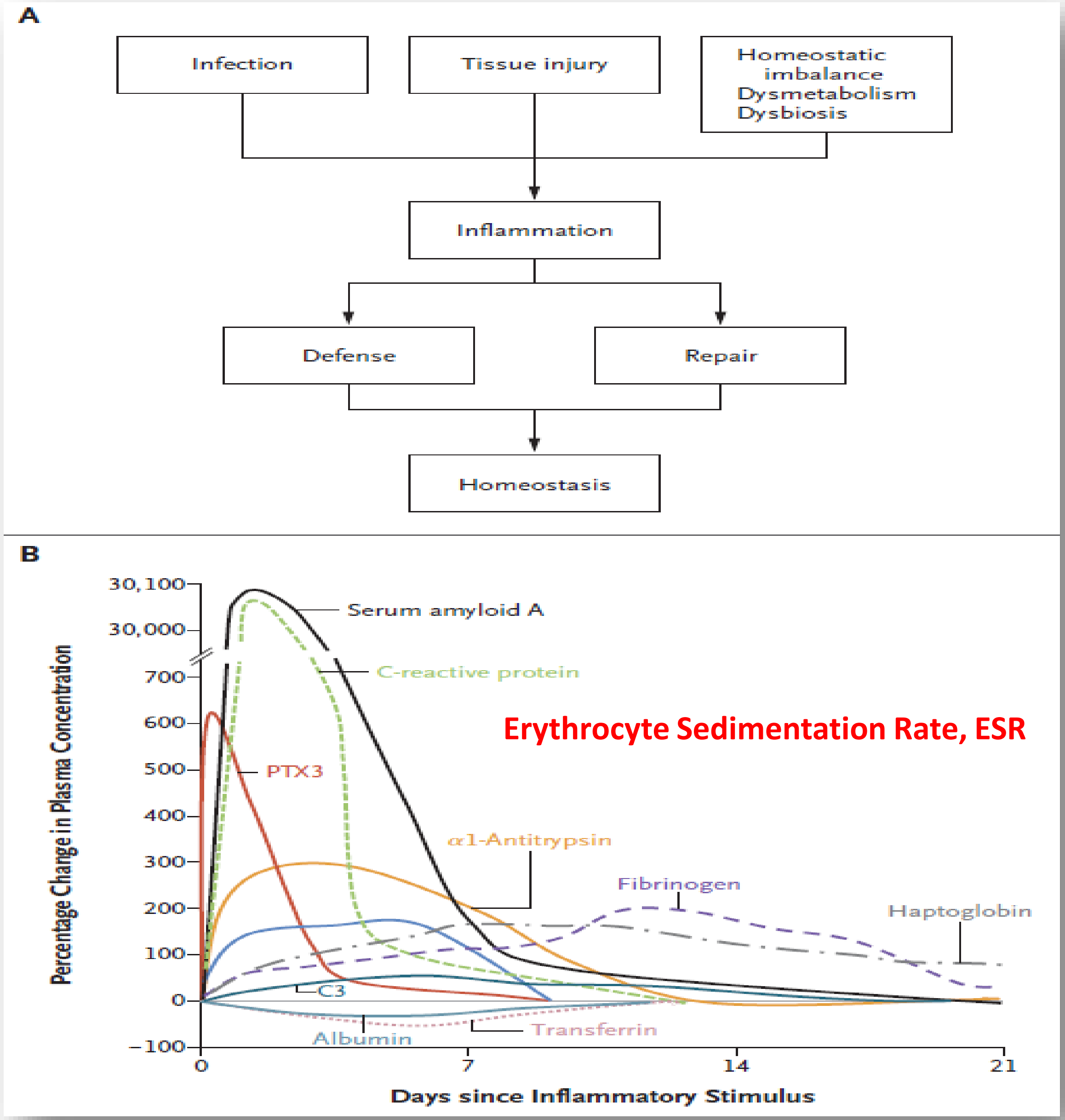
Disclosures

I bari

Michelangelo Merisi da Caravaggio, 1594:
I bari, cardsharps

- Inventor of patents related to PTX3 and other innate immunity molecules
- Royalties on IP and reagents
- Advisory Boards, lecturing, consultancy (Novartis, Roche, Ventana, Pfizer; Pierre Fabre, Verily, Abbvie, Compugen, Macrophage Therapeutics, Astra Zeneca, Biovelocita, BG Fund, Third Rock, Verseau, Myeloid Therapeutics; Kupando; Moderna; Imcheck; Montis; Hengenix, Kisoji, Hemera)

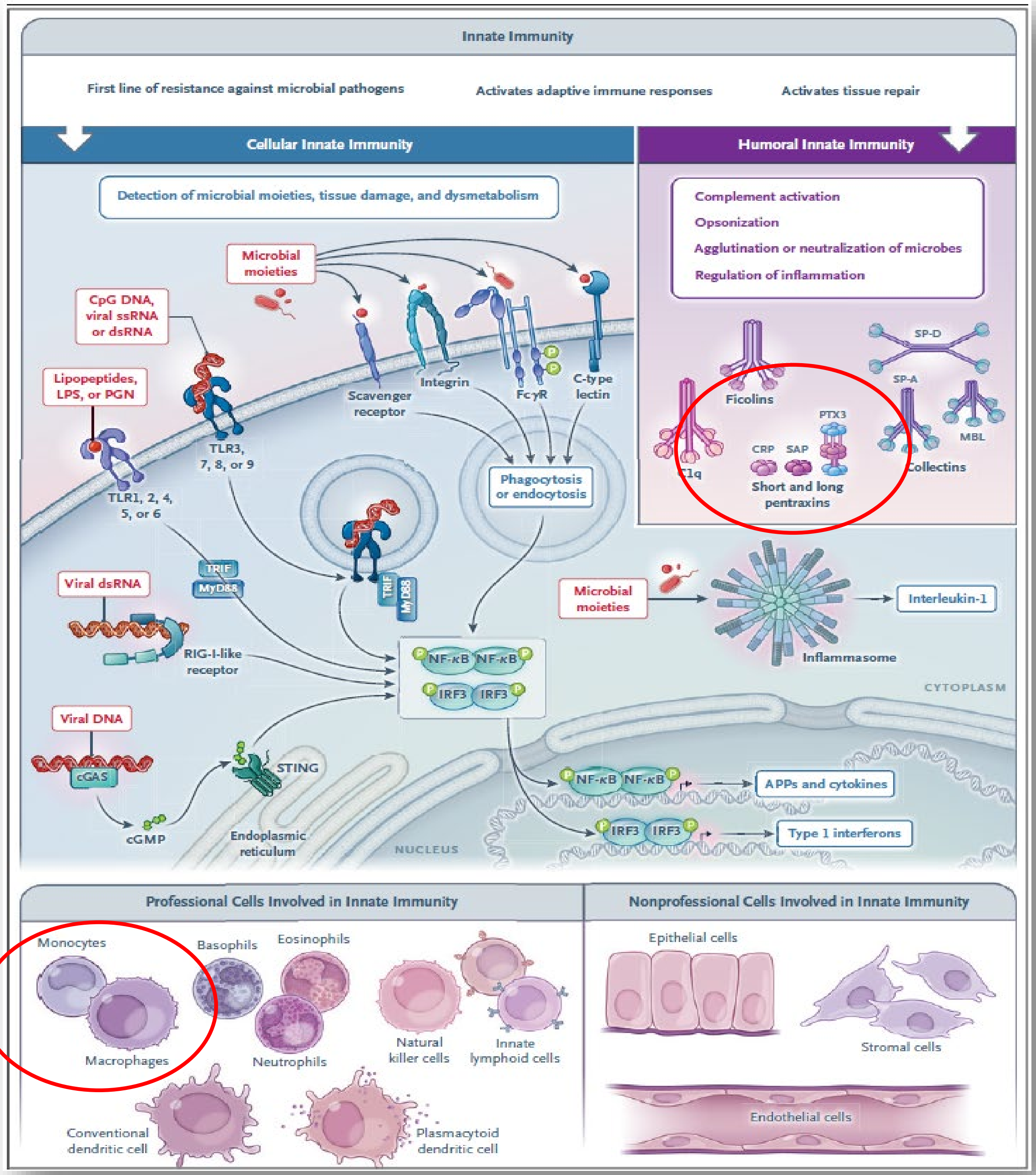
Role of Inflammation and Changes in the Circulation of Acute-Phase Proteins



Erythrocyte Sedimentation Rate, ESR

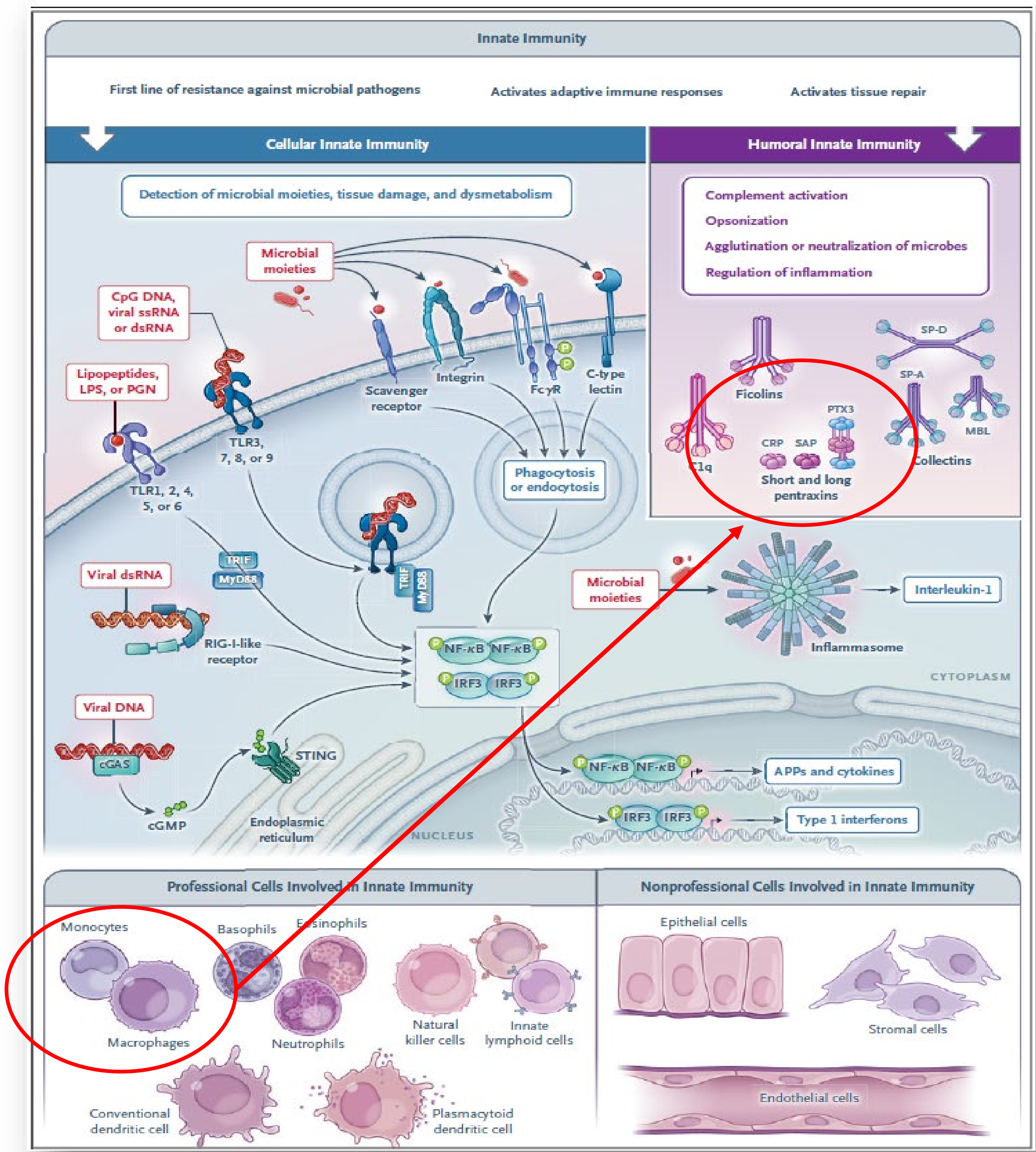
(Mantovani and Garlanda, New England J. Med. 2023)

Innate Immunity — a Cellular Arm and a Humoral Arm



(Mantovani and Garlanda, New England J. Med. 2023)

Innate Immunity — a Cellular Arm and a Humoral Arm



(Mantovani and Garlanda, New England J. Med. 2023)

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The Cytokine Cascade and Cellular Sources and Functions of Acute-Phase Proteins

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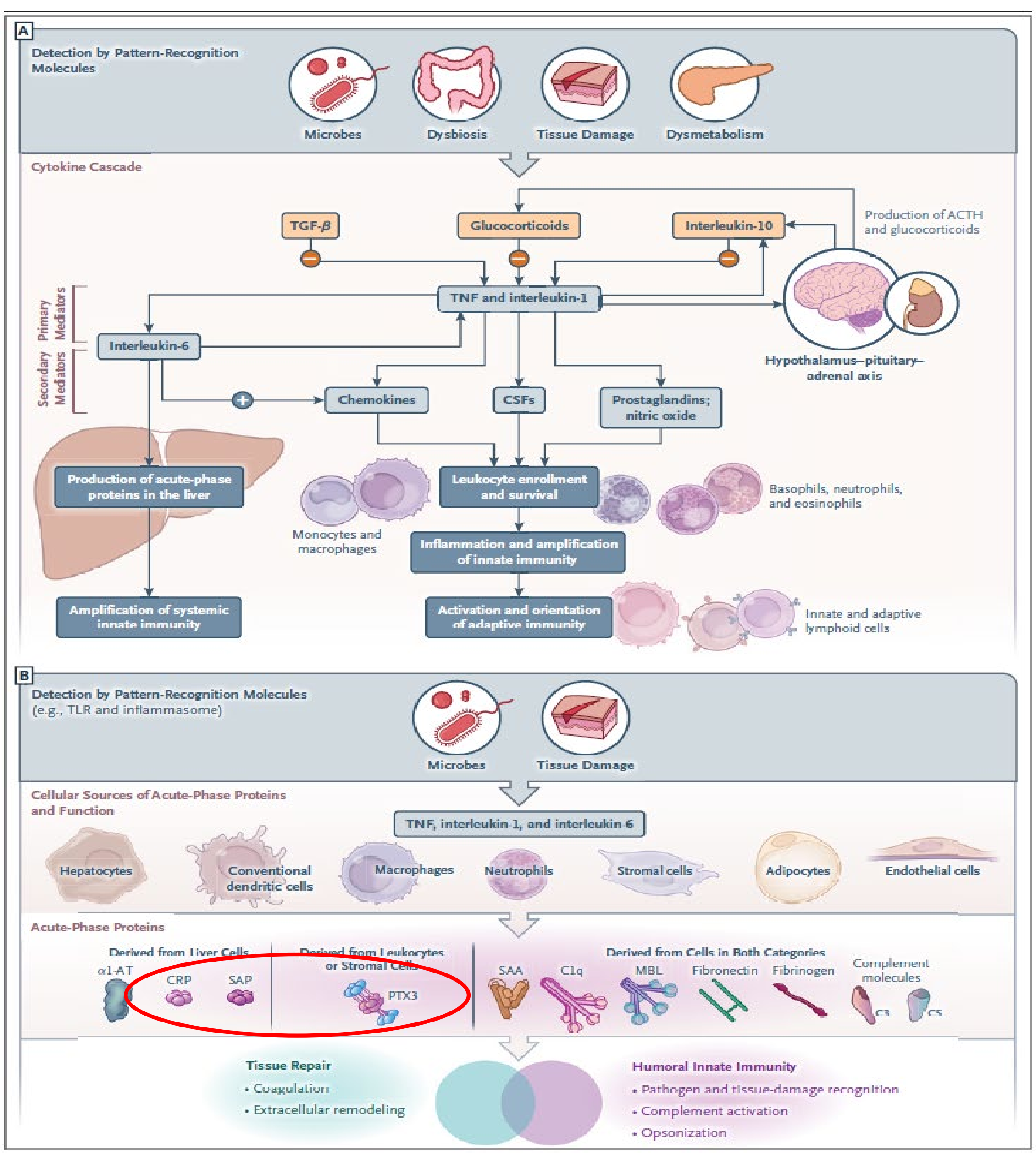
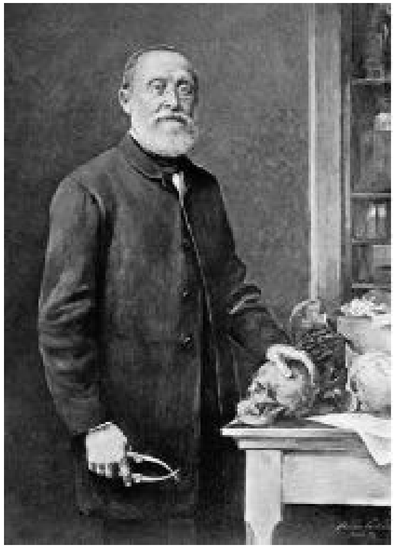


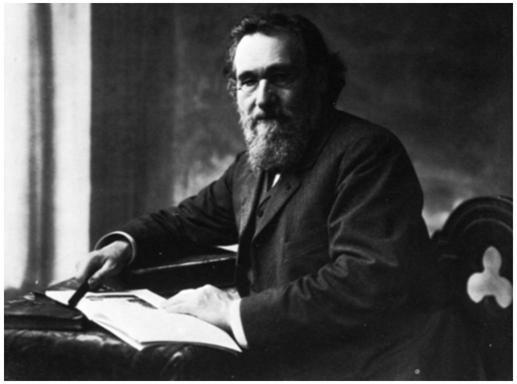
(Mantovani and Garlanda, New England J. Med. 2023)

INFLAMMATION, MACROPHAGES AND CANCER

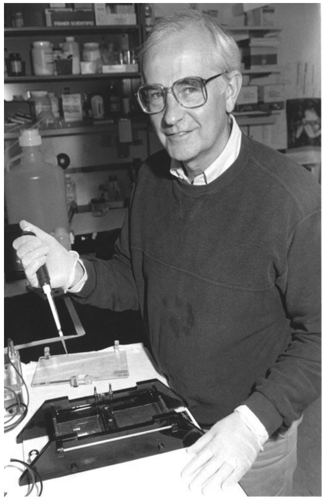


RUDOLF LUDWIG KARL VIRCHOW (1821-1902)

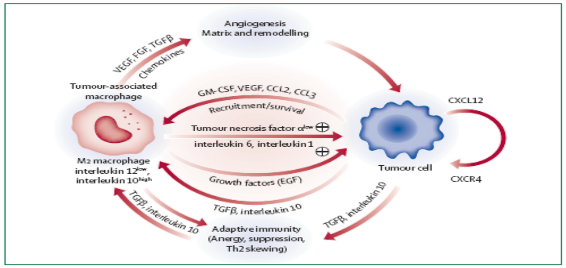
Balkwill and Mantovani, Lancet 2001



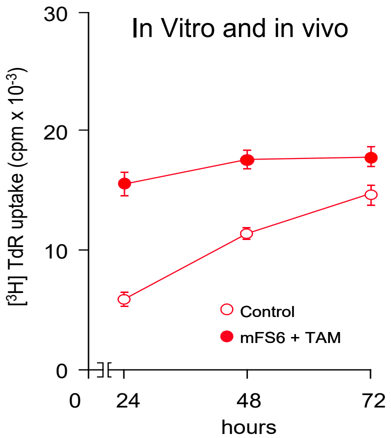
Ilya Mechnikov (1845-1916)
The Nobel Prize in Physiology and Medicine
1908



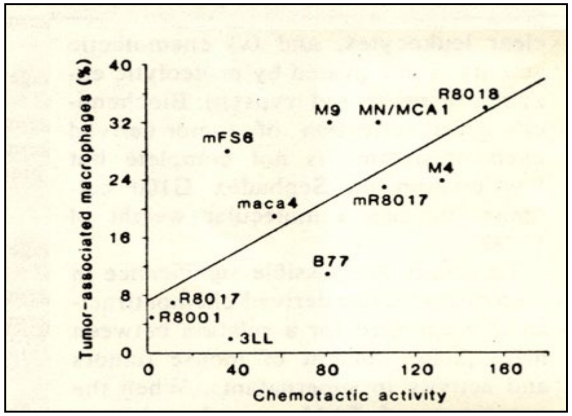
(TAM: Robert Evans, Transplantation, 1972; Evans and Alexander, Nature, 1970)



(Mantovani et al. Lancet 2008; Nature 2008)



(Mantovani A. 1978)



(Bottazzi et al Science 1983)

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M2-like

M1

M1-like

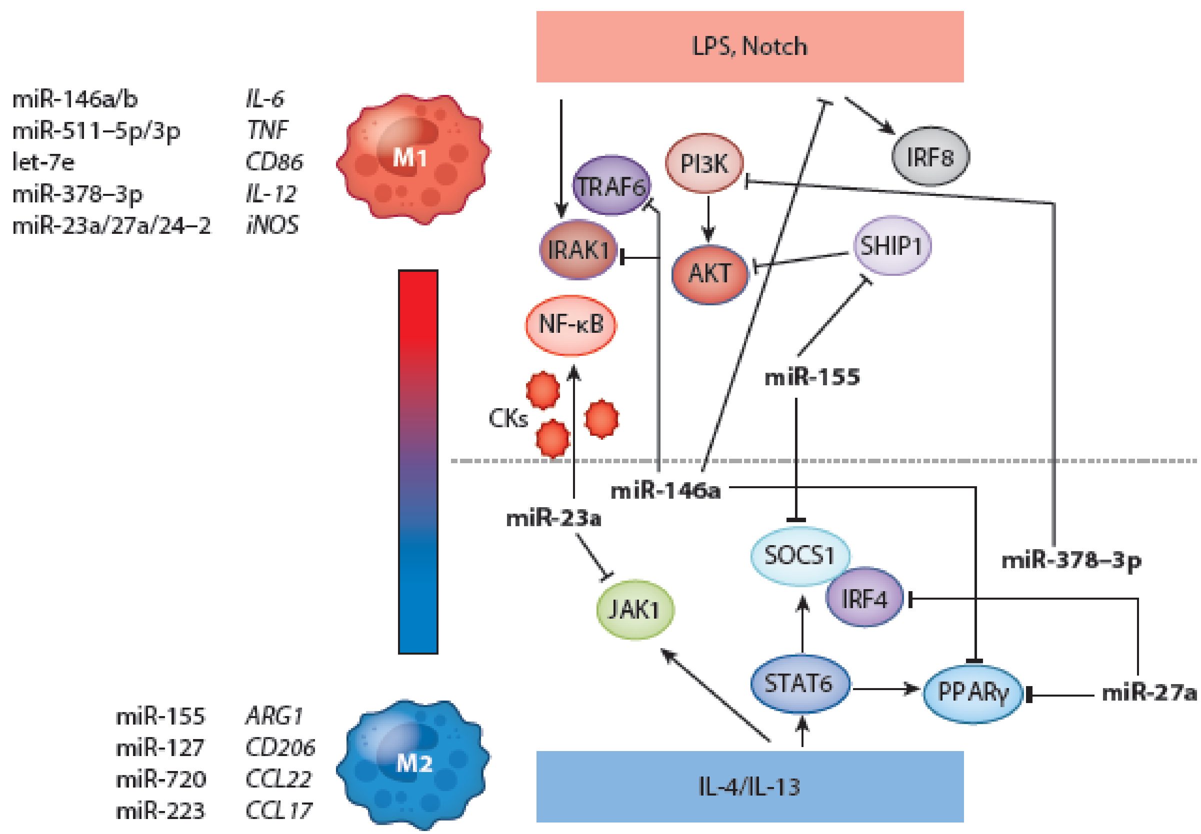
M2

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

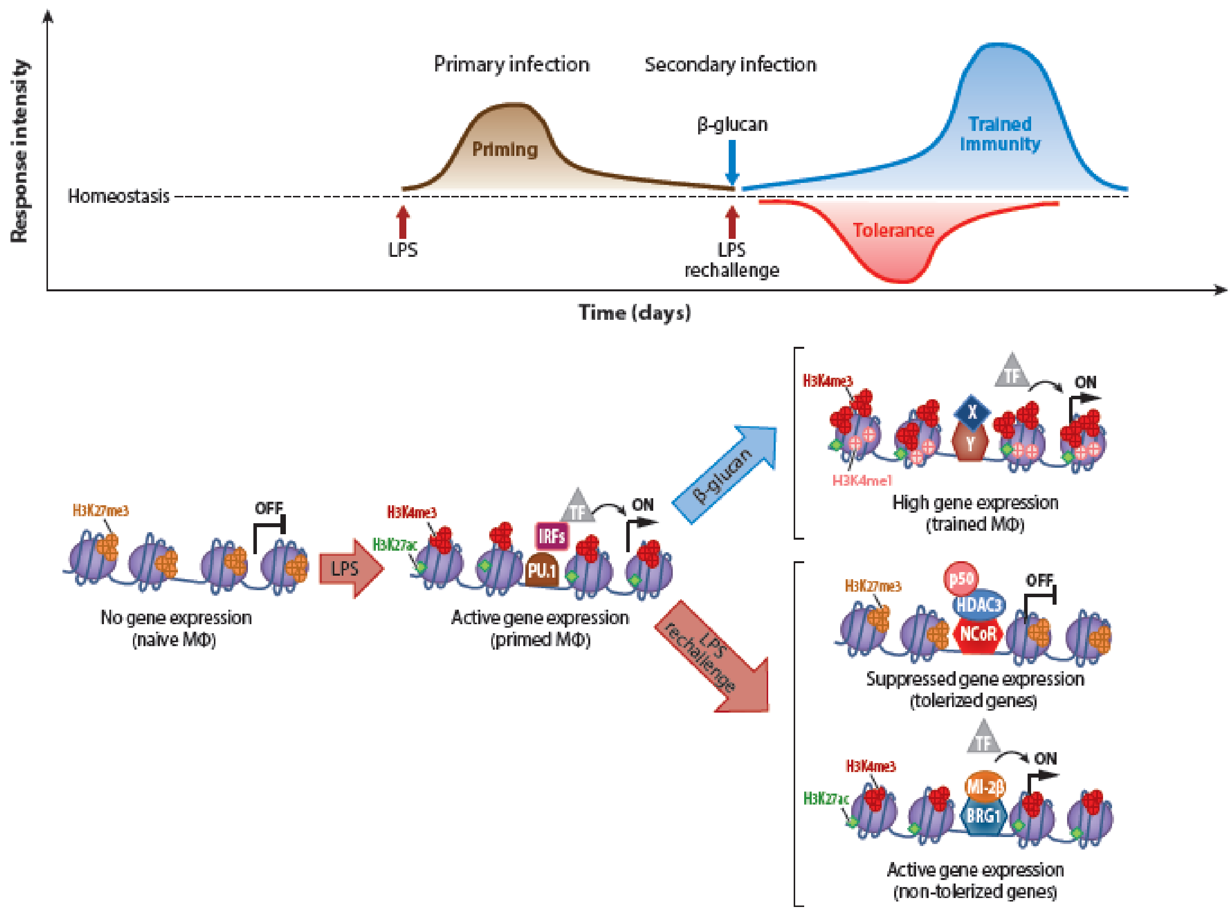
(Selected reviews: Sica and Mantovani J Clin Inv 2012; Biswas and Mantovani, Nature Immunol 2010; Murray et al Immunity 2014; Mantovani and Allavena J Exp Med 2015; Mantovani Nature Immmunol 2016; Locati et al, Annu. Rev. Pathol 2020)

MOLECULAR MECHANISMS UNDERLYING MACROPHAGE POLARIZATION



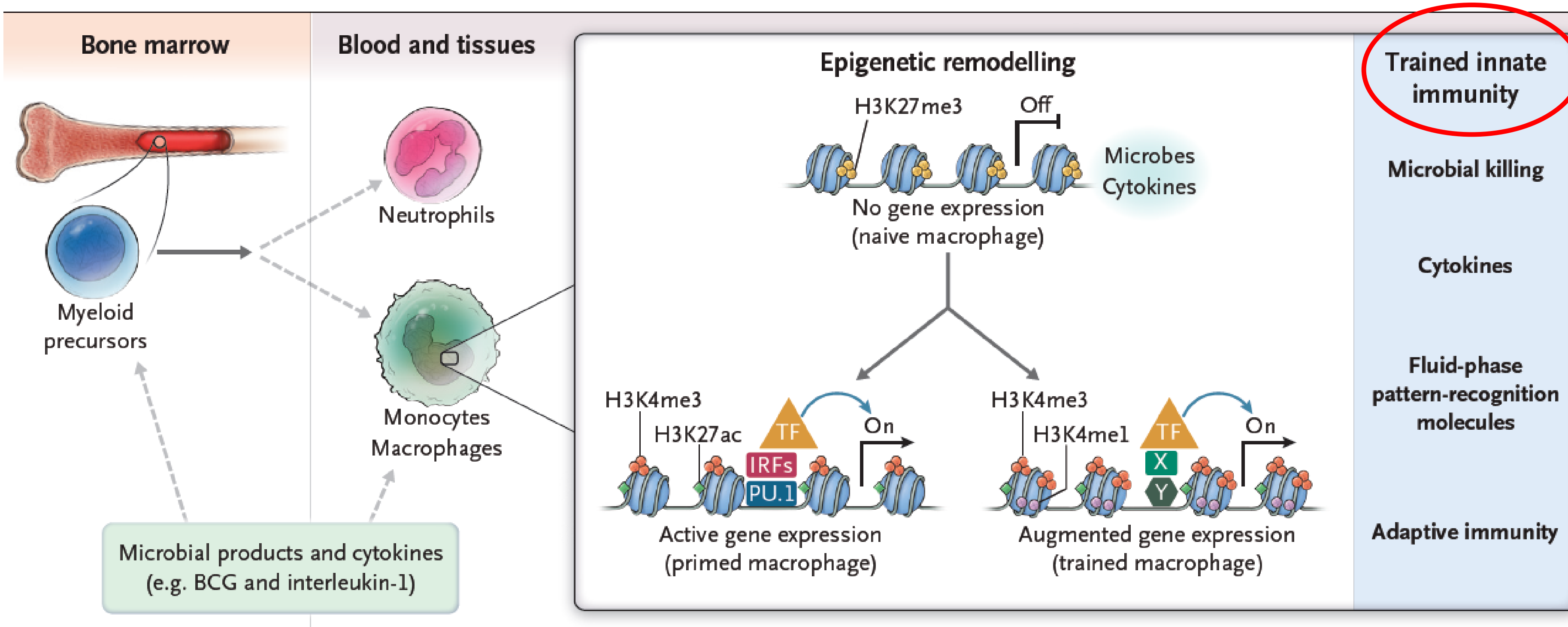
Locati et al. Annual Review of Pathology, 2020

DIVERSITY, MECHANISMS AND SIGNIFICANCE OF MACROPHAGE PLASTICITY

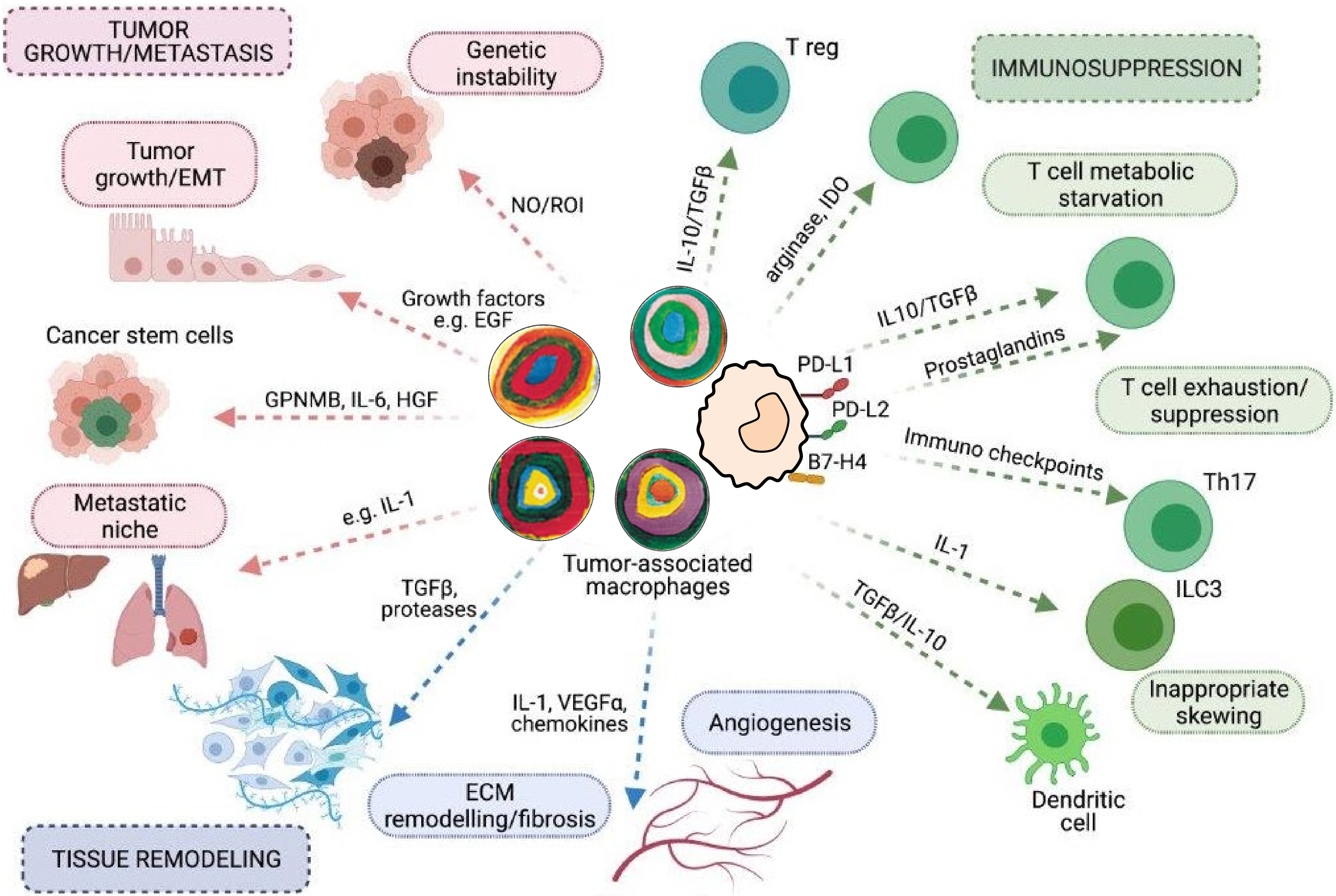


(Locati, Curtale and Mantovani, Annual Review of Pathology, 2020)

Cellular and Molecular Mechanisms Underlying Trained Innate Immunity in Response to Vaccines, Microbial Products and Cytokines



(Mantovani, Netea. Trained Innate Immunity, Epigenetics, and Covid-19, New England Journal of Medicine, 2020)



(modified from Farbstudie Quadrate, Wassily Kandinsky, 1913, modified from Mantovani, Allavena, Marchesi and Garlanda, Nature Rev Drug Discovery, 2022)

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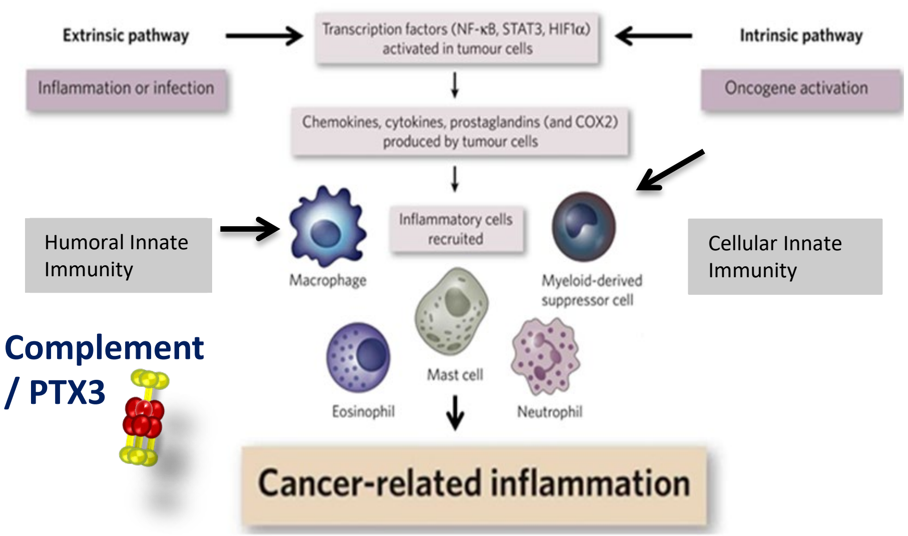
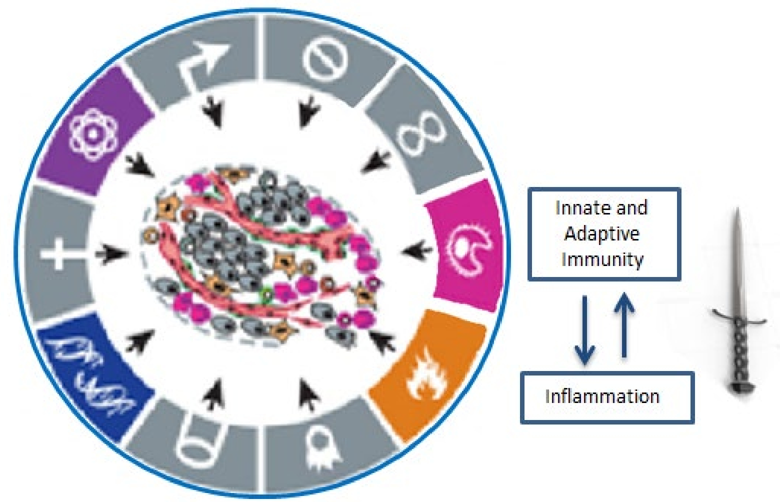
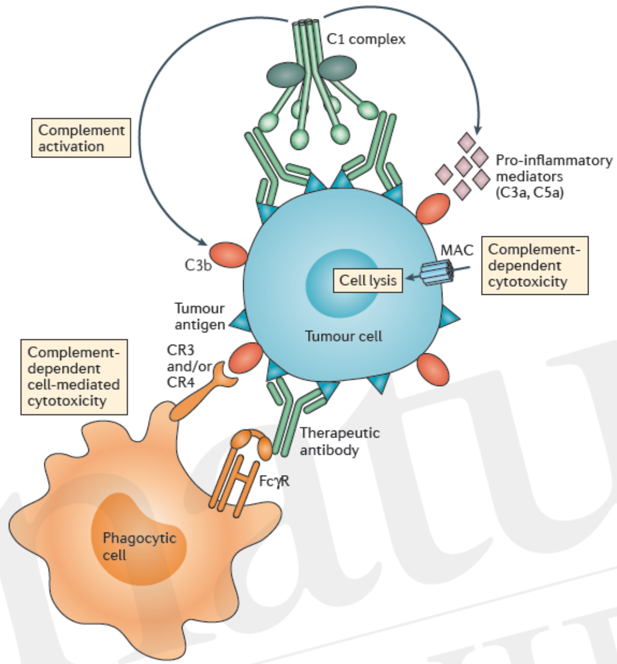




Hallmarks of Cancer
(modified from Hanahan and Weinberg 2011)

(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; Magrini et al, Nature Cancer 2021)

Complement in cancer: untangling an intricate relationship



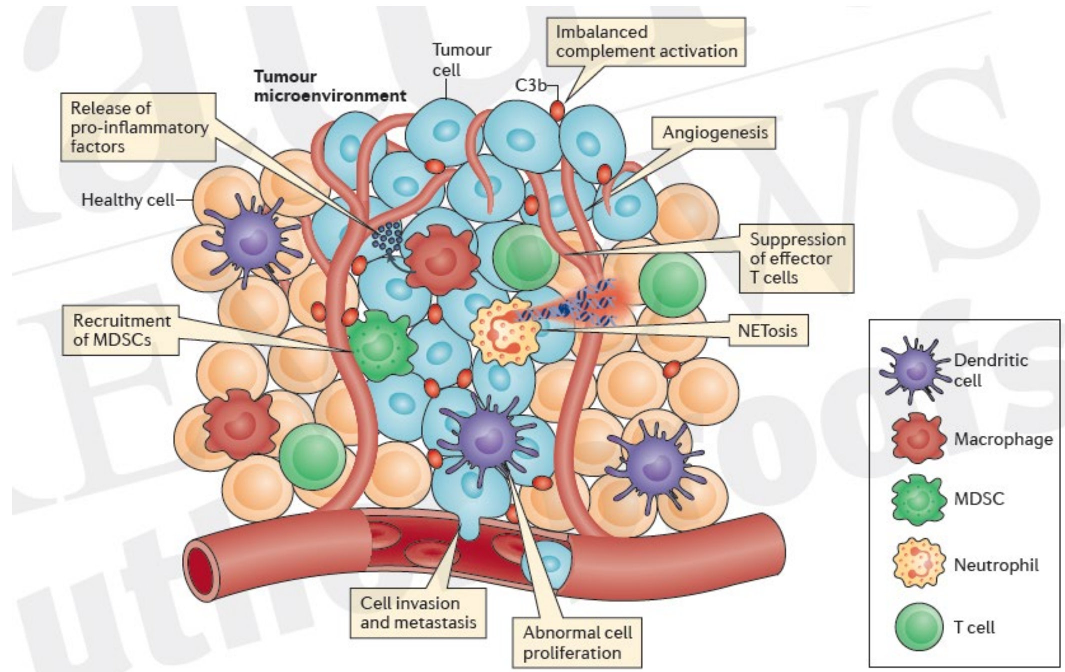


Figure 1
Complement mediates tumour cytolysis in the context of antibody-based immunotherapy

Figure 2
Complement activation in the tumour microenvironment promotes tumorigenesis

Reis, Mastellos, Ricklin, Mantovani, Lambris, Nature Rev Immunol, 2018; Ruben Pio et al 2019

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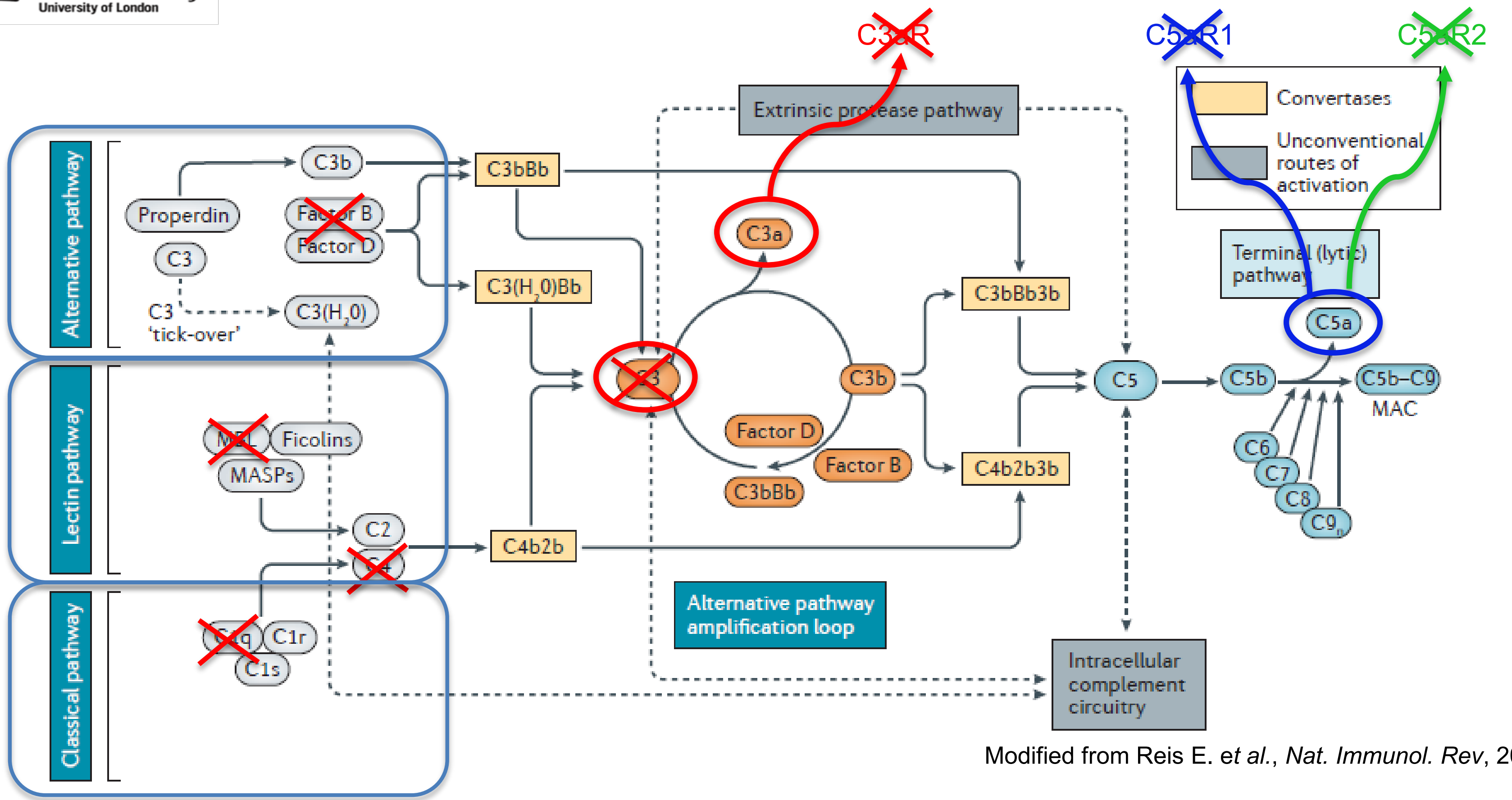
A systematic analysis of Complement activation pathways in sarcomagenesis



Modified from Reis E. *et al.*, *Nat. Immunol. Rev*, 2018.

C3-upstream mechanism(s)

Factor B$^{-/-}$ mice

MBL1/2$^{-/-}$ mice

C4$^{-/-}$ mice

C1q$^{-/-}$ mice

C3$^{-/-}$ mice

C3-downstream mechanism(s)

C3aR$^{-/-}$ mice

C5aR1$^{-/-}$ mice

C5aR2$^{-/-}$ mice

(Magrini et al Nature Cancer 2021)

The lectin pathway and the C3aR promote FS6 trasplantable sarcoma growth

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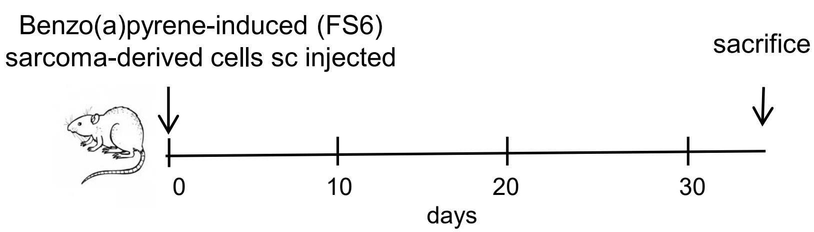
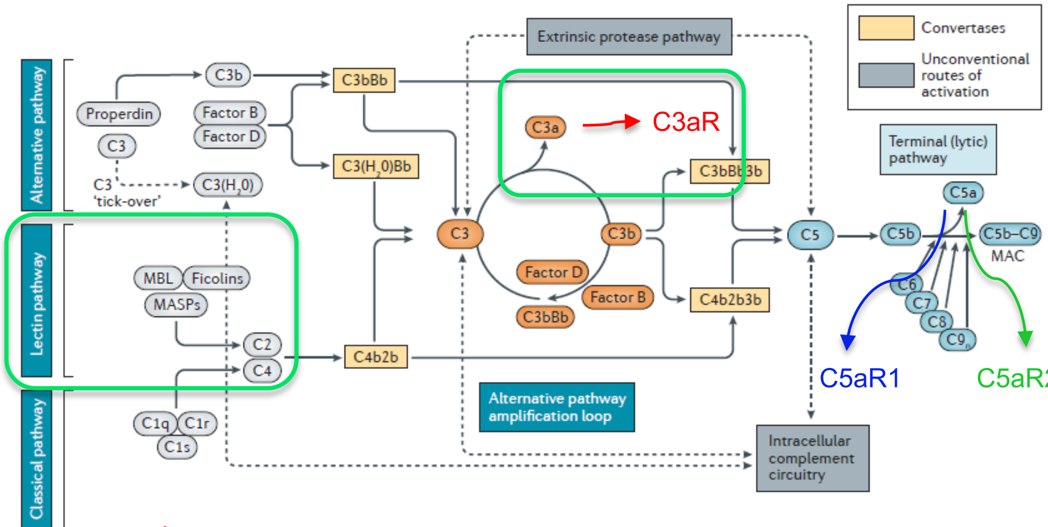
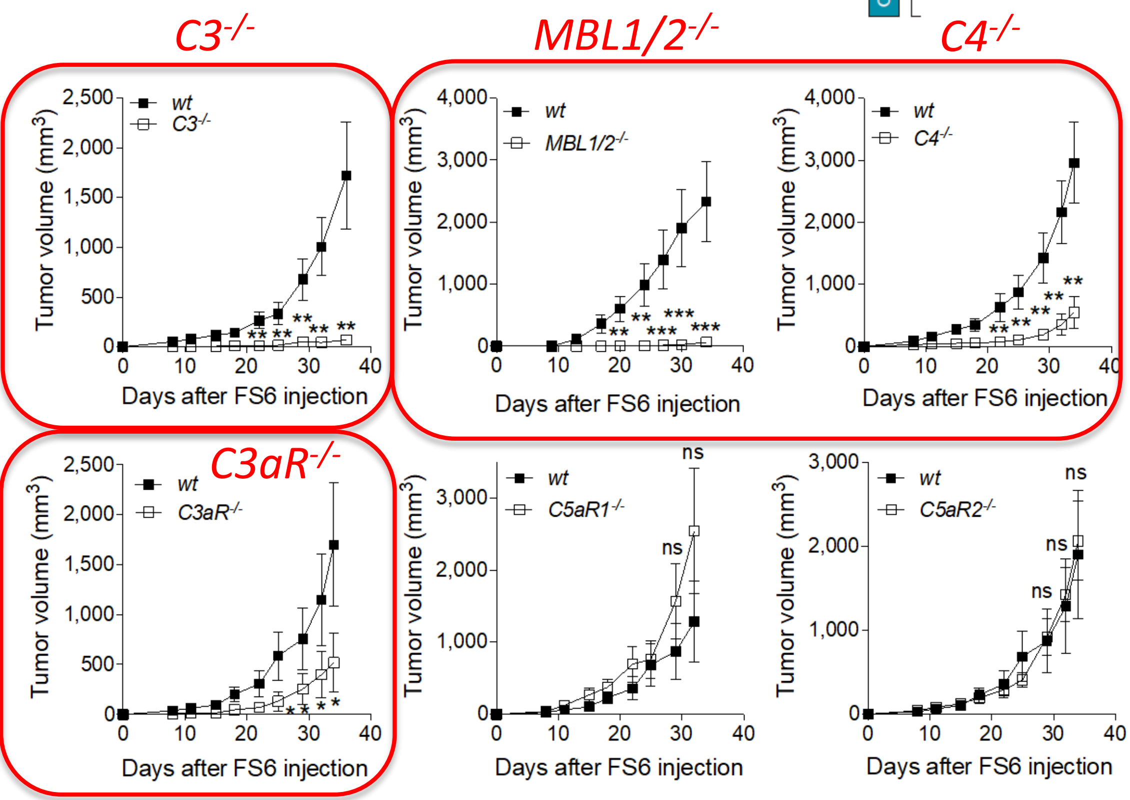
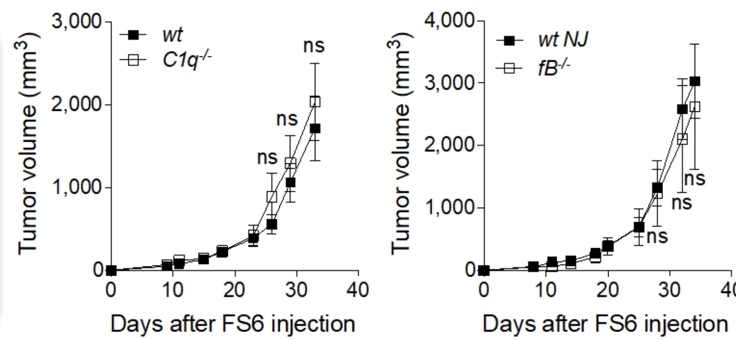
FS6 transplantable model



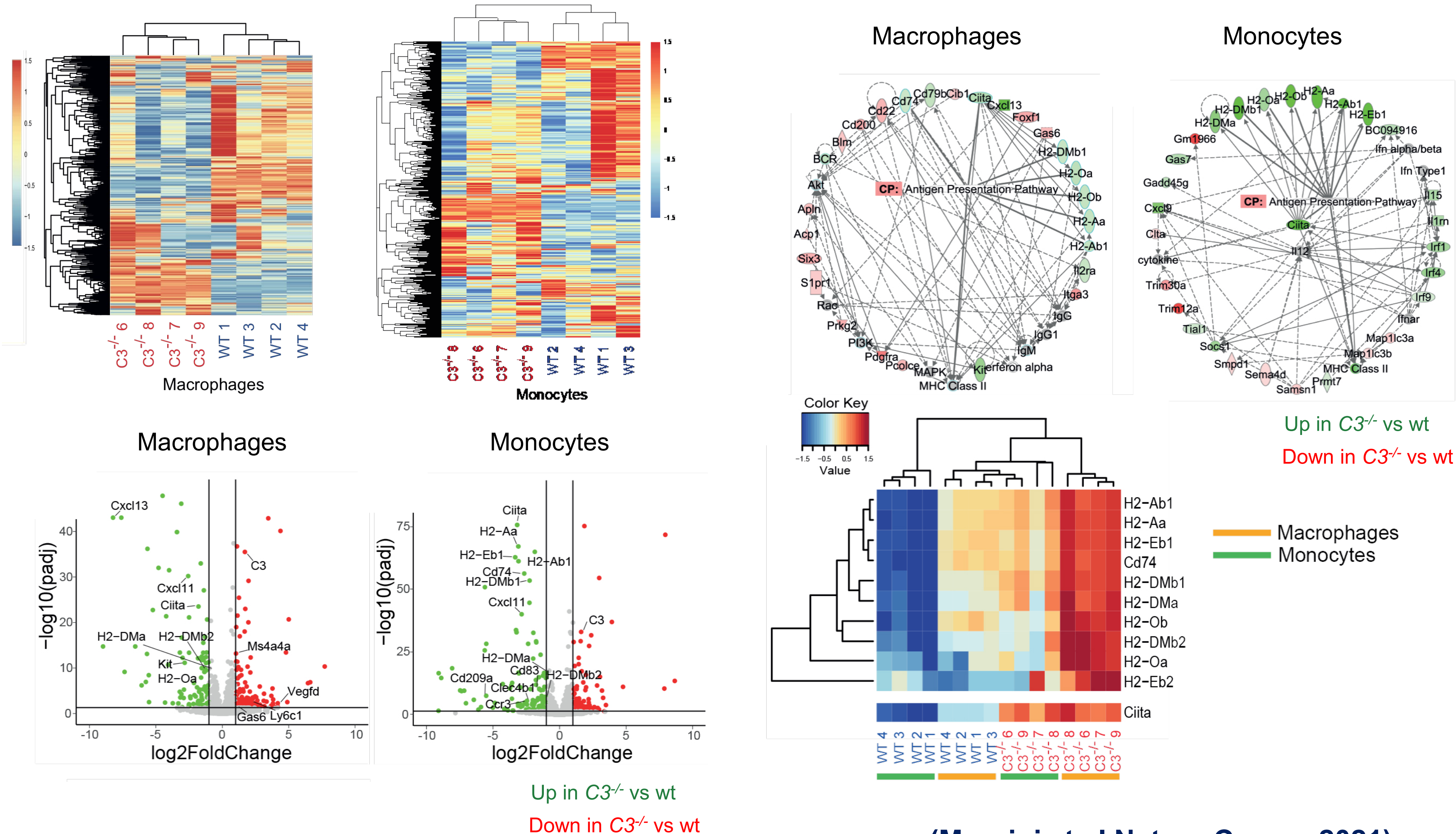






(Magrini et al Nature Cancer 2021)

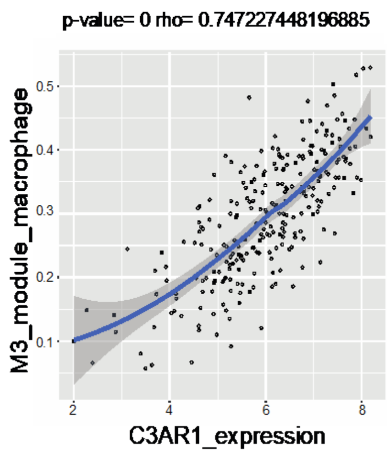
C3 deficiency was associated with gene expression reprogramming in tumor infiltrating leukocytes leading to increased antigen presentation

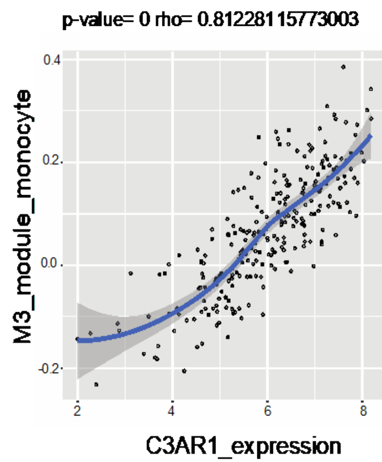


(Magrini et al Nature Cancer 2021)

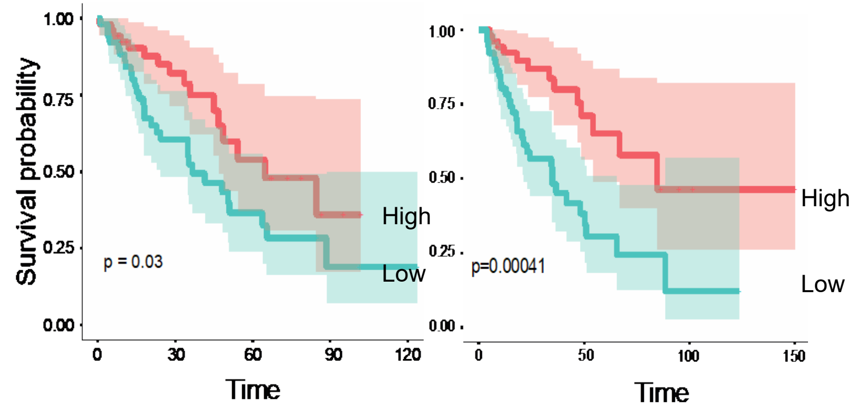
C3-deficiency associated genes have prognostic significance in human sarcoma

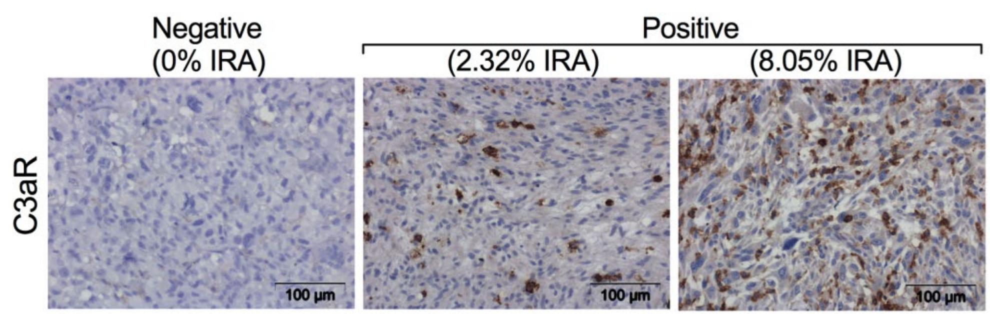
TCGA

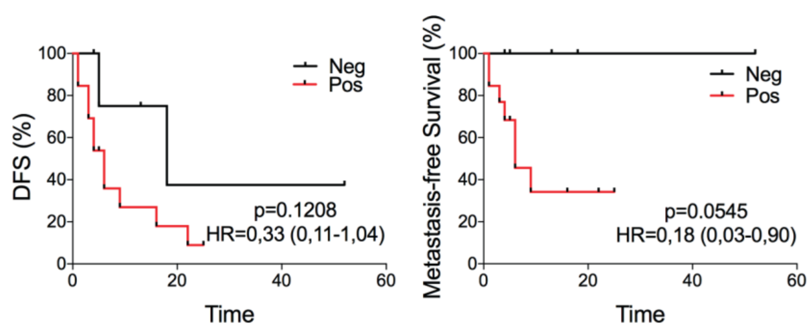




C3-deficiency signature of macrophages and monocytes



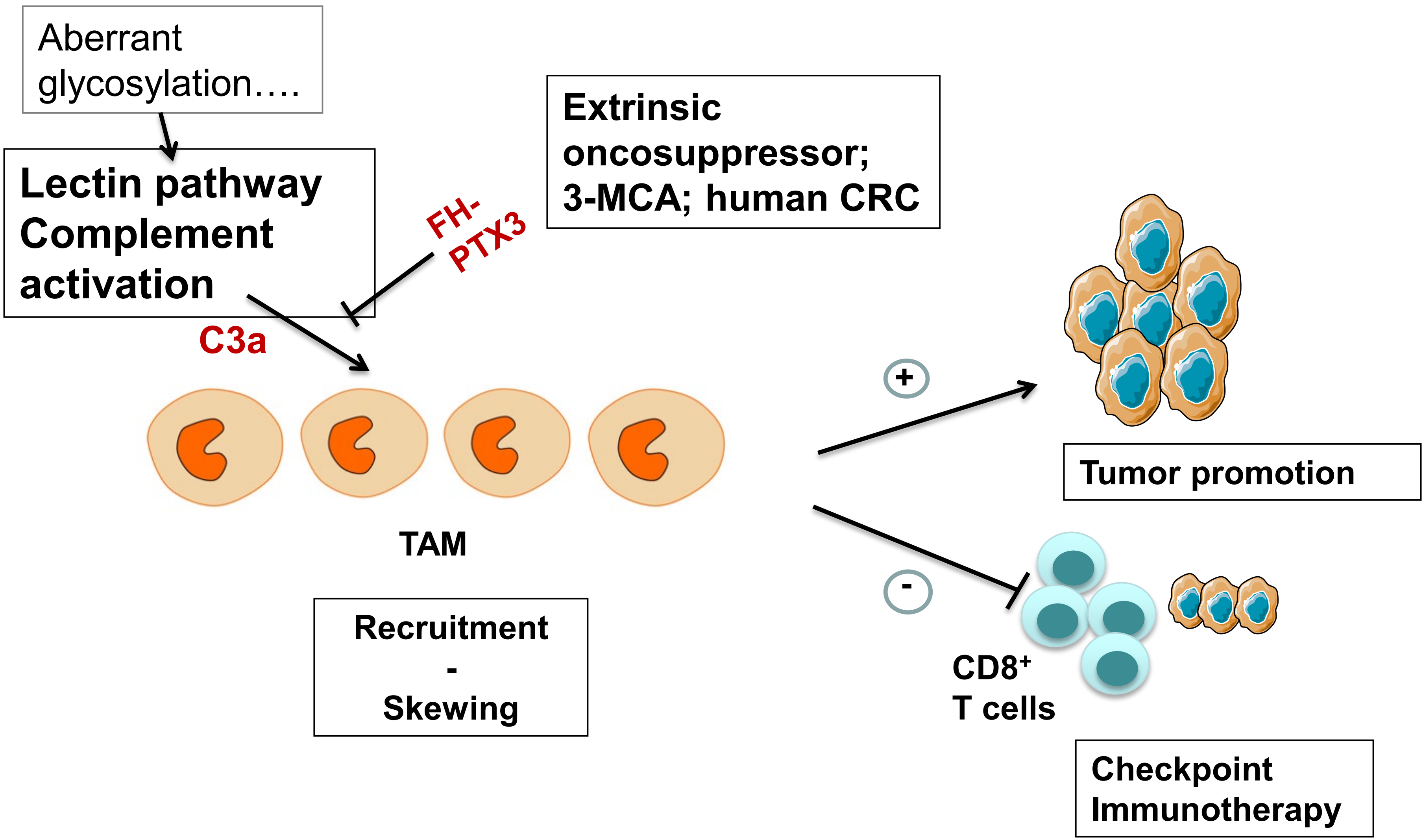




Undifferentiated pleomorphic sarcomas - UPS

(Magrini et al Nature Cancer 2021)

Complement and PTX3 in 3-MCA carcinogenesis and selected human tumors



(Bonavita et al, Cell, 2015;
Ries et al, Nature Rev Immunol, 2018
Magrini et al, Nature Cancer 2021 and unpublished data)

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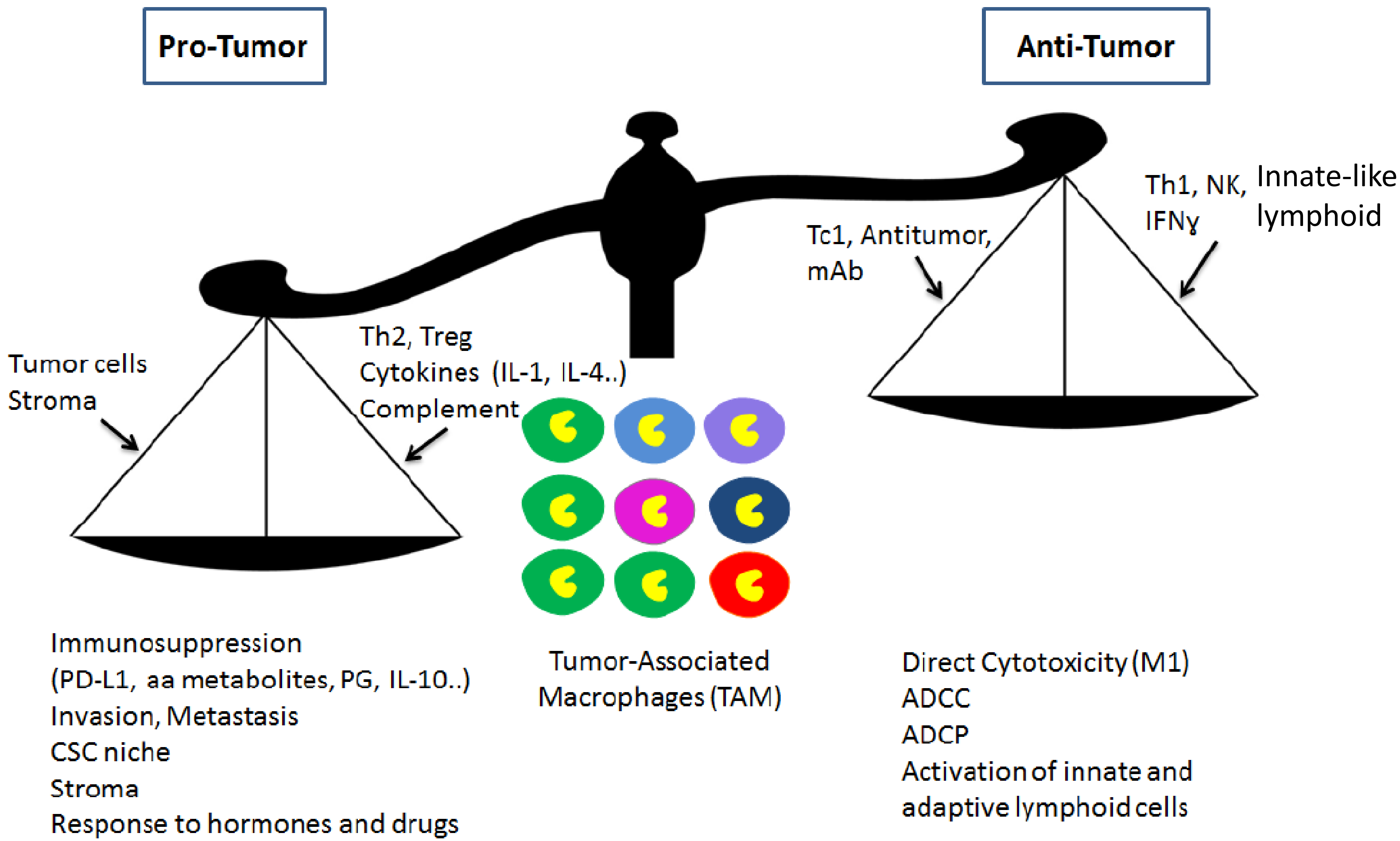
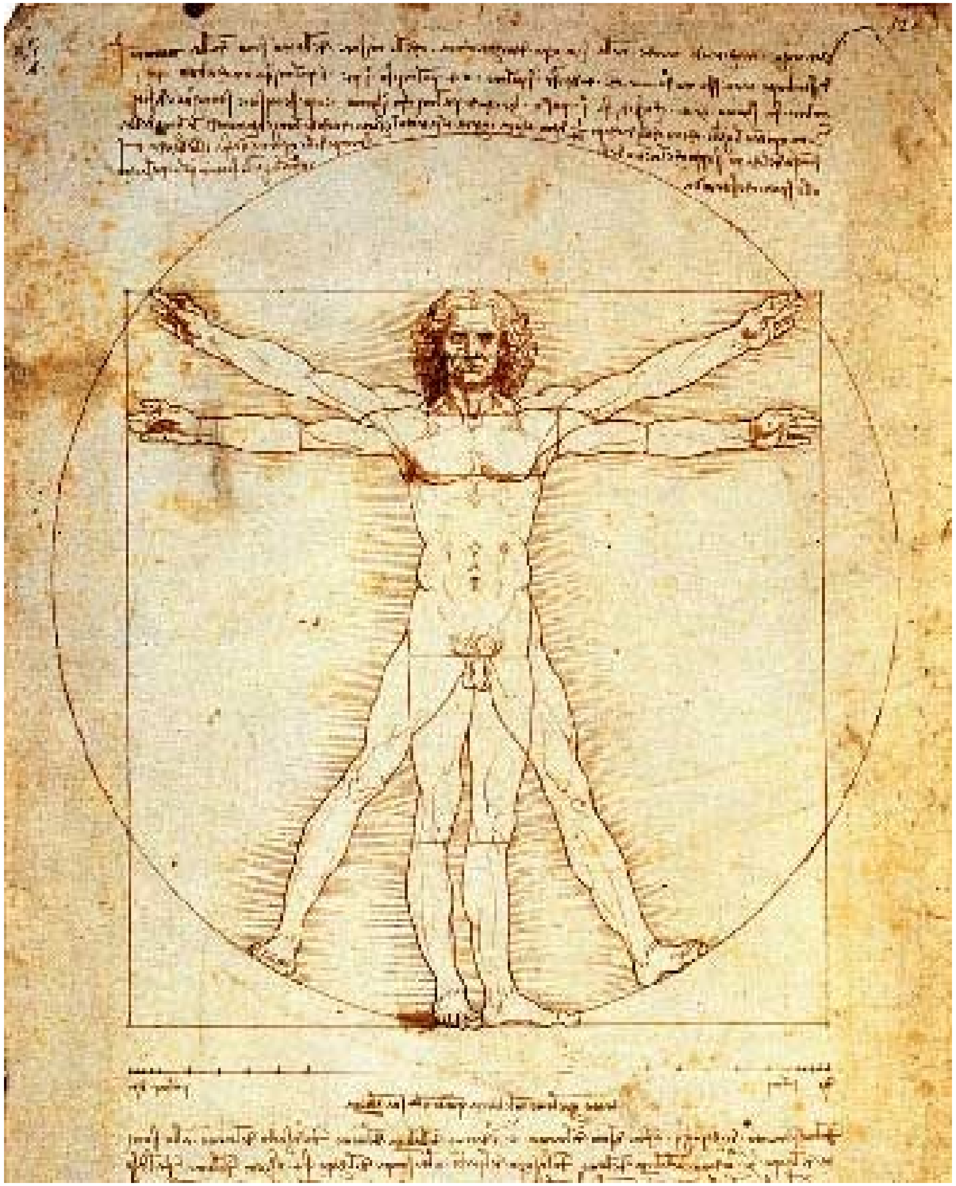
The macrophage balance in cancer



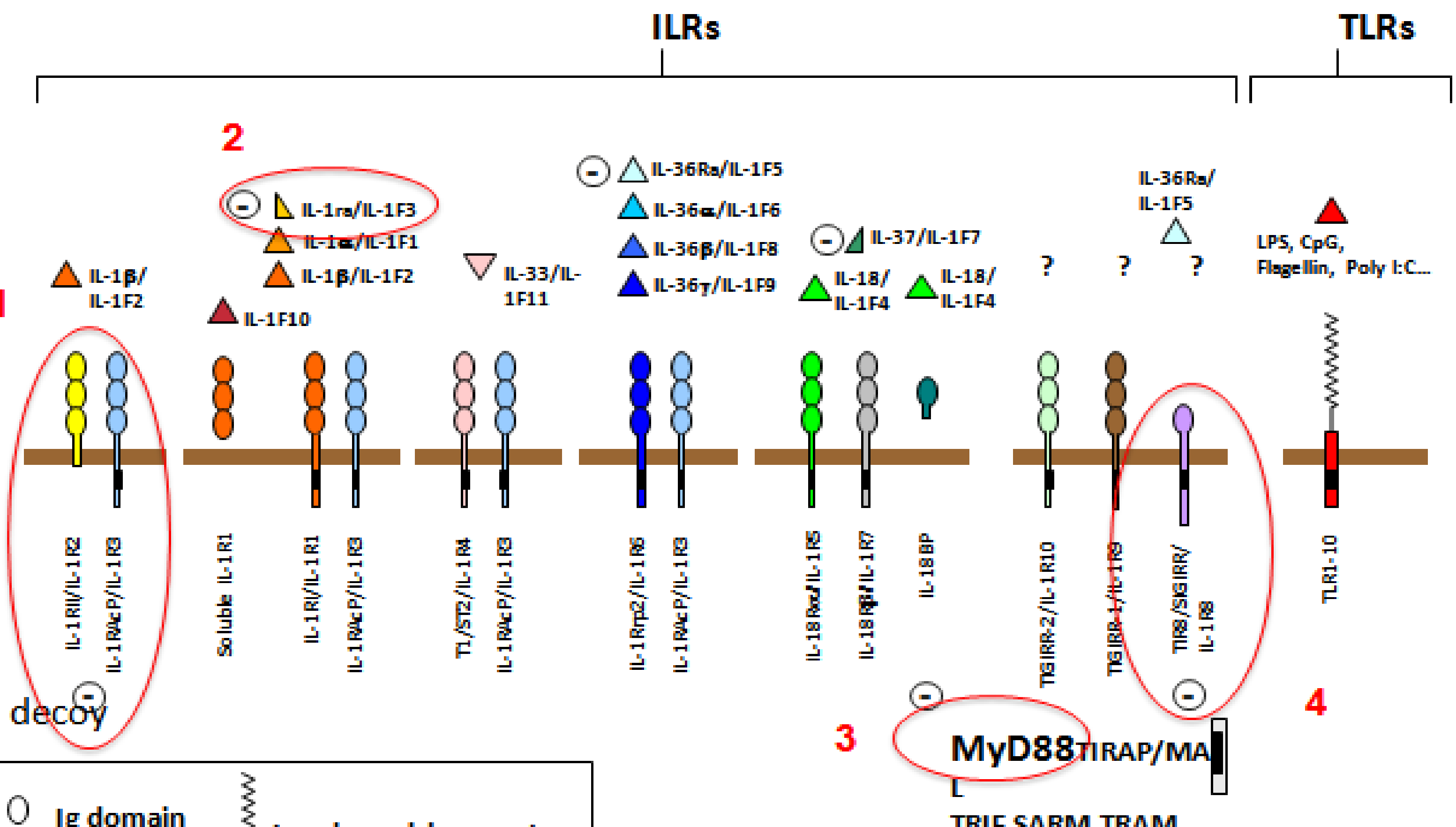
(Mantovani et al, Nature Rev. Clin. Oncol., 2017; Mantovani and Longo, New England J Med., 2018; Molgora et al Nature 2017; Locati et al, Annu Rev Pathol, 2020)

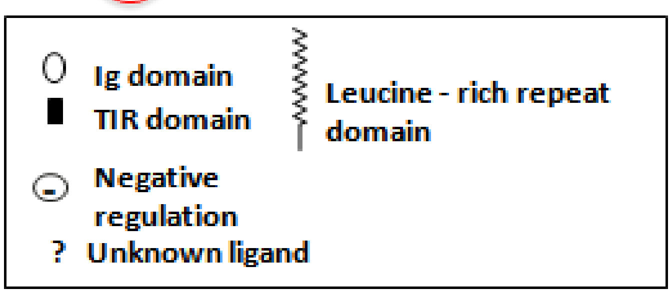
TAM, INFLAMMATION AND CANCER: TRANSLATION



1. **Pathology: prognostic vs predictive**
2. **Prevention/ Interception**
3. **Reeducation or targeting corrupted policemen**

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)

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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]

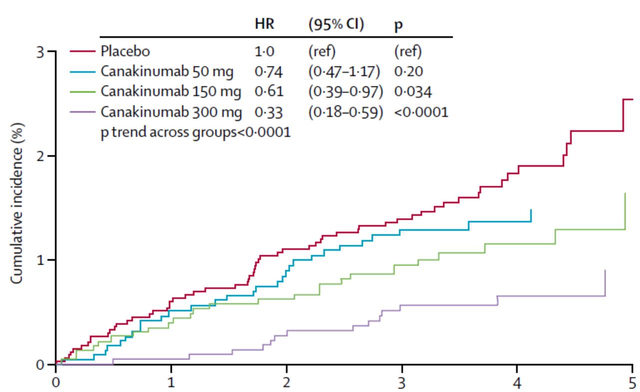
PNAS | March 4, 2003 | vol. 100 | no. 5 | 2645–2650

IL-1 is required for tumor invasiveness and angiogenesis

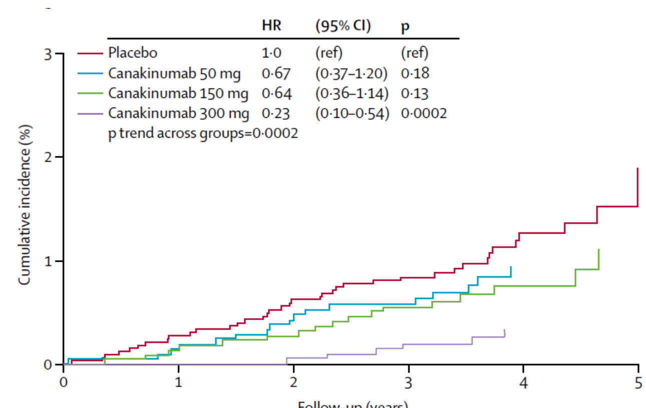
Elena Voronov*, Dror S. Shouval*, Yakov Krelin*, Emanuela Cagnano*, Daniel Benharroch*, Yoichiro Iwakura†, Charles A. Dinarello‡, and Ron N. Apte*§

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†*

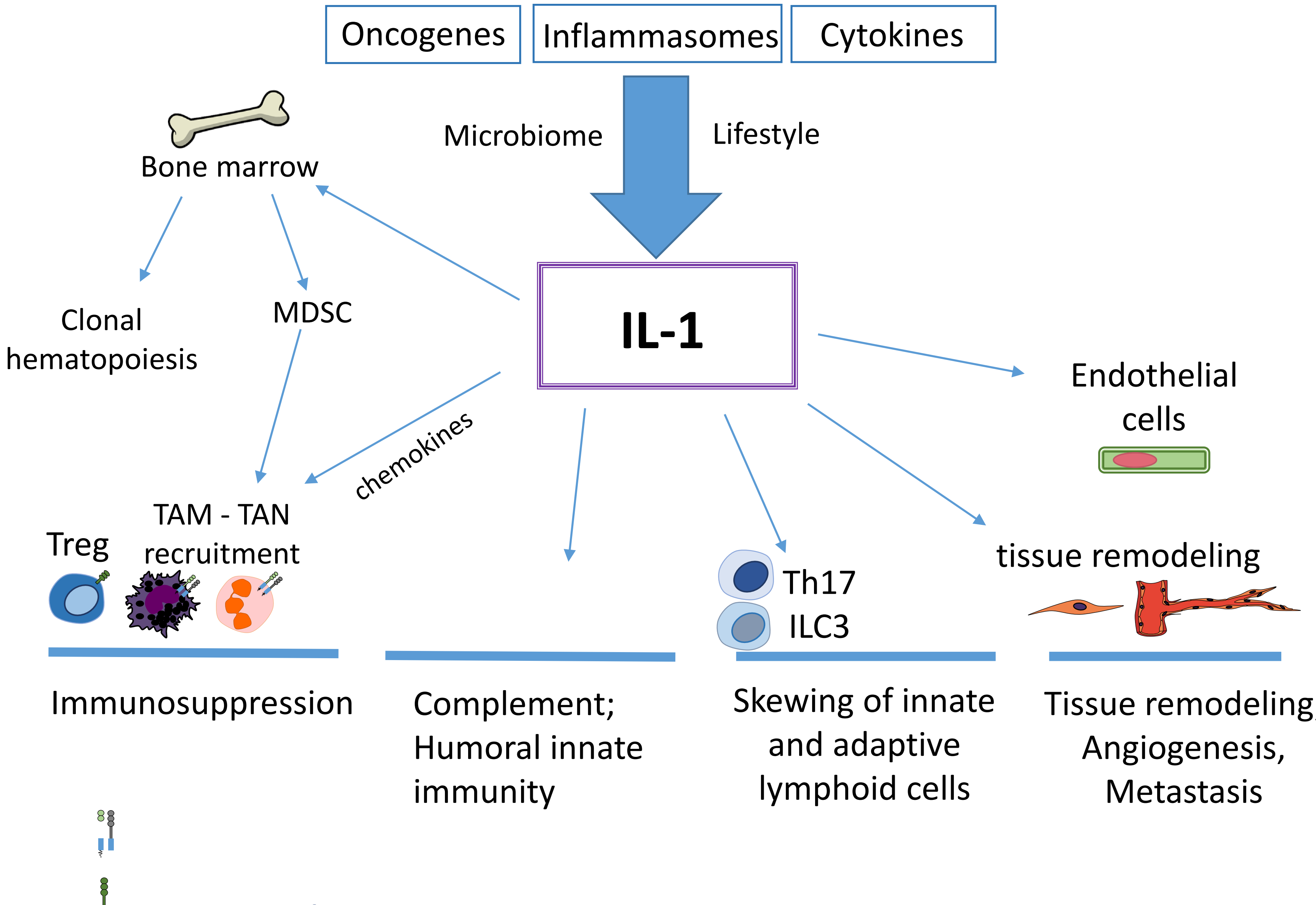


Number at risk	0	1	2	3	4	5
Placebo	3344	3241	3142	2835	1401	251
Canakinumab 50 mg	2170	2110	2047	1825	827	53
Canakinumab 150 mg	2284	2207	2148	1950	982	233
Canakinumab 300 mg	2263	2201	2128	1928	1002	222

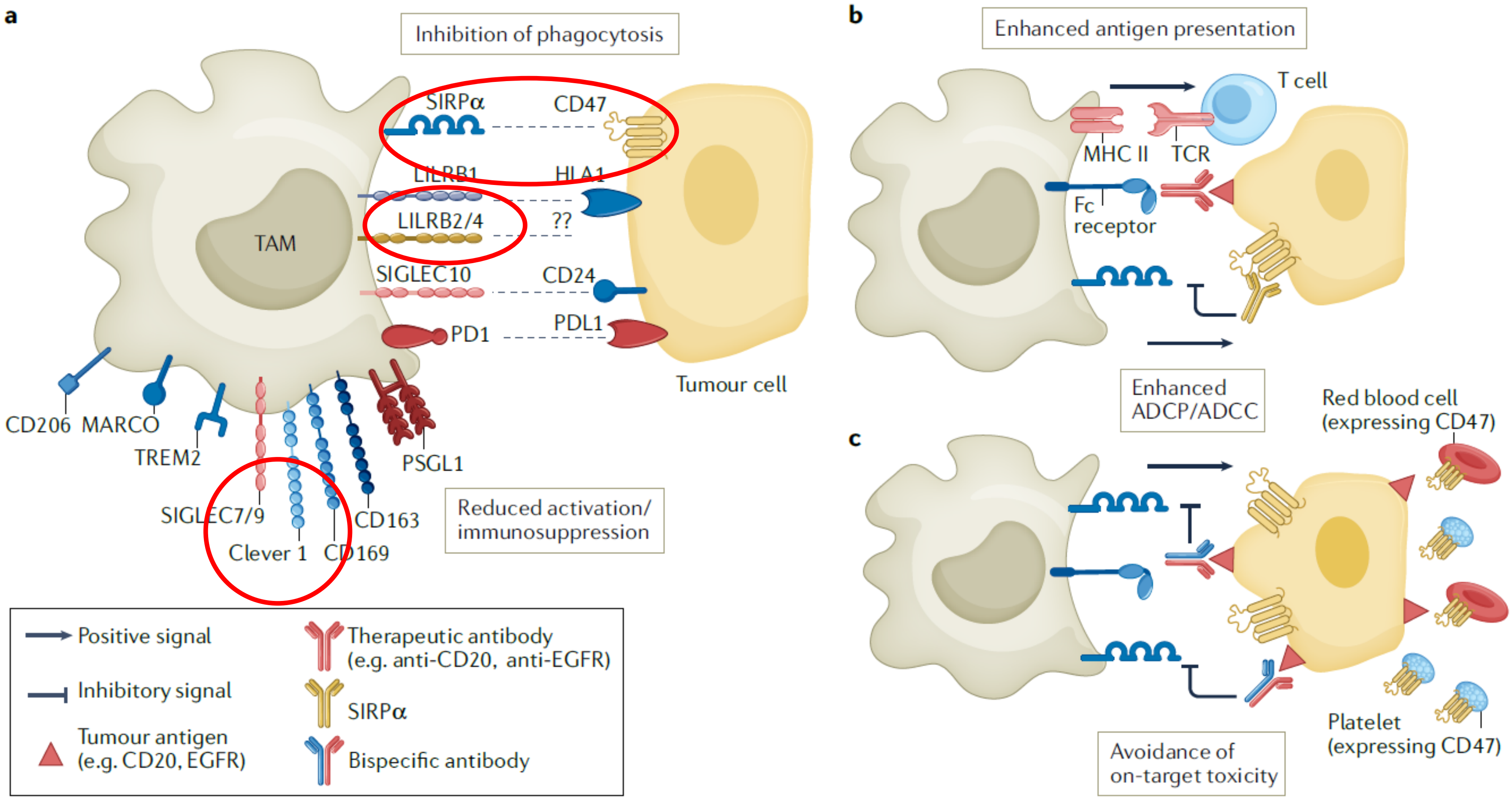


Number at risk	0	1	2	3	4	5
Placebo	3344	3255	3162	2868	1423	257
Canakinumab 50 mg	2170	2117	2054	1845	838	57
Canakinumab 150 mg	2284	2221	2163	1972	998	243
Canakinumab 300 mg	2263	2204	2139	1949	1013	227

INTERLEUKIN-1 IN TUMOR PROGRESSION, THERAPY AND PREVENTION

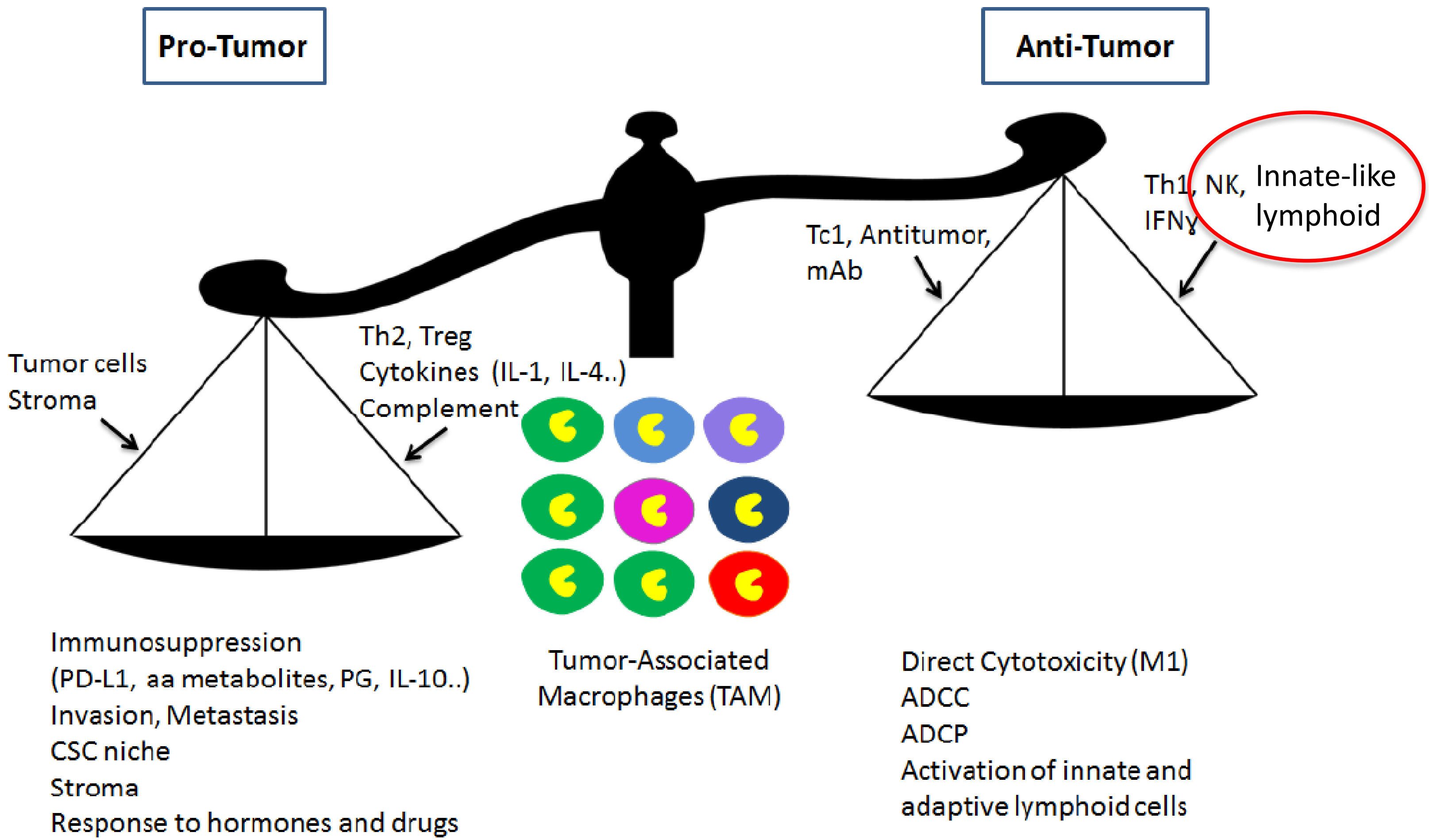


(Garlanda et al Immunity 2019; Garlanda and Mantovani, Cancer Cell 2021)



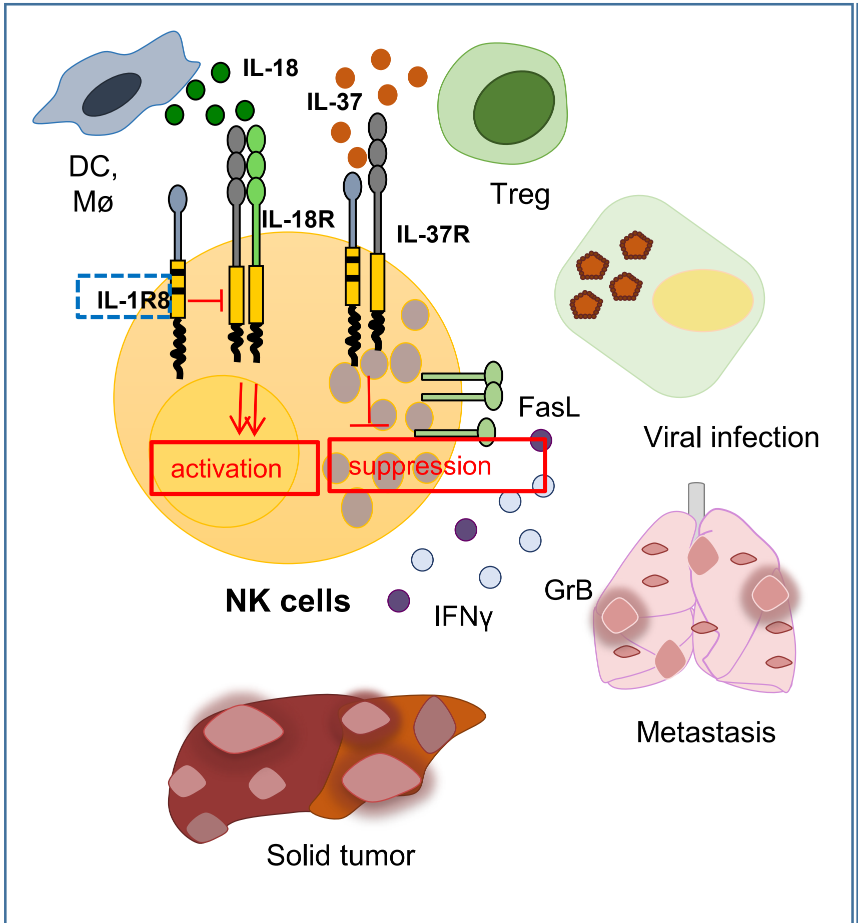
(Mantovani, Allavena, Marchesi and Garlanda, Nature Rev Drug Discovery, 2022)

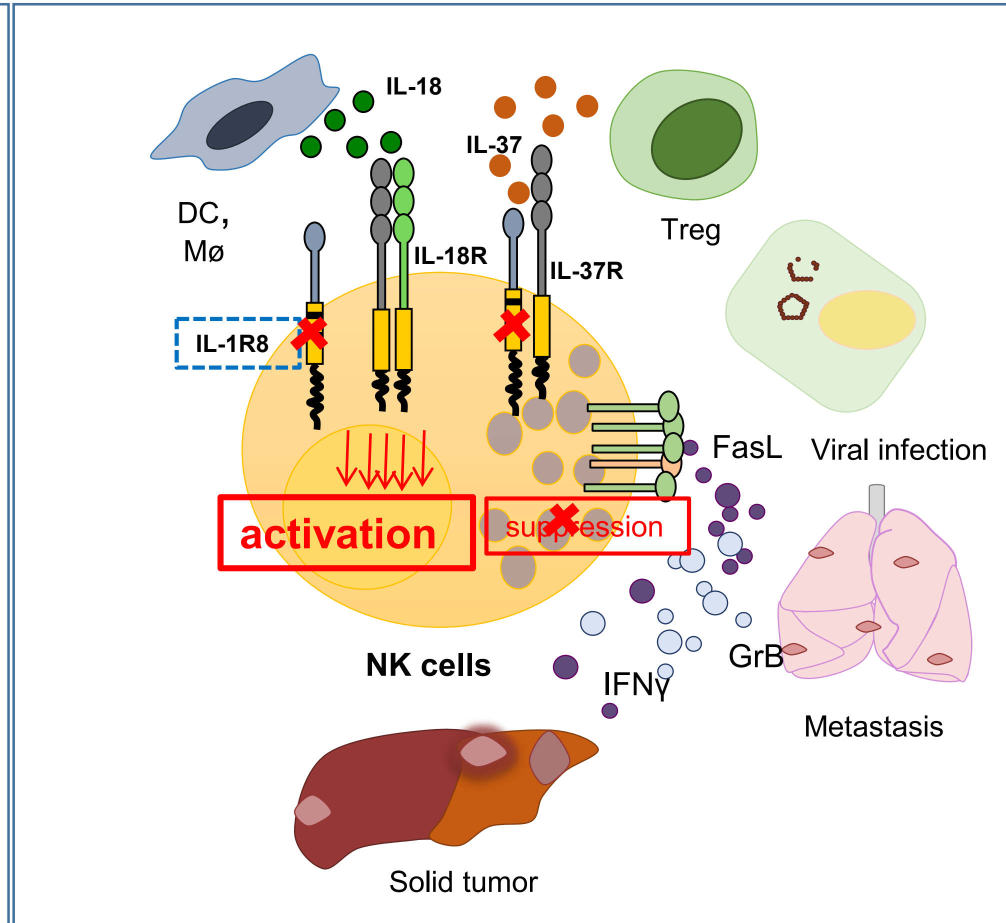
The macrophage balance in cancer



(Mantovani et al, Nature Rev. Clin. Oncol., 2017; Mantovani and Longo, New England J Med., 2018; Molgora et al Nature 2017; Locati et al, Annu Rev Pathol, 2020)

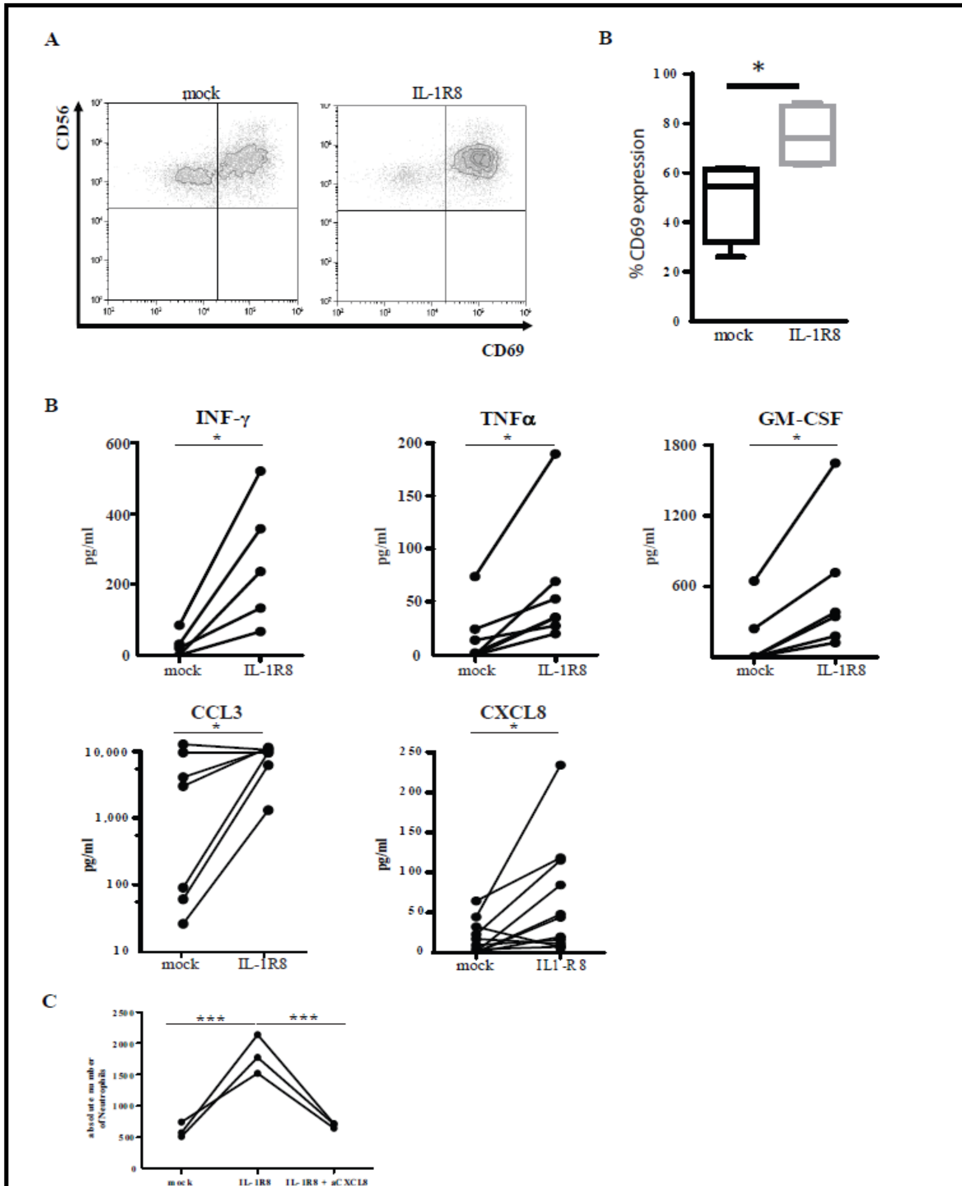
IL-1R8 as a checkpoint of NK cell anti-tumor and anti-viral activity





(Molgora et al. Nature 2017; Miller et al. Cancer Immunol Res 2018)

Effect of IL-1R8 silencing on NK cell effector function



(Landolina et al , J Immunotherapy of Cancer. 2022)

Profiling human monocyte-to-macrophage differentiation and polarization

C-type lectin receptors

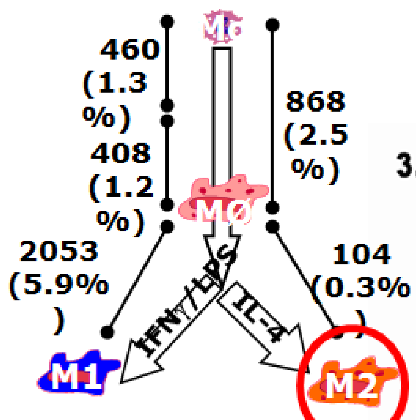
Mannose receptor	44
DC-SIGN	3.6
CLEC10A	2.5
DCL-1	3

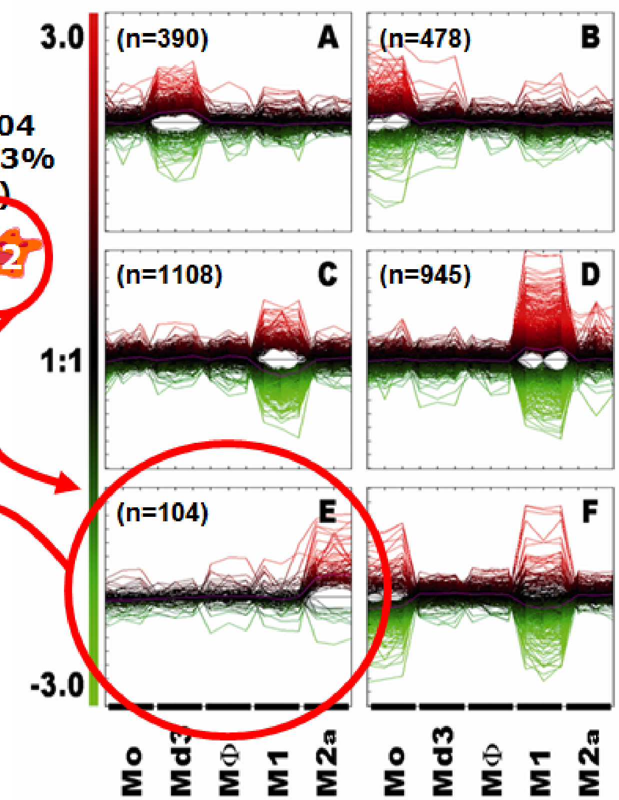
Scavenging receptors

Scavenging receptor A	9
Scavenger recceptor B	3
Stabilin 1	6
CD163	5

ECM molecules

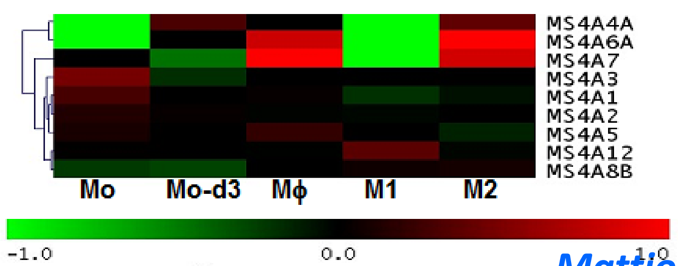
Ostoeactivin	83
Osteopontin	26
Factor XIII A1	11
FN1	7





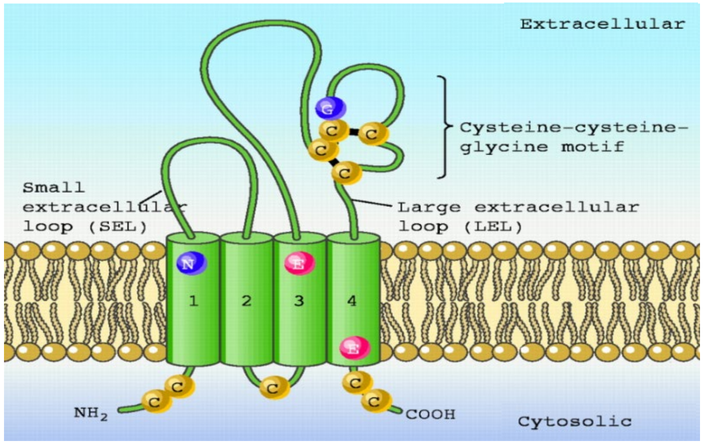
A-B: differentiation; C-D-F: M1; E: M2

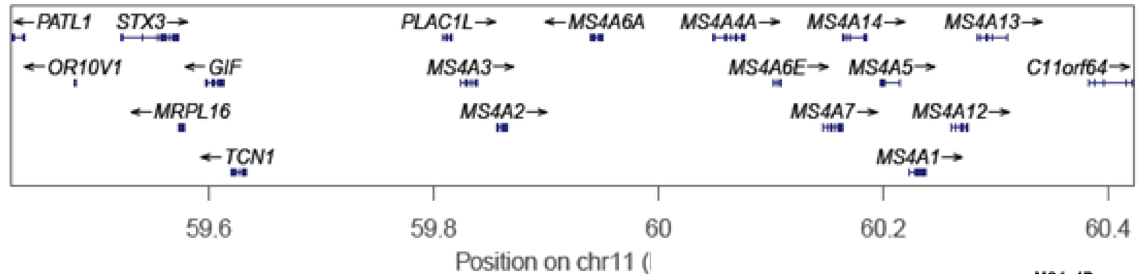
(transcriptional data from Martinez et al, J Immunol 2006)

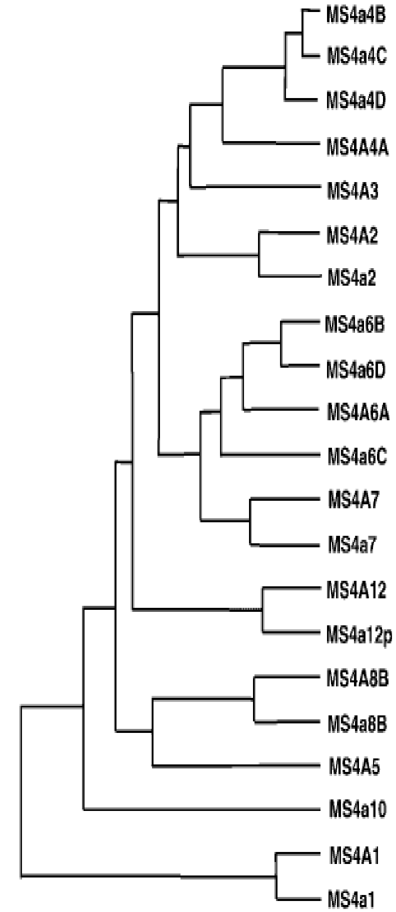


Mattiola, … Mantovani and Locati, Nature Immunol, 2019

MS4A proteins: a tetraspanin-like superfamily







MS4A1 (CD20)

B lymphocytes. Cell surface molecule involved in BCR signaling (transmembrane Ca^{++}conductance).

MS4A2 (FcεRIβ)

Mast cells. High affinity receptor for IgE involved in FcεRI signaling (ITAM domain).

Ms4a4b

T cells. Promotes Th1 function and enhances GITR signaling.

Ms4a8a

Marker of a TAM ubset in murine breast carcinoma and melanoma (Schmieder, 2012; Michel, 2013).

MS4A12

Colonic epithelial cells. Involved in cell differentiation

(Mattiola Mantovani and Locati Trends Immunol 2021)

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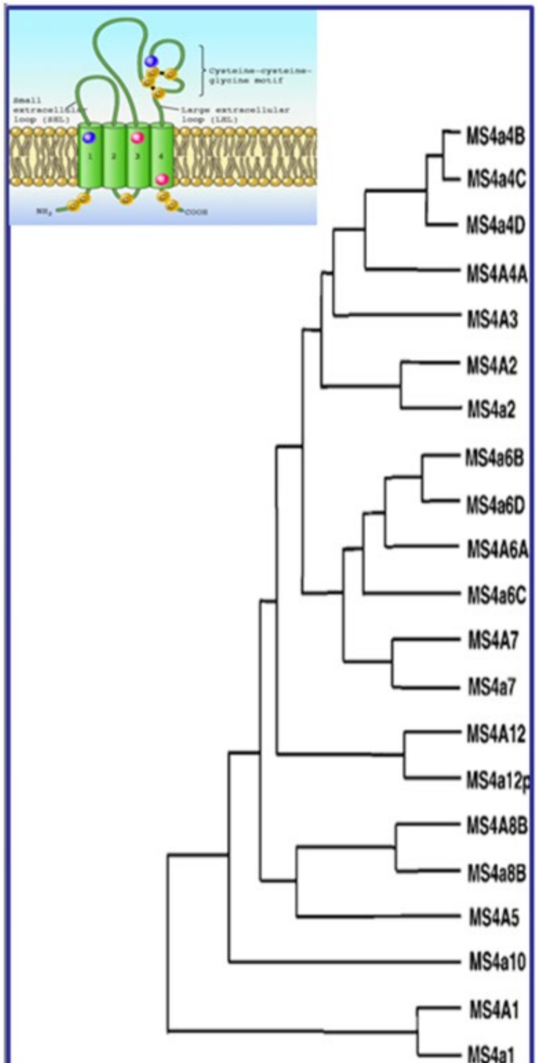
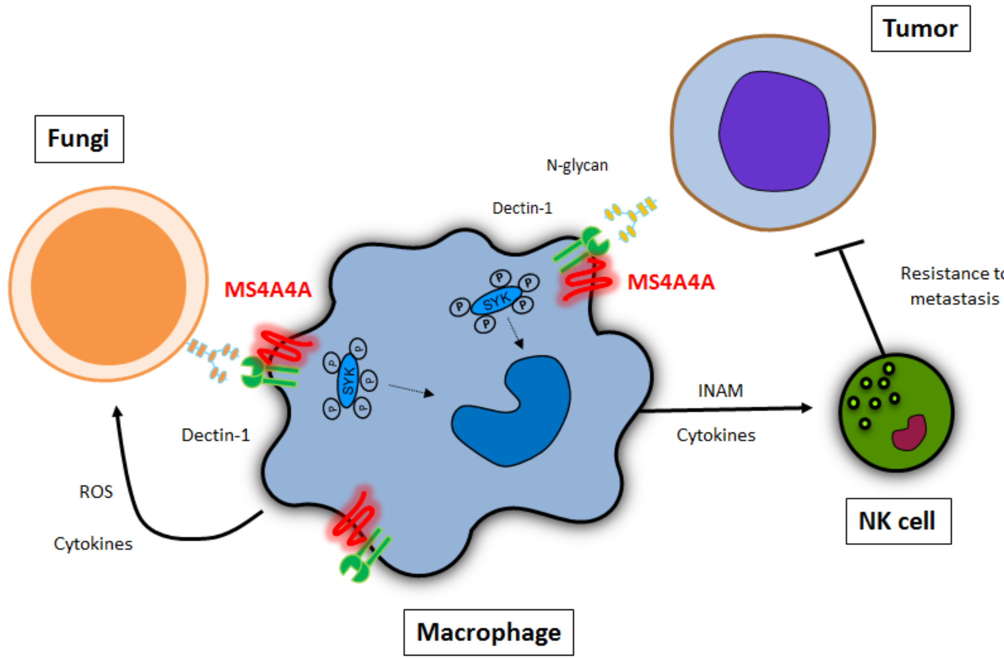
THE MACROPHAGE TETRASPAN MS4A4A:
FROM IGNOROME TO HUMAN DISEASES (including RA; Alzheimer)



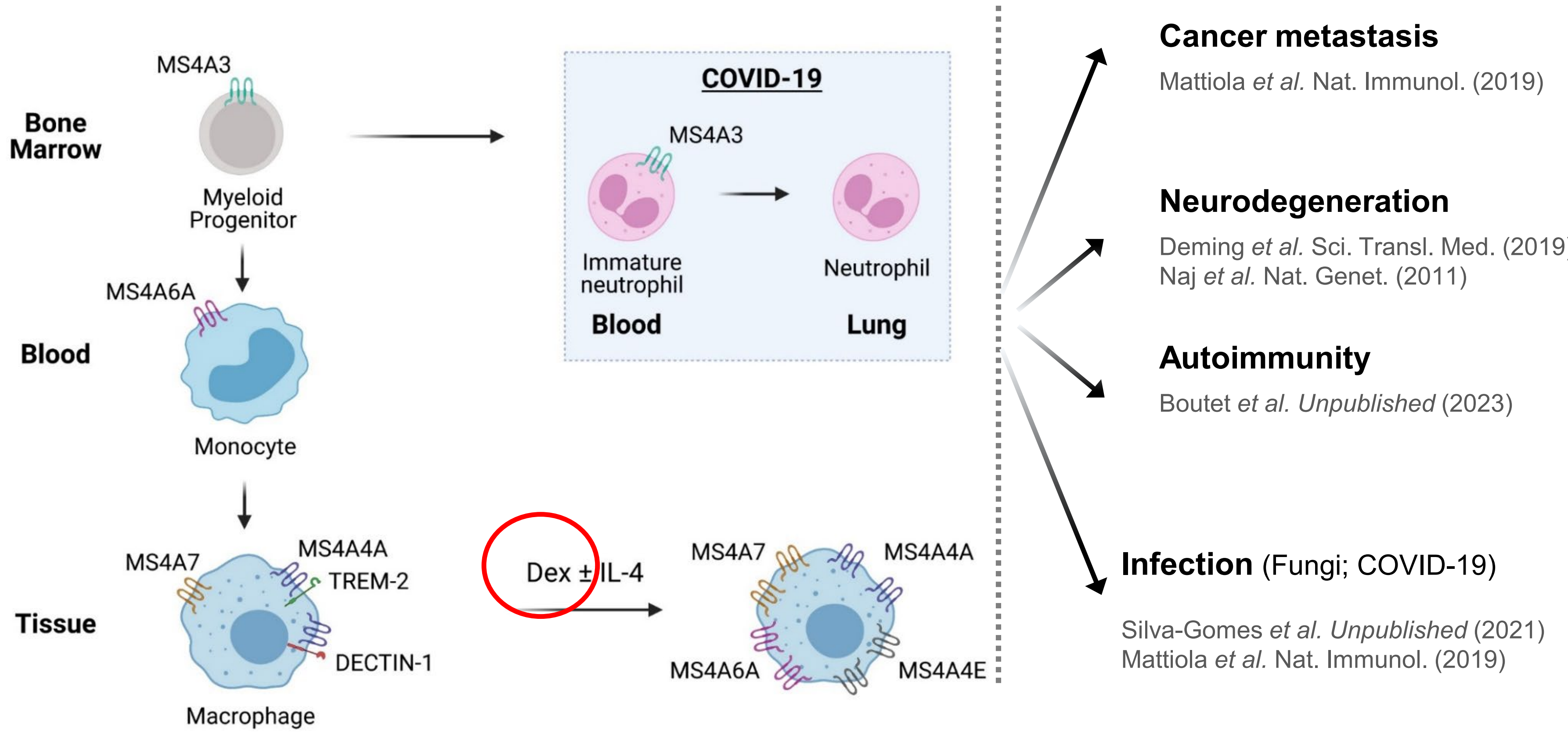


GENETIC ASSOCIATIONS WITH ALZHEIMER DISEASE

1) Naj AC, et al. Naure Genet 43:436-41, 2011.
2) Chouraki V, et al. Genetics of Alzheimer's disease. Adv Genet 87:245-94, 2014.
3) Hollingworth P, et al. Nature Genet 43:429–435, 2011.
4) Ma et al Aging Cell 2019
5) Deming et al bioRxiv 2018
6) Hou et al Neurobiol of Aging 2019

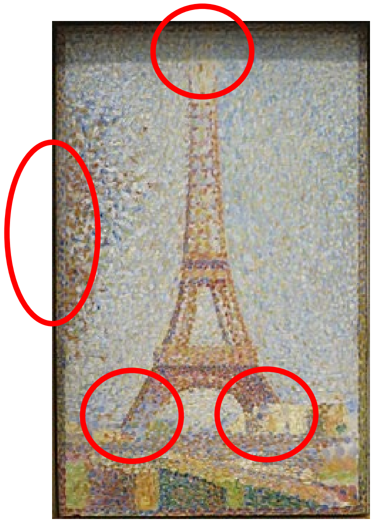
Martinez et al J. Immunol. 2006; Mattiola et al, Nature Immunol, 2019

Tetraspanin-like MS4A molecules in myeloid cells

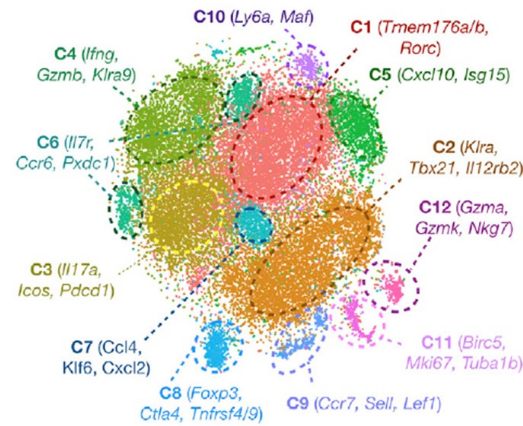


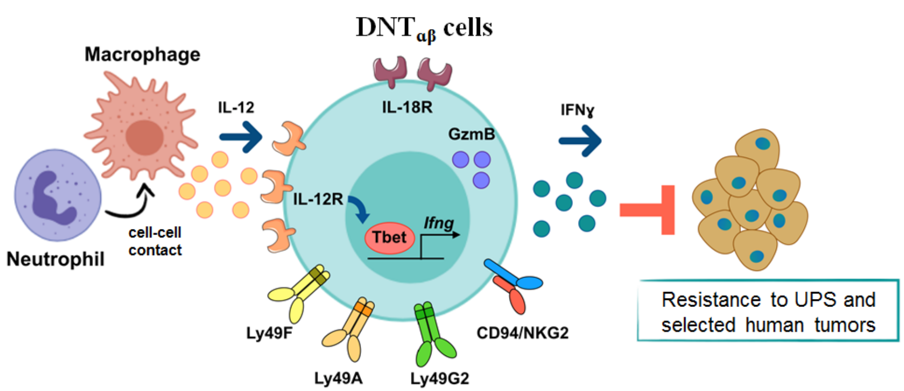
(Silva-Gomes et al. 2022; Mattiola, Mantovani and Locati Trends Immunol 2022)

FROM SINGLE CELL ANALYSIS TO BEDSIDE

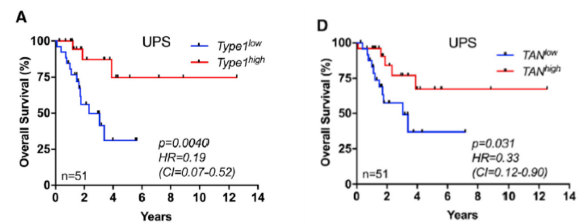


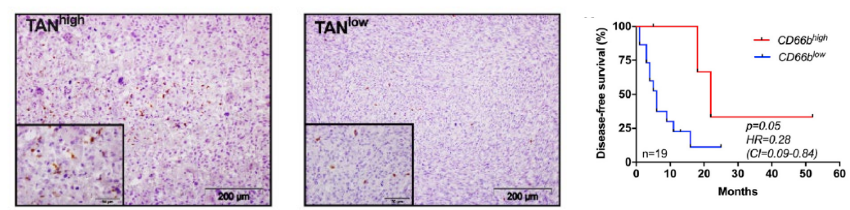
Georges Seurat (Pointillisme)





Insilico bioinformatics, TCGA





Ponzetta et al, Cell, 2019

Seminars in Immunology 48 (2020) 101408

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journal homepage: www.elsevier.com/locate/ysmim

Review

Prognostic significance of tumor-associated macrophages: past, present and future

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[d] Department of Medicine and Surgery, University of Parma, 43100 Parma, Italy
[e] Department of Biomedical Science, Humanitas University, Pieve Emanuele, Italy
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Tumor-Associated macrophages
Prognosis
Biomarkers
Single-Cell

ABSTRACT

Tumor tissues are populated by a multitude of macrophages, highly different in functional activity, localization and morphology. A clear contribution to disease progression has been shown in multiple cancer types, holding promise for the development of innovative macrophage-based prognostic tools. Current studies aimed at assessing the prognostic role of macrophages have documented the relevance of the macrophage population as a whole. However, dissecting the diversity of mononuclear phagocytes in tumor tissues has provided important information about the coexistence of distinct populations of macrophages with different prognostic significance. Here we summarize evidence of macrophage prognostic function in human cancer and focus on classical and modern strategies aimed at measuring macrophage features and deciphering their diversity. The wealth of new data generated will reshape our knowledge of macrophage complexity and hopefully foster the forthcoming development of these new metrics into prognostic tools as well as new therapeutic strategies.

1. Introduction

Recent years have witnessed a switch in perspective of prognostic markers in oncology. Increased recognition of the fundamental role of immune and stromal mediators in cancer biology has twisted our attention from traditional prognostic factors related to tumor cell characteristics (tumor size, local invasion, nodal involvement, spread to distant organs) to microenvironmental components, alongside clonal alterations. Patient stratification, which is essential to guide clinical management of cancer patients, is a complex process that requires identification of tumor features correlated with clinical variables. This operation becomes particularly important when nonconventional or combined therapeutic regimens - for which data collected on large cohorts of patients is not available yet - are adopted. In this scenario, fostered by the increasing evidence of an impact of leucocyte populations on the prognosis of cancer patients, the immune landscape is emerging as a promising tool to help in the stratification of clinical outcome [1–6].

A wealth of studies has revealed the association of specific immune parameters, with post-operative outcome of cancer patients. These studies have been primarily focused on T cells [1,2,4,5,7,8], while fewer studies are available on other immune types. However, by increasing our appreciation of the importance of immune profiles in dictating clinical outcome, these studies are slowly modifying our approach to cancer classification and set the foundations to explore whether macrophages, the most frequently found cells within the tumor microenvironment [9–13], hold potential to ameliorate the critical task of patient stratification. This effort goes along with studies testing the possibility to exploit macrophages as therapeutic targets. Here we review our current understanding of macrophage assessment tools to be exploited as new prognostic markers.

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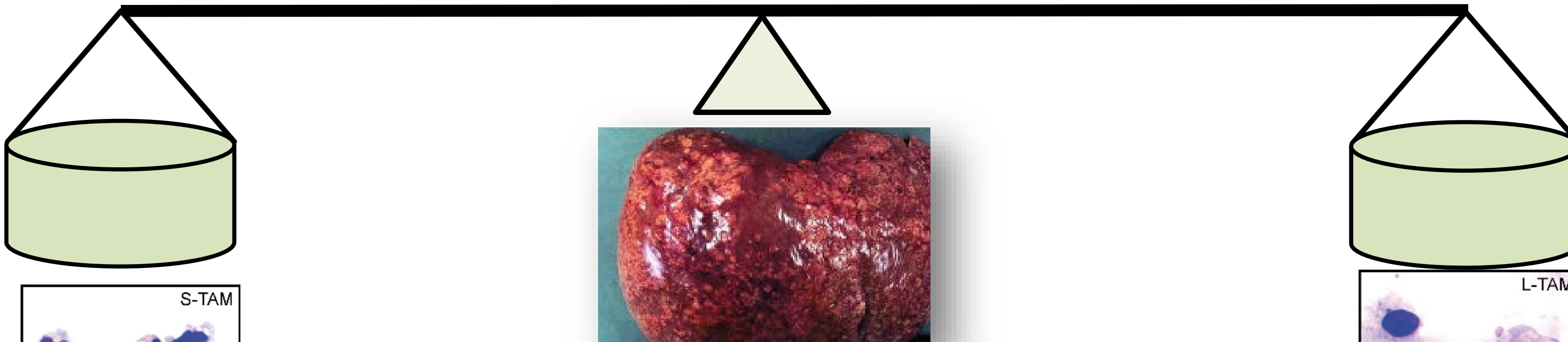
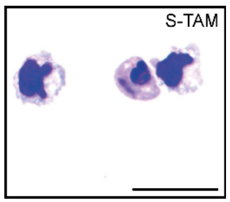
E-mail addresses: alberto.mantovani@humanitasresearch.it (A. Mantovani), federica.marchesi@humanitasresearch.it (F. Marchesi).

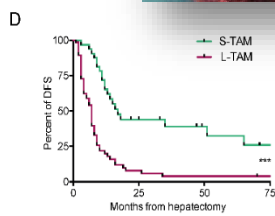
MACROPHAGE MORPHOLOGY and LOCALIZATION IN CRC METASTASIS AS A CORRELATE OF FUNCTION (SINGLE CELL) WITH PROGNOSTIC SIGNIFICANCE



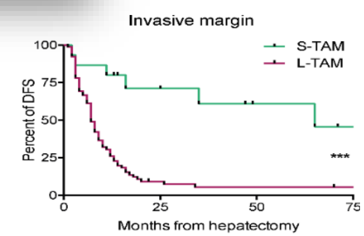


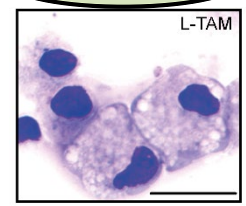
S-TAM

Anti-tumor?



	Number at risk			
Small TAMs	35	11	6	5
Large TAMs	66	4	2	1

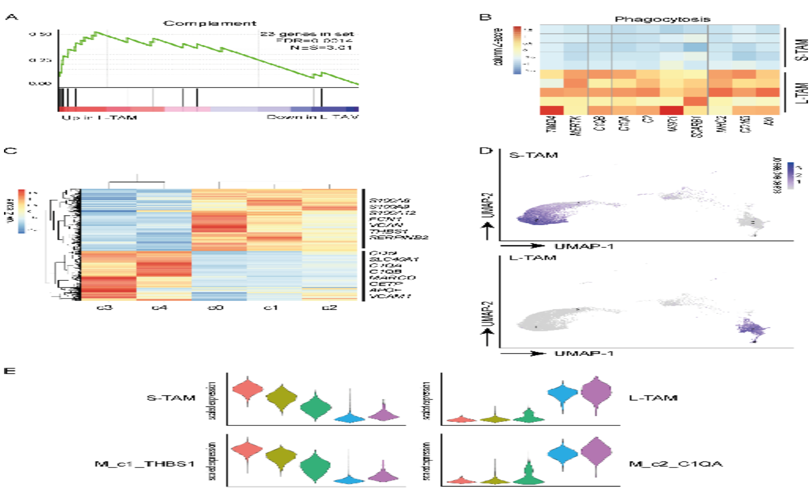




L-TAM

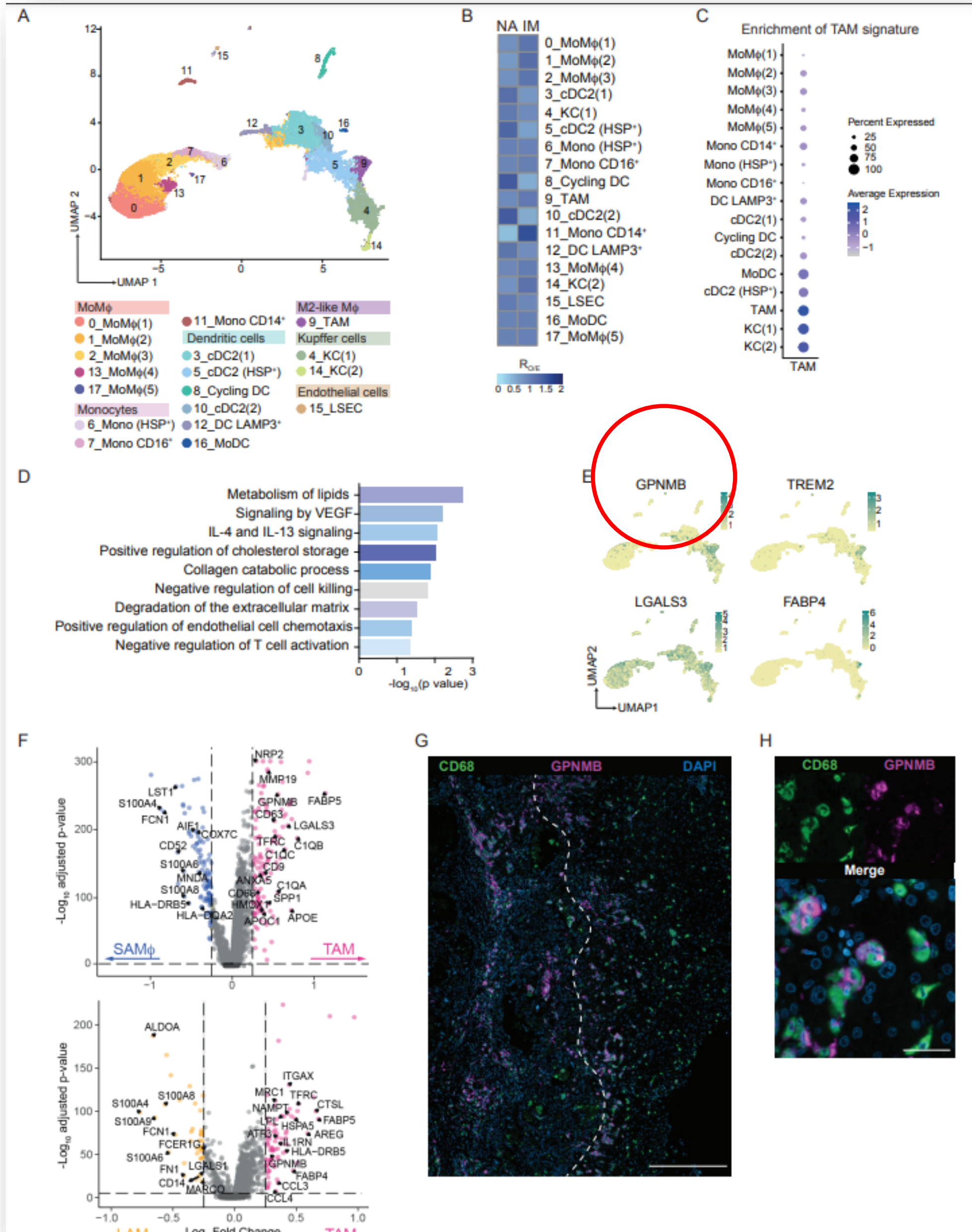
Pro-tumor

Lipid metabolism
Complement
....



(Donadon et al., J. Exp. Med. 2020;
Murray Editorial ibidem:
Cancian et al Deep Learning ..Cancers, 2021
Costa et al Int. J. Surg. 2023, in press)

Identification of GPNMB⁺ TAMs in the invasive margin of human CLM



Cortese et al. Cancer Immunol. Res, 2023

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In-depth characterization of inflammatory MoMϕ subsets and TAMs in CLM

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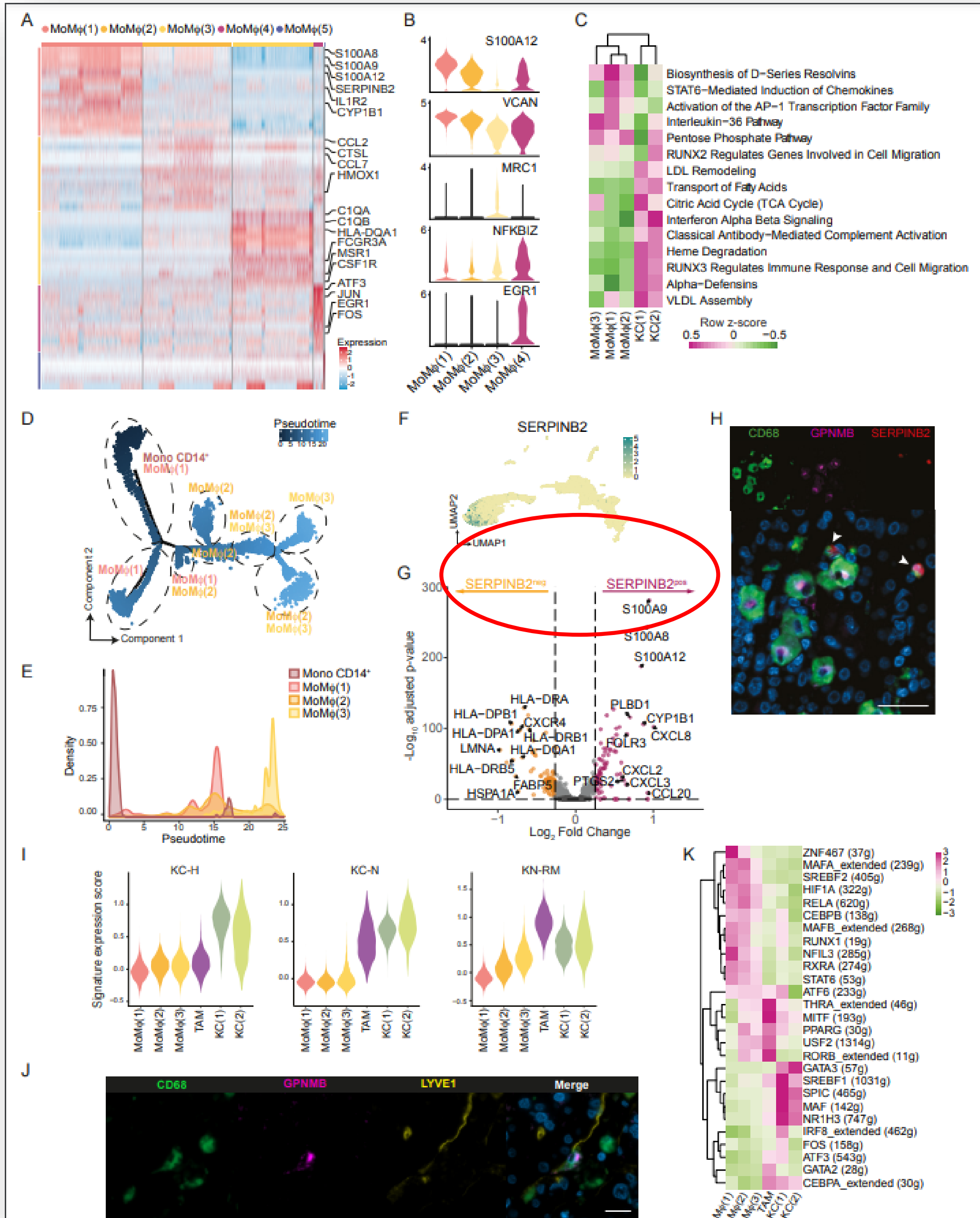
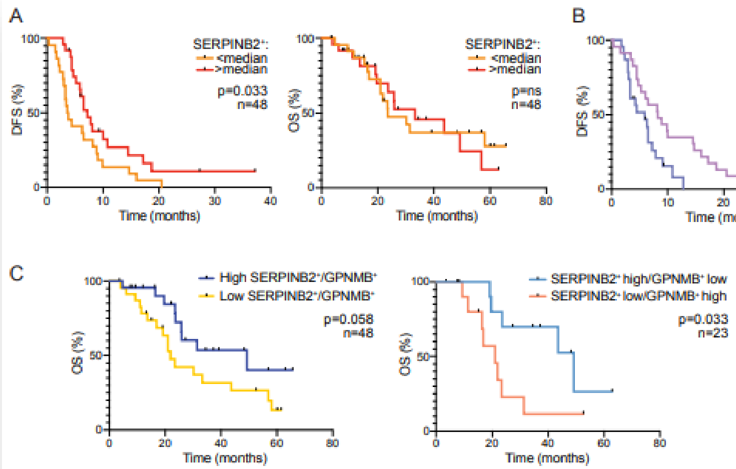
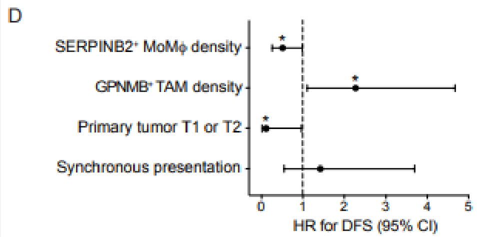
Queen Mary University of London



(Cortese et al. Cancer Immunol. Res, 2023)

Clinical relevance of SERPINB2^{+} MoMϕ and GPNMB^{+} TAMs in CLM and primary CRC

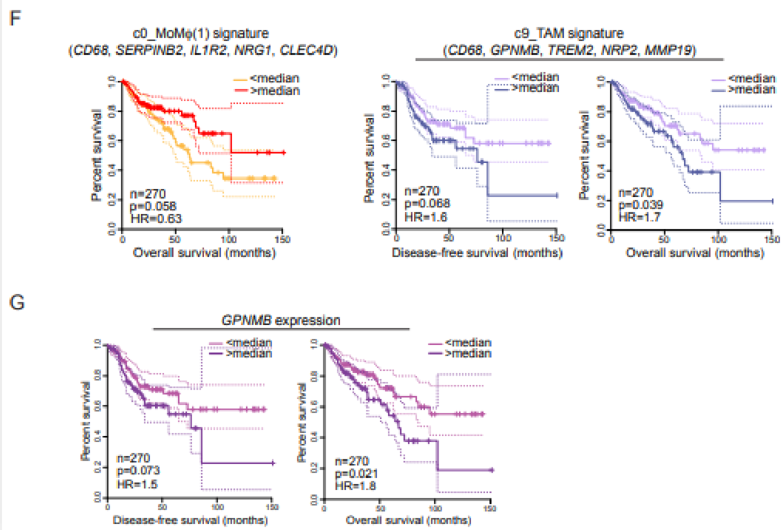




E

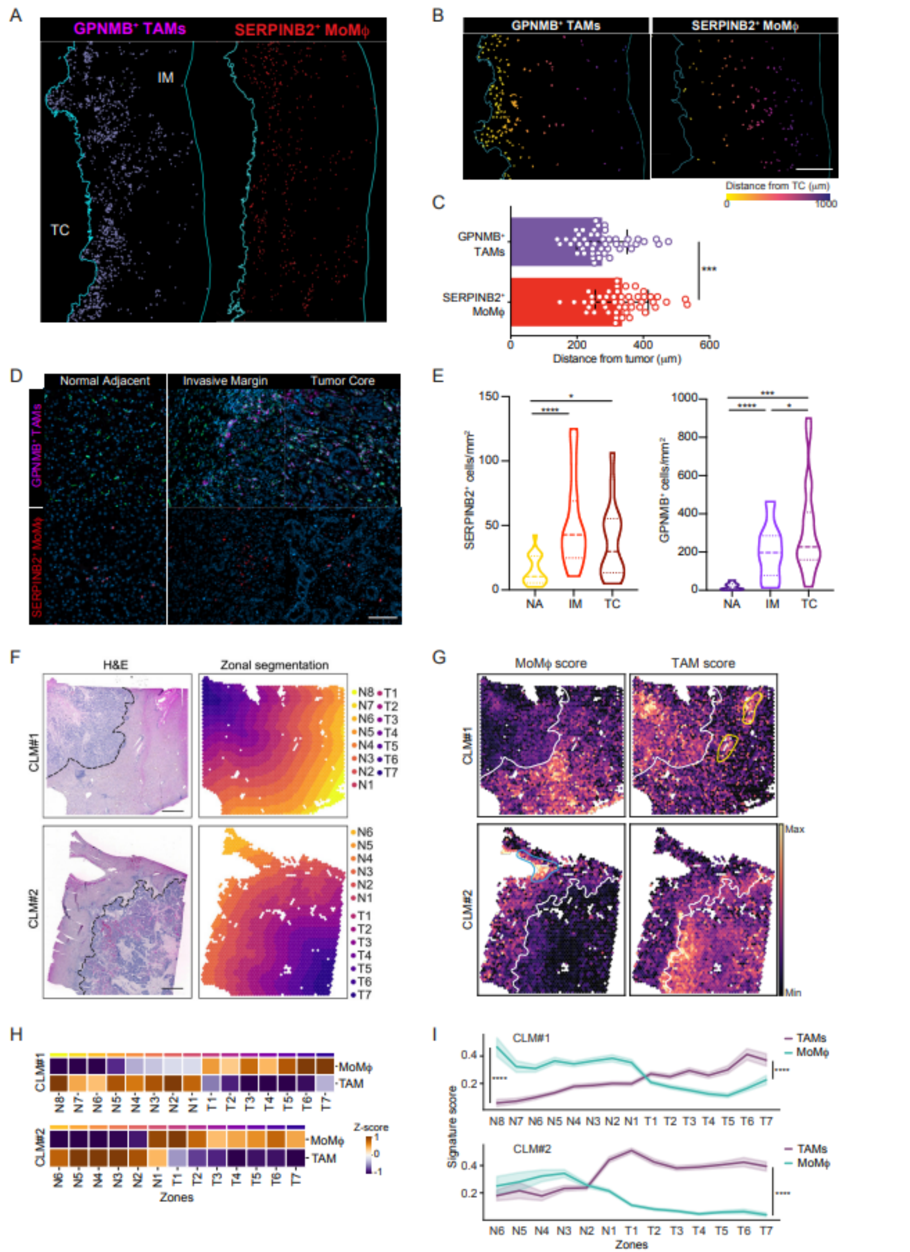
Multivariate analysis of prognostic factors for DFS

	HR	95% CI	P-value
SERPINB2⁺ MoMϕ density, <median vs >median	0.51	0.26 - 0.99	0.046
GPNMB⁺ TAM density, <median vs >median	2.27	1.11 - 4.66	0.025
T status of primary tumor, T1-2 vs T3-4	0.11	0.01 - 0.97	0.046
Synchronous presentation, Yes vs No	1.42	0.55 - 3.70	0.467



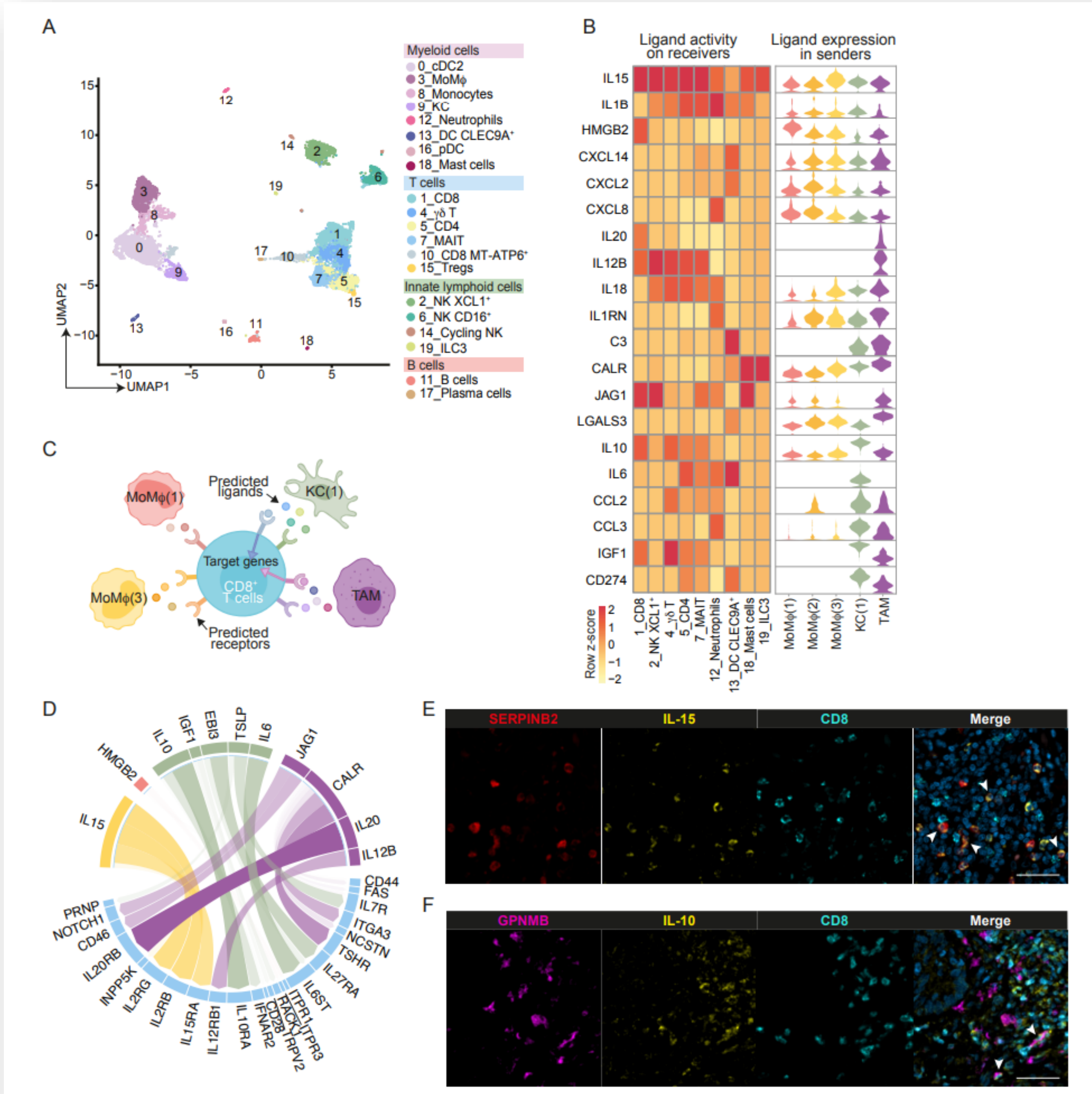
(Cortese et al. Cancer Immunol. Res, 2023)

Spatial assessment of MoMϕ and TAMs in the TME



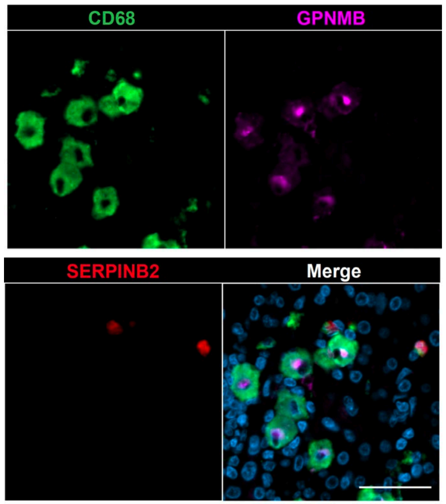
(Cortese et al. Cancer Immunol. Res, 2023)

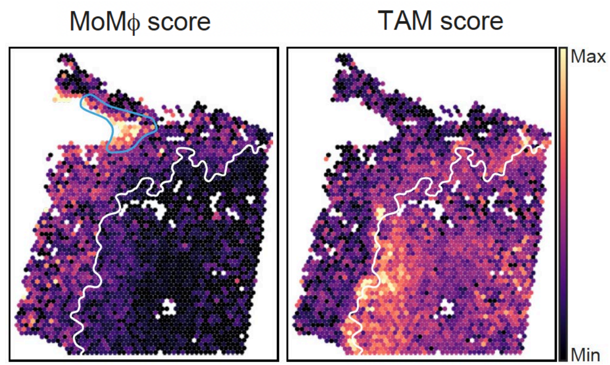
Cell-cell interaction networks of MoMϕ and TAMs in the TME

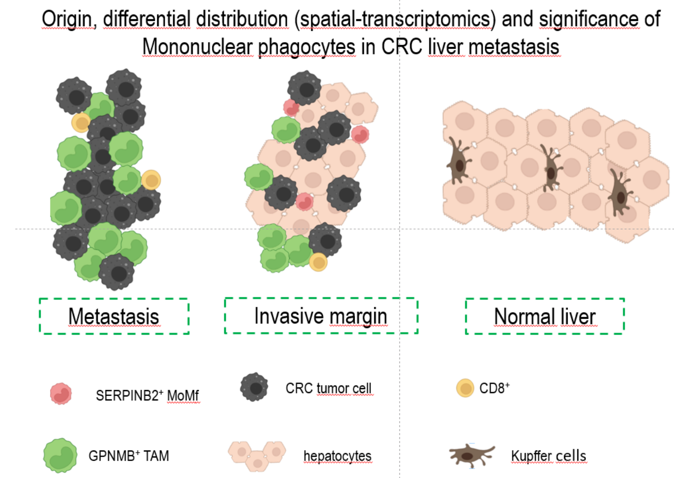


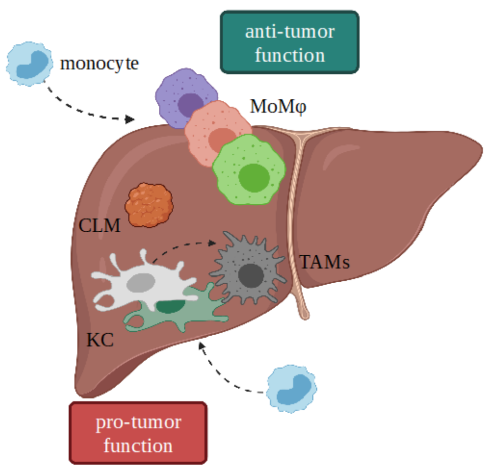
(Cortese et al. Cancer Immunol. Res, 2023)

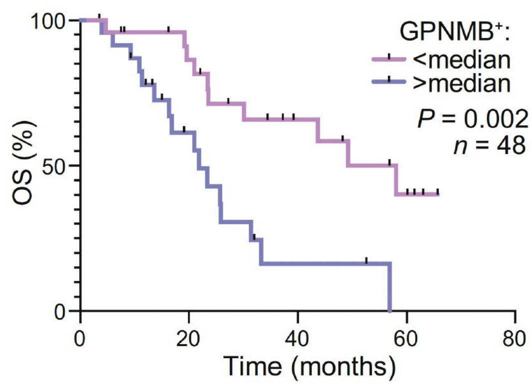
Origin, Spatial Distribution (mfIHC;Transcriptomics) and Significance of Mononuclear Phagocytes in Colorectal Cancer Liver Metastasis

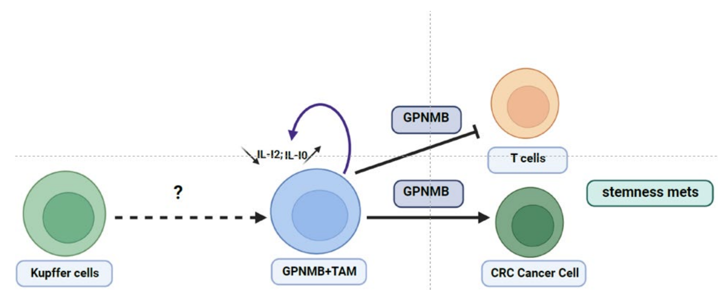






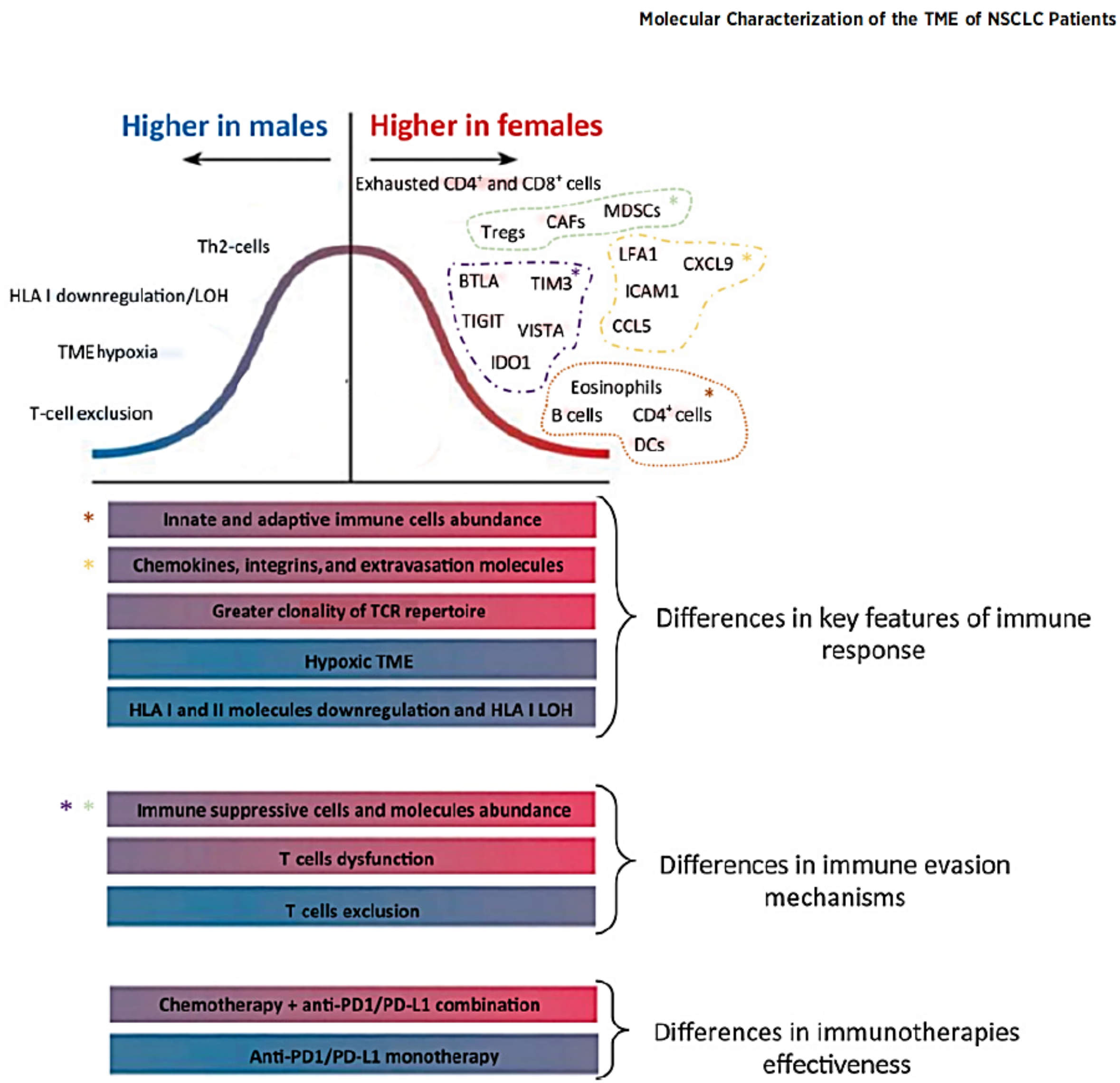






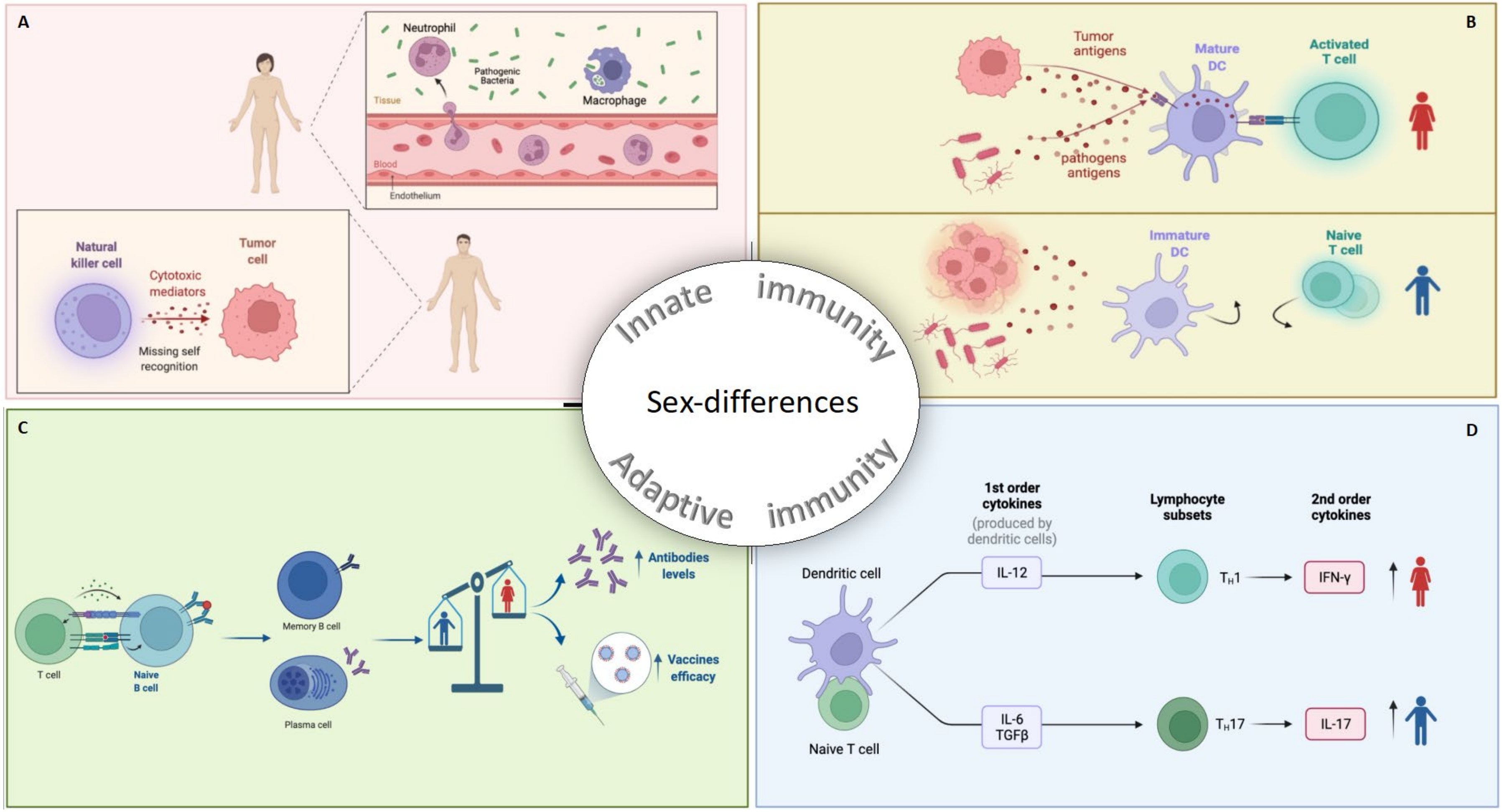
(Donadon et al J. Exp. Med. 2020; Costa et al Int. J. Surg. 2023; Cortese N, Carriero R, Cancer Imm. Res. 2023)

Sex-based differences of molecular mechanisms of anticancer immune response and immune evasion



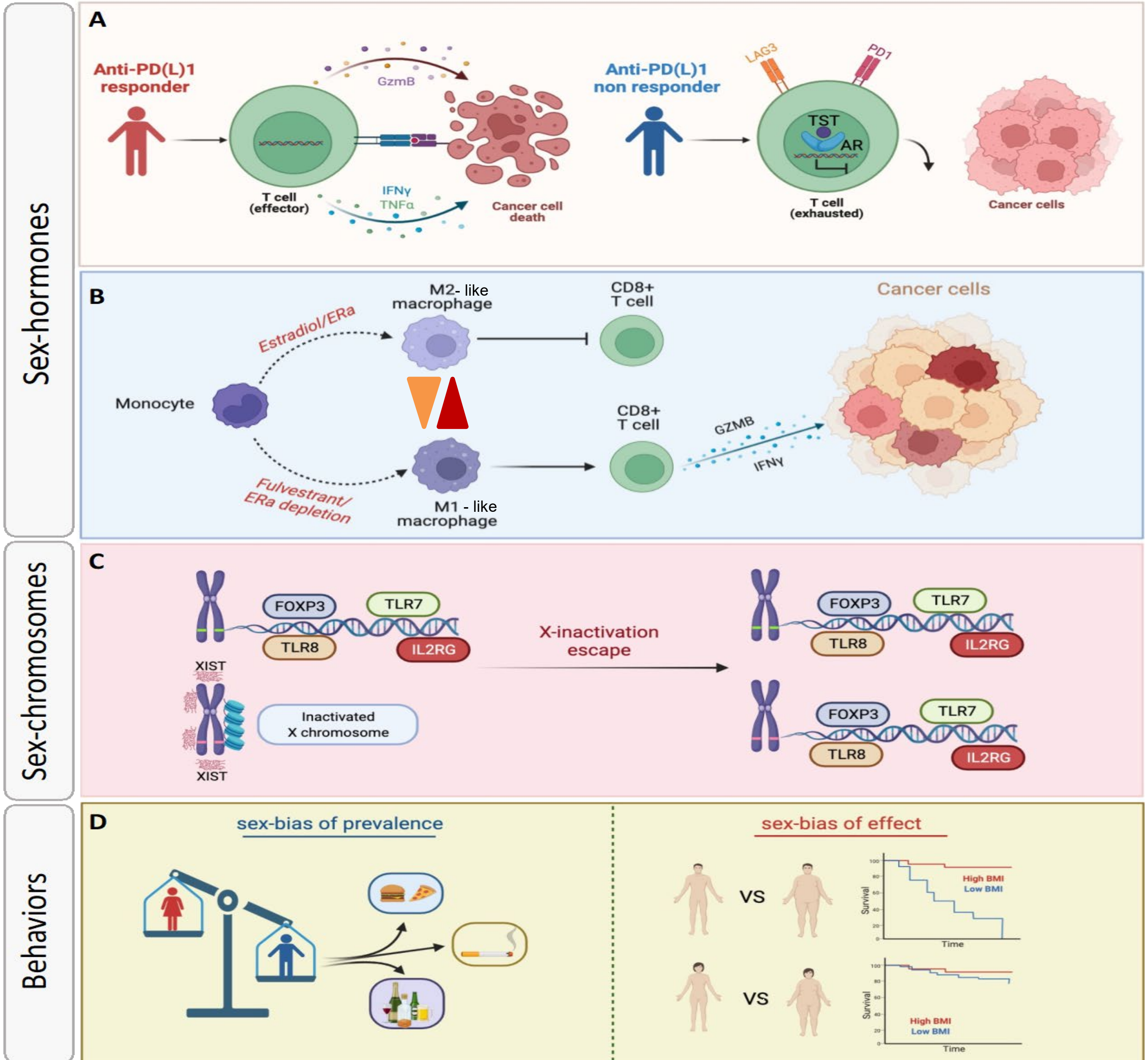
Conforti et al. *Clin Cancer Res*. 2021

Differences of innate and adaptive immune responses between healthy women and men



(Pala et al Cancer Cell 2022)

Molecular mechanisms underpinning the sex-based dimorphism of anticancer immune response



(Pala et al Cancer Cell 2022)

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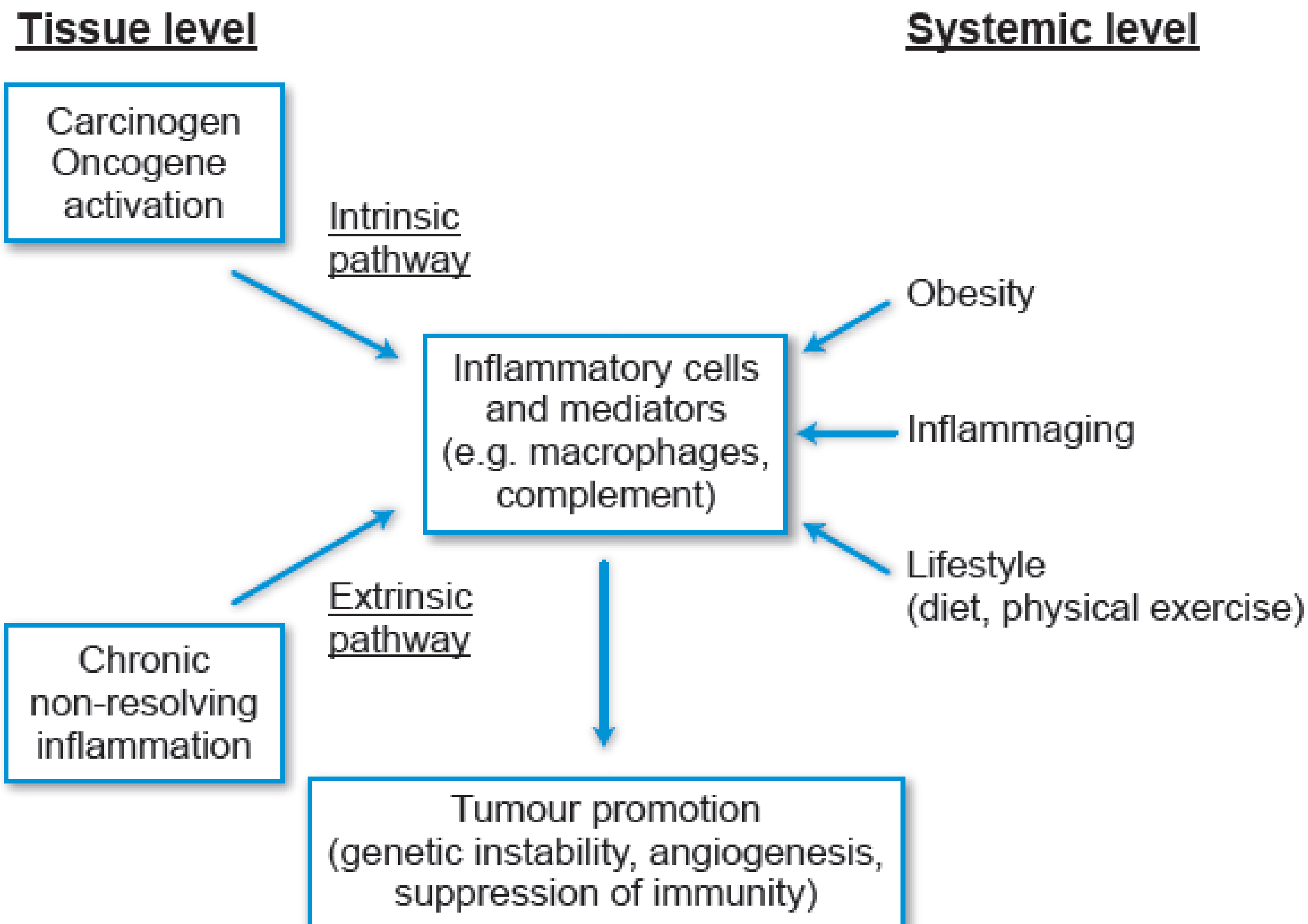
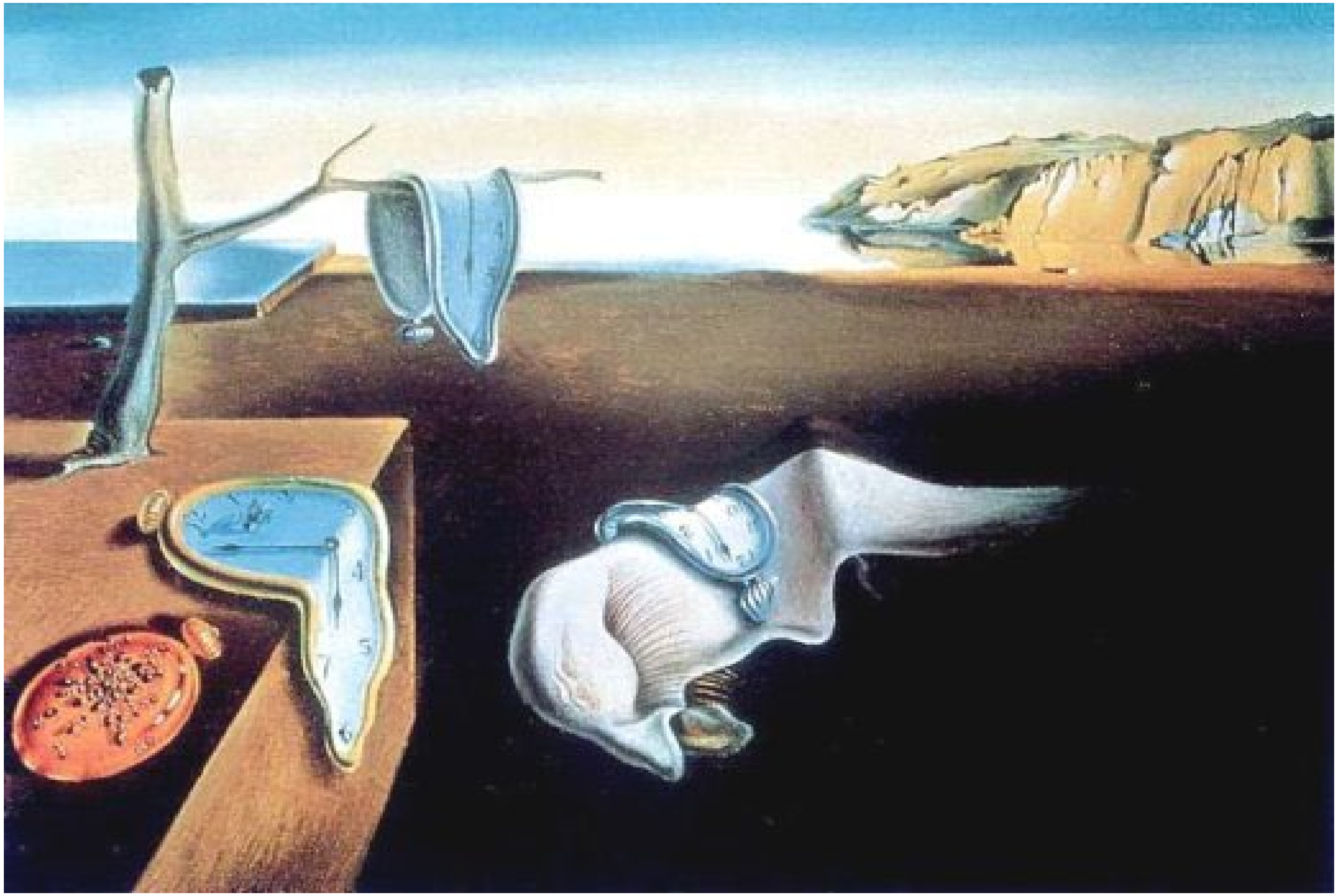
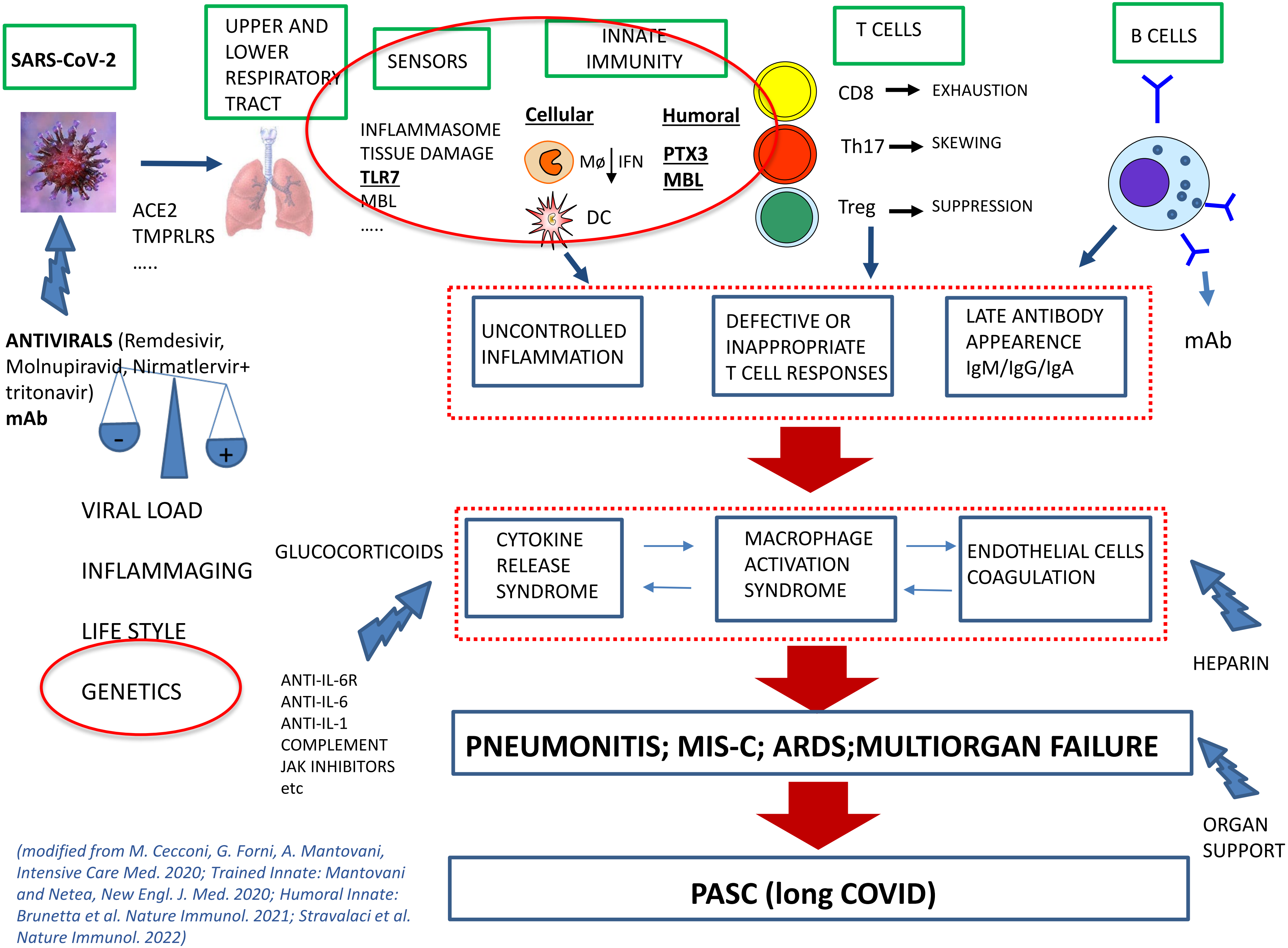
Pathways connecting inflammation and cancer at the tissue level and at the systemic level



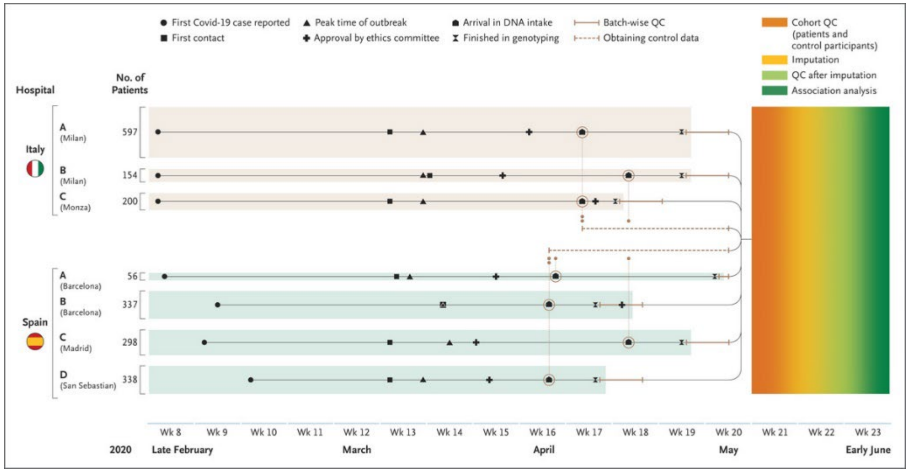
Mantovani et al, Nature, 2008; Nature, Rev Clin. Immunol., 2017; Mantovani, Bottazzi and Riboli, Seminars Immunology, 2018; World Cancer Report, IARC, Chapter 3.9 - Immune function, Mantovani, 2019



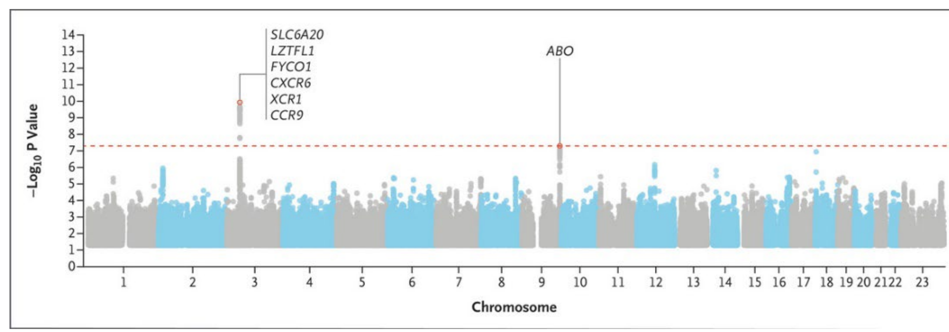


(modified from M. Cecconi, G. Forni, A. Mantovani, Intensive Care Med. 2020; Trained Innate: Mantovani and Netea, New Engl. J. Med. 2020; Humoral Innate: Brunetta et al. Nature Immunol. 2021; Stravalaci et al. Nature Immunol. 2022)

Timeline of rapid COVID-19 GWAS



Manhattan Plot of the meta-analysis highlighting the two susceptibility loci for Severe COVID-19 with Respiratory Failure



Ellinghaus D, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N Engl J Med*. 2020;NEJMoa2020283.

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Article

Mapping the human genetic architecture of COVID-19

https://doi.org/10.1038/s41586-021-03767-x

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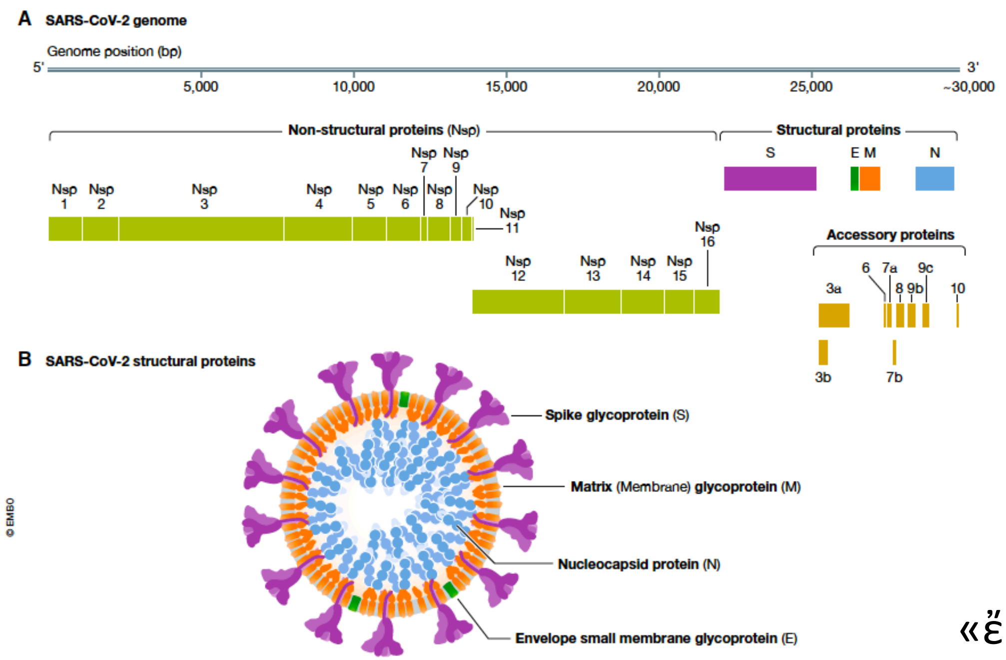
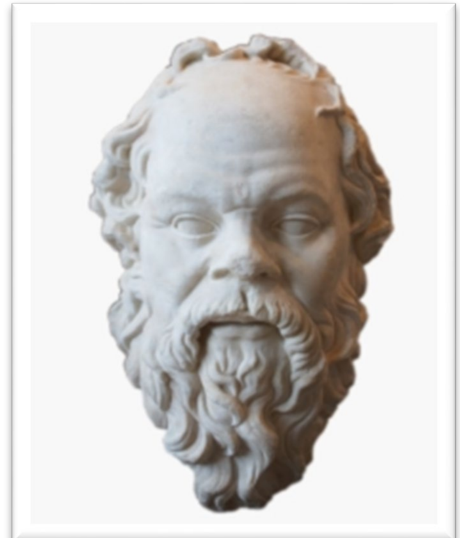
COVID-19 Host Genetics Initiative*

The genetic makeup of an individual contributes to susceptibility and response to viral infection. While environmental, clinical and social factors play a role in exposure to SARS-CoV-2 and COVID-19 disease severity[1,2], host genetics may also be important. Identifying host-specific genetic factors may reveal biological mechanisms of therapeutic relevance and clarify causal relationships of modifiable environmental risk factors for SARS-CoV-2 infection and outcomes. We formed a global network of researchers to investigate the role of human genetics in SARS-CoV-2 infection and COVID-19 severity. We describe the results of three genome-wide association meta-analyses comprised of up to 49,562 COVID-19 patients from 46 studies across 19 countries. We reported 13 genome-wide significant loci that are associated with SARS-CoV-2 infection or severe manifestations of COVID-19. Several of these loci correspond to previously documented associations to lung or autoimmune and inflammatory diseases[3–7]. They also represent potentially actionable mechanisms in response to infection. Mendelian Randomization analyses support a causal role for smoking and body mass index for severe COVID-19 although not for type II diabetes. The identification of novel host genetic factors associated with COVID-19, with unprecedented speed, was made possible by the community of human genetic researchers coming together to prioritize sharing of data, results, resources and analytical frameworks. This working model of international collaboration underscores what is possible for future genetic discoveries in emerging pandemics, or indeed for any complex human disease.

(Andrea Ganna and the COVID-19 Host Genetics Initiative, Nature, 2021)

THE CHANGING LANDSCAPE OF COVID-19





«ἔοικα γοῦν τούτου γε σμικρῷ τινι αὐτῷ τούτῳ σοφώτερος εἶναι, ὅτι ἃ μὴ οἶδα οὐδὲ οἴομαι εἰδέναι»

«Hence, I feel that I am wiser in this minor respect: what I do not know, I do not believe I know». Socrates

COVID-19: AT THE INTERCEPTION OF GENETIC PREDISPOSITION, IMMUNODEFICIENCY UNMASKED BY THE VIRUS, AUTOIMMUNITY AND UNCONTROLLED INFLAMMATION

(Platone, Apologia)

nature immunology

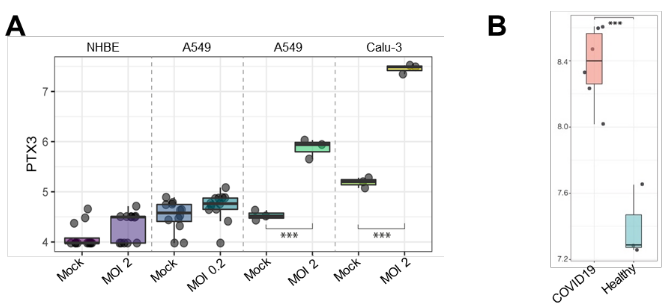
LETTERS

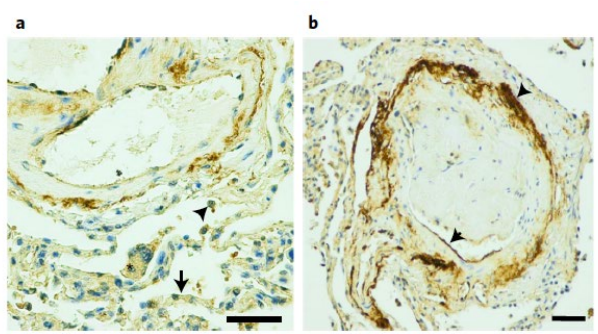
https://doi.org/10.1038/s41590-020-00832-x

Check for updates

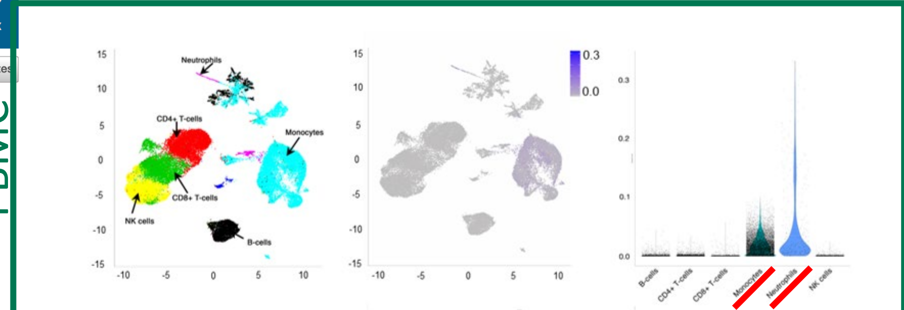
Macrophage expression and prognostic significance of the long pentraxin PTX3 in COVID-19

Enrico Brunetta[1,2,10], Marco Folci[1,2,10], Barbara Bottazzi[1,10], Maria De Santis[1], Giuseppe Gritti[3], Alessandro Protti[1,2], Sarah N. Mapelli[1], Stefanos Bonovas[1,2], Daniele Piovani[1,2], Roberto Leone[1], Ilaria My[1,2], Veronica Zanon[1], Gianmarco Spata[1], Monica Bacci[1], Domenico Supino[2], Silvia Carnevale[2], Marina Sironi[1], Sadaf Davoudian[1], Clelia Peano[1,4], Francesco Landi[3], Fabiano Di Marco[5,6], Federico Raimondi[5], Andrea Gianatti[7], Claudio Angelini[1], Alessandro Rambaldi[3,8]✉, Cecilia Garlanda[1,2]✉, Michele Ciccarelli[1]✉, Maurizio Cecconi[1,2]✉ and Alberto Mantovani[1,2,9]✉

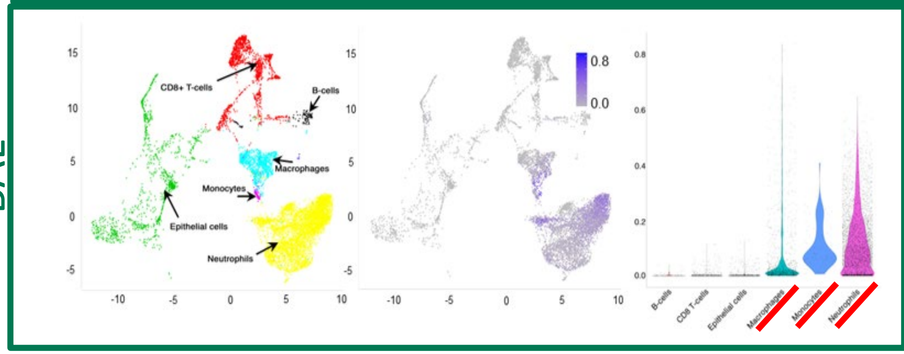


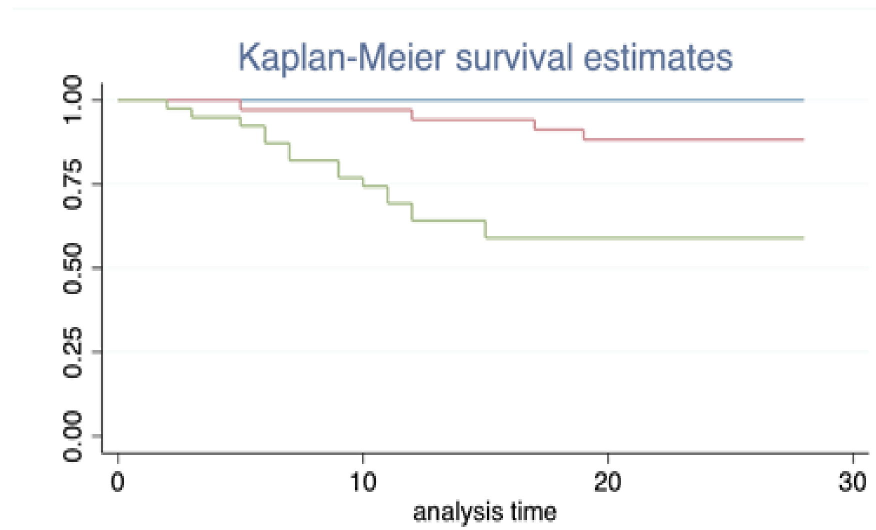


PBMC



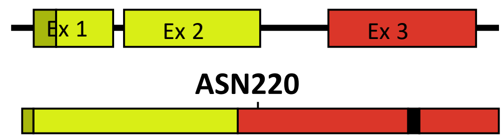
BAL

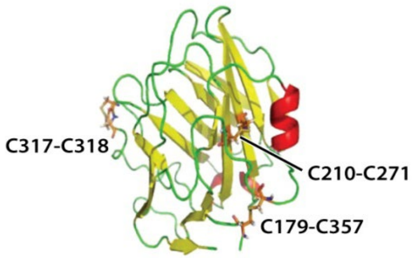




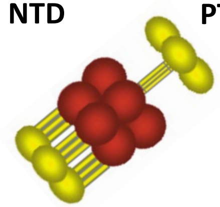
Chr 3q25
mRNA 1866 bp

Prot 381 aa

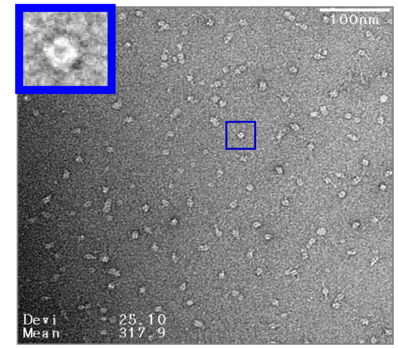




PTX3
C-terminal domain



PTX3



OmpA
Men B
components

Microbe recognition

FcγR

Opsonization

C1q
Factor H

C activation and regulation of inflammation

Ficolins
MBL

Repertoire synergism

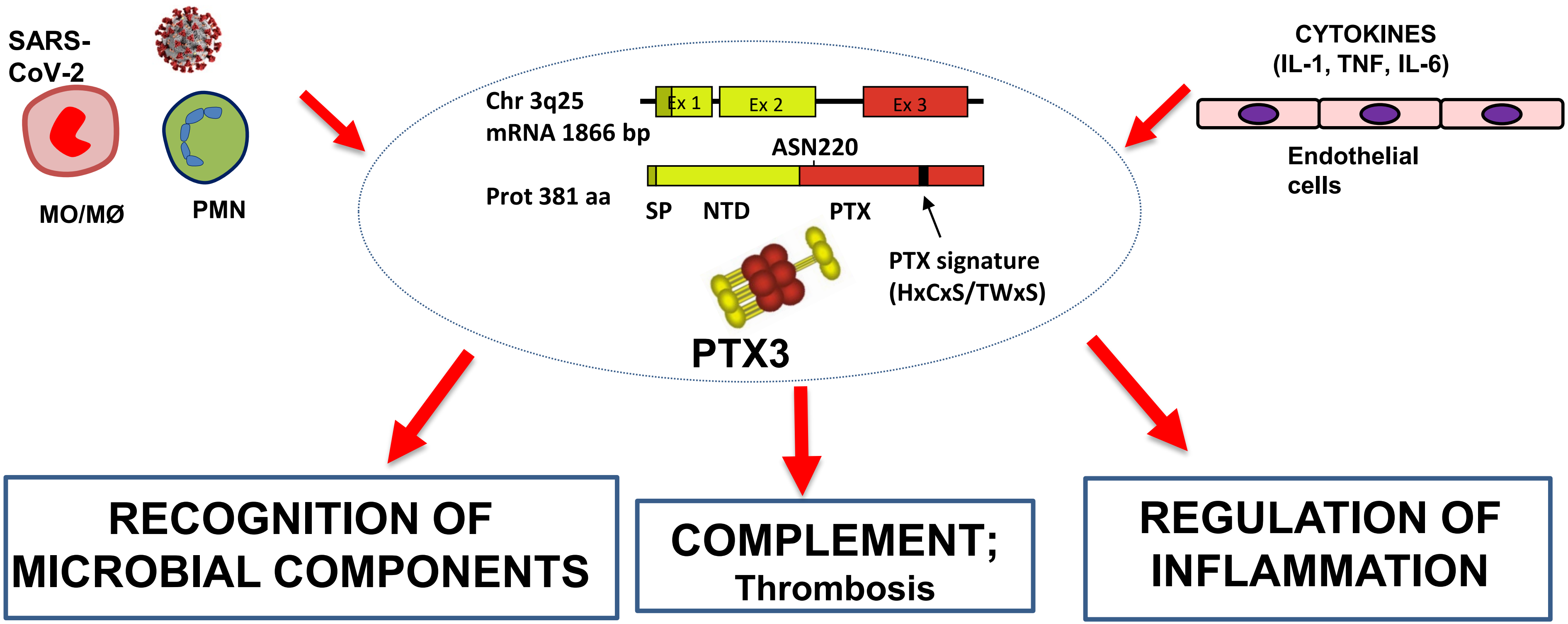
P-selectin

Regulation of leukocyte recruitment and inflammation

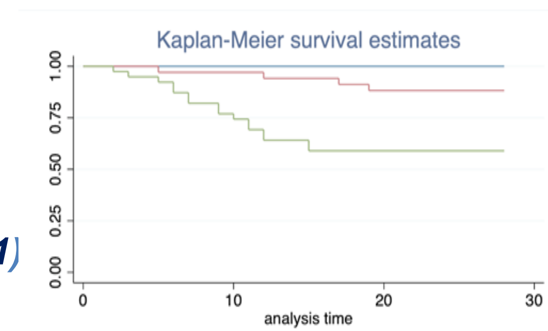
RESISTANCE TO SELECTED MICROBES (eg A. fumigatus, P. aeruginosa) – REGULATION OF INFLAMMATION and REPAIR – ADAPTIVE IMMUNITY

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

PROGNOSTIC SIGNIFICANCE OF PTX3: INTEGRATING MYELOMONOCYTIC CELL AND ENDOTHELIAL CELL RESPONSE



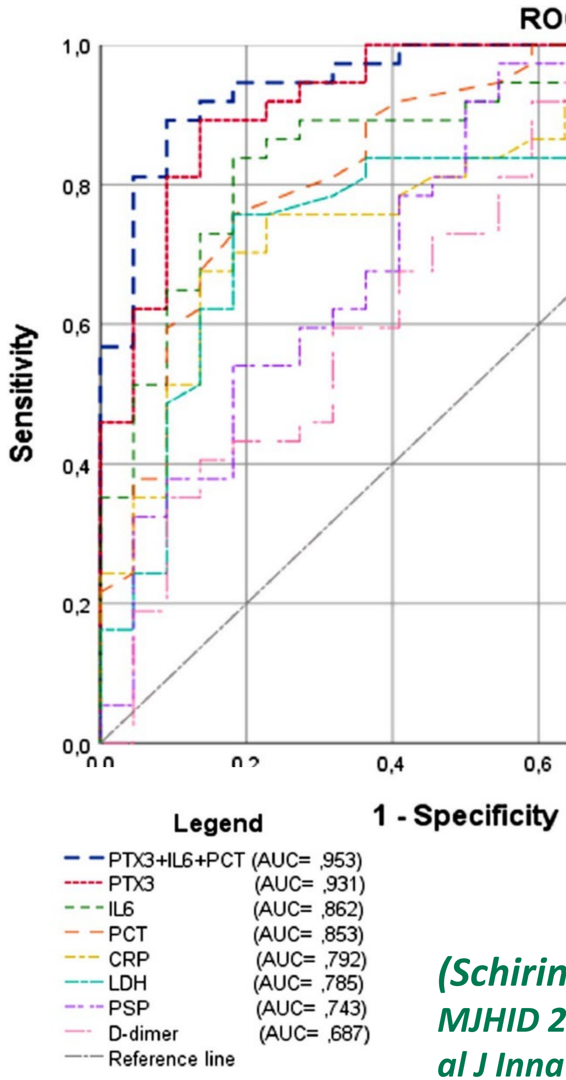
BIOMARKER;PROGNOSIS

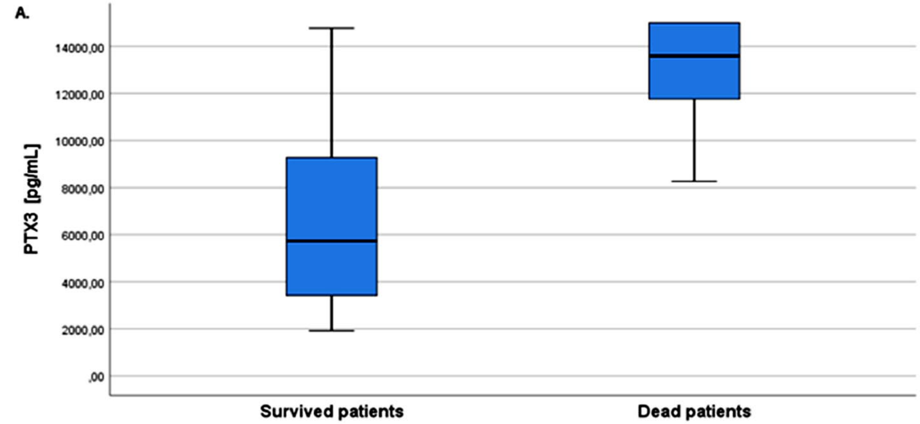


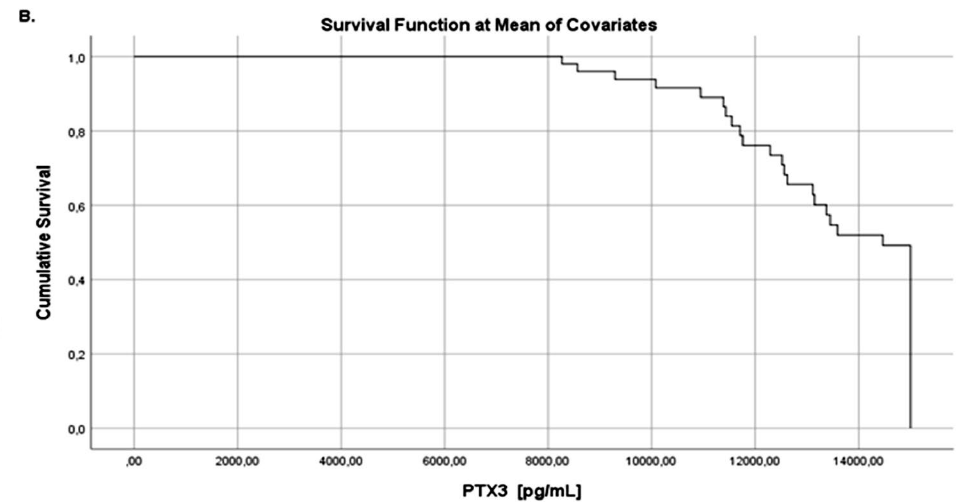
(Brunetta, Folci, Bottazzi et al., Nature Immunology, 2020; MedRxiv 2021)

(Confirmed and extended by: Schirinzi et al. The Journal of Infection, 2020; Tong et al MJHID 2020; Genc et al Tur J Med Sci 2020; Gutmann et al Nature Com. 2021; Hansen et al J Innate Immunity 2021; Lapadula et al Front. Immunol 2022; Long Covid: Phetsouphan et al Nature Med 2022)

PTX3 AS A PREDICTOR OF DEATH IN COVID-19







(Schirinzi et al. The Journal of Infection, 2020. Similar results on PTX3 in: Tong et al MJHID 2020; Genc et al Tur J Med Sci 2020; Gutmann et al Nature Com. 2021; Hansen et al J Innate Immunity 2021; Lapadula et al. Front Immunol 2022)

(PTX3 in Long Covid: Phetsouphan et al Nature Immunology 2022)

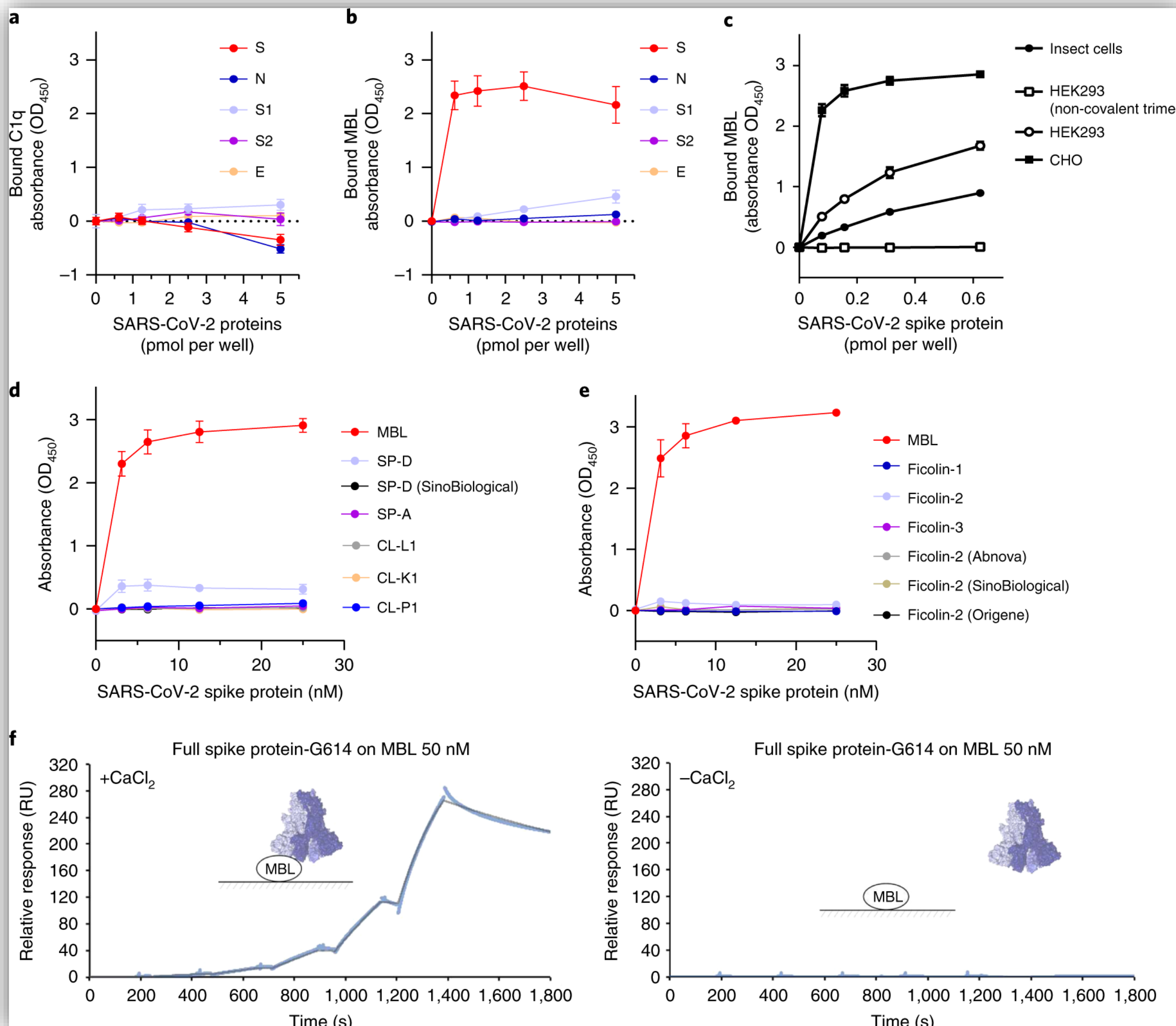
Main Acute-Phase proteins and their Role in Covid-19

Table 1. Main Acute-Phase Proteins and Their Role in Covid-19.*

Function and Protein or Proteins	Degree and Type of Change in Inflammatory Conditions†	Role or Roles in Covid-19 and Associated Conditions‡
Humoral innate immunity		
C-reactive protein	↑↑↑↑	Association with death, ICU admission, need for interleukin-6 inhibition, and PASC[11-14]
Serum amyloid P	↑ or →	ND
Serum amyloid A	↑↑↑↑	Association with severity[15]
PTX3	↑↑↑	Association with death, lung lesions on CT, response to interleukin-6 inhibition, intubation, thrombotic events, and PASC[16-19]
C1q, C3, and C4	↑	Association with pathogenesis[20,21]
C4-binding protein	↑	ND
Mannose-binding lectin	↑↑ or →	Viral inhibition, association with thromboembolism[22]
Interleukin-1Ra	↑↑	Association between anti–interleukin-1Ra autoantibodies and severity, MIS-C, or myocarditis after SARS-CoV-2 vaccination[23]
Coagulation or tissue repair and remodeling		
Fibrinogen	↑↑	Association of D-dimer with thromboembolism[14]
Prothrombin	→	ND
Fibronectin	↑ or →	ND
α2-Macroglobulin	↑	ND
Antithrombin III	↓	ND
α1-Antitrypsin	↑↑	ND
α1-Antichymotrypsin	↑↑	ND
Urokinase-type plasminogen activator	↑	ND
Thrombopoietin	↑↑	ND
Iron metabolism		
Transferrin	↓	ND
Ferritin	↑↑	Association with ICU admission and mechanical ventilation[14,24]
Haptoglobin	↑↑	ND
Hemopexin	↑	ND
Hepcidin	↑↑	ND
Other carrier proteins		
Albumin	↓	ND
Ceruloplasmin	↑ or →	ND
Apolipoproteins	↓	ND
α1-Acid glycoprotein	↑↑	ND

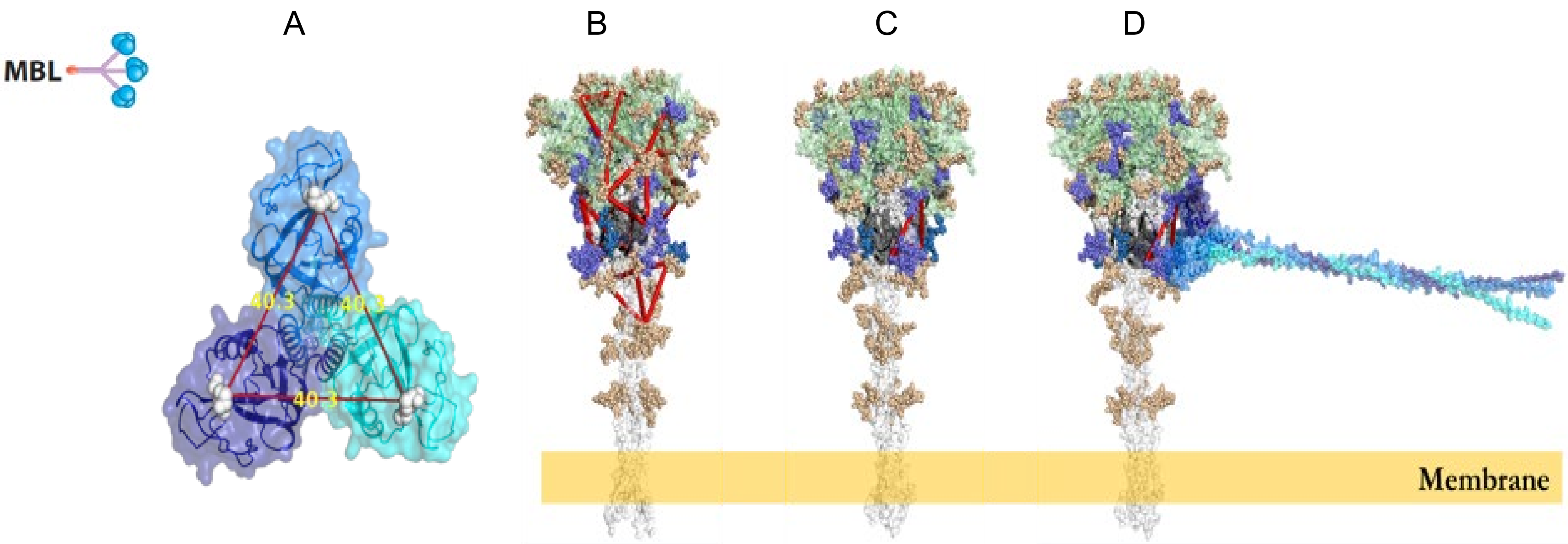
(Mantovani and Garlanda, New England J. Med. 2023)

Interaction of C1q, MBL, ficolins and surfactant proteins with SARS-CoV-2 proteins



Stravalaci, Pagani et al. Nature Immunol. 2022

Model of the interaction between MBL and Spike

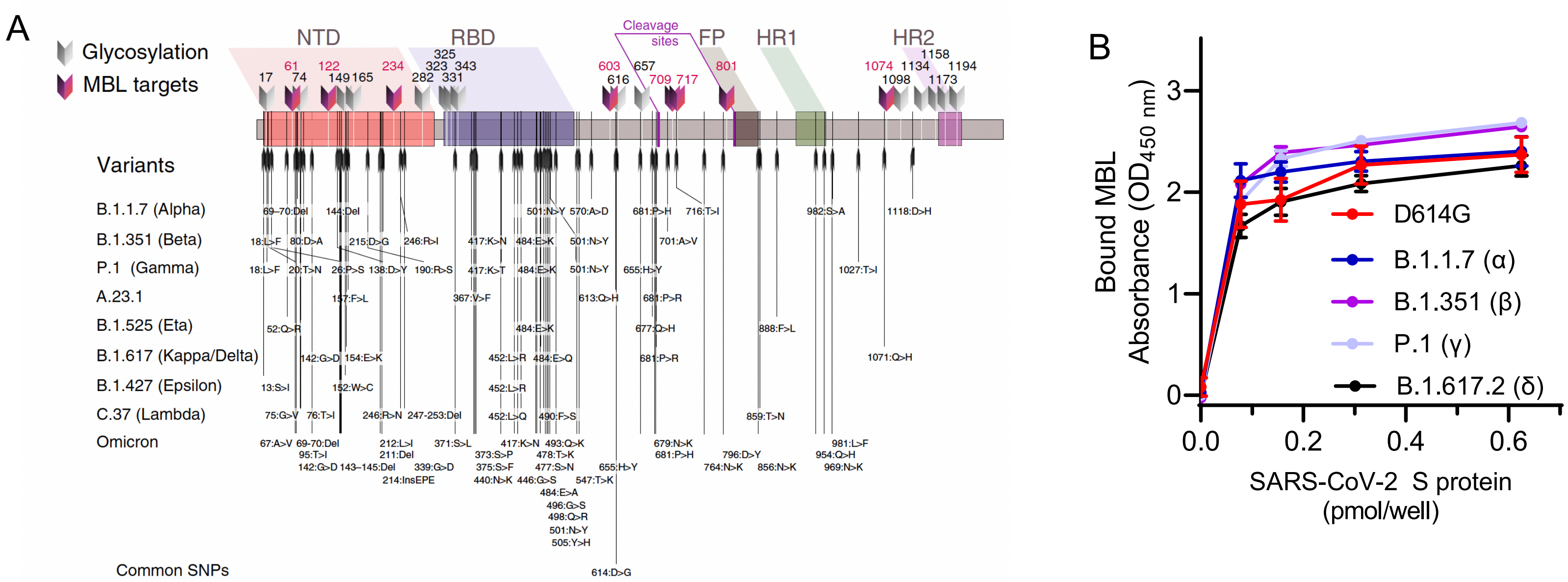


A- Trimeric MBL model shows the distance of approximately 40 Å between mannose-binding sites.
B- 14 mannose-binding sites in Spike, represented as red triangles.
C- Putative binding site of MBL (highest site-specific probability to be glycosylated with oligomannose).
D- Spike-MBL complex.
Glycosylation sites are colored according to the oligomannose glycosylation probability. Gold < 60%. Purple > 80% up until S2' region. Blue > 80% in the S2' region.

Stravalaci, Pagani *et al.*, *2022, Nature Immunology*

Andrea Cavalli

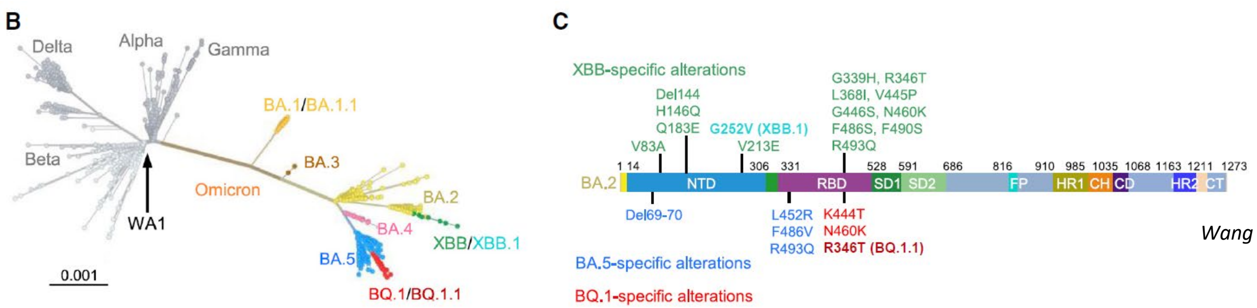
Mutations of SARS-CoV-2 Spike variants do not impact glycosylation sites and interaction with MBL



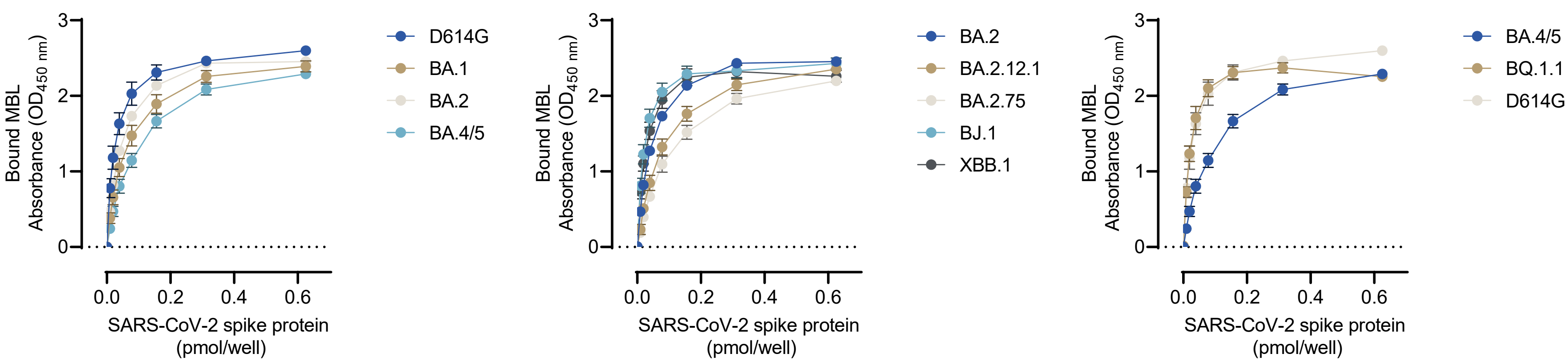
- **None of reported mutations involve the glycosylation sites**
- **Binding of MBL to S is not affected by mutations of variants**

This is in line with the role of innate immunity in recognizing conserved and essential microbial moieties (C. Janeway).

Binding of MBL to SARS-CoV-2 spike protein Omicron subvariants



Wang et al., 2023, Cell 186, 1–8



n=3 exp, mean ± SEM

(Stravalaci et al unpublished data)

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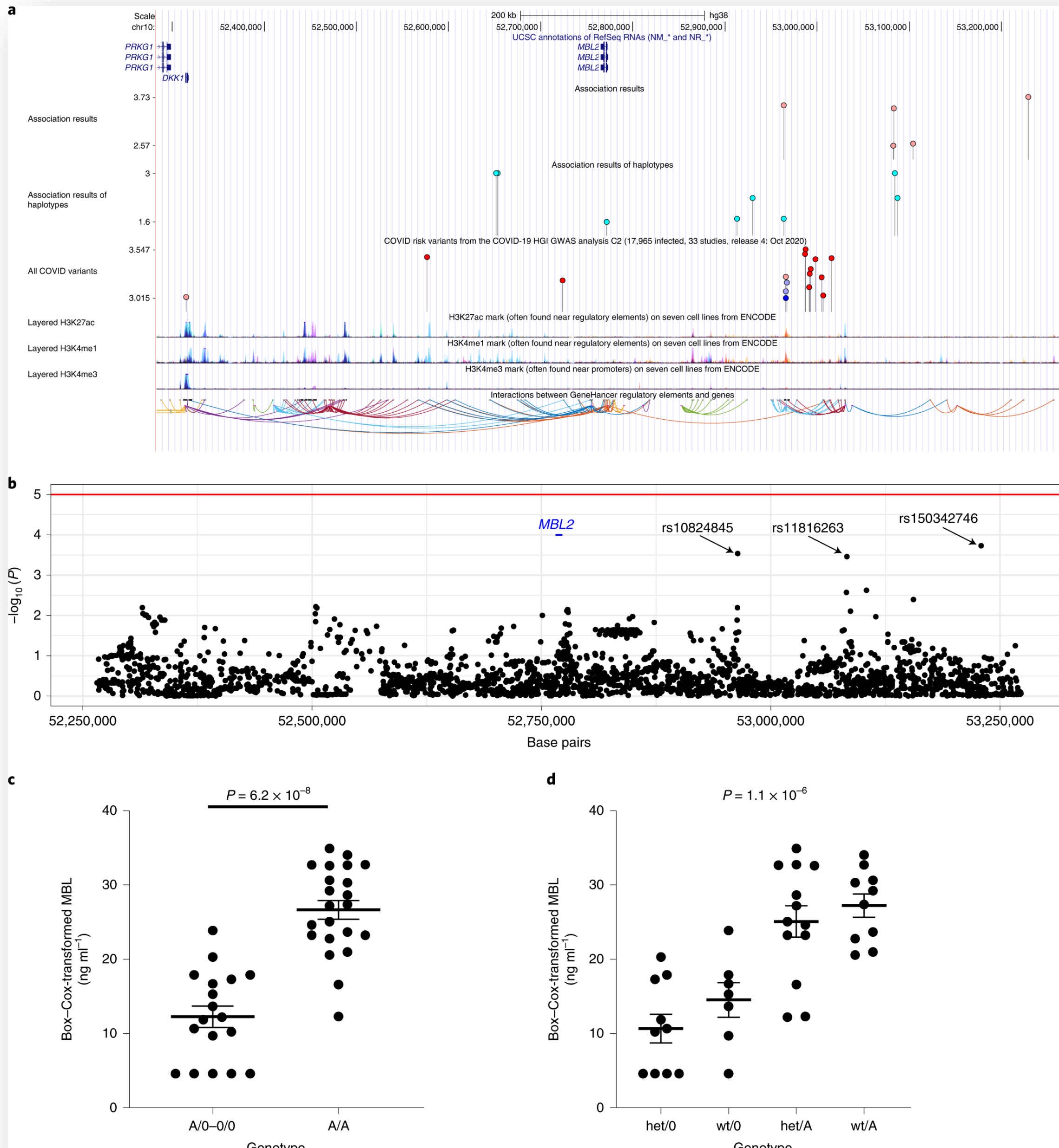
The *MBL2* locus: structure and main association signals with severe COVID-19



Stravalaci, Pagani et al. Nature Immunol. 2022; Asselta et al Nature Immunol. 2023

Matter arising

nature immunology

MATTERS ARISING

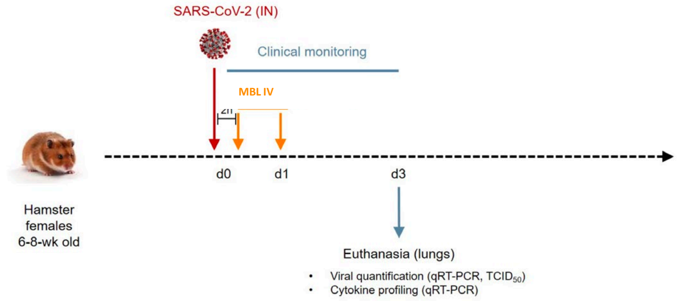
https://doi.org/10.1038/s41590-022-01227-w

Check for updates

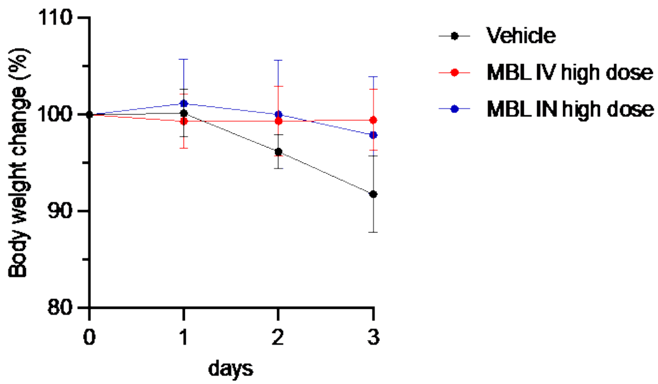
Genetic determinants of mannose-binding lectin activity predispose to thromboembolic complications in critical COVID-19

Michael Hultström[1,2,3,4,13], Robert Frithiof[1,13], Jonathan Grip[5,6,13], Linnea Lindelöf[7,13], Olav Rooijackers[5,6], Sara Pigazzini[8], Mari Niemi[8], Mattia Cordioli[8], Lindo Nkambule[8], Tomislav Maricic[9], Kristina Nilsson Ekdahl[7,10], Bo Nilsson[7], Miklós Lipcsey[1,11], Hugo Zeberg[9,12,13] ✉ and Oskar Eriksson[7,13] ✉

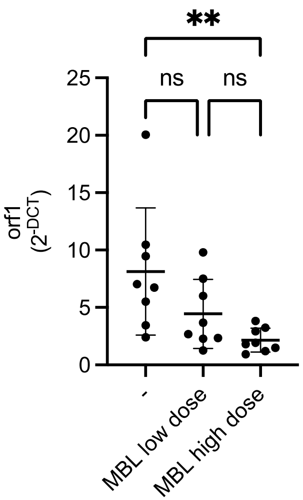
COVID-19 in vivo therapy with MBL



Body weight loss



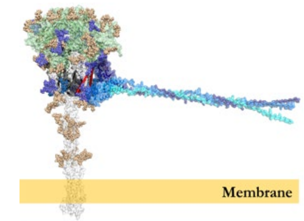
Viral load



MBL treatment protects SARS-CoV-2 infected hamsters

(Garlanda and European Research Biology Center, unpublished)

Binding of MBL to Spike protein



Early phase

Late phase

Protection:

-Mode of action?
Competition with C-type lectins
Fusion neutralization

Antiviral activity

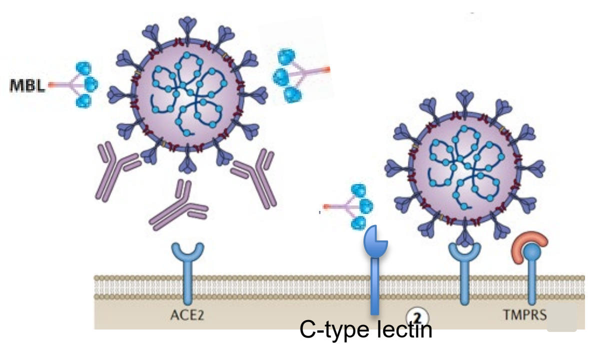
Prognostic:

MBL SNPs associated with susceptibility or thrombosis

Pathogenesis:

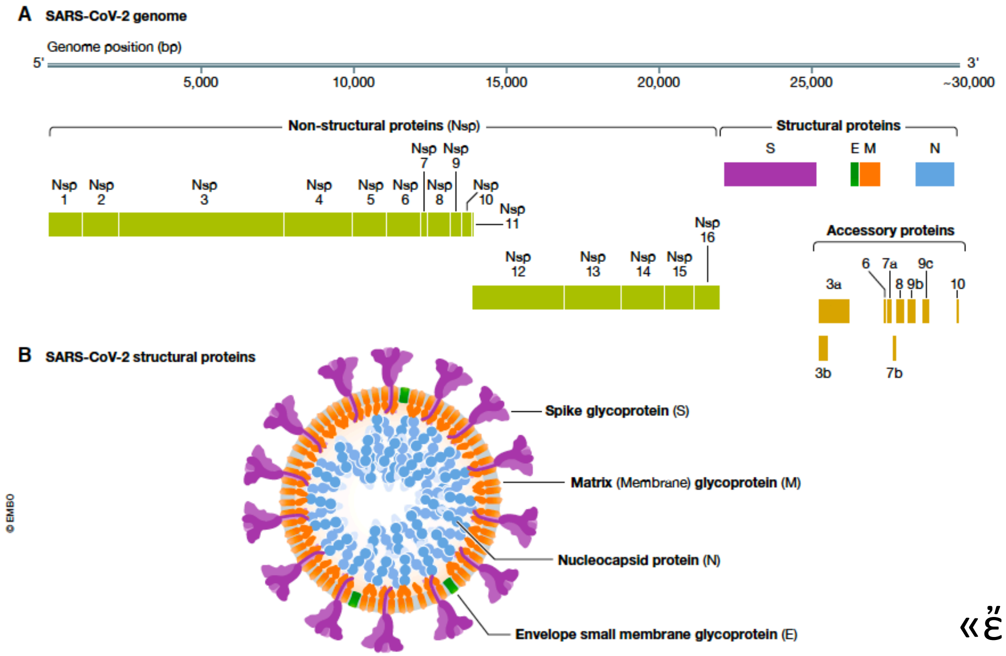
-Complement activation
-Thromboembolism
-Ante-antibody-dependent enhancement (A-ADE) phenomenon

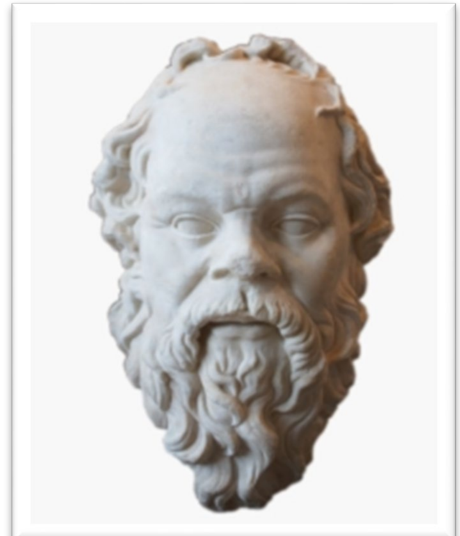
Tissue damage



(Stravalaci, Pagani et al. Nature Immunol. 2022; and unpublished data)

THE CHANGING LANDSCAPE OF COVID-19





«ἔοικα γοῦν τούτου γε σμικρῷ τινι αὐτῷ τούτῳ σοφώτερος εἶναι, ὅτι ἃ μὴ οἶδα οὐδὲ οἴομαι εἰδέναι»

«Hence, I feel that I am wiser in this minor respect: what I do not know, I do not believe I know». Socrates

COVID-19: AT THE INTERCEPTION OF GENETIC PREDISPOSITION, IMMUNODEFICIENCY UNMASKED BY THE VIRUS, AUTOIMMUNITY AND UNCONTROLLED INFLAMMATION

(Platone, Apologia)

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nature immunology

Letter

https://doi.org/10.1038/s41590-023-01445-w

Autoantibodies against chemokines post-SARS-CoV-2 infection correlate with disease course

Received: 11 July 2022

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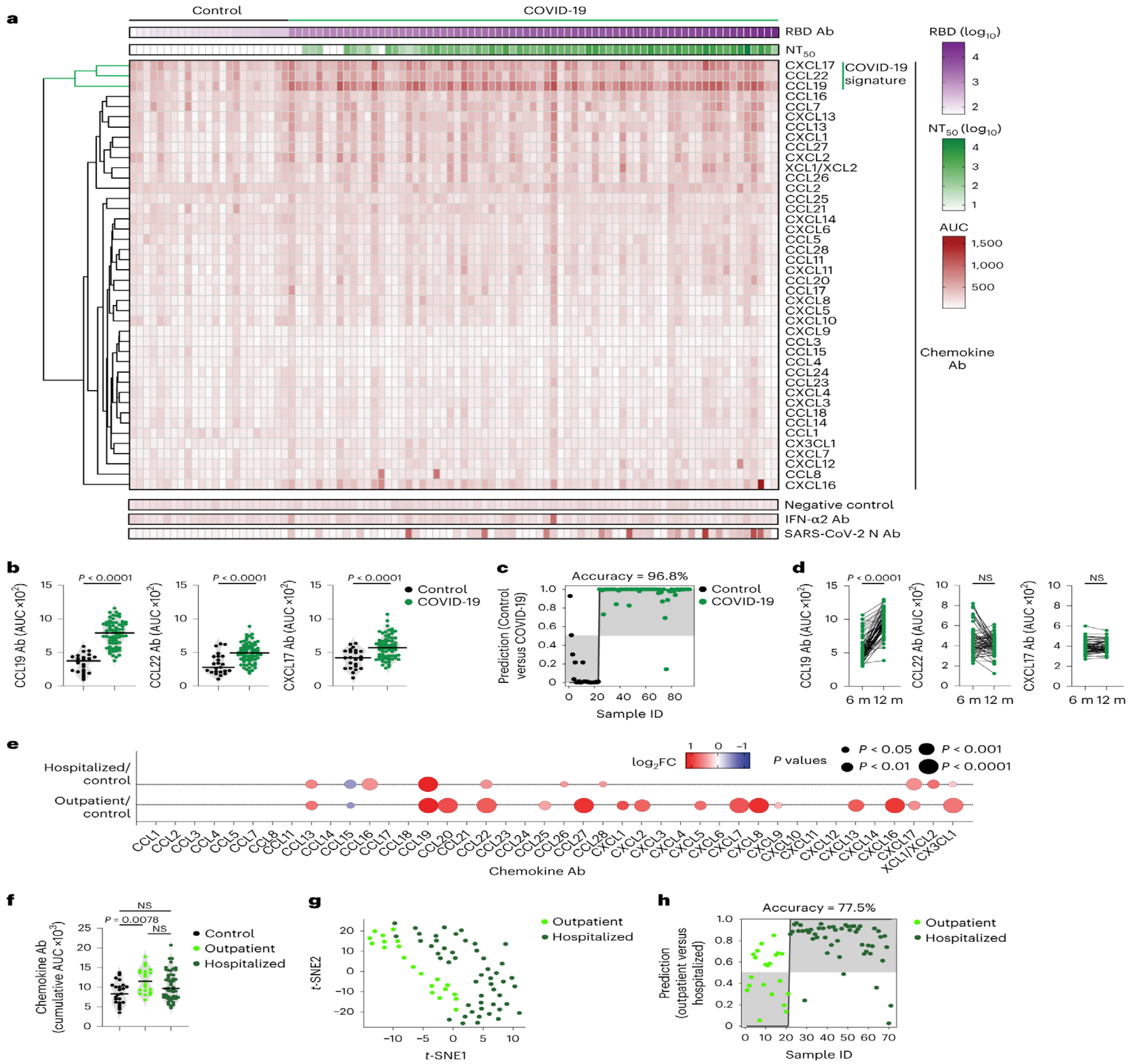
Check for updates

Jonathan Muri[1,23], Valentina Cecchinato[1,23], Andrea Cavalli[1,2] ✉, Akanksha A. Shanbhag[1], Milos Matkovic[1], Maira Biggiogero[3], Pier Andrea Maida[3], Jacques Moritz[1], Chiara Toscano[1], Elaheh Ghovehoud[1], Raffaello Furlan[4,5], Franca Barbic[4,5], Antonio Voza[4,6], Guendalina De Nadai[7], Carlo Cervia[8], Yves Zurbuchen[8], Patrick Taeschler[8], Lilly A. Murray[9], Gabriela Danelon-Sargenti[1], Simone Moro[1], Tao Gong[1], Pietro Piffaretti[1], Filippo Bianchini[1], Virginia Crivelli[1], Lucie Podešvová[1], Mattia Pedotti[1], David Jarrossay[1], Jacopo Sgrignani[1], Sylvia Thelen[1], Mario Uhr[10], Enos Bernasconi[11,12], Andri Rauch[13], Antonio Manzo[14], Adrian Ciurea[15], Marco B. L. Rocchi[16], Luca Varani[1], Bernhard Moser[17], Barbara Bottazzi[18], Marcus Thelen[1], Brian A. Fallon[9,19], Onur Boyman[8,20], Alberto Mantovani[4,18,21], Christian Garzoni[22], Alessandra Franzetti-Pellanda[3], Mariagrazia Uguccioni[1,4,24] ✉ & Davide F. Robbiani[1,24] ✉

Infection with severe acute respiratory syndrome coronavirus 2 associates with diverse symptoms, which can persist for months. While antiviral antibodies are protective, those targeting interferons and other immune factors are associated with adverse coronavirus disease 2019 (COVID-19) outcomes. Here we discovered that antibodies against specific chemokines were omnipresent post-COVID-19, were associated with favorable disease outcome and negatively correlated with the development of long COVID at 1 yr post-infection. Chemokine antibodies were also present in HIV-1 infection and autoimmune disorders, but they targeted different chemokines compared with COVID-19. Monoclonal antibodies derived from COVID-19 convalescents that bound to the chemokine N-loop impaired cell migration. Given the role of chemokines in orchestrating immune cell trafficking, naturally arising chemokine antibodies may modulate the inflammatory response and thus bear therapeutic potential.

ANTI-CHEMOKINE AUTOANTIBODIES IN COVID-19



(Muri…Robbiani Nature Immunol 2023)

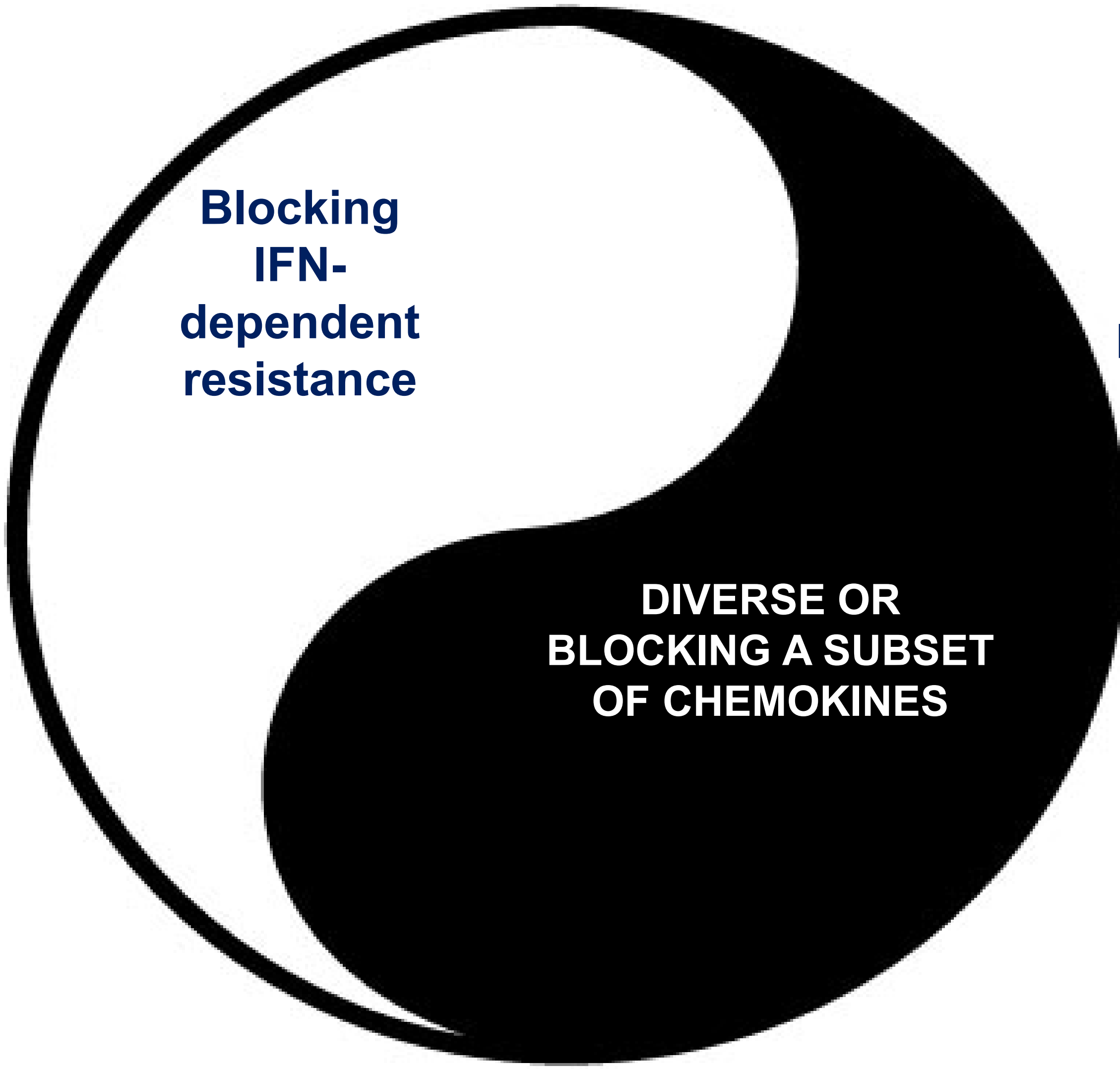
AUTOANTIBODIES AGAINST CHEMOKINES IN COVID-19

- **Omnipresent in COVID-19 in three independent cohorts (Lugano, Zurich, Milan)**
- **CXCL5, CXCL8, CCL25 autoantibodies were associated with protection against hospitalization in severe disease: Neutrophil trafficking?**
- **CCL21, CXCL13, CXCL16 autoantibodies were associated with no long COVID at 1year: T and B cell trafficking?**

(Muri…… Uguccioni and Robbiani Nature Immunol 2023)

THE YING-YANG AUTOIMMUNITY IN COVID-19

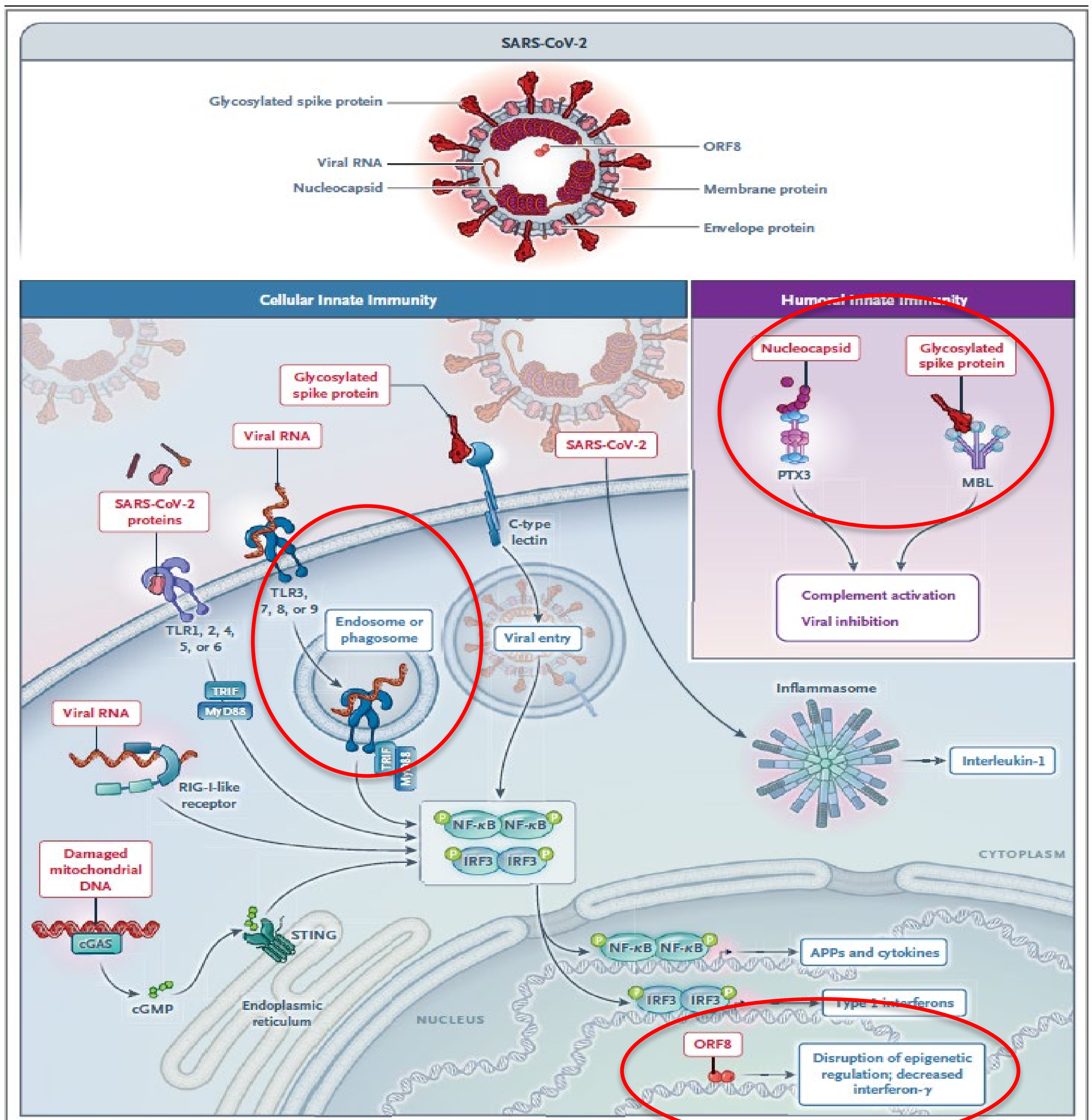
PROPENSITY TO SEVERE ACUTE DISEASE



PATHOGENESIS OR PROTECTION AGAINST LONG COVID

(eg Bastard et al Science 2020 ; Muri… Robbiani Nature Immunol. 2023)

Recognition of SARS-CoV-2 by Cellular and Humoral Pattern-Recognition Molecules, Including Acute-Phase Proteins



(Mantovani and Garlanda, New England J. Med. 2023)

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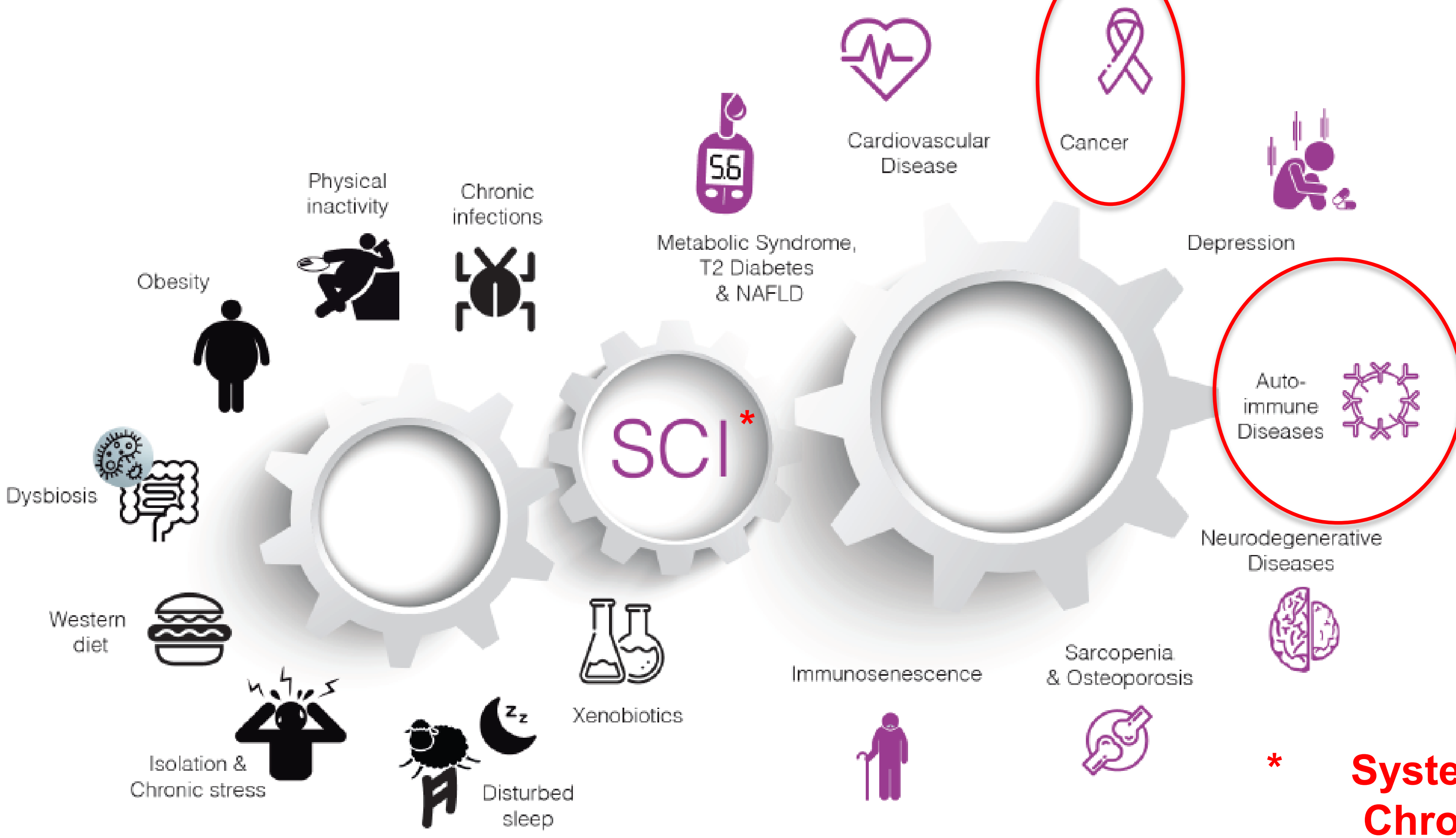
Inflammation and Immunity as a metanarrative of medicine



* **Systemic Chronic Inflammation**

(Mantovani et al, Immunity, 2019; Furman et al Nature Med., 2020)

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