

# Preface

The last 30 years or so has seen rapid growth in our understanding of the molecular basis of cancer. Many oncogenes and tumor suppressor genes have been discovered. The function of their protein products has been defined and they have been placed on signaling pathways and networks that are hijacked in cancer in ways that we can now comprehend. The three editions of *Principles of Molecular Oncology* have appeared during a period of unprecedented definition of the nature of molecular causation of cancer and the most rapid rational exploitation of this knowledge for the design of molecularly targeted cancer therapeutics.

Although still incomplete, we have assembled a considerable “parts list” for normal and malignant cells. The current and future challenge is to complete this parts list and to assemble the components into a model of the whole that is intellectually satisfying and also allows robust and accurate predications of how biological systems respond to perturbation, including pinpointing the best therapeutic approaches.

Of course, the sequencing of the human genome has made a major impact on the completion of the parts list. Technologies for gene resequencing and gene- and protein-expression profiling provide opportunities for genome-wide and proteome-wide searching. At the time of this writing, a debate rages, particularly in the United States, concerning the value for money of “big science,” “cancer genome anatomy” projects—which contribute further to the parts list and provide the tools for hypothesis generation—as distinct from individual investigator-led, hypothesis-driven “small science” that has been the traditional mechanism for basic research. This debate is healthy and is understandable in what is inevitably a cash-limited setting. However, in my view both approaches are important and are mutually beneficial. It is already almost impossible to imagine doing biomedical science without the human genome sequence. Similarly, accumulating the corresponding cancer genome sequences and other related information such as gene-expression patterns in cancer cells will make the ultimate understanding of the molecular basis of cancer much less difficult. At the same time, creative ideas generated by individual researchers remain crucial. A great

example of the mutual benefit of the two approaches is provided by the discovery of mutant *B-RAF* as an oncogene by high-throughput kinase mutation analysis and the subsequent functional and structural characterization, leading rapidly to drug discovery initiatives. The progression from gene to drug, along with the identification of the necessary biomarkers for diagnosis and prognosis and also pharmacodynamic endpoints for proof of concept, can now be accelerated by an array of powerful technologies [1]. These include RNA interference, high-throughput compound screening, chemical biology, and structural biology to name but a few.

Over the last 5–10 years, translational cancer research has accelerated tremendously, particularly in area of targeted molecular therapeutics. The successes with trastuzumab, imatinib, gefitinib, erlotinib, bevacizumab, and others have clearly exemplified the ability to exploit our knowledge of the molecular biology of cancer to produce drugs that have a real impact on patients’ lives.

This 3rd edition of the *Principles of Molecular Oncology* illustrates how far we have come in a short space of time. On the other hand, this edition also highlights the things that we need to do to move forward towards the goal of personalized medicine. Some have criticized the inevitable hype around the publication of the human genome sequence because of the somewhat inappropriate prediction that personalized medicines would simply fall into our hands. However, it is very clear that cancer is the therapeutic area in which individualized therapies based on genomic information on the particular patient concerned will be forthcoming over the next 5–10 years.

To achieve this we need to complete the parts list and to understand the systems biology of cancer. Characterization of the multiple genes and proteins contributing to each individual cancer will lead to the potential for mathematical modeling of the responses of normal and pathologic systems when perturbed by cancer genes and therapeutic agents. Improved biomarkers will need to be developed. Ideally these will be minimally invasive markers, and the prospects for the use of molecular imaging are clearly very bright. The multiple drivers of malignant progression, together with the plasticity of cancer genomes that predispose to the development of therapeutic

resistance will necessitate the development of combinatorial treatments. We can now clearly envisage the scenario in which, at some finite time in the future, a cancer patient will undergo a set of analyses—perhaps involving a whole genome scan—and the individualized therapy will be selected on that basis. The cancer treatment will no longer be based on anatomical location and the appearance of the tumor under the light microscope, but will be directly linked to molecular causation.

We will look forward to the rapid progress towards this ambitious scenario and reading about this in future editions of *Principles of Molecular Oncology*.

I would like to thank my co-editors, Miguel Bronchud, MaryAnn Foote, Giuseppe Giaccone, and Olufunmilayo Olopade. Particular thanks go Miguel for his tireless leadership of the project.

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## Reference

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