Introduction: Chronic rejection remains a major obstacle in transplant medicine. Efficient therapeutic strategies are lacking. Recent studies suggest a crucial role of the chemokine SDF-1 on neointima formation after injury. Here, we investigate the potential therapeutic effect of inhibiting the SDF-1/CXCR4/CXCR7 axis with an anti-SDF-1 Spiegelmer (NOX-A12) on the development of chronic allograft vasculopathy (CAV).

Methods: Two established experimental models of CAV were used. Heterotopic heart transplants (HTx) from H-2bm12 to B6 mice and fully MHC mismatched aortic transplants (AoTx) from Balb/c to B6 were performed. Mice were treated with NOX-A12. Control animals received a non-functional Spiegelmer (PoC). Samples were retrieved at different time points between 4-8 weeks after transplantation and analysed by histology, RT-PCR and proliferation assay.

Results: Blockade of SDF-1 caused a significant decrease in neointima formation as measured by intima/media ratio (1.0 ±0.1 vs. 1.8±0.1, p<0.001 AoTx; 0.35±0.05 vs. 1.13±0.27, p<0.05 HTx). In vitro treatment of primary vascular smooth muscle cells isolated from the thoracic aorta with NOX-A12 showed a significant reduction in proliferation as measured by BrdU incorporation (0.42 ± 0.04 vs. 0.24 ± 0.03, p<0.05). Cytokine levels as TGF-β, TNF-α and IL-6 were significantly reduced under SDF-1 inhibition (3.42±0.37 vs. 1.67±0.33, p<0.05; 2.18±0.37 vs. 1.0±0.39, p<0.05; 2.18±0.26 vs. 1.6±0.1, p<0.05).

Conclusion: SDF-1/CXCR4/CXCR7 plays a critical role for the development of chronic allograft vasculopathy (CAV). Therefore, pharmacological inhibition of SDF-1 with NOX-A12 may represent a therapeutic option to ameliorate chronic rejection changes.