Session 2: Acute Inflammation – Part 2

Characterizing and Targeting Acute Inflammation Following SARS-CoV-2 Infection

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Characterizing and targeting acute inflammation following SARS-CoV-2 infection

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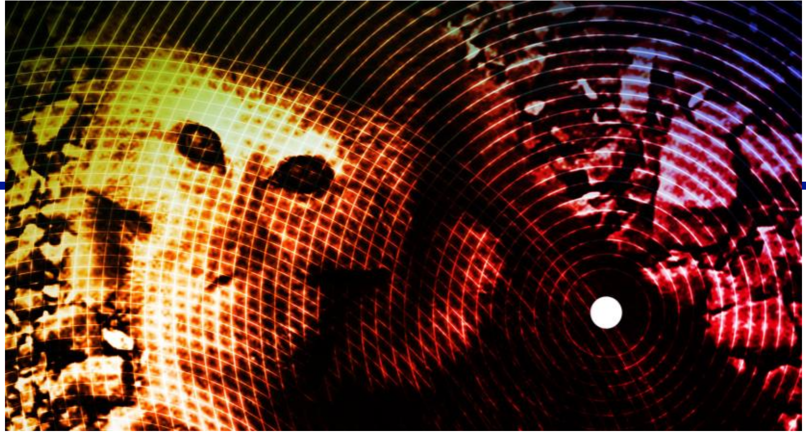
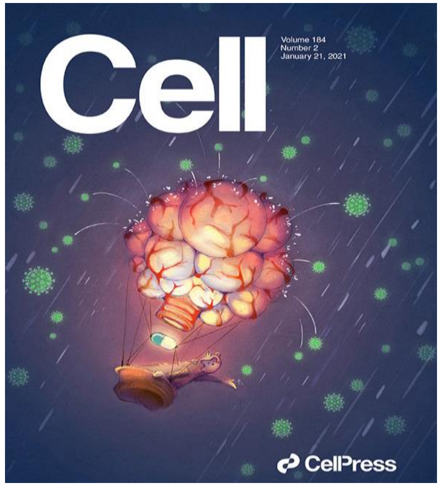
NHP models for SARS-CoV-2 infection



- Most early events are missed in patients with hospitalization
- Difficulty in studying lower airway during early clinical infections
- Discordance in time of sampling relative to exposure and exposure dose in human
- Ability to test therapies and vaccines rapidly before clinical trials
- The NHP model supports high levels of viral replication in the upper and lower airway; shares tissue distribution of ACE2 with humans; recapitulates mild (largely) to moderate COVID-19 that typically resolve by 10 days post infection

- **Can the NHP model recapitulate hallmarks of severe COVID-19?**
- **Can the NHP model provide utility as a benchmark for therapies?**

SARS-CoV-2 induces rapid Type I IFN responses in RMs



Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques

Timothy N. Hoang,[1,13] Maria Pino,[1,13] Arun K. Boddapati,[2,13] Elise G. Viox,[1] Carly E. Starke,[3] Amit A. Upadhyay,[2] Sanjeev Gumber,[4,5] Michael Nekorchuk,[3] Kathleen Busman-Sahay,[3] Zachary Strongin,[1] Justin L. Harper,[1] Gregory K. Tharp,[2] Kathryn L. Pellegrini,[2] Shannon Kirejczyk,[5] Keivan Zandi,[6] Sijia Tao,[6] Tristan R. Horton,[2] Elizabeth N. Beagle,[2] Ernestine A. Mahar,[1] Michelle Y.H. Lee,[1] Joyce Cohen,[7] Sherrie M. Jean,[7] Jennifer S. Wood,[7] Fawn Connor-Stroud,[7] Rachelle L. Stammen,[7] Olivia M. Delmas,[1] Shelly Wang,[1] Kimberly A. Cooney,[8] Michael N. Sayegh,[8] Lanfang Wang,[8] Peter D. Filev,[9] Daniela Weiskopf,[10] Guido Silvestri,[1,4] Jesse Waggoner,[8] Anne Piantadosi,[4,8] Sudhir P. Kasturi,[1] Hilmi Al-Shakhshir,[11] Susan P. Ribeiro,[11,14] Rafick P. Sekaly,[11,14] Rebecca D. Levit,[8] Jacob D. Estes,[3,12] Thomas H. Vanderford,[1] Raymond F. Schinazi,[6,14,*] Steven E. Bosinger,[1,2,4,*] and Mirko Paiardini[1,4,15,*]

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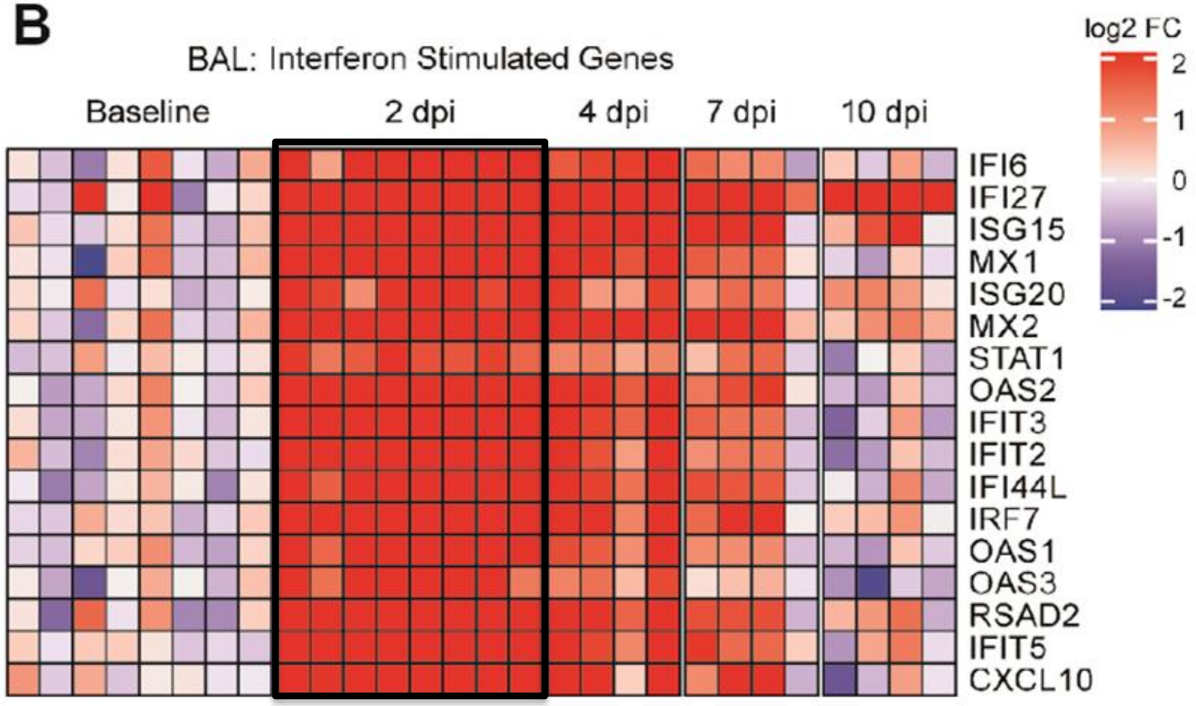
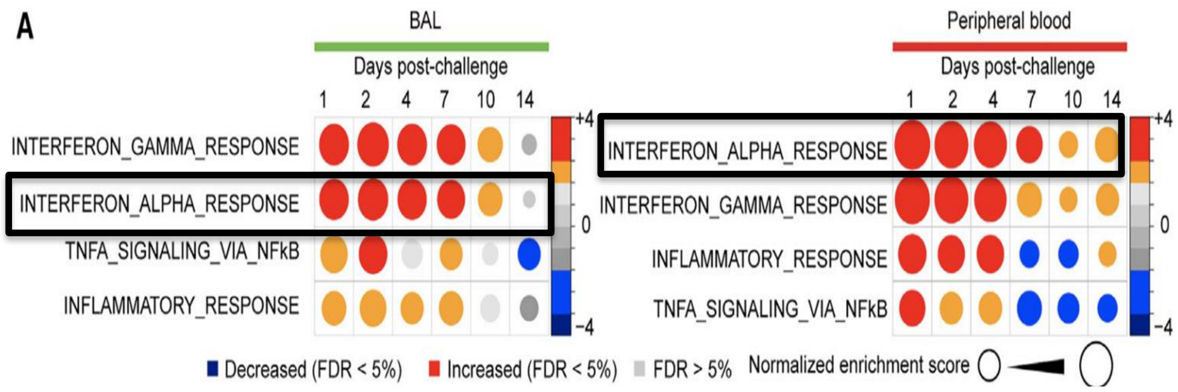
Article

Vascular Disease and Thrombosis in SARS-CoV-2-Infected Rhesus Macaques

Malika Aid,[1] Kathleen Busman-Sahay,[2] Samuel J. Vidal,[1] Zoltan Maliga,[3] Stephen Bondoc,[2] Carly Starke,[2] Margaret Terry,[2] Connor A. Jacobson,[3] Linda Wrijil,[4] Sarah Ducat,[4] Olga R. Brook,[5] Andrew D. Miller,[6] Maciel Porto,[10] Kathryn L. Pellegrini,[8] Maria Pino,[7] Timothy N. Hoang,[7] Abishek Chandrashekar,[1] Shivani Patel,[1] Kathryn Stephenson,[1] Steven E. Bosinger,[7,8,9] Hanne Andersen,[10] Mark G. Lewis,[10] Jonathan L. Hecht,[11] Peter K. Sorger,[3] Amanda J. Martinot,[1,4] Jacob D. Estes,[2] and Dan H. Barouch[1,12,13,*]





Singh DK et al; Coleman C et al; etc.

The role of type I IFN in COVID-19

- **Protective**
  - Individuals with severe COVID-19 were demonstrated to be more likely to have deficiencies to IFN-I responses:
    - Auto-antibodies against IFN-I (Bastard et al., 2020; Lopez et al., 2021; Wang et al., 2021)
    - Rare inborn errors of IFN-I immunity (Zhang et al., 2020; Pairo-Castineira et al., 2021)
    - Lack of production of IFN-I (Hadjadj et al., 2020; Combes et al., 2021; Ziegler et al., 2021)

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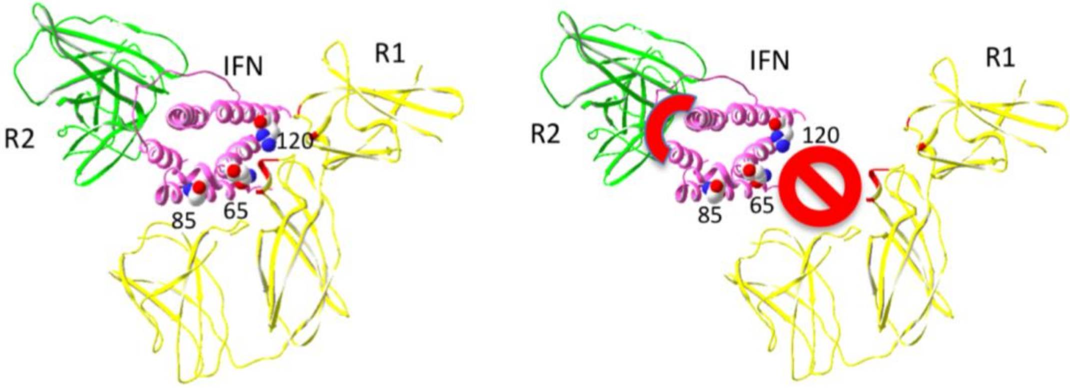
    - Lack of production of IFN-I (Hadjadj et al., 2020; Combes et al., 2021; Ziegler et al., 2021)

- **Deleterious**
  - High and/or sustained IFN-I expression associated with increased disease severity, susceptibility to bacterial infections, impaired lung epithelia repair (Blanco-Melo et al., 2020; Broggi et al., 2020; Major et al., 2020).
  - Association of IFITM 1-3, Siglec-1, and cGAS-STING signaling with increased SARS-CoV-2 infection (Prelli Bozzo et al., 2021; Lempp et al., 2021; Domizio et al., 2022)

Manipulating the IFN-I system to dissect the role of IFN-I in COVID-19

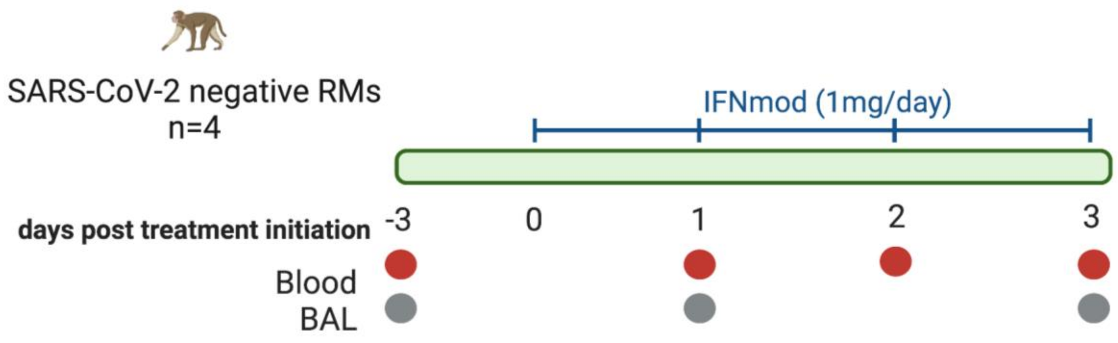
- IFNmod (previously referred to as IFN-1ant):
  - Mutated IFNα2 that binds with high affinity to IFNAR2, but markedly lower affinity to IFNAR1
  - Reduces the binding and signaling of all forms of endogenous IFN-I
  - Induces low-level stimulation of antiviral genes without induction of inflammatory genes when used *in vitro* in cancer cells (Levin *et al.*, 2014; Urin *et al.*, 2015)
  - blockade of the IFN-I receptor with the mutated IFNa2 caused accelerated CD4 T-cell depletion and progression to AIDS in SIV-infected RMs (Sandler *et al.,* 2014)



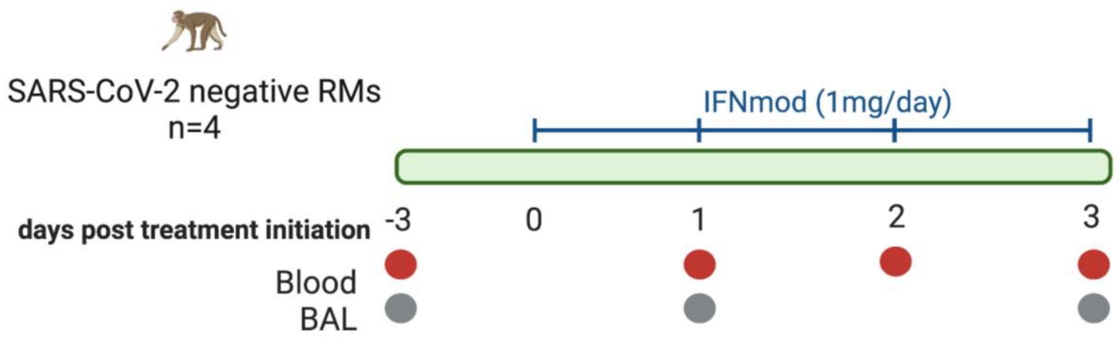
Mutated Arg 120 to Glu and adding the alpha8 tail, reducing its affinity for R1 to below detection level while increasing affinity for R2

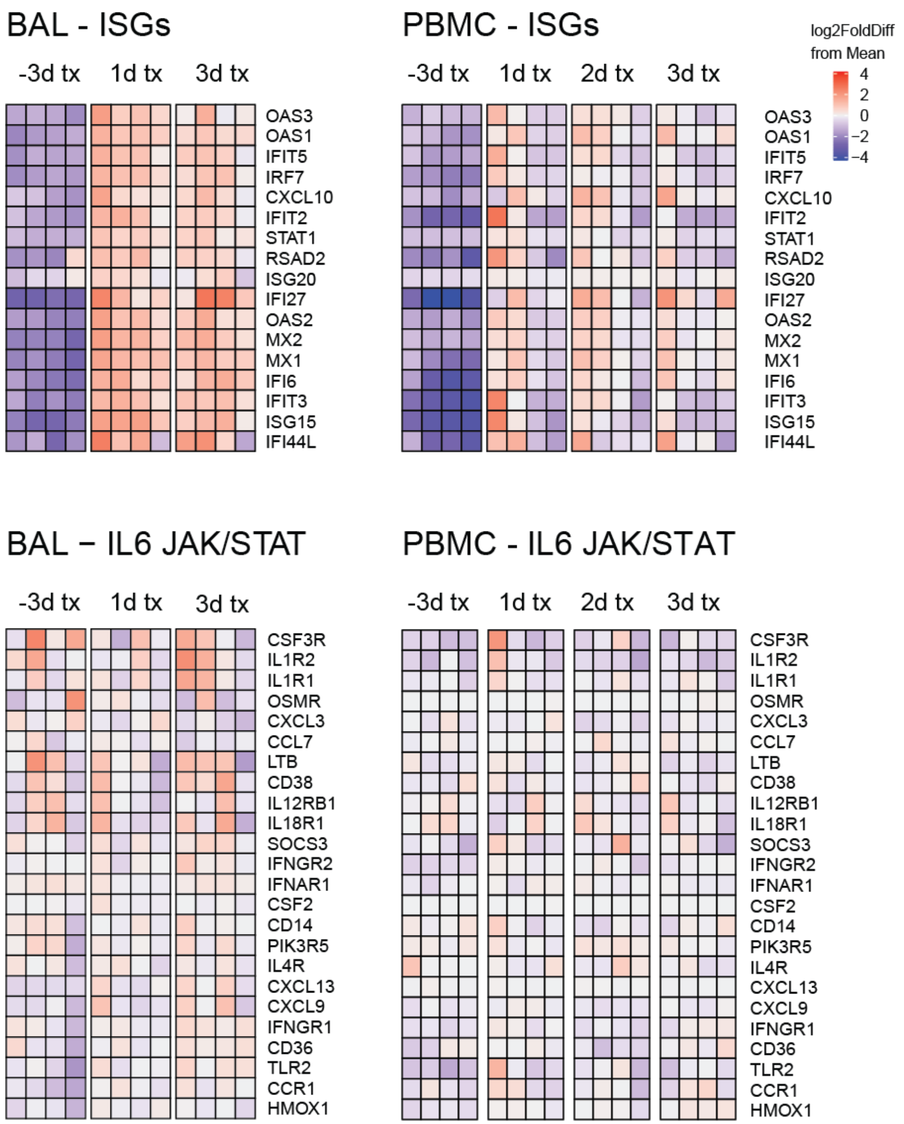
Provided by Gideon Schreiber

IFNmod treatment in uninfected RMs results in modest and specific upregulation of antiviral ISGs



IFNmod treatment in uninfected RMs results in modest and specific upregulation of antiviral ISGs





- **Multifaceted role: <u>modest upregulation of ISGs, without changes in pro-inflammatory genes</u>**

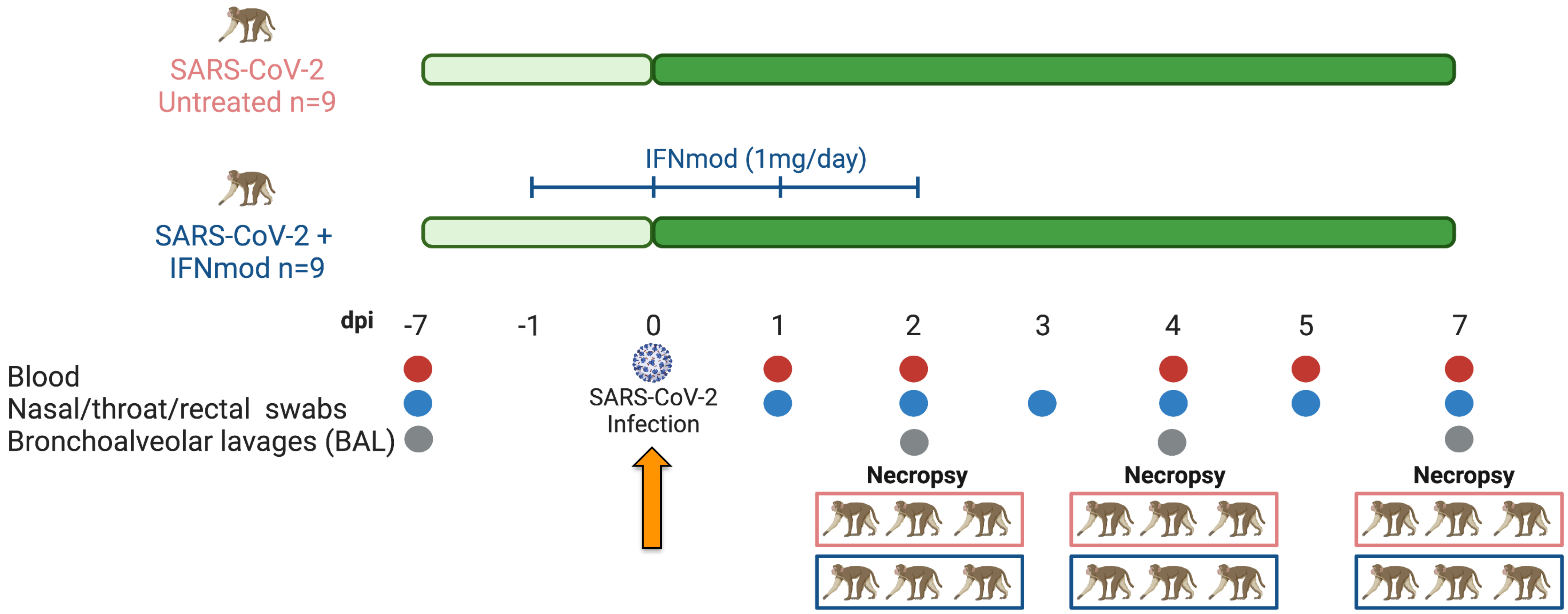
- **These results suggest that this compound could be ideal in the context of SARS-CoV-2 infection**

Determining how IFNmod affects COVID-19: Study Design

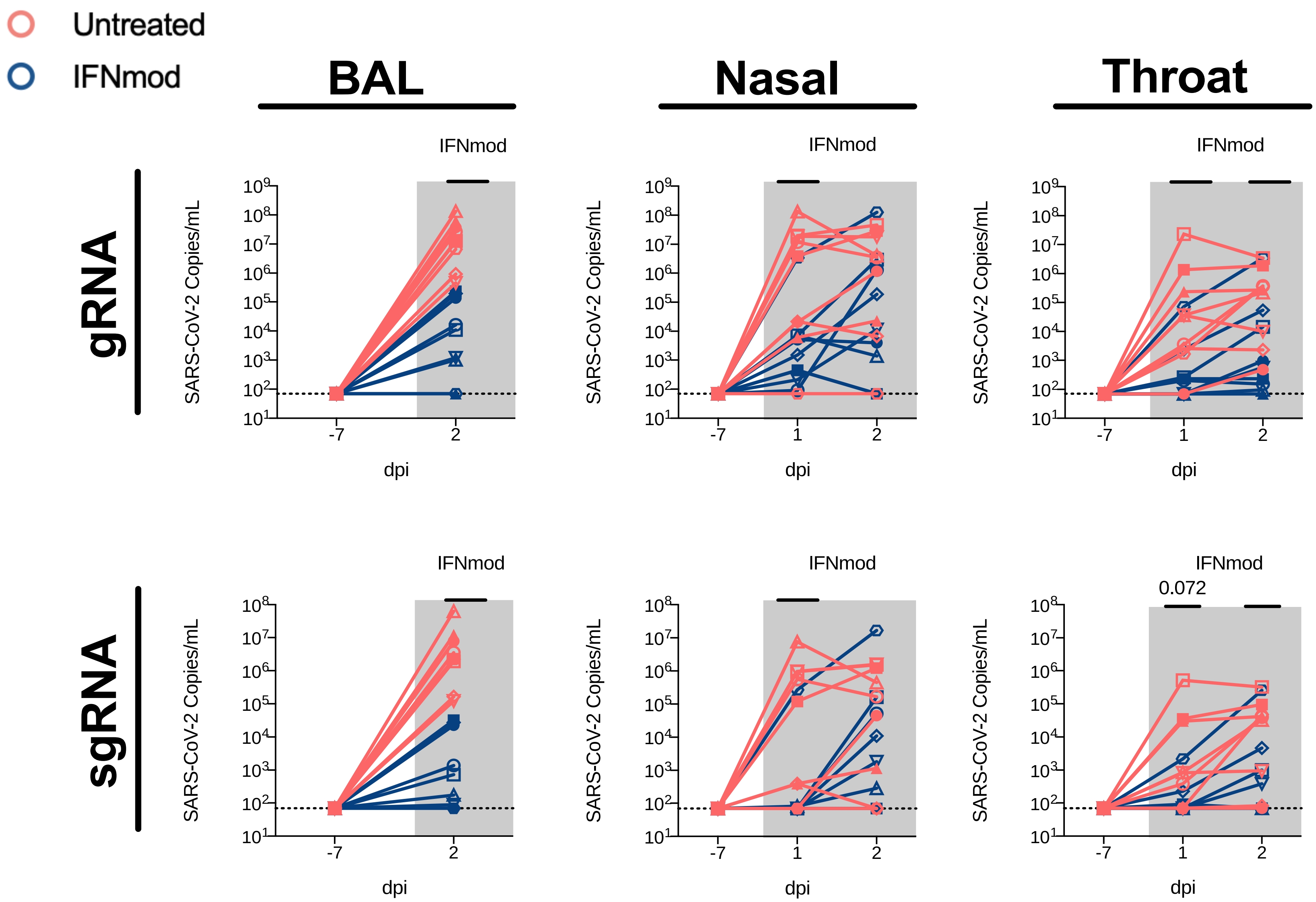
- SARS-CoV-2 isolate 2019-nCoV/USA-WA1/2020

- Intratracheal (I.T.) and Intranasal (I.N.) – dual route challenge

- 1.1 x 10^6 PFU (1 mL I.T. and 1 mL I.N.)

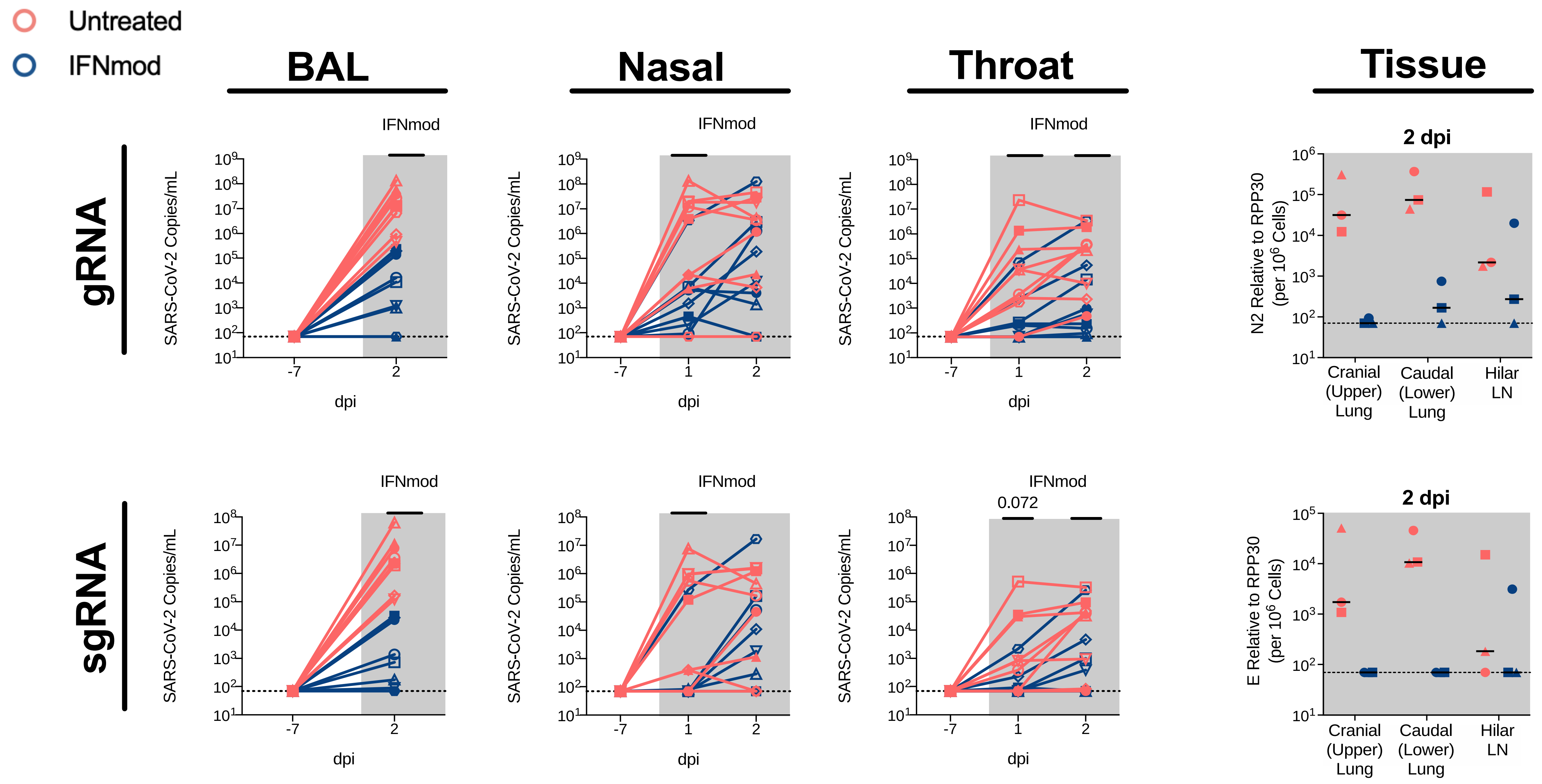


Lower viral loads in IFNmod treated RMs during dosing phase



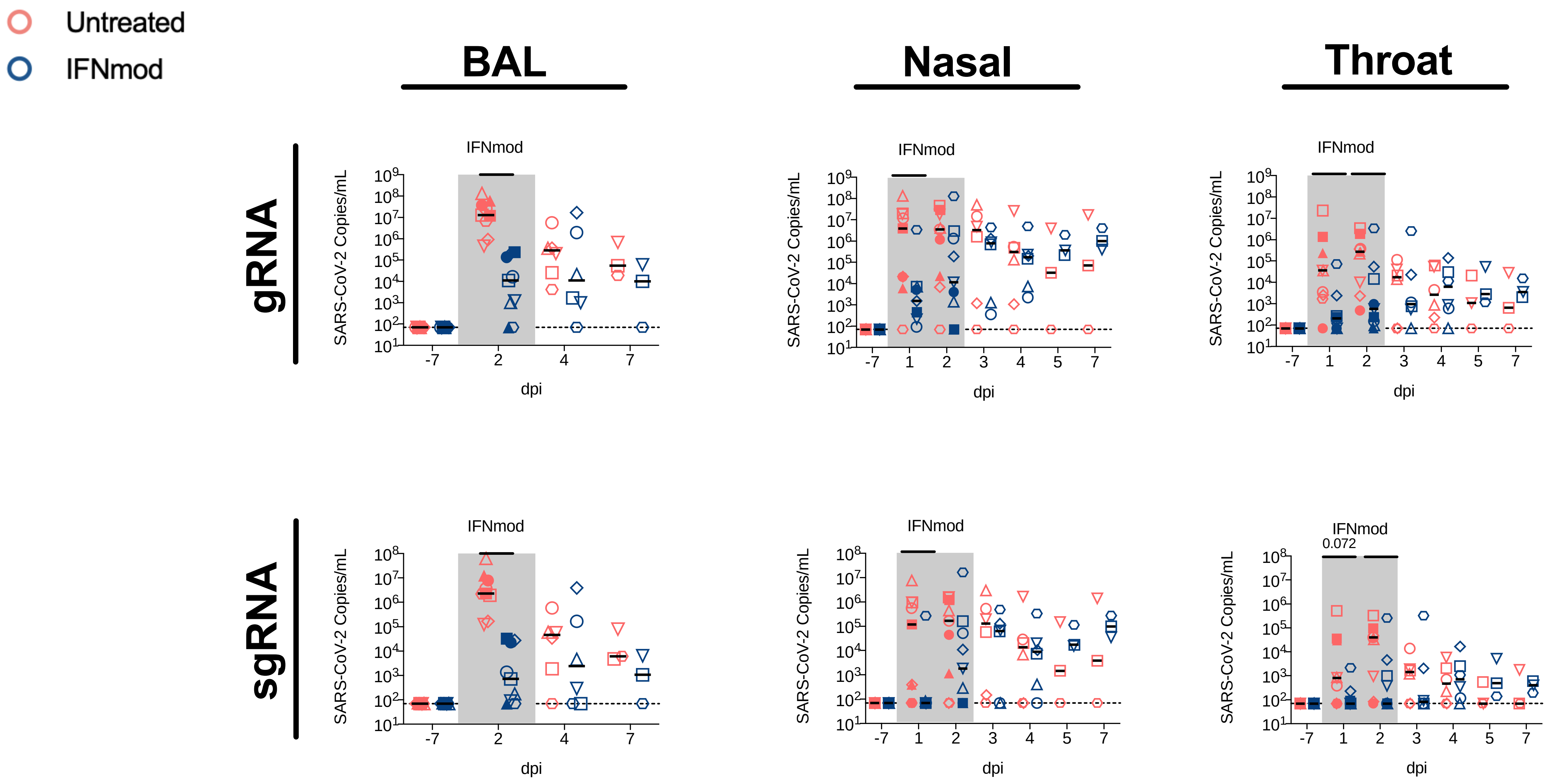
Lines depicted represent median

Lower viral loads in IFNmod treated RMs during dosing phase



Lines depicted represent median

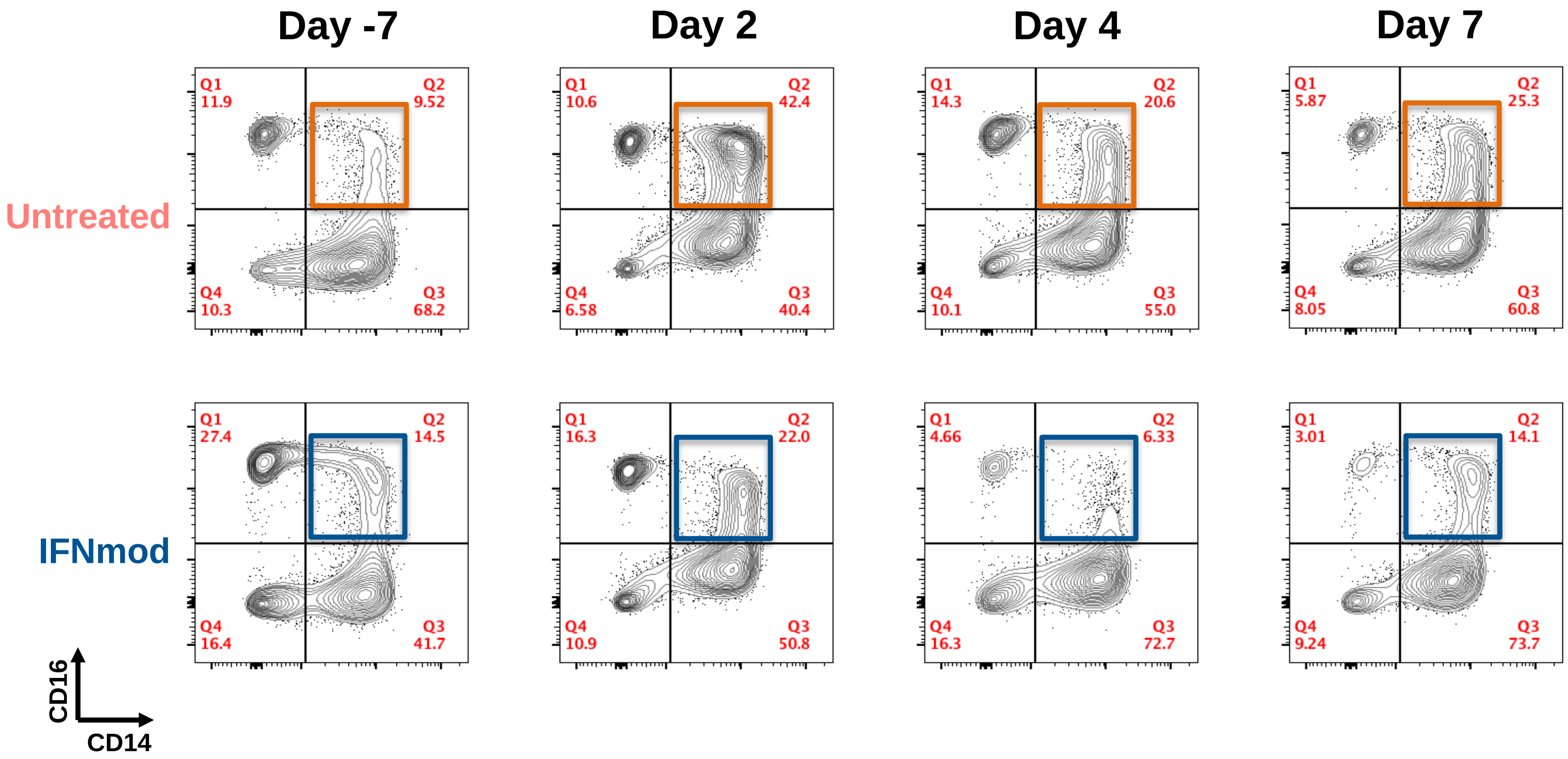
Viral loads remained stable in IFNmod treated RMs after treatment phase



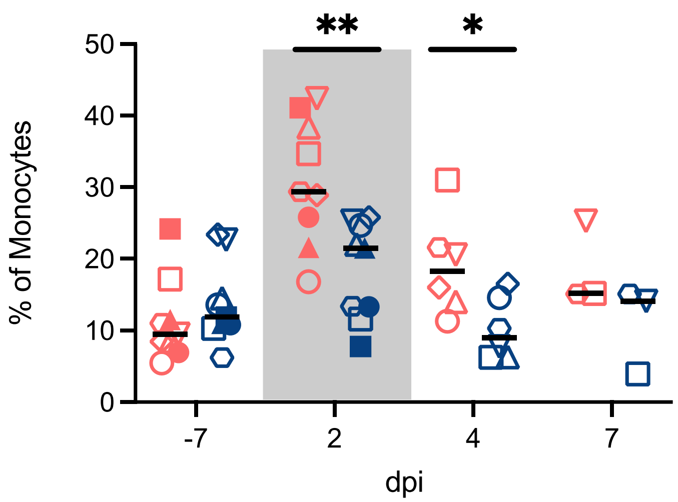
Lines depicted represent median

IFNmod treated RMs had lower expansion of inflammatory monocytes

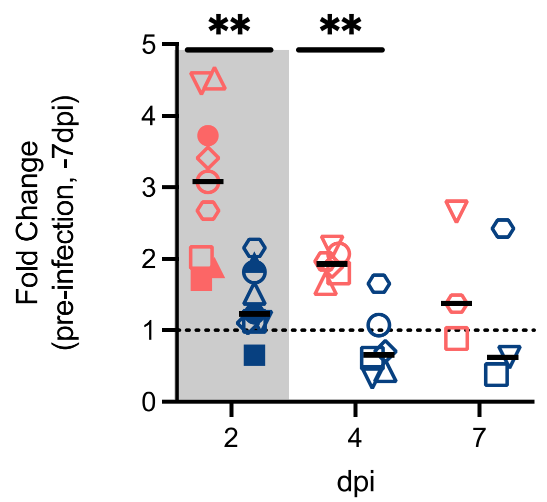
Untreated
IFNmod



CD14+ CD16+ Monocytes (Blood)



FC CD14+ CD16+ Monocytes (Blood)



Lines depicted represent median

Siglec-1 expression enhances SARS-CoV-2 infection and is associated with disease severity

nature
https://doi.org/10.1038/s41586-021-03925-1

Lectins enhance SARS-CoV-2 infection and influence neutralizing antibodies

https://doi.org/10.1038/s41586-021-03925-1
Received: 3 April 2021
Accepted: 18 August 2021
Published online: 31 August 2021

Florian A. Lempp[1], Leah B. Soriaga[1], Martin Montiel-Ruiz[1], Fabio Benigni[2], Julia Noack[1], Young-Jun Park[3], Siro Bianchi[2], Alexandra C. Walls[3], John E. Bowen[3], Jiayi Zhou[1], Hannah Kaiser[1], Anshu Joshi[3], Maria Agostini[1], Marcel Meury[1], Exequiel Dellota Jr[1], Stefano Jaconi[2], Elisabetta Cameroni[2], Javier Martinez-Picado[4,5,6], Júlia Vergara-Alert[7], Nuria Izquierdo-Useros[4,8], Herbert W. Virgin[1,9,10], Antonio Lanzavecchia[2], David Veesler[3], Lisa A. Purcell[11], Amalio Telenti[1,12] ✉ & Davide Corti[2,12] ✉

Monocyte CD169 Expression as a Biomarker in the Early Diagnosis of Coronavirus Disease 2019

Anne-Sophie Bedin,[1] Alain Makinson,[2,3] Marie-Christine Picot,[4,5] Frank Mennechet,[1] Fabrice Malergue,[6] Amandine Pisoni,[1,7] Esperance Nyiramigisha,[7] Lise Montagnier,[7] Karine Bollore,[1] Ségolène Debiesse,[1] David Morquin,[3] Pénélope Bourgoin,[6] Nicolas Veyrenche,[7] Constance Renault,[1] Vincent Foulongne,[1,7] Caroline Bret,[8] Arnaud Bourdin,[9,10] Vincent Le Moing,[2,3] Philippe Van de Perre,[1,7] Edouard Tuaillon[1,7]

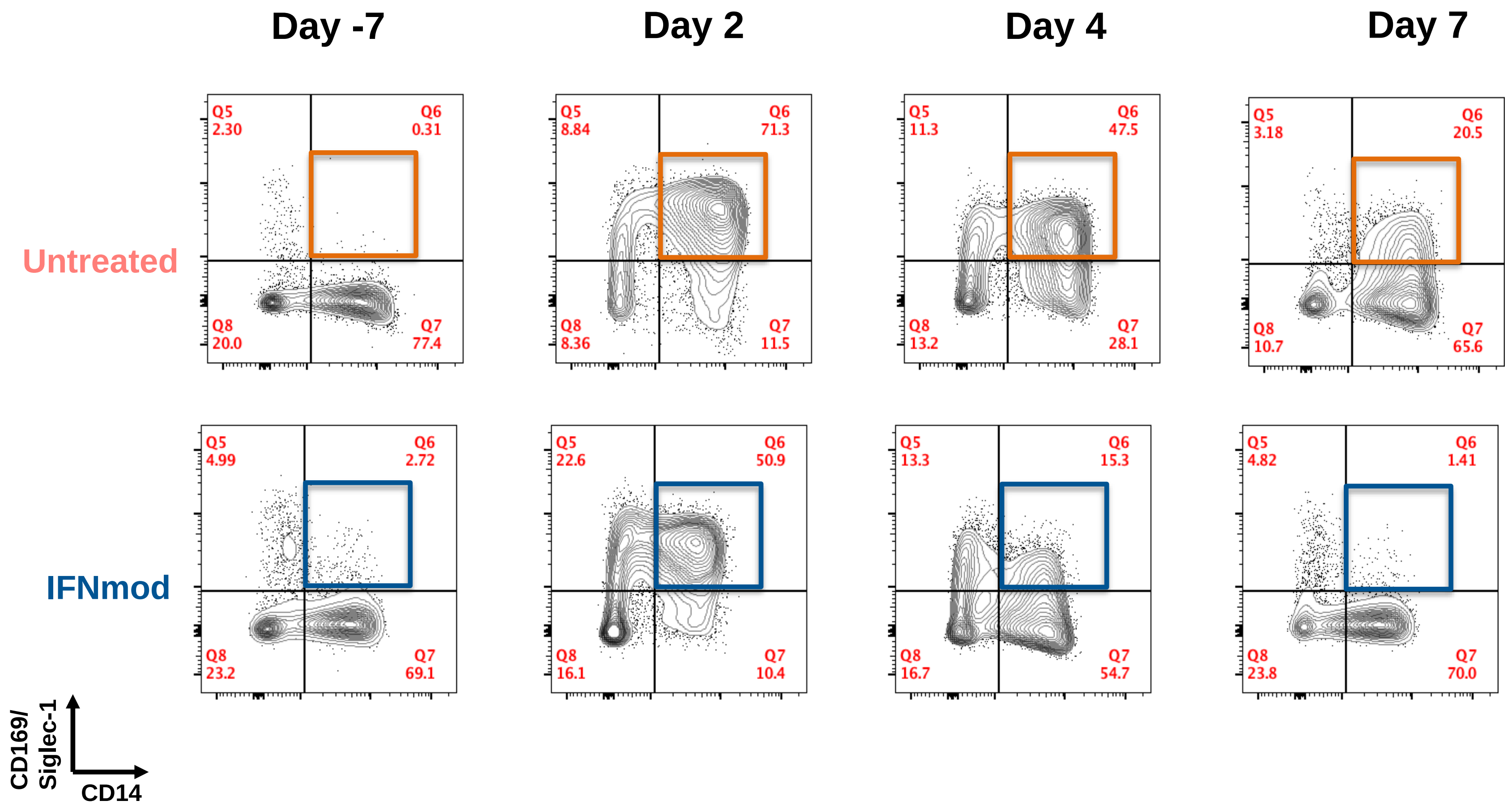
CD169/SIGLEC1 is expressed on circulating monocytes in COVID-19 and expression levels are associated with disease severity

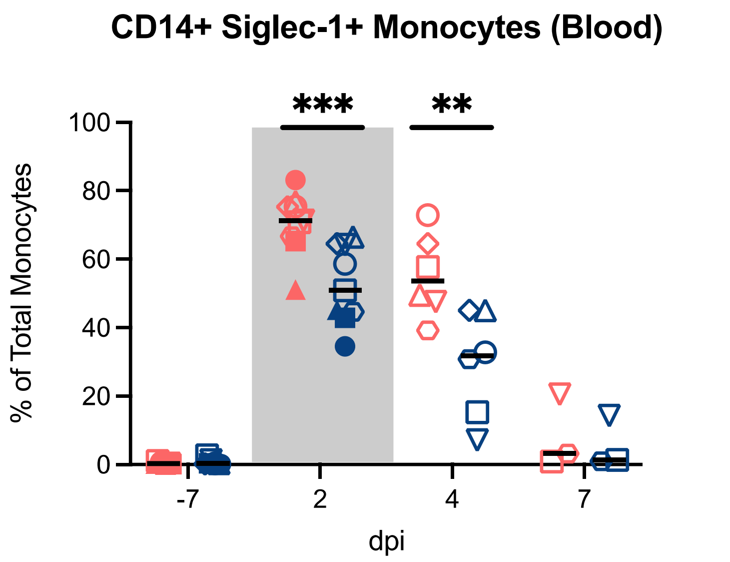
Jan-Moritz Doehn[1] · Christoph Tabeling[1,2,3] · Robert Biesen[4] · Jacopo Saccomanno[1] · Elena Madlung[1] · Eva Pappe[1] · Frieder Gabriel[1] · Florian Kurth[1,5] · Christian Meisel[6,7] · Victor M. Corman[8,9] · Leif G. Hanitsch[6] · Sascha Treskatsch[10] · Kathrin Heim[1] · Miriam S. Stegemann[1] · Christoph Ruwwe-Glösenkamp[1] · Holger C. Müller-Redetzky[1] · Alexander Uhrig[1] · Rajan Somasundaram[11] · Claudia Spies[12] · Horst von Bernuth[13] · Jörg Hofmann[7,8,9] · Christian Drosten[8,9] · Norbert Suttorp[1,14] · Martin Witzenrath[1,2,14] · Leif E. Sander[1,14] · Ralf-Harto Hübner[1]

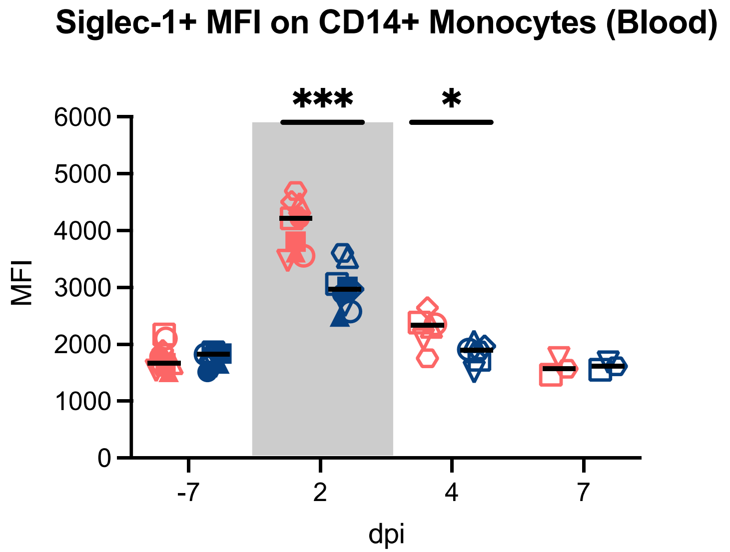
- Siglec-1, an IFN-I responsive protein, functions as an attachment receptor for SARS-CoV-2 and enhances SARS-CoV-2 infection (Lempp *et al.*, 2021; Perez-Zsolt et al., 2021).
- Siglec-1 expression on circulating monocytes is associated with disease severity (Doehn et al., 2021; Bedin et al, 2021)

IFNmod treated RMs had lower expression of Siglec-1+ CD14+ monocytes

○ Untreated
○ IFNmod

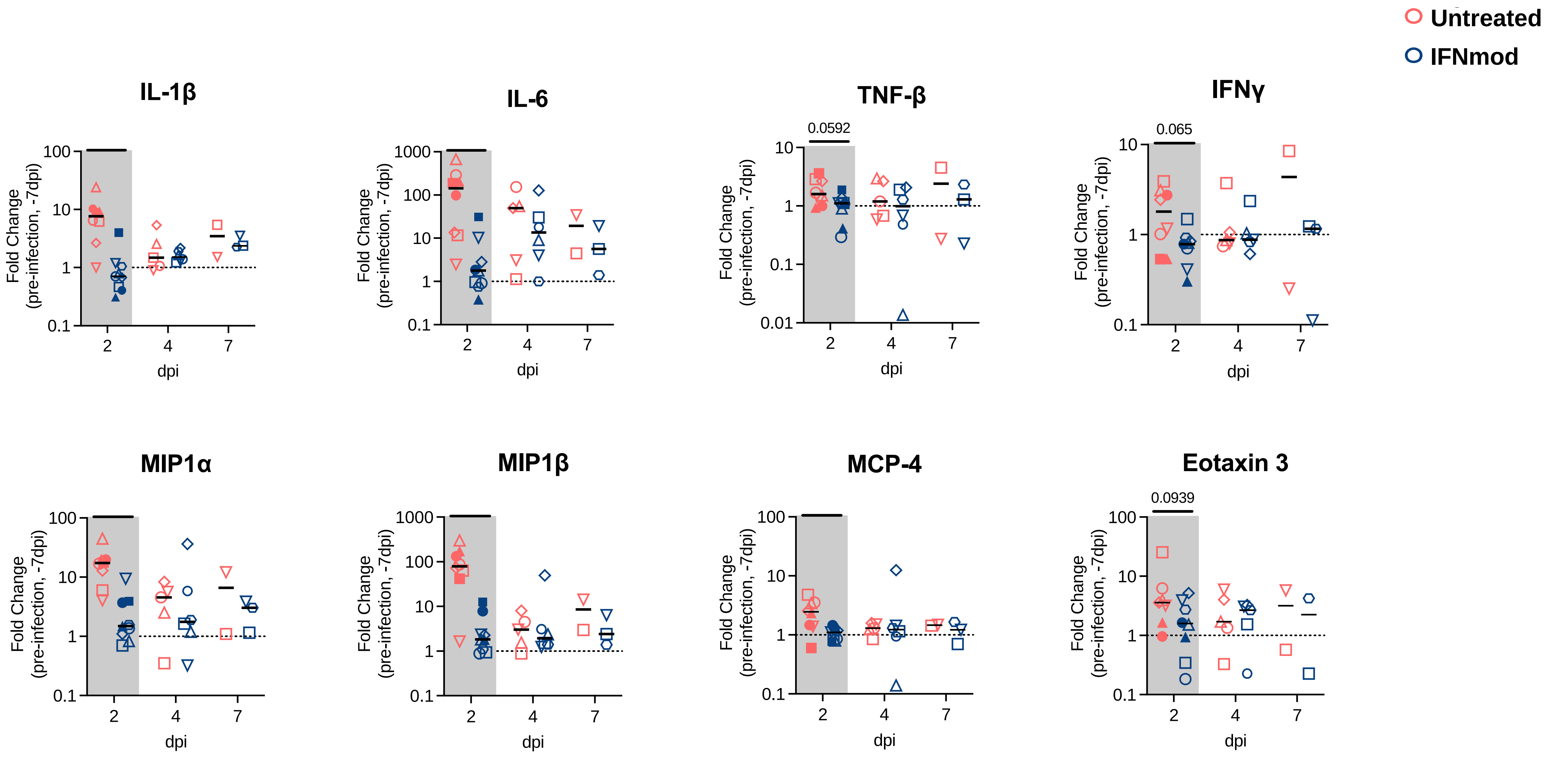




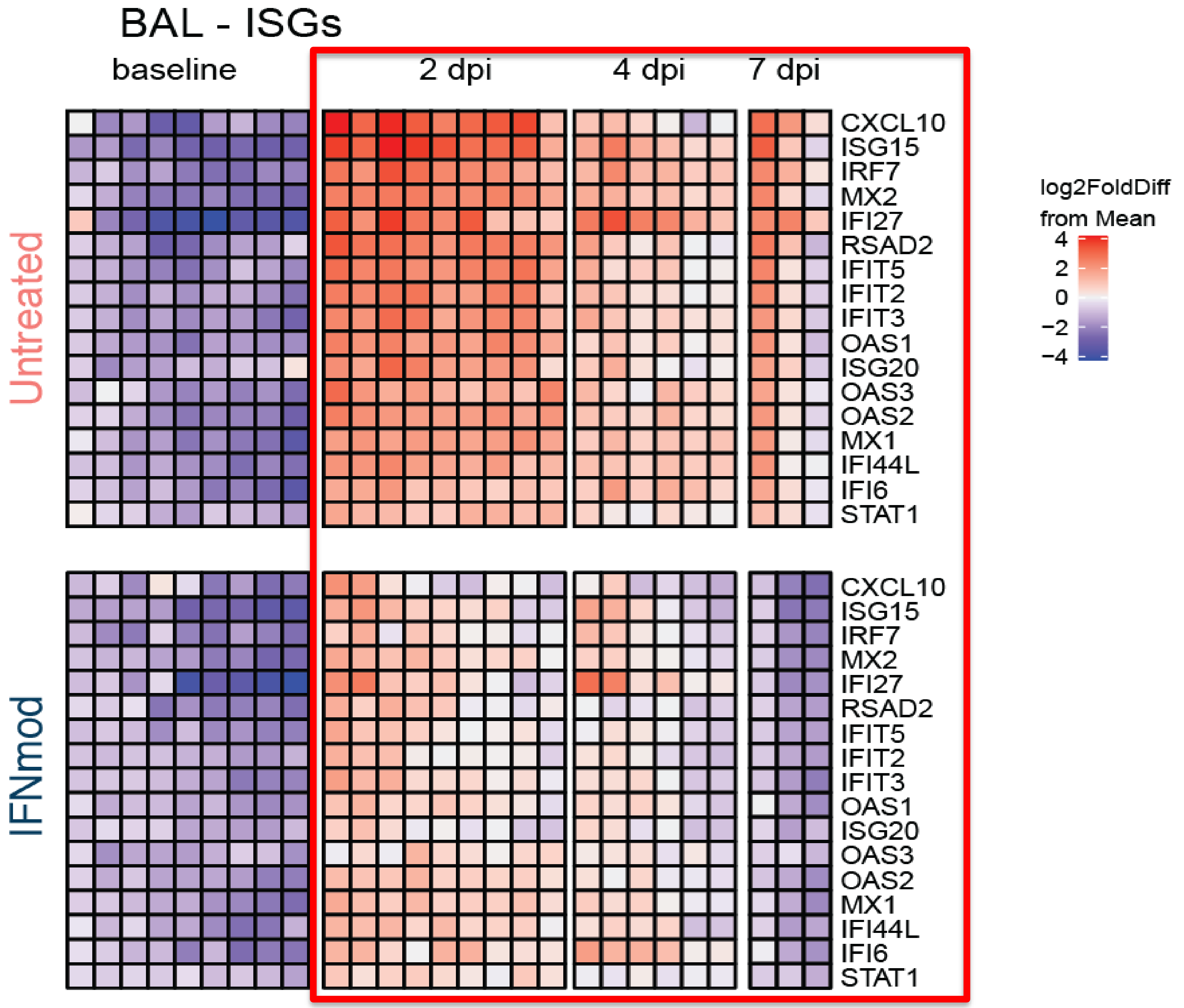


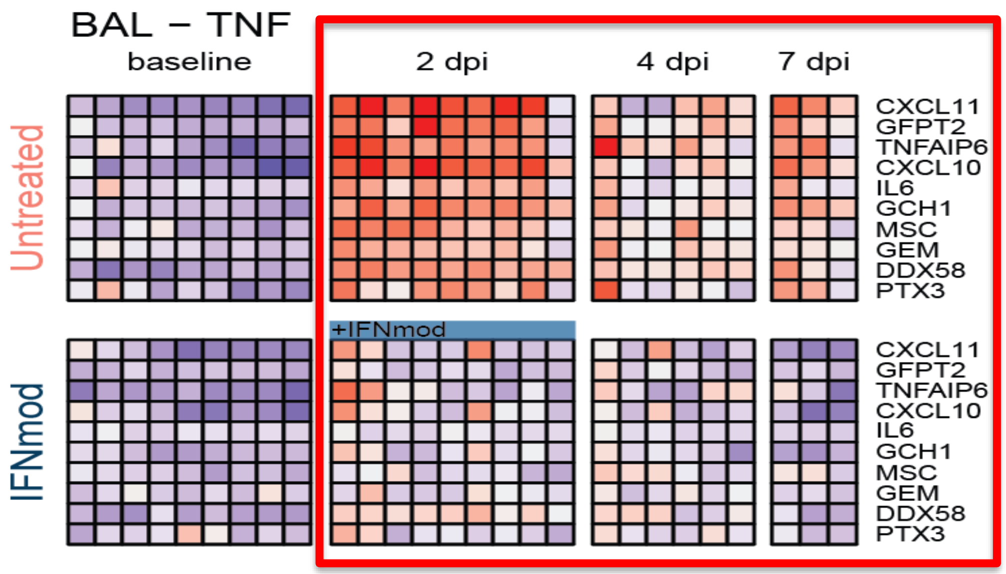
Lines depicted represent median

IFNmod treated RMs had lower level of inflammatory molecules in BAL



IFNmod inhibits the ISG response and pro-inflammatory signaling in the BAL of SARS-CoV-2 infected RMs





COVID-19 and the Inflammasome

Article | Published: 28 April 2022

Inflammasome activation in infected macrophages drives COVID-19 pathology

Esen Sefik, Rihao Qu, Caroline Junqueira, Eleanna Kaffe, Haris Mirza, Jun Zhao, J. Richard Brewer, Ailin Han, Holly R. Steach, Benjamin Israelow, Holly N. Blackburn, Sofia E. Velazquez, Y. Grace Chen, Stephanie Halene, Akiko Iwasaki, Eric Meffre, Michel Nussenzweig, Judy Lieberman, Craig B. Wilen, Yuval Kluger & Richard A. Flavell

Nature **606**, 585–593 (2022) | Cite this article

Article | Published: 06 April 2022

FcγR-mediated SARS-CoV-2 infection of monocytes activates inflammation

Caroline Junqueira, Ângela Crespo, Shahin Ranjbar, Luna B. de Lacerda, Mercedes Lewandrowski, Jacob Ingber, Blair Parry, Sagi Ravid, Sarah Clark, Marie Rose Schrimpf, Felicia Ho, Caroline Beakes, Justin Margolin, Nicole Russell, Kyle Kays, Julie Boucau, Upasana Das Adhikari, Setu M. Vora, Valerie Leger, Lee Gehrke, Lauren A. Henderson, Erin Janssen, Douglas Kwon, Chris Sander, ... Judy Lieberman

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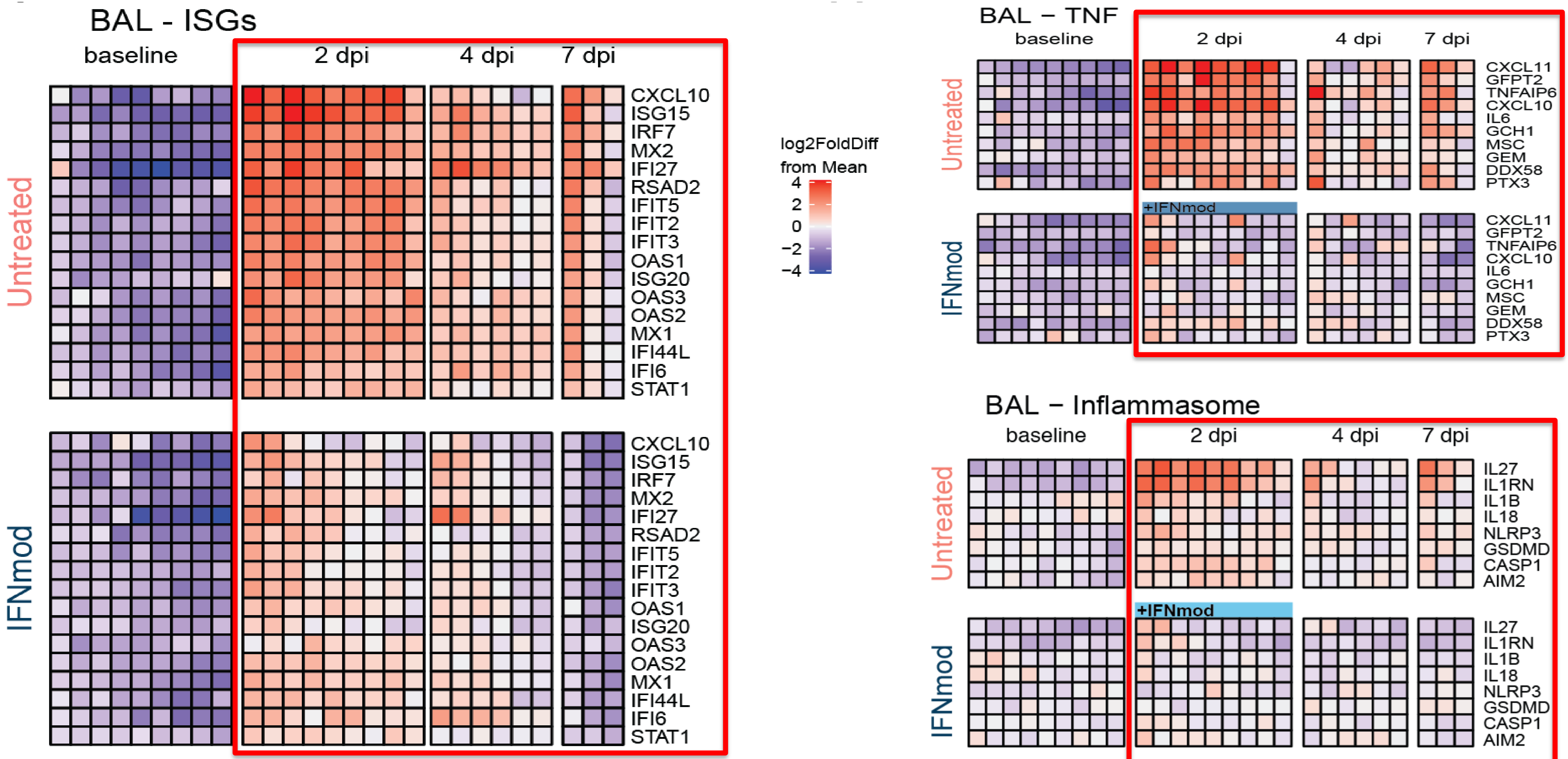
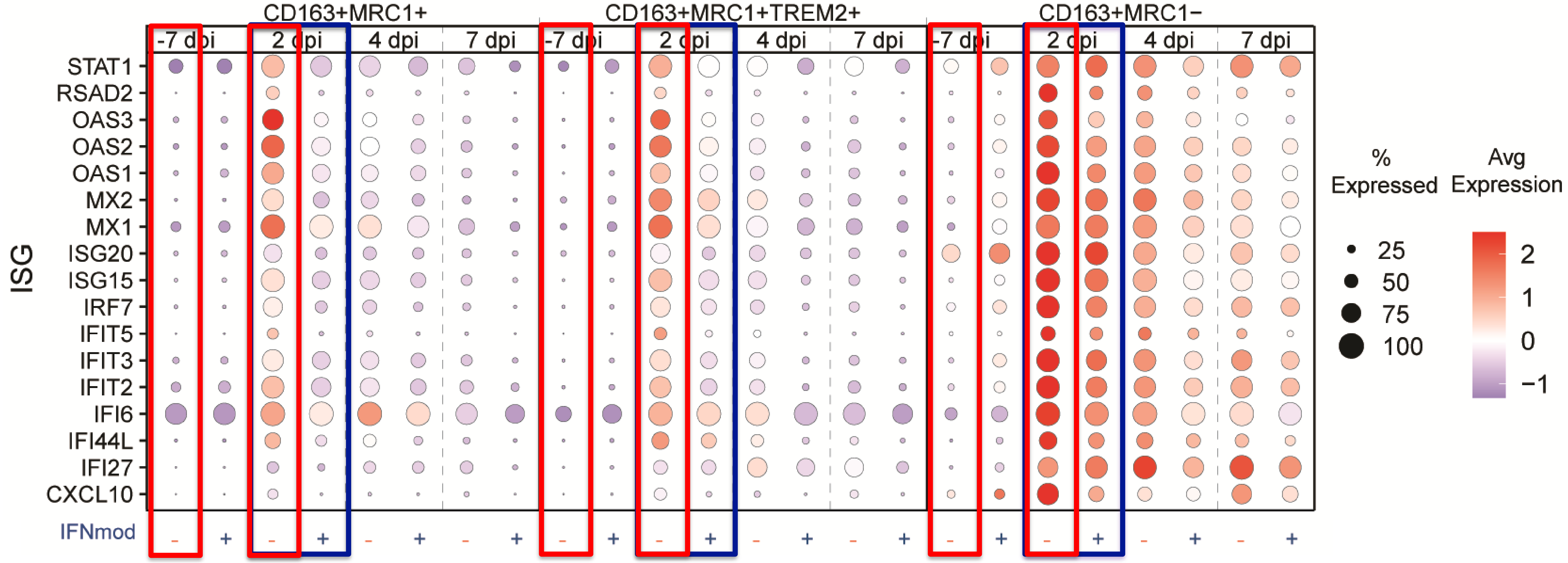
Nature **606**, 576–584 (2022) | Cite this article

A series of studies linked lower airway inflammation during SARS-CoV-2 infection to inflammasome activation specifically within infiltrating monocytes and resident macrophages

IFNmod inhibits the ISG response and pro-inflammatory signaling in the BAL of SARS-CoV-2 infected RMs

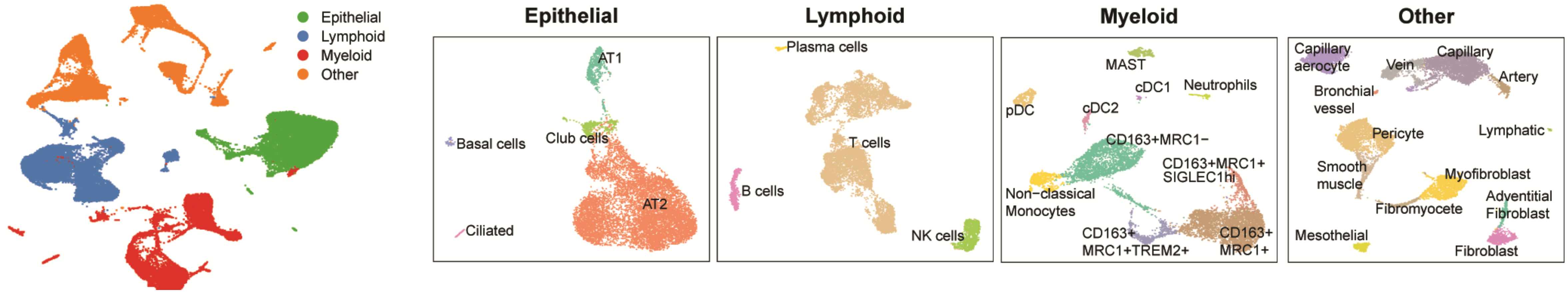


IFNmod treatment reduces ISG expression in macrophage subsets in the lower airway

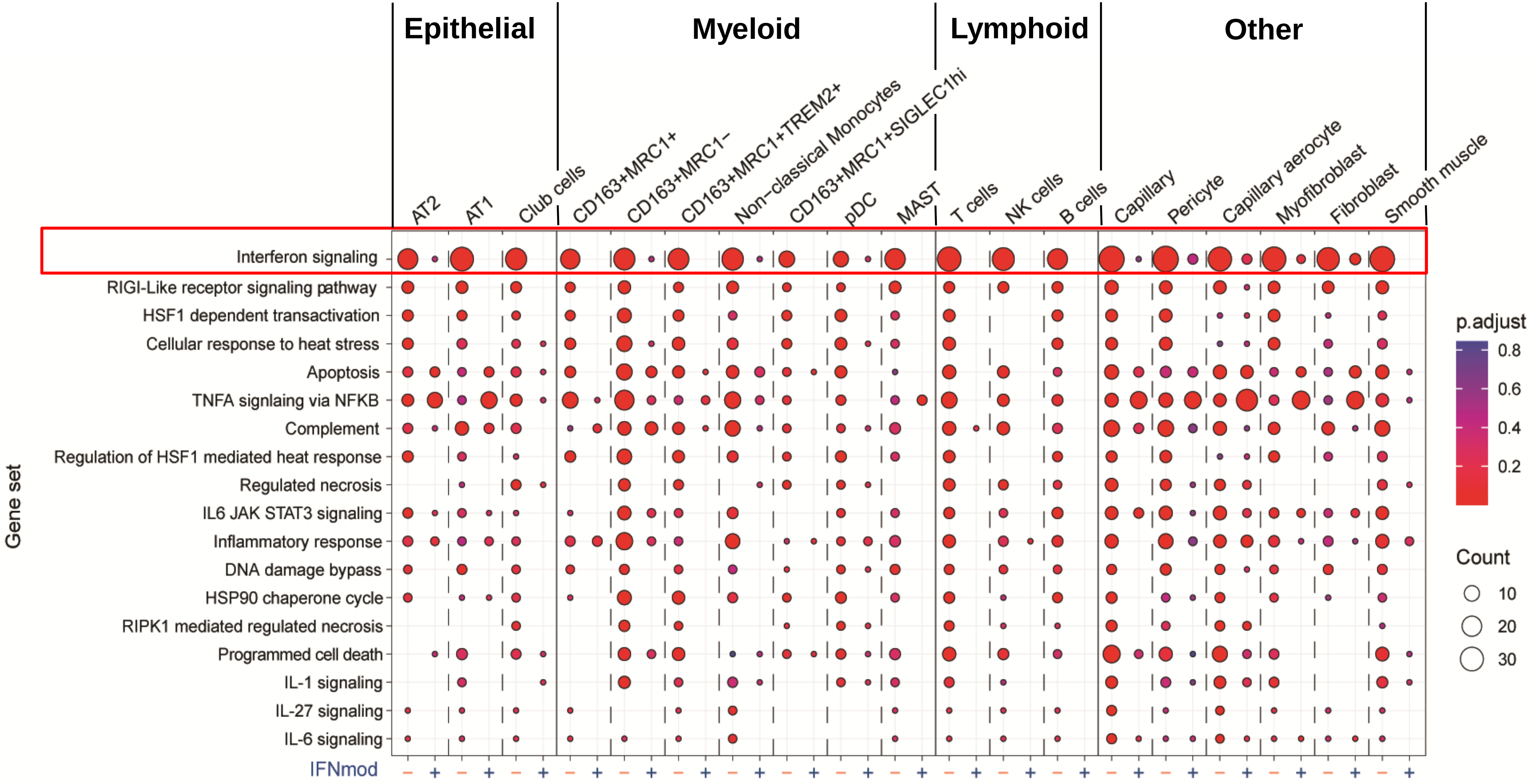


- IFNmod inhibits the accumulation of CD163^{+}MRC1^{-} inflammatory macrophages in the lower airway

sc-RNA-seq of the lower lung

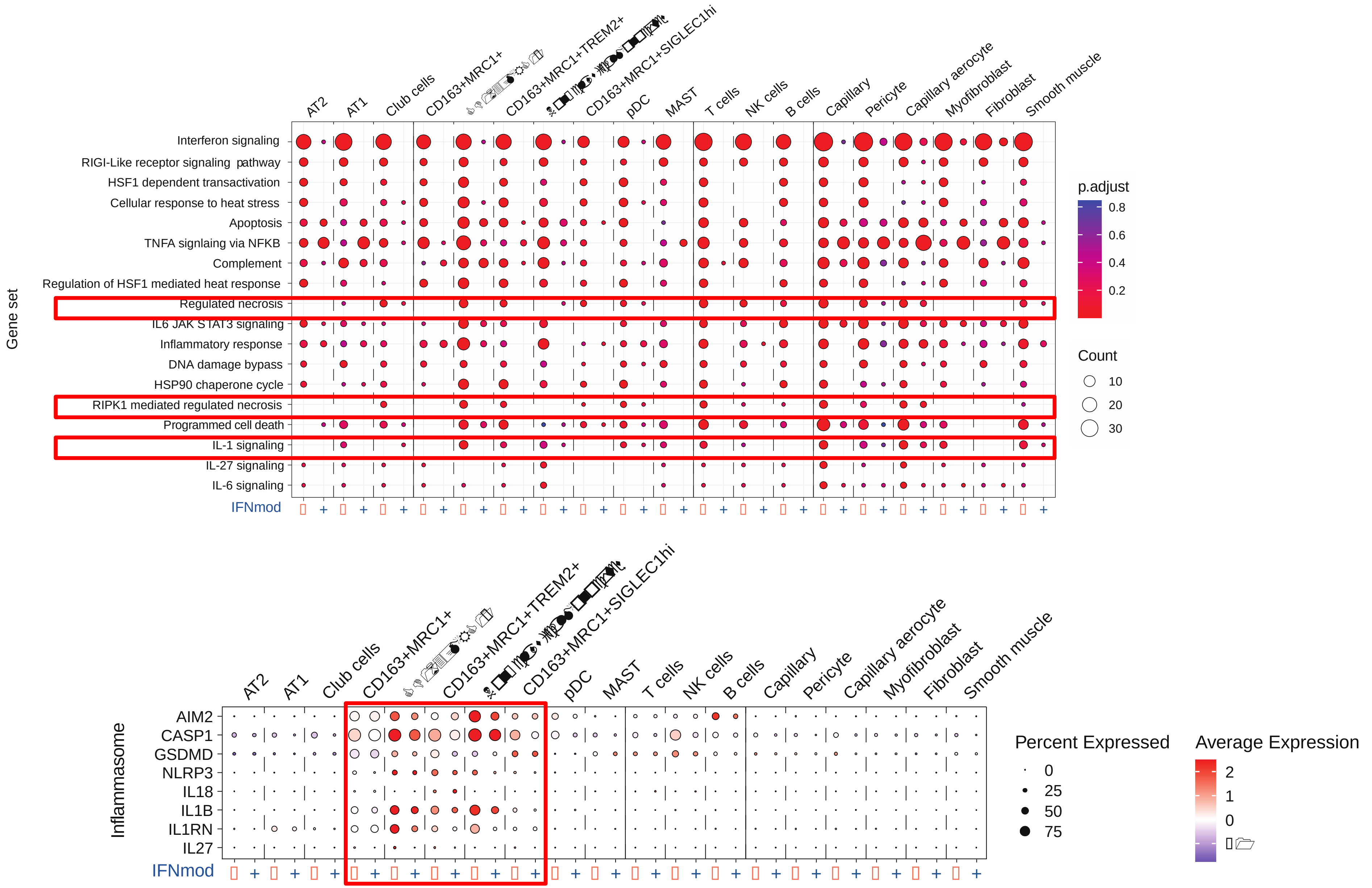


IFNmod treatment reduces IFN-I signaling in all cell subsets in the lung at 2 dpi



- 12-17 ISGs out of the panel of 17 ISGs were significantly lower ($p_{adj} < 0.05$) in IFNmod-treated RMs as compared to untreated RMs at 2dpi

Inflammasome activation largely restricted to monocyte/macrophages in the lung during SARS-CoV-2 infection and IFNmod treatment attenuates this inflammasome activation



Conclusions

Type I IFN pathway plays a key role in SARS-CoV-2 infection

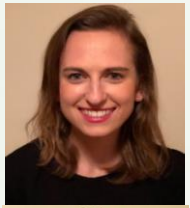
- **IFNmod** treated RMs had :
  - ~3 log reduction to viral loads during treatment, particularly in BAL and lung
  - Less expansion of inflammatory and Siglec-1$^+$ myeloid cells
  - Decreased mediators of inflammatory cell trafficking to the lung
  - Reduced accumulation of CD163+MRC1- macrophages
  - Attenuated antiviral and inflammatory ISGs in PBMCs, whole blood, BAL, and lung

Implications:

- Uncontrolled IFN signaling has detrimental impact on airway pathology and COVID-19 severity
- IFNmod treatment may provide sufficient levels of Type I IFN signaling that inhibits viral replication without inducing hyperinflammation.
- Future studies will help to determine the effects of IFNmod (i) when started post-infection, (ii) with different variants of concern and the effects of (iii) complete blockade of the type I IFN signaling

Acknowledgments

Paiardini Lab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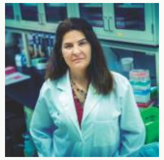

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Angela Birnbaum
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Weizmann Institute of Science

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Ulm University

Frank Kirchhoff
Konstantin Sparrer
Rayhane Nchioua
Maximilian Hirschenberger

OHSU
Jacob Estes
Kathleen Busman-Sahay

Funding
NIH COVTEN P51-OD011132-60S4
William and Lula Pitts Foundation
Fast Grants
Emory MP3 Grant
EPC Pilot Grant

MOLECULES PATHOGENS POPULATIONS PANDEMICS MP3

FAST — GRANTS COVID-19 RESEARCH FUNDING

NATIONAL INSTITUTES OF HEALTH

EMORY | NATIONAL PRIMATE RESEARCH CENTER

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August 29, 1992 - June 18, 2022