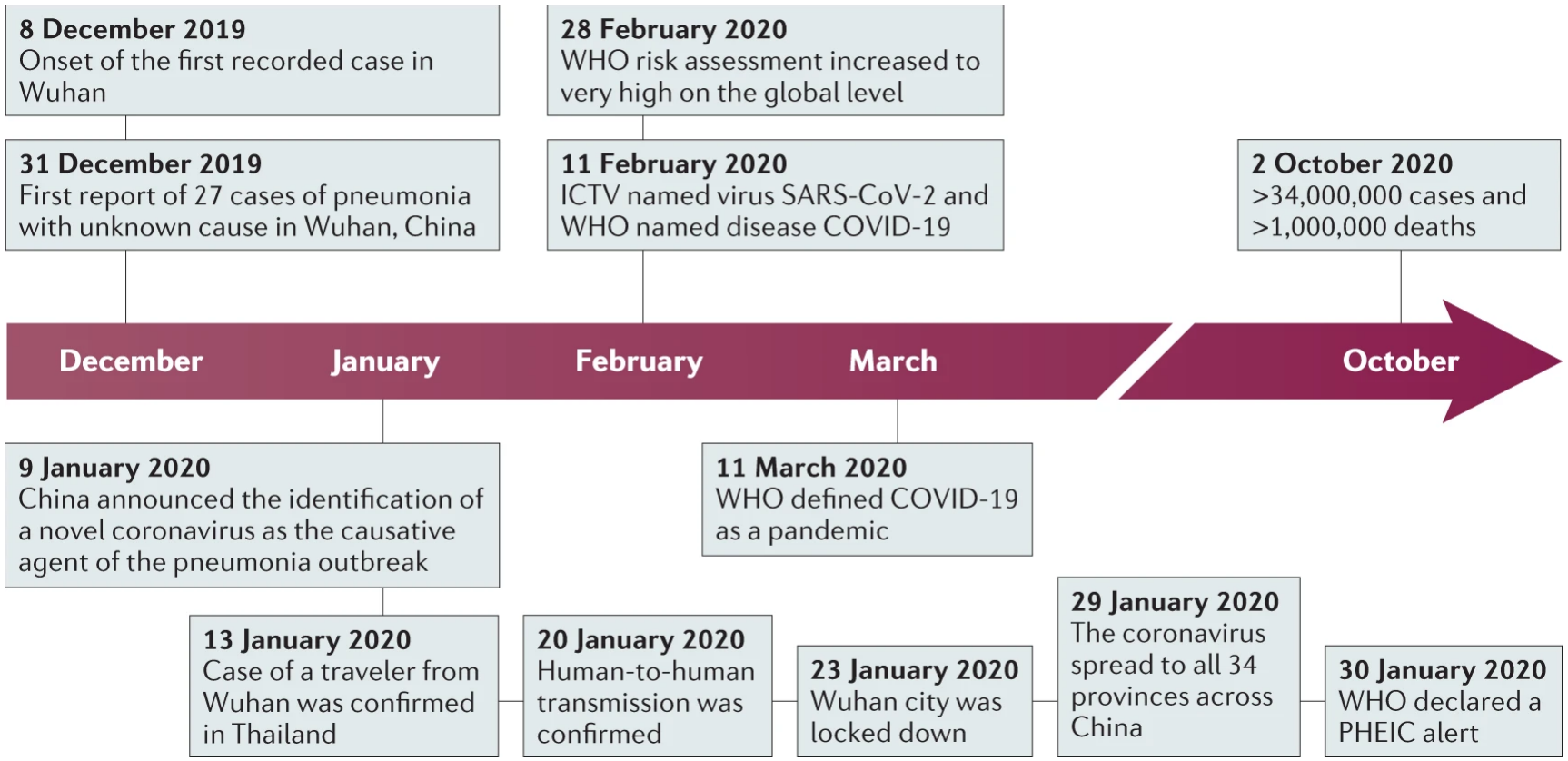
Anti-IFN au cours de l'infection par SARS-CoV2

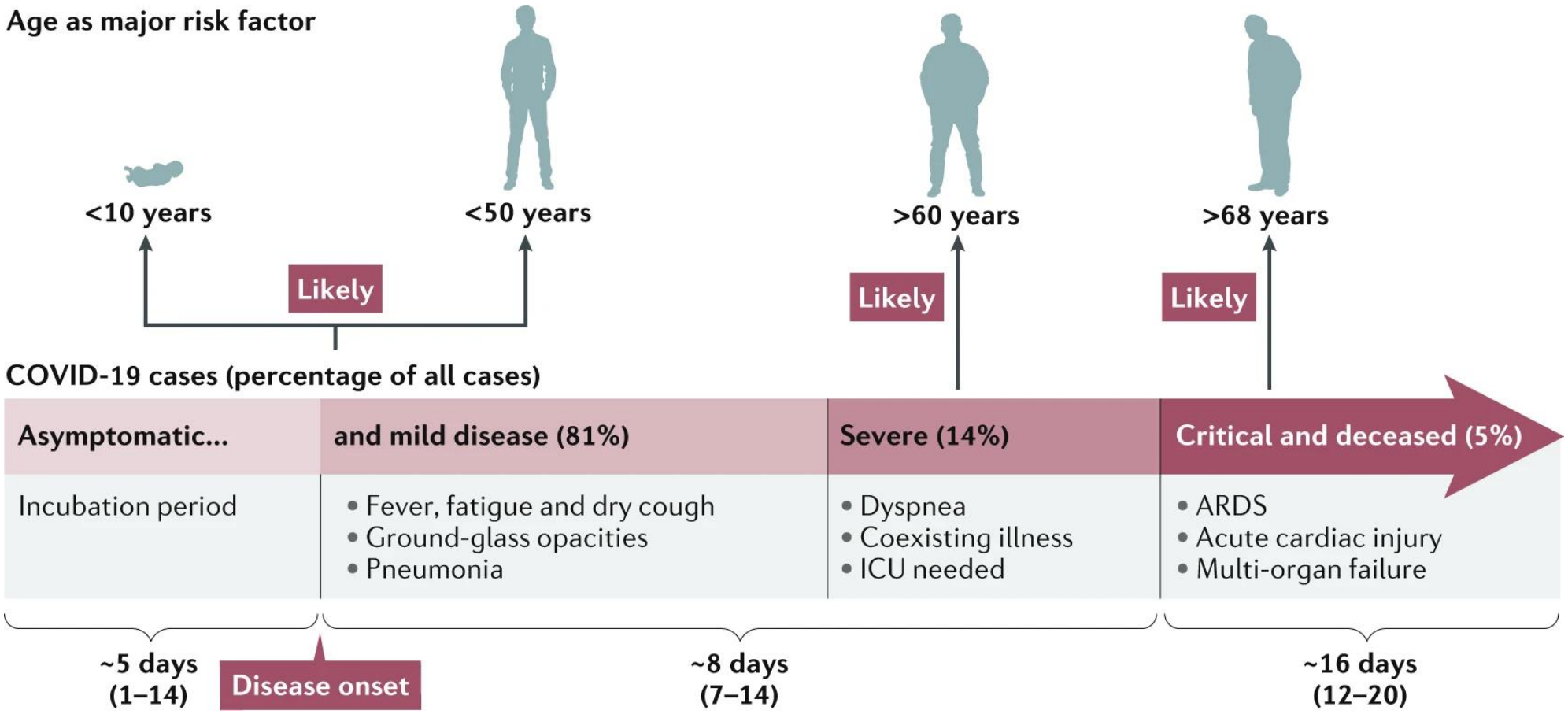
GEAI

14.12.2020

Timeline of the key events of the COVID-19 outbreak



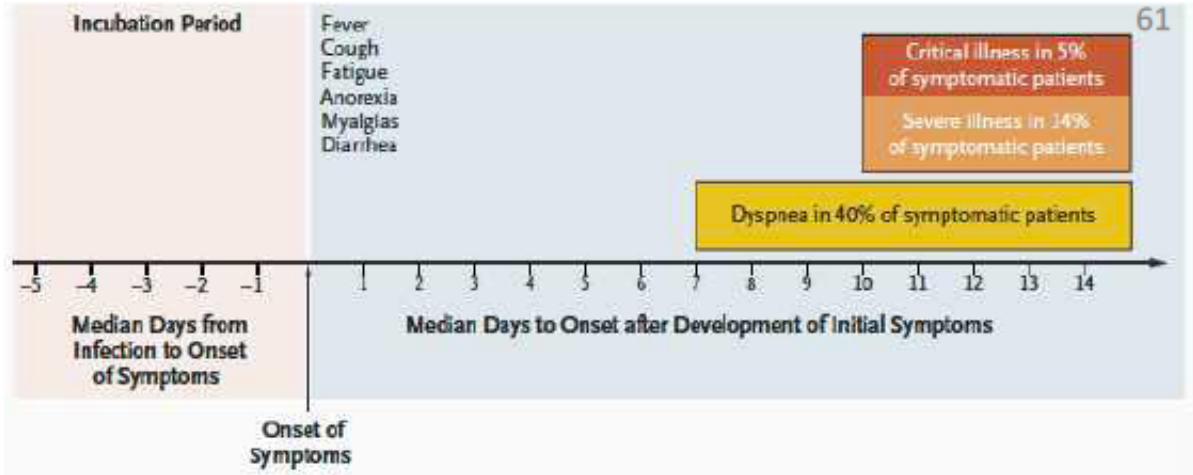
Clinical features of COVID-19

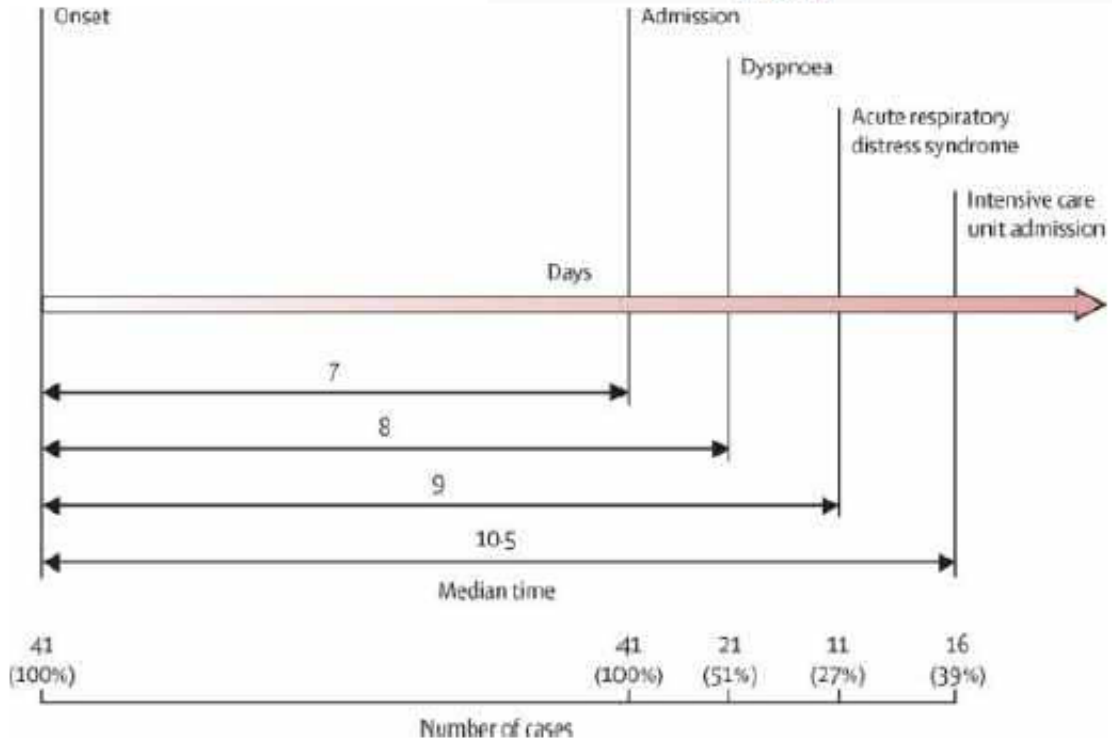


Clinical features

Median time (41 patients admitted to hospital)

- From onset of symptoms to first hospital admission
  - **7 days** [4,0–8,0]
- From illness onset to dyspnea
  - **8 days** [5,0–13,0]
- To ARDS
  - **9 days** [8,0–14,0]
- To ICU admission
  - **10,5 days**
- To mechanical ventilation
  - **10,5 days** [7,0–14,0]

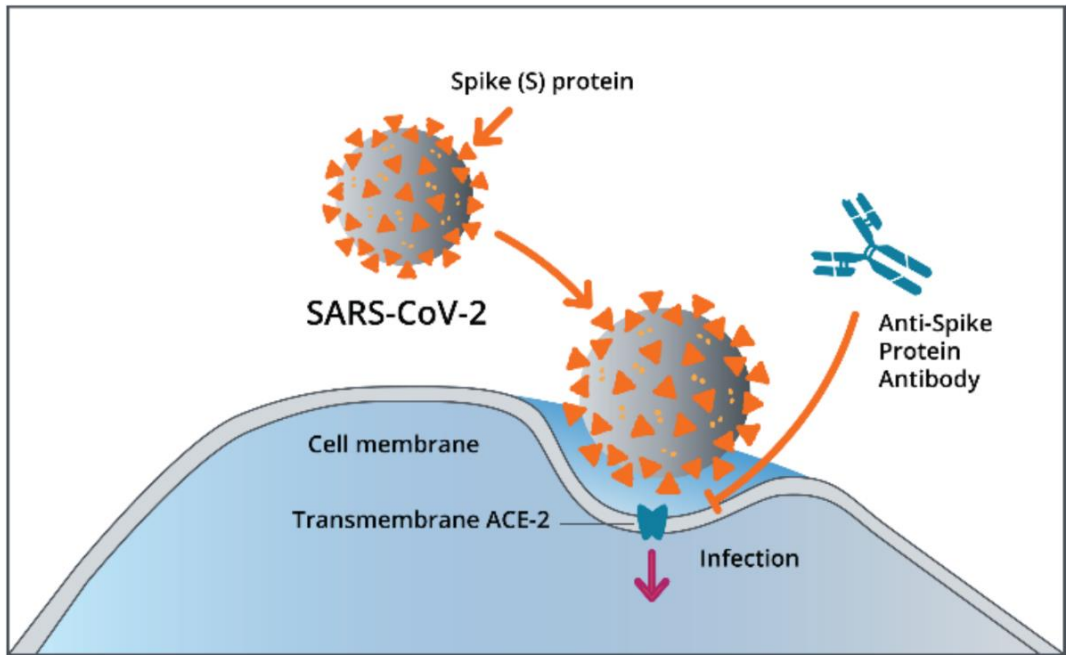


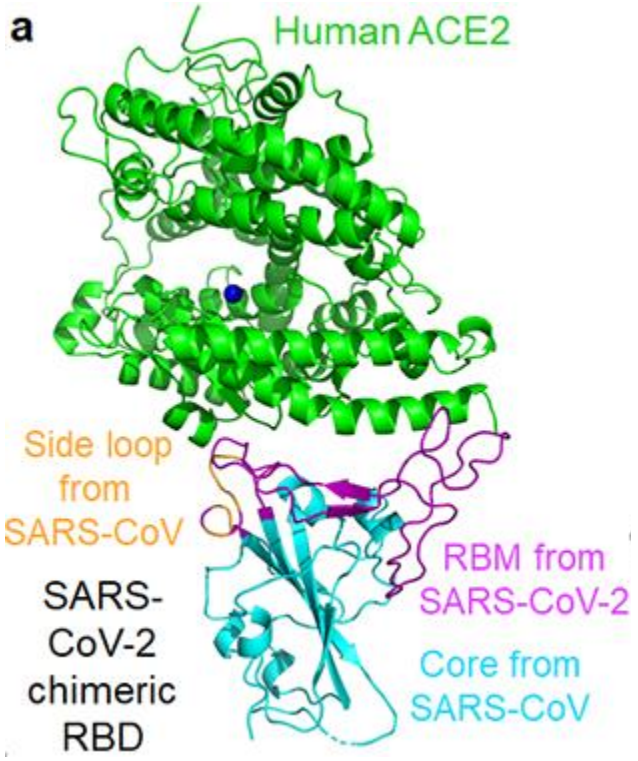


Huang C *et al. Lancet*. Feb 2020

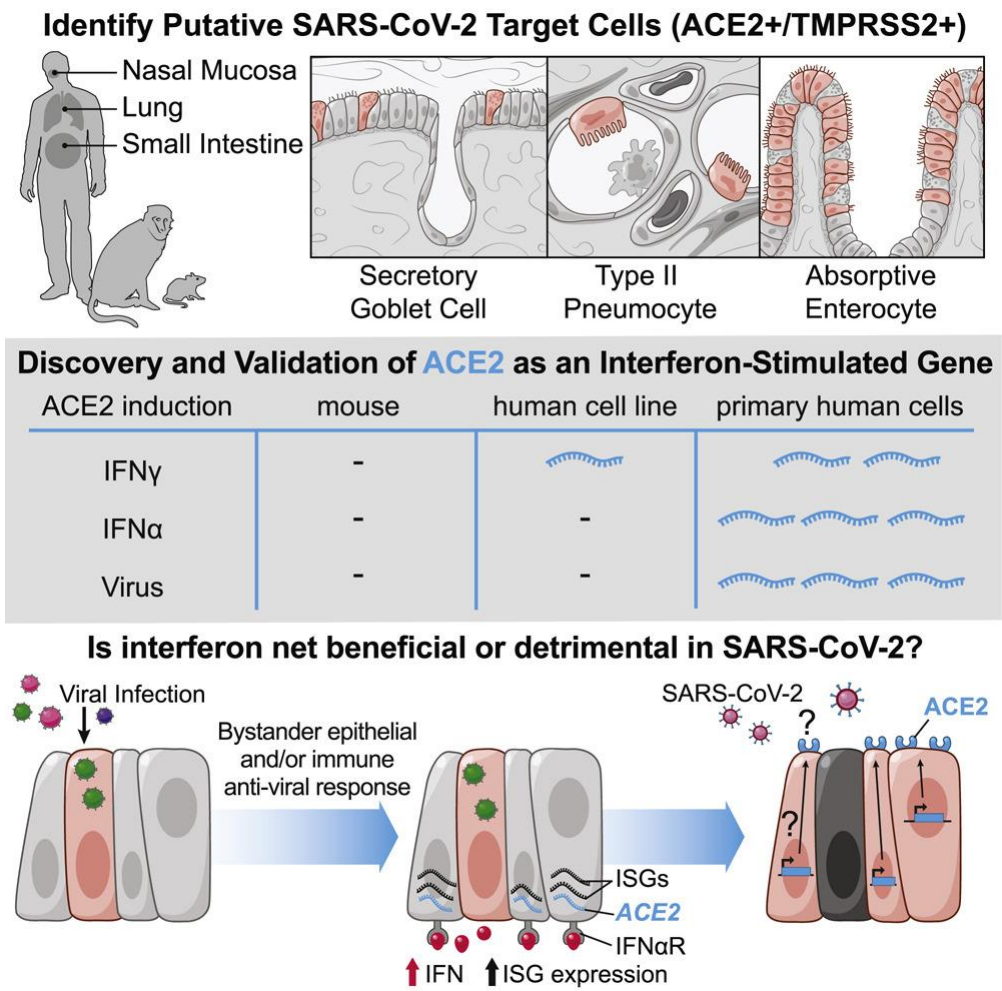
Berlin DA. *et al. NEJM*. May 2020

Structural basis of receptor recognition by SARS-CoV-2

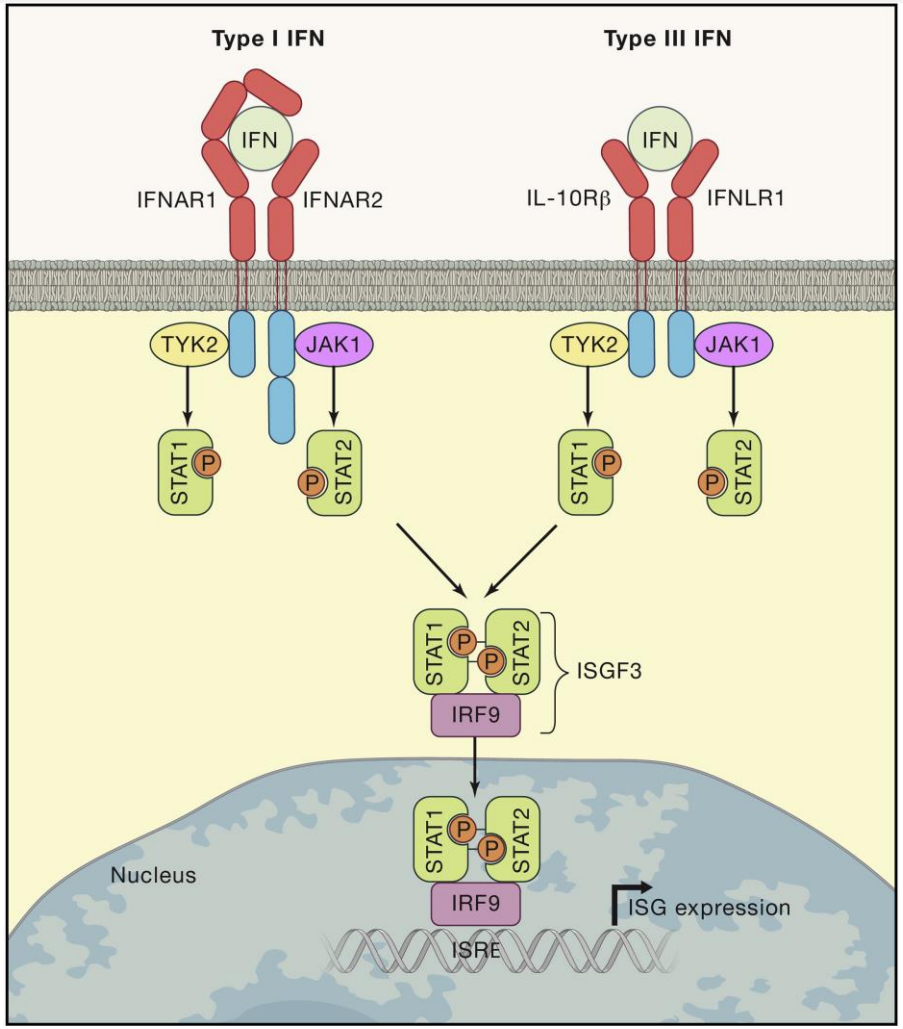




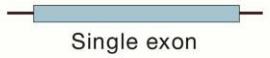
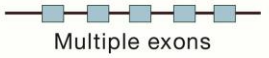
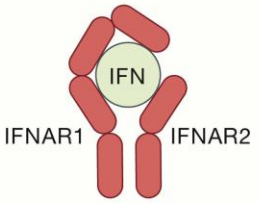
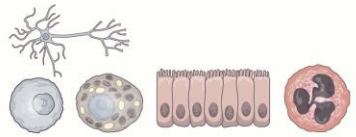
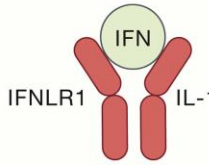
ACE2 is a human interferon-stimulated gene (ISG)



Canonical Type I and Type III IFN Signaling

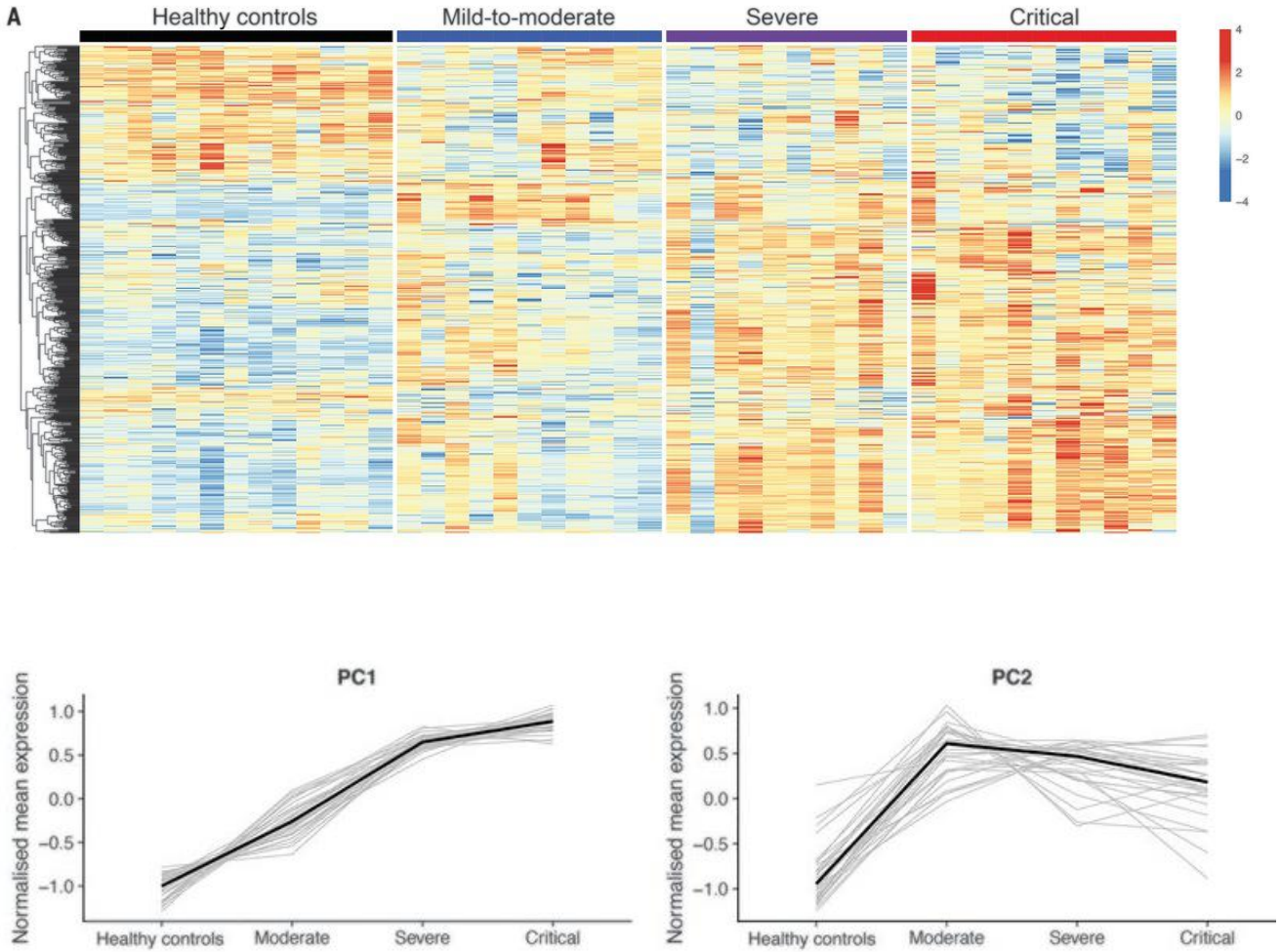


Comparison of Type I and Type III IFNs

	Type I IFN	Type III IFN
Gene	 Single exon	 Multiple exons
Members	Human α1, α2, α4, α5, α6, α7, α8, α10, α13, α14, α16, α17, α21, β, ε, κ, ω Mouse α1, α2, α4, α5, α6, α7, α9, α11, α12, α13, α14, α15, α16, αBβ, ε, κ, ζ	Human λ1, λ2, λ3, λ4 Mouse λ2, λ3
Receptor binding	 • High-affinity binding to IFNAR2, then recruits low-affinity IFNAR1 to form signaling competent ternary complex • Receptor subunits bind on opposite sides of cytokine, no stem/stem contacts • Receptor is ubiquitously expressed 	 • High-affinity binding to IFNLR1, then recruits low-affinity IL-10Rβ to form signaling competent ternary complex • Less cytokine surface exposed, more stem-stem contacts in recpetor • Receptor preferentially expressed on epithelial cells (and some immune cells, e.g., neutrophils) 
Response	• High potency • Rapid kinetics • Systemic • Inflammatory	• Lower potency • Slower kinetics • Anatomic barriers • Less inflammatory

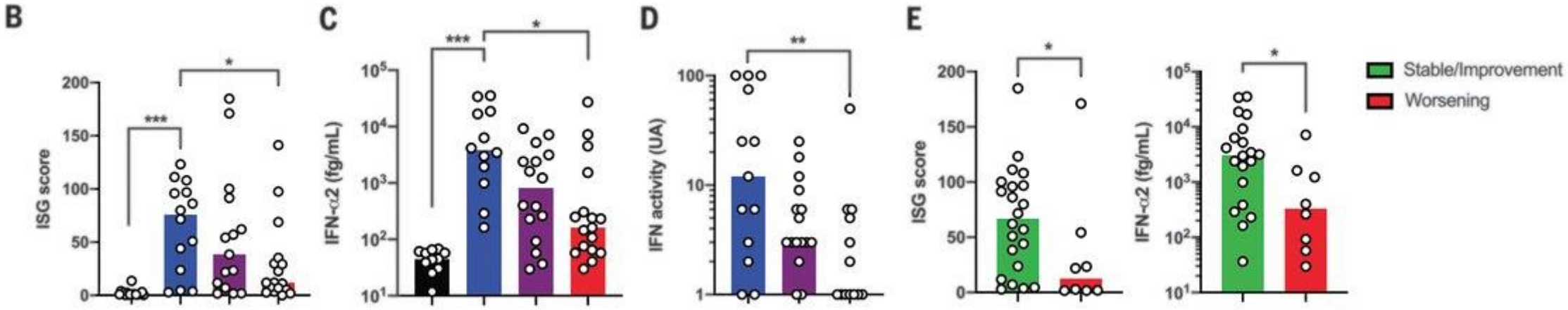
Altération de l'activité IFN de type I et réponses inflammatoires exagérées chez les patients sévères

- Identification de gènes exprimés différentiellement dans le sang périphérique en fonction des degrés de gravité de la Covid-19.
- Analyse en composante principale non supervisée selon le degré de sévérité:
  - PC1, enrichie en gènes codant pour les réponses immunes innées et inflammatoires (TLR, TNF, …)
  - PC2, enrichie en gènes codant pour les réponses interférons (IFN) de type I and type II



Hadjadj, Science, 2020

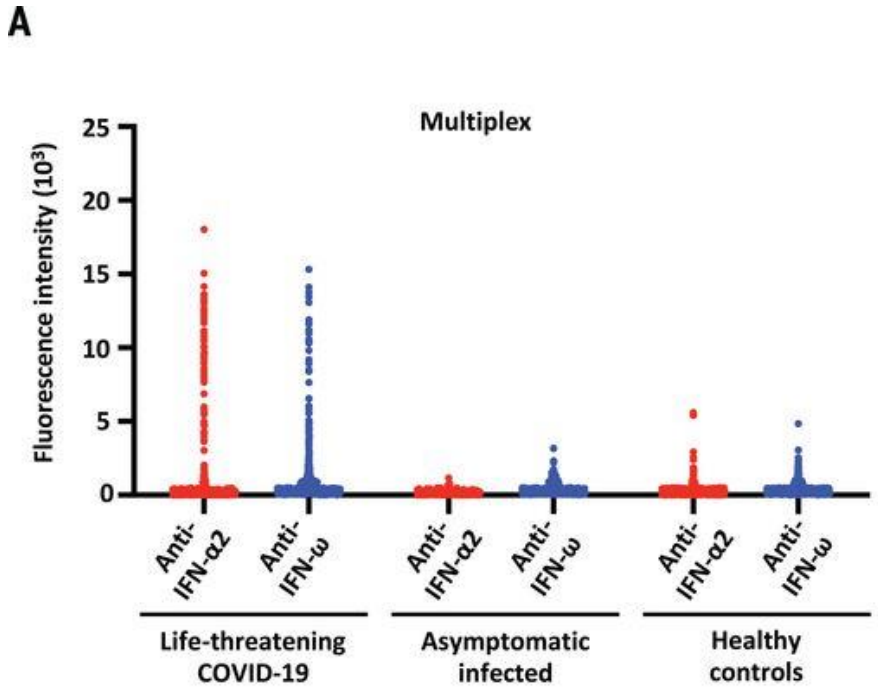
Défaut d'activité IFN de type I chez les patients sévères et critiques

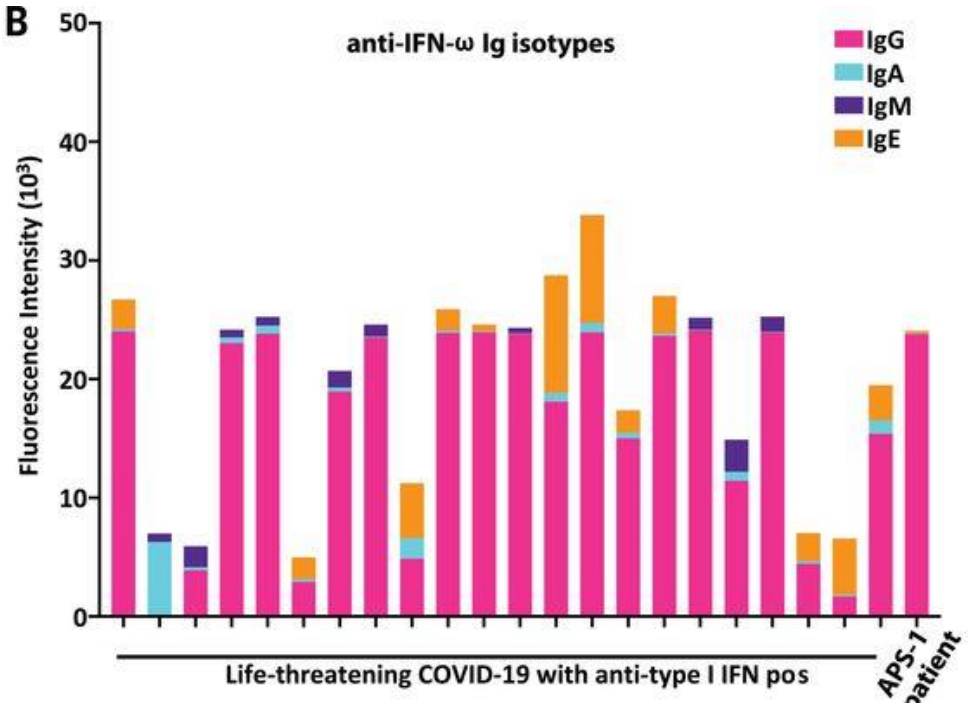


Diminution de l'ISG score, des taux d'IFN-α2 dans le plasma et de l'activité IFN chez les patients les plus sévères, comparativement aux formes modérés
Absence de détection d'IFN-β
Défaut d'activité IFN de type 1 précédant la détérioration clinique

Hadjadj, Science, 2020

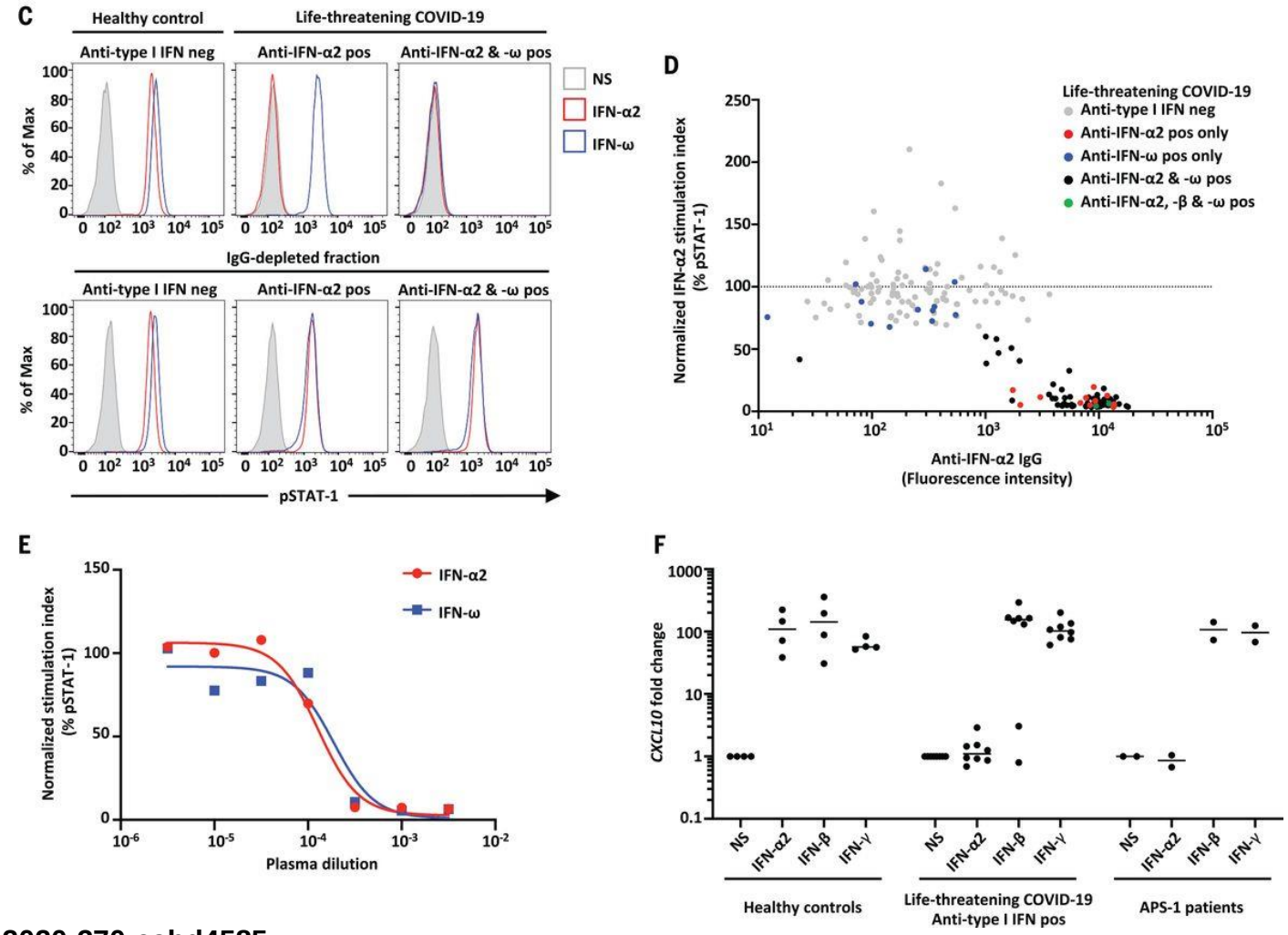
Auto-Abs against IFN-α2 and/or IFN-ω in patients with life-threatening COVID-19





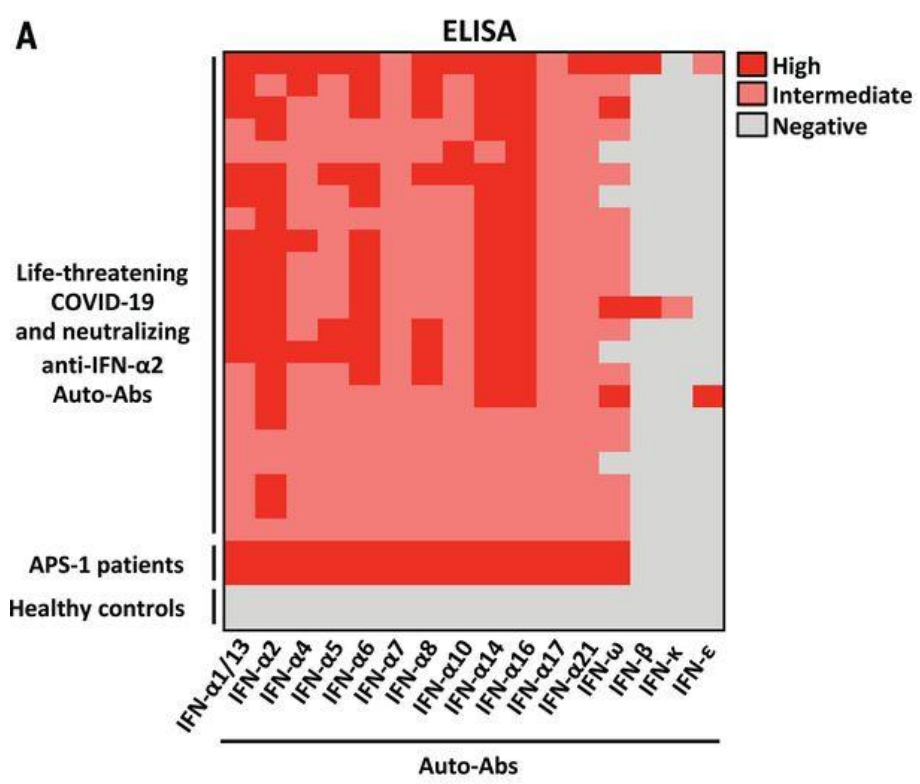
Paul Bastard et al. Science 2020;370:eabd4585

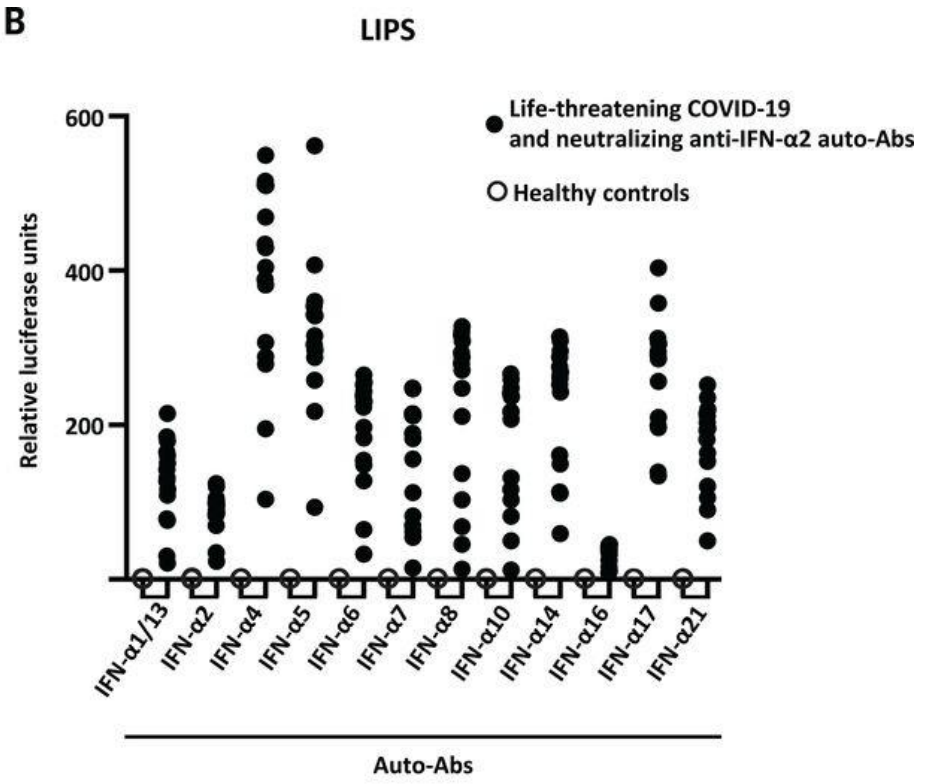
Neutralizing auto-Abs against IFN-α2 and/or IFN-ω in patients with life-threatening COVID-19



Paul Bastard et al. Science 2020;370:eabd4585

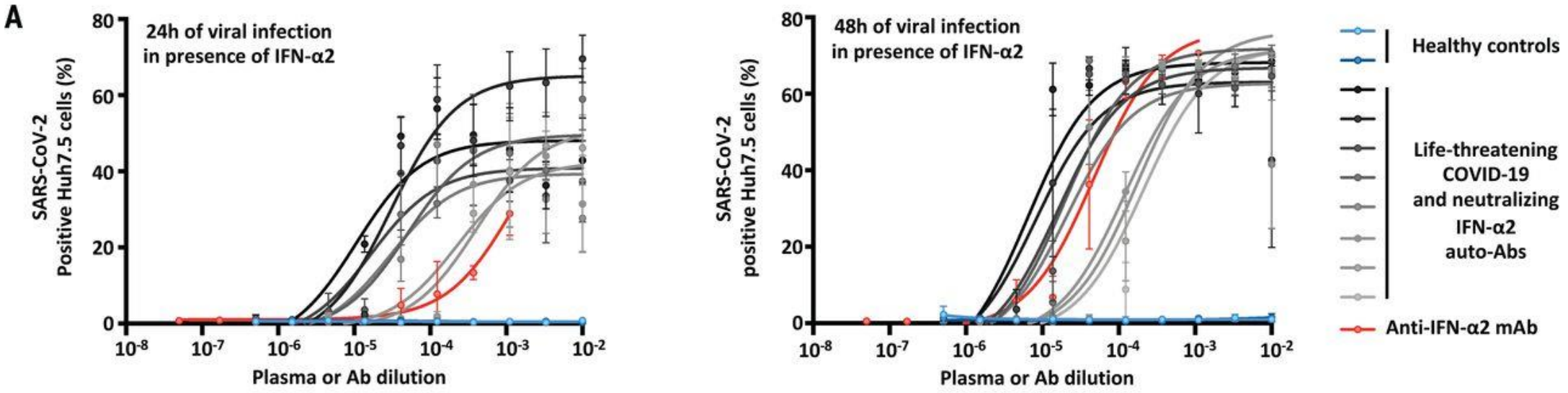
Auto-Abs against the different type I IFN subtypes





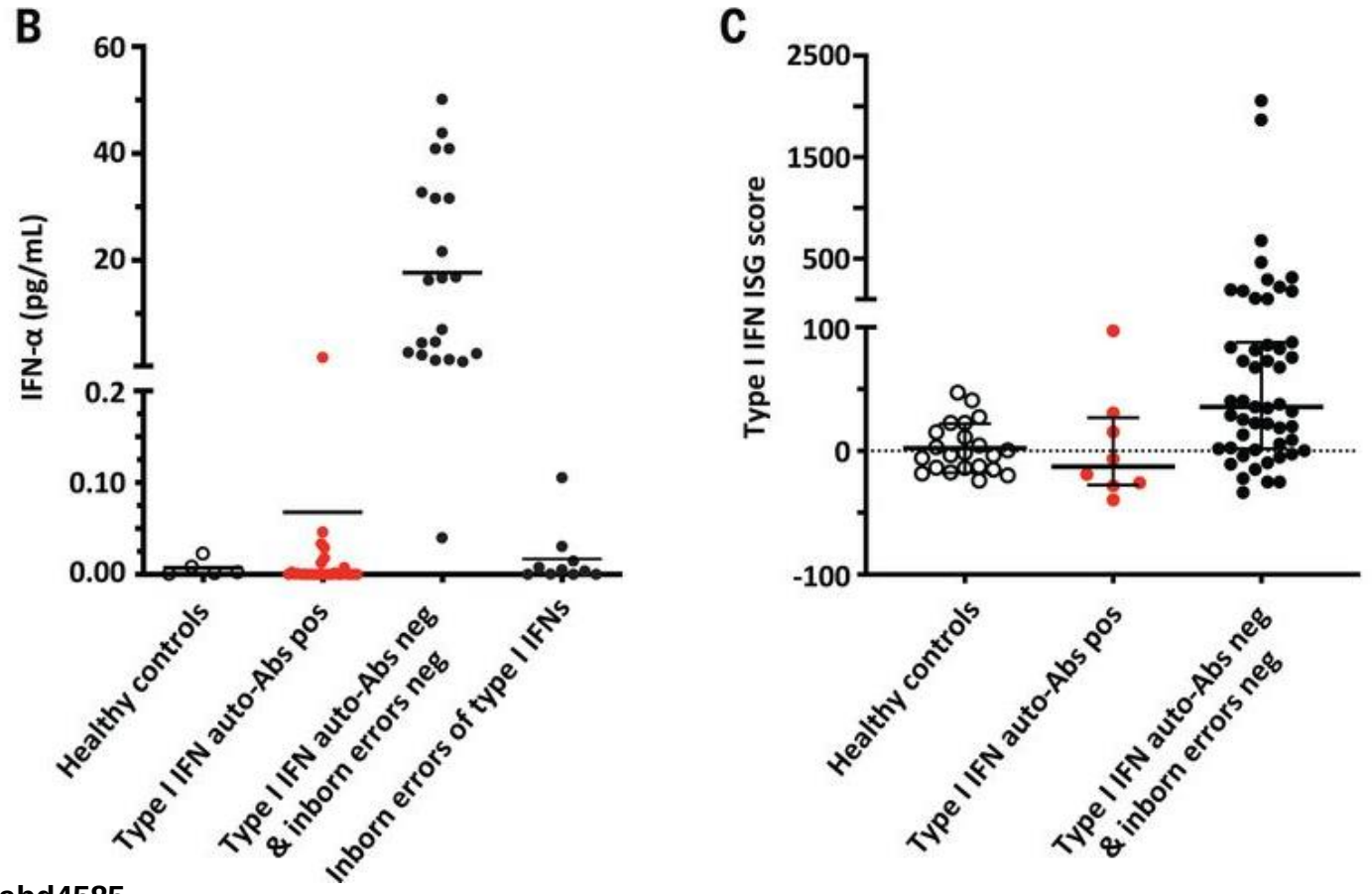
Paul Bastard et al. Science 2020;370:eabd4585

Enhanced SARS-CoV-2 replication, despite the presence of IFN-α2, in the presence of plasma from patients with auto-Abs against IFN-α2



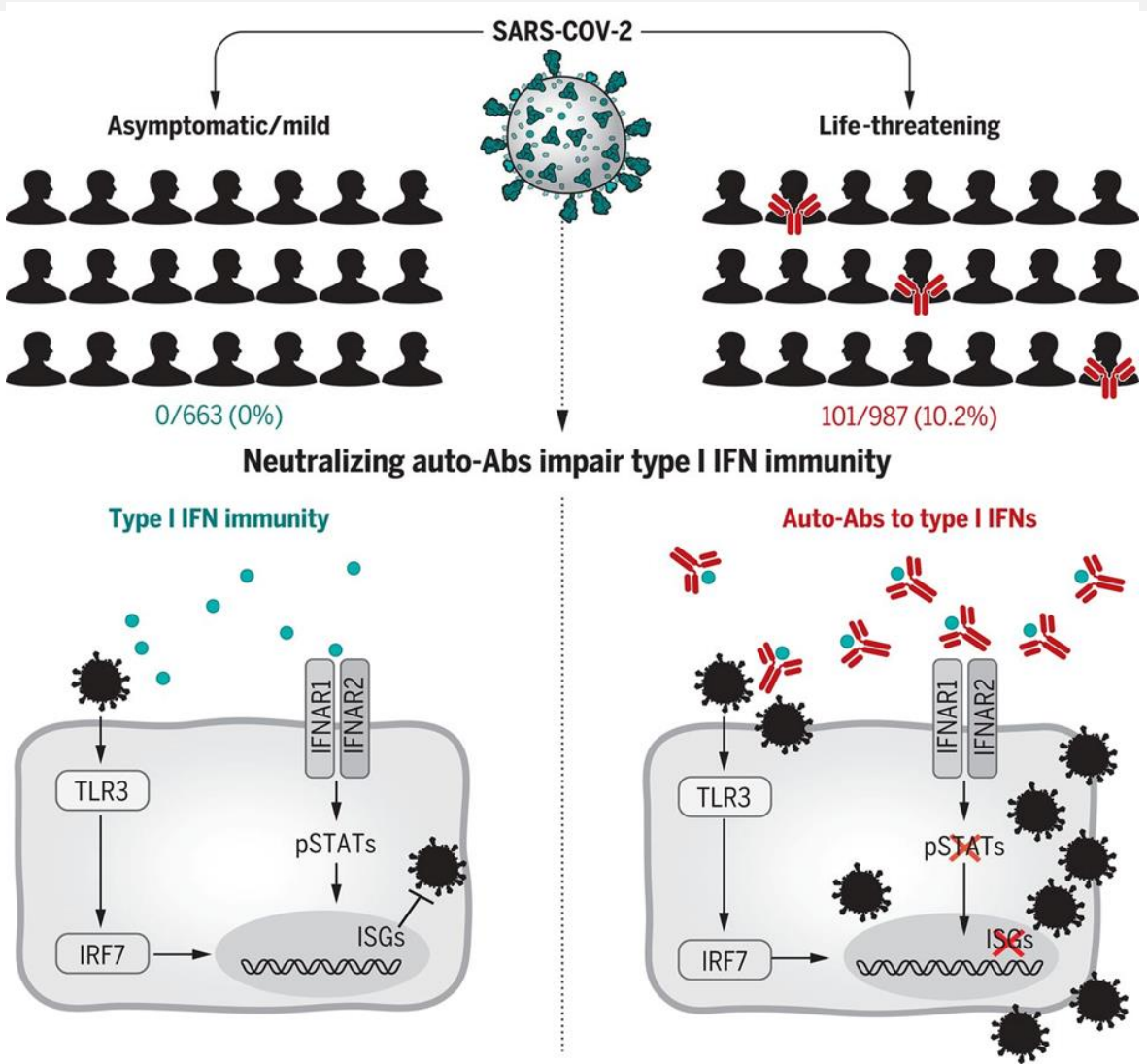
Paul Bastard et al. Science 2020;370:eabd4585

Low *in vivo* levels of IFN-α in patients with auto-Abs against IFN-α2 and

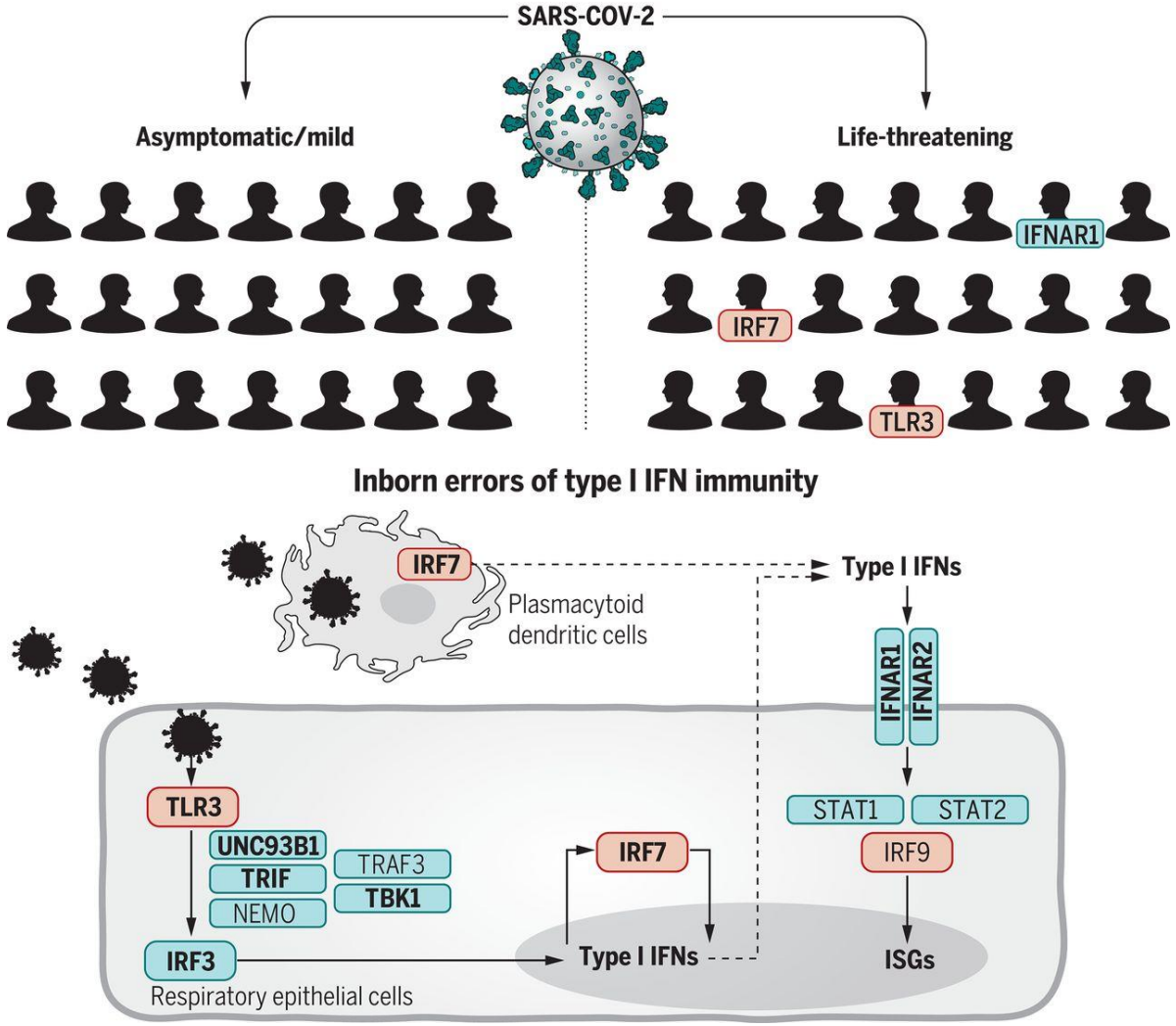


Paul Bastard et al. Science 2020;370:eabd4585

Neutralizing auto-Abs to type I IFNs underlie life-threatening COVID-19 pneumonia



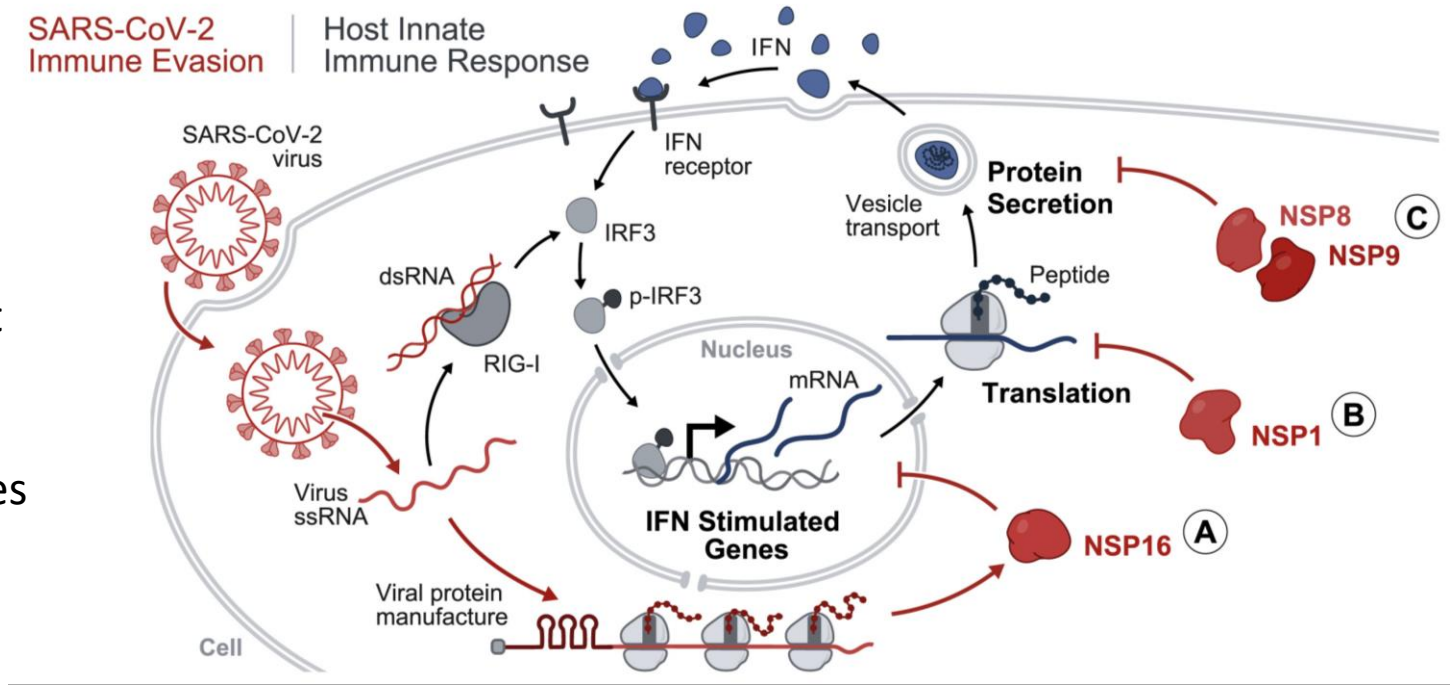
Inborn errors of TLR3- and IRF7-dependent type I IFN production and amplification underlie life-threatening COVID-19 pneumonia.



Zhang, Science, 2020

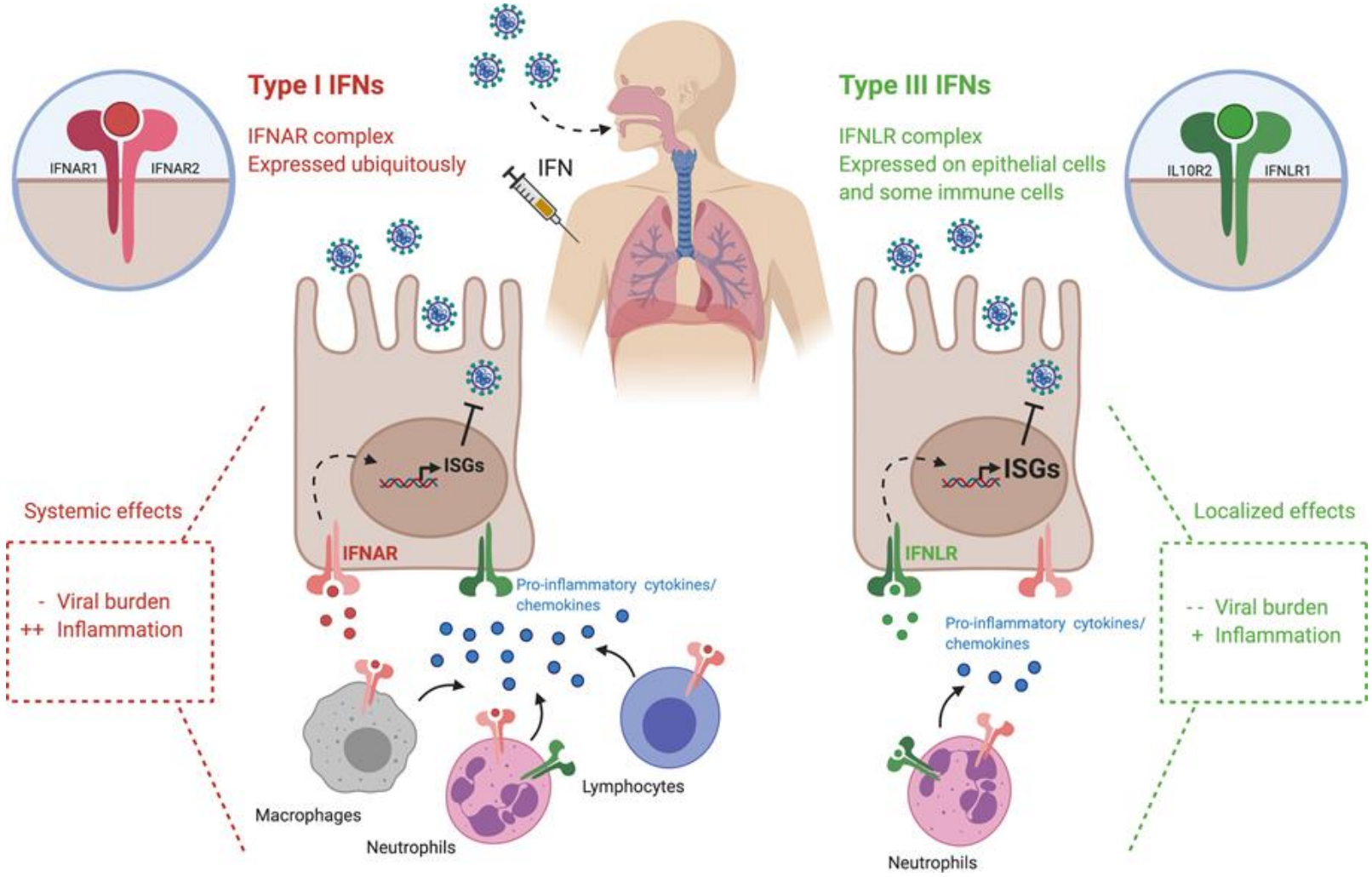
A model of how SARS-CoV-2 suppresses host immune responses through multi-pronged inhibition of core cellular functions

A. NSP16 diminue l'épissage des ARNm
B. NSP1 se fixe à l'ARN ribosomal 18S et diminue la traduction des ARNm
C. NSP8 et NSP9 diminue le trafic des protéines membranaires dépendantes de la SRP



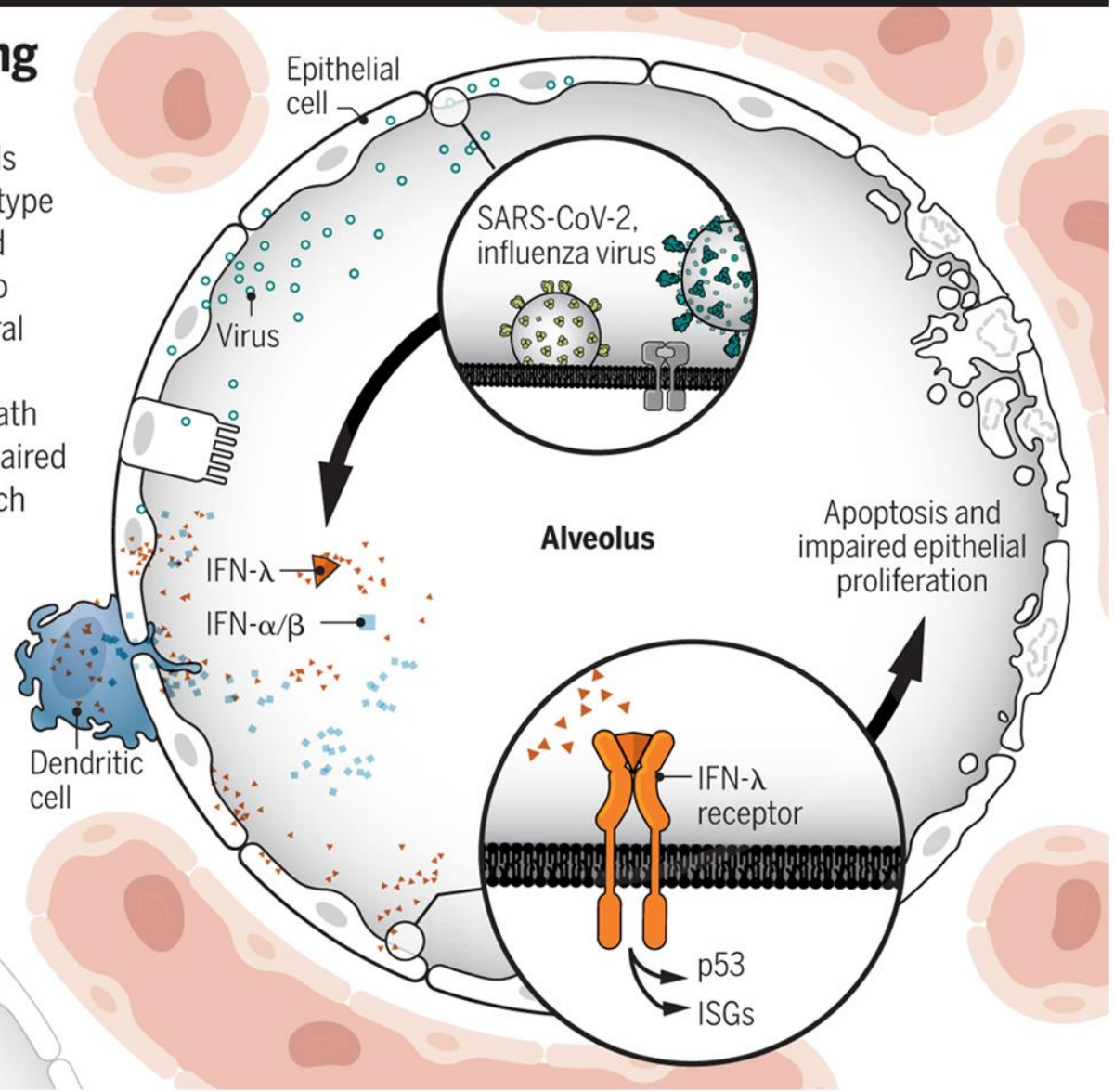
Banerjee, Cell, 2020

Responses to lung viral infections



Responses to lung viral infections

Lung alveolar epithelial cells and dendritic cells release type I interferons (IFN-α/β) and type III IFN-λ in response to viral infection. IFNs limit viral replication; however, IFN-λ signaling can cause cell death through apoptosis and impaired epithelial proliferation, which prevents tissue recovery.



ISGs, interferon-stimulated genes; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.