Protocol Name: Serum Level of S100A4 in Patients With Portopulmonary Hypertension

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A. Study Purpose and Rationale

Portopulmonary hypertension (PPHTN) refers to pulmonary arterial hypertension (PAH) in association with portal hypertension, and its prevalence has been estimated to be between 3-16% in patients with end-stage liver disease[1]. PPHTN is classified as a Group 1 PAH according to WHO which brought together a group of diseases with similar histopathologic features of pulmonary hypertension that includes idiopathic PAH, collagen-vascular disease, human-immunodeficiency virus, anorexigen, congenital-heart disease[1]. PAH as a group confers significant morbidity and mortality risks upon those afflicted, and few therapeutic options are emerging capable of changing its natural history. Numerous approaches have been undertaken to better define the pathophysiology of PAH with the goal of improving treatments, including defining the genetic susceptibility of PAH through candidate gene analysis. Dr. Steven Kawut in the Pulmonary and Critical Care Division at Columbia is involved in a multi-center collaboration to study the genetics, treatments, and outcomes of portopulmonary hypertension. A high-output genotype was carried out to define single-nucleotide polymorphisms (SNP) located within loci of candidate genes implicated in the pathophysiology of pulmonary hypertension. The genotype was performed with samples from patients with PPHTN (case) and portal hypertension without PAH (control) and SNP alleles were analyzed in a case-control study to identify SNPs with close association with PAH. One of the candidate genes with highly correlative SNPs was S100A4, encoding a cytsolic/nuclear protein involved in cellular motility and implicated in extracellular-matrix remodeling in tumor metastasis and tissue fibrosis[2]. S100A4 has also been identified as a secreted factor found in the serum of patients with inflammatory disorders[3]. Our study aims to examine the serum level of S100A4 in patients with PPHTN in comparison to portal hypertension alone to assess whether serum level of this gene product correlate with PAH, thus implicating S100A4 as a marker of disease with possible contribution to the pathophysiology.

B. Study Design and Statistical Analysis

The serum samples are collected from patients situated at multiple sites in the study and frozen according to protocol. Case and control subjects are defined according to the inclusion/exclusion criteria. The patient samples are anonymous and labeled with randomly generated 4-digit numbers and matched with their respective patient data. The laboratory personnel analyzing the serum of level of S100A4 will be blinded to the case-control status of the samples. Based on our best estimate of serum level of S100A4 according literature and pilot experiments, we included 20 cases and 60 controls with estimated effect size to be a difference of 70 ug/ml between the two groups with pre-determined level of significance of alpha < 0.05 and power = 80% according to the paired

t-test for sample size. Descriptive statistics will be utilized to calculate the mean, median, standard deviation and standard error of the serum values of the two groups for comparison.

C. Study Procedure

Quantitative measurement of the S100A4 level in serum samples will be performed by the The CircuLex™ S100A4 ELISA according to manufacturer protocol[4].

D. Study Drugs

None

E. Medical Device

None

F. Study Questionnaires

None

G. Study Subjects

Patients in this study are patients with portal hypertension undergoing liver transplant evaluation at the various sites in this study.

Inclusion Criteria: Patients with known intrinsic liver disease and documented portal hypertension by Doppler ultrasonagraphy. Pulmonary hypertension (case) is defined as a) mean pulmonary artery pressure of > 25 mm Hg, b) pulmonary vascular resistance > 120 dynes-sec-cm^{-5}, and c) pulmonary capillary wedge pressure ≤ 15 mm Hg on right heart catheterization.

Exclusion Criteria: Patients with co-existing medical conditions known to be associated with pulmonary hypertension (eg. HIV, collagen-vascular disease, chronic hypoxia, systolic dysfunction, valvular disease, congenital heart disease, chronic thromboembolic disease). Pt with renal failure. Pt who have received a lung or liver graft for transplant.

H. Recruitment of Subjects

Potential subjects will be identified by the respective investigators at the various sites who are evaluating patients for liver transplants. Potential subjects who are interested will be contacted by the study coordinator and screened for eligibility. Eligible patients will have their blood drawn at an outpatient appointment and their clinical data will be accessible to the investigators of the study.

I. Confidentiality of Study Data

Patients' samples are labeled with randomly generated 4 digit numbers that represents each patient in the study. The assigned numbers are then matched to the patient's clinical data without identifying information such as name, telephone number, SSN, phone numbers, or address. All clinical data are stored on pass-word encrypted computers accessible only to the investigators in the study.

J. Potential Conflict of Interest

None

K. Location of the Study

Serum samples are frozen in storage facilities assigned to the Pulmonary Critical Care Division at Columbia Presbyterian. All assays are performed within the premise of the Clinical Research Core Laboratory.

L. Potential Risks

Only procedures performed on the study subject will be routine phlebotomy to retrieve serum samples.

M. Potential Benefits

None

N. Alternative Therapty

None

References

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