Adhesion Molecules on High Endothelial Venules (HEVs) of Pancreatic Lymph Nodes (LNs) from Humans with Type 1 Diabetes

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Major goals of our research are to define the molecular mechanisms that control the migration of lymphocytes from blood vessels into tissues in:

1. mouse models of human autoimmune disease
2. people with autoimmune disease




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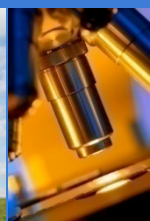

T Cell Migration in Type 1 Diabetes

Naive T cells

↓

Pancreatic LNs

+

Islet antigens

↓

Memory/effector T cells

↓

Islets



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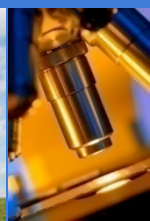
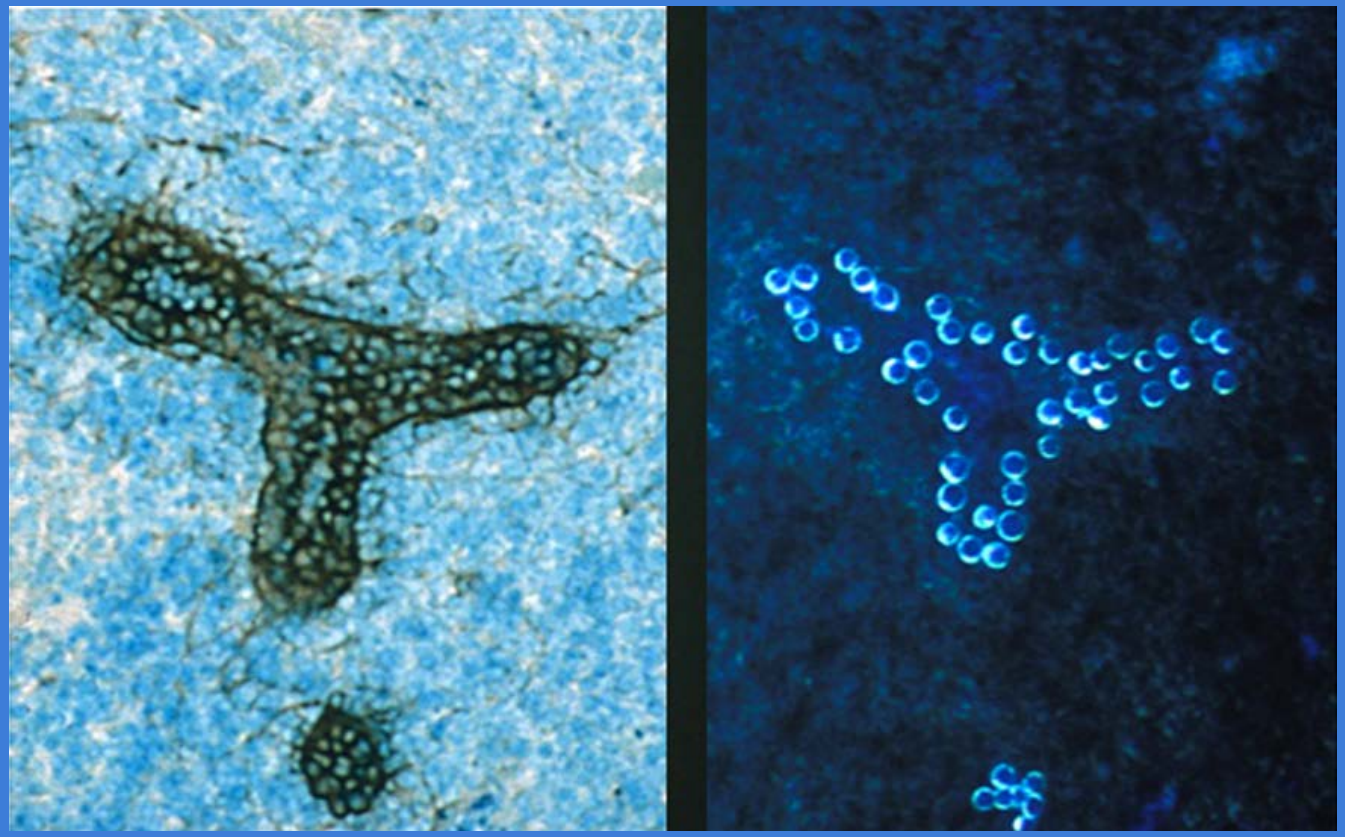


High endothelial venules (HEVs) express adhesion molecules and chemokines that bind lymphocytes



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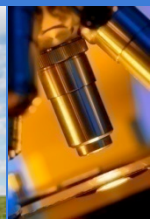

Mucosal addressin cell adhesion molecule-1 (MAdCAM-1)

- Expressed on HEVs in intestinal lymphoid tissues (Peyer's patches, appendix)
- Not expressed on HEVs in peripheral LNs

Peripheral node addressin (PNAd)

- Expressed on HEVs in peripheral LNs
- Not expressed on HEVs in intestinal lymphoid tissues (Peyer's patches, appendix)




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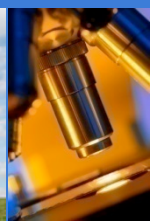
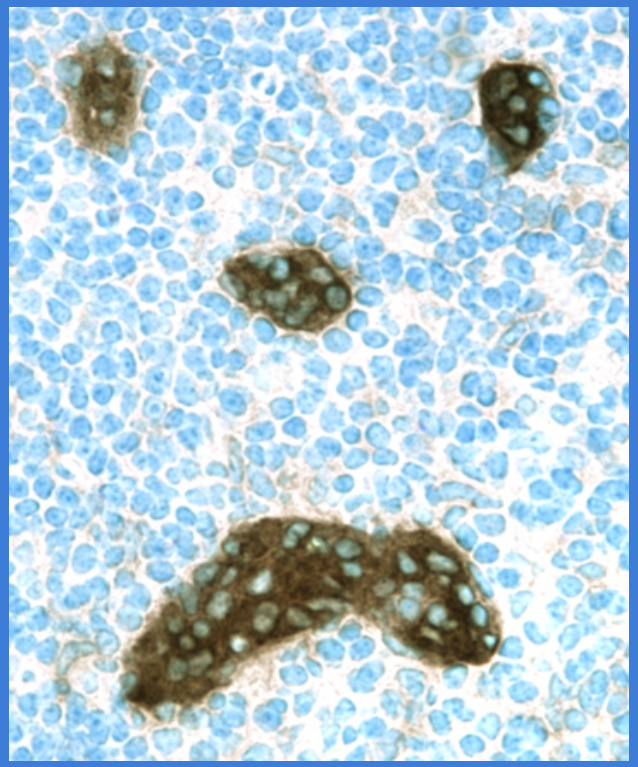


MAdCAM-1 is highly expressed on pancreatic LN HEVs in prediabetic NOD mice

- MAdCAM-1 was expressed on almost every HEV in every mouse

- PNAd expression varied with age

3-4 wk old	29+/-8.2% HEVs PNAd$^+$
8-12 wk old	53+/-23% HEVs PNAd$^+$



MAdCAM-1 on PanLN of 4 wk old NOD



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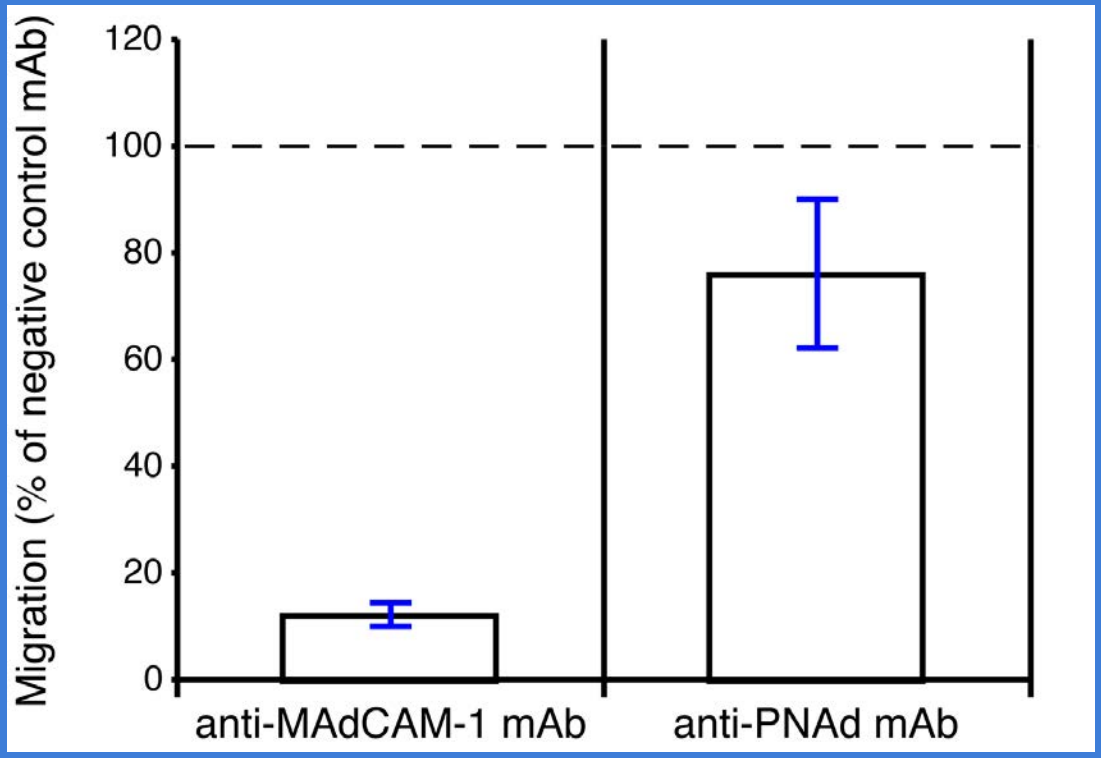
MAdCAM-1 is important for migration of naïve T cells into pancreatic LNs of NOD mice





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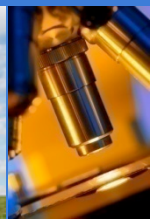

MAdCAM-1 is highly expressed on pancreatic LN HEVs in humans

- LNs from 18 cases
  - 7 donors with no diabetes
  - 4 autoantibody positive donors
  - 7 donors with T1D

- MAdCAM-1 was expressed >98% of HEVs in each group (mean)

- PNAd expression varied

Group	% of HEVs PNAd+
No T1D	50+/-28%
AutoAb^{+}	50+/-41%
T1D	65+/-32%

MAdCAM-1 on PanLN of 12 yr old boy with T1D for 1 yr (#6052)



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Summary

- MAdCAM-1 is highly expressed on HEVs in pancreatic LNs of humans and NOD mice
- MAdCAM-1 plays a major role in migration of naive T cells into pancreatic LNs of NOD mice
- PNAd is expressed on some HEVs in pancreatic LNs of humans and NOD mice
- These results suggest that NOD mice are a good model to study T cell migration mechanisms in type 1 diabetes




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