The Era of Cancer Discovery

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Realization of the need for a forum that would bring basic and translational scientists and clinical trials specialists together inspired the launch of Cancer Discovery.

A growing optimism that cancer research and treatment are entering a new era is taking hold. Since the late 1950s, when the first real cancer cures were achieved with combination therapies, progress in treating cancers has been painfully slow, and with a few notable exceptions, breakthroughs came from empirical observations in the clinic rather than from detailed understanding of the disease. We did not understand why certain therapies were successful in some subsets of cancers and failures in others. Most cancer drugs were being developed on the basis of their ability to kill cancer cells grown on plastic or in nude mice, with no real understanding of the mechanism of drug action. It is therefore not surprising that the majority of these investigational drugs ultimately failed when tested in large and expensive randomized trials, and those that did succeed typically extended lives by only a few months. In 1996, the 25th anniversary of the declaration of war on cancer, it was difficult to point to a single breakthrough in treatment that emerged from the tens of billions of dollars that had been spent on basic and clinical research.

Nevertheless, we learned a lot during those first 25 years. We discovered that cancer was, for the most part, caused by mutations in genes (oncogenes) that control cell proliferation, cell growth, cell survival, and cell differentiation. Importantly, we discovered that the types of cancers that had been historically defined based on tissue of origin and classical techniques of pathology could be further divided into dozens of subtypes when analyzed at the molecular level. This knowledge began to explain why 2 patients with the same disease diagnosis could respond so differently to the same therapy, but at that time this knowledge had not translated into new cures. In fact, awareness of this Pandora’s box of cancer diversity gave pause to the pharmaceutical industry. Given the historically high costs of drug development and the frequency of failures, was it even possible to make a profit on a drug that would be approved for only a minor subset of breast cancers or leukemias? The concept that one could cure (or even slow down) a cancer by targeting the oncogene that was mutated or aberrantly activated was not yet proven in humans, and it is fair to say that in 1996 most clinicians were doubtful that targeted approaches would succeed.

Early advances that persuaded clinicians and pharmaceutical companies to embrace targeted therapies were not initial home runs. Trastuzumab was approved for Her2-amplified breast cancers but rarely provides cures in advanced disease. Similarly, imatinib dramatically extends lives of patients with BCR-abl mutant chronic myelogenous leukemia (CML) but does not result in cures. However, these developments represent an important start—the first proof of the concept that therapies against oncogenes might be beneficial. With the discovery that resistance to imatinib could be explained by a mutation in the drug-binding pocket of BCR-abl, the oncology community became further convinced that these agents were interfering with the target’s function. Importantly, these early partial successes provided 3 motivations for pharmaceutical companies to invest in targeted therapies. First, they offered proof of the concept that cancers are more “addicted” to mutated oncogenes than are noncancerous tissues that express the same (nonmutated) genes, providing an efficacy–toxicity window. Second, these advances showed that, by excluding patients who lack mutations (or amplifications) in the oncogene being targeted in the clinical trial, it is possible to increase the odds of drug approval and decrease the number of patients and years required for approval. Third, in part because of funds that have been saved from fewer clinical trial failures and because patients survive and continue to take the drugs, it has become clear that it is possible to make a profit on drugs that target minor subsets of cancers.

We are now in an unprecedented time with regard to emerging cancer therapies. Advances in DNA-sequencing technologies have made it possible to sequence candidate oncogenes in cancers quickly and affordably, and dozens of tumors have been characterized by full exome or full genome sequencing. Soon the numbers will be in the thousands. These data provide critical information about the spectrum and frequencies of mutations in cancers and will facilitate the development of drugs against targets that are most frequently mutated. For the more frequently mutated “druggable” oncogenes, such as PI3K and BRAF, dozens of investigational agents are already in early-stage clinical trials. Because it is becoming simpler to identify patients with mutations, a rationale also exists for developing
drugs against targets that are rarely mutated. As a consequence, the number of new drugs entering trials is unprecedented, and competition to find sufficient numbers of patients to complete the trials will increase. Other important discoveries likely to be exploited therapeutically in the clinic concern the unique metabolism of cancer cells, post-translational (epigenetic) modifications, tumor heterogeneity, stroma–tumor interactions, and the immune response to tumor cells.

Despite the early successes of targeted therapies, it is also becoming evident that primary and acquired resistance will be major limitations. To begin with, most solid tumors will not yield to single-agent targeted therapies in the way that CML retreats from imatinib. Even in those cases in which a single agent dissolves the tumor, such as the effects of erlotinib on epidermal growth factor receptor mutant lung cancers or the effects of PLX4032 on BRAF mutant melanomas, the victory is short lived and the tumors re-emerge. More often, single-agent trials involving targeted therapies administered to solid tumors result in modest effects, or no responses, even when confined to patients who have mutations in the target oncogene. Clearly, we have much yet to understand about in vivo tumor biology. Do the drugs fail because the target oncogene develops a mutation in the drug-binding site? Is the failure due to the drug’s not reaching the target at high enough concentrations, to an alternative pathway that bypasses the target oncogene, to the survival signals provided by the stromal cells in the tumor environment, or to the drug’s adverse effects on the immune system? An understanding of resistance mechanisms is essential to decide what combination of drugs will treat resistant tumors or even to prevent the emergence of resistance.

In short, we have much to do, and the only logical way forward is for basic scientists with detailed knowledge of oncogene signaling pathways and tumor biology to collaborate with clinicians and other clinical trial specialists in designing biomarker-driven trials that test specific hypotheses about mechanisms of resistance. Not enough cancer patients exist in the world to randomly test all possible combinations of approved or investigational drugs in all forms of cancers. Instead, we need to choose drug combinations based on hypotheses that emerge from knowledge of the tumor biology and signaling pathways. These hypotheses need to be supported by experiments using model systems that better replicate the natural tumor environment, such as genetically engineered mouse models that mimic mutational events in human cancers or human tumors explanted into immune-compromised mice, to determine whether an efficacy–toxicity window is evident for the drug combination of choice. Human trials must be designed to ascertain whether the drugs are affecting the pathways they are designed to target, by tracking changes in the appropriate biomarkers detected in repeat biopsies or circulating tumor cells. Acute changes in tumor metabolism can be monitored by alterations in positron emission tomographic images using radiolabeled metabolites. Changes in appropriate serum biomarkers (e.g., proteins, RNA, lipids, or metabolites) might also be informative. We need technologies that tell us quickly whether the drug or drug combination is inducing the expected response in the tumor so that we learn as much from patients who fail to respond as we do from those who do respond. No single scientific discipline will be able to tackle this complex issue alone.

It is now possible to translate a discovery in a basic science laboratory into a new clinical trial at an unprecedented rate. Basic scientists need to become familiar with the complexities and potential answers to be found in clinical trials. In turn, clinicians would greatly benefit from acquainting themselves with the details of articles on oncogene signaling networks, tumor microbiology, tumor immunology, and cancer stem cells. We believe that Cancer Discovery can help bring these fields together by publishing high-impact, peer-reviewed articles describing major advances from the laboratory to the clinic to epidemiologic studies. We will also provide commentaries on these articles that explain the relevance to a more general audience. In addition, Cancer Discovery will include review articles, perspectives and commentaries, news, and Research Watch summaries of important journal articles published in other oncology journals. The journal has a distinguished team of scientific editors with expertise in all major areas of cancer research, as well as superb professional in-house editors. We strongly believe that Cancer Discovery will be an important tool in developing the field and look forward to providing the most timely and important information to you and the community.