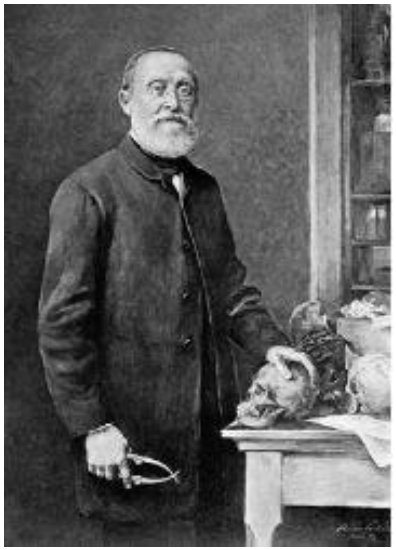
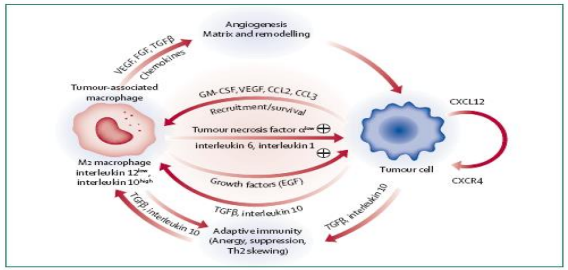
INFLAMMATION, MACROPHAGES AND CANCER

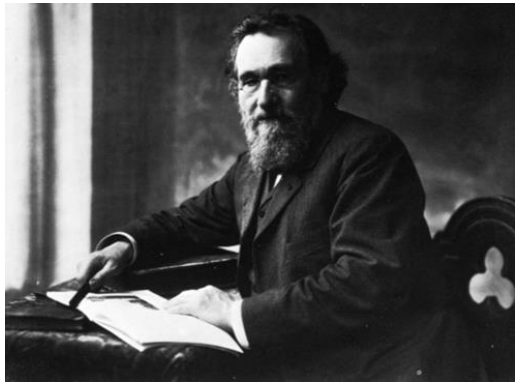


RUDOLF LUDWIG KARL VIRCHOW (1821-1902)

Balkwill and Mantovani, Lancet 2001

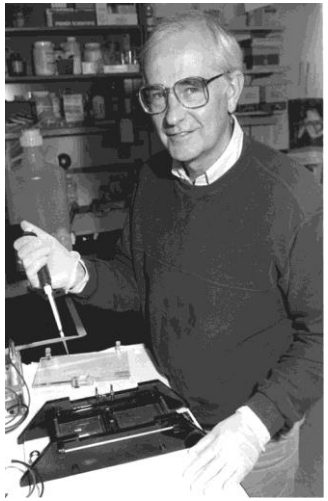


(Mantovani et al. Lancet 2008; Nature 2008)

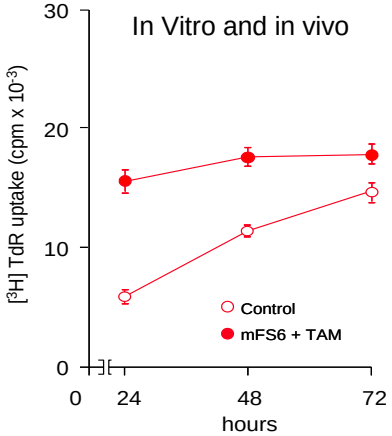


Ilya Mechnikov (1845-1916)

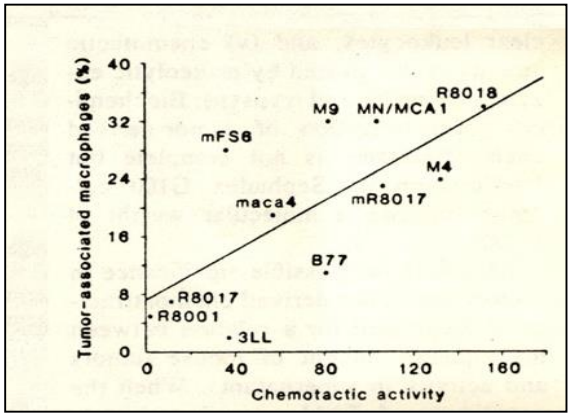
The Nobel Prize in Physiology and Medicine 1908



(TAM: Robert Evans, Transplantation, 1972; Evans and Alexander, Nature, 1970)



(Mantovani A. 1978)



(Bottazzi et al Science 1983)

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M1

M2-like

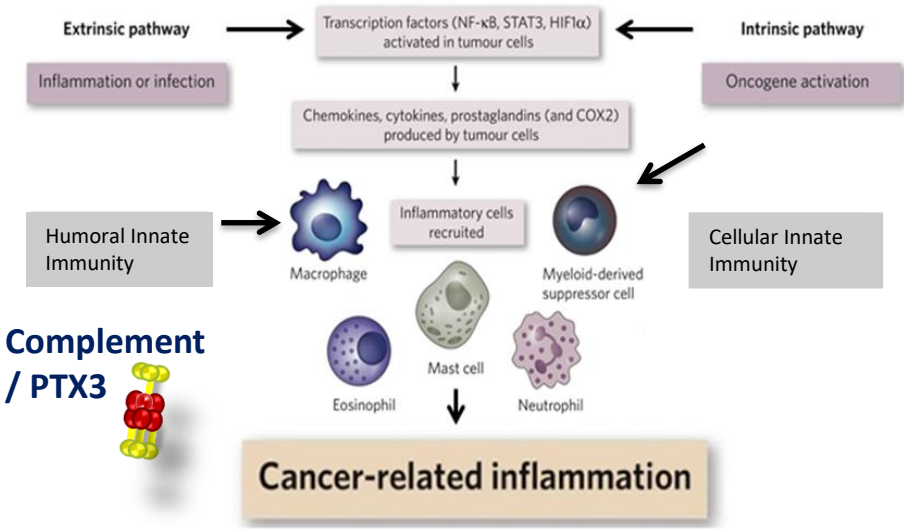
M1-like

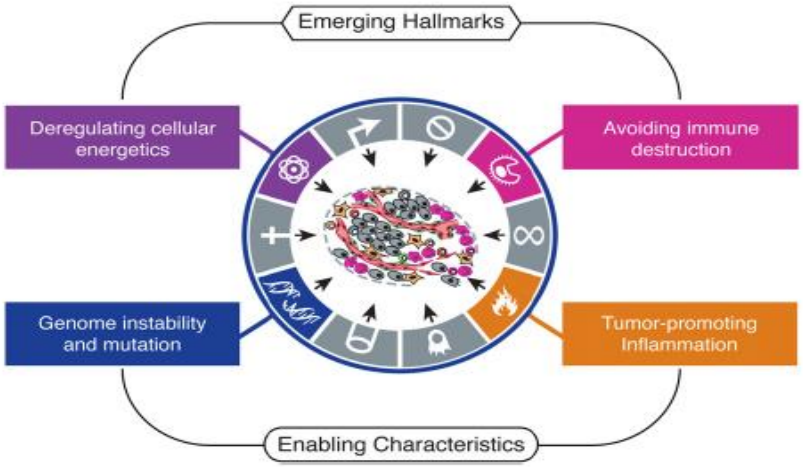
M2

Farbstudie Quadrate, Wassily Kandinsky, 1913

«A distinct and unique transcriptional program expressed by tumor-associated macrophages (defective NF-kappaB and enhanced IRF-3/STAT1 activation)»
Biswas et al., Blood 2006

(Selected reviews: Sica and Mantovani J Clin Inv 2012; Biswas and Mantovani, Nature Immunol 2010; Murray et al Immunity 2014; Mantovani and Allavena J Exp Med 2015; Mantovani Nature Immmunol 2016)





(e.g. Mantovani, Sica, Allavena, Balkwill, Nature, 2008; Mantovani, Nature, 2009; Hanahan and Weinberg, Cell, 2000; Cell, 2011; Reis et al, Nature Rev Immunol, 2018; Bonavita et al, Cell, 2015)

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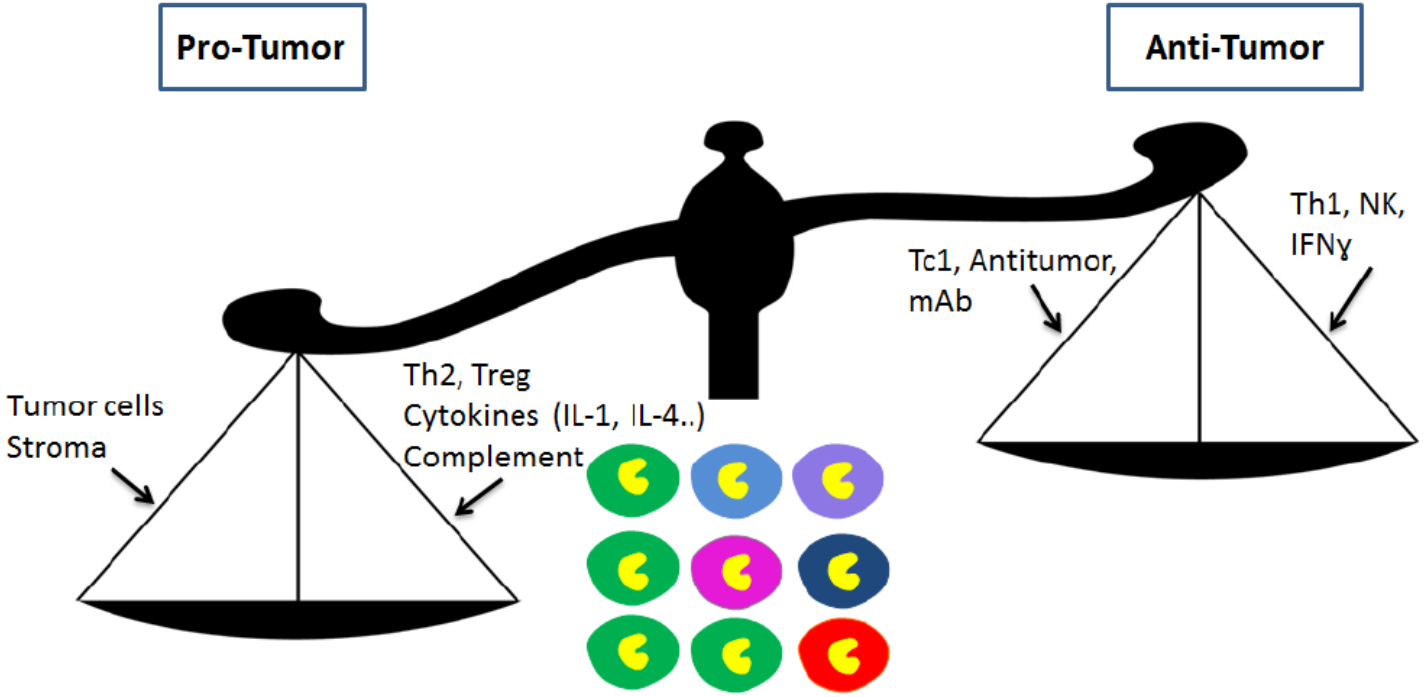
The macrophage balance in cancer



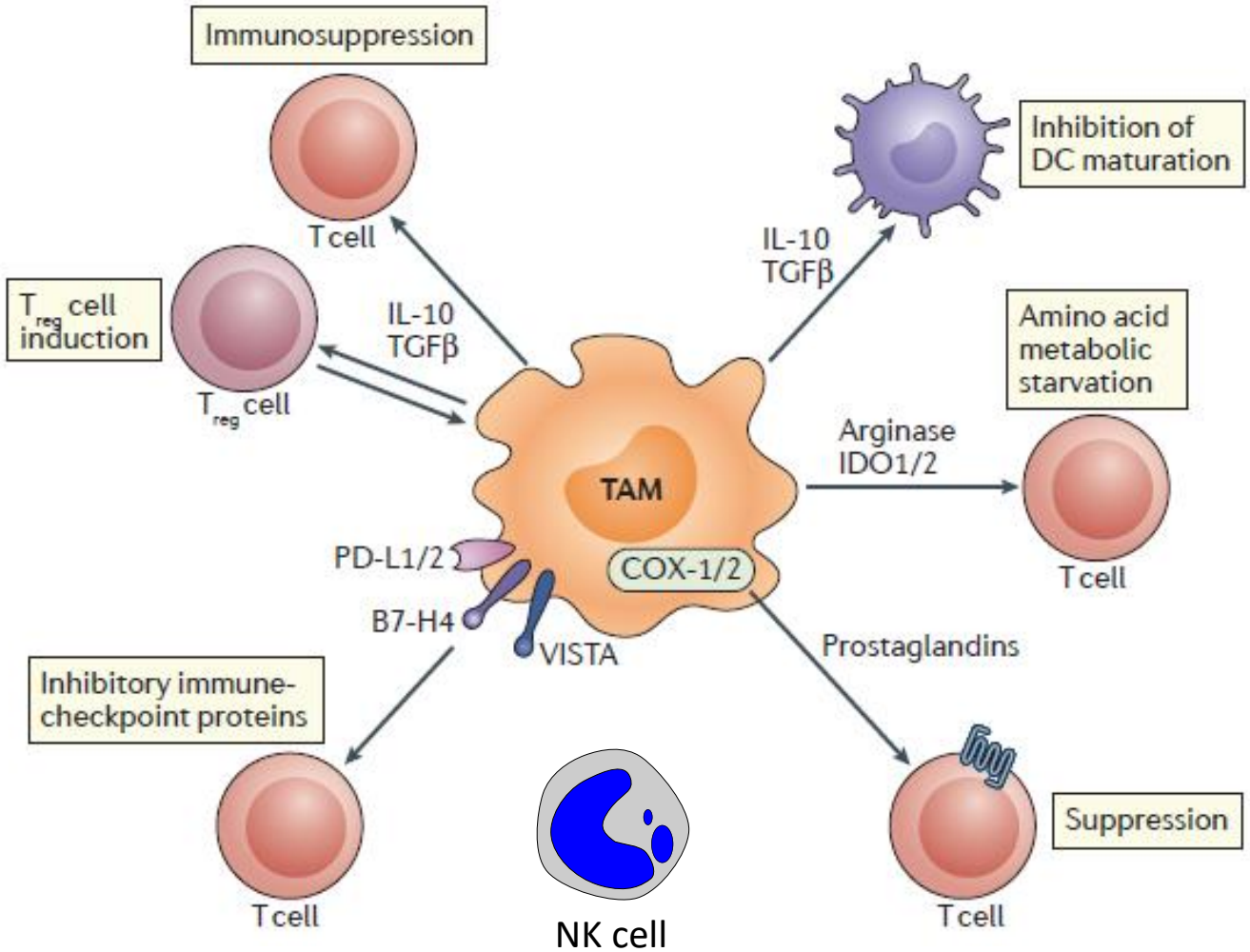
Immunosuppression
(PD-L1, aa metabolites, PG, IL-10..)
Invasion, Metastasis
CSC niche
Stroma
Response to hormones and drugs

Tumor-Associated
Macrophages (TAM)

Direct Cytotoxicity (M1)
ADCC
ADCP
Activation of innate and
adaptive lymphoid cells

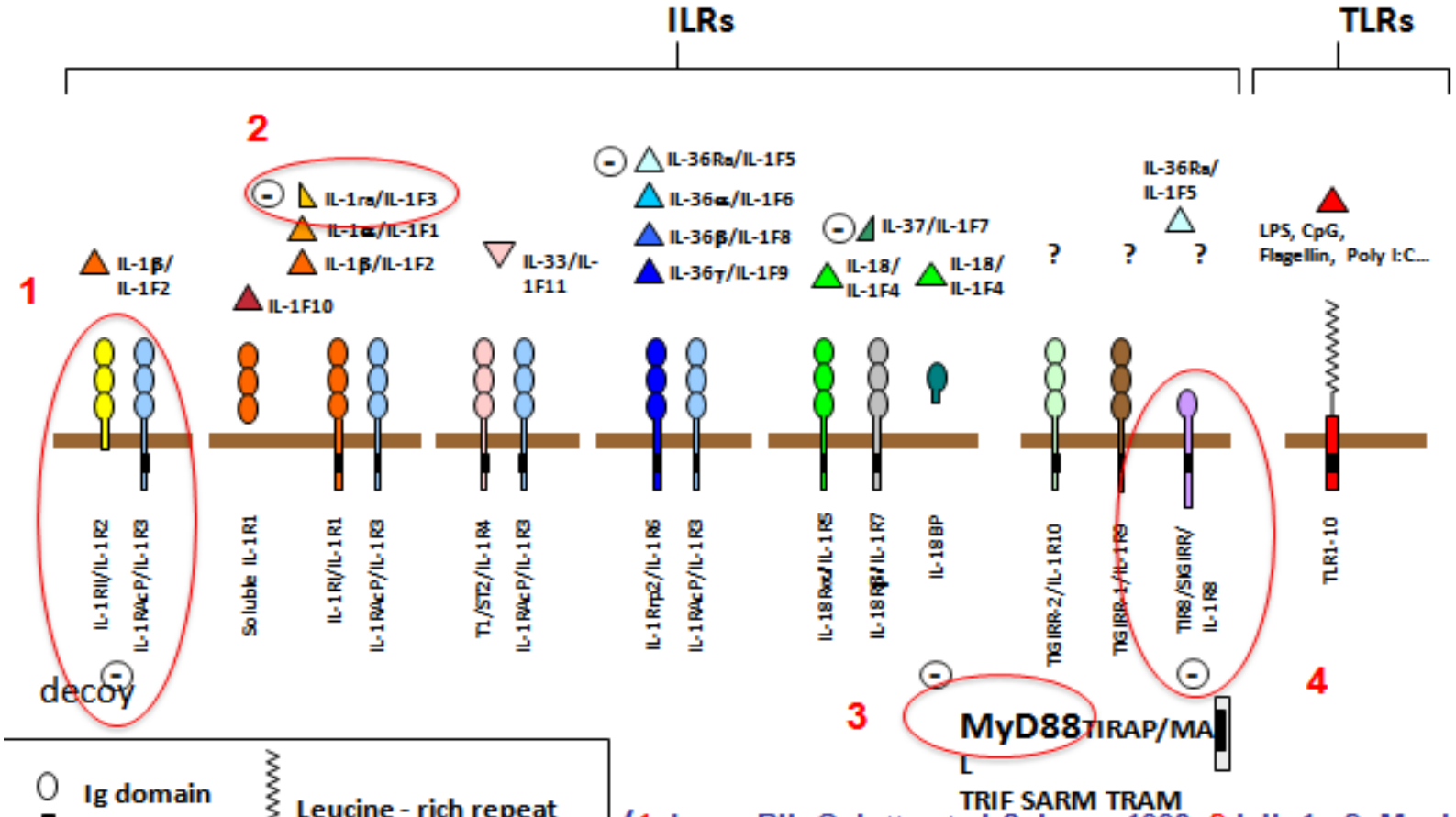
(Mantovani et al, Nature Rev. Clin. Oncol., 2017; Mantovani and Longo, New England J Med., 2018; Mantovani et al, Annu Rev Pathol, Under revision)

Mechanisms of TAM mediated immune suppression



(Mantovani et al, Nature Rev Clin Oncology, 2017; Mantovani and Ceresoli Lancet Oncol 2018)

THE IL-1 RECEPTOR (ILR)



(1 decoy RII: Colotta et al Science 1993; 2 icIL-1ra2: Muzio et al JEM 1998; 3 The hToll –MyD88 cascade: Muzio et al JEM 1998 4 TIR8: Garlanda, Anders and Mantovani Trends Immunol 2009)

(for a review on IL-1/IL-1R family Garlanda et al Immunity 2013; Immunity 2019 in press)

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[CANCER RESEARCH 50, 4771–4775, August 1, 1990]

Interleukin 1-induced Augmentation of Experimental Metastases from a Human Melanoma in Nude Mice[1]

Raffaella Giavazzi,[2] Angela Garofalo, Maria Rosa Bani, Mauro Abbate, Pietro Ghezzi, Diana Boraschi, Alberto Mantovani, and Elisabetta Dejana

[CANCER RESEARCH 53, 5051–5054, October 15, 1993]

Interleukin 1 Receptor Antagonist Inhibits the Augmentation of Metastasis Induced by Interleukin 1 or Lipopolysaccharide in a Human Melanoma/Nude Mouse System[1]

Renato G. S. Chirivi, Angela Garofalo, Ines Martin Padura, Alberto Mantovani, and Raffaella Giavazzi[2]

[CANCER RESEARCH 54, 2667–2672, May 15, 1994]

Interleukin-1 Receptor Blockade Reduces the Number and Size of Murine B16 Melanoma Hepatic Metastases[1]

Fernando Vidal-Vanaclocha, Cristian Amézaga, Aintzane Asumendi, Gilles Kaplanski, and Charles A. Dinarello[2]

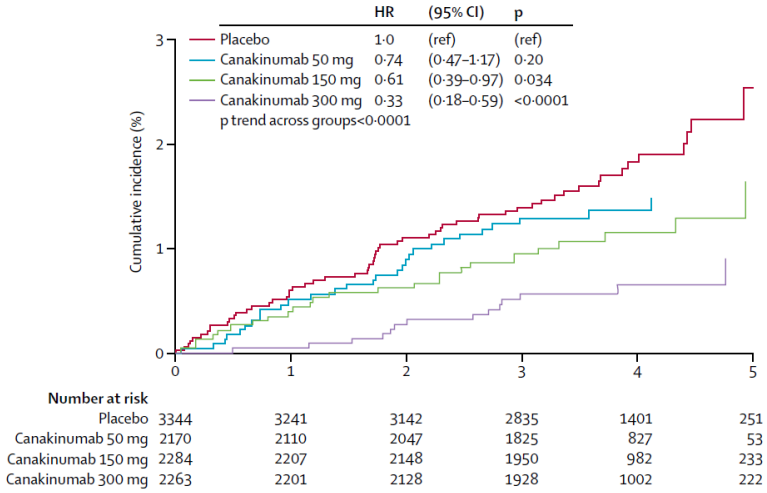
PNAS | March 4, 2003 | vol. 100 | no. 5 | 2645–2650

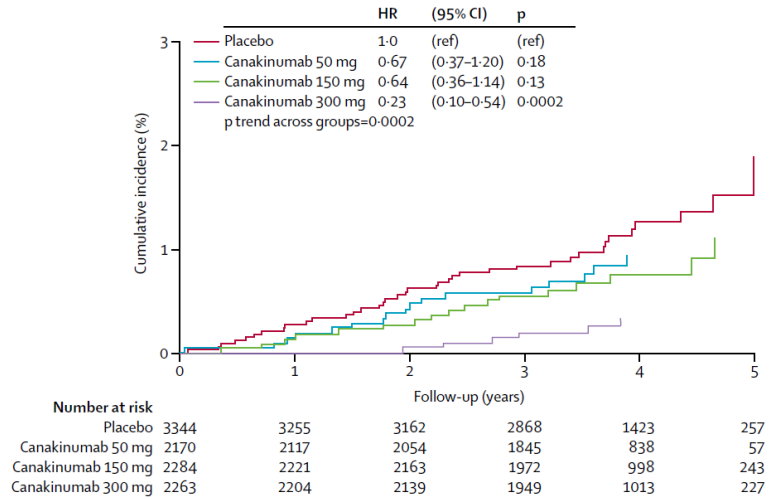
IL-1 is required for tumor invasiveness and angiogenesis

Elena Voronov*, Dror S. Shouval*, Yakov Krelin*, Emanuela Cagnano*, Daniel Benharroch*, Yoichiro Iwakura†, Charles A. Dinarello‡, and Ron N. Apte*§

Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial

Paul M Ridker, Jean G MacFadyen, Tom Thuren, Brendan M Everett, Peter Libby*, Robert J Glynn*, on behalf of the CANTOS Trial Group†





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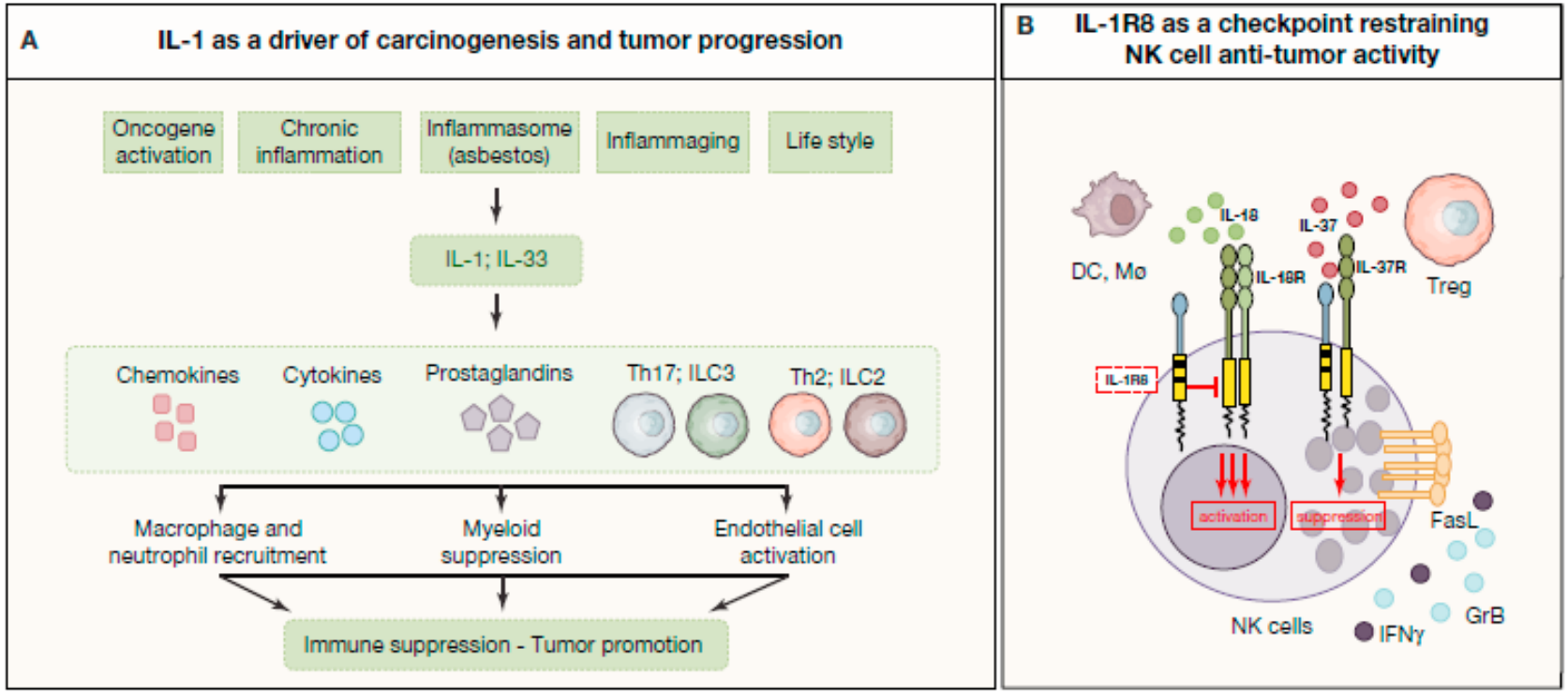
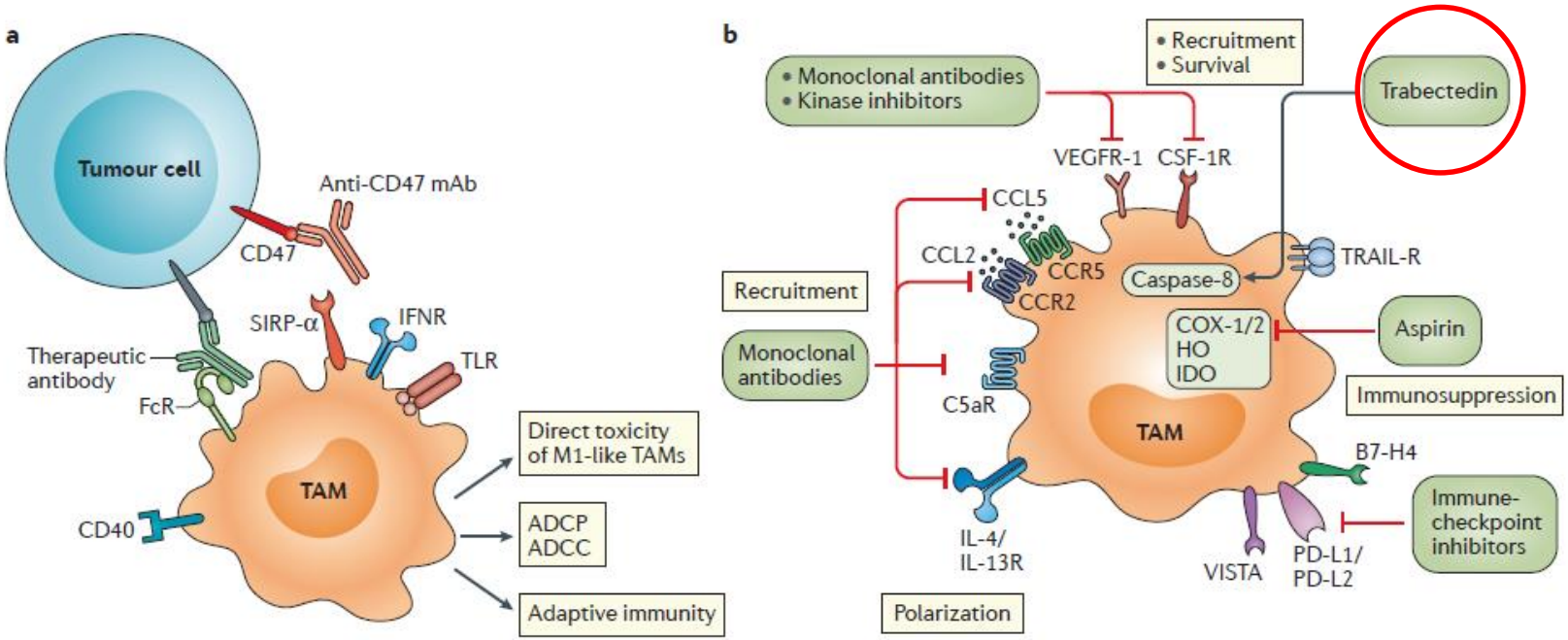
The dual role of IL-1 / IL-1R family members in cancer



(Mantovani et al, Immunity, 2019 In press)

Macrophage-targeting antitumour treatment approaches

Trabectedin: Chemo and macrophage targeting in one molecule
Germano, ...D'Incalci, Mantovani, Allavena Cancer Cell 2013;



Mantovani et al, Nature Rev Clin Oncol, 2017

Macrophage-targeting antitumour treatment approaches

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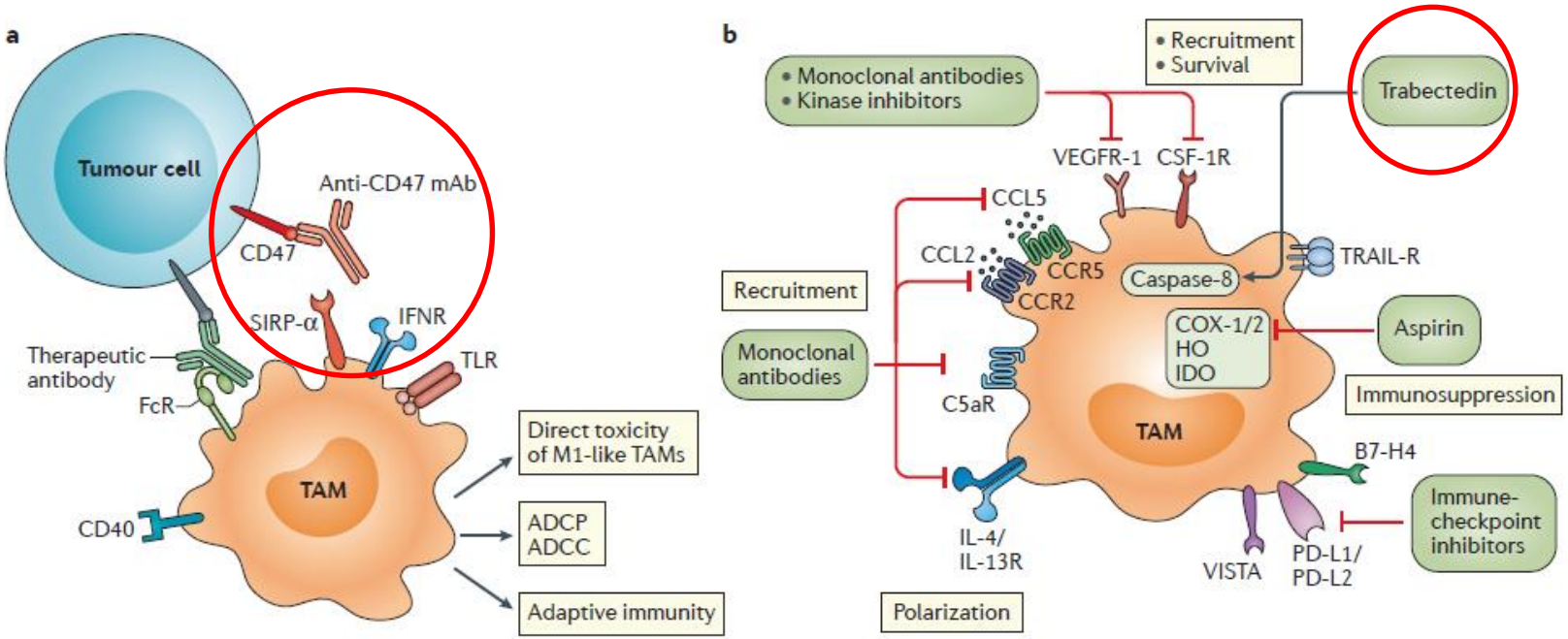
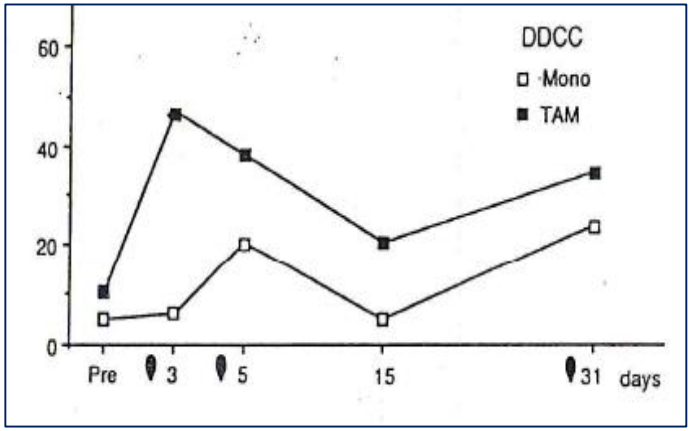


Mantovani et al, Nature Rev Clin Oncol, 2017

IFNγ IMMUNOTHERAPY IN OVARIAN CANCER PATIENTS WITH MINIMAL RESIDUAL DISEASE (i.p.)

Advanced cancer (7 pts)



Minimal residual disease

TABLE II – CLINICAL RESPONSES TO IMMUNOTHERAPY AND FOLLOW-UP

Patient	Tumor burden at second look (mm)	Toxicity	Clinical response third look	Follow-up (months)
1	5–10	Fever, malaise bowel perforation > transaminase	PR	20
2	<5	Fever, malaise > transaminase	CR	28[1]
3	<5	Fever, malaise	progr. disease	13
4	<5	Fever, malaise	SD	24[1]
5	<5	Fever, malaise > transaminase	progr. disease	7
6	5–10	Fever, malaise	SD	22[1]
7	5–10	Fever, malaise	progr. disease	8
8	<5	Fever, malaise	PR	11[1]

[1]Patient is still alive.

8 pts; full trial 108 pts

Biological response in minimal residual disease: Pt2 (CR)

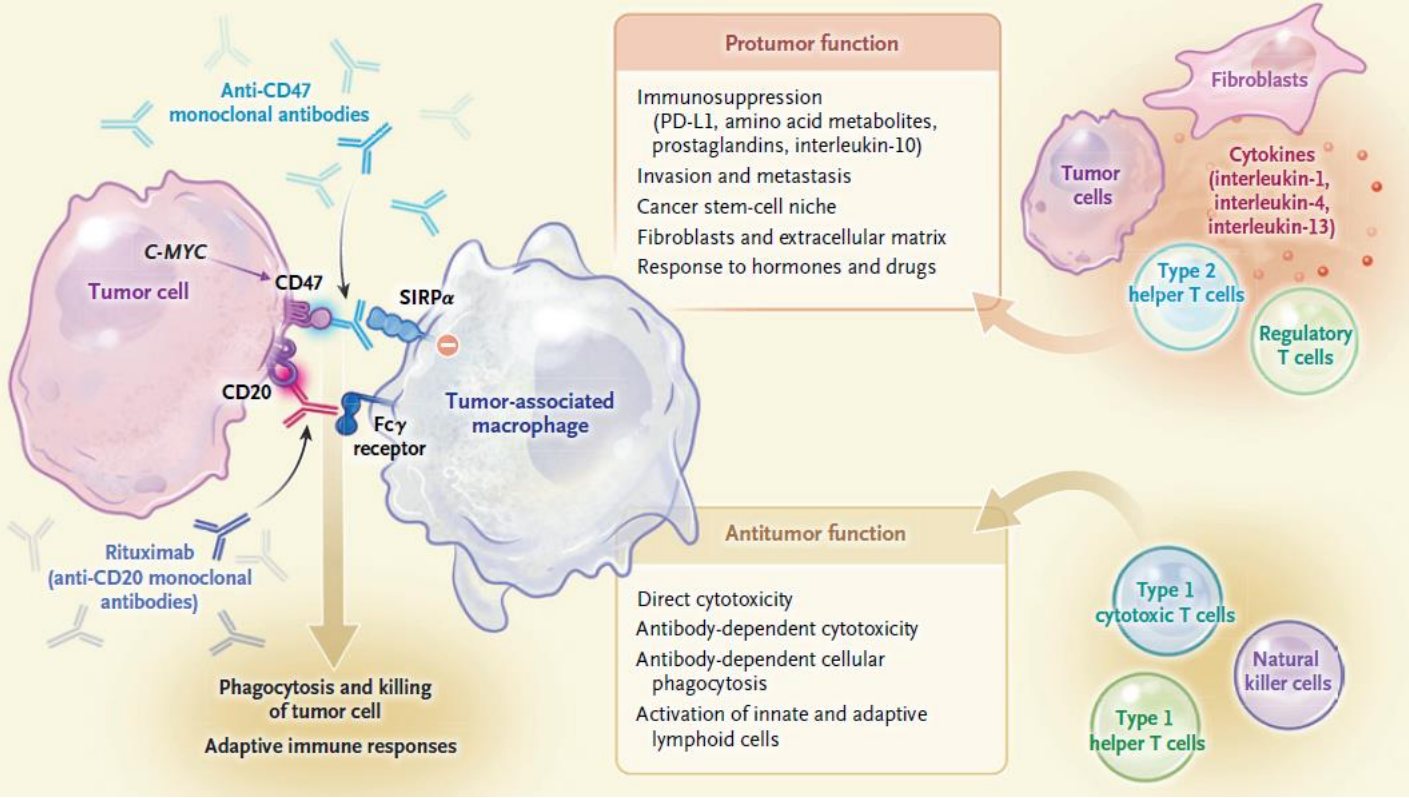
TABLE III – CYTOTOXIC ACTIVITY OF PERIPHERAL BLOOD AND TUMOR-ASSOCIATED EFFECTORS DURING I.P. THERAPY WITH IFN-γ

		NK[1]		DDCC[2]	
	Days[3]	TAL	PBL	TAM	Monocytes
PT.2	Pre	1.6 ± 1.7	14.2 ± 2.1	4.0 ± 2.3	16.2 ± 5.8
	4	17.4 ± 3.8*	15.3 ± 2.5	—	14.1 ± 2.9
	30	14.5 ± 0.3*	41.9 ± 3.0*	46.1 ± 1.8*	30.1 ± 3.4*
	60	28.8 ± 4.0*	37.4 ± 1.5*	30.7 ± 3.8*	28.1 ± 4.7*

Allavena et al., Cancer Res 1990; Colombo et al., Int J Cancer 1992; Pujade-Lauraine et al., Bull Cancer 1993; J C O, 1996

Macrophage Checkpoint Blockade in Cancer — Back to the Future

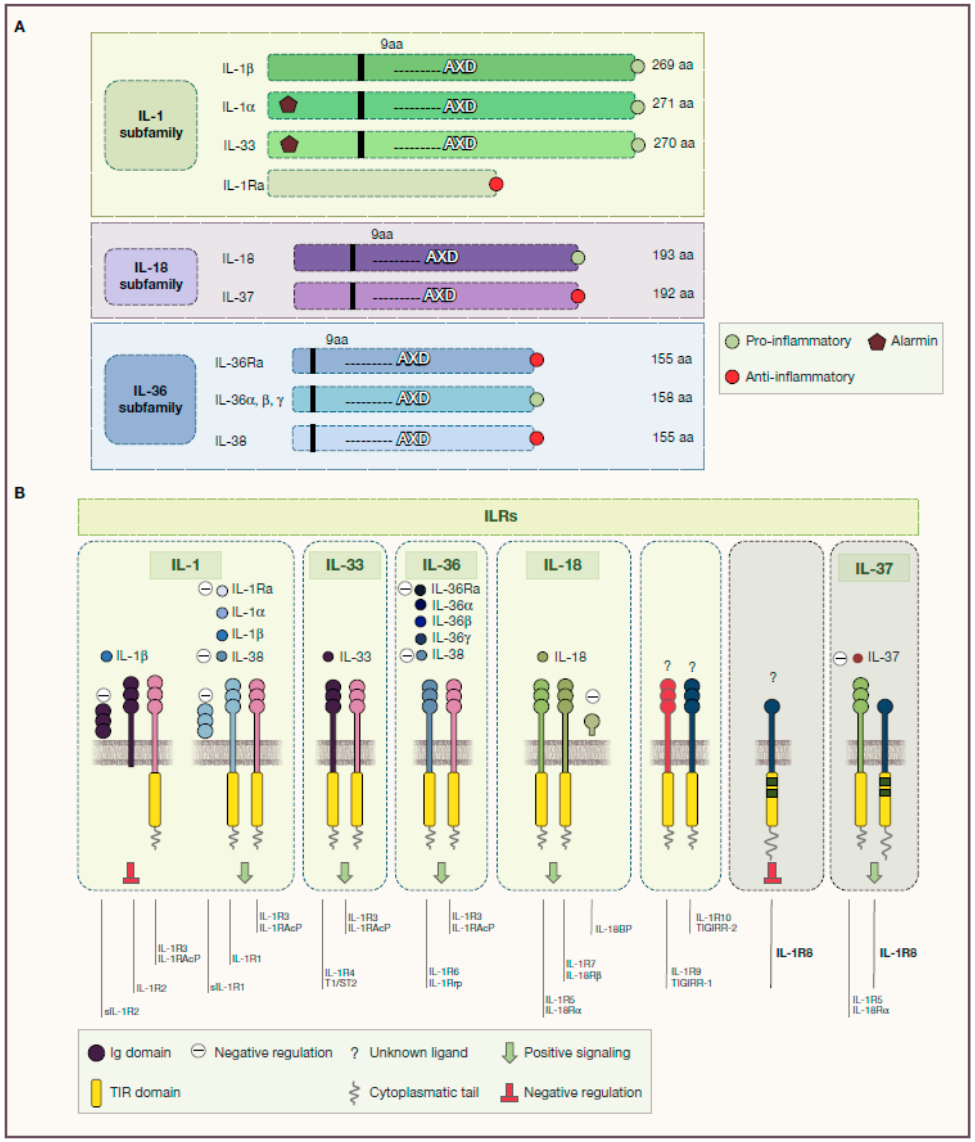
Alberto Mantovani, M.D., and Dan L. Longo, M.D.



Tumor-Associated Macrophages in Cancer Progression and as Therapeutic Targets.
Macrophages can exert dual function in patients with cancer, depending on the activation state and therapy. During tumor progression, protumor functions prevail. *C-MYC*, an oncogene that often drives the proliferation of neoplasms, also induces the expression of CD47. Negative signals delivered by the signal regulatory protein α (SIRPα) to macrophages through CD47 prevent their participation in tumor killing. In the presence of antitumor monoclonal antibodies (anti-CD20; rituximab), blocking the CD47–SIRPα checkpoint unleashes macrophage-mediated tumor-cell phagocytosis and killing. The same pathway activates effective adaptive immunity. PD-L1 denotes programmed death ligand 1.

(Mantovani and Longo, New England J. Med. 2018; on Advani et al NEJM 2018)

The IL-1 / IL-1R family



(Mantovani et al, Immunity 2019, in press)

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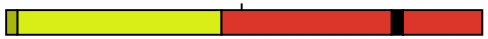
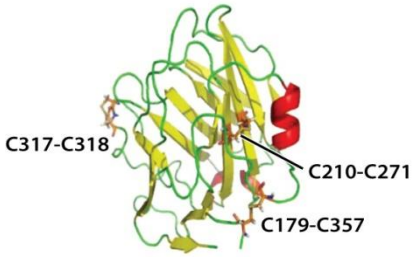
Chr 3q25
mRNA 1866 bp

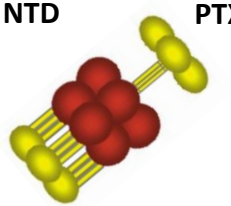
Prot 381 aa



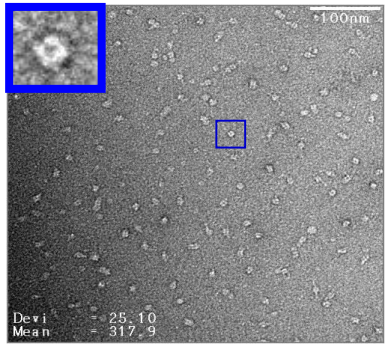
PTX signature
(HxCxS/TWxS)



PTX3
C-terminal domain



PTX3



OmpA
Men B
components

Microbe recognition

FcγR

Opsonization

C1q
Factor H

C activation and regulation of inflammation

Ficolins
MBL

Repertoire synergism

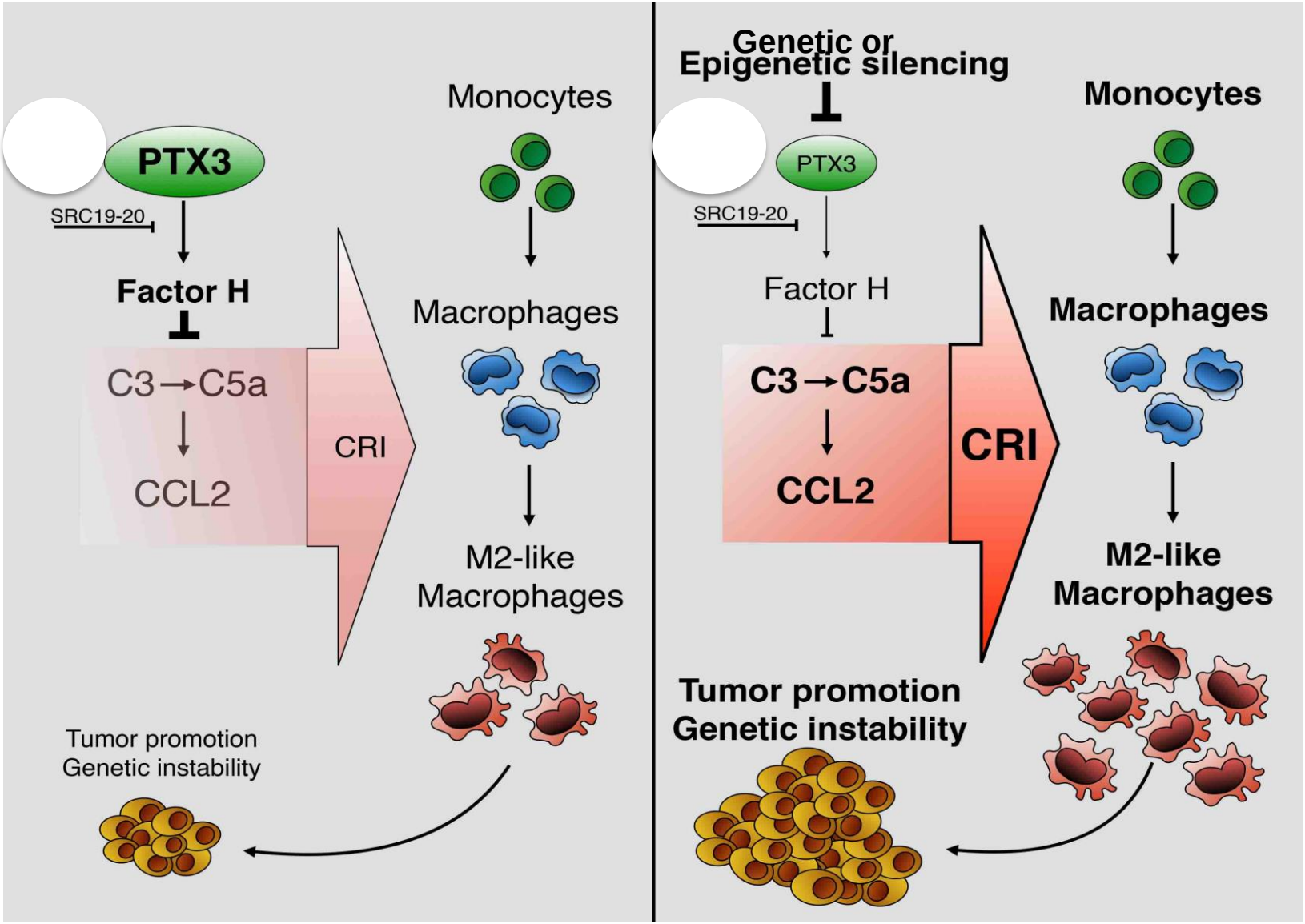
P-selectin

Regulation of leukocyte recruitment and inflammation

RESISTANCE TO SELECTED MICROBES (eg A. fumigatus, P. aeruginosa) – REGULATION OF INFLAMMATION and REPAIR – ADAPTIVE IMMUNITY

Garlanda et al Nature 2002; Deban al Nature Immunol 2010; Lu et al Nature 2009; Bottazzi et al Annu Rev Immunol 2010; Doni et al J Exp Med 2015; Bottazzi et al PLOSOne 2015; Chorny…Cerutti JEM 2016; Garlanda et al Physiol Rev 2018

PTX3 as an extrinsic oncosuppressor in mouse and human cancer: role of Complement



Bonavita et al Cell 2015; Rubino et al Oncoimmunology 2017; Reis et al Nature Rev Immunol 2018

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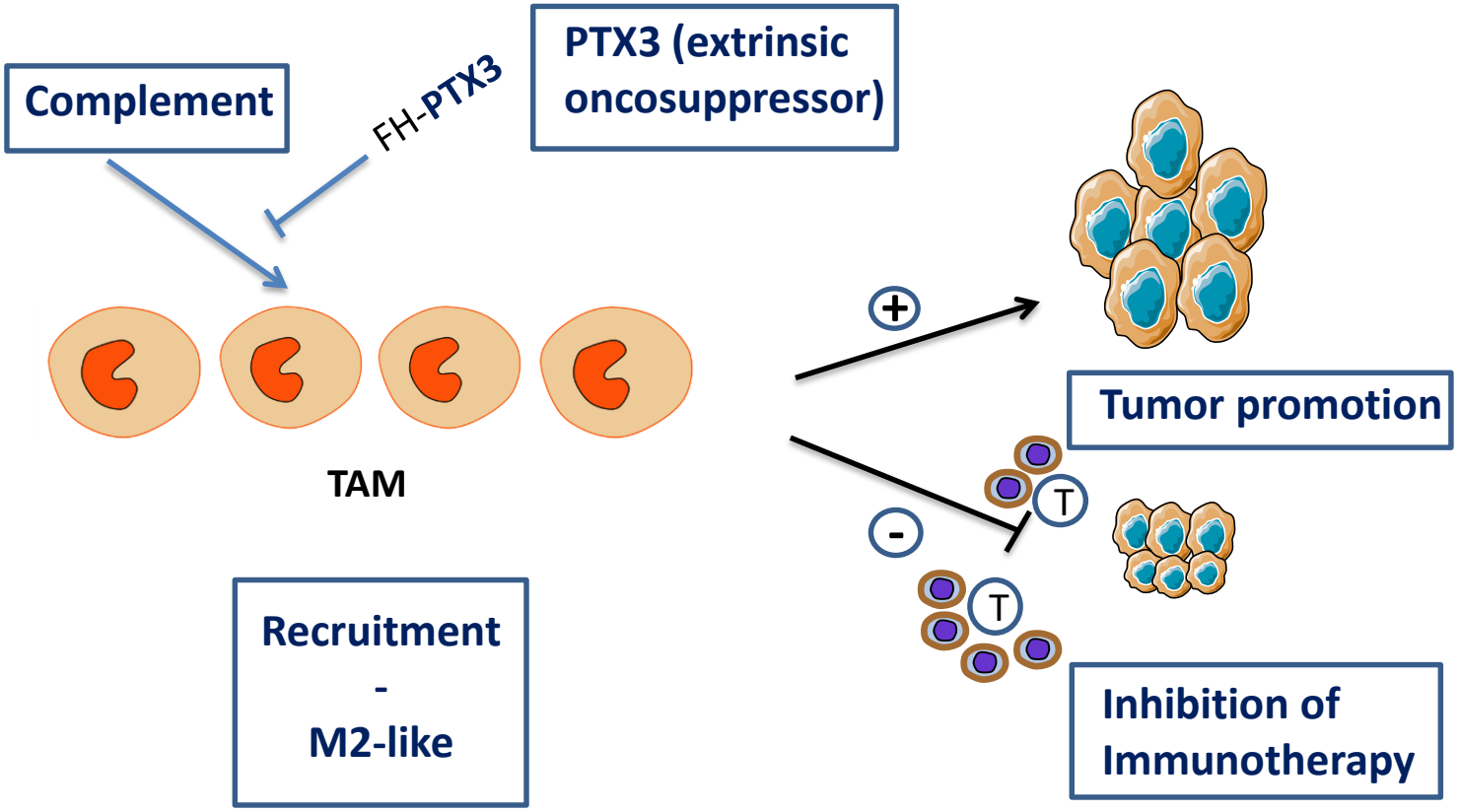
Complement and PTX3 in 3-MCA carcinogenesis and selected human tumors (e.g. CRC; leiomyosarcoma..)



Bonavita et al, Cell, 2015; Rubino et al Oncoimmunol. 2018; Magrini et al unpublished; Reis et al, Nature Rev Immunol, 2018; Ruben Pio et al Frontiers Immunol in press

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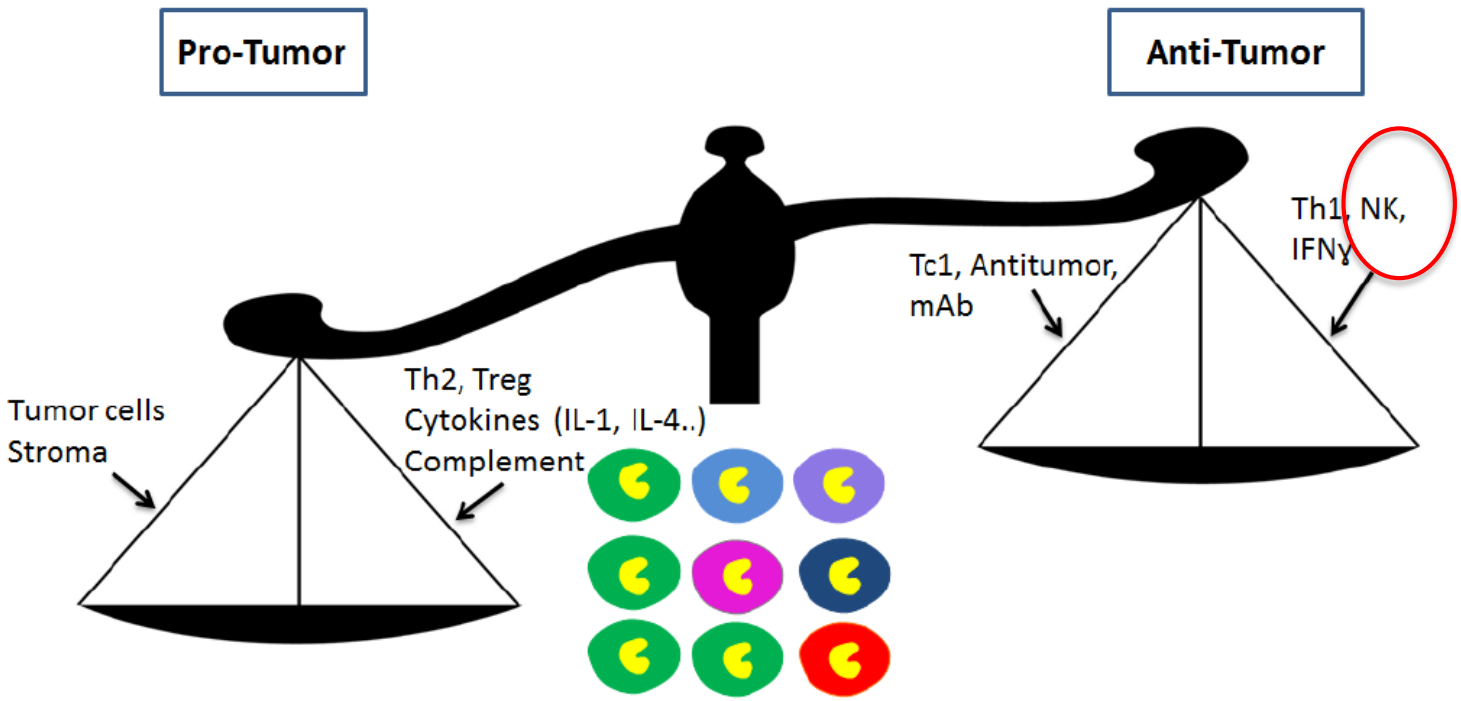
The macrophage balance in cancer



Immunosuppression
(PD-L1, aa metabolites, PG, IL-10..)
Invasion, Metastasis
CSC niche
Stroma
Response to hormones and drugs

Tumor-Associated
Macrophages (TAM)

Direct Cytotoxicity (M1)
ADCC
ADCP
Activation of innate and
adaptive lymphoid cells

(Mantovani et al, Nature Rev. Clin. Oncol., 2017; Mantovani and Longo, New England J Med., 2018; Mantovani et al, Annu Rev Pathol, Under revision)

IL-1R8/TIR8/SIGIRR

A member of the IL-1 receptor family, with regulatory function

(for a review on IL-1/IL-1R family: Mantovani, Molgora, Dinarello and Garlanda, Immunity 2019;
for IL-37R: Li et al PNAS; Nold-Petri et al Nature Immunol 2016)

IL-1R8/TIR8/SIGIRR

A member of the IL-1 receptor family, with regulatory function

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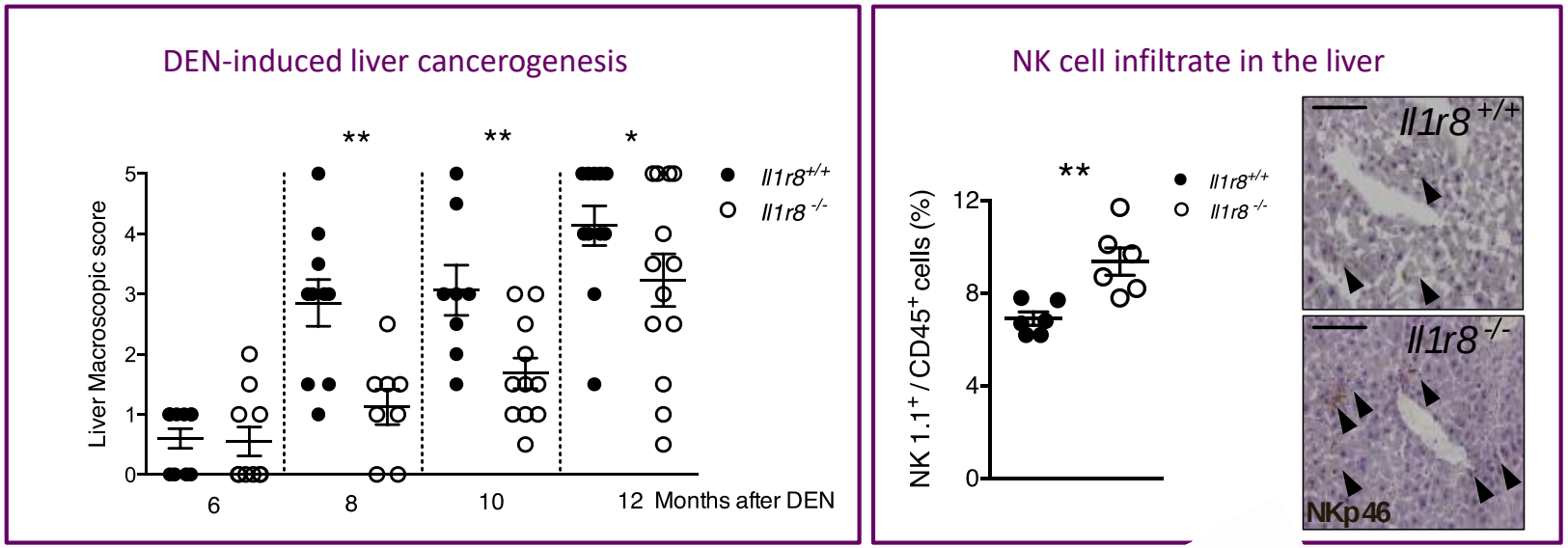
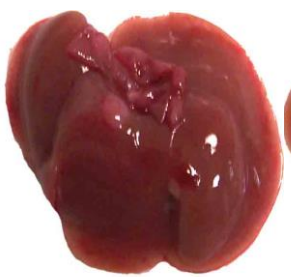
IL-1R8-deficient mice are protected against **HCC development**

Model of DEN-induced hepatocellular carcinoma (HCC)



6 Months

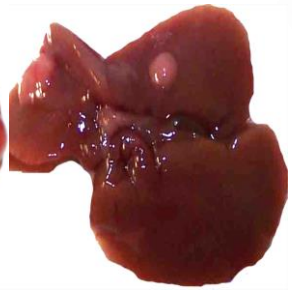


Il1r8$^{+/+}$

Il1r8$^{-/-}$

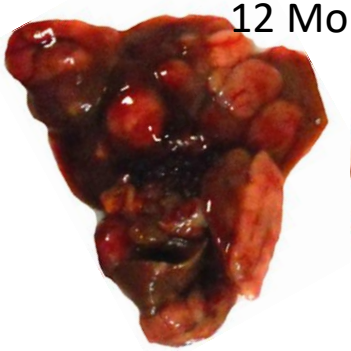
8-10 Months

Il1r8$^{+/+}$



Il1r8$^{-/-}$

12 Months

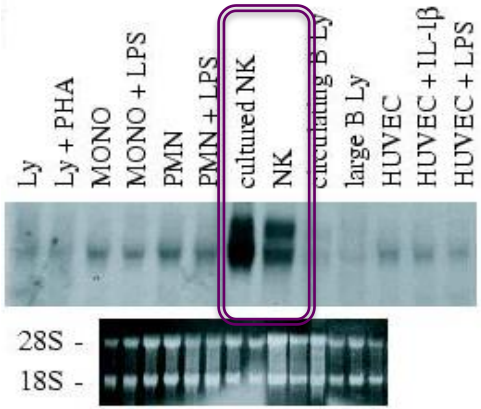


Il1r8$^{+/+}$

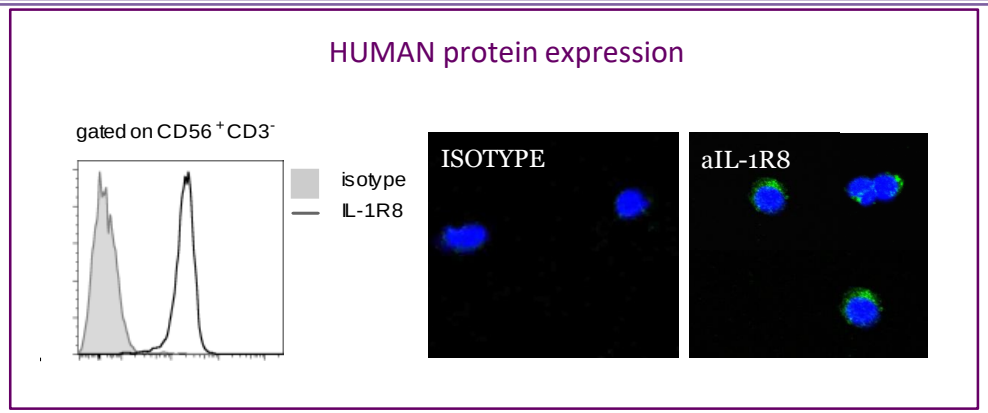
Il1r8$^{-/-}$

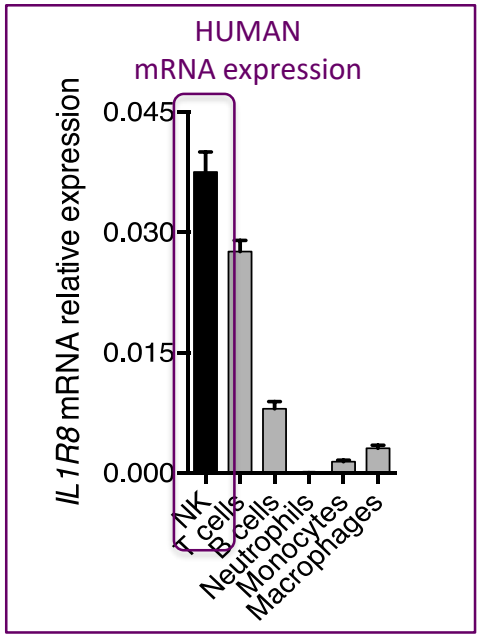
(Molgora, Bonavita et al, Nature 2017)

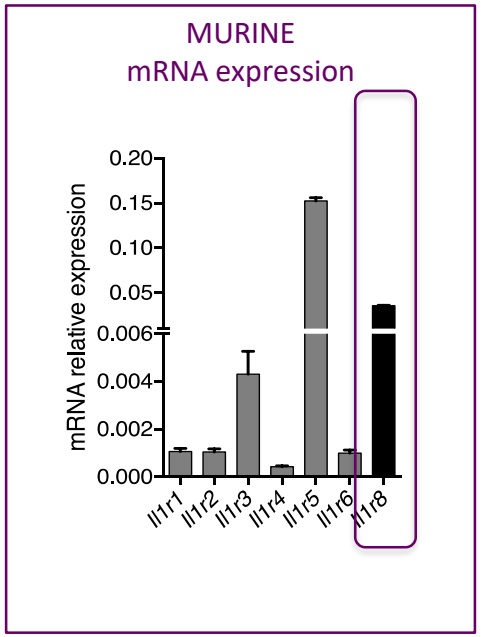
NK cells express high levels of IL-1R8



Polentarutti N. et al, Eur. Cytokine Netw. (2003)

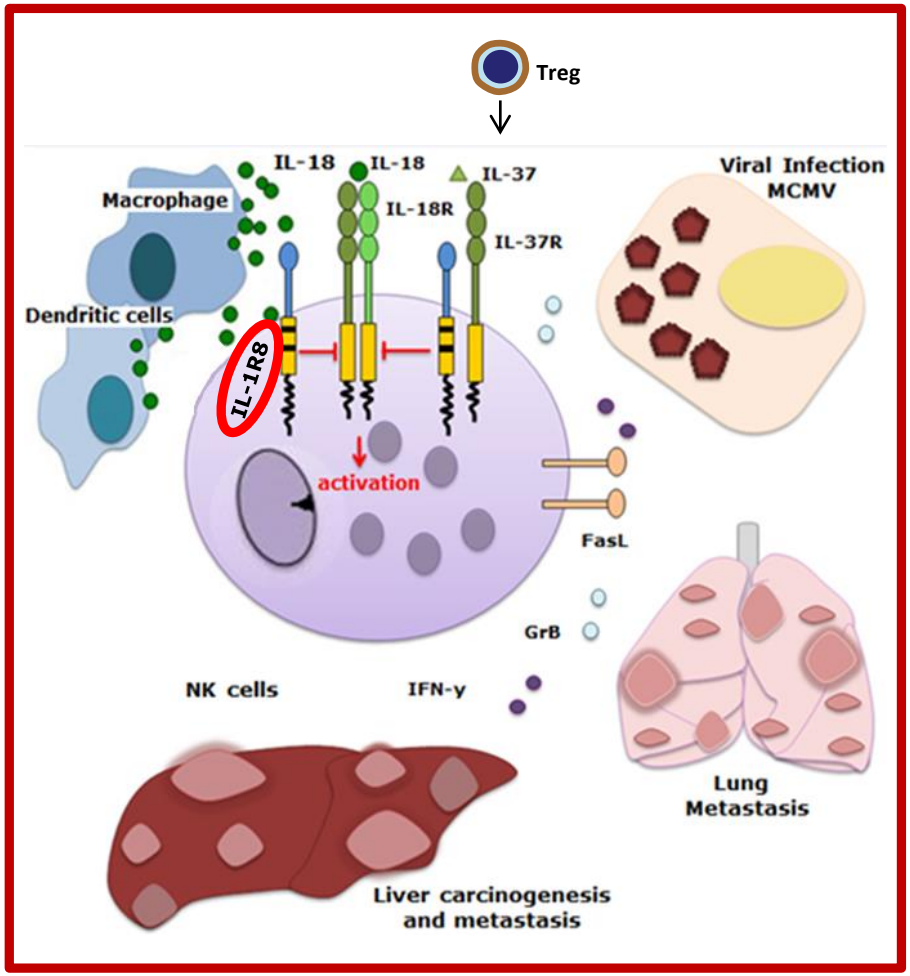


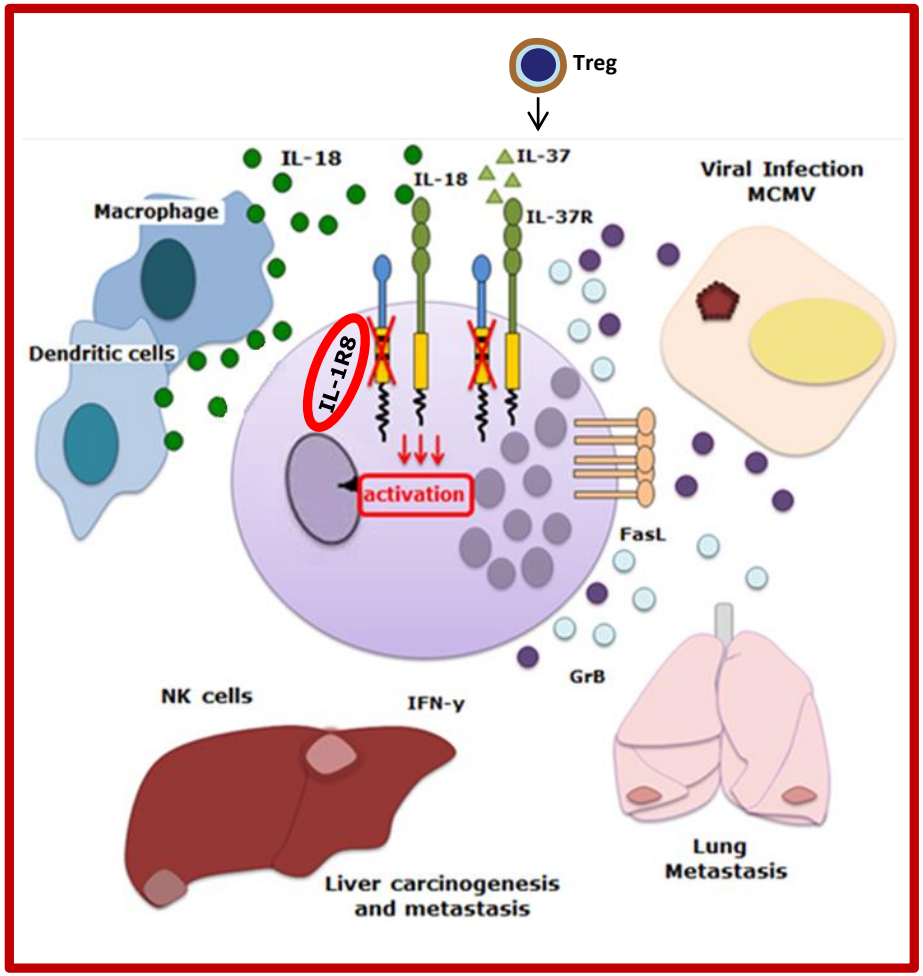




(Molgora, Bonavita et al Nature 2017)

IL-1R8 AS A KEY REGULATOR (CHECKPOINT) OF NK CELL DIFFERENTIATION AND FUNCTION





See also Serhan … Miller, Cancer Immunol Res, 2018; Treg/IL-37 – IL-1R8/NK

Molgora, Bonavita et al, Nature, 2017; Mantovani et al, Immunity, 2019, in press

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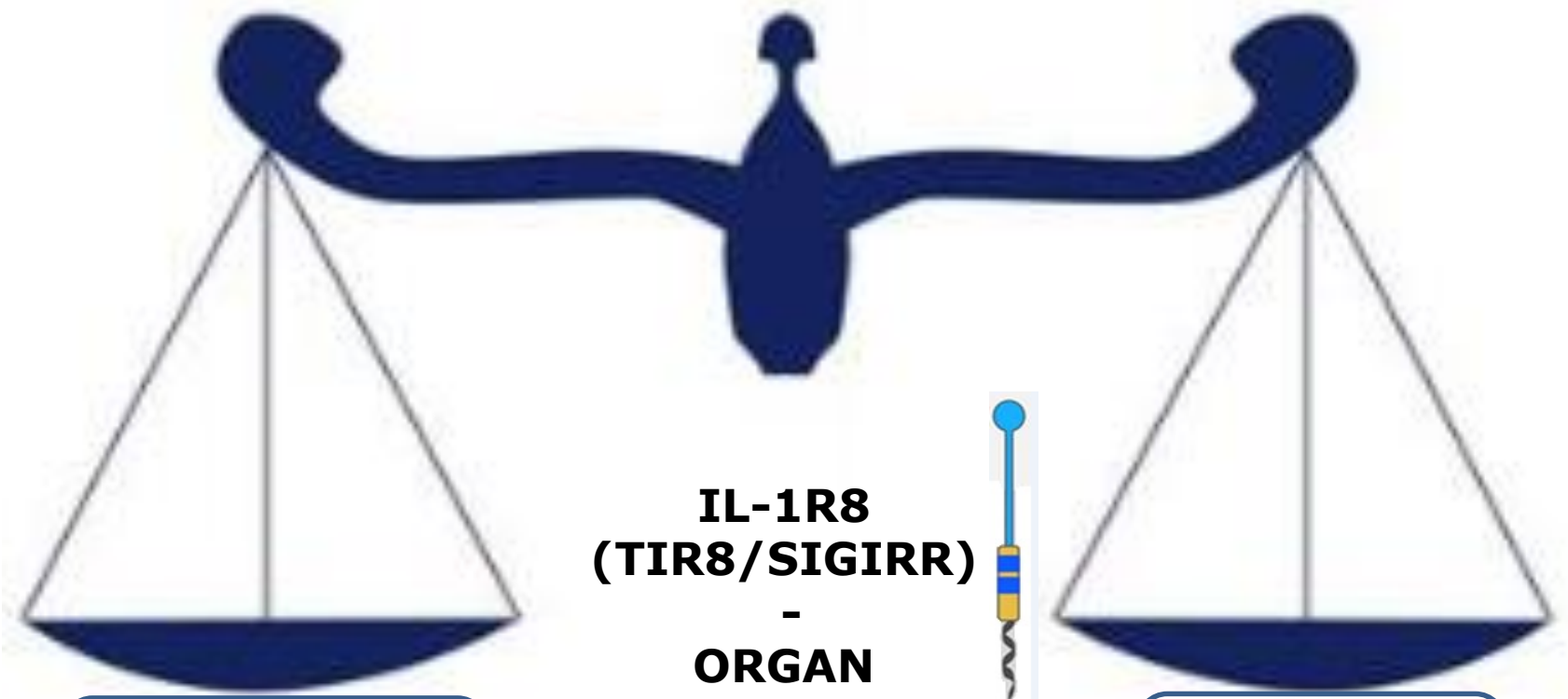
The Yin Yang of IL-1R8 in carcinogenesis and metastasis



IL-1R8 (TIR8/SIGIRR) - ORGAN IMMUNOLOGICAL CONTEXT

Tumor promoting INFLAMMATION

CHECKPOINT IN NK CELLS

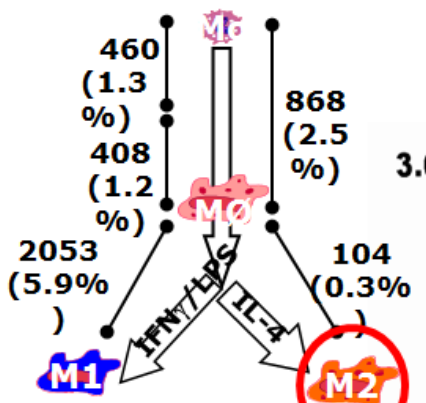
(Riva et al Cancer Immunol. Res. 2019 in press)

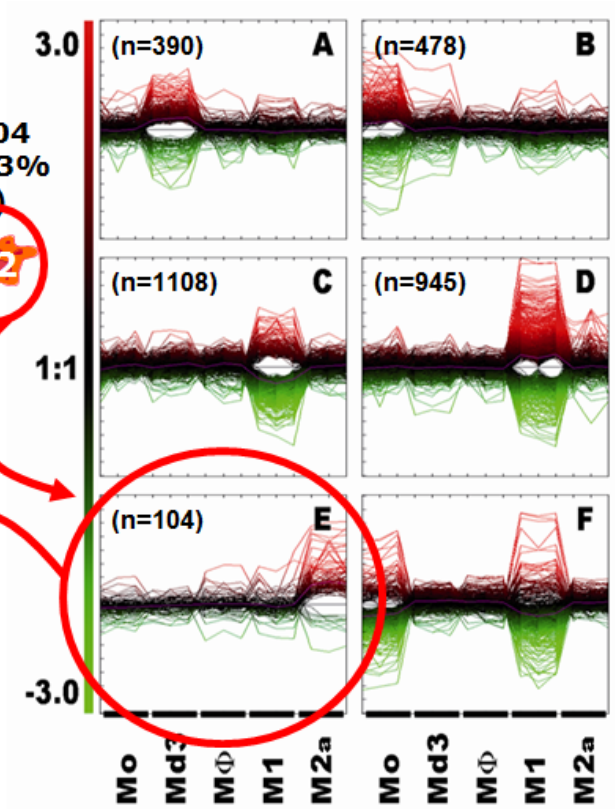
(Molgora, Bonavita et al Nature 2017; Campesato et al Oncotarget 2018)

UNLEASHED NK CELLS CAN MEDIATE RESISTANCE AGAINST SOLID TUMORS AT NK RICH ANATOMICAL SITES

Profiling human monocyte-to-macrophage differentiation and polarization

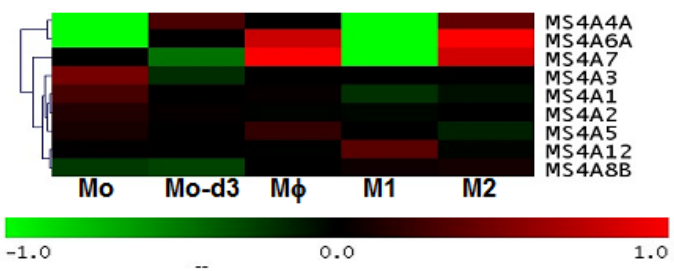
C-type lectin receptors		
Mannose receptor	44	
DC-SIGN	3.6	
CLEC10A	2.5	
DCL-1	3	
Scavenging receptors		
Scavenging receptor A	9	
Scavenger recceptor B	3	
Stabilin 1	6	
CD163	5	
ECM molecules		
Ostoeactivin		83
Osteopontin	26	
Factor XIII A1		11
FN1	7	





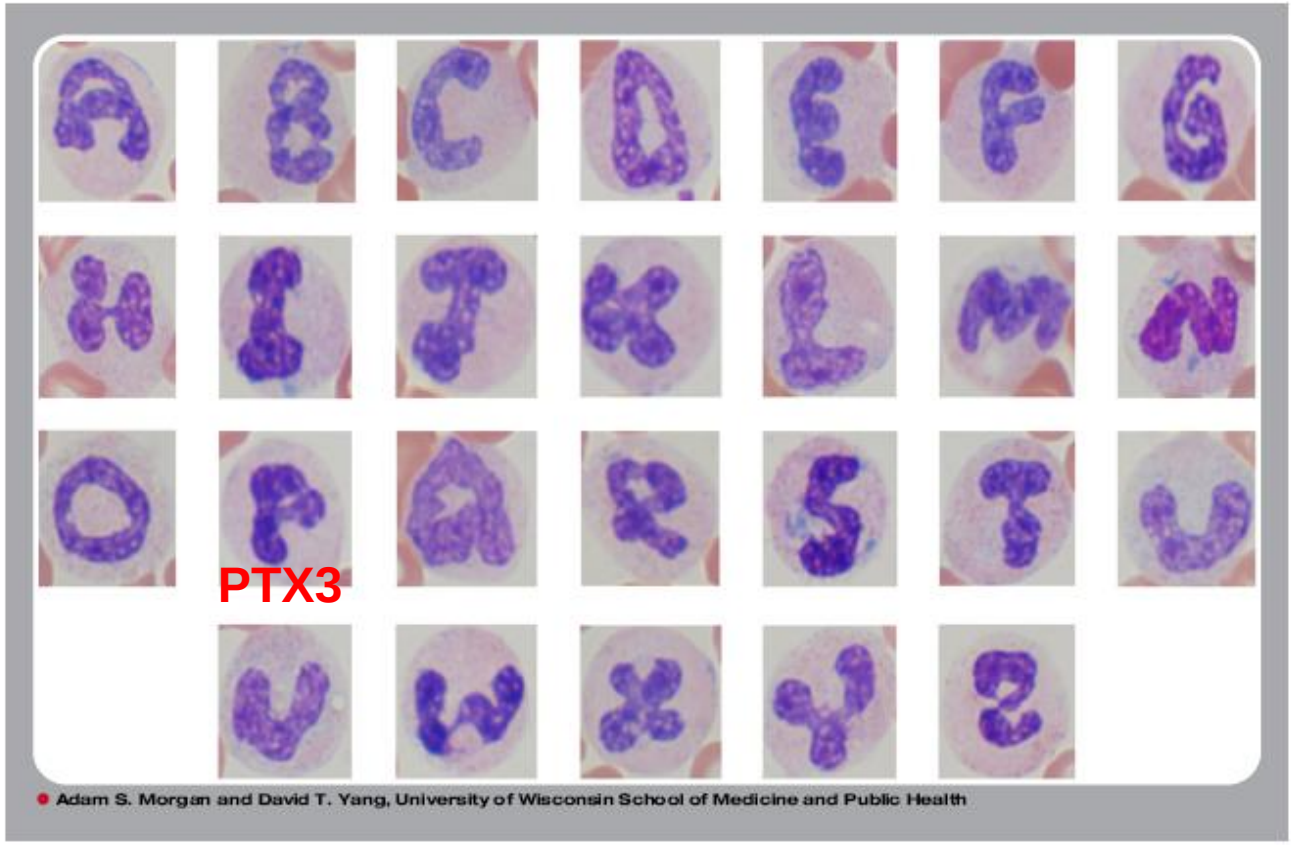
A-B: differentiation; C-D-F: M1; E: M2

(transcriptional data from Martinez et al, J Immunol 2006)



Mattiola, … Mantovani and Locati, Nature Immunol, in press

Neutrophil alphabet



Morgan AS and Yang DT, Blood 2013; 121:3546

NEVER UNDERESTIMATE THE POWER OF A NEUTROPHIL!

Mantovani, Locati, Cassatella, Immunity, 2009

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