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AWARDS

- American Heart Association, Established Investigator Award
- VA Merit Grant
- American Heart Association, Scientist Development Grant

PUBLICATIONS

Bastani S, Sherman W, Schnickel GT, Shieh GR, Bhatia R, Fishbein, MC, **Ardehali A**. Chemokine Receptor Blockade With a Synthetic Nonpeptide Compound Attenuates Cardiac Allograft Vasculopathy. Transplantation. 2009; 88(8): 995-1001.

Schnickel GT, Bastani S, Hsieh GR, Shefizadeh A, Bhatia R, Fishbein MC, Belperio J, **Ardehali A.** Combined CXCR3/CCR5 blockade attenuates acute and chronic rejection. J Immunol. 2008;180(7):4714-21.

Hsieh GR, Schnickel GT, Garcia C, Shefizadeh A, Fishbein MC, **Ardehali A.** Inflammation/oxidation in chronic rejection: Apolipoprotein A-I mimetic peptide reduces chronic rejection of transplanted hearts. Transplantation. 2007;84(2):238-43

Keane MP, Gomperts BN, Weight S, Xue YY, Burdick MD, Nakamura H, Zisman DA, **Ardehali A,** Saggar R, Lynch JP 3rd, Hogaboam C, Kunkel SL, Lukacs NW, Ross DJ, Grusby MJ, Strieter RM, Belperio JA. IL-13 is pivotal in the fibro-obliterative process of bronchiolitis obliterans syndrome. J Immunol. 2007;78(1):511-9

Schnickel GT, Hsieh G, Garcia C, Shefizadeh A, Fishbein MC, **Ardehali A**. Cytoprotective gene HO-1 and chronic rejection in heart transplantation. Transplant Proc. 2006;38(10):3259-61

Schnickel GT, Hsieh G, Kachikwu EL, Garcia C, Shefizadeh A, Fishbein MC, **Ardehali A**. Role of CXCR3 and CCR5 in allograft rejection. Transplant Proc. 2006;38(10):3221-4

Schnickel GT, Whiting D, Hsieh G, Yun JJ, Fischbein MP, Fishbein MC, Yao W, Shafizadeh A, **Ardehali A**. CD8 Lymphocytes are sufficient for the development of chronic rejection. Transplantation. 2004; 78(11):1634-1639

Immunobiology of Chronic Rejection

Chronic rejection or Cardiac allograft vasculopathy (CAV) is the leading cause of late death among heart transplant recipients. T-lymphocytes are known to play a major role in the development of CAV. The mediators of T-lymphocyte recruitment to the graft, leading to CAV, remain incompletely defined. Several groups and our group have shown that chemokine-chemokine receptor interactions may be important in T-lymphocyte recruitment in experimental CAV.

The focus of our ongoing projects are 2 fold:

1. To further define the role of chemokine receptors CXCR3 and CCR5 in the development of CAV.
2. To determine the role of regulatory T-cells in attenuation of CAV.

We utilize a murine model of CAV. In this model, heterotopic heart transplantation is performed by surgical residents. The donor hearts reproducibly develop CAV within 24-40 days post-transplantation.

To address project 1, we have utilized transgenic recipient mice to functionally examine the role of CXCR3 and CCR5 chemokine receptors. Our preliminary studies demonstrate that combined CXCR3 and CCR5 blockade, in addition to controlling mononuclear cell recruitment, also attenuate T-lymphocyte function and effector cytokine production. This intriguing observation is currently under further study. Additionally, we are analyzing the expression of CXCR3 and CCR5 on graft infiltrating T-lymphocytes in serial endomyocardial biopsies, to determine their predictive value in CAV development in human heart transplantation.

To address project 2, we are using adoptive transfer studies to RAG $^{-/-}$ recipient mice to delineate the role of naturally occurring and inducible regulatory CD4 lymphocytes. We have determined that naturally occurring regulatory T-cells attenuate CAV development and induce FoxP3 gene upregulation without additional immunosuppresion. Furthermore, we are investigating the specific mechanism of action of naturally occurring and inducible regulatory CD4 lymphocytes both in vivo and in vitro.

The long-term objectives of this project are to provide a basis for future clinical studies of chemokine receptor blockade and regulatory T-cells in prevention /control of CAV.