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miRNA-181 Promotes Granulosa Dendritic Cell Prolongation by Plasma Cells and T Regulatory Cells and Decreases B Cells Revealed by Mass Cytometry (CyTOF)

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I have no financial relationships with commercial interests to disclose

AND

My presentation does not include discussion of off-label or investigational use.

Introduction

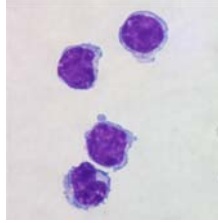
Dendritic Cells (DC)

Major subsets are the conventional (c)DC and plasmacytoid (p)DC

Adapted from KX Wang et al. Cytokine & Growth Factor Reviews 19 (2008) 333-345

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Plasmacytoid (p)DC

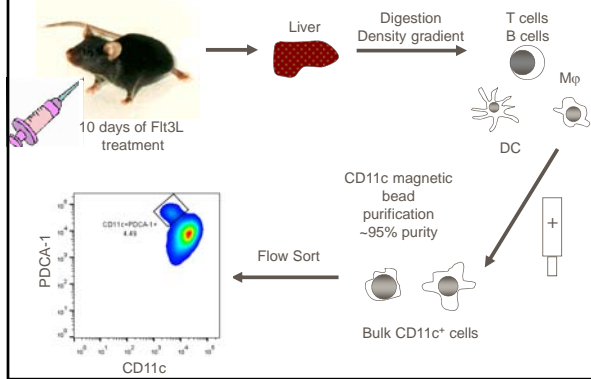


- Important in innate and adaptive T cell responses to viral infections
- Type 1 IFN-producing cells
- Regulate immune reactivity
 - shown to be involved in Treg generation
- Hepatic pDC express lower MHCII and CD86 as well as have poor allostimulatory capacity compared to splenic pDC

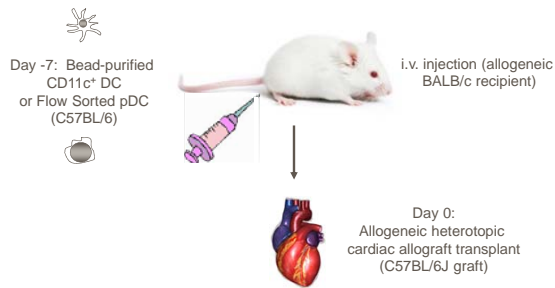
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Methods – Freshly-Isolated DC



Adoptive Transfer and Transplant

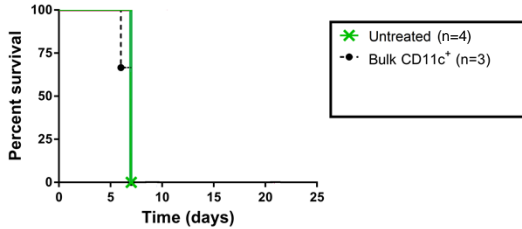


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<http://jaxmice.jax.org/strain/01803.html>
www.abnashheartcenter.com

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Hepatic pDC prolong cardiac allograft survival



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Liver transplant patients are more likely to attain tolerance to their graft

What properties are inherent to hepatic pDC which promote tolerance?

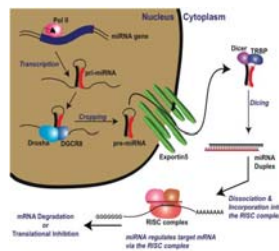
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microRNA

~22 nucleotides long single-stranded RNA

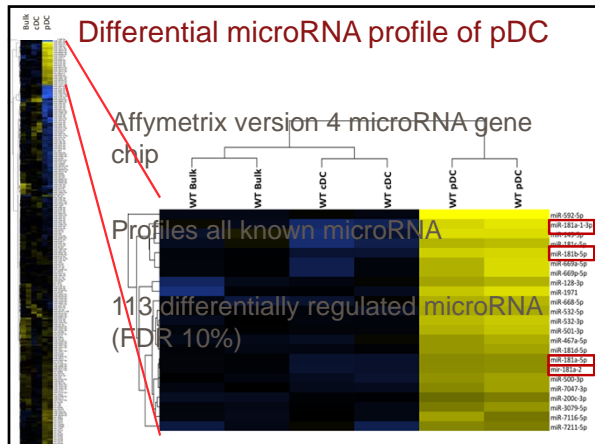
Regulate one or more target genes by binding and degrading mRNA

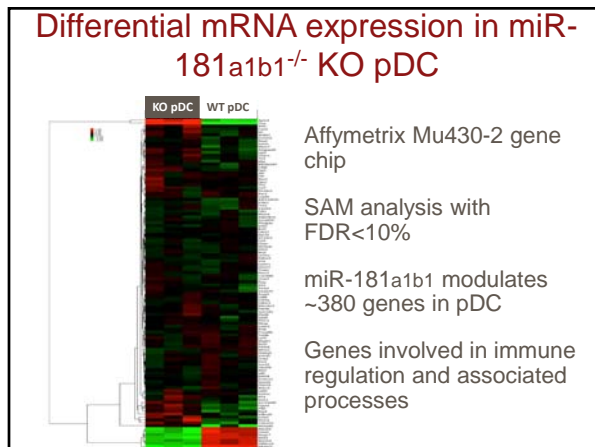


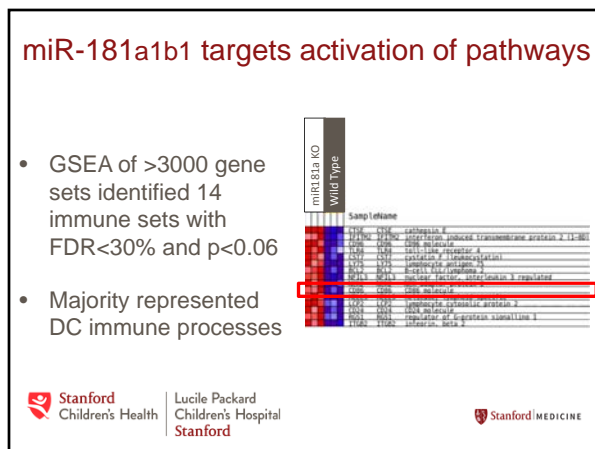
A Harris et al, American J Transplant 10 (2010) 713-719

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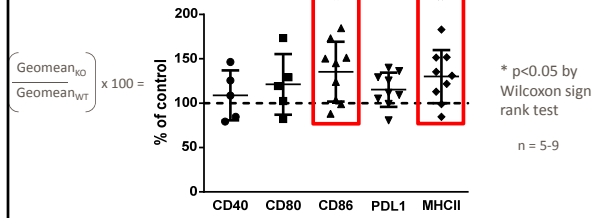
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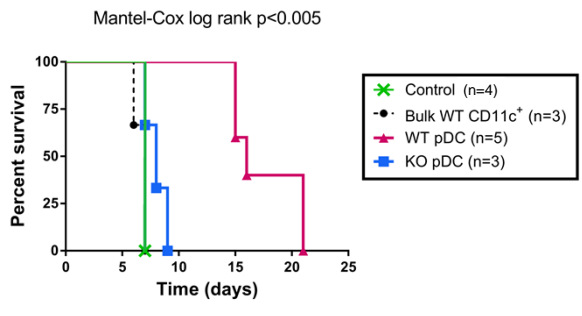


CD86 and MHCII are more highly upregulated on miR-181a1b1^{-/-} KO pDC

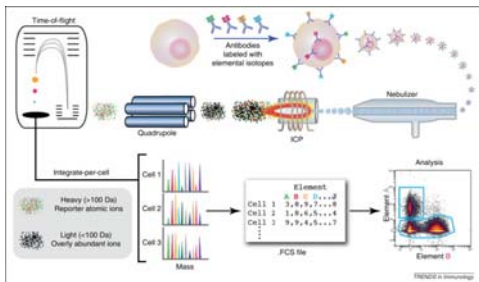


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Loss of miR-181a1b1 abrogates the tolerogenic properties of WT pDC

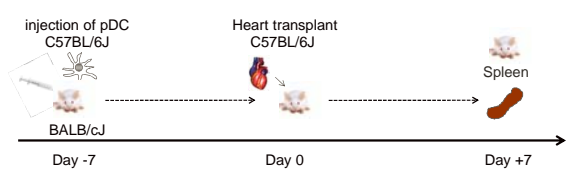


Analysis of Alloactivation by Cytometry Time-of-Flight (CyTOF, mass cytometry)



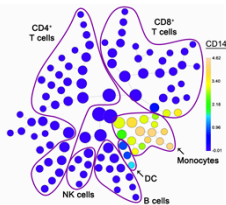
Bendall C *et al.* Trends Immunol. 2012

Examining the Alloimmune Response



Analysis of Mass Cytometry Data: Citrus

- a method for unsupervised identification of significant cellular populations, clustered on the basis of the expression of markers studied



Each node is a specific cell population

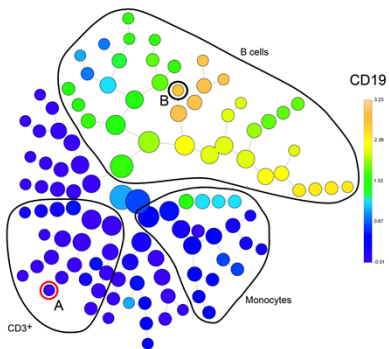
Color scale

Node size

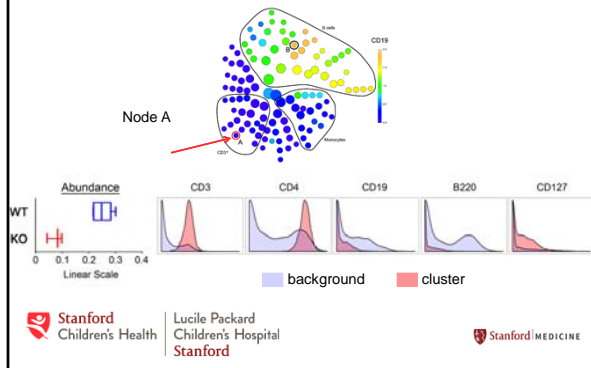
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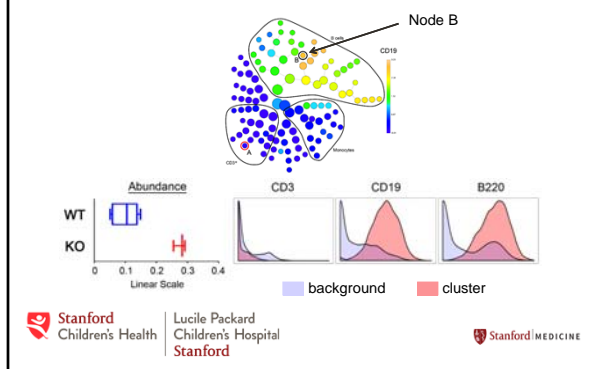
CytoF: Differing alloimmune response in mice pre-treated with miR-181a1b1^{-/-} pDC



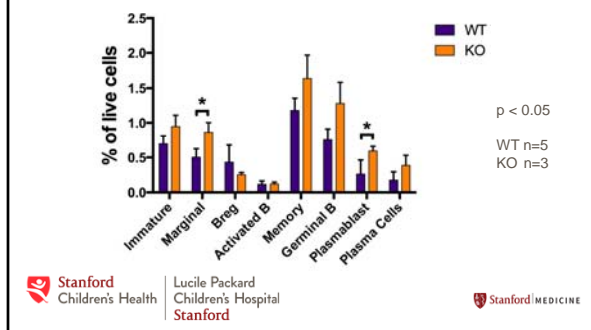
Increased CD3⁺CD4⁺CD127^{-/lo} T cells are detected in graft recipients that receive hepatic pDC



Increased B cells are detected in graft recipients that receive miR-181a1b1^{-/-} pDC



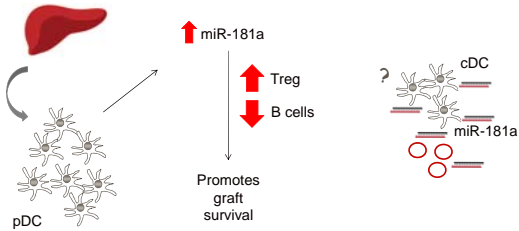
FACS: Marginal Zone B cells and Plasmablasts are decreased in miR-181a1b1-expressing pDC treated mice



CONCLUSIONS

miR-181a1b1 is a critical regulator of the tolerogenic properties of plasmacytoid dendritic cells

miRNA-181 promotes graft prolongation by pDC by increasing Treg cells and decreasing B cells



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