



Control of hyperinflammation due to dysregulation of the terminal complement pathway and the “lipid” mediated storm

Role of the innate immune system
Learnings from COVID-19
to prevent winter exacerbations from respiratory viral and bacterial infections

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October 27th 2021

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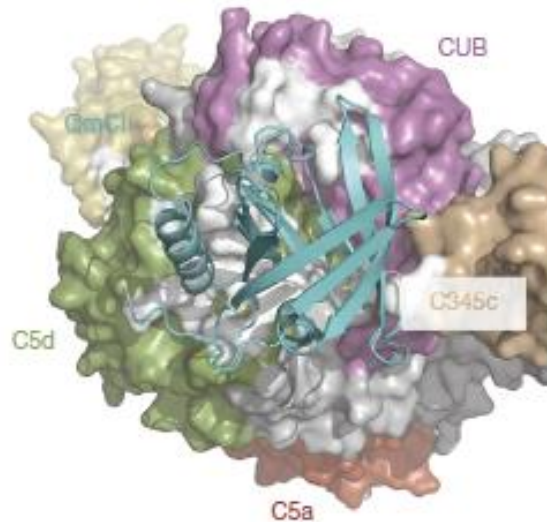
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Topics to be covered

- Introduction to nomacopan, learning from COVID–19 pneumonia about at-risk patient populations in order to control the wide range of winter respiratory viral & bacterial infections
- A focus on chronic lung diseases and winter infections – the lung as the site of initiation of “Hyper inflammatory state”
- Vascular Disease – Thrombotic Micro-Angiopathy (TMA) defining severity with a biomarker that helps to decide on who to treat
- Sepsis and trauma – biomarker needed to guide the choice of patients to treat and the effectiveness of dual inhibition of C5 and LTB4

Introducing nomacopan, a bifunctional anti-inflammatory protein that independently inhibits C5 & LTB4

Complement C5 binding
 K_D 0.1nM

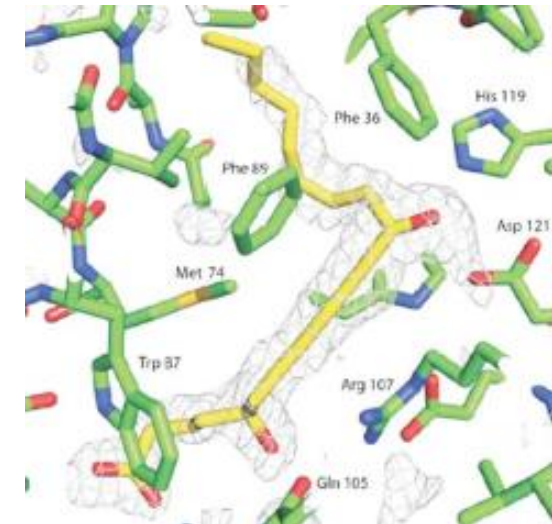


Top view of nomacopan (Cyan) bound to C5 Jore et al., Nat Struct Mol Biol. 2016

Independent C5 & LTB4 inhibitory activity

- Binds conserved region of C5 remote from eculizumab binding site
- Binding affinity tuned by natural selection:
 - a) Binds C5 at normal physiological levels, preventing release of C5a and formation of C5b-9 (the Membrane attack complex)
 - b) Binds LTB4 at the elevated levels (needed for cell activation) which occur at sites of inflammation due to synthesis of LTB4
- Inhibit the effects of 4 G-protein-coupled receptors (GPCRs: C5aR1, C5aR2, BLT1 and BLT2)

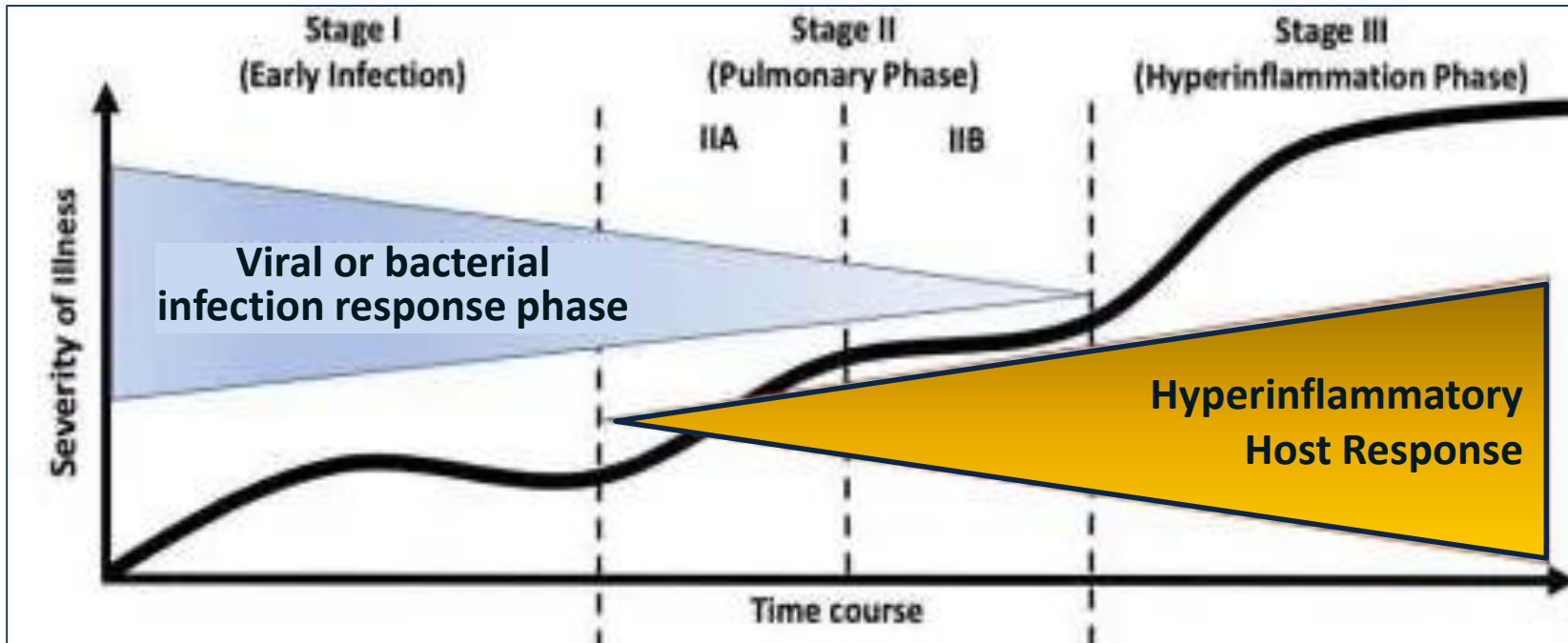
Eicosanoid LTB4 binding
 K_D 0.13nM



Detail nomacopan binding to LTB4 Roversi et al., J Immunol. 2013

Learning from COVID – the Patients & Diseases

In multiple respiratory infections (viral in particular) there are three overlapping phases



- **Stage 1** symptoms during the initial phase are often limited to fever, headache, sneezing and malaise. Initial innate immune response
- **Stage 2** the host inflammatory phase “kicks-in” with coughing and sore throat running nose and breathlessness may begin. Complement and leukotriene pathway may become dysregulated
- **Stage 3** - Hyperinflammation host response is characterised by development of respiratory failure and in some multi-organ failure for susceptible patients. Wide range of inflammatory mediators including cytokines

Who are at risk of the hyper-inflammation phase with a respiratory infection?

Multi- morbidity patients

Patients at risk of hyperinflammation phase usually have “winter exacerbations” of their chronic diseases. They are more often elderly and male.

They have chronic diseases e.g.: obesity, diabetes, coronary artery disease, hypertension, immune disease or chronic lung disease (**COPD** and **Asthma**) and Cancers

Elevated C5 and LTB4 found in all these illness including the Elderly

Hyperinflammation is disease agnostic

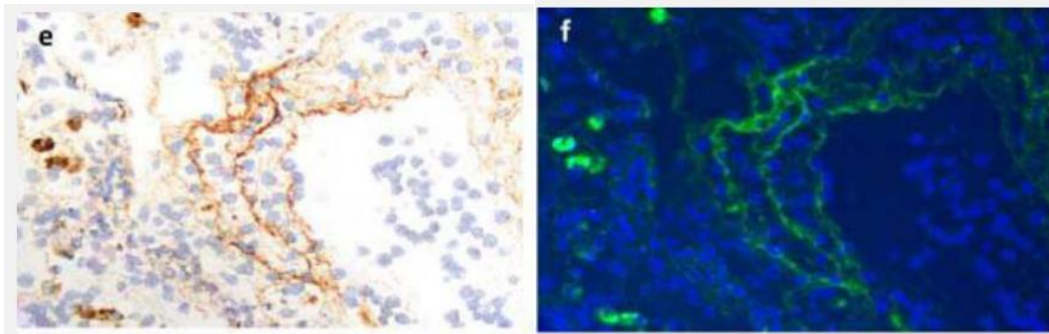


- **Williamson, E. J. et al. OpenSAFELY:** factors associated with COVID-19 death in 17 million patients. Nature <https://doi.org/10.1038/s41586-020-2521-4> Nature www.nature.com
- **WHO Sepsis** <https://doi.org/10.1038/s41586-020-2521-4> (2020).
- **Gotts JE, Matthay MA. Sepsis:** pathophysiology and clinical management. British Medical Journal 2016.
- **NICE guideline [NG51]** Published: 13 July 2016 Last updated: 13 September 2017 **Winter Hospital Admissions**

Complement terminal pathway dysregulation in COVID – 19 pneumonia (C5b-9 proposed as indicator of severity)

Complement C5b-9 associated microvascular injury pathogenesis of severe COVID-19 infection.

Magro C et al. J 2020;220:1-13

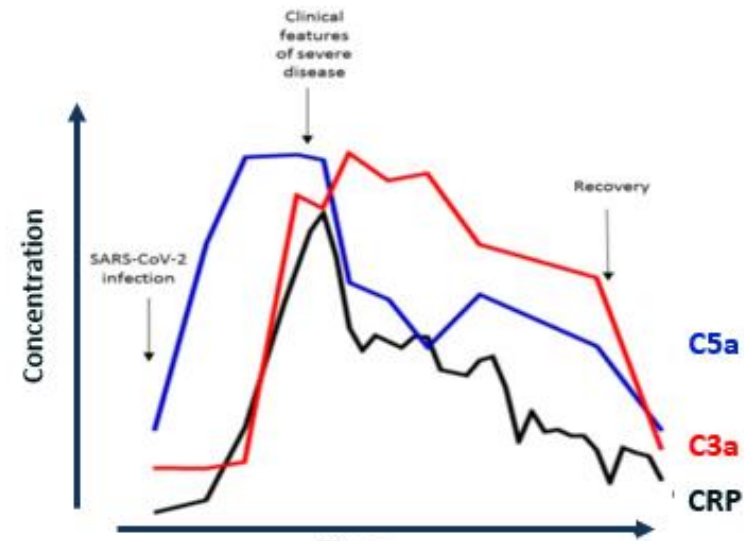


Staining of alveolar epithelium and endothelial cells plus fluorescence staining
Associated staining of systemic arteries

Dialysate levels in severe COVID-19 pneumonia

Predecki M, Clarke C, Medjeral-Thomas N et al.
Clin Kidney J 2020; R1

Pattern of C5a and C3a as severe respiratory disease

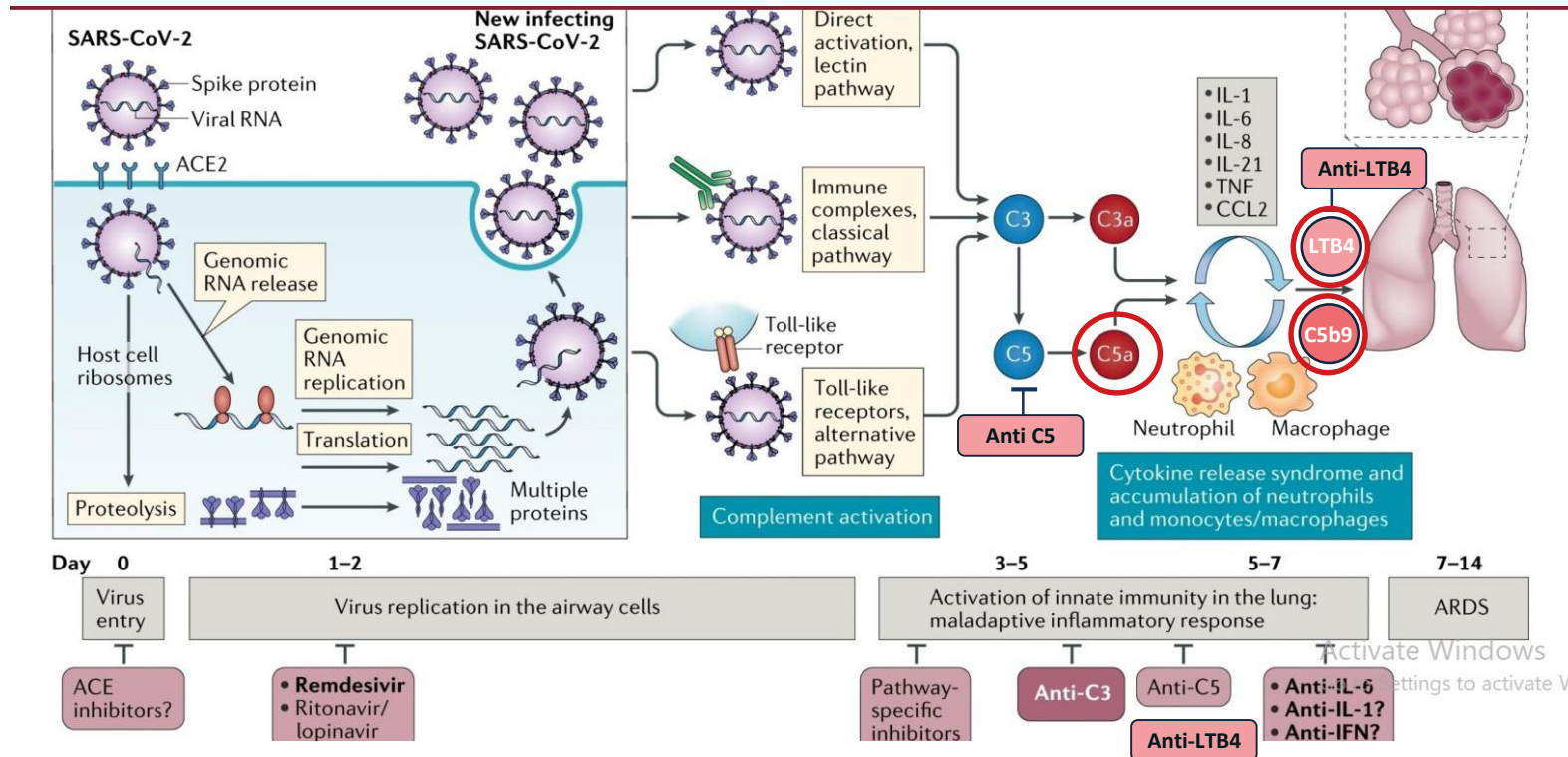


Relative time scale for the appearance of C5a and CRP during severe COVID-19 Pneumonia in renal failure patients

SARS-CoV-2 involves all complement pathways and leukotrienes leading to multiple cytokines elevations in serum and lung

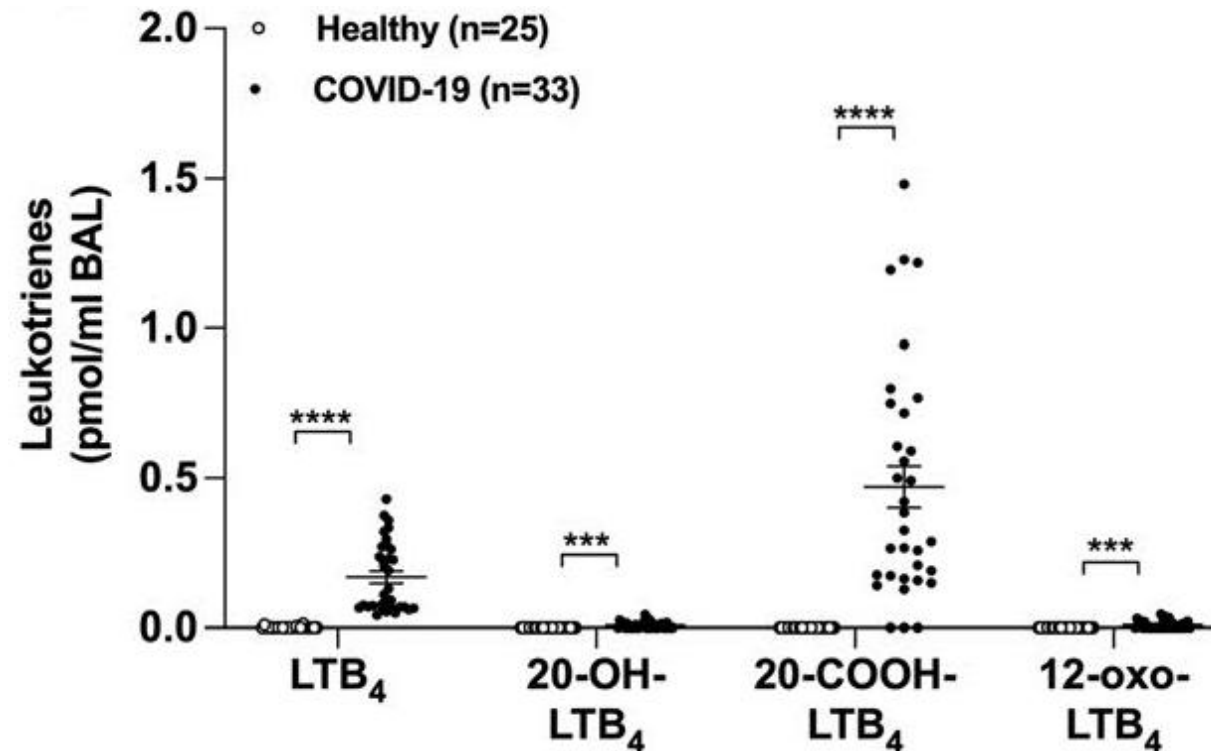
Targeting complement in SARS-CoV-2-associated lung injury. Complement activation may contribute to the “super” inflammatory response seen in some patients with severe COVID-19. Inhibition of C3 or C5 may have therapeutic potential. ARDS, acute respiratory distress syndrome

Amoretti, M., Amsler, C., Bonomi, G. *et al. Nature* **419**, 456–459 (2020). <https://doi.org/10.1038/nature01096>



High levels of eicosanoids and docosanoids, a lipid storm”, in the lungs of intubated COVID-19 patients

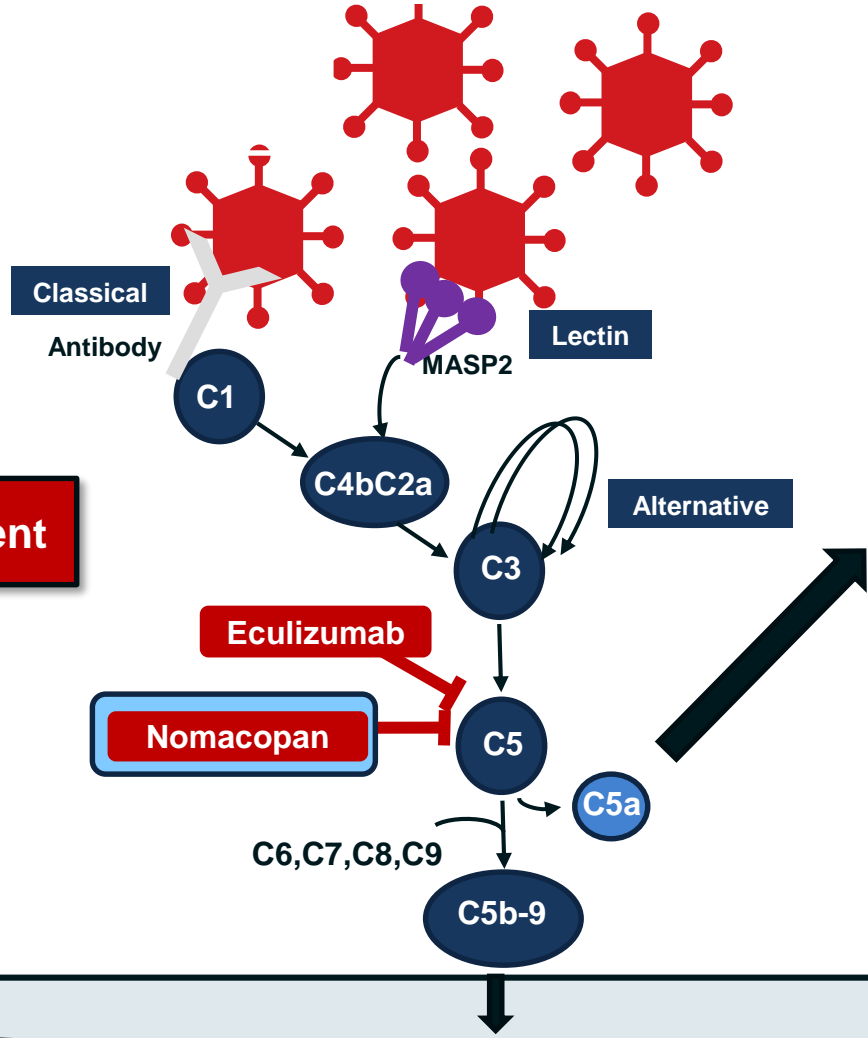
Elevated Lipides on Lipidomic analysis of Bronchoalveolar Lavage but not seen in plasma



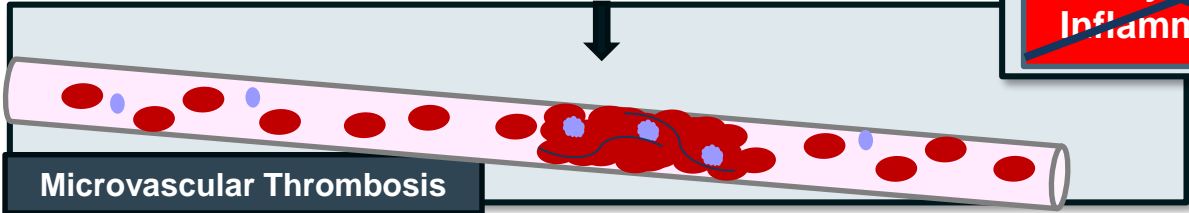
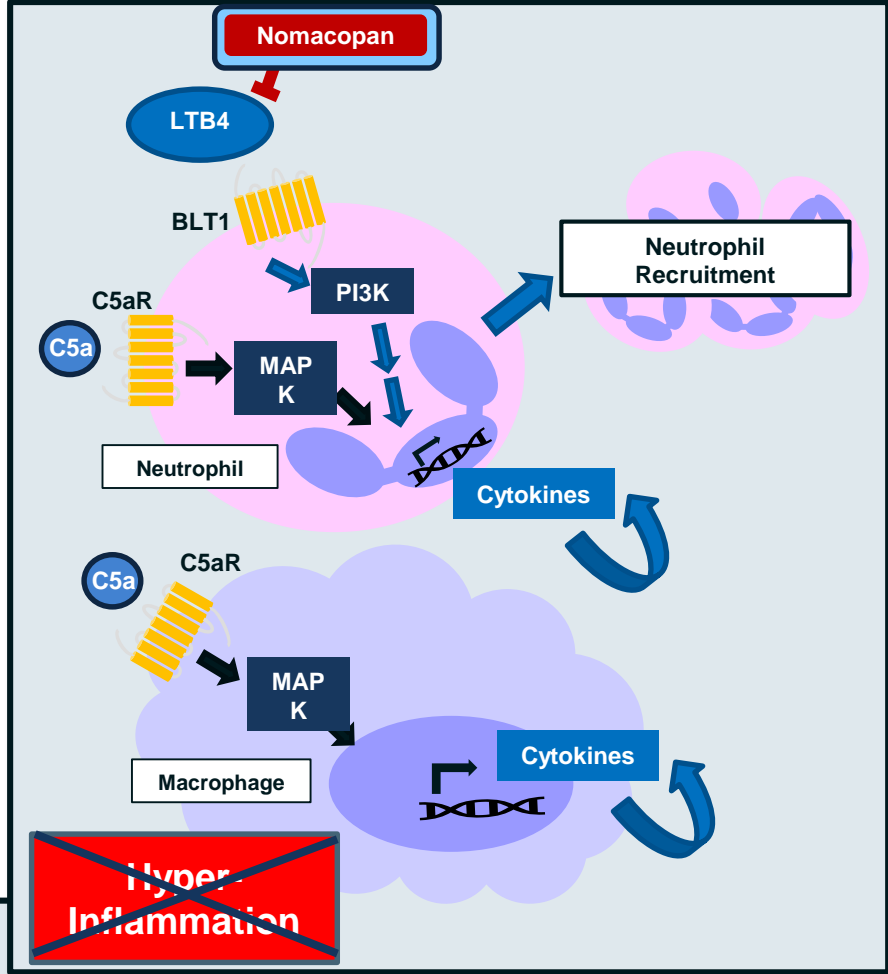
Anne-Sophie Archambault, Younes Zaid, Volatiana Rakotoarivelo..... Nicolas Flamand. The FASEB Journal. 2021;35:e21666. | <https://doi.org/10.1096/fj.202100540R>

Inhibiting hyperinflammation, the value of nomacopan's dual effects on complement and LTB4

Anti-Complement

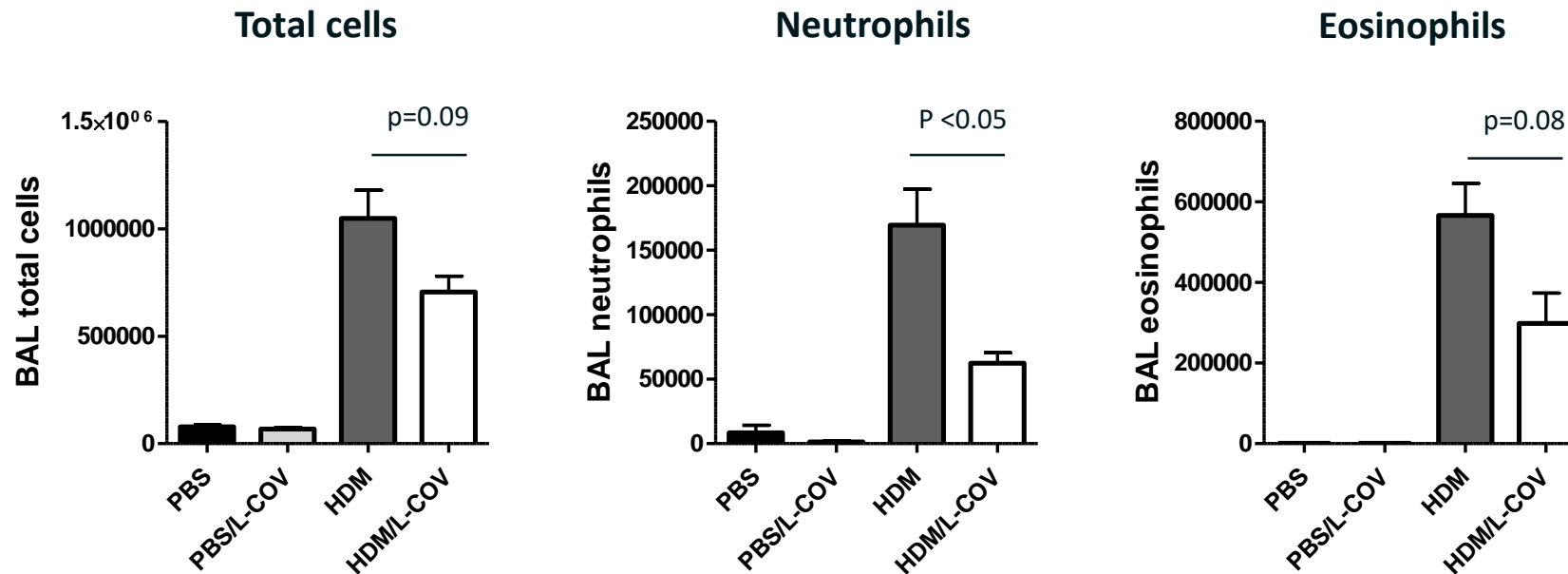


Anti-Leukotriene



Courtney Campbell WU, USA

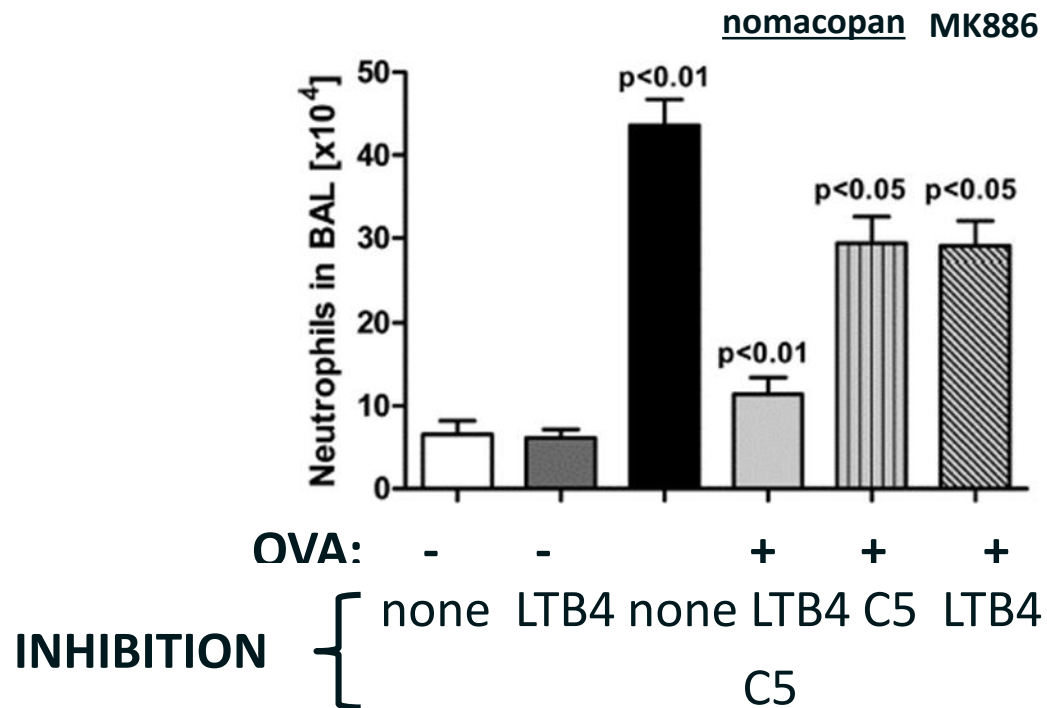
Inhibition of LTB4 leukotriene alone (here named L-COV) significantly reduced airway eosinophils and neutrophils (pre-clinical)



LTB4 inhibition alone significantly reduces leukocyte and Eosinophil recruitment to bronchoalveolar space after House Dust Mite challenge in Mice

Nomacopan's inhibition of both C5 & LTB4 shows additivity on inhibits neutrophil response in alveolitis (preclinical)

Lung model of immune-complex alveolitis - Dual inhibition superior to C5 or LTB4 inhibition alone



- Two forms of Nomacopan one inhibiting C5+LTB4, the other inhibiting C5 only (pre-saturated with LTB4)
 - LTB4 inhibition only is MK886 a leukotriene inhibitor that inhibits 5-lipoxygenase activator protein (FLAP)
- Roversi et al (2013) JBC 288: 18789 - 18802

Hyperinflammation seen during viral infections in patient populations with a wide range of chronic diseases – it is disease agnostic



Diseases/complement and Hyperinflammation

Diseases where genetic abnormalities are associated COVID-19 pneumonia

- Increased risk in patients with complement induced disease e.g., age-related macular degeneration (AMD)*
- Reduced risk in patients with complement deficiencies**

Chronic Inflammatory diseases with complement activation

- Severe Asthma (steroid requiring), COPD, Diabetes, Obesity, Coronary artery disease, Cancers, Immunological diseases (e.g., Rheumatoid Arthritis), Elderly people, Males and Deprivation
- Slow B lymphocyte antibody responses to infection

Extreme insults

- **Sepsis & Major Trauma**

* Ramlall V, Thangaraj PM, Meydan C et al., Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection Nat Med. 2020 October ; 26(10): 1609–1615. doi:10.1038/s41591-020-1021-2

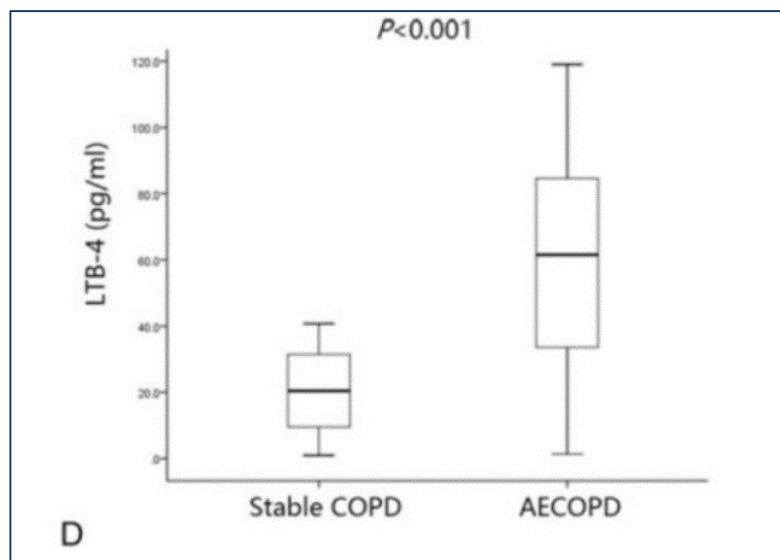
** Gavriilaki E, Asteris PG, Touloumenidou T, et al., Genetic justification of severe COVID-19 using a rigorous algorithm. Clin Immunol. 2021 May; 226: 108726. doi: [10.1016/j.clim.2021.108726](https://doi.org/10.1016/j.clim.2021.108726)

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Complement C5a and LTB4 in COPD exacerbations

Blood levels of LTB4 during exacerbations (AECOPD)

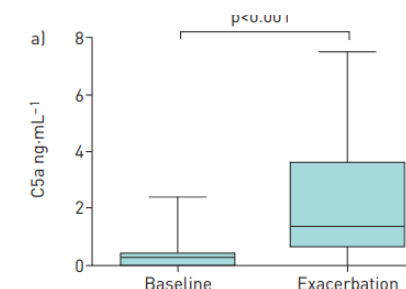


C5a is involved in response to infections

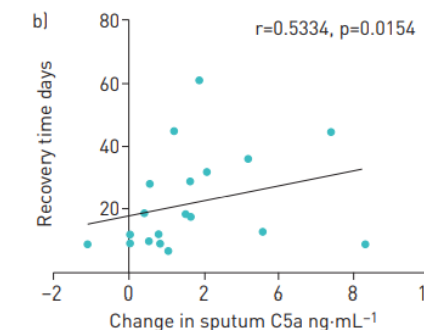
1. In exacerbations the C5a levels rise
2. Raised levels of C5a are also seen in the sputum
3. Elevated sputum levels predict a longer period to recover for the exacerbation
4. LTB4 is elevated in the blood of COPD patients with exacerbations

Hu H-L, Nie Z-Q, Lu Y, et.al., Medicine 2017; 96: 51(e9059) 4 August 2017.
<http://dx.doi.org/10.1097/MD.00000000000009059>

Sputum C5a levels in COPD exacerbations compared with stable COPD



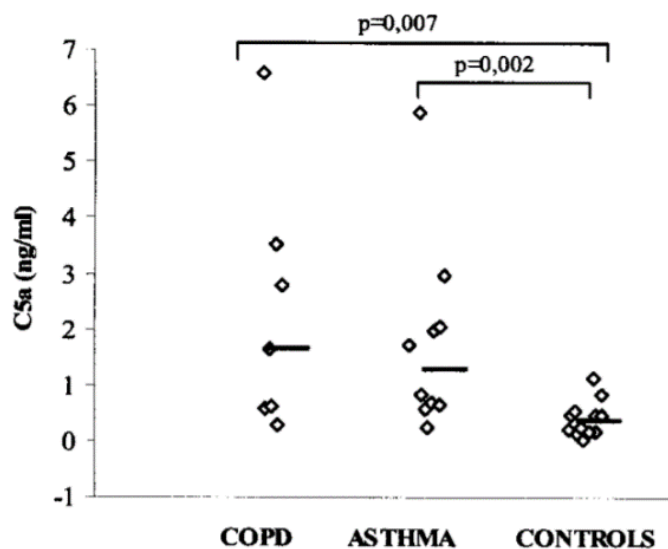
Sputum C5a levels in COPD patients enable prediction of the rate of recovery



Westwood J-P et al. ERJ Open Res 2016; 2: 00027-2016 | DOI: 10.1183/23120541.00027-2016.

Linkage between C5a and LTB4 in Asthma as well as in COPD

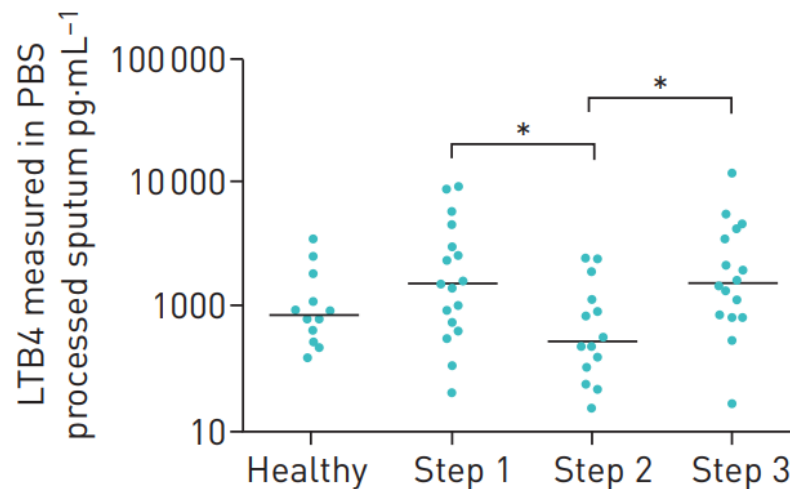
Marc MM, Korosec P, Kosnik M, et.al., Am. J. Respir. Cell Mol. Biol. 2004; 31: 216–219



C5a concentrations in sputum were significantly elevated in stable COPD (P 0.007), Asthma (P 0.002) patients compared to Controls

1. In asthma C5a are raised when stable as in COPD
2. C5a rises on allergen bronchial challenge in allergic asthmatics
3. LTB4 is elevated in “broncho dilator therapy” asthmatics and those experiencing repeated exacerbation

Higham A, Singh D, et.al., ERJ Open Res 2016; 2: 00088-2015 DOI:10.1183/23120541.00088-2015

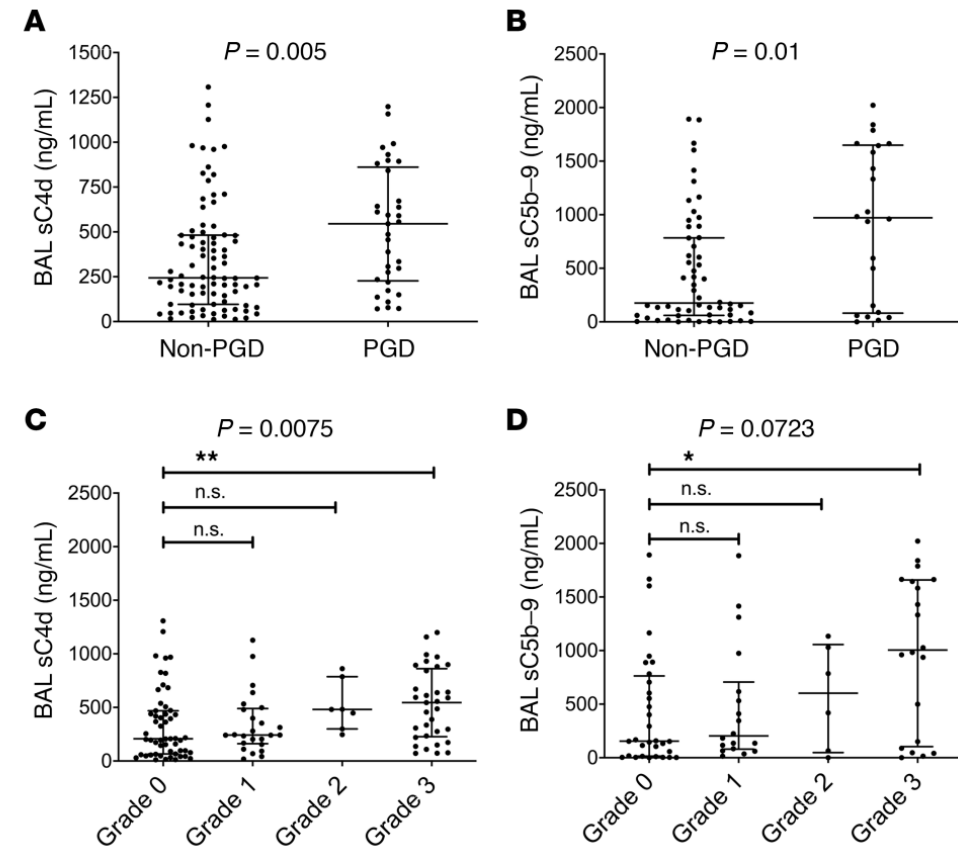


Sputum LTB4 levels are raised in patients were confined to GINA steps 1 and 3, and not step 2. This suggests a role for LTB4 those not using inhaled steroids and those with more continuous dual therapy for asthma

In a number of diseases, the lung seems to be the principle site of complement activation

Hrishikesh S. Kulkarni, Kristy Ramphal, Lina Ma et.al., **University of Pennsylvania and Washington study for primary graft failure in Lung Transplantation: JCI Insight. 2020;5(17):e138358. <https://doi.org/10.1172/jci.insight.138358>**

- Lung transplants' experience early graft failure that has proved difficult to diagnose and to treat.
- By measuring both blood and lavage in those patients on ventilation it has proved possible to show both lung & systemic activation of all three complement pathways occurs
- MBL and FCN-3 had a moderate-to-strong correlation with the terminal complement complex in the BAL but not in the plasma.
- Lung levels from bronchoalveolar lavage predict severity but not plasma
- Similar to COVID-19 Pneumonia C5b-9 is histological associated with the alveolar septum



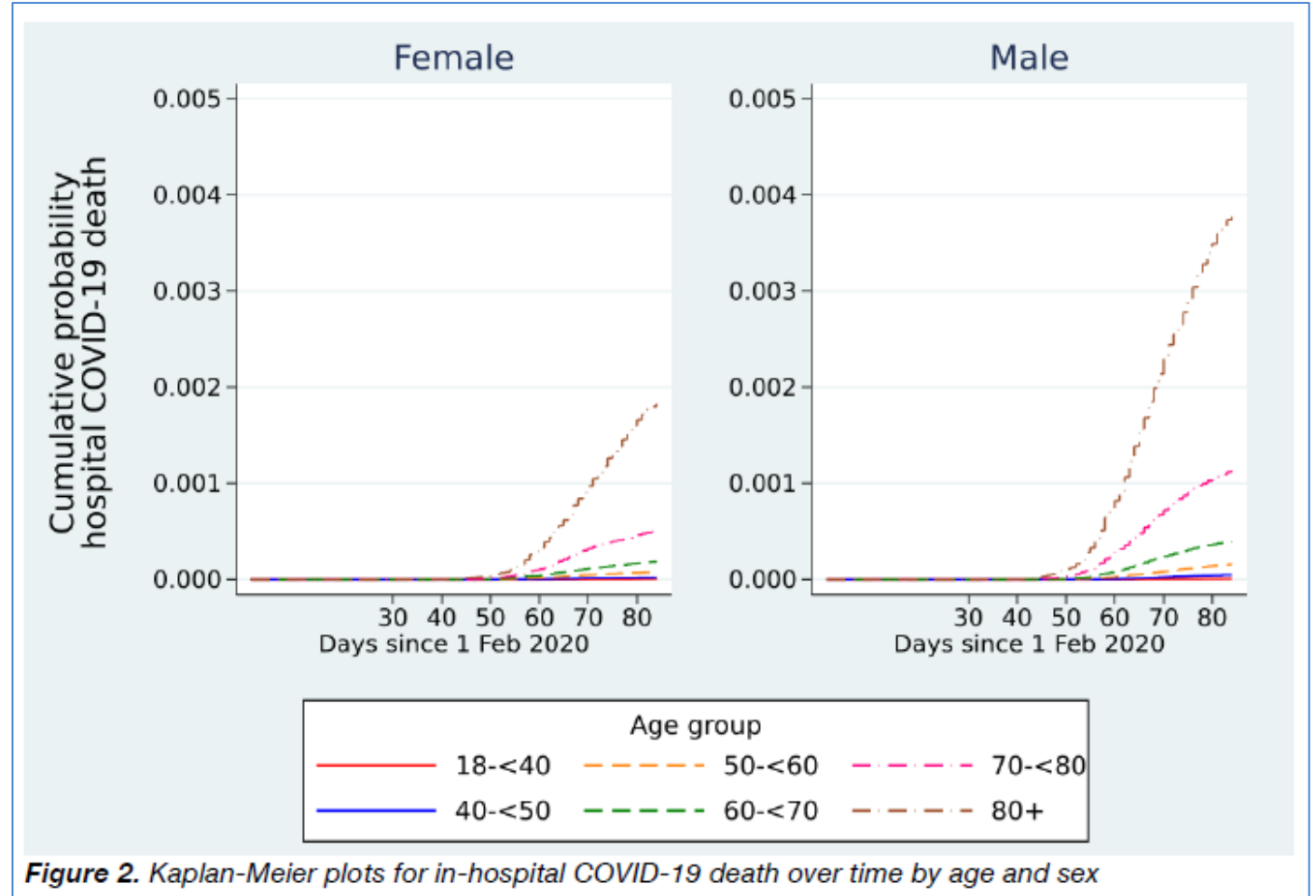
Hyperinflammation in COVID-19 was not confined to chronic lung disease - it is disease agnostic

Comorbidities associated with higher risk of COVID-19 hospital death:

- a) diabetes (with a greater HR for those with recent HbA1c ≥ 58 mmol/mol), b) asthma, c) respiratory disease, d) chronic heart disease, e) liver disease, f) stroke/dementia, g) reduced kidney function, autoimmune diseases, h) use of other immunosuppressive conditions

<https://opensafely.org/outputs/2020/05/covid-risk-factors/>

Persistently elevated levels of C3 or C5 plus leukotrienes incl. LTB4 found in all these diseases and age groups



Complement and LTB4, organ involvement, triggers, numbers susceptible and duration of treatment



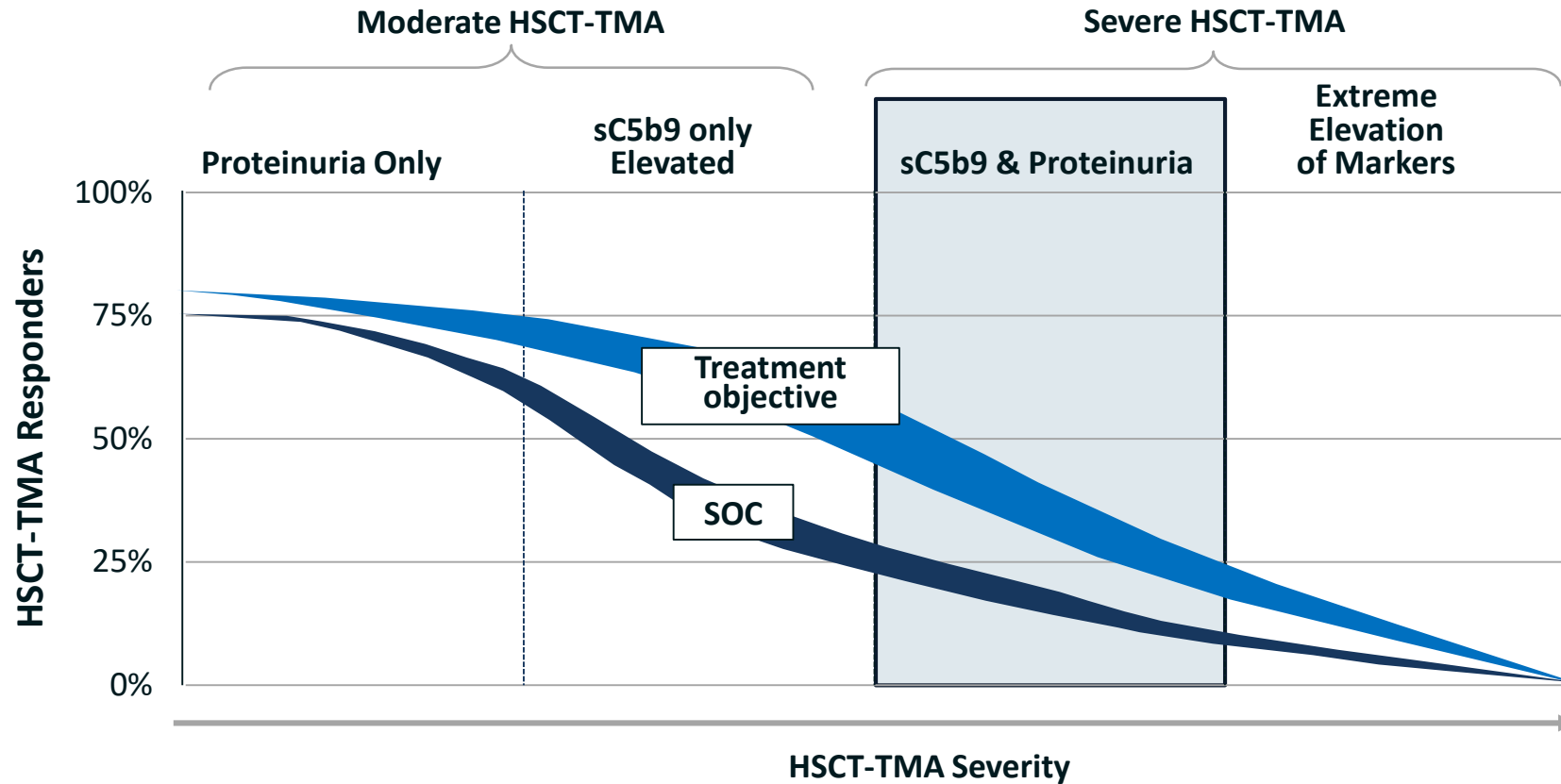
	C5a	C5b9	LTB4	Target	Triggers	Susceptible	Treatment
COVID pneumonia	XX	XX	XX	systemic and lung	SARS-CoV-2	0.1% with COVID	2-4 weeks
COPD exacerbation	XX	XX	XX	lung and systemic	winter virus / bacteria	20% COPD	2-4 weeks
Asthma exacerbation	XX	XX	XX	lung and systemic	winter virus / bacteria	3% asthmatics	2-4 weeks
TMA-HSCT	X	XX	X	systemic	unknown	10% of HSCT	12+ weeks
Sepsis	XX	X	XX	whole body	bacteria	unknown	1-4 weeks
Trauma	XX	XX	XX	systemic / brain	tissue injury	unknown	1-2 weeks

Subjects to be covered

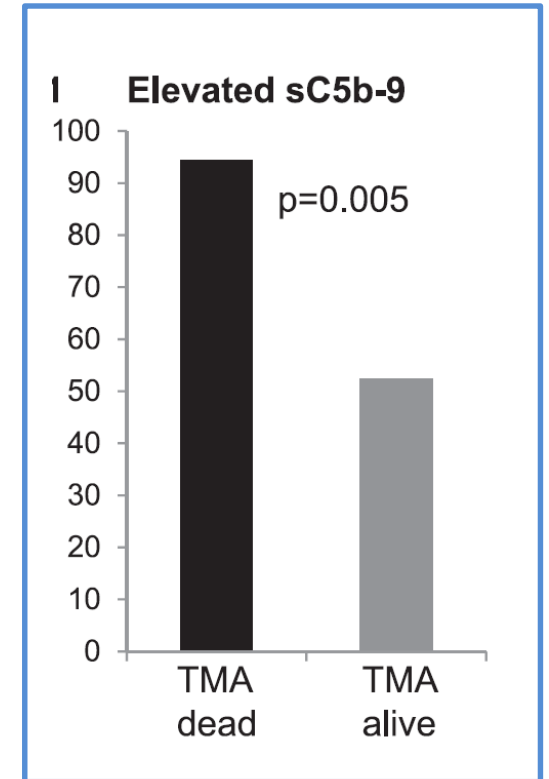
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- Sepsis and trauma – biomarkers needed to guide the choice of patients to treat and the effectiveness of dual inhibition of C5 and LTB4

Pediatric HSCT-TMA : production of the C5b-9 is a useful biomarker for start complement therapy

Conceptual Treatment Profile



Association between marker at time of TMA diagnosis and death at 1 year



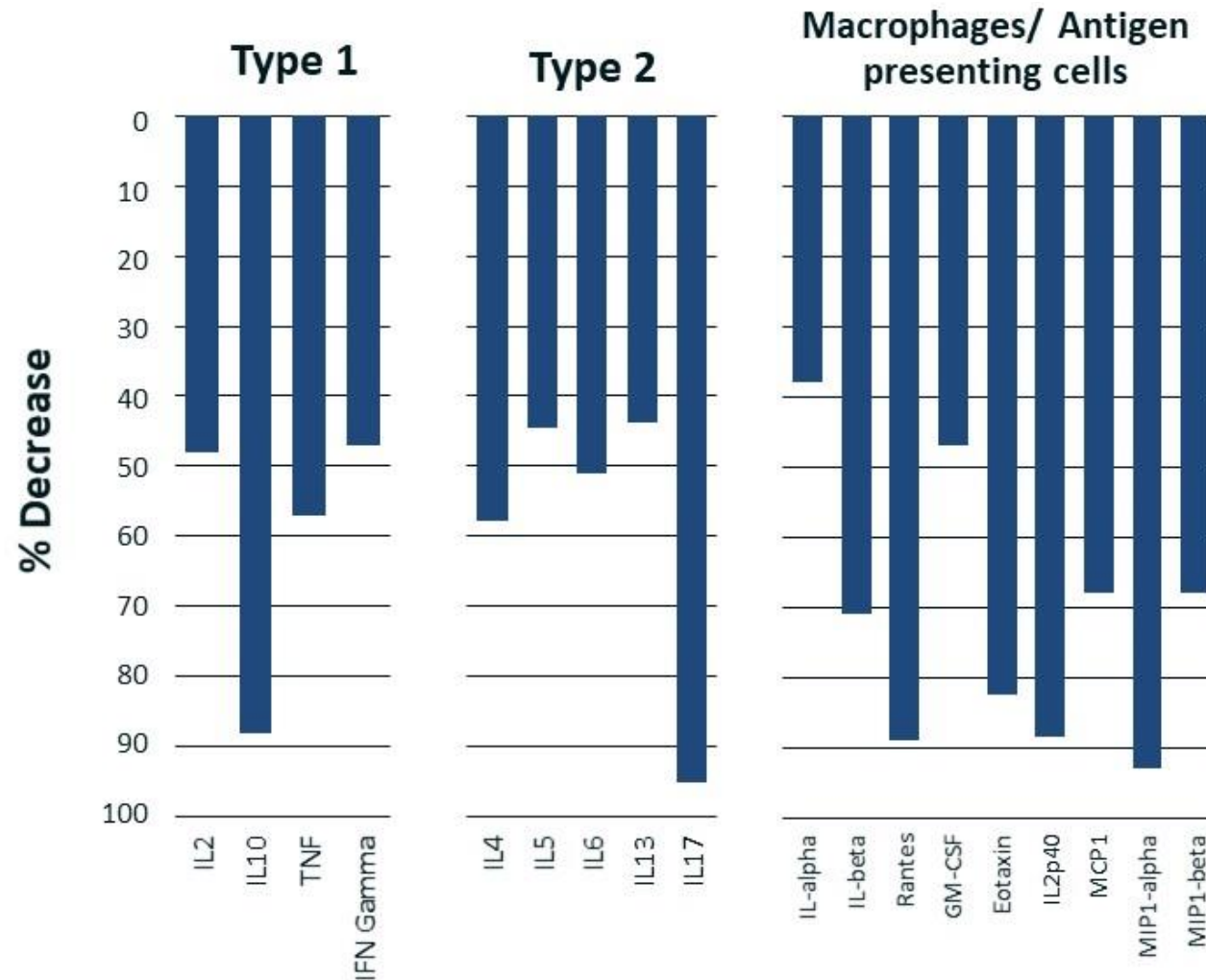
Conceptual graphic based on review of treatment renal failure literature, including Jodele et al Blood 2014 and Jodele et al Transfus Apher Sci 2016

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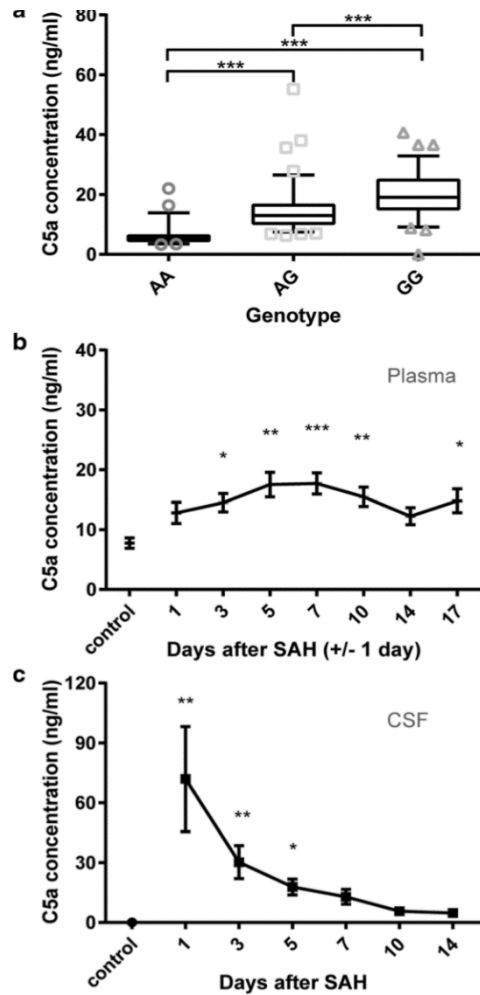
Nomacopan Inhibition drops levels a wide range of cytokines and neutrophils in sepsis and improves survival (pre-clinical)

Cytokines inhibited by nomacopan in polymicrobial sepsis mouse model

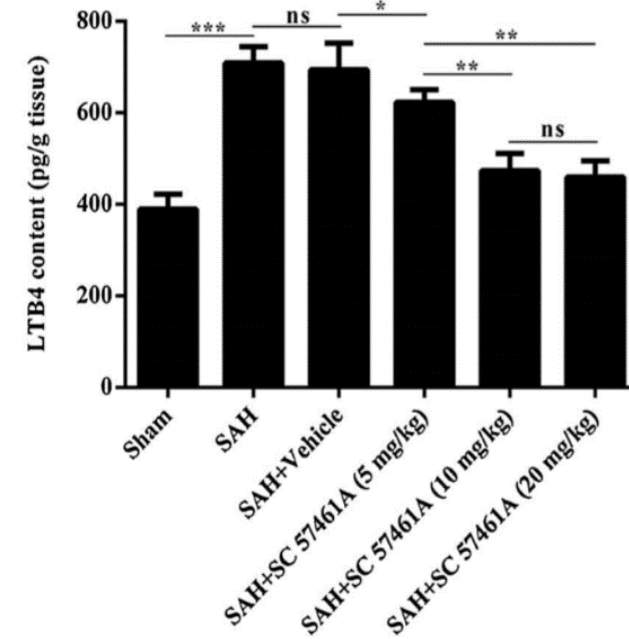


C5 and LTB4 in trauma (pre-clinical)

CSF C5 levels 1,400 x elevated vs control at Day 1 post-ictus



LTB4 induced influx of neutrophils after experimental stroke is associated with the development of early brain injury (EBI) in rats 24 hours after ictus using a model of SAH. Reduction of LTB4 reduce the signs of damage



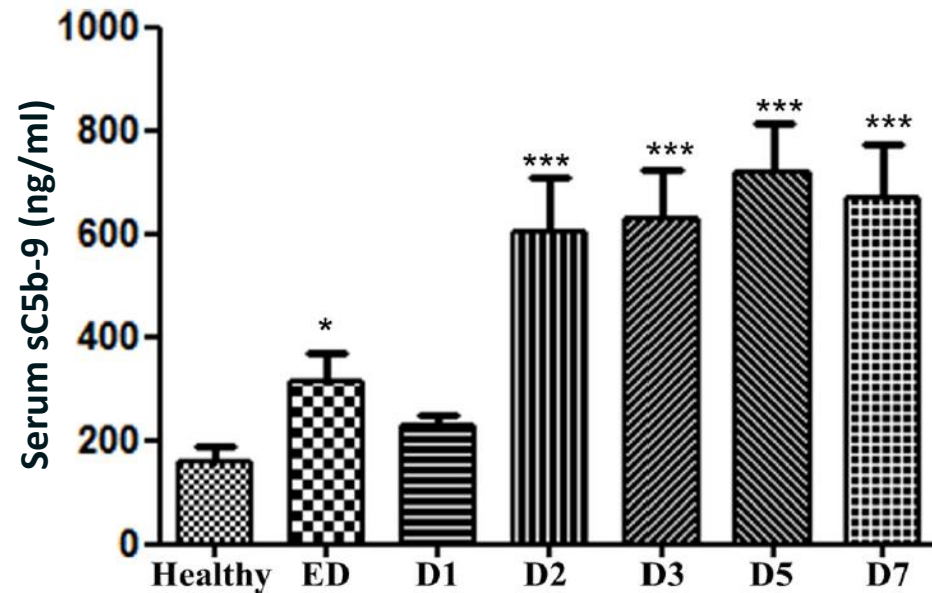
van Dijk B J et al, Translational Stroke Research (2020) 11:678- 699

Zhan-Nan Y et al. Behavioural Brain Research 339 (2018) 19-27

Complement and Leukotriene pathways both implicated in trauma (clinical and pre-clinical)

USAISR study of complement level in trauma patients

4x increase in sC5b-9 levels in trauma patients

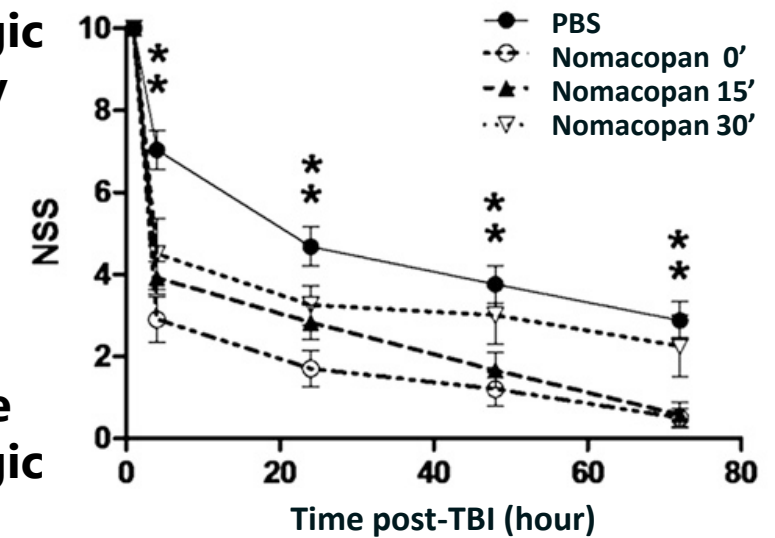


Li Y, et al. Trauma Surg Acute Care Open 2019;

Nomacopan reduces neural damage in mouse trauma model

complete neurologic disability

complete neurologic recovery



Conclusions and next steps

- At risk populations are annually afflicted with hyperinflammatory illnesses in the winters due to respiratory infections – **both viral and bacterial**
- There is emerging evidence that **both complement, and lipid mediators are responsible**
- In trauma and in sepsis there appears similar hyperinflammatory responses
- **Biomarkers such as C5b-9, C5a and LTB4 could be used to select patients for treatment with effective inhibitors**
- **Now is the time to use the learning from COVID-19 illnesses to focus on better care for patients at risk – we should move from supportive hospital and community care to medication for the hyperinflammation**
- **The ideal therapy is for short periods**

May I acknowledge and thank all the contributors



- Prof Joe Meollman Cincinnati Medical Centre
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- Prof Jonathan Bernstein Cincinnati Medical Centre
- Prof Courtney Campbell Ohio State University Hospital
- Dr Thomas Brown Consultant Portsmouth University Hospital
- Dr Sanjeev Khindri SMO Akari Tx Ltd
- Clive Richardson CEO Akari Tx Ltd



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Learnings from COVID-19
to prevent winter exacerbations
from respiratory viral and bacterial
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Thank you for your attention

October 26th to 27th 2021