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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 burnt-out T cells) was identified; these T cells exhibited features overlapping with those of exhausted T cells but were differentiated by their proliferative and apototic 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 Egrf-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.
Précis: In colorectal cancer, loss of optineurin led to increased lysosomal degradation of IFN\(\gamma\)
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


Précis: Deficiency of B2M, encoding the MHC-I component \(\beta_2\) 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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