

Sepsis - view into the future



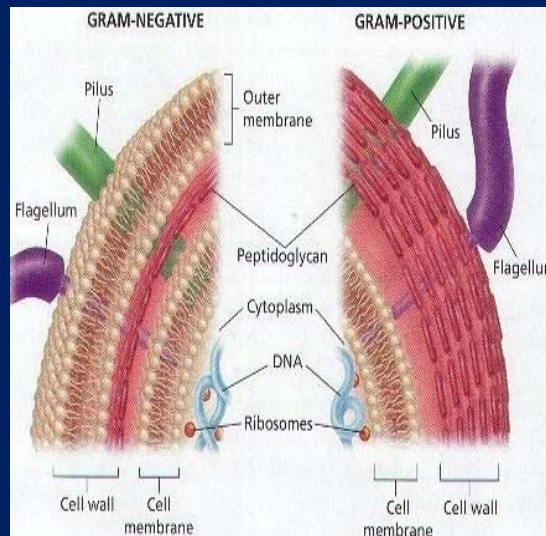
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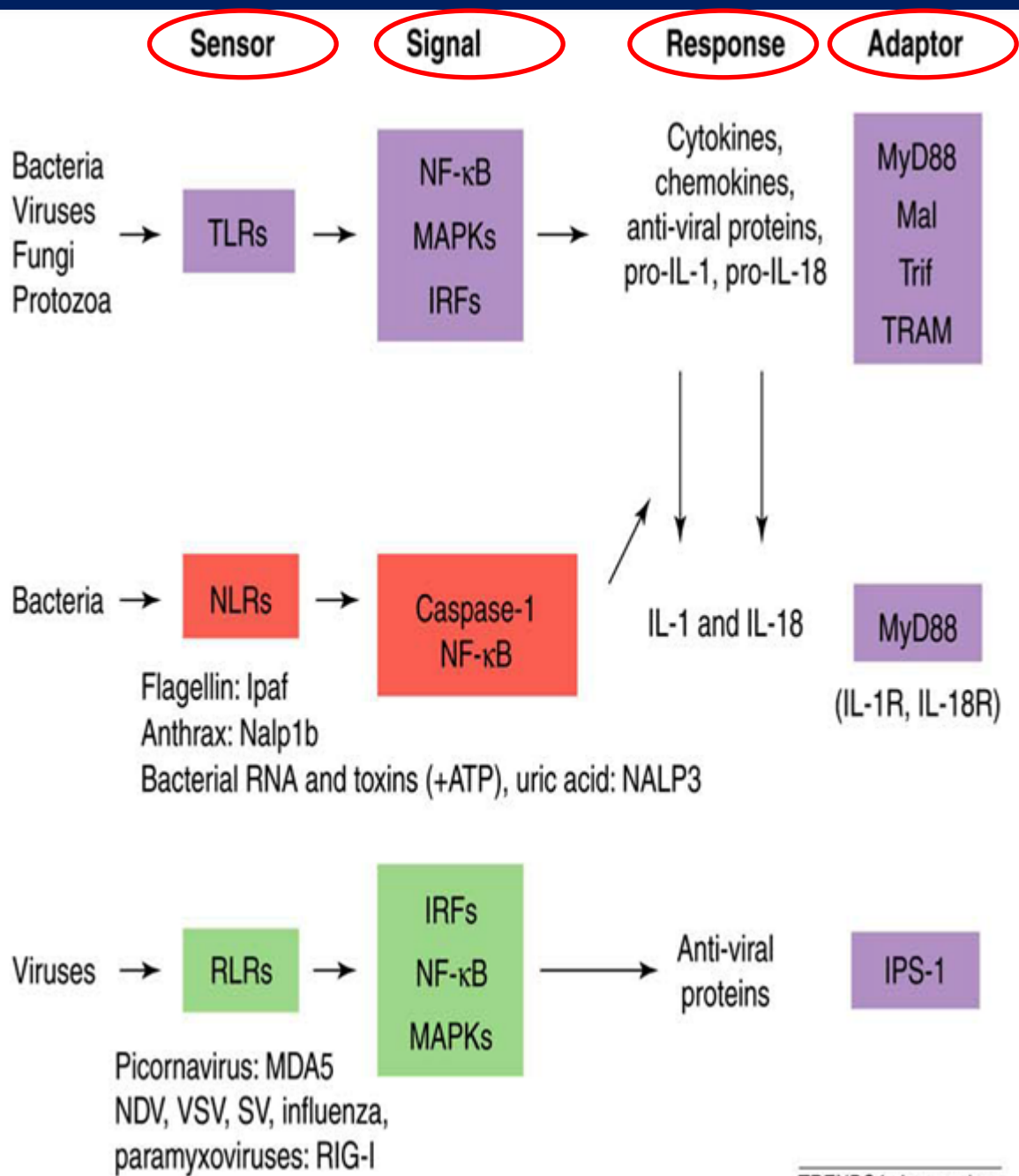
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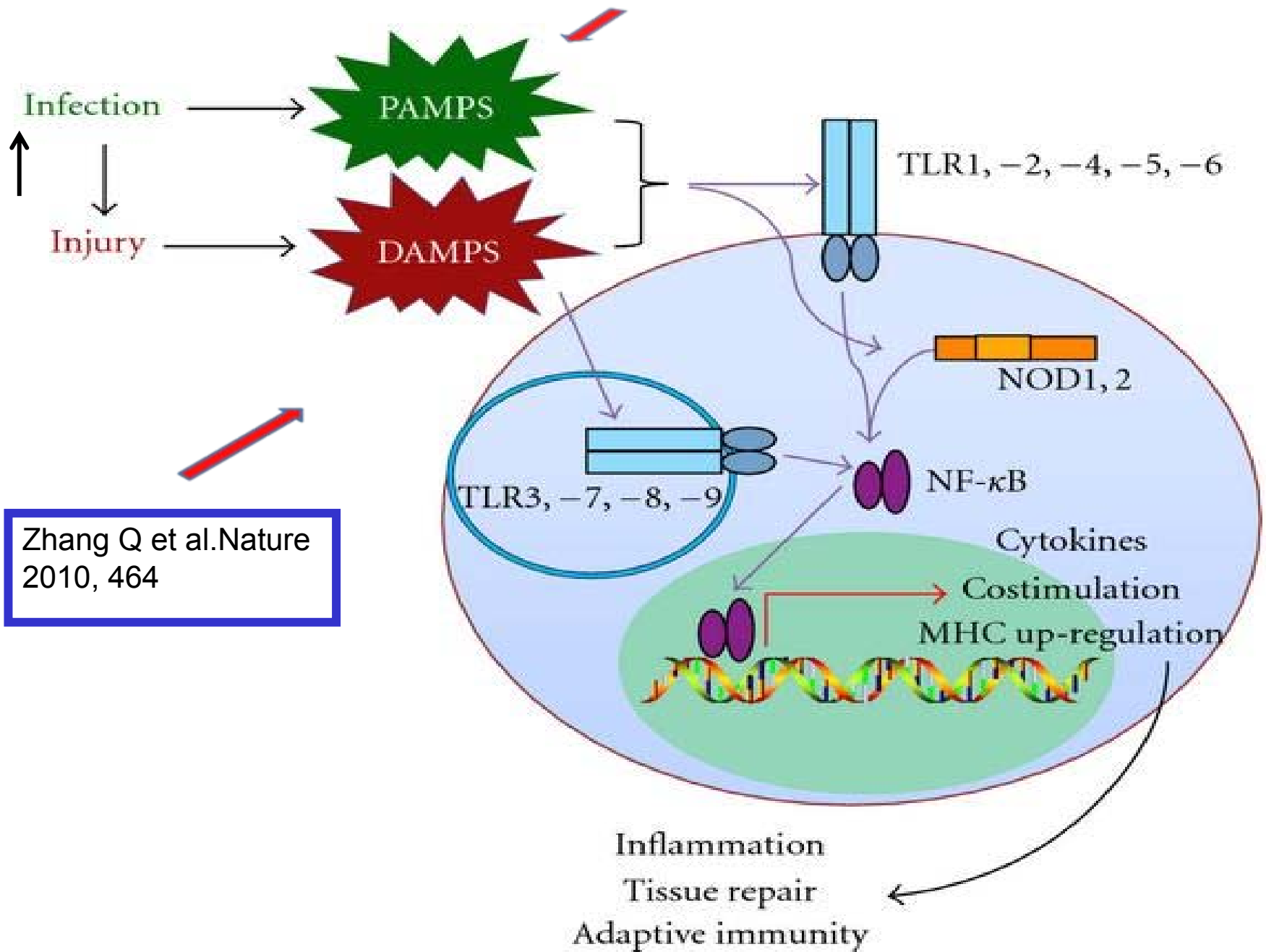
Sepsis represents a failure of innate and adaptive immunity



- Shift from Th1 to Th2 response – the different production of cytokines
- Increased apoptosis of immunocompetent cells
- Immunosuppression via neuroimmunomodulation





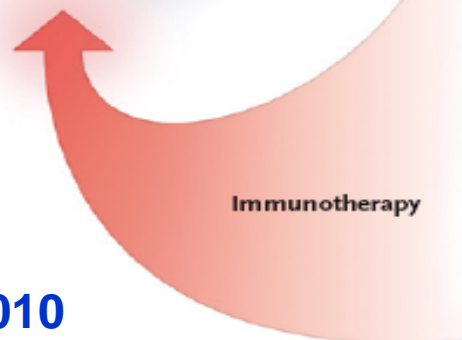
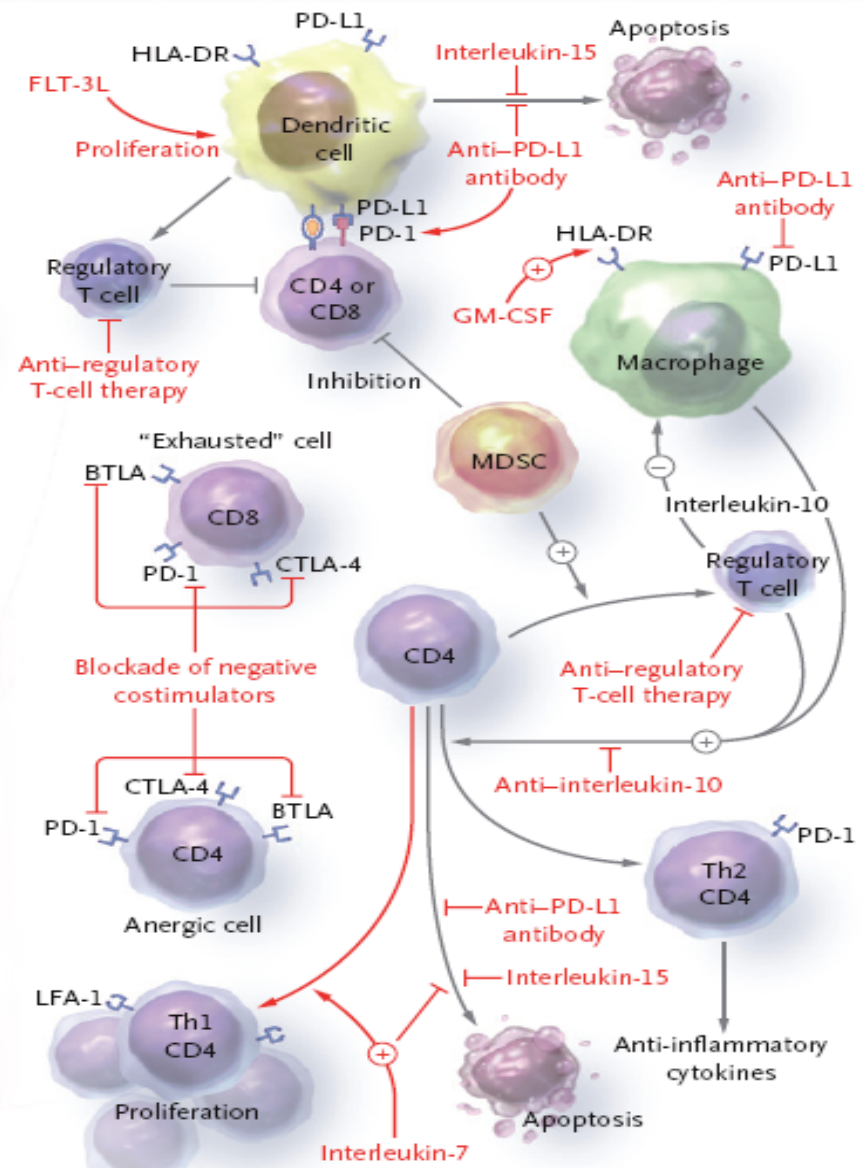
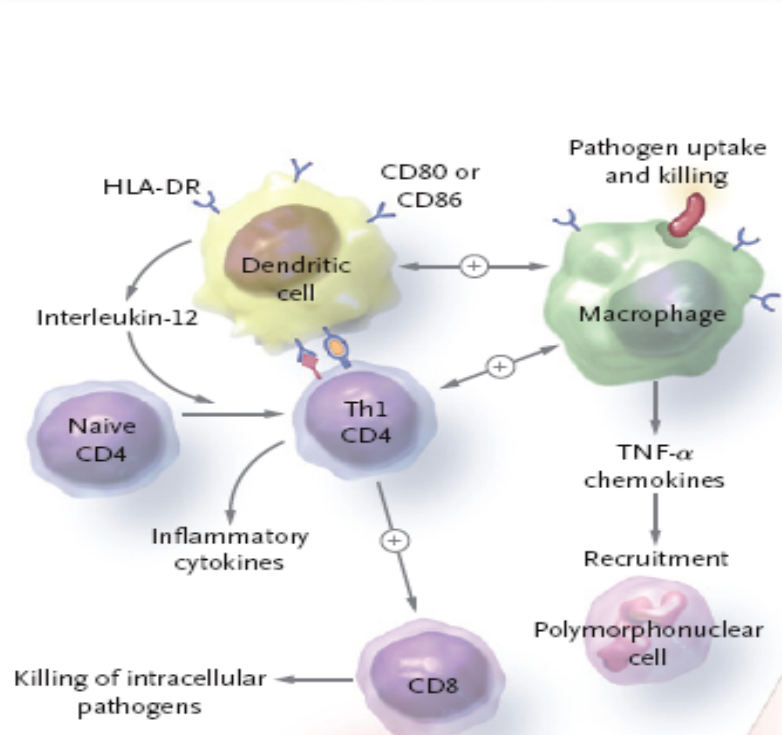


Zhang Q et al. Nature
2010, 464

Immune inflammatory response
(effective pathogen killing)

Sepsis progression

Immunosuppression
(pathogen persistence and superinfection)



Hotchkiss 2010

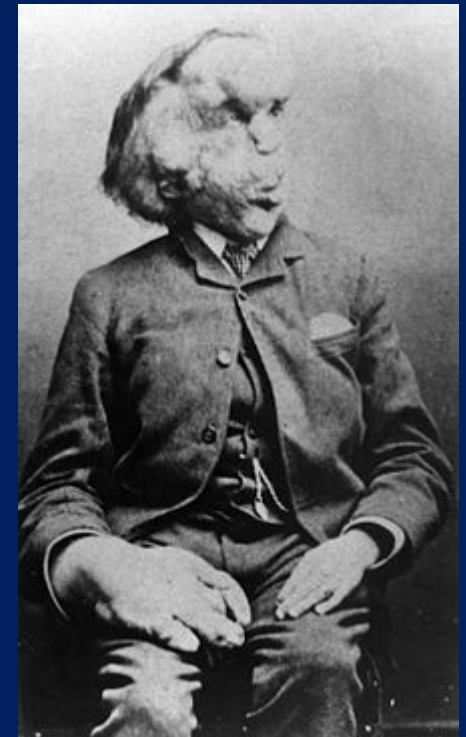
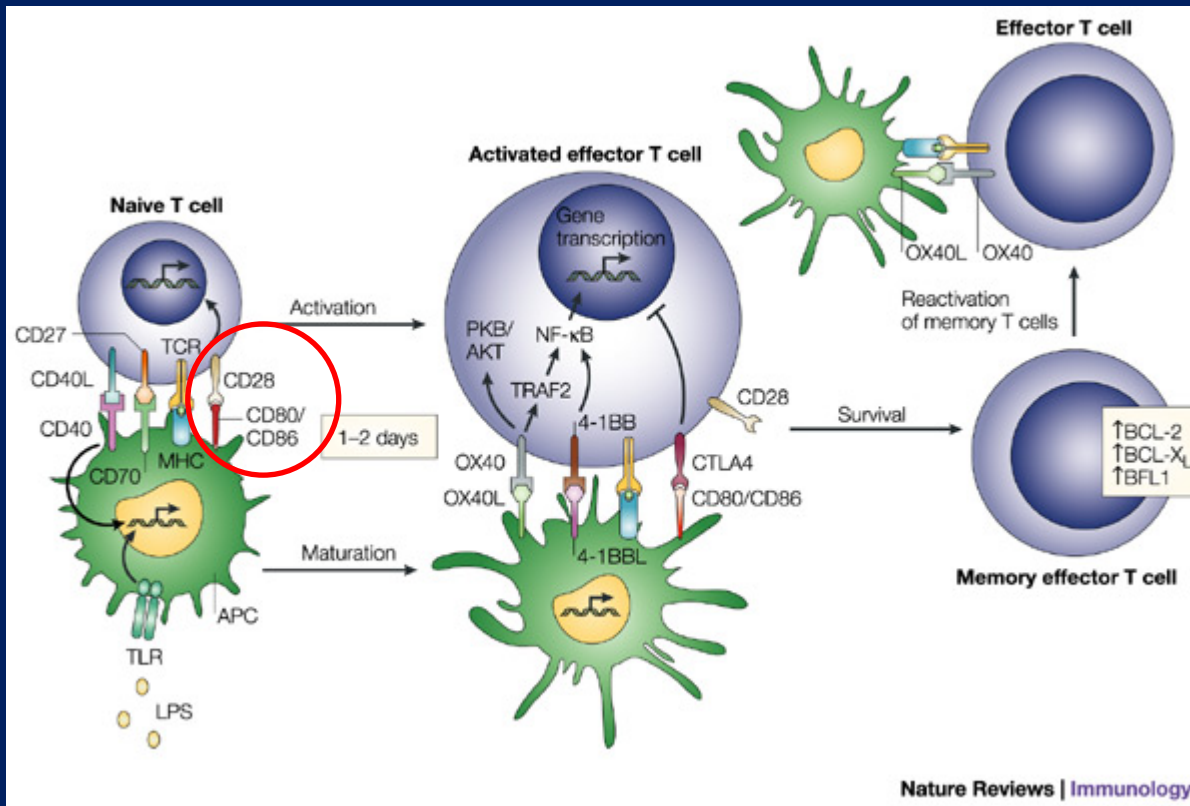
Co-stimulatory molecules

- Inflammation in sepsis is controlled primarily by the degree of macrophage activation.
- Costimulatory molecules are a class of receptors capable of macrophage activation in adaptive immunity. Ligation of macrophage expressed CD40, CD80/CD86 and ICAM by CD154, CD28/CTLA4 and LFA-1 on activated T-cell
- T cell co-stimulation is necessary for T cell proliferation, differentiation and survival. Activation of T cells without co-stimulation may lead to T cell anergy
- Orencia (abatacept) is a T cell co-stimulation modulator approved for the treatment of rheumatoid arthritis. Belatacept - Nulojix (Fc fragment IgG1 linked to extracellular domain of CTLA-4) is another novel molecule which is being tested for use in renal transplantation

Co-stimulatory molecules

Co-stimulation is required in addition to the antigen-specific signal from their antigen receptors

T cells activation is mediated: i) the interaction of T cell receptor and MHC molecule on APC; ii) the interaction of co-stimulatory molecule on APC and T cells.



Co-stimulatory molecules and their use in immunotherapy of sepsis - CD28

Nolan A et al: PLoS One 2009

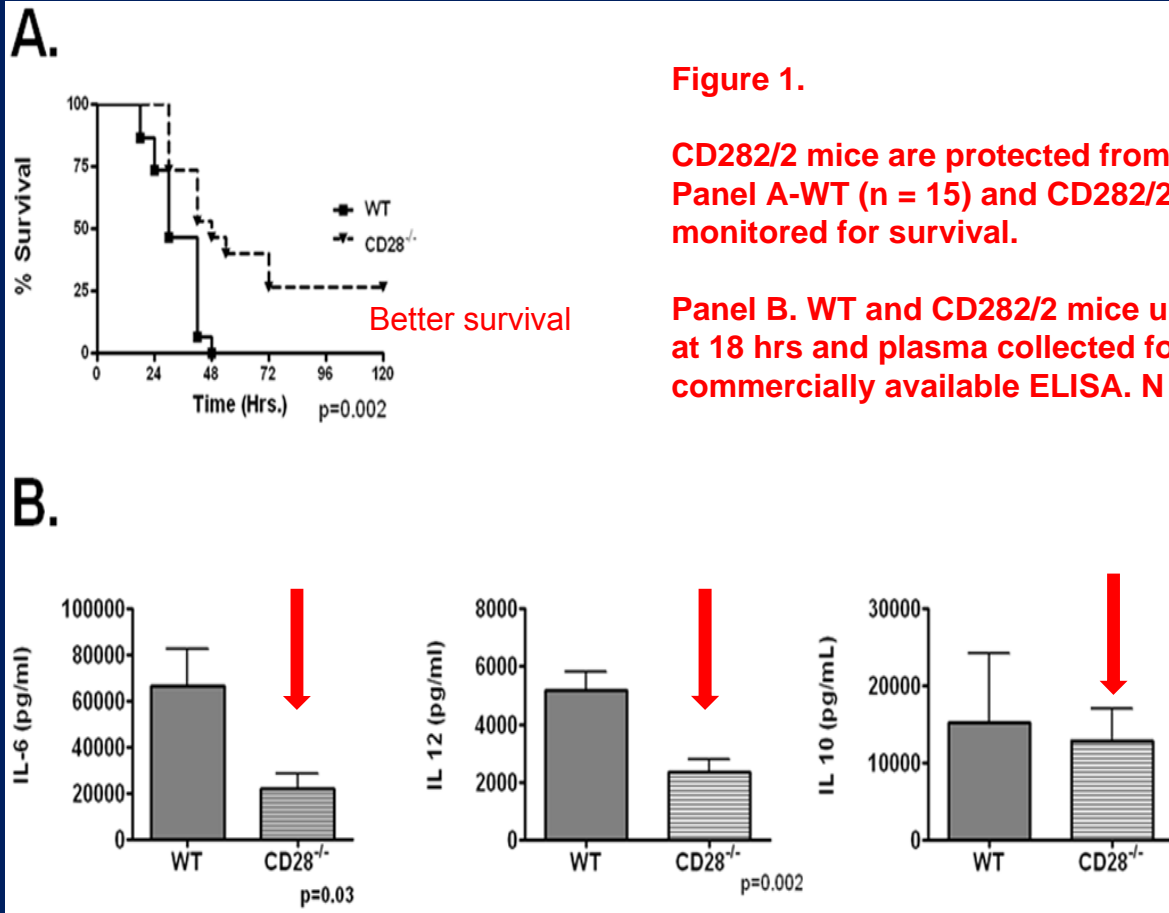
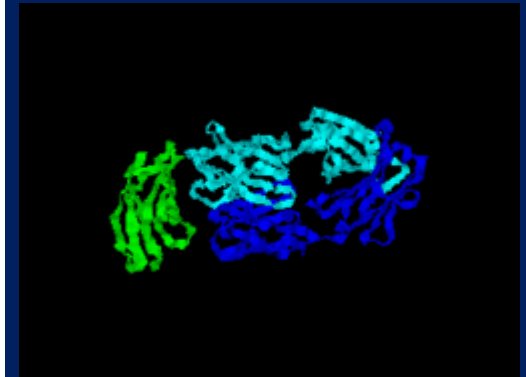


Figure 1.

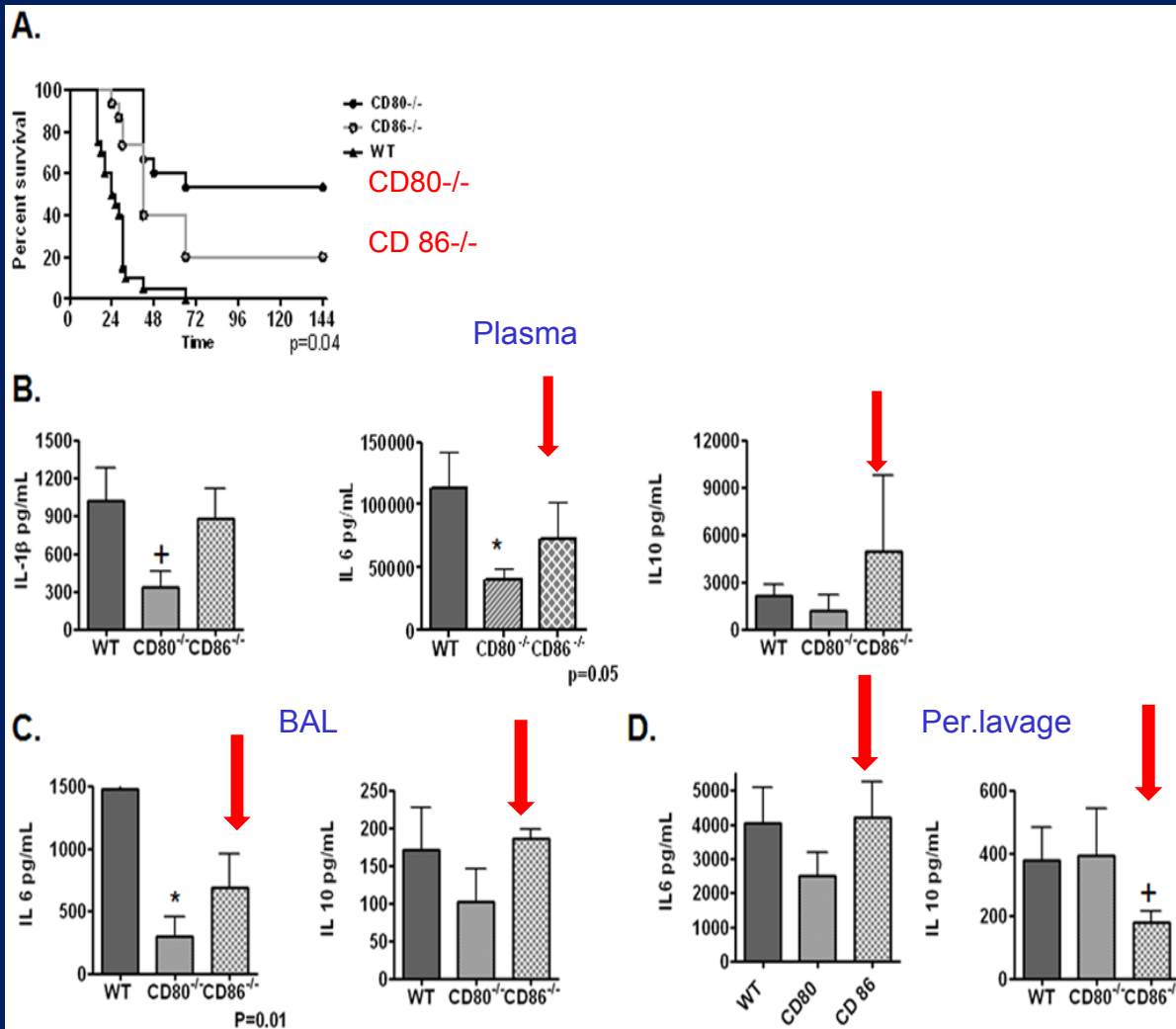
CD282/2 mice are protected from lethality of polymicrobial sepsis. Panel A-WT (n = 15) and CD282/2 (N = 15) underwent CLP and were monitored for survival.

Panel B. WT and CD282/2 mice underwent CLP and were sacrificed at 18 hrs and plasma collected for cytokine analysis via commercially available ELISA. N = 5/group.



Decreased production of pro-inflammatory cytokines

Co-stimulatory molecules and their use in immunotherapy of sepsis

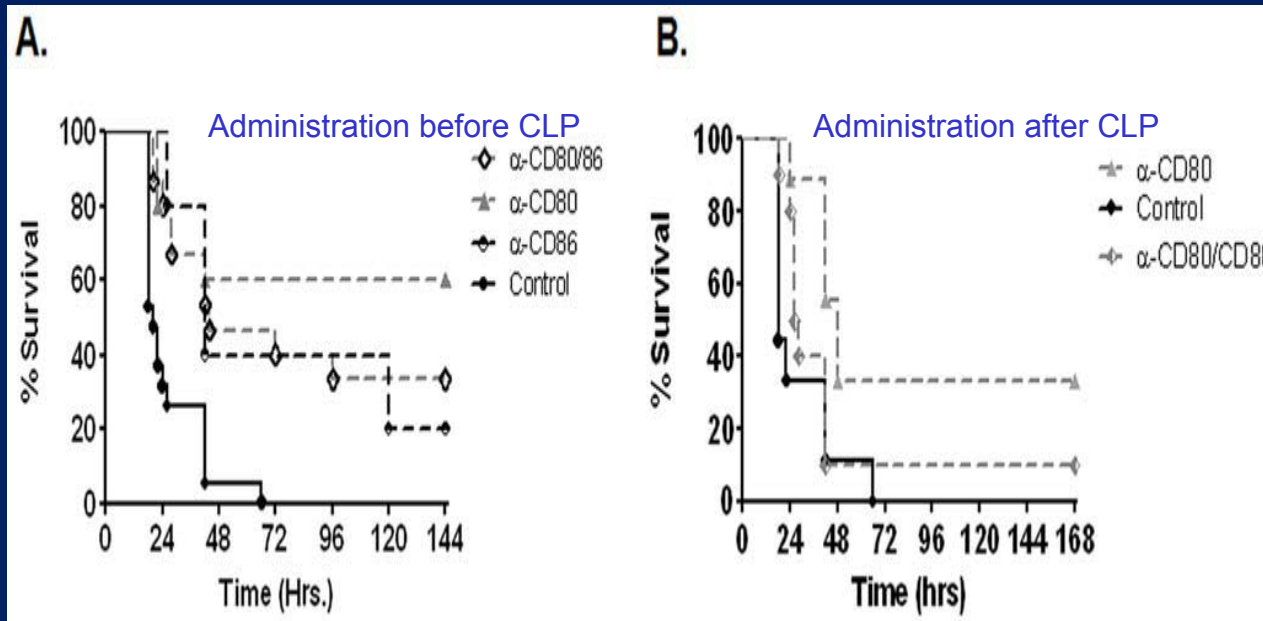


CD80 preferentially control lethality and inflammation in CLP.

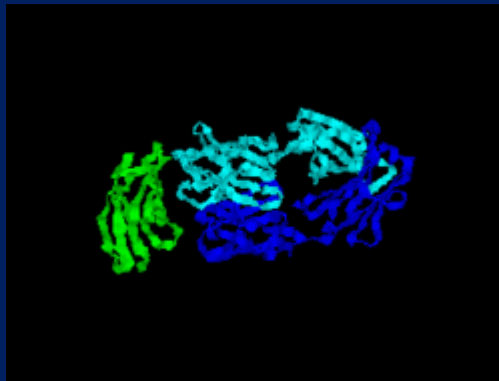
Panel A-WT (n = 20) and CD80^{-/-} (N = 15) and CD86^{-/-} (N = 15) underwent CLP and were monitored for survival. $P, 0.04$ (CD80^{-/-} vs. CD86^{-/-}), $p, 0.001$ (CD80^{-/-} vs. WT) and $p, 0.01$ (WT vs. CD86^{-/-}).

Panel B-D. WT and CD80^{-/-} and CD86^{-/-} mice underwent CLP and were sacrificed at 18 hrs and plasma (Panel B), BALF (Panel C) and PL (Panel D) were collected for cytokine analysis via commercially available ELISA. N = 8-10 mice/group. + =, 0.1, * =, 0.05.

Co-stimulatory molecules and their use in immunotherapy of sepsis



CD80 blockade preferentially improves survival after CLP.



Other experimental approaches

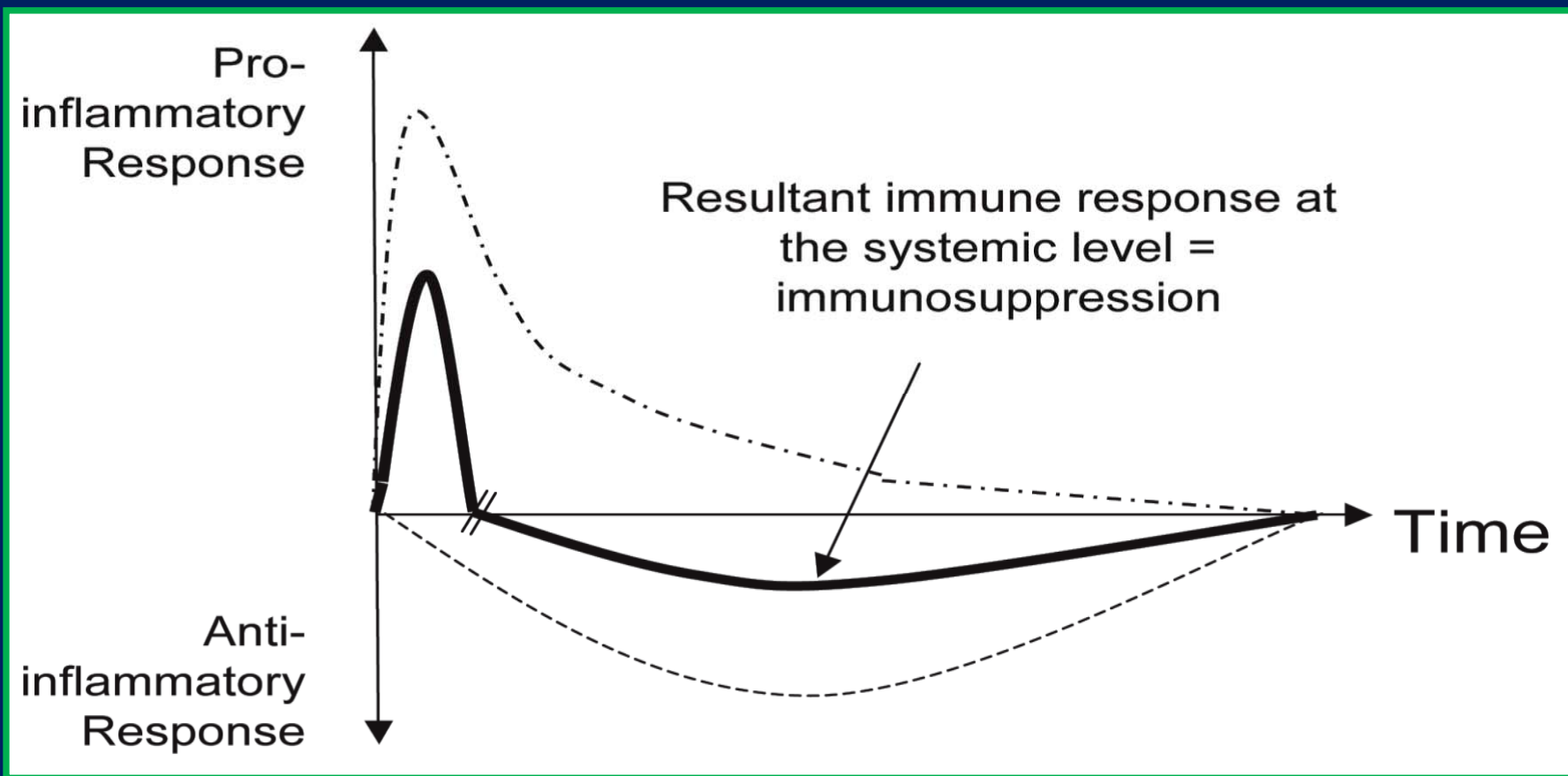
- Puneet P et al: **SphK1** regulates proinflammatory responses associated with endotoxin and polymicrobial sepsis; Science 2010
- Guignant C et al. **Programmed death/1** levels correlate with increased mortality, nosocomial infection and immune dysfunctions in septic shock patients; Crit.Care 2011
- Karulf M et al. **OX40 ligand** regulates inflammation and mortality in the innate immune response to sepsis J. Immunol. 2011

Critical notes to experimental model of sepsis

- Experimental model of sepsis is not identical to model „*in vivo*“
- We do not know the exact mechanisms responsible for immunosuppression in septic patients
- We do not have the sufficient possibility to assess the actual immune status not only in animals

Proinflammatory cytokines –
TNF, IL-6, IL-8

Immunoparalysis
Decreased expression HLA-DR/CD14
Increased apoptosis of immunocompetent cells
Decreased production antigen-specific
antibodies



Personal opinion – possible therapeutic approaches

- Early phase of sepsis – street's sepsis
- Blokation of mediators
- Anti-inflammatory therapy
- Anti-inflammatory agents were also significantly more efficacious in septic patients with higher risk of death and were harmful in those with low risk (Eichhacker et al 2002)

Personal opinion – possible therapeutic approaches

- Late phase of sepsis
- Immunostimulatory therapy (talactoferin)
- Elimination of mediators - endotoxin

Pediatric Sepsis Risk Model Biomarker [PERSEVERE])

- The 15 candidate outcome biomarkers have been selected using a genome-wide expression database of nearly 100 children with septic shock
- List of candidate outcome biomarkers by standard statistical approaches targeted at identification of genes differentially regulated between survivors and nonsurvivors of pediatric septic shock.
- The final 15 candidate outcome genes were selected from the intersection of the Venn diagram based on biological plausibility and the ability to reliably measure the genes' protein product in the serum
- Will provide unprecedented decision and stratification tool for the care of individual children with septic shock and for the conduct of interventional clinical trials

Pediatric Sepsis Biomarker Risk Model [PERSEVERE]

Table 1. Candidate biomarker gene list for derivation of Pediatric Sepsis Biomarker Risk Model (PERSEVERE).

Gene symbol	Description
<i>CCL3</i>	C-C chemokine ligand 3 (MIP-1 α)
<i>CCL4</i>	C-C chemokine ligand 4 (MIP-1 β)
<i>ELA2</i>	Neutrophil elastase 1
<i>FGL2</i>	Fibrinogen-like 2; acute phase protein similar to fibrinogen
<i>GZMB</i>	Granzyme B
<i>HSPA1B</i>	Heat-shock protein 70 kDa 1B
<i>IL1A</i>	IL-1 α
<i>IL8</i>	IL-8
<i>LCN2</i>	Lipocalin 2 (NGAL)
<i>LTF</i>	Lactotransferrin
<i>MMP8</i>	Matrix metalloproteinase 8
<i>ORM1</i>	Orosomucoid 1; acute-phase protein with unknown function
<i>RETN</i>	Resistin
<i>SULF2</i>	Sulfatase 2; extracellular modulator of heparan sulfate proteoglycans
<i>THBS</i>	Thrombospondin 1

Summary

- **We need the better diagnostics of immune status in septic patients to reach the tailored therapy**
- **Genomic and transcriptomic medicine is very promissfull tool**

Thank you for your attention !

感謝您的關注！

