THE FACULTY OF MEDICINE
Harvard University

Harold von Boehmer

Photograph courtesy of the Department of Cancer Immunology and Virology at the Dana-Farber Cancer Institute

Harald von Boehmer was a highly creative scientist and a visionary figure in the field of immunology. T cells are essential for human health – the diverse repertoire of antigens recognized by a diverse repertoire of T cells provides protective immunity against infectious agents and tumors. Dr. von Boehmer solved a challenging and fundamentally important scientific problem: given that T cells can recognize essentially any protein antigen, which cellular mechanisms prevent these immune cells from attacking the healthy cells of the body? The insights he gained have an immense impact on the field of immunology and ongoing translational research in autoimmunity, cancer immunology and infectious diseases.

Over the course of his scientific career, Dr. von Boehmer did research in four countries on three continents. After earning his M.D. degree from the Ludwig Maximilian University in Munich (1968), he moved to Melbourne where he obtained his Ph.D. under the mentorship of Dr. Ken Shortman (1974).

Shortly after receiving his Ph.D. he was recruited by Dr. Niels Jerne to the Basel Institute of Immunology, which at the time was a vibrant research center with a focus on basic immunology. At Basel, he performed highly creative experiments on the cellular and molecular mechanisms of T cell development in the thymus (1973-1996). From 1996-1999 he worked at the Institut Necker Enfants Malades, University Paris Descartes, before joining Harvard Medical School in 1999. He was a Professor of Pathology at Harvard Medical School and led a highly active research lab in the Department of Cancer Immunology and AIDS at the Dana-Farber Cancer Institute until his retirement in 2013.

T cells play a central role in human diseases and recognize antigens in the form of short peptides bound to MHC proteins. Each T cell expresses a unique T cell receptor (TCR) formed by gene rearrangement in the thymus, the site of T cell development. The resulting repertoire of T cells can recognize essentially any

peptide presented by MHC proteins, which of course includes the many peptides generated from self-antigens. How then can T cells efficiently detect and eliminate infectious agents, yet spare healthy cells? Dr. von Boehmer's work demonstrated that self-reactive T cells are eliminated during development in the thymus. The design of these groundbreaking experiments was highly creative. He used a T cell receptor specific for male antigen (H-Y), reasoning that such T cells could detect the antigen only in male but not female mice. These experiments were aided by the recent discovery of TCR genes and advances in the development of transgenic mice. He thus generated mice with a TCR specific for the male H-Y antigen and investigated the fate of the resulting T cells in male versus female mice. This ingenious experimental approach yielded a striking result: H-Y specific T cells were eliminated in the thymus of male but not female mice, a process he coined negative selection. This means that autoimmunity is prevented by purging of self-reactive T cells from the repertoire.

Another major challenge in understanding T cell development is the fact that MHC molecules are highly polymorphic. This means that the T cell repertoire needs to be personalized during development in the thymus. His team showed that the TCR of developing thymocytes needed to bind to MHC proteins to ensure their survival and further differentiation, a process called positive selection. These elaborate processes thus ensure that T cells in a given person can productively recognize MHC proteins (positive selection), but that potentially harmful T cells which strongly interact with MHC-bound self-peptides are eliminated (negative selection).

Another fascinating chapter of Dr. von Boehmer's work deals with the question of how functional T cells arise from random rearrangement of the gene elements that encode the building blocks of a TCR. The TCRβ chain rearranges first, and only T cells with a functional rearrangement proliferate and proceed to the next developmental step. How can a rearranged TCRβ chain induce such signaling events even though each TCR requires two chains? This question led to the discovery of the pre-TCR by the von Boehmer lab. The pre-TCRα chain associates with the TCRβ chain to form a functional heterodimer. Once the TCRα chain has been rearranged, a mature TCR heterodimer is formed that can recognize MHC – peptide complexes, enabling the subsequent steps of positive and negative selection. This elegant body of work has entered all textbooks of immunology.

During the last chapter of his career, Dr. von Boehmer investigated the implications on this basic biology for common human diseases, in particular autoimmunity. He discovered that regulatory T cells that protect against the development of type 1 diabetes can be elicited by sustained release of minute quantities of disease-relevant self-peptides. These studies thus closed the circle from discovering how autoimmunity is prevented in most individuals to devising a therapeutic strategy for dealing with those rogue T cells that escape this developmental process.

He received many awards for these groundbreaking contributions to immunology, including the Louis Jeantet Prize for Medicine (1990), the Avery-Landsteiner Prize of the German Society for Immunology (1990), the Paul Ehrlich and Ludwig Darmstädter Prize (1993) and the Körber European Science Prize

(1997).

Dr. von Boehmer was a larger than life person. In addition to his scientific brilliance, he was an excellent cellist who adored Pablo Casals and the music of Schumann. He and his charming wife Monica sometimes played together, he on the cello and she on the piano. Monica and Harald also excelled at hosting, and spent many evenings welcoming his colleagues and trainees into their home to entertain them over fantastic food and drink. Harald was uncompromising in the search for truth; this quality permeated his lab meetings and discussions and is one of the many he is remembered for. Among others are his scientific rigor, creativity and candor. Dr. von Boehmer passed away on June 24, 2018 at the age of 76. He is survived by Monica and their three children, Lisa, Lotta and Philip.

Respectfully submitted,

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