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"Platelet Kinetics in Acute Thrombus Formation in Healthy and VTE Patients"

The objective of this career development application is to seek additional mentored training to achieve my long-term goal of becoming an independent investigator studying thrombotic disease. To achieve this goal, I have developed a rigorous scientific proposal based on preliminary data which will allow me to gain technical and scientific expertise.

Venous Thromboembolism (VTE) presents an ongoing diagnostic challenge for physicians in the primary care and emergency department setting. Only a small minority of those with suspected VTE will end up being diagnosed with either a deep venous thrombosis (DVT) or pulmonary embolus (PE). Current biomarkers for VTE, such as the D-dimer assay, lack specificity and cannot be reliably used for rapid detection of acute VTE. In this career development award, I present compelling data to show that a platelet protein, platelet factor 4 (PF4) is markedly elevated and improves the performance of the D-dimer for diagnosis of VTE. In an observational cohort of 29 patients with VTE and 32 control patients, we show significant differences in PF4 and D-dimer levels in patients presenting with venous thrombosis as compared to controls. Receiving operator characteristic (ROC) analysis of PF4 and D-dimer levels show that combined use of biomarkers yield a c-statistic of 0.97. Data also reveal that PF4 and D-dimer assays did not correlate in patients with or without disease. Based on these findings, I will test the following interrelated hypotheses in my proposal: 1) PF4 and D-dimer biomarkers represent evolutionary stages of VTE and 2) the combined use of PF4 and D-dimer assay will improve diagnostic accuracy for VTE. **Aim 1: Examine the mechanisms and temporal relationship of PF4 and D-dimer release:** Using non-photobleachable fluorescent nanodiamonds and immunoassays, I will examine temporal expression of clotting markers in ex vivo thrombus from human blood and perform studies in an IVC thrombosis murine model. **Aim 2: Validate combined biomarkers (PF4 and D-dimer) for evaluation of suspected VTE.** I will enroll patients suspected of VTE and obtain D-dimer and PF4 values at time of suspected VTE and correlate these findings with clinical evaluation and outcomes as well as perform longitudinal assays of PF4 and D-dimer biomarkers in hospitalized VTE patients to assess kinetics of PF4/D-dimer release after initial presentation. By performing these studies, I will become facile in multiple new in vitro and in vivo techniques essential for achieving scientific independence.

VTE affects 600,000 people per year in the United States yet the work up of this disease process is fraught with false negative and positives, high costs, and associated morbidity and mortality. By better understanding the physiologic processes involved in acute thrombus formation, I hope to improve diagnostic work up and improve patient outcomes in the ED and primary care settings.