Preface

Over 22 million people are alive today suffering from cancer and half of those cancers share a precise common molecular feature. That feature is a mutation in the *p53* gene (see chapter by Olivier et al.) that alters its function. That these mutations play a major role in the development of malignancy is supported by the tragedy of Li-Fraumeni syndrome. This devastating cancer family syndrome is caused by germ line mutations in *p53* that predispose affected individuals to the early onset of a wide range of malignancies. It is the ubiquity of *p53* alterations in so many different types of human cancer that has focused such intense interest in understanding the *p53* gene and its protein product for the last 30 years.

An enormous amount has been learnt about how p53 functions to reduce the incidence of cancer (Zilfou and Lowe) and new therapies based upon our understanding of p53 are now in the clinic. The intensity of investigation has produced an intellectual dilemma, which the chapters in this book attempt to resolve. Is the ubiquity of p53 in non-neoplastic processes as apparently diverse as human reproduction (Hu), metabolism (Feng; Gottlieb and Vousden), development (Storer and Zon), drug and radiation toxicity (Gudkov and Komarova), and aging (Donehower) a unique feature of p53 as a transcription factor (Beckerman and Prives) or does it rather reflect the immense interconnections within signaling pathways in cells and the sensitivity of the tools developed in the p53 system to demonstrate these connections?

Starting with chapters (Belyi et al.; Rutkowski et al.) describing the origins and evolution of the *p53* family genes in invertebrates and vertebrates, which emphasize their high level of conservation, the book then explores the complexity with which that genetic information is expressed, producing many isoforms (Khoury and Bourdon) of the three family members p53, p63, and p73 (Dötsch et al.) in vertebrates.

Lack of p53 results in an increased incidence of cancer, while an overactive p53 can induce accelerated aging in vertebrates. The correct regulation of the p53 response to stress is vital for its effective function. The study of the control of p53 has been enormously exciting and at the cutting edge of modern molecular technology, from detailed structural investigations of its folding, stability, and oligomerization (Joerger and Fersht), through to analysis of its many post translational modifications (Meek and Anderson) and its molecular partners (Lu). Two negative regulators of p53 function, Mdm2 and Mdm4, play an essential role in controlling p53 and this has been elegantly explored in mouse models (Perry; Lozano). Remarkably, polymorphisms have been described in the p53 system in man that reflect on all these activities and the chapter by Grochola et al. updates the provocative observations that subtle human variations in p53 and Mdm2/Mdm4 activity can affect human cancer incidence and outcome. The pace of discovery in the field is quickening rather than slackening and it has become a model system of choice for many investigations in biology (Lane and Levine). The utility of these advanced studies is beginning to be realized both in disease diagnosis and prognosis (Robles and Harris) and in drug development (Lane et al.; Gudkov and Komarova), where a number of exciting pre-clinical molecules are under evaluation and p53 gene therapy approved in some countries. Indeed, the recent strong mouse model support for the earlier concepts that expressed mutant p53 proteins have new "gains of function" that can drive invasion and metastasis and block differentiation coupled with increased understanding of the control of expression of mutant p53 proteins may resolve long standing issues of interpretation of p53's role in tumor pathology (Oren and Rotter).

We hope that by bringing together a unique gathering of experts this volume will provide a great introduction to the field for newcomers to the p53 family and a starting off point for vigorous debate among the converted. The many unknowns in this system that are detailed and discussed in this volume provide us all with inspiration for future work.

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