



Impact van COVID-19 op auto-immuun en ontsteking gerelateerde huidaandoeningen.

Hok Bing Thio, Dermatologie, ErasmusMC,
Rotterdam, NL.

Webinar 16 november 2020
h.thio@erasmusmc.nl.

Photo illustration by Getty.

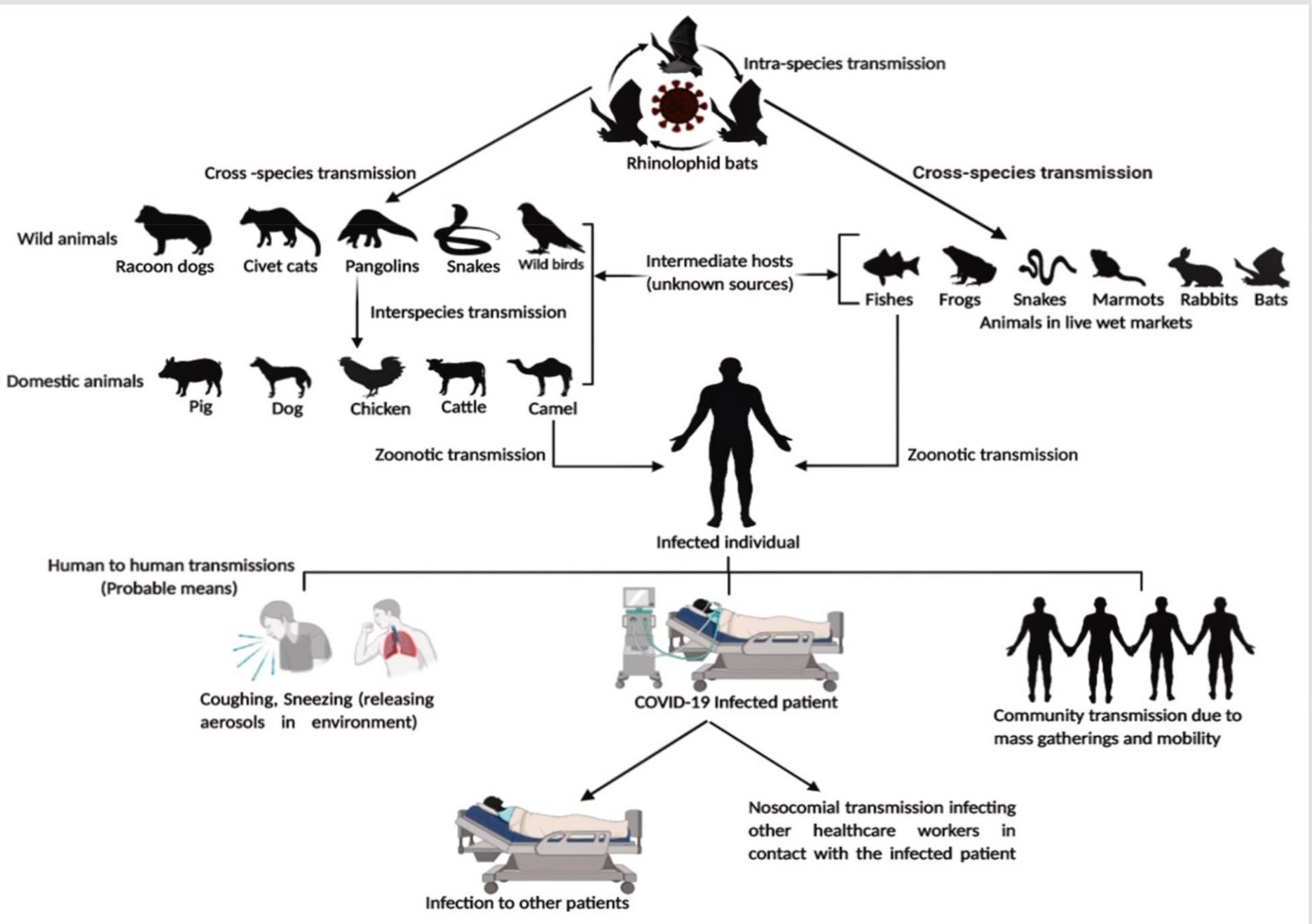
Disclaimer & Disclosure

The views as expressed in these slides are those of Hok Bing Thio.

The information shown in this slide deck may be outside the current indications of presented drugs. Please refer to the complete SmPCs for valid prescribing information.

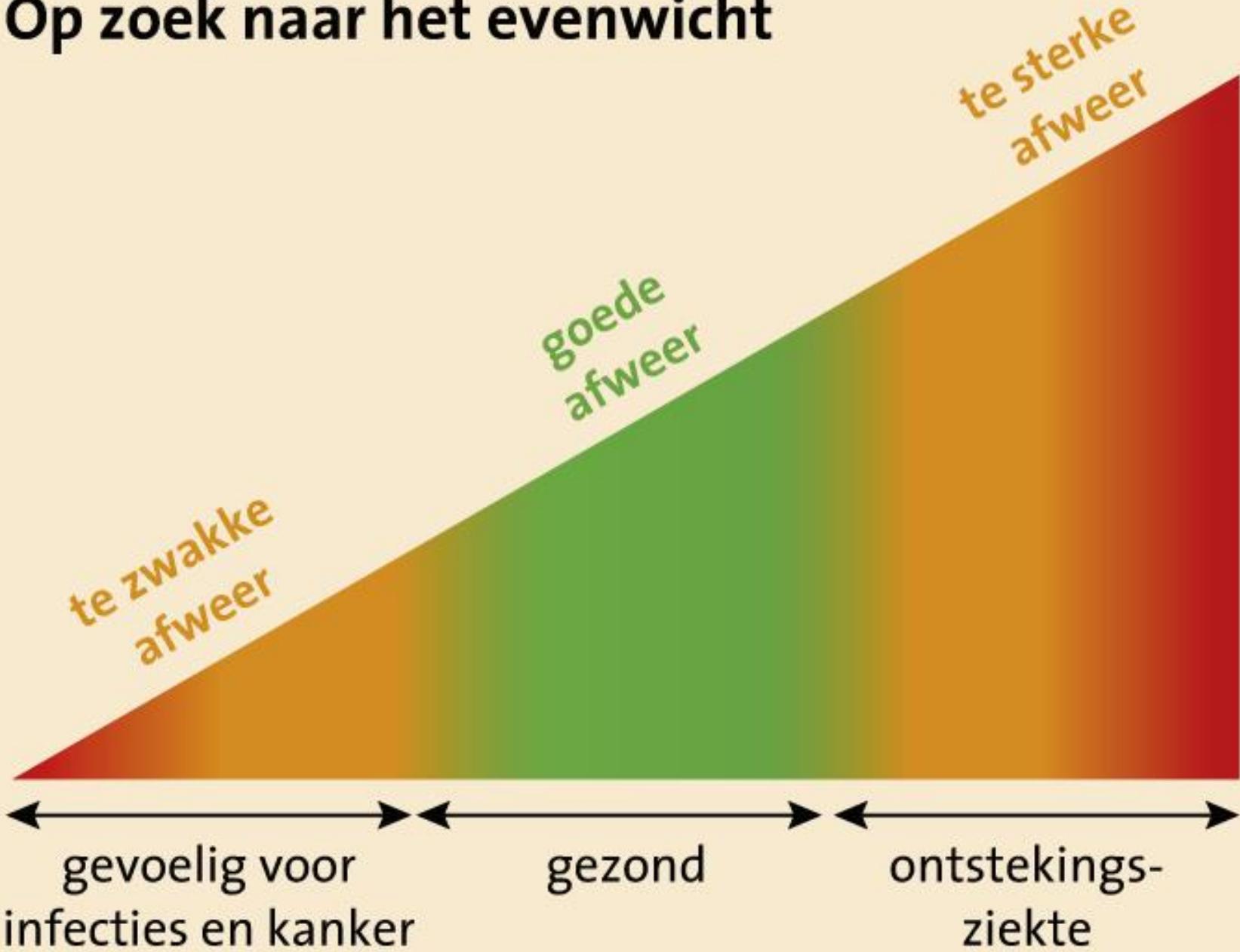
Hok Bing Thio has been a consultant and invited speaker for Dr. Reddy, Biogen, Janssen, AbbVie, Celgene, Biologix, Galderma, Leopharma, Lilly, Almirall, TEVA, UCB and Novartis. He has received educational and research grants from AbbVie, Celgene, Janssen and Biogen.

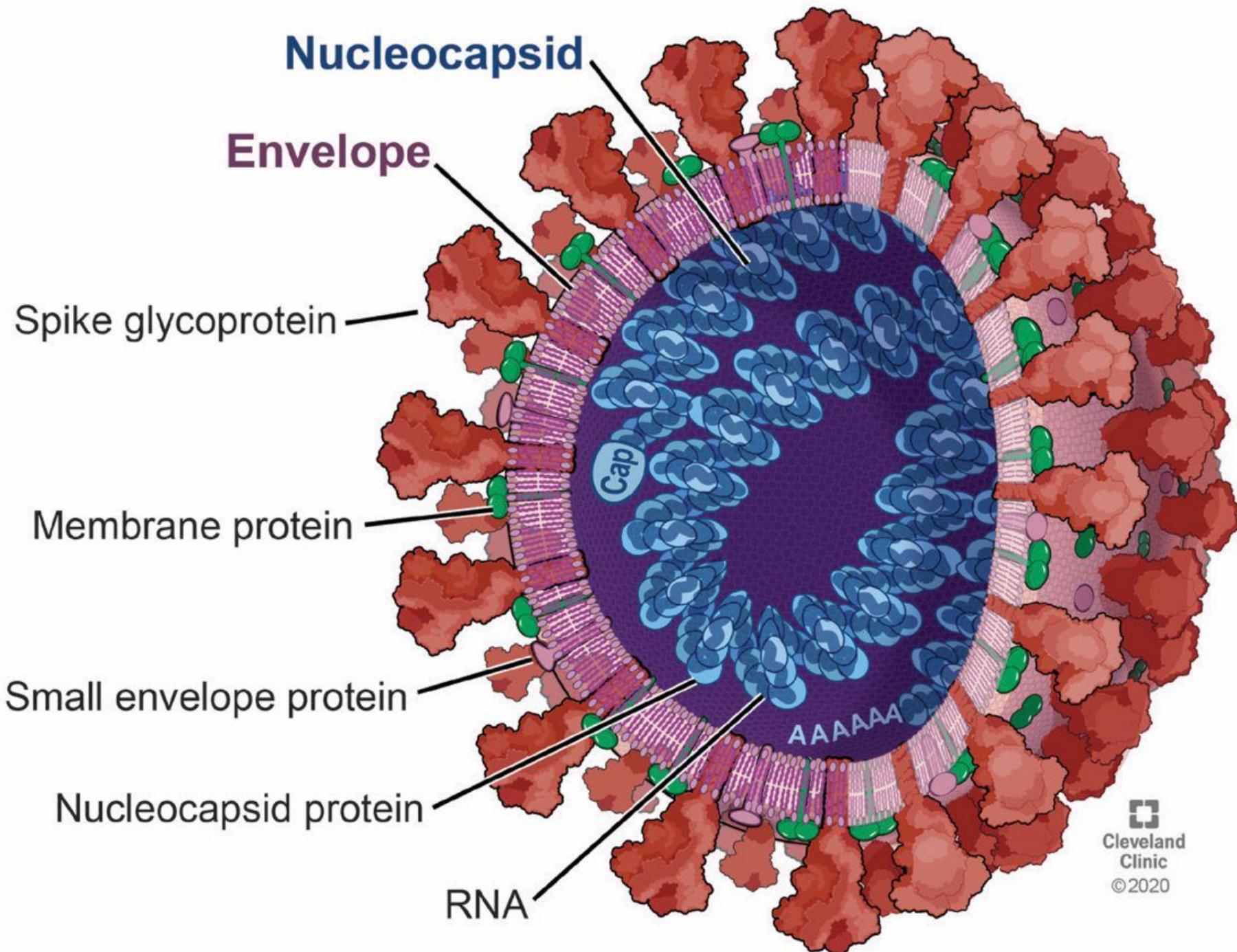




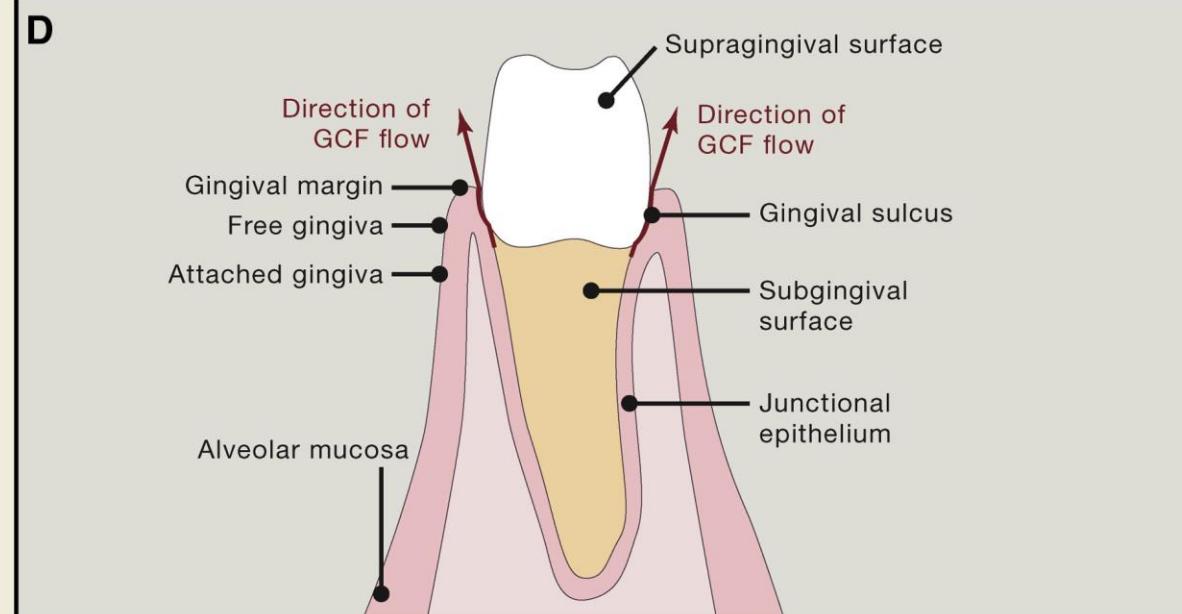
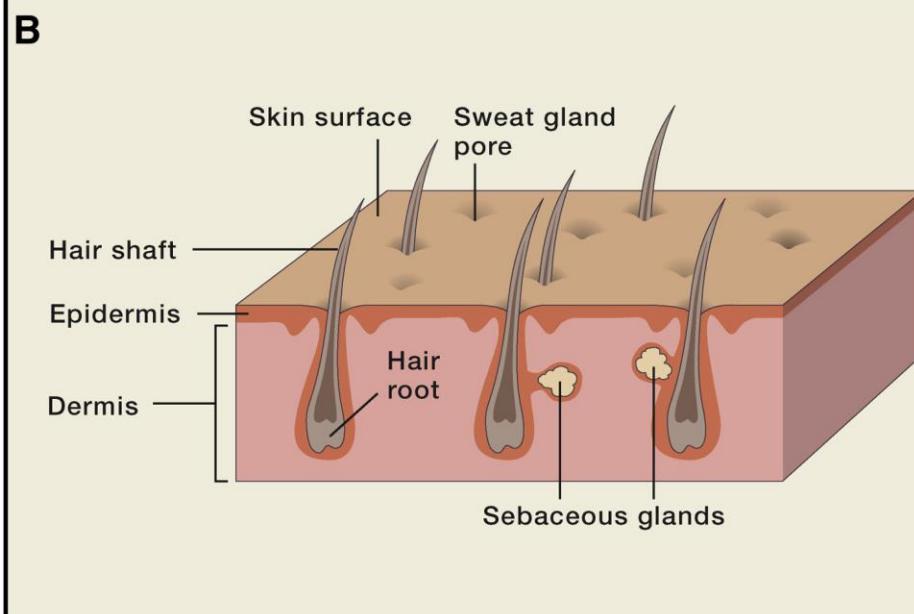
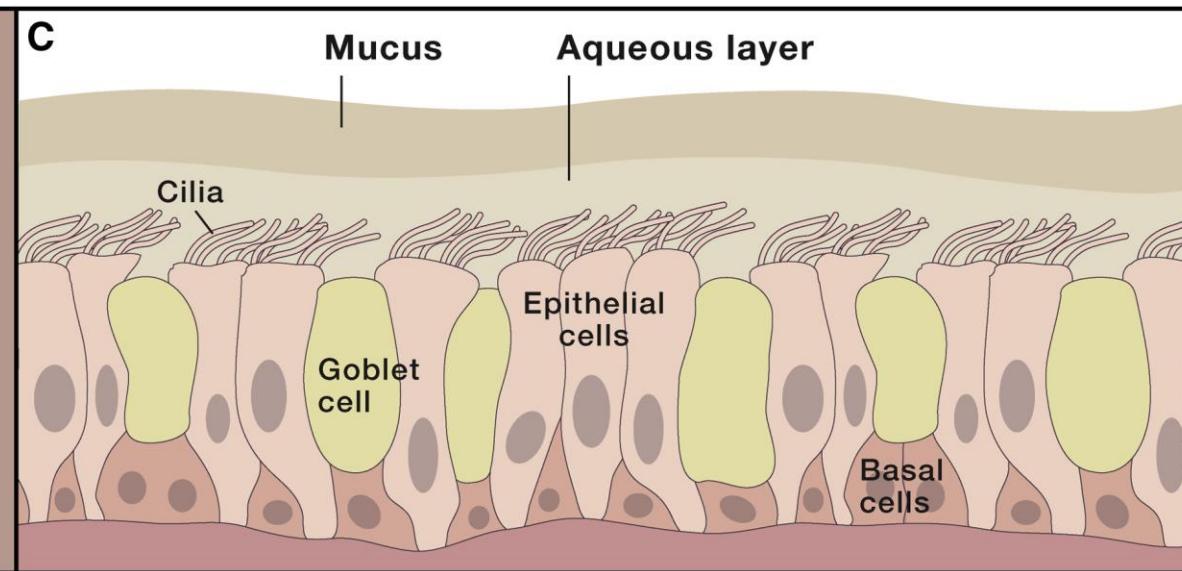
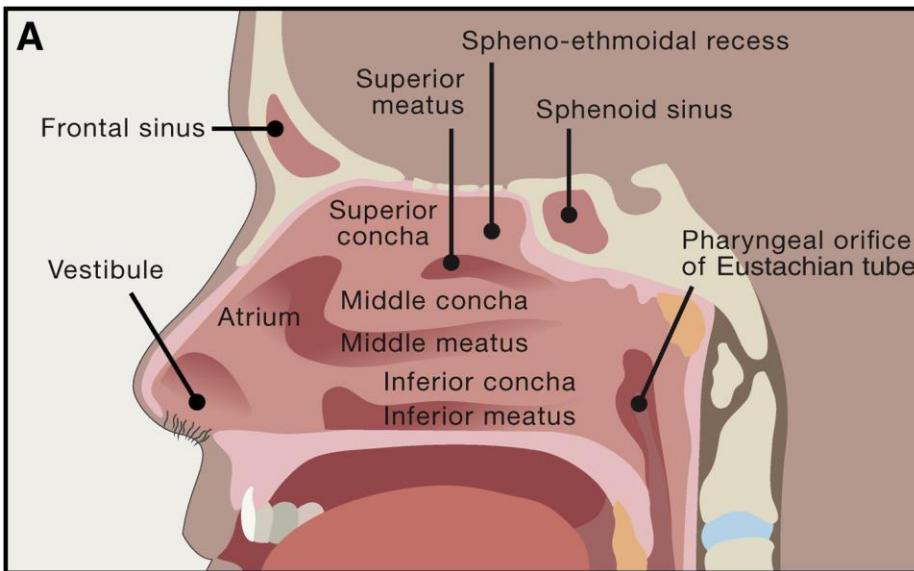
Ankit Kumar Dubey, Aakansha Singh,
Shardendu Prakash, Manoj Kumar,
Ashok K Singh,
Race to arsenal COVID-19 therapeutics:
Current alarming status and future
directions,
Chemico-Biological Interactions, Volume
332, 2020, 109298, ISSN 0009-2797,

Op zoek naar het evenwicht





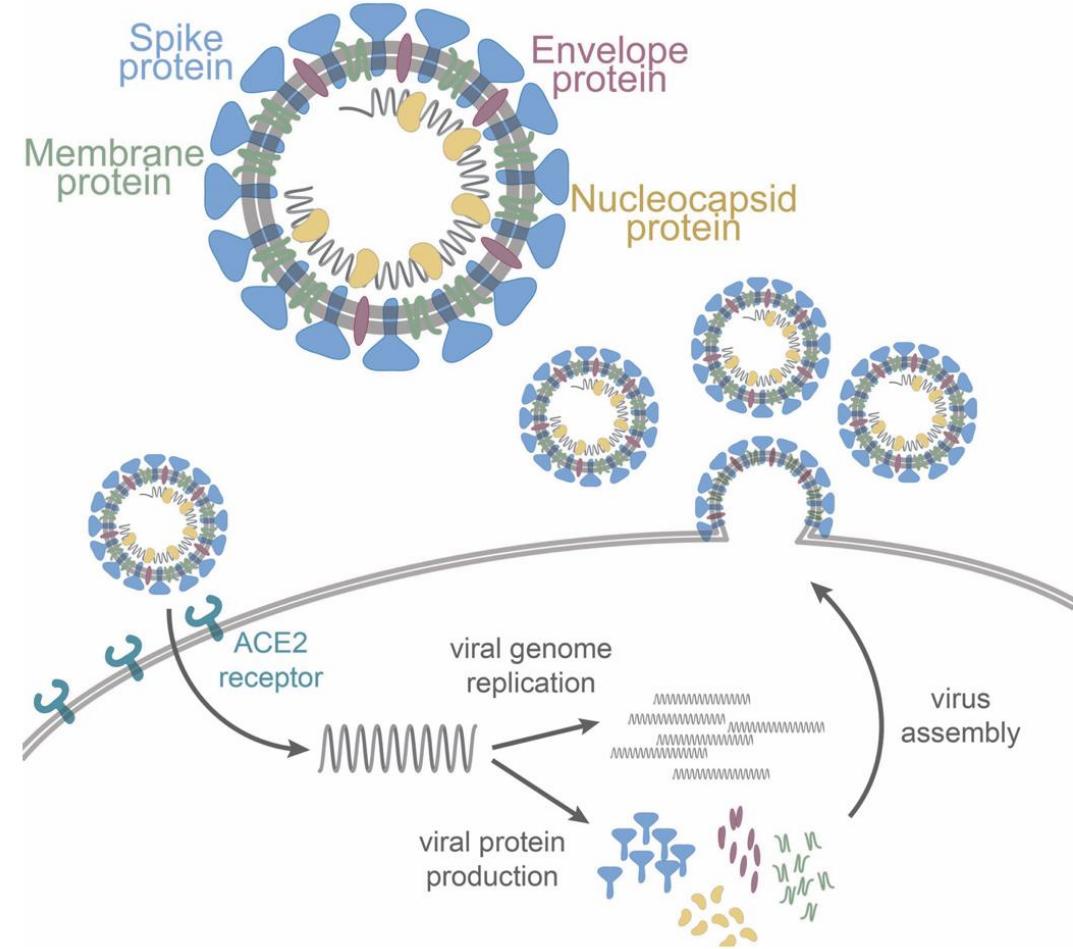
ENTRY

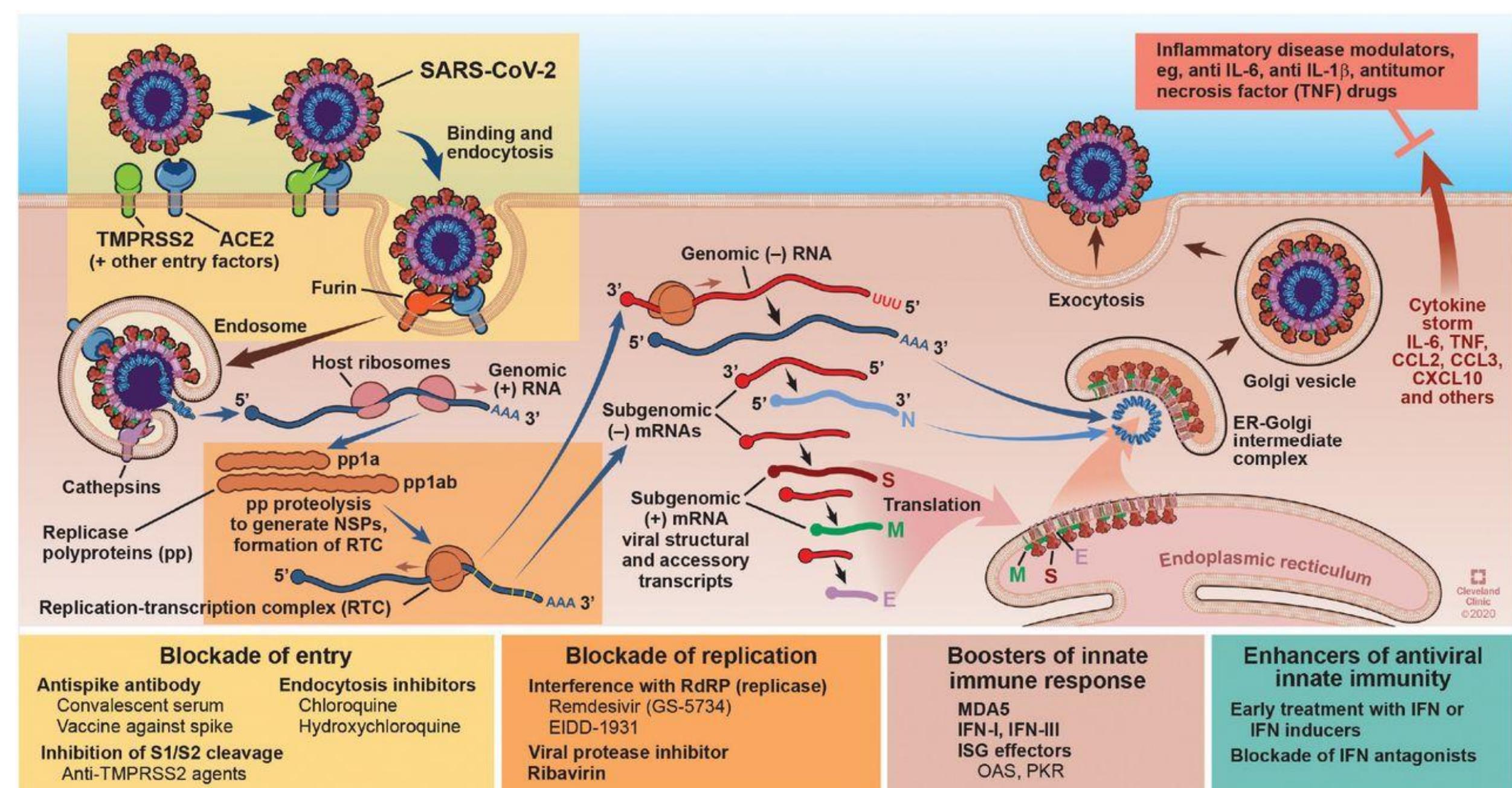


SARS-CoV-2 kan de smaak aantasten door binding aan angiotensin-converting enzyme-2 receptoren die aanwezig zijn op de tong en elders in de mondholte.

Smaakverlies treedt ongeveer in 50% van de COVID-19 patienten.

.

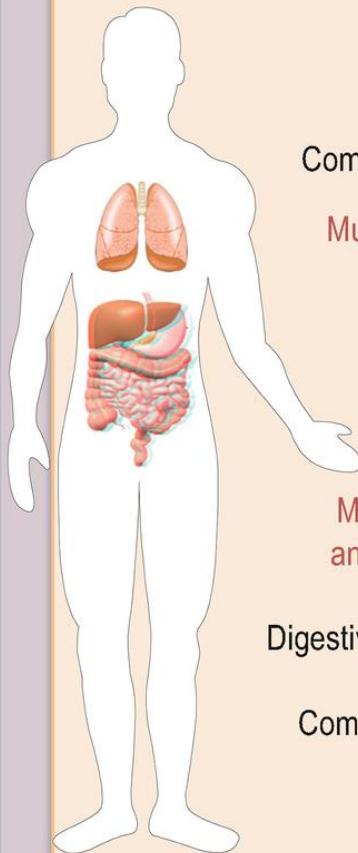




Adaptive immunity

Innate immunity

Physiological barriers



Eosinophil



NK cell



Complement



Activated B cell

PAMPs



TLRs



ROS



Cytokines



Chemokines



Neutrophils



Monocyte



DC



Macrophage



Antibodies



Plasma cell



Memory B cell



Cytotoxic T cell



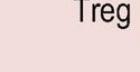
Helper T cell



Memory T cell

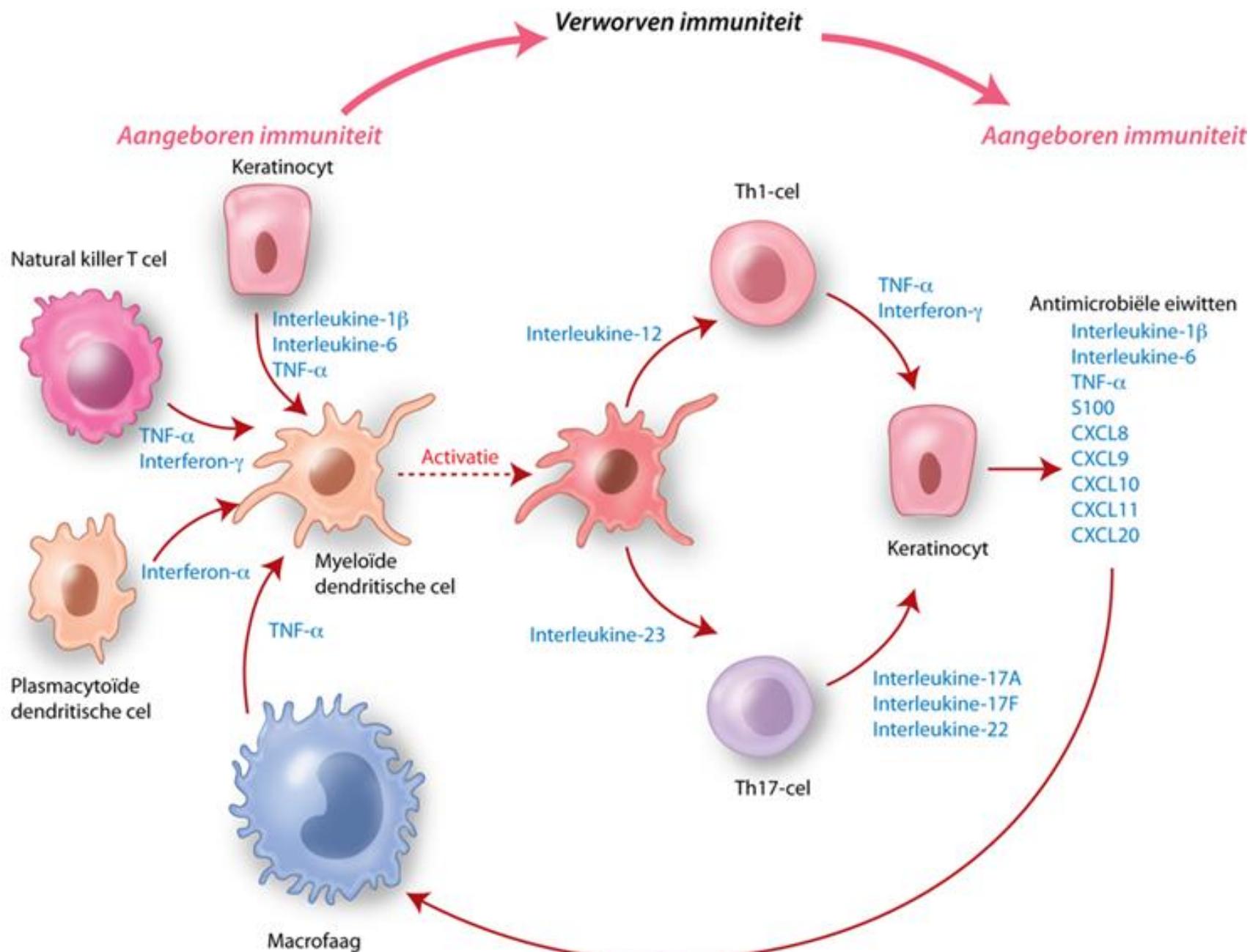


Treg



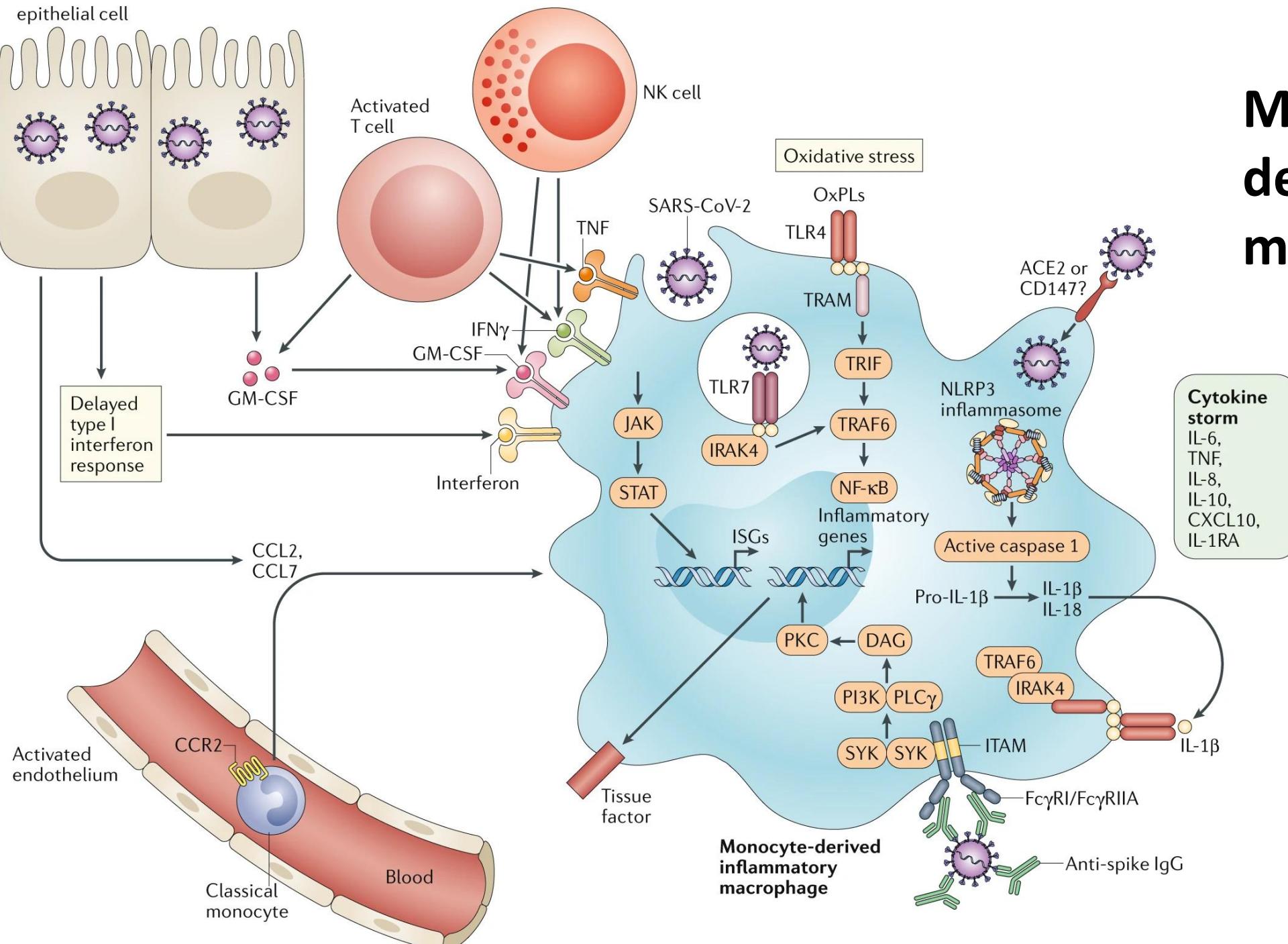
IMMUUN SYSTEM

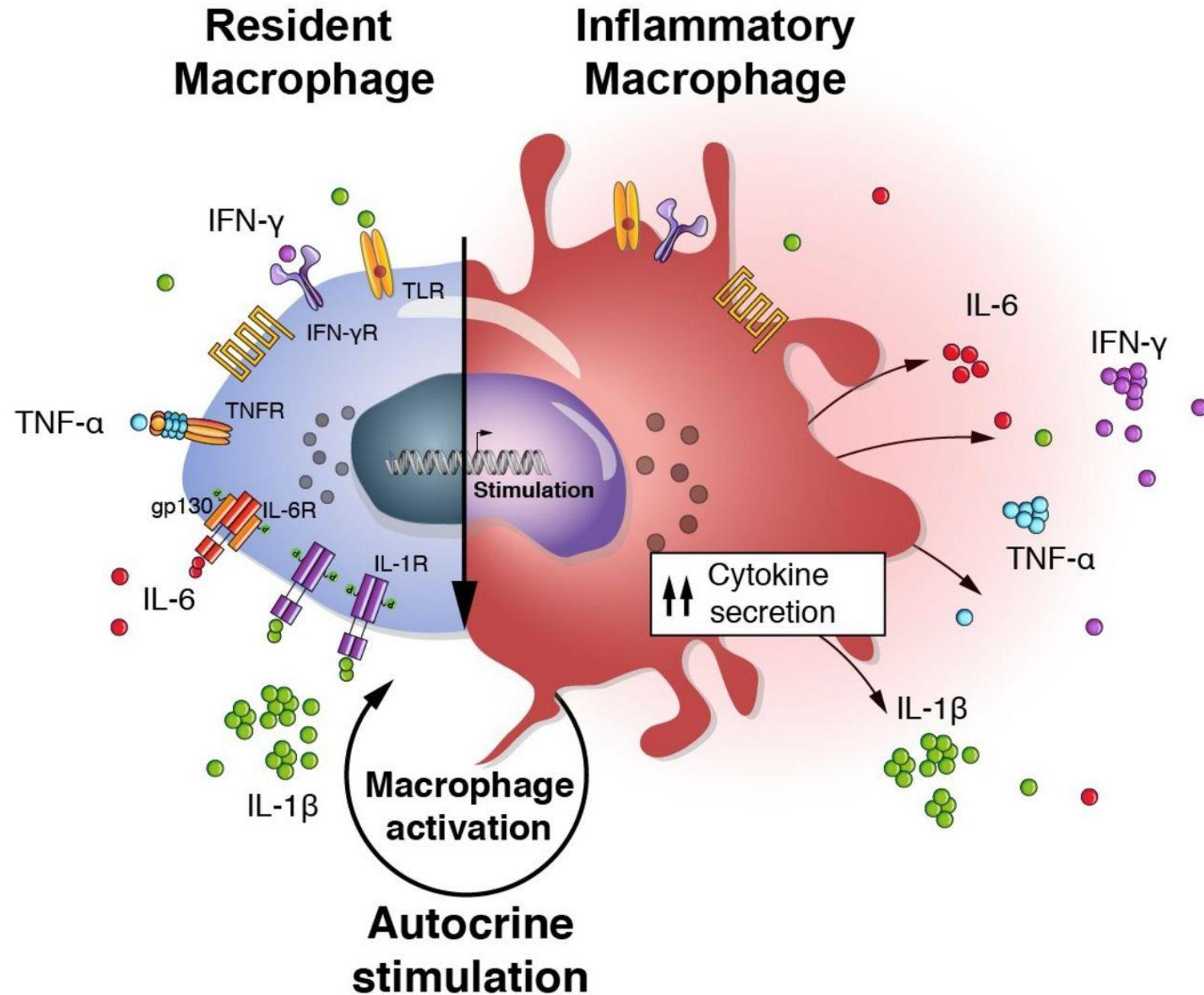
Müller L., Di Benedetto S., Pawelec G. (2019) The Immune System and Its Dysregulation with Aging. In: Harris J., Korolchuk V. (eds) Biochemistry and Cell Biology of Ageing: Part II Clinical Science. Subcellular Biochemistry, vol 91. Springer, Singapore



	aangeboren immuniteit	verworven immuniteit
specificiteit	patroonherkenning	antilichamen, T-celreceptoren
werking	direct	inductie
cellen	monocyten, macrofagen, granulocyten,	T- en B-lymfocyten, naturalkillerellen, dendritische cellen
geheugen	nee	ja
initiatie van de respons	ter plaatse	secundaire lymfoïde organen
effectormechanismen	fagocytose en intracellulaire doding	antilichamen, cytotoxische T-lymfocyten, helper-T-lymfocyten (Th1, Th2, Th17, Tfh en Treg)
effectoreiwitten	complement, defensinen, cytokinen,	antilichamen, cytokinen, perforine, granzymen andere eiwitten

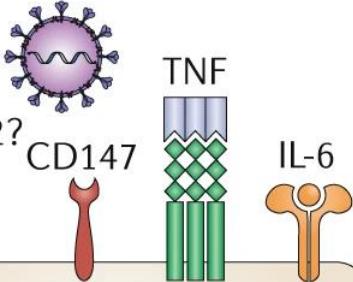
Monocyte-derived macrophages



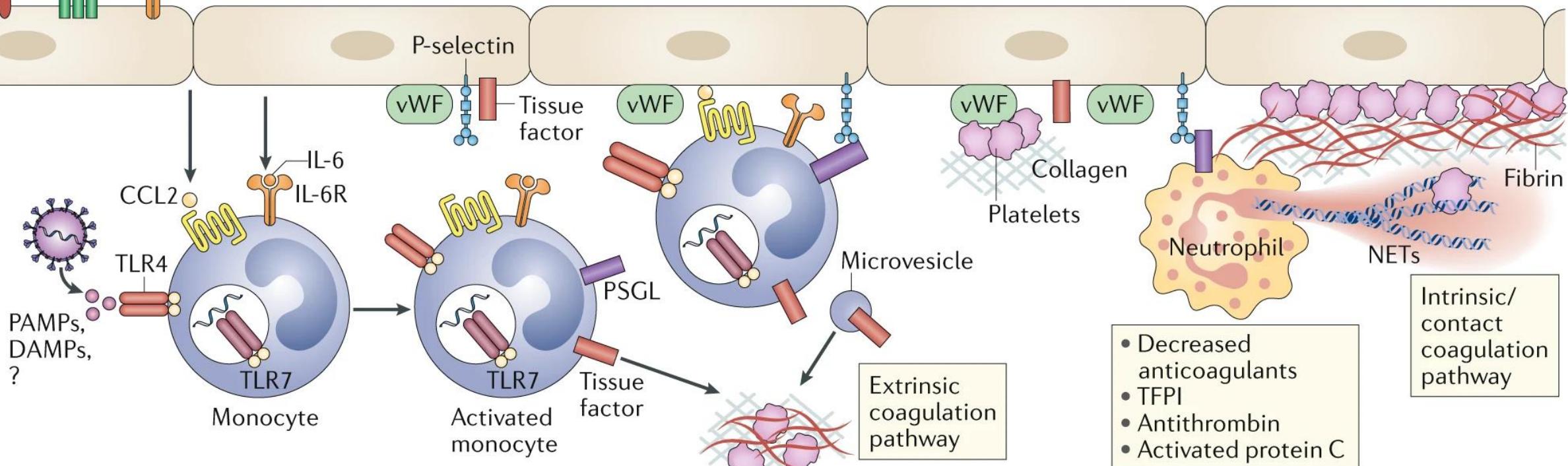


Addeo A, Obeid M, Friedlaender AC
COVID-19 and lung cancer: risks, mechanisms and treatment interactions
Journal for ImmunoTherapy of Cancer 2020;8:e000892. doi: 10.1136/jitc-2020-000892

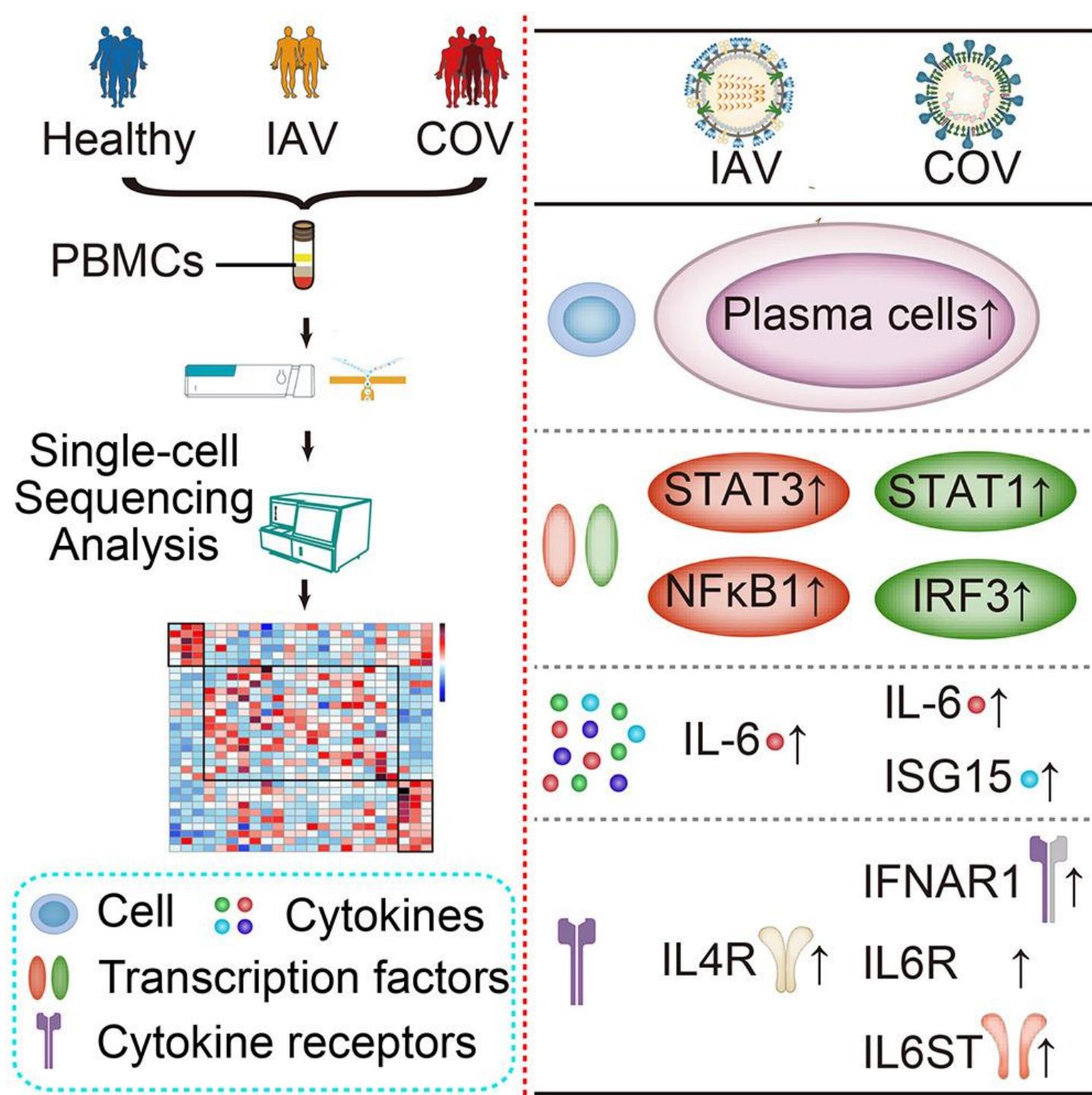
SARS-CoV-2



IMMUUN SYSTEEM EN STOLLING

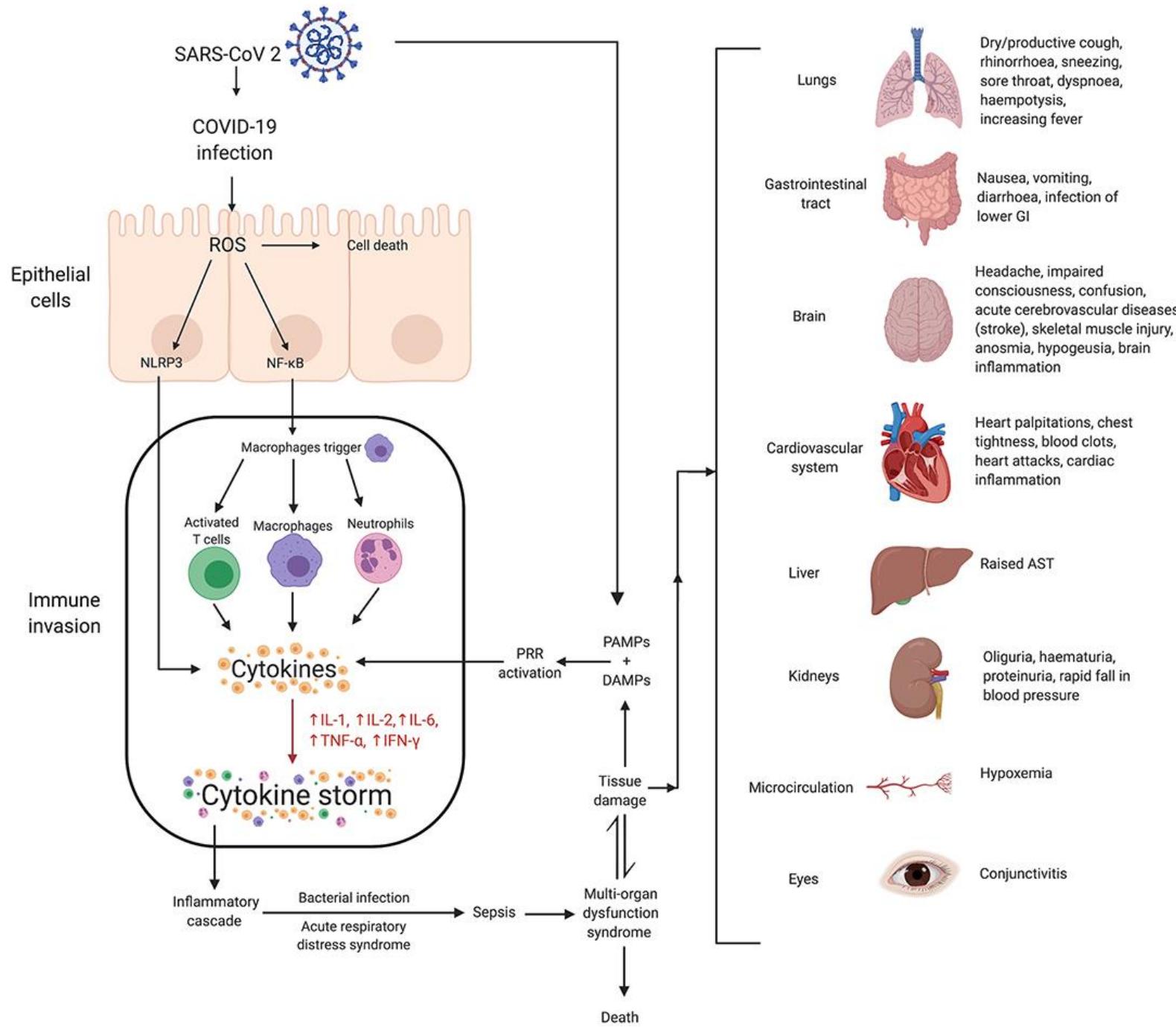


Merad, M., Martin, J.C. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 20, 355–362 (2020).
<https://doi.org/10.1038/s41577-020-0331-4>



Influenza A virus (IAV) vs SARS-CoV-2 (COV)

Single-cell sequencing of peripheral blood mononuclear cells reveals distinct immune response landscapes of COVID-19 and influenza patients. Linnan Zhu et al. Published: July 19, 2020 DOI: <https://doi.org/10.1016/j.jimmuni.2020.07.009>



Front. Immunol., 10 July 2020 |
<https://doi.org/10.3389/fimmu.2020.01648>
Cytokine Storm in COVID-19—Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper
Sonu Bhaskar et al.

COVID-19 en de huid



Medscape

Source: Jordan Lee

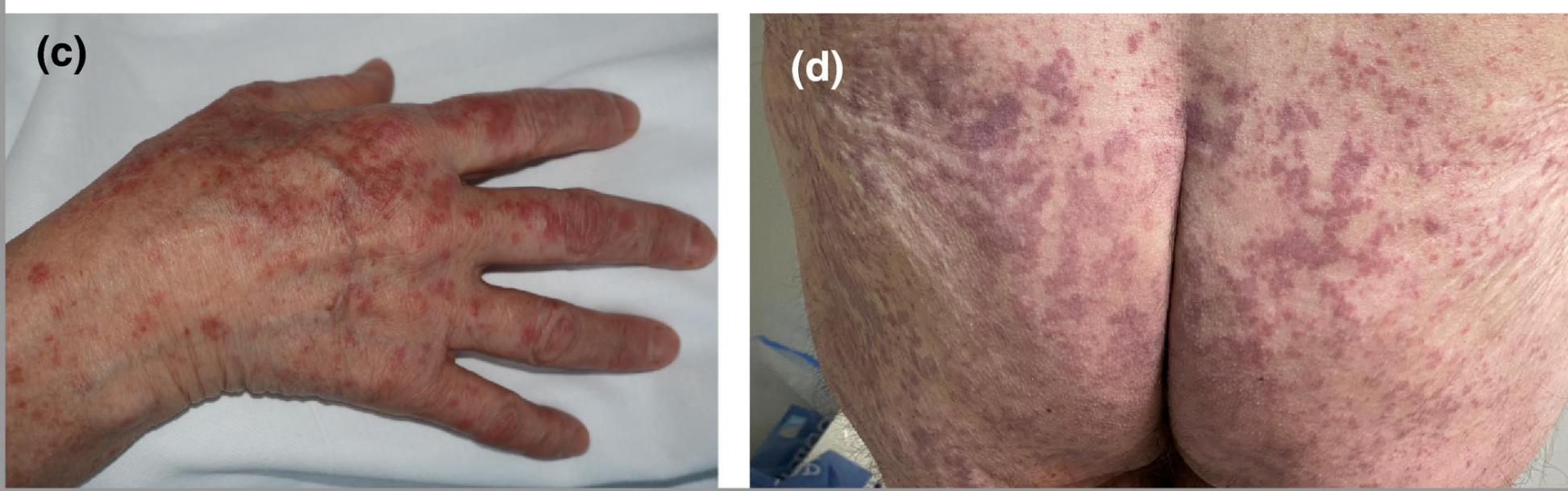
Dermatologic Changes With COVID-19: What We Know and Don't Know
Interviewer: Graeme M. Lipper, MD; Interviewee: Lindy P. Fox, MD
DISCLOSURES May 13, 2020



Mohan V, Lind R (July 17, 2020) Chilblains in COVID-19 Infection. *Cureus* 12(7): e9245. doi:10.7759/cureus.9245



[https://www.thestar.com.my/lifestyle/health/2020/06/04/unusual-covid-19-symptom
affect-taste-smell-skin-and-toes](https://www.thestar.com.my/lifestyle/health/2020/06/04/unusual-covid-19-symptom-affect-taste-smell-skin-and-toes)



All of the patients shown had confirmed COVID -19.

(a) Maculopapular eruption. Some of the lesions are perifollicular.

(b) Acral infiltrated papules (pseudovesicular).

(c) Acral papules (erythema multiforme like).

(d) Livedoid areas.

Galván Casas, C., et al. (2020), Classification of the cutaneous manifestations of COVID -19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. doi:10.1111/bjd.19163

(a)



(b)



(c)



(d)



All of the patients shown had confirmed COVID -19.

(a, b) Acral areas of erythema–oedema with vesicles or pustules (pseudo-chilblain).

(c) Monomorphic (i.e. at same stages) disseminated vesicles.

(d) Urticarial lesions.

Galván Casas, C., Català, A., Carretero Hernández, G., Rodríguez-Jiménez, P., Fernández-Nieto, D., Rodríguez-Villa Lario, A., Navarro Fernández, I., Ruiz-Villaverde, R., Falkenhain-López, D., Llamas Velasco, M., García-Gavín, J., Baniandrés, O., González-Cruz, C., Morillas-Lahuerta, V., Cubiró, X., Figueras Nart, I., Selda-Enriquez, G., Romaní, J., Fustà-Novell, X., Melian-Olivera, A., Roncero Riesco, M., Burgos-Blasco, P., Sola Ortigosa, J., Feito Rodriguez, M. and García-Doval, I. (2020), Classification of the cutaneous manifestations of COVID -19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. doi:10.1111/bjd.19163

Severity of COVID-19*



Pernio

- Feet (84%) and hands (32%)
- Pain/burning (71%) and pruritus (36%)
- After other COVID-19 symptoms (49%)
- Fever (35%), cough (35%); 19% asymptomatic
- 16% hospitalized

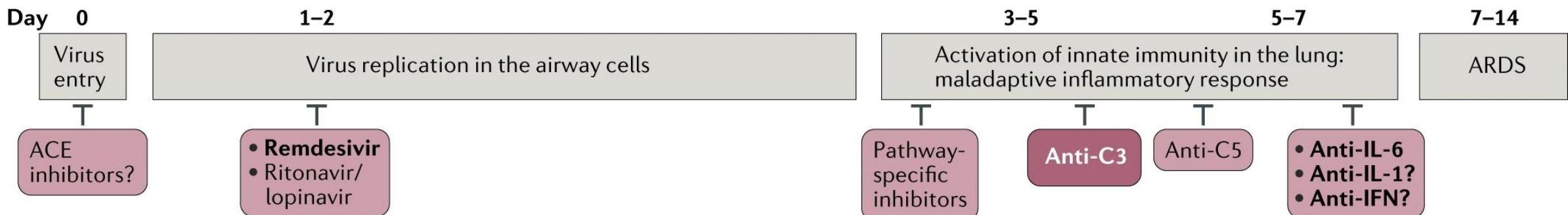
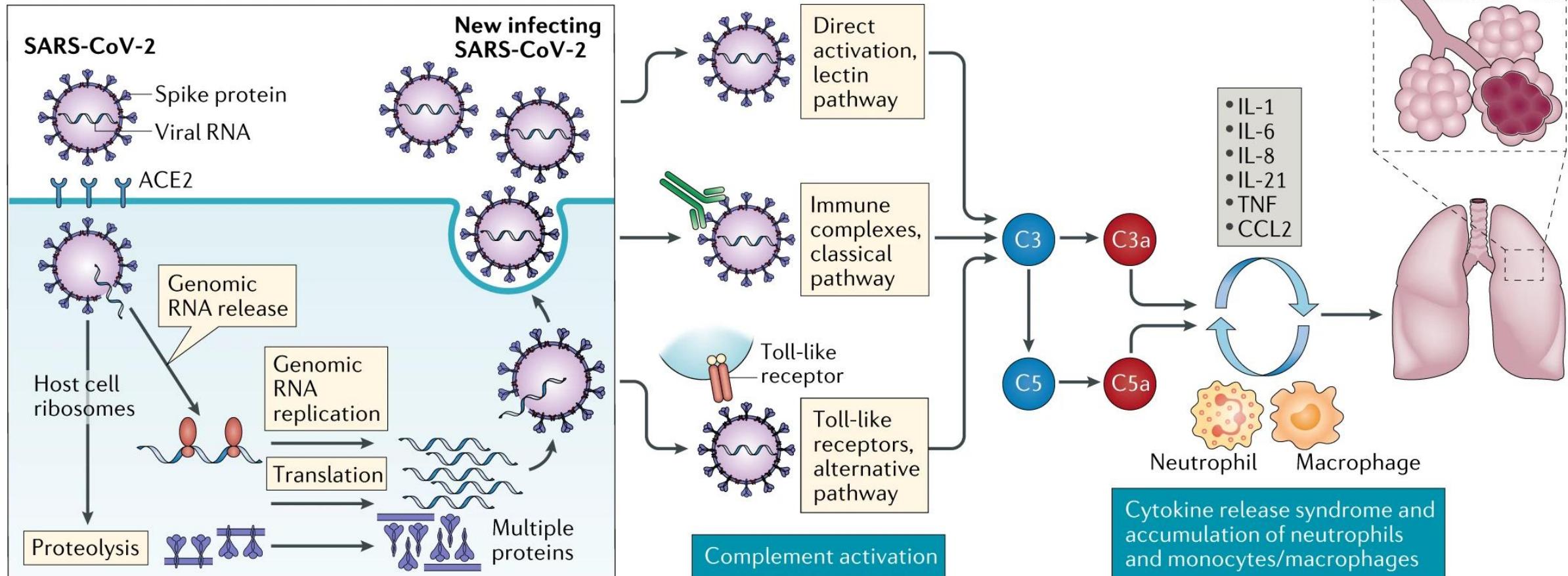
Vesicular/ Urticarial/ Macular Erythema/ Morbilliform

- Trunk and extremities
- Pruritus in 61-74%
- Typically after other COVID-19 symptoms (19%)
- Fever (65-74%), cough (52-66%), sore throat (39-50%), shortness of breath (28-45%)
- 22-45% hospitalized across groups

Retiform purpura

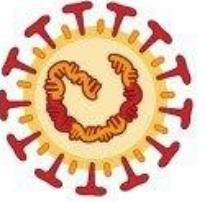
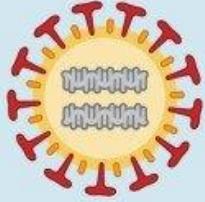
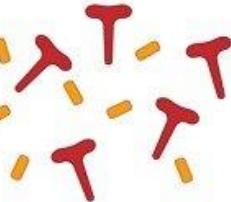
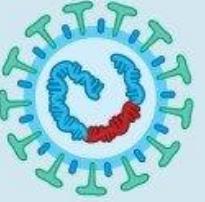
- Extremities and buttocks
- Often asymptomatic (73%)
- After other COVID-19 symptoms (91%)
- Fever (64%), cough (73%), and shortness of breath (73%)
- 100% hospitalized
- 82% with ARDS

*Severity calculated based on percentage of patients hospitalized for COVID-19

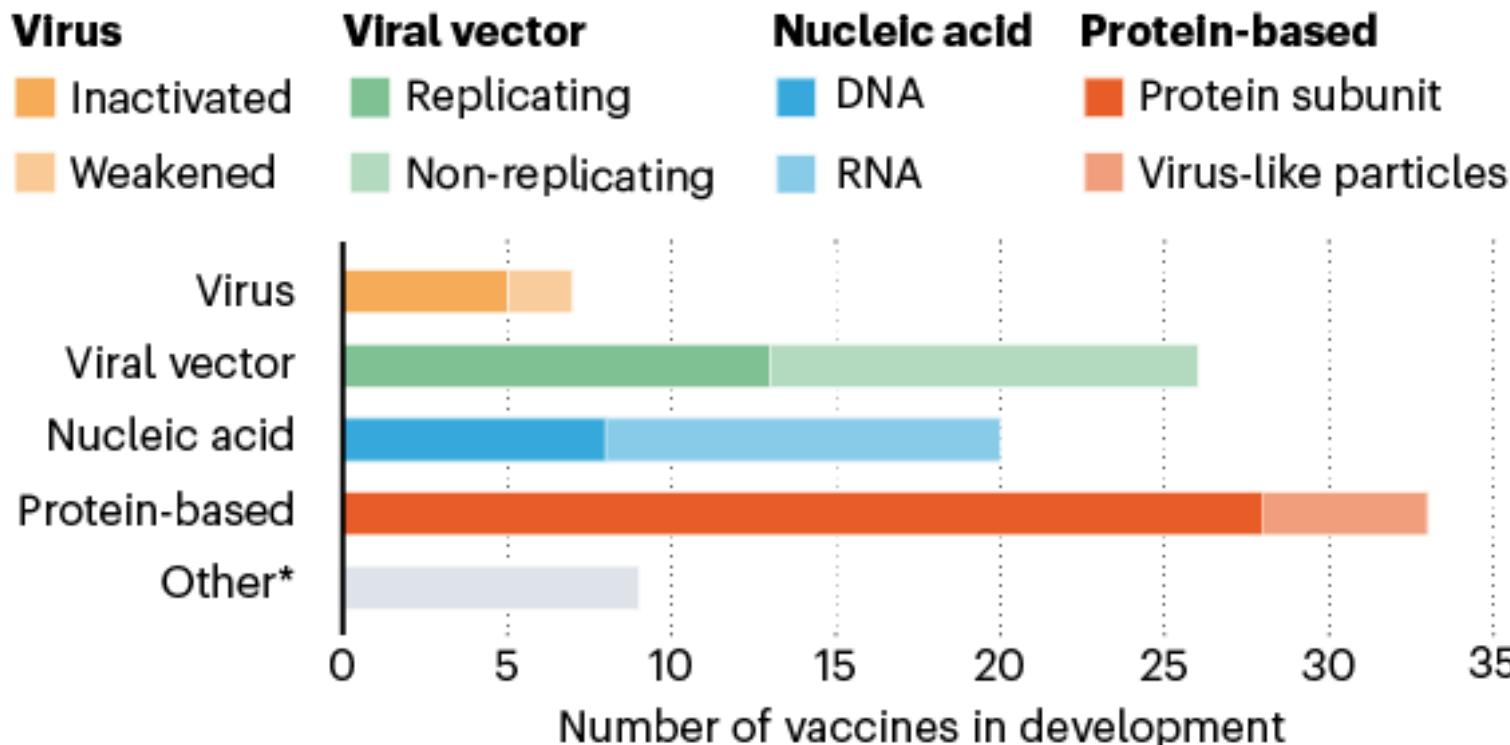


Types of coronavirus vaccine approaches

Scientists are casting a wide net to see what works best against the novel coronavirus.

Types of vaccines	DNA and RNA	Live attenuated	Inactivated	Subunit	Viral vector
How it works					
Advantages	This vaccine uses DNA or RNA molecules to teach the immune system to target key viral proteins.	This is a weakened version of the actual virus.	An inactivated vaccine uses the whole virus after it has been killed with heat or chemicals.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.
Disadvantages	Easy and quick to design.	Stimulates a robust immune response without causing serious disease.	Safe because the virus is already dead and is easy to make.	Focuses the immune response on the most important part of the virus for protection and cannot cause infection.	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.
Existing examples	<ul style="list-style-type: none"> None 	<ul style="list-style-type: none"> Measles, Mumps and Rubella Chickenpox 	<ul style="list-style-type: none"> Polio 	<ul style="list-style-type: none"> Pertussis Hepatitis C Human papillomavirus (HPV) 	<ul style="list-style-type: none"> Ebola Veterinary medicine
Group testing this approach for COVID-19	<ul style="list-style-type: none"> Moderna (RNA) Inovio (DNA) 	<ul style="list-style-type: none"> Codagenix Indian Immunologicals Ltd. 	<ul style="list-style-type: none"> Sinovac Sinopharm 	<ul style="list-style-type: none"> Novavax AdaptVac 	<ul style="list-style-type: none"> University of Oxford & AstraZeneca CanSino Biologics Johnson & Johnson

AN ARRAY OF VACCINES



* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity), or whether certain immune cells could be genetically modified to target the virus.

©nature



Newman AJ, Schneider A, Blumetti B, et alChronic cutaneous lupus erythematosus and topical clindamycinCase Reports 2018;2018:bcr-2018-226728.

**Clinical course of coronavirus disease 2019
(COVID-19) in a series of 17 patients with
systemic lupus erythematosus under long-term
treatment with hydroxychloroquine**

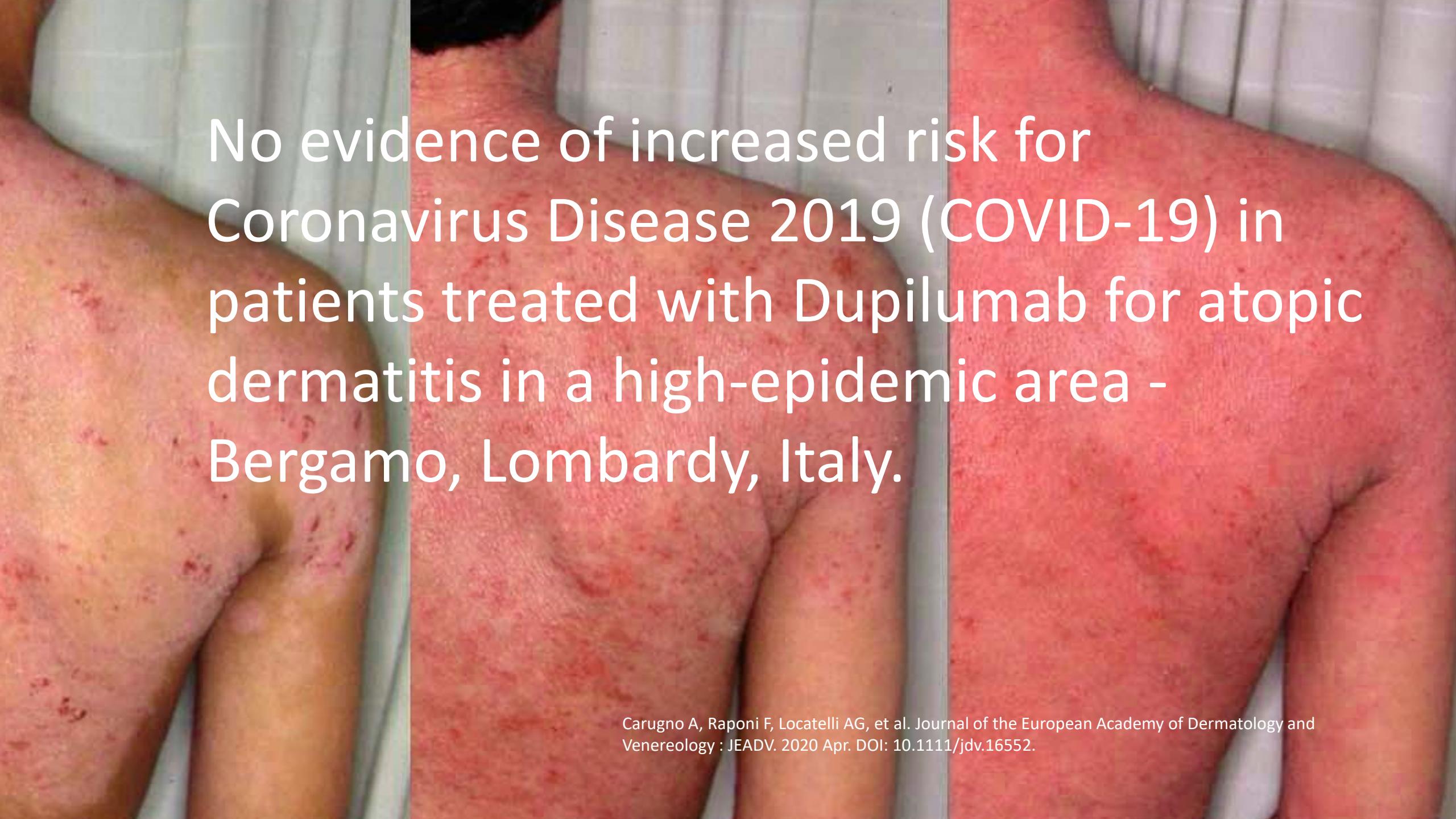
Patients
(N=17)

Signs and symptoms at baseline

Fever	17 (100)
Cough	14 (82)
Sputum	4 (24)
Shortness of breath	14 (82)
Respiratory rate >24 breaths per minute	9 (53)
Pulse >125 beats per minute	3 (18)
Myalgia	8 (47)
Confusion	1 (6)
Headache	10 (59)
Sore throat	6 (35)
Rhinorrhoea	4 (24)
Dysgeusia	5 (29)
Anosmia	5 (29)
Chest pain	4 (24)
Diarrhoea	7 (41)
Nausea and/or vomiting	3 (18)
Fever + cough + shortness of breath	13 (76)
Time from illness onset to fever, days	0 (0–12)



Atopic dermatitis. Weidinger, Stephan et al. 2015. *The Lancet*, Volume 387, Issue 10023, 1109 - 1122



No evidence of increased risk for
Coronavirus Disease 2019 (COVID-19) in
patients treated with Dupilumab for atopic
dermatitis in a high-epidemic area -
Bergamo, Lombardy, Italy.

Carugno A, Raponi F, Locatelli AG, et al. Journal of the European Academy of Dermatology and Venereology : JEADV. 2020 Apr. DOI: 10.1111/jdv.16552.



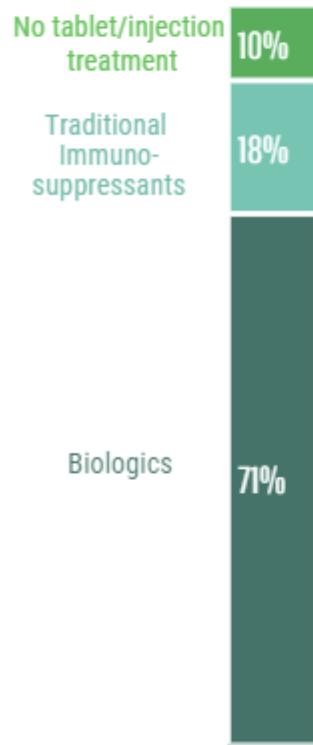
	Verona	Padua	Vicenza	Modena	Milan – Humanitas	Milan – San Donato	Turin	Total
Number of patients with psoriasis	1002	650	180	508	475	1093	1298	5206
Male sex, n (%)	631 (63)	461 (71)	130 (72)	340 (67)	299 (63)	66 (68)	896 (69)	2823 (67)
Age, years (mean ± SD)	56 ± 12·1	54 ± 10·2	58 ± 12·1	53 ± 13·2	48 ± 14·5	55 ± 10·1	49 ± 10·3	53·2 ± 11·2
Outcome measure, n								
Hospitalized for COVID-related disease	0	0	0	1	0	2	1	4
Deaths from COVID-related disease	0	0	0	0	0	0	0	0
Comorbidity, n (%)								
Obesity	301 (30)	162 (25)	54 (30)	193 (38)	133 (28)	197 (18)	273 (21)	1313 (25)
Cardiovascular disease	150 (15)	52 (8)	14 (8)	43 (8·4)	57 (12)	153 (14)	156 (12)	625 (12)
Hypertension	340 (34)	227 (35)	18 (10)	177 (34·9)	162 (34·1)	317 (29)	363 (28)	1604 (30·8)
Psoriatic arthritis	301 (30)	247 (38)	54 (30)	165 (32·5)	71 (15)	273 (25)	324 (25)	1435 (27·6)
Diabetes mellitus	120 (12)	78 (12)	22 (12)	45 (8·8)	57 (12)	131 (12)	182 (14)	635 (12·2)
Biological therapy, n (%)								
TNF-α inhibitors	501 (50)	312 (48)	108 (60)	188 (37)	57 (12)	240 (22)	273 (21)	1679 (32·2)
IL-17 inhibitors	280 (28)	175 (27)	27 (15)	183 (36)	190 (40)	492 (45)	649 (50)	1996 (38·3)
IL-12/23 inhibitor	170 (17)	162 (25)	36 (20)	99 (19·4)	185 (39)	361 (33)	376 (29)	1389 (26·7)
IL-23 inhibitors	50 (5)	–	9 (5)	39 (7·6)	43 (9)	–	–	141 (2·7)



PsoProtect

www.psoprotect.org

Impact of COVID-19 in People with Psoriasis Taking Drugs that Affect the Immune System: Findings from the PsoProtect Registry



Risk factors of hospitalization:



Male



Older age



Non-white ethnicity



Other health conditions (chronic lung disease, high blood pressure, heart disease)



21%

Hospitalized

79%

Not hospitalized



Death (2%)
Ongoing medical problems (5%)

93%

Full recovery

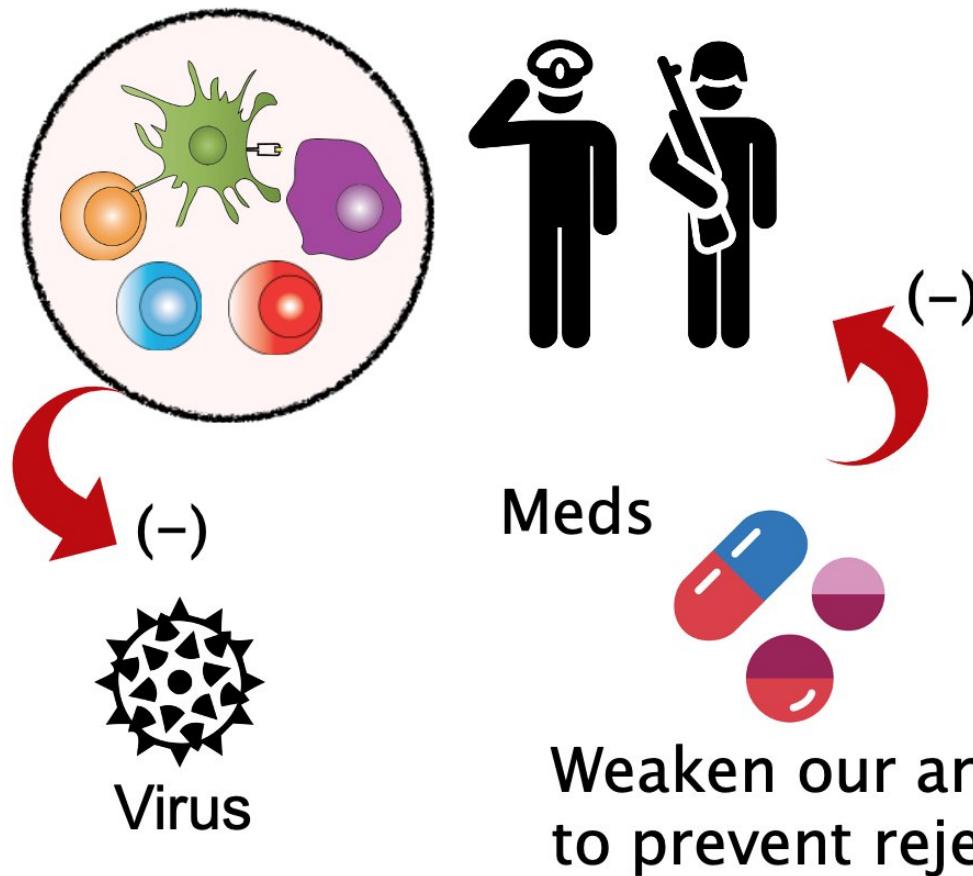
Study population:
374 people with moderate-severe psoriasis reported to PsoProtect from 25 countries

Hospitalized for COVID-19

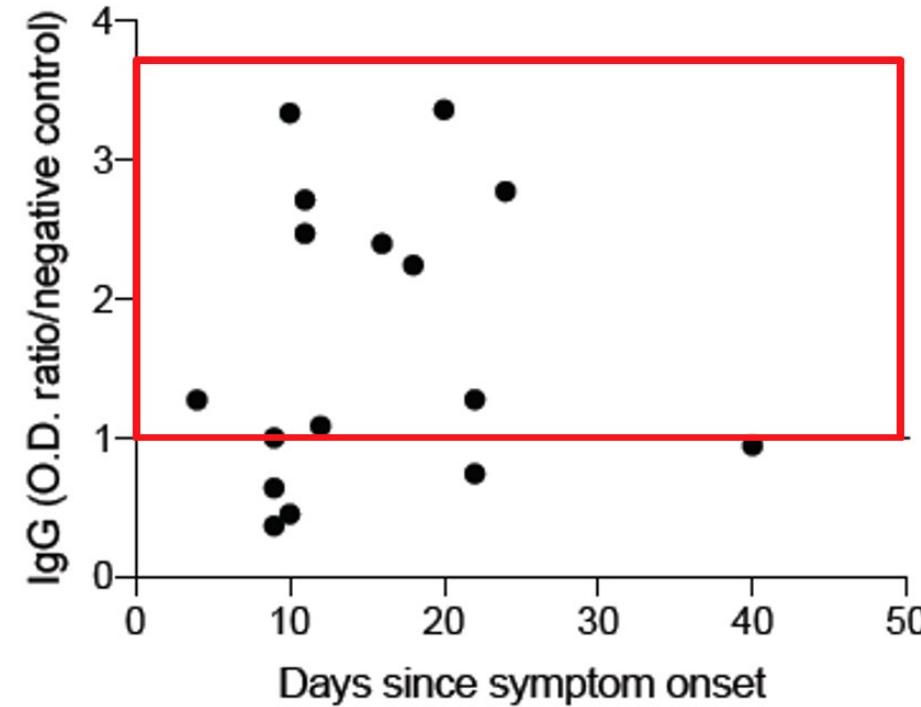
Overall Outcomes of COVID-19

Transplantation & antibody against SARS-CoV2

Our Army The Immune System



Majority of transplant patients are able to generate an antibody response against SARS-CoV2!



Hartzell et al. Am J Transp 2020



Nearly one-third of patients with systemic lupus erythematosus who discontinued immunosuppressants experienced a disease flare.

<https://www.rheumatologyadvisor.com/home/topics/systemic-lupus-erythematosus/disease-flares-common-after-discontinuing-immunosuppressants-in-systemic-lupus-erythematosus/>

Wij volgen het standpunt van de RIVM

Stop niet zonder overleg met uw arts met uw medicatie, gezien de risico's van een opvlamming.

Het is vooral van belang om het risico op besmetting zoveel mogelijk te beperken door:

(1) hygiëne maatregelen in acht te nemen:

- was de handen regelmatig
- hoest en nies in de binnenkant van de ellenboog
- gebruik papieren zakdoekjes en gooi deze na gebruik weg.

(2) mogelijke risicomomenten op contact met virus infecties te vermijden, dat wil zeggen:

- Niet reizen naar gebieden waar het virus is vastgesteld
- Niet op bezoek gaan bij mensen die recent (< 2 weken geleden) in gebieden zijn geweest waar het virus is vastgesteld
- Niet op bezoek gaan bij mensen met klachten van koorts, hoesten en kortademigheid
- Bezoek aan evenementen waar veel mensen zijn zoals concerten of beurzen vermijden.

Bij nieuwe klachten die kunnen passen bij een luchtweginfectie zoals hoesten of toenemende kortademigheid is het verstandig laagdrempelig de temperatuur te meten en bij temperatuurverhoging (>38 graden) in eerste instantie de huisarts telefonisch te raadplegen.

Informeer uw huisarts of andere zorgverlener altijd over welke medicatie (naam en dosering) u gebruikt. Als u voor uw huidaandoening biologische medicatie gebruikt raden wij u aan bij temperatuurverhoging de volgende injectie uit te stellen totdat u heeft overlegd met uw arts.

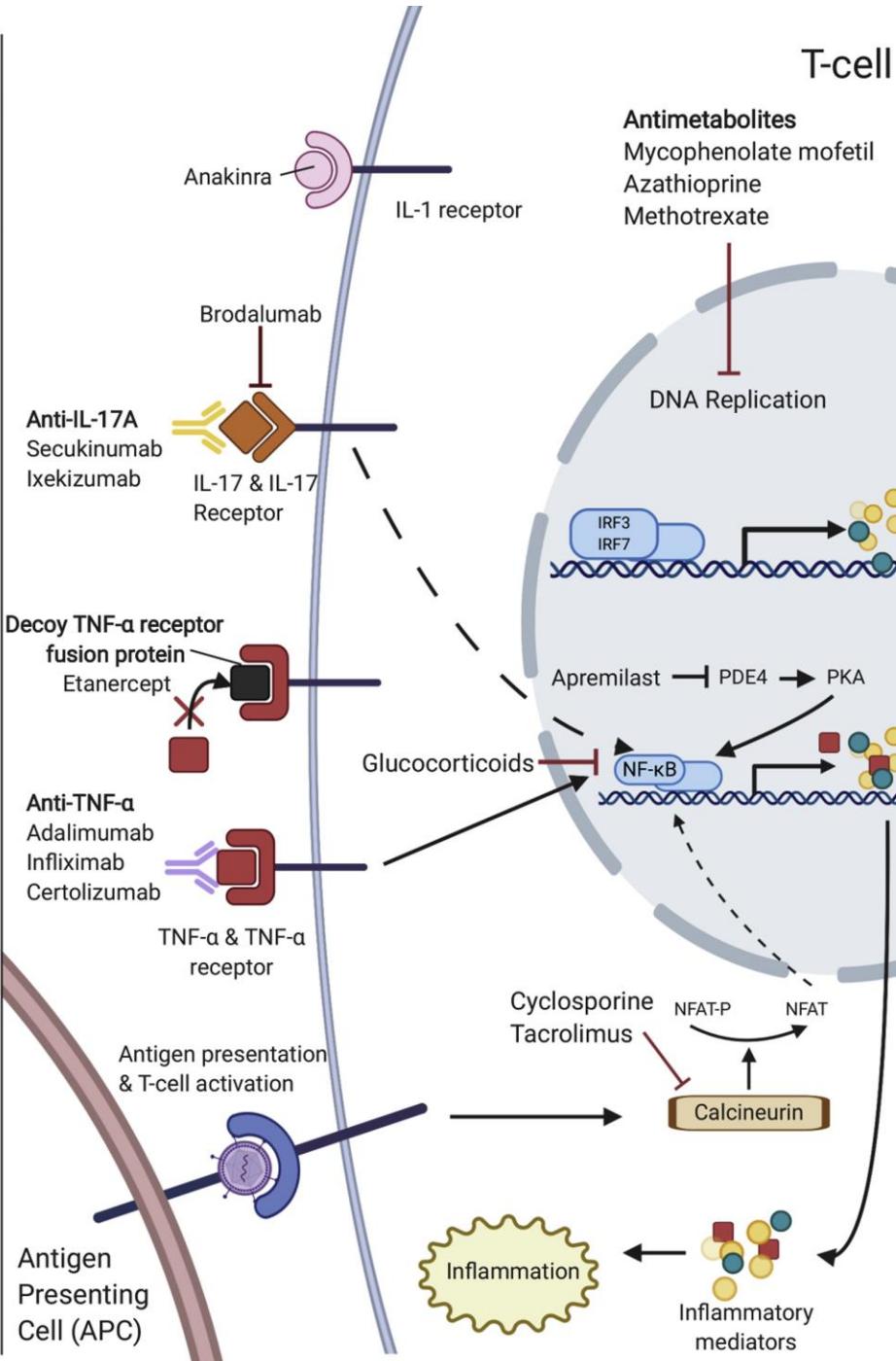
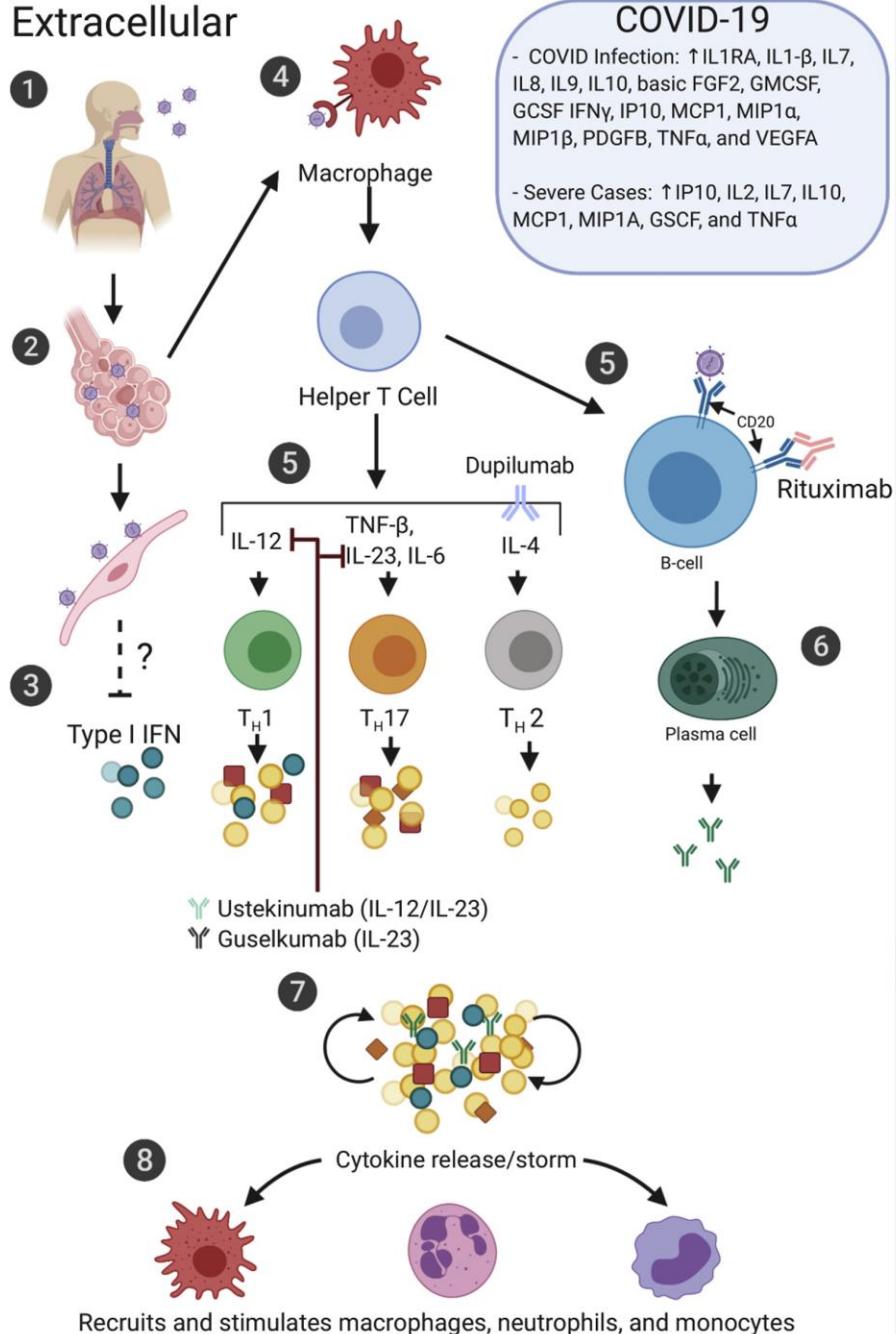
Table 1: Infectious Risk of Immunosuppressive Medications in Dermatology^a

	Therapies	Infectious Risk
Group A	Secukinumab (Cosentyx) Ixekizumab (Taltz) Brodalumab (Siliq) Guselkumab (Tremfya) Tildrakizumab-asmn (Ilumya) Risankizumab-rzaa (Skyrizi) Dupilumab (Dupixent)	No effect on viral immunity
Group B	Ustekinumab (Stelara) Apremilast (Otezla)	Theoretical effect on T _h 1/viral immunity, but no actual increased incidence of viral infections while on drug
Group C	Etanercept (Enbrel) Infliximab (Remicade) Adalimumab (Humira) Certolizumab pegol (Cimzia) Tofacitinib (Xeljanz) Baricitinib (Olumiant) Upadacitinib (Rinvoq)	Slight increased risk of infections in general, including viral infections
Group D	Prednisone Methotrexate Cyclosporine Azathioprine Mycophenylate mofitil	More broad-based immunosuppression, which would increase risk of infections, including viral infections

a) Data in this table is based on Dr Blauvelt's clinical experience and review of the literature.

<https://www.the-dermatologist.com/article/covid-19-dermatology>





COVID-19 and immunomodulator/immunosuppressant use in dermatology

JAAD, May 2020, Volume 82, Issue 5, Pages e173–e175
 COVID-19 and immunomodulator/immunosuppressant use in dermatology
 Kyla N. Price, BS, John W. Frew, MD, Jennifer L. Hsiao, MD, Vivian Y. Shi, MD

Considerations for commonly used immunomodulators and immunosuppressants for dermatologic conditions

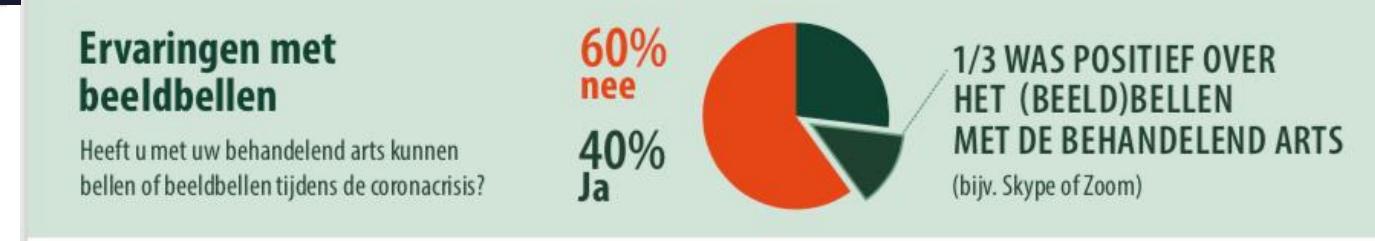
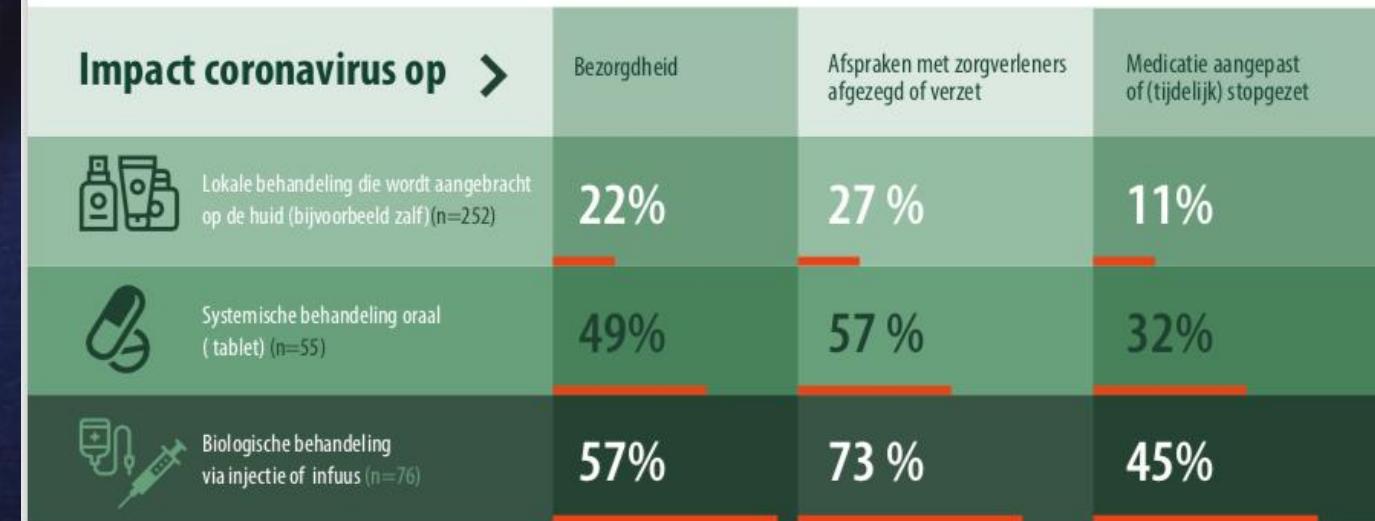
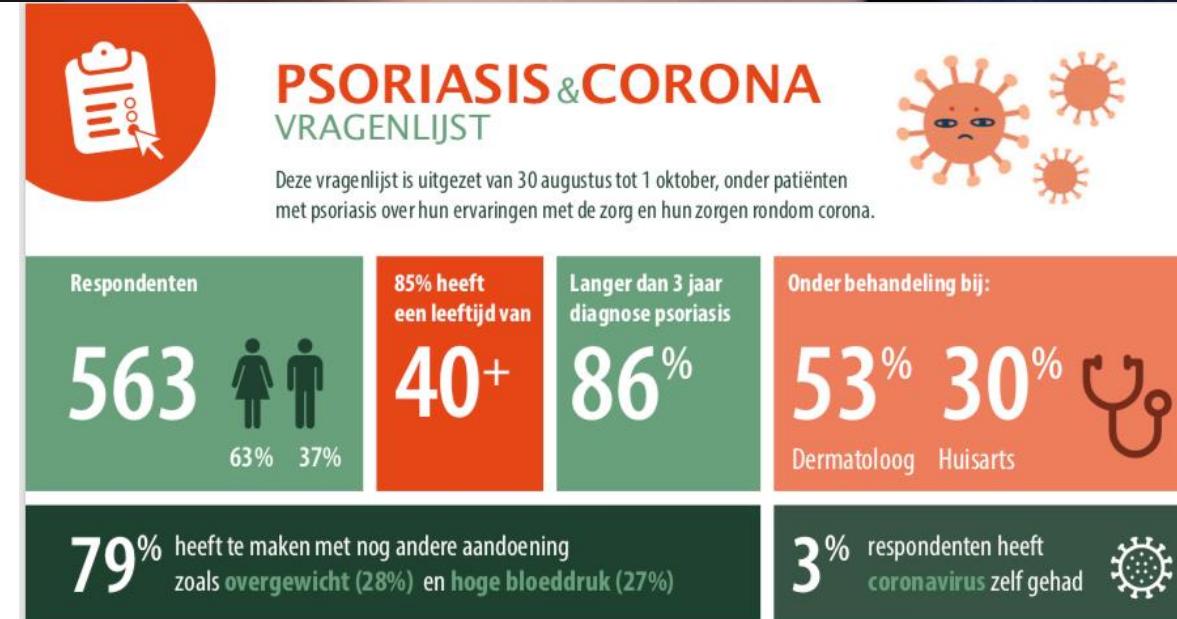
Drug class	Mechanism of action	Drug name	Risk	Comments/considerations*
Classic immunosuppressants				
	Inhibits NF-κB	Corticosteroids	Likely concerning risk	Consider stopping when viral symptoms present especially with known or potential exposure
	Calcineurin inhibitor	Tacrolimus		
		Cyclosporine		
Antimetabolites	Inhibits DNA replication	Mycophenolate mofetil		
		Azathioprine		
		Methotrexate		
Immunomodulators				
Monoclonal antibodies	TNF-α inhibition	Infliximab	Likely moderate risk	Continue if viral symptoms are mild, consider stopping if viral symptoms worsen or high fever develops
Receptor fusion protein		Etanercept		
Monoclonal antibodies		Certolizumab		
Monoclonal antibodies		Adalimumab		
IL receptor modulators	IL inhibition	Anakinra (IL-1)		
Monoclonal antibodies		Dupilumab (IL-4)		
Monoclonal antibodies		Brodalumab (IL-17)		
Monoclonal antibodies		Secukinumab (IL-17a)		
Monoclonal antibodies		Ixekizumab (IL-17a)		
Monoclonal antibodies		Ustekinumab (IL-12/23)		
Monoclonal antibodies		Guselkumab (IL-23)		
Monoclonal antibodies	Anti-CD20 antibody	Rituximab	Likely concerning risk	Consider stopping when viral symptoms present especially with known or potential exposure.
	PDE4 inhibition	Apremilast	Likely low risk	Continue unless severe symptoms present

Risk	Drug	Comments
	Systemic steroids	Strong dose-dependent risk of infection and existing evidence for harm in critically ill viral pneumonia patients although some preliminary evidence showing potential mortality benefit of dexamethasone in oxygen or ventilator dependent patients
	Rituximab	Prolonged B-cell depletion; consider potential impact on future vaccine immunity to COVID-19
	Cyclosporine	Frequent monitoring; multiple drug-drug interactions; risk of harm is likely dose-dependent
	Azathioprine and Mycophenolate mofetil	Association with viral infections, including HZV and CMV (transplant data)
	JAK inhibitors	Caution regarding use due to viral infection concern (HZV) and DVT/PE risk Potentially beneficial anti-viral effect with baricitinib and ruxolitinib, but not with tofacitinib
	TNF inhibitors	IFX likely highest risk among anti-TNF; caution with higher doses (e.g., IFX 10 mg/kg dosing)
	IL-17 inhibitors	Possible increased URI risk suggested in recent metanalysis of clinical trial data
	Methotrexate	Low overall risk of infections or infectious complications; may be associated with higher risk when used in combination therapy
	IL-12/23 inhibitor	Theoretical role of IL-12 in antiviral response, though not clearly implicated in COVID-19 pathology
	IL-23 (p19) inhibitors	
	Apremilast	
	Dupilumab	
	Hydroxychloroquine	No significant risk of infection or infectious complications; to date, no evidence for benefit in treatment of COVID-19
	Other:	Immunomodulatory agents (e.g. retinoids, dapsone, colchicine, etc.)
Evidence suggests harm - avoid if possible		CMV, Cytomegalovirus; DVT, deep venous thrombosis;
Mixed data - proceed with caution		HZV, herpes zoster virus; IL, interleukin; PE, pulmonary embolus; URI, upper respiratory infection.
Low risk of harm		
Not immunosuppressive		

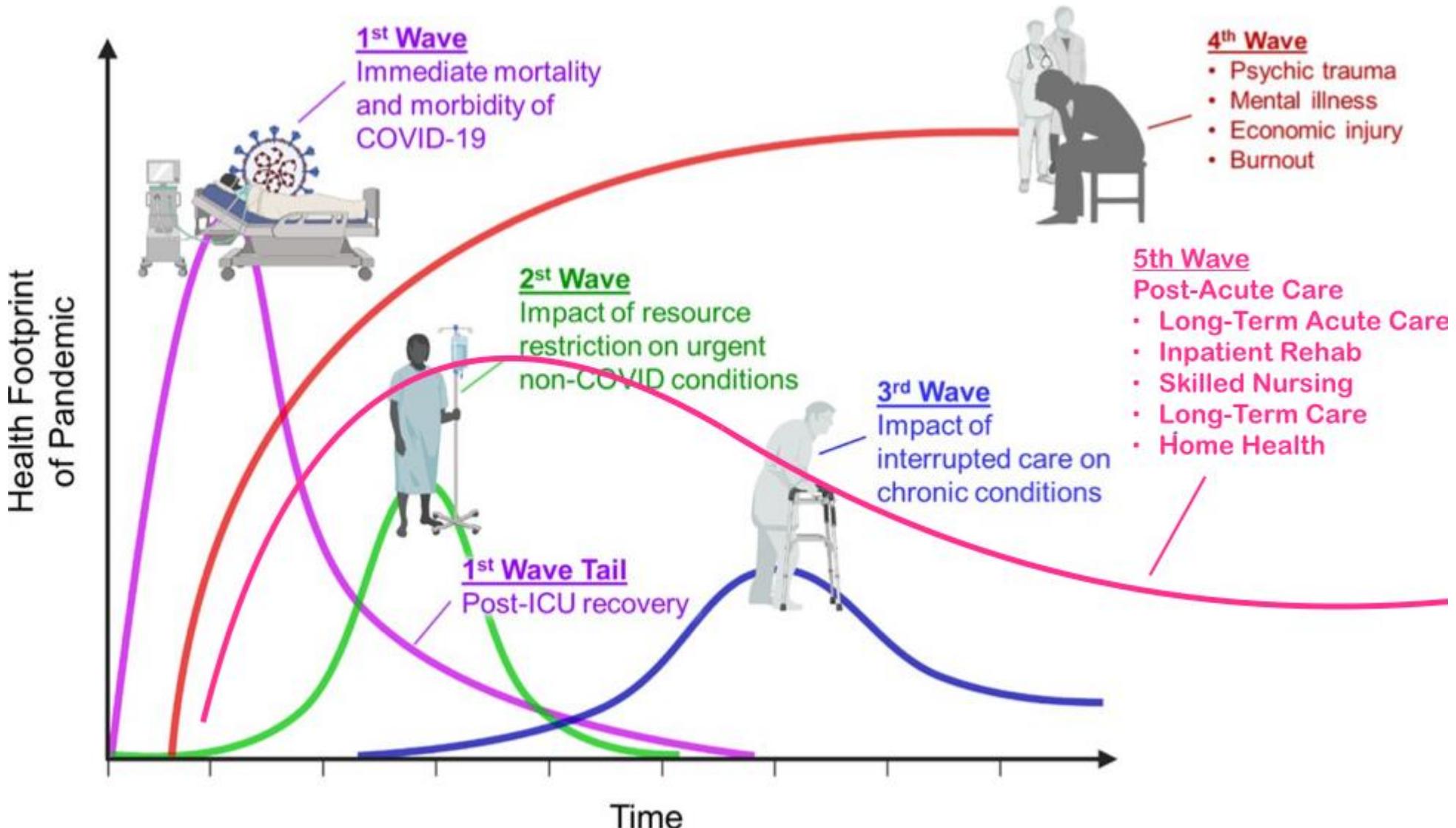
Omid Zahedi Niaki, et al.
 Navigating
 immunosuppression in a
 pandemic: A guide for the
 dermatologist from the
 COVID Task Force of the
 Medical Dermatology Society
 and Society of Dermatology
 Hospitalists,
 Journal of the American
 Academy of Dermatology,
 Volume 83, Issue 4, 2020,
 Pages 1150-1159,

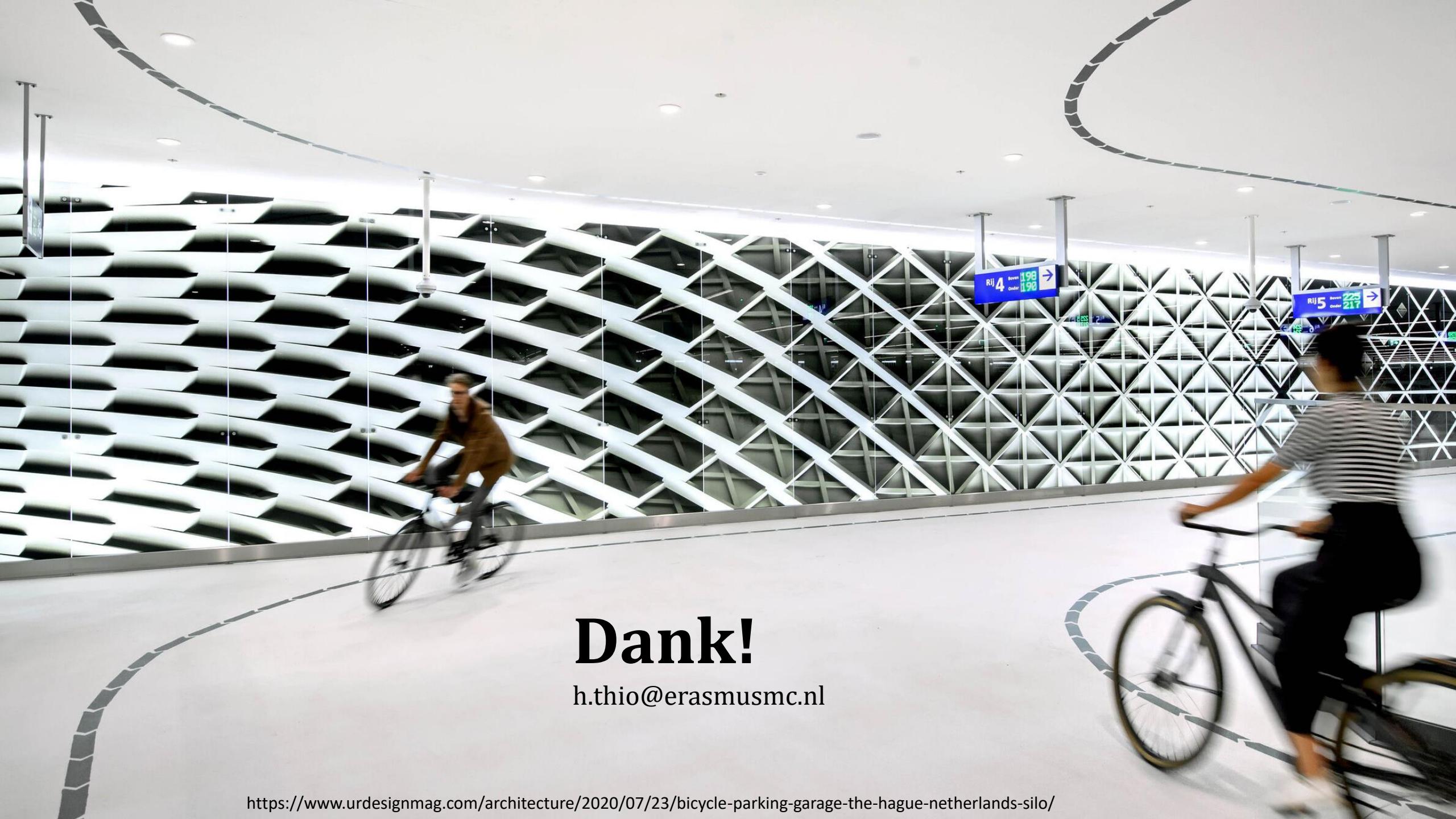


<https://pluscare.com/blog/psoriasis-vs-eczema/>



Long-Term consequences





Dank!

h.thio@erasmusmc.nl