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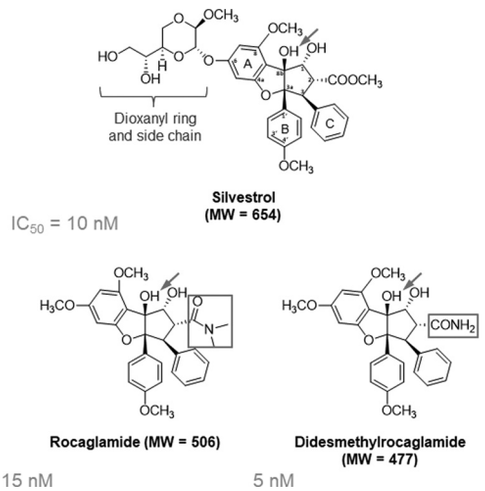
MOLECULAR CANCER THERAPEUTICS

HIGHLIGHTS

Selected Articles from This Issue

Rocaglamide and Didesmethylrocaglamide for Sarcoma Treatment



Chang *et al.* | Page 731

Malignant sarcomas, such as MPNST, Ewing sarcoma, and osteosarcoma, are highly refractory to current treatments. We identified two silvestrol-related eIF4A inhibitors, rocaglamide (Roc) and didesmethylrocaglamide, with comparable antiproliferative activity and the ability to inhibit expression of multiple oncogenic drivers and induce apoptosis and DNA damage response. Unlike silvestrol, these rocaglamides were insensitive to MDR1 efflux. Further, Roc had 50% oral bioavailability, exhibited potent anti-tumor effects in multiple sarcoma models, and did not induce pulmonary toxicity in dogs as found with silvestrol. These promising results indicate that these rocaglamides have potential to become viable treatments for MPNSTs and other malignant sarcomas.

Macrophage Syk-PI3K Axis in Tumor Immunity

Joshi *et al.* | Page 755

Syk kinase has been well-described for its role in adaptive immunity, but its role in macrophages is less clear. In this issue, Joshi and colleagues demonstrate the role of the Syk-PI3K axis in macrophage-generated immune suppression via genetic and pharmacologic inhibition. Specifically, they find that Syk and PI3K drives the polarization of immunosuppressive macrophages and results in an immunosuppressive tumor microenvironment. Applying this understanding of macrophage signaling, they designed a novel inhibitor of both Syk and PI3K (named SRX3207) that stimulated the release of pro-inflammatory cytokines (IL-1, IL-6, IFN-γ) and subsequently increased anti-tumor immunity.

Sialoglycan Monoclonal Antibody for Cancer Immunotherapy

Tivadar *et al.* | Page 790

Tumor cells exhibit modified glycosylation profiles compared to their normal couterparts. This modified glycoslation can generate immune evasion, increase proliferation, and support metastasis. Taking a cue from the original carbohydrate antigen (CA) 19.9, Tivadar and colleagues design a monoclonal antibody that targets sialyl-di-Lewisa-containing glycoproteins (FG129). FG129 and its human variant CH129 bound with nanomolar affinity to cancerous tissue while avoiding healthy tissue. Moreover, the antibody-bound glycoproteins were internalized, presenting an opportunity for antibody-drug conjugates. Monomethyl auristatin E (MMAE)- or maytansinoid (DM1 and DM4)-conjugated CH129 significantly reduced xenografted tumors. Therefore, antibodies targeted at sialyl-di-Lewisa glycoproteins are promising candidates for cancer therapy.

Combining FGFR and mTOR Inhibition in Cholangiocarcinoma

Krook *et al.* | Page 847

Fibroblast growth factor receptor (FGFR) kinase inhibitors are currently being assessed in clinical trials for treated FGFR-altered cholangiocarcinoma. In this study, Krook and colleagues present a bedside-to-bench investigation of an FGFR-altered patient who developed resistance to the FGFR inhibitor infigratinib (BGJ398) during a clinical trial. They hypothesize resistance was due to two kinase domain single nucleotide variants (SNVs): p.E565A and p.L617M. As p.E565A upregulated the PI3K/AKT/mTOR pathway, the mTOR inhibitor INK128 re-sensitized the resistant cells to FGFR inhibition. Taken together, the authors demonstrate mTOR inhibition as a viable route for combating resistance to FGFR inhibitors.