

Rapid Activation of Pro-Lymphangiogenic Phenotype and Consequent Increase of Lymphatic Density Occurs during the Development of Chronic Lung Allograft Dysfunction

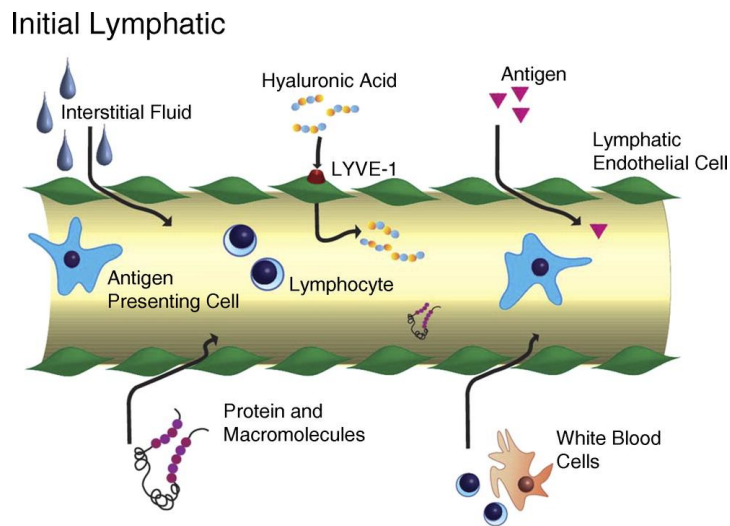
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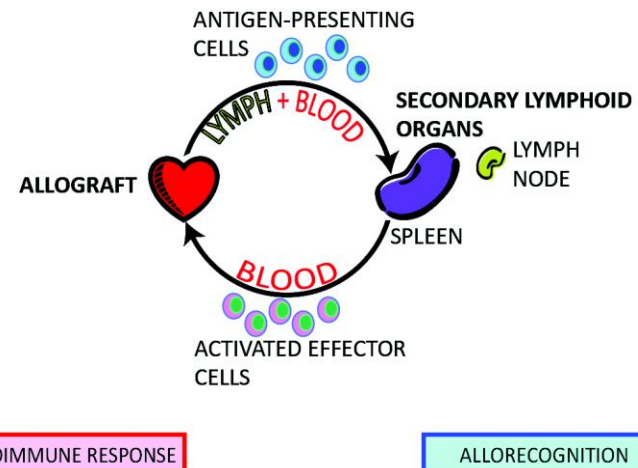
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Background

- Lung transplantation displays the worst long-term survival of all solid organ transplantations, due to chronic lung allograft dysfunction (CLAD).
- VEGFR3 signalling can activate lymphatic vessels, regulate interstitial drainage and leukocyte trafficking, therefore affects alloimmunity. But its role in CLAD development is unclear.



Stump B, *et al.* Am J Respir Cell Mol Biol. 2017

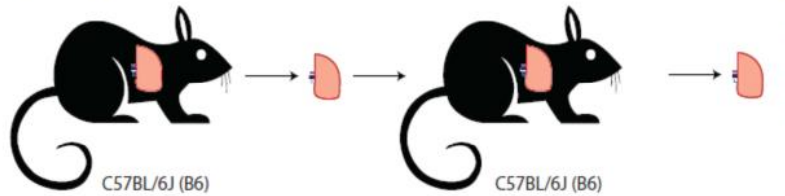


Dashkevich A, reprinted

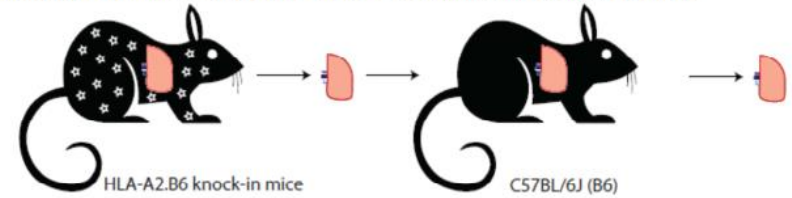
Methods

- Mouse orthotopic left lung transplantation with single mismatch

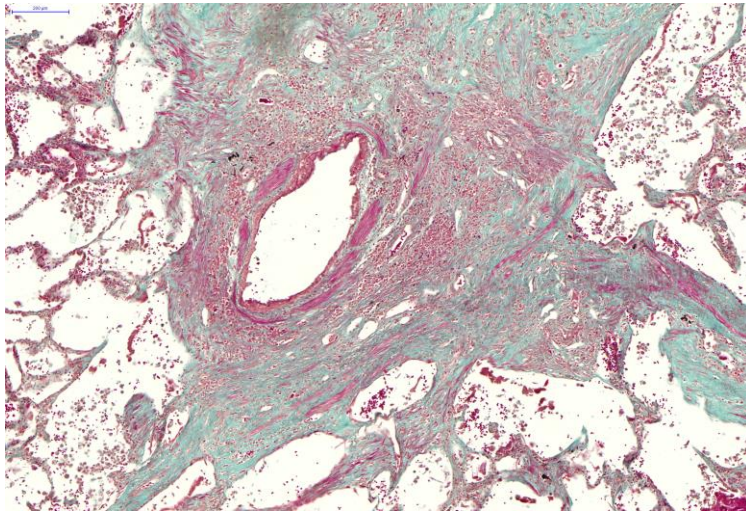
syngeneic LTx model



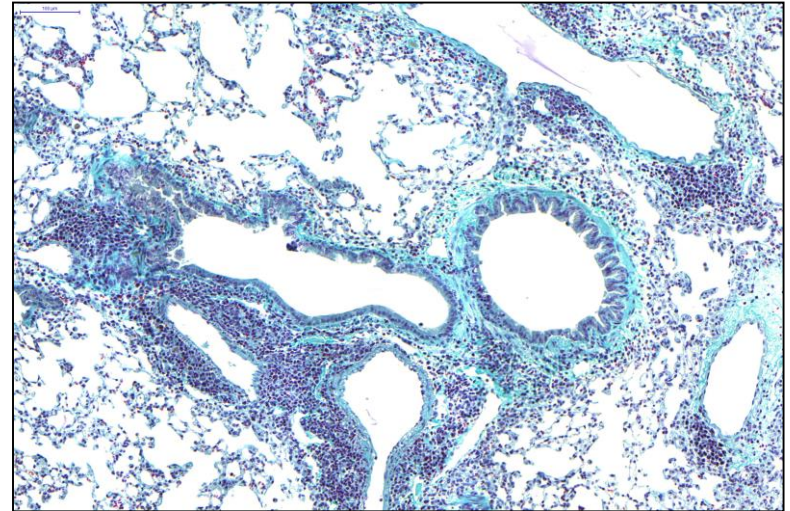
allogeneic HLA-mismatched LTx model (novel model of chronic rejection)



Human lymphocytic bronchiolitis



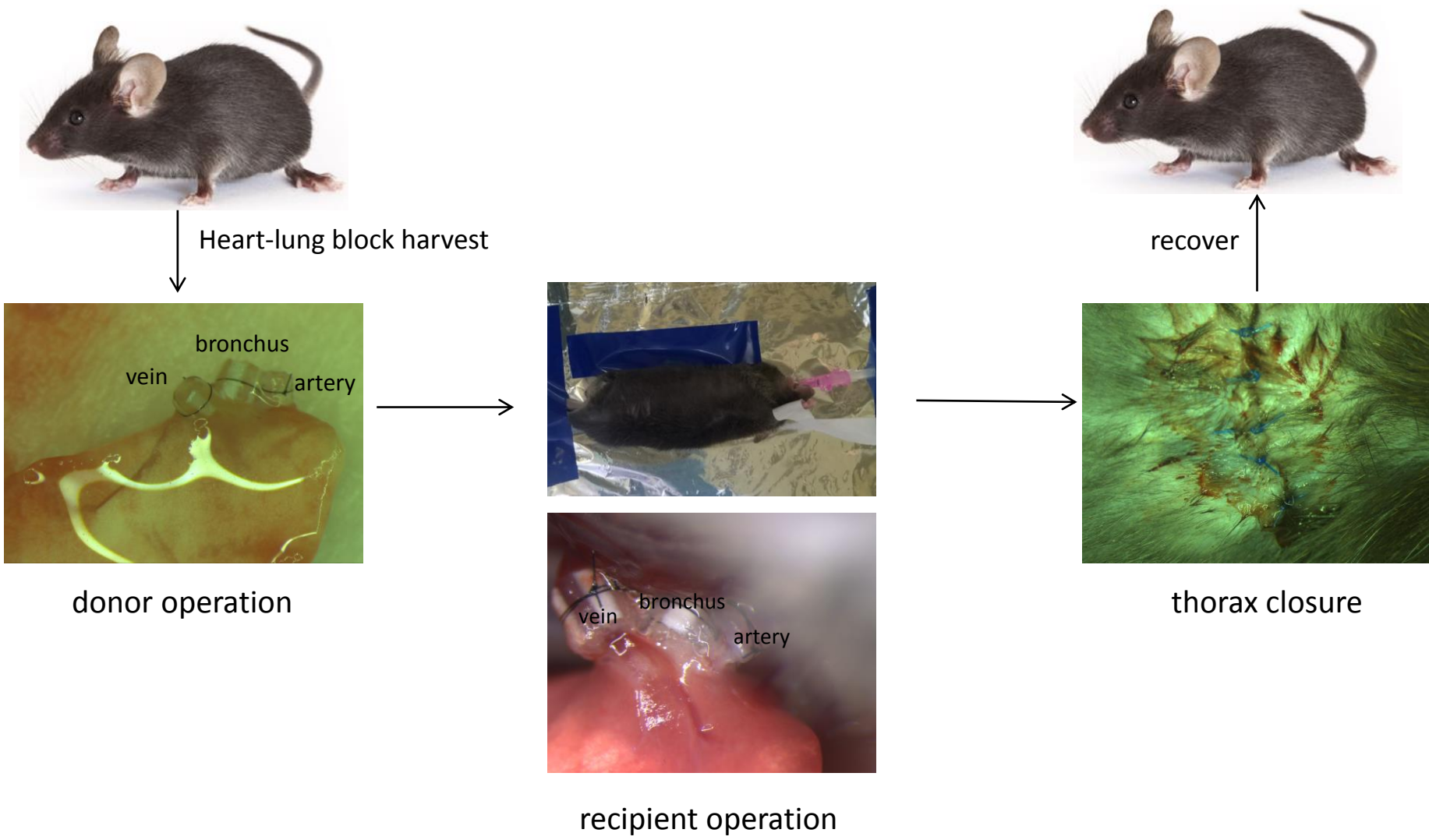
HLA-A2 -> B6 mouse orthotopic LTx, 2 months



Left lung transplantation in allogeneic model leads to bronchiolitis obliterans syndrome.

Methods

- Mouse orthotopic left lung transplantation



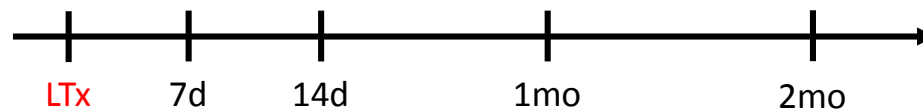
Methods:

- Evaluation of lung lymphatic activation and lymphatic density

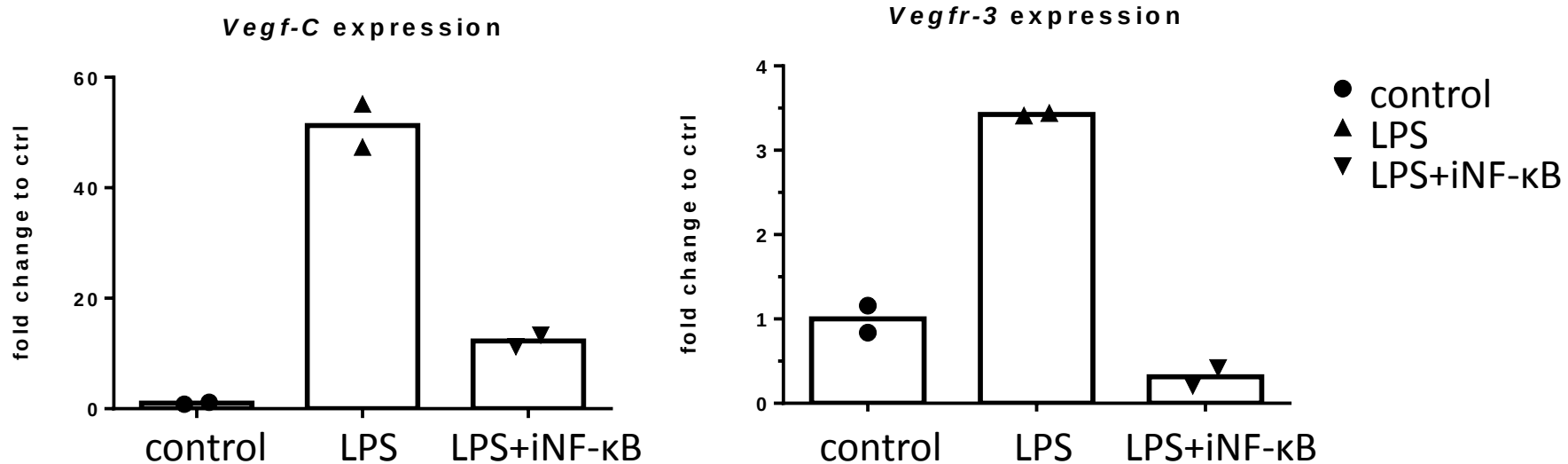
Lymphatic endothelial activation marker: LYVE-1, podoplanin, VEGFR3

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Analysis time points

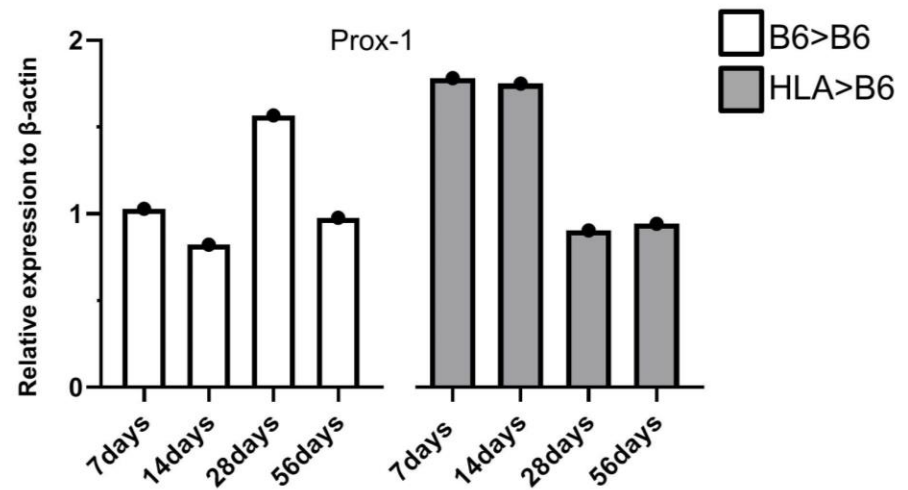
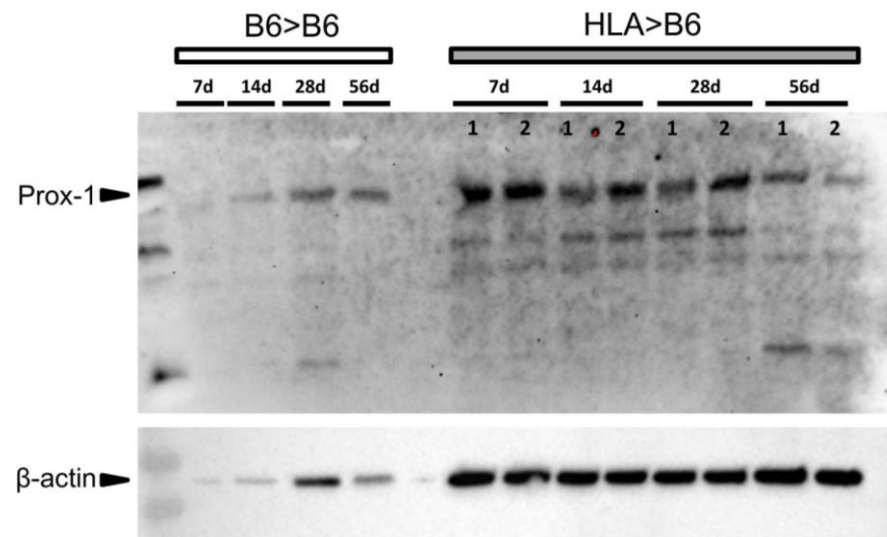


Results: In vitro model of ischemia-reperfusion injury illustrated activation of *Vegf-c* and *Vegfr-3* expression in macrophages via NF- κ B signalling.

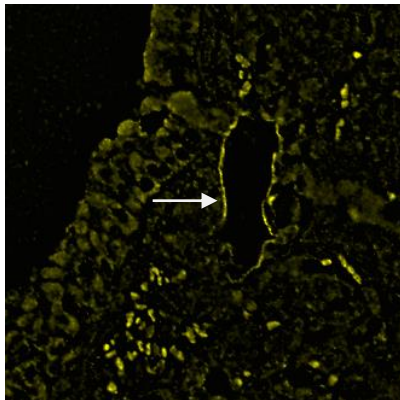
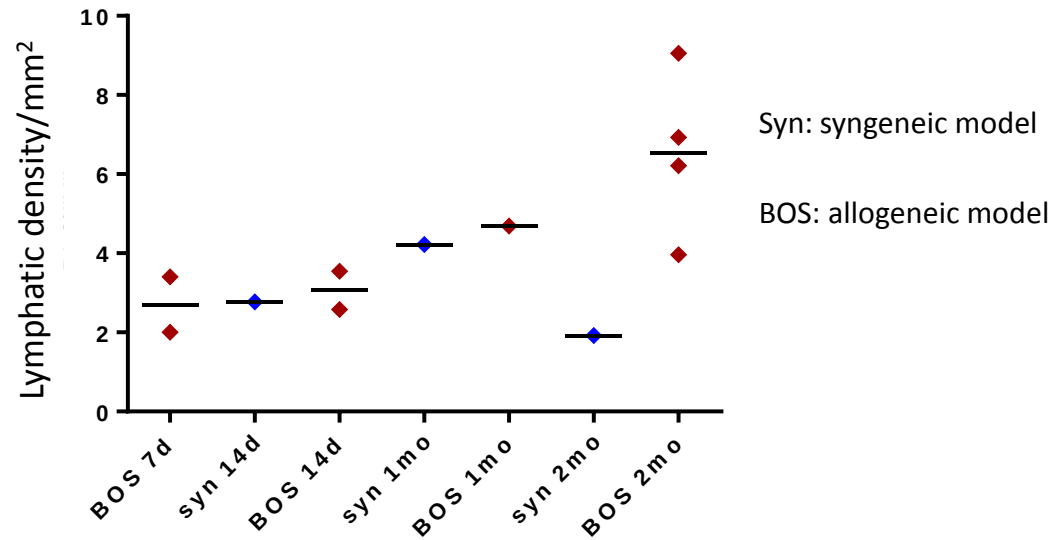
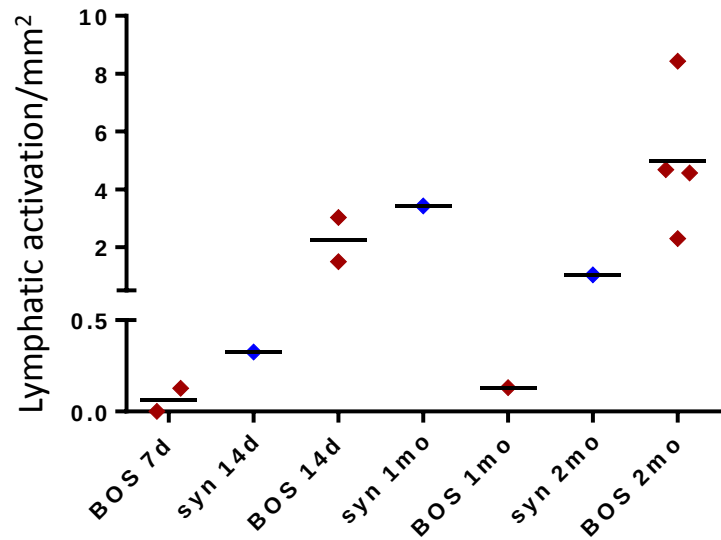


iNF- κ B: NF- κ B inhibitor Bay117082

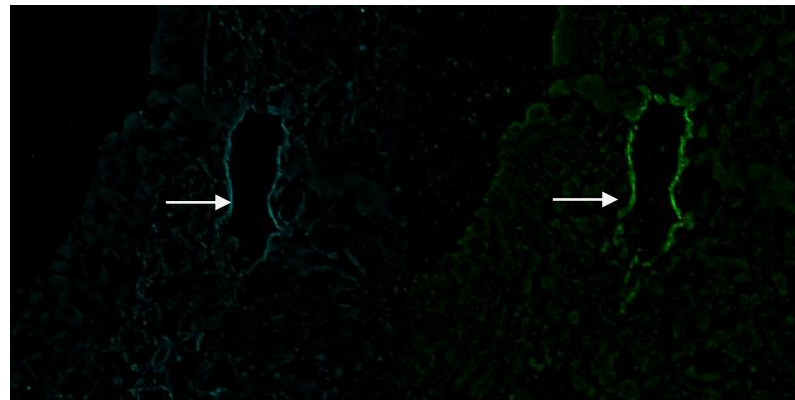
Results: Early activation of PROX-1 indicated rapid activation of lymphangiogenesis after lung transplantation in allogeneic model



Results: Rapid lymphatic activation led to elevated lymphatic density during CLAD development



VEGFR3



Podoplanin

LYVE1

Conclusion:

- In vitro IRI model proves *Vegfc* and *Vegfr3* expression in macrophages is activated via NF- κ B signaling.
- Lung transplantation leads to rapid activation of pro-lymphangiogenic phenotype with consequent increase of lymphatic activation and lymphatic density in CLAD model.
- The early activation of lymphangiogenesis during the CLAD development is associated with chronic alloimmune response.
- Therapeutic targeting of VEGF-C/VEGFR3 signaling in lung transplantation might prevent CLAD.