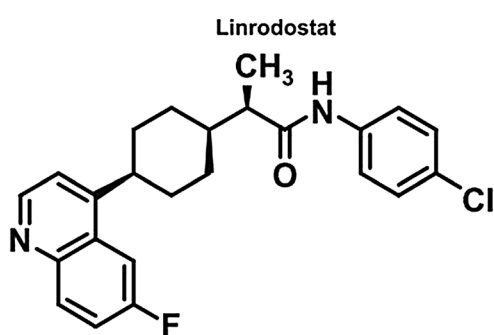


## MOLECULAR CANCER THERAPEUTICS

## HIGHLIGHTS

Selected Articles from This Issue

## Characterization of the IDO1 Inhibitor Linrodostat Mesylate

Balog *et al.* | Page 467

Indoleamine 2,3-dioxygenase 1 (IDO1) is a valuable target in therapeutics since it is highly expressed in many tumors and plays an active role in tumor immune evasion. Balog and colleagues outline linrodostat mesylate and its potent, selective inhibition of IDO1. Linrodostat suppressed kynurenine production without any activity against similar enzymes such as tryptophan 2,3-dioxygenase (TDO2) or indoleamine 2,3-dioxygenase 2 (IDO2). Linrodostat showed single-digit nanomolar potency *in vitro* and *in vivo*. Taken together, the authors offer strong support for the ongoing clinical development of linrodostat in immunotherapy.

## Anti-neoplastic Effects of a Novel CDK2/9 Inhibitor

Kawakami *et al.* | Page 477

Previous research revealed that antagonizing cyclin-dependent kinase 1 or 2 (CDK1 or CDK2) leads to missegregation and apoptosis in daughter cells in a mechanism termed anaphase catastrophe. To generate anaphase catastrophe using a clinical candidate, Kawakami and colleagues utilized the CDK2/9 inhibitor CYC065. They confirmed anaphase catastrophe in lung cancer murine syngeneic and PDX models. The anti-neoplastic effects were robust to KRAS expression. CYC065 is therefore a promising option for aneuploid cancers driven by KRAS expression. Clinical investigations are currently underway.

## Exosomes Expressing IL-12 Promote Antitumor Immunity

Lewis *et al.* | Page 523

The promise of Interleukin-12 as a cancer immunotherapy has yet to be fulfilled due to unwanted systemic exposure and related toxicities. Here, Lewis and colleagues generated exoIL-12™, a novel, engineered-exosome therapeutic candidate that displays functional IL-12 on exosome surface. In pre-clinical models, exoIL-12 was significantly more potent than rIL-12 and enabled systemic anti-tumor immunity by facilitating prolonged local pharmacology at the injection site with precisely quantified doses and undetectable systemic exposure. The improved therapeutic index achieved in pre-clinical models by localized exosome delivery support further clinical investigation, which may allow this potent cytokine to fulfill its clinical potential.

## Targeting Radiation-Resistant PCSCs by B7-H3 CAR T Cells

Zhang *et al.* | Page 577

Radiation therapy is a mainstay in prostate cancer, though it is counteracted by its induction of pancreatic cancer stem cells (PCSCs). Zhang and colleagues demonstrate that the immune checkpoint molecule B7-H3 is expressed at higher levels on PCSCs than on bulk prostate cancer (PCa) cells. Chimeric antigen receptor (CAR) T cells expressing B7-H3 were more potent against these PCSCs. As they showed fractionated radiation increased the expression of B7-H3 on both PCa bulk cells and PCSCs, it also increased their sensitivity to the B7-H3 CAR T cell. Moreover, radiation-induced B7-H3 fit into the optimal time-window for B7-H3 CAR T cell delivery. Their data demonstrates a novel, translational approach to overcome PCSC-driven treatment failure.