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T-regulatory cells in colon cancer.

Friend or Foe?

Increased frequency of regulatory T cells in peripheral blood and tumour infiltrating lymphocytes in colorectal cancer patients

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GASTROENTEROLOGY 2009;137:1270-1279

Intraepithelial Effector (CD3⁺)/Regulatory (FoxP3⁺) T-Cell Ratio Predicts a Clinical Outcome of Human Colon Carcinoma

FRANK A. SINICROPE,^{*,‡} RAFAELA L. REGO,^{*,‡} STEPHEN M. ANSELL,[§] KEITH L. KNUTSON,^{||} NATHAN R. FOSTER,[¶]
and DANIEL J. SARGENT[¶]

Antigen-specific Tregs control T cell responses against a limited repertoire of tumor antigens in patients with colorectal carcinoma

Andreas Bonertz,¹ Jürgen Weitz,² Dong-Ho Kim Pietsch,¹ Nuh N. Rahbari,² Christoph Schlude,¹ Yingzi Ge,¹ Simone Juenger,¹ Israel Vlodavsky,³ Khashayarsha Khazaie,⁴ Dirk Jaeger,⁵ Christoph Reissfelder,² Dalibor Antolovic,² Maximilian Aigner,² Moritz Koch,² and Philipp Beckhove¹

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- 5-10% of total “naïve” CD4 T cells.
- positively selected in the thymus
- CD25⁺ (IL2R α subunit)
- FOXP3⁺
- potent suppressors of antigen specific CD4 and CD8 T cell responses

- *potent suppressors of inflammation*

Tumor-Infiltrating FOXP3⁺ T Regulatory Cells Show Strong Prognostic Significance in Colorectal Cancer

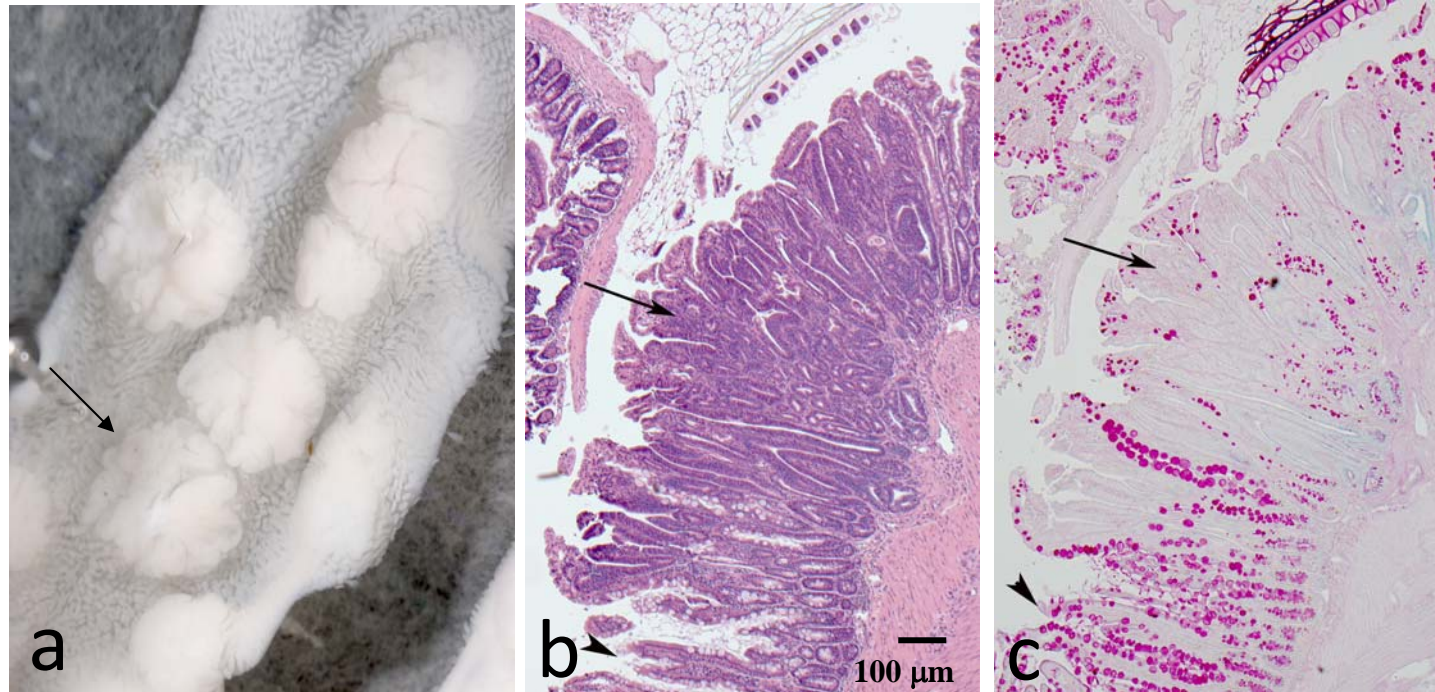
Paul Sakuma, Michael Phillips, Fabienne Griew, Melinda Morris, Nik Zeps, David Joseph, Cameron Platell, and Barry Iacopetta

Conclusion

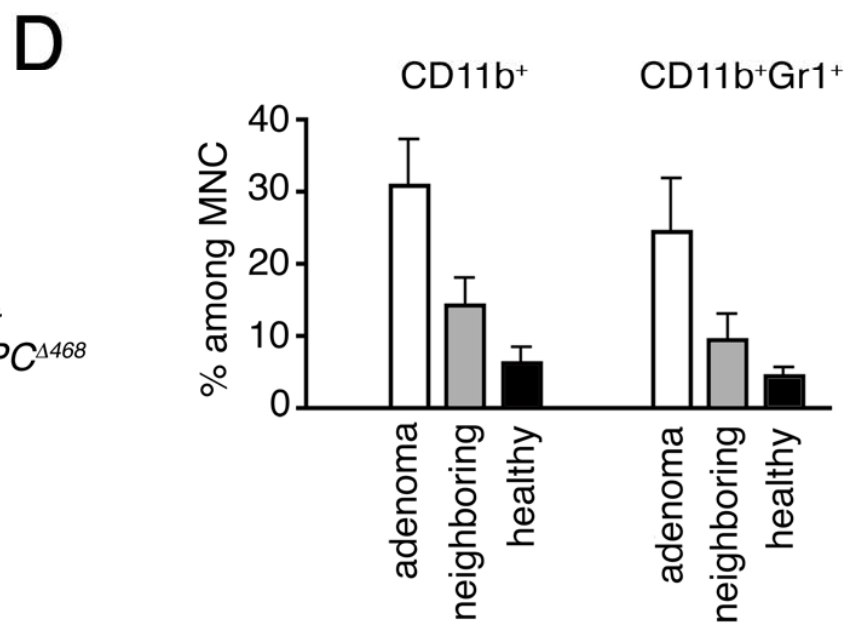
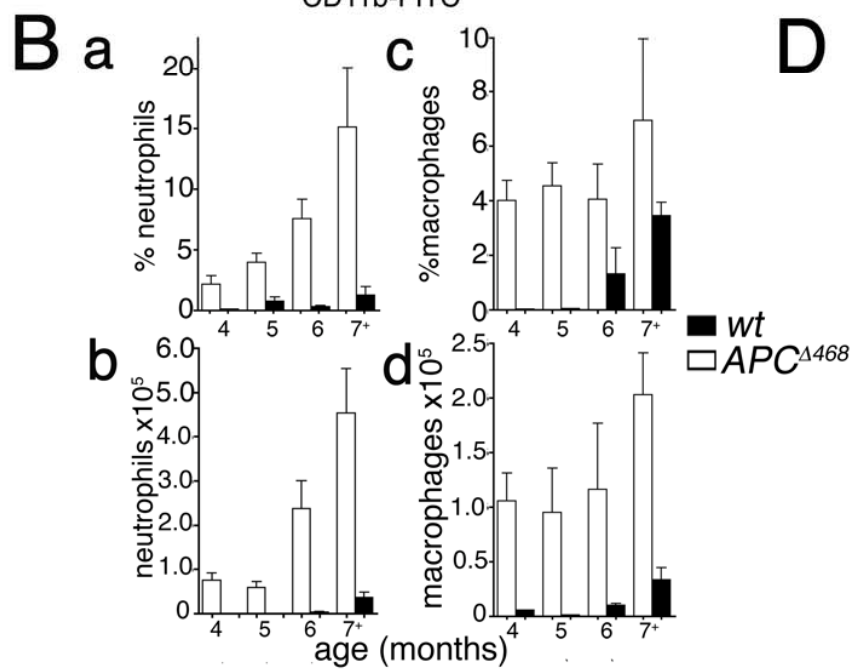
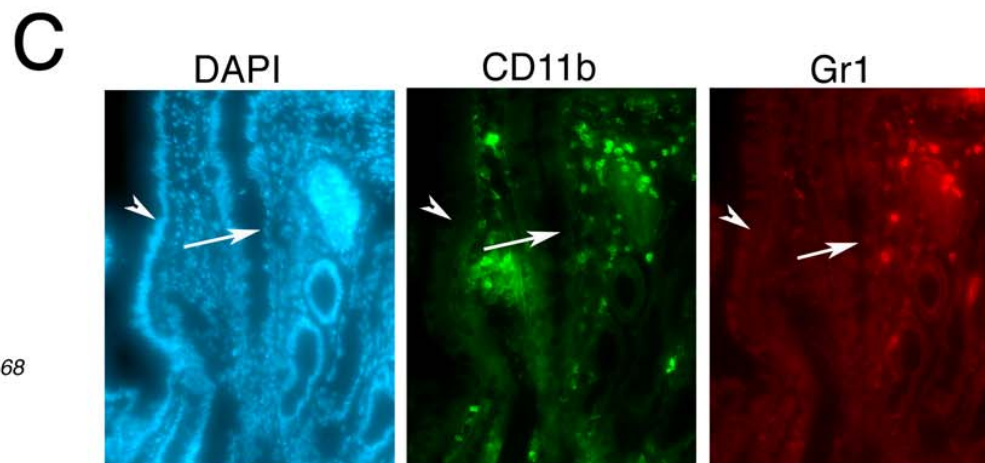
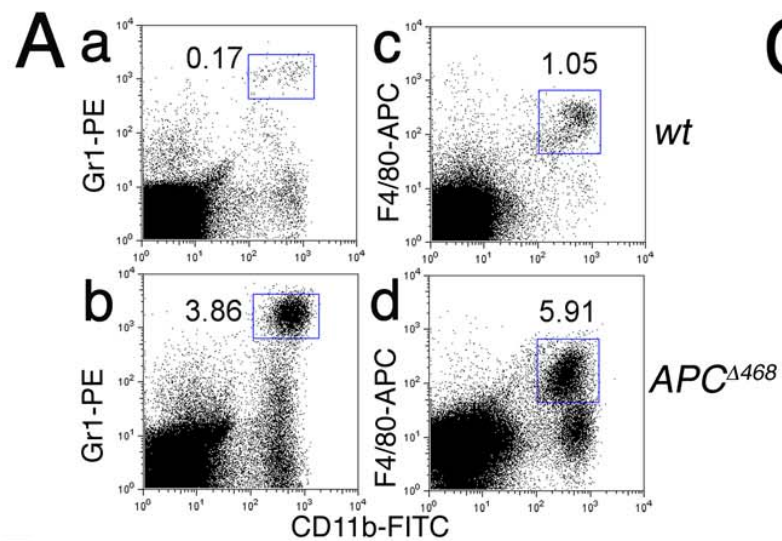
FOXP3⁺ Treg density in normal and tumor tissue had stronger prognostic significance in colorectal cancer compared with CD8⁺ and CD45RO⁺ lymphocytes. The finding of improved survival associated with a high density of tumor-infiltrating FOXP3⁺ Tregs in colorectal cancer contrasts with several other solid cancer types. The inclusion of FOXP3⁺ Treg density may help to improve the prognostication of early-stage colorectal cancer.

J Clin Oncol 27: 196-192. © 2009 by American Society of Clinical Oncology

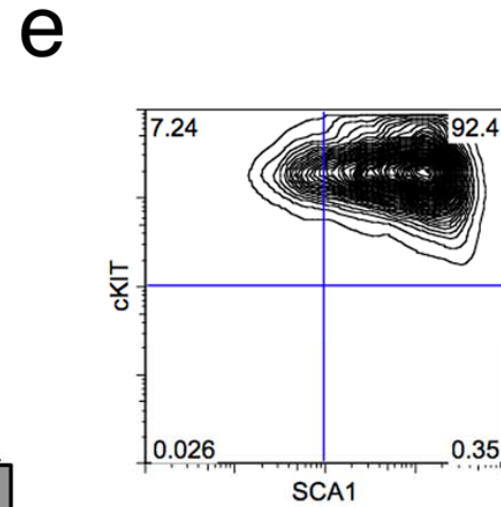
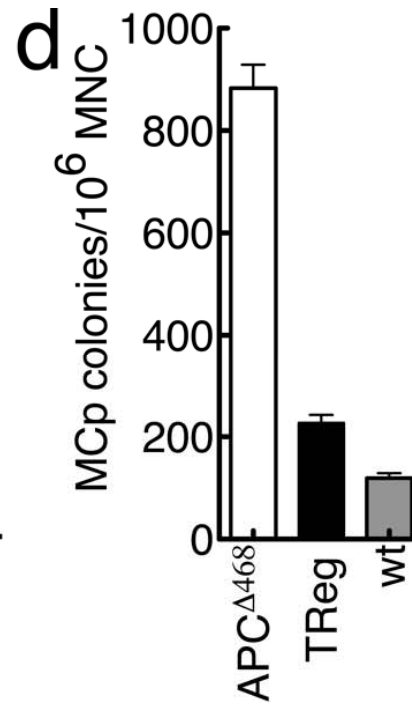
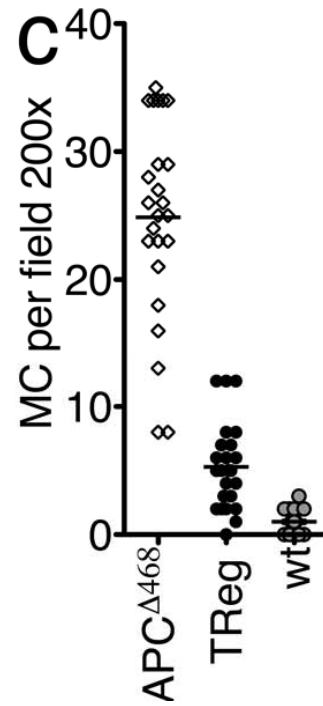
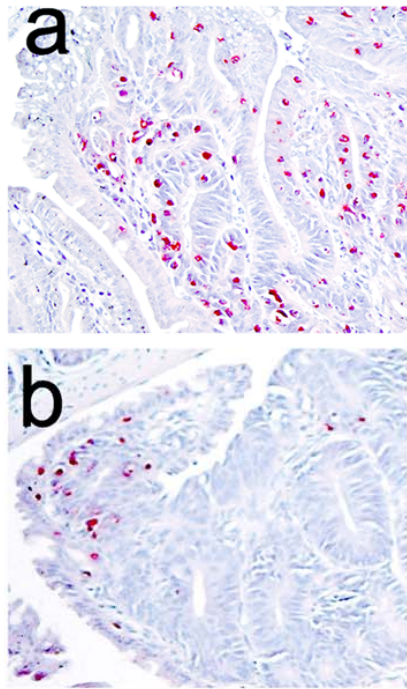
Typical histology of tubulovillous adenoma from small intestine



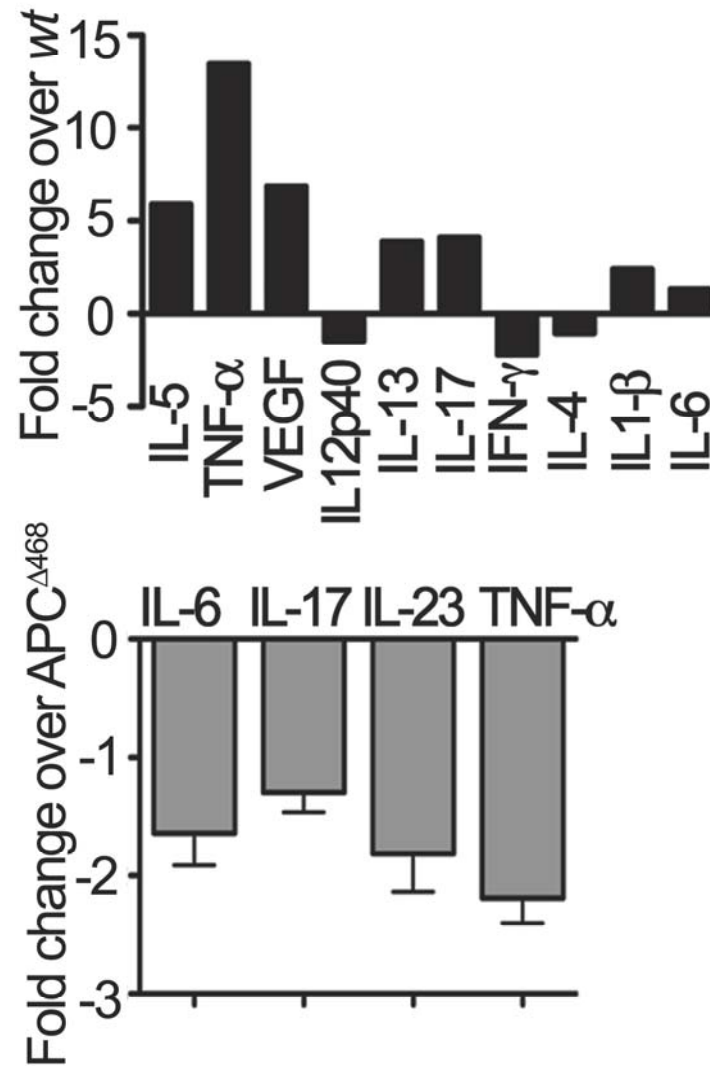
Tall, hyperchromatic disorderly cells with cigar-shaped nuclei and concomitant crypt budding, and absence of sulfomucin expressing goblet cells



Treg transfer suppresses cancer associated inflammation

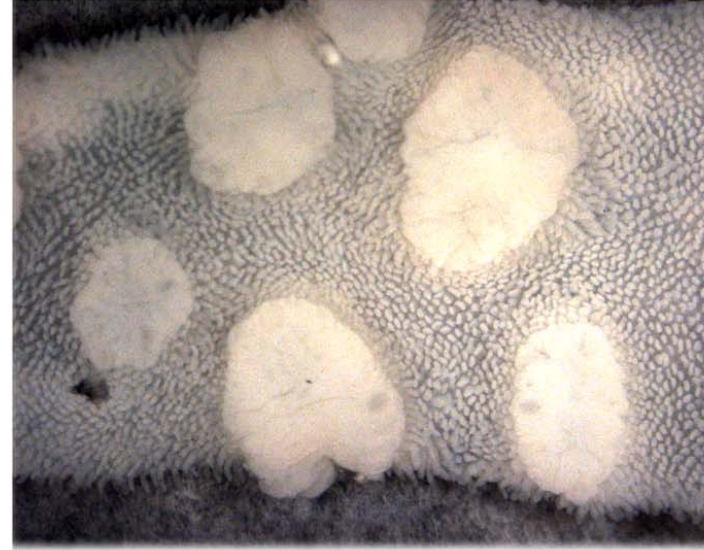


Adoptive Transfer of Healthy Treg



Transfer of 10^5 Treg: 4 weeks

untreated

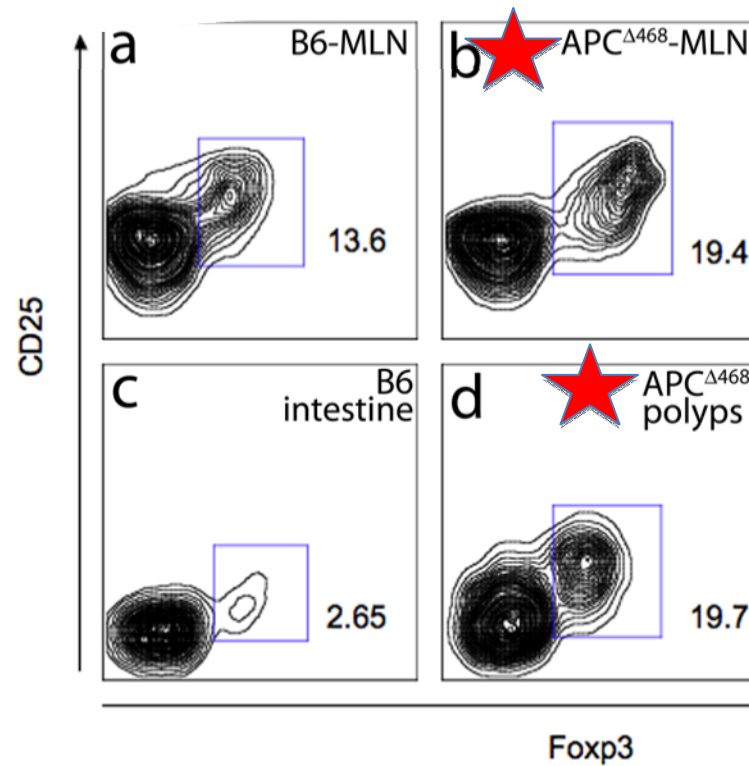


treated

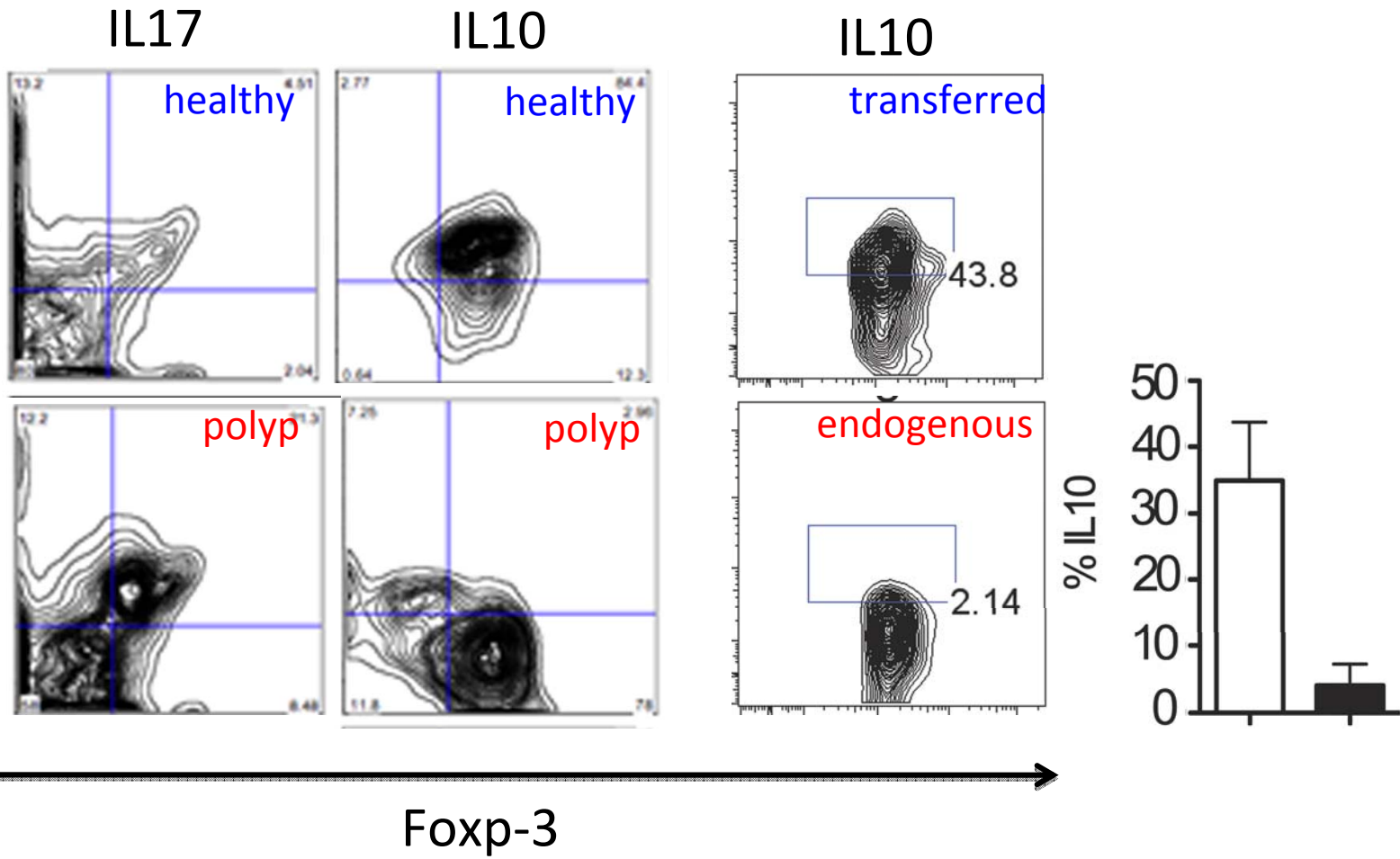


What about the endogenous Treg

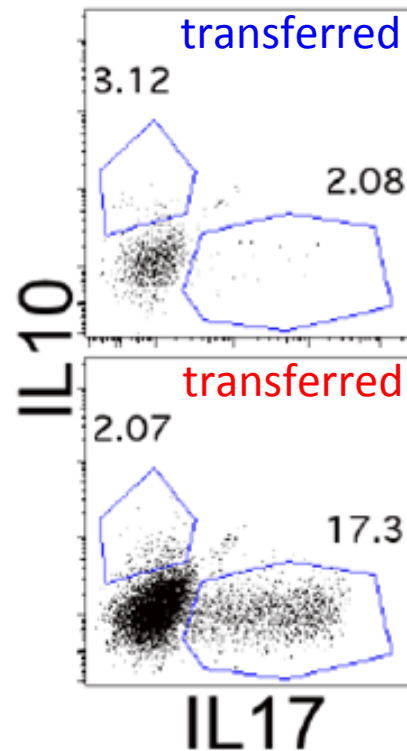
Treg in healthy mice < Treg in polyp mice



Treg are altered in polyposis



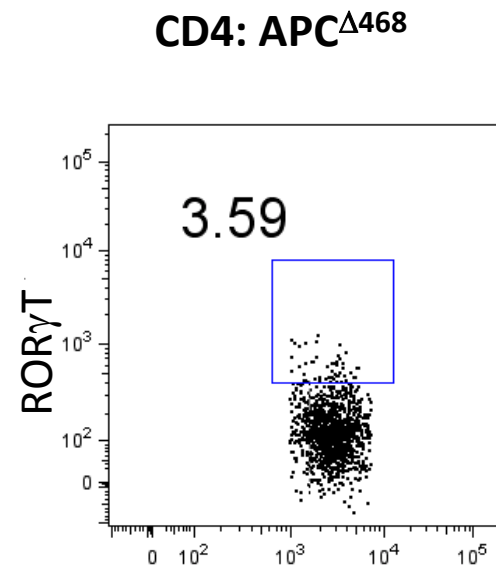
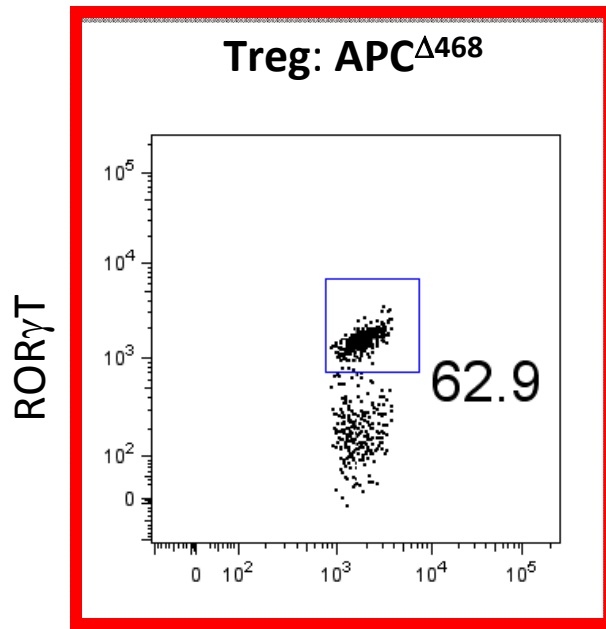
Adoptive Transfer in Rag^{-/-} mice



healthy donor

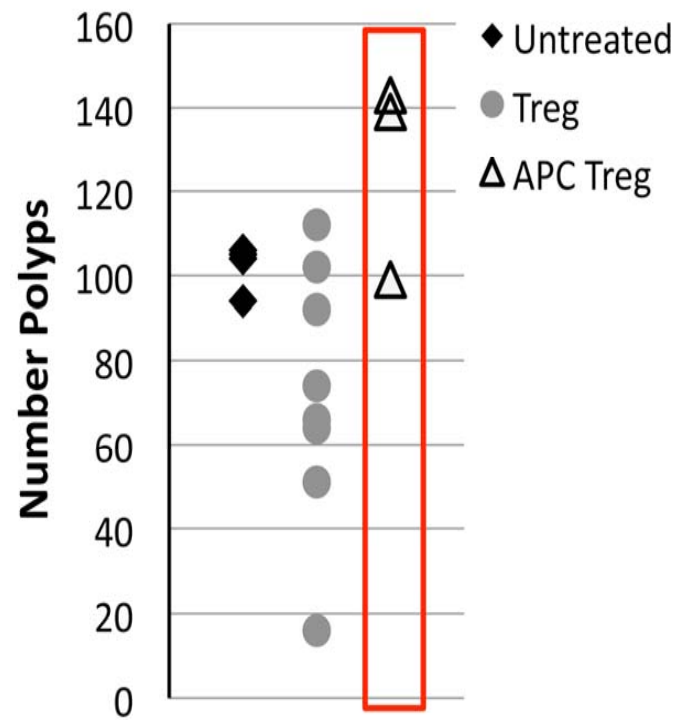
polyp-ridden donor

Δ Treg have TH17 characteristics (ROR γ T)

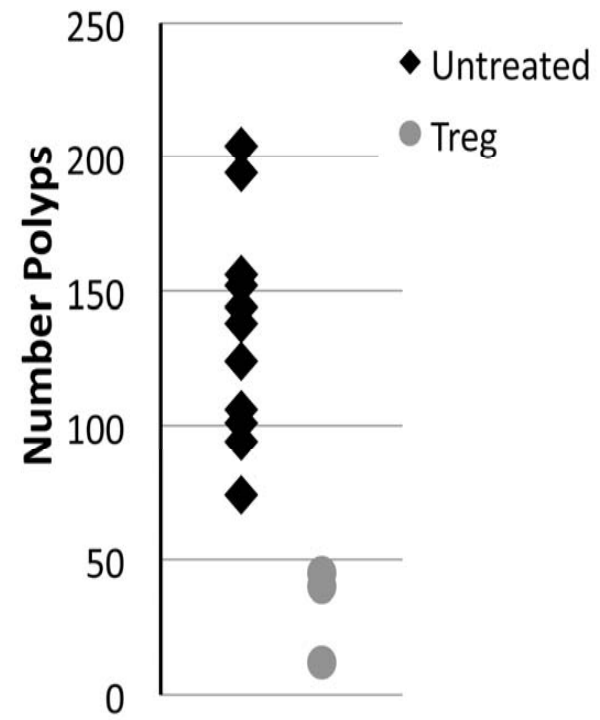


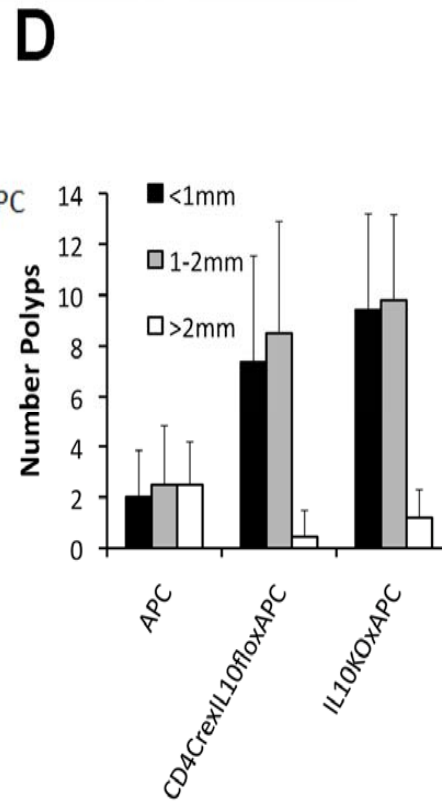
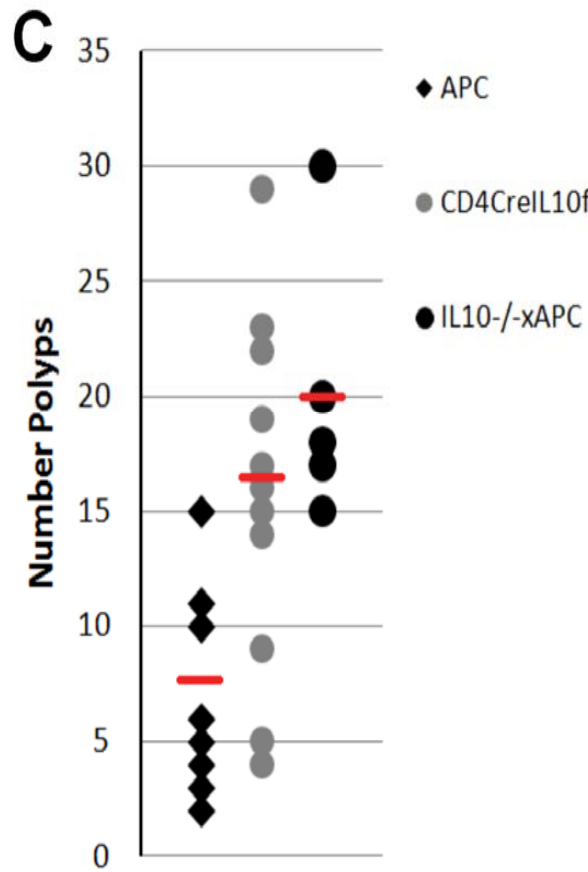
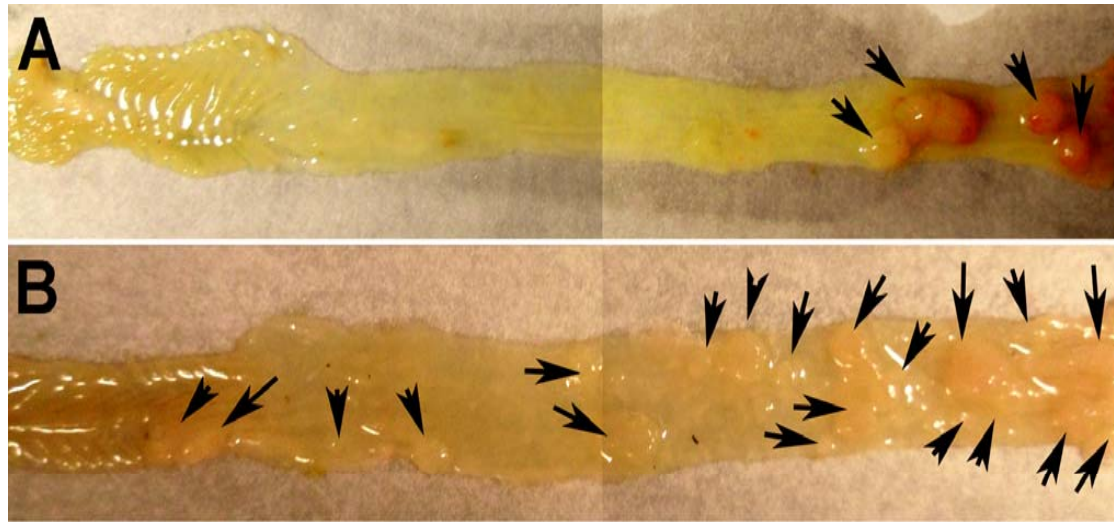
Gated on CD4⁺Foxp3⁺IRF4⁺

A Rag^{-/-}xAPC^{Δ468} Polyp Count

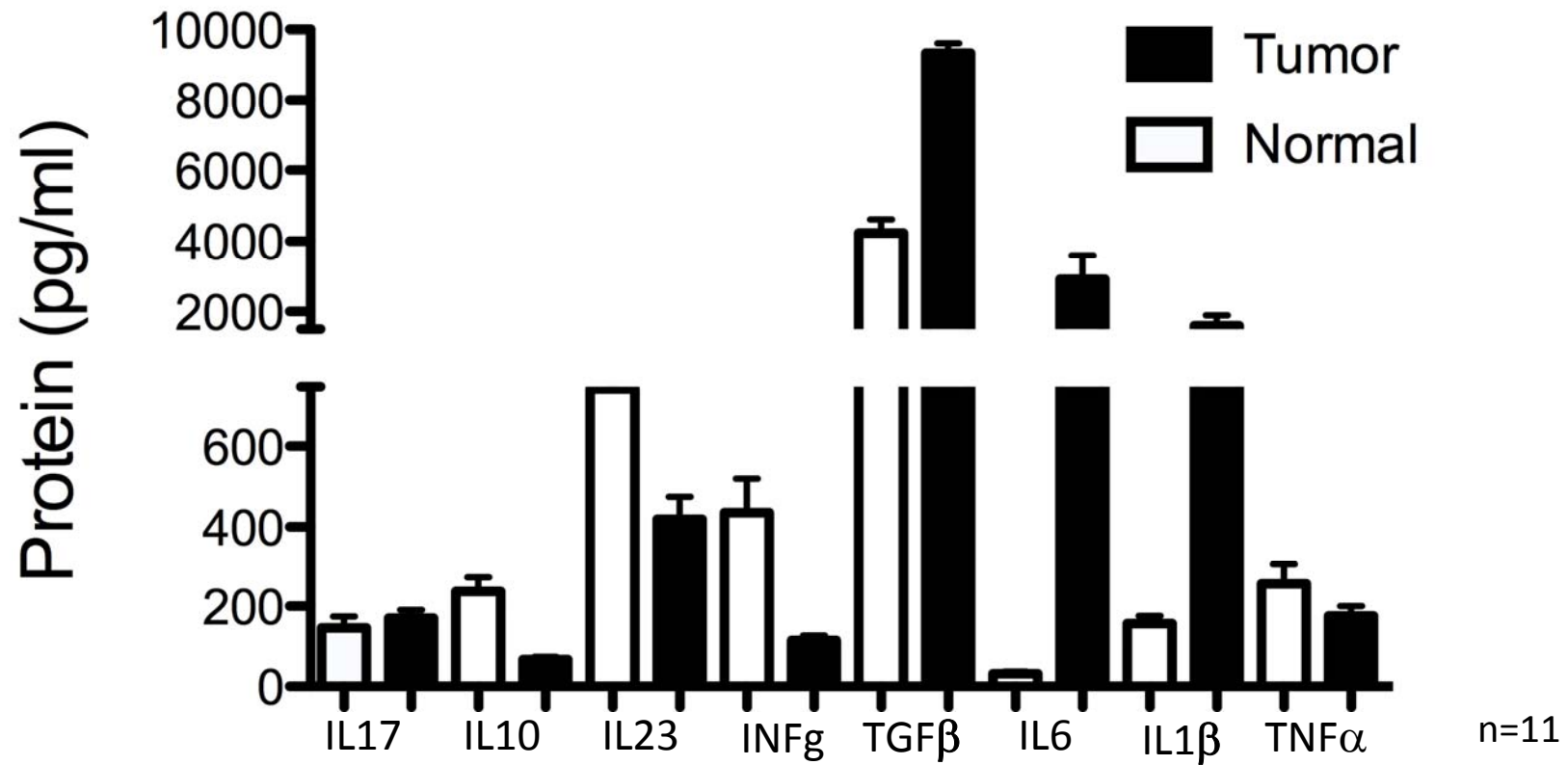


B APC^{Δ468} Polyp Count

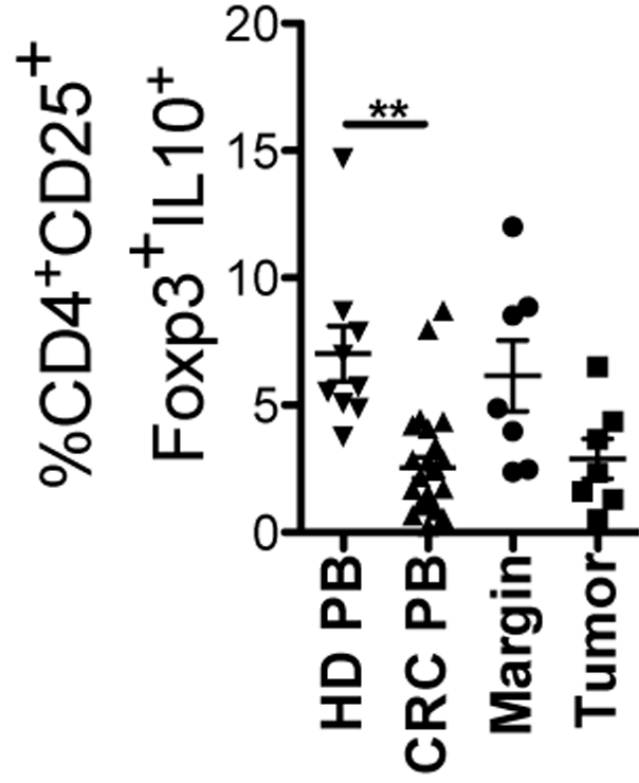
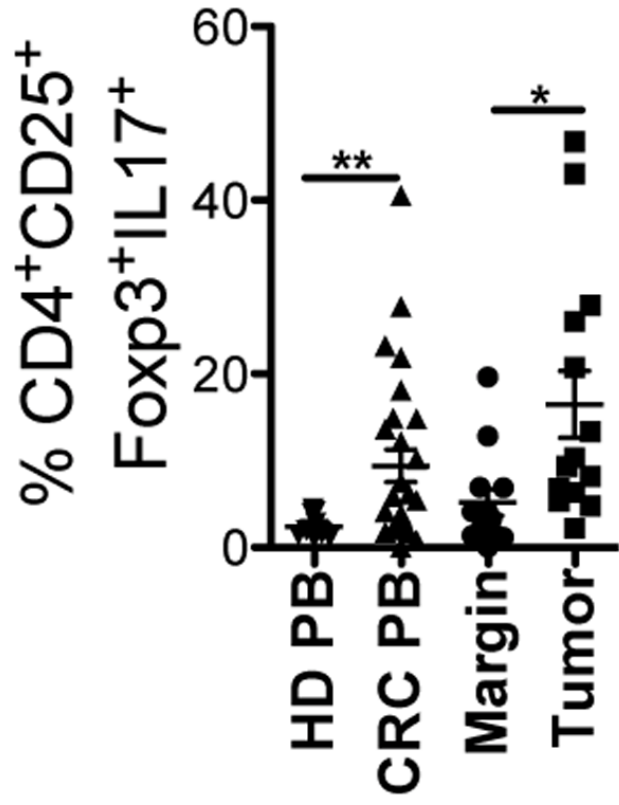


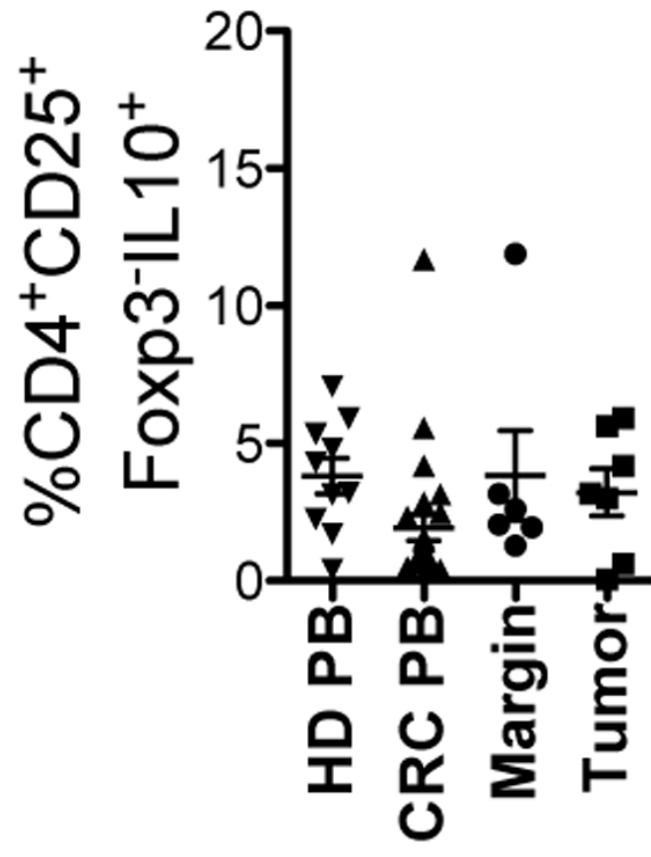
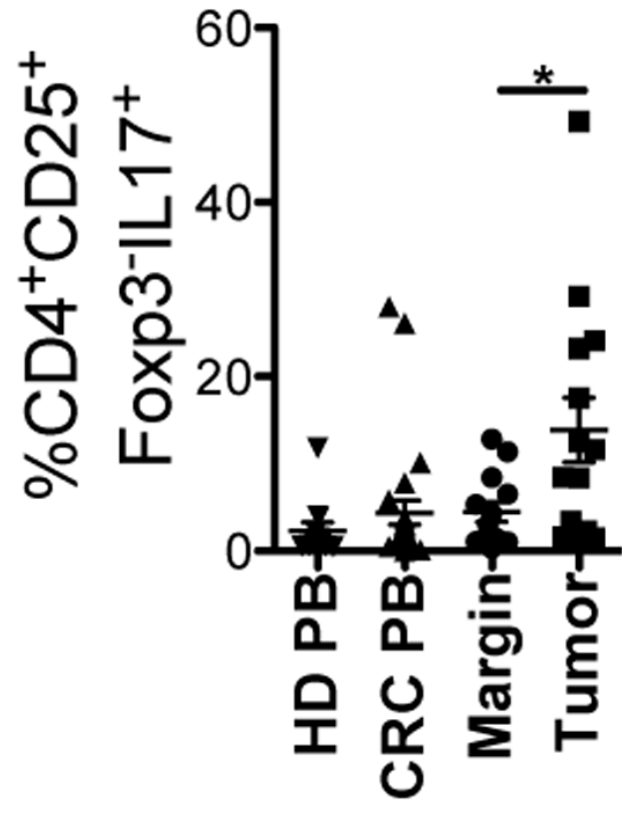


Cytokine milieu found in tumor lysates of CRC patients

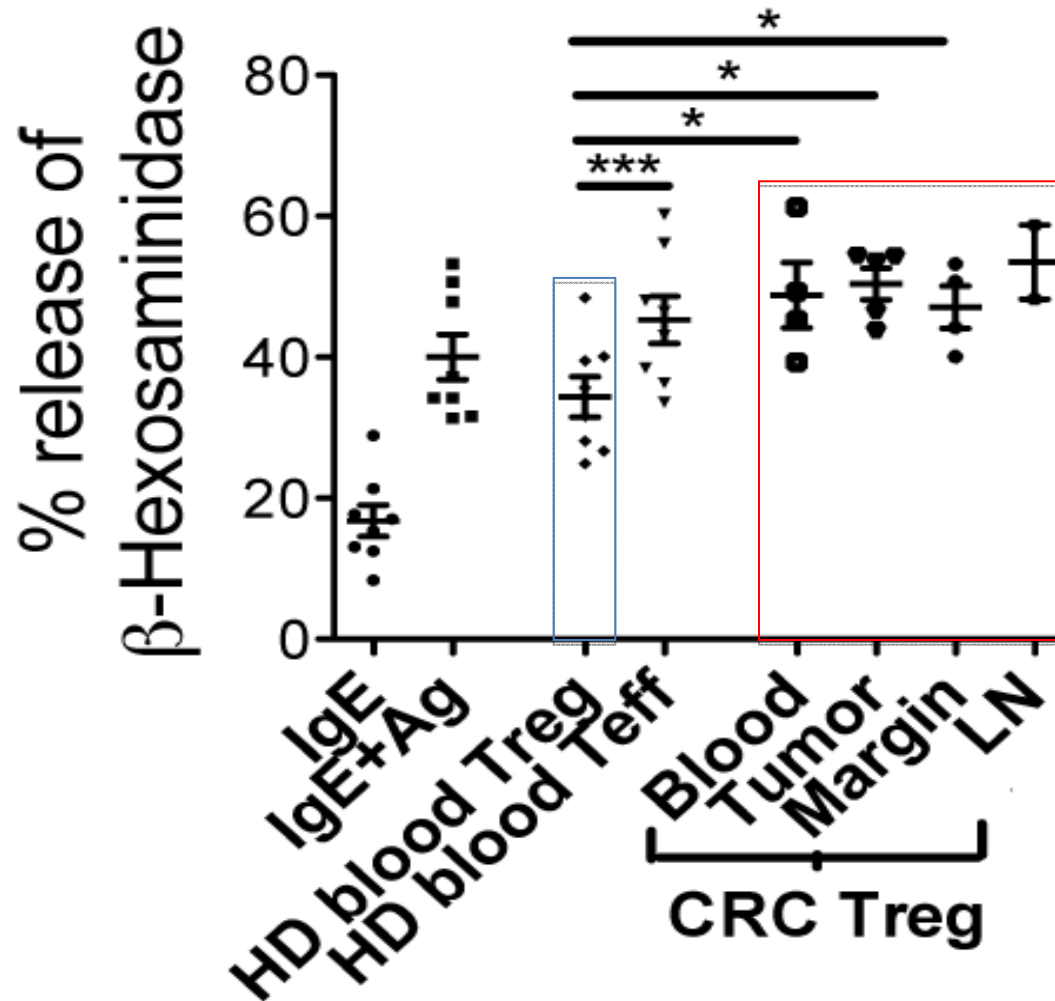


Increase in TGFβ, IL6 & IL1β supports IL17 conversion

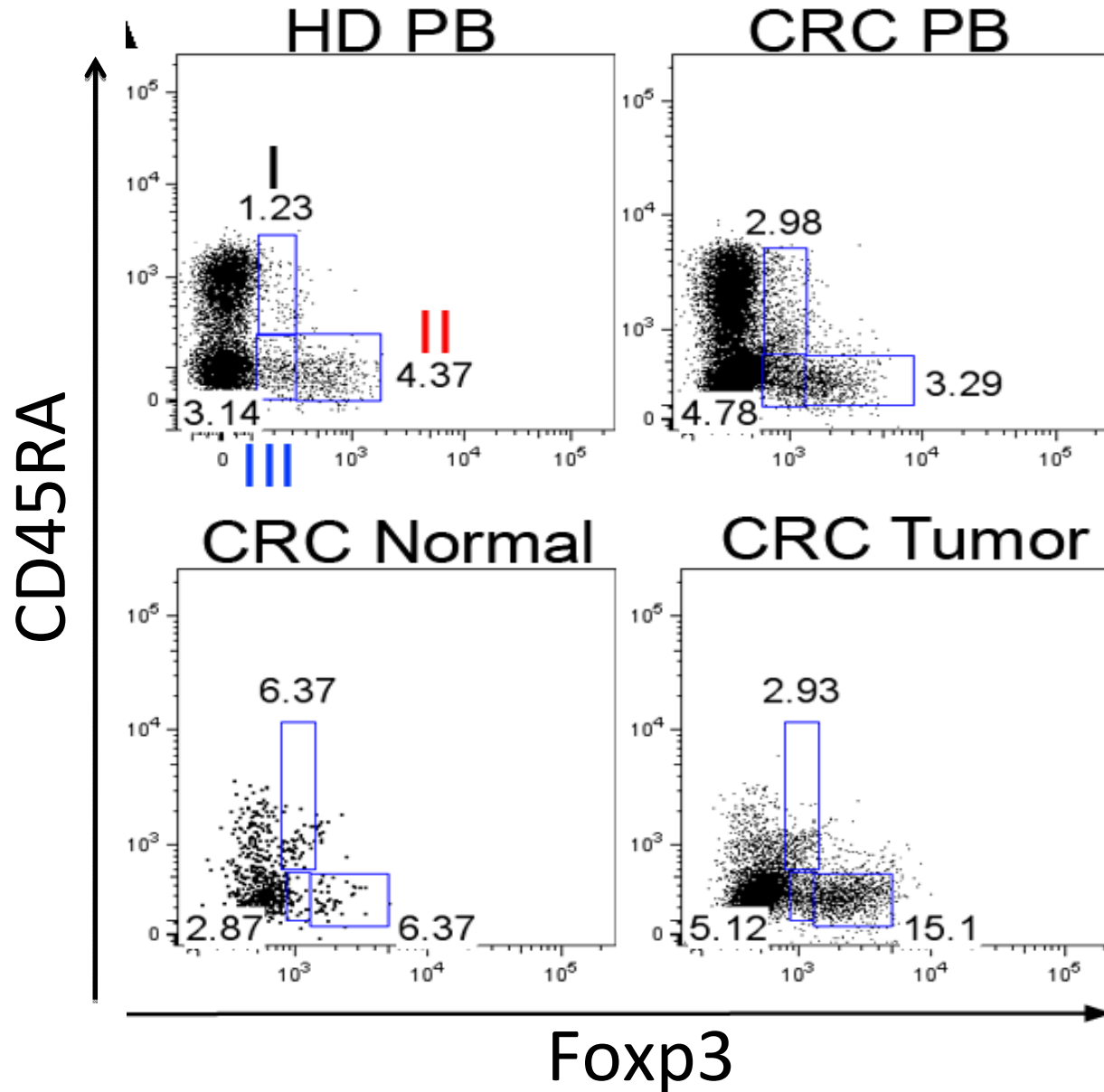


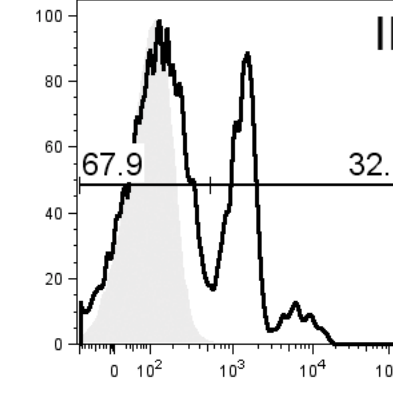
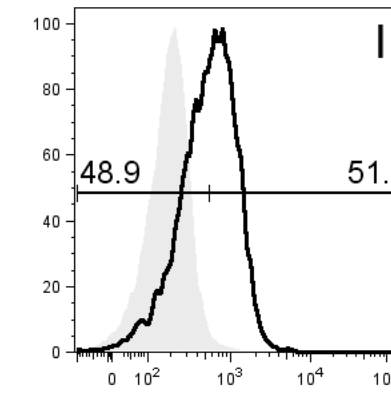
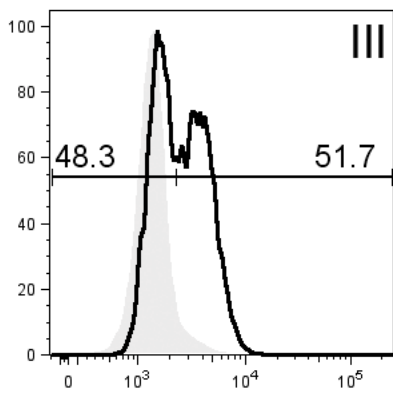
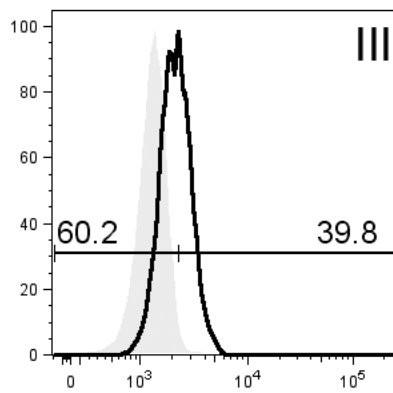
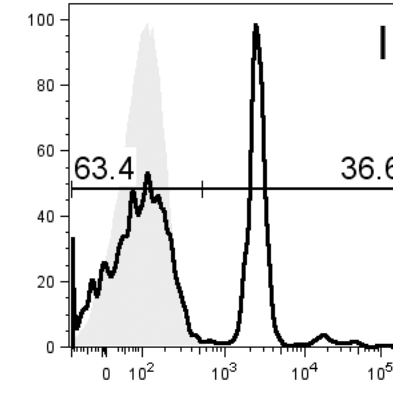
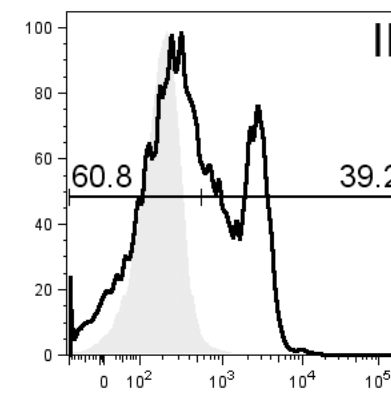
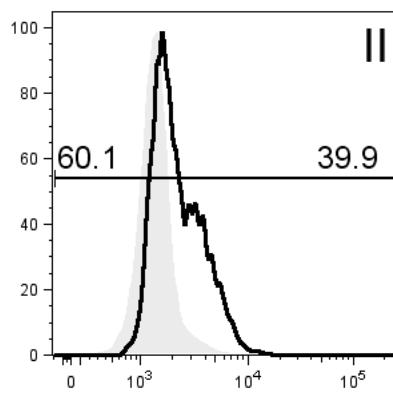
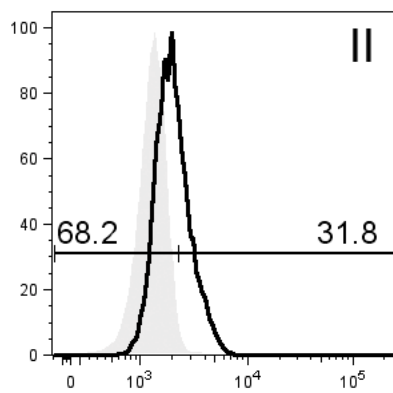
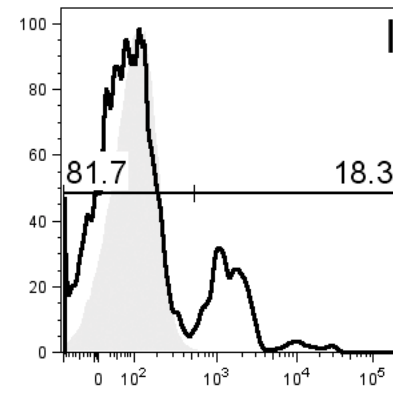
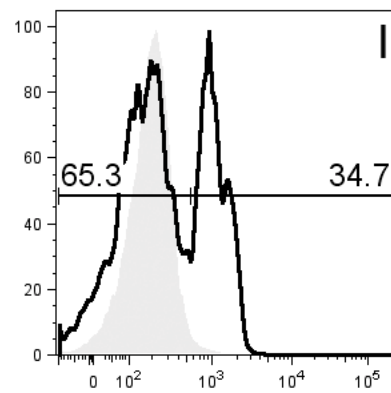
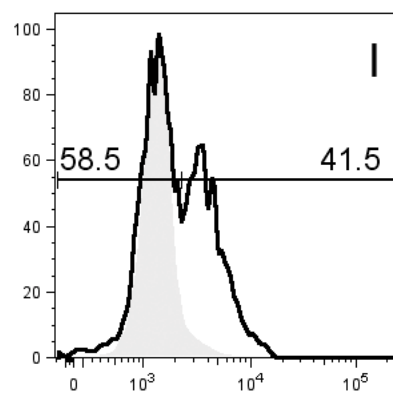
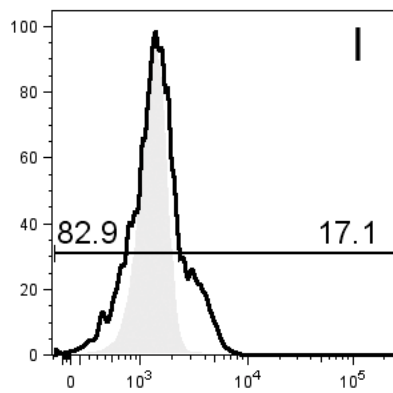


Treg from colon cancer patients are pro-inflammatory



Human Treg



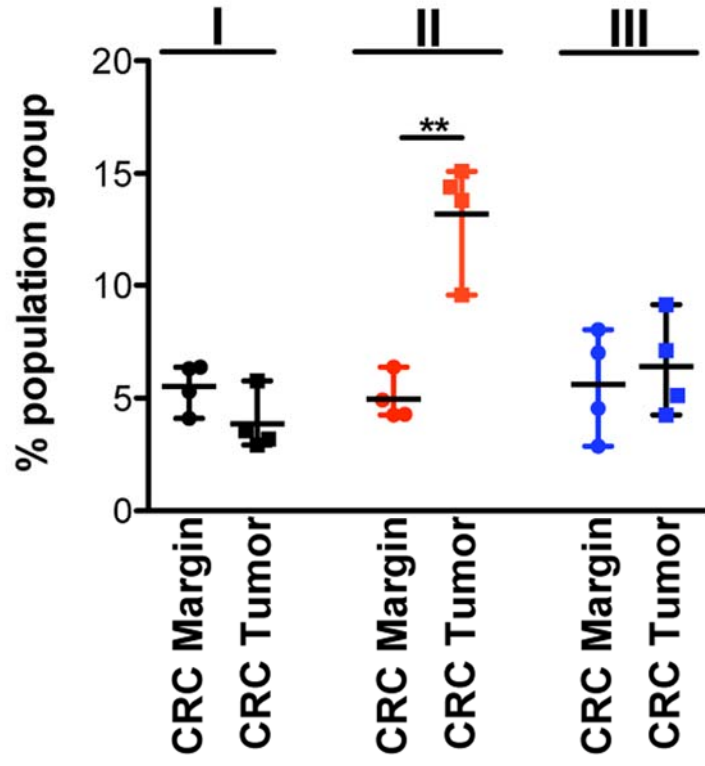
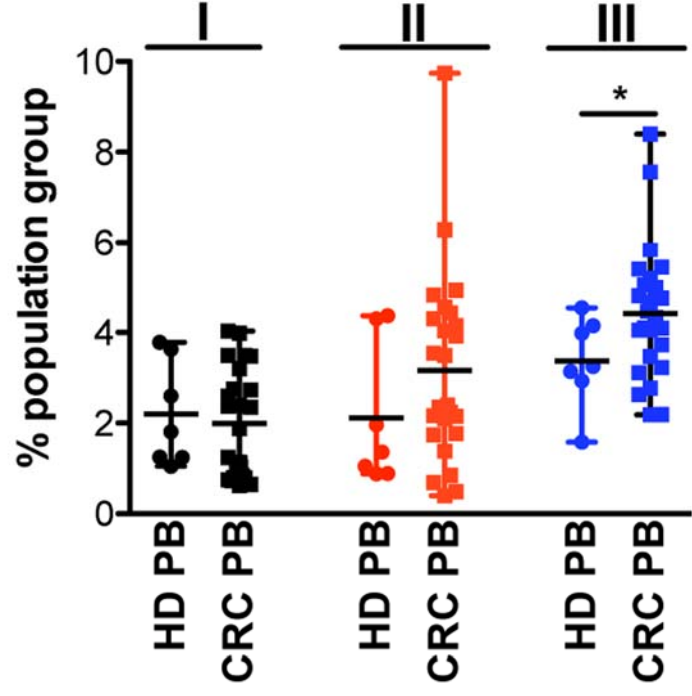


CCR6

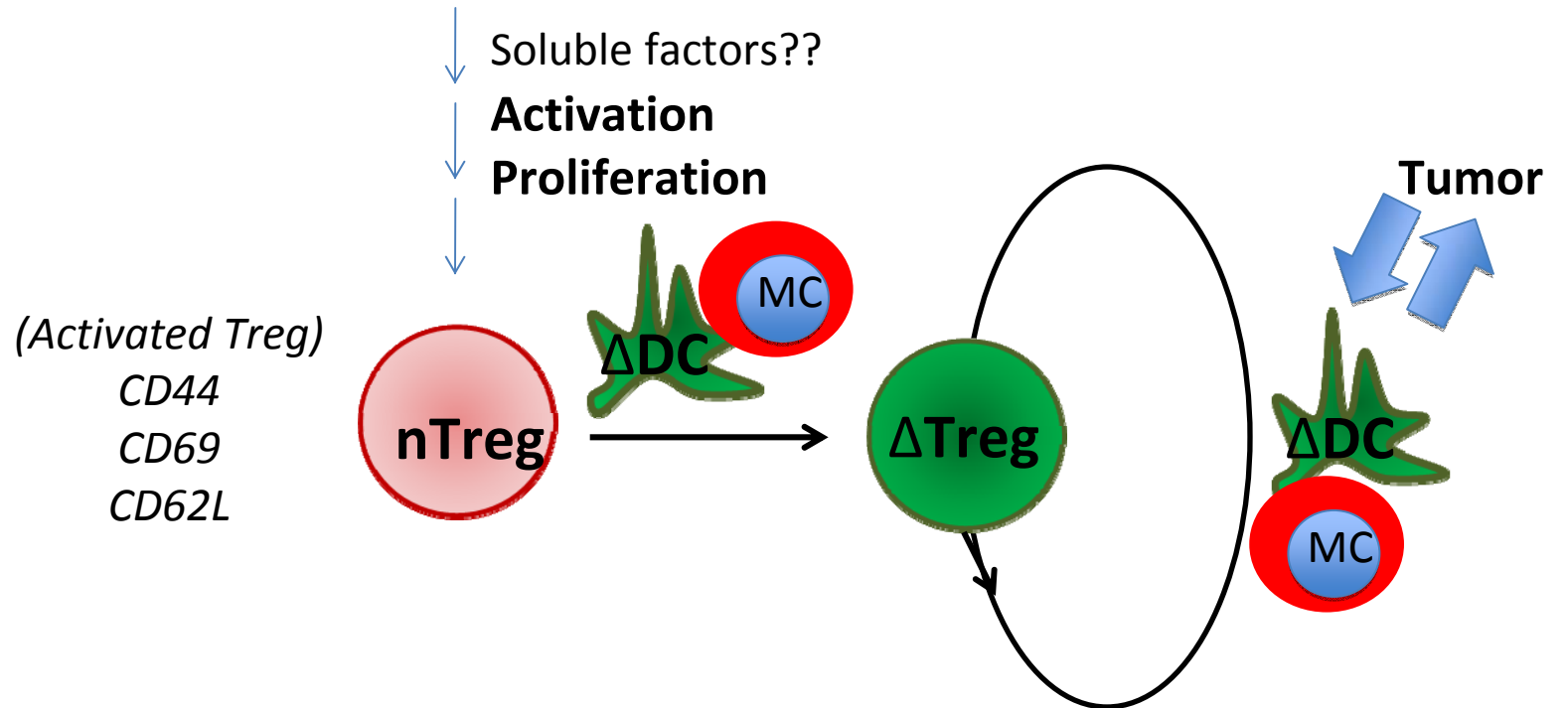
CXCR3

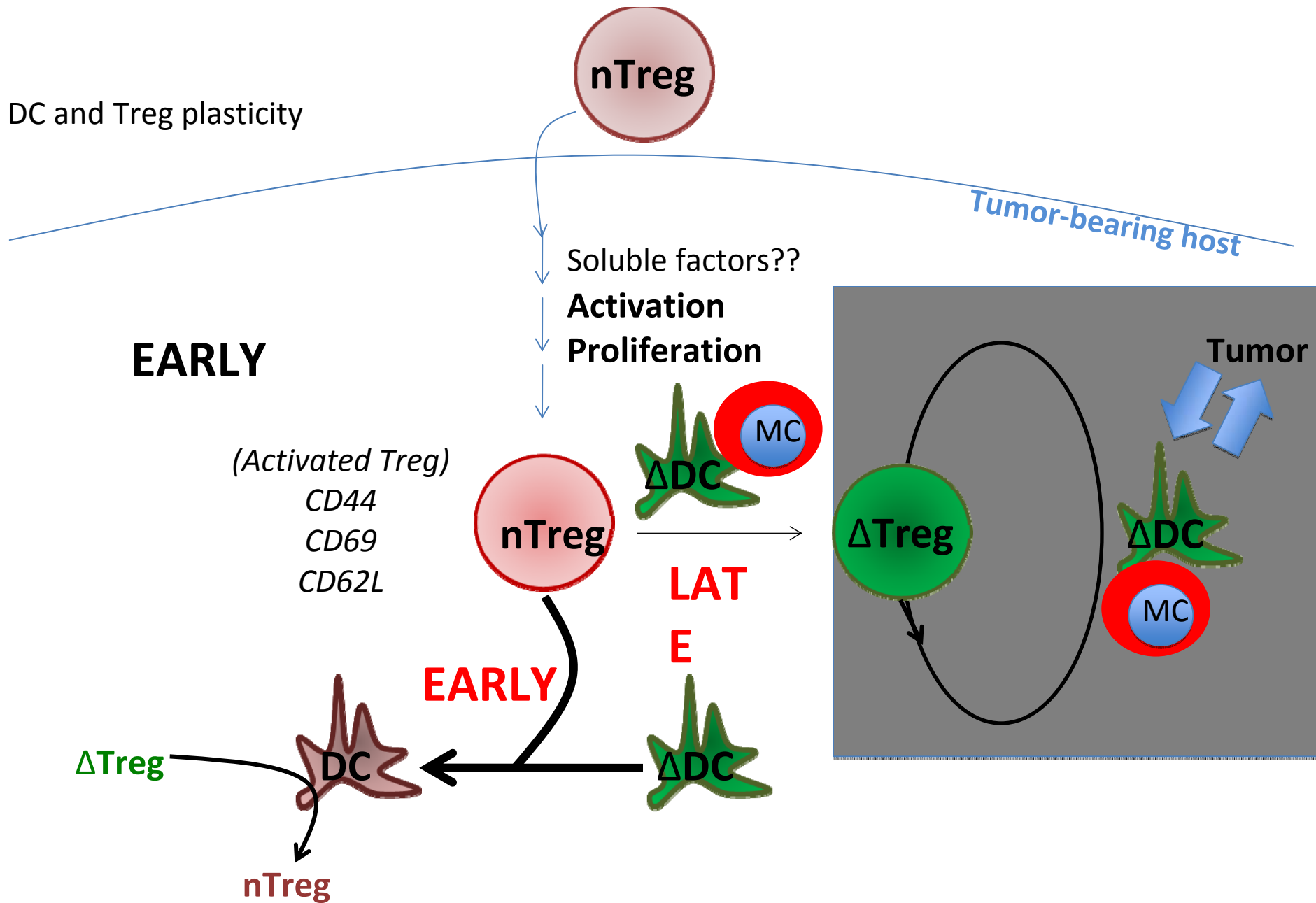
ROR γ t

IL17

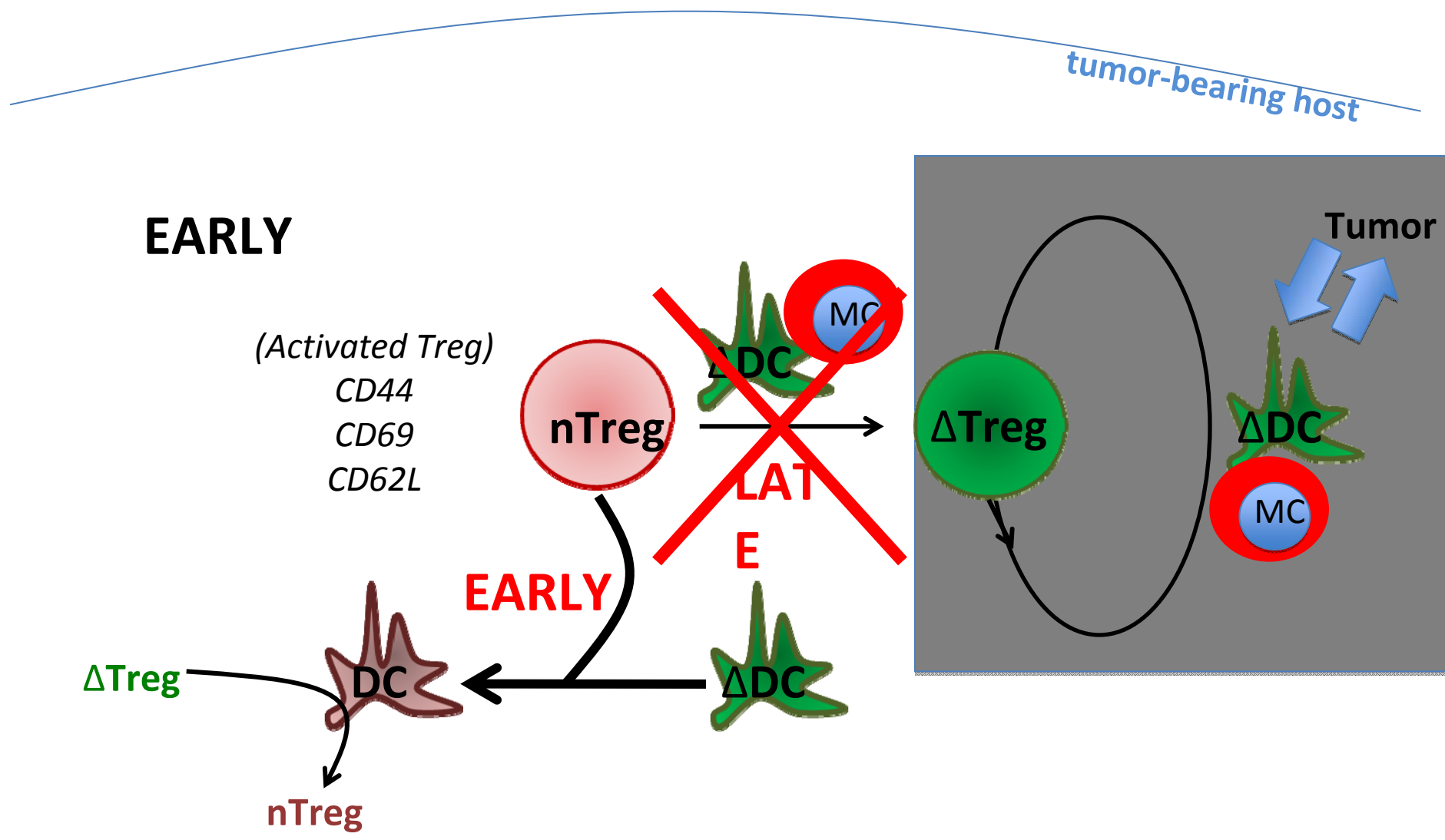


DC and Treg plasticity



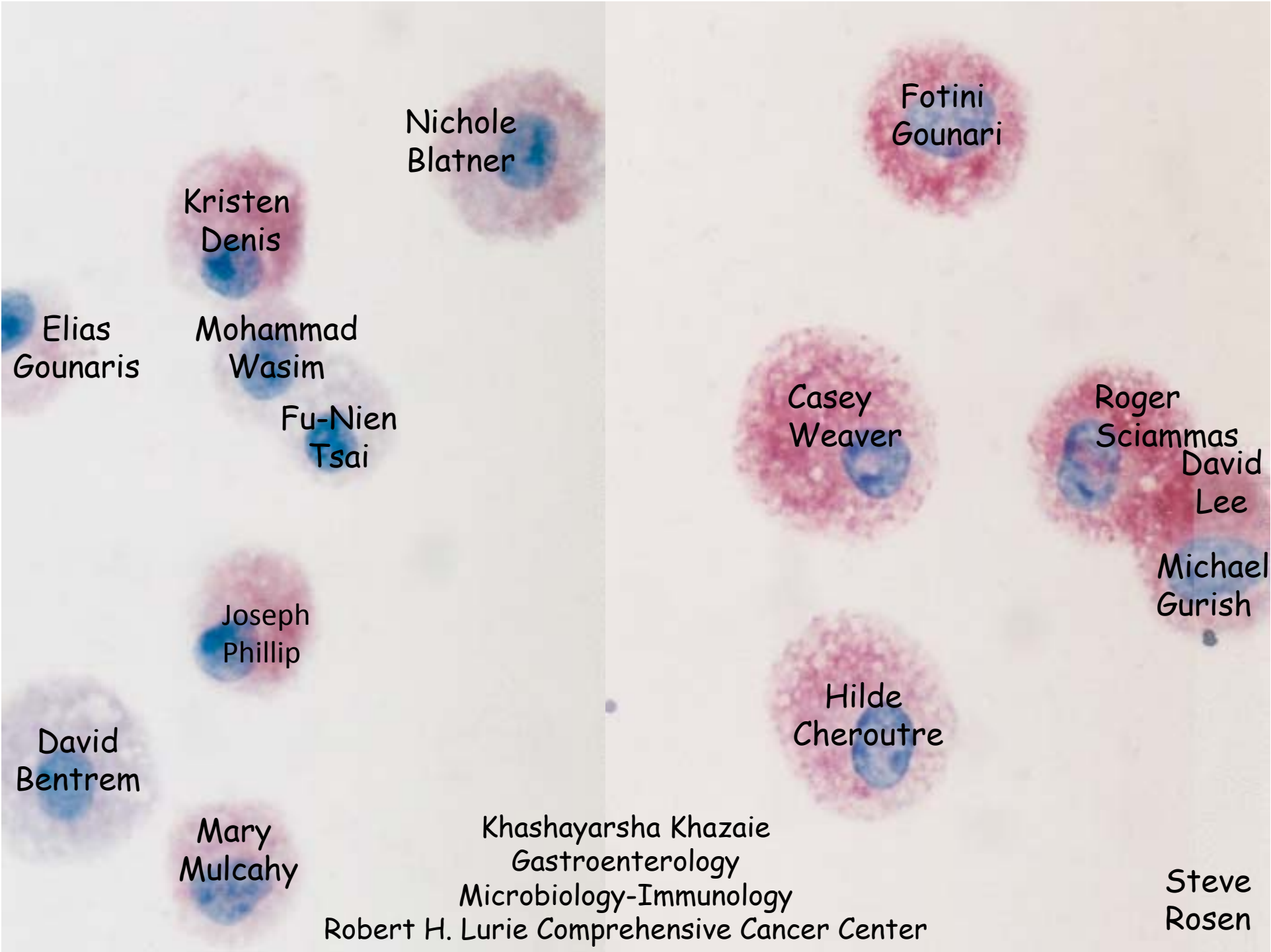


DC and Treg plasticity



Pro-inflammatory T-regulatory Cells in Colon Cancer.

- **Specific Aim 1: *Does the presence of “pathogenic” (pro-inflammatory Treg) in tumor correlate with clinical outcome?***
- **Specific Aim 2: *Do Treg pro-inflammatory properties segregate in different Treg sub-populations and are they reversible?***
- **Specific Aim 3: *What is the Gene Transcription Signature of CD4+Foxp3+ Treg in human colon cancer.***



Nichole
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