tissues of 37 HCC patients (20 MVI+ and 17 MVI-). We also investigated DNA methylation profiles of plasma samples from these 37 HCC patients and 30 normal individuals as controls to minimize the interference of random background DNA methylation signals. Tissue and plasma samples were prepared into DNA methylation library and sequenced on Illumina HiSeq X10 platform. Using methylation haplotype load (MHL) and unmethylation haplotype load (UMHL) as metrics, we quantified DNA methylation profiles on methylation haplotype blocks (MHBs) by computing the degree of linkage between methylated or unmethylated CpGs in HCC and adjacent normal samples to identify discriminatory markers. Grouping samples from our cohort into training and validation sets respectively, we employed two supervised machine learning algorithms, random forest (RF) and support vector machine (SVM) to train and cross-validate binary predictive models.

Results Supervised analyses identified 65 MHBs as classifiers for HCC tissues and adjacent normal liver tissues. Both RF- and SVM-built models were highly accurate in classifying HCC and normal liver tissues with AUC no less than 0.98 (AUC: 98%, CI: 97.3%~98.8% for RF model; AUC: 99.9%, CI: 99.9 ~ 99.9% for SVM model). We applied the RF-trained classification model to differentiate HCC plasma DNA from those of healthy controls, with AUC of 96% (CI: 95.1% - 96.9%). We further identified 6 MHL-quantified MHBs and 5 UMHL-quantified MHBs as classifiers for MVI- and MVI+ samples. Combining the MHBs' methylation scores as classifiers and applying RF method, we trained and cross-validated MVI- and MVI+ classification models. We found the AUC of these models is 85.9% (CI: 83.5% - 88.3%).

Conclusions These data showed that DNA methylation signatures can provide outstanding diagnostic accuracy for HCC and MVI.

IDDF2019-ABS-0320 TERMINALIA ARJUNA BARK EXTRACT PROTECTS AGAINST EARLY ALCOHOL-INDUCED LIVER INJURY IN THE RAT

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Background Terminalia arjuna, an indigenous plant used in ayurvedic medicine in India, primarily as a cardioprotective is also used in treating diabetes, anemia, tumors and hypertension. Oxidants have been shown to be involved in the alcohol-induced liver injury. Arjunolic acid (AA) is an oleanane triterpenoid found mainly in the heartwood of Terminalia arjuna. This study was designed to determine whether Terminalia arjuna bark (TAB) extract, composed mostly of ellagitannins oligomers, protects against early alcohol-induced liver injury in rats.

Methods Total fifty-eight male Wistar rats were fed high-fat liquid diets with or without ethanol (10–14 g/kg per day) and TAB extract (300 mg/kg per day) continuously for 4 weeks using an enteral feeding protocol.

Results Mean body weight gains (approximately 4 g/day) were not significantly different between treatment groups. TAB extract did not affect average daily urine ethanol concentrations (approximately 200 mg/dL). After 4 weeks, serum

alanine amino transferase levels of the ethanol group were increased nearly fourfold (110 ± 16 IU/L) compared to control values (35 ± 3 IU/L); this effect of ethanol was blocked by TAB extract (60 ± 6 IU/L). Additionally, enteral ethanol caused severe fat accumulation, mild inflammation, and necrosis in the liver; TAB extract significantly blunted these changes. Increases in liver TNF α protein levels caused by ethanol were completely blocked by TAB extract. Further, ethanol significantly increased the accumulation of protein adducts of 4-hydroxynonenal, a product of lipid peroxidation serving as an index of oxidative stress; again this was counteracted by the addition of TAB extract.

Conclusions The result indicates that the TAB extracts exhibit the antioxidant activity through correction of oxidative stress and validates the traditional use of Terminalia arjuna to prevent early alcohol-induced liver injury.

IDDF2019-ABS-0325 SUPERIOR EFFICACY AND LONG-TERM SURVIVAL BENEFIT OF HDAC8 AND PD-L1 CO-BLOCKADE IN LIVER CANCER IMMUNOTHERAPY

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Background The heterogeneous responses to immune-checkpoint blockade (ICB) therapy e.g. anti-programmed death-ligand 1 (PD-L1) antibody are attributable to the complex interplay between a range of cancer-cell-autonomous cues and immunosuppressive tumor microenvironment. Two recent phase I/II trials of PD-1 checkpoint inhibitors in patients with advanced hepatocellular carcinoma (HCC) have produced promising results, yet the objective response rates were relatively low (<20%). Accumulating evidence underscore the fundamental importance of epigenetic regulation in tumor immune evasion. We have previously elucidated a critical role of histone deacetylase 8 (HDAC8) in hepatic carcinogenesis (*Cancer Research* 2015;75:4803–16). Here, we aim to investigate the therapeutic potential of a HDAC8-specific inhibitor PCI-34051 in preclinical HCC models.

Methods The effect of PCI-34051 on tumorigenicity was investigated in orthotopic HCC mouse models. Immune profiling in tumor microenvironment was determined by multi-color flow cytometry. The underlying mechanism was investigated by integrative epigenomics analysis. The anti-tumor efficacy of combined therapy with PCI-34051 and anti-PD-L1 antibody was further determined.

Results PCI-34051 significantly suppressed tumorigenicity in immunocompetent but not immunodeficient mice, which was accompanied by increased effector T cell tumor infiltration. Mechanistically, tumor-intrinsic HDAC8 epigenetically silenced chemokine CCL4 expression via H3K27 deacetylation at the enhancer to inhibit T cell infiltration to tumor. Furthermore, PCI-34051 dramatically improved the therapeutic efficacy of