LA RÉPONSE DE L'HÔTE LORS D'UNE AGRESSION (INFECTIEUSE OU ORAGE CYTOKINIQUE) ET DÉFAILLANCE D'ORGANES

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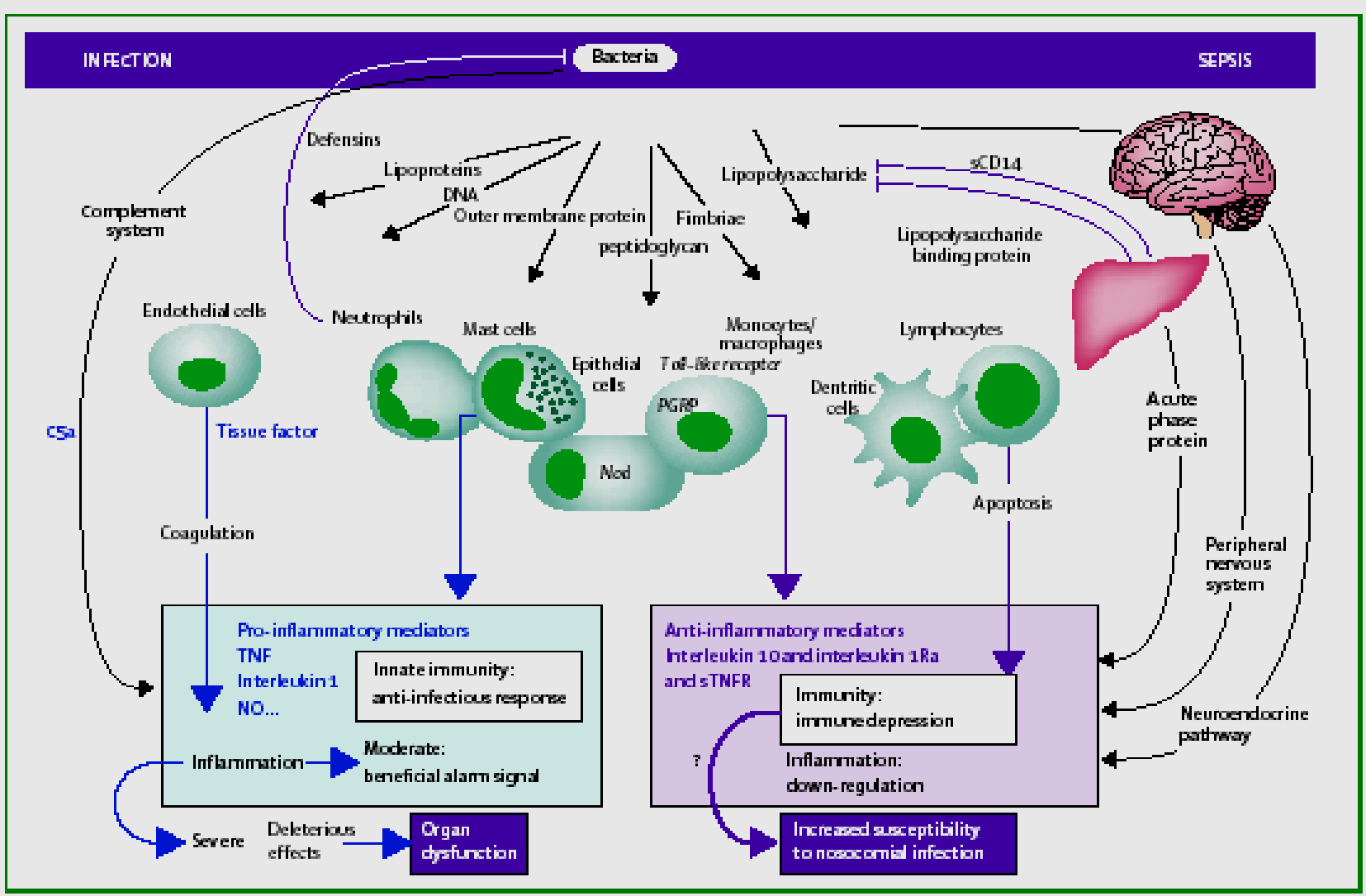
Conflict of Interest

- Financial:
  - since 1995 I have received multiple grants from French ministry of health, French ministry of higher education, research and innovation, various European research programs, from charity entities - french national programme d'investissement d'avenir: anr rhu 004
  - In 2021/2022/2023 I received honorarium to contribute to several advisory board (Pfizer, Baxter, Biomerieux, Janssen) and industry sponsored symposium (Baxter, Biomerieux, Alexion)
- Academic :
  - I contribute to SSC 2008/2012/2016 updates
  - I co-chair the Task Force of CIRCI/corticosteroids in the ICU guidelines, since 2008
  - Corticosteroids for acute inflammation is the main topic of research of my group since 1991

FHU SEPSIS
Personalized Interventions

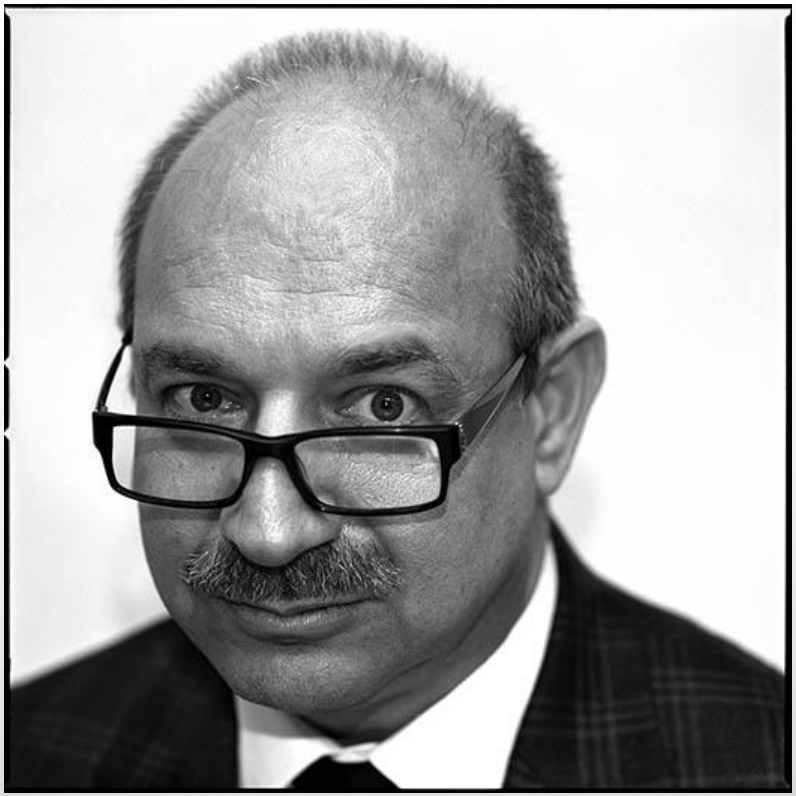
A life-threatening Disease

De la Bactérie au Choc septique

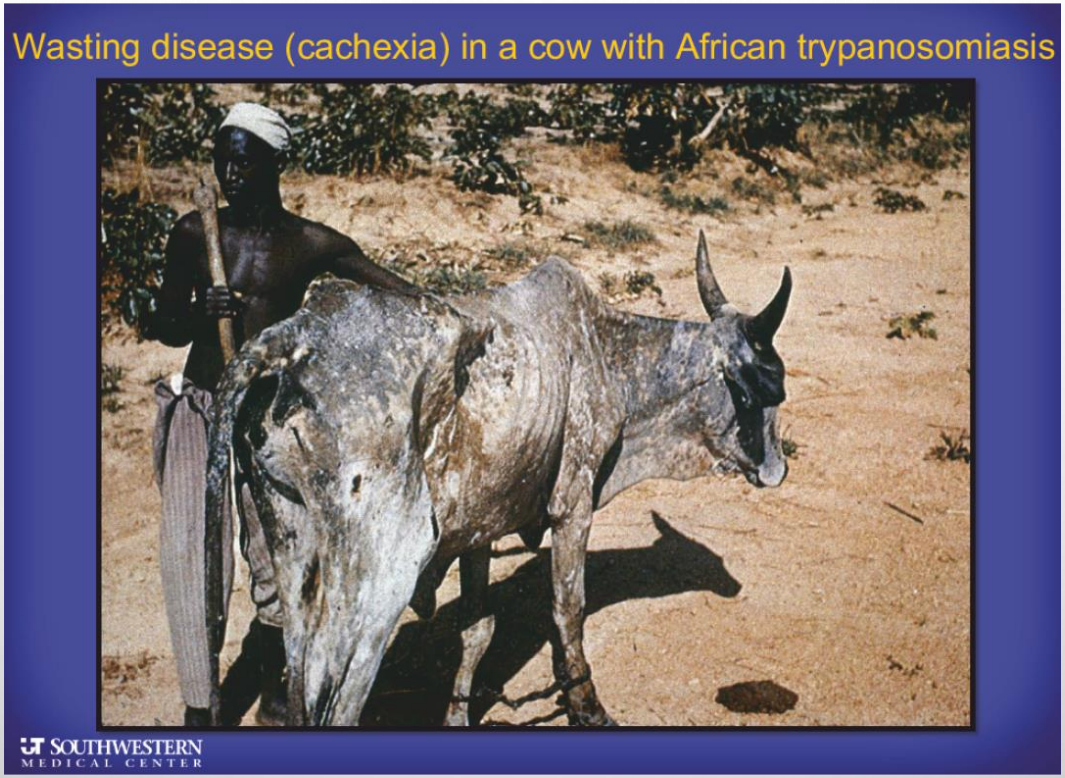


Annane Lancet 2005

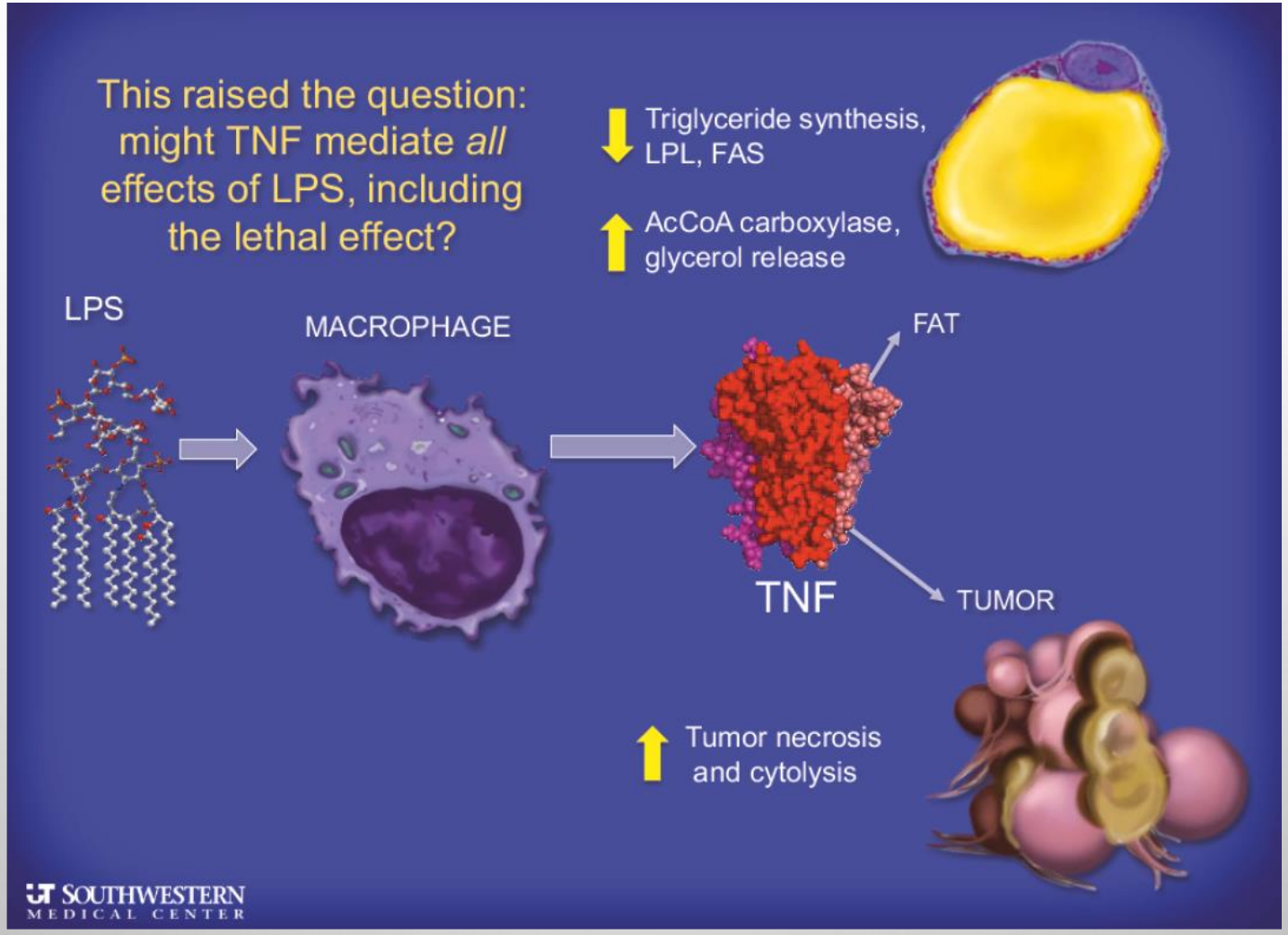
2011 Nobel Prize in Physiology or Medicine



Bruce Beutler

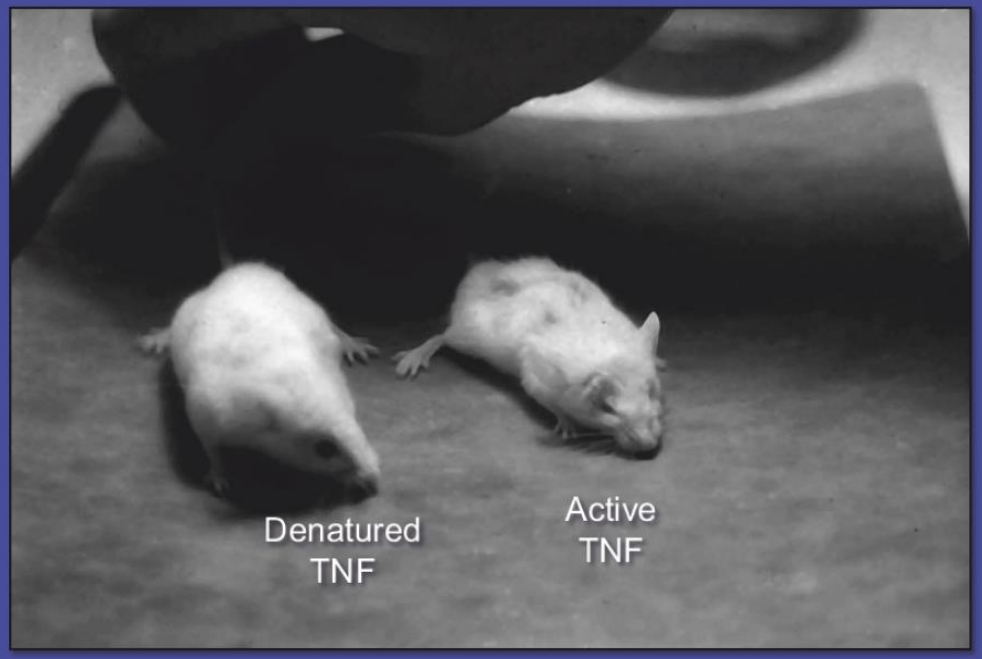


Beutler, Nobel Prize Lecture, 2011



Beutler, Nobel Prize Lecture, 2011

Purified TNF mimics LPS toxicity



1984

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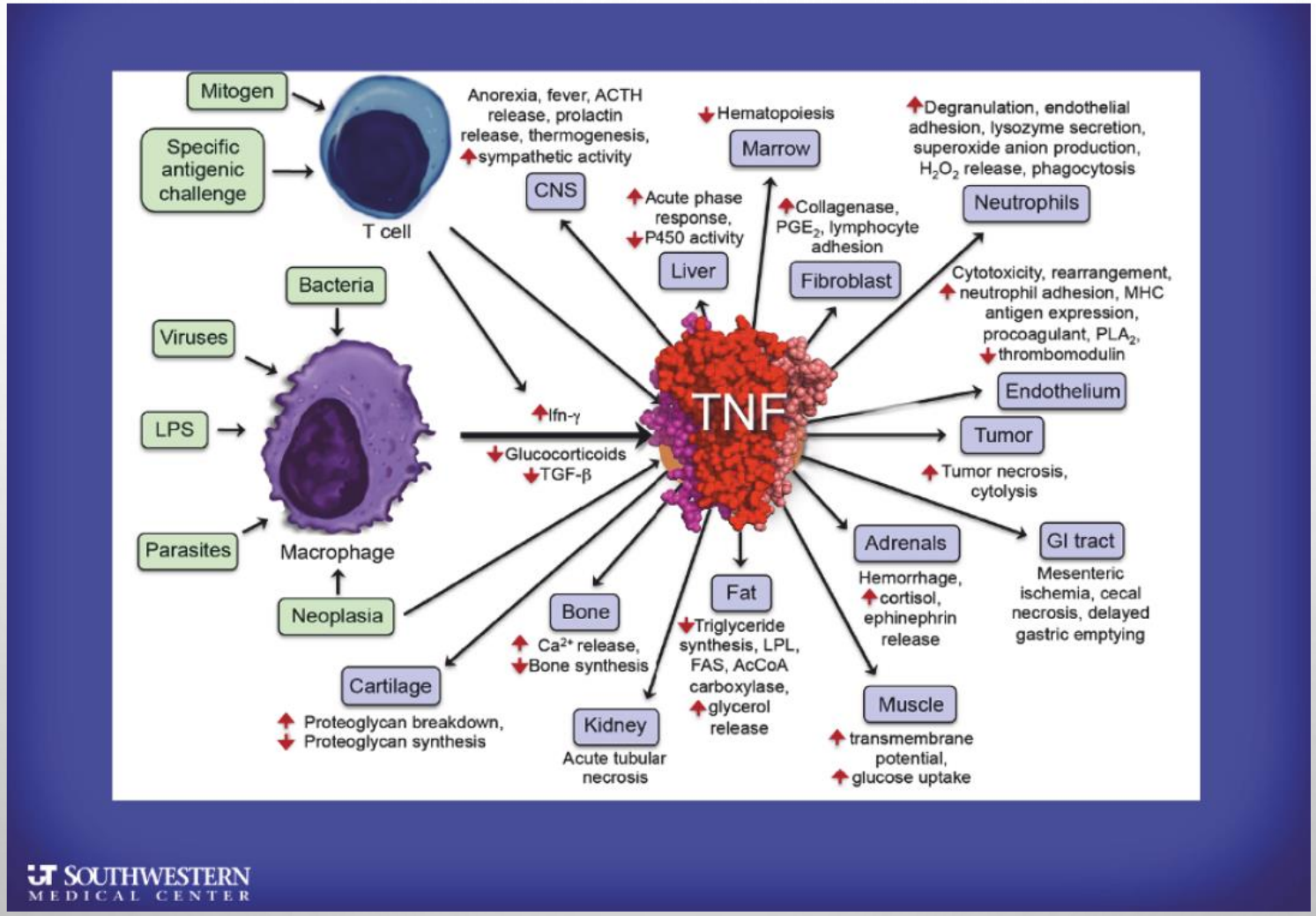
Beutler, Nobel Prize Lecture, 2011



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Beutler, Nobel Prize Lecture, 2011

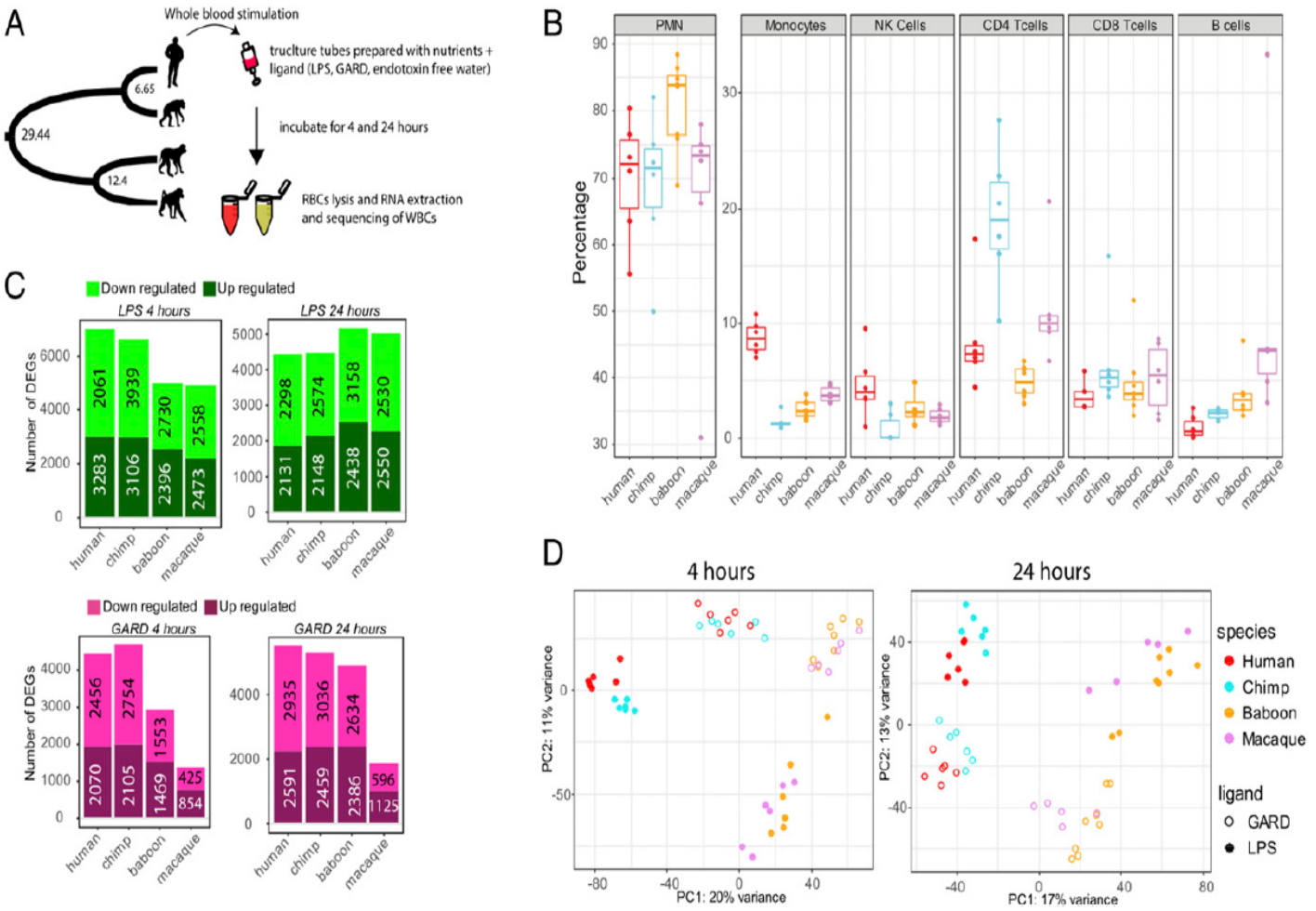


Fig. 1. Characterizing innate immune response upon viral and bacterial stimulation of primate white blood cells. (*A*) Schematic representation of the study design. Whole-blood samples from humans, common chimpanzees, rhesus macaques, and olive baboons were stimulated with bacterial or viral stimuli via venous draw directly into a media culture tube containing either LPS, single-stranded RNA viral mimetic GARD, or endotoxin-free water, as a negative control (Control). At 4 and 24 h poststimulation, white blood cells were isolated, and RNA was extracted for RNA-seq. (*B*) Cell proportions of six populations of

Hawash, PNAS 2021

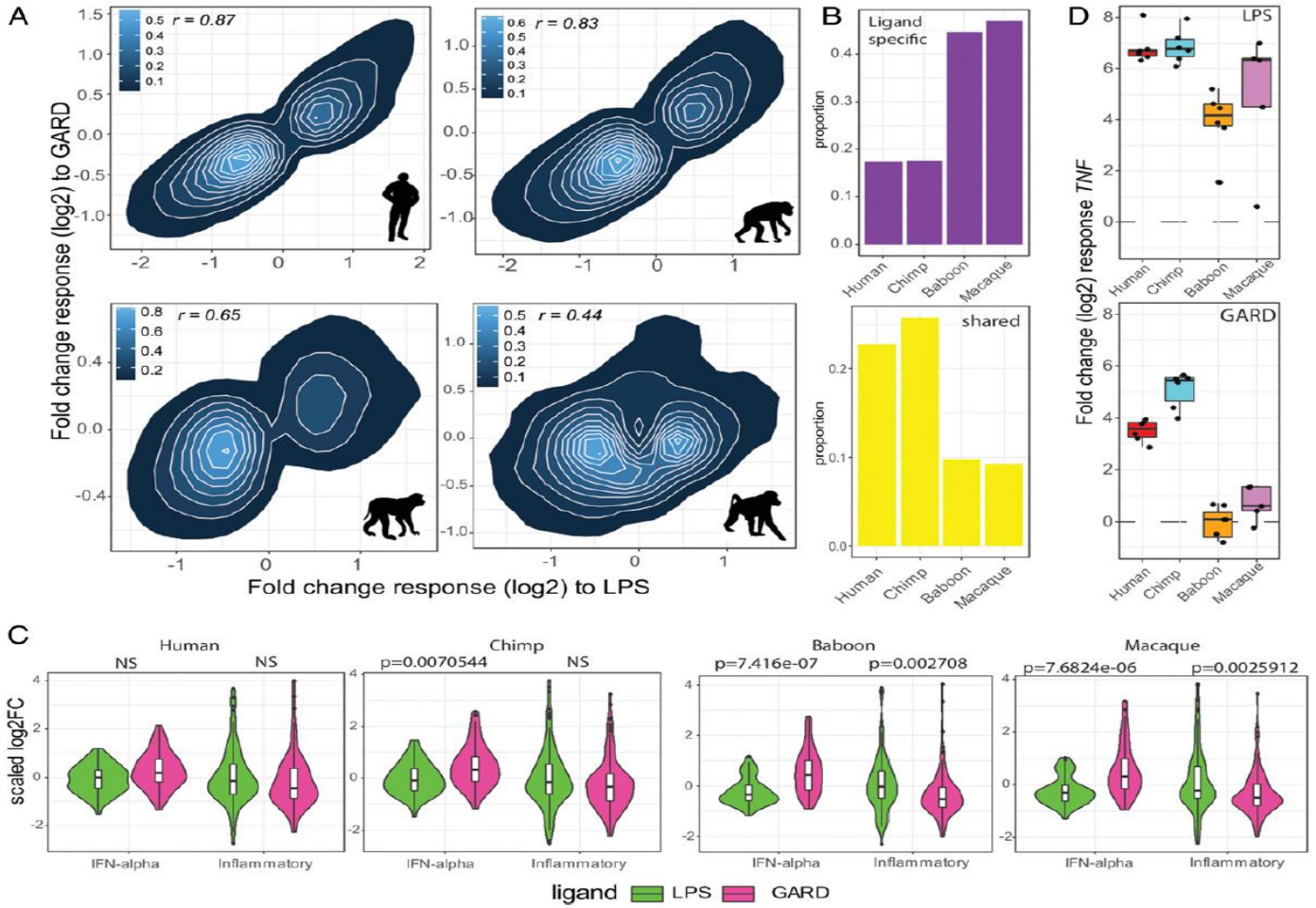


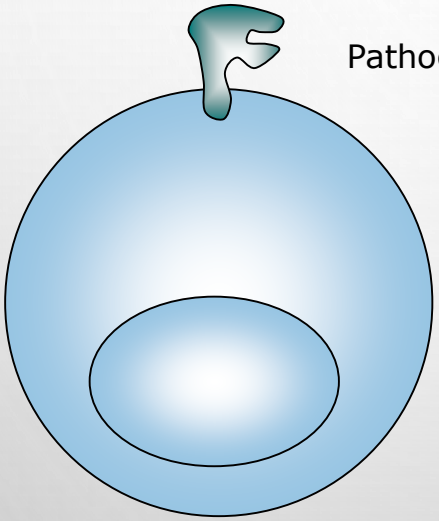
Fig. 5. Apes engage a less-specific innate immune response than AAMs. (*A*) Correlation plots of the magnitude of the fold-change responses between LPS (*x*-axis) and GARD-stimulated cells (*y*-axis). For each of the species, we only include genes that were differentially expressed (FDR < 0.05) in response to at least one of the stimuli (N = 7,862, 7,874, 6,585, and 5,430 genes for human, chimp, baboon, and macaque, respectively). High correlation was found in apes (~0.85), while modest correlation was found in baboon (0.44) and moderate in macaque (0.65). (*B*) Proportion of ligand-specific (i.e., genes that respond uniquely to either bacterial or viral stimuli) and shared genes (i.e., genes equally activated by both immune stimuli) across species. (*C*) Violin plots comparing (scaled) log2 fold-change responses to 4 h of LPS and GARD stimulation between genes belonging the hallmark pathways "Interferon (IFN) alpha" and "inflammatory response." The *P* values shown have been Bonferroni corrected for the number of tests performed. NS, nonsignificant (i.e., $P > 0.05$). (*D*) Boxplots of the log2 fold-change response (*y*-axis) of *TNF* in response to LPS and GARD stimulations across primates.

EVOLUTION

Hawash, PNAS 2021

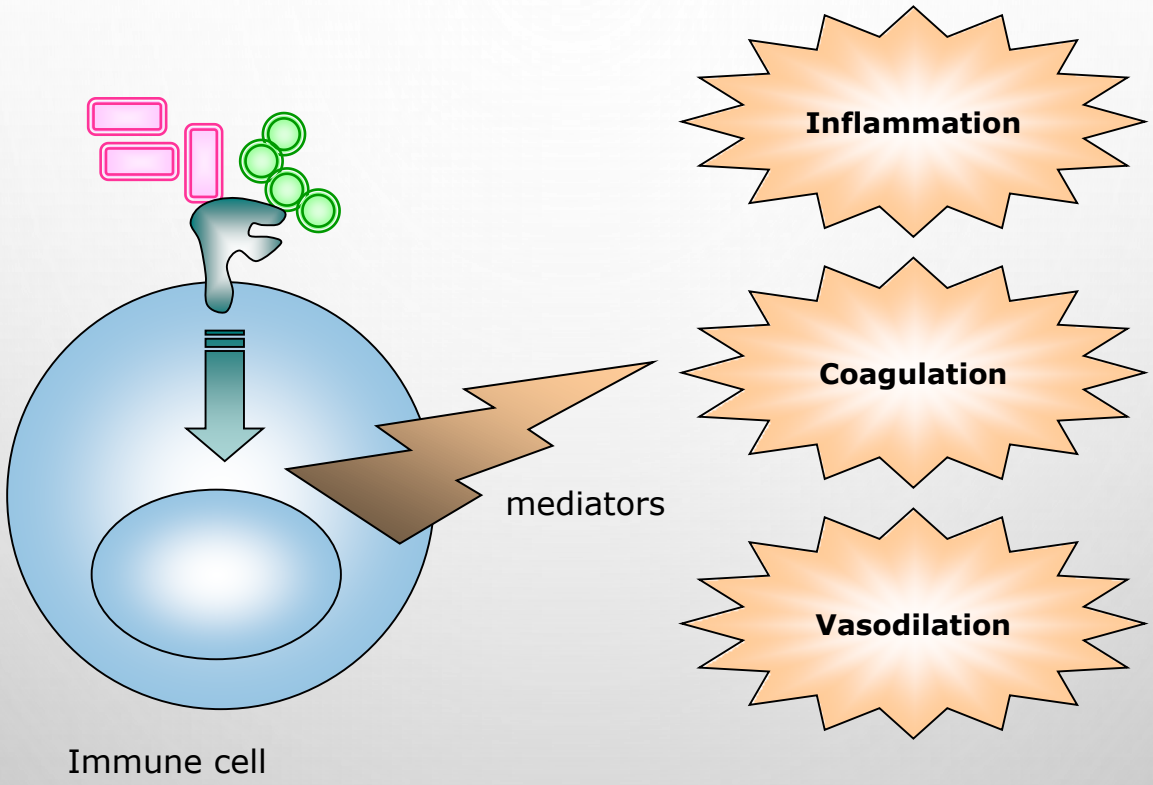
Host – pathogens interaction

Bacteria

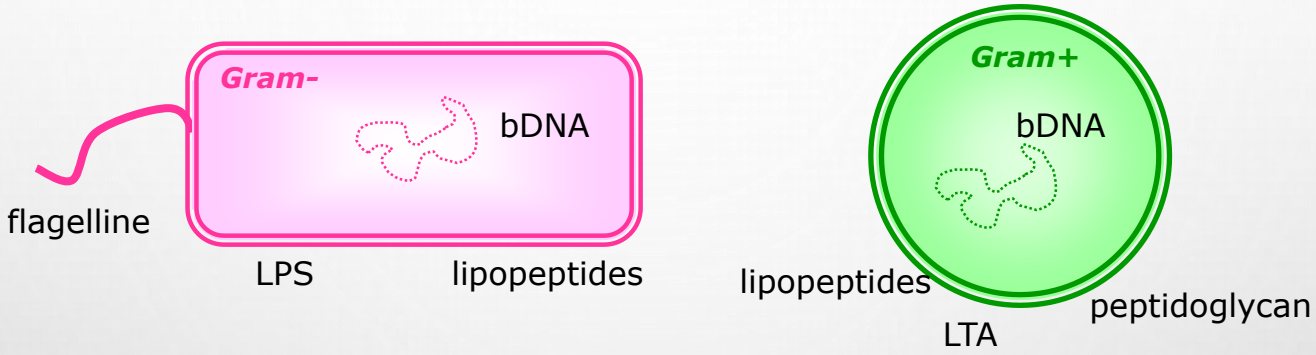


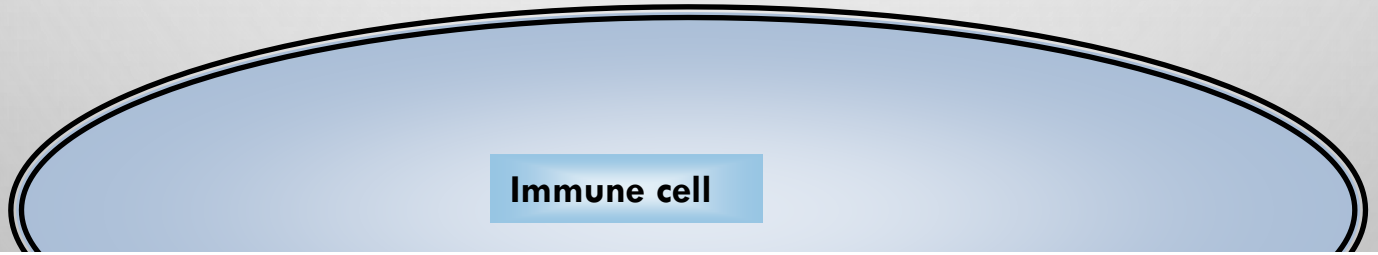
Pathogen Associated Mollecular Pattern

Immune cell

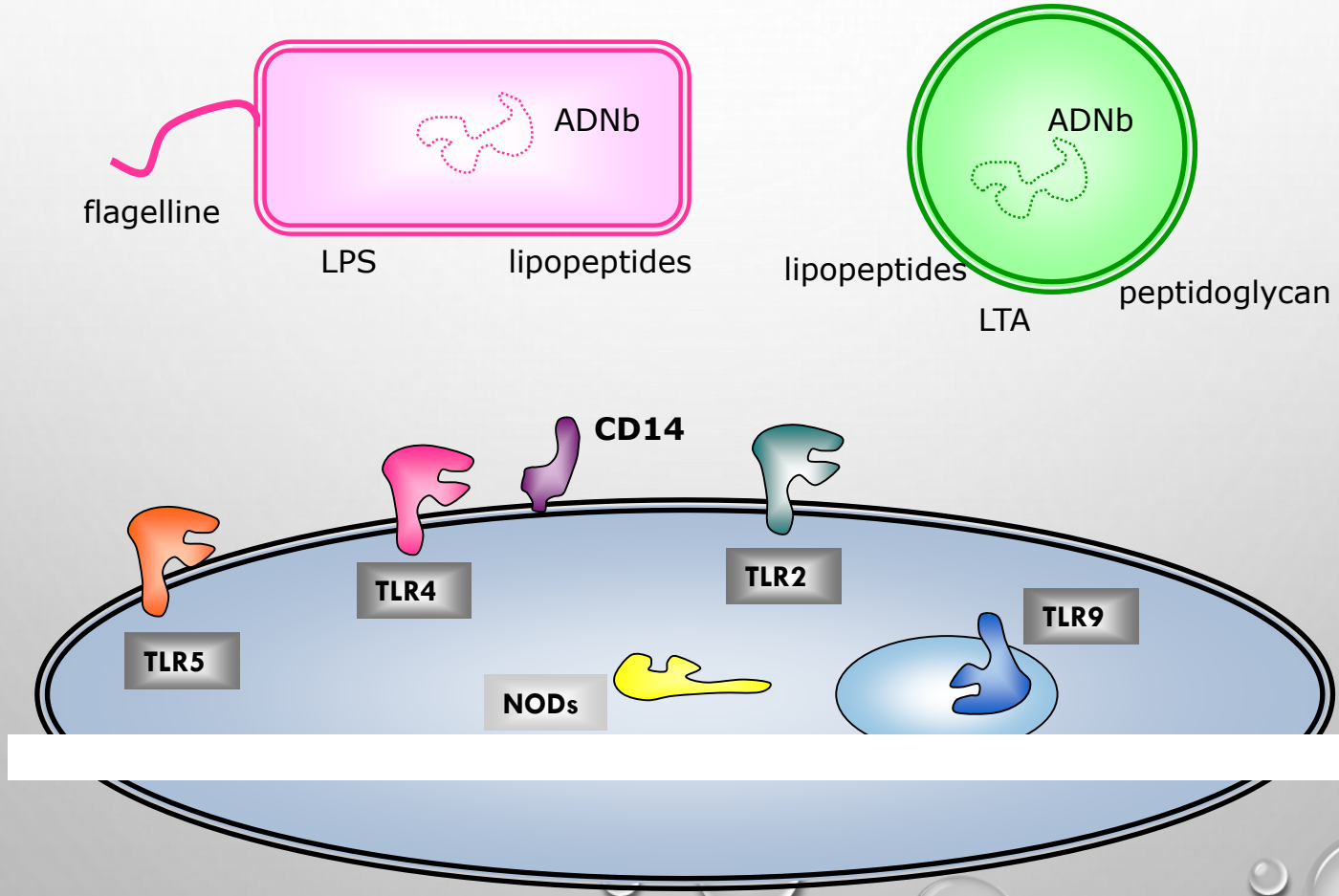

Inflammation
Coagulation
Vasodilation
mediators
Immune cell

Pathogen recognition

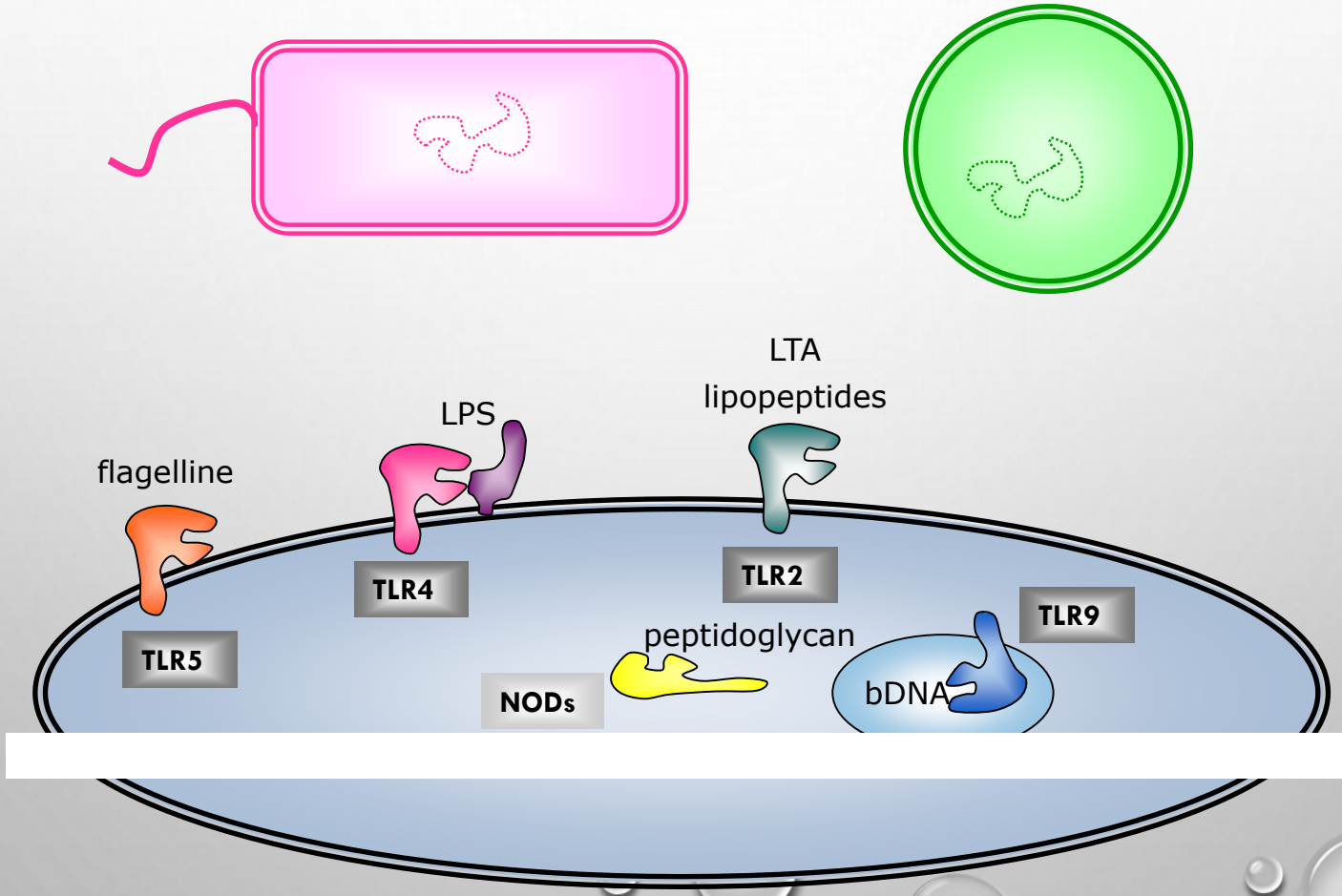


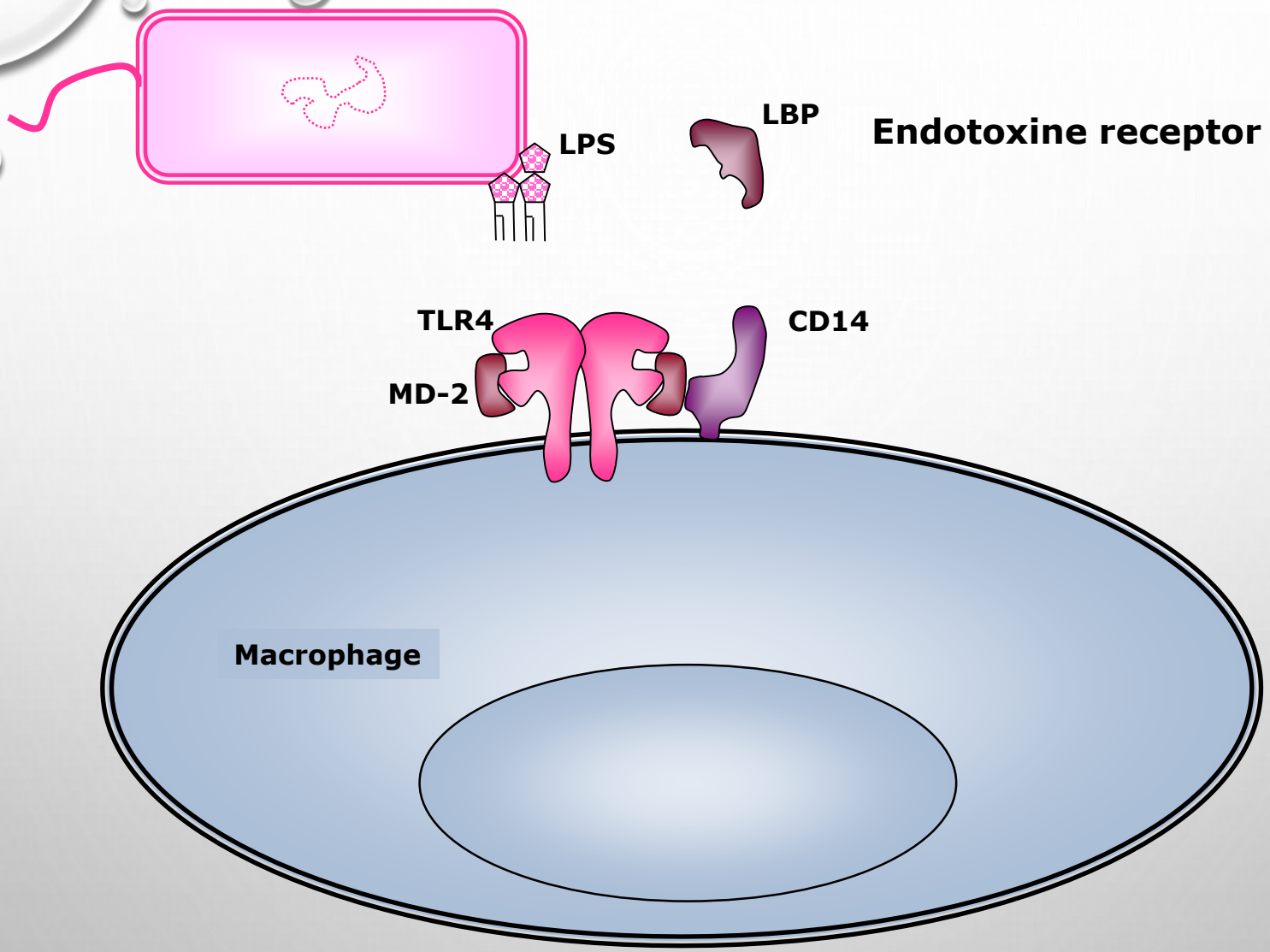


Pathogen recognition
Toll receptors

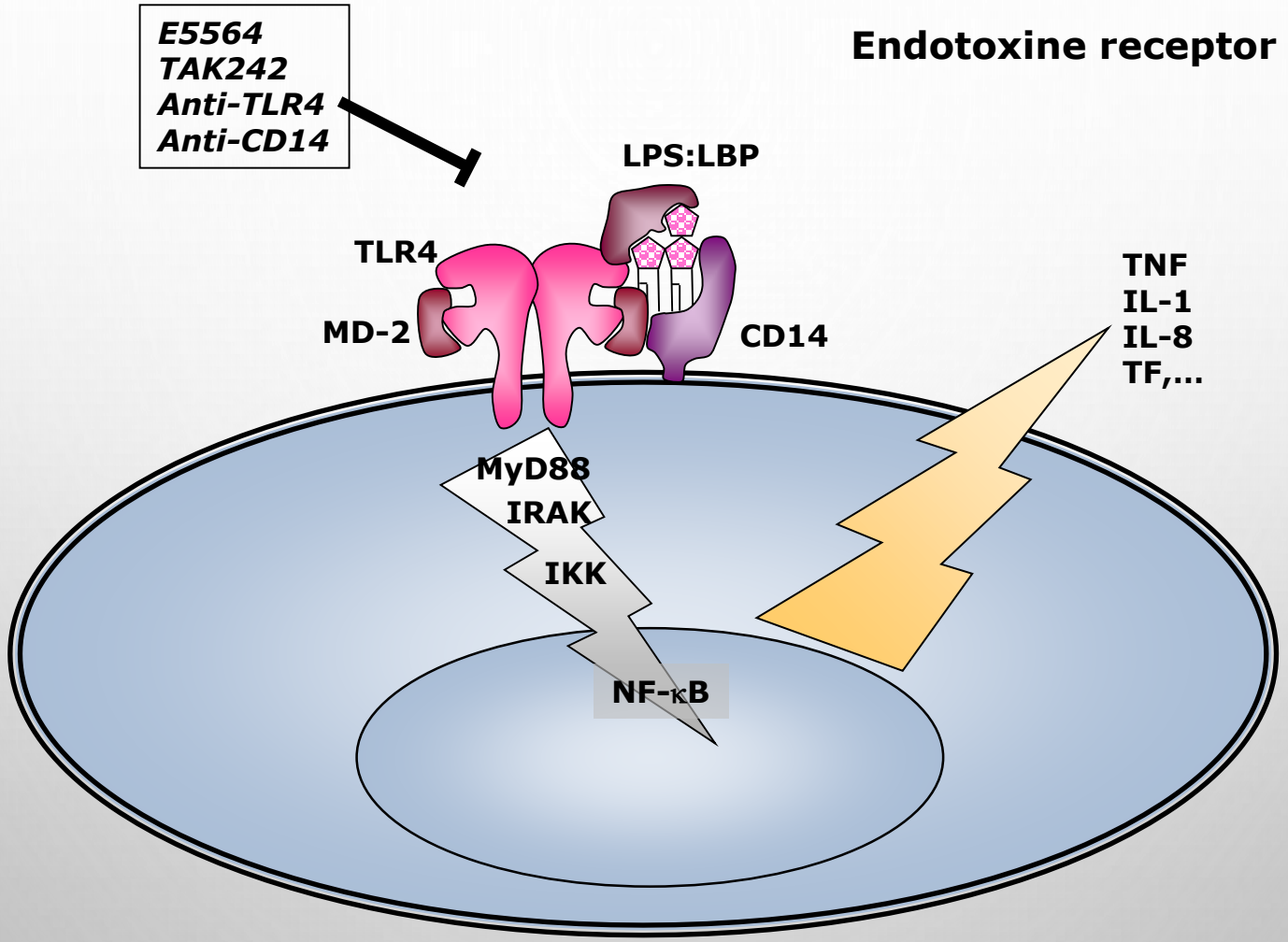


Pathogen recognition
Toll receptors




LPS
LBP
Endotoxine receptor
TLR4
CD14
MD-2
Macrophage

Endotoxine receptor



FHU SEPSIS
Personalized Interventions

Tissue damage/necrosis - shock/ischemia

DAMPs

Uric acid → **NALP3**

ATP_{ec} → **$P2X_7R$**

osmolality → **p38**

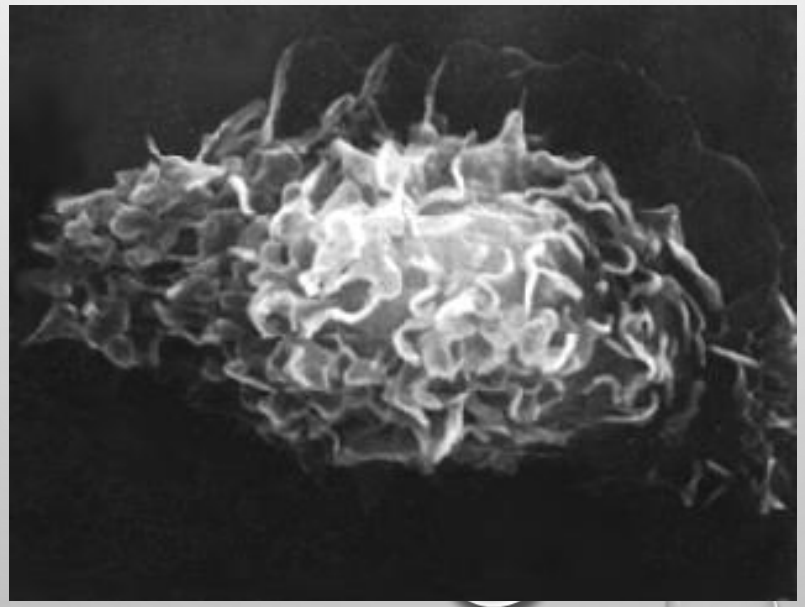
hypoxia → **ORE**

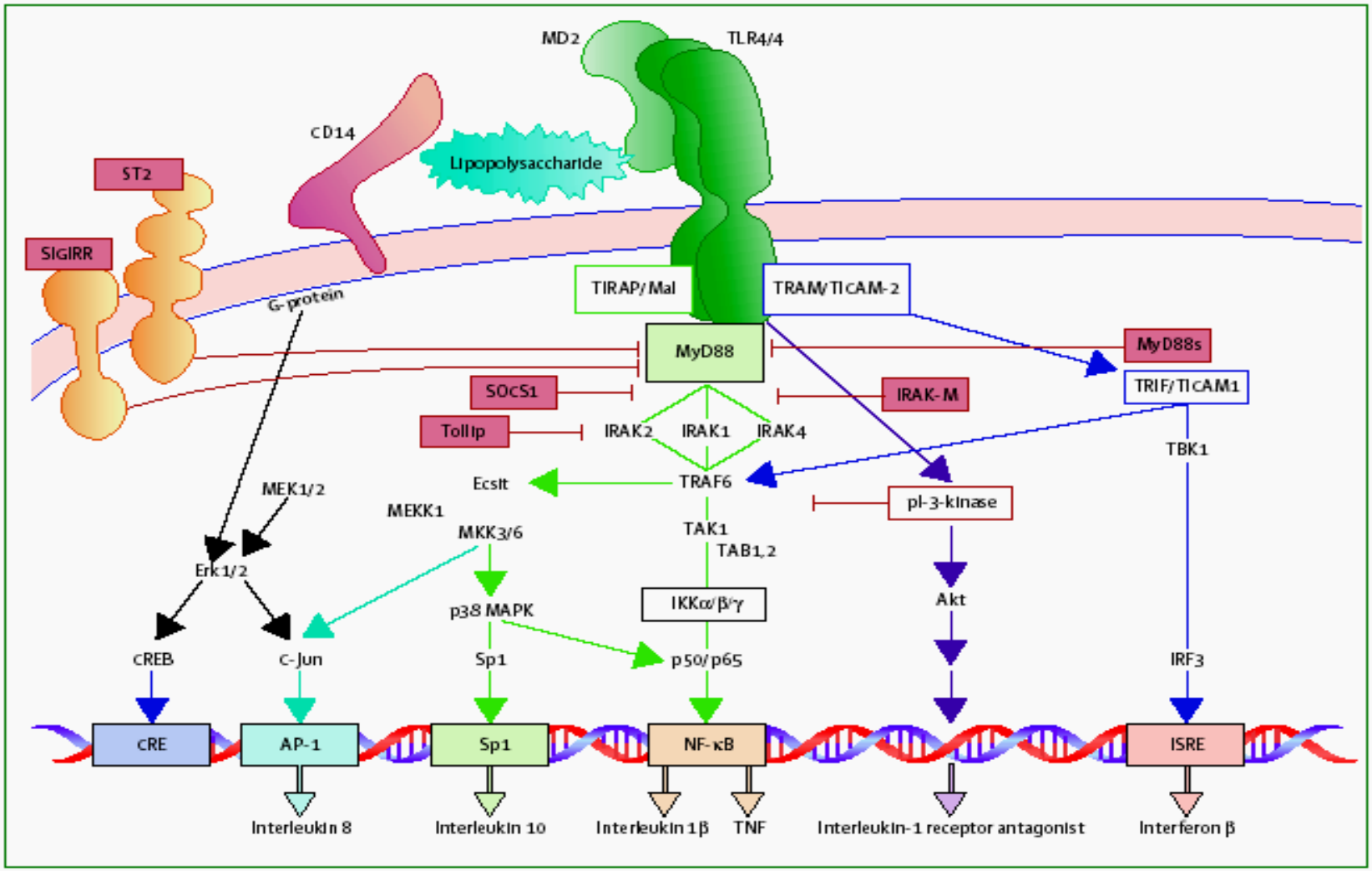
HSPs
HMGB-1 → **TLR2/4 RAGE**

substance P → **Récepteur NK-1**

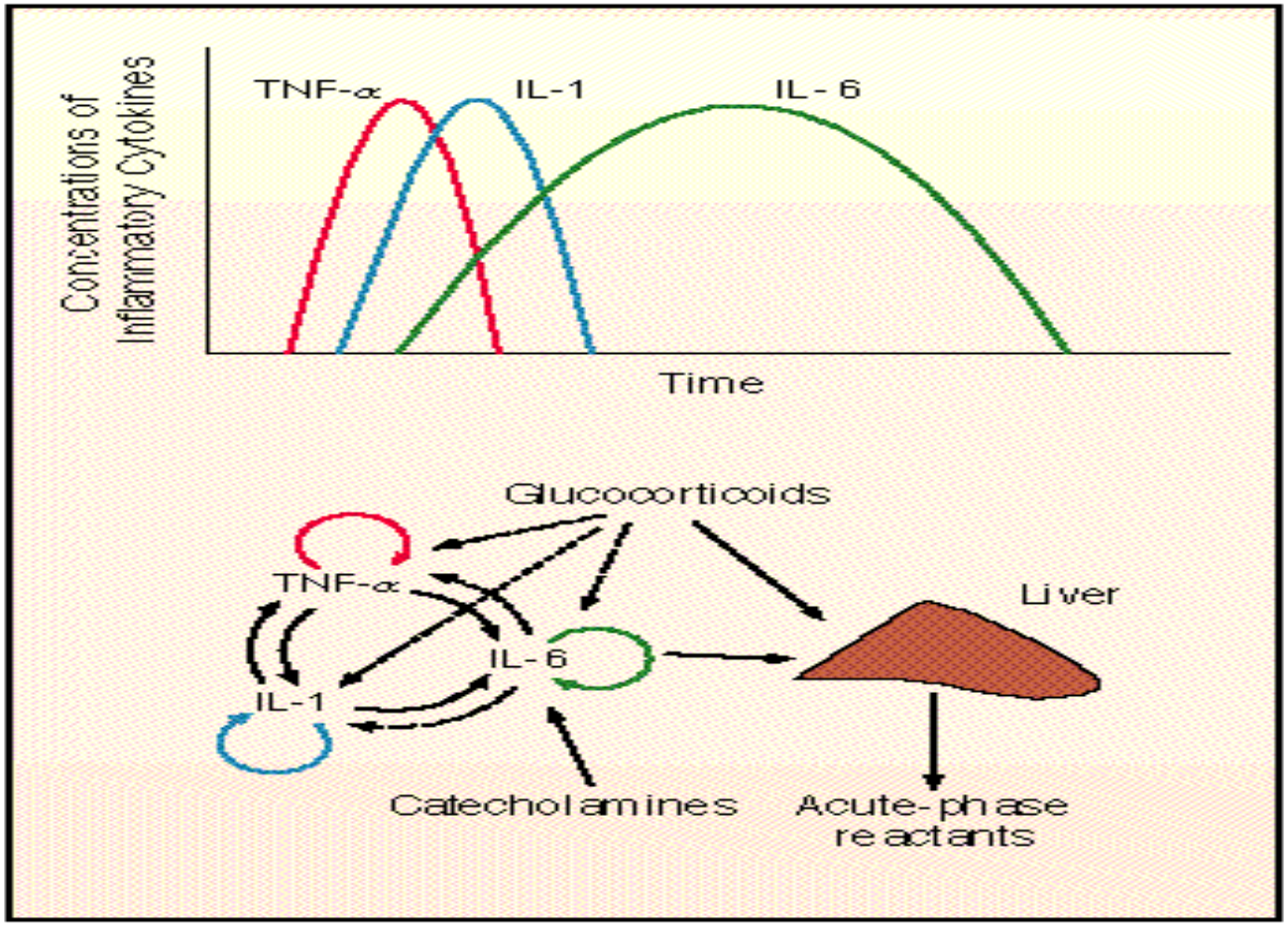
stretch → **Integrins FAK, MAPK NF-κB**

thrombine → **PAR**





Annane Lancet 2005


Concentrations of Inflammatory Cytokines
TNF-α
IL-1
IL-6
Time
Glucocorticoids
TNF-α
IL-6
IL-1
Liver
Catecholamines
Acute-phase reactants

BRIEF REPORT: SHOCK AND MULTIPLE-ORGAN DYSFUNCTION AFTER SELF-ADMINISTRATION OF SALMONELLA ENDOTOXIN

ANGELO M. TAVEIRA DA SILVA, M.D., PH.D.,
HELEN C. KAULBACH, M.D.,
FRANCIS S. CHUIDIAN, M.D.,
DAVID R. LAMBERT, M.D.,
ANTHONY F. SUFFREDINI, M.D.,
AND ROBERT L. DANNER, M.D.

cal signs and symptoms. We describe a patient who self-administered a single large dose of endotoxin and in whom the full clinical manifestations of septic shock syndrome developed.

CASE REPORT

A middle-aged laboratory worker was brought to the emergency department because of malaise, headaches, nausea, and vomiting. The patient was awake but listless with a pulse of 114 per minute, a blood pressure of 42/20 mm Hg, and an oral temperature of 40°C. The patient was treated with intravenous fluids, and a dopamine infusion was started at a dose of 5 μg per kilogram per minute. Blood cultures were obtained, and vancomycin and gentamicin were administered intravenously. The results of a urinalysis, chest roentgenography, and electrocardiography were normal. The patient was admitted to the medical intensive care unit with a presumptive diagnosis of septic shock.

Table 1. Hemodynamic Measurements and Vasopressor Administration after the Injection of *S. minnesota* Endotoxin.*

Hours after Endotoxin Injection	Weight	Cumulative Fluid Intake in Excess of Output	Dopamine	Norepinephrine	Mean Arterial Pressure	Pulmonary-Capillary Wedge Pressure	Cardiac Index	Systemic-Vascular-Resistance Index	Stroke-Volume Index	Left Ventricular-Stroke-Work Index
	kg	*ml*	*μg/kg/min*	*μg/min*	*mm Hg*		*liters/min/m²*	*dyn · sec · cm⁻⁵ · m²*	*ml/m²*	*g/min/m²*
5	66.4	4,000	5.0	—	47	—	—	—	—	—
12	—	5,000	12.4	9.4	60	3.0	5.0	800	46	29.4
17	—	6,900	12.4	9.4	77	4.0	4.6	1165	43	35.0
24	—	9,200	8.8	15.6	86	10.0	3.5	1896	40	47.8
28	—	10,300	4.4	15.6	78	12.0	3.3	1781	31	39.6
32	—	10,600	1.6	15.6	82	16.0	3.8	1560	40	42.4
44	—	14,600	1.6	2.1	71	21.0	4.9	933	46	44.4
50	76.5	14,900	1.6	—	78	15.0	4.3	1338	45	50.1
72	75.2	15,775	—	—	84	12.0	3.0	2000	39	44.5
Normal range†	—	—	—	—	70–105	2.0–10.0	2.6–4.2	1200–2800	30–65	30–90

*Hemodynamic variables were measured directly from strip-chart recordings or calculated with standard formulas.[7]
†The normal ranges for adults were obtained from Grossman.[10]

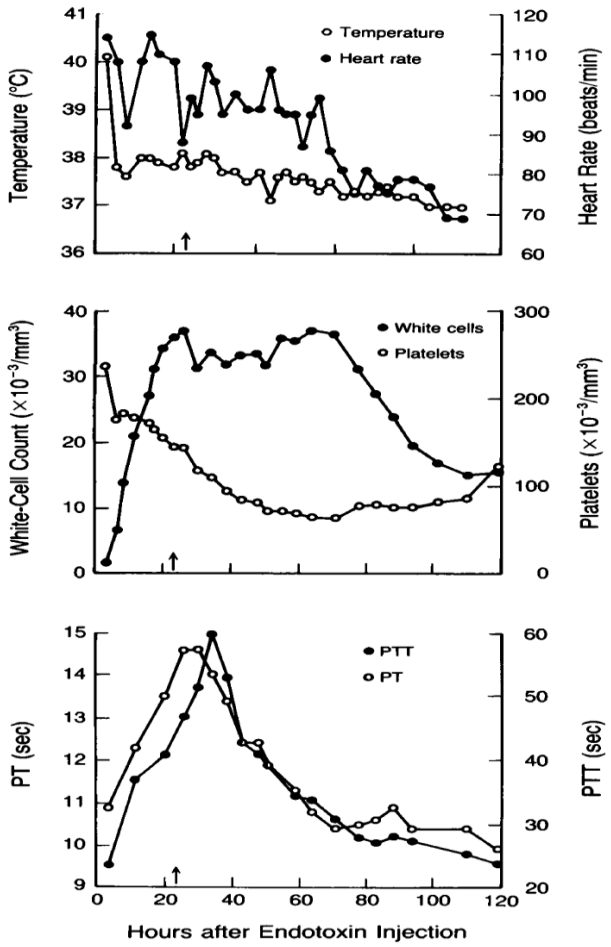


Figure 1. Serial Changes in Body Temperature and Heart Rate, Total White-Cell Count and Platelet Count, and Prothrombin Time (PT) and Partial-Thromboplastin Time (PTT) after the Intravenous Injection of Endotoxin.
The arrows denote the time at which HA-1A antibody was administered.

Table 2. Serial Serum Concentrations of Endotoxin and Cytokines after the Injection of *S. minnesota* Endotoxin.*

Hours after Endotoxin Injection	Endotoxin	TNF-α by ELISA	TNF-α by Bioassay	Interleukin-6	Interleukin-8	G-CSF
	EU/ml†	*pg/ml*				
3.6	NA	14,630	9,157	NA	NA	NA
6.8	0.38	147	17	263,510	16,410	NA
11.5	<0.05	NA	NA	51,910	3,190	NA
22.5	0.19‡	NA	NA	1,620	520	277,070
24.0	0.80‡	22	<10	927	380	230,690
24.5	<0.05	NA	NA	489	230	174,200
25.5	<0.05	16	<10	480	210	164,870
26.5	NA	<10	<10	590	650	10,630
48.0	NA	<10	<10	NA	NA	NA
Normal value§	<0.05	<10	<10	<100	<50	<100

*TNF-α was measured by bioassay and ELISA, interleukin-6 and granulocyte colony-stimulating factor by a double-ligand immunoassay, and interleukin-8 by ELISA. G-CSF denotes granulocyte colony-stimulating factor, and NA not available.

†1 EU = 0.1 ng of U.S. Standard Reference Endotoxin.

‡This value may represent exogenous contamination of the specimen.

§Normal values are based on product information from R&D Systems and studies in human volunteers.[4,14]

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P.,
Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A.,
Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

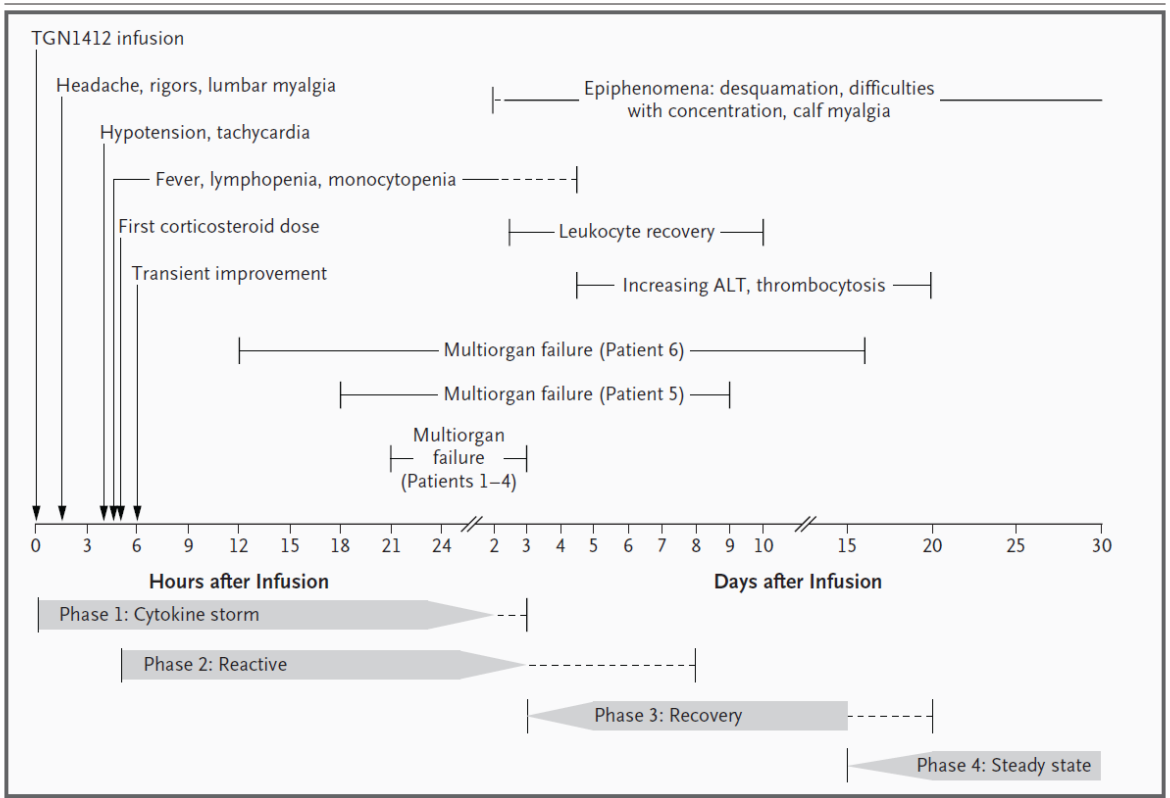
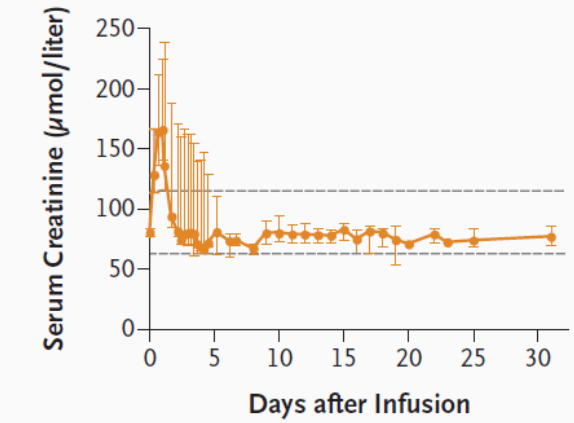
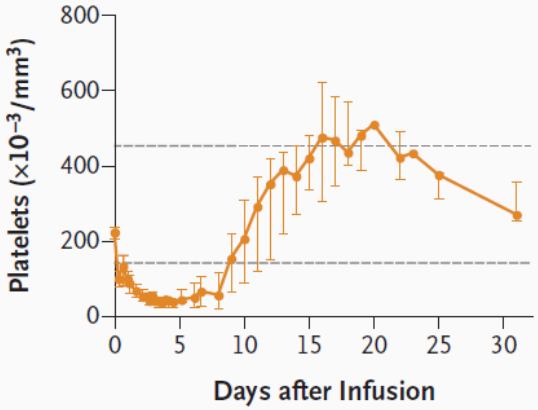
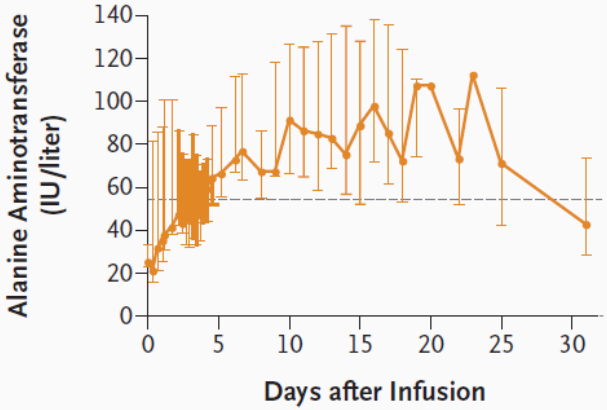


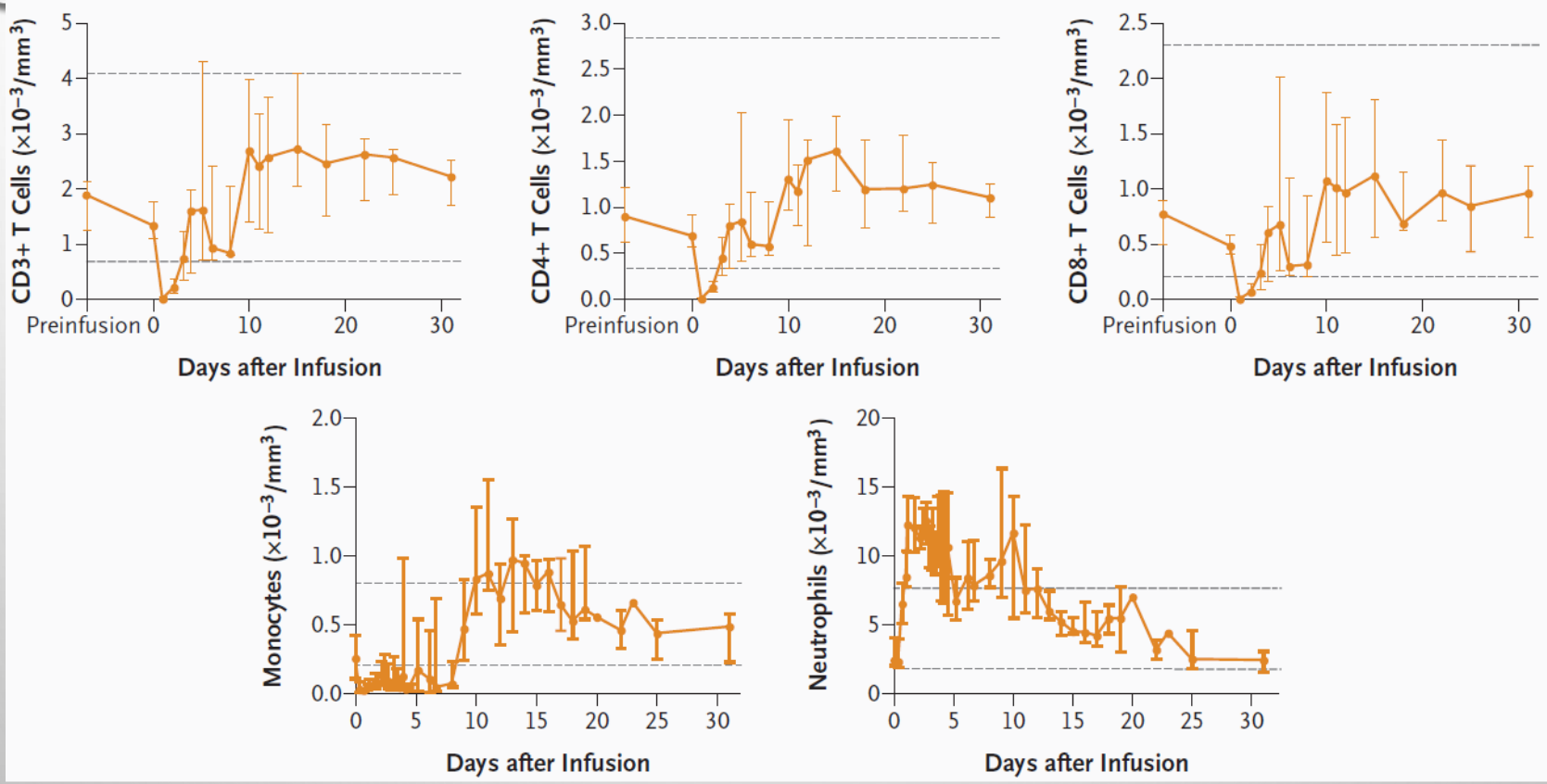
Figure 1. Summary Timeline of the Main Events after Infusion of TGN1412.

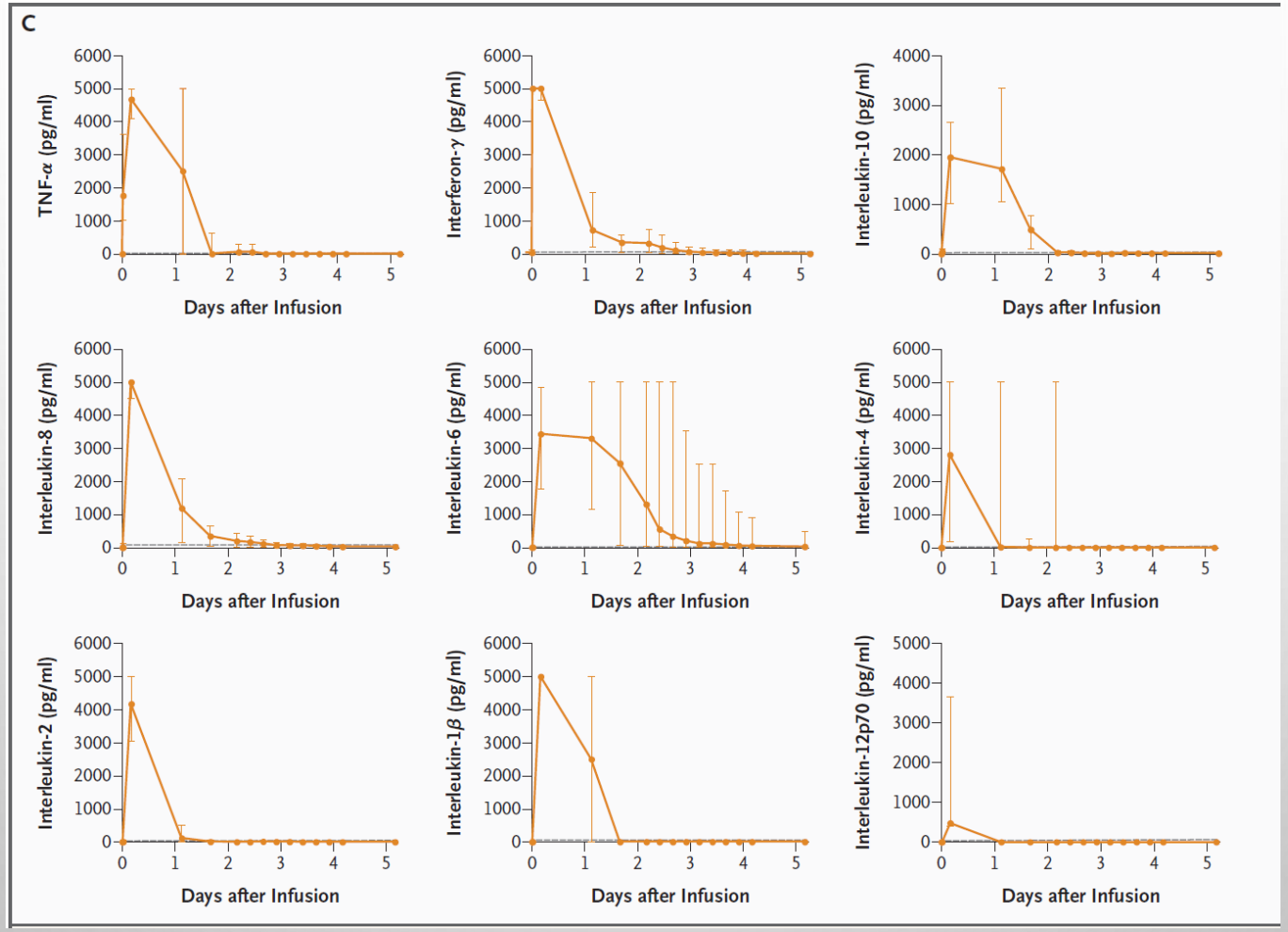
The course is divided into four phases: cytokine storm, reactive, recovery, and steady state. ALT denotes alanine aminotransferase. Dashed lines represent the responses of Patients 5 and 6 (who were the most seriously ill).

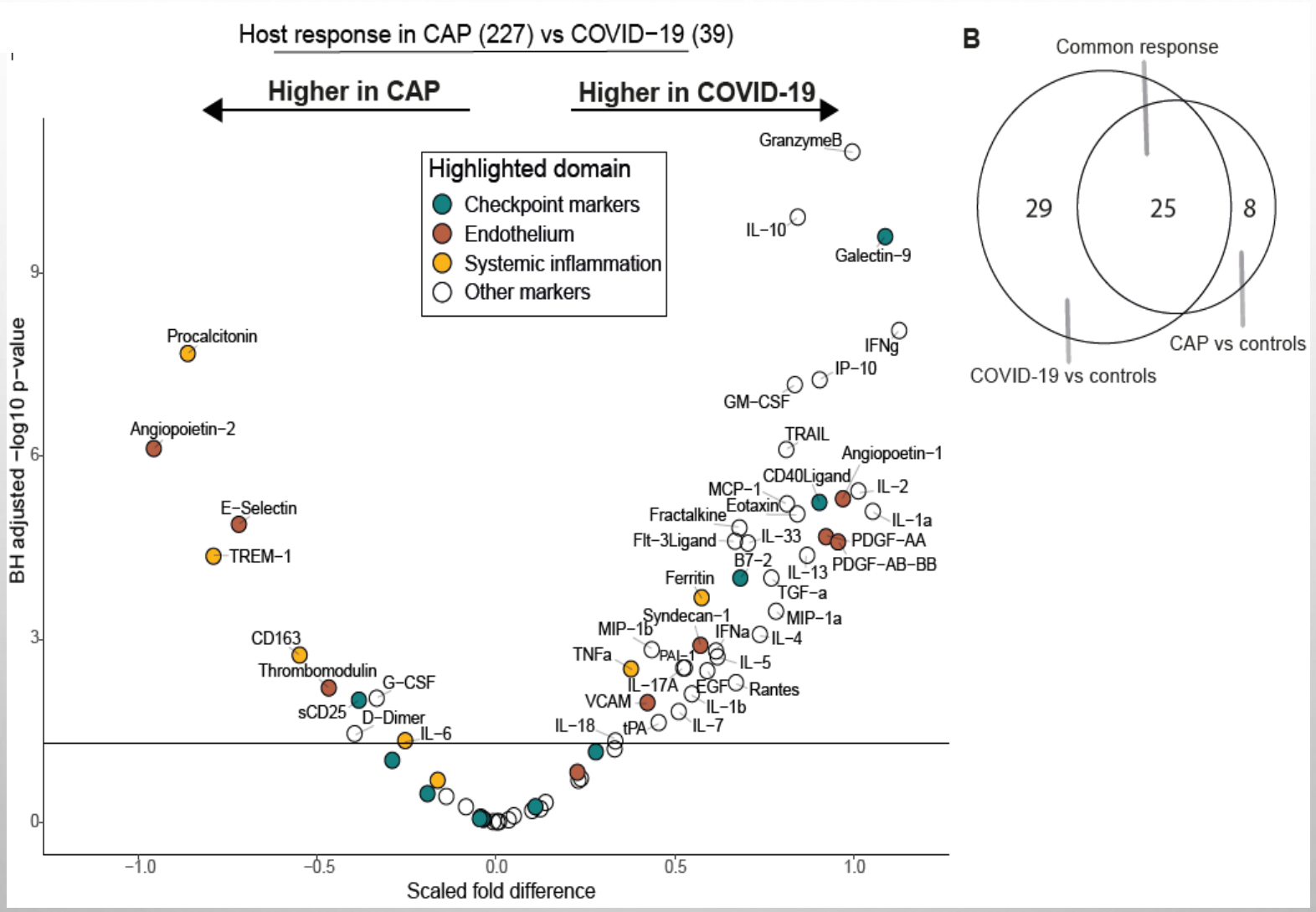

Serum Creatinine (μmol/liter)
250
200
150
100
50
0
0 5 10 15 20 25 30
Days after Infusion


Platelets (×10⁻³/mm³)
800
600
400
200
0
0 5 10 15 20 25 30
Days after Infusion


Alanine Aminotransferase (IU/liter)
140
120
100
80
60
40
20
0
0 5 10 15 20 25 30
Days after Infusion


CD3+ T Cells (×10⁻³/mm³)
Preinfusion 0
Days after Infusion
CD4+ T Cells (×10⁻³/mm³)
Preinfusion 0
Days after Infusion
CD8+ T Cells (×10⁻³/mm³)
Preinfusion 0
Days after Infusion
Monocytes (×10⁻³/mm³)
Days after Infusion
Neutrophils (×10⁻³/mm³)
Days after Infusion


C
TNF-α (pg/ml)
Interferon-γ (pg/ml)
Interleukin-10 (pg/ml)
Interleukin-8 (pg/ml)
Interleukin-6 (pg/ml)
Interleukin-4 (pg/ml)
Interleukin-2 (pg/ml)
Interleukin-1β (pg/ml)
Interleukin-12p70 (pg/ml)
Days after Infusion



Luminex protein panel

Alex Schuurman, eLife, 2021 and data in preparation

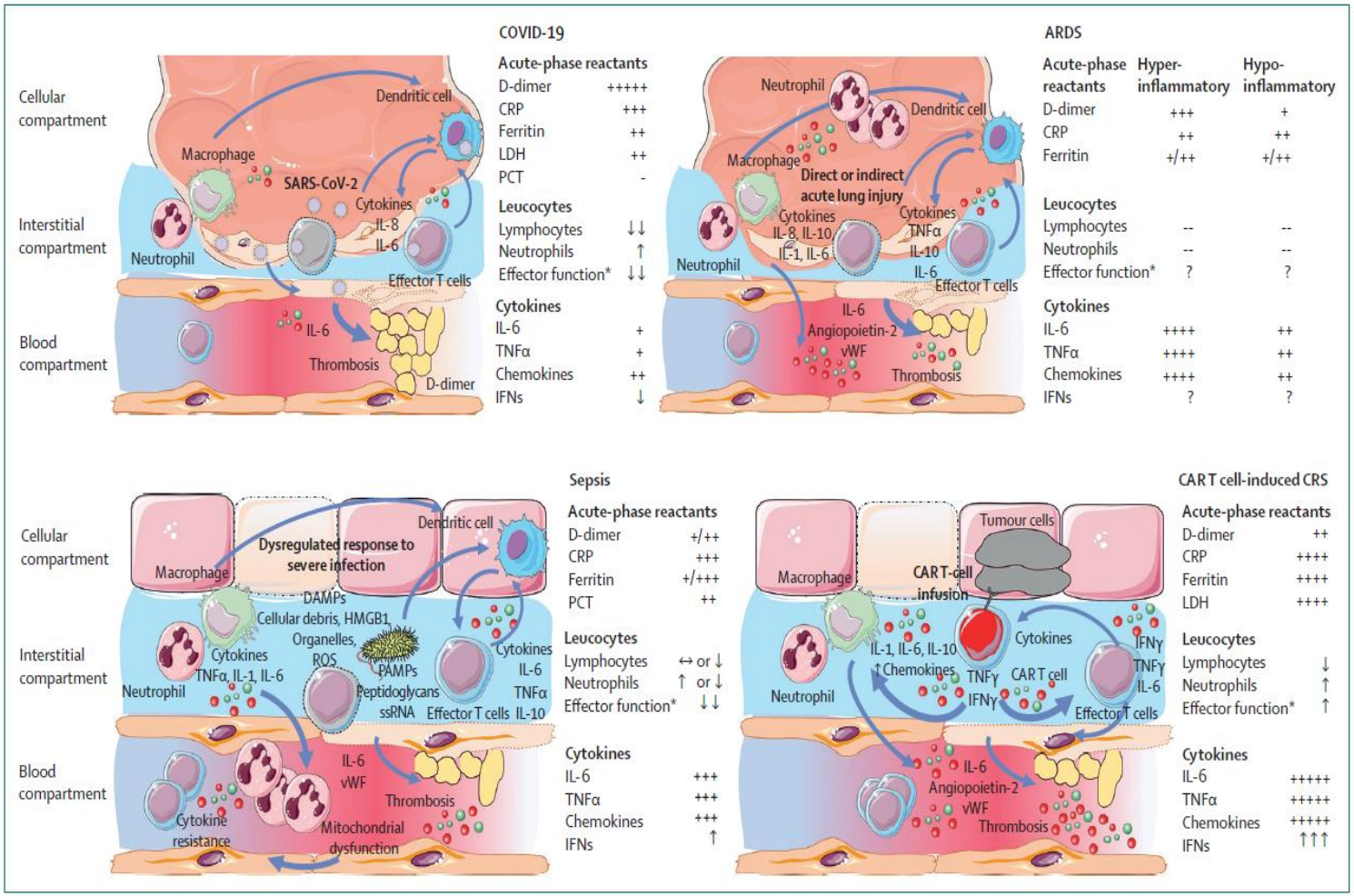
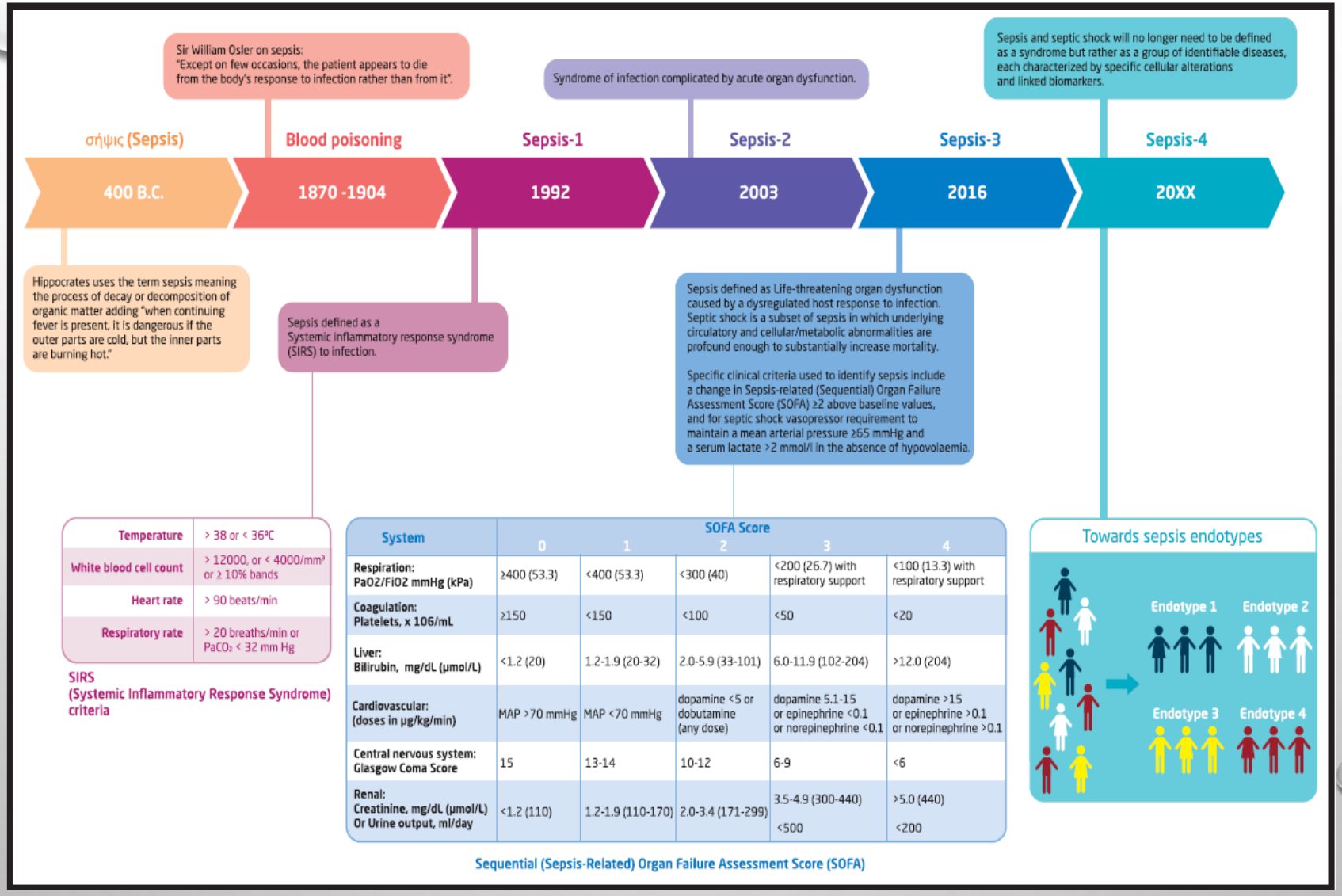


Figure 4: **Mechanistic comparison of inflammatory processes in patients with COVID-19 versus ARDS, sepsis, and CAR T cell-induced CRS**

ARDS=acute respiratory distress syndrome. CAR T cell-induced CRS=chimeric antigen receptor T cell-induced cytokine release syndrome. CRP=C-reactive protein. DAMPs=damage-associated molecular patterns. IFN=interferon. IL=interleukin. LDH=lactate dehydrogenase. PAMPs=pathogen-associated molecular patterns. PCT=procalcitonin. ROS=reactive oxygen species. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ssRNA=single-stranded RNA. vWF=von Willebrand factor. *Effector function measured by ex vivo functional assays.

Leisman, LRM 2020



Temperature	> 38 or < 36ºC
White blood cell count	> 12000, or < 4000/mm³ or ≥ 10% bands
Heart rate	> 90 beats/min
Respiratory rate	> 20 breaths/min or $PaCO_2$ < 32 mm Hg

SIRS (Systemic Inflammatory Response Syndrome) criteria

System	SOFA Score 0	1	2	3	4
Respiration: PaO2/FiO2 mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation: Platelets, x 106/mL	≥150	<150	<100	<50	<20
Liver: Bilirubin, mg/dL (µmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular: (doses in µg/kg/min)	MAP >70 mmHg	MAP <70 mmHg	dopamine <5 or dobutamine (any dose)	dopamine 5.1-15 or epinephrine <0.1 or norepinephrine <0.1	dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system: Glasgow Coma Score	15	13-14	10-12	6-9	<6
Renal: Creatinine, mg/dL (µmol/L) Or Urine output, ml/day	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500	>5.0 (440) <200

Sequential (Sepsis-Related) Organ Failure Assessment Score (SOFA)

Van der Poll Imunity 2021