The Immune System: The First Nobel Prize in Physiology or Medicine

Emil Adolph von Behring, 1901
Ilya Ilyich Machnikov and Paul Ehrlich, 1908
Jules Bordet, 1919
Sir Frank Macfarlane Burnet and Sir Peter Brian Medawar, 1960
Gerald M. Edelman and Rodney R. Porter, 1972
Niels K. Jerne, Georges J. F. Köhler and César Milstein, 1984
Susumo Tonegawa, 1987
Peter C. Doherty and Rolf M. Zinkernagel, 1996
Bruce A. Beutler, Jules A. Hoffmann and Ralph M. Steinman, 2011
Adolph Emil Behring, 1901

Winner of the FIRST Nobel Prize for Physiology or Medicine

"for his work on serum therapy, especially its application against diphtheria, by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and deaths"
Adolph Emil Behring

- **Born:** 15 March 1854, Hansdorf, Prussia (now Jankowa Żagańska, Poland)
- **Died:** 31 March 1917, Marburg, Germany
- **Affiliation at the time of the award:** Marburg University, Marburg, Germany
Adolph Emil Behring

Behring studied medicine at the Akademie für das militärärztliche Bildungswesen, Berlin between 1874 and 1878. First a military doctor, he later became Professor of Hygienics at the University of Marburg.

He discovered diphtheria antitoxin in 1890 and made many contributions to the study of immunity. He was awarded the first Nobel Prize in Physiology or Medicine in 1901 for the development of serum therapies against diphtheria and tetanus. The former had been a scourge of the population, especially children, whereas the other was a leading cause of death in wars, killing the wounded.

He married the then eighteen-year-old Else Spinola in December 1896 (he was 42). They had six sons. They held their honeymoon at villa Behring on Capri 1897, where Behring owned a vacation home.
Adolph Emil Behring

Behring was elected a Foreign Honorary Member of the American Academy of Arts and Sciences in 1902.

He died at Marburg, Hessen-Nassau, on 31 March 1917. His name survives with the Dade Behring organization, the world's largest company dedicated solely to clinical diagnostics (now part of the Siemens Healthcare Division), in CSL Behring (a manufacturer of plasma-derived biotherapies), in Behringwerke AG in Marburg, in Novartis Behring, in the Emil von Behring Prize of the University of Marburg, the highest endowed medicine award in Germany and in schools and gymnasiums.
Behring’s award was not without controversy

• The formal study of antibodies may be said to have begun in 1890 when Kitasato Shibasaburō (1853-1931) described antibody action against diphtheria and anthrax toxins. Shibasaburō had studied under Robert Koch (1843-1910, Nobel Prize 1905). He was the first person to grow the tetanus bacillus in pure culture, and used this in partnership with Behring in 1891 to demonstrate the effect of serum extracted from an animal which had been inoculated with tetanus toxin.

• Paul Ehrlich (1854-1915) was the first to coin the term “antibody” (Antikörper, in German) in his 1891 paper, “Experimental Studies on Immunity”.

• Behring effectively cheated Ehrlich out of recognition and financial reward for their collaborative development of a diphtheria serum produced by repeatedly injecting the deadly toxin into a horse. A chemical company preparing to undertake commercial production and marketing of the diphtheria serum offered a contract to both men, but von Behring maneuvered to claim all the considerable financial rewards for himself.

• Neither men were credited by Behring in his acceptance of the Nobel Prize. However Ehrlich did win the prize in 1908.
Ilya Ilyich Metchnikov and Paul Ehrlich, 1908, “in recognition of their work on immunity”

- Ilya Metchnikov (1845-1916): as graduate student he worked on the intracellular digestion in flatworms. This led later to his discovery of the phenomenon of phagocytosis, which he linked to the movement of leucocytes from blood to sites of infection. He proposed that this was a part of the immune system.

- Paul Ehrlich (1854-1915): demonstrated that antitoxins isolated from blood were highly specific for the toxins to which they would bind, and postulated that these toxin “receptors” were proteins and were produced by cells in the blood and were used by the cells to recognize and ingest the toxin. He further postulated that these cells produce the receptor proteins in excess and these were what was circulating in the blood.
We now know that a complex of proteins (C3 and C3-convertase) are synthesized in an inactive form by the liver, macrophages, monocytes, and epithelial cells of the genitourinary and gastrointestinal tracts. Upon activation by the presence of antigen-antibody complexes (the specific immune response), C3-convertase cleaves and activates component C3, creating a series of components with different immune responses. C3b binds to the surface of pathogens, leading to greater phagocytosis by leukocytes; C5a helps recruit these cells to the site of infection. Both C3a and C5a directly trigger degranulation of mast cells and increase vascular permeability and smooth muscle contraction. C5b initiates the membrane attack pathway, a complex of proteins that form a transmembrane channel in target cells causing osmotic lysis.

Jules Bordet, 1919 “for his discoveries relating to immunity”

- Bordet (1870-1961) worked in Metchnikov’s lab in 1895. He found that the immune response consists of two different actions. The first is the *innate immune response* or the *complement system*, and the second is the *adaptive immune response*. Bordet showed that the innate immune response is always present, whether the subject has been immunized or not.
We now know that while all the cells of the immune system are produced in bone marrow, early on they pass through the thymus gland, which rejects any which might react with self. Today immunosuppressive drugs (and sometimes radiation and/or surgery) are used to artificially suppress the immune response for cases involving transplantation or autoimmune diseases.*

*Joseph E. Murray and E. Donnall Thomas, 1990 “for their discoveries concerning organ and cell transplantation in the treatment of human disease”
Antibodies are proteins (either free in serum or cell-bound) that attach to a specific antigen (see Ehrlich, 1908).

- Antibodies consist of two heavy and two light chains (Edelman and Porter).
- The heavy chain determines the action of the antibody.
- Humans have five types ("isotypes") of heavy chains: IgA, IgD, IgE, IgG and IgM. IgM is the primary defense against invading pathogens. IgE is involved in allergic reactions.
- Both heavy and light chains each have a constant and a variable region. The constant region in the heavy chain determines the isotype. The variable regions in both chains determine the antigen specificity.

- If the antigen is free in the serum IgG antibodies inactivate it by agglutination and mark it for later elimination.
- If the antigen is found on a cell surface such as a bacterium they mark the cell for attack by macrophages or killer T-cells.
The heavy chain domain on the DNA of chromosome 14 has some 65 different segments. The light chain genes are found on chromosomes 2 and 22.

To form the exact gene coding for the variable region in either chain, gene segments are randomly combined before being expressed. This leads to many thousands of possible variable regions and thus to the ability of antibodies to bind to a vast variety of antigens.

Susumu Tonagawa, 1987 “for his discovery of the genetic principle for generation of antibody diversity”
Once a B-cell antibody attaches to an antigen and the B-cell proliferates, a process known as "somatic hypermutation and affinity maturation" takes place.

The genes for the variable regions mutate at the rate of around one nucleotide per generation. This leads to variations from the original successful antibody.

Some variants are worse than the original, while some are better.

The ones with higher affinity receive strong survival signals from other cells and proliferate, coming to dominate the population.
Monoclonal antibodies are antibodies highly specific for a single antigen. To produce them one collects antibody-producing immune cells, immortalizes them by fusing to cancer cells, then selects for the clone of cells that produces the most effective antibody.
Monoclonal Antibodies in Research
Therapeutic Uses of Monoclonal Antibodies:

- **Radioimmunotherapy (RIT)** involves the use of radioactively-conjugated murine antibodies against cellular antigens.

- **Antibody-directed enzyme prodrug therapy (ADEPT)** involves the application of cancer-associated monoclonal antibodies that are linked to a drug-activating enzyme. Systemic administration of a non-toxic agent results in the antibody's conversion to a toxic drug, resulting in a cytotoxic effect that can be targeted at malignant cells.

- **Immunoliposomes** are antibody-conjugated liposomes. Liposomes can carry drugs, and when conjugated with monoclonal antibodies, may be directed against malignant cells.

- **Checkpoint therapy** uses antibodies and other techniques to circumvent the defenses that tumors use to suppress the immune system. Each defense is known as a checkpoint. Compound therapies combine antibodies to suppress multiple defensive layers.

  - **Unleashing T cells against tumors**

List of therapeutic monoclonals
The process begins when a B-cell binds to an antigen. This may be on the surface of a bacterium or virus, may be free-floating, or may be expressed on the surface of a phagocyte or infected cell. Once the B-cell is activated (a process involving Helper T-cells), it produces antibodies specific to the antigen (thousands a second!). The B-cell divides and gives rise to more antigen-producing daughters ("plasma cells") and to long-lived "memory cells" ready to fight the next assault by the same antigen, even years later. This latter is what vaccines work on.

The committee was not aware that Steinman had died three days before the announcement, from pancreatic cancer. After deliberation, the committee decided that as the decision to award the prize "was made in good faith", it would remain unchanged. Steinman's daughter said that he had joked the previous week with his family about staying alive until the prize announcement. He said: "I know I have got to hold out for that. They don't give it to you if you have passed away. I got to hold out for that."