Preface

A major process of rediscovery has taken place in the field of Cellular Immunology over the past 12 years—subsets of T lymphocytes exist that are specifically dedicated to regulation or as it should be more appropriately termed suppression of all aspects of immune responses. It is certainly appropriate at this time to recall some of the history that lead to the development of the concept of immune regulation/suppression. Shortly after the term helper T cells was coined to described lymphocytes that "helped" both humoral and cell-mediated responses, studies from the laboratory of the late Professor Richard Gershon demonstrated that under certain conditions, antigen recognition by T lymphocytes also resulted in the development of cells that are able to suppress immune responses. Unfortunately, research in this field rapidly shifted from studies of the function of the suppressor T cells to studies of their soluble products that were thought to be shed or secreted T cell receptors. A number of highly complex suppressor cell pathways and cell circuits were developed and were the subjects of more than 5,000 papers during this era. In 1983–1984, this field completely collapsed as studies called into question the existence of the I-J region of the mouse major histocompatibility complex that was thought to encode one of the major chains of the suppressor T cell factors. The cloning of the T cell receptor at that time firmly established that the T cell receptor genes were completely unrelated to the genes encoding immunoglobulin heavy chains calling into question the existence of soluble T cell factors that contained immunoglobulin VH gene products. The number of papers in the literature dealing with suppressor cells fell from a high of 1,300–1,500/year in 1981 to 150–200/year by the end of the 1980s. At this point in time, most immunologists felt it was even inappropriate to use the term suppressor cell!

Although a number of workers in the period of 1970–1995 continued to focus their studies on T suppressor cells rather than soluble factors, their work was largely ignored by the immunologic community. The detailed history of their pioneering work will be covered in Chapter 1 by Professor Sakaguchi. Immunologists are somewhat obsessed with dividing what initially appears to be homogeneous population of cells, e.g, $CD4^+$ T lymphocytes, into multiple subpopulations with distinct functional properties, e.g, Th1 and Th2 cells. Ideally, most immunologists desire that each subpopulation could easily be identified and separated by the expression of a cell surface antigen unique to that subpopulation. Although immunologic

phenomena that appeared to be mediated by regulatory T cells were described in the literature in the early 1990s, what was really missing from this field was a cell surface marker that would allow immunologists to define a regulatory/suppressor cell. It was only after Prof. Sakaguchi identified the CD25 antigen in 1995 as a marker for a major population of T cells that had suppressor functions both in vitro and in vivo that the resurgence in the regulatory T cell area could begin.

The regulatory T cells field has grown dramatically over the past decade. It is now impossible to read a journal that does not contain numerous papers whose titles deal with regulatory T cells. More importantly, it is also difficult to submit a new research grant proposal in any area of immunologic research that does not include a section on analysis on the contribution of regulatory T cells to the subject matter under study. Regulatory/Suppressor T cells have come of age, again, hopefully this time to stay. Although it was initially thought that regulatory T cells functioned primarily in controlling autoreactive immune responses and several chapters in this volume are devoted to that topic, there is little doubt that the role of regulatory T cells in infection, cancer, and transplantation is just as important. Regulatory T cells even appear to play critical roles in cardiovascular disease in the pathogenesis of atherosclerosis. Many of the chapters in this volume with deal with the lineage of regulatory T cells that are defined by expression of CD25 and more importantly the transcription factor Foxp3. These cells were originally believed to be generated exclusively during T cell development in the thymus, but many recent studies indicate that they can be generated extrathymically. Cell types other than $CD4^+CD25^+Foxp3^+$ have also been shown to manifest regulatory properties and some of these unique cell types will be described in Chapters 23–30.

As in any rapidly moving field in science, many of the concepts and theories presented here will rapidly be modified or even discarded as new studies are performed and new questions are raised. For example, there are now at least a dozen proposed cellular mechanisms for the suppressive activity of the $CD4^+CD25^+Foxp3^+$ regulatory cells. Are all of these suppressive pathways actually used? Which ones are the most important? Which ones can be manipulated for therapeutic purposes? All of these questions should be answered in the next five years. Lastly, an important focus of this book is clinical application. Although numerous studies in animal models have strongly suggested that manipulation (augmentation or downregulation) of regulatory T cell function can be used for therapy of autoimmune, neoplastic, or infectious disease, we are now just on the threshold of translating some of the approaches from animals to man. Regulatory T cells can be best thought of today as "teenagers" ready to take on all the challenges of complex immune responses. In ten years, the field will certainly be more mature, and manipulation of regulatory T cell function by cellular biotherapy, antibodies and small molecules will be routine function of the clinical immunologist.

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