Treatment of Sepsis by Phenotyping:
a practical tool or wishful thinking?

Marcin Osuchowski

LUDWIG BOLTZMANN INSTITUTE
Traumatology
The Research Center in Cooperation with AUVA

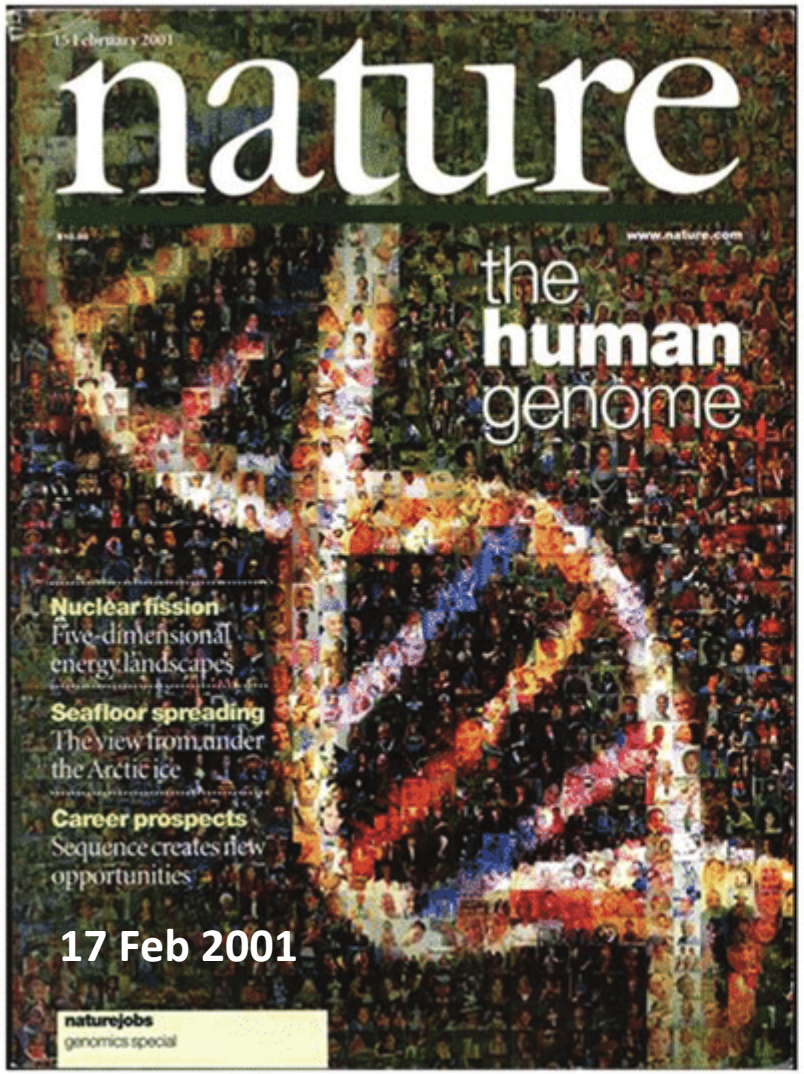
AUVA

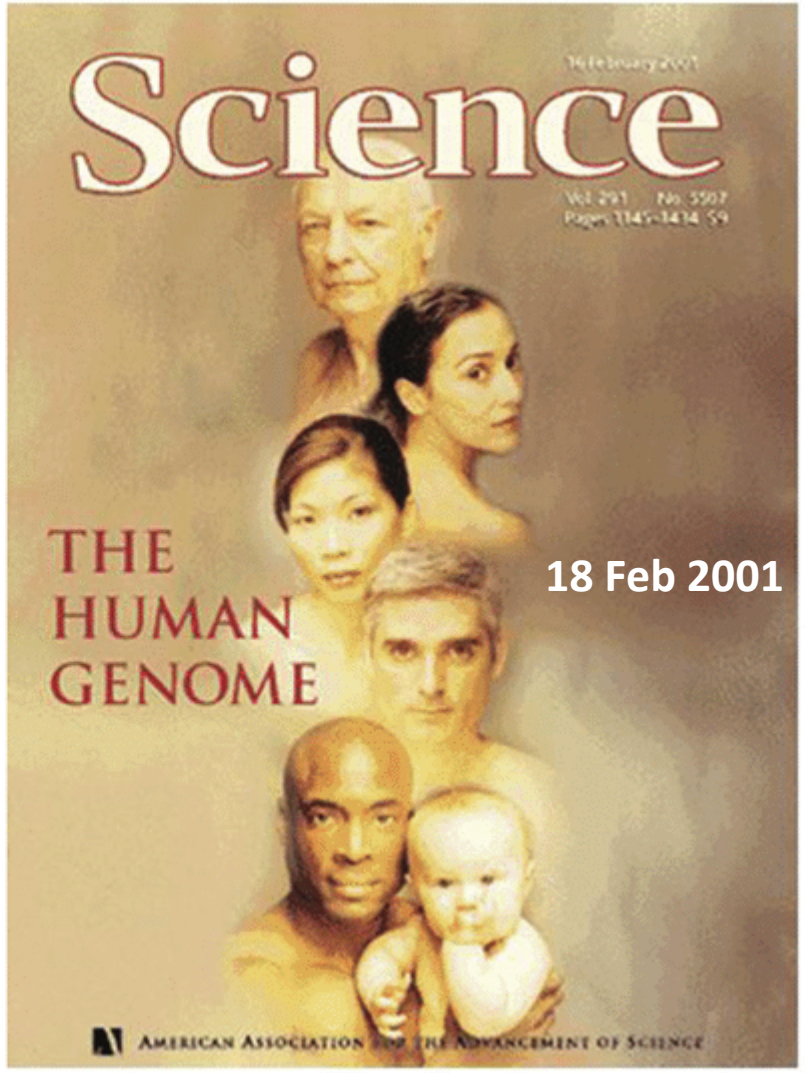
Disclosures

A Serious Moral Conflict to Declare for this Talk

Human Genome Project

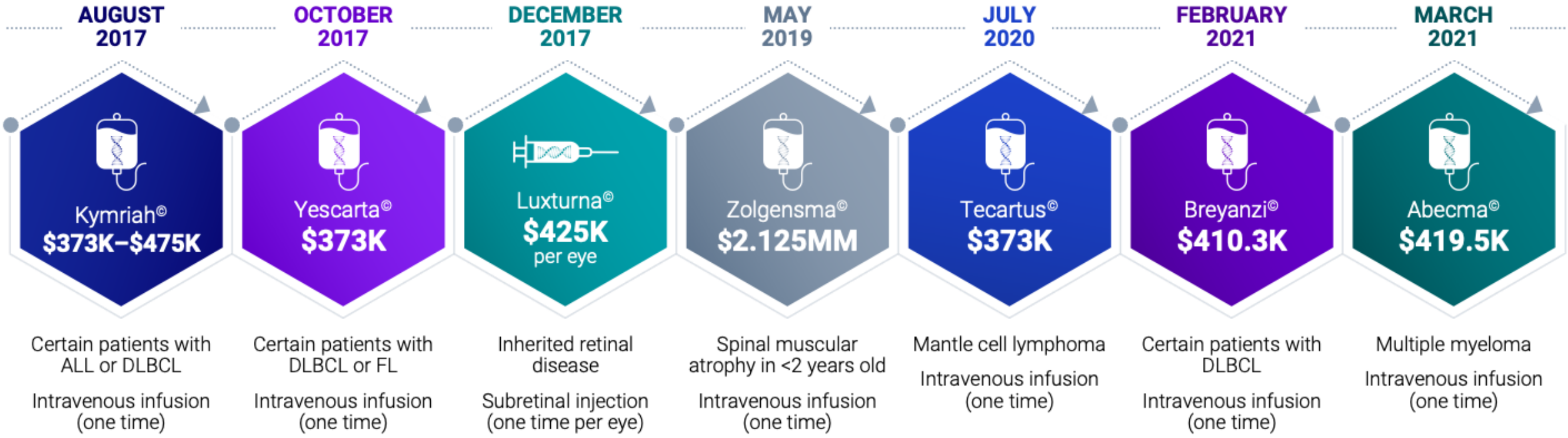
- initial analysis of the human genome sequence published in February 2001
- successful completion announced on April 14, 2003





20 Years Later…

Current FDA approved gene therapies.



ALL: acute lymphoblastic leukemia; **DLBCL:** Diffuse large B-cell lymphoma; **FL:** Follicular lymphoma;

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

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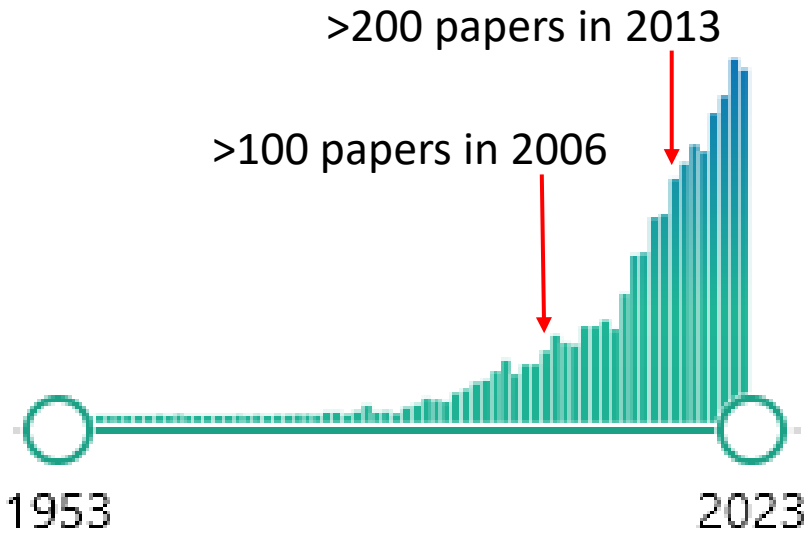
National Library of Medicine
National Center for Biotechnology Information

Query „sepsis (AND) phenotyping“

PubMed.gov

RESULTS BY YEAR



Total: 4535 papers

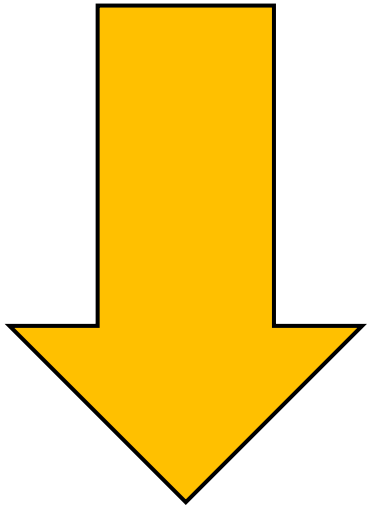
2020-yesterday: 1124 papers

Why do phenotyping?

Level 1: to (better) understand pathophysiology of a disease

Level 2: to better treat it thanks to that improved understanding

Level 1: do we know ENOUGH?



Level 2: to devise/implement effective treatments

Out of 67 Anti-sepsis Ph2/3 Human Trials listed: 58 w/o effect

5 benefit (never repeated)

4 harm

y of clinical trials of pharmacological interventions for the adjuvant treatment of sepsis, which have been reported since 1982

Fink MP., Virulence 2014

	Year	Patients (sample size)	Trial Acronym	Experimental agent	Effect on mortality[a]	References
	1994	Septic shock and Gram-negative bacteremia (621)	CHESS	HA-1A, a human mAb that binds the lipid A domain of LPS	No effect[c]	5
	1991	Gram-negative sepsis (486)		E5, a murine mAb that binds the lipid A domain of LPS	No effect	68
	1995	Gram-negative sepsis with organ dysfunction (847)		E5, a murine mAb that binds the lipid A domain of LPS	No effect	69
	2000	Severe sepsis due to Gram-negative infection (1090)		E5, a murine mAb that binds the lipid A		
	2003	Severe sepsis or septic and evidence due to presumed Gram-negative infection				
	2000	Children with severe meningococcal sepsis (393)				
	1997	Severe sepsis or septic shock (498)				
	2001	Severe sepsis or early septic shock (1342)				
	1996	Septic shock (141)		Etanercept, a recombinant fusion protein that is a dimer of the extracellular portion of the human p75 TNF receptor and the Fc portion of IgG1; it binds and neutralizes TNF	Harm	20
	1995	Sepsis (994)	NORASEPT I	BAY x 1351, a murine anti-TNF mAb	No effect	75
	1996	Sepsis (564)	INTERSEPT	BAY x 1351, a murine anti-TNF mAb	No effect	76
	1998	Septic shock (1878)	NORASEPT II	BAY x 1351, a murine anti-TNF mAb	No effect	77
	2006	Severe sepsis or septic shock (81)		CytoFab, F(ab) fragments of an ovine polyclonal antibody to TNF	No effect	78
	1996	Severe sepsis or septic shock (122)		Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	No effect	79
	2001	Severe sepsis and high serum concentration of IL-6 (446)	RAMSES	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	No effect	80
	2004	Severe sepsis and high serum concentration of IL-6 (998)	MONARCS	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	Benefit	9
	1995	Septic shock (42)		CDP571, a humanized anti-TNF mAb	No effect	81
	1993	Severe sepsis or septic shock (80)		CB0006, a murine anti-TNF mAb	No effect	82
	1994	Sepsis (262)		BN 52021, a small molecule PAF receptor antagonist	No effect	83
	1998	Severe sepsis suspected to be caused by Gram-negative infection (609)		BN 52021, a small molecule PAF receptor antagonist	No effect	84
	2000	Clinical suspicion of infection and APACHE II score between 15 and 35 (152)		BB-882, a small molecule PAF receptor antagonist	No effect	85

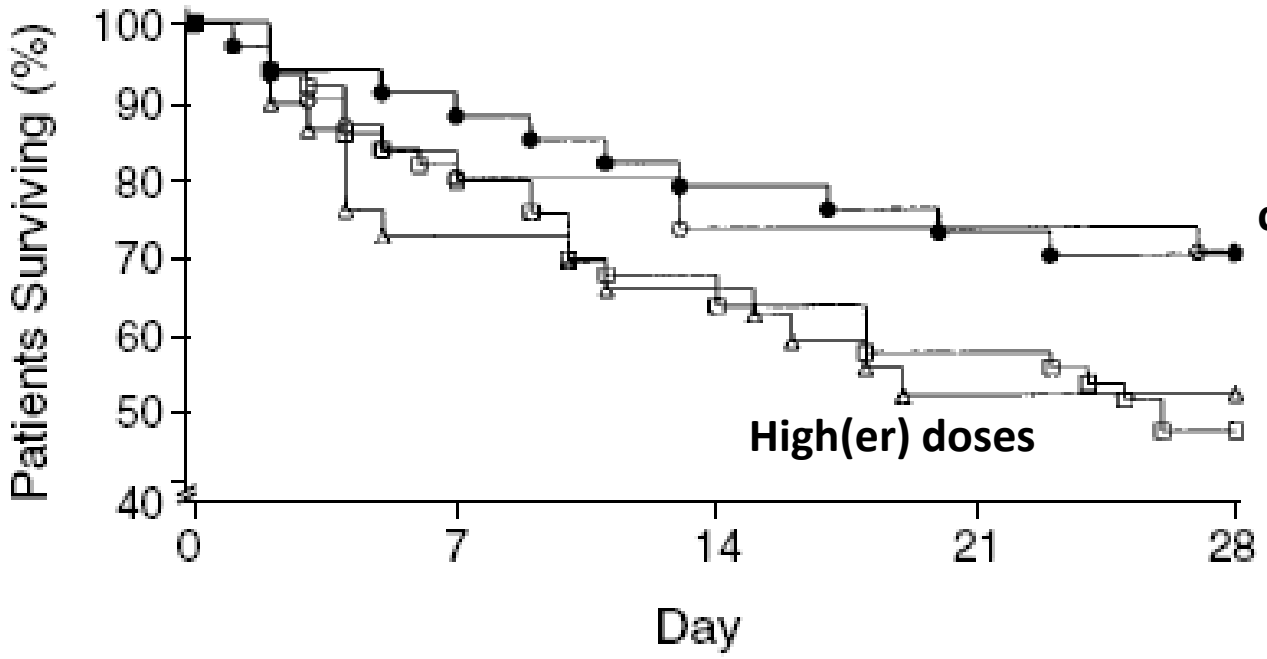
only two trial used biomarker-guided therapy

Reinhart	2001	Severe sepsis and high serum concentration of IL-6 (446)	RAMSES	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	No effect
Panacek	2004	Severe sepsis and high serum concentration of IL-6 (998)	MONARCS	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	Benefit

Year	Patients (sample size)	Trial Acronym	Experimental agent	Effect on mortality[a]	References
2000	Severe sepsis (131)		BB-882, a small molecule PAF receptor antagonist	No effect	86
1996	Systemic inflammatory response syndrome (29)		TCV-309, a small molecule PAF receptor antagonist	No effect	87
2000	Septic shock (98)		TCV-309, a small molecule PAF receptor antagonist	No effect	88
2003	Severe sepsis without established acute respiratory dis-		Pafase, recombinant human platelet activat-	Benefit	10
2009	Severe sepsis due to confirmed cted Gram- tion (1379)		GR270773, a phospholipids emulsion	No effect	93
2001	ere sepsis (210)		Tifacogin, recombinant human tissue factor pathway inhibitor	No effect	61
	evere sepsis and elevated international normalized ratio (1754)	OPTIMIST	Tifacogin, recombinant human tissue factor pathway inhibitor	No effect	60
011	Severe community acquired pneumonia (2138)		Tifacogin, recombinant human tissue factor pathway inhibitor	No effect	62
1994	Sepsis or septic shock (99)		Anakinra, recombinant human interleukin-1 receptor antagonist	Benefit	6
1994	Sepsis (893)		Anakinra, recombinant human interleukin-1 receptor antagonist	No effect	7
1997	Severe sepsis or septic shock (696)		Anakinra, recombinant human interleukin-1 receptor antagonist	No effect	8
1997	Systemic inflammatory response syndrome and presumed infection (504)		CP-0127, a small molecule bradykinin receptor antagonist	No effect	94
1995	Systemic inflammatory response syndrome and presumed infection (504)		CP-0127, a small molecule bradykinin receptor antagonist	No effect	
2001	Severe sepsis (1690)	PROWESS	Drotrecogin alfa, recombinant human activated protein C	Benefit	14
2007	Children with severe sepsis (477)	RESOLVE	Drotrecogin alfa, recombinant human activated protein C	No effect	16
2005	Severe sepsis and low risk of death	ADDRESS	Drotrecogin alfa, recombinant human activated protein C	No effect	15

Year	Patients (sample size)	Trial Acronym	Experimental agent	Effect on mortality[a]
2012	Infection, systemic inflammatory response syndrome and shock (1697)	PROWESS-SHOCK	Drotrecogin alfa, recombinant human activated protein C	No effect
			, small molecule isoform unselec- e cyclooxygenase inhibitor	No effect
			Antithrombin III	No effect
			Antithrombin III	No effect
			Antithrombin III	No effect
			Antithrombin III	No effect
			rednisolone or dexamethasone	No effect[d]
1987	Severe sepsis or septic shock (382)		Methylprednisolone	Harm[c]
1998	Septic shock (41)		Hydrocortisone	No effect
2005	Septic shock (41)		Hydrocortisone	No effect
2002	Septic shock and biochemical evidence of adrenal insufficiency (229)		Hydrocortisone and fludrocortisone	Benefit
2008	Septic shock (499)	CORTICUS	Hydrocortisone	No effect
2010	Septic shock and cirrhosis (75)		Hydrocortisone	No effect
1999	Septic shock (40)		Hydrocortisone	No effect
2003	Severe sepsis and bacterial pneumonia (701)		Filgrastim, recombinant human granulocyte colony stimulating factor	No effect
2002	Sepsis and respiratory dysfunction (18)		Sargramostim, recombinant human granulocyte macrophage colony stimulating factor	No effect
2006	Sepsis and abdominal infection (58)		Sargramostim, recombinant human granulocyte macrophage colony stimulating factor	No effect
2009	Severe sepsis and biochemical evidence of immunosuppression (38)		Sargramostim, recombinant human granulocyte macrophage colony stimulating factor	No effect
2009	Sepsis (319)		Unfractionated heparin	No effect
1998	Severe sepsis (51)		Pentoxifylline	No effect
2004	Septic shock (312)		546C88, small molecule isoform unselective nitric oxide synthase inhibitor	No effect
2004	Septic shock (797)		546C88, small molecule isoform unselective nitric oxide synthase inhibitor	Harm

The Harm – The Soluble TNF Receptor Sepsis Study Group



patients killed
by the treatment

Study Group	No. of Patients	No. of Deaths
Placebo (-●-)	33	10
0.15 mg/kg (-○-)	30	9
0.45 mg/kg (-△-)	29	14
1.5 mg/kg (-□-)	49	26

Figure 1. Kaplan–Meier Analysis of Survival in Patients with Sepsis Receiving Placebo or One of Three Doses of TNFR:Fc.

Fisher et al. N Engl J Med. 1996, 334(26):1697-702.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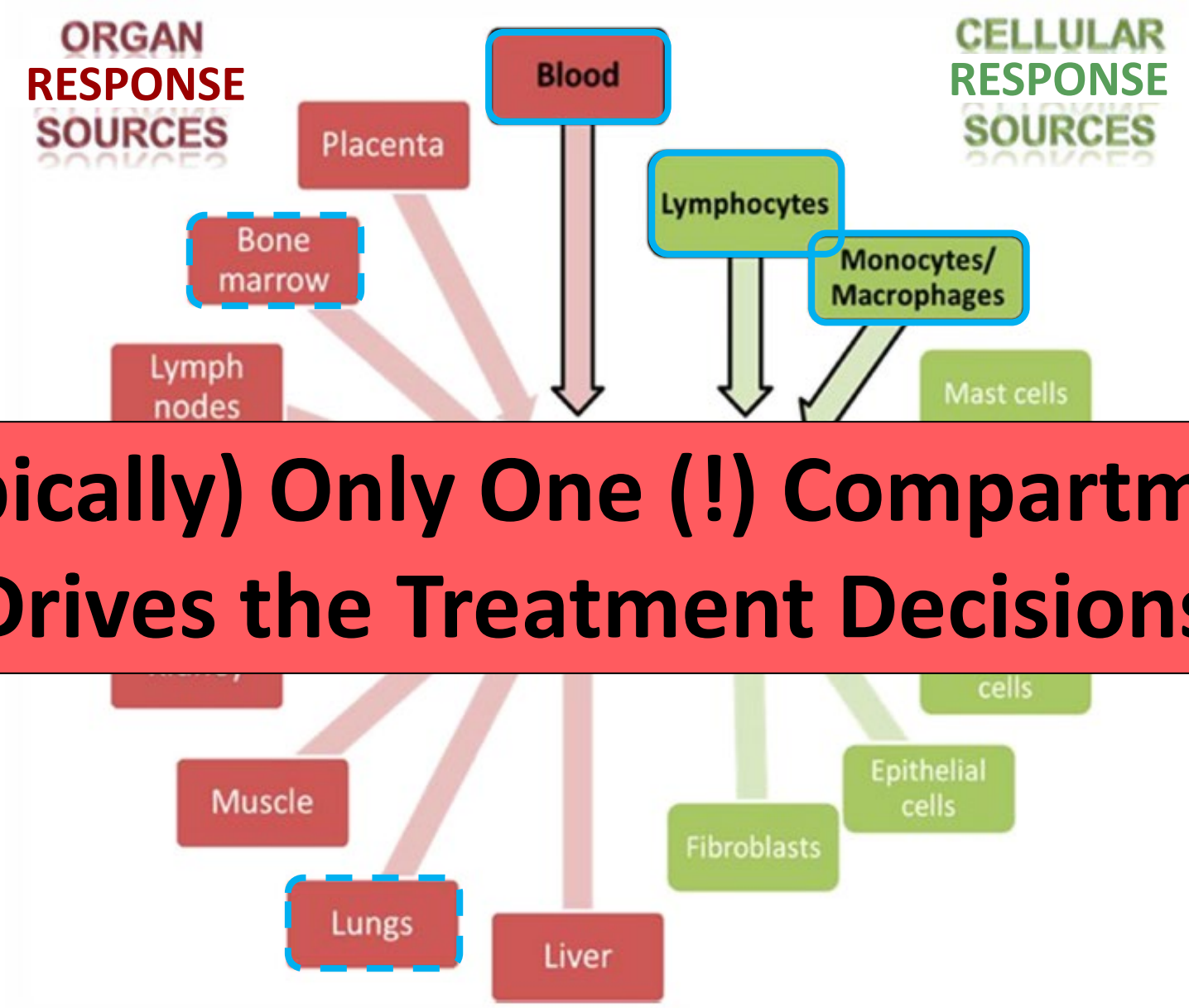


(Typically) Only One (!) Compartment Drives the Treatment Decisions

SHOCK, Vol. 41, No. 6, pp. 463–475, 2014

Operationalization of Phenotyping in Sepsis

Reducing patient heterogeneity to therapeutically exploit it

- Immuno-inflammatory status (i.e. robust response, immunosuppression)
- Sepsis severity/risk of death (high vs low)
- Responders/non-responders/harm (give treatment vs withhold t.)
- Infectious source/type of pathogen (e.g. abdominal vs pneumonia)
- Predispositions (e.g. based on age, comorbidities, genetics)

Operationalization of Phenotyping in Sepsis

„Simplicity is the ultimate sophistication“

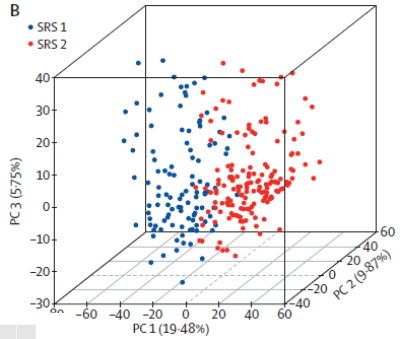
Leonardo da Vinci

„Make everything as simple as possible, but not simpler. “

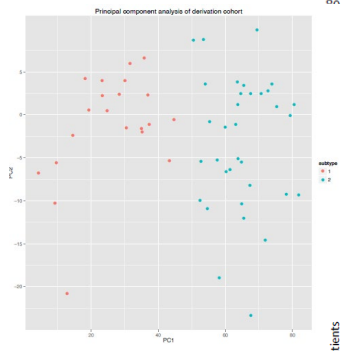
Albert Einstein

Phenotyping on the Genomic/Transcritomic Expression Level

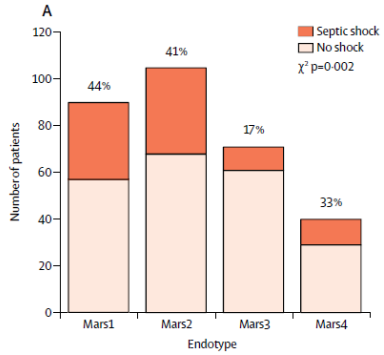
2012 Maslove et al.: <u>two</u> subtypes identified (n=166)



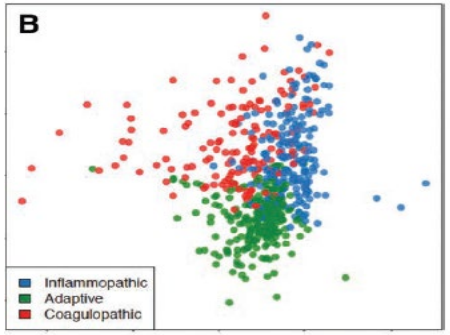
2016 Davenport et al.: <u>two</u> subtypes identified (n=384)



2017 Scicluna et al. (MARS): <u>four</u> subtypes identified (n=787)

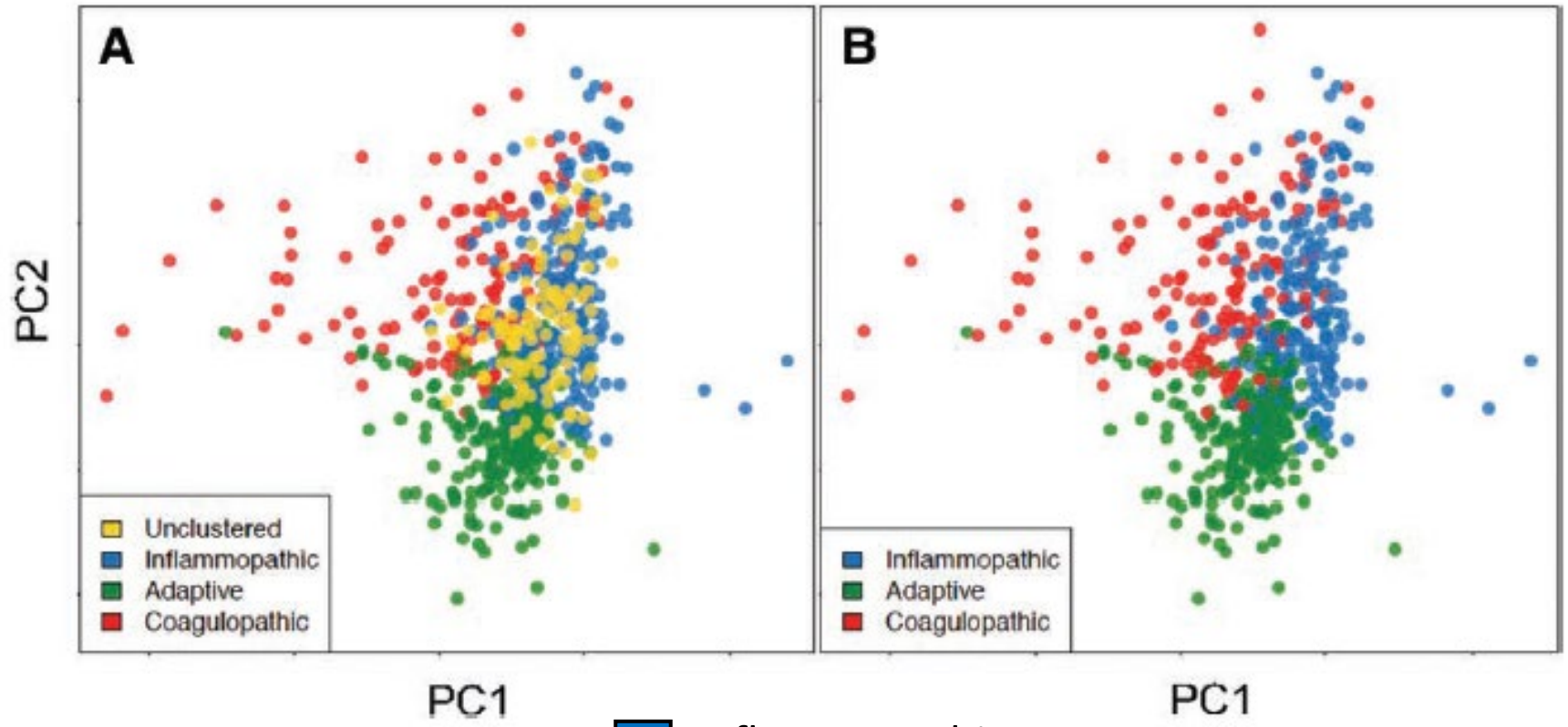


2018 Sweeney et al.: <u>three</u> subtypes identified (n=1300)



Critical Care Medicine 2018

Unsupervised Analysis of Transcriptomics in Bacterial Sepsis Across Multiple Datasets Reveals Three Robust Clusters



Inflammopathic

Adaptive

Coagulopathic

Phenotyping on the Level of Circulating Biomarkers

Research

JAMA. doi:10.1001/jama.2019.5791
Published online May 19, 2019.

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

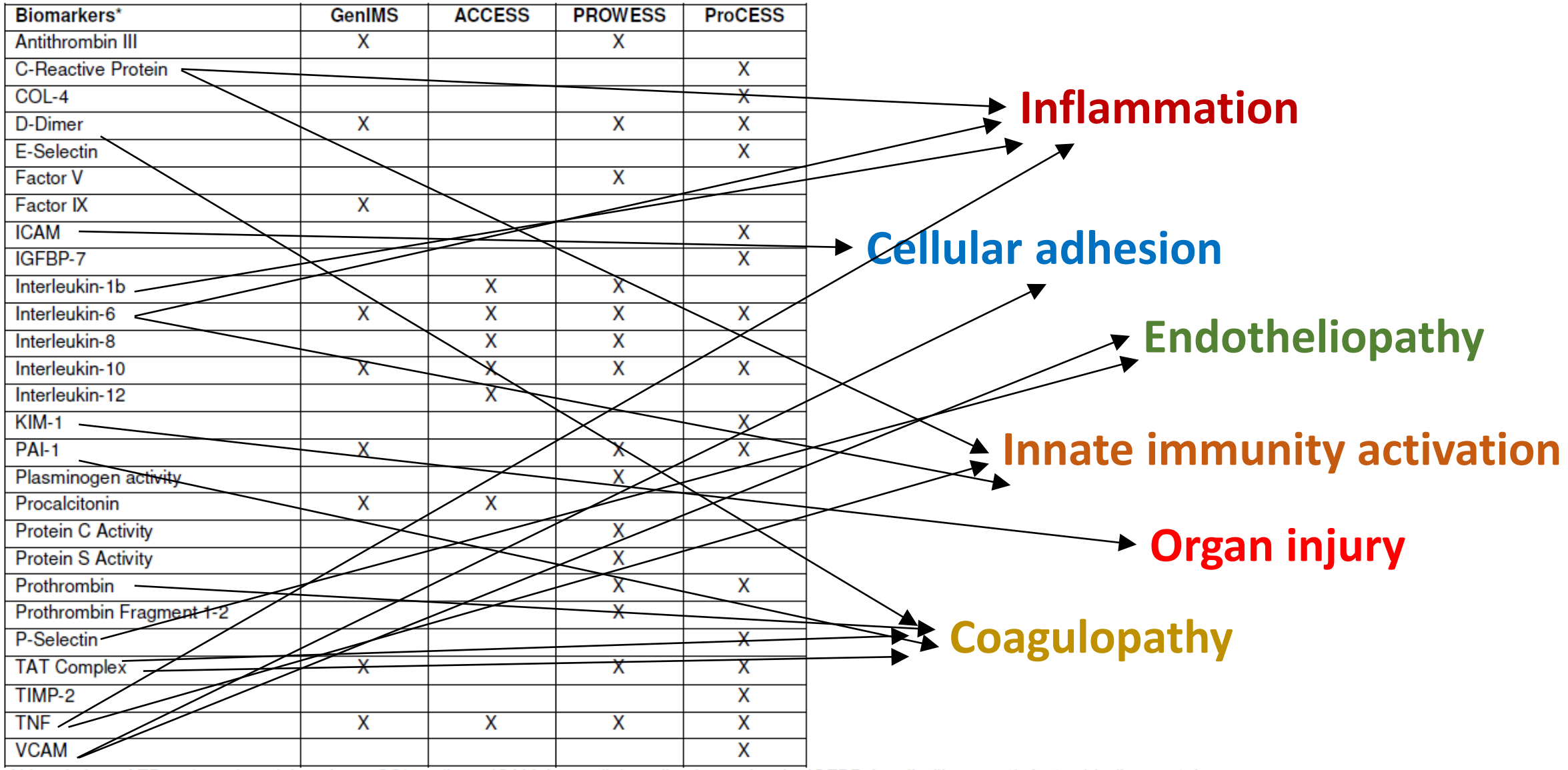
4 sepsis phenotypes identified: α, β, γ, δ.

- > 60k patients (derivation + validation cohorts)
- 3 observational trials & 3 RCTs

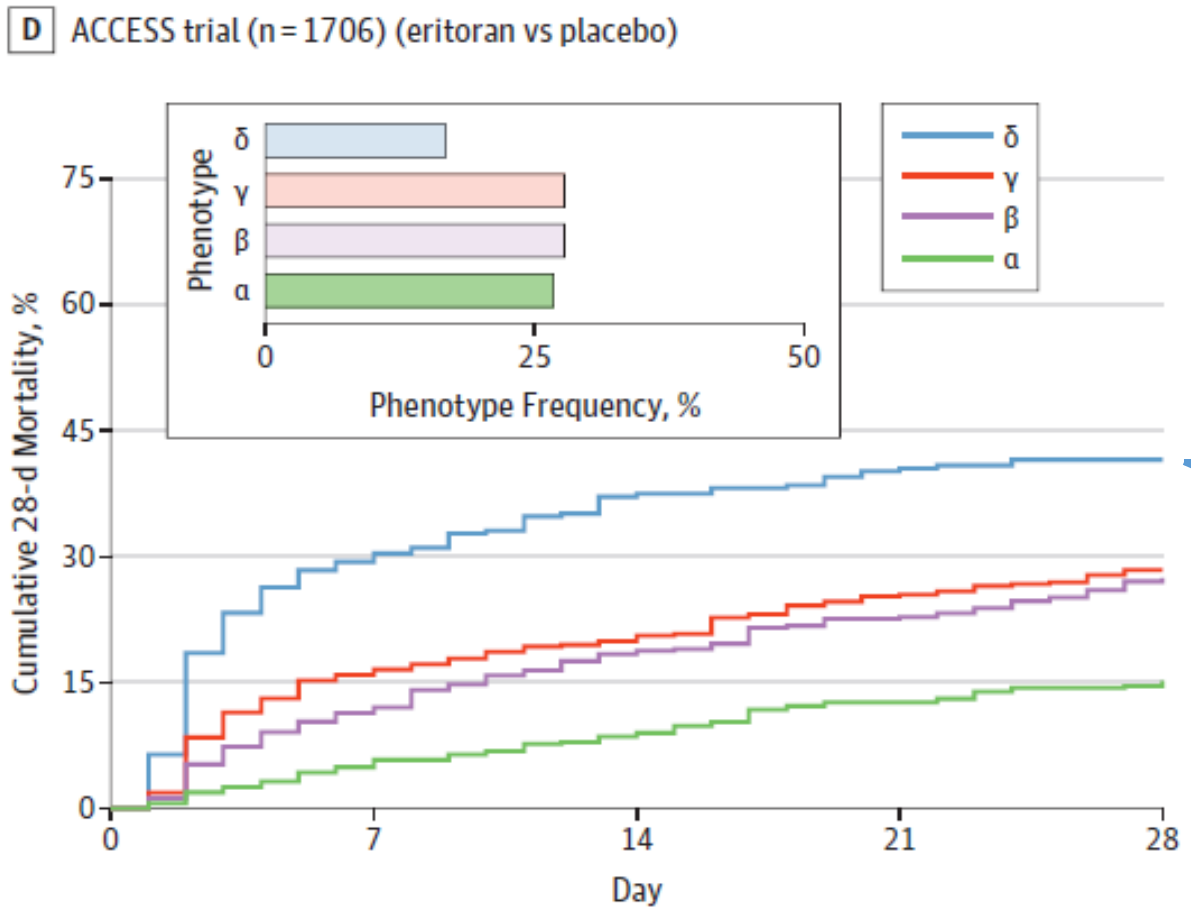
eTable 2. Availability of 27 biomarker measurements by dataset at baseline

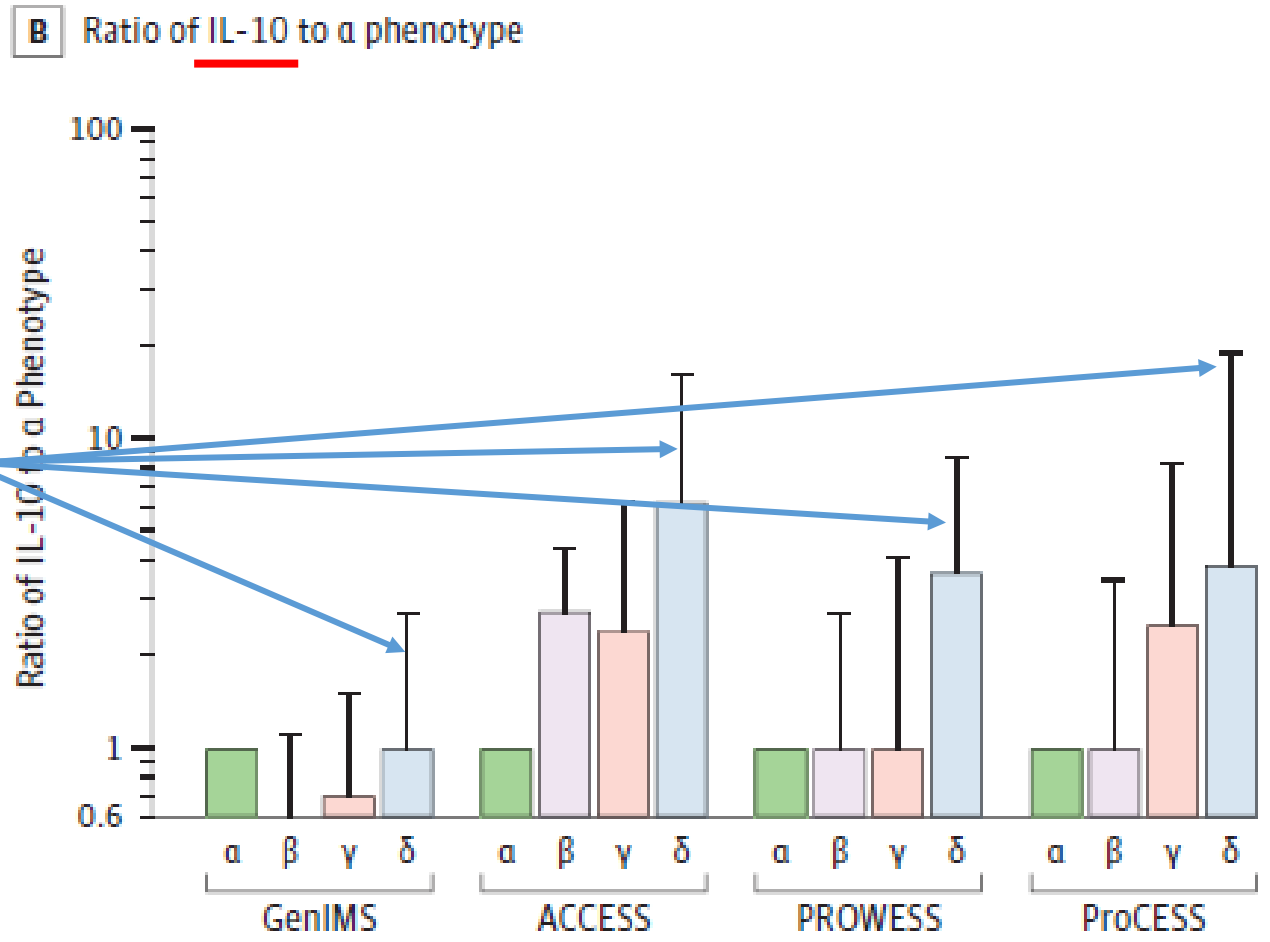
Biomarkers*	GenIMS	ACCESS	PROWESS	ProCESS
Antithrombin III	X		X	
C-Reactive Protein				X
COL-4				X
D-Dimer	X		X	X
E-Selectin				X
Factor V			X	
Factor IX	X			
ICAM				X
IGFBP-7				X
Interleukin-1b		X	X	
Interleukin-6	X	X	X	X
Interleukin-8		X	X	
Interleukin-10	X	X	X	X
Interleukin-12		X		
KIM-1				X
PAI-1	X		X	X
Plasminogen activity			X	
Procalcitonin	X	X		
Protein C Activity			X	
Protein S Activity			X	
Prothrombin			X	X
Prothrombin Fragment 1-2			X	
P-Selectin				X
TAT Complex	X		X	X
TIMP-2				X
TNF	X	X	X	X
VCAM				X

Abbreviations: ATP: adenosine triphosphate; COL: collage; ICAM: intracellular adhesion molecule; IGFBP: insulin-like growth factor-binding protein; KIM: kidney injury molecule; PAI: plasminogen activator inhibitor; TAT: Thrombin-Antithrombin; TIMP: tissue inhibitor of metalloproteinases TNF: tumor necrosis factor; VCAM: vascular adhesion molecule

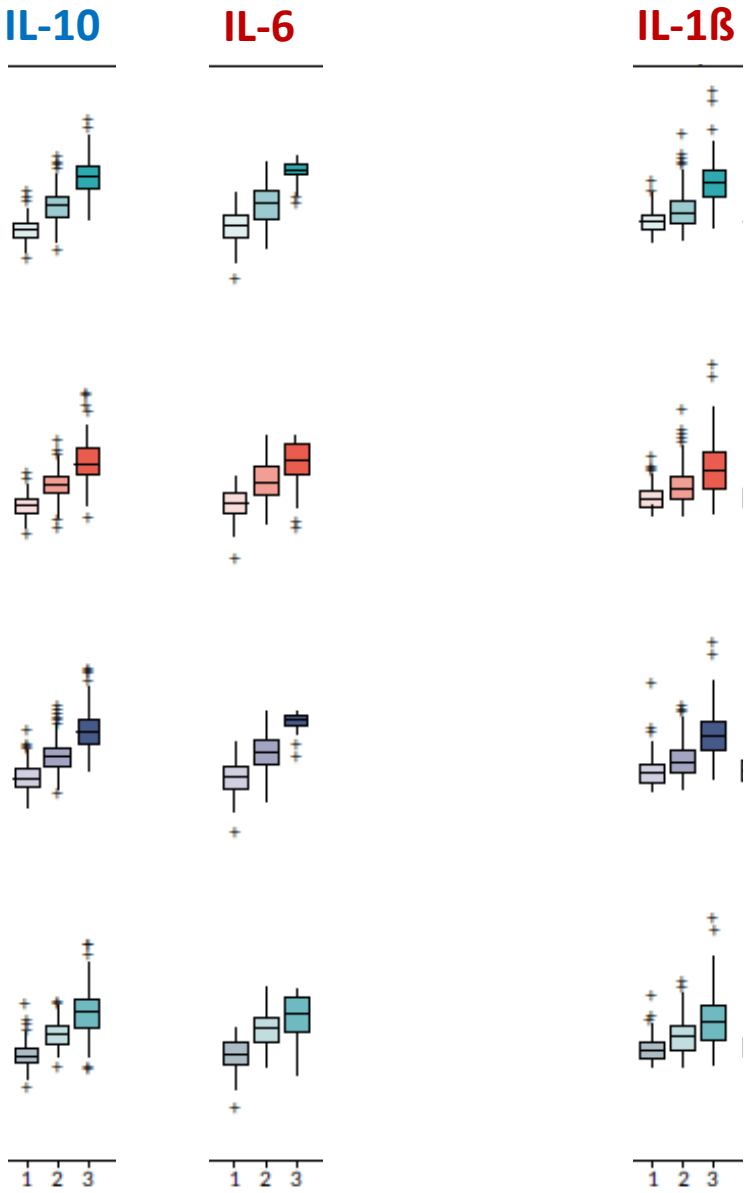


Higher Circulating IL-6 Correlates with Higher Mortality





LeoPARDS Trial (levosimendan) ISRCTN12776039



Efficacy and Mechanism Evaluation
Volume 8 • Issue 10 • July 2021
ISSN 2050-4365

Defining phenotypes and treatment effect heterogeneity to inform acute respiratory distress syndrome and sepsis trials: secondary analyses of three RCTs

Manu Shankar-Hari, Shalini Santhakumaran, A Toby Prevost, Josie K Ward, Timothy Marshall, Claire Bradley, Carolyn S Calfee, Kevin L Delucchi, Pratik Sinha, Michael A Matthay, Jonathan Hackett, Cliona McDowell, John G Laffey, Anthony Gordon, Cecilia M O'Kane and Daniel F McAuley

3 Endotypes in Sepsis-induced ARDS

Bruse *et al. Critical Care* (2022) 26:244
https://doi.org/10.1186/s13054-022-04118-6

Critical Care

BRIEF REPORT Open Access

Clinical sepsis phenotypes in critically ill COVID-19 patients

Niklas Bruse[1], Emma J. Kooistra[1], Aron Jansen[1], Rombout B. E. van Amstel[2], Nicolette F. de Keizer[3,4,5], Jason N. Kennedy[6], Christopher Seymour[6], Lonneke A. van Vught[2], Peter Pickkers[1] and Matthijs Kox[1*]

Results: Phenotype distribution was highly similar between COVID-19 and non-COVID-19 viral pneumonia sepsis cohorts, whereas the proportion of patients with the δ-phenotype was greater in both bacterial sepsis cohorts compared to the viral sepsis cohorts. The introduction of dexamethasone treatment was associated with an increased proportion of patients with the δ-phenotype (6% vs. 11% in the pre- and post-dexamethasone COVID-19 cohorts, respectively, $p < 0.001$). Across the cohorts, the α-phenotype was associated with the most favorable outcome, while the δ-phenotype was associated with the highest mortality. Survival of the δ-phenotype was markedly higher following the introduction of dexamethasone (60% vs 41%, $p < 0.001$), whereas no relevant differences in survival were observed for the other phenotypes among COVID-19 patients.

By a Retrospective Latent Class Analysis (LCA)

MEDICAL PROGRESS

The Pathophysiology and Treatment of Sepsis

Richard S. Hotchkiss, M.D., and Irene E. Karl, Ph.D.

Table 1. Potential Mechanisms of Immune Suppression in Patients with Sepsis.*

Shift from an inflammatory (Th1) to an antiinflammatory (Th2) response
Anergy
Apoptosis-induced loss of CD4 T cells, B cells, and dendritic cells
Loss of macrophage expression of major-histocompatibility-complex class II and costimulatory molecules
Immunosuppressive effect of apoptotic cells

NEJM 2003

Biomarker-guided Treatment Trials in Septic Patients

Immune cells	Markers and cut-off value	Intervention	Number of patients (to be enrolled)	Reference /Clinicaltrials.gov identifier	
Monocytes	HLA-DR expression < 8000 ABs/cell	GM-CSF	38	[97]	(Meisel et al., D)
	HLA-DR expression < 8000 ABs/cell at day 3	GM-CSF	166 *	NCT02361528	(GRID, FR)?
	HLA-DR MFI < 150 for 48 hours	GM-CSF	9	[96]	(Nierhaus et al., D)
	HLA-DR positive monocytes < 30%	IFNγ	9 278 *	[92] NCT03332225	(Döcke et al., D) (PROVIDE, GR)
	LPS-stimulated TNFα production < 160 pg/mL	GM-CSF	14	[98]	(Hall et al., Pediatric, USA)
Lymphocytes	< 0.9 *10^9 lymphocytes/L	IL-7	27	[104]	(IRIS-7, USA/FR)
Neutrophils	Phagocytic capacity < 50%	GM-CSF	64 *	NCT01653665	(GMCSF, UK)?

Niklas Bruse, Guus P. Leijte, Peter Pickkers & Matthijs Kox (2018) EXPERT REVIEW OF CLINICAL IMMUNOLOGY

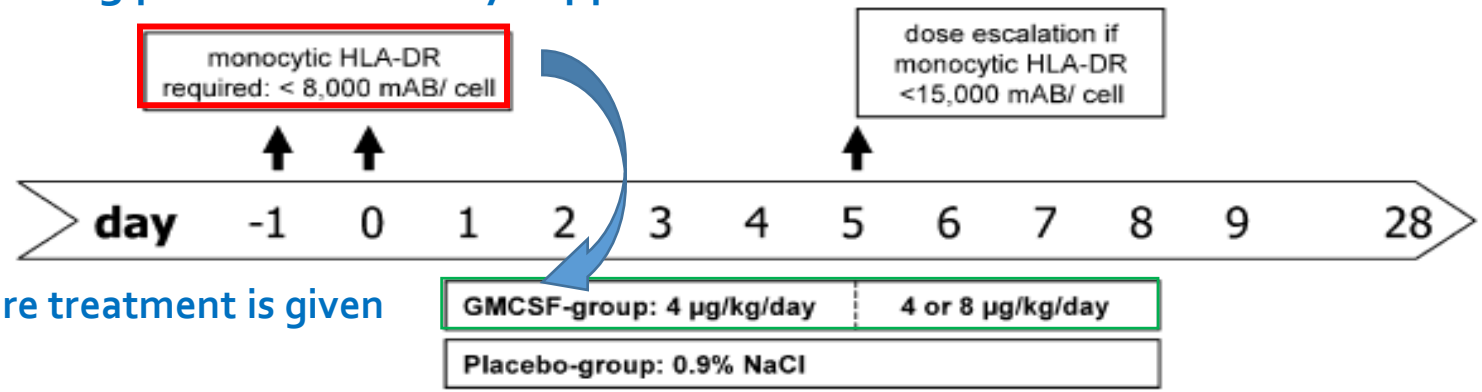
The first biomarker-based immuno-stimulatory trial (2009)

Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

A Double-Blind, Randomized, Placebo-controlled Multicenter Trial

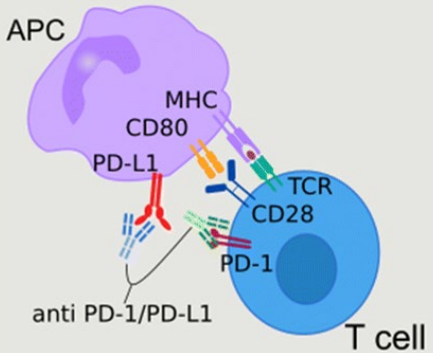
Christian Meisel[1]*, Joerg C. Schefold[2]*, Rene Pschowski[2], Tycho Baumann[1], Katrin Hetzger[1], Jan Gregor[3], Steffen Weber-Carstens[4], Dietrich Hasper[2], Didier Keh[4], Heidrun Zuckermann[3], Petra Reinke[2,5], and Hans-Dieter Volk[1,5]

confirming patients are really suppressed



Treatment restored monocytic immunocompetence & improved clinical endpoints (ventilation-free days, APACHE II)

Blocking wth Nivolumab/BMS-936559



T cell exhaustion reversed*

↓

Immunosuppression reduced

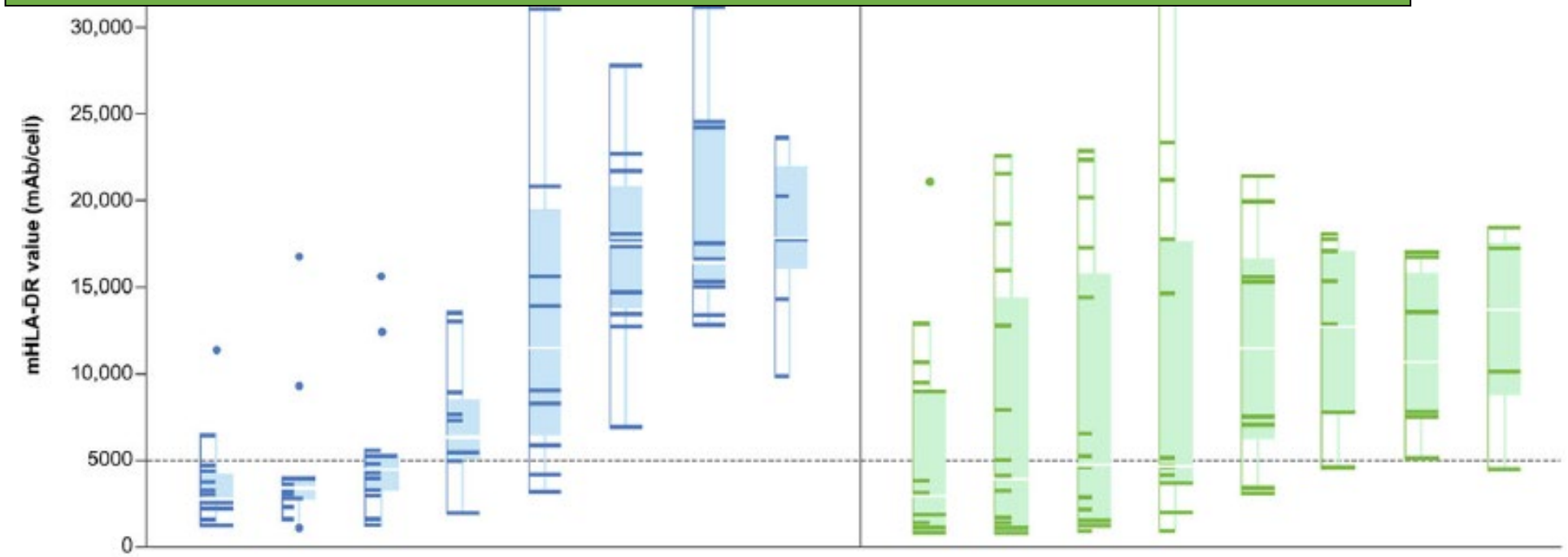
↓

Outcome?

Intensive Care Med. 2019 October ; 45(10): 1360–1371. doi:10.1007/s00134-019-05704-z.

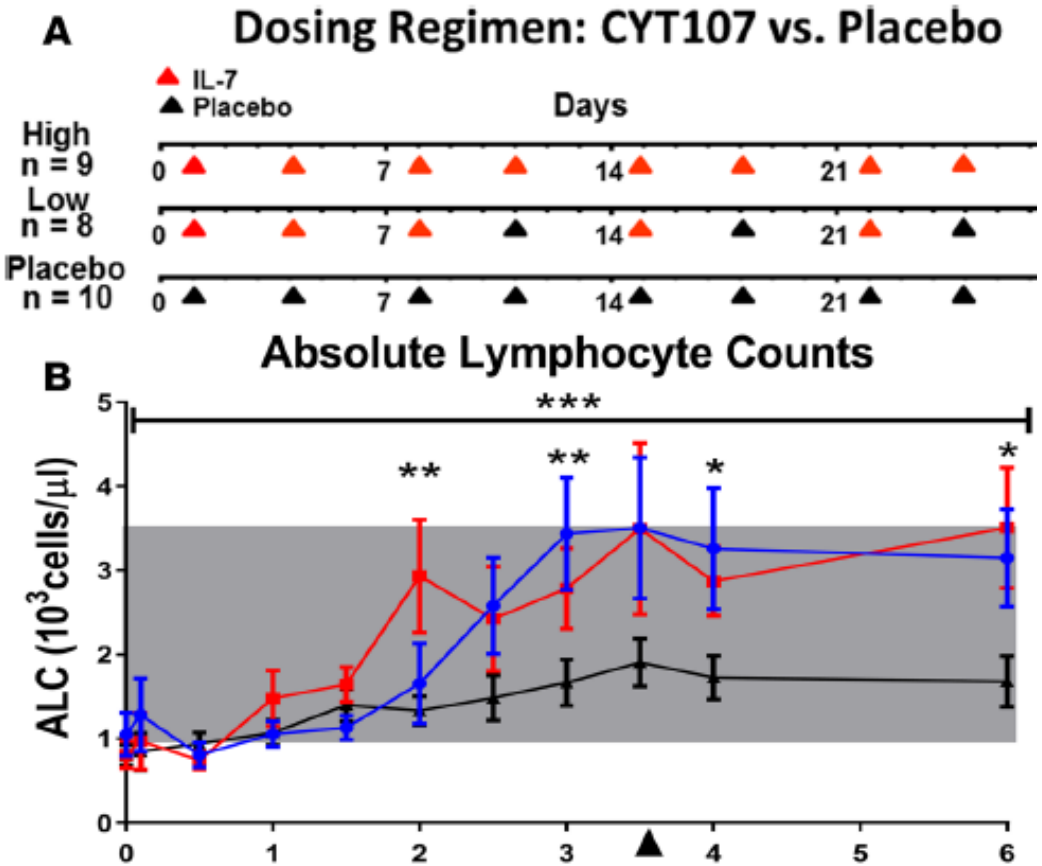
Immune checkpoint inhibition in sepsis: a Phase 1b randomized study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of nivolumab

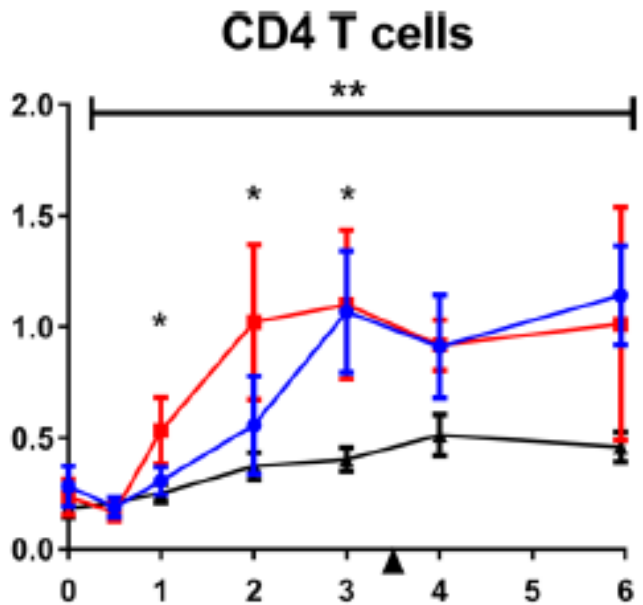
Restoration of HLA-DR on Monocytes; Increase of absolute LYM counts; No „Cytokine Storm“

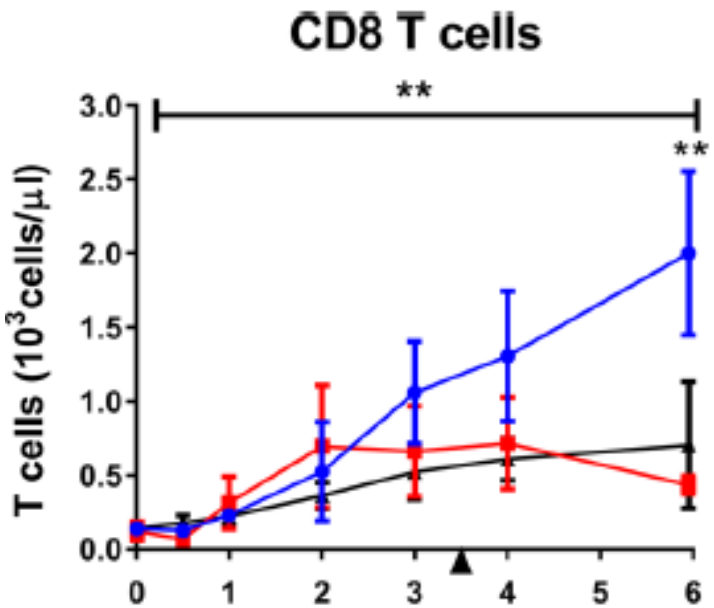


Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial

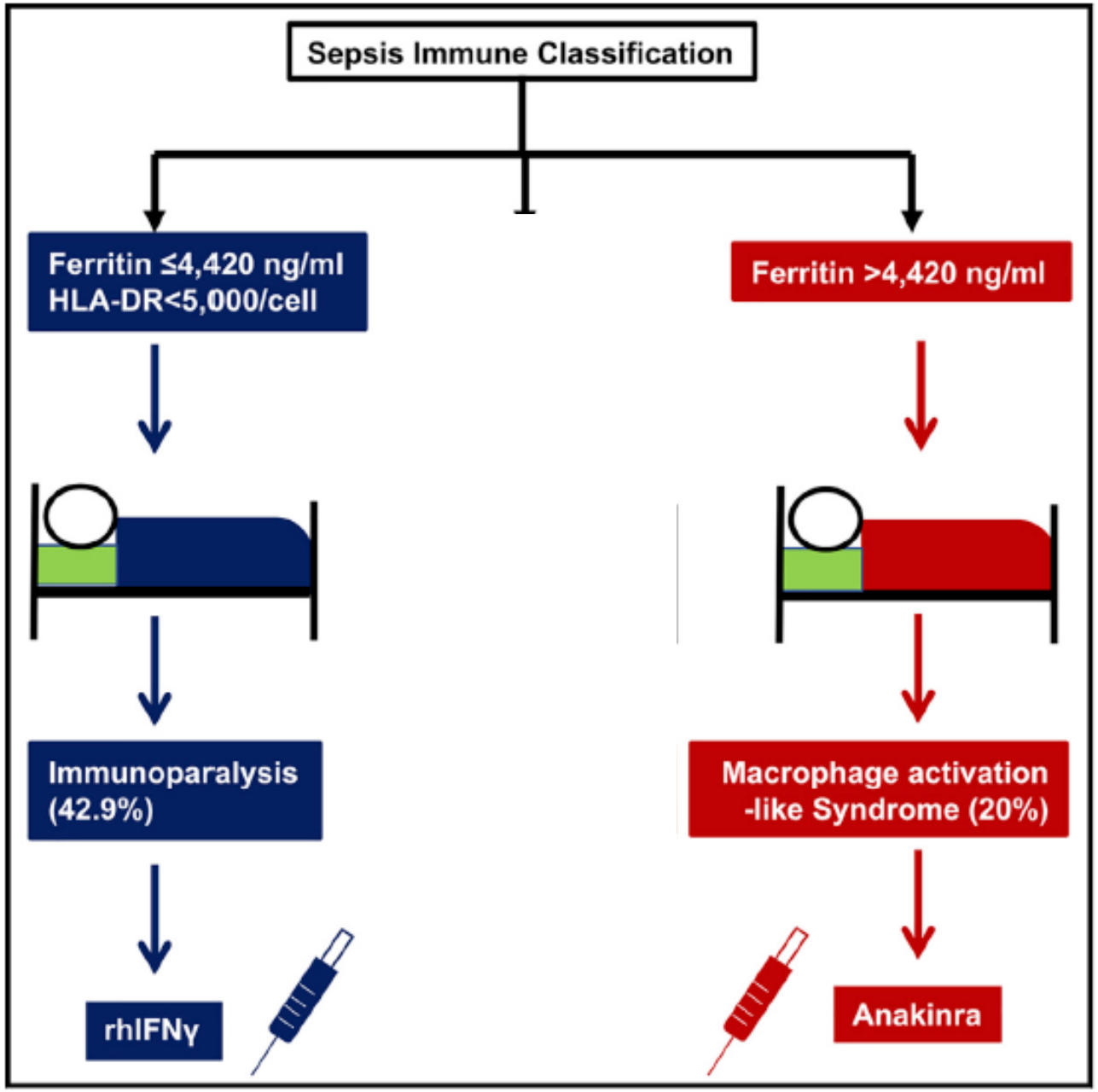
Bruno Francois,[1,2,3] Robin Jeannet,[2] Thomas Daix,[1,2] Andrew H. Walton,[4] Matthew S. Shotwell,[5] Jacqueline Unsinger,[4] Guillaume Monneret,[6,7] Thomas Rimmelé,[7,8] Teresa Blood,[4] Michel Morre,[9] Anne Gregoire,[9] Gail A. Mayo,[10] Jane Blood,[4] Scott K. Durum,[11] Edward R. Sherwood,[10,12] and Richard S. Hotchkiss[4,13,14]







JCI Insight. 2018;3(5):e98960.



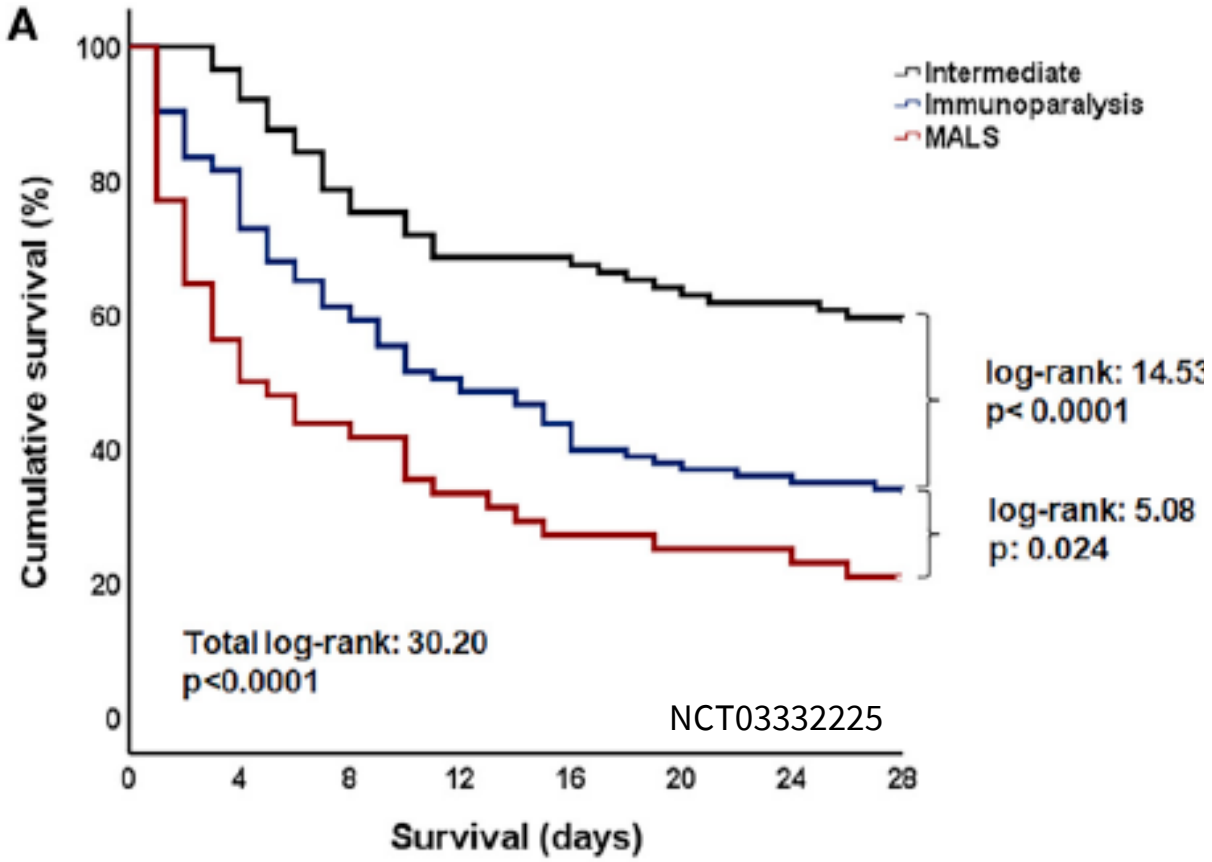
EudraCT number 2017-002171-26
ClinicalTrials.gov NCT03332225

↑Circulating ferritin & ↓HLA-DR expression (on CD14 monocytes)

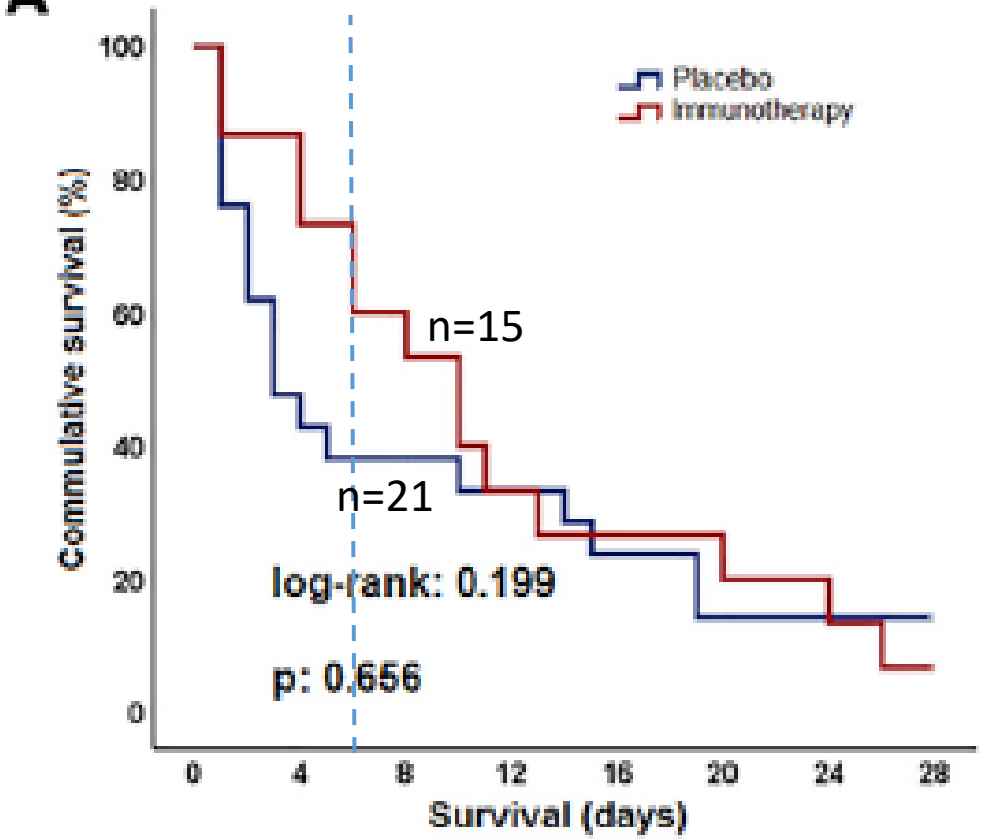
Cell Reports Medicine
Article

November 15, 2022

Toward personalized immunotherapy in sepsis: The PROVIDE randomized clinical trial



Only MALS/anakinra arm tested



Target: 280 participants/26 centers

ClinicalTrials.gov Identifier: NCT04990232

NIH U.S. National Library of Medicine
ClinicalTrials.gov

ARTICLES
https://doi.org/10.1038/s41591-021-01499-z

nature medicine

Check for updates

OPEN

Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial

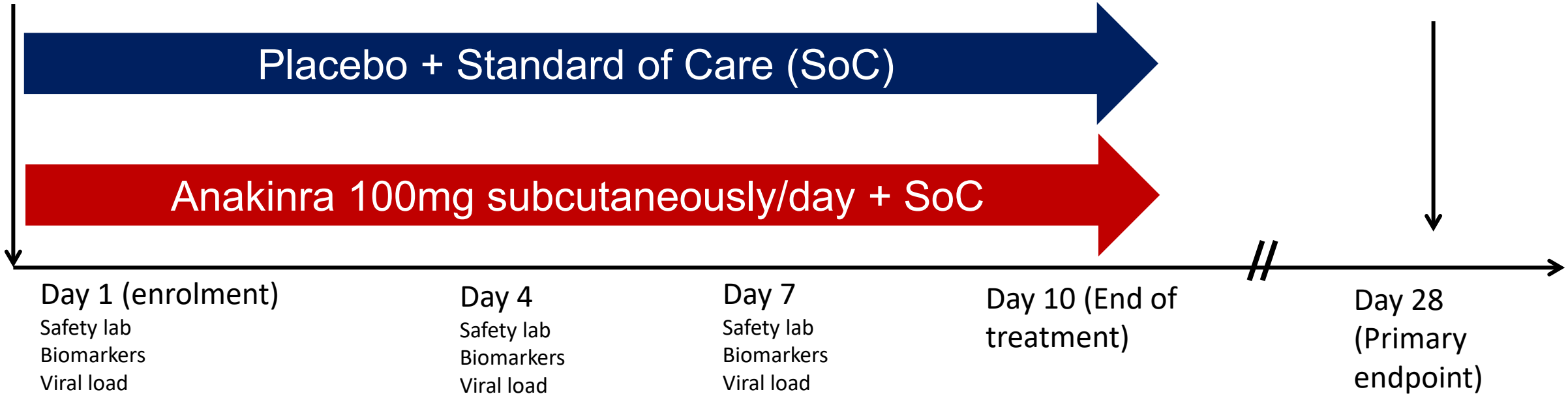
Evdoxia Kyriazopoulou[1], Garyfallia Poulakou[2], Haralampos Milionis[3], Simeon Metallidis[4], Georgios Adamis[5], Konstantinos Tsiakos[6], Archontoula Fragkou[7], Aggeliki Rapti[6], Christina Damoulari[1], Massimo Fantoni[8], Ioannis Kalomenidis[9], Georgios Chrysos[10], Andrea Angheben[11], Ilias Kainis[12], Zoi Alexiou[13], Francesco Castelli[14], Francesco Saverio Serino[15], Maria Tsilika[1], Petros Bakakos[16], Emanuele Nicastri[17], Vassiliki Tzavara[18], Evangelos Kostis[19], Lorenzo Dagna[20], Panagiotis Koufargyris[1], Katerina Dimakou[21], Spyridon Savvanis[7], Glykeria Tzatzagou[22], Maria Chini[23], Giulio Cavalli[20], Matteo Bassetti[24], Konstantina Katrini[1], Vasileios Kotsis[25], George Tsoukalas[26], Carlo Selmi[27], Ioannis Bliziotis[28], Michael Samarkos[29], Michael Doumas[30], Sofia Ktena[1], Aikaterini Masgala[31], Ilias Papanikolaou[32], Maria Kosmidou[3], Dimitra-Melia Myrodia[2], Aikaterini Argyraki[33], Chiara Simona Cardellino[11], Katerina Koliakou[34], Eleni-Ioanna Katsigianni[34], Vassiliki Rapti[2], Efthymia Giannitsioti[10], Antonella Cingolani[8], Styliani Micha[34], Karolina Akinosoglou[35], Orestis Liatsis-Douvitsas[34], Styliani Symbardi[36], Nikolaos Gatselis[37], Maria Mouktaroudi[1,34], Giuseppe Ippolito[17], Eleni Florou[34], Antigone Kotsaki[1], Mihai G. Netea[38,39], Jesper Eugen-Olsen[40], Miltiades Kyprianou[34], Periklis Panagopoulos[41], George N. Dalekos[37] and Evangelos J. Giamarellos-Bourboulis[1,34] ✉

THE SAVE-MORE RCT

Inclusion criteria

- Age ≥18 years, both genders, ICF
- Confirmed SARS-CoV-2 infection
- LRTI: positive chest-X-ray or CT
- **Plasma suPAR ≥6ng/ml**

PRIMARY ENDPOINT
11-point WHO ordinal scale



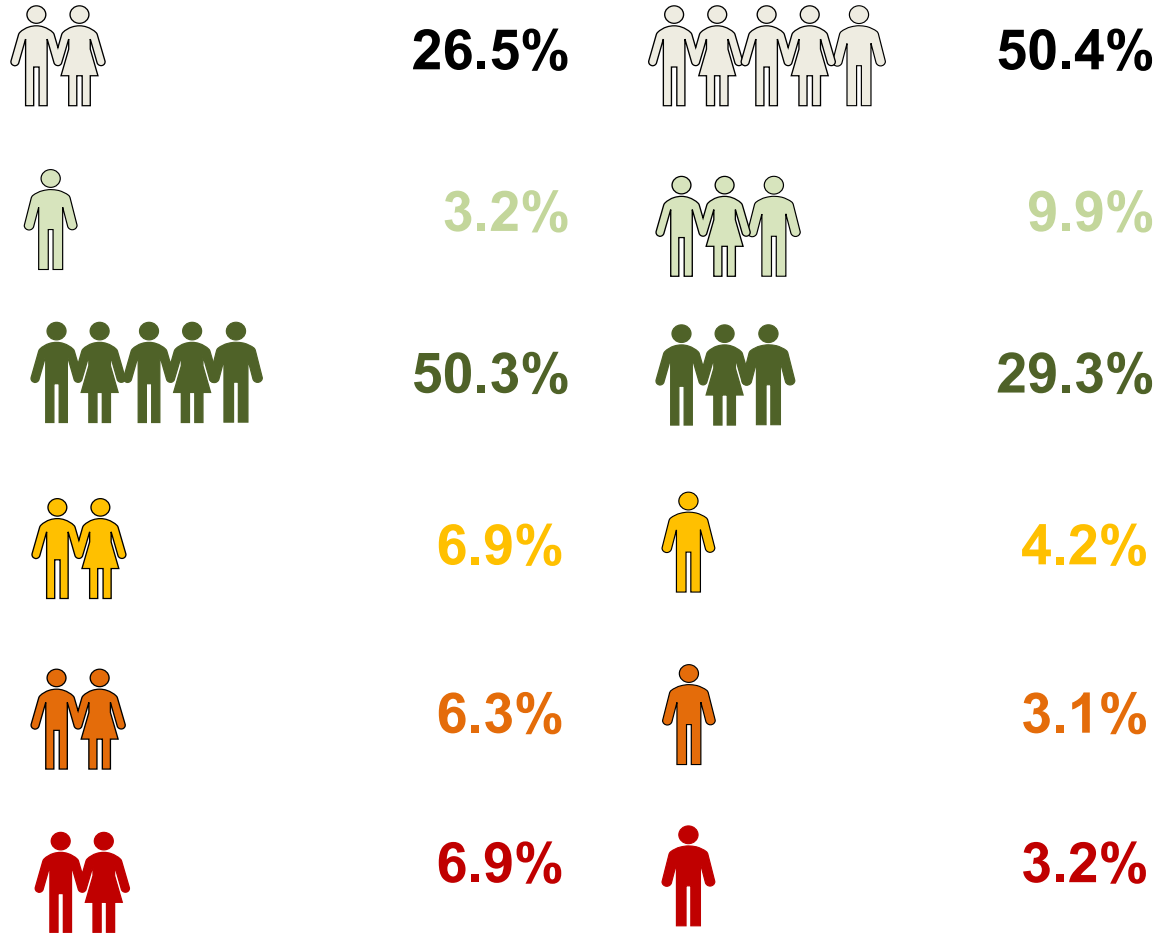
CT: computed tomography
ICF: written informed consent form
LRTI: lower respiratory tract infection
SOC: standard-of-care
suPAR: soluble urokinase Plasminogen Activator Receptor

Adding anakinra to current Standard-of-Care (SoC)

2.8 times more likely to improve overall clinical status

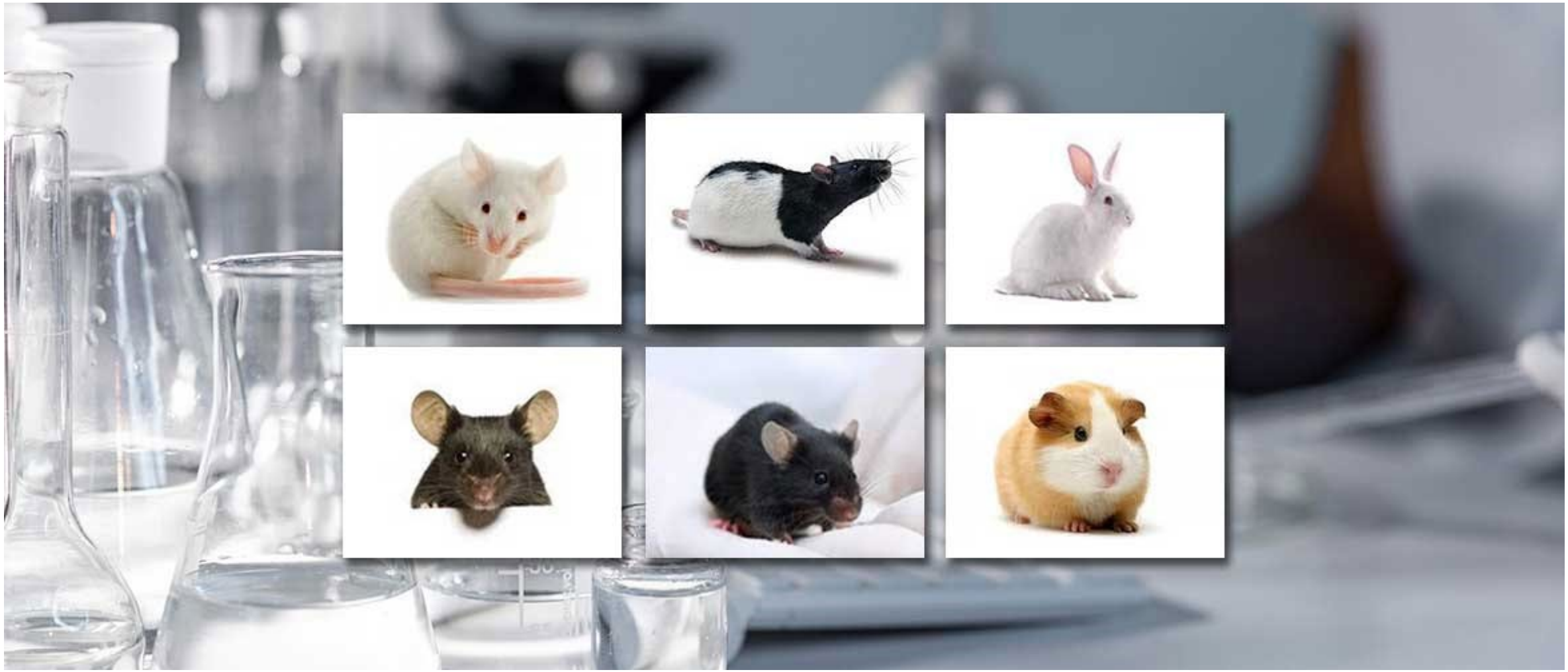
towards completely resolving the viral infection and preventing severe respiratory failure/death

Patient state	SoC + Placebo	SoC + Anakinra
Fully recovered, PCR(-)	26.5%	50.4%
Asymptomatic, PCR (+)	3.2%	9.9%
Ambulatory, with symptoms	50.3%	29.3%
Hospitalized, moderate disease	6.9%	4.2%
Hospitalized, severe disease	6.3%	3.1%
Dead	6.9%	3.2%



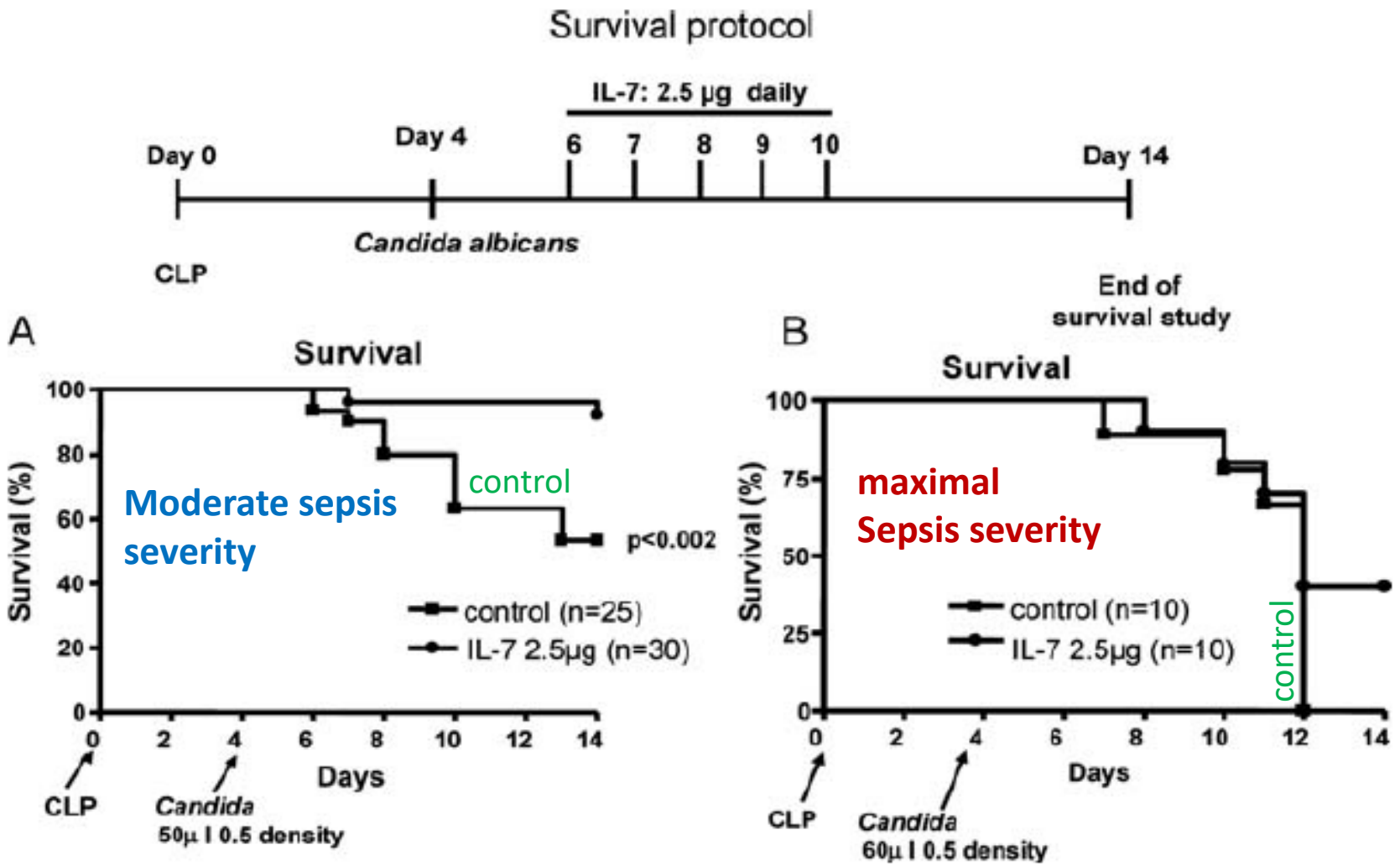
Kyriazopoulou E et al: Nat Med. 2021 Oct;27(10):1752-1760

Can Animal Models of Sepsis Aid in Testing the Phenotyping Concept?



Interleukin-7 Ameliorates Immune Dysfunction and Improves Survival in a 2-Hit Model of Fungal Sepsis

Jacqueline Unsinger,[1] Carey-Ann D. Burnham,[2] Jacquelyn McDonough,[1] Michel Morre,[3] Priya S. Prakash,[4] Charles C. Caldwell,[4] W. Michael Dunne, Jr.,[2] and Richard S. Hotchkiss[1,5,6]



Seymour *et al. Critical Care* (2019) 23:384
https://doi.org/10.1186/s13054-019-2655-7

Critical Care

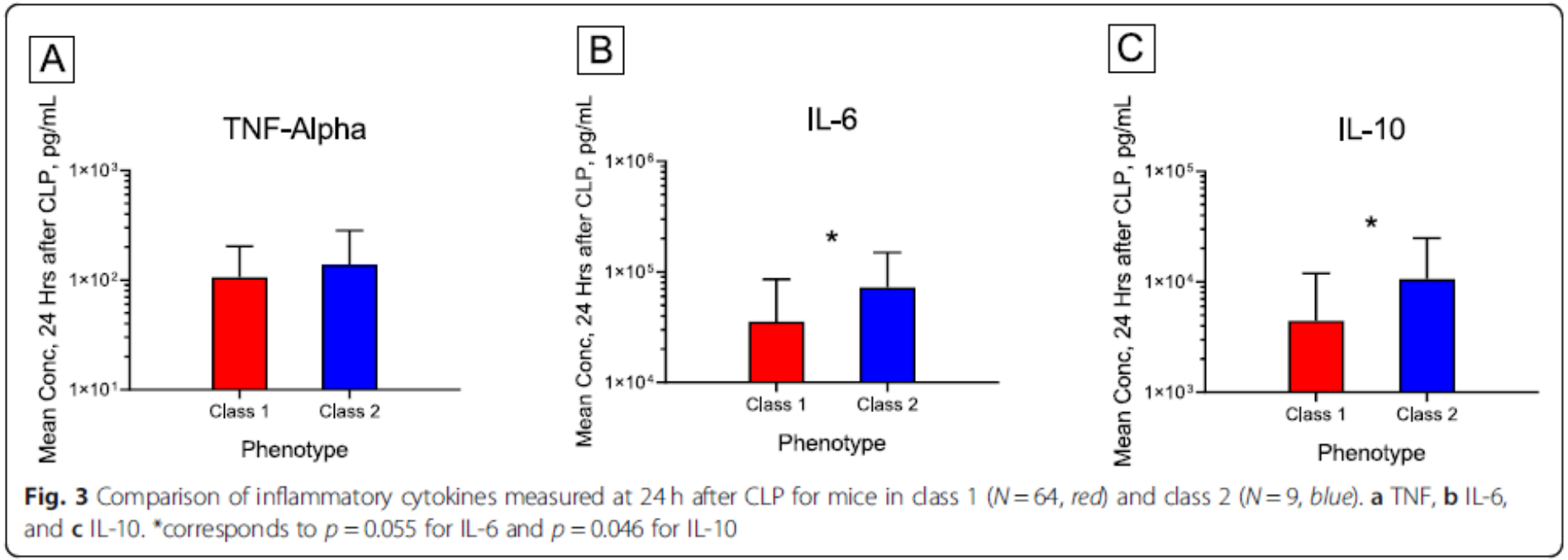
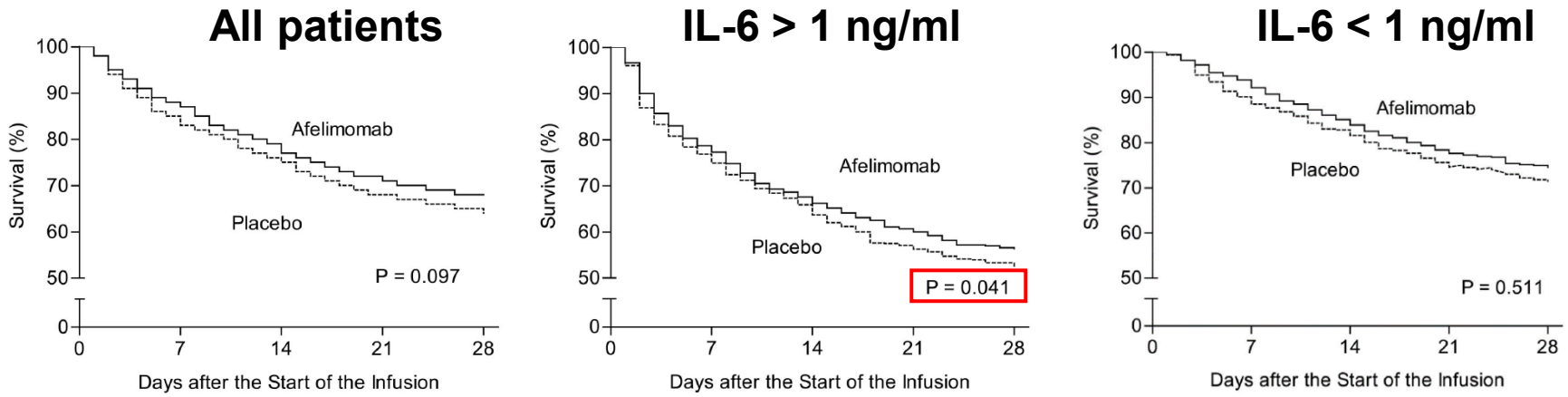


Fig. 3 Comparison of inflammatory cytokines measured at 24 h after CLP for mice in class 1 ($N = 64$, *red*) and class 2 ($N = 9$, *blue*). **a** TNF, **b** IL-6, and **c** IL-10. *corresponds to $p = 0.055$ for IL-6 and $p = 0.046$ for IL-10

Conclusions: We identified two sepsis phenotypes in a murine cecal ligation and puncture model, one of which is characterized by faster deterioration and more severe inflammation. Response to treatment in a randomized trial of immediate versus delayed antibiotics and fluids differed on the basis of phenotype.

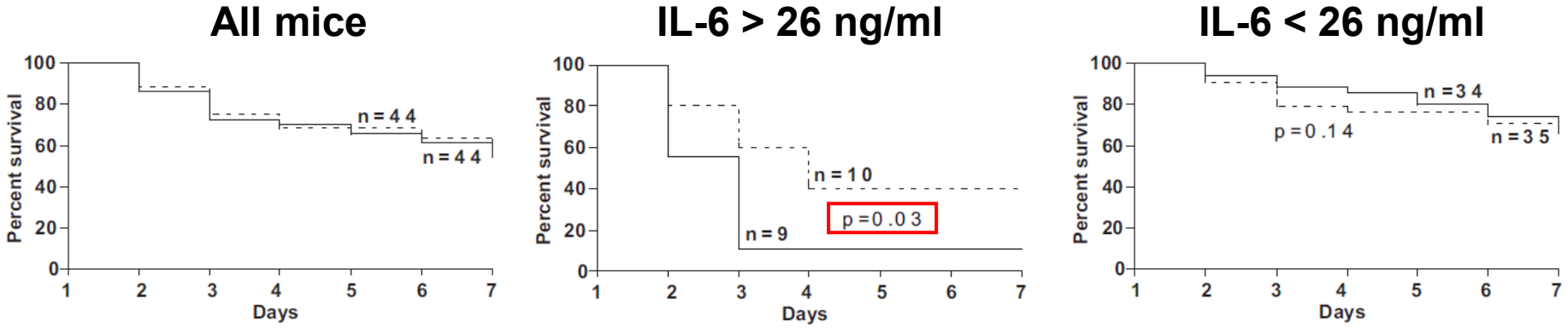
IL-6 – based Risk-Stratification for Sepsis Treatment

Clinical: anti-TNF (afelimomab) in severly septic patients



Panacek *et al.* Crit Care Med. 2004

Preclinical: corticosteroids (dexamethasone) in stratified septic mice



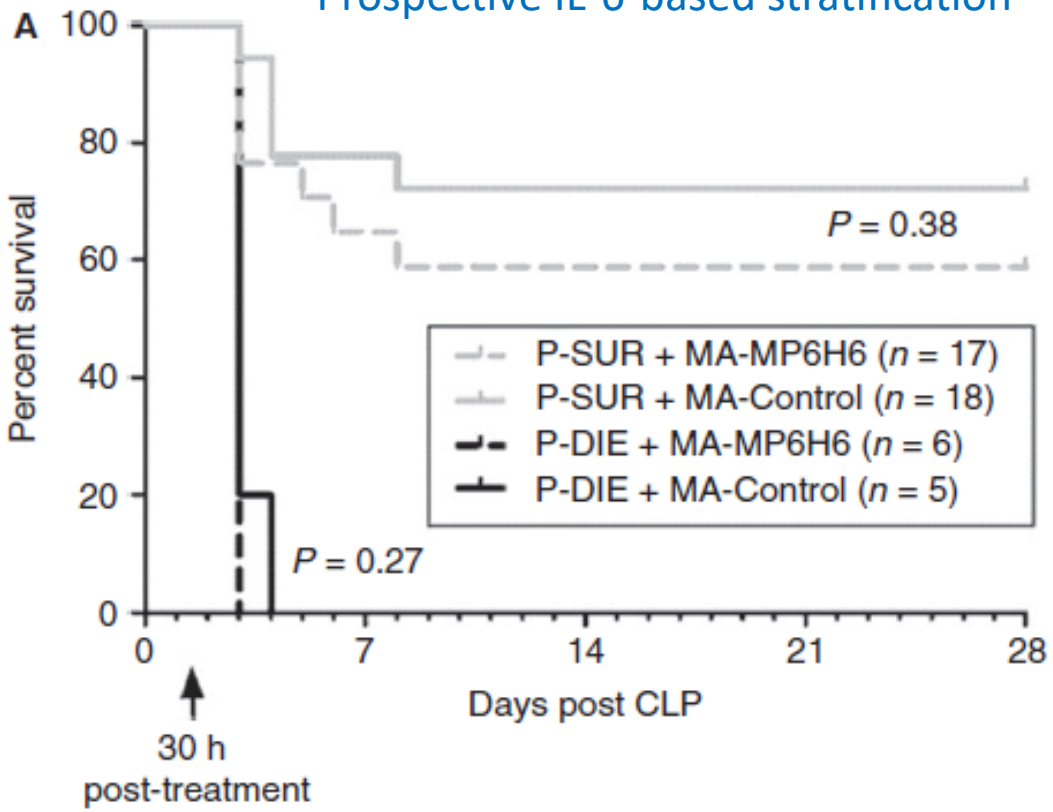
Osuchowski *et al.* Crit Care Med. 2009

J Thromb Haemost 2014; **12**: 958–69.

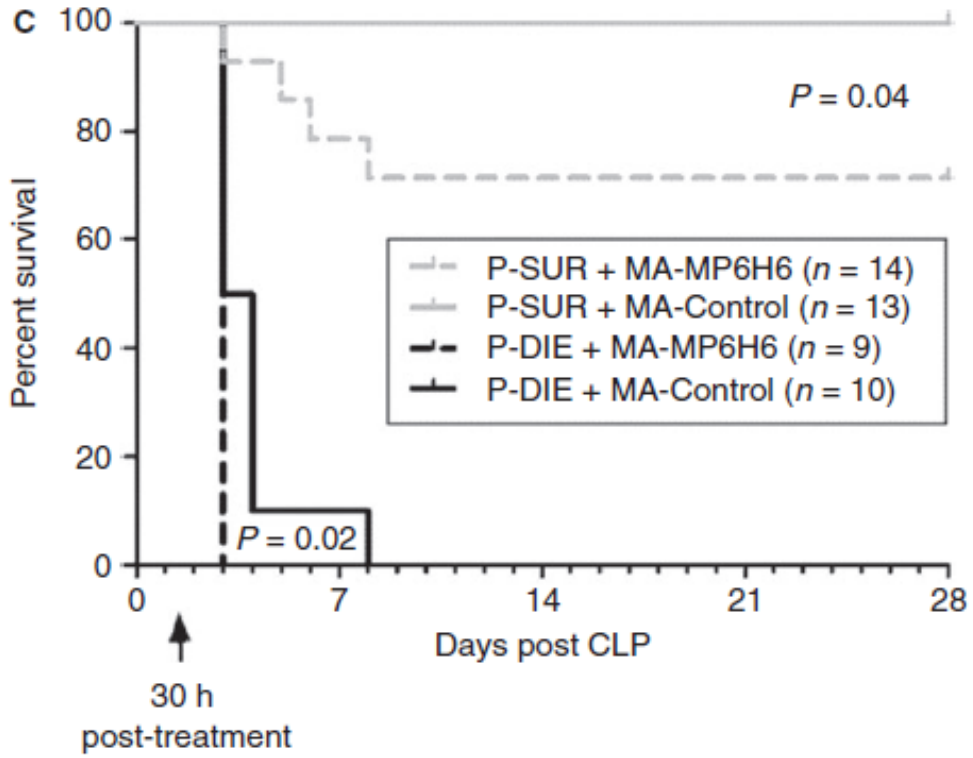
Systemic inhibition and liver-specific over-expression of PAI-1 failed to improve survival in all-inclusive populations or homogenous cohorts of CLP mice

P. RAEVEN,*§ S. DRECHSLER,* K. M. WEIXELBAUMER,* D. BASTELICA,† F. PEIRETTI,† A. KLOTZ,* M. JAFARMADAR,* H. REDL,* S. BAHRAMI,* M. C. ALESSI,† P. J. DECLERCK‡ and M. F. OSUCHOWSKI*

Prospective IL-6-based stratification



Retrospective (adjusted) IL-6-based stratification



Potential (near/distant) Options to Consider:

All septic patients → **“Extreme-end” patients**

Any septic patient → **Specific patients**
(e.g. only abdominal sepsis)

One-directional
(suppression or boosting) → **Two-directional**
(suppression & boosting)

Single markers → **Combinations of markers**

Classical RCTs → **Adaptive RCTs**

„Rough“ pre-clinical checks → **Diligent pre-clinical checks**

An Open Mind and Wide Perspective is a Must…

LUDWIG BOLTZMANN INSTITUTE
Traumatology
The Research Center in Cooperation with AUVA

AUVA

Tentative Program:
20th Congress of the European Shock Society, Vienna, Austria

Wed 20-9-23	Thursday 21-9-2023	Friday 22-9-2023	Saturday 23-9-2023

VS

ESS Board Meeting	*uences of Acute Illness*	*are Useful*	*Coagulopathy in Trauma, Sepsis and COVID-19*	Technological Palantir: *in Silico Modeling*
	Get-together: University of Vienna			
	Faculty Dinner		**Organ Concert**	

ESS General Assembly

ESS Gala Dinner: Vienna City Hall

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📰 Press news: SeptiCyte® RAPID 🔬🦠 Receives 510(k) clearance by US FDA ✅ 👉 First partner test fully ported + approved for commercialization on Idylla ✅ 👉 Congrats to our partner @Immunexpress! 👏 👉 Interested on bringing your test on Idylla? biocartis.com/en

5:43 PM · Nov 30, 2021

Rapid whole blood PCR-based platform for selected innate immunity gene expression

The Shock Society
@ShockSociety

IntelliSep® is the first FDA-cleared diagnostic tool to assess cellular host response to aid in identifying emergency department patients with sepsis and contribute to rapid life-saving decisions.

Continue Reading: ow.ly/HITC50MwnBQ

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Innate immunity activation endpoints in neutrophils & monocytes by microfluidics

SHOCK, Vol. 4, No. 2, pp. 89–95, 1995

J Immunol May 1, 1992, 148 (9) 2724-2730

BLOCKADE OF TUMOR NECROSIS FACTOR REDUCES LIPOPOLYSACCHARIDE LETHALITY, BUT NOT THE LETHALITY OF CECAL LIGATION AND PUNCTURE

Daniel Remick*, Prerana Manohar*, Gerald Bolgos*, Jorge Rodriguez*, Lyle Moldawer‡ and Gordon Wollenberg*

*‡Department of Surgery, University of Florida, Gainesville, Florida 32610; and *Departments of Pathology and Surgery, University of Michigan, Ann Arbor, Michigan 48109-0602*

ABSTRACT—Inhibition of tumor necrosis factor (TNF) bioactivity has afforded protection in several animal models of sepsis. We examined whether inhibition of TNF could improve survival after lethal lipopolysaccharide (LPS) or cecal ligation and puncture (CLP) in CD-1 or BALB\c mice. Neutralizing rabbit anti-TNF antisera were evaluated in CD-1 mice by injecting the antisera 3 h before intravenous (i.v.) LPS (600 μg). Implantable radiotransmitters were used for continuous monitoring of temperature. No decrease in mor-

inhibition of TNF fails to reduce mortality in a more clinically relevant model of sepsis.

performed followed by administration of antibiotics. -TNF did not decrease pulmonary neutrophil sequestration, improve survival, or prevent the decrea in temperature observed as sepsis developed. CLP was performed in the BALB\c mice using antibio plus anti-TNF antisera, but no protection was observed. Our results demonstrate that anti-TNF treatm prevents LPS mortality only when using certain strains of mice and inhibition of TNF fails to reduce mortality in a more clinically relevant model of sepsis.