Preface

This volume covers the exciting advances that have been made in our understanding of the generation of antibody diversity subsequent to the discovery of the activation-induced cytidine deaminase (AID). In this regard, the volume is organized into nine separate chapters, most of which focus on particular aspects of AID and the immunoglobulin gene diversification processes in which it functions. This short introductory overview summarizes some of the most relevant topics and points to particular chapters in which specific topics are covered. However, the reader is encouraged to go through all of the chapters to gain a complete understanding of this fascinating area of biology. In that regard, while individual chapters tend to focus on particular topics, they necessarily cover overlapping subject matter but often, given that this is still a developing field, from different viewpoints.

The AID protein is necessary and sufficient for the initiation of immunoglobluin heavy chain class switch recombination (CSR) and the initiation of somatic hypermutation (SHM) of immunoglobulin variable region exons. That one enzyme can induce the seemingly very different CSR and SHM mechanisms, and that this enzyme can also induce the process of gene conversion in chickens, was a very remarkable and unexpected finding. Moreover, the mechanism of SHM was considered by many as one of the last major frontiers of immunology, until the discovery that AID is the long sought mutator. Thus, the discovery of AID, about 7 years ago, revolutionized our understanding of the peripheral mechanism of immunoglobulin gene diversification and led to a huge body of additional work. The work that led to the discovery of AID is discussed in depth in Chapter 1 by Muramatsu *et al.* An in-depth review of CSR is presented in Chapter 6 by Chaudhuri *et al.* and a detailed introduction to SHM is presented in Chapter 4 by Yuan and Schatz.

AID is comprised of less than 200-amino acid residues and carries a cytidine deaminase motif. AID clearly is required to introduce DNA lesions into variable region exons and switch regions during SHM and CSR, respectively. However, many important questions remain concerning how AID leads to DNA cleavage. A long-debated question is the nature of the direct target of cytidine deamination *in vivo* by AID, DNA or RNA. AID is structurally related to APOBEC1, which is an RNA editing enzyme. However, biochemical studies

have shown that purified AID deaminates cytidines on single-strand DNA. Considerations relevant to DNA versus RNA models for AID activity are presented in depth in Chapter 1 by Muramatsu *et al.* and in Chapter 6 by Chaudhuri *et al.*

There are many other important questions regarding the function and regulation of AID. A key question is how AID-initiated lesions lead to mutation of variable region DNA and DNA double strand breaks within switch regions. In this context, another major question is the identification of modifications or cofactors that might influence AID activity and potentially channel AID functions into SHM or CSR. An extremely important question is the nature of the mechanisms that normally target the activities of this potent mutator to immunoglobulin genes and not other genes. These general topics are discussed in Chapter 1 by Muramatsu *et al.*, in Chapter 3 by Ramiro *et al.*, and in Chapter 6 by Chaudhuri *et al.* AID biochemistry is a particular focus of Chapter 5 by Goodman *et al.* while issues related to AID targeting are a focus of Chapter 4 by Yuan and Schatz, which also describes gene conversion.

The nature of the mechanisms that join AID-initiated breaks in the context of CSR has been a major area of study. Several studies have shown that general DNA double strand break repair mechanisms are harnessed to join AID-dependent breaks in switch regions. This topic is a particular focus of Chapter 3 by Ramiro *et al.* and is also covered in depth in Chapter 6 by Chaudhuri *et al.* AID also has been demonstrated to be involved in the initiation of translocations that arise in the context of IgH CSR, including oncogenic translocations found in certain B-cell lymphomas. Chapter 3 also discusses this topic in depth. Transgenic studies have further indicated that AID expression can lead to other types of tumors, raising the question of how broadly AID might function to generate certain forms of human cancer. This topic is discussed in Chapter 8 by Okazaki *et al.*

AID deficiency causes a severe immune deficiency in humans that is called hyper IgM syndrome type II. This disease causes the absence of IgH isotypes other than IgM and absence of hypermutation and, thereby, results in severe susceptibility to bacterial infection. As there are other forms of hyper IgM type II not yet fully characterized, the question arises whether further studies of these deficiencies may reveal other functions for AID or potential cofactors. The pathophysiology of AID deficiency in humans is the subject of Chapter 9 by Durandy *et al.*

Finally, an important question is whether AID might have functions beyond somatic mutation and CSR. This possibility is supported by findings that molecules related to AID in HIV resistance and that AID is induced after

infection by various viruses. This exciting new area of investigation is covered in Chapter 2 by Conticello *et al.* and in Chapter 7 by Rosenberg and Papavasiliou.

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