

Rethinking Cancer

A New Paradigm for the Postgenomics Era

Edited by Bernhard Strauss, Marta Bertolaso, Ingemar Ernberg, and Mina J. Bissell

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Preface

This book is published at an important juncture in the history of cancer research. Never before have we known so much about the individual cancer cell, yet never before has it been so unclear how to translate this knowledge into treatment success. This book is also published over a year into the global COVID-19 pandemic. Apart from its many other devastating consequences, the pandemic has caused many millions of cancer patients to have not been treated or diagnosed. Moreover, cancer research spending has dropped significantly. In October 2020 the UK's National Cancer Research Institute released figures projecting a 24 percent drop in the UK's overall cancer research spending, driven by a 46 percent fall in charity sector funding. The impact of the pandemic on cancer patients and cancer research will be felt for years to come, and will make it all the more important to determine what to focus on with the funds available.

Great technological progress over the past four decades has enabled earlier diagnosis, better surgery, disease monitoring, and follow-up, and it just begins to show in the cancer survival statistics. What is still hard to show is any significant extension of life span after treatment of late-stage disease, the real measure of our ability to effectively cure cancer. This is urgently needed, however, in the face of a worldwide, rapidly increasing cancer incidence. It seems that we are still waiting for the progress that was promised at the time of the “genomics revolution” by the sequencing of the first human genome twenty years ago.

The early 2000s were a time of great optimism in biomedical research, as it was generally assumed that once we know every single human gene, applications would be easy to engineer, and tangible benefits for human health would inevitably follow. But cures based on this “complete” knowledge of our genetic blueprint have remained largely elusive. Targeted therapy, as in precision cancer medicine (PCM), is still only applicable to small subsets of patients, and treatment outcomes are often not as expected. Cancer immunotherapy, after fifty years of basic research, could finally be translated into clinical practice during the last decade, but is so far successfully applicable to only a few types of cancer. Over the same time span, precise manipulation of the genome has become even easier than anybody would have thought back then. In addition, novel computational methods have enabled in-depth analysis of vast amounts of genomics data, be it at the single cell or tumor level, or in large

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cohorts of cancer patients, with the aim to uncover the genes and molecular pathways that cause cancer. The genomics era was characterized by a sense of relief, as one was under the impression that finally the protocol for understanding and manipulating life had truly arrived. It appeared that with a few minor technical optimizations, any problem in biology, including in humans, would become solvable, at least “in principle.”

In the second decade of the twenty-first century, however, it has become clear that simple correlations between genes, mutations, and cancer that have diagnostic or therapeutic value are not to be found exclusively at the DNA sequence level. It seemed that we had reached “peak genomics.” Even among cancer systems biologists, consensus started to build that understanding cancer as a perturbation in a complex multimodal, molecular network will not lead to straightforward actionable treatments, despite impressive recent advancements in computational powers and single-cell analysis methods. What these approaches have uncovered instead is enormous heterogeneity at the genomic level, often presented as “complexity”: not only between different cancers but also of the same cancer type in different patients, and even between the individual cancer cells within a single tumor in one patient. This ubiquitous observation has led to the declaration of a “complexity crisis” in the cancer genomics field. On the one hand, this admission has relativized the significance of the large amounts of cancer data that have been accumulated and was often used to explain the failures of new cancer drugs in the clinic; on the other hand, the implicit understanding was that doubling down on the acquisition of DNA sequence data and on throughput of analysis (using artificial intelligence) will lead to important breakthroughs in the foreseeable future.

Despite the persistence of the central causal narrative in cancer biology, which holds that cancer is caused by mutations in certain genes, many researchers have begun to doubt that DNA-level information is sufficient for understanding the cancer phenotype and have moved on to cancer epigenomics and other kinds of -omics. Hence, there is now widespread commentary about the arrival of the “postgenomics era” in cancer research. Originally, this term had an optimistic connotation, supposed to mean that things will be easier from then on, say with the ability to personalize treatments, and to tailor therapies to the exact specifications of a patient’s disease. Although indeed technically achievable, it now appears very unlikely that these approaches can ever become standard of care due to their enormous complexities and thus inevitable diagnostic and therapeutic uncertainties, not to mention the high costs of the methodologies involved. Meanwhile, data on the success rates of “targeted” drugs based on genomic information show that these drugs have overall been far less successful in the clinic than expected.

Perhaps, “postgenomics” really is meant to announce a reboot: we have tried genomics, with only modest success in curing cancer, and now need to move on to something else—but where to? This is what this book is about.

Applying loosely a historical framework as presented by Thomas S. Kuhn in his 1962 book *The Structure of Scientific Revolutions*, it appears that an increasing number of scientists would agree today that the current consensus that defines what is considered

“normal science” in cancer research, or its contemporary scientific “paradigm” in Kuhn’s terminology, has been insufficient to answer basic questions about carcinogenesis.

Emerging from this wider historic perspective and from the very concrete results of our own scientific work and that of others, the following two premises motivated the creation of this volume:

1) The current paradigm, namely that a number of specific genes, when mutated or mis-regulated, cause cancer, has not by itself led to a cure for cancer—a failure clearly not due to lack of financial investments or intellectual effort. Therefore, a new theoretical framework for causally understanding and treating cancer is required. (We are not criticizing the general understanding of how genes function and their causal role in biology.)

What went wrong? We believe that first and foremost, we have applied an incomplete or incorrect theoretical framework in our attempts to explain carcinogenesis. This concerns specifically how a simplistic understanding of the causal role of individual genes has been applied to cancer.

2) Several lines of evidence, supported by comprehensive data over the past two decades, can be identified that challenge the current paradigm. These are now converging toward a more widely accepted systems view of cancer and are presented in this volume along different “dimensions” of cancer. This view has, however, not yet led to a change in research practices or to fundamentally new experimental approaches in mainstream cancer research.

At the core of this premise is the understanding that models of linear causation, based on single (mutated) genes or networks thereof, “in principle” cannot explain the cancer phenotype and therefore cannot be used to formulate a cure. This view is now increasingly supported by the very data that were initially collected with the aim to find simple answers. However the logical structure of most current cancer research efforts still appears to follow a mind-set that wants to find *the* few most relevant cancer genes for a given tumor or *the* corresponding drug that targets such genes in a precise manner—while it is becoming more and more obvious that cancer is certainly more complex than that. To change this mind-set, we believe, requires active concerted efforts in order to translate alternative concepts into scientific practice—instead of waiting for “linear” science to take its course, while hoping that the relevant breakthroughs will emerge eventually “anyway.” From the patients’ perspective, that is certainly not good enough value for research money.

This volume aims to reemphasize the point that it is primarily novel conceptual or theoretical thinking that is required to drive progress in cancer research. Ultimately, only a clearly detectable change in research practices and funding policies will tell whether new thinking has arrived. New thinking becomes particularly important as currently, an increasing number of formerly “solid” fundamental concepts that are still constituting elements of the current paradigm, such as “oncogene,” “clonal expansion,” “tumor suppressor gene,” and “driver mutation,” to name a few, are becoming increasingly “softened” and attached with

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various disclaimers regarding their explanatory power, often by the very scientists who introduced them earlier. It seems therefore rather surprising that this has not led to a frantic search for additional conceptual building blocks, if not new frameworks.

This highlights also one central issue with theoretical thinking in cancer research: the fact that novel concepts emerge mainly in the basic sciences where they can be dynamic and evolving, but cancer clinicians remain suspended in the tension between their own empirical insights based on clinical practice and the concepts from the basic sciences they apply (usually with some delay) to the cancer context in humans. When clinical outcomes are not in agreement with the prevailing paradigm, for instance, when no plausible “cancer mutations” are found in a tumor, or rationally designed, target-selective drugs do not work as expected or even make the tumor more aggressive, then clinicians usually assume that the principles established in cell culture, animal models, or small cohorts may not apply, because humans might be just too complex and too diverse. They would certainly not question the scientific foundations that guide clinical practice, let alone assume flaws therein that needed addressing. Despite the fact that the number of clinician-scientists (MD-PhDs) is increasing, and integration between clinical and basic sciences is steadily improving, it seems by now quite clear that beyond such logistical advancements, theory-driven cancer biology needs to lead the way with conceptual innovation.

Over the past four decades, the dedication to explain cancer exclusively from the gene level up has been so all-encompassing that even trying to conceptualize alternative ideas has become difficult for at least two generations of cancer scientists. It has also discouraged research into other causally relevant processes beyond the single cancer cell level, depriving us of not only the theoretical but also the experimental tools to study them. But where do we start if we are to create a new theory framework, and what would its conceptual building blocks be?

Here we have gathered contributions from a number of theory-minded cancer scientists who present ideas and results that are covering many different aspects of cancer but are united by the view that it is paramount to revise the current somatic mutation paradigm if we are to make more progress in finding a cure for cancer. Their thinking comes from different areas of basic cancer cell biology, clinical research, and theoretical investigation, but they share a systemic and dynamic understanding of cancer that goes well beyond the idea that specific mutations in certain genes cause cancer and that assembling them into linear schemes of causation would be sufficient to explain carcinogenesis.

We are aware that this volume had to remain incomplete, as many colleagues who have contributed over the years with their work and theoretical thinking to a possibly emerging new paradigm could not be included here because of time and space constraints. In particular, the areas of inflammation and cancer immunology, two of the most dynamic fields in recent cancer research, are not explicitly represented, although references to relevant findings in these areas are made repeatedly by contributing authors throughout the book.

We believe that not only has sufficient solid evidence accumulated to warrant a change of the current paradigm based on scientific reasoning, but also that over the past decade the readiness for change has increased within the scientific community—despite the fact that funding agencies and mainstream research efforts still largely adhere to outdated concepts.

In this volume, we do not argue yet another critique of current research practices as this has been done by some of the authors and others in the past. Instead, we wish to present a number of conceptual stepping-stones that should lead the reader to a new vantage point from where a coherent new theory framework for cancer research might become visible.

The editors

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