confirm our hypothesis. We examined several additional mechanisms as possible causes of increased sensitivity to lovastatin, but found no correlation between expression of HMG CoA-reductase, Bcl-2, survivin or P-glycoprotein with the level of sensitivity. Similar sensitivity pattern of $CA3_{ST}$ and CK2 cells to lovastatin and statins with different lipophility and metabolic pathways suggests that altered intracellular accumulation of active drugs was not the cause of altered sensitivity.
**Conclusions:** Increased sensitivity of cDDP-resistant cells to lovastatin involves several geranylgeranylated proteins, among others Rac1 and Cdc42. Including lovastatin in the treatment of cancer patients could improve the success of chemotherapy for patients with cDDP-resistant tumors.

**1027** POSTER

**Sorafenib overcomes TRAIL resistance of hepatocellular carcinoma cells through the inhibition of signal transducers and activators of transcription 3**

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**Background:** Hepatocellular carcinoma (HCC) is one of the most common and lethal human malignancies. Recombinant tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a promising anti-tumor agent. However, many HCC cells show resistance to TRAIL-induced apoptosis. Sorafenib, a tyrosine kinase inhibitor, was recently approved by FDA for HCC. In this study, we showed that sorafenib sensitizes resistant HCC cells to TRAIL-induced apoptosis.
**Material and Methods:** HCC cell lines (PLC5, Huh-7, Sk-Hep1, and Hep3B) were treated with sorafenib and/or TRAIL and analyzed in terms of apoptosis, signal transduction.
**Results:** HCC cells, including PLC5, Huh-7, Hep3B and Sk-Hep1, showed significant resistance to TRAIL-induced apoptosis (up to 1000 ng/ml). The combination of sorafenib (starting at 5 μM) and TRAIL restored the sensitivity of HCC cells to TRAIL-induced apoptosis. Thorough comparisons of the molecular change before and after treatment with these agents, we found signal transducers and activators of transcription 3 (Stat3) played a significant role in mediating TRAIL sensitization of sorafenib. Our data showed that sorafenib down-regulated phospho-Stat3 (Tyr 705) and subsequently reduced the expression levels of two Stat3-related proteins, Mcl-1, and survivin, in a dose- and time-dependent manner in TRAIL-treated HCC cells. Knocking down Stat3 by RNA-interference reversed overcame apoptotic resistance to TRAIL in HCC cells, and ectopic expression of Stat3 in HCC cells abolished the TRAIL sensitizing effect of sorafenib, indicating Stat3 inactivation plays a key role in mediating the combination effect.
**Conclusions:** Sorafenib sensitizes resistant HCC cells to TRAIL-induced apoptosis at clinical achievable concentrations, and this effect is mediated via the inhibition of Stat3.
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**1028** POSTER

**Aloe emodin, a natural anthraquinone targeting multiple facets (migration, invasion, angiogenesis) of tumour metastasis**

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**Background:** The present study evaluated the apoptotic, antimetastatic and antiangiogenic property of a naturally occurring anthraquinone, aloe emodin (AE) in colon cancer cells. This compound is known to induce apoptosis in various other tumour cell types *in vitro*. Studies validating its role in influencing the regulatory molecules involved in metastasis and angiogenesis are rare. Colorectal tumors are one of the rapidly metastasizing tumours and a major cause for cancer deaths world wide.
**Methods:** Cell viability was assayed by MTT staining for the detection of the antiproliferative activity of drug. Ability of this drug to induce apoptosis was identified by annexin/propidium Iodide staining, loss of mitochondrial membrane potential and TUNEL assay. Inhibition of cancer cell migration was assessed by wound healing and transwell migration/transwell invasion assays. Cell growth inhibition and cell cycle distribution induced by AE was evaluated by FACS. Endothelial cell proliferation and migration assays as well as *in vitro* tube formation assays were used to evaluate the antiangiogenic activity of AE. Effect of AE on the expression of molecular players involved in apoptosis (caspases, PARP, MAPKs) migration (MMP2, MMP9, MAPKs) angiogenesis (VEGF) was assayed using substrate zymograpghy, PCR, western blot and fluorescent tagged peptide assay.
**Results:** Treatment with AE we observed positive annexin staining, loss of mitochondrial membrane potential and strong TUNEL positivity. The growth inhibitory capacity of AE was through induction of G2/M arrest. We have observed down regulation of phosphoERK1/2, activation of caspase and fragmentation of PARP on treatment with AE. Our results showed that a relatively non toxic level of AE suppressed the phorbol-12-myristyl-13-acetate (PMA) induced migration and expression/activity of MMP2/MMP9. We have also analyzed the involvement of signaling molecules (MAPKs) and specific transcription factors in AE mediated up regulation of MMP2/9. AE also inhibited Human Umbilical Vein Endothelial cells (HUVECs) proliferation migration/invasion and *in vitro* tube formation. We have also analyzed its effects on VEGF expression.
**Conclusion:** *In vitro* anticancer activity of AE on colon cancer cells depends on the ability to induce apoptosis, inhibit cell migration, *in vitro* tube formation and down regulation of key MMPs involved in metastasis. Thus AE can be projected as a prospective antitumor agent even though further research is warranted.

**1029** POSTER

**Improved distribution and efficacy of oncolytic virus in solid tumors by apoptosis-inducing pretreatments**

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**Background:** For successful eradication of the tumor by oncolytic gene therapy, initial widespread distribution of the virus within the tumor is crucial. However, viral distribution is limited by the large size of viral vectors, which limits their penetration through the interstitial matrix and the narrow spaces separating tumor cells. This study tested if the void space resulting from tumor cell apoptosis improves the distribution and efficacy of oncolytic HSV.
**Material and Methods:** We used two different approaches to induce apoptosis, which are 1) tet-regulated expression of apoptotic gene and 2) cytotoxic agents. For tet-regulated apoptosis system, MDA-MB-435S cells were transfected with tet-inducible CD8/Caspase-8 plasmids. For cytotoxic agents, paclitaxel or recombinant TRAIL was used. *In vivo*, MDA-MB-435S cells were implanted into the SCID mice and apoptosis was induced by doxycycline-regulated expression of CD8/Caspase-8 or cytotoxic agents. To study the effect of pretreatments on the viral distribution, oncolytic HSV expressing GFP was injected intratumorally following to different pretreatments. Finally the effect on tumor growth was assessed in MDA-MB-435S tumors.
**Results:** *In vitro,* both caspase-8 activaion and cytotoxic treatments induced significant apoptosis on tumor cells. Paclitaxel followed by TRAIL induced significantly more apoptosis than single treatment. In mice with MDA-MB-435S tumors, both the activation of caspase-8 and pretreatment with cytotoxic agents induced 9.0% and 4.0% apoptosis, respectively. In contrast to the limited viral distribution of 13% of the tumor section in control tumors, viral distribution was significantly improved by both caspase-8 activation (42.4%) and paclitaxel-TRAIL (30.3%). In tumor areas with a high density of apoptotic cells, the cellular shrinkage produced interstitial void spaces and channels that facilitated HSV distribution. We also show that the intratumoral injection of oncolytic HSV after caspase-8 activation or the paclitaxel plus TRAIL pre-treatment produces a significantly longer tumor growth delay than the administration of HSV before the induction of cell death, demonstrating the importance of sequence of the treatments.
**Conclusions:** Cancer cell death improves the intratumoral spread and therapeutic efficacy of oncolytic HSV. Thus the administration of cytotoxic agents before the injection of virus could significantly enhance the efficacy of oncolytic viral therapy.

**1030** POSTER

**Complementary treatment with (−)-epicatechin enhances the anti-cancer effect of etoposide in the spleen of Brown Norway rats with acute myeloid leukemia**

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**Background:** It has been proven that tea catechins possess antileukemic properties, which might be useful in complementary treatment. The aim of the study, was to examine whether the adjuvant therapy with (−)-epicatechin (EC) can affect the anti-cancer effect of etoposide (Eto) in Brown Norway rats with acute myeloid leukemia (BNML).