

## **Nobel Prize in Medicines 2011**



**Bruce A. Beutler**



**Jules A. Hoffmann**



**Ralph M. Steinman**

**The Nobel Prize in Physiology or Medicine 2011 was divided, one half jointly to Bruce A. Beutler and Jules A. Hoffmann "for their discoveries concerning the activation of innate immunity" and the other half to Ralph M. Steinman "for his discovery of the dendritic cell and its role in adaptive immunity"**

This year's Nobel Laureates have revolutionized our understanding of the immune system by discovering key principles for its activation.

Scientists have long been searching for the gatekeepers of the immune response by which man and other animals defend themselves against attack by bacteria and other microorganisms. Bruce Beutler and Jules Hoffmann discovered receptor proteins that can recognize such microorganisms and activate innate immunity, the first step in the body's immune response. Ralph Steinman discovered the dendritic cells of the immune system and their unique capacity to activate and regulate adaptive immunity, the later stage of the immune response during which microorganisms are cleared from the body.

The discoveries of the three Nobel Laureates have revealed how the innate and adaptive phases of the immune response are activated and thereby provided novel insights into

disease mechanisms. Their work has opened up new avenues for the development of prevention and therapy against infections, cancer, and inflammatory diseases.

Two lines of defense in the immune system

We live in a dangerous world. Pathogenic microorganisms (bacteria, virus, fungi, and parasites) threaten us continuously but we are equipped with powerful defense mechanisms (please see image below). The first line of defense, innate immunity, can destroy invading microorganisms and trigger inflammation that contributes to blocking their assault. If microorganisms break through this defense line, adaptive immunity is called into action. With its T and B cells, it produces antibodies and killer cells that destroy infected cells. After successfully combating the infectious assault, our adaptive immune system maintains an immunologic memory that allows a more rapid and powerful mobilization of defense forces next time the same microorganism attacks. These two defense lines of the immune system provide good protection against infections but they also pose a risk. If the activation threshold is too low, or if endogenous molecules can activate the system, inflammatory disease may follow.

The components of the immune system have been identified step by step during the 20<sup>th</sup> century. Thanks to a series of discoveries awarded the Nobel Prize, we know, for instance, how antibodies are constructed and how T cells recognize foreign substances. However, until the work of Beutler, Hoffmann and Steinman, the mechanisms triggering the activation of innate immunity and mediating the communication between innate and adaptive immunity remained enigmatic.

### **Discovering the sensors of innate immunity**

**Jules Hoffmann** made his pioneering discovery in 1996, when he and his co-workers investigated how fruit flies combat infections. They had access to flies with mutations in several different genes including Toll, a gene previously found to be involved in embryonal development by Christiane Nüsslein-Volhard (Nobel Prize 1995). When Hoffmann infected his fruit flies with bacteria or fungi, he discovered that Toll mutants died because they could not mount an effective defense. He was also able to conclude that the

product of the Toll gene was involved in sensing pathogenic microorganisms and Toll activation was needed for successful defense against them.

**Bruce Beutler** was searching for a receptor that could bind the bacterial product, lipopolysaccharide (LPS), which can cause septic shock, a life threatening condition that involves overstimulation of the immune system. In 1998, Beutler and his colleagues discovered that mice resistant to LPS had a mutation in a gene that was quite similar to the Toll gene of the fruit fly. This Toll-like receptor (TLR) turned out to be the elusive LPS receptor. When it binds LPS, signals are activated that cause inflammation and, when LPS doses are excessive, septic shock. These findings showed that mammals and fruit flies use similar molecules to activate innate immunity when encountering pathogenic microorganisms. The sensors of innate immunity had finally been discovered.

The discoveries of Hoffmann and Beutler triggered an explosion of research in innate immunity. Around a dozen different TLRs have now been identified in humans and mice. Each one of them recognizes certain types of molecules common in microorganisms. Individuals with certain mutations in these receptors carry an increased risk of infections while other genetic variants of TLR are associated with an increased risk for chronic inflammatory diseases.

**A new cell type that controls adaptive immunity**

Ralph Steinman discovered, in 1973, a new cell type that he called the dendritic cell. He speculated that it could be important in the immune system and went on to test whether dendritic cells could activate T cells, a cell type that has a key role in adaptive immunity and develops an immunologic memory against many different substances. In cell culture experiments, he showed that the presence of dendritic cells resulted in vivid responses of T cells to such substances. These findings were initially met with skepticism but subsequent work by Steinman demonstrated that dendritic cells have a unique capacity to activate T cells.

Further studies by Steinman and other scientists went on to address the question of how the adaptive immune system decides whether or not it should be activated when

encountering various substances. Signals arising from the innate immune response and sensed by dendritic cells were shown to control T cell activation. This makes it possible for the immune system to react towards pathogenic microorganisms while avoiding an attack on the body's own endogenous molecules.

From fundamental research to medical use

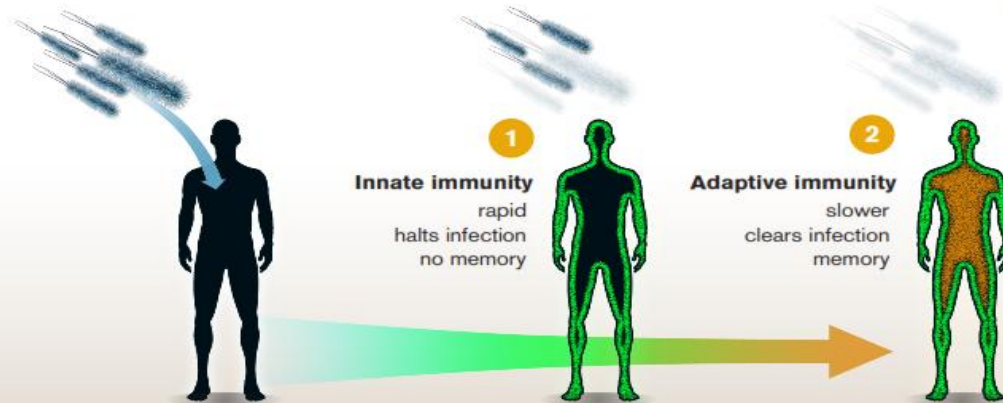
The discoveries that are awarded the 2011 Nobel Prize have provided novel insights into the activation and regulation of our immune system. They have made possible the development of new methods for preventing and treating disease, for instance with improved vaccines against infections and in attempts to stimulate the immune system to attack tumors. These discoveries also help us understand why the immune system can attack our own tissues, thus providing clues for novel treatment of inflammatory diseases.

**Bruce A. Beutler** was born in 1957 in Chicago, USA. He received his MD from the University of Chicago in 1981 and has worked as a scientist at Rockefeller University in New York, at UT Southwestern Medical Center in Dallas, where he discovered the LPS receptor, and the Scripps Research Institute in La Jolla, CA. Very recently, he rejoined the University of Texas Southwestern Medical Center in Dallas as professor in its Center for the Genetics of Host Defense.

**Jules A. Hoffmann** was born in Echternach, Luxembourg in 1941. He studied at the University of Strasbourg in France, where he obtained his PhD in 1969. After postdoctoral training at the University of Marburg, Germany, he returned to Strasbourg, where he headed a research laboratory from 1974 to 2009. He has also served as director of the Institute for Molecular Cell Biology in Strasbourg and during 2007-2008 as President of the French National Academy of Sciences.

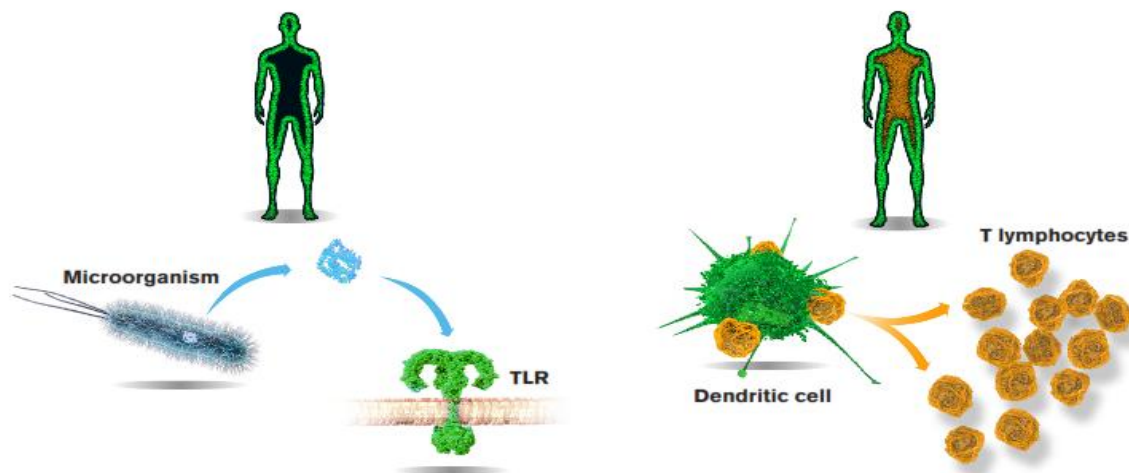
**Ralph M. Steinman** was born in 1943 in Montreal, Canada, where he studied biology and chemistry at McGill University. After studying medicine at Harvard Medical School in Boston, MA, USA, he received his MD in 1968. He was affiliated with Rockefeller University in New York since 1970, where he was professor of immunology from 1988. Sadly, Ralph Steinman passed away before the news of his Nobel Prize reached him.

## The Nobel Prize in Physiology or Medicine 2011



### The immune system

Infection of the human body by pathogenic microorganisms such as bacteria, viruses, parasites or fungi triggers the immune response. It occurs in a two-step process: innate immunity halts the infection, and adaptive immunity subsequently clears it.



### 1 Innate immunity

Components of microorganisms bind to Toll-like receptors located on many cells in the body. This activates innate immunity, which leads to inflammation and to the destruction of invading microorganisms.

### 2 Adaptive immunity

Dendritic cells activate T lymphocytes, which initiates adaptive immunity. A cascade of immune reactions follows, with formation of antibodies and killer cells.



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