Toward improved models of human cancer: Two perspectives

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INTRODUCTION

Given the continued high incidence rates of cancer despite numerous advances in treatment, there is little debate about the need for fundamental innovation leading to new approaches to study mechanisms of cancer progression, develop new therapeutic strategies, and provide the scientific basis for a more personalized approach to patient treatment. Currently, the scientific community looks to two complementary methodologies to address these critical issues: animal models, typically in the mouse, or in vitro models spanning a broad range of complexity from cells-in-a-dish to organs-on-a-chip. Here and in the two companion perspectives, we seek to foster an open discussion with the goal of identifying a clear pathway for future development.

Seeking to draw more physical scientists into the field of cancer research, the National Cancer Institute formed the Physical Sciences Oncology Network (PS-ON) in 2009. Since its inception, the program has grown in size and impact and has driven discussion of new and innovative ways in which we can study cancer, fostering a range of perspectives that improve our fundamental understanding of the disease process and promote innovative technologies to advance treatment. A recently formed sub-group of the PS-ON focuses on the development of “tissue engineered models,” platform assays that are often based on in vitro abstractions of human cancer. While still much in the minority (by a recent search in PubMed, 645 papers were published on “microfluidics + cancer,” compared with 14,575 publications on “cancer + mouse + model”), the cancer community is increasingly impacted by the insight that such models can provide.

ASSESSING THE NEED

While in vitro models have been used for decades in the study of cancer and dominate the initial steps in the process of drug development, for years, these were largely limited to simple assays based on experiments conducted on a single cell type cultured on glass or hard plastic. In vitro models have progressed and become increasingly sophisticated and realistic, however, utilizing 3D cultures of multiple cell types and often drawing upon microfluidics and new synthetic matrix materials to better recapitulate the in vivo tumor microenvironment. Success of these more complex assays has clearly demonstrated that in vitro models provide enormous value, and their central role in understanding fundamental biological processes and in drug screening is now widely recognized. In addition, these studies have raised the prospect that in vitro models should be more heavily utilized to supplement, or even someday replace, certain animal studies, and this has nurtured a healthy debate in the scientific community. While few question the need to reduce our reliance on animal testing, most still consider it to be the “gold standard” against which all in vitro models must be validated. Questions persist, however, regarding the usefulness of animals as models of human disease, and these especially apply in the case of immuno-oncology for the study of cancer. At the same time, some are not convinced that in vitro models can ever capture the essential complexity of human disease, given the reductionist approach that necessitates difficult decisions regarding the level of complexity of a model needed to develop an appropriate disease model to study fundamental mechanisms or discover new therapies. These questions have tremendous implications in general, but rise to prominence particularly in the context of drug discovery and screening by the pharmaceutical and biotech industries, where we see increasing investments in in vitro models but a reluctance to commit to wide adoption of microphysiological systems as an integral part of their drug development pipeline.

Addressing these essential issues requires an open dialog between proponents on both sides, those who develop microphysiological models of cancer along with leaders of the research community who focus on animal studies. This point-counterpoint perspective seeks to bring these issues to the forefront. For this purpose, we invited two leaders in their respective fields: one, David Beebe, with an emphasis on in vitro model development; and another, Alana Welm, whose work...
is based largely upon animal models. In this introduction to the perspectives, we adopt Beebe’s term, “bioengineered microscale organotypic models” (BMOMs), to include the wide variety of in vitro modeling approaches.

CURRENT STATE OF MODELING

One issue that likely contributes to the slow adoption of BMOMs is the wide diversity of existing platforms. While pharmacology and federal regulators seek standardization, the developed technologies vary dramatically in design and composition. This is both an advantage and a drawback of BMOMs. The advantage is that the model and device platform can be made to be only as complex as deemed necessary to address a particular problem. Researchers are, thus, able to maintain control over the critical variables, better monitor model function, and dissect out the roles of individual cell types or other factors in what might, otherwise, be a complex, often overwhelmingly so, process. So, while one model might take a patient tumor, sort its constituent cells, and reconstitute a subset of different cell types in a synthetic matrix with known ligand densities and mechanical properties, another might take a small fragment of the patient-derived tumor sample, suspend it in a natural or synthetic matrix material, and introduce it directly into a BMOM. Different questions require different models, and the flexibility of an in vitro system, combined with the ability to control and monitor critical variables, leading to a plethora of different approaches. The disadvantage of this, of course, is that it is often difficult to compare one model with another, and not surprisingly, they sometimes lead to conflicting conclusions based on their individual focus (raising the “streetlight bias” criticism), supporting the skepticism of the BMOM critics. This is also reflected in the diversity of commercial platforms being developed and marketed, further contributing to the reluctance of industry to invest in a single technology for fear that it will soon become obsolete.

Animal models, specifically mouse models, share many common features even though gene editing has facilitated the creation of a wide variety of models for specific diseases. They also benefit from the years of experience that researchers have gained in their use, leading to the current situation in which most of the advantages and limitations are well known. However, despite the considerable and growing recognition that the immune system plays a critical role in both the progression and treatment of cancer, the relevance of immune-humanized mouse models of human cancer, including PDX models, is not universally accepted. Despite many successes, there remains a high failure rate in humans of drugs that have tested favorably in mice, reported to be 96.6% in oncology. Finally, pressures from the society to minimize animal studies, and ban them in some cases, push researchers even more to consider in vitro alternatives.

MAPPING THE ROAD AHEAD

In order to foster an open and productive debate on these questions, as members of the cancer researcher community, we need to provide a balanced assessment of both the advantages and disadvantages of our models and should help guide users of both technologies in their choice of which is optimal for a given application. This starts with a clear statement of the critical issues to consider. In terms of application in either the pharmaceutical industry or clinical setting, these include the following:

- relevance to human disease and the questions being addressed;
- repeatability, standardization, and validation;
- efficiency/time;
- cost;
- ease of use;
- throughput; and
- ability to monitor response.

These are some of the issues discussed in the following perspectives in the context of current models. Beyond that, both papers look to the future and seek to identify where the field is headed and what are the important issues.

Barriers to progress exist, especially in the newer BMOM technologies. Questions regarding the alternative use of in vitro and in vivo models arise in the context of three major applications: disease models, drug screening, and personalized medicine or patient stratification according to the genetic profile or functional screens. The accompanying papers lead us through a reasoned discussion of these application areas and provide specific viewpoints of what is possible now and what we yet need to develop. Many key issues remain, such as the following:

- How far does one go in recreating the in vivo environment, balancing in vivo realism and multi-organ effects against increased challenges in interpreting the results?
- Do we work to minimize or control for intrinsic variability of model behavior based on cell source variations, or do we embrace it as a means of capturing the natural genetic profiles of different patient groups?
- How do we incorporate the human innate and adaptive immune systems with greater realism?
- An increased emphasis needs to be placed on metastatic disease as the dominant cause of death in cancer.

These and other issues are raised and discussed in these perspectives in a balanced way, helping us to understand the nuances of choosing between the various modeling approaches.

THE BOTTOM LINE

Somewhat surprisingly, despite their different backgrounds, Welm and Beebe arrive at remarkably similar conclusions about the future of cancer models and their use in drug development and personalized medicine for patient-specific therapies. Both foresee a time in the future when we will have developed an integrated approach to clinical trials and even the selection of personalized patient treatments. They envision tremendous potential in an integrated approach using a combination of in vitro, in vivo, and in silico (especially machine learning-based) models. In terms of research, new sensing/monitoring technologies will be developed with greater reliance on single cell genomics and computational methods. For discovery of new therapeutics, higher throughput methods that embrace and account for patient subpopulations, tumor heterogeneity, and the key role of the immune system are on the horizon. Finally, patient treatment is seen to benefit greatly from this combined approach, potentially using patient biopsy specimens as tumor surrogates, to be harvested and stored at the time of surgical removal of the tumor and drawn upon as needed to test response to alternate therapies, all with the goal of reducing cancer mortality.
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1See https://physics.cancer.gov/ for information on the National Cancer Institute Physical Sciences Oncology Network.

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