Inhibiting CXCL12 Blocks Fibrocyte Migration and Differentiation and Attenuates Bronchiolitis Obliterans in a Murine Heterotopic Tracheal Transplant Model.

David A. Harris B.S., Yunge Zhao M.D. Ph.D., Damien J. LaPar M.D. MSc, Abbas Emaminia M.D., John F. Steidle B.A., Mark Stoler M.D., Joel Linden M.D., Irving L. Kron M.D., Christine L. Lau M.D.

University of Virginia, Charlottesville, VA

92th Annual Meeting of the American Association of of Thoracic Surgery
San Francisco, CA
May 1, 2012
Presenter Disclosures
David Harris
The following relationships exist related to this presentation:

No relationships to disclose
What is a Fibrocyte?

- BM derived mesenchymal stem cells integral in fibroproliferative disease
- Undifferentiated phenotype = CD45+Col1+CXCR4+
- Preferentially traffic via the CXCR4/CXCL12 axis
- Differentiate into smooth muscle actin producing cells = CD45+CXCR4+αSMA+
- Immune Modulation vs. Reparative cell

Fibrocytes in Human BOS Post Lung Transplantation

Purpose

• Fibrocyte number correlates with BOS stage
• CXCR4/CXCL12 axis is integral fibrocyte trafficking
• Can immune-therapy directed against CXCL12 attenuate airway fibrosis and obliteration in a murine heterotopic tracheal transplant model?
Experimental Design

- Heterotopic subcutaneous tracheal transplant model of obliterative bronchiolitis

Donor: Balb/c (BC), MHC class I
Recipient: C57BL/6 (B6), MHC class II

Allografts: Zhao, 2010
A Close Look At Day 7... Trachea Allografts

CD45⁺Col-1⁺CXCR4⁺

CD45⁺Col-1⁺SMA⁺
Luminal Fibrosis

21 Days
Goat IgG  Anti-CXCL12

28 Days

Graph showing the integrated density units of trachea luminal fibrosis at 21 and 28 days for control and anti-CXCL12 treatments.
Conclusions

• Fibrocytes respond to tracheal tissue injury via CXCL12 chemotaxis and propagate a temporal fibrotic process
• Differences between control and experimental animals is most pronounced at day 7
• Anti-CXCL12 F(ab’)2...
  – Attenuates fibrocyte trafficking to & differentiation in trachea allografts
  – Mitigates graft disease progression & fibro-obliteration
  – Significant decrease in total luminal collagen deposition
Future Directions

Acknowledgements

• Dr. Christine Lau & Dr. Yunge Zhao: National Heart, Lung, and Blood Institute (1K08HL094704-01) and the CVRC Partner’s Grant
• Dr. Irving Kron (NIH - 5RO1HL092953)
• American Association for Thoracic Surgery (AATS)
  – 2010 Summer Intern Scholarship in cardiothoracic surgery