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**Title:** Immune and inflammatory cell involvement in the pathology of idiopathic pulmonary arterial hypertension

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**Body:** Pulmonary arterial hypertension (PAH) is characterized by vasoconstriction and vascular remodeling. Recent studies have revealed that immune/inflammatory responses play a crucial role in pathogenesis of IPAH. To systematically evaluate the number and distribution of inflammatory cells in different sizes of pulmonary arteries from explanted lungs of patients with IPAH versus healthy lungs and to demonstrate functional relevance by blocking stromal-derived factor-1 by the Spiegelmer NOX-A12 in MCT-induced PH in rats. Immunohistochemistry was performed on lung tissue sections from patients with IPAH and healthy donors. All positively stained cells in whole-lung tissue sections, surrounding vessels, and in the different compartments of the vessels were counted. To study the effects of blocking SDF-1, rats with MCT-induced PH were treated with NOX-A12 from Day 21 to Day 35 after MCT-administration. We found a significant increase of the perivascular number of macrophages (CD68), macrophages/monocytes (CD14), mast cells (toluidine blue), dendritic cells (CD209), T cells (CD3), cytotoxic T cells (CD8), and helper T cells (CD4) in vessels of idiopathic PAH lungs compared with control subjects. FoxP3+ cells were significantly decreased. In the MCT model, the NOX-A12-induced reduction of mast cells, macrophages, and T cells was associated with improvement of hemodynamics and pulmonary vascular remodeling. Our findings reveal altered perivascular inflammatory cell infiltration in pulmonary vascular lesions of patients with idiopathic pulmonary arterial hypertension. Targeting attraction of inflammatory cells by blocking SDF-1 may be a

novel approach for treatment of PAH.