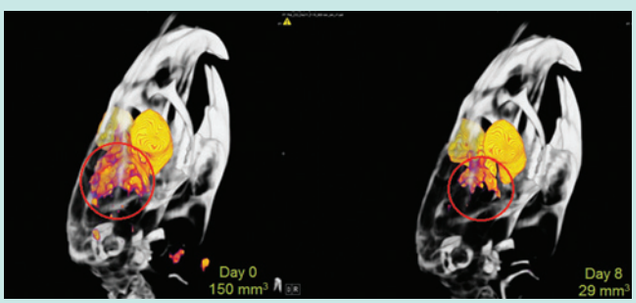
Molecular Cancer Therapeutics

Highlights

April 2015 • Volume 14 • Number 4

Selected Articles from This Issue



Potential New Therapeutic Strategy for Malignant Gliomas

Dave *et al.* Page 857

There is an immediate need to identify novel therapeutic options for the treatment of malignant gliomas. In this study, Dave and colleagues report that letrozole, an aromatase inhibitor widely used in the treatment of ER-positive breast tumors, caused cytotoxicity and considerably lowered the aromatase activity against several human and rat glioma cell lines that expressed aromatase. Furthermore, in a preclinical orthotopic glioma model, letrozole markedly reduced the active tumor volume as well as aromatase expression. These findings demonstrate a potential new target and a novel therapy for malignant gliomas.

PD-L1 IHC as a Predictive Biomarker in Cancer Immunotherapy

Patel and Kurzrok Page 847

Overexpression of PD-L1 in tumors, as determined by immunohistochemistry (IHC), is associated with significantly higher response rates (~36–100%) to PD-1/PD-L1–directed immunotherapy relative to PD-L1–negative tumors (~0–17%). Despite these results, robust responses in patients harboring PD-L1–negative tumors occur, albeit in a minority of patients, and reflect the complexity of the immune microenvironment. Here, Patel and Kurzrock review PD-L1 IHC as a predictive biomarker for anti–PD-1/PD-L1 therapy across tumor types. An improved understanding of the immune ecosystem may help further refine the application of PD-L1 in predicting response and therapeutic resistance.

Increased Sensitivity to WEE1 Inhibitor in Specific Cancer Types

Aarts *et al.* Page 865

Deregulation of cell-cycle checkpoints is a feature of many different cancer types. WEE1 kinase controls progression through S-phase and entry into mitosis by regulating the activity of CDK1 and CDK2. WEE1 inhibitors are currently being developed as anticancer drugs. However, insight into the specific vulnerabilities that increase sensitivity to WEE1 inhibitors is limited. Aarts and colleagues used siRNA screening to discover that cancer cells with defects in Fanconi anemia and homologous recombination pathways are more sensitive to WEE1 inhibition, causing increased replication stress and premature mitotic entry. These findings highlight the therapeutic potential of WEE1 inhibitors in these specific cancer subtypes.

Orphan Molecules AGR2 and C4.4A Are Cancer Confederates

Arumugam *et al.* Page 941

Anterior gradient 2 (AGR2) promotes cancer growth, metastasis, and resistance to therapy, but the mechanisms have been unknown. In this article, the orphan receptor C4.4A, another molecule known to increase cancer aggression by unknown mechanisms, was identified as the receptor for AGR2. AGR2 was shown to directly interact with C4.4A and knockdown of C4.4A blocked AGR2-stimulated cancer cell functions. Blocking monoclonal antibodies developed against AGR2 and C4.4A resulted in the regression of aggressive pancreatic xenograft tumors and dramatically increased survival of mice. These studies have thus identified the mechanisms of two cancer facilitators and demonstrated the therapeutic potential of interfering with their interactions.

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Mol Cancer Ther 2015;14:845.