Molecular Cancer Therapeutics

Highlights

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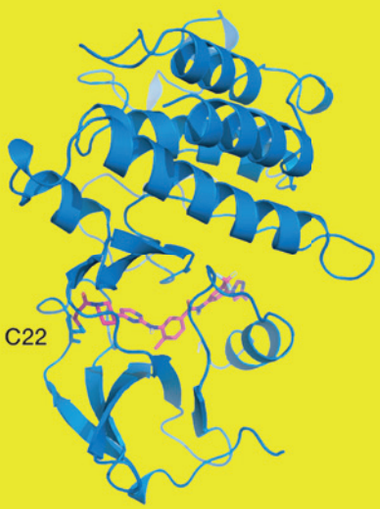
Selected Articles from This Issue



Radiosensitization of Medulloblastoma by an Inhibitor of MRK/ZAK

Markowitz and Powell *et al.*_____Page 1799

Current treatment of medulloblastoma often relies on the use of radiation, causing severe side effects that can greatly compromise the quality of life for these children. Markowitz, Powell, and colleagues identified the protein kinase MRK/ZAK as a radiosensitization target for medulloblastoma. The authors also designed an irreversible inhibitor of MRK/ZAK, M443 that effectively radiosensitizes patient-derived medulloblastoma cells both *in vitro* and *in vivo*. Further development of M443 may allow for lowering radiation doses delivered to patients, while preserving therapeutic efficacy.

ADCs with Potent DNA Alkylating Agents

Miller *et al.*_____Page 1870

In this study, Miller and colleagues developed a new class of DNA alkylating cytotoxic agents for use as payloads in antibody–drug conjugates (ADC), designed to extend the types of cancer potentially treatable with ADC therapeutics. Through innovative chemical design, a novel DNA-interacting compound was transformed from acting as a DNA cross-linker to an alkylator. Through this fundamental modification, and via linker optimization, DNA alkylating ADCs characterized by a high therapeutic index were created. These findings represent a major advancement in ADC technology, designed to ultimately offer cancer patients a more tolerable and highly active therapeutic option.

Macrophage-Mediated Trogocytosis Can Kill Cancer Cells

Velmurugan *et al.*_____Page 1879

Trogocytosis involves the ingestion of fragments of antibody-opsonized cells by effector cells such as macrophages through a "gnawing"-like process. The effects of this process on the survival of tumor cells are not well defined. Velmurugan and colleagues use a combination of advanced microscopy and cellular assays to demonstrate that persistent trogocytosis by macrophages can result in death of HER2-positive breast cancer cells in the presence of the HER2-specific antibody trastuzumab. This study extends the antitumor activities of macrophages to trogocytosis and has relevance to the use of therapeutic antibodies in cancer.

Potent Anticancer Effect of Afatinib for *HER4*-Mutated Cancers

Nakamura *et al.*_____Page 1988

A novel *HER4* mutation was identified in a head and neck squamous cell carcinoma cell line. This mutation is an activating oncogenic mutation with a transformation ability and tumorigenicity, and the growth of this cell line is dependent on this mutation. Afatinib exhibited dramatic anticancer effect against this cell line by inhibiting the HER4 signal, both *in vitro* and *in vivo*. These results provide a novel insight regarding afatinib as a HER4 inhibitor for *HER4*-mutated cancers, and a *HER4* mutation as a potential predictive biomarker for afatinib.

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