



2011 Abstracts



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The Role of Antibodies in the Pathogenesis of Pulmonary Arterial Hypertension

While the pathogenesis of pulmonary arterial hypertension (PAH) is likely multifactorial, there is increasing evidence that inflammation and immune dysregulation play a role in pulmonary vascular injury and remodeling. Previous studies have shown that athymic rats, which lack T cells, injected with the vascular endothelial growth factor receptor-2 (VEGFR-2) blocker, SU5416, develop severe PAH in normoxia and are characterized by perivascular infiltration of B cells and deposition of antibodies on the endothelium as seen in clinical disease. Preliminary data suggest that the susceptibility of these rats to PAH may be due to the lack of regulatory T cells. Hence, it has been postulated that loss of immune regulation leads to proliferation of autoreactive B cells. Pilot studies have shown that B cell depletion with an anti-CD20 antibody in athymic rats attenuates PAH, right ventricular hypertrophy (RVH), and pulmonary vascular remodeling. This proposal will evaluate the role of antibodies in the pathogenesis of PAH. The primary hypothesis is that the pathogenic property of the autoreactive B cell is its ability to produce autoantibodies against lung endothelial antigens which leads to persistent vascular injury, pulmonary vascular remodeling, and PAH. Furthermore, demonstration of this hypothesis will provide evidence that PAH may be considered an autoimmune disease. This premise will be addressed in two ways. First, the euthymic rat, which does not develop PAH with SU5416 injection in normoxia, will be used. Serum or purified antibodies from athymic rats with severe PAH will be transferred to euthymic rats after SU5416 injection. If



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antibodies are pathogenic, it is anticipated that these animals will develop elevated right ventricular pressures, RVH, and perivascular inflammation. Next, the pathogenicity of autoantibodies will be tested by depletion of antibodies by plasma exchange in athymic rats after SU5416 injection. It is anticipated that removal of pathogenic autoantibodies will attenuate PAH and vascular remodeling in these rats.