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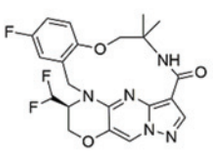
MOLECULAR CANCER THERAPEUTICS

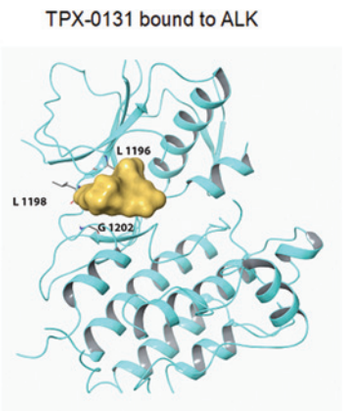
HIGHLIGHTS

Selected Articles from This Issue

TPX-0131, a Next-generation ALK Inhibitor



TPX-0131



Murray *et al.* | Page 1499

In this First Disclosure, Murray and colleagues describe TPX-0131, a compact macrocyclic ALK inhibitor designed to fit completely in the ATP-binding pocket and inhibit both wild-type ALK and drug-resistance mutations. Using a combination of biochemical, cellular, and *in vivo* preclinical assessments, TPX-0131 was shown to a CNS-penetrant molecule that potently inhibits wild-type ALK and a broad array of clinically relevant ALK mutants that limit the utility of previous generations of ALK inhibitors such as solvent front, gatekeeper, hinge region, and compound mutations. TPX-0131 currently is being evaluated in a phase 1/2 clinical study of TKI-pretreated patients with ALK+ NSCLC (NCT04849273).

SENTI-101 Induces Localized and Durable Anti-tumor Immunity

Gonzalez-Junca *et al.* | Page 1508

This First Disclosure describes the lead selection and preclinical research supporting the development of SENTI-101, a novel allogeneic cell therapy preclinical product candidate for the treatment of peritoneal carcinomatosis, including advanced ovarian cancer. SENTI-101 uses mesenchymal stromal cells innate capacity to traffic and localize to solid tumors to deliver two potent immune stimulatory cytokines (IL-12 and IL-21) to the tumor microenvironment. Studies conducted by Senti Bio demonstrate that, with this approach, scientists safely turned "cold" tumors "hot" resulting in long term anti-tumor immunity and rendered them susceptible to checkpoint inhibition. SENTI-101 demonstrates anti-tumor activity and proposes a cell modality that may address an unmet need for patients with ovarian cancer.

DNAPK Inhibition Radiosensitizes Tumor Cells in Vitro

Jiang *et al.* | Page 1663

Tumor hypoxia is a barrier to radiotherapy. It has been reported that DNAPK inhibition preferentially sensitizes tumor cells to radiation under hypoxia *in vitro*. However, whether DNAPK inhibition sensitizes hypoxic tumor cells to radiation *in vivo* has not been reported. In this study, Jiang *et al* show that transient DNAPK inhibition by a novel selective DNAPK inhibitor, NU5455 favorably compromises the repair of radiation-induced DNA DSBs in chronically hypoxic tumor cells *in vivo*, suggesting that DNAPK inhibition may preferentially sensitizes chronically hypoxic tumor cells to radiotherapy, which could form the basis for clinical trials investigating the impact of DNAPK inhibitors in radioresistant hypoxic tumors.

mRNA Encoding Anti-TIM-3 CAR T Cells to Treat AML

Lee *et al.* | Page 1702

Therapy-resistant leukemic stem cells can lead to the relapse of acute myeloid leukemia. In this study, Lee and colleagues target these residual cancer cells using mucin domain 3 (TIM-3) targeted chimeric antigen receptor (CAR) T cells. TIM-3 was selected due to its high expression on AML blasts and leukemic stem cells and its low expression on normal hematopoietic cells. Phage display was used to determine a TIM-3 antibody suitable for expression on the CAR T cells, which were subsequently tested on murine models and primary AML blasts. Although the consequences of TIM-3 targeting require further investigation, the authors demonstrate favorable anti-tumor activity by TIM-3 CAR T cells.

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Molecular Cancer Therapeutics

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