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Rational Treatment of Metastatic Colorectal Cancer: A Reverse Tale of Men, Mice, and Culture Dishes ................. 1644
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A Chimeric GM-CSF/IL18 Receptor to Sustain CAR T-cell Function ................. 1661
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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.

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Mobocertinib: A Potential Treatment for NSCLC with EGFR Exon 20 Insertions ................. 1617
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Triple Therapy to Outwit the BRAF Oncogene ................. 1620
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Optineurin Guards IFNγ Signaling in Cancer Cells ................. 1623
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José “Pepe” Baselga, MD, PhD: In Memoriam (1959–2021) ................. 1614
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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 burned-out 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 RAF for use in conjunction with a BRAFV600E 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: PTHLH (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 BRAFV600E generated tumors that recapitulated the biology of human BRAFV600E-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.

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