progression and monitored apoptosis *in vivo* using fluorescence molecular and micro-computed tomography (FMT, µCT).
Results: Single dose injection (0.2 mg/kg body weight) revealed a significant reduction of *Jnk2* on mRNA and protein levels in wildtype mice after 1 week. Moreover, 4 week *siJnk2* treatment had no influence in JNK1$^{\Delta hepa}$ livers. Next, we sought to investigate the effects in an acute model of Nemo$^{\Delta hepa}$ mice. Treatment with *siJnk2* caused hepatocyte hypertrophy, mitotic catastrophe, karyomegaly, exacerbated cell infiltration, hepatic fibrogenesis and ductular proliferation. These effects were evident by high alkaline phosphatase levels, cleaved caspase-3 positive cells alongside with increased compensatory proliferation. Furthermore, our data indicated that proinflammatory monocytes massively infiltrate the liver after hepatocyte-specific *Jnk2* inhibition. Interestingly, decreased compensatory proliferation, cleaved Caspase-3 protein levels and markers of hepatic stellate cell activation/matrix deposition were observed in a chronic model of Nemo$^{\Delta hepa}$ mice injected over 8 weeks.
Conclusions: *siJnk2* therapy successfully depleted the levels of *Jnk2* both *in vivo* and *in vitro*. *Jnk2* knockdown induced significant changes in liver parenchyma and a therapeutic option by reducing HCC progression. These results open ew opportunities for precision medicine of CLD treatment with potential translation into humans.

FRI-113
Histological subtypes of hepatocellular carcinoma are related to gene mutations and molecular tumor classification
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Background and Aims: Our increasing understanding of hepatocellular carcinoma (HCC) biology holds promise for personalized care, however its translation into clinical practice requires a precise knowledge of its relationship to tumor phenotype. We aimed at investigating molecular-phenotypic correlations in a large series of HCC.
Methods: Surgically resected HCC (n = 343) were investigated by pathological review, immunohistochemistry, gene expression profiling and sequencing.
Results: *CTNNB1* (40%) and *TP53* (21%) mutations were mutually exclusive and defined two major groups of HCC characterized by distinct phenotypes. *CTNNB1* mutated-tumors were large (P = 0.001), well-differentiated (P < 0.001), cholestastic (P < 0.001), with microtrabecular (P < 0.001) and pseudoglandular (P < 0.001) patterns and without inflammatory infiltrates (P < 0.001). *TP53* mutated-tumors were poorly-differentiated (P < 0.001) with compact pattern (P = 0.02), multinucleated (P = 0.01) and pleomorphic (P = 0.02) cells and frequent vascular invasion (P < 0.001). World Health Organization (WHO) histological subtypes were also strongly related to molecular features. The scirrhous subtype was associated with *TSC1/TSC2* mutations (P = 0.005), epithelial-to-mesenchymal transition and a progenitor expression profile. The steatohepatitic subtype showed frequent IL-6/JAK/STAT activation without *CTNNB1*, *TERT* and *TP53* pathway alterations (P = 0.01). Pathological review identified a novel subtype, designated as "macrotrabecular-massive" associated with HBV infection (P = 0.01), poor overall survival (P < 0.001), high alphafoeto-protein serum level (P = 0.01), angiogenesis activation (P = 0.007), *FGF19* amplifications (P = 0.02), *TP53* (P < 0.001) and *ATM* (P = 0.03) mutations. Finally, integration of HCC pathological characteristics with the transcriptomic classification showed phenotypically distinct tumor subclasses closely related to G1-G6 transcriptomic subgroups.
Conclusions: HCC phenotypes are tightly associated with gene mutations and transcriptomic classification. These findings may help in translating our knowledge of HCC biology into clinical practice.

FRI-114
Nanovesicle mediated delivery of combination of anticancer agents effectively induced cell death in Hepatocellular carcinoma cell lines
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Background and Aims: Hepatocellular carcinoma (HCC) is a primary malignant hepatic tumor and highly resistant to treatment owing to tumor heterogeneity. The current treatment modalities for HCC are not effective due to lack of efficient and organ specific drug delivery system. We studied the efficacy of milk-derived nanovesicles (MNV) to deliver the anticancer agent doxorubicin into HCC cells in culture as well as intrahepatic tumors induced in immunodeficient mice.
Methods: MNVs were isolated from skim milk using ultracentrifugation and characterized with nanoparticle tracking analysis (NTA) and electron microscopy. MNVs were loaded with doxorubicin (dox-MNV), purified by ultracentrifugation, and characterized using spectrophotometry and NTA. HepG2, Hep3B, and PLC/PRF/5 HCC cells in culture were treated with dox-MNV and evaluated the rate of cell death. Intrahepatic tumors induced in nude mice were injected with dox-MNV through tail vein and assessed tumor regression using in-vivo imaging system.
Results: Cellular uptake studies depicted plain and dox-MNV attained saturation within 4 h of treatment. Cell toxicity studies on HepG2, Hep3B, and PLC/PRF/5 HCC cells with MNV-dox at 1 µM depicted around 20% cell death at 24 h, 50% at 48 h, and 80% at 72 h. HepG2 cells treated with fluorescent-tagged dox-MNV exhibited nuclear disintegration and apoptosis within 24 h. Treatment of intrahepatic tumors with dox-MNV resulted in significant regression and increased survival rate in nude mice.
Conclusions: Our studies demonstrated that MNVs could be effectively used for successful delivery of anticancer agents into HCC cells and intrahepatic tumors. MNV mediated delivery of anticancer agents through intravenous system would be an effective method for the treatment of primary hepatic tumors.

FRI-115
Genetic and epigenetic bases of the relationship between reduced OCT1 expression and poor response to sorafenib in hepatocellular carcinoma and cholangiocarcinoma
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Background and Aims: The organic cation transporter-1 (OCT1, *SLC22A1* gene) plays a key role in sorafenib uptake and interaction with its molecular targets. Its expression has been found decreased both in hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA). Here we have aimed at characterizing the genetic and