Personalized immunotherapy in fungal infections

Frank van de Veerdonk

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Introduction

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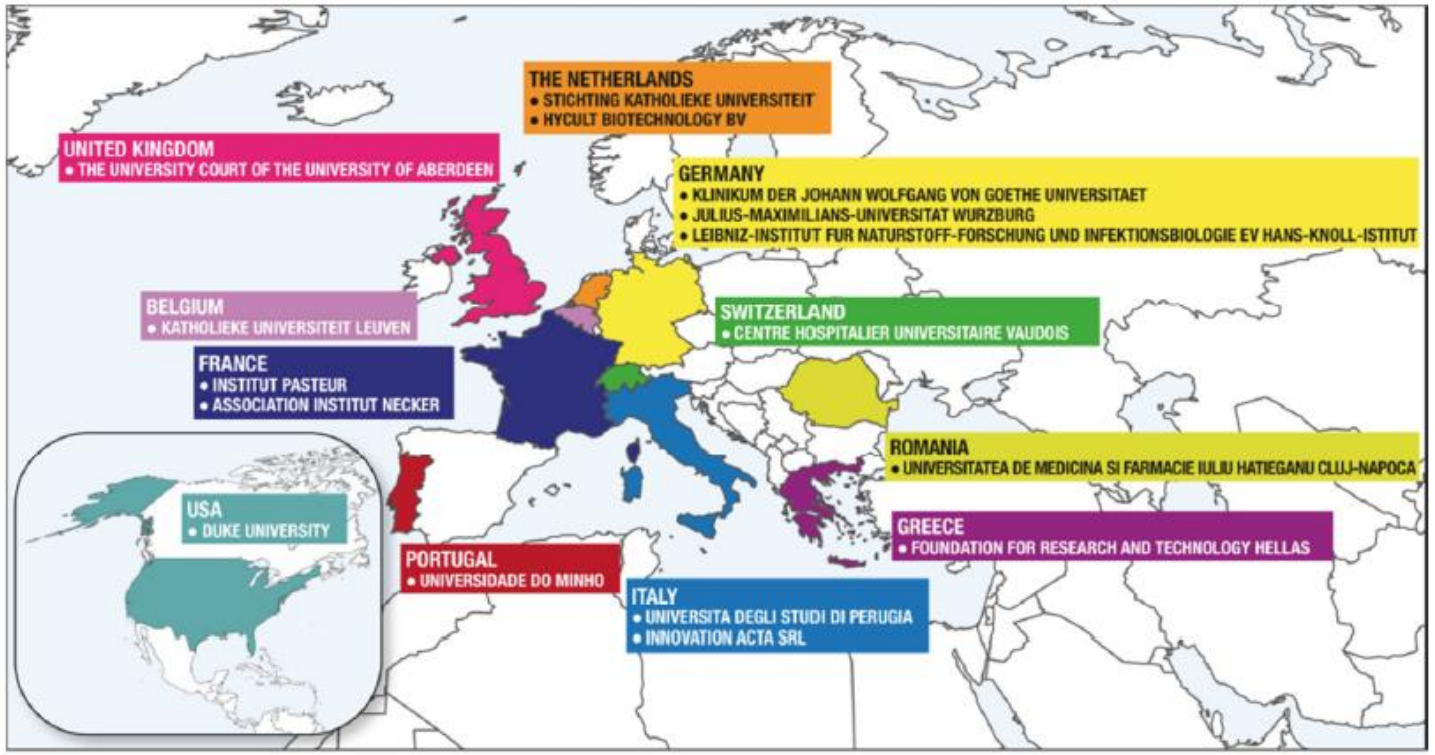
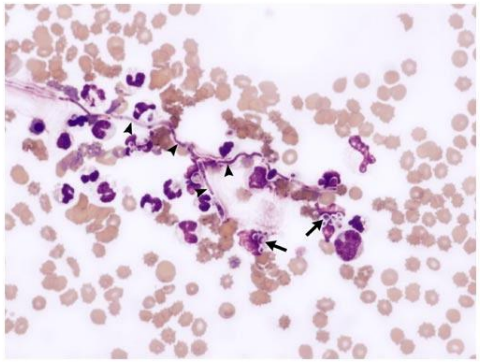
- **HDM-FUN project and trials**
- **Immunotherapy : IFNγ candidemia**
- **Effects of IFNγ on innate immune cells**
- **Anakinra in Influenza-aspergillosis**
- **Future perspectives**

Host-Directed Medicine in FUNgal infection

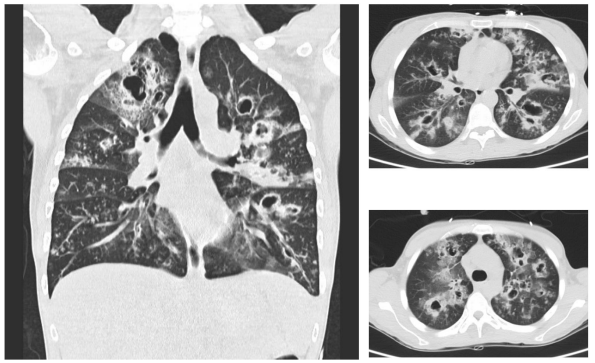




Candidiasis

HDM-FUN

16 partners



Aspergillosis (IAPA)

HDM-FUN

1. Identify host pathogen factors (HPFs) that correlate with disease and use them for stratification of treatment

2. Establish two clinical trials (intervention and prevention)

3. Central biobank and standardize procedures and analysis

4. Unique infrastructure and implementation of host-directed medicine in clinical setting and society

Timeline Immunotherapy Fungal

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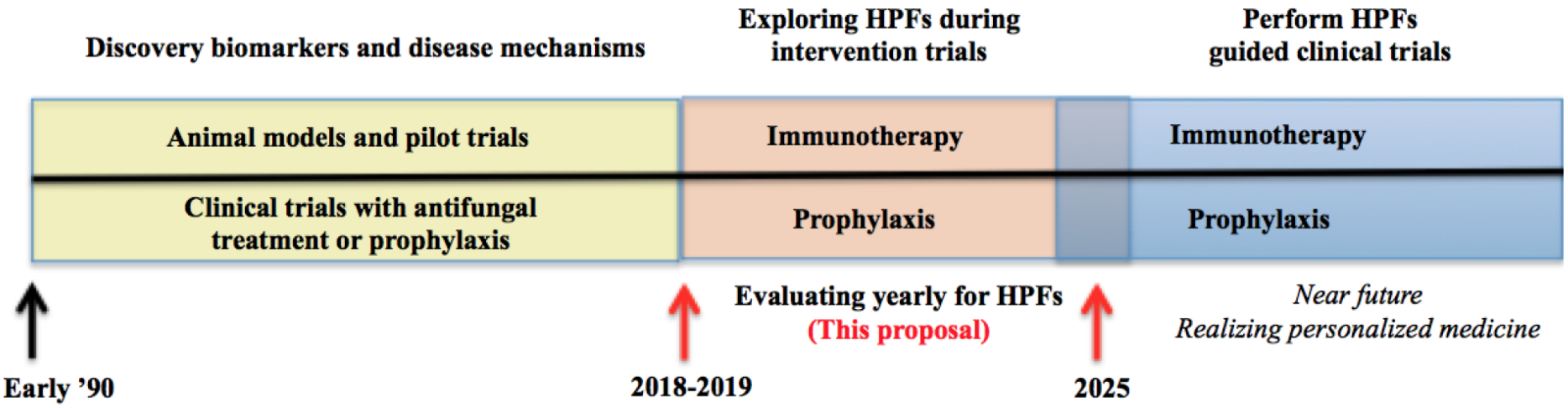

HDM-FUN

Who will benefit from immunotherapy?

Methodology

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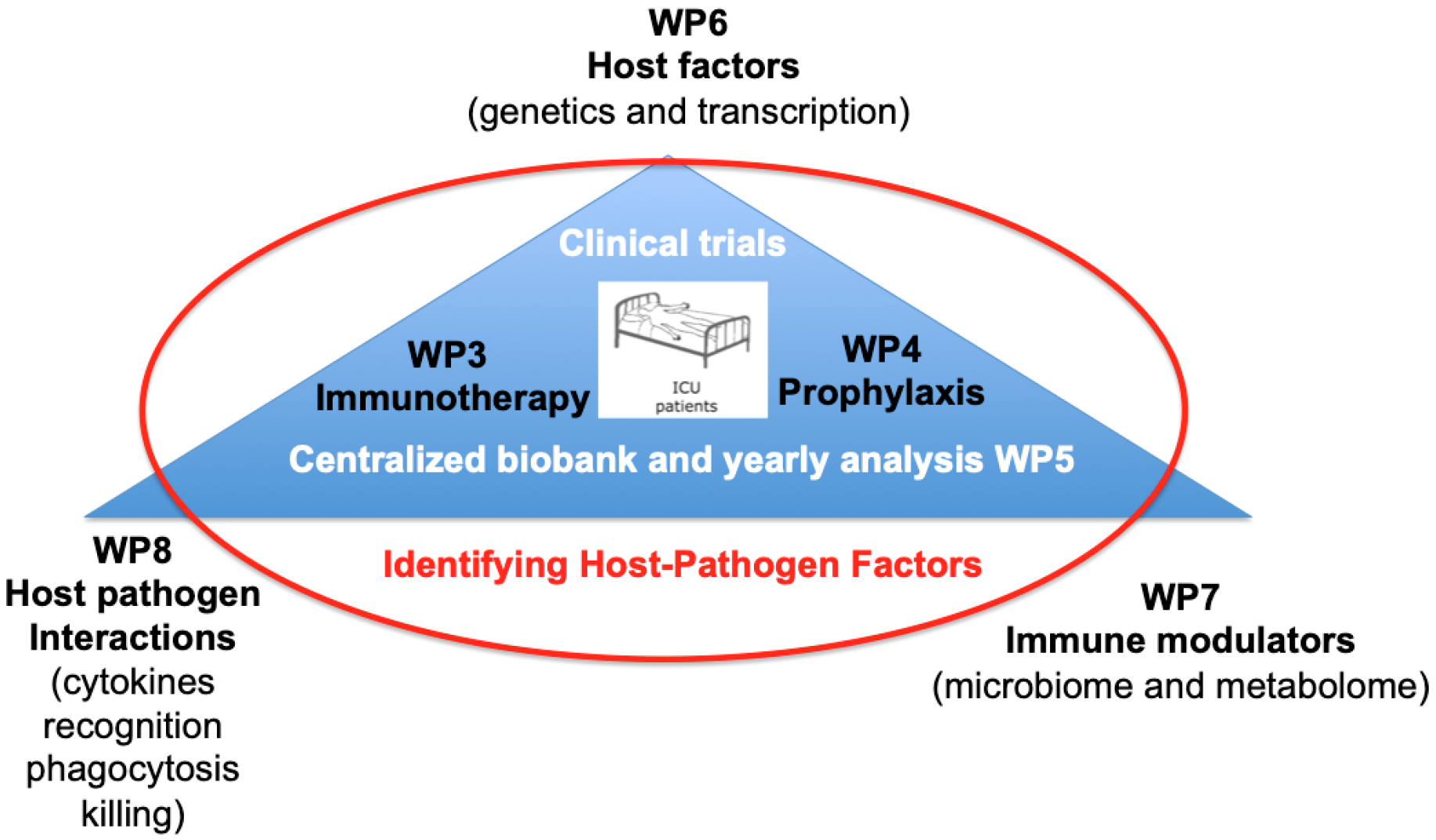
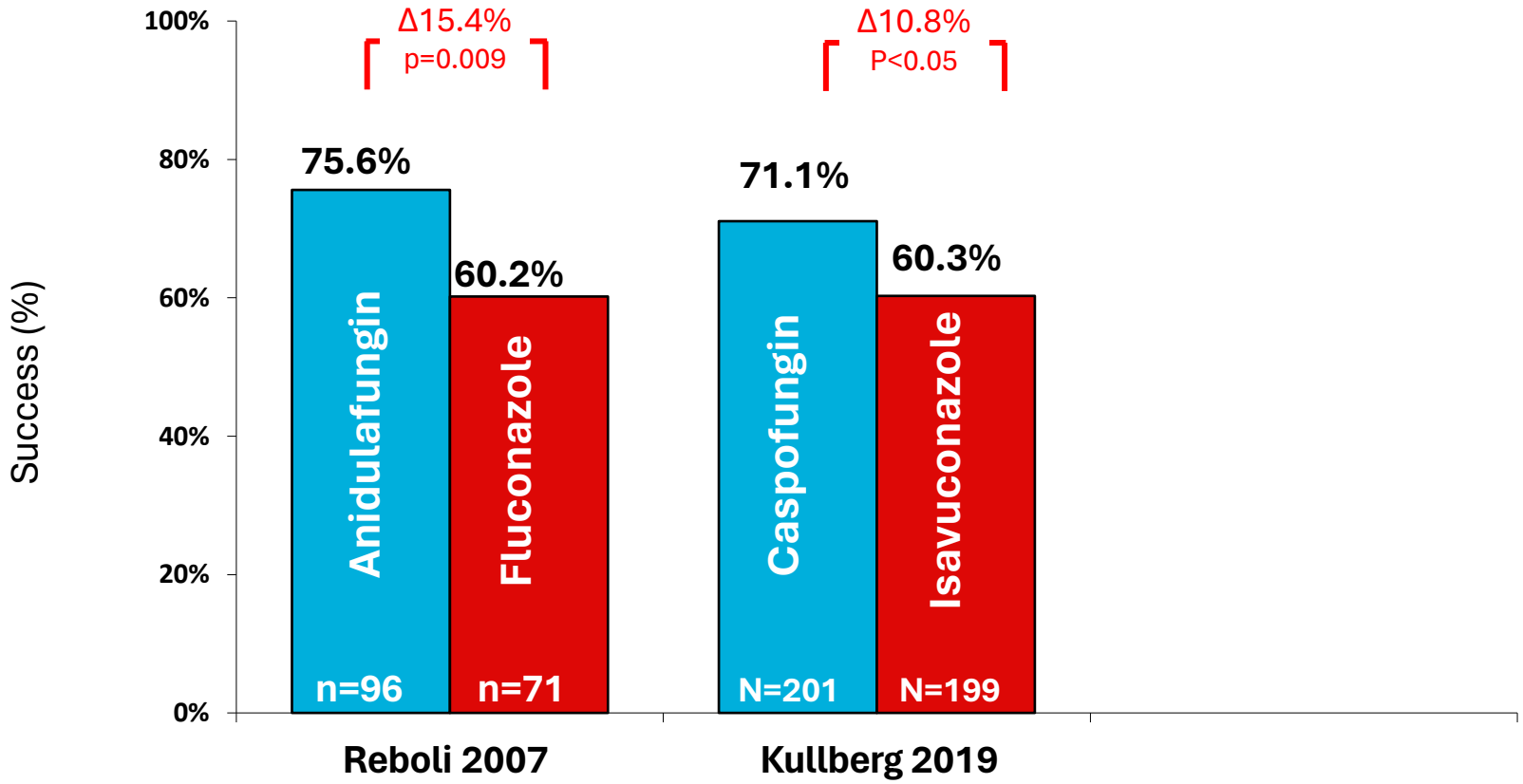


Candidemia 30% mortality



1. Reboli AC, et al. *N Engl J Med* 2007; 356(24):2472–82
2. Kullberg et al. *Clin Infect Dis* 2019; 68: 1981-9

Design candidemia trail

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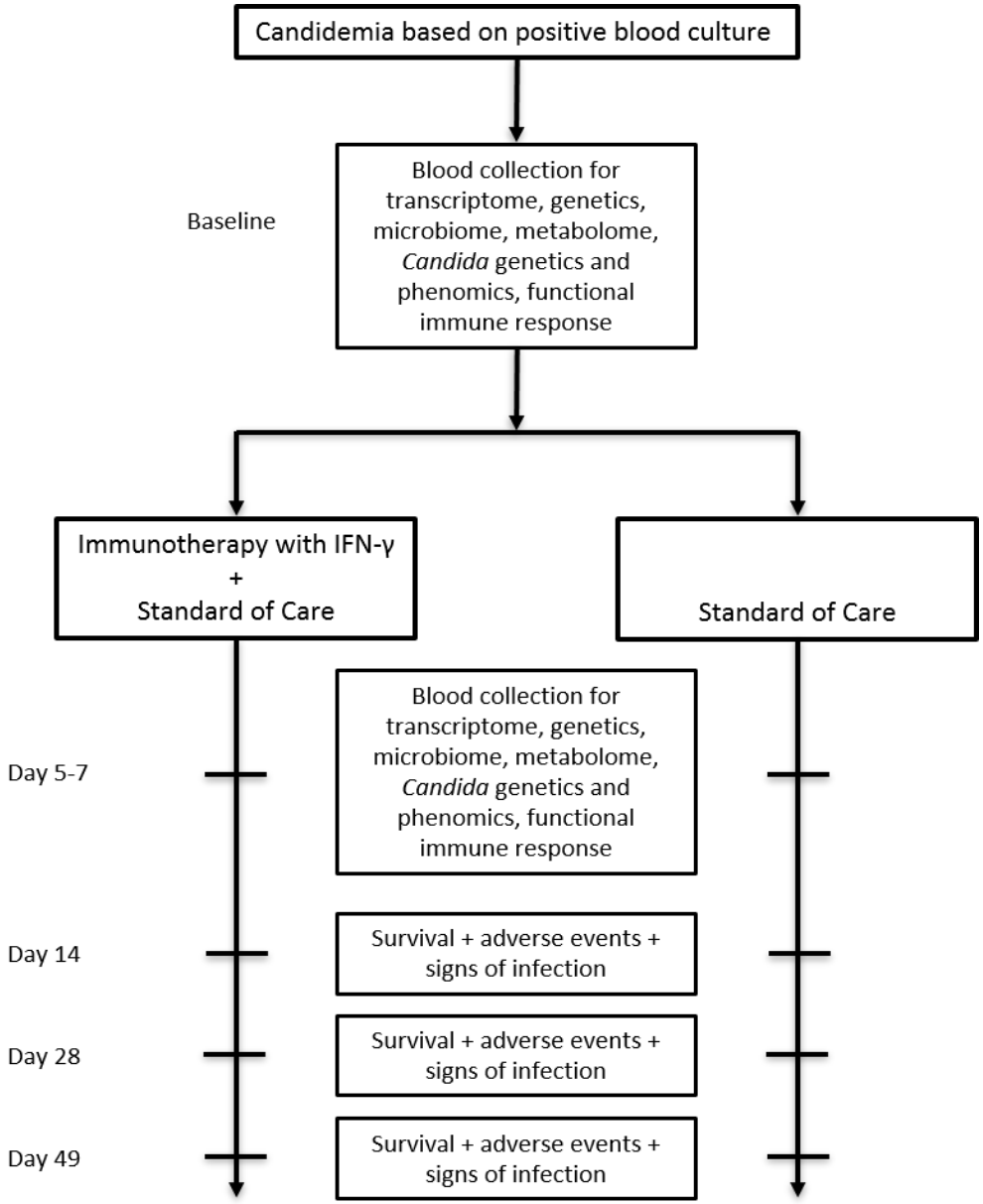

Primary endpoint

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The primary focus is on time to clearance.

A composite endpoint of clearance of candidemia and (in-hospital) mortality within 7 days using an ordinal scale indicating the number of days with negative blood culture and death as the worst outcome (labelled as -1)

Could trigger statistical significance at 75 patients per group (n=150)

Interim analysis from n=40 and every extra 20 patients thereafter

Progress

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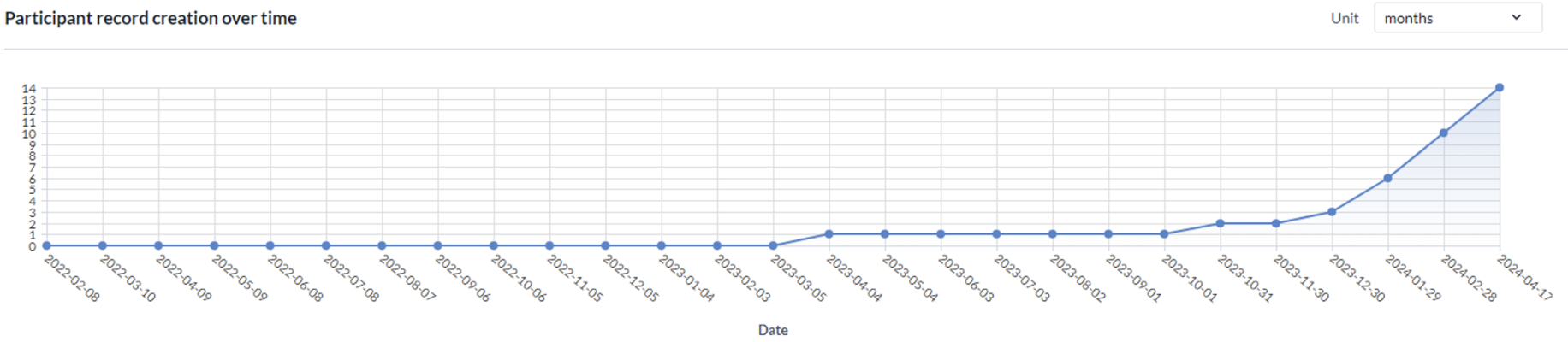
2.3 Clinical Study Recruitment

Recruitment rate/month	*3-5 per months, expected to stabilize to at learst 5 per month from Q2 2024.*
Current total enrollment up to	*14 includeded subjects up to March 2024* *(67 candidemia patients screened for inclusion, 53 did not meet inclusion criteria)*

2.3.1 Study Enrollment Cumulative Graph (month / number of enrollments):



Progress

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Participant status

Site	Total
Radboudumc	1
Klinikum Der Johann Wolfgang Von Goethe Universitaet	1
Universitatea de Medicina si Farmacie Iuliu Hatieganu Cluj-Napoca	1
"ATTIKON" University General Hospital, 4th Department of Internal Medicine	3
General University Hospital of Patras, Intensive Care Unit	1
General Hospital of Athens "KORGIALENIO-BENAKIO E.E.S", Intensive Care U	1
"Sotiria" Athens General Hospital of Thoracic Diseases, New Intensive Care Ur	1
General Oncological Hospital of Kifissia "Oi Agioi Anargyroi" Intensive Care U	2
General Hospital "Asklepieio Voulas", Intensive Care Unit	3
Total	14

End date : March 2026

Interferon gamma (IFNγ) and candidiasis

IFNγ candidiasis

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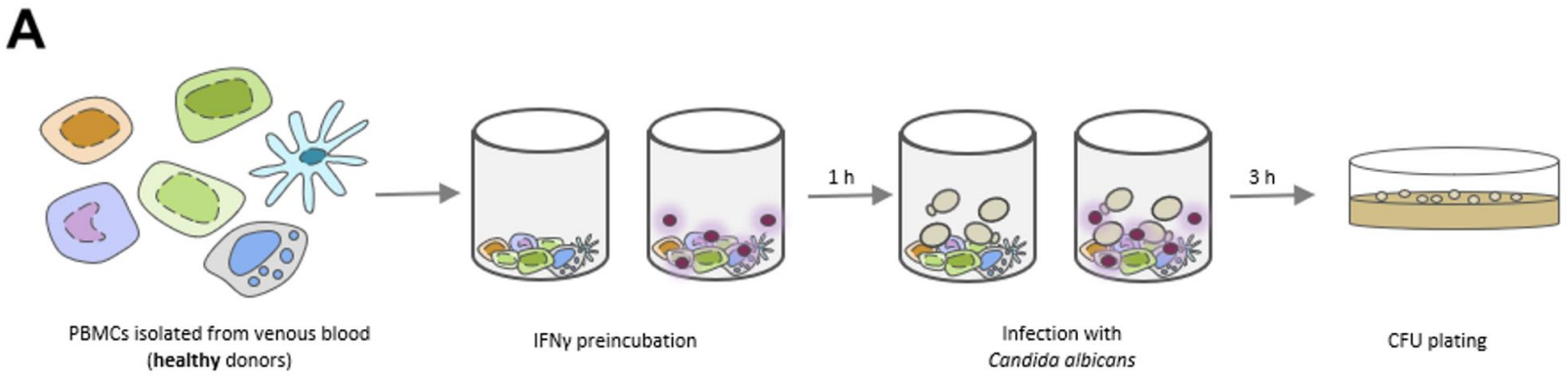
200 FG cohort

n=155 phagocytosis and killing

Candida +/- IFNγ



IFNγ candidiasis PBMCs

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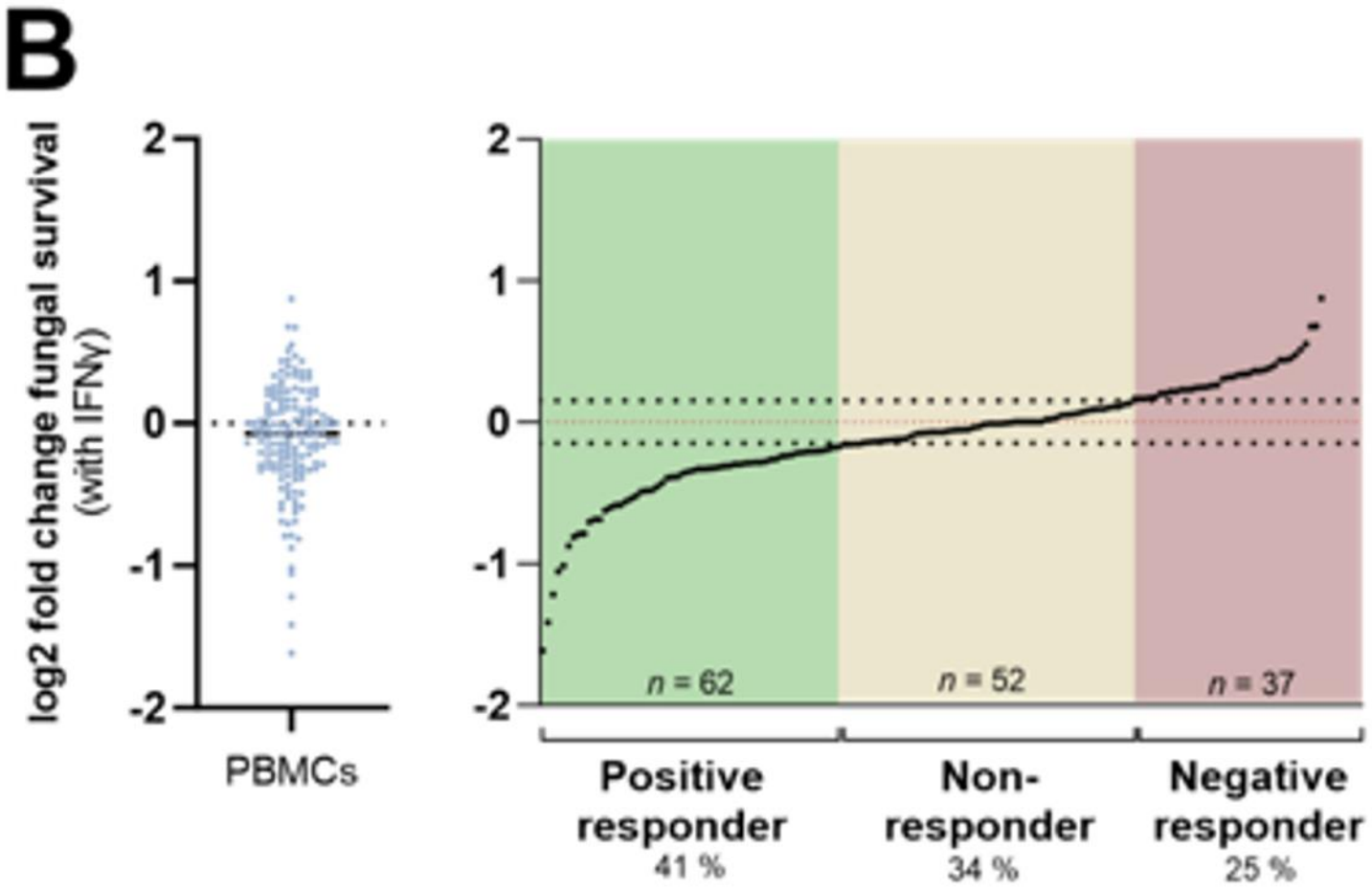

Interferon gamma candidiasis

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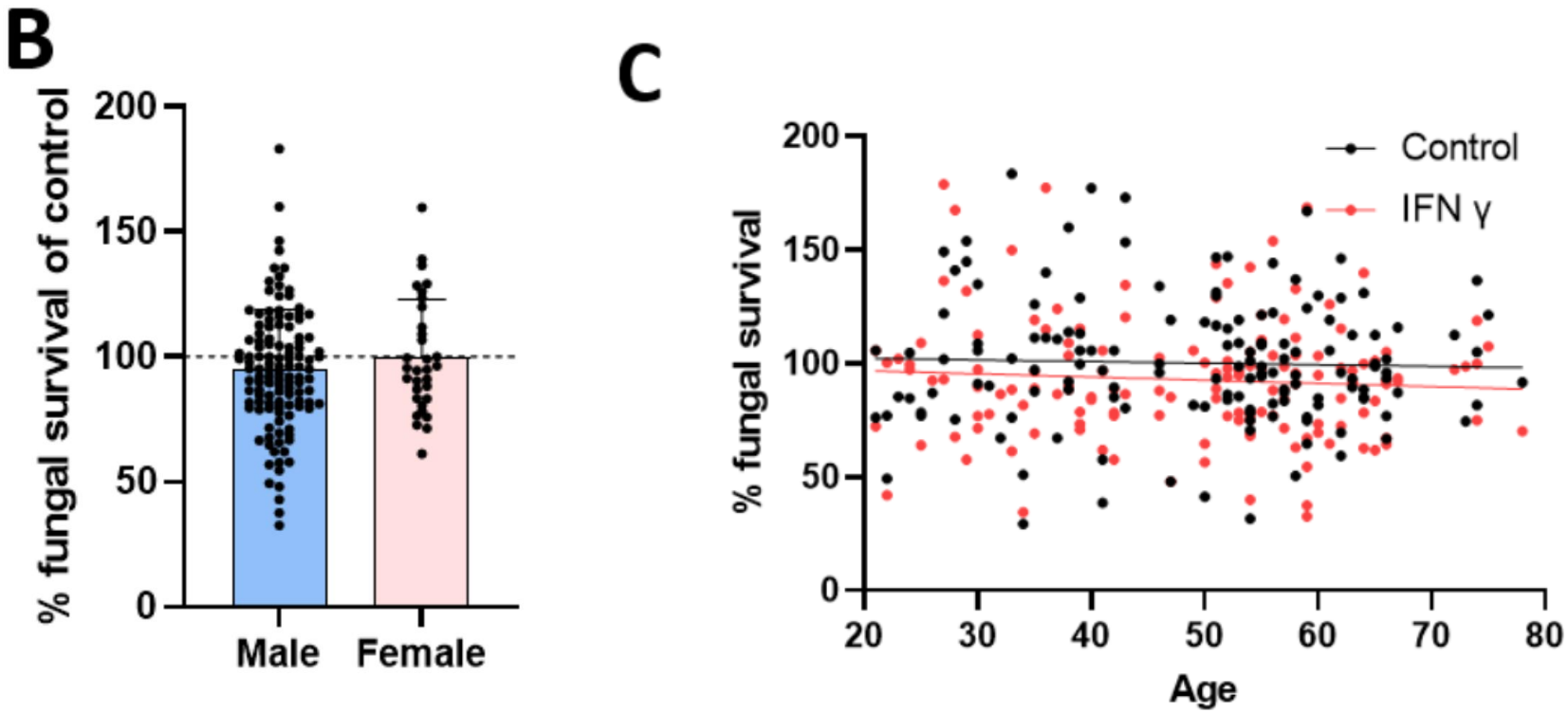

Interferon gamma candidiasis

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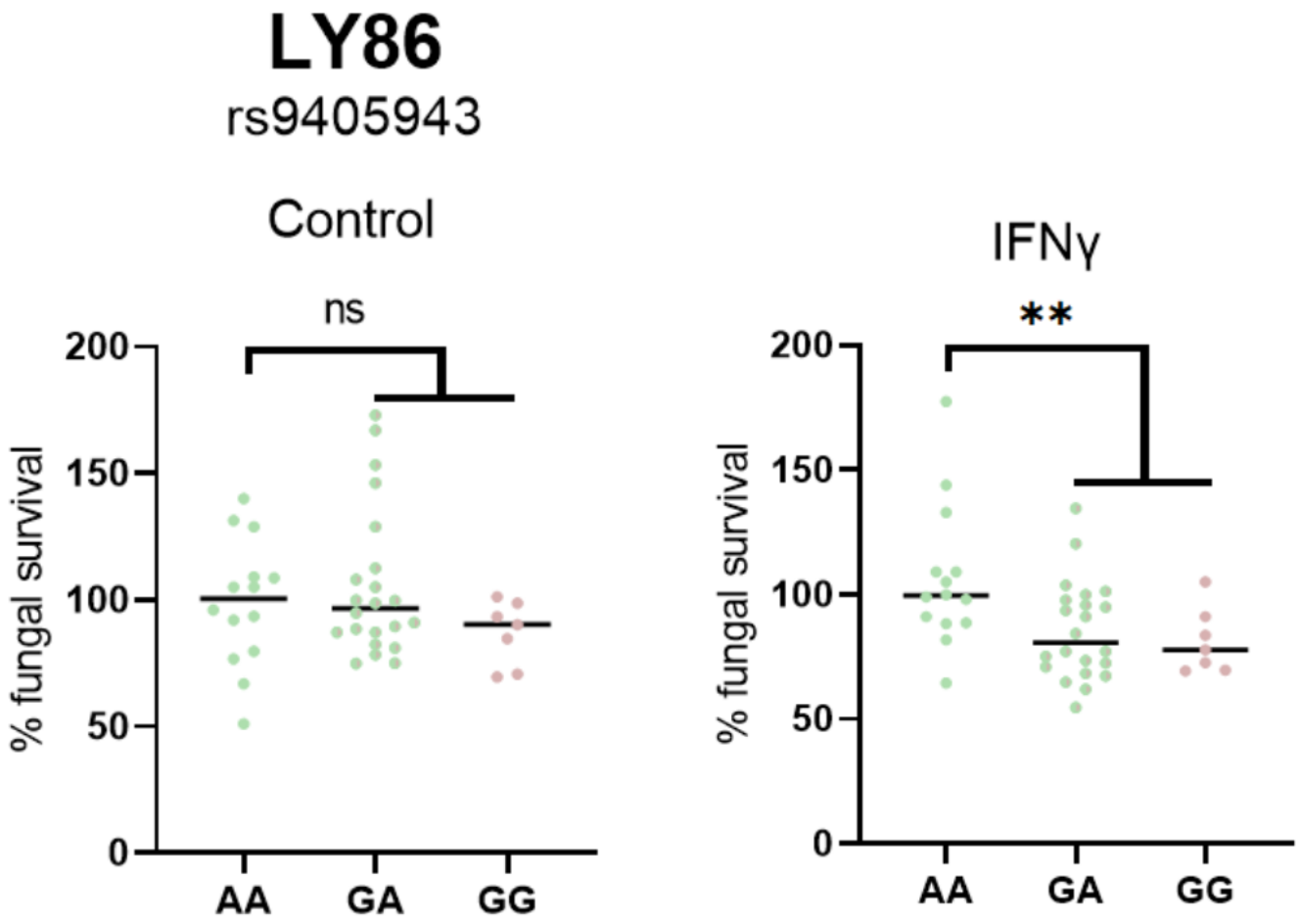

Interferon gamma candidiasis

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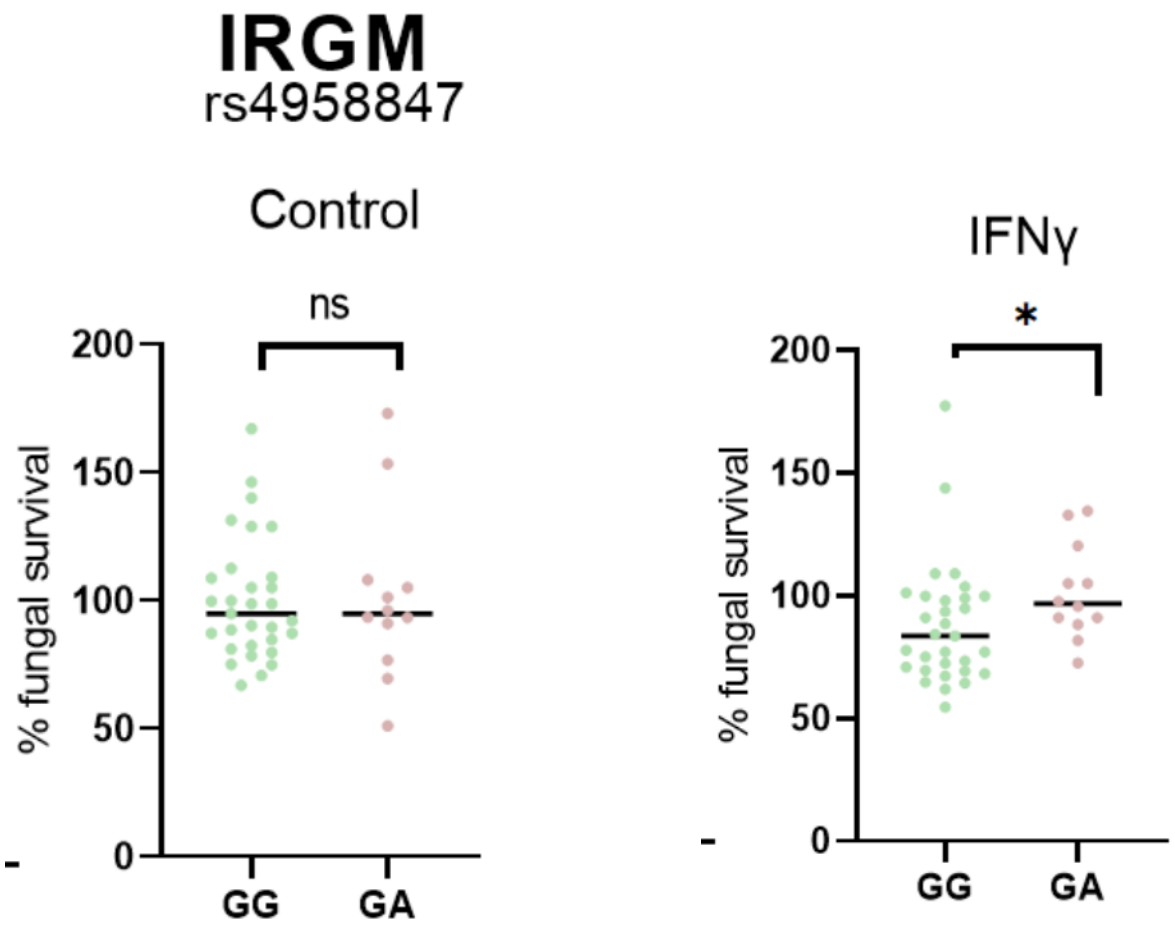

Interferon gamma candidiasis

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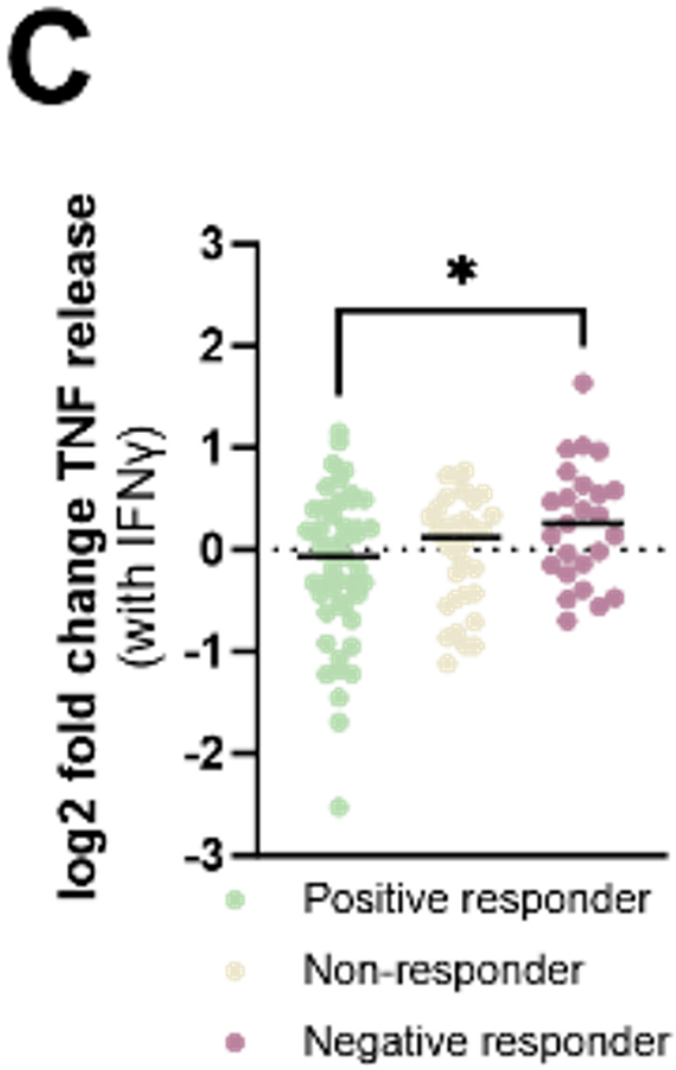

Interferon gamma candidiasis

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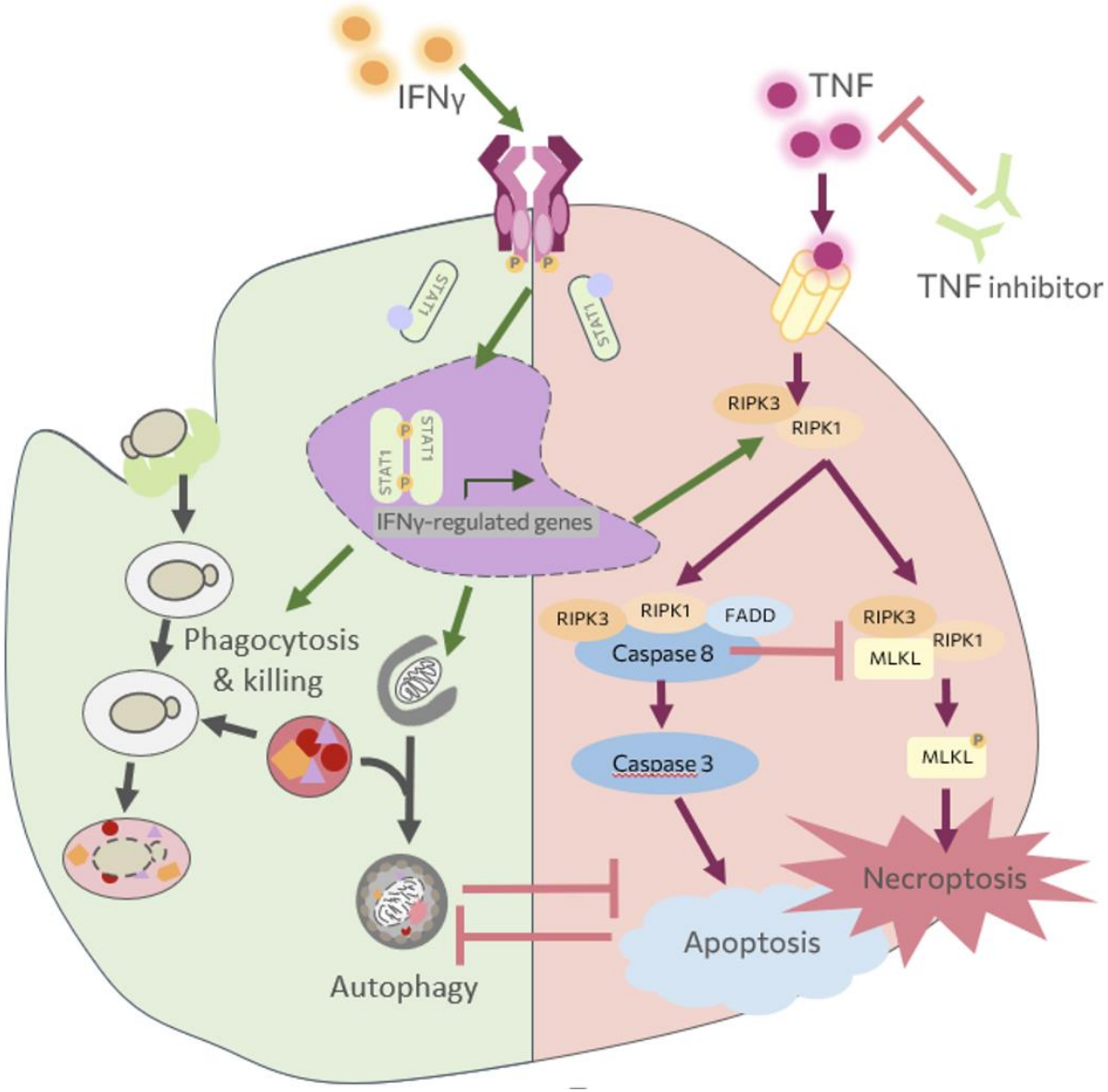

Interferon gamma candidiasis

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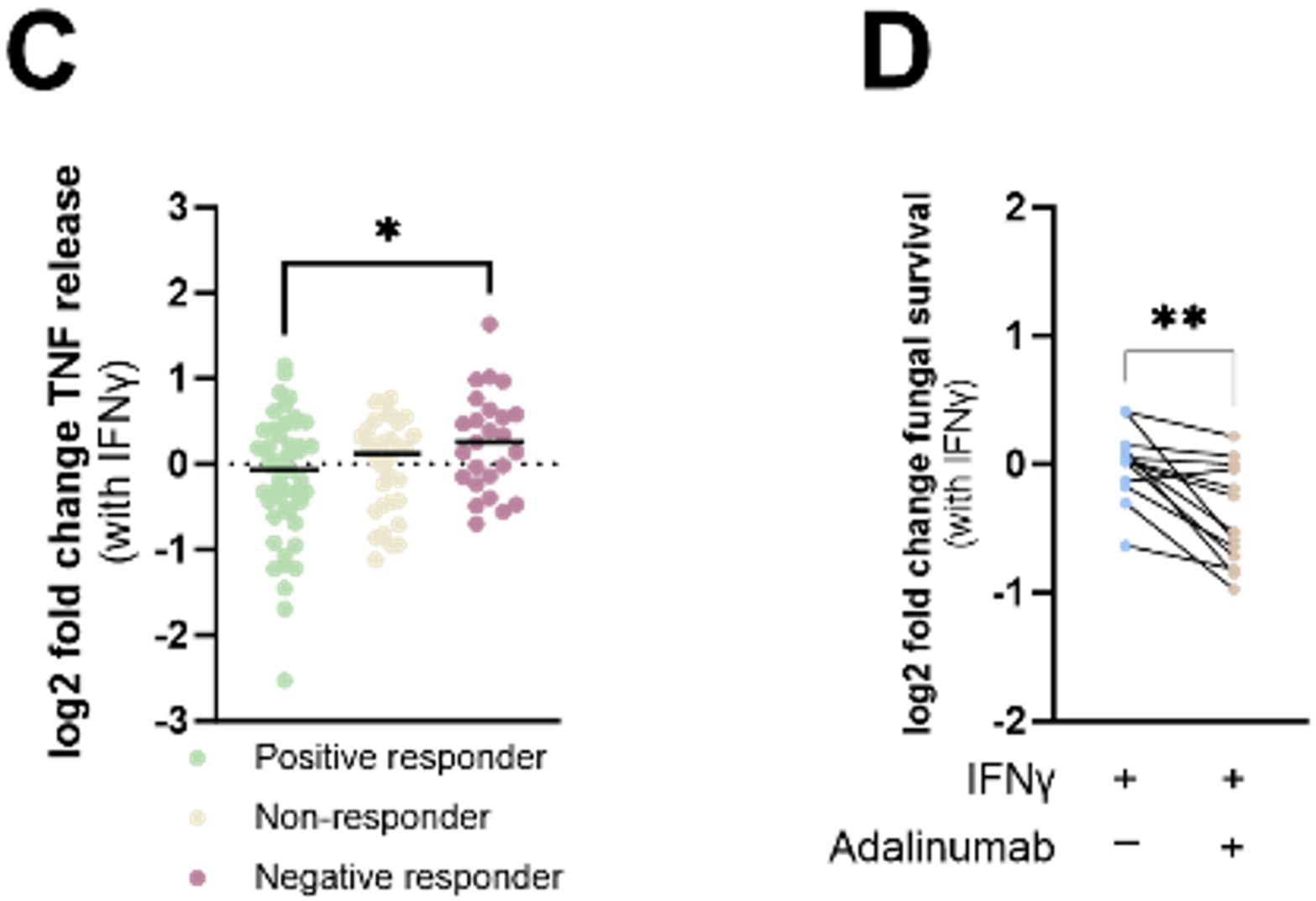

Conclusions 1

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- **Individual response to IFNγ on killing**
- **Associated on genetics and cytokine (TNF)**
- **Stratification?**
- **Develop functional assays**

Interferon gamma (IFNγ)

effect on innate immune cells

38 yr old women

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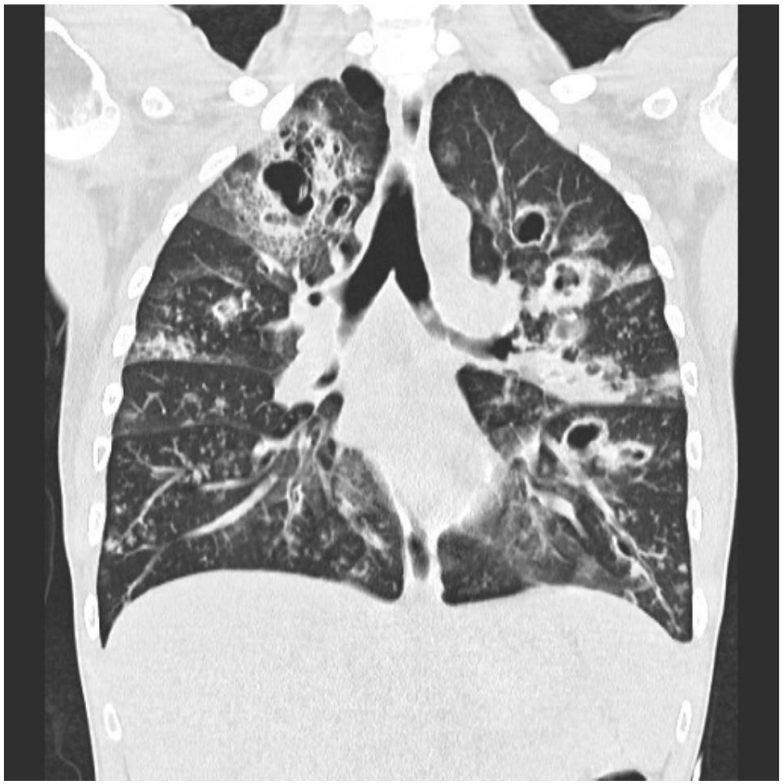
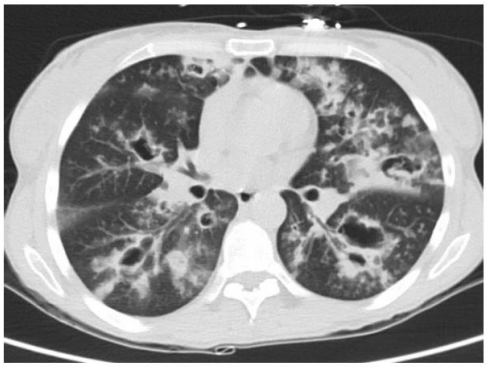
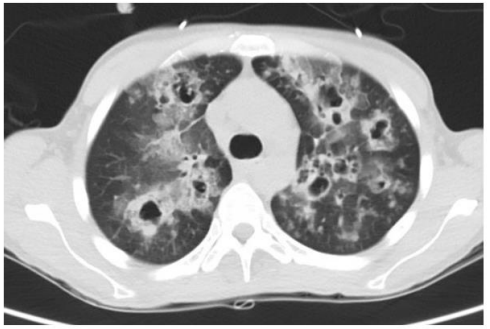
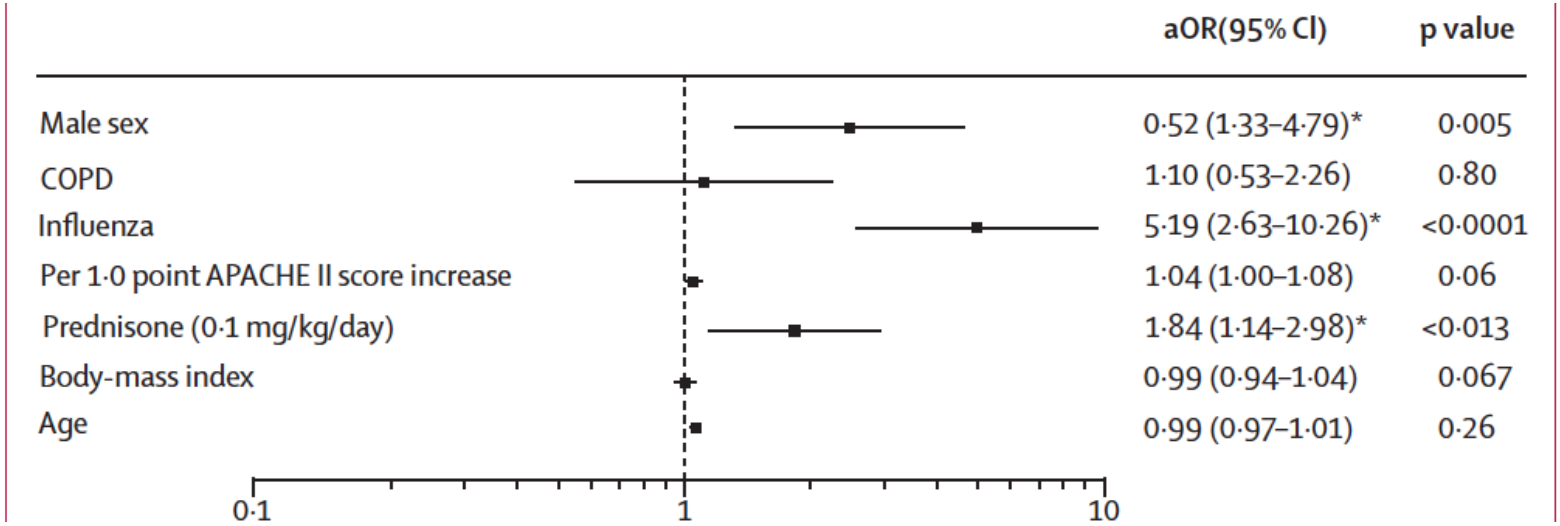






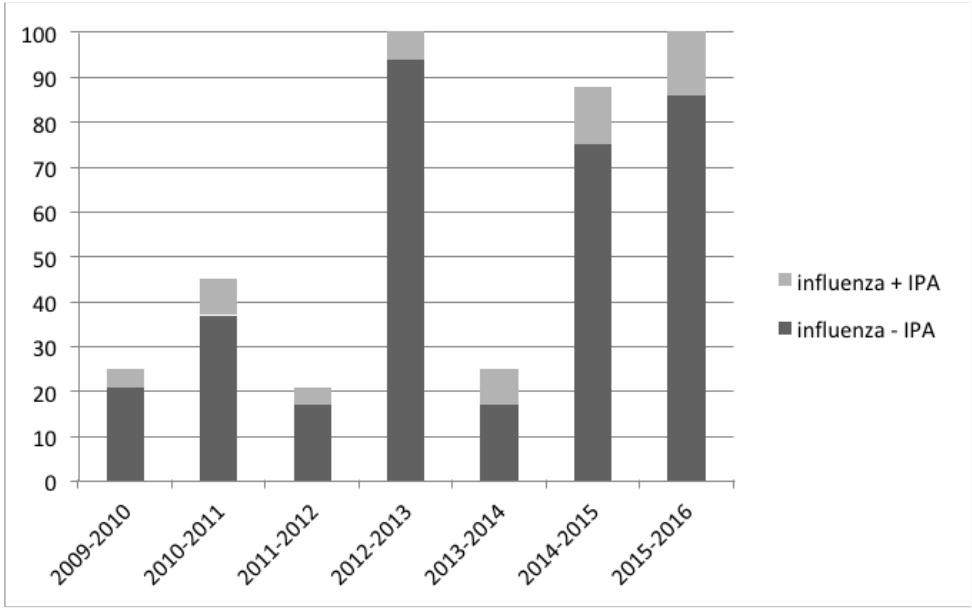
No medical history
influenza illness
admitted ICU

Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study



432 patients with influenza

83 invasive aspergillosis



Schauwvlieghe et al. 2018

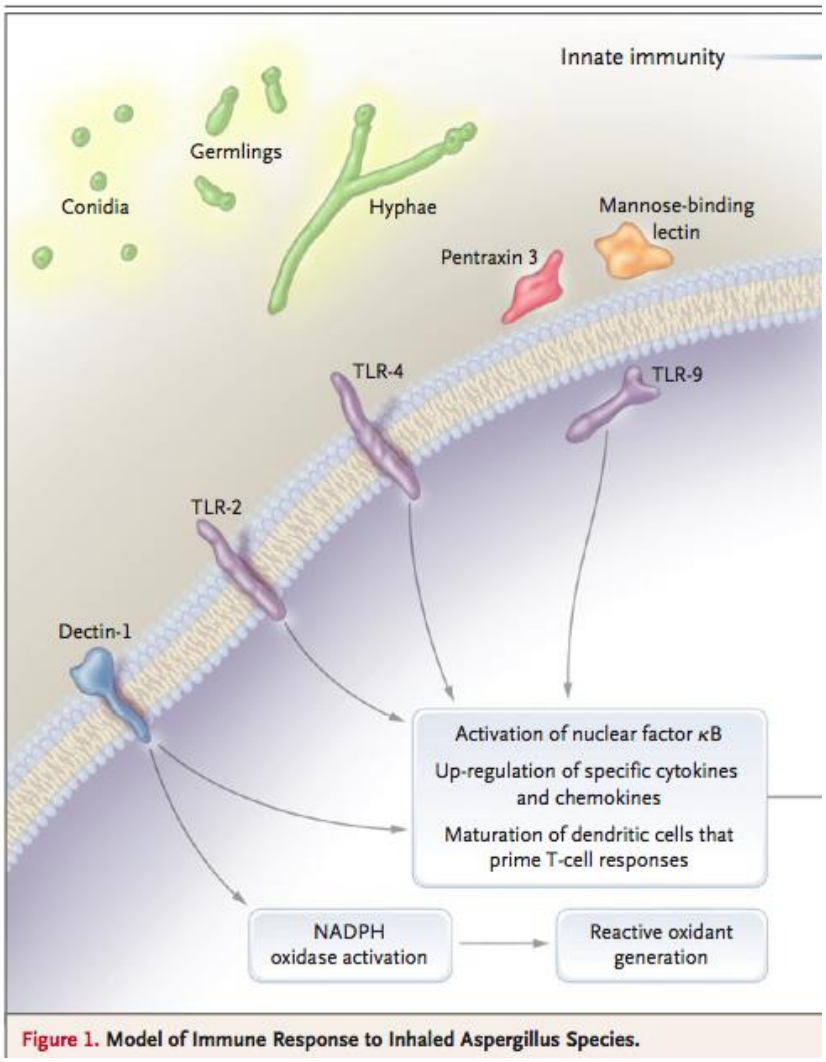


Figure 1. Model of Immune Response to Inhaled Aspergillus Species.

Host defense

Neutrophils

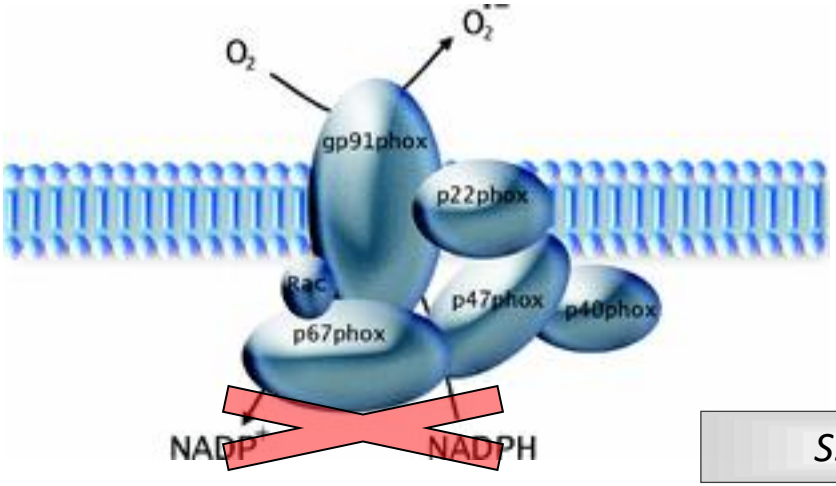
Pattern recognition

Cytokines/chemokines

NADPH-oxidase complex

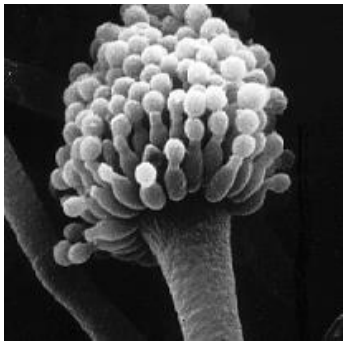
Chronic granulomateus disease (CGD)

Generation of
reactive oxygen species (ROS)

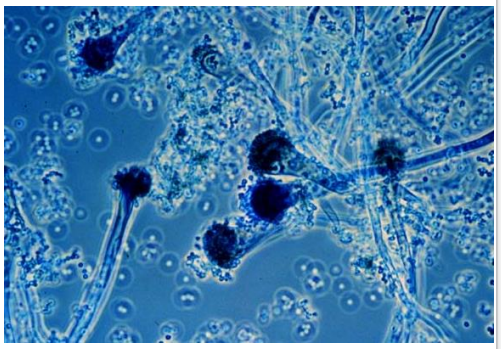


Mutation in NADPH
oxidase

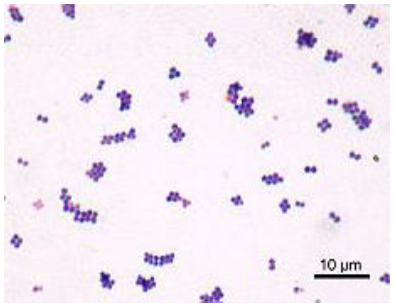
Aspergillus fumigatus



Aspergillus nidulans



S. aureus



NADPH-oxidase in IAPA

J Immunol. 2014 Apr 1;192(7):3301-7. doi: 10.4049/jimmunol.1303049. Epub 2014 Feb 21.

Influenza Infection Suppresses NADPH Oxidase-Dependent Phagocytic Bacterial Clearance and Enhances Susceptibility to Secondary Methicillin-Resistant Staphylococcus aureus Infection.

Sun K[1], Metzger DW.

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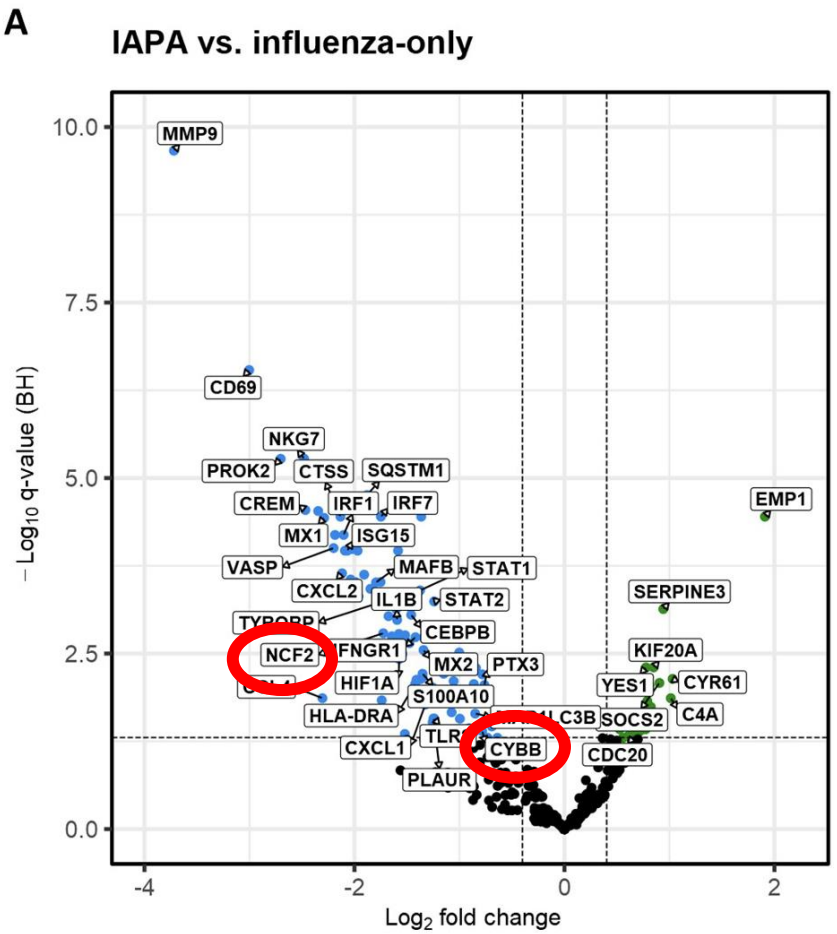

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The New England
Journal of Medicine

Volume 324 FEBRUARY 21, 1991 Number 8

A CONTROLLED TRIAL OF INTERFERON GAMMA TO PREVENT INFECTION IN CHRONIC GRANULOMATOUS DISEASE

THE INTERNATIONAL CHRONIC GRANULOMATOUS DISEASE COOPERATIVE STUDY GROUP*

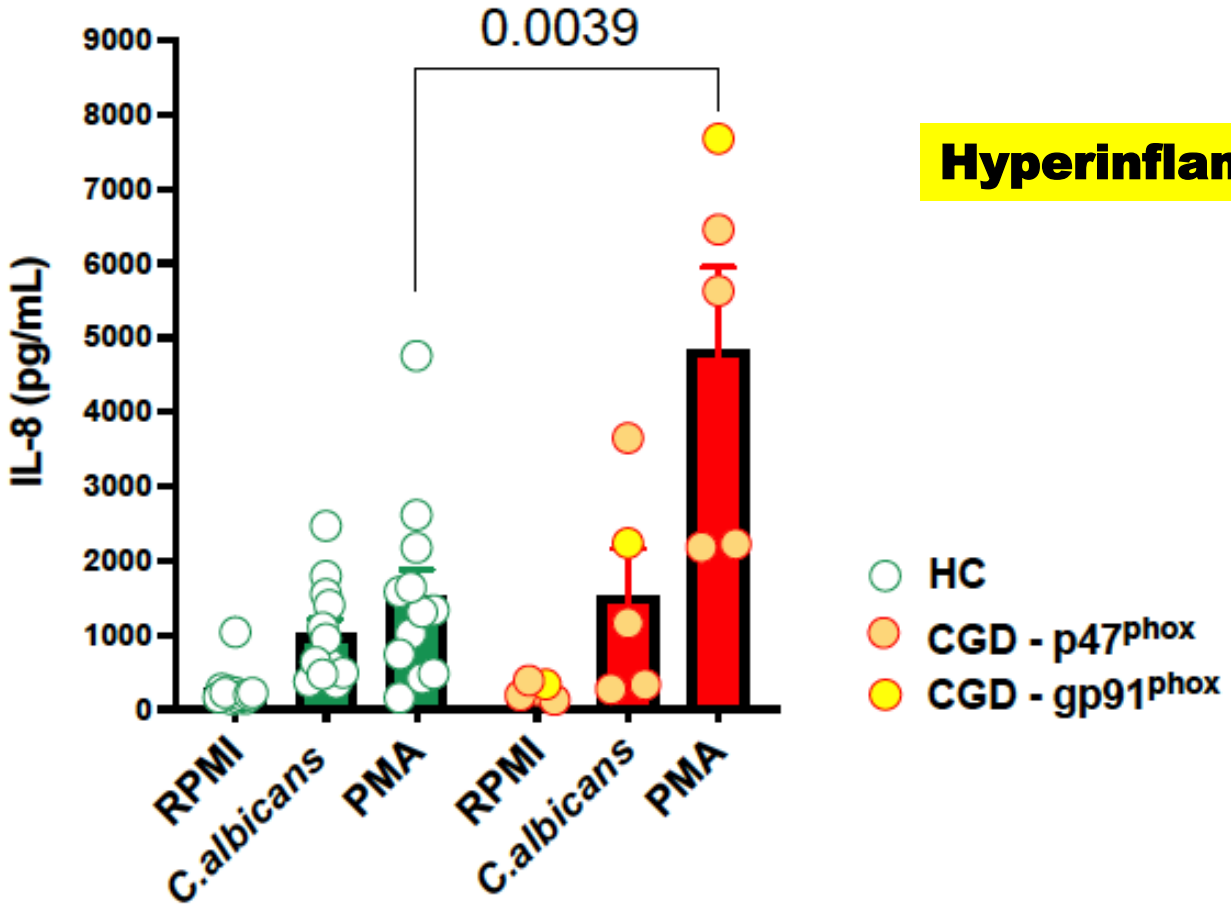
Abstract *Background.* Chronic granulomatous disease is an uncommon inherited disorder of phagocytes in which defective production of the reactive intermediates of oxygen predisposes patients to recurrent and severe pyogenic infections. Evidence from in vitro and in vivo studies indicates that interferon gamma can partially correct the metabolic defect in phagocytes. We assessed the efficacy of interferon gamma in decreasing the frequency of serious infections in patients with this disease.

Methods. We conducted a randomized, double-blind, placebo-controlled study in 128 patients with chronic granulomatous disease (median age, 15 years). Patients received interferon gamma (50 μg per square meter of body-surface area) or placebo subcutaneously, three times a week for up to a year. The primary end point of the study was the time to the first serious infection, defined as an event requiring hospitalization and parenteral antibiotics. Measures of phagocyte function were also monitored.

Results. In terms of the time to the first serious infection, there was a clear benefit from interferon as compared with placebo ($P = 0.0006$). Of the 63 patients assigned to interferon, 14 had serious infections, as compared with 30 of the 65 patients assigned to placebo ($P = 0.002$). There was also a reduction in the total number of serious infections — 20 with interferon as compared with 56 with placebo ($P<0.0001$). Interferon was beneficial regardless of age, the use or nonuse of prophylactic antibiotics, and the mode of inheritance (X-linked or autosomal recessive). However, there were no significant changes in the measures of superoxide production by phagocytes. Interferon therapy was well tolerated, and there was no evidence of serious toxicity.

Conclusions. For patients with chronic granulomatous disease, interferon gamma therapy is an effective and well-tolerated treatment that reduces the frequency of serious infections. (N Engl J Med 1991; 324:509-16.)

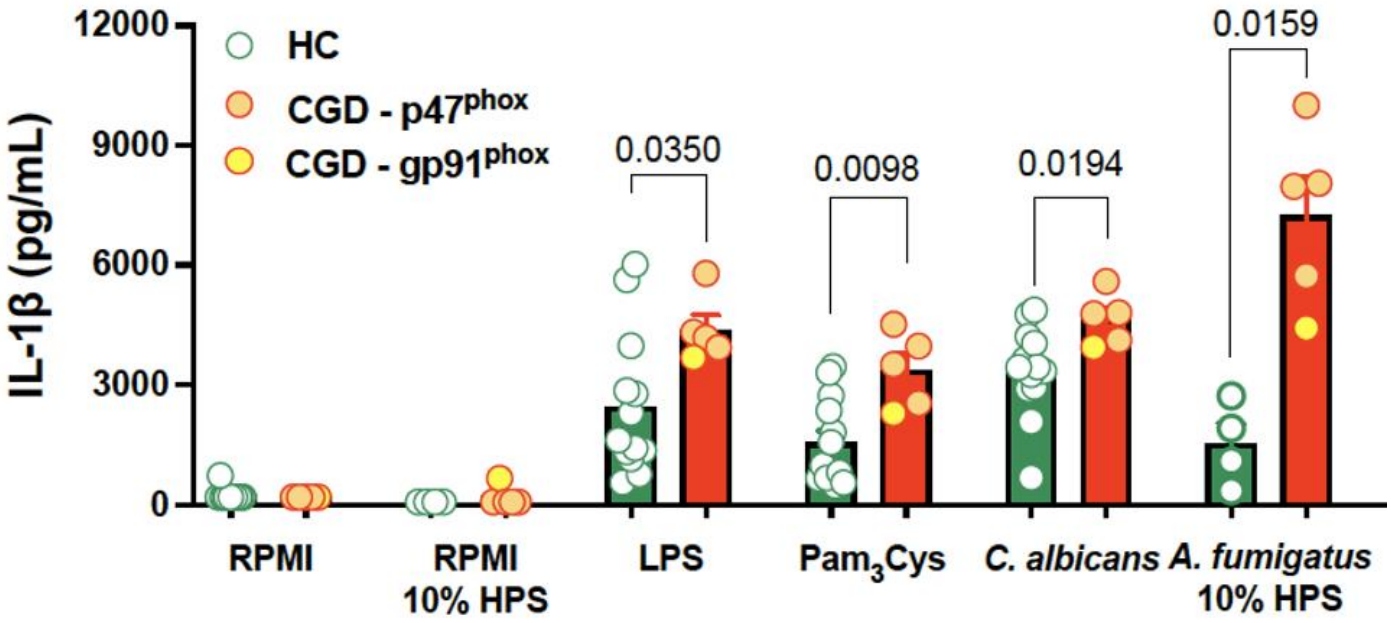
NADPH-oxidase (neutrophils)



Hyperinflammatory

Paradox in CGD (monocytes)

Hyperinflammatory



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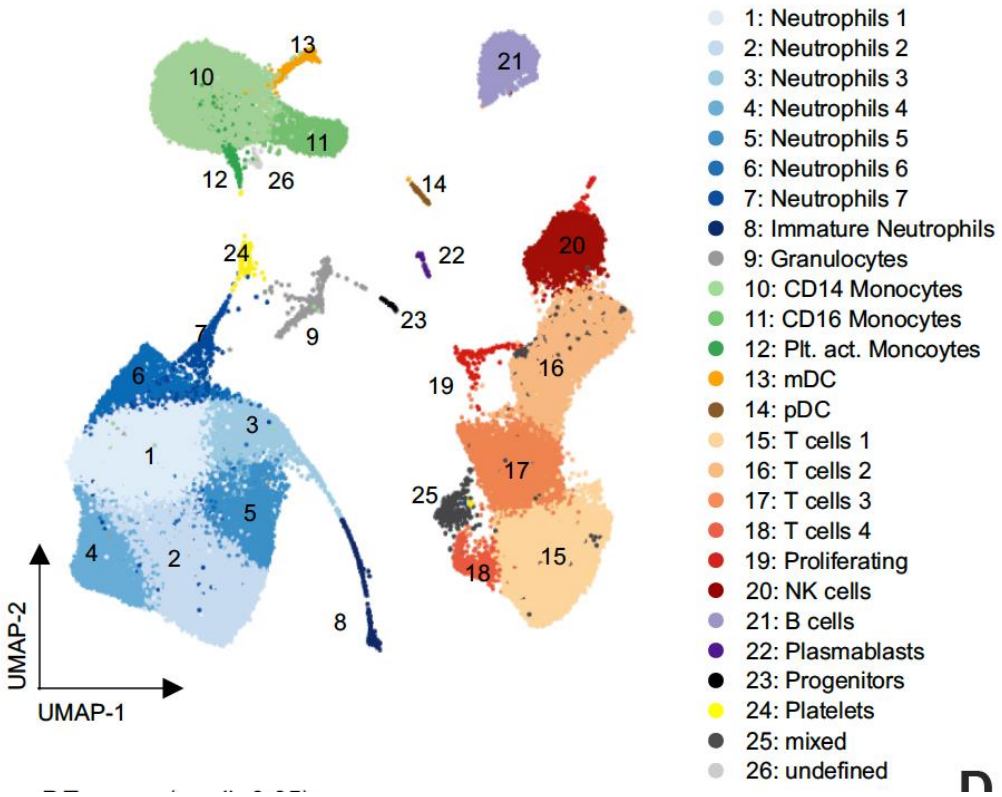
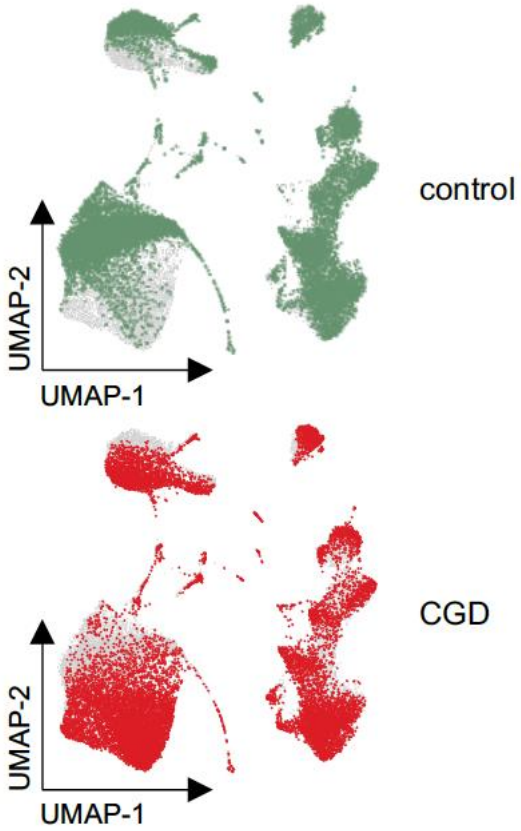
Paradox in CGD





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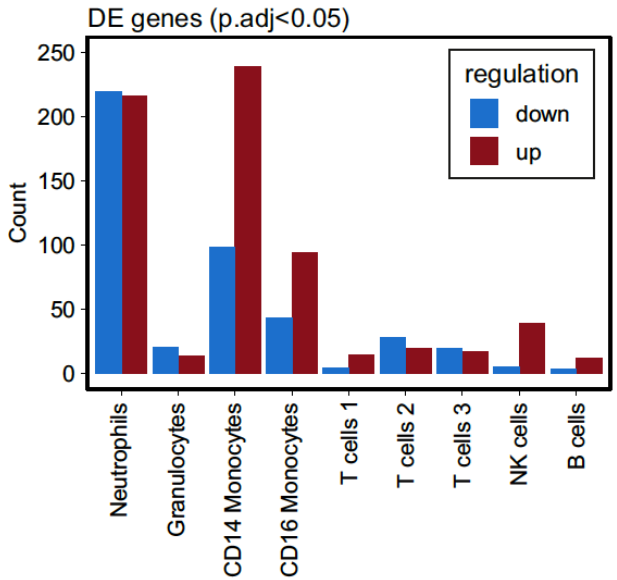
Paradox in CGD



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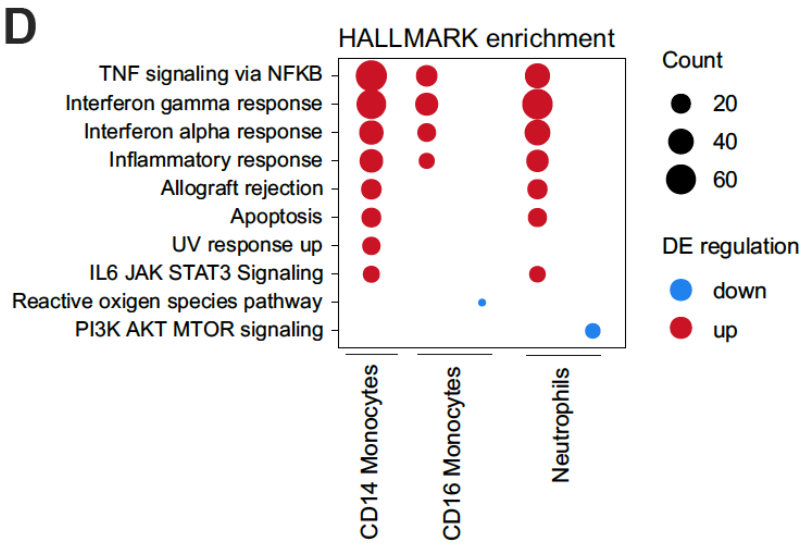

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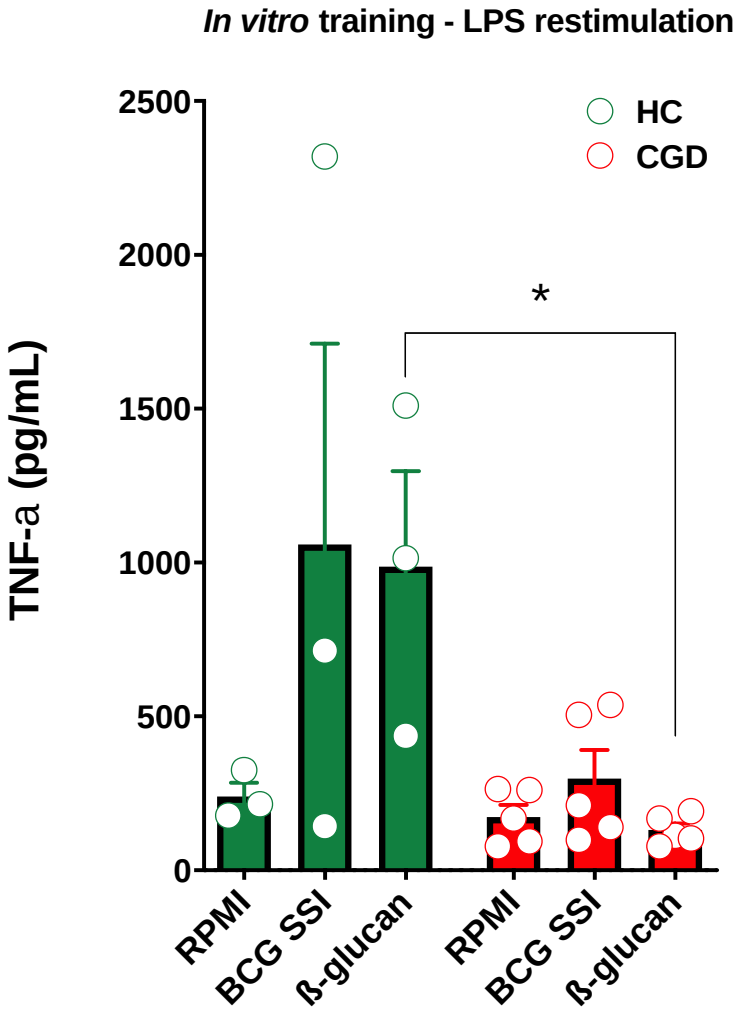
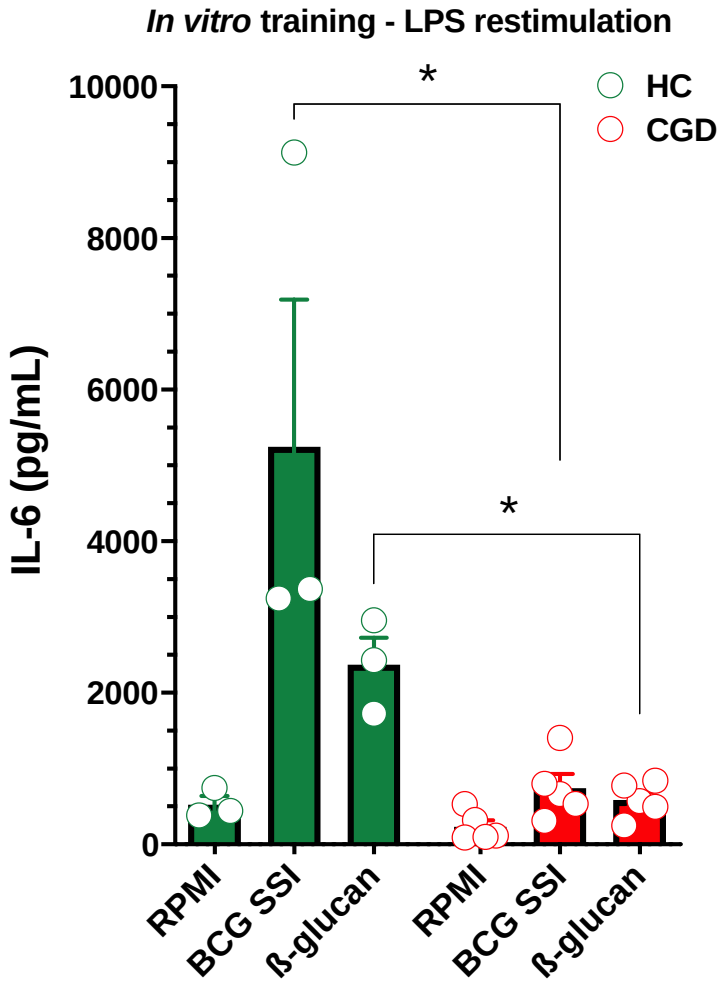
Trained immunity in CGD





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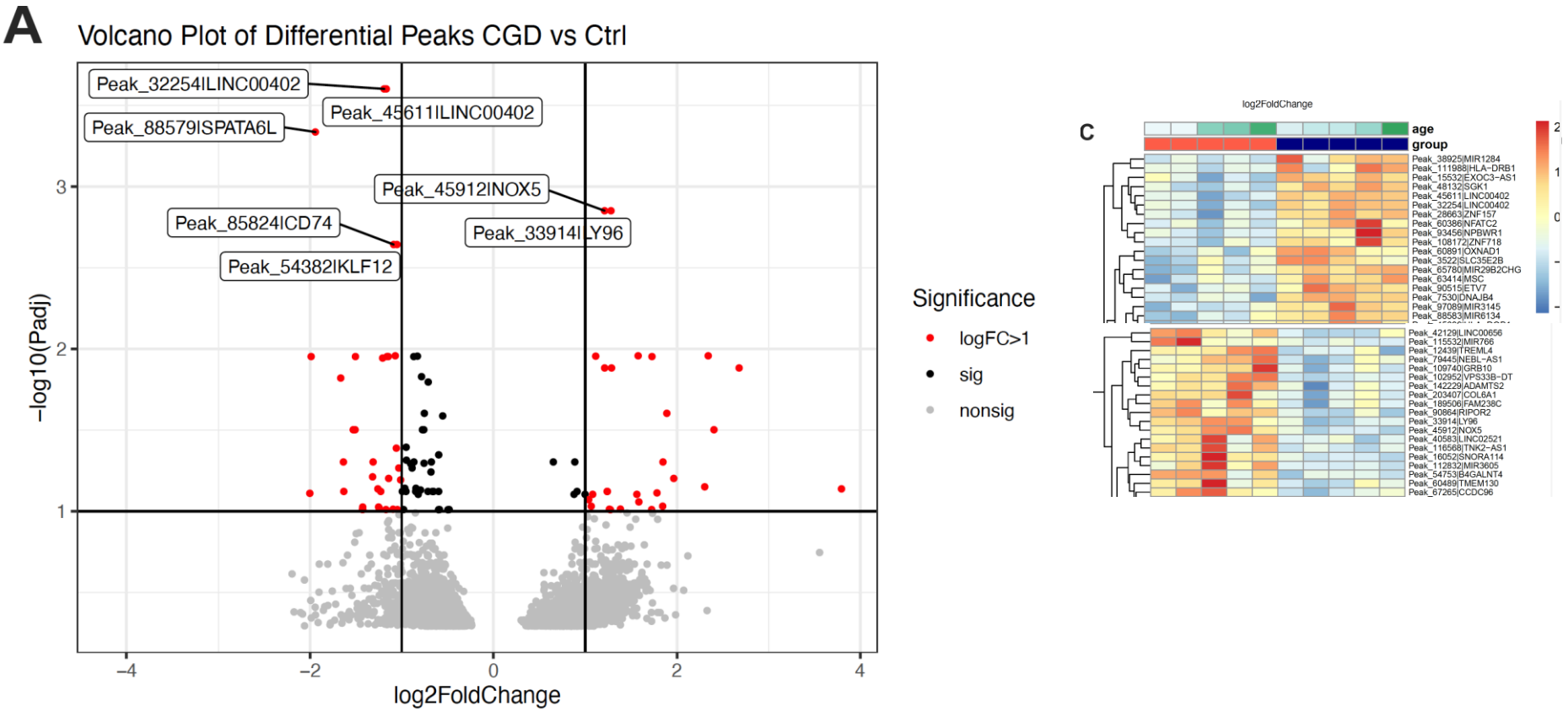
Epigenetic dysregulation in CGD



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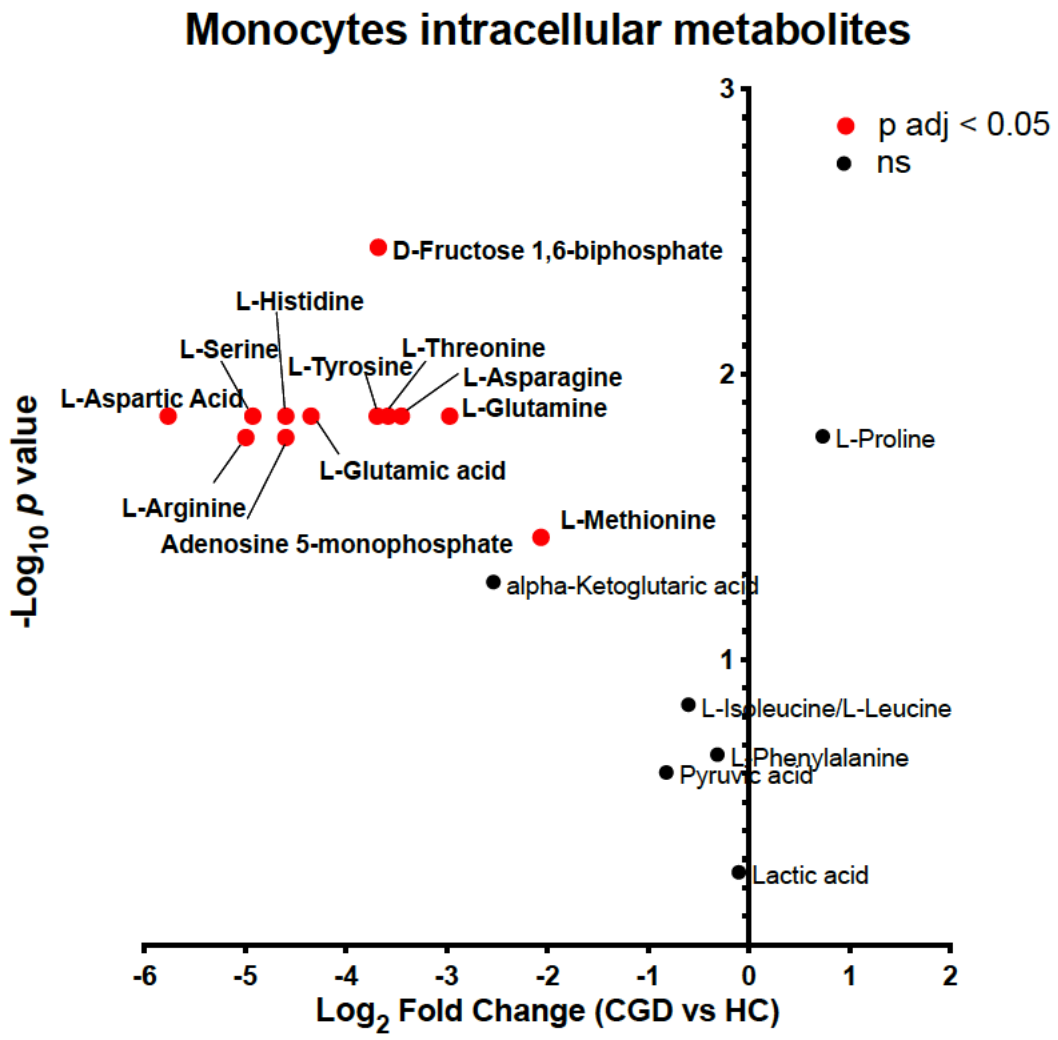
Metabolome in CGD



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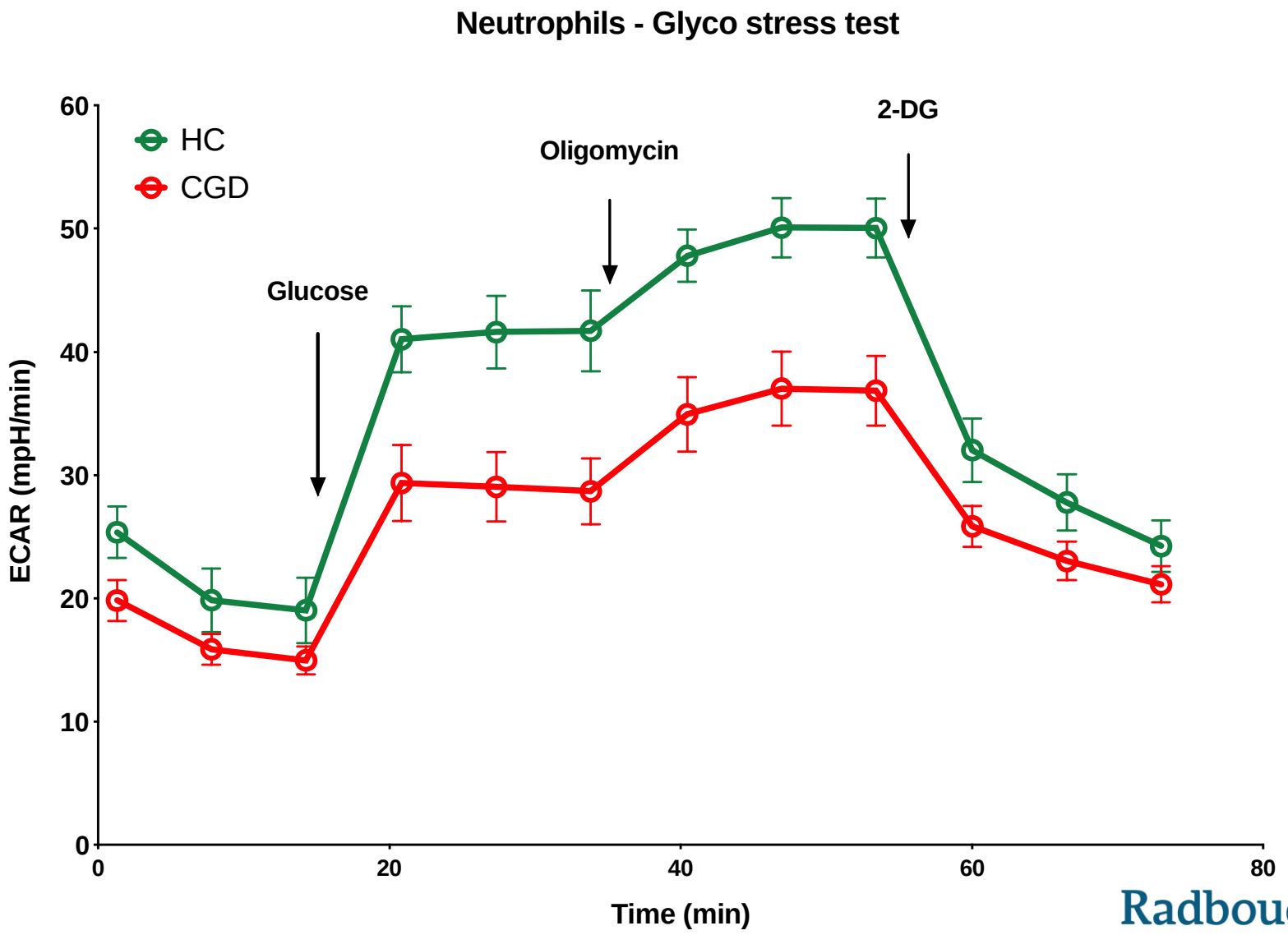
glycolysis in CGD neutrophils



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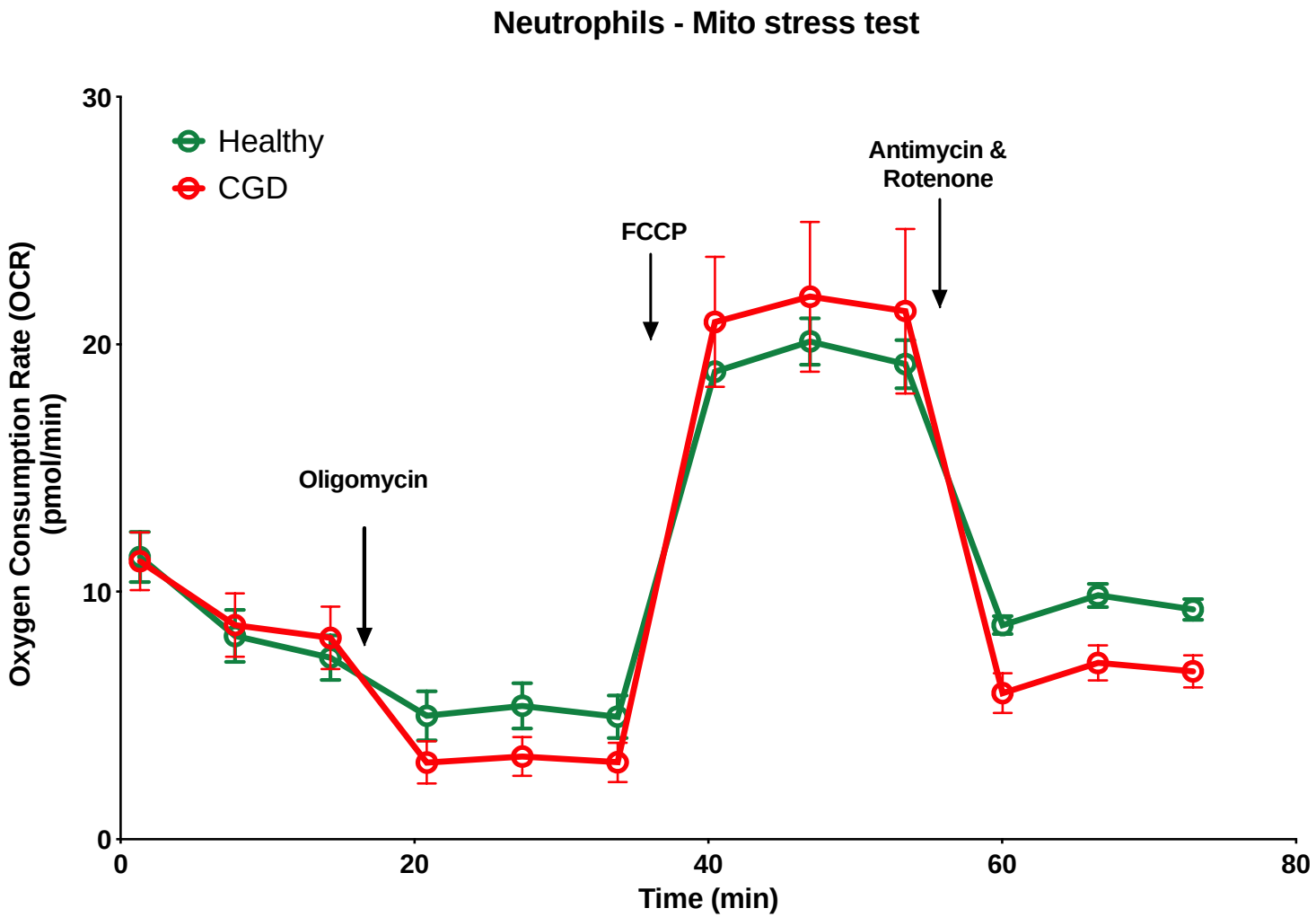
Mitochondrial respiration CGD neutrophils



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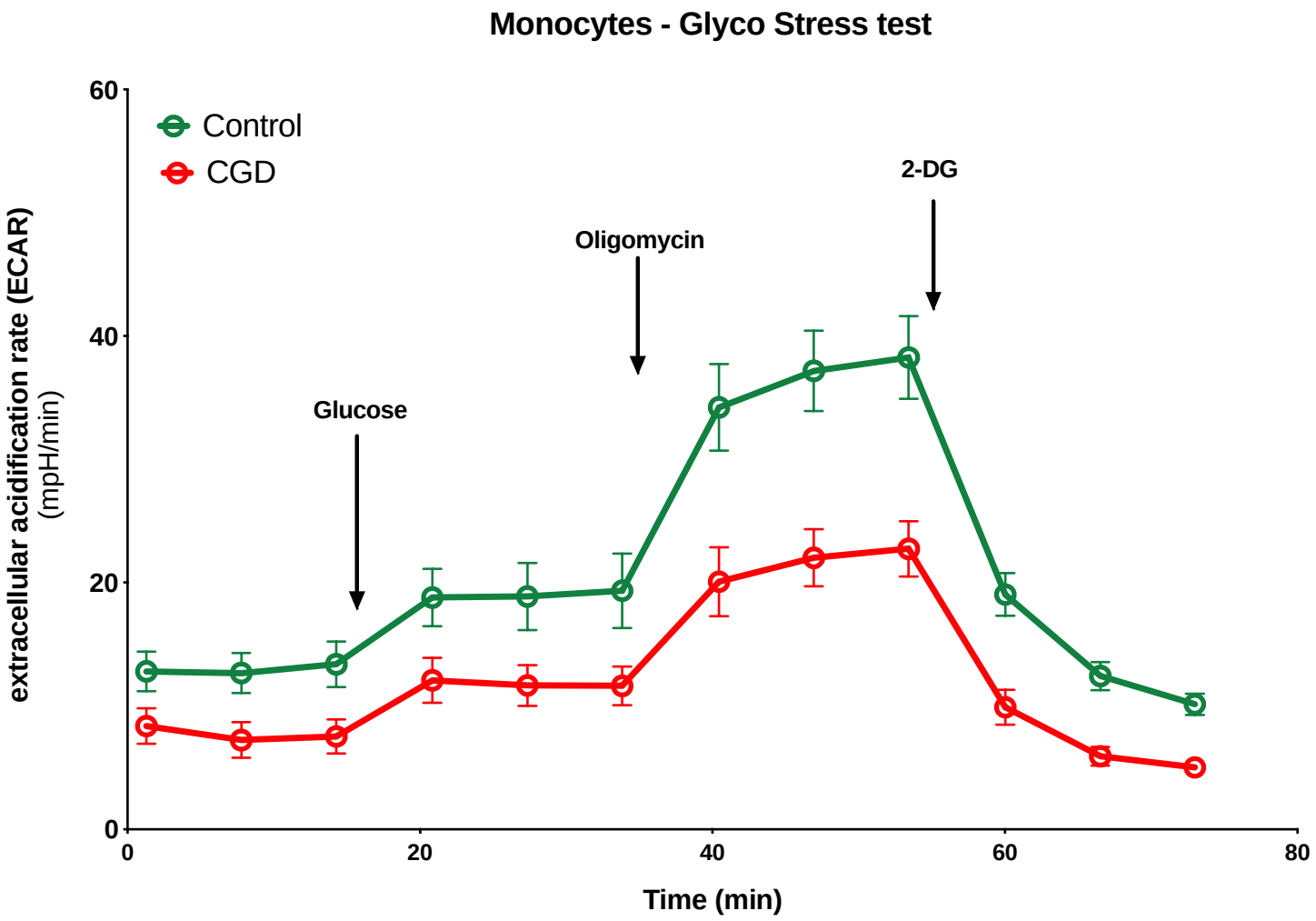
Glycolysis in CGD monocytes



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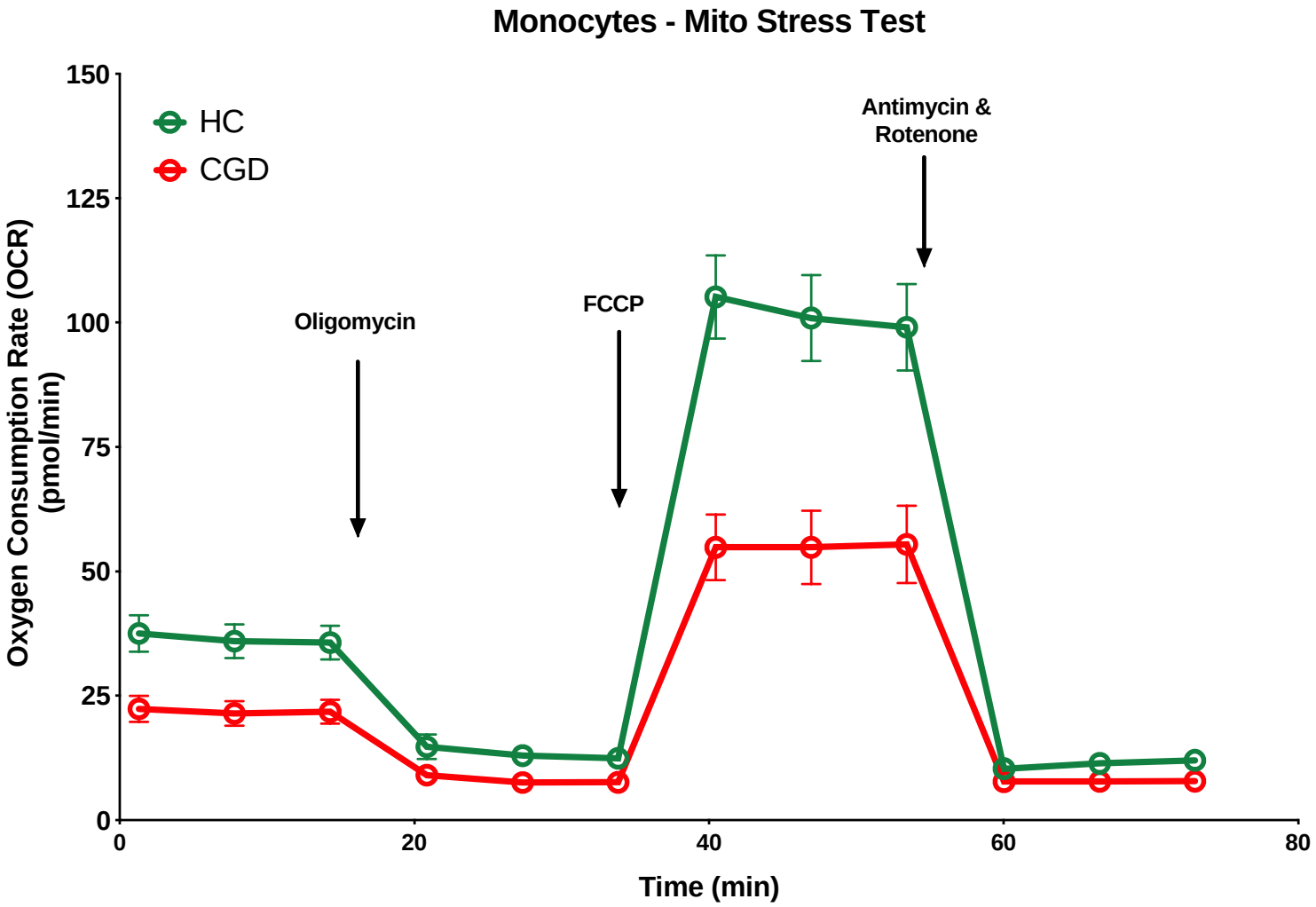
Mitochondrial respiration CGD monocytes



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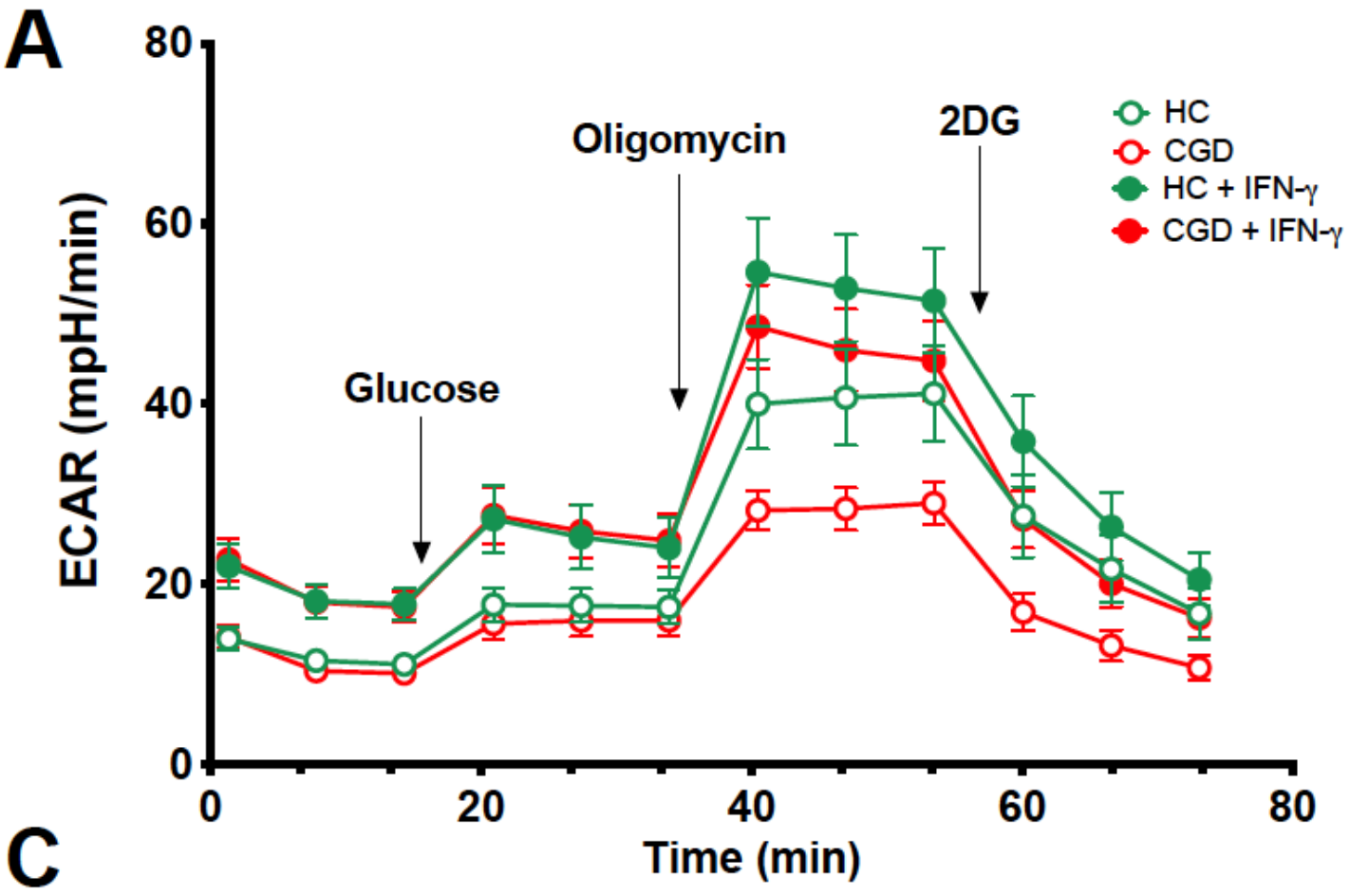
What is the effect of Interferon gamma (IFNγ)?

IFNγ restores metabolic function in CGD



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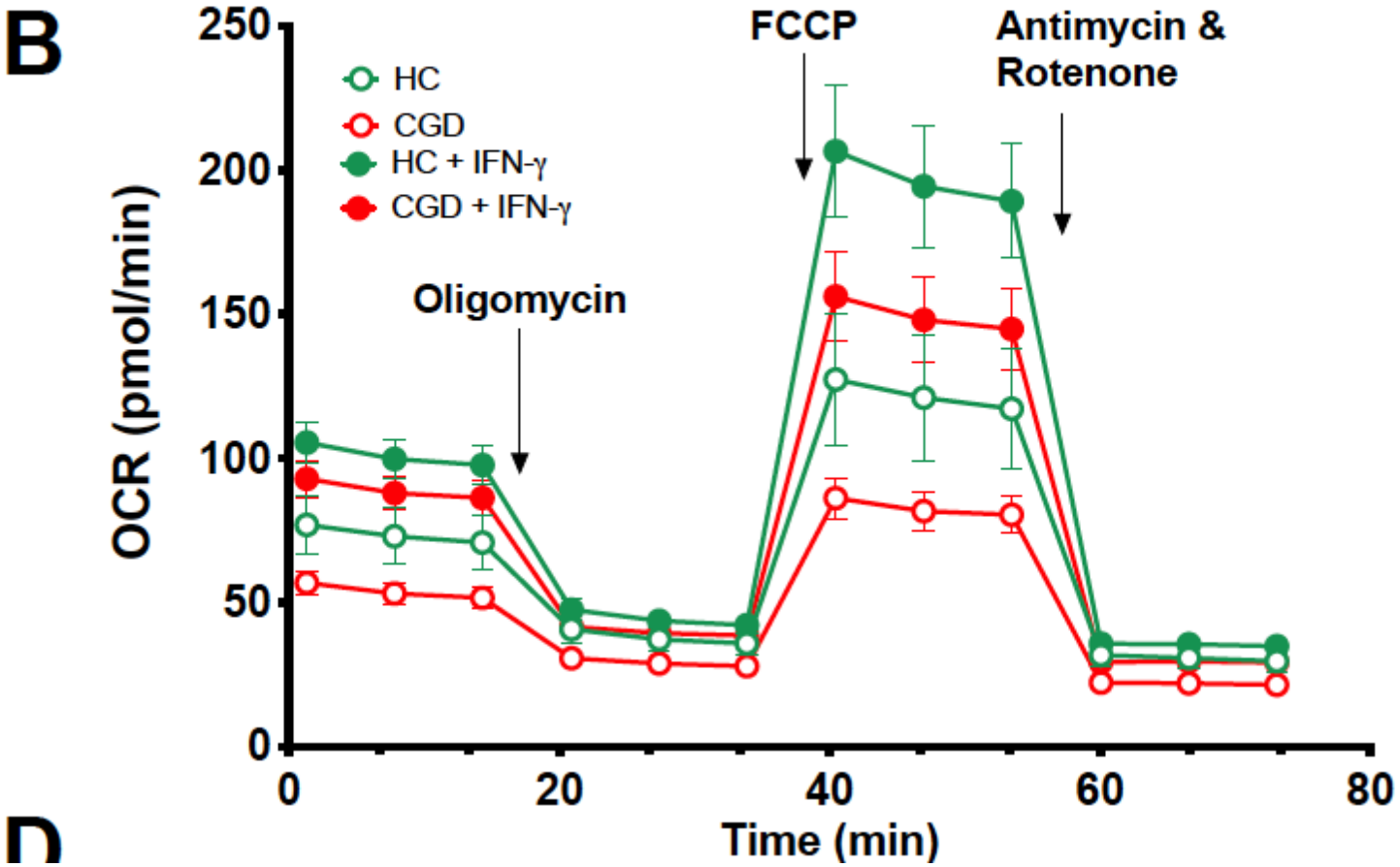
IFNγ restores metabolic function in CGD



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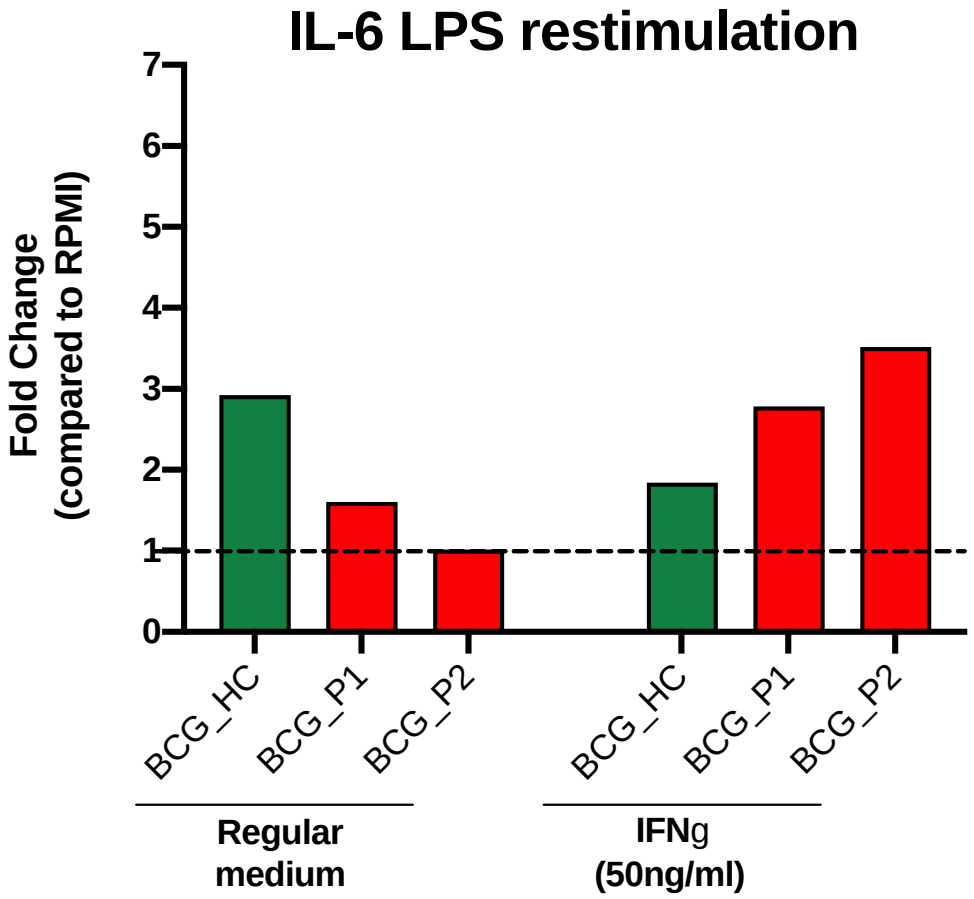
IFNγ restores training in CGD



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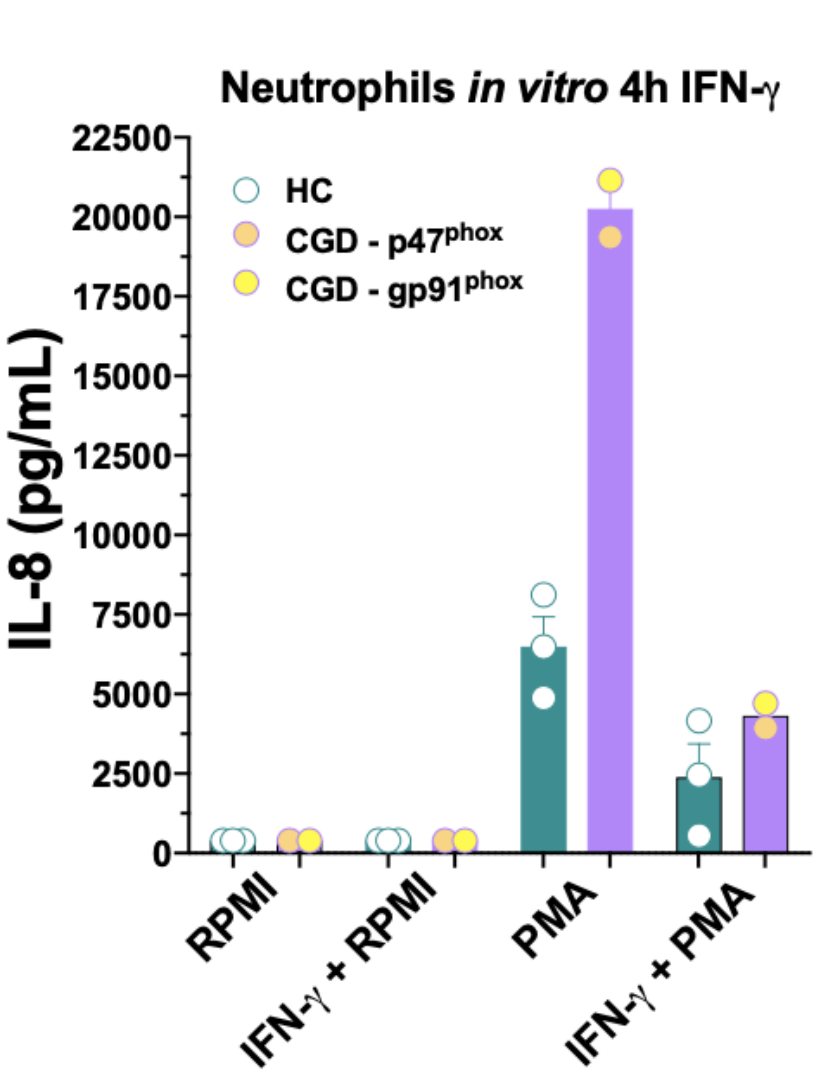
IFNγ restores in CGD

I



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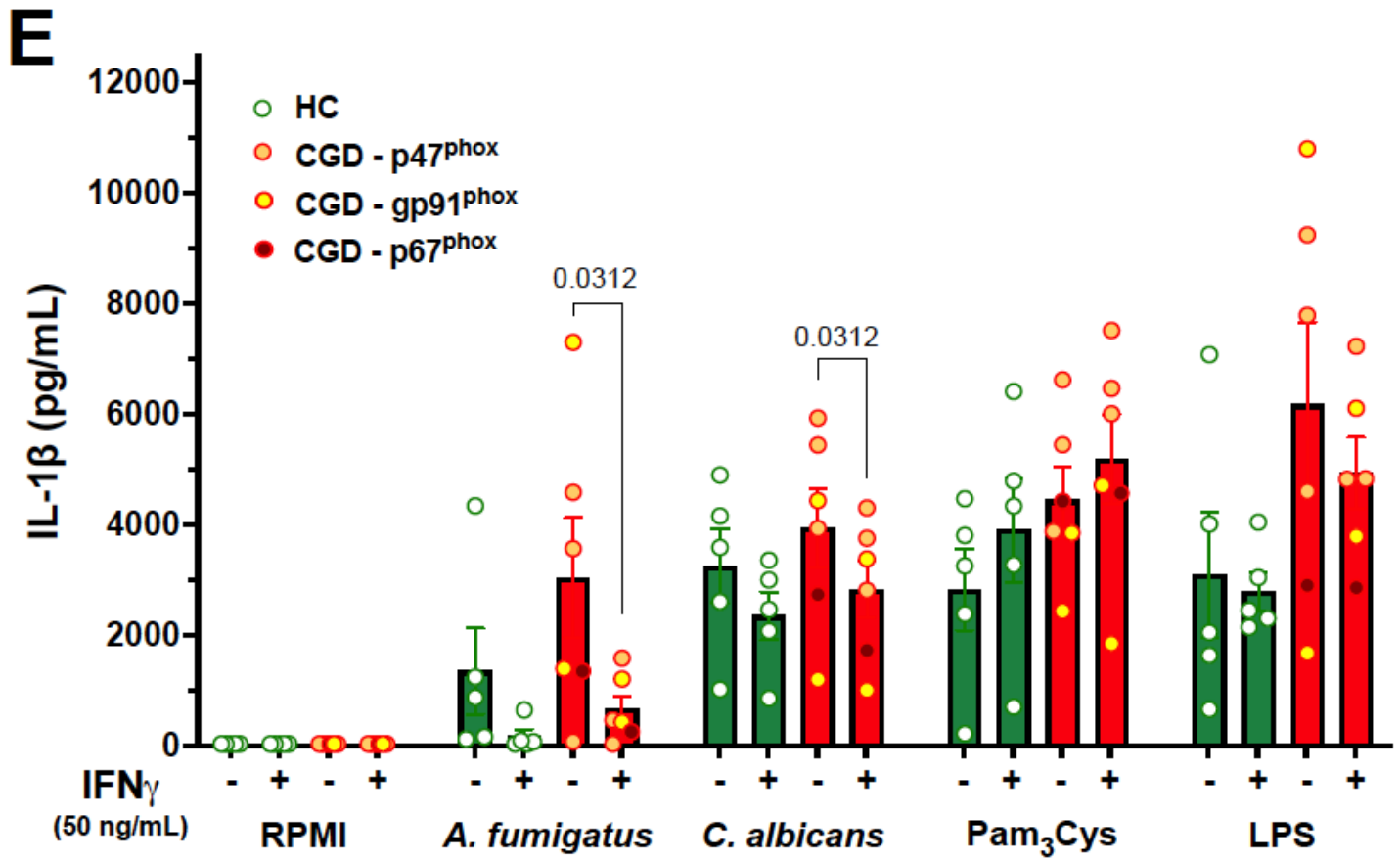
IFNγ restores in CGD



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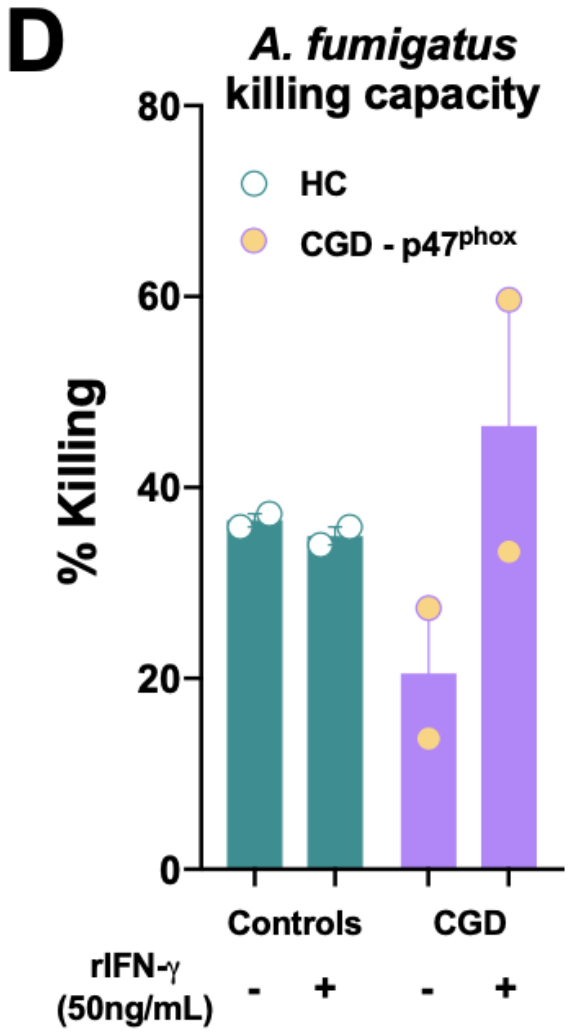
IFNγ restores in CGD



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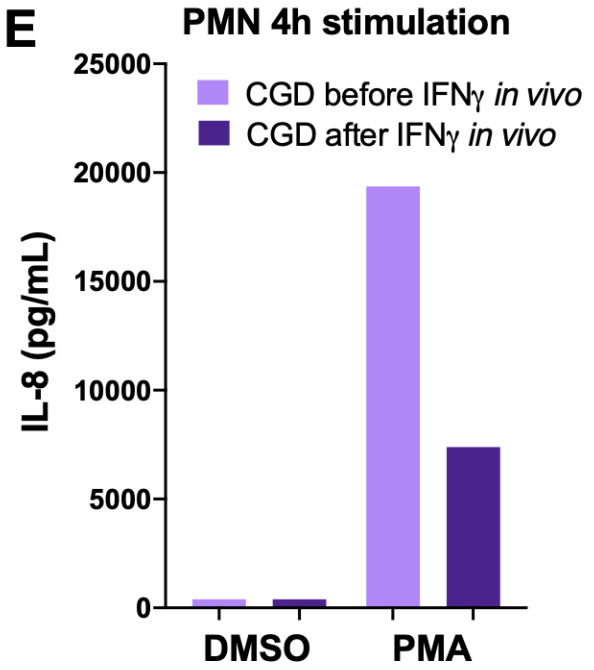
IFNγ in vivo CGD



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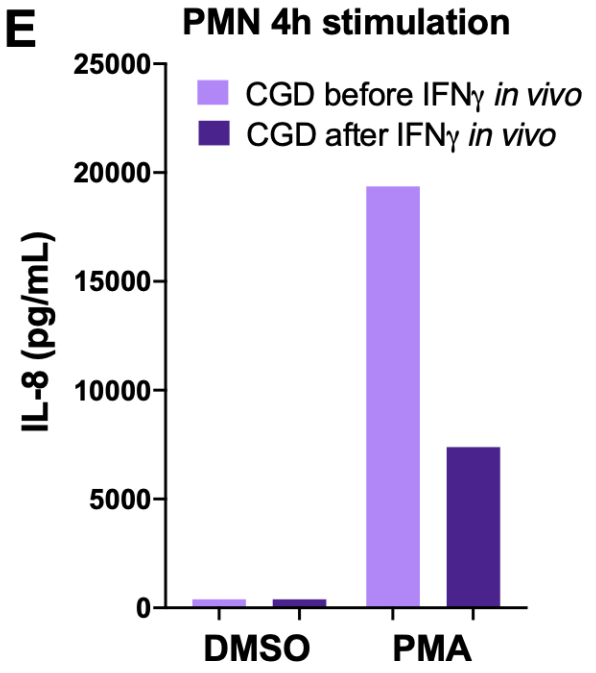
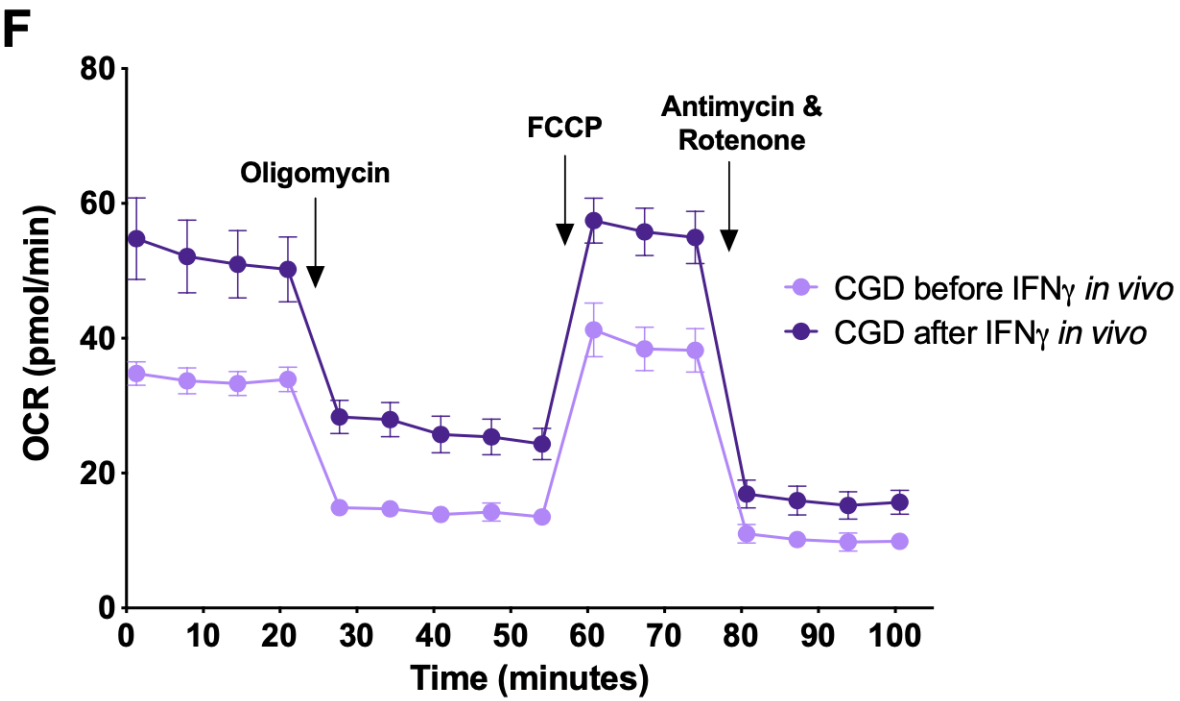
IFNγ in vivo CGD





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Conclusions 2

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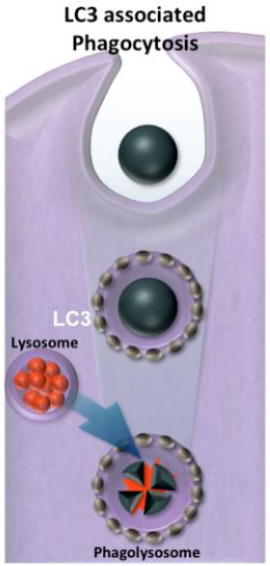
- IFNγ can restore killing and immunedysregulation
- Effects on immunometabolism innate cells
- Rapid effect in vivo (but short lasting) on innate
- Option for treating IAPA?

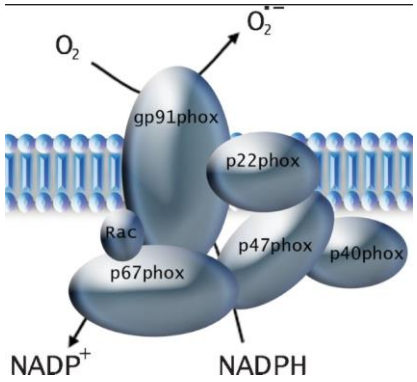
A role for anakinra?

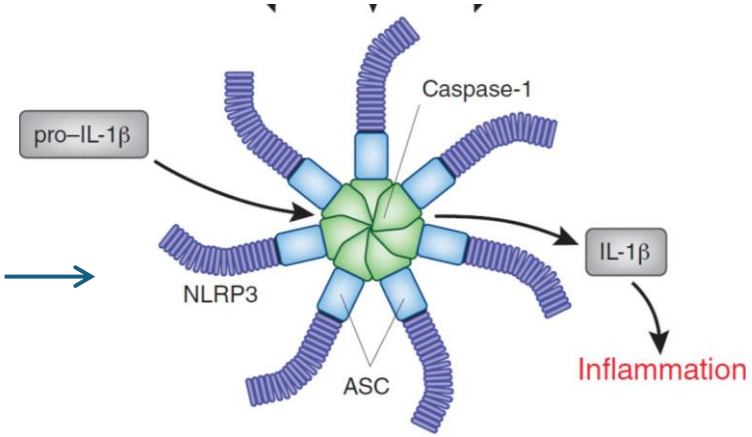
J Immunol. 2014 Apr 1;192(7):3301-7. doi: 10.4049/jimmunol.1303049. Epub 2014 Feb 21.

Influenza Infection Suppresses NADPH Oxidase-Dependent Phagocytic Bacterial Clearance and Enhances Susceptibility to Secondary Methicillin-Resistant Staphylococcus aureus Infection.

Sun K[1], Metzger DW.







T

Increased susceptibility aspergillosis

Hyper activation inflammasome with high IL-1 (MAS)

Inflammasome and IL-1 in CGD

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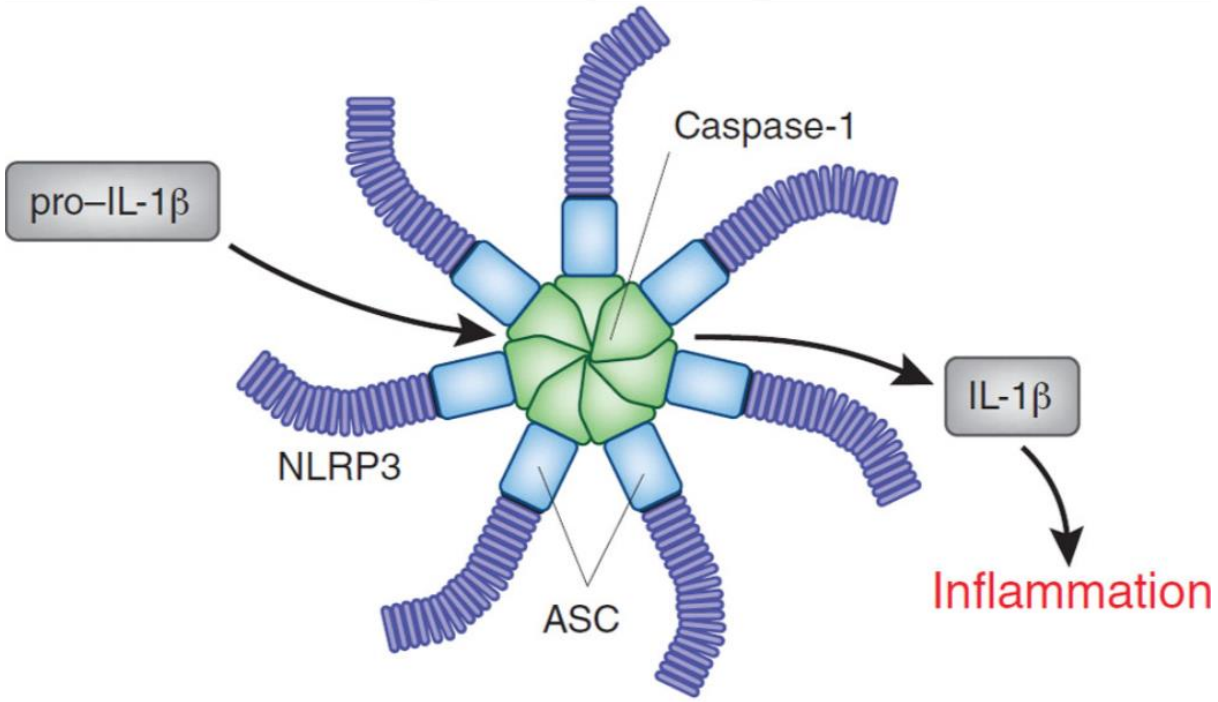
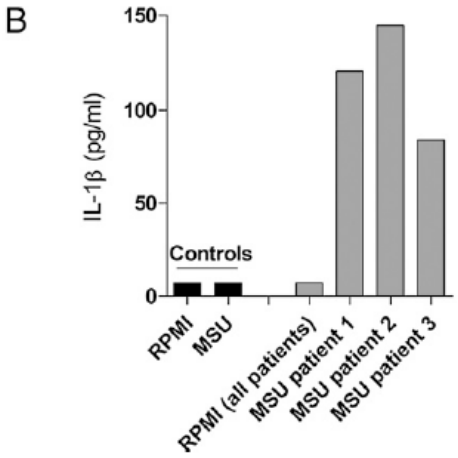
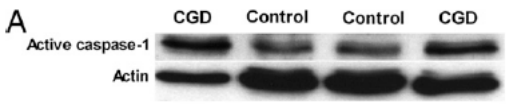
Hyperinflammation



Increased IL-1

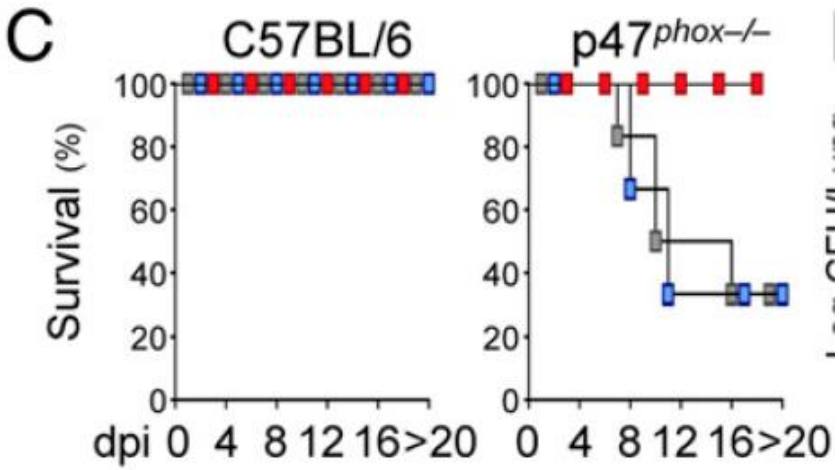


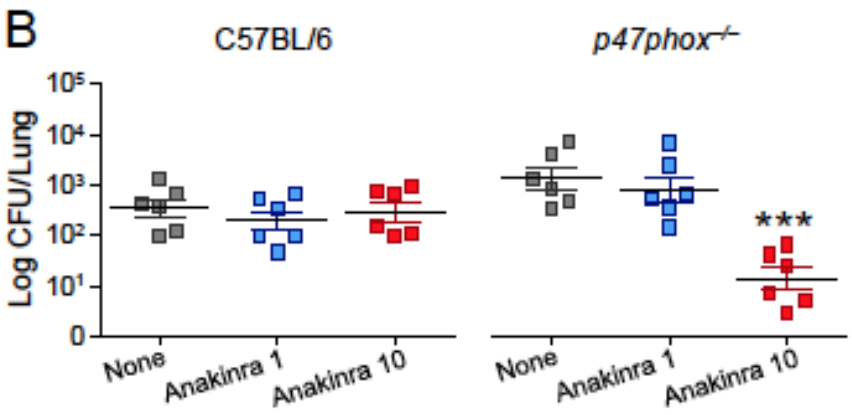


PNAS

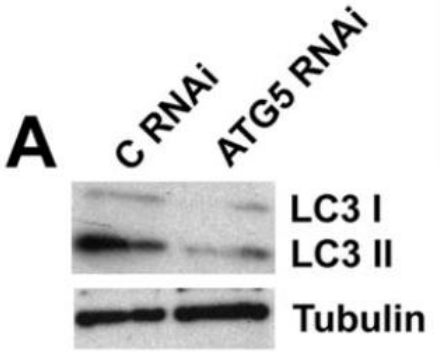
IL-1 receptor blockade restores autophagy and reduces inflammation in chronic granulomatous disease in mice and in humans

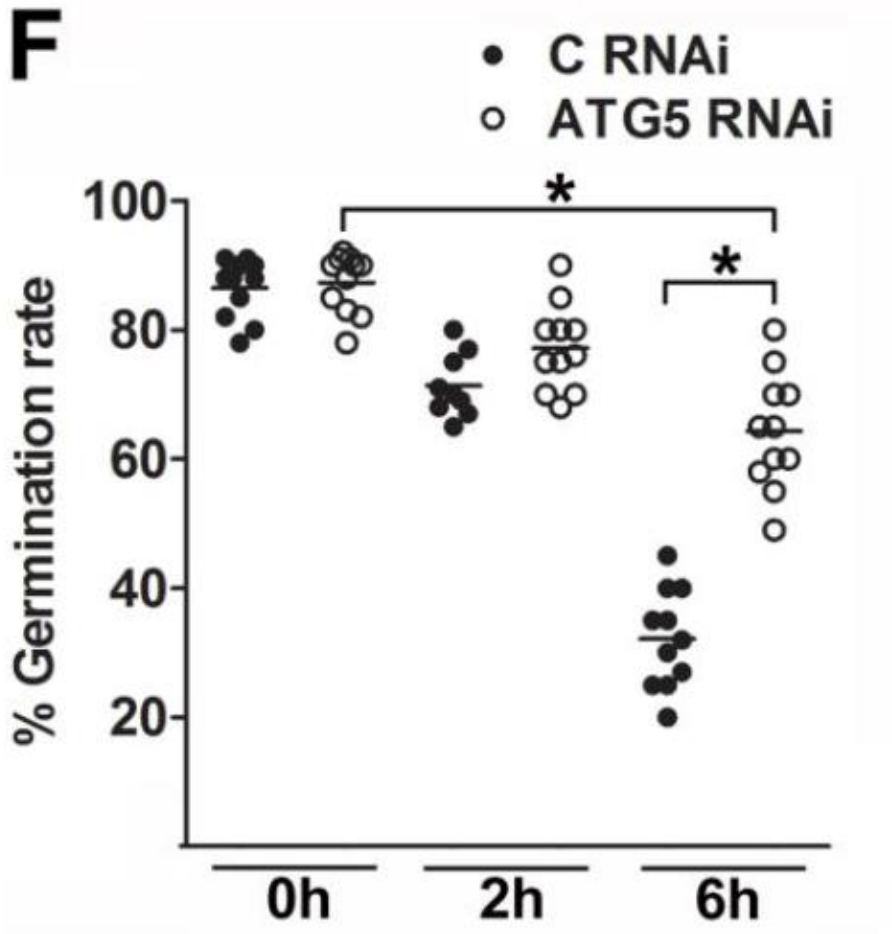
Antonella de Luca[a,1], Sanne P. Smeekens[b,c,1], Andrea Casagrande[a], Rossana Iannitti[a], Kara L. Conway[d], Mark. S. Gresnigt[b,c], Jakob Begun[d], Theo S. Plantinga[b,c], Leo A. B. Joosten[b,c], Jos W. M. van der Meer[b,c], Georgios Chamilos[e], Mihai G. Netea[b,c], Ramnik J. Xavier[d,f], Charles A. Dinarello[b,c,f,2], Luigina Romani[a,3], and Frank L. van de Veerdonk[b,c,g,2,3]



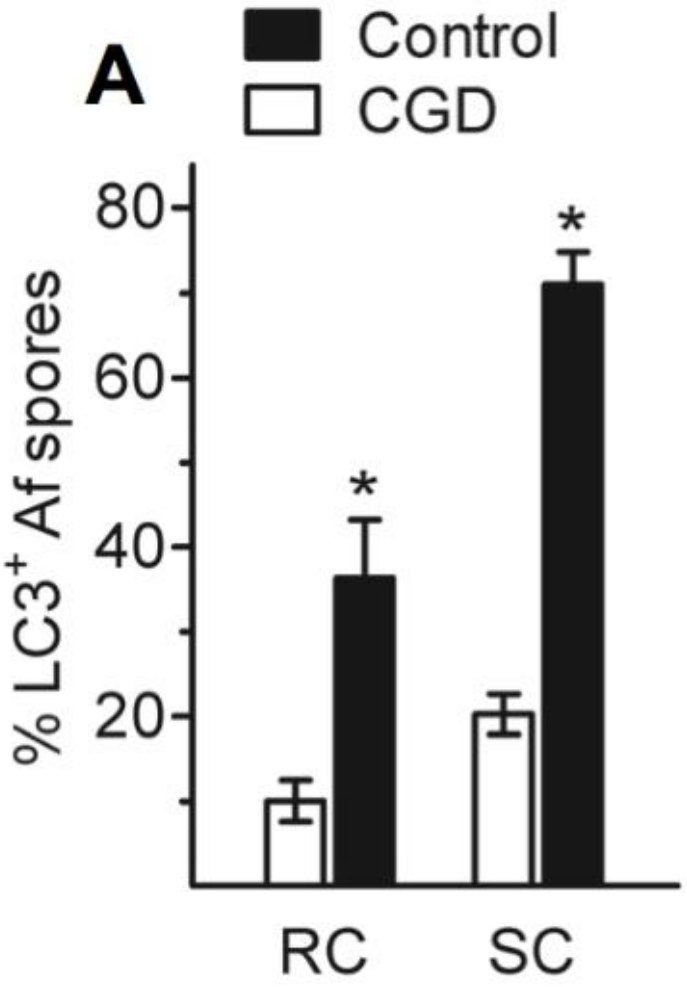


Autophagy important for killing aspergillus





Kyrmizi et al. 2013


A
Control
CGD
% LC3+ Af spores
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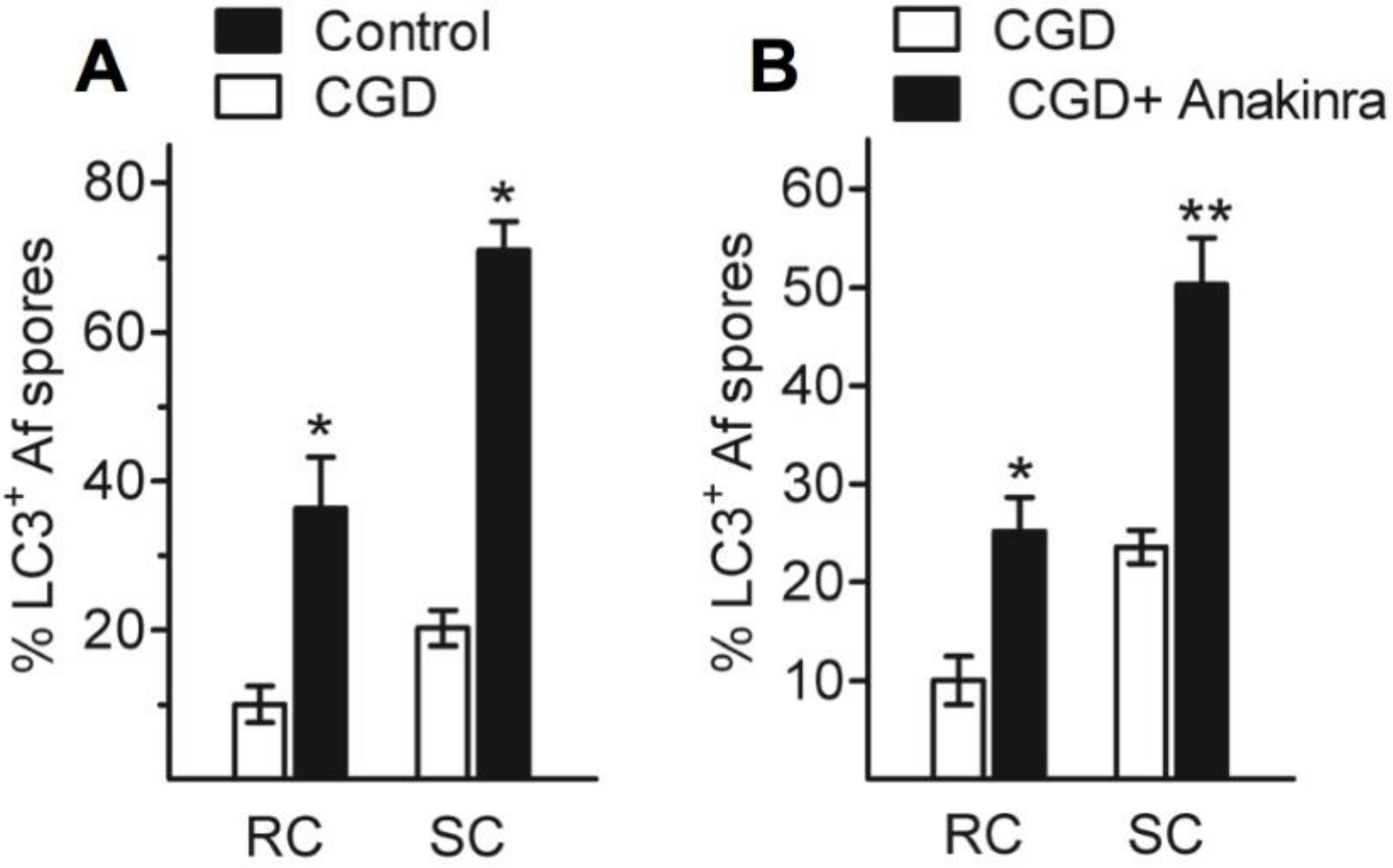
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% LC3+ Af spores
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RC
SC

IL-1 - Inflammasome and IAPA

Inflammasome IAPA

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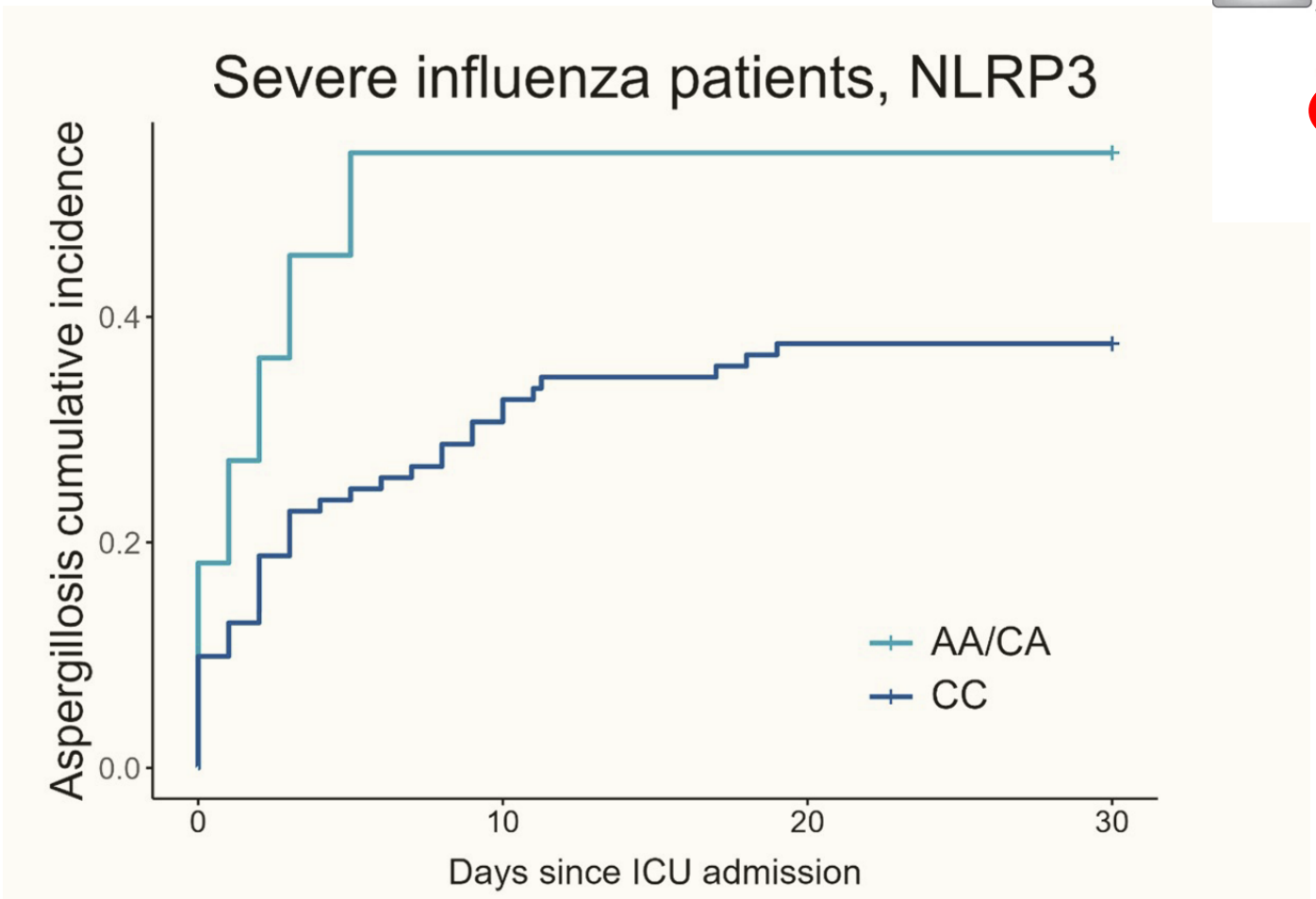
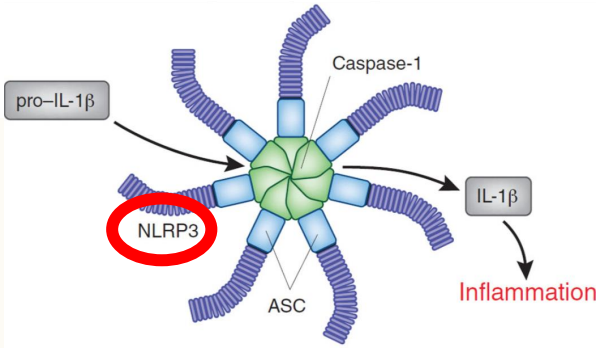
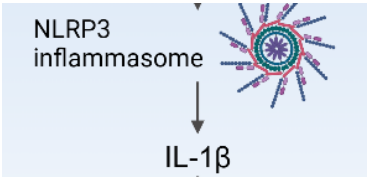


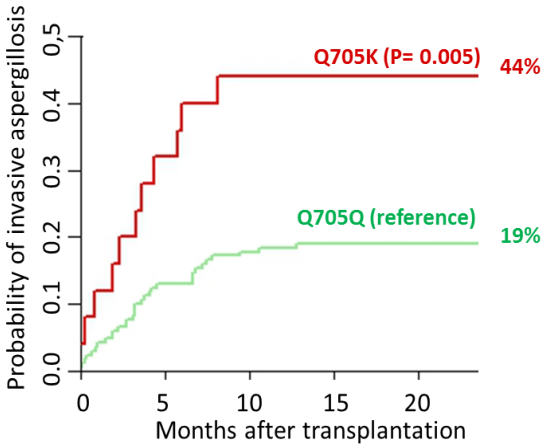


Q705K SNP in NLRP3 predisposes to IPA

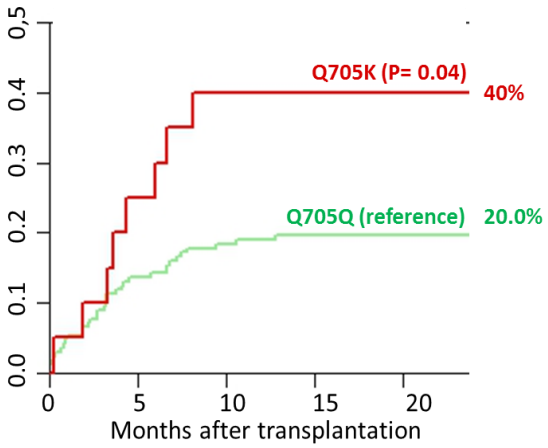


IFIGEN Cohort

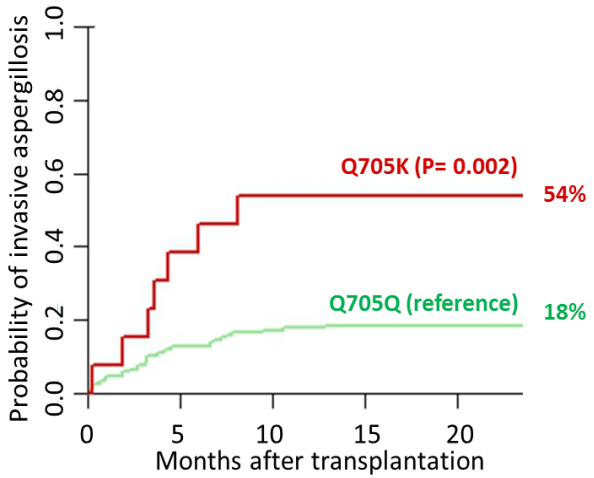
DONOR



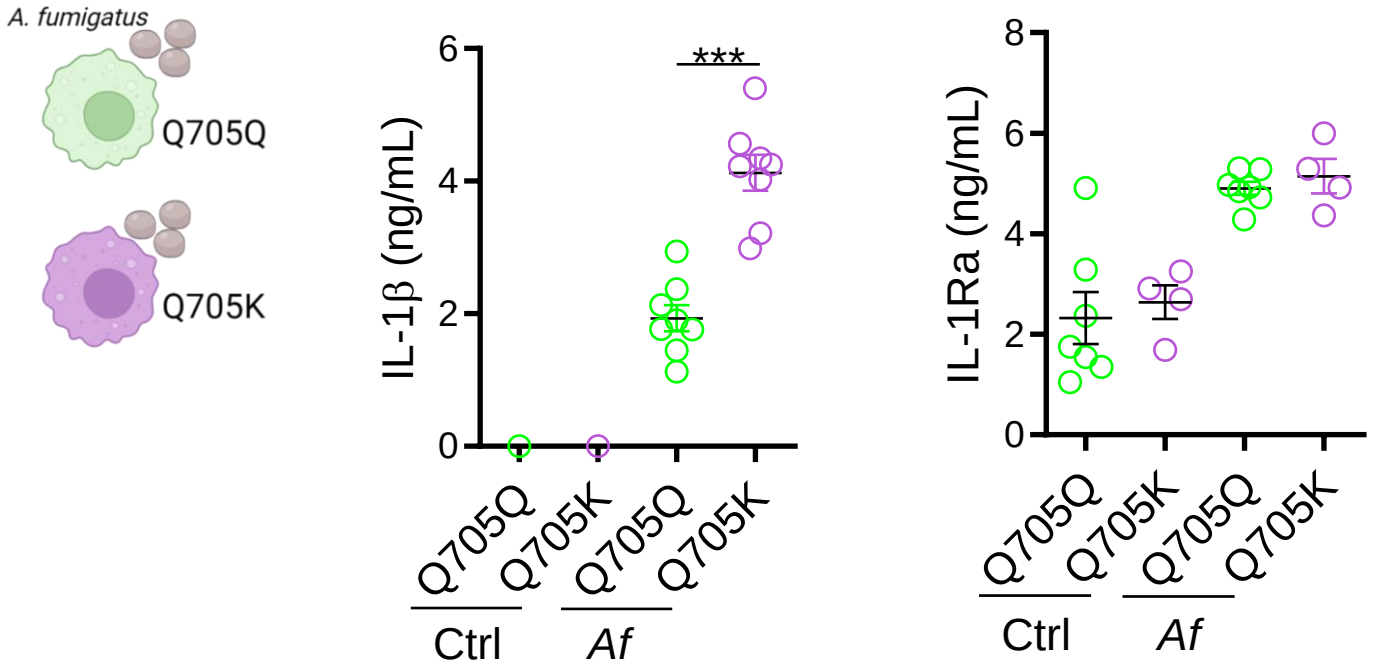
RECIPIENT



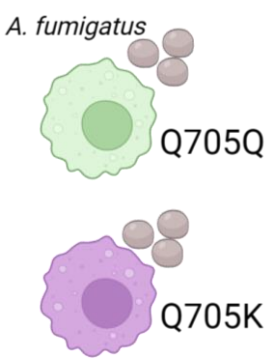
DONOR + RECIPIENT

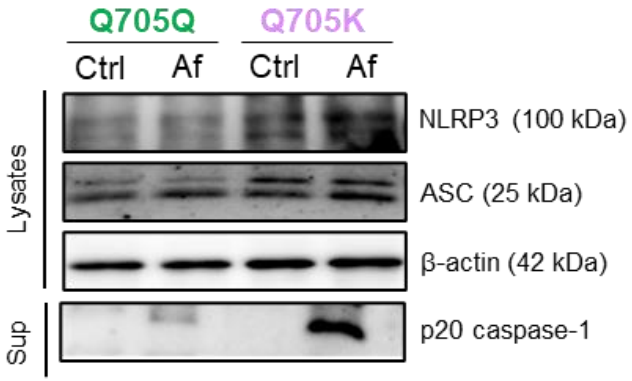


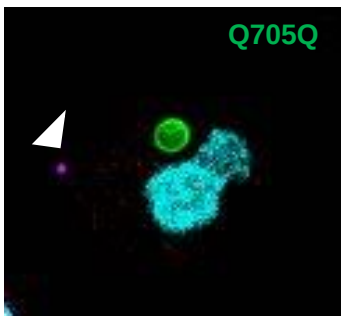
Q705K SNP underlies an hyperactivation of the NLRP3 inflammasome

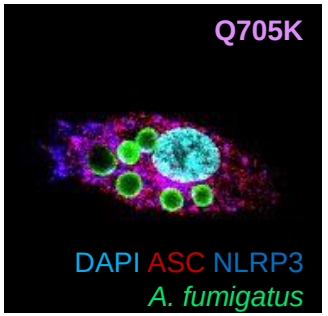


Q705K SNP underlies an hyperactivation of the NLRP3 inflammasome

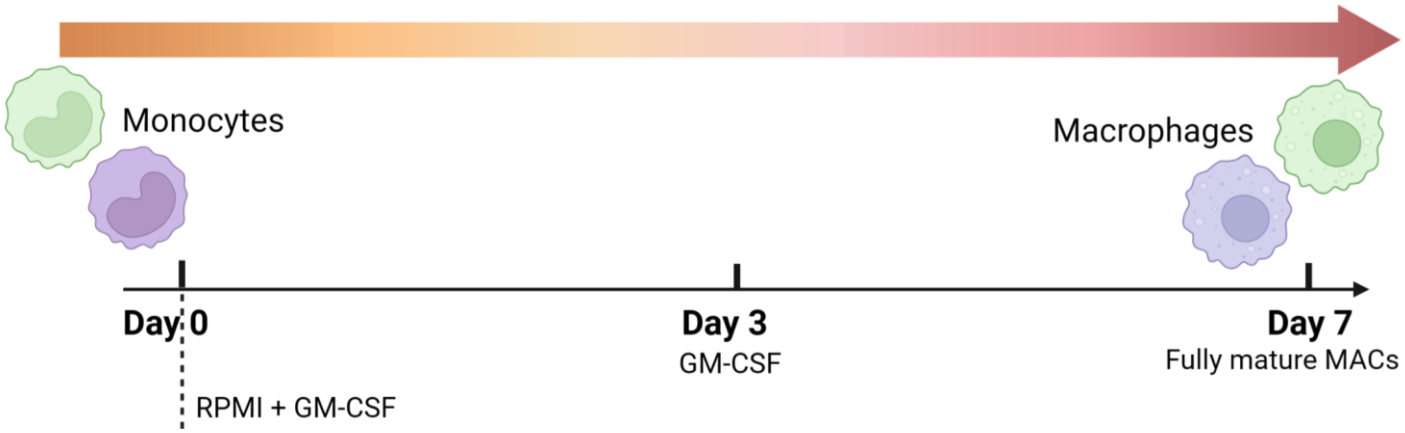




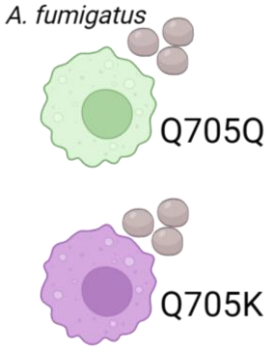


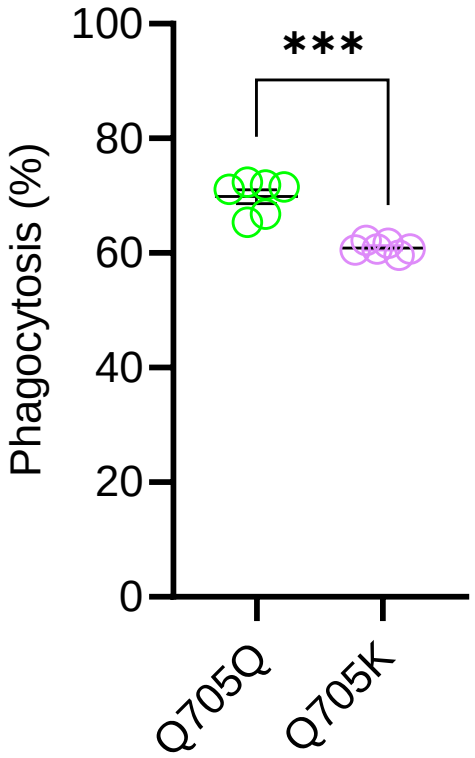


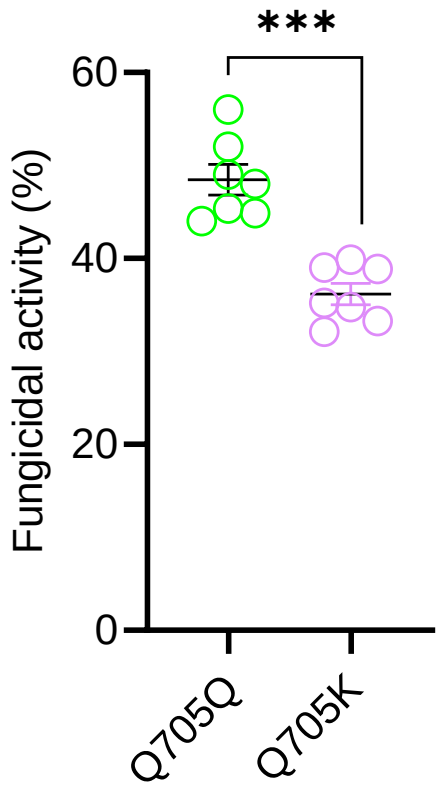
Q705K SNP underlies an hyperactivation of the NLRP3 inflammasome



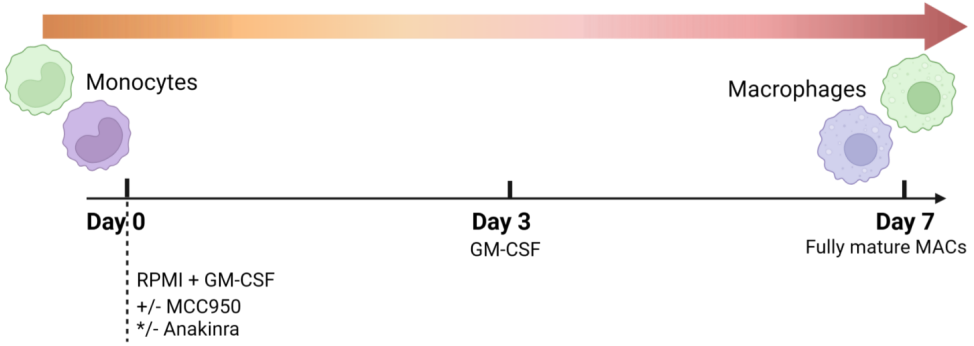
Q705K-driven hyperactivation of the NLRP3 inflammasome impairs antifungal effector functions

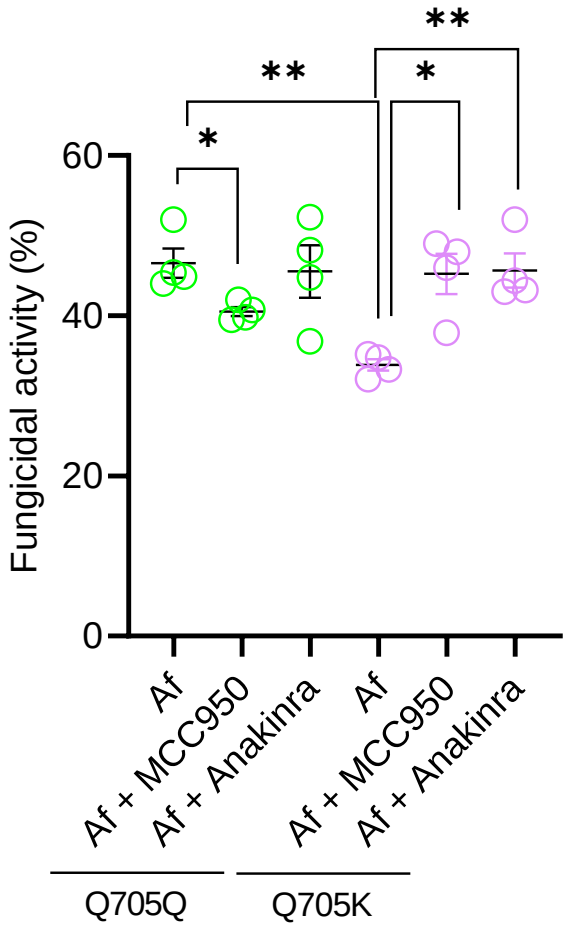






NLRP3/IL-1β inhibition restores antifungal mechanisms of Q705K macrophages





Mouse model IAPA

Mouse model IAPA

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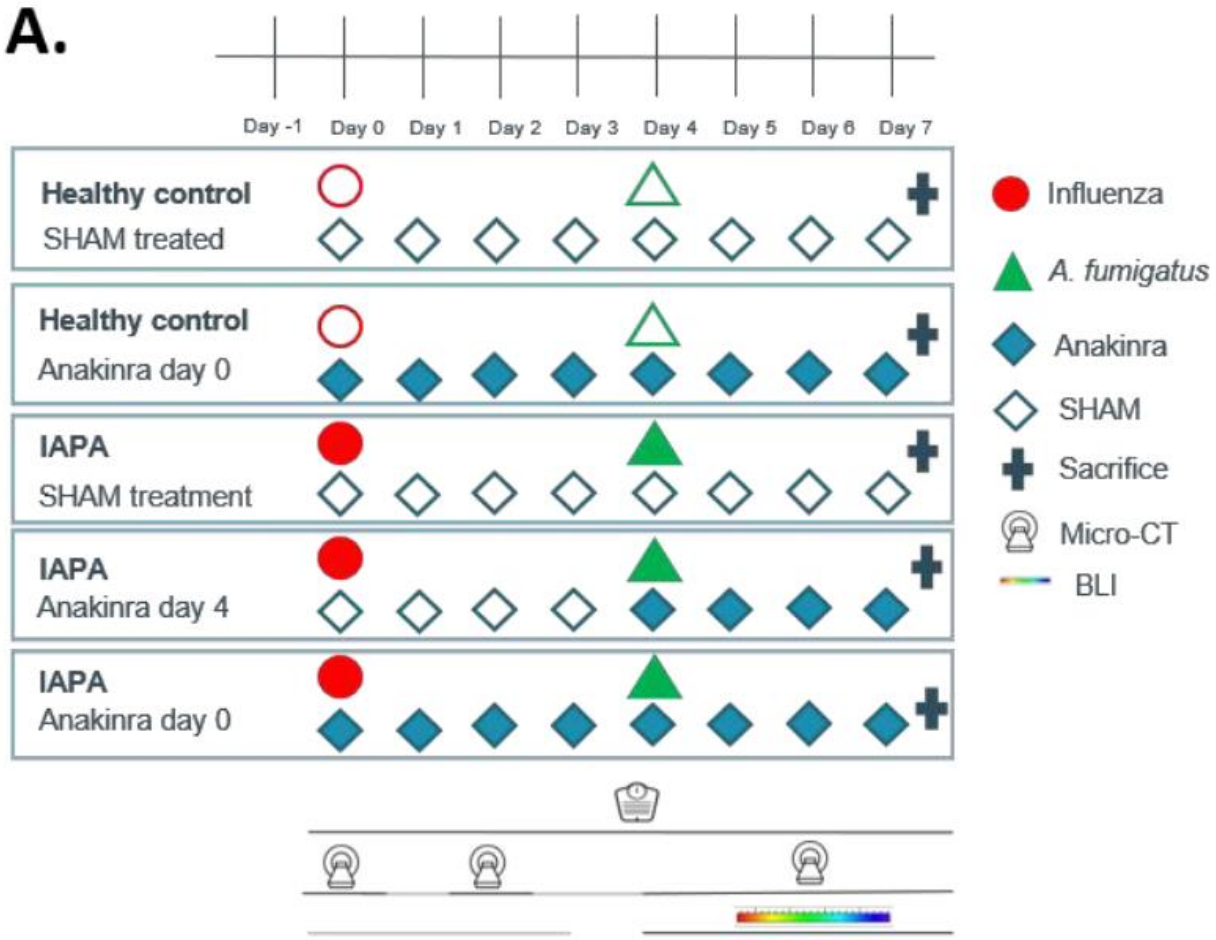

Mouse model IAPA

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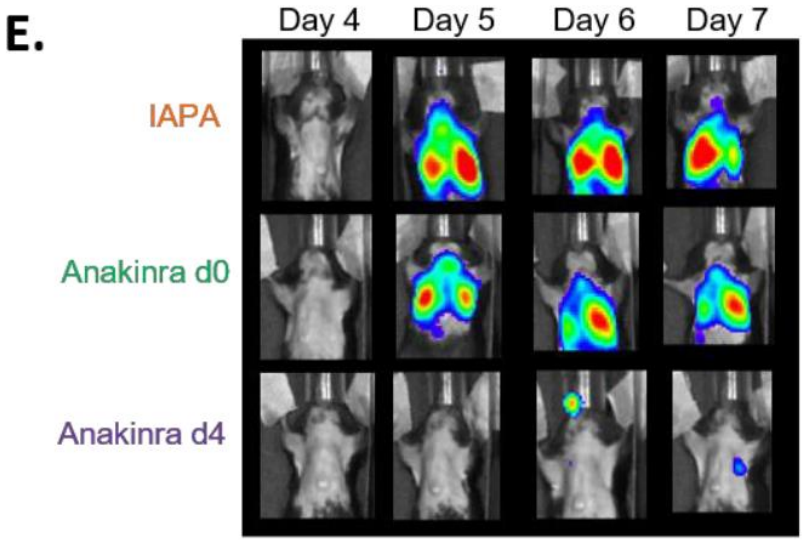

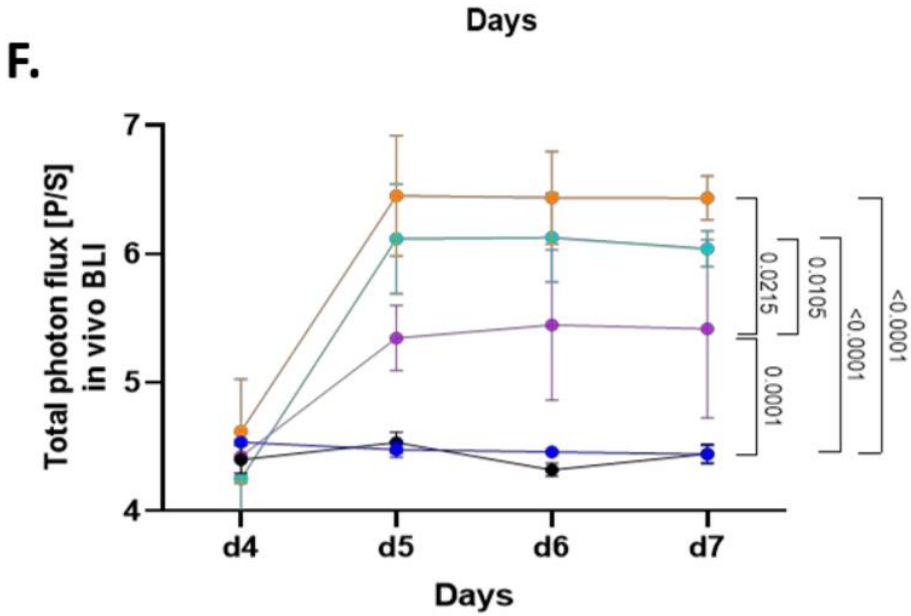

Mouse model IAPA

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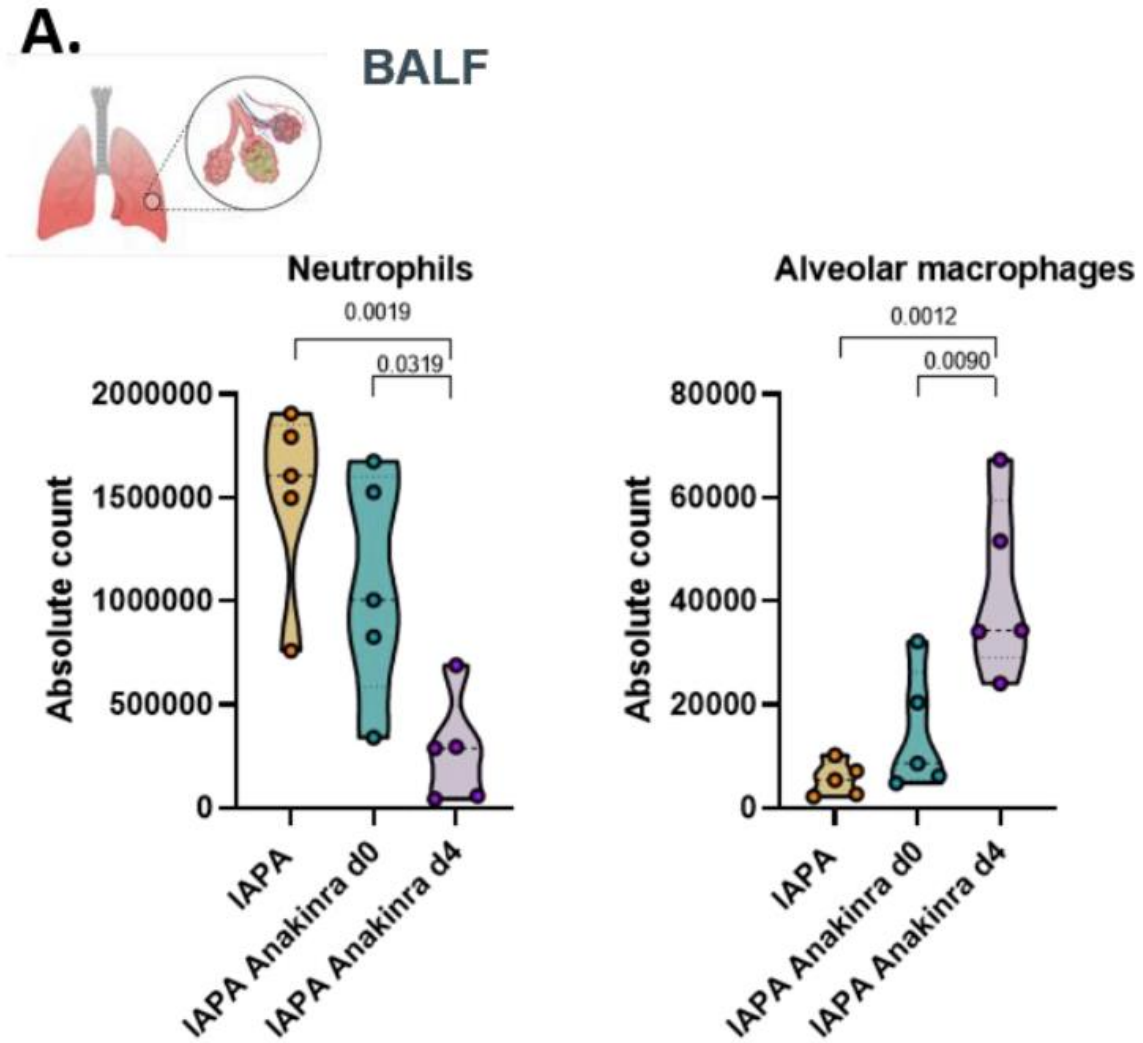

Mouse model IAPA

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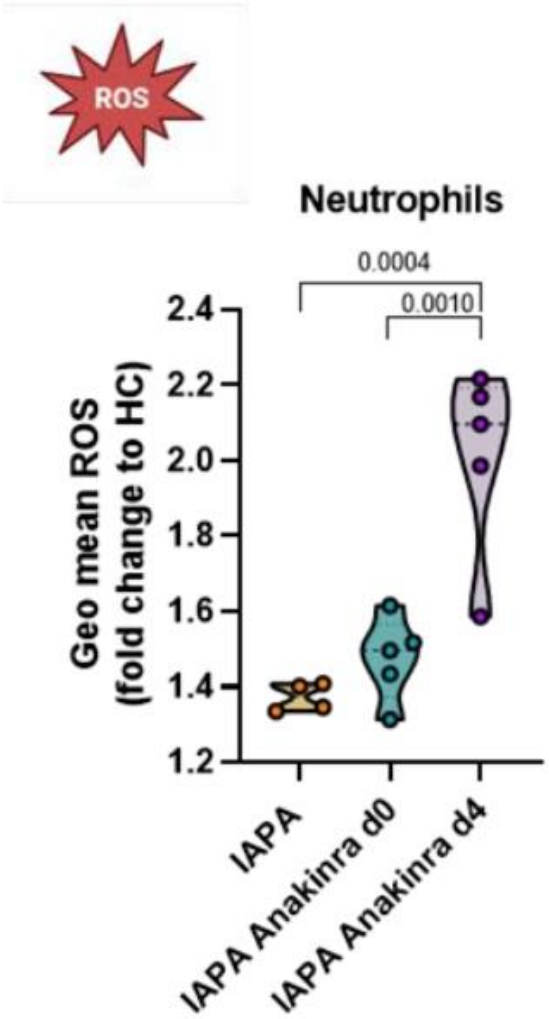
B.



Conclusions 3

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- **Inflammasome dysregulation a role in IAPA**
- **Seems amendable to anakinra**
- **Timing is important**
- **And probably dependent on host-status**

Galactin 3 SNP

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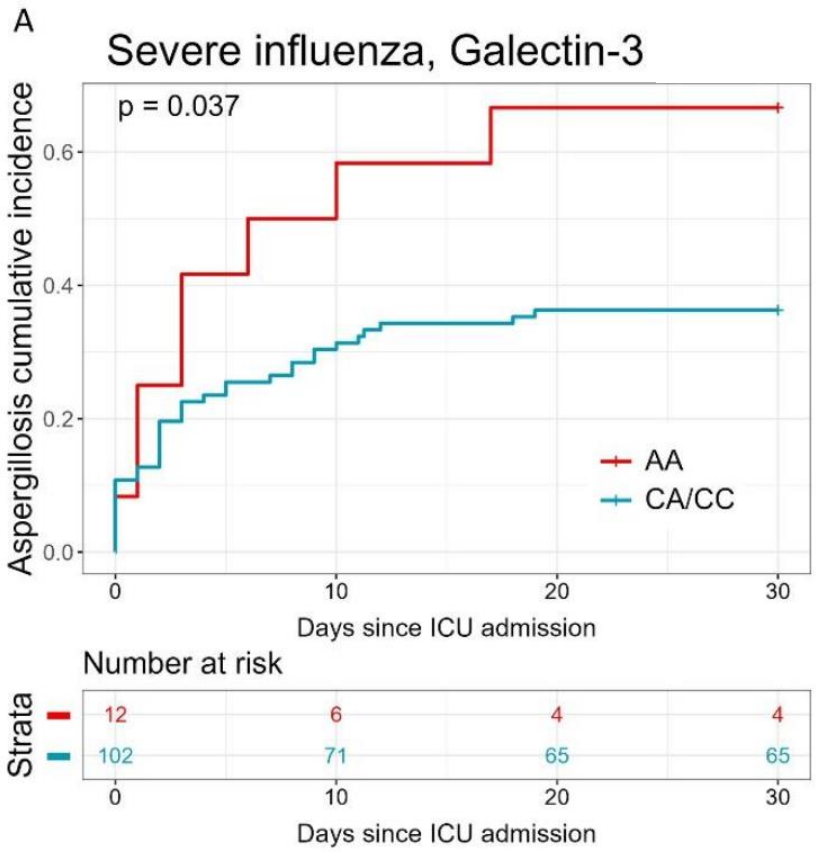

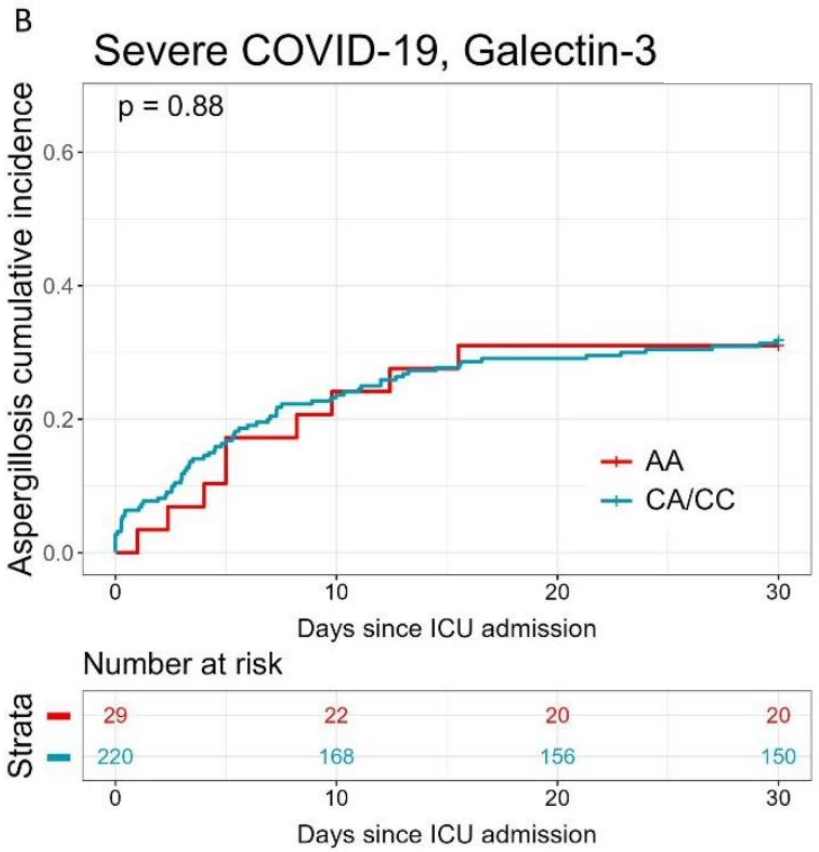

2 out of 3 with galactin-3 SNP >IAPA

Take home HDM-FUN

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Center for Infectious Diseases

- **Unique fungal translational clinical trial network**
- **IFNγ and anakinra potent immune modulators**
- **Will have a role in fungal infection**
- **Timing is important**
- **Guiding by functional assays and immune status**

Thanks

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Expertice Center for Mycology
Corlinda Kievit
Martin Jaeger
Intan Dewi
Nico Janssen
Mariolina Bruno
Rob Arts
Corine Delsing
James Cheng
Linda Davidson
Leo Joosten
Jos W.M. van der Meer
Reinout van Crevel
Bart Jan Kullberg
Jacques Meis
Roger Bruggeman
Paul Verweij
Mihai Netea

Dept. Intensive Care - Radboud
Matthijs Kox
Peter Pickkers

Athens University
Evangelos Giamarellos

University of Minho, Braga
Christina Cunha
Ricardo Silvestre
Fernando Rodrigues
Agostinho Carvalho

University of Colorado
Charles Dinarello

University of Aberdeen
Carol Munro

University of Exeter
Neil Gow
Gordon Brown
Al Brown

Institute Pasteur
Jessica Quintin
Vishu Aimanianda
Jean Paul Latge
Christophe D'Enfert

Hospital Necker
Fanny Lanternier
Olivier Lortholary

University of Leuven
Karin Thevissen
Lore Venderbeeke
Greetje van der Wal
Katrien Lagrou
Joost Wauters

University of Crete
George Hamilos

Leibniz HKI
Mark Gresnigt
Bernard Hube
Axel Brakhage

JMU Wurzburg
Oliver Kurzai

Hycult
Erik Toonen
Loek Willems

CHUV
Thierry Calandra

UH-GUF
Maria Vehreschild

University of Perugia
Luigina Romani

Duke University
Mellissa Johnson
John Perfect

InnACTA
Paola Cesaroni

Thanks!

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