FcγRIIIA (CD16)-expressing monocytes mediate the depletion of tumor-infiltrating Tregs via ipilimumab-dependent ADCC in melanoma patients

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Tumor Microenvironment and Immunosuppression

Disclosures

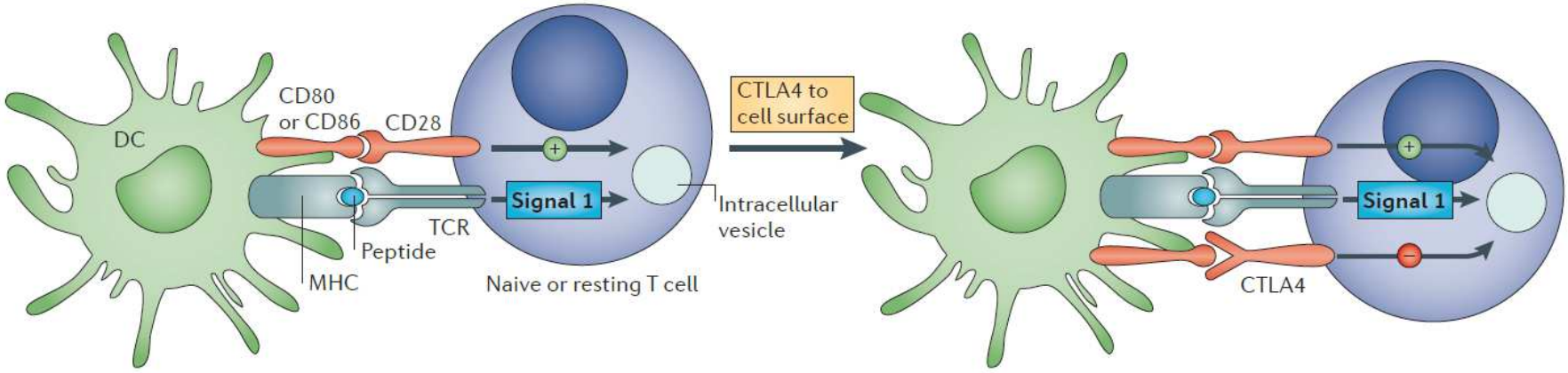
Emanuela ROMANO

The following relationships exist related to this presentation:

No Relationships to Disclose

CTLA-4 a key regulator of T cell activation and a failsafe against autoimmunity

ACTIVATION of T cell **MAINTENANCE of self-tolerance**



CTLA-4 (**cytotoxic T-lymphocyte-associated antigen 4**) is an immune checkpoint molecule that down regulates T-cell responses and is expressed at low levels on naïve T cells and constitutively expressed at regulatory T cells (T_{regs}).

Pardoll, 2012 | Nature Reviews

CTLA-4 a key regulator of T cell activation and failsafe against autoimmunity – mouse model data

1. CTLA-$4^{-/-}$ mice die at 3-4 wks due to systemic immune disregulation and lymphoprolipheration

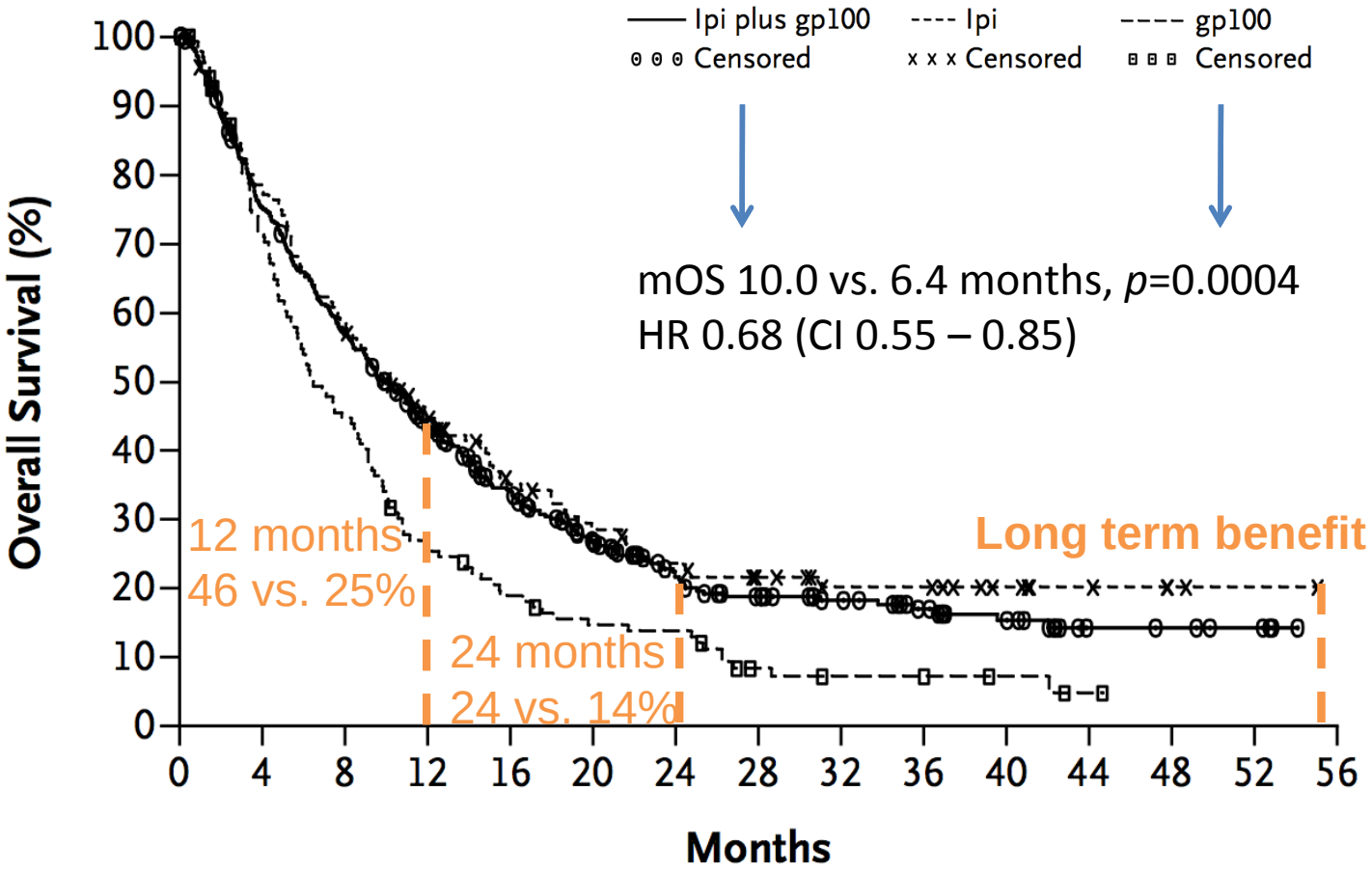
2. Disease in CTLA-$4^{-/-}$ mice was abrogated when CD28 pathway was interrupted by blockade or deficiency of their shared ligands CD80 and CD86

3. The notion of CTLA-4 as an intrinsic negative signal was challenged by CTLA-$4^{w/t}$ and CTLA-$4^{-/-}$ chimeras that showed a normal phenotype!

4. Treg-deficient and CTLA-$4^{-/-}$ mice share similar phenotype

5. CTLA-4 serves as a major mechanism of Treg suppression

Ipilimumab (human IgG1) phase III: survival data



Hodi & al, NEJM, 2010

CTLA-4 blockade increases CD8 T cell activation and CD8/Treg ratio in the TME

Research article

CTLA4 blockade and GM-CSF combination immunotherapy alters the intratumor balance of effector and regulatory T cells

Sergio A. Quezada, Karl S. Peggs, Michael A. Curran, and James P. Allison

Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.

2006

Cancer Therapy: Clinical

Clinical Cancer Research

CTLA4 Blockade Induces Frequent Tumor Infiltration by Activated Lymphocytes Regardless of Clinical Responses in Humans

Rong Rong Huang[1], Jason Jalil[2], James S. Economou[3,4], Bartosz Chmielowski[2], Richard C. Koya[3], Stephen Mok[3], Hooman Sazegar[2], Elizabeth Seja[2], Arturo Villanueva[2], Jesus Gomez-Navarro[5], John A. Glaspy[2,4], Alistair J. Cochran[1], and Antoni Ribas[2,3,4]

2011

PNAS

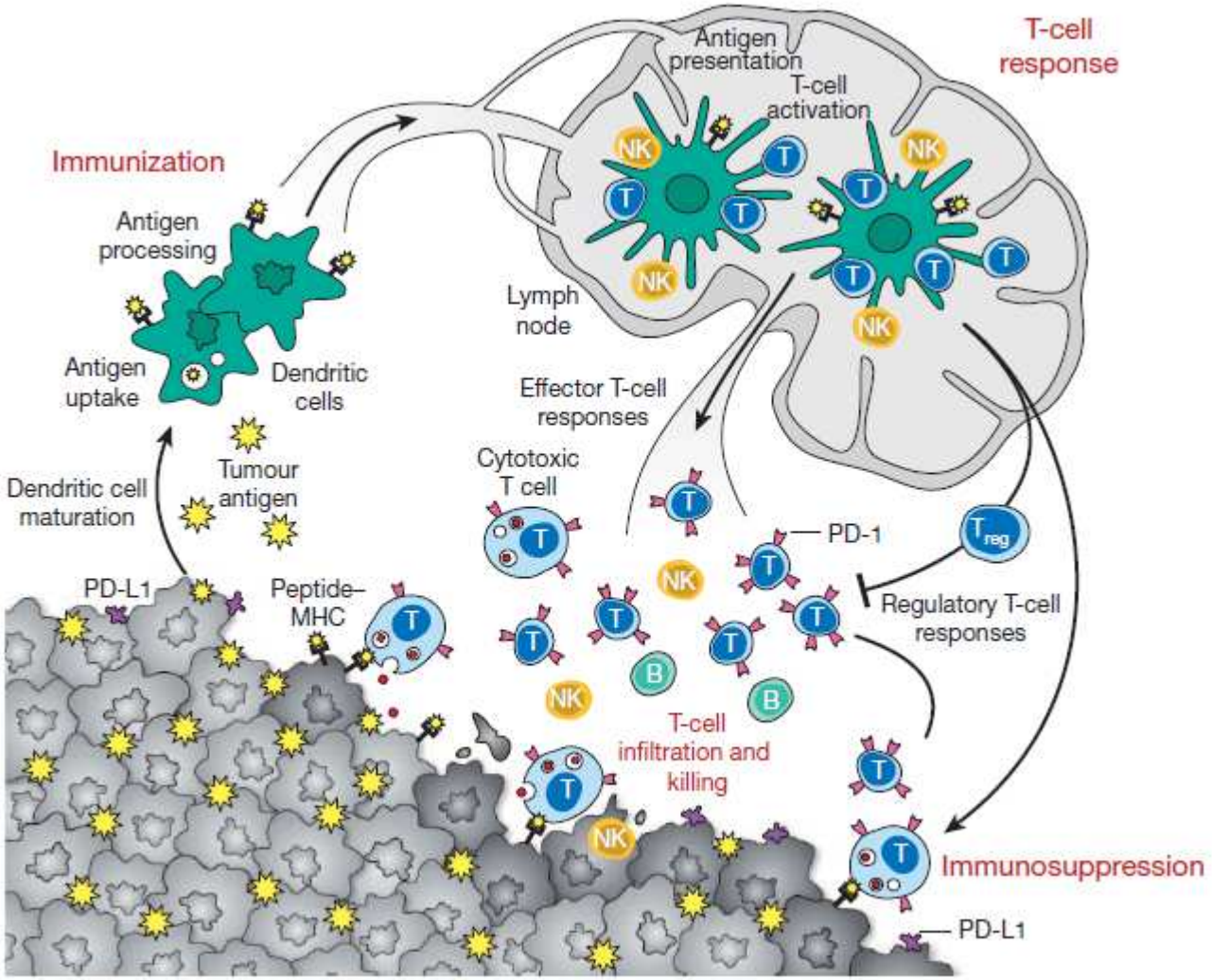
Immunologic and clinical effects of antibody blockade of cytotoxic T lymphocyte-associated antigen 4 in previously vaccinated cancer patients

F. Stephen Hodi[a,b], Marcus Butler[a], Darryl A. Oble[c], Michael V. Seiden[d,e], Frank G. Haluska[f], Andrea Kruse[a], Suzanne MacRae[a], Marybeth Nelson[a], Christine Canning[a], Israel Lowys[a], Alan Kormans, David Lautz[b], Sara Russell[b], Michael T. Jaklitsch[b], Nikhil Ramaiya[g], Teresa C. Chen[i], Donna Neuberg[k], James P. Allison[b,j], Martin C. Mihm[c], and Glenn Dranoff[a]

2008

What's the mechanism of such change in CD8/Treg ratio?

Cross-talk between tumor and immune cells



Mellman I, Nature 2011

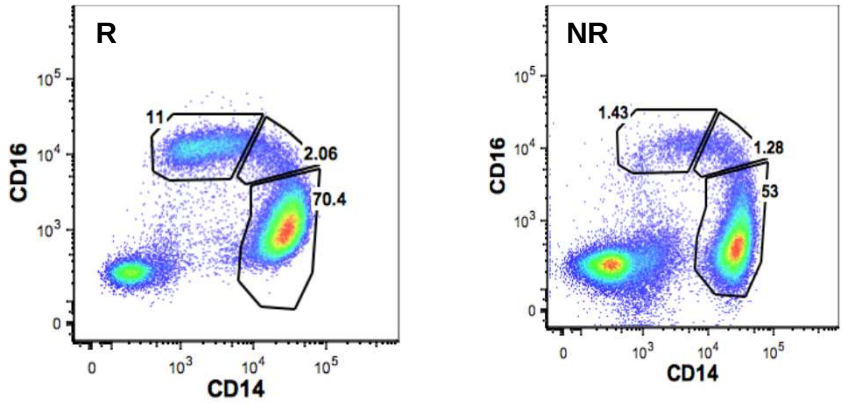
Immunological study in melanoma patients treated with Ipilimumab

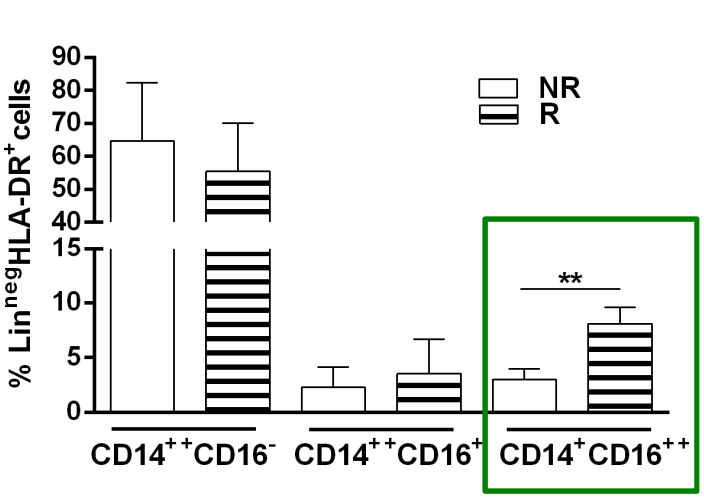
Patient population

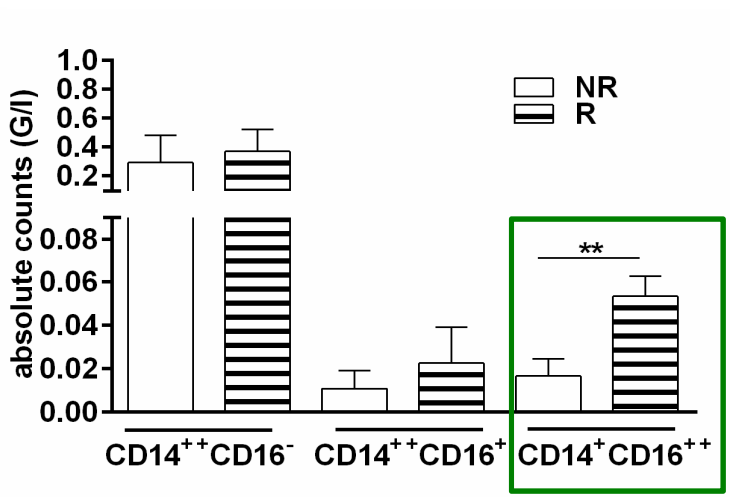
- 29 melanoma patients undergoing ipilimumab treatment
  - ✓ 14 non-responders (NR)
  - ✓ 15 objective responders (R)
- tumor response was assessed by immune-related response criteria

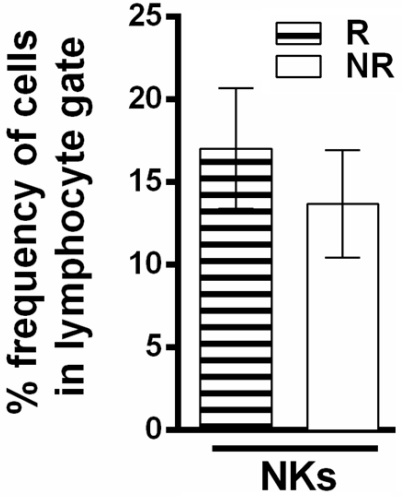
Variable	N (%)
Mean age - yr	62
Gender	
Male	21 (72%)
Female	8 (28%)
ECOG performance status	
0	17 (59%)
1	12 (41%)
M stage	
M1a	2 (7%)
M1b	6 (21%)
M1c	21 (72%)
No. of prior lines of systemic therapies for metastatic disease	
1	28 (97%)
2	1 (3%)
Ipilimumab cycles	
4	23 (79%)
3	3 (10%)
2	3 (10%)
1	0 (0%)

Patients responding to ipilimumab display the highest frequency of $CD14^{+}CD16^{++}$ monocytes at baseline!



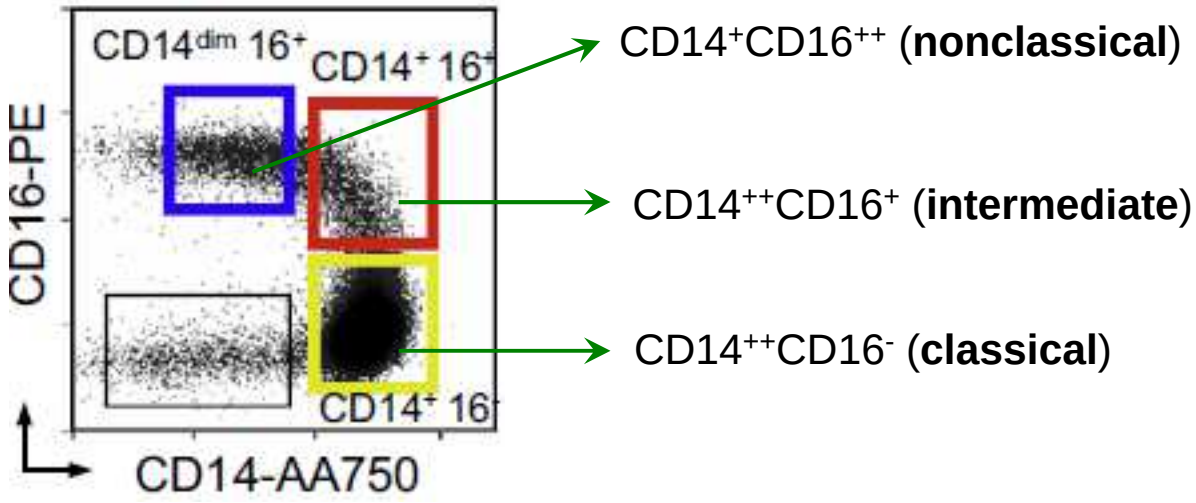






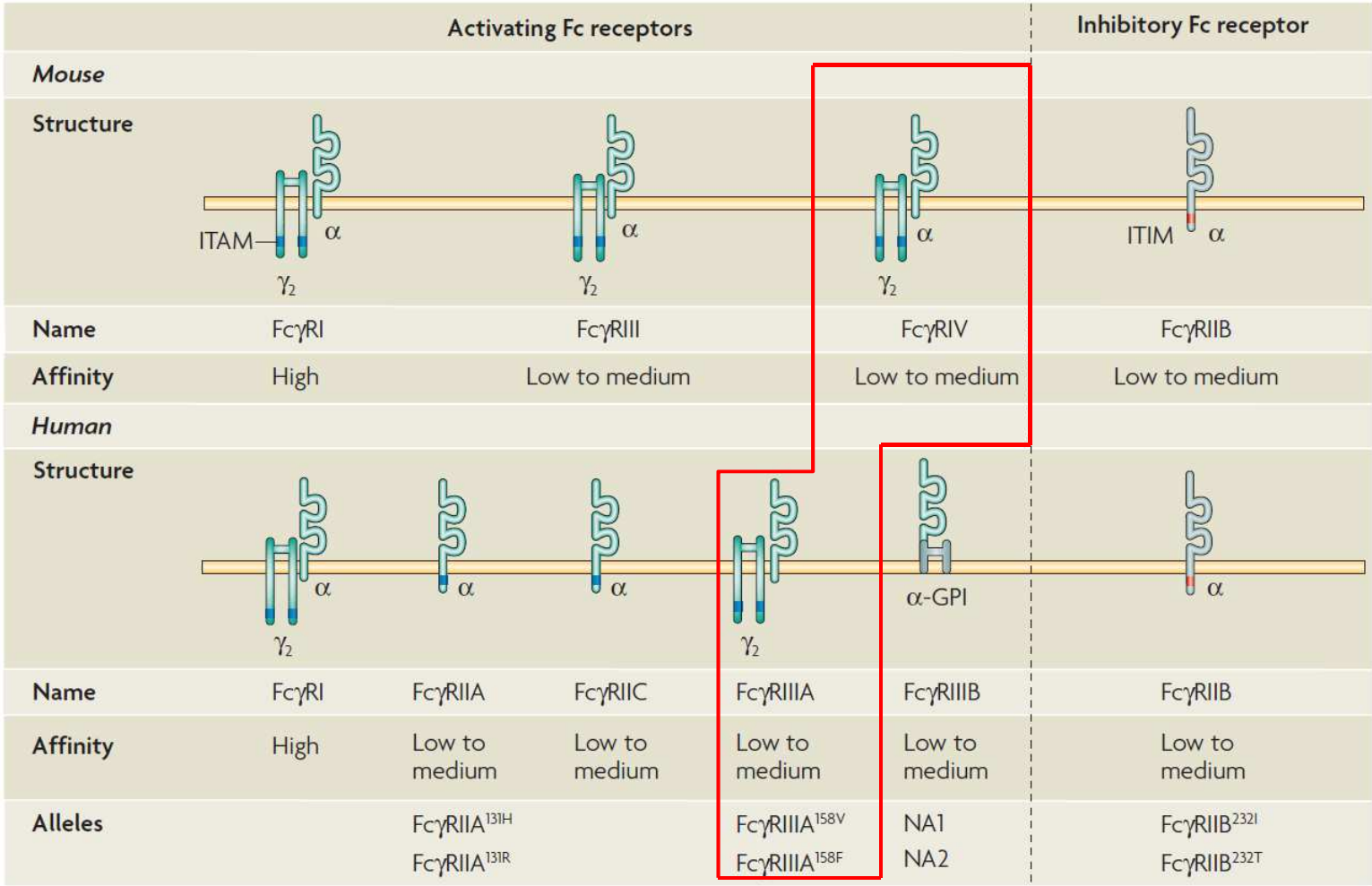
What do we need to know about monocytes?

- Human monocytes can be divided into three subpopulations
- Populations are characterized by different expression level of CD16 and CD14
- The classification has been approved by the Nomenclature Committee of the International Union of Immunological Societies



Cros et al., 2010 (*Immunity*); Ziegler-Heitbrock et al., 2010 (*Blood*)

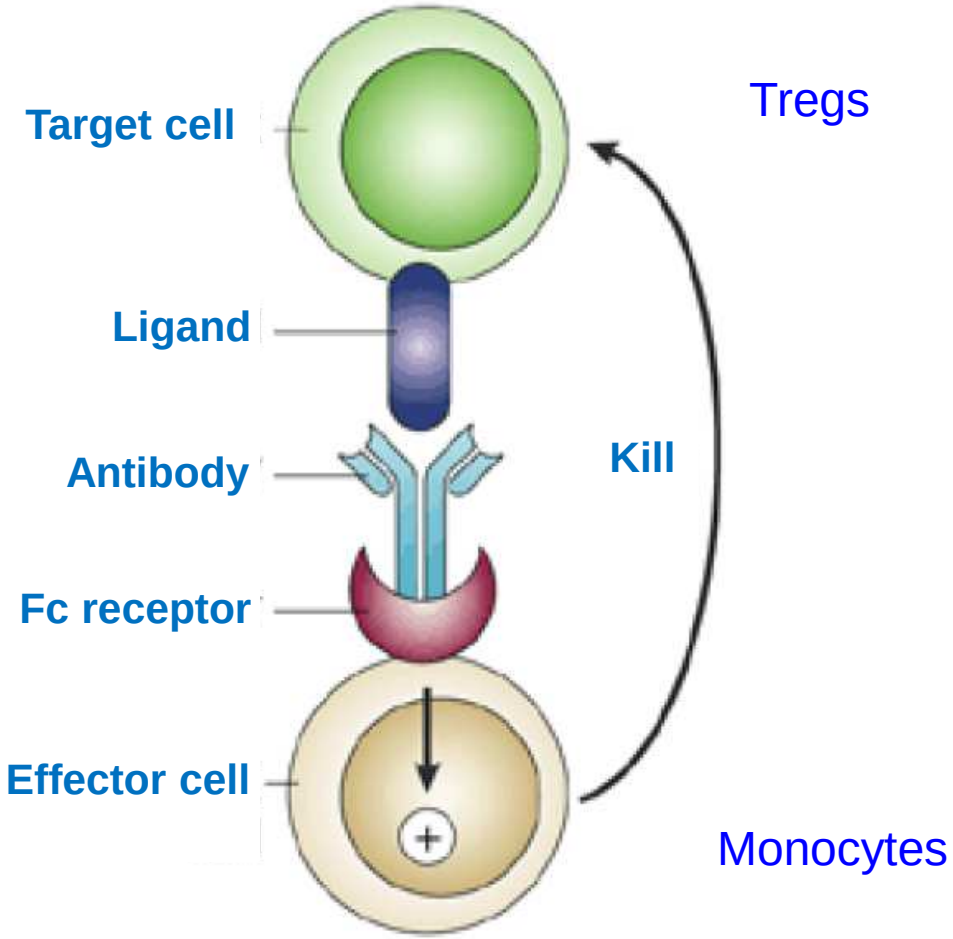
Human FcγRIIIA (CD16), a homologue of murine FcγRIV, is a major mediator of ADCC



Hypothesis

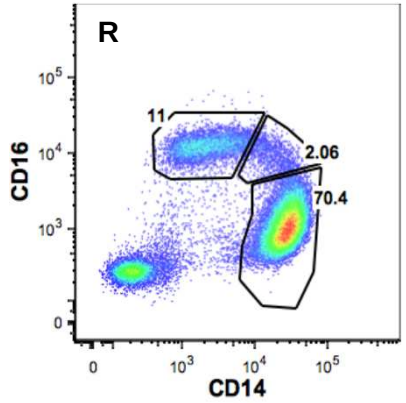
Nonclassical monocytes mediate the depletion of tumor infiltrating T_{regs} via ipilimumab-dependent ADCC in melanoma patients

Antibody-dependent cellular cytotoxicity (ADCC)

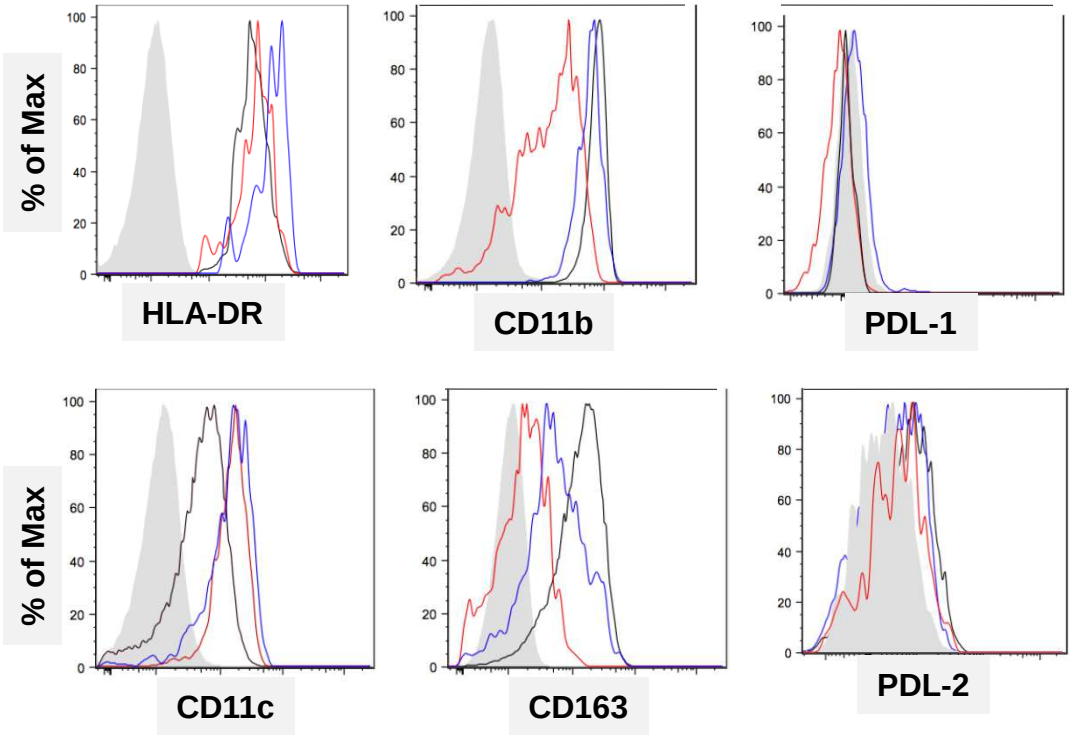


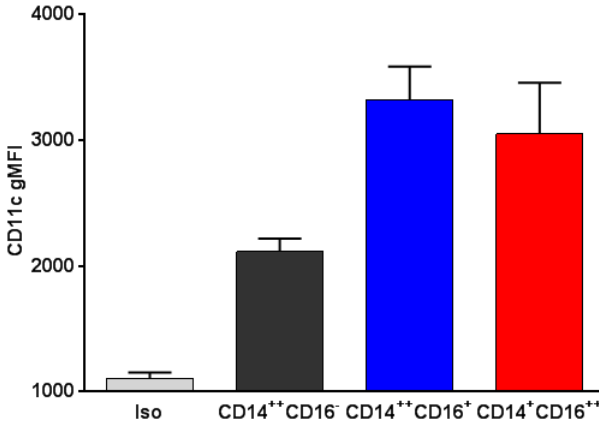
Adapted from Nature Reviews | Immunology

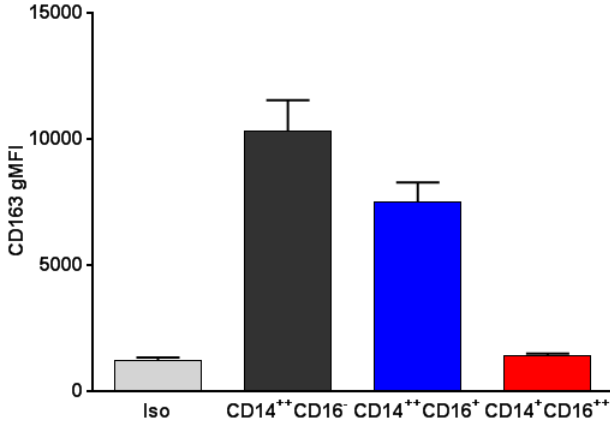
Phenotype of peripheral monocytes

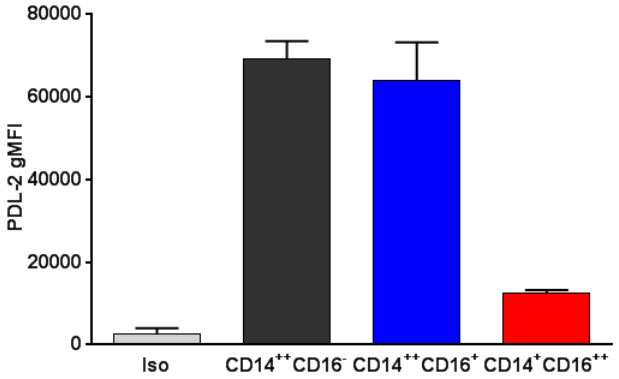


CD14^{+}CD16^{++}
CD14^{++}CD16^{+}
CD14^{++}CD16^{-}

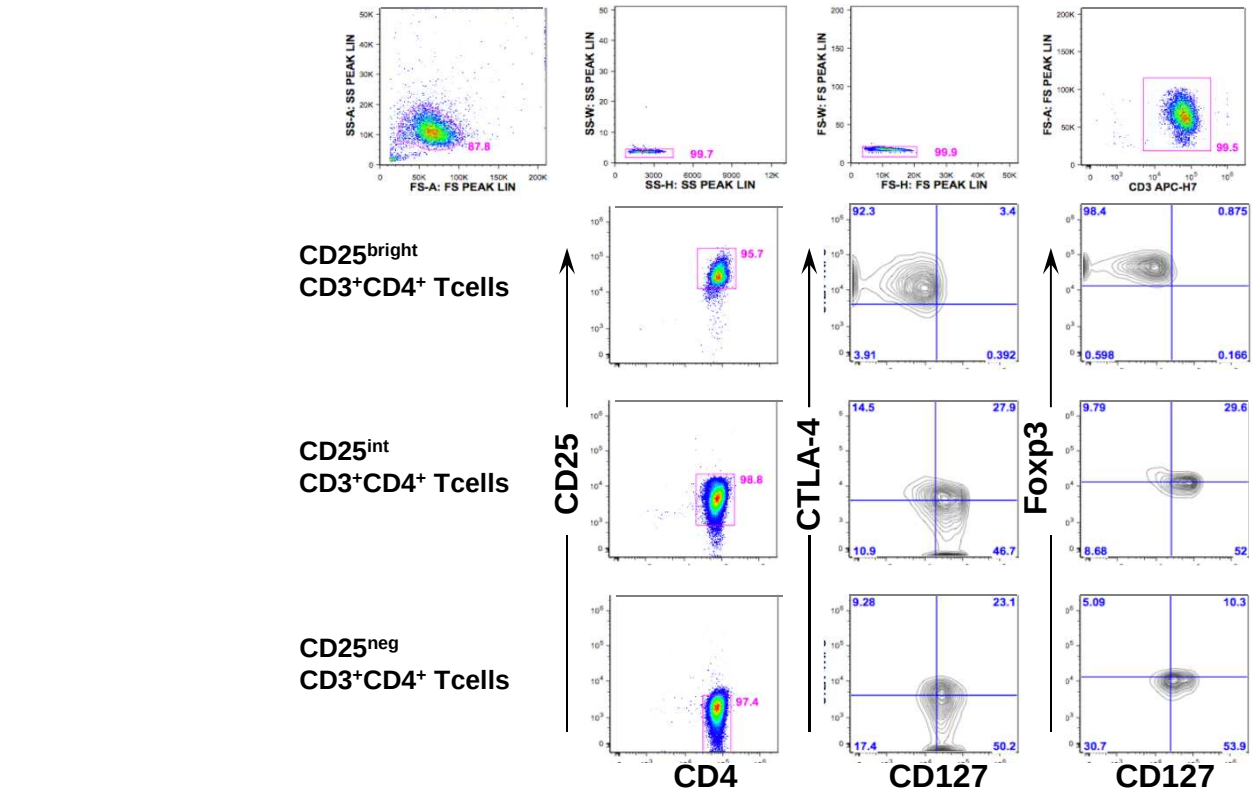




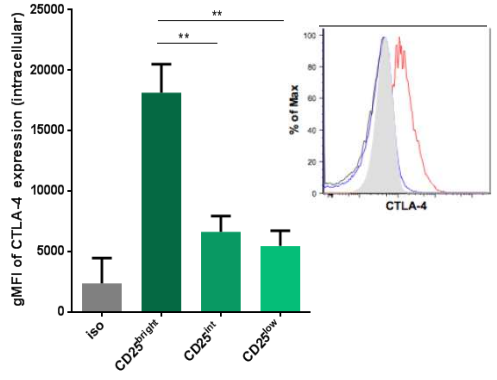




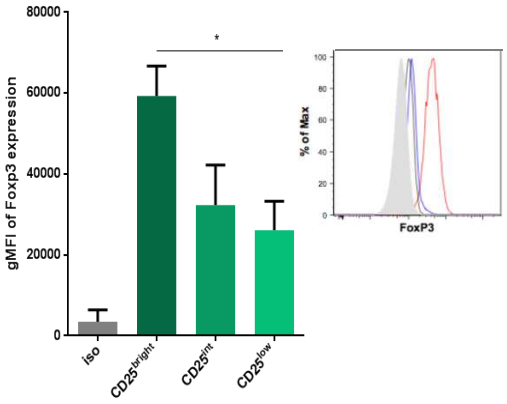
Postsort flow cytometric analysis of $CD3^{+}CD4^{+}CD25^{bright,int,neg}$ T cell subgroups



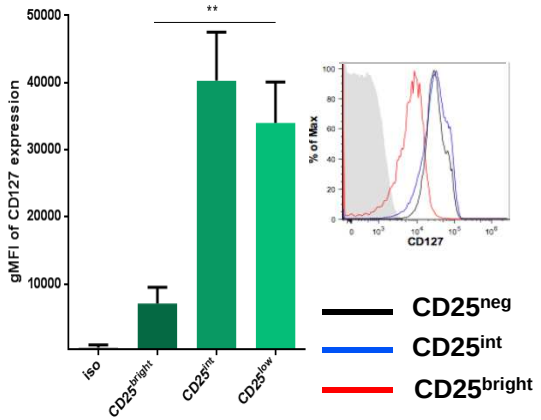
CTLA-4



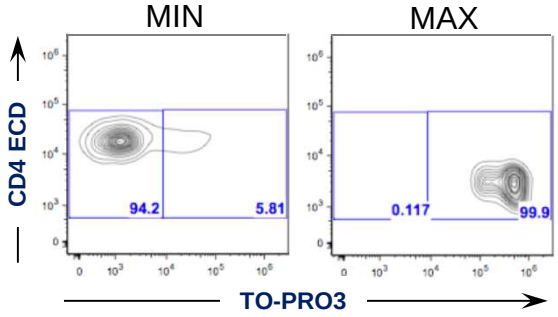
Foxp3

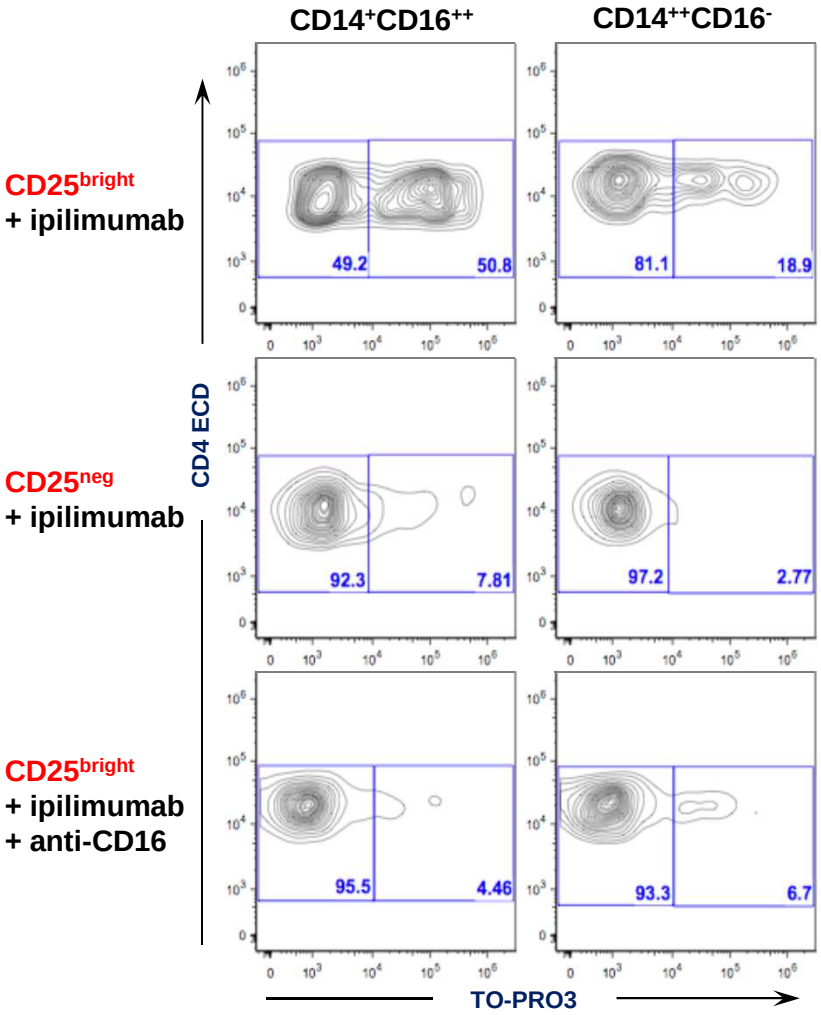


CD127

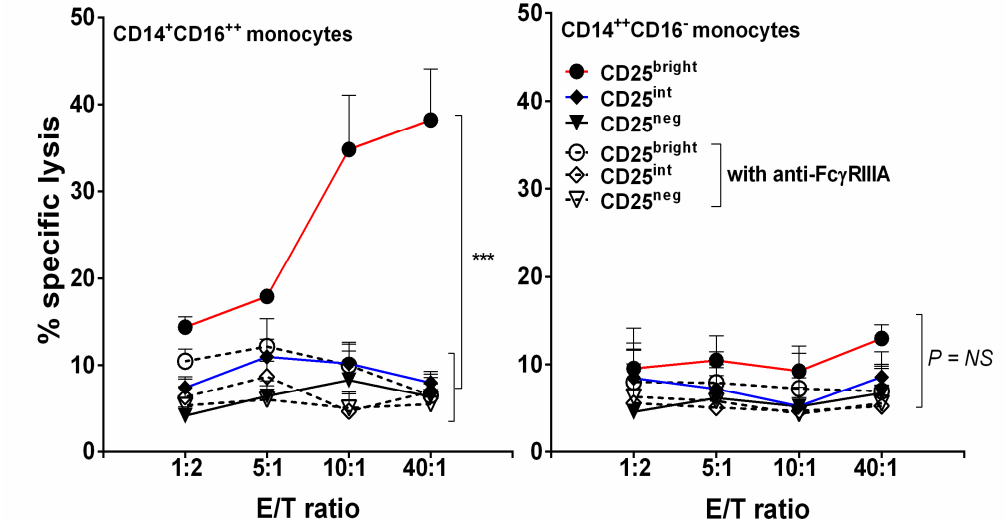


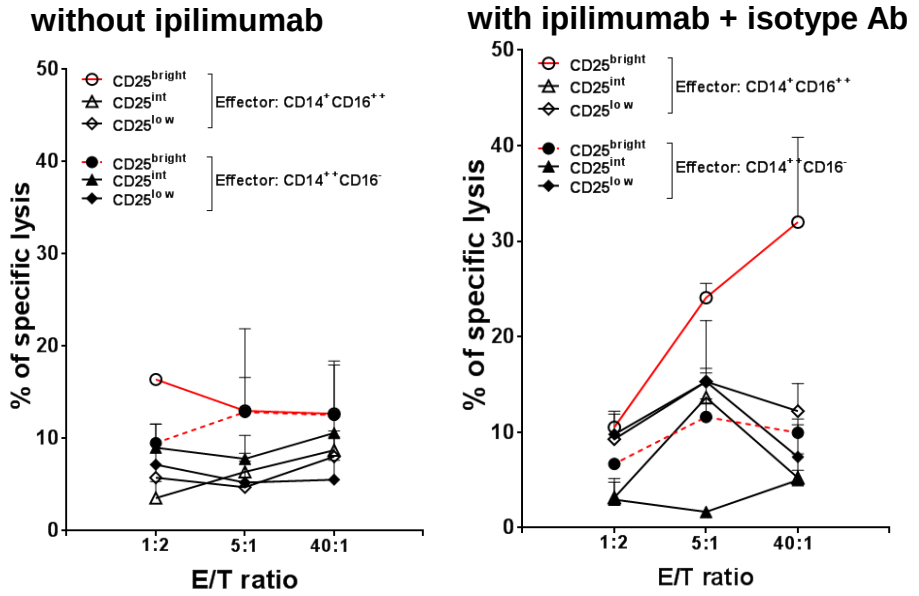
Selective killing of Tregs by $CD14^{+}CD16^{++}$ monocytes in the presence of ipilimumab





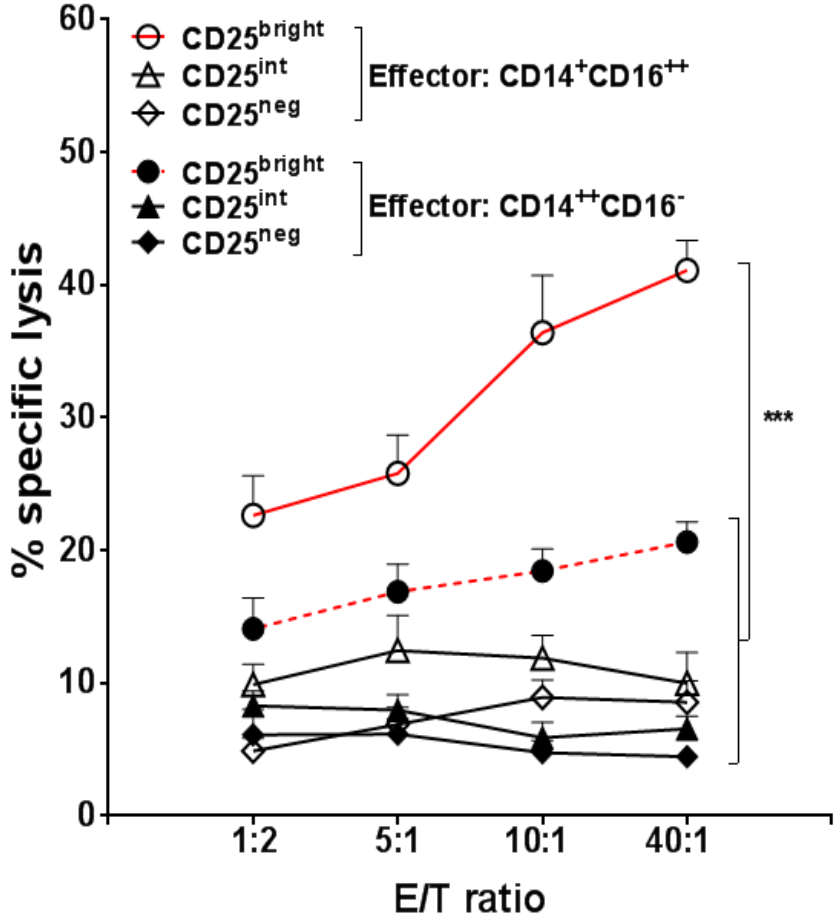
ADDC-dependent Treg depletion by $CD14^{+}CD16^{++}$ monocytes in normal donors





N= 5

ADDC-dependent Treg depletion by $CD14^{+}CD16^{++}$ monocytes in patients



N= 4

Article

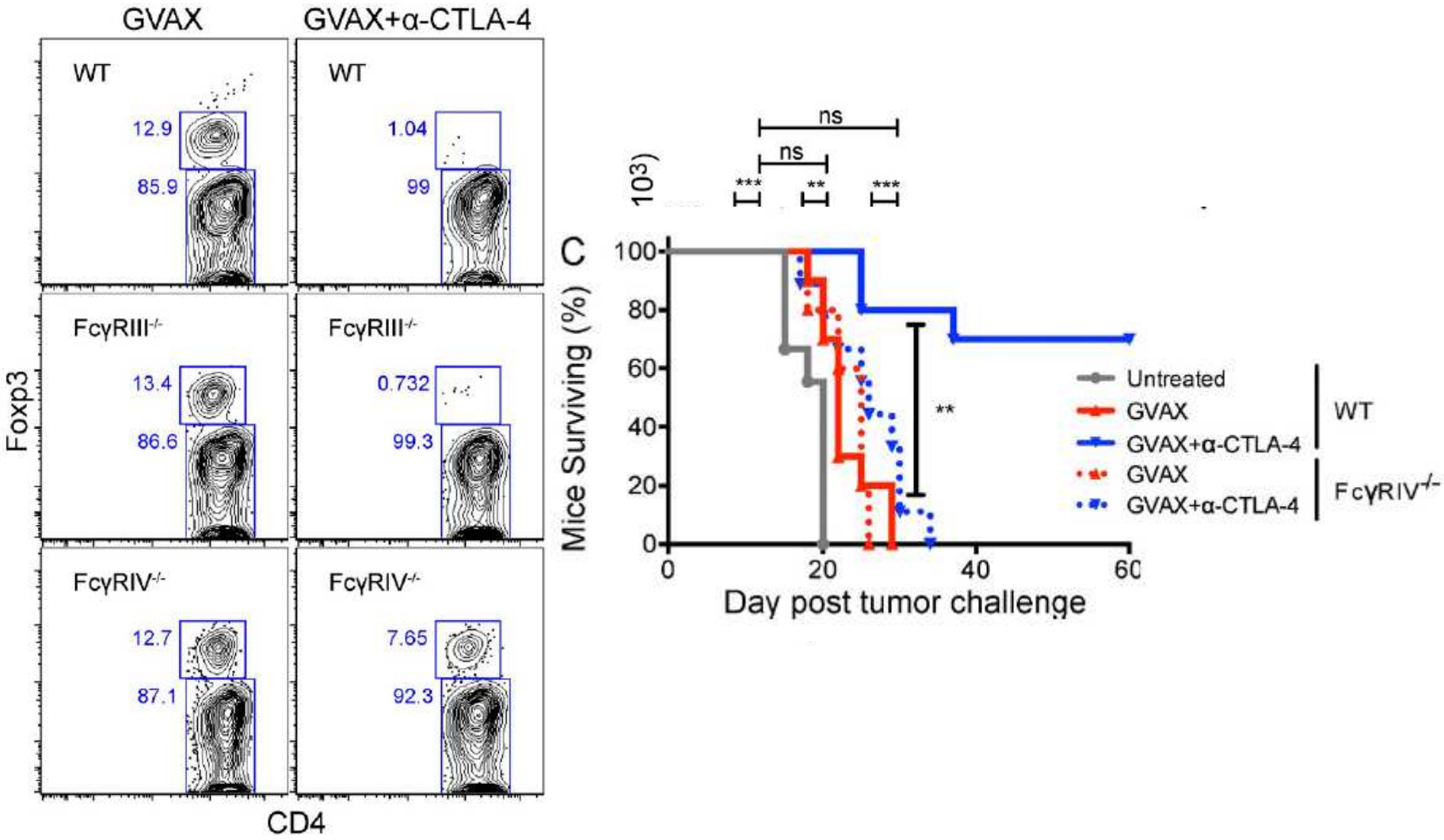
JEM

Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti–CTLA-4 therapy against melanoma

Tyler R. Simpson,[1,2,3] Fubin Li,[4] Welby Montalvo-Ortiz,[1] Manuel A. Sepulveda,[3] Katharina Bergerhoff,[6] Frederick Arce,[6] Claire Roddie,[6] Jake Y. Henry,[6] Hideo Yagita,[5] Jedd D. Wolchok,[3] Karl S. Peggs,[6] Jeffrey V. Ravetch,[4] James P. Allison,[1] and Sergio A. Quezada[6]

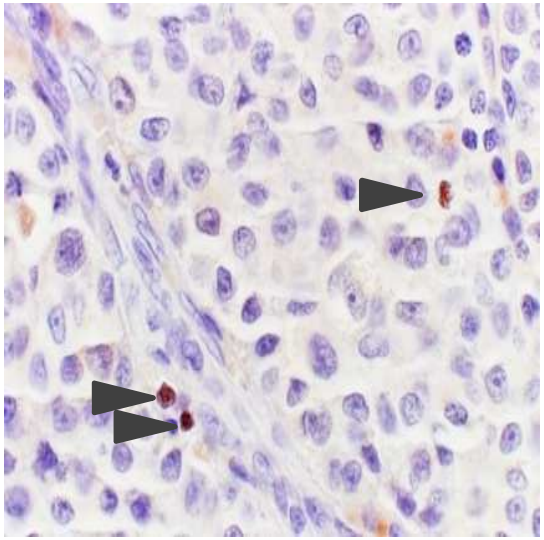
2013

Treg cell depletion is mediated largely by FcγRIV+ macrophages in the TME

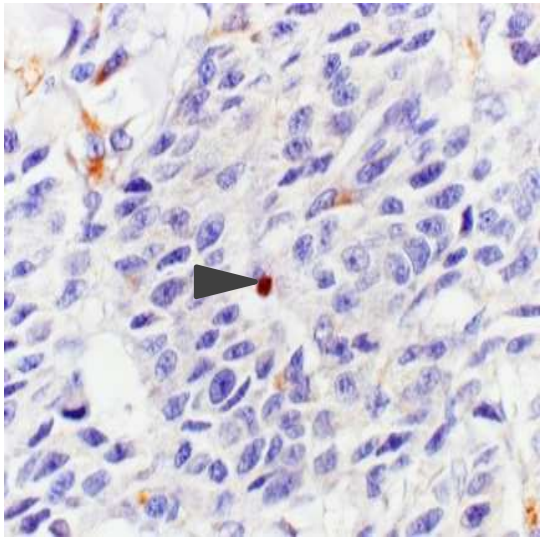


Decreased T_{regs} infiltration in patients responding to ipilimumab

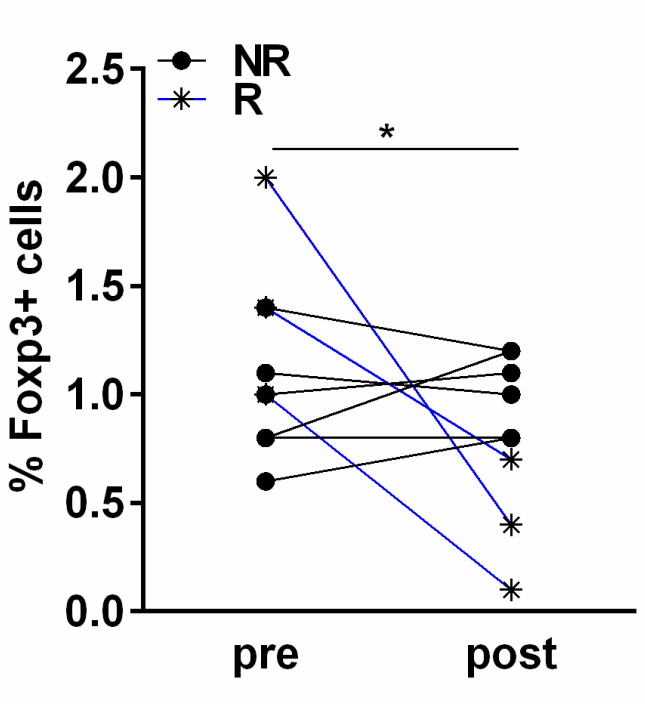
Pre-treatment



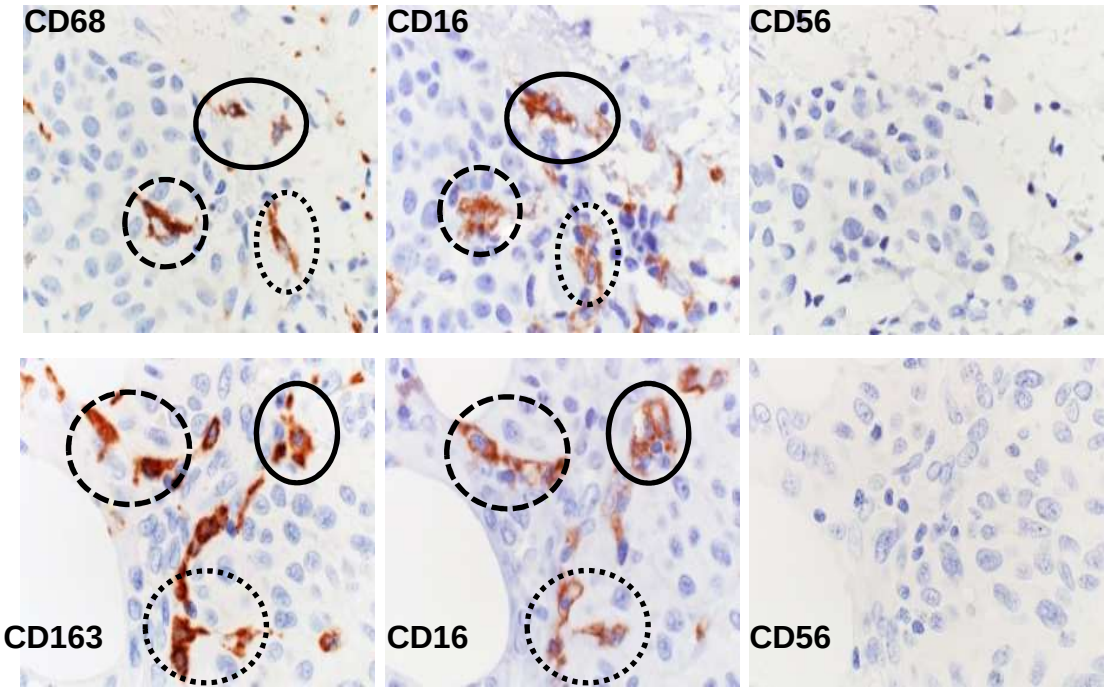
Post-treatment

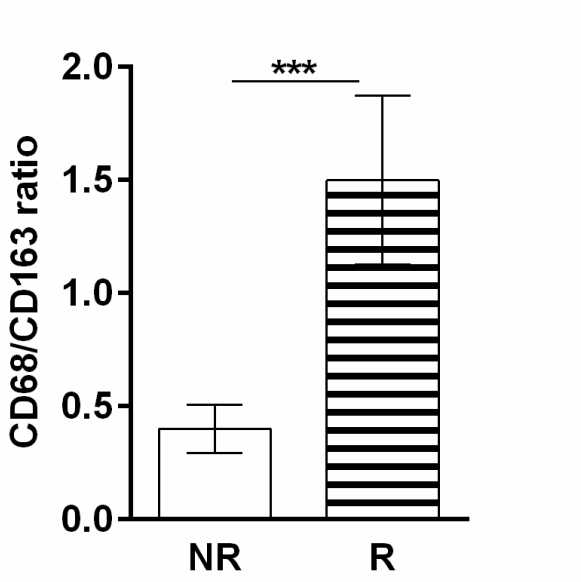


moAb Foxp3



The TME of R patients is enriched with $CD68^{+}CD16^{+}$ macrophages





Key Points

• Patients responding to ipilimumab displayed the highest baseline frequencies of circulating nonclassical $CD14^{+}CD16^{++}$ monocytes. This is a potential biomarker of response.

• $CD14^{+}CD16^{++}$ monocyte subpopulation is responsible for the depletion of Tregs

• Preferential depletion of Treg versus Teff is due to the high levels of surface CTLA-4 expression on Tregs

• Increased baseline ratio of CD68/CD163 cells within the TME correlated with decreased number of Tregs in R patients

•No difference in the frequency of peripheral NK cells between ipilimumab R and NR patients suggesting that these cells do not play a role in immune response to ipilimumab

Acknowledgments

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