

History and Development of Immunotherapies – Key Breakthroughs and Milestones, from Early Immunology to Contemporary Immunotherapy

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LEARNING OBJECTIVES

- Pay tribute to key authors who contributed to the understanding of the immune response, paving the ground for immunotherapy.
- Bridge preventive vaccinations to prophylactic ones.
- Describe the evolution of serotherapy to intravenous immunoglobulins and monoclonal antibodies therapies.
- Recall how non-specific stimulation by bacterial products can favour tumour regression.
- Explain why cytokines can be harnessed or neutralised to address cancer, infectious disease, and inflammatory disorders.

1.1 KEY MILESTONES IN THE HISTORY OF IMMUNOLOGY

The history of immunology extends back before the immune response itself was properly understood. Louis Pasteur (1822–1895) set up his vaccines with an erroneous view that vaccination with attenuated microbes would deprive the host's supply of essential trace nutrients necessary for their survival and growth [1]. Pasteur's close collaborators, Émile Roux (1853–1933) (Figure 1.1) and Charles Chamberland (1851–1908), noted that: '*M. Pasteur thought that in the case of fowl cholera, the non-recurrence was due to the disappearance of some substances consumed by the microbe*'. However, they recognised that immunity was an active process developed by the host, as they showed that injecting soluble substances produced by these microbes could also induce the refractory state [2].



FIGURE 1.1 Some founding fathers of immunology and serotherapy. Upper row – from left to right: Paul Ehrlich, the founding father of humoral immunity. Harris & Ewing Collection / The Library of Congress / Public domain; Elie Metchnikoff, the founding father of cellular immunity. Wellcome Collection / Wikimedia Commons / CC BY 4.0; Jules Bordet, the father of the complement system, used serotherapy in Pretoria against cattle plague. Pierre Petit / Wikimedia Commons / Public domain. All three were awarded the Nobel Prize. Lower row – from left to right: Emil von Behring, the founding father of serotherapy, Nobel Prize 1901. Harris & Ewing Collection / The Library of Congress / Public domain; Émile Roux, who used horses to prepare immune sera against diphtheria (115 nominations for Nobel Prize) © Institut Pasteur; Alexandre Yersin, who discovered *Yersinia pestis* and used immune sera against plague in China. Wellcome Collection / Wikimedia Commons / CC BY 4.0.

The foundations of humoral immunity were laid by Paul Ehrlich (1854–1915) (Figure 1.1) by his discovery of antibodies which awarded him a Nobel Prize in 1908 [3]. Although Ehrlich is credited to have demonstrated the transfer of protective immunity from pregnant mothers to their newborns in 1892 [4], an earlier demonstration occurred in 1883. Hippolyte Rossignol (1837–1919), although initially very sceptical of Louis Pasteur’s anthrax vaccine, welcomed his demonstration in the open field on his farm in Pouilly-Le-Fort. He reported that the immunity provided by the anthrax vaccine was transmissible from mother to foetus [5]. Ehrlich also coined the word ‘complement’ in 1899 [6] to describe the bactericidal capacity of the blood discovered in 1886 by the Hungarian physician and professor of epidemiology, Josef von Fodor (1843–1901) [7]. Later, Belgian medical doctor Jules Bordet (1870–1961) (Figure 1.1) further deciphered the complement system [8] and received the Nobel

Prize in 1919 [9]. Bordet, working in the laboratory of Elie Metchnikoff (1845–1916) (Figure 1.1), also investigated the relationship between the complement system and macrophages and described the process of opsonisation, a word later coined in 1903 by Sir Edward Almroth Wright (1861–1947) [10]. The identification of antibodies as immunoglobulins was discovered in 1959–1961 by Rodney Porter (1917–1985) and Gerald M. Edelman (1924–2014) [11, 12], a discovery that was recognised in 1972 with the Nobel Prize. The characterisation of the genetic mechanisms that allow antibody diversity by Susumu Tonegawa (1939–) in 1976 [13] was also awarded the Nobel Prize in 1987. Early attempts to identify the cellular origin of antibodies led to a conclusion that was later found to be false. Florence Rena Sabin (1871–1953) was a pioneering scientist who achieved many groundbreaking firsts: she was the first woman to hold a full professorship at Johns Hopkins School of Medicine, the first woman to direct a department in medical research at the Rockefeller Institute, and in 1925, the first female member of the National Academy of Sciences. In 1939, she claimed that macrophages were the source of antibodies [14]. In 1947, another woman, Astrid Fagraeus (1913–1997) from the Karolinska Institute, correctly identified plasma cells as the source of antibodies [15].

The study of cellular immunity started with the identification of blood cells. In 1674, a Dutch draper, Antoni van Leeuwenhoek (1632–1723), was the first to observe a drop of blood under a microscope and discovered red blood cells [16]. During the 18th century, two French doctors reported the presence of white blood cells. Joseph Lieutaud (1703–1780), physician of King Louis XVI, called them ‘*globuli albicantes*’ [17] and Jean-Baptiste de Sénac (1693–1770), a chemist and a cardiologist, referred to them as ‘white globules’, which he had observed in both blood and pus [18]. This finding was further advanced in 1845 by William Addison (1802–1881), who first described the process of diapedesis: ‘*Colourless blood cells are deposited all over the interior of the vessels; [...] and at length pass into the tissue; [...] These facts are all independent of any orifices, rupture or pores in the vessels, allowing the escape of cells*’ [19]. In 1865, Johann Sigismund Schultze (1825–1874) was the first to describe the main types of white blood cells which correspond to the lymphocytes, monocytes, eosinophils, and neutrophils we recognise today [20]. Although Paul Ehrlich is best known for his work in humoral immunology, he also made several key contributions to cellular immunity. With a background in chemistry, Ehrlich began his scientific career as a histologist, applying chemical dyes to stain cells selectively and was the first to identify eosinophils [21]. Metchnikoff later recognised this achievement, stating that ‘*The best proven result was provided by Mr. Ehrlich, who showed that the eosinophil leukocytes are mainly produced by bone marrow*’. Ehrlich’s research also led to the discovery of mast cells, further enriching the understanding of immune cell types [22]. Nevertheless, Elie Metchnikoff is the one often credited as the founder of cellular immunity [23]. In 1882, he observed the process of phagocytosis by macrophages and microphages (neutrophils) and understood and demonstrated its function in defence against pathogens [24, 25]. In addition, Metchnikoff discovered the process of efferocytosis and described specific immune cell types including alveolar macrophages and ‘neuronophages’ (microglial cells). In 1908, both Ehrlich and Metchnikoff received the Nobel Prize for their works. Macrophages constitute a heterogeneous population, depending on the tissues in which they reside [26]. The distinction between B- and T-lymphocytes was achieved by Max Cooper (1933–) in 1965 [27], and their collaboration for antibody

production was described by Jacques F. Miller (1931–) in 1968 [28]. Specific cytotoxic T cells were reported by Jean-Charles Cerottini (1938–) in 1970 [29], and the first subsets of T cells (Th1 and Th2) were mentioned in 1986 by Tim Mosmann (1949–) and Robert L. Coffman (1948–) [30]. Dendritic cells were discovered in 1973 by Ralph Steinman (1943–2011), who was awarded the Nobel Prize in 2011 [31]. Natural killer (NK) cells were first described in 1975 by Rolf Kiessling, Eva Klein, and Hans Wigzell [32]. Identified as non-T, non-B lymphocytes with the capability for ‘natural’ cytotoxicity, NK cells belong to a group of immune cells known as innate lymphoid cells which also exist as subsets [33].

1.2 VARIOLATION AND VACCINATION

Variolation and vaccination are not immunotherapeutic approaches *per se*, although the famous anti-rabies vaccine developed by Louis Pasteur was used therapeutically, since it was injected after the patient had been bitten by a rabid animal, and therefore administered after the infection [34]. Likewise, cancer vaccines are employed as immunotherapies [35].

To prevent smallpox, variolation was set up in China in 1014, and later introduced in Turkey (1718) and the United Kingdom (1721) by Lady Mary Wortley Montagu (1689–1762), writer and poet, and wife of the British ambassador in Constantinople. Remarkably, a similar approach was used to prevent syphilis, called ‘syphilisation’. This was first suggested in Norway by Carl Wilhelm Boeck (1808–1875) and in France by Joseph-Alexandre Auzias-Turenne (1812–1870). Amusingly, the latter’s book was kept hidden in a drawer of his desk by Pasteur. In 1796, Edward Jenner (1749–1823) documented his first vaccination against smallpox in a manuscript which he submitted to the Royal Society; however, the report was returned unread. Let’s mention the names of those ‘famous’ doctors who failed to realise the importance of this discovery that would save millions of people: Joseph Banks (1743–1820), John Southey (1765–1819), and Sir Everard Home (1756–1832)! Richard Dunning (1761–1851), a friend of Jenner, coined the word ‘vaccination’ in his book published in 1800 [36]. Henri Toussaint (1847–1890) and Pierre-Victor Galtier (1846–1908) were the precursors of Louis Pasteur’s vaccines against anthrax and rabies, respectively. In addition, Pasteur prepared a vaccine against fowl cholera and pig erysipelas. From 1880 to the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) vaccines developed in 2020, numerous infectious diseases have been prevented thanks to the advancement of vaccines (Figure 1.2). Only two vaccines have received a Nobel Prize: in 1951, the yellow fever vaccine developed by Max Theiler (1899–1972) and in 2023, the messenger ribonucleic acid (mRNA) vaccine against SARS-CoV-2 developed by Katalin Kariko (1955–) and Drew Weissman (1959–). Among the leaders in the field of vaccination, let’s mention Maurice Hilleman (1919–2005) who was responsible for the development of 40 different vaccines; among them, 8 are a part of the 14 vaccines regularly recommended in immunisation programmes in the United States. Estimates suggest that these vaccines prevent nearly eight million deaths annually, leading many to regard Hilleman as the scientist who has saved the most lives.

Cancer vaccines were first reported in 1902, in Germany, when Ernst von Leyden (1832–1910) and Ferdinand Blumenthal (1870–1941) used an autologous tumour cell suspension as a vaccine to treat patients with advanced metastatic cancer [37]. In 1959,

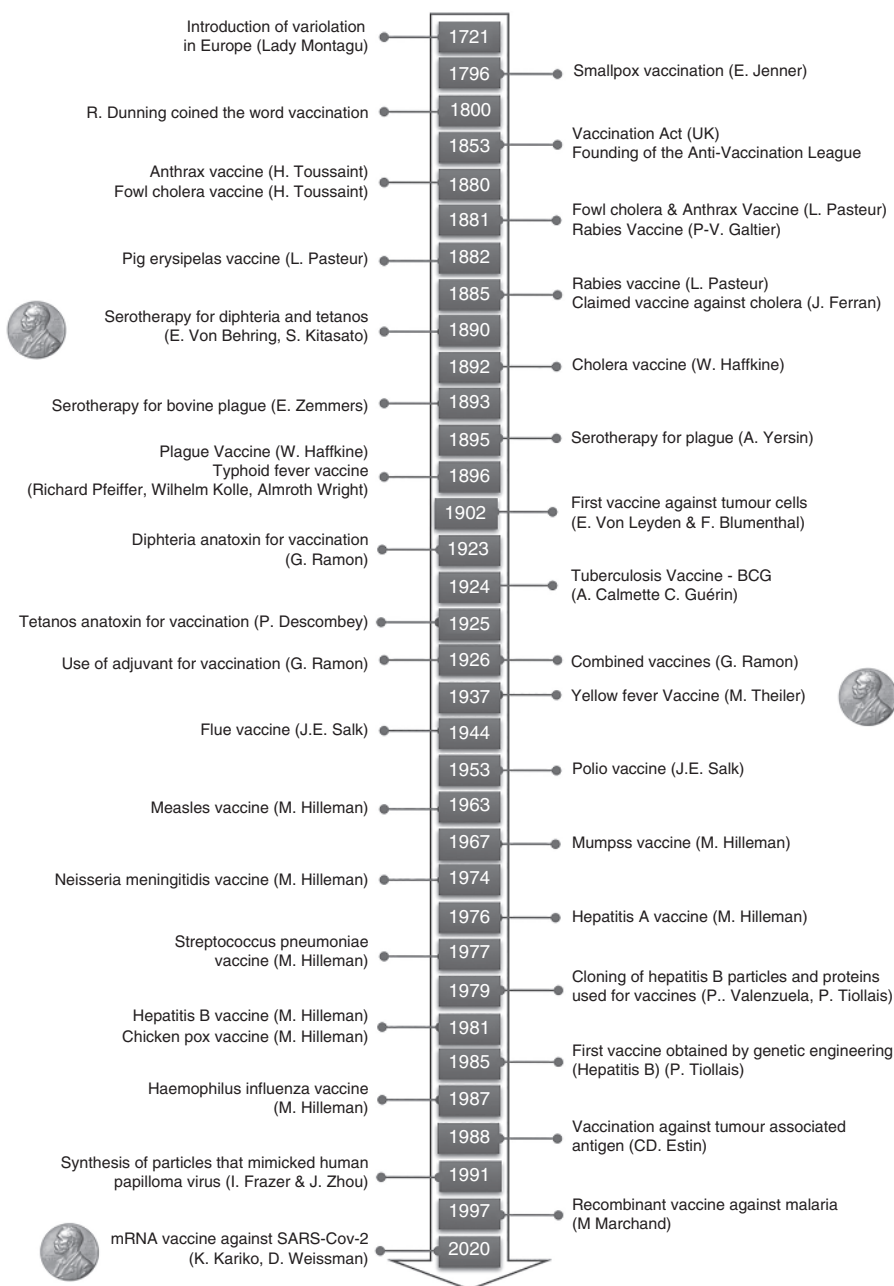


FIGURE 1.2 Timeline of immunoprophylaxis and immunotherapies by vaccination and serotherapies.

the husband-and-wife team of Ruth M. Graham (1917–1978) and John B. Graham published a cancer vaccine study on 114 gynaecologic cancer patients treated with tumour lysate associated with Freund's adjuvant [38]. In 1965, it was established that tumour cells could express specific antigens [39]. Accordingly, cancer vaccines could be designed to target tumour-associated antigens. Such an approach was achieved in 1988 using a recombinant vaccinia virus expressing human melanoma-associated antigen [40]. In the mid-1990s, tumour-specific glycopeptides, or tumour-associated carbohydrates such as gangliosides, were used in cancer vaccine formulations [41], and monoclonal antibodies (mAbs) targeting these structures were employed [42]. Of note, vaccines against certain viruses such as hepatitis B virus [43] or human papilloma virus [44] can prevent the occurrence of liver cancer and gynaecologic cancers, respectively.

1.3 SEROTHERAPY

By the late 1800s, diphtheria, nicknamed 'the child-strangling angel', killed thousands of children. A total of 1,639 children died of diphtheria in Paris alone in 1890. That same year, in Berlin, Emil von Behring (1854–1917) (Figure 1.1) and his Japanese colleague Shibasaburo Kitasato (1853–1931) showed that immune serum against the respective toxins protected against diphtheria and tetanus [45] (Figure 1.2). Later, Adolf Baginsky (1843–1918), a paediatrician who also served as Freud's mentor and established the 'Kaiser und Kaiserin Friedrich Kinderkrankenhaus' in Berlin, documented the earliest clinical trial involving diphtheria. In this study, 220 children with diphtheria were treated with intraperitoneal injections of immune serum, resulting in a 77% recovery rate [46]. In 1901, Emil von Behring earned the first Nobel Prize in Physiology and Medicine for this discovery. In France, Emile Roux, who together with Alexandre Yersin (1863–1943) (Figure 1.1) had identified the diphtheria toxin, was among the first to employ horses for producing immune serum. In 1894, working with Louis Martin (1864–1946) at the Institut Pasteur and Auguste Chaillou (1866–1915) at Necker Hospital, he reported a study treating 300 children which showed a 50% reduction in mortality [47]. This success received significant attention in the press, and 'Le Figaro' initiated a fundraising campaign that improved the poor financial status of the institute at that time. During World War I, Institut Pasteur produced a huge quantity of immune sera against diphtheria and tetanus. By the end of the war, 1,462 horses contributed to the production of 600,000 vials/month.

Serotherapy has also been applied to patients with plague. In 1894, Alexandre Yersin was sent to Hong Kong to investigate the ongoing plague epidemic. On 20 June of that year, he successfully identified and isolated the bacterium responsible, later named *Yersinia pestis* [48]. Upon returning to France, Yersin collaborated with Amédée Borrel (1867–1936) and Albert Calmette (1863–1933) to develop an anti-plague serum using horses [49]. During a subsequent outbreak in Guangzhou, China, in 1896, Yersin travelled there to administer the serum, achieving successful treatment outcomes [50]. Paul-Louis Simond (1858–1947) went to India to treat patients with the anti-plague immune serum [51].

Another successful treatment was achieved with serotherapy to treat cattle plague (Rinderpest). The disease started to spread to Africa from Egypt in 1875. By 1896, it had reached South Africa. In 1897, Robert Koch (1843–1910), the famous German microbiologist, who had isolated the bacillus of tuberculosis (1882), joined

Kimberley. He proposed a treatment with bile from convalescent animals. His colleague, Paul Kohlstock (1861–1901), applied the suggested treatment in Namibia, resulting in the death of 2,700 animals among the 6,200 treated livestock. Meanwhile, Institut Pasteur sent two of its collaborators to Pretoria, the Belgian medical doctor Jules Bordet and the Polish scientist Jan Danysz (1860–1928). There, they joined the Swiss veterinarian Arnold Theiler (1867–1936), the father of Max Theiler, who, as previously mentioned, developed the yellow fever vaccine [9]. All three of them decided to apply the serotherapy advocated by the Latvian microbiologist Eižens Zemmers (1843–1906) who had extensive expertise on cattle plague [52]. The treatment was a success, and amusingly it was referred to as ‘the methods of the French doctors’, even though none of them were French! Bordet and Danysz were asked by the South African government to stay to solve the problem of horse plague. However, for that specific disease, the team failed to find an appropriate treatment. Of note, on 28 June 2011, the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (WOAH) declared that bovine plague was eradicated from the planet. This is the first animal disease to have been eradicated (like smallpox for humans in 1979).

1.4 ANTI-TUMOUR ACTIVITY OF BACTERIA, BACTERIAL TOXINS, AND VIRUSES

The idea that bacterial infections and bacterial-derived products could boost the immune system non-specifically and then enhance its ability to control tumour cell growth emerged when two German physicians, Wilhelm Busch (1826–1881) and Friedrich Fehleisen (1854–1924), independently noticed tumour regression in patients with erysipelas infection in 1866 and later. Two years later, Busch deliberately injected erysipelas into a patient with cancer and observed a subsequent reduction in the tumour’s size. In 1882, Fehleisen replicated this approach and reported similar outcomes. The following year, he recognised *Streptococcus pyogenes* as the bacterium responsible for erysipelas [53, 54].

In 1891, William B. Coley (1862–1936) (Figure 1.3), a surgeon at the New York Cancer Hospital, began treating his cancer patients with *S. pyogenes*. He reported his first cases in 1893 [55]. He found that, in most patients, inducing erysipelas was extremely challenging, and among the few who developed an active infection, it was incredibly difficult to cure. In two cases, death resulted from widespread septicaemia rather than the patients’ underlying cancers [56].

Coley later treated 140 patients with inoperable sarcoma using ‘toxins’ from both *S. pyogenes* and *Bacillus prodigiosus* (i.e. *Serratia marcescens*); these were most likely the supernatants of cultures from these Gram-positive and Gram-negative bacteria. For 24 cases he obtained partial regression of the tumour and complete regression for 16 patients, including one chondrosarcoma and one osteosarcoma [57] (Figure 1.4). The effects of the toxins lasted from 7 months to 6 years. Dr. Coley was viewed with suspicion by many surgeons, and his observations were largely ignored for the next 25 years, possibly because the mechanism of action of his toxins was unknown. He believed the cure was possible because sarcoma was of microparasitic or infectious origin. It was only in 1909 that Paul Ehrlich hypothesised that host immune defences could prevent the development of cancers [58], a concept now known as immunosurveillance. This concept was proposed in 1957 by Frank Macfarlane



FIGURE 1.3 Some founding fathers of immunotherapy. Upper row – from left to right: William Coley (bacterial toxin to fight sarcoma). *Wellcome Collection / Wikimedia Commons / CC BY 4.0*; Israel Holmgren (BCG to treat cancer). *Gösta Florman / Västergötlands Museum / Public domain*; Ogden Carr Bruton (human immunoglobulin to treat people who have inherited antibody deficiencies). *U.S. Federal Government / Wikimedia Commons / Public domain*; Edward Donnall Thomas (anti-CD20 mAb to fight B-cell lymphoma). *Ca.garcia.s / Wikimedia Commons / CC BY-SA 4.0*. Lower row – from left to right: Steven A. Rosenberg (IL-2, LAK cells, TIL for cancer therapy); Sir Marc Feldmann (anti-TNF in rheumatoid arthritis); Donald Metcalf (the discoverer of the colony-stimulating factors). *Wikimedia Commons / Public domain*; Kevin Tracey (the vagal nerve control of inflammation). *Mike Denora / Wikimedia Commons / CC BY-SA 4.0*.

Burnet (1889–1985) [59], who was awarded the Nobel Prize in 1960 for his studies on immune tolerance, jointly with Sir Peter Brian Medawar (1915–1987). It was not until 1943 that Murray J. Shear (1899–1983) recognised that the anti-tumour activity of *S. marcescens* was caused by its endotoxin (lipopolysaccharide, LPS) [60]. Regarding the anti-tumour activity of *S. pyogenes* supernatant, it has been proposed that streptococcal exotoxins are the active molecules. Known as superantigens, they could activate cytotoxic T cells, as staphylococcal superantigens do, and thereby contribute to the anti-tumour effect [61].

Attenuated *Mycobacterium bovis* in the vaccine against tuberculosis prepared by Albert Calmette (1863–1933) and Camille Guérin (1872–1961), known as the ‘bacille de Calmette et Guérin’ (BCG), is another bacterium used to fight cancer. The idea was derived from an observation made in 1928 by Raymond Pearl (1879–1940), working at Johns Hopkins Hospital in Baltimore, who discovered through autopsy studies that cancer occurred less frequently in individuals with *Mycobacterium tuberculosis* [62]. In 1935–1936, Israel Frithiofsson Holmgren (1871–1961) (Figure 1.3) in Stockholm administered BCG vaccine to patients with cancer [63]. He delivered

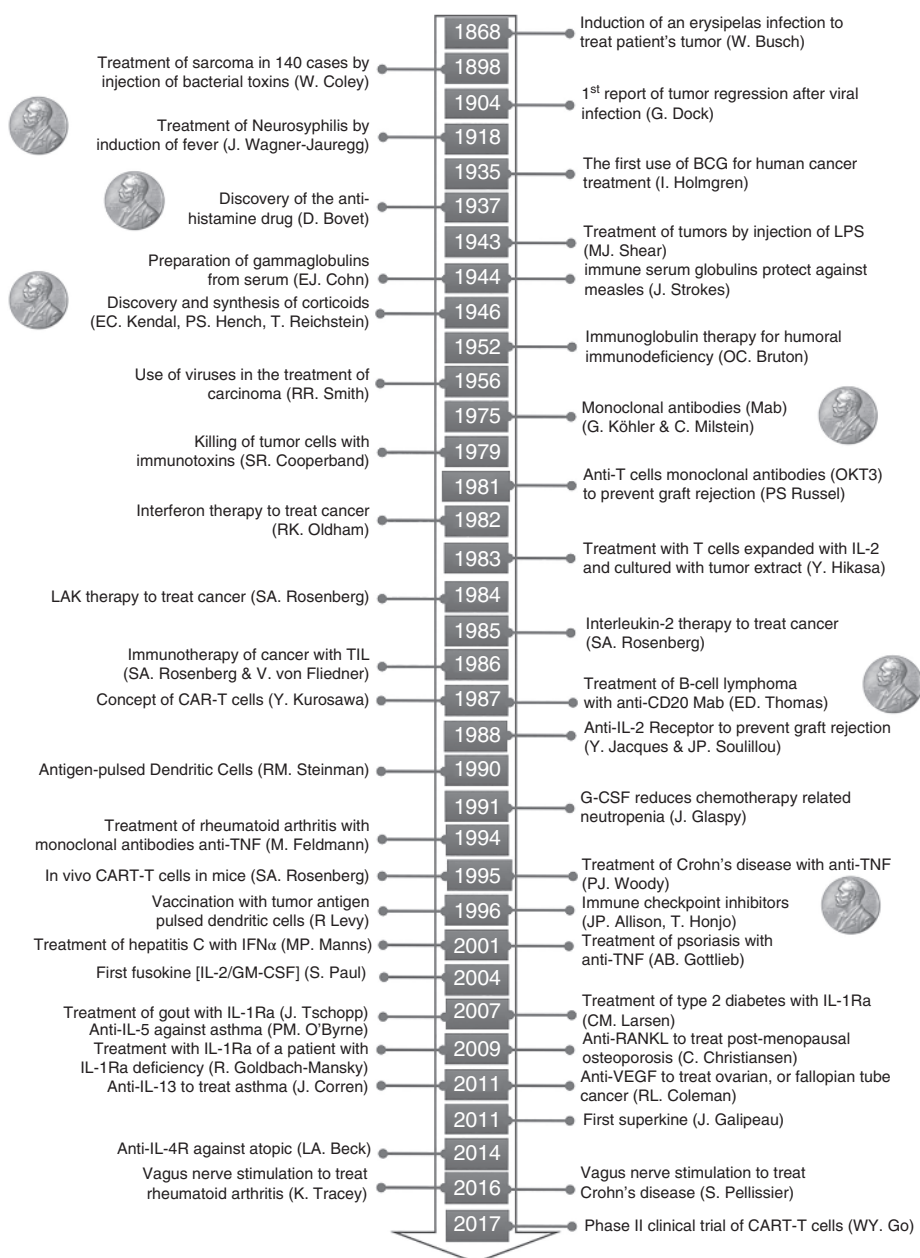


FIGURE 1.4 Timeline of the main achievements in immunotherapy.

intravenous injections of BCG to 33 individuals, most of whom had stomach cancer. One patient received as many as 37 injections, amounting to a total of 2.68 mg BCG over the course of more than a year. All patients developed fever accompanied by general malaise following treatment; however, some showed improvement in their overall condition. A similar approach was undertaken in the Philippines in the early

1960s for patients with advanced malignant disease [64] and in France in the late 1960s to treat patients with acute lymphoblastic leukaemia [65]. In 1976, Alvaro Morales (1938–) was the first to administer BCG to treat bladder cancer and reported favourable effects in reducing bladder cancer recurrence [66]. Since then, bladder cancer is still being treated with BCG.

Bacterial toxins have been engineered to offer specific tools to kill tumour cells. Diphtheria toxin or ricin (a plant toxin) has been chemically linked to purified anti-tumour antibodies [67] and mAbs [68]; called immunotoxins, these constructs were reported in 1976 and 1981, respectively. In 1987, another chimeric molecule combining diphtheria toxin and interleukin-2 (IL-2) was designed to target IL-2 receptor-positive cells [69] and treat cutaneous T-cell lymphoma (Denileukin diftitox). This treatment was approved by the US Food and Drug Administration (FDA) in 1999. Among other toxins employed to target tumour cells, let's mention the work of Calmette in 1933 who employed cobra venom [70].

Not surprisingly, transient improvements have also been observed in cancer patients following viral infections. The first report was published in 1904 [71], but the observation had previously been made on 29 December 1896, in a woman with leukaemia. She was the patient of a fascinating doctor, George Dock (1860–1951), when he worked at the University of Michigan Medical School. Dock wrote many articles, including some on Jenner and on vaccination. His oral notes for the students during his clinical sessions, recorded with a stenographer, resulted in 6,800 pages, gathered in 17 volumes. He noticed that *'two weeks after an attack of what was probably influenza, the leukocytes were found reduced from 367,070 to 7500, falling to 4775 in two weeks more [...]. The spleen was much smaller; the liver became smaller later'*. Two months later, the disease was back, and the patient passed away 18 months after the initial observation. In the early 1950s, few reports were published on the beneficial consequences of different types of viral infection on the growth of the tumours [72–76]. A fascinating case was reported in 1950 [77]: in May 1940, a primary lesion was removed from a 32-year-old woman with malignant melanoma. Two years later, three additional cutaneous melanotic nodules were removed. Following a dog bite in September 1943, she underwent a course of 14 rabies vaccine injections. By April 1948, two further melanotic nodules were excised, but since then, there had been no further evidence of recurrence. The author indicates that on purpose, he voluntarily vaccinated 12 of his patients with the rabies vaccine with some beneficial effects. Nowadays, one refers to oncolytic viruses while the concept of virotherapy emerged [78].

1.5 IMMUNOGLOBULIN, ANTIBODIES, AND MONOCLONAL ANTIBODIES

1.5.1 Ivlg

Intravenous immunoglobulins (IvIg) are the heirs of successful serotherapy. In 1944, the purification of serum gamma globulins from human plasma was achieved by Edwin Joseph Cohn (1892–1953) [79]. In the same year, Joseph Stokes (1896–1972) demonstrated that immune serum globulin (ISG) could either prevent or lessen the severity of measles in children exposed during outbreaks. He further noted that patients who had already begun to show symptoms appeared to respond better to

higher ISG doses and proposed that intravenous administration at an early stage of infection might offer therapeutic benefit [80]. In 1952, Ogden Carr Bruton (1908–2003) (Figure 1.3), chief of paediatrics at Walter Reed Army Hospital (Washington), used human immunoglobulin to treat people who had inherited antibody deficiencies [81]. The first commercially available IvIg was developed in 1962 by digesting ISG with pepsin. The main component of this product was the F(ab') fragment [82]. Nowadays, IvIg therapies are prepared from a pool of polyclonal immunoglobulins (antibodies) from the plasma of thousands of healthy donors. Commercial IvIg preparations contain a wide repertoire of antibody specificities, enabling neutralisation of a broad range of antigens. They contain >95% immunoglobulin G (IgG), <2.5% immunoglobulin A (IgA), and negligible amount of immunoglobulin M (IgM). They are now far less frequently used to treat infectious diseases despite a meta-analysis suggesting that their use in sepsis could be beneficial [83]. In contrast, another meta-analysis failed to demonstrate that IvIg were of any benefit when employed in COVID-19 patients [84]. They continue to be used to treat primary humoral immunodeficiency, haematologic disorders, neurologic disorders, and autoimmune disorders [85].

1.5.2 Anti-immune Cells and Anti-tumour Cells

mAbs are widely employed for various types of immunotherapies. They were conceived by Georges Köhler (1946–1995) and César Milstein (1927–2002) [86] in 1975. mAbs are produced using hybridoma technology that fuses together myeloma cells (to give cellular immortality), and antibody-producing B cells (from which they acquire the antibody specificity). Köhler and Milstein's paper has been cited more than 15,000 times (July 2025). Both received the Nobel Prize in 1984. Of note, the term 'hybridoma' was suggested by Leonard A. Herzenberg (1934–2012) during a sabbatical in César Milstein's laboratory in 1976/1977 [87]. In 1969, Herzenberg developed the fluorescence-activated cell sorting (FACS) machine [88], while flow cytometry was invented by Mack Fulwyler (1936–2001) in 1965 [89].

The first mAbs were fully murine, resulting in the generation of human antibodies targeting the mouse IgG in patients. Thus, different technologies have since been applied to humanise mAbs using transgenic mice [90, 91] or phage display [92], making it possible to now generate fully human mAbs [93].

In 1981, OKT3 (*Muromonab-CD3*), a mouse IgG2a, became the first mAb to be applied clinically for the treatment and prevention of renal allograft rejection, and it was approved by the FDA in 1986. It was a pan-T-cell mAb, proposed by Paul Snowden Russell (1925–), professor of Surgery at the Massachusetts General Hospital (MGH) [94]. Of note, the museum at MGH has been named in honour of Paul S. Russell. Alongside Russell in 1987, Edward Donnell Thomas (1920–2012) (Figure 1.3), professor at the University of Washington, produced the anti-CD20 mAb, a specific B-cell marker which has been used to treat individuals with B-cell lymphoma with great success [95], and was the first mAb to be approved for the treatment of cancer by the FDA in November 1997 (rituximab). Thomas received the Nobel Prize in Physiology and Medicine in 1990 for his work on transplants and immune rejection mechanisms. The major role of these mAbs, once on their target cells, is to bind via their Fc moiety to the Fc-receptor on NK cells and macrophages, triggering target cell death by antibody-dependent cellular cytotoxicity (ADCC). Interestingly, glycosylation of the Fc moiety was later proposed to offer a modified mAb with enhanced

affinity for receptor binding [96]. This new mAb (obinutuzumab) has now supplanted rituximab, with slightly higher efficacy [97]. Among the early mAbs used for human therapy, let's mention the anti-CD25 (IL-2R α subunit) mAb, reported in 1988 by Yannick Jacques (1950–) and Jean-Paul Soulillou (1944–) to prevent kidney graft rejection. This anti-CD25 mAb (daclizumab) was the first humanised antibody to be approved by the FDA in 1997 for renal transplant [98, 99].

1.5.3 Immune Checkpoint Inhibitors

CTLA-4 (cytotoxic T-lymphocyte-associated protein-4) was discovered concomitantly by two independent groups in 1995 [100, 101]. CTLA-4 is constitutively expressed on regulatory T cells (Treg) and functions as an inhibitory signal upon interacting with CD80 or CD86 on the antigen-presenting cell's surface. Programmed cell death protein 1 (PD-1) was discovered in 1992 [102]. PD-1 is displayed by effector T cells, and engagement with its ligands, PD-L1 and PD-L2, inhibits immune responses. PD-L1 is typically found on activated T- and B cells, macrophages, dendritic cells, and some epithelial cells, especially during inflammation. Tumour cells can also express PD-L1 as an adaptive mechanism to evade anti-tumour immunity. mAbs aimed to neutralise CTLA-4, PD-1, or PD-L1 are called immune checkpoint inhibitors and were shown in the early 2010s to be a potential treatment for certain cancers [103, 104]. The FDA's approval of the CTLA-4 inhibitor occurred in 2011, followed by approval of PD-1 inhibitors in 2014. James P. Allison (1948–) and Tasuku Honjo (1942–) received the 2018 Nobel Prize in Medicine for discovering cancer treatments that inhibit negative regulators of the immune system.

1.6 HARNESSING AND TARGETING CYTOKINES

1.6.1 A Brief History of Cytokines

Although the discovery of type I interferon (IFN) is often attributed to Alick Isaacs (1921–1967) and Jean Lindenmann (1924–2015) in 1957 [105], the truth is that this discovery was owed to Yasuichi Nagano (1906–1998) and Yasuhiko Kojima (1928–) in 1954 [106]. Their contribution was likely overlooked because of two mistakes: they published in a French-speaking journal and failed to create a neologism. IFN α was the first human cytokine to be cloned in 1980 [107] and the first human recombinant cytokine to be used in cancer patients in 1982 [108, 109] (Figure 1.5). The second cytokine to be discovered was the macrophage migration inhibitory factor (MIF) in 1966 by Barry Bloom (1937–2026) [110]. Bax69, an anti-MIF mAb, has entered Phase I/II clinical trials focusing on cancer treatment. Because MIF was not exclusively produced by lymphocytes and could also be secreted by fibroblasts, Stanley Cohen coined the word 'cytokine' in 1974 to replace the word 'lymphokine' [111]. The discovery of IL-1 started with the efforts of Valy Menkin (1901–1960) in 1944 to identify the endogenous molecular substance responsible for fever [112]. However, his isolated 'pyrexin' from inflammatory exudates appeared to be contaminated with endotoxin [113]. The endogenous pyrogen was finally isolated in 1953 by Ivan L. Bennet Jr. (1922–1990) and Paul Beeson (1908–2006) [114] and two years later by Elisha Atkins (1921–2005) and W. Barry Wood Jr. (1910–1971) [115]. When it

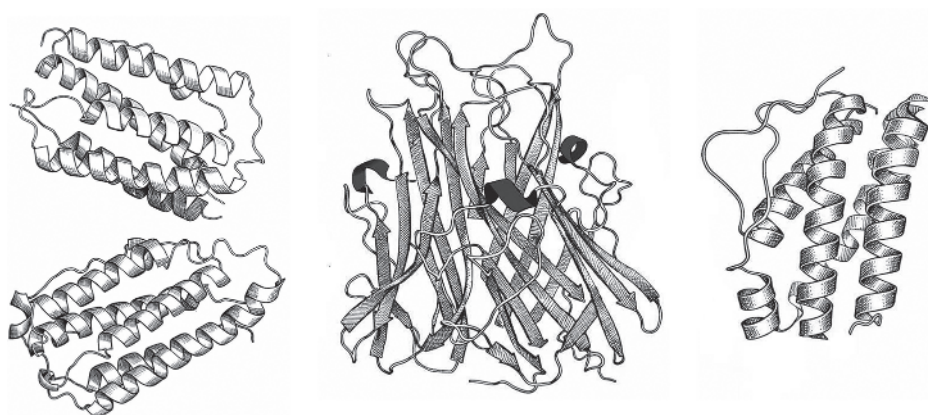


FIGURE 1.5 Cytokines used as recombinant molecules for their own properties to boost immune defences or as target of monoclonal antibodies to prevent their inflammatory properties. From left to right: Type I interferon (IFN) discovered in 1954 by Nagano, Y., & Kojima, Y.; Tumour necrosis factor (TNF) discovered in 1975 by Carswell EA, Old LJ and colleagues; and interleukin-2 (IL-2) discovered in 1976 by Morgan DA, Ruscetti FW, & Gallo R. Courtesy of Jingchen Zhou.

appeared that the endogenous pyrogen was identical to other identified molecules (namely, osteoclast activating factor, haemopoietin-1, catabolin, lymphocyte activating factor, epidermal cell-derived thymocyte activating factor), it was named 'IL-1'. In 1984, human IL-1 was first cloned by Charles Dinarello (1943–) [116] and murine IL-1 by Steven B. Mizel (1948–) [117]. While fever is an effective component of the immune response against infectious agents, inducing fever has also been used as a therapeutic approach to treat neurosyphilis. Julius Wagner-Jauregg (1857–1940) inoculated malaria to induce fever, followed by treatment with quinine. He claimed to have treated more than 150 patients using this method. In total, pyrotherapy cured about half of the patients who received the treatment, but approximately 15% died from malaria. Nevertheless, he received the Nobel Prize in 1927! IL-2 was discovered in 1976 in the laboratory of Robert Gallo (1937–) [118] (Figure 1.5). To date, there are now 41 identified ILs.

Another family of cytokines is that of tumour necrosis factor (TNF) (Figure 1.5). As mentioned earlier, LPS and BCG are microbial substances able to boost immunity against cancer cells. In 1975, TNF was identified in the serum of mice injected with BCG and LPS [119]. Ten years later, Bruce Beutler (1957–), who was awarded the Nobel Prize in 2011, showed that TNF was identical to cachectin, a molecule responsible for cachexia, isolated in the laboratory of Anthony Cerami (1940–) [120].

Among cytokines, there is a family of chemo-attractant molecules, which were named chemokines in 1992. In 1987, IL-8 was one of the first chemokines to have been characterised and extensively studied by Joost Oppenheim (1934–2022) [121].

To end this brief historical background, let's mention the amazing contribution of Donald Metcalf (1929–2014) (Figure 1.3) in Australia. Between 1965 and 1985, Metcalf's group characterised and isolated four distinct colony-stimulating factors (CSFs) which stimulate differentiation, growth, and other activities of macrophages

(M-CSF), granulocytes (G-CSF), both granulocytes and macrophages (GM-CSF), and the pluripotent multi-CSF (IL-3) [122]. The gene for GM-CSF was later cloned by Metcalf's team.

1.6.2 Cytokines Used to Restore or Boost the Immune System

Cytokines are often classified as proinflammatory or anti-inflammatory. This Yin-Yang view is far too simplistic [123] and may help to explain the side effects, or even the toxic effects, associated with their use or neutralisation. Several cytokines (IL-2, G-CSF, GM-CSF, IFN- α , IFN- β , IFN- γ , etc.) are already approved as disease therapeutics, and many other cytokines are being investigated for their anti-cancer, anti-microbial, and immunomodulatory properties in preclinical studies and trials.

IFN α was the first available recombinant cytokine and the first to be used in clinical trials in 1982, surprisingly not for viral infection, but instead in cancer patients [108, 109]. IL-2 was cloned in 1983 [124], and the first *in vivo* treatments were performed in 1984 for HIV patients [125], in 1985 in murine models of cancer [126], in 1986 in patients with hairy cell leukaemia [127], and in 1987 in patients with different types of malignancy [128]. G-CSF has been employed since the late 1980s to boost haematopoiesis to increase the number of haematopoietic stem cells for auto-transplantation [129] or to enhance haematopoiesis altered by chemotherapies during cancer treatment [130]. GM-CSF has been similarly employed, but because of its stimulatory properties, it has also been used to restore the altered immune status observed in sepsis patients [131]. A similar result was achieved in 1997 with IFN- γ [132], in 2012 with IL-7 [133], and in 2019 with anti-PD-1 [134]. Given the Yin-Yang properties of cytokines, the fact that the concept of immunosuppression in sepsis patients is largely based on analyses of circulating leucocytes (which represent only a small percentage of the total immune cells), and the compartmentalisation of the immune response during sepsis [135], we cautioned against the risks of globally boosting the entire immune cell population [136]. In fact, clinical trials of sepsis patients with IFN- γ [137] or IL-7 [138] had to be discontinued early due to safety concerns.

Despite its anti-tumour properties, TNF is difficult to use since it is a major proinflammatory cytokine. Nevertheless, it has been employed with melphalan, a chemotherapeutic medication in an isolated limb perfusion for locally advanced limb sarcomas. One hundred patients were treated, and a 36% complete remission rate was obtained [139].

When scientists wish to be smarter than nature, they invent new cytokines, named either superkines or fusokines. The concept emerged in 2012 when scientists from Zurich and Stanford universities engineered a CD25-independent version of IL-2 [140]. CD25 is the α -chain of the IL-2 receptor, which also contains a β - and a γ -chain. α -, β -, and γ -chains are displayed on Treg but cytotoxic CD8⁺ T cells and NK cells only express β - and γ -chains. Because Tregs are negative regulators of the immune system, and CD8⁺ and NK cells are important players in anti-tumour immunity, it made sense to generate a superkine that fails to activate Tregs but stimulates CD8⁺ and NK cells. This is the role of ALKS-4230 (Nemvaleukine), a fusion protein combining IL-2 with the extracellular domain of IL-2R α [141]. Clinical trials are now ongoing to study the molecule alone and in combination with other anti-cancer strategies. Other IL-2 superkines are under investigation including few pegylated

IL-2 (e.g. Bempegaldesleukin). Fusokines are engineered proteins created by joining two distinct cytokines into a single molecule. Compared with individual cytokines or combinations of different cytokines, these fusion proteins can offer enhanced bio-availability and therapeutic benefits, although they may also display unanticipated biological effects. The first fusokine to be reported was in 2004, which was a fusion between IL-2 and GM-CSF [142]; additional fusokines later reported were IL-2/IL-18 and IL-15/GM-CSF in 2005–2006 [143, 144]. Since then, many others have been produced and investigated (IL-4/GM-CSF, IL-7/GM-CSF, IL-9/GM-CSF, CCL2/GM-CSF, CXCL10/XCL1, and IL-21/anti-CD20) [145].

1.6.3 Neutralisation of Cytokines

In sepsis patients, a lot of efforts have been made to neutralise damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs) and their receptors, inflammatory mediators, and cytokines. Although therapies targeting molecules such as anti-high-mobility group box 1 (HMGB1), anti-triggering receptor expressed on myeloid cells 1 (TREM-1), anti-vascular endothelial growth factor (VEGF), anti-C5a and anti-CXC chemokines, anti-MIF, anti-IL-17, anti-IL-27, anti-IL-33, anti-IFN- γ , and anti-TNF have successfully rescued mice in sepsis models of limited clinical relevance, none of these approaches have proven effective in saving human patients [146]. While targeting cytokines might have seemed logical in a syndrome characterised by a cytokine storm, neutralisation of IL-1 or TNF (the two main drivers of the cytokine cascade) failed to display efficiency [147]. Fortunately for drug companies, success stories have been told for other patients suffering inflammatory pathologies.

I remember attending a lecture by Sir Marc Feldmann (1944–) (Figure 1.3) where he showed a film of a lady suffering from rheumatoid arthritis, sitting in a wheelchair, who after receiving the miraculous anti-TNF treatment was able to get up and go up and down stairs. That was spectacular! Since 1994, this approach has changed the lives of many patients [148]. Various antibodies have been designed and patented, humanised mAb, human mAb, and the extracellular domain of the TNF receptor connected to the Fc-portion of human IgG. In 2002, the anti-TNF adalimumab was the first fully human antibody, made via phage display, to be approved by the FDA for the treatment of rheumatoid arthritis.

Because the neutralisation of TNF is not free from side effects (e.g. increase in tuberculosis cases, cases of sepsis, increased incidence of lymphoma), other cytokines (IL-17, IL-6) have been targeted, but with limited efficiencies [149, 150]. Surprisingly, tocilizumab (anti-IL-6R gp80), which emerged from studies on rheumatoid arthritis, was used to fight SARS-CoV-2 infection with very limited rationale and has ultimately yielded unconvincing results. In 1995, the neutralisation of TNF was shown to be efficient in Crohn's disease [151, 152], and in 1997, it was found to be beneficial in psoriasis [153]. Psoriasis has also been successfully treated with anti-IL-4 [154], anti-IL-17 [155], anti-IL-17R [156], and anti-IL-12/23 p40 [157].

Other cytokines have been targeted in early studies against cancer, with, for example, mAbs against chemokines or chemokine receptors [158], VEGF [159], or IL-6 for multiple myeloma [160]. For allergies and asthma, anti-IL-5 [161], anti-IL-13 [162], IL-4Ra [163] mAbs have been proposed. Anti-IL-2R (CD25) mAbs have been used to prevent allograft rejection [164] and to treat multiple sclerosis [165]. Systemic lupus

erythematosus has been addressed with anti-IFN α mAb [166]. Osteoporosis was treated with anti-receptor activator of nuclear factor kappa-B ligand (RANK-L) [167]. Following these earlier studies, a large number of mAb anti-cytokines or anti-cytokine receptors have been patented.

1.7 TARGETING THE INFLAMMATORY PLAYERS

An earlier strategy to neutralise inflammatory cytokines came from the discovery and synthesis of glucocorticoids between 1936 and 1941 by Philip Showalter Hench (1896–1965), Edward Calvin Kendall (1886–1972), and Tadeusz Reichstein (1897–1996). In 1950, these three scientists received the Nobel Prize for their work on adrenal cortex hormones, including their structure, biological effects, and therapeutic potential in patients with inflammatory disorders [168]. A total of 2,766 different genes were reported as glucocorticoid regulated [169]. The capacity of glucocorticoids to inhibit the production of inflammatory cytokines was demonstrated in the mid-1980s for IL-1 [170], IL-2 [171], IL-3 [172], IFN- γ [173], and TNF [174]. Glucocorticoids inhibit the production of most cytokines but favour the release of MIF [175] and IL-10 [176]. Glucocorticoids also inhibit a large number of cytokine functions [177].

IL-1 receptor antagonist (IL-1Ra), a natural inhibitor of IL-1, is one of the cytokines being developed for clinical use. Initial studies of recombinant IL-1Ra (anakinra) in sepsis were unsuccessful [178], but a reanalysis of the data revealed that a subgroup of patients, those displaying a macrophage activation syndrome, may have benefited from the treatment [179]. This suggests that precision medicine could in the future identify sepsis patients who might benefit from such a treatment, thanks to biomarkers allowing for the identification of different endotypes. A similar approach has been successfully performed in COVID-19 patients [180]. IL-1Ra has also been used to treat patients with type 2 diabetes mellitus [181], gout [182], Behçet disease [183], post-acute myocardial infarction [184], and young children with IL-1Ra deficiency [185]. Another means to block IL-1 is the use of specific mAbs, as done in cryopyrin-associated periodic syndromes [186].

Among the numerous inflammatory mediators, histamine plays a central role, particularly in asthma and other atopic diseases. In 1937 at Institut Pasteur, in the laboratory of Daniel Bovet (1907–1992), a Swiss-born Italian medical doctor, Anne-Marie Staub (1914–2012), his trainee, was the first scientist to save a guinea pig from an anaphylactic shock thanks to the antihistamine properties of thymoxyethyldiethylamine (compound 929F) and phenolic ethers [187]. Unfortunately, the drug was toxic for humans. It was Bernard Halpern (1904–1978) at Rhône-Poulenc who discovered Antergan, the first antihistamine drug for humans.

1.8 CELLULAR THERAPIES FOR CANCER

Autologous T-lymphocytes isolated from cancer patients have been widely used *in vivo* to promote the fight against cancer. In 1983, the first report was published in Japan on the injection of T cells which display increased cytotoxicity after having

been expanded with IL-2 and cultured with autologous tumour extract [188]. In 1984, Steven A. Rosenberg (1940–) (Figure 1.3), a pioneer in the development of immunotherapy in cancer, took the lead in the development of ‘lymphokine-activated killer’ (LAK) cells, consisting mostly of NK, NK-T, and T cells [189, 190]. In 1986, Rosenberg developed the tumour-infiltrating lymphocytes (TILs) expanded in IL-2. They were tested in mice carrying micro-metastases from different tumour types. TILs demonstrated 50- to 100-fold greater therapeutic efficacy compared to LAK cells [191]. The same year, a team from the Ludwig Institute for Cancer Research, in Lausanne (Switzerland), obtained TILs from human solid tumour, but only 3 out of 22 expressed the IL-2 receptor [192]. In 1988, Rosenberg reported the first clinical trial of TIL for patients with metastatic melanoma [193]. To enhance efficacy and specificity of T cells, chimeric antigen receptor-engineered T cells (CAR-T cells) were developed. In 1987, Yoshikazu Kurosawa (1947–) and his team first described the concept of a chimeric T-cell receptor (TCR), created by fusing antibody-derived variable domains (VH and VL) with constant regions from the TCR [194]. In 1993–1995, Rosenberg then tested *in vitro* and *in vivo* the efficiency of these cells against tumours [195, 196]. A Phase II clinical trial involving 111 patients with diffuse large B-cell lymphoma reported an objective response in 82% of participants, with 54% achieving complete remission [197]. However, CAR-T cell therapy can be associated with cytokine release syndrome, a very serious and potentially life-threatening toxicity that requires careful management [198]. More recently, a comparable approach has been explored using CAR-NK cells [199].

Another cellular immunotherapy has been proposed by Steinman, who discovered dendritic cells. Steinman isolated dendritic cells and primed them with the appropriate antigen. Once injected into the patient, these dendritic cells allow for the development of antigen-responsive T cells in the draining lymphoid tissue [200]. Loaded with tumour antigens, these dendritic cells become highly effective antigen-presenting cells capable of activating tumour-specific T cells. In 1996, the first clinical trial in B-cell lymphoma-vaccinated patients with these autologous primed dendritic cells was reported [201]. Three out of four patients experienced complete or partial tumour regression. Having pancreatic cancer, Steinman applied his treatment to himself. However, he passed away a few days before the Nobel Committee for Physiology or Medicine announced he was awarded the Nobel Prize, alongside Bruce Beutler (1957–) and Jules A. Hoffmann (1941–). Although the prize is not awarded posthumously, an exception was made because the committee was unaware that he had passed away three days earlier.

1.9 NEUROMODULATION OF INFLAMMATION

Since the earlier works of Hans Selye (1907–1982), a Hungarian physician who made his career at Montreal University, it is known that stress sensed in the brain has significant consequences on the whole body including the immune system [202]. Selye wrote many books on the effect of stress on health and diseases. The crosstalk between the central nervous system and the peripheral immune system is particularly mediated by the vagal nerve. The main person to decipher the dialogue was Kevin Tracey (1957–) (Figure 1.3), a neurosurgeon, and president and CEO of the Feinstein

Institute for Medical Research (Manhasset, USA). His initial contributions were in the field of sepsis when he showed that anti-TNF could protect mice against an endotoxic shock and baboons against bacteraemia. He discovered that local inflammation is sensed in periphery by the afferent vagus nerve which transmits information to the brain. Then, the brain via the efferent vagal nerve sends signals that cause the production of acetylcholine which results in the release of epinephrine. Epinephrine acts on the β -adrenergic receptors on T cells, which then produce acetylcholine which acts on macrophages via the $\alpha 7$ -nicotinic receptor and inhibits the production of inflammatory cytokines (e.g. IL-1, TNF) [203]. In 2016, Tracey demonstrated that an implantable device stimulating the vagus nerve reduces the production of TNF, IL-1 β , and IL-6 in peripheral blood. In patients with rheumatoid arthritis, vagus nerve stimulation (administered up to four times daily) significantly suppressed TNF production for as long as 84 days and significantly improved their clinical score [204]. In July 2025, the FDA approved the SetPoint System, a groundbreaking implantable vagus nerve implant device offering a new treatment approach for rheumatoid arthritis. Furthermore, a French team using similar vagus nerve stimulation techniques obtained encouraging results in patients with Crohn's disease [205]. Vagus nerve stimulation also led to promising results in a porcine model of sepsis [206]. Transcutaneous auricular vagus nerve stimulation performed in patients with sepsis resulted in substantially lower serum proinflammatory cytokines and higher anti-inflammatory cytokines, but no differences in clinical score were obtained between the treated patients and the sham stimulation [207].

1.10 A PERSONAL CONCLUDING REMARK

Thanks to their keen observational skills, their desire to discover new therapeutic approaches, and their experimental expertise, highly motivated physicians and scientists have, over the years, offered new treatments to patients in need. Since the deciphering of the immune system and the understanding of its complex network of interactions between immune cells and molecular players, experimenters have helped improve and prolong the lives of patients with debilitating diseases or even save them. I would like to thank and congratulate specifically Edward Donnall Thomas [95], Pablo Umaña [96], and Donald Metcalf [122] whose contributions were of great use to me and allowed me to be alive and healthy to write this chapter. I would also like to thank Professor François Lemonnier and the nurses of Henri Mondor Hospital, who treated me with the most appropriate treatment, and the French Social Security system, which covered the cost of my treatment, including the obinutuzumab (€3,214 per infusion).

I would like to dedicate this text to my valued former collaborator, Dr. Minou Adib-Conquy, who supervised the thesis of Professor Fernando Guimaraes, and to Dr. Tomasz Skirecki (Warsaw), my spiritual son in the field of immunity to sepsis [208]. Both were not as lucky as I was and died of cancer at the age of 47 and 37, respectively. This illustrates how much researchers must continue their efforts and call upon their inventiveness to treat this disease which has become a major cause of mortality in developed countries, whereas 125 years ago, the main causes were tuberculosis and syphilis.

KEY TERMS & DEFINITIONS SIDEBAR

Cytokines Soluble mediators that allow the crosstalk between cells.

Immune checkpoint inhibitors Inhibitors that block key surface proteins involved in the negative regulation of the immune response.

Serotherapy Injection of immune serum to prevent infections.

Vaccination Injection of an antigen (microbial molecule, attenuated or killed bacteria or virus, etc.) to induce protective immunity against a given infection.

Variolation An injection of material sampled from a human with smallpox to prevent the infection.

LIST OF ABBREVIATIONS

BCG	bacille de Calmette et Guérin
CAR-T cells	chimeric antigen receptor-engineered T cells
CD	cluster of differentiation
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
COVID-19	coronavirus disease 2019
DAMPs	damage-associated molecular patterns
FDA	US Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HMGB1	high-mobility group box 1
IFN	interferon
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
IL-1Ra	IL-1 receptor antagonist
ISG	immune serum globulin
IvIg	intravenous immunoglobulins
LAK	lymphokine-activated killer
LPS	lipopolysaccharide
mAb	monoclonal antibody
M-CSF	macrophage-colony-stimulating factor
MIF	macrophage migration inhibitory factor
mRNA	micro ribonucleic acid
NK	natural killer
PAMPs	pathogen-associated molecular patterns
PD-1	programmed cell death protein 1

PD-L1	PD1 ligand 1
RANK-L	receptor activator of nuclear factor kappa-B ligand
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
TCR	T-cell receptor
Th	T helper cells
TIL	tumour-infiltrating lymphocytes
TNF	tumour necrosis factor
Treg	regulatory T cells
TREM-1	triggering receptor expressed on myeloid cells 1
VEGF	vascular endothelial growth factor

REVIEW QUESTIONS

1. What were the key contributions of Ehrlich and Metchnikoff to immunology?
2. How did Coley's observations on tumour regression after bacterial infection anticipate modern cancer immunotherapy?
3. What technological advance allowed the transition from polyclonal serotherapy to the use of monoclonal antibodies?
4. Give examples of cytokines, used a tool or as a target for immunotherapy.
5. What is the aim of vagal nerve stimulation?

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