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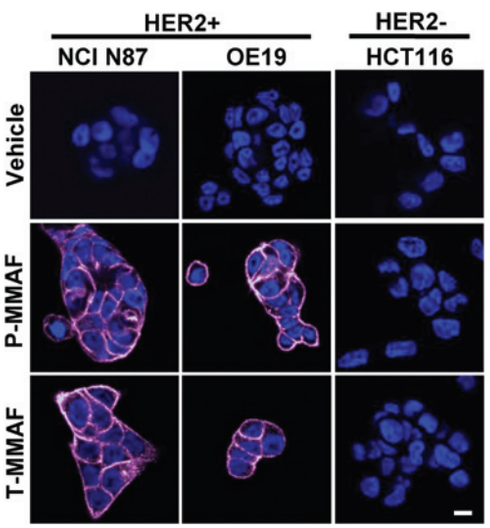
MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

Precision Chemo-radiotherapy Using MMAF Antibody Conjugates



Hingorani *et al.* | Page 157

Although cytotoxic chemotherapies improve the control of locally advanced, non-metastatic tumors with radiotherapy, their lack of targeting can increase the damage done to nearby normal tissue and induce systemic toxicities. To achieve a more targeted radiosensitization, Hingorani and colleagues combined anti-HER2 antibody-drug conjugates bearing monomethyl auristatin E (MMAE) or auristatin F (MMAF) with radiotherapy to treat various HER2-expressing tumors. Despite the decreased permeability of MMAF-conjugated antibodies, their administration alongside radiotherapy significantly enhanced tumor control and improved mouse survival. Anti-HER2 MMAF conjugates also demonstrated decreased bystander accumulation and off-target effects compared to MMAE. Taken together, the results demonstrate cell impermeable radiosensitizing warheads represent a potent application of antibody-drug conjugates.

Multi-functional Targeting Improves Systemic Cancer Control

Zhang *et al.* | Page 39

Organ destruction by metastatic cancer is a dominant clinical problem. Therapy directed at different functions that drive this process constitutes a rational approach to advance disease control. Zhang and colleagues demonstrate that combining inhibitors of cell motility with inhibitors of cell growth or with modulators of the bone microenvironment is highly efficacious across several clinically relevant models. Multifunctional therapy as a therapeutic strategy should be examined in humans. In the specific case of prostate cancer, combined inhibition of cell motility and modification of the bone microenvironment is highly efficacious.

Biomarkers of Response to Taselisib in Breast Cancer Models

Moore *et al.* | Page 292

Mutations in the alpha subunit of PI3K (PIK3CA) are common in breast cancer and result in constitutive activation of the PI3K signaling pathway. Taselisib (GDC-0032) potently inhibits PI3K while reducing the on-target PI3K toxicities of its predecessors (e.g. pictilisib, buparlisib). To guide Taselisib's clinical development, Moore and colleagues use an unbiased approach to determine biomarkers of taselisib response in preclinical breast cancer models. They associate the role of PIK3CA mutations with PTEN, HER2, and estrogen receptor (ESR1) status in determining sensitivity to Taselisib. Their results suggest that Taselisib use should occur in PIK3CA mutant settings and that combined therapy should be guided by the subtype.

Biomarkers for CDK4/6 Inhibitors

Schoninger and Blain | Page 3

CDK4 and CDK6 regulate the G1/S phase transition and serves as a downstream effector of many oncogenic signaling pathways. Therefore, a great deal of effort has been placed in inhibiting these critical regulators, and the FDA approval of Palbociclib, Abemaciclib and Ribociclib demonstrates this success. However, treatment with CDK4/6 inhibitors is challenged by primary or secondary resistance, highlighting a need for biomarkers that will identify the patients who would derive the most benefit. This review by Schoninger and Blain provides a roadmap for the development of potential CDK4i biomarkers, informed by the biological basis of CDK4/6 signaling and recent clinical support.

Molecular Cancer Therapeutics

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