CONTROLLING INFLAMMATION

Role of C5a in COVID-19 Pathogenesis

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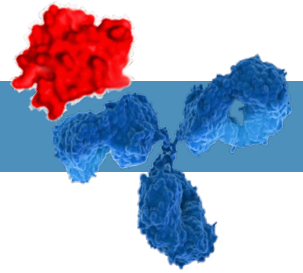
Company Program Updates



LEADING PROPRIETARY ANTI-C5A TECHNOLOGY

- Complete and selective blockade of the biological activity of C5a in vitro and in vivo
- Strong patent coverage on anti-C5a technology until end of 2030 / 2035 with extension

ESTABLISHED CLINICAL EFFICACY FOR LEAD DRUG IFX-1 (INN NAME: VILOBELIMAB)

- Proven anti-inflammatory effect in multiple Phase II studies; favorable safety profile & excellent tolerability in >300 patients
- Statistically significant reduction of inflammatory lesions in Phase IIb Hidradenitis Suppurativa (HS) study; impressive long-term efficacy
- HS full data analysis warrants continued development towards Phase III despite missing the primary endpoint (HiSCR) in Phase IIb study
- Encouraging data in Phase II part of Phase II/III study in patients with severe COVID-19 induced pneumonia

MULTIPLE ONGOING STUDIES AND INDICATION + PIPELINE EXTENSION

- **COVID-19 pneumonia**: Phase III part of study has initiated in EU; Additional sites to be added in the US, EU and other regions
- **HS**: End-of-Phase II meeting held with FDA; positive scientific advice from European Medicines Agency (EMA)
- **ANCA-associated vasculitis (AAV)**: Clinical studies ongoing with data readouts expected in 2021
- **Pyoderma Gangraenosum (PG)**: Clinical study ongoing with data readouts expected in 2021
- **Oncology**: Clinical proof of concept study in preparation
- Potential for **Pipeline Extension** in other inflammatory diseases

TOPICS COVERED IN THIS PRESENTATION:

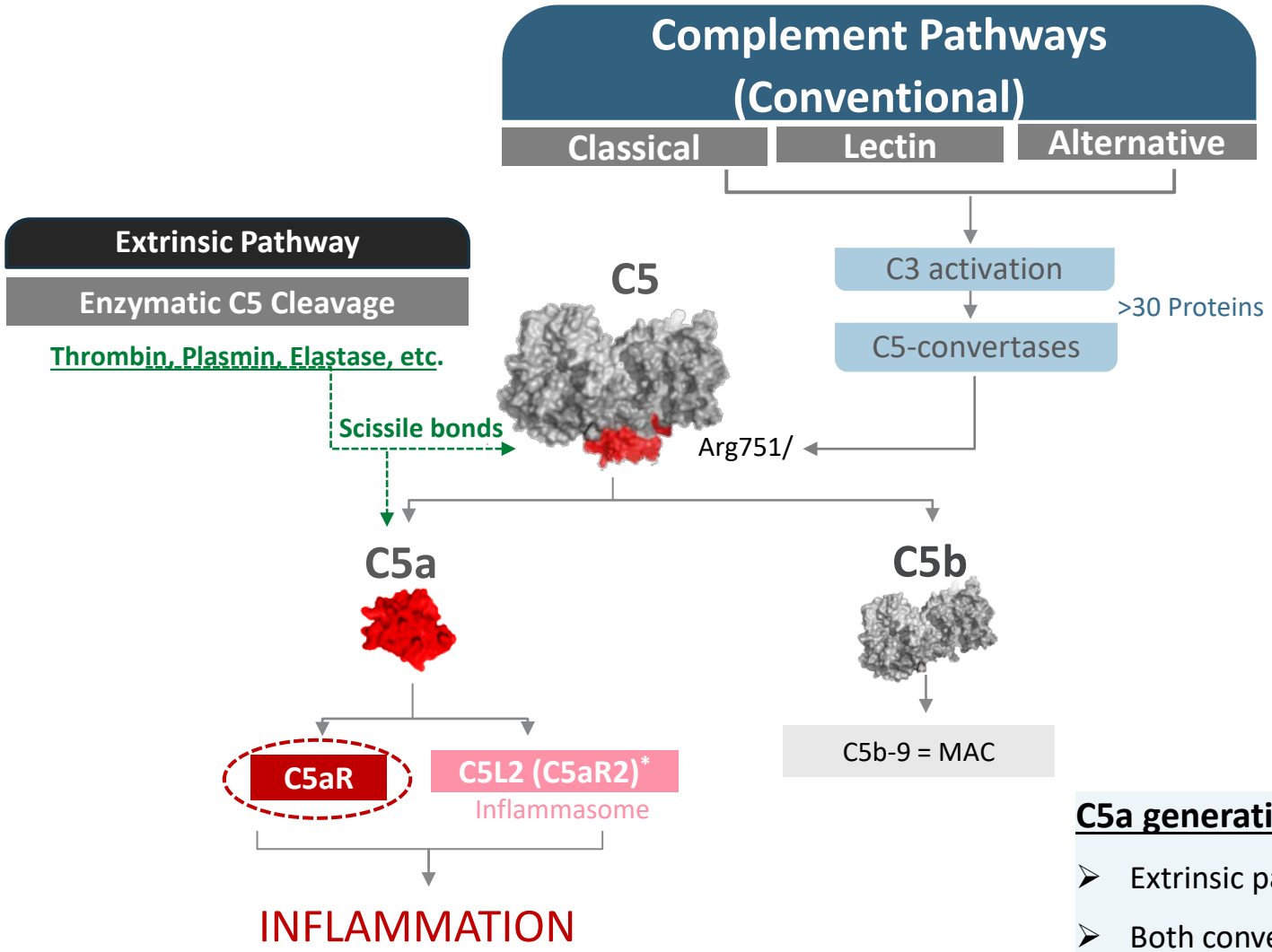
I. SOURCES OF C5A

II. REVIEW: ROLE OF C5A IN INFLAMMATION

III. COVID-19 PATHOGENESIS & POTENTIAL C5A INVOLVEMENT

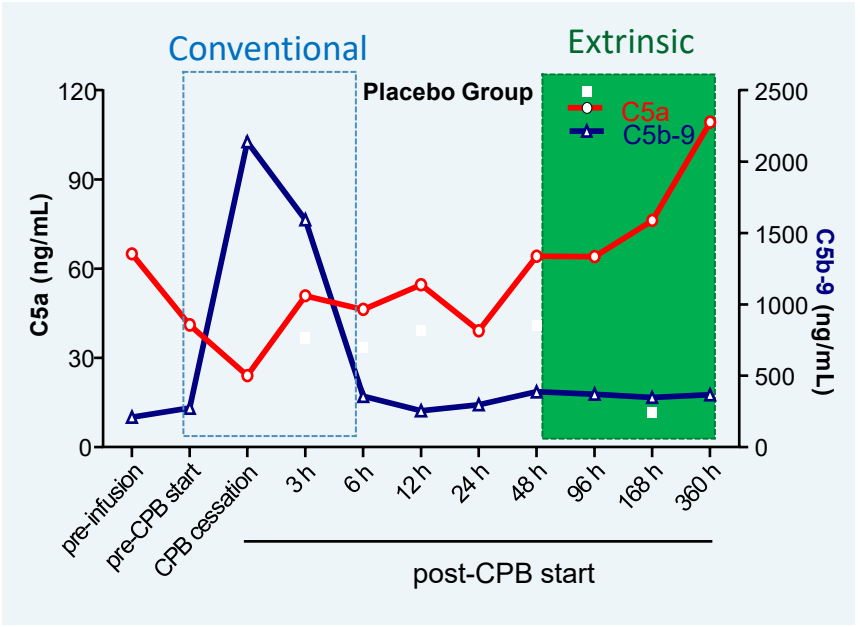
IV. PHASE II COVID-19 TRIAL RESULT & PHASE III PLAN WITH IFX-1

Complement Activation Pathways: Extrinsic Pathway as a Source of C5a



Cardiac Surgery under Cardiopulmonary Bypass

Com. Activation Profile in Placebo Patients (n=25)**



C5a generation:

- Extrinsic pathway occurs in disease condition
- Both conventional and extrinsic pathways could be the source of C5a

Colley et al. MABS. 2018,10 (1), 104; Yu, et al. JBC. 2019, 294 (21): 8384* * Guo R et al. Poster; 27th ICS International Complement Society 2018 Sept. 16th , Santa Fe, New Mexico, USA*

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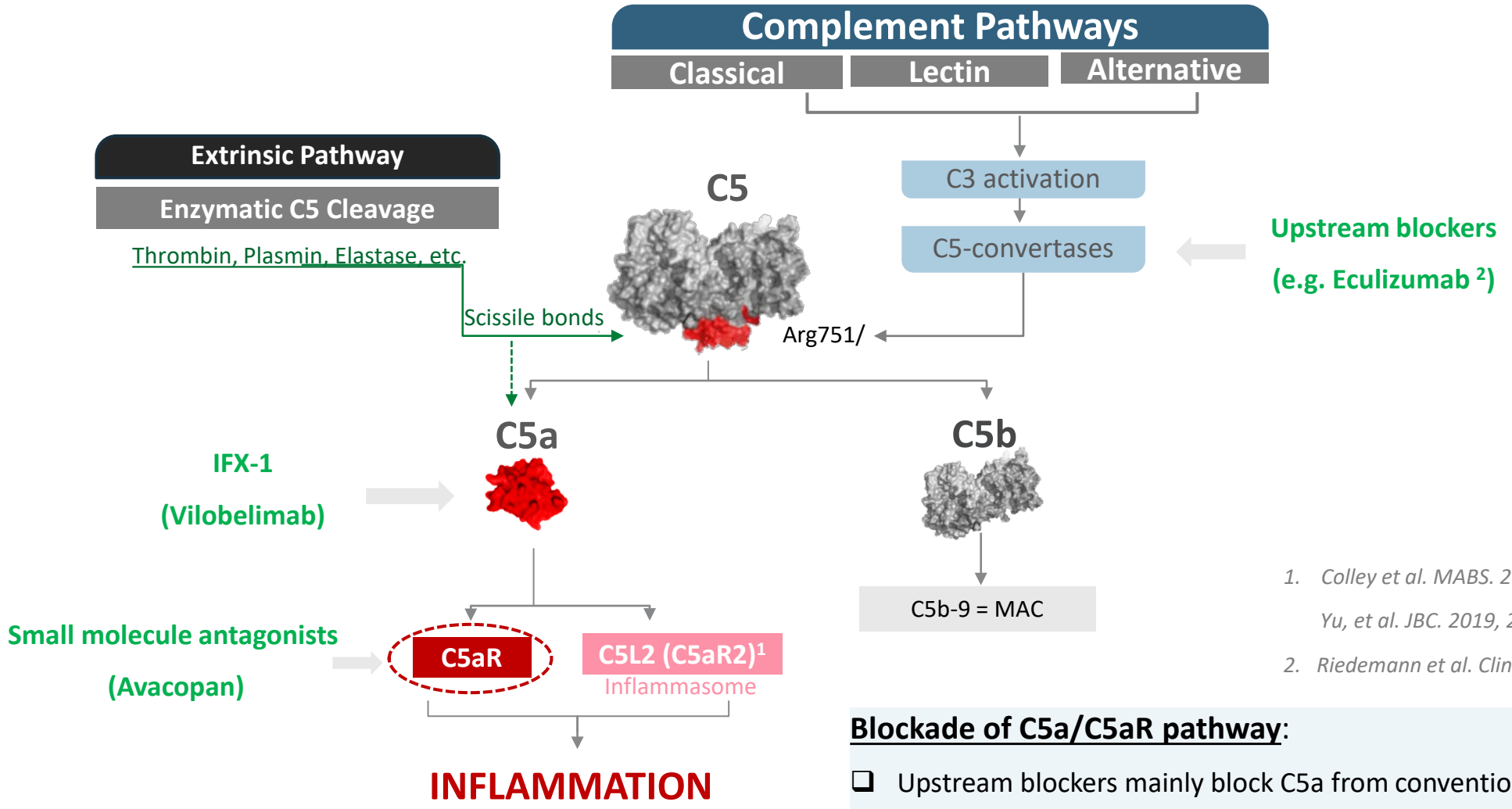
Complement Activation Pathways: Approaches to Block C5a Biological Effect



1. *Colley et al. MABS. 2018,10 (1), 104;*
   Yu, et al. JBC. 2019, 294 (21): 8384;
2. *Riedemann et al. Clin Immunol. 2017 Jul;180:25*

Blockade of C5a/C5aR pathway:

- ❑ Upstream blockers mainly block C5a from conventional pathways
- ❑ IFX-1 blockade: clearance of C5a out of system – rapid and complete
- ❑ C5aR compound blockade: competitive binding to C5aR with C5a

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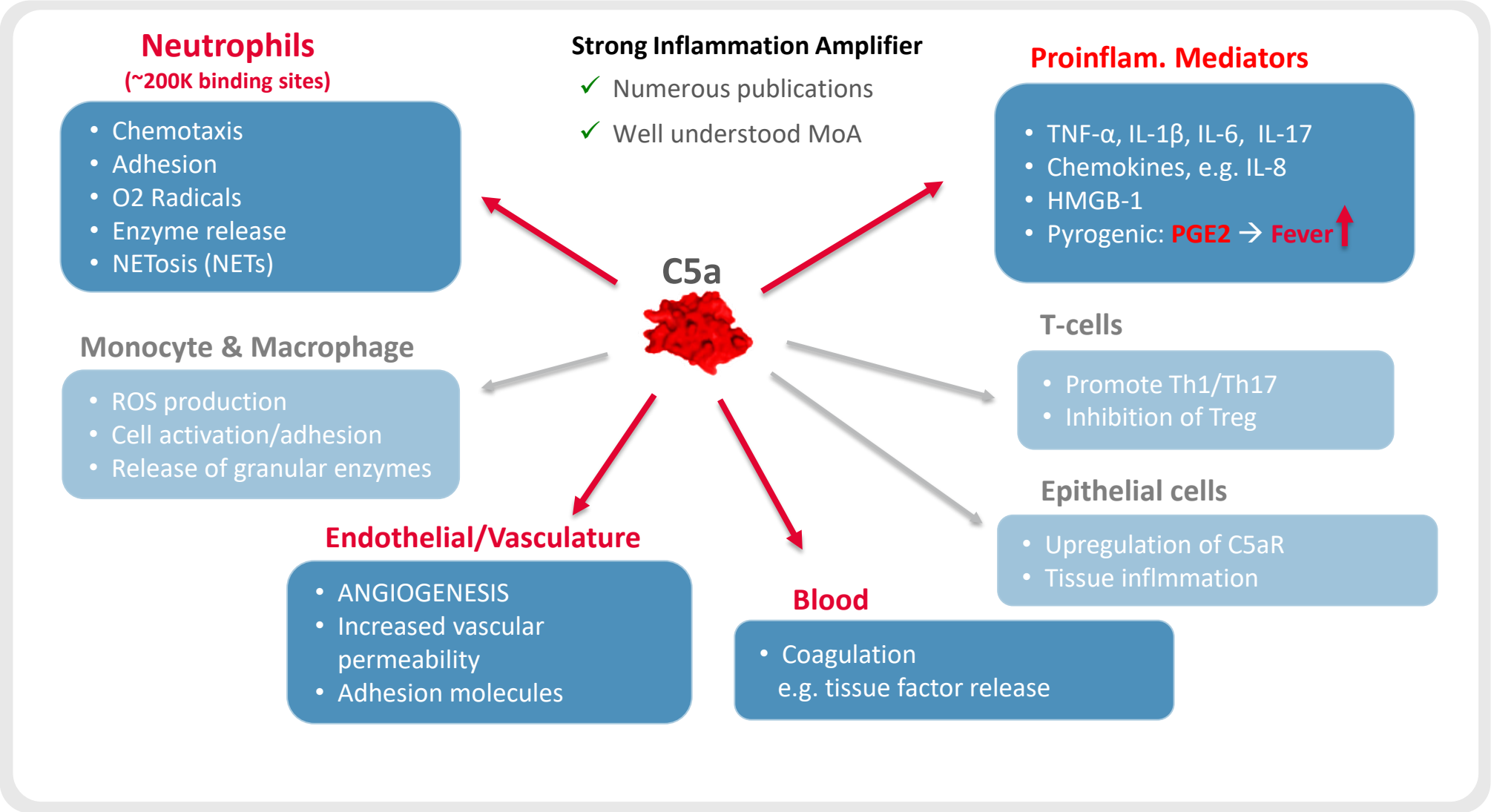
Biological Activity of C5a: Booster of Inflammation

> 5000 publications since the 1960th



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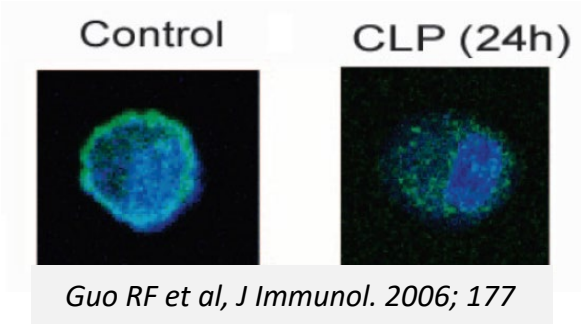
Partial Preclinical Research Summary (1999-2019): C5a/C5aR Axis in Bacterial and Viral Sepsis

Bacterial Sepsis: Role of C5a/C5aR interaction *(Rodent Sepsis Models, 1999-2007 at U of Michigan Ward Lab):*



Guo RF et al, J Immunol. 2006; 177

- ❑ C5aR internalizes in neutrophil – contribute to disease severity (*Guo et al, J Immunol. 2006; 177*)
- ❑ **Neutrophil dysfunction:** start with a hyperactive phase then to an immunosuppressive state

  (Riedemann et al, Immunity, 2003; 19; Huber-lang et al, J Immunol, 2002; 169)
- ❑ Prolonged lifespan of neutrophil due to delayed apoptosis *(Guo et al, JLB, 2006; 80)*
- ❑ Increased β2 and β1 integrins on neutrophil, increasing **pathogenicity** *(Guo et al, J Immunol. 2002; 169)*

- ❑ Contributes to thymocyte apoptosis via an indirect mechanism, leading to **lymphopenia** (*Guo et al, J Clin Invest. 2000; 106*)
- ❑ Excessive C5a Enhances **Coagulopathy** through tissue factor releases *(Laudes et al, A.J. Pathol, 2002; 160)*
- ❑ Blockade of C5a/C5aR signaling improves sepsis survival *(Riedemann et al, J Clin Invest. 2002; 110)*

C5a/C5aR pathway is critical in viral sepsis development *(Monkey and Mouse Models, 2013-2018; Res. Collaboration):*

- ❑ In a monkey model of **H7N9-induced viral pneumonia**, IFX-1 markedly improved lung injury and reduced viral load *(Sun et al, CID, 2015)*
- ❑ In a mouse model of **MERS-CoV-induced viral pneumonia**, anti-C5aR mAb remarkably improved lung pathology and reduced viral titer. (*Jiang et al., Emerging Microbes & Infections, 2018)*

C5a/C5aR blockade attenuates lung injury by reducing inflammatory cell infiltration & promotes virus CL by **preserving innate immunity**

Conclusion: C5a-induced neutrophil activation is a major pathogenic event in both bacterial and viral Sepsis

- *Neutrophil Facts: 40-60% in white blood cells; ~100 bn cells/day; Half-life in circulation: 6-12 hours; One cell has 200K binding sites for C5a*

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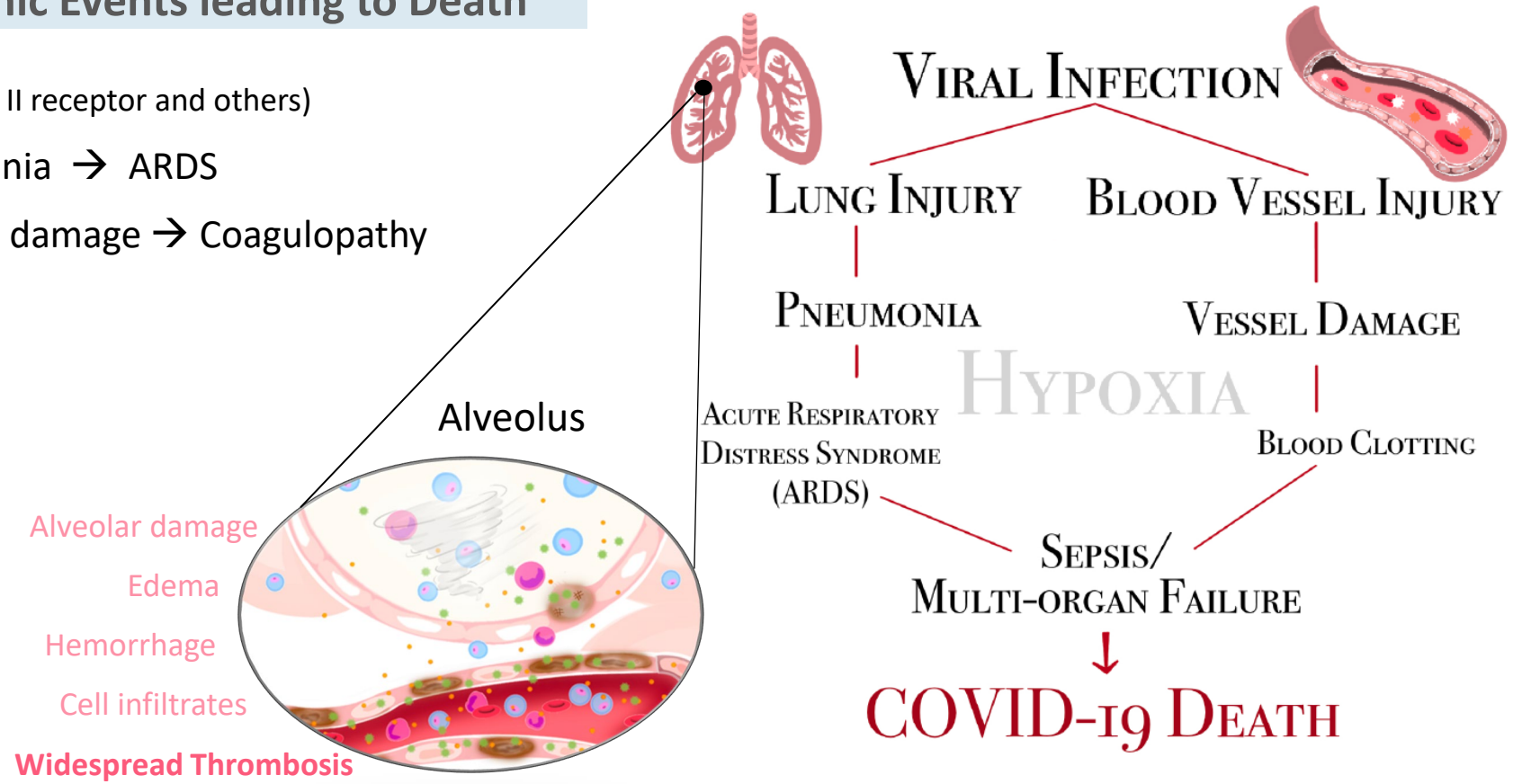
COVID-19 Pathogenesis: Overview

COVID-19: Critical Pathogenic Events leading to Death

- SARS-COV2 infection (via. ACE II receptor and others)
- Epithelial injury → Pneumonia → ARDS
- Endothelial injury → Vessel damage → Coagulopathy
- Hypoxia
- Viral Sepsis
- Multiorgan Failure
- Death



Almost all the COVID-19 deaths present with sepsis (100%), respiratory failure (98%) & ARDS (93%). *Zou et al., Lancet 2020 28; 395*

*Sepsis is a life-threatening organ dysfunction caused by a **dysregulated host response** to infection (WHO definition)*

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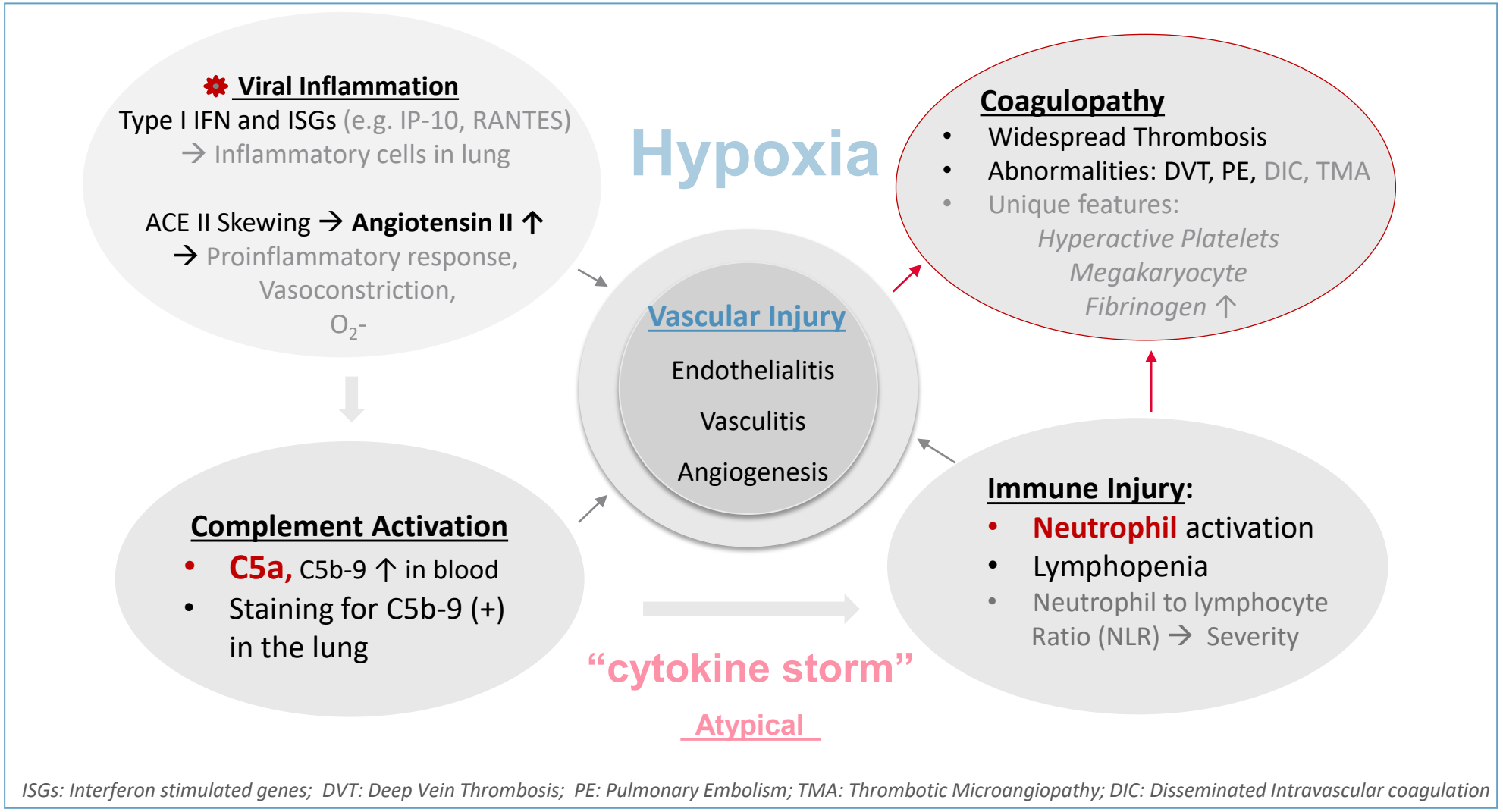
COVID-19 Pathogenesis : Interplay of Viral Inflammation and Host Response

Host Responses: Complement and Coagulation are highly dysregulated in COVID-19



ISGs: Interferon stimulated genes; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; TMA: Thrombotic Microangiopathy; DIC: Disseminated Intravascular coagulation

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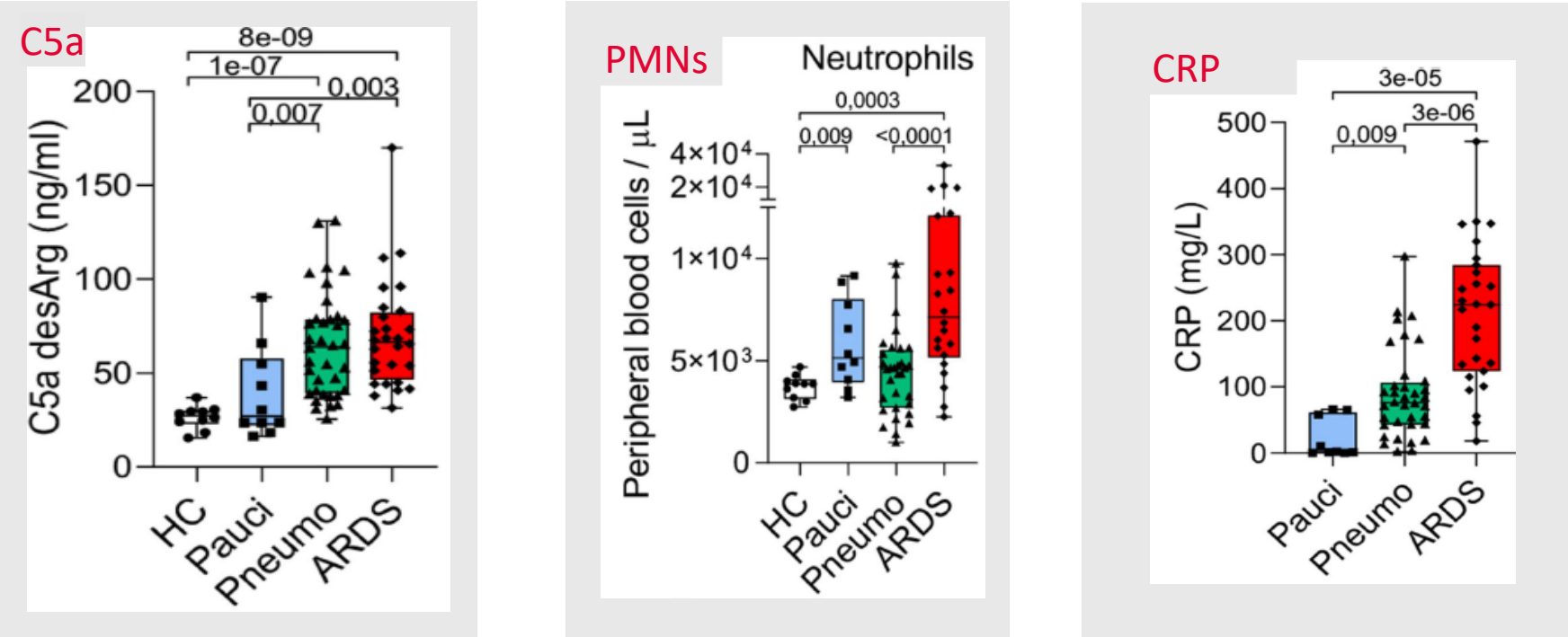
COVID-19 Pathogenesis: Potential Role of C5a

Complement Activation in COVID-19: C5a Level Predicts Disease Severity

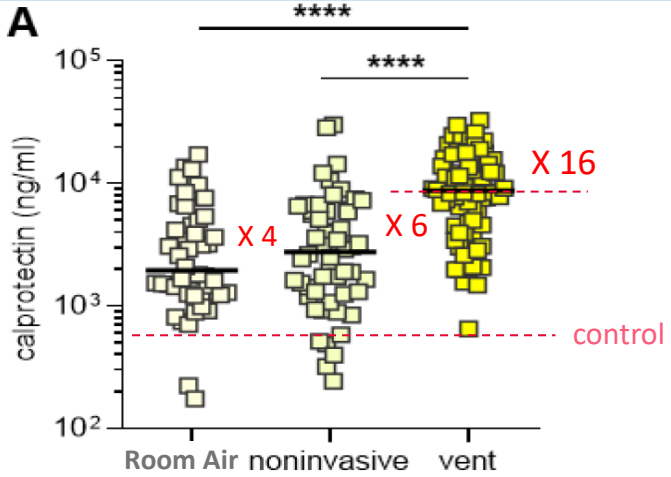


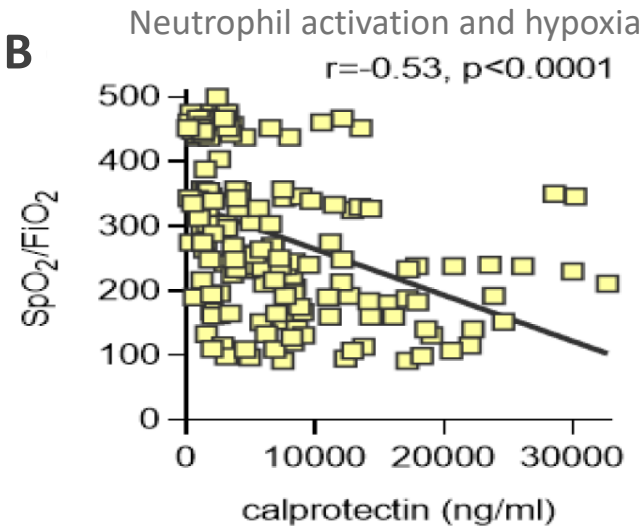
Carvelli et al, Nature, July 2020: doi: 10.1038/s41586-020-2600-6

- C5a levels were positively correlated with disease severity (*C5a was measured by BD ELISA*)
- Positive correlations among C5a, neutrophils, and CRP (inflammation) – Causal Role of C5a/Neutrophils in COVID-19

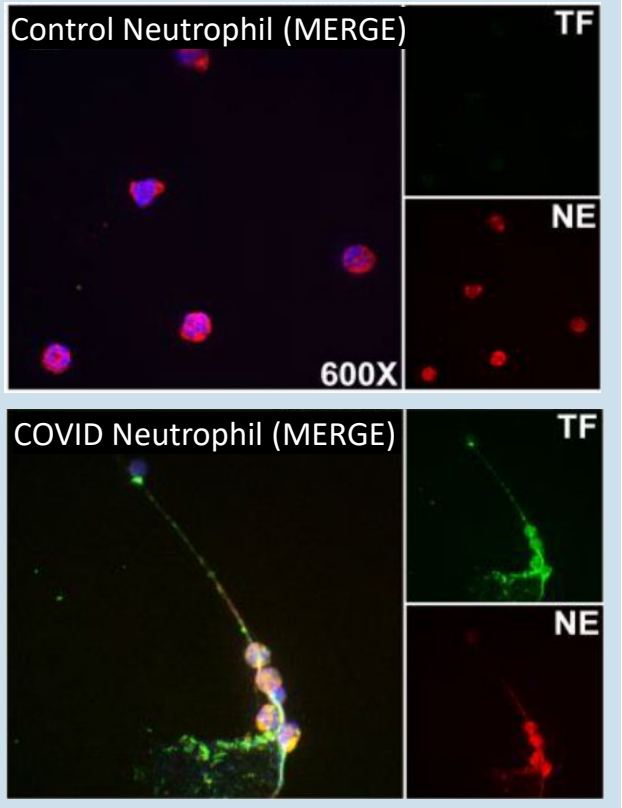
COVID-19 Pathogenesis: Potential Role of C5a and Neutrophil

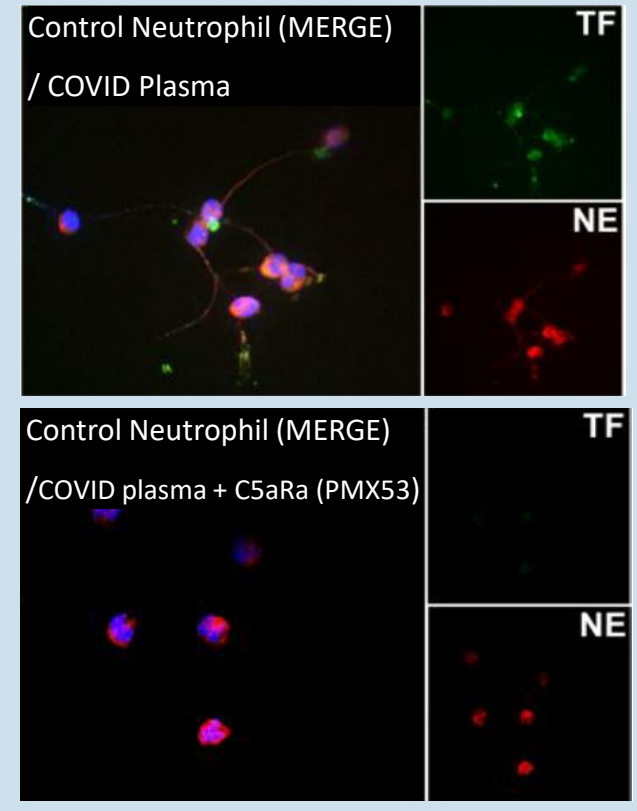
Neutrophil Activation In COVID-19





Neutrophil tissue factor (TF) generation and NETosis in COVID-19 are C5a-dependent processes





- In COVID-19, Neutrophil is highly activated, and its activation correlates with hypoxia
- Excessive C5a in COVID-19 patients leads to **tissue factor generation** and **Netosis**.

Conclusion: C5a-activated neutrophil is a major pathogenic cell in COVID-19

Shi et al. J Leukoc Biol. 2020 September; 1-6; *Skendros et al. J Clin Invest. 2020. August. Https://doi.org/10.1172/JCI141374.*

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IFX-1 Phase II/III Study in COVID-19 Pneumonia – Phase II Part

PHASE II PART DESIGN (EXPLORATORY)

- Adaptive, **open-label**, **randomized**, multicenter trial in EU
- IFX-1 + Best Supportive Care (BSC) vs. BSC alone
- 30 patients (15 IFX-1 vs. 15 BSC alone)
- **Primary endpoint:** Relative change (%) from baseline in Oxygenation Index (PaO2 / FiO2) to day 5
- **Key secondary endpoints:**
  - 28-day all-cause mortality rate
  - Frequency, severity, and relatedness to study drug of treatment-emergent adverse events (AEs) and serious adverse events (SAEs)

STUDY RESULTS

- **Baseline characteristics:** Comparable
  - Comorbidities (≥ 2): 4 in IFX-1 group, and 1 in BSC;
  - 10/15 on mechanical ventilator for each group at day 1
  - Deaths occurred only to the patients on mechanical ventilator

All-cause 28-day mortality analysis

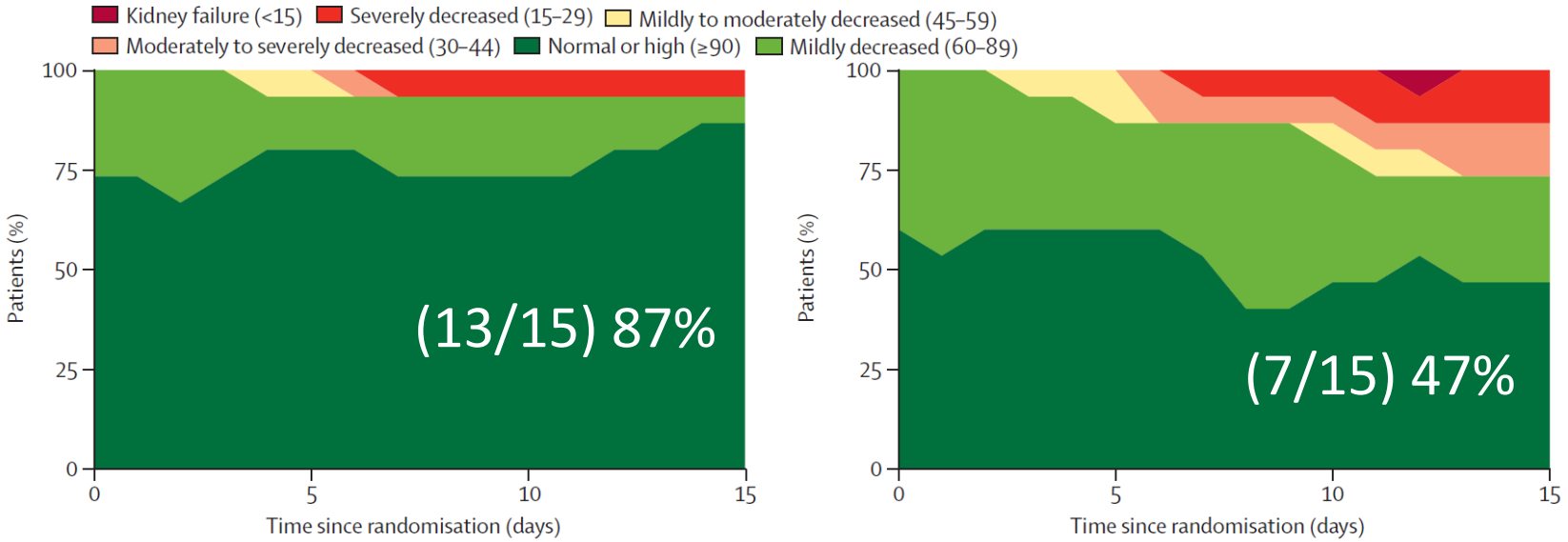
IFX-1 Treated	BSC Control
n= 15 (10 vent @day1)	n=15 (10 vent @day1)
2 deaths (20% Vent.)	**4 deaths (40% Vent.)**
No severe PE	3 severe PEs
1 severe COPD (Excl. Criteria)	All COVID-19 death
1 ventilator tube issue	with respiratory failure
2 PEs reported as SAE	**6 PEs reported as SAE**

PE: Pulmonary Embolism; COPD: Chronic obstructive pulmonary disease

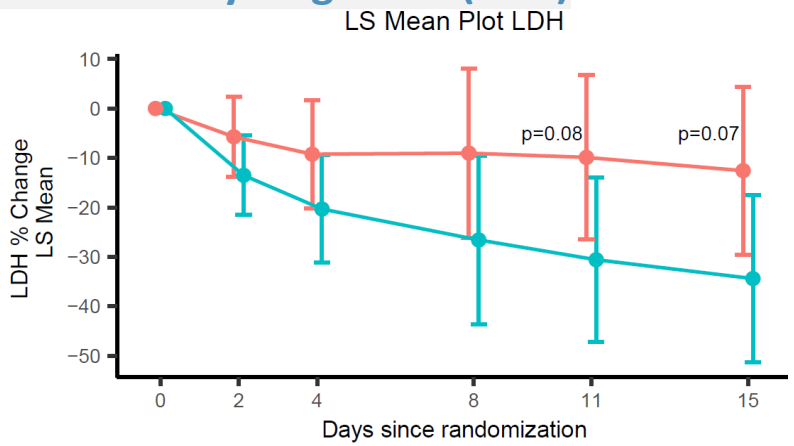
Vlaar, A et al. Lancet Rheumatol 2020. https://doi.org/10.1016/S2665-9913(20)30341-6

IFX-1 Phase II Study Results in COVID-19 – Tissue Injury & Organ Damage

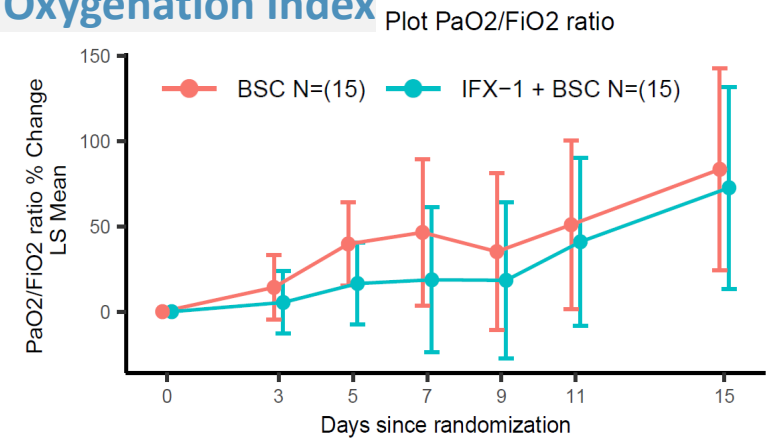
Kidney Function (eGFR): IFX-1 P=0.05 @Day 15 Control Group (BSC)



Lactate Dehydrogenase (LDH)



Oxygenation Index



Summary:

❑ **Kidney Function** (15-D Shift Plots):

BSC Control: At day 15, there were 4 patients with renal impairment; 7 of 15 patients showed normal eGFR values.

IFX-1 group: only 1 patient with renal impairment; 13 of 15 patients showed normal eGFR values; P=0.05.

❑ **Tissue injury Marker LDH:**

LDH/change curve showed a steady decline in IFX-1 group. (P=0.07 @d15)

❑ **Oxygenation Index (OI)**:

No statistically significant differences in chosen primary endpoint of PaO2/FiO2 ratio, likely due to the facts that:

OI measurements were dependent on patient positioning, in supine or in prone, leading to high variability

Vlaar, A et al. Lancet Rheumatol 2020. https://doi.org/10.1016/S2665-9913(20)30341-6

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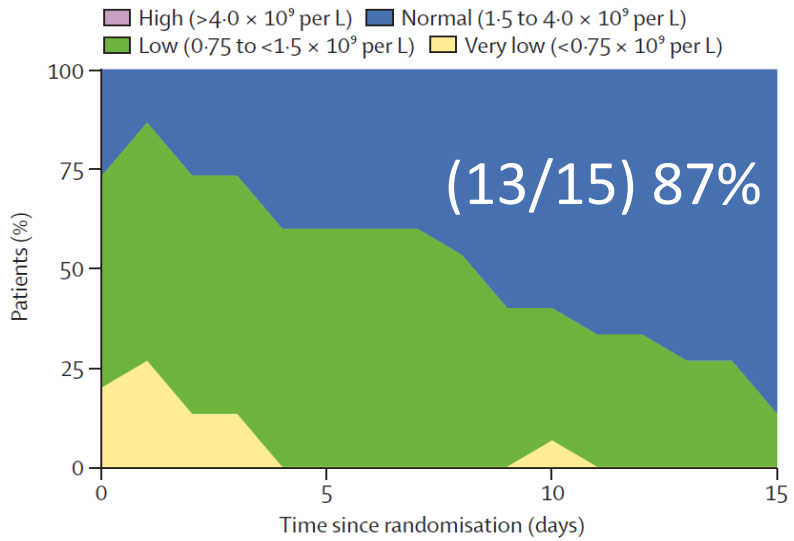
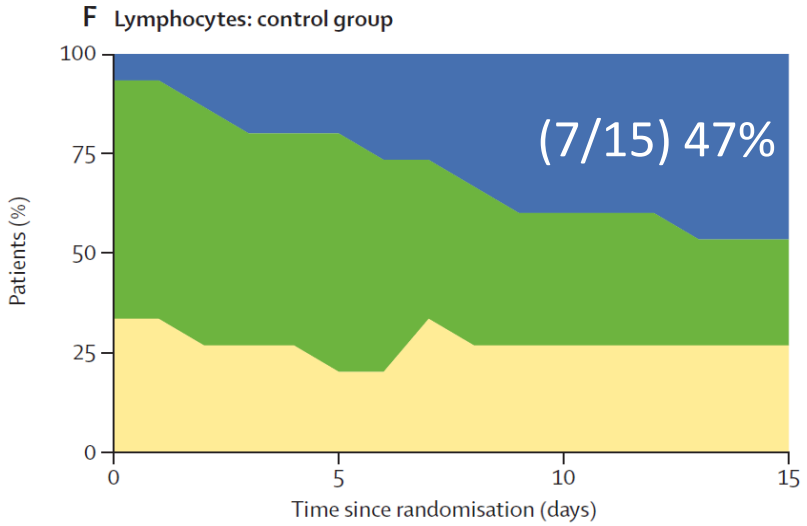
IFX-1 Phase II Study in COVID-19 : Lymphopenia and Fibrinolysis

Lymphocyte Counts: IFX-1 P=0.05 @Day 15 Control Group (BSC)





Data Summary

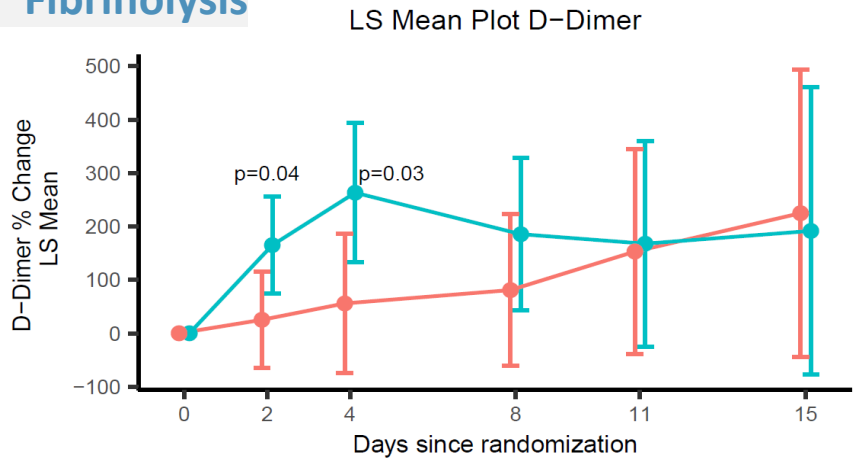
❑ **Lymphopenia** (15-D Shift Plots):

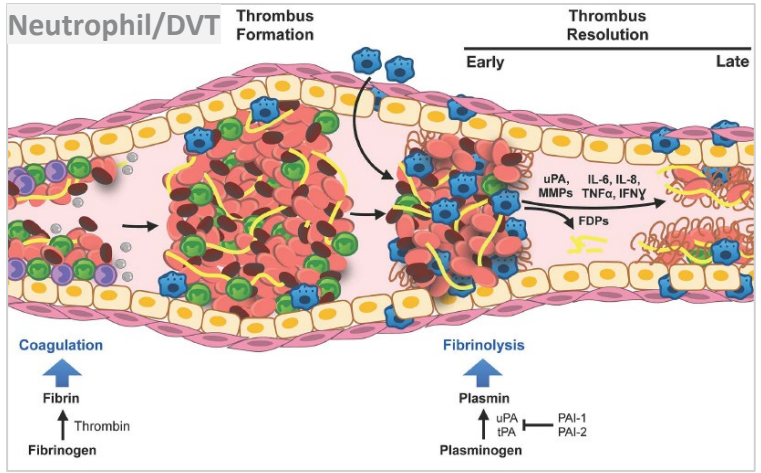
At day 15, in treatment group, 13 out of 15 showed the normal lymphocyte counts; in the control group, only 7 out of 15 showed the normal counts; P=0.05

❑ **Fibrinolysis (D-Dimer)**:

D-dimer, as a fibrin lysis product, reflects hyper-coagulable state **AND** hyper-fibrinolytic state. After IFX-1 treatment, D-dimer showed transient increases at day 2 and 4 (P<0.05) vs. control – suggesting high levels of clot lysis

Fibrinolysis





*Mukhopadhyay et al. Frontiers in Immunol, 2019 June

Innate Immune Cells in DVT*:

Thrombus infiltrating neutrophils and macrophages mobilize plasmin and matrix metalloproteinases (MMPs), promoting **fibrinolysis**

Vlaar, A et al. Lancet Rheumatol 2020.

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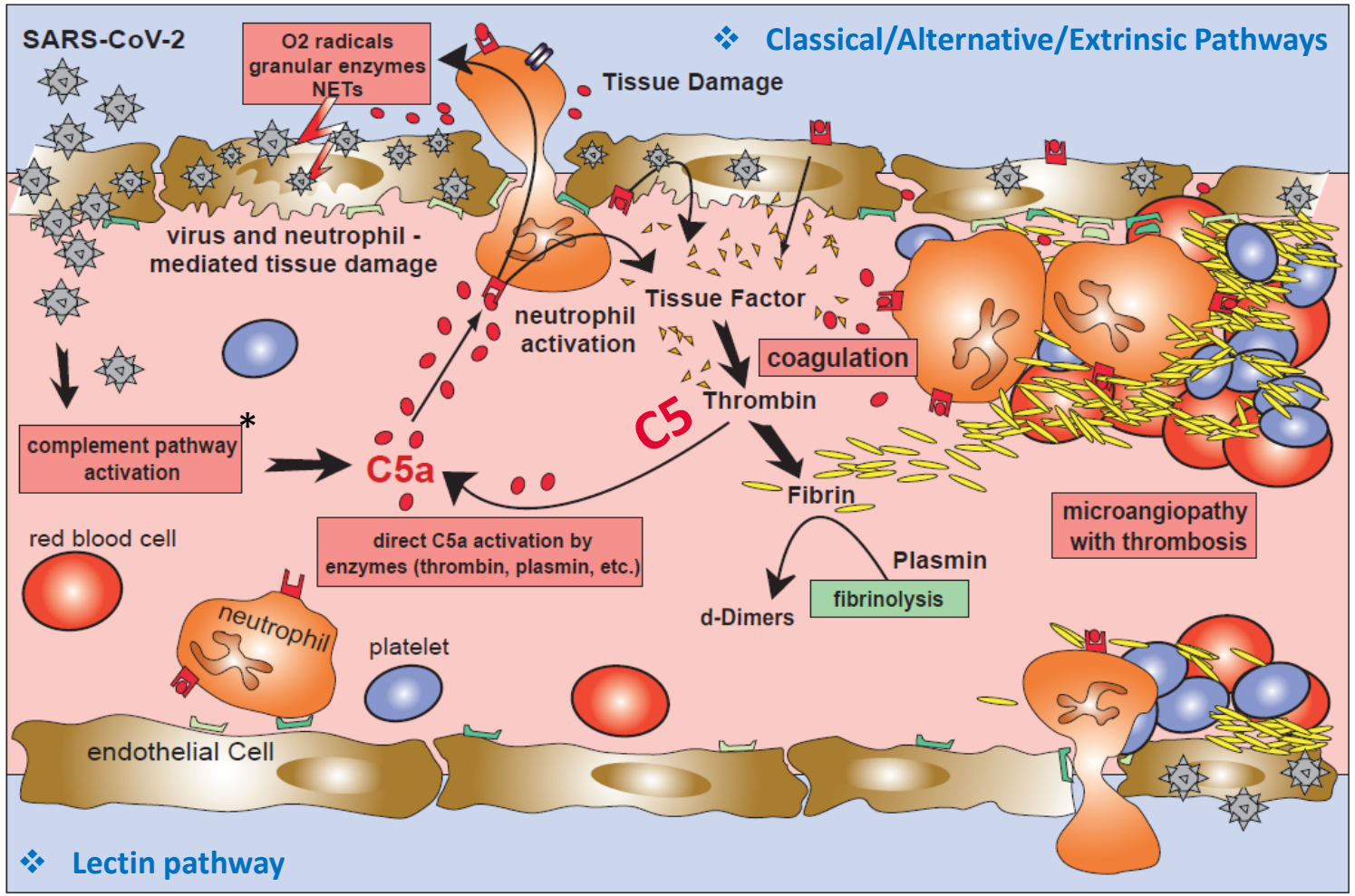
Potential Role of C5a in COVID-19 – *Proposed MOA of IFX-1*

Potential Role of C5a in COVID-19:

- SARS-CoV-2 infection activates the complement system leading to C5a generation via lectin pathway; Other pathways follow.
- C5a activates neutrophils leading to endothelial injury through generation of O_2 radicals, granular enzyme releases and NETs.
- C5a induces tissue factor release from neutrophils and endothelial cells, promoting coagulation.
- Thrombin, plasmin and other enzymes can further generate C5a through direct cleavage of C5, establishing a viscous cycle of "C5a-neutrophil-enthelial injury-thrombosis-C5a".



IFX-1 MOA - Immune Correction:

- ✓ Attenuate SARS-COV2 induced tissue damage (e.g. LDH, Kidney function)
- ✓ Mitigate the risk of coagulopathy, and facilitates fibrinolysis (e.g. D-dimer)
- ✓ Expediate the restoration of innate and adaptive immunity (e.g. D-dimer, lymphocyte counts)

**Gao et al, 2020 March; MedRXiv, 2020.03.29.20041962;* *Vlaar, A et al. Lancet Rheumatol 2020. https://doi.org/10.1016/S2665-9913(20)30341-6*

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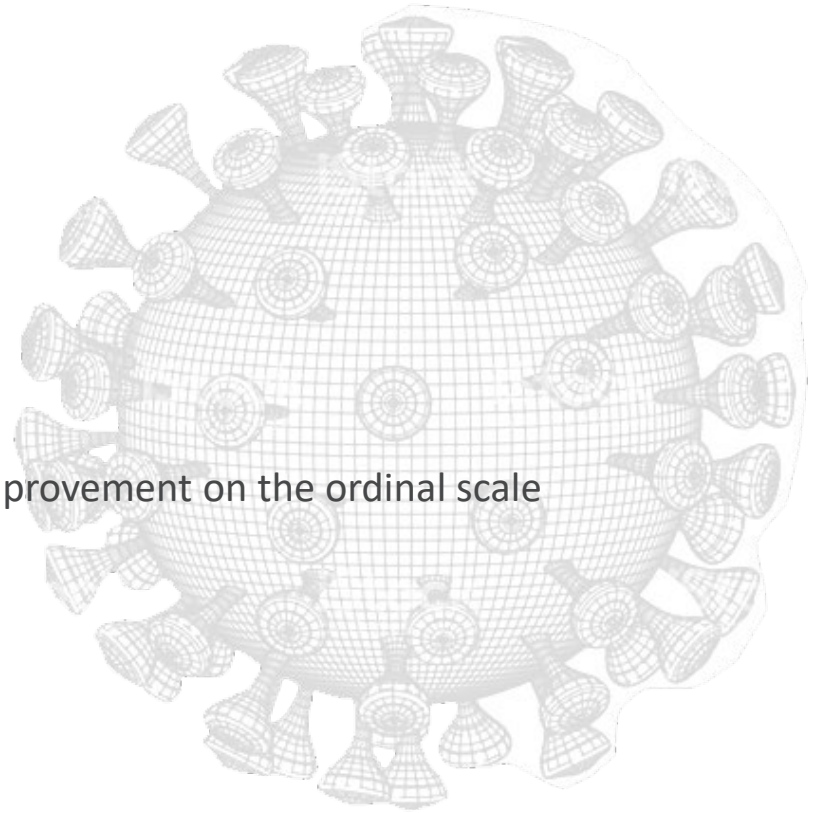
Phase III Part Initiated in COVID-19 Pneumonia

MOVING INTO PHASE III FOLLOWING ENCOURAGING TOPLINE RESULTS FROM PHASE II

STUDY DESIGN

- Double-blinded, randomized, placebo-controlled trial
  - Adequately powered for statistical analyses
- ~360 early intubated, critically ill patients with COVID-19 induced pneumonia
- Interim analysis currently planned after enrollment of 180 patients
  - Potential for an early stop for efficacy or futility
- Primary endpoint: 28-day all-cause mortality
- Other key endpoints include assessments of organ support, assessment of disease improvement on the ordinal scale
- First site initiated for enrollment in the Netherlands
  - Regulatory approval has been granted to start the trial in Germany
  - Additional sites to be added in the US, Europe and other regions



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