

From Koch to mRNA vaccines — Nobel Prizes and the development of medicine with a comparative analysis of the achievements of the 20th and 21st centuries (1901–2025)

Mila Bastać (1), Pavle Nežović (2), Dušan Bastać (2), Jasna Strajnić (1), Stanislav Tadić (1), Petar Basić (2)
(1) "MEDSCAN TADIĆ DIJAGNOSTIKA" ZAJEČAR; (2) INTERNAL MEDICINE PRACTICE "DR BASTAĆ" ZAJEČAR

Summary: The Nobel Prize in Physiology or Medicine is one of the most important international recognitions for scientific achievements that have shaped the development of modern medicine. Since it was first awarded in 1901, the prize has recognized scientific discoveries that have fundamentally changed the understanding of the human organism, the origin of diseases and the possibilities for their treatment. **The aim** of this paper on the history of medicine is to present the development of medical science through an analysis of the Nobel Prizes in Physiology or Medicine during the 20th and 21st centuries, with special reference to the most important discoveries and their impact on everyday clinical practice. The key achievements of the 20th century that laid the foundations of modern medicine — the discovery of insulin, penicillin and the structure of DNA — are analyzed, as well as their contribution to the development of endocrinology, infectious diseases, molecular biology and personalized medicine. An overview of the most important Nobel Prizes of the 21st century is also presented, among which research on the cell cycle, apoptosis, RNA interference, stem cells, immunotherapy of malignant diseases, mRNA technology and microRNA stand out. Today, checkpoint inhibitors (PD-1, PD-L1, CTLA-4) enable long-term survival in many patients with melanoma, lung cancer, kidney cancer and other tumors. The comparative analysis shows that in the 20th century Nobel Prizes were mainly directed toward discovering the causes of diseases and developing antibiotics, hormones and diagnostic methods, while in the 21st century research on molecular and cellular mechanisms, gene regulation, immunology and precision medicine dominates. From the discovery of insulin and penicillin to mRNA vaccines and tumor immunotherapy, Nobel laureates have contributed significantly to extending life expectancy and improving the quality of life of millions of people. There are several oversights by the Nobel Committee with regard to ultrasound diagnostics, innovative surgical techniques and new inventive drugs and therapies. Although these methods have saved or improved the quality of life of millions of patients, the Nobel Committee has traditionally rewarded fundamental biological discoveries much more often than the development of diagnostics, pharmacological therapy and surgical techniques. There is a significant difference between a scientific discovery and its clinical translation into everyday medical practice. That is why many scientific achievements of enormous public health importance remain outside its scope. The history of medicine cannot be viewed exclusively through the Nobel Prizes, but also through an assessment of the real impact of individual diagnostic and therapeutic methods on survival, quality of life and the reduction of the burden of disease in the general population. **CONCLUSION:** If the 20th century was the century of the scientific discovery of organs, microbes, hormones and antibiotics, then the 21st century is the century of molecular medicine, genomics and personalized treatment. In the 20th century, medicine answered the question "What causes disease?", and in the 21st century it is trying to answer the question "Why does the disease develop in this particular patient and how can it be treated in a targeted way?".

Keywords: Nobel Prize; history of medicine; insulin; penicillin; DNA; immunotherapy; mRNA vaccines; personalized medicine; molecular biology.

INTRODUCTION

The Nobel Prize is one of the most prestigious international recognitions for scientific, literary and peace achievements. Its history begins with the will of Alfred Nobel, a Swedish inventor and industrialist, who bequeathed his fortune to establish a fund that would reward "those who, during the preceding year, have conferred the greatest benefit to humankind" [1].

Alfred Nobel was born in 1833 in Stockholm. He spent most of his life as a chemist

and inventor. He patented a total of 355 inventions [2]. His best-known invention, dynamite, patented in 1867, brought him enormous wealth, but also his concern about the destructive use of explosives [2,3]. It is believed that precisely these reasons, as well as the influence of Bertha von Suttner, a prominent peace activist, prompted Alfred Nobel to dedicate most of his fortune to prizes that would serve the progress of humankind [4].

In his will, signed in 1895, Nobel specified that the income from his fortune should be divided into five equal parts and

awarded for outstanding achievements in the fields of physics, chemistry, physiology or medicine, literature and peace [1]. The prize in physiology or medicine was to go to the person who had made the most important discovery in these fields. For a large part of his life and business, Nobel was connected with France. He had a laboratory and an estate near Paris. His last will was signed precisely in Paris on 27 November 1895. Alfred Nobel died on 10 December 1896 in San Remo, and it was precisely this date that was later chosen as the day of the prize award ceremony [5]. With it, he practically dedicated most of his remaining fortune to a fund from whose income prizes would be awarded every year.

After lengthy negotiations (about 5 years), both with the French government and with members of the Nobel family, the first Nobel Prize award ceremony was held on 10 December 1901 [6]. That year, prizes were awarded in all five categories, and the first recipient of the Nobel Prize in Physiology or Medicine was Emil Adolf von Behring, a German physician and bacteriologist, for the discovery of serum therapy against diphtheria [3,7]. This discovery marked a turning point in the development of modern immunization methods and saved countless lives around the world [7].

The Nobel Prize in Physiology or Medicine, awarded since 1901, has become synonymous with the highest achievements in the biomedical sciences. During more than a century of its existence, this prize has recognized discoveries that have fundamentally changed the way we understand the human body, diseases and treatment [7].

The importance of the Nobel Prize in Medicine is reflected in several key aspects. First of all, the prize has recognized discoveries that directly contributed to saving millions of lives — from the discovery of insulin in 1923, through penicillin in 1945, to the development of mRNA vaccines in 2023 [7]. **Second, the Nobel Prize has served as a kind of map of the development of medical science, reflecting changes in research priorities — from the study of infectious diseases in the early decades, through molecular biology and genetics in the second half of the 20th century, to contemporary research at the subcellular and molecular level [8].**

In addition, the prize has institutionalized and affirmed scientific

excellence, encouraging international cooperation and the exchange of knowledge. An analysis of the laureates shows that most laureates came from the United States of America, Great Britain and Germany, but the discoveries had a global impact on medical practice [9]. Also, the prize has evolved from recognizing individual researchers toward recognizing teamwork — in the period from 1901 to 2019, as many as 71 of the total of 110 prizes in medicine were awarded to two or three scientists jointly [8].

The Nobel Prize in Physiology or Medicine is more than a mere recognition — it is a mirror of the progress of medical science and a witness to humankind's continuous striving for a better understanding of life and health. From the first recognition to Emil von Behring for serum therapy to the latest discoveries in the field of immunology and gene therapy, this prize documents the history of medicine and at the same time illuminates the path for future generations of researchers.

MATERIAL AND METHODS

This paper presents an overview of the development of medicine through an analysis of the Nobel Prizes in Physiology or Medicine, i.e. biomedical scientific achievements, awarded in the period from 1901 to 2025. Data on Nobel Prize laureates, years of award and the explanations of the awarded achievements were collected from the official database of the Nobel Prize Foundation and from the available scientific literature [1,2].

The analysis included discoveries that had a significant impact on the development of the biomedical sciences, diagnostic methods, therapeutic procedures and preventive medicine. Nobel Prize laureates were classified according to the dominant field of research (microbiology, immunology, genetics, molecular biology, pharmacology, neurology, cardiology and other fields), as well as according to their contribution to contemporary clinical practice.

A qualitative comparative analysis of the Nobel Prizes awarded during the 20th and 21st centuries was applied, with the aim of examining changes in the research priorities of medicine. Particular attention was paid to discoveries that led to a significant improvement in the diagnosis, treatment and prevention of diseases, as well as to their impact on life

expectancy and the quality of life of the population.

For the purposes of this paper, Nobel Prizes that led to changes in everyday clinical practice were analyzed in particular, including the discovery of insulin, blood groups, penicillin, electrocardiography, cardiac catheterization, the structure of DNA, computed tomography, magnetic resonance imaging, new surgical techniques and organ transplantation, immunotherapy of malignant diseases and mRNA technology.

NOBEL PRIZES OF THE 20TH CENTURY: Key discoveries that laid the foundations of modern medicine (Table 1)

Modern medicine, as we know it today, is the result of a series of revolutionary discoveries that have fundamentally changed the way we understand the human body, diseases and treatment. Among the most important achievements that shaped medical science in the 20th century, the discoveries of insulin, penicillin and the structure of DNA stand out. For most historians of medicine, the three greatest turning points are:

1. **Insulin (1923)** — saved millions of patients with diabetes.
2. **Penicillin (1945)** — dramatically reduced mortality from infections.
3. **The structure of DNA (1962)** — opened the era of molecular and personalized medicine.

The discovery of insulin (1921–1923)

The discovery of insulin is one of the greatest achievements of 20th-century medical science and the first time that modern medical science succeeded in providing a life-saving therapy for a disease that had previously been universally fatal [10]. Diabetes mellitus, a condition described as early as 1550 BC in the Ebers Papyrus, had been a medical mystery for thousands of years [11].

The research that led to the discovery of insulin was carried out in Toronto in 1921–1922 and was led by Frederick Banting and John Macleod, with the key contribution of Charles Best and James Collip [12]. Their revolutionary work demonstrated that a pancreatic extract could consistently lower blood glucose levels in diabetic dogs [12]. This discovery marked a turning point in the understanding of the

endocrine regulation of nutrient metabolism and the functions of other organs [12].

For this achievement, Banting and Macleod were awarded the Nobel Prize in Physiology or Medicine in 1923, and they shared their prize with Best and Collip [12]. The importance of the discovery of insulin is reflected in the fact that it has saved the lives of millions of people with type 1 diabetes worldwide [12]. This discovery also initiated a whole century of research aimed at the purification, isolation, structural characterization and genetic sequencing of insulin, which has continuously improved therapeutic formulations [10].

The discovery of penicillin (1928–1945)

The discovery of penicillin represents a turning point in the fight against infectious diseases and one of the most important contributions to modern medicine [13]. The history of penicillin comprises three key phases of development: Fleming's discovery, the success of Florey and his colleagues in obtaining penicillin in a relatively pure form and demonstrating its clinical application, and the American success in mass production of the drug [14].

Sir Alexander Fleming discovered penicillin by chance in 1928, but his discovery did not attract significant attention for more than a decade, and the active substance was not isolated [13]. It was only in 1939 that Sir Howard Walter Florey, together with Ernst Boris Chain, led a team of British scientists who successfully produced the drug from the liquid medium in which penicillin grows [13].

During the Second World War, penicillin production took place under extremely difficult conditions. In the Netherlands, scientists of the NG&SF company continued secret research despite the German occupation. Using Fleming's 1929 publication as a basis, they managed to isolate a substance which they code-named "Bacinal" in order to conceal its identity from the German authorities [15]. An interesting detail from this period is that the scientists kept a German guard tipsy during their work by "treating" him to gin, which enabled them to continue production [15].

In 1945, Fleming, Florey and Chain were awarded the Nobel Prize in Physiology or Medicine for the discovery of penicillin and its therapeutic value [16,17]. The development of

penicillin represents a turning point in the fight against infectious diseases and laid the foundations for the antibiotic era [13].

The discovery of the structure of DNA (1953)

The discovery of the molecular structure of deoxyribonucleic acid (DNA) is one of the most important scientific achievements of the 20th century and the foundation of modern molecular biology [18]. This discovery transformed the understanding of cell function and revolutionized fields such as medicine, forensics, bioinformatics and nanotechnology [19].

On 25 April 1953, James Watson and Francis Crick published in the journal *Nature* their revolutionary model of the DNA double helix [19]. In their paper they concluded that “the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material” [19]. This insightful statement marked the beginning of a new era in the understanding of heredity and the transmission of genetic information. The double helix model was the result of a synthesis of numerous studies. Watson and Crick used the data of many researchers, including Oswald Avery, who proved that DNA, and not proteins or

RNA, is the carrier of hereditary information, as well as Erwin Chargaff, who showed that in DNA the amount of adenine corresponds to the amount of thymine, while the amount of guanine corresponds to the amount of cytosine [20]. A key role was also played by Rosalind Franklin, a British biophysicist and crystallographer, whose X-ray images provided key information that Watson and Crick used to build their model [19]. The structure of the double helix is antiparallel and complementary, with the bases located inside the molecule, adenine bonded to thymine and guanine to cytosine by hydrogen bonds, while the phosphates and deoxyribose are on the outside [20]. This structure in itself reveals its function — the way in which genetic information is copied and passed on to offspring [20].

Watson, Crick and Maurice Wilkins, their collaborator from King's College, were awarded the Nobel Prize in Physiology or Medicine in 1962 for this epochal discovery [16,17,19]. Elucidating the structure of DNA enabled the development of molecular biology into its “golden age”, creating structural biology and laying the foundations for the sequencing of the human genome twenty years later [18].

Table 1. The Nobel Prize in Physiology or Medicine (1901–2000)

Year	Laureate(s)	Discovery / contribution
1901	Emil von Behring	Serum therapy against diphtheria
1902	Ronald Ross	Transmission of malaria by mosquitoes
1903	Niels Finsen	Phototherapy (light treatment)
1904	Ivan Pavlov	Physiology of digestion
1905	Robert Koch	Tuberculosis and its causative agent
1906	Camillo Golgi, Santiago Ramón y Cajal	Structure of the nervous system and neurons
1907	Alphonse Laveran	Protozoa as causes of disease
1908	Ilya Mechnikov, Paul Ehrlich	Immunity (cellular and humoral)
1909	Theodor Kocher	Physiology and surgery of the thyroid gland
1910	Albrecht Kossel	Nucleic acids and cell chemistry
1911	Allvar Gullstrand	Optics of the eye
1912	Alexis Carrel	Vascular anastomoses and transplantation
1913	Charles Richet	Anaphylaxis
1914	Robert Bárány	Vestibular apparatus and balance
1915–1918	—	Prize not awarded
1919	Jules Bordet	Immunology and the complement system
1920	August Krogh	Regulation of capillary circulation
1921	—	Prize not awarded
1922	Archibald Hill, Otto Meyerhof	Energy metabolism of muscle
1923	Frederick Banting, John Macleod	Discovery of insulin
1924	Willem Einthoven	Electrocardiography (ECG)
1925	—	Prize not awarded
1926	Johannes Fibiger	Experimental carcinogenesis*
1927	Julius Wagner-Jauregg	Malaria therapy of neurosyphilis
1928	Charles Nicolle	Typhus
1929	Christiaan Eijkman, Frederick Hopkins	Vitamins and deficiency diseases
1930	Karl Landsteiner	ABO blood groups

1931	Otto Warburg	Cellular respiration
1932	Charles Sherrington, Edgar Adrian	Function of neurons
1933	Thomas Hunt Morgan	Chromosomes and heredity
1934	George Whipple, George Minot, William Murphy	Treatment of pernicious anemia
1935	Hans Spemann	Embryology and the organizer of development
1936	Henry Dale, Otto Loewi	Chemical transmission of nerve impulses
1937	Albert Szent-Györgyi	Vitamin C and cellular metabolism
1938	Corneille Heymans	Regulation of respiration
1939	Gerhard Domagk	Sulfonamides (Prontosil)
1940–1942	—	Prize not awarded
1943	Henrik Dam, Edward Doisy	Vitamin K
1944	Joseph Erlanger, Herbert Gasser	Functions of nerve fibers
1945	Alexander Fleming, Ernst Chain, Howard Florey	Penicillin
1946	Hermann Muller	Mutations induced by X-rays
1947	Carl Cori, Gerty Cori, Bernardo Houssay	Glucose and glycogen metabolism
1948	Paul Müller	DDT as an insecticide
1949	Walter Hess, Egas Moniz	Hypothalamus; psychosurgery
1950	Edward Kendall, Tadeus Reichstein, Philip Hench	Corticosteroids and their application
1951	Max Theiler	Yellow fever and vaccine development
1952	Selman Waksman	Streptomycin
1953	Hans Krebs, Fritz Lipmann	Krebs cycle and coenzyme A
1954	John Enders, Thomas Weller, Frederick Robbins	Cultivation of poliovirus in tissue cultures
1955	Hugo Theorell	Oxidation enzymes
1956	André Cournand, Werner Forssmann, Dickinson Richards	Cardiac catheterization
1957	Daniel Bovet	Antihistamines
1958	George Beadle, Edward Tatum, Joshua Lederberg	Role of genes in biochemical processes
1959	Severo Ochoa, Arthur Kornberg	Biosynthesis of RNA and DNA
1960	Frank Macfarlane Burnet, Peter Medawar	Acquired immunological tolerance
1961	Georg von Békésy	Mechanism of hearing
1962	Francis Crick, James Watson, Maurice Wilkins	Structure of DNA
1963	John Eccles, Alan Hodgkin, Andrew Huxley	Ionic mechanisms of the nerve impulse
1964	Konrad Bloch, Feodor Lynen	Metabolism of cholesterol and fatty acids
1965	François Jacob, André Lwoff, Jacques Monod	Genetic regulation of enzyme synthesis
1966	Peyton Rous, Charles Huggins	Tumor viruses and hormonal treatment of prostate cancer
1967	Ragnar Granit, Haldan Hartline, George Wald	Physiology of vision
1968	Robert Holley, Har Gobind Khorana, Marshall Nirenberg	Deciphering of the genetic code
1969	Max Delbrück, Alfred Hershey, Salvador Luria	Replication and genetics of viruses
1970	Julius Axelrod, Ulf von Euler, Bernard Katz	Neurotransmitters and synaptic transmission
1971	Earl Sutherland	cAMP as a second messenger
1972	Gerald Edelman, Rodney Porter	Structure of antibodies
1973	Karl von Frisch, Konrad Lorenz, Nikolaas Tinbergen	Foundations of ethology
1974	Albert Claude, Christian de Duve, George Palade	Structure and organization of the cell
1975	David Baltimore, Renato Dulbecco, Howard Temin	Interaction of tumor viruses and genetic material
1976	Baruch Blumberg, Daniel Gajdusek	Hepatitis B and new mechanisms of infectious diseases
1977	Roger Guillemin, Andrew Schally, Rosalyn Yalow	Hypothalamic hormones and radioimmunological methods
1978	Werner Arber, Daniel Nathans, Hamilton Smith	Restriction enzymes
1979	Allan Cormack, Godfrey Hounsfield	Computed tomography (CT)
1980	Baruj Benacerraf, Jean Dausset, George Snell	Genetic control of the immune response (MHC/HLA)
1981	Roger Sperry, David Hubel, Torsten Wiesel	Functional organization of the brain
1982	Sune Bergström, Bengt Samuelsson, John Vane	Prostaglandins
1983	Barbara McClintock	Mobile genetic elements
1984	Niels Jerne, Georges Köhler, César Milstein	Monoclonal antibodies
1985	Michael Brown, Joseph Goldstein	Cholesterol metabolism and LDL receptors
1986	Stanley Cohen, Rita Levi-Montalcini	Cell growth factors (NGF, EGF)
1987	Susumu Tonegawa	Genetic mechanisms of antibody diversity
1988	James Black, Gertrude Elion, George Hitchings	Rationally designed drugs
1989	J. Michael Bishop, Harold Varmus	Proto-oncogenes
1990	Joseph Murray, E. Donnall Thomas	Organ and cell transplantation

1991	Erwin Neher, Bert Sakmann	Function of single ion channels
1992	Edmond Fischer, Edwin Krebs	Reversible protein phosphorylation
1993	Richard Roberts, Phillip Sharp	Discovery of split genes (introns)
1994	Alfred Gilman, Martin Rodbell	G proteins and cell signaling
1995	Edward Lewis, Christiane Nüsslein-Volhard, Eric Wieschaus	Genetic control of early embryonic development
1996	Peter Doherty, Rolf Zinkernagel	Specificity of the cell-mediated immune response
1997	Stanley Prusiner	Prions
1998	Robert Furchgott, Louis Ignarro, Ferid Murad	Nitric oxide (NO)
1999	Günter Blobel	Signal sequences for protein transport
2000	Arvid Carlsson, Paul Greengard, Eric Kandel	Signal transduction in the nervous system

The importance of fundamental scientific discoveries for the development of cardiology **The five Nobel Prizes with the greatest impact on cardiology:**

- 1924 — Einthoven (ECG) — the most frequently used diagnostic method in cardiology.
- 1956 — Cardiac catheterization — enabled coronary angiography, PCI and modern invasive cardiology.
- 1964 — Cholesterol metabolism — the basis for the prevention of atherosclerosis.

- 1985 — LDL receptor — the direct scientific foundation of statins, ezetimibe and PCSK9 inhibitors.
- 1998 — Nitric oxide (NO) — changed the understanding of endothelial dysfunction, coronary disease and pulmonary hypertension.

The most important discoveries in the history of medicine in the 20th century (Table 2).

Table 2. The most important discoveries in the history of medicine

Year	Laureate(s)	Discovery	Impact on everyday medical practice
1901	Emil von Behring	Serum therapy	The beginning of modern immunotherapy and vaccinology.
1905	Robert Koch	Tuberculosis	Founded medical microbiology and the etiological diagnosis of infections.
1908	Mechnikov and Ehrlich	Immunity	The basis of modern immunology, vaccines and biological therapy.
1923	Banting and Macleod	Insulin	Turned type 1 diabetes from a fatal into a chronic disease.
1924	Willem Einthoven	Electrocardiogram (ECG)	The foundation of modern cardiological diagnostics.
1930	Karl Landsteiner	ABO blood groups	Enabled safe transfusions and the development of transplantation.
1945	Fleming, Chain and Florey	Penicillin	A revolution in the treatment of bacterial infections.
1952	Selman Waksman	Streptomycin	The first effective drug against tuberculosis
1956	Forssmann, Cournand and Richards	Cardiac catheterization	The basis of invasive cardiology, coronary angiography and hemodynamics
1960	Burnet and Medawar	Immunological tolerance	Enabled the development of transplant medicine.
1962	Watson, Crick and Wilkins	Structure of DNA	The foundation of molecular medicine, genetics and personalized therapy)
1964	Bloch and Lynen	Cholesterol metabolism	Laid the foundations for statins and the prevention of atherosclerosis.
1968	Holley, Khorana and Nirenberg	Genetic code	The basis of genetic engineering and modern biotechnology.
1977	Rosalyn Yalow	Radioimmunoassays (RIA)	The forerunner of modern laboratory diagnostics of hormones and biomarkers.
1979	Cormack and Hounsfield	Computed tomography (CT)	A revolution in radiological diagnostics
1984	Köhler, Milstein and Jerne	Monoclonal antibodies	The foundation of biological therapy in oncology, rheumatology and hematology.
1985	Brown and Goldstein	LDL receptor	Understanding of hyperlipidemia and the development of modern lipidology.
1988	Black, Elion and Hitchings	Rational drug design	Contributed to the development of beta-blockers, anti-ulcer drugs and numerous other drugs.
1990	Murray and Thomas	Organ transplantation	Routine transplantation of the kidney, heart, liver and bone marrow.
1998	Furchgott, Ignarro and Murad	Nitric oxide (NO)	Understanding of endothelial function, hypertension and atherosclerosis, and the development of sildenafil therapy.

WINNERS OF THE NOBEL PRIZE IN MEDICINE IN THE 21ST CENTURY

The twenty-first century has brought accelerated development of the biomedical

sciences, and the Nobel Prize in Physiology or Medicine has become a mirror of that progress (Table 3). From discoveries that shed light on the basic mechanisms of the functioning of cells,

through the understanding of the immune system, to revolutionary therapies that saved millions of lives during the COVID-19 pandemic,

the laureates of the 21st century have continued the tradition of exceptional achievements that have shaped modern medicine.

Table 3. Nobel Prizes in Medicine in the 21st century (2001–2025)

Year	Laureates	Discovery	Clinical significance
2001	Hartwell, Hunt, Nurse	Regulation of the cell cycle	Understanding the origin of malignant diseases
2002	Brenner, Horvitz, Sulston	Programmed cell death (apoptosis)	Oncology, neurodegenerative diseases
2003	Lauterbur, Mansfield	Magnetic resonance imaging (MRI)	A revolution in the diagnosis of the CNS, heart and soft tissues
2004	Axel, Buck	Odorant receptors	Neurobiology and sensory medicine
2005	Marshall, Warren	<i>Helicobacter pylori</i>	Peptic ulcer becomes a curable infectious disease
2006	Fire, Mello	RNA interference	Modern gene therapy
2007	Capecchi, Evans, Smithies	Knockout mice	Disease models and drug development
2008	zur Hausen; Barré-Sinoussi; Montagnier	HPV and HIV	Prevention of cervical cancer, AIDS
2009	Blackburn, Greider, Szostak	Telomeres and telomerase	Aging, carcinogenesis
2010	Robert Edwards	In vitro fertilization	Treatment of infertility
2011	Beutler, Hoffmann, Steinman	Innate immunity and dendritic cells	Vaccines and immunotherapy
2012	Gurdon, Yamanaka	Induced pluripotent stem cells	Regenerative medicine
2013	Rothman, Schekman, Südhof	Vesicular transport in the cell	Diabetes, neurological diseases
2014	O'Keefe, Moser, Moser	The brain's GPS system	Dementias and neurology
2015	Campbell, Ōmura, Tu Youyou	Therapy of malaria and parasitic diseases	Millions of lives saved
2016	Yoshinori Ohsumi	Autophagy	Cancer, neurodegeneration
2017	Hall, Rosbash, Young	Circadian rhythm	Sleep medicine, metabolism
2018	Allison, Honjo	Tumor immunotherapy	One of the greatest revolutions in oncology
2019	Kaelin, Ratcliffe, Semenza	Cellular response to hypoxia	Anemia, cancer, cardiology
2020	Alter, Houghton, Rice	Hepatitis C virus	Elimination of post-transfusion hepatitis
2021	Julius, Patapoutian	Receptors for temperature and touch	Chronic pain
2022	Svante Pääbo	Paleogenomics	Evolutionary medicine
2023	Karikó, Weissman	mRNA technology	COVID vaccines and a new era of vaccination
2024	Ambros, Ruvkun	microRNA	Regulation of gene expression
2025	Brunkow, Ramsdell, Sakaguchi	Peripheral immune tolerance	Autoimmune diseases and transplantation

Key areas of research in the 21st century

An analysis of the winners of the Nobel Prize in Physiology or Medicine in the 21st century shows several dominant directions in the development of biomedical research.

1. Gene regulation and RNA biology

The Nobel Prizes awarded for RNA interference (2006) and microRNA (2024) point to the central importance of RNA in the regulation of gene expression. These discoveries showed that the control of gene activity does not take place exclusively at the level of DNA, but also through complex mechanisms of post-transcriptional regulation. Understanding these processes has opened new possibilities for the development of diagnostic methods, targeted therapy and gene medicine. The discovery of RNA interference showed that cells possess natural mechanisms for the selective “silencing” of genes, while research on microRNA revealed an additional regulatory layer that controls protein synthesis and cell function. Today,

disorders of these mechanisms are associated with numerous diseases, including malignant, metabolic and neurodegenerative disorders.

2. Immunology

One of the most important areas of modern medicine is immunology. The Nobel Prizes of 2011, 2018 and 2025 shed light on key mechanisms of innate immunity, immune regulation and peripheral tolerance. The discoveries of Toll-like receptors and dendritic cells explained how the organism recognizes pathogens and triggers an immune response. The later identification of immune checkpoints enabled the development of modern immunotherapy of malignant diseases, while research on regulatory T lymphocytes and peripheral tolerance has significantly advanced the understanding of autoimmune diseases, transplant medicine and immune homeostasis.

3. Cell biology

Advances in cell biology have enabled a deeper understanding of the basic mechanisms

of the functioning of living systems. The Nobel Prizes for vesicle transport (2013) and autophagy (2016) clarified the processes of intracellular transport, intercellular communication and the recycling of cellular components. These mechanisms play a key role in maintaining cellular balance, the response to stress and adaptation to changes in the external environment. Their disorders are associated with the development of numerous diseases, including neurodegenerative disorders, diabetes, cardiovascular diseases and malignant tumors.

4. Radiological diagnostics, translational and applied medicine

A special characteristic of 21st-century medicine is the successful translation of fundamental scientific discoveries into clinical practice. The Nobel Prizes for magnetic resonance tomography (2003), in vitro fertilization (2010) and mRNA technology (2023) are examples of how basic research can lead to revolutionary diagnostic and therapeutic achievements.

These technologies have significantly advanced diagnostics, reproductive medicine and the prevention of infectious diseases, confirming that the greatest progress in medicine is often achieved by linking basic research with clinical application.

The winners of the Nobel Prize in Physiology or Medicine in the 21st century have continued the tradition of great scientific discoveries, but at the same time they have directed medicine toward new concepts of molecular biology, immunology and personalized therapy. Unlike many achievements of the 20th century, which were focused on individual diseases or organs, contemporary research increasingly reveals universal molecular and cellular mechanisms that link various physiological and pathological processes. Such an approach is the basis of modern precision medicine and the future development of new diagnostic and therapeutic strategies.

THE FIVE GREATEST MEDICAL REVOLUTIONS OF THE 21ST CENTURY

1. Immunotherapy of malignant diseases (Nobel 2018)

Before 2010, metastatic melanoma was one of the deadliest diagnoses in oncology. Patients with advanced melanoma had a five-year survival of only about 5%, and therapeutic

options were limited to surgery, radiation and cytotoxic chemotherapy, which rarely produced lasting results. Tumor cells managed to evade attack by the immune system by using their own “brakes” that prevent excessive activation of T cells.

The key discovery came from two independent directions in the 1990s. James Allison discovered that the CTLA-4 protein on the surface of T cells acts as an inhibitory receptor — a kind of “brake” that prevents full activation of the immune response. By blocking CTLA-4 with antibodies, his team showed that T cells can be “released” and directed to destroy tumor cells. Tasuku Honjo independently discovered another inhibitory receptor, PD-1, which binds to PD-L1 on tumor cells; this interaction sends a signal to the T cell to withdraw from the attack. Many tumors overexpress PD-L1 precisely as a strategy for evading the immune system [21,22].

Checkpoint inhibitors became the first class of drugs that does not attack the tumor directly, but rather “releases the brakes” of the immune system. In 2011, ipilimumab (anti-CTLA-4) was approved for metastatic melanoma, followed by anti-PD-1 drugs such as pembrolizumab (Keytruda) and nivolumab (Opdivo). The results were revolutionary: combined anti-PD-1 and anti-CTLA-4 therapy extended long-term survival in metastatic melanoma from 5% to about 50% in the latest reports [23]. Today, these drugs are used for melanoma, cancer of the lung, kidney, urinary bladder, head and neck, as well as for Hodgkin lymphoma [21].

However, challenges remain: only some patients have a lasting response, and the therapy can cause autoimmune side effects. New checkpoints (LAG-3, TIM-3) and combinations with other treatment modalities are being investigated [23]. Today, checkpoint inhibitors (PD-1, PD-L1, CTLA-4) enable long-term survival in many patients with melanoma, lung cancer, kidney cancer and other tumors.

2. mRNA vaccines (Nobel 2023)

For the first time in history, a vaccine does not require the cultivation of viruses or bacteria. The genetic information for producing the protective antigen is sufficient. This has opened the possibility of developing vaccines against malignant diseases, HIV and numerous infections.

Traditional vaccines required the cultivation of viruses or bacteria under laboratory conditions — a lengthy, expensive and technically demanding process. Even after identification of the pathogen, it took weeks or months to produce a sufficient amount of attenuated or inactivated virus. The mRNA approach changed this completely: instead of producing the antigen itself in the laboratory, it is enough to know the genetic sequence that encodes the protective protein, and the patient's body becomes a "factory" that produces that protein and triggers an immune response [24,25].

The key scientific breakthrough occurred in 2005, when Katalin Karikó and Drew Weissman discovered how to modify mRNA so that it does not cause an undesirable immune reaction. Namely, the synthetic mRNA that scientists produced in the laboratory was recognized by innate immune receptors (Toll-like receptors) as a foreign body, which caused a strong inflammatory reaction and degradation of the mRNA before it could reach the ribosomes. Karikó and Weissman showed that replacing uridine — one of the four basic nucleotides — with pseudouridine (its isomer) dramatically reduces immunogenicity and at the same time increases the translational efficiency of mRNA [26].

This discovery enabled the development of mRNA vaccines against COVID-19 in record time. Unlike traditional vaccines, mRNA vaccines do not require the cultivation of the virus; the genetic information is sufficient. The Pfizer-BioNTech and Moderna vaccines showed an efficacy of about 95% in preventing symptomatic COVID-19 disease, including in older people, who usually respond less well to vaccines [25]. This technology is extremely flexible: when a new variant of the virus appears, the mRNA sequence can be quickly adapted. The same principle opens the possibility of developing vaccines against HIV, Zika virus and influenza, as well as therapeutic vaccines against malignant diseases — for example, against melanoma, where mRNA can be programmed to encode neoantigens specific to the patient's tumor [24,27].

3. Genomics and molecular medicine

From the discovery of the structure of DNA in 1953 (Nobel 1962) to the present day, genomics has traveled the path from fundamental research to routine clinical

application. The Human Genome Project, completed at the beginning of the 21st century, was a turning point: for the first time, the complete sequence of the human genome was read. Today, genome sequencing is no longer a special event — it is becoming a ubiquitous resource in medicine. Whole-genome sequencing (WGS) has been recognized as a priority diagnostic method for detecting rare genetic diseases, because it enables analysis of the non-coding parts of the genome, which make up about 98,5% of our DNA and contain regulatory elements key to controlling gene expression [28,29]. In oncology, this has led to a paradigm shift: tumors are today classified not only according to the organ of origin, but according to molecular mutations. Next-generation sequencing (NGS) enables simultaneous analysis of a multitude of genes from a limited amount of sample, **identifying "driver" mutations** that drive tumor growth, translocations, amplifications and other genetic changes [30]. For example, lung cancer is routinely tested for EGFR, ALK, ROS1 and other mutations, because each of them has a corresponding targeted therapy. **Personalized cancer vaccines are designed on the basis of the unique mutations of the patient's tumor**, and liquid biopsy (analysis of circulating tumor DNA from the blood) enables early detection of recurrence [28].

Genomics also enables pharmacogenomics — adjusting the dose and choice of drugs on the basis of the genetic profile of the patient. This reduces side effects and increases the efficacy of therapy, especially in pediatrics and oncology [29]. However, challenges remain: the reference genome is incomplete and does not represent the genetic diversity of humankind well enough, which is why the concept of a "pangenome" is being developed that would encompass both copies of the chromosomes and variations within populations [28]. Interpreting the enormous amount of data also requires sophisticated bioinformatic tools and multidisciplinary teams.

4. Regenerative medicine

Until 2006, the dominant view in biology was that cell differentiation is an irreversible process — that a mature, specialized cell cannot return to the stem cell state. Shinya Yamanaka called this dogma into question. Yamanaka's induced pluripotent STEM cells made it possible to return mature cells to an

embryonic state, opening the possibility of regenerating tissues and organs.

His team showed that mature, differentiated cells can be reprogrammed into a pluripotent state by simply introducing only four transcription factors (known as the Yamanaka factors: Oct4, Sox2, Klf4 and c-Myc). The cells created in this way were named induced pluripotent stem cells (iPS cells) [31,32].

This discovery revolutionized the understanding of development and opened the door to regenerative medicine. iPS cells have two key properties: they can divide indefinitely and they can differentiate into any cell type in the body — neurons, cardiomyocytes, hepatocytes, pancreatic cells. Unlike embryonic stem cells, iPS cells can be created from the patient's own cells (e.g. from skin or blood), thereby avoiding ethical issues and the risk of immunological rejection. In 2012, Yamanaka received the Nobel Prize for this discovery, together with John Gurdon, whose pioneering nuclear transfer experiments in frogs decades earlier had laid the foundations [33,31].

The clinical potential of iPS cells is enormous. They can be used for disease modeling in the laboratory (e.g. creating neurons from patients with ALS or Parkinson's disease), for drug screening, and — most ambitiously — for the regeneration of damaged tissues and organs. The first clinical studies have already been conducted: transplantation of iPS-derived retinal cells in macular degeneration, and research for heart disease, type 1 diabetes and spinal cord injuries [33]. **However, challenges remain: the risk of tumor (teratoma) formation if remaining undifferentiated iPS cells are transplanted,** the efficiency of reprogramming, and long-term safety. Nevertheless, iPS technology has already changed the way we think about cellular plasticity and has opened the way to personalized regenerative medicine.

5. Precise gene regulation

RNA interference and microRNA have shown that genes are not just “switched on or off”, but that there is a complex network regulating their activity. This represents the basis of future gene therapies.

For a long time it was believed that genes are simply “switched on” or “switched off” — that gene expression is regulated primarily at the level of transcription, through transcription factors that bind to DNA. The discovery of RNA

interference (RNAi) in 1998 (Nobel 2006) showed that there is a completely different layer of regulation that acts at the level of the RNA itself, after transcription has already taken place [34]. Andrew Fire and Craig Mello discovered that double-stranded RNA can activate cellular mechanisms that specifically degrade the mRNA that matches it in sequence, thereby “silencing” gene expression before the protein is even formed [34].

MicroRNAs, discovered in 1993 but recognized with the Nobel Prize in 2024, represent an even finer layer of regulation [35]. These small RNA molecules (about 22 nucleotides long) do not degrade mRNA directly, but bind to it and inhibit translation or promote its gradual destruction [35]. One microRNA can regulate hundreds of different mRNAs, creating a complex network of mutual interactions [36]. The human genome encodes more than 1000 microRNAs, and their dysregulation is associated with numerous diseases — from cancer to neurodegenerative disorders [36].

These findings form the basis of future gene therapies. RNAi is already used as a research tool for gene silencing, and the first drugs based on this principle have been approved (e.g. patisiran for hereditary transthyretin amyloidosis) [37]. MicroRNAs are being investigated as therapeutic targets: inhibition of oncogenic microRNAs or the addition of tumor-suppressor microRNAs could become a new strategy for treating cancer [36]. The key challenge remains the delivery of these molecules to target cells in vivo, as well as avoiding off-target effects [37]. Nevertheless, the understanding that genes are not binary switches, but exist in a complex network of regulation, fundamentally changes the way we approach gene therapy and drug development [38].

COMPARATIVE ANALYSIS of the Nobel Prizes in Physiology or Medicine during the 20th and 21st centuries

An analysis of the Nobel Prizes in Physiology or Medicine during the 20th and 21st centuries provides a unique insight into the development of medical science and changes in research priorities over more than a century [1,2]. Viewed through the prism of the awarded discoveries, a transition can clearly be seen from research aimed at identifying the causes of diseases and basic physiological processes toward the study of molecular mechanisms, gene

regulation and an individualized approach to treatment [8].

The first half of the 20th century was marked by discoveries that laid the foundations of modern medicine. The work of Robert Koch, Ronald Ross and Alphonse Laveran enabled an understanding of the etiology and transmission of infectious diseases [1,2], while Landsteiner's discovery of blood groups, Banting's discovery of insulin and Fleming's discovery of penicillin directly changed clinical practice and significantly reduced mortality [10,12,13]. In the same period, key diagnostic methods, such as electrocardiography, emerged, which enabled an objective assessment of organ function and laid the foundations of modern diagnostics [1,2].

The second half of the 20th century represents the era of molecular biology. The discovery of the structure of DNA in 1962 marked the beginning of a new epoch in medicine [19,20]. The following decades brought an understanding of the genetic code, the mechanisms of cell signaling, cholesterol metabolism, receptor function and the regulation of the immune response [1,2]. During this period, medicine moved from the level of organs and tissues to the level of the cell and the molecule. At the same time, advanced diagnostic methods were developed, among which computed tomography represents one of the most important technological revolutions in medicine [1,2].

Unlike in the 20th century, the Nobel Prizes in the 21st century have been predominantly directed toward research on regulatory mechanisms within the cell. Discoveries of apoptosis, RNA interference, telomeres, stem cells, autophagy, microRNA and immune checkpoints have been awarded [34,35,36,40]. The common feature of this research is the study of processes that determine cell behavior, gene expression and the interaction of the organism with disease at the molecular level [8].

A particularly important trend of the 21st century is the development of personalized

medicine. While the therapeutic approaches of the 20th century were mainly based on the principle of "one disease — one drug", modern medicine strives to individualize diagnosis and therapy on the basis of the genetic, molecular and immunological characteristics of each patient [28,29]. Immunotherapy of malignant diseases, awarded the Nobel Prize in 2018, is one of the best examples of this concept, because it enables activation of the immune system against the tumor, with a significant improvement in survival in certain malignancies [21,23,38].

In addition, the Nobel Prize for the development of mRNA technology in 2023 showed how fundamental research can lead to the rapid development of new therapeutic and preventive strategies [24,25,39]. During the COVID-19 pandemic, mRNA vaccines enabled unprecedentedly rapid production of effective vaccines, thereby confirming the practical value of decades of basic research [25,27,39].

Viewed as a whole, the Nobel Prizes of the 20th century were focused on discovering the causes of diseases and developing antibiotics, hormones, vaccines and diagnostic methods, while the Nobel Prizes of the 21st century reflect the transition of medicine toward understanding the molecular and genetic mechanisms of disease [8]. This change marks the transformation of medicine from a predominantly reactive discipline toward predictive, preventive and personalized medicine [28,29].

It can be concluded that the Nobel Prizes represent a kind of history of the development, i.e. the evolution, of biology, especially physiology and medicine (Table 4.). From microorganisms, hormones and antibiotics to the genome, immunotherapy and mRNA technology, the awarded discoveries show how the focus of medicine over the last 125 years has shifted from treating manifest disease toward its early detection, prevention and an individualized therapeutic approach [1,2,8].

Table 4. The development or evolution of medicine through the Nobel Prizes

Characteristic	20th century	21st century
Dominant diseases	Infectious diseases	Chronic non-communicable diseases and malignancies
Level of research	Organ and tissue	Cell, genome and molecule
Main discoveries	Insulin, penicillin, ECG, DNA	Immunotherapy, mRNA, microRNA, stem cells
Goal of therapy	Treatment of disease	Prediction, prevention and personalization
Concept of medicine	"One drug for many"	"The right drug for the right patient"
Dominant technology	Microbiology and biochemistry	Genomics, bioinformatics and artificial intelligence

Through this table we see that the Nobel Prizes are a kind of mirror of the development of medicine from 1901 to the present day.

DISCUSSION

The Nobel Prize is awarded for a fundamental scientific mechanism in diagnostics and therapy, and not for the development of diagnostic and therapeutic methods and techniques or the development of new drugs. For example, in 2023 the prize was not awarded for a particular vaccine against COVID-19, but for the discoveries that enabled the development of mRNA vaccines.

However, in the discussion we would like to emphasize our view that there are several oversights by the Nobel Committee with regard to new modalities of ultrasound, MDCT scanner, PET scan and magnetic resonance diagnostics, as well as revolutionary innovative surgical techniques and new revolutionary inventive drugs and therapies. Although these methods have saved or improved the quality of life of millions of patients, the Nobel Committee has traditionally rewarded fundamental biological discoveries much more often than the development of diagnostics, pharmacological therapy and surgical techniques.

Table 5. The most important pioneers of ultrasound diagnostics and the Nobel Prizes

Field	Pioneers	Nobel Prize
Echocardiography (1953)	Inge Edler and Hellmuth Hertz	No
Doppler echocardiography	Shigeo Satomura	No
Pulsed Doppler	Peter Wells, Paul Peronneau, Donald Baker	No
Two-dimensional echocardiography	Bom, Lancée, Roelandt, Kisslo and others	No
Color Doppler	Developed by several research groups during the 1970s and 1980s	No
Three-dimensional echocardiography	Dekker, Roelandt and numerous later researchers	No
Strain / Speckle Tracking	Developed during the 1990s and 2000s by several groups	No

While other revolutionary diagnostic methods in medicine received this prestigious recognition, echocardiography and medical ultrasound remained without a Nobel Prize, despite the fact that they completely changed modern clinical practice [41,42].

Although Inge Edler (a cardiologist) and Hellmuth Hertz (a physicist) successfully applied

Thus, there is a significant difference between a scientific discovery and its clinical translation into everyday medical practice. The Nobel Prize traditionally favors fundamental mechanisms and biological principles, while many achievements of enormous public health importance remain outside its scope. Therefore, the history of medicine cannot be viewed exclusively through the Nobel Prizes, but also through an assessment of the real impact of individual therapies on survival, quality of life and the reduction of the burden of disease in the general population.

ULTRASOUND DIAGNOSTICS. None of the key pioneers of medical ultrasound, echocardiography, Doppler, color Doppler, three-dimensional echocardiography and speckle-tracking (strain) echocardiography, or of ultrasound-guided therapeutic interventions, received the Nobel Prize in Physiology or Medicine, or in Physics, for these achievements [41,42]. In fact, ultrasound diagnostics is one of the most important medical technologies that has never been awarded a Nobel Prize [41] (Table 5).

ultrasound to examine cardiac structures as early as 1953 at Lund University, and Shigeo Satomura soon afterwards developed the Doppler technique for analyzing blood flow, the Nobel Committee never awarded them [41]. The two of them (Inge Edler and Hellmuth Hertz) received the prestigious Lasker Award in 1977, which is often called the “American Nobel Prize for medicine” [41].

Table 6. Comparison with other major imaging methods that were awarded the Nobel Prize in Physiology or Medicine (or Physics)

Diagnostic method	Laureates	Year of award	Contribution
X-radiation (X-rays)	Wilhelm Conrad Röntgen	1901. (Physics)	Discovery of X-rays, which enabled the first insight into the interior of the human body.
Electrocardiography (ECG)	Willem Einthoven	1924.	Invention of the ECG apparatus and recording of the electrical activity of the heart.
Computed tomography (CT)	Allan Cormack and Godfrey Hounsfield	1979.	Development of computer-assisted tomography for three-dimensional imaging of tissues.
Magnetic resonance imaging (MRI)	Paul Lauterbur and Peter Mansfield	2003.	Discoveries concerning the visualization of structures by means of magnetic resonance.

Historians of medicine cite several reasons why a Nobel Prize was never awarded for ultrasound: the gradual evolution of the technology, the focus on clinical application, and the fact that ultrasound diagnostics is not the work of one person but of a large number of physicists, engineers and physicians over several decades, so it was difficult to designate one or at most three laureates, as the Nobel rules require [41,42]. Gradual evolution of the technology — medical ultrasound developed step by step, through the adaptation of existing industrial and military technology (such as sonar for detecting submarines), so it may have been difficult for the Committee to single out one or two individuals who made a definitive scientific breakthrough [41]. Focus on clinical application — the Nobel Prize in Physiology or Medicine often favors fundamental, basic scientific discoveries (such as genetics, immunology or cell biology) over engineering and technological achievements in medical practice [41,42].

Nevertheless, in medical circles the absence of this prize for ultrasound is considered one of the greatest oversights in the history of the Nobel Committee, given that it is the most accessible, completely safe (non-ionizing) and today irreplaceable method for examining the heart and the whole body [41].

The most important pioneers of medical ultrasound who did not receive the Nobel Prize

1. Karl Theodor Dussik (Austria) - He is considered one of the first researchers to attempt to use ultrasound to image the human body. As early as 1942, he used ultrasonic waves in an attempt to diagnose brain tumors with a method he called "hyperphonography".
2. George Ludwig (USA) - He was the first to show that ultrasound can be used to detect gallstones and other structures in tissues. His work from the late 1940s is considered the first practical medical application of ultrasound.
3. John J. Wild (1914–2009) - Often called "**the father of medical ultrasound**". He was the first to use ultrasound to distinguish normal from tumor tissue, especially in the breast and the gastrointestinal tract. He developed the first ultrasound images of breast tumors and participated in the development of transrectal and transvaginal probes.
4. John Reid - An engineer who, together with Wild, constructed the first practical ultrasound devices for imaging breast tumors. He later also

participated in the development of Doppler technology.

5. Douglas Howry (1920–1969) - A radiologist who developed B-mode ultrasound imaging and produced the first high-quality two-dimensional cross-sectional images of the human body. He is considered one of the founders of modern abdominal ultrasonography.

6. Joseph Holmes - Together with Howry, he developed the first 2D B-mode scanners and laid the foundations of modern imaging of the abdominal organs.

7. Ian Donald (1910–1987) - Known as "**the father of obstetric and gynecological ultrasound**". His work enabled the routine use of ultrasound in pregnancy and in the diagnosis of abdominal masses and gynecological diseases. In 1958, he published a famous paper on the use of ultrasound in the diagnosis of abdominal tumors and cysts.

8. Tom Brown - An engineer who, with Ian Donald, developed the first practical contact B-mode scanners, without the need to immerse the patient in water.

Scientists working on the Doppler effect found themselves in a similar situation. The Doppler effect was described by the Austrian physicist Christian Doppler as early as 1842. He did not receive the Nobel Prize because he died long before the Nobel Prizes were established (1901). The 1919 Nobel Prize in Physics was not awarded to Doppler, but to Johannes Stark for experimental research on the Doppler effect in canal rays and for the Stark effect [1,2].

Revolutionary surgical techniques and operations

It is also a great oversight in the awarding of the Nobel Prize, in our opinion and in the opinion of many historians of medicine, that the innovative surgeons who revolutionized operative medicine in the second half of the 20th century and in the 21st century did not receive the Nobel Prize, although their methods changed everyday surgical practice more than many Nobel-awarded discoveries. Outside transplant surgery, very few surgeons have received the Nobel Prize for the development of operative techniques: Alexis Carrel – Nobel Prize in Medicine 1912 for vascular suturing and transplant surgery; Joseph Murray – Nobel 1990 for organ transplantation.

However, no Nobel Prize has been awarded for laparoscopy, minimally invasive surgery, video surgery, endoscopic surgery,

arthroscopy, robotic surgery or modern oncological operations, despite the fact that their revolution in surgery has permanently changed almost all surgical disciplines and has become the standard of modern operative medicine [43,44].

Pioneers of laparoscopy who did not receive the Nobel Prize:

1. Kurt Semm (1927–2003) - Most often considered one of the most important figures in the history of minimally invasive surgery: first laparoscopic appendectomy (1980), developed the electronic CO₂; developed numerous laparoscopic instruments; developed training simulators for laparoscopic training. His work was initially ridiculed, and later became the basis of modern laparoscopic surgery.

2. Erich Mühe (1938–2005) - Performed the first laparoscopic cholecystectomy in 1985 in Germany. Initially he was not recognized by the surgical community, and his pioneering work was officially recognized only many years later.

3. Philippe Mouret (1942–2008) - A French surgeon who in 1987 popularized laparoscopic cholecystectomy and launched the worldwide "laparoscopic revolution".

4. Camran Nezhat - One of the pioneers of video laparoscopy. His idea of performing the operation while watching a monitor instead of looking directly through the optics represented a turning point that enabled the development of modern laparoscopic surgery.

Many of these surgeons received the highest professional recognitions: the SAGES Pioneer in Endoscopy Award, the Jacobaeus Award, the Semm Award, honorary memberships of the world's leading surgical societies, medals of the American College of Surgeons (ACS), and European and world awards for minimally invasive surgery. Toward the end of his life, Kurt Semm received the "**Pioneer in Endoscopy**" recognition, which is considered one of the highest recognitions in the field of endoscopic surgery. Nor did the pioneers of the following fields receive the Nobel Prize: arthroscopy (Masaki Watanabe); modern colorectal total mesorectal excision (Bill Heald); laparoscopic hernioplasty; video-assisted thoracoscopic surgery (VATS); endovascular surgery; robotic surgery (the da Vinci era).

Although these methods have saved or improved the quality of life of millions of patients, the Nobel Committee has traditionally rewarded fundamental biological discoveries

much more often than the development of surgical techniques [43,44].

Revolutionary innovative drugs

Many inventors of drugs in the 20th and 21st centuries did receive the Nobel Prize, but most often not for the drug itself as a product, but for the discovery of the biological mechanism or principle on which the drug is based. The Nobel Committee has traditionally valued **a fundamental discovery** more than the development of an individual preparation. In Nobel's will, the key terms are "the most important discovery" and "the greatest benefit to humankind".

Drugs and therapies that brought the Nobel Prize:

Insulin - Banting and Macleod (1923).

Penicillin - Fleming, Chain and Florey (1945).

Sulfonamides (Prontosil) - Gerhard Domagk (1939).

Streptomycin (the first effective drug against tuberculosis) - Selman Waksman (1952).

Corticosteroids - Hench, Kendall and Reichstein (1950).

Beta-blockers and H₂ antagonists - James Black (1988).

Rational drug design - Gertrude Elion and George Hitchings (1988), whose work led to numerous drugs (azathioprine, allopurinol, acyclovir and others).

Aspirin, prostaglandins and mechanisms of action - John Vane (1982).

Cancer immunotherapy (checkpoint inhibitors) - James Allison and Tasuku Honjo (2018).

mRNA vaccines - Katalin Karikó and Drew Weissman (2023).

Why, then, did many great drug inventors not receive the Nobel Prize?

The first reason: the Nobel is awarded for a discovery, not for the development of a product. For example, the development of statins, ACE inhibitors or ARB drugs involved dozens of research groups, companies and clinical trials. It is difficult to single out at most three people, and the Nobel can be shared among at most three laureates. **The second reason** is that many drugs are created through teamwork. In the 21st century, the development of a new drug often involves hundreds of researchers, pharmacologists, biochemists and clinicians. The Nobel system was created at the beginning of the 20th century, when discoveries were more often linked to individuals. **The third reason** is the long-term testing and monitoring of drug effects,

and decades are needed to confirm the importance of the effects and adverse effects of drugs, so the Nobel Committee often waits 20–40 years to see whether a discovery has really changed medicine. Because of this, many researchers die before they could be awarded, and the Nobel is generally not awarded posthumously. An important fact is that the Nobel Prize is awarded for the fundamental scientific mechanism of action of a drug and not for the development of the drug. For example, in 2023 the prize was not awarded for a particular vaccine against COVID-19, but for the discoveries that enabled the development of mRNA vaccines.

Many cardiologists consider the discovery of statins to be among the greatest achievements of modern medicine, comparable in impact to insulin. The Japanese biochemist Akira Endo discovered the first HMG-CoA reductase inhibitor, but never received the Nobel Prize. However, he received numerous other prestigious international awards.

SGLT2 inhibitors (empagliflozin, dapagliflozin, canagliflozin and others) represent one of the greatest therapeutic revolutions of the last 20 years. They were originally developed as antidiabetic drugs, and it was then shown that they reduce hospitalizations for heart failure, slow the progression of chronic kidney disease and reduce cardiovascular risk even in patients without diabetes. Interestingly, however, it is still not fully clarified even today which is the dominant mechanism of their cardioprotective and nephroprotective action.

GLP-1 receptor agonists (liraglutide, semaglutide, dulaglutide and others) also have a strong case for the Nobel Prize. This group of drugs has changed the treatment of: type 2 diabetes, obesity, cardiovascular risk in obese persons. However, it is more likely that Nobel recognition, if it comes, would be linked to: the discovery of the incretin system, the biology of the GLP-1 receptor, new knowledge about the regulation of appetite and body weight,

The list of the greatest therapeutic discoveries of the 20th and 21st centuries by impact on mortality comprises: Insulin, Antibiotics (penicillin and later antibiotics), Vaccines, statins, diuretics and antihypertensive therapy, corticosteroids, antiplatelet and anticoagulant therapy, Antiretroviral therapy for HIV, Immunotherapy of malignant diseases SGLT

inhibitors and GLT agonists. However, only some of these achievements have been awarded the Nobel Prize, because the Nobel primarily rewards **the discovery of a scientific principle**, and not necessarily the therapy that later had the greatest clinical effect.

Great medical achievements without a Nobel Prize

The history of medicine shows that the Nobel Prize, despite its enormous importance, has not encompassed all the achievements that have fundamentally changed the course of modern clinical practice. The reason for this lies in the fact that the Nobel Prize is most often awarded for fundamental scientific discoveries, while many revolutionary achievements arise as the result of the long-term work of large research teams, decades of technological development and the gradual improvement of existing methods. [53,54]. One of the most important examples is statins. The discovery of the first HMG-CoA reductase inhibitor by the Japanese biochemist Akira Endo opened a new era in the prevention and treatment of atherosclerotic cardiovascular disease. Over the last few decades, statins have contributed to a significant reduction in the incidence of myocardial infarction, stroke and cardiovascular mortality worldwide. However, the Nobel Prize was not awarded for the discovery of statins as such; instead, Brown and Goldstein were awarded for fundamental discoveries of the mechanisms regulating cholesterol metabolism, which enabled the development of modern lipid-lowering therapy [50,54].

A similar example is angiotensin-converting enzyme inhibitors (ACE inhibitors). The work of David Cushman and Miguel Ondetti led to the development of captopril, the first ACE inhibitor, which started a new era in the treatment of arterial hypertension, heart failure and diabetic nephropathy. Despite its enormous impact on reducing morbidity and mortality, this achievement was not awarded the Nobel Prize.

Beta-blockers represent an interesting exception. Although the Nobel Prize was not awarded for propranolol itself, rather James Black was awarded in 1988 for discovering the basic principles of rational drug development that led to the creation of beta-blockers and H2 antagonists. In this way, the Nobel Committee rewarded a scientific concept rather than an individual drug [49,54].

The development of heart transplantation represents another achievement that fundamentally changed medicine. After the first successful heart transplant performed by Christiaan Barnard in 1967, transplant surgery became a standard therapeutic option for end-stage heart failure. However, the Nobel Prize was never awarded for this achievement, partly due to the fact that numerous researchers and surgeons contributed to the development of transplant medicine, including Norman Shumway, Richard Lower and many others.

Coronary revascularization represents one of the greatest therapeutic successes of cardiovascular medicine. The development of coronary artery bypass grafting (CABG), associated with René Favaloro, enabled effective surgical treatment of coronary heart disease. Later, Andreas Grüntzig developed percutaneous transluminal coronary angioplasty (PCI), which marked the beginning of modern interventional cardiology, particularly refined with the development of coronary STENT technology. Both methods have significantly extended the lifespan of millions of patients, but their creators did not receive the Nobel Prize. *sv.*

The first Stents were **self-expanding Wallstent** systems. In 1986 the first coronary stent in humans was developed by **Ulrich Sigwart and Jacques Puel**. The first Wallstent implantations were performed in **Lausanne (Switzerland) and Toulouse (France)**. **Jacques Puel** was the first to implant a Wallstent in a coronary artery in **Toulouse**, while **Ulrich Sigwart** was simultaneously performing the first implantations in **Lausanne**. Their stent was a **self-expanding mesh metal prosthesis**, unlike the later balloon-expandable stents. **Julio Palmaz**, together with **Richard Schatz**, developed one of the most important early **balloon-expandable coronary stents - the Palmaz-Schatz stent**. The concept originated in the late 1970s, and clinical development took place during the 1980s. The first **Palmaz-Schatz stent in a coronary artery** was implanted **in 1987 in São Paulo, Brazil**, by a team consisting of **Julio Palmaz, Richard Schatz and Eduardo Sousa**. However, even earlier in 1987, the first implantations of other balloon-expandable stents were performed.

Similarly, the implantable cardioverter-defibrillator (ICD), developed by Michel Mirowski, enabled the prevention of sudden cardiac death in high-risk patients and

represents one of the most important achievements of modern arrhythmology. The first successful implantable cardioverter-defibrillator in a human was implanted on 4 February 1980 at Johns Hopkins Hospital in Baltimore, USA. The device was developed by the cardiologist **Michel Mirowski**, together with Morton Mower and colleagues. The first implantation was performed by the cardiac surgeon **Levi Watkins Jr.** Despite its enormous clinical importance, this discovery was not awarded the Nobel Prize.

A special example is in vitro fertilization (IVF). For the development of this method, Robert Edwards received the Nobel Prize in 2010, after his method had enabled the birth of millions of children around the world and opened a completely new chapter in reproductive medicine. This example shows that the Nobel Committee occasionally also rewards clinical innovations when their importance becomes indisputable and confirmed in the long term [54]. During the last decades, antiretroviral therapy for HIV infection has also gained great importance. Although Françoise Barré-Sinoussi and Luc Montagnier received the Nobel Prize for the discovery of HIV in 2008, the development of modern combined antiretroviral therapy, which turned HIV infection from a fatal into a chronic disease, was not the subject of Nobel recognition [54].

An analysis of these examples shows that there is a significant difference between a scientific discovery and its clinical translation into everyday medical practice. The Nobel Prize traditionally favors fundamental mechanisms and biological principles, while many achievements of enormous public health importance remain outside its scope. Therefore, the history of medicine cannot be viewed exclusively through the Nobel Prizes, but also through an assessment of the real impact of individual therapies on survival, quality of life and the reduction of the burden of disease in the general population [49,50,51,53,54].

From the perspective of the history of medicine, among the modern therapies that have the potential to one day be associated with the Nobel Prize because of their impact on mortality and morbidity, the following are often cited:

- SGLT2 inhibitors and their cardiorenal mechanisms.
- GLP-1 receptor agonists and the regulation of metabolism/obesity.

- Immunotherapy of malignant diseases (already awarded in 2018).
- mRNA platforms (already awarded in 2023).
- CRISPR gene therapy (Nobel Prize in Chemistry 2020, but medical applications are yet to come).

If the long-term effects of SGLT2 inhibitors on the heart and kidneys prove comparable to the historical impact of statins or ACE inhibitors, this group of drugs could represent one of the greatest therapeutic achievements of the beginning of the 21st century, regardless of whether their creators ever receive the Nobel Prize - **they represent a potential area of future Nobel-awarded discoveries**. The current literature particularly emphasizes that the mechanisms of cardiorenal protection of SGLT2 inhibitors have not yet been fully clarified.

SGLT2 inhibitors and GLP-1 receptor agonists – potential candidates for future Nobel recognition

SGLT2 inhibitors represent one of the most important pharmacotherapeutic achievements of the beginning of the 21st century. Although they were originally developed as drugs for lowering blood glucose concentration in patients with type 2 diabetes mellitus, large randomized clinical trials have shown that their benefit goes far beyond glycemic control. This group of drugs reduces the risk of hospitalization for heart failure and slows the progression of chronic kidney disease, and certain effects are also seen in patients without diabetes [55–58]. It is particularly important that the results of the EMPA-REG OUTCOME study with empagliflozin showed a reduction in cardiovascular and total mortality, as well as in hospitalizations for heart failure, in patients with type 2 diabetes and high cardiovascular risk. These results were unexpected, because the benefit was considerably greater than could be explained by improved glycemic control alone [55]. Further research showed that SGLT2 inhibitors provide cardiorenal protection independently of the presence of diabetes. In the DAPA-HF and DAPA-CKD studies and other large randomized trials, their benefit was confirmed in patients with heart failure and chronic kidney disease, including populations without diabetes [56–58].

The mechanism by which SGLT2 inhibitors achieve such broad effects has not yet

been fully clarified. Increased natriuresis and osmotic diuresis, a reduction in intravascular volume and arterial blood pressure, restoration of tubuloglomerular feedback and a reduction in intraglomerular pressure are considered important. In addition, effects on the energy efficiency of the myocardium and kidneys, tissue oxygenation, metabolism of energy substrates, inflammation and cardiac remodeling have been proposed [55,59,60].

Precisely the fact that a single group of drugs shows simultaneous metabolic, cardiac and renal effects represents a particularly interesting scientific problem. Current data indicate that their action cannot be reduced merely to the inhibition of glucose reabsorption in the proximal tubule, but that there is a complex interaction between the kidneys, heart, metabolism and neurohumoral mechanisms [59–61].

Therefore, any future Nobel recognition would more likely be associated with the discovery of a fundamental mechanism explaining the broad cardiorenal effects of SGLT2 inhibition than with the development of an individual drug itself, such as empagliflozin or dapagliflozin. Such a scenario would be consistent with the traditional pattern of the Nobel Prize, which is primarily awarded for fundamental discoveries and new biological principles, and not for the commercial development of an individual pharmaceutical product.

The second great therapeutic revolution of the beginning of the 21st century is associated with GLP-1 receptor agonists. Understanding the incretin system and the physiological role of GLP-1 enabled the development of drugs that simultaneously affect insulin secretion, glucagon, gastric emptying, food intake and the regulation of body weight [62]. GLP-1 receptor agonists, including liraglutide, dulaglutide and semaglutide, were first developed for the treatment of type 2 diabetes, but their use expanded significantly after evidence of a pronounced effect on body weight and cardiovascular outcomes. The development of this therapeutic group is an example of how fundamental research on hormone physiology can lead to a completely new class of drugs [62,63]. Of particular importance are the results of the SELECT study, in which semaglutide reduced the incidence of major cardiovascular events compared with placebo in overweight or

obese persons without diabetes. These results further extended the importance of GLP-1 receptor agonists beyond the traditional treatment of diabetes and pointed to the possibility that pharmacological control of body weight is an important component of cardiovascular prevention [63,64]. Therefore, the GLP-1 system can be viewed as another potentially important candidate for a future fundamental discovery that could be recognized with the highest scientific honors. However, any Nobel Prize would more likely be linked to a new fundamental understanding of the regulation of metabolism, appetite, energy homeostasis and the action of the GLP-1 receptor than to semaglutide itself or any other individual drug. SGLT2 inhibitors and GLP-1 receptor agonists thus represent an interesting example of modern medicine in which the boundary between diabetology, cardiology, nephrology and metabolic medicine is increasingly blurred. Their clinical importance has already been confirmed by large randomized studies, while the fundamental mechanisms of their pleiotropic effects remain the subject of intensive research [55–64].

If future research identifies a fundamental biological mechanism that explains the broad spectrum of metabolic, cardiovascular and renal effects of these therapeutic groups, it is precisely such a discovery, and not the drug itself, that could form the basis for one of the future great recognitions in the field of physiology or medicine.

CONCLUSION

Viewed from the perspective of modern medicine, the most influential therapeutic achievements of the 20th and early 21st centuries by impact on mortality include antibiotics, insulin, vaccines, corticosteroids, organ transplantation, statins, antihypertensive drugs, coronary revascularization, ICD therapy, antiretroviral drugs, immunotherapy of malignant diseases, Immunotherapy of malignant diseases with checkpoint inhibitors, sodium-glucose cotransporter type 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, mRNA vaccines and siRNA directed at the degradation of PCSK9 mRNA - gene therapy . However, only some of these achievements have been awarded the Nobel Prize, because the Nobel primarily rewards **the discovery of a scientific principle**, and not

necessarily the therapy that later had the greatest clinical effect, which confirms that the importance of an individual medical discovery need not always be proportional to its Nobel recognition [45–54].

If the 20th century saved millions of people thanks to insulin, antibiotics, blood transfusion, the ECG and transplantation, the 21st century strives to provide each patient with therapy based on their genome, immunological profile and the molecular characteristics of the disease [1,2,8].

The 20th century discovered the causes of diseases. The 21st century is learning how to treat them precisely, in a targeted and individualized way [8,28,29].

The key differences between the 20th and 21st centuries are:

- *Focus on basic mechanisms:* While discoveries in the 20th century were often directed at specific diseases and their causes (e.g. penicillin, poliovirus), the 21st century is increasingly focused on understanding the basic biological mechanisms underlying health and disease [8].
- *Genetics and molecular biology:* The 21st century has brought a revolution in genetics. Discoveries such as RNA interference (2006) and the role of genes in the development of cells and diseases (e.g. the discovery of FOXP3 gene mutations that lead to autoimmune diseases) represent enormous progress compared with earlier understandings of genetics [34,35,36].
- *Immunology and therapy:* The understanding of the immune system has significantly advanced. The discovery of regulatory T cells and peripheral immune tolerance (2025) is key to understanding autoimmune diseases and developing new therapies [40]. Also, the discovery of HIV (2008) and the development of mRNA vaccines (2023) are examples of the direct application of this knowledge in medicine [24,25,39].
- *Technological progress:* The development of new technologies has enabled scientists to investigate things that were previously unimaginable. An example is the sequencing of

Neanderthal DNA (2022), which opened a completely new field in the study of

human evolution [41].

REFERENCES:

- Nobel Foundation. Nobel Prize Facts [Internet]. Stockholm: Nobel Prize Outreach AB; 2025 [cited 2026 Sep 11]. Available from: <https://www.nobelprize.org>
- Nobel Prize Outreach AB. All Nobel Prizes in Physiology or Medicine [Internet]. Stockholm: Nobel Prize Outreach AB; 2025 [cited 2026 Sep 11]. Available from: <https://www.nobelprize.org/prizes/medicine>
- Nobel Prize Outreach AB. Alfred Nobel [Internet]. Stockholm: Nobel Prize Outreach AB; 2025 [cited 2026 Sep 11]. Available from: <https://beta.nobelprize.org/alfred-nobel/>
- Skole.hr. Nobelova nagrada [Internet]. Zagreb; 2025 [cited 2026 Sep 11]. Available from: <https://www.skole.hr/nobelova-nagrada/>
- Nobel Prize Outreach AB. The Nobel Prize Award Ceremonies and Banquets [Internet]. Stockholm: Nobel Prize Outreach AB; 2025 [cited 2026 Sep 11]. Available from: <https://www.nobelprize.org/ceremonies/the-nobel-prize-award-ceremonies-and-banquets/>
- Nobel Prize Outreach AB. From the First Nobel Prize Award Ceremony, 1901 [Internet]. Stockholm: Nobel Prize Outreach AB; 2025 [cited 2026 Sep 11]. Available from: <https://www.nobelprize.org/ceremonies/from-the-first-nobel-prize-award-ceremony-1901/>
- Nobel Prize Outreach AB. The Future of Health [Internet]. Stockholm: Nobel Prize Outreach AB; 2025 [cited 2026 Sep 11]. Available from: <https://www.nobelprize.org/stories/article-future-of-health/>
- PMC7927541. The Nobel Prize in Physiology or Medicine: A Century of Discovery [Internet]. 2021 [cited 2026 Sep 11]. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC7927541/>
- Europe PMC. The Nobel Prize in Physiology or Medicine: A Century of Discovery [PDF]. 2021 [cited 2026 Sep 11]. Available from: <https://dev.europepmc.org/backend/ptpmcrender.fcgi?accid=PMC7927541&blobtype=pdf>
- BVS Brasil. Discovery of Insulin [Internet]. 2021 [cited 2026 Sep 11]. Available from: <https://pesquisa.bvsalud.org/brasil/resource/pt/mdl-33393501>
- OUCI. History of Diabetes Mellitus [Internet]. 2021 [cited 2026 Sep 11]. Available from: <https://ouci.dntb.gov.ua/en/works/4rN1rKY4/>
- American Journal of Physiology-Endocrinology and Metabolism. The Discovery of Insulin [Internet]. 2020 [cited 2026 Sep 11]. Available from: <https://journals.physiology.org/doi/full/10.1152/ajpen.00496.2020>
- PubMed. The History of Penicillin [Internet]. 2004 [cited 2026 Sep 11]. Available from: <https://pubmed.ncbi.nlm.nih.gov/15185195/>
- JAMA. The Discovery of Penicillin [Internet]. 2018 [cited 2026 Sep 11]. Available from: <https://jamanetwork.com/journals/jama/article-abstract/270514>
- CDC. The Secret Production of Penicillin During WWII [Internet]. 2017 [cited 2026 Sep 11]. Available from: https://wwwnc.cdc.gov/eid/article/23/5/16-1556_article
- Britannica. Nobel Prize in Physiology or Medicine [Internet]. 2025 [cited 2026 Sep 11]. Available from: <https://www.britannica.com/topic/Nobel-Prize/Physiology-or-Medicine>
- Britannica. Winners of the Nobel Prize for Physiology or Medicine [Internet]. 2025 [cited 2026 Sep 11]. Available from: <https://www.britannica.com/science/Winners-of-the-Nobel-Prize-for-Physiology-or-Medicine-1856944>
- TMGL. The Discovery of DNA Structure [Internet]. 2021 [cited 2026 Sep 11]. Available from: <https://busqueda.tmg.org/portal/resource/pt/biblio-1584005>
- IUPAC. The Double Helix: A Personal View [Internet]. 2012 [cited 2026 Sep 11]. Available from: <http://www.list.iupac.org/publications/ci/2012/3405/si.html>
- PMC10599781. DNA Structure and Function [Internet]. 2023 [cited 2026 Sep 11]. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10599781/>
- C&EN. Cancer Immunotherapy Pioneers Win 2018 Nobel Prize [Internet]. 2018 [cited 2026 Sep 11]. Available from: <https://cen.acs.org/biological-chemistry/cancer/Cancer-immunotherapy-pioneers-win-2018-Nobel-Prize-in-Physiology/96/web/2018/10>
- AIP. Two Share 2018 Nobel Prize in Physiology or Medicine for Cancer Discoveries [Internet]. 2018 [cited 2026 Sep 11]. Available from: <https://www.aip.org/inside-science/two-share-2018-nobel-prize-in-physiology-or-medicine-for-cancer-discoveries>
- PubMed. Immune Checkpoint Blockade in Cancer Therapy [Internet]. 2019 [cited 2026 Sep 11]. Available from: <https://pubmed.ncbi.nlm.nih.gov/31783990/>
- Cedars-Sinai. mRNA Vaccines Explained [Internet]. 2023 [cited 2026 Sep 11]. Available from: <https://www.cedars-sinai.org/stories-and-insights/innovation-and-research/mrna-vaccines-explanation>
- Yale Medicine. Understanding COVID-19: How mRNA Vaccines Work [Internet]. 2023 [cited 2026 Sep 11]. Available from: <https://medicine.yale.edu/media-player/understanding-covid-19-how-mrna-vaccines-work/>
- PMC10758357. Suppression of RNA Recognition by Toll-like Receptors [Internet]. 2023 [cited 2026 Sep 11]. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10758357/>
- Harvard Health. What Are mRNA Vaccines? [Internet]. 2023 [cited 2026 Sep 11]. Available from: <https://www.health.harvard.edu/healthy-aging-and-longevity/what-are-mrna-vaccines>
- Stanford Medicine. How Scientists Are Rethinking Genome Sequencing [Internet]. 2026 [cited 2026 Sep 11]. Available from: <https://med.stanford.edu/news/insights/2026/09/how-scientists-are-rethinking-genome-sequencing-to-bolster-prec.html>
- Liječnički Vjesnik. Pedijatrijski kongres 2023 [PDF]. 2023 [cited 2026 Sep 11]. Available from: https://lijecnicki-vjesnik.hlz.hr/pdf/supplement/supl_Pedijatrijski%20kongres_2023.pdf
- HAZU. Irena Drmić-Hofman [PDF]. 2023 [cited 2026 Sep 11]. Available from: https://www.info.hazu.hr/upload/File/aba/0000000000Irena-Drmic-Hofman_prezentacija.pdf
- Nature. Induced Pluripotent Stem Cells [Internet]. 2013 [cited 2026 Sep 11]. Available from: <https://preview-www.nature.com/articles/nrm3463>
- Nobel Prize Outreach AB. Advanced Information: 2012 Nobel Prize in Physiology or Medicine [Internet]. 2012 [cited 2026 Sep 11]. Available from: <https://www.nobelprize.org/prizes/medicine/2012/advanced-information/>
- NHLBI. Shinya Yamanaka Selected to Receive Nobel Prize [Internet]. 2012 [cited 2026 Sep 11]. Available from: <https://www.nhlbi.nih.gov/directors-messages/shinya-yamanaka-selected-receive-nobel-prize>
- Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature*. 1998;391(6669):806-11.
- Ambros V, Ruvkun G. The 2024 Nobel Prize in Physiology or Medicine: microRNA — a new dimension in gene regulation. *Nobel Prize Outreach AB*; 2024 [cited 11.09.2026]. Available from:

- <https://www.nobelprize.org/prizes/medicine/2024/advance-d-information/>
36. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*. 2004;116(2):281-97.
 37. Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21.
 38. Allison JP. Immune checkpoint blockade in cancer therapy: the 2018 Nobel Prize in Physiology or Medicine. *Nat Rev Cancer*. 2019;19(2):56-8.
 39. Karikó K, Weissman D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the origin of mRNA therapeutics. *Immunity*. 2023;56(6):1185-98.
 40. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N. Regulatory T cells and human disease. *Annu Rev Immunol*. 2020;38:541-66.
 41. Edler I, Hertz CH. The use of ultrasonic reflectoscope for the continuous recording of movements of heart walls. *Kungl Fysiogr Sällsk Lund Förh*. 1954;24(5):40-58.
 42. Feigenbaum H. Evolution of echocardiography. *Circulation*. 1996;93(7):1321-7.
 43. Semm K. Endoscopic appendectomy. *Endoscopy*. 1983;15(2):59-64.
 44. Nezhat C, Nezhat F, Nezhat C. Operative laparoscopy (minimally invasive surgery): state of the art. *J Gynecol Surg*. 1992;8(3):111-41.
 45. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 1923 – Frederick G. Banting and John Macleod for the discovery of insulin. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/medicine/1923/summary/>
 46. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 1945 – Alexander Fleming, Ernst B. Chain and Howard W. Florey for the discovery of penicillin and its curative effect in various infectious diseases. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/medicine/1945/summary/>
 47. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 1950 – Edward C. Kendall, Tadeus Reichstein and Philip S. Hench for discoveries relating to the hormones of the adrenal cortex. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/medicine/1950/summary/>
 48. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 1952 – Selman A. Waksman for the discovery of streptomycin. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/medicine/1952/summary/>
 49. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 1988 – Sir James W. Black, Gertrude B. Elion and George H. Hitchings for discoveries of important principles for drug treatment. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/medicine/1988/summary/>
 50. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 1985 – Michael S. Brown and Joseph L. Goldstein for discoveries concerning the regulation of cholesterol metabolism. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/medicine/1985/summary/>
 51. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 2018 – James P. Allison and Tasuku Honjo for discovery of cancer therapy by inhibition of negative immune regulation. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/medicine/2018/summary/>
 52. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 2023 – Katalin Karikó and Drew Weissman for discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/medicine/2023/summary/>
 53. Nobel Prize Outreach. The Nobel Prize in Physiology or Medicine 1901–2000. Stockholm: Nobel Prize Outreach; 2000. Available from: <https://www.nobelprize.org/prizes/themes/the-nobel-prize-in-physiology-or-medicine-1901-2000/>
 54. Nobel Prize Outreach. All Nobel Prizes in Physiology or Medicine. Stockholm: Nobel Prize Outreach; 2026. Available from: <https://www.nobelprize.org/prizes/lists/all-nobel-laureates-in-physiology-or-medicine/all/>
 55. Sattar N, McLaren J, Kristensen SL, Preiss D, McMurray JJV. SGLT2 inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? *Diabetologia*. 2016;59(7):1333-9. doi:10.1007/s00125-016-3956-x. (PubMed)
 56. Cherney DZI, Verma S. Sodium glucose cotransporter 2 inhibitors: a novel treatment for type 2 diabetes mellitus. *Circulation*. 2016;134(18):1430-9.
 57. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-46.
 58. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008.
 59. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia*. 2018;61(10):2108-17.
 60. Pollock C, Neuen BL. Sodium-glucose cotransporter 2 inhibition: rationale and mechanisms for kidney and cardiovascular protection in people with and without diabetes. *Adv Chronic Kidney Dis*. 2021;28(6):503-10. doi:10.1053/j.ackd.2021.02.006. (PubMed)
 61. Verma S, Mudaliar S. Potential underlying mechanisms explaining the cardiorenal benefits of sodium-glucose cotransporter 2 inhibitors. *Cardiovasc Diabetol*. 2023;22:293. (PubMed)
 62. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 2006;368(9548):1696-705. doi:10.1016/S0140-6736(06)69705-5. (PubMed)
 63. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-22.
 64. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221-32.