

REPRODUCING SEPSIS ENDOTYPES IN ANIMAL MODELS



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Panagiotis Koufargyris, Evangelia Karagianni,
Konstantinos Leventogiannis, Evangelos J Giamarellos-Bourboulis



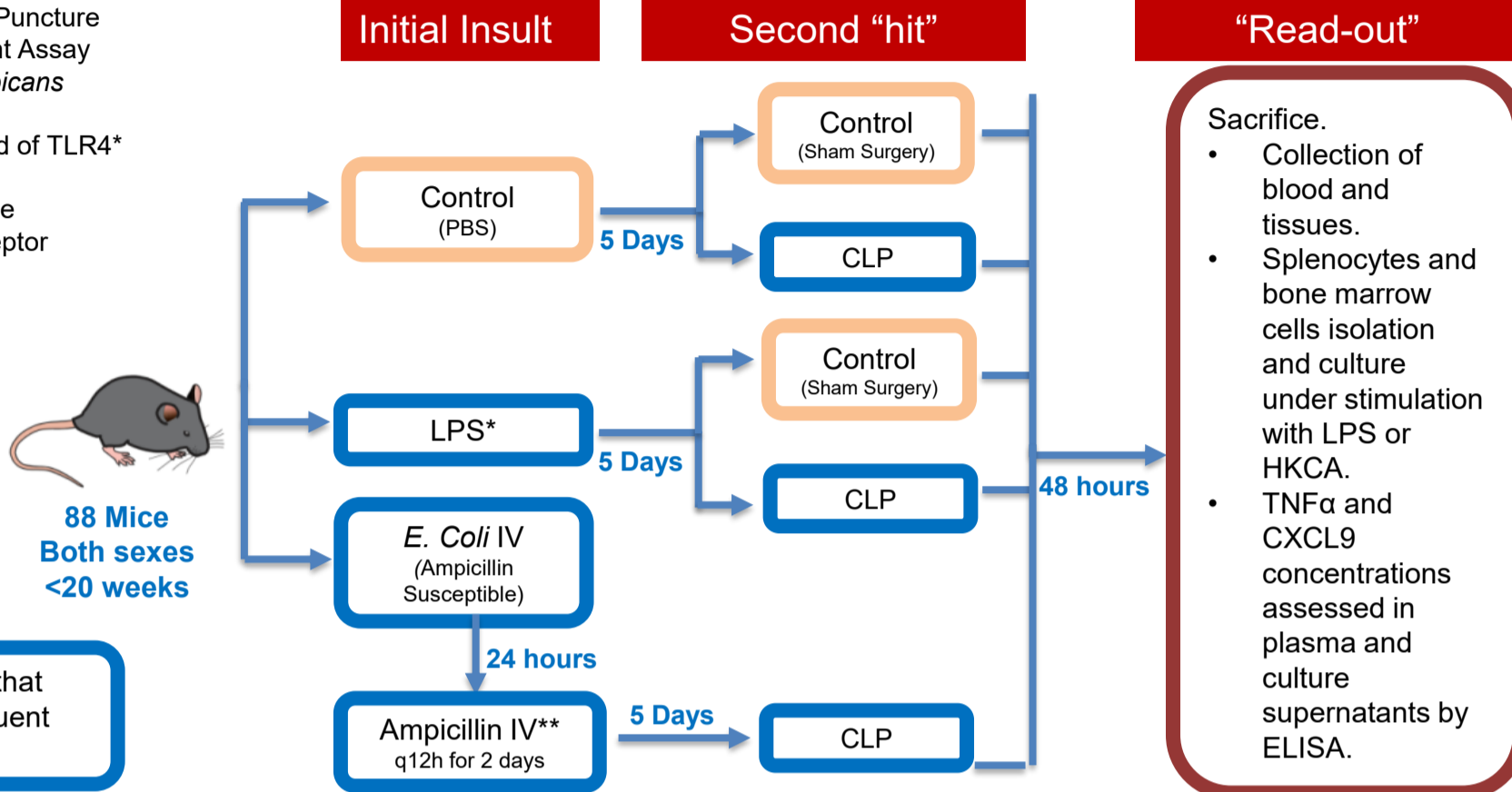
4th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Greece

Introduction

Two of the most clinically relevant functional endotypes are sepsis-induced immunoparalysis (SII) characterized by immune exhaustion, reduced monocyte HLA-DR expression and diminished production of pro-inflammatory cytokines; and IFN γ -driven sepsis (IDS), characterized by the overexpression of the CXCL9 chemokine under the influence of excessive IFN γ biosynthesis.¹ Given the lack of established preclinical models for sepsis endotypes, we tried different combinations of consecutive immunogenic interventions via a “two-hit” approach, aiming to develop mice models mimicking SII and IDS.

Animal and Methods: Two-hit approach mimicking severe immune dysregulation of human sepsis

CLP: 50% Cecal Ligation and Puncture
ELISA: Enzyme Immunosorbent Assay
HKCA: Heat-Killed *Candida albicans*
IV: Intravenous
LPS: Lipopolysaccharide; ligand of TLR4*
M ϕ : Macrophages
PBS: Phosphate Buffered Saline
PPR: Pattern Recognition Receptor
q: every
TNF α : Tumor necrosis factor α



Results

Primary measure used for sepsis endotype classification

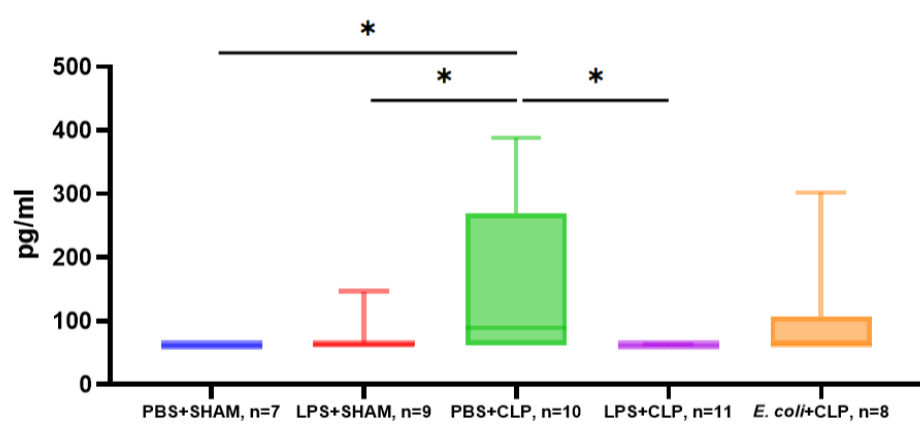
IDS Hallmark:

Elevated presence of CXCL9 in biological fluids

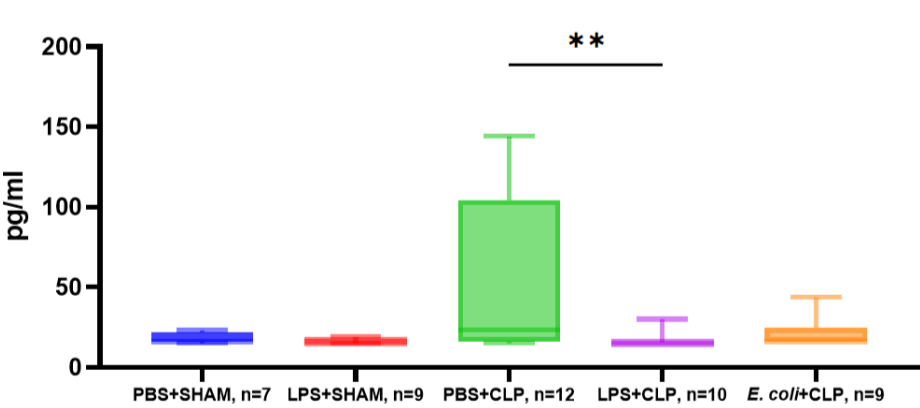
SII Hallmark:

Exhausted *ex vivo* TNF α production

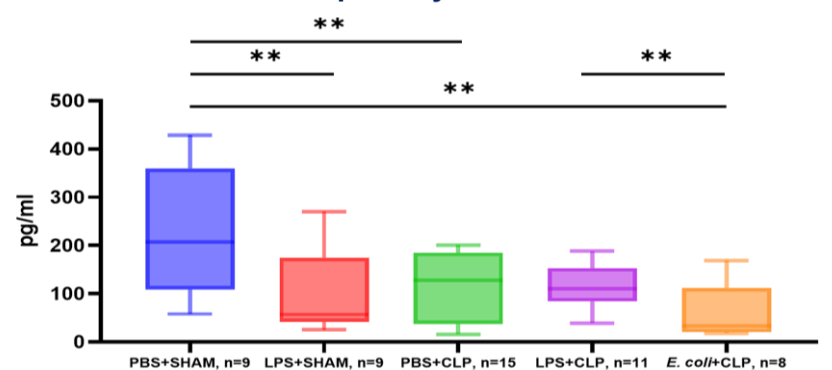
Plasma CXCL9



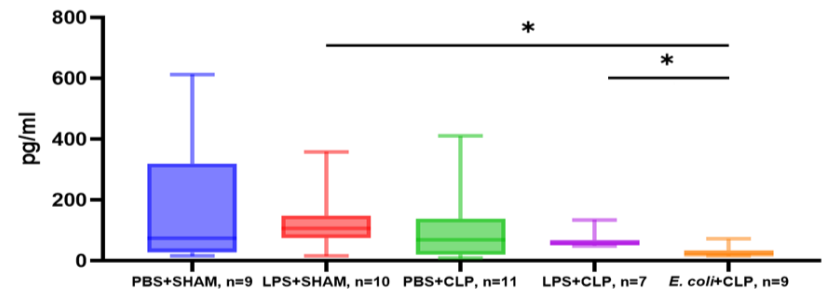
Peritoneal CXCL9



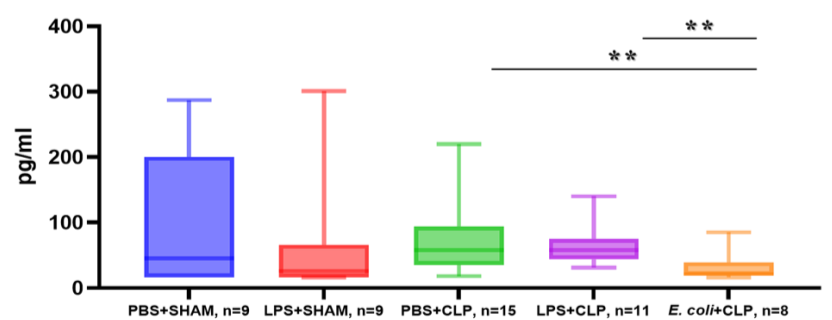
TNF α - Splenocytes with LPS



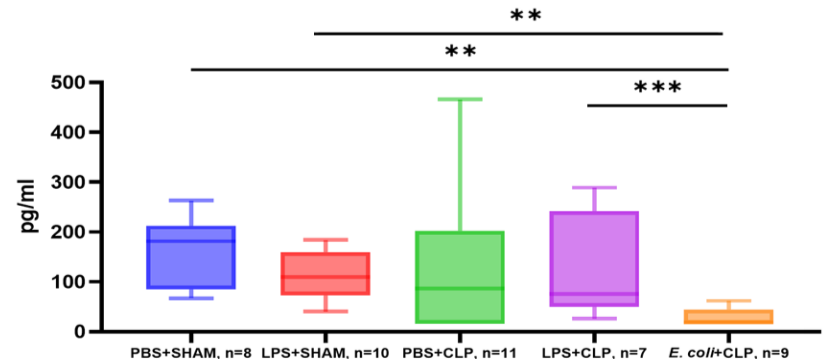
TNF α - Bone marrow cells with LPS



TNF α - Splenocytes with HKCA



TNF α - Bone marrow cells with HKCA



CLP: Cecal Ligation and Puncture

E. coli: *Escherichia coli*

LPS: Lipopolysaccharide

PBS: Phosphate Buffered Saline

HKCA: Heat-Killed *Candida albicans*.

*: *p* value < 0.05

** : *p* value < 0.01

***: *p* value < 0.001

- E. coli* IV and CLP surgery (*E. coli*+CLP)**, exhibited the lowest TNF α production under *in vitro* LPS and HKCA stimulation, by both splenocytes and bone marrow cells # significant immune exhaustion, consistent with SII.
- PBS and CLP surgery (LPS+CLP)** group had the highest concentration of CXCL9 both in plasma and peritoneal lavage fluid # consistency with IDS.

Conclusions

- Infection by *E. coli* followed by step 1) antibiotic treatment; and step 2) by resuscitation by CLP surgery mimics SII
- Pre-treatment with PBS followed by CLP mimics IDS.

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¹ Giamarellos-Bourboulis, E. J. et al. eBioMedicine 2024; 109: 105414

This research was supported by Swedish Orphan Biovitrum AB; the funder had no role in study design, data collection and analysis.