

BRUCE ALAN BEUTLER



American immunologist and geneticist

Together with Jules A. Hoffmann, he received one-half of the 2011 Nobel Prize in Physiology or Medicine, for „their discoveries concerning the activation of innate immunity” (the other half went to Ralph M. Steinman for „his discovery of the dendritic cell and its role in adaptive immunity”).

CAREER

Beutler majored in biology as an undergraduate at the University of California, San Diego, where he graduated in 1976 at the age of 18. He attended medical school at the University of Chicago. From 1981 to 1983 Beutler continued his medical training at the University of Texas Southwestern Medical Center in Dallas, Texas, as an intern in the Department of Internal Medicine, and as a resident in the Department of Neurology. Between 1983 and 1985 he was a postdoctoral fellow at Rockefeller University in the laboratory of Anthony Cerami. He became an assistant professor at Rockefeller University in 1985. He was also an associate physician at the Rockefeller University Hospital between 1984 and 1986.

Beutler returned to Dallas in 1986 as an assistant professor in the Department of Internal Medicine of the University of Texas Southwestern Medical Center at Dallas, and an assistant investigator at the Howard Hughes Medical Institute, where he retained a position for the next 14 years. He became an associate professor and an associate investigator with HHMI in 1990, and a professor in 1996.

In 2000, Beutler moved to The Scripps Research Institute in La Jolla, California, as a professor in the department of immunology. In 2007, he became chairman of the newly created Department of Genetics at Scripps Research. In 2011, Beutler returned to UT Southwestern Medical Center to become director of the Center for the Genetics of Host Defense.

Beutler is best known for his pioneering molecular and genetic studies of inflammation and innate immunity. He was the first to isolate mouse tumor necrosis factor-alpha (TNF), and to demonstrate the inflammatory potential of this cytokine, proving its important role in endotoxin-induced shock. Subsequently, he invented recombinant molecules expressly designed to neutralize TNF, fusing the binding portion of TNF receptor proteins to the heavy chain of an immunoglobulin molecule to force receptor dimerization. These molecules were later used extensively as the drug Etanercept in the treatment of rheumatoid arthritis, Crohn's disease, psoriasis, and other forms of inflammation. Interested in the mechanism by which LPS activates mammalian immune cells, Beutler used TNF production as a phenotypic endpoint to identify the LPS receptor. Identification of the receptor hinged on the positional cloning of the mammalian *Lps* locus, which had been known since the 1960s as a key genetic determinant of all biological responses to LPS. Beutler thus discovered the key sensors of microbial infection in mammals, demonstrating that one of the mammalian Toll-like receptors, TLR4, acts as the membrane-spanning component of the mammalian LPS receptor complex. The TLRs (of which ten are now known to exist in humans) are now widely known to function in the perception of microbes, each detecting signature molecules that herald infection. These receptors also mediate severe illness, including shock and systemic inflammation as it occurs in the course of an infection. They are central to the pathogenesis of sterile inflammatory and autoimmune diseases such as systemic lupus erythematosus. The research on TLRs won him the Nobel Prize in 2011.

The positional cloning of *Lps* was completed in 1998. Beutler thereafter continued to apply a forward genetic approach to the analysis of immunity in mammals. In this process, germline mutations that alter immune function are created through a random process using the alkylating agent ENU, detected by their phenotypic effects, and then isolated by positional cloning. His work disclosed numerous essential signaling molecules required for the innate immune response, and helped to delineate the biochemistry of innate immunity.

ENU mutagenesis was also used by Beutler and colleagues to study the global response to a defined infectious agent. By screening mutant mice for susceptibility to mouse cytomegalovirus (MCMV), they identified a large number of genes that make a life-or-death difference during infection, and termed this set of genes the MCMV

„resistome“. These genes fall into „sensing“, „signaling“, „effector“, „homeostatic“, and „developmental“ categories, and some of them were wholly unexpected. For example, $K_{ir}6.1$ ATP-sensitive potassium channels in the smooth muscle of the coronary arteries serve an essential homeostatic role during infection by this microbe, and mutations that affect them cause sudden death during infection.

In the course of their work, Beutler and his colleagues identified genes required for other important biological processes, including the regulation of iron absorption, hearing, and embryonic development, since their disruption by ENU created strikingly abnormal visible phenotypes.

PROFESSIONAL ACHIEVEMENTS

On October 4, 2011, Beutler was named regental professor of the University of Texas System.

- 2001 – Institute for Scientific Information has listed Beutler as an ISI highly cited researcher since the year 2001, marking him as an influential figure in the field of immunology. He has also been listed by Thomson-Reuters as a Citation Laureate.
- 2004 – Robert Koch Prize of the Robert Koch Foundation, Germany (shared with Jules A. Hoffmann and Shizuo Akira).
- 2006 – William B. Coley Award of the Cancer Research Institute, US (shared with Shizuo Akira).
- 2006 – Grand Prix Charles-Leopold Mayer of the Académie des Sciences, France.
- 2007 – Balzan Prize for Innate Immunity (shared with Jules A. Hoffmann).
- 2007 – Doctor of Medicine Honoris causa from the Technical University of Munich Germany.
- 2009 – Will Rogers Institute Annual Prize for Research
- 2009 – Albany Medical Center Prize (shared with Charles A. Dinarello and Ralph M. Steinman)[20]
- 2011 – Shaw Prize (shared with Jules A. Hoffmann and Ruslan M. Medzhitov)
- 2011 – Nobel Prize in Physiology or Medicine (shared with Jules A. Hoffmann and Ralph M. Steinman)
- 2012 – Member of the German Academy of Sciences Leopoldina
- 2013 – Stanley J. Korsmeyer Prize
- 2015 – Doctor honoris causa of the Norwegian University of Science and Technology, Norway.
- 2019 – Doctor honoris causa of the University „Magna Graecia“ of Catanzaro, Italy.