Molecular Cancer Therapeutics

Highlights

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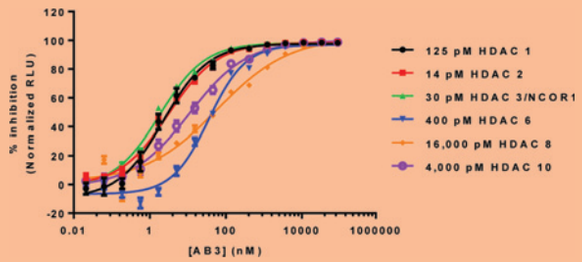
Selected Articles from This Issue



Tumor Suppressor Role of Notch3 in Medullary Thyroid Carcinoma (MTC)

Jaskula-Sztul *et al.* Page 499

The transmembrane receptor Notch3 may act as a tumor suppressor or as an oncogene in human cancers, depending upon the cellular context. To elucidate its role in medullary thyroid cancer (MTC), Jaskula-Sztul and colleagues created a gain-of-function model in a MTC cell line containing a doxycycline-inducible Notch3 intracellular domain and validated the function of Notch3 overexpression by exposure to a novel class I HDAC inhibitor, AB3. The forced expression of Notch3 in MTC altered malignant phenotype by triggering apoptosis and reducing neuroendocrine tumor markers. These studies document the tumor suppressor role of Notch3 in MTC and propose it as a potential therapeutic target.

High-Throughput Drug Screening for Novel Radiosensitizers

Goglia *et al.* Page 326

Double-strand break (DSB) repair pathways are emerging as a clinically relevant target for cancer therapy. However, previous drug screening campaigns have focused on single target proteins with *in vitro* assays. In this issue, Goglia and colleagues describe a cell-based, high-throughput small molecule screen for novel DSB repair inhibitors. They utilized a unique assay permitting the simultaneous analysis of two key DSB repair pathways, non-homologous end joining (NHEJ) and homologous recombination (HR). The authors report numerous novel DSB repair inhibitors, many of which were FDA-approved compounds. One of their hits was subsequently translated into a Phase I trial as a glioma radiosensitizer.

VEGF-Grab: Engineering of VEGFR1 for More Potent Antiangiogenic Cancer Therapy

Lee and Kim *et al.* Page 470

Vascular endothelial growth factor (VEGF) is critical for physiologic and pathological angiogenesis, particularly in cancer. To date, several antiangiogenic therapies neutralizing VEGF have been successfully developed for clinical use. Here, Lee and colleagues created a novel glycosylated VEGF decoy receptor, called VEGF-Grab. VEGF-Grab contains VEGFR1 D2-D3 domain, the positively charged patches of which are engineered to reduce the isoelectric point. VEGF-Grab exhibited more potent decoy activity against VEGF-A and placental growth factor (PlGF), and had prolonged pharmacokinetic profiles. These advancements lead to stronger and more durable antiangiogenic and antitumor efficacy, suggesting that VEGF-Grab is a promising therapeutic candidate for antiangiogenic cancer therapy.

Hyaluronan (HA) Accumulation in the Tumor Microenvironment

Singha *et al.* Page 523

A complex network of hyaluronan (HA) and proteoglycans in a tumor microenvironment with high levels of HA (HA^{high}) forms a physical barrier capable of inhibiting access of therapeutic monoclonal antibodies (mAbs) and immune cells to tumor cells, resulting in a more aggressive tumor phenotype in several solid tumor types. HA depletion by PEGPH20 removes this barrier, which allows increased access of mAb and immune cells to the tumor cell, resulting in efficient ADCC-dependent tumor cell killing. Microscopic live cell imaging shows that a physical barrier in HA^{high} tumor cells restricts live human NK cells from accessing the tumor cells.