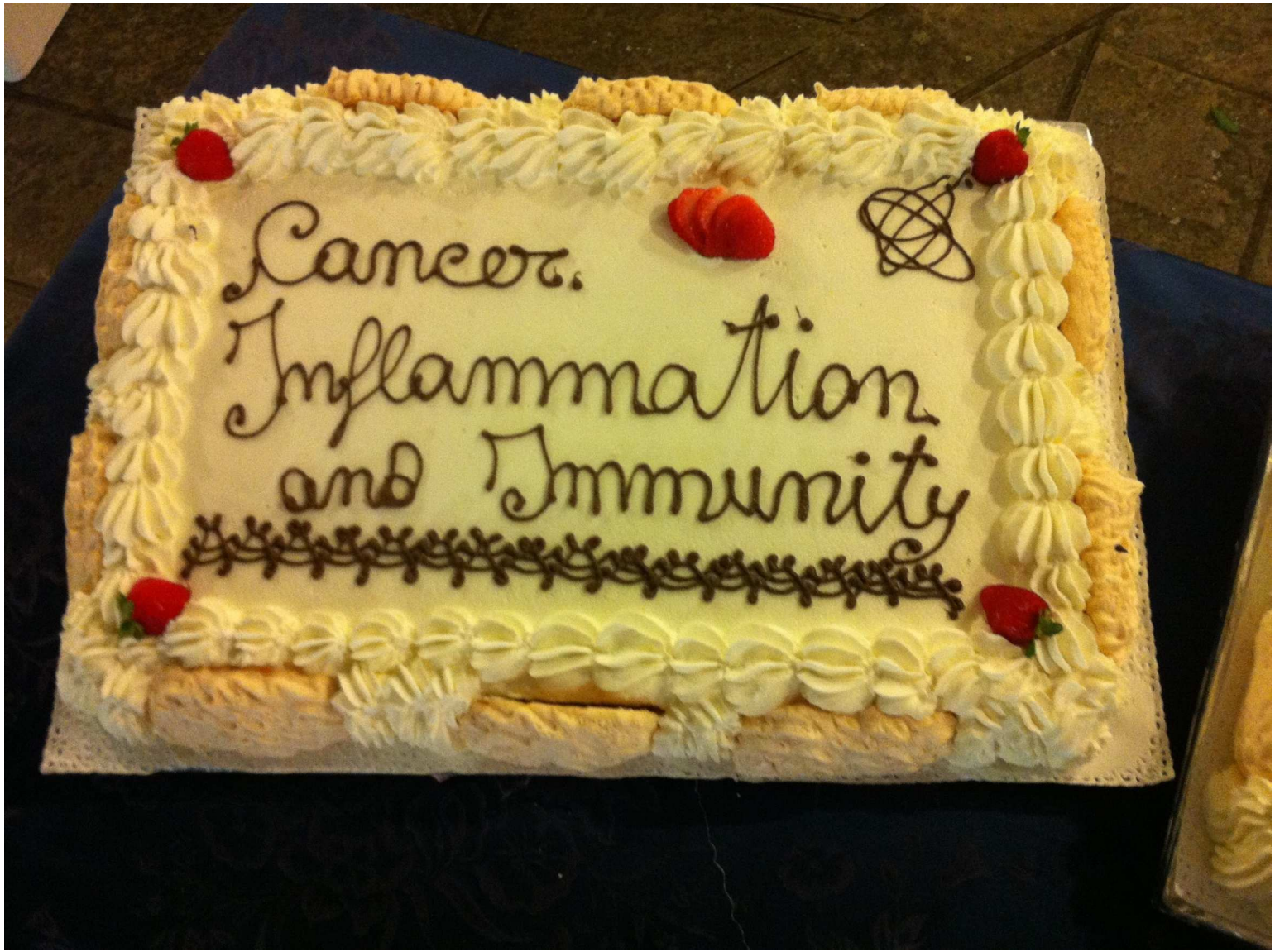
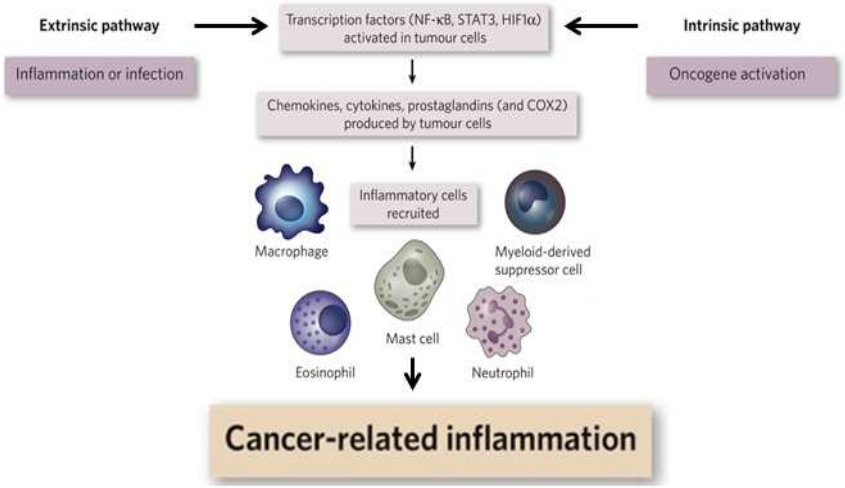
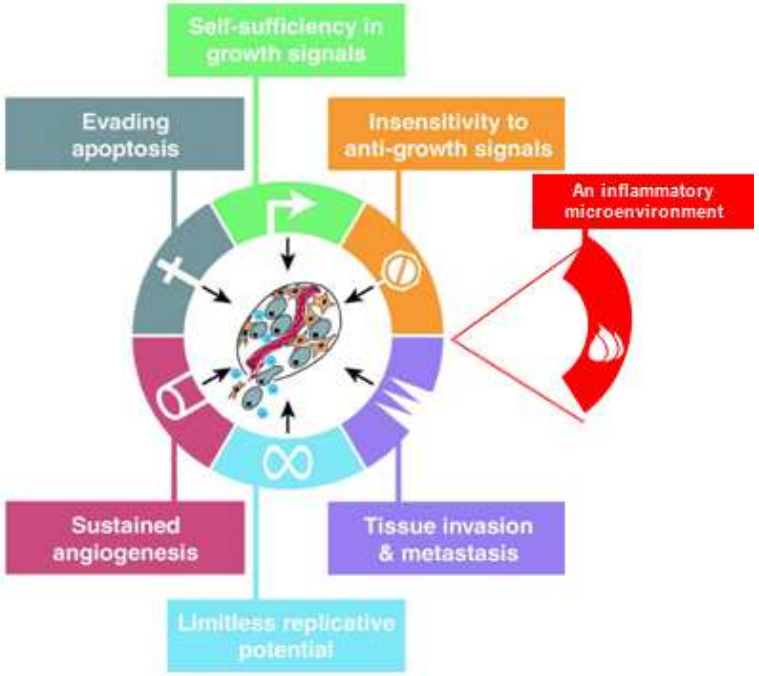


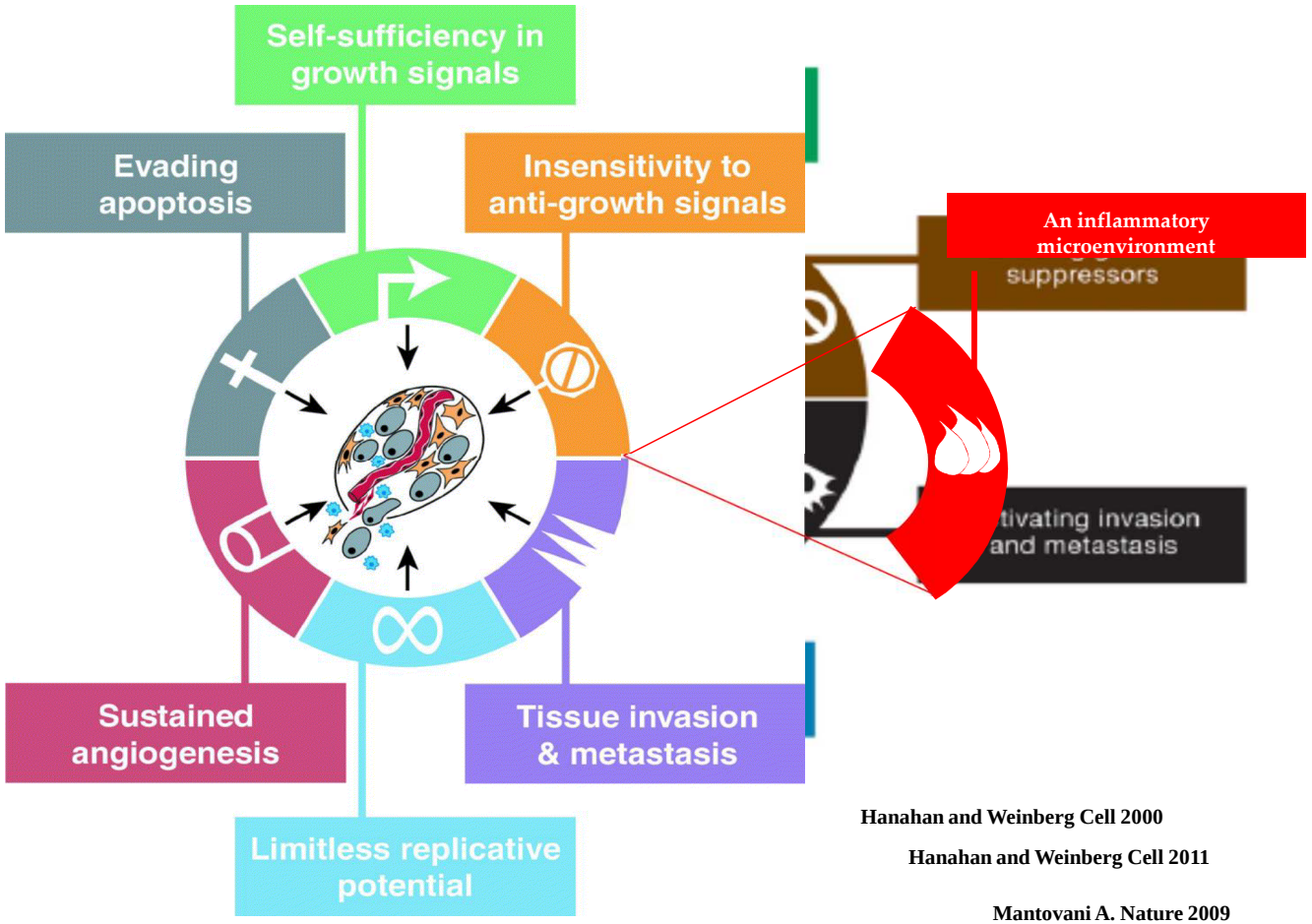
Finalborgo 2015





(Mantovani, Sica, Allavena, Balkwill Nature 2008; Mantovani Nature 2009)

The Hallmarks of Cancer



Hanahan and Weinberg Cell 2000

Hanahan and Weinberg Cell 2011

Mantovani A. Nature 2009

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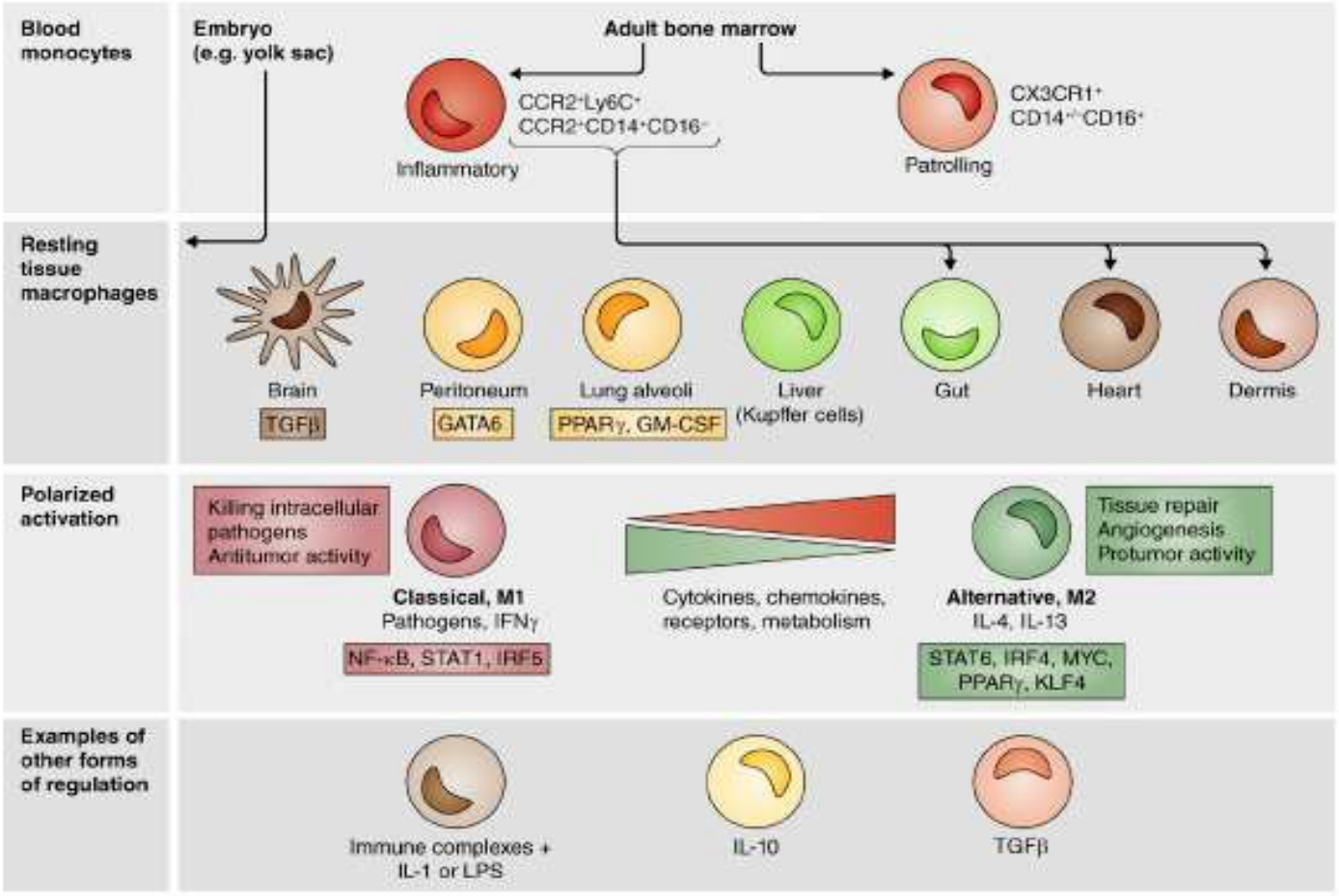
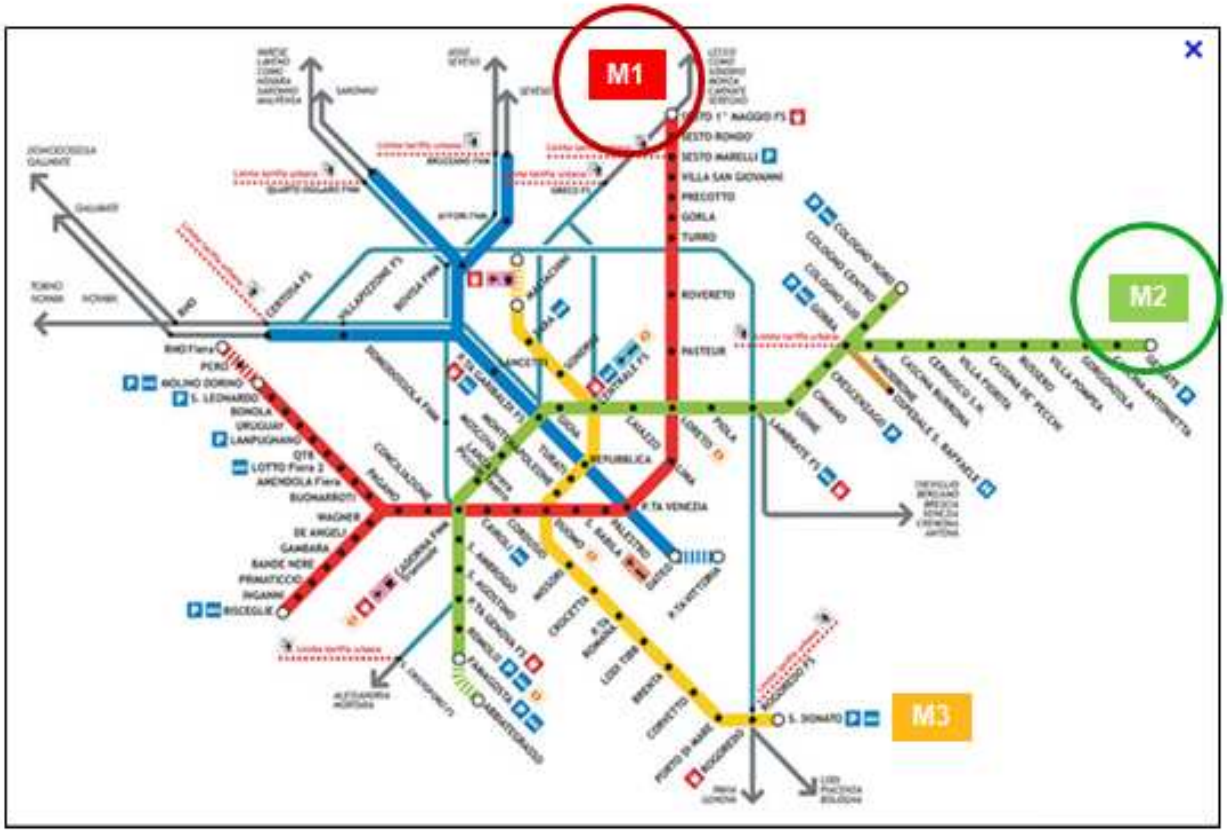
Ontogeny and regulation of cells of the monocyte-macrophage lineage



Mantovani and Allavena , J. Exp . Med 2015

Macrophage Polarization as seen in the Milano Metro Map



Inspired by Luke O'Neill

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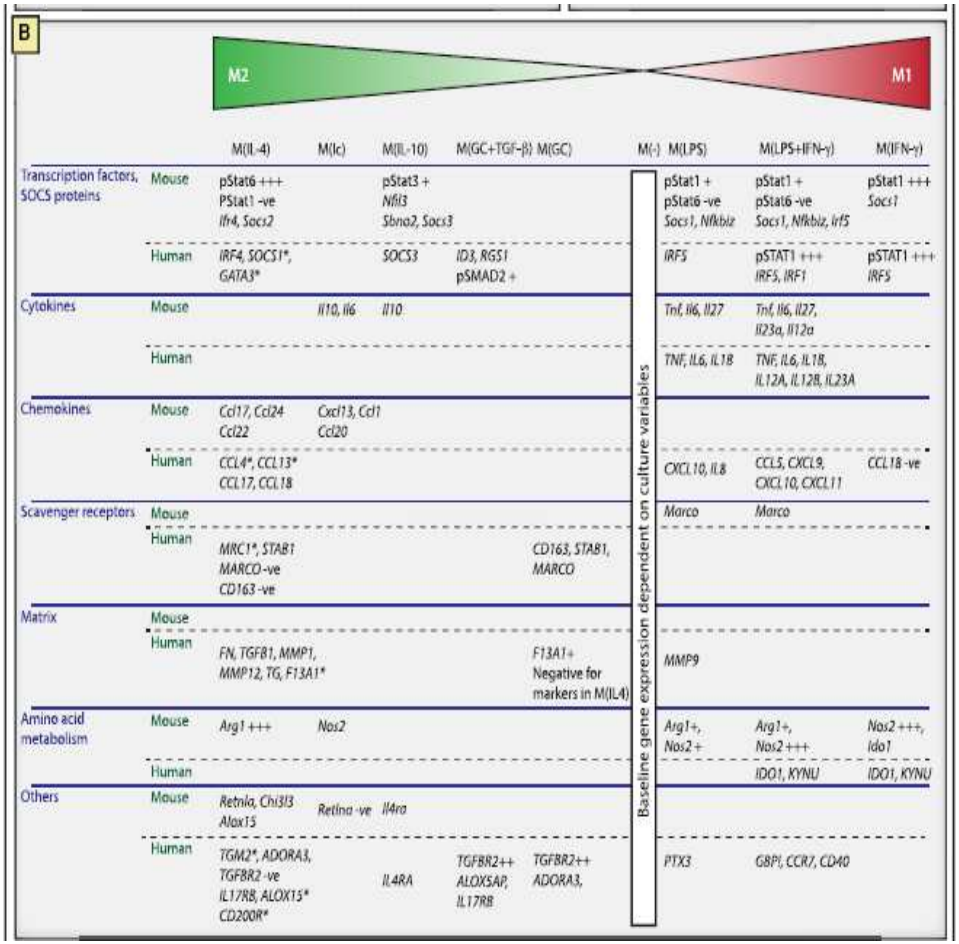

Murray et al, Immunity 2014

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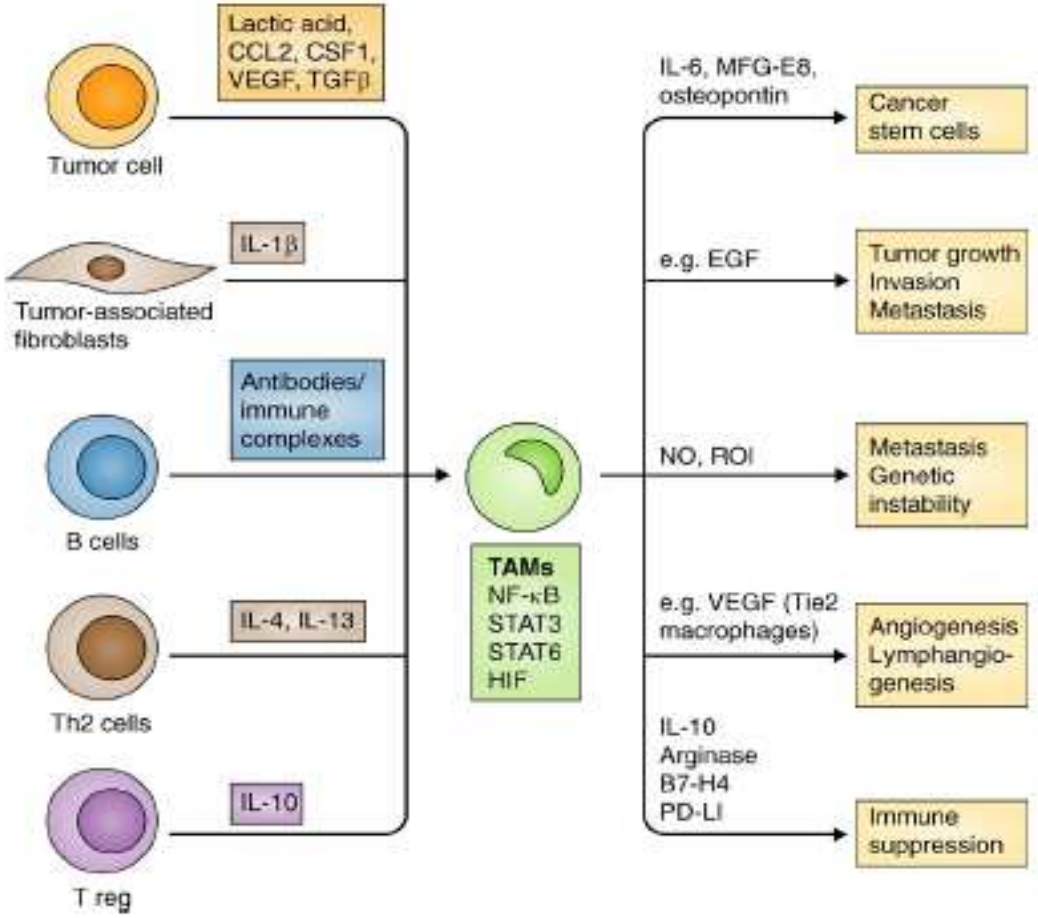
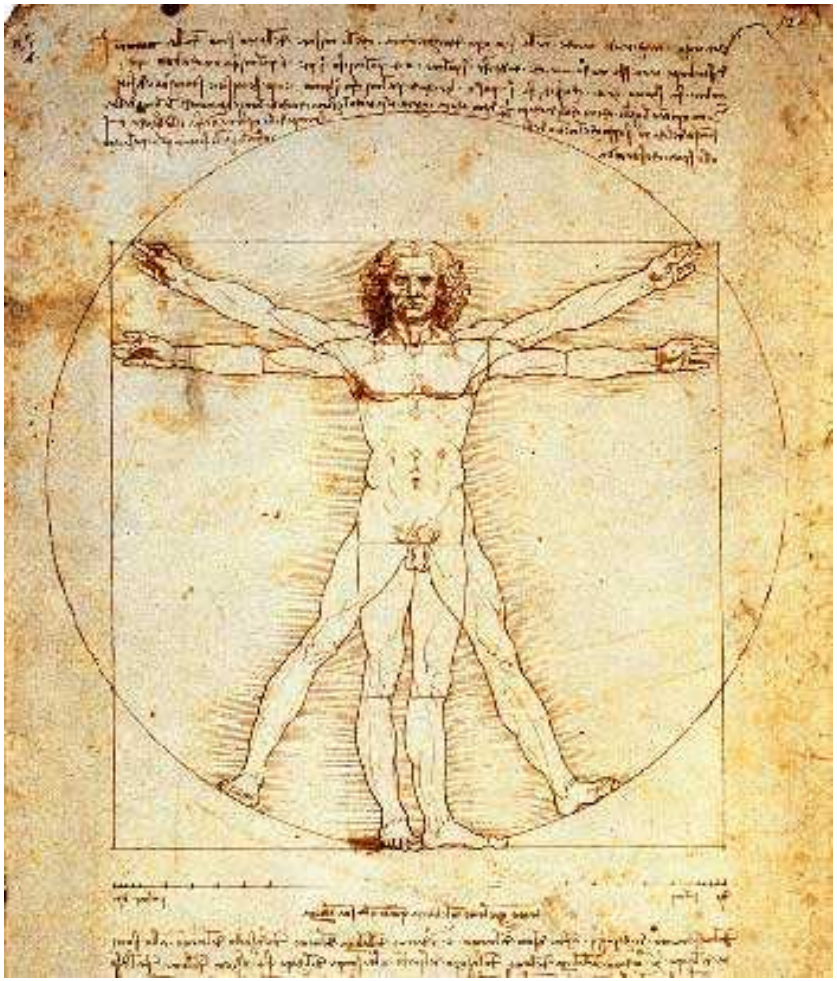
Tumor-associated macrophages (TAMs) in tumor progression



Mantovani and Allavena J. Exp. Med. 2015



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TARGETING CANCER-RELATED INFLAMMATION: Trabectedin

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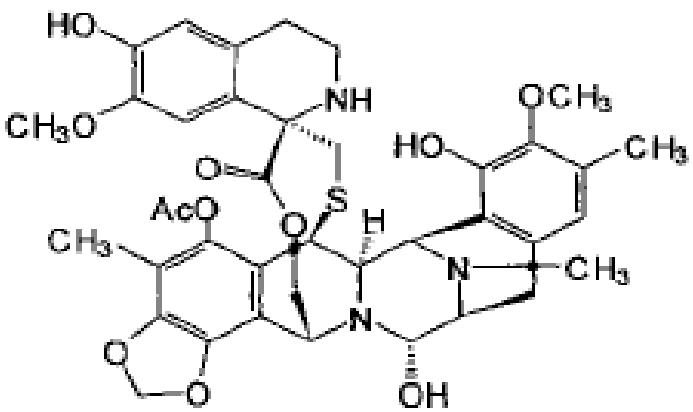
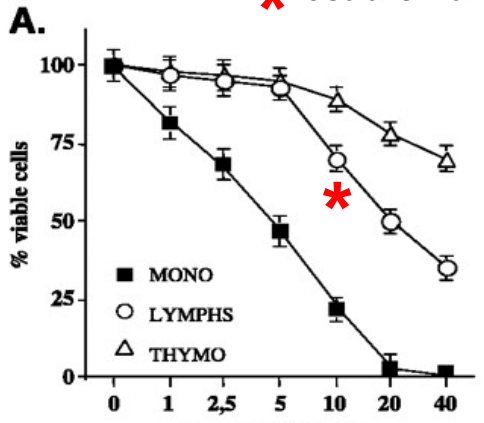


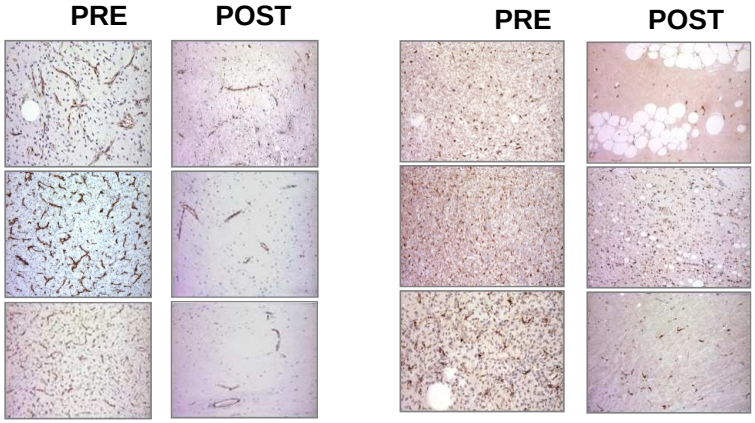
TRABECTEDIN

* IC 50 on tumor cells



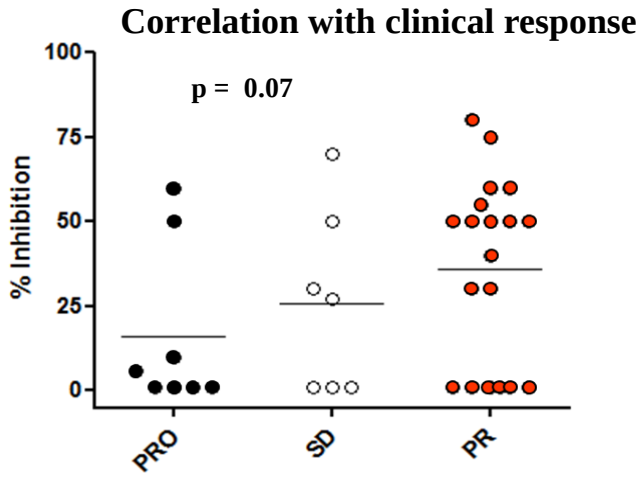
Germano et al Cancer Res 2005; 2010; Cancer Cell, 2013; D'Incalci Mol Cancer Ther 2010

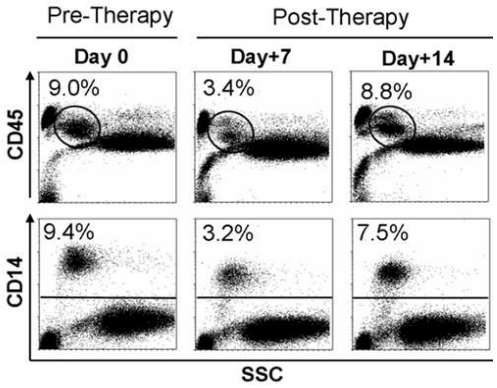
Tumor macrophages and vessels are reduced in treated STS patients



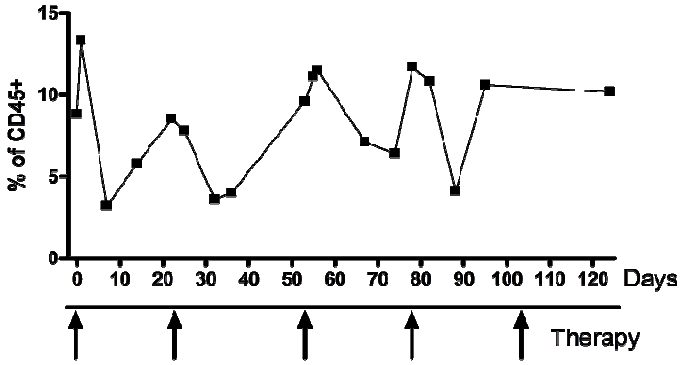
CD31 vessels **CD163 macrophages**

(PRE: biopsy before surgery; POST: tumor sample at surgery, after therapy)





Blood monocytes



(Germano et al Cancer Cell 2013)

Targeting TAM is a key component of the antitumor activity of Trabectedin

- **Trabectedin is preferentially toxic for cells of the monocyte-macrophage lineage. In these cells it activates a TRAIL-R dependent extrinsic pathway of apoptosis**
- **TAM depletion is sufficient for the anti-tumor activity of Trabectedin (resistant lines; macrophage rescue)**
- **First evidence that targeting tumor-promoting TAM is involved in the anti-tumor activity of a clinically approved agent (sarcomas; ovarian carcinoma)**
- **This finding provides proof of principle for TAM targeting in human cancer treatment and has implications for combination therapy and design**

Germano et al Cancer Cell 2013

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THE YIN-YANG OF TAM IN ANTI-TUMOR THERAPY

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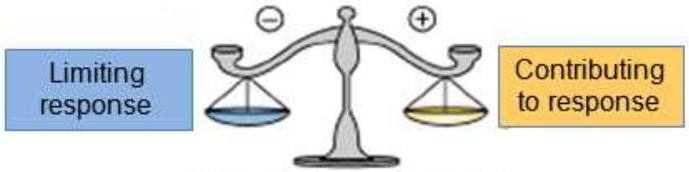


A misdirected macrophage-orchestrated tissue repair response limiting response to chemotherapy, targeted therapy and radiotherapy

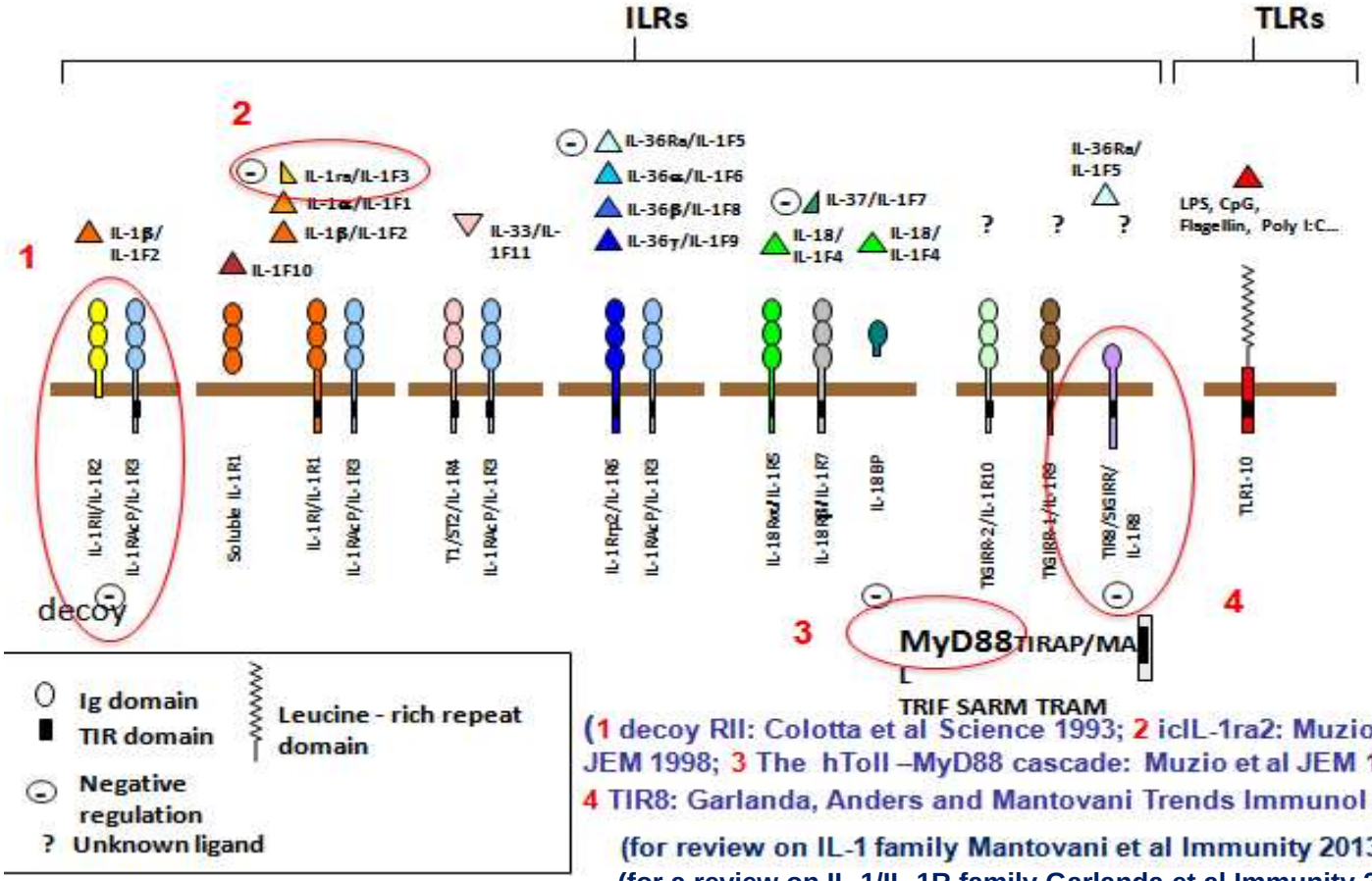
Mechanism limiting response	Example agent
Misguided tissue repair	Doxorubicin
Protumor skewing (M2-like polarization)	Platinum
Increased CSF-1 and CCL2 production, protumor skewing (M2-like polarization), suppression of CD8+ antitumor responses	Paclitaxel
Skewing of adaptive immunity (tumor-promoting Th17 responses)	Gemcitabine 5-FU
Chemoprotection of cancer stem cells by macrophages	

Mechanism contributing to response	Example agent
Myeloid cell recruitment, differentiation into APCs and activation of immune responses	Doxorubicin
Immunogenic tumor cell death	Doxorubicin
Antitumor M1-like macrophage polarization	CpG Anti-CSF1R (Emactuzumab) and kinase inhibitors
MSDC depletion	Doxorubicin Gemcitabine
Reduced TAM numbers	Trabectedin Anti-CSF1R (Emactuzumab) and kinase inhibitors Anti-chemokines (CCLS2)
ADCC against tumor cells or T reg cells	Anti-CD20 Anti-CTLA4
Eat-me	Anti-SIRPα and CD46

Note: Trabectedin approved for clinical use in Europe and USA (Germano et al., Cancer Cell 2013

Modified from Mantovani A and Allavena P, J Exp Med 2015

The IL-1 receptor (ILR) superfamily



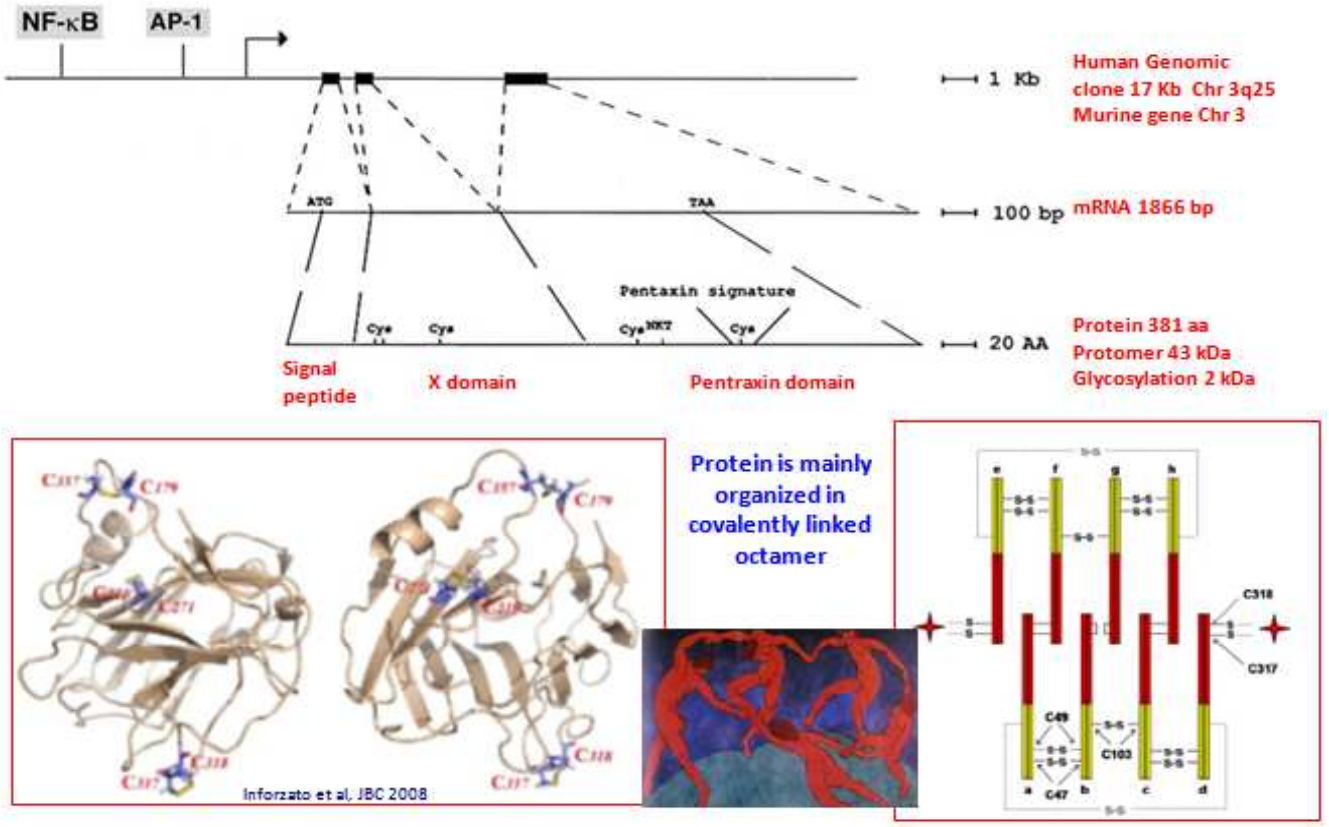
(1 decoy RII: Colotta et al Science 1993; 2 icIL-1ra2: Muzio et al JEM 1998; 3 The hToll –MyD88 cascade: Muzio et al JEM 1998
4 TIR8: Garlanda, Anders and Mantovani Trends Immunol 2009)

(for review on IL-1 family Mantovani et al Immunity 2013)

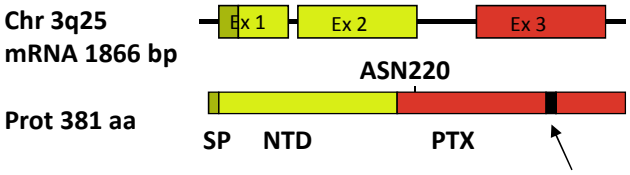
(for a review on IL-1/IL-1R family Garlanda et al Immunity 2013)

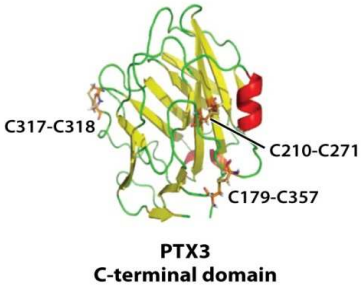
I pesci, Museo Archeologico Nazionale di Napoli

The prototypic long pentraxin PTX3

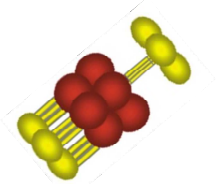


(Garlanda et al Annu Rev Immunol 2005, 2010; Bottazzi et al Curr Op Immunol, 2006, 2008)

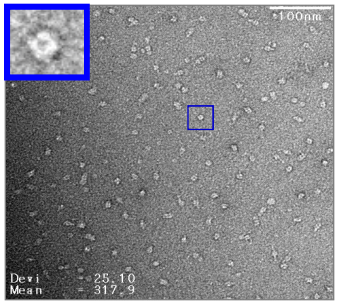


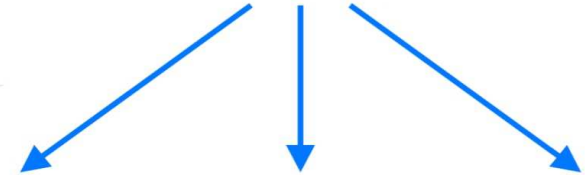


PTX3
C-terminal domain



PTX3





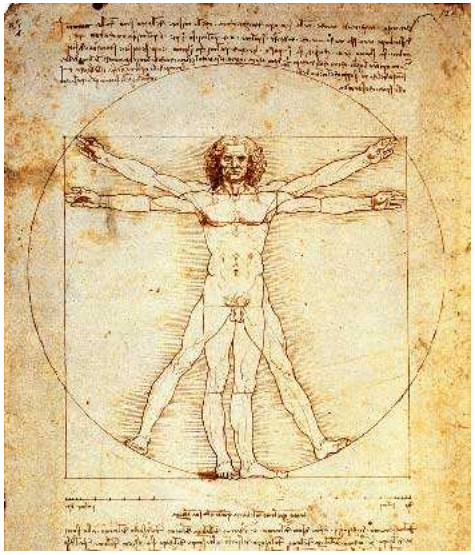
OmpA Men B components	FcγR	C1q Factor H	Ficolins MBL	P-selectin
Microbe recognition	Opsonization	C activation and regulation of inflammation	Repertoire synergism	Regulation of leukocyte recruitment and inflammation

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

Garlanda et al Nature 2002; Deban al Nature Immunol 2010; Lu et al Nature 2009; Bottazzi et al Annu Rev Immunol 2010

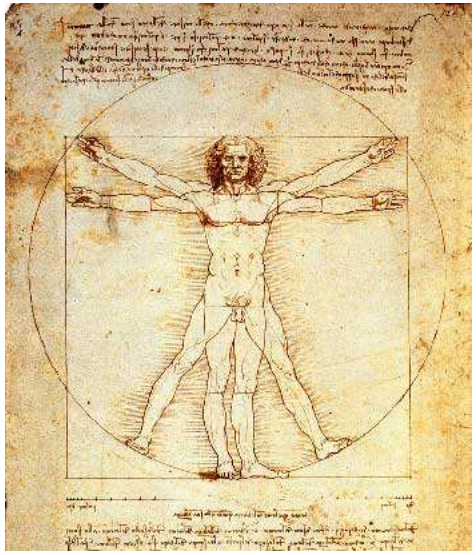
PTX3 translation

- Diagnostic/prognostic (ELISA, genetics): earlier marker and better related to prognosis compared to CRP
- Therapy (**A. fumigatus**; P. aeruginosa)



PTX3 translation - Genetics

- **IN HUMANS GENETIC POLYMORPHISMS ASSOCIATED WITH SUSCEPTIBILITY TO INFECTION (TB+, P. AERUGINOSA*, UROPATHOGENIC E. COLI#, A.FUMIGATUS$)**



*** Chiarini, Genes Immun 2010**
+ Olesen, Genes Immun. 2007
 # Jaillon et al Immunity 2014

$ Cunha et al New Engl J Med 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic PTX3 Deficiency and Aspergillosis in Stem-Cell Transplantation

Cristina Cunha, Ph.D., Franco Aversa, M.D., João F. Lacerda, M.D., Ph.D., Alessandro Busca, M.D., Oliver Kurzai, M.D., Matthias Grube, M.D., Jürgen Löffler, Ph.D., Johan A. Maertens, M.D., Ph.D., Alain S. Bell, Ph.D., Antonio Inforzato, Ph.D., Elisa Barbati, Ph.D., Bruno Almeida, Ph.D., Pedro Santos e Sousa, M.D., Anna Barbui, M.D., Leonardo Potenza, M.D., Ph.D., Morena Caira, M.D., Ph.D., Fernando Rodrigues, Ph.D., Giovanni Salvatori, Ph.D., Livio Pagano, M.D., Mario Luppi, M.D., Ph.D., Alberto Mantovani, M.D., Andrea Velardi, M.D., Luigina Romani, M.D., Ph.D., and Agostinho Carvalho, Ph.D.

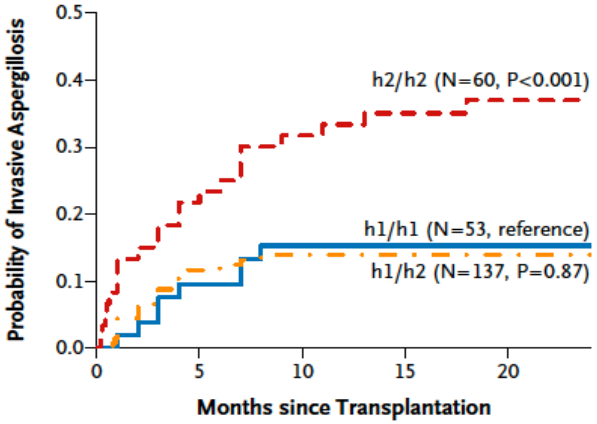
PTX3 polymorphisms were associated with susceptibility to *A. fumigatus* infection in patients undergoing hematopoietic stem cell transplantation

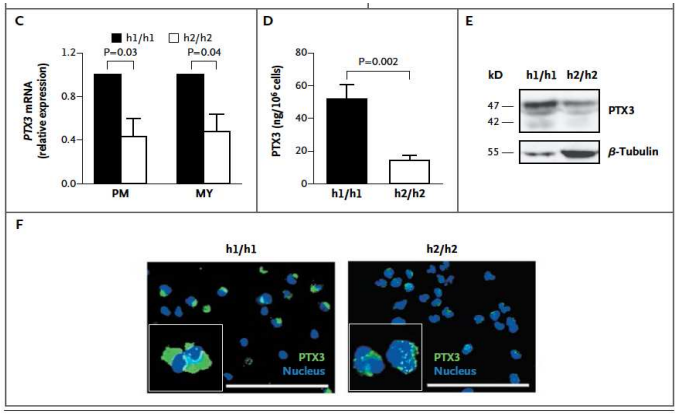
- **Haplotype AC was associated with increased protein expression**

Results confirmed and extended in 1101 pts in the Swiss Organ Transplantation cohort, 2015

(Wójtowicz A, et al, Clin Infect 2015)

N Engl J Med. 2014 Jan 30;370(5):421-32.





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Increased susceptibility to carcinogenesis of PTX3$^{-/-}$ mice

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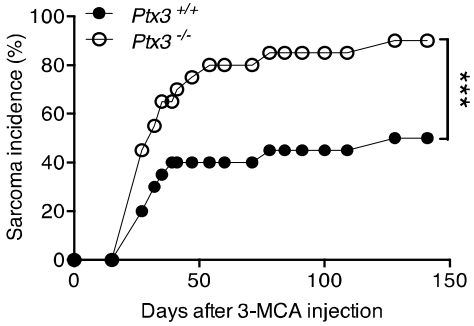

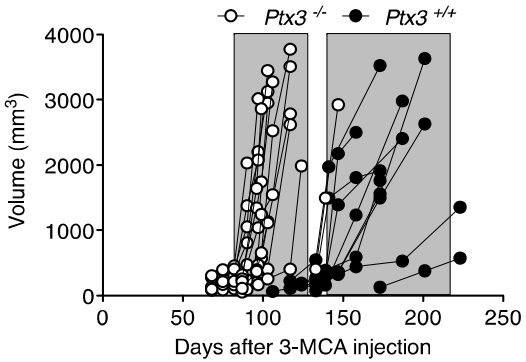

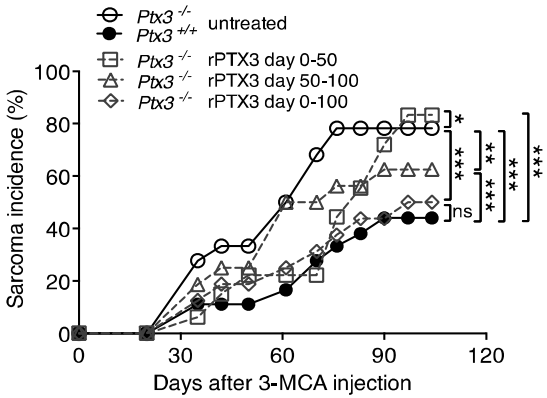

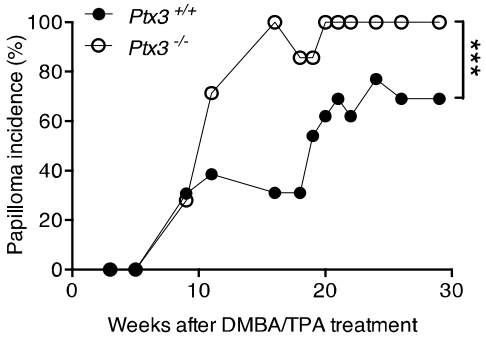

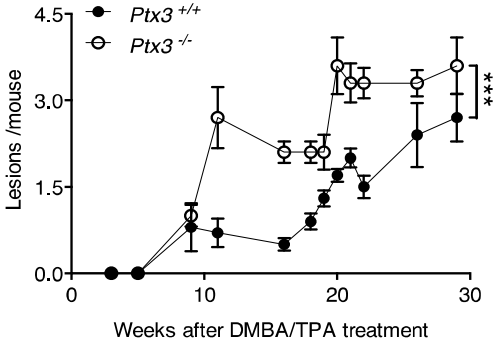

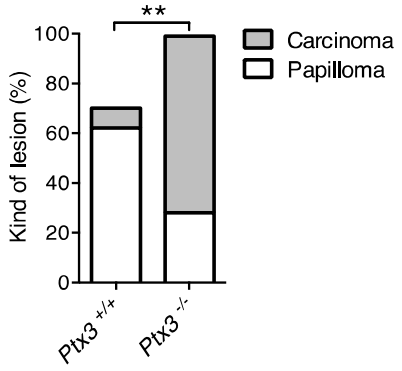

Bonavita et al Cell 2015

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IL-1 dependent production of PTX3 during carcinogenesis

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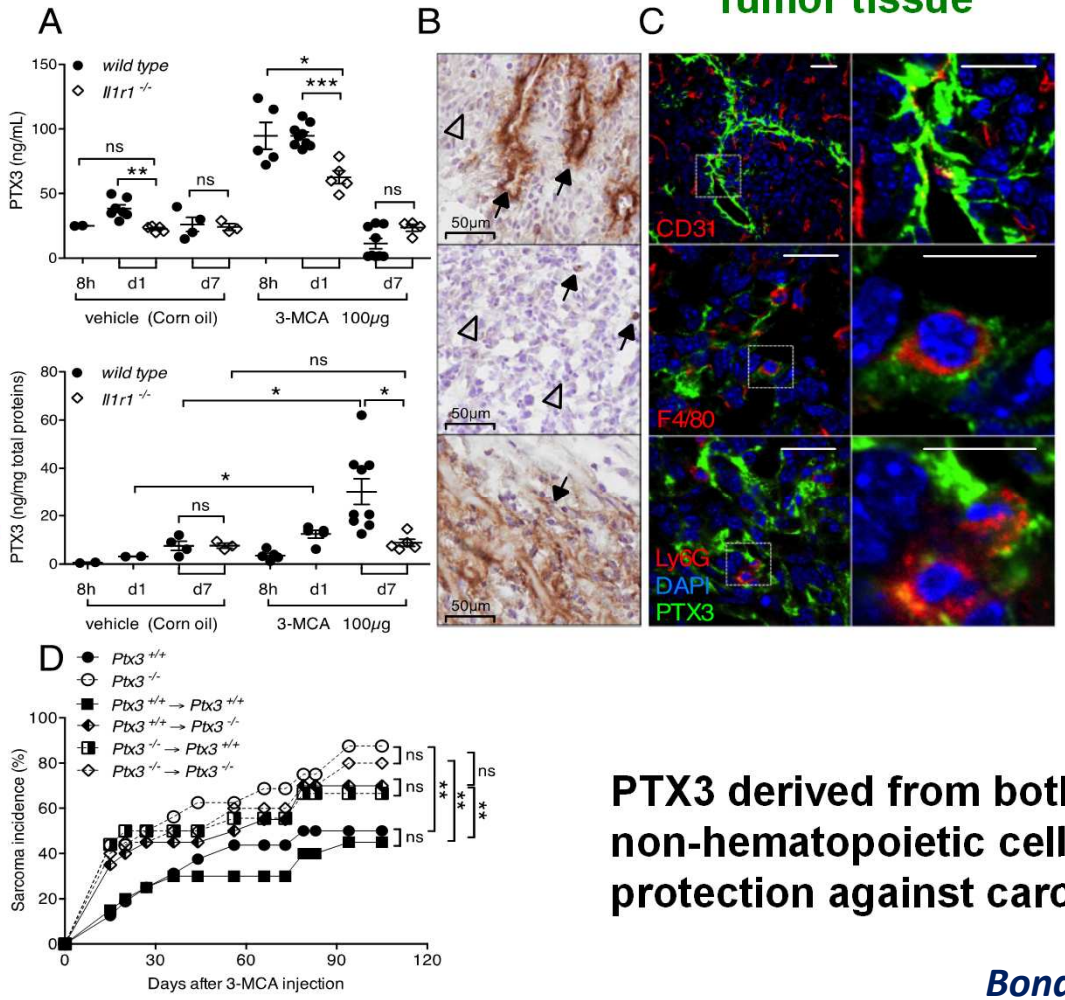
Tumor tissue

Serum

Injection site



PTX3 derived from both hematopoietic and non-hematopoietic cells contributes to protection against carcinogenesis

Bonavita et al Cell 2015

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PTX3-deficiency is associated to increased cancer-related inflammation

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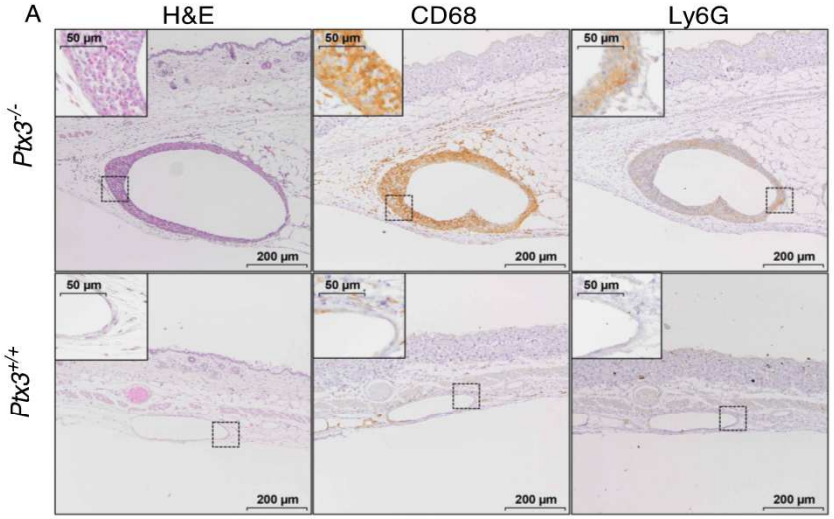
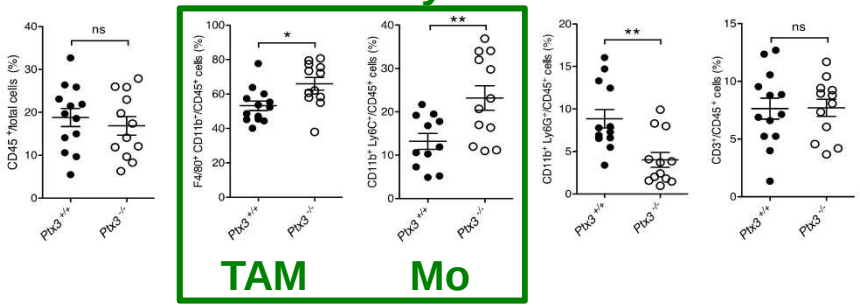
Injection site



C

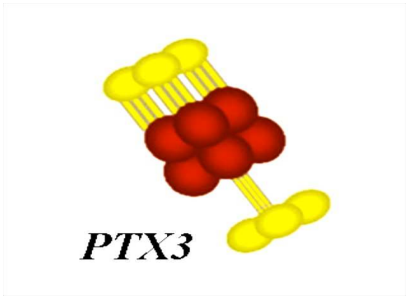
FACS analysis of Tumor



		$Ptx3^{+/+}$ Mean (±SEM)	$Ptx3^{-/-}$ Mean (±SEM)	p Value [a]
Tumor [c] (ng/mg total proteins)	CCL2	26.46 (±12.01)	92.25 (±21.99)	**0.04**
	CXCL1	0.77 (±0.12)	0.72 (±0.22)	ns
	CXCL2	0.18 (±0.06)	0.03 (±0.01)	**0.03**
	CXCL12	0.34 (±0.18)	0.29 (±0.09)	ns
	TNFα	0.03 (±0.01)	0.13 (0.04)	**0.003**
	IL-1β	0.21 (±0.10)	1.39 (±0.31)	**0.007**
	IL-1α	0.45 (±0.11)	1.46 (±0.37)	0.07
	IL-6	2.05 (±0.30)	4.67 (±1.02)	**0.02**
	VEGF	0.11 (±0.24)	0.77 (±0.51)	**0.01**
	TGFβ	5.21 (±0.30)	10.67 (±1.02)	0.10
	IL-17	n.d.	n.d.	n.a
	IL-23	n.d.	n.d.	n.a

Bonavita et al. Cell 2015

Which are the mechanisms?



P-selectin (leukocyte recruitment)

Complement activation and regulation (C1q; Factor H)

(Deban et al Nature Immunol 2010; Jaillon et al Immunity 2014; Bonavita et al Cell 2015)

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PTX3-deficiency was associated to higher tumor incidence regardless of P-selectin competence

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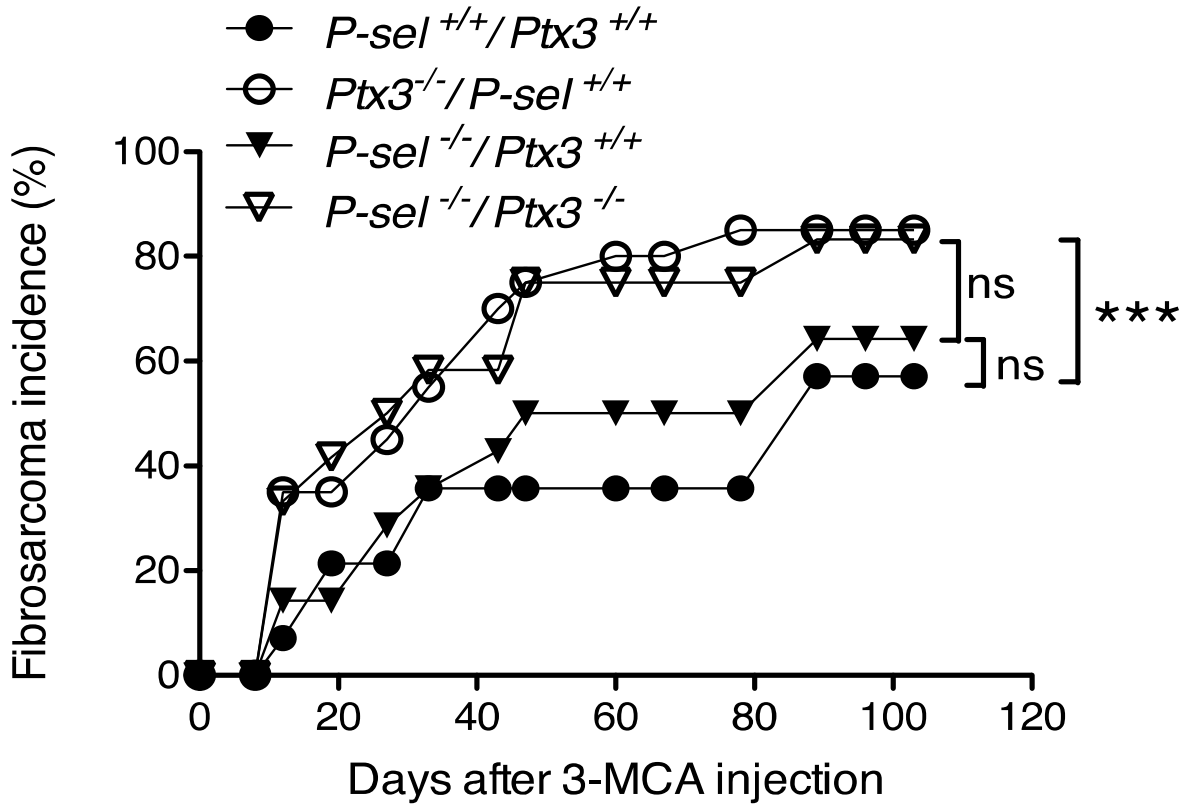

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PTX3-deficiency is associated to increased Complement activation

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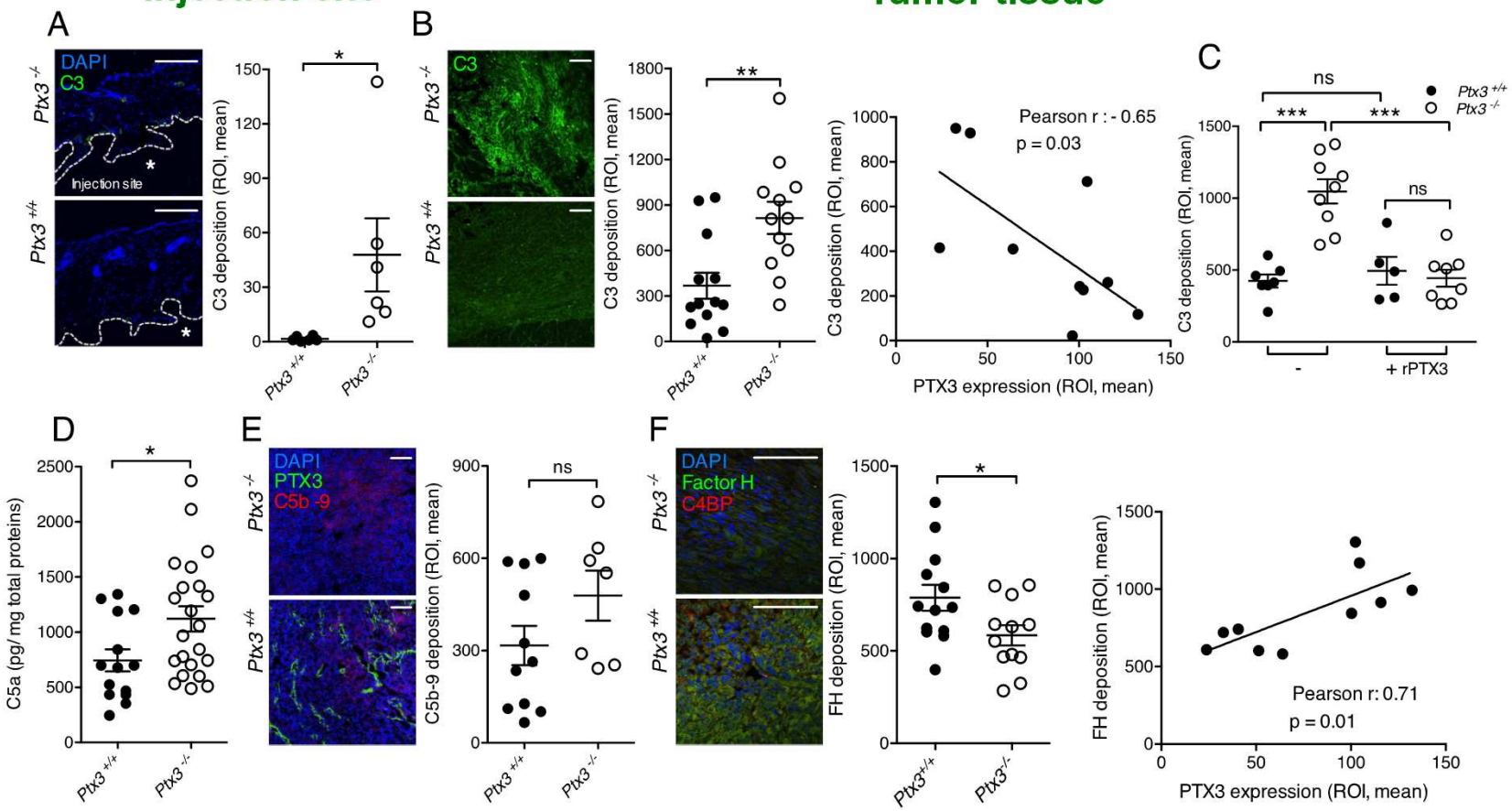
Injection site

Tumor tissue



Bonavita et al Cell 2015

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Role of C3 and interaction with Factor H: lack of PTX3-mediated recruitment of the negative regulator Factor H is responsible for exacerbated C3 deposition

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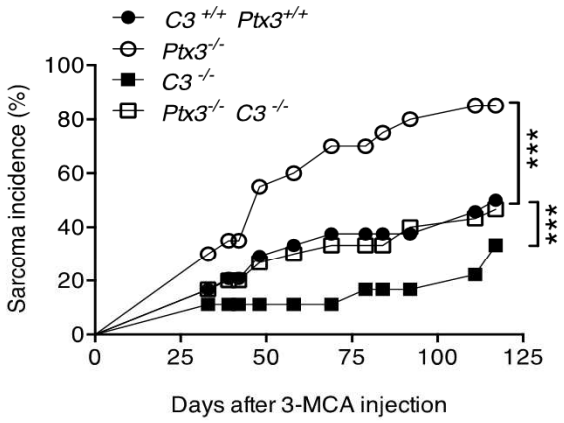

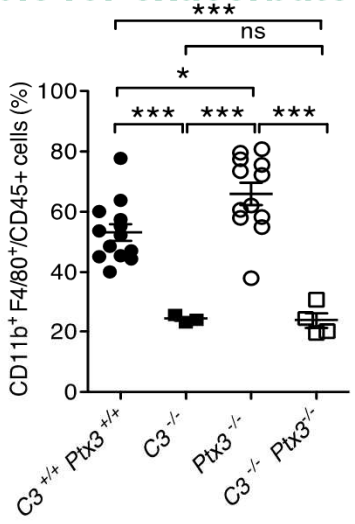

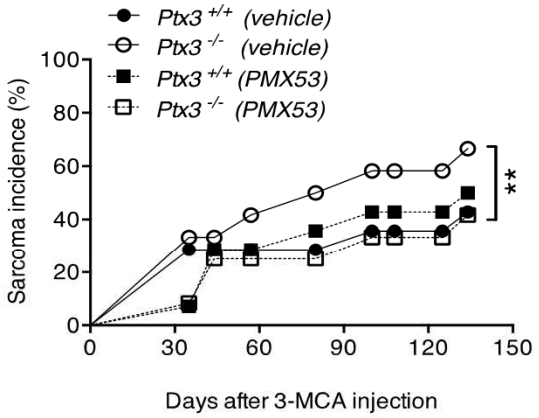

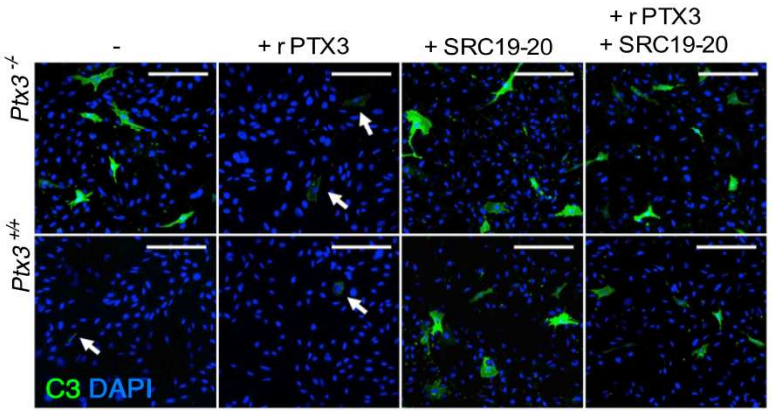

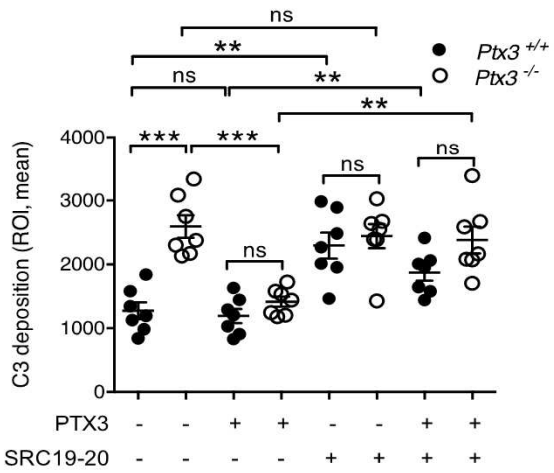

SRC 19-20, an inhibitor of PTX3-FH interaction, dampens inhibition of C3 deposition by PTX3

Bonavita et al Cell 2015

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C3 gene targeting reduces susceptibility to papillomas development

[DMBA/TPA-induced carcinogenesis model]

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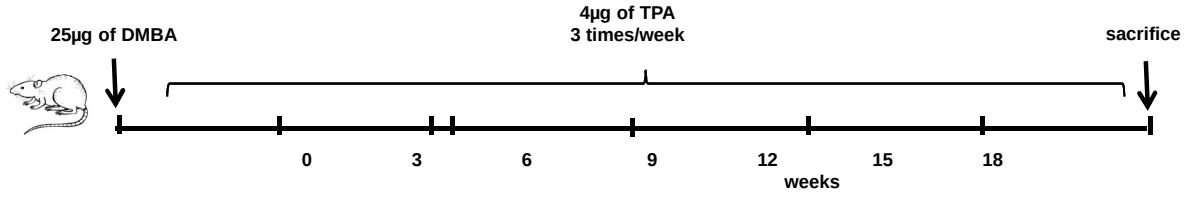

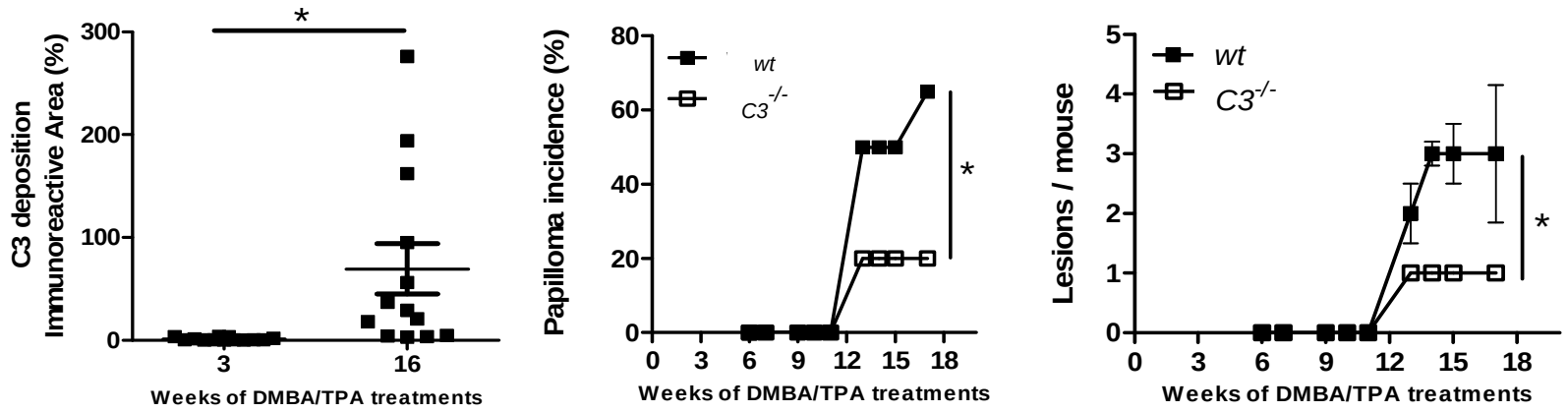

(Elena Magrini, unpublished data)

*p < 0.05, t test

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CCL2 plays a key role in promoting cancer-related inflammation associated to PTX3-deficiency

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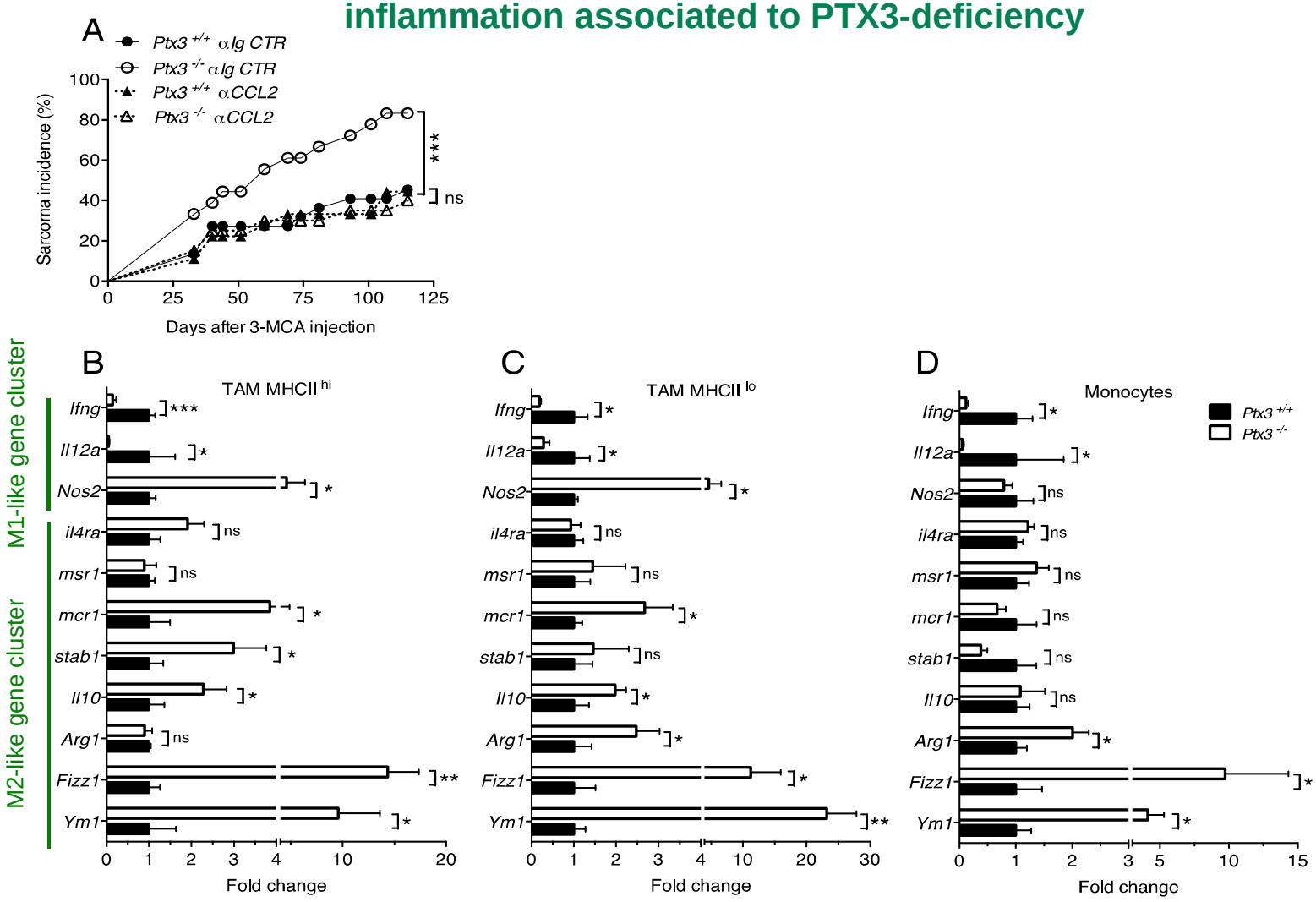

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PTX3-deficiency is associated to increased gene instability and higher DNA-damage response (DDR)

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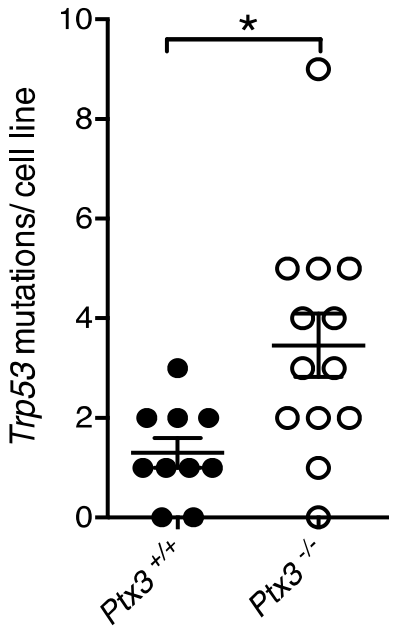

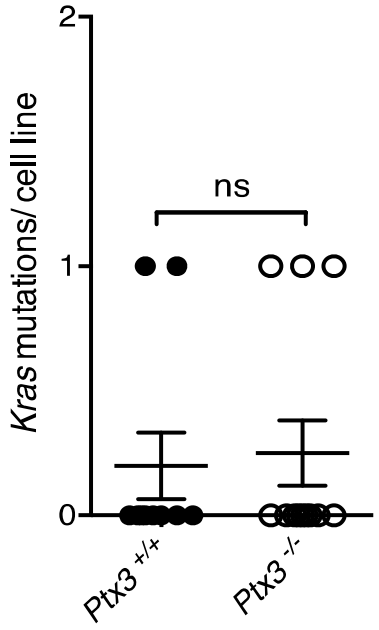

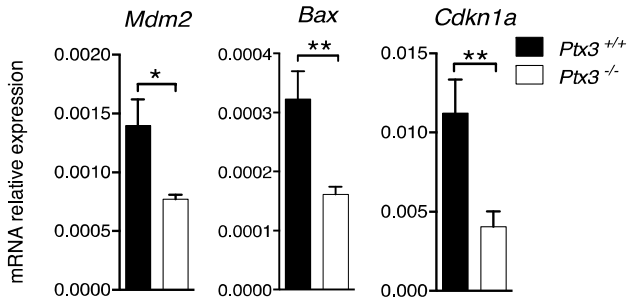

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PTX3-deficiency is associated to increased gene instability and higher DNA-damage response (DDR)

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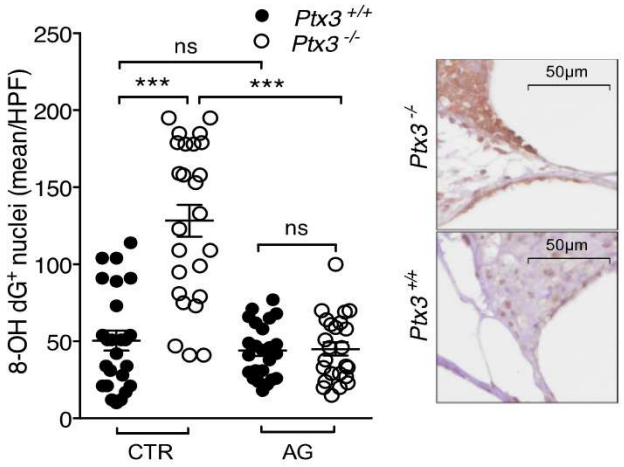

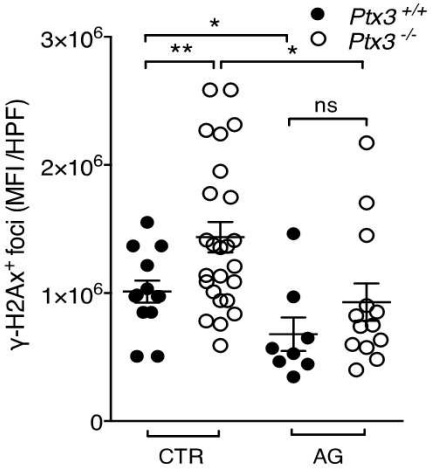

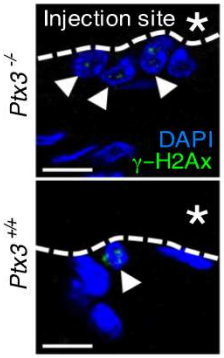

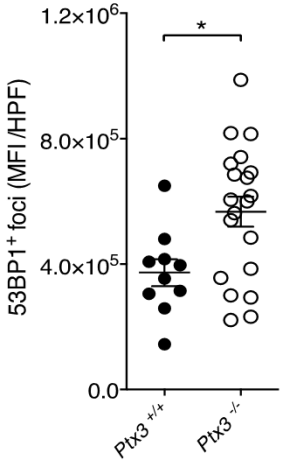

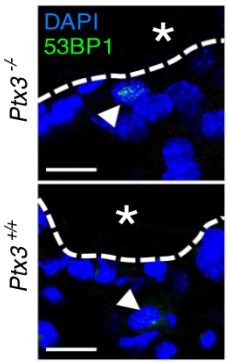

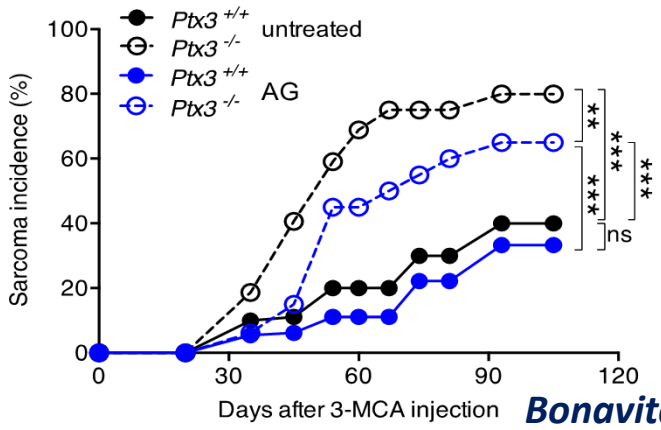

Bonavita et al Cell 2015

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Methylation of the PTX3 gene in human cancer

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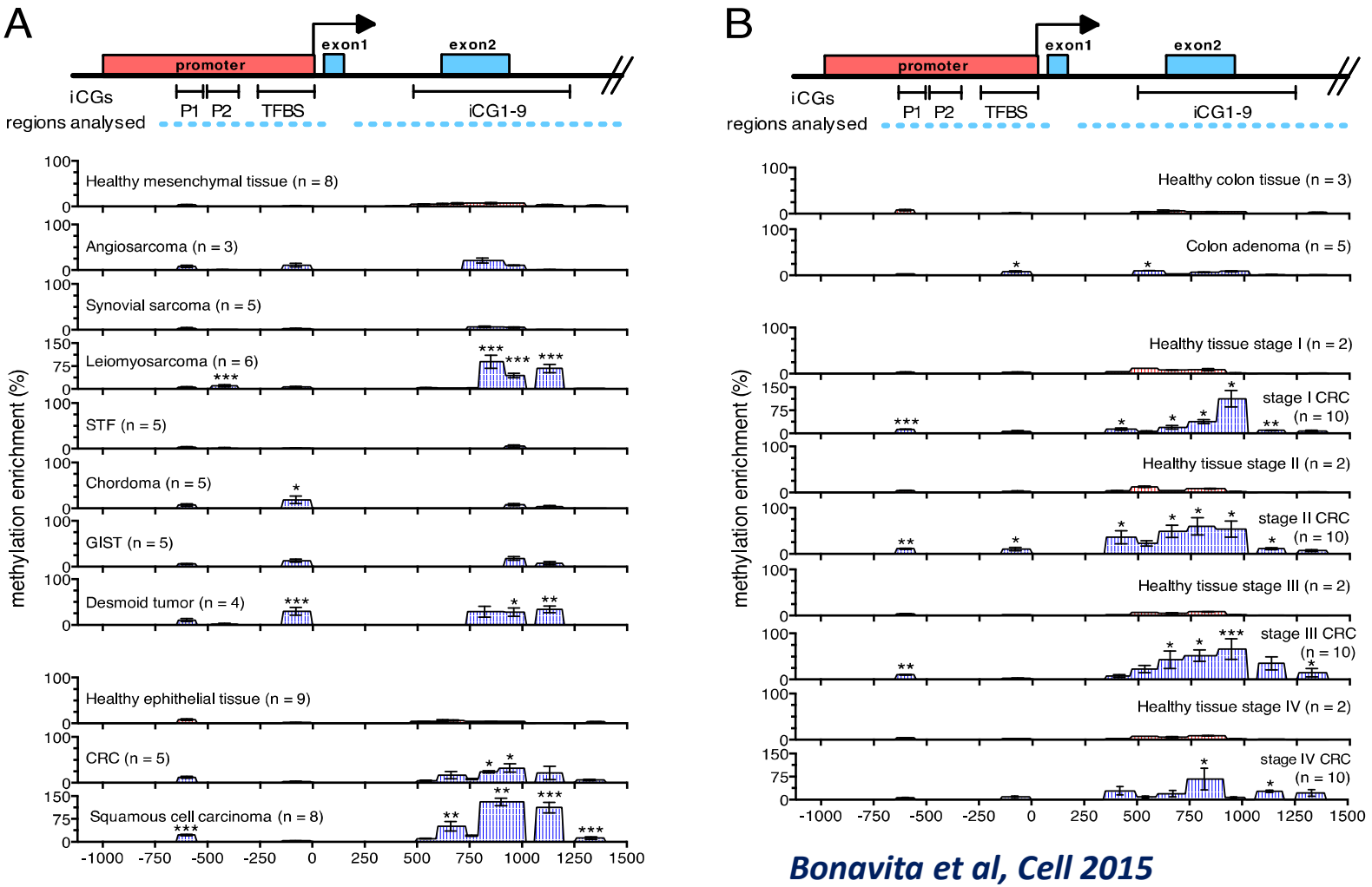

Bonavita et al, Cell 2015

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Silencing by methylation of the PTX3 gene in selected human tumors

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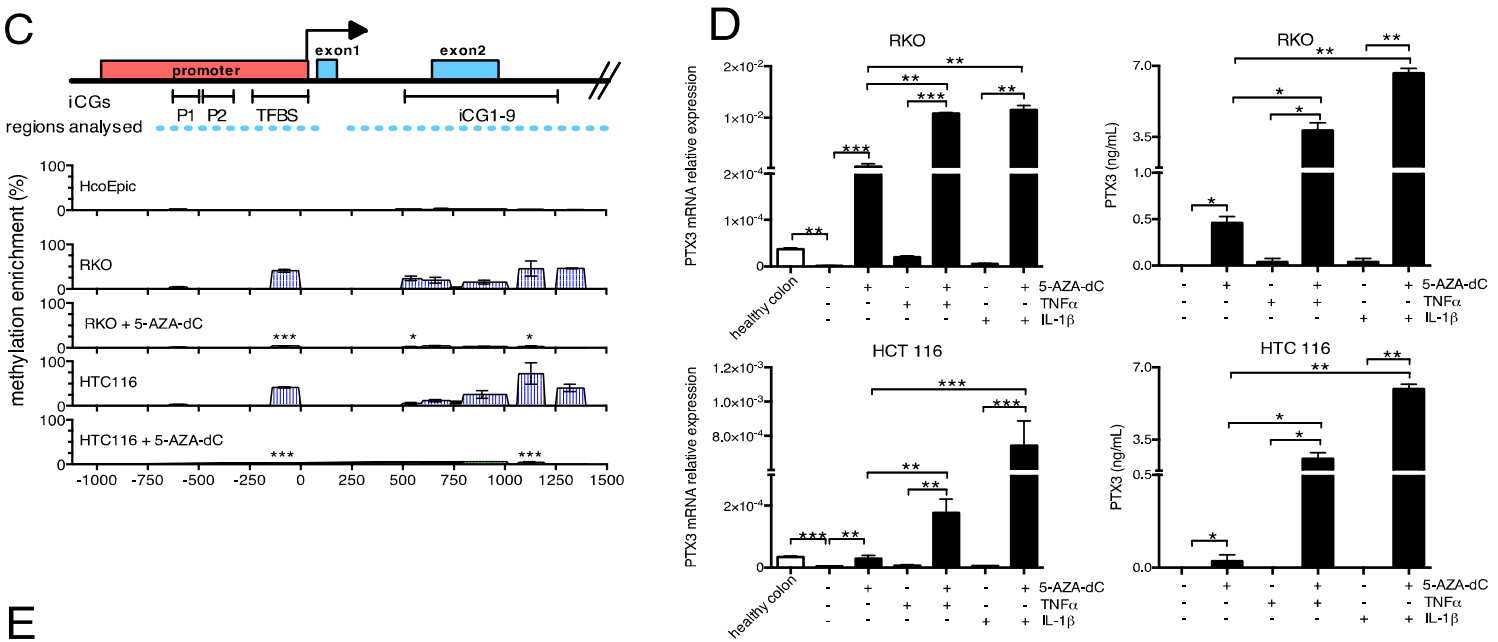

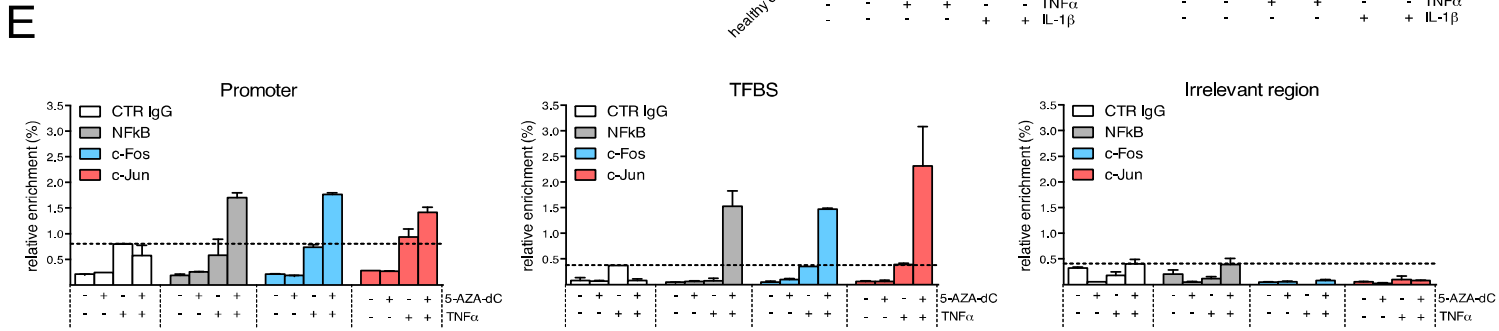

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PTX3 as an extrinsic oncosuppressor in mouse and human cancer

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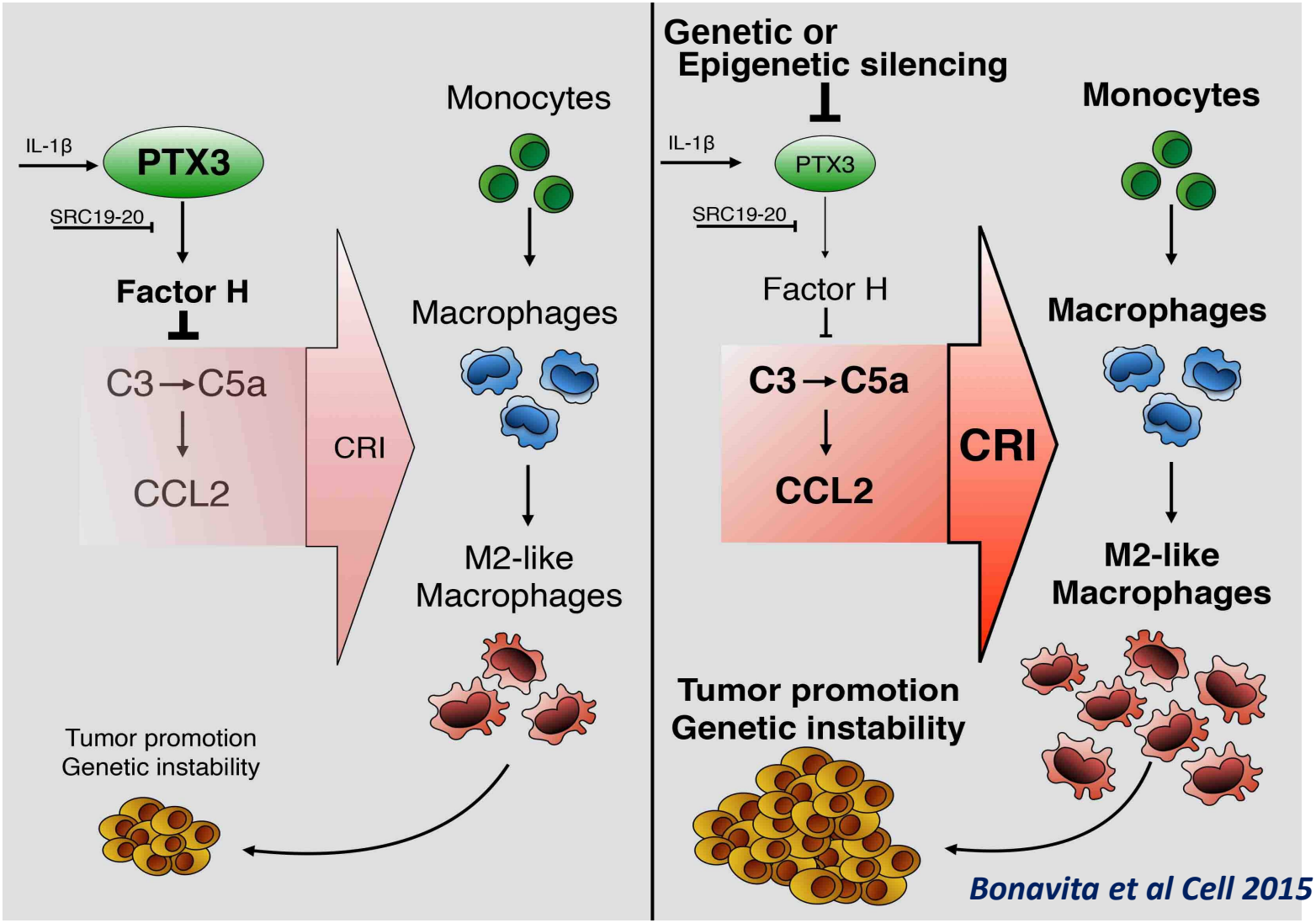
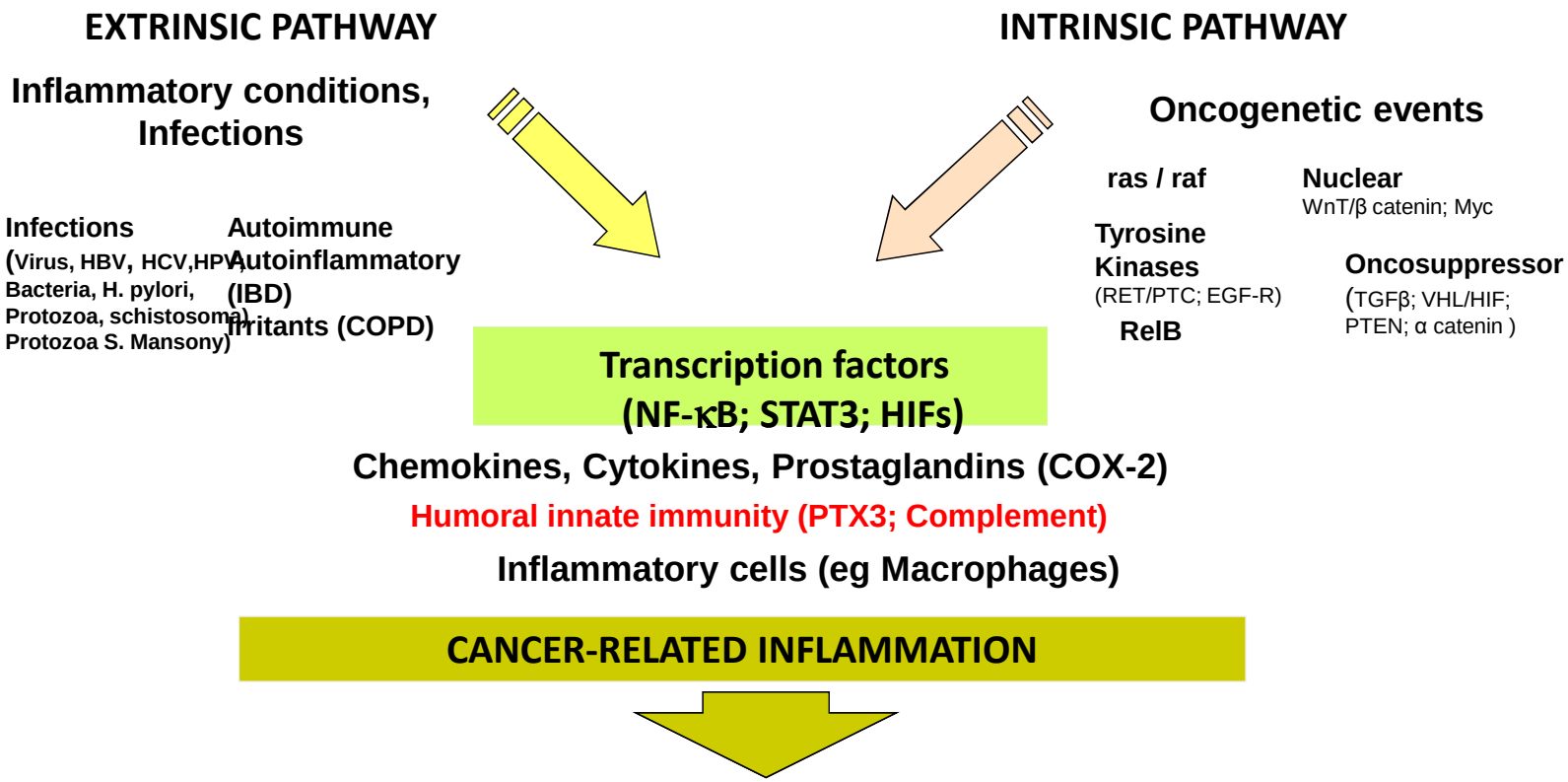


Bonavita et al Cell 2015

Two pathways link inflammation and cancer



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FONDAZIONE PER LA RICERCA

(Bonavita et al Cell 2015)

Mantovani A, Allavena P, Sica A, and Balkwill F, Nature2008

Humanitas Clinical and Research Center

Eduardo Bonavita
Stefania Gentile
Marcello Rubino
Virginia Maina
Francesca Feruglio
Martina Molgora
Ilaria Laface
Silvia Tartari
Andrea Doni
Fabio Pasqualini
Elisa Barbati
Polentarutti Nadia
Maria Rosaria Galdiero
Sebastien Jaillon
Cecilia Garlanda

Collaborators:

Pathology, University of Milan

Manuela Nebuloni

Humanitas Clinical and Research Center / Institute of Genetics and Biomedical Research, National Research Council

Roberto Papait
Paolo Kunderfranco
Gianluca Basso
Luigi Laghi

Department of Pathology and Laboratory Medicine, University of Pennsylvania,

John D. Lambris

University of Helsinki
Seppo Meri

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PTX3 in carcinogenesis: an extrinsic oncosuppressor taming tumor promoting inflammation

- **MCA and DMBA carcinogenesis in PTX3 deficient mice:**
  - **earlier appearence; increased growth; early increase in TAM; increased angiogenesis; increased p53 mutations; complement/CCL2 mediated tumor promotion**

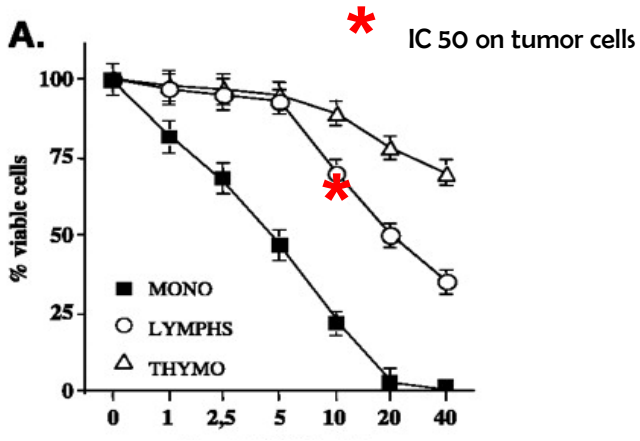
- **Methylation-dependent gene silencing in selected human tumors (eg leiomyosarcomas; CRC)**

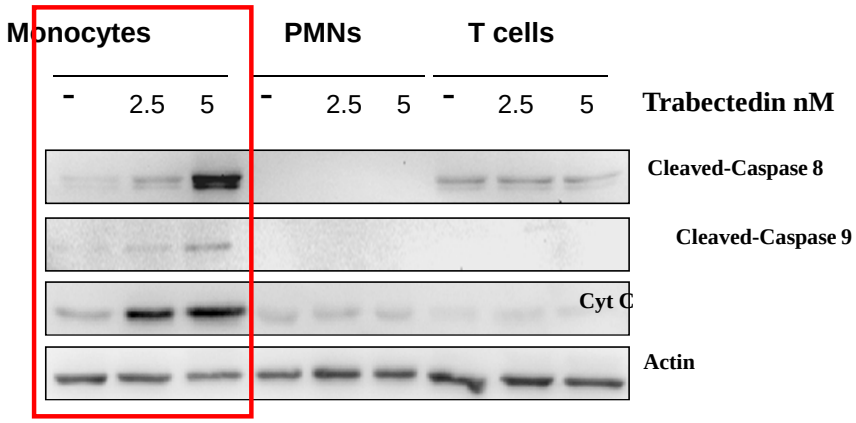
- **The humoral pattern recognition molecule PTX3 acts as an extrinsic oncosuppressor by regulating Complement-dependent tumor-promoting inflammation**

- **Complement is a key component of cancer-related inflammation**

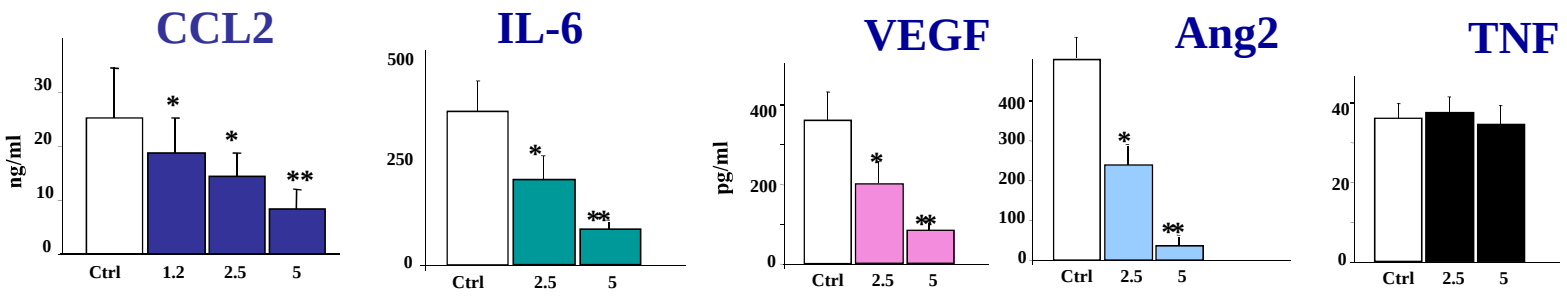
- **An effector molecule in innate immunity is a cancer gene (extrinsic oncosuppressor): a missing link in the connection between inflammation and cancer**

Trabectedin is selectively cytotoxic for Monocytes and reduces some inflammatory cytokines



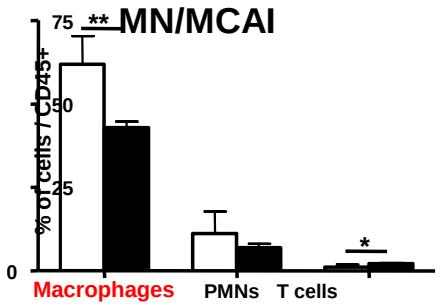


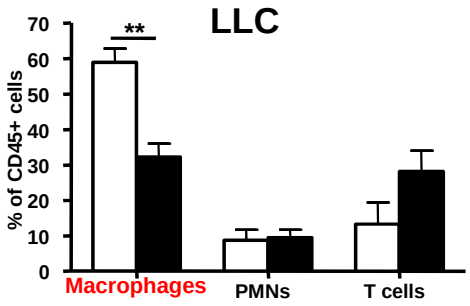
Allavena et al Cancer Res, 2005, 2010

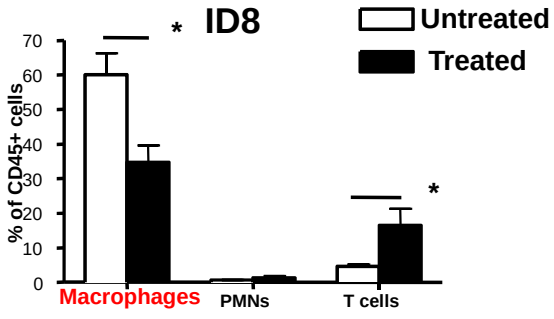


(Germano et al Cancer Cell 2013)

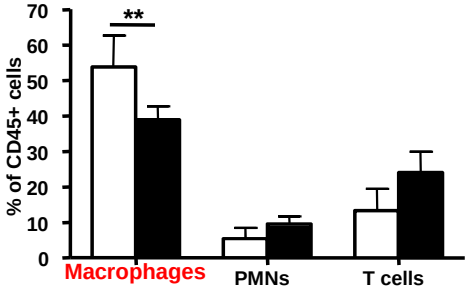
Tumor-associated macrophages but not T cells are decreased in tumors

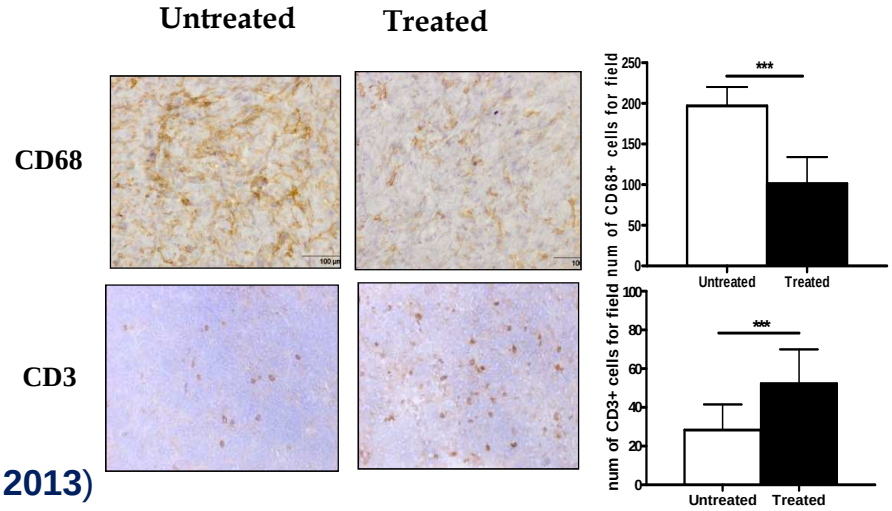






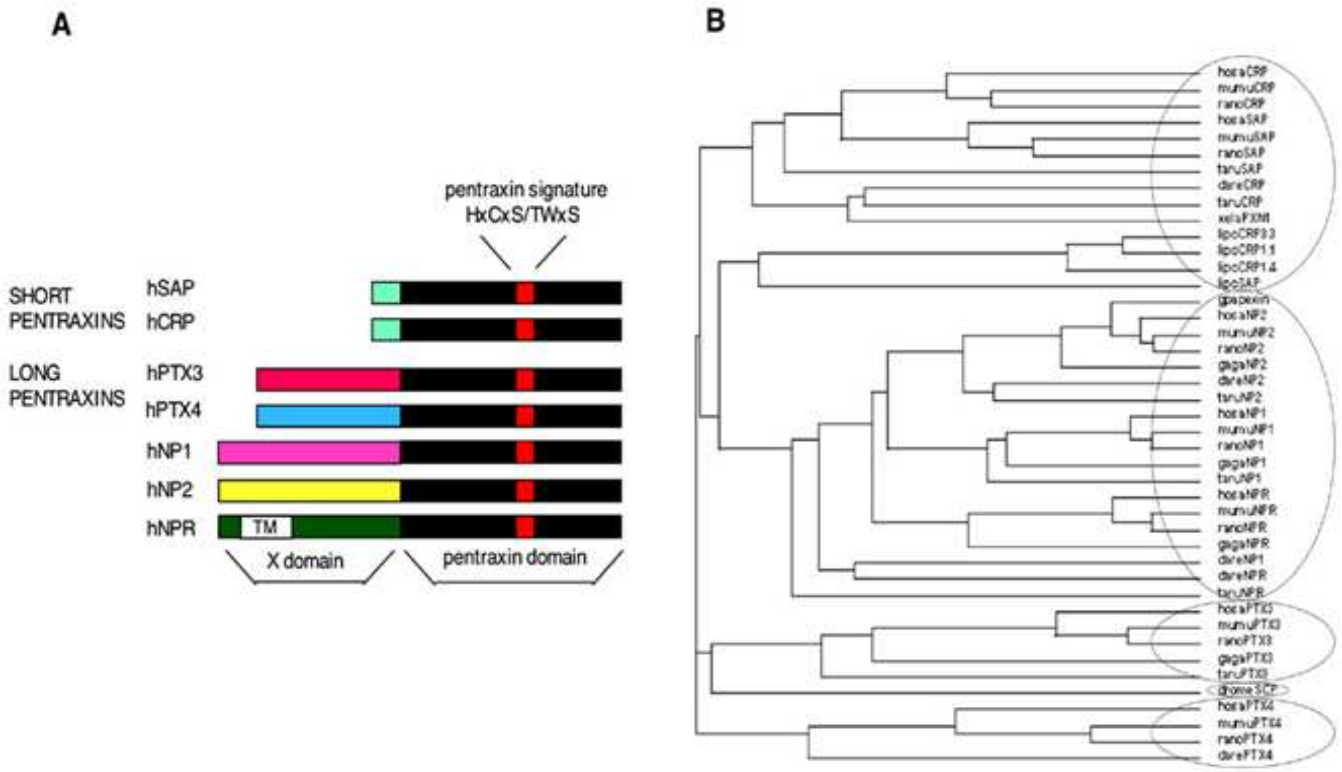
MCA-induced fibrosarcoma





(Germano et al Cancer Cell 2013)

The pentraxin superfamily



(Garlanda, Bottazzi and Mantovani, Annu Rev Immunol 2005, 2010)

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Conflict of Interest

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Michelangelo Merisi da Caravaggio, 1594

- Inventor of patents related to PTX3 and other innate immunity molecules
- Royalties on IP and reagents
- Advisory Boards, lecturing, consultancy (Sigma-Tau, ACRAF, Efranat, Novartis, Roche)
- Grant support: Sigma-Tau, Roche, Novartis, Compugen, Dompé