

## Preface

**D**ESPITE THE FACT THAT THEODOSIUS DOBZHANSKY wrote his famous quote “Nothing in biology makes sense except in the light of evolution” in 1973, and Peter Nowell published his landmark essay on the clonal evolution of cancer in 1976, the principles of Darwinian evolution have been largely ignored by cancer biologists and oncologists. However, over the last 5 years there has been a major shift in the way in which we view and manage human cancer, brought about by our improved ability to probe and monitor tumors over space and time. Evolution and adaptation, although familiar to those working in ecology and infectious disease, have until recently, not been given sufficient consideration in cancer medicine. This was in part due to the lack of technologies that allow for the dissection of cellular and molecular changes within the tumor at unprecedented depth and lack of recognition that cancer is truly a systemic disease, as even early stage tumors appear to induce significant alterations in the host. The realization that cancer biology only makes sense through an evolutionary lens is rapidly altering the way in which we examine tumor biology, comprehend the mechanisms through which the microenvironment constrains cancer growth, and the way in which scientists approach cancer biomarker discovery and the delivery of therapeutics. Although the clinical translation of the rapidly increasing knowledge still remains a challenge, progress made in the past few years gives us hope that evolutionary principles will increasingly guide the clinical management of cancer patients.

We have invited leaders in the field to contribute their insights in order to distill the challenges and opportunities to leverage experience in evolutionary biology and mathematical modeling for patient benefit. The book covers several major themes, including mathematical modeling of cancer evolution, genome instability as a driver of cellular diversity and selection, the tumor immune and stromal microenvironment, and therapeutic approaches to mitigate cancer evolution and forestall drug resistance. The chapters in the book can be divided into four major parts. The first few chapters discuss general principles of evolution and ecology as they apply to cancer, methods that can be used to study intratumoral heterogeneity and subclonal evolution, and mathematical models including neutral evolution and the “big bang” models that attempt to frame the experimental data.

The following few chapters focus on the molecular mechanisms that underlie genetic heterogeneity within tumors including chromosomal instability, aneuploidy, and cancer treatment-induced mutagenesis. Although each one of these mechanisms primarily shapes the cancer genome, they have profound effects on cellular phenotype, which is the substrate for selection. Experimental data in recent years also revealed that in contrast to the previously proposed model of tumor progression where alterations progressively accumulate in a step-wise manner, one can observe global rearrangements of the cancer genome in a single step leading to sudden dramatic changes in cellular fitness.

Subsequent chapters describe the roles of the microenvironment and spatial heterogeneity within tumors that provide selection pressures and drive the coevolution of cancer cells with their microenvironment. Non-cell-autonomous factors, in general, have not been considered as “cancer drivers” as the genes involved are rarely mutated and often produced by various stromal cells present within tumors. However, the almost miraculous success of immunotherapies in curing even advanced metastatic disease highlights the importance of host factors in limiting cancer evolution.

The next few chapters provide examples of how to incorporate novel technologies such as liquid biopsy into clinical practice to enable more effective detection and monitoring of tumors during treatment. Last, but not least, the final chapters discuss how to integrate evolutionary principles

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into the design of cancer therapies to decrease the chance of progression to resistant disease. Although clinical evidence has repeatedly shown that even the most promising targeted therapy eventually leads to resistance and recurrence of the disease and we know that stronger selection likely speeds up evolution, we still keep applying single drugs at maximum tolerated doses, even in patients with advanced-stage highly heterogeneous disease. Combining therapeutic agents with different mechanisms of action in the most optimal dose and sequence at the earliest possible stages of tumor development will be required to make significant improvements in clinical outcomes.

We hope that this book will serve as a primer in cancer evolution and appeal to scientists and clinicians alike, challenging current paradigms in disease biology and clinical trial design. We also hope that it will stimulate and provoke bold attempts to develop approaches to limit genome instability, target evolving subclones, influence the tumor environment, and design rational combination therapies to decrease the probability of therapeutic resistance to improve clinical outcomes.

Last, we are grateful to the outstanding scientists who so enthusiastically contributed to this book. We could not have put this together without their dedicated work and commitment. We also thank Richard Sever and Barbara Acosta at Cold Spring Harbor Laboratory Press for conceiving the idea and managing the book, respectively.

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