TIMELINE OF IMMUNOLOGY

- **1549 – The earliest account of inoculation of smallpox (variolation) occurs in Wan Quan's (1499–1582)**
- **1718 – Smallpox inoculation in Ottoman Empire realized by West. Lady Mary Wortley Montagu,** the wife of the British ambassador to Constantinople, observed the positive effects of variolation on the native population and had the technique performed on her own children.
- **1796 – First demonstration of smallpox vaccination (Edward Jenner)**
- 1837 – Description of the role of microbes in putrefaction and fermentation (Theodore Schwann)
- 1838 – Confirmation of the role of yeast in fermentation of sugar to alcohol (Charles Cagniard-Latour)
- **1840 – Proposal of the germ theory of disease (Jakob Henle)**
- 1850 – Demonstration of the contagious nature of puerperal fever (childbed fever) (Ignaz Semmelweis)
- 1857–1870 – Confirmation of the role of microbes in fermentation (Louis Pasteur)
- **1862 – Phagocytosis (Ernst Haeckel)**
- 1867 – Aseptic practice in surgery using carbolic acid (Joseph Lister)
- 1876 – Demonstration that microbes can cause disease-anthrax (Robert Koch)
- 1877 – Mast cells (Paul Ehrlich)
- 1878 – Confirmation and popularization of the germ theory of disease (Louis Pasteur)
- **1880 – 1881 -Theory that bacterial virulence could be attenuated by culture in vitro and used as vaccines. Proposed that live attenuated microbes produced immunity by depleting host of vital trace nutrients. Used to make chicken cholera and anthrax "vaccines" (Louis Pasteur)**
- **1883 – 1905 – Cellular theory of immunity via phagocytosis by macrophages and microphages (polymorhonuclear leukocytes) (Elie Metchnikoff)**
- **1885 – Introduction of concept of a "therapeutic vaccination". Report of a live "attenuated" vaccine for rabies (Louis Pasteur and Pierre Paul Émile Roux).**
- 1888 – Identification of bacterial toxins (diphtheria bacillus) (Pierre Roux and Alexandre Yersin)
- 1888 – Bactericidal action of blood (George Nuttall)
- **1890 – Demonstration of antibody activity against diphtheria and tetanus toxins. Beginning of humoral theory of immunity. (Emil von Behring) and (Kitasato Shibasaburō)**
- **1891 – Demonstration of cutaneous (delayed type) hypersensitivity (Robert Koch)**
- 1893 – Use of live bacteria and bacterial lysates to treat tumors-"Coley's Toxins" (William B. Coley)
- 1894 – Bacteriolysis (Richard Pfeiffer)
- **1896 – An antibacterial, heat-labile serum component (complement) is described (Jules Bordet)**
- **1900 – Antibody formation theory (Paul Ehrlich)**
- **1901 – Blood groups (Karl Landsteiner)**
- **1902 – Immediate hypersensitivity anaphylaxis (Paul Portier) and (Charles Richet)**

- 1903 – Intermediate hypersensitivity, the "Arthus reaction" (Maurice Arthus)
- 1903 – Opsonization
- 1905 – "Serum sickness" allergy (Clemens von Pirquet and (Bela Schick)
- **1909 – Paul Ehrlich proposes "immune surveillance" hypothesis of tumor recognition and eradication**
- 1911 – 2nd demonstration of filterable agent that caused tumors (Peyton Rous)
- **1917 – Hapten (Karl Landsteiner)**
- **1921 – Cutaneous allergic reactions (Otto Prausnitz and Heinz Küstner)**
- 1924 – Reticuloendothelial system
- **1938 – Antigen-Antibody binding hypothesis (John Marrack)**
- **1940 – Identification of the Rh antigens (Karl Landsteiner and Alexander Weiner)**
- **1942 – Anaphylaxis (Karl Landsteiner and Merill Chase)**
- 1942 – Adjuvants (Jules Freund and Katherine McDermott)
- 1944 – hypothesis of allograft rejection
- 1945 – Coombs test a.k.a. antiglobulin test (AGT)
- 1946 – Identification of mouse MHC (H2) by George Snell and Peter A. Gorer
- **1948 – Antibody production in plasma B cells**
- 1949 – Growth of polio virus in tissue culture, neutralization with immune sera, and demonstration of attenuation of neurovirulence with repetitive passage (John Enders) and (Thomas Weller) and (Frederick Robbins)
- 1951 – vaccine against yellow fever
- **1953 – Graft-versus-host disease**
- 1953 – Validation of immunological tolerance hypothesis
- **1957 – Clonal selection theory (Frank Macfarlane Burnet)**
- **1957 – Discovery of interferon by Alick Isaacs and Jean Lindenmann**
- 1958–1962 – Discovery of human leukocyte antigens (Jean Dausset and others)
- **1959–1962 – Discovery of antibody structure (independently elucidated by Gerald Edelman and Rodney Porter)**
- 1959 – Discovery of lymphocyte circulation (James Gowans)
- 1960 – Discovery of lymphocyte "blastogenic transformation" and proliferation in response to mitogenic lectins-phytohemagglutinin (PHA) (Peter Nowell)
- **1961–1962 Discovery of thymus involvement in cellular immunity (Jacques Miller)**
- **1960 – Radioimmunoassay – (Rosalyn Sussman Yalow)**
- 1961 – Demonstration that glucocorticoids inhibit PHA-induced lymphocyte proliferation (Peter Nowell)
- 1963 – Development of the plaque assay for the enumeration of antibody-forming cells in vitro by Niels Jerne and Albert Nordin
- 1963 – Gell and Coombs classification of hypersensitivity
- 1964–1968 – T and B cell cooperation in immune response
- 1965 – Discovery of lymphocyte mitogenic activity, "blastogenic factor" (Shinpei Kamakura) and (Louis Lowenstein) (J. Gordon) and (L.D. MacLean)
- **1965 – Discovery of "immune interferon" (gamma interferon) (E.F. Wheelock)**
- **1965 – Secretory immunoglobulins**
- **1967 – Identification of IgE as the reaginic antibody (Kimishige Ishizaka)**
- 1968 – Passenger leukocytes identified as significant immunogens in allograft rejection (William L. Elkins and Ronald D. Guttmann)

- 1969 – The lymphocyte cytolysis Cr51 release assay (Theodore Brunner) and (Jean-Charles Cerottini)
- **1971 – Peter Perlmann and Eva Engvall at Stockholm University invented ELISA**
- **1972 – Structure of the antibody molecule**
- **1973 – Dendritic Cells first described by Ralph M. Steinman**
- **1974 – Immune Network Hypothesis (Niels Jerne)**
- **1974 – T-cell restriction to MHC (Rolf Zinkernagel and (Peter C. Doherty)**
- **1975 – Generation of monoclonal antibodies (Georges Köhler) and (César Milstein)**
- **1975 – Discovery of Natural Killer cells (Rolf Kiessling, Eva Klein, Hans Wigzell)**
- **1976 – Identification of somatic recombination of immunoglobulin genes (Susumu Tonegawa)**
- **1980–1983 – Discovery and characterization of interleukins, 1 and 2 IL-1 IL-2 (Robert Gallo, Kendall A. Smith, Tadatsugu Taniguchi)**
- **1983 – Discovery of the T cell antigen receptor TCR (Ellis Reinherz) (Philippa Marrack) and (John Kappler) (James Allison)**
- 1983 – Discovery of HIV (Luc Montagnier) (Françoise Barré-Sinoussi) (Robert Gallo)
- 1985–1987 – Identification of genes for the T cell receptor
- **1986 – Hepatitis B vaccine produced by genetic engineering**
- **1986 – Th1 vs Th2 model of T helper cell function (Timothy Mosmann)**
- 1988 – Discovery of biochemical initiators of T-cell activation: CD4- and CD8-p56lck complexes (Christopher E. Rudd)
- 1990 – Gene therapy for SCID
- 1991 – Role of peptide for MHC Class II structure (Scheherazade Sadegh-Nasseri & Ronald N. Germain
- 1992 – Discovery of transitional B cells (David Allman & Michael Cancro)
- **1994 – 'Danger' model of immunological tolerance (Polly Matzinger)**
- 1995 – James P. Allison describes the function of CTLA-4
- **1995 – Regulatory T cells (Shimon Sakaguchi)**
- **1995 – First Dendritic cell vaccine trial reported by Mukherji et al.**
- **1996 – 1998 – Identification of Toll-like receptors**
- **2000 – Characterization of M1 and M2 macrophage subsets by Charles Mills**
- **2001 – Discovery of FOXP3 – the gene directing regulatory T cell development**
- **2005 – Development of human papillomavirus vaccine (Ian Frazer)**
- 2006 – Antigen-specific NK cell memory first reported by Ulrich von Andrian's group after discovery by Mahmoud Goodarzi
- **2008 - Françoise Barré-Sinoussi and Luc Montagnier win the Nobel Prize in Physiology or Medicine for their discovery of human immunodeficiency virus**
- 2010 – The first autologous cell-based cancer vaccine, PROVENGE, is approved by the FDA for the treatment of metastatic, asymptomatic stage IV prostate cancer. The treatment is marketed at a cost of $93,000 and imparts, on average, only an extra four months of life expectancy. The manufacturer, Dendreon Inc, declares bankruptcy in 2014.
- 2010 – First immune checkpoint inhibitor, ipilimumab (anti-CTLA-4), is approved by the FDA for treatment of stage IV melanoma
- 2011 – Carl H. June reports first successful use of CAR T-cells expressing the 4-1BB costimulatory signaling domain for the treatment of CD19+ malignancies

- 2014 – A second class of immune checkpoint inhibitor (anti-PD-1) is approved by the FDA for the treatment of melanoma. Two different drugs, pembrolizumab and nivolumab are approved within months of each other.
- 2016 – Halpert and Konduri first characterize the role of dendritic cell CTLA-4 in Th-1 immunity
- 2016 – A third class of immune checkpoint inhibitor, anti-PD-L1 (atezolizumab), is approved for the treatment of bladder cancer
- 2017 – The first autologous CAR T-cell therapy tisagenlecleucel also known as Kymriah is approved for the treatment of pediatric B-ALL. Marketed at a cost of $475,000, the treatment provides an 83% rate of durable remission among poor prognosis patients for whom a bad outcome would otherwise be expected.
- **2017 – The Indian government approves Apceden, the first potentially curative dendritic cell vaccine for the treatment of prostate, ovarian, colon, and lung cancers.**
- 2018 – James P.Allison and Tasuku Honjo won the Nobel Prize in Physiology or Medicine for their discovery of cancer therapy by inhibition of negative immune regulation

NOBLE PRIZES IN IMMUNOLOGY (MEDICINE)

- **1901- Emil Adolf von Behring**, "for his serum therapy to treat diphtheria"
- 1908- **Eli Metchnikof and Paul Ehrlich**, "for study of the immune system"
- **1919- Jules Bordet**, "for discovery of the complement system in the immune system"
- **1930- Karl Landsteiner**, "for discovery of human blood types"
- **1960- Medawar and Burnet**, "for the discovery that the immune system of the fetus learns how to distinguish between self and non-self"
- **1972- Edelman and Porter**, "for discovering the chemical structure of antibodies"
- **1980- Benacerraf, Dausset and Snell**, "for discovery of the Major histocompatibility complex genes"
- **1984- Jerne, Köhler and Milstein,** "for work on the immune system and the production of monoclonal antibodies"
- **1987- Susumu Tonegawa**, "for the generation of antibody diversity"
- **1989- Bishop and Varmus**, "for discovering the cellular origins of retroviral oncogenes"
- **1996- Peter C. Doherty and Rolf M. Zinkernagel**, "for describing how MHC molecules are used by white blood cells to detect and kill virus-infected cells."
- **2011- Bruce Beutler, Jules A. Hoffmann** "for their discoveries concerning the activation of innate immunity" and **Ralph Marvin Steinman,** "for his discovery of the dendritic cell and its role in adaptive immunity"
- **2018- James P. Allison and Tasuku Honjo** "for their discovery of cancer therapy by inhibition of negative immune regulation."