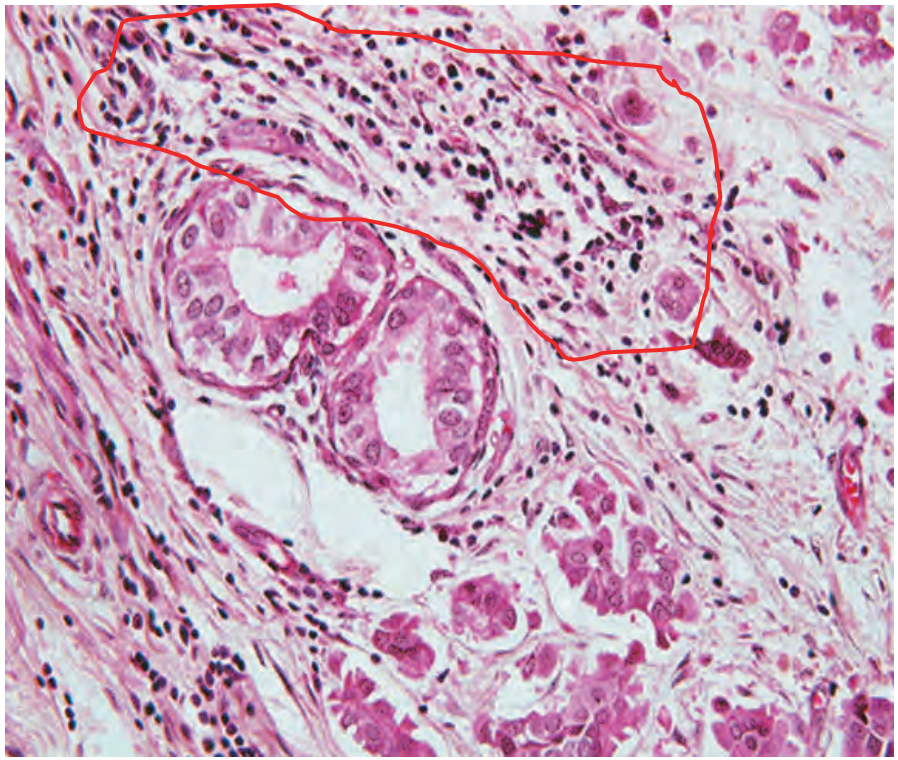
Host Tumor Relationship

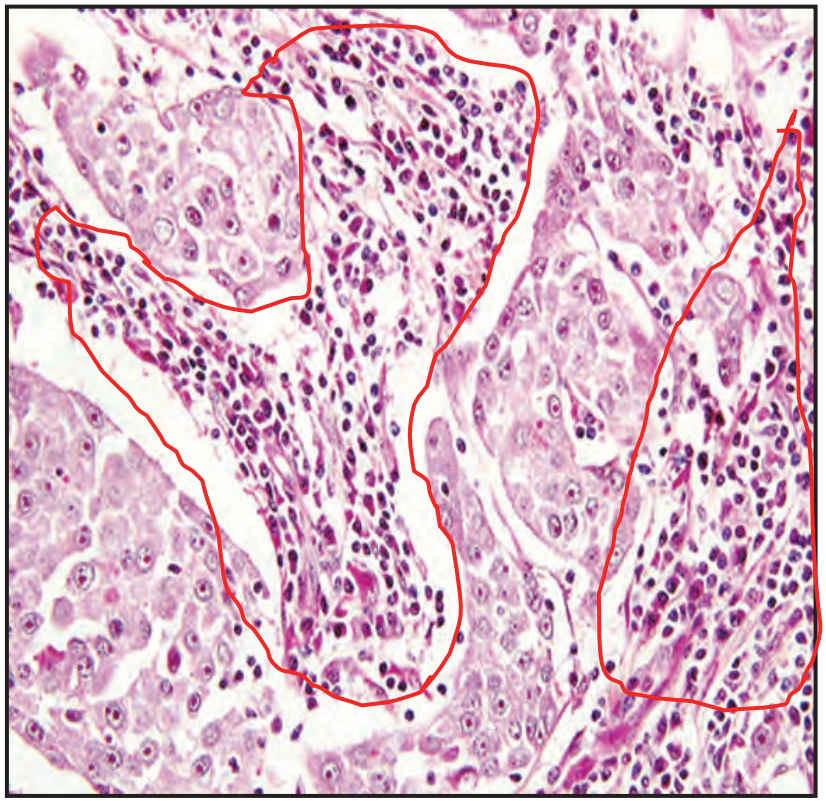
Augusto C. Ochoa, M.D.
Stanley Scott Cancer Center
Louisiana State University
New Orleans

Inflammation and Cancer: What are the cells doing there?

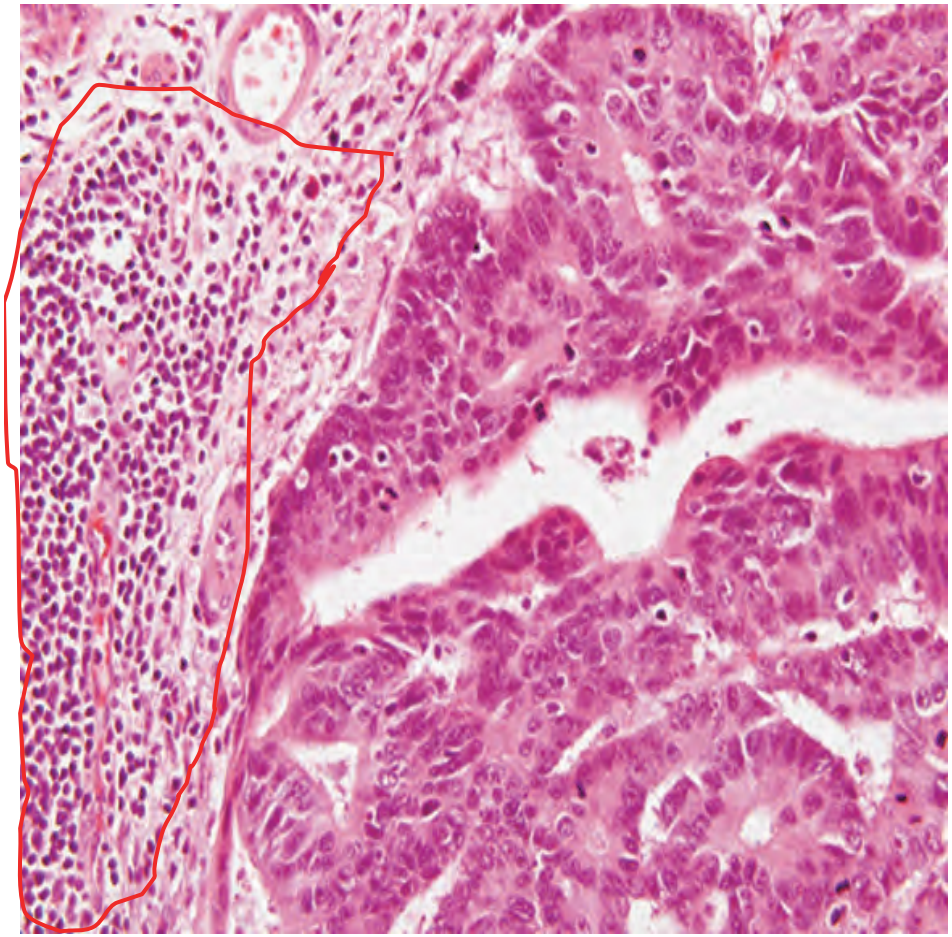
Breast Medullary CA



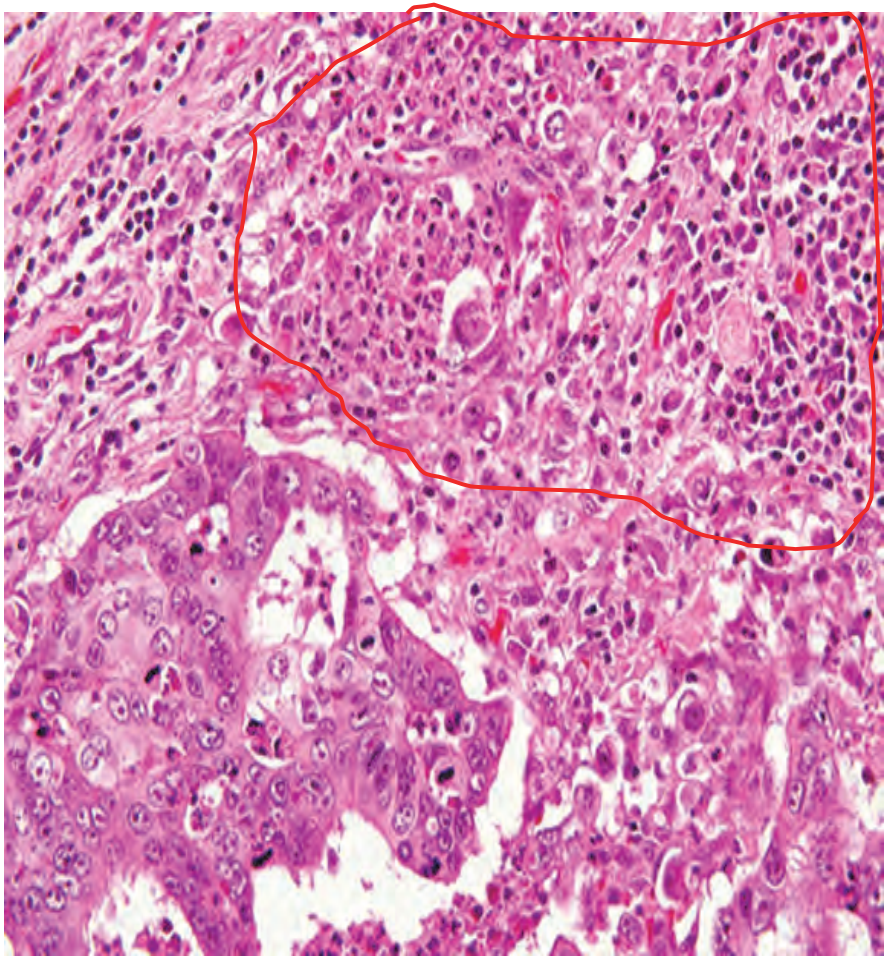
Breast Ductal CA

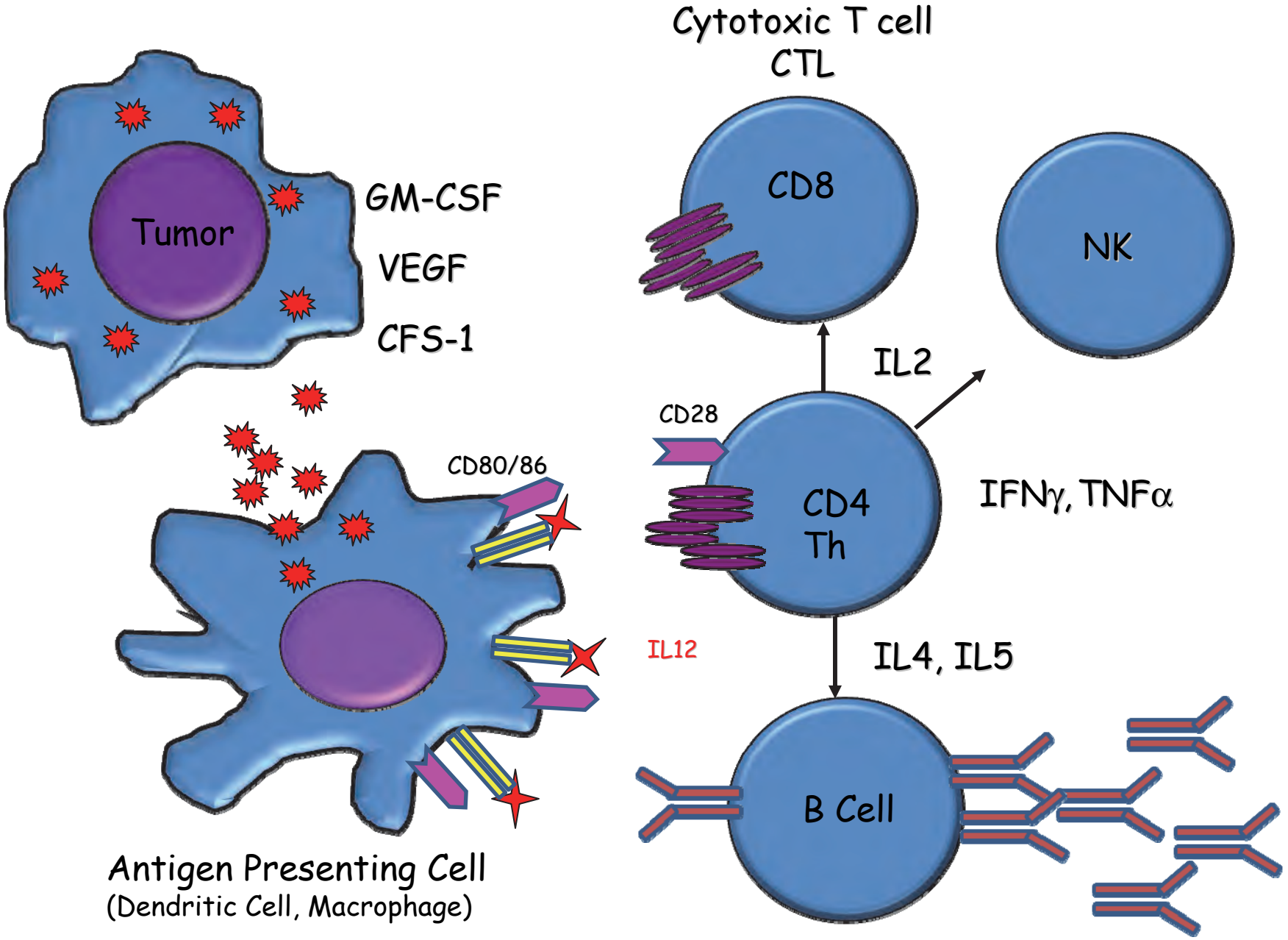


Colon Adenocarcinoma



Glioblastoma




Cytotoxic T cell
CTL
Tumor
GM-CSF
VEGF
CFS-1
CD8
NK
IL2
CD28
CD80/86
CD4
Th
IFNγ, TNFα
IL12
IL4, IL5
B Cell
Antigen Presenting Cell
(Dendritic Cell, Macrophage)

Inflammation (Immunity) and Cancer

Prevent or Treat

- At least 20% of cancers have a preventable infectious component: HPV, HBV, H. pylori
- NK and T cells can eradicate established tumors (renal and melanoma)

Promote

- "Cancer originates in sites of chronic inflammation" Virchow 1863
- Chronic inflammatory cells promote tumor growth (Coussens et al Imm. Rev 2008)
- NSAIDS prevent colon CA
- Hodgkin's disease: Loss of DTH to DNCB and candida *(Hersch and Oppenheim – 1963)*

Cellular Immunotherapy

3-5 days

Immunotherapy:
cytokines, T cells

Anti-tumor response

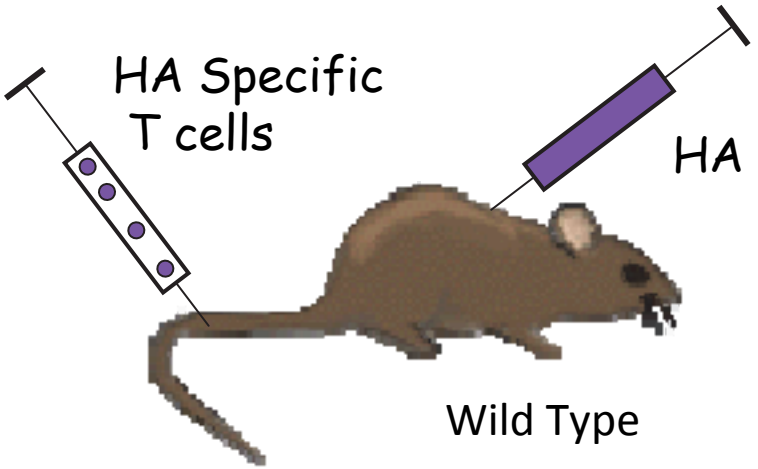
Cancer Patient

Immunotherapy:
cytokines, T cells

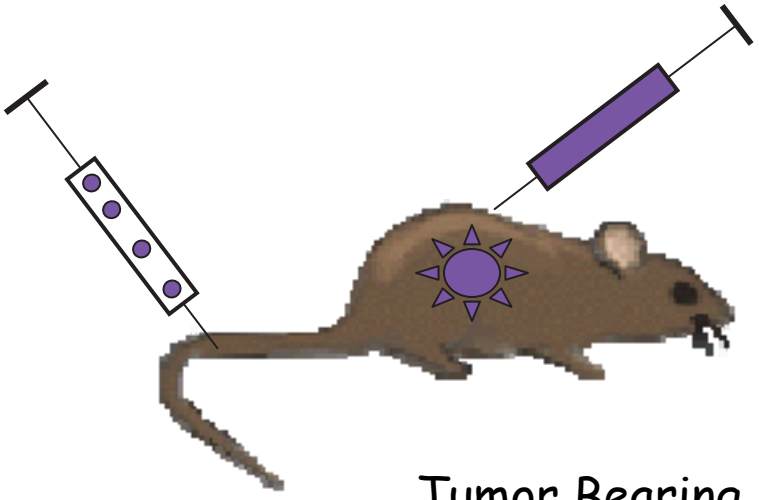
Few Responses

Immune Tolerance

Tumor Induced Tolerance



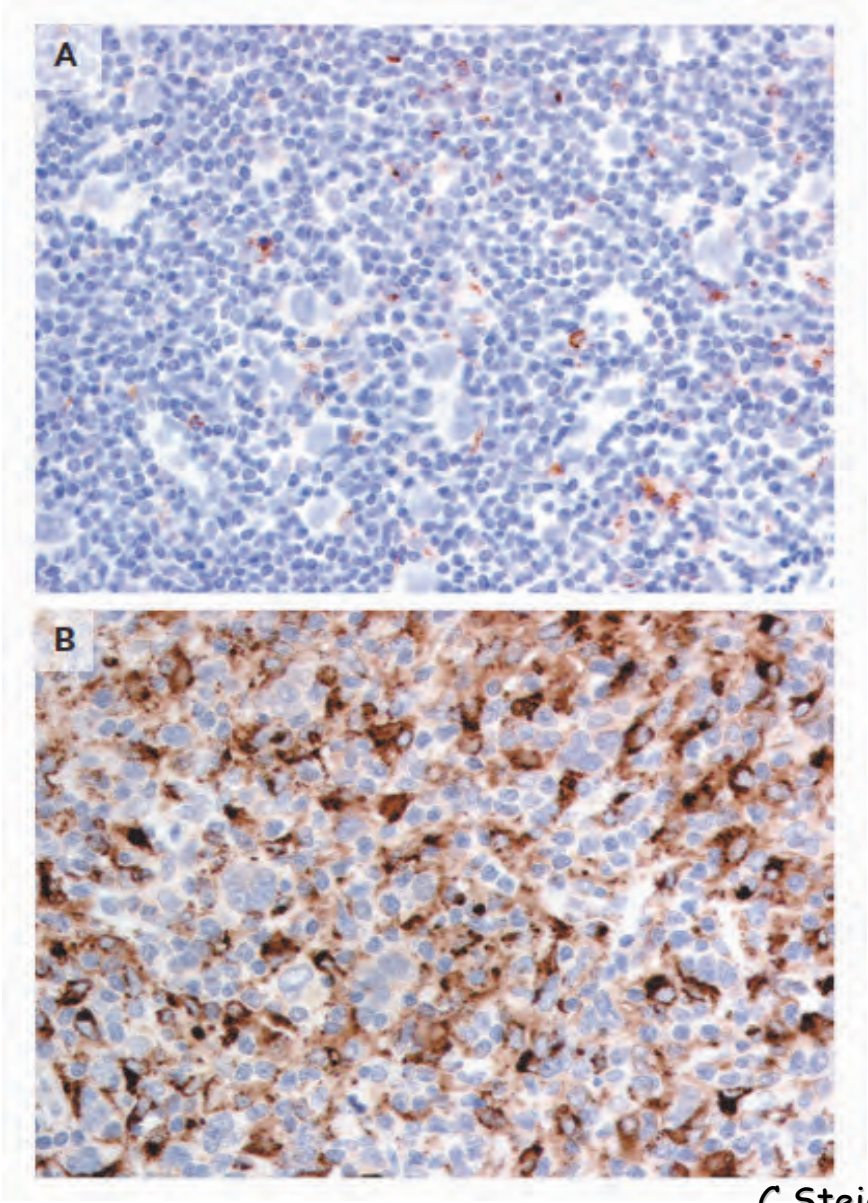
Proliferation +++++
Cytokine Production +++++



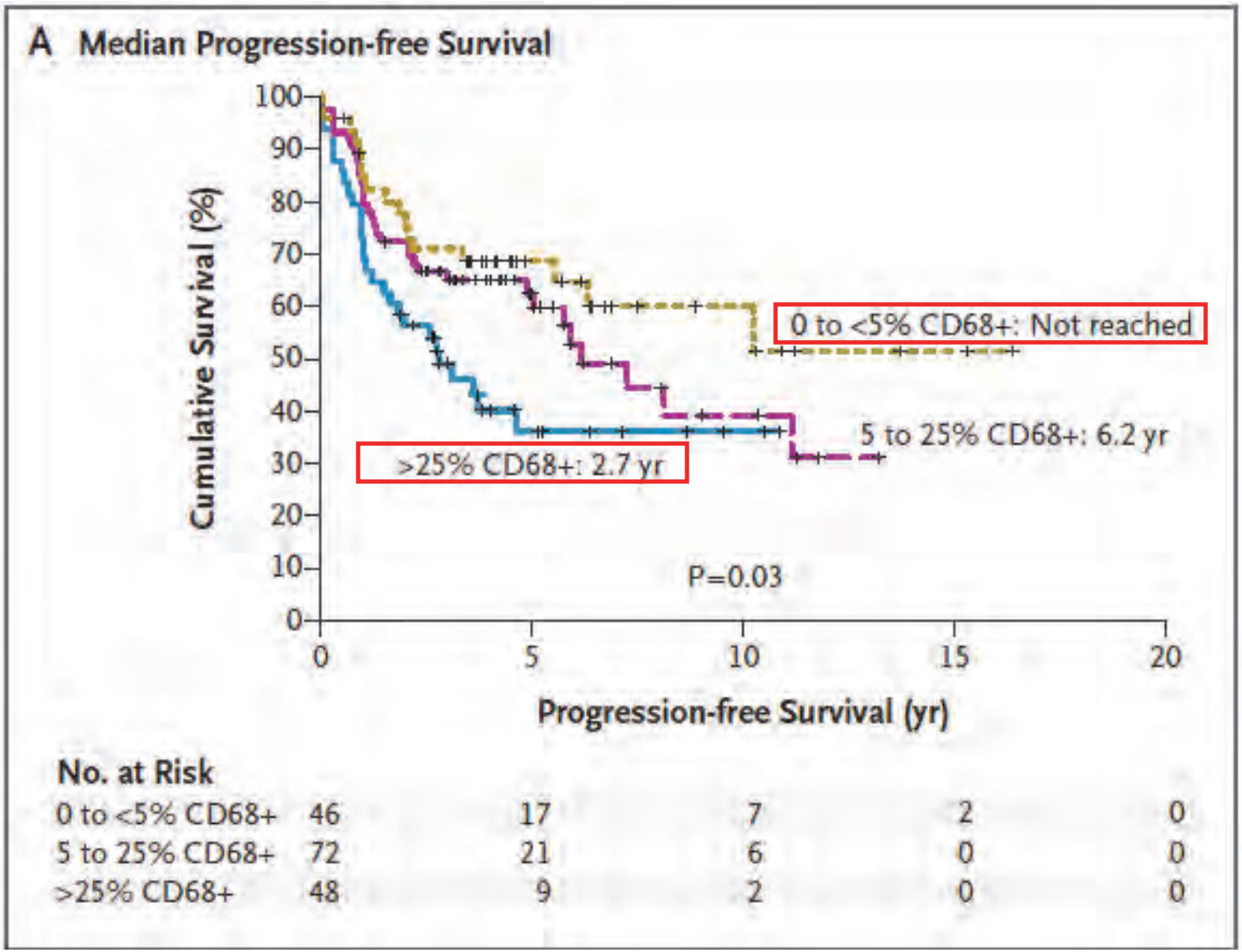
Proliferation +/-
Cytokine Production +/-

Staveley-O'Carrol, Sotomayor, Levitsky. PNAS 95-1178

Tumor Associated Macrophages (TAM) in Hodgkins Lymphoma

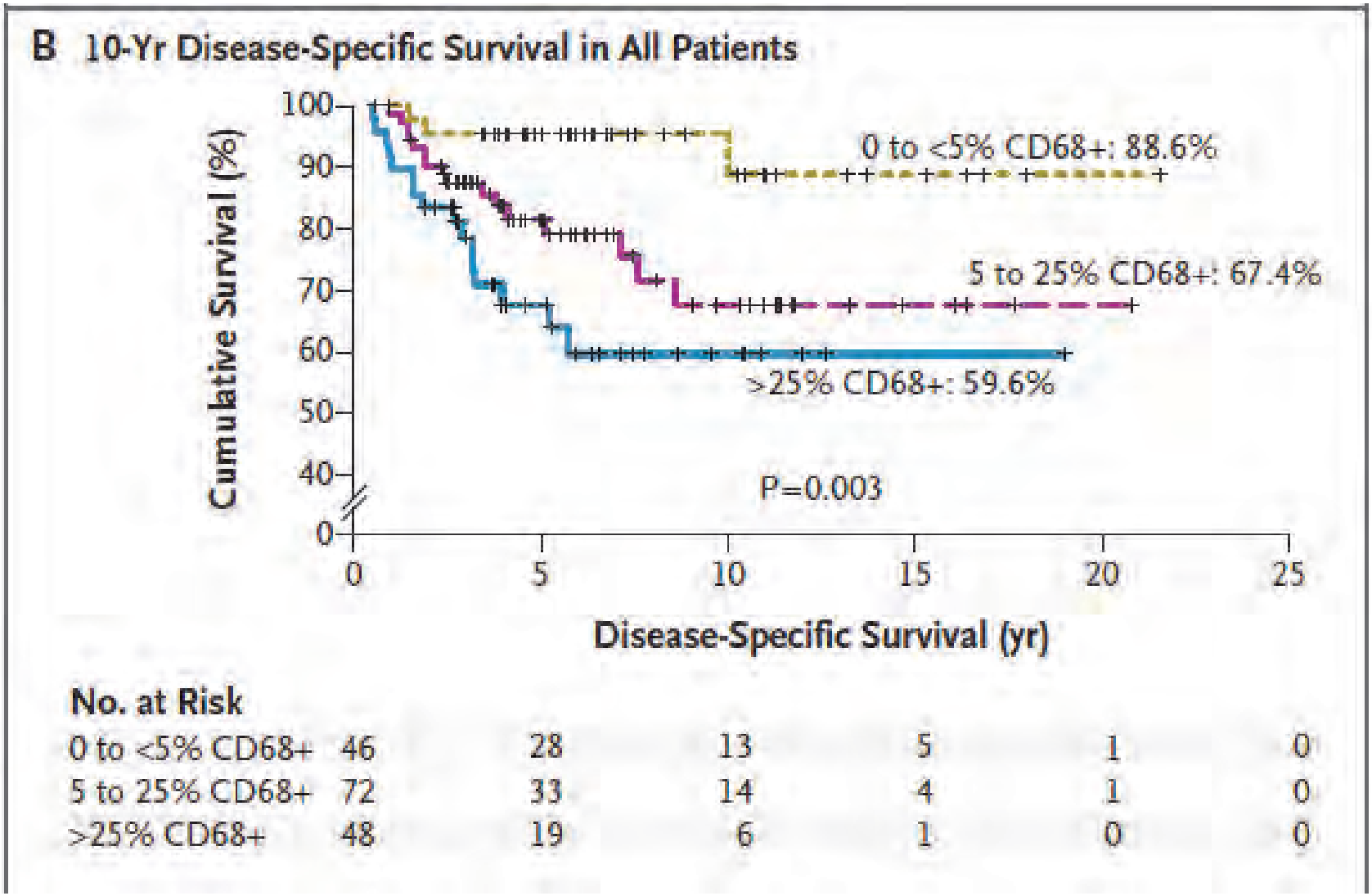


C Steidl, et al, NEJM, 362:10, 2010

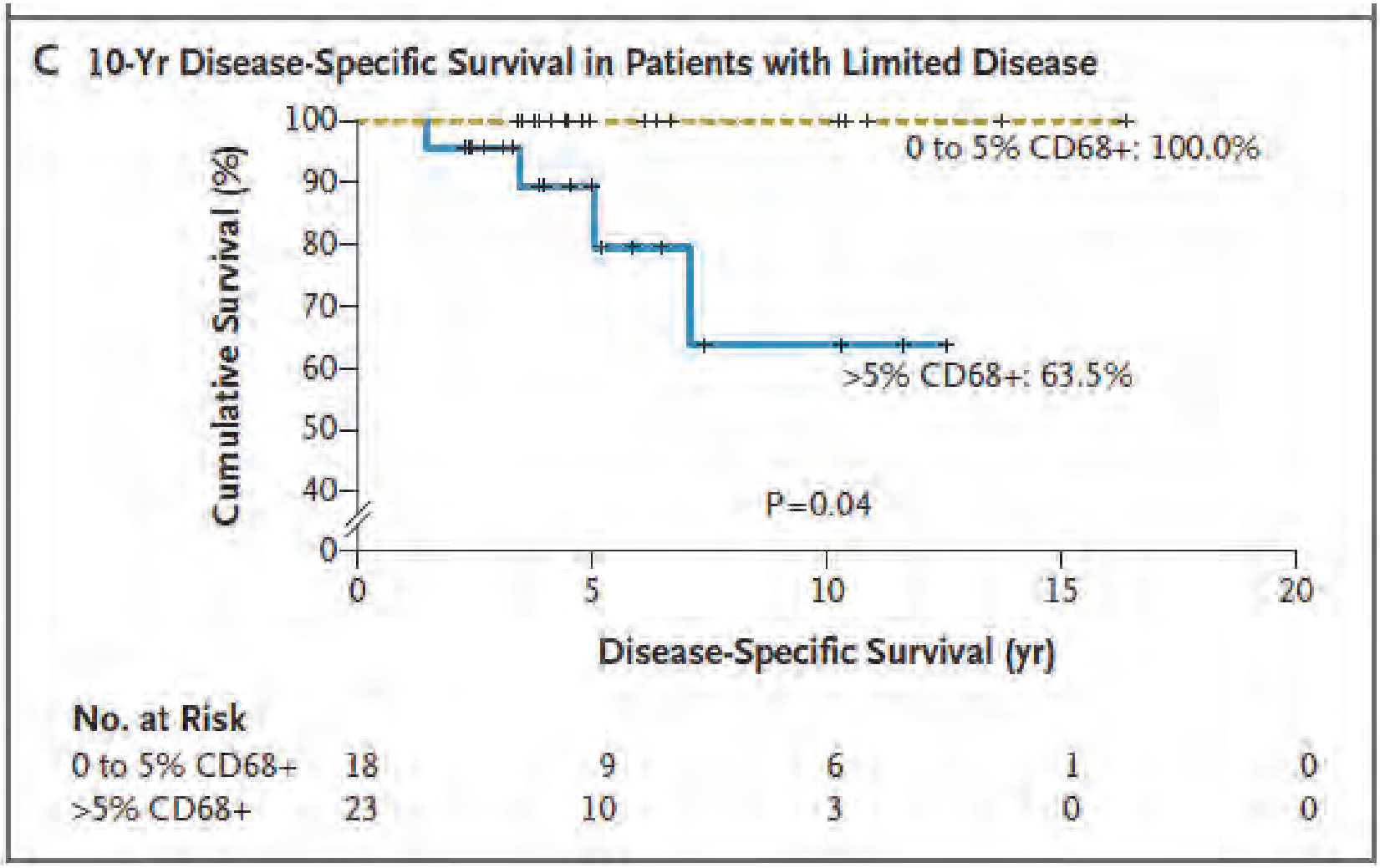


Validating cohort , n=166
Screening cohort, n=130

C Steidl, et al, NEJM, 362:10, 2010
British Columbia + U Nebraska

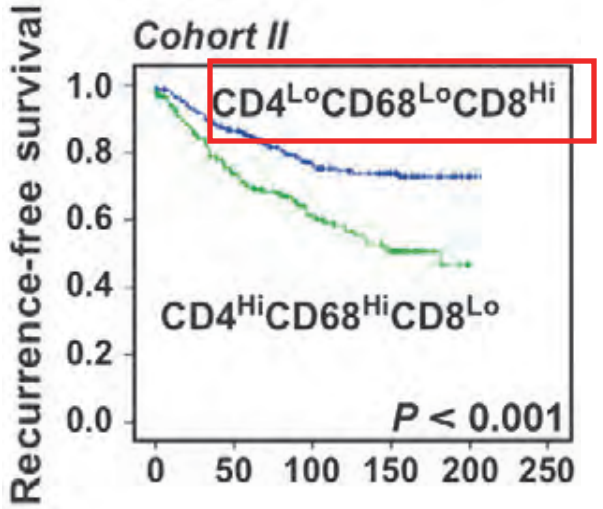


C Steidl, et al, NEJM, 362:10, 2010

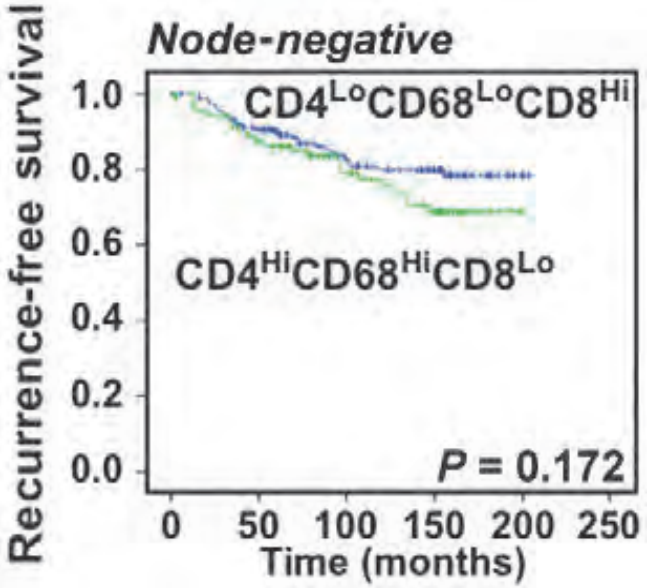


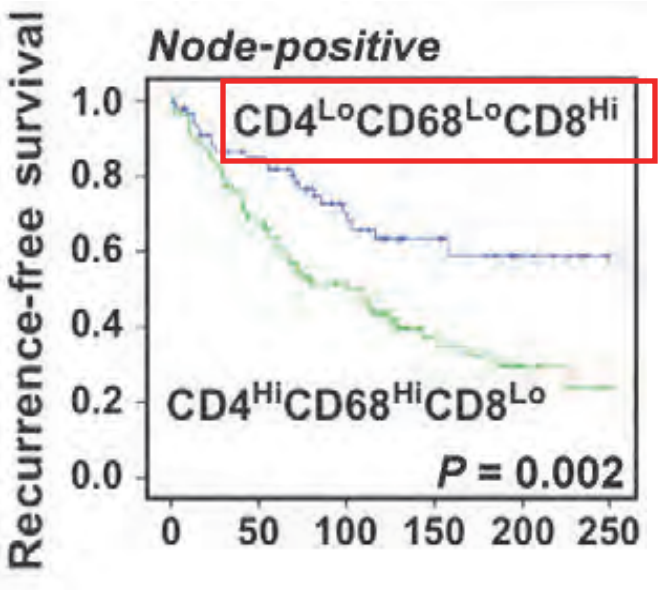
Christian Steidl, M.D, NEJM, 362:10, 2010

Immune Infiltrates and RFS in Breast Cancer



n=498
Validating Cohort





David DeNardo et al Cancer Discovery 2011

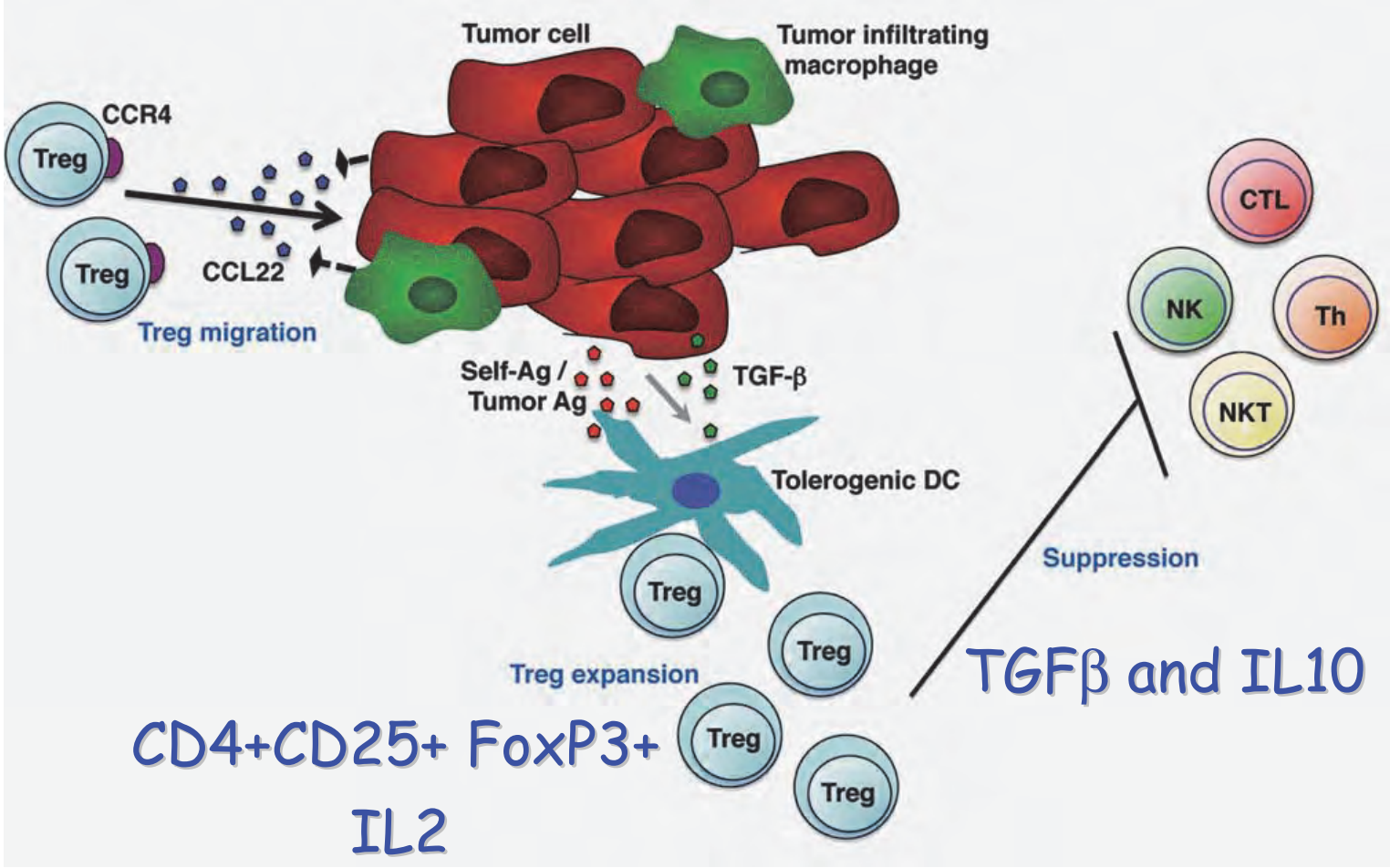
Mechanisms of Tumor Escape
1990-2010

- Factors produced by the tumors
  - TGFβ, IL10 ,IL17

- Intrinsic changes in the tumor
  - Loss of MHC (immuno-editing)
  - Lack of co-stimulatory signals B7.1, B7.2
  - Expression of checkpoint signals B7H1, B7H4 (CTLA4), PD-1

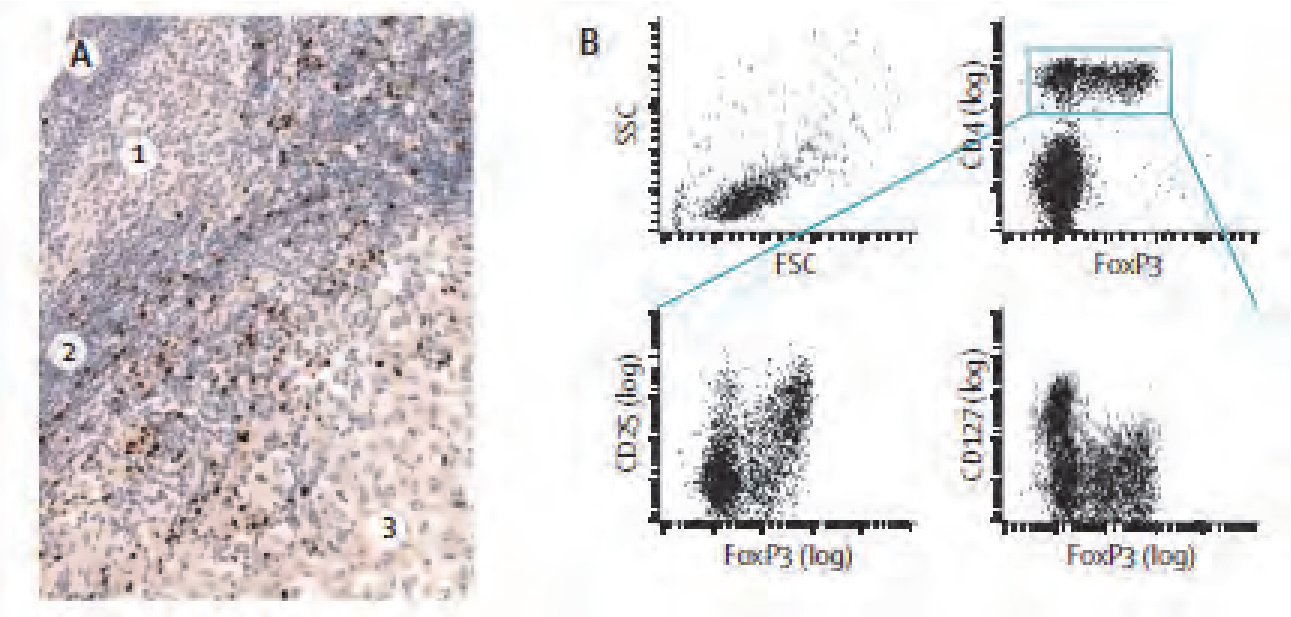
- Immunosuppressive cells stimulated by tumors
  - Regulatory T cells (T-regs)
  - Plasmacytoid dendritic cells producing IDO
  - Myeloid-derived suppressor cells (MDSC)
  - Tumor Associated Macrophages (TAM)

Regulatory T cells in Cancer



Nishikawa and Sakaguchi, Int. J. Cancer 127 (2010)

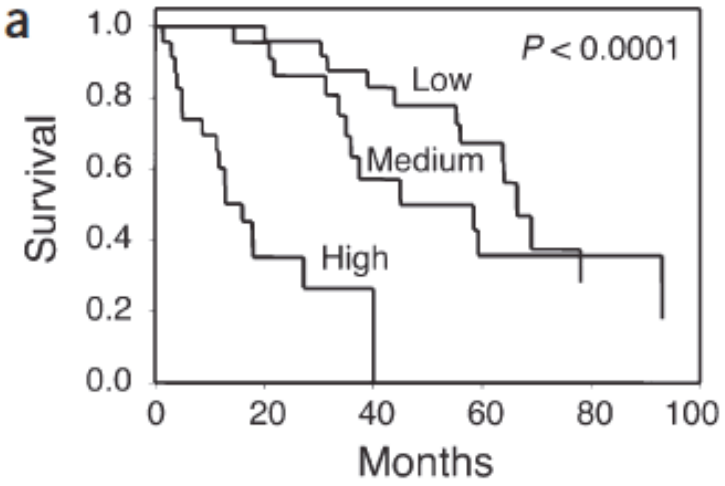
Regulatory T cells (T-Regs) in Melanoma



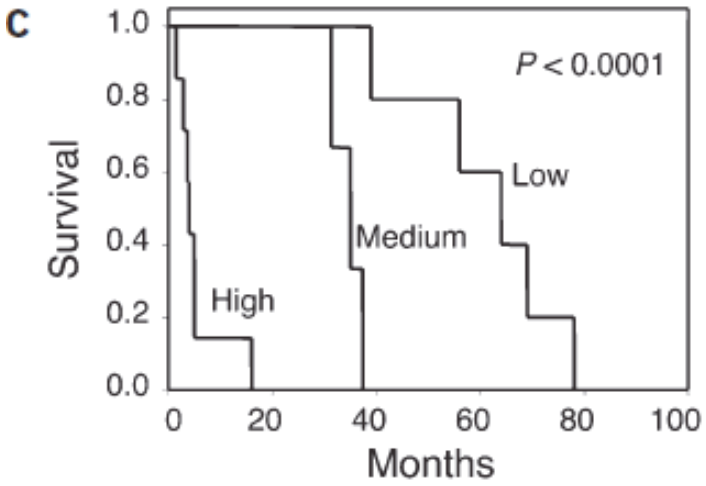
Jacobs JFM et al, The Lancet 13, 2012

T-Reg Infiltration and Survival in Ovarian CA

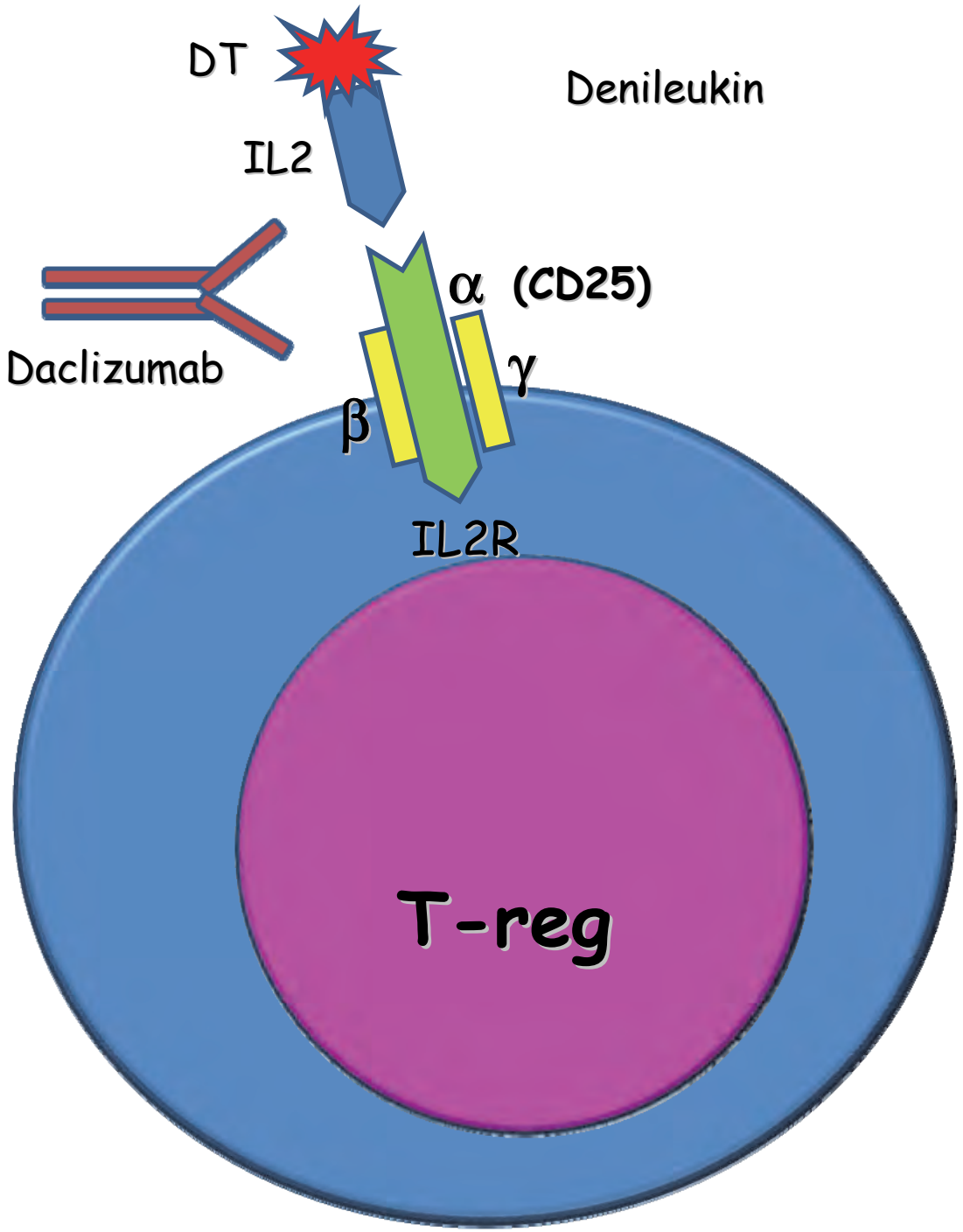
Stages I – IV
N=70



Stage IV

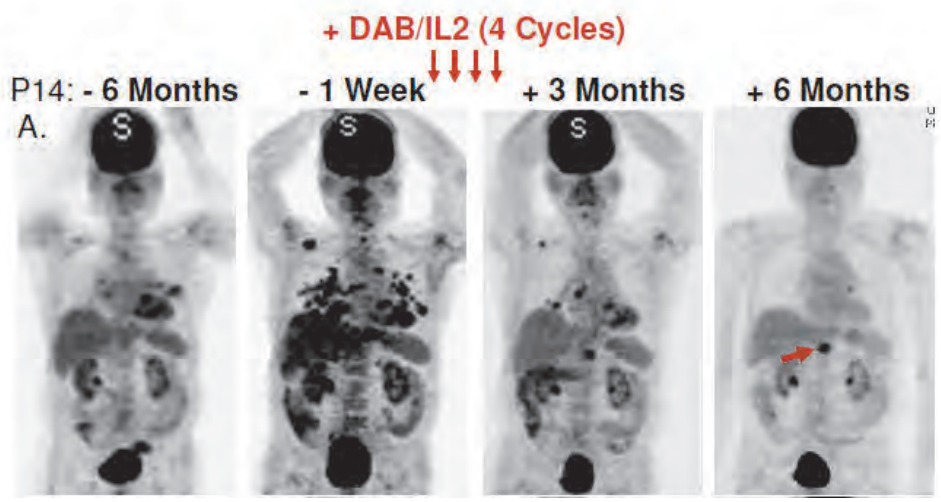


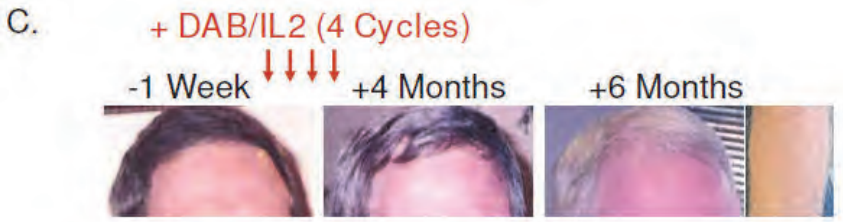
Curiel T, Nature Med 10(9), 2004


DT
Denileukin
IL2
Daclizumab
α (CD25)
γ
β
IL2R
T-reg

Denileukin Difitox in Melanoma

S. Telang et al BioMed Central 11, 2011





Denileukin Difitox in NHL

NH Dang et al, JCO 20, 2004

CR + PR = 24%

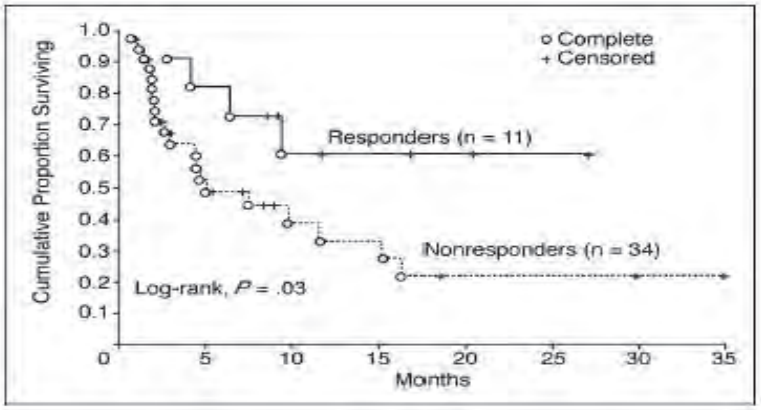
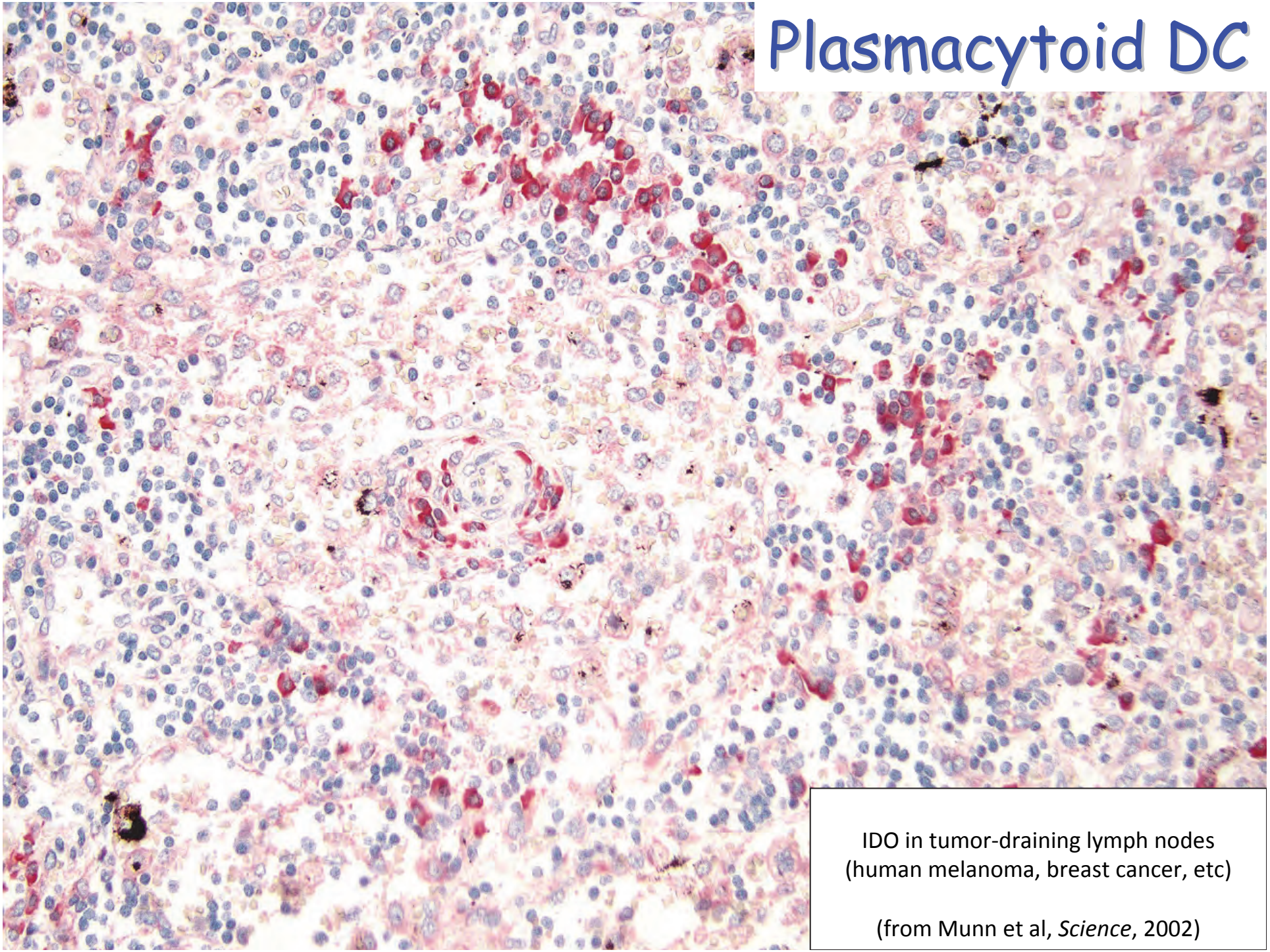


Fig 2. Overall survival comparison between patients responding and not responding to denileukin diftitox, based on Kaplan-Meier estimates.

Plasmacytoid DC

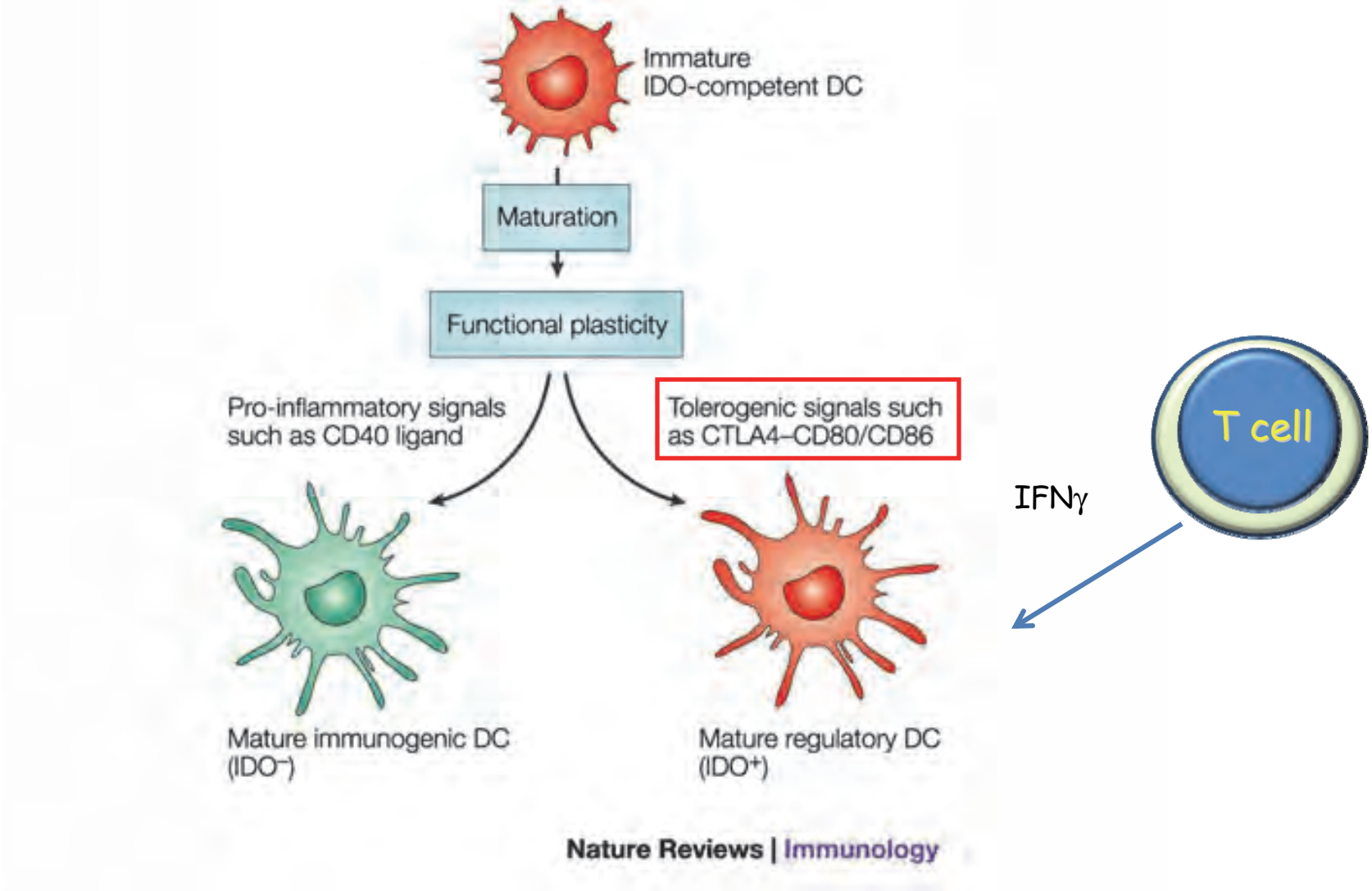


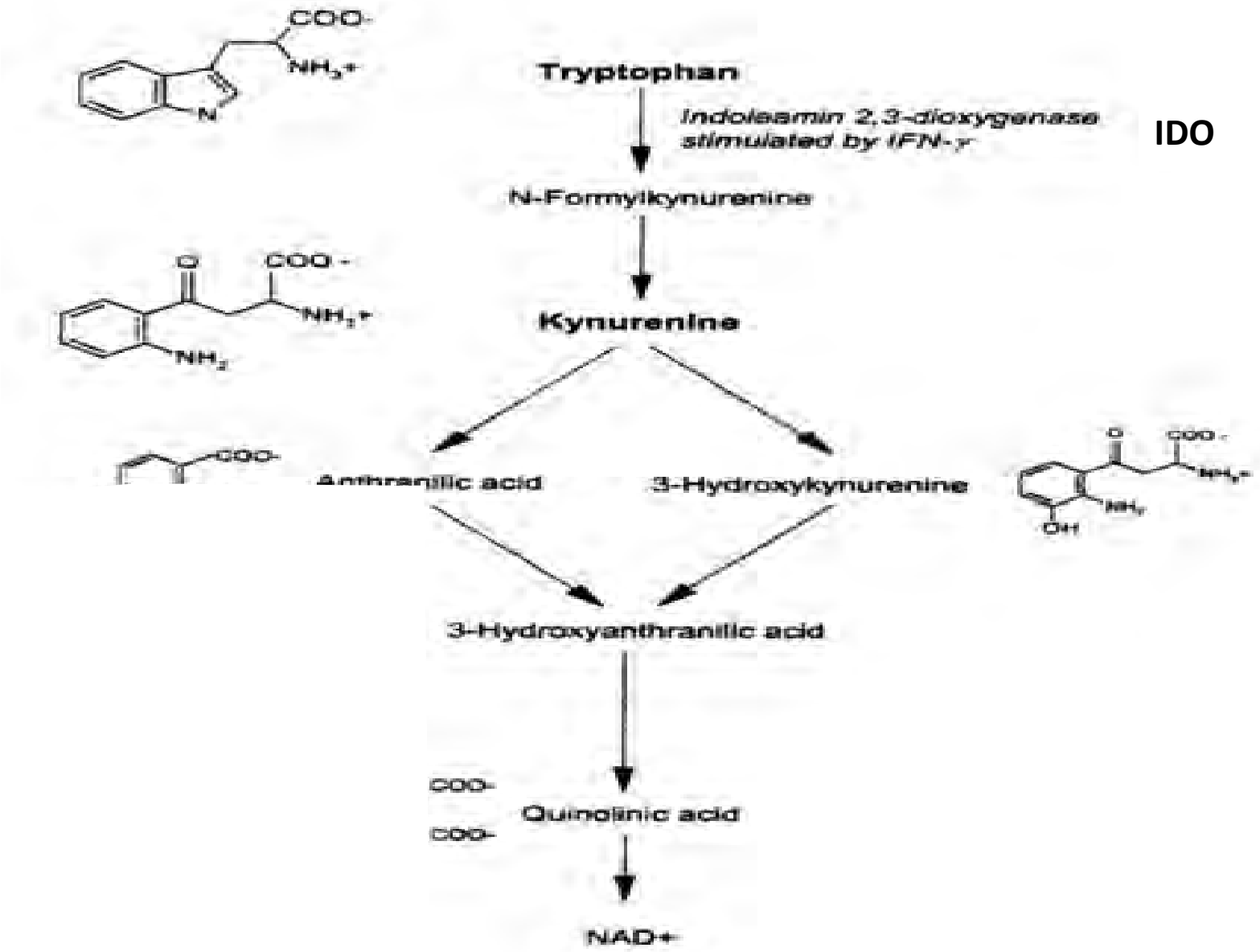
IDO in tumor-draining lymph nodes
(human melanoma, breast cancer, etc)

(from Munn et al, *Science*, 2002)

IDO (Indoleamine 2,3-dioxygenase)

David H. Munn and Andrew L. Mellor





IDO

David Munn

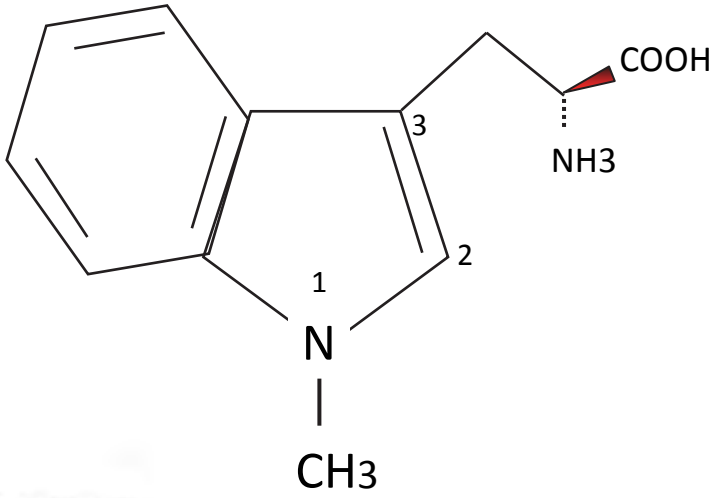
Indoleamine 2,3-dioxygenase (IDO)

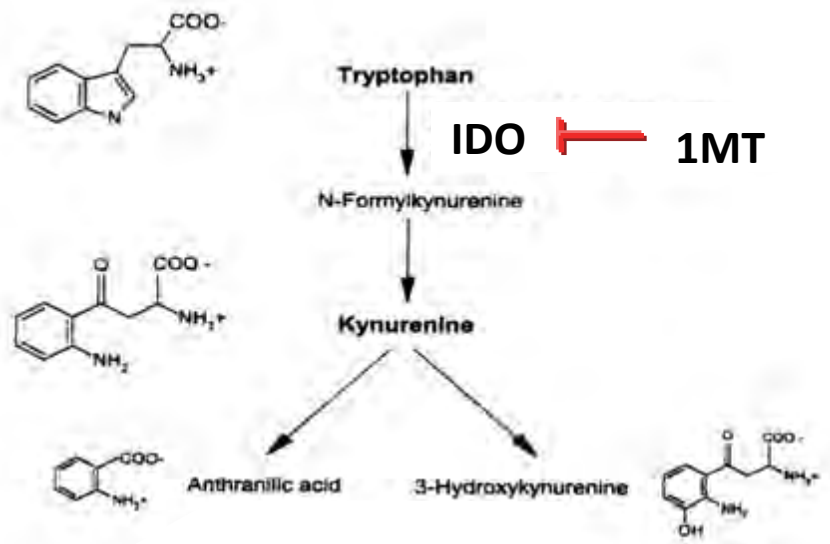
- IDO depletes tryptophan from the microenvironment
- IDO can create acquired peripheral tolerance *de novo*
- IDO is counter-regulatory (induced by inflammation but suppresses immune responses)
- IDO regulates both innate and adaptive responses
  - Control of local inflammation, IL-6, etc
  - Activates Tregs

David Munn

IDO-inhibitor drug (NSC-721782):

1-methyl-[D]-tryptophan





David Munn

ASCO American Society of Clinical Oncology
www.asco.org
Abstract # 3004
2009

Phase I Trial of 1-methyl-D-tryptophan

PI: Scott Antonia MD PhD
Co PI: Hatem Soliman MD
Dan Sullivan MD

Moffitt Cancer Center/Southeast Phase II Consortium

Chuck Link MD
Nick Vanahanian MD
William Ramsey MD PhD

NewLink Genetics Inc

- Hypophysitis seen in 3 patients
  this was a recall toxicity associated with prior ipilimumab therapy (anti-CTLA4 mAb)
- otherwise 1MT was well tolerated

Myeloid-derived Suppressor Cells (MDSC) Tumor Associated Macrophages (TAM)

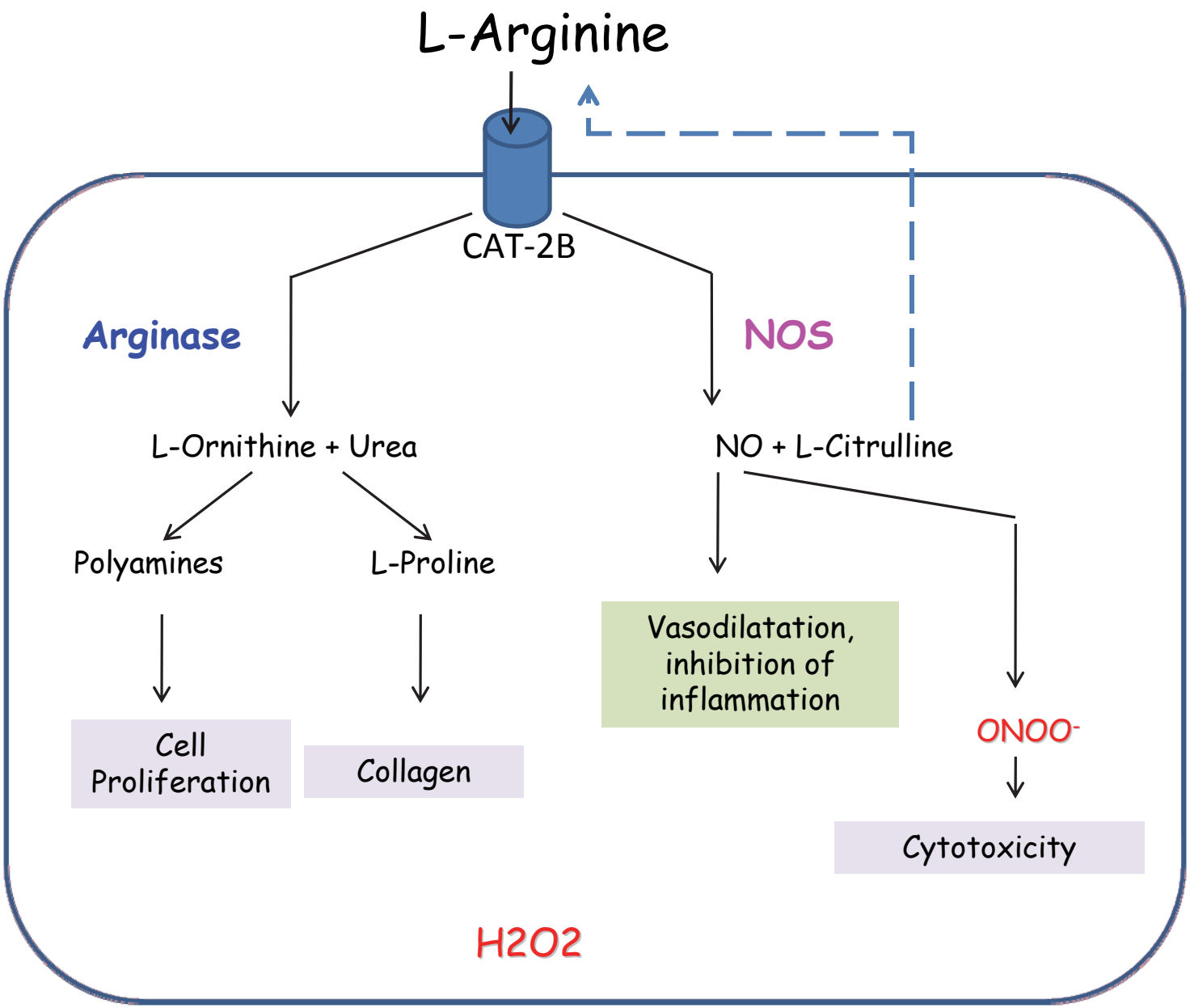
- CD11b+,GR1+ myeloid cells H&N pts (R. Young) and tumor-bearing mice (D. Gabrilovich)
- Immature DC to mature granulocytes: CD11b+,CD33+,CD68+,IL4rα
- Increased in Renal Cell Carcinoma (A. Zea) , Pancreatic CA (O. Finn), Head and Neck (S Chen), Breast CA (S. Ostrand-Rosenberg), Colon CA (R. Kiessling)
- Produce Arginase 1, Nitric Oxide or H_2O_2 (Bronte E., Ochoa A, Ostrand-Rosenberg S)

Effect of MDSC on OT-1/OT-2 T cells

	No MDSC	Plus MDSC	Plus non-MDSC
No Stimuli	33	48.5	88.5
OVA 257-264	20,713 →	217	23842
OVA 323-339	17,073 →	164	15159

Inhibit IFNγ production and CD3ζ chain expression

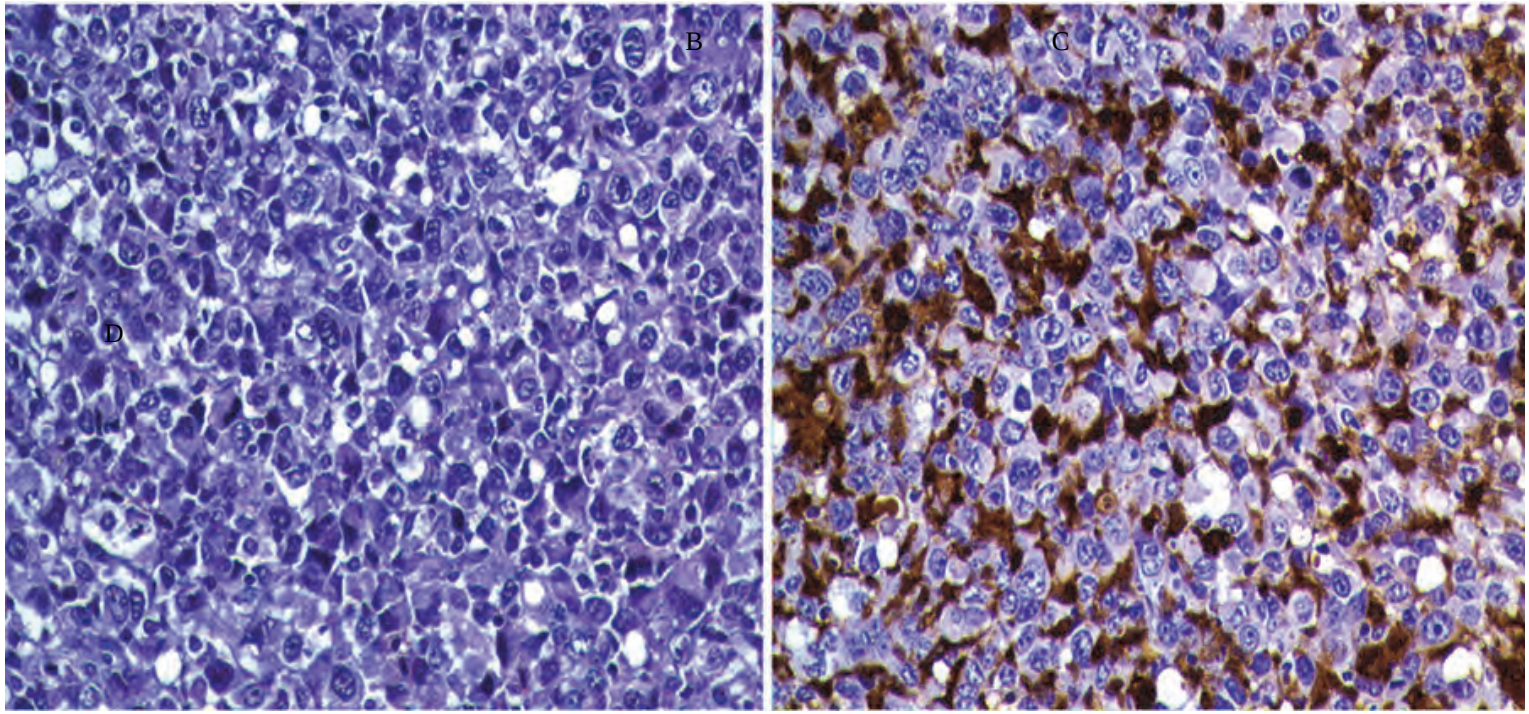
Decrease the therapeutic efficacy of radiation and chemotherapy


L-Arginine
CAT-2B
Arginase
NOS
L-Ornithine + Urea
NO + L-Citrulline
Polyamines
L-Proline
Vasodilatation, inhibition of inflammation
ONOO-
Cell Proliferation
Collagen
Cytotoxicity
H2O2

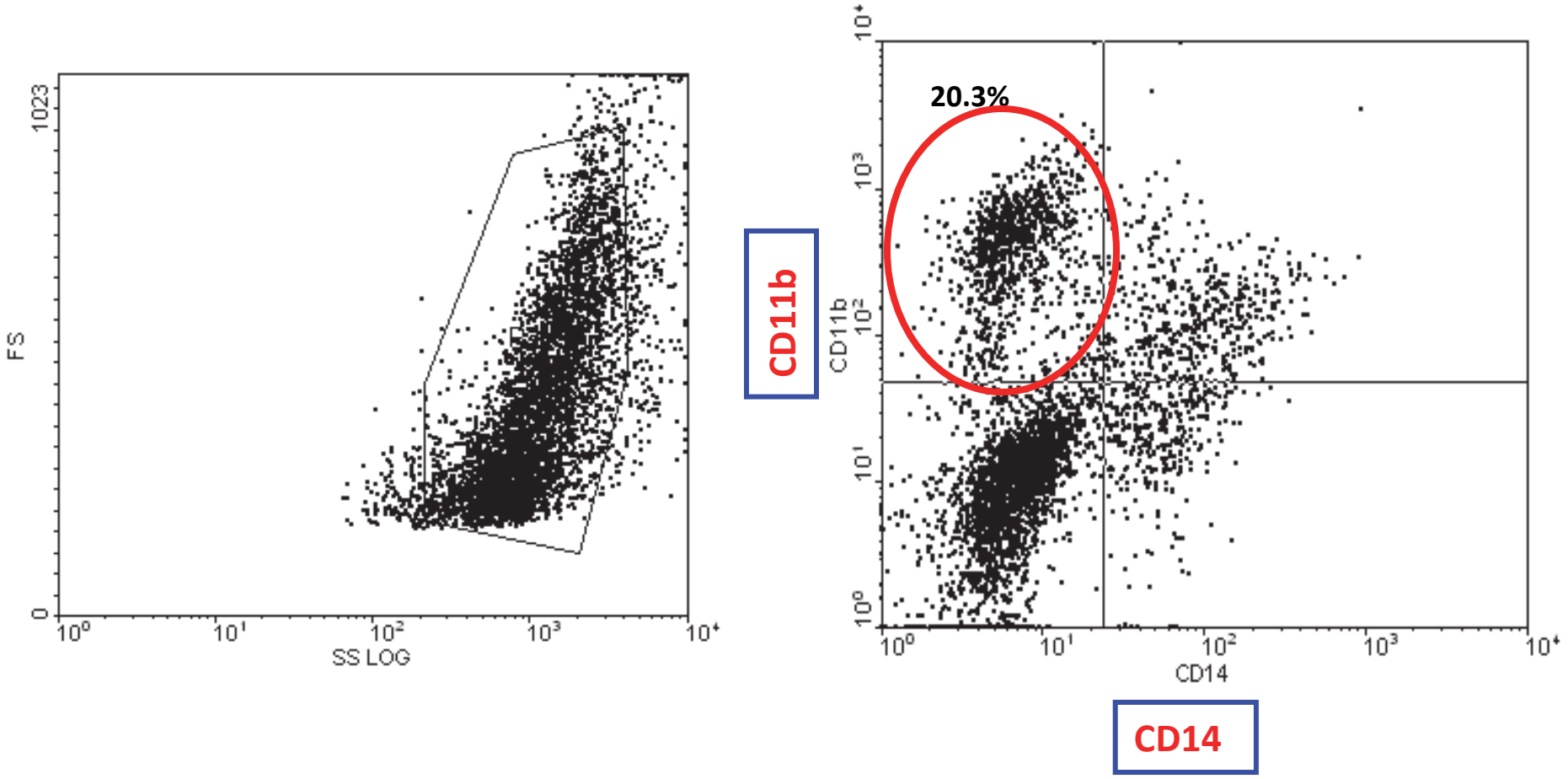
Arginase I Expression in 3LL Tumor

Isotype

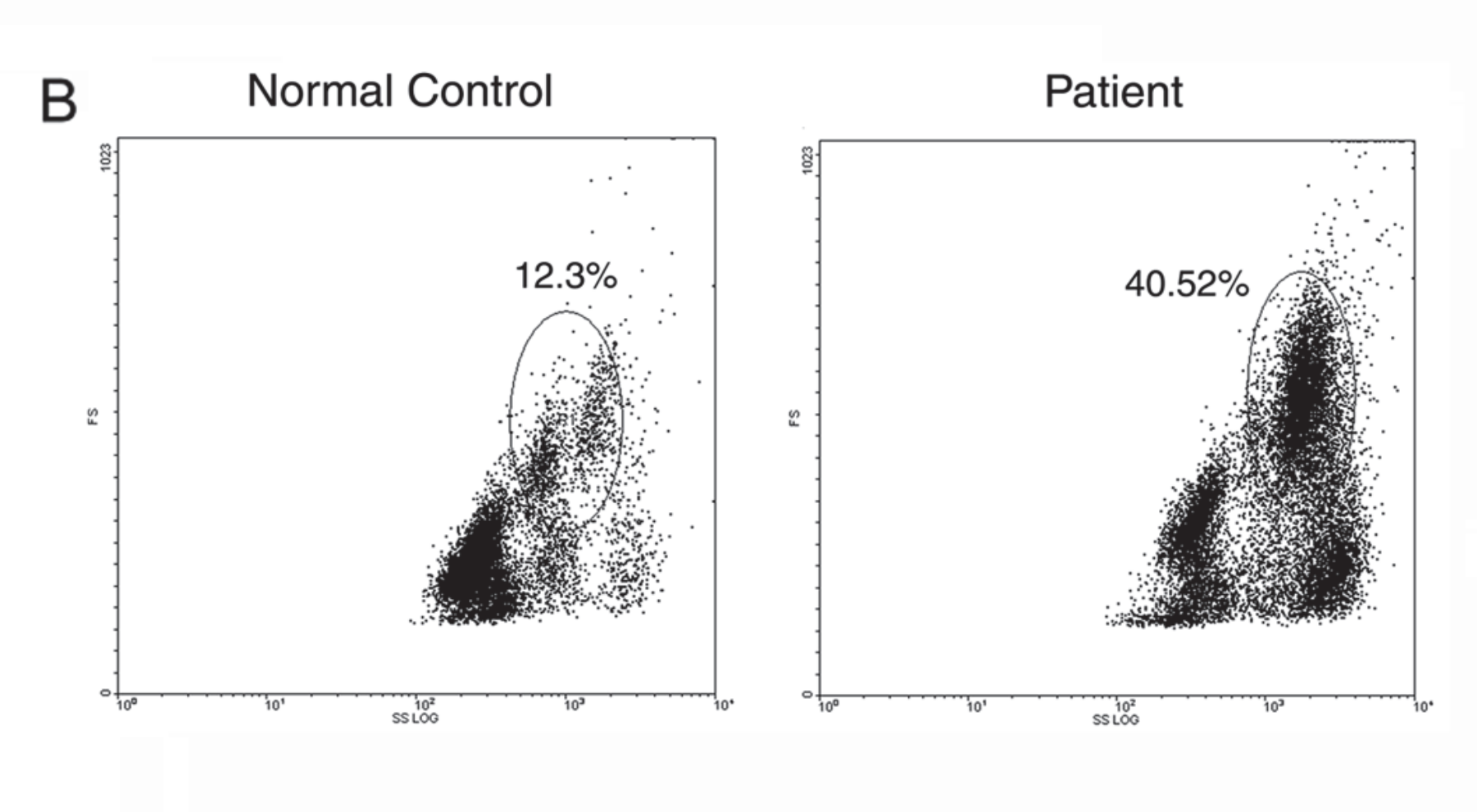
Arginase I



MDSC Infiltrating RCC

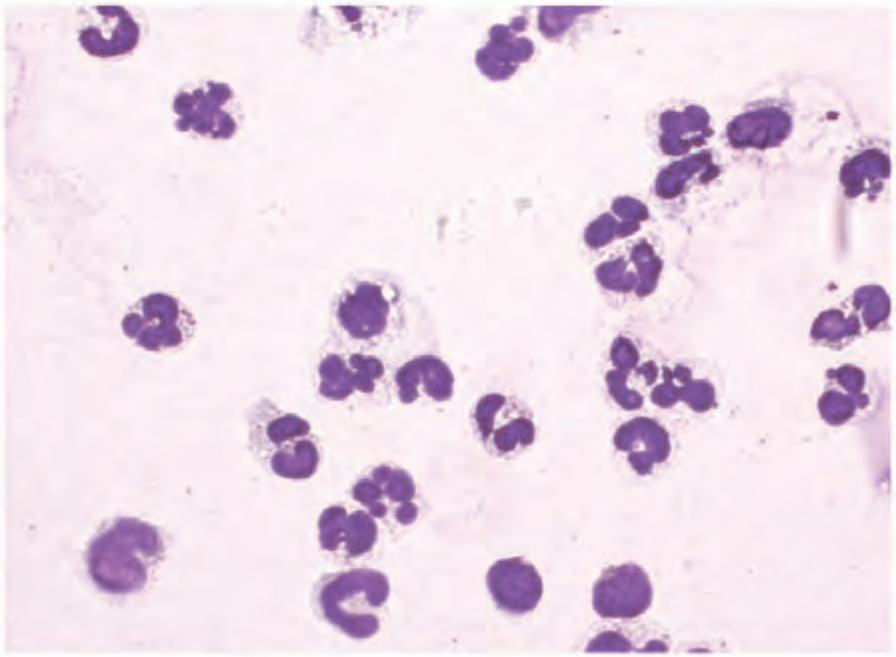


MDSC in RCC Patient



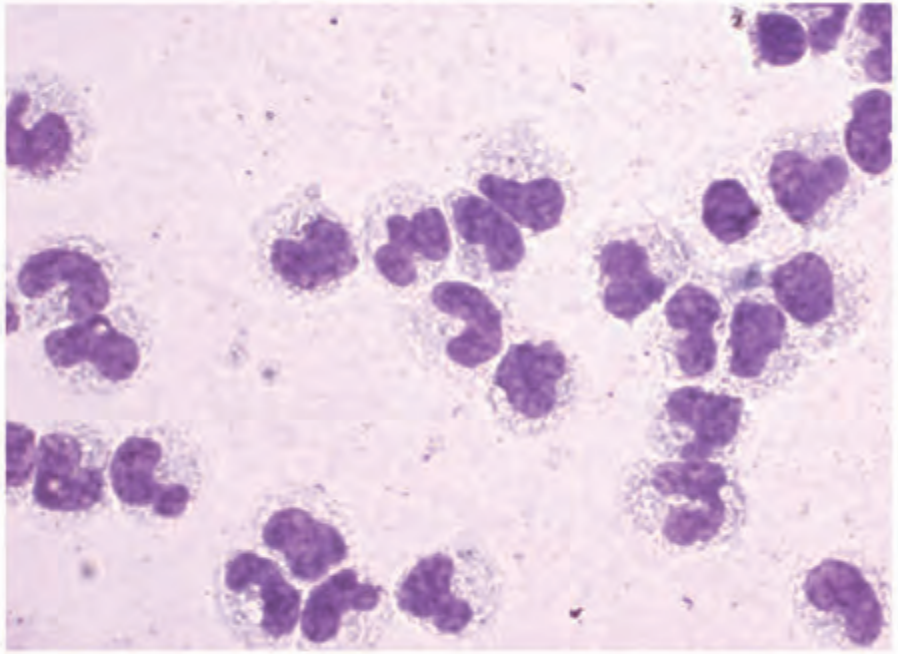
MDSC

CD11b^{+}/CD14^{-}

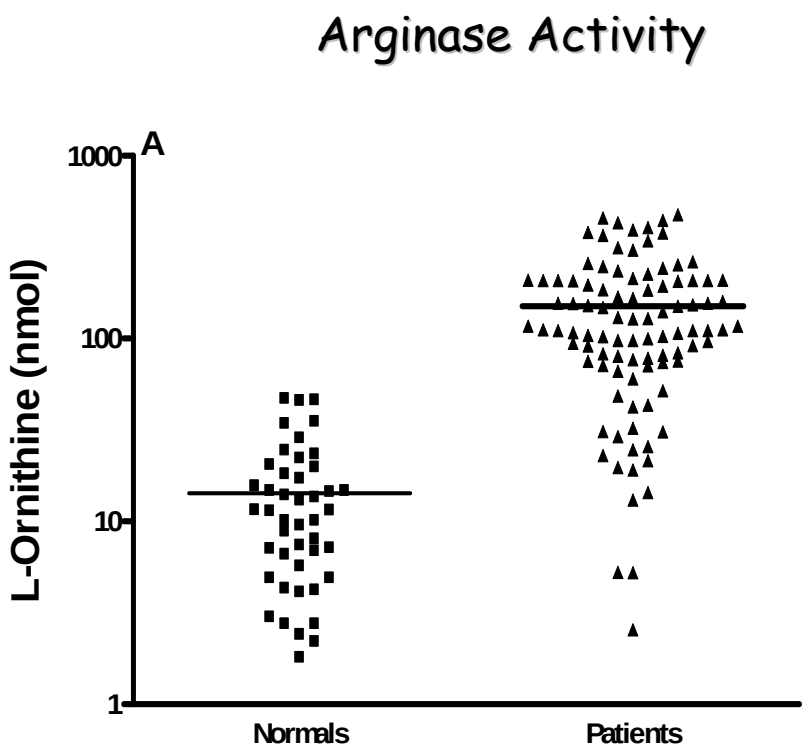


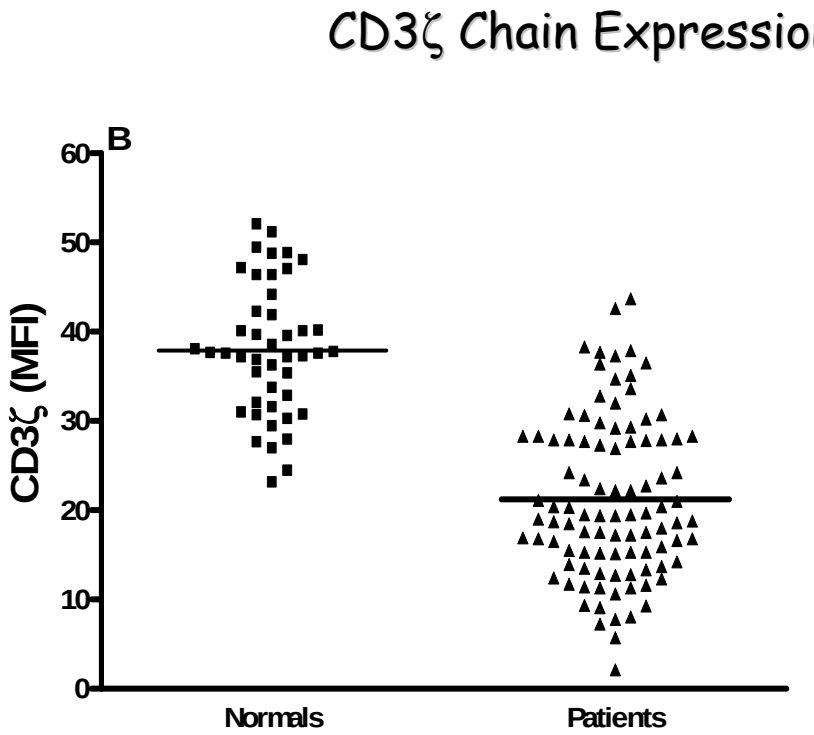
Macrophages

CD11b^{+}/CD14^{+}



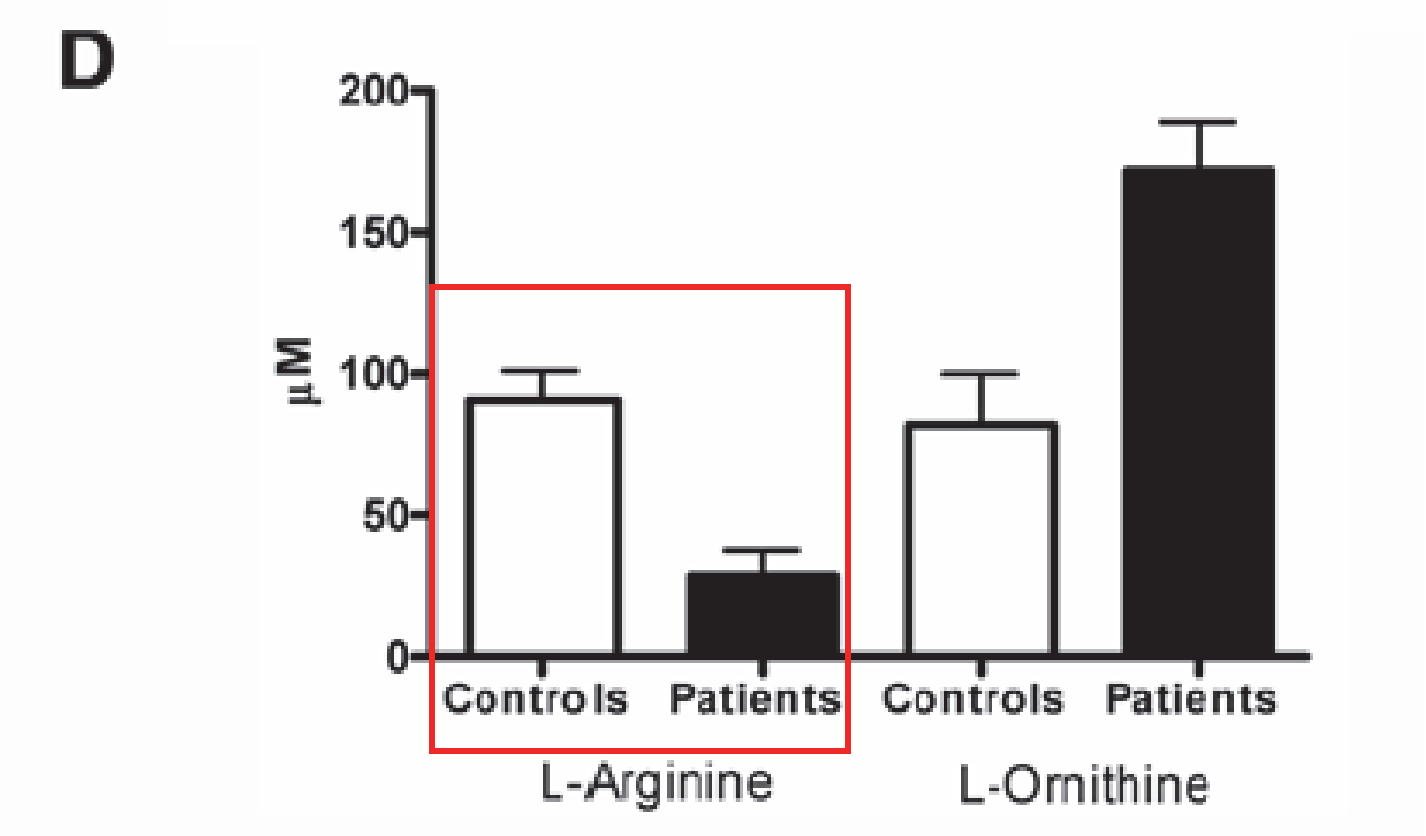
Arginase Activity in RCC Patients



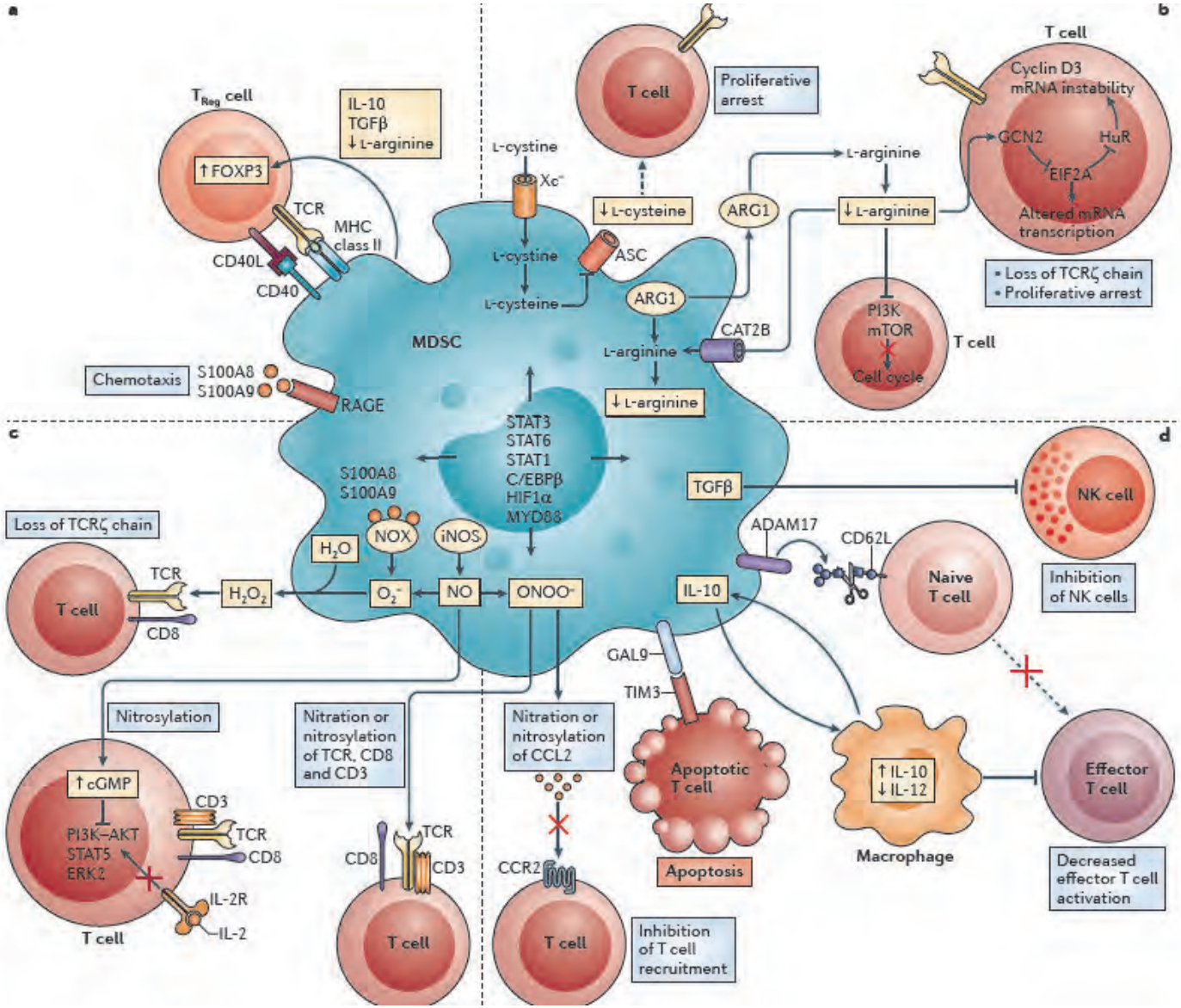


Zea et al.

Arginine and Ornithine in Plasma of RCC Patients



Zea et al.

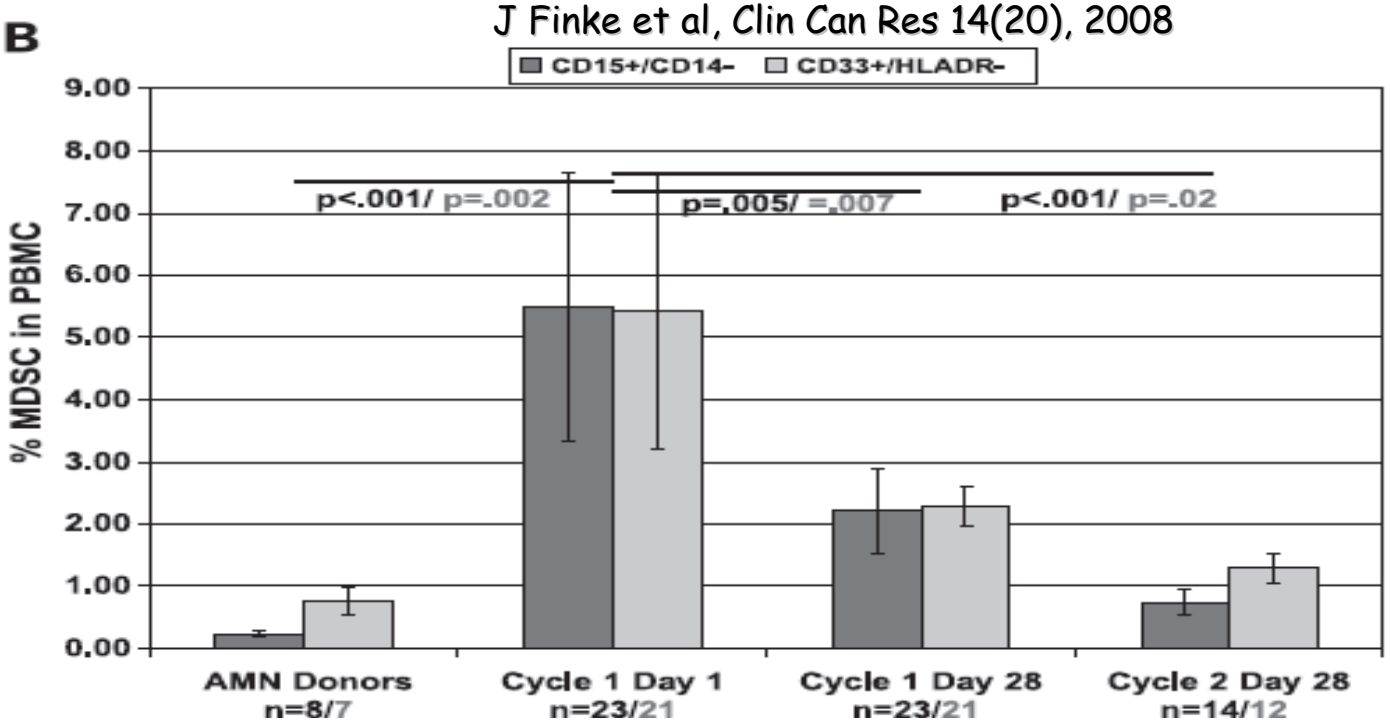

a
b
c
d
T cell
Proliferative arrest
Cyclin D3
mRNA instability
GCN2
HuR
EIF2A
Altered mRNA transcription
• Loss of TCRζ chain
• Proliferative arrest
T cell
PI3K
mTOR
Cell cycle
T cell
L-arginine
↓ L-arginine
ARG1
CAT2B
L-cystine
Xc⁻
↓ L-cysteine
L-cystine
L-cysteine
ASC
ARG1
L-arginine
↓ L-arginine
MDSC
STAT3
STAT6
STAT1
C/EBPβ
HIF1α
MYD88
S100A8
S100A9
RAGE
Chemotaxis
T_Reg cell
↑ FOXP3
IL-10
TGFβ
↓ L-arginine
TCR
MHC class II
CD40L
CD40
S100A8
S100A9
NOX
iNOS
H2O
O2⁻
NO
ONOO⁻
H2O2
Loss of TCRζ chain
T cell
TCR
CD8
TGFβ
NK cell
Inhibition of NK cells
ADAM17
CD62L
Naive T cell
IL-10
GAL9
TIM3
Apoptotic T cell
Apoptosis
↑ IL-10
↓ IL-12
Macrophage
Effector T cell
Decreased effector T cell activation
Nitrosylation
↑ cGMP
PI3K–AKT
STAT5
ERK2
CD3
TCR
CD8
IL-2R
IL-2
T cell
Nitration or nitrosylation of TCR, CD8 and CD3
CD8
TCR
CD3
T cell
Nitration or nitrosylation of CCL2
CCR2
T cell
Inhibition of T cell recruitment

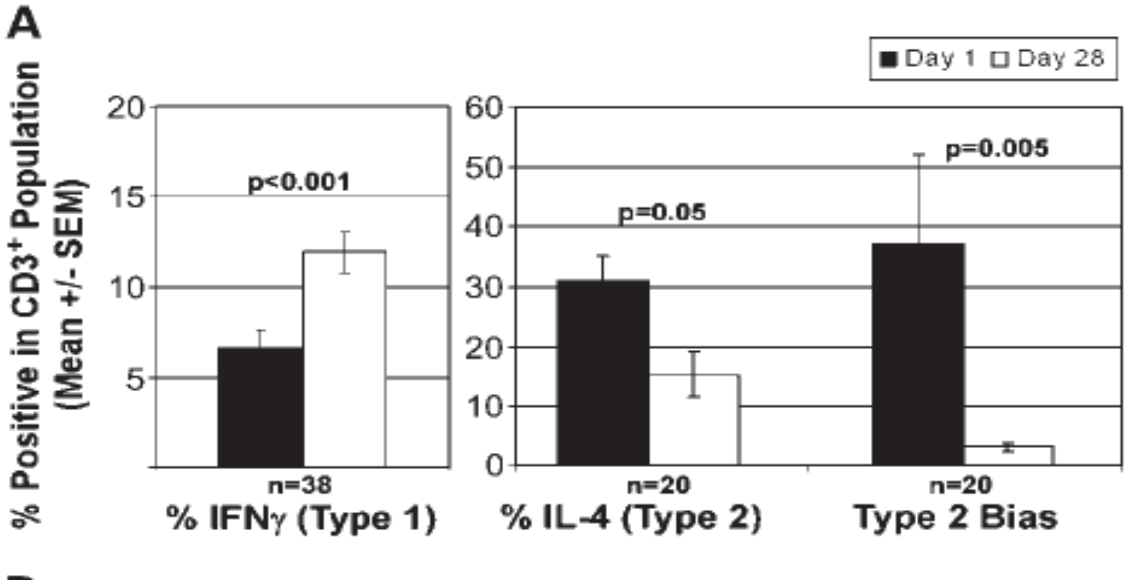
Blocking MDSC

- Arginase inhbitors: Nor-NOHA, BEC and ABH - D. Christiansen
- Tyrosine kinase inhibitors – Sunitinib – J. Finke
- PDE5 inhibitors (Viagra and Cialis): I. Borrello
- NOS2/Arginase inhibitors (nitroaspirin) - E. Bronte
- All-Trans-retinoic acid (ATRA) D. Gabrilovich
- Anti-CD11b – D. Denardo

Sunitinib and MDSC in RCC

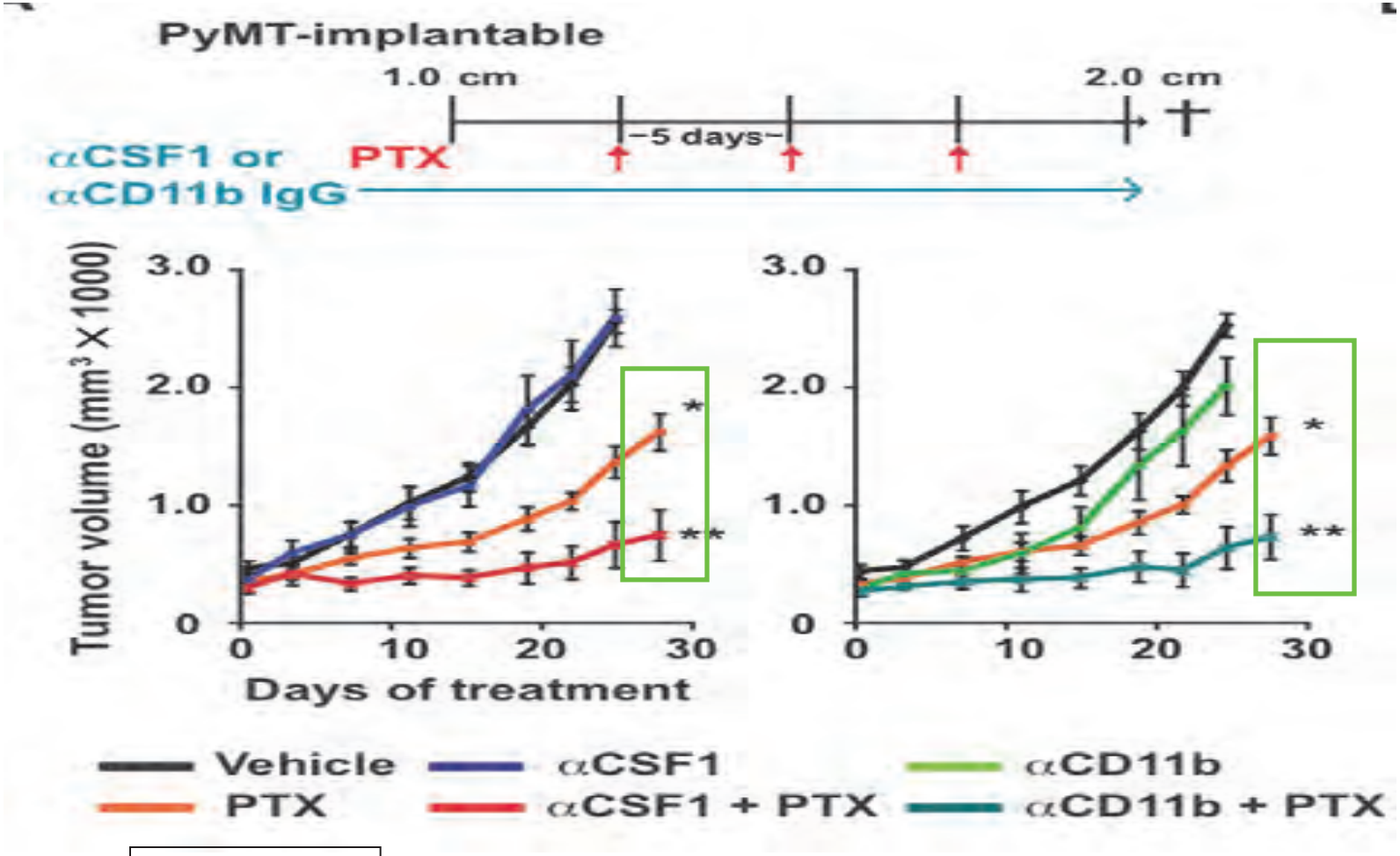
J Finke et al, Clin Can Res 14(20), 2008



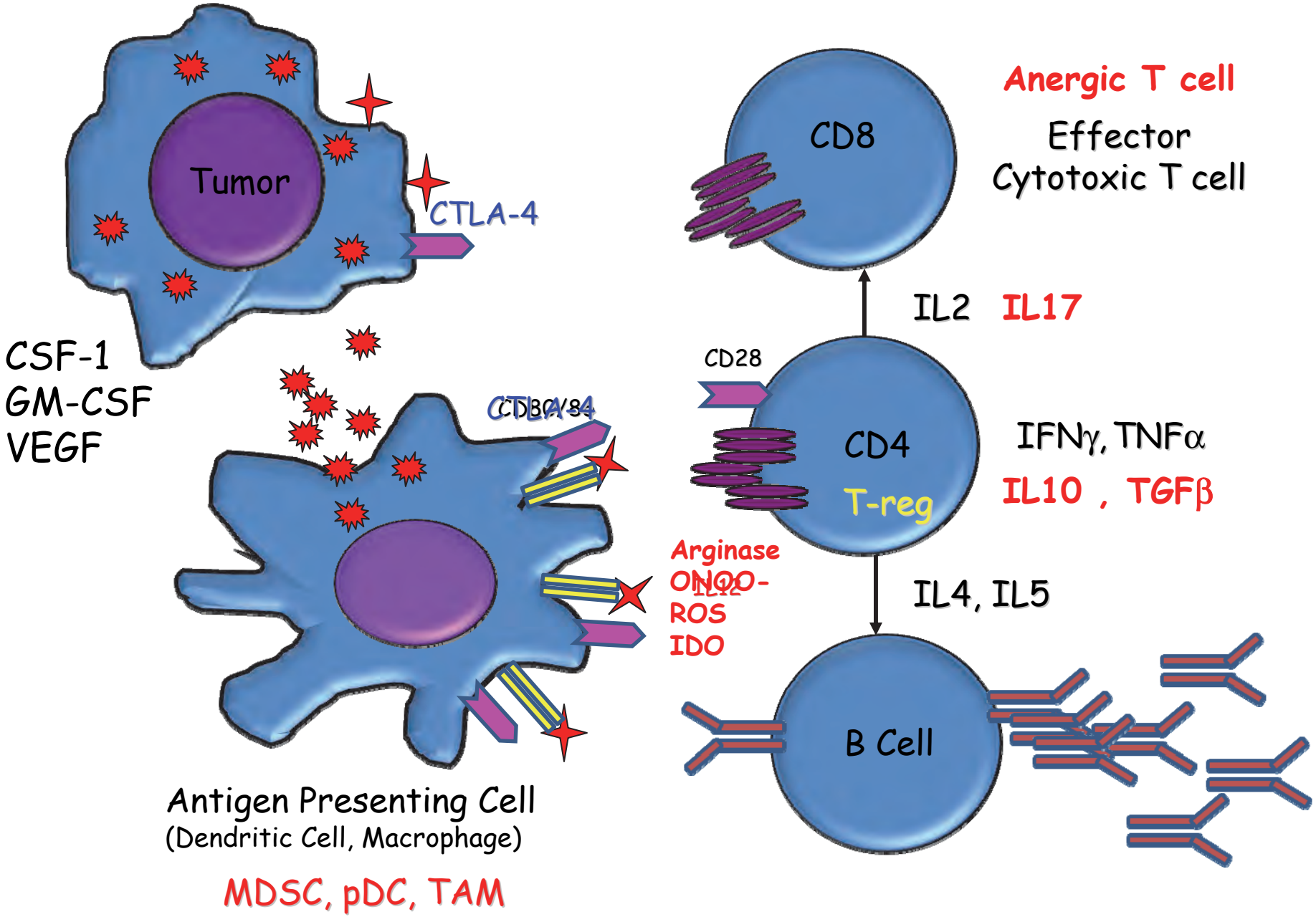


Myeloid Cell Inhibition and Chemotherapy

DeNardo et al. Cancer Discovery 2011



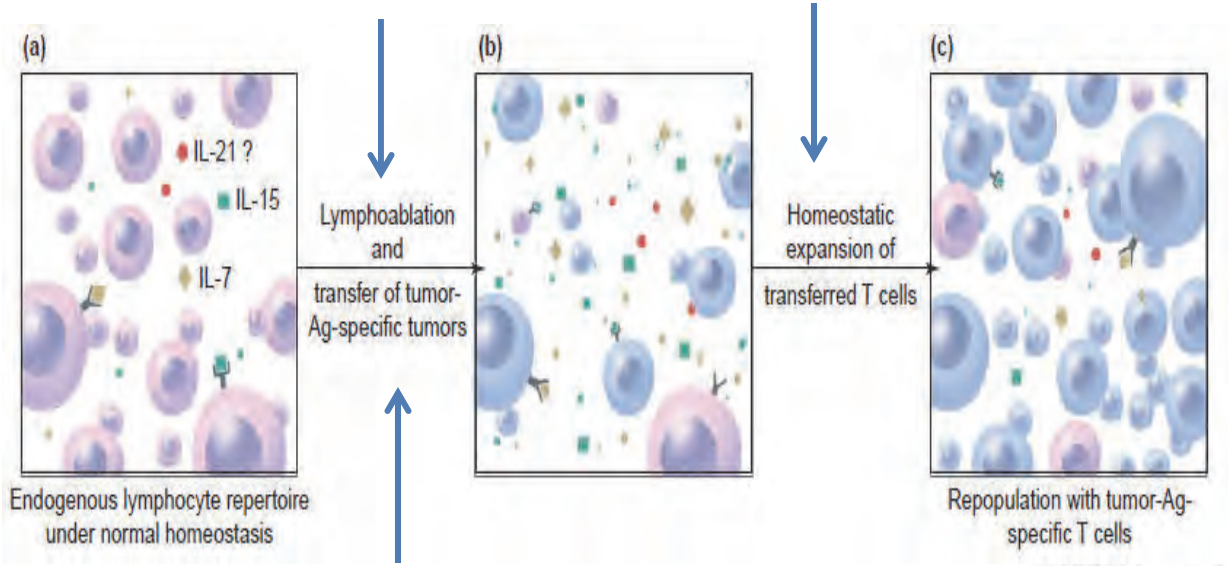
PTX – Paclitaxel


Tumor
CTLA-4
CSF-1
GM-CSF
VEGF
CD80/84
Antigen Presenting Cell
(Dendritic Cell, Macrophage)
MDSC, pDC, TAM
Arginase
ONOO-
IL12
ROS
IDO
CD8
Anergic T cell
Effector
Cytotoxic T cell
IL2
IL17
CD28
CD4
T-reg
IFNγ, TNFα
IL10 , TGFβ
IL4, IL5
B Cell

Lymphodepletion in Adoptive Cellular Therapy

Cytoxan
Fludarabine
TBI

Adoptive Cell Transfer



Depletion of MDSC, T-regs
Eliminate "cytokine sink"

Adapted from Klebanoff et al, Trends in Immunol 26,2005

Research Question

- What is the hierarchy and/or sequence of these suppressor mechanisms?
- What type of tumors and tumor-derived signals determine the type of suppressor cell?
- What is the combination of chemo-immuno therapy that will block the immunosuppressive cells and induce a therapeutic anti-tumor response?

Chronic Inflammation : Turning Friend into Foe