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Induced immunological defects in virus-associated pulmonary aspergillosis (VAPA)

AAAM 2024, Milano

Joost Wauters, MD, PhD

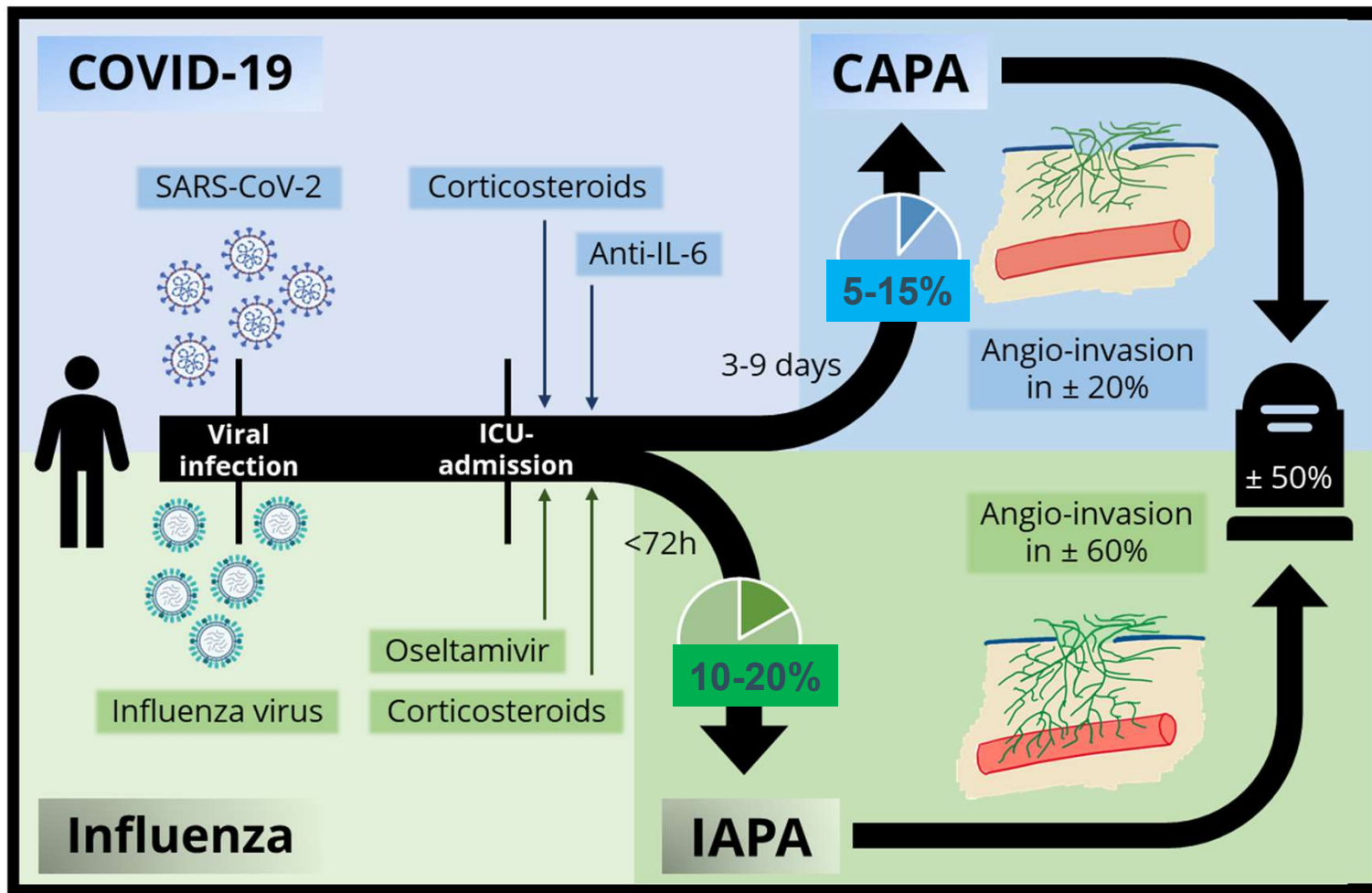
Simon Feys, MD and Laura Seldeslachts, MSc

✉ Joost.wauters@uzleuven.be

Disclosures



- This is the PhD work of **Dr. Simon Feys** (human data) and **Ing. Laura Seldeslachts** (mouse data)
- I am not an immunologist
- Investigator-initiated grants, travel grants and speakers fees from Pfizer, Gilead, MSD

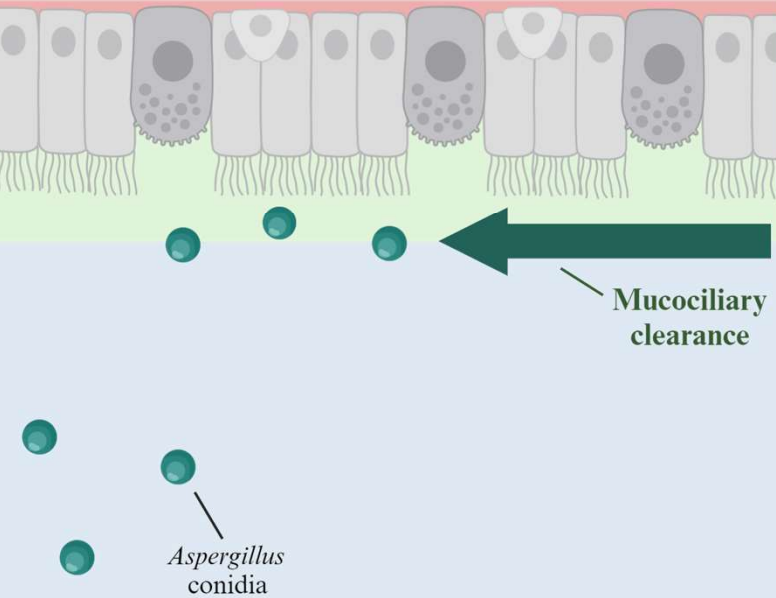


20-25% tracheobronchitis

Why does VAPA exist?

How does severe viral pneumonia impair
anti-*Aspergillus* ***innate*** immunity?

1. Epithelial barrier disruption

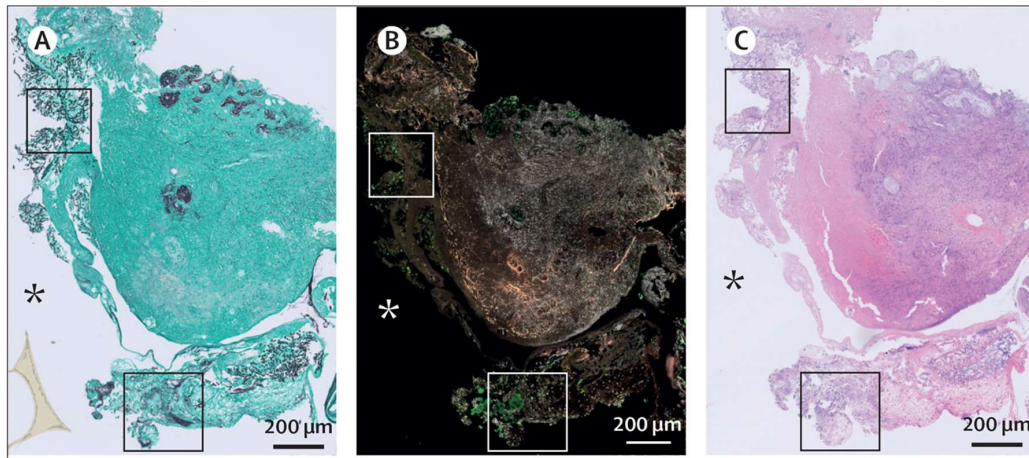


Epithelial barrier disruption

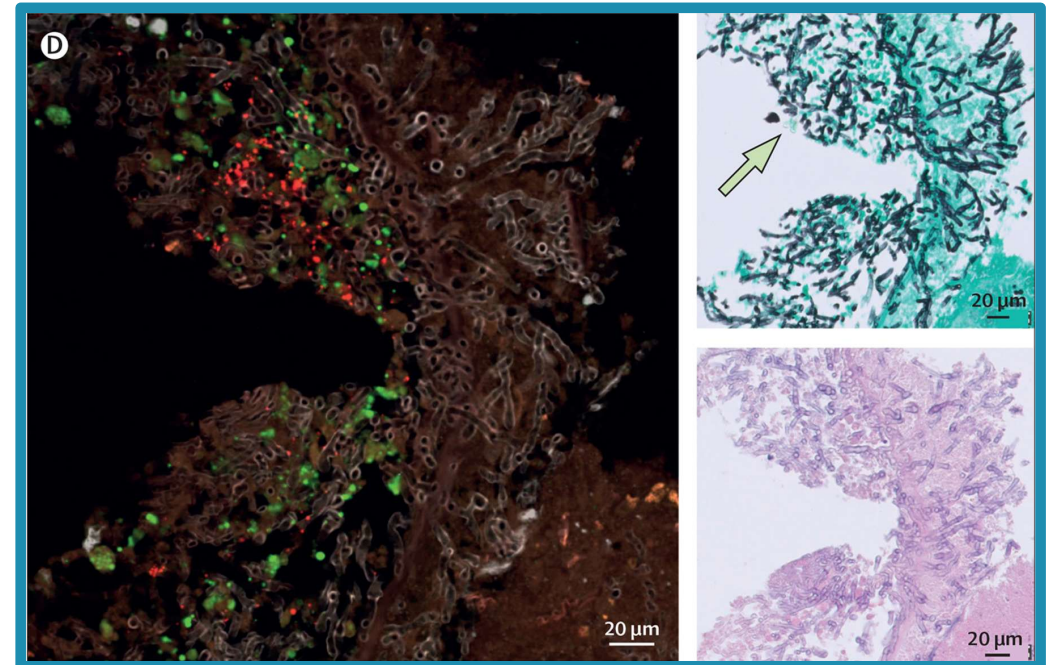


Virus-induced epithelial barrier disruption paves the way for tissue-invasive VAPA

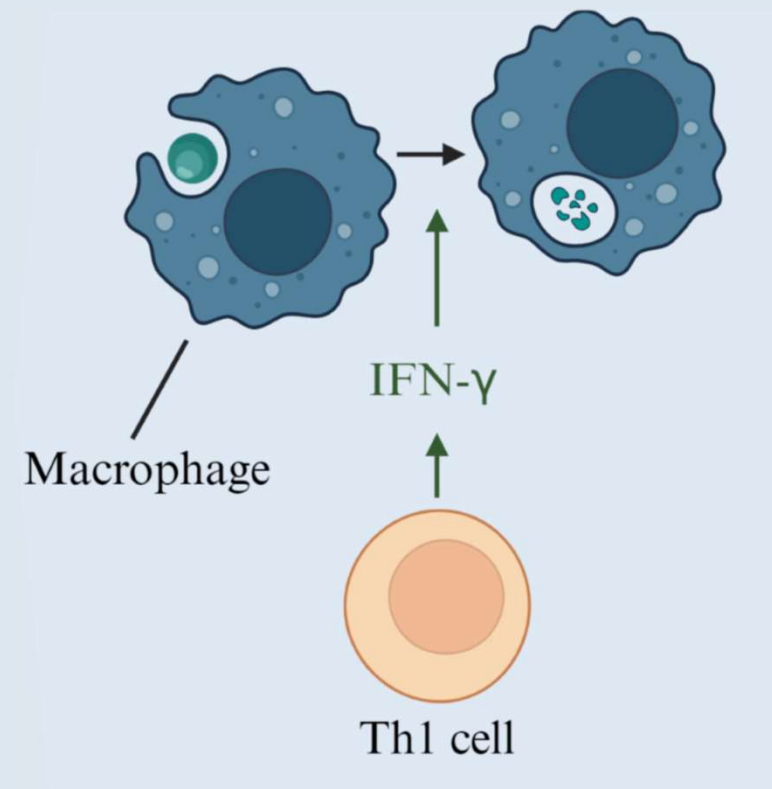
Epithelial immune function impaired?



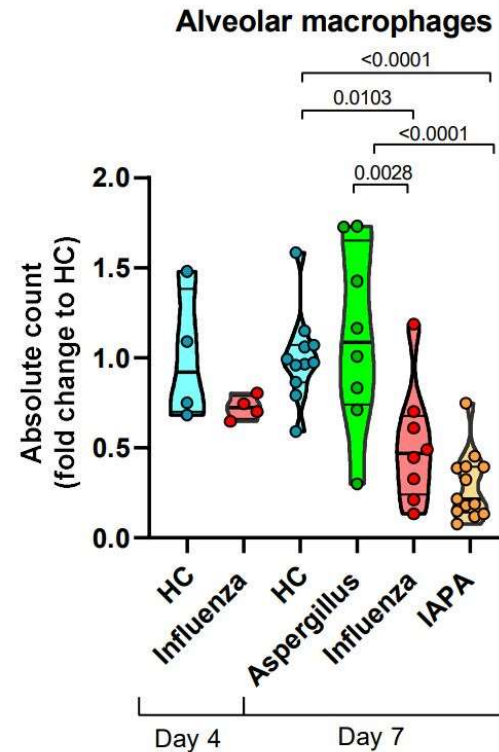
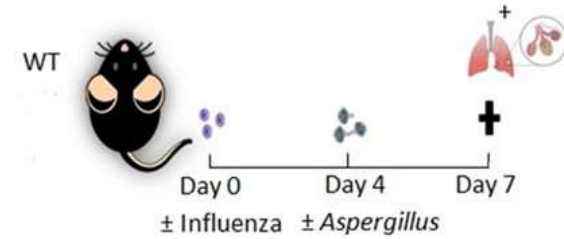
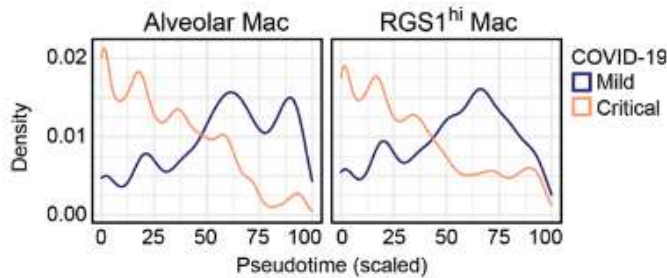
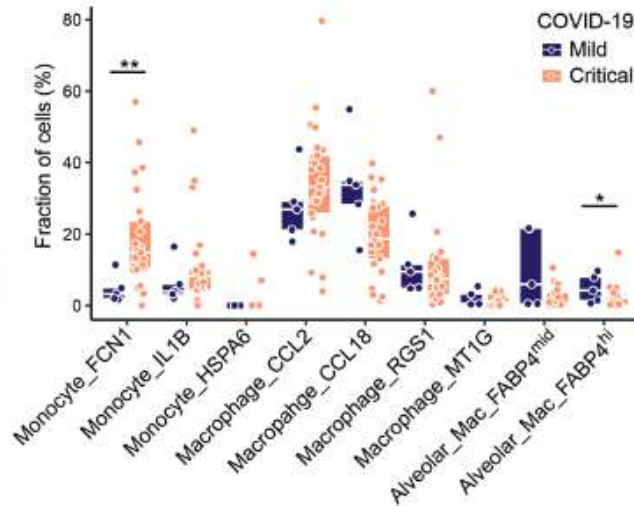
Mucociliary clearance impaired in CAPA (& IAPA)?



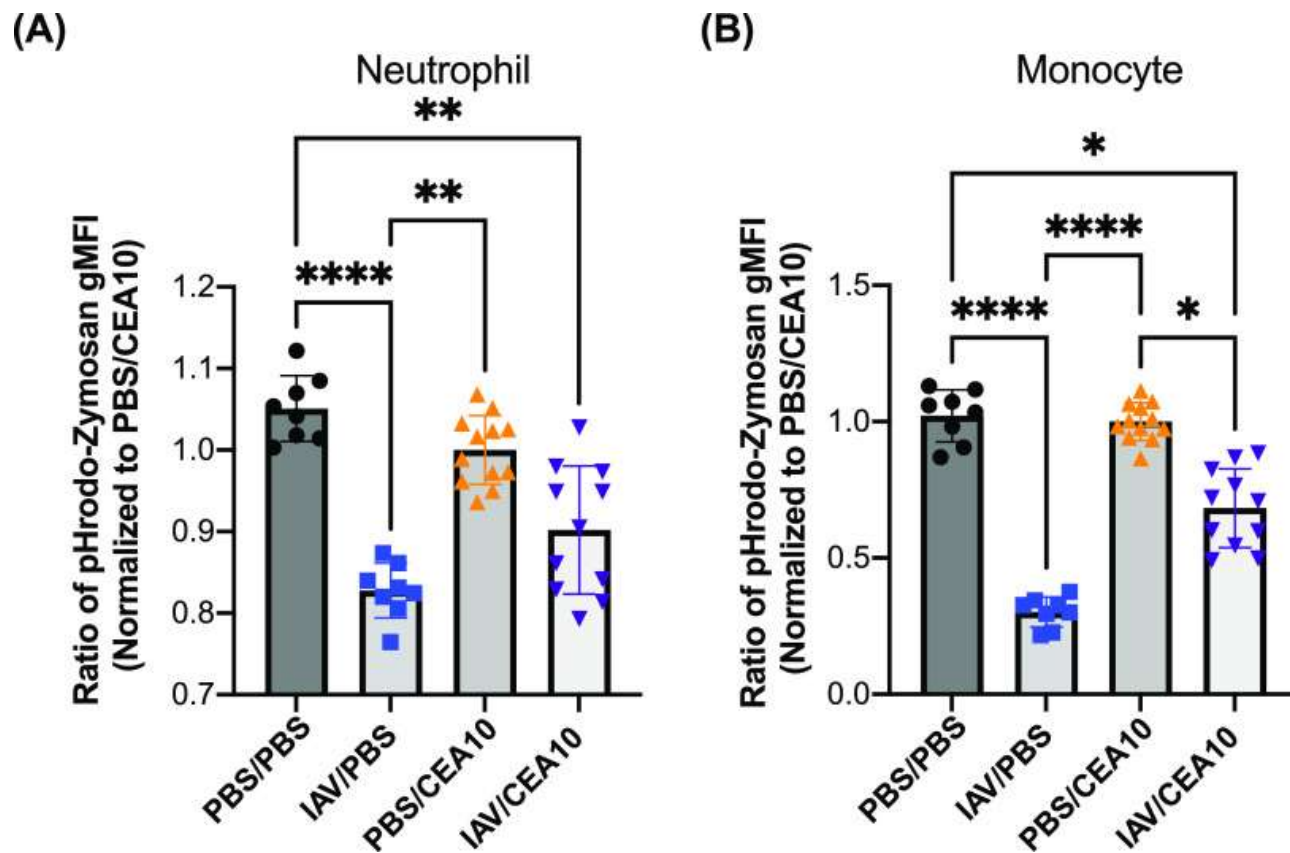
2. Phagocytosis & phagolysosomal killing



Alveolar macrophage depletion in viral pneumonia



Impaired phagolysosome maturation in influenza

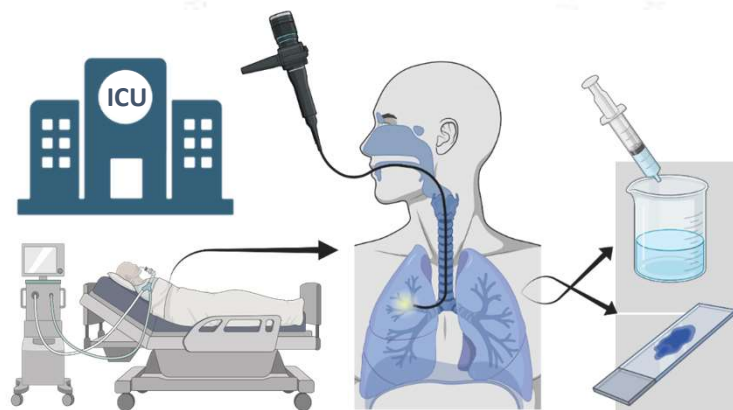


Role for impaired IFN- γ signaling in ICU?



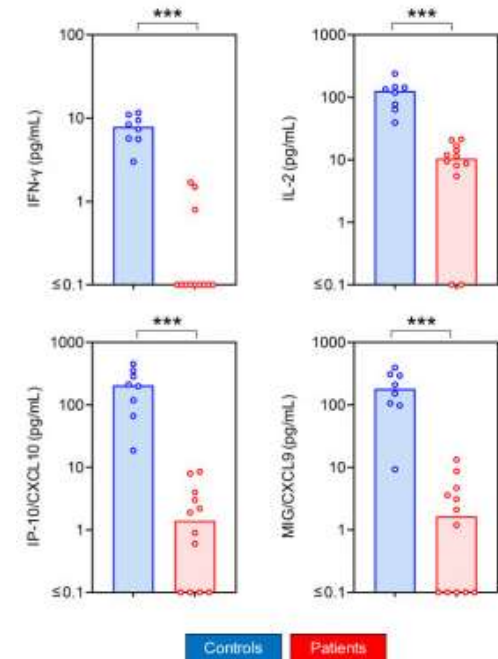
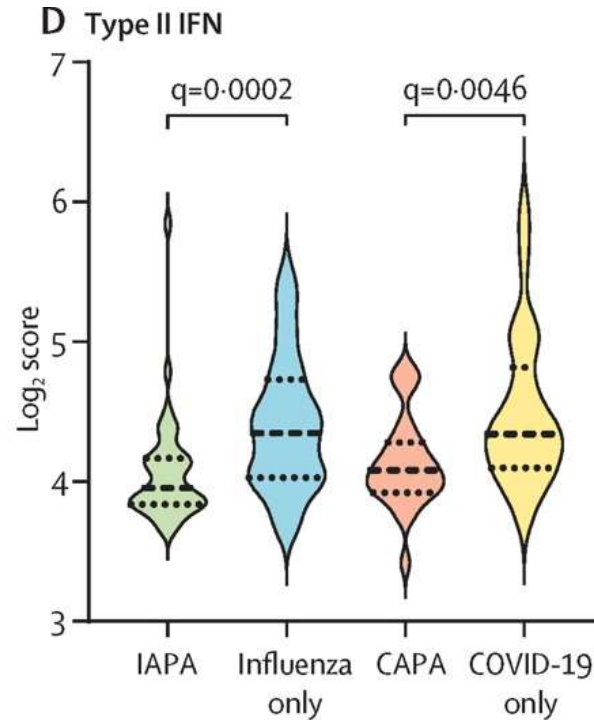
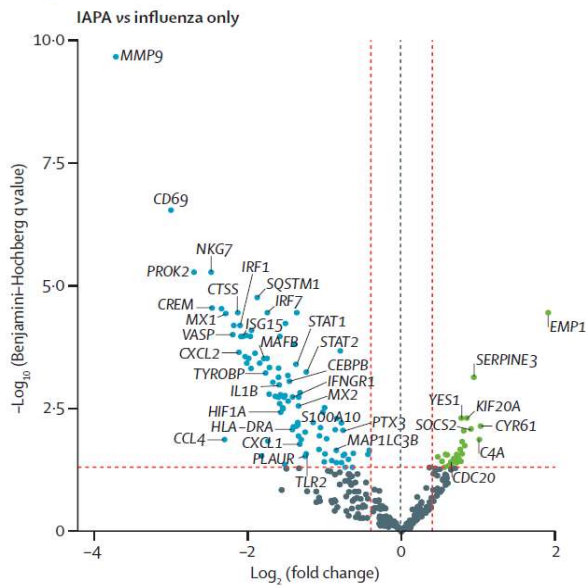
Lung epithelial and myeloid innate immunity in influenza-associated or COVID-19-associated pulmonary aspergillosis: an observational study

Simon Feys, Samuel M Gonçalves*, Mona Khan*, Sumin Choi*, Bram Boeckx, Denis Chatelain, Cristina Cunha, Yves Debaveye, Greet Hermans, Marjan Hertoghs, Stephanie Humblet-Baron, Cato Jacobs, Katrien Lagrou, Lukas Marcelis, Julien Maizel, Philippe Meersseman, Rémy Nygå, Laura Seldeslachts, Marick Rodrigues Starick, Karin Thevissen, Christophe Vandembriele, Lore Vanderbeke, Greetje Vande Velde, Niels Van Regenmortel, Arno Vanstapel, Sam Vanmassenhove, Alexander Wilmer, Frank L Van De Veerdonk, Gert De Hertogh, Peter Mombaerts, Diether Lambrechts, Agostinho Carvalho†, Johan Van Weyenbergh†, Joost Wauters†



	IAPA	Influenza-only	CAPA	COVID-19 only	Total
Gene expression	38	35	27	34	134
Protein levels	40	52	32	38	162
RNAscope					
Spatial transcriptomics	2		2		4

Role for impaired IFN- γ signaling?



Gene module score: downregulation genes IFN type I/II signaling

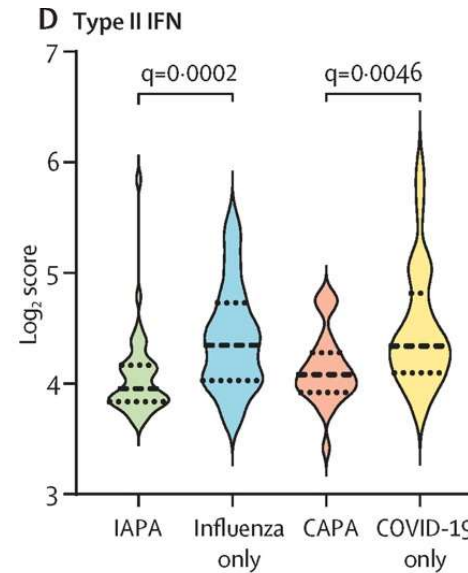
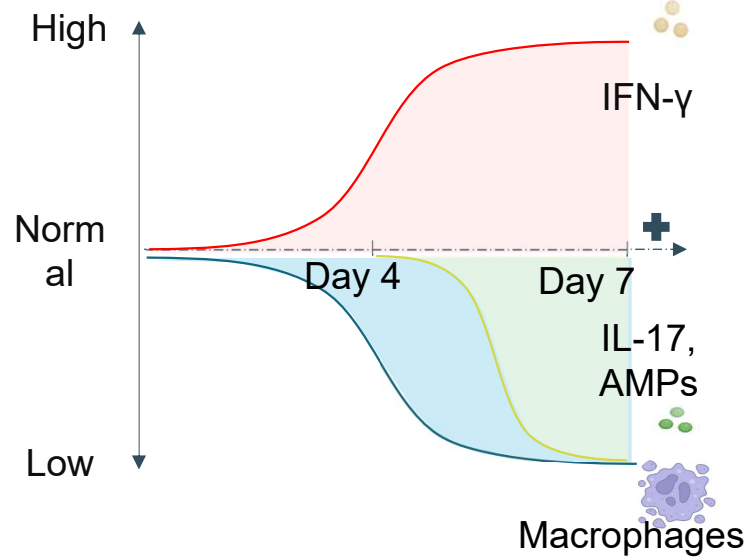


Human versus murine IAPA



INFg blocker

rINFg



Start flu symptoms

ICU admission

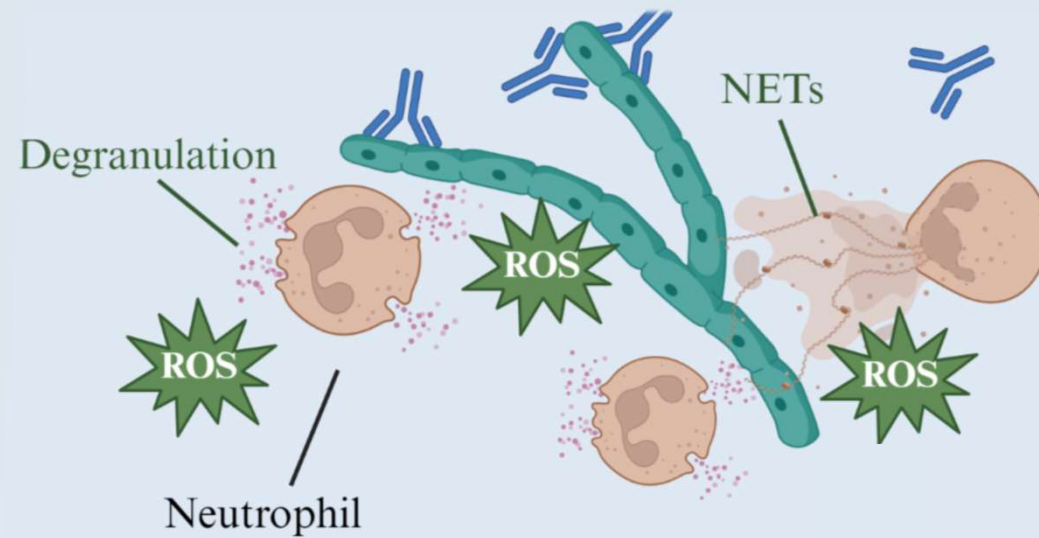
ICU day 7

ICU discharge



± 1 week



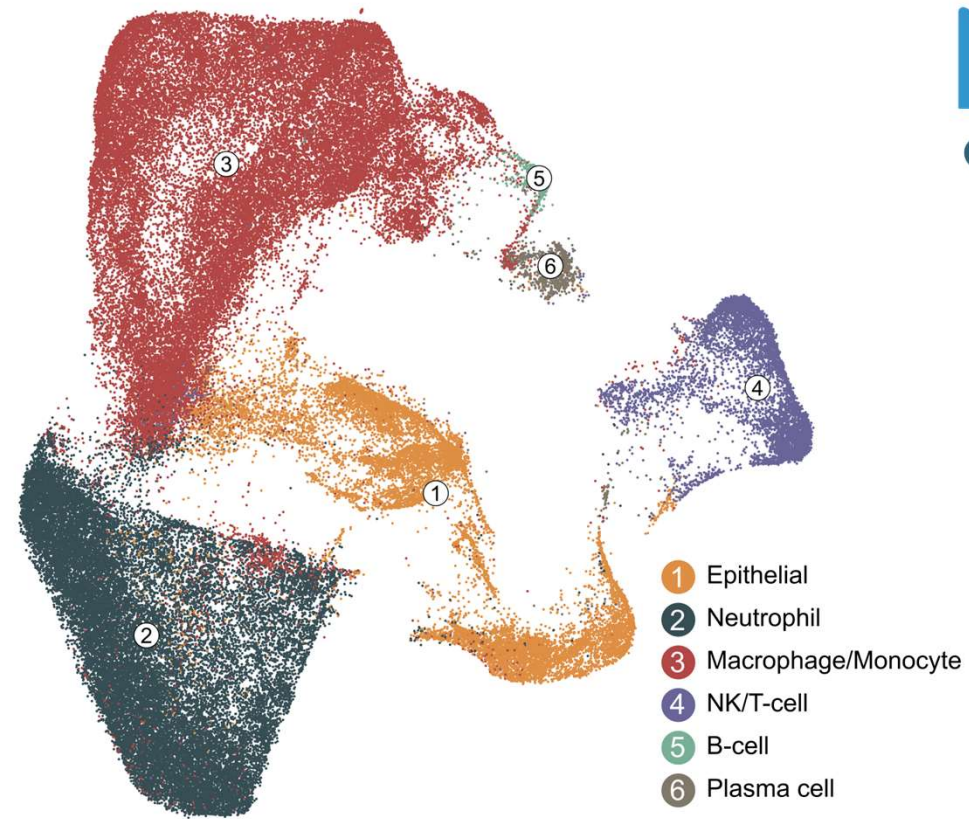
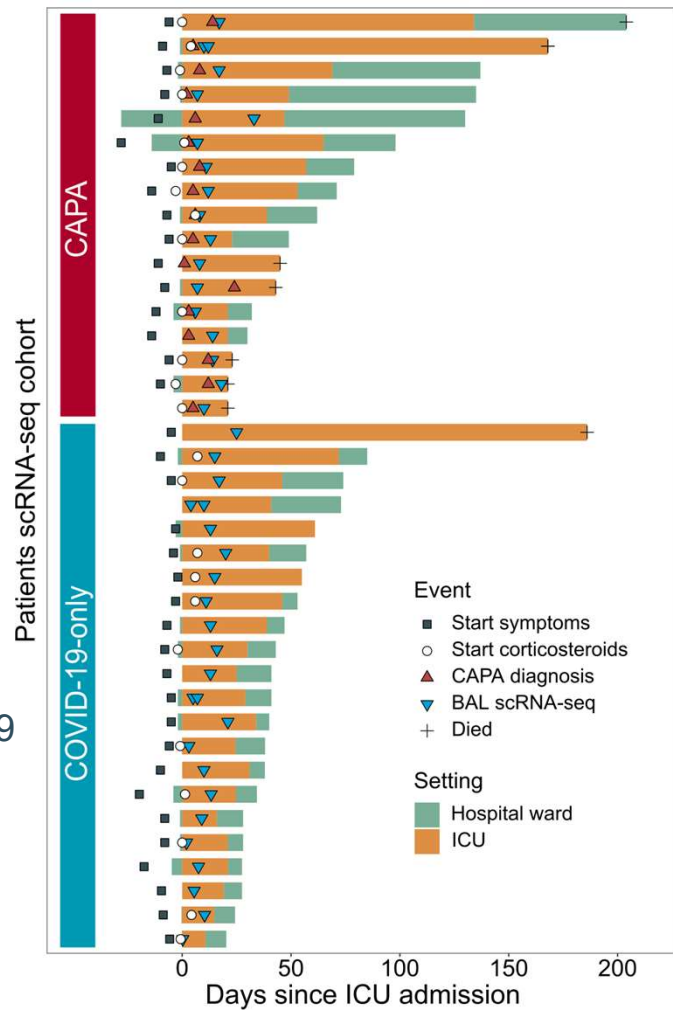


3. Neutrophil killing of hyphae



n=17
Proven/
probable
CAPA

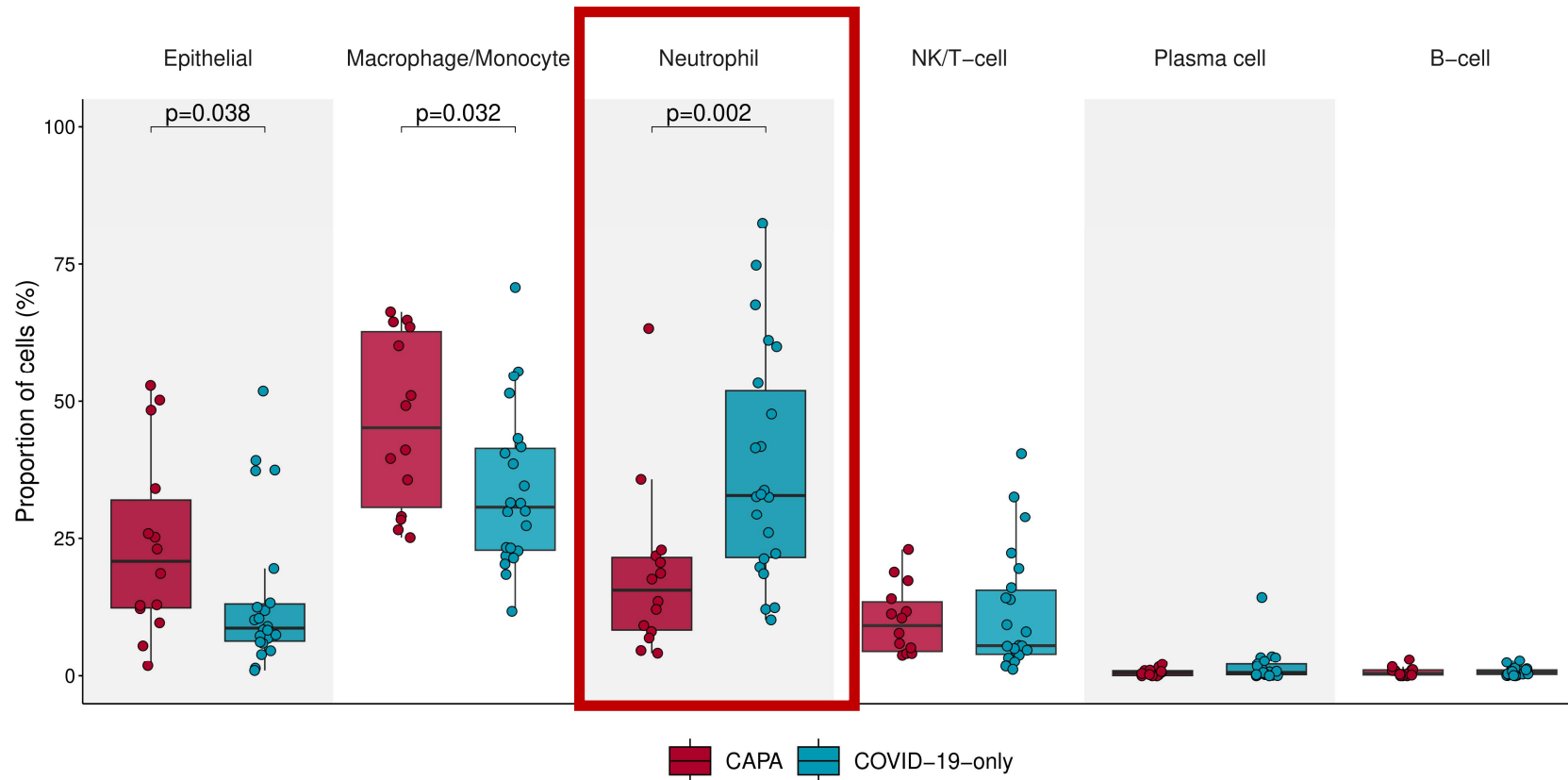
n=22
COVID-19
only



scRNA-seq of BAL of severe
COVID-19 patients

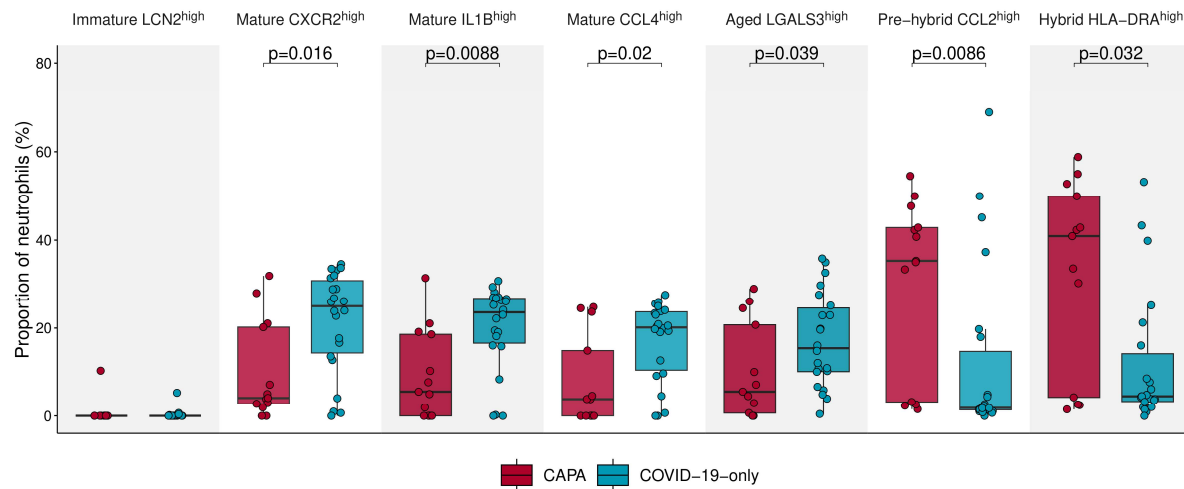
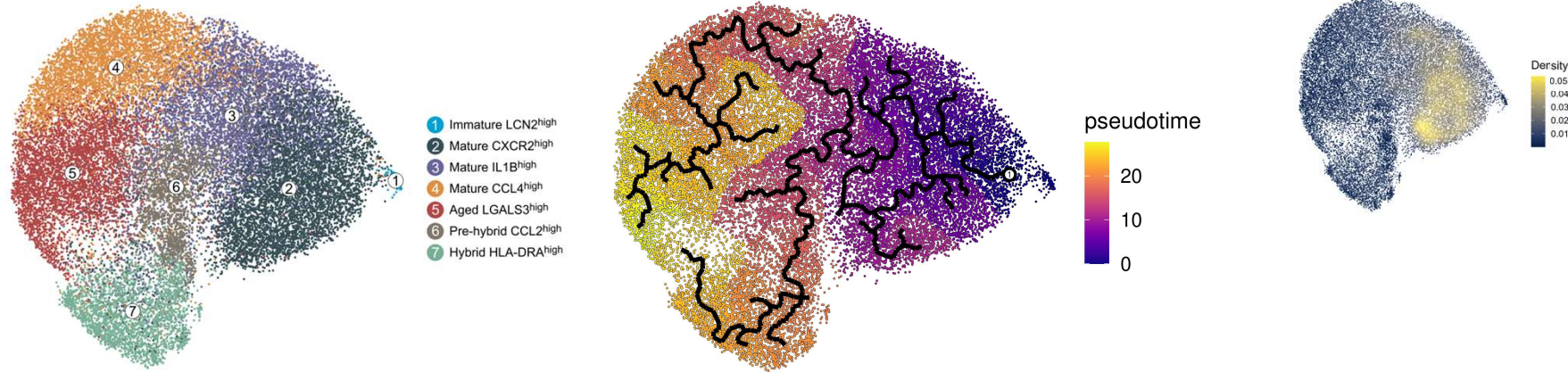
Major cell types

Significantly lower neutrophil fractions
in CAPA vs. COVID-19 only

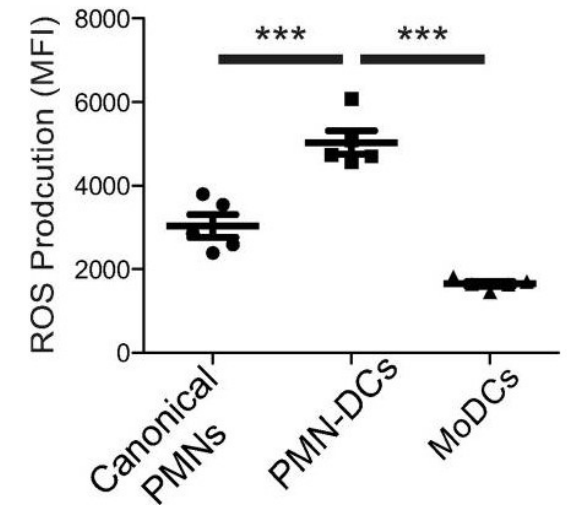
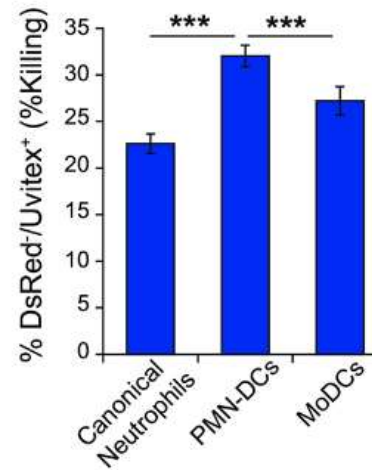
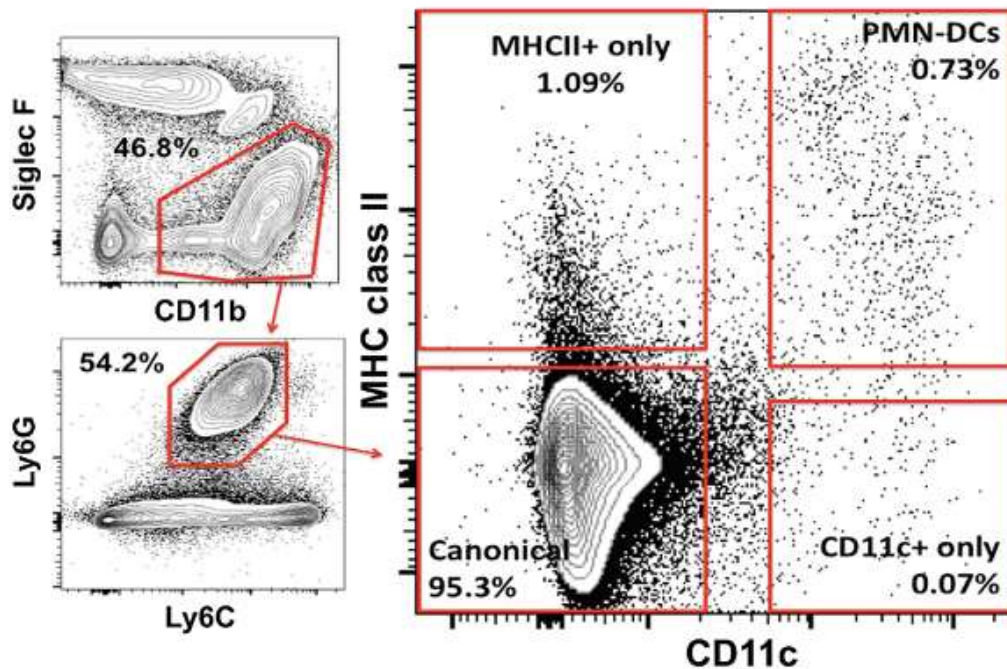


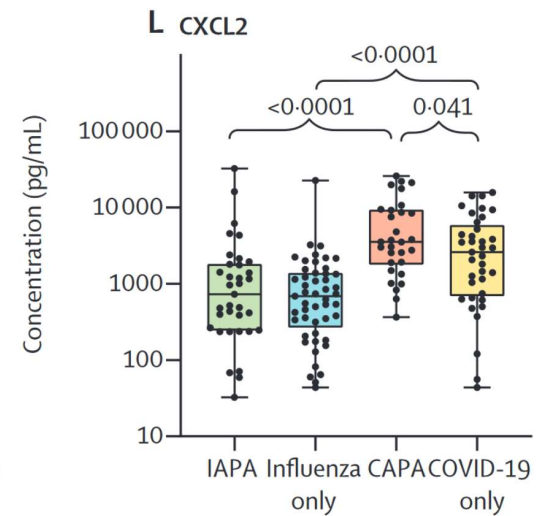
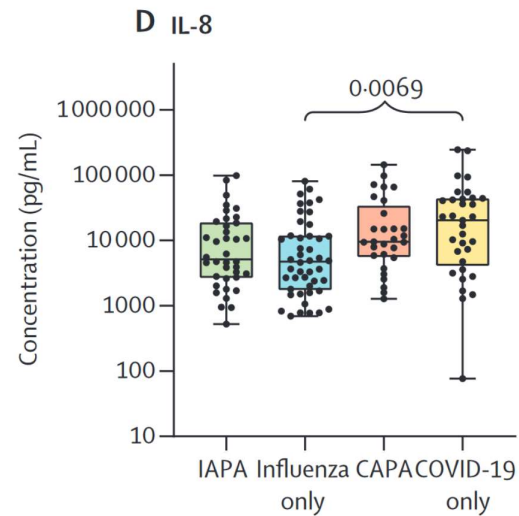
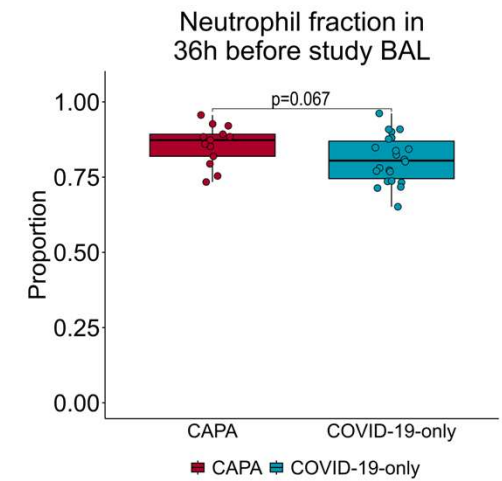
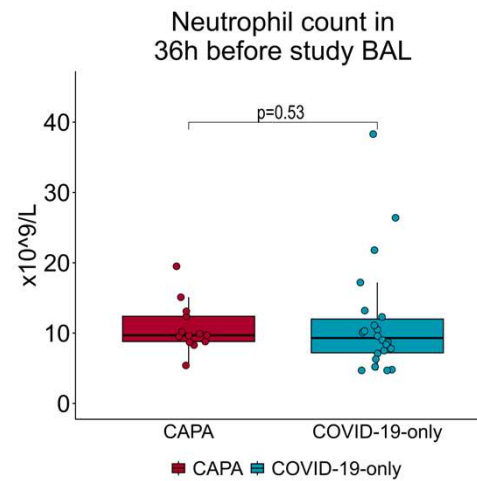
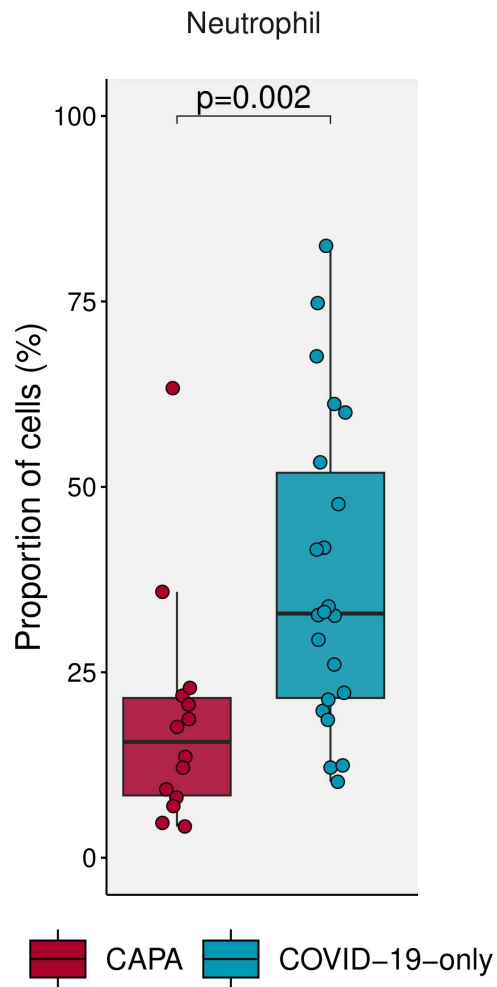
Neutrophils

Hybrid trajectory preferred in CAPA

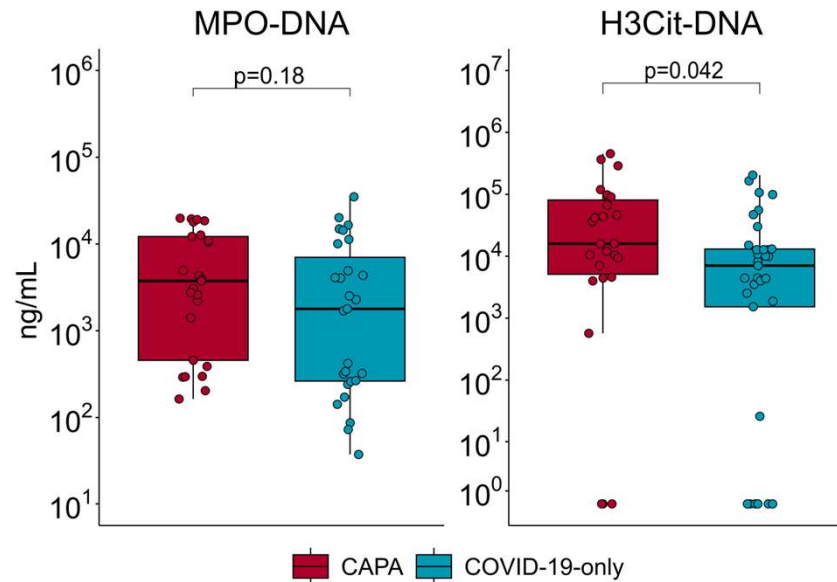
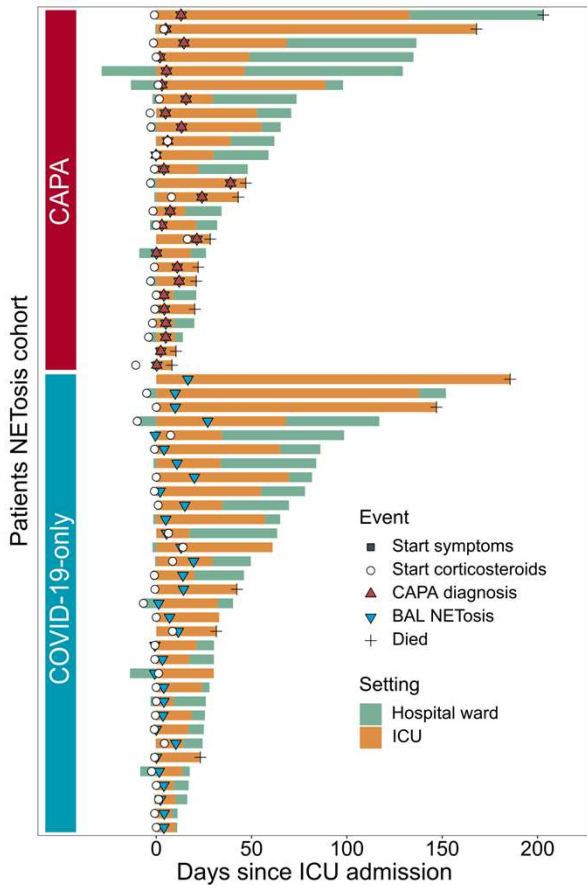


Hybrid neutrophils

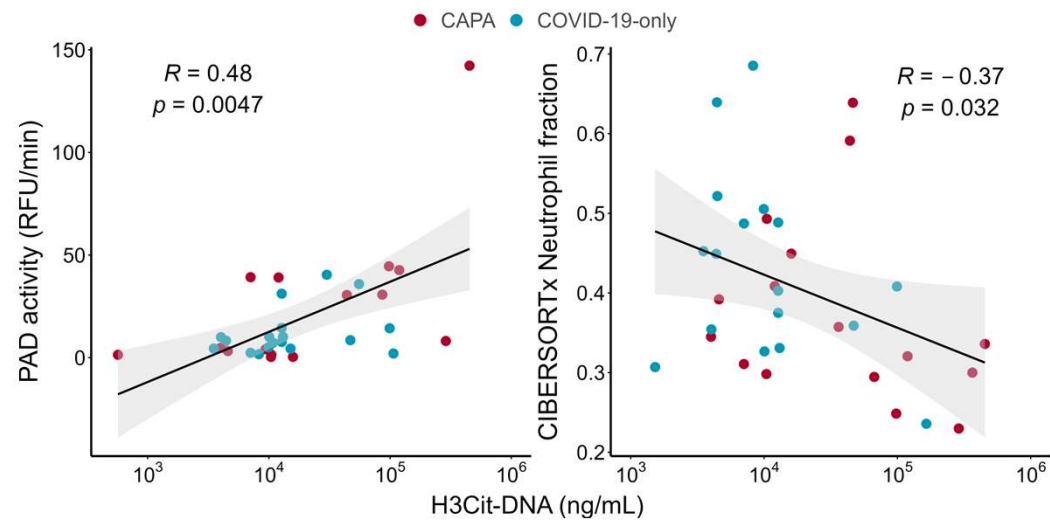




NETs

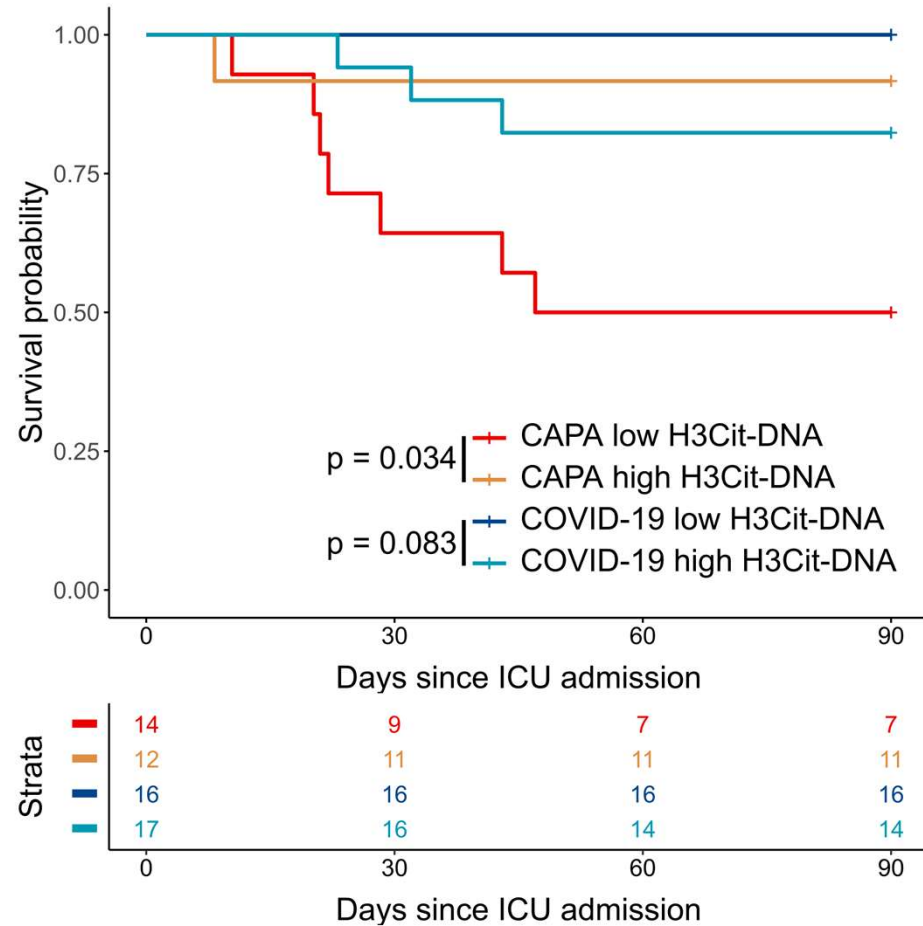


More NETs in CAPA
 → Lower neutrophil fractions detected by scRNA-seq

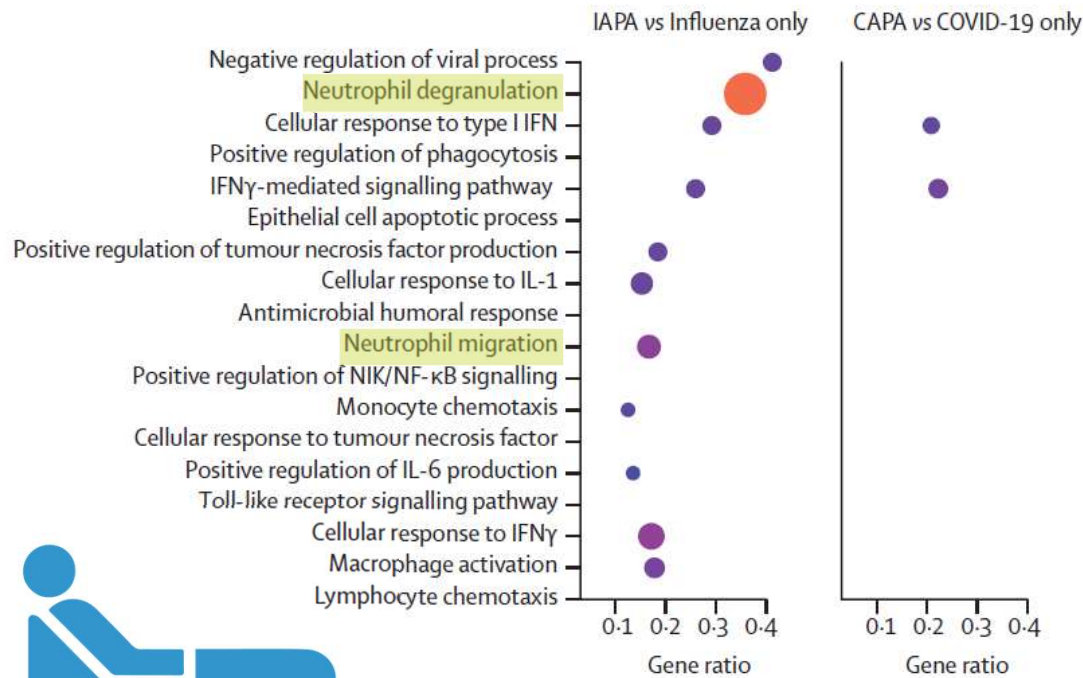


NETs

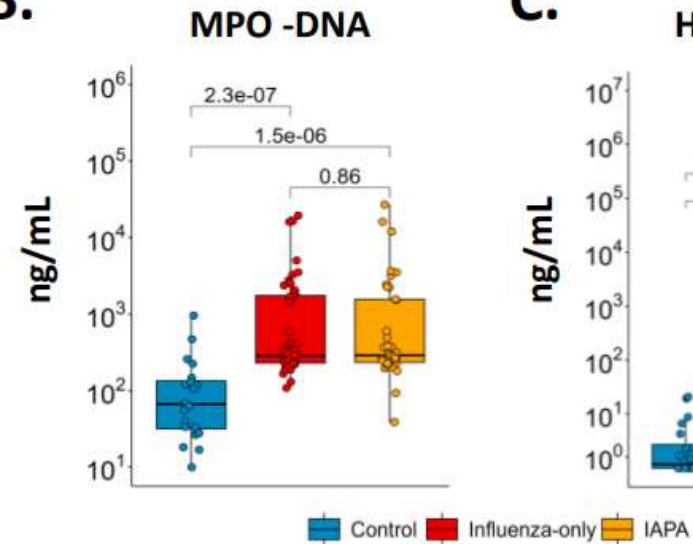
Lower H3Cit-DNA NETs associate with mortality in CAPA



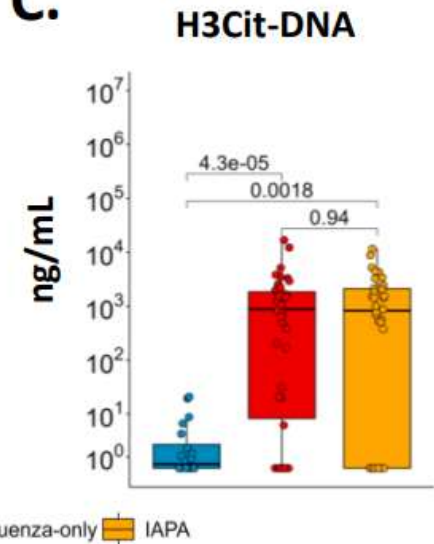
IAPA & neutrophils/NETosis



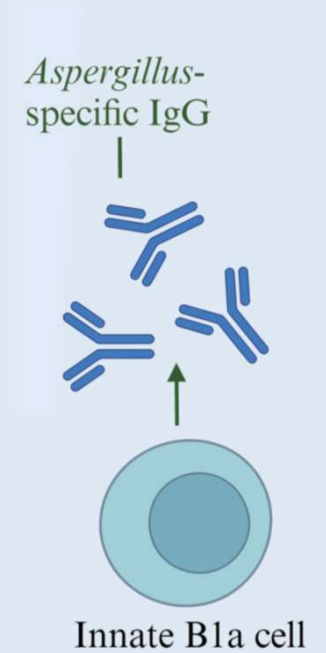
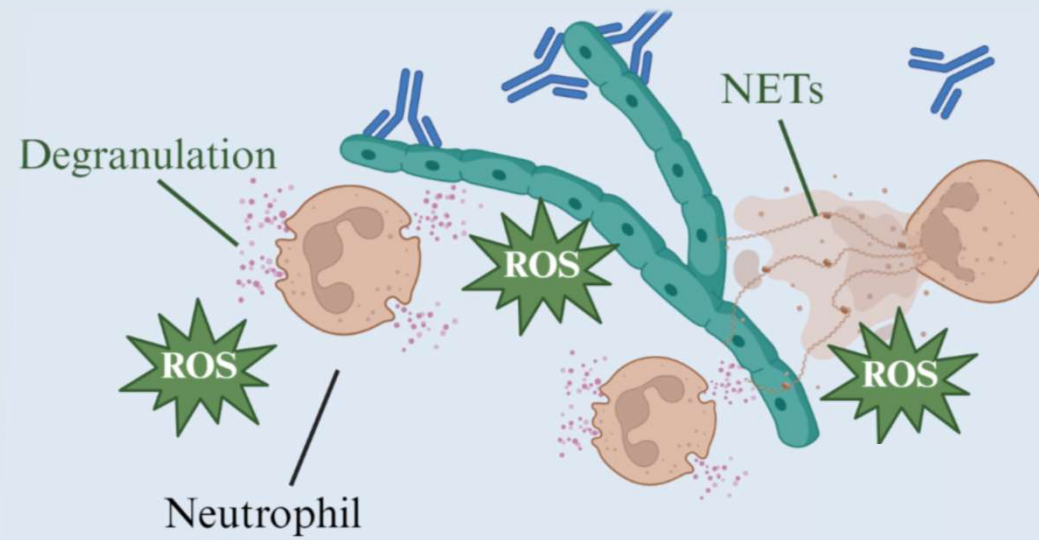
B.



C.



Antifungal neutrophil response affected in IAPA > CAPA?



3. Neutrophil killing of hyphae

FUNGAL INFECTIONS

A B1a–natural IgG–neutrophil axis is impaired in viral- and steroid-associated aspergillosis

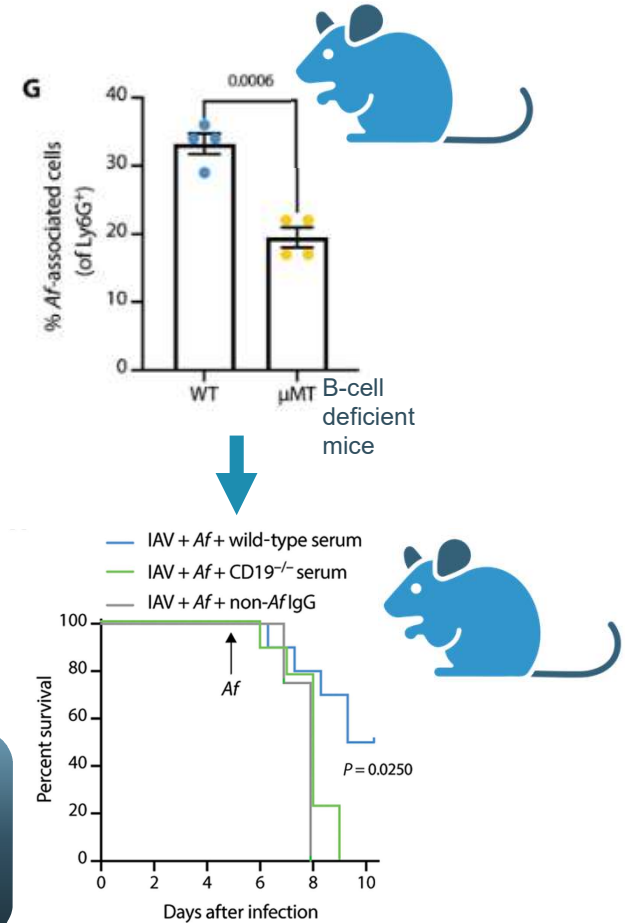
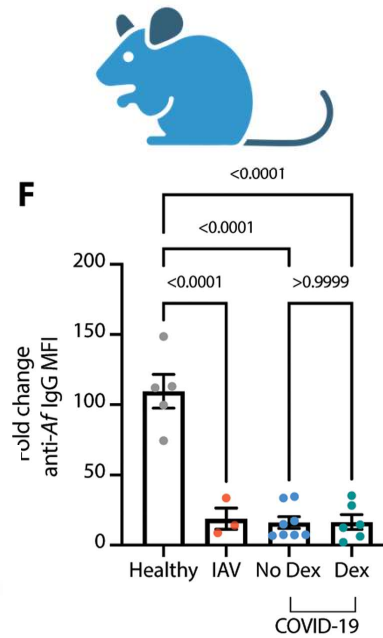
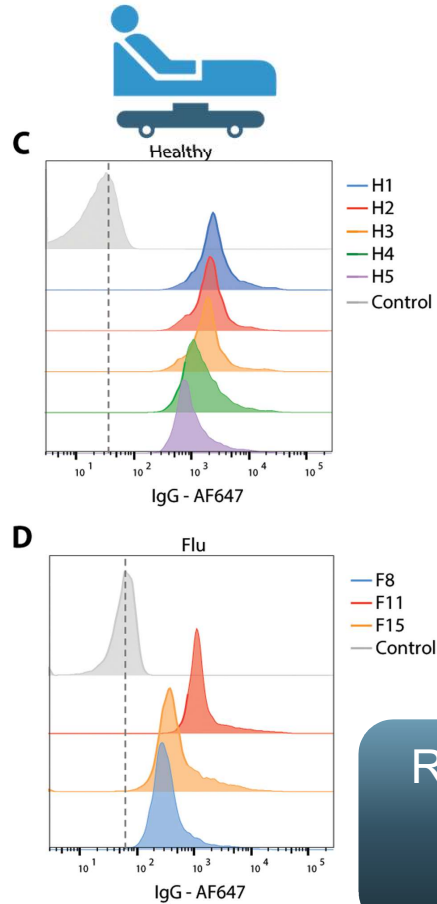
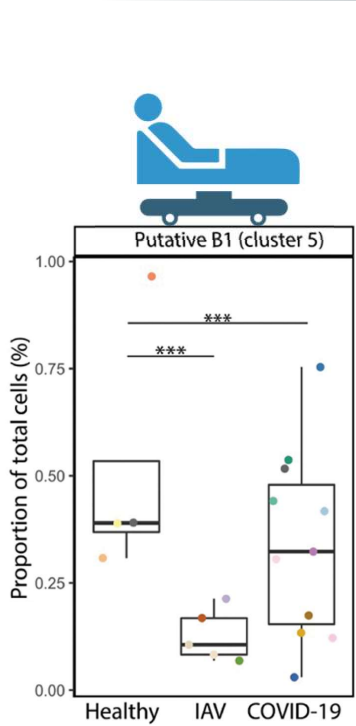
Nicole Sarden^{1,2}, Sarthak Sinha³, Kyle G. Potts⁴, Erwan Pernet^{5,6}, Carlos H. Hiroki^{1,2}, Mortaza F. Hassanabad^{1,2}, Angela P. Nguyen^{1,2}, Yuefei Lou^{1,2}, Raquel Farias^{1,2}, Brent W. Winston^{1,2}, Amy Bromley⁷, Brendan D. Snarr⁶, Amanda Z. Zucoloto^{1,2}, Graciela Andonegui¹, Daniel A. Muruve¹, Braedon McDonald^{1,2}, Donald C. Sheppard^{6,8}, Douglas J. Mahoney⁴, Maziar Divangahi^{5,6}, Nicole Rosin³, Jeff Biernaskie³, Bryan G. Yipp^{1,2*}

- Neutrophils are essential for host defense against *Aspergillus*, but *Aspergillus* seems not to be captured/killed by recruited neutrophils
- Sarden et al. found, in animals, that B1 innate lymphocytes and their production of naturally-occurring anti-*Aspergillus* IgG antibodies are essential for enhancement of neutrophil-mediated phagocytosis

Innate B1a cell depletion in viral pneumonia

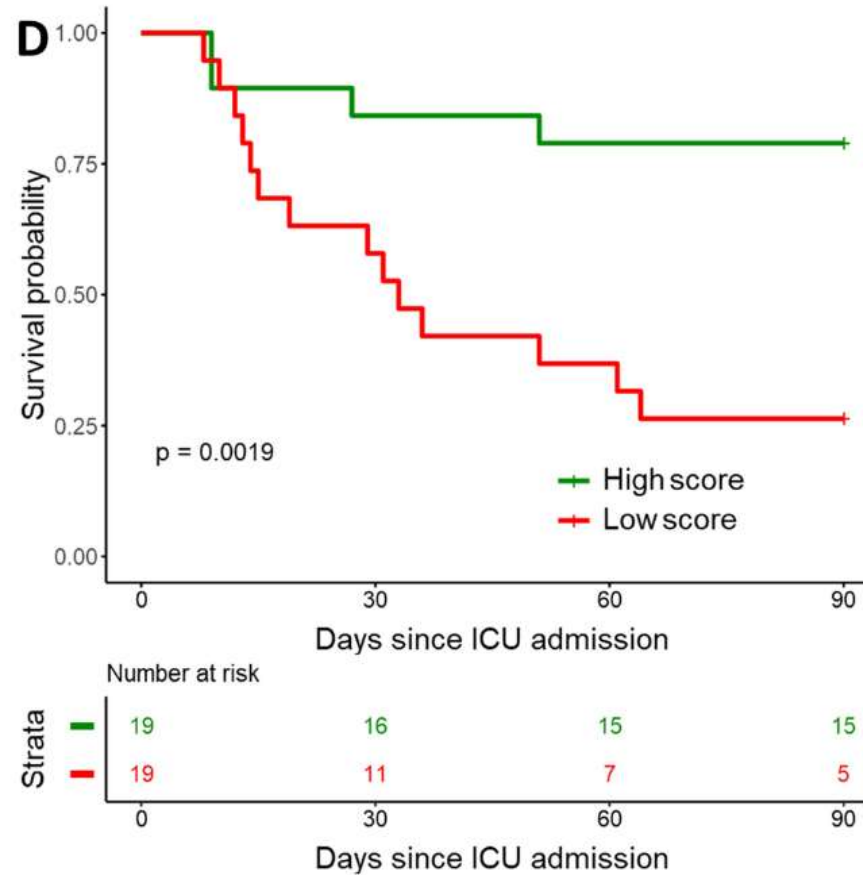
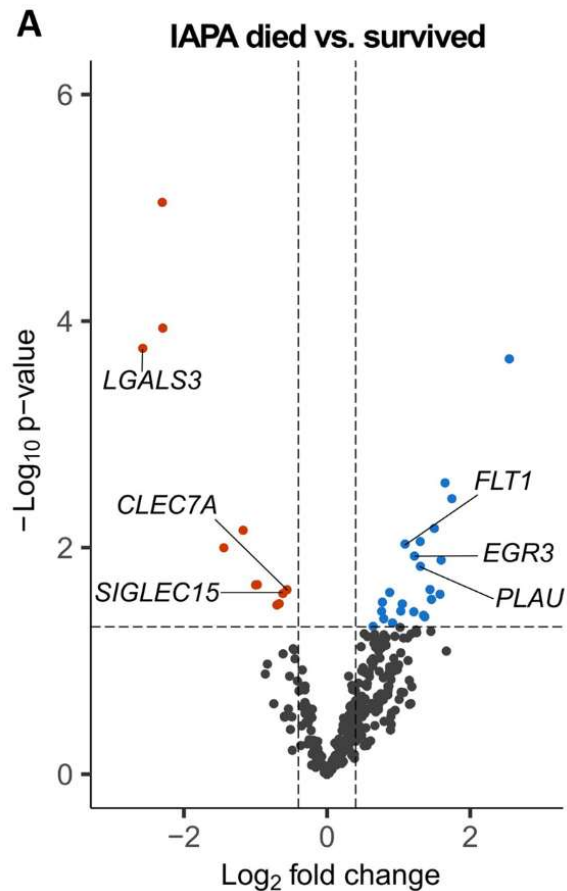
Reduced natural anti-*Af* IgG

Reduced fungal recognition of *Af*



Repleting anti-*Af*-IgG as immunity-restoring therapy in VAPA?

Impaired fungal recognition in IAPA?



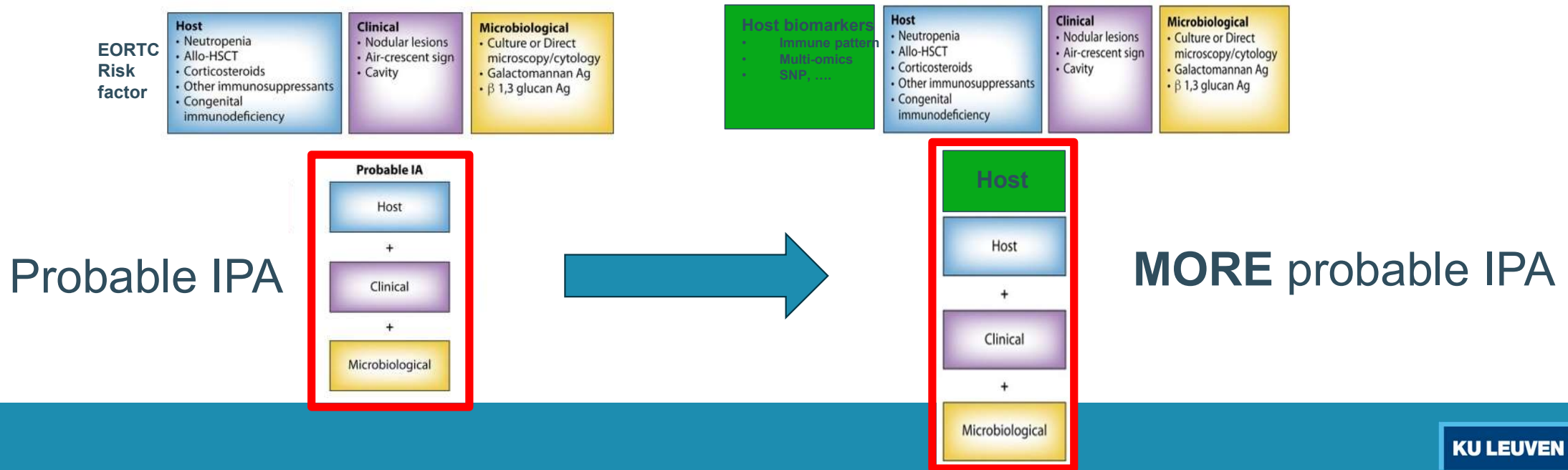
Decreased fungal recognition leads to worse outcome in IAPA?



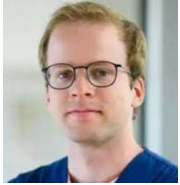
Take home message

- Increasing knowledge on pathophysiology VAPA:
 - Impaired epithelial barrier
 - Defects in phagocytosis and killing of conidia and hyphae

=> TRANSLATE towards novel biomarkers and therapeutic targets !!



Team work



Simon Feys



Laura Seldeslachts



Agostinho Carvalho,
Braga



Kim Martinod



Sam Vanmassenhove



Frank Van de Veerdonk,
Nijmegen



Diether Lambrechts



Cato Jacobs



Johan Van Weyenbergh



Sirima Kraisin



Greetje
Vandevelde



Lore Vanderbeke



Johan Maertens



Katrien Lagrou



Georgios Chamilos,
Crete



Karin
Thevissen



Stephanie Humblet-
Baron



Hanne Moon
Lauwers



Jannes Heylen



Joost Wauters



And many
more...

