10° WORKSHOP NAZIONALE CISAI

MILANO

PREVENZIONE E GESTIONE DELLE CO-MORBIDITÀ ASSOCIATE ALL'INFEZIONE DA HIV

PRESIDENTI
PAOLO BONFANTI
ANTONIO DI BIAGIO

30 SETTEMBRE
1 OTTOBRE
2021

CISAI

FONDAZIONE ASIA

COVID-19 e infezione da HIV: legami pericolosi

Paolo Maggi
Università della Campania, Luigi Vanvitelli
UOC Malattie Infettive e Tropicali AORN Caserta

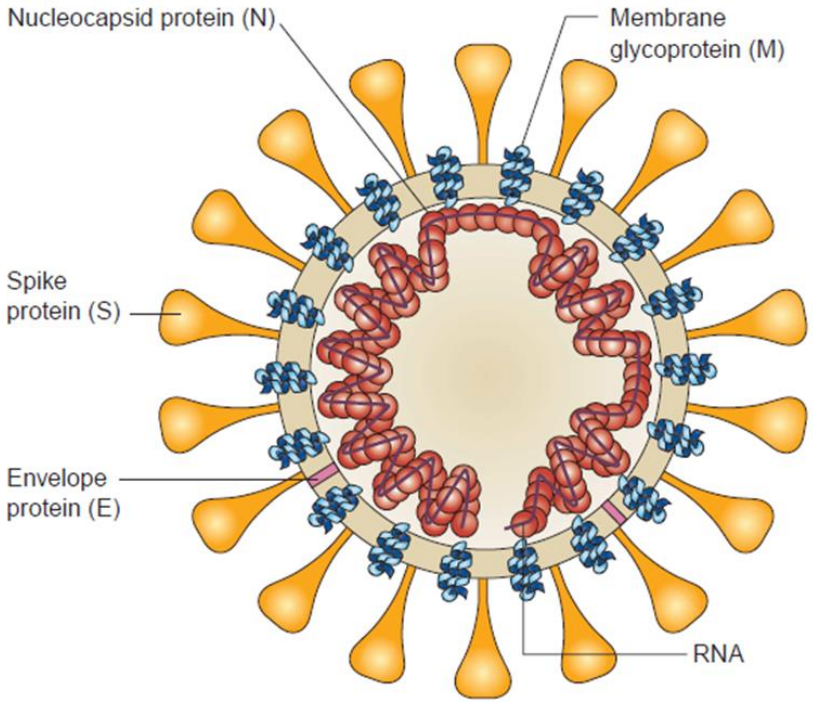
Potenziale conflitto d'interessi da dichiarare

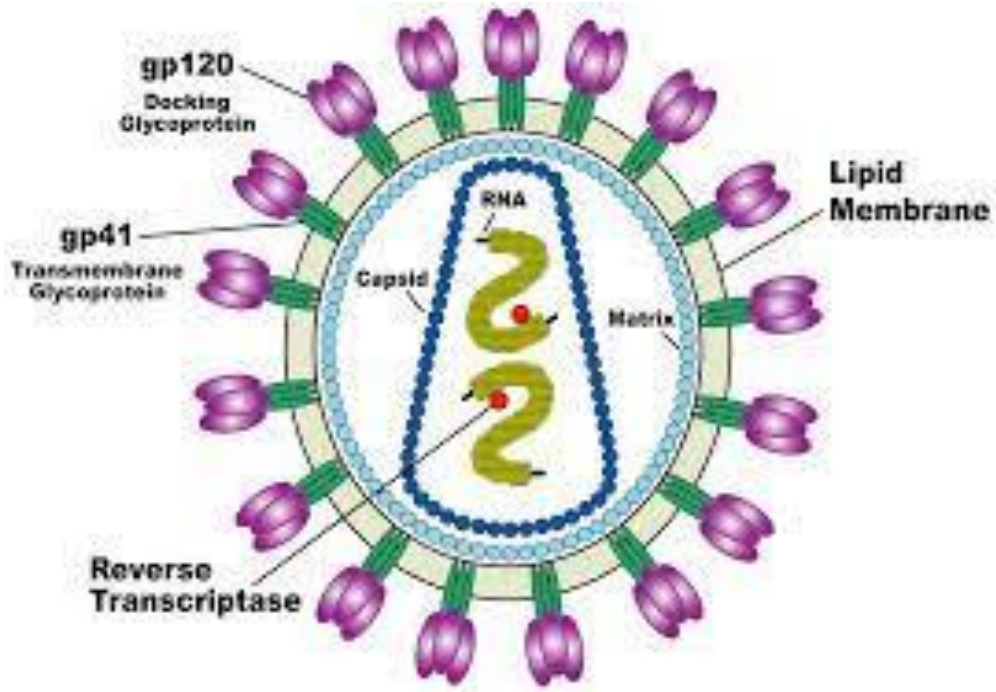
Tipo di affiliazione o supporto finanziario	Sponsor
Grant for publication, Advisory board fees, speakers' honoraria Conference hospitality,	Gilead Science
Advisory board fees	ViiV Healthcare
Advisory board fees, speakers' honoraria	MSD
Advisory board fees, speakers' honoraria	Janssen
Conference hospitality	Abbvie

CISAI
FONDAZIONE ASIA

In persons living with HIV (PLWH), levels of **immune activation and inflammation** remain elevated even when viral suppression is maintained, and this may contribute to the insurgence of several comorbidities.

On the other hand, residual immune dysregulation can hamper the immune response to infections.





Immune activation and inflammation seem to play a pivotal role also in SARS-CoV-2, and some comorbidities are tied to a worse outcome in this disease,

Although it is still unclear if PLWH experience a worse outcome in the case of COVID- 19 [1,2].

1)Karmen-Tuohy S 2020.Geretti 2020.

Dangerous liaisons? The role of inflammation and comorbidities in HIV and SARS-CoV-2 infection

Paolo Maggi , Elena Ricci , Vincenzo Messina , Angela Salzillo , Filomena Simeone , Angelo Iodice & Giuseppe Vittorio Socio

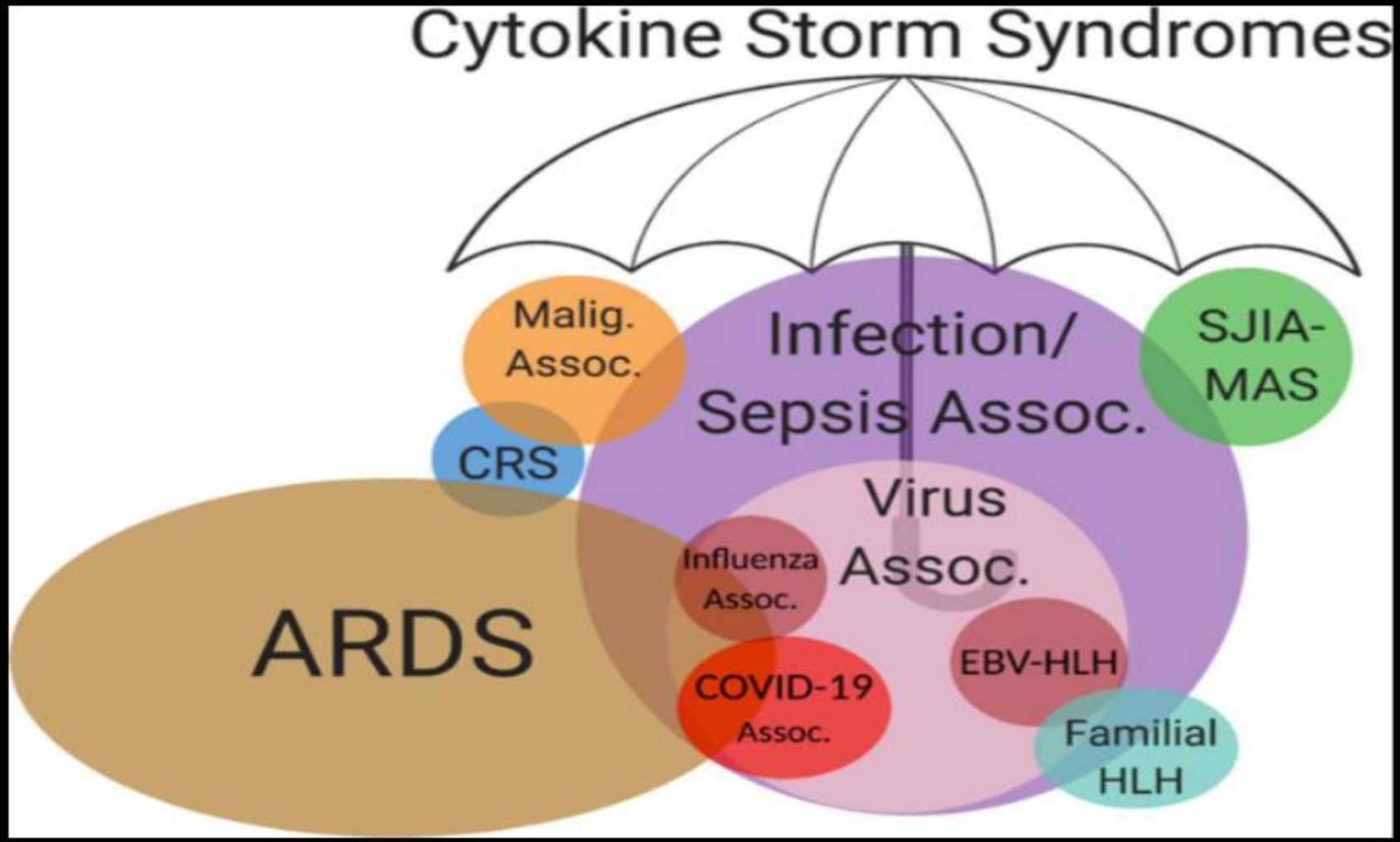
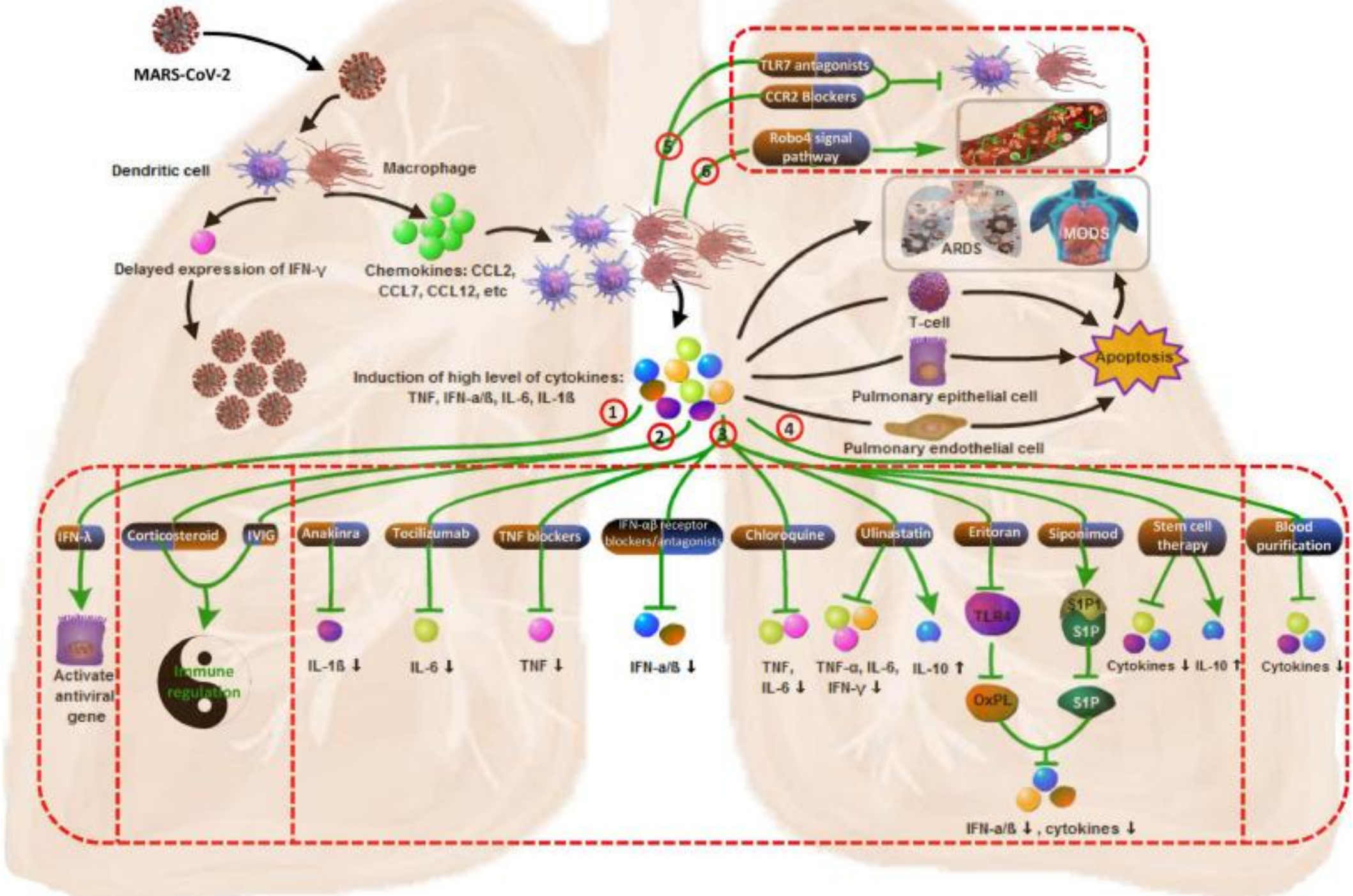
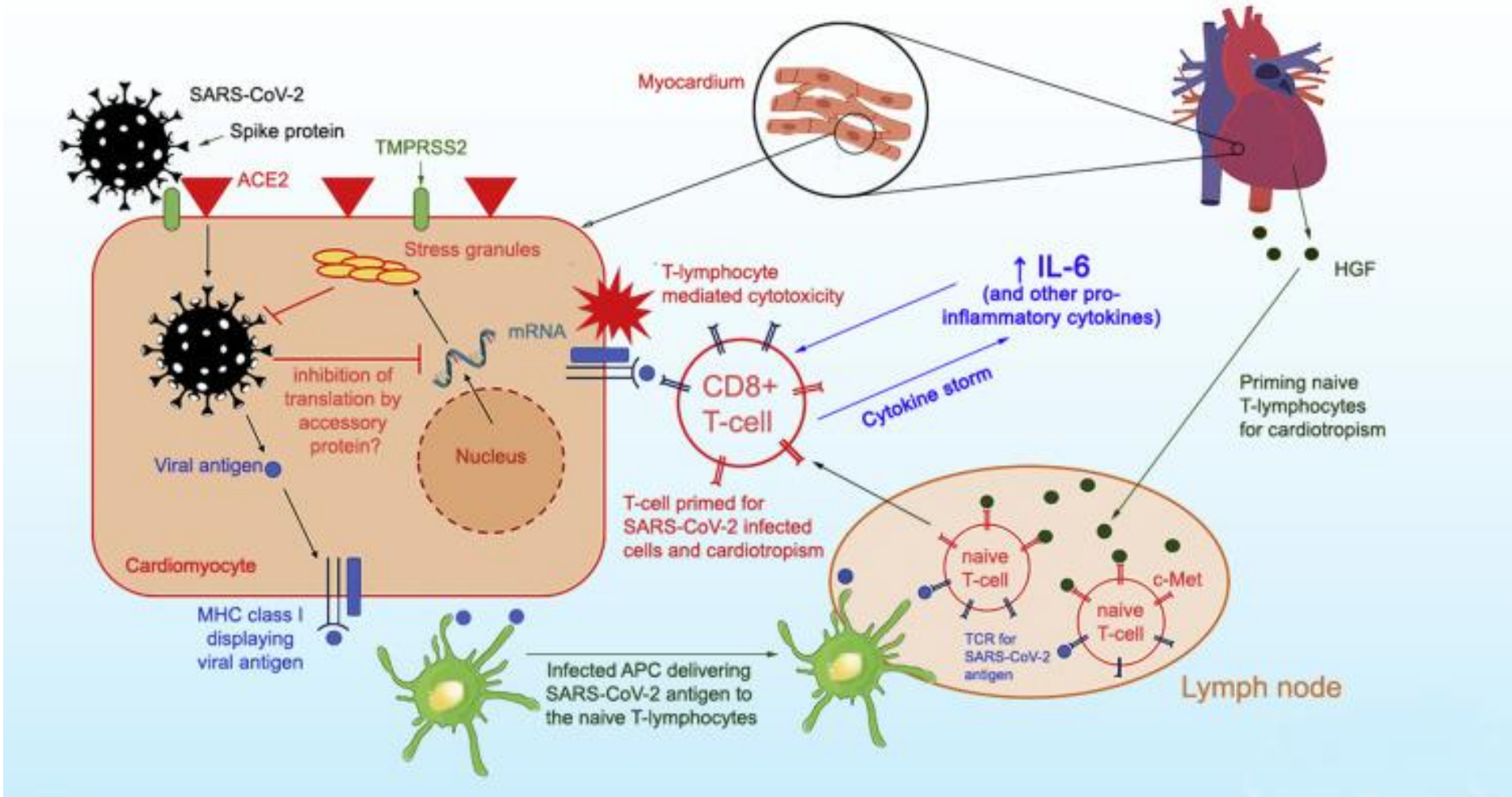


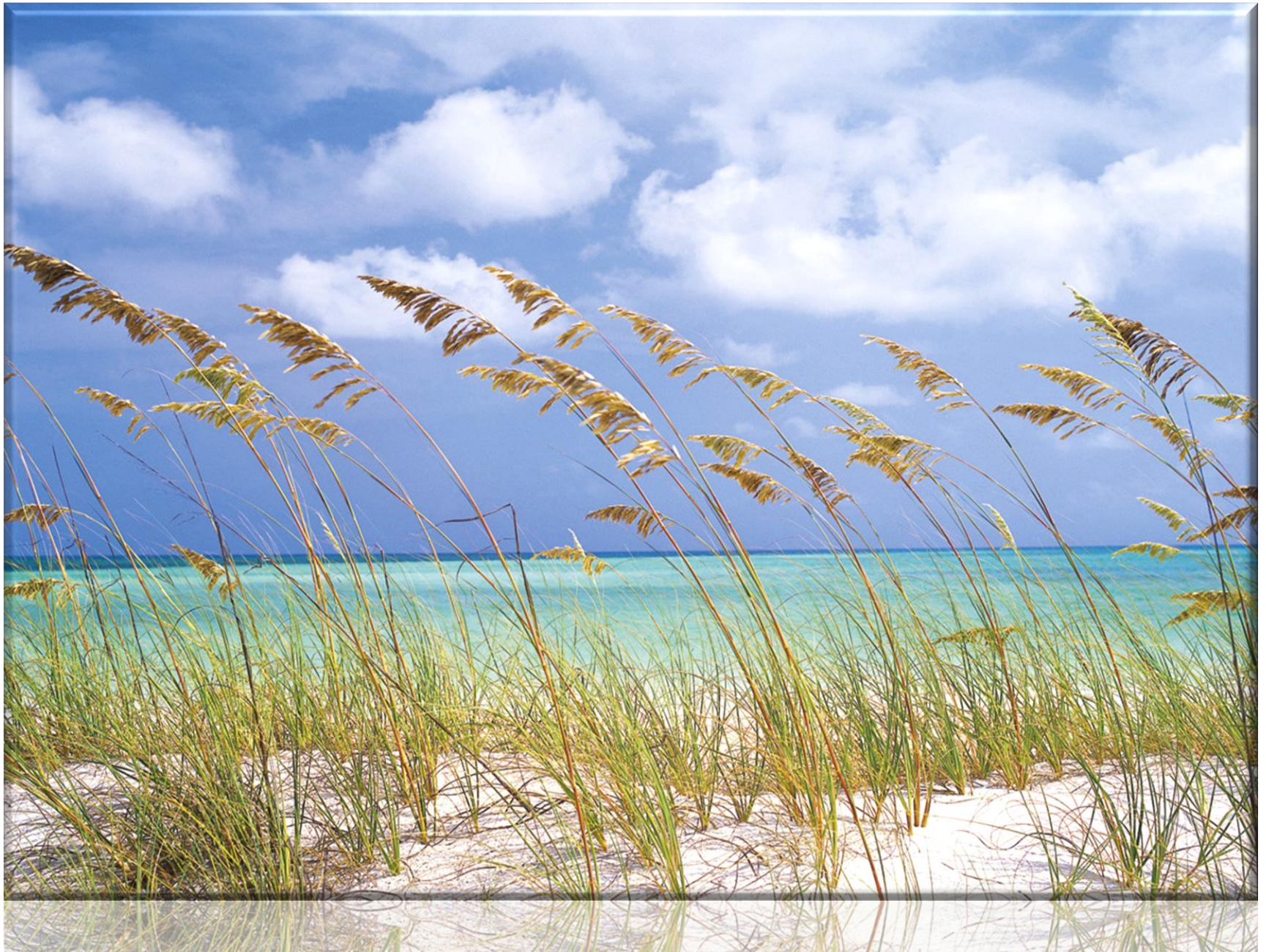
Figure 1 The family of conditions characterized by cytokine storm. Malig. = malignancy; Assoc. = associations; SJIA = systemic juvenile idiopathic arthritis; MAS = macrophage activation syndrome; CRS = cytokine release syndrome; ARDS = acute respiratory distress syndrome; EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis.

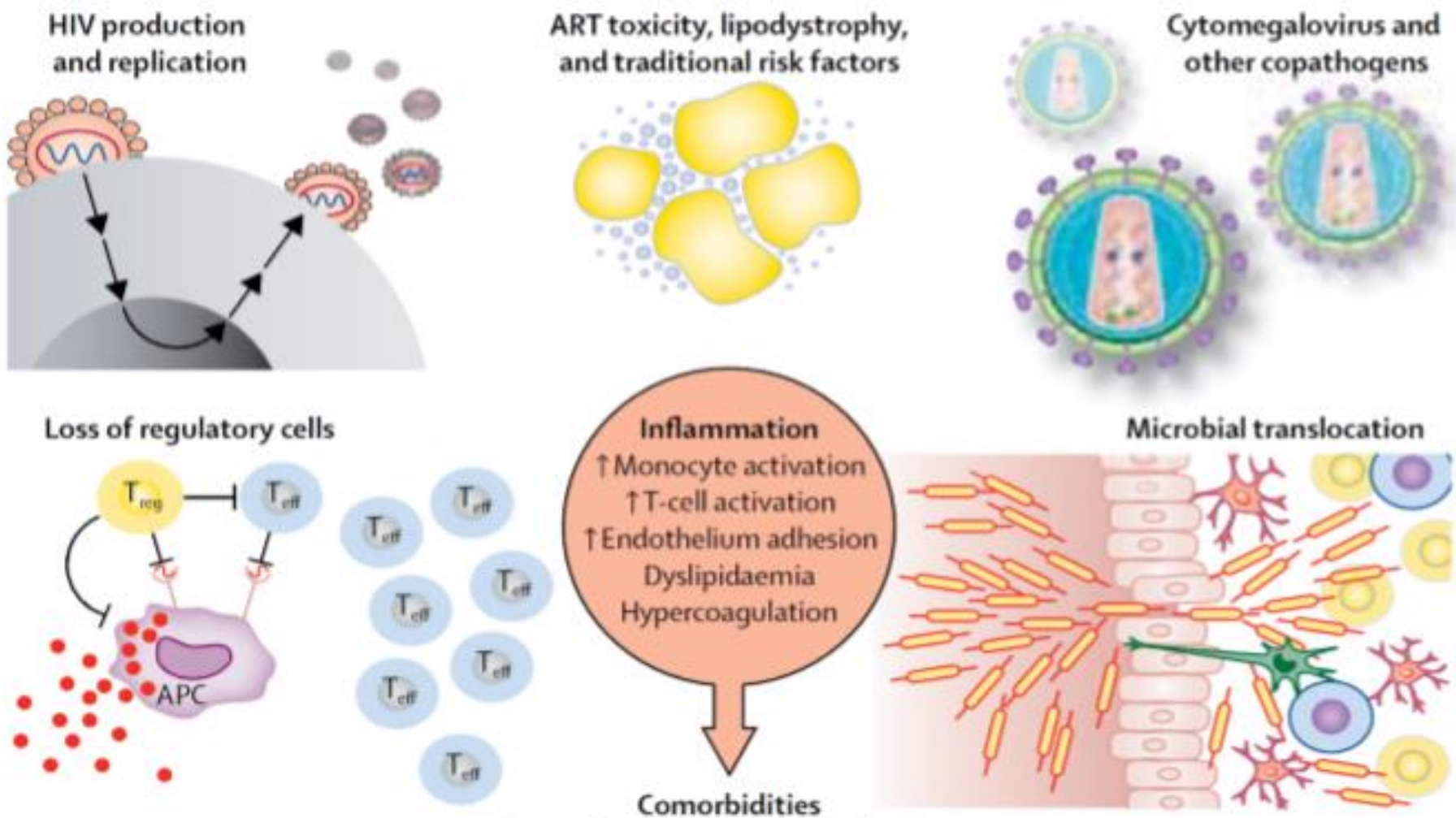
Too much of a good thing….


MARS-CoV-2
Dendritic cell
Macrophage
Delayed expression of IFN-γ
Chemokines: CCL2, CCL7, CCL12, etc
Induction of high level of cytokines: TNF, IFN-a/ß, IL-6, IL-1ß
TLR7 antagonists
CCR2 Blockers
Robo4 signal pathway
ARDS
MODS
T-cell
Pulmonary epithelial cell
Pulmonary endothelial cell
Apoptosis
IFN-λ
Activate antiviral gene
Corticosteroid
IVIG
Immune regulation
Anakinra
IL-1ß ↓
Tocilizumab
IL-6 ↓
TNF blockers
TNF ↓
IFN-αβ receptor blockers/antagonists
IFN-a/ß ↓
Chloroquine
TNF, IL-6 ↓
Ulinastatin
TNF-α, IL-6, IFN-γ ↓
IL-10 ↑
Eritoran
TLR4
OxPL
Siponimod
S1P1
S1P
S1P
Stem cell therapy
Cytokines ↓ IL-10 ↑
Blood purification
Cytokines ↓
IFN-a/ß ↓, cytokines ↓
1
2
3
4
5
6


SARS-CoV-2
Spike protein
TMPRSS2
ACE2
Stress granules
mRNA
inhibition of translation by accessory protein?
Viral antigen
Nucleus
Cardiomyocyte
MHC class I displaying viral antigen
Myocardium
HGF
T-lymphocyte mediated cytotoxicity
↑ IL-6
(and other pro-inflammatory cytokines)
Cytokine storm
CD8+ T-cell
T-cell primed for SARS-CoV-2 infected cells and cardiotropism
Priming naive T-lymphocytes for cardiotropism
naive T-cell
c-Met
naive T-cell
TCR for SARS-CoV-2 antigen
Lymph node
Infected APC delivering SARS-CoV-2 antigen to the naive T-lymphocytes

HIV: a cytokine breeze





Deeks, Lancet 2013

Inflammation and comorbidity in HIV

- DC signs. (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin)
- sCD14 (macrophages), sCD163 (monocytes/macrophages)
- D-dimer
- Soluble TNF receptors 1 and 2
- IL-6

1) Bowman E 2019. 2) De Francesco 2019

Summary table. Markers of inflammation and comorbidities in SARS-CoV-2 and HIV infection.

Marker	SARS-CoV-2	HIV
IL-2 r	Increased	Reduced
IL-6	Increased	Increased
TNF-a	Increased	Increased
IL-17	Increased	Reduced
D-dimer	Increased	Increased
DC SIGNS	Favors CRS	Favors HIV access
CD4+ cells	Decreased	Decreased
Th17	Increased	Decreased
Comorbidity		
Diabetes	Favors CRS	Favored by HIV
Cardiovascular disease	Favors CRS	Favored by HIV
Coagulation disturbances	Favors CRS	Favored by HIV
Metabolic syndrome	Favors CRS	Favored by HIV
Vitamin D deficiency	Favors CRS (?)	Favors disease progression

Maggi P et al. 2021

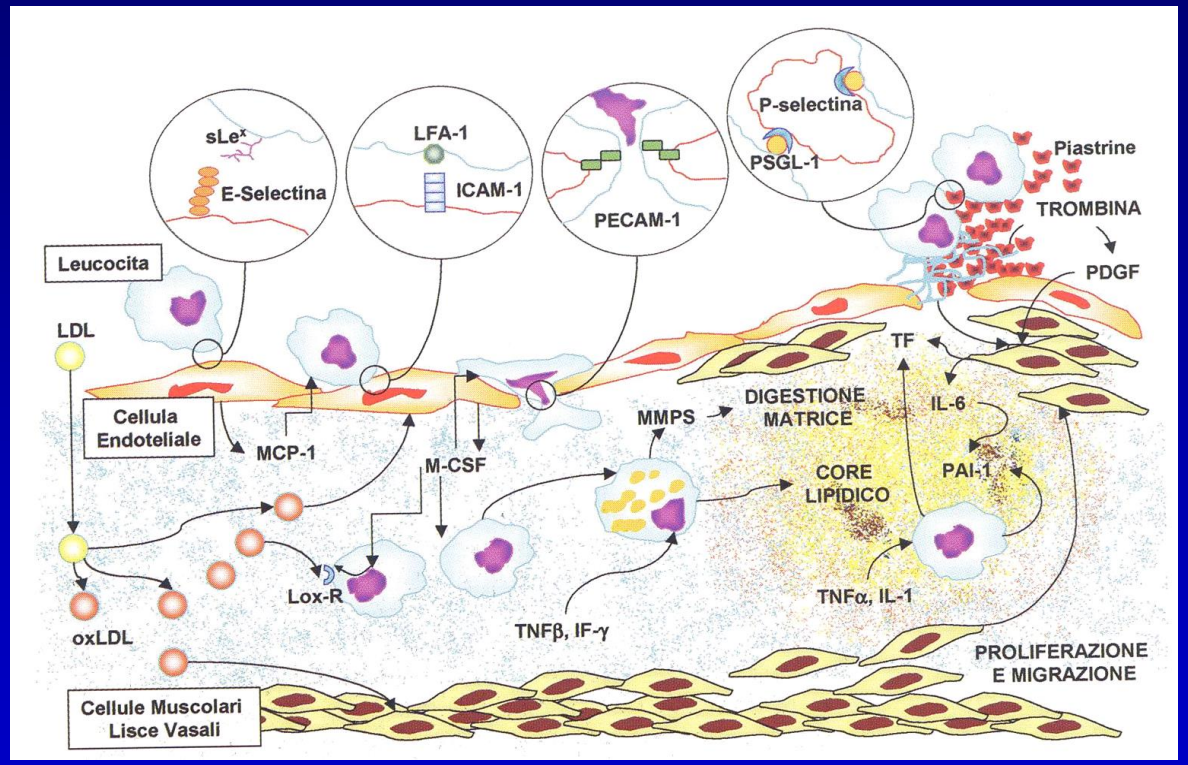
Effetti sull'Endotelio del Processo Infiammatorio

Ridotta biodisponibilità di NO

Aumentata sintesi di Endotelina-1

Effetto protrombotico attivazione del TF

Aumento di O_2 – e dei ROS



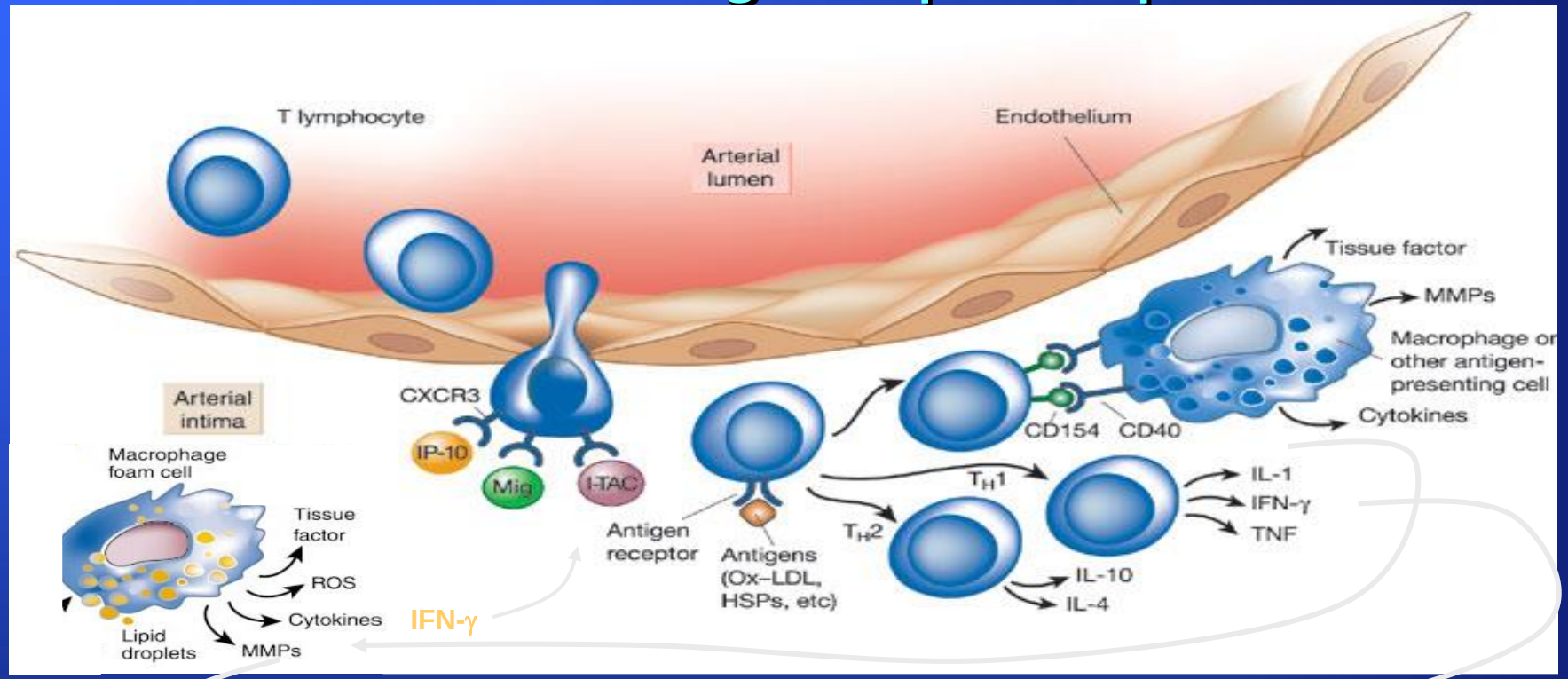
Aumentata migrazione e proliferazione delle CML. Attivazione del PDGF

Aumentata adesività tra Leucociti e Endotelio. Aumentata produzione di IL-6 e di CRP

Attivazione della Matrix Metalloproteinasi e attivazione dei Macrofagi

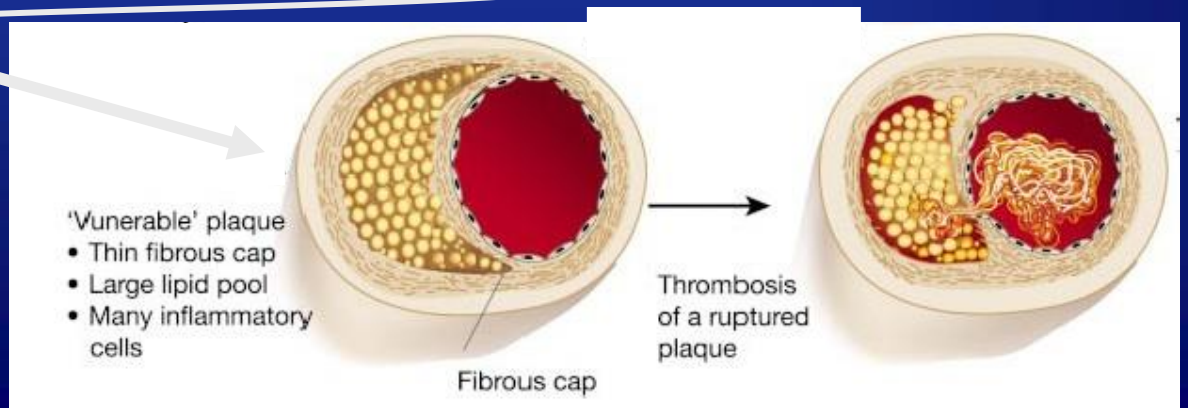
Bonetti, Eur Heart J 2003

T-lymphocytes and Macrophages Interact In Promoting Plaque Rupture

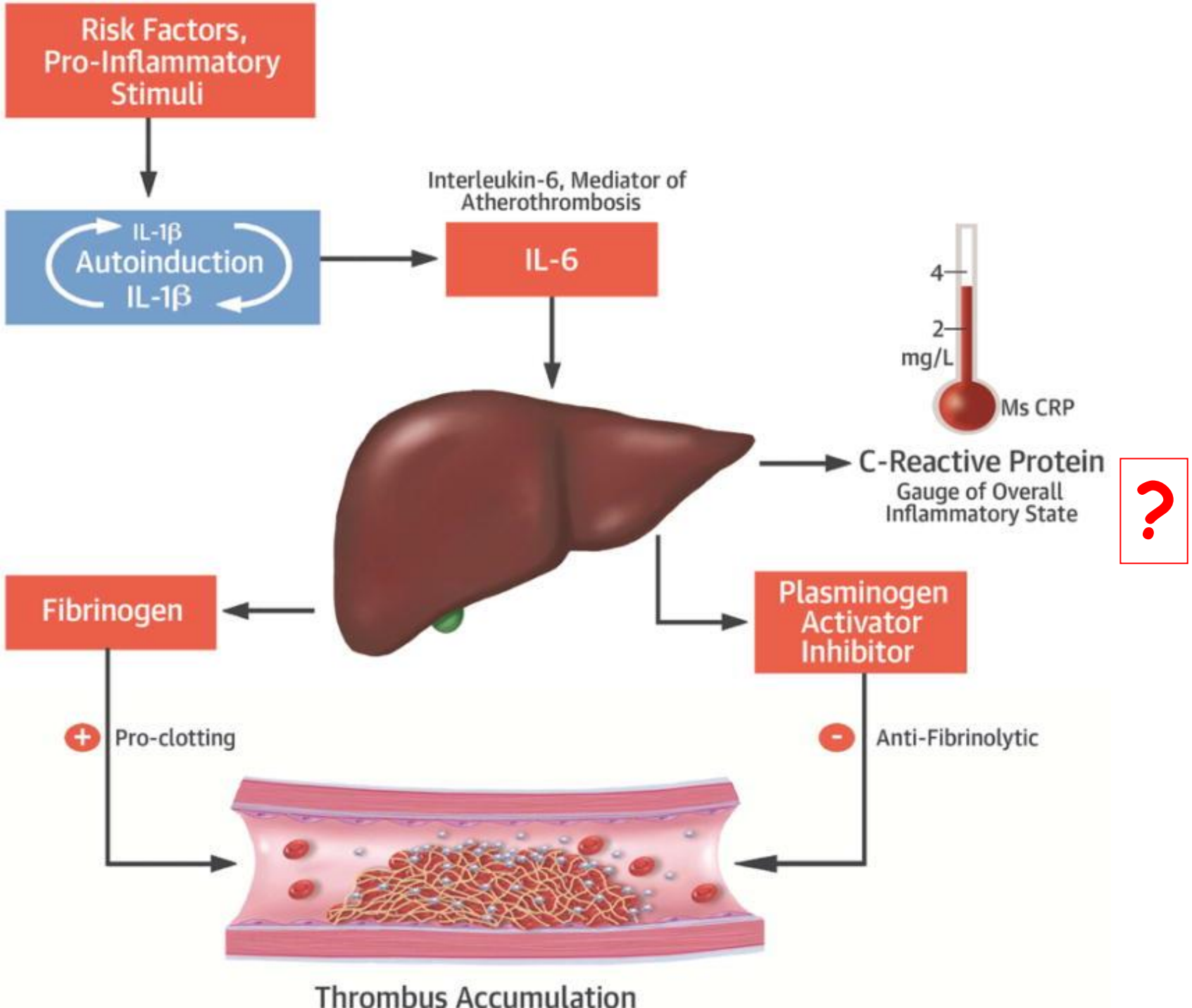


Collagen degrading enzymes↑

Collagen formation↓



Adapted from Libby P Nature 2002


Risk Factors, Pro-Inflammatory Stimuli
IL-1β Autoinduction IL-1β
Interleukin-6, Mediator of Atherothrombosis
IL-6
4
2
mg/L
Ms CRP
C-Reactive Protein
Gauge of Overall Inflammatory State
?
Fibrinogen
Plasminogen Activator Inhibitor
+
Pro-clotting
-
Anti-Fibrinolytic
Thrombus Accumulation

Can we measure the inflammation?

RESEARCH ARTICLE

Association between Immune Markers and Surrogate Markers of Cardiovascular Disease in HIV Positive Patients: A Systematic Review

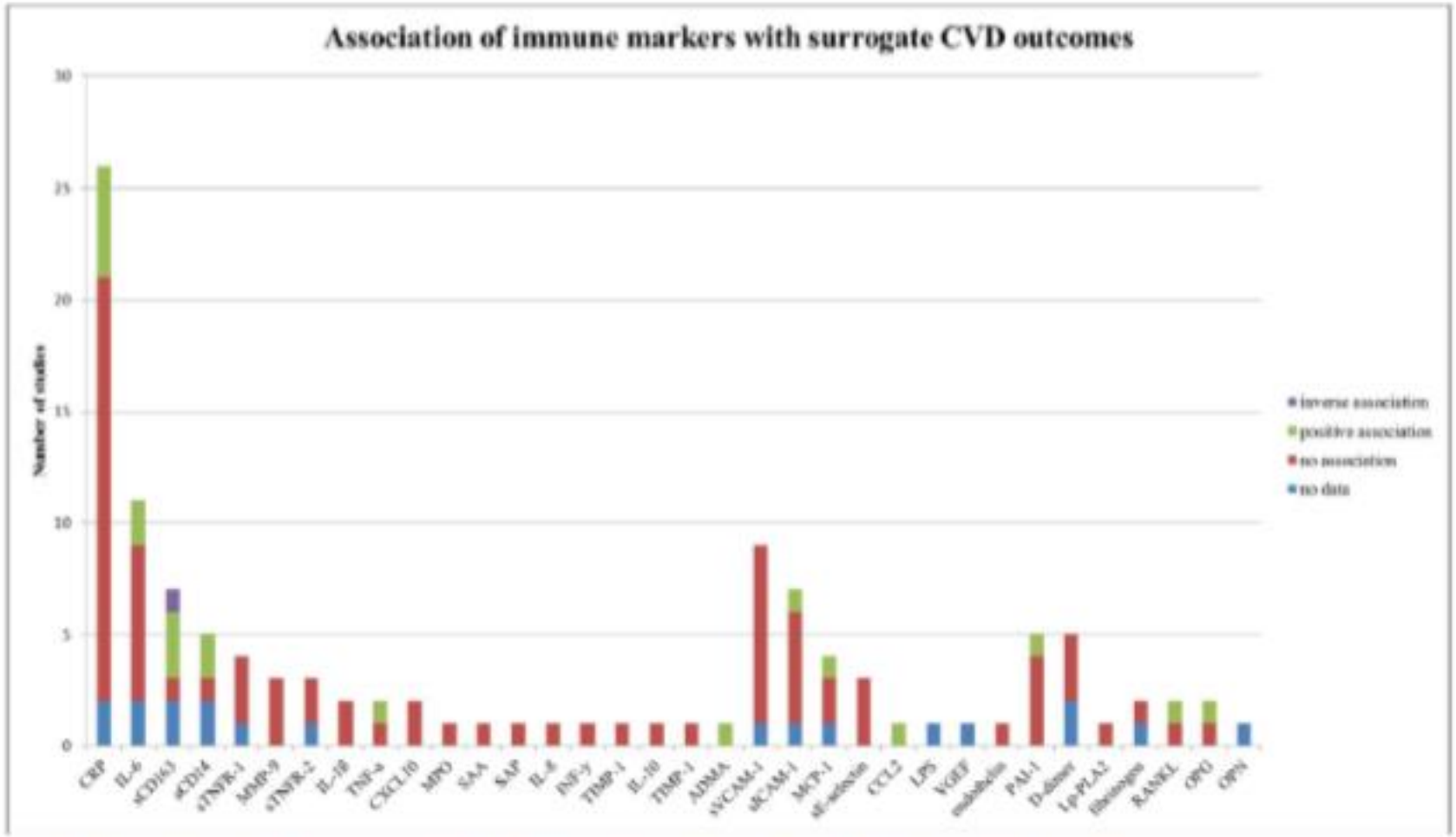


Fig 3. Association of immune markers with surrogate CVD outcomes. CVD: cardiovascular disease.

Vos, PlosOne 2017

SARS-COV2: Diagnosi precoce? Poco si può fare…..

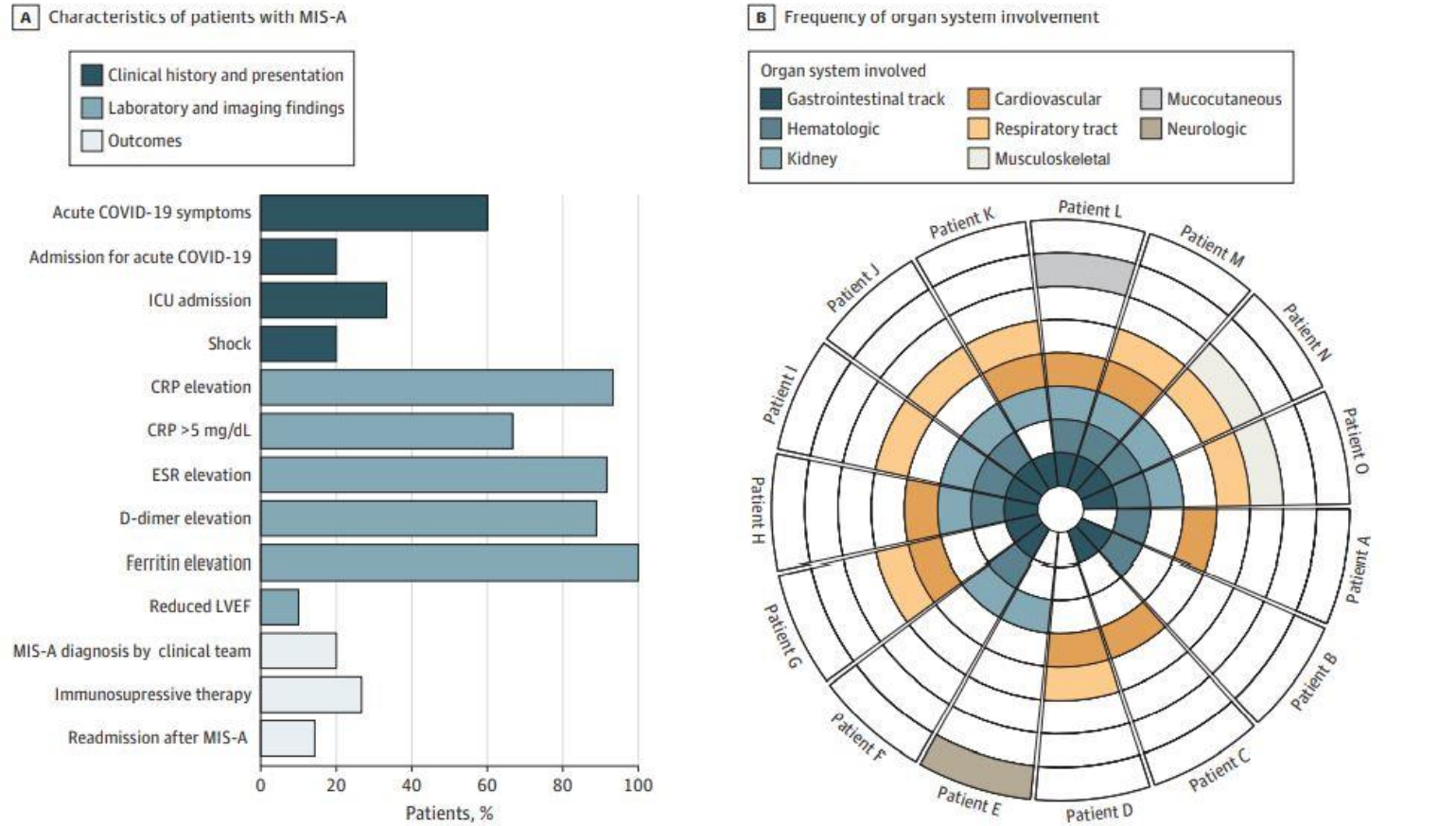
Table 1

Biomarkers of cytokine storm syndrome (CSS)[a]

Biomarker	Biology	Status in hyperinflammation	Status in COVID-19	Test availability
CRP	Hepatic release in response to IL-6	Nonspecific, useful for monitoring, blunted by IL-6 blockade	Associated with severity, ARDS	A
Complete blood cell count	Multifactorial cytopenias	May be indicative of CSS (especially thrombocytopenia)	Associated with severity, ARDS	A
↑ D-dimer, ↓ fibrinogen	Fibrin degradation product, reflective of DIC	May be indicative of active CSS	Associated with severity, ARDS	A
LDH, AST, ALT	Tissue injury, hepatitis	May be indicative of active CSS	Associated with severity, ARDS	A
Ferritin	Macrophage/hepatocyte activation	Integral part of CSS diagnosis, predictive of sepsis mortality	Associated with severity, ARDS	A
Ferritin:ESR ratio	ESR falls with fibrinogen consumption	Higher specificity than ferritin alone	Not assessed	A
Procalcitonin	Adipokine	Nonspecific, useful for monitoring	Variably associated with severity, ARDS	A, S
IL-2Ra (CD25)	Cleaved from T cells by inflammatory proteases	Part of HLH diagnostic criteria, useful for monitoring	Associated with severity	S
IL-6	Pleiotropic inflammatory cytokine	Elevated, nonspecific	Associated with severity	S
Neopterin	Metabolite of GTP induced by IFNγ	Elevated in blood and CSF	Not assessed	S
IFNγ	Classic type 1/Th1 cytokine	Elevated, but poor dynamic range	Elevated compared with healthy control	S, R
CXCL9	Chemokine induced by IFNγ	Elevated in most CSS, useful for monitoring	Not assessed	S
IL-1β	Inflammasome-activated	Elevated, but poor dynamic range	Variably elevated with severity	S, R
IL-18	Inflammasome-activated, IFNγ inducing	Very high levels may indicate MAS, not useful for monitoring	Not assessed	S
ADA-2	Released by IFNγ-activated monocytes	Elevated in most CSS, useful for monitoring	Not assessed	S, R
S100 proteins	Neutrophil/monocyte activation	Elevated in active systemic JIA and MAS, and in some ARDS	Not assessed	S, R
CD163	Cleaved from tissue macrophages	Elevated in active systemic JIA and MAS, and in ARDS	Not assessed	S, R

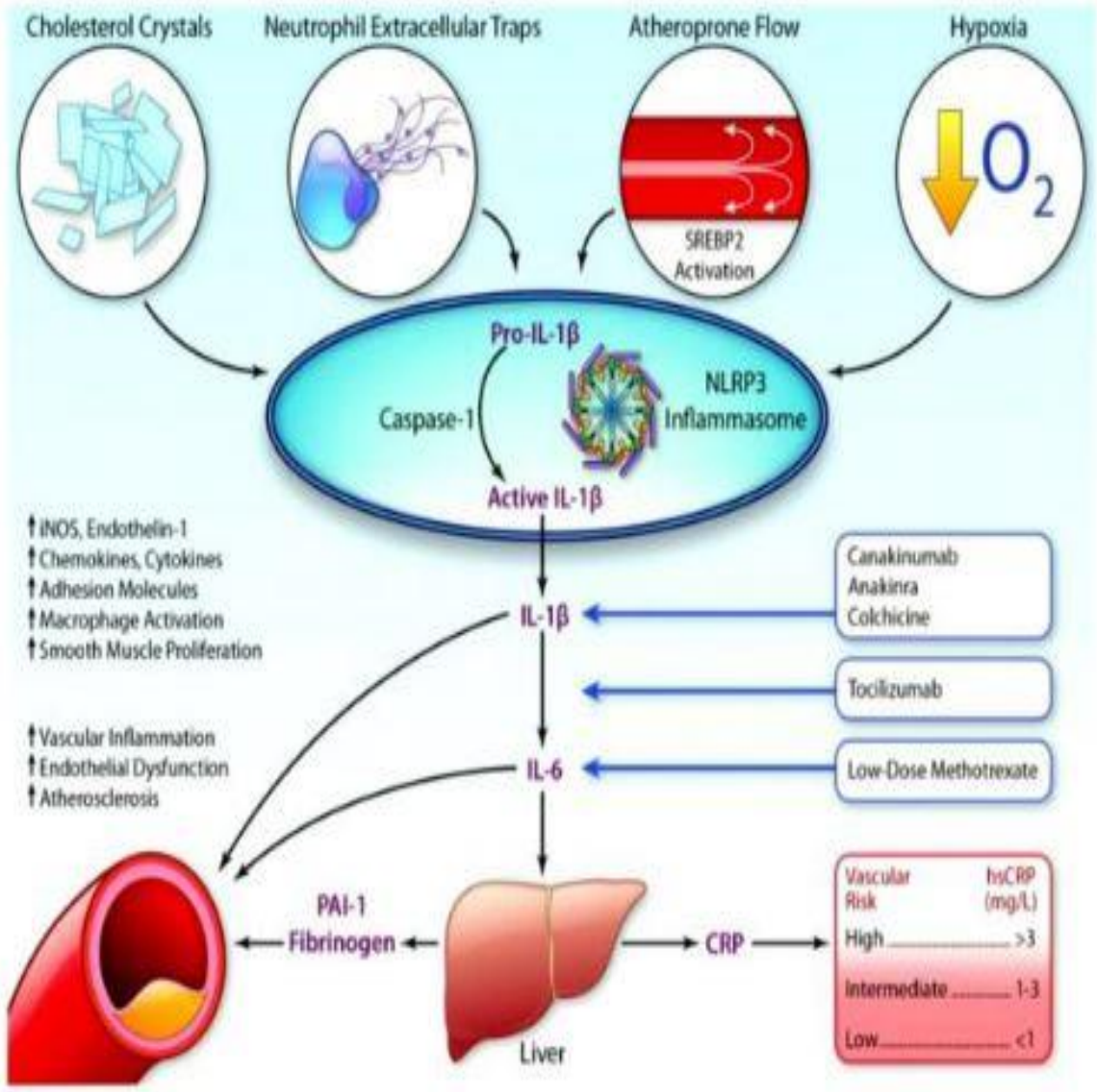
[a]Relevant citations are provided in Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41285/abstract). COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; IL-6 = interleukin-6; ARDS = acute respiratory distress syndrome; A = widely available; DIC = disseminated intravascular coagulation; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ESR = erythrocyte sedimentation rate; S = typically send-out; IL-2Ra = IL-2 receptor antagonist; HLH = hemophagocytic lymphohistiocytosis; IFNγ = interferon-γ; CSF = cerebrospinal fluid; R = may be available only on a research basis; MAS = macrophage activation syndrome; ADA-2 = adenosine deaminase 2; JIA = juvenile idiopathic arthritis.

Figure. Clinical Presentation and Organ Involvement of Patients Identified With Multisystem Inflammatory Syndrome in Adults (MIS-A)



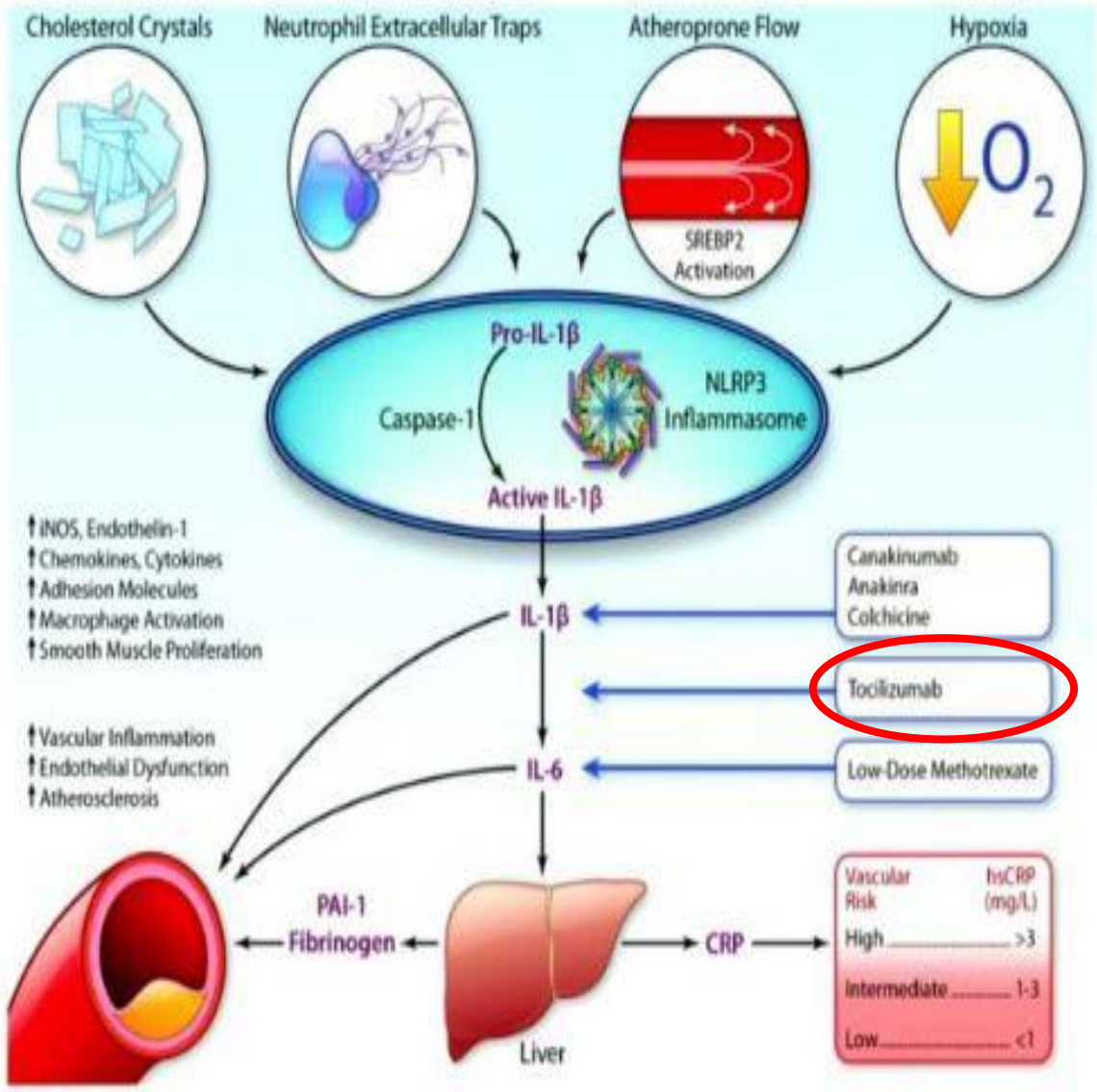
A, Data were available for left ventricular ejection fraction (LVEF) from 10 patients, for erythrocyte sedimentation rate (ESR) from 12, for D-dimer level from 9; and for ferritin level from 8. To convert C-reactive protein (CRP) level from milligrams per deciliter to milligrams per liter, multiply by 10. B, Each wedge represents a single patient, and each concentric ring represents an organ system, organized from inside out by frequency of involvement. ICU indicates intensive care unit.

Targeting inflammation: Moving upstream



Ridker P Circulation Research 2016

Targeting inflammation: Moving upstream



Ridker P Circulation Research 2016

The NEW ENGLAND JOURNAL of MEDICINE

Tocilizumab in Patients Hospitalized with Covid-19

DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

242
Patients with confirmed SARS-CoV-2 infection

	Tocilizumab	Placebo
	N=161	N=81
Mechanical ventilation or death within 28 days	10.6%	12.5%
	HR, 0.83; 95% CI, 0.38 to 1.81; P=0.64	
Clinical worsening of disease within 28 days	19.3%	17.4%
	HR, 1.11; 95% CI, 0.59 to 2.10; P=0.73	

Tocilizumab was not effective for preventing mechanical ventilation or death among moderately ill patients hospitalized with Covid-19

J.H. Stone et al. 10.1056/NEJMoa2028836

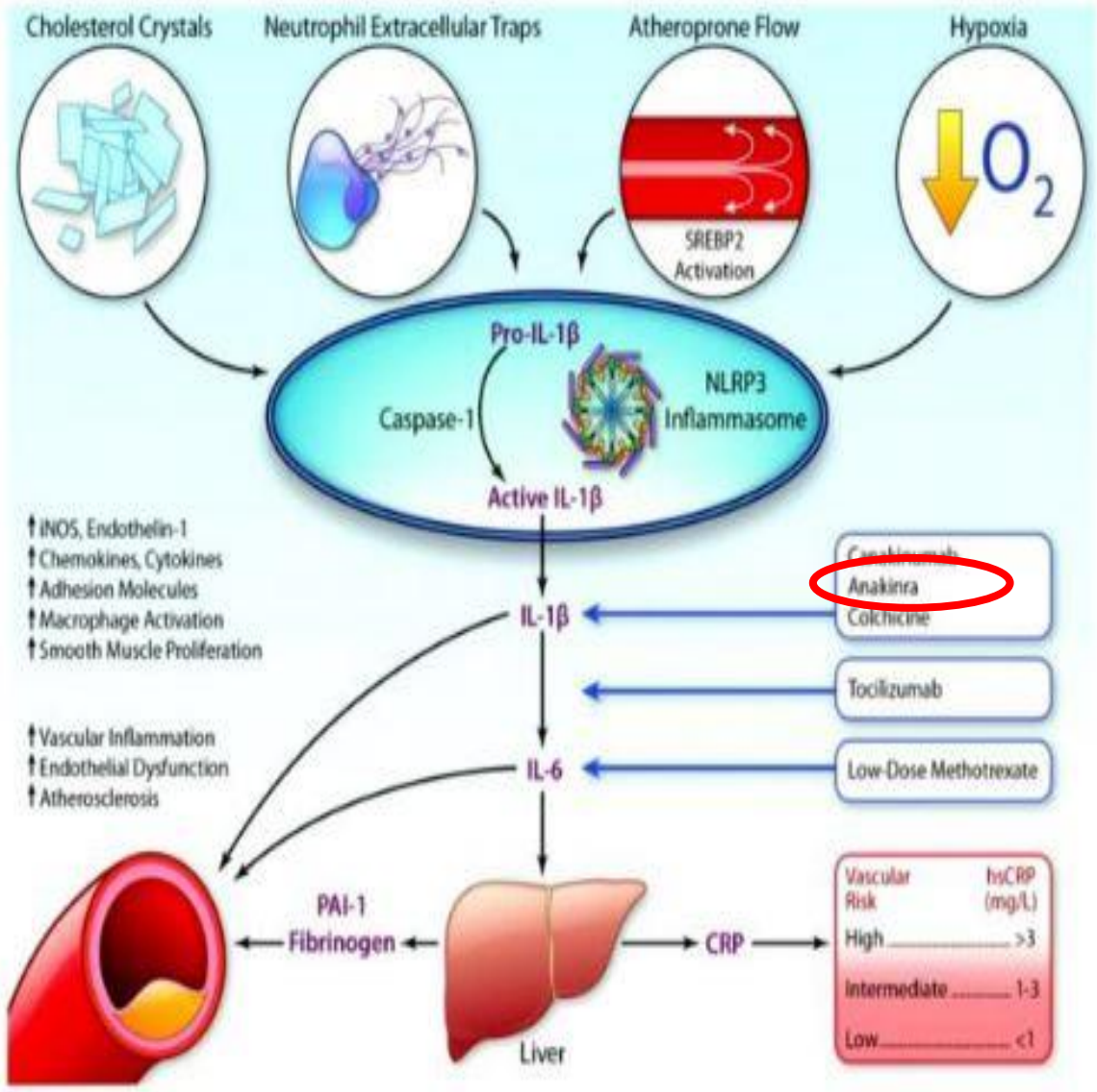
› Lancet Respir Med. 2021 Mar 4;S2213-2600(21)00099-0. doi: 10.1016/S2213-2600(21)00099-0.
Online ahead of print.

Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial

François-Xavier Lescure [1], Hitoshi Honda [2], Robert A Fowler [3], Jennifer Sloane Lazar [4], Genming Shi [4], Peter Wung [4], Naimish Patel [5], Owen Hagino [4], Sarilumab COVID-19 Global Study Group

Interpretation: This trial did not show efficacy of sarilumab in patients admitted to hospital with COVID-19 and receiving supplemental oxygen. Adequately powered trials of targeted immunomodulatory therapies assessing survival as a primary endpoint are suggested in patients with critical COVID-19.

Targeting inflammation: Moving upstream



Ridker P Circulation Research 2016

Lancet Rheumatol 2020;
2: e393–400

Published Online
May 29, 2020
https://doi.org/10.1016/
S2665-9913(20)30164-8

Anakinra for severe forms of COVID-19: a cohort study

Thomas Huet, Hélène Beaussier, Olivier Voisin, Stéphane Jouveshomme, Gaëlle Dauriat, Isabelle Lazareth, Emmanuelle Sacco, Jean-Marc Naccache, Yvonnick Bézie, Sophie Laplanche, Alice Le Berre, Jérôme Le Pavec, Sergio Salmeron, Joseph Emmerich, Jean-Jacques Mourad, Gilles Chatellier, Gilles Hayem

Interpretation Anakinra reduced both need for invasive mechanical ventilation in the ICU and mortality among patients with severe forms of COVID-19, without serious side-effects. Confirmation of efficacy will require controlled trials.

The **SAVE-MORE** is a pivotal, confirmatory, phase III RCT aiming to evaluate the efficacy and safety of early start of anakinra guided by suPAR (soluble urokinase plasminogen activator receptor) in patients with LRTI by SARS-CoV-2 in improving the clinical state of COVID-19 over 28 days

Immunology and Inflammation, Medicine

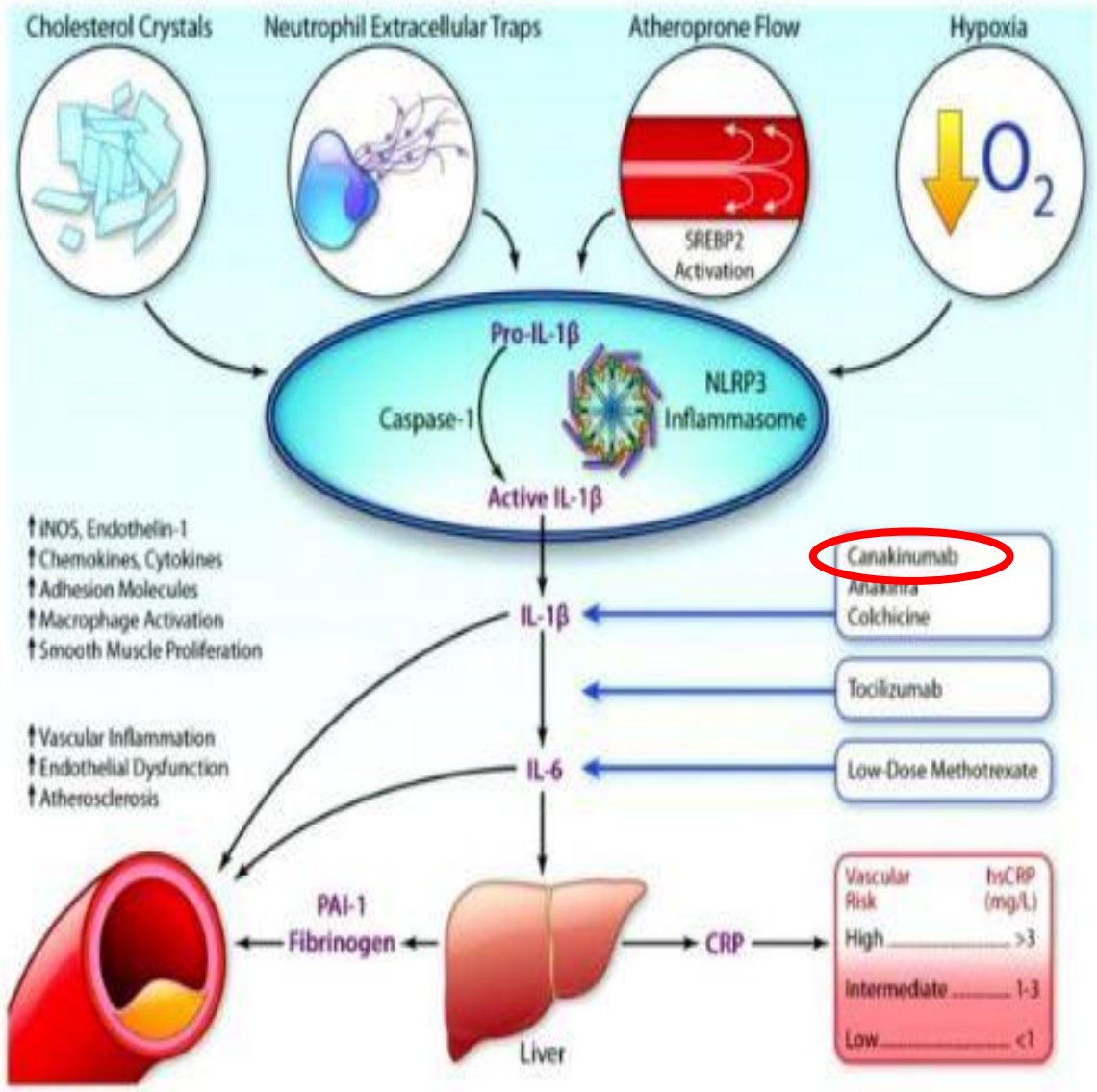
An open label trial of anakinra to prevent respiratory failure in COVID-19

Evdoxia Kyriazopoulou, Periklis Panagopoulos, Symeon Metallidis, George N Dalekos, Garyphallia Poulakou, Nikolaos Gatselis, Eleni Karakike, Maria Saridaki, Georgia Loli see all »

National and Kapodistrian University of Athens, Medical School, Greece; Democritus University of Thrace, Medical School, Greece; Aristotle University of Thessaloniki, Medical School, Greece; National Expertise Center of Greece in Autoimmune Liver Diseases, General University Hospital of Larissa, Greece; Univeristy of Ioannina School of Medicine, Greece; University of Ioannina, School of Health Sciences, Faculty of Medicine, Greece; General Hospital of Kerkyra, Greece; University of Patras, Greece; Radboud University Medical Centre, Netherlands see all »

Research Article · Mar 8, 2021

Targeting inflammation: Moving upstream



Ridker P Circulation Research 2016

Journal of the American College of Cardiology
Volume 72, Issue 22, 4 December 2018, Pages 2809-2811

Letters

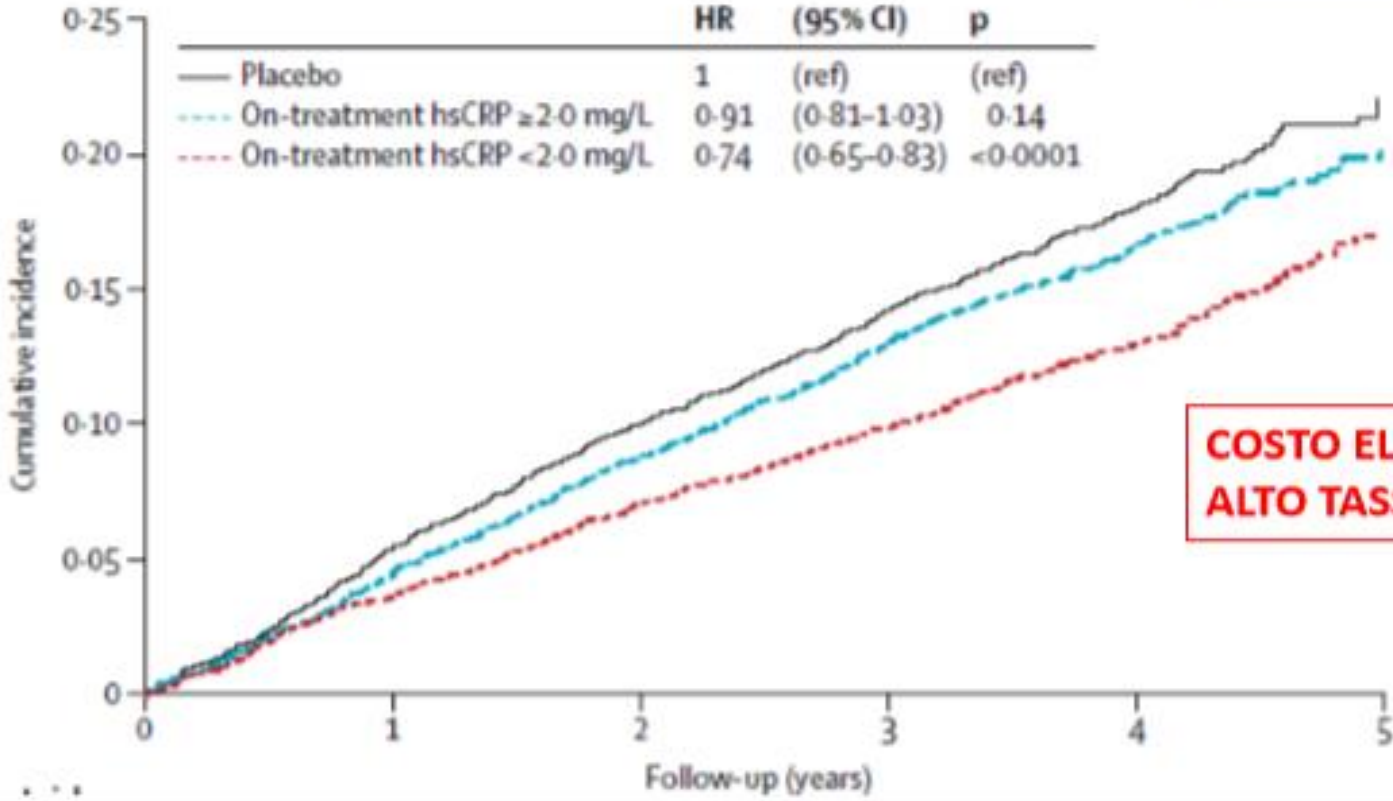
IL-1β Inhibition Reduces Atherosclerotic Inflammation in HIV Infection

Priscilla Y. Hsue MD, Danny Li BS, Yifei Ma MS, Amorina Ishai MD, Maura Manion MD, PhD, Matthias Nahrendorf MD, Peter Ganz MD, Paul M Ridker MD, Steven G. Deeks MD, Ahmed Tawakol MD

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

CANTOS study

- 10,061 pts with previous MI AND hsCRP ≥2mg/l
- Primary end point: non fatal MI, non fatal stroke, or CV death



COSTO ELEVATO ($200.000/anno)
ALTO TASSO DI INFEZIONI FATALI

Ridker, Lancet 2018

Summary table. Markers of inflammation and comorbidities in SARS-CoV-2 and HIV infection.

Marker	SARS-CoV-2	HIV
IL-2 r	Increased	Reduced
IL-6	Increased	Increased
TNF-a	Increased	Increased
IL-17	Increased	Reduced
D-dimer	Increased	Increased
DC SIGNS	Favors CRS	Favors HIV access
CD4+ cells	Decreased	Decreased
Th17	Increased	Decreased
Comorbidity		
Diabetes	Favors CRS	Favored by HIV
Cardiovascular disease	Favors CRS	Favored by HIV
Coagulation disturbances	Favors CRS	Favored by HIV
Metabolic syndrome	Favors CRS	Favored by HIV
Vitamin D deficiency	Favors CRS (?)	Favors disease progression

Maggi P et al. 2021

PLOS ONE

PLoS One 2020;15:e0238215 Ssentongo P, et al. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis.

the presence of:

- cancer
- CVD
- congestive heart failure
- hypertension
- diabetes
- and CKD

increased the mortality risk in COVID-19 patients.

Diabetes Metab.
2020 Oct;46(5):403-405. doi: 10.1016/j.diabet.2020.05.005.

Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients.

Marfella R, Paolisso P, Sardu C, Bergamaschi L, D'Angelo EC, Barbieri M, Rizzo MR, Messina V, **Maggi P**, Coppola N, Pizzi C, Biffi M, Viale P, Galié N, Paolisso G.

on 475 patients positive for COVID-19, it was observed that hyperglycemic patients (even if on-diabetic) vs. normoglycemic patients had higher IL-6 levels, persisting after TCZ administration. In hyperglycemic patients, higher L-6 levels lessened the effects of TCZ while the TCZ effect lost significance when IL-6 levels were added to the Cox regression model. In both diabetic and non-diabetic patients, evidence suggested that COVID-19 was not optimally managed during hyperglycemia.

Diabetes Care
2020 Jul;43(7):1408-1415. doi: 10.2337/dc20-0723.

Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control?

Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, **Maggi P**, Coppola N, Paolisso G, Marfella R.

Diabetes Obes Metab
Marfella R, D'Onofrio N, Sardu C, Scisciola L, **Maggi P**, Coppola N, et al.
2021 Sep 8. doi: 10.1111/dom.14547.

Does poor glycemic control affect the immunogenicity of COVID-19 vaccination in patients with Type 2 Diabetes: The CAVEAT study.

J Am Heart Assoc.
2020 Sep;9(17):e016948. doi: 10.1161/JAHA.120.016948

Sardu C, **Maggi P**, Messina V, Iuliano P, Sardu A, Iovinella V, Paolisso G, Marfella R.

Could Anti-Hypertensive Drug Therapy Affect the Clinical Prognosis of Hypertensive Patients With COVID-19 Infection? Data From Centers of Southern Italy

Anti-hypertensive drugs didn't affect the prognosis in patients with COVID-19. Lowest values of left ventricle ejection fraction predicted deaths, while **highest values of interleukin-6** predicted the admission to intensive care unit, mechanical ventilation, heart injuries, and deaths

Front Oncol
2021 May 7;11:662746.
Monari C, Sagnelli C, **Maggi P,** et al.

More Severe COVID-19 in Patients With Active Cancer: Results of a Multicenter Cohort Study.

AB0 groups may affect the coagulation processes

1. Ohira T, et al. ABO blood group, other risk factors and incidence of venous thromboembolism: The Longitudinal Investigation of Thromboembolism Etiology (LITE). J Thromb Haemost 2007;5:1455–61.
2. Storry JR, Olsson ML. The ABO blood group system revisited: A review and update. Immunohematology 2009;25:48–59.

The AB0 blood group plays a functional role in some viral infections, such as Norwalk virus infection or SARS. It has also been observed that individuals with 0 blood group had lower risk of being infected with COVID-19 when compared to individuals with non-0 blood groups

Lindesmith L, et al. Human susceptibility and resistance to Norwalk virus infection. Nat Med 2003;9:548–53.

Cheng Y, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. J Am Med Assoc 2005;293:1450–1.

Zhao J, et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. Clin Infect Dis 2020.

BMC Cardiovasc Disord

2020;20:373. https://doi.org/10.1186/s12872-020-01658-z.

Sardu C, Marfella R, **Maggi P**, Messina V, Cirillo P, Codella V, et al.

Implications of AB0 blood group in hypertensive patients with covid-19.

Overall, these data indicate that individuals with hypertension and COVID-19 had significantly **higher values of prothrombotic indexes**, as well as **higher rates of cardiac injury and deaths**, if they were **in the non-0 blood group**, in comparison to the 0 group.

Th17 cells during HIV and Covid-19

The **paucity of Th17 cells during HIV infection** is caused by the infection itself, but also by an altered Th17 differentiation, survival, and trafficking into mucosal sites.

This causes major alterations in mucosal barrier integrity, microbial translocation, and disease progression.

Unless initiated during the early acute infection phases, ART fails to restore the frequency and functionality of mucosal Th17 cells.

It has been recently hypothesized that the altered functional characteristics of **COVID-19 patient-derived neutrophils result in skewed Th1/Th17 adaptive immune response**, thus contributing to disease pathology.

In the COVID-19 neutrophil/T cell cocultures, neutrophils caused a strong polarity NOS-dependent shift toward Th17.

Neutrophils, the known modulators of adaptive immunity, skew the polarization of T cells toward the Th17 promotion and Th1 suppression in COVID-19 patients, contributing to the dyscoordinated orchestration of immune response against SARSCoV-2.

As IL-17 and other Th17-related cytokines have previously been shown to correlate with the disease severity, targeting neutrophils and/or Th17 could represent a potentially beneficial therapeutic strategy for severe COVID-19 patients.

Horby PW, Mafham M, Bell JL, et al.

Lancet. 2020;396: 1345-1352.

Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.

The RECOVERY trial showed that, in patients admitted to hospital with COVID-19, lopinavir-ritonavir, used in the first phase of the pandemic, was not associated with reduction in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death

AIDS
2020; Oct 1;34(12):1775-178034:1775–80

Inciarte A, et al.

Clinical characteristics, risk factors, and incidence of symptomatic coronavirus disease 2019 in a large cohort of adults living with HIV: a single-center, prospective observational study.

PLWH diagnosed with COVID-19 **were not different from the rest of the Barcelona HIV cohort**. Clinical presentation, severity of the disease, and mortality did not depend on HIV-related or ART-related factors. **The standardized incidence rate of COVID-19 was lower in PLWH than in the Barcelona general population**, although no comparison of mortality rates was performed between the two groups.

JAIDS
2020 Sep 1;85(1):6-10.

Karmen-Tuohy S, et al.

Outcomes among HIV-positive patients hospitalized with COVID-19.

This finding was confirmed in a study comparing 42 HIV-negative and 21 HIV-positive COVID-19 patients. (NY City) **SARS-CoV-2-HIV coinfection did not have a significant impact on clinical features, course of hospitalization, or outcomes** as compared to SARS-CoV-2 infection alone.

AIDS
2020; Nov 34:F3–8
Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR.
Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study.

In a study comparing COVID-19 outcome between PLWH and non-HIV subjects crude COVID-19 mortality (West Virginia) resulted higher in PLWH. However, as regards COVID-19 outcomes, propensity matched analyses revealed no difference in HIV infection status, suggesting that **higher mortality was likely driven by higher number of comorbidities**.

Clin Infect Dis. 2020

Geretti AM, et al.

Outcomes of COVID-19 related hospitalization among people with HIV in the ISARIC WHO clinical characterization protocol (UK): a prospective observational study.

On the contrary, a comparison between HIV-negative and positive patients, admitted in 207 hospitals across the United Kingdom, showed a **higher day 28 mortality in PLWH**, after considering potential risk factors such as age, sex,comorbidities and need for oxygen at presentation. **In particular, in people aged less than 60 years the adjusted hazard ratio was 2.87 an increased risk due to HIV status**

AIDS.

2020 Nov 1;34(13):1983-1985

Di Biagio A, Ricci E, Calza L, Squillace N, Menzaghi B, Rusconi S, Orofino G, Bargiacchi O, Molteni C, Valsecchi L, Cenderello G, Ferrara S, Saracino A, **Maggi P**, Falasca K, Taramasso L, Bonfanti P; CISAI Study group.

Factors associated with hospital admission for COVID-19 in HIV patients.

Di Biagio et al. described the epidemiological, clinical features and the outcomes of 69 HIV patients with confirmed SARSCoV-2 in a network of Italian centers. Characteristics of patients and median days between symptoms and diagnosis were similar by hospital admission. **Admitted patients had lower current lymphocytes count and nadir CD4 cells, values that also correlated to the worse outcome of COVID-19. Antiretroviral drugs and disease severity did not seem to be associated.**

HIV Med. 2021 Oct;22(9):867-876.

Díez C, et al.

COVID-19 in hospitalized HIV-positive and HIV-negative patients: A matched study.

Well-controlled HIV infection does not modify the clinical presentation or worsen clinical outcomes of COVID-19 hospitalization

Behavioral aspects could play a role:

- Many PLWH are **aware** of their immune deficiency conditions and may protect themselves better than the general population.
- In several countries, **the median age** of PLWH is lower than non-coinfected COVID-19 patients.
- PLWH are frequently **more treated and monitored for hypertension and diabetes at an earlier stage** than their non co- infected counterparts.

1 Conclusions

- **Both these viruses are able to activate inflammatory pathways**.
  - This capacity influences the acute or **hyperacute phase of SARSCoV- 2**
  - In the case of HIV, inflammation dominates **the chronic phase**
- The **comorbidities** seem to represent,
  - in the case of SARS-CoV -2, a contributory cause of primary importance in the **outcome of the disease**
  - In the case of HIV an effect of the **virus-induced damage**.

2 Conclusions

- **Inflammation and comorbidities** represent nowadays two fundamental aspects in the pathogenesis of several infectious diseases, previously generally underestimated.
- From now on, an in-depth knowledge of **immune mechanisms** at the base of several viral diseases will be mandatory, aimed both at preventing the negative outcomes of these diseases and at designing effective therapeutic strategies, especially for new pathogens, such as SARS-CoV-2.
- In the near future, **therapies targeted to interfere with inflammatory patterns** will be associated with antiviral or antibiotic treatments.

3 Conclusions

- **The role of comorbidities** in modifying the natural history of viral diseases is another crucial point
- Nowadays it is mandatory to obtain, from our first clinical approach to the patient, **a comprehensive awareness of his comorbidities, even at subclinical stages!**
- Moreover a **prompt and effective treatment of comorbidities** could substantially modify the clinical outcome of a number of infections and could prevent the most severe complications
- The contribution of **immunology** to infectious disease research is essential, but we should also be aware that only interactive teams composed by infectious disease specialists supported by **cardiologist, diabetologists, geriatricians,** could effectively address all the diagnostic and therapeutic needs of these patients.