**Ralf Ludwig**

# The long road from basic research to innovation: The example of NMR

The debate over the importance of basic research and applied research has always played a central role in science policy and research funding. At its core, the issue is how limited resources should be allocated and what kind of research yields the greatest benefits for society, the economy, and science. Unjustly, basic research is coming under increasing pressure. The demand from politics and business for immediate benefits from research is growing. Yet knowledge-driven research leads to new insights and understanding that can result in technological breakthroughs and innovations in the medium and long term. For example, quantum mechanics first advanced our understanding of nature at the atomic level before later making microchips, transistors, lasers, and LEDs possible. The history of nuclear magnetic resonance (NMR) is also a prime example of how knowledge-driven research first yields fundamentally new insights before, after a time lag, leading to new developments and applications. The long journey from the discovery of the nuclear spin to magnetic resonance imaging (MRI or nuclear magnetic resonance imaging) as an established medical imaging technique can be clearly traced through five Nobel Prizes awarded in Physics, Chemistry, and Medicine.

In 1944, American physicist Isidor Isaac Rabi was awarded the Nobel Prize in Physics for developing the resonance method for studying the magnetic properties of atomic nuclei. Just a few years later, in 1952, Edward Mills Purcell and Felix Bloch (USA) were also awarded the Nobel Prize in Physics for developing new methods for precise nuclear spin measurement and for the related discoveries. Further fundamental discoveries in the field of magnetic resonance led to two Nobel Prizes in Chemistry. In 1991, Richard Ernst of the Laboratory of Physical Chemistry at ETH Zurich was honored for his contributions to the development of high-resolution nuclear magnetic resonance spectroscopy. In 2002, Kurt Wüthrich, also from ETH Zürich, received the Nobel Prize for his development of nuclear magnetic resonance spectroscopy to determine the three-dimensional structure of biological macromolecules in solution. The following year, Paul C. Lauterbur (USA) and Sir Peter Mansfield (UK) were awarded the 2003 Nobel Prize in Medicine in recognition of their discoveries in the field of MRI.

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DOI-Nr.: 10.26125/5mkq-9472

The Nobel Prize award ceremony traditionally takes place every year on December 10, the anniversary of the death of the founder, Alfred Nobel. The prizes for Physics, Chemistry, and Medicine are presented at the Stockholm Concert Hall. The King of Sweden presents the prizes to the respective laureates. In the evening, the formal Nobel Banquet takes place at City Hall. The laureates' lectures are held in the Aula Magna at Stockholm University (Chemistry, Physics) and at the Karolinska Institute (Medicine). In these lectures, the Nobel laureates present their award-winning research. They outline the historical development of their work and reflect on the future significance of their achievements. The lectures are made available as PDF files by the Nobel Foundation and published in journals such as Angewandte Chemie.




**Fig. 1:** **Five Nobel Prizes in Physics, Chemistry, and Medicine related to NMR technology illustrate the long journey from basic research to innovation.**

## Nobel Prize in Physics awarded to Isaac Isidor Rabi in 1944

Protons and neutrons in atomic nuclei behave like tiny, rotating magnets. Atoms and molecules therefore align themselves in a magnetic field. In 1938, Isaac Isidor Rabi passed a beam of molecules through a magnetic field. When the beam was irradiated with radio waves, the direction of spin could be changed, though only in specific steps, as predicted by quantum mechanics. When the atoms returned to their original positions, they emitted electromagnetic radiation at uniquely characteristic frequencies. For the development of the resonance method for determining the magnetic properties of atomic nuclei, the American physicist was awarded the Nobel Prize in Physics in 1944. World War II was still raging. The Swedish Academy states on its website that "Professor I.I. Rabi did not deliver a lecture [1]." Rabi received the Nobel Prize jointly with Otto Stern, who had been honored a year earlier for his contribution to the development of the molecular beam method and his discovery of the proton's magnetic moment. Professor E. Hulthén from Stockholm presented the groundbreaking work of Stern and Rabi in a radio lecture on December 10. In closing, the chairman of the Nobel Prize Committee for Physics paid tribute to Rabi's work with the following statement: "By this method, Rabi has literally established radio connections with the most subtle particles of matter - with the world of the electron and the atomic nucleus."

## Nobel Prize in Physics awarded to Edward M. Purcell and Felix Bloch in 1952

In his Nobel Lecture, "Research in Nuclear Magnetism," delivered on December 11, 1952, Edward M. Purcell explained the physical principles of nuclear magnetic resonance [2, 3]. Atomic nuclei with a nonzero nuclear spin possess a magnetic moment. When placed in an external magnetic field, their magnetic moments align and precess at a characteristic frequency, the Larmor frequency. If electromagnetic radiation matches this resonance frequency exactly, the nuclei absorb energy and transition between their quantized energy states. The resulting resonance signals enable an extremely precise determination of nuclear physical properties.

A key focus of the lecture is the determination of nuclear magnetic moments. Purcell demonstrates that the resonance frequency provides a direct indication of an atomic nucleus's magnetic moment. In particular, the ratios of the magnetic moments of different isotopes can be determined with great precision, since measurements of relative frequencies are significantly more accurate than absolute magnetic field measurements. This method provided fundamental information about nuclear spin, nuclear structure, and isotopic properties, and became an important tool in nuclear physics. Furthermore, Purcell describes how NMR provides insights into the immediate surroundings of atomic nuclei. The electron shell partially shields the external magnetic field, thereby slightly altering the resonance frequency. The chemical shift allows conclusions to be drawn about the electronic structure and the chemical bonding of an atom. Although this application was still in its infancy at the time of his lecture, Purcell already recognized its great potential for chemistry and materials research. As a result, NMR evolved into a universal method for the analysis of liquids, solids, and other condensed-state materials.

In his Nobel Lecture, "Nuclear Induction," Felix Bloch explained the physical principles and experimental development of nuclear induction, a phenomenon discovered by his research group [4–6]. Together with the work of Edward M. Purcell, this method forms the basis of modern NMR. The lecture focuses on the description of the experimental procedure, the underlying physical processes, and the scientific possibilities arising from the observation of magnetic nuclear moments. Bloch first explains the fundamental physical principle of nuclear induction. When atomic nuclei with a magnetic moment are placed in a strong external magnetic field, their spins preferentially align along this field. By exciting them with a high-frequency electromagnetic field, the nuclear spins can be displaced from their equilibrium state. After the excitation pulse is turned off, the resulting magnetization precesses around the direction of the external magnetic field and induces an electrical voltage in a receiving coil. This induced signal constitutes the experimental evidence of nuclear resonance and forms the basis of all modern NMR experiments.

A central component of the lecture is the mathematical description of the magnetization of macroscopic samples. Bloch introduces the differential equations now known as the Bloch equations, which describe the temporal evolution of magnetization under the influence of external magnetic fields and relaxation processes. In doing so, he distinguishes between longitudinal relaxation ($T_1$ time), which describes the return of magnetization

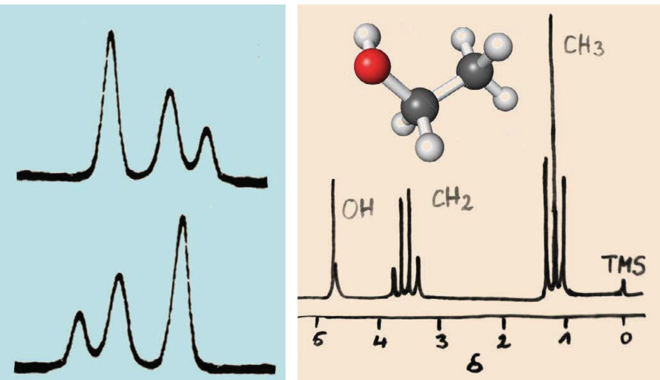


**Fig. 2:** The first recorded NMR spectrum of ethanol shows three lines that arise from the $CH_3$, $CH_2$ and OH protons (top left, in Hz) [2, 3]. The resonances are sensitive to the chemical environment of non-equivalent protons, an effect known as the chemical shift. In addition, the spectrum already exhibits a rough intensity ratio of 3:2:1. Today, the highly resolved $^1H$ spectrum provides the spin multiplets arising from spin-spin coupling with neighboring active nuclei. The spectra are displayed in parts per million (ppm) from that of tetramethylsilane (TMS), a convenient standard assigned the reference value (right).

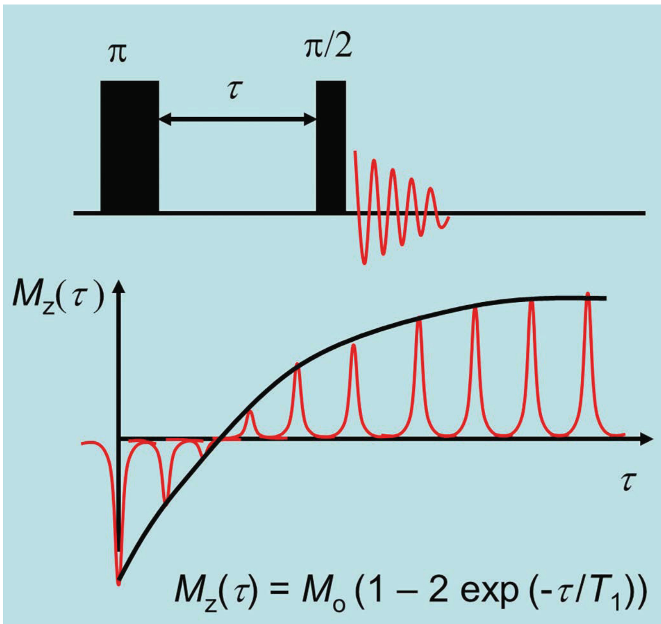


**Fig. 3:** In the inversion recovery experiment, the nuclei are first allowed to relax fully to their equilibrium states along the z-axis. A 180° pulse is then applied, which inverts the signals. The signals are then allowed to relax for a length of time $\tau$ that is varied between experiments. After each variable time, a 90° pulse is applied, and an NMR spectrum is recorded in which the peak intensities are a function of the variable delay $\tau$ and the individual $T_1$ relaxation rates.

toward the static magnetic field, and transverse relaxation ($T_2$ time), which characterizes the loss of phase coherence among the spins. To this day, these equations form the theoretical basis of NMR spectroscopy and magnetic resonance imaging (MRI).

Furthermore, Bloch demonstrated that important information about the properties of the material under investigation can be obtained from resonance frequencies and relaxation times. The resonance frequency depends on the strength of the magnetic field as well as on the gyromagnetic ratio of the respective atomic nucleus. At the same time, molecular interactions and motions influence the relaxation times, thereby providing insights into the dynamics of liquids and solids.

### Nobel Prize in Chemistry awarded to Richard R. Ernst in 1991

In his Nobel Lecture, “Nuclear Magnetic Resonance Fourier Transform Spectroscopy,” delivered on December 9, 1992, Richard R. Ernst describes the scientific development of NMR spectroscopy from its physical origins to its emergence as a high-resolution analytical method for chemistry, biology, and medicine [7, 8]. The lecture focuses on the methodological innovations that fundamentally transformed the capabilities of NMR and enabled its application to complex molecular systems. Ernst places particular emphasis in his lecture on the introduction of Fourier-transform NMR (FT-NMR). Until the 1960s, NMR spectra were recorded by continuously scanning through individual frequencies, a process that was time-consuming and relatively insensitive. Short radio-frequency pulses made it possible to excite all resonance frequencies simultaneously. The resulting time signal - known as the free induction decay (FID) - contains all spectral information and is converted into a frequency spectrum using the Fourier transform. This method significantly increased sensitivity, shortened measurement times, and allowed for the averaging of many individual measurements to improve the signal-to-noise ratio. The introduction of FT-NMR was certainly a turning point in the history of NMR spectroscopy.

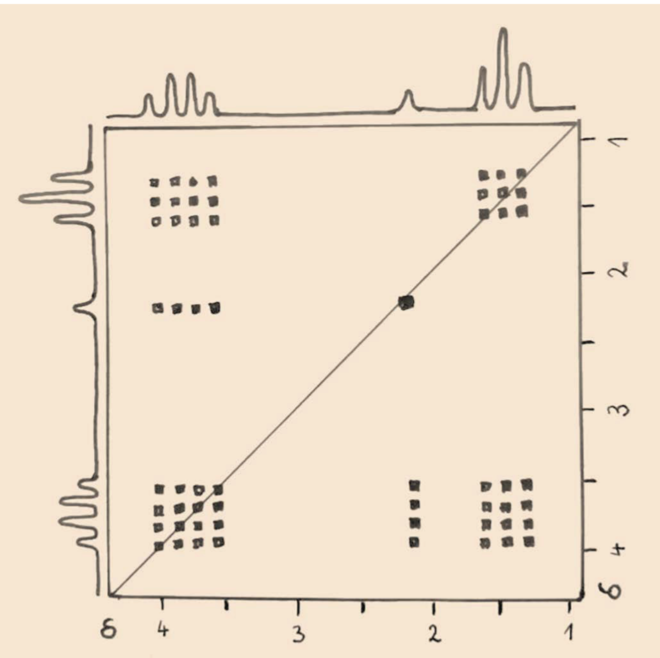


**Fig. 4:** A COSY (correlated spectroscopy) spectrum of ethanol in solution. The two-dimensional spectrum shows which of the $CH_3$, $CH_2$ and OH protons are coupled to one another via chemical bonds. It allows to determine the exact structure of molecules and the proximity of atoms.

The development of multidimensional NMR techniques can also be attributed to Ernst. The use of multiple radiofrequency pulses delivered in sequence, combined with multidimensional Fourier transforms, made it possible to study interactions between atomic nuclei. Methods such as COSY, NOESY, and other two-dimensional experiments now allowed for the unambiguous assignment of signals even in highly complex spectra. These multidimensional techniques opened up new possibilities for determining the structures of organic molecules, natural products, and, in particular, biological macromolecules such as proteins and nucleic acids.

### Nobel Prize in Chemistry Awarded to Kurt Wüthrich in 2002

In his Nobel Lecture, “NMR Studies of Structure and Function of Biological Macromolecules,” Kurt Wüthrich explains the development of NMR spectroscopy into one of the most important methods in modern structural biology [9, 10]. His lecture focuses on the question of how the three-dimensional structure of biological macromolecules - particularly proteins - can be determined under physiologically relevant conditions. Wüthrich begins by describing what sets NMR spectroscopy apart from X-ray crystallography. While the latter requires the crystallization of a protein, NMR allows for the study of proteins and nucleic acids directly in solution. This makes it possible not only to determine static structures but also to analyze molecular movements, conformational changes, and interactions with ligands or other biomolecules. According to Wüthrich, NMR therefore provides both structural and dynamic information that is crucial for understanding biological functions.

Wüthrich then describes the scientific challenges that stood in the way of the routine application of NMR to proteins in the 1970s. The spectra of biological macromolecules contain a large number of overlapping signals, which initially made it nearly impossible to unambiguously assign the resonances. To solve this problem, his research group developed the concept of sequential resonance assignment. In this approach, adjacent amino acids along the polypeptide chain are linked together step by step, so that each NMR signal can be assigned

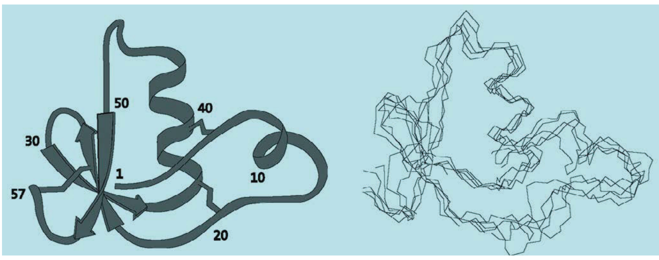


**Fig. 5:** One of the first three-dimensional NMR solution structures determined by Wüthrich, in 1985 [11]. The structures were calculated from distance constraints obtained from two-dimensional NOESY spectra and structural constraints such as torsion angles. The average structure is calculated from five possible structures using the constraints.

to a specific atom in the protein. This method represented a decisive breakthrough for structural biology and remains the foundation of numerous NMR analyses of proteins to this day.

Another focus of the lecture is the determination of three-dimensional protein structures using distance information between atomic nuclei. Wüthrich explains that the Nuclear Overhauser Effect (NOE), in particular, can be used to determine distances between protons in a molecule [11]. From a large number of measured distances, three-dimensional structural models can be calculated using computer simulations. Using several examples, he demonstrates that protein structures can be determined in this way with atomic resolution, with accuracy comparable to the results of X-ray crystallography. Furthermore, Wüthrich emphasizes that NMR goes far beyond mere structural determination. The method enables the investigation of protein movements, folding processes, ligand binding, and the thermodynamic and kinetic properties of biological macromolecules.

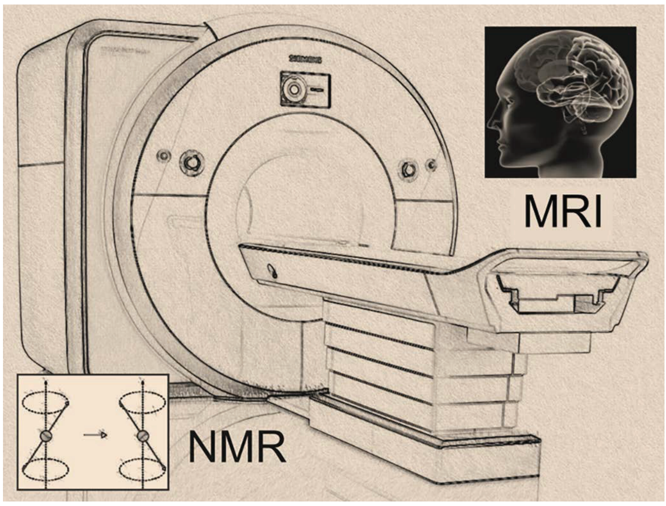


**Fig. 6:** **Magnetic resonance imaging (MRI) is an imaging technique that uses a strong magnetic field and radio waves to produce cross-sectional images of our body. Today, MRI machines provide clear and accurate images of organs such as the brain, the spine, and the entire musculoskeletal system.**

## Nobel Prize in Medicine awarded to Paul C. Lauterbur and Sir Peter Mansfield in 2003

In his Nobel Lecture, "All Science is Interdisciplinary – From Magnetic Moments to Molecules to Men," Paul C. Lauterbur describes the scientific developments that led to magnetic resonance imaging (MRI) [12, 13]. He emphasizes that scientific progress rarely arises within a single discipline, but is rather the result of close collaboration among various fields. The development of MRI, he notes, was only possible through the interplay of physics, chemistry, biology, medicine, and engineering.

At the beginning of his scientific career, Lauterbur focused on the application of NMR for determining the structure of molecules. While working with NMR spectrometers, he realized that introducing spatial magnetic field gradients would allow him to obtain not only chemical information but also positional information. This idea emerged in 1971 and led to the fundamental concept of magnetic resonance imaging. Instead of merely obtaining a spectrum of the entire sample, it became possible to spatially localize the origin of the NMR signal and reconstruct two-dimensional images from it.

Lauterbur describes how this idea was initially met with skepticism. The journal "Nature" initially rejected his manuscript because the medical significance of the method was not immediately recognized. The paper was published only after it had been revised. Looking back, Lauterbur cites this experience as an example of how scientific breakthroughs and their implications are often underestimated [14].

He also emphasized the importance of technical advancements. It was only through numerous contributions from other scientists - particularly in the fields of magnetic field gradients, mathematical image reconstruction, and computer technology - that his original idea could be developed into a clinically viable procedure. He pays special tribute to Peter Mansfield, whose work on rapid image reconstruction was instrumental in advancing the practical application of MRI.

In his Nobel Lecture, "Snap-Shot MRI," delivered by Sir Peter Mansfield on December 8, 2003, he describes the scientific and technical developments that transformed magnetic resonance imaging (MRI) from a physical concept into a clinically applicable imaging technique [15, 16]. While Paul C. Lauterbur developed the fundamental idea of spatial encoding using magnetic field gradients, Mansfield focuses on the mathematical, physical, and technical innovations that made fast, high-resolution imaging possible.

First, Mansfield provides a theoretical description of the spatial encoding of NMR signals and demonstrates that magnetic field gradients alter the resonance frequency of the nuclear spins in a position-dependent manner. This allows frequency and phase information to be mathematically analyzed to reconstruct the spatial distribution of the signals. This work laid the physical foundation for the frequency and phase encoding techniques used in MRI today.

Mansfield then explains his development of the echo-planar imaging (EPI) technique. Unlike the methods commonly used at the time, in which data was acquired line by line, EPI allows for the capture of nearly all image information after just a single radiofrequency pulse. This made it possible to reduce scan times from several minutes to a few seconds or even milliseconds. Mansfield describes this development as a decisive step toward real-time imaging and emphasizes that, for the first time, it made it possible to significantly reduce motion artifacts and study dynamic processes within the human body.

Mansfield also describes the significant experimental challenges of early MRI development. The design of fast gradient systems, the development of suitable receiver electronics, and the processing of large amounts of data presented significant technical hurdles. Despite initial skepticism about the new method, his research group succeeded in producing the first high-resolution MRI images of the human body, thereby impressively demonstrating the practical applicability of the technology.

Finally, Mansfield highlights the medical significance of MRI. The rapid imaging techniques he developed made it possible to examine moving organs such as the heart and brain and, later, to develop functional techniques, including functional magnetic resonance imaging (fMRI). As a result, MRI has become an indispensable diagnostic tool in neurology, oncology, cardiology, and many other medical specialties.

### Lessons to learn: Good things take time

The lectures delivered by the Nobel laureates in NMR underscore the great importance of basic research, which is driven by scientific curiosity rather than by a targeted search for applications. It was not uncommon for new knowledge to initially be met with great skepticism. Groundbreaking manuscripts were rejected by renowned scientific journals because their significance was not immediately recognized. It also becomes clear that new discoveries in physics and chemistry rely heavily on advances in other disciplines and fields of research, such as mathematics, electrical engineering, and computer science. It was only the development of powerful computers that made the fast Fourier transform and thus the practical application of FT-NMR possible. The development of MRI further demonstrates that innovation arises from openness to new ideas, interdisciplinary collaboration, and scientific curiosity. In this context, the greatest advances in science are often achieved at the intersections of different disciplines. Interdisciplinarity and international collaboration also allow for a holistic view of complex problems and, ultimately, their solution. The much-discussed academic freedom is aimed specifically at protecting basic research. It is not specific results, societal benefits, or applications that should be given special protection, but rather the evidence-based and open-ended pursuit of knowledge.

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Ralf Ludwig studied physics at RWTH Aachen University. He switched to physical chemistry for his diploma's thesis, and in 1991, Ludwig earned his doctorate in Manfred Zeidler's research group. After an inspiring stint as a postdoctoral researcher at the University of Wisconsin in Madison (USA) in Tom Farrar's research group and within Frank Weinhold's circle, he decided to pursue a career in academia and physical chemistry. In 1999, Ludwig completed his habilitation at TU Dortmund University in the group of Alfons Geiger. In 2004 accepted a professorship in Theoretical Chemistry at the University of Rostock. In 2011, he declined an offer to move south and instead took up the Chair of General Physical and Theoretical Chemistry in Rostock. His research focuses on elucidating the structure and dynamics of clusters, liquids, and solutions, as well as on developing a mechanistic understanding of chemical reactions. He actively contributes this work to the interdisciplinary faculty at the University of Rostock and, as an associated professor, to the Leibniz Institute for Catalysis. Ludwig is a member of the Senate of the German Research Foundation (DFG) and the NFDI expert committee. Recently, he served as president of the German Bunsen Society for Physical Chemistry.