Preface

The last four decades of the 20th century saw the discovery of the heat shock or cell stress response and the identification of the proteins produced by cells in response to adverse environmental conditions. In 1987, the term 'molecular chaperone' was coined to describe several unrelated protein families which had the ability to assist the correct folding and assembly/disassembly of other proteins. The past 20 years have seen the elucidation of the structural mechanisms of protein chaperoning by several key molecules including chaperonin (Hsp) 60 and Hsp70 and the realisation that not all molecular chaperones are cell stress proteins and vice versa. The genesis of molecular chaperones was contemporaneous with the identification of these highly conserved proteins as paradoxical immunodominant antigens that appeared to be important in microbial infection and autoimmunity. Indeed, the administration of molecular chaperones such as Hsp60 and Hsp70 was found to inhibit experimental autoimmune disease. By the 1990s, it was realised that correct protein folding was the key to cellular homeostasis and the paradigm that developed was that molecular chaperones were intracellular proteins whose function was to assist in protein folding. The paradoxical immunogenicity and immunomodulatory effects of molecular chaperones remained unexplained.

Another strand of the molecular chaperone story began to develop in the late 1980s and early 1990s with reports of the appearance of certain molecular chaperones on the surface of cells. Later, reports began to appear that molecular chaperones when applied exogenously to cells in culture had effects similar to those of pro-inflammatory cytokines. Molecular chaperones, such as early pregnancy factor (chaperonin 10), Hsp27, and BiP can also have anti-inflammatory/immunosuppressive actions. In addition to having direct effects on cells, there is mounting evidence that certain molecular chaperones can bind peptides and present these to antigen-presenting cells to modulate T lymphocyte responses.

This rapidly expanding body of literature is suggesting a new paradigm in which molecular chaperones are moonlighting proteins – that is, proteins with more than one function that are able to interact with many cell types to produce a range of effects. Support for this paradigm comes from studies revealing the presence of a number of molecular chaperones in the body fluids of man and animals.

Molecular Chaperones and Cell Signalling provides the reader with an overview of our current understanding of the biological roles of extracellular molecular chaperones. The book is divided into a number of sections. The first provides an overview of the structure and function of molecular chaperones, their role in the cellular response to stress, and their disposition within the cell. It also questions the basic paradigm of molecular chaperone biology – that these proteins are, first and foremost, protein-folding molecules. A key concern of those working on molecular chaperones as extracellular signals is the mechanism of secretion from cells. Section 2 reviews the current paradigms of protein secretion from cells and discusses the evolving concept of proteins (such as molecular chaperones) as multi-functional molecules for which the term "moonlighting proteins" has been introduced. In Section 3, attention turns to the role of exogenous molecular chaperones as cell regulators. Section 4 describes the physiological and pathophysiological roles that molecular chaperones play, and in Section 5, the potential therapeutic use of molecular chaperones is described. The final chapter of this volume brings out the crystal ball and asks, 'What does the future hold for the extracellular biology of molecular chaperones?'.

This book will be of interest to biologists, biochemists, cell biologists, clinicians, immunologists, pharmacologists, and pathologists at both the graduate and postgraduate levels.