Trends in
Cancer

Special Issue: Quantitative Cancer Biology

Editorial

Quantifying Cancer: More Than Just a Numbers Game

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In his famous essay, 'The Transformation of Oncology', the former National Cancer Institute (NCI) Director and Nobel-laureate Harold Varmus described how cancer was relegated to a minor place in the medical curriculum in the 1960s [1]. However, this view has dramatically changed since then. Today, we have targeted therapies as part of precision medicine and treatment is based on tremendous progress in developing methods to determine and understand a patient's cancer genome.

Have we been successful in dealing with cancer much less curing it? Unfortunately, the answer, at least in most cases, is a sobering, 'No!' Despite all the progress and the hype regarding early detection and precision medicine, we still are faced with the nettlesome problem: cancer is a moving target. Even within an individual tumor, deep sequencing analyses now indicate multiple, genetically distinct subpopulations whose representation seems to vary significantly from one stage to the next as the tumor progresses. Similarly, single cell transcriptomics has revealed the wide variation of expression patterns available to cells with common genotypes. With the deluge of data generated in recent times, it seems that we have we have come full circle, from endless complexity to simplicity and back again [2].

A deeper understanding of cancer is needed to provide novel insight to personalize treatments and to address therapeutic resistance by administering 'adaptive' (intermittent) therapy rather than the standard (continuous) therapy that typically, albeit inadvertently, encourages emergence of drug-resistant tumors. Technological advances that enable a quantitative view of the key processes in tumorigenesis can address these gaps. Single cell and single molecule studies, the availability of powerful computing platforms, and the application of evolutionary game theory to discern group behavior have galvanized multiscale modeling. These efforts have served as a powerful means to investigate biological phenomena more comprehensively in experimentally relevant ways.

Mathematical modeling and systems biology approaches are bridging the gap between mechanism and treatment, providing researchers with tools to better predict treatment response and resistance. However, many researchers and clinicians are not well versed in these tools and physical science concepts, making their wider acceptance within the field a major barrier to be overcome. Experts in the field acknowledge these and other bottlenecks, but all agree that quantitative approaches need to be embraced to propel forward the treatment of cancer. In this special issue, we are excited to feature perspectives that reflect the challenges and opportunities of integrating quantitative approaches into the landscape of cancer research. The articles embodied in this compendium present new ideas and concepts outlining how a quantitative understanding of cancer can provide deeper insight and how recognizing the importance of both genetic and nongenetic mechanisms may hold the key to fully comprehend how cancer arises and progresses. As well, we highlight mechanisms of resistance that will ultimately play a role in designing better therapeutics.

From the beginning, cancer was always considered to be a genetic disease underscoring the role of the genome in specifying the malignant phenotype. The idea that interactions between the

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genome and the environment shape the phenotype, as envisaged by Conrad Hal Waddington [3] in the developmental biology context, was simply nonexistent among cancer biologists. Furthermore, the discovery of 'driver' mutations and 'actionable' genes added further credence to the genetic underpinning and fueled the era of omics approaches starting from tissue to the single-cell. Together with the reductionist perspective, these new developments revealed that cancer is a complex and heterogeneous disease, driven by genetic mutations. Zhaoqi Liu and Raul Rabadan explore the computational tools to study alternative splicing actuated by mutant splicing factors expressed in cancer, one facet of these genetic events.

That cancer is a complex system, and that going from the genotype to the phenotype at both the single cell and tissue levels requires a nonlinear dynamics perspective, was relegated to the wayside. However, it has now become evident that, in addition to genetic mutations, intratumoral heterogeneity can also arise through nongenetic mechanisms and that the malignant phenotype results from complex interactions between genetic and nongenetic mechanisms. Furthermore, these interactions contribute to the functional changes across multiple spatiotemporal scales, from the molecular to cellular and tissue level, creating a heterogeneous cancer cell population. Intra- and interindividual heterogeneities are the main challenge for studying cancer as well as in treating the disease appropriately. Several reviews in this special issue tackle the role of tumor heterogeneity in cancer progression and treatment resistance. Sui Huang provides a framework for unifying genetic and nongenetic dynamics in tumor progression. Supriyo Bhattacharya and colleagues further expand on the impact of nongenetic interactions and discuss how group behavior can influence drug resistance. Aritro Nath and Andrea Bild discuss recent advances in single cell technologies that have revolutionized how we understand tumor heterogeneity and clonal evolution and that could be applied when developing personalized therapeutic strategies. Despite studies of genetic, epigenetic, and transcriptomic cellular heterogeneity, we still know little about phenotypic heterogeneity. Emma Lundberg and colleagues describe the use of imaging-based spatial proteomic technologies that characterize phenotypic states for individual cancer cells at subcellular resolution.

Among nongenetic environmental components, the immune system is now recognized as a major contributor to tumor heterogeneity and treatment resistance. However, many of the mechanisms by which the immune system influences cancer progression remains unknown. Aleksandra Karolak and colleagues suggest the use of information theory to define and to guide new concepts regarding the function of interconnected components of the immune system in cancer. Jason George and Herbert Levine propose that mathematical models of the tumor–immune interaction and subsequent coevolution can optimize immunotherapies and accelerate our understanding of these interactions for cancer treatment.

While experiments with data collected at fixed end points provide a binary answer at best, imaging of live single cells in real time can provide a quantitative picture of the underlying mechanisms. Indeed, such studies have revealed that cells can send and receive information by controlling the temporal behavior (dynamics) of their signaling molecules, which can ultimately impact on cell fate decisions. Galit Lahav and colleagues propose that combining dynamic measurements of signaling with complementary measurements, such as transcriptomic and proteomic assessment, can bridge the timescale gap between short-term dynamics and long-term outcomes.

The deluge of data on the complexity, heterogeneity, and dynamics of cancer combined with various treatment options can present challenges for decision-making in oncology. Among all this data, clinicians are faced with the daunting task of identifying which therapy to use for a specific patient at a specific time point, while keeping in mind the future course of the disease.

Dalit Engelhardt and Franziska Michor discuss how mathematical modeling and machine learning can be combined to construct dynamic, optimal cancer treatment strategies. As outlined by Jonathan Wan and colleagues, machine learning is also likely to increase the sensitivity and specificity of liquid biopsies, which can be used in the early detection of cancer and residual disease, treatment selection, and monitoring of disease burden. However, the power of machine learning for treating cancer can only be realized if publicly available data are accompanied by the sharing of standardized metadata. Ariel Hippen and Casey Greene argue the need for computationally derived metadata to enhance the power of genomic data.

Many of the articles herein identify important questions that can only be realized by the power of quantitative studies. We hope that this Special Issue encourages cross-pollination of ideas between clinicians, basic science researchers, and physical scientists interested in integrating both theoretical and experimental approaches to study cancer and to address these outstanding questions for the field. Our fond hope is that this knowledge can potentially lead to a more fundamental understanding of cancer so that more effective therapeutics can be developed.

The idea for this Special Issue of *Trends in Cancer* germinated from a Symposium, *Mathematical Oncology and Cancer Systems Biolog*y, organized by Ravi Salgia, Andrea Bild, and Prakash Kulkarni, that was to be held in March 2020 at City of Hope. Unfortunately, the symposium was cancelled due to the impending COVID-19 pandemic. However, we are delighted to have many of the invitees of this meeting kindly agree to contribute to this Special Issue. We thank all the authors and reviewers for their contributions to the special issue and we thank you for reading it. Your comments and ideas are always welcome; you can contact us with feedback or questions at trendscancer@cell.com or @trendscancer.

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