IMMUNOMODULATORS IN THE CRITICALLY ILL

SHORT COURSE IN CRITICAL ILLNESS
SCCI 2023

Sanjay Swaminathan
Dept of Clinical Immunology and Allergy

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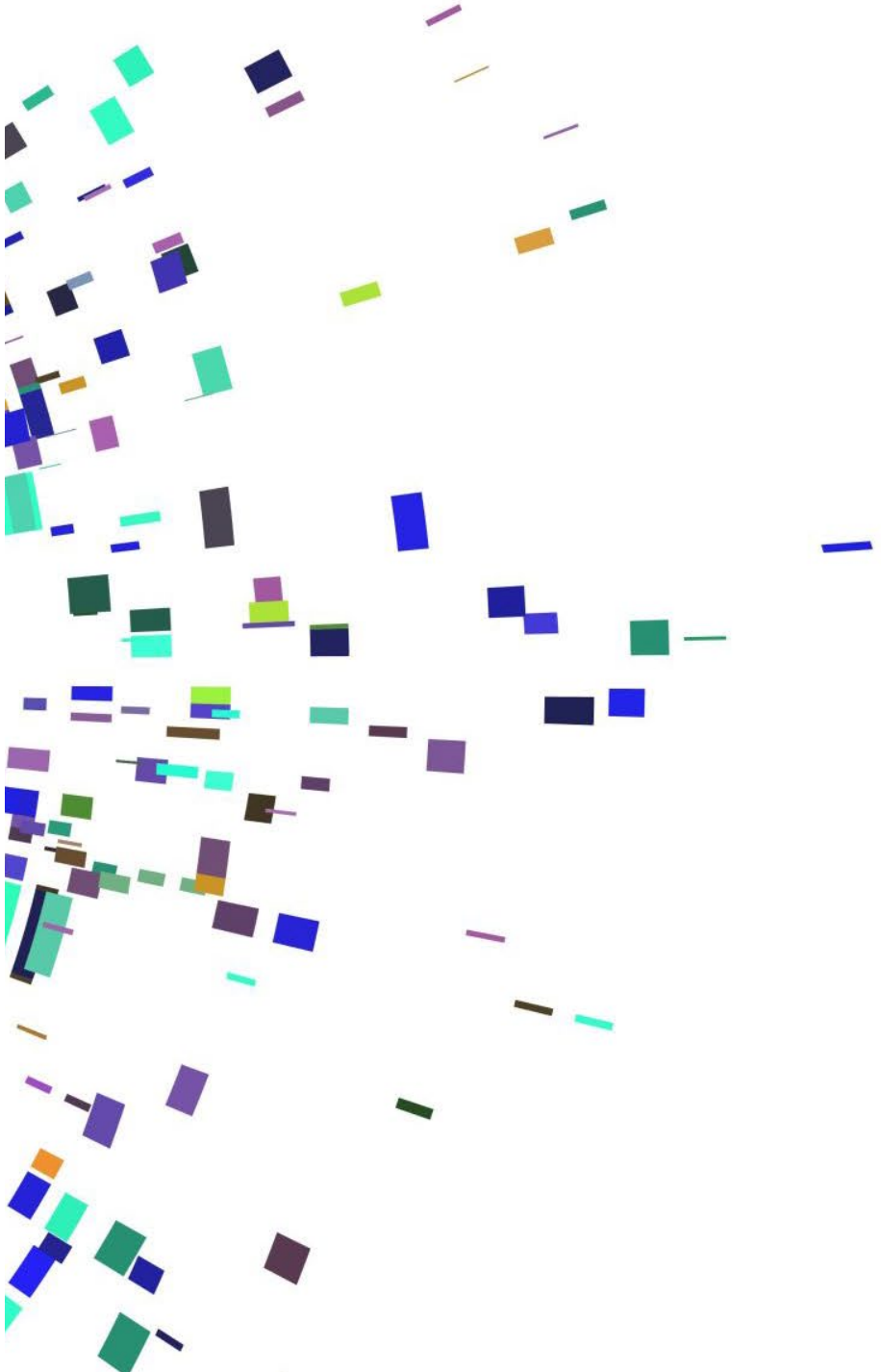


Talk Outline

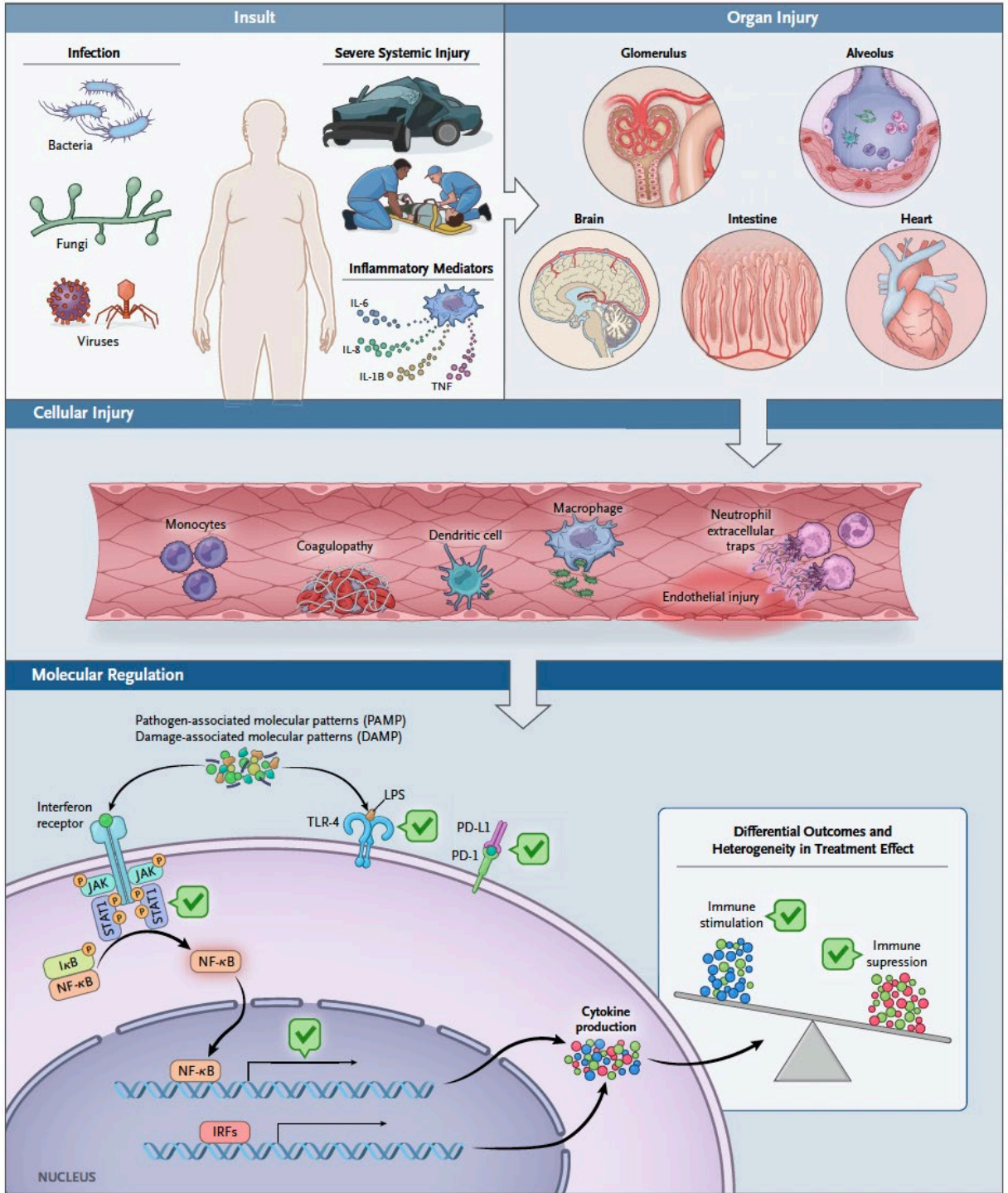
- Biologic and clinical heterogeneity in the ICU patient
- Immune suppression versus immunomodulation versus immune stimulation
- Types of drugs/agents available
- Importance of Covid-19 in furthering this area
- Future trends
- Questions

Connection between immunomodulation in Sepsis and ARDS

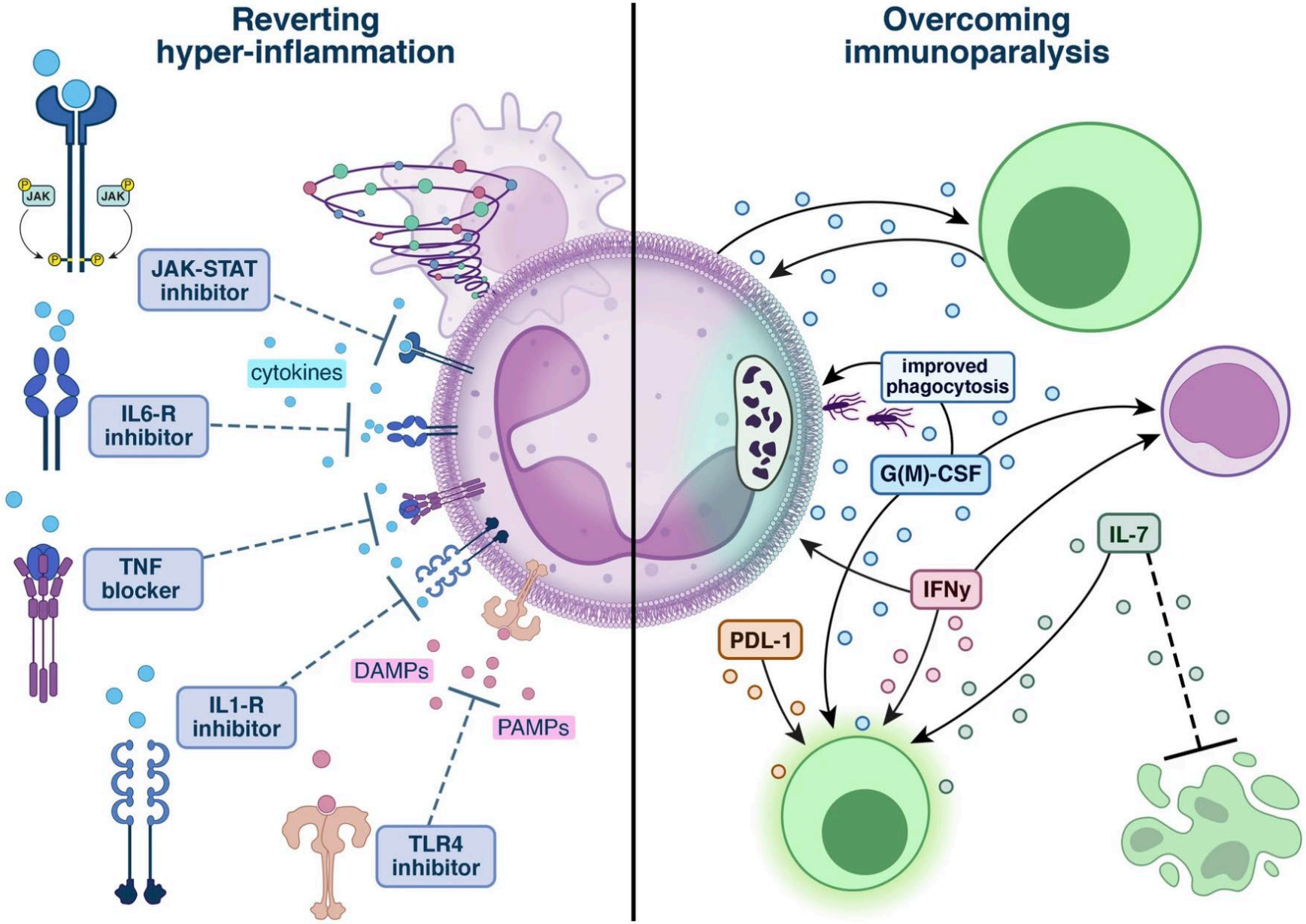
- A dysregulated host response to infection is the basis of the 2016 Sepsis-3 definition
- The immune response in sepsis and ARDS is complex and varies from patient to patient
- Early response to pathogens is via innate immunity (neutrophils, monocytes, dendritic cells)
  - Also pattern recognition receptors recognize DAMPs and PAMPs
  - Lead to cascades of inflammatory cytokines which aim to get control of the infection
- However uncontrolled inflammation can lead to tissue damage, and immune cell exhaustion
- Endothelial activation, either by inflammation or directly via pathogens, contributes to endothelial barrier disruption which can lead to coagulopathy, microthrombi formation, fluid shifts and tissue hypoxia (in both sepsis and ARDS)

NEJM Evidence

Leligdowicz et al, 2022



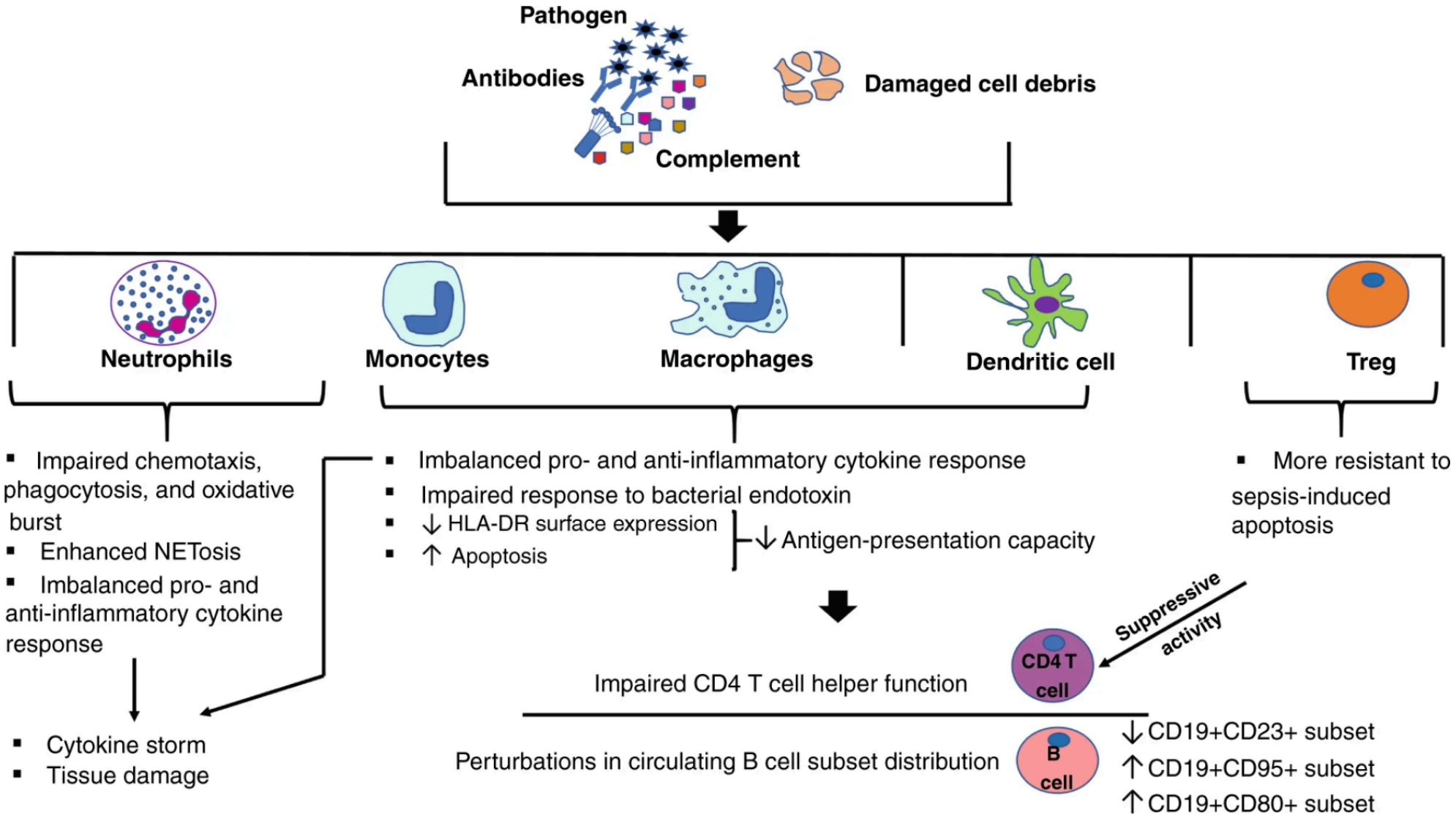
From: Targeted immunomodulation: a primer for intensivists



Targets for immunomodulation

Fig. 1: Pathways of immune dysfunction associated with sepsis.

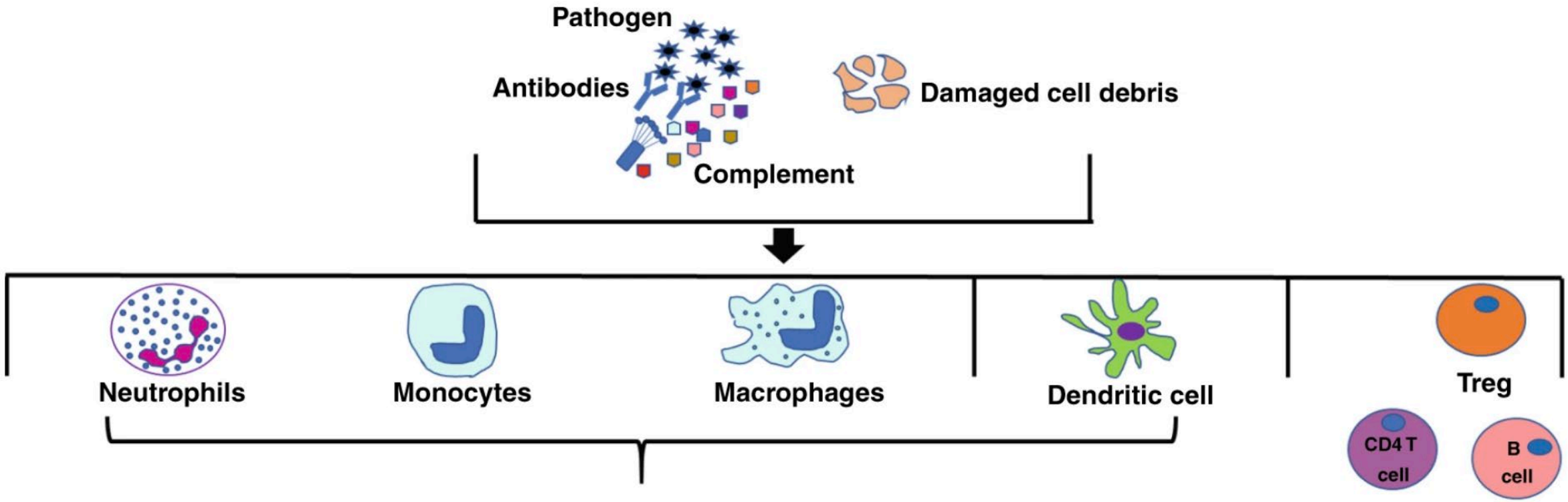
From: Mechanisms and modulation of sepsis-induced immune dysfunction in children



The illustration depicts dysregulation at the levels of the innate immune response (complement, neutrophils, monocytes-macrophages) as well as the adaptive immune response (T cells and B cells) that characterizes the immunopathology observed in the setting of sepsis.

Fig. 2: Targeted immunomodulatory therapies in sepsis.

From: Mechanisms and modulation of sepsis-induced immune dysfunction in children



Clinical heterogeneity in sepsis and ARDS

- Whilst targeting the immune system (by suppressing or stimulating) may help the individual patient, the diagnosis of both syndromes still use non specific signs and symptoms at the bedside
  - This makes it harder to work out where the immune dysfunction is occurring and to what degree

- In sepsis, there is a variety of organisms and location of infections, which lead to a wide range of responses
  - Sepsis from *S.aureus* is associated with twice the mortality of sepsis with *E.coli* as an example
  - Not all pathogens are the same (outcomes vary with virus type as an example)
  - Pathogen load and virulence factors can also be important variables

- There are host differences in immune responses (partly controlled by HLA), differences in co-morbidities, timing of interventions

Therapies for modulating the immune system

- Immune suppression
  - Corticosteroids
  - TNF blockade
  - IL-1 receptor blockade
  - JAK/STAT inhibition

- Immune stimulation
  - G-CSF or GM-CSF
  - PD-1 and PD-L1 manipulation
  - Use of Interferons (Type 1 and gamma IFN)

- Other immune modulators
  - IVIg

Corticosteroids

- The idea of steroids use in ARDS dates back >50 years, with >400 trials being completed
- Problems: Different types of steroids (various classes), varying doses/duration, heterogeneity of patients have shown inconsistent benefits between completed trials
- As as example, 2 recently completed landmark trials in vasopressor dependent septic shock tested 2 different regimens: continuous hydrocortisone infusion (Venkatesh, NEJM 2018) versus intermittent hydrocortisone plus fludrocortisone (Annane et al, NEJM 2018)
- In these trials, corticosteroid use contributed to faster reversal of shock and decreased duration of mechanical ventilation, however mortality was only affected in trial where sicker patients were enrolled
- A systematic review in 2019 (>11,000 patients) showed that steroids slightly reduced 28 day mortality, which forms the current guidelines for sepsis suggesting steroids be initiated in vasopressor dependent shock
- Similar trials in ARDS suggest similar outcomes with steroids in these patients
- But there are caveats: in the late steroid rescue trial (LaSRS), where steroids were given >14 days after ARDS onset, there was an increased mortality (similar story with use of steroids in H1N1 influenza)

Corticosteroids

- Variability in results may be due to selection bias in smaller trials or inclusion of steroid responsive diffuse lung diseases (such as cryptogenic organizing pneumonia)

- Steroids also confer potential risks
  - Secondary infections
  - ICU critical myopathy
  - Hyperglycemia
  - Delirium etc

- Concerns about:
  - Class of steroids
  - Timing of drug initiation
  - Duration and dosing regimen

Targeting TNF and IL-1 receptor

- These are attractive targets as they are upregulated during an acute inflammatory response plus we have agents that can target them
- However, trials (in non-Covid patients), have been disappointing in septic shock
- Treatment of septic shock with a TNF receptor:Fc fusion protein (Fisher NEJM 1996), failed to show any mortality benefit with this approach
- Similar studies have shown little benefit in antagonsing the IL-1 receptor
  - Although there may be mortality benefits from using a recombinant IL-1 receptor antagonist in sepsis by correlating with initial IL-1 receptor antagonist plasma concentration
  - Argues for a more nuanced approach to using these agents

Immune stimulation

- G-CSF or GM-CSF
- PD-1 and PD-L1 manipulation
- Use of Interferons (Type 1 and gamma IFN)

G-CSF and GM-CSF

- Expressed by immune, endothelial, epithelial and fibroblasts/chondroblasts leading to mobilization of immune cells from bone marrow and promoting their survival and migration to site of infection

- GM-CSF may offer broader effects than G-CSF (such as increasing monocyte HLA-DR expression)

- However, a meta analysis of 12 clinical trials failed to show a benefit from 12 RCTs in patients treated with these agents in sepsis

- Ongoing clinical trial looking at role of GM-CSF in patients with immunoparalysis (ex-vivo LPS induced TNF < 200 pg/ml)

PD-1 -PD-L1 blockade

- PD-1 and PD-L1 proteins negatively regulate lymphocyte function and therefore blockade has been successfully used in the oncology space to activate the immune system (and target cancer)
- Theoretically immune activation could aid the immune paralysis seen in some patients with sepsis
- Phase 1b RCT of anti-PD-L1 therapy suggested a restoration of immune status (as measured by T cell gamma interferon and T cell proliferation) without the induction of a cytokine storm in patients with sepsis associated immunosuppression (lymphocyte count < 1100/ul)

Interferons

- Endogenous antiviral and immunomodulating agents
- Small studies suggested that IFN-beta may be associated with lower 28 day mortality, however when a larger group was studied, no mortality benefit was seen
- IFN-gamma produced in response to viral pathogens in particular
- Current open label prospective study looking at role of IFN-g in sepsis, suggesting it might improve monocyte function and survival, with benefit in patients with low monocyte HLA-DR expression and low ex-vivo induced TNF production
- However, none of these strategies have sufficient evidence to support their use outside the trial space

Other approaches

- IVIg is pooled immunoglobulin and has been studied in sepsis and Covid-19
- Meta analysis of 43 trials suggested benefit as an adjunct in septic shock but is not considered standard of care with a consensus that more work is required
- No benefit seen in Covid-19

Lessons from Covid-19

- Success of corticosteroids demonstrated in numerous trial
- IL-6 blockade hadn't been looked at in sepsis before but in Covid-19 shown to be of benefit
- JAK inhbitors (baricitinib, tofacitinib) provided mortality benefit in patients treated with remdesivir
- Perhaps an easier group to study given the diagnostics and high degree of suspicion for disease and early initiation of treatment

Table 1. Summary of Selected Landmark Trials of Immunomodulating Therapies for Covid-19.*

Class	Reference	Drug	Trial Group	Trial Design	Sample Size	Outcome
Corticosteroids	RECOVERY Collaborative Group[105]	Dexamethasone 6 mg every 24 hours	RECOVERY[106]	Randomized platform trial	6425	Lower mortality in patients receiving oxygen/ventilatory support
	Angus et al.[107]†	Hydrocortisone 50 mg every 6 hours	REMAP-CAP[18]	Bayesian randomized embedded multifactorial adaptive platform trial	403	Possible superiority in odds of improvement in organ support–free days within 21 days
	Dequin et al.[108]†	Hydrocortisone 200 mg/d as continuous infusion	CAPE-COVID	Randomized clinical trial	149	No benefit
	Tomazini et al.[109]†	Dexamethasone 20 mg for 5 days, then 10 mg for 5 days every 24 hours	CoDEX	Randomized clinical trial	299	Increase in ventilator-free days over 28 days
	The COVID STEROID 2 Trial Group[110]	Dexamethasone 6 mg vs. 12 mg every 24 hours	COVID STEROID 2	Randomized clinical trial	1000	No difference in days alive without life support at 28 days
IL-6 receptor inhibition	The REMAP-CAP Investigators[111]	Tocilizumab and sarilumab	REMAP-CAP[18]	Bayesian randomized embedded multifactorial adaptive platform trial	803	Improved survival
	RECOVERY Collaborative Group[112]	Tocilizumab	RECOVERY[106]	Randomized platform trial	4116	Improved survival
JAK1/2 inhibitions	Marconi et al.[113]	Baricitinib	COV-BARRIER	Randomized clinical trial	1525	Lower mortality
	Kalil et al.[114]	Baricitinib + remdesivir	ACTT[115]	Adaptive randomized trial	1033	Faster recovery
	Guimarães et al.[116]	Tofacitinib	STOP-COVID	Randomized clinical trial	289	Lower mortality or respiratory failure at 28 days
IL-1 receptor antagonists	Tharaux et al.[117]	Anakinra	CORIMUNO-19	Bayesian randomized clinical trial	116	No benefit
IL-1β inhibitors	Caricchio et al.[118]	Canakinumab	CAN-COVID	Randomized clinical trial	454	No benefit
GM-CSF inhibitors	Temesgen et al.[119]	Lenzilumab	LIVE-AIR	Randomized clinical trial	479	Improved survival without invasive mechanical ventilation
Interferons	Hung et al.[120]	IFN-β-1b + lopinavir-ritonavir + ribavirin	—	Randomized clinical trial	127	Faster improvement
	Kalil et al.[121]	IFN-β-1a + remdesivir	ACTT[115]	Adaptive randomized clinical trial	969	No benefit
	Alavi Darazam et al.[122]	Lopinavir/ritonavir + hydroxychloroquine + IFN-β-1a or IFN-β-1b	COVIFERON	Randomized clinical trial	60	Faster improvement with IFN-β-1a
CD14 inhibition	PR Newswire[123]	IC14 (anti-CD14)	I-SPY COVID[20]	Randomized platform trial	142	No benefit

Moving forwards

- Most RCTs are designed to assess the overall treatment effect which is the average treatment effect across all patients in a trial population

- But, when studying patients with sepsis or ARDS, it's likely that some patients will experience benefit, some harm and others with little effect
  - Overall effect could be negligible but there could be individual benefits
  - Key is finding the subgroups of patients who may benefit from immunomodulation

- Identifying biologic derangements in real time with point of care tests to identify patient biologic response groups on the basis of the predominant biologic mechanism (ie immune activation or exhaustion, endothelial or epithelial injury)

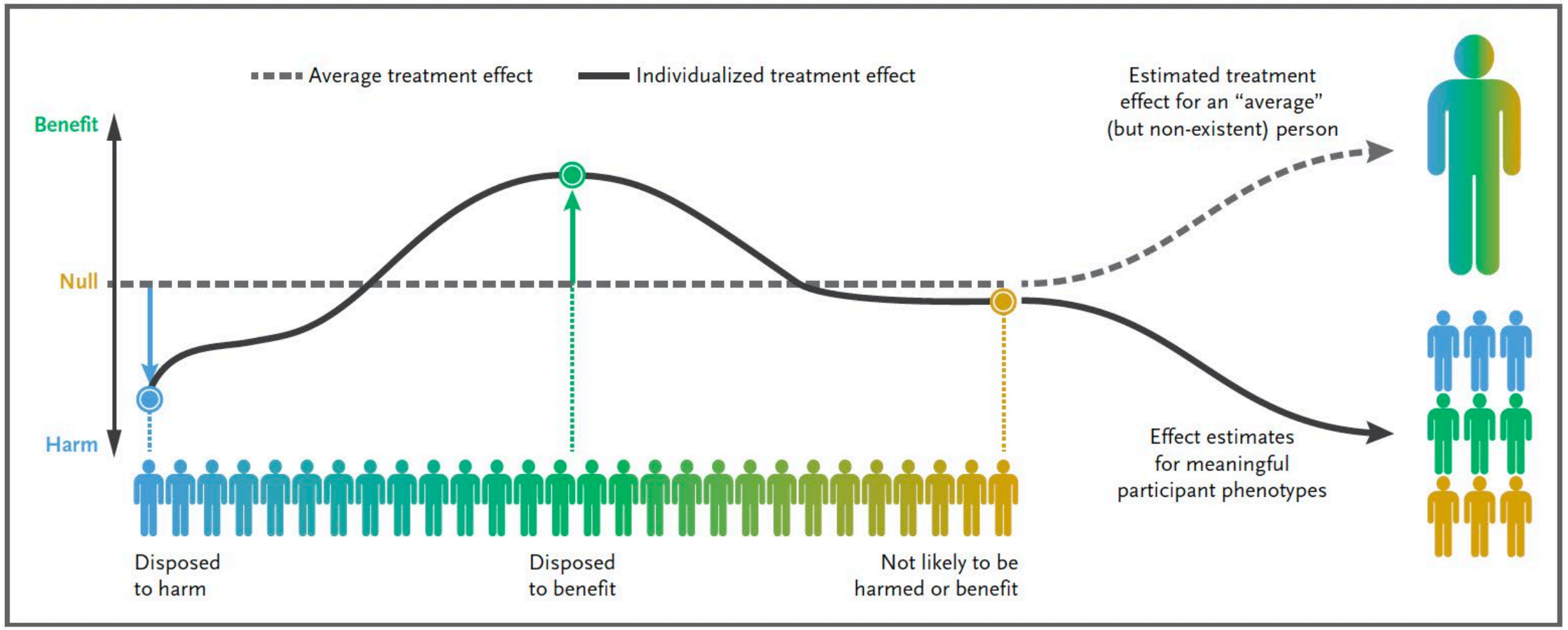


Figure 2. Patient Heterogeneity in Past Trial Interpretation and Precision Trial Design.

NEJM Evidence

Leligdowicz et al, 2022

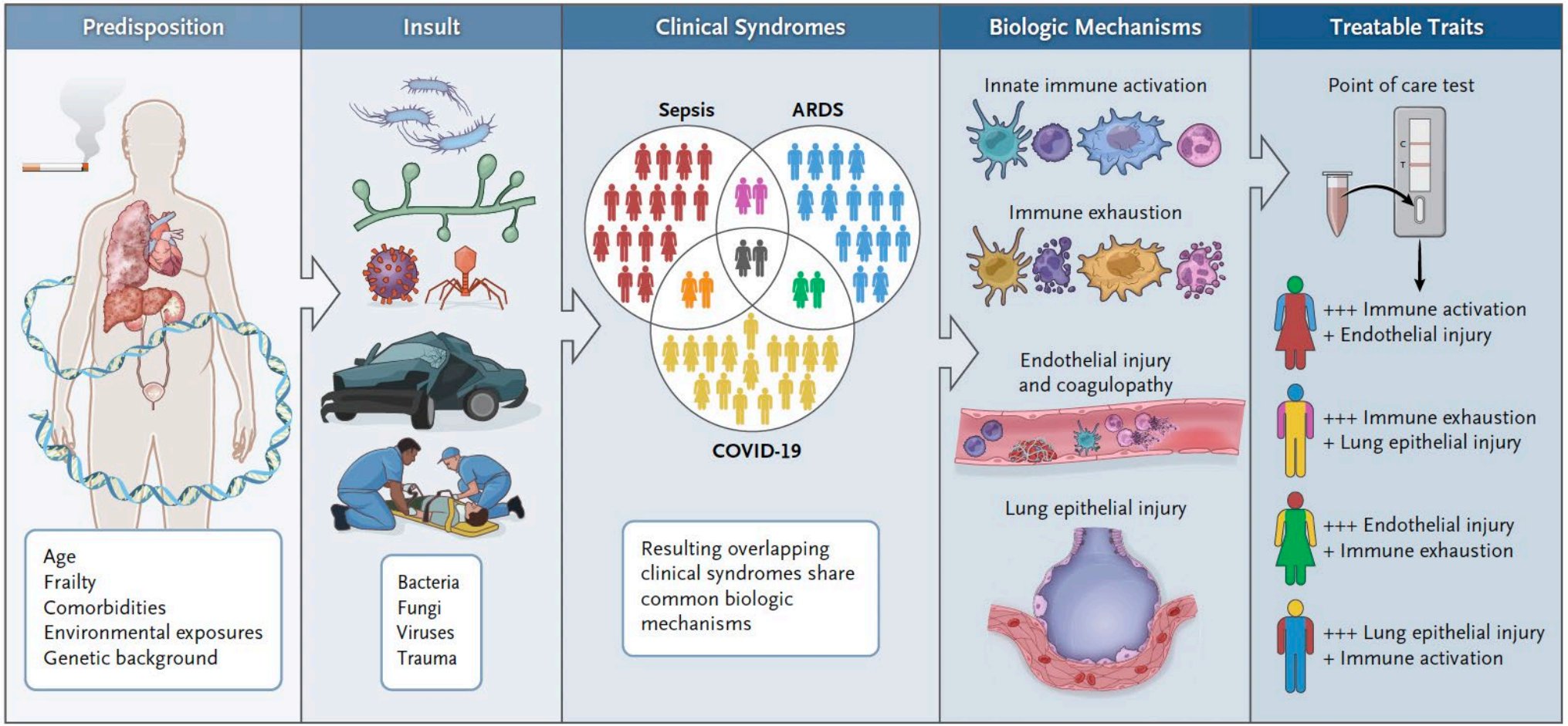


Figure 3. Potential Paradigm Shift From Clinical Syndromes (Current Paradigm) to Treatable Biologic Traits (Potential Future Paradigm).

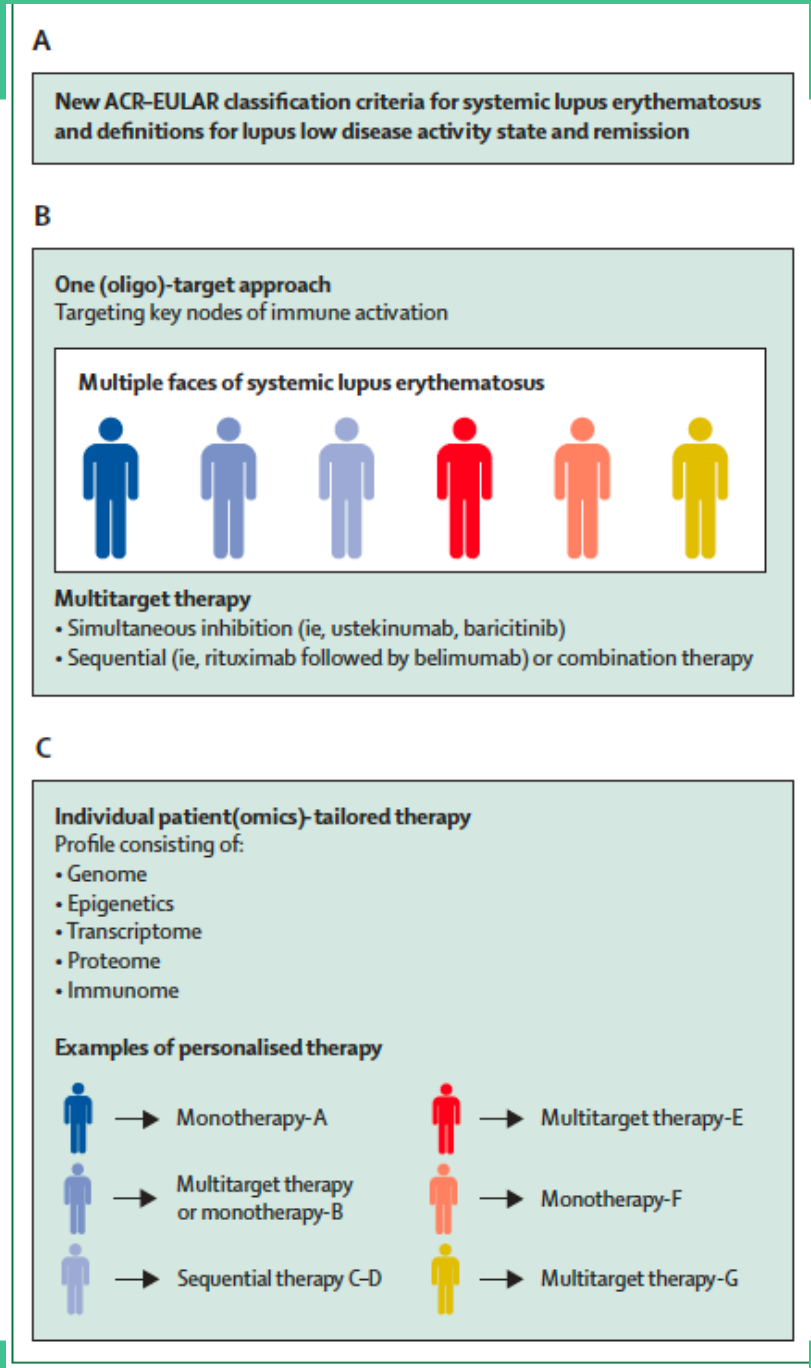


Figure 4: **Concepts to improve therapeutic outcomes in systemic lupus erythematosus**


WHEN WE TESTED THIS DRUG ON MICE, NOBODY NOTICED ANY SIDE EFFECTS.
SCHWADRON

Questions?

- Suggested reading

- Immune Modulation in Sepsis, ARDS and Covid-19 – the Road travelled and the Road ahead
- NEJM Evidence 2022; 1(11) Aleksandra Leligdowicz et al