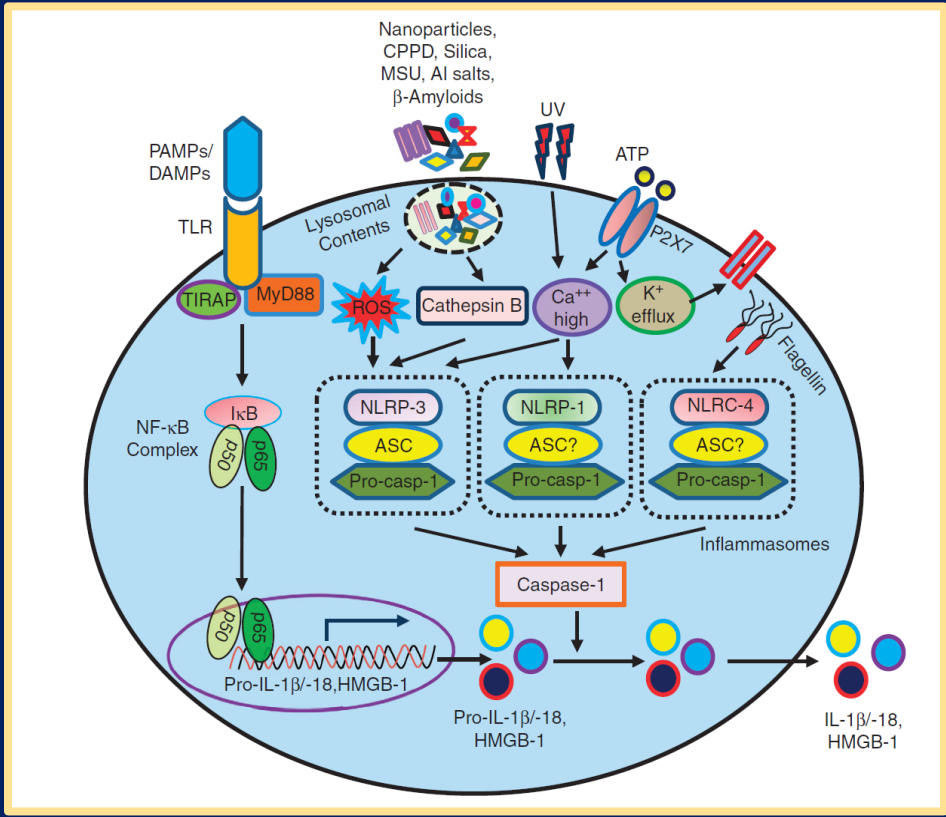
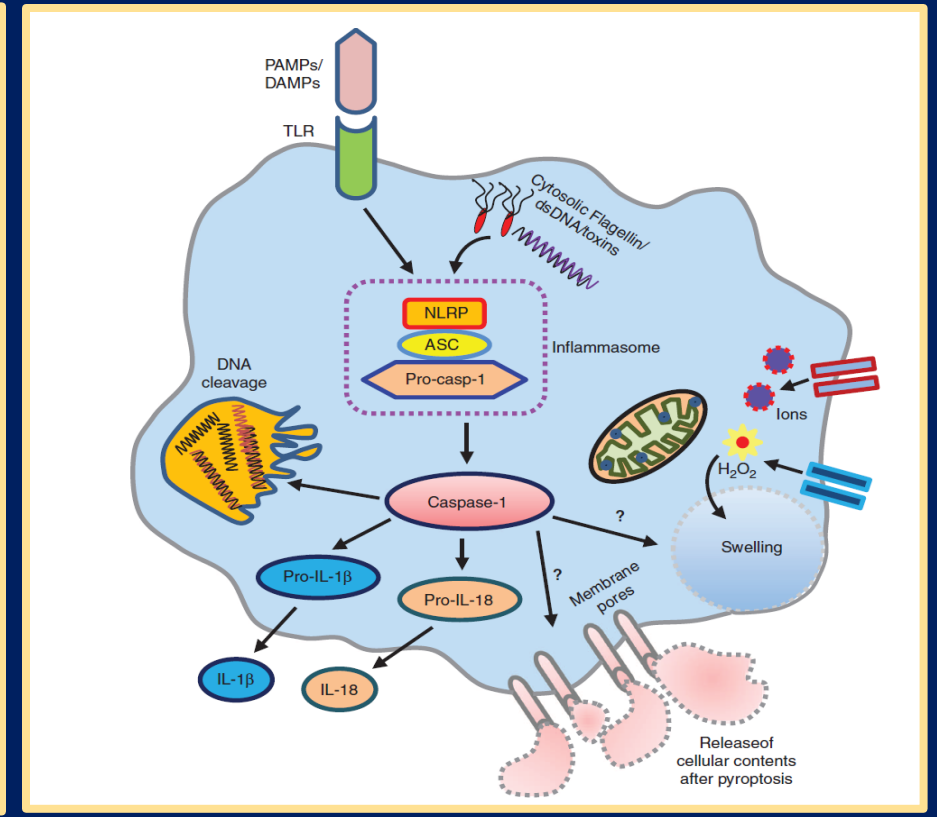
Od PAMPs a DAMPs k biomarkerům sepse

Antonín Jabor, Janka Franeková
IKEM Praha a 3. LF UK Praha

Imunopatogeneze sepse





OPEN

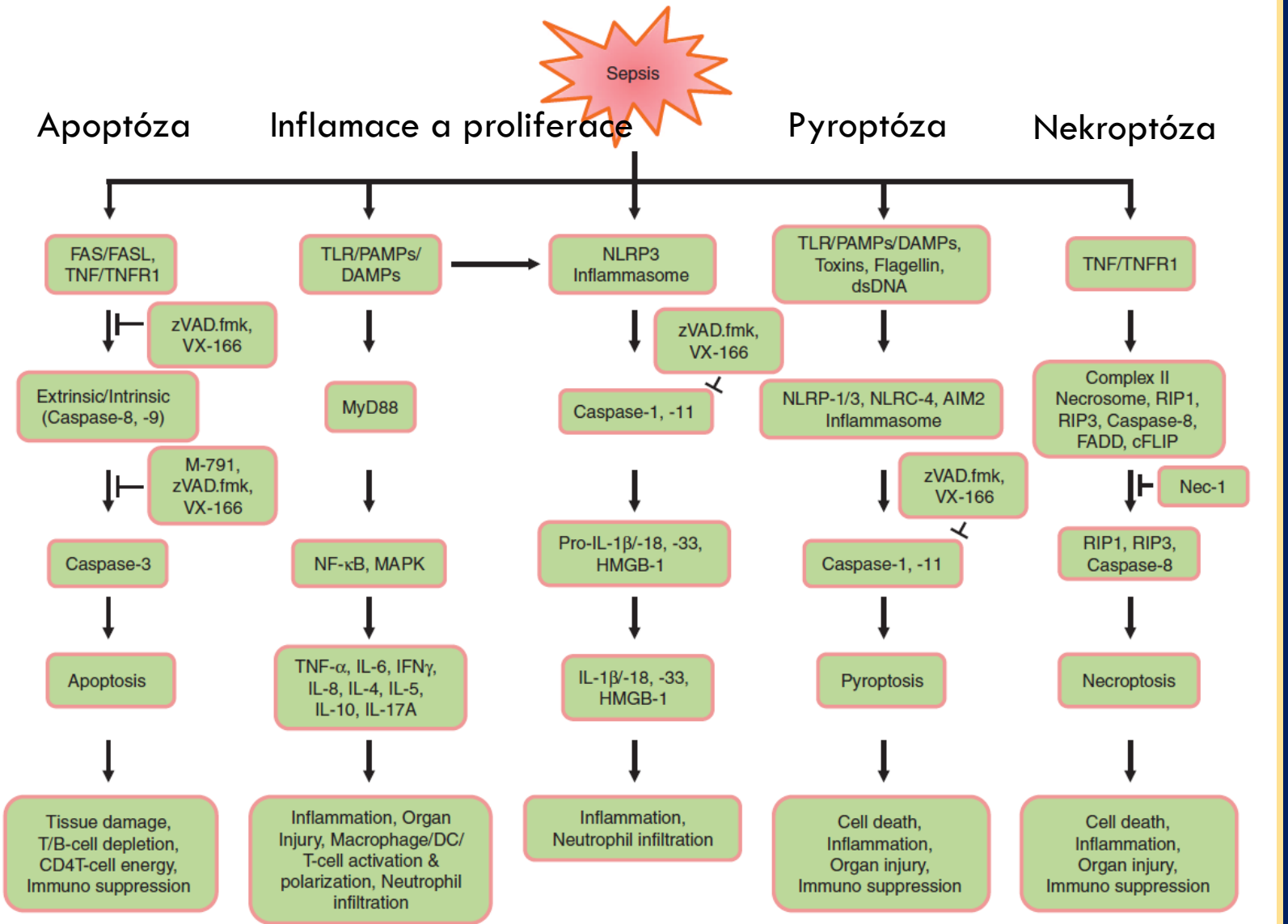
Citation: Cell Death and Disease (2014) 5, e1526; doi:10.1038/cddis.2014.488

www.nature.com/cddis

Review

Revisiting caspases in sepsis

M Aziz[1,2], A Jacob[1,2] and P Wang*[,1,2]



OPEN

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Review

Revisiting caspases in sepsis

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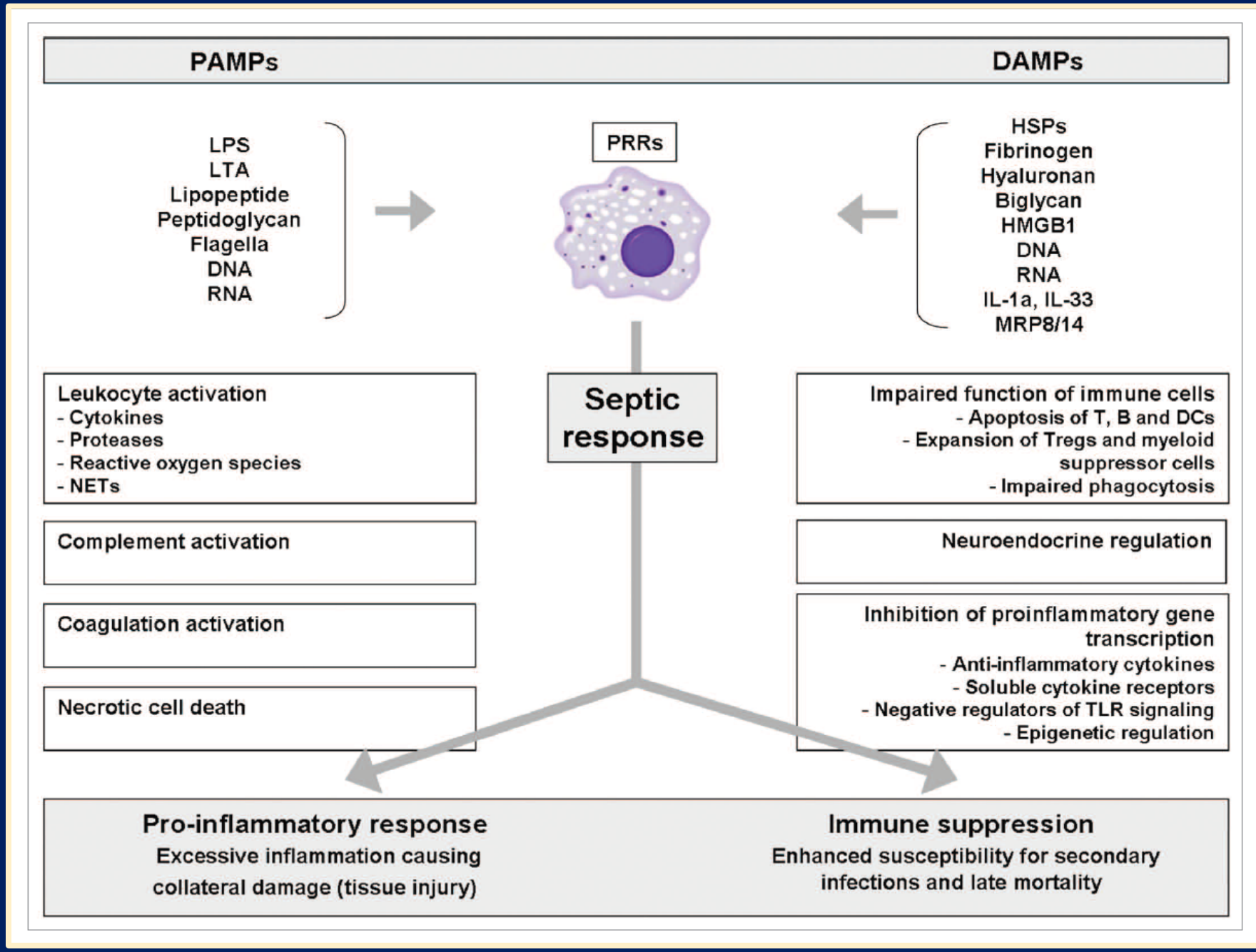
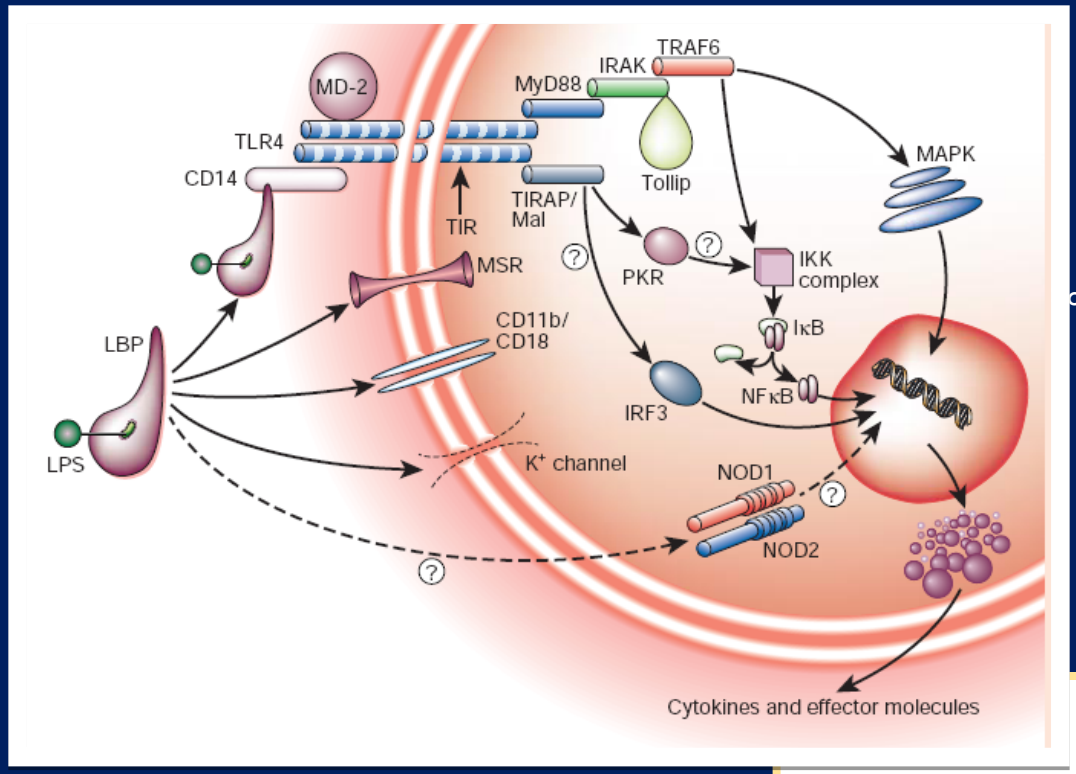
PAMPs a DAMPs



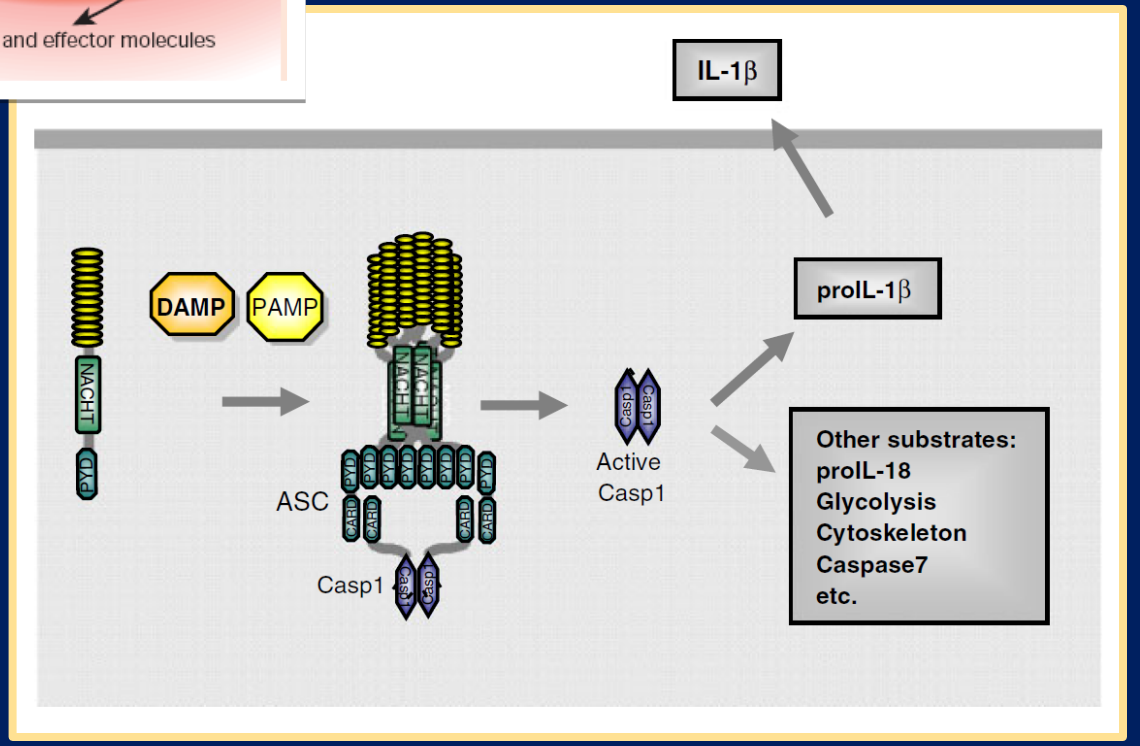
Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence. 2014 Jan 1;5(1):36-44. doi: 10.4161/viru.25436. Epub 2013 Jun 17.

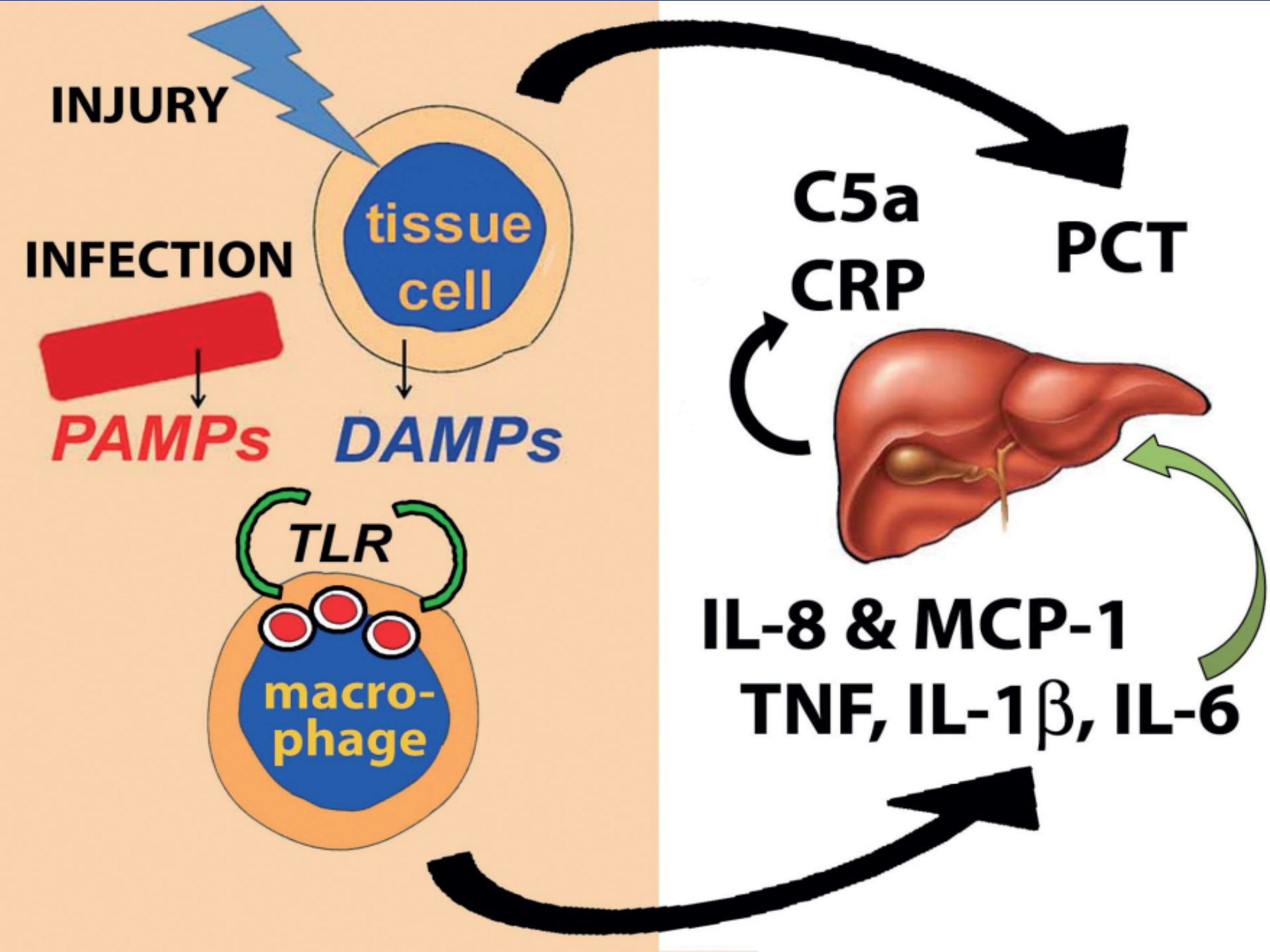
Extrinsic pathway: Toll-like receptory



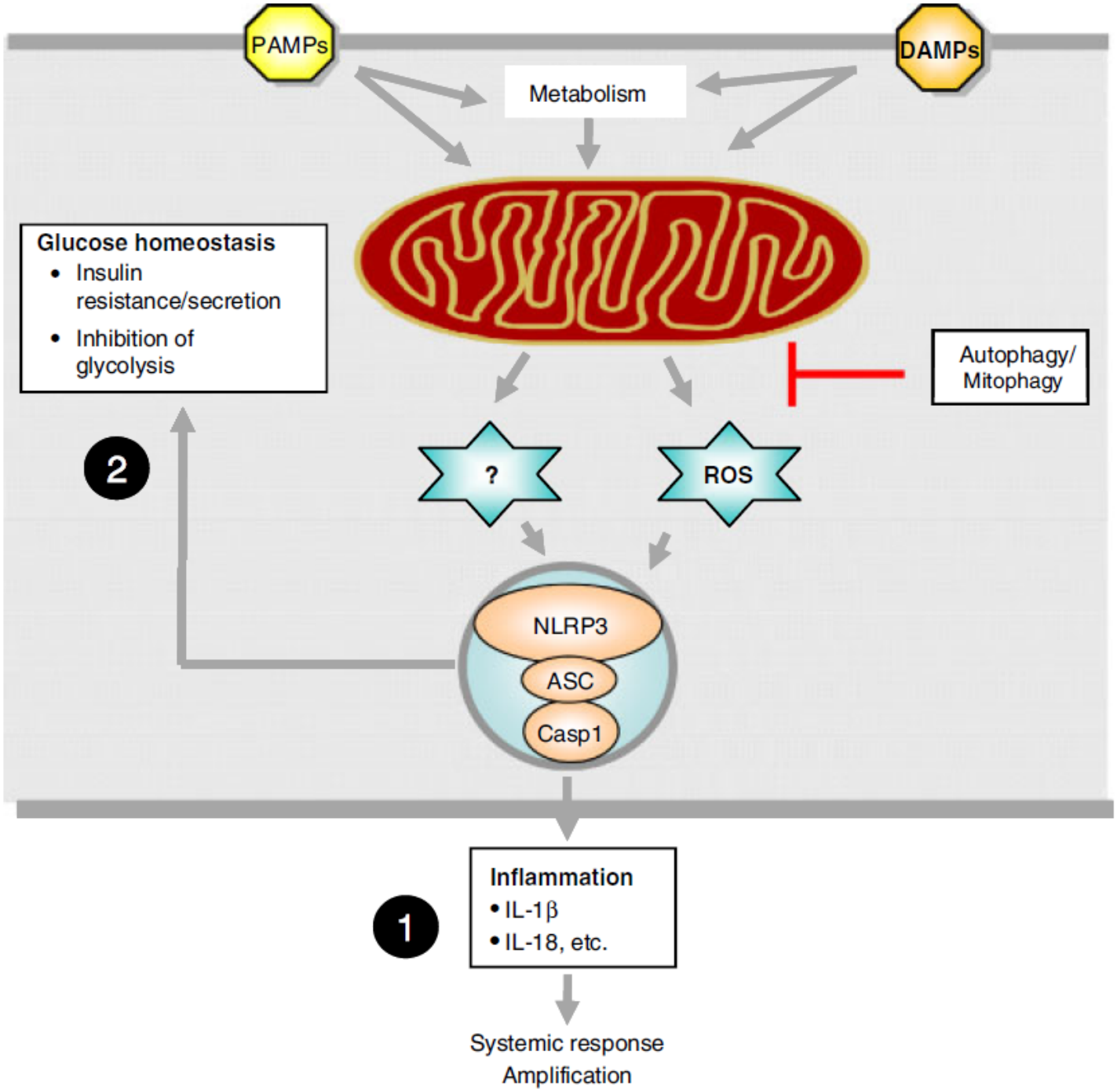
ohen J. The immunopathogenesis of sepsis. Nature. 2002 Dec 19-26;420(6917):885-91.

Intrinsic pathway: Nod-like receptory




INJURY
INFECTION
tissue cell
PAMPs
DAMPs
TLR
macro-phage
C5a
CRP
PCT
IL-8 & MCP-1
TNF, IL-1β, IL-6

Centrální role mitochondrií v patogenezi sepse?


PAMPs
DAMPs
Metabolism
Glucose homeostasis
• Insulin resistance/secretion
• Inhibition of glycolysis
Autophagy/ Mitophagy
2
?
ROS
NLRP3
ASC
Casp1
1
Inflammation
• IL-1β
• IL-18, etc.
Systemic response
Amplification

Terapie

Inátní imunita

- **zasahovat?**
  - **komplikované vztahy**
  - **unikátní jedinci**
  - **unikátní kombinace patogen + hostitel**
  - **akce + reakce**
  - **proteáza + antiproteáza**
  - **poškození + úklid**
    - apoptóza
    - pyroptóza
    - nekroptóza
    - zánětlivá reakce
    - proliferace

CARING FOR THE CRITICALLY ILL PATIENT

Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis

The ACCESS Randomized Trial

Steven M. Opal, MD
Pierre-Francois Laterre, MD
Bruno Francois, MD
Steven P. LaRosa, MD
Derek C. Angus, MD, MPH
Jean-Paul Mira, MD, PhD
Xavier Wittebole, MD
Thierry Dugernier, MD
Dominique Perrotin, MD
Mark Tidswell, MD
Luis Jauregui, MD
Kenneth Krell, MD
Jan Pachl, MD
Takeshi Takahashi, MD
Claus Peckelsen, MD
Edward Cordasco, DO
Chia-Sheng Chang, MD
Sandra Oeyen, MD
Naoki Aikawa, MD, PhD
Tatsuya Maruyama, MD, PhD
Roland Schein, MD
Andre C. Kalil, MD, MPH
Marc Van Nuffelen, MD
Melvyn Lynn, PhD
Daniel P. Rossignol, PhD
Jagadish Gogate, PhD
Mary B. Roberts, MS
Janice L. Wheeler, BS, RN
Jean-Louis Vincent, MD, PhD
for the ACCESS Study Group

Importance Eritoran is a synthetic lipid A antagonist that blocks lipopolysaccharide (LPS) from binding at the cell surface MD2-TLR4 receptor. LPS is a major component of the outer membrane of gram-negative bacteria and is a potent activator of the acute inflammatory response.

Objective To determine if eritoran, a TLR4 antagonist, would significantly reduce sepsis-induced mortality.

Design, Setting, and Participants We performed a randomized, double-blind, placebo-controlled, multinational phase 3 trial in 197 intensive care units. Patients were enrolled from June 2006 to September 2010 and final follow-up was completed in September 2011.

Interventions Patients with severe sepsis (n=1961) were randomized and treated within 12 hours of onset of first organ dysfunction in a 2:1 ratio with a 6-day course of either eritoran tetrasodium (105 mg total) or placebo, with n=1304 and n=657 patients, respectively.

Main Outcome Measures The primary end point was 28-day all-cause mortality. The secondary end points were all-cause mortality at 3, 6, and 12 months after beginning treatment.

Results Baseline characteristics of the 2 study groups were similar. In the modified intent-to-treat analysis (randomized patients who received at least 1 dose) there was no significant difference in the primary end point of 28-day all-cause mortality with 28.1% (366/1304) in the eritoran group vs 26.9% (177/657) in the placebo group (P=.59; hazard ratio, 1.05; 95% CI, 0.88-1.26; difference in mortality rate, −1.1; 95% CI, −5.3 to 3.1) or in the key secondary end point of 1-year all-cause mortality with 44.1% (290/657) in the eritoran group vs 43.3% (565/1304) in the placebo group, Kaplan-Meier analysis of time to death by 1 year, P=.79 (hazard ratio, 0.98; 0.85-1.13). No significant differences were observed in any of the prespecified subgroups. Adverse events, including secondary infection rates, did not differ between study groups.

Conclusions and Relevance Among patients with severe sepsis, the use of eritoran, compared with placebo, did not result in reduced 28-day mortality.

Trial Registration clinicaltrials.gov Identifier: NCT00334828

JAMA. 2013;309(11):1154-1162 www.jama.com

SEVERE SEPSIS, A SYNDROME OF acute infection complicated by organ dysfunction, is caused by a dysregulated systemic inflammatory response. Sepsis can progress to

Author Affiliations are listed at the end of this article.
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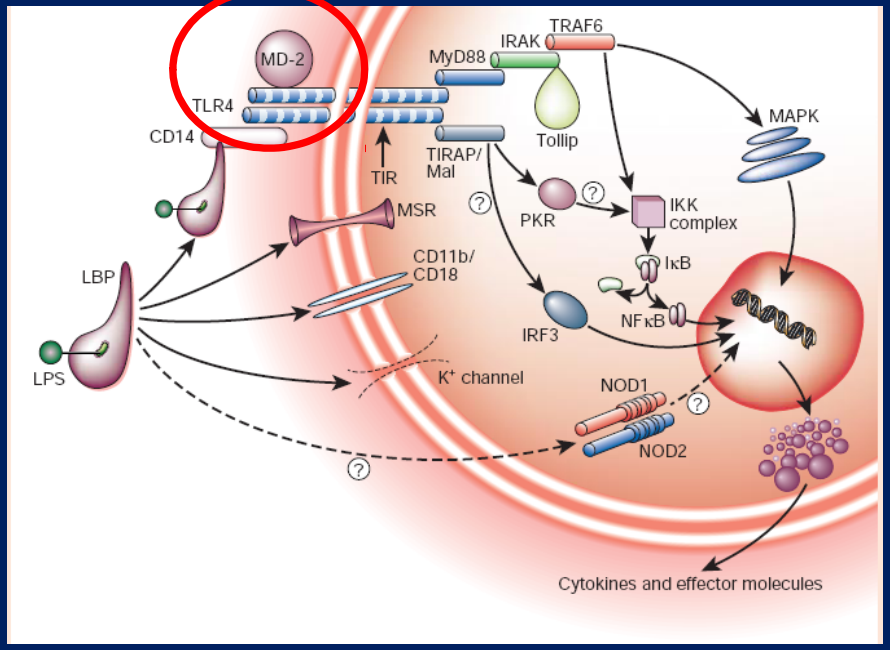
Caring for the Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, *JAMA*

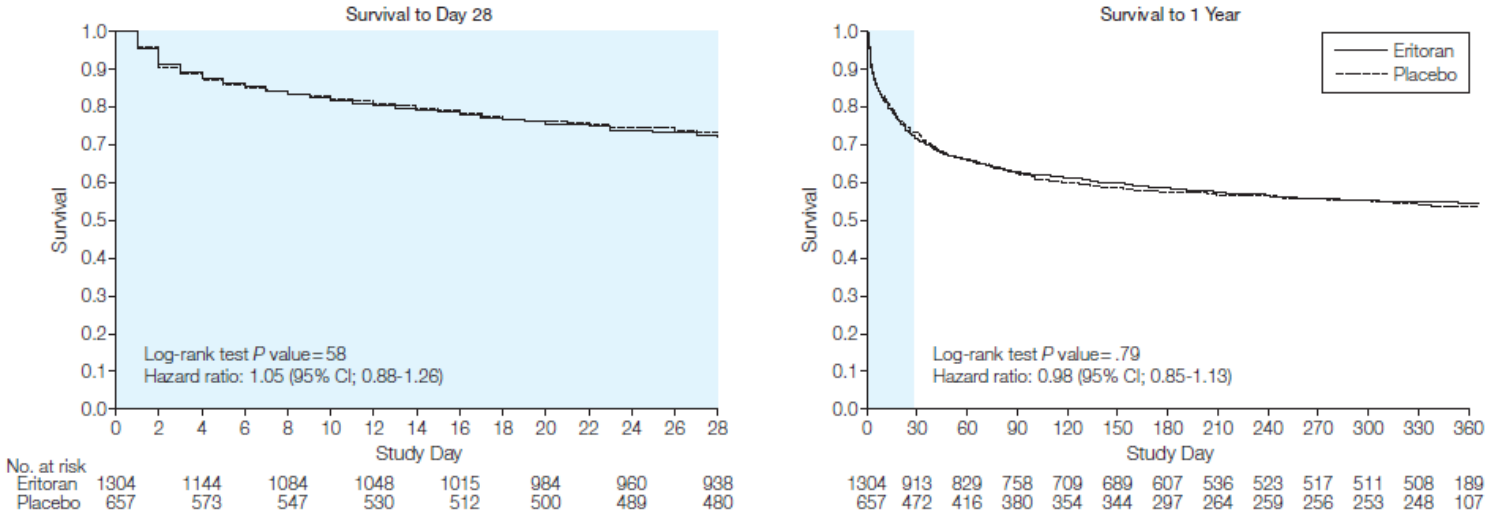


Cohen J. The immunopathogenesis of sepsis. Nature. 2002 Dec 19-26;420(6917):885-91.

„In summary, in this phase 3 trial eritoran did not significantly improve outcome for patients with severe sepsis and septic shock. Eritoran joins a long list of other experimental sepsis treatments that do not improve outcomes in clinical trials in these critically ill patients."

Opal SM ..... Vincent JL; ACCESS Study Group. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. JAMA. 2013 Mar 20;309(11):1154-62

Figure 2. Kaplan-Meier Analysis of Time to Death by (A) Day 28 and (B) 1 Year in the MITT Population Who Received Eritoran or Placebo



Patients who were alive past day 28 and at 1 year were censored at day 28 or at 1 year, respectively. Patients who did not die and were lost to follow-up within 28 days or 1 year were censored at their last contact date. Plot areas tinted blue indicate data for days 0 through 28.

Eritoran: bez vlivu na 28denní i roční mortalitu.

„In summary, in this phase 3 trial eritoran did not significantly improve outcome for patients with severe sepsis and septic shock. Eritoran joins a long list of other experimental sepsis treatments that do not improve outcomes in clinical trials in these critically ill patients."

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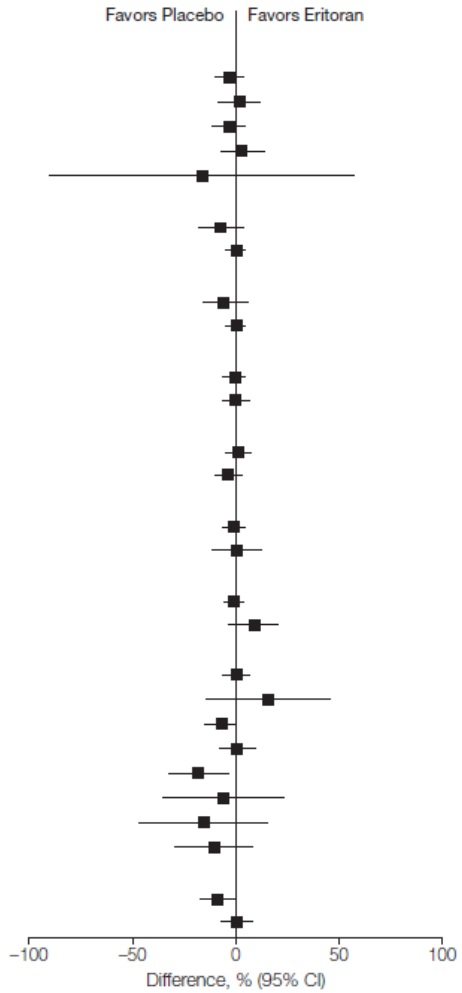
Figure 3. Mortality (28-Day) in Subpopulations in the Modified Intention to Treat Population Who Received Eritoran or Placebo

	No. of Patients		Mortality, No. (%)		Difference in % Mortality (95% CI)	*P* Value
	Placebo	Eritoran	Placebo	Eritoran		
APACHE II group						
<21	0	5	0 (0.0)	0 (0.0)		
≥21-≤24	209	441	40 (19.1)	99 (22.4)	−3.3 (−10.1 to 3.4)	.34
>24-≤26	122	219	36 (29.5)	62 (28.4)	1.2 (−8.8 to 11.2)	.81
>26-≤31	194	371	50 (25.8)	108 (29.1)	−3.3 (−11.1 to 4.5)	.40
>31-≤37	128	265	49 (38.3)	95 (35.8)	2.4 (−7.7 to 12.6)	.64
>37	4	3	2 (50.0)	2 (66.7)	−16.7 (−90.7 to 57.4)	.66
SOFA scores-cardiovascular						
0-1	98	203	20 (20.4)	56 (27.6)	−7.2 (−17.7 to 3.3)	.18
2-4	557	1101	156 (28.0)	310 (28.2)	−0.1 (−4.7 to 4.4)	.95
SOFA scores-respiratory						
0-1	94	174	20 (21.3)	46 (26.4)	−5.2 (−16.0 to 5.6)	.35
2-4	549	1098	154 (28.1)	307 (28.0)	0.1 (−4.5 to 4.7)	.97
SOFA scores-CNS						
0-1	362	685	88 (24.3)	172 (25.1)	−0.8 (−6.3 to 4.7)	.78
2-4	278	588	83 (29.9)	177 (30.1)	−0.2 (−6.8 to 6.3)	.94
SOFA scores-renal						
0-1	288	617	62 (21.5)	127 (20.6)	0.9 (−4.7 to 6.6)	.74
2-4	360	669	111 (30.8)	233 (34.8)	−4.0 (−10.0 to 2.0)	.20
SOFA scores-coagulation						
0-1	443	839	105 (23.7)	208 (24.8)	−1.1 (−6.0 to 3.9)	.67
2-4	95	191	35 (36.8)	70 (36.6)	0.2 (−11.7 to 12.1)	.97
SOFA scores-hepatic						
0-1	556	1083	144 (25.9)	298 (27.5)	−1.6 (−6.2 to 2.9)	.49
2-4	83	172	28 (33.7)	44 (25.6)	8.2 (−3.6 to 19.9)	.18
Infection site						
Lung	329	671	97 (29.5)	200 (29.8)	−0.3 (−6.4 to 5.7)	.92
Primary bloodstream	12	38	5 (41.7)	10 (26.3)	15.4 (−14.4 to 45.1)	.31
Genitourinary	149	268	25 (16.8)	64 (23.9)	−7.1 (−15.3 to 1.1)	.09
Abdomen	159	305	47 (29.6)	89 (29.2)	0.4 (−8.3 to 9.1)	.93
Skin/soft tissue	55	122	9 (16.4)	43 (35.2)	−18.9 (−33.4 to −4.4)	.01
CNS	14	31	4 (28.6)	11 (35.5)	−6.9 (−36.7 to 22.8)	.65
Catheter-related bacteremia	11	35	2 (18.2)	12 (34.3)	−16.1 (−47.3 to 15.1)	.31
Other	31	82	7 (22.6)	28 (34.1)	−11.6 (−30.7 to 7.5)	.24
Infection type						
Gram positive	182	349	45 (24.7)	118 (33.8)	−9.1 (−17.4 to −0.8)	.03
Gram negative	215	421	48 (22.3)	92 (21.9)	0.5 (−6.3 to 7.3)	.89



CNS indicates central nervous system.

Opal SM ..... Vincent JL; ACCESS Study Group. Effect of eritoran, an antagonist of MD2-TLR4, on mortality in patients with severe sepsis: the ACCESS randomized trial. JAMA. 2013 Mar 20;309(11):1154-62

	Mechanism of action	Developmental status
Specific bacterial vaccines	Promote antimicrobial clearance of common pathogens (*Meningococcal* spp, *Pneumococcal* spp, and *Haemophilus* spp)	In standard clinical practice to decrease bloodstream infection[286,287]
Vaccine against bacterial lipopolysaccharide	Prevents endotoxin-mediated activation of the host immune response	Preclinical investigations[288]
Vaccines against streptococcal or staphylococcal superantigens	Attenuates superantigen-induced activation of CD4+ T lymphocytes and antigen-presenting cells	Preclinical investigations[289]
Recombinant gelsolin	Protein that clears extracellular actin filaments, has immunomodulatory activity, and binds bacterial toxins	Early clinical trials in pneumonia and sepsis[290]
Polymyxin B perfusion columns, other blood purification strategies	Clears bacterial lipopolysaccharide, inflammatory cytokines, HMGB1, and other inflammatory mediators	In phase 3 clinical trials[291]
Immunonutrition strategies	Can induce inhibitory phenotype of macrophages and lymphocytes	Preclinical investigations[292]
Mitochondrial-sparing drugs	Improves cellular energetics and restricts apoptosis	Preclinical investigations[27,268]
Monoclonal antibodies to bacterial virulence factors and to common multidrug-resistant pathogens	Block bacterial virulence factors from invasive pathogens and promote immune clearance of pathogens	Early clinical trials[286,293]
Anti-HMGB1 monoclonal antibody	Prevents HMGB-1 mediated inflammatory effects and endothelial barrier breakdown	Preclinical investigations[268]
Soluble TREM-like transcript-1	Blocks TREM-1 signalling on innate immune cells, restricting leucocyte activation in sepsis	Preclinical trials[294]
Protease inhibitors; monoclonal antibody to PCSK9	Block proprotein convertases that activate endogenous proteases or impair lipopolysaccharide clearance by the LDL receptor	Preclinical studies and observational studies in human beings[295,296]
New formulations of intravenous immunoglobulins	IgM concentrates that have immune-modulatory effects, bacterial clearance, and C' clearance	Early clinical trials in pneumonia and sepsis[297]
Proresolving drugs	Lipooxygenase-derived lipidated mediators that promote resolution of inflammation, tissue repair, and clearance of damaged immune cells	Preclinical investigations[298]
Low-dose corticosteroids	Anti-inflammatory effects and reduce the synthesis of acute phase proteins	Large phase 3 trials[299]
β blockers for septic shock	Cardiac rate control during haemodynamic monitoring for myocardial protection	Phase 2 testing[300]
Orally administered protease inhibitors	Prevention of pancreatic enzyme-mediated gut luminal injury, resulting in increased intestinal permeability	In phase 2 trials[301]
Thymosin α 1	Short peptide that is a T-cell adjuvant and immunostimulant for sepsis-induced immunosuppression	Phase 2 clinical trials[302]
Mesenchymal stem cell therapy	Cells traffic to sites of injury and promote anti-inflammatory effects, and tissue repair by paracrine secretion of soluble factors	Phase 2 testing in other indications;[303] pilot studies in patients with acute respiratory distress syndrome and sepsis[304]

HMGB1=high mobility group box 1. TREM=triggering receptor expressed on myeloid cells. PCSK9=proprotein convertase subtilisin kexin type 9. IgM=immunoglobulin M. C'=complement.

Table 7: **Other potential new treatment options to prevent or treat sepsis**

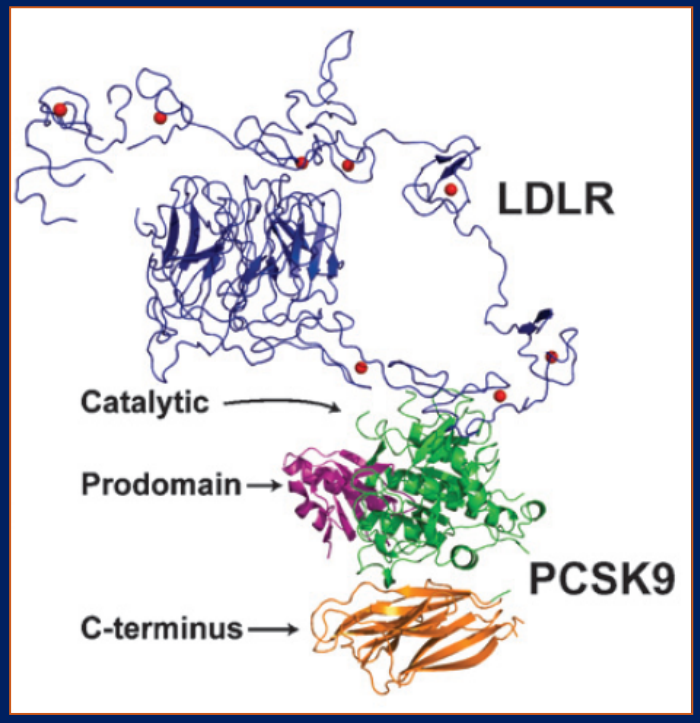
Inhibitory PCSK9

http://global-sepsis-alliance.org/

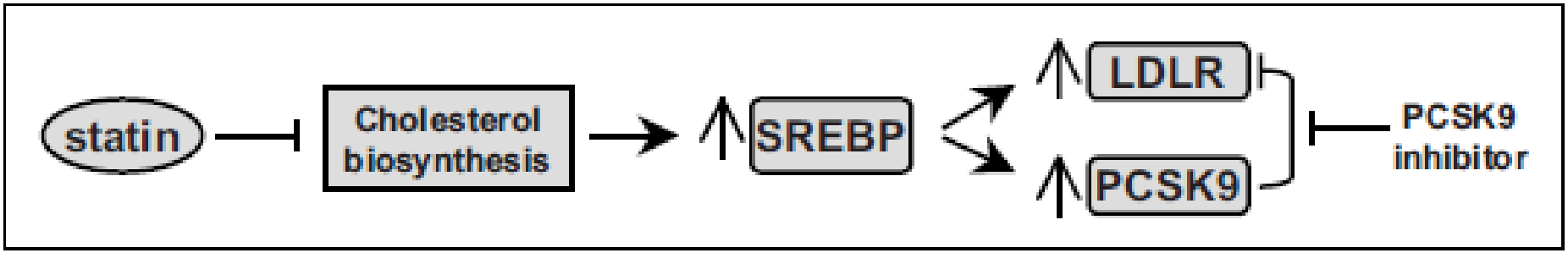
Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, Jaton K, Giulieri S, Delaloye J, Opal S, Tracey K, van der Poll T, Pelfrene E. Sepsis: a roadmap for future research. Lancet Infect Dis. 2015 May;15(5):581-614.

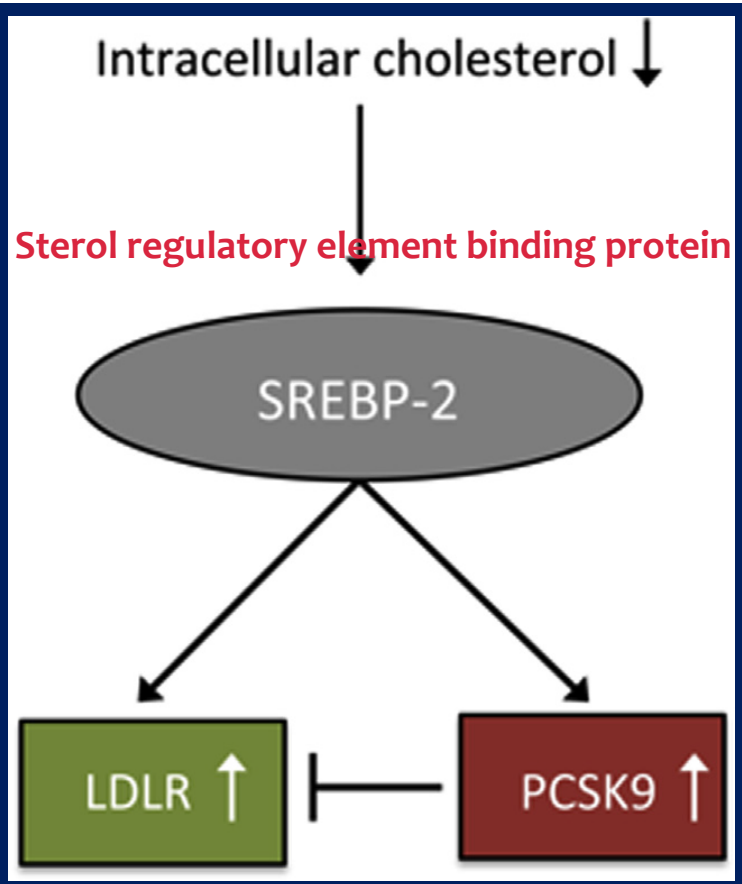
Sepse a inhibitory PCSK9?

Inhibitory PCSK9 (evolokumab, alirocumab)



Proprotein convertase subtilisin kexin 9: the third locus implicated in autosomal dominant hypercholesterolemia
Kara N. Maxwell and Jan L. Breslow





SREBP zprostředkuje transkripci LDLR a PCSK9

ale

1. PCSK9 degraduje LDLR
2. zvýšení PCSK9 může limitovat statiny indukovaný vzestup LDLR
3. PCSK9 inhibitory tak mohou maximálně zvýšit LDLR a snížit LDL cholesterol

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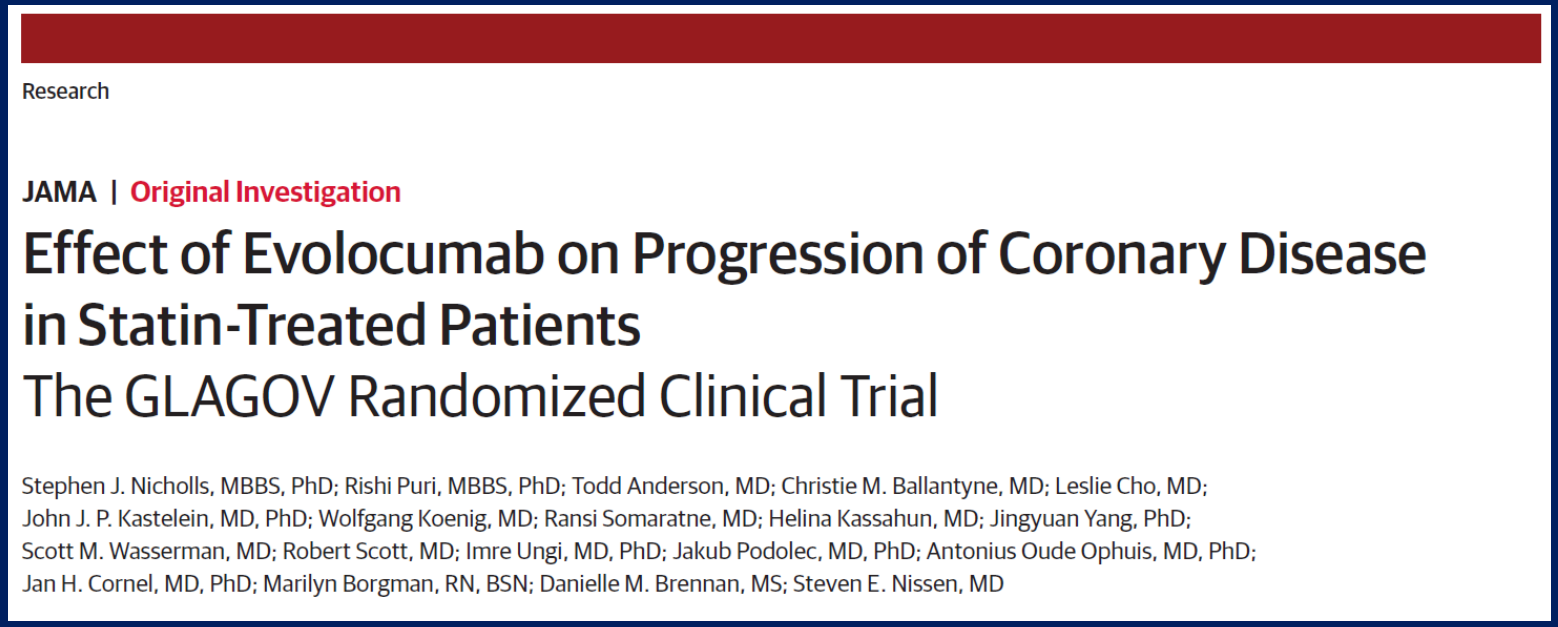
STATE-OF-THE-ART PAPER

Targeting the Proprotein Convertase Subtilisin/Kexin Type 9 for the Treatment of Dyslipidemia and Atherosclerosis

Daniel Urban, MD, Janine Pöss, MD, Michael Böhm, MD, Ulrich Laufs, MD
Homburg/Saar, Germany

Mechanism of Action	Agent	Company/Sponsor	Phase
Monoclonal antibodies	SAR236553/REGN727	Sanofi/Regeneron	3
	AMG 145	Amgen	3
	RN316	Pfizer	2
	RG7652	Roche/Genentech	2
	LGT-209	Novartis	2
	1D05-IgG2	Merck	Pre-clinical
	1B20	Merck	Pre-clinical
	J10, J16	Pfizer	Pre-clinical
	J17	Pfizer	Pre-clinical
Adnectins	BMS-962476	Bristol-Myers Squibb/Adnexus	1
Mimetic peptides	EGF-AB peptide fragment	Schering-Plough	Pre-clinical
	LDLR (H306Y) subfragment	U.S. National Institutes of Health	Pre-clinical
	LDLR DNA construct	U.S. National Institutes of Health	Pre-clinical
Small-molecule inhibitors	SX-PCK9	Serometrix	Pre-clinical
	TBD	Shifa Biomedical	Pre-clinical
Antisense oligonucleotides	ISIS 394814	Isis	Pre-clinical
	SPC4061	Santaris-Pharma	Pre-clinical
	SPC5011	Santaris-Pharma	1 (terminated)
RNA interference	ALN-PCS02	Alnylam	1

Studie GLAGOV: regrese ateromu



Research

JAMA | Original Investigation

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

The GLAGOV Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helina Kassahun, MD; Jingyuan Yang, PhD; Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD, PhD; Jakub Podolec, MD, PhD; Antonius Oude Ophuis, MD, PhD; Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Danielle M. Brennan, MS; Steven E. Nissen, MD

The GLAGOV Randomized Clinical Trial

Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound

Nicholls SJ et al.: Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients. The GLAGOV Randomized Clinical Trial.
JAMA. doi:10.1001/jama.2016.16951 Published online November 15, 2016.

Research

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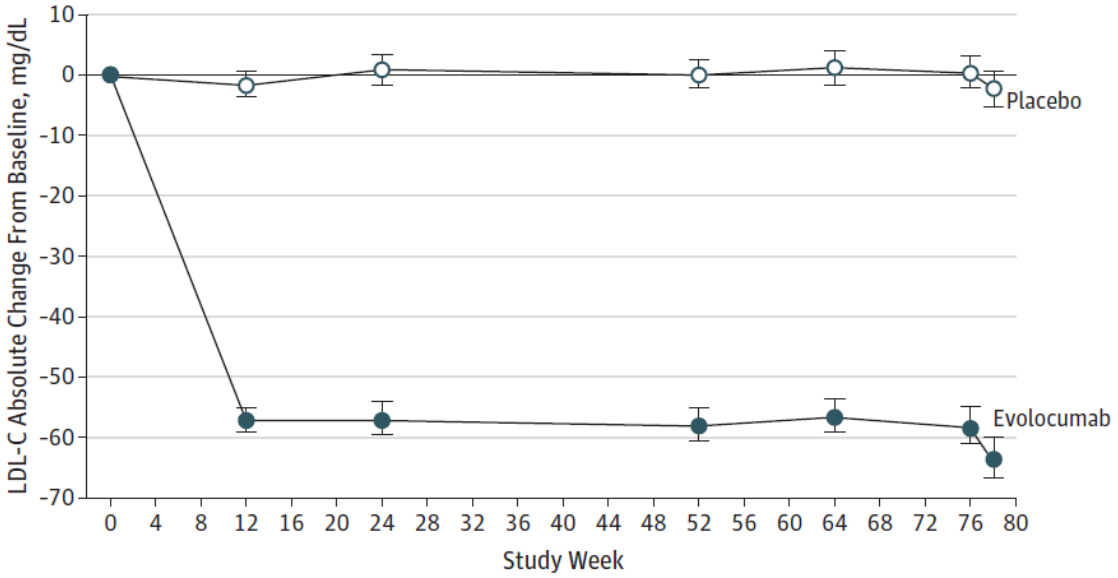
Figure 2. Mean Absolute Change in LDL-C Level



No. of patients						
Placebo	484	446	441	447	441	425 418
Evolocumab	484	456	452	444	449	426 434

Nicholls SJ et al.: Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients. The GLAGOV Randomized Clinical Trial. JAMA. doi:10.1001/jama.2016.16951 Published online November 15, 2016.

Research

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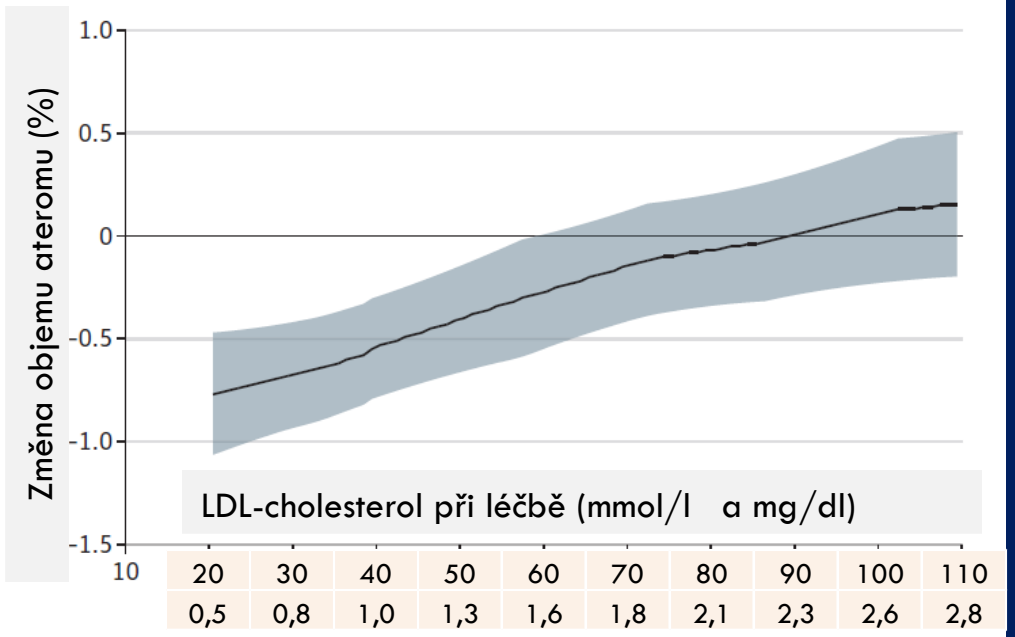
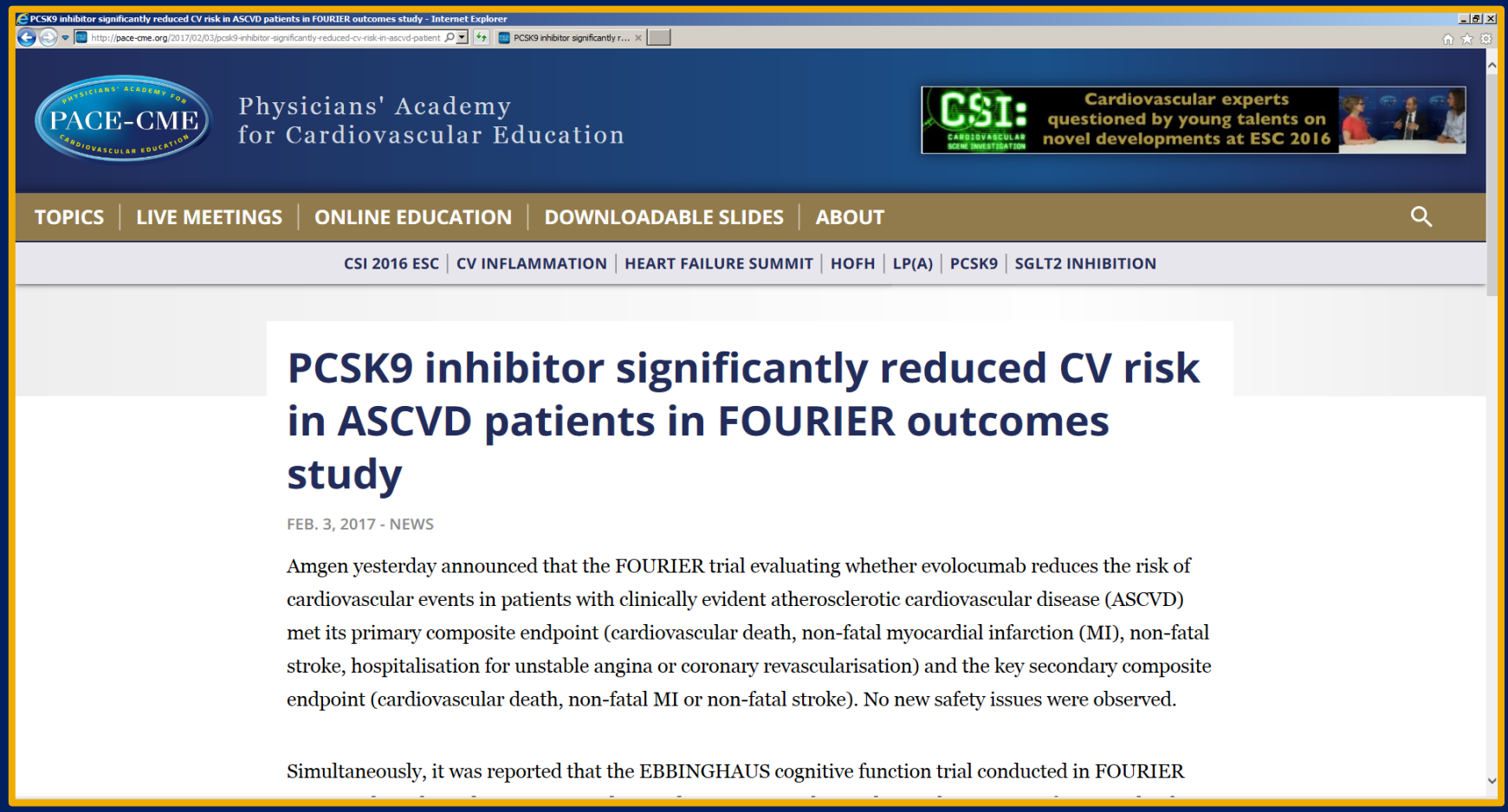
Figure 4. Post Hoc Analysis Examining the Relationship Between Achieved LDL-C Level and Change in Percent Atheroma Volume

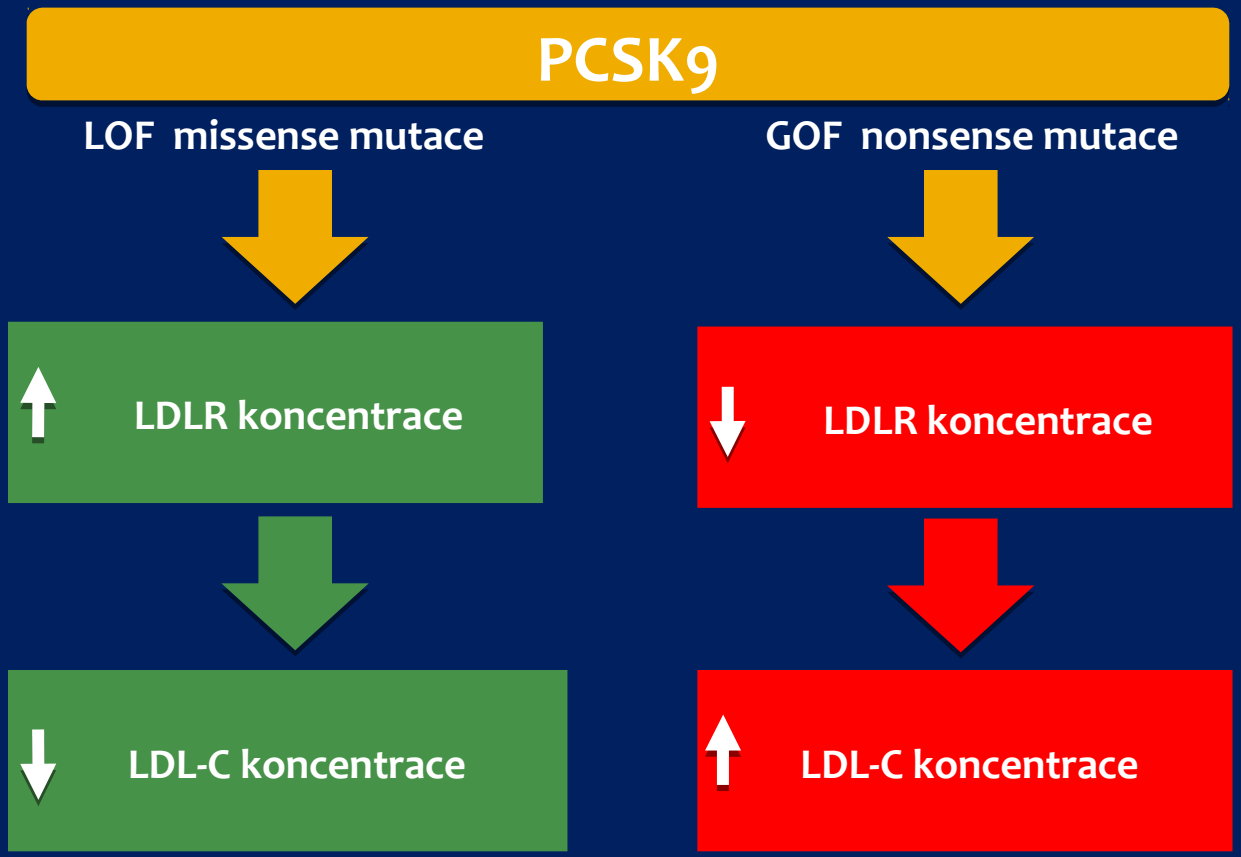


Nicholls SJ et al.: Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients. The GLAGOV Randomized Clinical Trial. JAMA. doi:10.1001/jama.2016.16951 Published online November 15, 2016.



"In the GLAGOV study, we demonstrated that evolocumab has an effect on atherosclerosis, the underlying cause of cardiovascular disease. These FOURIER results show unequivocally the connection between lowering LDL cholesterol with evolocumab and cardiovascular risk reduction, even in a population already treated with optimised statin therapy," said Sean E. Harper, M.D., executive vice president of Research and Development at Amgen.

Genetické mutace PCSK9

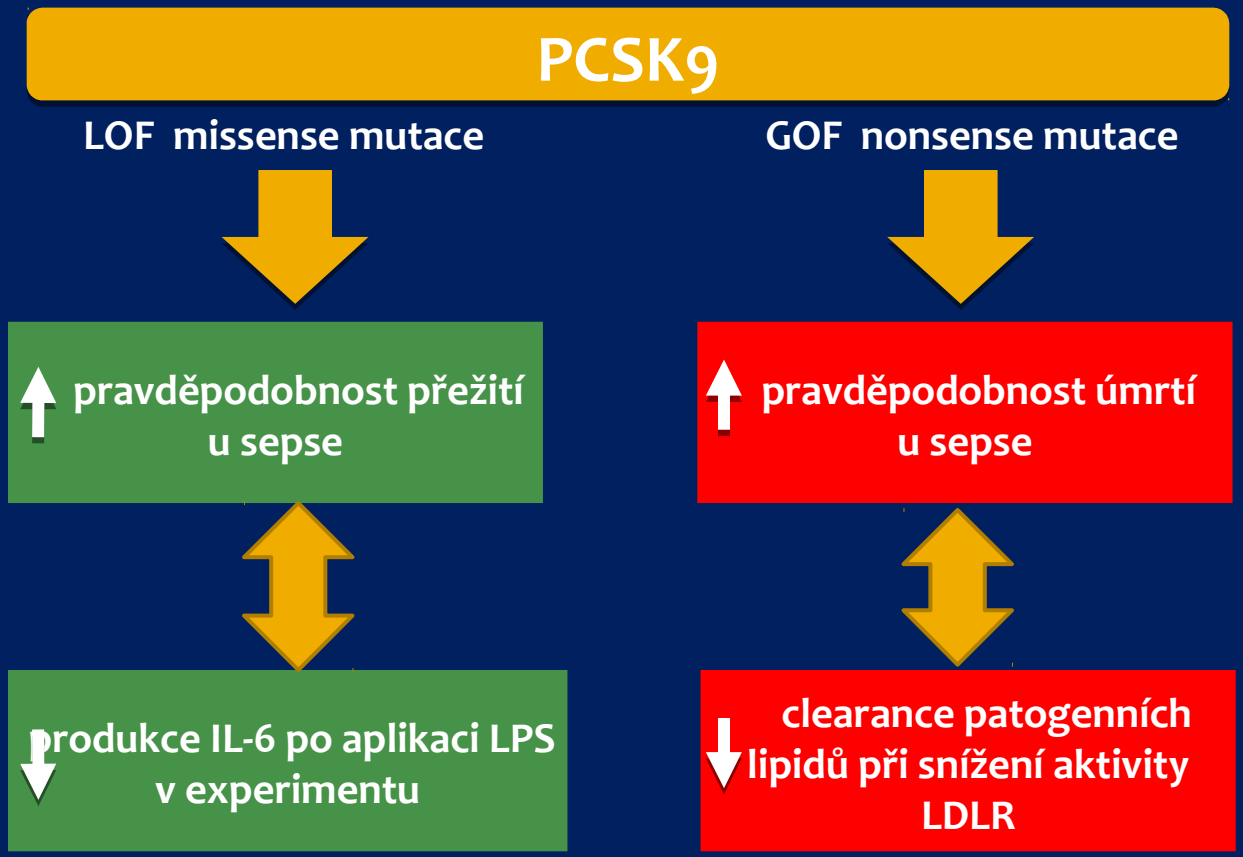


PCSK9 mutace mohou být homozygotní, nebo heterozygotní

GOF, gain of function; LOF, loss of function

Abifadel M et al. *Human Mutation*. 2009;30:520–529; 2. Horton JD et al. *J Lipid Res*. 2009;50:S172–S177

Genetické mutace PCSK9



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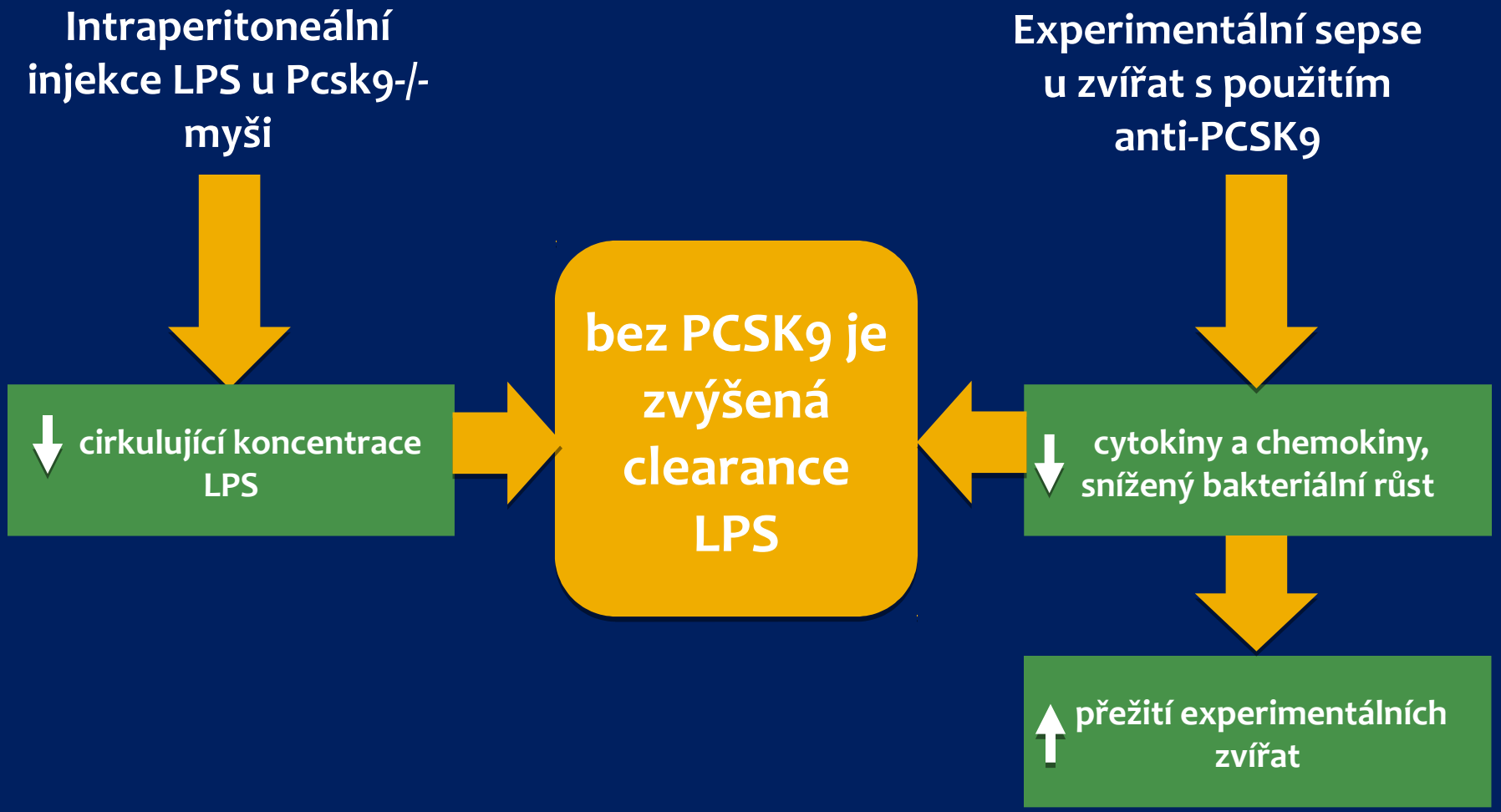
Walley, KR et al.: PCSK9 is a critical regulator of the innate immune response and septic shock outcome. Sci Transl Med, 2014; 6:258.

Animální model sepse a PCSK9



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MINI-REVIEW

PCSK9 at the crossroad of cholesterol metabolism and immune function during infections

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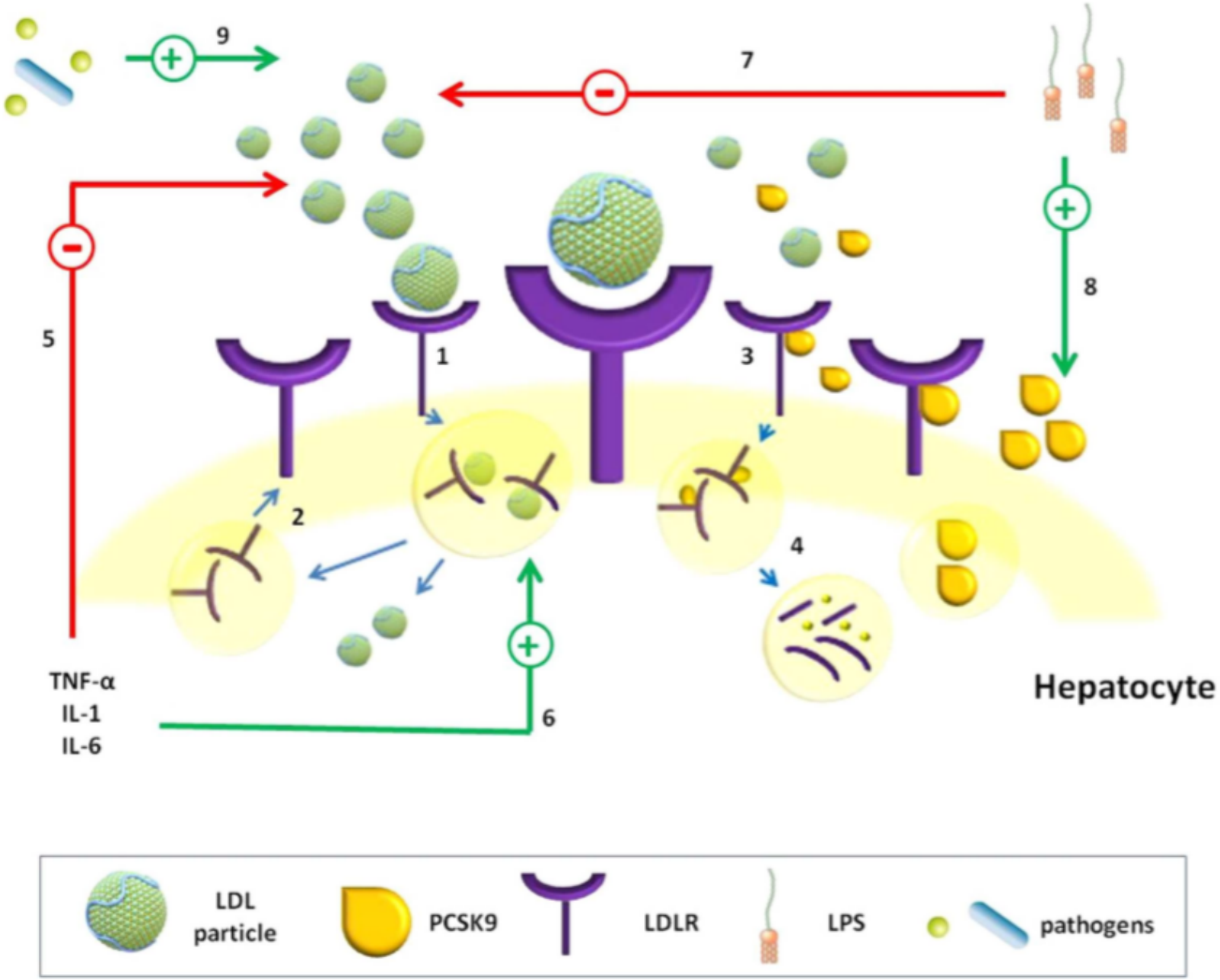
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7
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8
1
3
2
4
6
TNF-α
IL-1
IL-6
Hepatocyte
LDL particle
PCSK9
LDLR
LPS
pathogens

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EDITORIAL

PCSK9 inhibitors in sepsis: a new potential indication?

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KEYWORDS PCSK9; Alirocumab; Evolocumab; LDL receptor; Lipopolysaccharide; Sepsis

Conclusion

Available evidence shows a strong association between PCSK9 levels and septic symptoms, which can be attributed to the cross talk between PCSK9 and liver LDLR. Overexpressed PCSK9 is found to decrease LPS clearance and increase inflammatory cytokines, while PCSK9 deficiency is shown to enhance LPS clearance and ameliorate sepsis-related inflammatory responses. Lack of efficient therapeutic approaches to modify inflammation in septic patients calls for new strategies to enhance clearance of pathogenic lipids and mitigate inflammatory responses.

Závěry

Od PAMPs a DAMPs k biomarkerům sepse

- PAMPs i DAMPs mohou být biomarkery
  - DNA/RNA patogenů, Heat Shock Protein...
- PAMPs a DAMPs jsou na počátku dráhy s řadou biomarkerů
  - od CD znaků přes interleukiny a chemokiny až k prokalcitoninu a reaktantům akutní fáze
- Biomarkery orgánových funkcí
  - troponiny, bilirubin, koagulační faktory...
- a také SOFA je kombinovaný biomarker!
- monitorování terapie zasahující vhodné dráhy?

Děkuji za pozornost