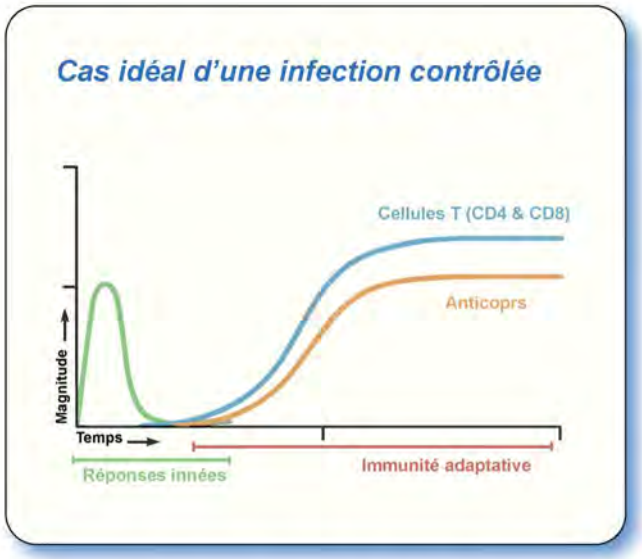
Mécanismes pathogènes dans le COVID Long

Hypothèses immunitaires et virologiques

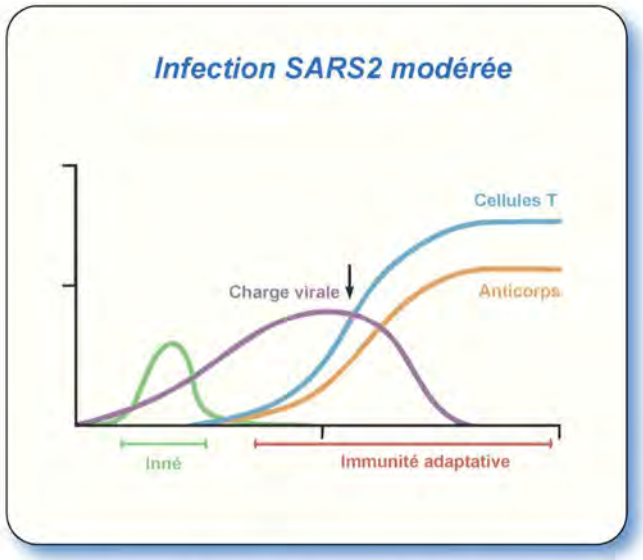
Lisa A. Chakrabarti
Groupe CIVIC, Unité Virus & Immunité
19 nov. 2021

INSTITUT PASTEUR

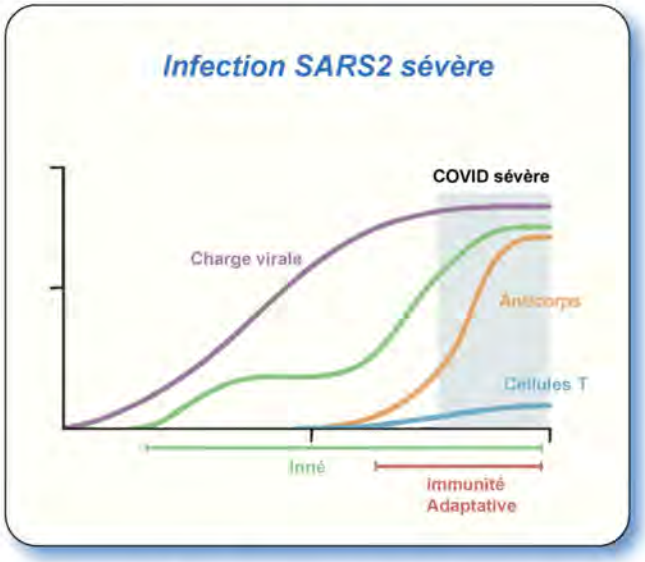
Différentes cinétiques de la réponse immune antivirale dans l'infection par le SARS-CoV-2



Contrôle viral efficace



Retard de la réponse innée



Retard et faible intensité de la réponse T

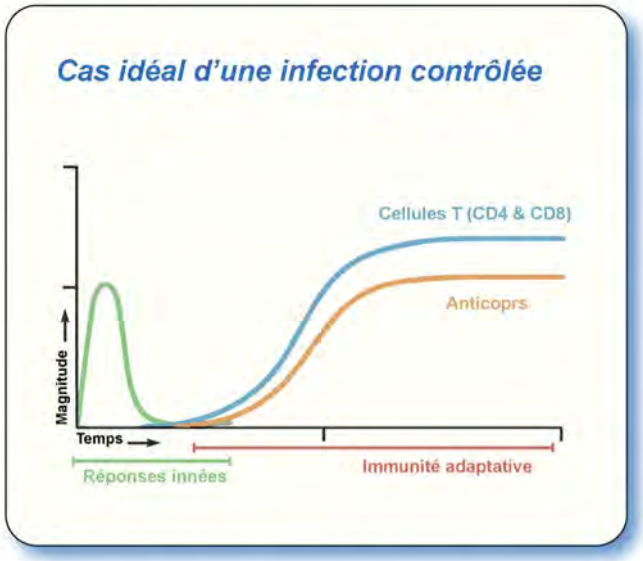
Adapté de: A. Sette and S. Crotty, Cell 184:861, 2021

Tan / Bertoletti, Cell Reports 34:108728, 2021

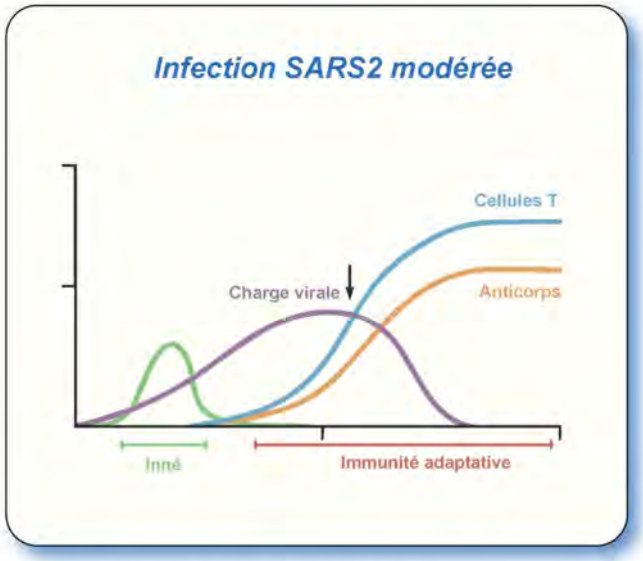
Rydyznski / Crotty, Cell 183:996, 2020

Swadling / Maini, medRxiv 2021.06.26.21259239

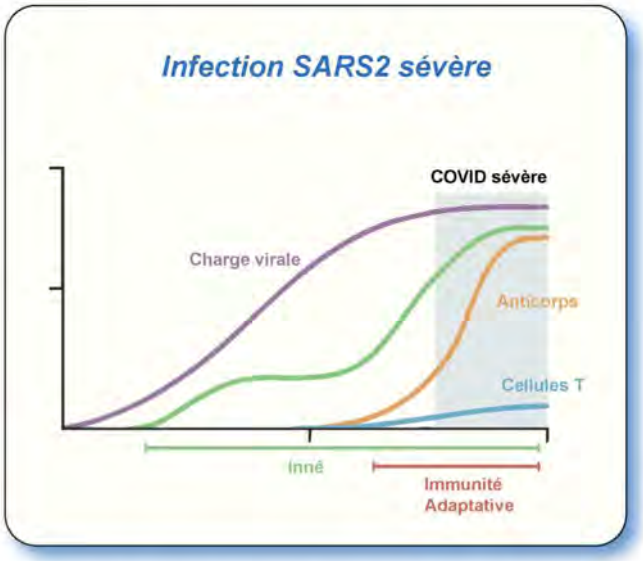
Différentes cinétiques de la réponse immune antivirale dans l'infection par le SARS-CoV-2



Contrôle viral efficace



Retard de la réponse innée



Retard et faible intensité de la réponse T

Réplication virale persistante

Réponse innée persistante -> inflammation

Adapté de: A. Sette and S. Crotty, Cell 184:861, 2021

Réponses immunes exacerbées dans le COVID Long ?

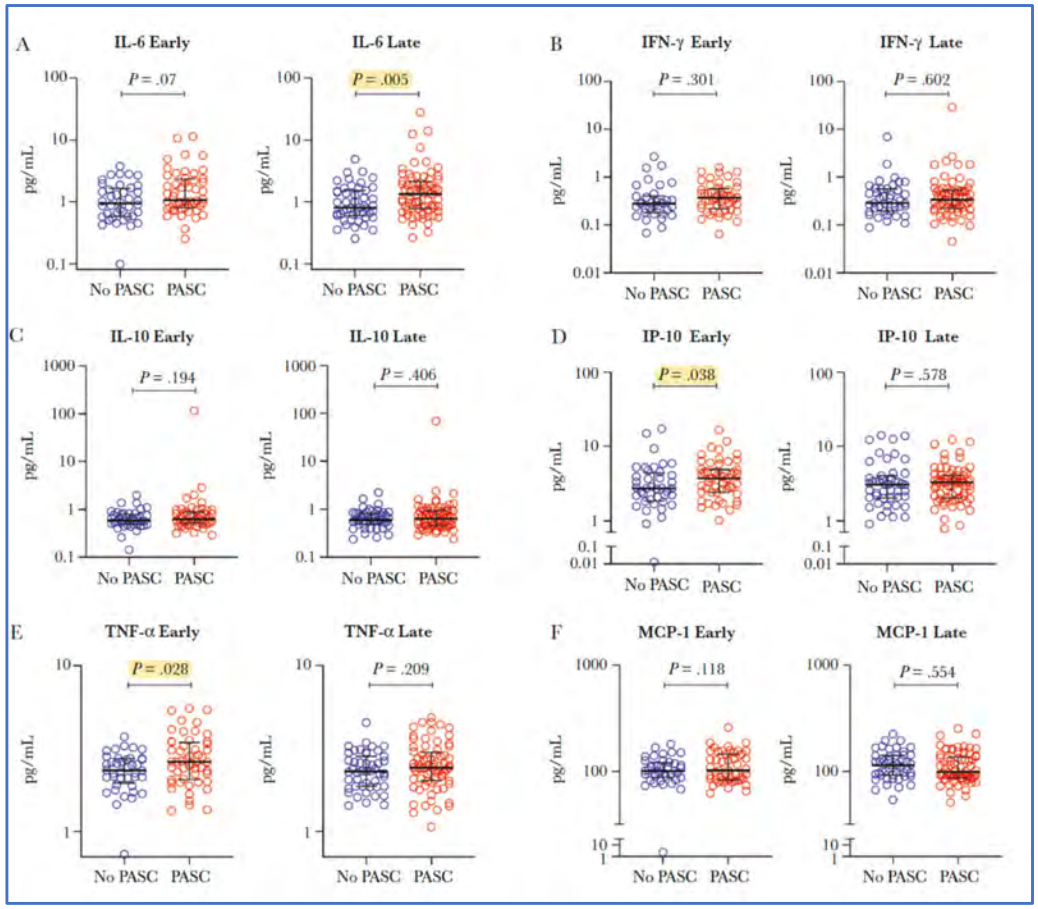
- Inflammation persistante?
- Autoimmunité?

The Journal of Infectious Diseases *Sept. 2021*

MAJOR ARTICLE

Markers of Immune Activation and Inflammation in Individuals With Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Michael J. Peluso,[1,©] Scott Lu,[2] Alex F. Tang,[1] Matthew S. Durstenfeld,[3] Hsi-en Ho,[4] Sarah A. Goldberg,[2] Carrie A. Forman,[1] Sadie E. Munter,[5] Rebecca Hoh,[1] Viva Tai,[1] Ahmed Chenna,[6] Brandon C. Yee,[6] John W. Winslow,[6] Christos J. Petropoulos,[6] Bryan Greenhouse,[1] Peter W. Hunt,[5] Priscilla Y. Hsue,[3] Jeffrey N. Martin,[2] J. Daniel Kelly,[2] David V. Glidden,[2,©] Steven G. Deeks[1,a], and Timothy J. Henrich[5,a]



- n=121 patients (n=48 no PASC; n=73 PASC)
- Documented SARS-CoV-2 infection
- PASC : at least 1 symptom at >90 days
- 78% not hospitalized
- History of autoimmune disease:
  - No PASC : 2%
  - PASC: 11% (P=0.08)

Persistent immune activation may be associated with Long COVID

Open Forum Infectious Diseases *March 2021*

MAJOR ARTICLE

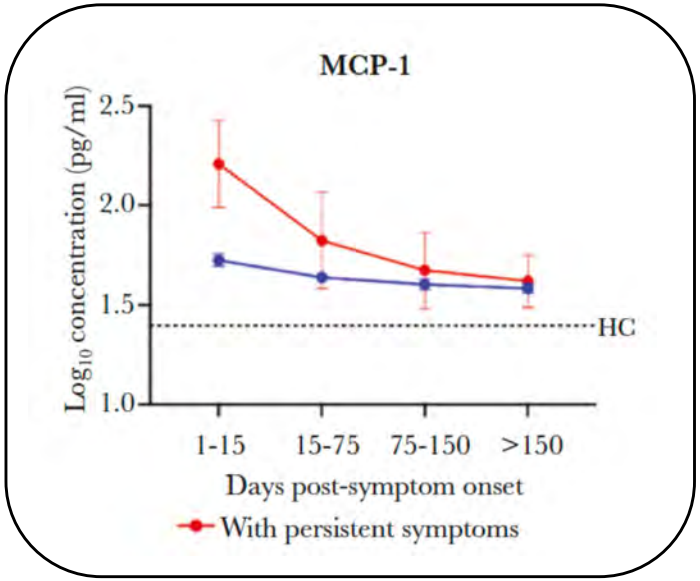
Persistent Symptoms and Association With Inflammatory Cytokine Signatures in Recovered Coronavirus Disease 2019 Patients

Sean Wei Xiang Ong,[1,2,a] Siew-Wai Fong,[3,4,a] Barnaby Edward Young,[1,2,5] Yi-Hao Chan,[3,4] Bernett Lee,[6] Siti Naqiah Amrun,[3,4] Rhonda Sin-Ling Chee,[3,4] Nicholas Kim-Wah Yeo,[3,4] Paul Tambyah,[6,7] Surinder Pada,[8] Seow Yen Tan,[9] Ying Ding,[1] Laurent Renia,[3,4] Yee-Sin Leo,[1,2,5,7] Lisa F. P. Ng,[3,4,7,10] and David Chien Lye,[1,2,5,7]

1 National Centre for Infectious Diseases, Singapore

Variable	All Patients (n = 183)	No Persistent Symptoms (n = 161)	Persistent Symptoms at Day 90 or 180 (n = 22)	*P* Value[a]
Demographics				
Female sex	45 (24.6)	38 (23.6)	7 (31.8)	.43
Age, years	44 (33–56)	43 (31–55)	50.5 (39–66)	**.042**
Severity				**.040**
Mild[b]	81 (44.3)	75 (46.6)	6 (27.3)	
Moderate	47 (25.7)	43 (26.7)	4 (18.2)	
Severe	55 (30.1)	43 (26.7)	12 (54.6)	

Patients with persistent symptoms: 7% at day 90, 11% at day 180
(lower than in European and American cohorts)



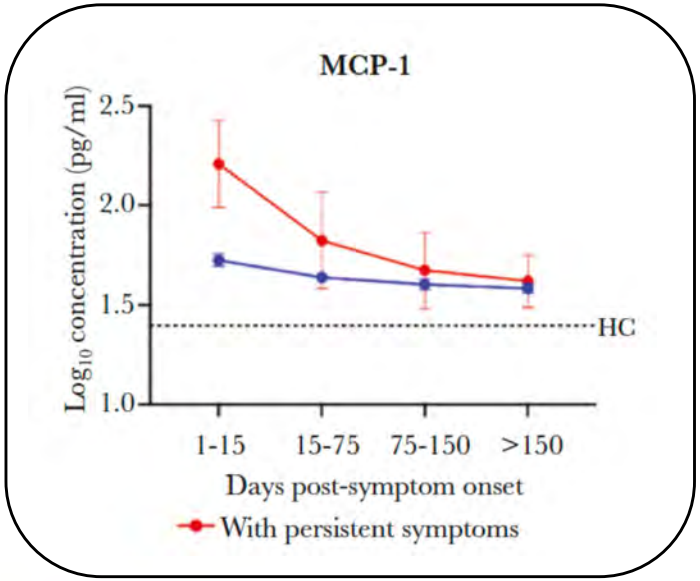
Stronger inflammation during acute infection in patients who develop persistent symptoms

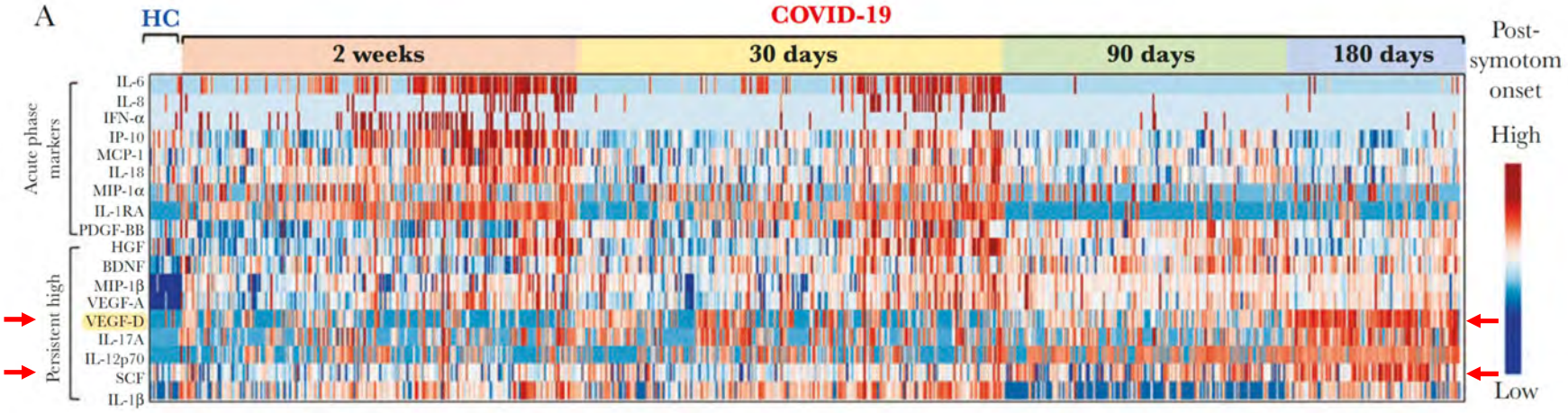
Open Forum Infectious Diseases *March 2021*

MAJOR ARTICLE

Persistent Symptoms and Association With Inflammatory Cytokine Signatures in Recovered Coronavirus Disease 2019 Patients

Sean Wei Xiang Ong,[1,2,a] Siew-Wai Fong,[3,4,a] Barnaby Edward Young,[1,2,5] Yi-Hao Chan,[3,4] Bernett Lee,[4] Siti Naqiah Amrun,[3,4] Rhonda Sin-Ling Chee,[3,4] Nicholas Kim-Wah Yeo,[3,4] Paul Tambyah,[6,7] Surinder Pada,[8] Seow Yen Tan,[9] Ying Ding,[1] Laurent Renia,[3,4] Yee-Sin Leo,[1,2,5,7] Lisa F. P. Ng,[3,4,7,10] and David Chien Lye,[1,2,5,7]





Angiogenesis / endothelial inflammation during the late recovery phase?

Syndrome d'Activation des Mastocytes (SAMA) dans le COVID Long ?

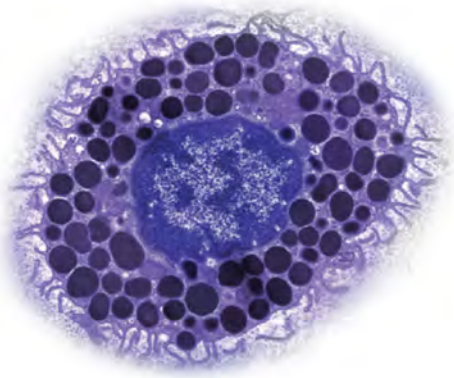
MCAS: inappropriate activation of mastocytes

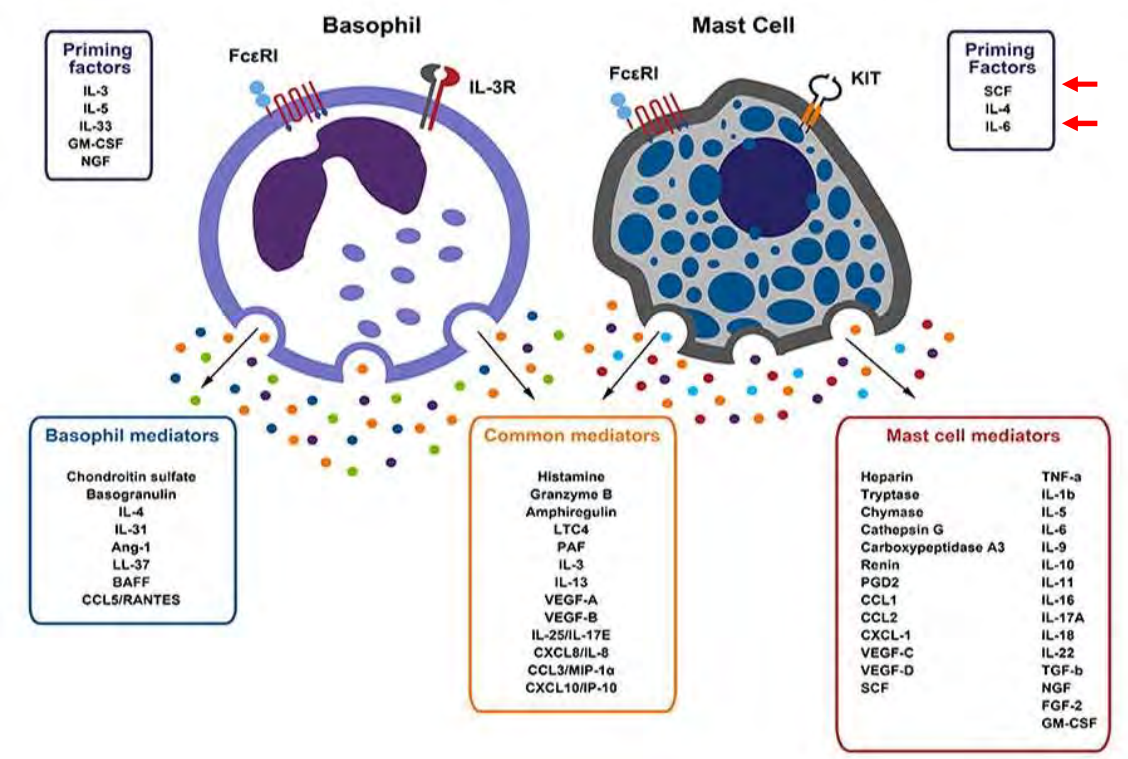
- Release of granule content, including histamine, heparin, proteases (such as tryptase), …
- De novo synthesis of arachidonic metabolites (prostaglandin D2, leukotriene E4, …)
- Chemokine and cytokine secretion (TNF-a, …)

MCAS associated symptoms:

- Tachycardia, hypotension, syncope
- Pruritus, urticaria, angioedema
- Wheezing, shortness of breadth
- Gastrointestinal symptoms

→ POTS?





https://www.thermofisher.com/fr/fr/home/life-science/cell-analysis/cell-analysis-learning-center/immunology-at-work/granulocyte-cell-overview/mast-cell-overview.html

Original research

Long COVID following mild SARS-CoV-2 infection: characteristic T cell alterations and response to antihistamines

Paul Glynne,[1] Natasha Tahmasebi,[2] Vanya Gant,[3] Rajeev Gupta [4,5]

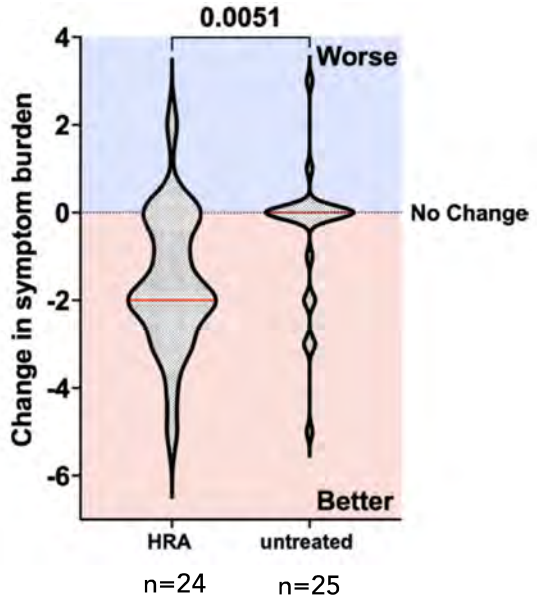
Glynne P, *et al*. *J Investig Med* 2021;**0**:1–7. doi:10.1136/jim-2021-002051

Table 1 Clinical features of study participants

Clinical characteristics	Long COVID (symptomatic, n=49)	Post-COVID controls (asymptomatic, n=16)
Age range (median)	25–65 (43)	25–72 (34.5)
Female (%)	30 (61.2%)	8 (50%)
Allergy or atopy	16 (32.7%)	1 (5.8%)
Mean days from acute COVID to study testing	271.8 days	321.6 days
Vaccination history at time of recruitment (at least one dose)	1/49 (2.0%)	14 (87.5%)
SARS-CoV-2 antibodies detected	20/49 (40.8%)	13/16 (81.3%)

Treatment with Histamine Receptor Antagonists (HRA)

Combination of H1 (loratadine) and H2 (famotidine or nizatidine) HRA for > 4 weeks



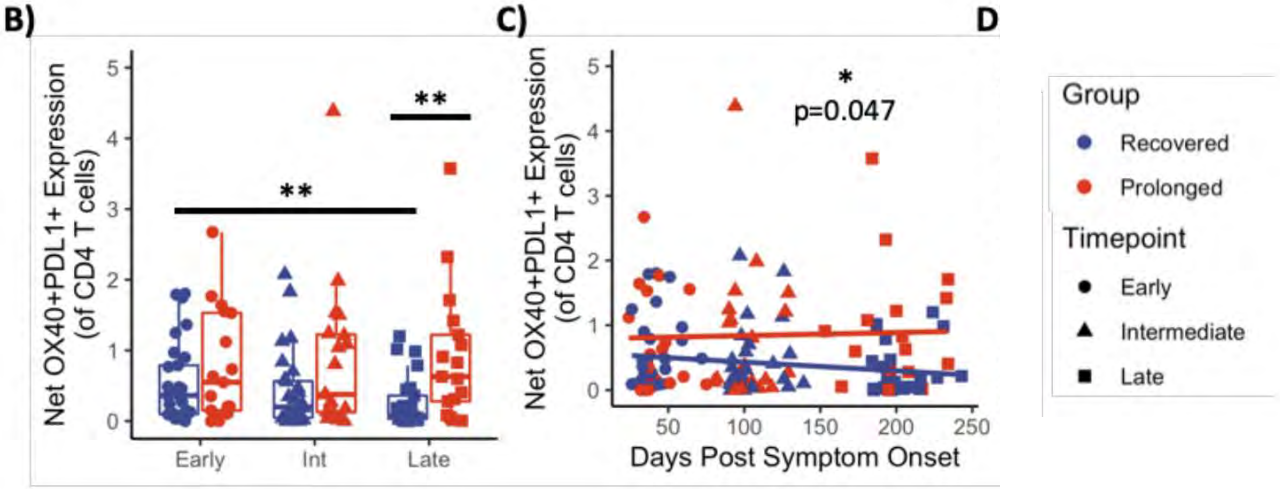
Possible beneficial effects of HRA in Long COVID

JCI insight

Duration of post-COVID-19 symptoms are associated with sustained SARS-CoV-2 specific immune responses

Jacob K. Files, … , Paul A. Goepfert, Nathan Erdmann

JCI Insight. 2021. https://doi.org/10.1172/jci.insight.151544.



Persistence of a high frequency of spike-specific CD4+ T cells in Long COVID patients

JCI insight

Duration of post-COVID-19 symptoms are associated with sustained SARS-CoV-2 specific immune responses

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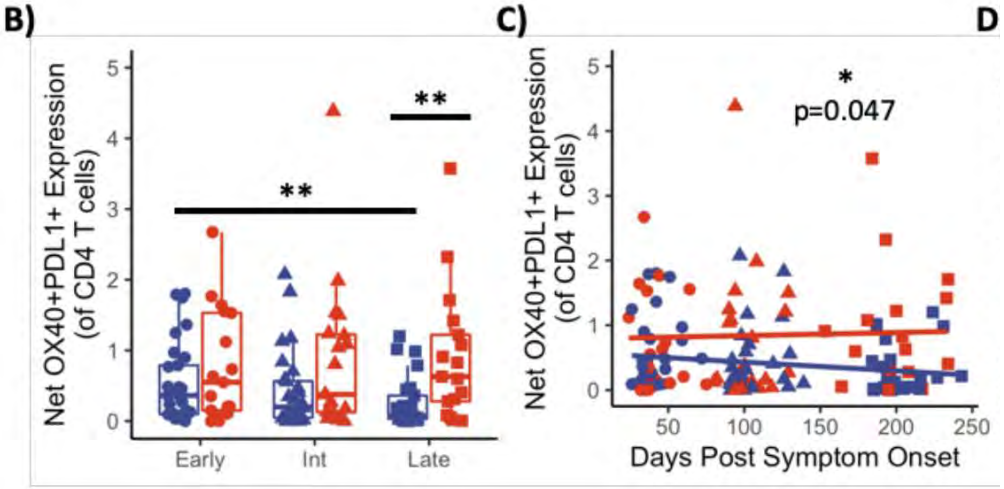
JCI Insight. 2021. https://doi.org/10.1172/jci.insight.151544.

Possible confounder: difference in severity of the original SARS-CoV-2 infection between groups



-	Overall (n=50)	Prolonged (n=20)	Recovered (n=30)
Symptom Duration	14 (1-208)	73.5 (30-208)	10 (1-20)
Hospitalized during COVID-19 infection	10 (20%)	10 (50%)	0 (0%)
Peak Ordinal Score	2 (2-7)	3 (2-7)	2 (2-2)
Age	51 (20-86)	51.5 (27-86)	50.5 (20-82)

Persistence of a high frequency of spike-specific CD4+ T cells in Long COVID patients

Science Immunology

RESEARCH ARTICLES

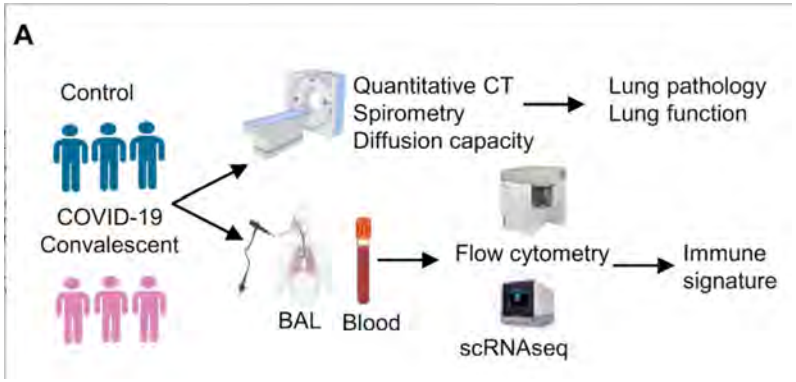
Cite as: I. S. Cheon *et al.*, *Sci. Immunol.* 10.1126/sciimmunol.abk1741 (2021).

CORONAVIRUS

Immune signatures underlying post-acute COVID-19 lung sequelae

Cheon IS[1,2]*, Li C[1,2]*, Son YM[1,2]*, Goplen NP[1,2], Wu Y[1,2], Cassmann T[1,2], Wang Z[1,2], Wei X[1,2], Tang J[1,2], Li Y[3], Marlow H[1], Hughes S[1], Hammel L[1], Cox TM[1], Goddery E[2], Ayasoufi K[2], Weiskopf D[4], Boonyaratanakornkit J[5], Dong H[2], Li H[6], Chakraborty R[2,7], Johnson AJ[2], Edell E[1], Taylor JJ[5], Kaplan MH[8], Sette A[4,9], Bartholmai BJ[10], Kern R[1], Vassallo R[1,11]* and Sun J[1,2,11-14]*†

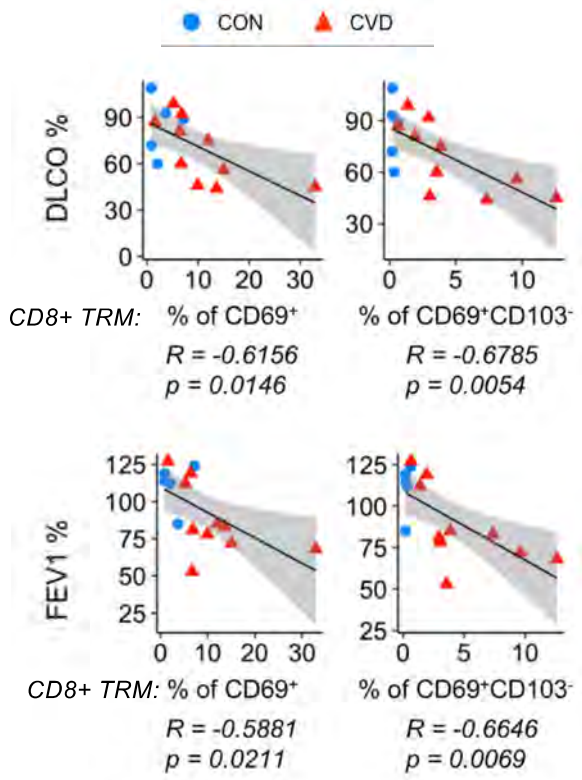
COVID patients
- > 60 years old
- had severe pneumonia
- Experience persistent respiratory dysfunction



	Controls n=5	COVID n=10
Sex	4M/1F	7M/3F
Age (Avg)	69.6 ± 6.18	68.4 ± 6.62
TLC (%, Avg)	100.5 ± 11.5	70.4 ± 11.4
FVC (%, Avg)	118 ± 17.9	85.5 ± 22.7
DLCO (%, Avg)	84 ± 17.0	68.5 ± 19.8
FEV1 (%, Avg)	110.8 ± 13.6	87.8 ± 22.6
Dyspnea (MRC score)		2.1 ± 1.14
Cough (%)		30
Fatigue (%)		50
Inability to return to work (%)		30

DLCO: diffusion capacity for carbon monoxyde

FEV1: forced expiratory volume in 1 s



Inverse association between the presence of activated Tissue Resident Memory CD8+ T cells and pulmonary function

Science Immunology

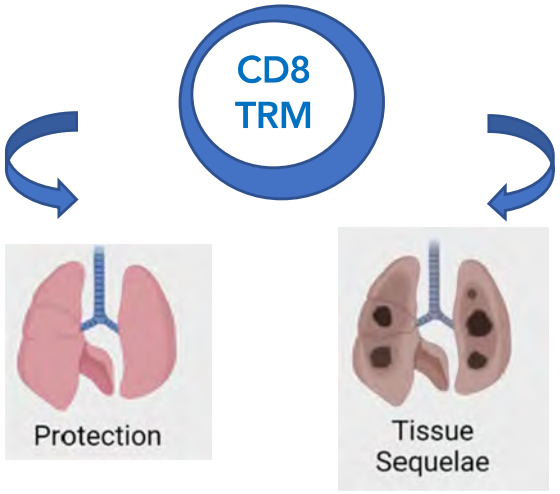
RESEARCH ARTICLES

Cite as: I. S. Cheon *et al.*, *Sci. Immunol.* 10.1126/sciimmunol.abk1741 (2021).

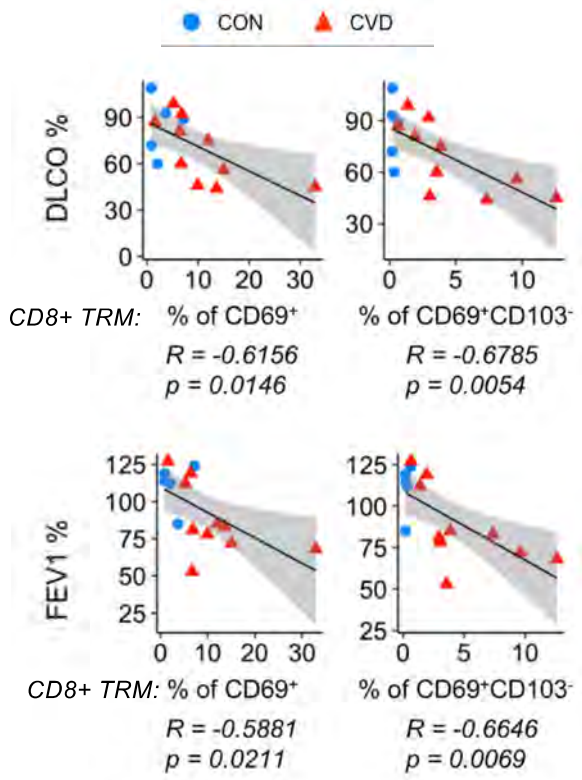
CORONAVIRUS

Immune signatures underlying post-acute COVID-19 lung sequelae

Cheon IS[1,2*], Li C[1,2*], Son YM[1,2*], Goplen NP[1,2], Wu Y[1,2], Cassmann T[1,2], Wang Z[1,2], Wei X[1,2], Tang J[1,2], Li Y[3], Marlow H[1], Hughes S[1], Hammel L[1], Cox TM[1], Goddery E[2], Ayasoufi K[2], Weiskopf D[4], Boonyaratanakornkit J[5], Dong H[2], Li H[6], Chakraborty R[2,7], Johnson AJ[2], Edell E[1], Taylor JJ[5], Kaplan MH[8], Sette A[4,9], Bartholmai BJ[10], Kern R[1], Vassallo R[1,11#] and Sun J[1,2,11-14 #†]



Role of cytotoxic TRM in persistent pulmonary lesions?



Inverse association between the presence of activated Tissue Resident Memory CD8+ T cells and pulmonary function

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.journals.elsevier.com/journal-of-translational-autoimmunity/

Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms

Gerd Wallukat [a,b,*], Bettina Hohberger [c], Katrin Wenzel [b], Julia Fürst [d], Sarah Schulze-Rothe [b], Anne Wallukat [b], Anne-Sophie Hönicke [b], Johannes Müller [b]

Table 1
Overview of post-COVID-19 symptoms and accompanying GPCR-$_f$AABs.

Patient no.	Gender	Age (years)	Running no.	Symptom class		Symptoms		Neuro-active $_f$AABs	Vasoactive $_f$AABs			Neuro- and vasoactive $_f$AABs	RAS-specific $_f$AABs	
				Neuro*	Cardiovasc**	Neuro*	Cardiovasc**	Noc-$_f$AAB[§]	β_2-$_f$AAB[$]	α_1-$_f$AAB[&]	ETA-$_f$AAB[+]	M_2-$_f$AAB[%]	AT1-$_f$AAB[?]	MAS-$_f$AAB[#]
1	F	48	1	x	x	Fatigue, Alopecia, Anomic aphasia	Tachycardia	x	x		x	x	x	x
7	F	55	2	x	x	Fatigue, Alopecia	Tachycardia	x	x	x	x	x	x	x
11	F	39	3	x	x	Fatigue, Alopecia	Tachycardia	x	x			x	x	x
19	F	34	4	x	x	Fatigue, PoTS, Tremor	Tachycardia		x	x		x	x	x
22	F	34	5	x	x	Fatigue, Alopecia	Tachycardia		x	x		x	x	x
29	F	49	6	x	x	PoTS	Tachycardia		x	x		x	x	x
26	M	28	7	x	x	PoTS	Tachycardia, Hypertension	x	x			x	x	x
30	M	55	8	x	x	PoTS	Bradycardia		x			x	x	x
27	M	69	9	x	x	PoTS, Attention deficit	Tachycardia	x	x			x	x	x
31	M	44	10	x	x	Attention deficit	Bradycardia		x			x	x	x
3	F	56	11	x	x	Fatigue, Attention deficit	Tachycardia,	x	x		x	x	x	x
21	F	28	12	x	x	Attention deficit, Tremor, Dysautonomia	Arrhythmia		x			x	x	x
18	F	53	13	x	x	Tremor, Attention deficit	Tachycardia		x			x		
20	M	54	14	x	x	Attention deficit	Tachycardia, Hypertension						x	x
14	F	57	15	x	x	Fatigue, Anomic aphasia	Arrhythmia, Hypertension	x	x			x	x	x
23	F	50	16	x	x	Eczema, Alopecia	Myocarditis		x		x	x	x	x
28	M	65	17	x	x	Smell/Taste disorder.	Tachycardia, Myocarditis	x	x			x	x	x
24	F	33	18	x	x	Fatigue, PoTS	n.a.	x	x	x		x	x	x
2	M	42	19	x	–	Fatigue, Alopecia	n.a.		x			x	x	x
4	M	50	20	x	–	Fatigue	n.a.		x			x	x	x
5	F	45	21	x	–	Fatigue	n.a.		x			x	x	x
6	F	36	22	x	–	Tremor, Alopecia, Dysautonomia	n.a.	x	x	x	x	x	x	x
9	F	50	23	x	–	Fatigue	n.a.	x	x			x	x	x
10	F	48	24	x	–	Fatigue	n.a.		x		x	x	x	x
12	F	53	25	x	–	Fatigue, Attention deficit	n.a.	x	x			x	x	x
15	F	46	26	x	–	Fatigue, Alopecia, Polyneuropathy	n.a.	x	x			x	x	x
17	F	49	27	x	–	Fatigue, PoTS, Tremor	n.a.		x			x		
25	F	58	28	x	–	Attention deficit, Neuropathy	n.a.		x		x	x	x	x
13	F	26	29	x	–	Fatigue	n.a.		x			x	x	x
8	M	71	30	–	–	Symptom free	Symptom free		x	x	x	x	x	x
16	M	54	31	–	–	Symptom free	Symptom free	x	x			x	x	x

Neuro* = neurological symptoms; Cardiovasc** = cardiovascular symptoms, n.a. = not applicable, PoTS = postural orthostatic tachycardia syndrome; NOC-$_f$AAB[§] = functionally active autoantibody against the nociceptin receptor, β_2-$_f$AAB[$] = autoantibody targeting the beta$_2$-adrenoceptor, α_1-$_f$AAB[&] = autoantibody targeting the alpha1-adrenoceptor, ETA-$_f$AAB[+] = autoantibody targeting the endothelin receptor, M_2-$_f$AAB[%] = autoantibody targeting the muscarinic receptor, AT1-$_f$AAB[?] = autoantibody targeting the angiotensin II AT1 receptor, MAS-$_f$AAB[#] = autoantibody targeting the MAS receptor.

Detectable autoantibodies against multiple GPCRs in Long COVID patients

Contribution to dysautonomia and cardiovascular symptoms?

Réponses immunes antivirales inefficaces dans le COVID Long?

- Persistance virale?
- Lésions tissulaires induites par le virus?

The Lancet Regional Health - Europe 6 (2021) 100122

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The Lancet Regional Health - Europe

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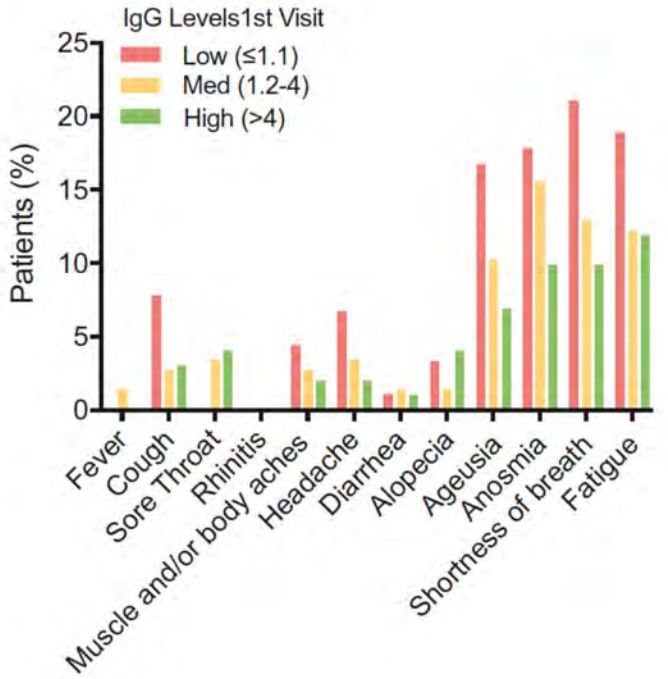
Research paper

Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study

Max Augustin, MD[a,b,c,1], Philipp Schommers, M.D. PhD.[a,c,d,1], Melanie Stecher, Ph.D.[a,c,1], Felix Dewald, M.D.[d], Lutz Gieselmann, M.D.[d], Henning Gruell, M.D.[d], Carola Horn, M.D.[a,b,c], Kanika Vanshylla, Ph.D.[d], Veronica Di Cristanziano, M.D.[d], Luise Osebold[a], Maria Roventa[a], Toqeer Riaz[a], Nikolai Tschernoster, M.Sc[e], Janine Altmueller, M.D.[e], Leonard Rose, M.D.[f], Susanne Salomon, Ph.D.[d], Vanessa Priesner, M.D.[a], Jan Christoffer Luers, Prof.[g], Christian Albus, Prof.[h], Stephan Rosenkranz, Prof.[b,i,j], Birgit Gathof, Prof.[f], Gerd Fätkenheuer, Prof.[a,c], Michael Hallek, Prof.[a,b,k,l], Florian Klein, Prof.[b,d], Isabelle Suárez, M.D.[a,c,2], Clara Lehmann, Prof.[a,b,c,2,*]

- Longitudinal study of PCR+ patients with no or mild symptoms during acute SARS-CoV-2 infection

- 353 patients completed the 3 visits:
  - 123 with persistent symptoms
  - 230 without symptoms



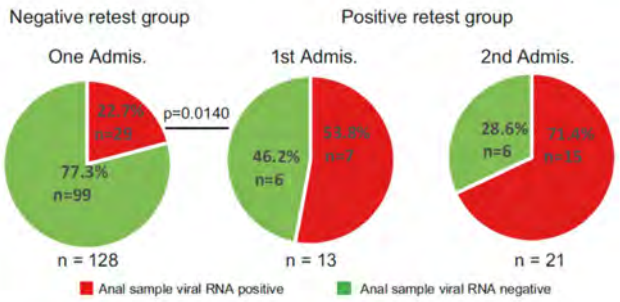
Low SARS-Cov-2-specific IgG at the first visit is associated with persistent symptoms at the third visit (month 7)

ARTICLE OPEN

A compromised specific humoral immune response against the SARS-CoV-2 receptor-binding domain is related to viral persistence and periodic shedding in the gastrointestinal tract

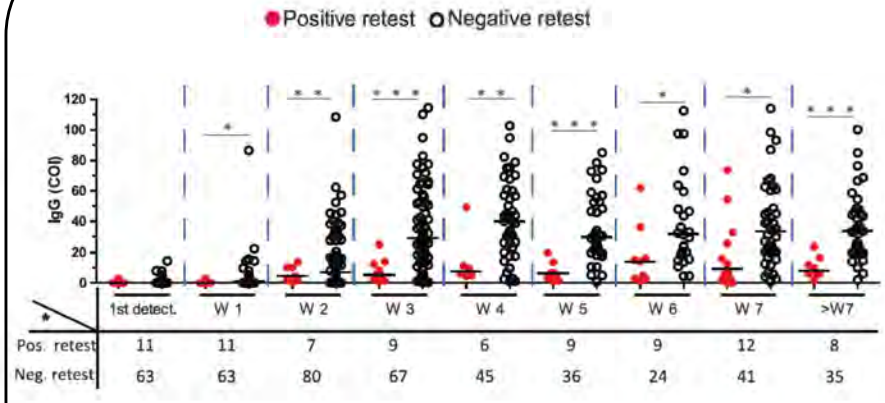
Fengyu Hu[1], Fengjuan Chen[1], Zhihua Ou[2], Qinghong Fan[1], Xinghua Tan[1], Yaping Wang[1], Yuejun Pan[1], Bixia Ke[3], Linghua Li[1], Yujuan Guan[1], Xiaoneng Mo[1], Jian Wang[1], Jinlin Wang[1], Chun Luo[1], Xueliang Wen[1], Min Li[2,4], Peidi Ren[2], Changwen Ke[3], Junhua Li[2,5], Chunliang Lei[1], Xiaoping Tang[1] and Feng Li[1]

Cellular & Molecular Immunology (2020) 17:1119–1125; https://doi.org/10.1038/s41423-020-00550-2



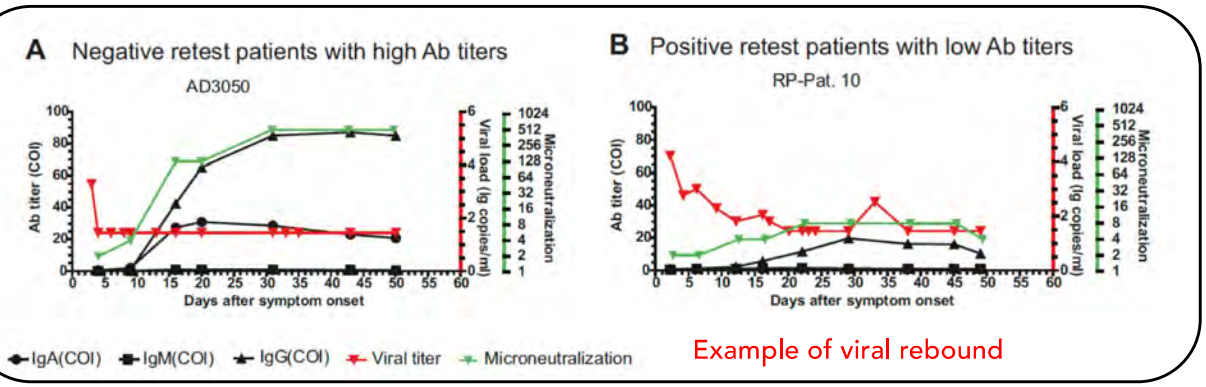
More frequent detection of SARS-CoV-2 viral RNA in anal samples of patients who retest PCR+ after the acute stage

Preferential persistence of SARS-CoV-2 in the gastrointestinal tract?



Lower RBD-specific IgG in patients with viral rebound

Lack of a robust antibody response may be associated with viral persistence



Example of viral rebound

Science Translational Medicine RESEARCH ARTICLES

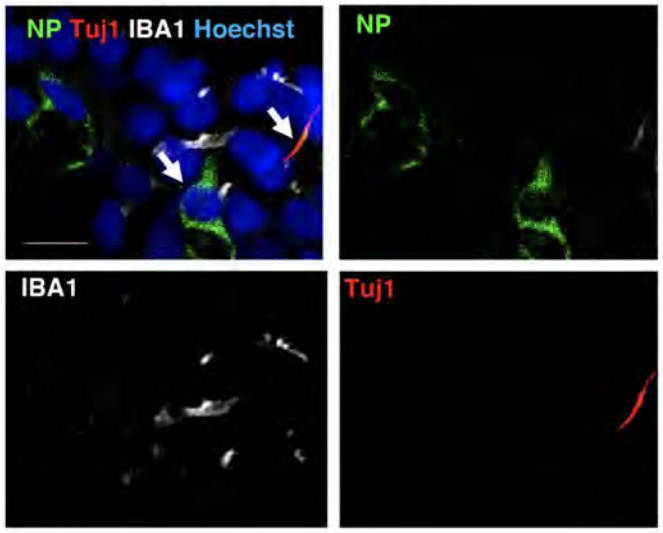
Cite as: G. D. de Melo *et al.*, *Sci. Transl. Med.* 10.1126/scitranslmed.abf8396 (2021).

CORONAVIRUS

COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters

Guilherme Dias de Melo[1‡], Françoise Lazarini[2‡], Sylvain Levallois[3‡], Charlotte Hautefort[4‡], Vincent Michel[2,5], Florence Larrous[1], Benjamin Verillaud[4], Caroline Aparicio[6], Sebastien Wagner[2], Gilles Gheusi[2,7], Lauriane Kergoat[1], Etienne Kornobis[8,9], Flora Donati[10,11], Thomas Cokelaer[8,9], Rémi Hervochon[12], Yoann Madec[13], Emmanuel Roze[14], Dominique Salmon[15], Hervé Bourhy[1*], Marc Lecuit[3,16*], Pierre-Marie Lledo[2*]

Post-COVID-19, Case # 10 with persistent signs



Persistence of viral antigen (NP+) in the olfactory epithelium

Inflammation: presence of Iba1+ MF/microglia in the epithelium

Link with anosmia?

Table S4. Individual features at inclusion of the participants with persistent olfactory dysfunction.

Patient	COVID #6	COVID #8	COVID #9	COVID #10	CONTROL: Normosmic COVID #7
Years/Sex	24/M	43/F	71/F	56/F	47/M
Clinical features at the 1st episode	Anosmia -Ageusia	Anosmia -Ageusia	Anosmia -Ageusia	Anosmia -Ageusia-Vertigo	Normosmia-headache
Long lasting clinical features at inclusion	Anosmia-Parosmia-Ageusia	Intermittent anosmia-Asthenia-Burning sensations-Stereotypical crises: wriggling nose, left arm pain, left intercostal pain	Hyposmia-Ageusia-Paresthesia-memory loss-concentration	Hyposmia-asthenia-vertigo-queasiness paresthesia-burning sensations-memory loss-hyperemotivity thoracic oppression diarrhea, oesophageal pain	Normosmia Dysgeusia-vertigo-paresthesia-asthenia-tremor-tingling of the face, nose, arms, legs
Treatments	-	Antiviral(hydroxychloroquine)-antihistaminic-Zinc	Antidepressant (fluoxetine)-B-bloquant	-	Antalgic (aspirine)-antiepileptic
Comorbidities[a]	-	Flammer syndrome- Allergy	Overweight-allergy	-	-
Smoking status	Nonsmoker	Nonsmoker	Previous (24years ago)	Nonsmoker	Current
Time between the first disease symptoms[b] and inclusion	110	136	158	196	141
Time between the first disease symptoms[b] and olfactory loss	15	45	35	0	Not applicable
SARS-CoV-2 PCR in the nasopharynx	Neg	Neg	Neg	Neg	Neg
SARS-CoV-2 PCR in the olfactory mucosa[c]	Pos	Pos	Pos	Pos	Pos
RdRp gene, genomic RNA (copy number/µL[d])	(<200)	($3.43.\ 10^5$)	($4.35.\ 10^5$)	($1.68.\ 10^5$)	($1.88.\ 10^5$)
E gene, genomic RNA (copy number/µL[d])	(<200)	($2.20.\ 10^4$)	($4.54.\ 10^4$)	($1.80.\ 10^4$)	($1.16.\ 10^4$)
E gene, subgenomic RNA (copy number/µL[d])	(<2000)	(<2000)	(<2000)	(<2000)	(<2000)
OMP RNA PCR	Pos	Pos	Pos	Pos	Pos
SARS-CoV-2 antigens in the olfactory mucosa	Yes	Yes	No	Yes	No
SARS-CoV-2 serology	Neg	Pos	Pos	Pos	Neg

Detection of SARS-CoV-2 RNA in the olfactory mucosa of Long COVID patients

Infect Dis Ther (2021) 10:1747–1763
https://doi.org/10.1007/s40121-021-00484-w

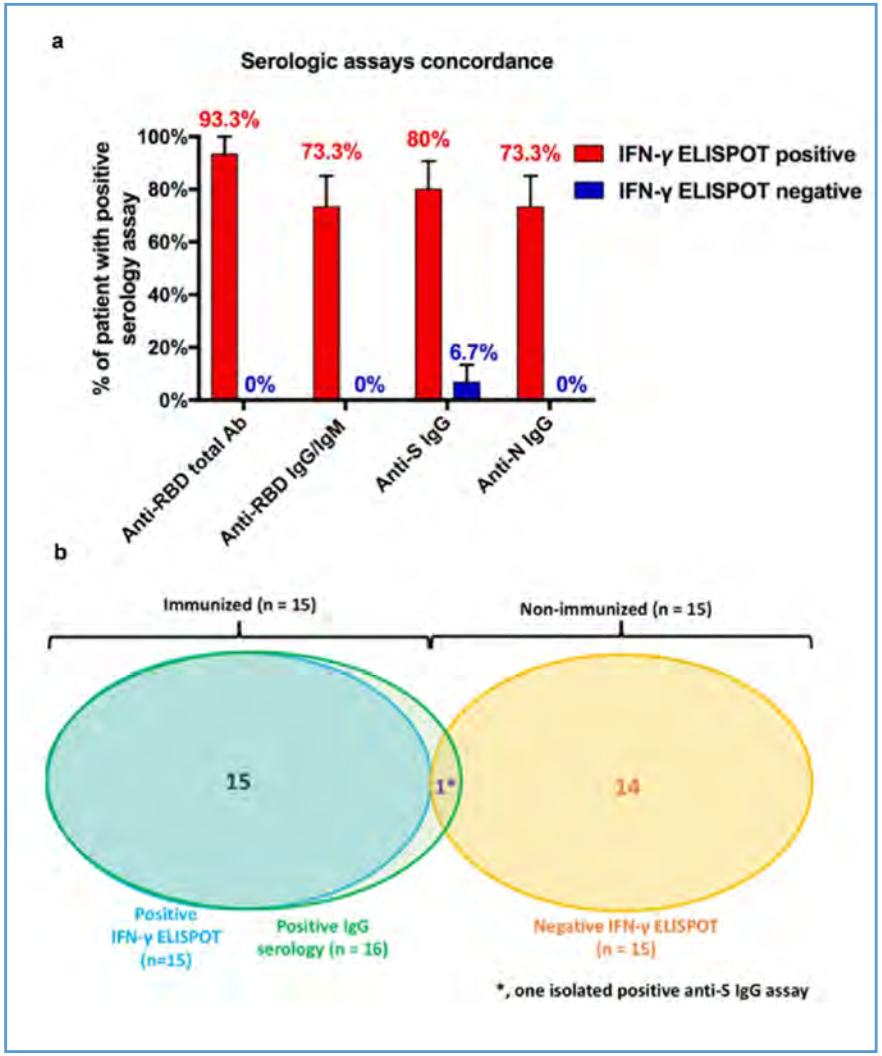
ORIGINAL RESEARCH

Refining "Long-COVID" by a Prospective Multimodal Evaluation of Patients with Long-Term Symptoms Attributed to SARS-CoV-2 Infection

Marc Scherlinger · Renaud Felten · Floriane Gallais · Charlotte Nazon · Emmanuel Chatelus · Luc Pijnenburg · Amaury Mengin · Adrien Gras · Pierre Vidailhet · Rachel Arnould-Michel · Sabrina Bibi-Triki · Raphaël Carapito · Sophie Trouillet-Assant · Magali Perret · Alexandre Belot · Seiamak Bahram · Laurent Arnaud · Jacques-Eric Gottenberg · Samira Fafi-Kremer · Jean Sibilia

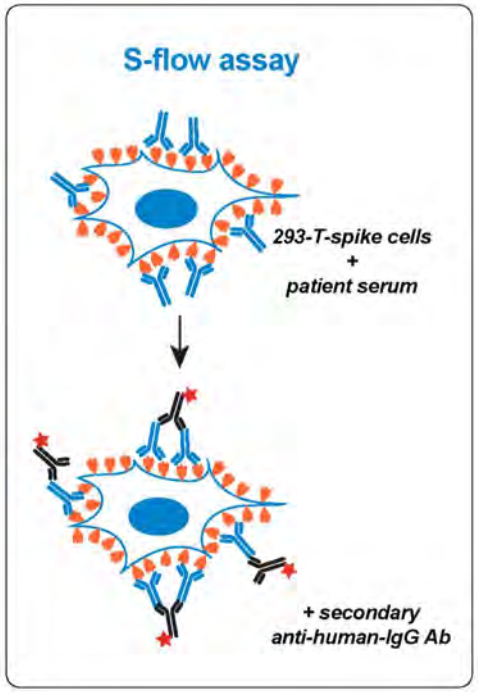
Characteristics, % (*n*/*N*)	Total (*N* = 30)	Immunized (*N* = 15)	Non-immunized (*N* = 15)	Convalescent COVID-19 (*N* = 17)
Demographics				
Age (median, (IQR))	40 (35–54)	40 (31–58)	39 (35–45)	40 (31–45)
Female sex	60 (18/30)	46.7 (7/15)	73.3 (11/15)	76.4 (13/17)
Close contact with confirmed COVID-19 patients	43.3 (13/30)	46.7 (7/15)	40 (6/15)	29.4 (5/17)

- Two groups of Long COVID patients: with or without detectable adaptive responses
- No significant differences in symptoms except for higher thoracic oppression in the « non-immunized » group

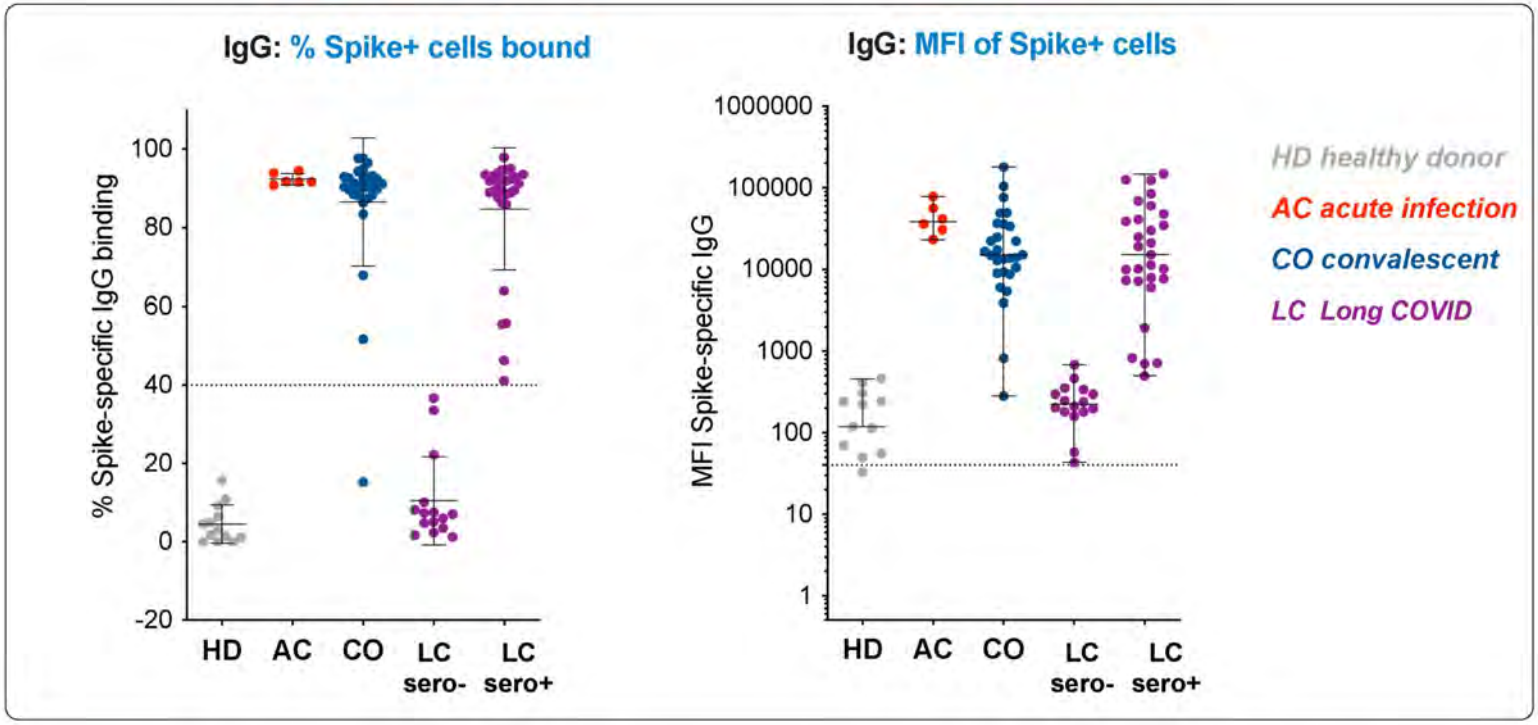


PERSICOT study

Antibody responses in Long COVID patients



S-flow assay by I. Staropoli
in O. Schwartz Unit



➡ *Antibody measurements distinguish two groups of Long COVID patients*

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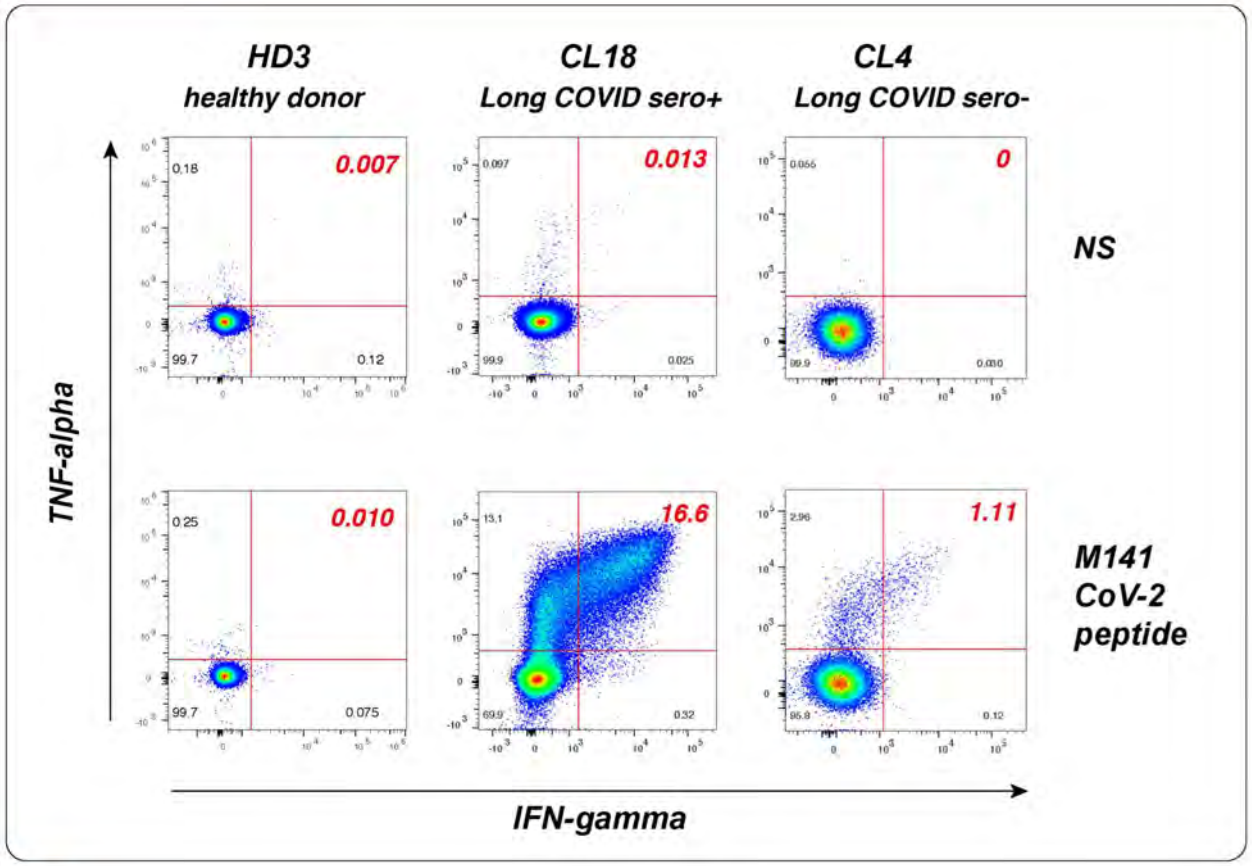
PERSICOT study

CD4+ T cell responses in Long COVID patients



Examples of primary CD4+ T cell line responses to a SARS-CoV-2 M peptide

- *strong response to M141 in one seropositive Long Covid patient*
- *weaker but detectable response in one seronegative Long Covid patient*

Suggests previous infection in the seronegative patient

INSTITUT PASTEUR

J Kervevan, D. Salmon-Ceron

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-26479-2 OPEN

Anti-spike antibody response to natural SARS-CoV-2 infection in the general population

Jia Wei[1,2], Philippa C. Matthews[1,3], Nicole Stoesser[1,3,4,5], Thomas Maddox[6], Luke Lorenzi[6], Ruth Studley[6], John I. Bell[7], John N. Newton[8], Jeremy Farrar[9], Ian Diamond[6], Emma Rourke[6], Alison Howarth[1,5], Brian D. Marsden[1,10], Sarah Hoosdally[1], E. Yvonne Jones[1], David I. Stuart[1], Derrick W. Crook[1,3,4,5], Tim E. A. Peto[1,3,4,5], Koen B. Pouwels[1,2,4,11,22], A. Sarah Walker[1,2,4,12,22], David W. Eyre[2,3,4,5,22] & the COVID-19 Infection Survey team*

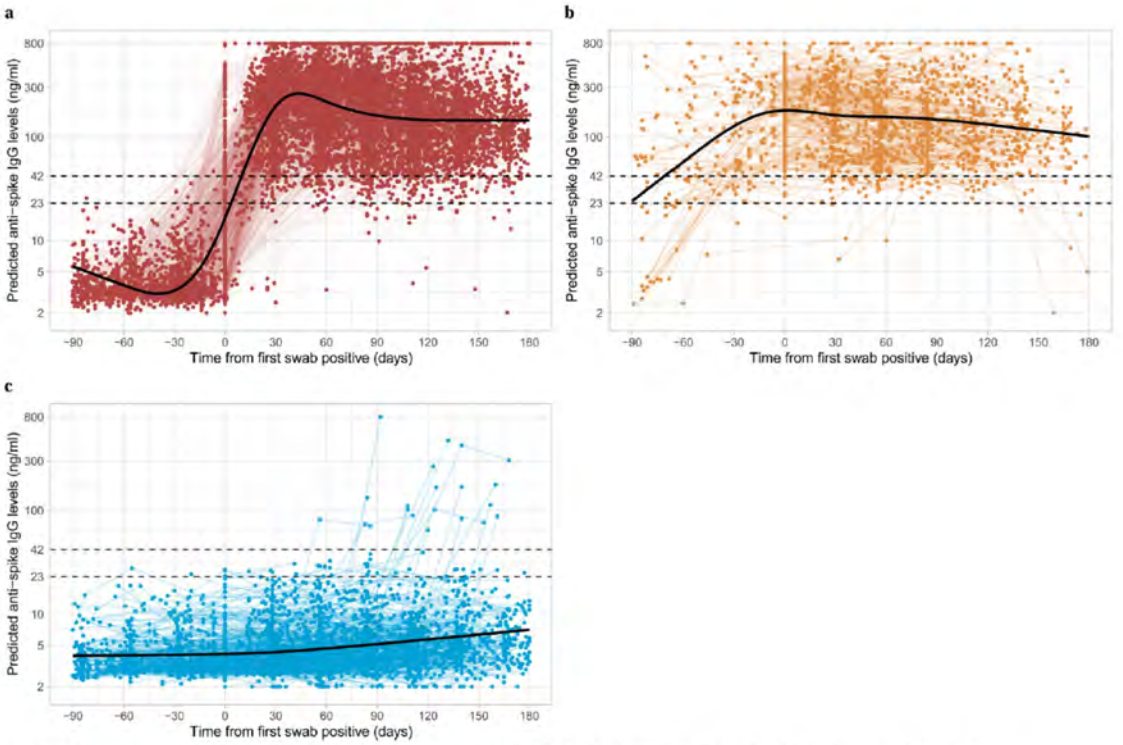


Fig. 1 Individual trajectories for 7256 participants infected with SARS-CoV-2 by class identified from latent class mixed models.

- 7,256 UK COVID-19 Infection Survey participants who were PCR+
- 24% were seronegative
  - Older
  - Lower initial viral load
  - Fewer symptoms

Persistently low or absent antibodies in a significant fraction of the SARS-CoV-2 infected population

Evaluer l'effet de la vaccination dans le COVID Long

- Persistance virale ?

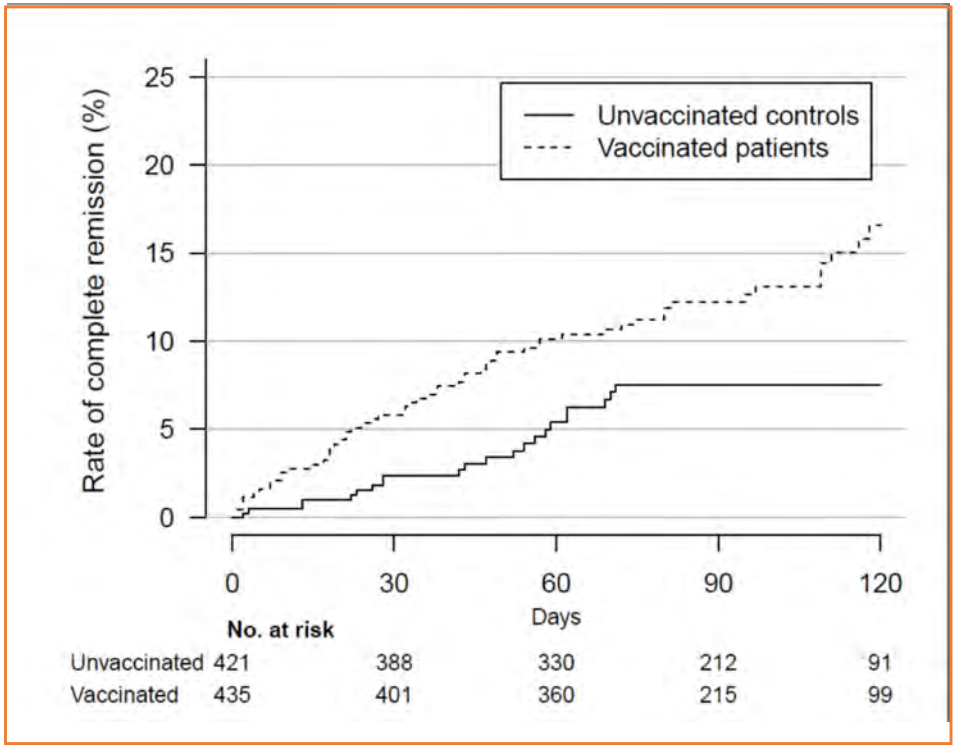
- Clairance virale ?
- Inflammation controlée ?

Preprints with THE LANCET

Efficacy of COVID-19 Vaccination on the Symptoms of Patients With Long COVID: A Target Trial Emulation Using Data From the ComPaRe e-Cohort in France

17 Pages • Posted: 29 Sep 2021

Viet-Thi Tran
Center for Research in Epidemiology and Statistics Sorbonne Paris Cité (CRESS- UMR 1153) - METHODS Team; Universite Paris Descartes; Universite Paris Descartes - Center for Clinical Epidemiologie
...
Philippe Ravaud
Columbia University - Department of Epidemiology

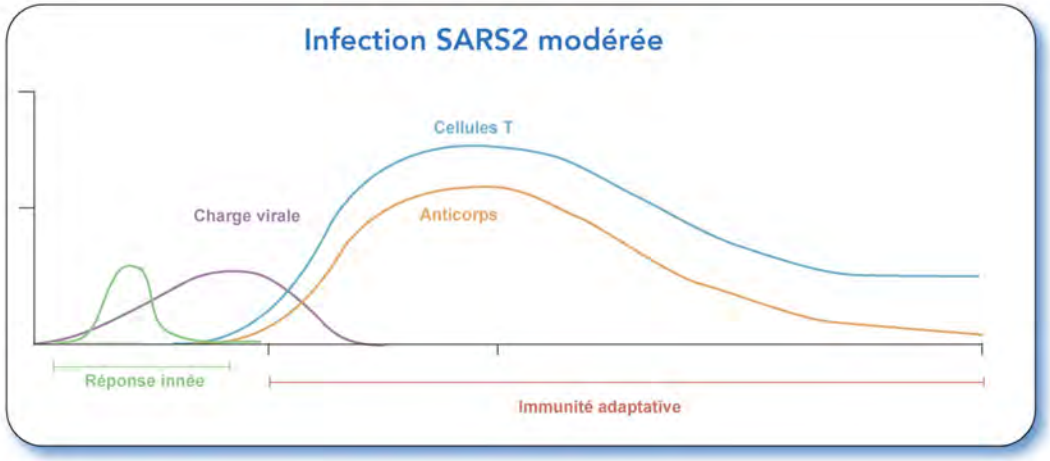


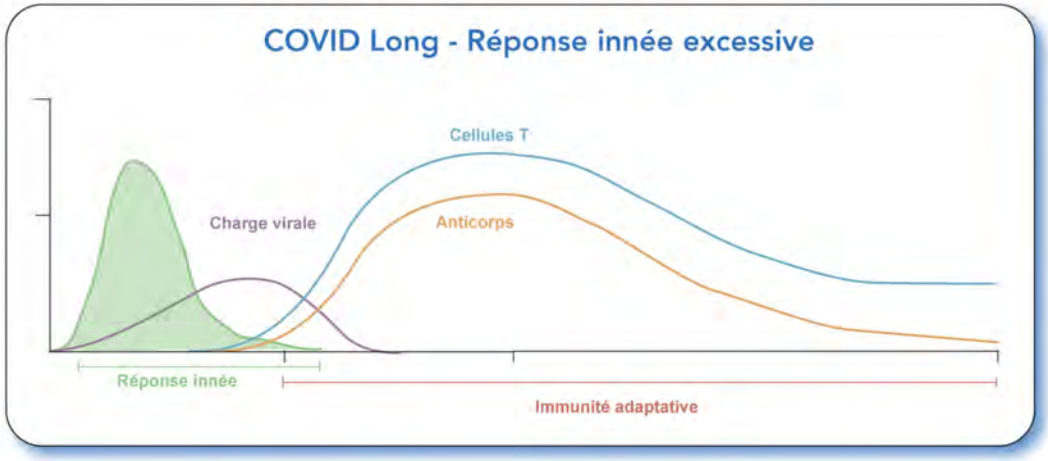
An immunological component to Long COVID that may be amenable to intervention

Vaccination doubled the rate of Long COVID patients in complete remission at 120 days

Conclusions :

Possibles mécanismes pathogènes du COVID Long (1)

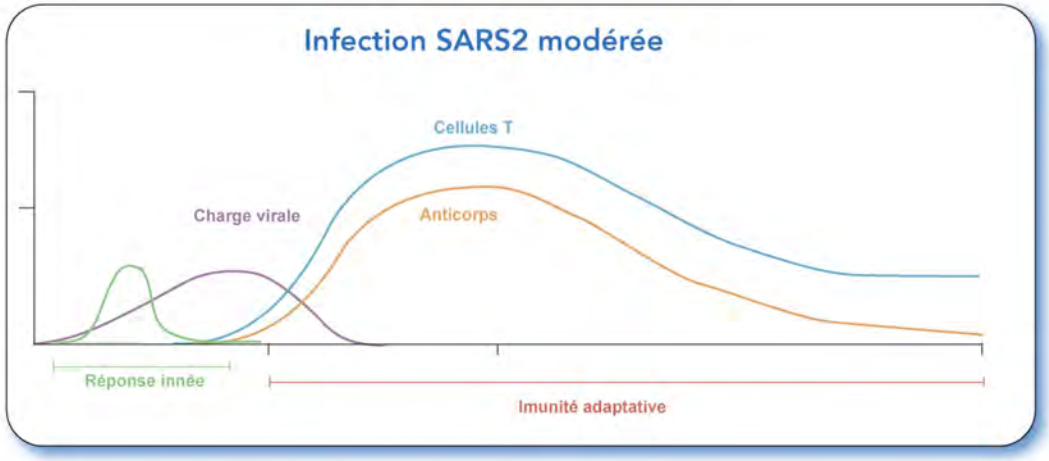


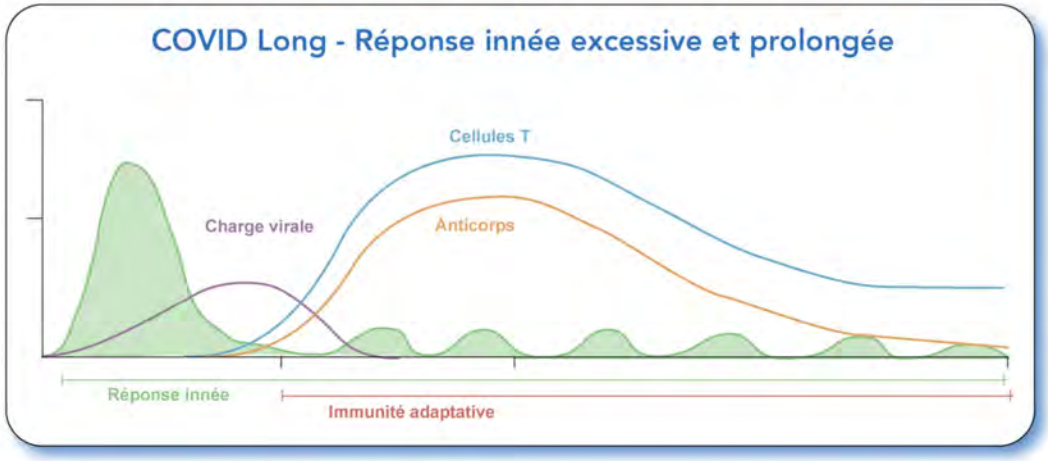


Effets délétères d'une inflammation précoce :

- Micro-caillots dans les capillaires ?
- Dommage neuronal ou vasculaire ?
- Autre ?

Possibles mécanismes pathogènes du COVID Long (2)

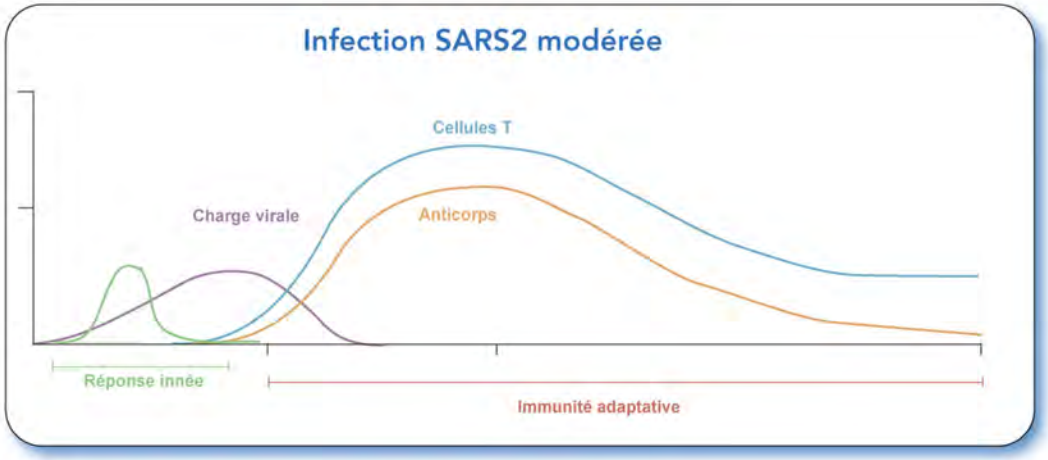


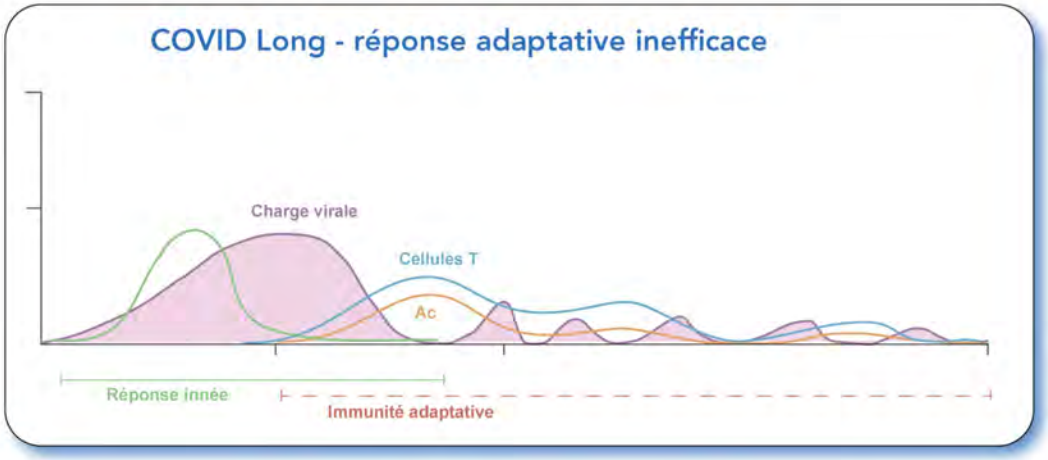


- Traitement anti-inflammatoire ?
- Traitement anti-histaminique ?

- Inflammation chronique ?
- Activation des mastocytes ?
- Risque accru d'autoimmunité ?

Possibles mécanismes pathogènes du COVID Long (3)

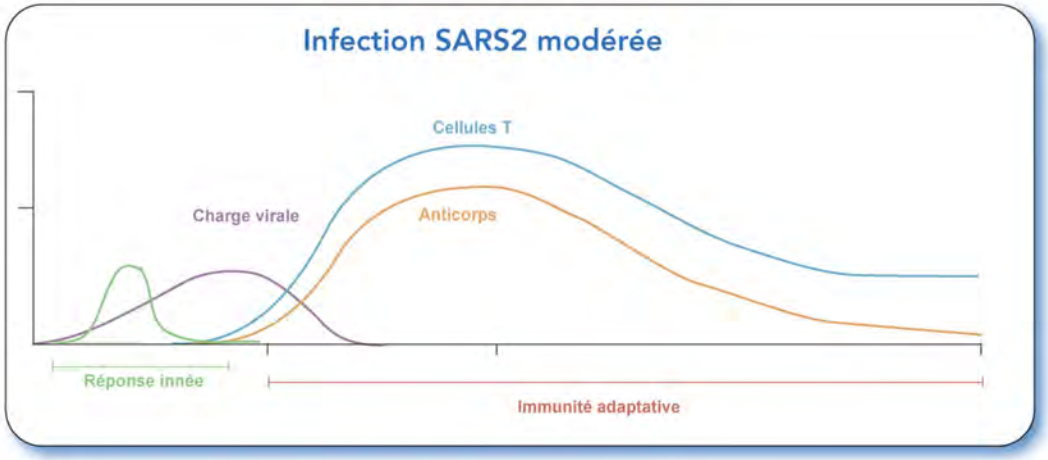


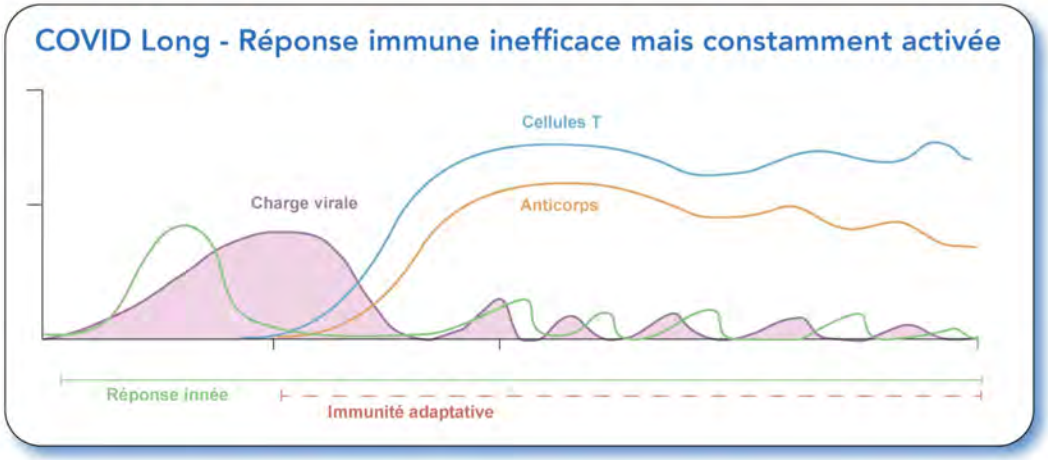


- Vaccination ?
- Traitement antiviral ?

- Faibles réponses des cellules T et B
- Persistance virale dans sites sanctuaires?
- Dommage tissulaire localisé ?

Possibles mécanismes pathogènes du COVID Long (4)





- Différents types de COVID Long ?
- Besoin d'analyser la qualité des réponses immunes antivirales

- Réponses adaptatives de forte intensité mais de faible qualité
- Persistance virale dans sites sanctuaires ?
- Inflammation persistante

Etude PERSICOT

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