Preface

As mentioned in the preface to the first edition of *Cytokine Knockouts* (1998) by the editors S. K. Durum and K. Muegge, "The technique of gene targeting or 'knockout' has swept through biomedical research of the 1990s as if it were the Occam's razor of biology. The technique provides an acid test of the function of a gene." In the years since the first edition of *Cytokine Knockouts* was published, several factors have contributed to expand the use of gene-deficient mice in research. Advances in molecular biology techniques have facilitated gene cloning and the building of DNA constructs. Furthermore, the possibility of generating conditional or tissue-specific knockouts, as well as knock-in mice, has opened new avenues for more sophisticated use of gene-modified animals in research. At the same time, many universities and research centers have organized core laboratories for the generation of knockout and transgenic mice, therefore making this technique available even to nonexperts. These two factors have contributed to the incredibly rapid increase in the number of new knockout mice created every year and have led to a marked reduction in the time between the cloning of a new gene and generating the corresponding deficient mouse, thus speeding up the appreciation of the in vivo role of any given new gene. The commercial availability of several strains of gene-deficient mice has been the third factor greatly contributing to widening the use of knockout mice. After an initial characterization, a large number of investigators decided to make their mice available through commercial providers. This choice has allowed laboratories without expertise in molecular biology, but oftentimes with a great deal of knowledge in the characterization of in vivo processes, to have easy access to gene-deficient mice. In this way, a sort of long-distance collaboration has narrowed the gap between molecular biology and in vivo studies, a much appreciated result given the ever increasing technical specialization of many laboratories. Approximately 10% of the more than 300 different types of knockout mice that are currently commercially available is represented by cytokine- or cytokine receptor-deficient mice.

Research in the closely intertwined fields of immunology, infection, and inflammation is proceeding at a pace faster than ever before. Among the many types of mediators involved in the regulation of phenomena as varied as resistance to infectious pathogens, fever, pain, wound healing, autoimmune reactions, hematopoiesis, angiogenesis, and tumor surveillance—to cite only a few—the family of cytokines can, without any doubt, be considered one of the most prominent. Paraphrasing an Italian saying, "Cytokines are like parsley," you can find them everywhere. In fact, as attested by the reviews collected in this volume, the variety of physiological and pathological conditions in which cytokines have been implicated is staggering. Thanks to the factors mentioned above, the use of cytokine knockouts in research has literally exploded in the past 5 to 10 years. A PubMed search with the terms "cytokine" and "knockout mice" provides a list of approximately 4000 scientific reports, more than 3000 of which were published since 1998, the year of the first edition of *Cytokine Knockouts*.

As the reader will appreciate, several new types of cytokine knockout mice have been generated since the first edition was published. Thus, to cite only a few examples,

osteoprotegerin (or RANK) ligand, a major player in bone metabolism and one of the most promising cytokines in terms of therapeutic developments, had just been cloned when the first edition of *Cytokine Knockouts* appeared; the generation of RANK and RANK- ligand-deficient mice soon followed (*see* Chapter 23). Despite the long history of Interleukin (IL)-1, reports describing the generation of IL-1α and double IL-1α/IL-1β knockouts were only published in 1998, the same year of the first report on IL-18-deficient mice (*see* Chapters 6 and 18). Moreover, novel important data have been published by investigators studying new phenomena in "old" knockouts. To cite only a few examples, the critical role for IL-1Ra in maintaining control of inflammatory responses had been reported by two separate groups in 2000 (*see* Chapter 7), a more detailed characterization of the pathogenesis of colitis development in IL-2- and IL-10-deficient mice appeared over the course of the past 5 years (*see* Chapter 14), the role of tumor necrosis factor-α and lymphotoxin in the development of germinal centers has been further clarified (*see* Chapter 25), and so have the roles of IL-2, IL-7 and the common γ chain of their receptor in lymphopoiesis (Chapters 8 and 9). From these and the many more examples that might have been listed, it is clear that the time is right for a new edition of *Cytokine Knockouts*.

Structure of the Volume

Cytokine Knockouts is comprised of two sections, *Cytokine Knockouts in Models of Human Disease*, and *Cytokine Knockout Mice*. Although both sections are addressed to researchers interested in the field of cytokines, Part I could also serve as an introduction to the use knockout mice for scientists who are not familiar with cytokine research.

Part I contains chapters dedicated to the use of cytokine knockout mice in different fields of research. Rather than providing a comprehensive overview of results obtained using each available knockout mouse, the intent of this first set of reviews is to present a constructive discussion of ways in which cytokine knockout mice have been employed in various fields, with clarification of the relative advantages and disadvantages of their use.

Several important points are raised by the authors of these chapters. Thus, the reader is reminded of how the use of different experimental models is subject to the "fashion" of the moment, so that novel cytokines or novel cytokine-deficient mice are rarely tested for "old" parameters of pro-inflammatory activities, such as induction of fever. At the same time, it is critical to use caution when trying to interpret data derived from different studies, given the variability of results obtained using apparently similar experimental models. We also need to use caution when trying to directly infer results for clinical practice, and avoid creating misleading interpretations. When dealing with knockout mice, researchers should always take into account the possible effects of redundancy and of unspecific perturbations of the immune (and other) systems when a single gene is deleted. The importance of crossing gene-deficient animals into different background strains appropriate for the study of various conditions is also touched upon in Part I. I am sure this section will be a helpful tool to stimulate reflection and discussion about research methodology and data interpretation.

Part II includes chapters dealing with individual cytokines. To avoid excessive repetition, some cytokines are grouped and presented in families. Similarly, to provide the reader with a "concentrated" source of information, mice knockouts for a given

cytokine are generally discussed together with mice knockouts for that cytokine's receptor(s). Rather than presenting a brief summary of each of the chapters contained in Part II, I will point out how many unexpected discoveries were made possible by the use of cytokine knockout mice, and of gene-deficient models in general. Given the extreme pleiotropy and functional redundancy of many cytokines, it was only after the generation of mice deficient for each cytokine and each cytokine receptor that the specific in vivo role of a given molecule could be determined. As detailed in the various chapters, almost without exception there were big surprises awaiting investigators studying cytokine knockout mice. New phenotypes are being continually discovered, and some of them do not apparently have a relationship with immune responses, such as the recently described spontaneous obesity of IL-6 knockout mice (*see* Chapter 13). When working with cytokine-deficient mice, thus, one has to keep an open mind, be a careful observer and be ready to share results and materials with researchers in other disciplines. When these measures are carried out, cytokine knockout mice laboratories flourish and important results can quickly reach an eager audience.

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