

## **Laudatio by Prof. Dr. Andreas Radbruch for Prof. Dr. Tasuku Honjo**

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This year's Robert Koch Research Award goes to Professor Tasuku Honjo, Kyoto University. He receives this prestigious award for his unique contributions to molecular immunology and medicine.

Antibody forming B lymphocytes are unique in that they diversify their antigen receptor genes by somatic hypermutation (SHM) and class switch recombination (CSR) during immune responses. These two processes, SHM and CSR, are fundamental to the quality of an antibody response. Tasuku Honjo has been an exceptionally creative and productive leader in deciphering the molecular basis of these processes.

SHM introduces point mutations in the variable regions of antibody genes creating a large number of clonally related antibody variants. These variants or mutants then can be selected for higher antigen binding affinity during the germinal center reaction, resulting in the very large increase in affinity that characterizes B cell memory. CSR is a region specific DNA recombination reaction that joins two Ig switch regions. This reaction diversifies antibody responses by producing related clones of B cells in which a single variable region exon is combined with different constant regions. This results in distinct antibody effector functions, pertinent for example to allergy, mucosal immunity, complement fixation, and the opsonization for immune complex receptors on many cell types.

Honjo was first to examine the molecular basis for class switch recombination. His pioneering contribution in this area was to demonstrate that CSR is a deletional recombination reaction. I rank this contribution equal with Tonegawa's Nobel-Prize winning demonstration of rearrangement of antibody variable region gene rearrangements in B lymphocytes. Tasuku Honjo used molecular probes corresponding to constant region genes to show that constant regions are deleted during the class switch reaction. He proposed that pieces of the Ig locus would be looped out during the reaction, and that it would proceed through double stranded DNA break intermediates. Honjo along with others provided the proof for the looping-out deletion model of switching, by cloning and characterizing the deleted switch.

This major discovery was followed by the elucidation of the structure and function of switch regions, and the demonstration of the organization and structure of Ig heavy chain genes. These fundamental findings were accompanied by the characterization of two critical cytokines involved in the regulation of CSR as well as lymphocyte differentiation, namely interleukins 4 and 5. Furthermore, Honjo demonstrated that CSR is mediated by recognition of the secondary rather than the primary structure of DNA, followed by nicking-type cleavage. At last, the mysterious but basic process of antibody isotype switching has a mechanistic basis at the genetic level.

Although those past achievements would already justify the Robert-Koch Prize, more recently Tasuku Honjo topped his achievements with another discovery of equal if not

superior relevance. Honjo's most exciting recent breakthrough was the discovery of activation-induced cytidine deaminase (AID), a relative of the APOBEC genes which serve as intracellular anti-viral defence line. He showed that AID is required for both CSR and SHM. This surprising discovery demonstrated that these physically different reactions are initiated by a single shared intermediate and opened the way towards a molecular understanding of CSR and SHM. Gene conversion was later shown to be regulated by AID. AID is a cytidine deaminase that is structurally related to an RNA editing enzyme. In collaboration with Michel Nussenzweig, Honjo showed that it is required for the cleavage step of CSR. Further, he showed that AID is the only B cell specific component required to induce CSR in non-lymphoid cells. Together with a team of investigators, he established that a deficiency in AID is the cause of the autosomal recessive form of the hyper-IgM syndrome type II.

The regulation of CSR and SHM are the most critical steps in the antigen-specific antibody response. These steps impact on many clinical applications including vaccination, antibody-based therapy, and treatment of allergy. In addition, the genetic alteration mechanisms involved in CSR and SHM have been postulated by Honjo and others to be closely related with those for tumorigenesis through chromosomal translocations and mutations. Honjo has recently shown that ectopic expression of AID induces T cell lymphomas by the accumulation of mutations in transgenic mice. He is now approaching the biochemical mechanisms for AID function. In summary, Honjo has proposed and demonstrated the conceptual framework of almost all aspects of CSR, finally linking CSR with SHM at the molecular level, with ramifications into cancer.

What is overwhelming is the breadth and impact of Honjo's work in a variety of fields in immunobiology. First, he developed the conceptual framework to understand the molecular mechanism of CSR. Unlike VDJ recombination, which is a well-characterized type of site-specific recombination, CSR is a region-specific recombination, which is unique and unprecedented. Second, he has developed novel strategies to isolate new cytokines and receptors; the expression library method in *Xenopus* oocytes for cloning IL-4 and IL-5, and the signal sequence trap method for cloning of SDF-1, fibulin-5 and many other cytokines and receptors. Third, in addition to his monumental discoveries in CSR and SHM, which are the focus of this summary, he has made outstanding contributions to related fields of immunology: the isolation and characterization of a negative costimulatory molecule PD-1, which is proving to be essential to peripheral immune tolerance and to be a potential therapeutic target of tumor immunotherapy; the isolation and characterization of a DNA binding protein RBP-J involved in Notch signaling; the isolation of IL-2 receptor alpha chain cDNA.

Honjo's scientific achievements are not only superlative in immunology but also are of fundamental importance as well as an incentive to the broader fields of molecular biology and cancer biology. Congratulations on his truly amazing achievements which have paved new avenues for looking at Immunology as we know it.