**EDITORIAL**

A Decade of Cancer Discovery

Luis A. Diaz\(^1\) and Lewis C. Cantley\(^2\)

**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 the past decade focused on identifying actionable alterations (1–3) or mechanisms of therapeutic resistance (see review by Soria and colleagues on page 874). 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 KRAS\(^{G12C}\) 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 on page 858).

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

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Cancer Discov 2021;11:795-7

doi: 10.1158/2159-8290.CD-21-0082

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little more than 10 years ago, and though initially this labo-
rious 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 on page 798). Immune-check-
point therapies, including anti-CTLA4, anti–PD-1, and anti-
PD-L1 (see review by Sharma and colleagues on page 838),
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 pemb-
rolizumab in unresectable or metastatic, MSI-high or mis-
mismatch repair–deficient solid tumors.

The clinical success of immune therapy has been accom-
panied by a much deeper appreciation of the roles of various
types of immune and stromal cells in the tumor microenvi-
ronment (see review by Joyce and colleagues on page 933).
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 sequenc-
ing of single cells (see review by Suvà and colleagues on
page 960), 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 on page 916). 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 Massagué
on page 971).

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 on page 801), continued break-
throughs in drug discovery as the list of targets in cancer
previously considered “undruggable” continues to shrink (see
Perspective by Malek and colleagues on page 815), and innov-
ative approaches to clinical trial design in oncology with
next-generation targeted therapies (see review by Siu and col-
leagues on page 822 and In Focus by Peters and colleagues on
page 810). We also anticipate more widespread application of
artificial intelligence–based approaches to guide drug develop-
ment, facilitate diagnosis, and probe real-world data (see review
by Elemento and colleagues on page 900), 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 on page 805).

As Editors-in-Chief of Cancer Discovery, it has been thrill-
ning 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 pro-
cess 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. This is in large part due
to our founding co–Editor-in-Chief, the late José Baselga, a
true visionary with a keen sense for the types of preclinical
and clinical studies that were most likely to benefit patients.
Our founding Executive Editors, Mark Landis and Judy
Quong, also made enduring contacts with the community
from the journal’s inception and laid much of the ground-
work for the journal’s success. We are grateful to our current
team of Editors, including Robert Kruger, Elizabeth McK-
enna, 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 edi-
torial process. We are also extremely thankful 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 impor-
tant 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 develop-
ments 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 vil-
lage 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
be sharing throughout the year highlighting some of the most
impactful work published in the journal over the past decade.
We also hope you will join us for our upcoming 10th Anniver-
sary Symposium to be held virtually June 21–22, 2021, which
we intend to be a forward-looking discussion of emerging
topics in cancer research and therapy. We close the first decade
of Cancer Discovery with gratitude to our authors, reviewers,
editors, and readers and excitement for the opportunity to
continue to serve the research community and advance break-
throughs to benefit patients for decades to come.

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 inven-
tor 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.

Published first February 22, 2021.

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Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-21-0082

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