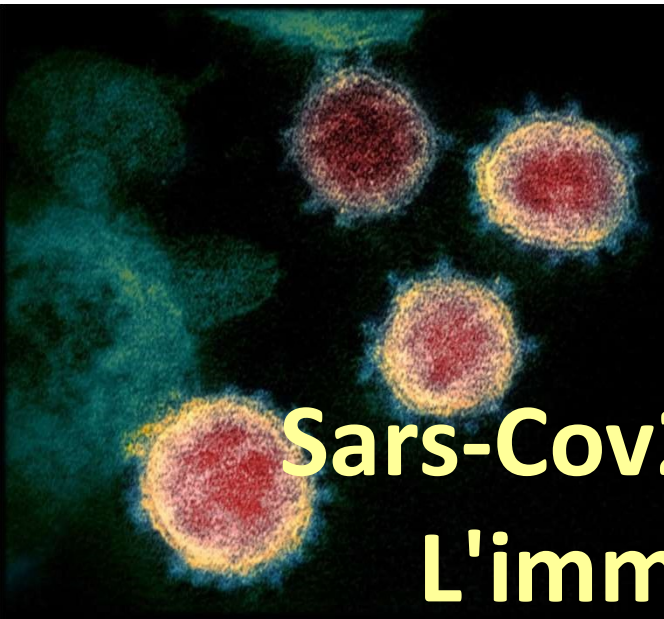


Sars-Cov2, Covid-19, qu'a-t-on appris ? L'immunopathologie "en direct"

Jean Sibilia

Rhumatologie, CHU de Strasbourg

Centre national de référence "Maladies auto-immunes systémiques rares"

Laboratoire d'ImmunoRhumatologie Moléculaire, INSERM UMR S1109

Fédération Hospitalo-Universitaire (FHU) OMICARE

Fédération de Médecine Translationnelle de Strasbourg (FMTS)

Winterschool

Strasbourg, 25 novembre 2021

Liens d'intérêt

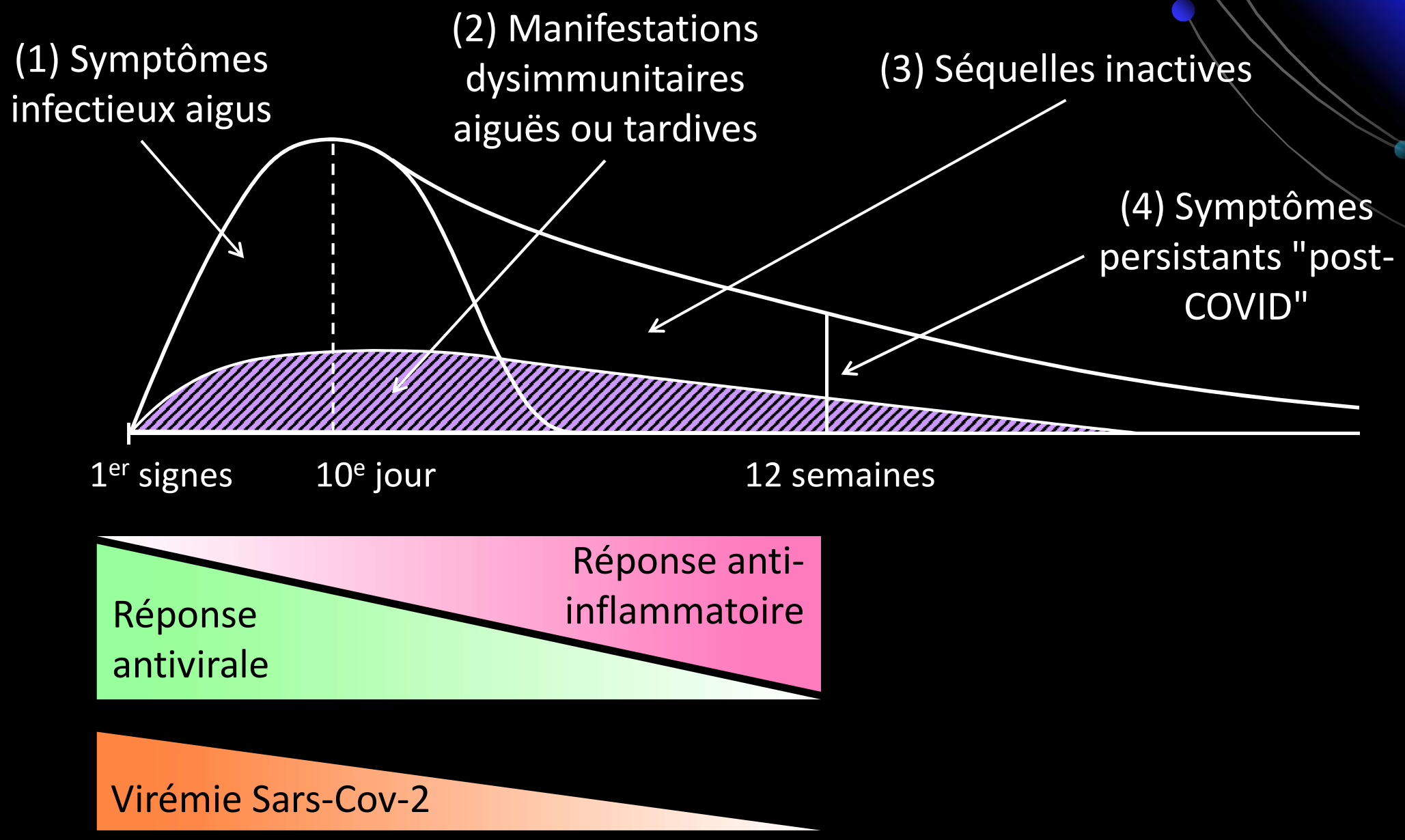
- Aucun lien d'intérêt avec le sujet
- Interventions ponctuelles (expertises, conseils, symposiums, études cliniques, formations) : Roche, Chugai, Bristol-Myers Squibb, UCB, GSK, LFB, Actelion, Pfizer, MSD, Novartis, Amgen, Abbvie, Sandoz, Gilead, Lilly, Sanofi Genzyme, Janssen, Mylan, Galapagos, Sobi
- Intérêts indirects (subvention de recherche) : Roche, Pfizer, MSD, BMS

Une expérience d'immunopathologie "en direct"

- "Cytokine storm" ou "cytokine summer thunderstorm"
- Déficit en IFN ou auto-Ac anti-IFN ?
- PIMS ou Kawasaki ?
- HIT ou VITT ?
- Syndrome post-covid "hit and hide" ou "hit and run" ?

BFM TV. LCI C NEWS

De l'infection à Sars-Cov2 à la Covid-19



La réponse immunitaire anti-Sars-Cov2 :
une "cytokine summer thunderstorm" plus qu'une "cytokine storm"

THE LANCET
Respiratory Medicine
Volume 8, Issue 12, December 2020, Pages 1233-1244

Rapid Review

Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes

Daniel E Leisman MD [b, c, d, †], Lukas Ronner MD [b, e, †], Rachel Pinotti MLIS [a], Matthew D Taylor MD [d, f, g], Pratik Sinha PhD [h, i], Prof Carolyn S Calfee MD [h, i, j], Alexandre V Hirayama MD [k], Fiore Mastroiani MD [l], Prof Cameron J Turtle MBBS [k], Michael O Harhay PhD [m], Prof Matthieu Legrand MD [h], Prof Clifford S Deutschman MD [d, f, g]

Sars-Cov2 "cytokine summer thunderstorm"…
et pourquoi Homo sapiens ?

Primate innate immune responses to bacterial and viral pathogens reveals an evolutionary trade-off between strength and specificity

Mohamed B. F. Hawash[a,b], Joaquin Sanz-Remón[c,d], Jean-Christophe Grenier[e], Jordan Kohn[f,g], Vania Yotova[a], Zach Johnson[h], Robert E. Lanford[i], Jessica F. Brinkworth[j,k,1], and Luis B. Barreiro[a,l,1]

Proc Natl Acad Sci U S A. 2021 Mar 30;118(13):e2015855118.

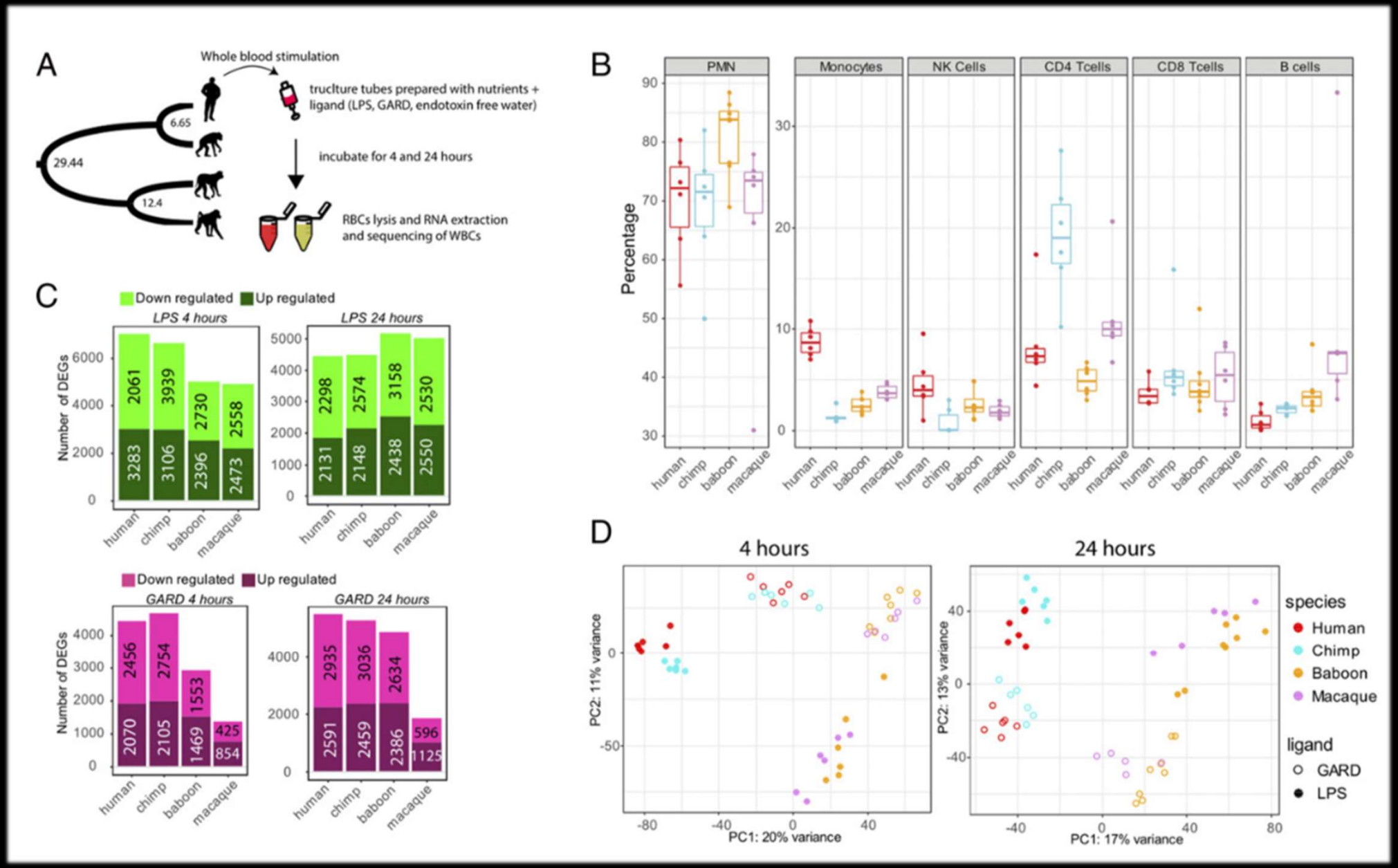
Sars-Cov2 "cytokine summer thunderstorm"…
et pourquoi Homo sapiens ?

Etude whole-genome transcriptomique ← stimulation bactérienne et virale

- Une hyperexpression inflammatoire anti-infectieuse précoce chez l'homme et le chimpanzé → intense mais à spectre "réduit"
  - ⚠ Modification de ≈ 40% des gènes, en particulier des gènes de la voie des IFN
  - ⚠ Homo sapiens a une réponse immunitaire anti-infectieuse intense et précoce, ce qui lui confère un bénéfice pour se défendre mais au détriment d'un risque de lésions tissulaires "inflammation drivers"

Hawash et al. Proc Natl Acad Sci U S A. 2021;118(13):e2015855118.

Sars-Cov2 "cytokine summer thunderstorm"… et pourquoi Homo sapiens ?



Hawash et al. Proc Natl Acad Sci U S A. 2021;118(13):e2015855118.

Sars-Cov2 "cytokine summer thunderstorm"…
très différente des autres réponses anti-infectieuses

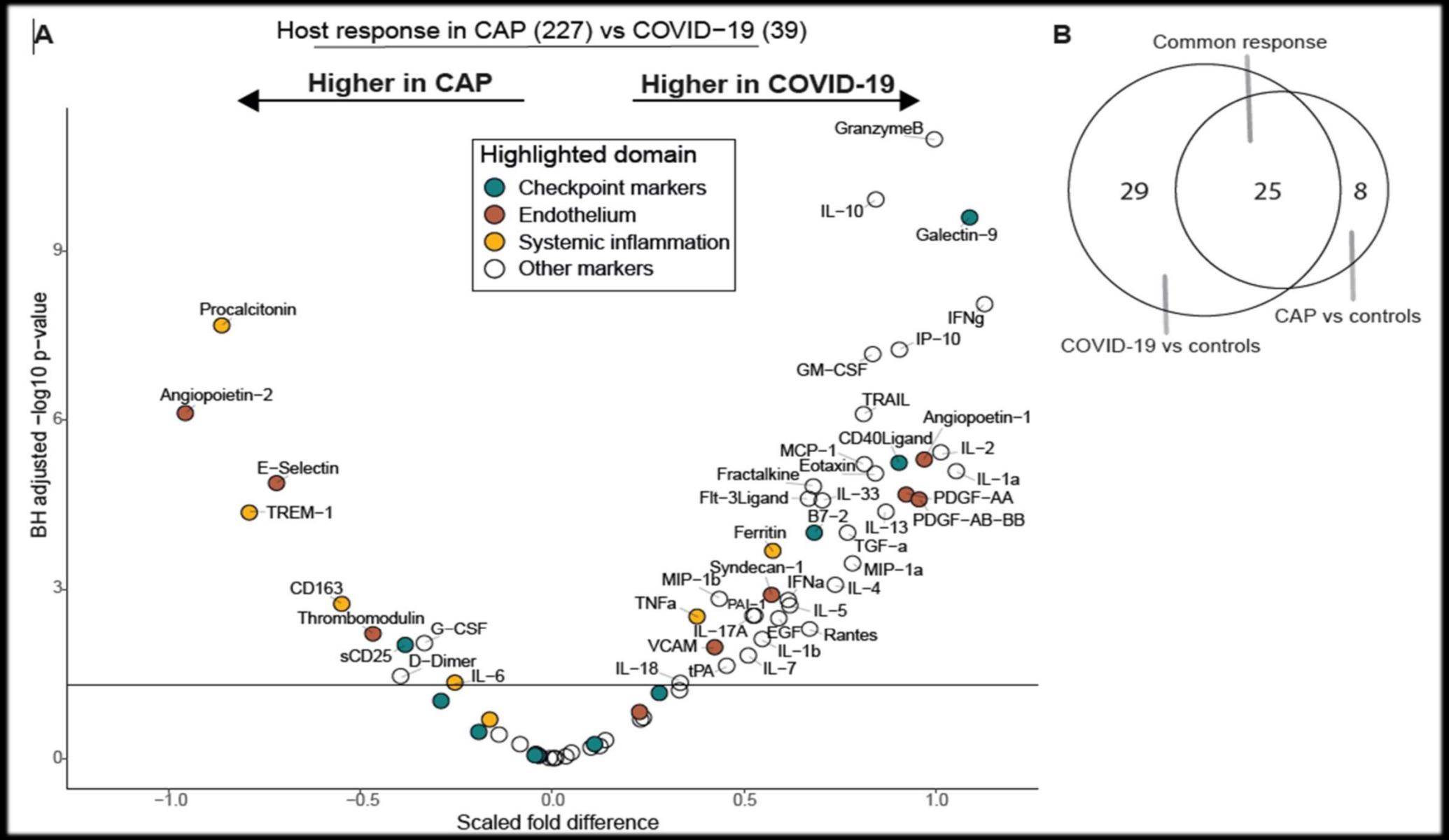
eLife. 2021; 10: e69661.
Published online 2021 Aug 23. doi: 10.7554/eLife.69661

PMCID: PMC8382293
PMID: 34424199

Integrated single-cell analysis unveils diverging immune features of COVID-19, influenza, and other community-acquired pneumonia

Alex R Schuurman,[#1,2,‡] Tom DY Reijnders,[#1,2,‡] Anno Saris,[1,2] Ivan Ramirez Moral,[1,2] Michiel Schinkel,[1,2] Justin de Brabander,[1,2] Christine van Linge,[1,2] Louis Vermeulen,[3] Brendon P Scicluna,[1,4] W Joost Wiersinga,[1,2,5] Felipe A Vieira Braga,[#3,†] and Tom van der Poll[#1,2,5,†]

Sars-Cov2 "cytokine summer thunderstorm"…
très différente des autres réponses anti-infectieuses



Schuurman et al. eLife 2021; 10: e69661.

Quelles voies et cellules de l'inflammation clés ?

ARTICLES
https://doi.org/10.1038/s41590-021-00870-z

nature immunology

NATURE IMMUNOLOGY | VOL 22 | MARCH 2021 | 322–335

Check for updates

Outcome of SARS-CoV-2 infection is linked to MAIT cell activation and cytotoxicity

Héloïse Flament[1,2,17], Matthieu Rouland[3,17], Lucie Beaudoin[3,17], Amine Toubal[3,17], Léo Bertrand[3], Samuel Lebourgeois[4,5], Camille Rousseau[3], Pauline Soulard[3], Zouriatou Gouda[3], Lucie Cagninacci[3], Antoine C. Monteiro[4,5], Margarita Hurtado-Nedelec[1,2], Sandrine Luce[3], Karine Bailly[3], Muriel Andrieu[3], Benjamin Saintpierre[3], Franck Letourneur[3], Youenn Jouan[6,7], Mustapha Si-Tahar[6], Thomas Baranek[6], Christophe Paget[6], Christian Boitard[3,8], Anaïs Vallet-Pichard[3,9], Jean-François Gautier[10], Nadine Ajzenberg[11,12], Benjamin Terrier[13], Frédéric Pène[3,14], Jade Ghosn[5,15], Xavier Lescure[5,15], Yazdan Yazdanpanah[5,15], Benoit Visseaux[4,5], Diane Descamps[4,5], Jean-François Timsit[5,16], Renato C. Monteiro[1,2] and Agnès Lehuen[3] ✉

⚠ Quid des ILCs (1, 2, 3), NK, iNKT, mastocytes ?

La Covid-19 : une dérégulation complexe de l'IFN ?

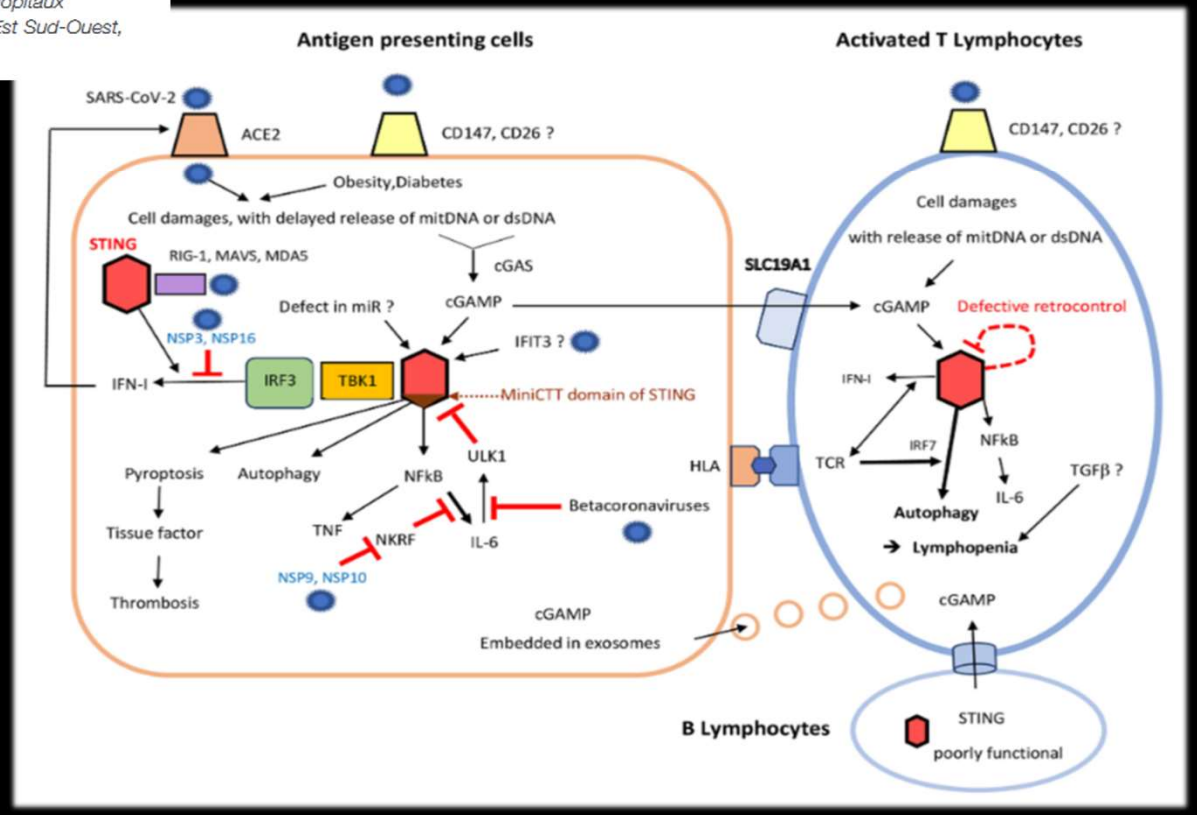
frontiers in Immunology

December 2020 | Volume 11 | Article 607069

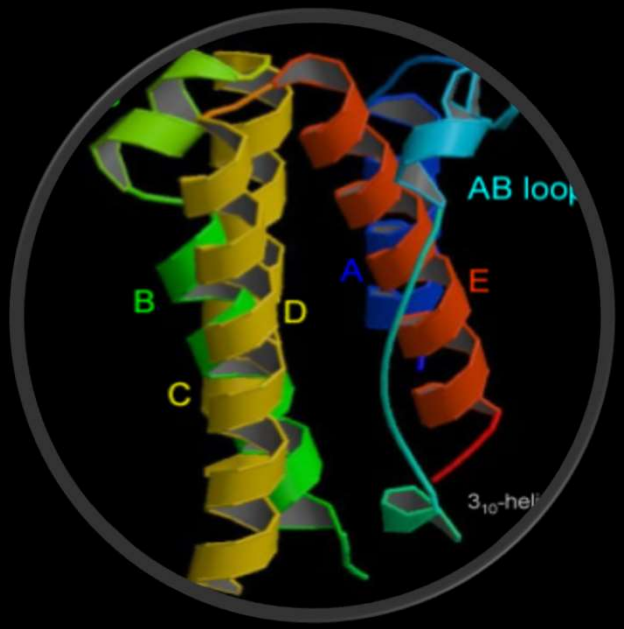
Lymphocyte Changes in Severe COVID-19: Delayed Over-Activation of STING?

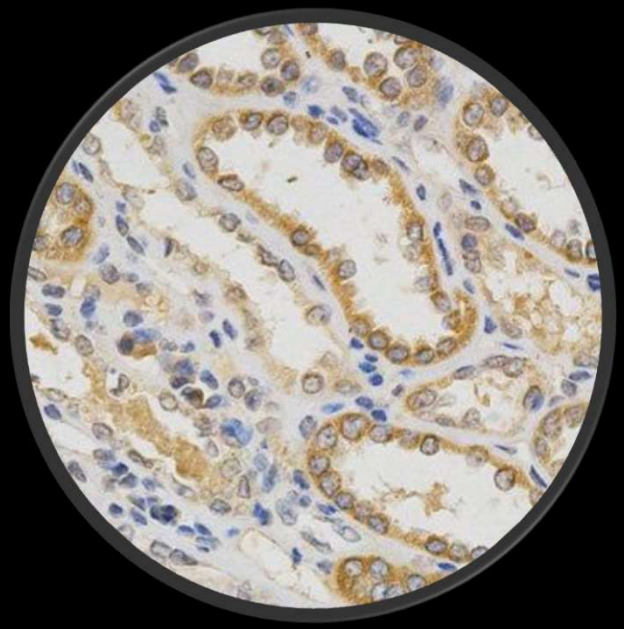
Jean-Marie Berthelot[1], Frédéric Lioté[2], Yves Maugars[1] and Jean Sibilia[3,4]*

[1] Rheumatology Department, Nantes University Hospital, Nantes, France, [2] Rheumatology Department & Inserm UMR 1132 (centre Viggo Petersen), Hôpital Lariboisière, Université de Paris, Paris, France, [3] Service de rhumatologie, Hopitaux Universitaires de Strasbourg, RESO: Centre de Reference des Maladies Autoimmunes Systemiques Rares Est Sud-Ouest, Strasbourg, France, [4] INSERM UMR_S1109, Universite de Strasbourg, Strasbourg, France



La susceptibilité à une Covid-19 sévère
Déficit en IFN ou auto-Ac anti-IFN ?





… les 2, mon capitaine !

La susceptibilité à une Covid-19 sévère : déficit en IFN ou auto-Ac anti-IFN ?

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Autoantibodies against type I IFNs in patients with life-threatening COVID-19

Paul Bastard*† and Lindsey B. Rosen† *et al.*

Science. 2020 Oct 23;370(6515):eabd4585.

Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths

PAUL BASTARD, ADRIAN GERVAIS, TOM LE VOYER, JÉRÉMIE ROSAIN, QUENTIN PHILIPPOT, JÉRÉMY MANRY, ELEFTHERIOS MICHAILIDIS, HANS-HEINRICH HOFFMANN, SHOHEI ETO, [...] JEAN-LAURENT CASANOVA +190 authors Authors Info & Affiliations

SCIENCE IMMUNOLOGY • 20 Aug 2021 • Vol 6, Issue 62 • DOI: 10.1126/sciimmunol.abl4340

X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19

TAKAKI ASANO, BERTRAND BOISSON, FANNY ONODI, DANIELA MATUOZZO, MARCELA MONCADA-VELEZ, MAJISTOR RAJ LUXMAN MAGLORIUS RENKILARAJ, PENG ZHANG, LAURENT MEERTENS, ALEXANDRE BOLZE, [...] JEAN-LAURENT CASANOVA +106 authors Authors Info & Affiliations

SCIENCE IMMUNOLOGY • 20 Aug 2021 • Vol 6, Issue 62 • DOI: 10.1126/sciimmunol.abl4348

La Covid-19 : une maladie immunologique complexe

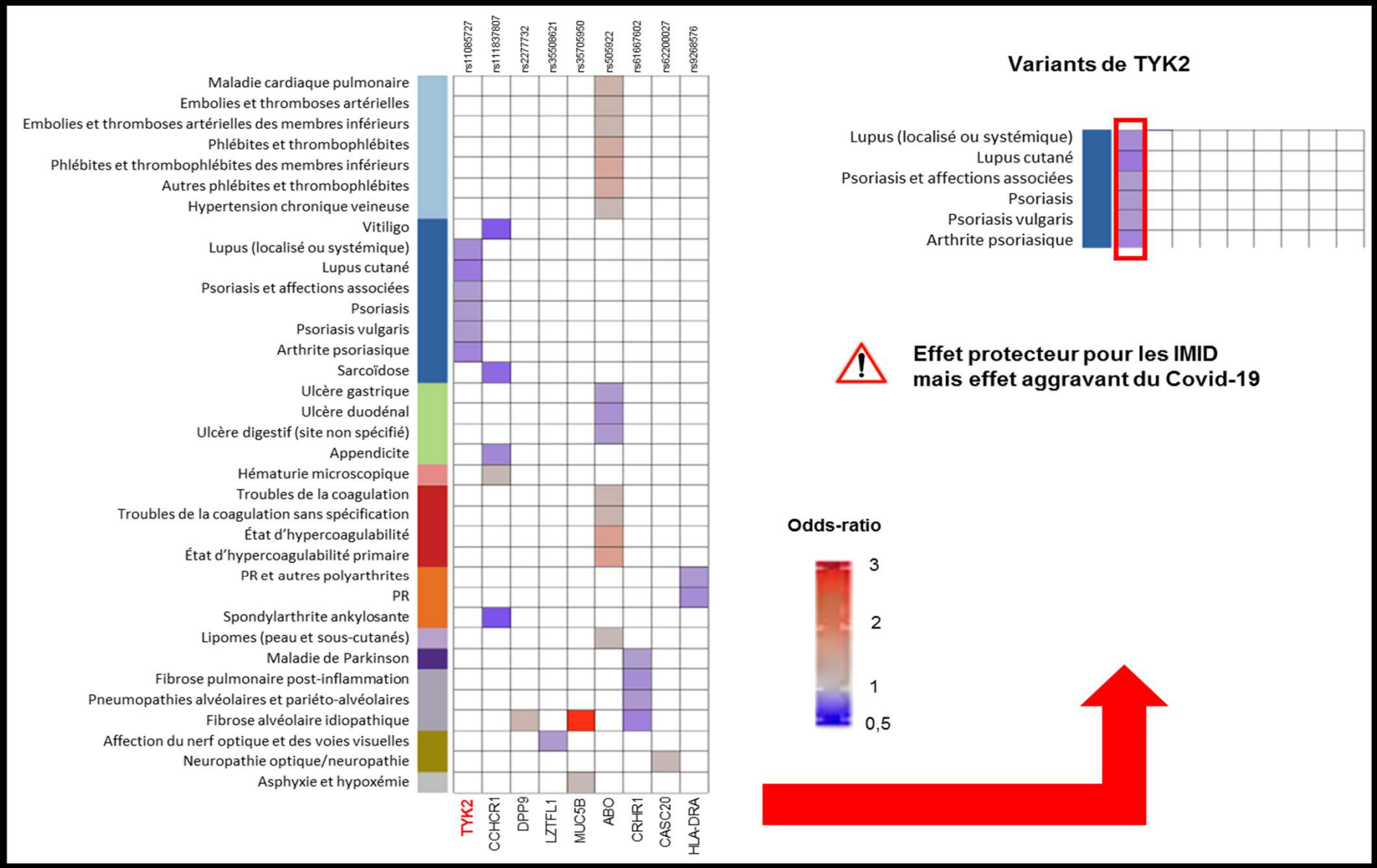
Susceptibilité génétique aux Covid sévères : Analyse PheWAS (Phenome-wide association study)

- **2 cohortes comportant des données génétiques et phénotypiques**
  - Cohorte exploratoire : Veteran Administration (VA) Million Veteran Program (MVP) (n = 455 683)
  - Cohorte de validation : United Kingdom Biobank (UKBB)
- **Génotypage de 87 variants précédemment identifiés comme associés à une évolution péjorative du Covid-19 (n = 48) ou à une hospitalisation (n = 39)**

Pairo-Castineira E et al. Nature 2021;591(7848)92-8 ; COVID-19 Host Genetics Initiative. Nature 2021
ACR 2021 - D'après Verma A et al., abstr. 1938, actualisé

La Covid-19 : une maladie immunologique complexe

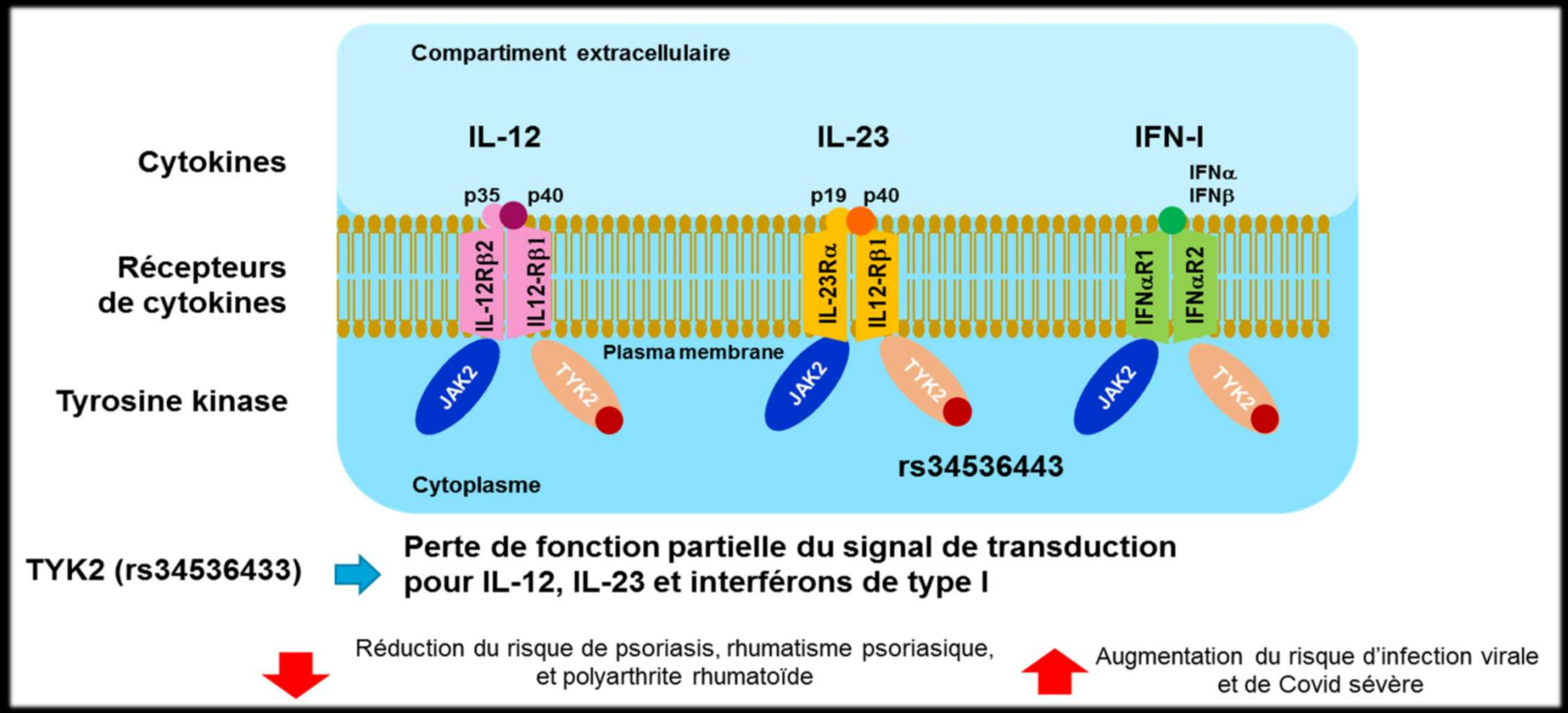
Susceptibilité génétique aux Covid sévères : Analyse PheWAS (Phenome-wide association study)



ACR 2021 - D'après Verma A et al., abstr. 1938, actualisé

La Covid-19 : une maladie immunologique complexe

Susceptibilité génétique aux Covid sévères : Analyse PheWAS (Phenome-wide association study)



- **Architecture génétique partagée entre facteurs de sévérité du Covid et facteur de thrombose ou d'asthme**
- **Balance opposée entre la sévérité du Covid et le facteur génétique de prédisposition aux IMID pour variant fonctionnel localisé dans le locus de TYK2**

ACR 2021 - D'après Verma A et al., abstr. 1938, actualisé

La Covid-19 : une maladie immunologique complexe

doi:10.1093/brain/awab337

BRAIN 2021: Page 1 of 15 | 1

BRAIN
ORIGINAL ARTICLE

A genetic link between risk for Alzheimer's disease and severe COVID-19 outcomes via the *OAS1* gene

Naciye Magusali,[1,†] Andrew C. Graham,[1,†] Thomas M. Piers,[2] Pantila Panichnantakul,[1] Umran Yaman,[1] Maryam Shoai,[1,3] Regina H. Reynolds,[3,4,5] Juan A. Botia,[3,6] Keeley J. Brookes,[7] Tamar Guetta-Baranes,[8] Eftychia Bellou,[9] Sevinc Bayram,[10] Dimitra Sokolova,[1] Mina Ryten,[3,4,5] Carlo Sala Frigerio,[1] Valentina Escott-Price,[9] Kevin Morgan,[8] Jennifer M. Pocock,[2] John Hardy[1,3] and Dervis A. Salih[1]

La Covid-19 : une maladie immunologique complexe

Science Translational Medicine

RESEARCH ARTICLES

Cite as: R. Carapito *et al.*, *Sci. Transl. Med.* 10.1126/scitranslmed.abj7521 (2021).

CORONAVIRUS

Identification of driver genes for critical forms of COVID-19 in a deeply phenotyped young patient cohort

Raphael Carapito[1,2,3,†], Richard Li[4†], Julie Helms[1,3,5], Christine Carapito[3,6], Sharvari Gujja [4], Véronique Rolli[1,2,3], Raony Guimaraes[4], Jose Malagon-Lopez[4], Perrine Spinnhirny[1,3], Alexandre Lederle[1,3], Razieh Mohseninia[7], Aurélie Hirschler[3,6], Leslie Muller[3,6], Paul Bastard[8,9,10], Adrian Gervais[9,10], Qian Zhang[8,9,10], François Danion[1,3,11], Yvon Ruch[3,11], Maleka Schenck[3,12], Olivier Collange[3,13], Thiên-Nga Chamaraux-Tran[3,14], Anne Molitor[1,3], Angélique Pichot[1,3], Alice Bernard[1,3], Ouria Tahar[2,3], Sabrina Bibi-Triki[1,3], Haiguo Wu[4], Nicodème Paul[1,3], Sylvain Mayeur[1,3], Annabel Larnicol[1,3], Géraldine Laumond[1,3], Julia Frappier[1,3], Sylvie Schmidt[1,3], Antoine Hanauer,[1,3], Cécile Macquin[1,3], Tristan Stemmelen[1,2,3], Michael Simons[15], Xavier Mariette[16,17], Olivier Hermine[10,18], Samira Fafi-Kremer[1,3,19], Bernard Goichot[3,20], Bernard Drenou,[21], Khaldoun Kuteifan[22], Julien Pottecher[3,14], Paul-Michel Mertes[3,13], Shweta Kailasan[23], M. Javad Aman[23], Elisa Pin[24], Peter Nilsson[24], Anne Thomas[25], Alain Viari[25], Damien Sanlaville[25], Francis Schneider[3,12], Jean Sibilia[1,3,26], Pierre-Louis Tharaux[27], Jean-Laurent Casanova[8,9,10,28], Yves Hansmann[3,11], Daniel Lidar[7,29], Mirjana Radosavljevic[1,2,3], Jeffrey R.Gulcher[4], Ferhat Meziani[3,5], Christiane Moog[1,3], Thomas W. Chittenden[4,30]*, Seiamak Bahram[1,2,3]*

La Covid-19 : une maladie immunologique complexe

Etude multiomique de 47 "Covid-19 sévères" chez des sujets < 50 ans sans facteur de risque versus 25 Covid non critiques et 22 témoins

- Whole-genome sequencing
- Whole-blood RNA sequency
- Plasma and blood mononuclear cells proteomes
- Cytokine profiling and high-throughput immunophenotyping

IA

Quantique

⚠ Excès d'activation des compartiments lymphoïdes et myéloïdes

⚠ Signature génomique avec une surexpression d'ADAM9

- Confirmée dans une cohorte de réplication
- Confirmée en transcriptomique et prolongée

La Covid-19 : une maladie immunologique complexe

ADAM 9 → ex vivo

- Impliqué dans la réplication de Sars-Cov2 dans les cellules épithéliales
- Impliqué dans des mécanismes immunopathologiques importants

ADAM9 enhances Th17 cell differentiation and autoimmunity by activating TGF-β1

Masataka Umeda[a,1], Nobuya Yoshida[a,1], Ryo Hisada[a], Catalina Burbano[a], Seo Yeon K. Orite[a], Michihito Kono[a], Vasileios C. Kyttaris[a], Suzanne Krishfield[a], Caroline A. Owen[b], and George C. Tsokos[a,2]

PNAS 2021 Vol. 118 No. 18 e2023230118

HIT ou VITT ?

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med. 2021 Jun 10;384(23):2254-2256.

EDITORIAL

SARS-CoV-2 Vaccine–Induced Immune Thrombotic Thrombocytopenia

Douglas B. Cines, M.D., and James B. Bussel, M.D.

HIT : heparin-induced thrombocytopenia
VITT : vaccine-induced thrombosis and thrombocytopenia

HIT ou VITT ?

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med. 2021 Jun 3;384(22):2124-2130.

BRIEF REPORT

Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination

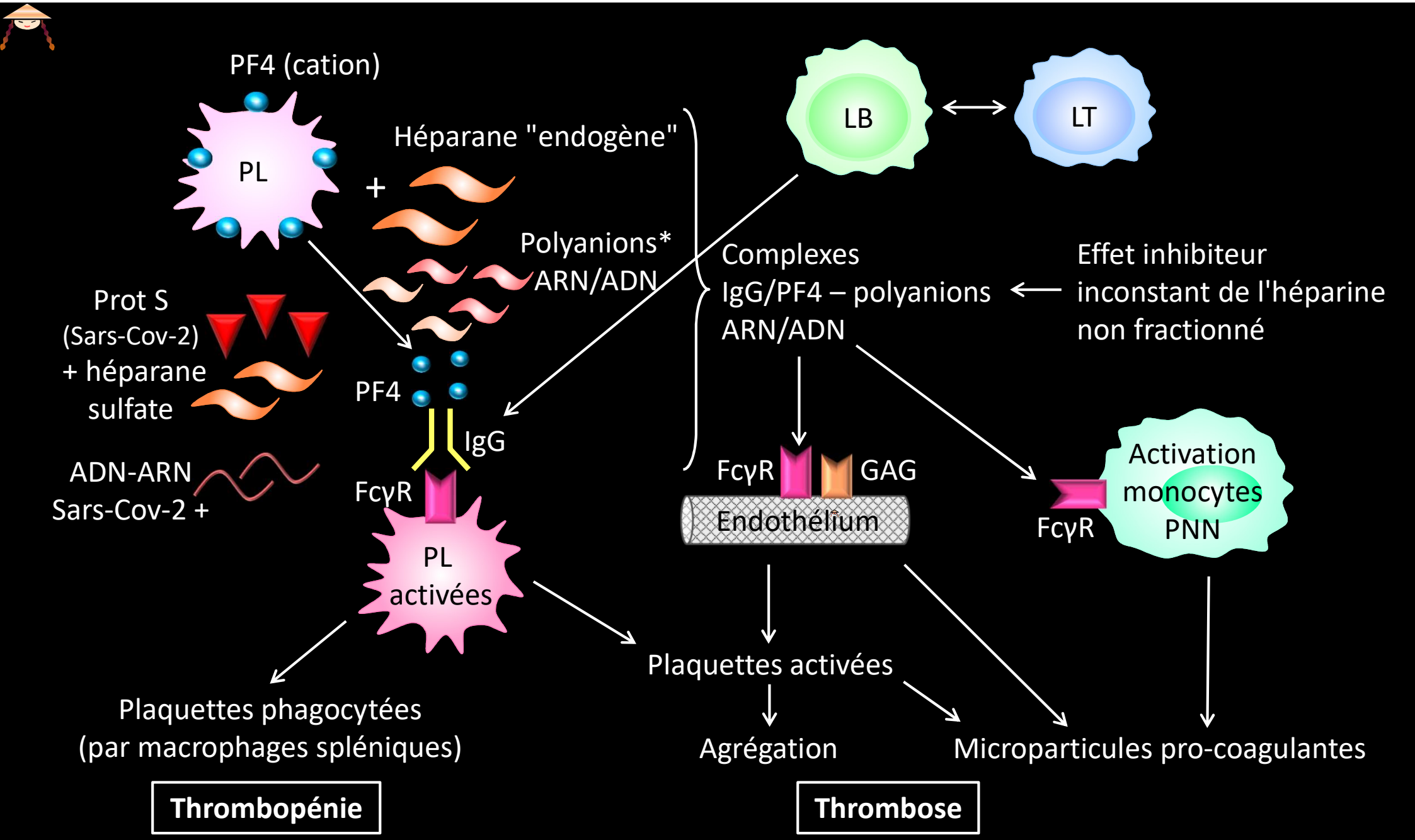
Nina H. Schultz, M.D., Ph.D., Ingvild H. Sørvoll, M.D., Annika E. Michelsen, Ph.D., Ludvig A. Munthe, M.D., Ph.D., Fridtjof Lund-Johansen, M.D., Ph.D., Maria T. Ahlen, Ph.D., Markus Wiedmann, M.D., Ph.D., Anne-Hege Aamodt, M.D., Ph.D., Thor H. Skattør, M.D., Geir E. Tjønnfjord, M.D., Ph.D., and Pål A. Holme, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med. 2021 Jun 3;384(22):2092-2101.

ORIGINAL ARTICLE

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination

Andreas Greinacher, M.D., Thomas Thiele, M.D., Theodore E. Warkentin, M.D., Karin Weisser, Ph.D., Paul A. Kyrle, M.D., and Sabine Eichinger, M.D.



Greinacher et al. N Engl J Med. 2021 (Online ahead of print).
Schultz et al. N Engl J Med. 2021 (Online ahead of print).
Yu et al. Blood 2020; 136 : 2080-9.
Jaax et al. Blood 2013; 122: 272–281.

* Médicaments polyanioniques : Pentosan, polysulfate, agent anti-angiogénique

Ann Intern Med. 2021 Oct;174(10):1468-1469.

Annals of Internal Medicine

EDITORIAL

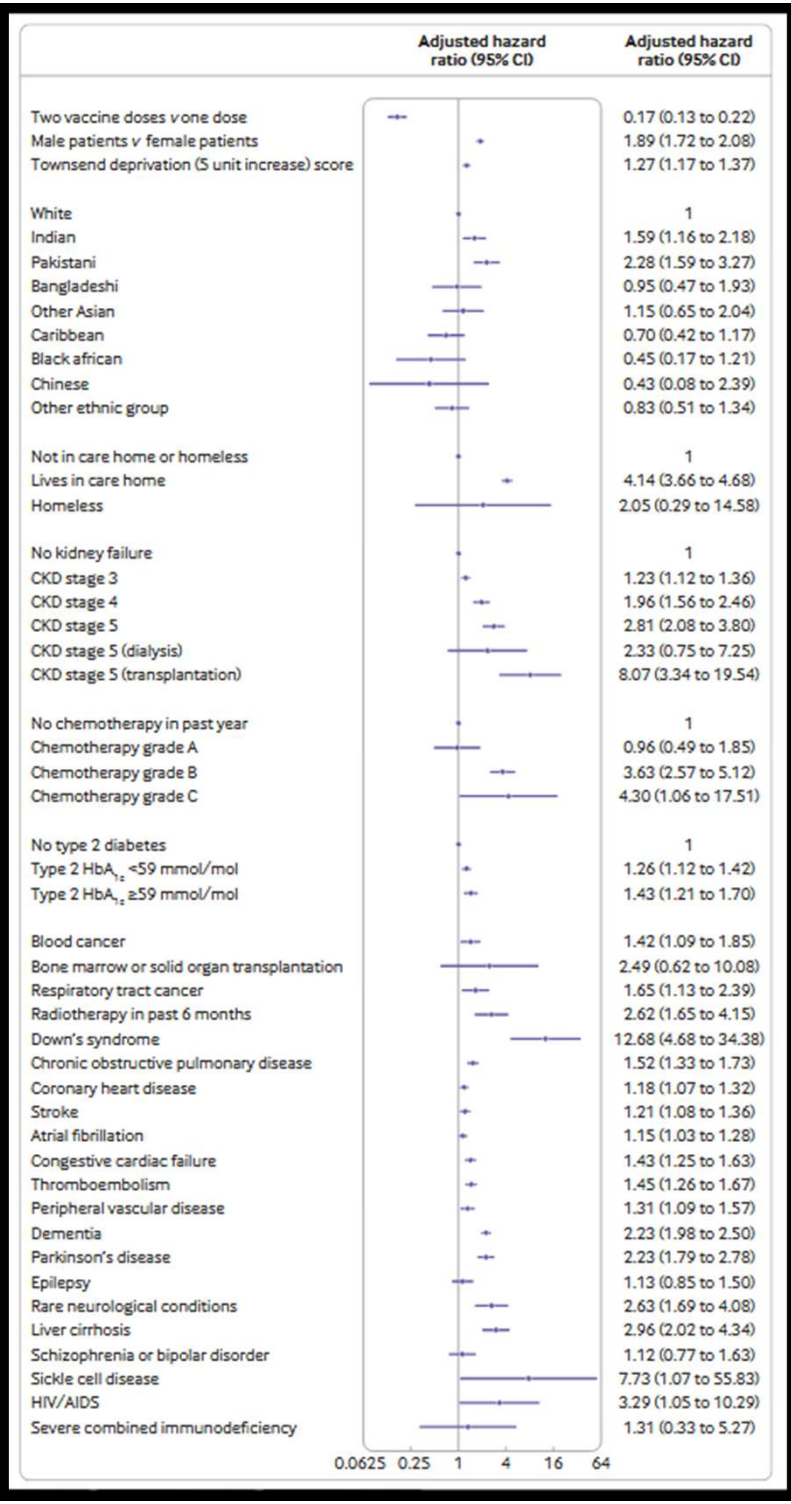
Thrombosis After Vaccination With Messenger RNA–1273: Is This Vaccine-Induced Thrombosis and Thrombocytopenia or Thrombosis With Thrombocytopenia Syndrome?

Allyson M. Pishko, MD
Adam Cuker, MD, MS

Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study

Julia Hippisley-Cox,[1] Carol AC Coupland,[1,2] Nisha Mehta,[3] Ruth H Keogh,[4] Karla Diaz-Ordaz,[4] Kamlesh Khunti,[5] Ronan A Lyons,[6] Frank Kee,[7] Aziz Sheikh,[8] Shamim Rahman,[9] Jonathan Valabhji,[10] Ewen M Harrison,[8] Peter Sellen,[9] Nazmus Haq,[9] Malcolm G Semple,[11] Peter W M Johnson,[10] Andrew Hayward,[12] Jonathan S Nguyen-Van-Tam[2,9]

| *BMJ* 2021;374:n2244



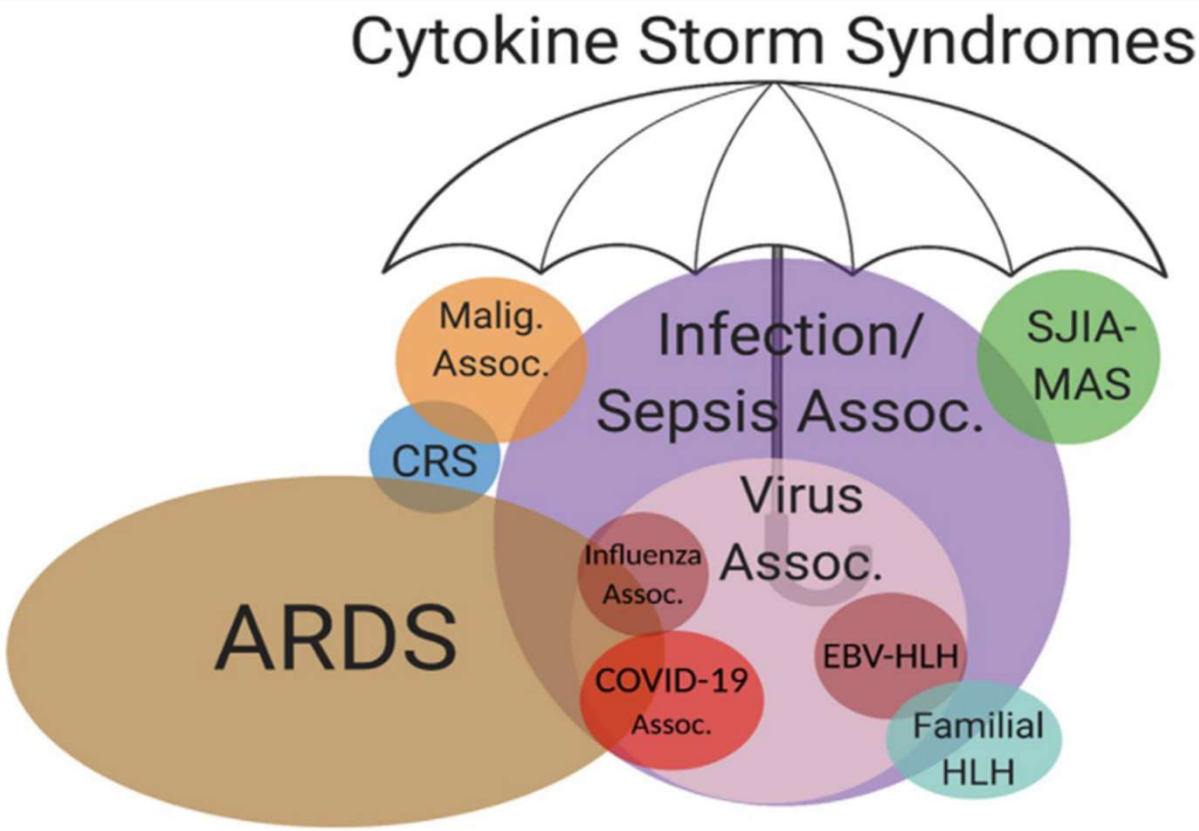
Arthritis & Rheumatology
Vol. 72, No. 7, July 2020, pp 1059–1063
DOI 10.1002/art.41285
© 2020, American College of Rheumatology

American College of Rheumatology
Empowering Rheumatology Professionals

NOTES FROM THE FIELD

On the Alert for Cytokine Storm: Immunopathology in COVID-19

Lauren A. Henderson,[1] Scott W. Canna,[2] Grant S. Schulert,[3] Stefano Volpi,[4] Pui Y. Lee,[1] Kate F. Kernan,[2] Roberto Caricchio,[5] Shawn Mahmud,[6] Melissa M. Hazen,[1] Olha Halyabar,[1] Kacie J. Hoyt,[1] Joseph Han,[7] Alexei A. Grom,[3] Marco Gattorno,[4] Angelo Ravelli,[8] Fabrizio De Benedetti,[9] Edward M. Behrens,[10] Randy Q. Cron,[11] and Peter A. Nigrovic[12]



PIMS ou KAWA ?

PIMS : Paediatric Inflammatory Multisystem Syndrome
ou MIS-C : Multisystem inflammatory syndrome in children

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med. 2020 Jul 23;383(4):347-358.

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in Children in New York State

Elizabeth M. Dufort, M.D., Emilia H. Koumans, M.D., M.P.H., Eric J. Chow, M.D., M.P.H., Elizabeth M. Rosenthal, M.P.H., Alison Muse, M.P.H., Jemma Rowlands, M.P.H., Meredith A. Barranco, M.P.H., Angela M. Maxted, D.V.M., Ph.D., Eli S. Rosenberg, Ph.D., Delia Easton, Ph.D., Tomoko Udo, Ph.D., Jessica Kumar, D.O., Wendy Pulver, M.S., Lou Smith, M.D., Brad Hutton, M.P.H., Debra Blog, M.D., M.P.H., and Howard Zucker, M.D., for the New York State and Centers for Disease Control and Prevention Multisystem Inflammatory Syndrome in Children Investigation Team*

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med. 2020 Jul 23;383(4):334-346.

ORIGINAL ARTICLE

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

L.R. Feldstein, E.B. Rose, S.M. Horwitz, J.P. Collins, M.M. Newhams, M.B.F. Son, J.W. Newburger, L.C. Kleinman, S.M. Heidemann, A.A. Martin, A.R. Singh, S. Li, K.M. Tarquinio, P. Jaggi, M.E. Oster, S.P. Zackai, J. Gillen, A.J. Ratner, R.F. Walsh, J.C. Fitzgerald, M.A. Keenaghan, H. Alharash, S. Doymaz, K.N. Clouser, J.S. Giuliano, Jr., A. Gupta, R.M. Parker, A.B. Maddux, V. Havalad, S. Ramsingh, H. Bukulmez, T.T. Bradford, L.S. Smith, M.W. Tenforde, C.L. Carroll, B.J. Riggs, S.J. Gertz, A. Daube, A. Lansell, A. Coronado Munoz, C.V. Hobbs, K.L. Marohn, N.B. Halasa, M.M. Patel, and A.G. Randolph, for the Overcoming COVID-19 Investigators and the CDC COVID-19 Response Team*

An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study

Lancet 2020; 395: 1771–78

Lucio Verdoni, Angelo Mazza, Annalisa Gervasoni, Laura Martelli, Maurizio Ruggeri, Matteo Ciuffreda, Ezio Bonanomi, Lorenzo D'Antiga

Le PIMS

- **En France : 727 cas (sept 2021)**
  ⚠️ 44.6 cas/millions d'enfants de < 18 ans
- **Age médian : 7 ans (25% ≤ 4 ans) – surtout 4-11 ans**
- **Suivi 4 à 6 semaines après l'infection**
- **Surtout des garçons – origine africaine et hispanique**
- **Tableau "systémique" :**
  - T° : 39-40°C (≈ des cas)
  - AEG, asthénie, hypoTA, choc
  - Signes digestifs (douleurs, diarrhée)
  - Irritation conjonctivales, glossite, chéléite
  - Éruption, prurit, œdème souvent palmo-plantaire avec parfois une desquamation
  - Myocardite et parfois péricardite
  - Signes neurologiques et respiratoires inconstants

PIMS ou KAWA ?

- **PIMS : des différences**
  - → plus âgé
  - → plus grande fréquence des sujets africains
  - → plus de myocardite et des signes digestifs et systémiques
  - → plus d'inflammation (CRP↗↗, PNN↗↗↗)

The Journal of Clinical Investigation RESEARCH ARTICLE
J Clin Invest. 2021 Mar 15;131(6):e144554.

Similarities and differences between the immunopathogenesis of COVID-19–related pediatric multisystem inflammatory syndrome and Kawasaki disease

Ana Esteve-Sole,[1,2,3] Jordi Anton,[3,4,5] Rosa Maria Pino-Ramirez,[6] Judith Sanchez-Manubens,[3,5,7] Victoria Fumadó,[3,4,8] Claudia Fortuny,[3,4,8,9,10] María Rios-Barnes,[8] Joan Sanchez-de-Toledo,[3,11,12] Mónica Girona-Alarcón,[13] Juan Manuel Mosquera,[3,5] Silvia Ricart,[4,6] Cristian Launes,[3,4,6,9] Mariona Fernández de Sevilla,[6,9] Cristina Jou,[3,14,15] Carmen Muñoz-Almagro,[3,9,16,17] Eva González-Roca,[18,19] Andrea Vergara,[18,20] Jorge Carrillo,[21] Manel Juan,[2,4,19] Daniel Cuadras,[3,22] Antoni Noguera-Julian,[3,4,8,9,10] Iolanda Jordan,[3,4,9,13] and Laia Alsina[1,2,3,4]

⚠ Profil cytokinique comparable avec une réponse IFNγ (IFNγ, IL-18 et IP10) et monocytaire (MCP-1, IL-1α, IL-1RA) avec un sous-groupe de PIMS avec une réponse immunitaire (IFNγ, IL-18, GM-CSF, IP10, IL-12 et SDF-1 plus élevés avec une part d'activation macrophagique)

PIMS ou KAWA ?

Med
Volume 2, Issue 9, 10 September 2021, Pages 1072-1092.e7
CellPress

Clinical and Translational Article

A monocyte/dendritic cell molecular signature of SARS-CoV-2-related multisystem inflammatory syndrome in children with severe myocarditis

Camille de Cevins [1, 2], Marine Luka [1, 3, 30], Nikaïa Smith [4, 30], Sonia Meynier [5, 30], Aude Magérus [5, 30], Francesco Carbone [1, 3, 31], Víctor García-Paredes [1, 3, 31], Laura Barnabei [5, 31], Maxime Batignes [1], Alexandre Boullé [1], Marie-Claude Stolzenberg [5], Brieuc P. Pérot [1], Bruno Charbit [6], Tinhinane Fali [1], Vithura Pirabakaran [5], Boris Sorin [5], Quentin Riller [5], Ghaith Abdessalem [1] ... Mickaël M. Ménager [1, 3, 32, 33]

- 30 PIMS dont 21 myocardites
- 13 KAWA non Sars-Cov2
- Contrôles

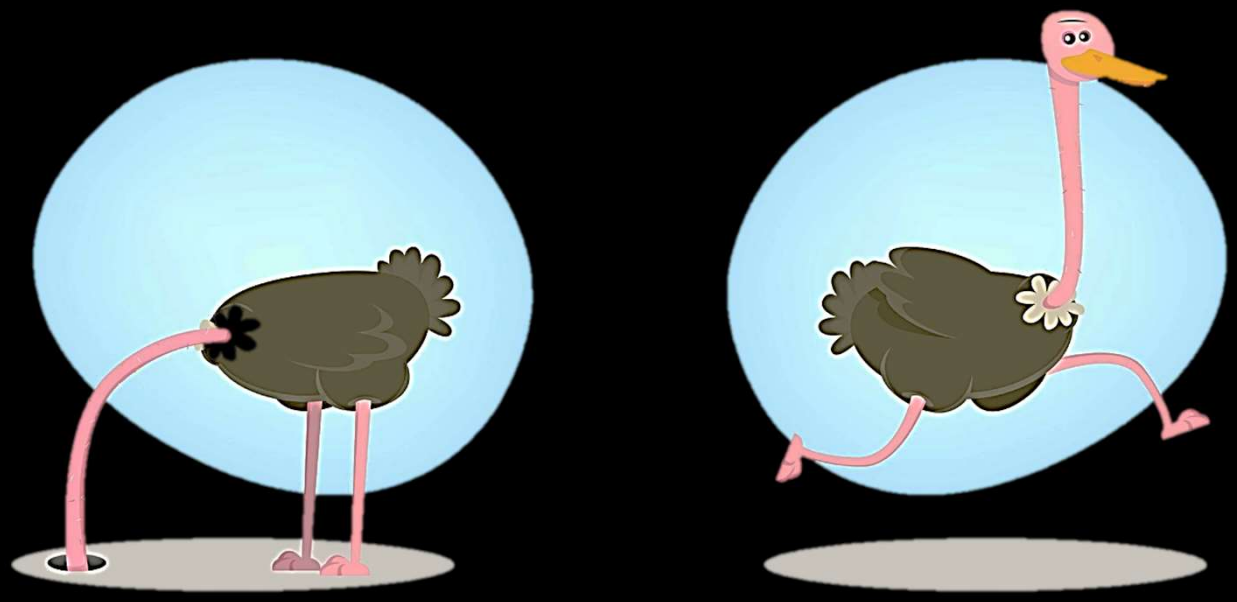
} Etudes cytokiniques immunophénotypiques et transcriptomiques

⚠ Myocardites "signature de 25 gènes monocytaires"

→ Défaut d'inhibition de la voie NF-KB
→ Surproduction de TNF
→ Défaut de réponse aux IFN type 1 et 2

Syndrome post-Covid "hit and hide" ou "hit and run"

- Les "séquelles" inactives
- Les lésions "post-infectieuses"
  - → avec une infection persistante "hit and hide"
  - → avec une réponse immunitaire "hit and run"
    - ⚠ Auto-immunisation ?

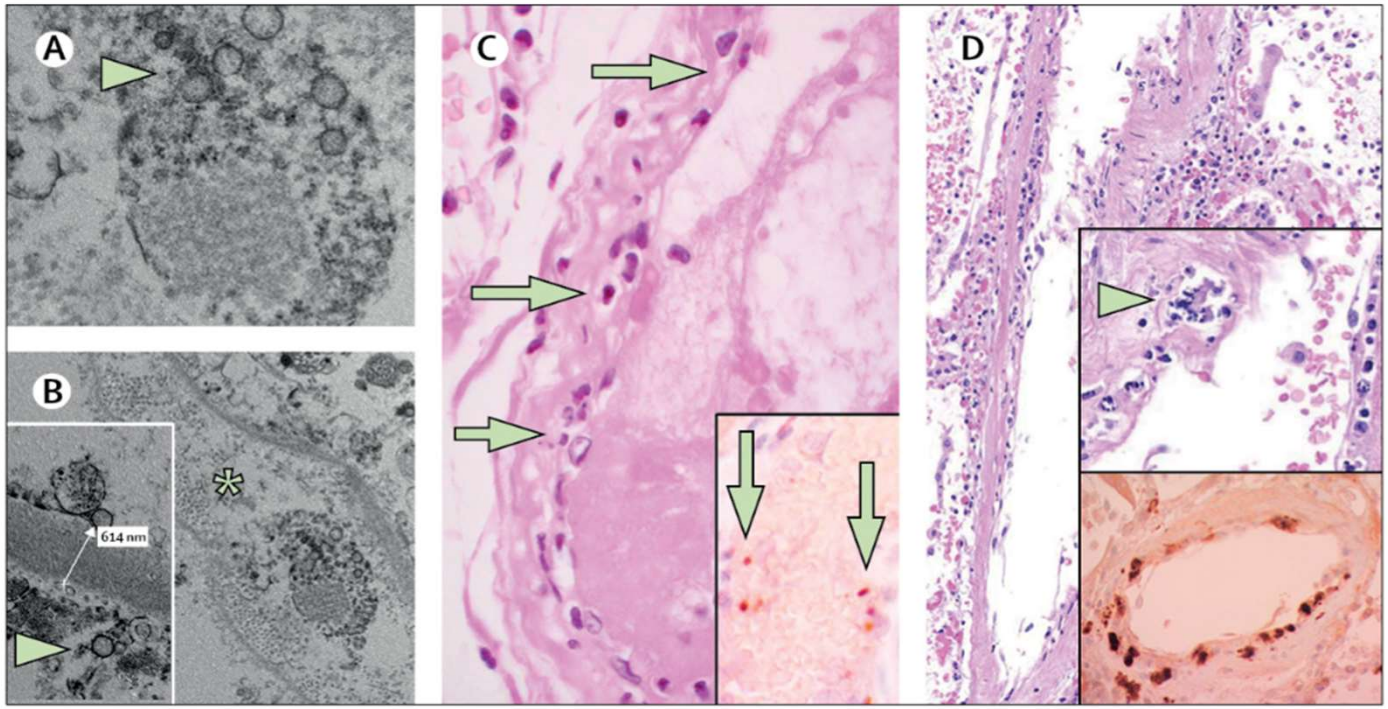


Syndrome post-Covid :
le "poids" de l'endothélite et de ses conséquences

Lancet. 2020 2-8 May; 395(10234): 1417–1418.
Published online 2020 Apr 21. doi: 10.1016/S0140-6736(20)30937-5
PMCID: PMC7172722
PMID: 32325026

Endothelial cell infection and endotheliitis in COVID-19

Zsuzsanna Varga,[a] Andreas J Flammer,[b] Peter Steiger,[c] Martina Haberecker,[a] Rea Andermatt,[c] Annelies S Zinkernagel,[d] Mandeep R Mehra,[e] Reto A Schuepbach,[c] Frank Ruschitzka,[b] and Holger Moch[a]



A-B : ME : inclusion virale dans l'espace péritubulaire et les cellules endothéliales des capillaires glomérulaires
C : coloration HE d'intestin grêle réséqué pour une ischémie mésentérique avec un infiltrat mononucléaire de l'intima des vaisseaux
D : coloration HE d'un poumon avec un infiltrat mononucléaire d'un vaisseau (marquage caspase 3 (apoptose) des monocytes et cellules endothéliales)

Syndrome post-Covid :
le "poids" de l'endothélite et de ses conséquences

ARTICLES
https://doi.org/10.1038/s41593-021-00926-1

nature neuroscience

VOL 24 | NOVEMBER 2021 | 1522–1533 | Check for updates

OPEN

The SARS-CoV-2 main protease M^{pro} causes microvascular brain pathology by cleaving NEMO in brain endothelial cells

Jan Wenzel[1,2,24], Josephine Lampe[1,2,24], Helge Müller-Fielitz[1,24], Raphael Schuster[1], Marietta Zille[1,2], Kristin Müller[1], Markus Krohn[1,2], Jakob Körbelin[3], Linlin Zhang[4,5], Ümit Özorhan[1,2], Vanessa Neve[1], Julian U. G. Wagner[2,6], Denisa Bojkova[7], Mariana Shumliakivska[6], Yun Jiang[1], Anke Fähnrich[8,9], Fabian Ott[8,9], Valentin Sencio[10], Cyril Robil[10], Susanne Pfefferle[11], Florent Sauve[12], Caio Fernando Ferreira Coêlho[12], Jonas Franz[13,14,15], Frauke Spiecker[1], Beate Lembrich[1], Sonja Binder[1], Nina Feller[1,2], Peter König[16,17], Hauke Busch[8,9], Ludovic Collin[18], Roberto Villaseñor[18], Olaf Jöhren[1], Hermann C. Altmeppen[19], Manolis Pasparakis[20], Stefanie Dimmeler[2,6], Jindrich Cinatl[7], Klaus Püschel[21], Matija Zelic[22], Dimitry Ofengeim[22], Christine Stadelmann[13], François Trottein[10], Ruben Nogueiras[23], Rolf Hilgenfeld[4,5], Markus Glatzel[19], Vincent Prevot[12] and Markus Schwaninger[1,2] ✉

Syndrome post-Covid :
le "poids" de l'endothélite et de ses conséquences

Nat Rev Rheumatol. 2021 Jun;17(6):315-332.

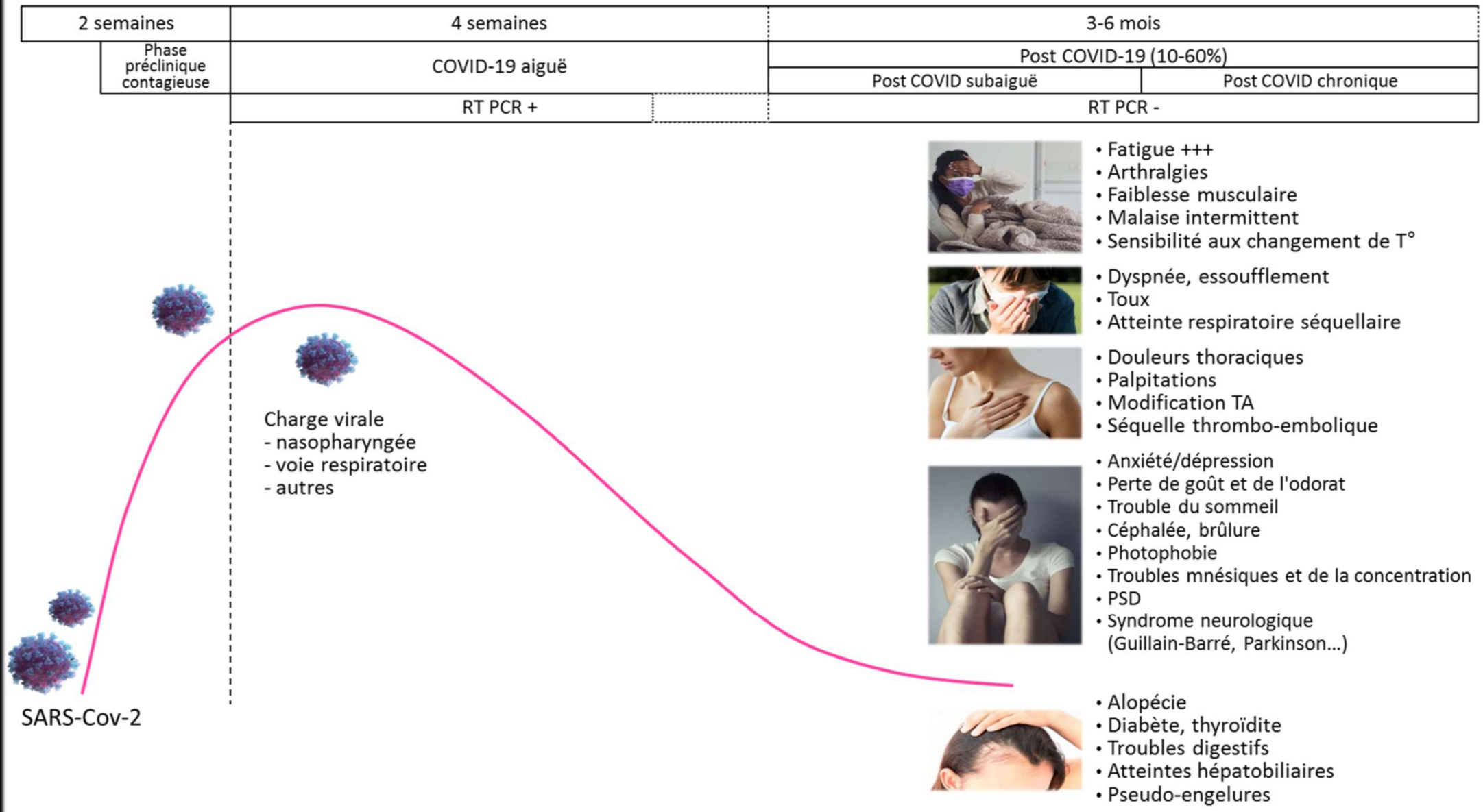
REVIEWS

Check for updates

Systemic and organ-specific immune-related manifestations of COVID-19

Manuel Ramos-Casals[1,2], *Pilar Brito-Zerón*[3] *and Xavier Mariette*[4]

Les manifestations post-Covid



D'après Nalbandian et al. Nat Med 2021

Syndrome post-Covid : quid des phénomènes d'auto-immunisation ?

Des homologies d'épitopes entre Sars-Cov2 et des auto-anticorps ?

antibodies
Antibodies (Basel). 2020 Jul 16;9(3):33.
MDPI

Article

From Anti-SARS-CoV-2 Immune Responses to COVID-19 via Molecular Mimicry

Darja Kanduc
Department of Biosciences, Biotechnologies, and Biopharmaceutics, University of Bari, 70125 Bari, Italy; dkanduc@gmail.com

SARS-CoV-2 epitopes with sequences shared with human proteins marked in capital letters.

A [1]	B [2]	C [3]	A [1]	B [2]	C [3]
956	N	AEGSRGGSQA	37,515	N	lLLLDRLNql
999	S	aeiRASANLA	37,544	S	lLLQYGSfc
1220	S	aevqidrli	37,583	orf1b	Llmpiltlt
1221	S	aevqidrlit	37,724	S	LLQYGSfct
1349	ORF7b	AFLLFLVLI	37,766	orf1a	LLSAGIFGA
1350	ORF7b	AFLLFLVLIMLIIFw	38,043	orf1b	Lmierfvsl
1946	orf1a	AIILASFSA	38,353	S	lntLVKQLSSNFGAi
2027	orf1b	aimtrclav	38,831	S	LQDVVNQNAQALNTL
2431	N	ALALLLLDr	38,855	S	Lqipfamqm
2682	orf1b	ALLADKfpv	38,874	orf1b	LQLGFSTGv
2801	S	alntlvkql	38,881	N	LQLPQGttl
2802	N	ALNTPKdhi	38,990	S	lqslqtyvtQQLIRA
2855	orf1a	aLRANSAvk	39,003	S	lqtyvtQQLIRAAEI
2998	orf1a	alweiqqvv	39,576	N	Lsprwyfyy
3589	S	aphgvvflhv	40,459	orf1b	LVLSVNpyv
3810	N	APSASAFFgm	40,677	M	Lwllwpvtl
3939	S	aQALNTLvk	40,685	M	lWPVTLAcf
3956	N	AQFAPSASA	41,962	ORF7b	mLIIFWFSL
3982	S	aqkfnGLTVLPPLLT	42,093	orf1b	Mlwckdghv
4307	N	asaffgmsr	42,128	orf1b	Mmisagfsl
4321	S	ASANLAATk	42,260	orf1a	Mpaswvmri
4936	N	ATEGALNTPK	42,648	N	msriGMEVTPSGTWl
5149	M	aTSRTLSYY	42,873	S	mTSCCSCLk
5150	M	aTSRTLSYYK	42,972	orf1b	mvMCGGSLyv
5209	orf1b	ATVVIGtsk	43,024	M	mwSFNPETni
5447	orf1a	AVLQSGFRK	44,501	N	nkhidayktFPPTEP
5908	S	ayrfngiGVTQNVly	44,814	S	nlnESLIDL
6184	ORF7a	celyhyqecv	44,913	M	nlVIGFLFL
6668	S	cmTSCCSCLk	60,380	N	sQASSRSSSR

[1] A: Epitopes listed as IEDB ID number and detailed at IEDB [16]. [2] B: SARS-CoV-2 proteins [18]. [3] C: Hexapeptides shared with human proteins are given in capital letters.

Syndrome post-Covid : quid des phénomènes d'auto-immunisation ?

RHEUMATOLOGY ADVANCES IN PRACTICE

Rheumatology Advances in Practice 2021;00:1–14
doi:10.1093/rap/rkaa081

Review

Anti-phospholipid syndrome and COVID-19 thrombosis: connecting the dots

Moon Ley Tung [1,2,*], Bryce Tan[3], Robin Cherian[2,4] and Bharatendu Chandra[2,5,*]

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Distinct Autoimmune Antibody Signatures Between Hospitalized Acute COVID-19 Patients, SARS-CoV-2 Convalescent Individuals, and Unexposed Pre-Pandemic Controls

Nahid Bhadelia, Anna C. Belkina, Alex Olson, Thomas Winters, Patricia Urick, Nina Lin, Ian Rifkin, Yachana Kataria, Rachel R. Yuen, Manish Sagar, Jennifer E. Snyder-Cappione

doi: https://doi.org/10.1101/2021.01.21.21249176

RESEARCH ARTICLE

PLoS One. 2021 Sep 3;16(9):e0257016.

Development of ACE2 autoantibodies after SARS-CoV-2 infection

John M. Arthur[1,2☯*], J. Craig Forrest[3,4,5☯], Karl W. Boehme[3,4,5☯], Joshua L. Kennedy[4,6], Shana Owens[3], Christian Herzog[1], Juan Liu[7], Terry O. Harville[1,7☯]

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Article

Nature | Vol 595 | 8 July 2021 | 283

Diverse functional autoantibodies in patients with COVID-19

https://doi.org/10.1038/s41586-021-03631-y

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Published online: 19 May 2021

Check for updates

Eric Y. Wang[1,16], Tianyang Mao[1,16], Jon Klein[1,16], Yile Dai[1,16], John D. Huck[1], Jillian R. Jaycox[1], Feimei Liu[1], Ting Zhou[1], Benjamin Israelow[1], Patrick Wong[1], Andreas Coppi[2], Carolina Lucas[1], Julio Silva[1], Ji Eun Oh[1], Eric Song[1], Emily S. Perotti[1], Neil S. Zheng[1], Suzanne Fischer[1], Melissa Campbell[3], John B. Fournier[3], Anne L. Wyllie[4], Chantal B. F. Vogels[4], Isabel M. Ott[4], Chaney C. Kalinich[4], Mary E. Petrone[4], Anne E. Watkins[4], Yale IMPACT Team*, Charles Dela Cruz[5], Shelli F. Farhadian[3], Wade L. Schulz[2,6], Shuangge Ma[7], Nathan D. Grubaugh[4], Albert I. Ko[3,4], Akiko Iwasaki[1,4,8] & Aaron M. Ring[1,9]

Syndrome post-Covid : quid des phénomènes d'auto-immunisation ?

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CORONAVIRUS

Sci Transl Med. 2020 Nov 18;12(570):eabd3876.

Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19

Yu Zuo[1], Shanea K. Estes[1], Ramadan A. Ali[1], Alex A. Gandhi[1], Srilakshmi Yalavarthi[1], Hui Shi[1,2], Gautam Sule[1], Kelsey Gockman[1], Jacqueline A. Madison[1], Melanie Zuo[3], Vinita Yadav[4], Jintao Wang[5], Wrenn Woodard[6], Sean P. Lezak[6], Njira L. Lugogo[7], Stephanie A. Smith[8], James H. Morrissey[8], Yogendra Kanthi[4,5]*, Jason S. Knight[1]*

SN Comprehensive Clinical Medicine
https://doi.org/10.1007/s42399-020-00521-8

SN Compr Clin Med. 2020 Sep 19;1-11.

COVID-19

Immune Thrombocytopenia Secondary to COVID-19: a Systematic Review

Sukrita Bhattacharjee[1] · Mainak Banerjee[2]

ELSEVIER

Journal of Translational Autoimmunity
Volume 4, 2021, 100100

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]

frontiers in Medicine

CASE REPORT
published: 18 November 2021
doi: 10.3389/fmed.2021.754667

Case Report: Neutralization of Autoantibodies Targeting G-Protein-Coupled Receptors Improves Capillary Impairment and Fatigue Symptoms After COVID-19 Infection

Bettina Hohberger[1†], Thomas Harrer[2,3†], Christian Mardin[1†], Friedrich Kruse[1†], Jakob Hoffmanns[1†], Lennart Rogge[1†], Felix Heltmann[1†], Michael Moritz[1†], Charlotte Szewczykowski[1†], Julia Schottenhamml[1†], Martin Kräter[2,3†], Antonio Bergua[1†], Matthias Zenkel[1†], Andreas Gießl[1†], Ursula Schlötzer-Schrehardt[1†], Robert Lämmer[1†], Martin Herrmann[2,3†], Annekathrin Haberland[4†], Peter Göttel[4†], Johannes Müller[4†] and Gerd Wallukat[4†]*

EUROPEAN RESPIRATORY JOURNAL
RESEARCH LETTER
M. ZUNIGA ET AL.

Autoimmunity to annexin A2 predicts mortality among hospitalised COVID-19 patients

Eur Respir J. 2021 Oct 21;58(4):2100918.

Syndrome post-Covid… rien n'est simple !

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

Check for updates

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

JAMA Internal Medicine | Original Investigation

JAMA Intern Med. 2021 Nov 8;e216454.

Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results With Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic

Joane Matta, PhD; Emmanuel Wiernik, PhD; Olivier Robineau, MD, PhD; Fabrice Carrat, MD, PhD; Mathilde Touvier, PhD; Gianluca Severi, PhD; Xavier de Lamballerie, MD, PhD; Hélène Blanché, PhD; Jean-François Deleuze, PhD; Clément Gouraud, MD, MSc; Nicolas Hoertel, MD, PhD; Brigitte Ranque, MD, PhD; Marcel Goldberg, MD, PhD; Marie Zins, MD, PhD; Cédric Lemogne, MD, PhD; for the Santé, Pratiques, Relations et Inégalités Sociales en Population Générale Pendant la Crise COVID-19–Sérologie (SAPRIS-SERO) Study Group