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Supported by an Independent Educational Grant from BAYER

RATIONAL TO TARGET IMMUNE CHECKPOINTS IN DISEASES

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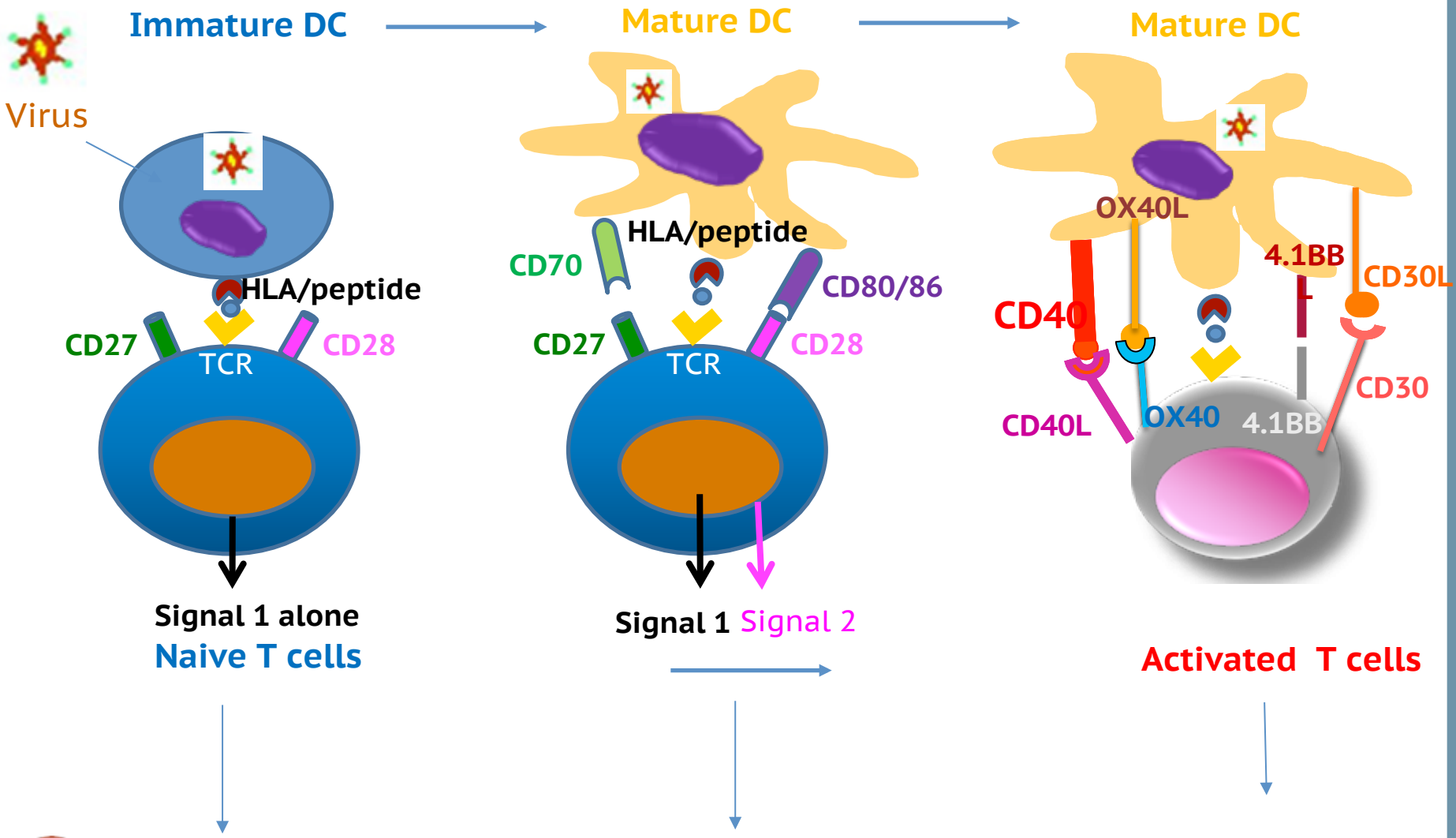
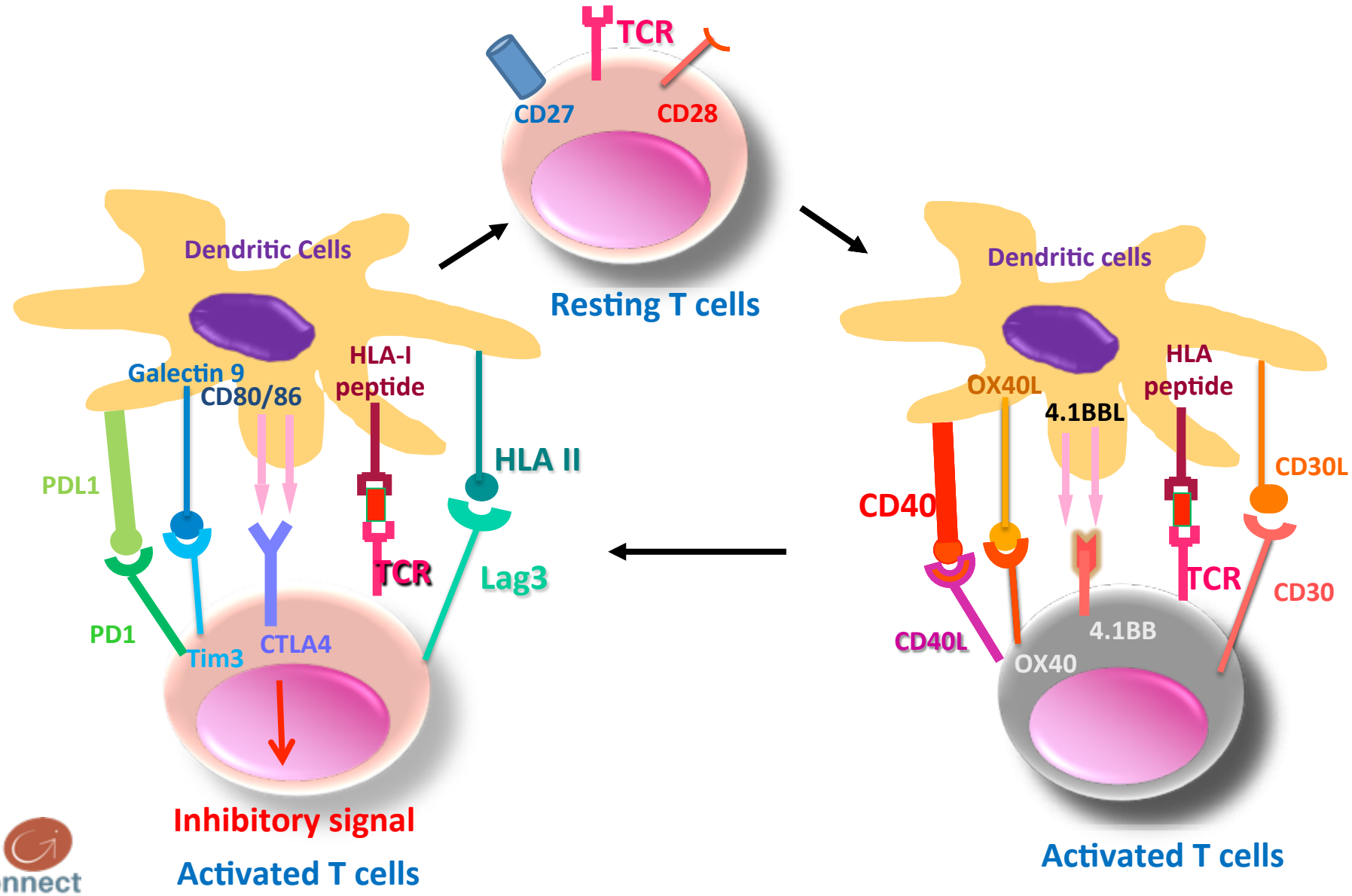
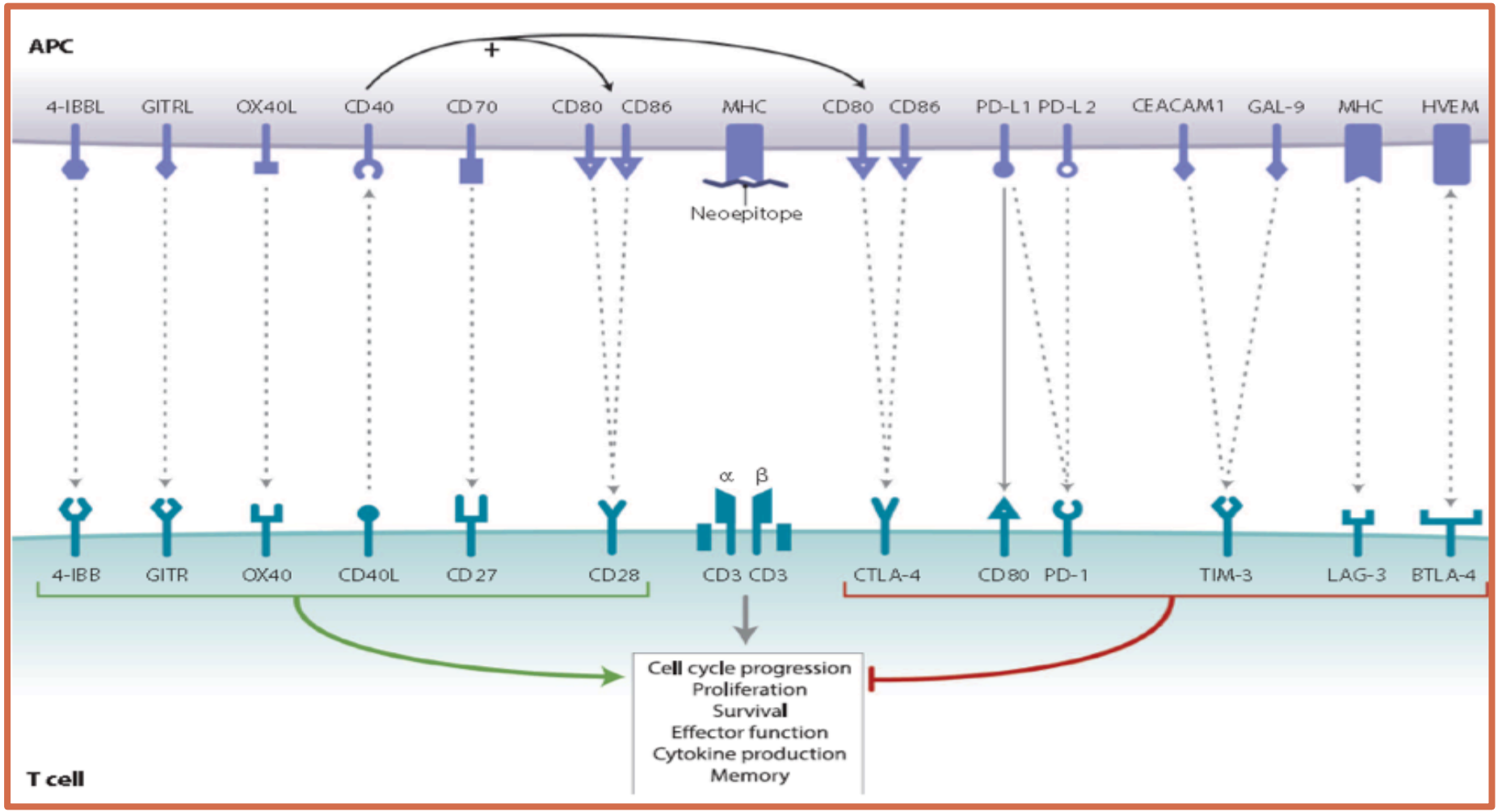
COSTIMULATORY ACTIVATING MOLECULES ARE REQUIRED FOR T CELL PRIMING



INHIBITORY RECEPTORS REGULATE NORMAL ACTIVATION OF T CELLS

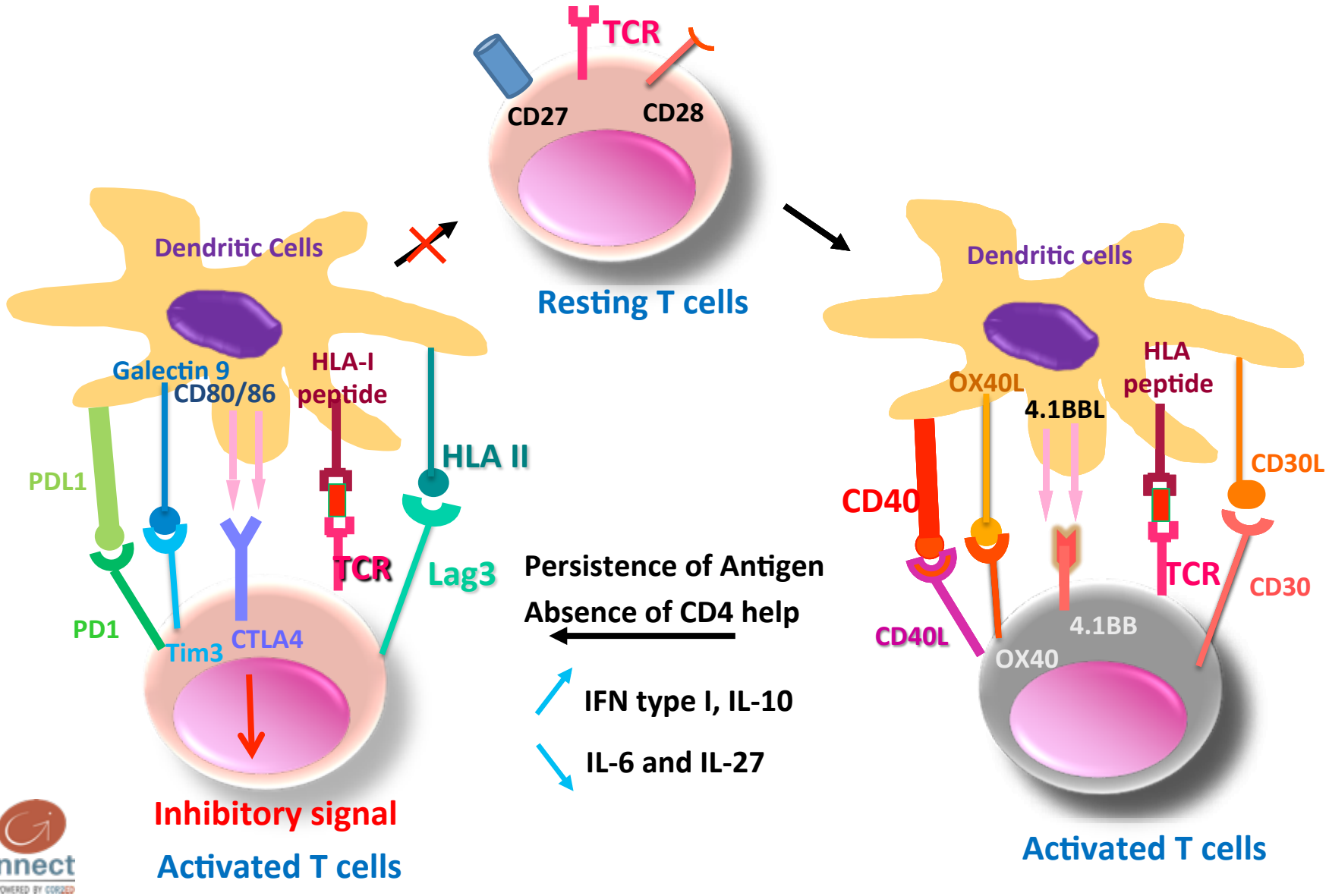


MULTIPLE CO-SIGNALING MOLECULES REGULATE ALL PHASES OF THE T CELL LIFE CYCLE



Lesokhin AM Sci Transl Med 2015

SUSTAINED INHIBITORY RECEPTORS EXPRESSION LEADS TO EXHAUSTED T CELLS



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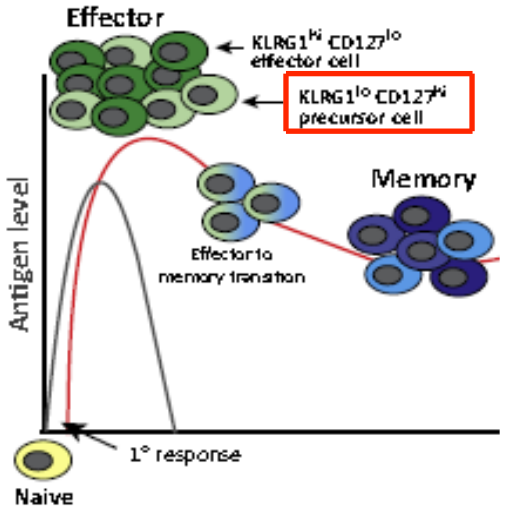
MEMORY AND EXHAUSTED T CELLS

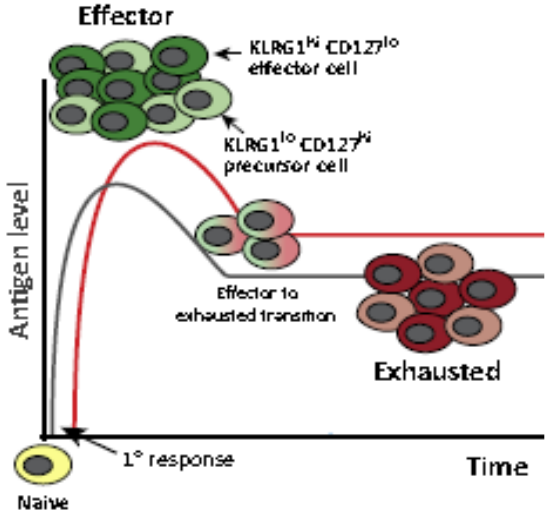
(A) Acute antigen/functional memory



- CD127 (IL-7R)
- CD122 (IL-2Rβ)
- CXCR3
- CD62L

- Proliferation potential +++
- Cytokine production +++
- IL-7 or IL-15 driven self renewal +++
- Antigen dependency -

(B) Chronic antigen/exhaustion



Inhibitory receptors

PD-1, Lag3, Tim3, CD160, TIGIT, 2B4

- Proliferation potential +/-
- Cytokine production +/-
- IL-7 or IL-15 driven self renewal -
- Antigen dependency ++

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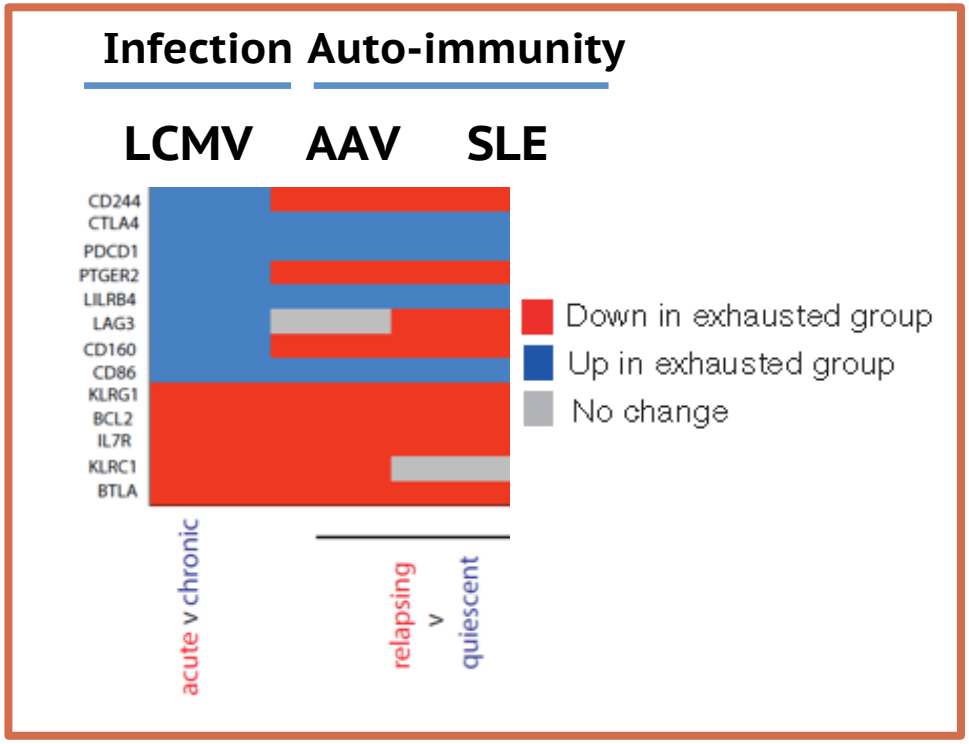
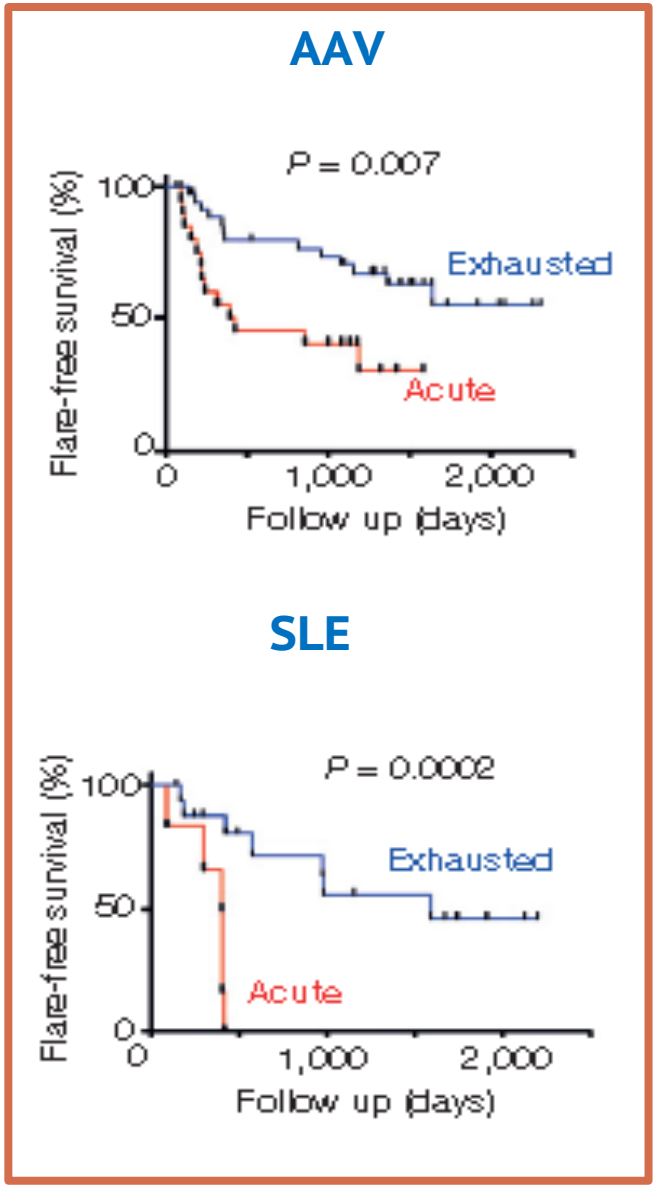
Adapted from Pauken KE Trends Immunol 2015

CLINICAL ROLE AND SIGNIFICANCE OF EXHAUSTED T CELLS DEPEND ON PATHOLOGICAL CONTEXT

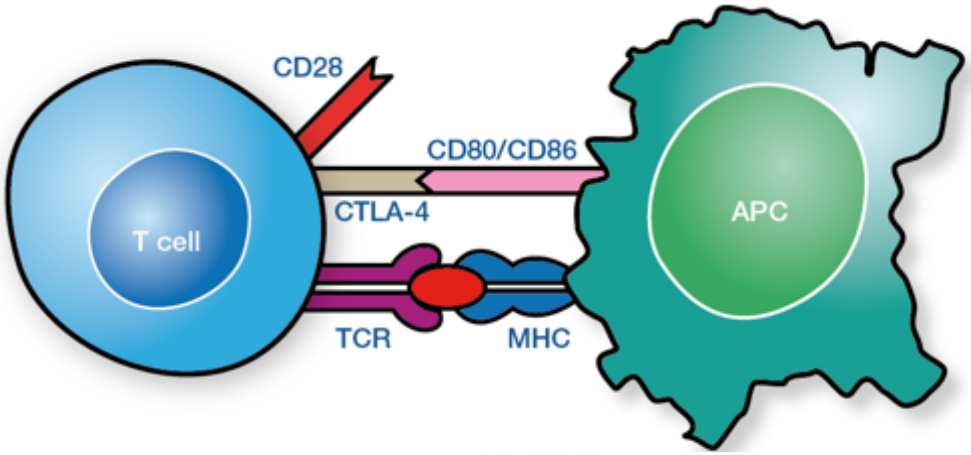




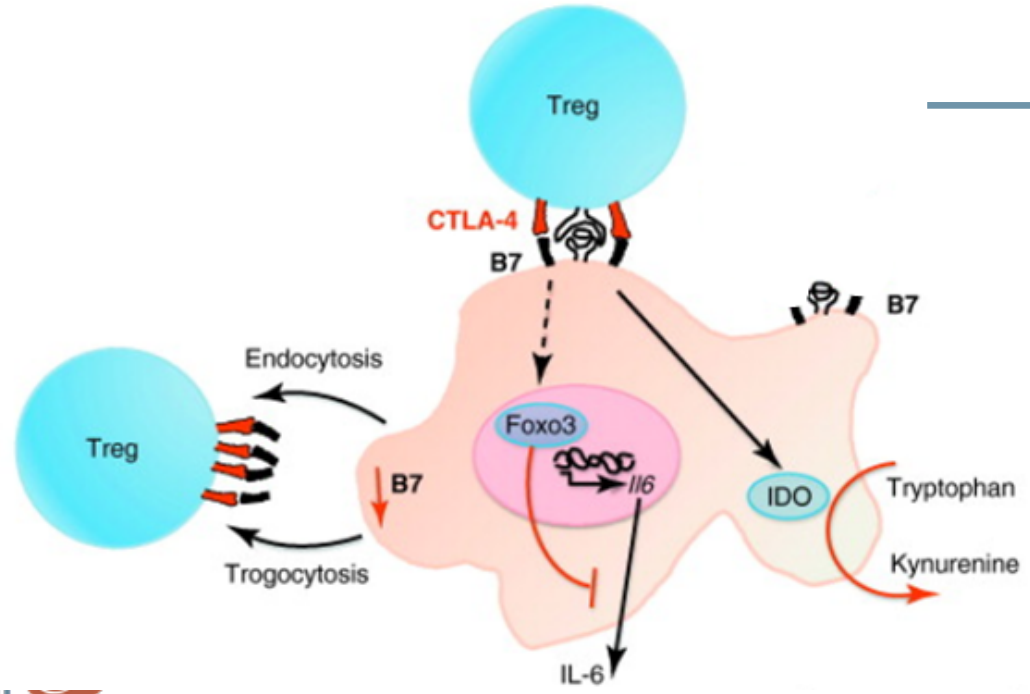
AAV: Antineutrophil cytoplasmic antibody-associated vasculitis
SLE: Systemic lupus erythematosus
LCMV: Lymphocytic Choriomeningitis Virus

McKinney EF Nature 2015

FOCUS ON CTLA-4 AND PD1/PD-L1 TARGETS OF APPROVED DRUGS IN ARTHRITIS AND CANCERS



CTLA-4 competes favorably with CD28 for binding to CD80/ CD86 (higher avidity) and delivers negative signal to T cells



Inhibition T cell activation

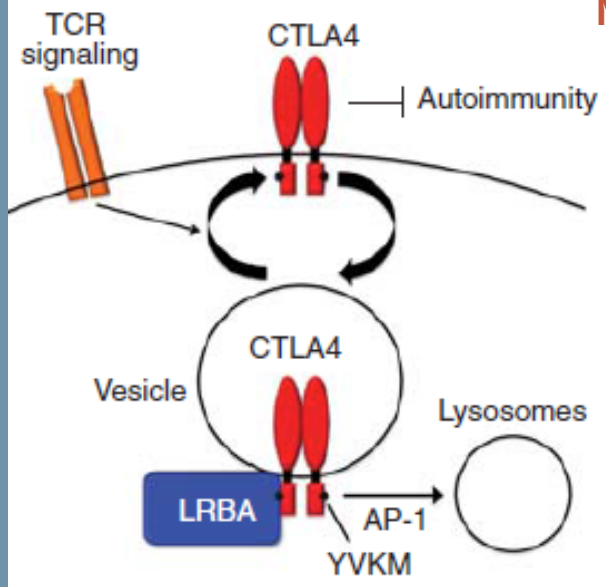
Inhibition T cell activation

Wing K Trends Immunol 2011

DEFECT IN CTLA-4 LEADS TO T CELL ACTIVATION AND AUTOIMMUNITY

- Heterozygous mutations CTLA-4

Impaired Foxp3^{+}regulatory T cell function
Hyperactivation of effector T cells
Autoimmune cytopenia/autoimmune enteropathy



Mutation LRBA leads to increase CTLA-4 degradation in lysosome

↓

Autommunity, Lymphoproliferation

↓

Clinical improvement with CTLA4-Ig (Abatacept)

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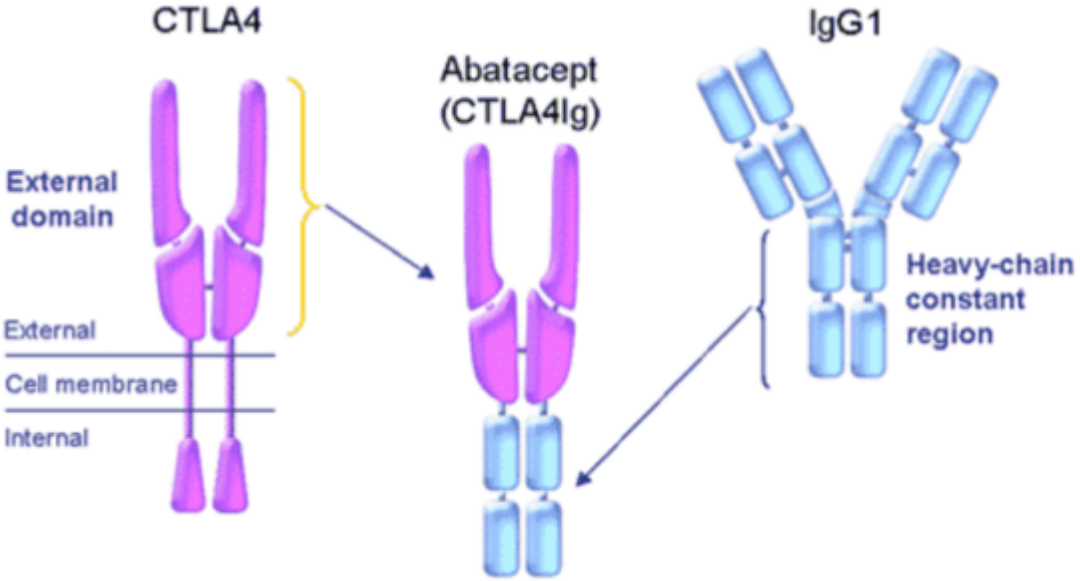
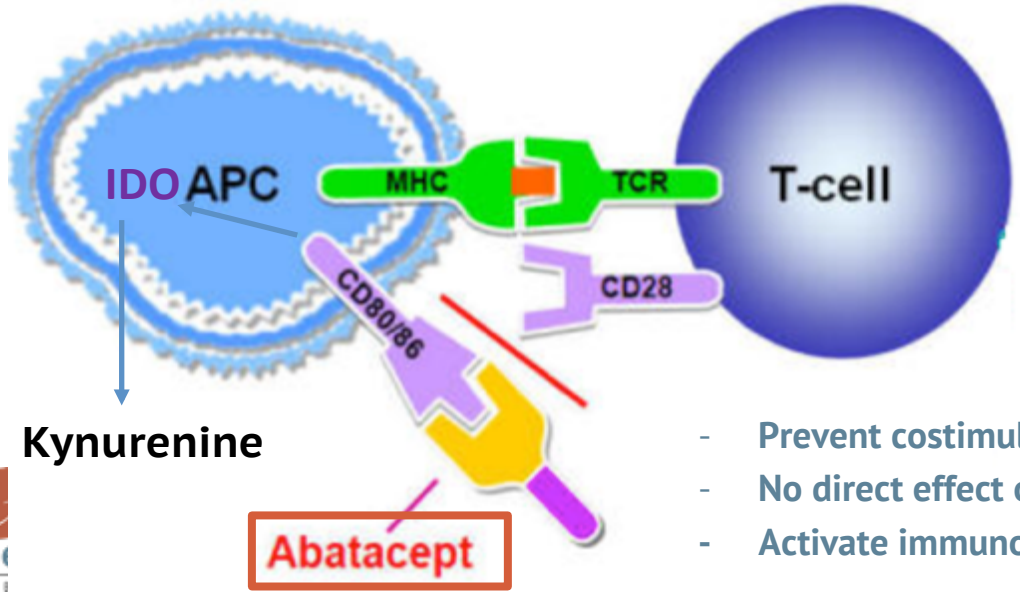
Kuehn HS et al Science 2014; Schubert D Nat Med 2014; Lo B Science 2015

ABATECEPT (ORENCIAR): STRUCTURE AND MECHANISMS OF ACTION

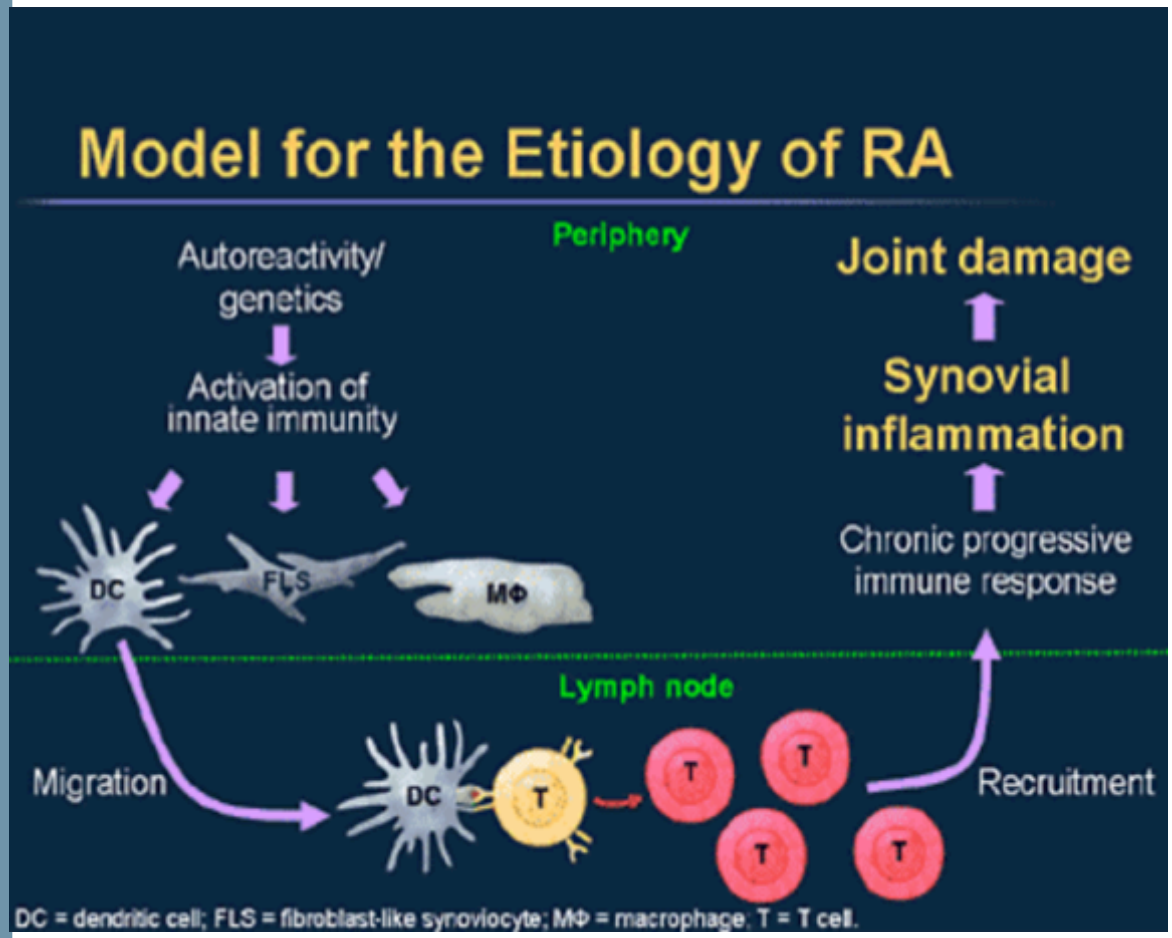


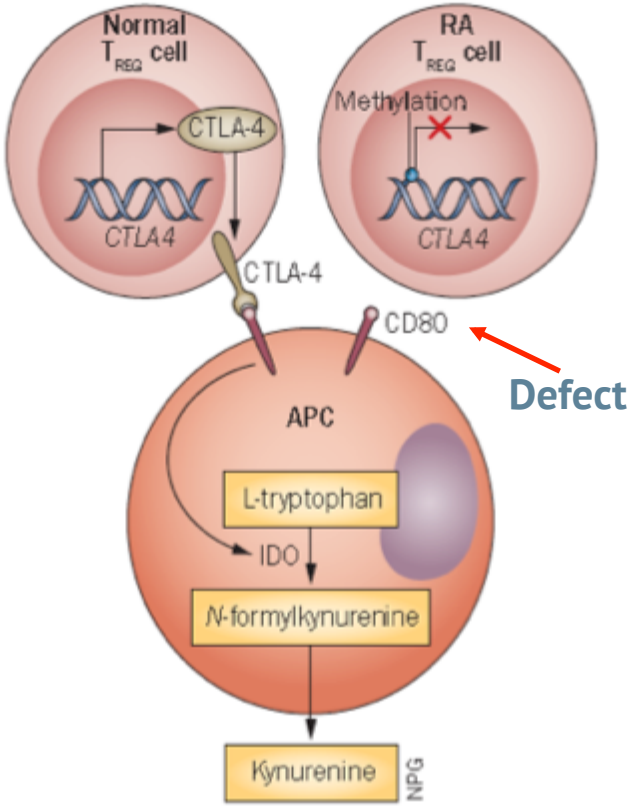
Fusion protein : Extracellular domain of hCTLA-4 linked to a modified Fc domain of IgG1 which does not fix Fc receptor and does not activate complement (Clinically approved in Rheumatoid Arthritis (RA) and Juvenile Idiopathic Arthritis).



- Prevent costimulatory binding of CD28 on naive T cells
- No direct effect on T cells (?)
- Activate immunosuppressive regulatory network on APC

HYPERACTIVATION OF T CELLS AND DEFECT IN TREG FUNCTION SECONDARY TO LOW CTLA-4 EXPRESSION ARE HALLMARKS OF RHEUMATOID ARTHRITIS (RA)



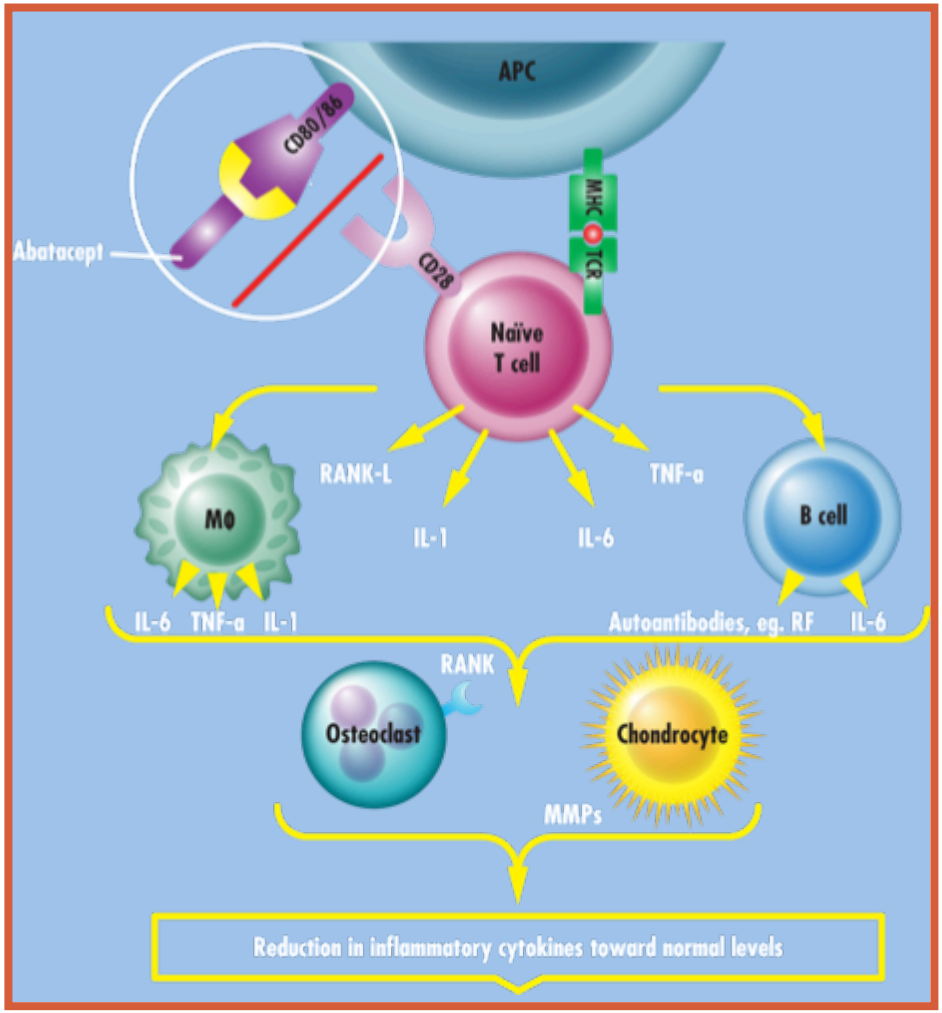


Moreland LW Medscape. Bernard RJ Nat Rev Rheumatol 2014

ABATACEPT WORKS EARLY ON IN THE INFLAMMATORY CASCADE

Decrease T-cell activation and proliferation

Decrease pro-inflammatory cytokine secretion from activated synovial macrophages



Upstream modulation

Decrease autoantibody

(e.g. RF) reduces clonal expansion

Downstream impact

RF=rheumatoid factor; APC=antigen-presenting cell; MHC=major histocompatability complex; TCR=T-cell receptor; MΦ=macrophage

Adapted from Choy EH, et al. NEJM 2001;344:907–16; Adapted from Linsley PS, et al. J Exp Med 1991;174:561–9

CANCER IMMUNOTHERAPY : FROM CONCEPT TO CLINICAL PRACTICE

Immunotherapy was often considered as only efficient to cure tumors in mice !

Anti-CTLA-4

Anti-PD-1

Approved in metastatic melanoma and non-small-cell lung cancer

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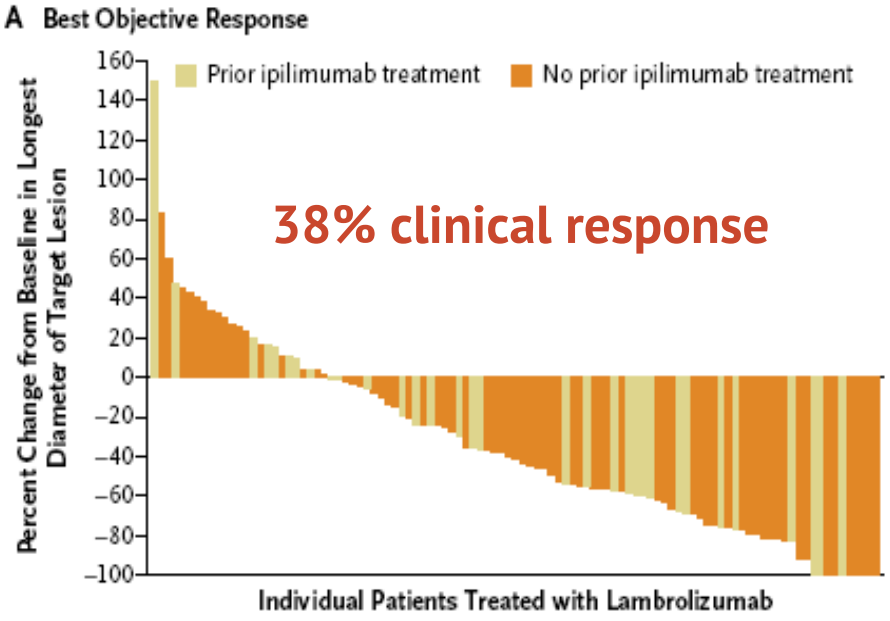
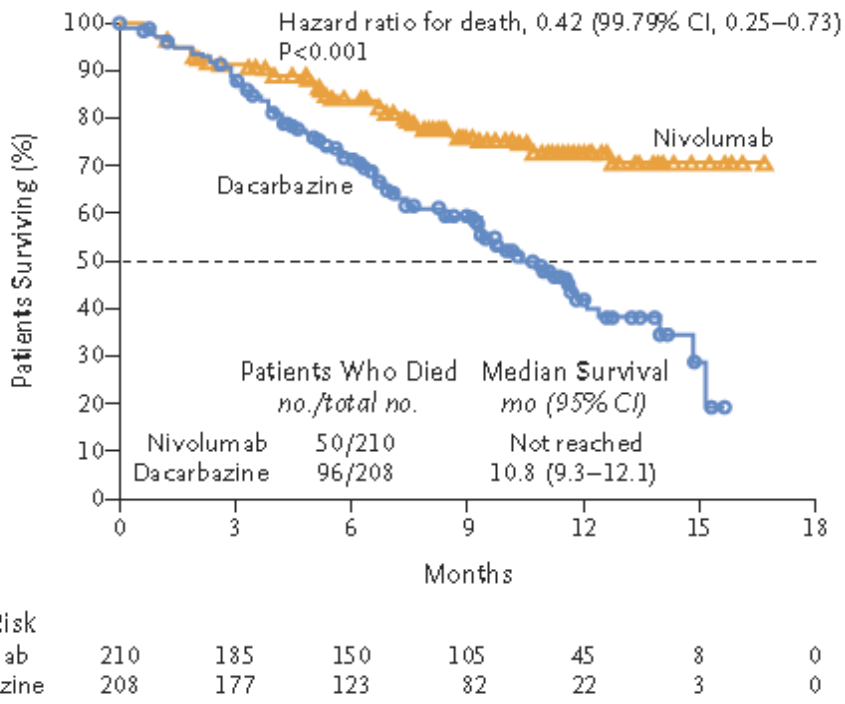
BLOCKADE OF PD-1-PD-L1 AXIS LED TO DRAMATIC CLINICAL RESPONSES IN MELANOMA PATIENTS

Melanoma





Hamid O N Engl J Med 2013

Robert C et al N Engl J Med 2014

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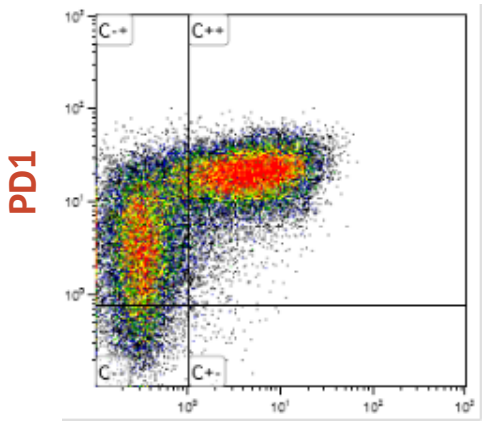
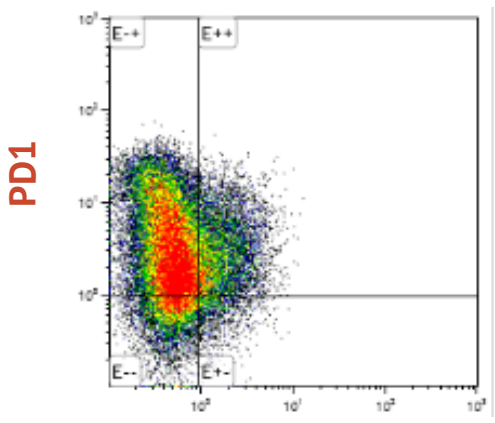
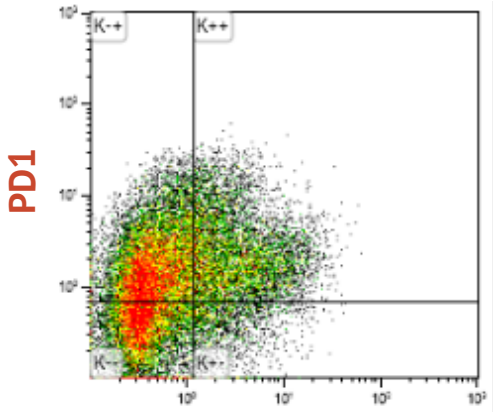
EXPRESSION OF INHIBITORY COSTIMULATORY MOLECULES BY INFILTRATING T CELLS IN THE TUMOR MICROENVIRONMENT MAY EXPLAIN THEIR FAILURE TO ERADICATE TUMORS



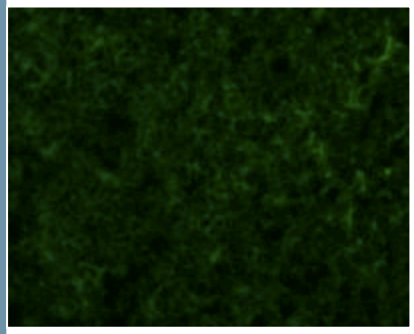
Tim3



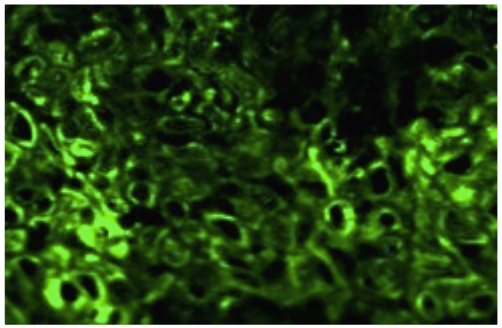
LAG3



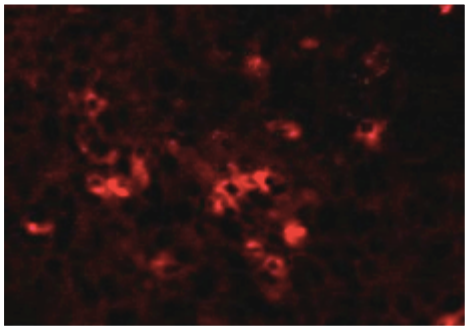
CTLA-4



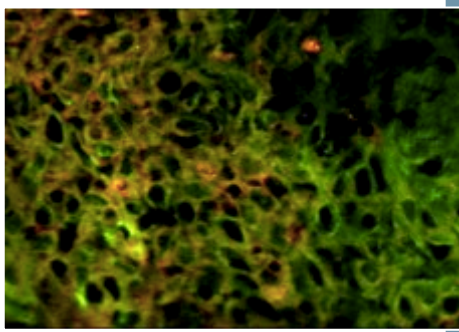
PD-L1
isotype control



PD-L1
(tumor cells)



PD-1
T cells



PD-L1/PD-1

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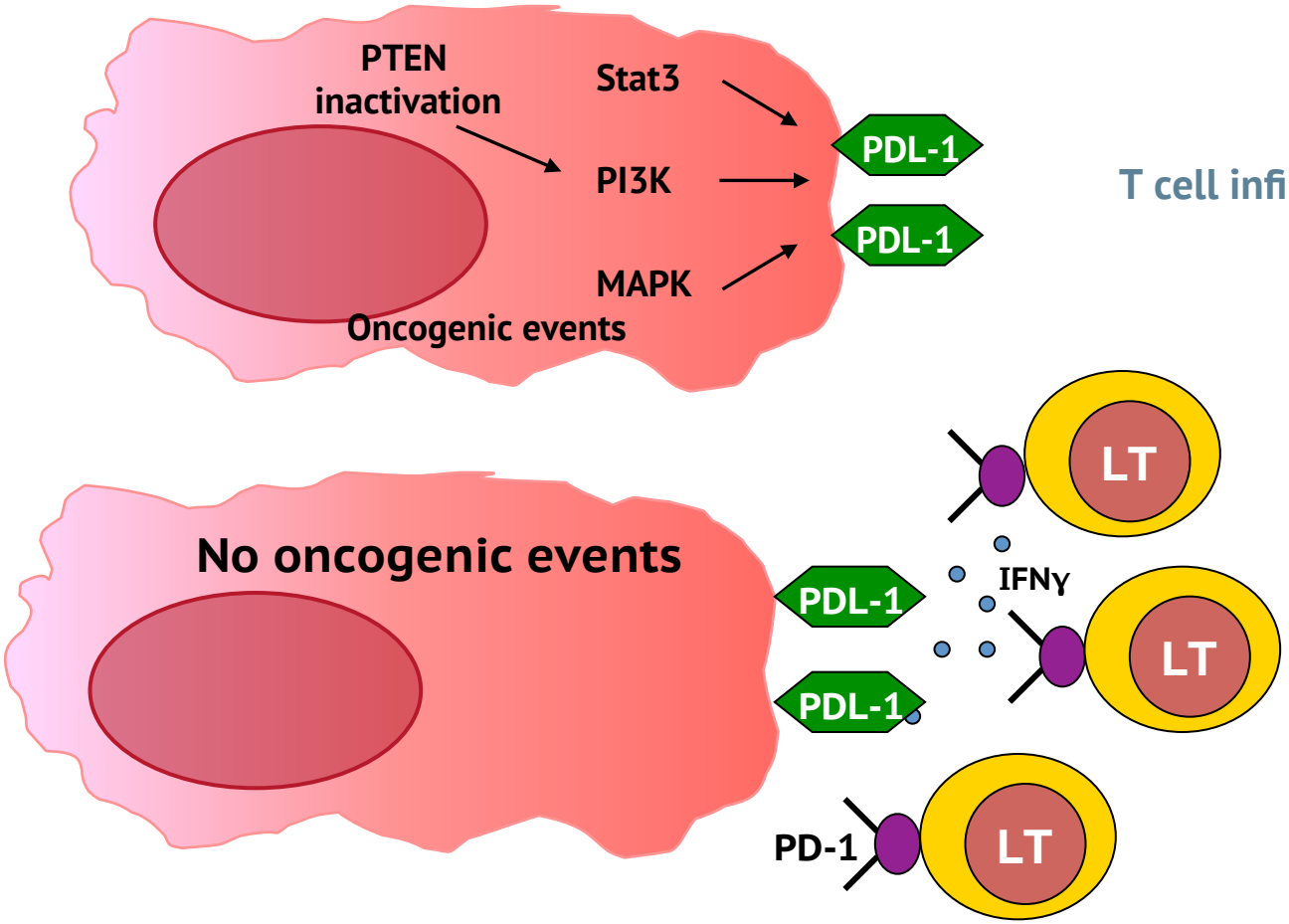
Badoual C et al Cancer Res 2013

SIGNIFICANCE OF PD-L1 AND PD-1 EXPRESSION IN HUMAN CANCERS

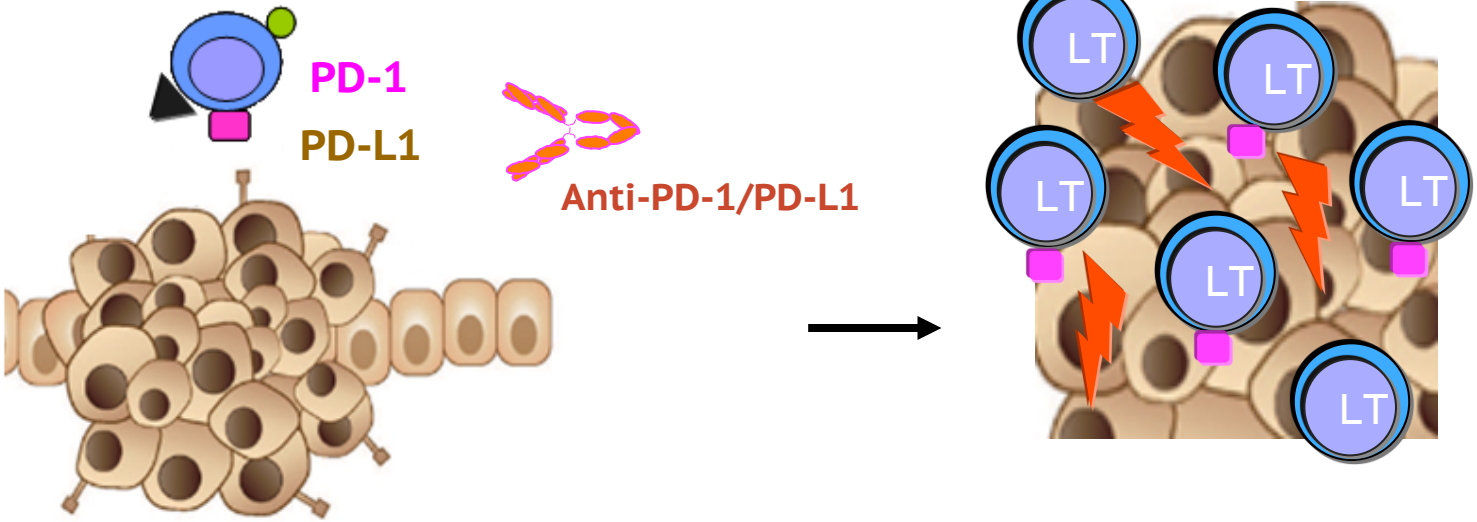


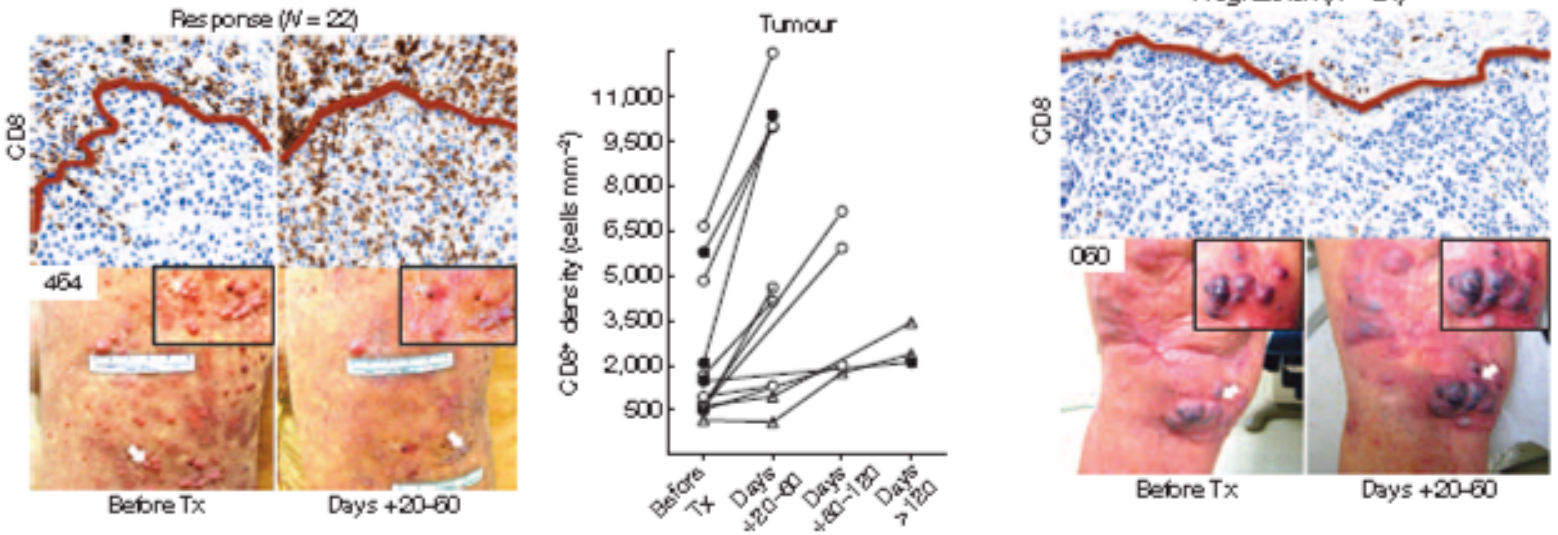
T cell infiltration not required

Upregulation of PD-L1 by IFNg
producing T cells recognizing tumor cells

Badoual C et al Med Sci 2013

BLOCKADE OF PD-1-PD-L1 PATHWAY REVERSE T CELL ANERGY LEADING TO PROLIFERATION OF PRE-EXISTING ANTI-TUMOR T CELLS

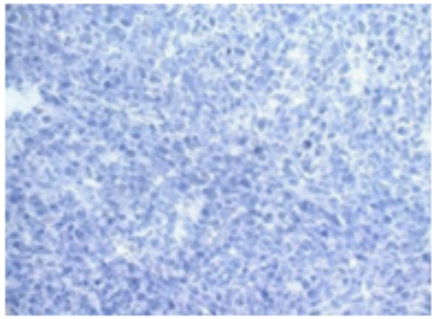


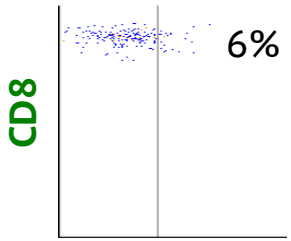


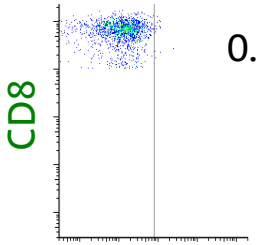
Tumey PC et al Nature 2014

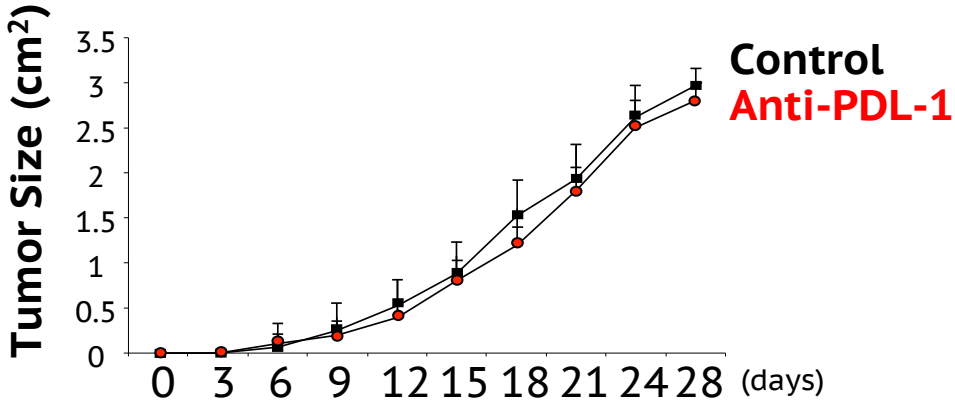
OTHER ARGUMENTS ABOUT THE REQUIREMENT OF THE EXISTENCE OF PRE-EXISTING T CELLS FOR THE SUCCESS OF PD-1-PD-1 BLOCKADE

TC1 : epithelial tumor expressing E6-E7 and PDL-1







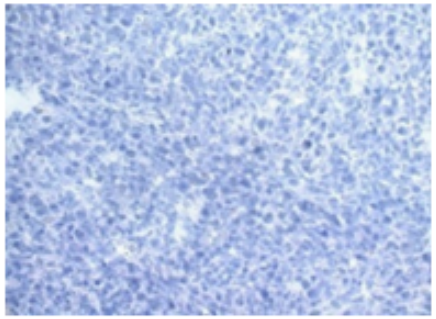


Badoual C et al, Cancer Res, 2013

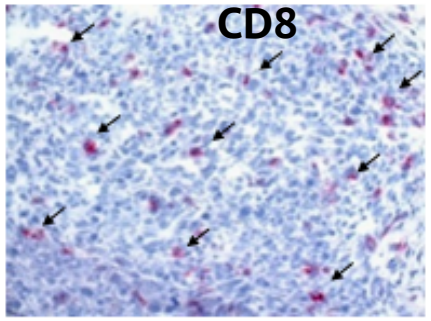
SYNERGY BETWEEN A THERAPEUTIC ANTI-HPV CANCER VACCINE AND THE BLOCKADE OF PD-1-PDL-1 INTERACTION

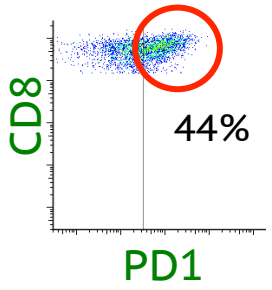
TC1 : epithelial tumor expressing E6-E7 and PDL-1

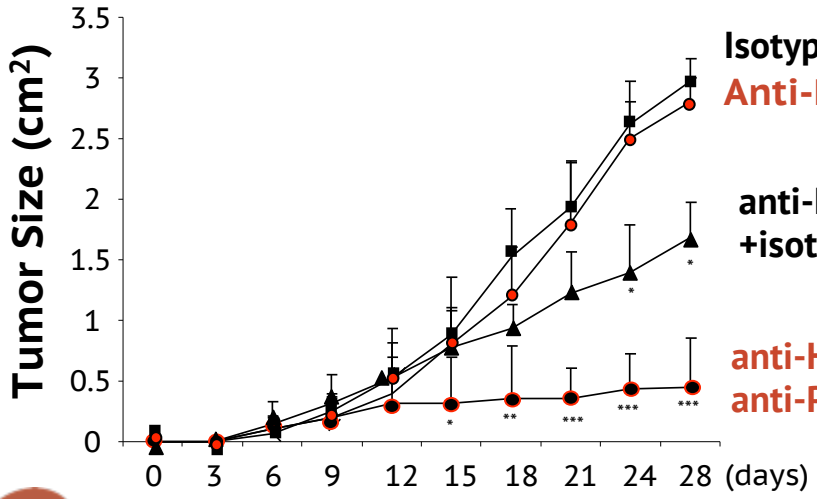
Not vaccinated



HPV vaccine



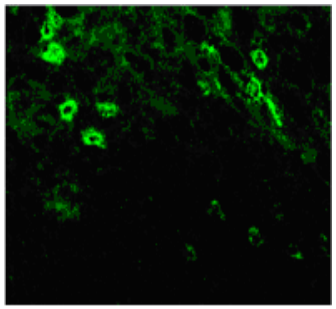




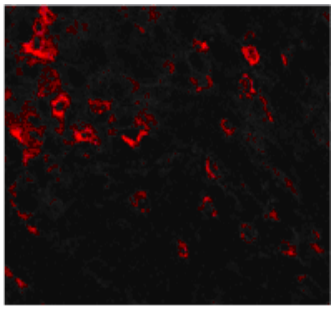
Endogenous specific CD8⁺ T cell response correlates with anti-PDL-1 clinical efficacy

Badoual C et al, Cancer Res, 2013

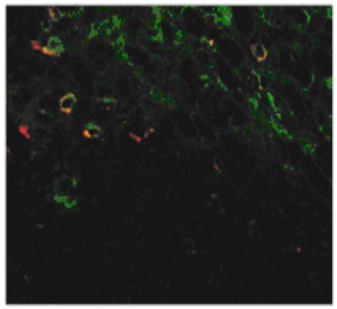
IN SITU IMMUNOFLUORESCENCE ANALYSIS OF TUMOR CELLS AND INFILTRATING IMMUNE CELLS



CD8

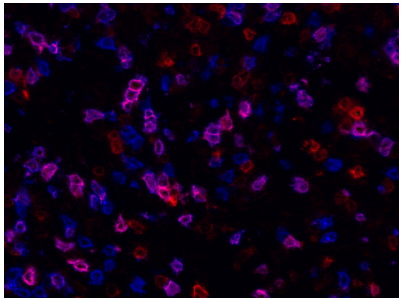


PD-1



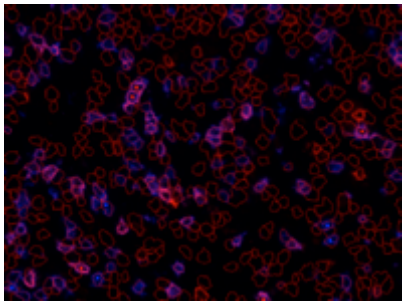
CD8-PD-1

Head and neck

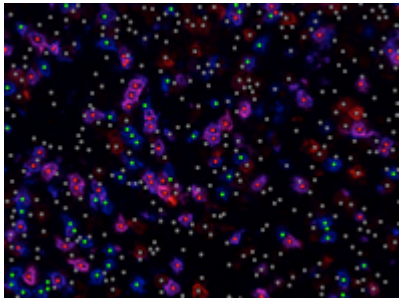


Kidney (RCC)

CD8
PD1



Cell segmentation



Cell phenotyping

Predictive biomarker of response to checkpoint inhibitors

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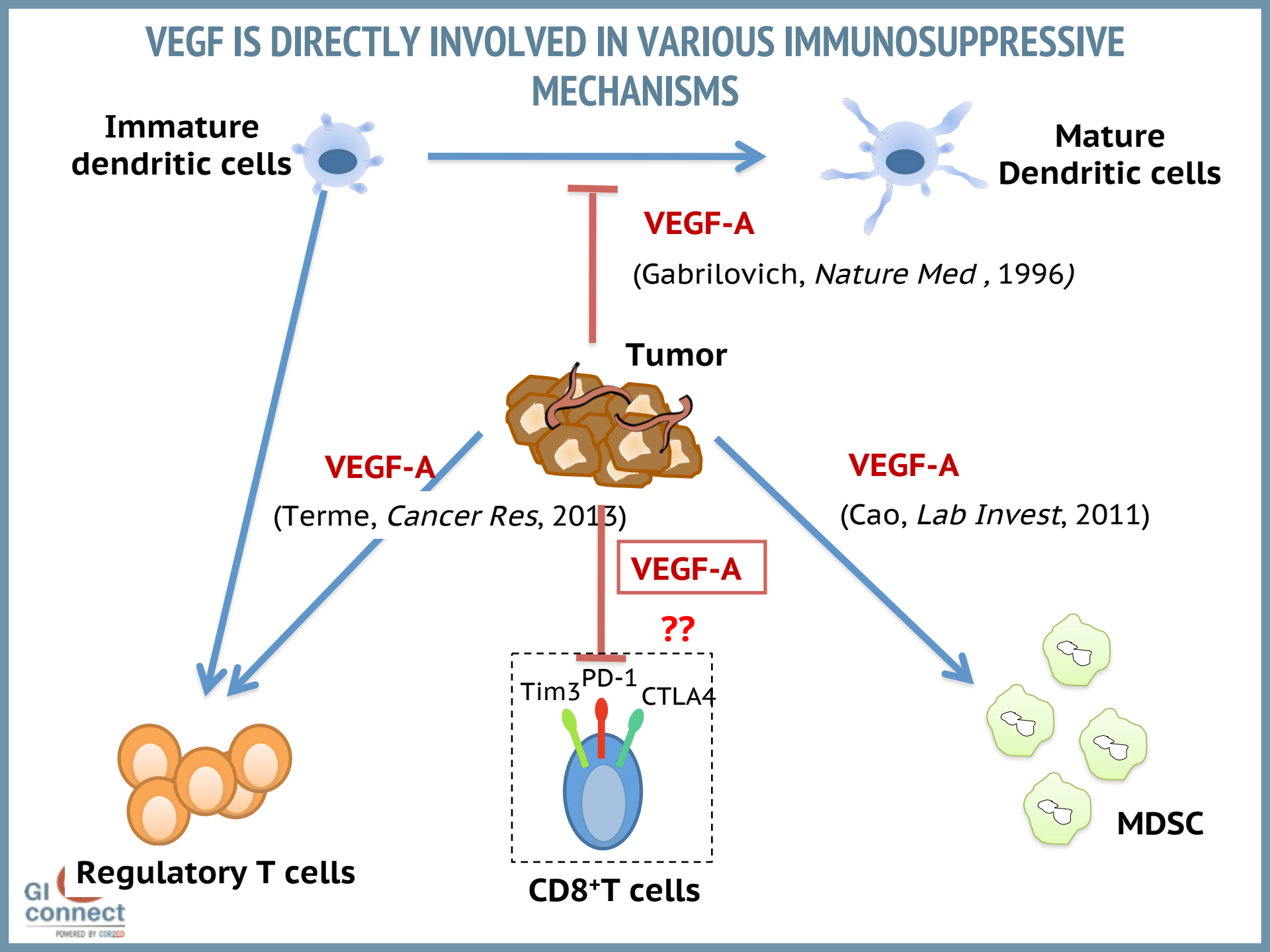
Badoual C et al, Cancer Res, 2013

- Activating inhibitory receptor pathways demonstrate their efficacy in auto-immune diseases (**Abatecept** approved in **Rheumatoid arthrisis** and **JIA**) and transplantation (**betalacept** in **kidney transplantation**)

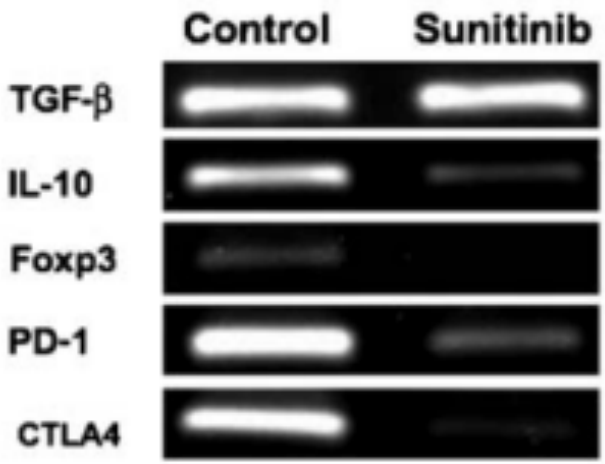
- Blockade of the interaction of checkpoint with their ligands (**ipilimumab**, **nivolumab, pembrolizumab**) constitutes a new validated therapeutic approach in **melanoma** and **NSCLC** and raising high hopes in many others cancers **(bladder cancer, gastric cancer, renal cancer, Hodgkin lymphoma)**

- Preexisting anti-tumor T cells represent a prerequisite for therapeutic response to immunomodulators.

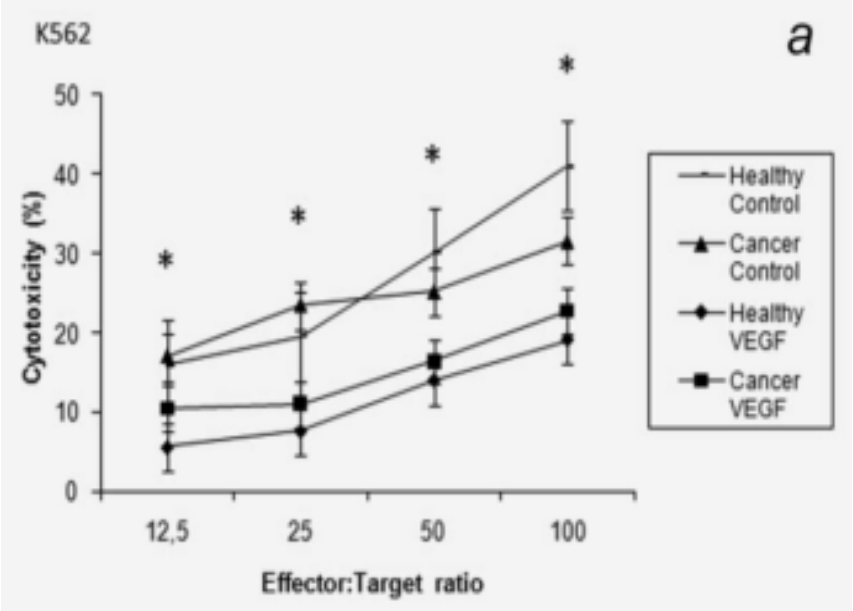
VEGF IS DIRECTLY INVOLVED IN VARIOUS IMMUNOSUPPRESSIVE MECHANISMS



REGULATION OF PD-1 EXPRESSION AND OTHER CHECKPOINT INHIBITORS BY VEGF AND ITS ROLE IN T CELL EXHAUSTION



(Ozao-Choy, Cancer Res, 2009)



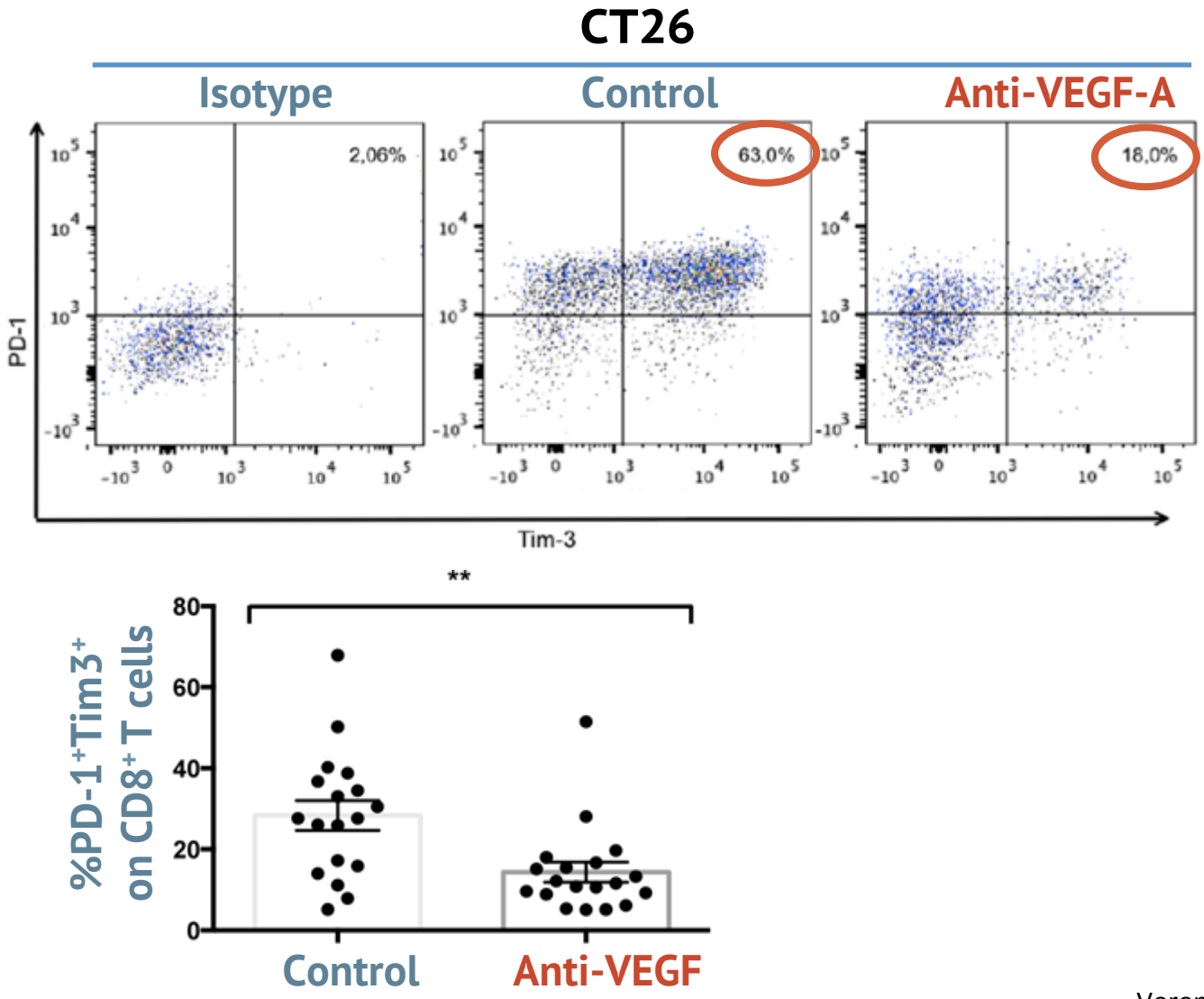
(Ziogas, Int J Cancer, 2012)

Decrease of mRNA encoding PD-1 after sunitinib therapy

Role of VEGF in the decrease of PD-1 ?

What are the targets (T cells) of this inhibition ?

ANTI-VEGF DECREASES THE CO-EXPRESSION OF PD-1-TIM3 ON CD8+ T CELLS



Voron, Terme, J Exp Med, 2015

HOW TO EXPLAIN THE PRESENCE OF EXHAUSTED T CELLS IN THE TUMOR MICROENVIRONMENT ?

- Chronic activation of T cells secondary to the persistence of tumor cells
- Presence of inflammatory mediators (IFN) upregulating checkpoint inhibitors and their ligands
- Role of angiogenesis

PBS | VEGF : 5 ng/ml | VEGF : 20 ng/ml | VEGF : 50 ng/ml | VEGF : 100 ng/ml

Number of checkpoint inhibitors (PD-1, Tim3, CTLA-4, Lag3) expressed by *in vitro* activated T cells in the presence of an increase concentration of VEGF

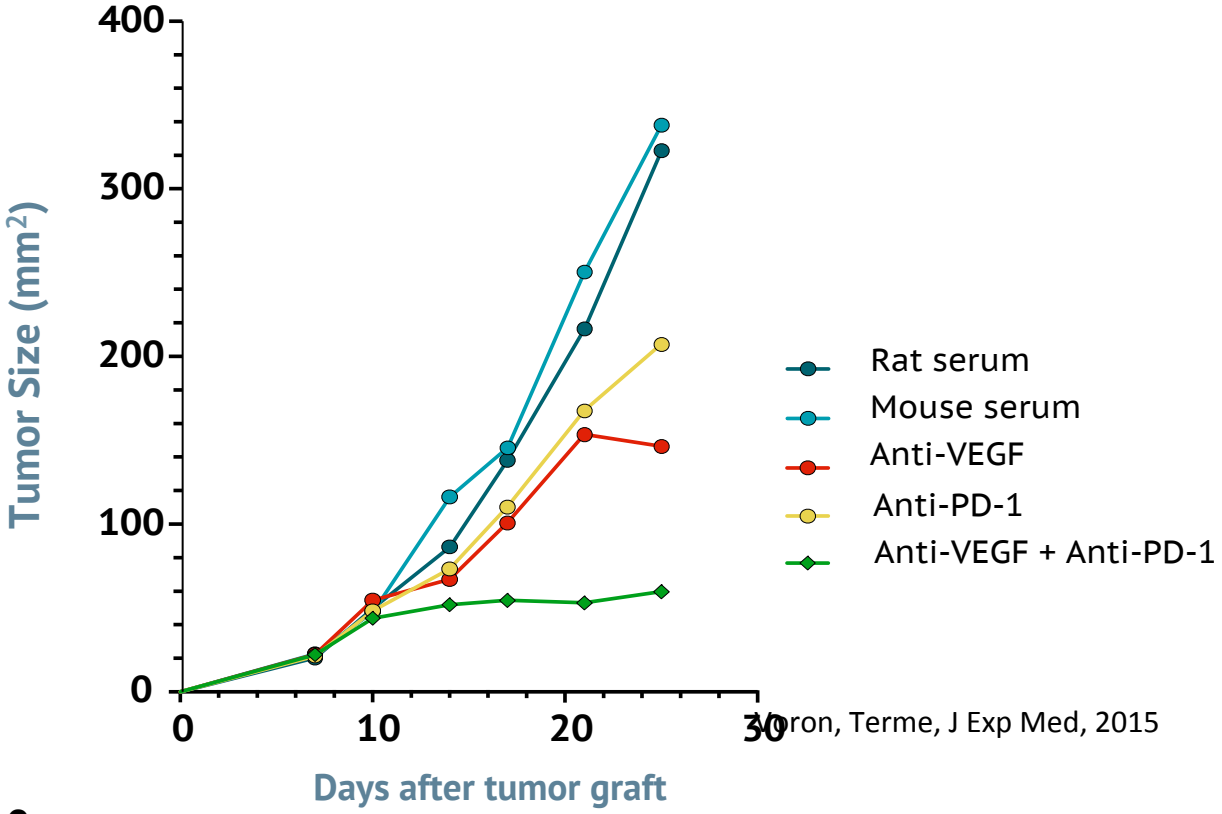
No treatment

Anti-VEGF (14 days)

Expression of inhibitory checkpoints on intratumor CD8$^+$ T cells without or after anti-VEGF treatment

Voron, Terme, J Exp Med, 2015

SYNERGY IN A PRECLINICAL MODEL BETWEEN THE COMBINATION OF ANTI-VEGF AND ANTI-PD-1



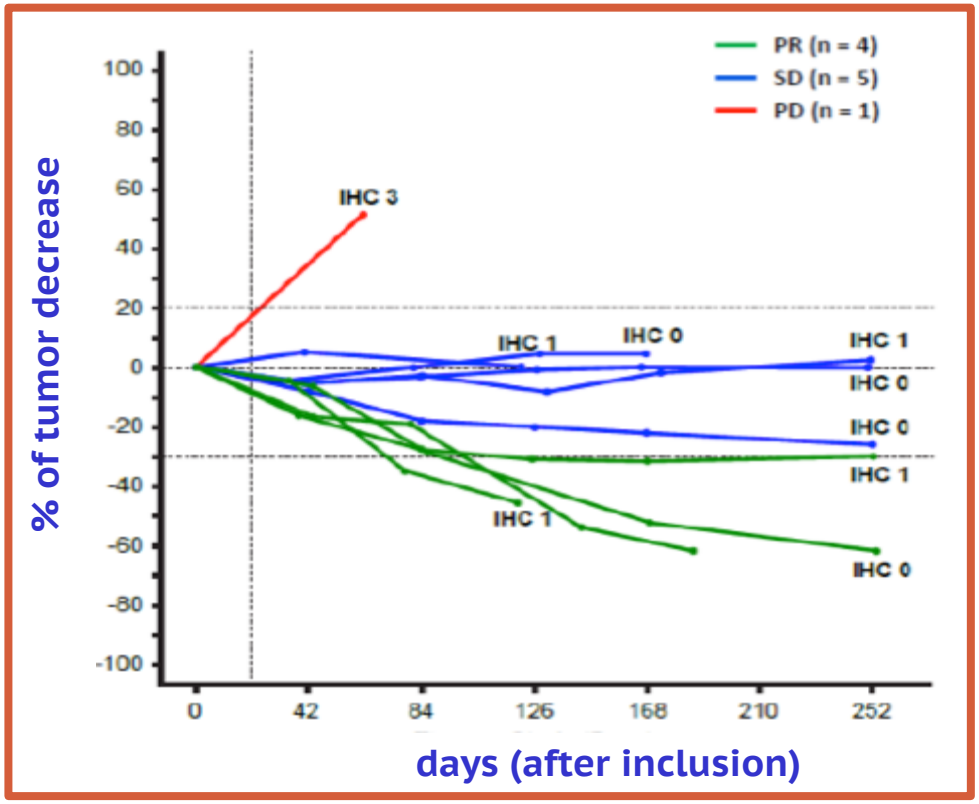
Huron, Terme, J Exp Med, 2015

ASCO 2014 Abst 5010

Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC).

→ **Durable (more than 1 year) ORR response in 45-52% patients**

SYNERGY BETWEEN AN ANTI-VEGF (BEVACIZUMAB) AND AN ANTI-PD-L1 (MPDL3280A) IN PATIENTS WITH METASTATIC RENAL CELL CARCINOMA



4/10 (40%) Overall objective responses

5/10 (50%) Stable disease

Ongoing clinical trials:

Phase 3: First line : anti-PDL-1 (MPDL3280A) + Bevacizumab (&VEGF) *vs* Sunitinib: **Renal K (NCT02420821)**

Phase 2: Anti-PD-1 (Pembrolizumab) in combination with Bevacizumab: **Renal K (NCT02348008)**

Phase 2: Anti-PD-1 (Pembrolizumab) +/- Bevacizumab: **Multiple Glioblastoma (NCT02337491)**

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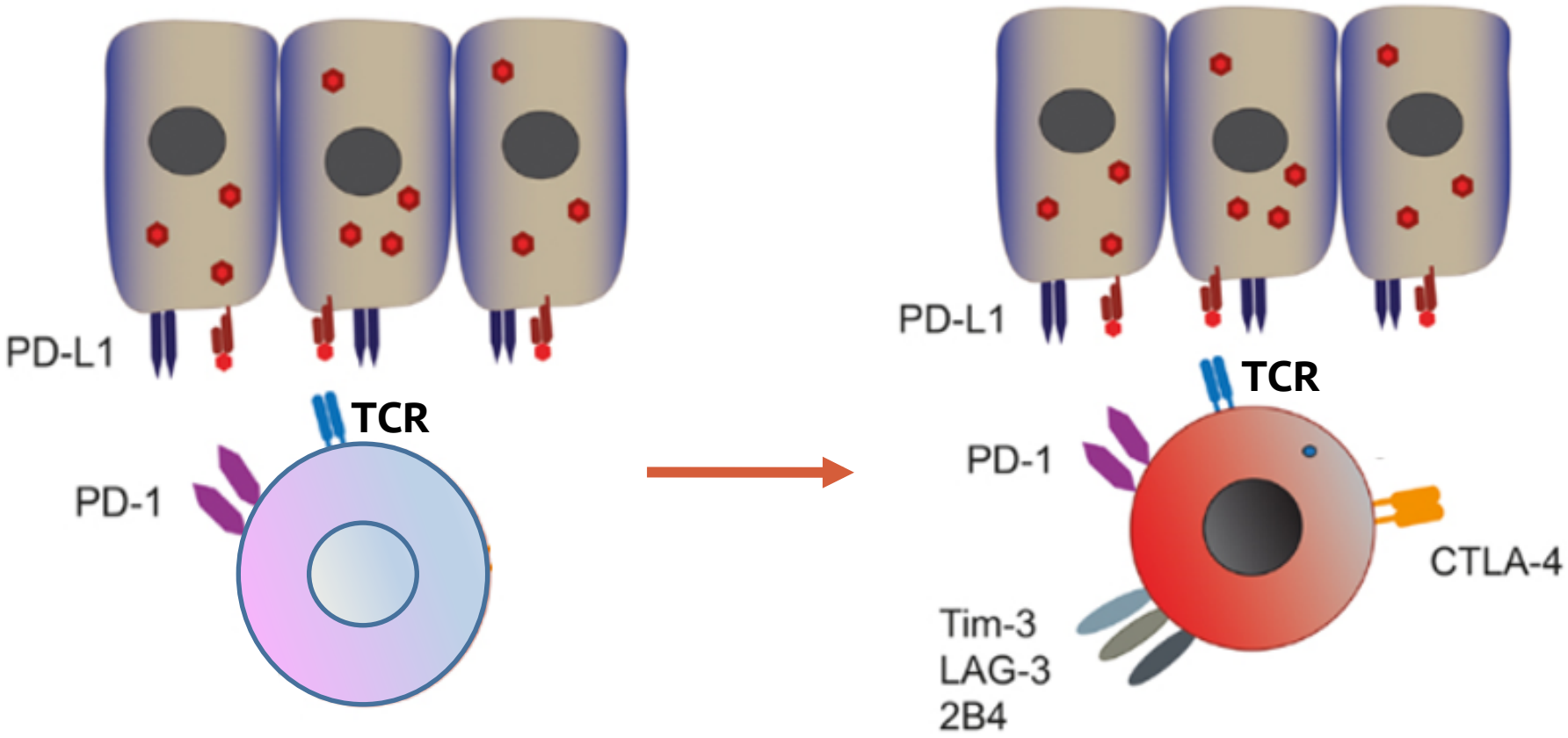
Mc Dermott, ESMO, 2014. Lieu , Abst 10490

SIMULTANEOUS CO-EXPRESSION OF VARIOUS INHIBITORY COSTIMULATORY MOLECULES MAKE T CELLS MORE EXHAUSTED



Moderate « Exhaustion »
T cells can be reactivated

Severe « Exhaustion »
Pre-apoptotic cells

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Adapted from Schurich, Front Immunol, 2014

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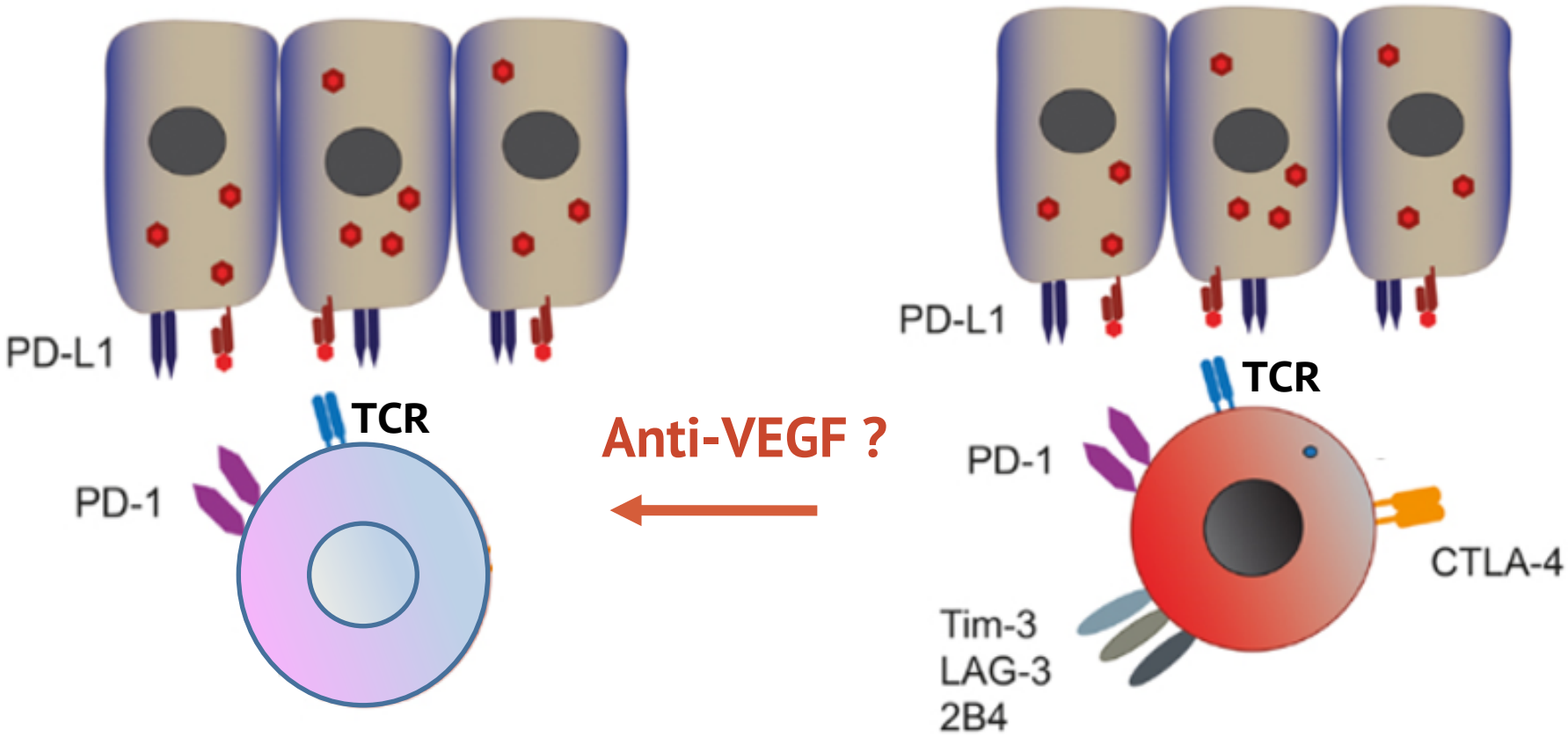

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Severe « Exhaustion »
Pre-apoptotic cells

Adapted from Schurich, Front Immunol, 2014

CONCLUSIONS

- Blockade of VEGF reverses various immunosuppressive mechanisms present in the tumor microenvironment
- VEGFR2 is expressed by some immune cells ($CD8^+$ T cells and Treg) in the tumor microenvironment
- VEGF acts as a costimulatory molecules to increase the expression of multiple checkpoint inhibitors (PD-1, Tim3…) on $CD8^+$ T cells

All these results constitute a strong rationale for combination of anti-angiogenic molecules and immunotherapy
(i.e anti-PD-1/PD-L1)

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