Molecular Cancer Therapeutics

Highlights

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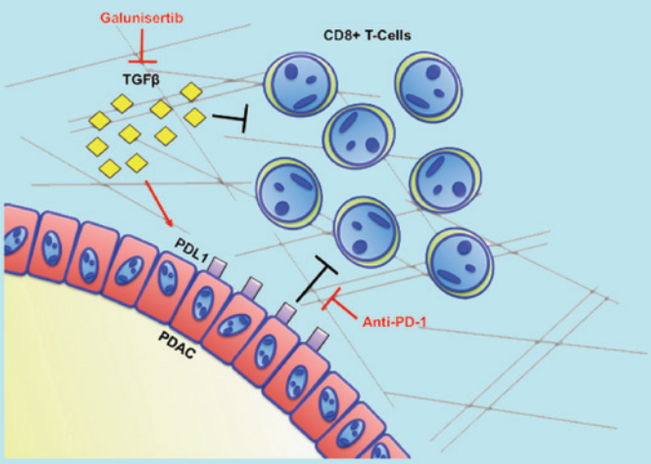
Selected Articles from This Issue



TGFβ blockade augments PD-1 inhibition in pancreatic cancer

Principe *et al.* Page 613

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, and most patients have poor responses to conventional therapy. TGFβ signaling is required for evasion of the cytotoxic immune program in PDAC. However, pharmacologic inhibition of TGFβ signaling failed to promote an anti-tumor immune response in clinical trials. In murine PDAC, TGFβ signal inhibition similarly failed to alter disease course, and enhanced expression of the immune checkpoint molecule PD-L1. Concomitant TGFβ and PD-L1 pathway inhibition led to a significant reduction in the neoplastic phenotype, improving survival and reducing disease-associated morbidity *in vivo*. Hence, combined TGFβ/PD-L1 inhibition warrants therapeutic consideration in PDAC patients.

Targeting MELK with its inhibitor OTS167 in neuroblastoma

Chlenski *et al.* Page 507

High-risk neuroblastoma patients currently witness survival rates less than 50% as well as the potential for treatment-related late effects. There is therefore a need to identify exploitable targets in neuroblastoma that increase treatment efficacy and decrease toxicity. In this manuscript, Chlenski and colleagues investigated the Maternal Embryonic Leucine Zipper Kinase (MELK) as one such target. Inhibiting MELK with OTS167 significantly decreased the growth of neuroblastoma tumors *in vivo*. Furthermore, OTS167 prolonged the survival of mice whose tumors had previously achieved minimal residual disease via treatment with cyclophosphamide. OTS167 also synergized with the DNA damaging agent CPT and with radiation therapy. These results outline the potential efficacy of combining OTS167 with current therapies in neuroblastoma.

miR-708 mimetic in TNBC therapy

Ramchandani *et al.* Page 579

Triple-negative breast cancer (TNBC) remains a difficult subtype due to the high rates of recurrence and metastatic spread. To combat this, Ramchandani, Lee, and colleagues have designed the first gold nanoparticle-delivered miRNA mimetic for TNBC. The nanoparticle utilizes a novel layer-by-layer construction that incorporates miR-708 and successfully delivers it to the primary tumor. By using a fluorescent reporter of the SOX2 and OCT4 response elements, they demonstrated miR-708 gold nanoparticles reduced the migration properties of invasive TNBC cell populations. Furthermore, administration of miR-708 nanoparticles *in vivo* reduced formation of metastatic nodules. Nanoparticles containing miR-708 therefore represent a potential anti-metastatic therapy for TNBC.

MEK and BCL-2/XL combination therapy and biomarkers in HGSOC

Iavarone *et al.* Page 642

Most patients with high-grade serous ovarian cancer (HGSOC) develop resistance to chemotherapy. In this work, Iavarone and colleagues demonstrated administration of the MEK inhibitor cobimetinib (GDC-0973) primed cells from patient-derived xenografts models for BCL-2-regulated apoptosis through the upregulation of BIM. Combining GDC-0973 with the BCL-2/X_L inhibitor ABT-263 therefore led to significant reductions in cell number and was well-tolerated *in vivo*. Intuitively, combined therapy was efficacious in models for which BIM was either initially highly expressed or was induced with GDC-0973 treatment and was not efficacious in models where BIM was not induced. These data indicate a mechanistic rationale for the combined use of MEK and BCL-2/X_L inhibitors in high-grade serous ovarian cancer.

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