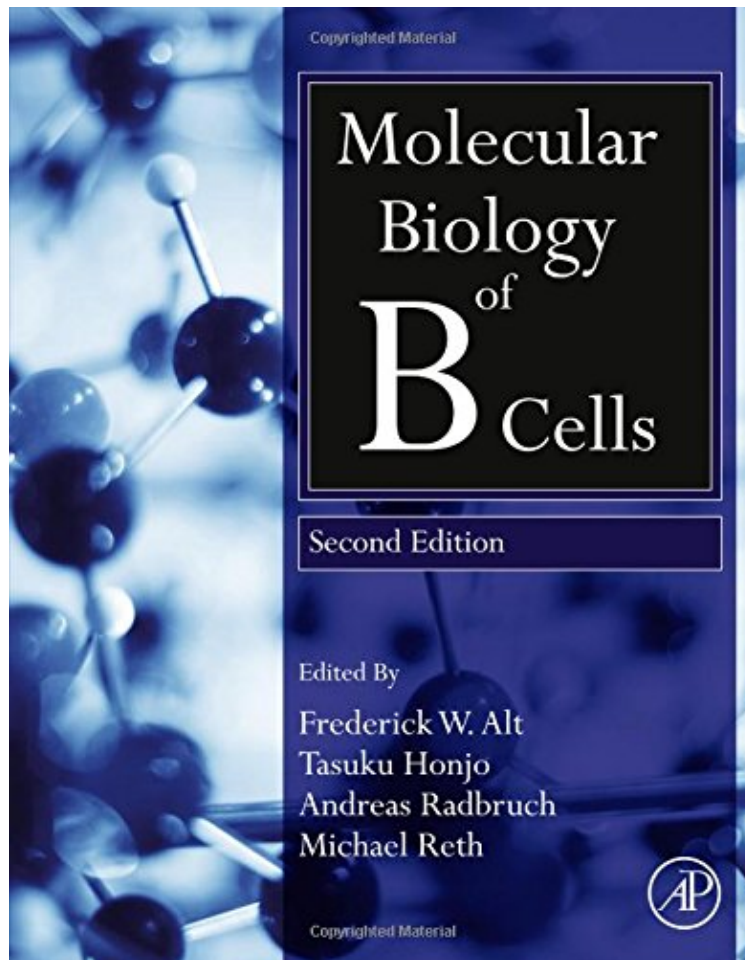


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## Molecular Biology of B Cells, Second Edition

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**About the Author**  
Dr. Tasuku Honjo graduated from Kyoto University Faculty of Medicine in 1966 (M.D.). After obtaining his Ph.D. in Biochemistry (Dr. O. Hayaishi), he spent 4 years in the U.S.A. as a postdoctoral fellow first in Carnegie Institution of Washington (Dr. D. Brown), and then in NIH (Dr. P. Leder) where he initiated studies on immunoglobulin genes. He returned to Tokyo University as an assistant professor in 1974, and then moved to Osaka University School of Medicine as Professor of Genetics in 1979. He succeeded to Dr. O. Hayaishi after his retirement at the Department of Medical Chemistry in Kyoto University. He also served as Dean of Medical School (1996-2000 and 2004-2005), and Executive Member of Council for Science and Technology Policy, Cabinet Office (2006-2012). Currently, he is Professor of Department of Immunology and Genomic Medicine, Kyoto University, and also Chairman of Board of Directors, Shizuoka Prefectural University Corporation. Dr. Honjo is well known for his discovery of activation-induced cytidine deaminase that is essential for class switch recombination and somatic hypermutation. He has established the basic conceptual framework of class switch recombination starting from discovery of DNA deletion (1978) and S regions (1980), followed by elucidation of the whole mouse immunoglobulin heavy-chain locus. His contribution further extended to cDNA cloning of IL-4 and IL-5 cytokines involved in class switching and IL-2 receptor alpha chain. Aside from class switching recombination, he discovered PD-1 (program cell death 1), a negative coreceptor at the effector phase of immune response and showed that PD-1 modulation contributes to treatments of viral infection, tumor and autoimmunity. In addition, he is known to be a discoverer of RBP-J, a nuclear protein that interacts with the intracellular domain of Notch in the nucleus. Notch/RBP-J signaling has been shown to regulate a variety of cell lineage commitment including T and B cells. For these contributions, Dr. Honjo has received many awards, including the Noguchi Hideyo Memorial Prize for Medicine (1981), Imperial Prize, Japan Academy Prize (1996), Robert Koch Prize (2012), and Order of Culture (2013). He is an honorary member of the American Association of Immunologists. He has been honored by the Japanese Government as a person of cultural merits (2000). He has also been elected as a foreign associate of National Academy of Sciences, USA in 2001, as a member of Leopoldina, the German Academy of Natural Scientists in 2003, and as a member of Japan Academy in 2005.

**Prof. Dr Michael Reth** has won the Paul Ehrlich and Ludwig Darmstaedter Prize, awarded by the Paul Ehrlich Foundation, for his research on the immune system. For the first time since 1996, the prize goes to a scientist working in Germany. Dr Reth is Professor for Molecular Immunology at the Institute of Biology III of the University of Freiburg and Scientific Director of the Cluster of Excellence BIOSS, Centre for Biological Signalling Studies. He is also head of the department for Molecular Immunology at the Max Planck Institute of Immunobiology and Epigenetics (MPI-IE). The prize is endowed with 100,000 and is one of the highest honours in science in Germany. By awarding the prize to Dr Reth, the Foundation has chosen to honour a scientist who, like Nobel laureate Paul Ehrlich, decodes how immunity operates at a molecular level, in order to find new therapies for cancer and infectious diseases. This award is a great honour for me, because I deeply admire Paul Ehrlich's work in immunology, Dr Reth said. He was one of the first scientists to consider the molecular level in this field. Following Ehrlich's scientific tradition, Dr Reth chose to focus his research on how the human body recognises foreign substances. Due to the success of vaccinations, which was one of the greatest achievements in medicine, immunology has been an applied science from the beginning. However, we still do not fully understand the processes that underlie immunisation, Dr Reth remarks. That is why his research revolves around the B cell component of the immune system. When activated, these blood cells produce antibodies to fight off infection. Dr Reth investigates the structure and organisation of the B cell antigen receptors. These molecules on the surface of B cells recognise foreign substances, so-called antigens, and trigger the activation of the immune system. Dr Reth was able to describe the basic structure of the antigen receptor of B cells for the first time in 1989. Together with his research group, he developed a new model for the activation of this receptor and recently provided further experimental evidence for this model. Furthermore Dr Reth has shown that receptors on the plasma membrane have a more complex structure than previously assumed. They are not freely diffusing on the cell surface but are organized in 50 to 150 nanometre sized membrane patches also called protein islands. The detailed analysis of the organization of receptors on the cellular membrane is a focus of research at the BIOSS Centre for Biological Signalling Studies, the cluster of excellence directed by Dr Reth since 2007. Located in the Signalhaus in Freiburg, BIOSS brings together engineers and biologists to investigate signalling processes using methods of synthetic biology. In the spirit of BIOSS's motto from analysis to synthesis, researchers re-construct signalling cascades or develop new kinds of systems altogether - for example, hydrogels that release medication in a temporally controlled way, or signalling proteins that can be switched on and off with light.

**About Michael Reth:** In 1989 Michael Reth joined Nobel laureate George Köhler's laboratory at the MPI and later on was appointed Chair of Molecular

Immunology at the University of Freiburg. He was awarded the Gottfried Wilhelm Leibniz Prize of the German Research Foundation in 1995 and the EFIS-Schering-Plough European Immunology Prize in 2009. In 2012, Michael Reth was awarded an advanced grant by the European Research Council (ERC). Andreas Radbruch did his PhD at the Genetics Institute of the Cologne University, Germany, with Klaus Rajewsky. He later became Associate Professor there and was a visiting scientist with Max Cooper and John Kearney at the University of Alabama, Birmingham. In 1996, he became Director of the German Rheumatism Research Centre Berlin, a Leibniz Institute, and in 1998, Professor of Rheumatology at the Charit, the Medical Faculty of the Humboldt University of Berlin. A biologist by education, Andreas Radbruch early on worked on somatic variants in myeloma and hybridoma cells lines, modeling antibody class switching and somatic hypermutation. In this context, his lab originally developed the MACS technology. Andreas Radbruch then showed that recombination is the physiological mechanism of class switching *in vivo*, in plasmablasts isolated *ex vivo*. Moreover, he could show that *in vivo*, class switch recombination is targeted to the same Ig class on both IgH loci of a cell, reflecting a tight control of targeting of recombination. An essential element of this control is transcription of recombinogenic sequences, and the processing of these switch (germline) transcripts, as became evident from targeted deletion of the control regions involved. The switch transcripts are induced by cytokines of T helper cells, e.g. interleukin-4. The Radbruch lab contributed essentially to our current understanding of the polarization and imprinting of T helper cells expressing interleukin-4 (Th2) versus those expressing interferon- (Th1). The lab then addressed the organization of immunological memory as such. First they identified longlived (memory) plasma cells, mostly residing in bone marrow but also in secondary lymphoid organs and in inflamed tissues. They could show that these cells individually persist in dedicated survival niches, organized by CXCL12-expressing mesenchymal stroma cells. They identified different, dedicated niches for CD4+ and CD8+ memory T cells in the bone marrow, too, and could show that, at least in immune responses to vaccines, memory T cells are mostly maintained in bone marrow, resting in terms of proliferation and gene expression. Thus memory niches organize and maintain memory, and bone provides a privileged environment for resting memory cells. In chronic antibody-mediated diseases, Andreas Radbruchs lab identified pathogenic antibody-secreting memory plasma cells as critical mediators of chronicity, refractory to conventional immunosuppression, and thus representing a novel therapeutic target. Similarly, in chronic T cell-mediated diseases, the pathogenic T cells induce and adapt to chronicity. Recently, the Radbruch group has identified Twist1, HopX and the microRNAs miR-182 and miR148a as molecular adaptations of proinflammatory T cells to chronicity, and innovative therapeutic targets. Andreas Radbruchs work has been recognized by the Carol Nachman Prize for Rheumatology (2011), an Advanced Grant of the European Research Council (ERC, 2010), the Federal Cross of Merit (2008) and the Aronson Award (2000). He is a member of the Berlin-Brandenburg Academy of Sciences and Humanities (BBAW), the European Molecular Biology Organization (EMBO) and the German National Academy of Sciences Leopoldina.

Frederick Alt received his Ph.D. in Biology from Stanford University in 1977 where he worked with Robert Schimke and discovered gene amplification and genomic instability in mammalian cancer cells. Alt moved to MIT for postdoctoral work with David Baltimore, where he helped elucidate basic principles of recombination in the immune system. His work with Baltimore included the discovery that production of membrane versus secreted immunoglobulin is achieved via differential RNA processing and the discovery that allelic exclusion of Immunoglobulin (Ig) gene rearrangements is controlled by feedback from protein products. With Baltimore, Alt also elucidated major aspects of the V(D)J recombination mechanism, including involvement of site-specific DNA double strand breaks (DSBs) that are end joined, and the discovery of N regions, which represent a major source of antigen receptor diversity. Dr. Alt moved to Columbia University in 1982 as Assistant Professor of Biochemistry. He became Professor of Biochemistry and Molecular Biophysics in 1985 and HHMI Investigator in 1987. At Columbia, he established the role of Ig chains in regulating B cell development and discovered that antigen receptor genes are assembled by a common V(D)J recombinase. He then elucidated a role for non-coding gene transcription and "chromatin accessibility" as means to target the lineage, stage, and allele specific activity of the V(D)J recombinase. He extended that work to show that IgH class switch recombination (CSR) in B cells to particular IgH classes is directed by activation of non-coding transcription units that contain the CSR target sequences. At Columbia, he also discovered N-myc, based on its amplification in human neuroblastomas and he characterized the Myc cellular oncogene family. In 1991, Dr. Alt moved to Boston Children' Hospital (BCH) and Harvard Medical School as a Professor of Genetics and HHMI Investigator. He also became a Senior Investigator at the Immune Disease Institute (IDI). He was appointed Charles A. Janeway Professor of Pediatrics in 1993, Scientific Director of IDI in 2005, and Director of the Program in Cellular and Molecular Medicine (PCMM) at Children's Hospital in 2008. He also became President of IDI in 2010 and continues to serve as director since the merger of IDI with BCH where it remains the PCMM. At CHB and IDI, Dr. Alt's group confirmed his earlier proposal with Baltimore that N regions are added by terminal deoxynucleotidyl transferase, demonstrating that TdT is a V(D)J recombinase component. They also discovered that the joining activity of the V(D)J recombinase is carried out by a multi-component general cellular non-homologous DNA end joining (NHEJ) pathway. Subsequently, Dr. Alt was involved in the discovery of a number of the NHEJ factors and he then went on to discover the key role of NHEJ proteins in maintenance of genomic stability. Dr. Alt continues to elucidate many new aspects of the mechanism and

control of V(D)J recombination and IgH CSR and also continues to elucidate mechanisms that generate and suppress genomic instability, most recently through development of high through-put methods to study DSBs and chromosomal translocations. In 1994, Dr. Alt was elected to the U.S. National Academy of Sciences, the American Academy of Arts and Sciences, and the American Academy of Microbiology; in 1999 he was elected to the European Molecular Biology Organization; in 2010 he was elected a Fellow of the American Association for Advancement of Sciences; and in 2011 he was elected to the Institute of Medicine. In 2004, Alt received the Clowes Memorial Award from AACR; in 2005 he received the Rabbi Shai Shacknai Prize from Hebrew University, the Pasarow Foundation Prize for Extraordinary Achievement in Cancer Research, the Leukemia Lymphoma Society de Villiers International Achievement Award, and the Irvington Institute Award. In 2007, Alt received the NCI Alfred K. Knudson Award for pioneering contributions that have revolutionized Cancer Genetics, the AAI-Huang Meritorious Career Award, and the Novartis Basic Immunology Prize for his discoveries on B cell development and antigen responses. In 2009, he received the Cancer Research Institute William B. Coley Award for Distinguished Research in Basic Immunology for fundamental contributions to understanding of B-cell development and B cell lymphomagenesis. For his overall contributions, he most recently received the 2012 Arthur Kornberg and Paul Berg Award for Lifetime Achievement in Biomedical Sciences from Stanford University Medical School. Dr. Alt serves on numerous editorial boards and is Editor in Chief of *Advances in Immunology*. He also has served on various national and international advisory boards and is currently Chair, of the SAC of the Cold Spring Harbor Laboratory. Dr. Alt has mentored over 100 students and research fellows, many of whom have become leaders in immunology, genetics, or cancer biology and he received the 2003 American Association of Immunologists Excellence in Mentoring Award. The Cancer Research Institute of New York annually presents the Frederick W. Alt Award for New Discoveries in Immunology.