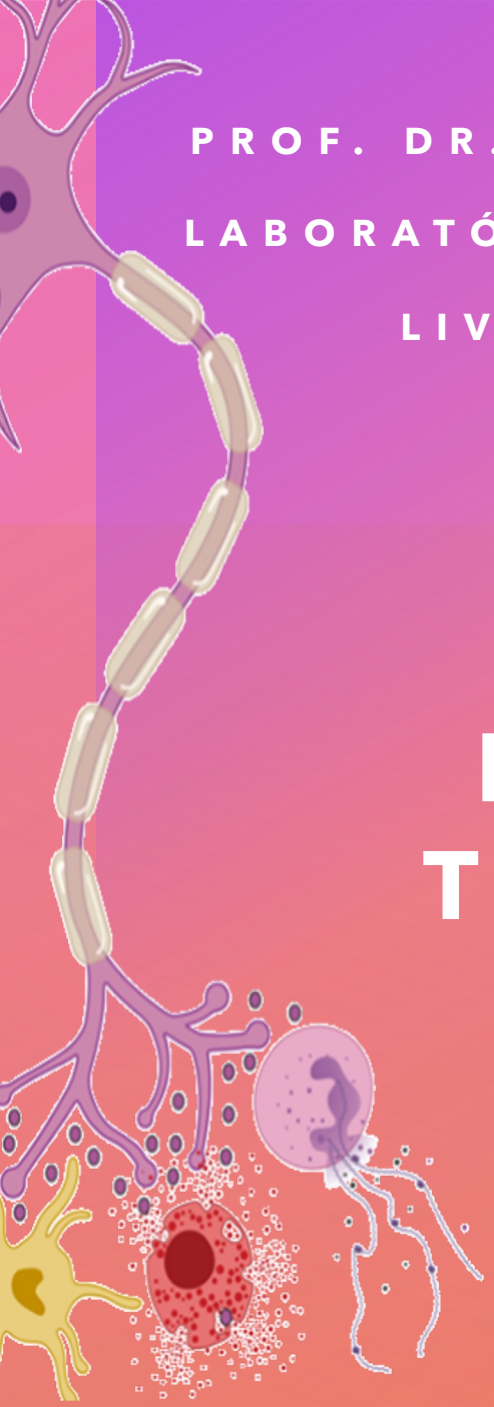
PROF. DR. JEAN PIERRE SCHATZMANN PERON

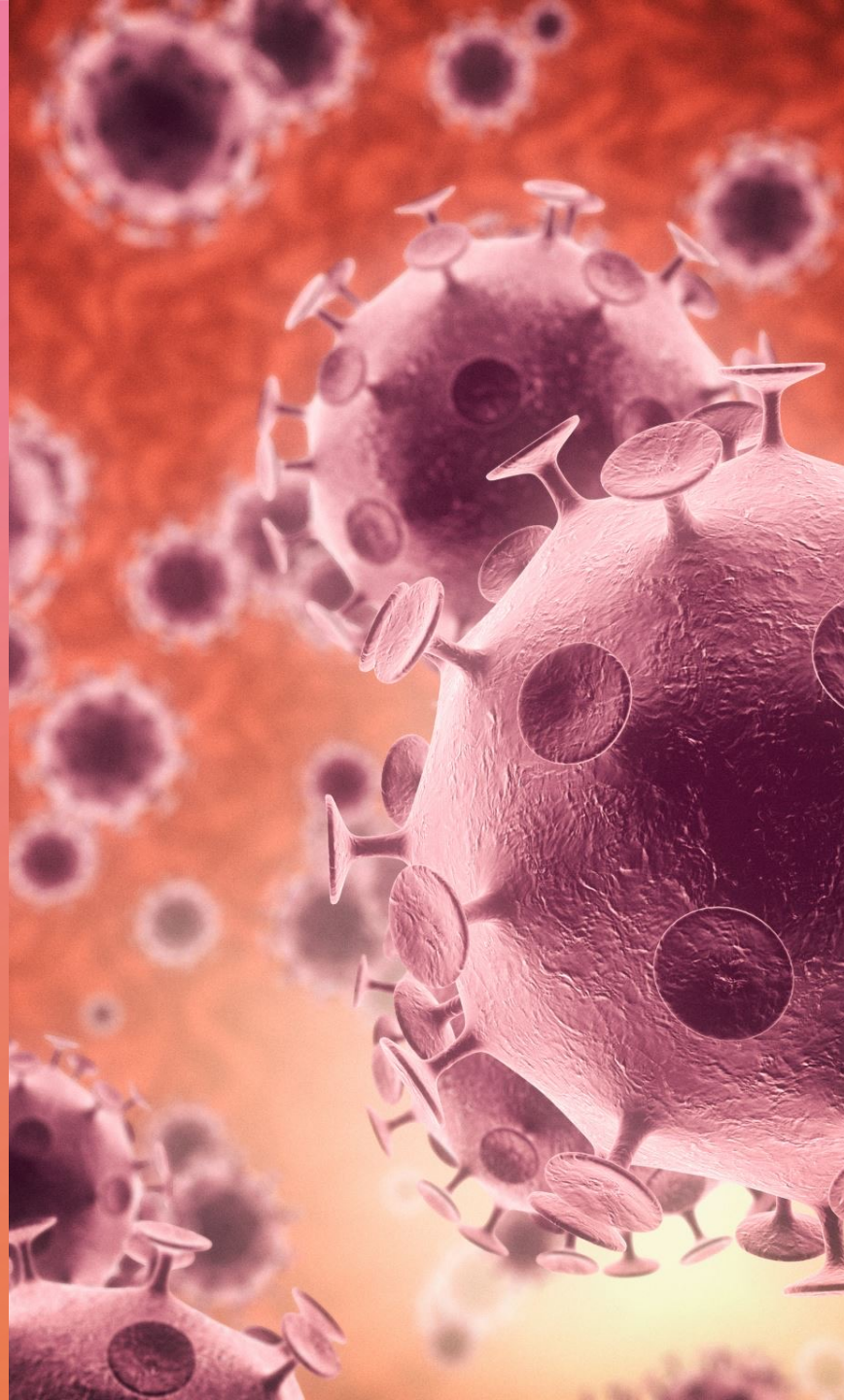
LABORATÓRIO DE INTERAÇÕES NEUROIMUNES

LIVRE-DOCENTE DEPARTAMENTO

IMUNOLOGIA- USP

COVID-19: PATOGÊNESE TRATAMENTOS E VACINAS





Laboratory of Neuroimmunology of Arboviruses

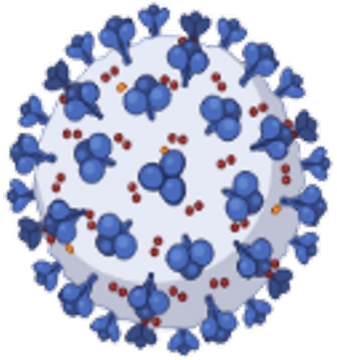
DEPARTAMENTO DE Imunologia
INSTITUTO DE CIÊNCIAS BIOMÉDICAS | USP

Institut Pasteur USP
Scientific Platform Pasteur USP

Laboratório de Interações Neuroimunes

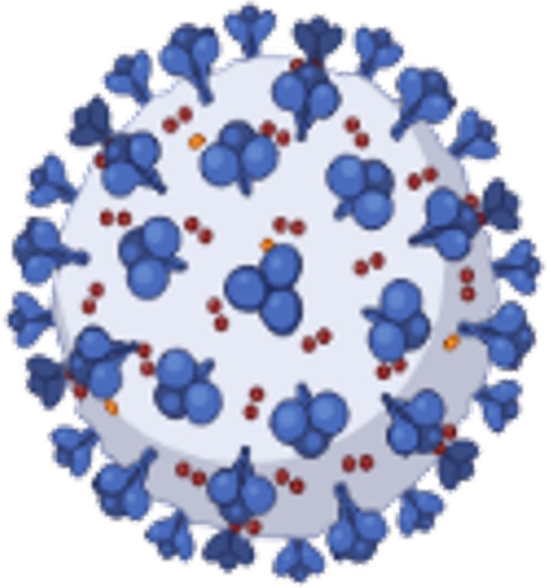
Neuroimmune Interactions Laboratory

OBJETIVOS

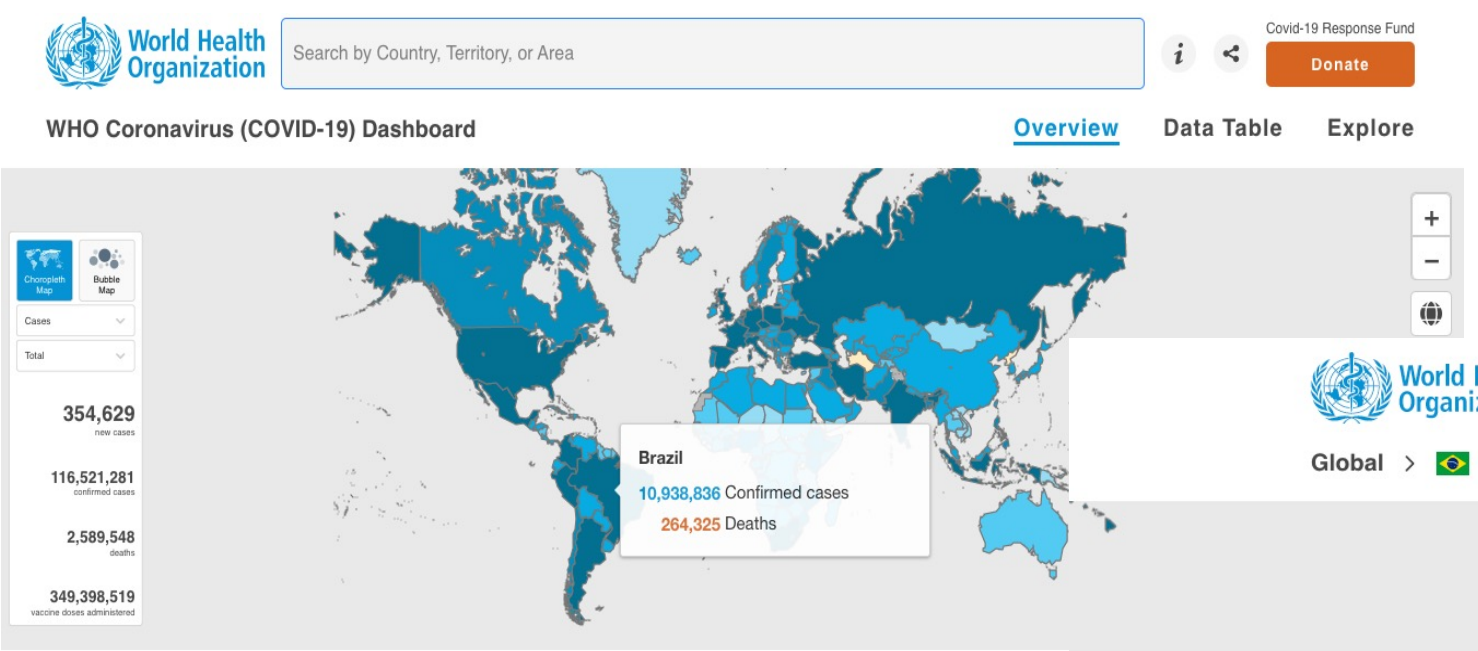


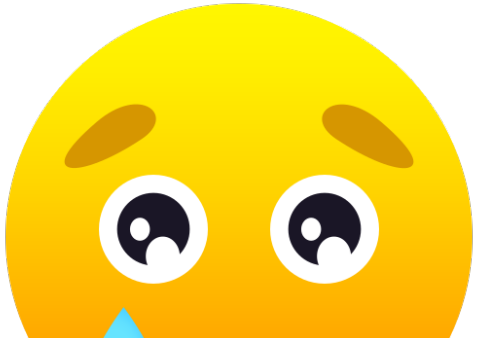
- Resposta imune inata
  - Receptores de padrão – TLRs, NLRs, inflamassomas...
- Resposta imune adaptativa
  - Linfócitos T e Linfócitos T, anticorpos neutrlizantes, CD8 citotóxicos
- Imunopatogênese
  - *Cytokine storm,* imunocomplexos, coagulopatia.

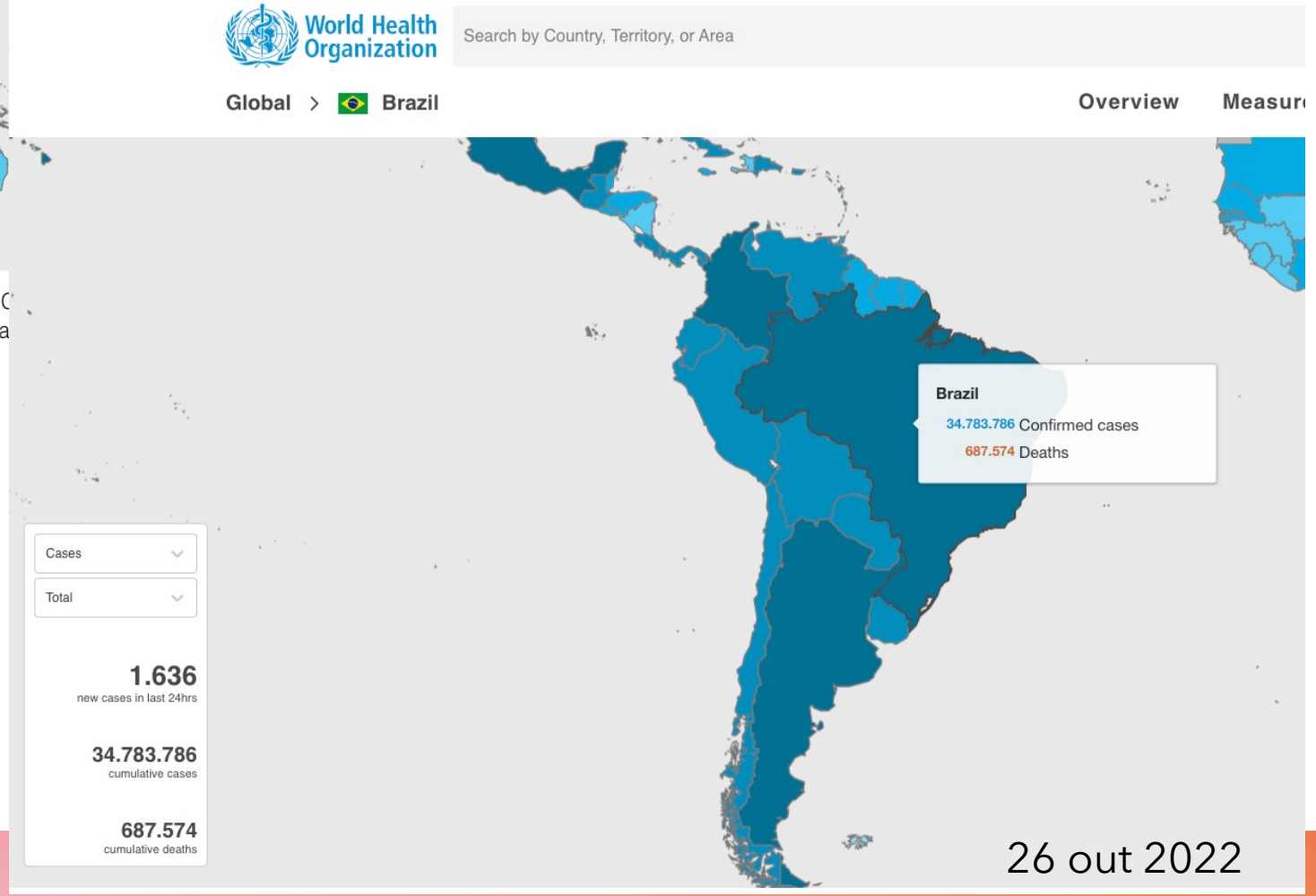
OBJETIVOS



- Tratamentos –
  - Diretos e Indiretos
  - Diretos: Anti-virais
  - Indiretos: Paliativos – glicocorticóides, anti-coagulantes, mAbs.
- Vacinas
  - Quais são os tipos de vacinas ?
  - Qual a resposta imune que elas desencadeiam?
  - O que são variantes de escape?







Globally, as of **6:02pm CET, 8 March 2021**, there have been **116.521.281 confirmed cases** of C
deaths, reported to WHO. As of **8 March 2021**, a total of **349.398.519 vaccine doses** ha

26 out 2022

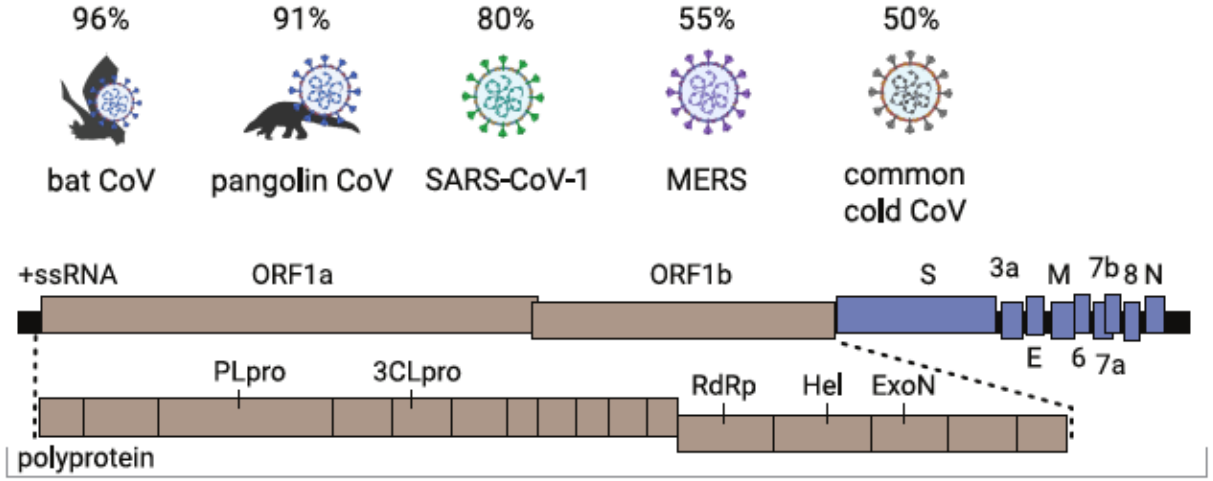
SARS-CoV-2 (COVID-19) by the numbers

Yinon M. Bar-On[1], Avi Flamholz[2], Rob Phillips[3,4], and Ron Milo[1*]
[1]Weizmann Intitute of Science, Rehovot 7610001, Israel [2]University of California, Berkeley, CA 94720, USA
[3]California Institute of Technology, Pasadena, CA 91125, USA [4]Chan Zuckerberg Biohub, San Francisco, CA 94158, USA
*Corresponding author: ron.milo@weizmann.ac.il.
Comments are welcome; this article is being updated on an ongoing basis at: https://bit.ly/2WOeN64

eLife
published in eLife, March 31st, 2020
https://elifesciences.org/articles/57309

Genome

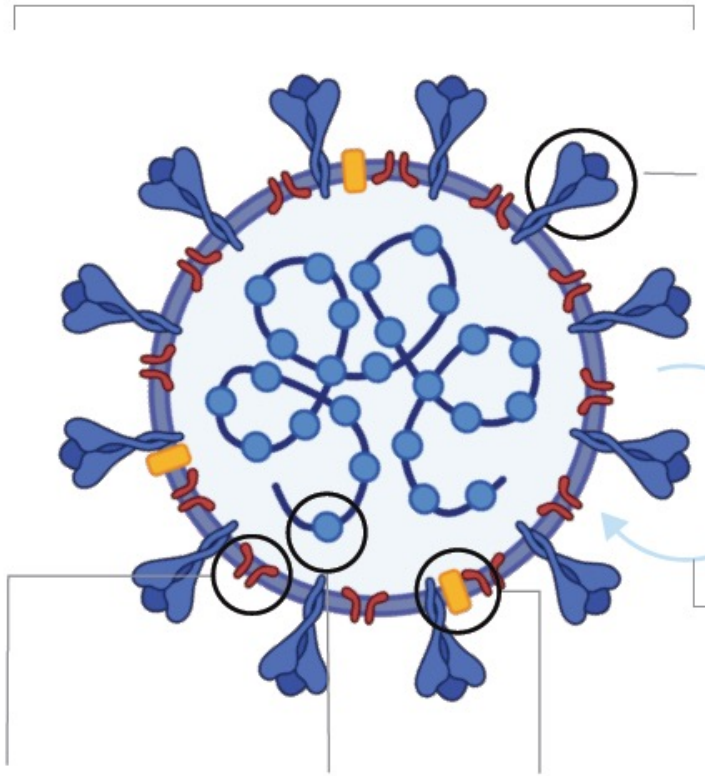
Nucleotide identity to SARS-CoV-2



Length: ≈30kb; β-coronavirus with 10-14 ORFs (24-27 proteins)

Size & Content

Diameter: ≈100 nm
Volume: ~10^6 nm^3 = 10^{-3} fL
Mass: ~10^3 MDa ≈ 1 fg



Spike trimer
Length: ≈10 nm
Copies per virion: ≈100
(300 monomers, measured for SARS-CoV-1)
Affinity to ACE2 receptor K_d: ≈1-30 nM
primed by TMPRSS2

Membrane protein
≈2000 copies
(measured for SARS-CoV-1)

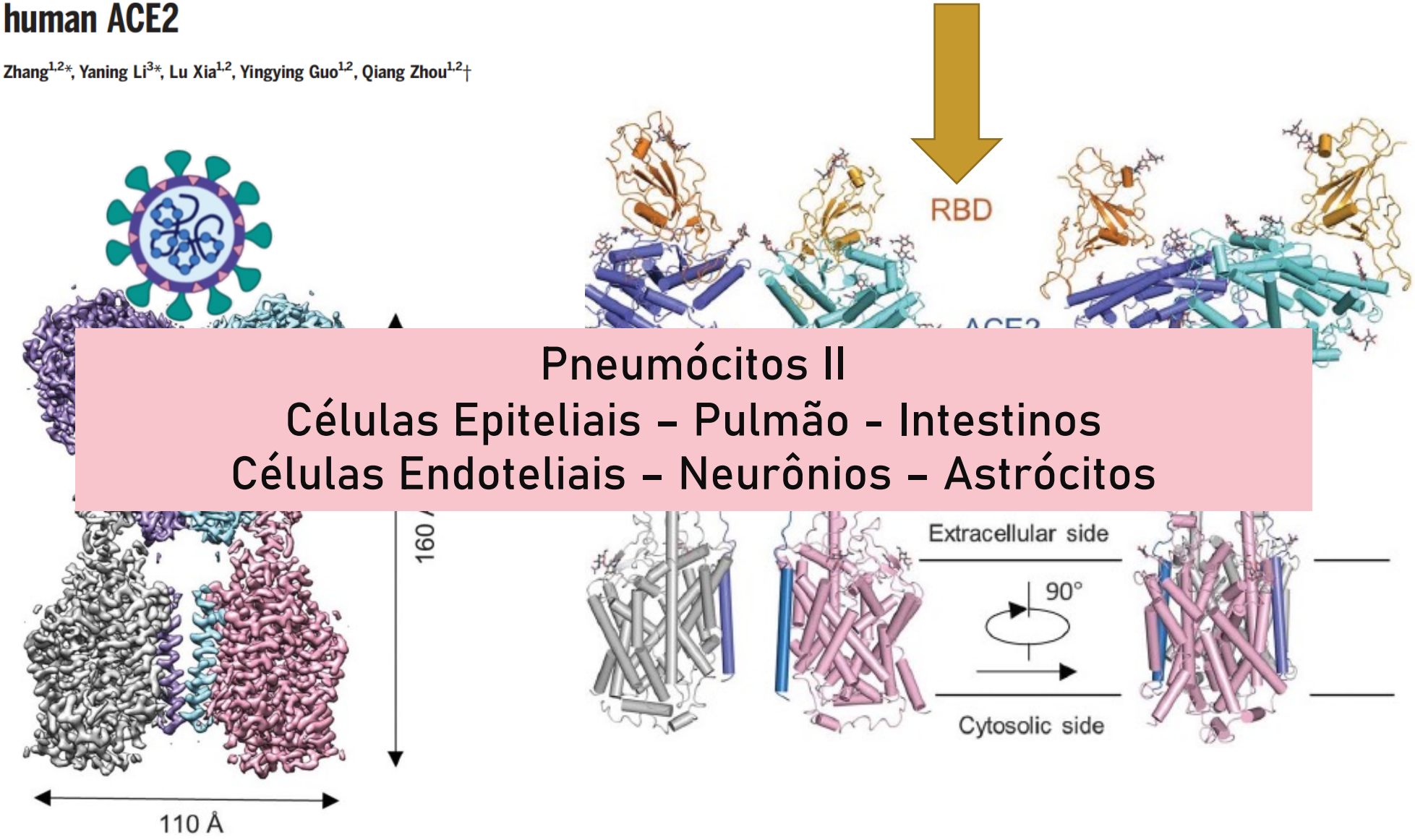
Nucleoprotein
≈1000 copies
(measured for SARS-CoV-1)

Envelope protein
≈20 copies
(100 monomers, measured for TGEV coronavirus)

CORONAVIRUS

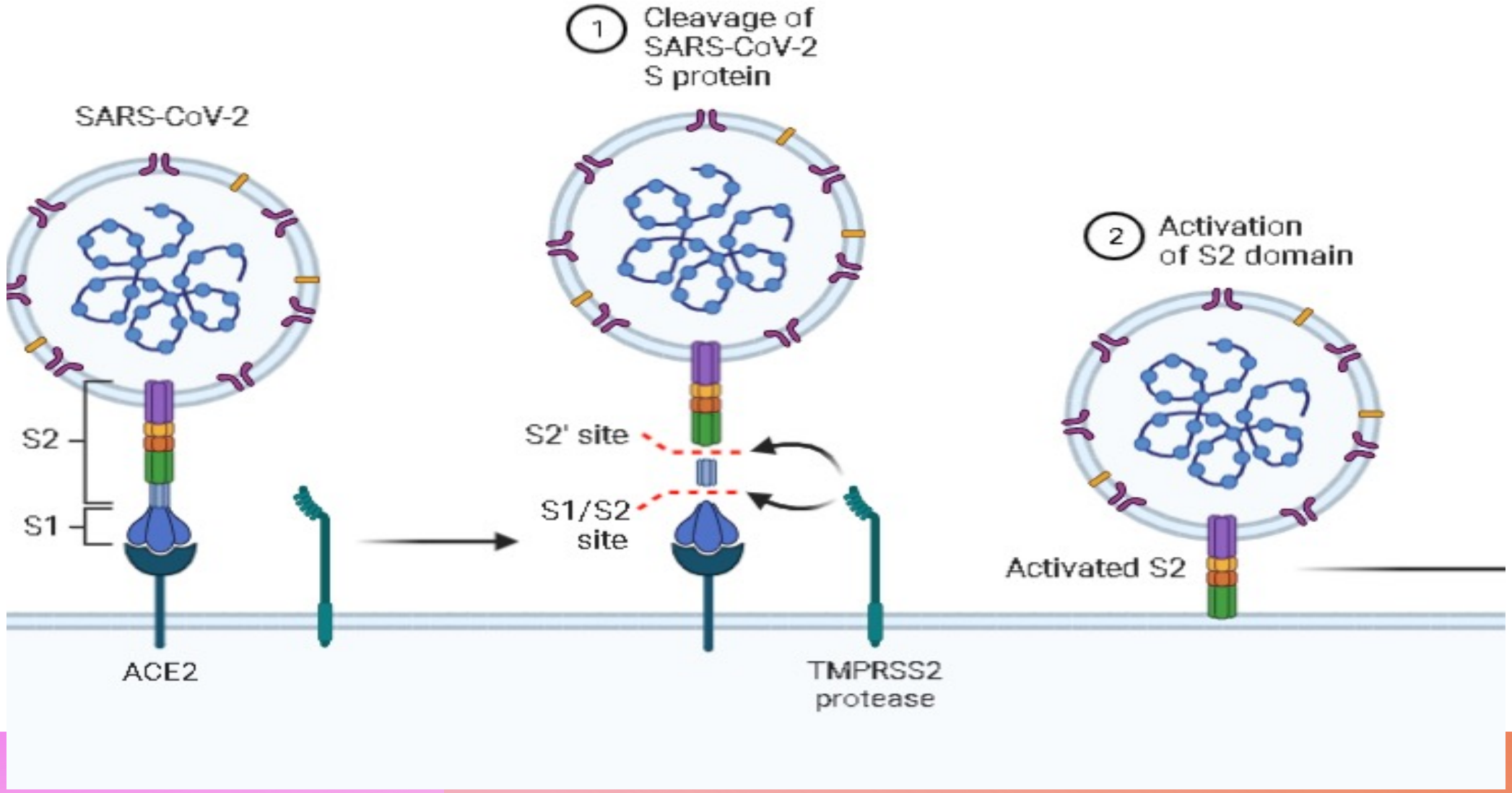
Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2

Renhong Yan[1,2], Yuanyuan Zhang[1,2]*, Yaning Li[3]*, Lu Xia[1,2], Yingying Guo[1,2], Qiang Zhou[1,2]†

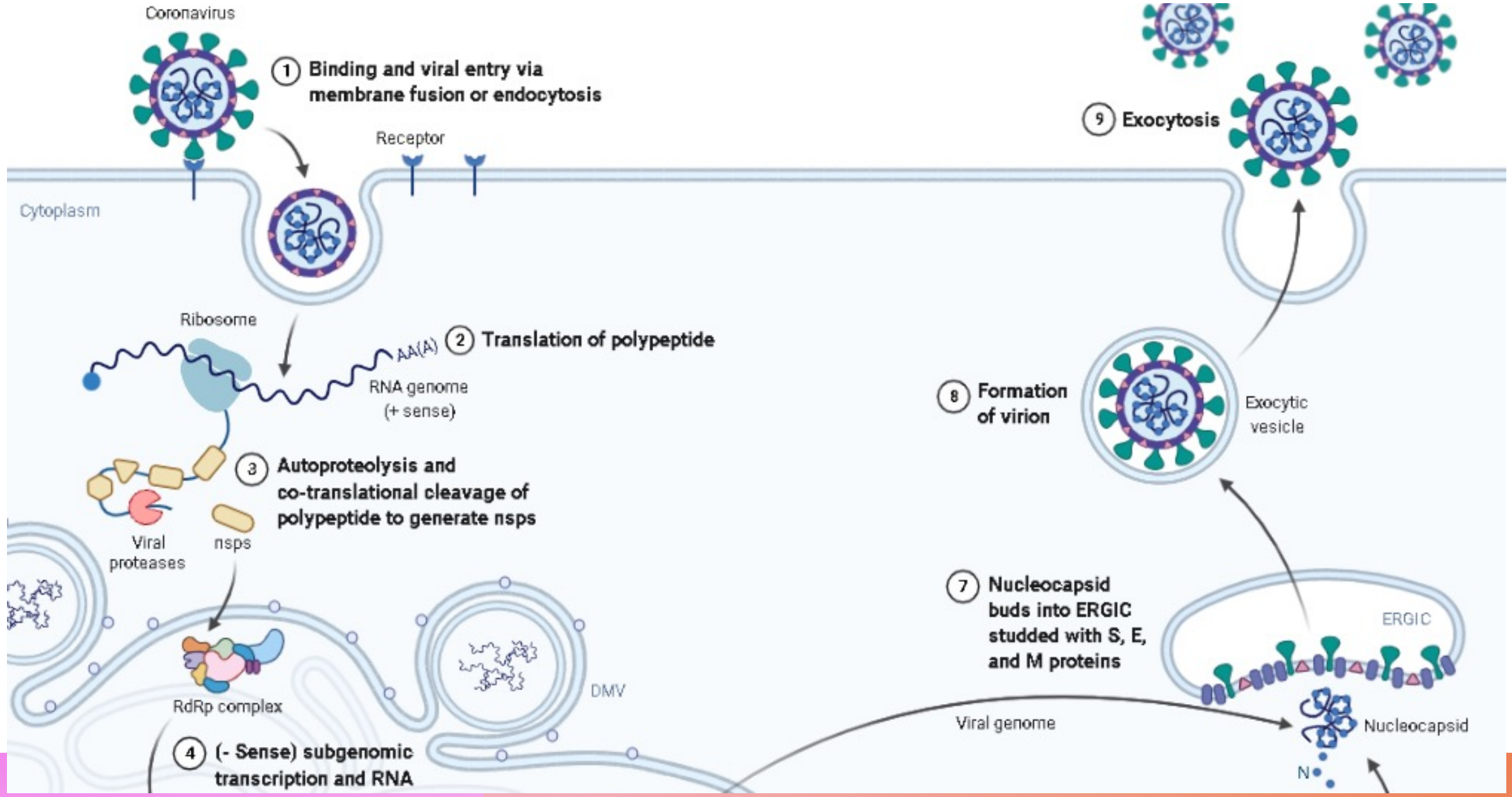


Pneumócitos II
Células Epiteliais – Pulmão - Intestinos
Células Endoteliais – Neurônios – Astrócitos

ADESÃO E INVASÃO CELULAR
ACE-2 + TMPRSS2

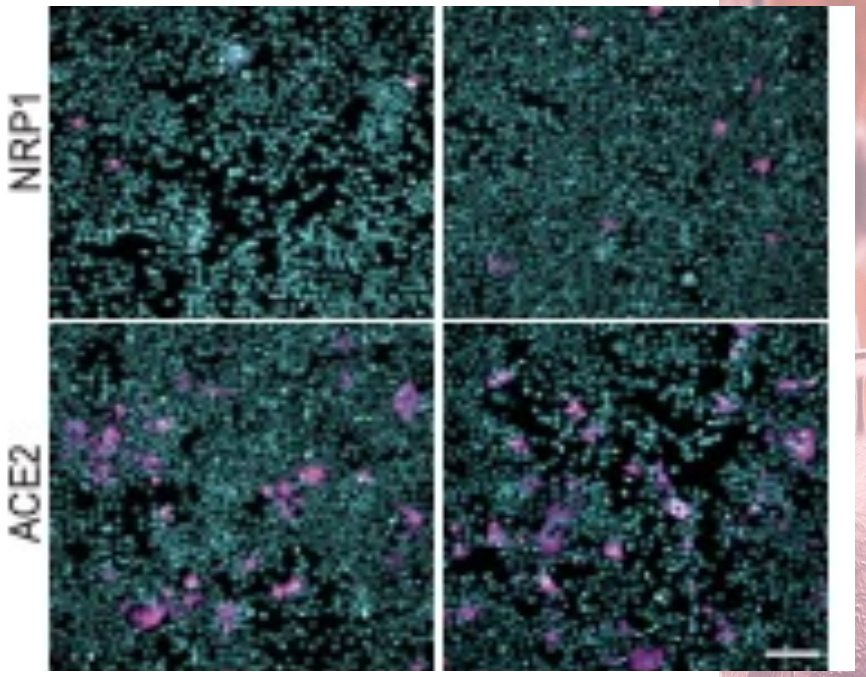


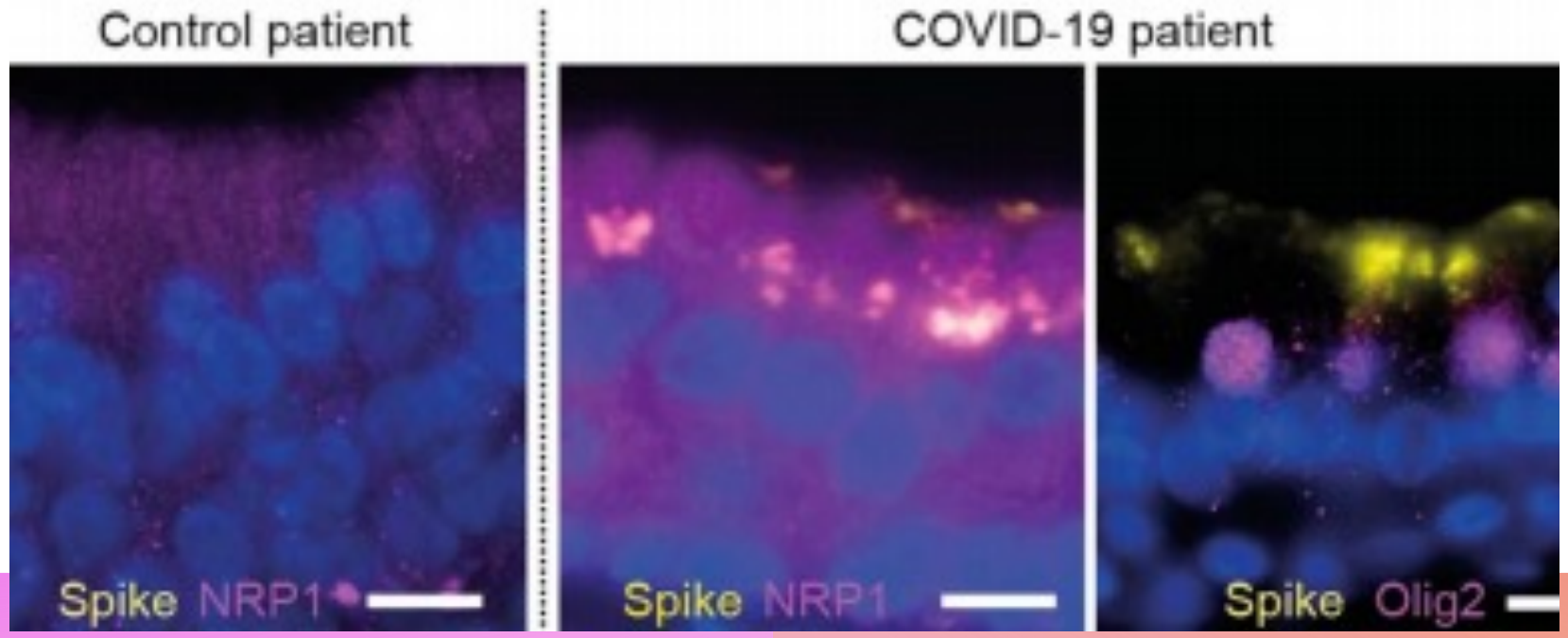
REPLICAÇÃO SARS-CoV2

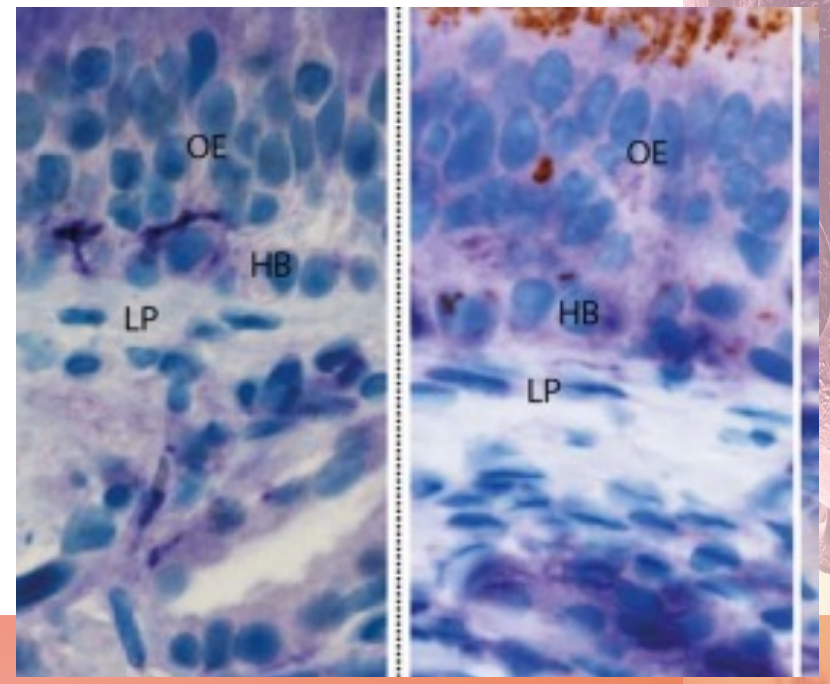


Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity

Ludovico Cantuti-Castelvetri[1,2]*, Ravi Ojha[3]*, Liliana D. Pedro[1,2]*, Minou Djannatian[1,2]*, Jonas Fran
Suvi Kuivanen[7]*, Franziska van der Meer[4], Katri Kallio[3], Tuğberk Kaya[1,2,8], Maria Anastasina[3,9],
Teemu Smura[7], Lev Levanov[7], Leonora Szirovicza[7], Allan Tobi[10], Hannimari Kallio-Kokko[11],
Pamela Österlund[12], Merja Joensuu[13], Frédéric A. Meunier[13], Sarah J. Butcher[3,9],
Martin Sebastian Winkler[14], Brit Mollenhauer[15,16], Ari Helenius[17], Ozgun Gokce[8],
Tambet Teesalu[3,19,20], Jussi Hepojoki[5,21], Olli Vapalahti[7,11,22], Christine Stadelmann[4],
Giuseppe Balistreri[3,18]†, Mikael Simons[1,2,23]†







Como é a resposta imune ao SARS-CoV2?

2 COMPONENTES

1 – imunidade Inata

2- Imunidade Adaptativa

Popular Latest

The

HEALTH

Immunology Is ... Die

Which is too bad bec... ...n reacts to the coronavirus.

ED YONG AUGUST 5, 2...

THE ATLANTIC

Editor's Note: The Atlantic *is making vit... ...so all readers. Find the collection here.*

Dinâmico

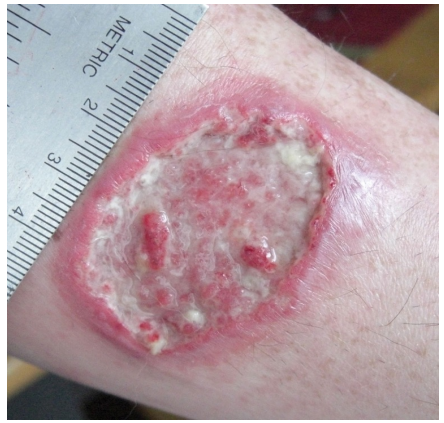
Imprevisível

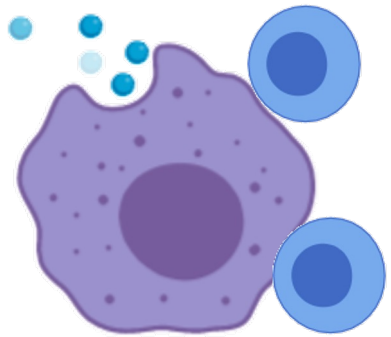
Varia de Intensidade

DANGER

Resposta imune é uma resposta ao PERIGO

Endógeno ou Exógeno





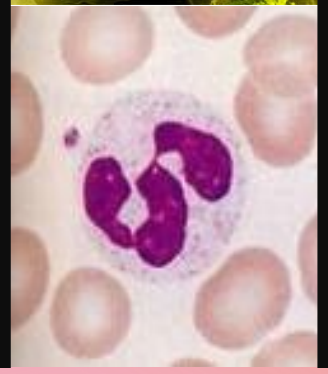
Padrões Moleculares

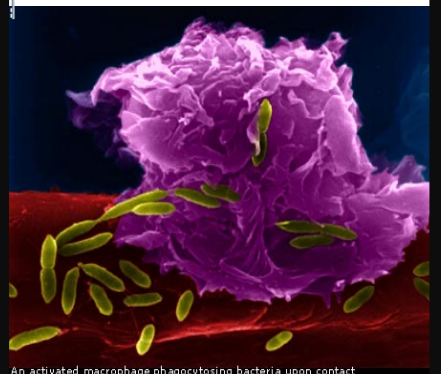
PAMPs – Pathogen Associated Molecullar Patterns

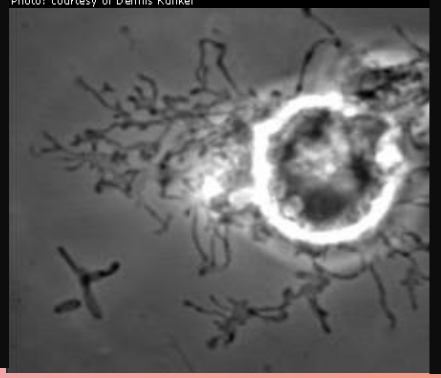
DAMPs – Danger Associated Molecular Pattern6

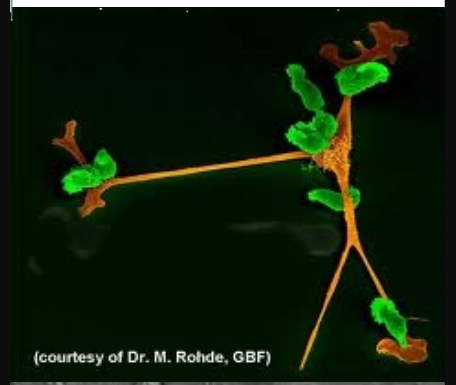
RESPOSTA IMUNE INATA E SUAS CÉLULAS

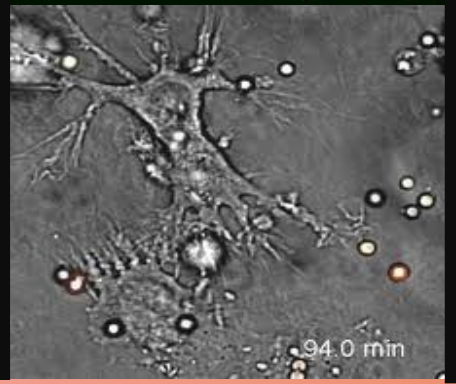
Tipo celular	Neutrófilo	Macrófago	Células dendríticas	Célula *natural killer*
Função	Fagocitose Espécies reativas de oxigênio e nitrogênio Peptídeos antimicrobianos	Fagocitose Mediadores inflamatórios Apresentação de antígenos Espécies reativas de oxigênio e nitrogênio Citocinas Proteínas do complemento	Apresentação de antígeno Sinais co-estimuladores Espécies reativas de oxigênio Interferon Citocinas	Lise da célula infectada por vírus Interferon Ativação de macrófagos

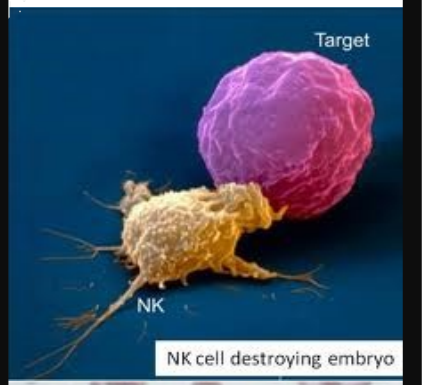


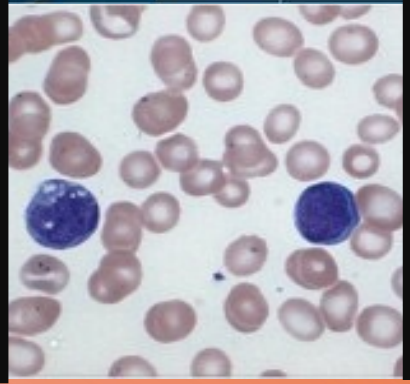












Prêmio Nobel Medicina – Fisiologia - 2011

Photo: The Scripps Research Institute

Photo: CNRS Photo Library/Pascal Disdier

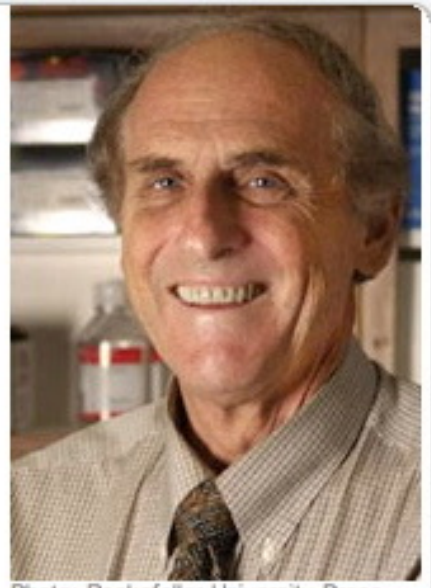


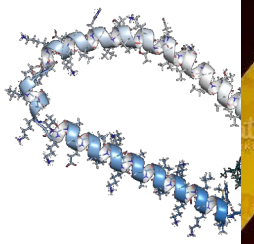
Photo: Rockefeller University Press

Bruce A. Beutler **Jules A. Hoffmann** **Ralph M. Steinman**

The Nobel Prize in Physiology or Medicine 2011 was divided, one half jointly to Bruce A. Beutler and Jules A. Hoffmann *"for their discoveries concerning the activation of innate immunity"* and the other half to Ralph M. Steinman *"for his discovery of the dendritic cell and its role in adaptive immunity"*.

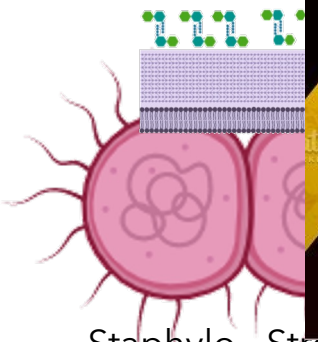
Charles Janeway **Ruslan Medzhitov**

"for their discoveries concerning the activation of innate immunity"



Alpha-synuc

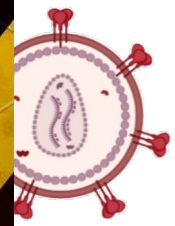
TLR-2
Monocyte



Staphylo - Strepto

DNA

TLR-9
pDCs



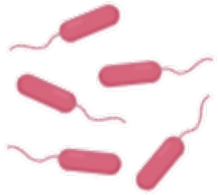
ZIKV

ZIKV

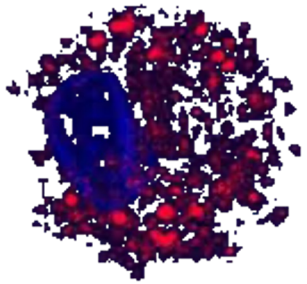
E. coli

DANGER

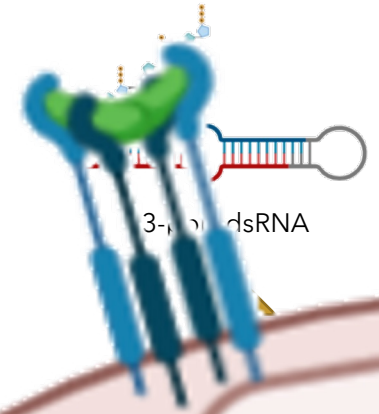
RECEPTORES TOLL-LIKE



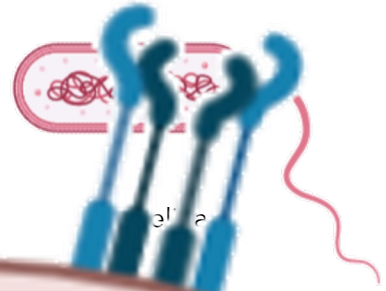
Sistema s de Secreção
SSTI/IIP

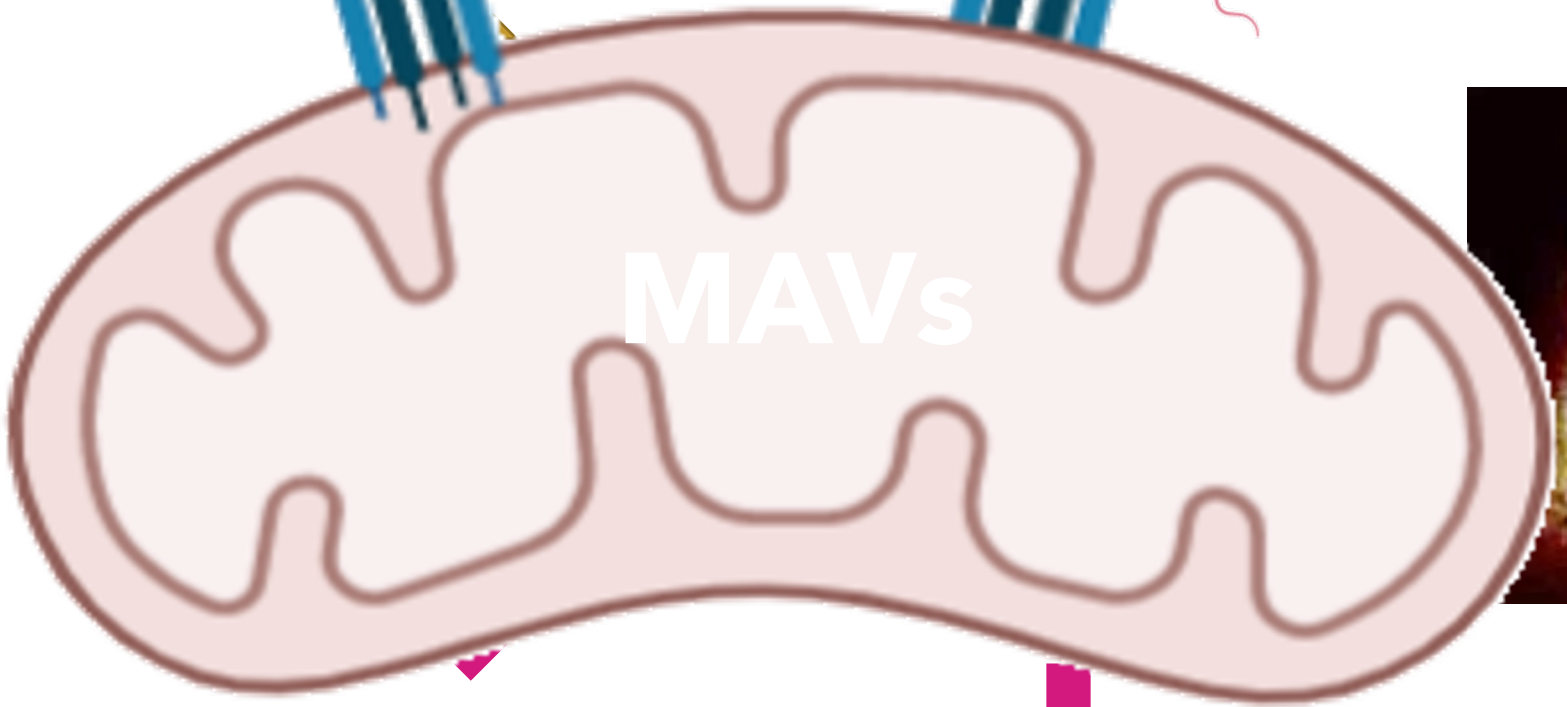


NLRP3
Monocytes



3-p dsRNA

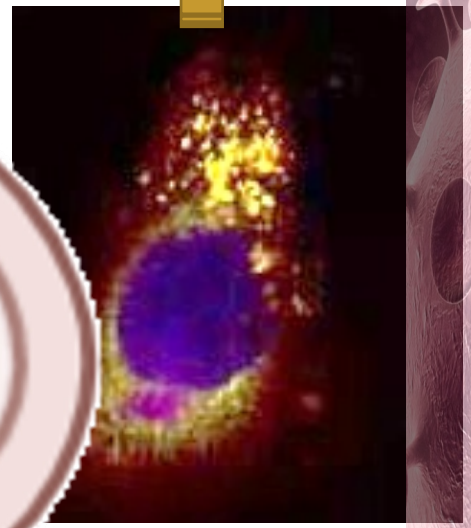




?

?

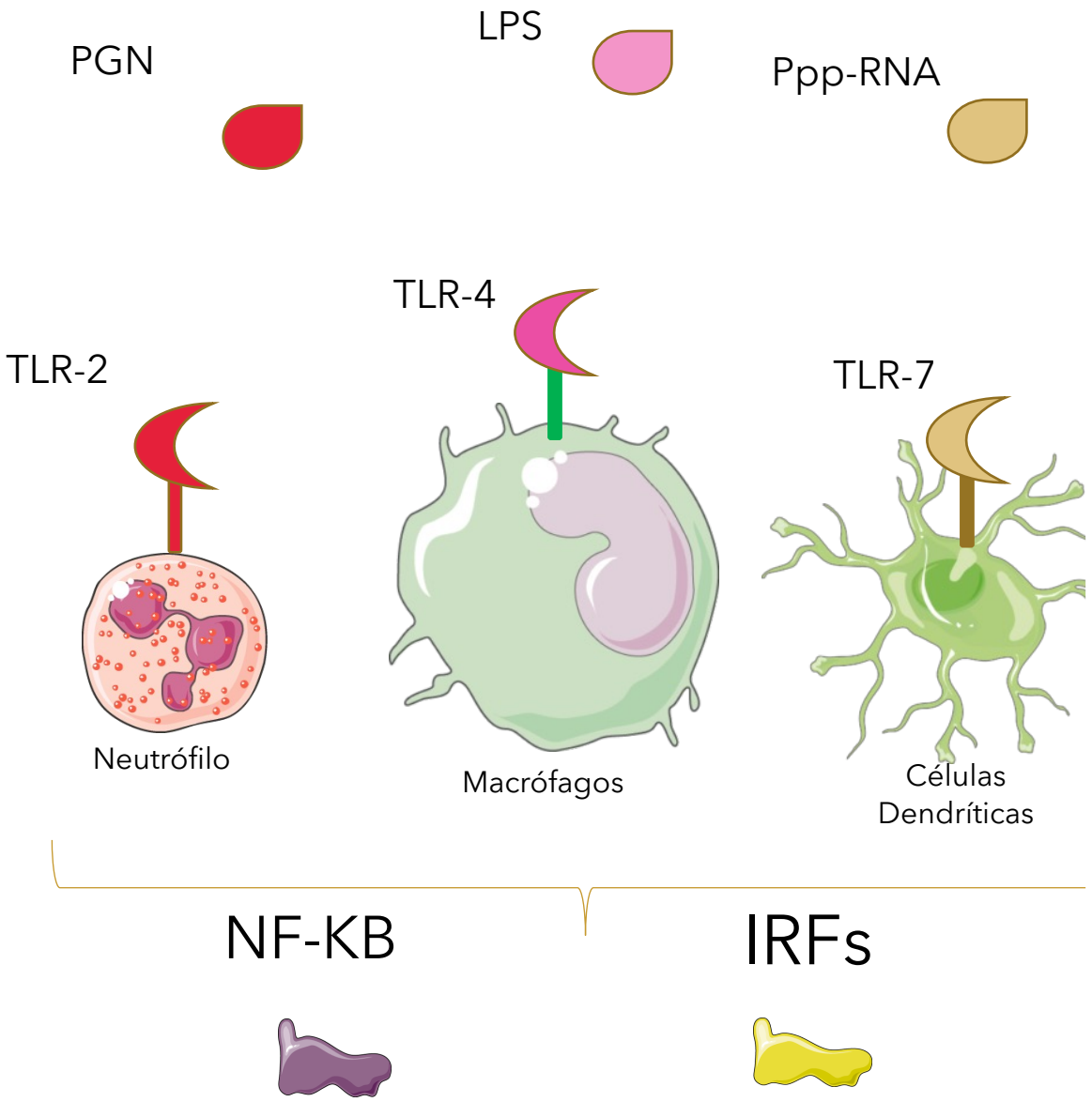
dsRNA



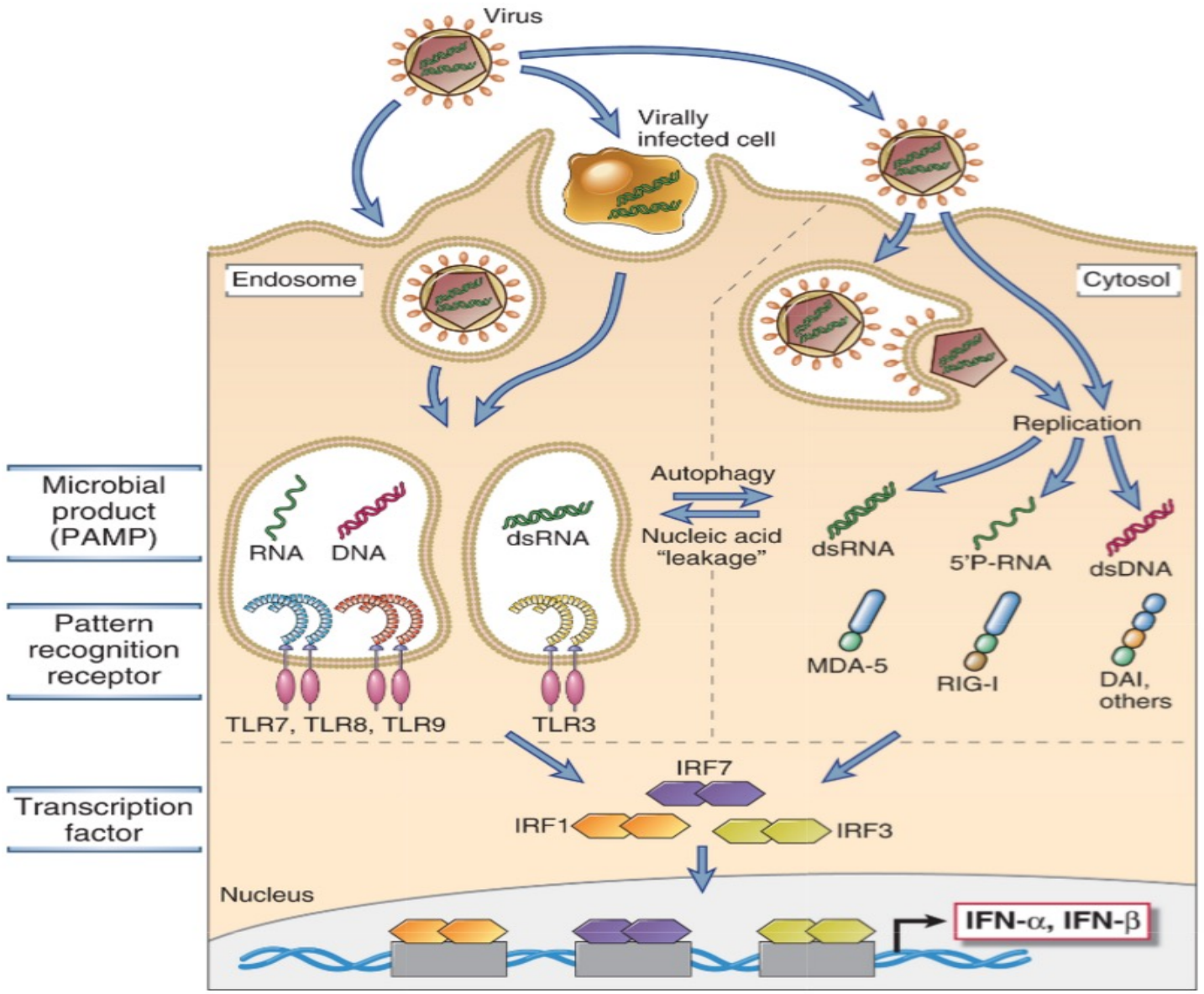
MDA-5
Monocytes

?

Ativação da Imunidade Inata
Sinaliza via NF-KB



Citocinas inflamatórias-IL-6, TNF-α, IFN-a/b
Moléculas de Adesão – Integrinas, MHC I/II
Mediadores Lipídicos – Cox-2, 5-LO
Quimiocinas – CCL2, CXCL5, CXCL12



Sensores de Ácidos Nucléicos no Citoplasma

TLR-3
TLR-7
TLR-8
TLR-9

MDA-5

RIG-I

MAVs

INTERFERONS TIPO I

Mas qual a importância dessas vias de sinalização intracelular?

E dessas citocinas ?

Quais são seus efeitos
BIOLÓGICOS ?

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cytokine Storm

David C. Fajgenbaum, M.D., and Carl H. June, M.D.

IL-1

IL-6

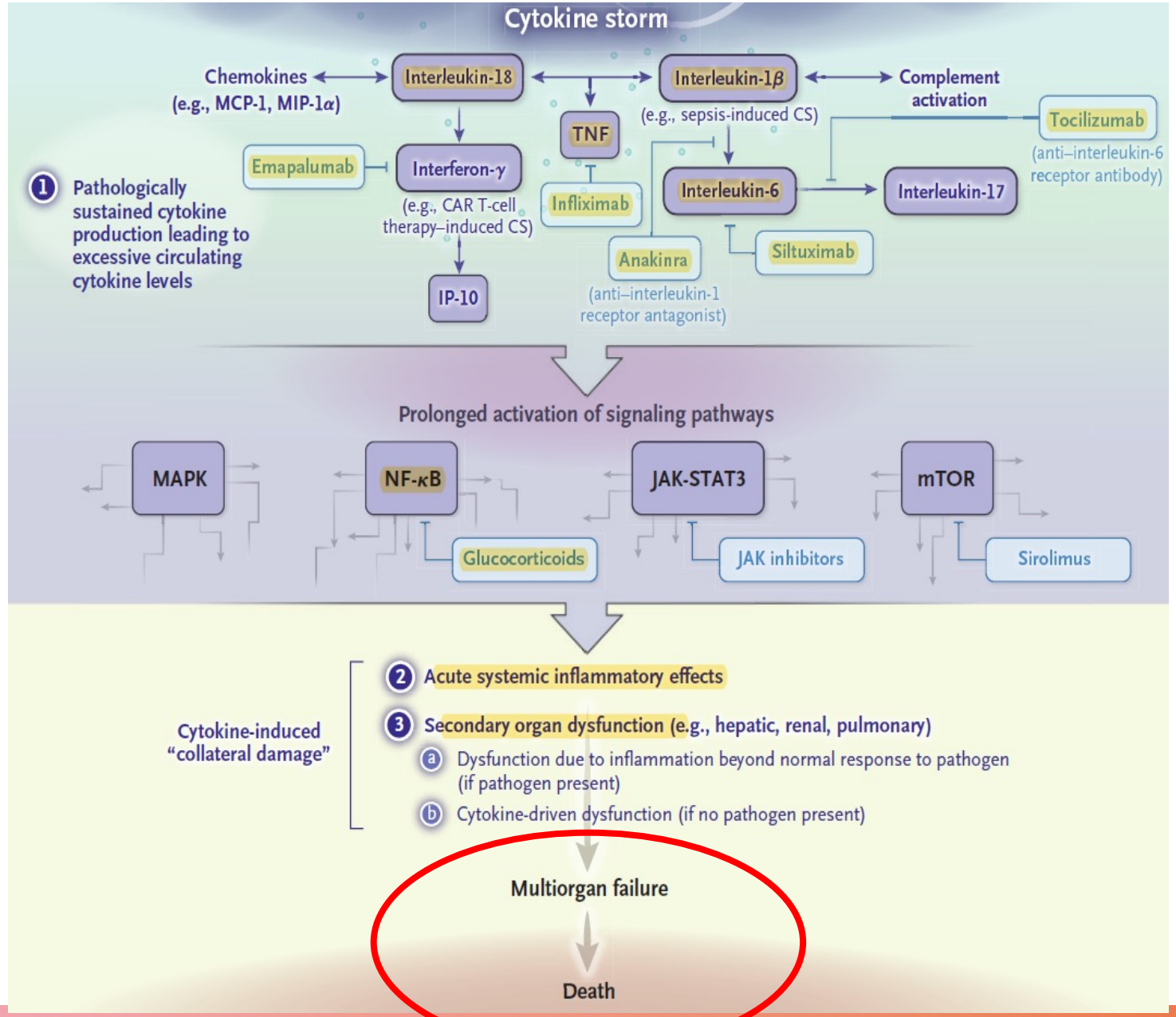
TNF-alpha

Interferons Tipo I

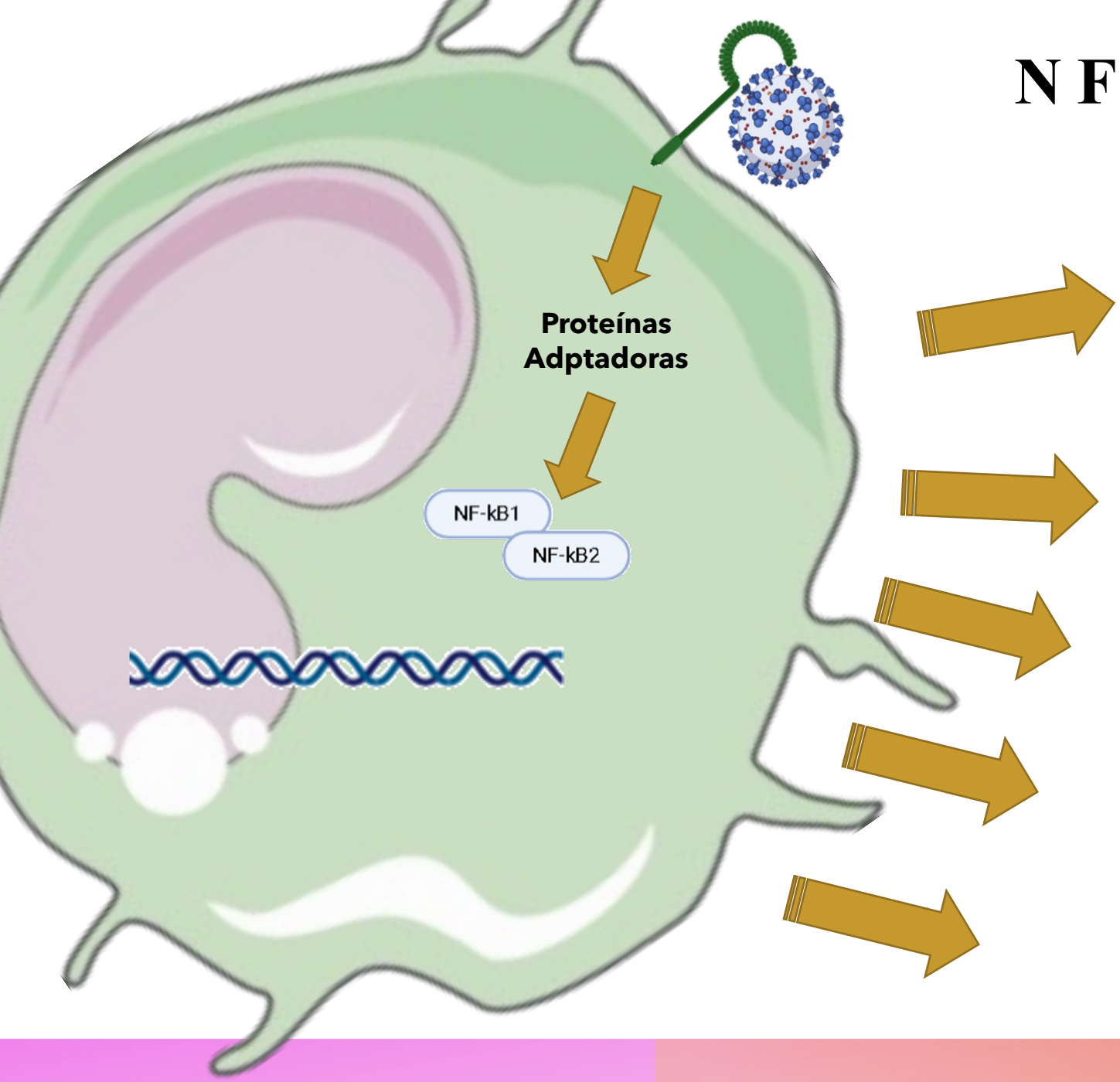
IFN-alpha
IFN-beta

Interferon Tipo II

IFN-gamma



NF-KB E SEUS GENES ALVO



Citocinas inflamatórias
IL-6, IL-12, TNF-α

Moléculas de Adesão
Integrinas, selectinas, proteoglicanas.

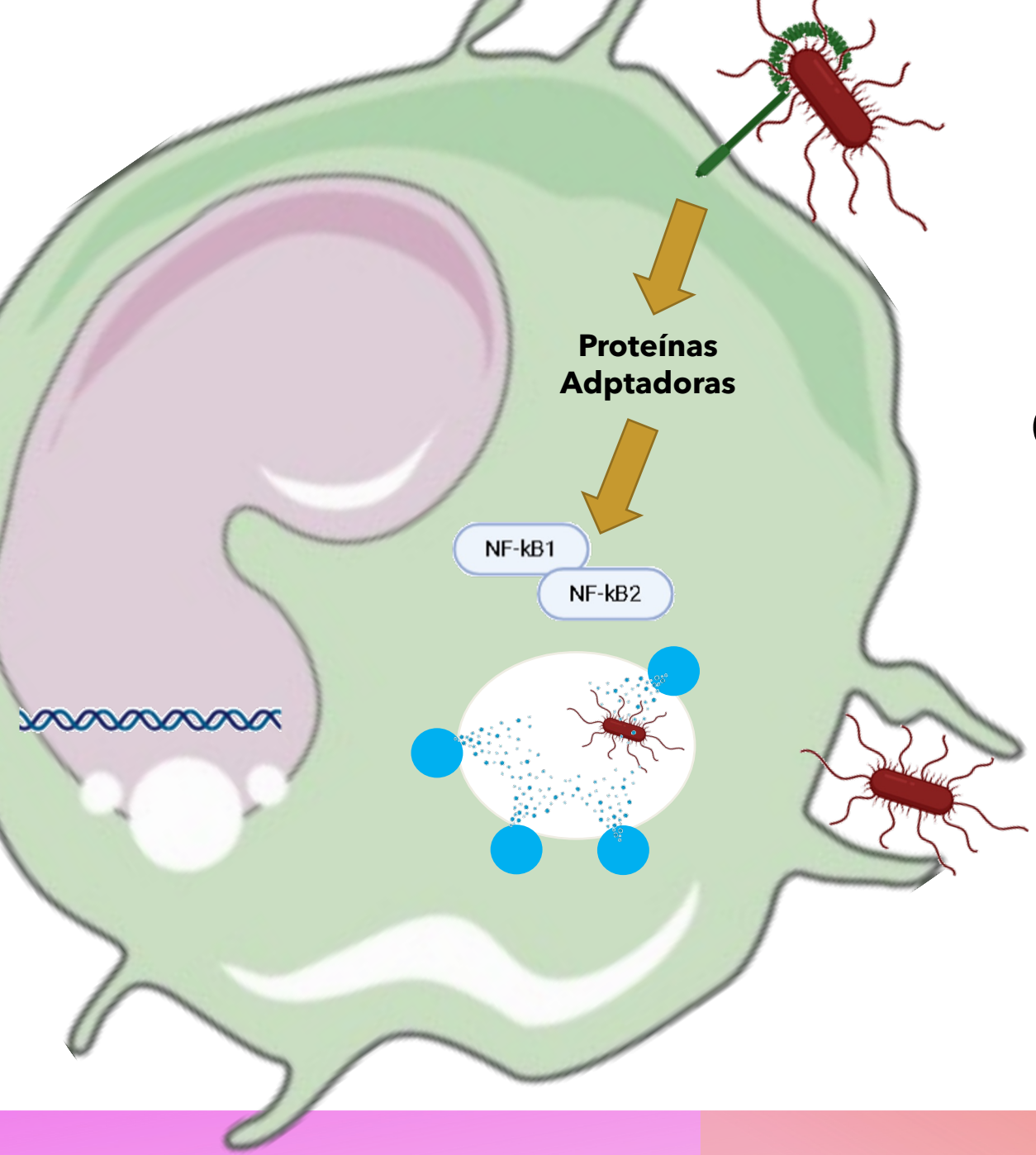
Moléculas de Apresentação de Ags MHC I/II

Mediadores Lipídicos
Cox-2, 5-LO

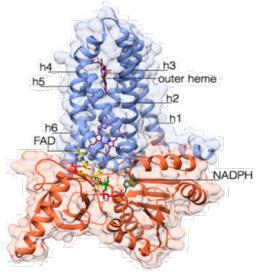
Quimiocinas
CCL2, CXCL5, CXCL12

Proteínas de FASE AGUDA
PROTEÍNAS DA COAGULAÇÃO

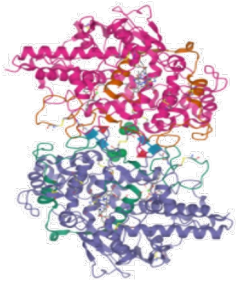
NF-KB – E SEUS GENES ALVO
SISTEMA NADPH OXIDASE
SUPERÓXIDO DISMUTASE
MIELOPEROXIDASE



O_2 → O_{2-} → H_2O_2 → H_2O + O_2



NADPHOx



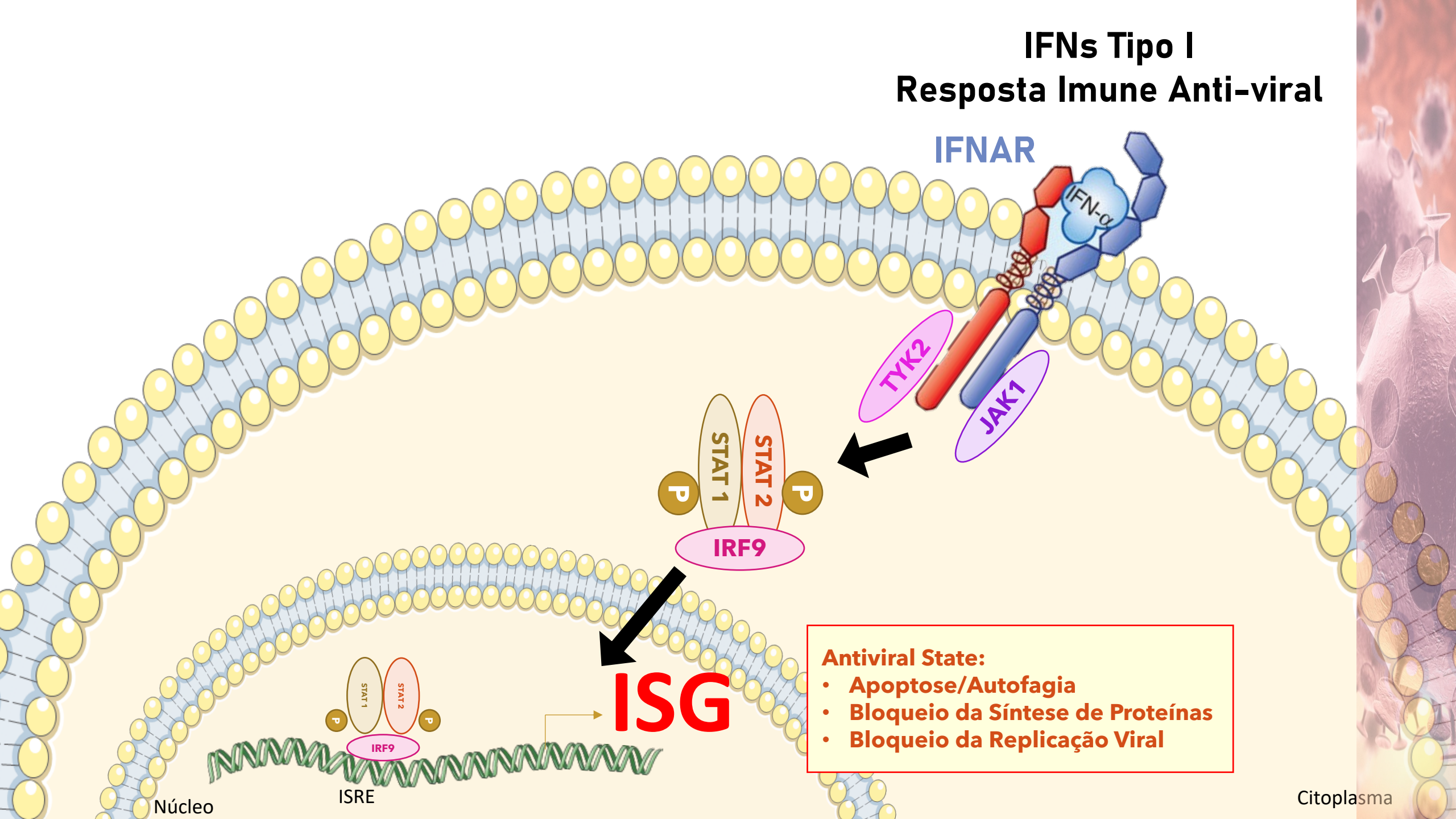
Mieloperoxidase

Crystal structures and atomic model of NADPH oxidase

Francesca Magnani, Simone Nenci, Elisa Millana Fananas, Marta Ceccon, Elvira Romero, Marco W. Fraaije, and Andrea Mattevi

PNAS June 27, 2017 114 (26) 6764-6769; first published June 12, 2017 https://doi.org/10.1073/pnas.1702293114

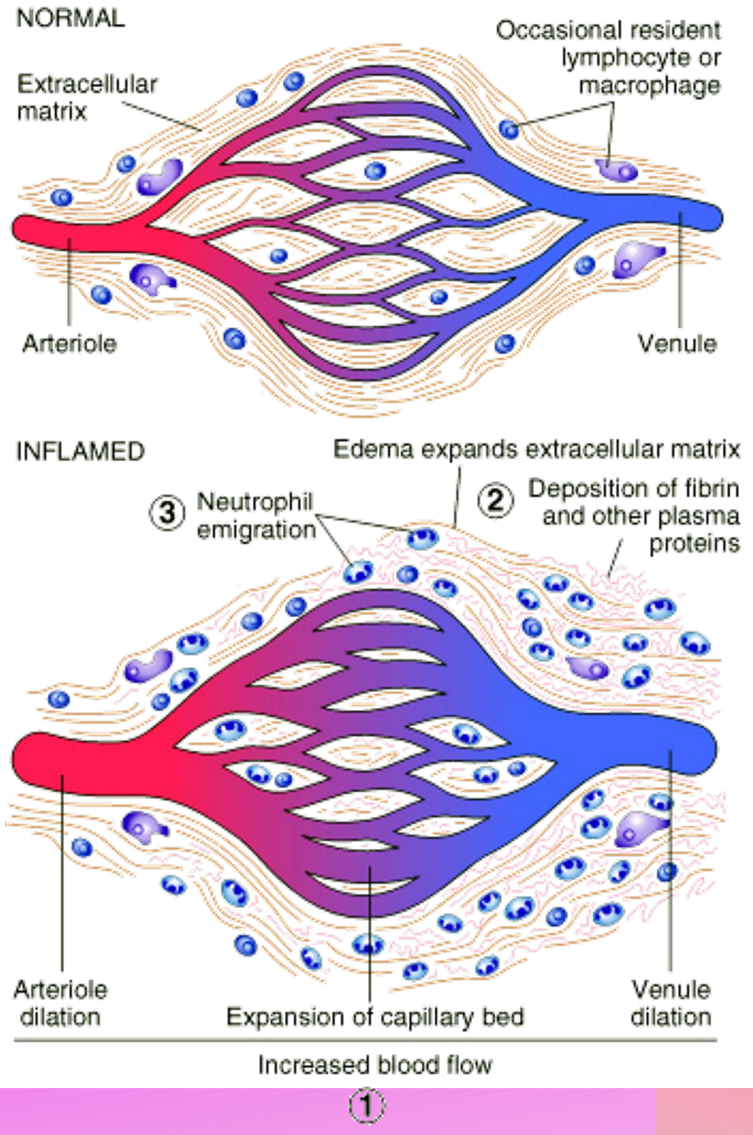
IFNs Tipo I
Resposta Imune Anti-viral

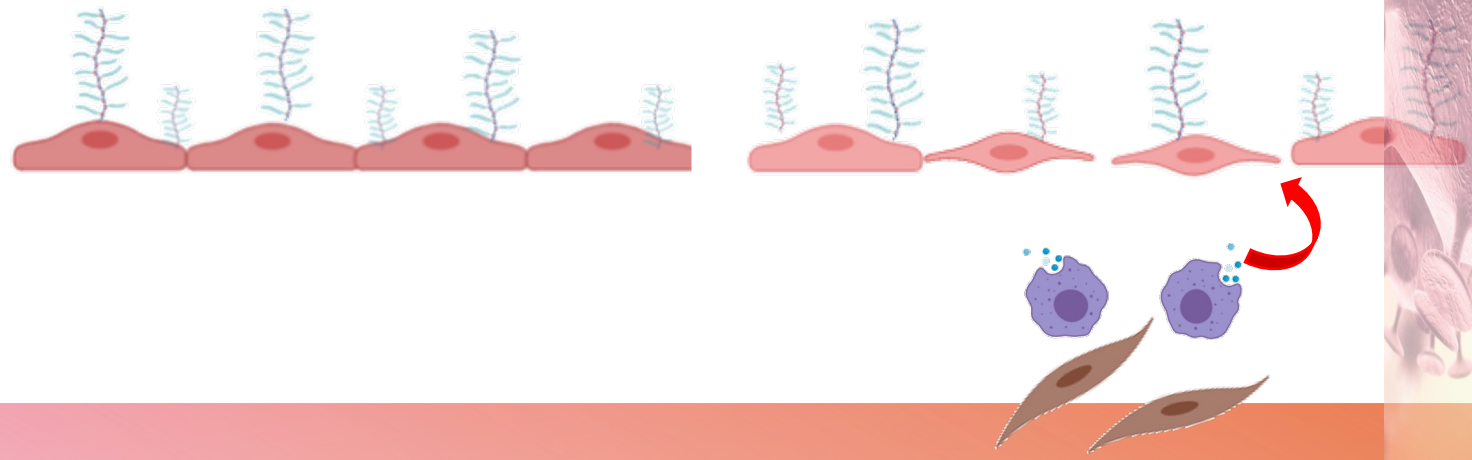


Antiviral State:

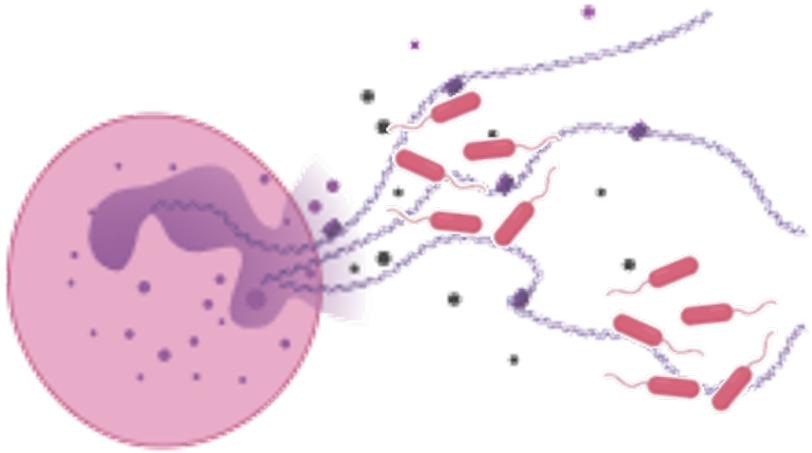
- **Apoptose/Autofagia**
- **Bloqueio da Síntese de Proteínas**
- **Bloqueio da Replicação Viral**

ALTERAÇÕES NO FLUXO SANGUÍNEO E MIGRAÇÃO DE LEUCÓCITOS



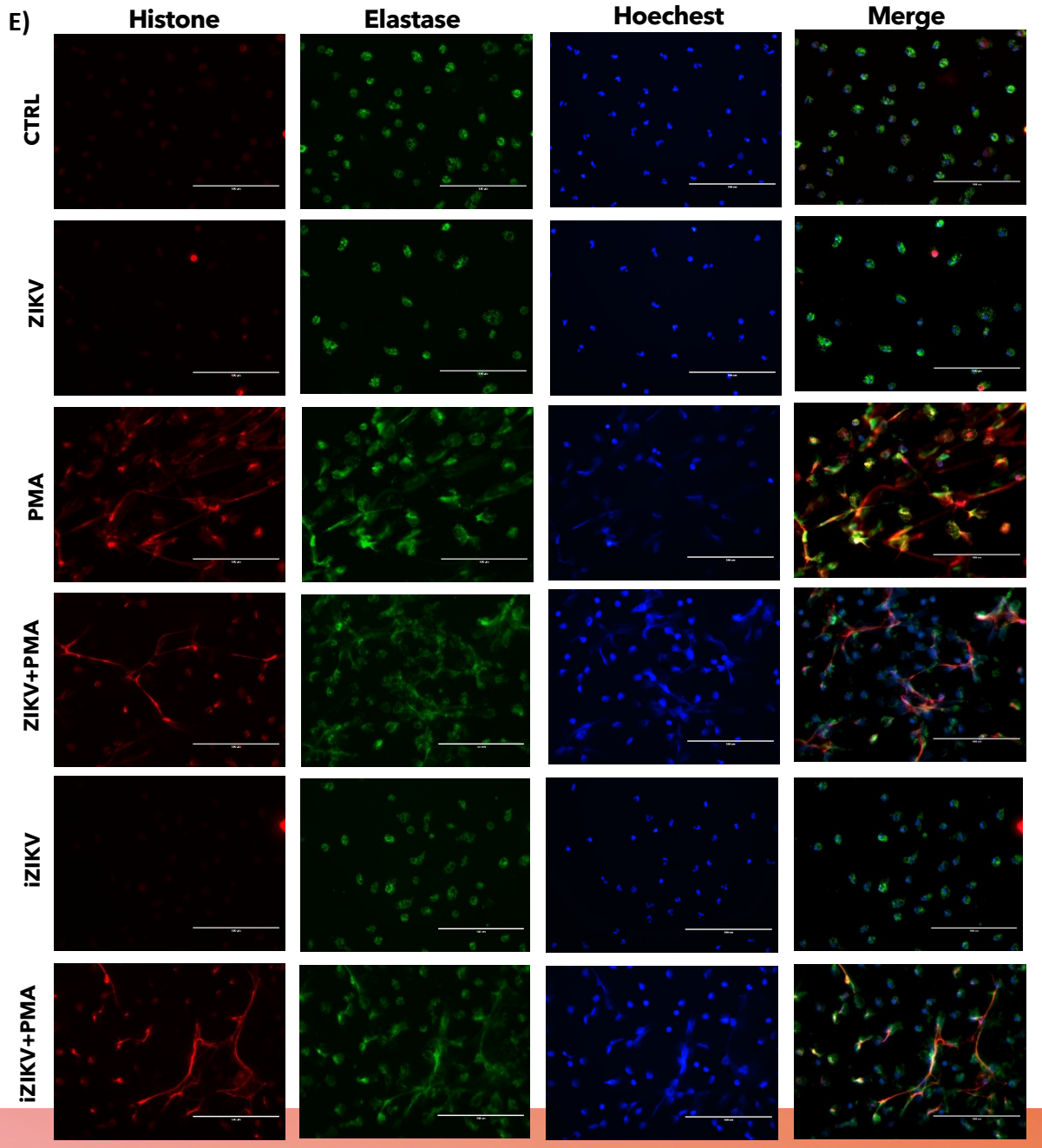


NETOSIS
OU *DNA TRAPS*

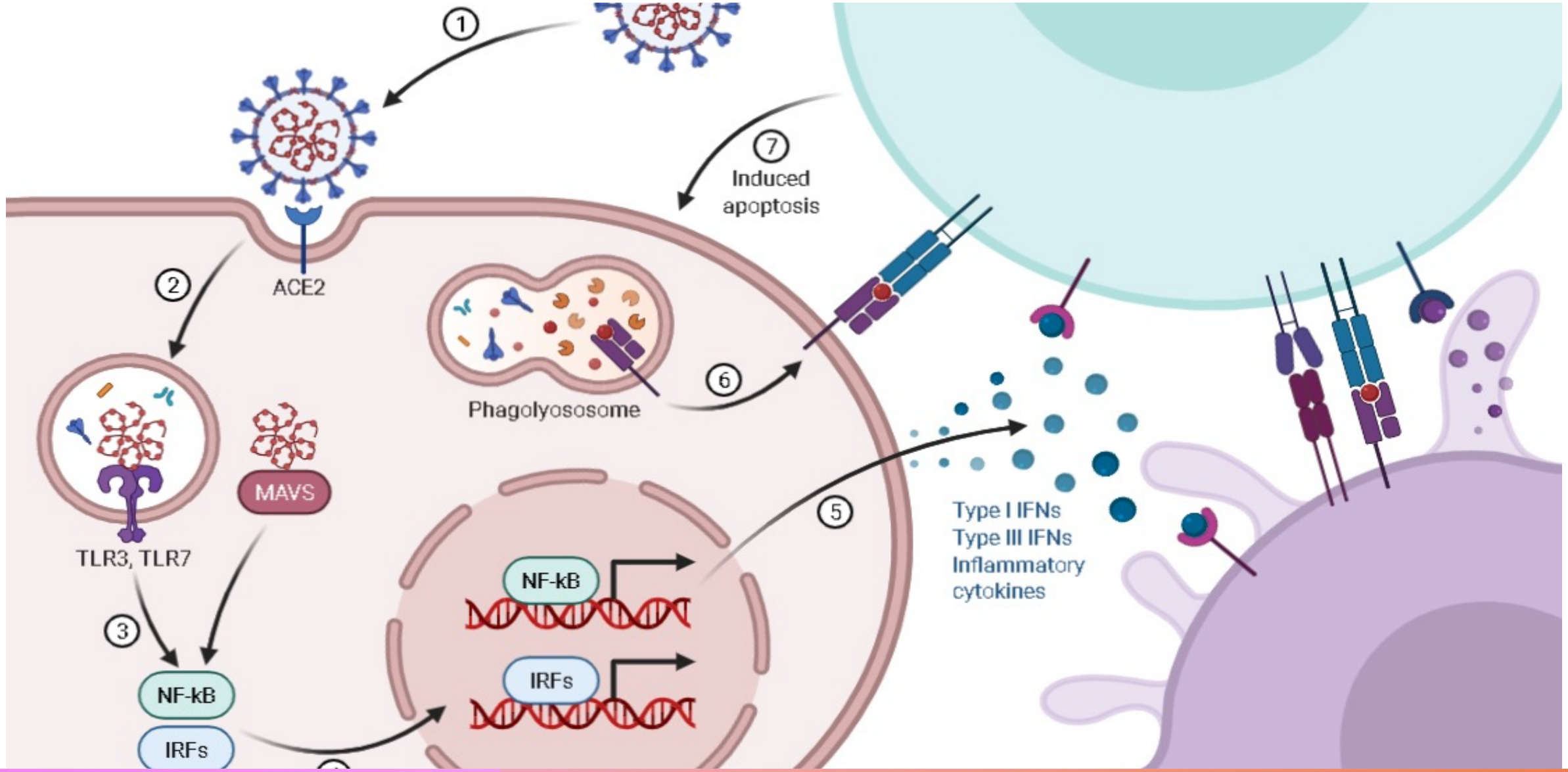


Extravasamento do material
Nuclear + Citoplasmático

PAD4 / ROS / MPO



RESUMINDO – SARS-COV2 ATIVA VIAS DA IMUNIDADE INATA PRODUTORAS DE CITOCINAS INFLAMATÓRIAS



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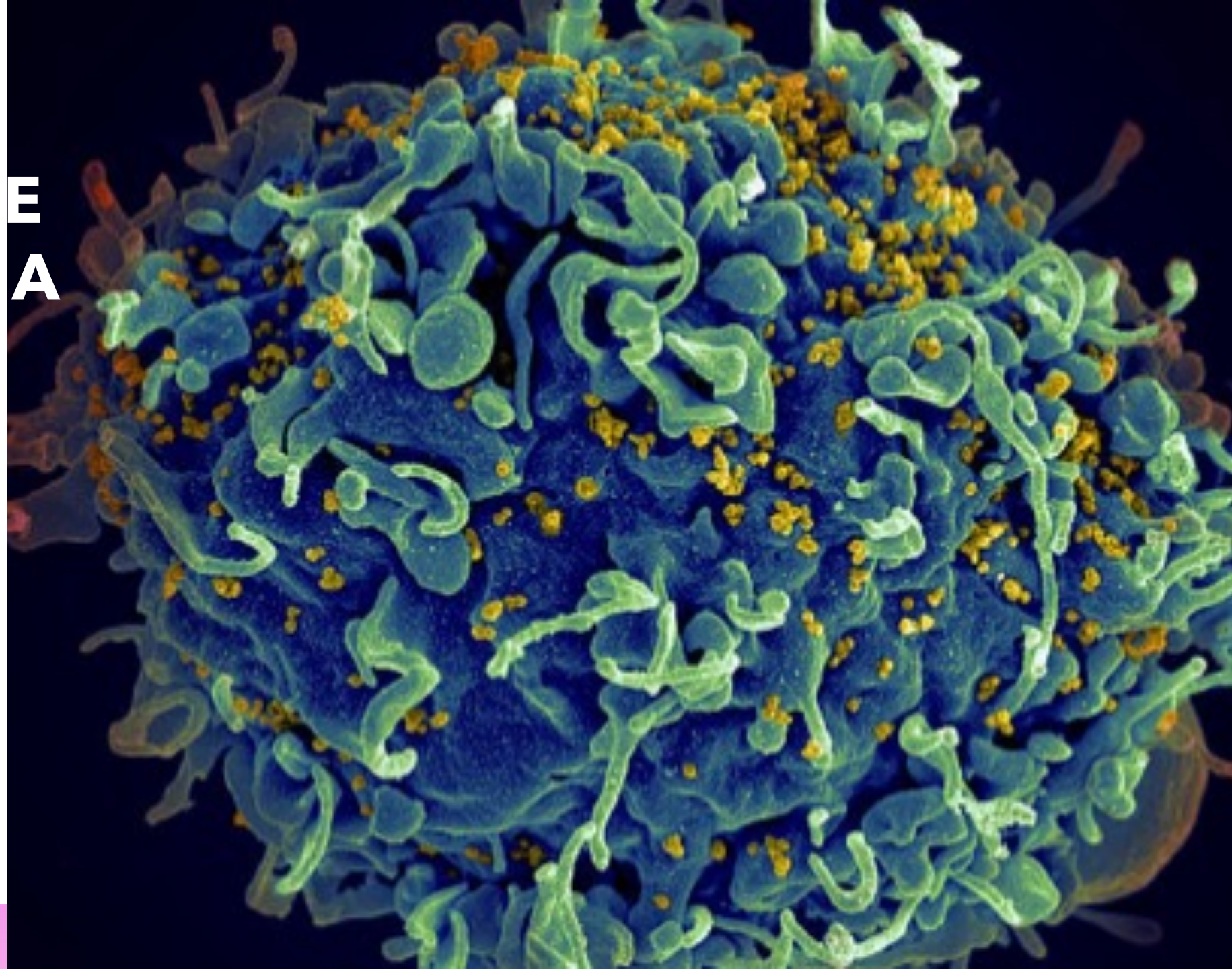
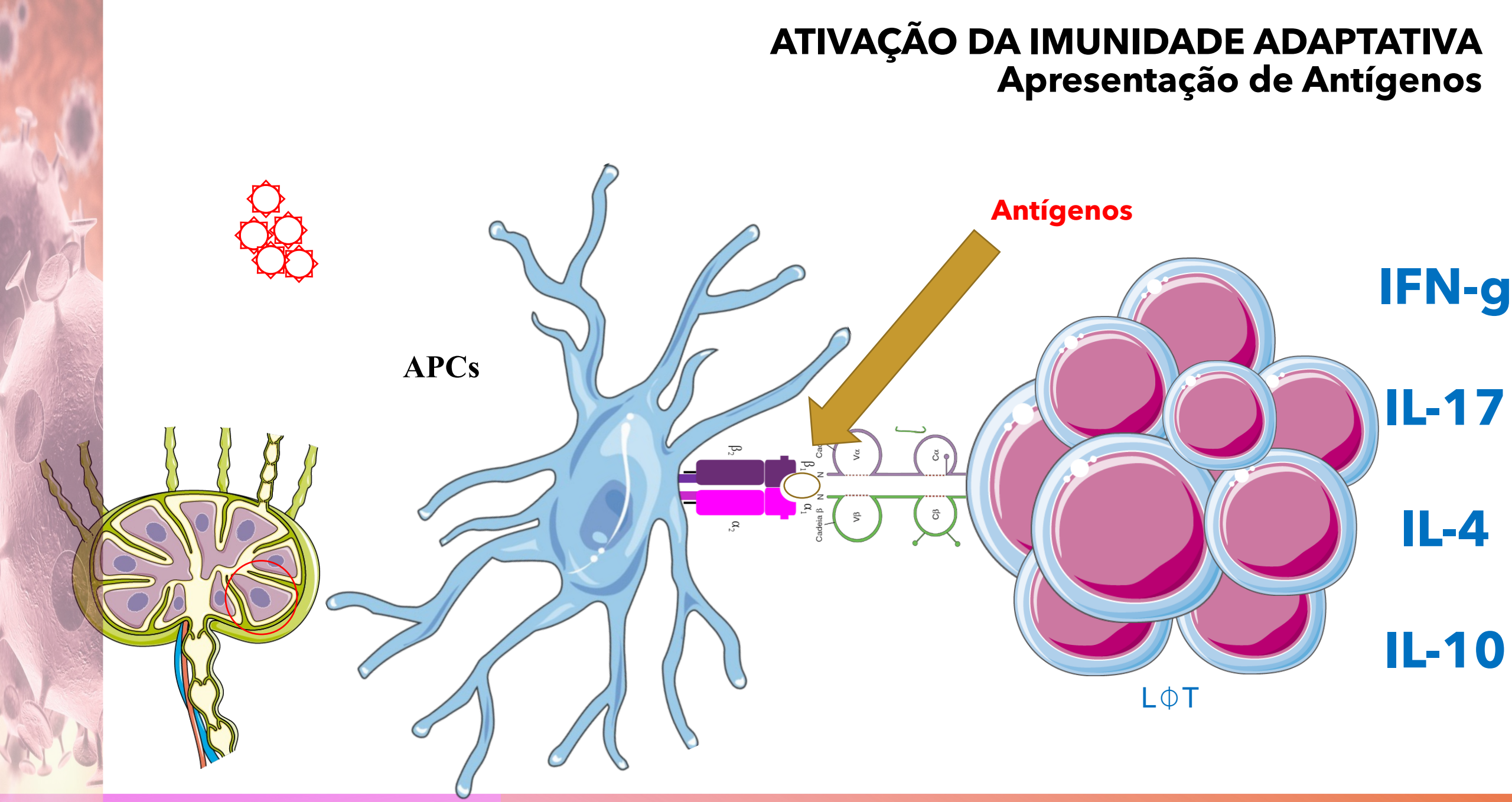


E QUAL O PAPEL DA IMUNIDADE ADAPTATIVA ?

LINFÓCITOS B

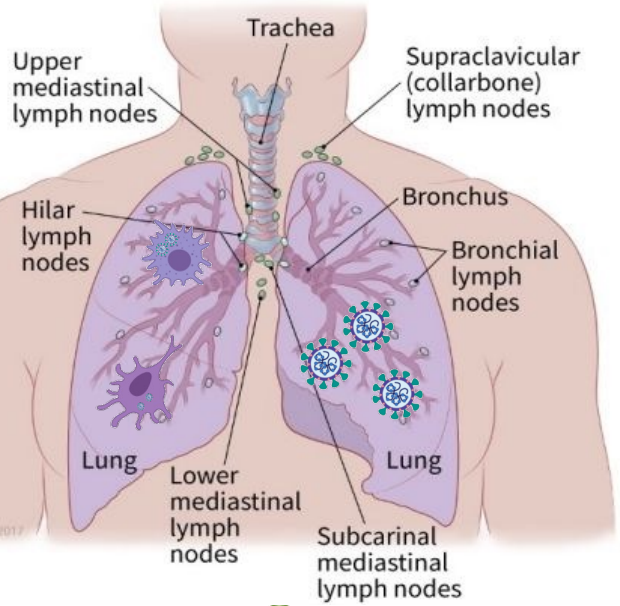
LINFÓCITOS T

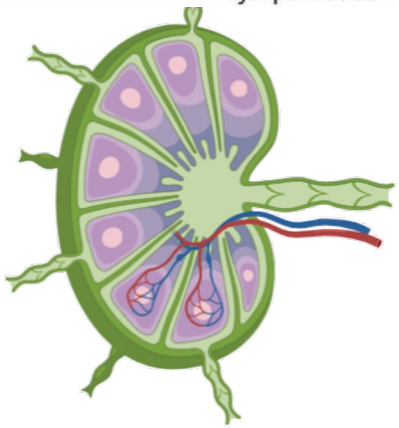
ATIVAÇÃO DA IMUNIDADE ADAPTATIVA
Apresentação de Antígenos

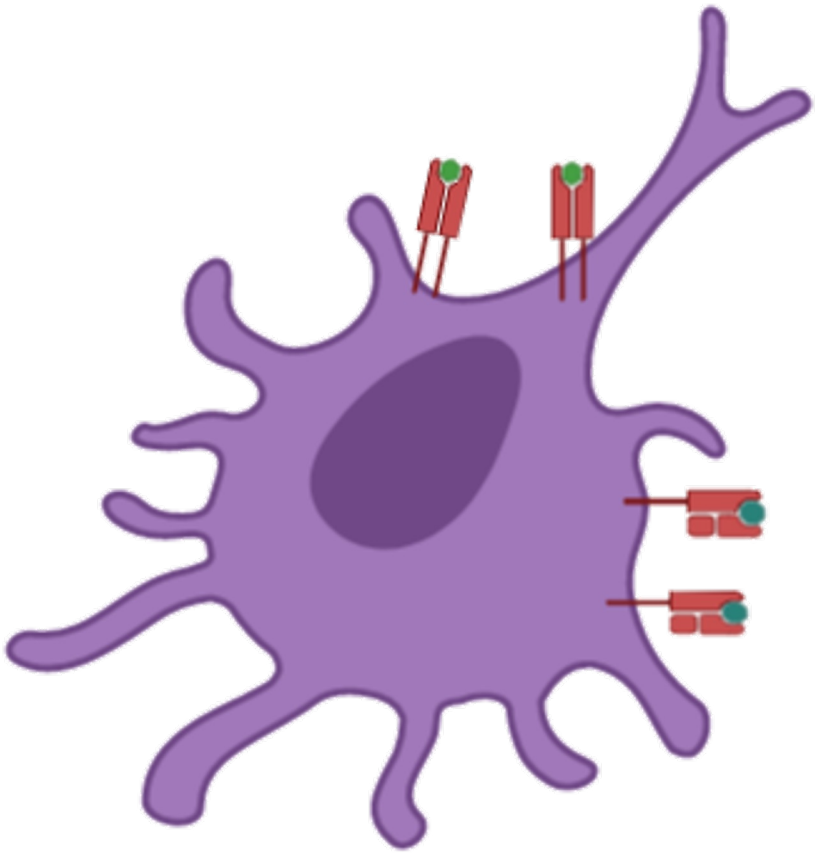


Van Kaer L et al 2019

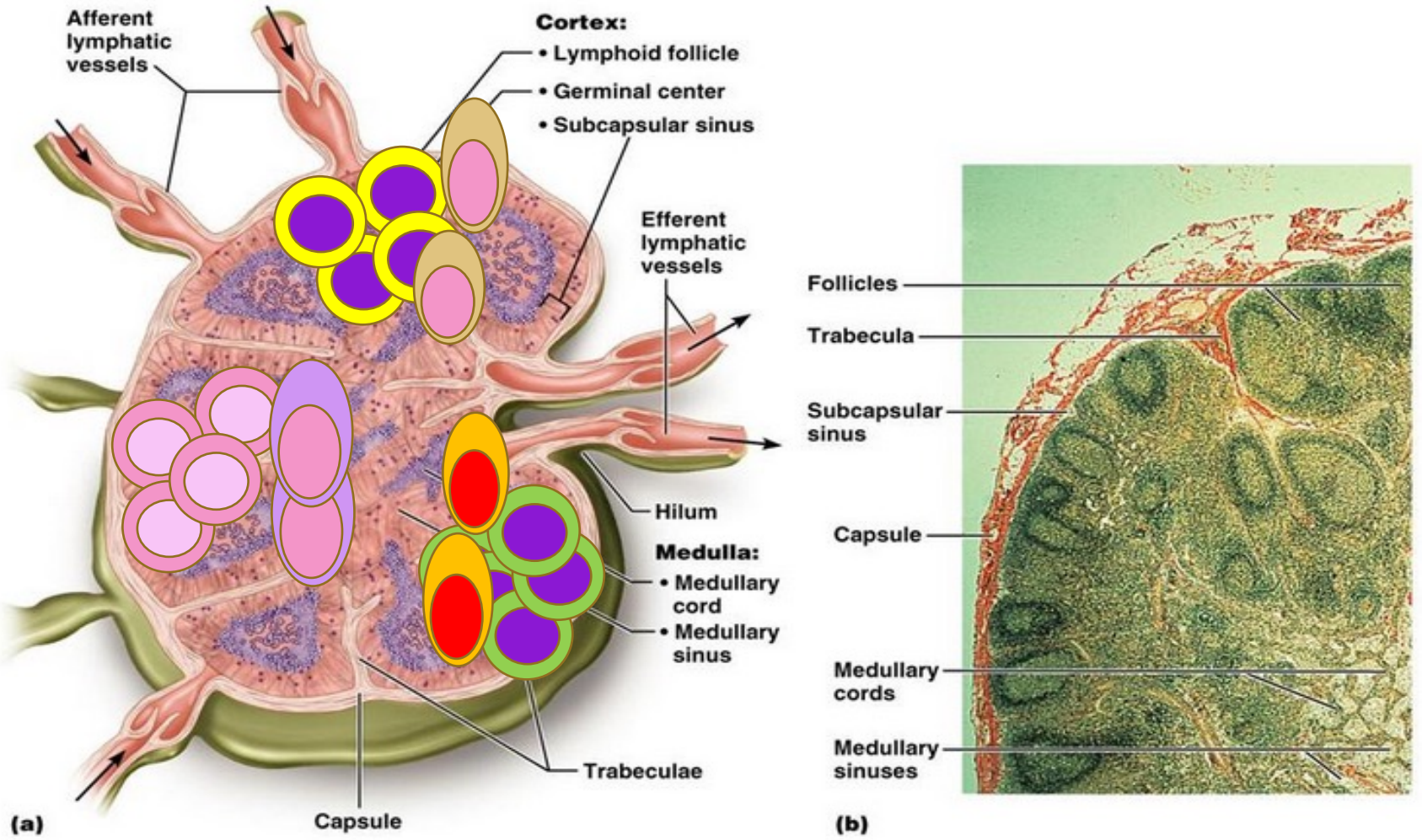
Ativação da Imunidade Adaptativa
Linfonodos, Baço e no Sítio da Infecção



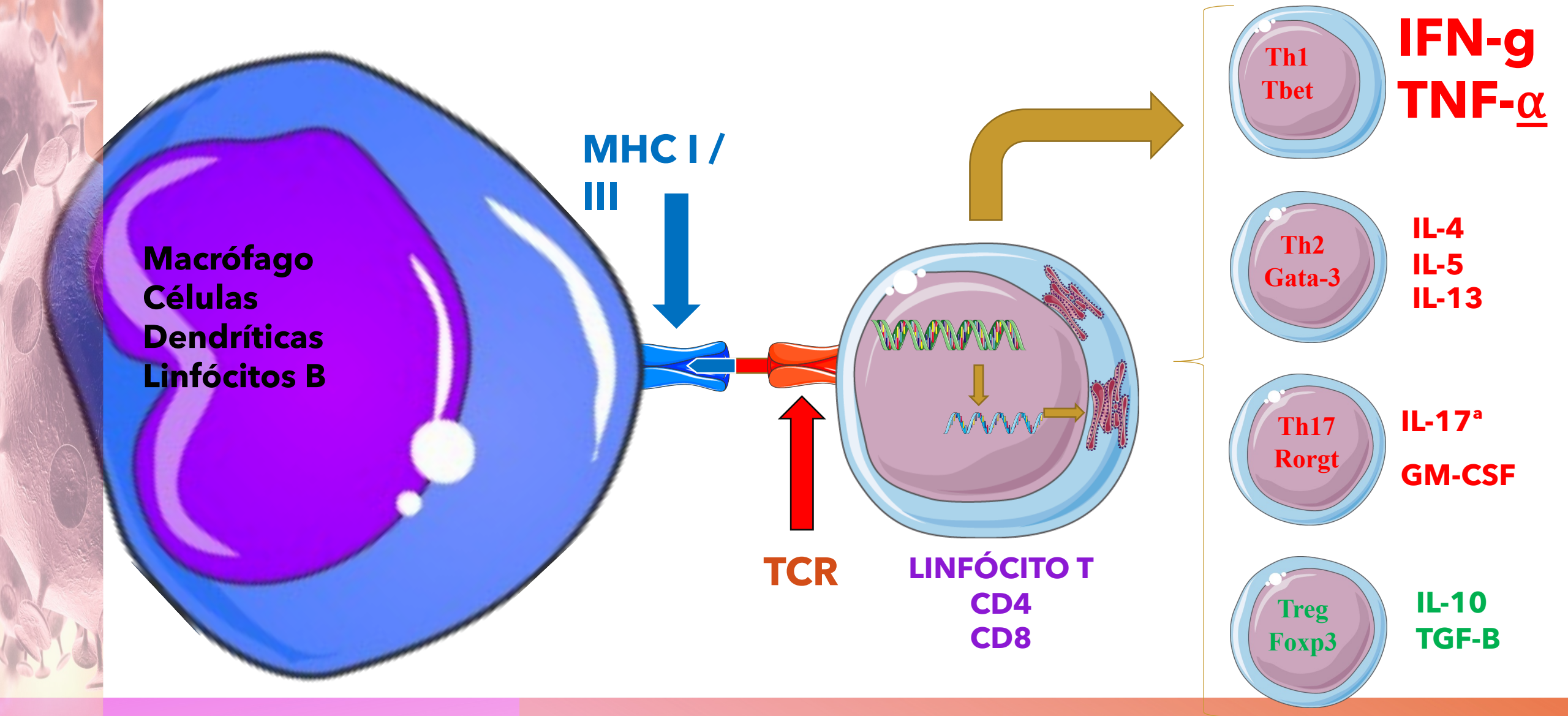




Drenagem Antígenos aos Linfonodos – Antígenos Proteicos

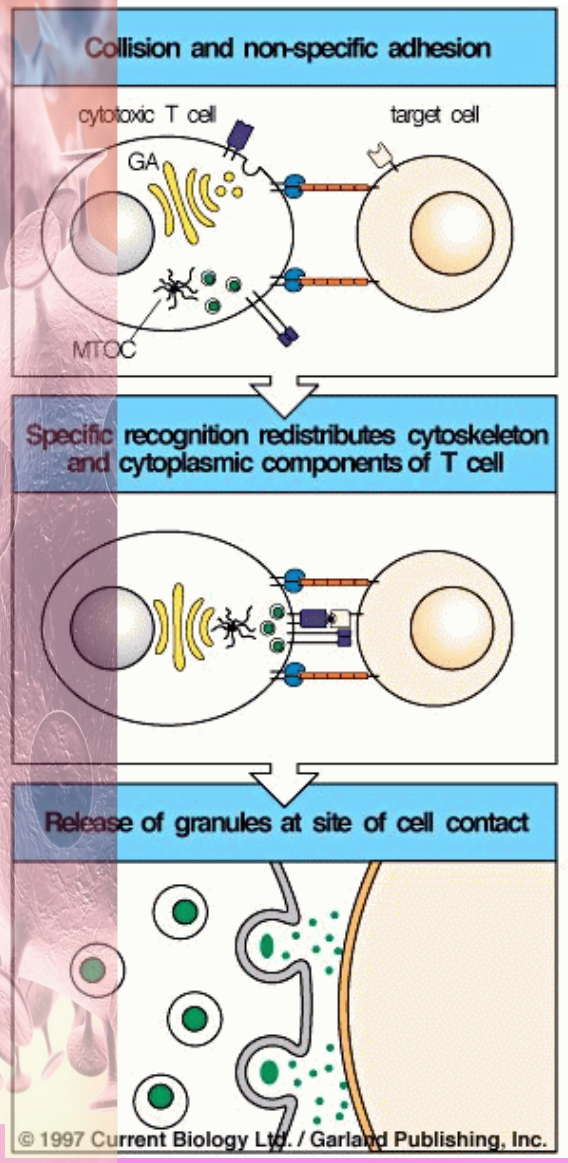


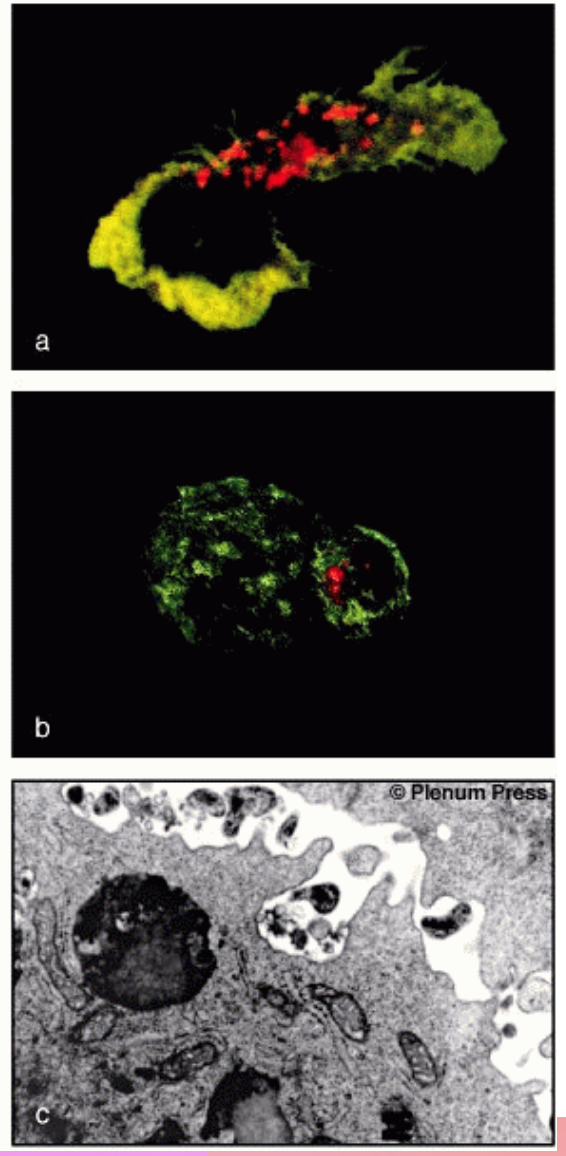
DIFERENCIAÇÃO FUNCIONAL DE LINFÓCITOS T



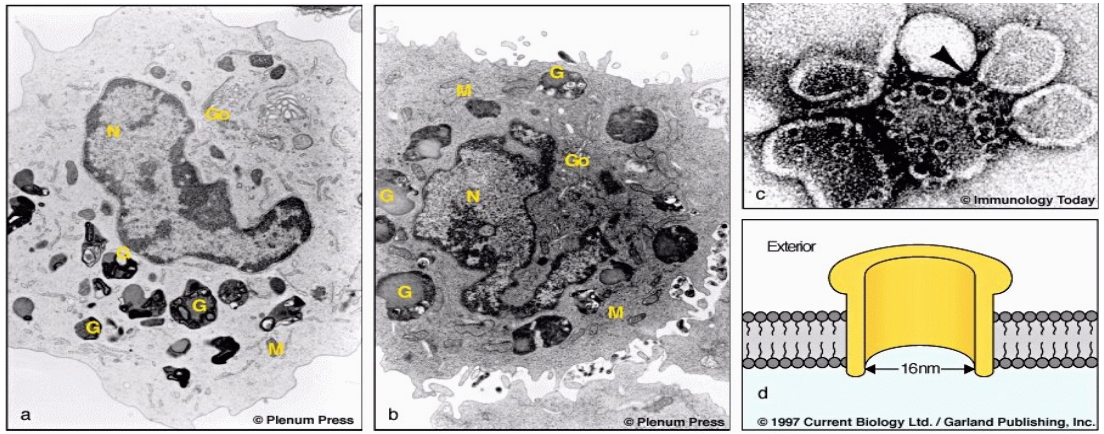
Imunobiologia de Janeway. 8ª Ed.
Abbas A:Imunologia celular e molecular. 8ª Ed.

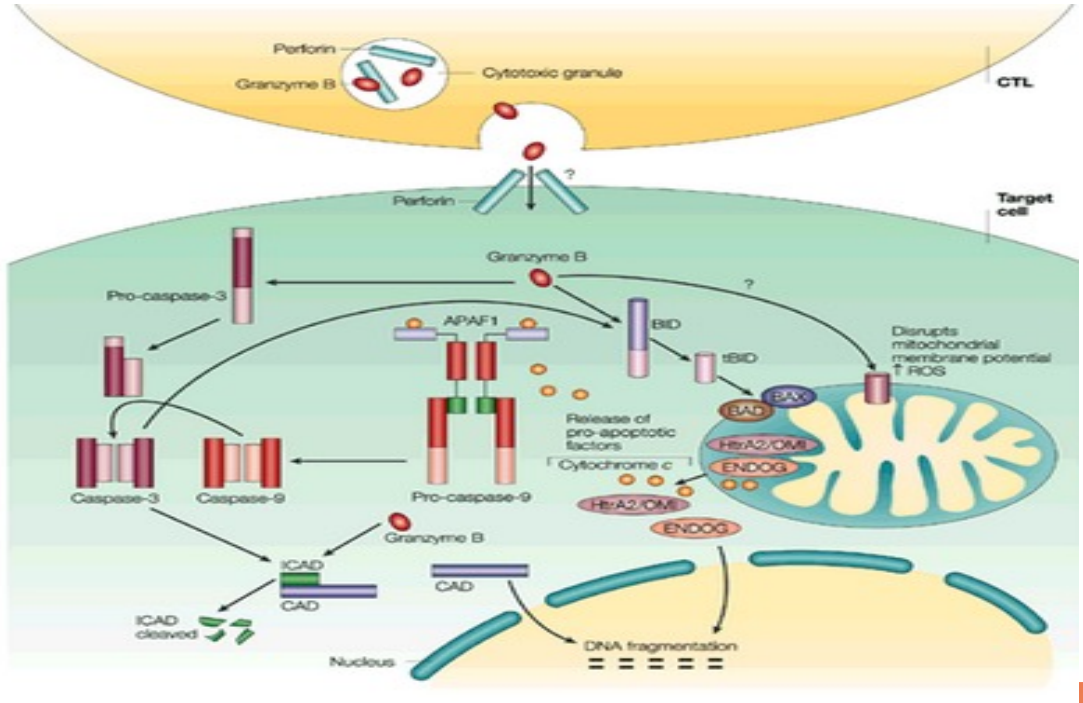
Linfócitos T CD8 - Citotóxicos

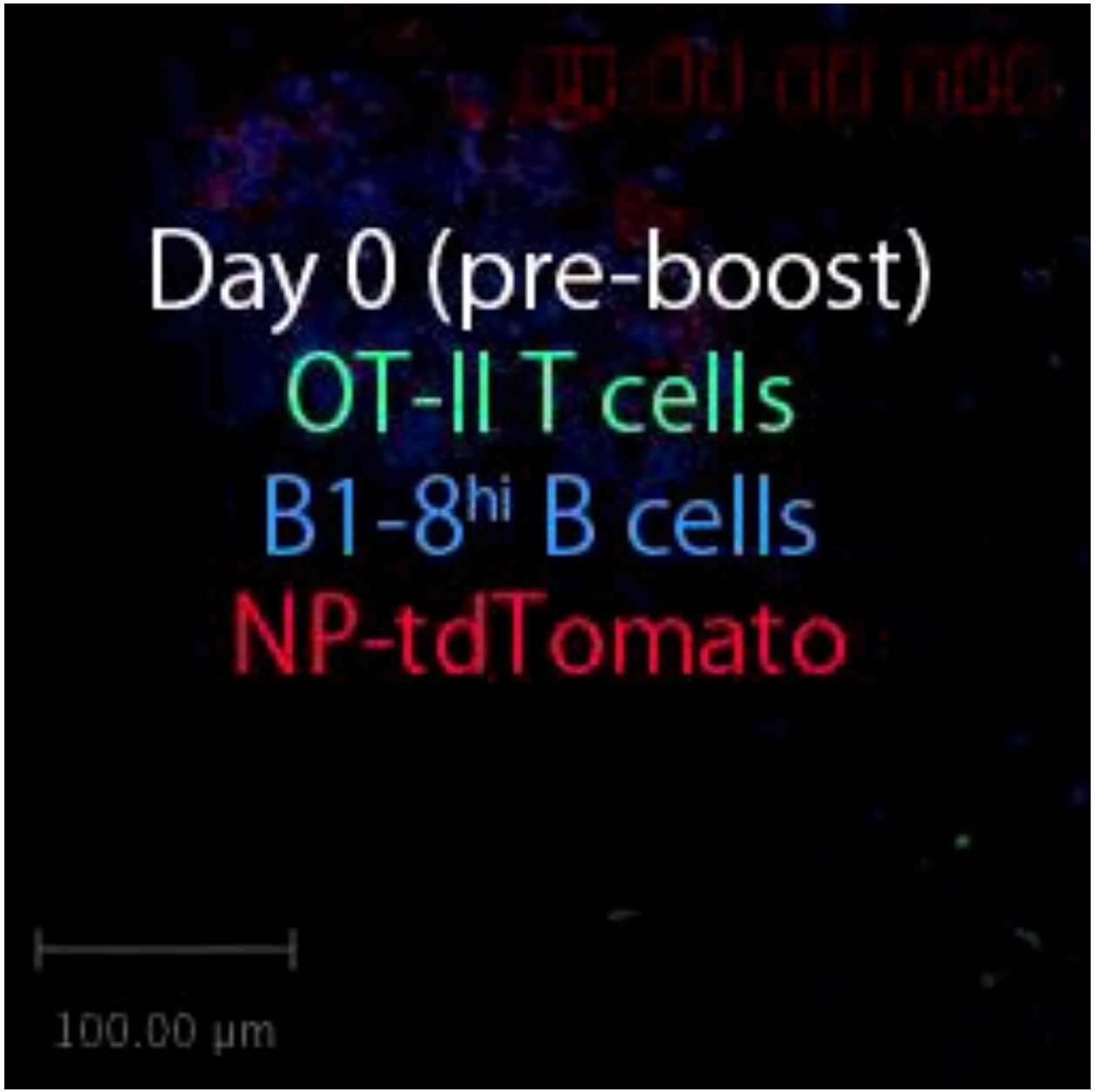




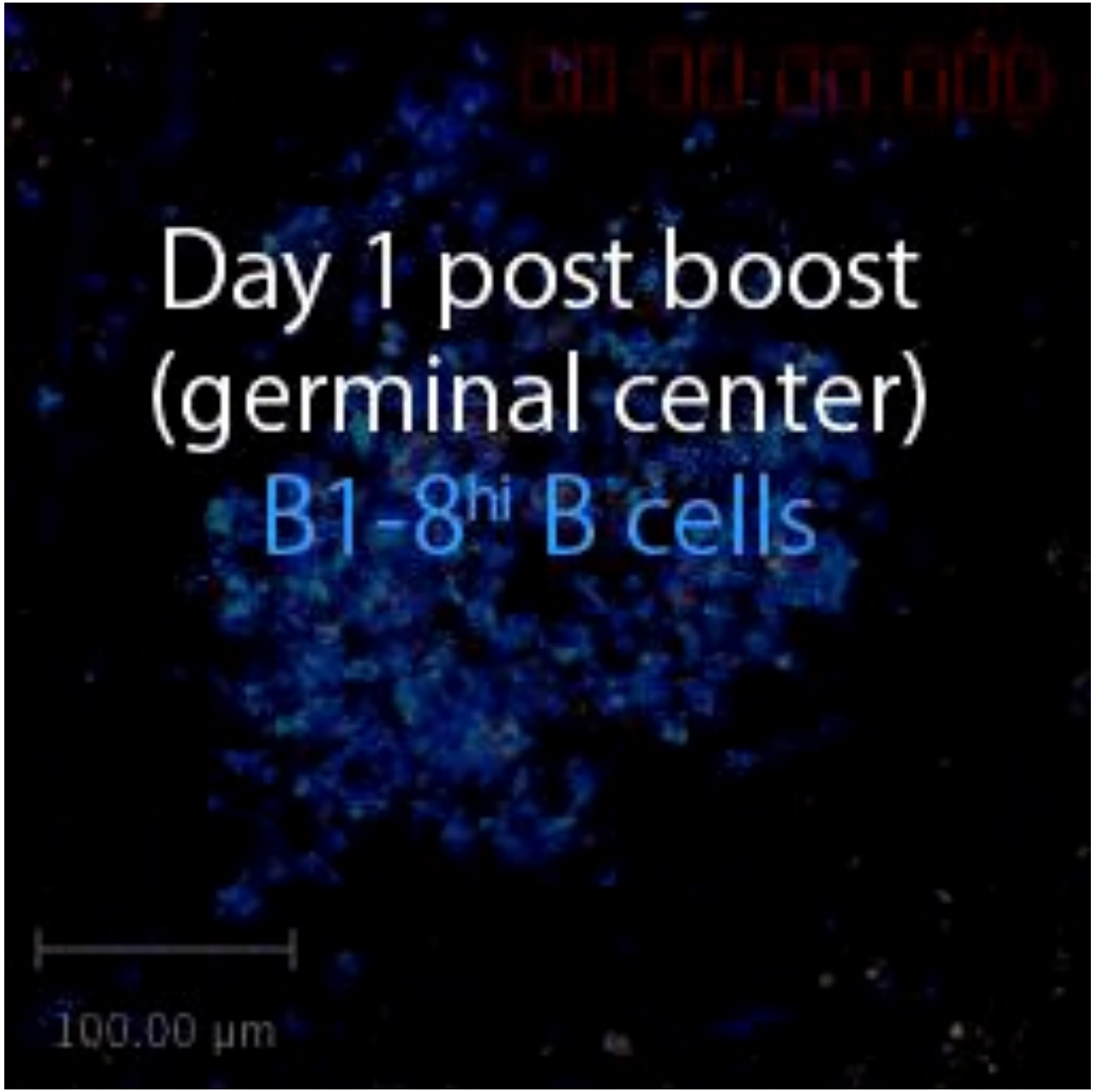
Granzimas e Perforinas



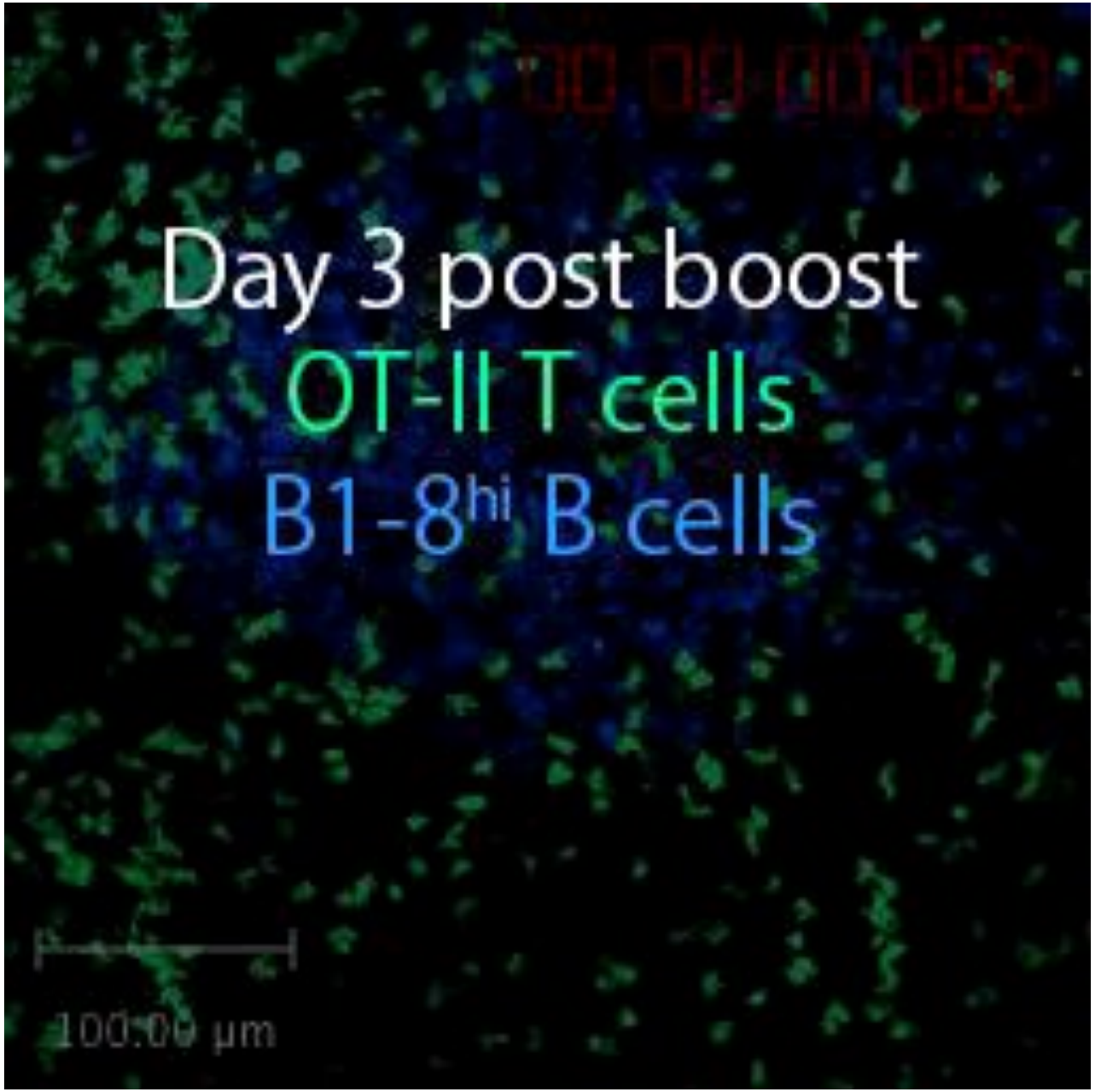




T follicular helper cell dynamics in germinal centers. Shulman Z et al. Science. 2013 Aug 9;341(6146):673-7.

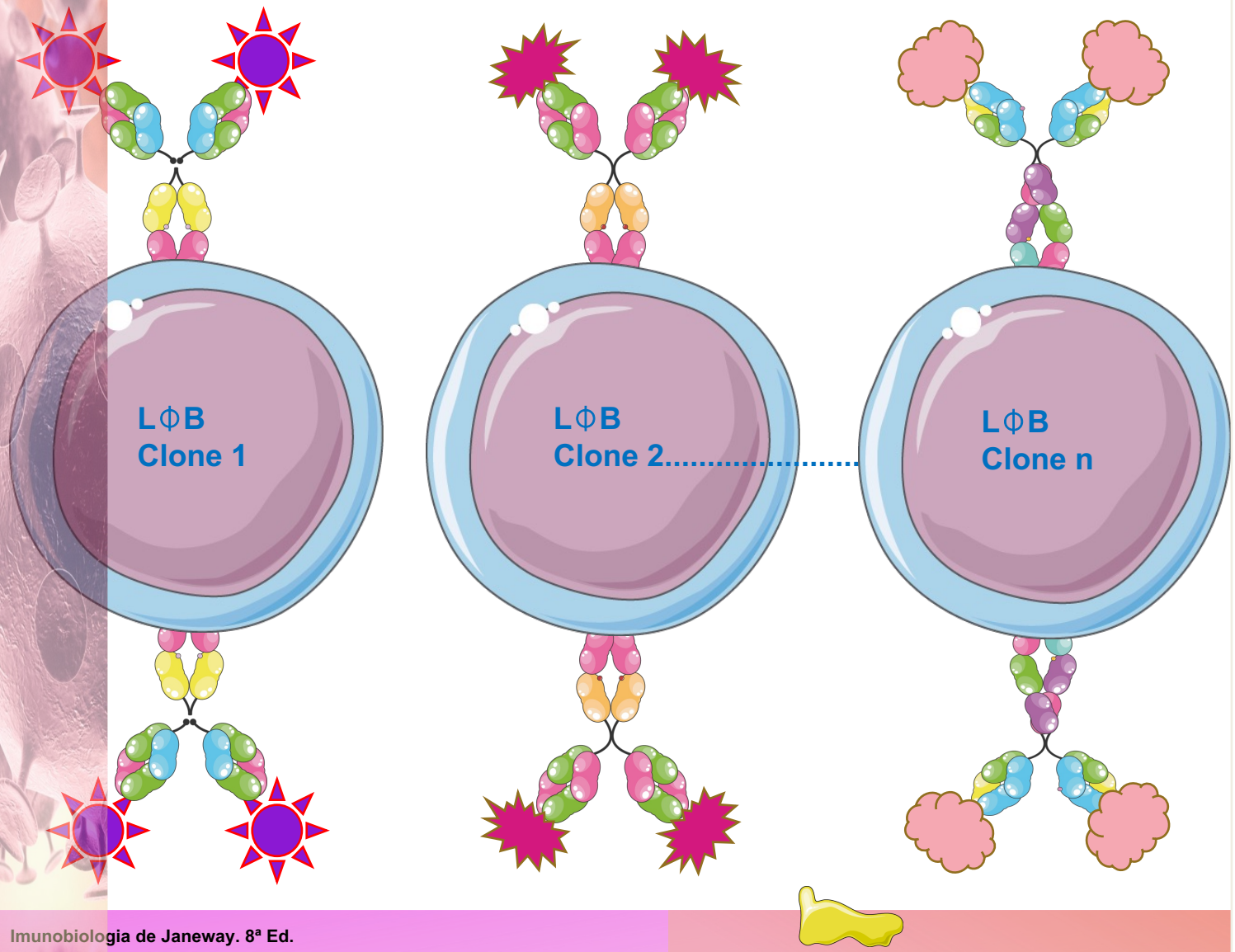


T follicular helper cell dynamics in germinal centers. Shulman Z et al. Science. 2013 Aug 9;341(6146):673-7.



T follicular helper cell dynamics in germinal centers. Shulman Z et al. Science. 2013 Aug 9;341(6146):673-7.

ATIVAÇÃO IMUNIDADE ADAPTATIVA LINFÓCITOS B - ANTÍGENOS SOLÚVEIS DE QUALQUER NATUREZA

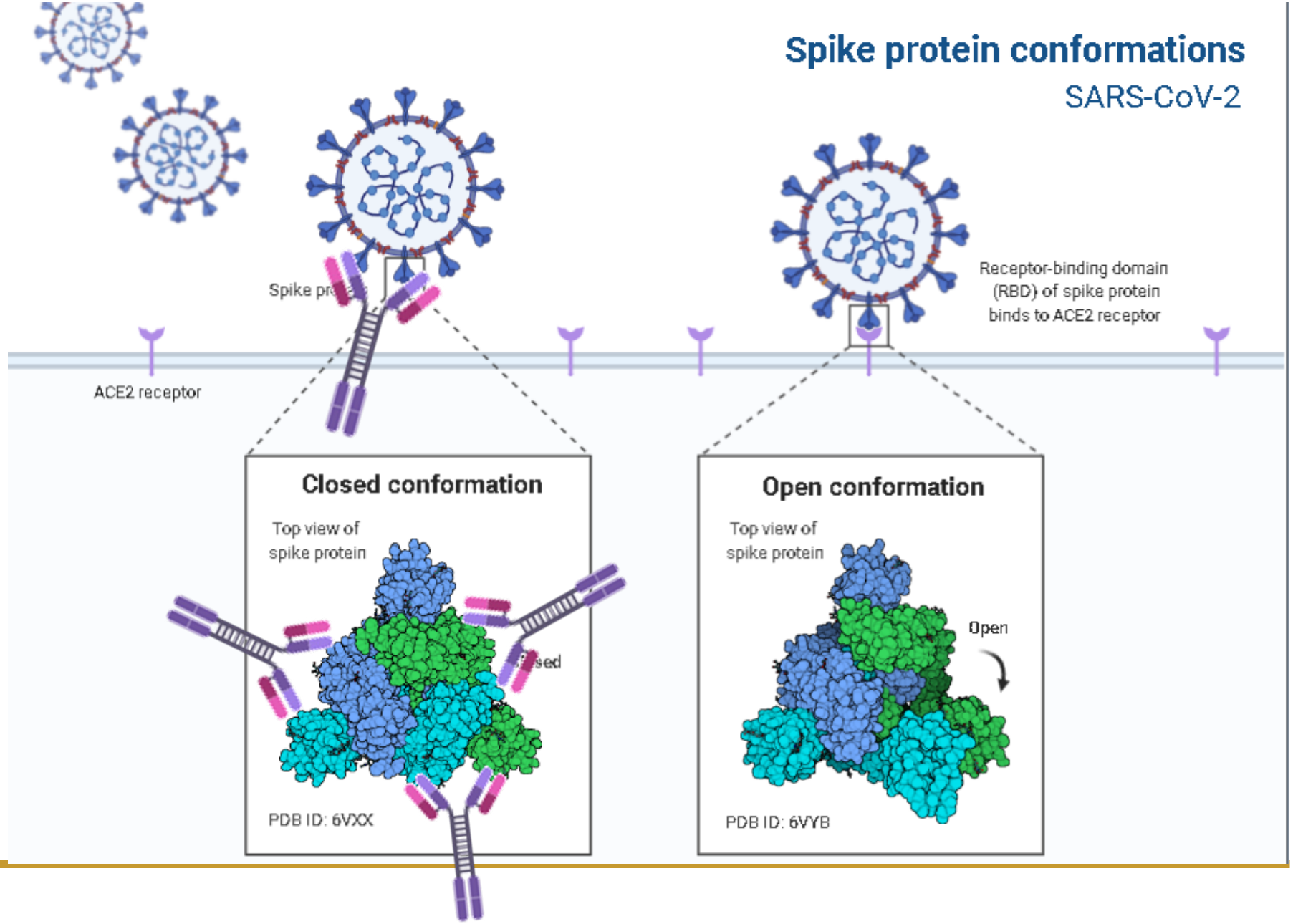


Imunobiologia de Janeway. 8ª Ed.
Abbas A:Imunologia celular e molecular. 8ª Ed.

ANTICORPOS NEUTRALIZANTES

Anti-SPIKE

Evitar a ADESÃO à Superfície da Célula e Invasão Viral



Então...como seria um **resumo** de

tudo isso no **PULMÃO**?

Ambiente Pulmonar – Alvéolos

PNEUMÓCITOS E MACRÓFAGOS EXPRESSAM

ACE-2 / TMPRSS2

TLRs
NLRs
MAVS

aço Alveolar
Ar

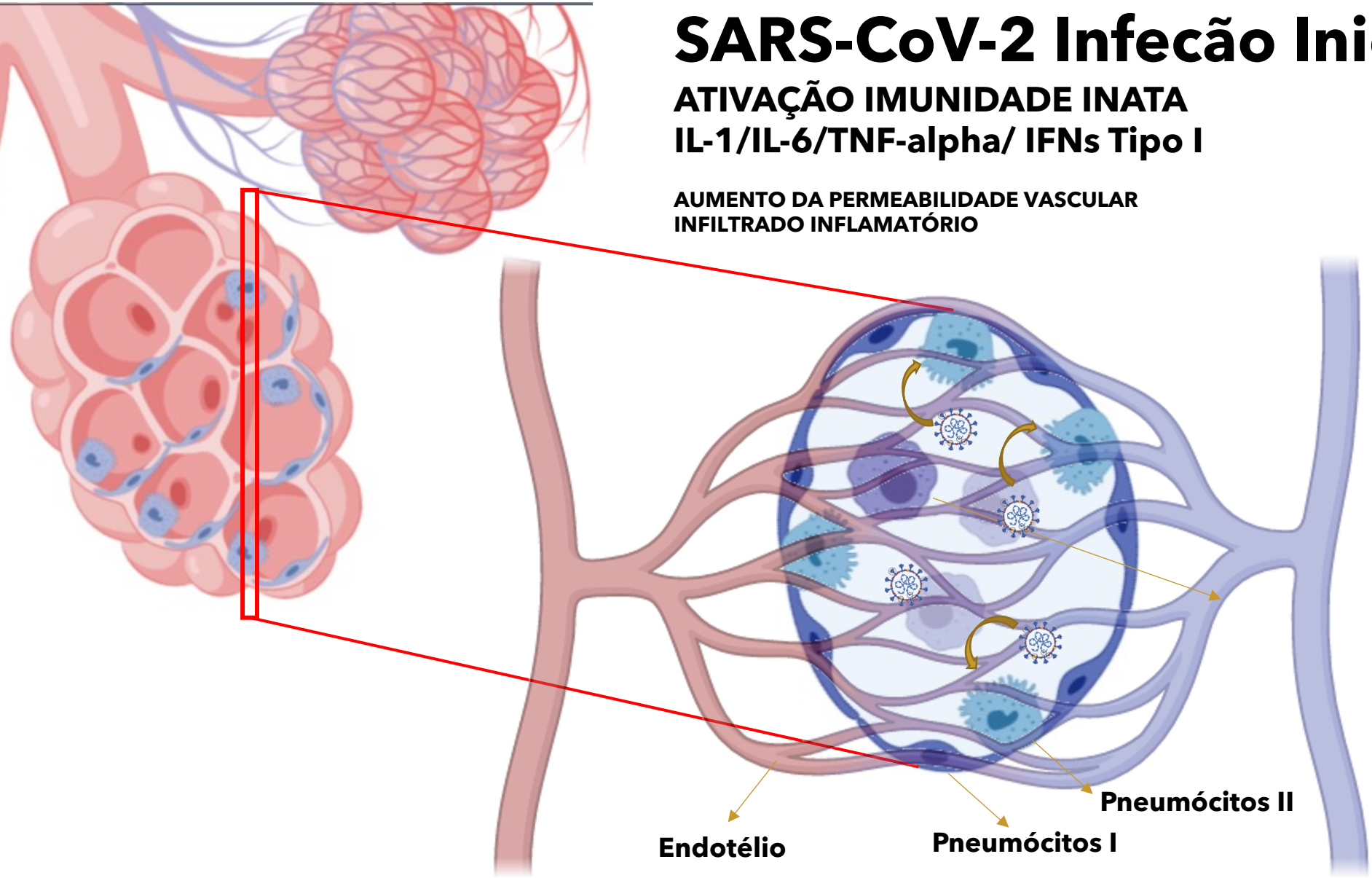
Moléculas
Surfactante
Proteínas

Células
Macrófagos
mócitos I e II
s Endoteliais

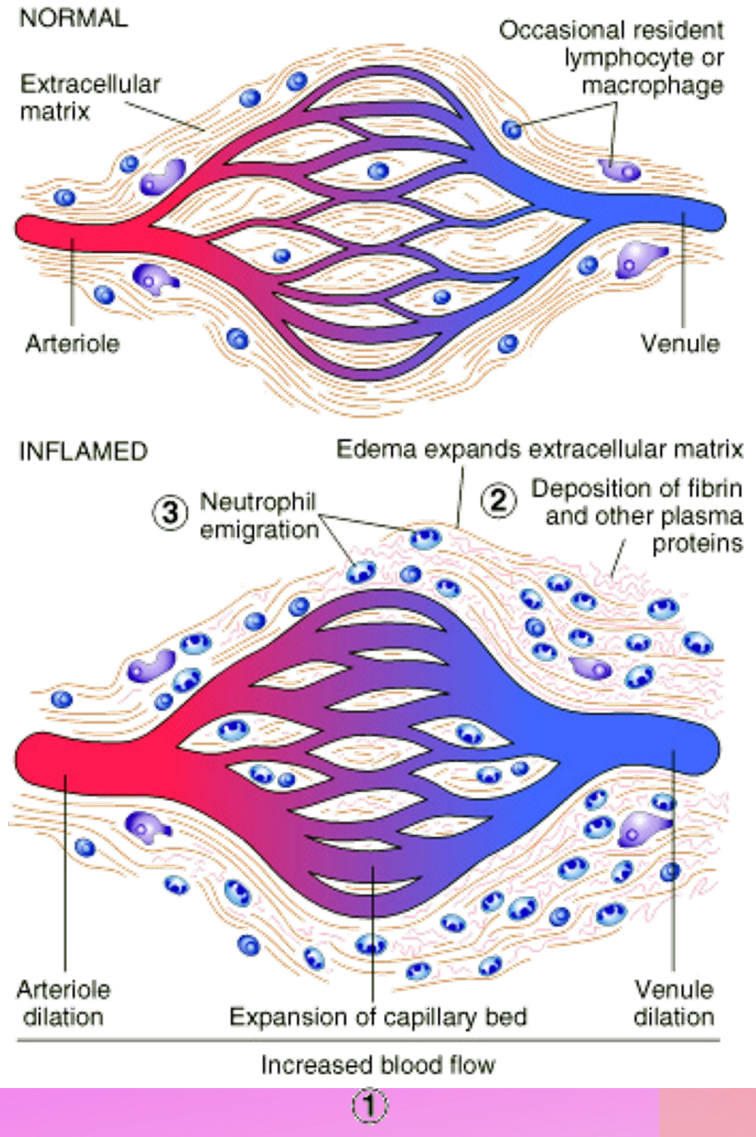
SARS-CoV-2 Infecão Inicial

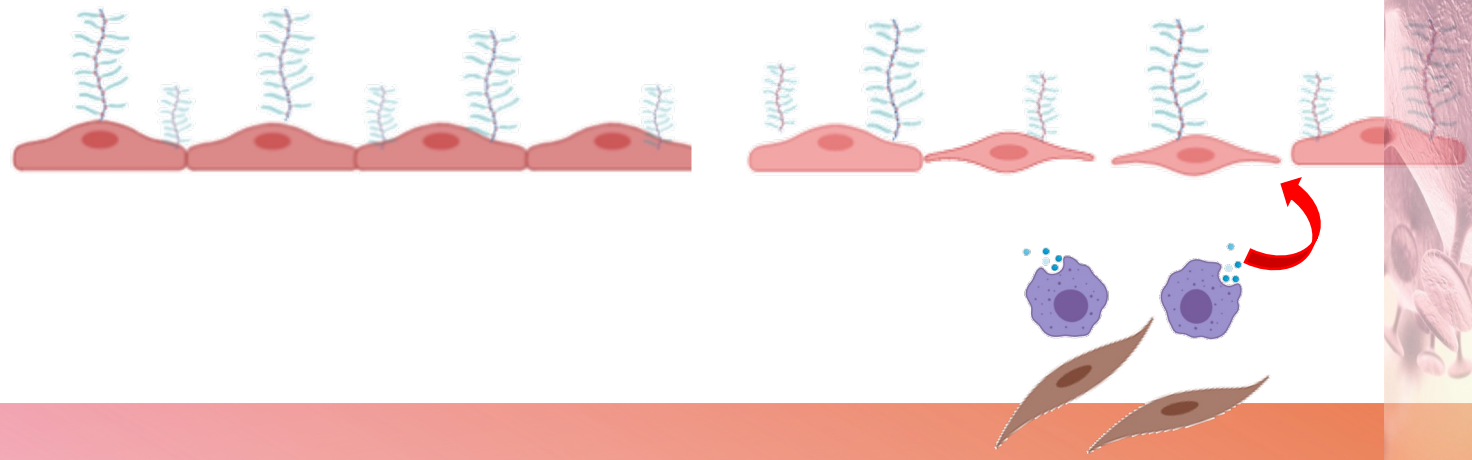
ATIVAÇÃO IMUNIDADE INATA
IL-1/IL-6/TNF-alpha/ IFNs Tipo I

AUMENTO DA PERMEABILIDADE VASCULAR
INFILTRADO INFLAMATÓRIO



ALTERAÇÕES NO FLUXO SANGUÍNEO E MIGRAÇÃO DE LEUCÓCITOS

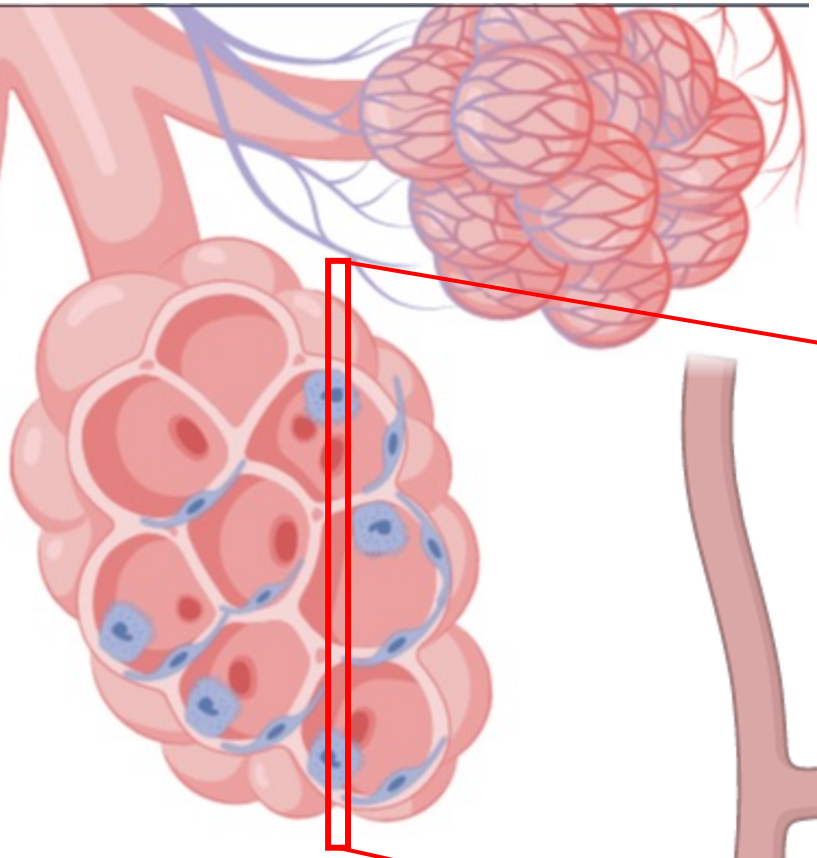


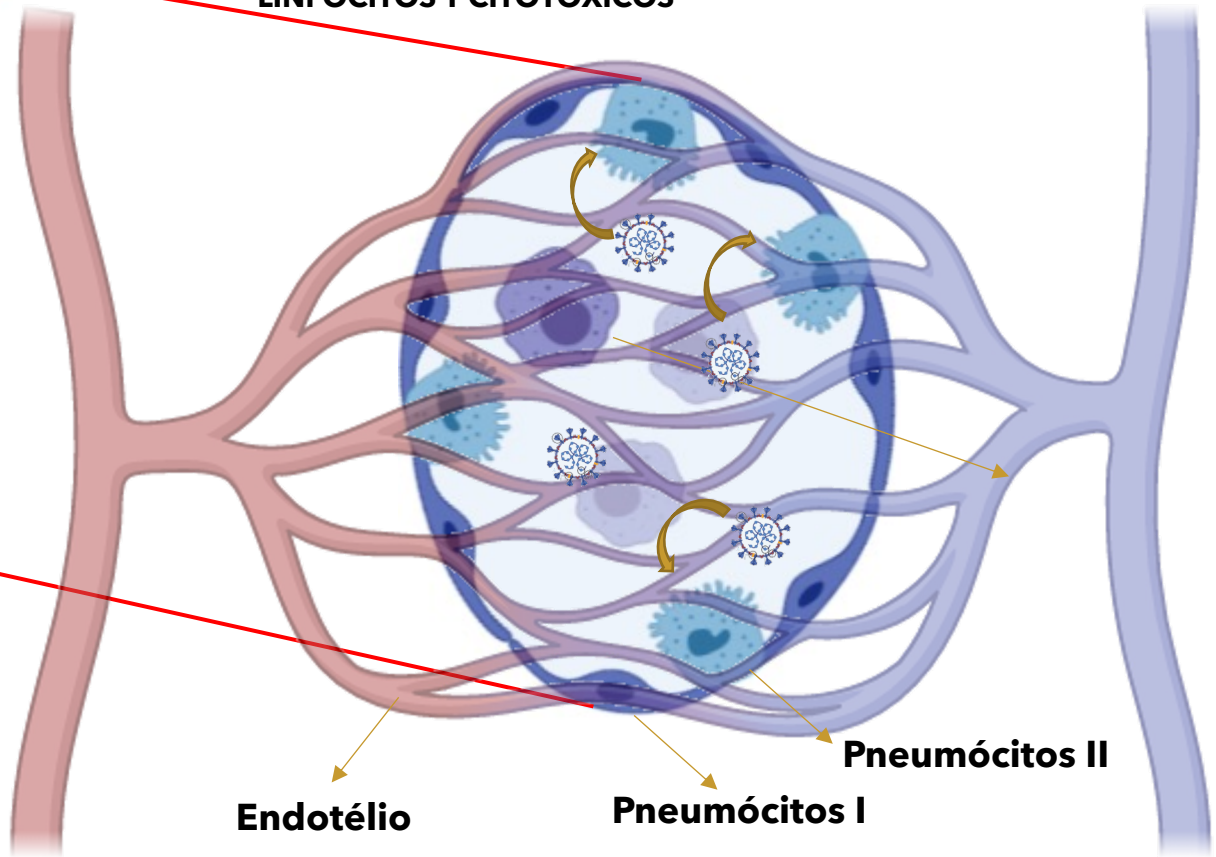


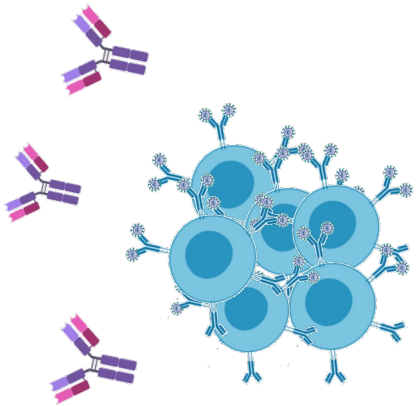
EVOLUÇÃO DA INFECÇÃO

ATIVAÇÃO IMUNIDADE INATA + ADAPTATIVA
IL-1/IL-6/TNF-alpha/ IFNs Tipo I + IFN-G + ANTICORPOS

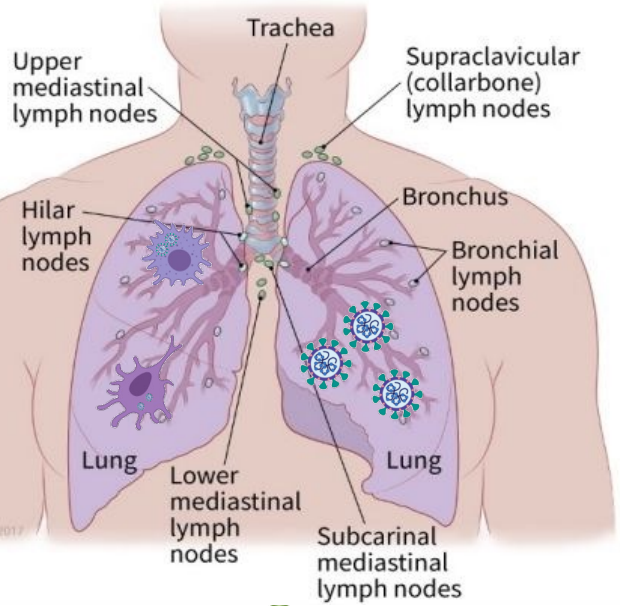
AUMENTO DA PERMEABILIDADE VASCULAR
INFILTRADO INFLAMATÓRIO
ANTICORPOS NEUTRALIZANTES
LINFÓCITOS T CITOTÓXICOS

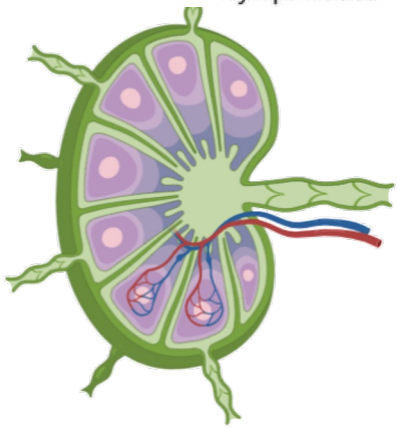


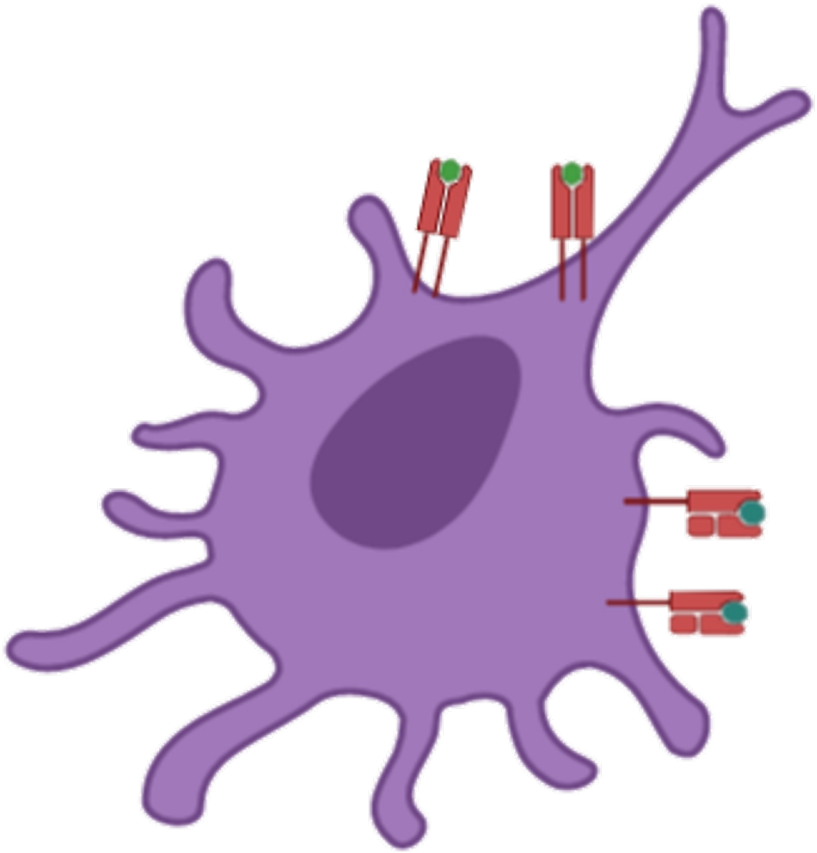


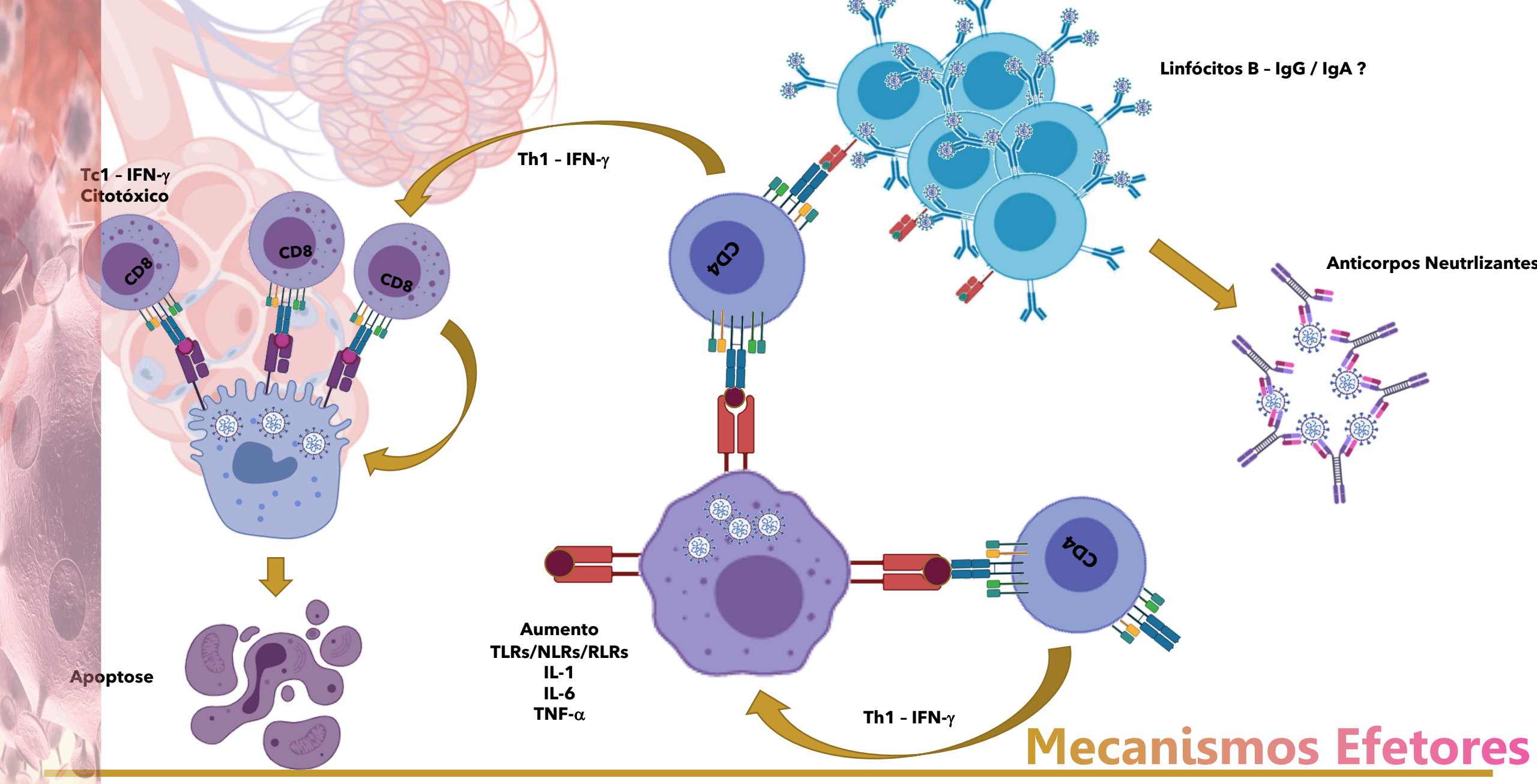


Ativação da Imunidade Adaptativa
Linfonodos, Baço e no Sítio da Infecção





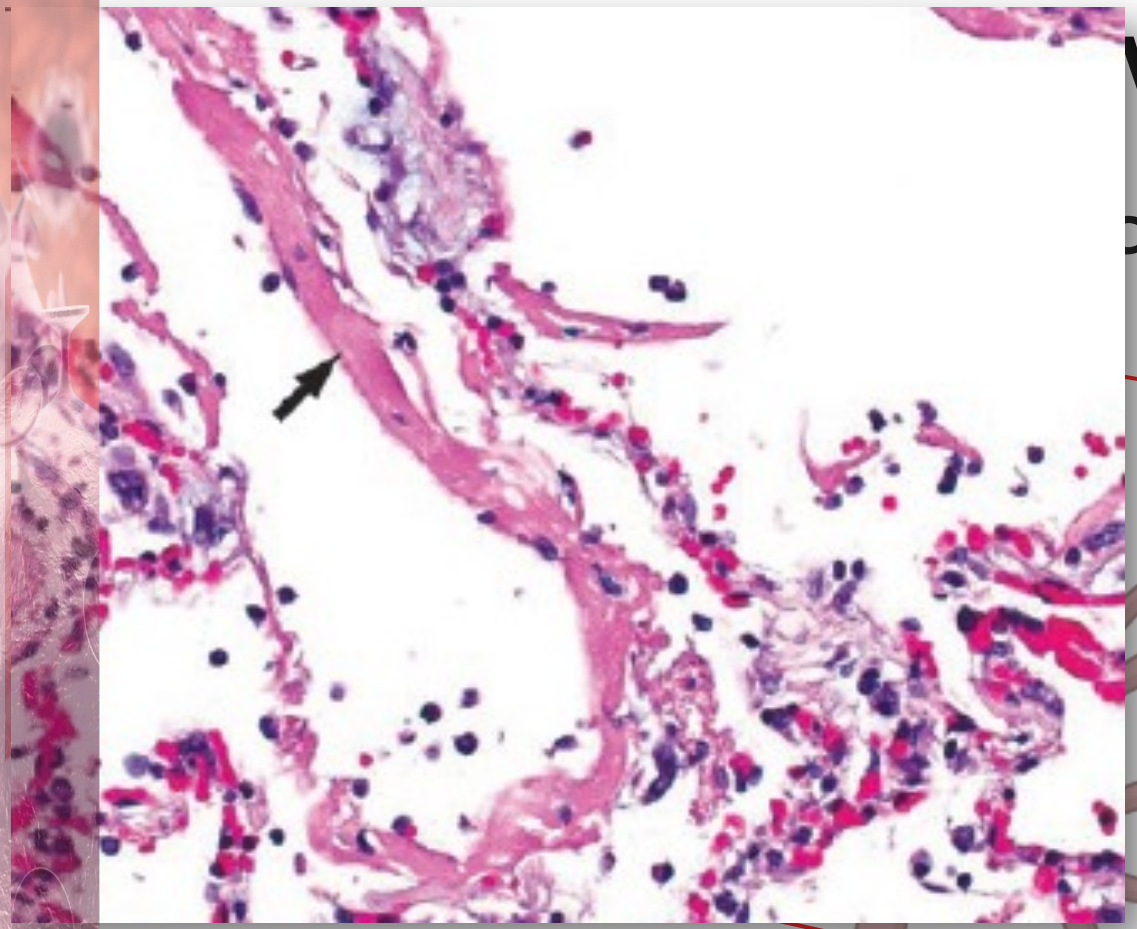


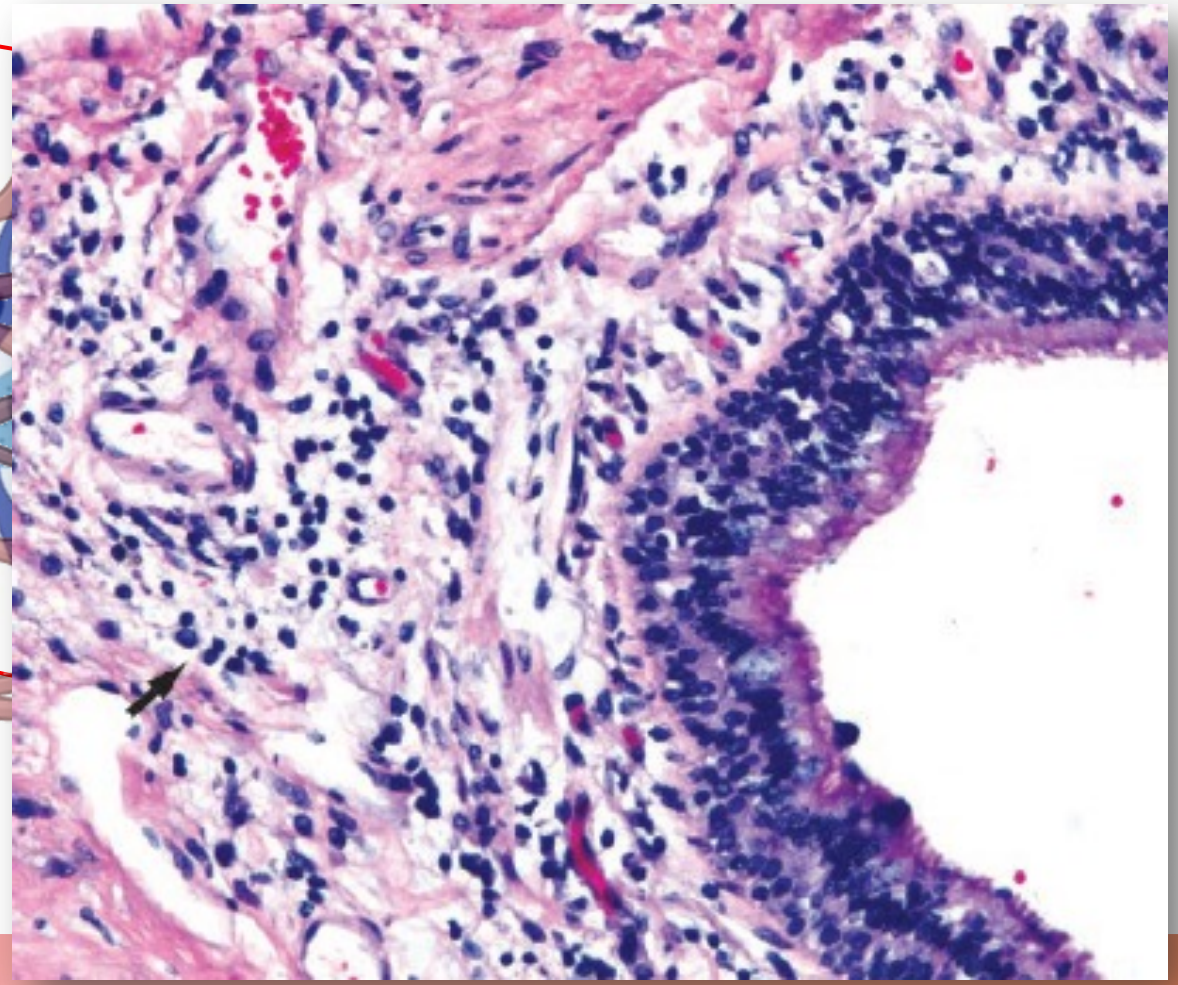


Mecanismos Efetores

VID-19 GRAVE

CERBAÇÃO DA RESPOSTA IMUNE



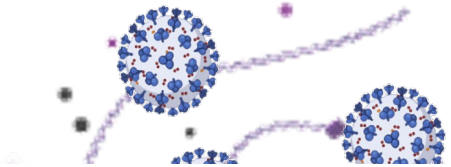


Endotélio

COVID-19 Autopsies, Oklahoma, USA

Lisa M. Barton, MD, PhD,[1] Eric J. Duval, DO,[1] Edana Stroberg, DO,[1] Subha Ghosh, MD,[2] and Sanjay Mukhopadhyay, MD[2,o]

INFLAMASOMAS E COVID-19

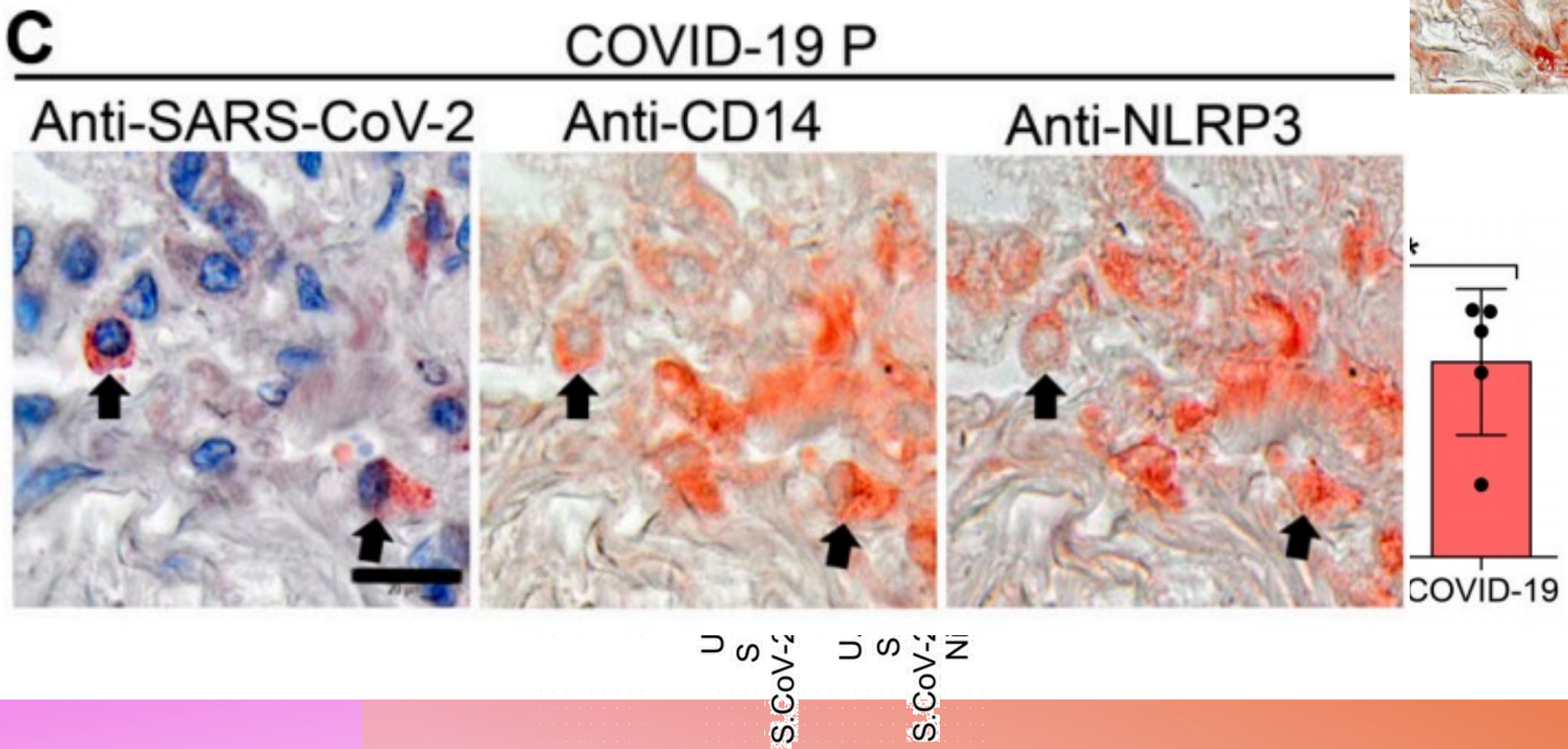


BRIEF DEFINITIVE REPORT

Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients

Infla

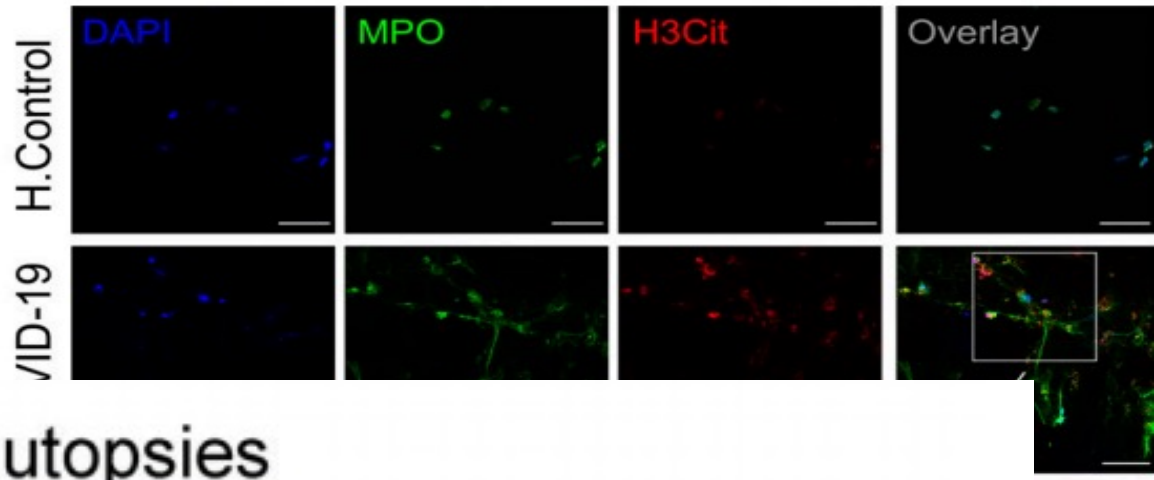
Secreç

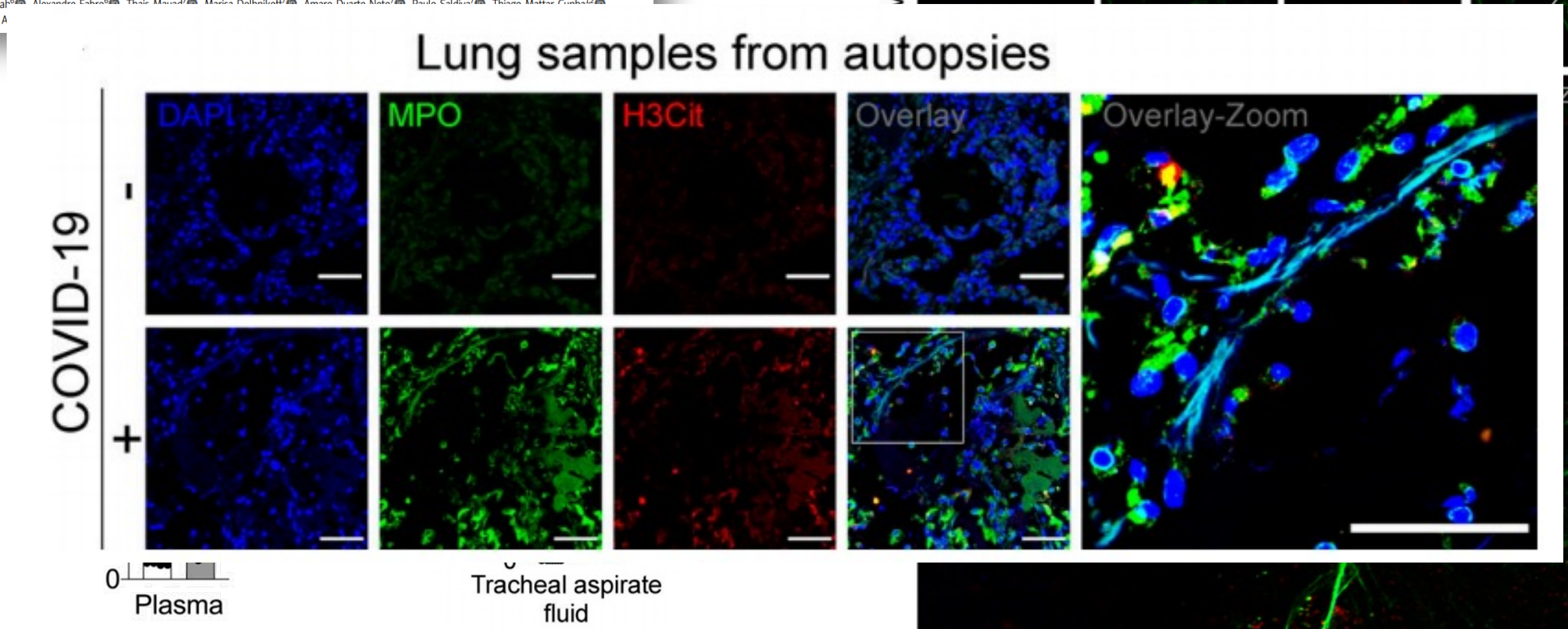


BRIEF DEFINITIVE REPORT

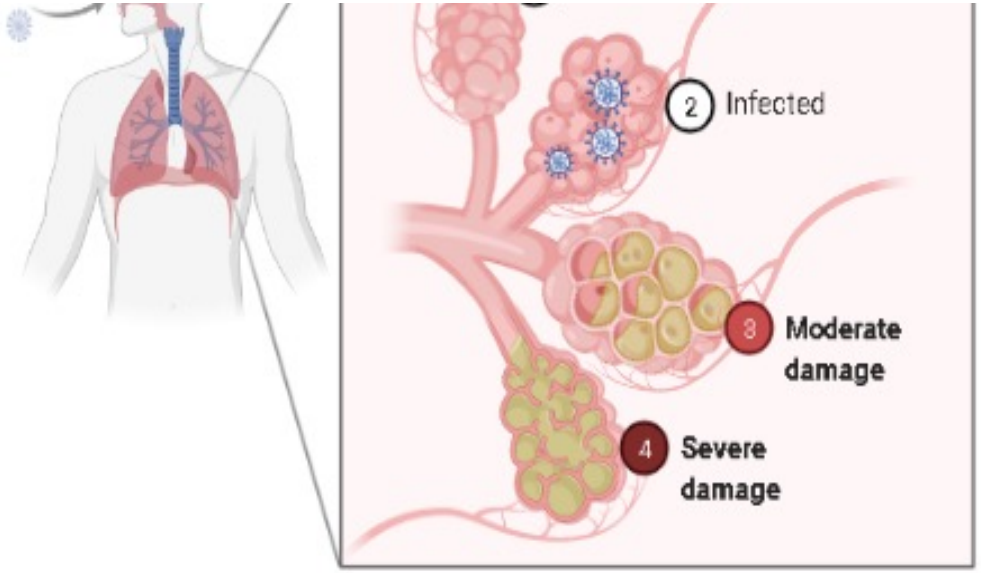
SARS-CoV-2–triggered neutrophil extracellular traps mediate COVID-19 pathology

Flavio Protasio Veras[1,2], Marjorie Cornejo Pontelli[3,4], Camila Meirelles Silva[1,2], Juliana E. Toller-Kawahisa[1,2], Mikhael de Lima[1,2], Daniele Carvalho Nascimento[1,2], Ayda Henriques Schneider[1,2], Diego Caetité[1,2], Lucas Alves Tavares[3,4], Isadora M. Paiva[1,2], Roberta Rosales[4], David Colón[1,2], Ronaldo Martins[3,4], Italo Araujo Castro[3,4], Glaucia M. Almeida[1,2], Maria Isabel Fernandes Lopes[5], Maíra Nilson Benatti[5], Letícia Pastorelli Bonjorno[5], Marcela Cavichioli Giannini[5], Rodrigo Luppino-Assad[5], Sérgio Luna Almeida[5], Fernando Vilar[5], Rodrigo Santana[5], Valdes R. Bollela[5], Maria Auxiliadora-Martins[5], Marcos Borges[5], Carlos Henrique Miranda[5], Antônio Pazin-Filho[5], Luis Lamberti P. da Silva[3,4], Larissa Dias Cunha[4], Dario S. Zamboni[1,4], Felipe Dal-Pizzol[8], Luiz O. Leiria[1,2], Li Siyuan[6], Sabrina Batah[6], Alexandre Fabro[6], Thais Mauad[7], Marisa Dolhnikoff[7], Amaro Duarte Neto[7], Paulo Saldiva[7], Thiago Mattar Cunha[1,2], José Carlos A

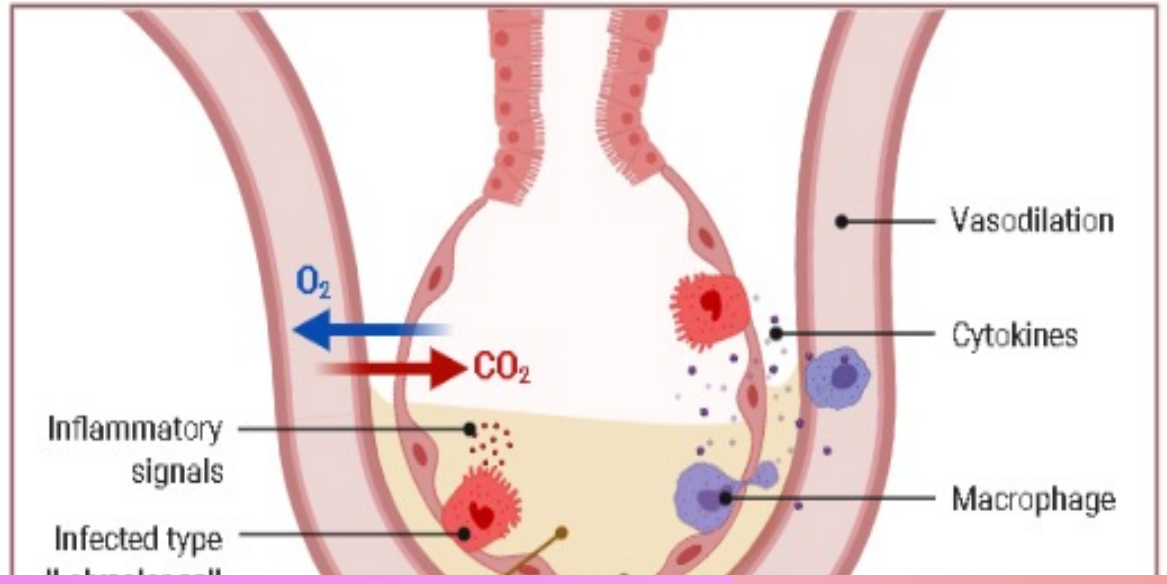




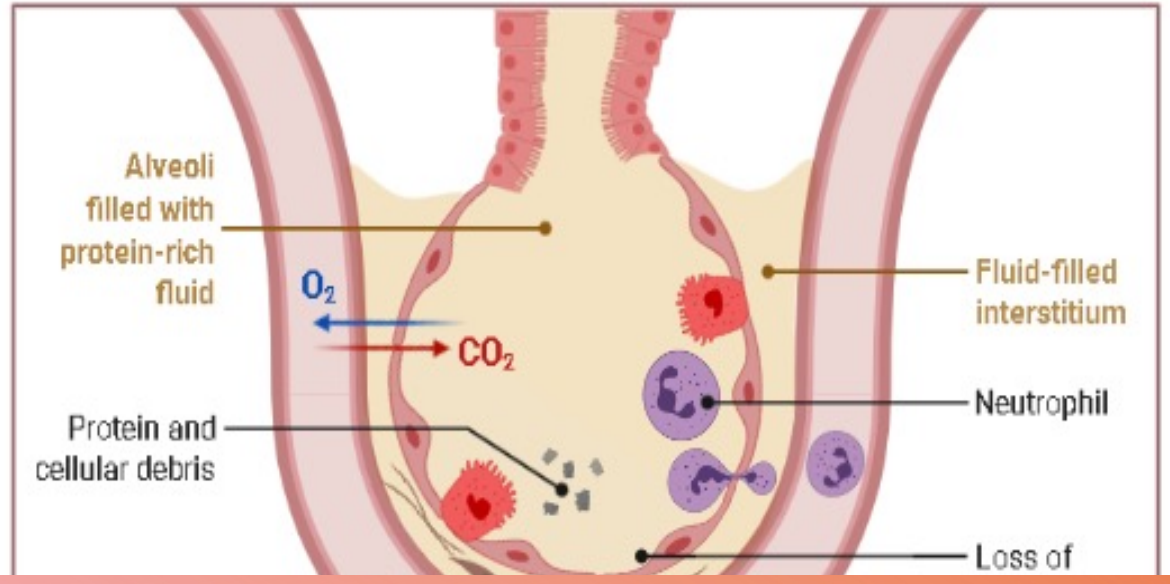
Effects of SARS-CoV-2 on respiration



3 Moderate damage: Accumulating fluid, reduced gas exchange



4 Severe damage: Build up of protein-rich fluid, very limited gas exchang

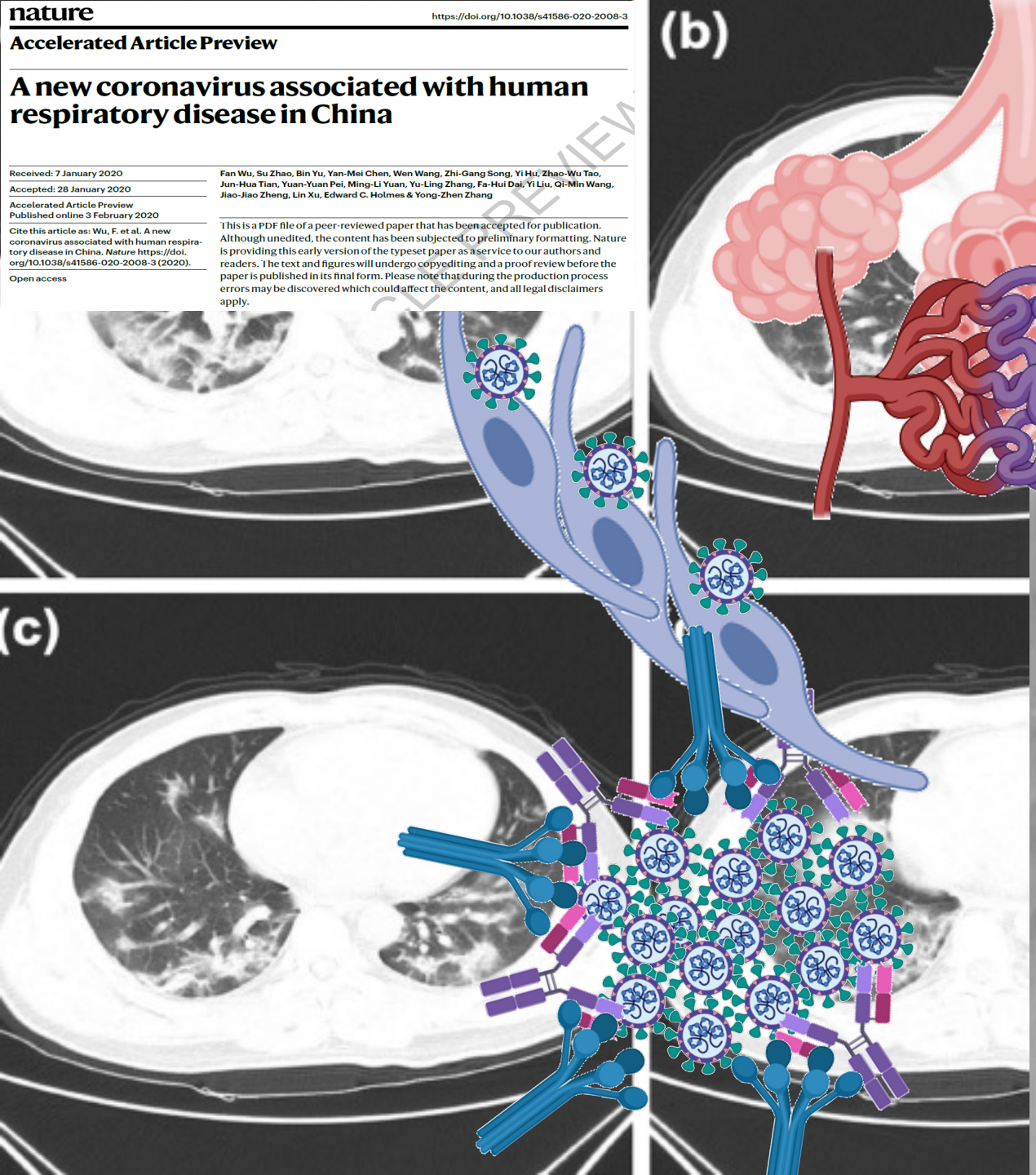


nature
https://doi.org/10.1038/s41586-020-2008-3
Accelerated Article Preview

A new coronavirus associated with human respiratory disease in China

Received: 7 January 2020
Accepted: 28 January 2020
Accelerated Article Preview
Published online 3 February 2020
Cite this article as: Wu, F. et al. A new coronavirus associated with human respiratory disease in China. *Nature* https://doi.org/10.1038/s41586-020-2008-3 (2020).
Open access

Fan Wu, Su Zhao, Bin Yu, Yan-Mei Chen, Wen Wang, Zhi-Gang Song, Yi Hu, Zhao-Wu Tao, Jun-Hua Tian, Yuan-Yuan Pei, Ming-Li Yuan, Yu-Ling Zhang, Fa-Hui Dai, Yi Liu, Qi-Min Wang, Jiao-Jiao Zheng, Lin Xu, Edward C. Holmes & Yong-Zhen Zhang



Cytokine Storm
IL-1
IL-6
TNF-a

Imunocomplexo?
Complemento

Microtrombos

Cytokine Storm

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cytokine Storm

David C. Fajgenbaum, M.D., and Carl H. June, M.D.

IL-1

IL-6

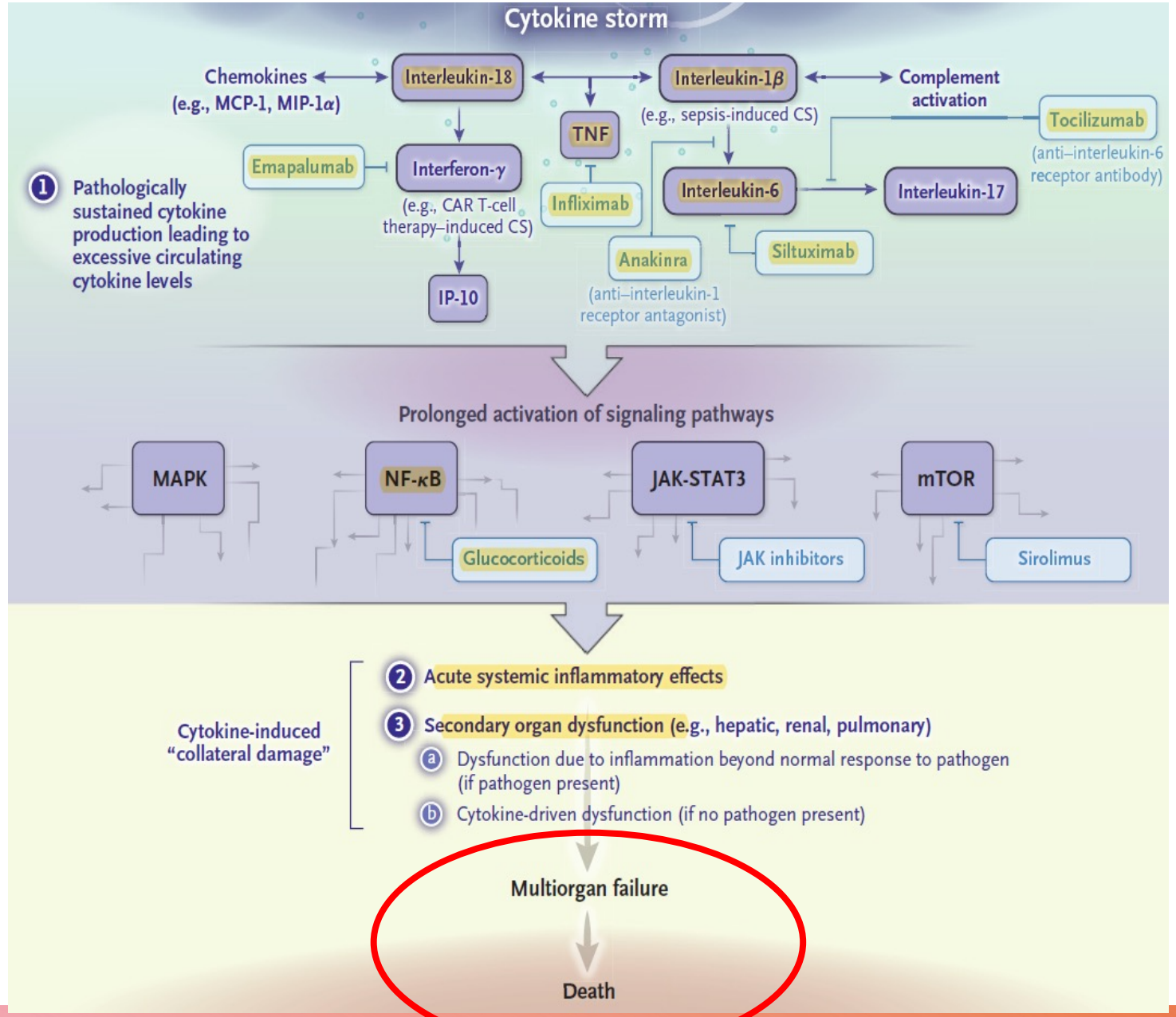
TNF-alpha

Interferons Tipo I

IFN-alpha
IFN-beta

Interferon Tipo II

IFN-gamma

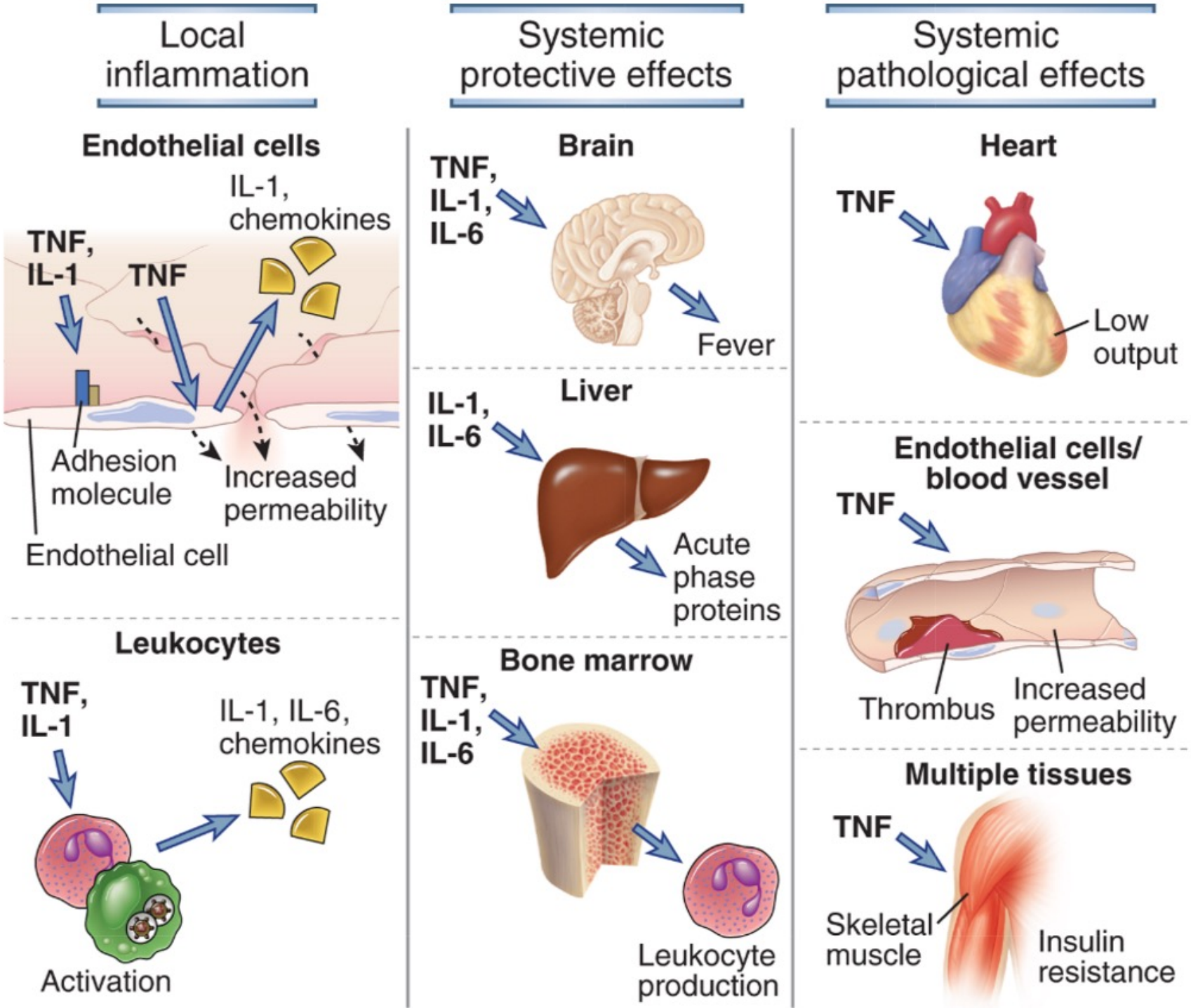


Efeitos

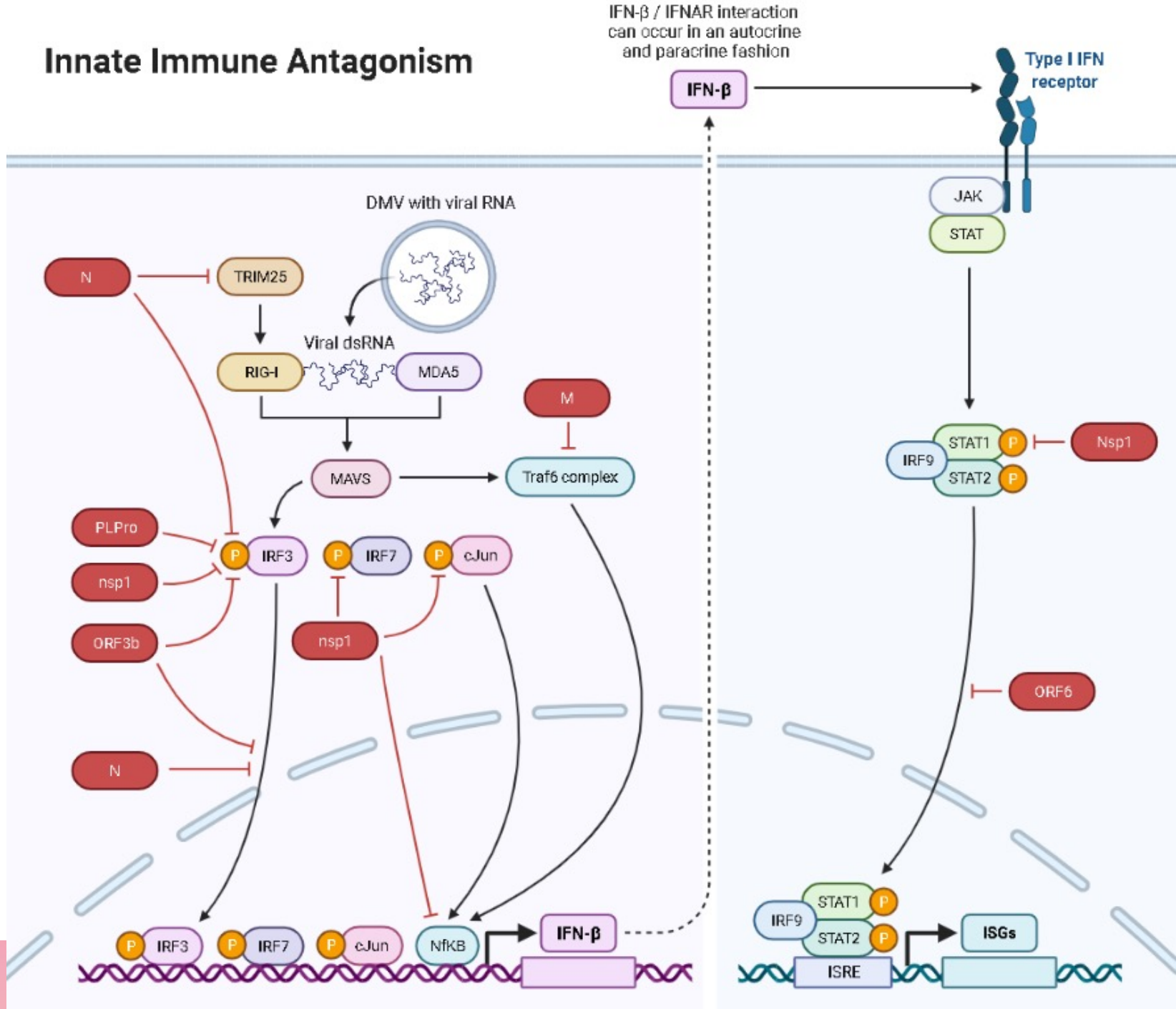
Locais

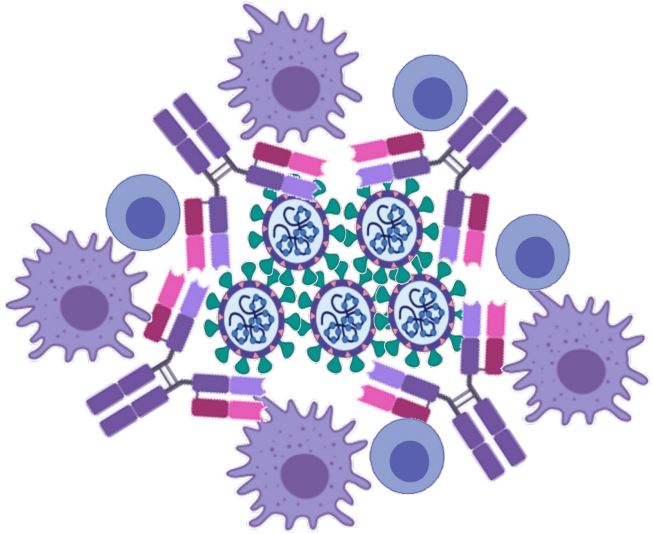
E

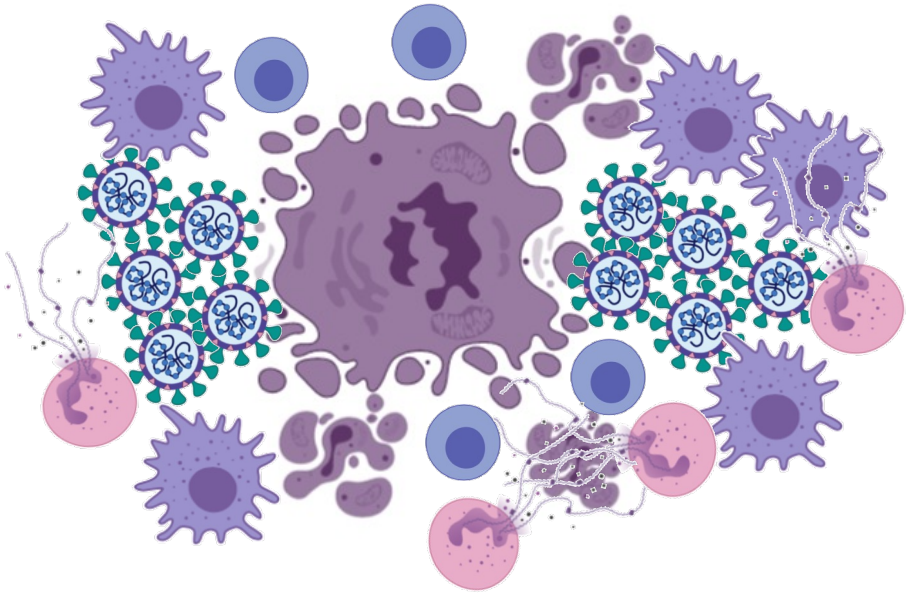
Sistêmicos



Como o SARS-CoV2 Escapa Do Sistema Imune ?







Resposta Imune Efetora
Proteção - Cura

Resposta Imune Exacerbada ou Deficiente
Imunopatologia

De onde ele tirou ISSO ?

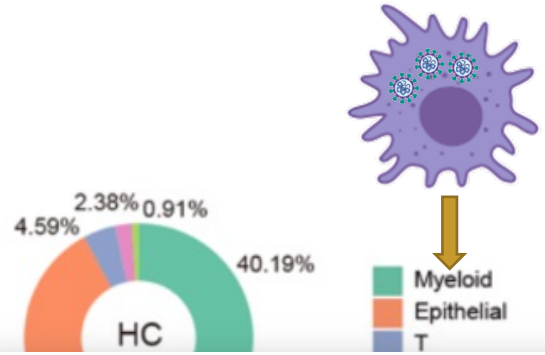
ARTIGOS INTERESSANTES

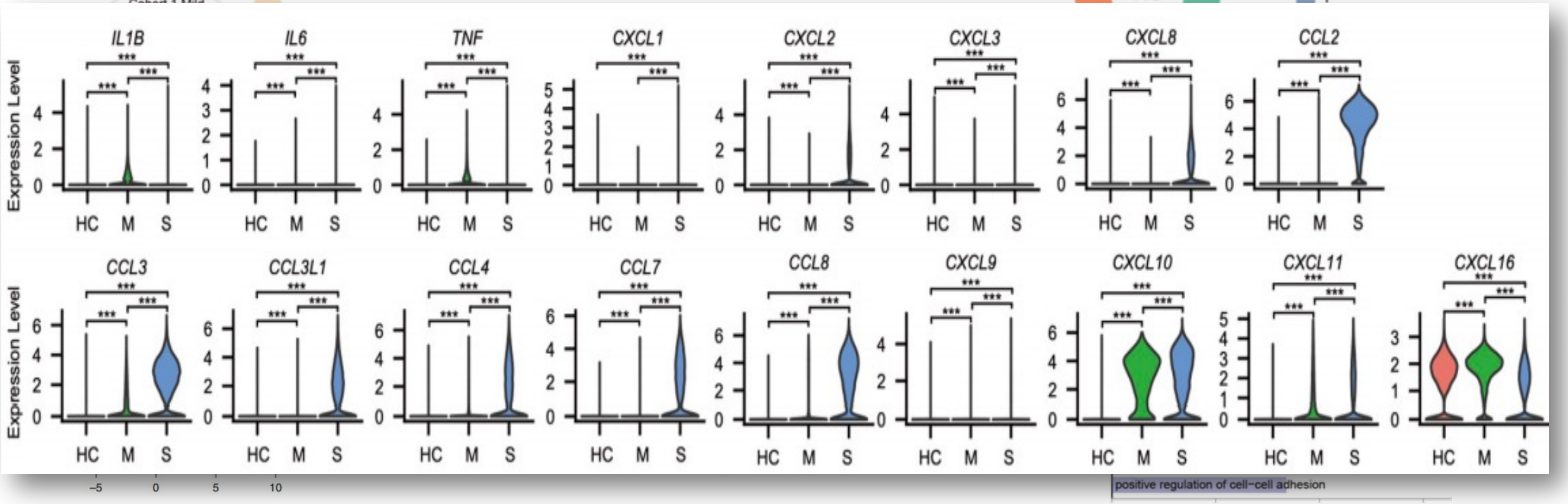
nature medicine
BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-020-0901-9
Check for updates

Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19

Mingfeng Liao[1,6], Yang Liu[1,6], Jing Yuan[2,6], Yanling Wen[1], Gang Xu[1], Juanjuan Zhao[1], Lin Cheng[1], Jinxiu Li[2], Xin Wang[1], Fuxiang Wang[2], Lei Liu[1,3]✉, Ido Amit[4]✉, Shuye Zhang[5]✉ and Zheng Zhang[1,3]✉

3 Clusters de Macrófagos



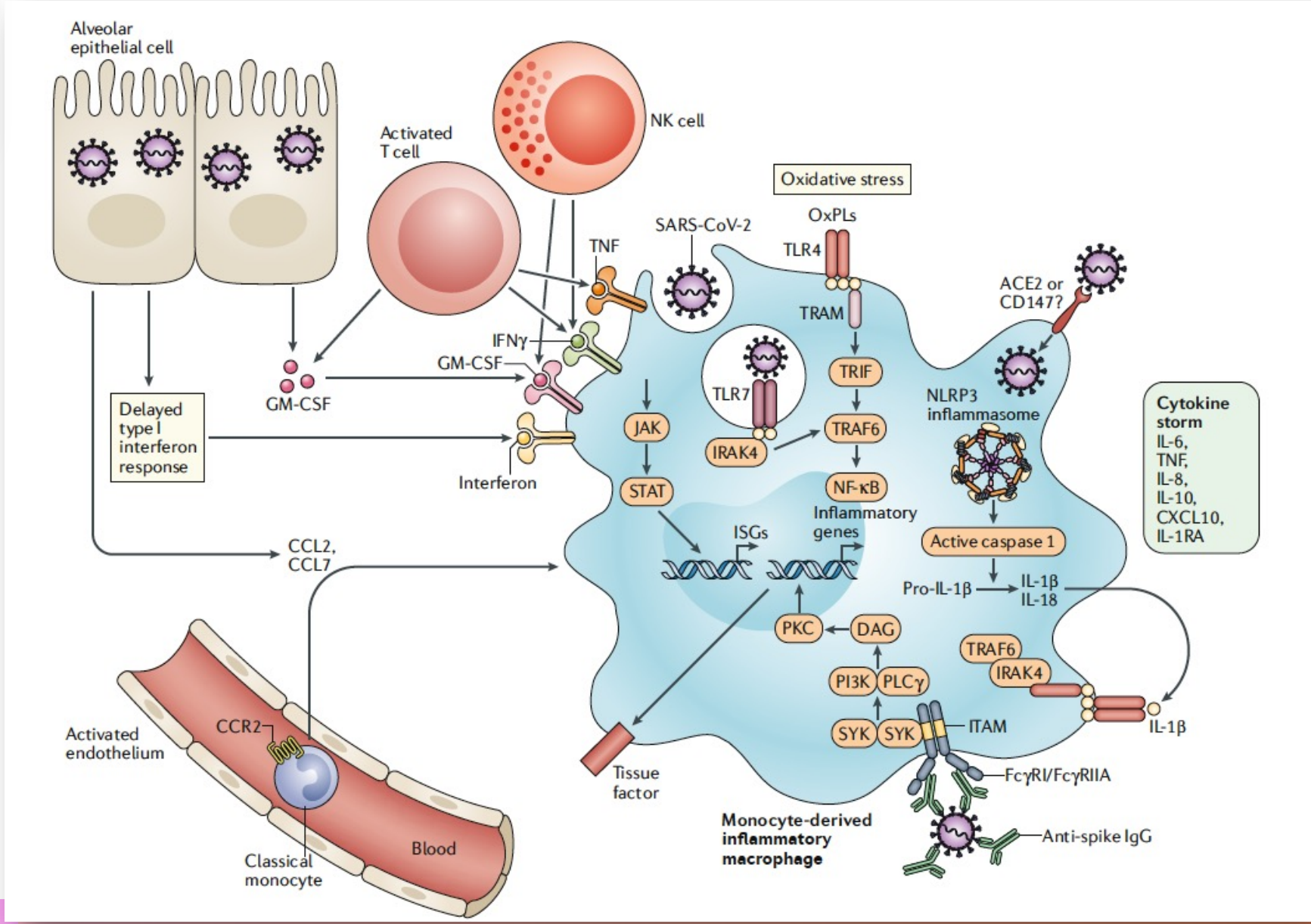


Resposta Imune Efetora
Proteção - Cura

Resposta Imune Exacerbada ou Deficiente
Imunopatologia

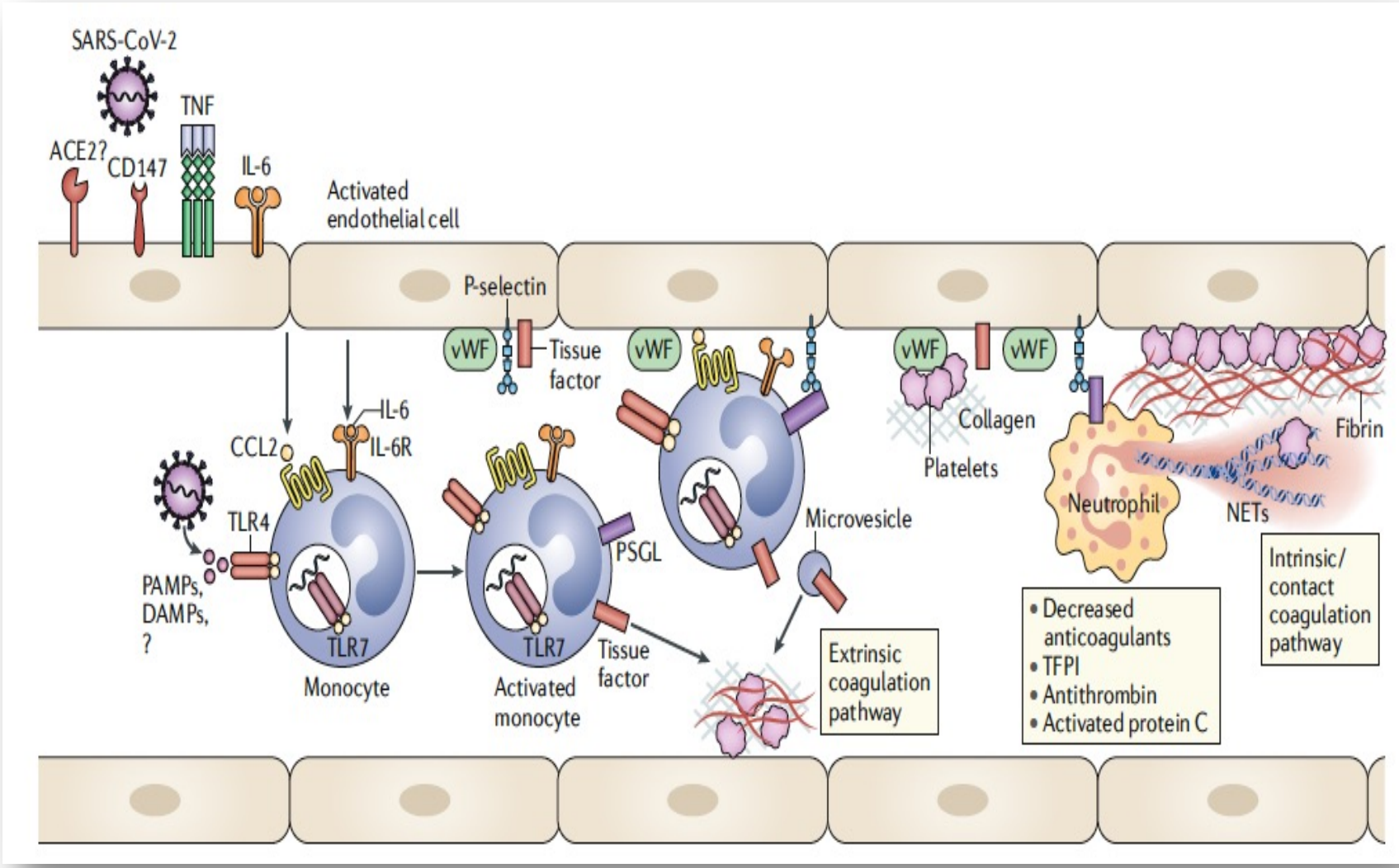
Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages

Miriam Merad and Jerome C. Martin



Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages

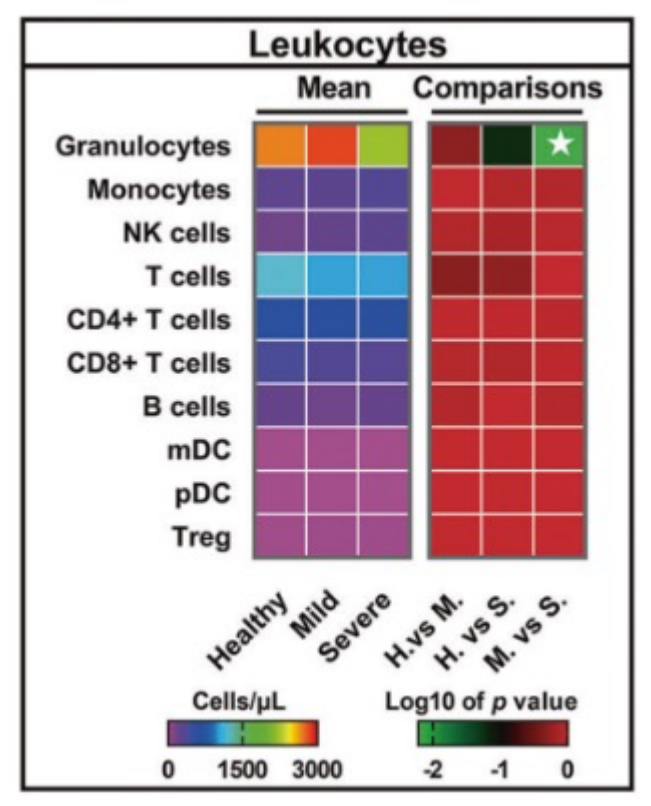
Miriam Merad and Jerome C. Martin



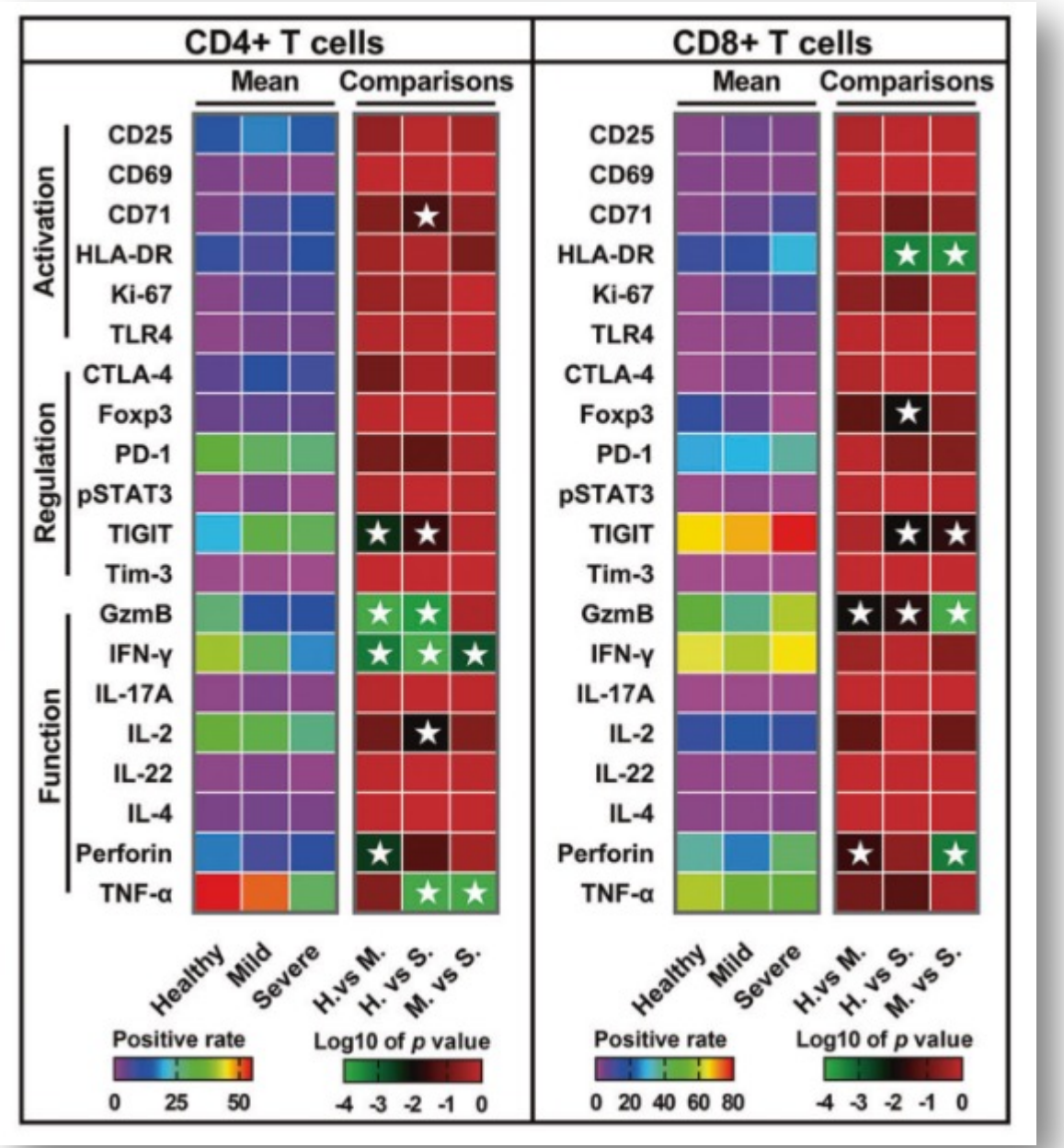
CORRESPONDENCE

Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients

Hong-Yi Zheng[1], Mi Zhang[2], Cui-Xian Yang[2], Nian Zhang[2], Xi-Cheng Wang[2], Xin-Ping Yang[2], Xing-Qi Dong[2] and Yong-Tang Zheng[1]



Restrição de Repertório ???



Aumento de Populações - Redução da diversidade funcional

SARS-COV-2 – ACE-2

AUMENTO ACE-2 EM COMORBIDADES

ADE – IGG E FCGR

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ACE2 Expression is Increased in the Lungs of Patients with Comorbidities Associated with Severe COVID-19

Posted March 27, 2020.

Bruna GG Pinto, Antonio ER Oliveira, Youvika Singh, Leandro Jimenez, Andre NA Goncalves, Rodrigo LT Ogava, Rachel Creighton, Jean PS Peron, Helder I Nakaya

doi: https://doi.org/10.1101/2020.03.21.20040261

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Susceptibility of the Elderly to SARS-CoV-2 Infection: ACE-2 Overexpression, Shedding and Antibody-dependent Enhancement (ADE)

Views 540 | Downloads 294
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Jean Pierre Schatzmann Peron * and Helder Nakaya

Version 1 : Received: 25 March 2020 / Approved: 27 March 2020 / Online: 27 March 2020 (02:48:01 CET)

How to cite: Schatzmann Peron, J.P.; Nakaya, H. Susceptibility of the Elderly to SARS-CoV-2 Infection: ACE-2 Overexpression, Shedding and Antibody-dependent Enhancement (ADE). *Preprints* **2020**, 2020030400 (doi: 10.20944/preprints202003.0400.v1).

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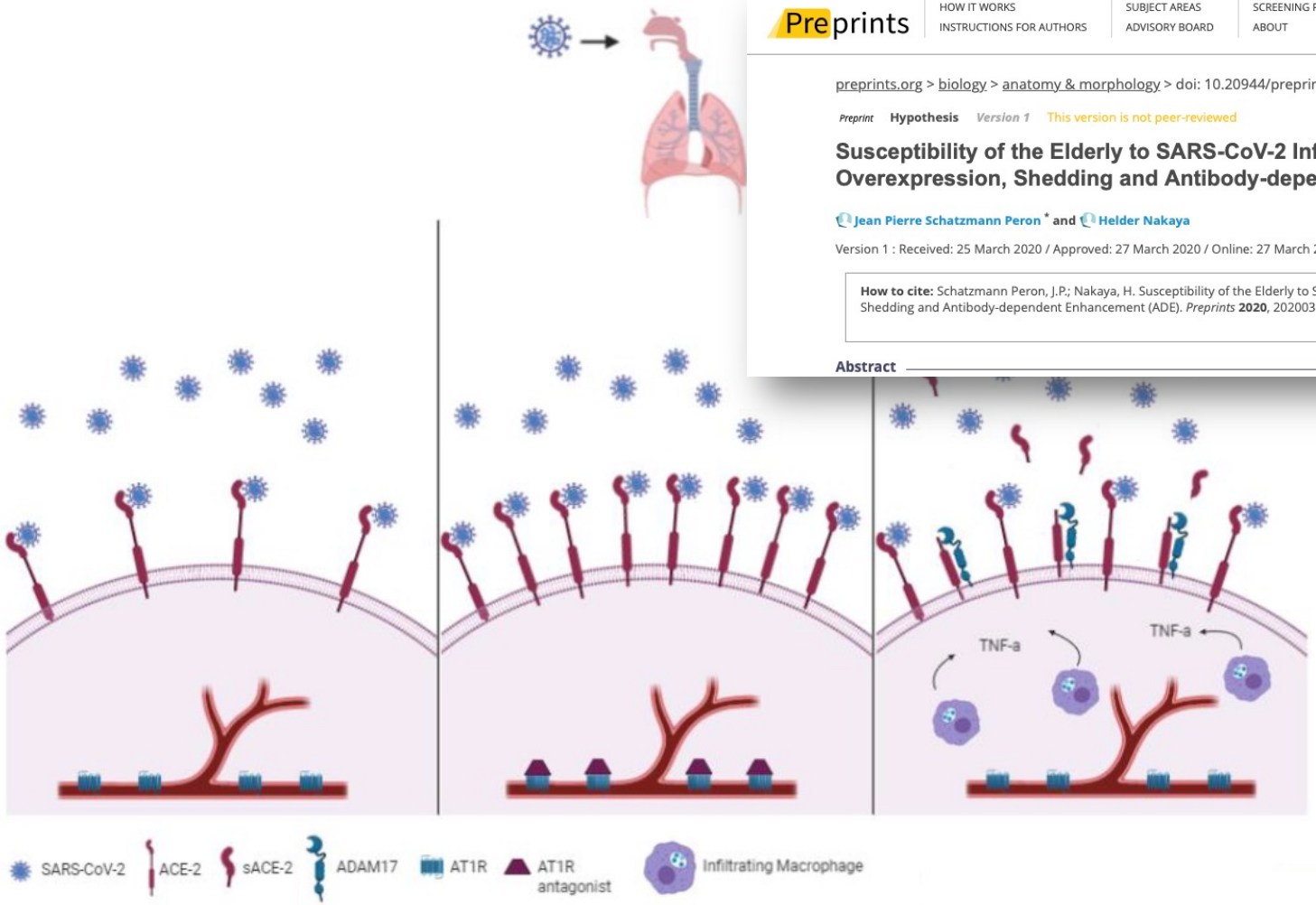
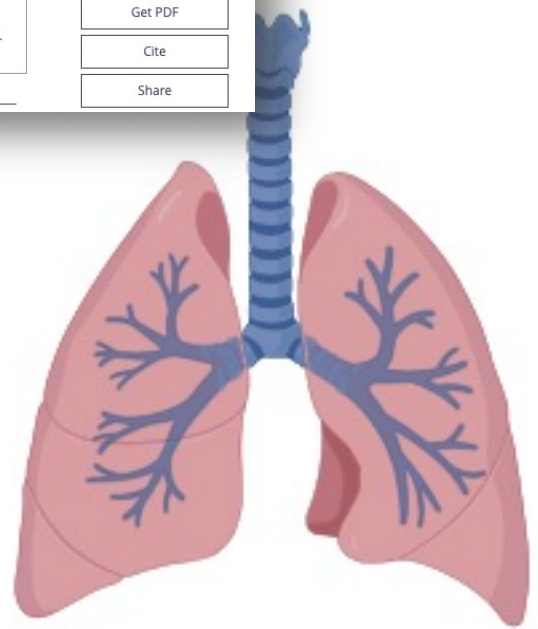
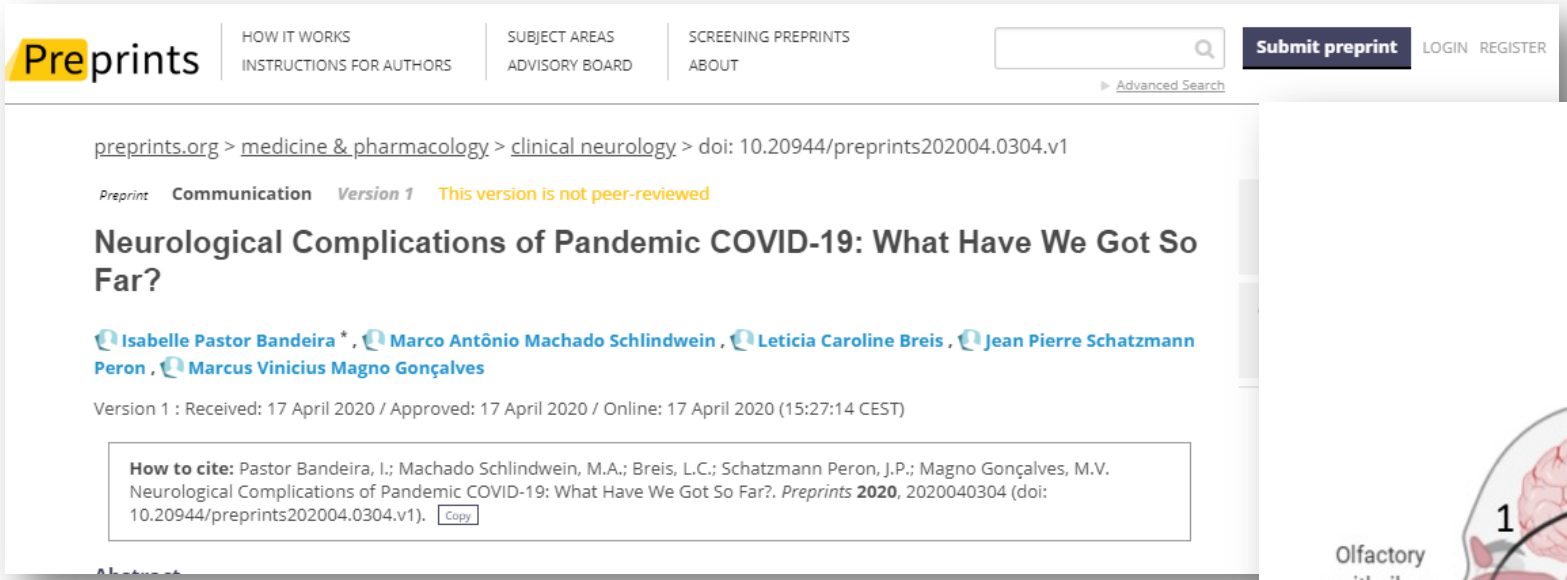
Abstract







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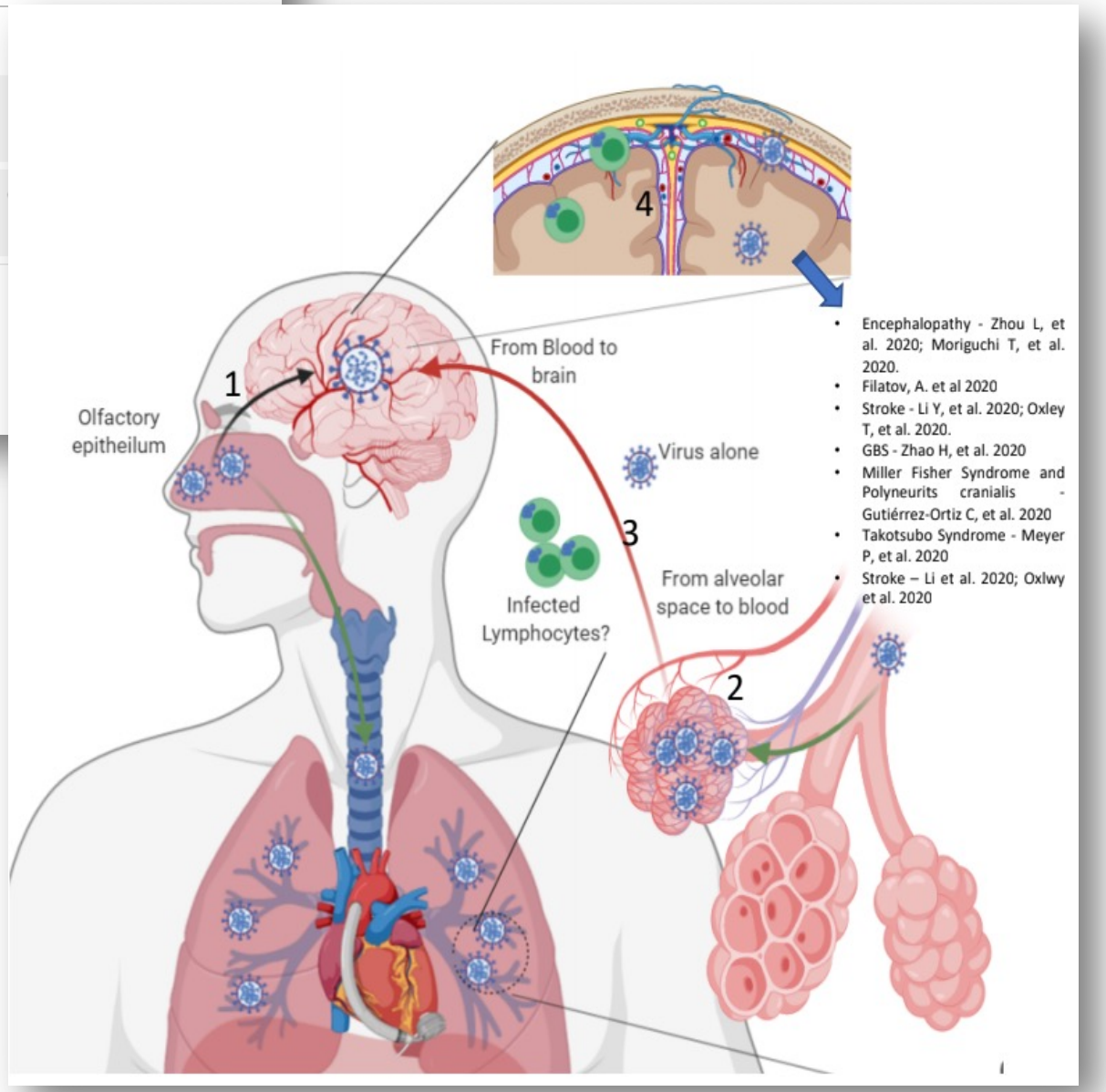
Neurological Complications of Pandemic COVID-19: What Have We Got So Far?

Isabelle Pastor Bandeira *, Marco Antônio Machado Schlindwein, Leticia Caroline Breis, Jean Pierre Schatzmann Peron, Marcus Vinicius Magno Gonçalves

Version 1 : Received: 17 April 2020 / Approved: 17 April 2020 / Online: 17 April 2020 (15:27:14 CEST)

How to cite: Pastor Bandeira, I.; Machado Schlindwein, M.A.; Breis, L.C.; Schatzmann Peron, J.P.; Magno Gonçalves, M.V. Neurological Complications of Pandemic COVID-19: What Have We Got So Far?. *Preprints* **2020**, 2020040304 (doi: 10.20944/preprints202004.0304.v1). Copy



SNC

Encefalite
Leptomeningite
ADEM
AVC
Vírus no líquor

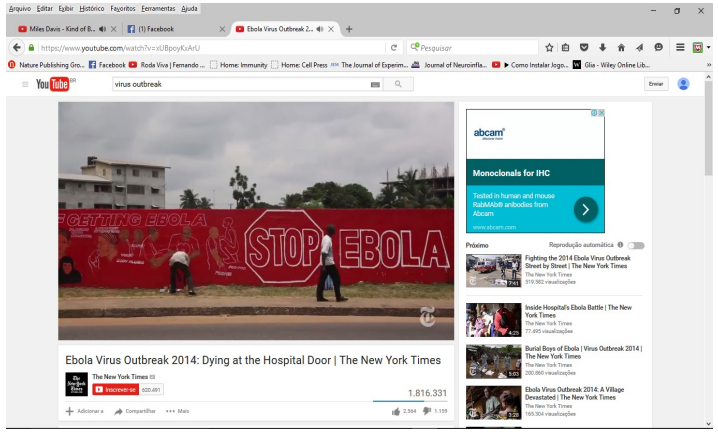
SNP

Guillain-Barré
Síndrome Takotsubo
Miller Fisher

GRANDES MAZELAS DA HUMANIDADE - INFECÇÕES

EBOLA

https://www.youtube.com/watch?v=xUBpoyKxArU



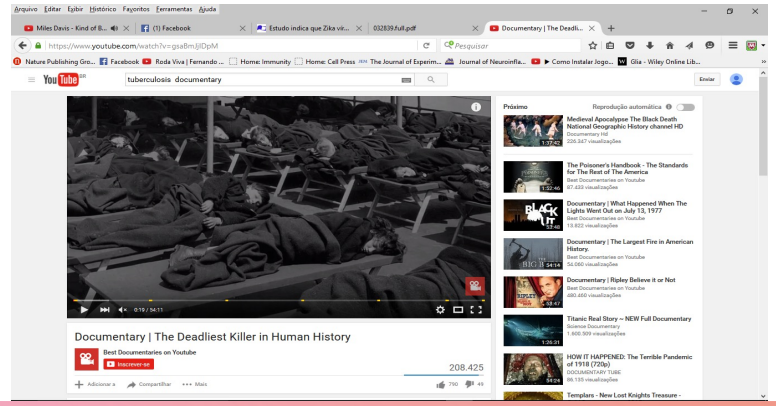
https://www.youtube.com/watch?v=Py2HkKUI5hI

Malária

SARS

https://www.youtube.com/watch?v=JBagOaneLeo

https://www.youtube.com/watch?v=gsaBmJjIDpM



Tuberculose

Influenza

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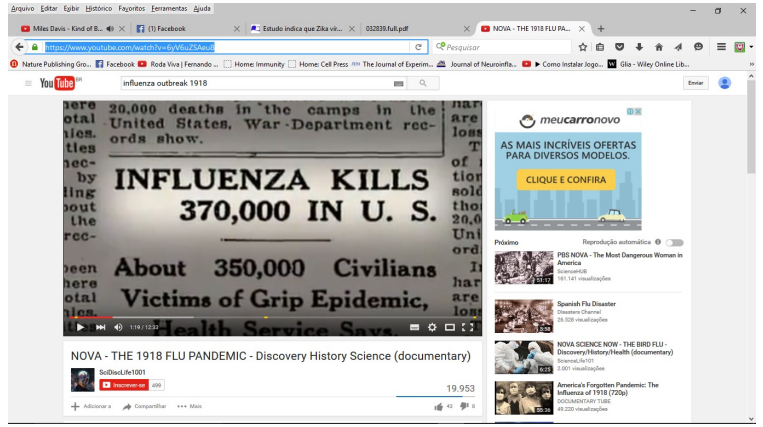

https://www.youtube.com/watch?v=ugdPBvTSYPQ

HIV

TRATAMENTOS – COVID-19

Diretos – Anti-virais

Remdesivir
Sofosbuvir

HCQ
Ivermectina

Indiretos – Sintomas
Inflamação

Glicocorticóides
Enoxaparina

Imunobiológicos
Anakinra – IL-1Ra
Tocilizumab – anti-IL-6

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Patients get tested for COVID-19 in India, one of 30 countries that took part in the Solidarity trial. AP PHOTO/ALTAF QADRI

Remdesivir and interferon fall flat in WHO's megastudy of COVID-19 treatments

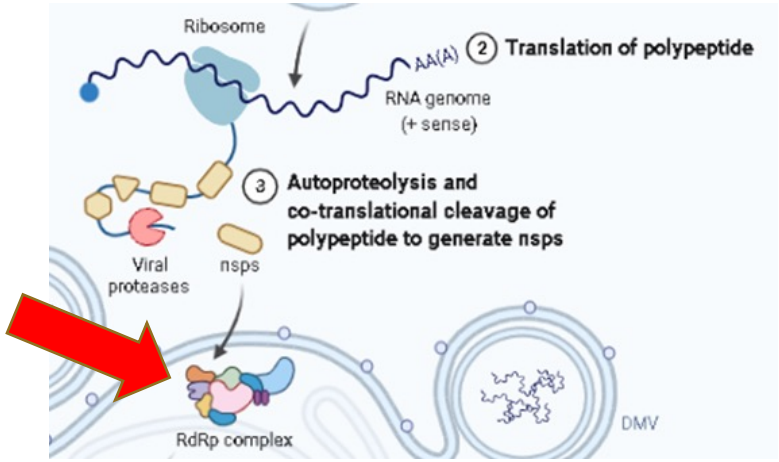
By Kai Kupferschmidt | Oct. 16, 2020 , 3:45 AM

ARTICLE

https://doi.org/10.1038/s41467-020-20542-0 OPEN

Mechanism of SARS-CoV-2 polymerase stalling by remdesivir

Goran Kokic[1,4], Hauke S. Hillen[1,2,4], Dimitry Tegunov[1,4], Christian Dienemann[1,4], Florian Seitz[3,4], Jana Schmitzova[1], Lucas Farnung[1], Aaron Siewert[3], Claudia Höbartner[3✉] & Patrick Cramer[1✉]



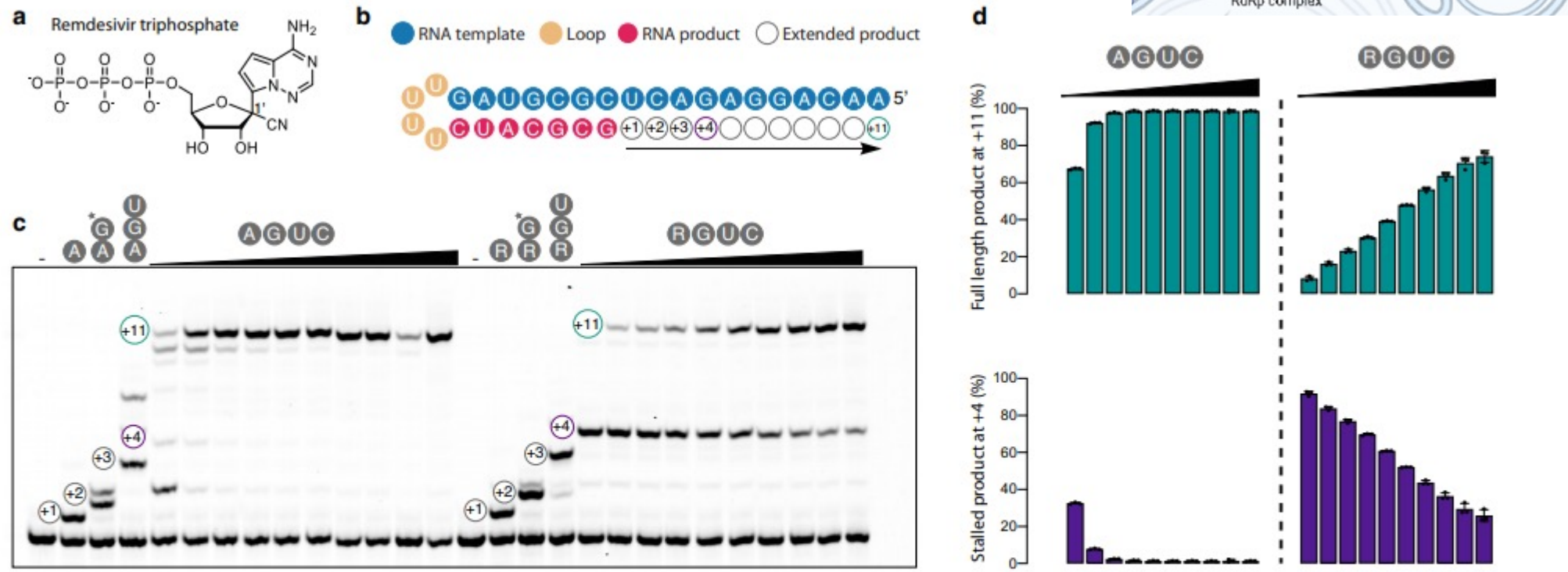


Fig. 1 Remdesivir impairs RNA elongation by RdRp. a Chemical structure of remdesivir triphosphate (RTP) showing the ribose 1′ cyano group. **b** RNA template-product duplex. The direction of RNA elongation is indicated. **c** Remdesivir-induced RdRp stalling. Replacing ATP with RTP leads to an elongation barrier after addition of three more nucleotides. The barrier can be overcome at higher NTP concentrations. The RNA 5′-end contains a fluorescent label. Asterisk indicates 3′-dGTP. Source data are provided as a Source Data file. **d** Quantification of the experiment in panel **c** after triplicate measurements. Standard deviations are shown. Source data are provided as a Source Data file.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

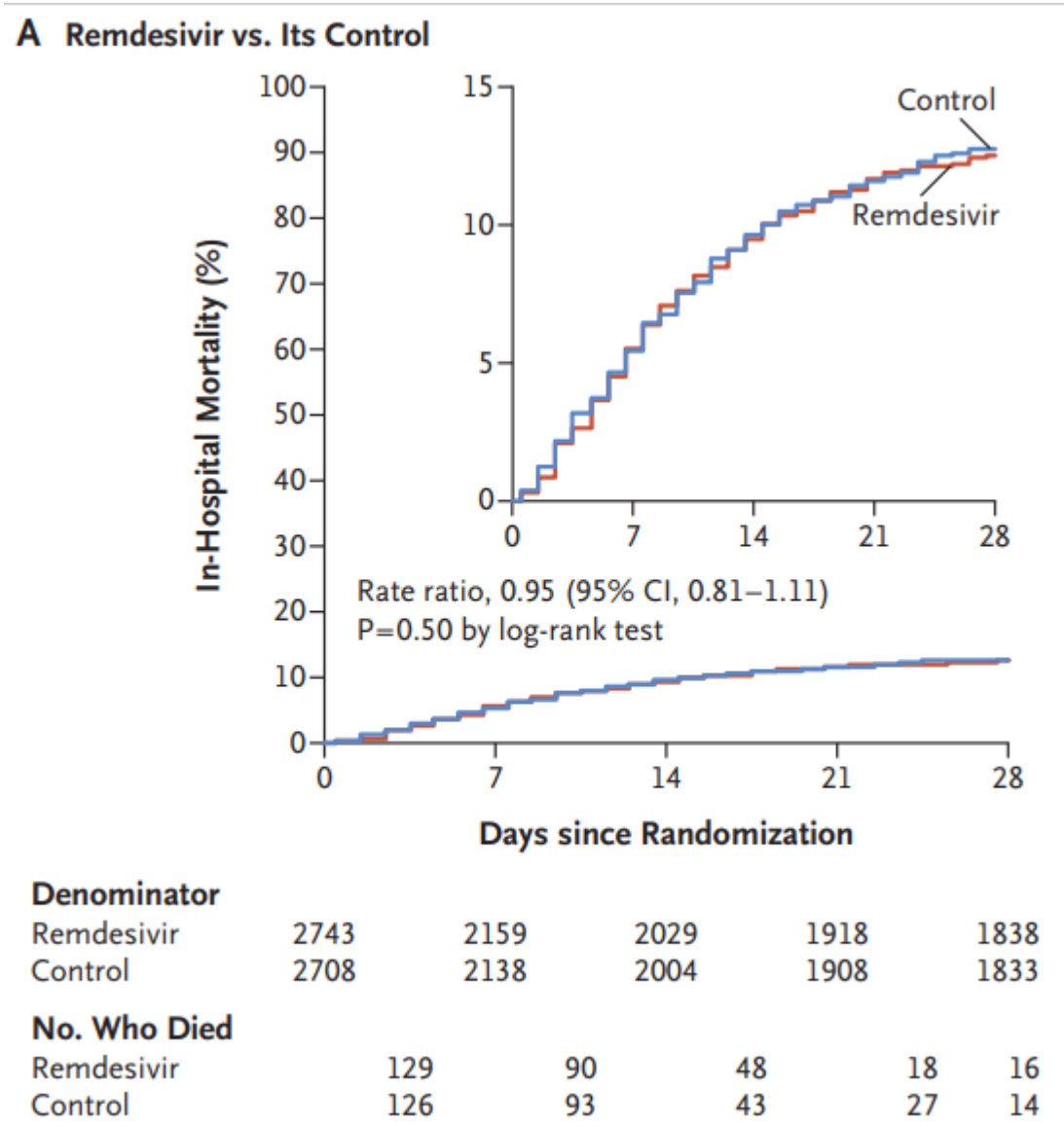
Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

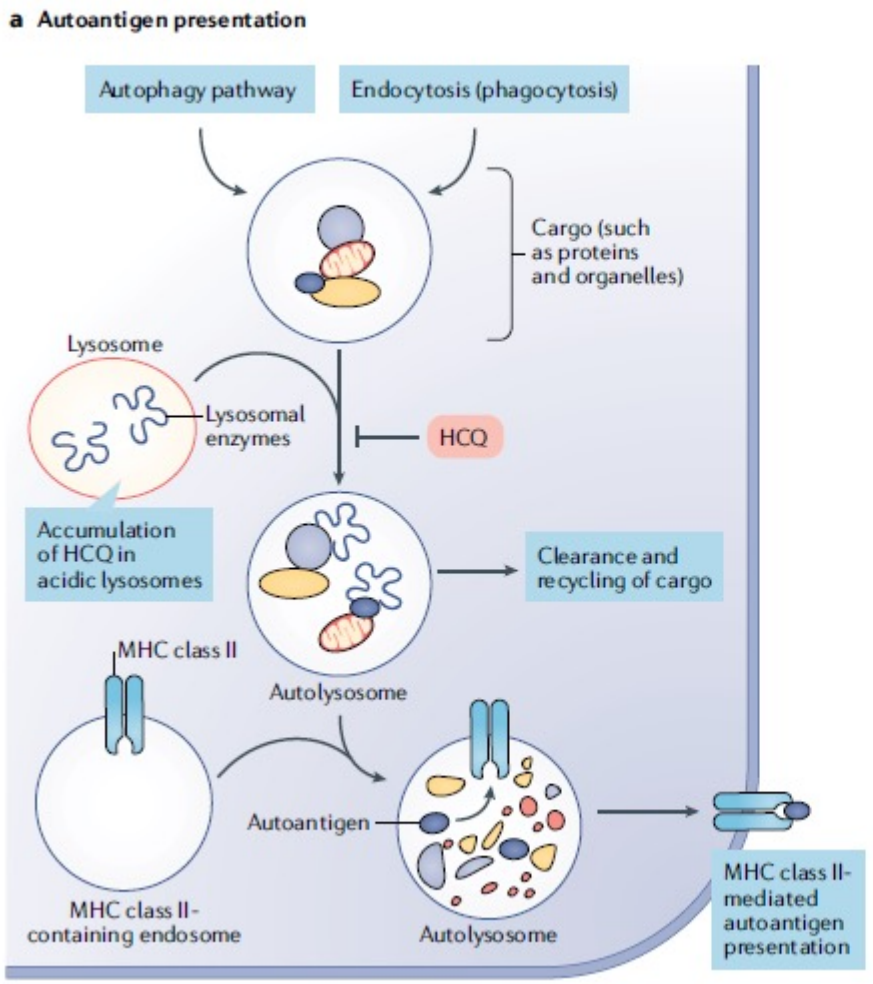
CONCLUSIONS

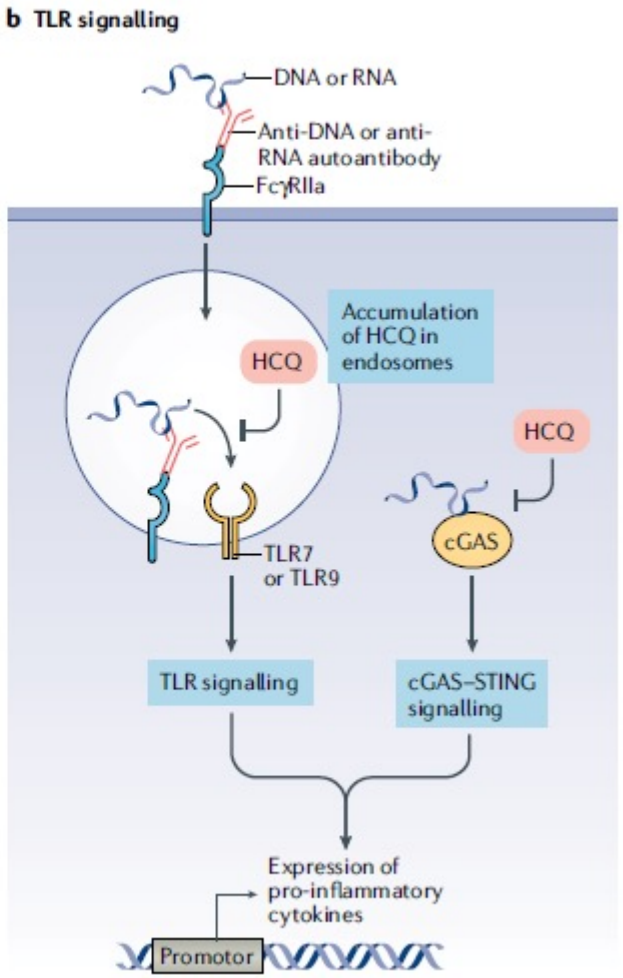
These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay. (Funded by the World Health Organization; ISRCTN Registry number, ISRCTN83971151; ClinicalTrials.gov number, NCT04315948.)

The trial drugs were remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a (given with lopinavir until July 4). The hydroxychloroquine, lopinavir, and interferon regimens were discontinued for futility on, respectively, June 19, July 4, and October 16, 2020. Participants were ran-




EMS
sulfato de hidroxicloroquina
400 mg
USO ORAL
USO ADULTO E PEDIÁTRICO ACIMA DE 6 ANOS
Medicamento Genérico
VENDA SOB PRESCRIÇÃO MÉDICA


a Autoantigen presentation
Autophagy pathway
Endocytosis (phagocytosis)
Cargo (such as proteins and organelles)
Lysosome
Lysosomal enzymes
HCQ
Accumulation of HCQ in acidic lysosomes
Clearance and recycling of cargo
Autolysosome
MHC class II
Autoantigen
MHC class II-containing endosome
Autolysosome
MHC class II-mediated autoantigen presentation


b TLR signalling
DNA or RNA
Anti-DNA or anti-RNA autoantibody
FcγRIIa
Accumulation of HCQ in endosomes
HCQ
HCQ
cGAS
TLR7 or TLR9
TLR signalling
cGAS–STING signalling
Expression of pro-inflammatory cytokines
Promotor

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ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

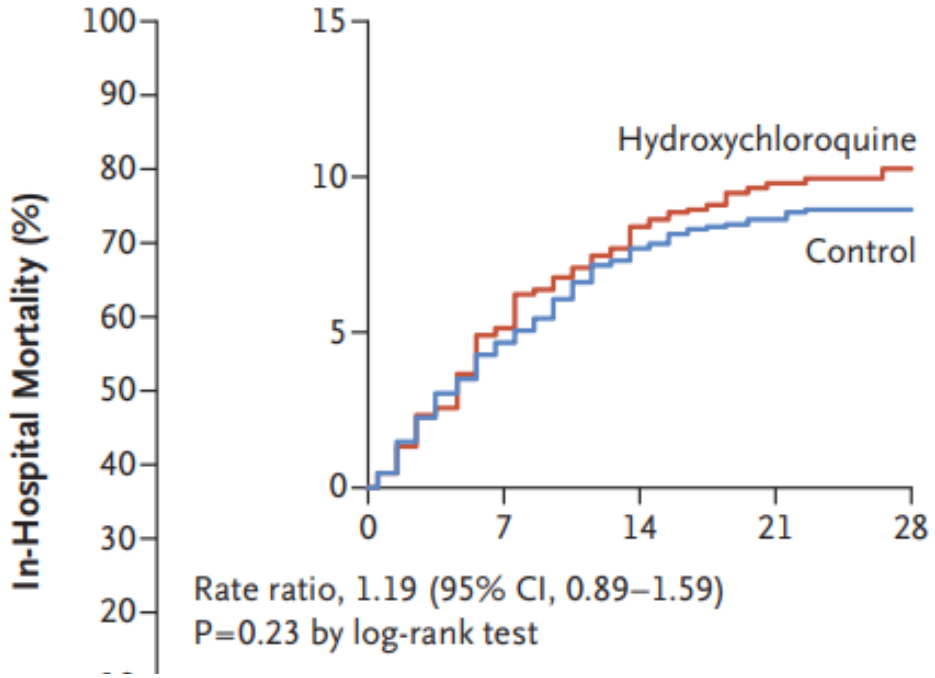
WHO Solidarity Trial Consortium*

ORIGINAL ARTICLE

Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19

Alexandre B. Cavalcanti, M.D., Ph.D., Fernando G. Zampieri, M.D., Ph.D., Regis G. Rosa, M.D., Ph.D., Luciano C.P. Azevedo, M.D., Ph.D., Viviane C. Veiga, M.D., Ph.D., Alvaro Avezum, M.D., Ph.D., Lucas P. Damiani, M.Sc., Aline Marcadenti, Ph.D., Letícia Kawano-Dourado, M.D., Ph.D., Thiago Lisboa, M.D., Ph.D., Debora L. M. Junqueira, M.D., Pedro G.M. de Barros e Silva, M.D., Ph.D., et al., for the Coalition Covid-19 Brazil I Investigators*

B Hydroxychloroquine vs. Its Control



Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure [illegible] Care Workers

A Randomized

Benjamin S. Abella, MD, MPhil[1]; El

» Author Affiliations | Article Information

JAMA Intern Med. 2021;181(2):195-202. doi:10.1001/jamainternmed.2020.6319

Meaning Among hospital-based health care workers, daily hydroxychloroquine did not prevent SARS-CoV-2 infection, although the trial was terminated early and may have been underpowered to detect a clinically important difference.

8

Days since Randomization

Denominator					
Hydroxychloroquine	947	889	854	838	833
Control	906	853	823	814	809
No. Who Died					
Hydroxychloroquine	48	31	13	6	6
Control	42	27	8	4	3

November 9, 2020

Misguided Use of Hydroxychloroquine for COVID-19

The Infusion of Politics Into Science

Michael S. Saag, MD[1]

» Author Affiliations | Article Information

JAMA. 2020;324(21):2161-2162. doi:10.1001/jama.2020.22389

AUTORES ???

Ivermectin is effective for COVID-19: real-time meta analysis of 46 studies

Covid Analysis, Nov 26, 2020 (Version 47, **Mar 17, 2021**)

@CovidAnalysis Share Tweet PDF Studies Adoption

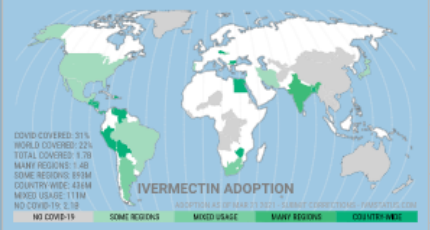
- 100% of the 46 studies to date report positive effects (22 statistically significant in isolation). Random effects meta-analysis for early treatment and pooled effects shows an 79% reduction, RR 0.21 [0.10-0.44], and prophylactic use shows 89% improvement, RR 0.11 [0.05-0.23]. Mortality results show 75% lower mortality, RR 0.25 [0.15-0.44] for all treatment delays, and 84% lower, RR 0.16 [0.04-0.63] for early treatment.
- 100% of the 24 Randomized Controlled Trials (RCTs) report positive effects, with an estimated 70% improvement, RR 0.30 [0.19-0.47].
- The probability that an ineffective treatment generated results as positive as the 46 studies to date is estimated to be 1 in 70 trillion (p = 0.000000000000014).
- All data to reproduce this paper and the sources are in the appendix. See *[Bryant, Hill, Kory, Lawrie, Nardelli]* for other meta analyses confirming effectiveness.

	Improvement	Studies	Authors	Patients
Early treatment	**79%** [56-90%]	16	152	1,684
Late treatment	**52%** [35-64%]	19	145	6,785
Prophylaxis	**89%** [77-95%]	11	74	7,011
Mortality	**75%** [56-85%]	17	152	7,267
RCTs only	**70%** [53-81%]	24	215	3,414
All studies	**72%** [64-79%]	**46**	**371**	**15,480**

WHO ivermectin approval status *[Kory (8)]*

Indication	Studies	Patients	Effect size	Status
Scabies	6	613	35% [22-46%]	Approved
COVID-19	46	15,480	72% [64-79%]	Pending

Global adoption: 31%

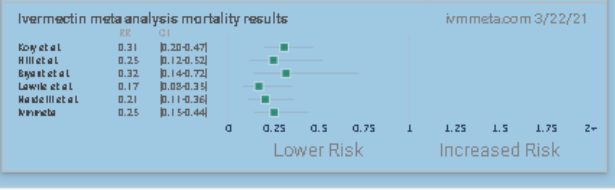


Other meta analyses:
Bryant, Hill, Kory, Lawrie, Nardelli

Resources: FLCCC, one-page summary

Show results for:

- All studies
- With exclusions
- Mortality results
- COVID-19 cases
- Viral clearance
- Peer reviewed
- RCT mortality
- All RCTs



Meta-Analysis > J Pharm Pharm Sci. 2020;23:462-469. doi: 10.18433/jpps31457.

Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta-analysis

Biswa Mohan Padhy [1], Rashmi Ranjan Mohanty [2], Smita Das [3], Bikash Ranjan Meher [1]

Affiliations + expand

PMID: 33227231 DOI: 10.18433/jpps31457

Free article

Abstract

The current management of COVID-19 is mostly limited to general supportive care and symptomatic treatment. Ivermectin is a broad-spectrum anti-parasitic drug used widely for the treatment of onchocerciasis and lymphatic filariasis. Apart from its anti-parasitic effect it also exhibits antiviral activity against a number of viruses both in vitro and in vivo. Hence, we conducted this systematic review and meta-analysis to assess the currently available data on the therapeutic potential of ivermectin for the treatment of COVID-19 as add on therapy. A total of 629 patients were included in the 4 studies and all were COVID-19 RT-PCR positive. Among them, 397 patients received ivermectin along with usual therapy. The random effect model showed the overall pooled OR to be 0.53 (95%CI: 0.29 to0.96) for the primary outcome (all-cause mortality) which was statistically significant (P=0.04). Similarly, the random effect model revealed that adding ivermectin led to significant clinical improvement compared to usual therapy (OR=1.98, 95% CI: 1.11 to 3.53, P=0.02). However, this should be inferred cautiously as the quality of evidence is very low. Currently, many clinical trials are on-going, and definitive evidence for repurposing this drug for COVID-19 patients will emerge only in the future.

JAMA | Original Investigation

Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19

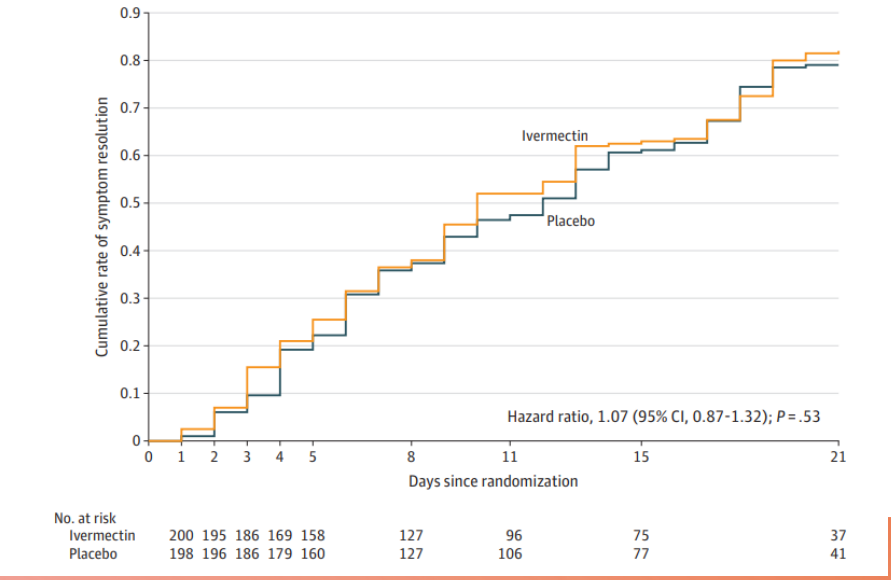
A Randomized Clinical Trial

Eduardo López-Medina, MD, MSc; Pío López, MD; Isabel C. Hurtado, MD; Diana M Dávalos, MD, MPH, DrPH; Oscar Ramirez, MD, MPhil; Ernesto Martínez, MD; Jesus A. Díazgranados, MD; José M. Oñate, MD; Hector Chavarriaga, MD, MS; Sócrates Herrera, MD; Beatriz Parra, PhD; Gerardo Libreros, PhD; Roberto Jaramillo, MD; Ana C. Avendaño, MD; Dilian F. Toro, MD; Miyerlandi Torres, DrPH; Maria C. Lesmes, MD; Carlos A. Rios, MD; Isabella Caicedo, MD

CONCLUSION AND RELEVANCE Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04405843

Figure 2. Time to Resolution of Symptoms in the Primary Analysis Population



Critical Reviews™ in Immunology

DOI: 10.1615/CritRevImmunol.2020036242
pages 537-542

COVID-19 Pandemic and Dysbiosis: Can the Ivermectin Hysteria Lead to an Increase of Autoimmune Neuroinflammatory Diseases?

J. P. S. Peron
Neuroimmune Interactions Laboratory, Institute of Biomedical Sciences, Department of Immunology, University of Sao Paulo, São Paulo, Brazil; Scientific Platform Pasteur, University of São Paulo (USP), São Paulo, Brazil; Immunopathology and Allergy Post Graduate Program, School of Medicine, University of São Paulo (USP), São Paulo, SP CEP 01246-903 Brazil

H. I. Nakaya
Scientific Platform Pasteur, University of São Paulo (USP), São Paulo, Brazil; Department of Clinical and Toxicological Analyses, School of Pharmaceutical Sciences, University of São Paulo (USP), São Paulo, Brazil

M. A. M. Schlindwein
Department of Medicine, University of the Region of Joinville (UNIVILLE) Joinville, Brazil

Marcus Vinicius Magno Gonçalves
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ABSTRACT

The pandemic caused by the SARS-CoV-2 has made new treatments a goal for the scientific community. One of these treatments is Ivermectin. Here we discuss the hypothesis of dysbiosis caused by the use of Ivermectin and the possible impacts on neuroinflammatory diseases after the end of the pandemic.

Sobre o uso da Proxalutamida no tratamento da covid-19

FÁBIO REIS CORONAVÍRUS | COVID-19 22 MARÇO 2021
ÚLTIMA ATUALIZAÇÃO: 22 MARÇO 2021

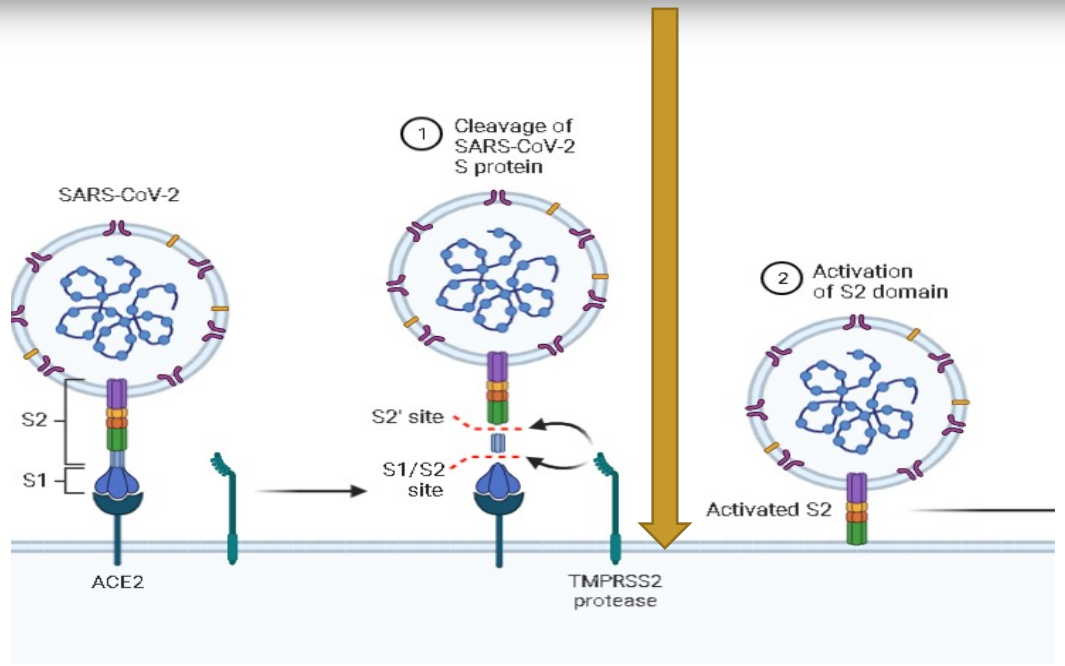
A proxalutamida (GT-0918) medicamento usado no tratamento de câncer de próstata e de mama está sendo testada para o tratamento da covid-19.

A proxalutamida (GT-0918 - 普克鲁胺) é um medicamento oral em testes para o tratamento de câncer de próstata e de mama. Ele foi desenvolvido pela indústria farmacêutica chineesa Suzhou Kintor Pharmaceuticals, uma subsidiária da Kintor Pharmaceutical Limited, e atualmente está em testes para o tratamento da COVID-19.

A proxalutamida está em estudos de fase III para mCRPC (Câncer de próstata) como monoterapia e em combinação com abiraterona. Nos Estados Unidos, está em um estudo de fase II como monoterapia para mCRPC. Também está em fase I em testes para Câncer de mama.

Em 5 março o FDA dos EUA aprovou o pedido de investigação para novos fármacos (IND) para uso da proxalutamida em infecções causada pelo coronavírus SARS-CoV-2.

O proxalutamida é um antiandrogênio não esteróide (NSAA) - especificamente, um antagonista silencioso de alta afinidade seletivo do receptor de androgênio (AR).



Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Active, not recruiting	**Proxalutamide** Treatment for Hospitalized **COVID-19** Patients	• **Covid19** • SARS (Severe Acute Respiratory Syndrome)	• Drug: **Proxalutamide** • Drug: Standard of Care	• Centro Clínico Advance, SGAS 915, Lote 69/70, Sala 262 Brasília, DF, Brazil
2	☐	Completed Has Results	Anti-Androgen Treatment for **COVID-19**	• **COVID-19** • **SARS-CoV2** • Androgenetic Alopecia • (and 3 more...)	• Drug: **Proxalutamide** • Other: Standard of Care	• Corpometria Institute Brasilia, Brazil

Criteria

Inclusion Criteria:

1. Male age ≥18 years old
2. Laboratory confirmed positive SARS-CoV-2 rtPCR test within 7 days prior to randomization
3. Clinical status on the COVID-19 8-point Ordinal Scale of 1 or 2
4. Coagulation: INR ≤ 1.5×ULN, and APTT ≤ 1.5×ULN
5. Subject (or legally authorized representative) gives written informed consent prior to any study screening procedures
6. Subject (or legally authorized representative) agree that subject will not participate in another COVID-19 trial while participating in this study

All-Cause Mortality

	Standard Care	Proxalutamide + Standard Care
	Affected / at Risk (%)	Affected / at Risk (%)
Total	2/128 (1.56%)	0/134 (0.00%)

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events: 5%

	Standard Care		Proxalutamide + Standard Care	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	78/128 (60.94%)		45/134 (33.58%)	
Cardiac disorders				
Tachycardia †1	11/128 (8.59%)	11	4/134 (2.99%)	4
Ear and labyrinth disorders				
Ear pain †1	13/128 (10.16%)	13	8/134 (5.97%)	8
Gastrointestinal disorders				
Diarrhea †1	11/128 (8.59%)	11	28/134 (20.90%)	28
Nausea †1	8/128 (6.25%)	8	19/134 (14.18%)	19
Abdominal pain †1	7/128 (5.47%)	7	16/134 (11.94%)	16
Abdominal discomfort †1	8/128 (6.25%)	8	12/134 (8.96%)	12
Dyspepsia †1	3/128 (2.34%)	3	15/134 (11.19%)	15
General disorders				
Fatigue †1	57/128 (44.53%)	57	3/134 (2.24%)	3
Fever †1	26/128 (20.31%)	26	5/134 (3.73%)	5
Disease progression †1	69/128 (53.91%)	69	7/134 (5.22%)	7
Musculoskeletal and connective tissue disorders				
Back pain †1	15/128 (11.72%)	15	13/134 (9.70%)	13
Nervous system disorders				
Ageusia †1	15/128 (11.72%)	15	5/134 (3.73%)	5
Anosmia †1	17/128 (13.28%)	17	6/134 (4.48%)	6
Headache †1	12/128 (9.38%)	12	3/134 (2.24%)	3
Respiratory, thoracic and mediastinal disorders				
Shortness of breath †1	46/128 (35.94%)	46	6/134 (4.48%)	6

1 Term from vocabulary, MedDRA (19.0)

† Indicates events were collected by systematic assessment

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Cytokine Storm

David C. Fajgenbaum, M.D., and Carl H. June, M.D.

IL-1

IL-6

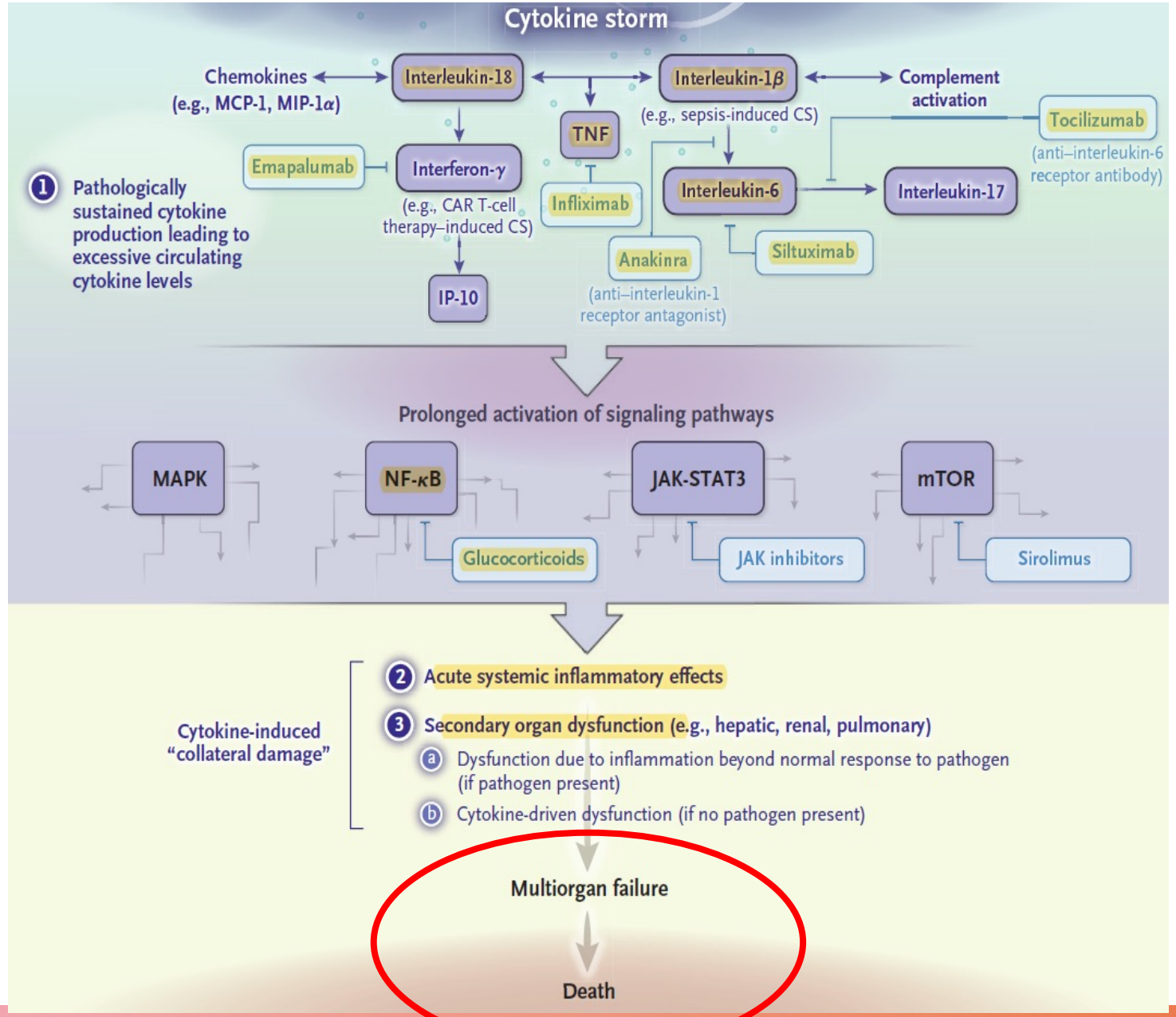
TNF-alpha

Interferons Tipo I

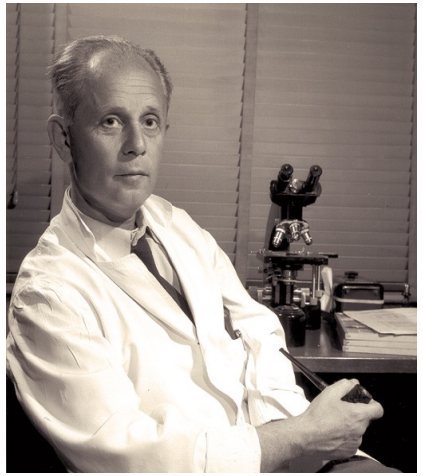
IFN-alpha
IFN-beta

Interferon Tipo II

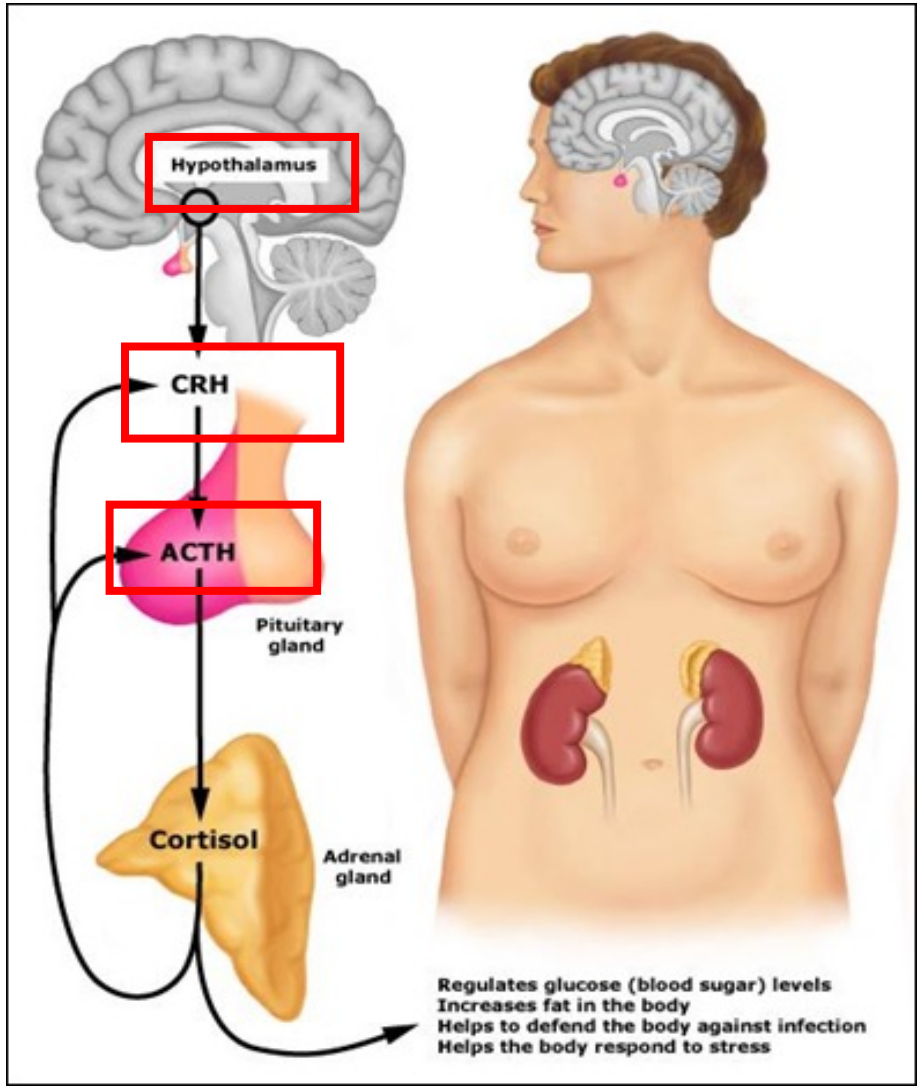
IFN-gamma

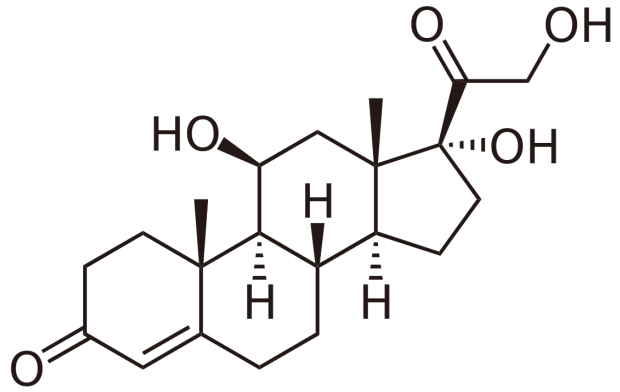


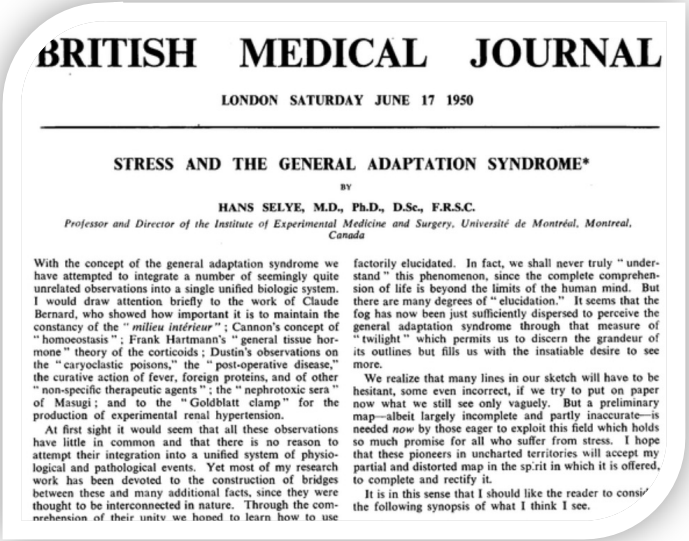
EIXO HIPOTÁLAMO - HIPÓFISE - ADRENAL - STRESS



Hans Selye - 1936







BRITISH MEDICAL JOURNAL

LONDON SATURDAY JUNE 17 1950

STRESS AND THE GENERAL ADAPTATION SYNDROME*

BY

HANS SELYE, M.D., Ph.D., D.Sc., F.R.S.C.

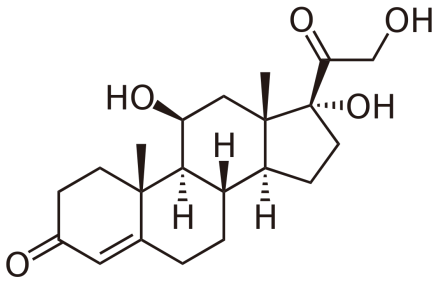
Professor and Director of the Institute of Experimental Medicine and Surgery, Université de Montréal, Montreal, Canada

With the concept of the general adaptation syndrome we have attempted to integrate a number of seemingly quite unrelated observations into a single unified biologic system. I would draw attention briefly to the work of Claude Bernard, who showed how important it is to maintain the constancy of the "*milieu intérieur*"; Cannon's concept of "homoeostasis"; Frank Hartmann's "general tissue hormone" theory of the corticoids; Dustin's observations on the "caryoclastic poisons," the "post-operative disease," the curative action of fever, foreign proteins, and of other "non-specific therapeutic agents"; the "nephrotoxic sera" of Masugi; and to the "Goldblatt clamp" for the production of experimental renal hypertension.

At first sight it would seem that all these observations have little in common and that there is no reason to attempt their integration into a unified system of physiological and pathological events. Yet most of my research work has been devoted to the construction of bridges between these and many additional facts, since they were thought to be interconnected in nature. Through the comprehension of their unity we hoped to learn how to use factorily elucidated. In fact, we shall never truly "understand" this phenomenon, since the complete comprehension of life is beyond the limits of the human mind. But there are many degrees of "elucidation." It seems that the fog has now been just sufficiently dispersed to perceive the general adaptation syndrome through that measure of "twilight" which permits us to discern the grandeur of its outlines but fills us with the insatiable desire to see more.

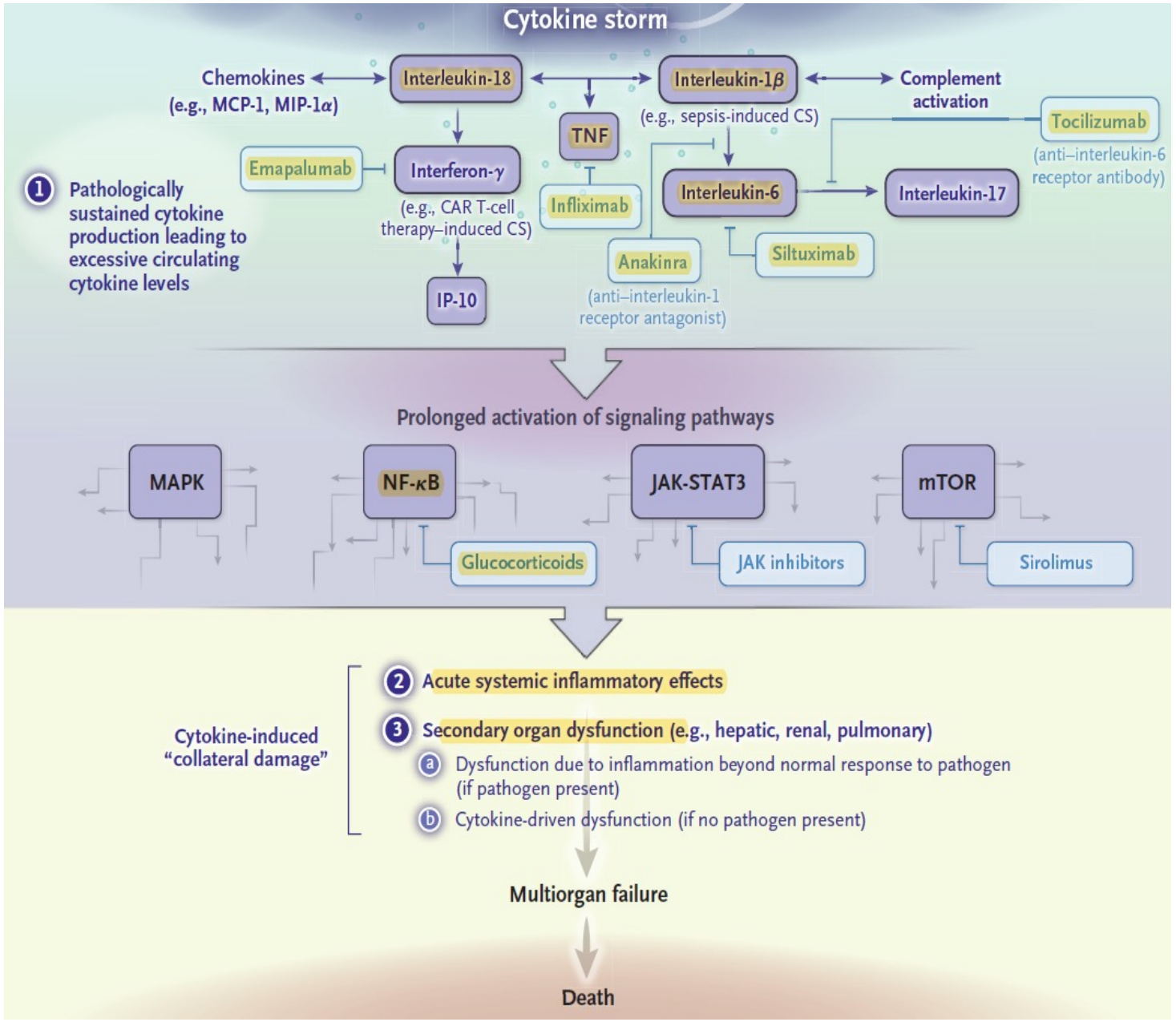
We realize that many lines in our sketch will have to be hesitant, some even incorrect, if we try to put on paper now what we still see only vaguely. But a preliminary map—albeit largely incomplete and partly inaccurate—is needed *now* by those eager to exploit this field which holds so much promise for all who suffer from stress. I hope that these pioneers in uncharted territories will accept my partial and distorted map in the spirit in which it is offered, to complete and rectify it.

It is in this sense that I should like the reader to consi/ the following synopsis of what I think I see.



Prednisona
Prednisolona

Dexametasona
Betametasona



GLICOCORTICÓIDES EFEITOS GENÔMICOS E NÃO GENÔMICOS

NÃO-GENÔMICOS

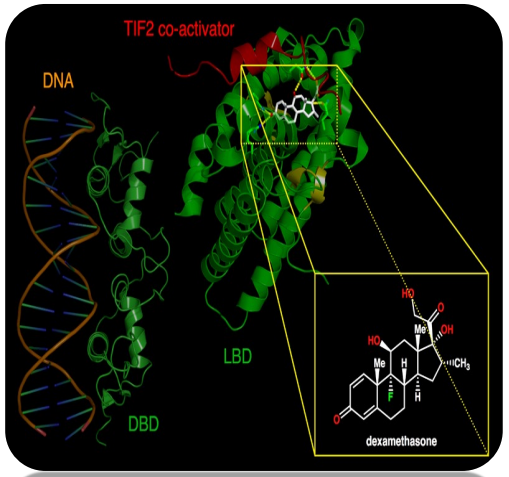
BLOQUEIAM **NF-KB E AP-1**

GENÔMICOS

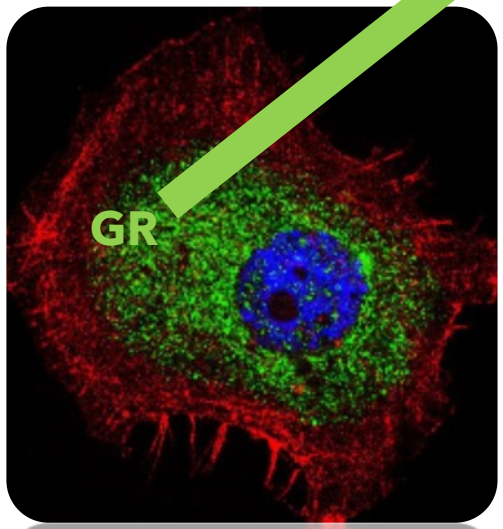
TRANSCRIÇÃO DE GENES ANTI-INFLAMATÓRIOS
MKP-1 / ANEXINA-A1/IDO

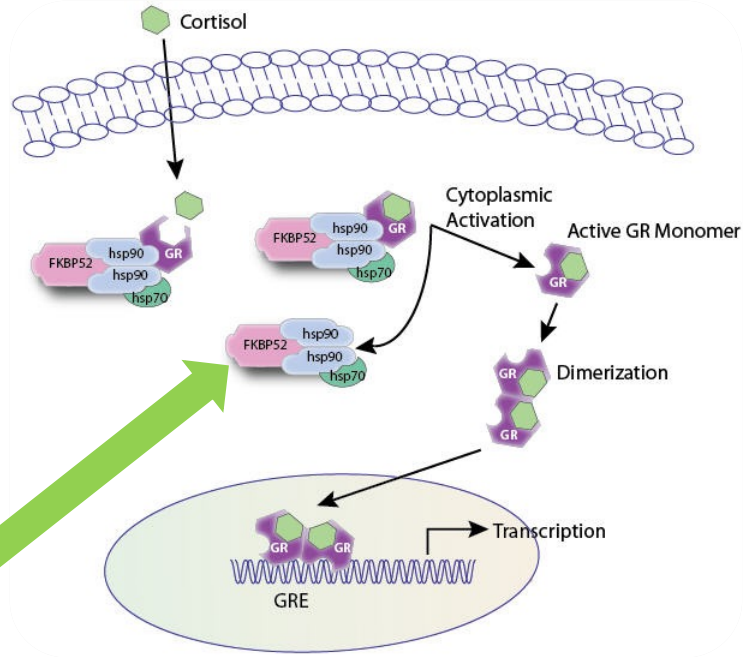
HISTONA DESACETILASE

BLOQUEIAM ACESSO DA RNA POLIMERASE AO GENE



Cortisol + GR





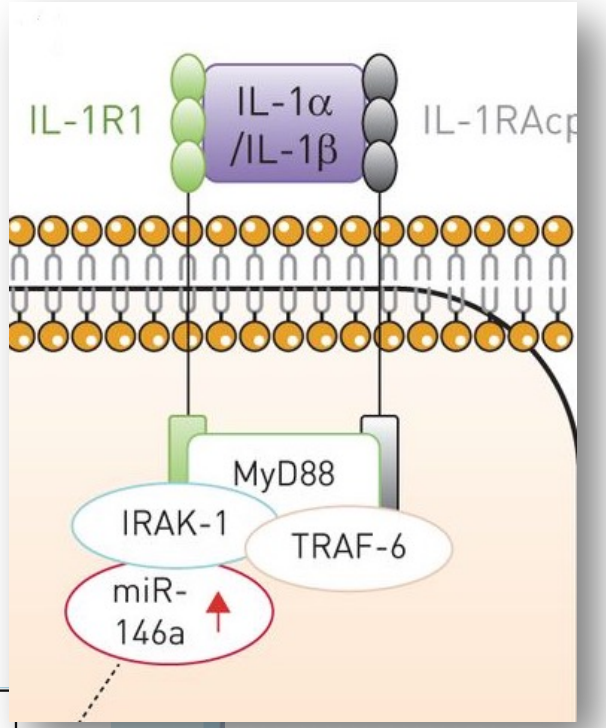
Inativação de **NF-κB** e **AP-1**

1500 genes pró-inflamatórios

são bloqueados

Anakinra – IL-1ra – Análogo recombinanto do receptor de IL-1 solúvel –

Scavenger RECEPTOR



Showing: 1-35 of **35** studies 100 studies per page

Row	Saved	Status	Study Title	Conditions	
1	☐	Recruiting	suPAR-Guided **Anakinra** Treatment for Management of Severe Respiratory Failure by **COVID-19**	• **Covid19**	• Drug: **Anakinra** • Drug: Placebo

UniProt UniProtKB

BLAST Align Retrieve/ID mapping Peptide search SPARQL Help Contact

UniProtKB - P01584 (IL1B_HUMAN)

Basket

Display Help video

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Entry
Publications
Feature viewer
Feature table

None

Function
Names & Taxonomy
Subcellular location
Pathology & Biotech
PTM / Processing
Expression

Protein Interleukin-1 beta
Gene IL1B
Organism *Homo sapiens (Human)*
Status Reviewed - Annotation score: ●●●●● - Experimental evidence at protein level[1]

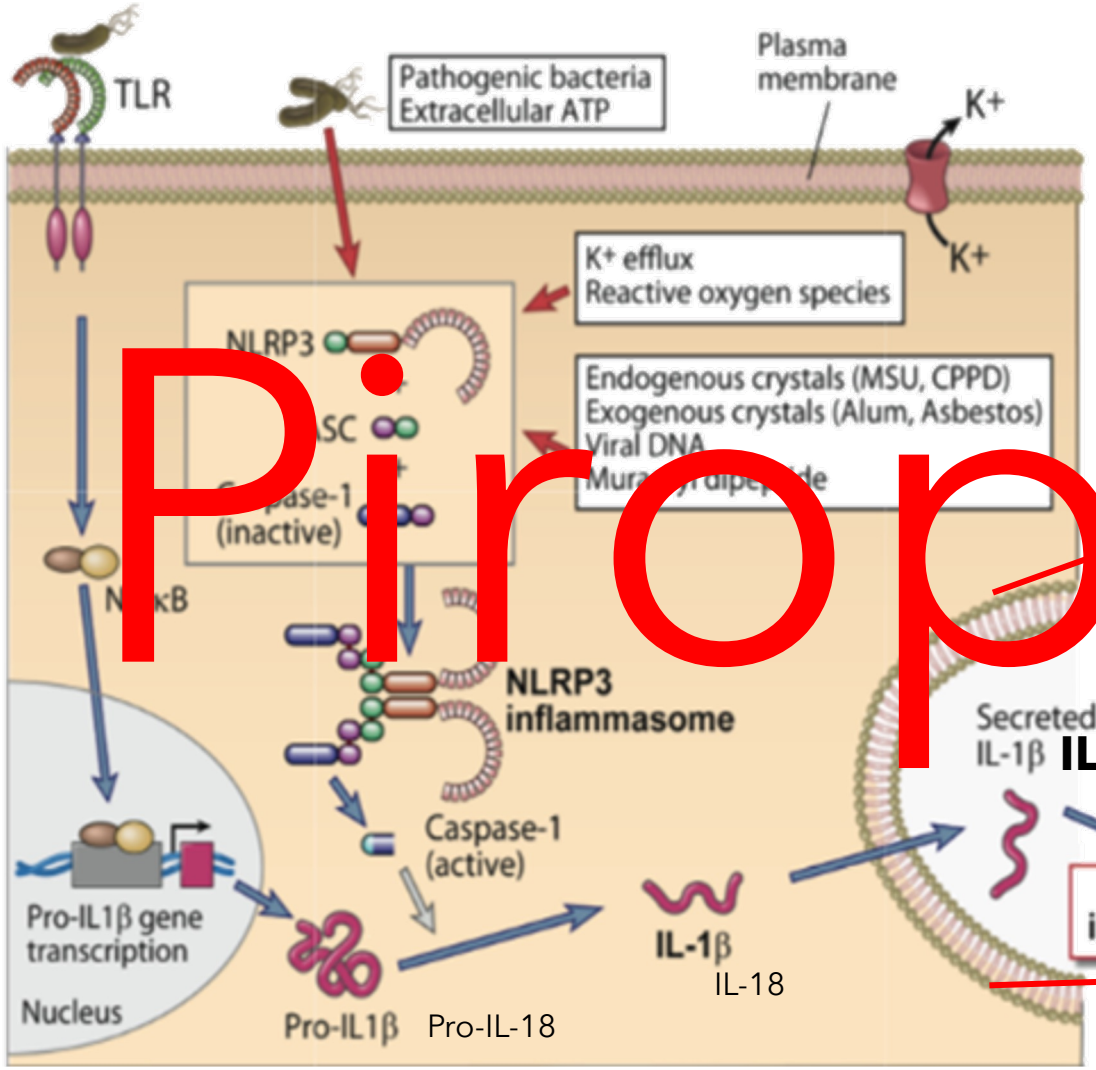
Function[1]

Potent proinflammatory cytokine. Initially discovered as the major endogenous pyrogen, induces prostaglandin synthesis, neutrophil influx and activation, T-cell activation and cytokine production, B-cell activation and antibody production, and fibroblast proliferation and collagen production. Promotes Th17 differentiation of T-cells. Synergizes with IL12/interleukin-12 to induce IFNG synthesis from T-helper 1 (Th1) cells (PubMed:10653850). Plays a role in angiogenesis by inducing VEGF production synergistically with TNF and IL6 (PubMed:12794819). 3 Publications

Miscellaneous

The IL1B production occurs in 2 steps, each being controlled by different stimuli. First, inflammatory signals, such as LPS, stimulate the synthesis and promote the accumulation of cytosolic stores of pro-IL1B (priming). Then additional signals are required for inflammasome assembly, leading to CASP1 activation, pro-IL1B processing and eventually secretion of the active cytokine. IL1B processing and secretion are temporarily associated.
1 Publication

IL-1 – Inflamasoma e Piroptose

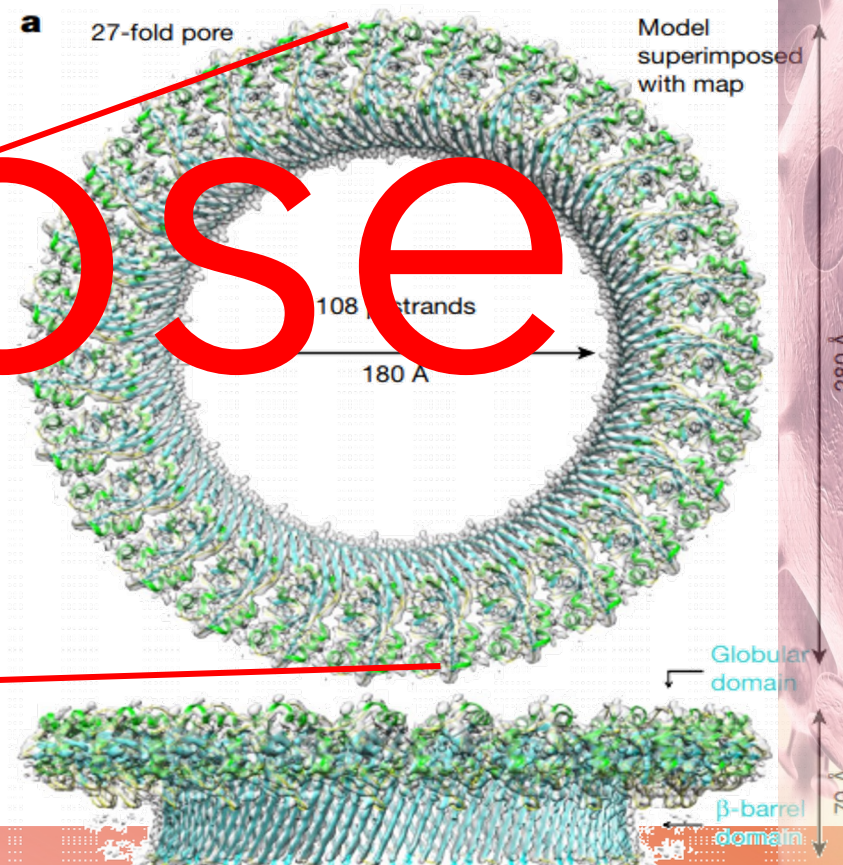


Piroptose

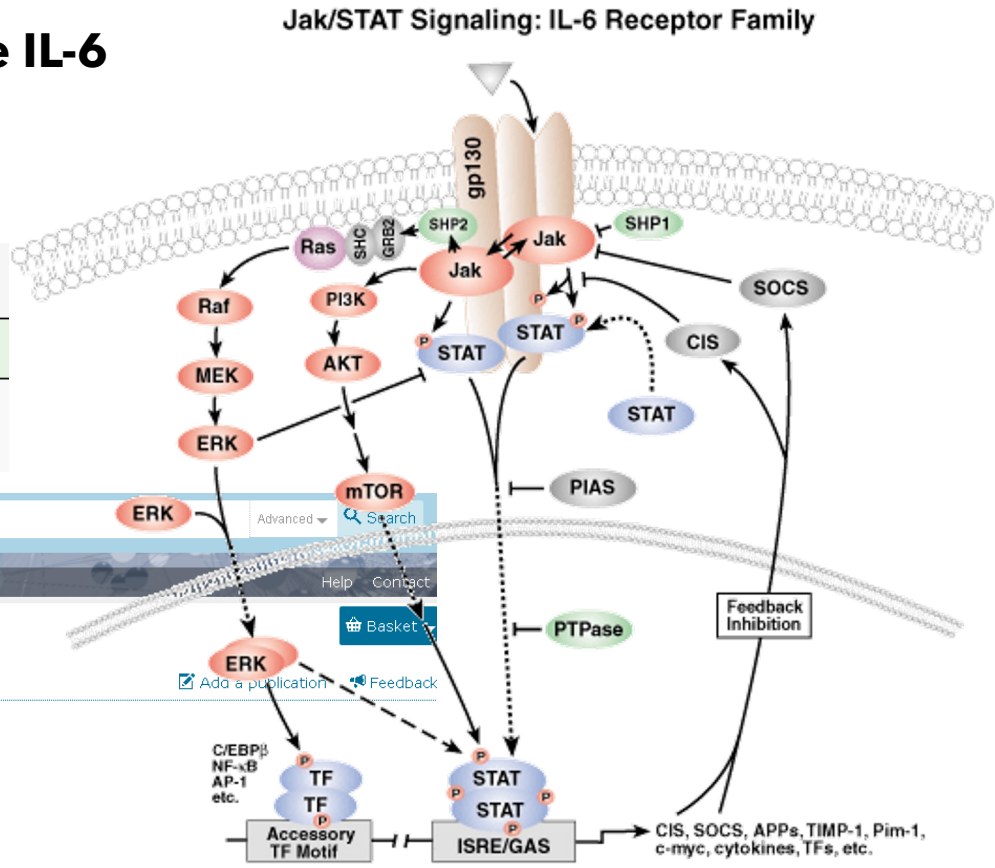
Cryo–EM structure of the gasdermin A3 membrane pore

Jianbin Ruan[1,2], Shiyu Xia[1,2], Xing Liu[1,3], Judy Lieberman[1,3] & Hao Wu[1,2]*

ten in mice, including three GSDMAs. GSDMs are cleaved by regulated processing that removes an inhibitory C-terminal fragment (GSDM-CT) to allow the N-terminal fragment (GSDM-NT) to bind to acidic lipids in the inner leaflet of mammalian cell membranes or on bacterial membranes to form pores. GSDMD is a substrate of inflam-



TOCILIZUMAB - mAb contra o receptor de IL-6



Showing: 1-78 of **78** studies 100 studies per page

Row	Saved	Status	Study Title	Conditions	
1	☐	Completed	Clinical Trial to Evaluate the Effectiveness and Safety of **Tocilizumab** for Treating Patients With **COVID-19** Pneumonia	• **COVID-19**	• Drug: **Tocilizumab**

UniProt

UniProtKB ▾ Advanced ▾ Search

BLAST Align Retrieve/ID mapping Peptide search SPARQL Help Contact

Basket ▾

UniProtKB - P05231 (IL6_HUMAN)

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BLAST Align Format Add to basket History Add a publication Feedback

- Entry
- Publications
- Feature viewer
- Feature table

None

- ☑ Function
- ☑ Names & Taxonomy
- ☑ Subcellular location
- ☑ Pathology & Biotech
- ☑ PTM / Processing
- ☑ Expression
- ☑ Interaction
- ☑ Structure
- ☑ Family & Domains
- ☑ Sequences (1+)

Protein Interleukin-6

Gene IL6

Organism *Homo sapiens (Human)*

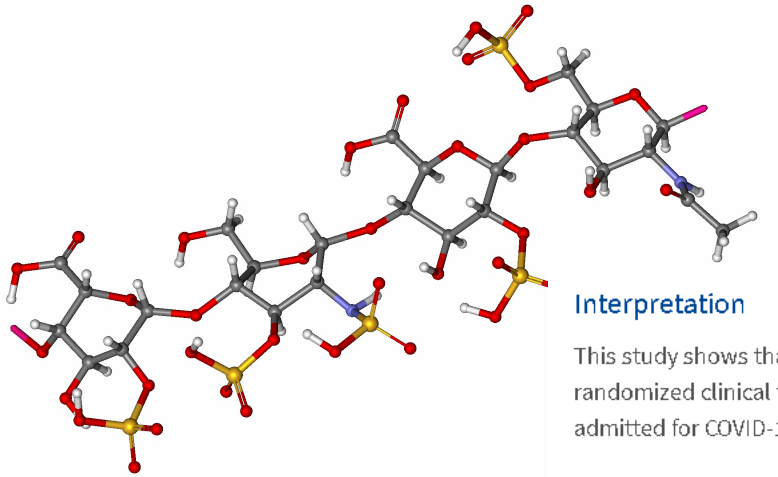
Status Reviewed - Annotation score: ●●●●● - Experimental evidence at protein level[i]

Function[i]

Cytokine with a wide variety of biological functions in immunity, tissue regeneration, and metabolism. Binds to IL6R, then the complex associates to the signaling subunit IL6ST/gp130 to trigger the intracellular IL6-signaling pathway (Probable). The interaction with the membrane-bound IL6R and IL6ST stimulates 'classic signaling', whereas the binding of IL6 and soluble IL6R to IL6ST stimulates 'trans-signaling'. Alternatively, 'cluster signaling' occurs when membrane-bound IL6:IL6R complexes on transmitter cells activate IL6ST receptors on neighboring receiver cells (Probable). 1 Publication

IL6 is a potent inducer of the acute phase response. Rapid production of IL6 contributes to host defense during infection and tissue injury, but excessive IL6 synthesis is involved in disease pathology. In the innate immune response, is synthesized by myeloid cells, such as macrophages and dendritic cells, upon recognition of pathogens through toll-like receptors (TLRs) at the site of infection or tissue injury (Probable). In the adaptive immune response, is required for the differentiation of B cells into immunoglobulin-secreting cells. Plays a major role in the differentiation of $CD4^+$ T cell subsets. Essential factor for the development of T follicular helper (Tfh) cells that are required for the induction of germinal-center formation. Required to drive naive $CD4^+$ T cells to the Th17 lineage. Also required for proliferation of myeloma cells and the survival of plasmablast cells (By similarity). By similarity 1 Publication

Acts as an essential factor in bone homeostasis and on vessels directly or indirectly by induction of VEGF, resulting in increased angiogenesis activity and vascular permeability (PubMed:17075861, PubMed:12794819). Induces, through 'trans-signaling' and synergistically with IL1B and TNF, the production of VEGF (PubMed:12794819). Involved in metabolic controls, is discharged into the bloodstream after muscle contraction increasing lipolysis and improving insulin resistance (PubMed:20823453). 'Trans-signaling' in central nervous system also regulates energy and glucose homeostasis (By similarity). Mediates, through GLP-1, crosstalk between insulin-sensitive tissues, intestinal L cells and pancreatic islets to adapt to changes in insulin demand (By similarity). Also acts as a myokine (Probable). Plays a protective role during liver injury, being required for maintenance of tissue regeneration (By similarity). Also has a pivotal role in iron metabolism by regulating HAMP/hepcidin expression upon inflammation or bacterial infection (PubMed:15124018). Through activation of IL6ST-YAP-NOTCH pathway, induces inflammation-induced epithelial regeneration (By similarity). By similarity 1 Publication 4 Publications



EClinicalMedicine 27 (2020) 100562

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Research Paper

Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study

Filippo Albani[a,*], Lilia Sepe[a], Federica Fusina[a], Chiara Prezioso[a,b], Manuela Baronio[a], Federica Caminiti[a], Antonella Di Maio[a], Barbara Faggian[a], Maria Elena Franceschetti[a], Marco Massari[a], Marcello Salvaggio[a], Giuseppe Natalini[a]

[a] Department of Anesthesia and Intensive Care, Fondazione Poliambulanza Hospital, via Bissolati, 57, Brescia 25124, Italy
[b] Department of Intensive Care Medicine and Anaesthesiology, Fondazione Policlinico Universitario A. Gemelli, Università Cattolica del Sacro Cuore, Rome, Italy

Interpretation

This study shows that treatment with enoxaparin during hospital stay is associated with a lower death rate and, while results from randomized clinical trials are still pending, this study supports the use of thromboprophylaxis with enoxaparin in all patients admitted for COVID-19. Moreover, when enoxaparin is used on the wards, it reduces the risk of Intensive Care Unit admission.

ıronaVirus 2 (SARS-CoV-2) infection is associated with
othelial cells and\or proinflammatory cytokine release.
ed by current guidelines, but evidence is still weak. The
ıoprophylaxis with enoxaparin on hospital mortality in
OVID-19). The effects of enoxaparin on intensive care
l as secondary outcomes.
cted from patients admitted to Poliambulanza Founda-

Table 2
Outcomes in the Enoxaparin cohort and no-Enoxaparin cohort.

		No-Enoxaparin treatment	Enoxaparin	p value
In-hospital mortality	N (%)	154 (25·5)	200 (25)	0·98
ICU admission	N (%)	74 (11)	72 (10·4)	0·79
Hospital length of stay	days	5 (3–7)	9 (6–15)	<0·001

Factor variables are expressed as count (%), continuous variables as median (1st - 3rd Quartiles).

Table 3
Thrombotic and hemorrhagic events.

		No Enoxaparin treatment	Enoxaparin (prophylactic)	Enoxaparin (therapeutic)	p value
Patients	N (%)	604 (43)	487 (35)	312 (22)	
Thrombotic events	N (%)	13 (2·2)	12 (2·5)	51 (16)	<0·001
Pulmonary Embolism		1	3	29	
Venous thromboembolism		2	1	14	
Acute myocardial infarction		6	4	6	
Cerebral infarction		4	4	2	
Hemorrhagic events	N (%)	15 (2·5)	6 (1·2)	10 (3·2)	0·12

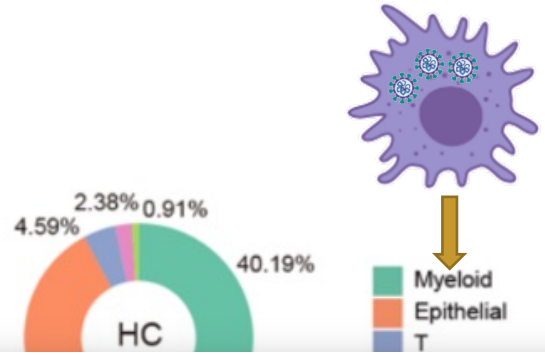
Recorded thrombotic and hemorrhagic events in the two cohorts. Patients in the enoxaparin cohort are divided according to dosage of received: prophylactic ≤ 40 mg a day or therapeutic > 40 mg a day. P values were computed with Fisher's exact test.

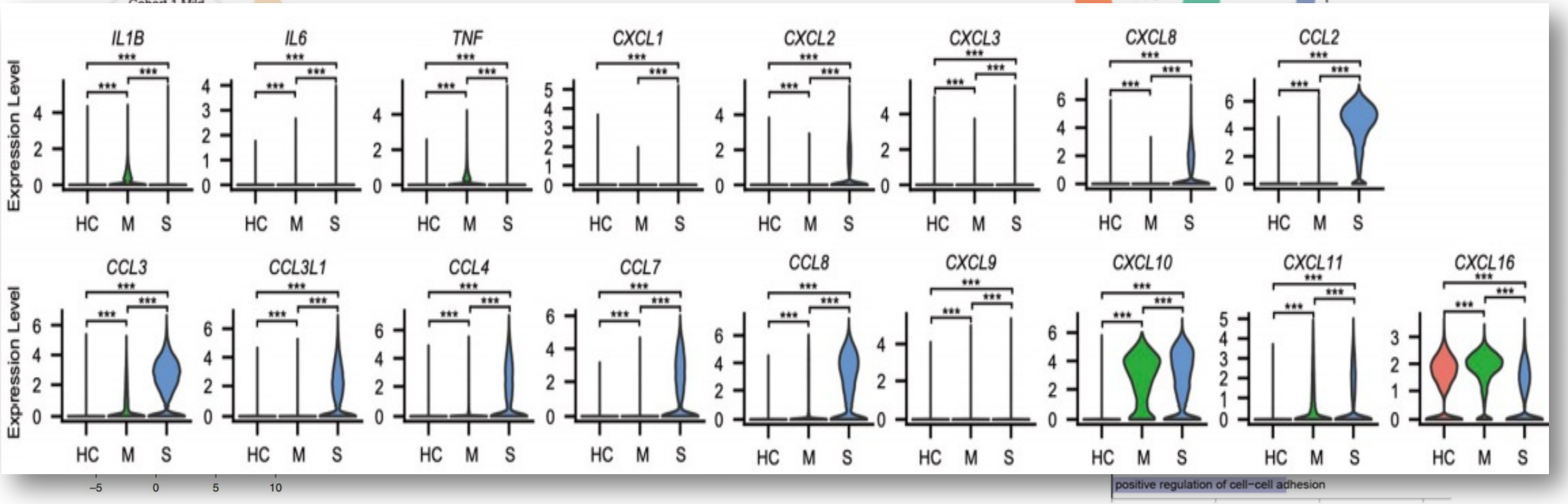
nature medicine
BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-020-0901-9
Check for updates

Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19

Mingfeng Liao[1,6], Yang Liu[1,6], Jing Yuan[2,6], Yanling Wen[1], Gang Xu[1], Juanjuan Zhao[1], Lin Cheng[1], Jinxiu Li[2], Xin Wang[1], Fuxiang Wang[2], Lei Liu[1,3]✉, Ido Amit[4]✉, Shuye Zhang[5]✉ and Zheng Zhang[1,3]✉

3 Clusters de Macrófagos



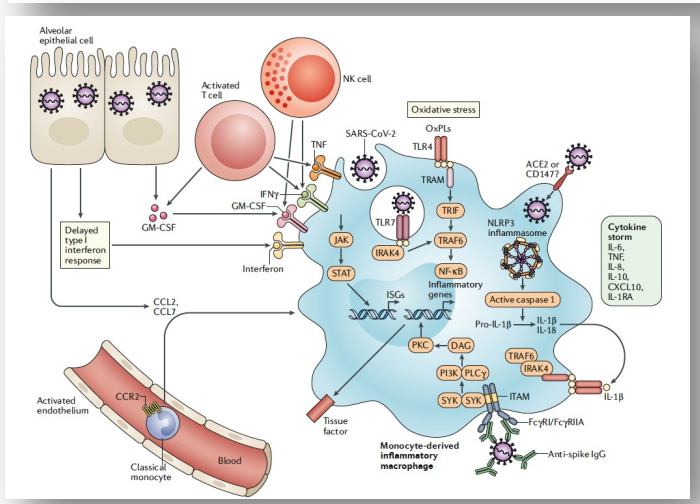


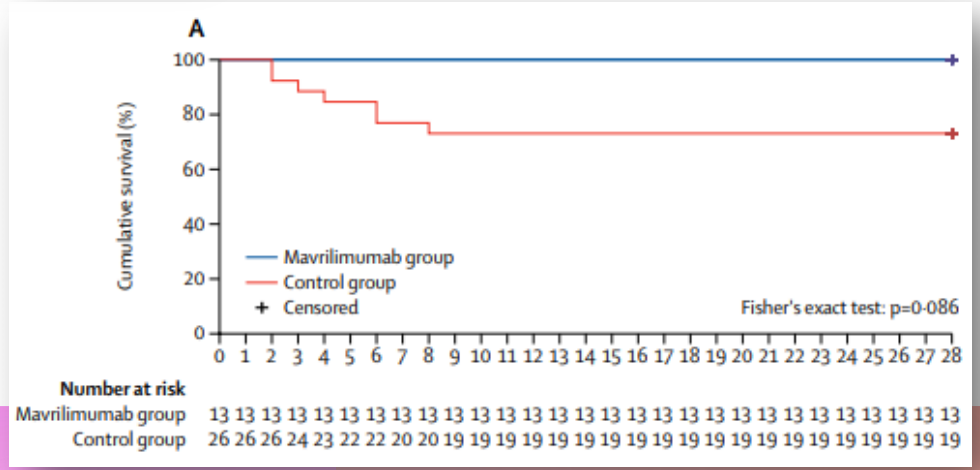
Resposta Imune Efetora
Proteção - Cura

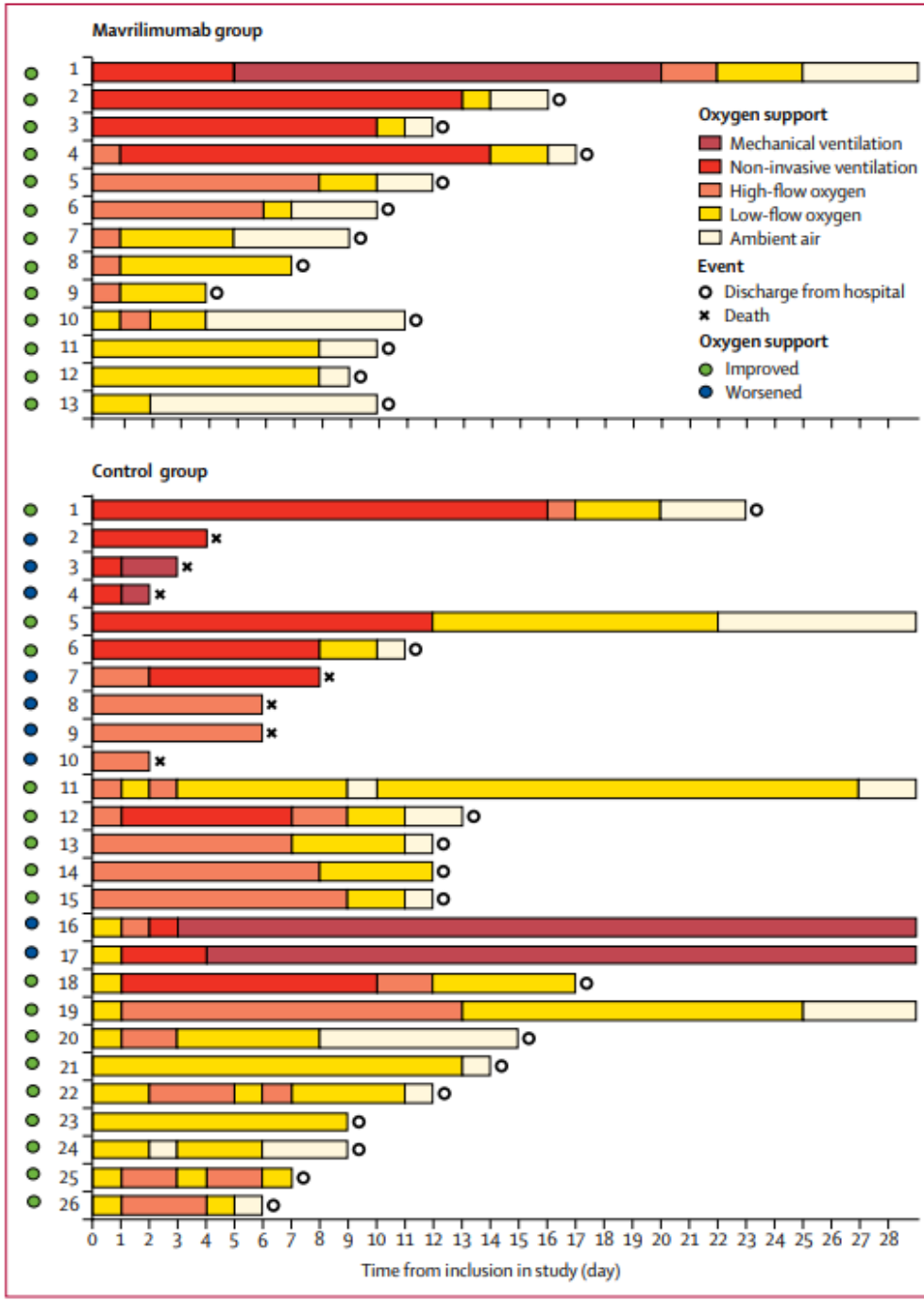
Resposta Imune Exacerbada ou Deficiente
Imunopatologia

GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study

Giacomo De Luca, Giulio Cavalli, Corrado Campochiaro, Emanuel Della-Torre, Piera Angelillo, Alessandro Tomelleri, Nicola Boffini, Stefano Tentori, Francesca Mette, Nicola Farina, Patrizia Rovere-Querini, Annalisa Ruggeri, Teresa D'Aliberti, Paolo Scarpellini, Giovanni Landoni, Francesco De Cobelli, John F Paolini, Alberto Zangrillo, Moreno Tresoldi, Bruce C Trapnell, Fabio Ciceri, Lorenzo Dagna

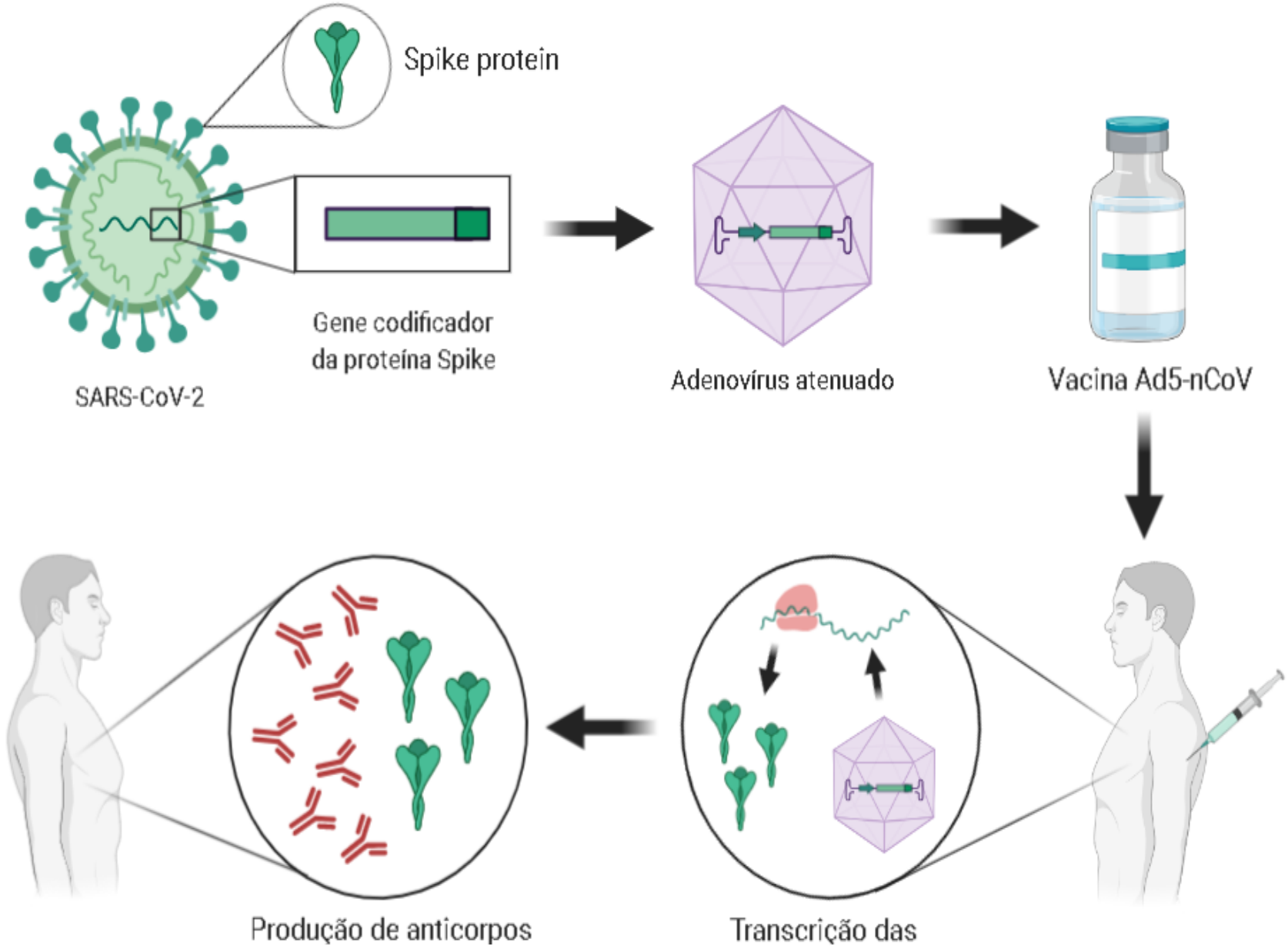






VACINAS
DNA
RNA
Vírus Inativado

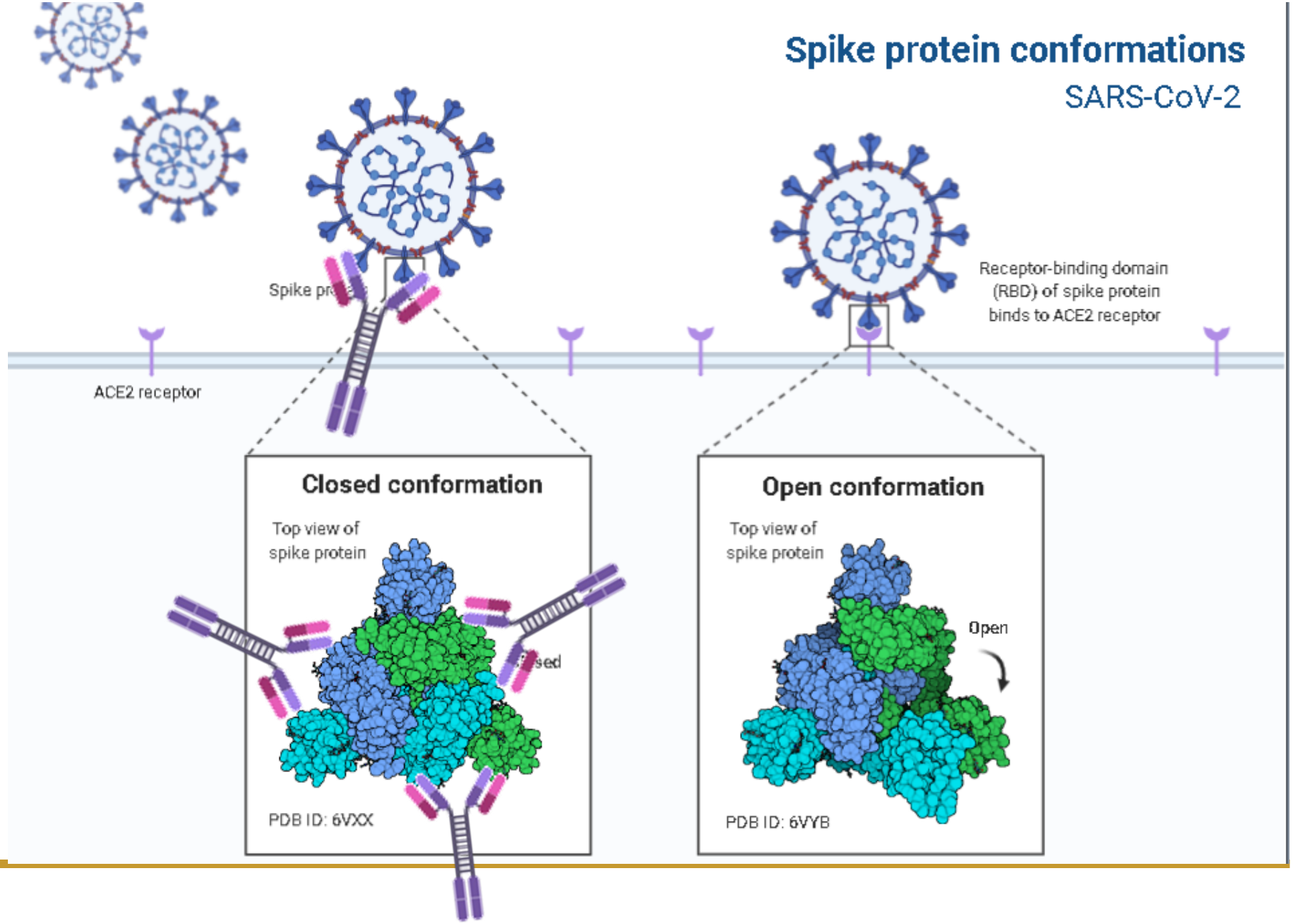
VACINAS
DNA
RNA
Vírus Inativado

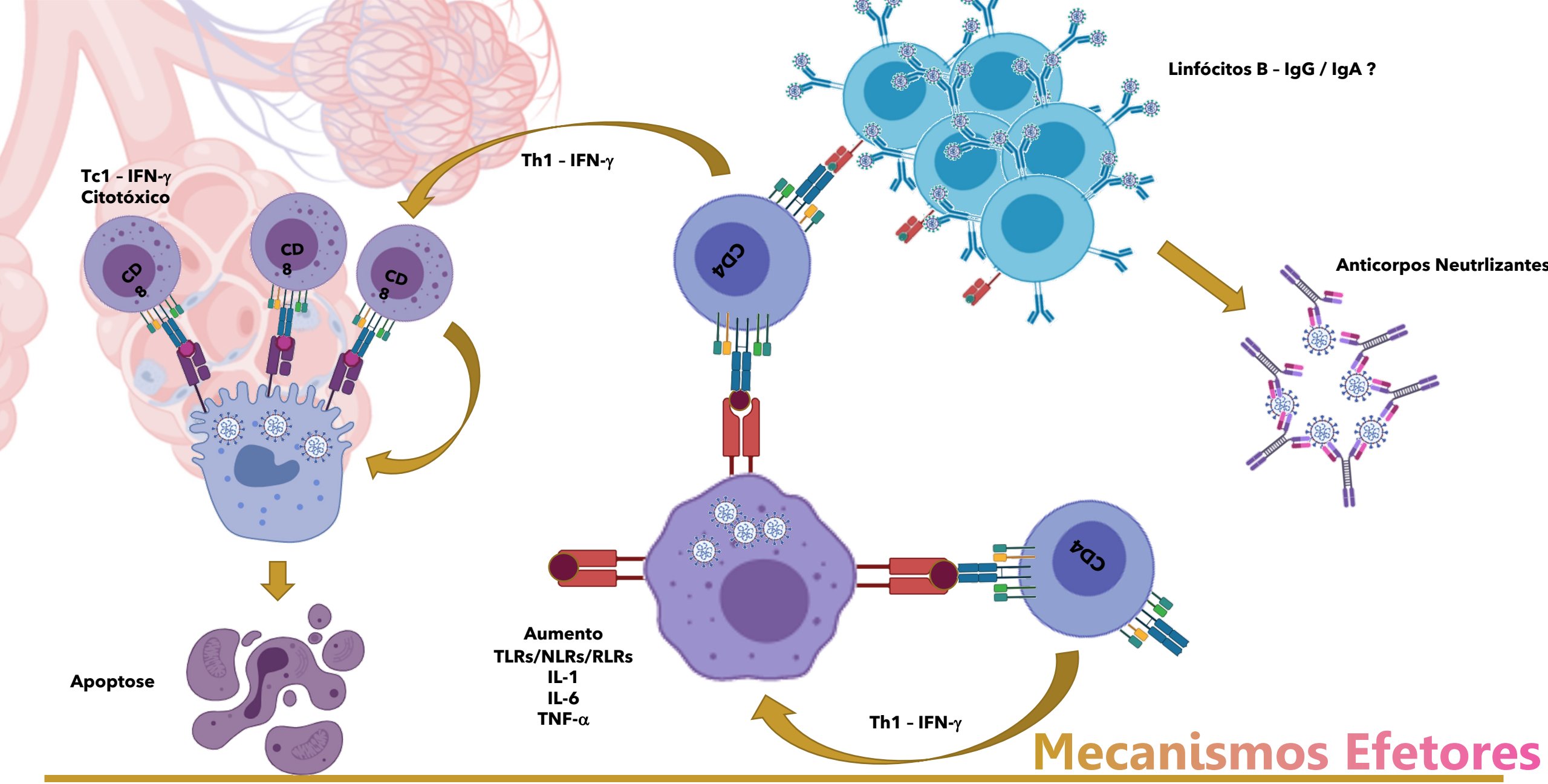


ANTICORPOS NEUTRALIZANTES

Anti-SPIKE

Evitar a ADESÃO à Superfície da Célula e Invasão Viral





Mecanismos Efetores

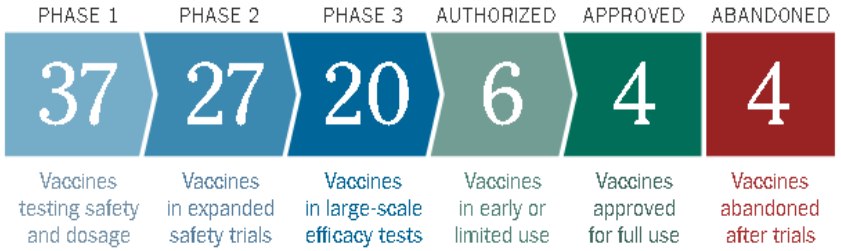
The New York Times

rus Outbreak › | LIVE Latest Updates | Maps and Cases | See Your Local Risk | New Variants Tracker | Vaccine Rollout

U.S.A. | World | Health

Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated Feb. 11, 2021



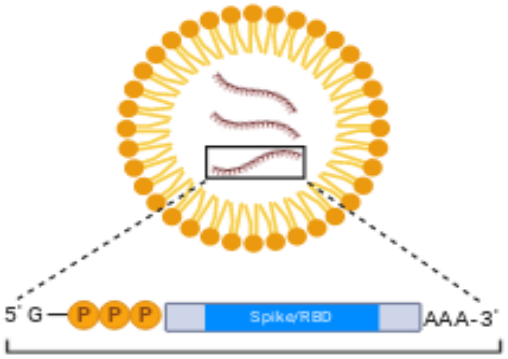
Vaccines typically require years of research and testing before reaching the clinic, but in 2020, scientists embarked on a race to produce safe and effective coronavirus vaccines in record time. Researchers are currently testing **69 vaccines** in clinical trials on humans, and 20 have reached the final stages of testing. At least 89 preclinical vaccines are under active investigation in animals.

Leading vaccines

Developer	How It Works	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in several countries. Emergency use in U.S., E.U., other countries.
Moderna	mRNA	3	Approved in Switzerland. Emergency use in U.S., U.K., E.U., others.
Gamaleya	Ad26, Ad5	3	Early use in Russia. Emergency use in other countries.
Oxford-AstraZeneca	ChAdOx1	2 3	Emergency use in U.K., E.U., other countries.
CanSino	Ad5	3	Limited use in China.
Johnson & Johnson	Ad26	3	**Approoved USA**
Vector Institute	Protein	3	Early use in Russia.
Novavax	Protein	3	
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in Egypt, other coutries.
Sinovac	Inactivated	3	Approved in China. Emergency use in Brazil, other countries.
Sinopharm-Wuhan	Inactivated	3	Limited use in China, U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India.

BioNTech (BNT162: a1, b1, b2, c2)

Delivery vehicle:
Lipid nanoparticle

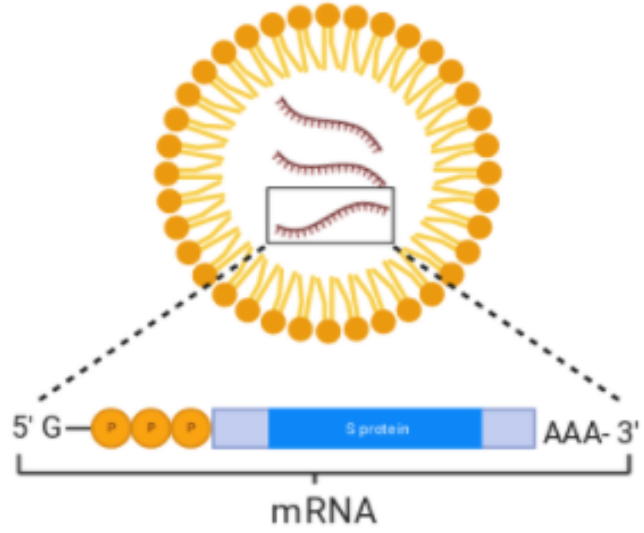


Nucleoside modified RNA (modRNA)
Uridine containing mRNA (uRNA)
Self-amplifying mRNA (saRNA)

Platform: Four individual LNP-encapsulated mRNA vaccines (2 modRNA, 1uRNA, 1 saRNA) encoding Spike protein or Receptor Binding Domain (RBD).

Moderna (mRNA-1273)

Lipid nanoparticle



Platform: LNP-encapsulated mRNA encoding S protein.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 31, 2020 VOL. 383 NO. 27

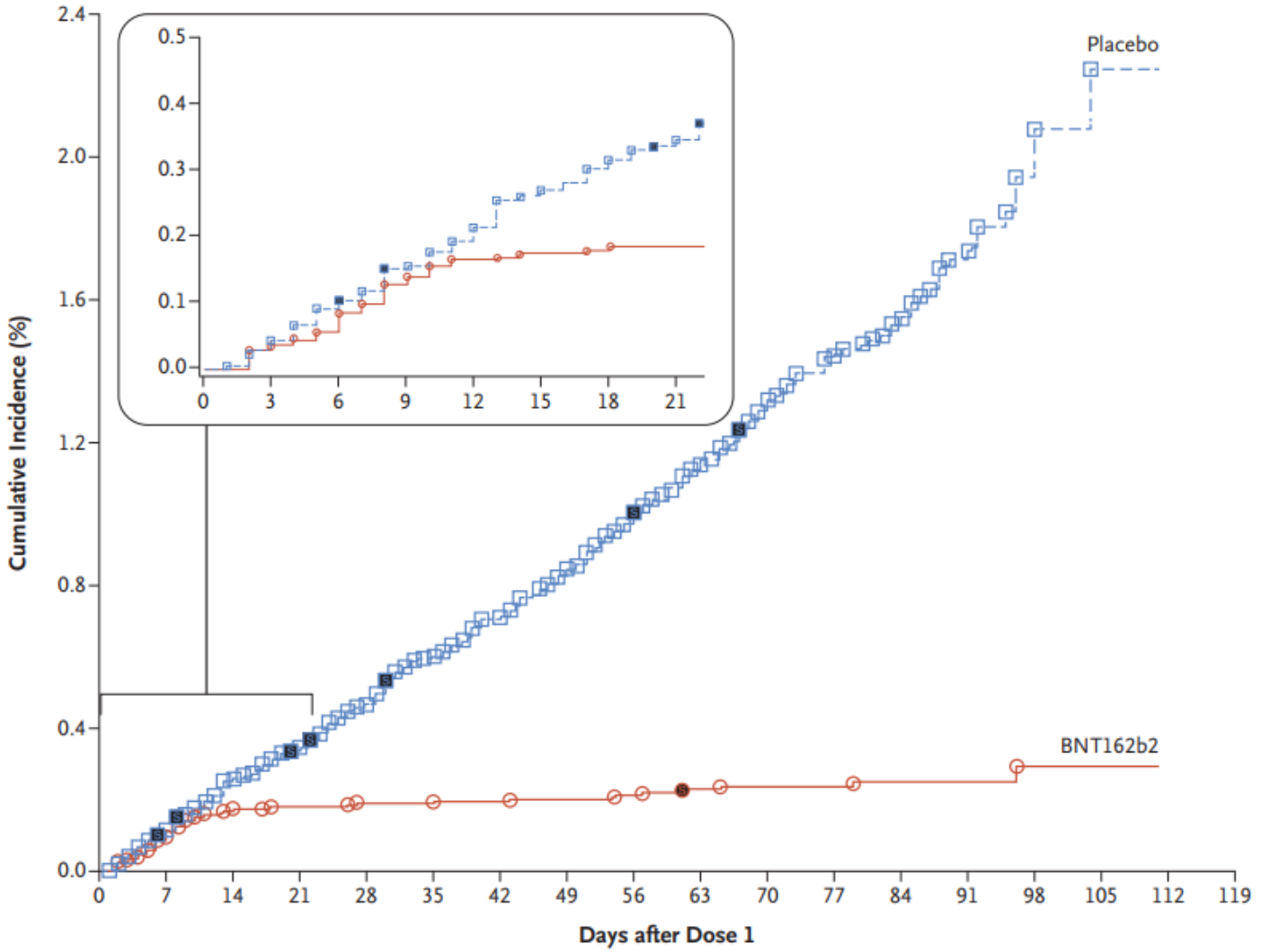
Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

PFIZER

Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
	(N=18,198)		(N=18,325)			
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
	(N=19,965)		(N=20,172)			
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

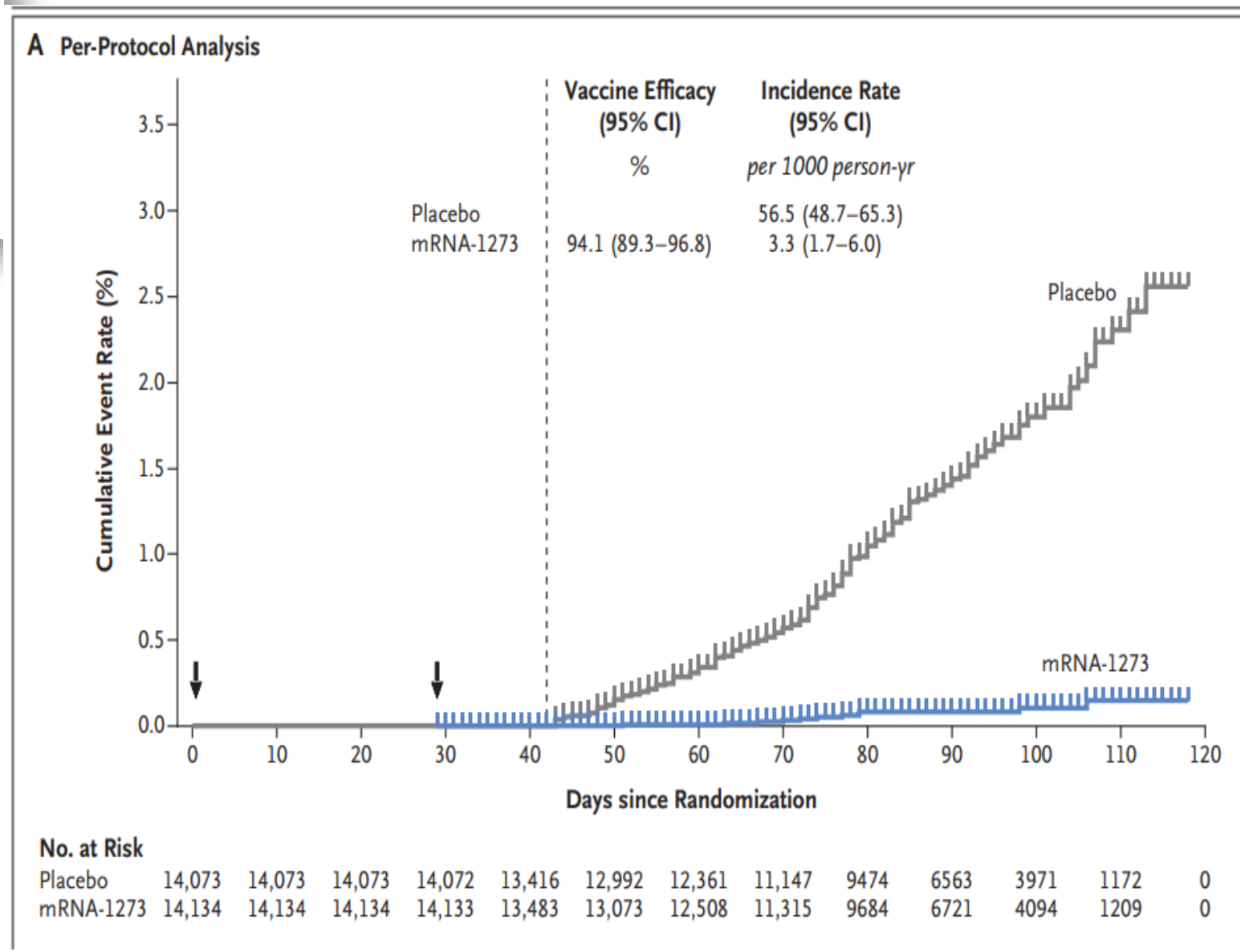
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 4, 2021 VOL. 384 NO. 5

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

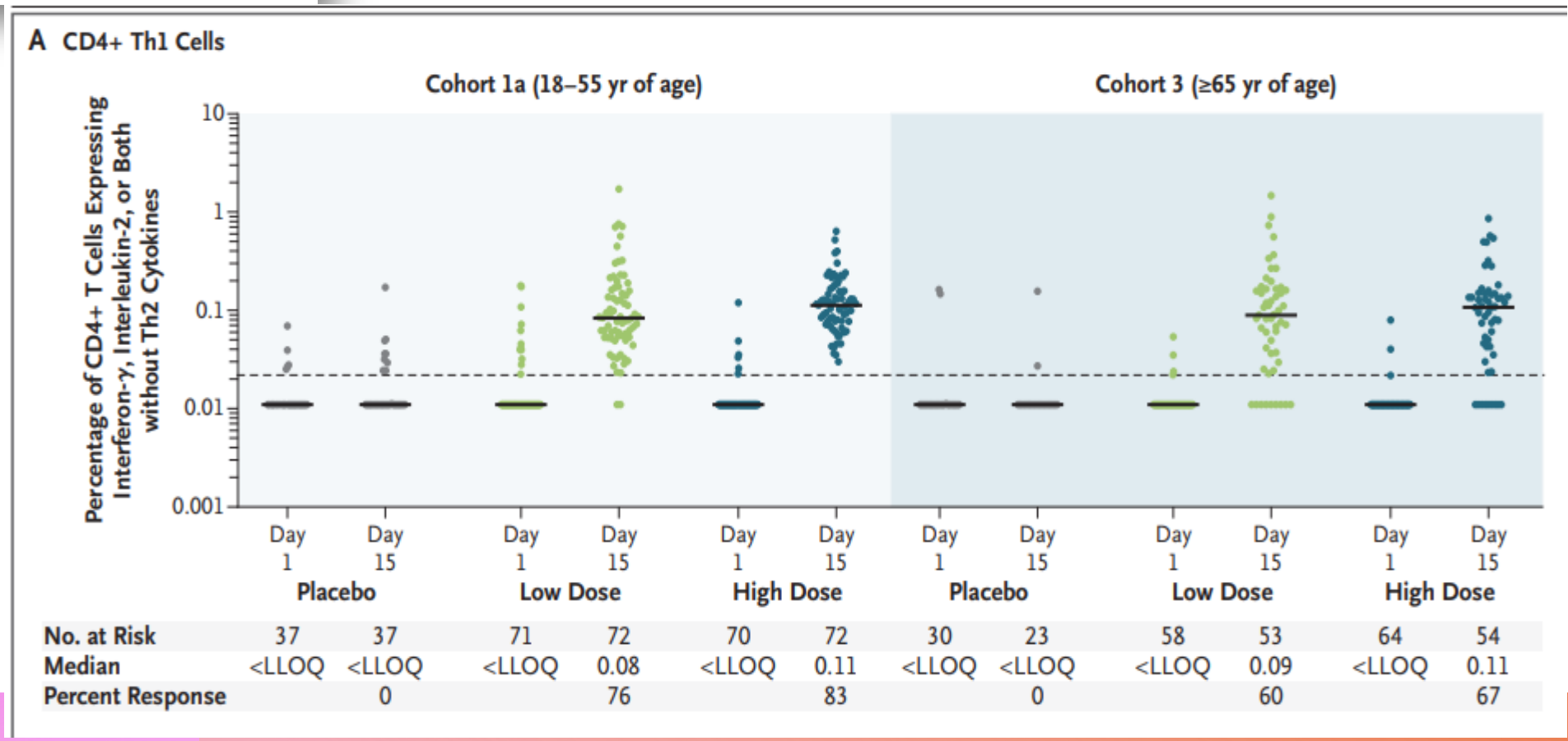
MODERNA

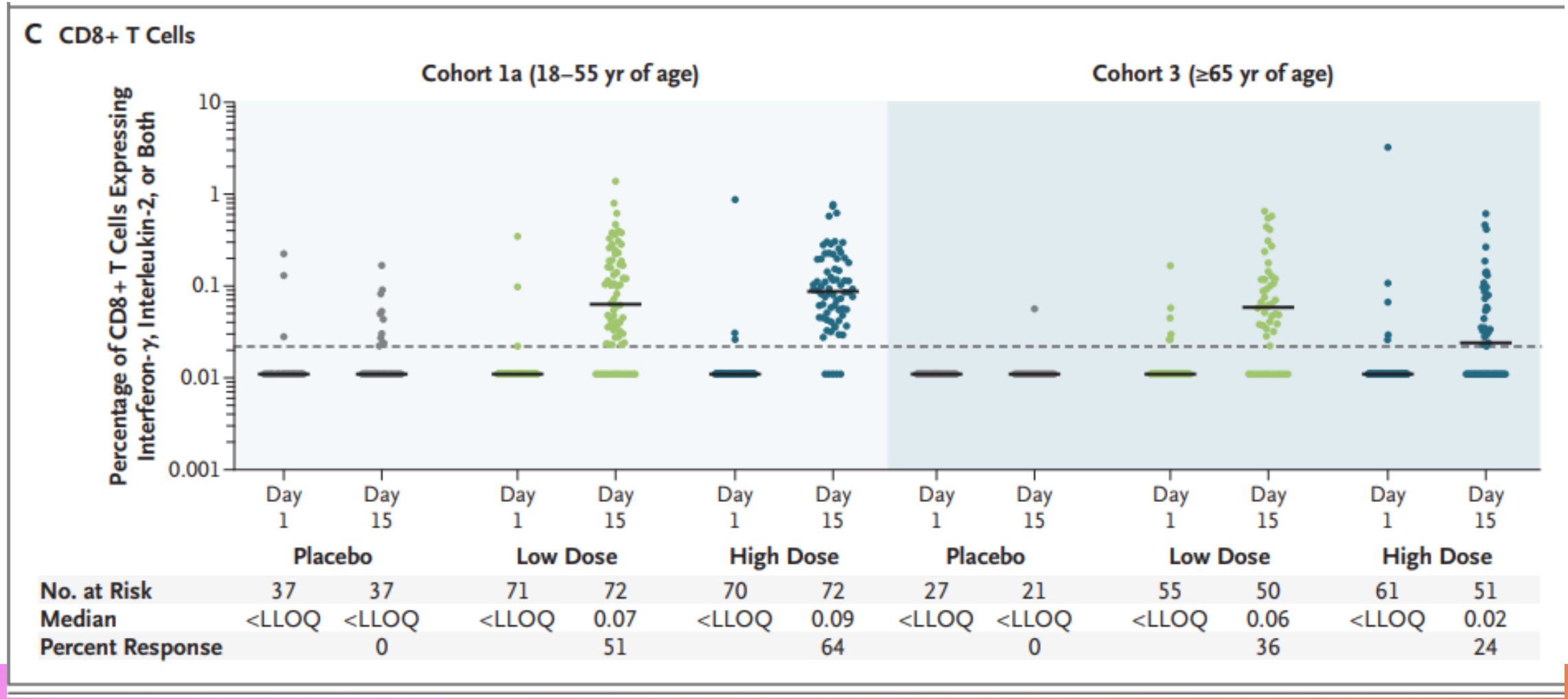


ORIGINAL ARTICLE

Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine

J. Sadoff, M. Le Gars, G. Shukarev, D. Heerwegh, C. Truyers, A.M. de Groot, J. Stoop, S. Tete, W. Van Damme, I. Leroux-Roels, P.-J. Berghmans, M. Kimmel, P. Van Damme, J. de Hoon, W. Smith, K.E. Stephenson, S.C. De Rosa, K.W. Cohen, M.J. McElrath, E. Cormier, G. Scheper, D.H. Barouch, J. Hendriks, F. Struyf, M. Douoguih, J. Van Hoof, and H. Schuitemaker




C CD8+ T Cells
Cohort 1a (18–55 yr of age)
Cohort 3 (≥65 yr of age)
Percentage of CD8+ T Cells Expressing Interferon-γ, Interleukin-2, or Both
10
1
0.1
0.01
0.001
Day 1
Day 15
Placebo
Low Dose
High Dose
No. at Risk 37 37 71 72 70 72 27 21 55 50 61 51
Median <LLOQ <LLOQ <LLOQ 0.07 <LLOQ 0.09 <LLOQ <LLOQ <LLOQ 0.06 <LLOQ 0.02
Percent Response 0 51 64 0 36 24

AZD1222 US Phase III trial met primary efficacy endpoint in preventing COVID-19 at interim analysis

PUBLISHED
22 March 2021

22 March 2021 07:00 GMT

79% vaccine efficacy at preventing symptomatic COVID-19

100% efficacy against severe or critical disease and hospitalisation

Comparable efficacy result across ethnicity and age, with 80% efficacy in participants aged 65 years and over

Favourable reactogenicity and overall safety profile

https://www.astrazeneca.com/media-centre/press-releases/2021/astrazeneca-us-vaccine-trial-met-primary-endpoint.html

ARTICLE OPEN

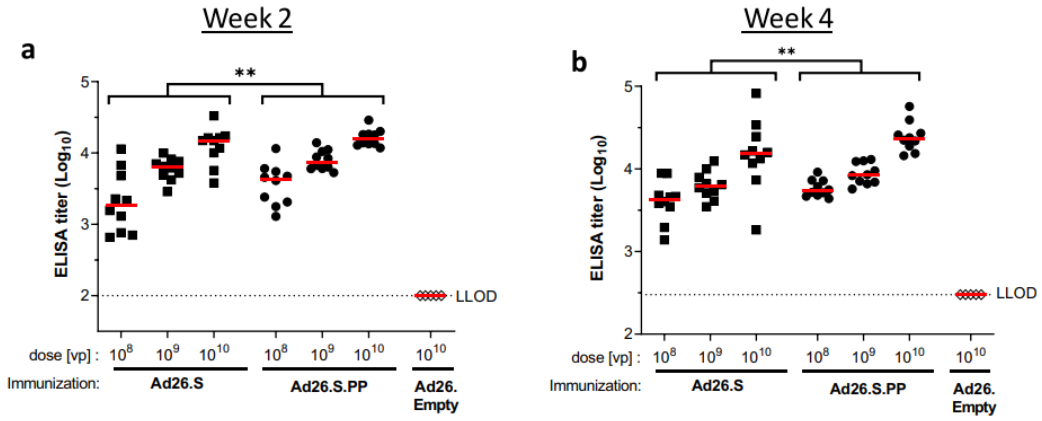
Check for updates

Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen induces potent humoral and cellular immune responses

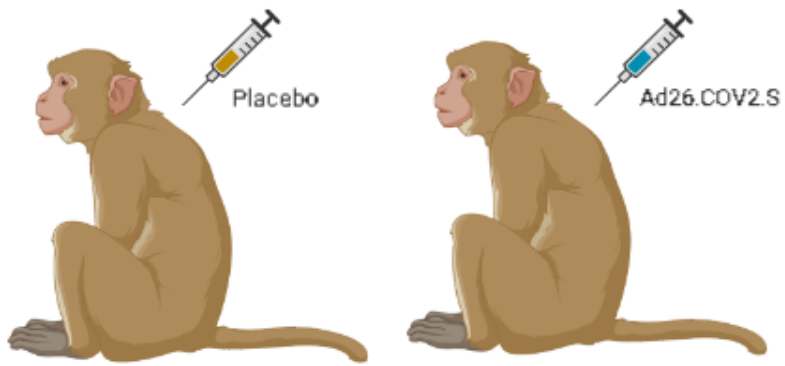
Rinke Bos[1,4], Lucy Rutten[1,4], Joan E. M. van der Lubbe[1,4], Mark J. G. Bakkers[1], Gijs Hardenberg[1], Frank Wegmann[1], David Zuijdgeest[1], Adriaan H. de Wilde[1], Annemart Koornneef[1], Annemiek Verwilligen[1], Danielle van Manen[1], Ted Kwaks[1], Ronald Vogels[1], Tim J. Dalebout[2], Sebenzile K. Myeni[2], Marjolein Kikkert[2], Eric J. Snijder[2], Zhenfeng Li[3], Dan H. Barouch[3], Jort Vellinga[1], Johannes P. M. Langedijk[1], Roland C. Zahn[1], Jerome Custers[1] and Hanneke Schuitemaker[1]✉

Adenovírus que entrega a proteína spike do SARS-CoV-2 para as células hospedeiras

Ad26.COV2.S

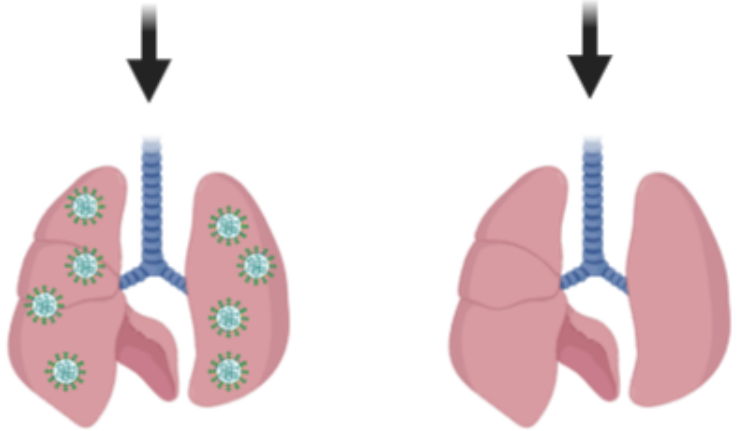


Macacos Rhesus



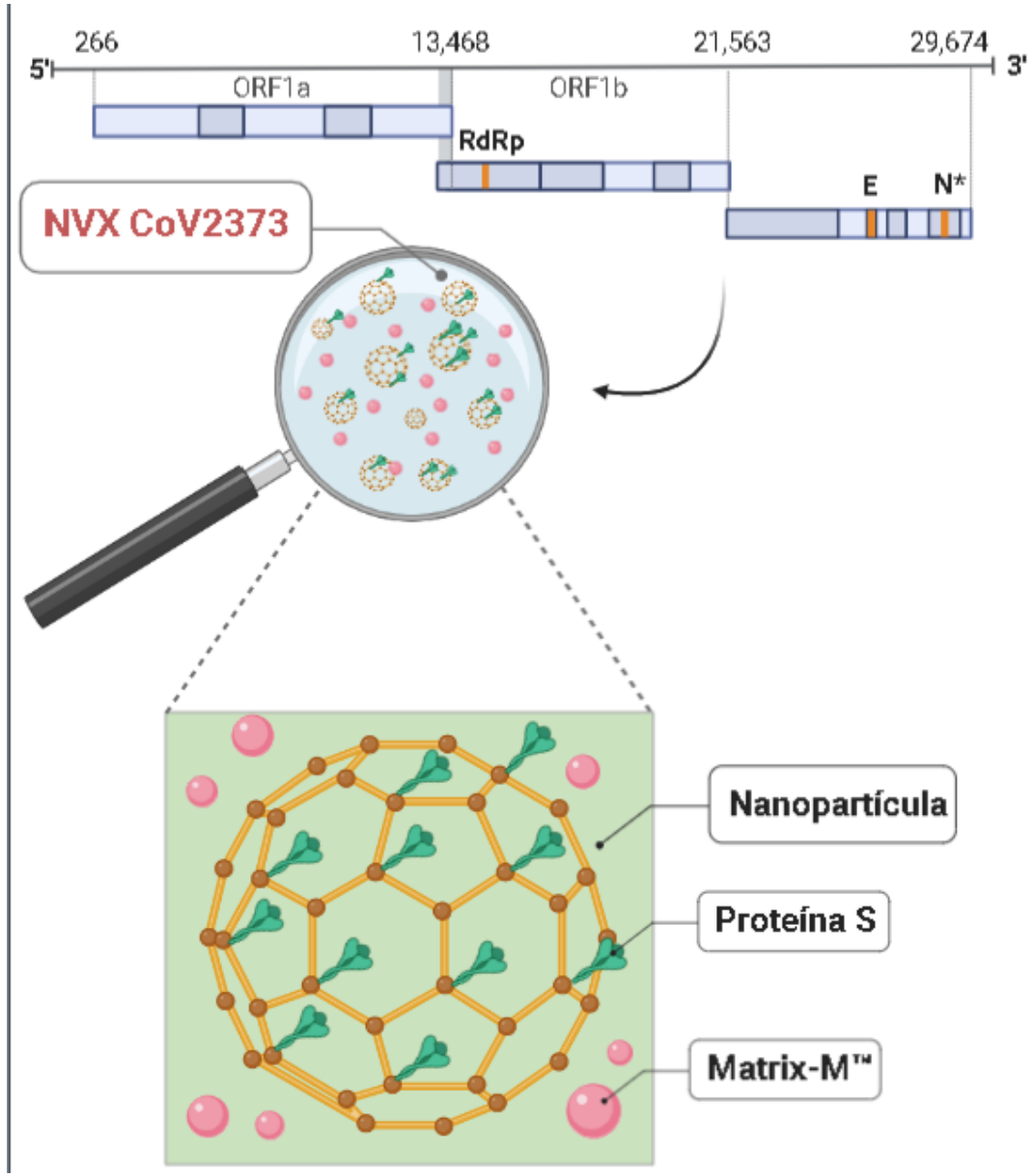
20 animais controle

32 animais vacinados com dose única



Os animais foram infectados e apresentaram altos níves de vírus no pulmão e no swab nasal.

Os animais não apresentaram vírus no pulmão e produziram altas concetrações de anticorpos neutralizantes.



Ensaio Clínico Fase I

150 participantes

Ensaio Clínico Fases Subsequentes

?? participantes

CORONAVIRUS | UPDATED JAN. 25, 2021

What We Know About the New P.1 Strain of the Coronavirus

By Chas Danner

A patient arrives at the 28 de Agosto Hospital in the city of Manaus, Brazil, on January 14, amid the a devastating second surge of COVID-19 cases in the region. Photo: Michael Dantas/AFP via Getty Images

Where and when did the P.1 variant emerge?

The P.1 variant was first detected in samples from Manaus in the Amazonas state in northern Brazil in mid-December. The researchers who discovered it published their findings on January 12, noting that they detected the strain in 42 percent of the samples they tested and that it had also been detected in a few recent coronavirus cases in Japan among people who had traveled to Manaus. It is not clear precisely when the variant evolved, but the researchers noted that it had not been present in the publicly available genome-surveillance samples that were collected in Manaus between March to November.

The reason the researchers started sequencing samples from Manaus was because they wanted to investigate why there had been a startling resurgence of the coronavirus in the city, where a study has estimated as much as 76 percent of the population had already been infected with COVID-19, which would theoretically infer a high level of immunity among its inhabitants.

What makes the P.1 variant so worrisome?

The P.1 variant (also known as B.1.1.248) concerns scientists for a few reasons, starting with how it has two notable mutations that may make it more dangerous.

First, it has a spike protein mutation that may make the variant more infectious. This mutation, known as N501Y (or "Nelly"), is also present in the B.1.1.7 variant, which is fast overtaking the U.K., as well as the B.1.351 (also known as 501.V2, or N501Y.V2) variant that has emerged in South Africa. The mutation enables the virus's spike proteins to more easily bind with human cells, which may make it more infectious. Research has suggested that the B.1.1.7 variant may be more than 50 percent more transmissible than previously dominant strains — which is why scientists and public-health officials are so worried about it.

The P.1 variant also has an "escape mutation" known as E484K, which also exists in the B.1.351 variant from South Africa and which in lab experiments has been found to help the coronavirus evade protective antibodies generated by earlier infections, as well as less susceptible to antibody drugs. In other words, it's possible that someone who has already been infected with an earlier strain of the coronavirus could be reinfected by a variant with this mutation and that the mutation may enable the coronavirus to evade antibodies generated by COVID vaccines.

More Resources

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Global COVID-19 +

Science & Research −

Science Agenda: Building the Evidence Base for Ongoing COVID-19 Response, 2020-2023

Science Briefs −

Background Rationale and Evidence for Public Health Recommendations for Fully Vaccinated People

Transmission of SARS-CoV-2 in K-12 schools

Emerging SARS-CoV-2 Variants

Options to Reduce Quarantine Using Symptom Monitoring and Diagnostic Testing

Use of Cloth Masks to Control the Spread of SARS-CoV-2

Science Brief: Emerging SARS-CoV-2 Variants

Updated Jan. 28, 2021 Languages Print

Multiple SARS-CoV-2 variants are circulating globally. Several new variants emerged in the fall of 2020, most notably:

- In the United Kingdom (UK), a new variant of SARS-CoV-2 (known as 20I/501Y.V1, VOC 202012/01, or B.1.1.7) emerged with a large number of mutations. This variant has since been detected in numerous countries around the world, including the United States (US). In January 2021, scientists from UK reported evidence[1] that suggests the B.1.1.7 variant may be associated with an increased risk of death compared with other variants. More studies are needed to confirm this finding. This variant was reported in the US at the end of December 2020.
- In South Africa, another variant of SARS-CoV-2 (known as 20H/501Y.V2 or B.1.351) emerged independently of B.1.1.7. This variant shares some mutations with B.1.1.7. Cases attributed to this variant have been detected in multiple countries outside of South Africa. This variant was reported in the US at the end of January 2021.
- In Brazil, a variant of SARS-CoV-2 (known as P.1) emerged that was first was identified in four travelers from Brazil, who were tested during routine screening at Haneda airport outside Tokyo, Japan. This variant has 17 unique mutations, including three in the receptor binding domain of the spike protein. This variant was detected in the US at the end of January 2021.

Scientists are working to learn more about these variants to better understand how easily they might be transmitted and the effectiveness of currently

Previous update:
Dec. 29, 2020

US COVID-19 Cases Caused by Variants

View a map showing the number of confirmed cases in each state.

View Cases

nature medicine

LETTERS

https://doi.org/10.1038/s41591-021-01255-3

Check for updates

Sixteen novel lineages of SARS-CoV-2 in South Africa

Houriiyah Tegally[1,23], Eduan Wilkinson[1,23], Richard J. Lessells[1], Jennifer Giandhari[1], Sureshnee Pillay[1], Nokukhanya Msomi[2], Koleka Mlisana[3], Jinal N. Bhiman[4], Anne von Gottberg[4,5], Sibongile Walaza[4,6], Vagner Fonseca[1], Mushal Allam[4], Arshad Ismail[4], Allison J. Glass[5,7], Susan Engelbrecht[8], Gert Van Zyl[8], Wolfgang Preiser[8], Carolyn Williamson[9], Francesco Petruccione[10,11], Alex Sigal[12,13,14], Inbal Gazy[1], Diana Hardie[9], Nei-yuan Hsiao[9], Darren Martin[15], Denis York[16], Dominique Goedhals[17], Emmanuel James San[1], Marta Giovanetti[18], José Lourenço[19], Luiz Carlos Junior Alcantara[18,20] and Tulio de Oliveira[1,21,22] ✉

The first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in South Africa was identified on 5 March 2020, and by 26 March the country was in full lockdown (Oxford stringency index of 90)[1]. Despite the early response, by November 2020, over 785,000 people in South Africa were infected, which accounted for approximately 50% of all known African infections[2]. In this study, we analyzed 1,365 near whole genomes and report the identification of 16 new lineages of SARS-CoV-2 isolated between 6 March and 26 August 2020. Most of these lineages have unique mutations that have not been identified elsewhere. We also show that three lineages (B.1.1.54, B.1.1.56 and C.1) spread widely in South Africa during the first wave, comprising ~42% of all infections in the country at the time. The newly identified C lineage of SARS-CoV-2, C.1, which has 16 nucleotide mutations as compared with the original Wuhan sequence, including one amino acid change on the spike protein, D614G (ref. [3]), was the most geographically widespread lineage in South Africa by the end of August 2020. An early South African-specific lineage, B.1.106, which was identified in April 2020 (ref. [4]), became extinct after nosocomial outbreaks were controlled in KwaZulu-Natal Province. Our findings show that genomic surveillance can be implemented on a large scale in Africa to identify new lineages and inform measures to control the spread of SARS-CoV-2. Such genomic surveillance presented in this study has been shown to be crucial in the identification of the 501Y.V2 variant in South Africa in December 2020 (ref. [5]).

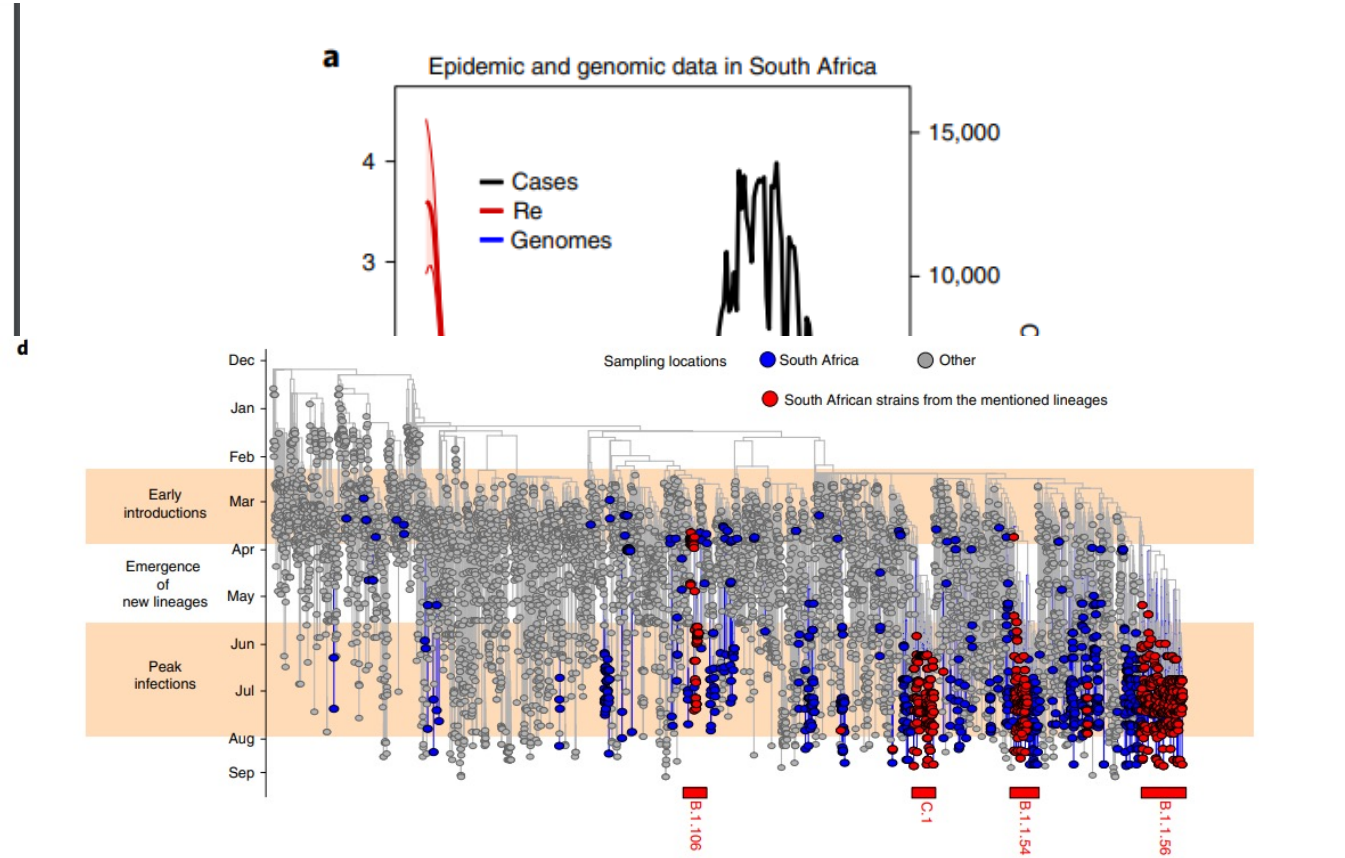


Fig. 1 | Monitoring the SARS-CoV-2 epidemic in South Africa using genomic sequencing. a, Epidemiological curve showing the progression of daily COVID-19 numbers in South Africa, changes in R_e estimations (mean estimated median R_e with upper and lower bounds of the 95% confidence interval shown), lockdown levels and the timing of genomic sampling in South Africa from the beginning of the epidemic to 15 September. **b**, Estimated numbers introductions into South Africa colored by region of origin. **c**, Overall sampling of genomes in South Africa colored by whether the genomes are associate with introduction events (origins outside South Africa) or not (origins in South Africa). **d**, MCC tree of 7,213 global genomes including 1,365 South Africa sequences, indicating a period of early introductions and a period of peak infection separated by a period of emergence of new lineages. The three larges monophyletic lineage clusters in South Africa, along with the early B.1.106 South African lineage, are labeled.

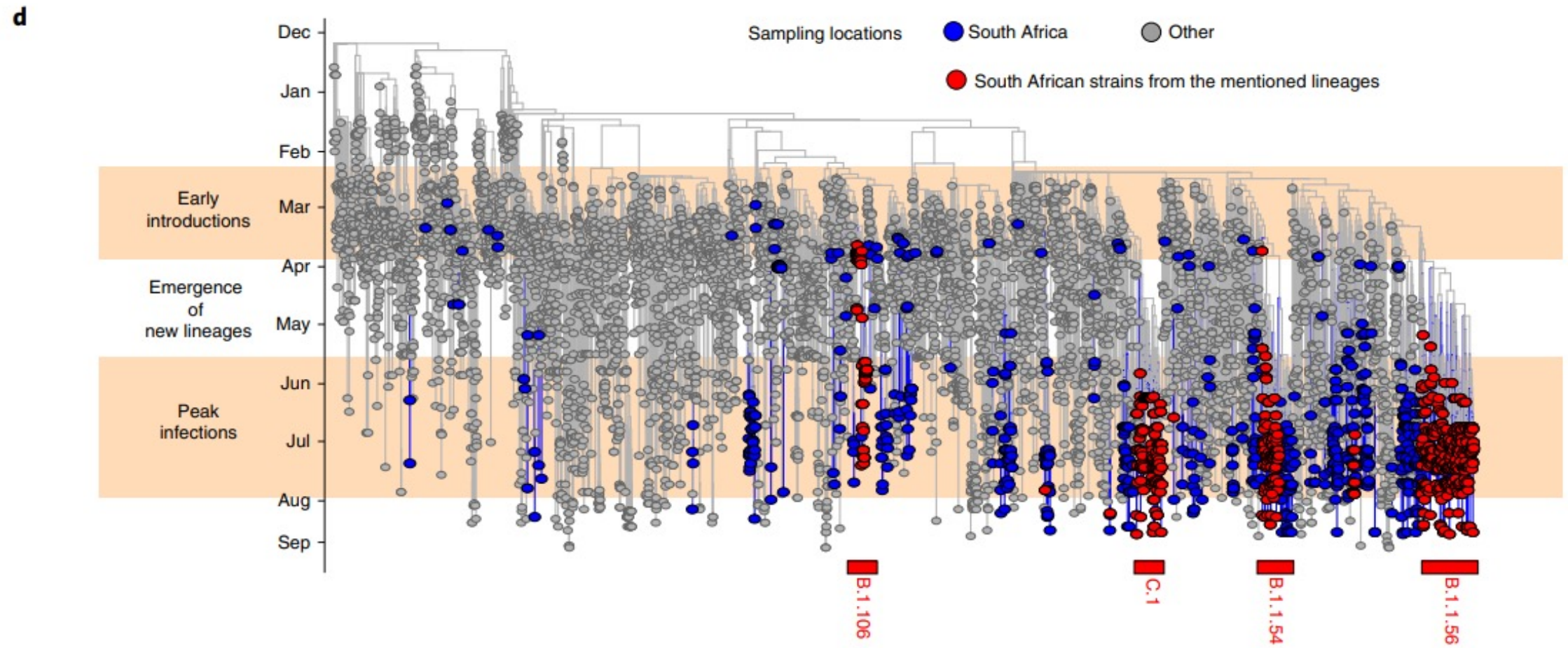
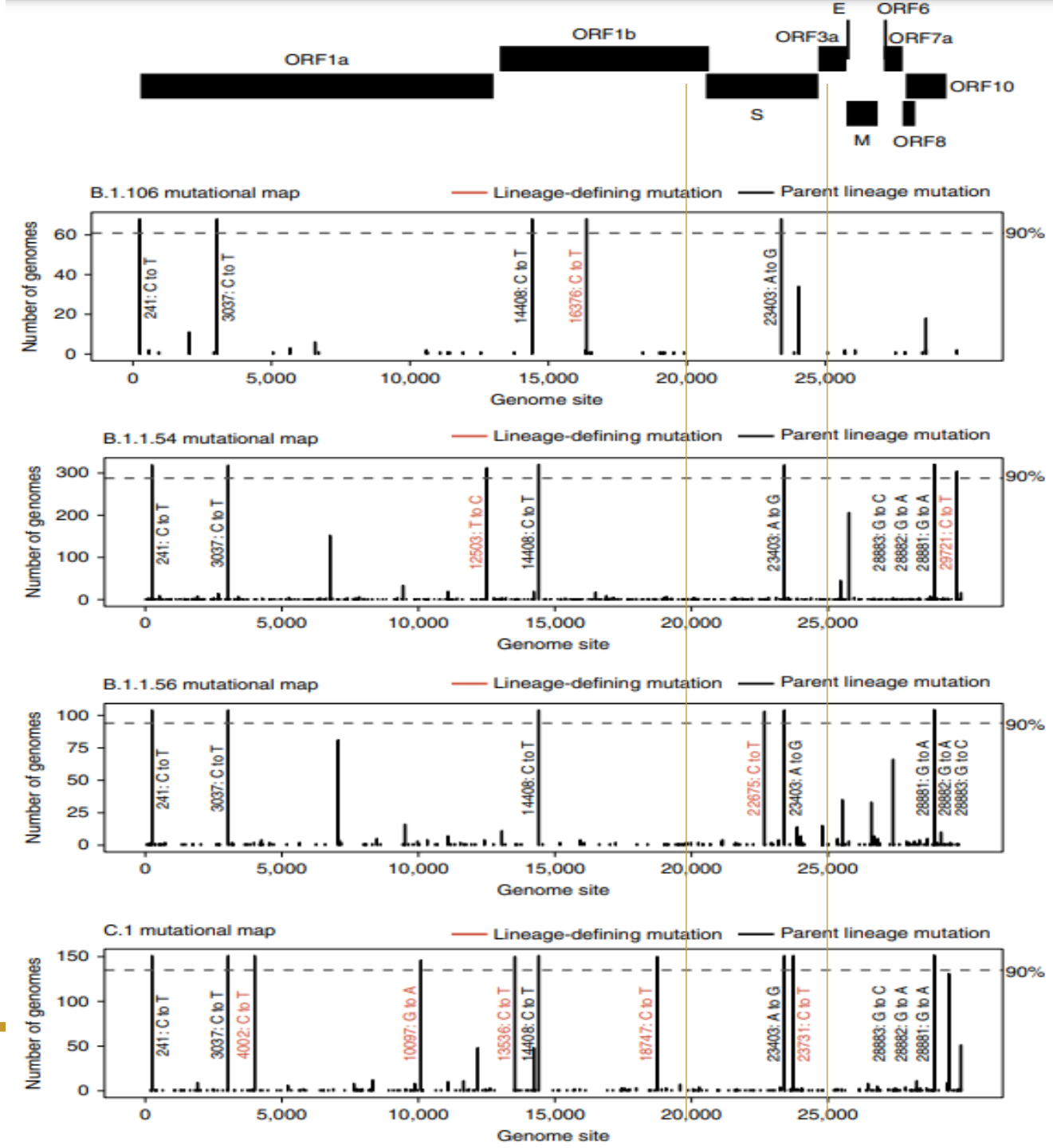


Fig. 1 | Monitoring the SARS-CoV-2 epidemic in South Africa using genomic sequencing. a, Epidemiological curve showing the progression of daily COVID-19 numbers in South Africa, changes in R_e estimations (mean estimated median R_e with upper and lower bounds of the 95% confidence interval shown), lockdown levels and the timing of genomic sampling in South Africa from the beginning of the epidemic to 15 September. **b**, Estimated numbers introductions into South Africa colored by region of origin. **c**, Overall sampling of genomes in South Africa colored by whether the genomes are associate with introduction events (origins outside South Africa) or not (origins in South Africa). **d**, MCC tree of 7,213 global genomes including 1,365 South Africa sequences, indicating a period of early introductions and a period of peak infection separated by a period of emergence of new lineages. The three larges monophyletic lineage clusters in South Africa, along with the early B.1.106 South African lineage, are labeled.

Mutações

Spike e Não Spike



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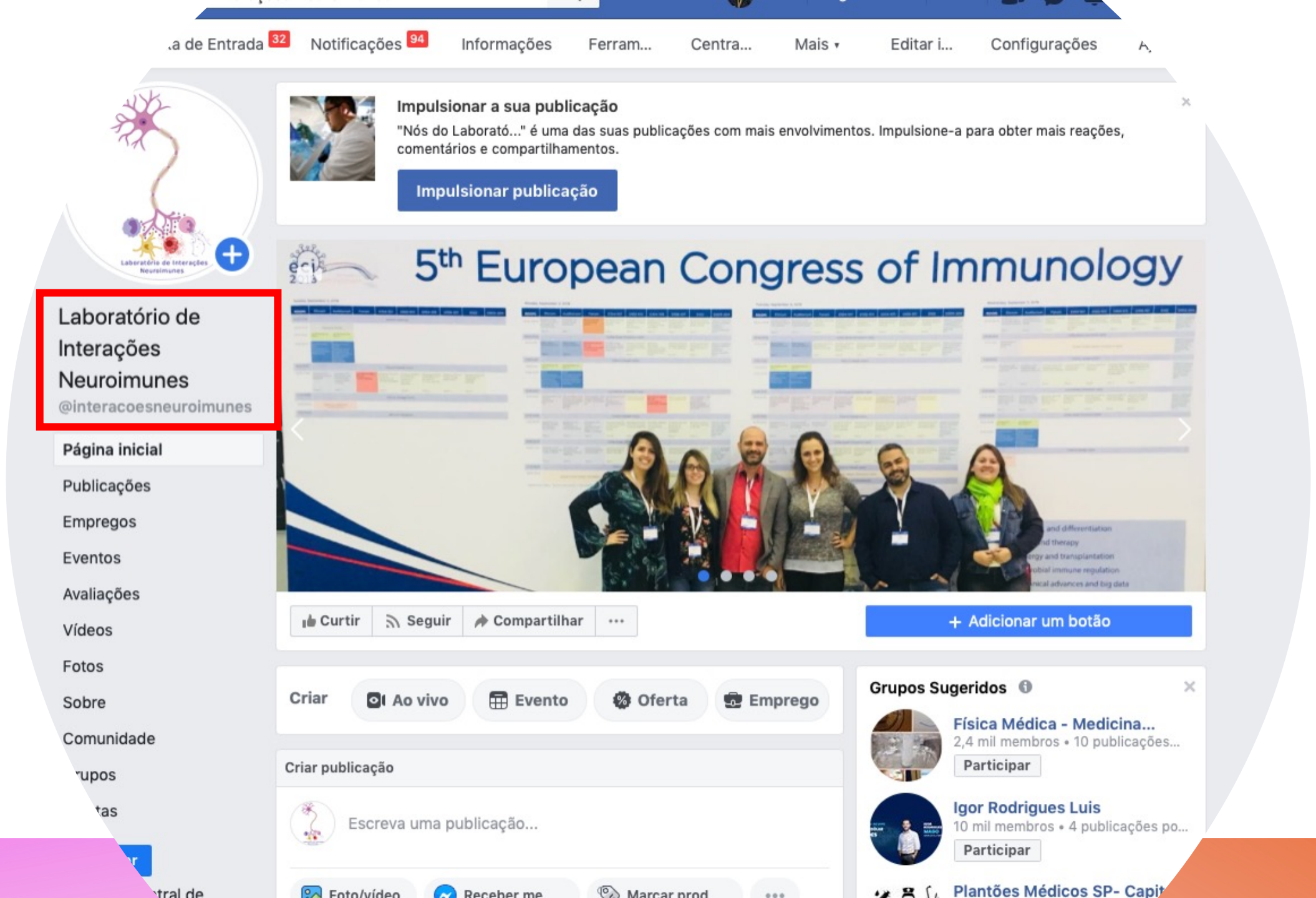
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