IN THIS ISSUE
Highlighted research articles .......................... 1601

NEWS IN BRIEF
Important news stories affecting the community ......... 1604

NEWS IN DEPTH
COVID-19 Reshapes Cancer Clinical Research ........... 1608

RESEARCH WATCH
Selected highlights of recent articles of exceptional significance from the cancer literature .......... 1609

ONLINE
For more News and Research Watch, visit Cancer Discovery online at http://cancerdiscovery.aacrjournals.org/CDNews.

VIEWS
Obituary

José “Pepe” Baselga, MD, PhD: In Memoriam (1959–2021) .... 1614
J. Tabernero, D.M. Hyman, and J.-C. Soria

In the Spotlight

Mobocertinib: A Potential Treatment for NSCLC with EGFR Exon 20 Insertions .... 1617
J.M. Pacheco
See article, p. 1672
See article, p. 1688

Triple Therapy to Outwit the BRAF Oncogene ............ 1620
C. Zhang and G. Bollag
See article, p. 1716

Optineurin Guards IFNγ Signaling in Cancer Cells .......... 1623
C. Salvagno and J.R. Cubillos-Ruiz
See article, p. 1826

MINI REVIEWS
Synthetic Lethality in Cancer Therapeutics: The Next Generation .................. 1626
J. Setton, M. Zinda, N. Riaz, D. Durocher, M. Zimmermann, M. Koehler, J.S. Reis-Filho, and S.N. Powell

The Complex Integration of T-cell Metabolism and Immunotherapy .......... 1636
M.Z. Madden and J.C. Rathmell

REVIEW
Rational Treatment of Metastatic Colorectal Cancer: A Reverse Tale of Men, Mice, and Culture Dishes ............ 1644
M. Avolio and L. Trusolino

RESEARCH BRIEF
A Chimeric GM-CSF/IL18 Receptor to Sustain CAR T-cell Function ......... 1661
S. Lange, L.G.L. Sand, M. Bell, S.L. Patil, D. Langfitt, and S. Gottschalk
Précis: Chimeric antigen receptor T cells designed to target the cytokine GM-CSF (abundant in solid tumors) and bind IL18, which supports T-cell function and persistence, showed in vivo efficacy against solid tumors.

RESEARCH ARTICLES
Mobocertinib (TAK-788): A Targeted Inhibitor of EGFR Exon 20 Insertion Mutants in Non–Small Cell Lung Cancer ............ 1672
Précis: Structure-guided design was used to develop mobocertinib, a selective, irreversible inhibitor of EGFR harboring exon 20 mutations; this drug yielded substantial reductions in non–small cell lung cancer tumor sizes in vivo.
See commentary, p. 1617
Activity and Safety of Mobocertinib (TAK-788) in Previously Treated Non–Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations from a Phase I/II Trial .......................... 1688
Précis: In a phase I/II clinical trial, mobocertinib—which selectively inhibits EGFR with oncogenic exon 20 insertions—produced objective responses in 43% of previously treated patients with non–small cell lung cancer harboring these mutations.

See commentary, p. 1617

A Burned-Out CD8+ T-cell Subset Expands in the Tumor Microenvironment and Curbs Cancer Immunotherapy ................................. 1700
Précis: A tumor-infiltrating CD8+ T-cell subset (dubbed burnout T cells) was identified; these T cells exhibited features overlapping with those of exhausted T cells but were differentiated by their proliferative and apoptotic nature.

Exploiting Allosteric Properties of RAF and MEK Inhibitors to Target Therapy-Resistant Tumors Driven by Oncogenic BRAF Signaling ............................. 1716
Précis: In silico experiments and biochemical assays were used to develop an inhibitor of dimeric BRAF for use in conjunction with a BRAF*V600E inhibitor and a MEK inhibitor; this combination exhibited safety and tolerability in vivo.

See commentary, p. 1620

Genetic Determinants of EGFR-Driven Lung Cancer Growth and Therapeutic Response In Vivo .......................... 1736
Précis: Some inactivating mutations in genes known to act as tumor suppressors in Kras-driven mouse lung adenocarcinoma models had the opposite effect in Egfr-driven lung cancer models, instead restricting tumor growth.

A Functional Taxonomy of Tumor Suppression in Oncogenic KRAS–Driven Lung Cancer ............ 1754
Précis: An innovative in vivo screening technique revealed that inactivation of various tumor suppressor genes had dramatically different effects on cancer development and progression in oncogenic Kras–driven mouse models of lung cancer.

PTHrP Drives Pancreatic Cancer Growth and Metastasis and Reveals a New Therapeutic Vulnerability ................................. 1774
Précis: PTHHLH (encoding PTHrP) was amplified in patient metastatic pancreatic cancer tumors, and loss of Pthlh or treatment with neutralizing antibodies to PTHrP reduced primary tumor growth, diminished metastasis, and increased survival time in vivo.

Bacterial-Driven Inflammation and Mutant BRAF Expression Combine to Promote Murine Colon Tumorigenesis That Is Sensitive to Immune Checkpoint Therapy ................................. 1792
Précis: In a mouse model of colorectal cancer driven by enterotoxigenic bacteria, expression of oncogenic human BRAF*V600E-generated tumors that recapitulated the biology of human BRAF*V600E-mutant tumors and were sensitive to anti–PD-L1 treatment.
Macropinocytosis in Cancer-Associated Fibroblasts Is Dependent on CaMKK2/ARHGEF2 Signaling and Functions to Support Tumor and Stromal Cell Fitness .......................... 1808
Y. Zhang, M.V. Recouvreux, M. Jung, K.M.O. Galenkamp, Y. Li, O. Zagnitko, D.A. Scott, A.M. Lowy, and C. Commissio

Précis: Under the glutamine-limiting conditions common in pancreatic ductal adenocarcinomas, cancer-associated fibroblasts activated macropinocytosis to engulf extracellular materials, enabling them to survive as well as secrete glutamine for use by tumor cells.

Loss of Optineurin Drives Cancer Immune Evasion via Palmitoylation-Dependent IFNGR1 Lysosomal Sorting and Degradation .......................... 1826

Précis: In colorectal cancer, loss of optineurin led to increased lysosomal degradation of IFNγ receptor 1 (IFNGR1), providing an explanation for the immunotherapy resistance; pharmacologic inhibition of a step in IFNGR1 lysosomal trafficking overcame this effect.

See commentary, p. 1623

CD4+ T Cell-Dependent Rejection of Beta-2 Microglobulin Null Mismatch Repair-Deficient Tumors ............... 1844

Précis: Deficiency of B2M, encoding the MHC-I component β2-microglobulin, is common in colorectal cancer, but CD4+ T cell–mediated antitumor immunity in mismatch repair–deficient colorectal cancer caused sensitivity to immune checkpoint blockade.

Together with the rest of the cancer research community, Cancer Discovery mourns the untimely death of José Baselga, founding co–Editor-in-Chief of the journal and a luminary in clinical and translational oncology. The Editors-in-Chief have chosen to honor him on this month’s journal cover (portrait by Nicolle Fuller of SayoStudio). Read the obituary by Scientific Editors Josep Tabernero, David M. Hyman, and Jean-Charles Soria on page 1614.