Introduction to Physics in Cancer Research

Herbert Levine

The Physics of Living Systems Community has collectively become excited at the possibility of contributing to a better understanding of and better treatment options for cancer. For example, sessions on the physics of cancer are now commonplace at international meetings and several special issues of physics journals have been devoted to this topic. And, there is definitely some reciprocal interest. The NCI has been running a Physical Science-Oncology program for the past 5 years, explicitly devoted to bringing physical scientists into contact with the cancer biology and clinical oncology communities. As another example, the Cancer Research and Prevention Institute of Texas has shown a remarkable willingness to fund researchers (such as several contributors to this special section) who are trying to contribute to this area.

So, what is the logic behind these events? The answer lies in the hope that physical science can offer both tools and concepts that could help deal with the amazingly complex story of cancer as it has come to be appreciated. Aside from some special cases, attempting to cure cancer by following the simple path of finding a single defect (perhaps one key driver mutation leading to constitutive activity of a specific signaling protein and downstream pathway) and subsequently devising a small-molecule therapy just has not proven to be a powerful enough strategy. In fact, cancers often respond to such treatment with short-term retraction that is followed inexorably by long-term renewed vigor. This defeat of therapy can occur through a variety of individual cell changes (for example, resistance mutations), through collective changes within the entire tumor, and through recruitment of surrounding normal cells; the details are sorely absent. Surely, coupled to this is the fact that cancers are remarkably heterogeneous in their cells; the details are sorely absent. Surely, coupled to this is the fact that cancers are remarkably heterogeneous in their genomic profiles and in their physical manifestations; there are many redundant pathways leading to similar dire consequences. We as a society are thus faced with the prospect of spending hundreds of thousands of dollars per patient on drugs that increase life expectancy by merely a few months. It may be the height of hubris to think that physicists can make progress on topics that have resisted the best efforts of the oncology community, but there is certainly a strong motivation to try.

In this special section of Cancer Research, we have asked a small number of prominent researchers from the physics of cancer community to explain some of their methods, ideas, and directions to cancer research professionals. As can be seen, there is not one unique aspect of the cancer problem that specifically attracts the interest of the physical science community. Instead, mathematical modeling and controlled quantitative experimentation are contributing across the research spectrum, from fundamental issues about the genetic circuitry underlying cell decisions correlated with increasingly intractable disease, and the complex role of the chemical and mechanical microenvironment in tumor progression, to the statistical analysis of large-scale "omics" data, to advanced imaging modalities, and finally to attempt to glean more insight from clinical trial response curves. Our potential contributions should not be compartmentalized, as if there were one identifiable part of each project that somehow needs physics and mathematics whereas the rest can proceed "normally." We are not just advanced informatics technicians. Experience in other areas of biological physics has shown that integrated multidisciplinary efforts are hard to arrange and maintain, but well worth the effort. We hope that this journal section will help in this regard and that here too it will prove to be well worth the effort.

The article by Lu and colleagues focuses on the genetic logic underlying the epithelial–mesenchymal (EMT) transition and its coupling to other cell changes that collectively allow for the various parts of metastatic spread. The article aims for a general framework for making sense of disparate data, not for a precise characterization of one type of tumor with one specific set of data. Underlying this type of work is a strong commitment to the vision espoused by Hanahan and Weinberg in their updated classic work on the hallmarks of cancer; that vision is that we can aim toward "cancer research as an increasingly logical science, in which myriad phenotypic complexities are manifestations of a small set of underlying organizing principles."

The hallmark of tissue invasion is not just a change in the state of the transcriptional and translational regulatory network. The genetic changes of course have specific biophysical consequences, which is of course the whole point of EMT from the cell's perspective. Unlike most in vitro studies, however, tissue invasion necessitates studying how the cells move within a complex extracellular matrix (ECM). Interactions between cells and the ECM are the subject discussed in two articles, by Sander and Rubashkin and colleagues. The first focuses on mechanical aspects, especially the feedback between forces generated by the cell and the alignment of the fibrous proteins underlying ECM structure. The other article adds to this, the clearly important signaling aspects of this interaction, explicitly focusing on the manner in which ECM affects adhesion complexes and strongly alters signaling therefrom. All this effort follows the seminal ideas of Mina Bissell, who has long focused attention on the

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bidirectional crosstalk that exists between a cell and its surrounding ECM (a "dynamic reciprocity"), in which the ECM influences cell behavior and the cell, in turn, remodels the ECM, which then further acts on the cell.

Much of cancer research is focused on the genetic basis for the aberrant behavior seen in cell decision-making, cell metabolism, and cellular interactions with the microenvironment. The article by Domany reviews how statistical methods originating from physical science have been used to construct prognostic classifiers, using correlation to help overcome shortcomings in more mechanistic approaches. We suspect that a fusion of purely informatic ideas applied to "omics-scale" data with detailed systems and biophysical models will help overcome the roadblocks that to date have prevented the knowledge of individual cancer genotypes from translating into individualized cancer therapeutics. Unfortunately, the gap between the scale of networks that can be quantitatively understood, as demonstrated in the articles by Lu and colleagues and Rubashkin and colleagues, and this omics scale remains quite formidable.

When one considers possible roles for physical science in clinical oncology, one immediately thinks of the development of improved noninvasive measurement techniques. Two articles in this section review MRI as an imaging modality, Kalpathy-Cramer and colleagues from a general perspective and White and colleagues focusing more specifically on methods that use water diffusion physics as a framework to construct more powerful approaches. As explained clearly, one main challenge here is to distinguish among the many effects arising from treatment so as to be able to accurately evaluate efficacy. The fact that modern therapies often operate in nontraditional manners, such as by "regularizing" the vasculature or by activating tumor-infiltrating immune system cells, can often lead to the wrong interpretation of images, mistaking inflammation for progression, or conversely perfusion reduction for shrinkage. This research is therefore critically needed and will become even more crucial as we learn to conduct a modern information-based war on tumors and not just continue to assume that success is merely a matter of counting the dead cells. Eventually, advanced algorithms will be combined with the data analysis strategies discussed in the article by Blagoev and colleagues, leading to more effective clinical trials and more rapid assessment of the promise of new treatment options.

The last article returns to one of the most basic questions and indeed to the one with which we started this discussion, namely the ability of tumors to develop resistance to the some of the best drugs in our arsenal. This work discusses possible approaches to using clinical data and carefully designed \textit{in vitro} experiments to unravel the dynamics of resistance. What is needed here are critical tests of the assumption that has gone into many resistance models, namely that the preexisting genetic heterogeneity of the tumor allows for the selection of resistant subclones, without any need for more complex mechanisms. This idea, although certainly correct in some cases, does not take into account phenotypic variability leading to drug tolerance (for example, of "stem-like" subpopulations), does not allow for a more active role for genetic instabilities (for example, as might be enhanced by treatment-induced hypoxia), and just plain seems too simple given what we have learned about the sophistication of cancer cells and the tumors they inhabit. But, these arguments are no substitute for obtaining and fitting real data, and this article takes some initial steps along this path.

Finally, it is important to be realistic about what can be accomplished by enlisting physics and mathematics to the cause. One should not imagine that there are waiting off-the-shelf techniques and technologies that just need to be applied to the problems at hand. Instead, these disciplines provide a conceptual framework replete with motivated practitioners, in which understanding slowly emerges from detailed investigations and applications slowly emerge from understanding. In a field in which there is a recurrent boom-bust cycle for magic bullet cures, perhaps it makes sense to invest some resources in a long-haul strategy.

\textbf{See all articles in this Cancer Research section, "Physics in Cancer Research."}

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