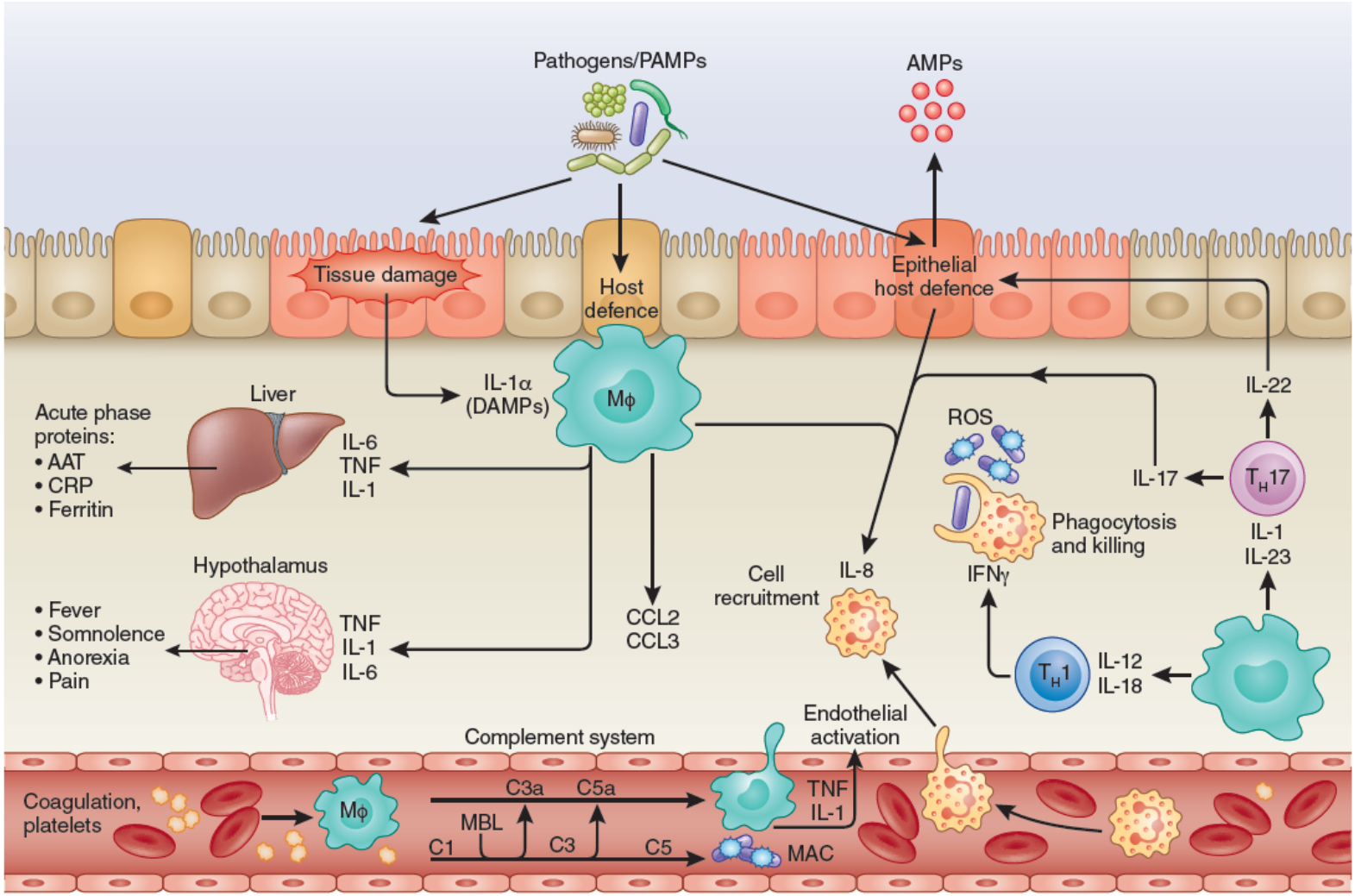
# A guiding map for Inflammation




*Netea et al, Nature Immunol, 2018*

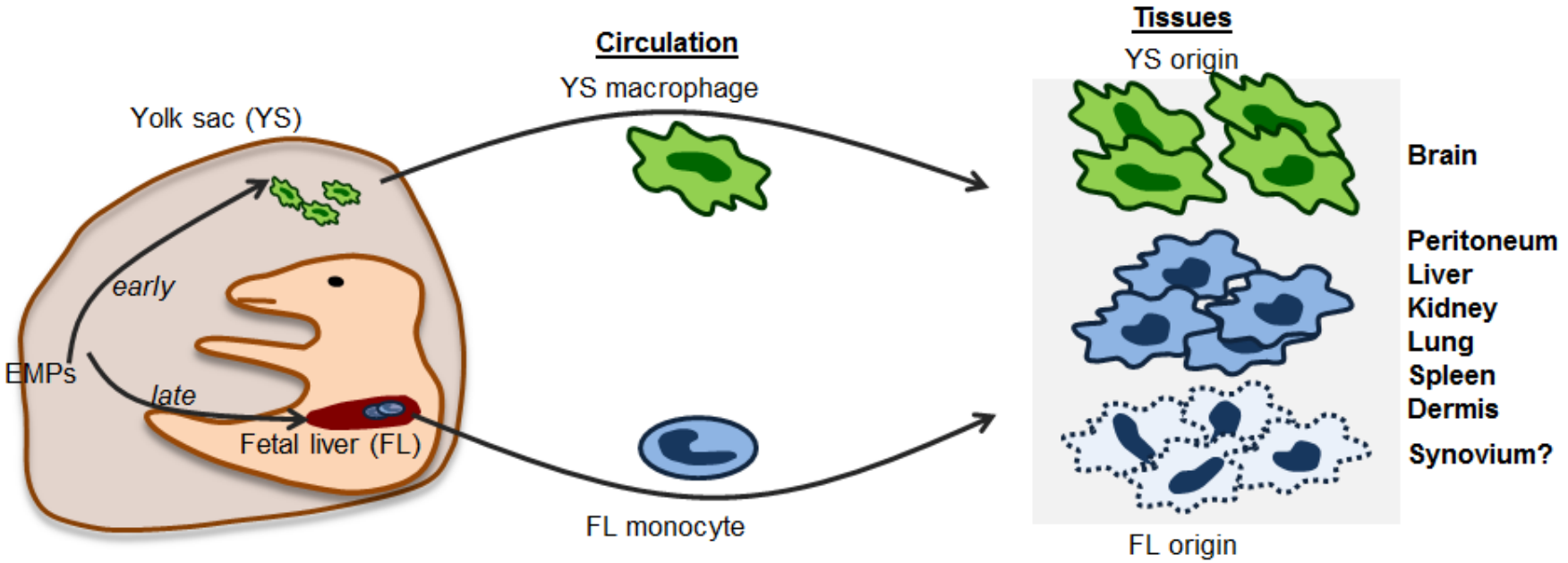



**FIGURE 2: Embryonic origins of tissue resident macrophages.**
The majority of tissue resident macrophages are seeded during embryonic development. YS macrophages arise first from primitive haematopoiesis and seed the embryonic tissues including the brain as early as E9.0. A wave of YS derived EMPs **( ? DEFINE EMPS**) seeds the FL where definitive haematopoiesis is established on E11.0. The FL is the main site of haematopoiesis until birth. On E12.5, FL derived monocytes populate the embryo and dilute the YS derived populations However, YS macrophages remain the sole source of microglia, the brain's resident macrophages, likely due to prior establishment of the blood brain barrier. In other tissues, resident macrophages are exclusively derived from FL monocytes. The fate mapping of tissue resident synovial macrophages has not yet been done.

**(Udalova I, Mantovani A, Feldmann M, Nature Rev Rheumatol 2016)**

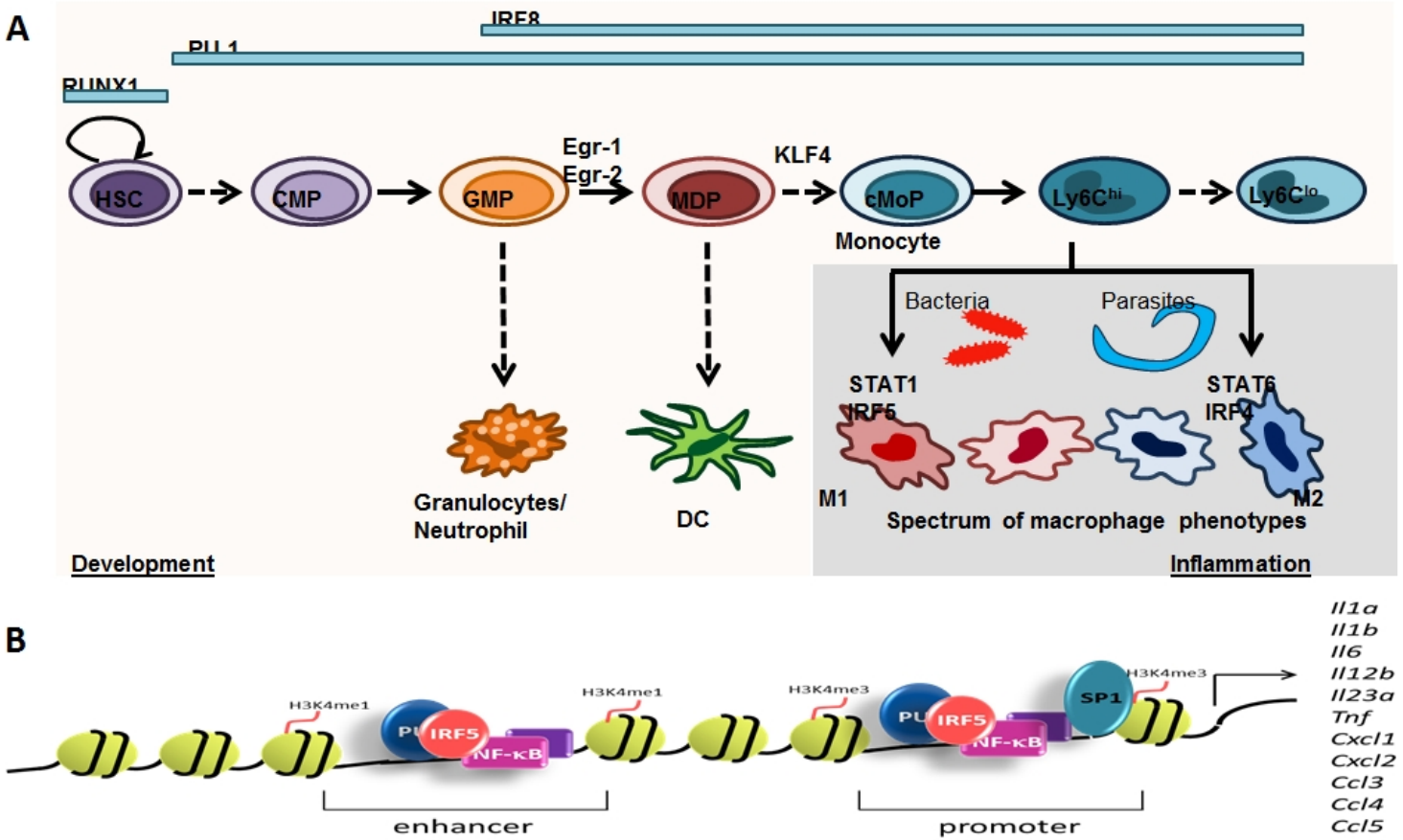
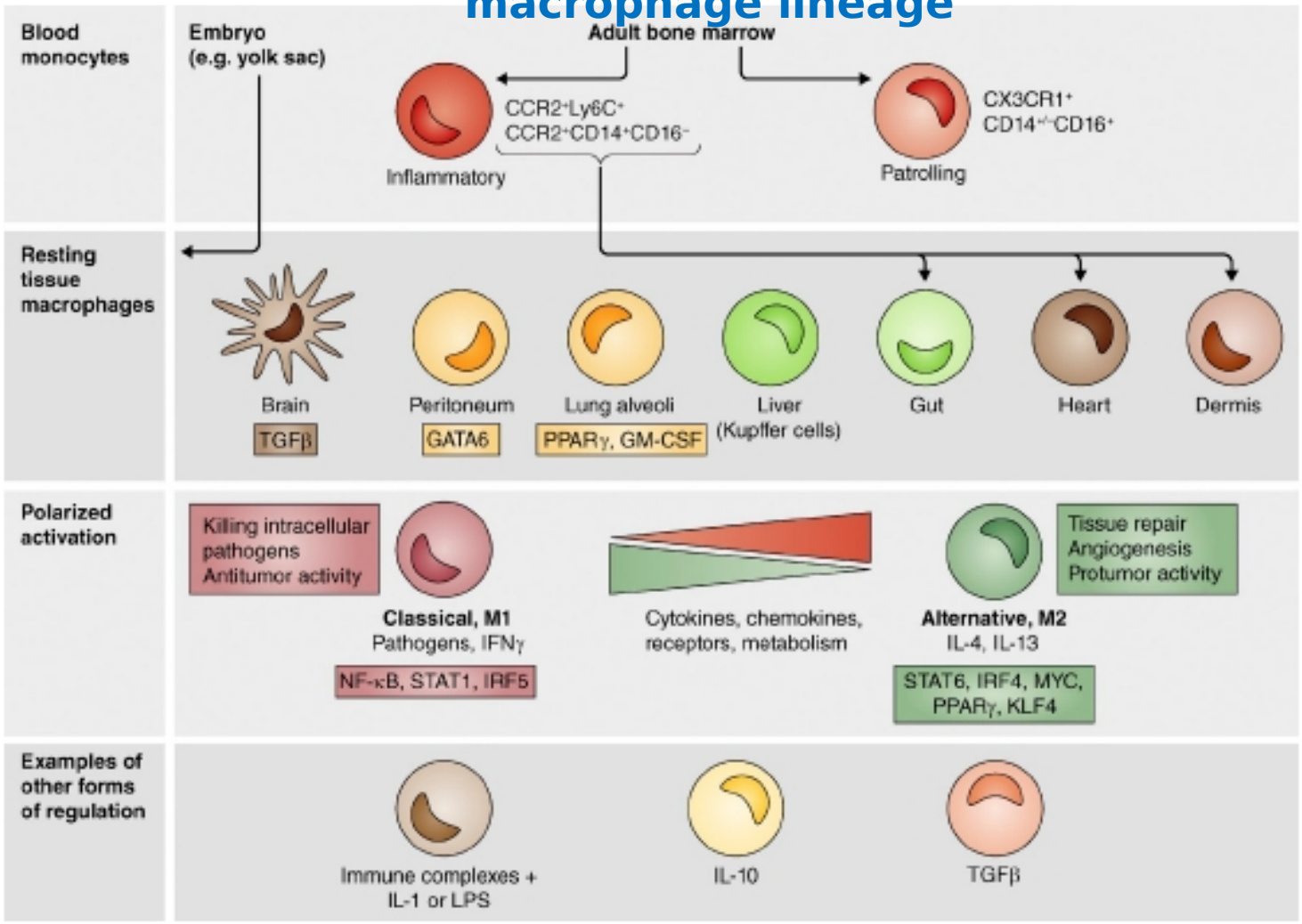



**FIGURE 4: PU.1 in the transcriptional control of macrophage development and activation.**

(A) RUNX1 is required during early development in HSCs followed by the onset of PU.1 expression. PU.1 is the master regulator of the myeloid lineage and crucial throughout differentiation. IRF8, Egr-1 and Egr-2 are involved in supressing granulocyte and neutrophil genes while promoting macrophage fate. KLF4 is required for monocyte/macrophage differentiation. During inflammation macrophages are shaped by the cytokine environment which depends on the nature of the infectious insult. Bacterial pathogens on the other hand cause a Th1 or Th17 type response which leads to STAT1 and IRF5 activation (classically activated M1 phenotype). Parasites lead to a Th2 driven disease activating STAT6 and IRF4 in macrophages (alternatively activated M2 phenotype). Importantly, macrophage phenotypes *in vivo* are manifold and thus represented as a spectrum. (B) Typical composition of PU.1 marked enhancers and promoters in classically activated M1 macrophages.

**(Udalova I, Mantovani A, Feldmann M, Nature Rev Rheumatol 2016)**

# Ontogeny and regulation of cells of the monocyte-macrophage lineage




*Mantovani and Allavena , J. Exp . Med 2015*

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

**ected reviews: Sica and Mantovani J Clin Inv 2012; Biswas and Mantovani, Nature Immunol 20**
**y et al Immunity 2014; Mantovani and Allavena J Exp Med 2015; Mantovani Nature Immmunol**

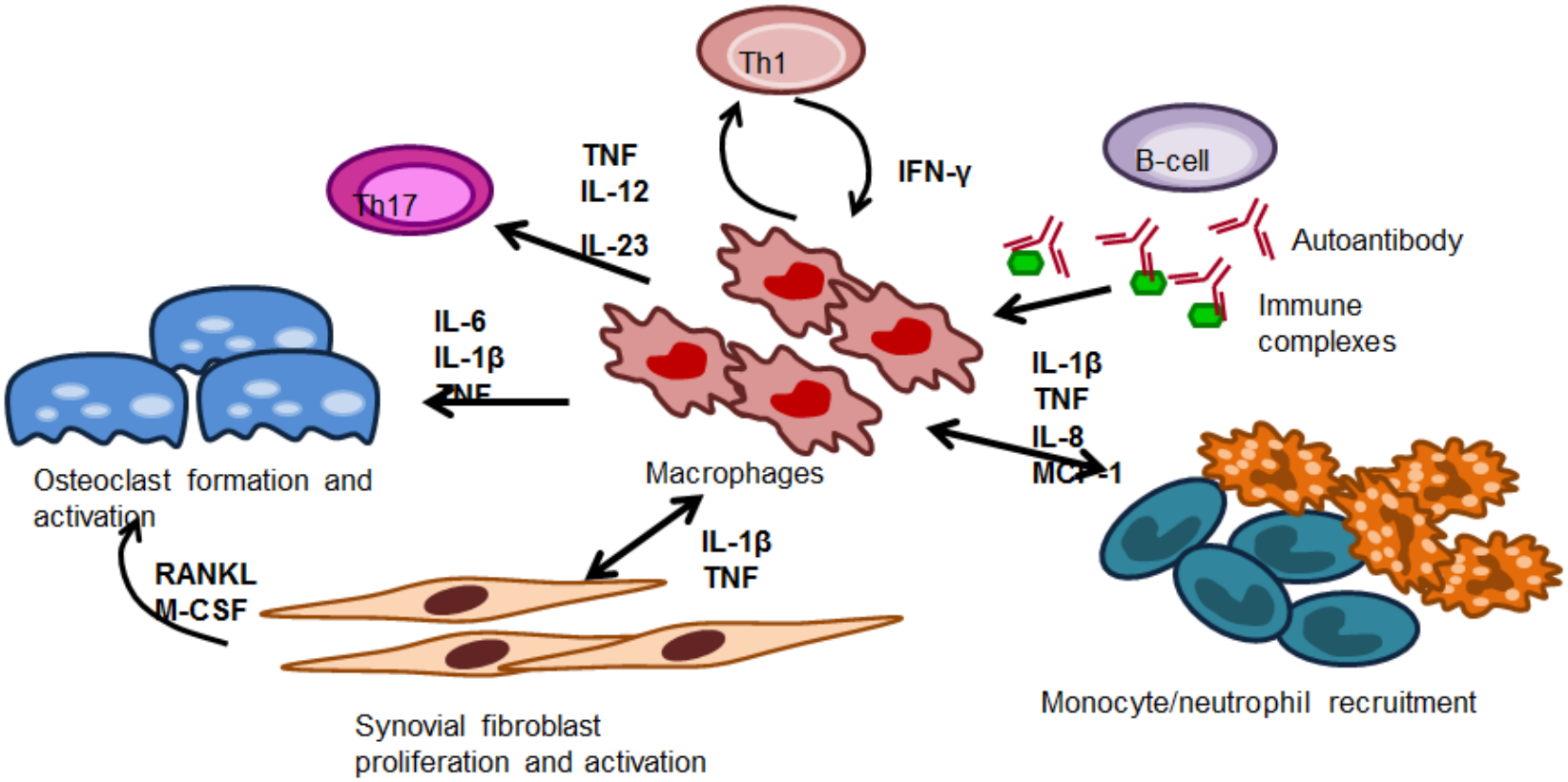
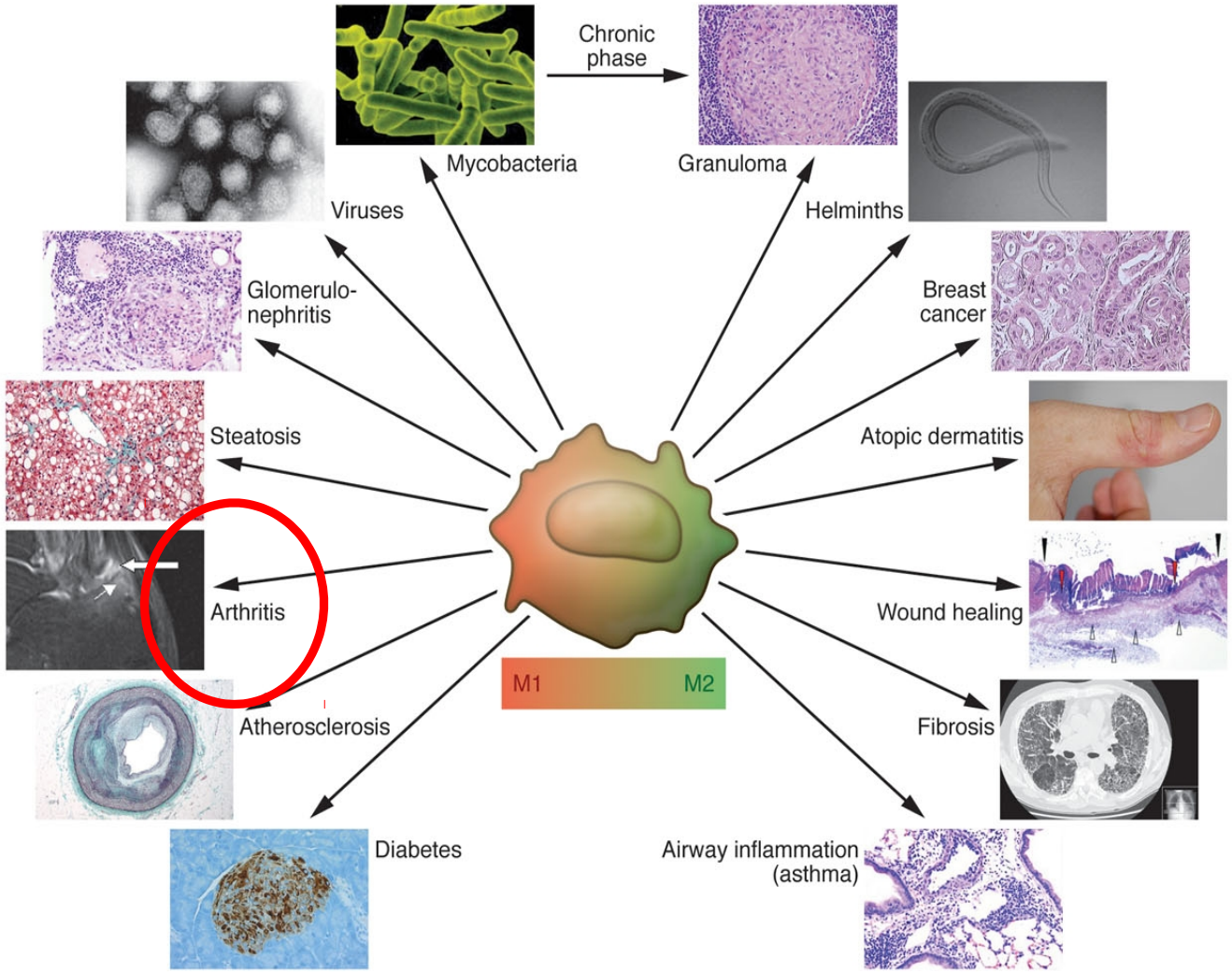



**FIGURE 1: Overview of the role of macrophages in RA.**
Macrophages produce cytokines which in turn promote inflammation by recruitment of additional immune cells, T-cell polarisation and fibroblast activation. Activated fibroblast secrete RANKL and M-CSF inducing osteoclast differentiation which is enhanced by macrophage derived TNF and others. Immune complexes formed by autoantibodies and antigens activate macrophages. Additionally, macrophages are influenced by cell-cell contact or cytokines produced by T-cells, fibroblasts and innate immune cells.

**(Udalova I, Mantovani A, Feldmann M, Nature Rev Rheumatol 2016)**

# Macrophage plasticity and polarization in pathology: in vivo veritas

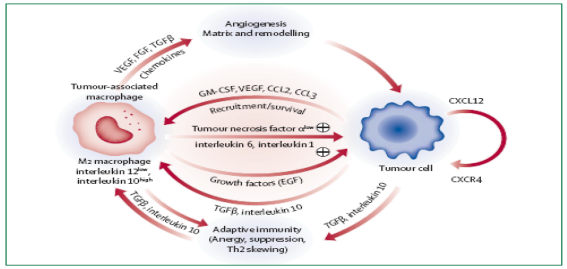



Sica A and Mantovani A. J. Clin. Invest. 2012

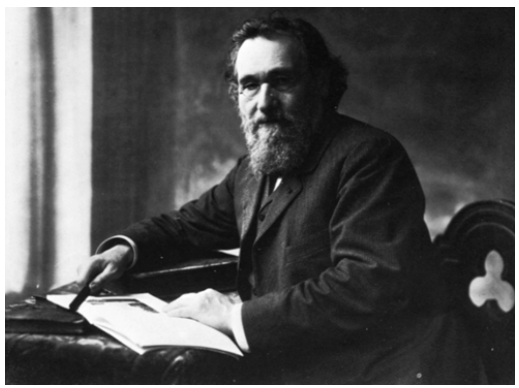
# INFLAMMATION, MACROPHAGES AND CANCER

**RUDOLF LUDWIG KARL VIRCHOW (1821-1902)**

***Balkwill and Mantovani, Lancet 2001***

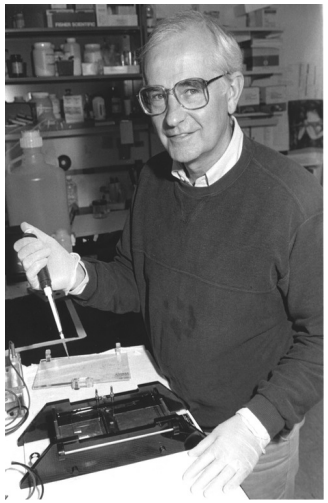



***(Mantovani et al. Lancet 2008; Nature 2008)***

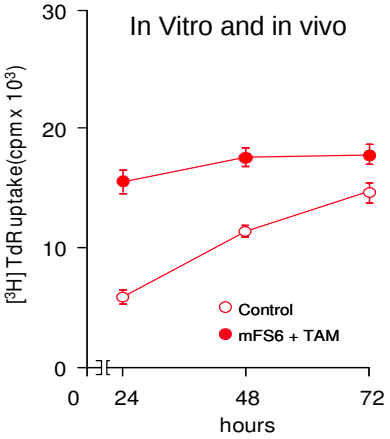


**Ilya Mechnikov (1845-1916)**

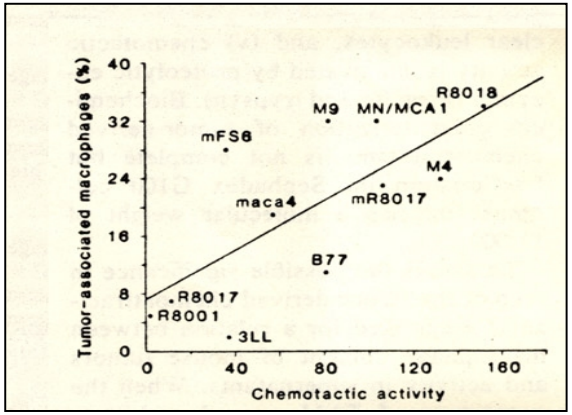
The Nobel Prize in Physiology and Medicine 1908



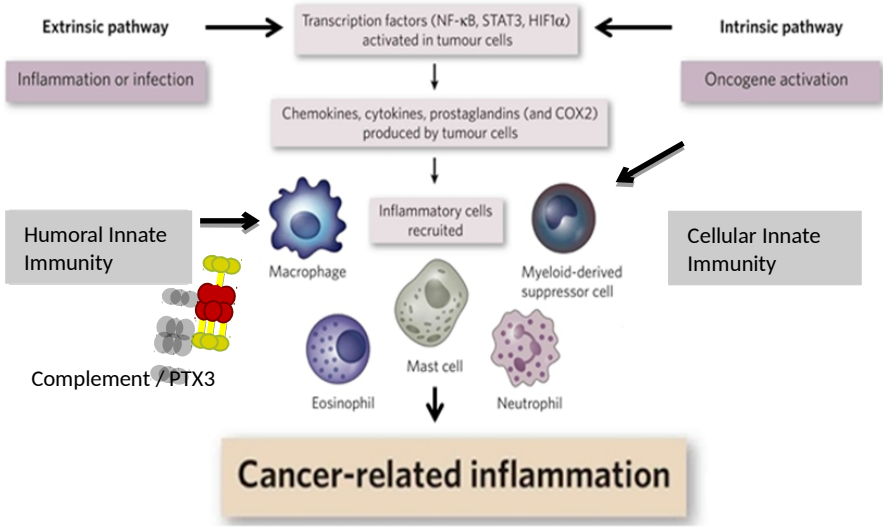
**(TAM: Robert Evans, Transplantation, 1972; Evans and Alexander, Nature, 1970)**

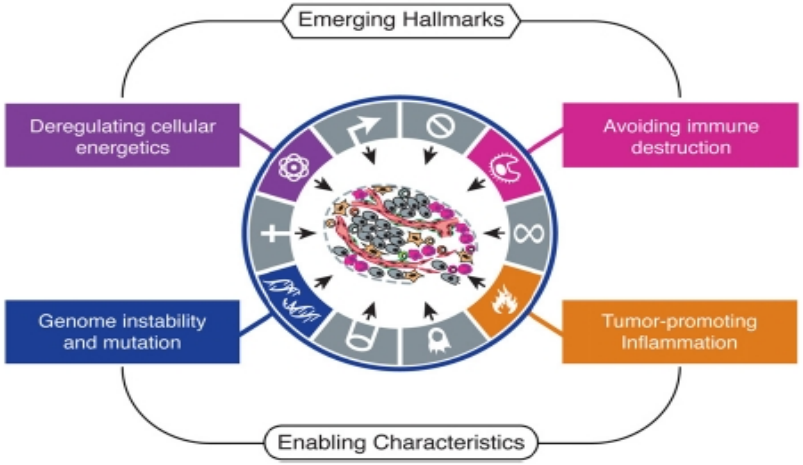



**(Mantovani A. 1978)**



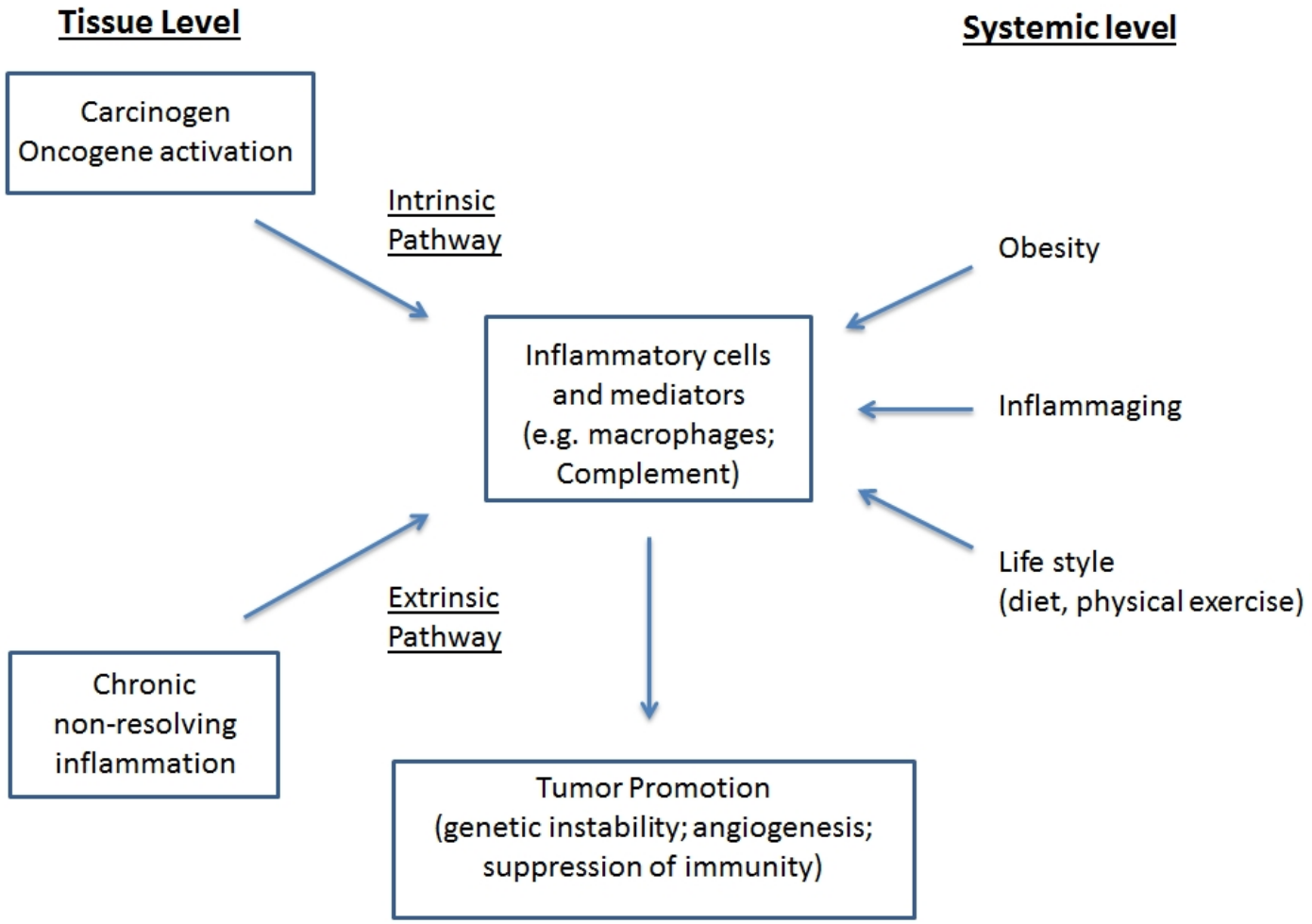

**(Bottazzi et al Science 1983)**



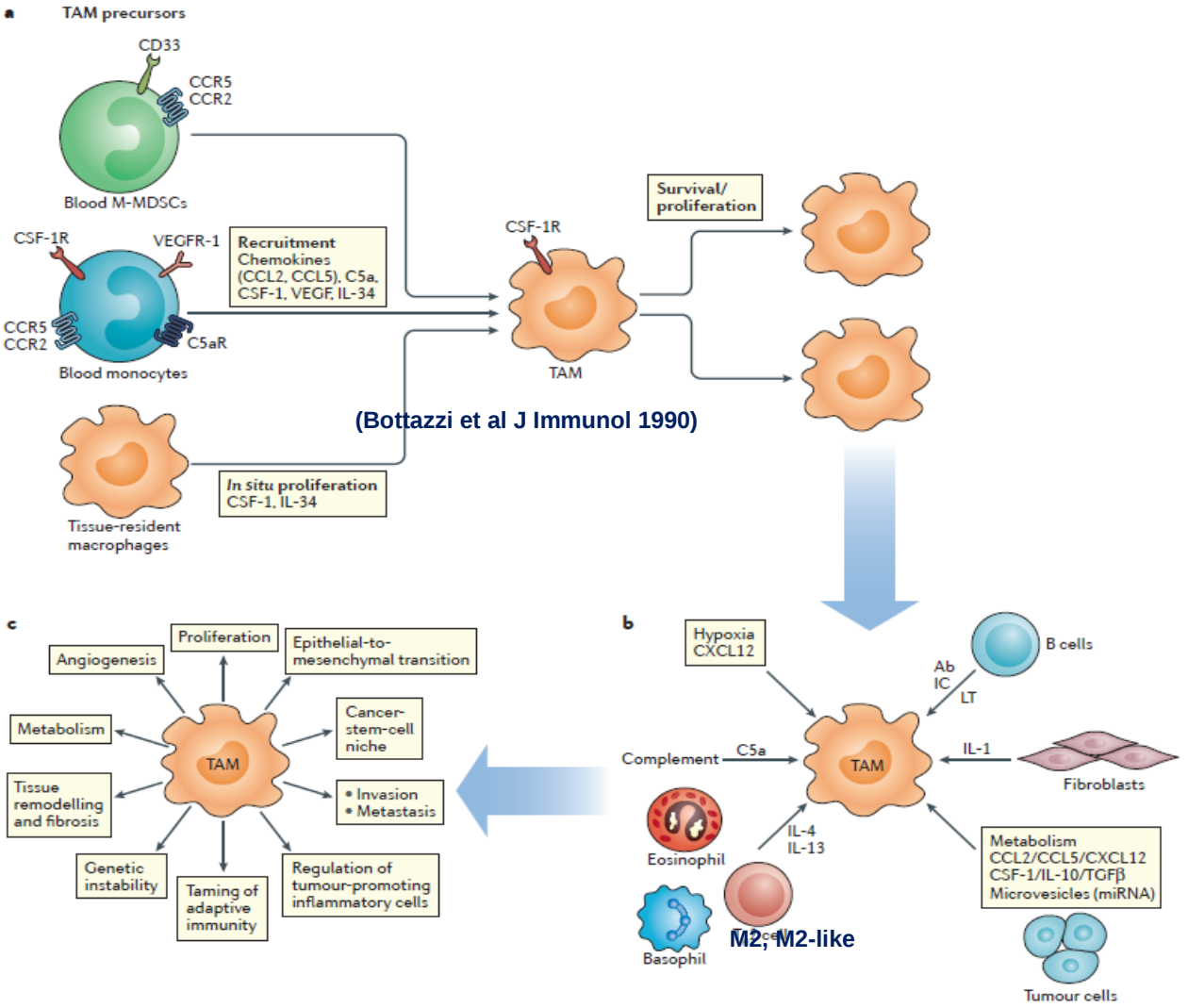

*(e.g. Mantovani, Sica, Allavena, Balkwill, Nature, 2008; Mantovani, Nature, 2009; Hanahan and Weinberg, Cell, 2000; Cell, 2011; Reis et al, Nature Rev Immunol, 2018; Bonavita et al, Cell, 2015)*

# Pathways linking inflammation and cancer




*Mantovani et al, Nature, 2008; Nature, Rev Clin. Immunol., 2017; Seminars Immunology, 2018*

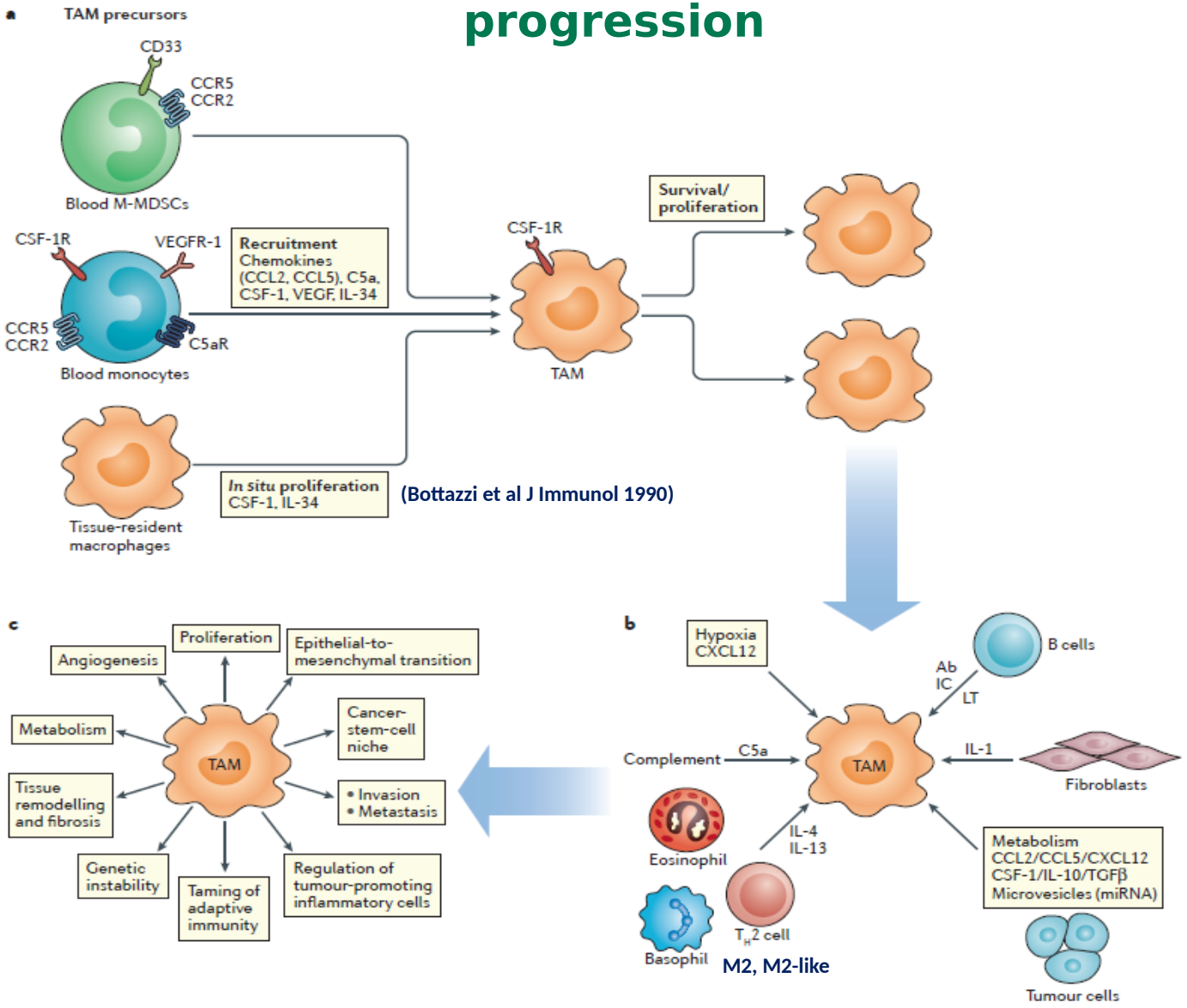
# The role of TAMs in tumour progression




*Mantovani , Marchesi..Allavena, Nature Reviews Clinical Oncology, 2017*

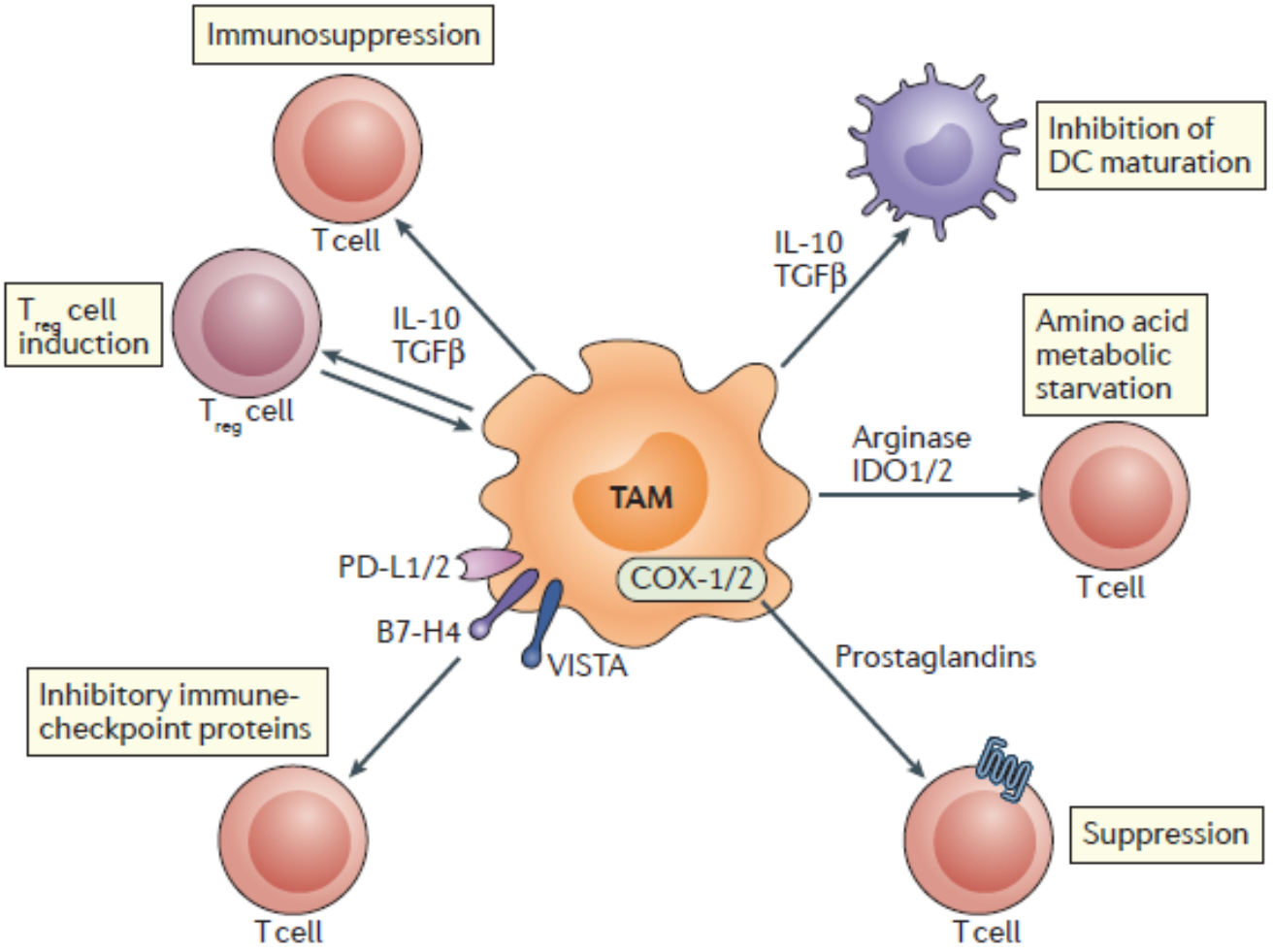

**(Mantovani…. Ruco, Immunol Today 1992)**

# The role of TAMs in tumour progression

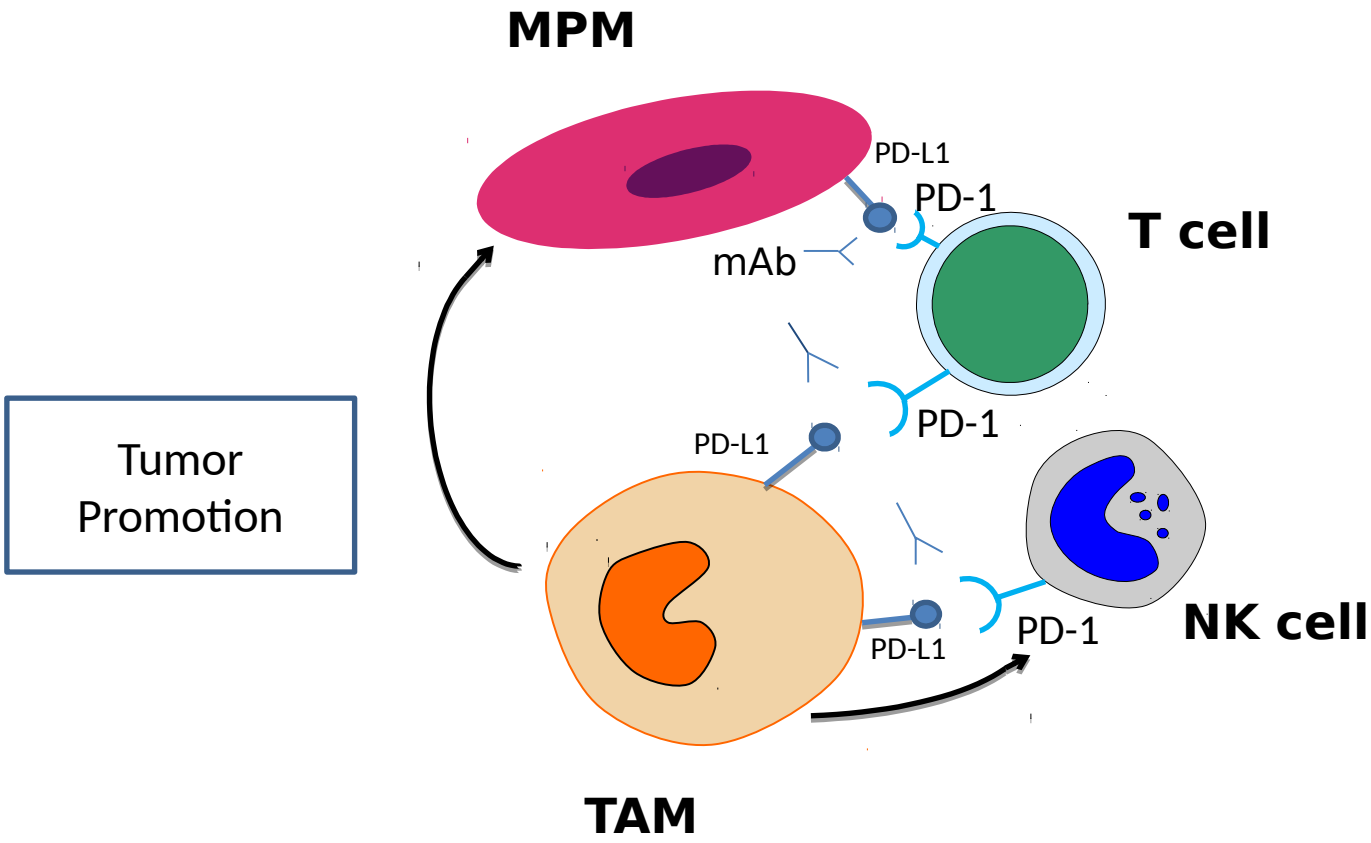



*(Mantovani , Marchesi..Allavena, et al Nature Reviews Clinical Oncology, 2017)*

# Mechanisms of TAM mediated immune suppression




*(Mantovani et al, Nature Rev Clin Oncology, 2017)*




*(Ceresoli and Mantovani, Lancet Oncol., 2018)*

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# TAM, INFLAMMATION AND CANCER: TRANSLATION

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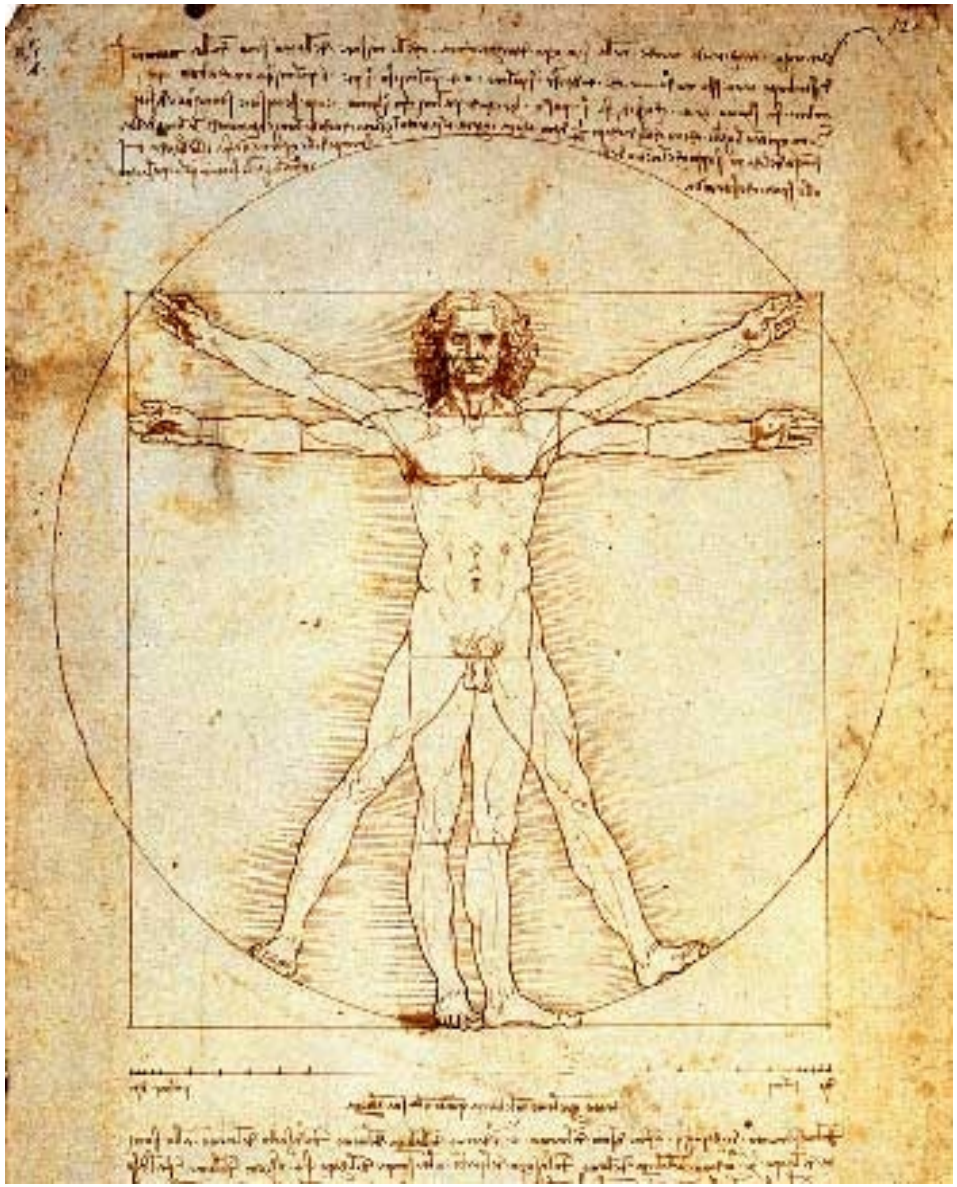

1. **Pathology: prognostic vs predictive**

2. **Prevention**

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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**

*Mario Negri Institute for Pharmacological Research, Via Gavazzeni 11, 24100 Bergamo [R. G., A. G., M. R. B., M. A.], and Via Eritrea 62, 20157 Milano [P. G., A. M., E. D.], and Sclavo Research Center, 53100 Siena [D. B.], Italy*

[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]**

*Mario Negri Institute for Pharmacological Research, Via Gavazzeni 11, 24125 Bergamo [R. G. S. C., A. G., R. G.], and Via Eritrea 62, 20152 Milano [I. M. P., A. M.], Italy*

[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]**

*Department of Cellular Biology and Morphological Sciences, School of Medicine and Dentistry, University of the Basque Country, Leioa, 48940-Vizcaya, Spain [F. V-V., C. A., A. A.], and Tufts University School of Medicine and New England Medical Center, Boston, Massachusetts 02111 [G. K., C. A. D.]*

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*§

*Departments of Microbiology and Immunology, and Pathology, Faculty of Health Sciences, The Cancer Research Center, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel; †Institute of Medical Science, University of Tokyo, Minato-Ku 108-8639, Japan; and ‡University of Colorado Health Sciences Center, Denver, CO 80262

Contributed by Charles A. Dinarello, December 27, 2002

# 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†*

## Summary

**Background** Inflammation in the tumour microenvironment mediated by interleukin 1β is hypothesised to have a major role in cancer invasiveness, progression, and metastases. We did an additional analysis in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), a randomised trial of the role of interleukin-1β inhibition in atherosclerosis, with the aim of establishing whether inhibition of a major product of the Nod-like receptor protein 3 (NLRP3) inflammasome with canakinumab might alter cancer incidence.

**Methods** We did a randomised, double-blind, placebo-controlled trial of canakinumab in 10 061 patients with atherosclerosis who had had a myocardial infarction, were free of previously diagnosed cancer, and had concentrations of high-sensitivity C-reactive protein (hsCRP) of 2 mg/L or greater. To assess dose–response effects, patients were randomly assigned by computer-generated codes to three canakinumab doses (50 mg, 150 mg, and 300 mg, subcutaneously every 3 months) or placebo. Participants were followed up for incident cancer diagnoses, which were adjudicated by an oncology endpoint committee masked to drug or dose allocation. Analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, NCT01327846. The trial is closed (the last patient visit was in June, 2017).

**Findings** Baseline concentrations of hsCRP (median 6·0 mg/L *vs* 4·2 mg/L; p<0·0001) and interleukin 6 (3·2 *vs* 2·6 ng/L; p<0·0001) were significantly higher among participants subsequently diagnosed with lung cancer than among those not diagnosed with cancer. During median follow-up of 3·7 years, compared with placebo, canakinumab was associated with dose-dependent reductions in concentrations of hsCRP of 26–41% and of interleukin 6 of 25–43% (p<0·0001 for all comparisons). Total cancer mortality (n=196) was significantly lower in the pooled canakinumab group than in the placebo group (p=0·0007 for trend across groups), but was significantly lower than placebo only in the 300 mg group individually (hazard ratio [HR] 0·49 [95% CI 0·31–0·75]; p=0·0009). Incident lung cancer (n=129) was significantly less frequent in the 150 mg (HR 0·61 [95% CI 0·39–0·97]; p=0·034) and 300 mg groups (HR 0·33 [95% CI 0·18–0·59]; p<0·0001; p<0·0001 for trend across groups). Lung cancer mortality was significantly less common in the canakinumab 300 mg group than in the placebo group (HR 0·23 [95% CI 0·10–0·54]; p=0·0002) and in the pooled canakinumab population than in the placebo group (p=0·0002 for trend across groups). Fatal infections or sepsis were significantly more common in the canakinumab groups than in the placebo group. All-cause mortality did not differ significantly between the canakinumab and placebo groups (HR 0·94 [95% CI 0·83–1·06]; p=0·31).

**Interpretation** Our hypothesis-generating data suggest the possibility that anti-inflammatory therapy with canakinumab targeting the interleukin-1β innate immunity pathway could significantly reduce incident lung cancer and lung cancer mortality. Replication of these data in formal settings of cancer screening and treatment is required.

**Funding** Novartis Pharmaceuticals.

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*These authors contributed equally

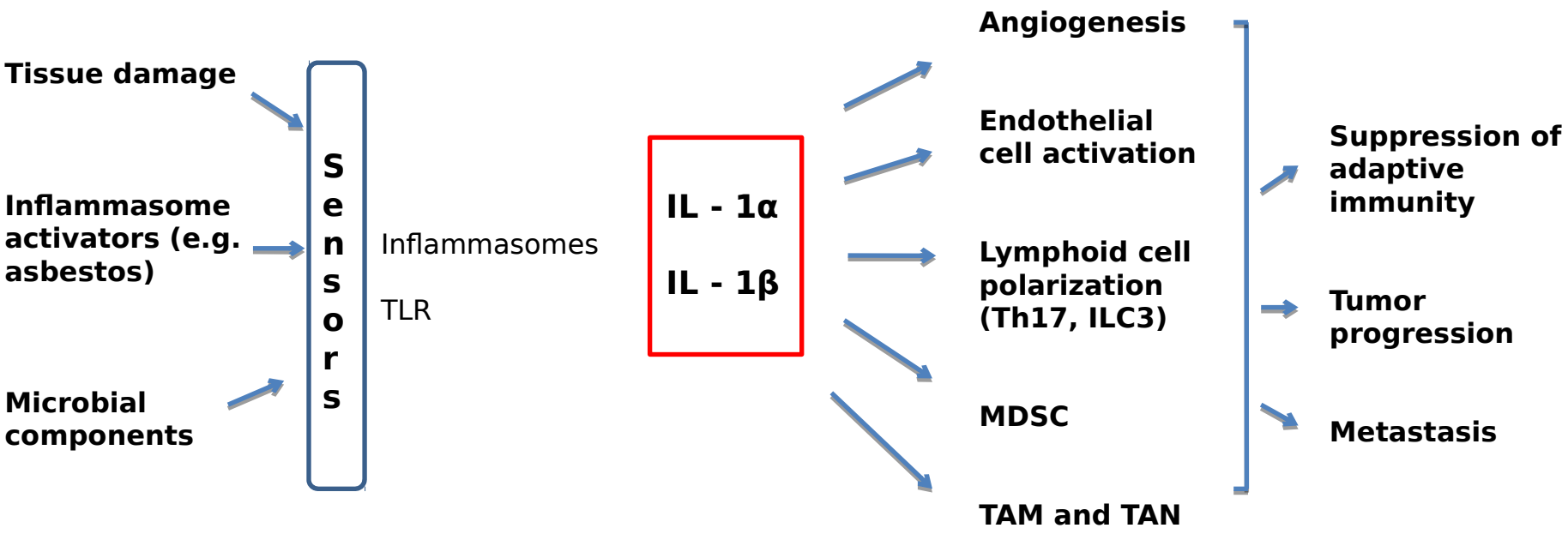
†CANTOS Trial Group listed in the apendix

**Center for Cardiovascular Disease Prevention** (Prof P M Ridker MD, J G MacFadyen BA, B M Everett MD, Prof R J Glynn ScD) **and Cardiovascular Division** (Prof P M Ridker, B Everett, Prof P Libby MD), **Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; Novartis Pharmaceuticals, East Hanover, NJ, USA** (T Thuren MD); **and Novartis Pharmaceuticals, Basel, Switzerland** (T Thuren)

Correspondence to:
Prof Paul M Ridker, Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, 900 Commonwealth Avenue, Boston, MA 02215, USA
**pridker@partners.org**

See Online for appendix

# IL-1 in cancer related inflammation




*Mantovani et al, Immunol Rev, 2018; Seminars Immunol, 2018*

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# TAM, INFLAMMATION AND CANCER: TRANSLATION

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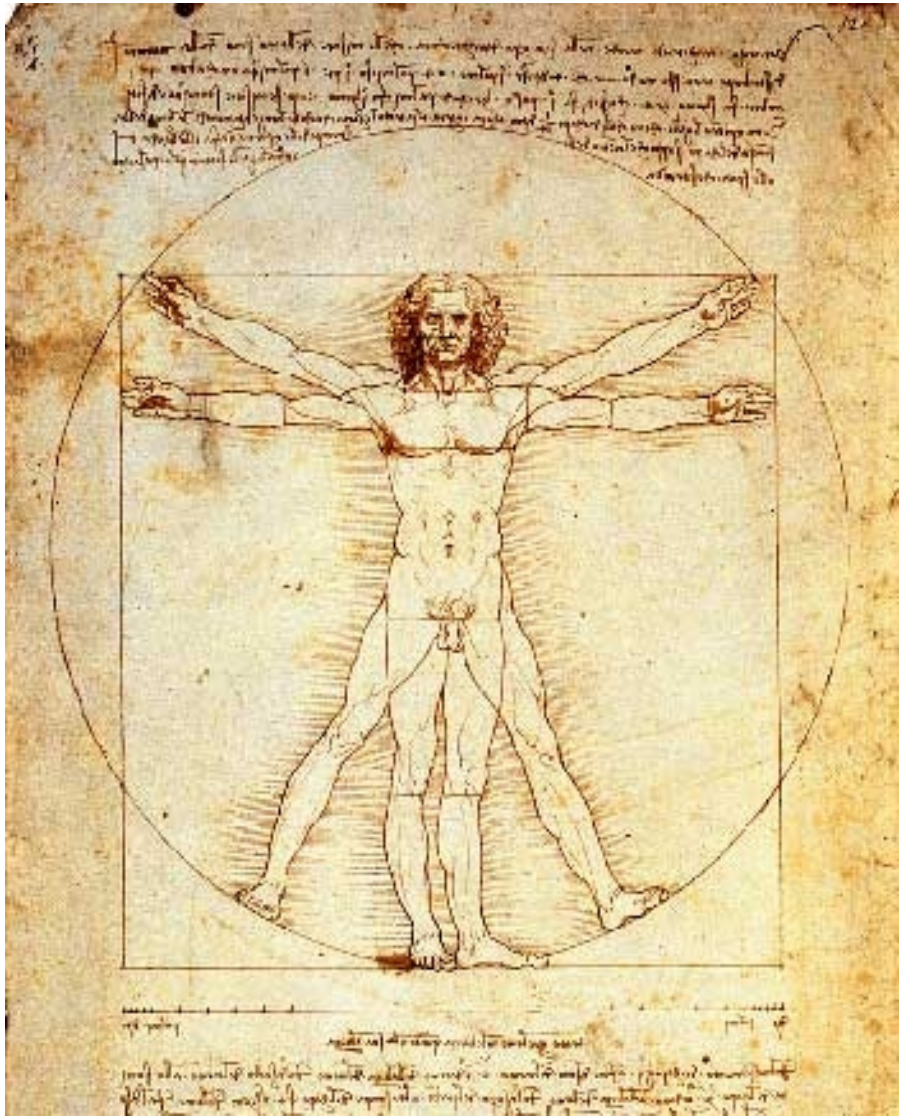
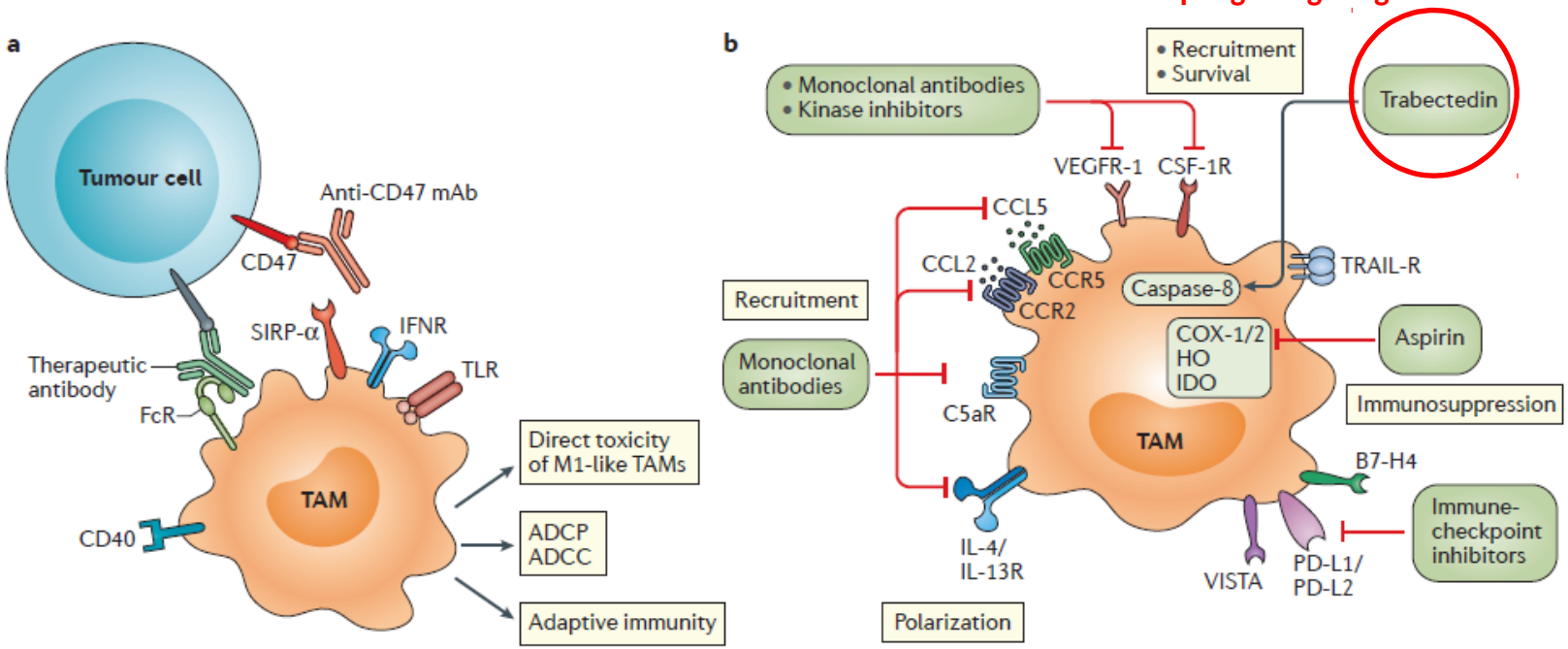


1. **Pathology: prognostic vs predictive**
2. **Prevention**
3. **Therapy: reeducation and targeting corrupted policemen**

# Macrophage-targeting antitumour treatment approaches

**Trabectedin approved by FDA and EMA, Germano et al Cancer Cell 2013; Chemo and macrophage targeting in one molecule**




*Mantovani et al, Nature Rev Clin Oncol, 2017*

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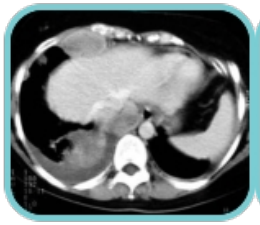
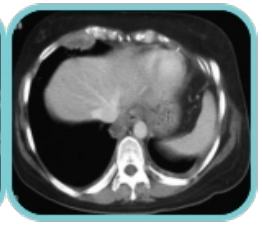
# Clinical patterns of response to Trabectedin: Chemo and more

## Classical pattern

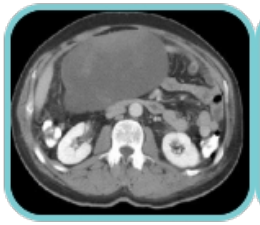
Pre-treatment



Cycle 2



Pre-treatment



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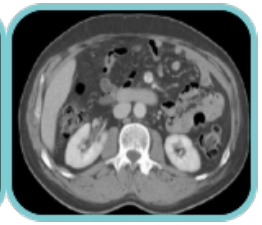
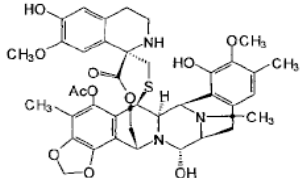
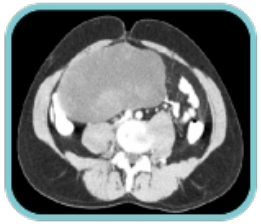




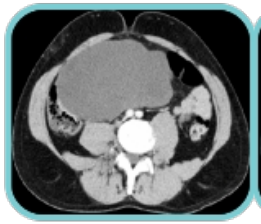

TRABECTEDIN

## Atypical pattern of response

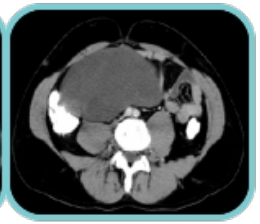
Pre-treatment



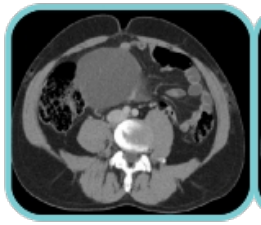
Cycle 1



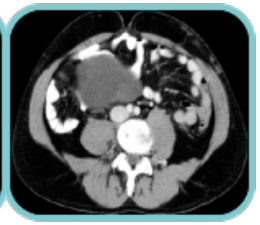
Cycle 5



Cycle 8



Cycle 11



Adapted from F. Grosso et al, Lancet Oncology 2007

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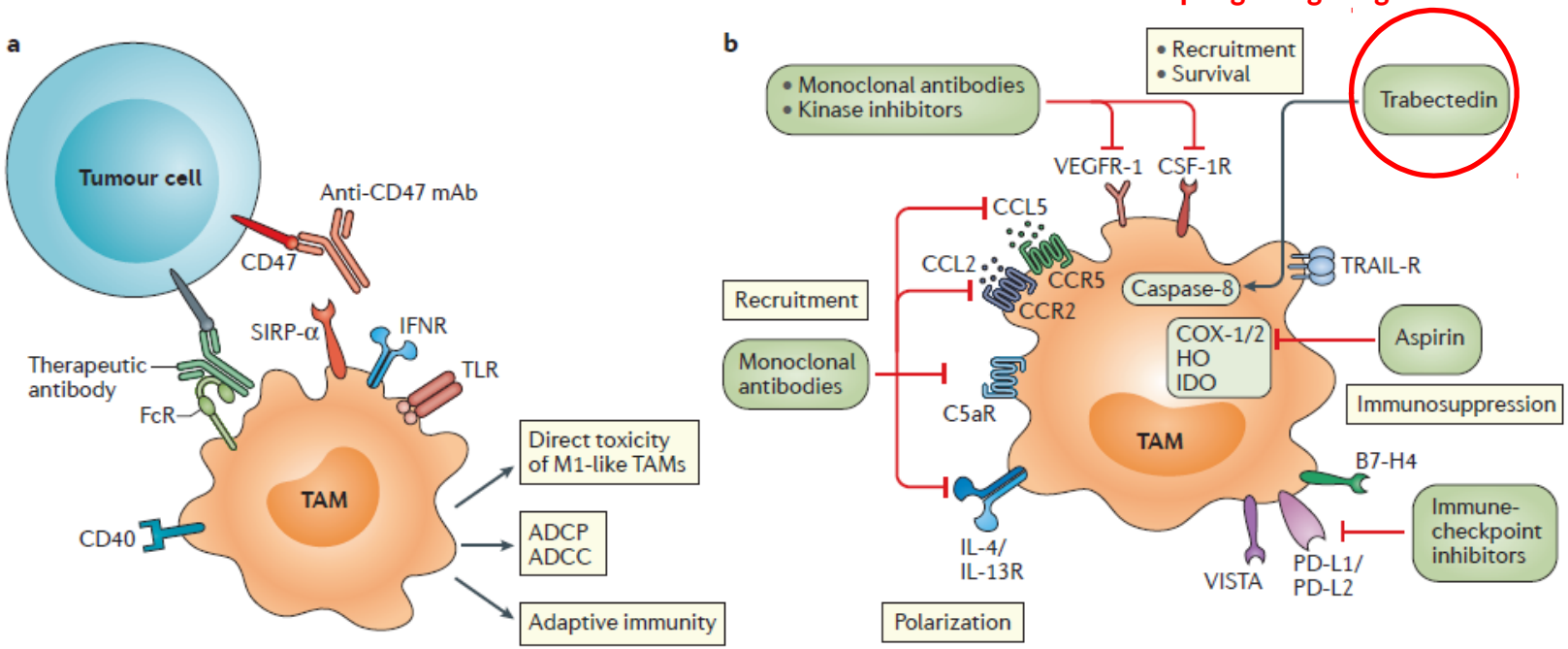
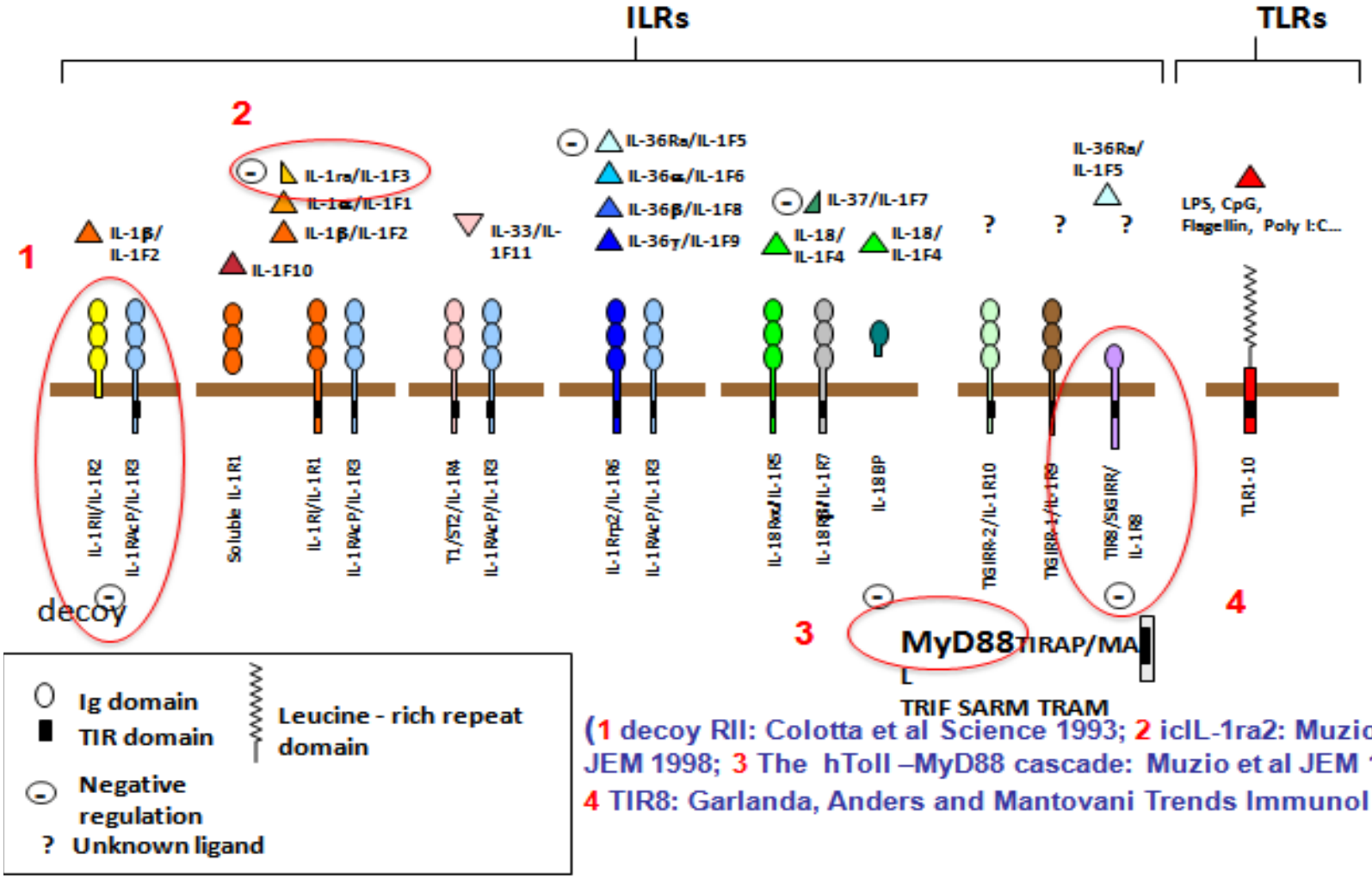
**Trabectedin approved by FDA and EMA, Germano et al Cancer Cell 2013; Chemo and macrophage targeting in one molecule**




*Mantovani et al, Nature Rev Clin Oncol, 2017*

## THE IL-1 RECEPTOR (ILR) FAMILY




(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, Dinarello and Mantovani, Immunity 2013)

Bardo Museum, Tunis

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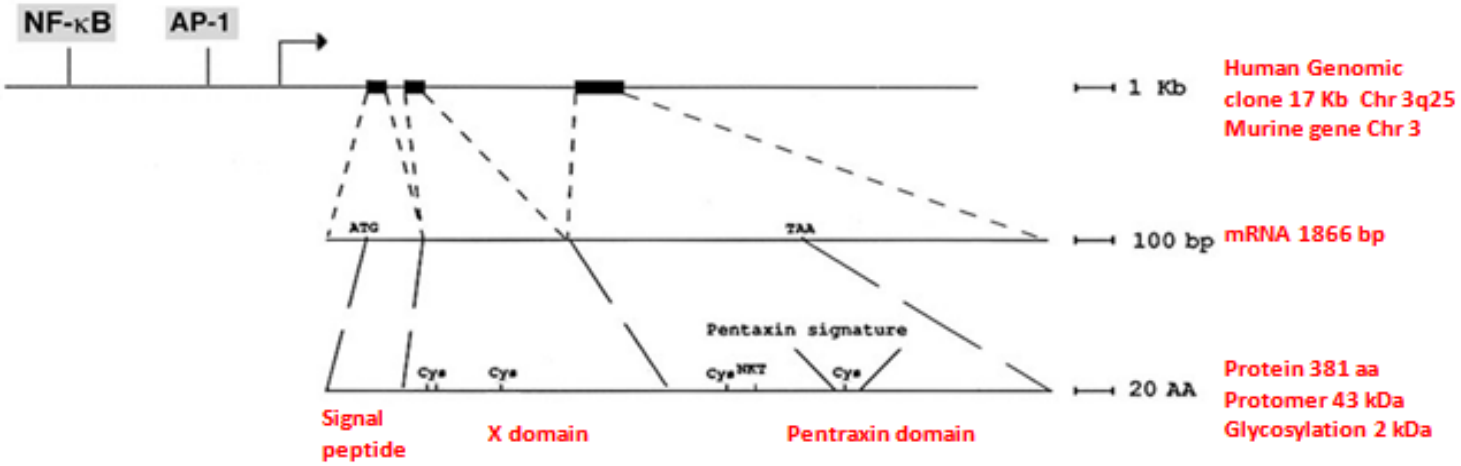
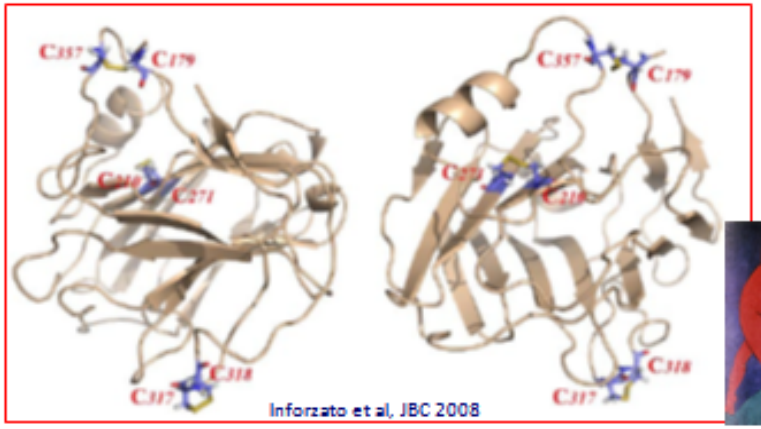
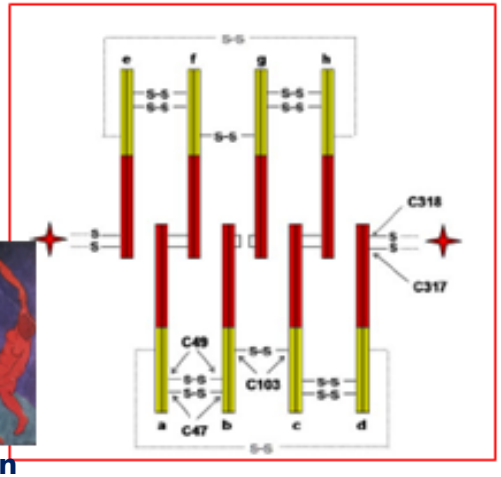
# THE PROTOTYPIC LONG PENTRAXIN PTX3



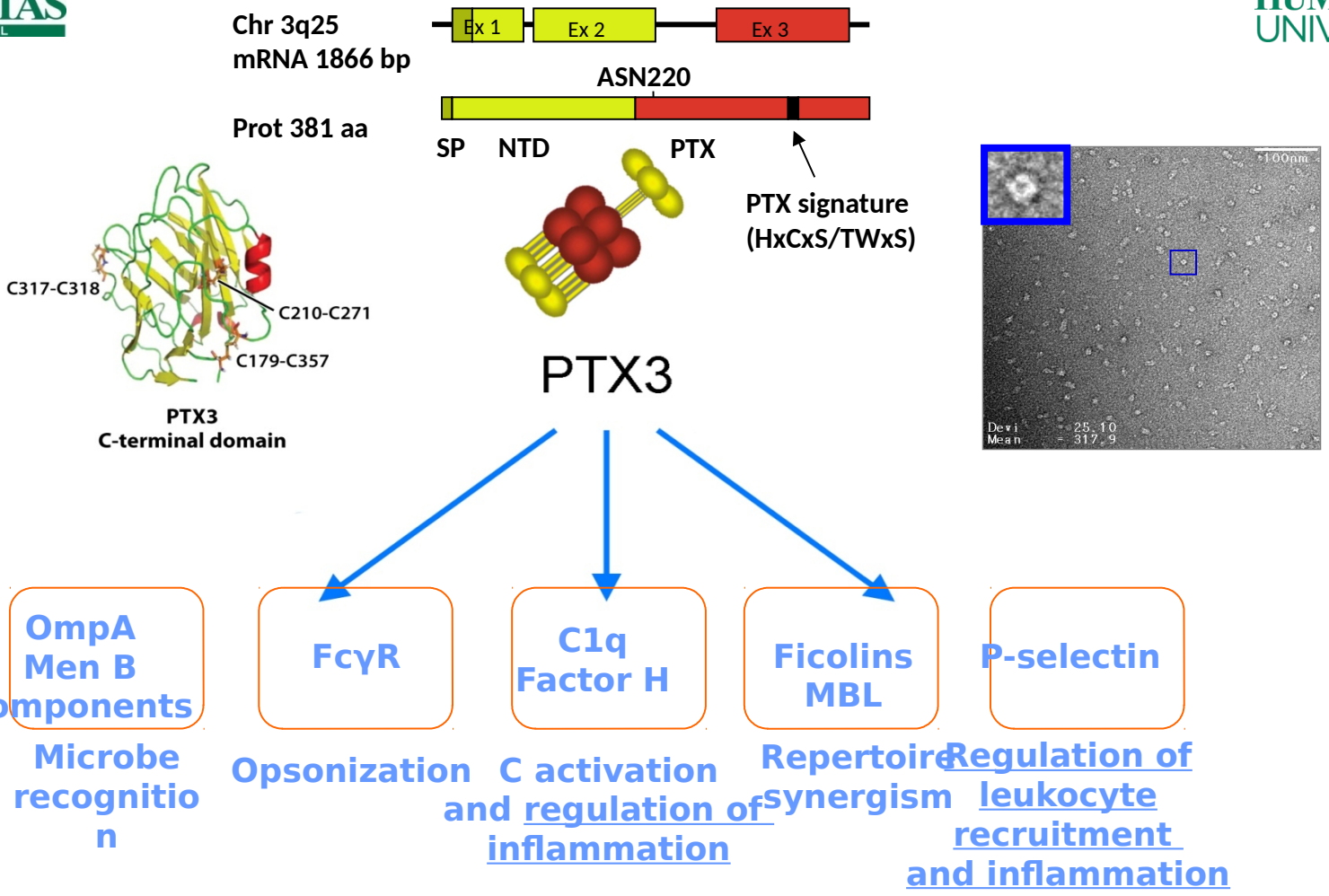




Protein is mainly organized in covalently linked octamer




**C Reactive Protein**

(Garlanda et al Annu Rev Immunol 2005, 2010; Bottazzi et al Curr Op Immunol, 2006, 2008, 2015; Immunol Rev 2017; Garlanda et al Physiol Rev 2017 in press)

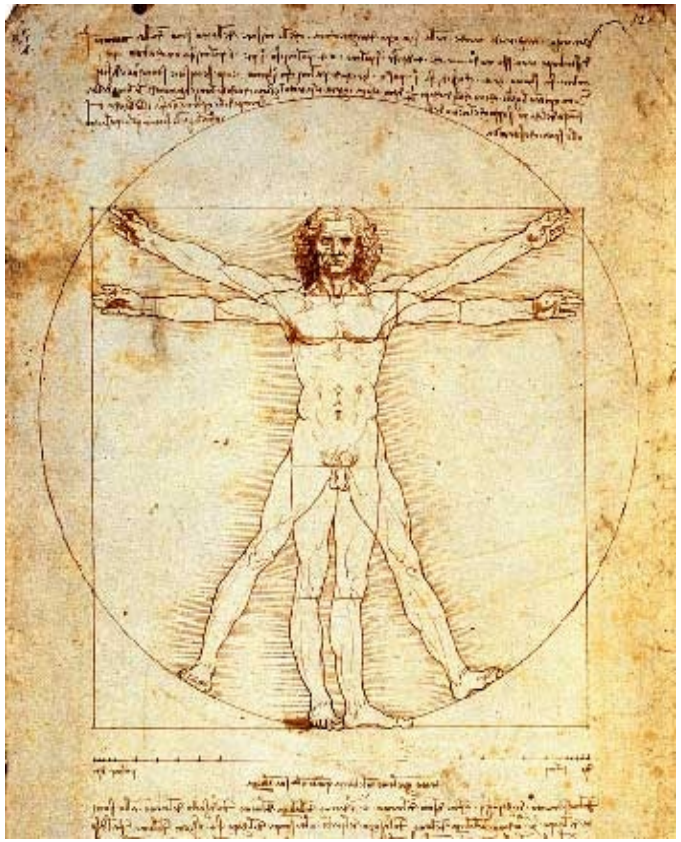



**RESISTANCE TO SELECTED MICROBES (eg A. fumigatus, P. aeruginosa) – REGULATION OF INFLAMMATION and REPAIR – ADAPTIVE IMMUNITY**

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

# 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**

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The NEW ENGLAND JOURNAL of MEDICINE

HUMANITAS UNIVERSITY

ORIGINAL ARTICLE

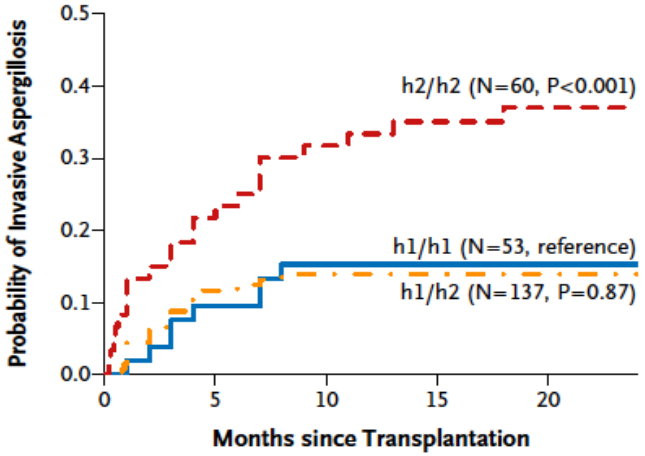
# Genetic PTX3 Deficiency and Aspergillosis in Stem-Cell Transplantation

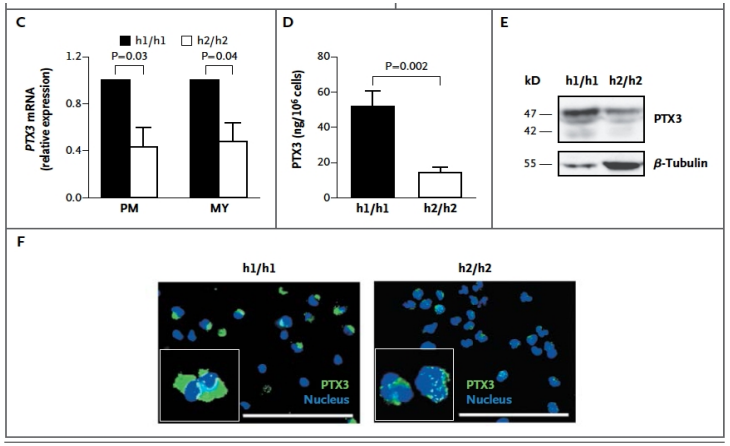
Cristina Cunha, Ph.D., Franco Aversa, M.D., João F. Lacerda, M.D., Ph.D., Alessandro Busca, M.D., Oliver Kurzai, M.D., Matthias Grube, M.D., Jürgen Löffler, Ph.D., Johan A. Maertens, M.D., Ph.D., Alain S. Bell, Ph.D., Antonio Inforzato, Ph.D., Elisa Barbati, Ph.D., Bruno Almeida, Ph.D., Pedro Santos 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**

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




Results confirmed and extended in 1,101 pts in the Swiss Organ Transplantation cohort (Wójtowicz A, et al, Clin Infect 2015), a lung transplantation cohort (Cunha et al 2015), 2,609 HCT pts at FHCR (Fisher et al Blood 2017), 185 chemo/mold pts (Brunel et al Haematologica 2018)

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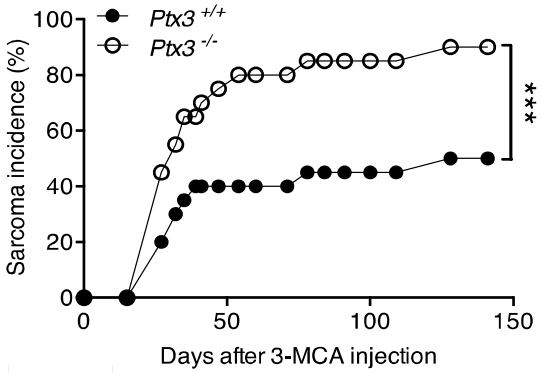
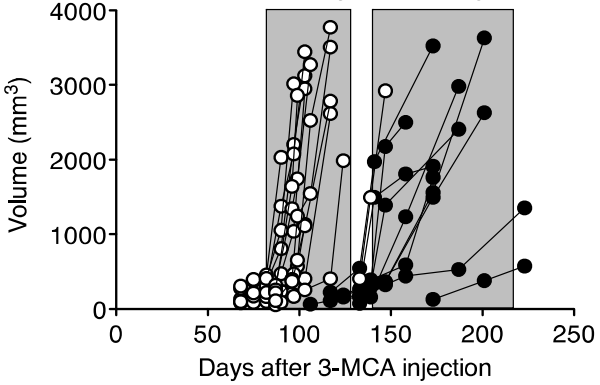
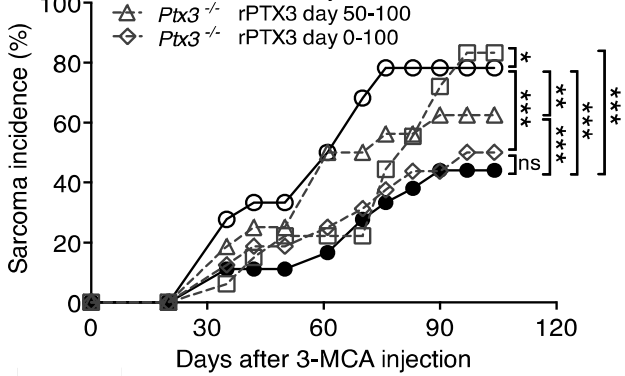
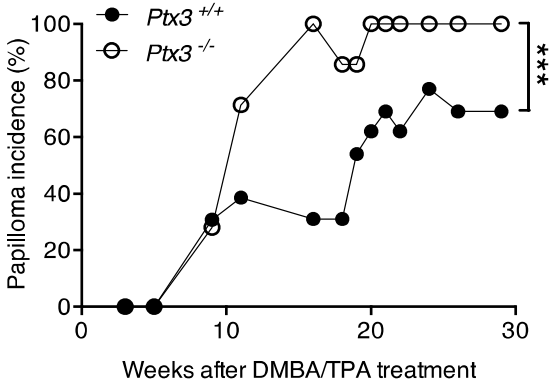
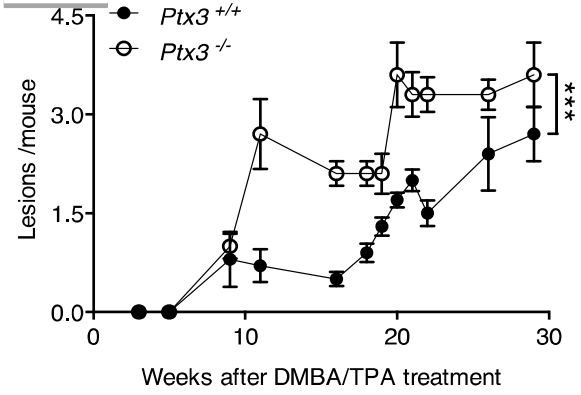
# Increased susceptibility to carcinogenesis of PTX3$^{-/-}$ mice

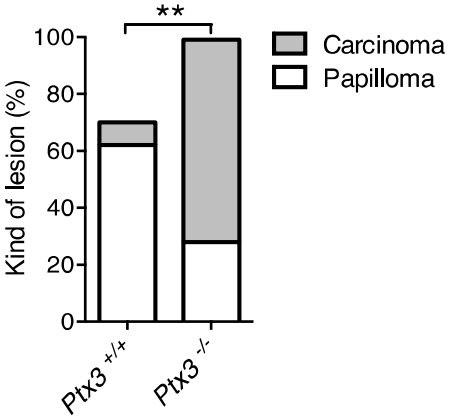



*Bonavita et al. Cell 2015*

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# PTX3 as an extrinsic oncosuppressor in mouse and human cancer

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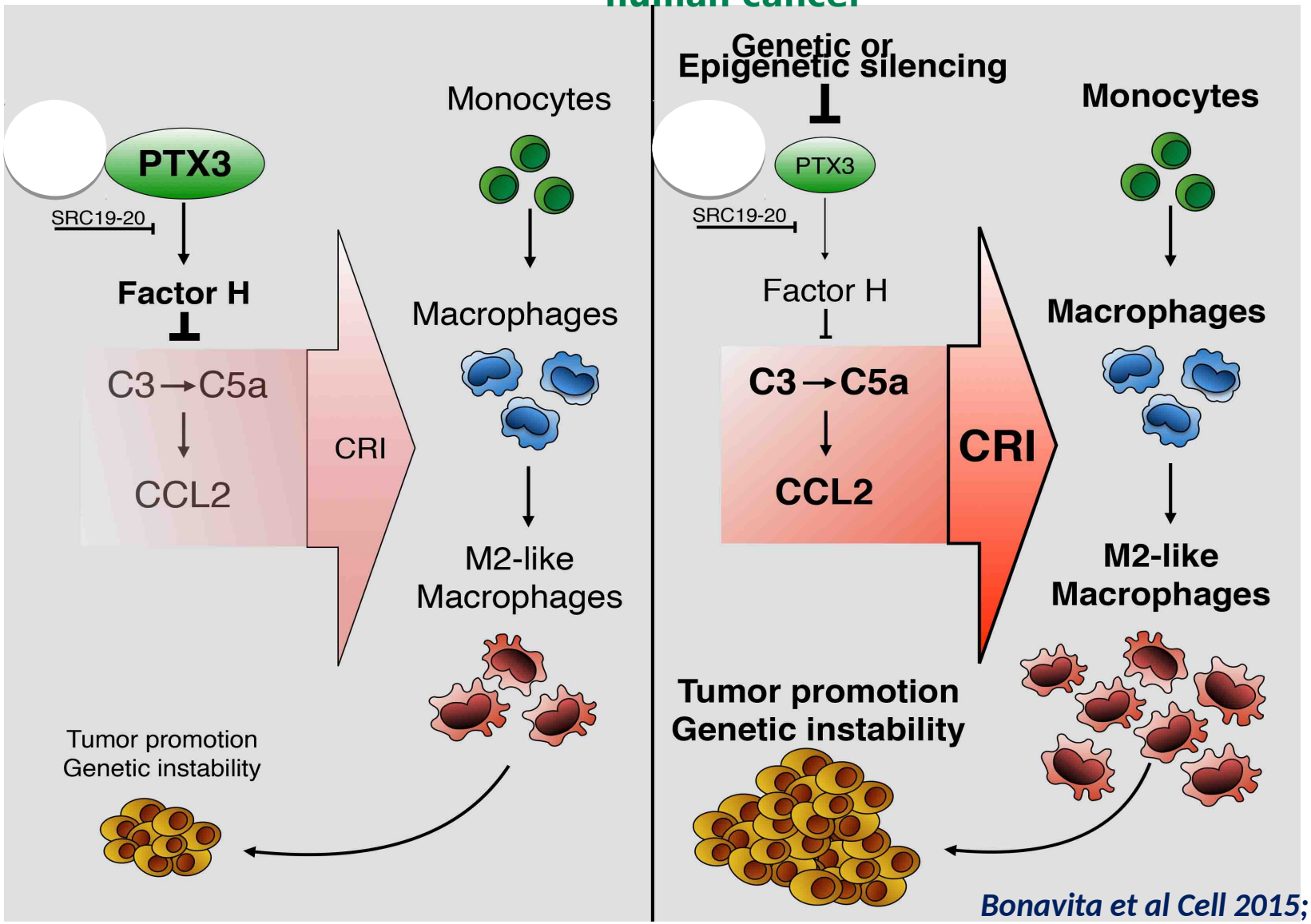


*Bonavita et al Cell 2015; Rubino et al Oncoimmunology 2017; Reis et al Nature Rev Immunol. 2018*

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# C3 deficiency protects against sarcoma tumor growth and metastasis

[transplanted MN/MCA1– sc injection]

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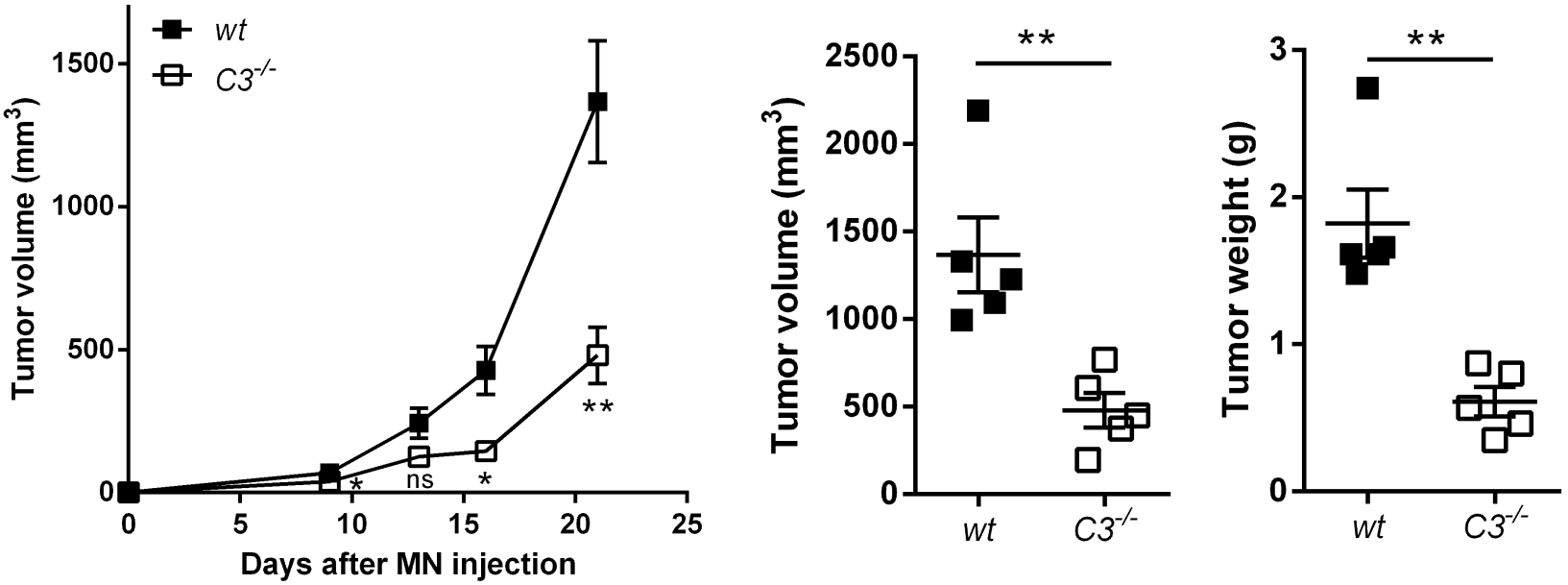


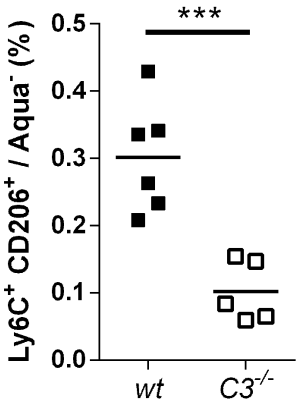

(Magrini et al unpublished)

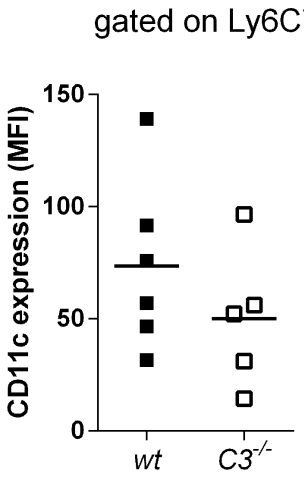
*p < 0.05, **p < 0.01, ns=not significant, t test

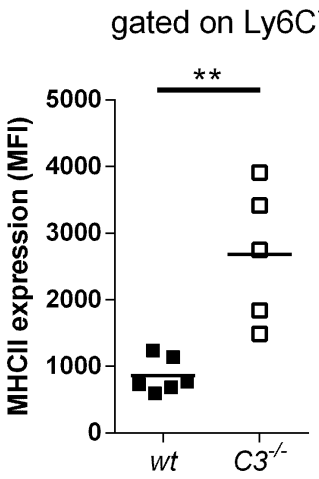
# Macrophage polarization in C3 deficient mice

[trasplantable sarcoma tumor model – im injection]

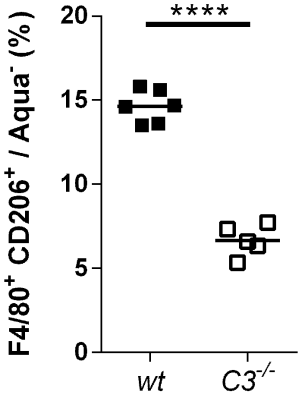
Mono

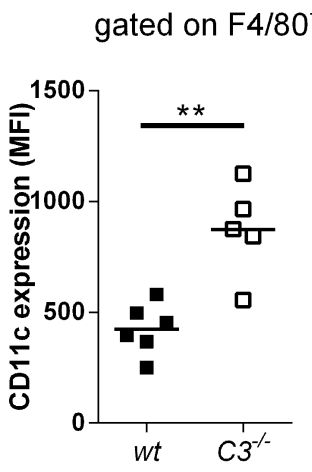


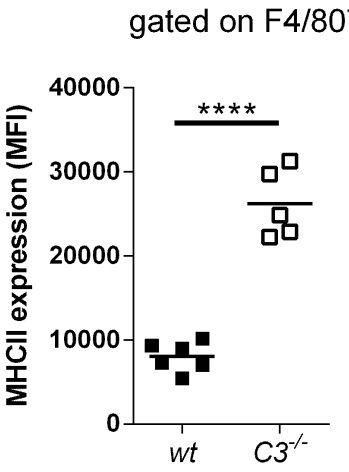




Mφ



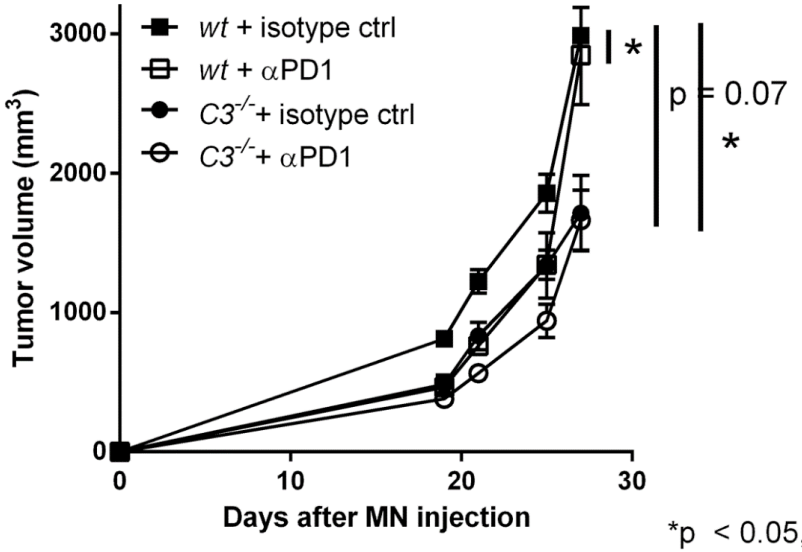




M2-like

M1-like associated molecules

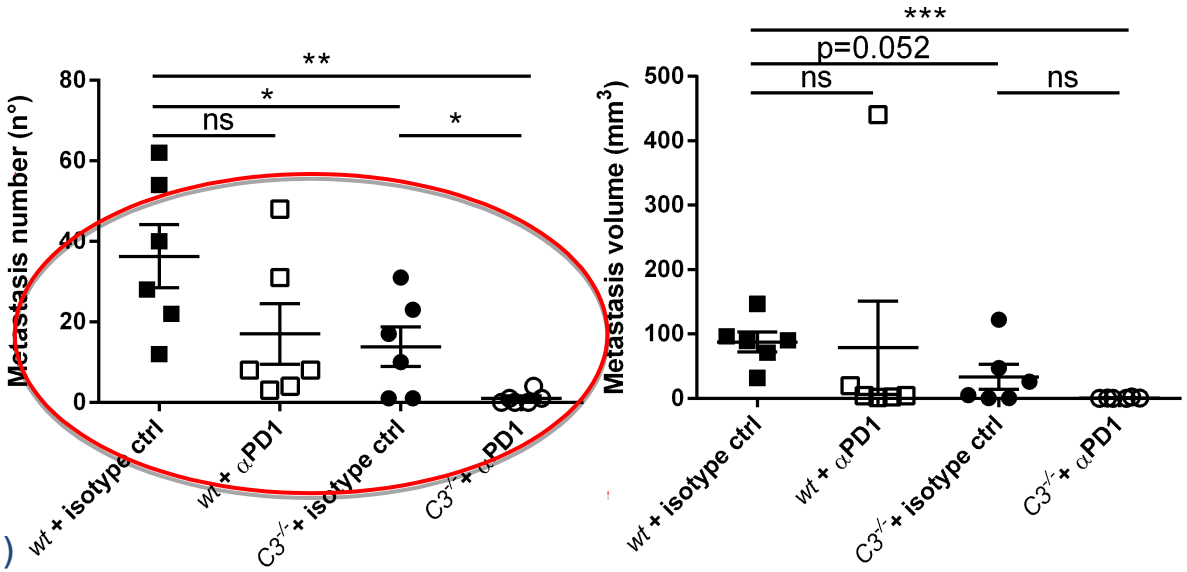
# Increased anti-metastatic activity of anti-PD1 in C3 deficient mice
## [trasplantable sarcoma tumor model – im injection]

1ary tumor




*p < 0.05, paired t test

Lung metastasis




*p < 0.05,**p < 0.01, ***p < 0.001, unpaired t test

(Magrini et al unpublished)

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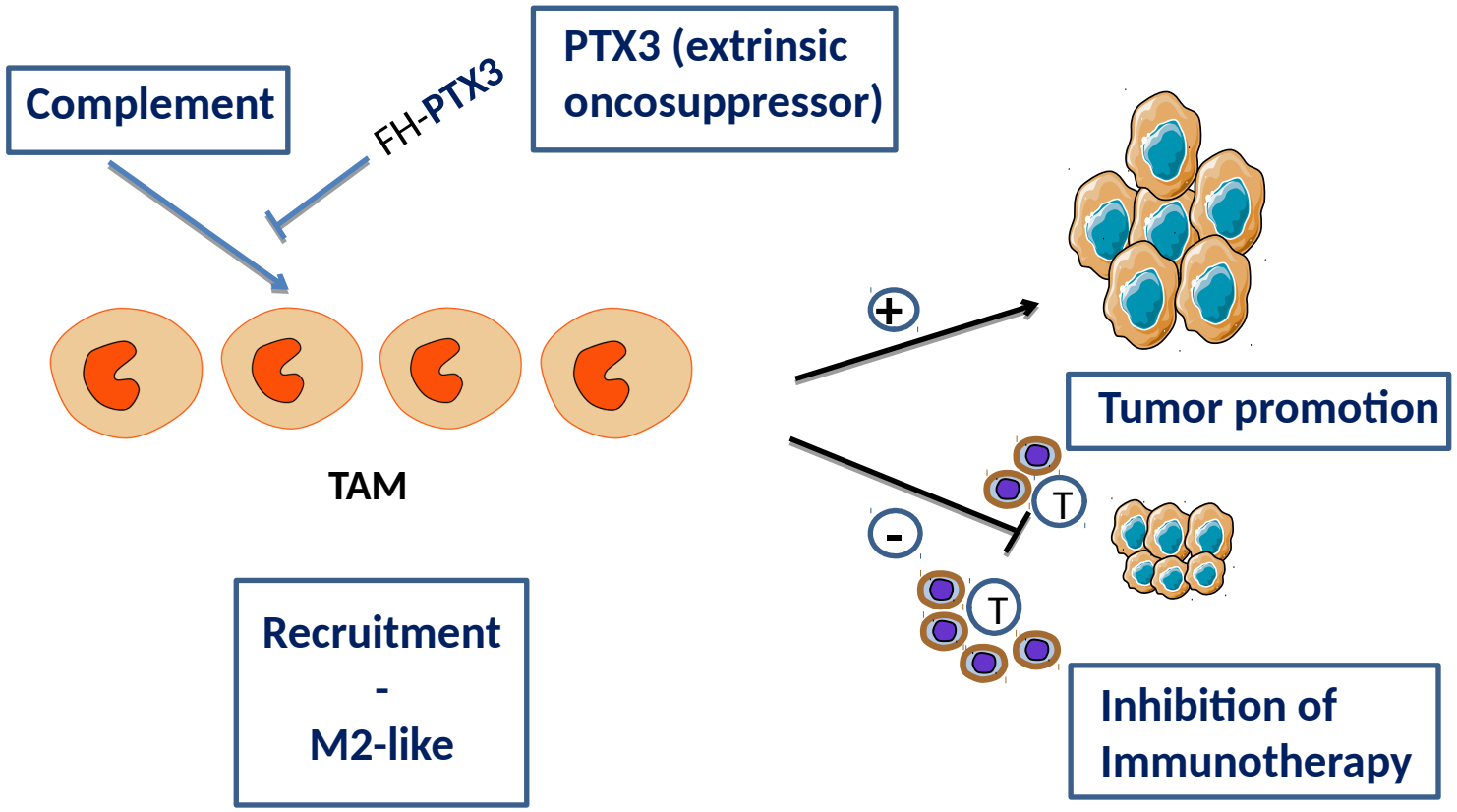
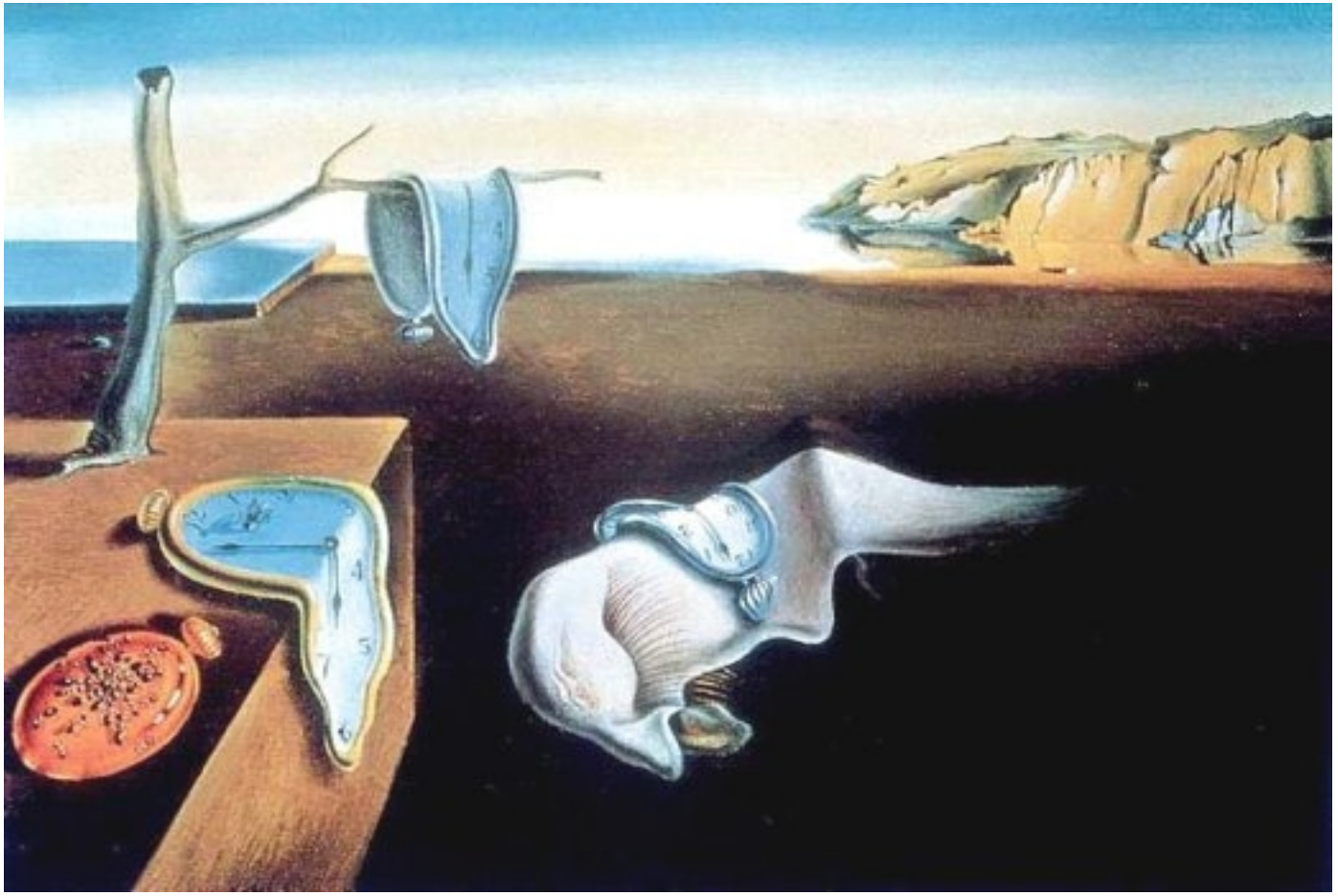
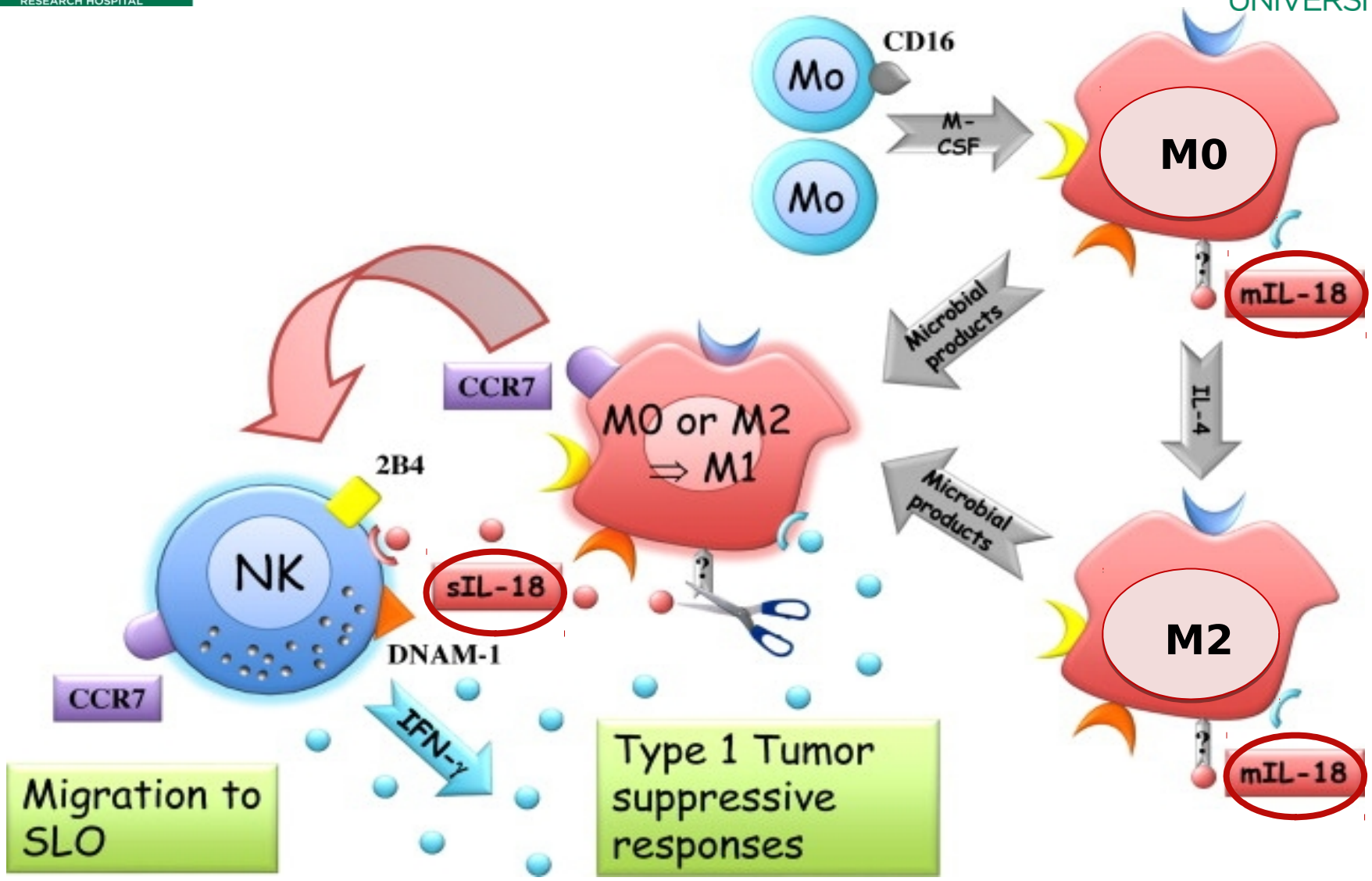
# Complement and PTX3 in 3-MCA carcinogenesis and selected human tumors (e.g. CRC)




*Bonavita et al, Cell, 2015; Magrini et al unpublished; Reis et al, Nature Rev Immunol, 2018*






*Modified from review Bottino C. et al Immunol Lett. 2014; Originals: Bellora et al, PNAS, 2010; Eur J Immul, 2012 and 2014*

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# IL-1R8/TIR8/SIGIRR

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


(for a review on IL-1/IL-1R family: Garlanda, Dinarello and Mantovani, Immunity 2013, Molgora et al Front. Immunol 2016; for IL-37R: Li et al PNAS; Nold-Petri et al Nature Immunol 2016)

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# IL-1R8/TIR8/SIGIRR

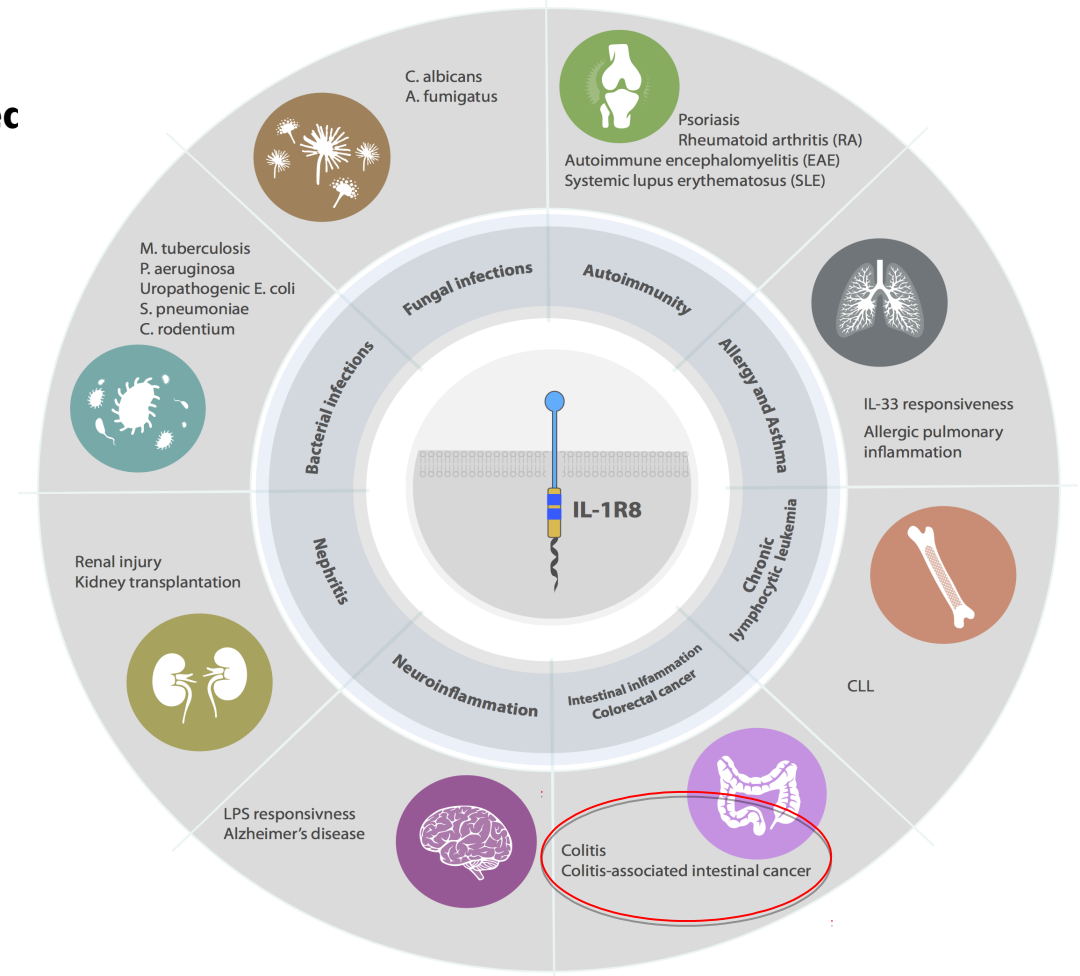
**, a negative regulator balancing amplification of immunity and tissue d**

**IL-1R8 is expressed in:**

- Kidney
- Liver
- Lung
- **Intestinal tract**

Immune cells:

- Lymphocytes
- Monocytes
- DCs
- **Macrophages**
- **NK cells**

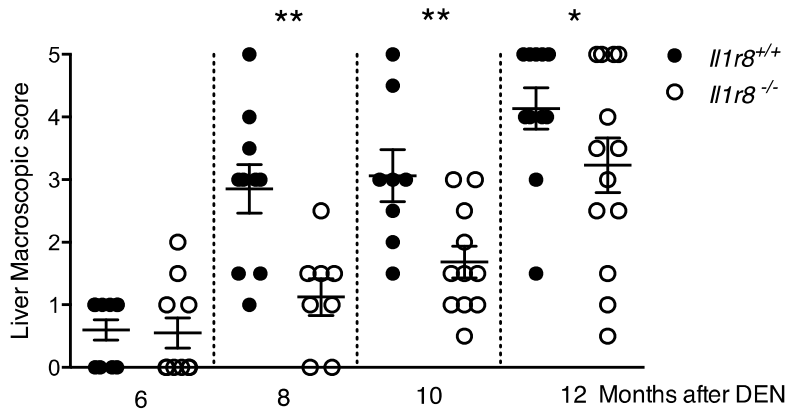



(for review on IL-1/IL-1R family: Garlanda, Dinarello and Mantovani, Immunity 2013; Molgora et al Front Immunol 2016)

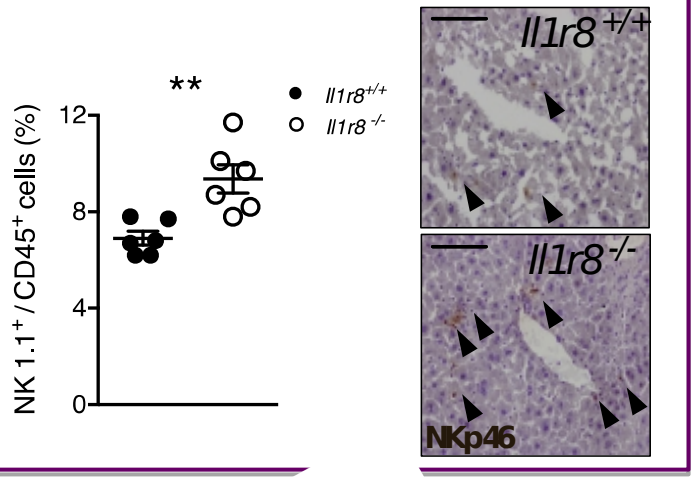
# IL-1R8-deficient mice are protected against **HCC development**

Model of DEN-induced hepatocellular carcinoma (HCC)

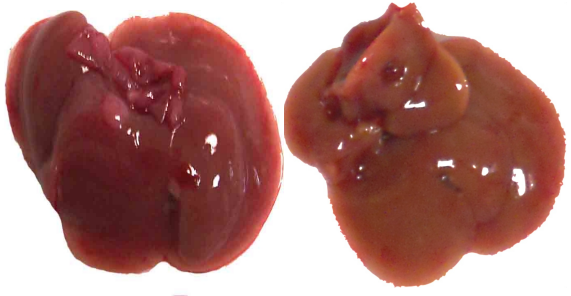
## DEN-induced liver cancerogenesis




## NK cell infiltrate in the liver

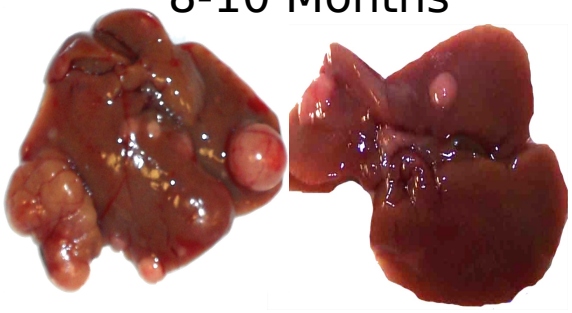



6 Months



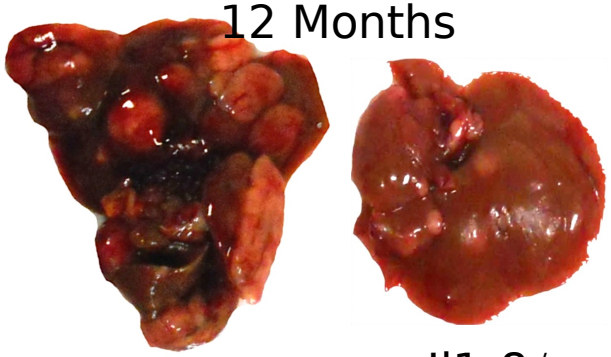
Il1r8$^{+/+}$ Il1r8$^{-/-}$

8-10 Months



Il1r8$^{+/+}$ Il1r8$^{-/-}$

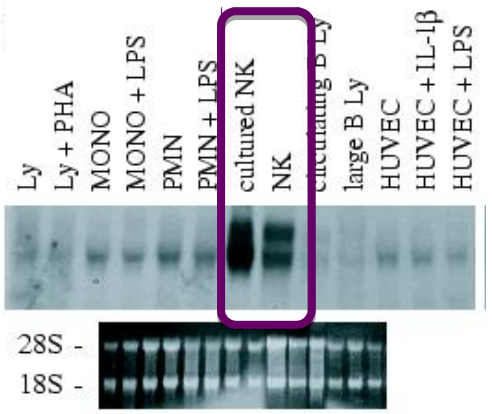
12 Months



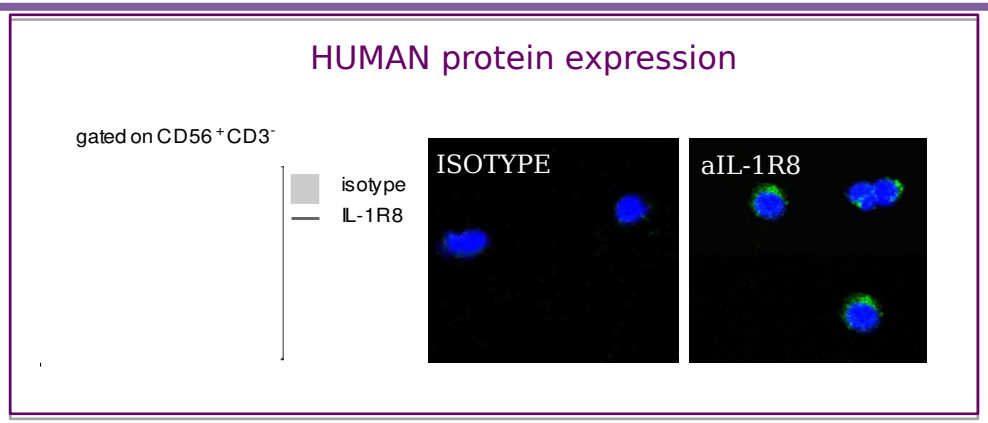
Il1r8$^{+/+}$ Il1r8$^{-/-}$

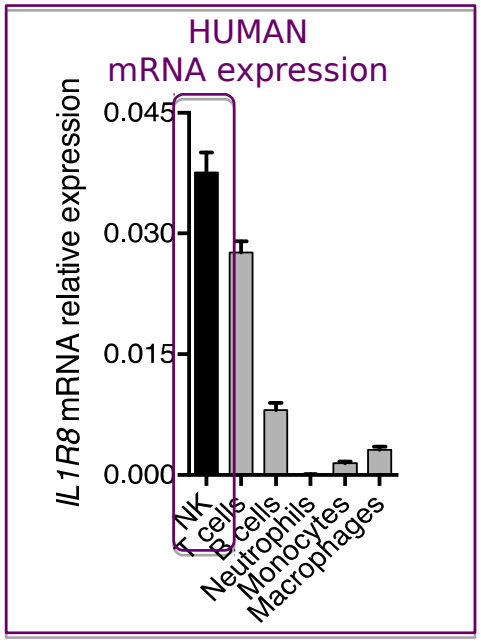
(Molgora, Bonavita et al, Nature 2017)

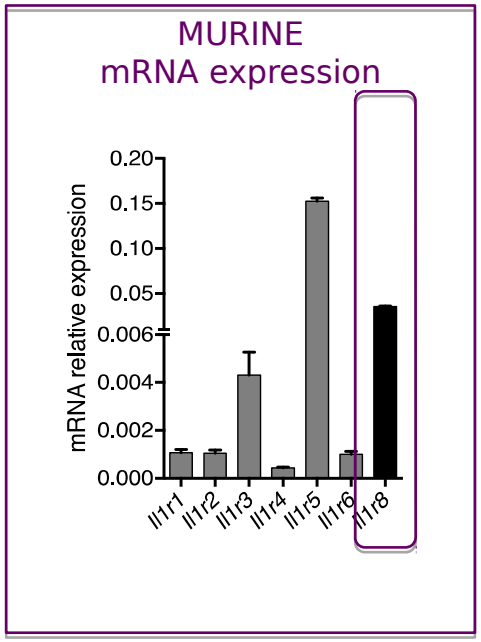
# NK cells express high levels of IL-1R8




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

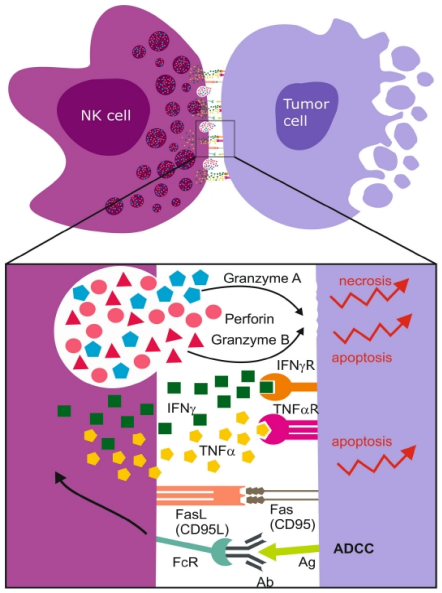


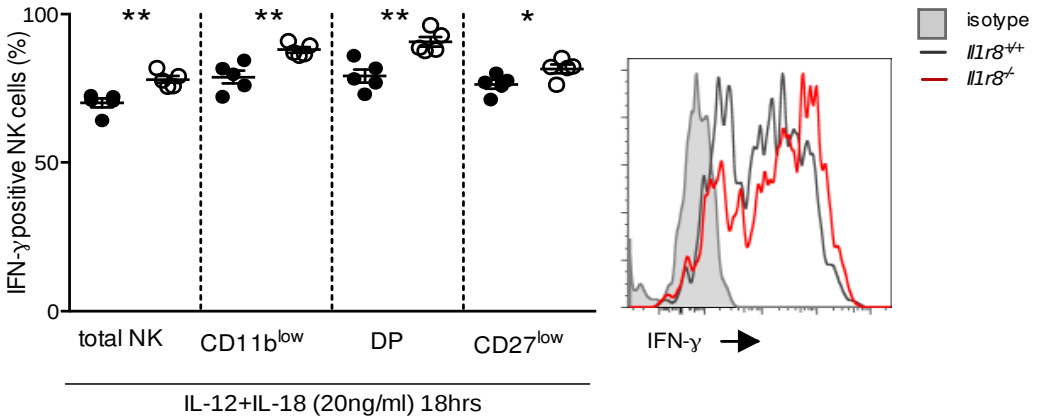

**(Molgora, Bonavita et al Nature 2017)**

# *IL-1R8*-deficiency is associated with higher **IFN-γ production and cytotoxic potential**

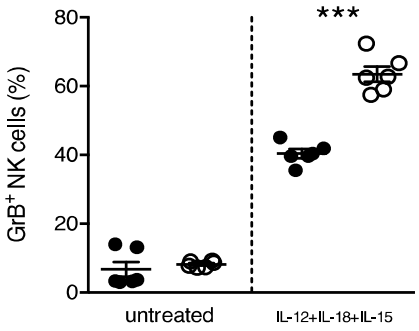



DNAM-1, Ly49H, NKG2D

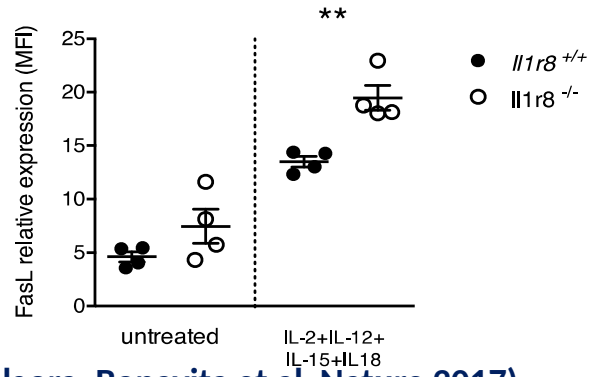
## IFN-γ




## Granzyme B

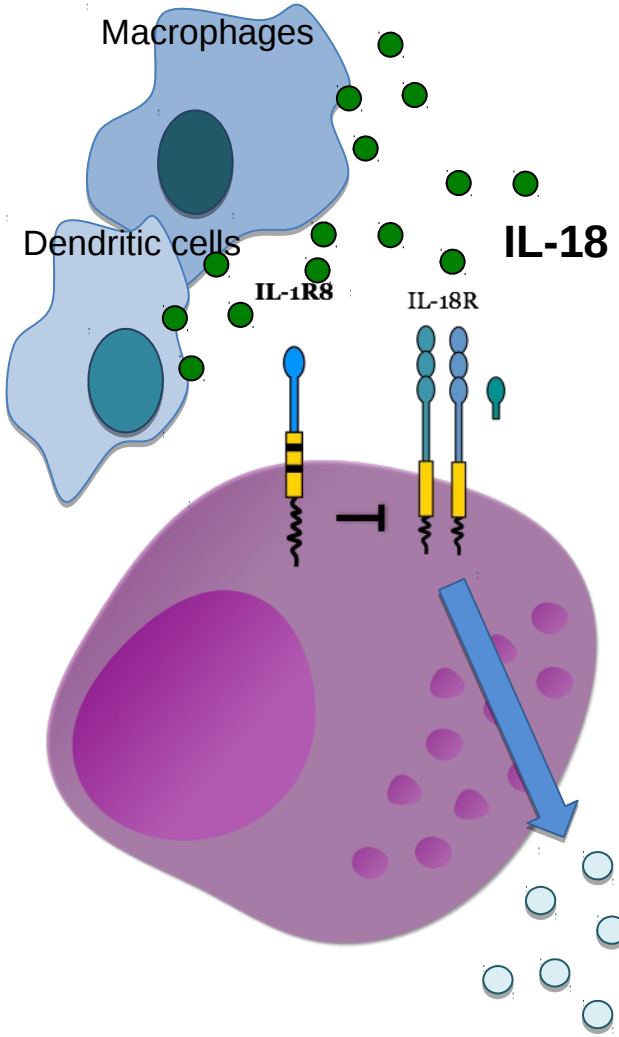


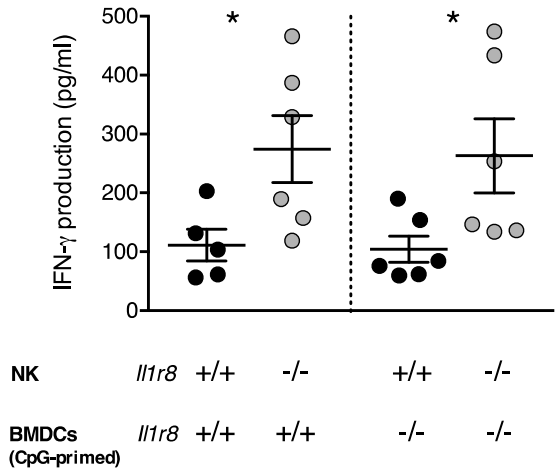

## Fas Ligand

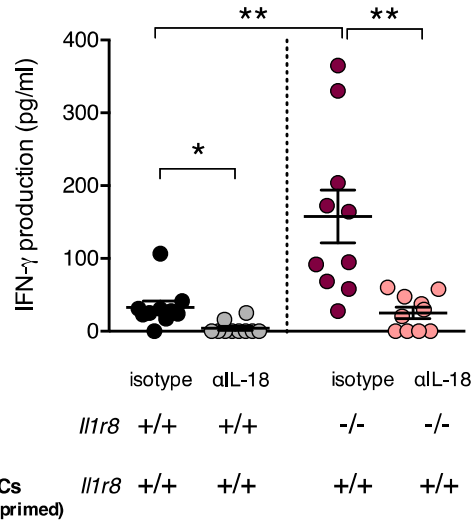



**(Molgora, Bonavita et al Nature 2017)**

# IL-1R8 modulates IL-18 dependent NK cell activation

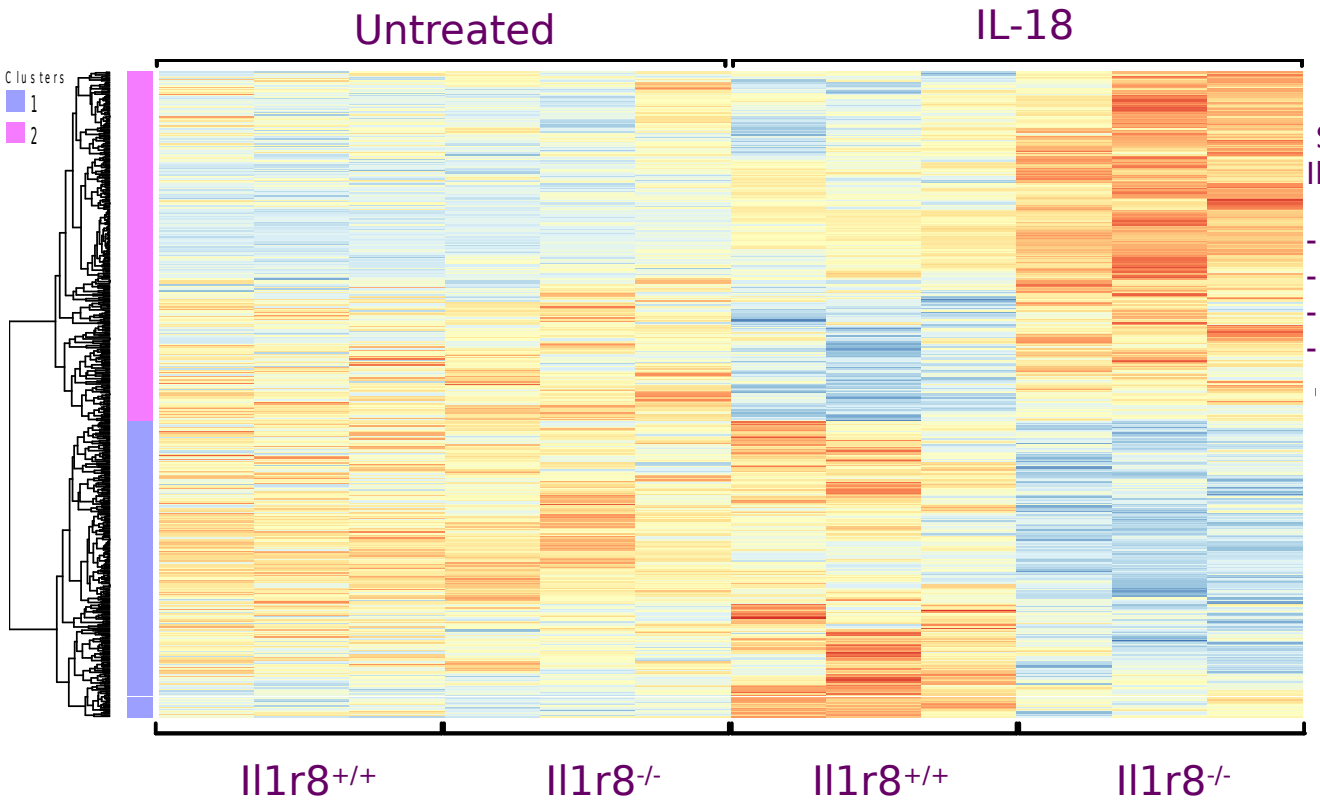



**(Molgora, Bonavita et al, Nature 2017)**

# Responsiveness to IL-18 was dramatically different in IL-1R8$^{-/-}$ NK cells (RNAseq)



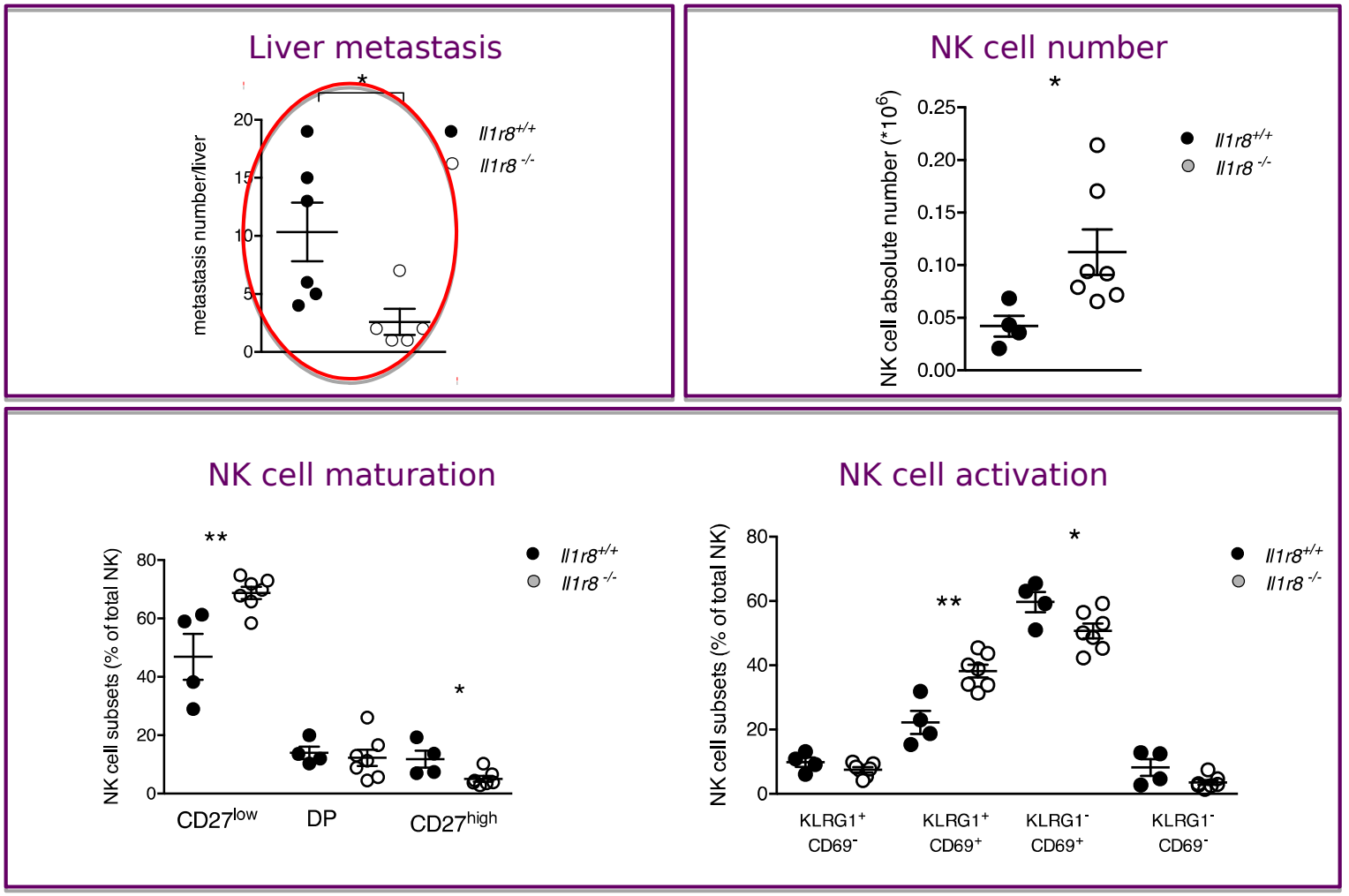

Some enriched pathways in Il1r8$^{-/-}$ NK:

- p38 MAPK , MAPK
- Leukocyte degranulation
- Cytokine chemokine production
- ICAM1, CD69.....

**(Molgora, Bonavita et al, Nature in press)**

# IL-1R8-deficiency significantly reduced colorectal cancer-derived **liver metastasis**

Model of colon carcinoma (MC38 cell line)-derived liver metastasis

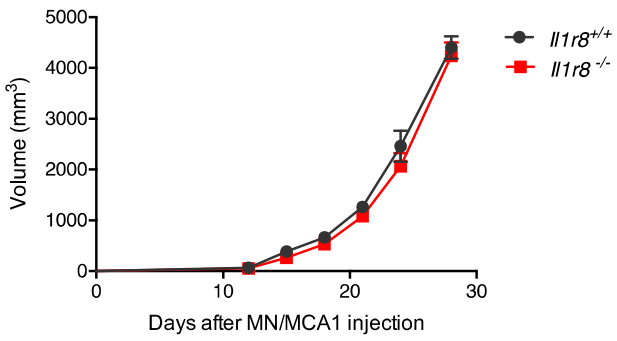



**(Molgora, Bonavita et al, Nature 2017)**

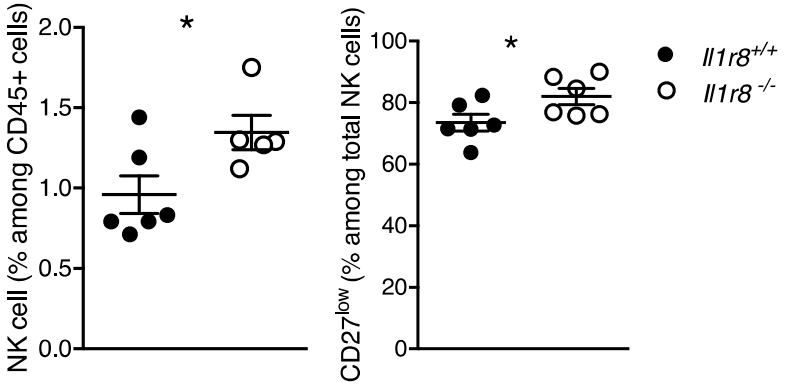
# IL-1R8-deficiency significantly reduced sarcoma-derived **lung metastasis**

Model of MCA-derived sarcoma metastasis

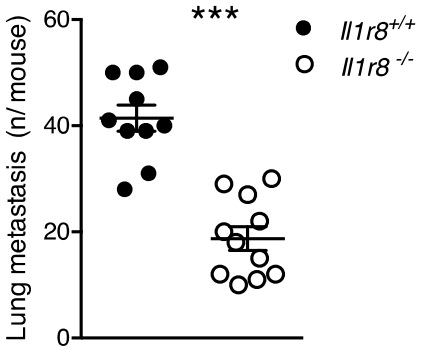
## Primary tumor



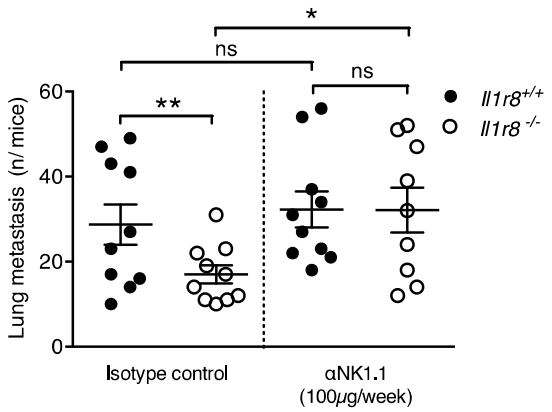

## NK cells in the lung




## Lung metastasis




## Depletion of NK cells




**(Molgora, Bonavita et al, Nature 2017)**

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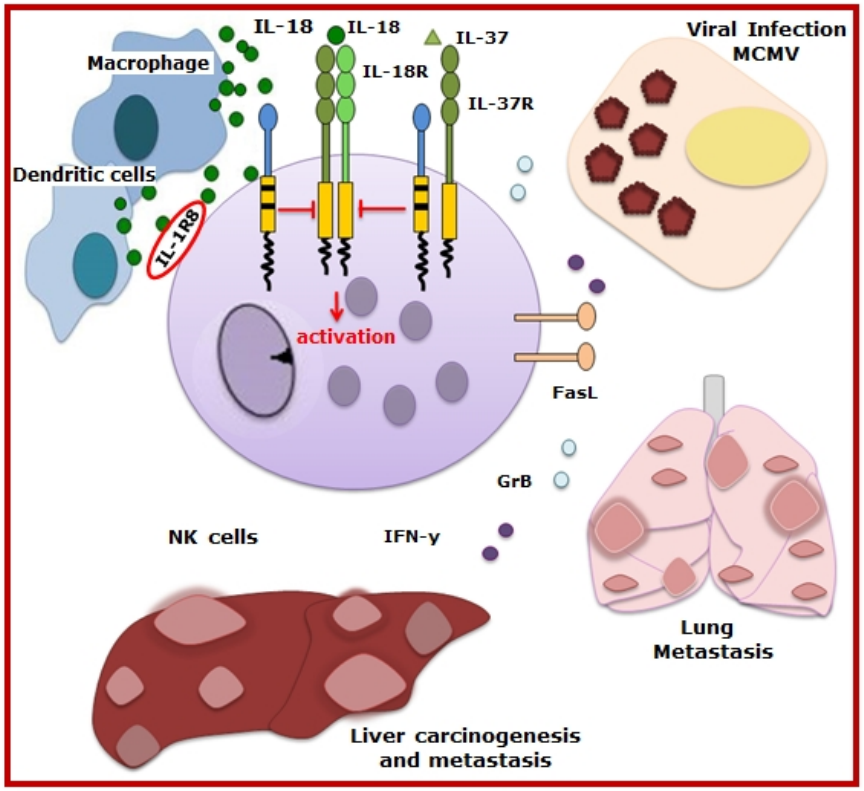
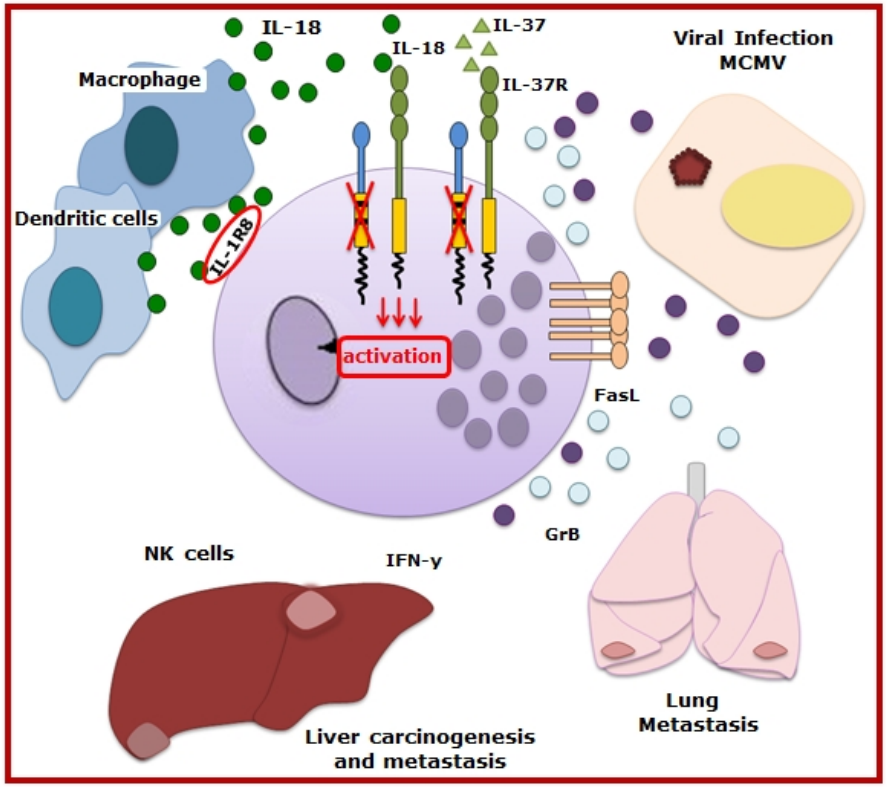
# IL-1R8 AS A KEY REGULATOR (CHECKPOINT) OF NK CELL DIFFERENTIATION AND FUNCTION

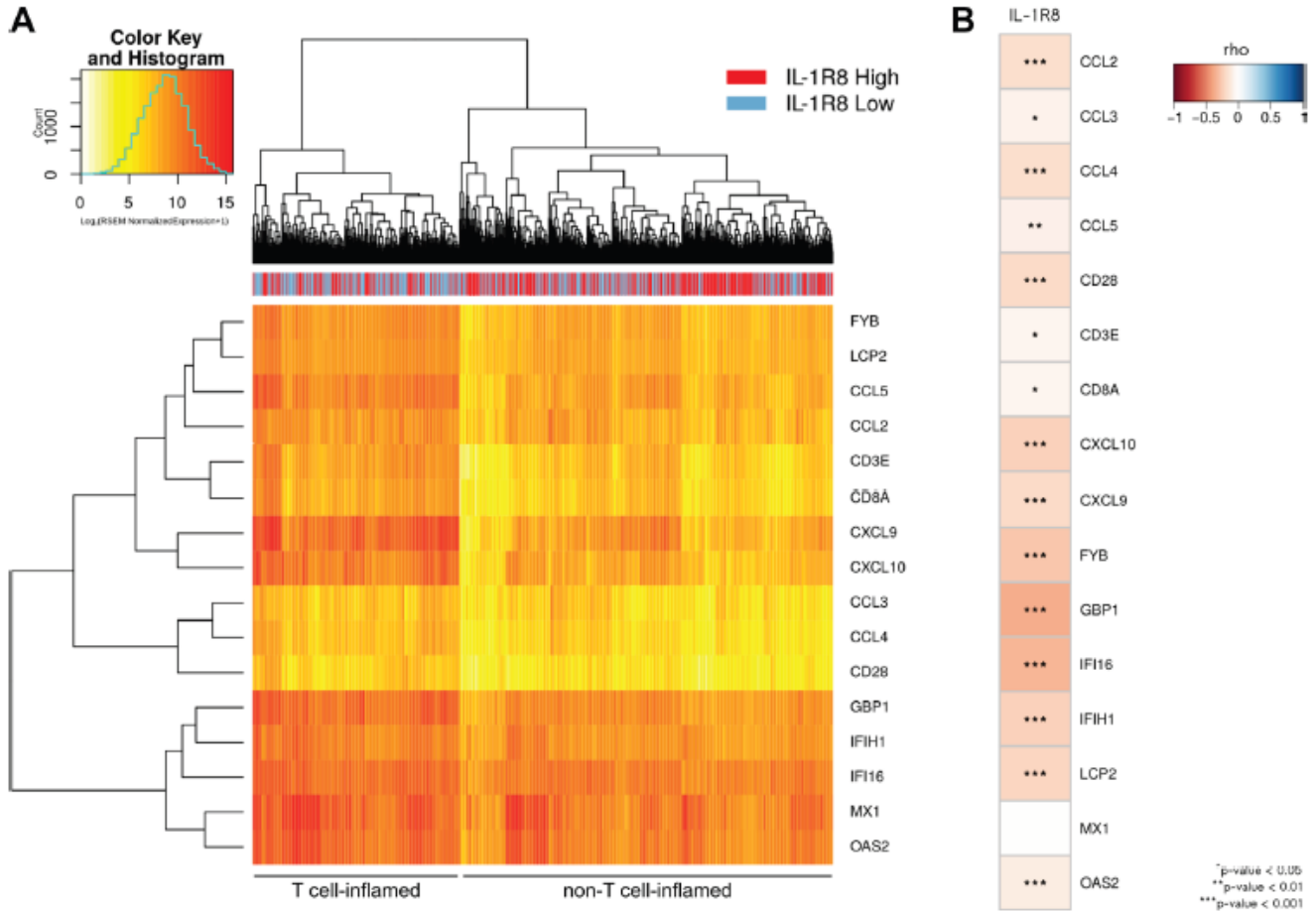



*See also Serhan…..Miller, Cancer Immunol Res, 2018; Treg/IL-37- IL-1R8/ NK*

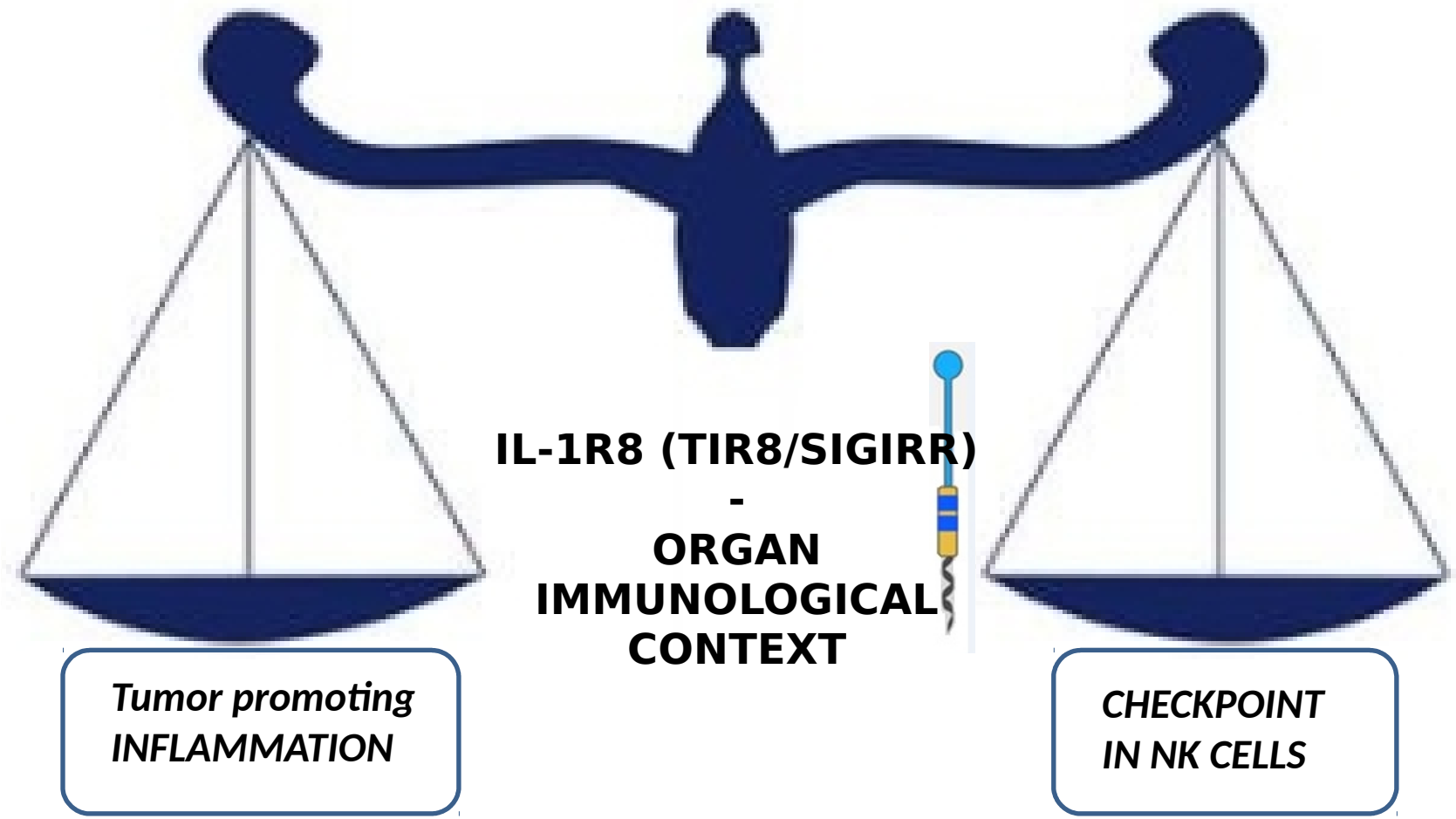
*Molgora, Bonavita et al, Nature, 2017*

## High IL-1R8 expression is associated with a non-T/NK cell inflamed molecular signature in primary breast tumors




*Campesato …..Camargo. Oncotarget 2017*

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




**UNLEASHED NK CELLS CAN MEDIATE RESISTANCE AGAINST SOLID TUMORS AT NK RICH ANATOMICAL SITES** (Molgora, Bonavita et al Nature 2017)

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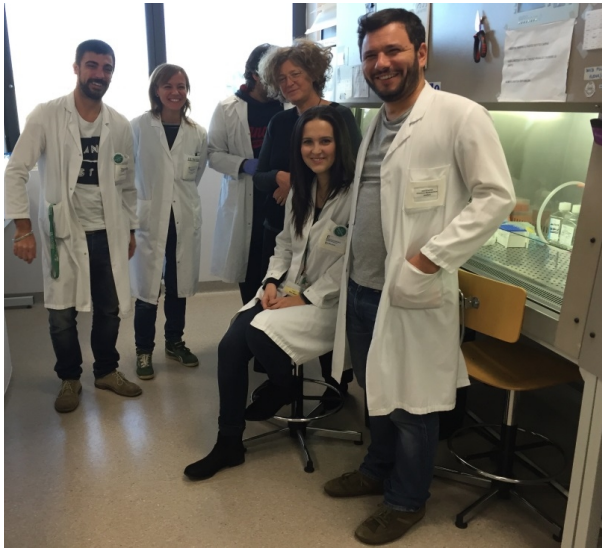

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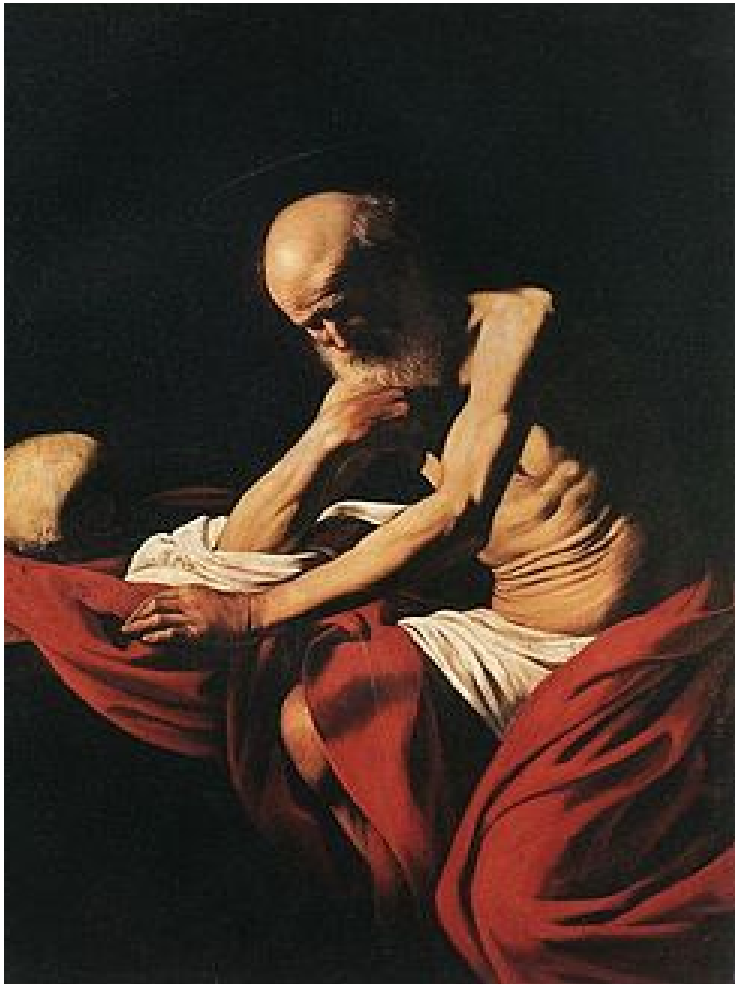
# San Gerolamo in meditazione



***Michelangelo Merisi detto il Caravaggio***

***Museo del Monasterio de Santa Maria, Montserrat, 1605 circa***

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