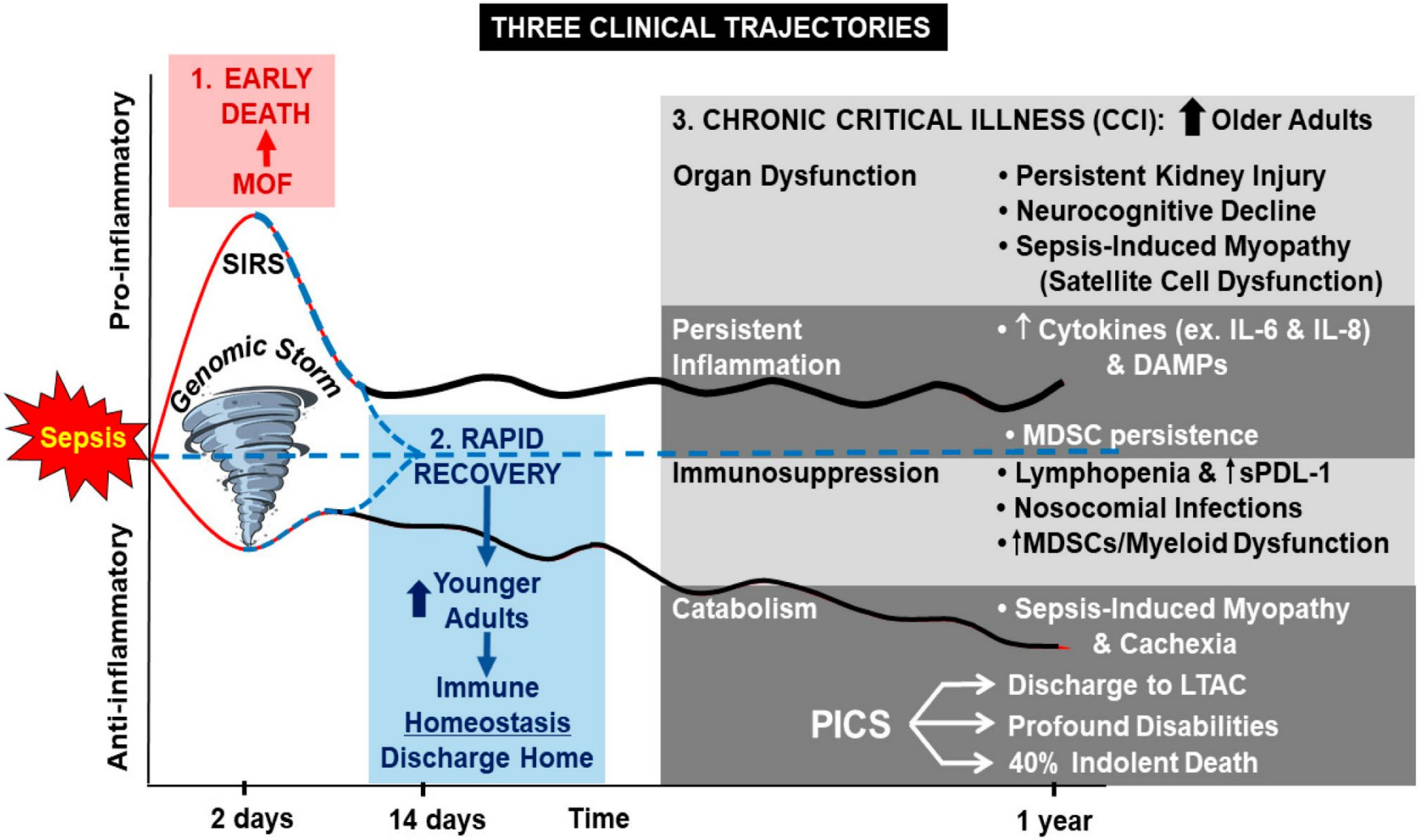
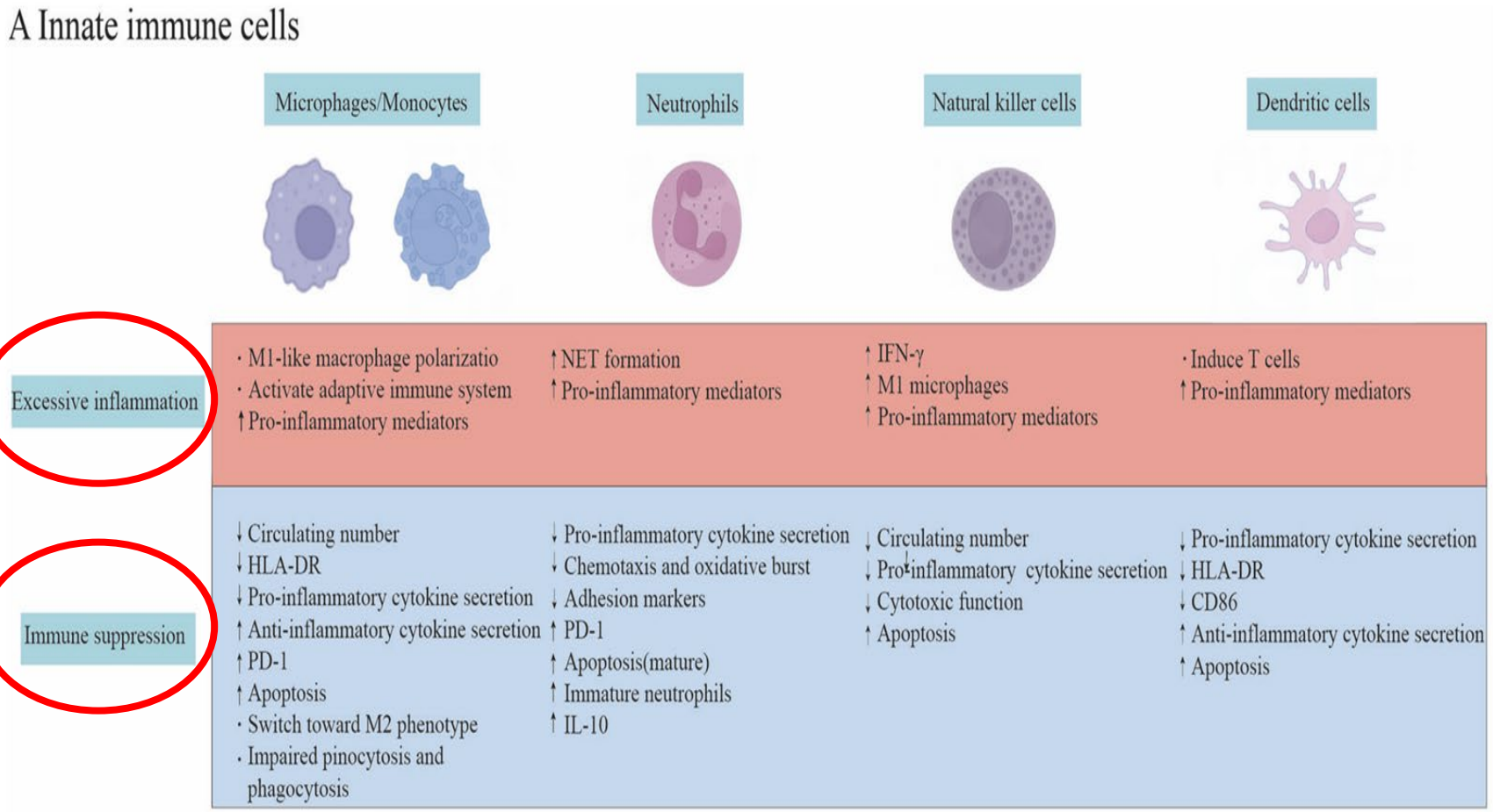
IMUNITNÍ ODPOVĚĎ U SEPSE

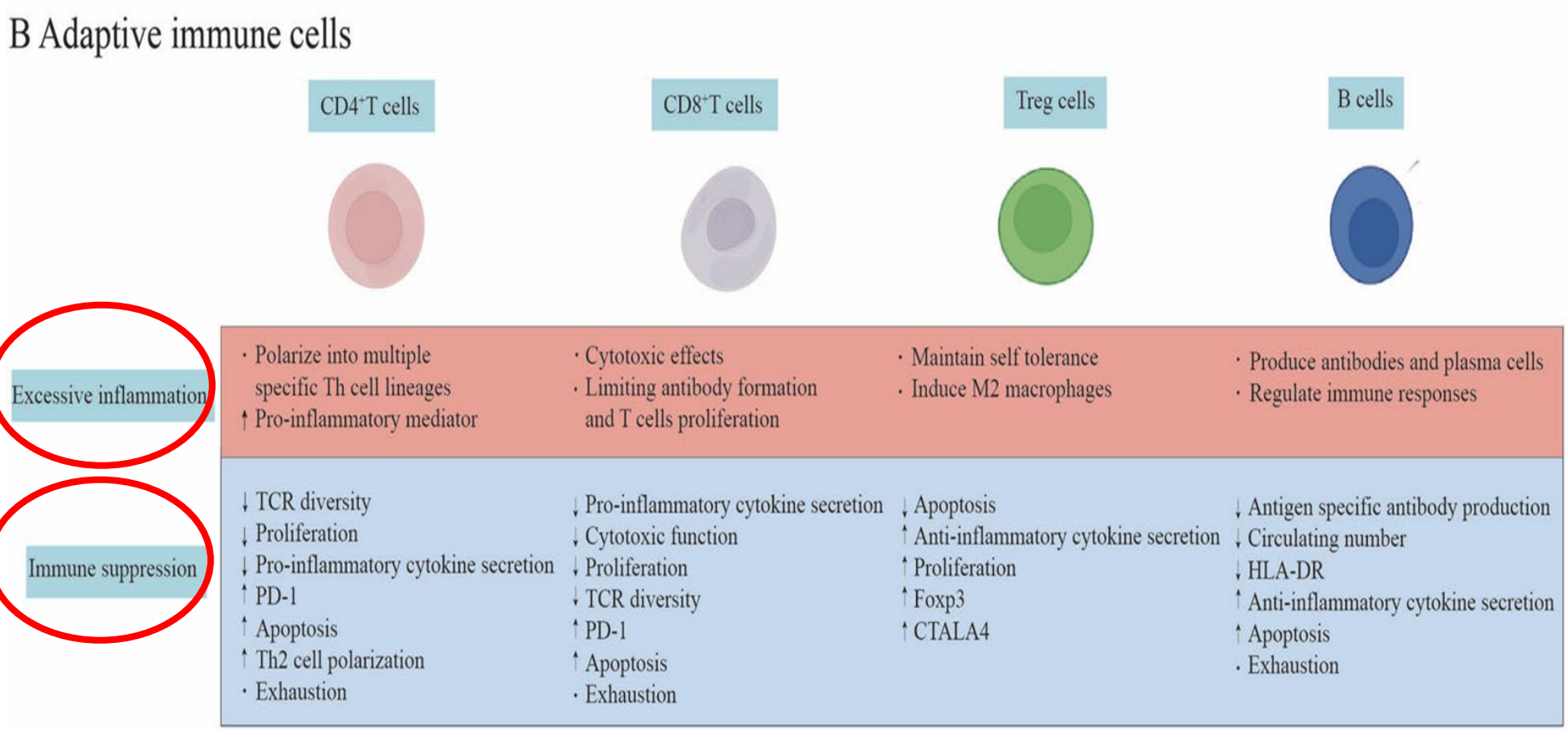
Miroslav Průcha
Nemocnice Na Homolce


THREE CLINICAL TRAJECTORIES
1. EARLY DEATH
MOF
Pro-inflammatory
Anti-inflammatory
SIRS
Genomic Storm
Sepsis
2. RAPID RECOVERY
Younger Adults
Immune Homeostasis
Discharge Home
3. CHRONIC CRITICAL ILLNESS (CCI): Older Adults
Organ Dysfunction
• Persistent Kidney Injury
• Neurocognitive Decline
• Sepsis-Induced Myopathy (Satellite Cell Dysfunction)
Persistent Inflammation
• ↑ Cytokines (ex. IL-6 & IL-8) & DAMPs
• MDSC persistence
Immunosuppression
• Lymphopenia & ↑sPDL-1
• Nosocomial Infections
• ↑MDSCs/Myeloid Dysfunction
Catabolism
• Sepsis-Induced Myopathy & Cachexia
PICS
Discharge to LTAC
Profound Disabilities
40% Indolent Death
2 days
14 days
Time
1 year

BUŇKY VROZENÉHO IMUNITNÍHO SYSTÉMU U SEPSE

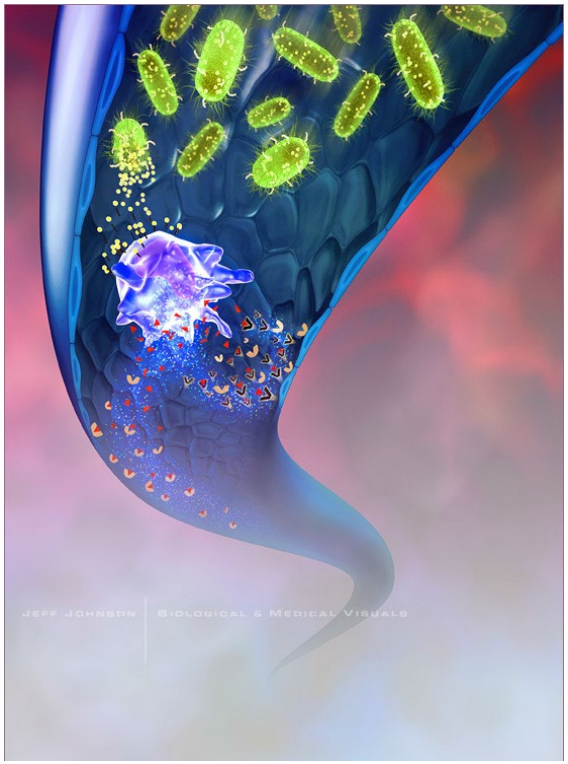


BUŇKY ADAPTIVNÍHO SYSTÉMU IMUNITY

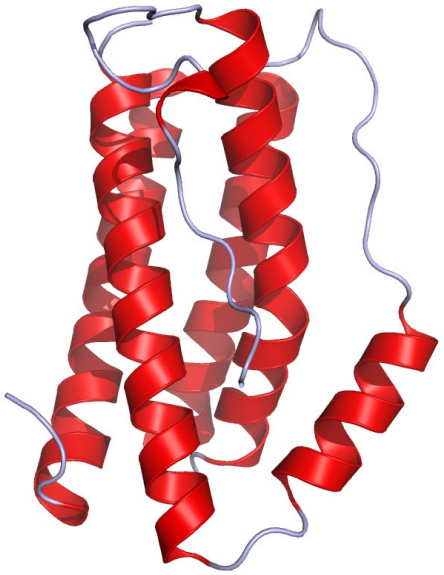


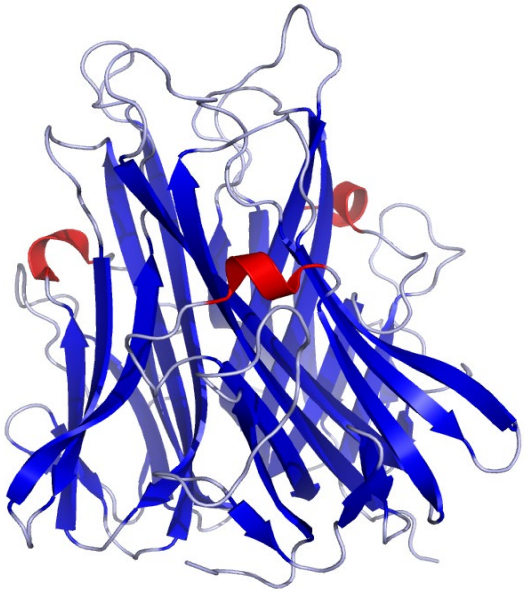
IMUNITNÍ SYSTÉM U SEPSE

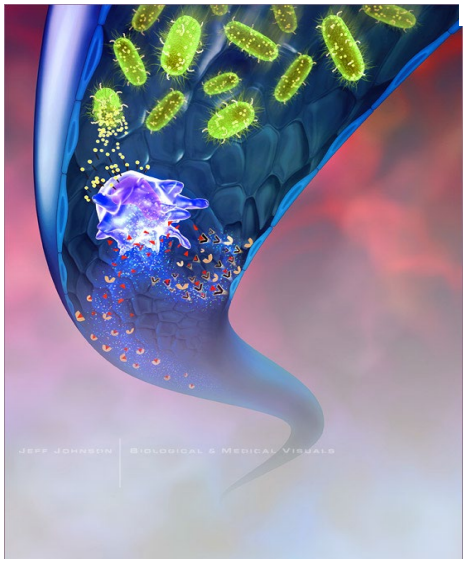
1. **Zvýšená apoptóza buněk vrozeného a adaptivního systému imunity**
2. **Vyčerpání T buněčného fenotypu**
3. **Deaktivace monocytů se snížením HLA-DR exprese**
4. **Zvýšení T regulačních buněk**
5. **Zvýšení negativních a snížení pozitivních kostimulačních molekul**
6. **Přesmyk Th 1 do Th2 odpovědi**

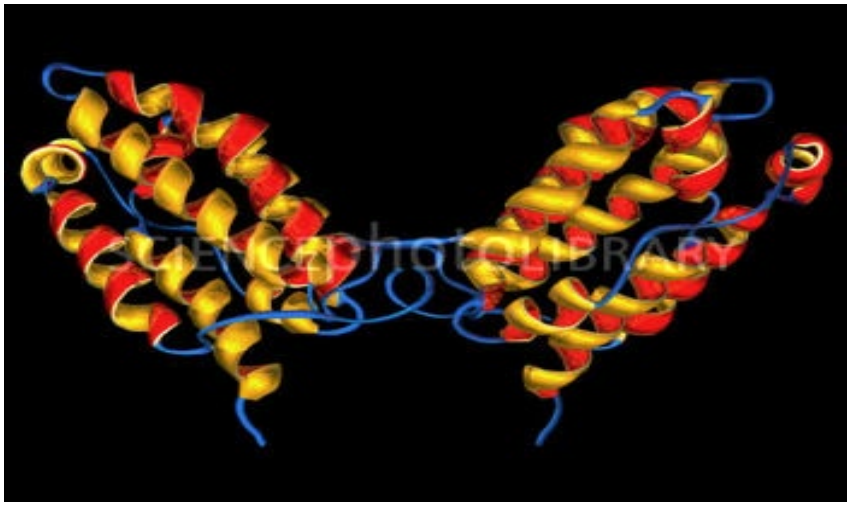


SEPSE JAKO MEDIÁTOROVÉ ONEMOCNĚNÍ



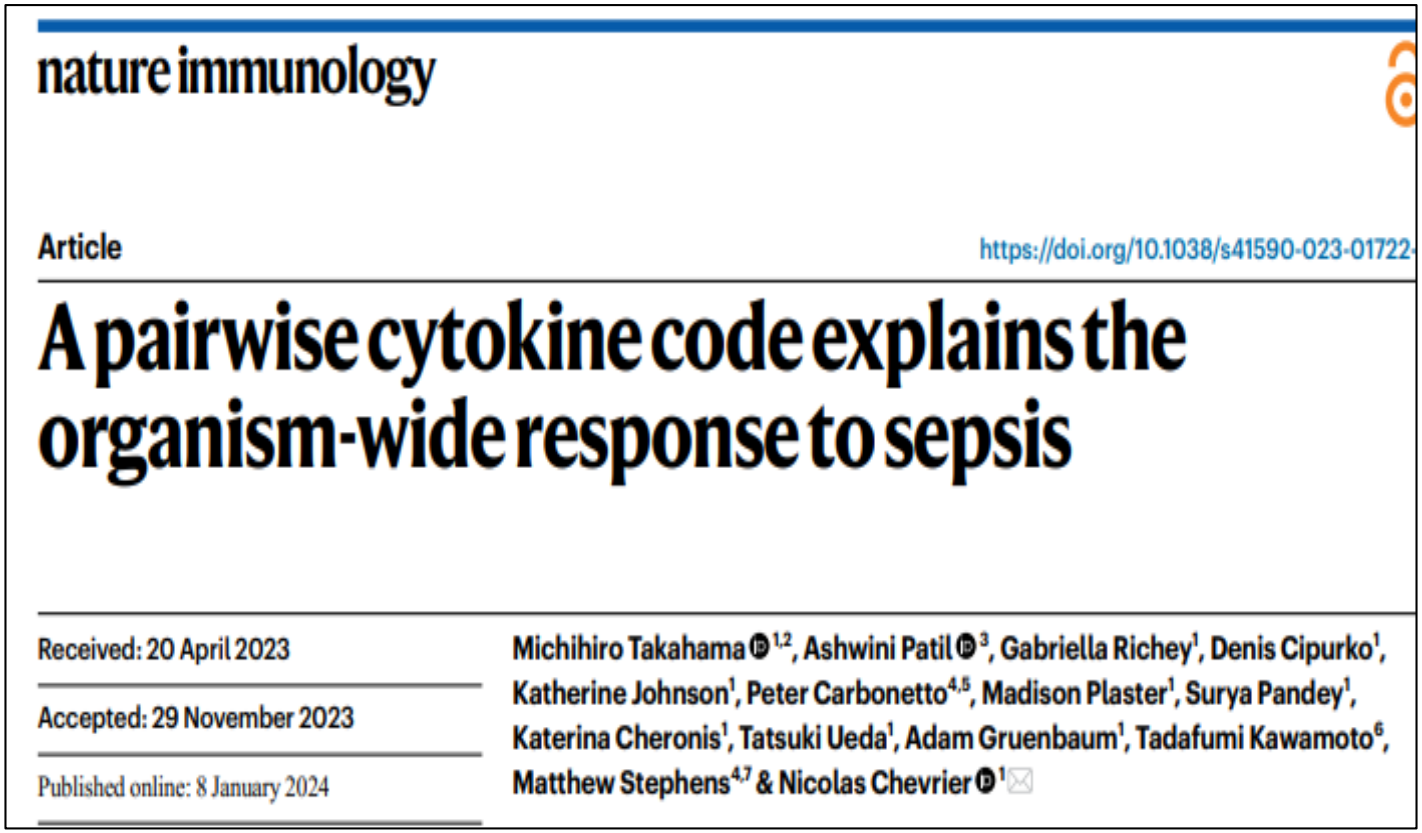






DIAGNOSTIKA OMICSOVÉ TECHNOLOGIE A TERANOSTIKA

Nejsme na konci cesty



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Article

https://doi.org/10.1038/s41590-023-01722-

A pairwise cytokine code explains the organism-wide response to sepsis

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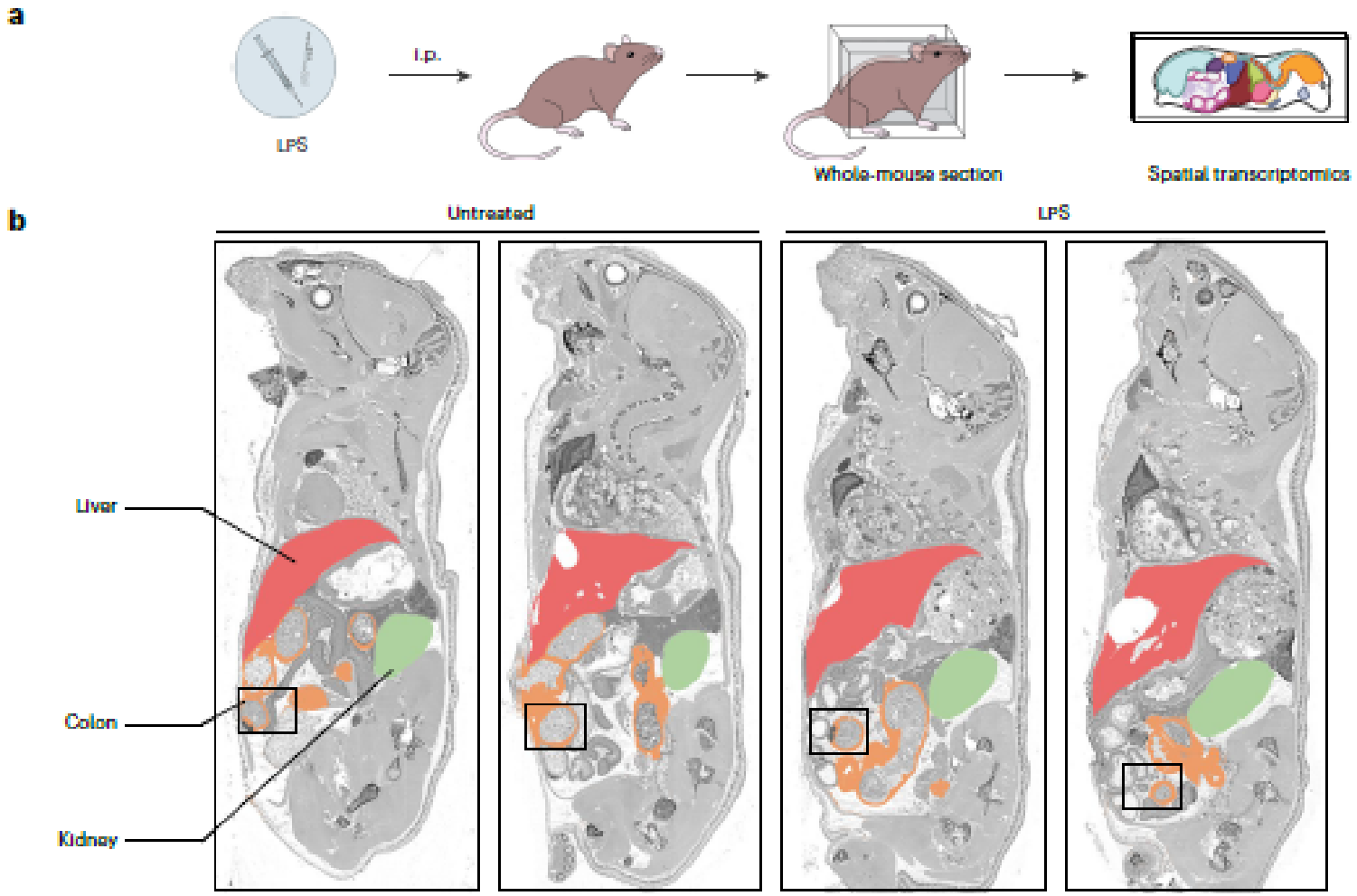
Michihiro Takahama[1,2], Ashwini Patil[3], Gabriella Richey[1], Denis Cipurko[1], Katherine Johnson[1], Peter Carbonetto[4,5], Madison Plaster[1], Surya Pandey[1], Katerina Cheronis[1], Tatsuki Ueda[1], Adam Gruenbaum[1], Tadafumi Kawamoto[6], Matthew Stephens[4,7] & Nicolas Chevrier[1]



Testovali 15 párů cytokinů – jejich produkce po injekci LPS v jednotlivých orgánech

VÝSLEDKY

- V rámci celého organismu panuje při sepsi „chaos“
- Existuje ale určitá hierarchie „zásadních„ cytokinů, které regulují imunitní odpověď
- Jsou to**: TNF, IL-18, IL 1β, IFN - gamma**
- Další cytokiny jsou „cíleněji“ zaměřeny v rámci jednotlivých orgánů
- Tyto 2 dvojice resp. 4 cytokiny regulují nejvíce genů ve všech orgánech - vyšší jednotky tisíc, zatímco zbývajících 12 dvojic pouze menší stovky

- **Individualizace terapie podle „vybraných parametrů“**

- **Již proběhlo v minulosti - určité podskupiny pacientů profitovaly z anti-TNF terapie**

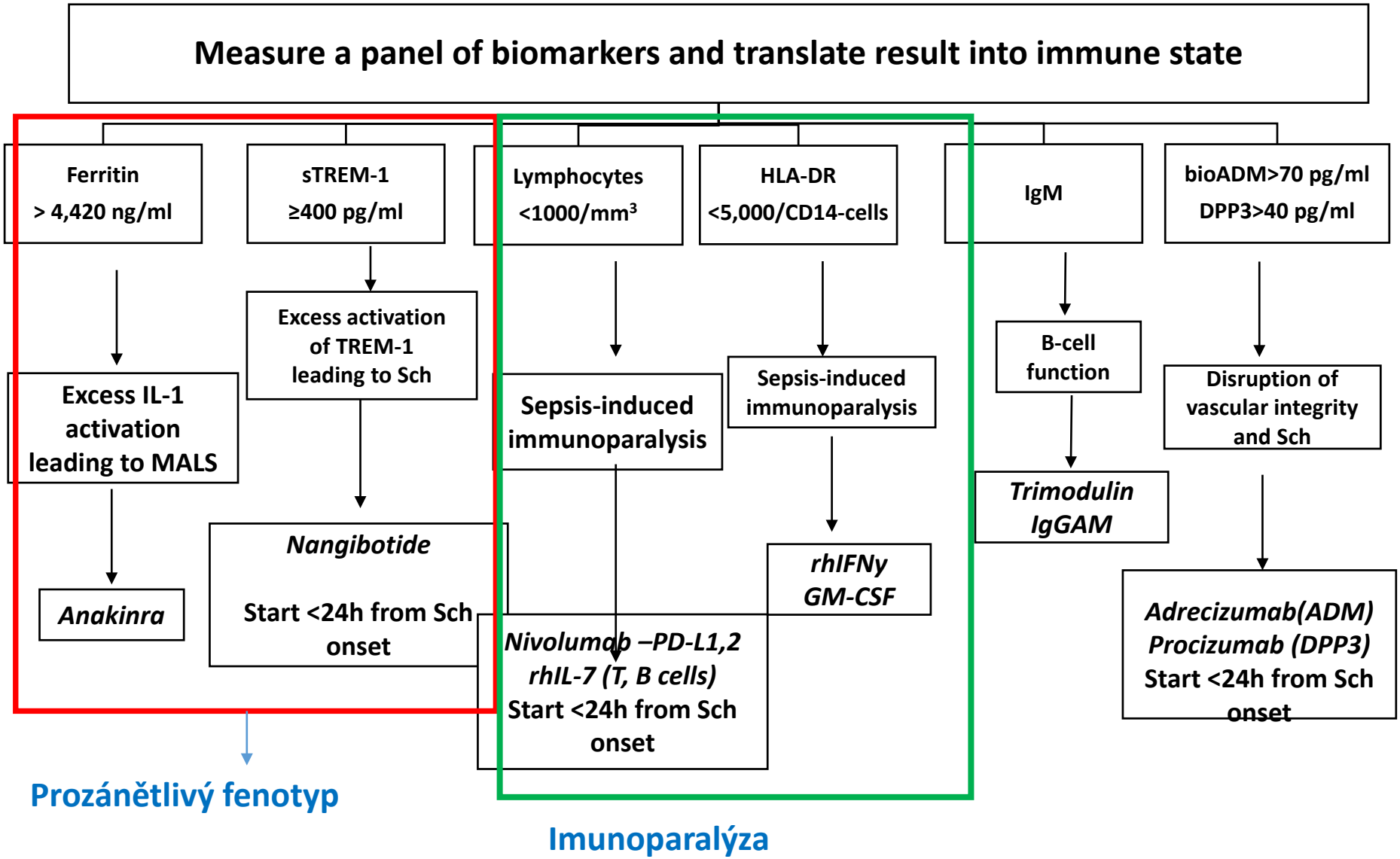
IMUNOFENOTYPY U SEPSE

- **Scicluna, B. P. et al**. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. Lancet Respir. Med. 5, 816–826 (2017).
- **Davenport, E. E. et al.** Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Lancet Respir. Med. 4, 259–271 (2016).
- **Sweeney, T. E. et al**. Unsupervised analysis of transcriptomics in bacterial sepsis across multiple datasets reveals three robust clusters. Crit. Care Med. 46, 915–925 (2018)

- S1, S2, MARS1-MARS4, inflammopathic, adaptive, coagulopathic
- V průběhu času se může endotyp měnit, proto je nutný „timing“ imunoterapie

IMUNITNÍ ODPOVĚĎ V DIAGNOSTICE A TERAPII

Burns & Trauma, 2025, vol. 13, tkaf001



SPRÁVNÁ LÉČBA KE „SPRÁVNÝM“ PACIENTŮM

Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of the macrophage activation syndrome: Re-analysis of a prior Phase III trial

B Shakoory , JA Carcillo , W W Chatham, R L Amdur , H Zhao , CA Dinarello , RQ Cron , SM Opal

Published in final edited form as: Crit Care Med. 2016 Feb;44(2):275–281. doi: 10.1097/CCM.0000000000001402

ANAKINRA – MAS
(macrophage activating sy)

Design

Re-analysis of deidentified data from the phase III randomized interleukin-1 receptor antagonist trial in severe sepsis (Opal, et. al. Crit Care Med. 1997 Jul;25(7):1115–24).

Setting

Multi-center study recruiting through 91 centers from 11 countries in Europe and North America.

Participants

Sepsis patients with MODS and/or shock (original study) were re-grouped based on presence or absence of concurrent HBD and DIC as features of MAS (HBD/DIC group). The “non-HBD/DIC” group included patients with only HBD, only DIC or neither.

ANAKINRA - MAS

Data were available for 763 adults from the original study cohort, randomized to receive either anakinra or placebo. Concurrent HBD/DIC was noted in 43 patients (5.6% of total, ages 18–75; 47% women). **The 28-day survival was similar in both anakinra and placebo-treated non-HBD/DIC patients** (**71.4% vs. 70.8%, *p*=.88**). Treatment with anakinra was associated with significant improvement in the 28-day **survival rate** in HBD/DIC patients (**65.4% anakinra vs. 35.3% placebo**), with HR for death 0.28 (0.11–0.71, p = 0.0071) for the treatment group in Cox regression.

Conclusions and Relevance

In this subgroup analysis, IL-1 receptor blockade was associated with significant improvement in survival of patients with sepsis and concurrent HBD/DIC. A prospective randomized trial using features of MAS for mortality risk stratification should be undertaken to confirm the role of IL-1 blockage.

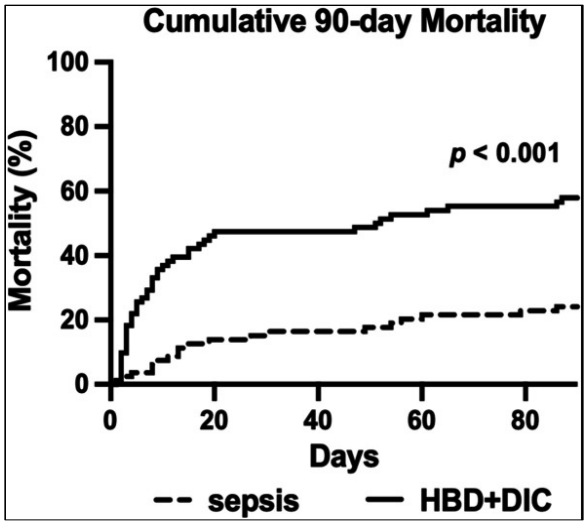
POTVRZENÍ

› Intensive Care Med Exp. 2022 Feb 21;10(1):6. doi: 10.1186/s40635-022-00433-y.

Sepsis with liver dysfunction and coagulopathy predicts an inflammatory pattern of macrophage activation

Renee R Anderko [# 1], Hernando Gómez [# 2 3], Scott W Canna [4 5], Bita Shakoory [6], Derek C Angus [1], Donald M Yealy [7], David T Huang [1], John A Kellum [1 8], Joseph A Carcillo [1 8]; ProCESS Investigators

In comparison with controls, HBD + DIC patients experienced higher in-hospital (43% vs 10%, $p < 0.001$) and 90-day mortality (56% vs 23%, $p < 0.001$)



VÝZNAM A ÚLOHA IMUNITNÍ ODPOVĚDI V DIAGNOSTICE (kdy, proč, jak, co)

- **Monitorování individuálně**
- **V závislosti na anamnéze(autoimunitní onemocnění, biologická léčba, sekundární ID)**
- **V závislosti na klinickém průběhu**
- **V diagnostice a následně již vliv na terapii**
- **Ig, imunoparalýza, vybrané cytokiny – IL-6**

DĚKUJI ZA POZORNOST