How the Pandemic has transformed the ARDS Drug Development & recent updates on ARDS treatment

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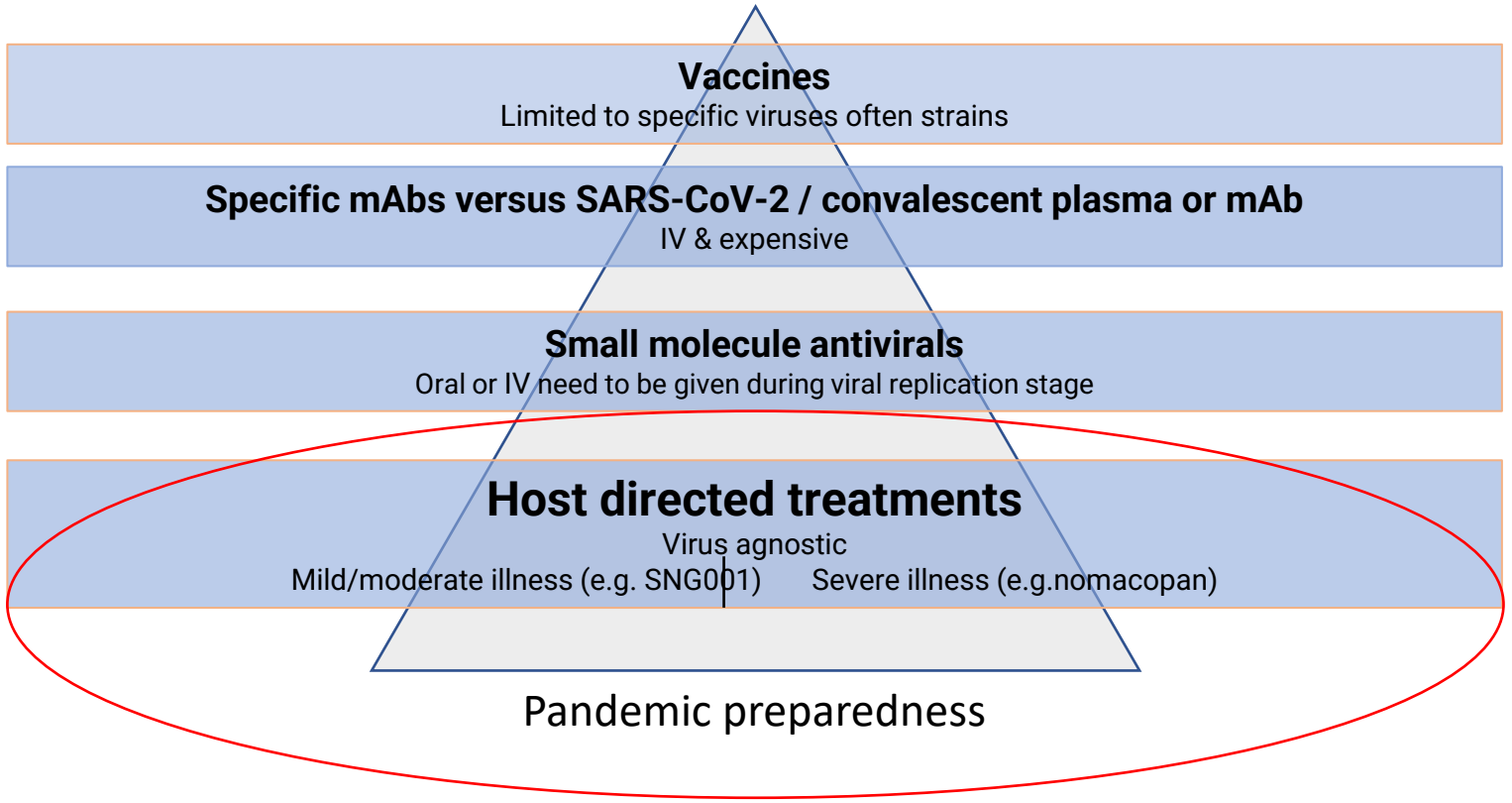
Disclosures:
I work for Akari Therapeutics
I hold patents in medicinal gas delivery devices of Camcon Medical Ltd

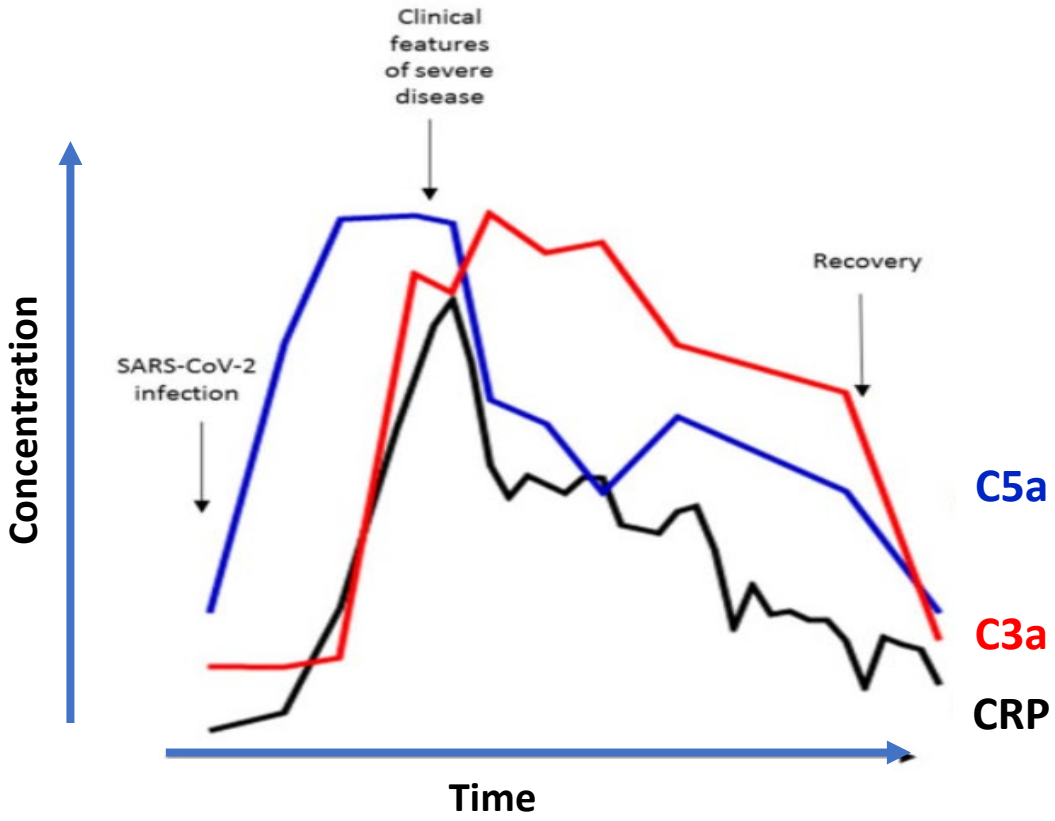
Spectrum of activity of antivirals in COVID-19
Importance of host directed treatments



The quest for effective host directed treatments in COVID-19

1. Inhibitors of the complement pathways
    - Unique pattern of complement activation in COVID-19
    - The clinical phenotype of severe COVID-19 pneumonia has many aspects of dysregulation of complement pathways
    - A question for a place for complement inhibition in other serious infections and winter exacerbations of chronic disease
    - Other parts of the Innate immune response are likely to be involved for which dual acting molecules should be considered
2. Ensuring adequate oxygenation
    - Some limited improvement in survival of COVID-19 pneumonia patients
    - Can we optimise oxygen delivery to respiratory failure patients to lessen the need for IMV?
    - An adaptive medicinal gas delivery device - BIMOD

In COVID-19 pneumonia the rise in serum C5a closely precede C3a &CRP in COVID-19 pneumonia and is followed by rise of cytokines



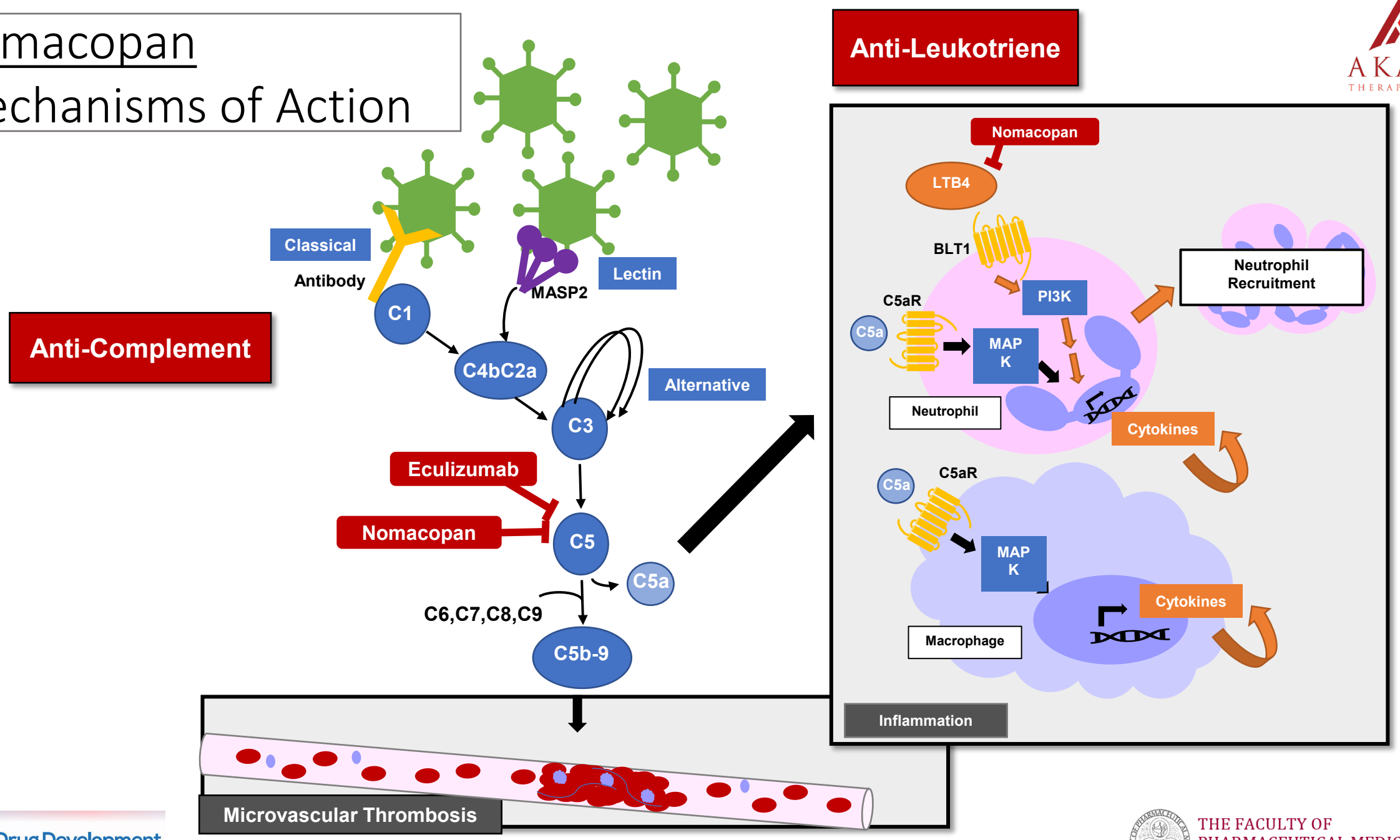
Dialysate levels in severe COVID-19 pneumonia Prendecki M, Clarke C, Medjeral-Thomas N et al. Clin Kidney J 2020; R1

Evidence of importance of Complement in COVID-19

1. Complement deficient patients have low risk of dying whilst patients with complement induced diseases are at high risk of dying
2. Early-onset and age-related macular degeneration (AMD) patients have a high risk of death with COVID-10 pneumonia

Ramlall V, et al, Nature Medicine. 2020; 26 1609–1615 | www.nature.com/naturemedicine

Nomacopan
Mechanisms of Action



AKARI THERAPEUTICS

ARDS Drug Development Summit

THE FACULTY OF PHARMACEUTICAL MEDICINE
of the Royal Colleges of Physicians of the United Kingdom

Early clinical and preclinical studies with nomacopan

1. SARS
   - *Pre-clinical* model demonstrated additive effect of inhibiting C5 and LTB4
2. COVID-19
   - Compassionate program/safety study: no drug related SAEs and clinical response reported (not randomised)
   - Requirement for increased dosing to compensate for significantly elevated complement levels in patients
3. Sepsis
   - *Pre-clinical* model demonstrated a significant reduction across a wide range of cytokines
4. TMA-HSCT
   - Elevated C5b-9 used as a marker for treatment
   - Ongoing phase III study
5. Severe asthma
   - *Pre-clinical* allergen model demonstrated additive effect of inhibiting C5 and LTB4

Over a long period of time - studies have associated asthma exacerbations to complement activation

1. **Exacerbations**:

   Plasma C5a levels reflect allergic respiratory disease severity as assessed by physicians and correlate with Asthma Quality of Life Questionnaire scores. Changes in C3a and C5a levels after immunotherapy reflect cutaneous allergic responses, especially to dust mite allergen.

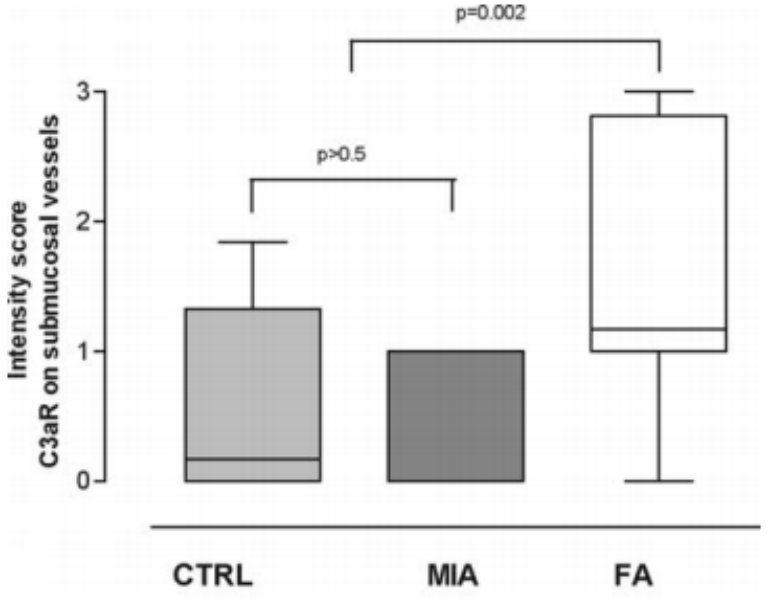
   Bowers et.al. Ann Allergy Asthma Immunol. 2010 Jan;104(1):42-9. doi: 10.1016/j.anai.2009.11.021.

2. **Fatal Asthma**:

   C3aR was expressed on airway epithelium, smooth muscle, submucosal, and parenchymal vessels. C5aR was expressed on myeloid cells infiltrating the submucosa and on airway epithelium.

   Fregonese L et. al. J Allergy Clin Immunol 2005;115: 1148-54.

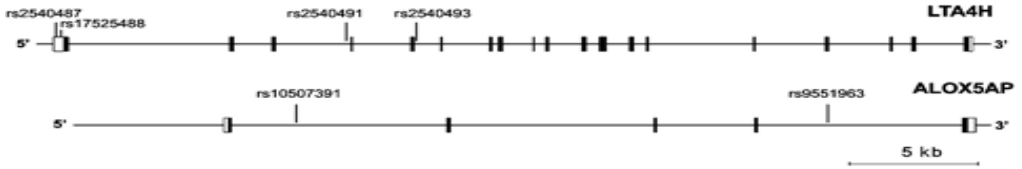
Fatal asthma exacerbations



Box-whisker plots of C3aR in submucosal vessels of control (CTRL), Mild asthma (MIA), and Fatal asthma (FA)

The value of a dual acting therapy as LTB_4 has a clear role in asthma pathophysiology

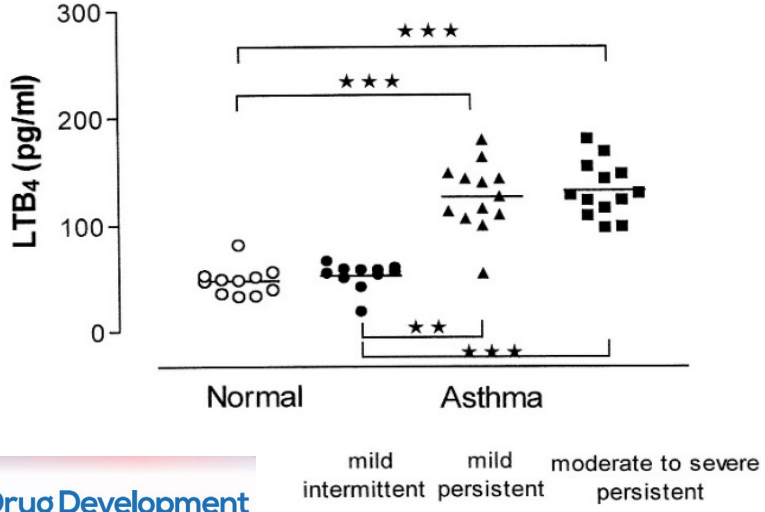
Polymorphisms in genes for LTB_4 – generating enzymes associated with asthma severity

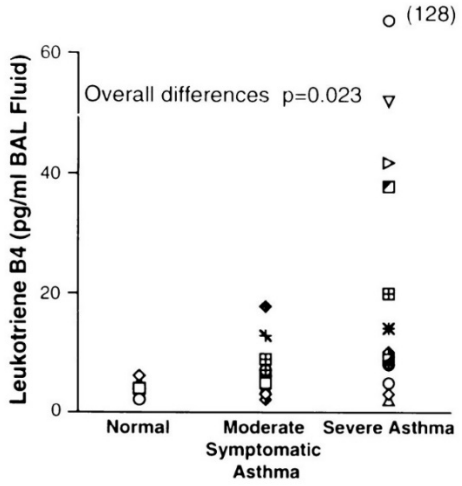


- Holloway, J. W. *et al*, Eur. J. Allergy Clin. Immunol. 2008.
- Tcheurekdjian, H. *et al*, J. Allergy Clin. Immunol. 2010.
- Via, M. *et al*, *Clin. Exp. Allergy* . 2010.

LTB_4 levels elevated in BAL, sputum, EBC, blood and urine of asthmatics

- associations reported with persistent, severe and neutrophilic asthma





Elevated levels of LTB_4-generating enzymes in asthmatics

- Seymour, M. L. *et al*, AJRCCM. 2001.
- Zaitsu, M. *et al*, J. Asthma . 2003.