25th December 2013

2013-2014 Kenneth W. Warren Fellowship Progress Report 1
Re: High Endothelial Venules and Hepatocellular Carcinoma

Dear IHPBA research committee,

I would like to thank the IHPBA Research Committee for awarding me the 2013-2014 Kenneth Warren Fellowship in support of my study on High Endothelial venules (HEV) and Hepatocellular carcinoma (HCC) under the mentorship of Dr. Ronald DeMatteo and Dr. William Jarnagin.

I am happy to report the progress of our study to date. Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and its mortality mirrors its incidence, emphasizing the high fatality rate of this aggressive disease.[1, 2] Most patients have advanced disease at diagnosis, and only a minority is eligible for curative surgery.[3] Moreover, HCC is notoriously resistant to chemotherapy and other systemic treatments. Immunotherapy has emerged recently as an attractive alternative to traditional therapies because of the immense potential and capacity of the immune system, not just for the primary tumor but also to prevent recurrence, but mechanisms governing infiltration of lymphocytes in HCC remain poorly characterized.[4-11] Tumor-infiltrating lymphocytes(TIL) and tumor-associated macrophages (TAM) are involved and modulate the key processes in tumor progression and metastasis.[12] Studies have demonstrated that regulatory T cells (Tregs) are associated with HCC invasiveness and poor outcome; cancers with extensive infiltration of cytotoxic T cells (CTL) generally have a better clinical outcome and the intratumoral balance of regulatory and cytotoxic T cells is a promising independent prognostic predictor in HCC.[13-17].

High endothelial venules (HEVs) are specialized post-capillary venules that normally exist in lymphoid tissues and play a role in lymphocyte trafficking.[18-21] Recently, HEVs have been discovered in several human cancers, including breast cancer, colon cancer, and melanoma. Whereas HEVs normally are involved in "lymphocyte trafficking" in lymph nodes, they may also play a role in "tumor cell trafficking" given their presence within tumors.[19-21] In some cancers, HEVs correlated with intratumoral lymphocyte infiltration, disease-free survival and overall survival. It has been demonstrated that T cell trafficking facilitated by HEVs is required for tumor control after the depletion of Tregs, but the role and importance of HEVs in HCC is unknown.[20, 22-24] We aim to evaluate the cancer-induced vascular changes in HCC by studying the morphological and functional alterations of HEVs and their correlation with pathological features such as the tumor's microenvironment immunoprofile like T cell infiltration and clinical outcome.

The study is based on 172 patients with HCC who underwent primary surgical treatment at Memorial Sloan-Kettering Cancer Center (MSKCC) from January 1992 to December 2010. After approval was obtained from our Institutional Review Board and Human Biospecimen Utilization Committee, a review

of the patients' pathological and clinical data was performed and completed from a prospective database. Histological confirmation of HCC was performed and reviewed by 2 independent pathologists to select the appropriate representative slides for paraffin block retrieval and tissue microarrays (TMA) construction. The immunohistochemical protocol was optimized and performed on a pilot group of patients for HEVs with a MECA-79 antibody, the current standard for identifying HEVs.

Our preliminary data revealed the presence of HEVs in HCC and its lymph node; this is previously not reported in literature. Based on our pilot sample, we found that that HEVs in the HCC stroma have marked lymphocyte aggregation around it. (Figure 1) In addition, interestingly, we discovered that the HEV marker (MECA-79) also stains benign bile ducts and proliferating bile ductules in the benign liver that surrounds HCC in all the cases of the pilot population. (Figure 2) MECA-79 also stains both the biliary ducts and HEV in the stroma in a cholangiocarcinoma case we used as a control. (Figure 3) In the next few months, after the IHC of all the selected blocks, high-power-field image analysis will be performed as we have done previously.[7, 19, 22] Various HEV parameters, its density and the immune cells characteristics will be analyzed with correlation to the patients' clinicopathological features.[19] We will also investigate the significance of HEV and MECA-79 in other liver malignancies such as intrahepatic cholangiocarcinoma and colorectal liver metastases in view of our preliminary findings.

Thank you for your support and I look forward to keep IHPBA updated on the findings of the study and present our results in the future.

Happy Holidays

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Figure 1

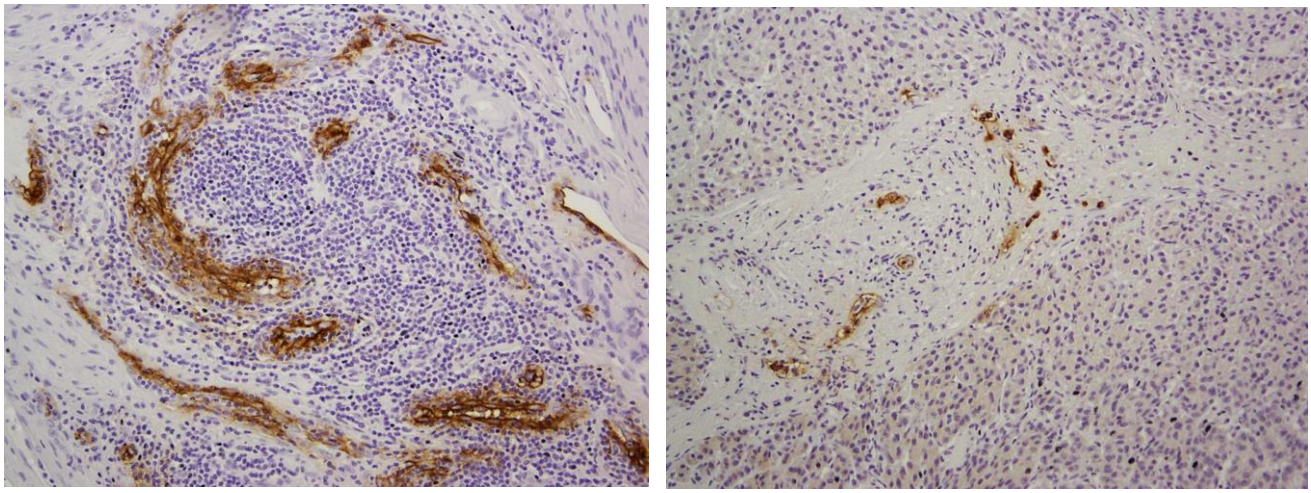


Figure 2

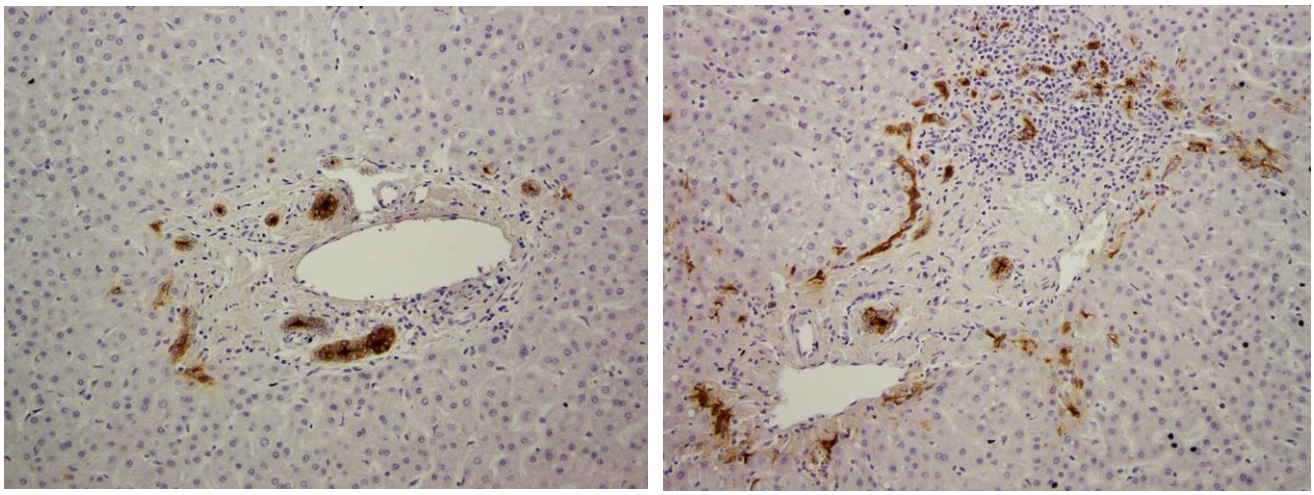
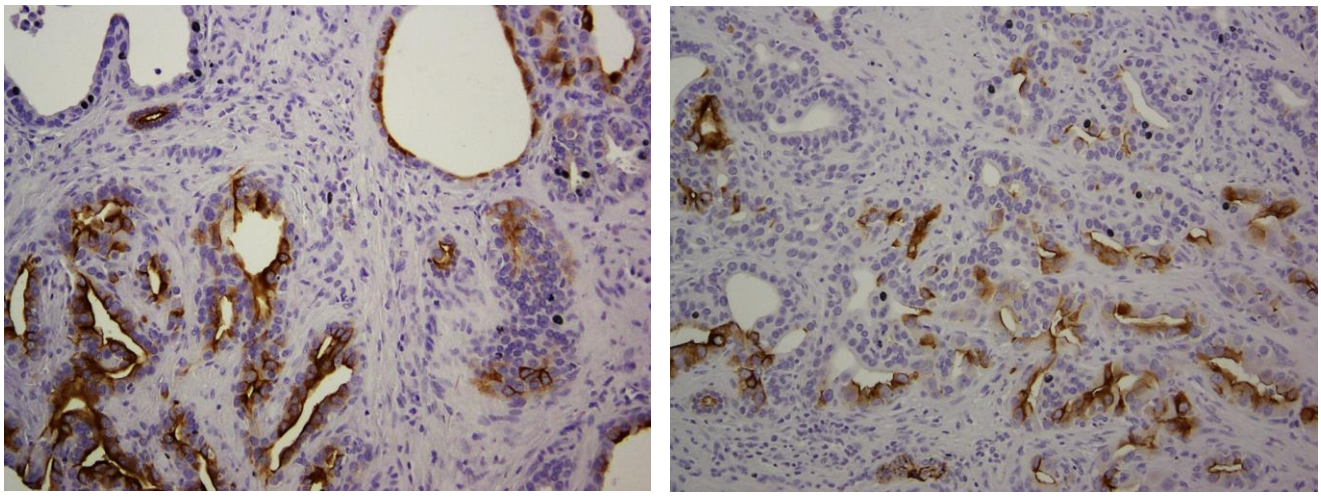


Figure 3



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