Molecular Cancer Therapeutics

Highlights

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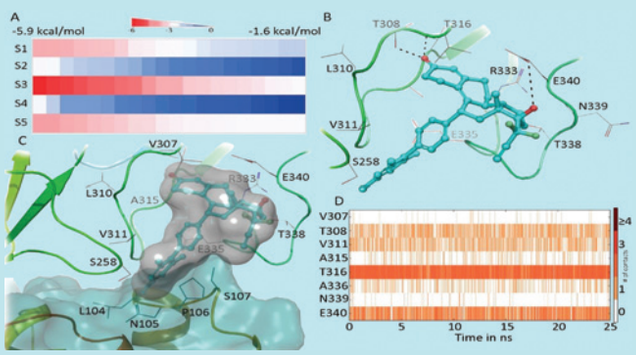
Selected Articles from This Issue



Novel small molecule inhibitor of LIFR

Viswanadhapalli *et al.*_____Page 1341

Leukemia inhibitory factor (LIF) is the most pleotropic member of the IL-6 family of cytokines, and its signaling through LIF receptor (LIFR) activates signaling pathways including JAK, STAT, MAPK, AKT, and mTOR. Therefore, inhibiting LIFR may provide a strong benefit to overall survival in multiple solid tumors. To accomplish this, Viswanadhapalli and colleagues optimized compounds using the crystal structure of LIF/LIFR, balancing the binding of LIFR against off-target binding to the glucocorticoid receptor. The resulting compound, EC359, inhibited LIFR downstream signaling and reduced the stemness of triple negative breast cancer (TNBC) cells. EC359 showed potent anti-tumor activity *in vivo* in mouse xenografts and *ex vivo* in patient-derived explants. Taken together, EC359 is a potent LIFR inhibitor prepared for translation into clinical TNBC patients.

Context specificity of KRAS signaling: clinical implications

Stewart *et al.*_____Page 1396

Dynamic signaling patterns caused by targeted therapy in *KRAS* mutant ($KRAS^M$) cell lines and patient samples derived from different tumor types i.e. colorectal cancer (CRC), non-small cell lung cancer (NSCLC) and pancreatic adenocarcinoma (PDAC) were studied herein by Stewart and colleagues. There were differences in signaling patterns depending on the tissue of origin of the $KRAS^M$ cells. For example, when exposed to a PI3K inhibitor $KRAS^M$ NSCLC cells showed significantly less upregulation of p-MEK compared to $KRAS^M$ CRC and PDAC cell lines. Tissue of origin of $KRAS^M$ cancers influences dynamic signaling patterns and should be taken into consideration while designing clinical trials.

Oncolytic Sendai virus suppresses micrometastasis in HNSCC

Tanaka *et al.*_____Page 1430

The control of lymph node metastasis (LNM) is one of the most important prognostic factors in head and neck squamous cell carcinoma (HNSCC) treatment. The objective of this study by Tanaka and colleagues was the sentinel lymph node (SLN)-targeted therapy using the oncolytic Sendai virus, "BioKnife". BioKnife migrated into SLNs after its injection into the primary tumor and effectively suppressed not only the primary tumor but also LNM by induction of apoptosis in HNSCC metastasis model. These results suggest that SLN-targeted therapy using BioKnife has great potential to provide a novel and promising alternative to conventional surgery with neck dissection in cN0 HNSCC patients.

Mutational landscape of canine cancer cell lines

Das *et al.*_____Page 1460

Comparative oncology in companion animals is expanding the scope of treatment opportunities and the ability to conduct clinical trials in an immune competent environment. To apply precision medicine in dog trials, a database of tumor mutations is essential. In this article, using whole exome sequence data from canine cancer cell lines, Das and colleagues have identified several oncogenic drivers, dysregulated signaling pathways, and drug sensitivity between dog cancer cell lines and human tumors. Significantly, this database of canine variants can inform preclinical studies of drug sensitivity in cell lines, which in turn can direct clinical trials in dogs.

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