A Decade of Cancer Discovery

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Summary: As Cancer Discovery turns 10, we reflect on the journal’s success and look ahead to the future.

Entering the second decade of publishing Cancer Discovery, we cannot help but reflect on the progress that has been made over the past 10 years both in understanding how cancers occur and in developing new therapeutic approaches. We are optimistic that the breakthroughs in cancer research and therapy herald even greater discoveries to come, and in this 10th anniversary special issue, we have asked leaders in some of the most rapidly evolving areas of the field to discuss some of the biggest unanswered questions to be addressed. The 10th anniversary of the journal also provides an excellent opportunity to reflect on the contributions that Cancer Discovery has made to the cancer research field, both in its paradigm-shifting content that has been at the forefront of the most important developments in cancer over the past 10 years and in its ethos of providing the highest level of author service in support of the cancer research community. We could not be prouder of the level of success the journal has achieved, which would not have been possible without the immediate and sustained support from the cancer research community.

From its outset, we sought to make Cancer Discovery a uniquely broad forum for the cancer community, featuring emerging insights in basic, translational, and clinical research. By 2011, as genome sequencing became more commonplace, it became clear that most cancers were driven by gain-of-function mutations or amplifications in oncogenes or loss-of-function mutations or deletions in tumor suppressor genes. More importantly, it was becoming clear that novel drugs that either block the function of the oncogene that was mutated or create a synthetic lethality upon loss of a tumor suppressor could be effective in treating cancers. Precision medicine was just beginning to have an impact on cancer research and treatment, and with the strong support of basic researchers, physician-scientists, and clinicians, Cancer Discovery was uniquely poised to present these advances to the community.

Many of the most impactful manuscripts published in Cancer Discovery over this past decade focused on identifying actionable alterations (1–3) or mechanisms of therapeutic resistance (see review by Soria and colleagues in our upcoming 10th Anniversary Special Issue). Over the past 10 to 15 years, clinical trial designs switched focus from the tissue of origin to patient selection based on genomic alterations (e.g., the BATTLE Trial, published in the very first issue of Cancer Discovery; ref. 4). As a consequence, there was a dramatic increase in clinical trials involving targeted therapies, and importantly, an increase in the fraction of studies that led to new drug approvals. In the 1980s, cancer drug approvals accounted for 4% of all new drugs approved, whereas over the past decade cancer drug approvals account for more than 25% of new drugs (5).

We are incredibly proud of the role Cancer Discovery has played in several such practice-changing advances. We published the first disclosure, preclinical characterization, and proof of concept of clinical efficacy for AZD9291/osimertinib [ref. 6; now approved by the FDA for first-line treatment of EGFR-mutant non–small cell lung cancer (NSCLC)], BLU-667/pralsetinib (ref. 7; now approved by the FDA for RET fusion–positive NSCLC), and most recently for MRTX849/adagrasib (8), one of the first KRASG12C inhibitors to enter the clinic. Preclinical and clinical studies published in Cancer Discovery also paved the way for the approval of venetoclax in acute myeloid leukemia (9, 10). Early-phase clinical trials with a strong scientific rationale and compelling biomarker analyses have been a key component of the journal since its launch, and we are pleased to welcome more clinical submissions along these lines as well as later-stage trials as ideas the journal has championed in preclinical and early-phase trials in its first decade come to fruition.

Dramatic improvement in techniques for sequencing DNA and RNA accounts for much of the progress in targeted therapies. A decade ago, it was rare for a tumor from a patient with cancer to be evaluated by DNA or RNA sequencing because of the cost and low probability of clinically actionable results. Today, it is becoming routine at major cancer centers to sequence focused panels of 200 to 400 genes or to do full exome sequencing of all genes in cancers where standard of care is unlikely to be curative. Sequencing of RNA has also revealed higher rates of gene fusions driving cancers than had been anticipated. The increased sensitivity of DNA sequencing is leading to dramatic improvements in identifying cell-free cancer DNA in plasma from patients with cancer, a potential new way to monitor response to therapy or reemergence of disease. This technology may eventually become a routine test to facilitate early detection of cancers of any origin and monitor recurrence (see review by Alix-Panabières and Pantel in our upcoming 10th Anniversary Special Issue).

Undoubtedly, the greatest breakthrough in cancer treatment over the past decade has been in immunotherapy.
Chimeric antigen receptor (CAR) T cells entered the clinic a little more than 10 years ago, and though initially this laborious and expensive approach was expected to have a small impact on cancer, improvements in CAR T-cell design and in manufacturing are leading to greater expectations for this approach (see In Focus by Ribas in our upcoming 10th Anniversary Special Issue). Immune-checkpoint therapies, including anti–CTLA4, anti–PD-1, and anti–PD-L1 (see review by Sharma and colleagues in our upcoming 10th Anniversary Special Issue), have had an immediate impact particularly on cancers that have high mutational burdens, with research published in Cancer Discovery showing that microsatellite instability (MSI)–positive tumors have a “hot” immune microenvironment (11) presaging the first tissue-agnostic FDA approval, for pembrolizumab in unresectable or metastatic, MSI-high or mismatch repair–deficient solid tumors.

The clinical success of immune therapy has been accompanied by a much deeper appreciation of the roles of various types of immune and stromal cells in the tumor microenvironment (see review by Joyce and colleagues in our upcoming 10th Anniversary Special Issue). We are learning that cancers coerce such cells, especially a subset of myeloid-derived suppressor cells, to protect them from T cells. This knowledge, derived in part from recent advances in technologies for conducting RNA sequencing of single cells (see review by Suva and colleagues in our upcoming 10th Anniversary Special Issue), will likely lead to yet additional approaches for enhancing immune attack of tumors and understanding tumor heterogeneity and evolution (see review by Swanton and colleagues in our upcoming 10th Anniversary Special Issue). Advances in understanding how tumors evade immune surveillance as well as new insights into tumor cell plasticity and dormancy have also provided key insights into how tumors metastasize and highlighted potential vulnerabilities (see review by Ganesh and Massague in our upcoming 10th Anniversary Special Issue).

In the coming years, we look forward to the development of more faithful tumor models to provide needed insight into underlying biological mechanisms and therapeutic responses (see In Focus by Tuveson in our upcoming 10th Anniversary Special Issue), continued breakthroughs in drug discovery as the list of targets in cancer previously considered “undruggable” continues to shrink (see In Focus by Malek in our upcoming 10th Anniversary Special Issue), and innovative approaches to clinical trial design in oncology with next-generation targeted therapies (see review by Siu and colleagues and In Focus by Peters and colleagues in our upcoming 10th Anniversary Special Issue). We also anticipate more widespread application of artificial intelligence–based approaches to guide drug development, facilitate diagnosis, and probe real-world data (see review by Elemento and colleagues in our upcoming 10th Anniversary Special Issue), and look forward to redoubled efforts into understanding and addressing the underlying causes of racial disparities in outcomes of patients with cancer (see In Focus by Davis and colleagues in our upcoming 10th Anniversary Special Issue).

As Editors-in-Chief of Cancer Discovery, it has been thrilling to follow this revolution in both the understanding and the treatment of cancer as cutting-edge manuscripts from basic, translational, and clinical research have arrived at the journal. Given the increasingly rapid rate of progress in this field, our approach from the journal’s onset—and what we hope has been one of Cancer Discovery’s most significant contributions to the cancer research community—has been to move only manuscripts that meet our criteria for novelty, significance, and clinical relevance into the peer-review process and to only consider manuscripts through one round of experimental revision to avoid unproductive and time-consuming review and revision processes. We do our best to serve the community by ensuring that papers that provide a significant advance are reviewed as rapidly as possible and, importantly, to work closely with authors to publish papers in a timely fashion.

It has been extremely gratifying to watch the growth of the journal, and in just 10 short years, Cancer Discovery has become the preeminent venue for basic, translational, and clinical cancer research and news. We are indebted to our founding co-Editor-in-Chief, José Baselga, and our founding Executive Editors, Mark Landis and Judy Quong, who laid much of the groundwork for the journal’s success. We are also grateful to our current team of Editors, including Robert Kruger, Elizabeth McKenna, Michele Hartsough, I-Mei Siu, and Avital Lev, who decide which manuscripts to review and work closely with authors and reviewers to shepherd papers through the editorial process. We are also extremely grateful to our group of external Scientific Editors who serve in an advisory role and who have supported the journal since its inception. Our News and Research Watch sections have served as important resources for the community, and we are grateful to Suzanne Rose, Catherine Caruso, and Nicole Haloupek for their efforts to keep readers updated on the latest developments in the field. Finally, we could not continue to present Cancer Discovery to the community without the support of numerous AACR colleagues and AACR Publications staff, particularly Ingrid Lin and Julie Ehlers—it truly takes a village to run a successful journal.

We look forward to celebrating the 10th anniversary of Cancer Discovery with you throughout the year, and we hope you enjoy our special reviews issue as well as content we will continue to serve the community by ensuring that papers that provide a significant advance are reviewed as rapidly as possible and, importantly, to work closely with authors to publish papers in a timely fashion.

Authors’ Disclosures

L.A. Diaz is a member of the board of directors of Personal Genome Diagnostics (PGDX) and Jounce Therapeutics. He is a compensated consultant to PGDX, 4Paws (PetDX), Innovatus CP, Se’er, Kinnate, and Neophore. He is an uncompensated consultant for Merck but has received research support for clinical trials from Merck. He is an inventor of multiple licensed patents related to technology for circulating tumor DNA analyses and mismatch repair deficiency for diagnosis and therapy from Johns Hopkins University. Some of
these licenses and relationships are associated with equity or royalty payments directly to him and to Johns Hopkins University. He holds equity in PGDx, Jounce Therapeutics, Thrive Earlier Detection, Se’er, Kinnate, and Neophore. L.C. Cantley is a consultant for Cell Signaling Technologies, Agios, Volastra, Faeth, Larkspur, Scorpion, and EIP Pharmaceuticals. He is a stockholder of Petra Pharmaceuticals, Agios, Cell Signaling Technologies, Volastra, Faeth, Scorpion, Larkspur, Geode, and EIP Pharmaceuticals. In addition, L.C. Cantley’s wife is on the Board of Directors of Bristol Myers Squibb and has stock in this company.

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REFERENCES
