of California, Berkeley, and Virginijus Šikšnys of Vilnius University.

“CRISPR-Cas9 is a breakthrough nanotool that will considerably enhance our understanding of genetic mechanisms. This great invention confers to society enormous capabilities for positive innovations,” says Arne Brataas, head of the nanoscience prize committee.

With their teams, Charpentier and Doudna, and independently Šikšnys invented a new tool that allows researchers to identify specific sequences in the genome and edit them, thereby changing the instruction manual of living things. Their breakthrough was found in combining CRISPR (“Clustered Regularly Interspaced Short Palindromic Repeats”), an element of the immune system of bacteria, with the Cas9 protein to precisely edit DNA.

The pioneering work has unleashed global interest among scientists and the public in a field of research with enormous potential to address disease-causing mutations in humans and improve agriculture. It has also sparked a conversation around the ethical challenges that must be addressed when altering genes.

More details available at the Kavli Prize website.

**Neuro: Unlocking the Mystery of Hearing**

The Kavli Prize in Neuroscience is shared between A. James Hudspeth, of the Rockefeller University, Robert Fettiplace, of the University of Wisconsin, Madison, and Christine Petit, of Collège de France/Pasteur Institute, for their scientific discoveries of the molecular and neural mechanisms of hearing. The Laureates used complementary approaches to unravel the mechanisms by which hair cells in the inner ear transform sound into electrical signals that can be deciphered by the brain.

"They have provided fundamental new insights into how our inner ear transforms sound into electrical signals - the basis of hearing - and have unveiled genetic and molecular mechanisms underlying hearing loss," says Ole Petter Ottersen, head of the neuroscience prize committee. "Their work serves as a sterling example of how concerted efforts across disciplines and technologies can revolutionize our understanding of complex neurobiological processes."

Hudspeth's research has provided much of the framework for our understanding of how sound is converted into neural signals through hair cells and their ion channels. Fettiplace showed that each hair cell in the cochlea of the inner ear is sensitive to a specific range of sound frequencies and discovered the mechanistic basis of this. By exploring the genetics of hereditary deafness, Christine Petit has furthered our understanding of hair cell biology and informed deafness diagnosis and counseling. Combined, these Laureates' work has unraveled the sense of hearing.

More details available at the Kavli Prize website.
About the Kavli Prize:
The Kavli Prize is a partnership between the Norwegian Academy of Science and Letters, the Kavli Foundation (USA) and the Norwegian Ministry of Education and Research. First awarded in 2008, the Kavli Prize has honored 47 scientists from 11 countries – France, Germany, Japan, Lithuania, The Netherlands, Norway, Russia, Sweden, Switzerland, the United Kingdom and the United States.

The Kavli Prize recognizes scientists for pioneering advances in our understanding of existence at its biggest, smallest, and most complex scales. Presented every two years in the fields of astrophysics, nanoscience and neuroscience, each of three prizes consists of USD $1 million and a gold medal. Laureates are nominated by committees whose members are recommended by The Chinese Academy of Sciences, The French Academy of Sciences, The Max Planck Society (Germany), The National Academy of Sciences (US), The Royal Society (UK) and the Norwegian Academy of Science and Letters. Winners receive gold medals in Oslo, Norway, in a ceremony presided over by His Majesty King Harald. A banquet takes place at Oslo’s City Hall, the venue of the Nobel Peace Prize ceremony.

The 2018 Kavli Prizes will be awarded on Tuesday, September 4 in Oslo, Norway.

For more detailed information on each of the prizes, the 2018 Laureates and their work, and the Kavli Prize events, please visit www.kavliprize.org

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We live in a universe where molecules are omnipresent and play a key role in the physical processes that lead to the formation of stars, planets, and life. Observing these molecules also allows astronomers to probe cold and obscured interstellar clouds in the Milky Way and other galaxies where these processes take place.

Our understanding of cosmic chemistry has been revolutionized by a combination of measurements with new observatories on the ground and in space, laboratory experiments, and theoretical studies of the relevant processes. Among the researchers who have contributed to this revolution, Ewine van Dishoeck stands out.

Among the many advances made by van Dishoeck and her collaborators are seminal contributions to our understanding of the formation and destruction of interstellar molecules. Their pioneering work on carbon monoxide has been essential for determining the physical processes that drive the evolution of the cold components of the interstellar medium, from diffuse to dense clouds in the Milky Way, as well as the cold star-forming gas in galaxies across cosmic time.

Through laboratory experiments, van Dishoeck's group has advanced the quantitative understanding of the chemical processes governing the growth and evolution of interstellar ices. This work includes investigations of photo-processing of ices composed of water, nitrogen, carbon monoxide and carbon dioxide. Such studies serve as the basis for modelling the effects of photo-desorption and processing of astrophysical ices, key steps in the evolution of molecular clouds and the subsequent formation of stars, protoplanetary disks, and planets. This work also helps to elucidate the chemical evolution of our Solar System, where comets and primitive meteoritic materials preserve the composition of the original cloud of gas and dust.

Recently van Dishoeck and colleagues have extended this approach in an effort to connect the chemical composition of the comet visited by the Rosetta mission with that of young Solar-type stellar systems.

Ewine van Dishoeck has masterfully applied spectroscopic tools across a broad range of wavelengths with a superb exploitation of the most capable astronomical measurement techniques. She used the Infrared Space Observatory (ISO) to study molecules previously not accessible by microwave spectroscopy, the Herschel Space Observatory to follow the trail of water throughout star formation, and more recently the Atacama Large Millimeter and sub-millimeter Array (ALMA) to provide the first view of dust traps in disks around young stars, observationally constraining planet formation theories.

These examples illustrate the remarkable breadth of her approach to these fundamental problems, encompassing cutting-edge astronomical observations, physical and chemical theory, and laboratory experiments. Ewine van Dishoeck is leading the transformation of astrochemistry into a growing, quantitative discipline.
To repair a defect in the genome of an organism, one would have to remove, alter, or insert a genetic code at atomically precise locations in the DNA sequence. This vision is now a reality with CRISPR-Cas9, a nanotool that opens a door towards curing hereditary diseases and boosting agriculture. CRISPR-Cas9 constitutes a revolutionary innovation compared to prior techniques, which were tedious, imprecise, and costly.

CRISPR-Cas9 is simple to use. A small RNA molecule is synthesized to encode the address of the DNA sequence to be altered. This RNA molecule is attached to a Cas9 protein to form a CRISPR-Cas9 complex. The complex attaches to the target DNA. Cas9 then opens and cleaves the DNA at exactly the desired location. As the DNA segments reconnect, genes may be inserted or defunctionalized. In this way, disease-causing mutations can be corrected by changing the underlying genetic code. CRISPR-Cas9 works on many organisms, including plants, fungi, animals, and humans.

The breakthrough of CRISPR-Cas9 builds on the discovery and exploration of CRISPR. CRISPR stands for “clustered regularly interspaced short palindromic repeats,” a DNA base-pair sequence used by the immune system of bacteria against viral attacks. With their teams, Emmanuelle Charpentier and Jennifer A. Doudna, and independently Virginijus Šikšnys invented a way to develop CRISPR and Cas9 into a powerful nanotool. Their pioneering work and further great advances by a growing number of researchers continue to unleash the enormous potential of CRISPR-Cas9.

This great invention not only offers tremendous opportunities but also carries responsibilities and risks that affect all humankind. Profound ethical challenges must be addressed and resolved.

CRISPR-Cas9 confers to society enormous capabilities for positive innovations. Possible benefits are wide-ranging in scope and value. From a fundamental perspective, CRISPR-Cas9 is a breakthrough nanotool for research in the life sciences that will greatly enhance our understanding of genetic mechanisms. It enables the detailed study of many hitherto genetically intractable organisms. Potential applications of CRISPR-Cas9 are to optimize agriculture with regard to breeding crops and livestock having desired properties.

Potential medical applications include the capability of correcting disease-causing mutations and using gene therapy to cure serious diseases such as muscular dys-
The CRISPR-Cas9 nanotool initiates a revolution in genetic engineering with great potential benefits and pressing ethical challenges.

trophy, sickle-cell anemia, and some forms of blindness and cancer.
Hearing is an important sense that contributes to human communication. The three Kavli Prize laureates used complementary approaches to unravel the mechanisms by which nerve cells transform sounds into electrical signals. This process is performed in the inner ear by sensory receptors called hair cells. The unique cellular, molecular and biophysical properties of these cells enable them to detect small air vibrations across a wide range of frequencies. The electrical signals generated by hair cells are then transmitted into the brain, allowing them to be interpreted as language, music, or noise.

A. James Hudspeth has provided the major framework for our understanding of the process that transduces sound into neural signals. Extending from each hair cell is a bundle of fine processes that act as sensors. Hudspeth used ingenious methods to reveal how sound-induced vibrations, which set the hair bundle in motion, evoke an electrical response in the hair cells through a direct mechanical connection between the hair bundle and ion channels. He also revealed how sound signals, which can be extremely small, are amplified within the inner ear.

Robert Fettiplace has made fundamental contributions to our understanding of sound transduction and demonstrated that each hair cell in the cochlea of the inner ear is sensitive to a specific range of sound frequencies. His experiments revealed that hair cells are organized along the cochlea in a pattern that reflects their frequency selectivity. Using sensitive physiological measurements and theoretical modeling, he discovered that this selectivity reflects an intrinsic electrical property of the cell, set by the density and kinetics of its ion channels that induce a resonance at a particular frequency.

Christine Petit has explored the genetics of hereditary deafness in humans and identified more than twenty genes that are required for hearing and inner ear development. She elucidated the mechanisms through which these mutations cause hearing deficits, thus illuminating the unique biology of hair cells and informing deafness diagnosis and counseling. Several of the genes she identified form major components of the hair cell mechanotransduction machinery. Collectively the breakthroughs made by this year’s Kavli Prize laureates have unveiled the molecular and cellular mechanisms that underlie hearing and deafness.
readily destroyed by ultraviolet starlight. The density of particles within interstellar clouds is higher than in surrounding space but would still be so low, the reasoning went, that any molecules that do survive would be far too thinly spread to be detectable.

Then in 1968, the physicist Charles Townes and colleagues pointed a radio telescope at the Sagittarius B2 molecular cloud, on the basis that if molecular hydrogen existed in interstellar space – as some scientists had proposed – then maybe other molecules did as well. That hunch was vindicated when the researchers first found signals from ammonia molecules and then from water. Following a slew of detections by other researchers since the 1970s, scientists have to date established the existence of around 200 types of molecule in the interstellar medium. These discoveries implied that interstellar clouds contained at least 1000 molecules per cubic centimetre, rather than the 1-10 atoms per cubic centimetre previously thought from observations of atomic hydrogen. It also
became clear that these molecular clouds contained a lot of interstellar dust – particles of matter from previous generations of exploded stars – that effectively blocks ultraviolet radiation. This extra protection and the higher densities reinforced the idea that stars could form when pockets of gas collapse in on themselves. However, this molecular basis for star formation threw up problems of its own. For atoms to combine to form molecules in the low densities of space they need to attract one another over long distances. In other words, ions are better at forming molecules than neutral atoms are. Those ions can be created when cosmic rays slam into atoms and create ion-electron pairs. Another way for molecules to form inside molecular clouds is for atoms to stick to the surfaces of dust particles, migrate and over time come together to form new molecules.

But that still leaves the problem of how molecules survive at all in the presence of ultraviolet starlight. It was a problem that vexed theorists and where van Dishoeck first made a name for herself, in research carried out during and after her PhD in the 1980s. She showed that although some molecules are indeed broken up, others, such as water and carbon monoxide (CO), manage to “self-shield” the inner parts of molecular clouds by selectively absorbing the destructive ultraviolet radiation in the outer layers. The self-shielding and the absorption by surrounding dust allow molecules deeper in the cloud to go on and form stars.

In carrying out this research, van Dishoeck considered the case of CO, which is far less abundant in space than hydrogen but emits radiation much more efficiently. Given a certain cloud density, she calculated the probability of a given molecule being excited – through rotation, vibration or electronic transition – when struck by another molecule in the gas. By taking into account starlight’s destruction of molecules, and how that varies throughout the volume of the gas, she arrived at probabilities that closely matched the intensity of radiation observed using radio telescopes (the radiation being emitted when molecules are excited).

However, having started her career as a theorist, van Dishoeck began to work increasingly with observational data. In particular, she studied infrared emissions from water detected by a series of ever more sophisticated space telescopes. Water is formed when reactants are relatively plentiful, so although rare in interstellar space generally it is abundant in star-forming regions. However, its emissions are almost entirely absorbed by the water in our own atmosphere, which means space-based observatories are needed to study it.

Scientists got their first view of the rich molecular world at infrared wavelengths with the launch of the European Space Agency’s Infrared Space Observatory in 1995. van Dishoeck used the Dutch-German built short-wavelength spectrometer to study the formation of water on the surface of dust grains, discovering that in dense molecular clouds the grains become completely covered with water ice and carbon monoxide ice.

From 2003, she then turned to NASA’s Spitzer Space Telescope to study chemical reactions in relatively light stars similar to our sun (having previously been limited to heavier objects). She and her colleagues also discovered water and other molecules in the dusty rotating disks created around still-forming stars that provide the stars with raw material from the surrounding gas and are the potential birth places of new planets.

Her observations of water intensified following the launch of an even more powerful far-infrared/submillimetre telescope, ESA’s Herschel Space Observatory, in 2009. This too she used to study a “protoplanetary disc”, the water in which binds dust grains...
together so that they eventually become solid bodies such as very young planets or comets, which themselves are thought to transport water to planets.

In 2011 van Dishoeck and colleagues reported measurements of cold water vapour emanating from across the disc surrounding a young and fairly close star known as TW Hydrae. Based on the strength of the infrared signals recorded by Herschel, they estimated that the vapour is being released from a reservoir of ice within the disc having a mass several thousand times that of the water covering Earth.

Using ALMA, van Dishoeck and her colleagues have observed protostellar discs around newly-formed stars on their way to forming new planetary systems in the Milky Way. They have obtained some striking images of complex dusty ring structures that perhaps point the way to individual planets within these discs. In addition to these chemistry- and physics-based studies, however, the researchers are also doing work with biological implications.

Last year, van Dishoeck’s group and an Italian/Spanish team reported having used ALMA to spot a number of emission lines from the organic molecule methyl isocyanate. This “prebiotic” molecule was located in the dust and gas surrounding several very young Sun-like stars about 400 light-years away in the Ophiuchus constellation. Since it is involved in the synthesis of peptides and amino acids, the researchers say that this molecule might help astronomers work out how life arose on our planet.

That optimism is mixed with caution, however. Although methyl isocyanate is far from the only complex organic molecule to have been detected in interstellar clouds, it is still not clear to what extent all the molecules needed for life are present in newly-made planets. In particular, despite significant searching, no-one has yet found unambiguous evidence for amino acids themselves in star-forming regions.

Many discoveries of new molecules in space need to be backed up with supporting laboratory work, so that researchers know the precise wavelengths at which those molecules emit or absorb electromagnetic radiation as well as having detailed information on molecules’ collision properties, among other things. Indeed, experiments carried out as part of the latest work showed that methyl isocyanate can form on icy particles in very cold conditions like those in interstellar space.

Those experiments were carried out in a laboratory at Leiden University that was set up by experimental astrochemist Mayo Greenberg in the 1970s. One of
the few labs of its type in the world, it provides the very low-density, low-temperature and stable conditions needed to approximate interstellar space. The vacuum created is still many orders of magnitude more dense than that in space but a number of tricks help bridge the gap, such as extending the lifetime of ions by embedding them in a neutral fluid.

Although van Dishoeck doesn't carry out the lab work herself, Reinhard Genzel, an astrophysicist at the Max Planck Institute for Extraterrestrial Physics in Munich, says that her familiarity with that work allows her to make ever more sophisticated predictions of interstellar chemistry. "This balance between theoretical and observational work is astounding in terms of breadth," he says.

By Edwin Cartlidge, science writer
During the following years, the CRISPR sequence was observed in other types of prokaryotic system. It became clear that the spacers were in fact copies of viral DNA that the cell could use to detect and eliminate viruses. Importantly, it was demonstrated that the number of spacers increases when bacteria were exposed to viruses. In other words, the CRISPR sequence provides the organism with an adaptive immune system.

The way in which the cell uses CRISPR sequences as a defence mechanism involves an enzyme known as Cas — short for CRISPR-associated — linked to a strand of RNA molecule generated as a copy of one of the spacers in the CRISPR DNA. Once a virus with a specific DNA sequence enters the cell this is matched by the RNA and deactivated by the Cas enzyme.

Research up to 2012 had provided essential information about the way CRISPR works. In that year however, two independent research groups showed how to harness and control the CRISPR-Cas system — more specifically, the version using a specific type of Cas enzyme known as Cas9.

One team was led by Jennifer Doudna from Berkeley and Emmanuelle
Charpentier, then at Umeå in Sweden. The other was led by Virginijus Šikšnys based in Vilnius, Lithuania. Both groups reported the isolation of Cas9–RNA complexes from bacteria and the demonstration in vitro that Cas9 could be used to cut out a segment of an external double strand DNA sequence that matched the sequence of the RNA (Figure 1). Effectively the results showed that the Cas9 enzyme can be used as a pair of nanoscale scissors to selectively cut out the pieces selected by the RNA.

In general, once DNA is broken, the cell will repair it, either by stitching together the loose ends, or by inserting a new segment. This process forms the basis of gene editing. Before the results found by Doudna, Charpentier and Šikšnys, gene editing had been approached with complicated systems involving binding between DNA proteins, primarily zinc-finger nucleases and transcription activator-like effector nuclease. Being based only on DNA–RNA linking, the CRISPR-Cas9 approach is much simpler. Already at the beginning of 2013, a few reports confirmed that through CRISPR-Cas9 it was possible to affect human and plant DNA, providing further evidence of the potential of the technique in gene editing.

Given the simplicity of CRISPR-Cas9, many teams around the world have been exploring its potential in a variety of biomedical applications. Gene editing has the potential to treat genetic diseases by removing the mutation that causes the disease from a patient’s DNA. Initial demonstrations in vitro were followed by in vivo experiments in which CRISPR-Cas9 was injected in animal models. One of the early examples was the treatment of Duchenne muscular dystrophy in mice. Other studies have focused on cystic fibrosis. Applications in certain types of cancer have also been explored, which has already led to one clinical study approved by the National Institutes of Health in the US, and several ongoing ones, primarily in China.

The anti-viral origin of CRISPR-Cas9 inspired studies exploring its use in fighting viral infections such as papillomavirus and hepatitis B. Encouraging results have also been obtained for the HIV virus, which was shown to regress in a number of animal models.

Aside from therapeutic applications, we can imagine that gene editing can be used on animals and plants for other purposes. By modifying or simply eliminating a gene responsible for a certain trait in a species it is possible to eliminate that trait, whether it is the appearance (Figure 2), or, more interestingly, the ability to carry a virus. Experiments have already demonstrated, for example, the possibility of using CRISPR-Cas9 to mutate Anopheles mosquitoes and make them resistant to the malaria parasite. Most importantly, the mutation was carried out in such a way that it could be transferred to the offspring of every insect. If pursued, this type of research could have enormous consequences on the spread of diseases carried by insects.

The possibility of mutating traits also has interesting potential for breeding livestock, for example by making animals stronger or more resistant to viruses. The latter has already been shown in pigs. In a similar way, by mutating genes in plants it is possible to improve agriculture. Experimental work has already shown the generation of crops with improved resistance to pests or to adverse weather conditions such as drought. More generally, even the quality of fruit and vegetables, in terms of size, colour or taste can be affected.

It should be mentioned that the great potential of the CRISPR-Cas9 gene editing tool also calls for responsibility in its use. The benefits could be enormous, especially because of the relative simplicity of the technique that can be applied by a large number of scientists and indeed commercial enterprises. However, there are serious concerns about its potential misuse and negative effects. Just imagine the ethical dilemmas that could be generated by the modification of genes in embryos to change specific traits in people, or by the introduction of mutations that can be inherited by offspring.

Even without going that far, changing animals or plants, even if for potentially beneficial purposes, could lead to catastrophic effects on entire ecosystems. Research is ongoing to understand potential unwanted effects of introducing gene mutations in any type of species. The situation is complicated by the fact that the views of the public and of policymakers on gene editing are different in different countries, and it is difficult to establish a unique regulatory system. The good news is that scientists are all too aware of these issues and are
working with regulators to ensure the mitigation of negative effects.

Beyond real world applications, CRISPR-Cas9 represents a powerful tool for scientific research. Just to name a couple of examples, in order to study the function of a gene, scientists can use CRISPR-Cas9 to mutate or even silence it, thus observing the effect it has on an organism. Alternatively, the DNA of an animal model could be modified with humanized mutations to perform studies that cannot be carried out on humans because it is too dangerous or unethical.

In less than six years since the work by Doudna, Charpentier and Šikšnys, CRISPR-Cas9 has developed into one of the most powerful tools in genetics. As Professor Arne Brataas, of the Norwegian University of Science and Technology, and chairman of the Kavli Prize in Nanoscience Committee said “CRISPR-Cas9 is a breakthrough nanotool that will considerably enhance our understanding of genetic mechanisms. This great invention confers to society enormous capabilities for positive innovations”.

By Fabio Pulizzi, science writer

Figure 3: Effect of two gene mutations induced by CRISPR-Cas9 on tomatoes. The upper panel shows the wild type with only two locules; the centre and lower panels show the results of two different gene mutations, producing 6 and 12 locules respectively. From Nature Genetics 47, 784–792 (2015). Image courtesy of Macmillan Publishers Ltd
Listening to music, a person talking, or an animal rustling through leaves, all depend on our sensitive hearing. The human ear is as sensitive for sound as eyes are for a photon of light. But how do we distinguish sounds, whether faint or loud, distant or near?

The 2018 Kavli Prize for Neuroscience has gone to scientists who have shed light on the fundamental processes of hearing, and helped to explain deafness.

Until a few decades ago, little was known about hearing beyond basic anatomy and physiology. Sound waves enter the ear canal of the outer ear and cause the eardrum to vibrate; the vibrations travel through the bones of the middle ear to the cochlea, in the inner ear. This tiny organ, shaped like a snail’s shell, is just a few millimeter wide, and 32 mm long in humans. Sound pressure waves travel through its fluid-filled chambers, and trigger electrical impulses to be sent to the brain via the auditory nerve. Scientists suspected that cells known as hair cells might be the key sensors of sound signals.

There are only around 16,000 hair cells in the cochlea, lining the basilar membrane, which separates the fluid-filled ducts of the cochlea. Microscopy shows that over a lifetime, these can become damaged and lost following exposure to drugs such as streptomycin, infections such as rubella or toxoplasmosis, or loud sounds, and do not regenerate, which could account for hearing loss.

The 2018 Kavli Neuroscience prizewinners, A. James Hudspeth, Robert Fettiplace and Christine Petit, have independently investigated the role of hair cells in hearing. Hair cells are named for their tufts of hair-like projections visible on electron microscopy. These tufts, called hair bundles, consist of 20 to 300 individual projections called stereocilia, arranged in neat rows of different height, and are embedded in a jelly-like overlay called the tectorial membrane.

Starting in the late 1970s, Hudspeth and Fettiplace came from biophysics backgrounds, and were curious about whether movement of the hair bundles, due to vibrations of the cochlear membranes, led to electrical signaling. In order to access the cochlea – which in mammals is embedded inside the temporal bone of the skull – they both chose initially to work on cochlea from exotic animals such as bull frogs (Hudspeth) and turtles (Fettiplace). These are fairly large and easy to maintain in the laboratory because, coming from cold-blooded creatures they can withstand temperature fluctuations. They then had to delicately peel off the tectorial membrane without tearing the hair bundle structures.

Hudspeth fashioning a very fine glass fibre, with a diameter of 0.5 to 0.8 micrometers, with which to push gently...
against the tips of individual hair bundles. He used a piezoelectric actuator for precise control of the glass fibre, and equally fine microelectrodes to measure changes in electrical potential of individual hair cells. He was the first to show that mechanical displacement of a hair cell bundle in the direction of the tallest row of stereocilia, triggered a change in electrical charge (depolarization) of the cell membrane. The amount of displacement needed was so miniscule, that Hudspeth likened it to being the equivalent of a thumb-wide movement at the tip of the Eiffel Tower.

Hudspeth found that the electrical response required the flow of potassium and calcium ions through the membrane at tips of the stereocilia, and proposed that the movement of stereocilia mechanically pulls open membrane channels to allow positively charged ions to flow in.

He drew inspiration from electron microscopy images of short rod-like structures connecting neighbouring stereocilia Tip-links, he suggested, were stretched by the movement of stereocilia and exerted a force that opened the ion channels. When moved in the opposite direction, the tip-links slackened and the ion channels closed. This would be consistent with the idea that sound waves pulsating through the fluid ducts of the cochlea, cause the basilar and tectorial membranes to vibrate and move across one another, creating a shearing force on hair bundles.

For the next three decades, Hudspeth developed his system and revealed more of the biophysical and biochemical properties of hair cells and their putative ion channels. He revealed a phenomenon that was like a public address system being turned up too far: rather than being passive receivers of sound, hair bundles actively twitch, which confers a 100- to 1000-fold greater sensitivity to sound vibrations. In other words, have a built-in amplifier system. It is this amplification that is lost first with aging.

Robert Fettiplace investigated the turtle cochlea, and in 1980, reported that the sensitivity to different sound frequencies could be mapped along the basilar membrane – rather like the keys of a piano. By recording electrical changes in inner hair cells, he revealed a spectrum of sound sensitivity, called a tonotopic map, in which individual hair cells were tuned to resonate with just a narrow range of sound frequencies, according to their position along the membrane. Hair cells at the narrower, stiffer base of the cochlea, responded to high frequencies, while those at the wider and more floppy apex of the membrane responded to low frequencies. Fettiplace predicted – and over the next two decades showed experimentally - that the fine tuning of each hair cell is due to the numbers and speed of opening and closing of different ion channels, which influences the hair cell’s electrical and mechanical properties. Hair cells at the two ends of the cochlea differ in their composition of ion channels and the height of their hair bundles. The identity of the ion channels, and how they open and close, remain a mystery.

Fettiplace later found that in mammals, the amplification of sound sensitivity is due to the movements of outer hair cells, which enhance vibrations locally in the basilar membrane.

By the early 1990s, Hudspeth, Fettiplace and others had made major strides in understanding the biophysics and physiology of the auditory system, but little was known about the molecular mechanisms. This was especially difficult to study because the cochlea has so few hair cells specific to each sound frequency.

This is where Christine Petit’s research compliments that of Hudspeth and Fettiplace. Trained in medicine in France, she was interested in the genetic basis for inherited forms of deafness. Petit worked extensively to build collaborations with doctors in Syria, Lebanon, Algeria, Tunisia, Morocco and Jordan, where profound deafness appeared to be particularly prevalent in some large families. One form is Usher syndrome, featuring progressive blindness and hearing defects, and which Petit found involved several different genes. There are over a hundred such inherited syndromes, and many different genetic mutations involved.

Through genetics, molecular biology and biochemical analysis, Petit has identified over 20 distinct genes whose absence or mutation disrupts hearing, mainly by affecting the development and function of hair cells. Some encode proteins found in tip-links (known as cadherin-related proteins), in hair bundles, the ankle-links at the base of hair cells, and machinery involved in the release of the neurotransmitter glutamate, and other hair
cell components. There are hints too that some of the genes may also be involved in the wiring of the auditory cortex, where the brain decodes the information about sound.

Petit’s work pinpointed the proteins at the heart of the molecular machinery proposed by Hudspeth and Fettiplace, and has also provided an explanation of some of the hundreds of different forms of human hearing loss. The work of the 2018 prizewinners may even have a practical application in future through gene therapy, or regeneration of hair cells in the inner ear to replace those that become damaged over time.

Medical applications aside, the Kavli Neuroscience Prize of 2018 honours curiosity-driven basic research that advances our understanding of hearing. According to Christine Dulac, a member of the Kavli Prize Neuroscience Committee, the prizewinners demonstrate, “without any shadow of a doubt, that there is this inter-dependence between this basic research and clinical research. Those different realms of science are inextricably intertwined.”

By Julie Clayton, science writer
Ewine van Dishoeck

Ewine van Dishoeck studied chemistry at Leiden University in the Netherlands and then switched to astrochemistry following a brief spell studying with physicist Alexander Dalgarno at Harvard University in the US in 1980. Completing a PhD at Leiden on the excitation and breaking up of molecules within interstellar gas clouds, she then went back across the Atlantic to take up a position in Harvard’s Society of Fellows in order to pursue her research on the interstellar medium under Dalgarno.

After carrying on her research at Princeton University and the California Institute of Technology, she moved back to the Netherlands in 1990. Here she was able to take advantage of the impending launch of the European Space Agency’s Infrared Space Observatory, a vital asset for studying the emission from interstellar water molecules that in the end took off in 1995. In the meantime, she took charge of Mayo Greenberg’s astrophysics laboratory at Leiden in order to carry out experiments for interpreting space-based observations.

While continuing with her own theoretical research and overseeing the experimental work, van Dishoeck became ever more prominent as a scientific leader. She coordinated a programme to study water molecules in a wide range of protostars using ESA’s Herschel Space Observatory and from 1999 onwards took up a number of key positions overseeing development of the first truly international astronomical observatory – the Atacama Large Millimeter/submillimeter Array in Chile.

According to astrophysicist Reinhard Genzel, van Dishoeck’s role in ALMA may well have been decisive, since it was she who persuaded scientists from many different nations to work together on the project. “She has a way that is very persuasive and positive,” he says. “And she has been able to communicate this positivity to young people and science organisations. It is a terrific gift.”
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See also:
The Kavli Prize
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The Kavli Foundation
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Emmanuelle Charpentier

Emmanuelle Charpentier is a French biochemist, microbiologist and geneticist. She studied at the Pierre and Marie Curie University in Paris, receiving a degree in biochemistry in 1991, and obtained her PhD in microbiology at the Pasteur Institute there in 1995.

Between 1996 and 2002 she continued her research in the United States, first in New York and then in Memphis. Returning to Europe she established her own group at the University of Vienna, where, in 2006, she became Lab Head at the Max F. Perutz Laboratories.

In 2009 she moved to the University of Umeå in Sweden, where she established a project on the CRISPR sequences. Charpentier discovered the essential role of the so-called trans-activating CRISPR RNA (tracrRNA) molecule in the immune systems in bacteria. These results led to a collaboration with Jennifer Doudna and to the demonstration, in 2012, of the potential of the CRISPR-Cas9 system for gene editing.

After Umeå, Charpentier moved to Germany and since 2015 has been Director of the Max Plank Institute for Infection Biology in Berlin. For her work she has received a large number of prizes, including the Breakthrough Prize in Life Sciences, the Warren Alpert Foundation Prize and the Novozymes Prize.

Jennifer A. Doudna

Jennifer Doudna is an American biochemist. She obtained her Bachelor of Arts in biochemistry at Pomona College, California, in 1985, before moving to Harvard University where she obtained her PhD in 1989.

After several postdoctoral positions she moved to Yale in 1994, where she would remain until 2000, leading a team that focused on solving the three-dimensional structure of RNA ribozymes.

After two more years at Harvard she moved to Berkeley as Professor of Biochemistry and Molecular Biology, where her research focused on understanding RNA functions via structural and biological methods. While at Berkeley she began a collaboration with Emmanuelle Charpentier. Their work led to a milestone publication in 2012.
that marked the development of the CRISPR-Cas9 system as a simple gene-editing tool.

Doudna is still based at the University of California, Berkeley where she is a professor of chemistry and of molecular and cell biology, and an investigator at the Howard Hughes Medical Institute. She has been awarded numerous prizes for her work, including the Breakthrough Prize in Life Sciences, the Gruber Genetics Prize and the Warren Alpert Foundation Prize.

Virginijus Šikšnys is a Lithuanian biochemist. He studied organic chemistry at Vilnius University and obtained his Masters degree in 1978. He then moved to the Lomonosov Moscow State University to study enzyme kinetics, where, in 1983, he obtained a Candidate of Sciences degree, equivalent to a PhD.

After Moscow, Šikšnys went back to Vilnius to work at the Institute of Applied Enzymology. Aside from a brief period in 1993 when he was a visiting scientist at the Max Planck Institute for Biochemistry, in Martinsried, Germany, he has spent his entire career in the Lithuanian capital.

Šikšnys's main research interests focused for many years on the role of restriction enzymes in combating viruses. Inspired by a 2007 paper that reported the adaptive immune system provided by the CRISPR DNA sequence in bacteria, he began working on understanding the role of the enzyme Cas9 in CRISPR. His work led to the publication of a paper in 2012 that demonstrated how the CRISPR-Cas9 system can be used in gene editing.

Šikšnys is now Head of the Department of Protein-DNA Interactions at the Vilnius University Institute of Biotechnology. For his work he has received numerous awards, including the Warren Alpert Foundation Prize and the Novozymes Prize.
A. James Hudspeth

Originally from Texas, Hudspeth went to Harvard University where he studied biochemical sciences, followed by a PhD in neurobiology (1973) and a medical degree (1974). Here he learned about the neuroscience of hearing and electron microscopy, both important for his future research. After a year at the Karolinska Institute, Stockholm, he moved to Harvard Medical School and then in 1982, to the California Institute of Technology, where he first showed that direct mechanical displacement of hair bundles led to an electrical response.

From 1983 to 1995 he did research at the University of California San Francisco and the University of Texas Southwestern Medical Centre before becoming Professor and Director of the FM Kirby Centre for Sensory Neuroscience at Rockefeller University. He continues to study the neural mechanisms of hearing including through a recently designed microscope that can take a million measurements a second, with subnanometer resolution. He is also exploring the possibility of hair cell regeneration as treatment for hearing loss.

His awards include the W. Alden Spencer Award (1985), the Ralph W. Gerard Prize, Society for Neuroscience (2003) and the Guyot Prize, University of Groningen 2010 for ‘important discovery in the field of otology’.

Robert Fettiplace

Robert Fettiplace began his studies at Cambridge University, with a degree in medical sciences (1968) then a PhD in biophysics. In 1974 he joined Denis Baylor to work on the mechanism of hearing in the turtle cochlea. He became a Fellow of the Royal Society in 1990, and in the same year, moved to the USA to become Professor of Neuroscience, University of Wisconsin (UW), Madison. Here, Fettiplace continued making advances in recording and measuring the motions of hair bundles and the properties of hair cell ion channels, including on the role of mammalian outer hair cells in sound signal amplification. He was Steenbock Professor of Neural & Behavioural Sciences, UW-Madison, from 1991-2011. In 2011 he became Fellow of the American Academy of Arts and Sciences.

Christine Petit

Christine Petit studied medicine at Pierre et Marie Curie University, Paris, and basic biological sciences, genetics and biochemistry at Orsay University, and
gained her Ph.D at Institut Pasteur. In 2002 she was appointed Professor in Genetics and Cellular Physiology at College de France. She is now head of the Genetics and Physiology of Hearing Laboratory at Institut Pasteur.

Her early work included research on human sex chromosome inversion, smell and vision. In 1994 she began publishing work on hereditary deafness, leading to new experimental models with which she has revealed the roles of various genes in sound processing. In 2018, she oversaw the opening of the new Hearing Institute, Paris, for interdisciplinary neuroscience research around hearing.

Honours include the Ernst Jung Prize for Medicine (2001), the Louis-Jeantet Prize for Medicine (2006), and foreign member of the National Academy of Sciences (USA, 2016).
I was born in 1955 in Leiden, the Netherlands, the city in which I would spend most of my life. My father was a medical doctor and in his later years professor of ear, nose, throat at Leiden University. He met my mother, who was an elementary school teacher and considerably younger, during the second world war when she provided a hiding place during the German occupation. My parents clearly had an academic career for me in mind: my birth announcement shows a baby wearing a stethoscope crawling toward the university with the motto ‘vires acquirit eundo’ (‘she will gather strength along the way’; from Virgilius’ Aeneid). This turned out to be a very appropriate quote. My parents got only one aspect wrong: I never had any inclination to study medicine.

My childhood was a happy and carefree period; my mother’s teaching philosophy was that play was more important than study for young children. I was enrolled in a Montessori elementary school, which encourages self-study and collaborative play. I also started to play the violin during this time. Among my schoolfriends was Jette van de Hulst, daughter of the famous astronomer Hendrik van de Hulst (who predicted the 21 cm radiation of hydrogen). Birthday parties took place in the domes at the Sterrewacht in the center of Leiden, where van de Hulst and Oort lived. It was my first encounter with astronomy, but little did I know then that the Sterrewacht would become so important in my later life. For high school, I went to the Stedelijk Gymnasium (‘Grammar School’), well known for its high academic level. For the first few years, lectures consisted mostly of Latin and Greek, together with modern languages and mathematics. I still enjoy the benefits from studying the classics in depth, since it teaches one to concentrate and properly dissect any piece of text.

My first encounter with science came in spring 1969, after my father had retired from Leiden University and the family went on a six month work visit to San Diego. I was enrolled in the public Horace Mann junior high school and chose subjects that I did not (yet) have in Leiden, most notably science, which was taught by an inspiring female African-American teacher (only in hindsight did I realize how special that must have been at that time). We enjoyed the sunny life in California, the era of the pop music, often visited the San Diego Zoo, and travelled to the Grand Canyon. Summer was spent in Mexico where we saw the Moon landing from a hotel room.

Shortly after we returned to Leiden my father passed away suddenly, on the eve of my 15th birthday. By the end of high school I had become fascinated with chemistry at the molecular
level thanks to a very good teacher, Gerard Desar. I therefore started studying chemistry at Leiden University in 1973, but quickly discovered that I liked physics just as much. After my bachelor degree in chemical physics, I felt that I would benefit from more mathematics and got my bachelor degree in mathematics a year later.

My first years at the University were clearly filled to the rim with course and practical work, but I continued to enjoy music. Since 1971 I played in the Leiden Youth Orchestra and in the gypsy music orchestra Csárdás, playing Hungarian and Romanian folk music. We had many ‘gigs’ at parties and other festivities. It is there that I met my future husband, Tim de Zeeuw, with both of us playing the violin. Tim studied astronomy and mathematics in Leiden so we also had a number of courses in common. We enjoyed long vacations together as students, one trip to Greece to visit all the historic sites that we had studied in high school, and one six-week trip to the western US which included a brief visit to Caltech. Our love for the spectacular mountains and forests in that area was born during that trip, and over the next 40 years we have continued to go camping and hiking every summer somewhere in the western US.

One of the research projects for my MSc degree was in theoretical quantum chemistry on the photodissociation pathways of the CH4+ ion under the guidance of Marc van Hemert. He inducted me into the field, always ensured that state-of-the-art quantum chemistry software was running on the then biggest computer (an IBM mainframe, still using punch cards), and would become one of my long term collaborators. Photodissociation has continued to be one of the main themes throughout my career with a major review in 2017.

Quantum chemistry suited me well, so I was convinced by 1979 that I wanted to continue in that direction for my PhD research. Unfortunately, the professor of theoretical chemistry at Leiden had just died and it became clear that there was not going to be a successor. So they advised me to look elsewhere. By chance, Tim had just taken the Interstellar Medium course from Harm Habing, which included a lecture on interstellar molecules. ‘Isn’t that something for you?’ he asked. Habing brought me in contact with his colleague, Teije de Jong, who recommended that I go to Harvard to the group of Alexander Dalgarno, world-leading in the new field of astrochemistry. In summer 1979, Tim and I were camping in Canada in the Mt Tremblant National Park, where the first symposium of the International Astronomical Union (IAU) on Interstellar Molecules took place. There I met Dalgarno who kindly invited me to spend some months at Harvard to get a start and work on photodissociation processes of astrophysically relevant molecules, most notably OH. Dalgarno would become my PhD supervisor and lifelong mentor: he set the tone with his phenomenal knowledge, his clarity, his love of science and constant drive for excellence and integrity, and his agility in moving easily between molecular physics and astronomy. He treated everyone with fairness, respect, generosity and encouragement (both in science and sports!).
In the meantime, Habing was able to convince the Netherlands Foundation for Scientific Research, NWO, to provide me with a grant to continue my PhD in Leiden, with regular visits to Harvard. There I also met John Black, then a postdoc, who patiently introduced me to the physics and chemistry of interstellar clouds. In June 1982 I went to Chile to do observations of interstellar C2 to test the models that John and I had developed: a fantastic experience that transformed me from a pure quantum chemist to an astronomer. Tim joined at the end of the run and we subsequently traveled for three weeks through Bolivia and Peru. This included taking the famous narrow gauge train from Calama in Chile to La Paz in Bolivia; we crossed the high-altitude plain at 5000m not too far from where three decades later the Atacama Large Millimeter/submillimeter Array (ALMA) would be inaugurated.

1982 was also the year in which I first participated in a conference on a far-infrared-submillimeter telescope in space, then called FIRST, organized by Thijs de Graauw from the Netherlands Institute for Space Research, SRON. This mission, which ultimately became the Herschel Space Observatory, would be important throughout my career as further described below, but I did not realize then that the first data would only appear in 2009! It illustrates the very long timescales of astronomical facilities, from conception to actual operation, of typically 25-30 years. It alerted me early on to the need for long term planning, looking decades ahead and making sure science stays in step with instrumentation along the way.

On June 19 1984 Tim and I graduated on the same day cum laude at Leiden University. On July 26 we were married and in late August we moved to the US for our postdoctoral fellowships at Harvard and Princeton. Tim’s mentor, Martin Schwarzschild, had given us good advice to take the steepest trajectory early on in one’s career to have more options later on, even if that meant living apart in two places for a number of years. John Bahcall kindly gave me a visiting position at the Institute for Advanced Study, but after 2.5 years we had enough of the long commute. I then obtained an NSF visiting professorship for women to spend a year at the astrophysics department of Princeton University, getting there also my first taste of lecturing. Several of my most cited papers were written in this period, most notably on CO photodissociation in 1988 and H2 excitation in 1987, both with John Black. We also defined in 1989 a new type of clouds, translucent clouds, as the transition between the traditionally studied diffuse and dense clouds. These clouds, which are rich in H2 but poor in CO, became known as ‘CO-dark clouds’ decades later.

By early 1988, we started to look for faculty positions. Several places were interested in both of us, but none of them was an optimal match. I was then encouraged by the California Institute for Technology to apply for one of their cosmochemistry positions, a new line of research initiated by Gerald Wasserburg in the Geology and Planetary Sciences (GPS) department. The first
hire was Geoffrey Blake, like me a chemist-turned-astronomer, and it was clear that our scientific interests matched well. Thus I became the first female faculty member in GPS. My two-year stay at Caltech was formative in switching to planetary system formation and learning how big science was done. Tom Phillips introduced me to hands-on submillimeter observations at the new Caltech Submillimeter Observatory (CSO), gradually shifting my interests from diffuse and translucent clouds to the denser star-forming regions of the interstellar medium. Within GPS, David Stevenson stimulated Geoff Blake and myself to put our astrochemical studies in the context of solar system formation, which led to decades long joint observing programs. Most astrochemistry studies had so far focused on the bright and massive Orion star-forming region, but an interesting low-mass source, IRAS16293-2422, had just been identified and proved to be a goldmine for determining the chemical inventory of an analog of our own young Solar System. The latest ALMA results show the source to be even chemically richer than expected.

In 1990, Tim received an offer from Leiden to become professor of theoretical astronomy. I was offered a senior lectureship (equivalent of associate professor with tenure), together with a big personal grant to start a group. Moreover, Thijs de Graauw had offered me some guaranteed time on the Short-Wavelength Spectrometer (SWS) on the Infrared Space Observatory (ISO), an ESA mission that would for the first time obtain infrared spectra of astronomical objects unhindered by the Earth’s atmosphere. As hard as it was to leave Caltech, going back to Leiden proved to be a unique scientific opportunity.

So far, my research had focused on gaseous molecular processes, which can be described and computed accurately by the laws of quantum mechanics. However, in cold and dense regions the atoms and molecules freeze-out onto the tiny dust particles, where chemical reactions can take place that normally do not happen in cold gas, such as hydrogenation reactions and producing complex molecules under the influence of UV irradiation. Leiden had in fact pioneered this area by attracting Mayo Greenberg in 1975, who established the first laboratory astrophysics group as a joint Leiden physics-astronomy program. Although I had contacts with the Greenberg lab in the 1980s, grain surface chemistry was too ‘messy’ for my taste then. However, with the prospect of the upcoming ISO mission, it was clear that the lab data would be crucial for the interpretation of the ice spectra. Greenberg had however retired in 1992 and neither physics nor astronomy wanted to commit to a new hire. The only option was to take the lab under my scientific responsibility, with two senior postdocs, Willem Schutte and Pascale Ehrenfreund, responsible for the day-to-day operation. Together they ran many key experiments and established the first version of the Leiden ice database which would be widely used by astronomers and highly cited.

Two key developments made a longer term commitment to the lab possible. First, Raymond and Beverly Sackler made a donation to the lab. Second, the Netherlands Research School for
Astronomy (NOVA), the alliance of all university astronomy institutes in the Netherlands, received a major 10-year grant in 1998 for new instrumental programs. The lab was fortunate to receive funding for starting two new experiments, taking the lab in a new direction by using ultra-high vacuum techniques from surface science to study the underlying chemical reactions on icy surfaces and their dependence on physical parameters. Harold Linnartz took over the lab in 2005, and under his energetic leadership the lab has blossomed and further expanded. I stayed closely involved through joint PhD students, and providing the link with observations. A beautiful example is the combined laboratory-modeling-observational study of the formation of water from reactions of H with O, O2 and O3, testing routes that Xander Tielens had proposed 30 years earlier. Similarly the hydrogenation of CO to form CH3OH (methanol) has been demonstrated in the lab and shown to be a key step in making even more complex organic molecules like glycolaldehyde (a simple sugar), glycolaldehyde and tri-carbon species like glycerol now being observed with ALMA and also seen in comets. The lab has also trained a next generation of laboratory astrophysicists, most notably Karin Öberg.

Over the past decades, the overarching science goal of my group has been to follow the physics and chemistry from star-forming clouds to planet-forming disks. It has been my joy and privilege to have (co-)supervised a very talented set of nearly 80 graduate students and postdocs. Much of my success is to their credit, their hard work and creativity. Progress is driven by major new advances in instrumentation, so projects were centered every 5 years around a new facility at infrared or millimeter wavelengths where molecules have their primary transitions. Following ISO, I co-led several major observational programs on the James Clerk Maxwell Telescope, the European Southern Observatory (ESO) Very Large Telescope, the Spitzer Space Telescope, Herschel and ALMA. Together these instruments allow us to zoom in on future solar systems, from scales of a few thousand AU in the 1980s to scales of just a few AU today (1 AU=distance Sun-Earth, the orbit of Neptune is around 30 AU). The ‘golden triangle’ of combining these observations with models and laboratory experiments (including quantum chemistry) in-house was a further key to the success.

With JCMT, VLT and most notably Spitzer, studies of samples of low- and high-mass protostars became possible. How typical was IRAS16293-2422 and what were the similarities and differences with high-mass protostars like Orion? Much of this research culminated in three ARAA reviews, in 1998 (with Geoff Blake), 2003 and 2009 (with Eric Herbst). We also started to probe the chemistry in protoplanetary disks, and established their ‘sandwich’ chemical structure with Yuri Aikawa (Japan). Tools for computing the molecular excitation and line radiative transfer needed for the analysis of the data were developed, allowing us to obtain quantitative (rather than qualitative) results; their public release and the molecular data base have served the worldwide astrophysical community up to today.
When I returned to Europe in 1990, I was asked by Reinhard Genzel (MPE) to join the ESA Herschel Science team. This cornerstone mission was finally approved in 1998 and launched in 2009. I was fortunate to lead the ‘Water in Star-forming regions with Herschel’ (WISH) key program, a collaboration of some 70 scientists across the world. The main goal was to follow the trail of water (a key ingredient for life elsewhere in the Universe) from its formation in cold clouds to its incorporation into disks and ultimately planets. We enjoyed a wonderful collaborative team spirit, especially once the Herschel data started to ‘rain’ in 2010.

This was also a period of significant personal changes: Tim was offered his dream position, to become the Director General of ESO starting in 2007. With headquarters in Garching near Munich, this meant that we had to face once again the challenge of living in two places at a time when my aging mother needed more care. Fortunately, Genzel kindly offered me a visiting position at MPE, which proved very fruitful in the Herschel and ALMA era.

It was clear since the early 1980s that a new generation of millimeter interferometers was needed to zoom in on solar system scales. In 1993, I was asked to serve on the US scientific advisory committee of their next generation Millimeter Array. At the same time, Europe was developing the concept of the Large Southern Array. It became clear by the mid 1990s that neither continent would have the resources to put together an array powerful enough to address the top-level science goals. Scientists involved in discussions on both sides of the ocean like myself managed to convince the NSF and ESO to join forces in 1997 to build ALMA; the Japanese joined a few years later. ALMA thus became the first modern world-wide collaboration in astronomy. Making ALMA into a reality became a major part of my efforts in the early 2000s, first as member and chair of the ALMA Science Advisory Committee (ASAC, 1999-2005) and later as member of the ALMA Board (2006-2012). Moreover, the then ESO Director General Catherine Cesarsky asked me to step in during 2001-2002 as interim European Project Scientist to help guide the project and set the specifications. This included Band 9 (650 GHz) as a first-light receiver, the development and construction of which was led by NOVA using technology from Herschel. ALMA finally opened its scientific eyes in 2012, with data quality that exceeded everyone’s expectation, with our favorite low-mass protostar IRAS16293-2422 as one of the first targets.

ALMA continues to surprise us. Our first ALMA image of a transitional disk with an inner dust cavity was utterly surprising: instead of a full dust ring, we found a highly asymmetric cashew nut-shaped feature offset from the star. What we had found was the first observational evidence for a dust trap created by a gas pressure maximum likely due to an embedded planet. These traps provide a location where tiny dust grains can grow to comet-sized bodies. Another ALMA surprise is that the gas lines in disks are much weaker than expected. Either disks have gas/dust mass ratios much lower than the canonical value of 100, or CO has been transformed into...
other species like methanol and CO2, as demonstrated in the lab.

The next chapter in our field is JWST, with which I have been associated since 1997. Riding on the success of ISO, we saw an opportunity to convince NASA and ESA to include a mid-infrared instrument, MIRI. As Dutch co-PI, I was heavily involved in the building of MIRI in 2000-2010 and am looking forward to first data in late 2021. MIRI will allow us to make the link from disks to planets, the logical next step after the clouds to disks trail.

Throughout my career I have been fortunate to receive many prizes and major grants at critical moments that have allowed my group to harvest the science from new instruments and embark on risky projects. Much thanks goes to NWO, ERC, KNAW, Leiden and MPE. My hobbies continue to include reading, cooking, camping, hiking, skiing and art, especially links between astronomy and art.

Administration is an inevitable part of scientific life, but can also be seen as an opportunity to advance the field. I succeeded Tim as scientific director of NOVA in 2007, and will become president of the IAU in August 2018. I look forward to stimulating astronomy and its benefits to society worldwide and remind people that we all live on a small planet under the same beautiful starry sky.
It all started with toads. When I was five years old, my family moved to half a hectare of unlandscaped land at the edge of Houston, Texas. Because this property abutted the largest natural park in the city, I encountered a rich selection of wildlife. By spending much of my free time wandering about the yard, and later the park, I became acquainted with hundreds of animals and their habits. My parents were surprised that I knew where each of the neighborhood toads was to be found at any time of the day or night: I was surprised that they didn’t know!

So I was born a naturalist. My younger brother and I amassed a menagerie that included not only dogs and cats, but also a raccoon, ducks, a crow, opossums, armadillos, anole lizards, horned “frogs,” venomous and non-venomous snakes, salamanders, tarantulas, and various local and tropical fishes. We specialized in box turtles, which we initially collected, but which subsequently appeared at the fence surrounding the turtle pen, begging for access to the food, water, and companionship that we provided. We eventually boarded more than a hundred of the creatures, which bred prolifically to produce wonderful miniature replicas, each with a tiny egg-tooth. After I departed for college, my brother gradually repatriated over 200 animals to the wild.

Seeking to inculcate a work ethic in his first-born, my father employed me in his law office during summers from an age of eleven years. This experience helped to focus my interests: I learned to hate typing, filing, mailing, and such chores. At this point I encountered the first of several individuals who shaped my career: Peter Kellaway, one of my father’s clients. A distinguished pediatic electroencephalographer at Baylor College of Medicine, he provided me with summer jobs from the age of thirteen years until I began college. I learned to fix, section, mount, and stain brain slices; to fabricate electrodes for medical-student demonstrations; and to assist with animal surgery and experiments. I loved it!

My education was a mess. Because I was—and am—quite shy, I spoke little enough in the lower grades of school that I was eventually tested for brain damage, then advanced a grade when none was apparent. In addition to performing photography for an award-winning yearbook in highschool, I organized an amateur crime ring that eventually got me expelled, then reinstated because no authority could determine exactly what I had done. I attended Harvard College during the Viet Nam War, which enlivened the educational process with the threat of being shipped abroad to inflict democracy on the unwilling.
Graduate school was also shadowed by that conflict. With the kindly help of the Registrar, I evaded military service by shifting back-and-forth between Harvard’s Graduate School of Arts and Sciences and its Medical School. As a graduate student I served as a teaching assistant in courses for medical students; when I then took the same courses as a medical student, my familiarity with the material enabled me to skip the lectures and return to the laboratory. Sustained by sex, drugs, and rock-and-roll, I somehow received an MD as well as a PhD.

Although my graduate preceptors paid little attention to me—the first graduate student to survive their tutelage—they had a good excuse: Torsten Wiesel and David Hubel were then in the thick of their amazingly productive collaboration to delineate how the cerebral cortex processes visual information. Both consummate scientists, they provided outstanding role models of scientific acumen, rigorous analysis, and precise writing. David was also as great as a lecturer as he was dismal as a department chairman; Torsten was precisely the opposite. I learned an immense amount from both, most of it painfully.

To complete my questionable education, I undertook a postdoctoral fellowship at the Karolinska Hospital in Stockholm with one of the few individuals who was interested in the cell biology of the inner ear. He unfortunately suffered a psychiatric breakdown within a few months of my arrival—not my fault, this time—so I was left to experience the boreal winter without funding, equipment, or guidance. Although it should have been clear by then that I was not destined to be a scientist, I received an offer of a faculty position and headed for California.

The next seven years at Caltech were a great relief. Working very hard, quite literally night and day, my colleagues and I discovered many of the processes by which the ear’s sensory receptors—hair cells—transduce mechanical stimuli into electrical signals. We also ascertained how the activity of ion channels tunes individual hair cells specific frequencies of stimulation.

This effort continued during the subsequent seven years at the University of California, San Francisco, which was then at its peak as the world’s premier site of biomedical research. In a highly stimulating and collaborative environment, my associates and I progressed from descriptions of hair-cell activity to insights into the biophysical underpinnings. As a matter of necessity, and as a considerable pleasure, I began to remediate my woeful lack of training in physics.

I was next attracted by the alleged opportunity to establish a premier neuroscience program at an institution in Dallas that—like Mordor or Voldemort—should not be named lest it gain uncanny strength. Here again I encountered toads, these in positions of great power. When I expressed dismay that the professorships that I had been promised in writing as recruitment tools were not forthcoming, my office was relocated to a basement, across the hall from the...
gross-anatomy laboratory and morgue. That year I was the only inductee into the National Academy of Sciences who was so honored by his institution.

Fortunately enough, I was saved from investigatorial purgatory by Max Cowan and Purnell Chopin, who graciously invited me to join Howard Hughes Medical Institute. And I was rescued from Dallas by Torsten Wiesel, who as President of The Rockefeller University offered me a position on the faculty of that illustrious institution. After weighing the alternatives for several milliseconds, I accepted.

One might ask why, through all of the foregoing, I kept going. Gifted with a fairly depressive character, I certainly asked as much, many times. A good part of the answer was the support of more people than I can acknowledge in this space. Some were the colleagues with whom I have conducted research: 30 graduate students, 13 of them MD-PhDs, and 44 postdoctoral fellows. Most of these are excellent scientists now enjoying successful careers of their own. In view of the importance of research experience early in my life, I have also strived to support the development of younger scientists. Each summer our group accommodates several students—eight during each of the past two years—at stages from high school to Master's programs. Apprenticed to the group's postdoctoral fellows and graduate students, these individuals both contribute to our research and strengthen their vocations as scientists.

My family has also kept me functional and largely under control. My first wife, Maurine, was for 47 years a source of inspiration, kindness, and patience; she accordingly remains my favorite and only wife. Our son James shares her delightful personality and vocation as a physician. He not only serves as an outstanding hospitalist but also organizes and conducts medical teaching in Haiti, India, and elsewhere. Our daughter Ann inherited a personality more like my own—but she got better. After fleeing the United States at the outset of its current wars (this may sound familiar), she is now debating whether to decamp from the imploding United Kingdom for Norway: better check her visa!

There was also a more abstract reason for continuing. Was it mankind's eternal quest for the meaning of it all? Well, yes, some of that. Was it the hope of overcoming deafness? I admit that as well. But mostly it was something else, which I think is the mainspring of true science: aesthetics. The orderliness of nature and the relationship between things is limitlessly beautiful. As a disinterested inquiry into the natural world, science stands alongside art as an embellishment of our species. Both enterprises involve attempts to grasp something ineffable, something beyond the ordinary and obvious. Both are frustrating: a serious scientist or committed artist fails more-or-less daily, with the occasional success serving as a reminder of how much more failure remains to be experienced. And the rewards are sparse, but very real. A gold medal is doubtlessly nice to have, but it scratches easily and must be dusted from time to time. A new scientific insight is both more exciting and more durable.
I was born in Laignes, a small village in northern Burgundy close to the sources of the Seine. This village, home to my father’s family, is located in a highly forested region. Its stone houses call to mind a golden age of forges and the industrial and domestic complex created by the great 18th century naturalist, the Comte de Buffon, embodies the spirit of the Age of Enlightenment. My mother came from southern Burgundy, with its sun-drenched hillsides and very famous wines. Her family had been established as vintners in Chassagne-Montrachet for generations. I was greatly influenced by my father, a brilliant physical engineer and pianist, and his passion for scientific discoveries. I was also marked by the frustration of my paternal grandmother, who, although an excellent pupil, was denied the chance to become a teacher, in an epoch in which women’s destinies were predetermined.

My interest in science began early. I trained as a physician at Paris VI University and Pitié-Salpêtrière Hospital, a historic cradle of neurology. I soon realized that I would need additional basic science training to reach the depth of understanding I sought in biological science. I attended additional courses in parallel and graduated with a Masters in genetics and biochemistry from Paris XI University of Sciences at Orsay, in 1973. I was lucky enough to be taught by Georges Rizet, a pioneer of genetic training in France, who revealed to me the rational power and heuristic value of genetics. I took microbiology and virology courses at Institut Pasteur in Paris, in 1974, at the end of which I was offered a position at the Institute. I initially worked towards my doctoral degree in science with Gunnar Lindahl in the laboratory of the Nobel laureate François Jacob, where I studied bacterial immunity to bacteriophages lambda and P2. I then moved to an immunology laboratory, where I obtained my doctorate in 1982. After a short stint at the Institute of Immunology in Basel, Switzerland, I moved to the CNRS center at Gif-sur-Yvette, where I focused on identifying genes regulating cell differentiation, through a genetic approach involving microcell hybrids. I returned to Institut Pasteur as a staff scientist in 1985.

At the time, new opportunities were emerging for deciphering human gene function and dysfunction by identifying disease-causing genes. This possibility, which had long been a dream for me, was finally becoming a reality, thanks to new methods for analyzing the human genome. I first addressed the molecular mechanisms underlying sex inversions in humans with my colleague Jacqueline Levilliers and Jean Weissenbach. We found that most cases of XX maleness and some cases of XY femaleness result from abnormal terminal exchanges between the short arms of the X and Y chromosomes (Xp and Yp) including SRY, the sex-determining gene,
promoted by X-Y homologous sequences persisting outside the pseudoautosomal region within which normal Xp Yp recombinations occur.

By 1993, I had established my own laboratory at Institut Pasteur. Fascinated by the amazing performances of sensory perception, I decided to use a human genetic approach to investigate olfactory system development. Kallmann’s syndrome is the only hereditary syndrome known to cause complete anosmia, a lack of the sense of smell. We identified the first causal gene for Kallmann’s syndrome, KAL1 and contributed to the discovery of three others: FGFR1, PROK2, and PROKR2. We then showed that the protein encoded by KAL1, ANOSMIN-1, is an extracellular matrix glycoprotein involved in axon guidance and promoting the branching essential for the patterning of olfactory bulb output neuron projections onto the olfactory cortex.

Through systematic explorations of the molecular mechanisms underlying the development and physiology of the other sensory systems, I came to realize, soon after discovering KAL1, that we actually knew next to nothing about the molecular physiology of the auditory system. Hearing is a sense intimately linked to the cognitive functions of human communication through language and music, and many concepts had already been developed concerning the principles of its functioning, mostly by physicists. So why was so little known about its functioning at the molecular level, even within the sensory organ, the cochlea? The answer lay in the very small number of each type of cochlear cell, incompatible with the resolution of the available biochemical and classical molecular genetic methods. Such constraints do not apply to the genetic approach. I thus opted for a neurogenetic dissection of the structure and function of the auditory system, focusing on the inherited forms of sensorineural deafness. However, several obstacles precluded a straightforward genetic approach. We overcame them by studying large consanguineous families affected by deafness and living in geographic isolation, mostly in North Africa and the Middle East. We thus mapped the first two loci for autosomal recessive hearing impairment, DFNB1 and DFNB2, to human chromosomes; a number of other laboratories subsequently initiated genetic studies of deafness using the same strategy. In these early days of disease-gene identification, with the human genome only partially sequenced, we developed an invaluable source of candidate genes by pulling out genes preferentially or specifically expressed in the cochlea. We thus rapidly identified a number of genes responsible for severe-to-profound non-syndromic (isolated) or syndromic deafness, about 20 genes in all. Unsurprisingly, the first genes we identified were those responsible for the most frequent forms of deafness and almost all encoded previously unknown proteins. Most turned out to be components of the sensory hair cells of the inner ear. They included proteins of the hair bundle, the mechanoreceptive structure responding to sound stimulation, such as the PDZ domain-containing proteins HARMONIN, WHIRLIN, NHERF-1, NHERF-2 and another scaffolding protein, SANS, the transmembrane and membrane-associated extracellular proteins VEZATIN, PHR1 and STEREOCILIN, the unconventional myosin MYOSIN-VIIA and the kinociliary...
protein, CDC14A. They also included the hair-cell synapse proteins KCNQ4 and OTOFERLIN, the components of the tectorial membrane (a gel overlying and stimulating the hair bundle) OTOGELIN and OTOANCORIN, the major otoconial protein OTOCONIN-95, and a number of other proteins, including PEJVAKIN, EYA1, SIX1 and AK2.

The physiological insight gained from audiometric tests in humans is too rudimentary to elucidate the function of these proteins, nevertheless an in vivo context is required to evaluate the interplay between the various sound-induced mechanical forces in cochlear sound processing. The cochlea is highly conserved in mice and humans. Engineered mouse models of human deafness, conditional knockout mice and mice carrying particularly informative missense mutations, analysed in details and combined with multidisciplinary studies, proved to be the most effective tools for exploring the molecular mechanisms of hearing based on “deafness genes”. To this end, scientists with complementary expertise, specifically in biochemistry, electrophysiology and biophysics joined the laboratory, and long-term collaborations were established with physicists, especially Paul Avan.

Unsurprisingly, the identification of “deafness genes” revealed principally the molecular mechanisms underlying cochlea-specific functions. The frequent targets in hair cells are the hair bundle, a tuft of microvillus-like structures called stereocilia that processes sound and operates mechanoelectrical transduction (MET), hair cell-to-cell junctions which are particularly resilient to continuous sound-induced mechanical stress, and the hair cell synapses which display highly temporally precise, rapid and sustained neurotransmitter release.

Assuming that causal genes for syndromic forms of deafness encode proteins from the same network, we began deciphering cochlear protein complexes by studying the proteins encoded by genes defective in Usher syndrome (sensorineural deafness associated with blindness) type 1. We showed that MYOSIN-VIIA, HARMONIN, CADHERIN-23, and SANS form a complex anchoring the embryonic hair bundle lateral fibrous links and, subsequently, the tip links, to the actin filaments of stereocilia. We found that SANS is essential for tip-link maintenance and HARMONIN- b for preventing full tip-link relaxation. We demonstrated that protocadherin-15, which forms the basal part of tip-links, switches from several functionally redundant isoforms during embryogenesis to a single specific isoform in adults, revealing the existence of a process of MET machinery maturation. Our studies of inter- and intramolecular interactions showed how MYOSIN-VIIA, HARMONIN and SANS operate at the F-actin insertion point of the upper part of the tip-link, consisting of cadherin-23. We uncovered the presence of the Usher-1 adhesion protein complex in photoreceptors too, accounting for the retinitis pigmentosa observed in this syndrome. It forms an adhesion belt associated with calyceal processes, (neglected microvillus-like structures) involved in regulating disk and lamella sizes in photoreceptor outer segments.
Beyond this reductionist view, this approach captured a broader picture of integrated physiology. Mouse models of Usher-1 syndrome revealed relationships between the MET machinery and stereocilium size. Hair-bundle morphology regulates hair-bundle activity, and we thus showed the converse to be true. We found that the various fibrous links between hair-bundle stereocilia, which had previously been largely ignored, are essential for hair-bundle sound processing and morphogenesis. The lateral fibrous links of embryonic hair bundles are required for early stereociliary cohesion during hair-bundle development; the ankle links, composed of proteins encoded by causal genes for Usher syndrome type 2, are essential for the development of the hair-bundle functional polarity. Our discovery of stereocilin, also encoded by a deafness gene, revealed the key role of the uppermost lateral links (the top connectors) and the crown of the outer hair-cell hair bundles in tectorial membrane attachment. By a further genetic dissection of the top-connectors and attachment links we recently showed these links to have a similar molecular composition, and therefore presumably also similar mechanical characteristics. The top-connectors ensure OHC stereociliary bundle cohesion, allowing the parallel gating of mechanotransduction channels required for the generation of large distortion products of oto-acoustic emissions (DPOAEs) in the ear canal. This touches on one of the many medical applications arising from our results. Audiometric tests frequently include DPOAE recordings, the interpretation of which has been clarified by these advances.

We also revealed the existence of a specific exocytotic molecular machinery at the first auditory system synapse, the inner hair-cell synapse, which is glutamatergic. This machinery includes OTOFERLIN, encoded by a deafness gene, a multi-C2-domain transmembrane protein of synaptic vesicles. Its synthesis begins when synaptotagmins 1 and 2 are no longer detected. We revealed a key role for otoferlin in synaptic release, as a Ca\(^{2+}\) sensor for neurotransmitter release and synaptic vesicle replenishment in the active zone at the inner hair-cell ribbon synapse. Ferlins are considered to be ancestral to synaptotagmins. The similarity between the roles of otoferlin and synaptotagmins should prompt studies of interactions between otoferlin and other synapse components, including the synaptic SNARE complex, the v- and t-SNARE proteins of which remain unidentified.

Another facet of the auditory system was also brought to light by studies of “deafness genes”. We found that peroxisomes protect the auditory system against the deleterious effects of overexposure to noise, the major environmental cause of hearing loss. Loud sounds induce an adaptive proliferation of peroxisomes triggered by PEJVAKin, we identified as a redox sensor encoded by a noise susceptibility gene.

Finally, we have recently begun to focus on developing gene therapy for preventing and curing hearing impairment, providing proof-of-concept for the efficacy of this approach in several mouse models of human deafness. However, all methods for hearing restoration acting on the
peripheral auditory system are dependent on auditory cortex plasticity. It is generally assumed that defects of the peripheral auditory system are not associated with intrinsic defects of the central auditory system. Our recent findings challenge this view, by showing that the tip-link components cadherin-23 and protocadherin-15 are expressed by the precursors of a parvalbumin-positive interneuron population restricted to the auditory cortex, and demonstrating the requirement of these proteins for the embryonic migration of these cells. This finding raises many questions about the evolution of this sensory system and has major potential implications for patient management. Could this also be the start of the extension of genetic dissection to the central auditory system?

These advances are the fruit of real teamwork. They owe much to the excellence of my co-workers.

I would like to thank my husband, Jacques, for our life together since our first year at university. I appreciate how lucky I have been, thanks to him, to have been able to enjoy both a highly active professional life and a happy family life, with a daughter who is now a doctor, a son who is a jazz cellist, and many long-standing friends with whom we have shared a great deal.
I was born in December 1968, at the height of the student and civil protest movements and grew up in a small and relatively quiet town about 25 kilometers south of Paris. I have always been encouraged by my parents to explore my own academic interests. In school, I was an enthusiastic and aspiring student, always eager to acquire knowledge and to achieve excellence and therefore, I took my studies seriously. During my time at primary school, the oldest of my two sisters entered university and I understood already early on that academia was a place where one could continue to study, do research, teach and transfer knowledge. I therefore wanted to follow her path and was even more motivated to continue my studies.

Although it was not clear at the time that I would eventually study biology, I showed an interest in science very early on. In fact, I was interested not only in pure sciences and mathematics, but also in the human sciences — psychology, sociology and philosophy. My father liked to explain to me the Latin names of many plants. Maybe this motivated me to pursue natural sciences with later a direction towards medically-oriented questions, influenced by my mother's interests. I also remember that when I had to decide on a host laboratory for my Master's degree, I told my mother that I had selected the Pasteur Institute. She then recalled that I had come back home from school at the age of twelve and said that I would work at the Pasteur Institute one day. I myself do not remember our conversation in detail, but I suppose that my biology teacher at the time must have discussed a topic in school that triggered my interest in microbiology at a young age already.

After I finished my secondary education, I moved to Paris in 1986 to study biochemistry, microbiology and genetics – first at the University Pierre and Marie Curie. Later, my curiosity about micro-organisms and infectious diseases brought me to the Pasteur Institute where I obtained my Ph.D. in Microbiology in 1995. My projects during my Master and PhD theses with Patrice Courvalin as my mentor combined medical microbiology and the genetics of traits of bacteria such as antibiotic resistance and mobile genetic elements. Here, it became clear to me that understanding fundamental science is the basis of innovation.

I felt a strong attraction to the field of microbiology, not only because of its importance given the rapid emergence of antibiotic resistance at the time, but also because I simply enjoyed the process of experimentation, from planning to execution and analysis. I felt at home in the laboratory. I was given a lot of independence and responsibility for my projects already at an early stage of my student life. Looking back, I think this had a very positive influence on my career,
because I identified myself very early on as a scientist rather than as a student – as someone creating knowledge rather than simply absorbing it. It seems small, but this change of mindset made me more curious and perceptive of the qualities and career paths of the established scientists at the Pasteur Institute. I was inspired by their enthusiasm of and advocacy for basic research in microbiology. I realized that being a research scientist would fit the many aspects of my personality — my curiosity, intellectual drive for knowledge, enjoyment of communicating knowledge to others and working as a team, and my desire to turn complex scientific discoveries into practical applications that would help society. I was excited about being a scientist.

The education I received in France, my mentors and the wonderful scientists that have been accompanying me, have made me the scientist I am today: curious, persistent and always trusting my instinct that I have to concentrate on the basic science, and the rest will follow eventually. I also never questioned whether women were entitled to a career in a same way as men. At home, my parents were always very supportive with all the choices I made in the course of my career. The same applies for my academic life: I had both male and female mentors. I learned a lot from all of them, and their gender was never an issue. On the other hand, they all realized very early that I would continue with a scientific career and therefore strongly encouraged me to follow my path.

Looking back today at 25 years as a scientist – or, more precisely, as a microbiologist, I have come to understand that my private and professional lives are deeply shaped by interdisciplinarity, mobility and international exchange. Much like microbiology itself, which encompasses the fields of molecular biology, genetics, immunology and biochemistry, interdisciplinary research draws knowledge from various scientific fields – sometimes close, sometimes very far from one’s own — to create new concepts by thinking across borders.

Crossing borders, in a literal sense, has been a highlight of my career. I have worked as an independent principal investigator in Austria and Sweden, and I am now based in Germany. I never thought that my career path would take me to these countries when I first started my postdoctoral studies in the US.

But after my time as a PhD student, I understood very fast that I also needed to go abroad. I knew that staying in France – as comfortable as that may have been – was not an option if I wanted to expand my personal and academic horizons. So, after sending out dozens of letters to different microbiology laboratories in the US, I decided to join the group of Elaine Tuomonen at the Rockefeller University in New York.

This was in 1996, when I was 27 years old. I moved into a shoe box of an apartment in New York. It was, in fact, a very exciting and happy time of my life and career. In many ways, New
York is a melting pot, and it gives you the feeling that you are free to re-invent yourself. This was perhaps part of the reason why I let my curiosity and intuition lead me through several other academic institutions, again with inspiring mentors: Pamela Cowin at the New York University Medical Center, Richard Novick at the Skirball Institute and Elaine Tuomanen at St. Jude Children’s Research Hospital in Memphis, Tennessee. The academic spirit in the United States certainly allowed me to explore different fields of research, ranging from bacterial pathogenicity to the genetic analysis of skin development in mice – and I greatly enjoyed this freedom. As new molecular and cellular technologies became available in the early 1990s, I turned my focus to the study of how bacterial pathogens infect and interact with their hosts and environment. I studied molecular mechanisms of regulation involved in gene and protein expression during infection. My aim was to find new pathways that could be further harnessed for the benefit of medicine and biotechnology. It was during my stays in Elaine Tuomanen’s and Richard Novick’s laboratories that I understood the need for more precise genetic tools, which I developed in order to facilitate the genetics in bacterial pathogens. The choice for a second postdoc with Pamela Cowin was mainly motivated by my wish to gain experience in the genetics and study of higher organisms. I chose to work on skin as I wanted to focus on bacterial pathogens that infect skin such as the human pathogen Streptococcus pyogenes. This bacterium has become a model organism for the past fifteen years of my laboratory’s research. It was through the generation of transgenic mouse models and the study of proteins involved in skin cell-cell adhesion and signal transduction that I came to realise the lack of easy-to-use and precise genetic tools for eukaryotic systems. Especially in the late 1990’s, there was no possibility to directly modify the DNA of human cells, which are critical to study in the context of human infectious diseases caused by bacterial pathogens.

Following this experience, I came back to focus on the more molecular aspects of regulation in bacteria but always kept in mind that I would take any opportunity in my future path to develop genetic tools for human cells if I had the chance to do so. CRISPR-Cas9 revealed to be the mechanism that led me indeed achieve this goal, and I expect more models to study infectious diseases based on the CRISPR-Cas9 technology to continue to develop.

One crucial aspect of my experiences in New York and Memphis was the chance to be surrounded by people that shared my level of ambition and my enthusiasm for basic science, and this was very enjoyable. I met so many researchers there who loved what they were doing and wanted to achieve major breakthroughs for themselves and for science. These were people that saw science as their vocation. Research was a fundamental part of their lives.

Moreover, as a medical microbiologist coming from a more conservative European research tradition, it was incredibly inspiring for me to witness how the research environment in the United States builds bridges between the academic world and the biotech sphere and pharma-
ceutical industry. I learned a lot from the American way of doing science, and the country’s enterprising spirit. Although I had a very clear motivation for each move – there was either a specific topic that I wanted to study or a method that I wanted to learn – you also have to approach the unexpected when you move to a new country, which is part of why mobility can be such an enriching experience.

Nevertheless, I returned to Europe in 2002 to establish my own research group as an Assistant and Associate Professor at the Max F. Perutz Laboratories of the University of Vienna in Austria where I also habilitated in the field of Microbiology. I found myself in an historically rich and beautiful city. I was pleasantly surprised by the international spirit that was blowing through the academic institutions at the Vienna BioCenter. Science was managed in a way that nobody felt excluded regardless of which country she or he was from. In Vienna, I developed several projects aiming to identify and decipher RNA- and protein-mediated regulatory mechanisms mainly in the bacterial pathogen S. pyogenes. One of these projects consisted of identifying more RNAs with regulatory functions, others than the few we were already focusing on at the time. And this is how my research on bacterial CRISPR-Cas systems started. In 2006, Maria Eckert and Karine Gonzales from my laboratory performed a bioinformatics screen to search for new molecules of small RNA nature in S. pyogenes and identified CRISPR RNAs of the CRISPR-Cas9 system as well as tracrRNA among other RNAs. At that time, CRISPR (“clustered regularly interspaced short palindromic repeats”) was hypothesized to act as an adaptive immune system in bacteria and archaea that would involve RNA-guided proteins to target the genomes of invaders such as viruses or plasmids. The hypothesis still needed to be tested and nothing was known about the mechanisms that would then be involved in such immunity. I saw this fundamental topic of microbiology as an opportunity to discover new types of RNA interference mechanisms that could be exploited to silence and recombine genomes of cells and organisms. One type of RNA, tracrRNA, retained the attention of my laboratory. Our focus on this RNA led us to demonstrate that it could have a regulatory function on the expression of a critical virulence factor, CAMP, but experiments failed to demonstrate such a function.

After six years in Vienna, I was appointed Associate Professor at the Laboratory for Molecular Infection Medicine Sweden (MIMS, part of the Nordic European Molecular Biology Laboratory (EMBL) Partnership for Molecular Medicine) at Umeå University where I habilitated in the field of Medical Microbiology and was active as a Visiting Professor until 2017. Being very far north in Umeå was a completely different experience. I was in a very remote environment and living through extreme winters. But I found state-of-the-art facilities and excellent working conditions with a great sense of respect for junior scientists. This framework enabled me to do some of my best research there. With my move to Umeå, I decided to focus more on the CRISPR-Cas9 system known at the time as the Csn1 system. My group had identified tracrRNA (trans-acting CRISPR RNA) (mentioned above) as an RNA encoded in the vicinity of the...
type II CRISPR-Cas9 system, and I was interested in investigating whether tracrRNA was an integrative part of or would have a regulatory function on the system. No one knew the details of how CRISPR-Cas9 was working as a genome targeting machinery. But it was very clear for us at early stages that if a CRISPR-Cas system would be attractive to be exploited for genetic purposes, then the minimal CRISPR-Cas9 system with an enzyme guided by a duplex of RNA would offer a simple way to cleave DNA and harness it as a genetic tool. The other CRISPR-Cas systems described at the time were too complex.

In 2011, my group published a breakthrough paper in Nature that laid the foundation of our entire work on CRISPR-Cas9, whereby we identified the critical role that tracrRNA performs in the development of the CRISPR-mediated viral defense mechanism. I am grateful to have worked with highly enthusiastic and productive students, mainly Elitza Deltcheva and Krzysztof Chylinski, and to have collaborated with the group of Joerg Vogel in Germany on this study. A year later, we were indeed able to demonstrate that CRISPR-Cas9 is a dual-tracrRNA-CRISPR RNA enzyme that cleaves DNA sequence-specifically. The system was then developed into a precise gene-editing tool that can correct defective DNA, much like a text editing software can edit or correct typos in a document. The details of the DNA targeting mechanism by the CRISPR-Cas9 system and the guidelines how to use it as a versatile genetic tool were published in the journal Science in 2012 within the frame of a collaboration with Martin Jinek in Jennifer Doudna’s laboratory in the US.

These ground-breaking findings in the field of RNA-mediated regulation based on the CRISPR-Cas9 system have revolutionized life sciences research and are opening whole new opportunities in biomedical gene therapies. Just a couple of months after the 2012 Science article, a number of studies were published, demonstrating the success of CRISPR-Cas9 as a technology that modifies DNA in human cells, plants and model organisms such as zebrafish and flies. The field of CRISPR-Cas9 continues to develop at dazzling speed, with exciting new developments emerging almost weekly.

At the same time, my career as a senior scientist was evolving very fast. Between 2013 and 2015, I was Professor at the Medical School of Hannover in Germany and established a new research department as Head of the Department of Regulation in Infection Biology at the Helmholtz Centre for Infection Research, Braunschweig. In 2013, I was honored with an Alexander von Humboldt Professorship, which I held in 2014 and 2015. In 2015, the Max Planck Society appointed me Scientific Member and Director of the Department of Regulation in Infection Biology at the Max Planck Institute for Infection Biology in Berlin, Germany. This meant that I had to move my laboratory for the third time in only a few years. A year later, I became Honorary Professor at Humboldt University.
When I left France and went to the United States, I lost a part of myself, but more importantly, I gained something new. I left America and moved to Vienna; I kept the best of the United States, and left the rest behind. Although not easy, it is important to find the right balance between staying true to oneself and avoiding complete assimilation on the one hand, and respecting and integrating into a new environment on the other, at the same time building on and being receptive to new ideas. A few iterations of this cycle—five in my case—and one is left with the essence of self that is imbued with one’s experiences. This has helped me realise what my core values are as a person and as a scientist.

My restless years, in which I changed institutions and countries, have now come to an end. I have found a home in Berlin and within the Max Planck Society. In early 2018, I founded a new institute, the Max Planck Unit for the Science of Pathogens which allows me to expand my research on the fundamental processes of infection and immunity to other types of pathogens as well. I am very happy and extremely grateful to create a completely new institute from the very beginning, and I hope it will give a home to many talented and ambitious young scientists from all over the world to work on the many questions of basic biological research on pathogens that are still unanswered.

People outside science are often surprised when they learn that the discovery of the CRISPR-Cas9 gene editing technology is a result of basic science. Being a microbiologist, I sometimes see my field of research overlooked or not given the public attention and funding it deserves. But, the CRISPR-Cas9 discovery is a very good example why basic science is fundamentally important. Without the deep understanding of its basic mechanisms, we would not have been able to develop it into the innovative technology it is today.

The fact that the work of my laboratory was honored with numerous prizes all over the world makes me very happy, not only on a personal level, but also because it gives fundamental research the public attention and recognition it needs. Despite the fact that it is arduous work, experiments fail on a regular basis, and it often takes years until results are finally visible. I would like to motivate the new generation of researchers to be persistent, curious and passionate about basic science. I would like to encourage them to take risks and cross as many borders as they possibly can—because what lies behind these borders, expands your mind-set and is a very enriching experience. For me, it was a process of refinement and has made me the scientist I am today.

An Autobiography by:
Emmanuelle Charpentier
Kavli Prize Laureate in Nanoscience 2018

The Kavli Prize
My parents grew up in different parts of the United States: Mom was from Connecticut, where her dad practiced real estate law; Dad grew up in Kentucky, where his dad worked as a civil engineer. They met at Oberlin College in Ohio, but because they were both traveling and working, and Dad was drafted to serve in the army during the Korean war, they did not marry until 10 years after college. They began their married life together in Washington DC, where I was born, then moved to northern Michigan so Dad could teach at a small college. When the college closed, Dad enrolled in a PhD program at the University of Michigan in Ann Arbor. Once their third daughter was born, Dad was hired as an assistant professor of English at the University of Hawaii at Hilo. My parents moved the family to Hilo in 1971: I was 7, my sister Ellen was 4 and the youngest, Sarah, was 3 months old. This move was a turning point in many ways: Hilo in the ‘70s was not always a friendly place for haole people like us, but we did make lifelong friends, experienced the wonders of Polynesian and Asian cultures and explored the incredible geology and biology of the Hawaiian islands. My parents were intellectuals, Dad with his teaching and writing career and Mom with an avid interest in Asian history that led her to get a Masters’ degree and begin teaching at the local community college. We spent many evenings reading, playing Scrabble, listening to music and debating political events. Weekends were for hiking, mostly in and around Hawaii Volcanoes National Park.

I went to public schools all the way through high school, with a brief two-year stint at a local Catholic school during grades 7-8. During 9th grade Dad was on sabbatical in Ann Arbor Michigan and I had the good fortune to attend a fabulous public school there with a wonderful English teacher who challenged us kids to read and write about our own ideas. But my favorite class was Math – I loved solving problems and working through proofs, and I began to imagine doing work that would engage my quantitative leanings. In 10th grade, back at Hilo High School, I had Ms. Wong for Chemistry class. She taught us kids that Chemistry is about figuring things out, and I loved the process of discovery. What if I could become a scientist who worked on discovering things about the natural world, maybe things no one had ever known before? The idea was tantalizing, especially because no one I knew, and certainly no one in my family, was a scientist.

As an undergraduate at Pomona College, I worked with Sharon Panasenko on cell-cell communication in bacteria, and went on to graduate school at Harvard in the fall of 1985. I had the good fortune to work in the lab of Jack Szostak, a brilliant young geneticist who had recently
turned his attention to understanding something seemingly unknowable: the molecular origin of life. Working in his lab on catalytic RNAs that might help reveal how self-replicating genetic systems first arose, I was in my element. It was incredibly exciting to be living and working in the intellectual hotbed of the Cambridge/Boston corridor, with MIT just across the Charles River from my lab at the Massachusetts General Hospital. As a graduate student I studied the function of self-splicing introns, which were one of the first examples of RNA molecules capable of conducting chemical reactions in cells. My PhD thesis project involved generating forms of the intron RNA that could produce copies of RNA templates, showing that RNA has the capacity to copy itself. Jack Szostak taught all of us in the lab to focus on doing our very best work, to do careful controls and to think creatively about our experiments. I deeply admired his passion for science and his willingness to think differently than others. In retrospect, I can see that Jack Szostak also found ways to validate his students’ ideas and bolster our self-confidence as scientists.

In 1991 I moved to Boulder Colorado to do postdoctoral work with Tom Cech, a recent Nobel laureate recognized for his discovery of self-splicing introns. I went to his lab with the goal of crystallizing the intron RNA in order to determine its molecular structure using X-ray crystallography. No one knew whether RNA molecules could be crystallized, or even whether RNA molecules had defined 3D shapes – there was just one example of an RNA (tRNA) whose structure had been determined, and that work had been done in the 1970s. The Cech lab offered a great environment in which to work on this risky but incredibly exciting project: Tom Cech gave all of us in the lab a lot of freedom to pursue our ideas, and he had assembled a fantastic group of talented people with whom to interact. I teamed up with Anne Gooding, Elaine Podell and Jamie Cate to figure out how to crystallize intron and other kinds of RNA, and eventually, we succeeded in obtaining crystals of the large P4-P6 domain of the self-splicing intron. It took until the first two years of my independent faculty position at Yale University to solve the P4-P6 domain structure, but the wait was well worth it! It was a fantastically interesting structure, showing how RNA can fold up into a distinct architecture that explained its biological and chemical behavior. Sadly, as we were completing the structure, my dad fell ill with terminal cancer. I was glad that I could share with him the joy of determining the P4-P6 RNA structure, and what it hinted about the role of RNA in the evolution of life, before he died.

Yale was a great place for me to establish myself as a new faculty member and to continue exploring the 3D structures of RNA molecules. With Adrian Ferré-D’Amaré, my first postdoctoral associate, we solved structures of another catalytic RNA, the hepatitis delta virus ribozyme. Methods of determining RNA structures developed in our lab were later used by the Steitz and Ramakrishnan labs to solve structures of the ribosome, the molecular machine that cells use to read the genetic code to make proteins. I loved being part of Yale’s Department of Molecular Biophysics and Biochemistry, surrounded by incredible colleagues and students who consistent-
ly encouraged and challenged me. Our lab went on to study other kinds of RNA and protein-RNA complexes, including the signal recognition particle (SRP) used in all cells to direct proteins to the correct cellular location, and internal ribosome entry sites that enable viruses to hijack ribosomes to make viral proteins. With each new structure and the accompanying biochemical experiments used to test hypotheses about function, I felt we were uncovering new principles about RNA that pertained to its many biological activities. But I was also eager to connect these findings to cellular and organismal behavior.

In 2002 I decided to move my laboratory to the University of California at Berkeley, where I began working on very small RNA molecules that control when and what kinds of proteins are made in animal and plant cells, a process known as RNA interference (RNAi). A few years later I met Jill Banfield, a colleague who had uncovered examples of bacterial immune systems known as CRISPRs. These DNA sequences, found in specific regions of bacterial genomes, contained bits of viral sequences that could be copied into RNA and used to protect cells from viral infection. I was fascinated by the possibility that CRISPR systems in bacteria operate similarly to RNAi in animal and plant cells – and with postdoctoral associate Blake Wiedenheft and graduate student Rachel Haurwitz, we began studying how CRISPR RNAs are made and how they work together with CRISPR-associated (Cas) proteins to find and destroy viral DNA. Based on this research I went to a meeting in 2011 to present our work and there I met Emmanuelle Charpentier, a medical microbiologist studying a different kind of CRISPR system that depended on the function of a protein called Cas9. In a wonderful and fateful collaboration, we teamed up to figure out the function of Cas9. Martin Jinek in my lab and Kryz Chylinski in Emmanuelle’s lab worked together to uncover the fundamental activity of Cas9, which turned out to be a dual-RNA guided enzyme that cuts double stranded DNA at sequences matching the 20-nucleotide sequence of the guide RNA. By engineering the dual RNAs into a single-guide RNA containing both the DNA-binding sequence and the Cas9-associating constant region, we turned the CRISPR-Cas9 enzyme into a robust technology for inducing genome editing based on its ability to cut DNA at desired sites. The programmable nature of Cas9 made it easy to adapt for a wide range of genome editing applications, which happened quickly after the publication of our work in June of 2012.

Studying how bacteria fight viral infections may sound like a niche area of biology, and it was. But this curiosity-driven research led in directions that none of us anticipated at the start of the project. Six years after the publication of our work, the range of applications of CRISPR-Cas9 technology is breathtaking. Genetic diseases have been cured in laboratory animals, clinical trials have begun for treating cancer and eye diseases and multiple companies have been established that are worth billions of dollars and employ hundreds of people. Corn, wheat and rice plants, as well as tomatoes, mushrooms and many other agriculturally important crops have been altered using CRISPR-Cas9 to introduce traits like drought and pest resistance and improved
yield. And the explosion of research using genome editing as a core technology has been exponential. Accompanying this progress are ethical and societal challenges that I have struggled to understand and communicate about, and there will be dilemmas and decisions that must be faced in the near future regarding human embryo editing, gene drives and different cultural norms.

My life has changed forever, and I sometimes miss my pre-Cas9 days: weekend trips to the Oakland Zoo with my young son and my mom, Saturday afternoons in my garden, weeknights reading to my son and helping him with homework. Now, my days, nights and weekends are a jumble of trying to keep up with the pace of the science in our lab and elsewhere, launching research projects and programs through the Innovative Genomics Institute that I co-founded with colleagues at UC Berkeley and UCSF, and answering a vast number of inquiries from people around the globe who are curious about CRISPR-Cas9 technology and applications. I am humbled by this experience, and feel grateful to be part of such a fascinating journey into the future.

Science is a wonderful career choice – one’s days are spent uncovering new knowledge, and doing so in the company of other likeminded souls who share a passion for understanding the natural world. I never imagined, at the beginning of my career, how my scientific pursuits would lead me to friendships and collaborations with people around the world. My lab is also fortunate to benefit from the intellectual freedom provided by the Howard Hughes Medical Institute, which enables our most risky forays into new biology.

I share my life with my husband Jamie Cate, also a professor of molecular and cell biology and of chemistry at UC Berkeley, and our teenage son Andy. Home life for us often revolves around science, and we also enjoy cooking and traveling together, reading and taking hikes on weekends. My garden is still my retreat, and I treasure the occasional afternoon when I can enjoy time among the flowers, blueberries and bees.
The Fettiplace surname is reputed to be derived from ‘faîtes place’, an old French term for an usher. History indicates my ancestors accompanied William the Conqueror during the French invasion of England in 1066, and they were subsequently rewarded with much land in Oxfordshire and Berkshire, one becoming mayor of the city of Oxford in 1245. They are commemorated in trios of striking stone effigies of reclining Tudor and Stuart knights in St. Mary’s Church in Swinbrook, near Oxford. However, the dynasty fell on hard times in the 1700’s, and the family manor was occupied by highwaymen and subsequently burned to the ground. The last of the Oxford Fettiplaces expired in 1805, but a line had earlier escaped north and flourished in Nottingham, where I was born in 1946 to Bob and Maisie Fettiplace. I was educated at Nottingham High School, a boy’s private school known as a direct grant school, that accepted a fraction of poor students funded by the local education authority. I was one of these, having been accepted based on my scores in the now defunct “eleven-plus” examination. It was an excellent school where I learned in detail all physical sciences (but not biology), mathematics and several foreign languages. My favorite teacher was Mr. Pitts, a maths teacher, who encouraged and challenged me with many problems, including the famous four-color map problem (not finally proven until 1997); and mechanics problems, such as why moving bicycles do not fall over. My great grandfather and grandfather were both gamblers and off track bookmakers (illegal in England until 1960), which may account for my interest in mathematics! Besides mathematics, a preoccupation during this period was music. I had no formal musical education but, like many teenagers at that time, learnt to play the guitar influenced by Lonnie Donegan, Buddy Holly, the Shadows and ultimately the Beatles. I built my own imitation red Fender-Stratocaster electric guitar, and played in a rock group called ‘The Boys’ throughout school. My best friend was Alan Jones, a clarinetist, saxophonist and guitarist, whom I accompanied in several folk rock bands at college and later. I believe my passion for music partly fostered my later interest in the auditory system. The family appetite for music later continued with my son David, who was a cellist in the state youth orchestra; my son Michael, who, with his brother as bassist, was lead singer in a Madison rockabilly band; and my grandson Callum who currently plays bass in a jazz band.

In 1965, I was accepted to Cambridge University to read Mathematical Physics, where I was initially taught by John Horton Conway, who invented the cellular automaton called ‘The Game of Life’. But mathematics seemed very dull, so in my second year, I switched to the Medical Sciences Tripos. This involved learning biology and taking a formal ‘A level’ biology exam, which was my first introduction to amazing topics such as cells, and genes, the brain and evolution, to fire my imagination. In my final undergraduate year, I took Physiology, taught at the
famous Physiological Laboratory, with particular emphasis on neuroscience, graduating with an MA in medical sciences. The faculty in that department had included Nobel laureates Edgar Adrian, Alan Hodgkin and Andrew Huxley. Hodgkin, along with his student Huxley, elucidated the mechanism underlying the nerve action potential, and first proposed the existence of ion channels, protein pores that regulate flow of ions across the plasma membrane. He was a genius, the cleverest person I have ever met. He had a unique way of thinking about biological problems, which ones were subject to mathematical analysis and therefore potentially solvable, and which ones were not, and he had an enormous influence on my scientific thinking. I continued as a research student at the Physiological Laboratory, investigating the structure and permeability of artificial lipid bilayers with Denis Haydon. In addition, I worked two seasons on the effects of channel-forming antibiotics such as the calcium-permeable nystatin on squid axons at the Plymouth Marine Biological Station. During my time at Plymouth, I met Denis Baylor and Andrew Crawford, both of whom later influenced my scientific career. In 1974, after receiving a PhD in membrane biophysics, I joined Denis Baylor at Stanford University, where we worked on synaptic transmission in the turtle retina. This involved performing simultaneous recordings from photoreceptors (rods and cones) and ganglion cells. From these experiments, we determined that electrical signals of just a few millivolts in the photoreceptors could be transmitted through the retinal synaptic pathway to elicit action potentials in the ganglion cells. Furthermore, the pathway from rods had slower kinetic properties to the one from cones, so slow signals of time course comparable to the rod light responses were better conveyed via the rod pathway. Denis had previously produced four exceptional papers on photoreceptor transduction with Alan Hodgkin, and he handed on to me Alan’s inimitable experimental philosophy. While at Stanford, I also met my future wife, Merriel Kruse, and returned with her to Cambridge in 1976.

In searching for a new project at the Physiological Laboratory, I resolved that the field of photoreceptor research was too crowded and, furthermore, I decided, mistakenly as it turned out, that there was not much left to do in that area. I spent much time talking with Andrew Crawford, often in the Eagle pub in Cambridge, about what other research problems in sensory transduction to attack. At the time studying sensory receptors was considered a good inroad to exploring neural signaling, if only because it was possible to precisely control the stimulus, unlike the often used cerebellum or hippocampus, where the physiological inputs are largely unidentified. We turned to auditory transduction in hair cells, about which little was known. There were rumors that the narrow frequency discrimination endowed by cochlear processing was vulnerable to lack of oxygen, suggesting that some active cellular mechanism contributed a ‘sharp second filter’. The obvious preparation to exploit was the turtle auditory papilla, because nerve cell preparations from this reptile could survive for a long time due to an ability for anaerobic metabolism. The robustness of the preparation had been recognized by Edgar Adrian who, in 1938, recorded from the auditory nerves of both tortoise and alligator. Andrew Craw-
ford and I developed an isolated turtle half-head preparation with access to the auditory hair cells of inner ear, but where the middle and external ears were intact and could be stimulated with sound. We described the sound sensitivity and frequency selectivity of the hair cells, and discovered that each hair cell behaves as an electrical resonator, intrinsically tuned to a narrow frequency range set by its electrical properties. My work over the next decade, along with Jon Art and Paul Fuchs, demonstrated that the variation in resonant frequency along the turtle papilla (the tonotopic map) arose from systematic differences in the numbers and speed of calcium-activated potassium channels, and that the tuning could be modulated by stimulation of a cholinergic efferent synapse.

In discovering electrical tuning, we believed we had stumbled across the ‘second filter’, but this proved incorrect. Electrical tuning was subsequently reported in auditory hair cells of amphibians, other reptiles and birds, but never in mammals. The most likely explanation for the difference is that evolution of small nocturnal mammals in a dinosaur dominated world required an expansion of the auditory range to frequencies too high for potassium channels to follow. The upper frequency limit of hearing for most birds is 5 kHz, whereas for small primitive mammals, it can be 10 to 20 times higher. An alternative mechanism for a ‘second filter’ might be some kind of fast electro-mechanical process, and discoveries in this area emerged during the 1980’s. One such process was the electrically-induced contraction of outer hair cells, first studied by Bill Brownell and Jonathan Ashmore, and extensively characterized by Peter Dallos and his colleagues, culminating in their cloning of the piezoelectric membrane motor ‘prestin’ in 2000. A second process was active motion of the hair cell stereociliary bundle. Andrew Crawford and I first addressed this possibility by projecting images of stereociliary bundles on a pair of photodiodes, differentially recorded to follow rapid motion of the bundle with small nanometer-scale amplitude. Using this technique, we concluded that turtle stereociliary bundles possess an active force generating mechanism. We subsequently characterized active bundle motion in more detail in hair cells of turtles, chickens and rats. However, the mechanism was most clearly explained by the experiments of Jim Hudspeth and coworkers, who showed that active force generation was linked to activation and adaptation of the mechanically sensitive ion channels that normally transduce sound into electricity. Whether this process contributes in mammalian cochlear hair cells is still unclear.

In 1990, I was made a Fellow of the Royal Society of London, at an awe-inspiring ceremony which involved signing a registry book containing signatures of all previous fellows, including Sir Isaac Newton. In the same year, I moved to the USA, partly to be closer to my wife’s family, and I became Steenbock Professor of Neural Sciences in the Department of Neurophysiology at the University of Wisconsin in Madison. The Department of Neurophysiology was distinguished for its achievements in auditory physiology, and contained researchers such as Jerzy Rose, John Brugge and Joe Hind, (who described auditory nerve phase-locking), Bill Rhode
(first to measure the narrow tuning of the basilar membrane with the Mössbauer effect), Tom Yin (who described the brainstem sound localization pathway) and Donata Oertel (first produced tissue slices of the cochlear nucleus). My work during my time here has focused mainly on characterizing the properties, location and identity of the mechanically-sensitive channels, often referred to as mechanoelectrical transducer (MET) channels. Although the work was begun in turtle hair cells, I later switched to rat cochlear hair cells. Employing patch clamp techniques, we devised methods for isolating and stimulating single MET channels, which was very exciting since it revealed a tonotopic gradient in their properties. These ion channels are challenging to study because they exist in very small numbers and must be mechanically connected to other parts of the cell to function. One of my most thrilling experiments was to use calcium-imaging to localize the MET channels. High speed video imaging, done in collaboration with Maryline Beurg and Tony Ricci at Stanford, provided unequivocal proof that the channels were at the tips of all but the tallest stereocilia, most likely in a complex demarcated as an opaque region in electron micrographs. This result constrained the method by which they were stimulated, but it gave no insight to their molecular identity. The study of mutations that cause deafness led to the elucidation by Christine Petit and others of many of the components of this protein complex within which the transducer channel is tethered. Until recently, however, it remained unclear which proteins form the channel. Discoveries of the effects of mutation by Andrew Griffith and colleagues at the NIDCD (National Institute on Deafness and other Communication Disorders) pointed to the transmembrane channel-like protein, TMC1, as a crucial element. My work has shown that the size of the single MET channel conductance, its variation along the tonotopic axis, its selectivity to calcium ions and its adaptive behavior are all modified in mutations of TMC1. This provides strong evidence that TMC1 forms the mechanoelectrical transducer channel.

One other line of research I have pursued since being in the USA is understanding the regulation of intracellular calcium, both as an important cytoplasmic messenger and as a potential source of hair cell damage. We were one of the first to apply real-time confocal microscopy to describe the spatial spread of calcium throughout the cytoplasm. This allowed me, in collaboration with Jon Art and Tom Tucker, to see calcium ‘hotspots’ around the synaptic release sites, and to characterize the mechanism of calcium extrusion via an ATP driven calcium pump. The importance of calcium turnover in hair cells is highlighted by the discovery that mutations of this pump, thus impairing calcium extrusion, underlie certain forms of deafness. Another indicator of the significance of calcium is the high levels of calcium binding proteins in the hair cell cytoplasm. In an extended collaboration with Carole Hackney, from Keele University in the UK, we documented the identities and concentrations of such calcium buffers. Carole was a superb electron microscopist who was one of the first to report tip links underlying force transmission to the MET channel. She used an ingenious method to quantify cytoplasmic proteins from their immunological labeling in electron micrographs. By measuring the density of the
immune-gold particles in tissue sections and in gels containing known amounts of the protein under study, she could accurately determine their concentration in the cytoplasm. A surprising finding was that one particular protein, oncomodulin, related to the parvalbumin occurring in skeletal muscle, is present at millimolar levels in outer hair cells. It was recently shown that oncomodulin knockout mice display progressive hearing loss, consistent with a central role for calcium.

Throughout my research, my aim has been to use different preparations and devise new techniques to study hair cells. The experiments have often been technically challenging, but have enabled us to be first to acquire different types of data. They were followed up by later quantitative analysis and coupled with modeling to complete the story. However, the results of electrophysiological experiments are usually evident immediately, which can be exciting to experience. It makes one feel like an explorer who turns a corner in the forest to encounter a new and unexpected artifact. Furthermore, many such experiments have involved only one or two other people working at the equipment rig at the same time. While in the USA, I have been particularly fortunate to work first with Tony Ricci and more recently with Maryline Beurg, who are both good friends. My research was rewarded with election as a Fellow of the American Academy of Arts and Sciences, the oldest learned society in USA, founded in 1780, not much later than the Royal Society. I was accompanied to the election ceremony in 2012 by my son, Michael, who has become a physician and is practicing at Massachusetts General Hospital, and sharing the occasion with him made me feel very proud. For over 20 years at the University of Wisconsin, I have enjoyed teaching a neuroscience course attended by both undergraduates and graduate students. The students are so enthusiastic about neuroscience. Interactions with them and with my colleagues persuade me that I can still make a valuable contribution, and that keeps me sufficiently young to continue with the laboratory research.
I was born and grew up in Šiauliai, an old city located in the northern part of Lithuania. My parents had met, got married and settled in Šiauliai soon after the WWII and started their carriers as financial accountants/bookkeepers. Presumably due to my parents’ occupation, I was quickly introduced to numbers and enjoyed occasional visits to my father’s office where I had a unique chance to explore mechanical calculators that helped to crunch numbers.

In the secondary school I became interested in mathematics, physics and chemistry first of all because of great teachers. Ms. Genovaite Jagminiene, a chemistry teacher sparked my interest in chemistry by classroom demonstrations and experiments. I became fascinated by it and curious to understand how these things happen. The teacher often encouraged me to solve chemistry problems often beyond the curriculum and soon I entered students’ chemistry competitions, both on city and country level. This opened the door to the chemistry lab in the school where I got the opportunity to do my first experiments.

After school graduation I had no doubts what to study and entered the Faculty of Chemistry of Vilnius University, where I became fascinated by organic chemistry. From my first years at the University I joined the Stereochemistry lab, headed by Prof. Petras Kadziauskas and started to work under the guidance of Prof. Eugenijus Butkus on the stereochemistry of bicyclo[3.3.1] nonanes. These studies developed my synthetic chemistry skills and sparked an interest in the mechanisms of chemical reactions.

At the beginning of the 80’s biochemistry and molecular biology started to get pace in Lithuania, boosted by the establishment of the Institute of Applied Enzymology in Vilnius. The potential and rapid development of life sciences captivated my attention, and motivated me to enter a PhD program at the Department of Chemical Enzymology of Lomonosov’s Moscow State University. At that time, this was probably the best place for PhD studies in the former Soviet Union. It was a time when many chemists at the Lomonosov’s Moscow University turned into biochemists, bringing with them a rigorous understanding of the kinetics and mechanisms of chemical reactions into biochemistry. There, for the first time I became familiar with big names in the field like William Jencks, Myron Bender, Stephen Benkovic who were behind the “iron curtain” at that time, but whom I had a pleasure to meet many years later. Surprisingly, PhD studies also exposed me to an international environment as much - as it was possible at that time - simply because my PhD advisor Prof. Karel Martinek was from Czecho-
slovakia, a country that does not exist anymore. During my PhD I focused on the mechanisms of thermoinactivation of proteolytic enzymes and acquired a solid background in the mechanisms of enzymatic reactions.

After getting my PhD in chemical kinetics and catalysis from Moscow University, I returned to Vilnius and joined the lab of Prof. Gervydas Dienys at the Institute of Applied Enzymology as a junior researcher (postdoc). Prof. Dienys had very wide research interests, but always looked for quantitative chemical explanations behind biological phenomena. The major focus of his lab was on enzyme immobilisation and mechanisms of proteolytic enzymes. During my time in the lab I developed a chemical modification approach that allowed dramatically increase thermostability of proteolytic enzymes. It resulted in several publications in international journals.

Nearly at the same time Prof. Arvydas Janulaitis at the Institute of Applied Enzymology initiated research on restriction-modification enzymes that provide defense against phages in bacteria. He soon became interested in the molecular mechanisms of restriction enzymes and invited me to join his lab. It was the right place to learn about the mechanisms protein-nucleic acid interactions. It was also an exciting time, since in 1990 Lithuania restored its independence and suddenly boarders opened for scientific collaboration. I captured this opportunity to initiate research collaboration with Prof. Steven Halford at the University of Bristol and Prof. Alfred Pingoud in Giessen, who were experts in the biochemistry of restriction enzymes. I quickly realized that in order to understand the structure and function of restriction enzymes we need a combination of biochemical and structural approaches. X-ray crystallography was not available at that time in Lithuania, but luckily at one of the FEBS meetings I had met Prof. Robert Huber, Nobel Laureate in Chemistry, who showed an interest in the crystallographic studies of restriction enzymes. In 1993 he invited me to join his lab at the Max-Planck-Institut für Biochemie in Martinsried, Germany as a visiting scientist.

In 1995 I became Chief scientist and Head of the lab of Protein-DNA Interactions at the Institute of Biotechnology. For more than two decades my research interests were focused on the structure-function relationships of enzymes involved in nucleic acids metabolism. Together with colleagues from the UK, Poland, Germany and other countries, we performed biochemical characterization of more than 20 restriction endonucleases, and solved approximately one third (~15 out of ~50) of currently available restriction endonuclease structures. We had thought that by deciphering the mechanism of sequence specificity of restriction enzymes we would be able to engineer tailor made restriction enzymes. Although we succeeded to establish some general rules of restriction enzyme specificity, structure guided reprogramming of restriction enzymes remained a challenging task that required a lot of protein engineering and not always produced desired variants.
Since 2007 I switched to mechanistic studies of CRISPR-Cas, the newly discovered bacterial antiviral system. CRISPR-Cas immediately caught my attention when a paper co-authored by Rodolphe Barrangou and Philippe Horvath reporting the CRISPR-Cas system of Streptococcus thermophilus appeared in Science in 2007. We immediately jumped on it, driven by desire to understand molecular mechanisms behind this novel antiviral defense system. We first showed that the Type II CRISPR-Cas system was a discrete and portable entity that could be transferred from one species to another and function correctly in the latter (Sapranauskas et al., 2011: Nucl. Acids Res. 39, 9275-9282). Next, we showed that the system could be established in vitro with just a single protein, Cas9, and the appropriate RNA species (Gasiunas et al. 2012: Proc. Natl. Acad. Sci. 109, 15539-15540); and the action in vitro could be tailored to target any DNA sequence of choice by selecting the corresponding RNA guide sequence. These in vitro reconstruction experiments laid the groundwork for the translation of CRISPR from a bacterial immune system into a powerful genome-editing tool.

My scientific career would never have been the same without the students and my lab team. I always had the privilege to work with brilliant students that not only did excellent science in the lab, but also created a fantastic atmosphere. During my scientific journey I always felt support from my family. My wife Dangira who also has a PhD in chemistry was often the first who heard about new discoveries and failures in the lab. My daughter Jurga have chosen a different career path, becoming a manager, but I hope that the scientific discussions she was exposed to in the family left at least an epigenetic footprint.