

GM-CSF is a Pro-Inflammatory Cytokine in Experimental Vasculitis of Medium and Large Arteries

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Disclosure

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Granulocyte-macrophage colony-stimulating factor (GM-CSF)

➤ Cellular sources

T cells, B cells, macrophages, neutrophils, endothelial cells and fibroblasts

➤ Functions

Development and maintenance of macrophages

Neutrophil activation

Angiogenesis

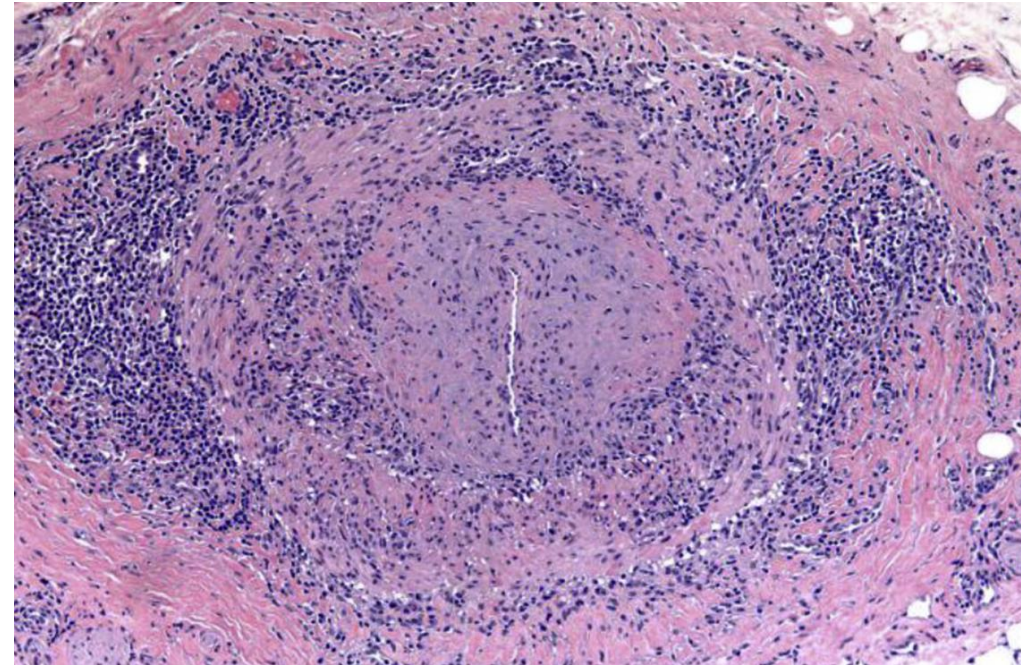
Anti-GM-CSF receptor antibody as an immuno-regulatory agent

- Mavrimumab (anti-GM-CSF receptor antibody) competes with GM-CSF for binding to the GM-CSF receptor α chain
- Therapeutic benefit in clinical trial of Rheumatoid arthritis (Burmester et al., *Ann Rheum Dis* 2013; 72: 1445-1452)

Giant cell arteritis (GCA)

- Medium/large vessel vasculitis
- Affects the elderly (>50 years)
- Infiltration of CD4 T cells and macrophages;
giant cell formation
vascular remodeling
- **High expression of GM-CSF mRNA
in temporal arteries affected by GCA**
Ann Intern Med. 1994

Temporal arteritis



Weyand CM, et al.
Clin Immunol. 2019

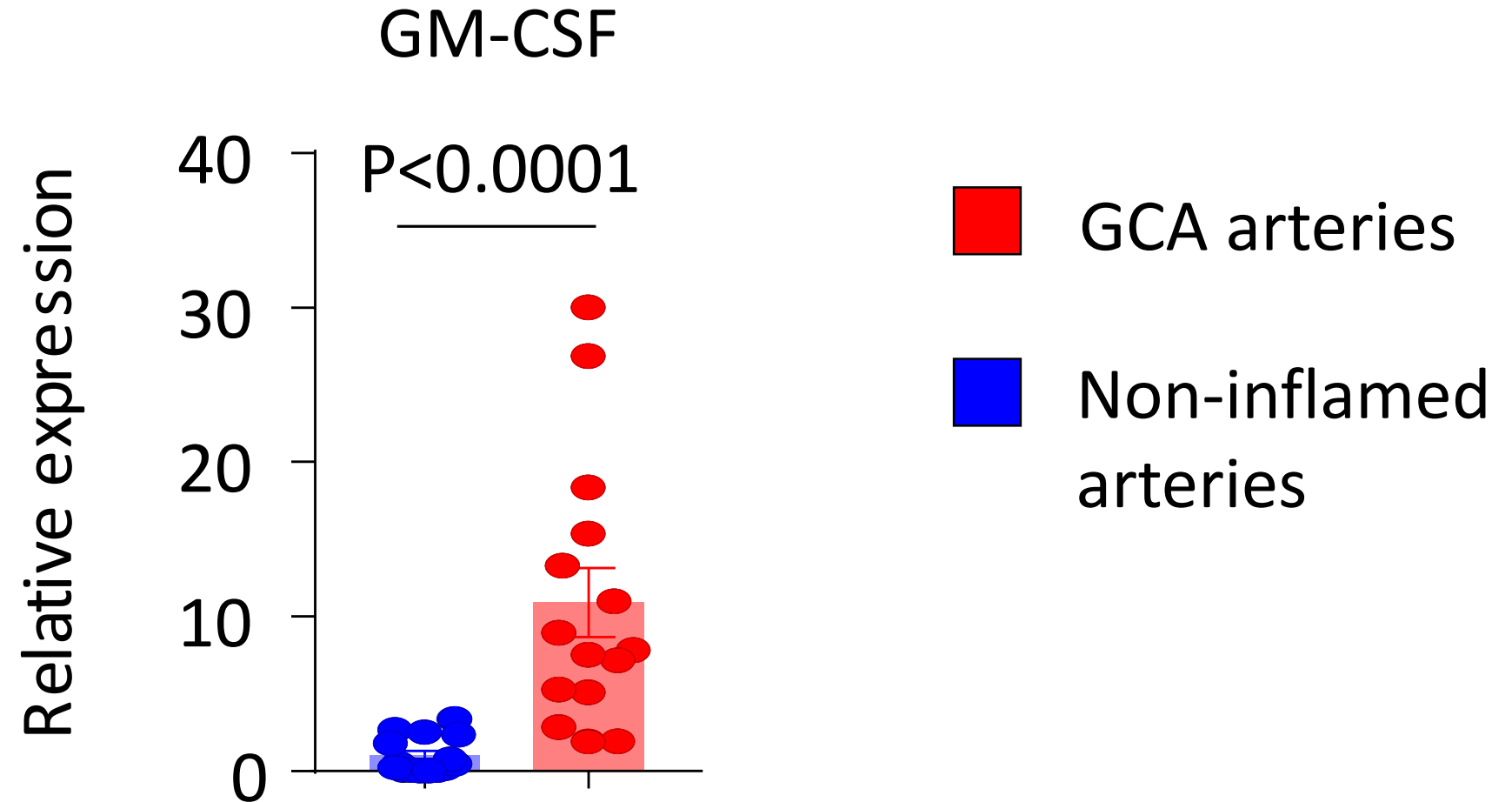
Hypothesis

GM-CSF functions as an amplifier of vascular inflammation

Methods

- GM-CSF expression
 - in tissue biopsies from patients with GCA
 - in vivo: human artery-SCID chimeric mice.
- Blocking GM-CSF activity
 - Mavrimumab, KPL-301; a monoclonal anti-GM-CSF receptor antibody
 - (300 µg given over one week in established vasculitis)

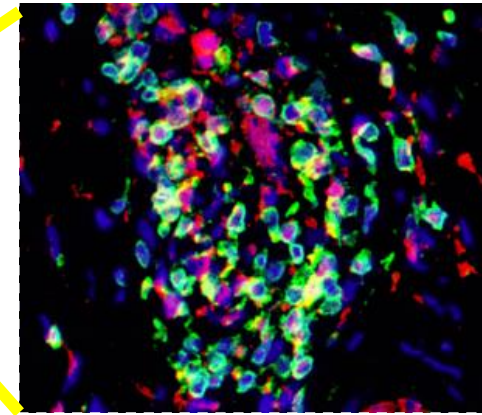
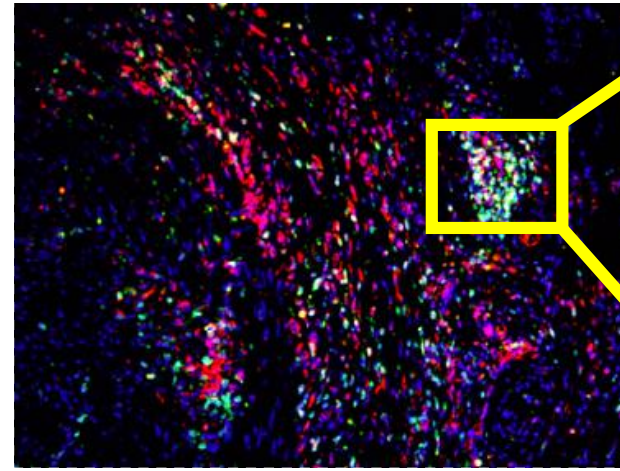
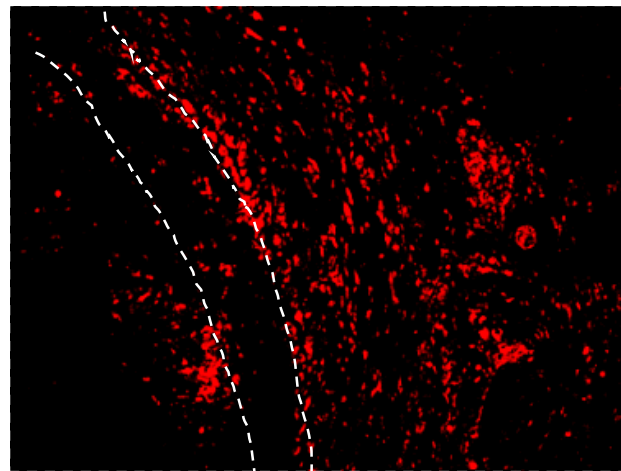
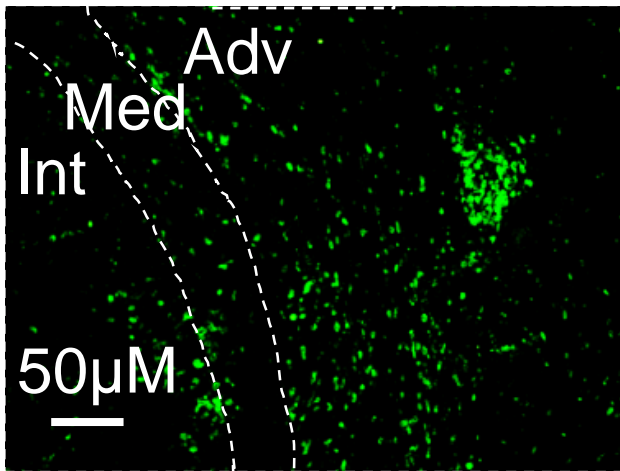
GM-CSF mRNA expression in temporal artery biopsies



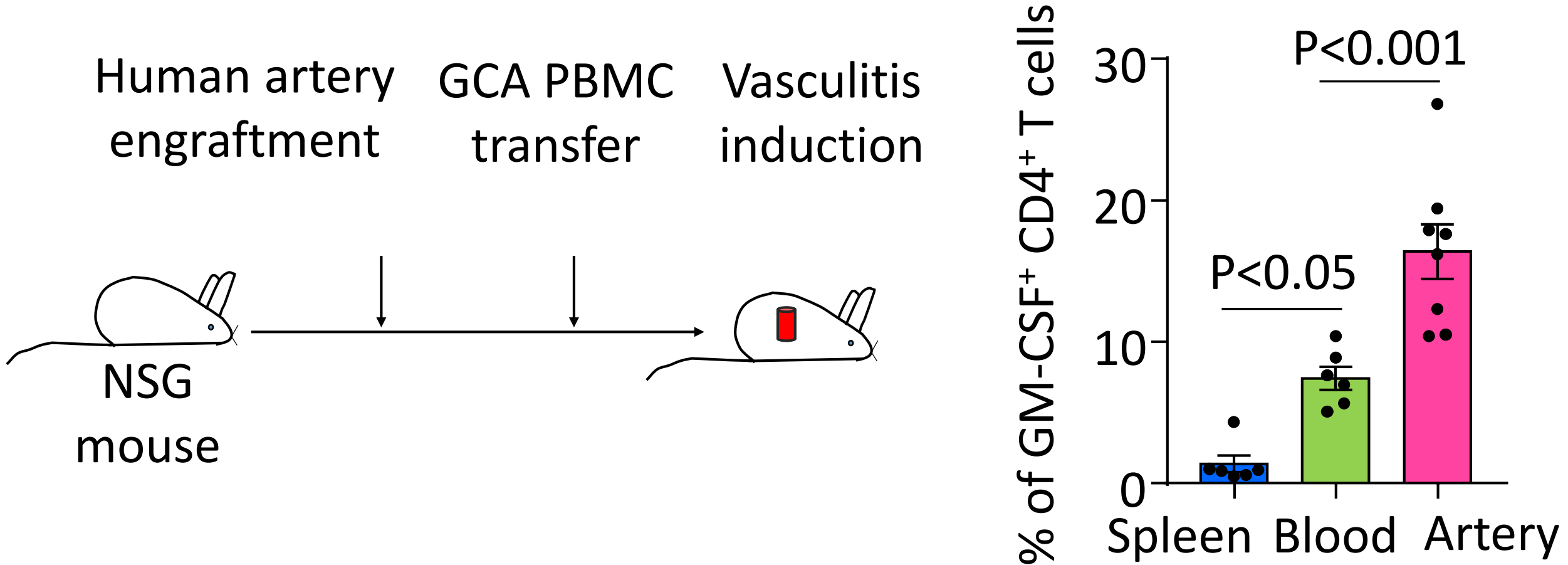
GM-CSF-producing T cells in vasculitic lesions

CD3

GM-CSF

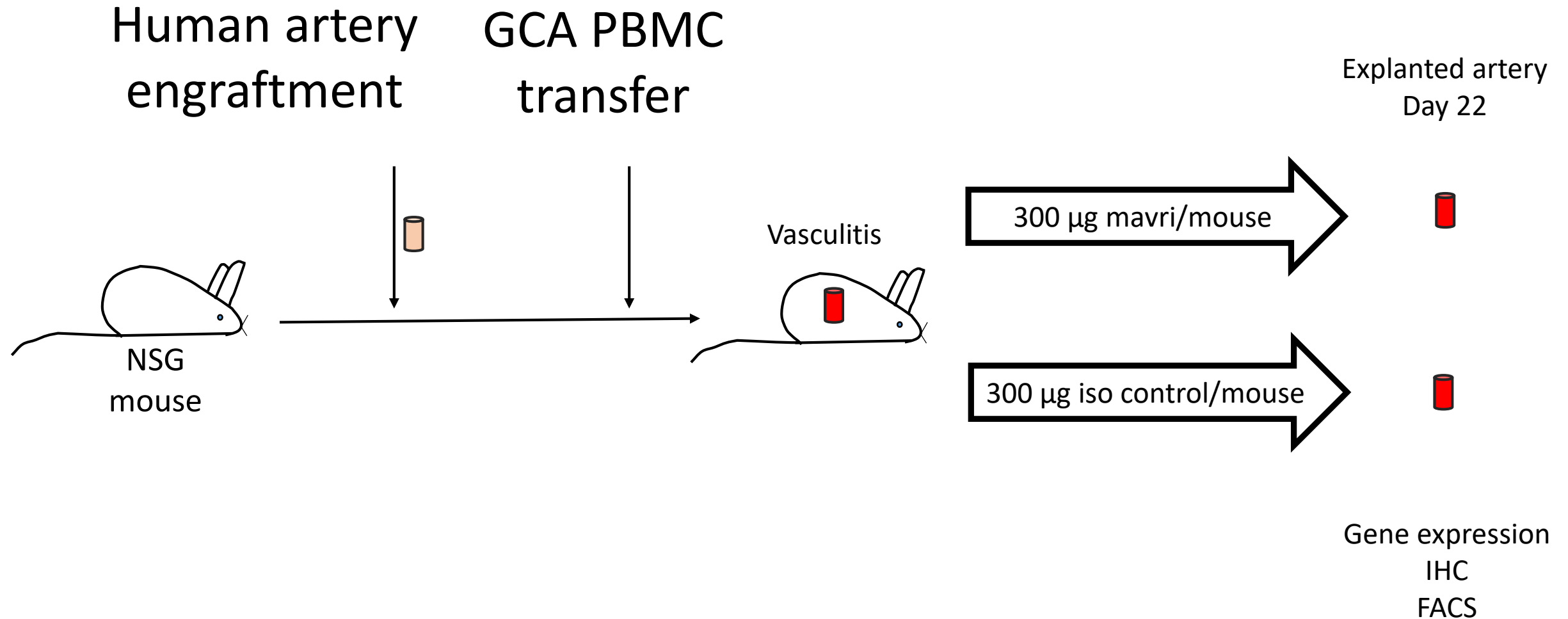


GM-CSF-producing T cells are selectively recruited to the inflamed vessel wall



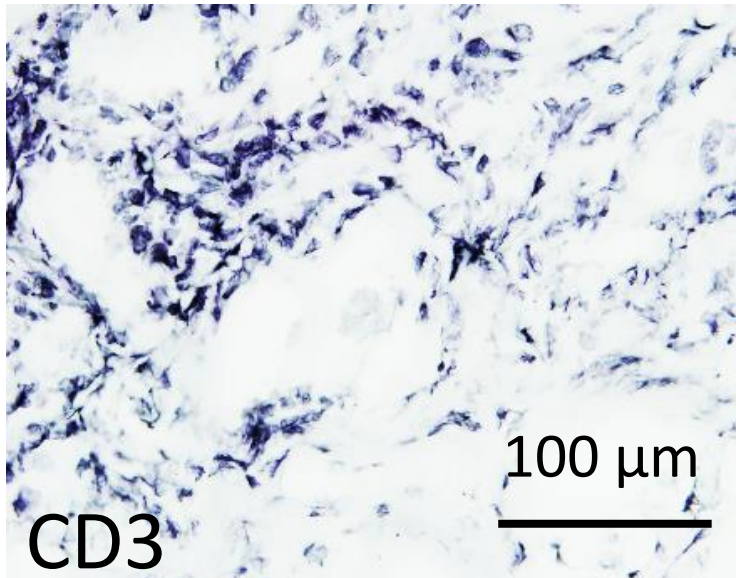
* GM-CSF⁺ CD4⁺ T cells measured by intracellular cytokine stain

Can Mavrimumab suppress vasculitogenic activity in vivo?

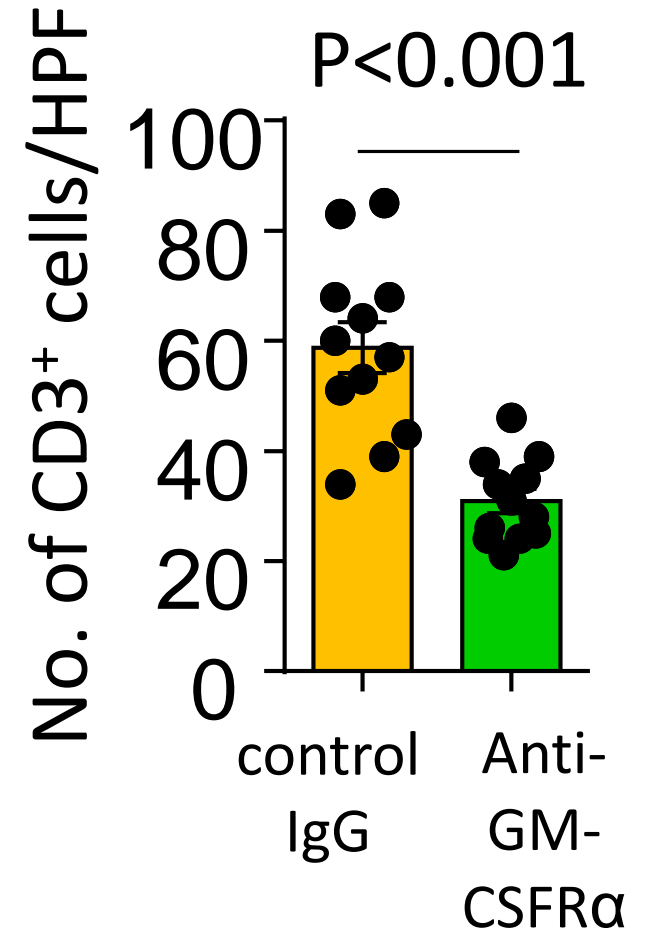
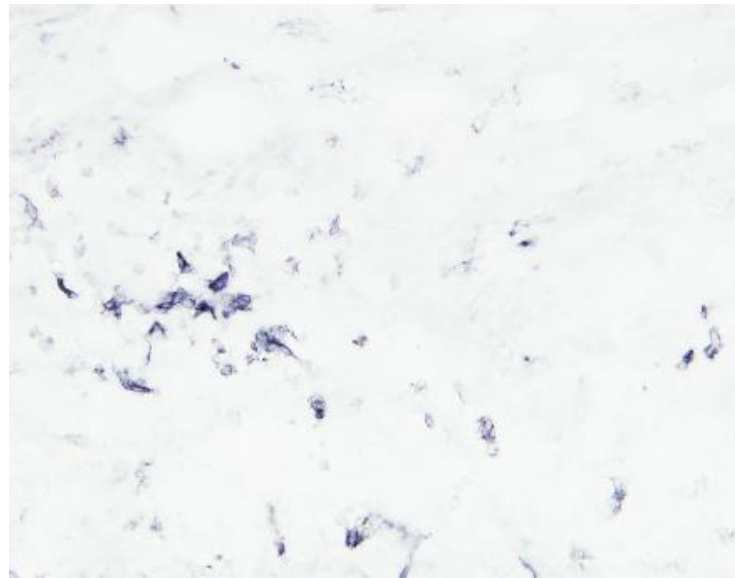


Anti-GM-CSFR Ab reduces vessel wall inflammation

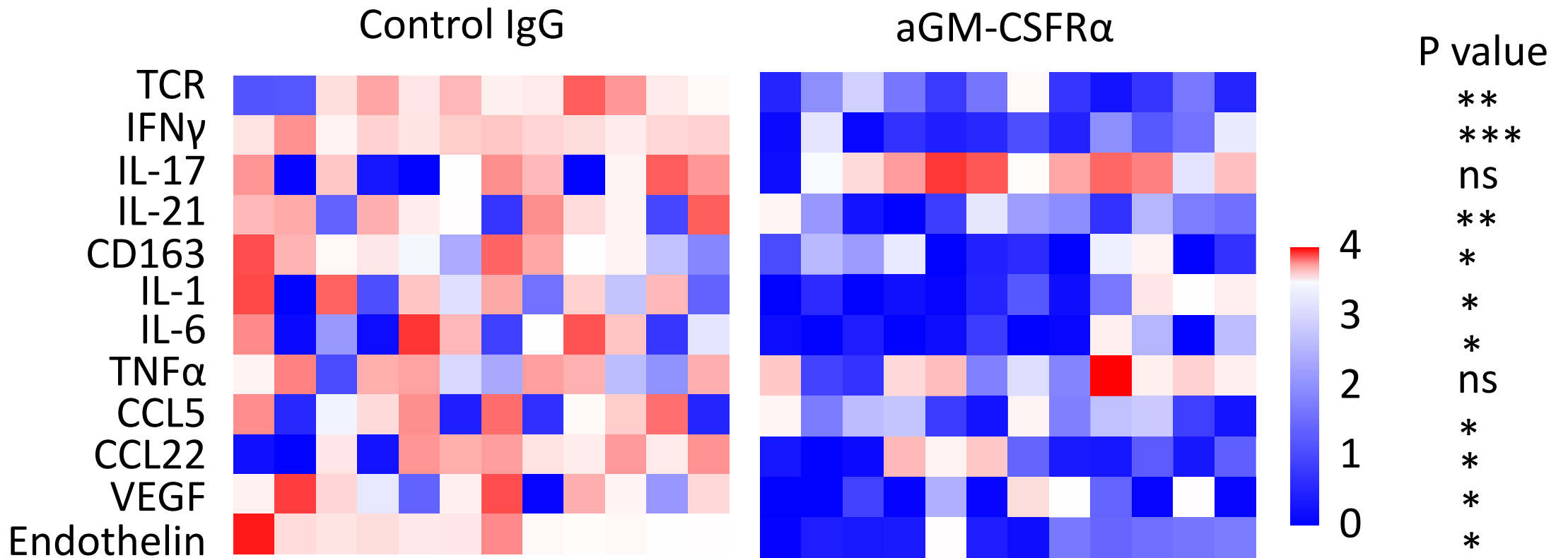
control IgG



Anti-GM-CSFR α

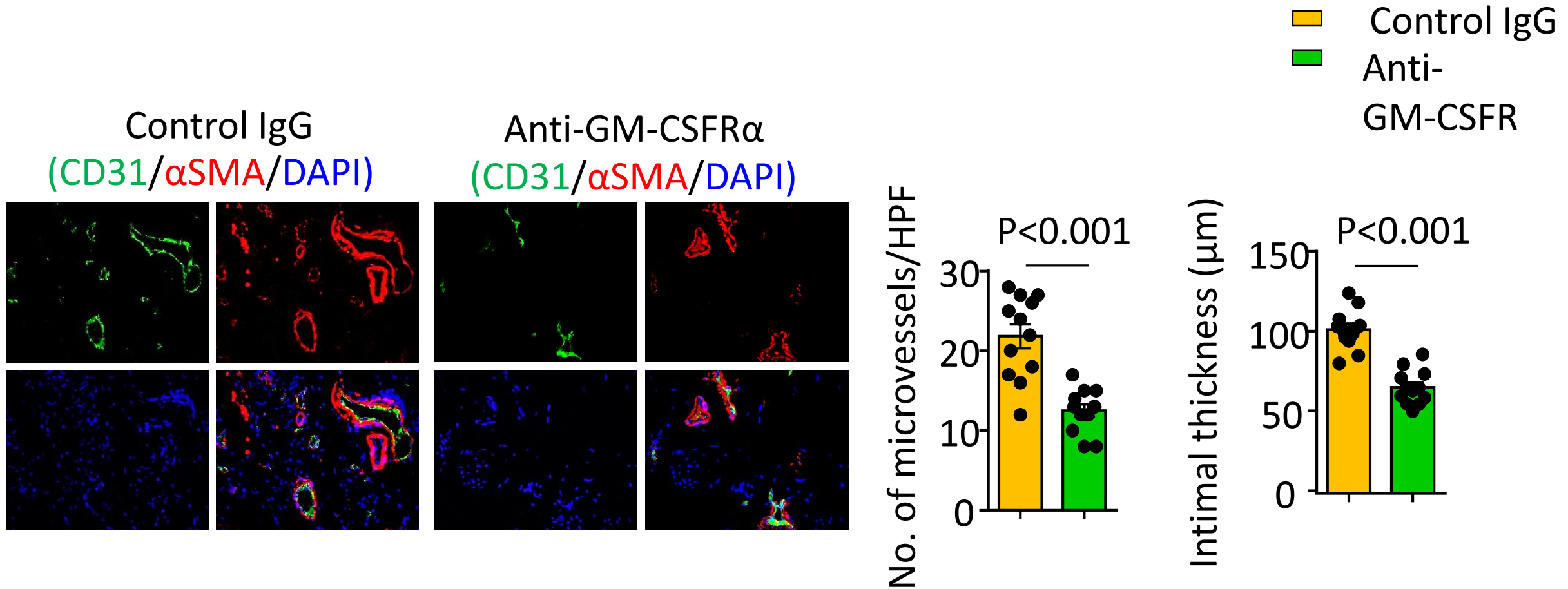


Anti- GM-CSFR Ab suppresses vessel wall inflammation



* P<0.05, ** P<0.01, *** P<0.001

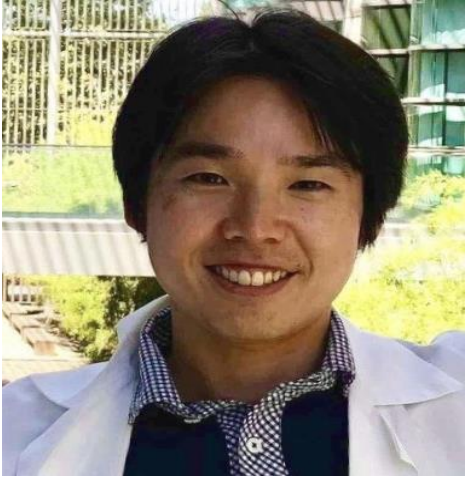
GM-CSF signaling promotes neoangiogenesis and intimal hyperplasia



Summary

1. GM-CSF mRNA is abundant in GCA-affected arteries.
2. The major sources of GM-CSF in the inflamed artery are CD4 T cells.
3. GM-CSF promotes innate and adaptive immunity in the vessel wall lesions and amplifies tissue vascularization and intimal hyperplasia.
4. Mavrilimumab, an anti-GM-CSF receptor antibody, is highly effective in suppressing vasculitis and the vasculitis-associated wall remodeling.

Acknowledgements



R Watanabe, MD PhD



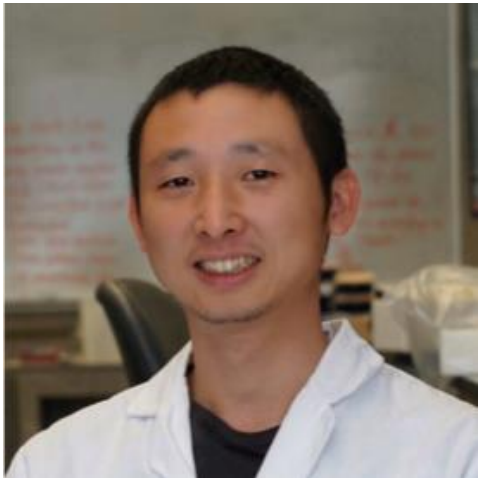
CM Weyand, MD PhD



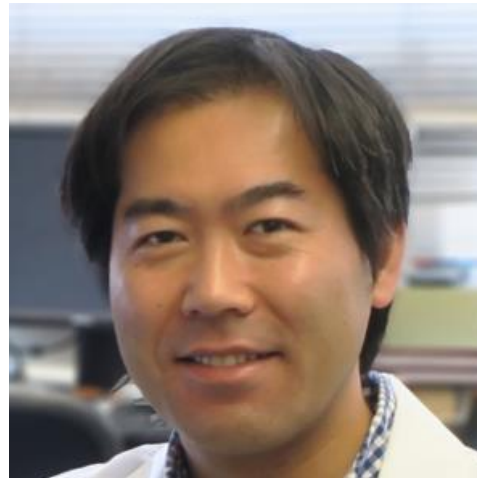
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