Preface

THE IMPORTANCE OF *RAS* GENES AND THE PROTEINS they encode in human cancer was firmly established in the 20th century, but more than 30 years later, we are still working to understand precisely how RAS proteins cause cancer and how we can intervene therapeutically. The contributions from the authors included in this volume highlight many of the complexities that have to be faced when we consider RAS proteins as drug targets and the progress that is being made toward effective therapies.

RAS proteins are essential for signal transduction in all cells, and oncogenic mutants are structurally very similar to their normal counterparts. This is one of many challenges. RAS proteins are also members of a broader superfamily of closely related proteins that play essential roles in many aspects of cell biology. Therapies aimed at oncogenic RAS proteins therefore need to avoid targeting these relatives as well as RAS proteins in normal cells. The RAS proteins themselves do not offer obvious opportunities for drug targeting, as they do not have active sites which can be exploited by traditional medicinal chemistry. Early efforts that instead targeted RAS processing failed, but new insights into the enzymes that regulate their critical posttranslational modification as well as a better understanding of how RAS proteins interact with lipid components in the membrane may yet lead to targeting opportunities.

Targeting pathways downstream is a strategy that may dodge the problems of targeting RAS proteins directly. Fortunately, the two major pathways downstream of RAS, the Raf/MAPK pathway and the PI3-kinase pathway, present many tractable drug targets, many of which have already been tested in the clinic. However, these pathways have proven unexpectedly complicated, with layers of redundancy and feedback that have, so far, defeated attempts to exploit them. Furthermore, tonic activation of these pathways by mutant RAS does not present a clear therapeutic window relative to transient activation in normal cells, so that drugs blocking enzymes in these pathways have, so far, been unacceptably toxic. Unbiased approaches to find vulnerabilities in RAS-driven cancers have also been disappointing in terms of identifying druggable enzymes that RAS tumors depend on uniquely, but again, new technologies and approaches are being applied that may identify opportunities in some RAS-driven cancers at least. Any new targets obviously have to be validated, preferably in vivo. Here again, new technologies offer far superior systems for testing the importance of potential targets and will certainly be critical to the development of the next generation of therapeutic candidates. Finally, the dream of harnessing the immune system to eradicate RAS-driven cancers is beginning to become reality and is also discussed in this volume.

It is our sincere hope that effective strategies for killing RAS-driven cancers will be in clinical practice before the 21st century advances much further. The editors, along with all of the excellent contributors to this volume and the entire RAS research community will continue to try and make this happen. We are very grateful to Barbara Acosta and her colleagues at Cold Spring Harbor Laboratory Press for all their patient efforts in assembling this volume, and we hope that some of the ideas and challenges described here will inspire others to join the fight to eliminate RAS-driven cancers.

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