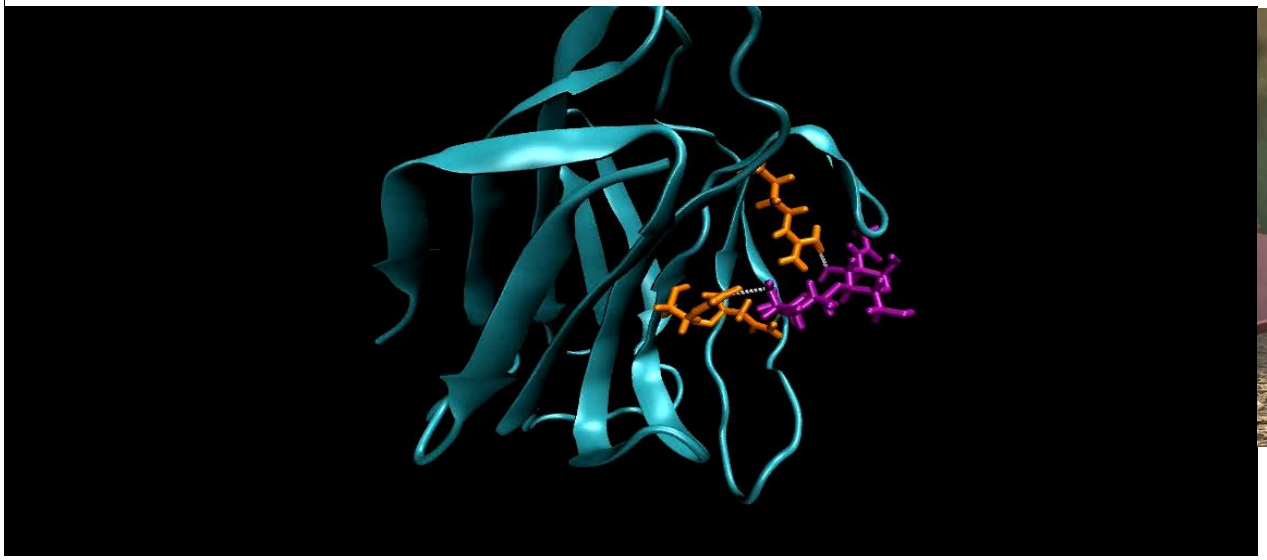
Inspire2Live World Campus

Galectins: emerging therapeutic targets in cancer and autoimmune inflammation

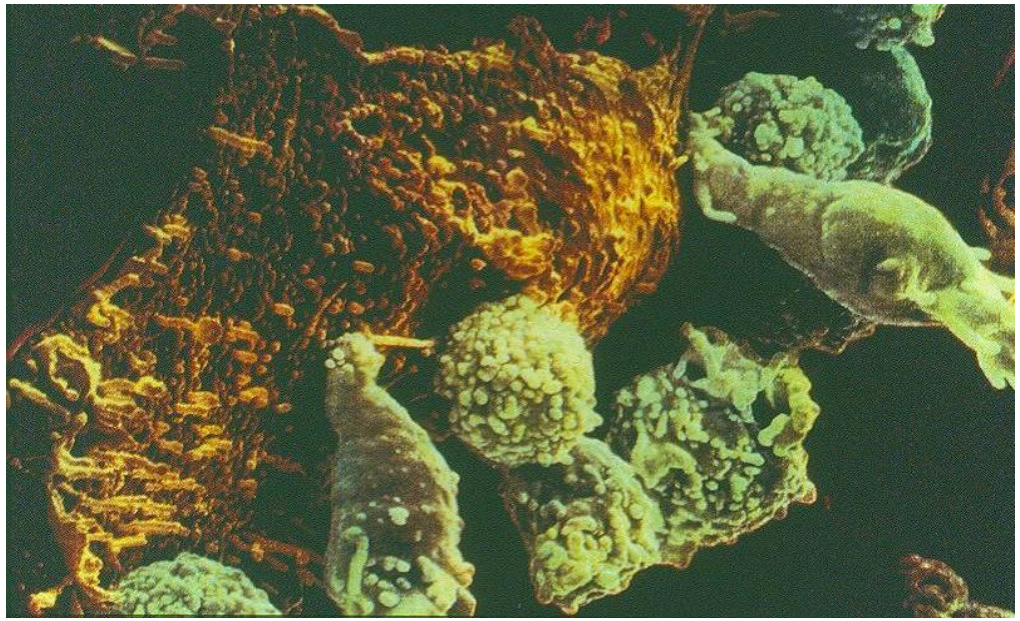
A Sweet Adventure South of the Equator

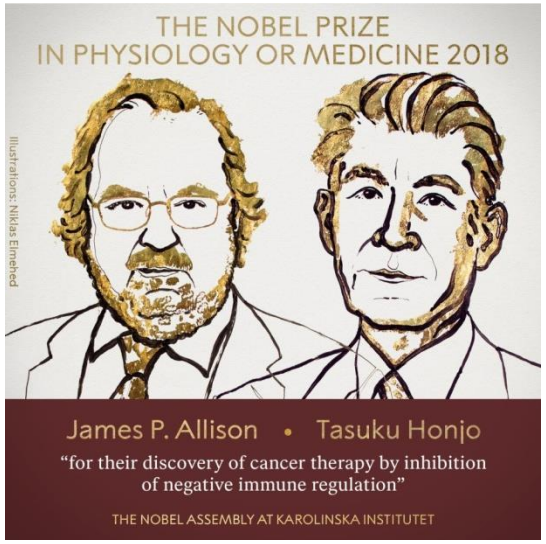


Gabriel Rabinovich et al

Laboratorio de Glicomedicina. Instituto de Biología y Medicina Experimental, CONICET y Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Argentina

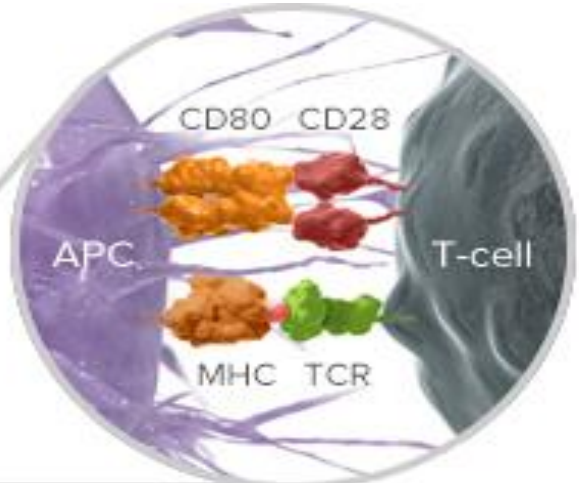
The Revolution of Cancer Immunotherapy





How does our immune system sense and eliminate tumors?

Antigen-presenting cells: Dendritic cells

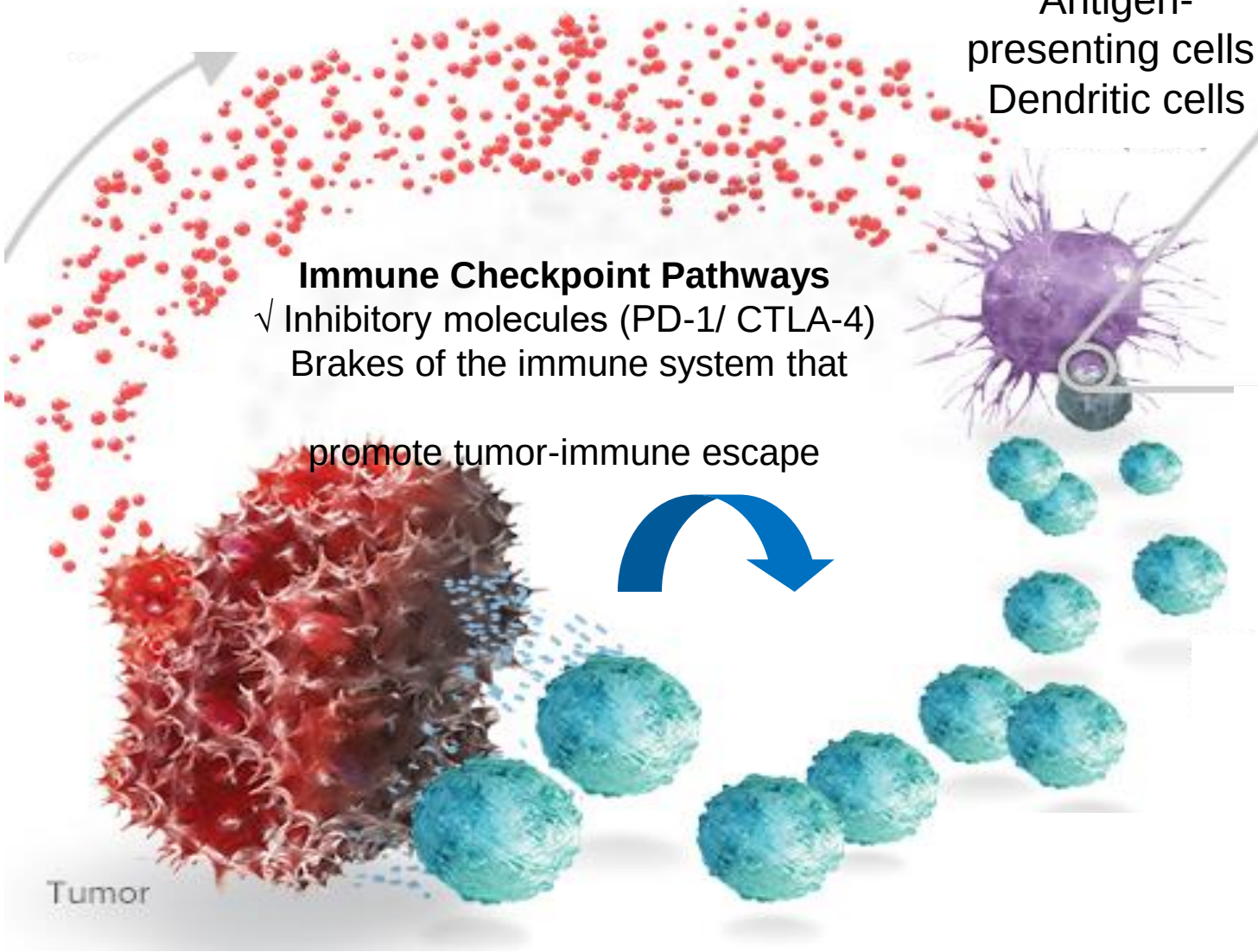


Immune Checkpoint Pathways

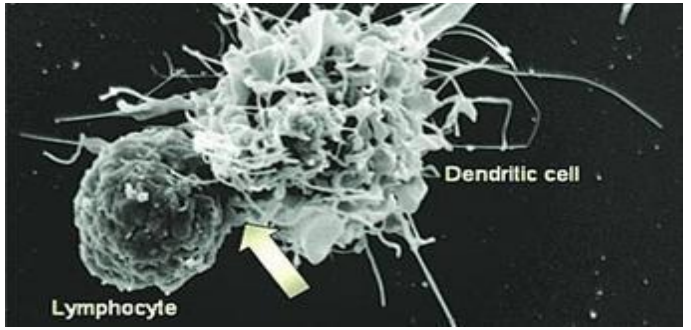
√ Inhibitory molecules (PD-1/ CTLA-4)

Brakes of the immune system that

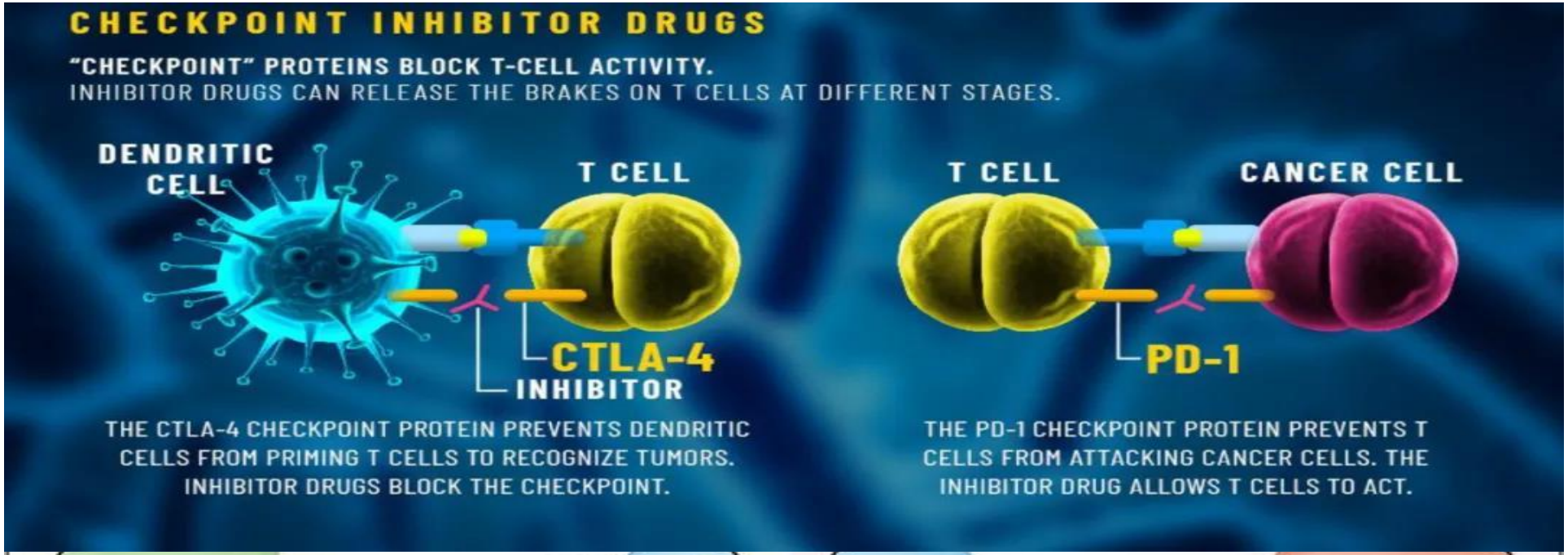
promote tumor-immune escape

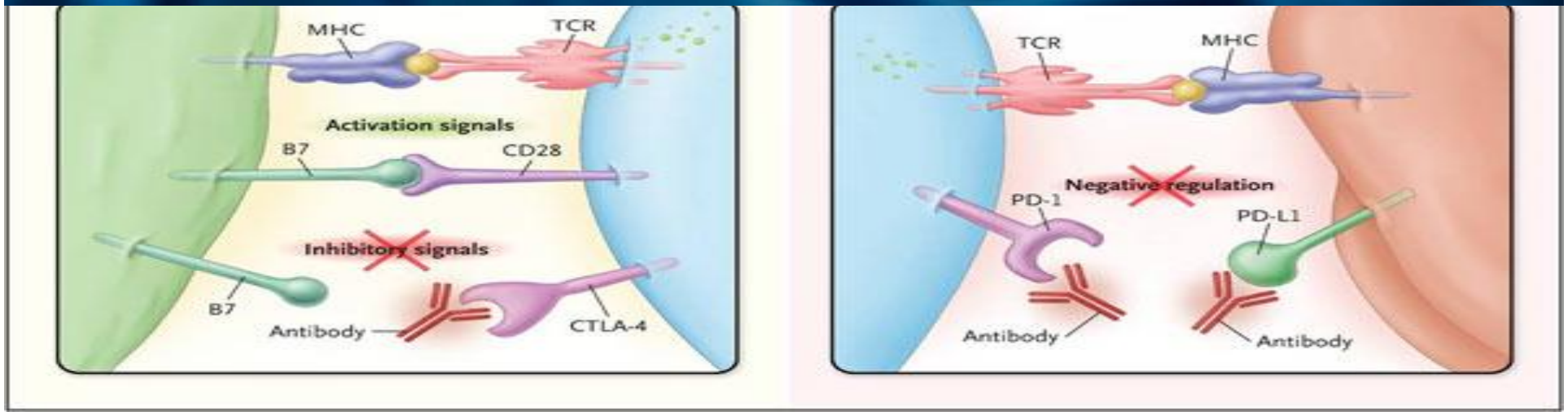


T-cell activation
T-cell trafficking



How do immune checkpoint inhibitors work?





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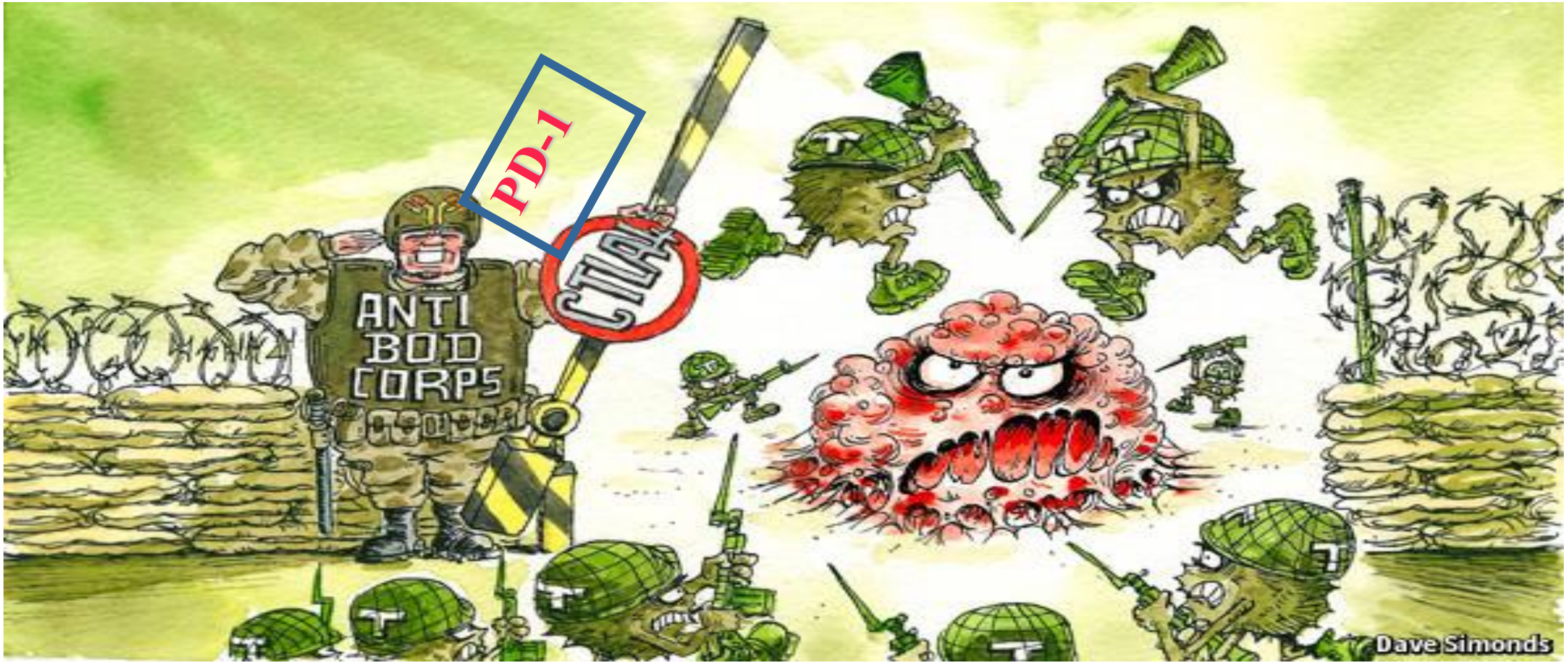
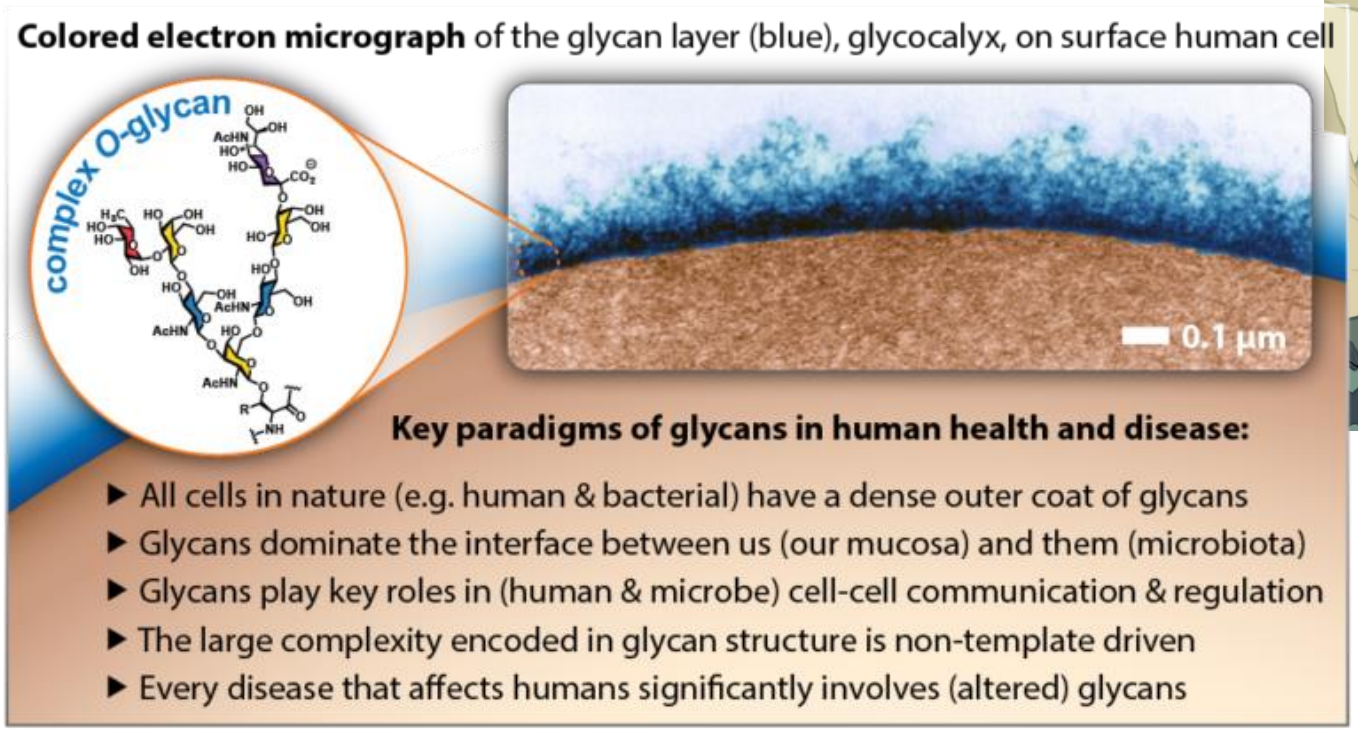
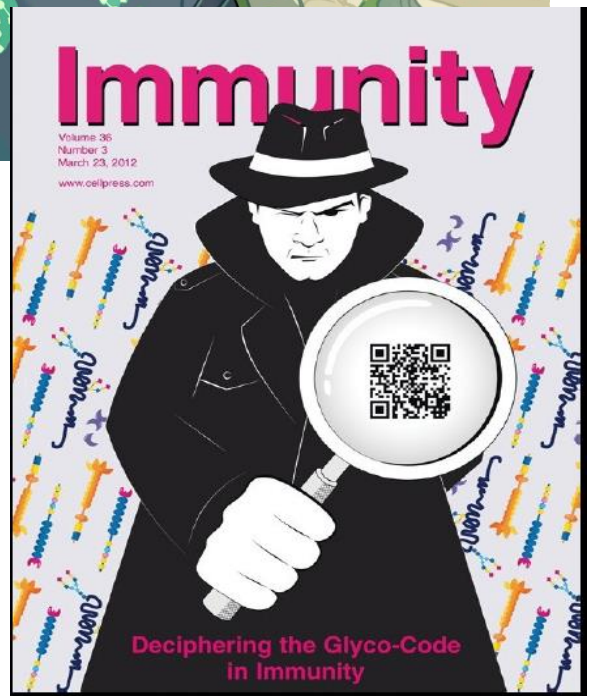


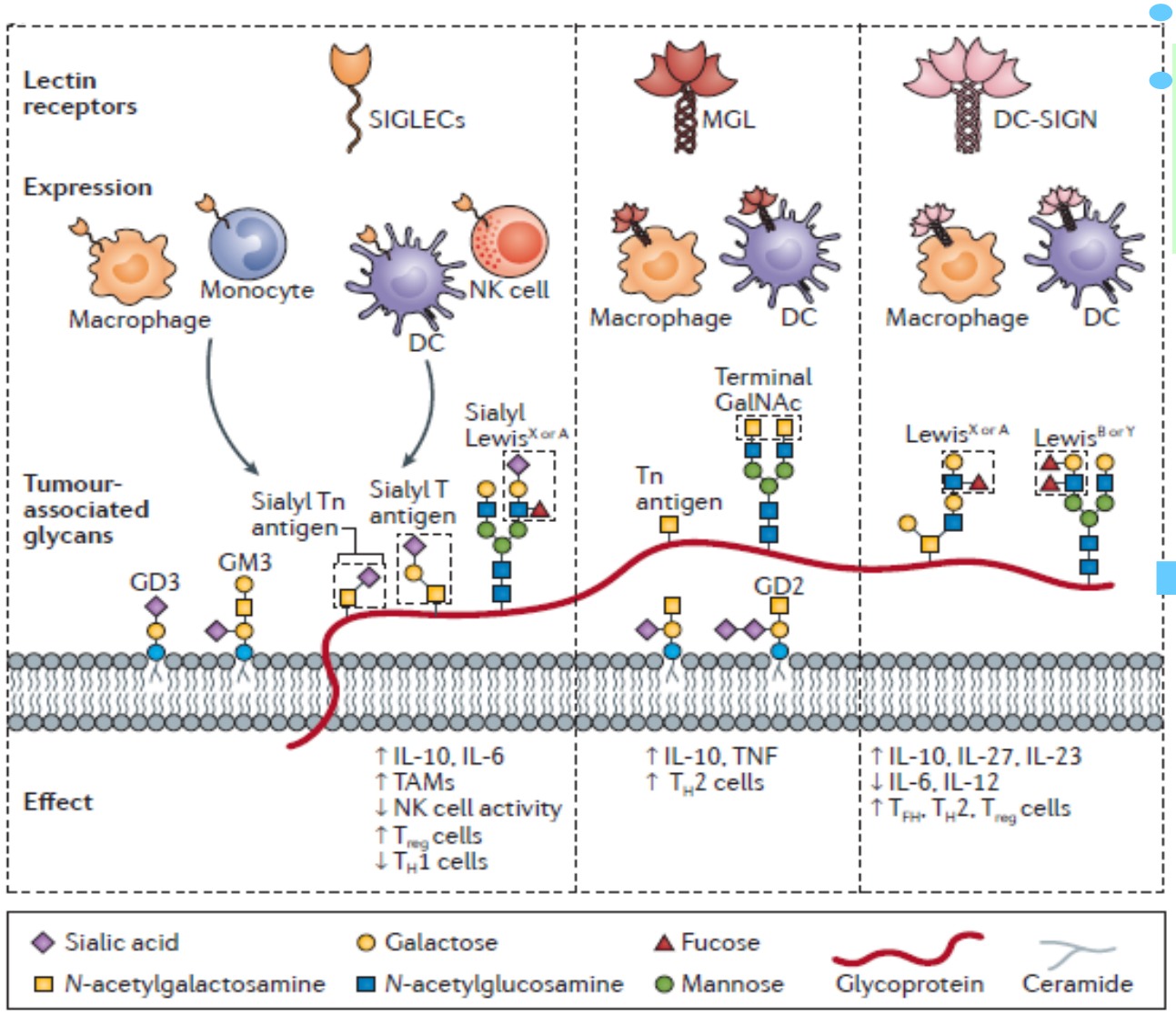
Deciphering the sugar code: Glyco-checkpoints in immunity





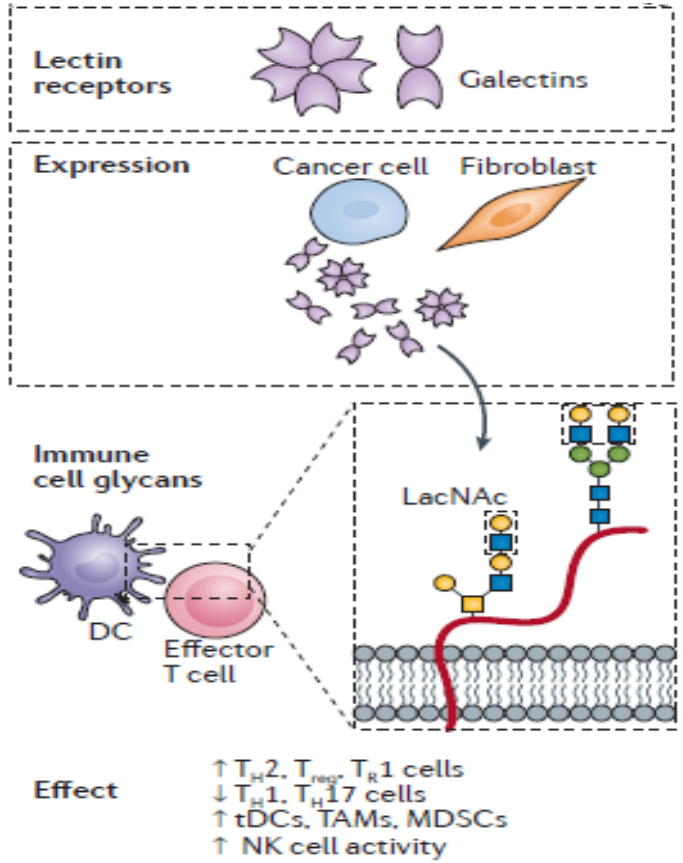
Rabinovich et al, Immunity 2012

Deciphering the Sugar Codes: Glycocheckpoints in Immunity



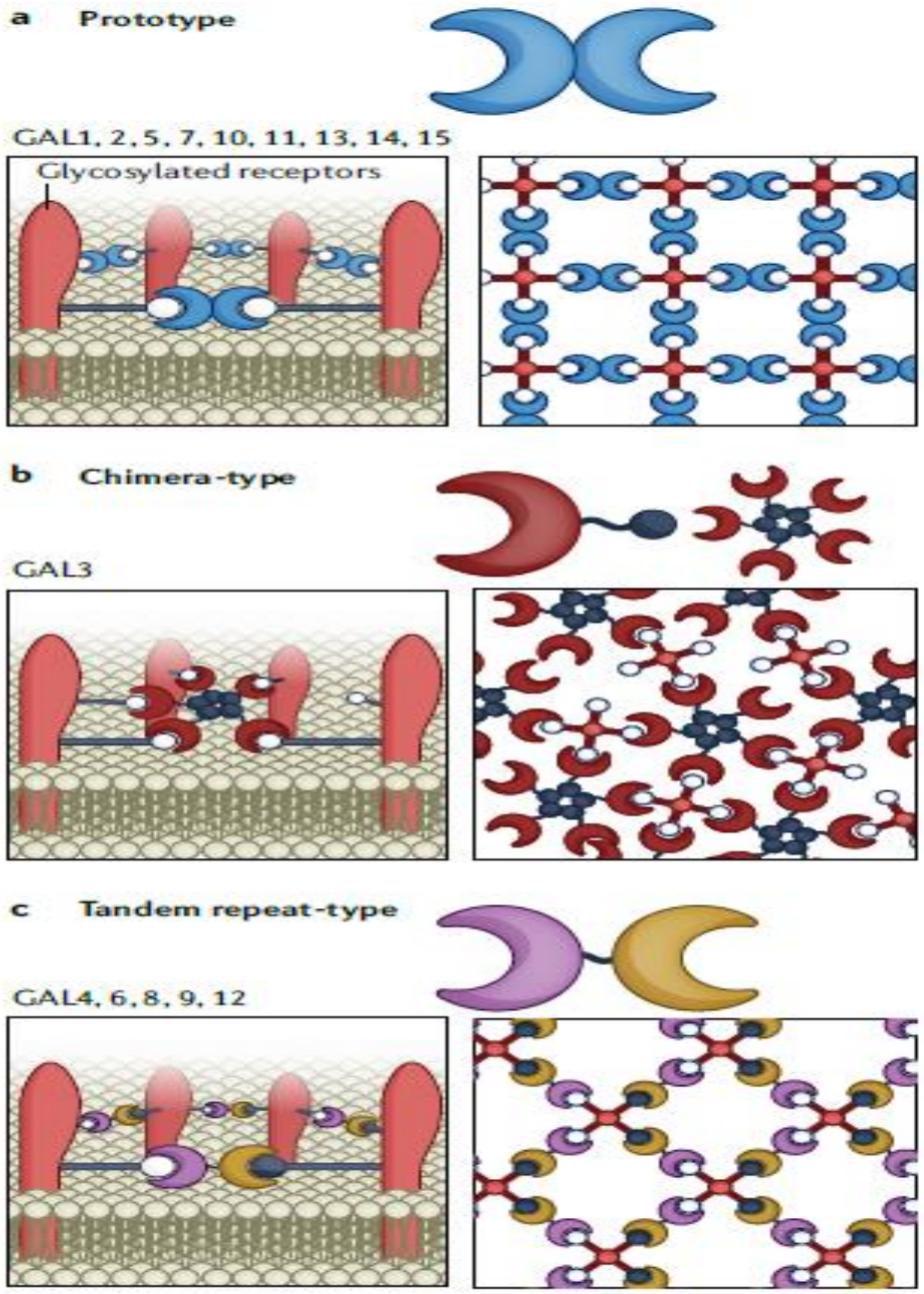
GLYCAN-BINDING PROTEINS OR LECTINS:

1. **SIGLECS**
2. **C-TYPE LECTINS**
3. **GALECTINS**



Rabinovich et al, Immunity 2012, Mendez Huergo et al, Curr Opin Immunol 2017

Galectins



- Galectins are a family of soluble glycan-binding proteins that preferentially recognize N-acetyl-lactosamine (Galβ1-4GlcNAc) units on different cell surface receptors

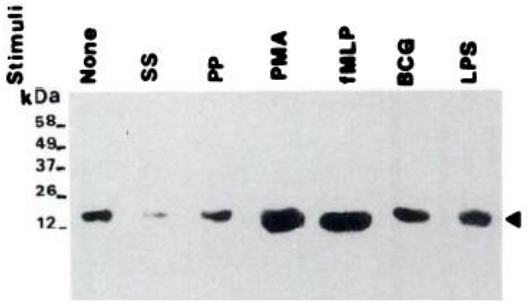
- They establish multivalent interactions with glycosylated receptors and control immune cell fate (activation, differentiation and survival).

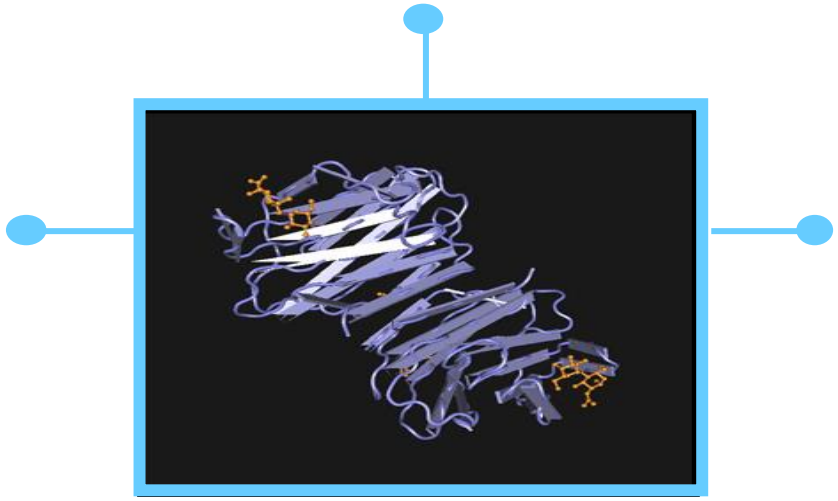
Rabinovich et al, Nature Rev Immunol 2009

An unexpected finding:
Galectin-1 (Gal-1): an inhibitory sugar-binding protein in the immune system

Broad immune inhibitory activity

Identification of a 14.5 kDa β-galactoside-binding protein in activated macrophages

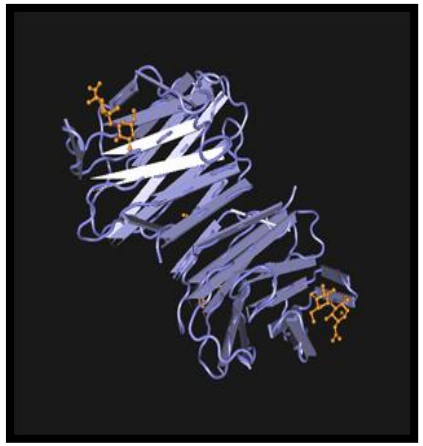


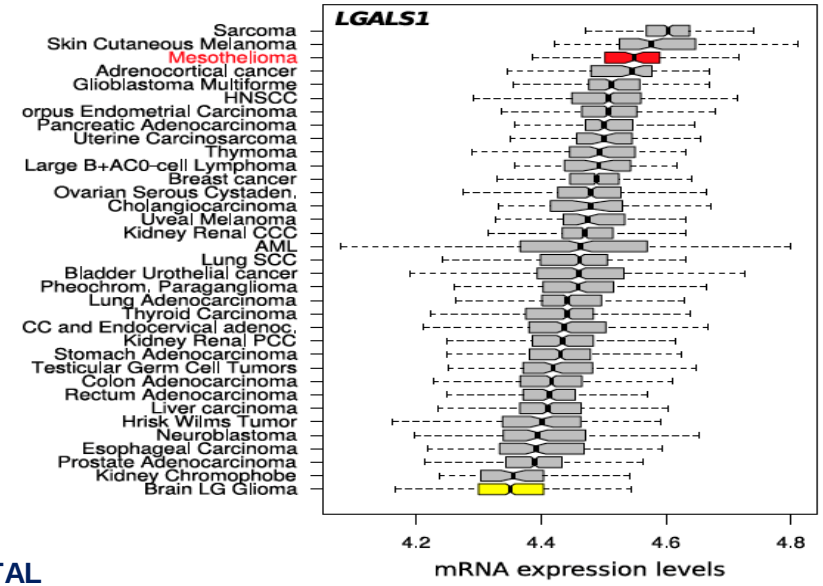


Up-regulated in tumor tissues

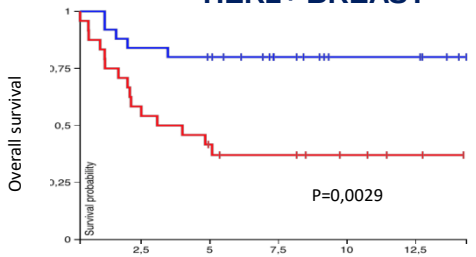
Rabinovich et al, J Leukoc Biol 1996; JB 1997; J Immunol 1998; J Exp Med 1999; Immunology 1999; Eur J Immunol 2000

Galectin-1 (Gal-1) expression: an indicator of poor survival in human cancer

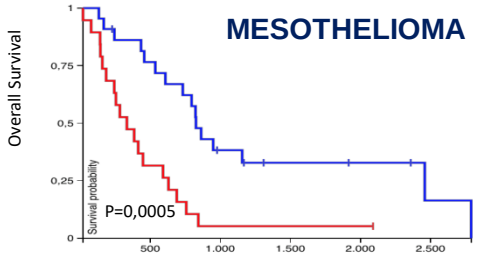




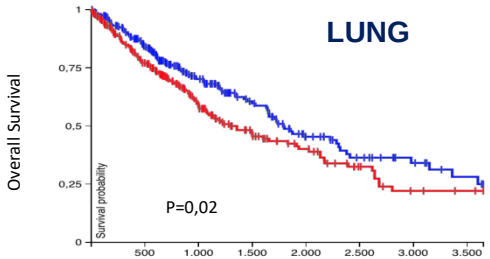
HER2+ BREAST



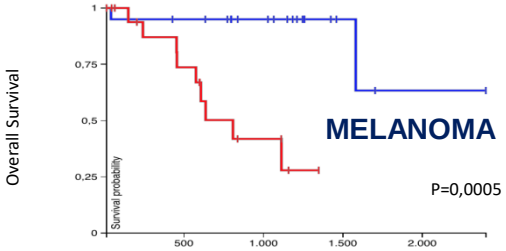
MESOTHELIOMA



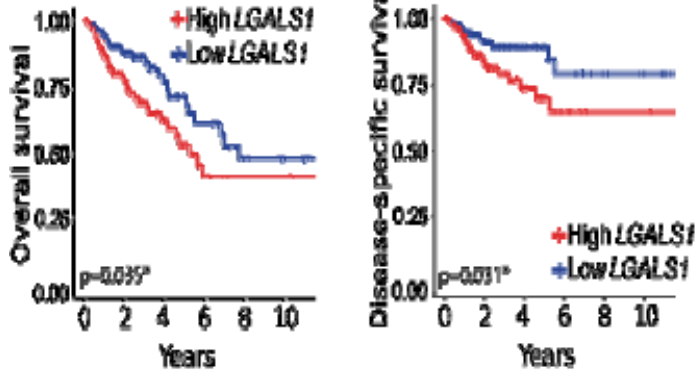
LUNG



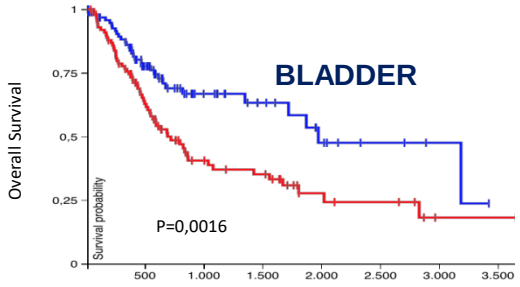
MELANOMA



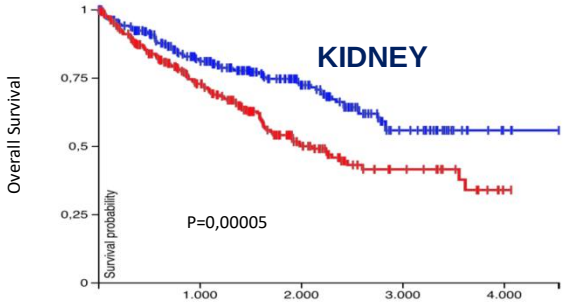
COLORECTAL



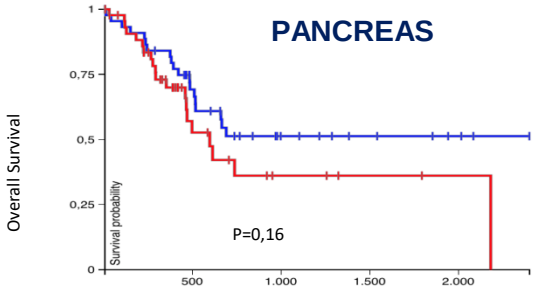
BLADDER



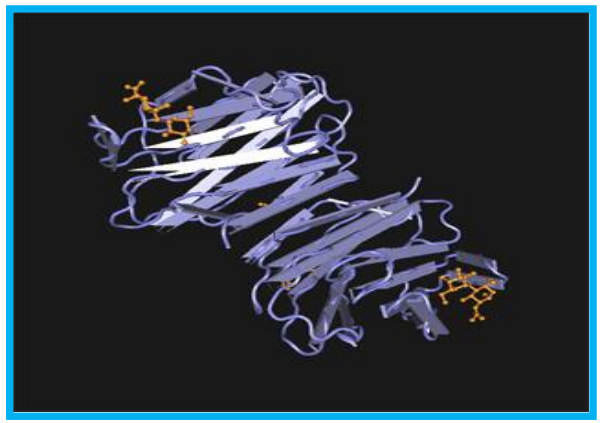
KIDNEY



PANCREAS

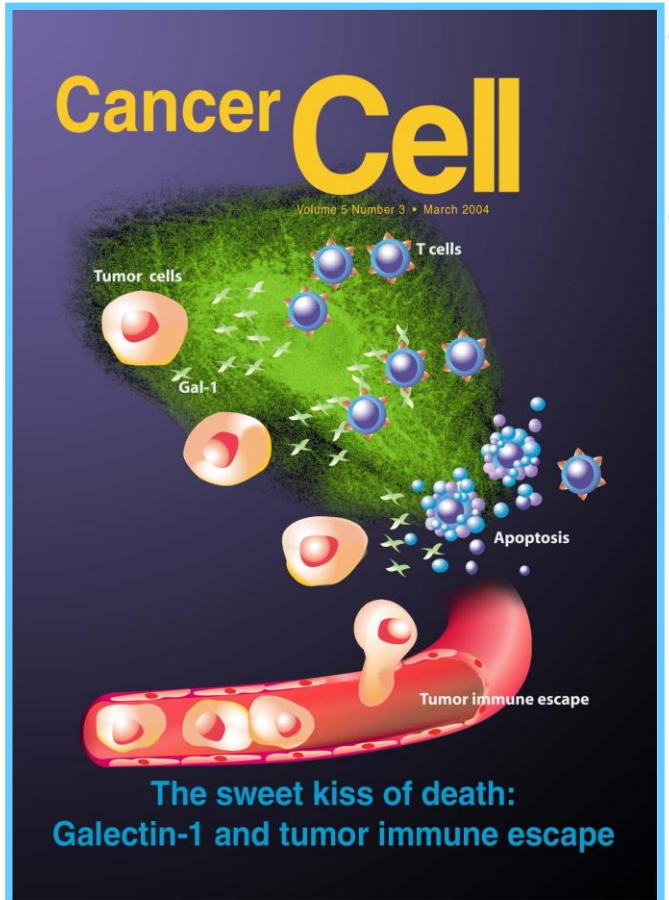


(TCGA Database)



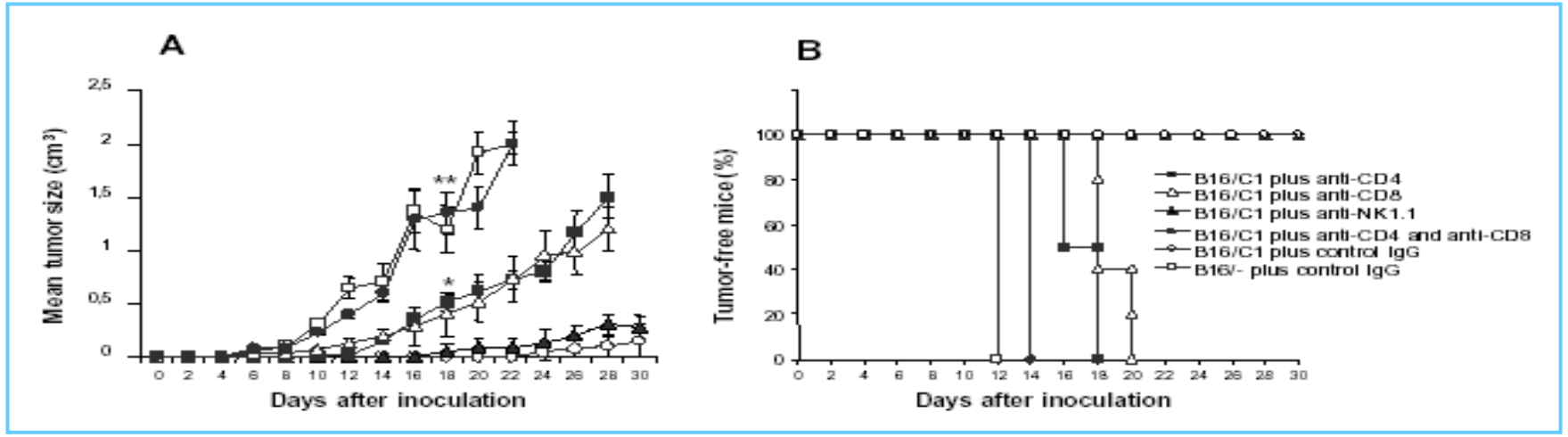
Tumors elude antitumor immunity by secreting Gal-1

- Expression of Gal-1 in human melanoma correlates with poor prognosis and acquisition of metastatic phenotype



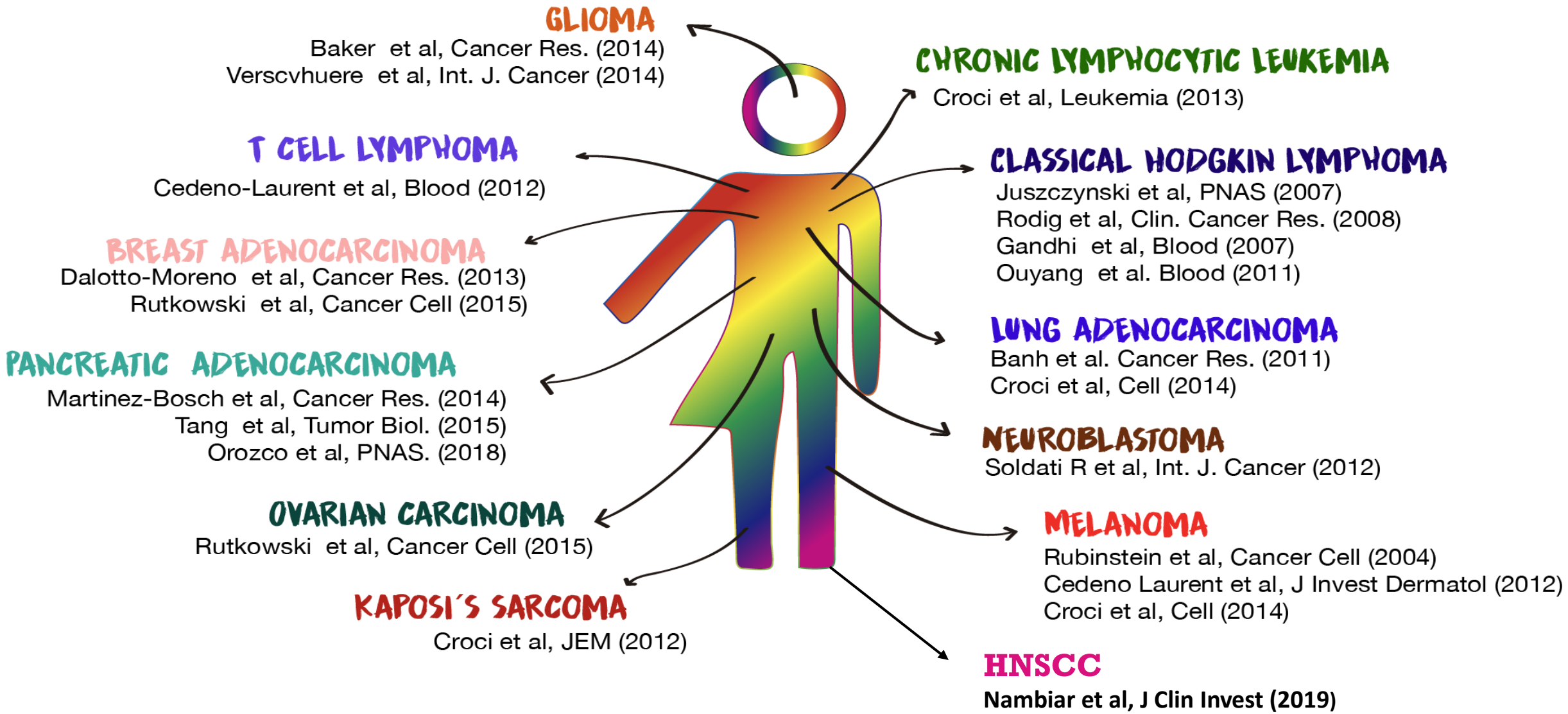
- Gal-1 contributes to the immunosuppressive activity of melanoma cells

- Blockade of Gal-1 leads to $CD4^+$ and $CD8^+$ T cell-mediated tumor rejection that was highly dependent on IFN-γ

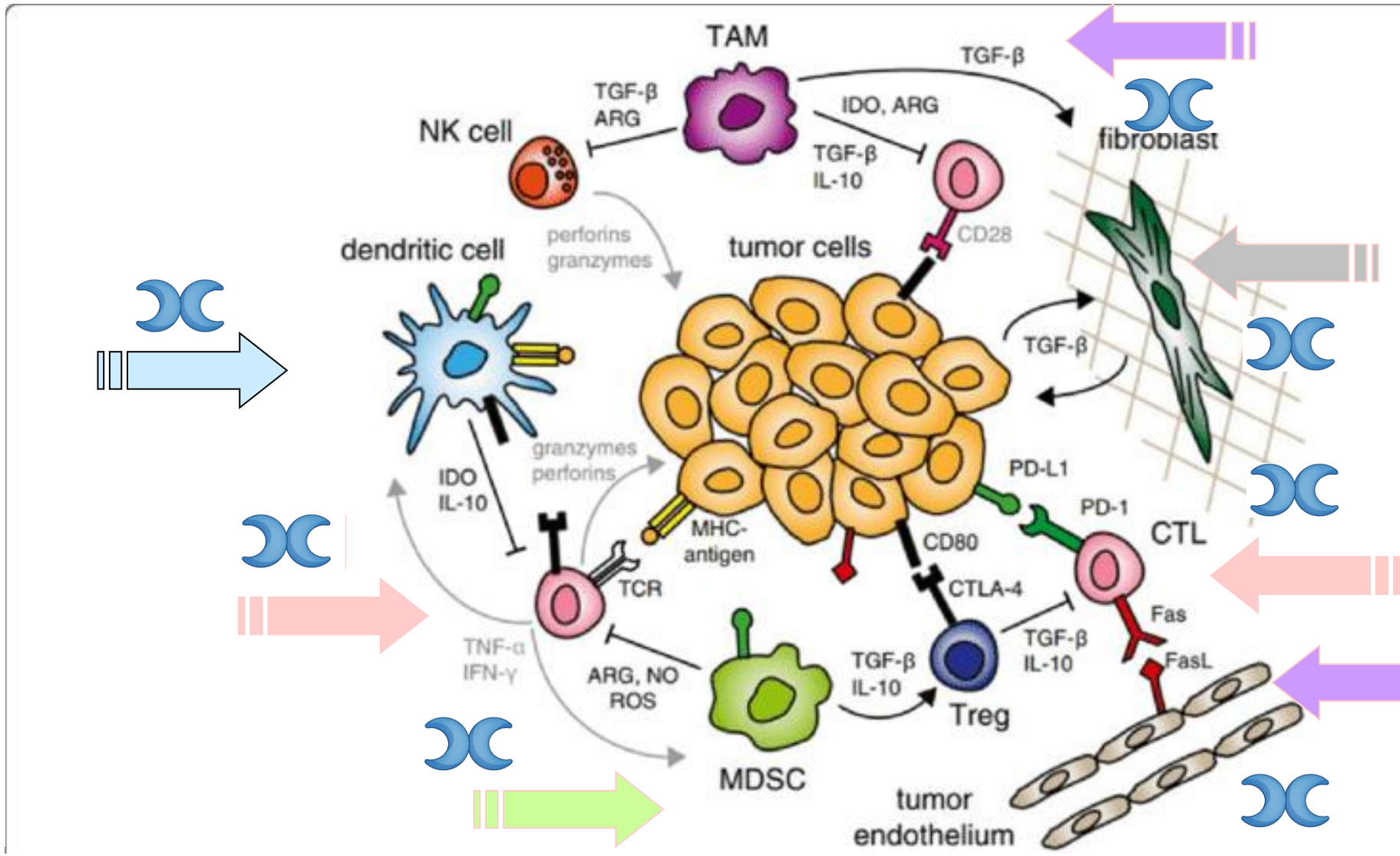


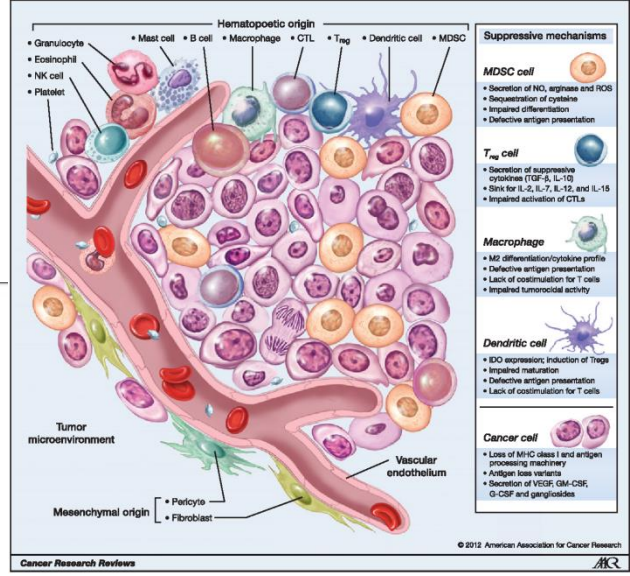
Rubinstein et al, Cancer Cell 2004

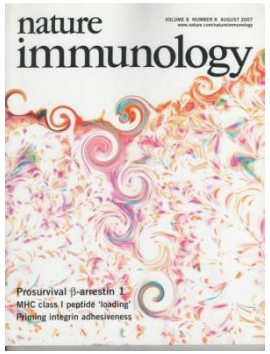
Gal-1 activates immune evasive programs in several tumor types



How does Gal-1 shape the tumor-immune microenvironment?

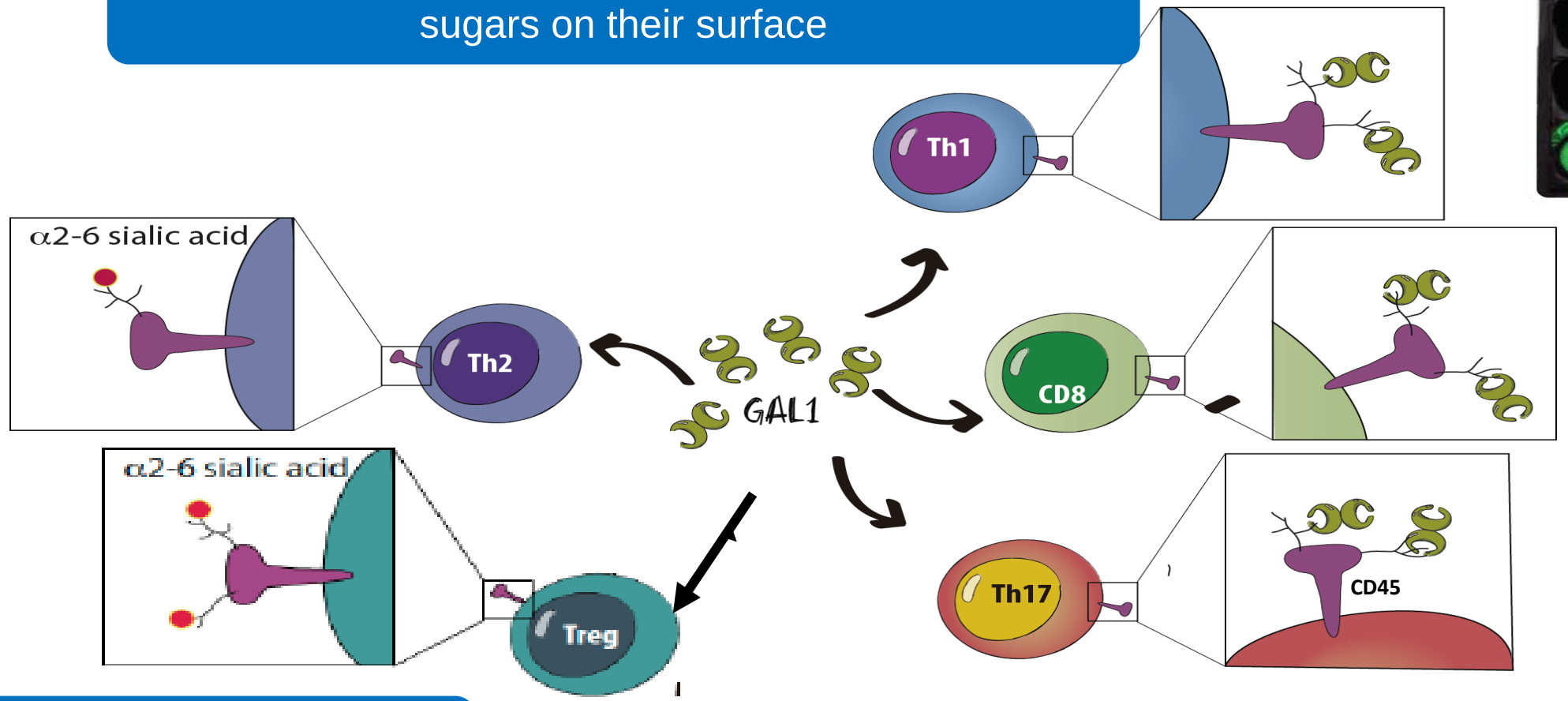






Gal-1 selectively kills effector T lymphocytes

Gal-1 kills effector T cells through binding to specific sugars on their surface

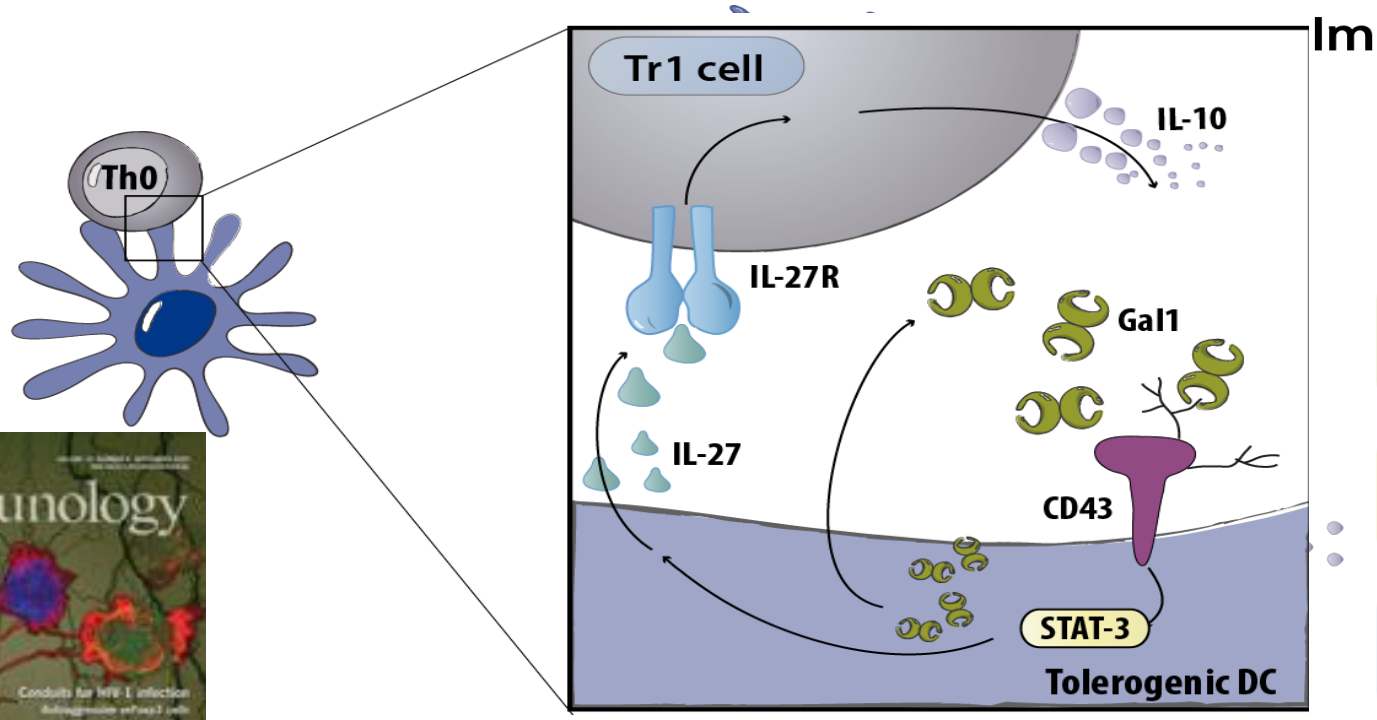


Gal-1 cannot bind and kill anti-inflammatoryTh2 and regulatory T cells

Bad for cancer ! Good for autoimmune diseases

Toscano et al, Nature Immunol 2007

Gal-1 induces tolerogenic dendritic cells and shut-off antitumor T cell responses

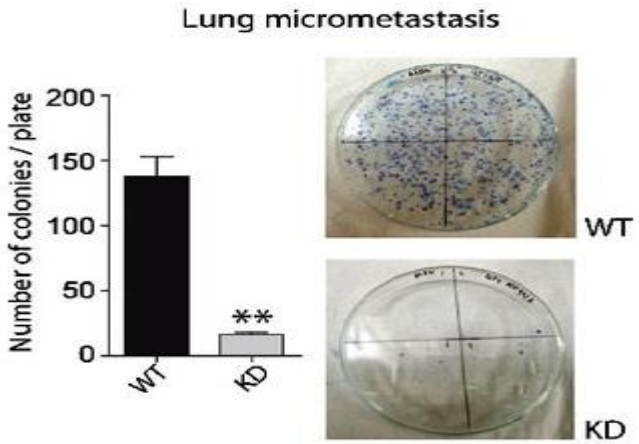


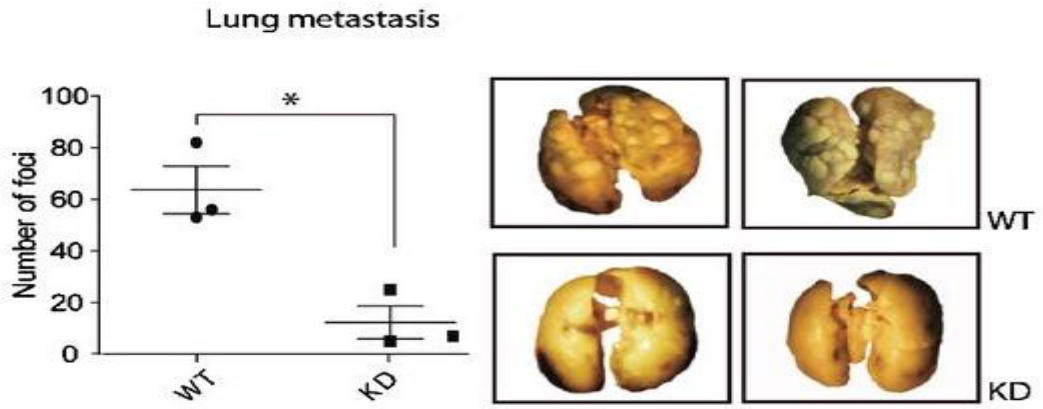
Immunoregulatory circuit

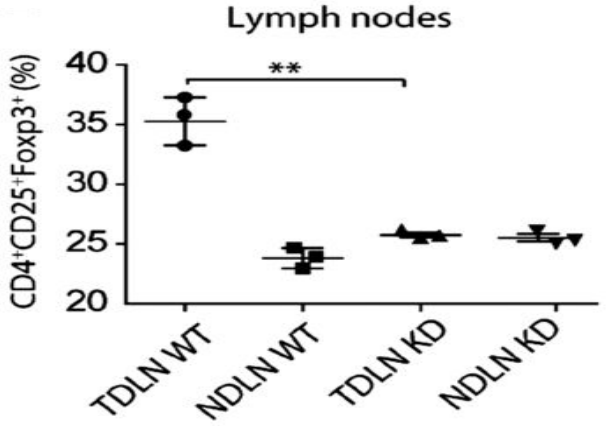
	Therapeutic strategy
Autoimmunity Favours resolution and remission	Activation
Infection Impairs resolution	Blockade
Cancer Promotes tumor-immune escape and metastasis	Blockade

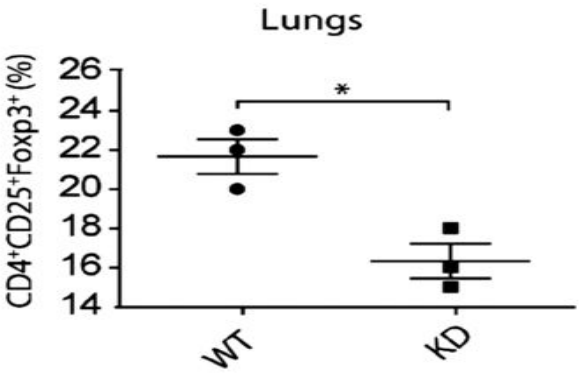
Ilarregui et al, Nature Immunol 2009, Tesone et al, Cell Rep 2016

Gal-1 favors metastasis by inducing immunosuppressive regulatory T cells



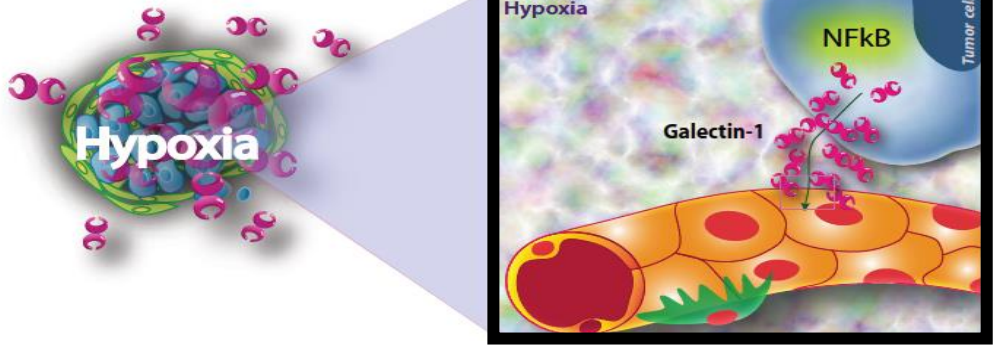


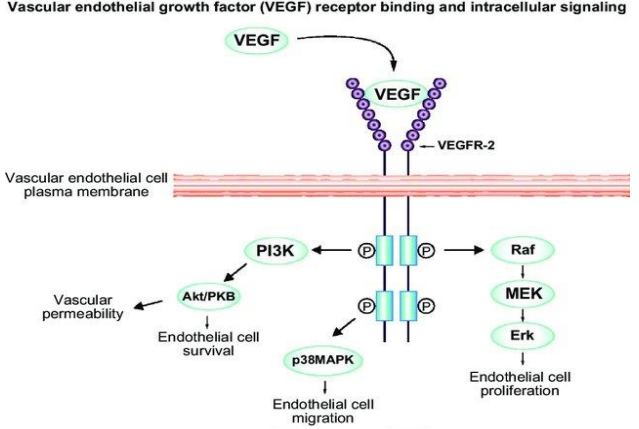


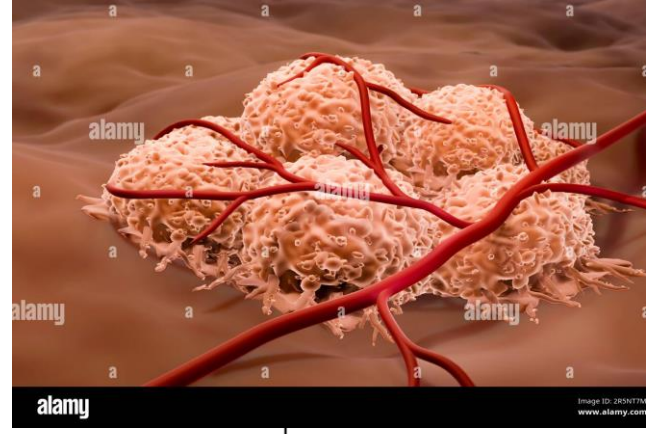


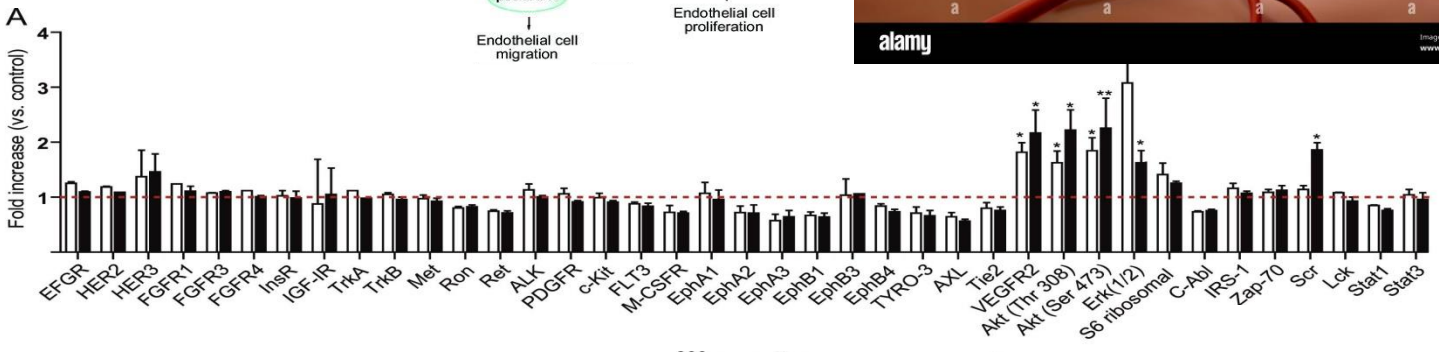
Dalotto Moreno et al, Cancer Res 2013

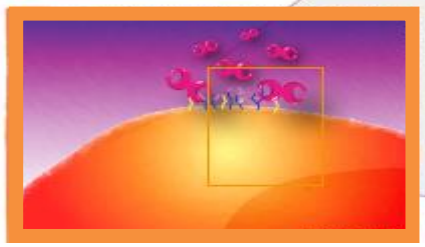
Gal-1 promotes the formation of aberrant tumor-vascular networks

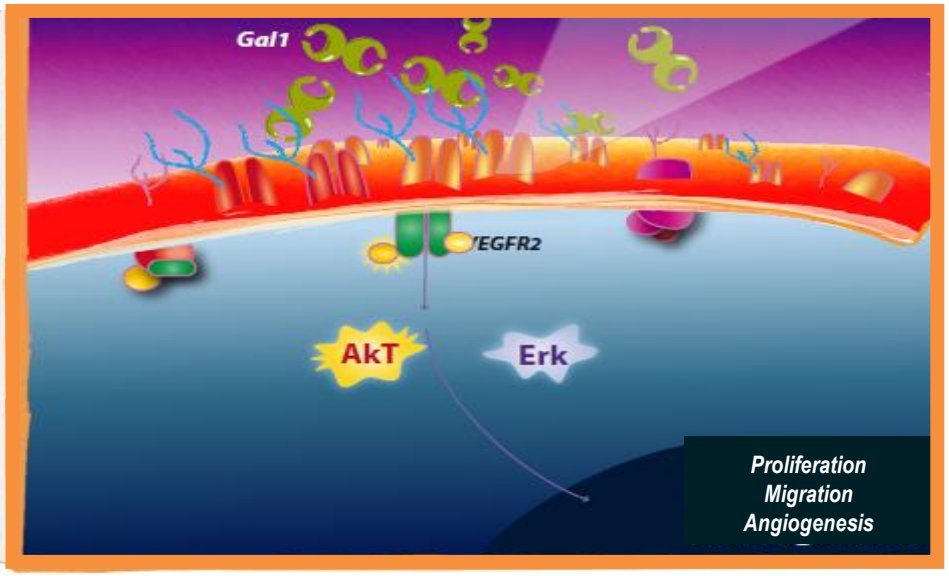








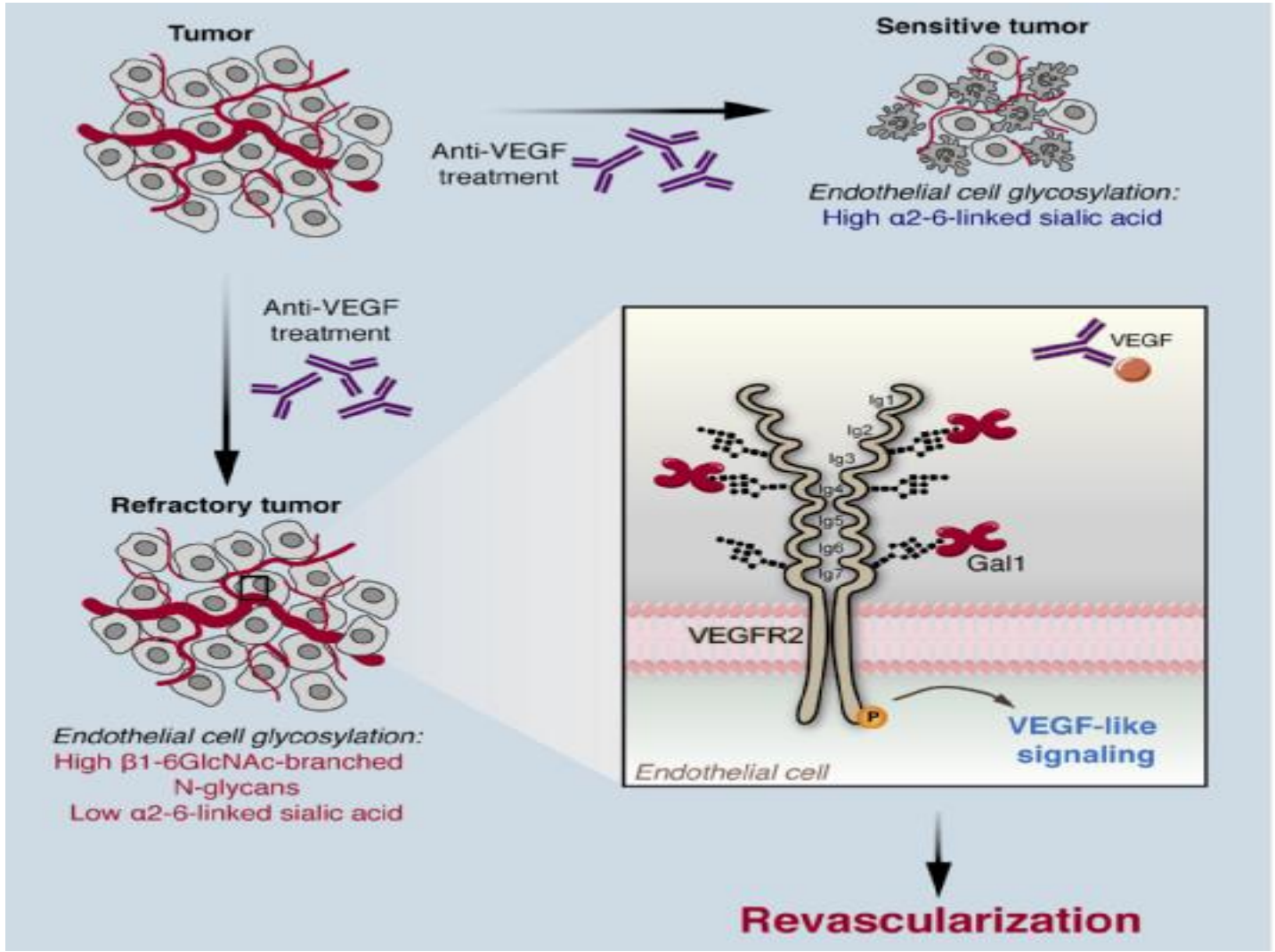


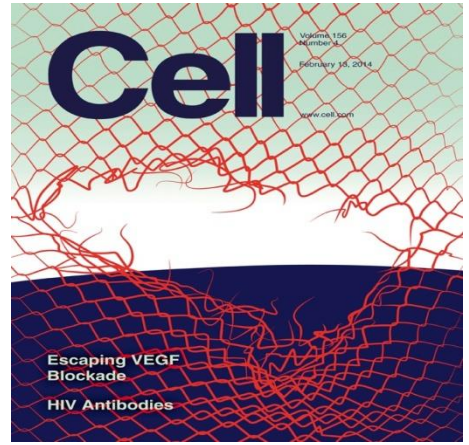


VEGF-like signaling

Croci et al, Cell 2014; Croci et al, JEM 2012

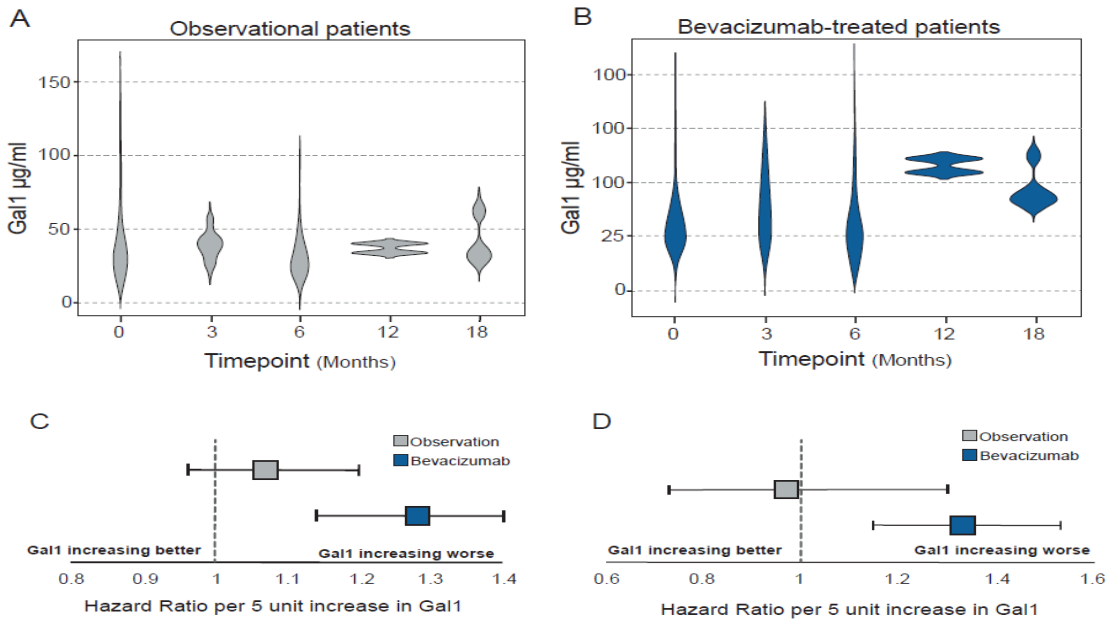
Gal-1 confers resistance to anti-angiogenic therapies

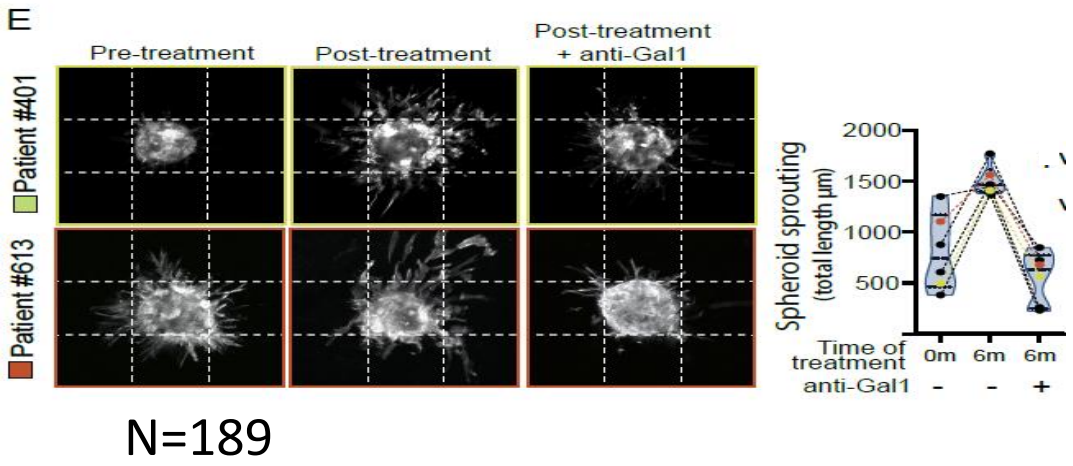




Croci et al, Cell 2014; Croci et al, J Exp Med 2012

Circulating Gal-1 levels delineate resistance to anti-angiogenic therapies



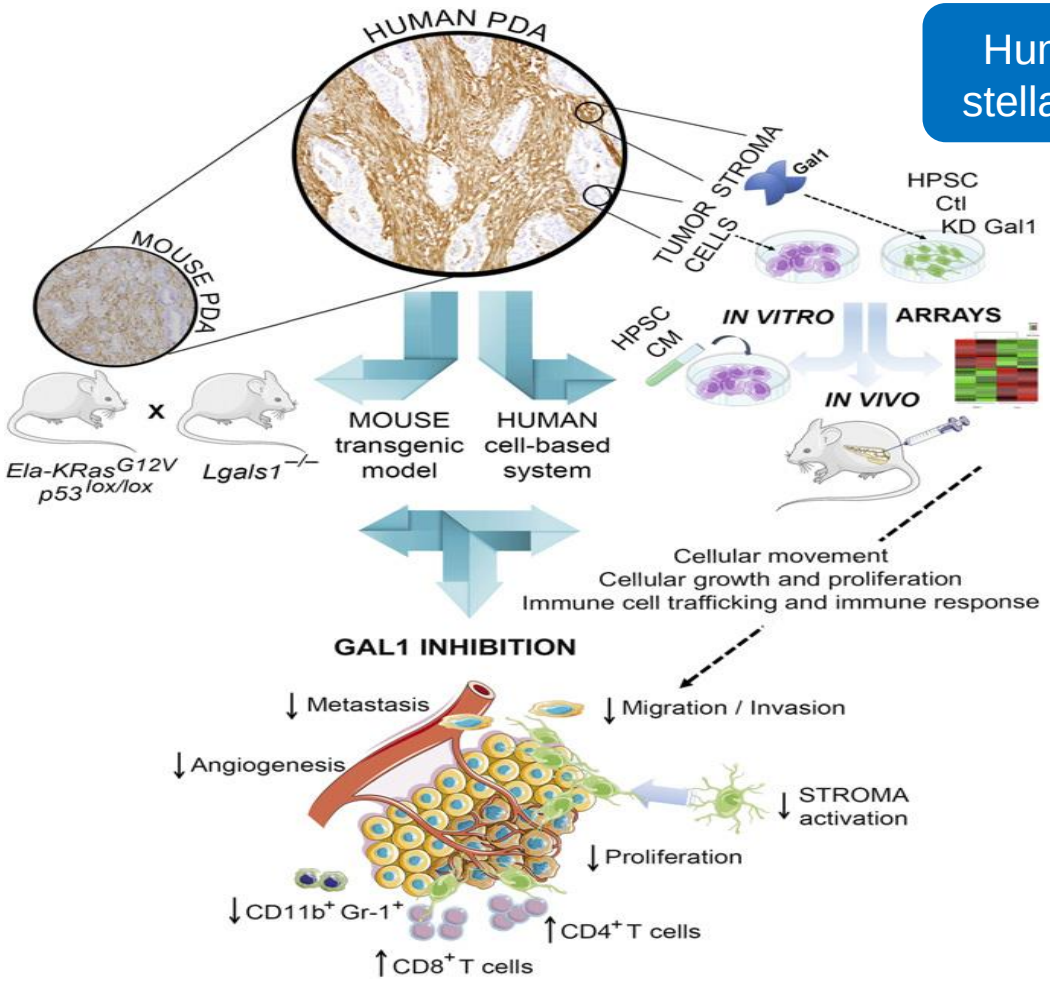


N=189

- Gal1 is elevated in plasma from bevacizumab-treated patients participating in AVAST-M: a phase 3 clinical trial of adjuvant bevacizumab versus standard surveillance.
- Increasing Gal1 levels over time in patients on the bevacizumab arm, but not on the observation arm, significantly increased risks of recurrence and death.
- Plasma from bevacizumab-treated non-responding patients can reprogram endothelial cell biology through a Gal1 pathway .

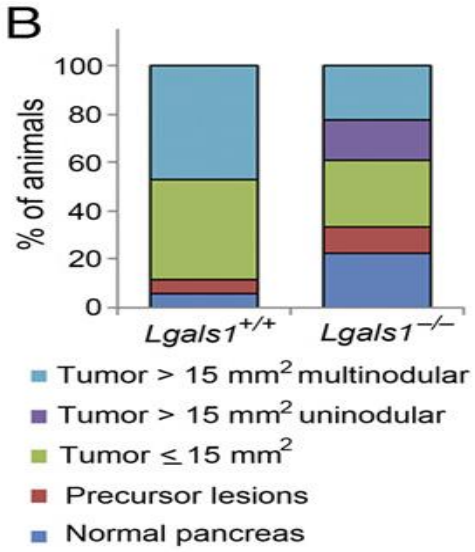
Bannoud et al, Proc Natl Acad Sci USA 2023

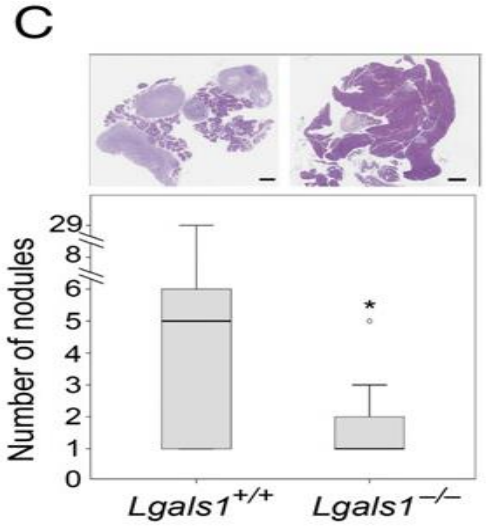
Targeting Gal-1 inhibits progression of pancreatic adenocarcinoma by modulating tumor stroma-immune cross-talk



Human Pancreatic stellate cells (HPSC)

- **Lowest survival rates**
- **Poorest prognosis**
- **Resistant to immunotherapy**

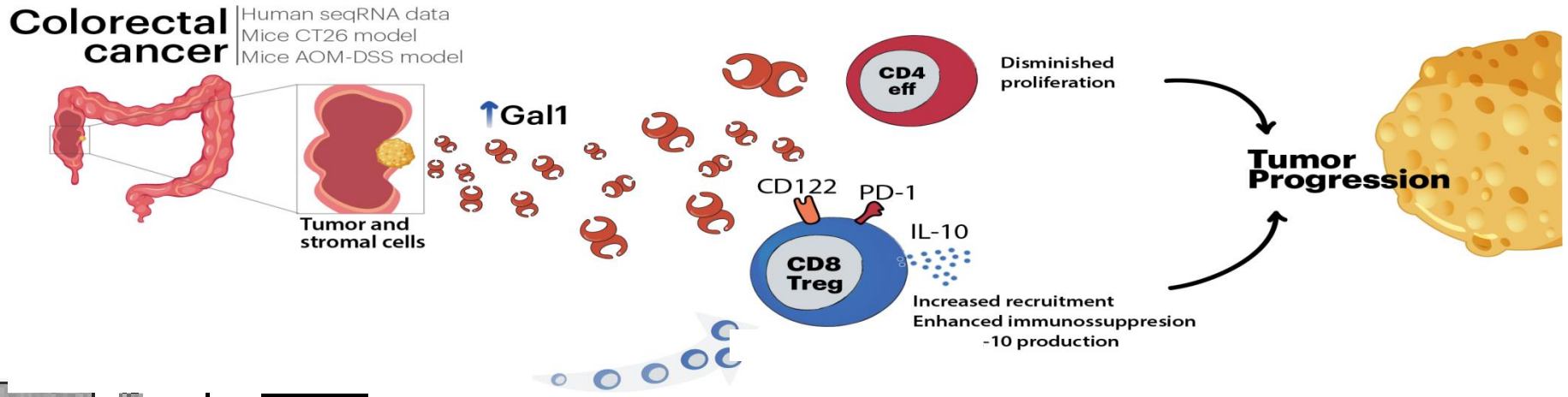




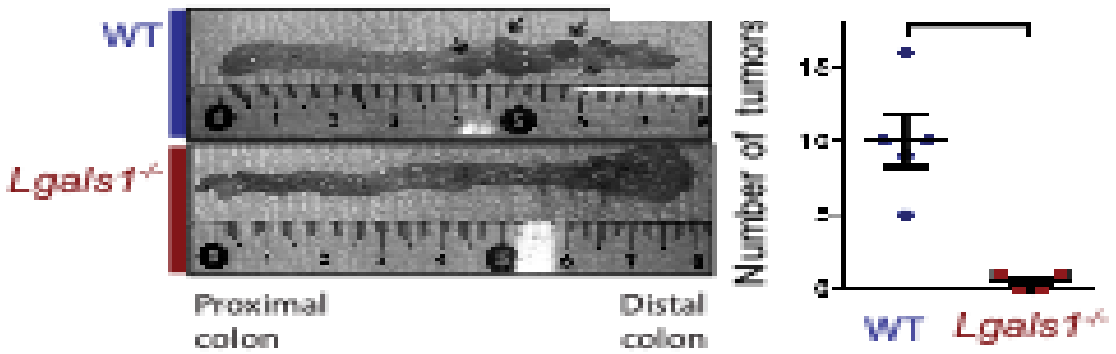
Orozco et al, Proc Natl Acad Sci USA 2018

Gal-1 fosters an immunosuppressive microenvironment in colorectal cancer

- **Expression of Gal-1 was independent of microsatelite Instability (MSI) or mismatch repair deficiency (dMMR)**
- **Gal-1 confers immune privilege to colorectal cancer by increasing the frequency of immunosuppressive CD8 T cells.**



Colorectal
er



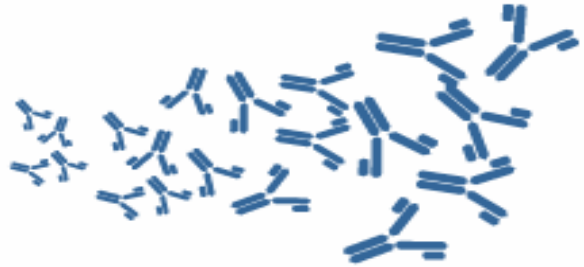
Cagnoni et al, Proc Natl Acad Sci USA 2021

Gal1 as an emerging immunotherapeutic target

GAL-1 blockade

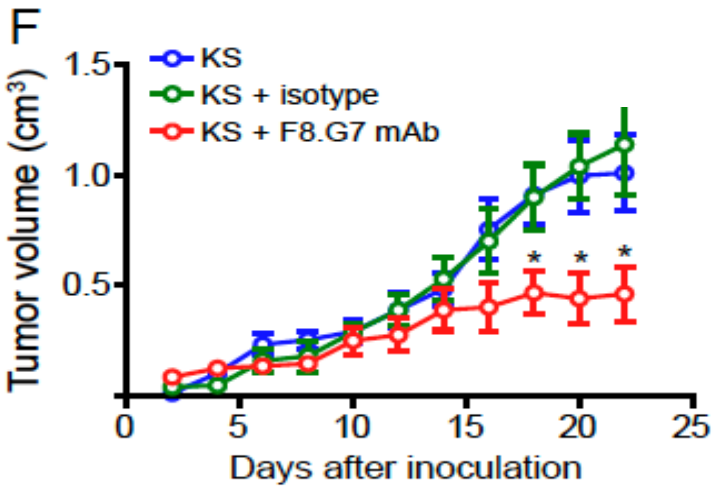
- Stimulates antitumor immune responses
- Mitigates abnormal tumor angiogenesis

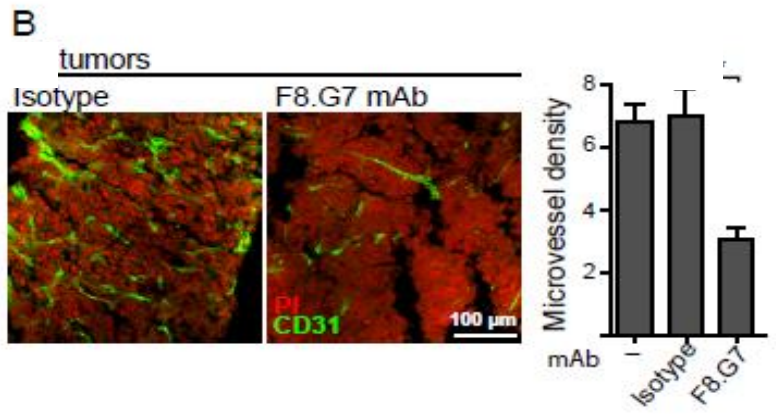
Anti-Gal-1 neutralizing mAb

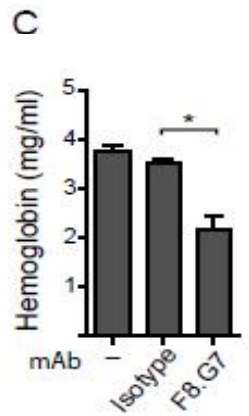


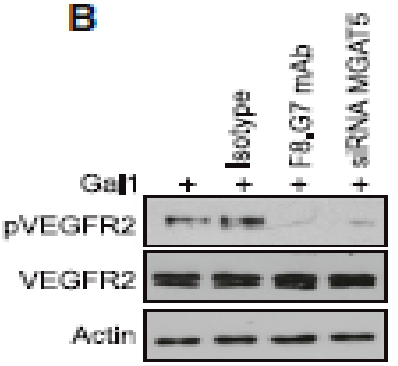
Mariño et al, Nature Reviews Drug Discovery 2023

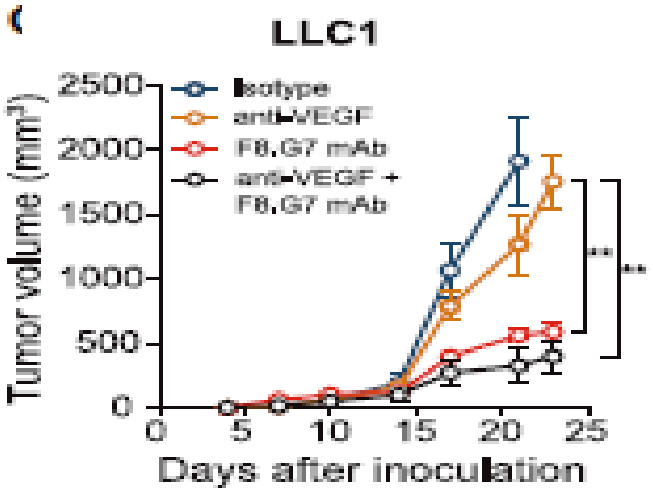
Anti-Gal1 mAb inhibits tumor growth, angiogenesis and counteracts resistance to anti-VEGF treatment

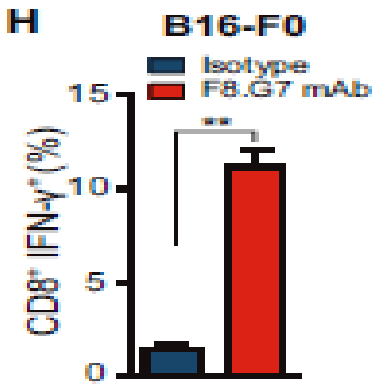


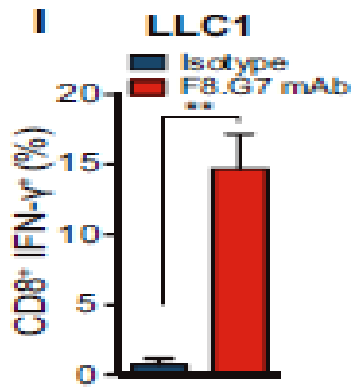


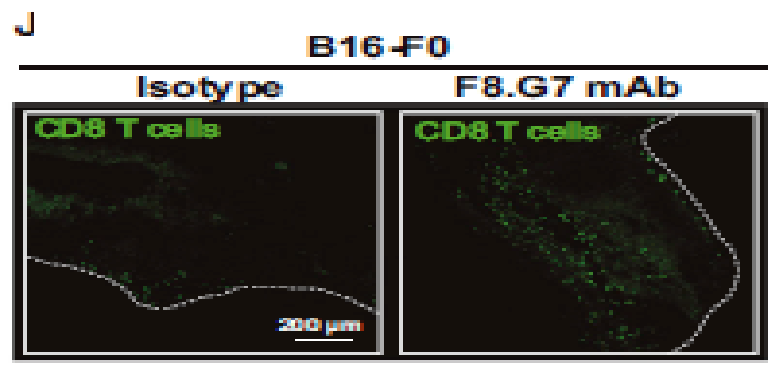








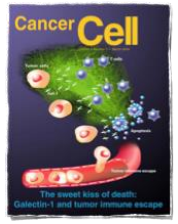




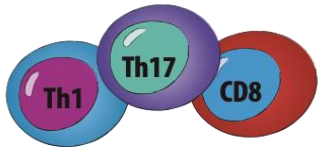
Gal-1: an immune escape strategy and therapeutic target in cancer

Promotes tumor-immune escape

Rubinstein et al, Cancer Cell. 2004
Juszczynski et al, PNAS 2007
Orozco et al, PNAS 2018
Dalotto et al, Cancer Res 2013

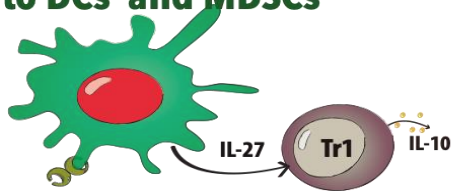


Induces selective death of Th1, Th17 and CD8 T cells via glycosylation-dependent mechanisms



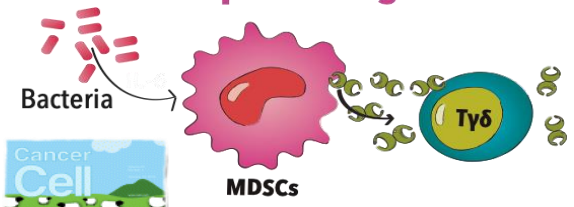
Toscano et al, Nat Immunol. 2007

Delivers tolerogenic signals to DCs and MDSCs

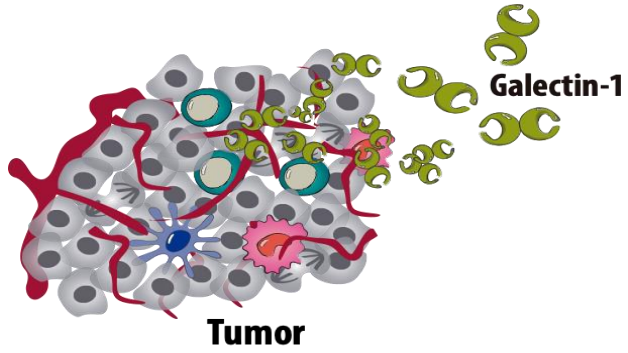


Ilarregui et al, Nat. Immunol. 2009
Tesone et al, Cell Rep. 2016
Blidner et al, under review

Links commensal microbiota to tumor-promoting inflammation

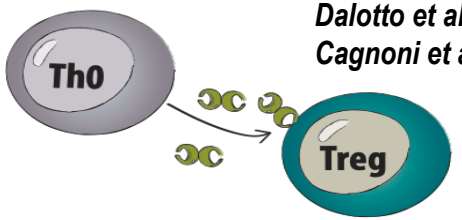


Rutkowski et al, Cancer Cell. 2015

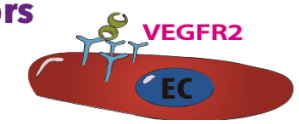


Favors Treg expansion

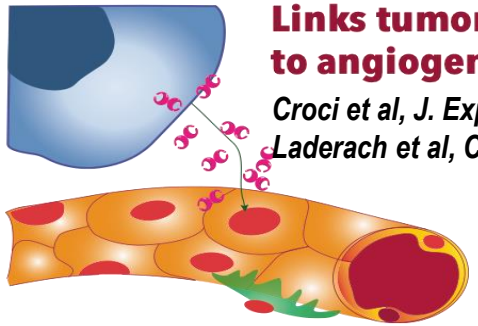
Blois et al, Nat. Med. 2008
Dalotto et al, Cancer Res. 2013
Cagnoni et al, PNAS 2021



Activates VEGFR2 signaling and preserves angiogenesis in anti-VEGF resistant tumors

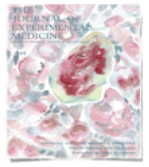


Croci et al, Cell 2014



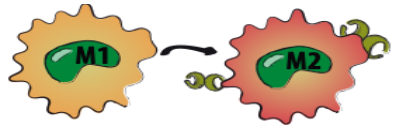
Links tumor hypoxia to angiogenesis

Croci et al, J. Exp. Med. 2012
Laderach et al, Cancer Res . 2013



Promotes M2 macrophages polarization

Starossom et al, Immunity 2012;

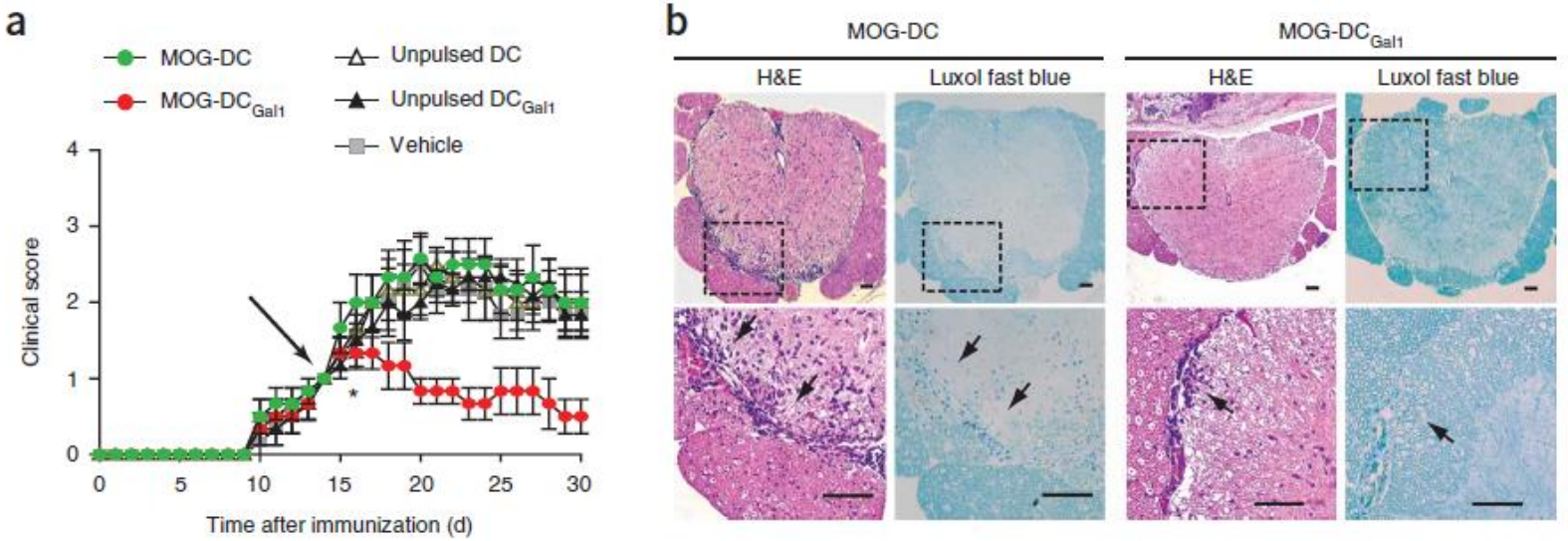


Gal-1 suppresses autoimmune inflammation: another side of the same coin

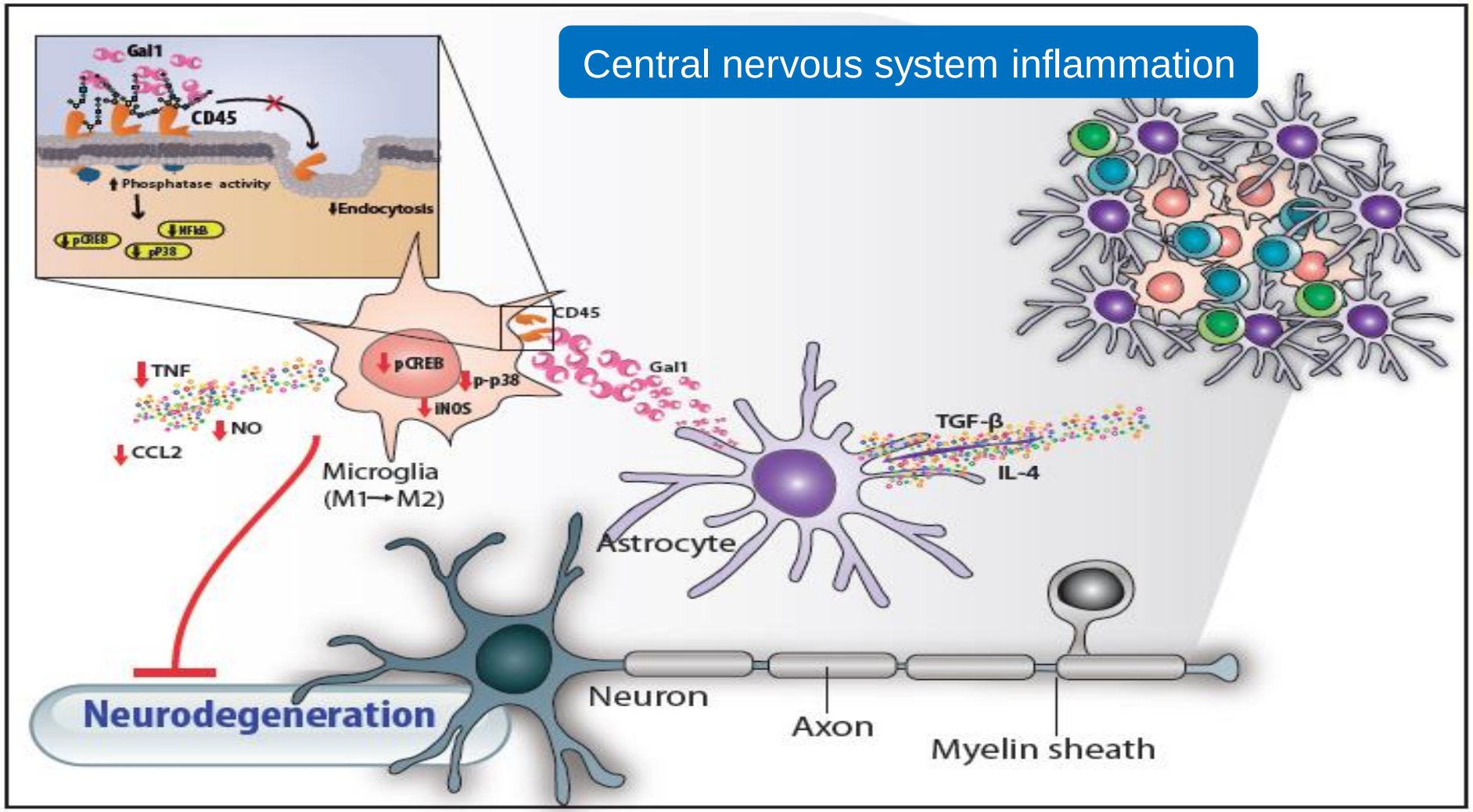
Protein or genetic delivery of Gal-1 suppresses inflammation in different models of autoimmune and inflammatory disorders

- √ **Arthritis** *(Rabinovich et al, J Exp Med 1999)*
- √ **Uveitis** *(Toscano et al, J Immunol 2006)*
- √ **Multiple Sclerosis** *(Toscano et al, Nat Immunol 2007; Ilarregui et al, Nat Immunol 2009; Starossom et al, Immunity 2012)*
- √ **Orchitis** *(Pérez et al, Sci Rep 2015)*
- √ **Diabetes** *(Perone et al, J Immunol 2007; Sundblad et al, Glycobiology 2021)*

EAE (Experimental autoimmune encephalomyelitis): a model of multiple sclerosis

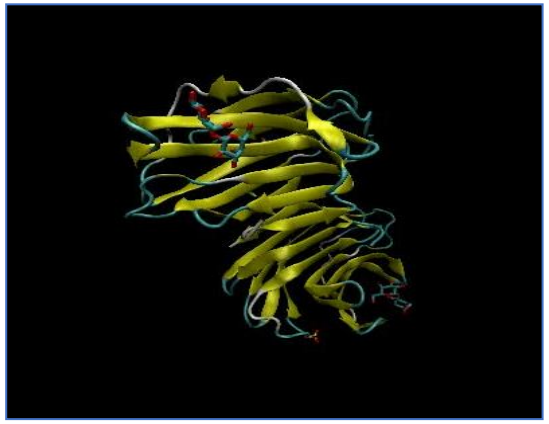


Gal-1 prevents inflammation-induced neurodegeneration



Starossom et al., Immunity 2012

Gal-1 as a potential therapeutic agent in autoimmune inflammation: challenges to overcome

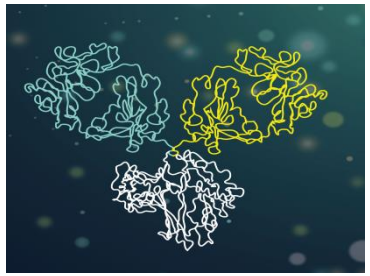


√ **High concentrations are needed for its immunosuppressive activity**

√ **Very unstable at sites of inflammation**

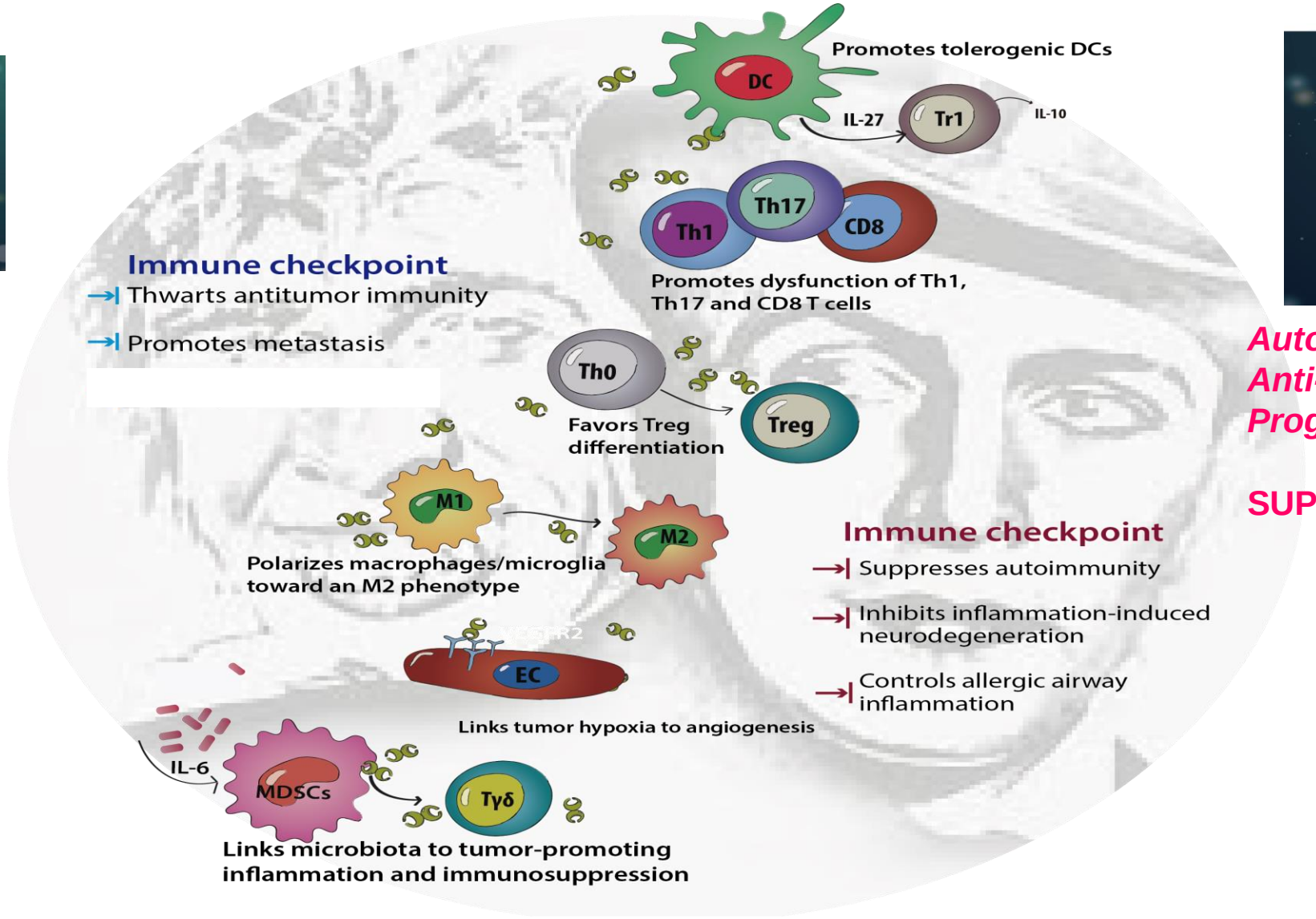
?

Gal-1: The ‘sweet case’ of Dr. Jekyll and Mr. Hyde



Inmuno-Oncology
Anti-angiogenesis
Program

(Anti-Gal-1 mAb)



Autoimmunity
Anti-inflammatory
Program

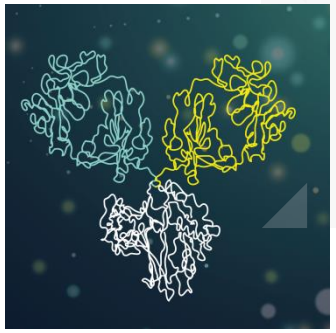
SUPER-GAL1 variant

Galtec

The future of health is sweet

MISION: *Translate scientific discoveries, based on modulation of galectins and its glycosylated ligands, into novel technologies and therapeutic opportunities for patients with cancer and autoimmune inflammatory diseases*

Galectin-1-based Technology Platforms



Platform 1: IMMUNO-ONCOLOGY (Human anti-Gal1 neutralizing mAbs)

- Stimulate antitumor immune responses
- Counteract aberrant tumor angiogenesis

TWO IN ONE THERAPY

Platform 2: AUTOIMMUNITY AND CHRONIC INFLAMMATION (Super-Gal1)

Immunoregulatory Gal1 variants engineered to overcome the adverse conditions of inflammatory microenvironments.

These Super-Gal1 variants target different cells implicated in autoimmune inflammation (Th1, Th17, CD8, dendritic cells, microglia)

THANKS SO MUCH!

Ferioli, Ostry and Caraballo Families- Patients

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