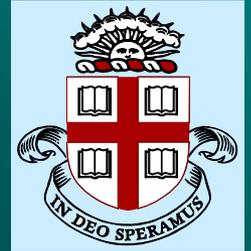


The Immunology of Sepsis

The problem of sepsis and non-resolving inflammation/infection

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Brown University
Providence, RI



FDA workshop
Washington DC-16/Oct/2015

Sepsis: Defining a Disease Continuum: 1992-2014

Infection/
Trauma

SIRS

Sepsis

Severe Sepsis

Sepsis with ≥ 1 organ
dysfunction

- Cardiovascular
(refractory
hypotension)
- Renal
- Respiratory
- Hepatic
- Hematologic
- CNS
- Metabolic acidosis

Shock

Draft Sepsis definitions: the 2015-6 version

- ❖ Infection: interaction with a microorganism that induces a local or a systemic host response (old term-sepsis); if no host response-colonization or contamination
- ❖ Sepsis: A deleterious host response to infection resulting in organ dysfunction remote from the site of infection (old term-severe sepsis)-deleting “SIRS”
- ❖ Septic Shock: sepsis complicated by diffuse cardiac and microvascular dysfunction with fluid non-responsive hypotension (SBP<90mmHg), need for vasopressors to maintain BP, and elevated blood lactate (>2 mmol/L)

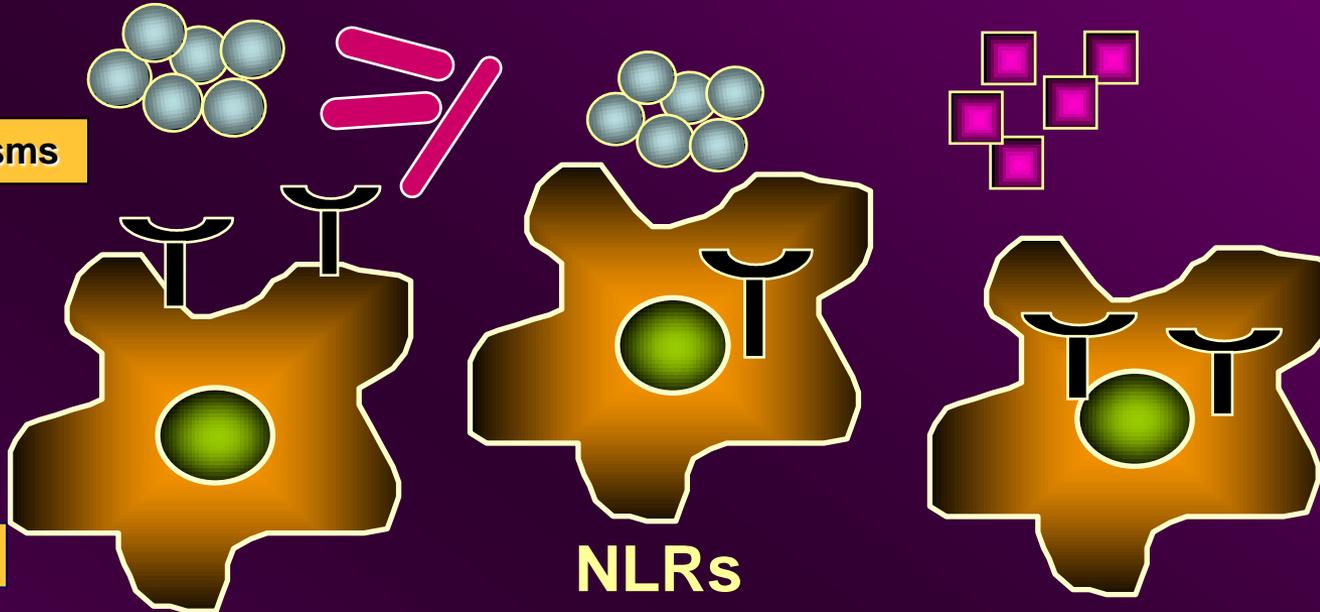
Innate Immunity in Early Sepsis

PAMPs

DAMPs

- HSP
- Heparan
- Hyaluronate
- Fibrinogen
- Biglycan
- Surfactant A
- HMGB-1
- Heme
- mtDNA
- Histone

Microorganisms



5 PRRs

NLRs

TLRs

CLRs

CDRs

RLHs

Signalosome Pathway

Inflammasome Pathway

NF- κ B

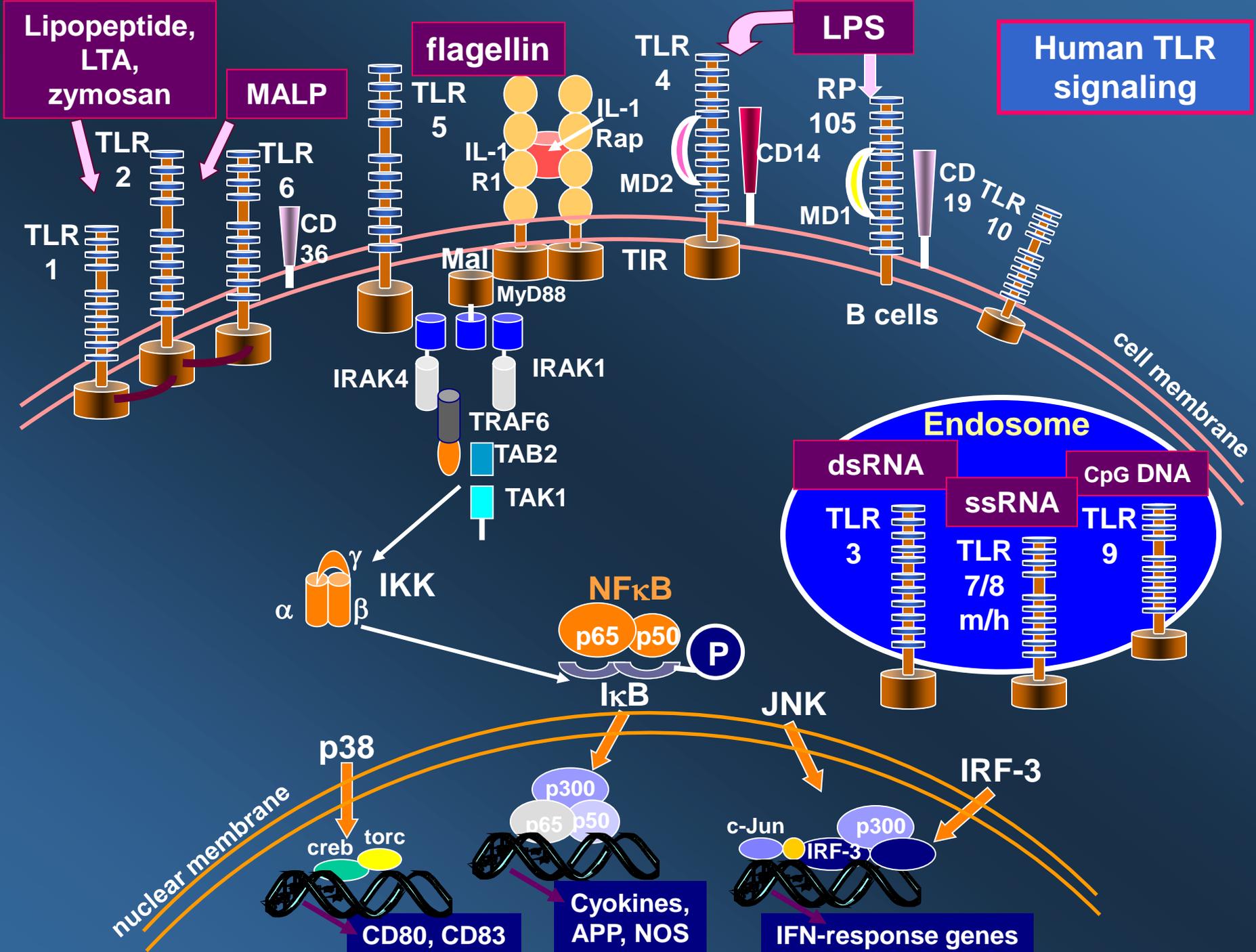


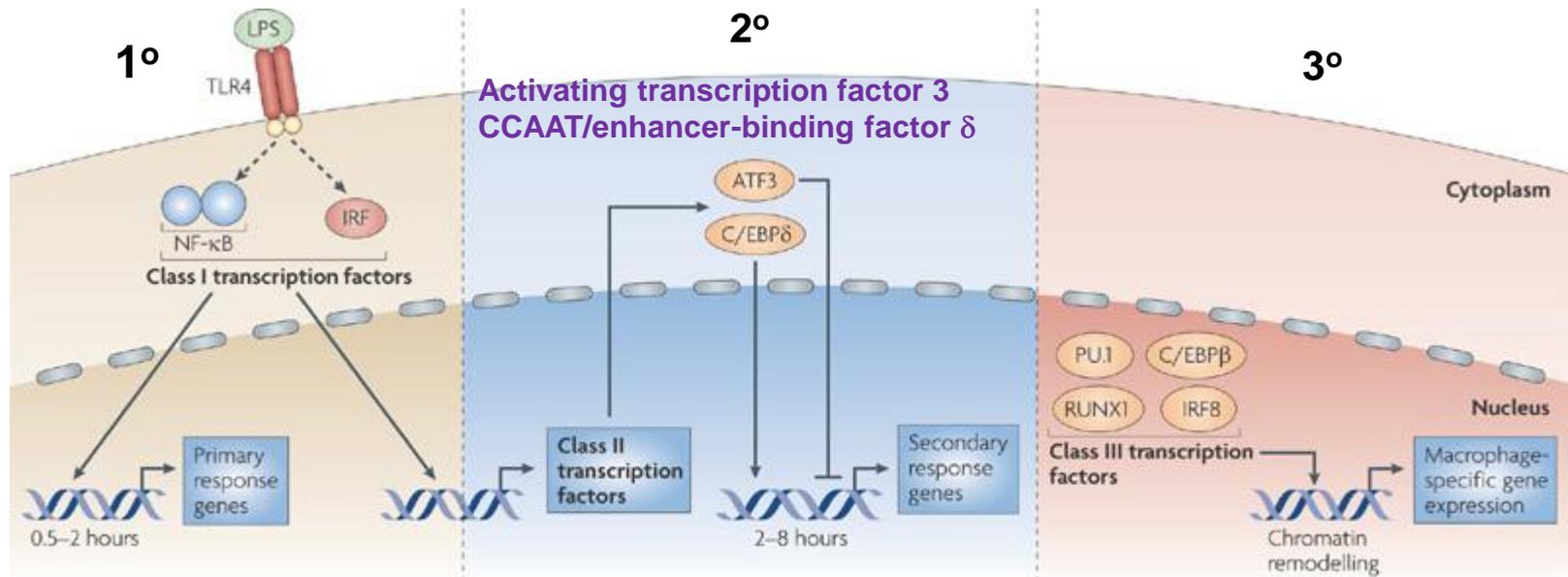
Caspase-1 & 5
ASC
NALP1 & 3
Pyrin

Host-derived mediators

INFLAMMATION

Cinel and Opal CCM 2009;291-
courtesy of T. Calandra





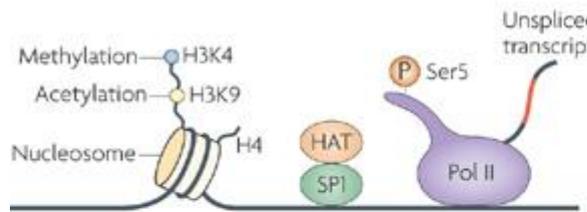
Minutes: proinflammatory

Hours: anti-inflammatory + host defense genes

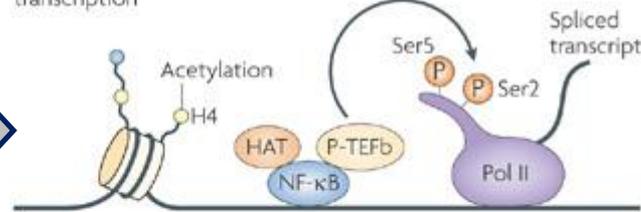
Days: mixed response + metabolic genes

1° response genes

Basal transcription



Stimulus-dependent transcription

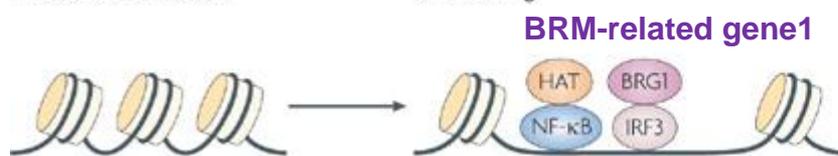


Positive-transcription elongation factor b

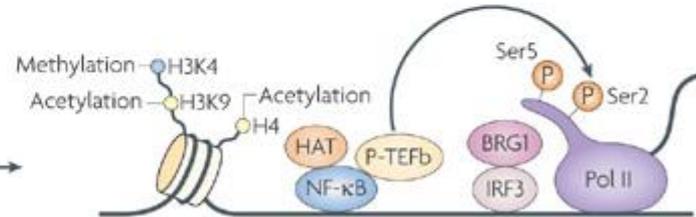
2°/3° response genes: de novo synthesis

Inaccessible chromatin

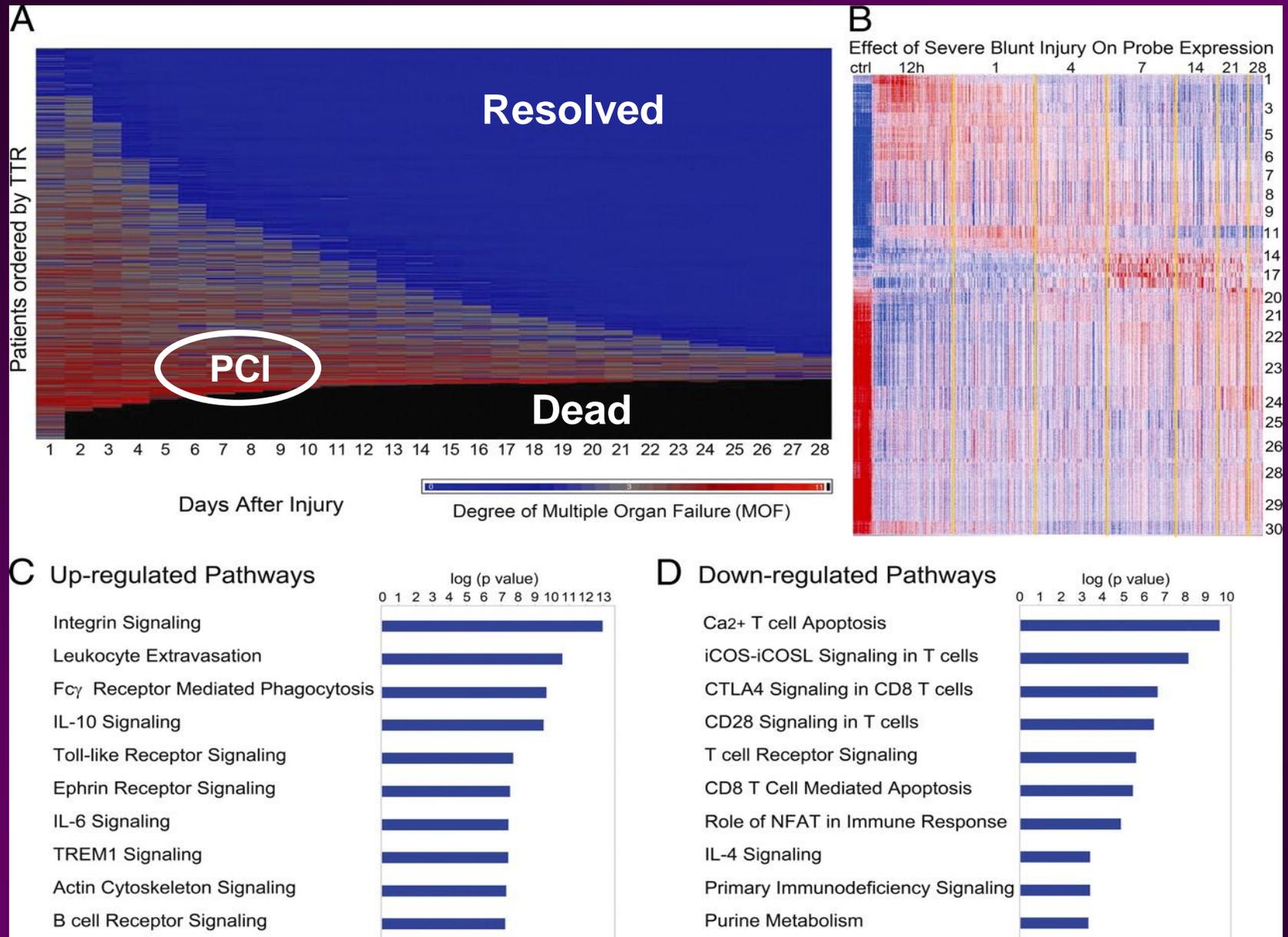
Remodelling



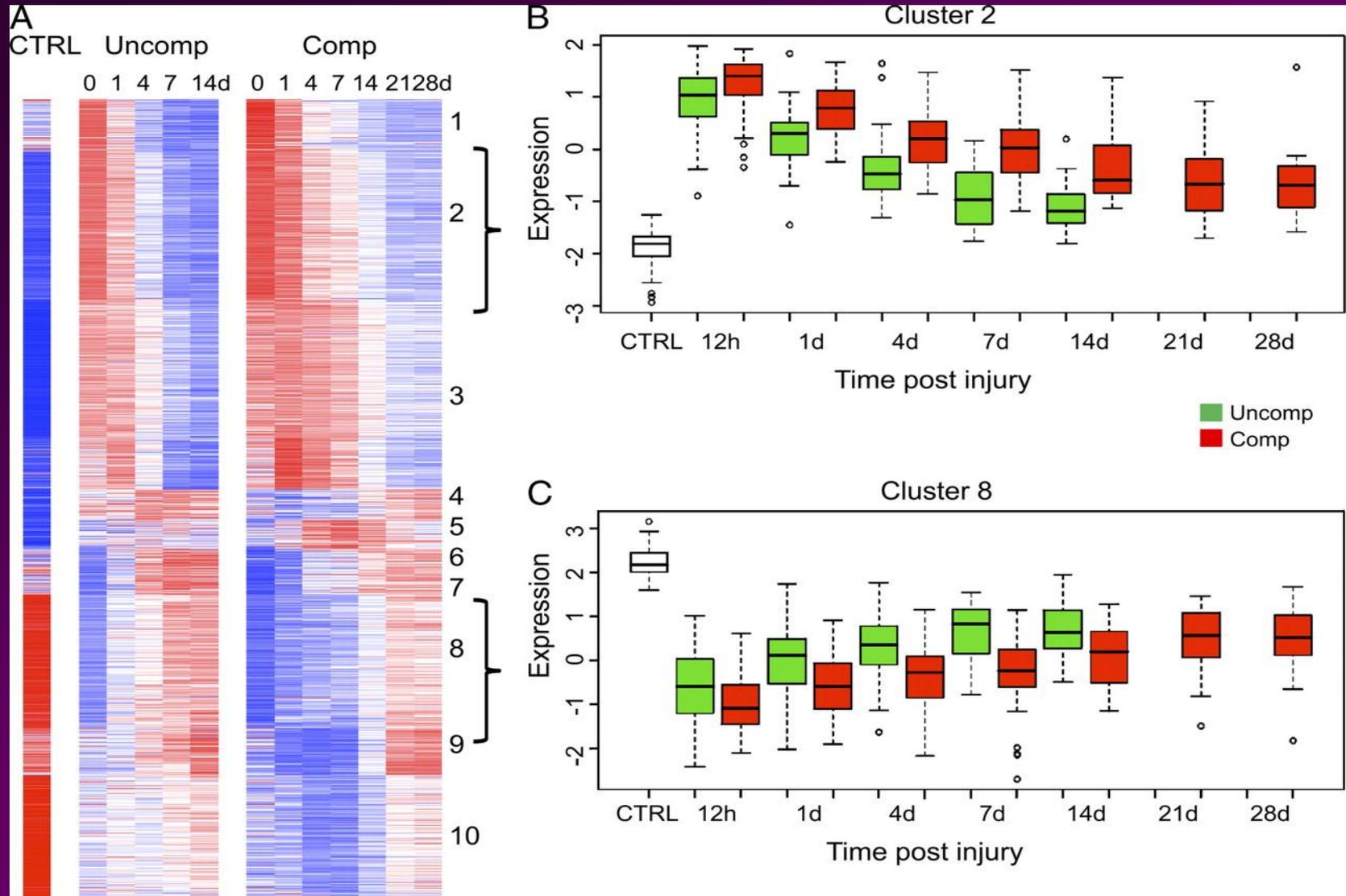
Transcriptional start site



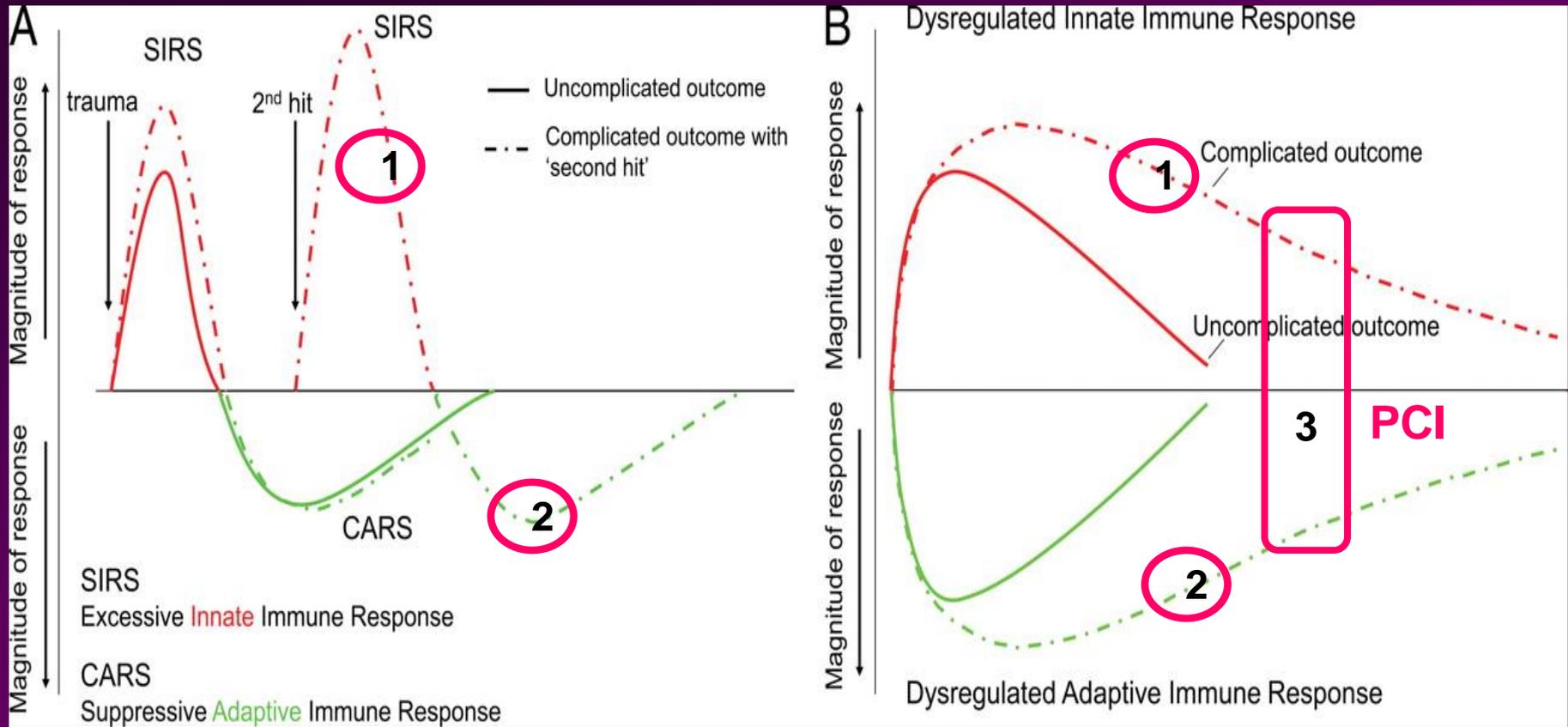
Human acute inflammatory patterns following “sterile” injury



Differences in gene expression: complicated vs. uncomplicated recovery following severe trauma



The “two hit model” vs. the “monopolar” immune response in sepsis



The T and B cell lymphopenia of sepsis (apoptosis and extravascular distribution)

Table 1

Comparative study of absolute cell numbers of lymphocyte subpopulations between septic shock patients and healthy individuals.

Cells/mL	Septic patients	Healthy volunteers
Total lymphocytes	1239 ± 237	3113 ± 739
CD3 ⁺ T lymphocytes	626 ± 58	1352 ± 86
CD4 ⁺ T lymphocytes	428 ± 74	836 ± 49
CD4 ⁺ CD25 ⁺ (Treg)	168 ± 32	173 ± 13
CD4 ⁺ CD25 ⁻	260 ± 44	663 ± 41
γδ T lymphocytes	16 ± 4	56 ± 9
Others (including B, CD8 ⁺ , NK)	613	1761

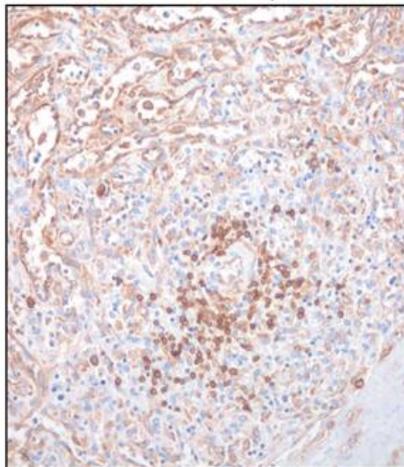
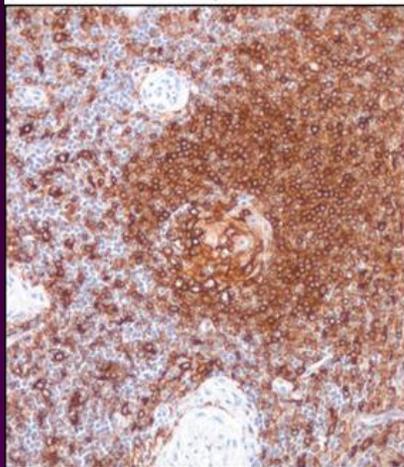
Data (mean ± SEM) from Lyon clinical studies ([126](#), [127](#)) were extracted to provide a global picture of the absolute count of lymphocyte subpopulations measured in whole blood from septic shock patients between days 3 and shock and from healthy individuals.

Sepsis - induced effector cell apoptosis in spleen tissue

A Immunohistochemical staining for HLA-DR

Control patient

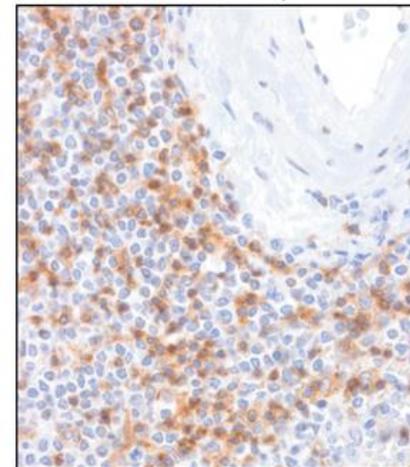
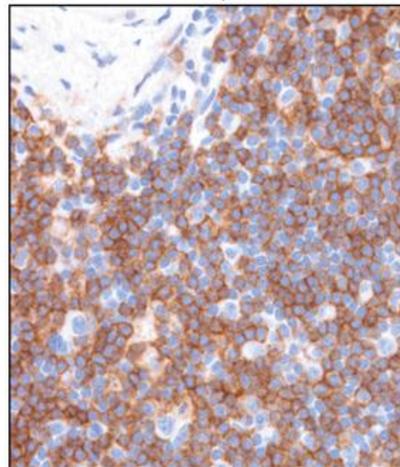
Patient with sepsis



B Immunohistochemical staining for CD4

Control patient

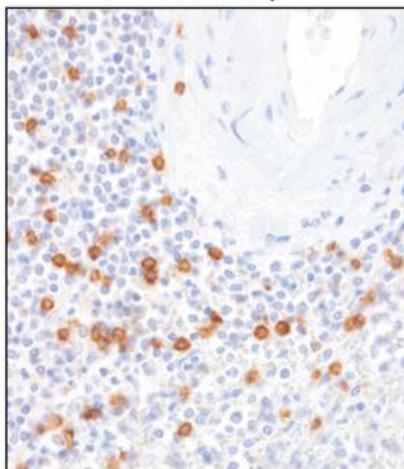
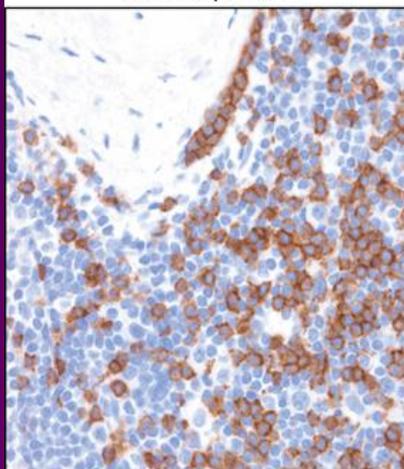
Patient with sepsis



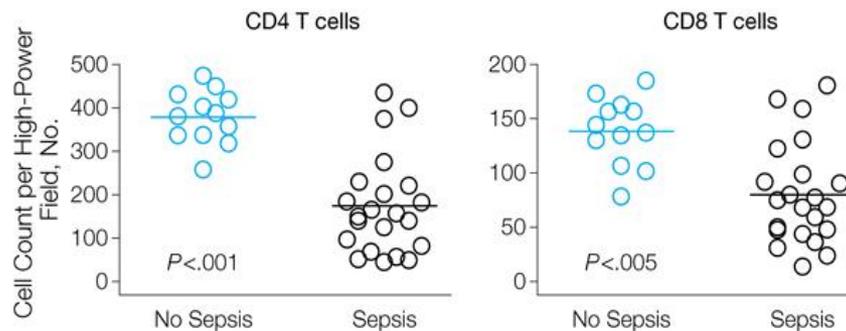
C Immunohistochemical staining for CD8

Control patient

Patient with sepsis

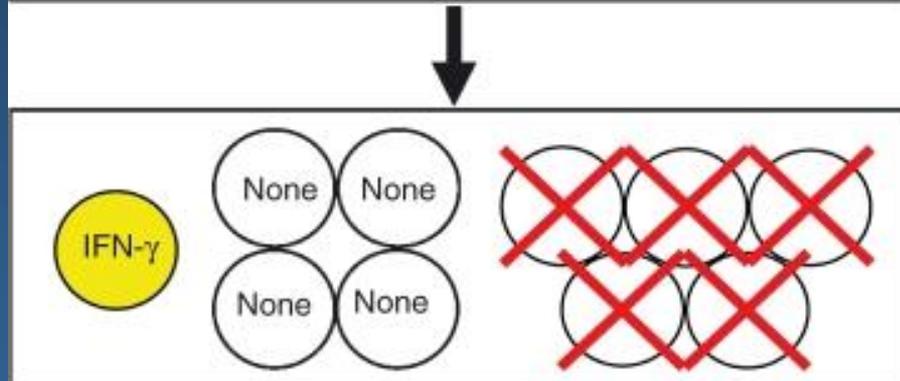
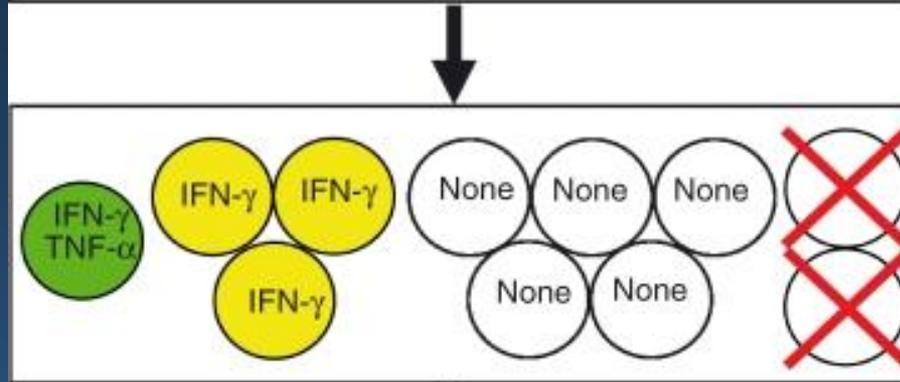
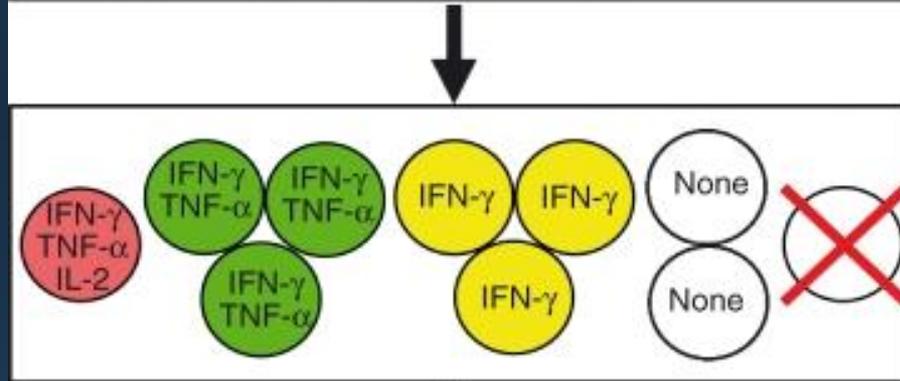
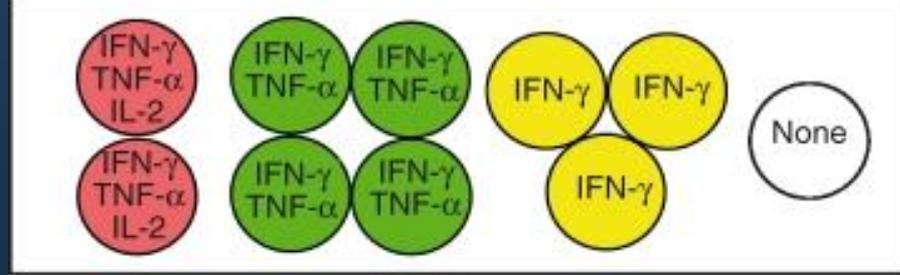


D T-cell counts



T cell exhaustion

Progressive loss of function along with excess apoptosis

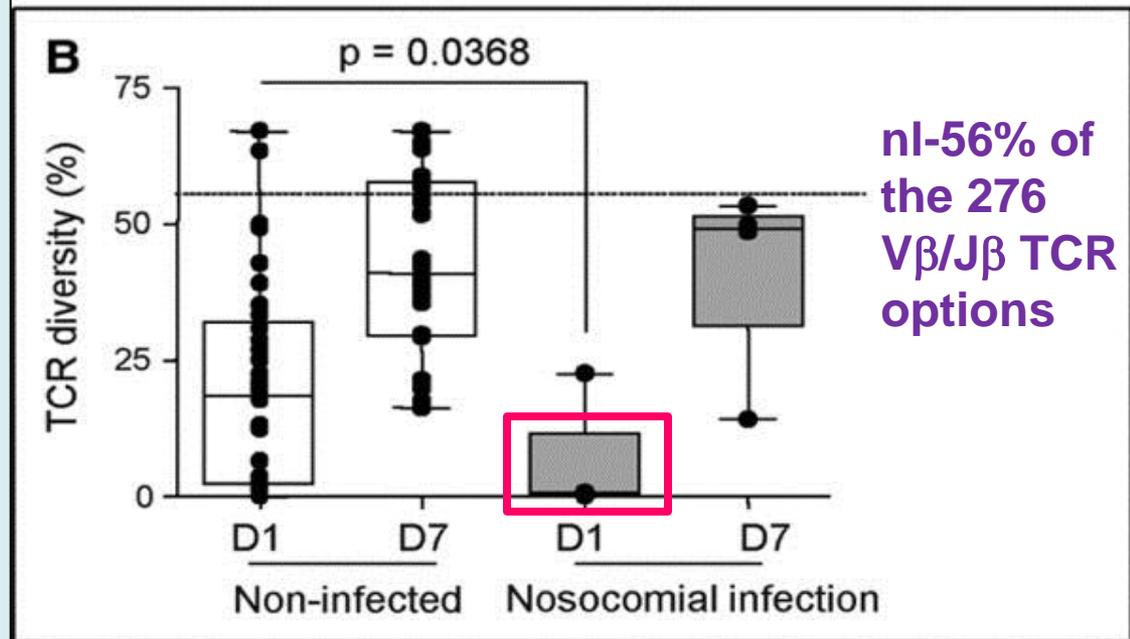
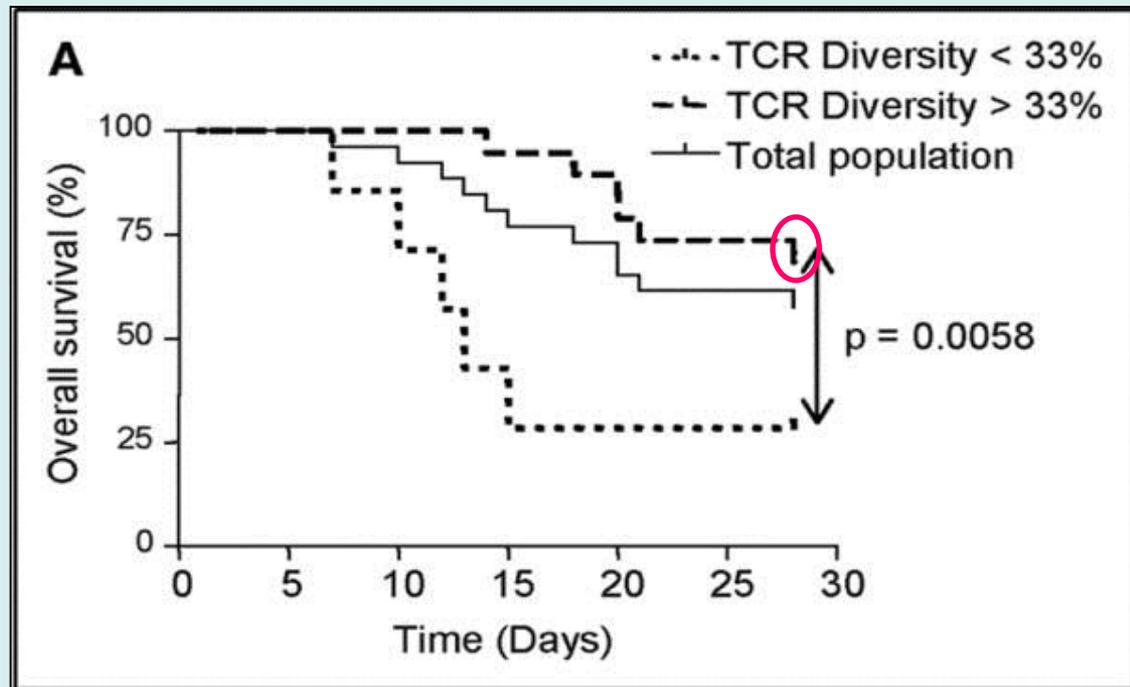


Non-resolving sepsis

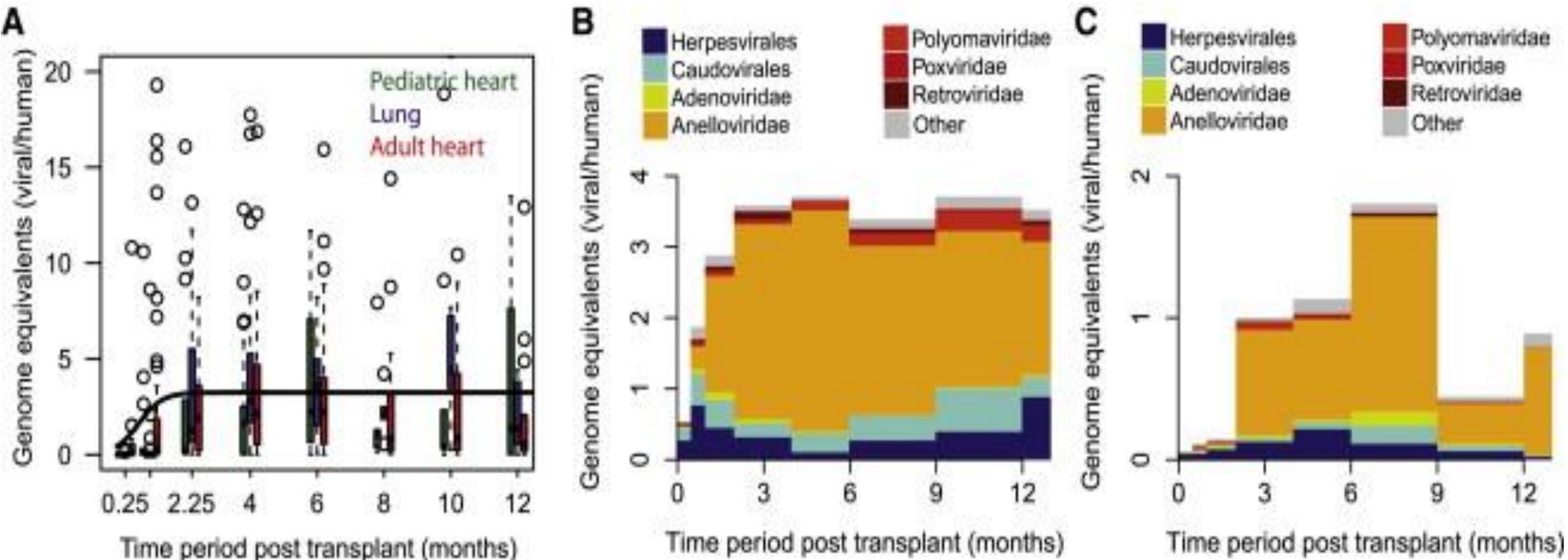
T cell receptor diversity

- outcome in septic shock
- risk of nosocomial infection (n=41)

Adaptive immunity is dysfunctional in sepsis; does it make any difference and is it correctable?



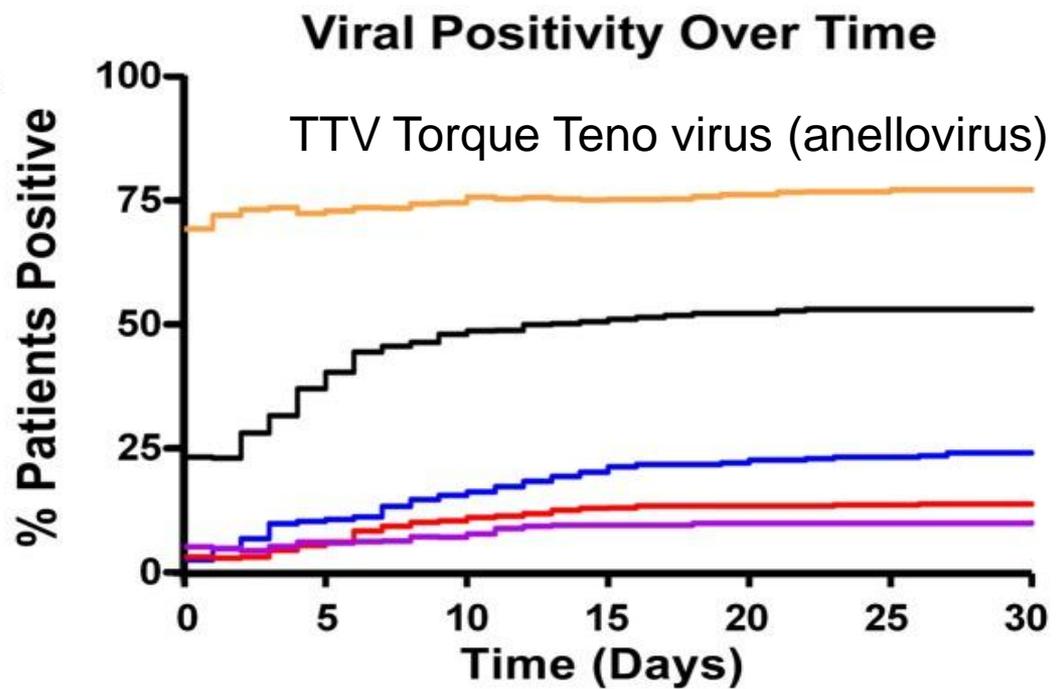
The full complement of viruses in human blood: the Virome



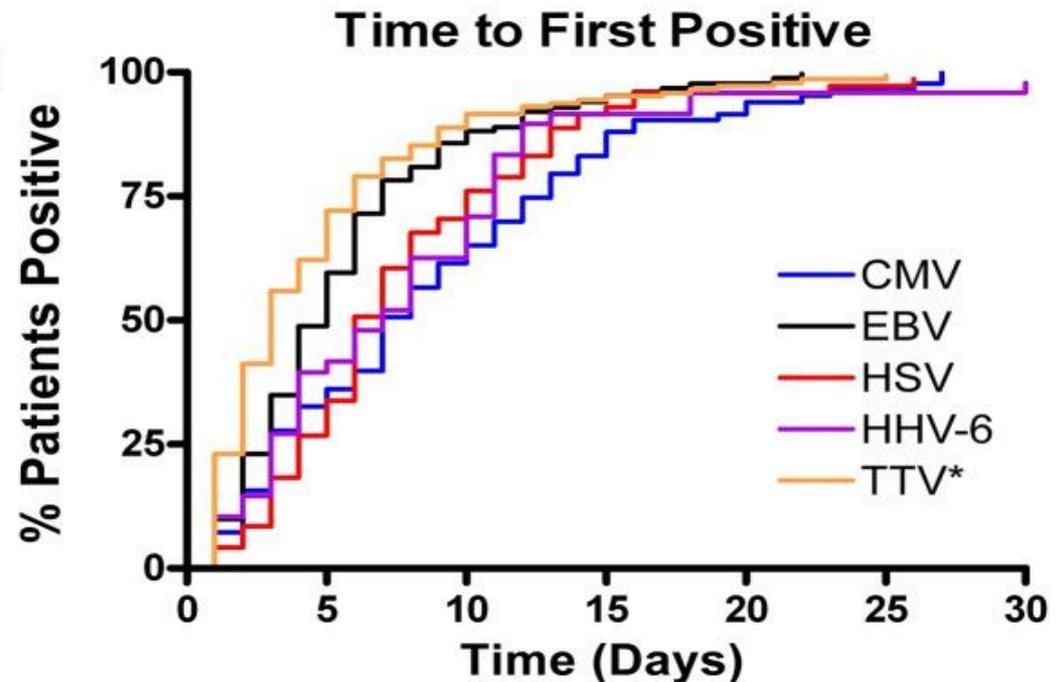
The human virome markedly expands S/P post transplantation from Immunosuppressive agents to prevent rejection

Prospective virome study of 560 septic vs. 161 critically ill, non septic, and 164 age-matched controls

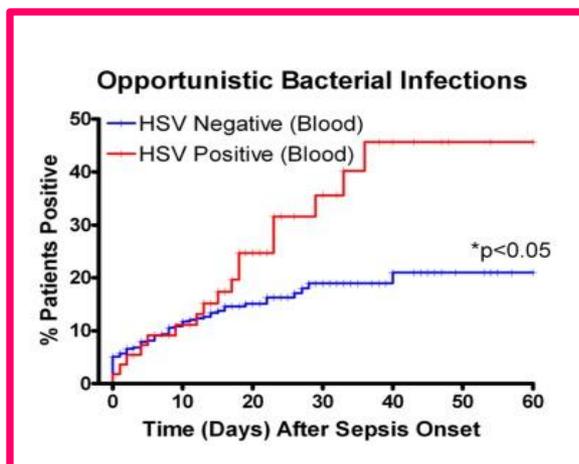
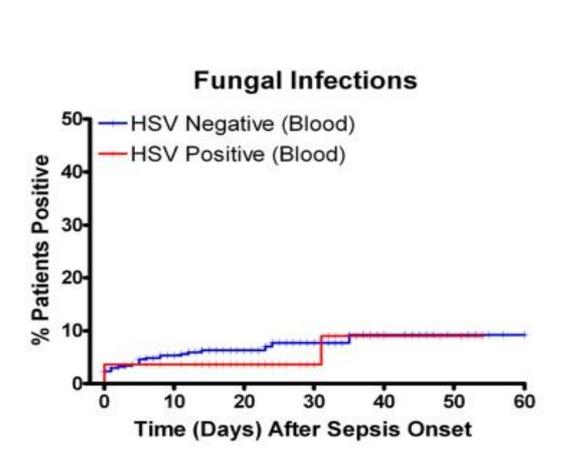
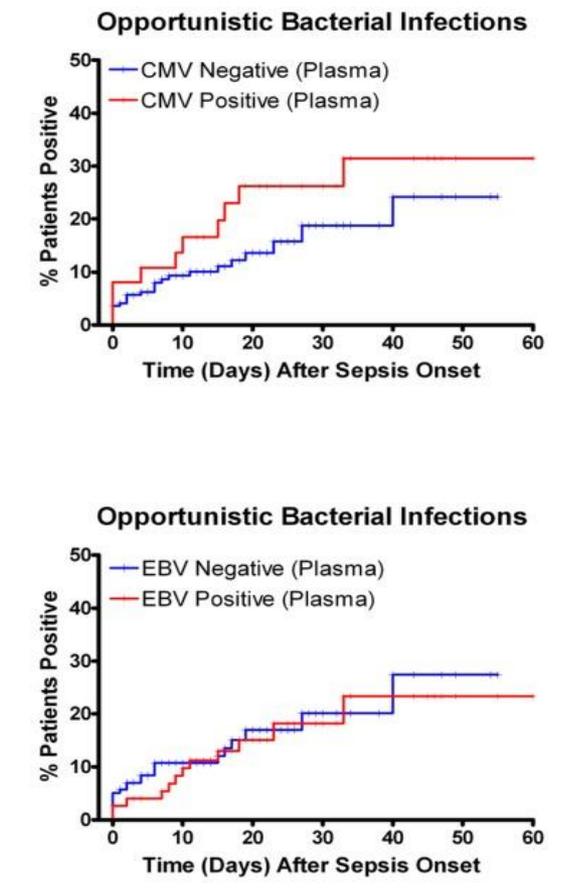
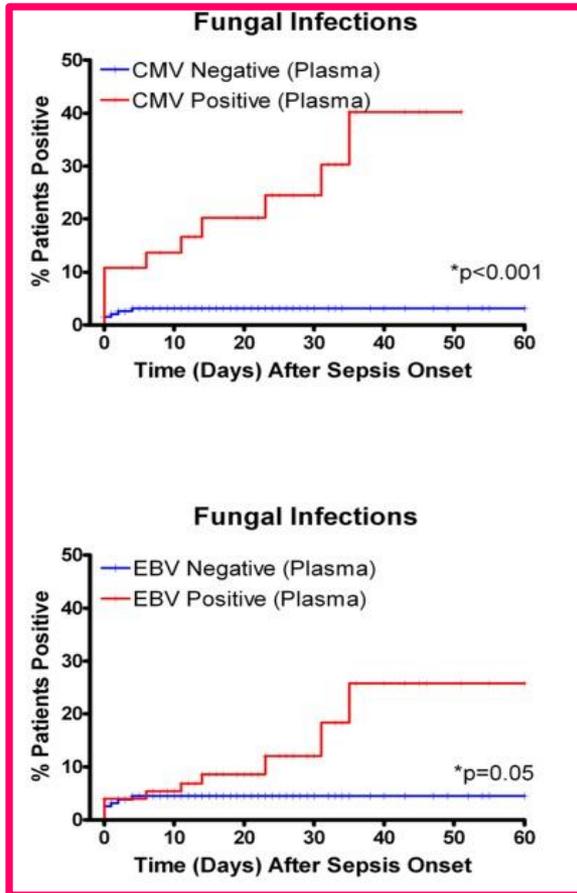
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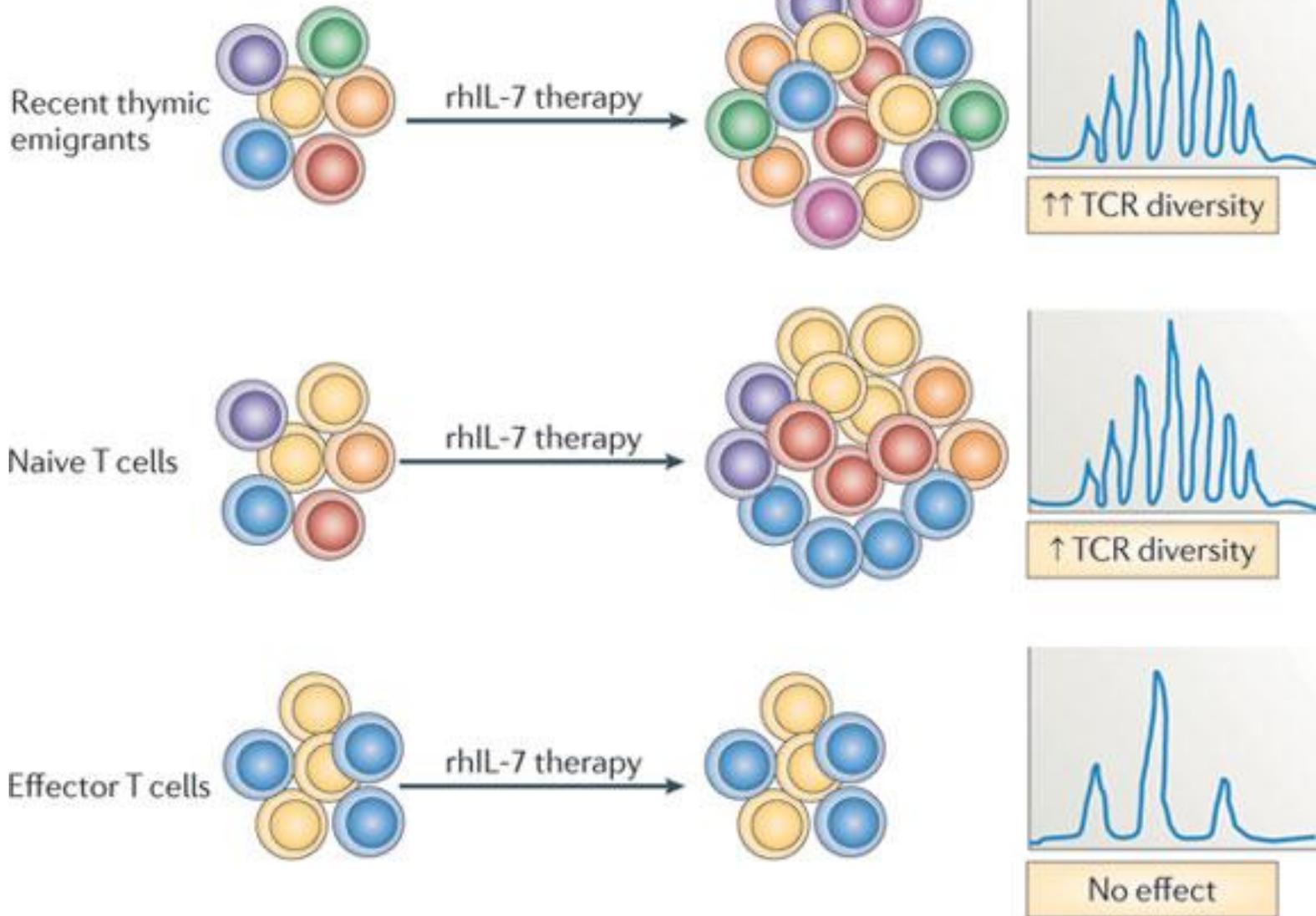
B



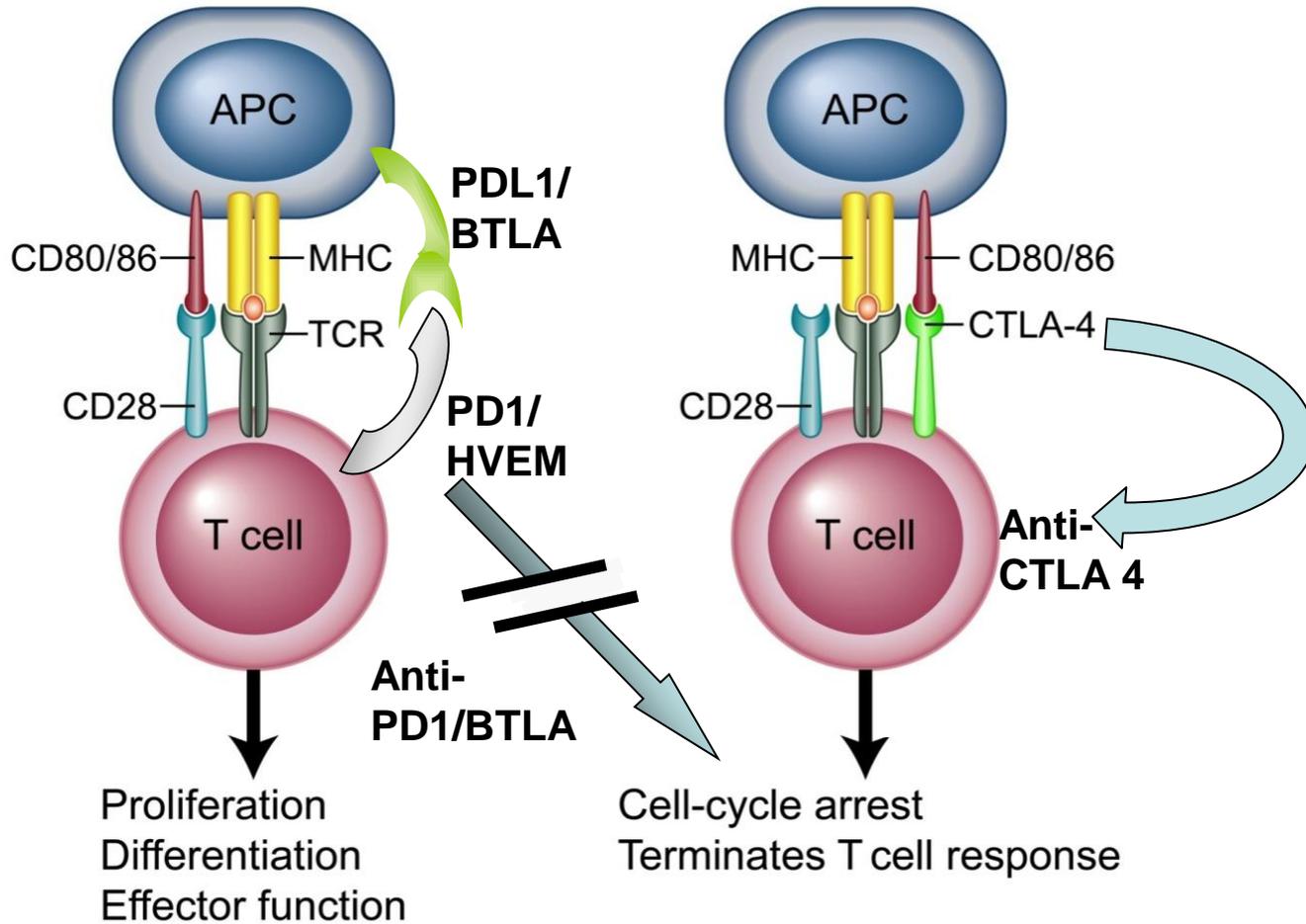
Herpes viral DNAemia predicts risk of opportunistic infections in septic patients



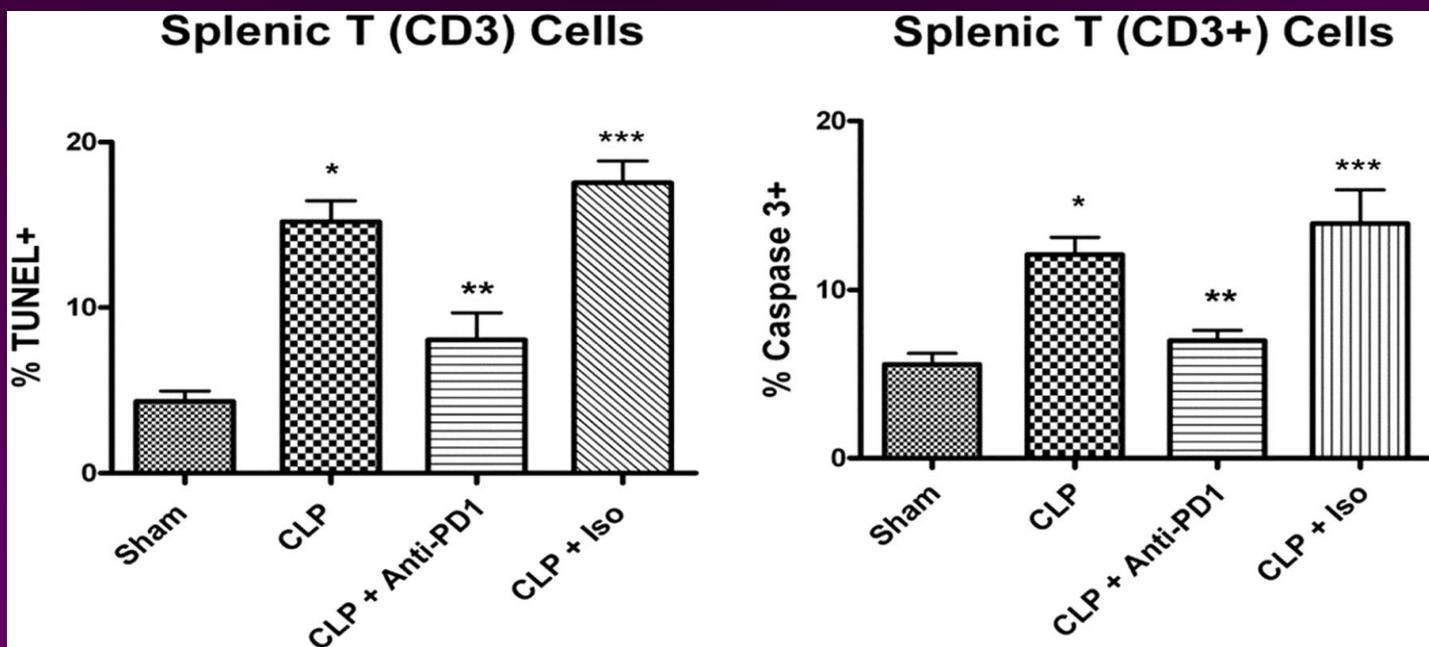
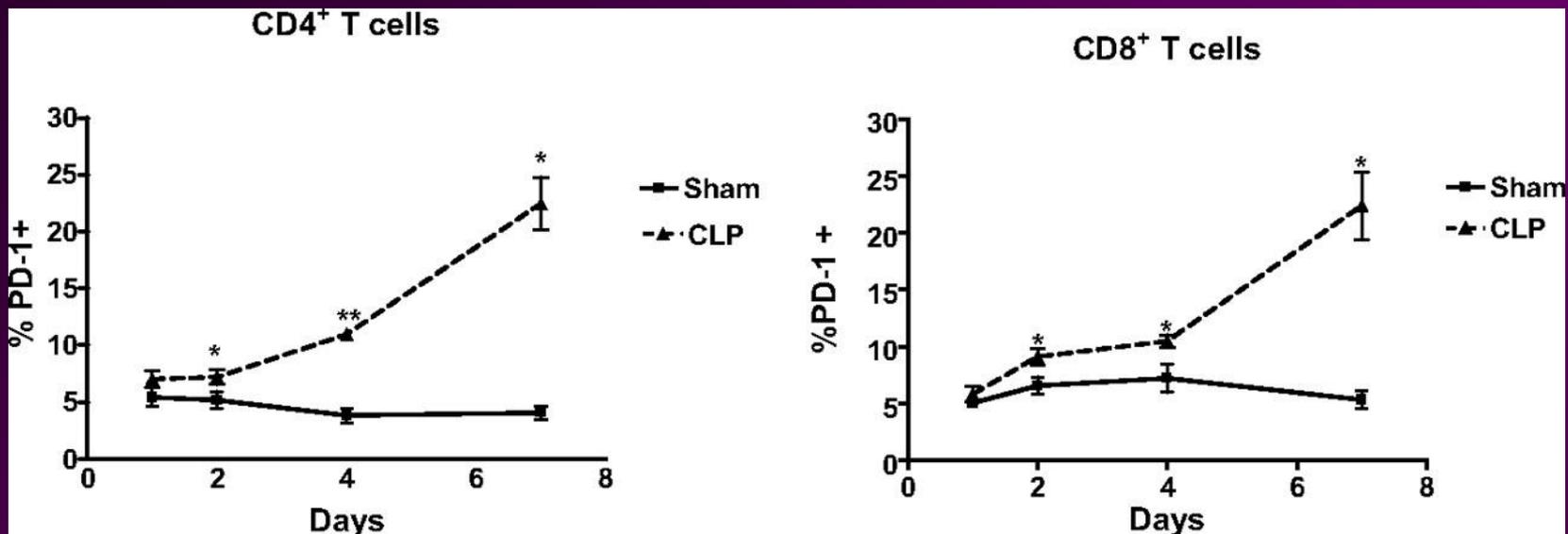
Any treatment options?



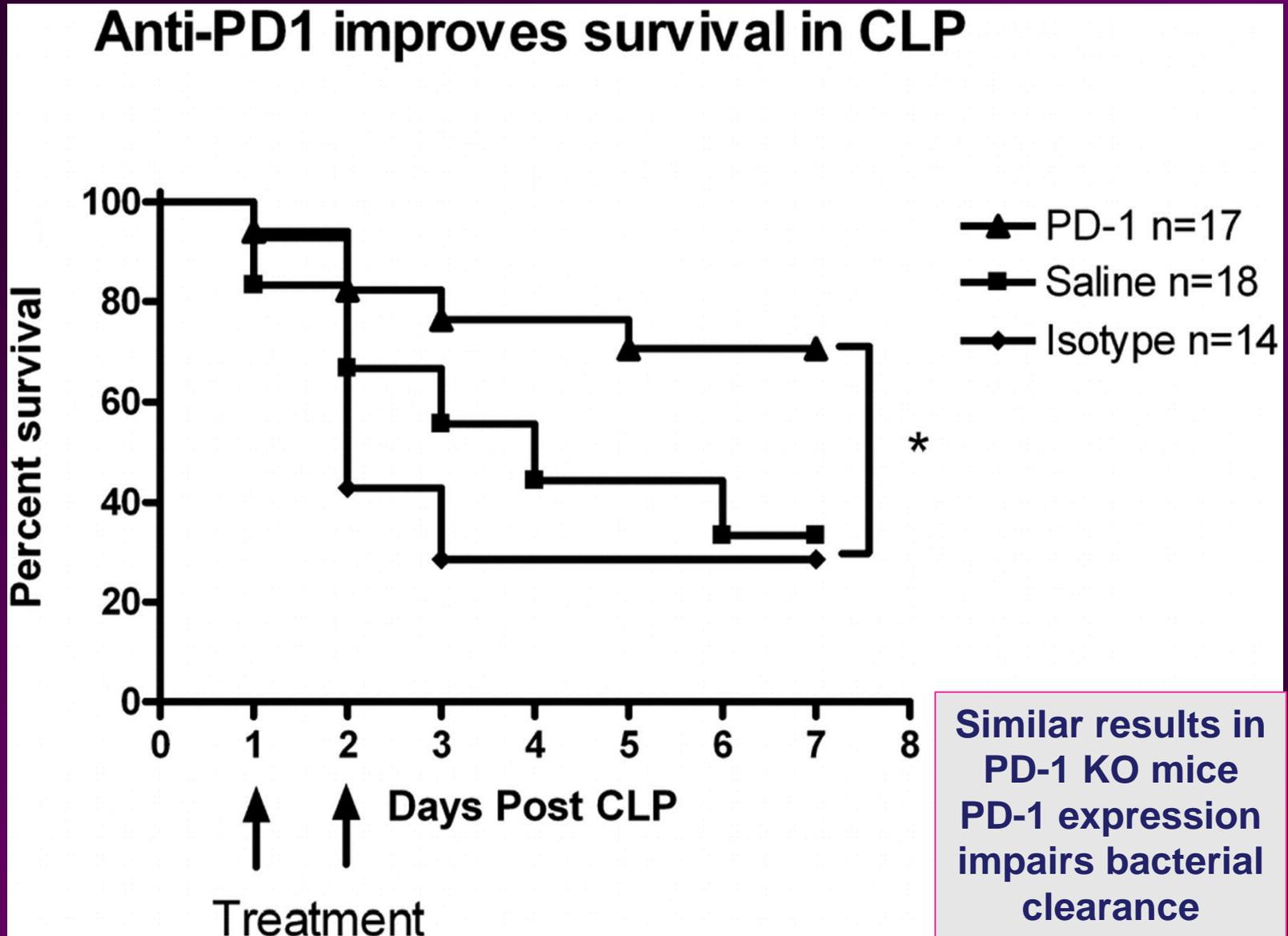
Blockade of Negative Co-stimulatory Molecules on T Cells



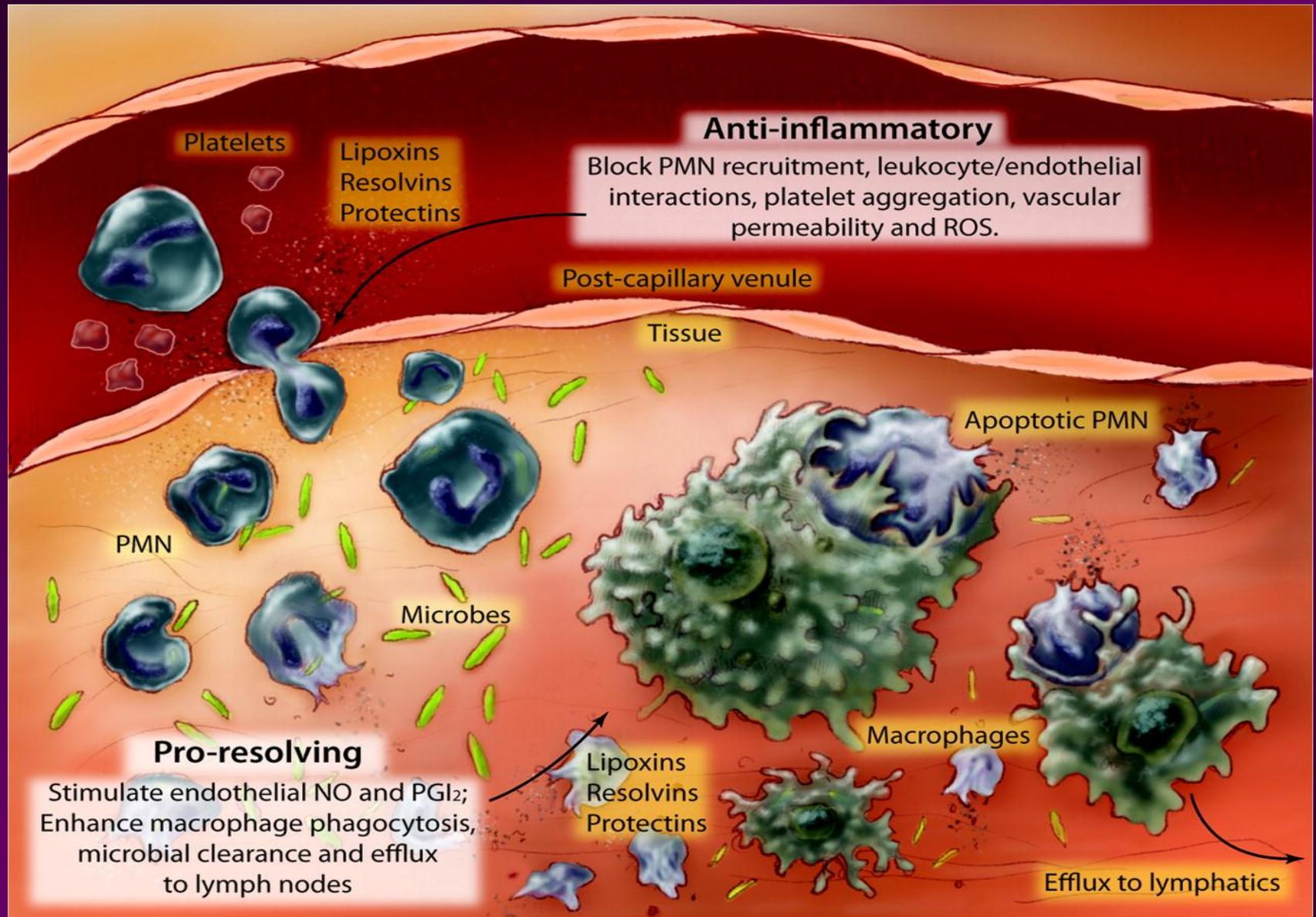
PD-1 expression increases in CD4+/CD8+ T cells in sepsis



Anti-PD-1 aB improves survival S/P CLP (given 24, 48 hr)



Resolving inflammation is an active process: proresolving actions of lipooxygenase-derived lipoxins, resolvins, and protectins



Can we restore immune tranquility in Sepsis ?
**Yes, but its complicated and we need rapid methods to identify
who is infected and who is developing organ injury**

