Diagnostic et traitement des chocs cytokiniques

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FHU SEPSIS
Personalized Interventions

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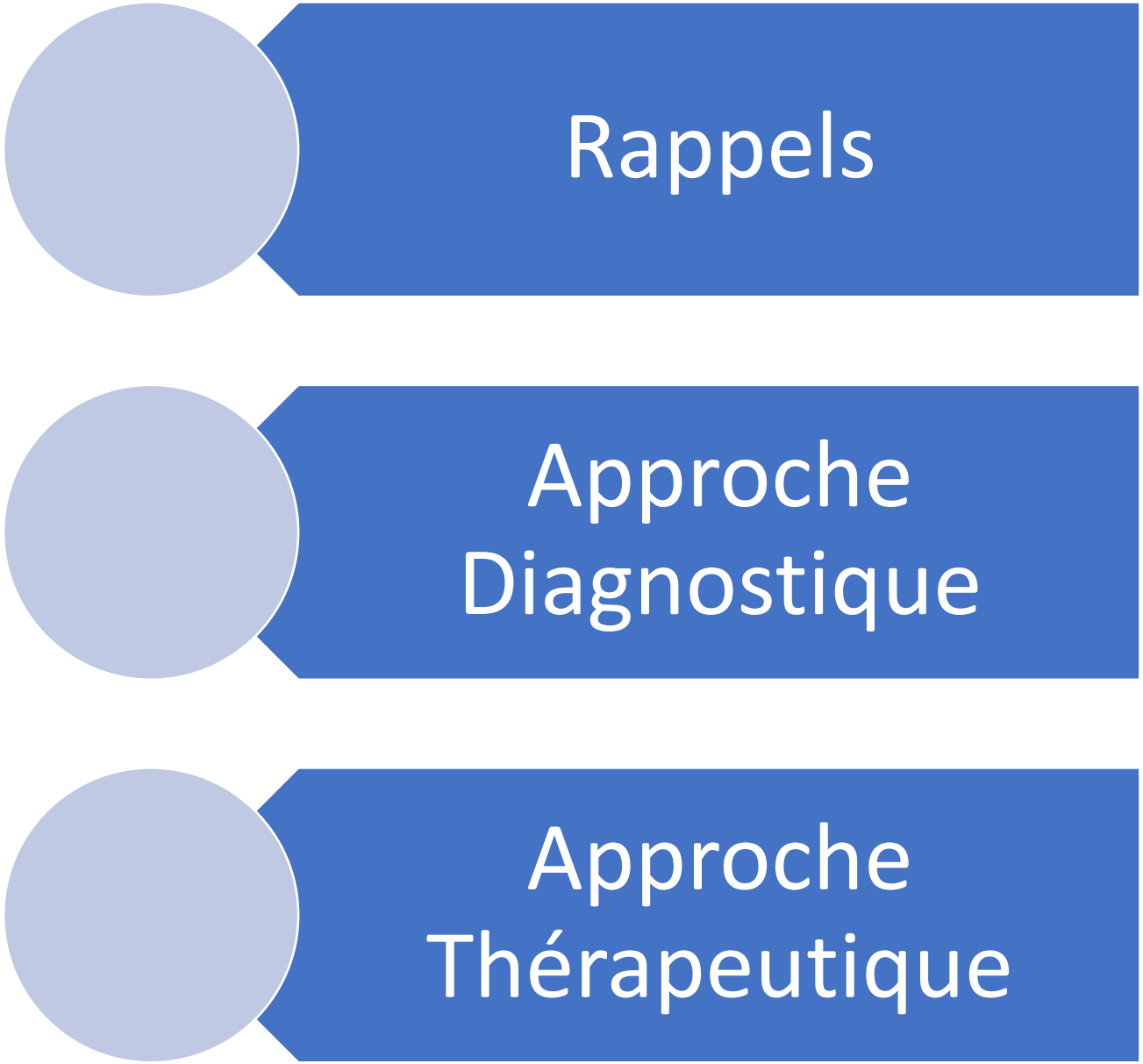
Sous l'égide de :

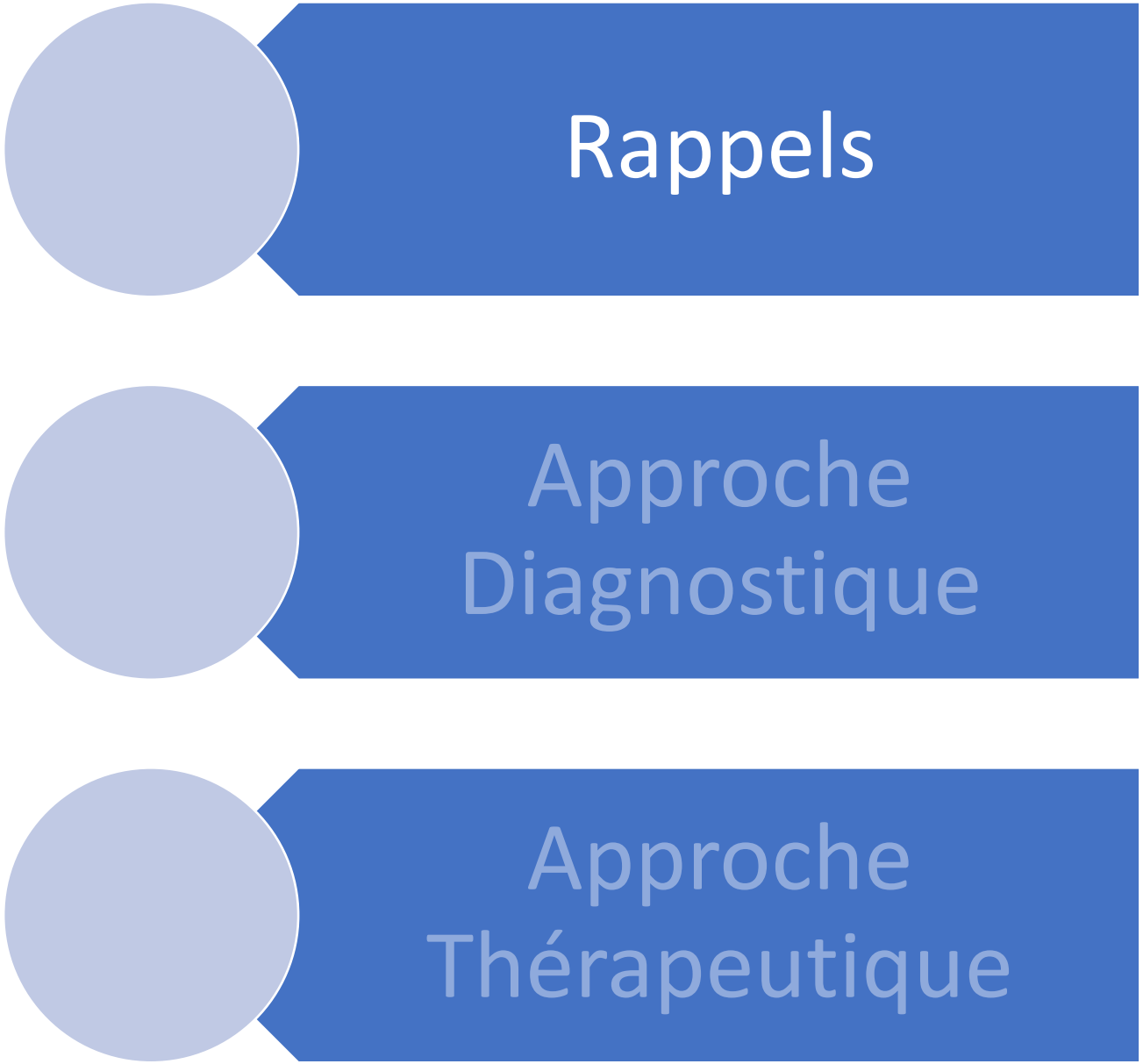
Déclaration d'Intérêt

- Financements publiques: ANR, PHRC, Horizon2020
- Académique: chair ESICM/SCCM TF for 2018 Guidelines on CIRCI, member of SSC guidelines panel for 2008, 2012 & 2016 revisions

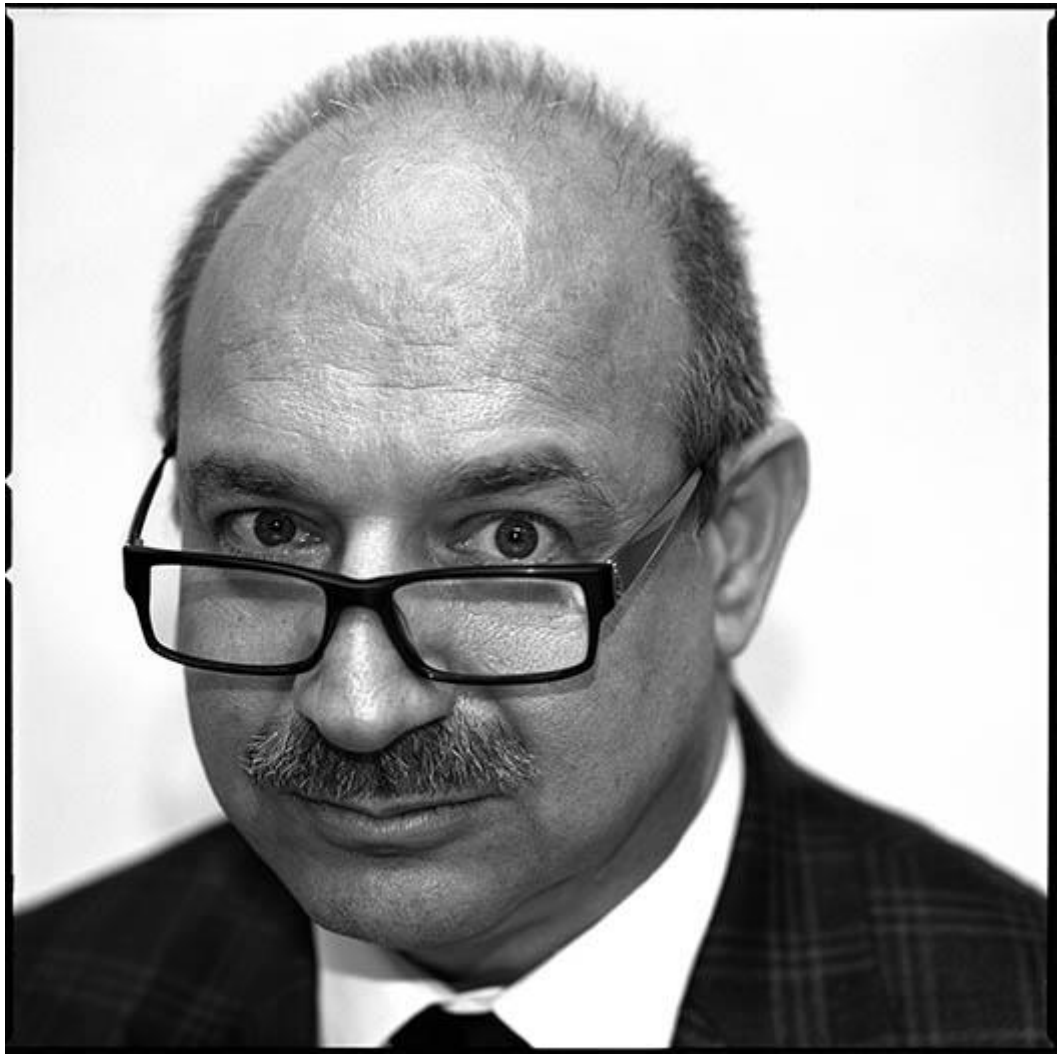
Plan



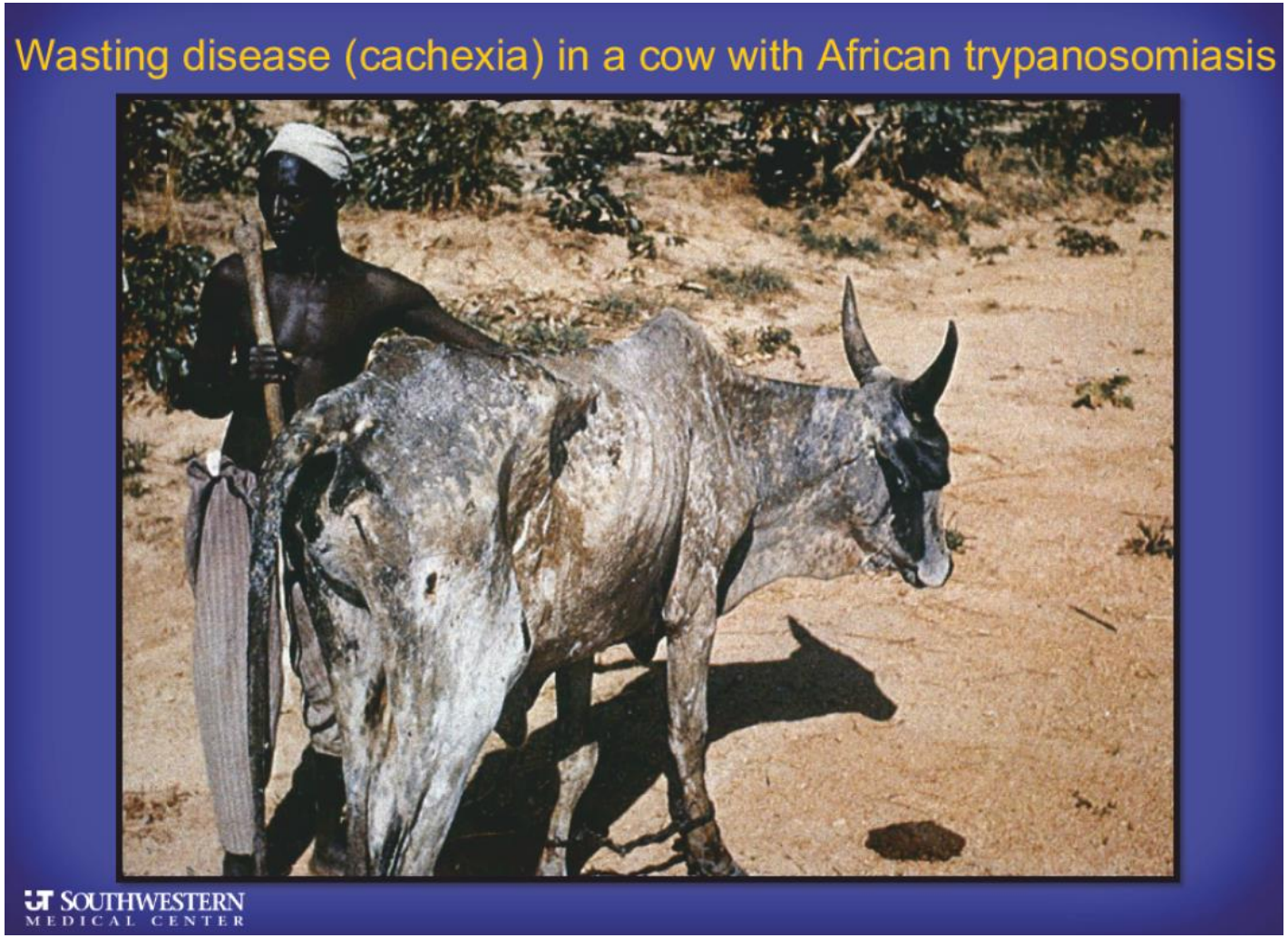
Plan



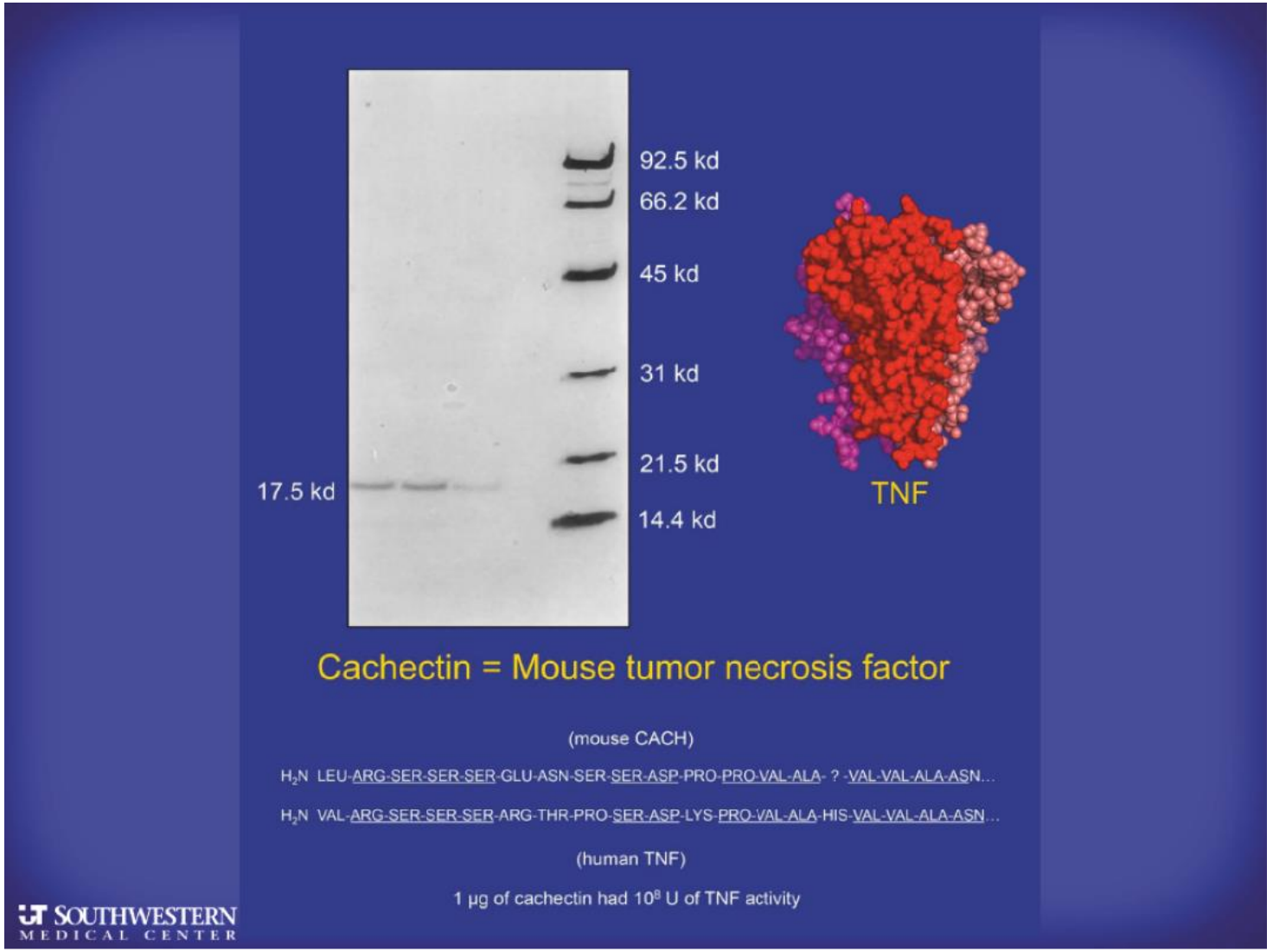
2011 Nobel Prize in Physiology or Medicine



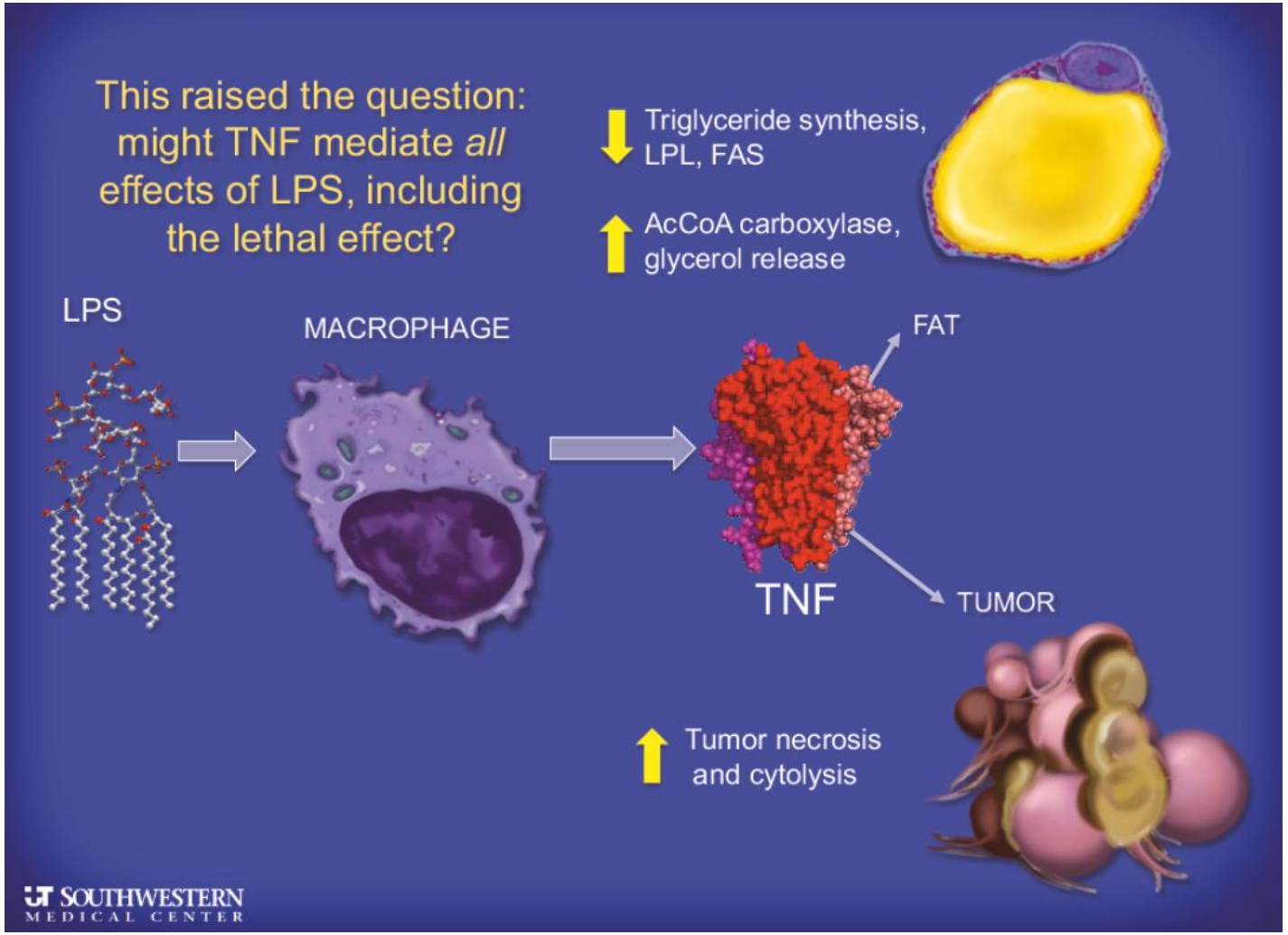
Bruce Beutler



Beutler, Nobel Prize Lecture, 2011

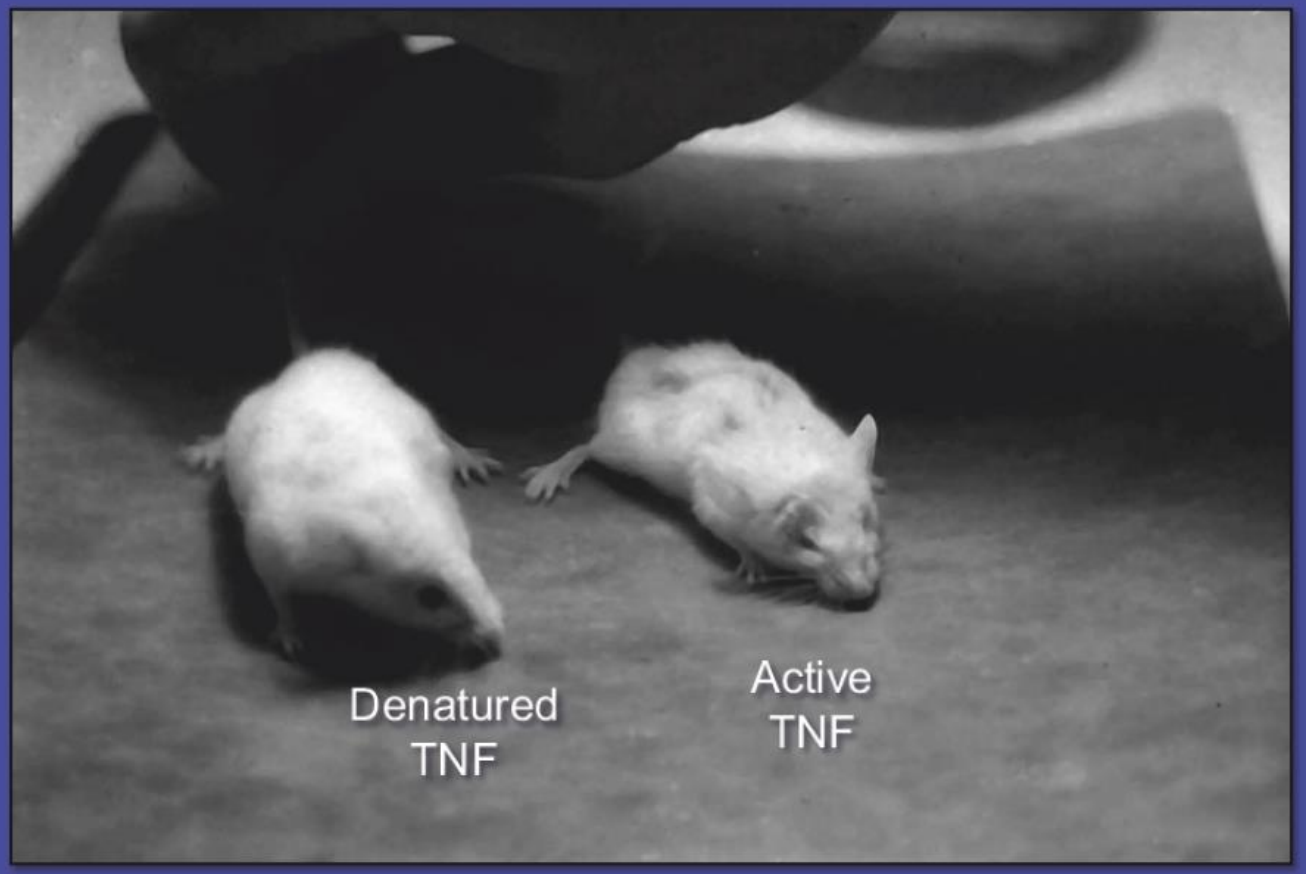


Beutler, Nobel Prize Lecture, 2011



Beutler, Nobel Prize Lecture, 2011

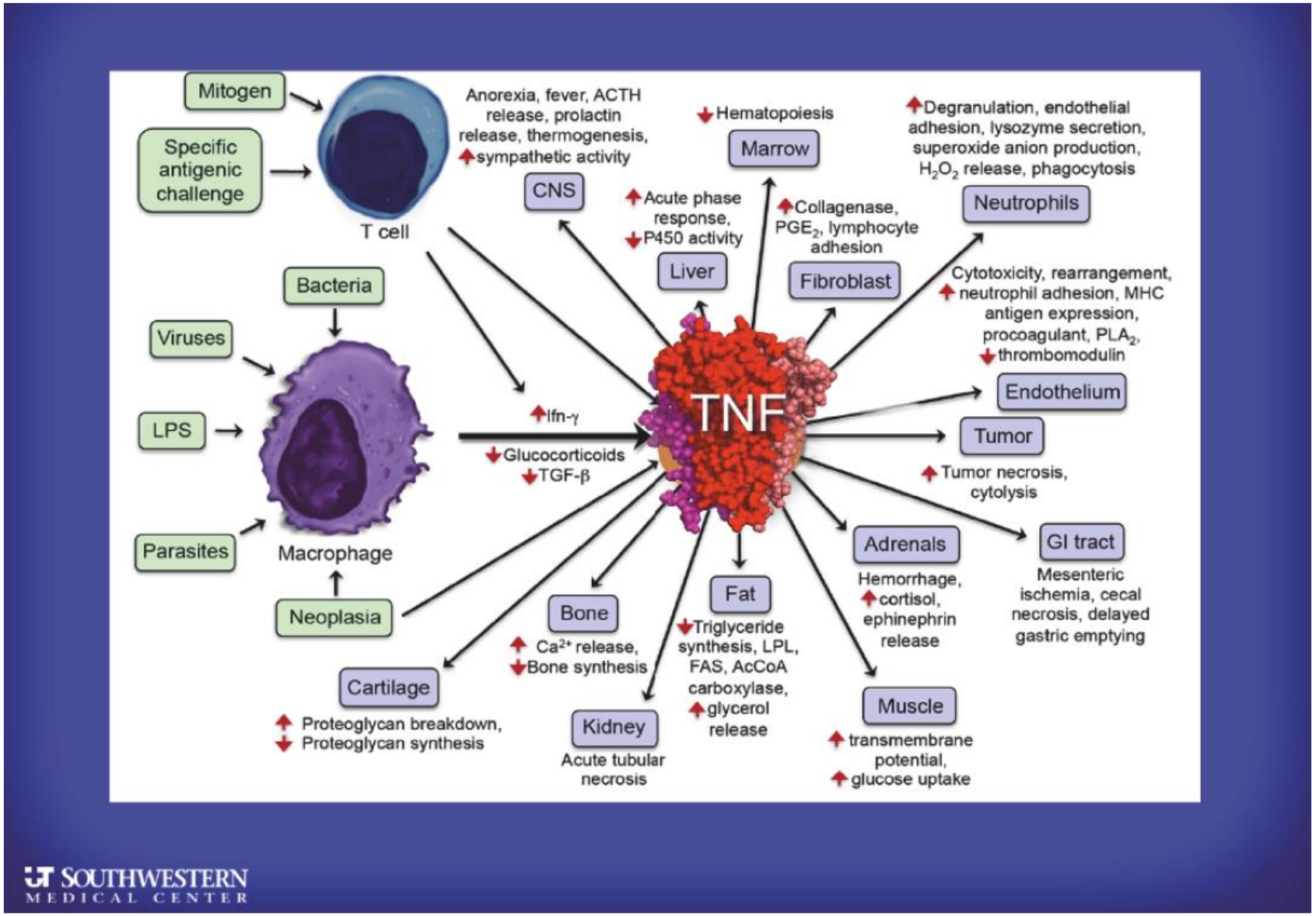
Purified TNF mimics LPS toxicity



1984

UT SOUTHWESTERN
MEDICAL CENTER

Beutler, Nobel Prize Lecture, 2011



Beutler, Nobel Prize Lecture, 2011

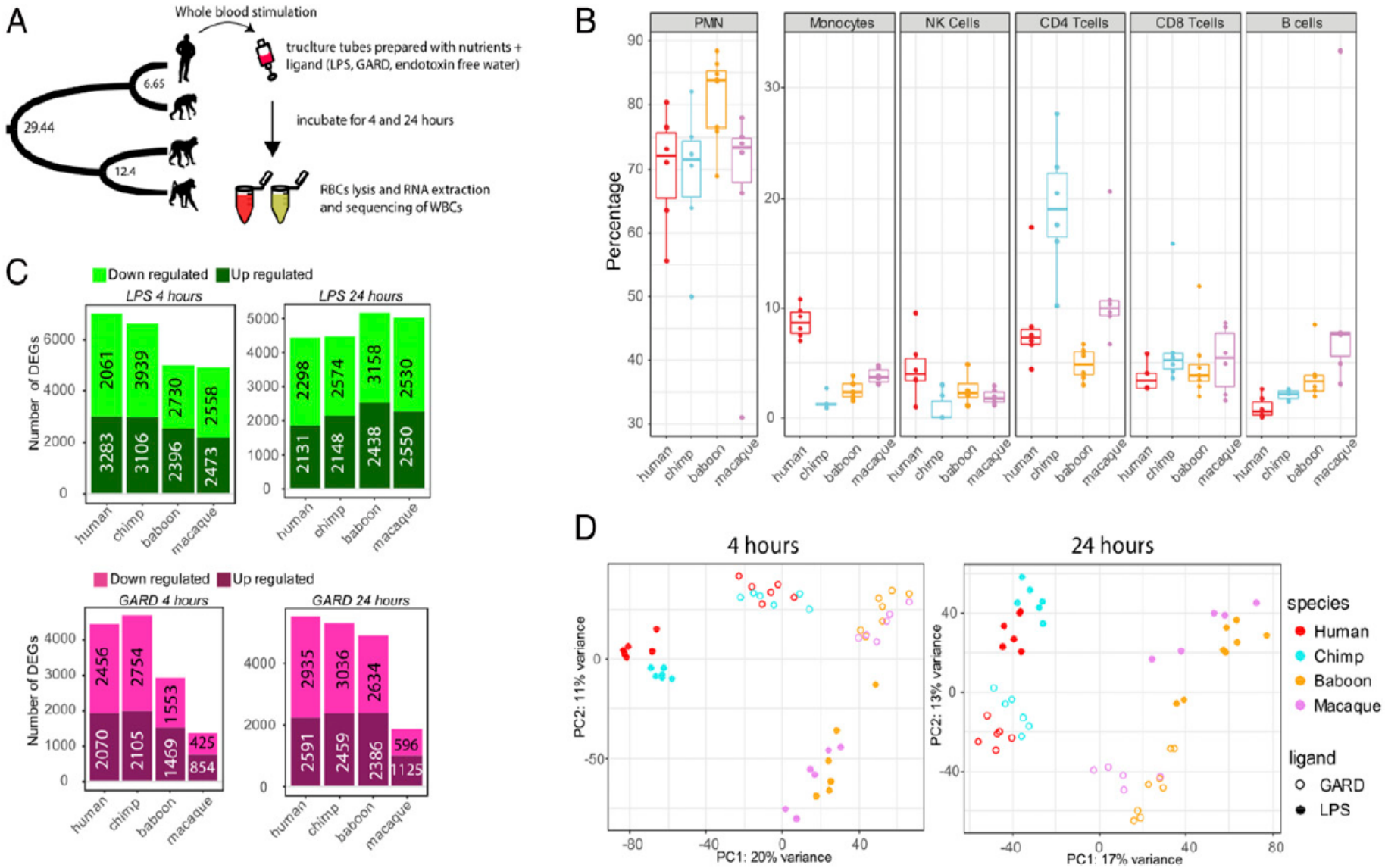


Fig. 1. Characterizing innate immune response upon viral and bacterial stimulation of primate white blood cells. (*A*) Schematic representation of the study design. Whole-blood samples from humans, common chimpanzees, rhesus macaques, and olive baboons were stimulated with bacterial or viral stimuli 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

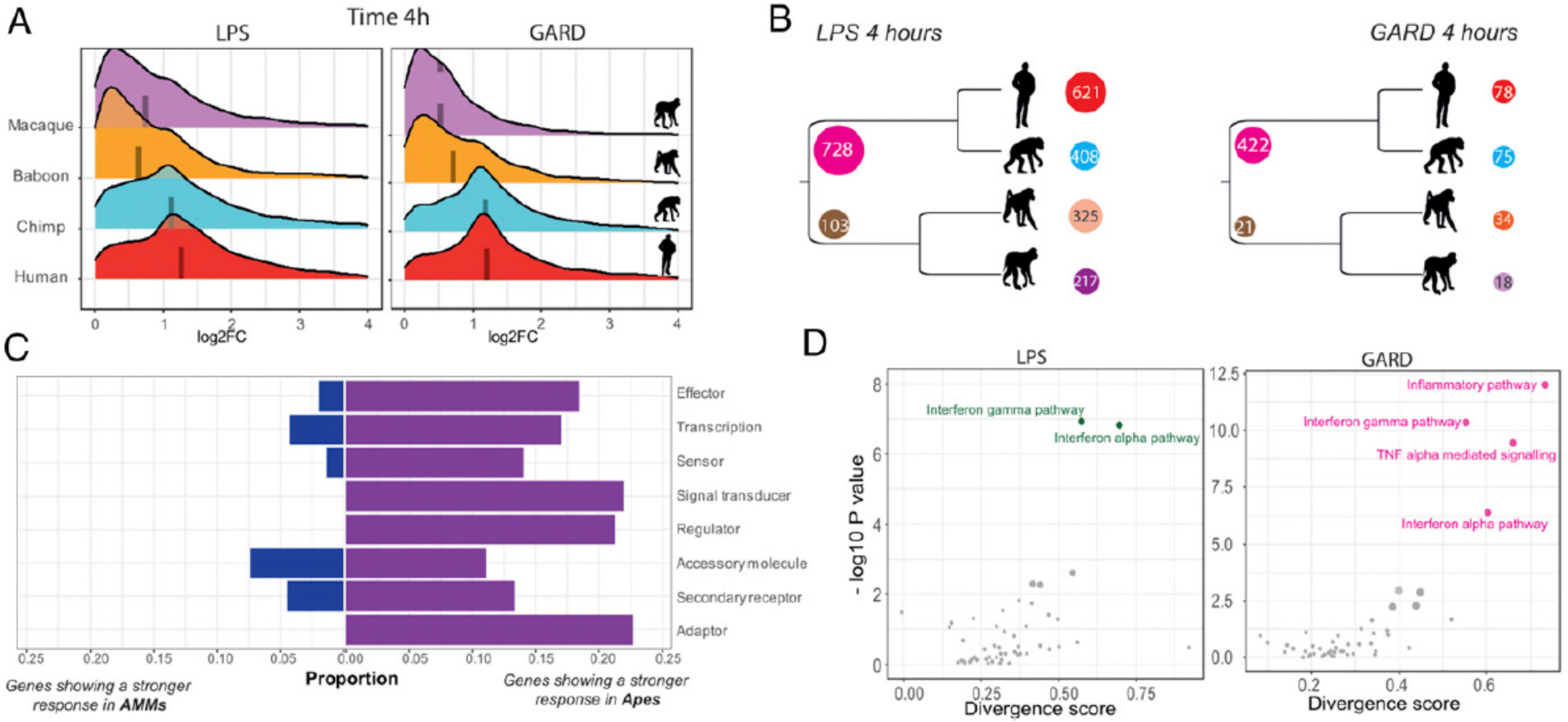


Fig. 2. Stronger early innate immune response in apes than monkeys. (*A*) For each combination of stimulus and time point, we show the distribution of the log2 fold changes (*x*-axis) among genes that respond to that treatment in at least one of the species. The median log2 fold-change responses in each species is represented by a dashed line. (*B*) Number of DRGs that are clade- or species-specific differently regulated genes at 4 h post-LPS (*Left*) and GARD (*Right*) stimulation. For c-DRG, we report the number of genes that show a stronger response in a specific clade at the beginning of the ancestral branch of the tree. For example, in response to LPS, we identified 831 c-DRGs from which 728 show a stronger response in apes and 103 in AAMs. For species-specific responsive genes, numbers are given in front of each species. The color codes for each species are red for human, cyan for chimp, orange for baboon, and violet for macaque. (*C*) Bar plots represent the proportions of different classes of innate immunity genes that are classified as c-DRGs with a higher response in apes (dark violet) or in AAMs (dark blue). (*D*) Scatter plot displaying total divergence scores of hallmark pathways for LPS (green) and GARD (pink) at 4 h stimulations. For a given pathway, the total divergence is given by divergence score (DS) on the *x*-axis and −log10 *P* values for each DS is on the *y*-axis. The pathways names, DS values, and corresponding *P* values are shown in Dataset S6. We highlight the pathways showing the most significant divergence scores for both the response to LPS and GARD.

Hawash, PNAS 2021

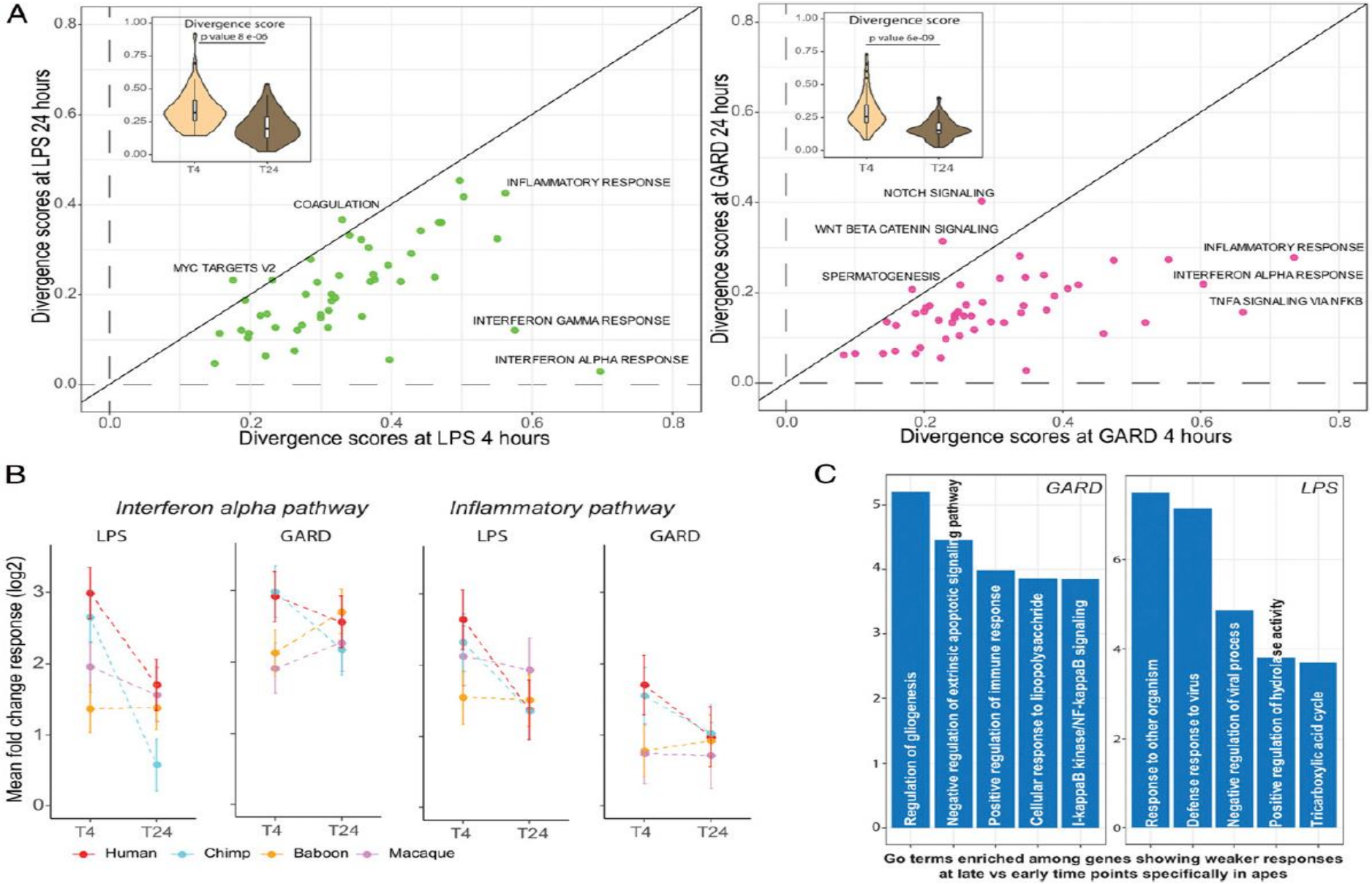


Fig. 4. Divergence of immune response is reduced at later time point. (*A*) Scatter plots of divergence scores of hallmark pathways at early (*x*-axis) and later time points (*y*-axis) for LPS (green) and GARD (maroon) stimulations. The inset boxplots contrast the distribution of divergence scores among all pathways between the two time points. *P* values were obtained using Mann–Whitney *U* test. (*B*) Estimates of the mean response at the two time points for each species (± SE) across genes bellowing to the interferon alpha and inflammatory response hallmark pathways. (*C*) GO enrichment analysis for genes that showed significant decrease in response in apes only (FDR < 0.05 in apes and FDR > 0.05 in monkeys) for LPS and GARD. Top significant GO terms are given as indicated by −log10 *P* value on the *x*-axis.

Hawash, PNAS 2021

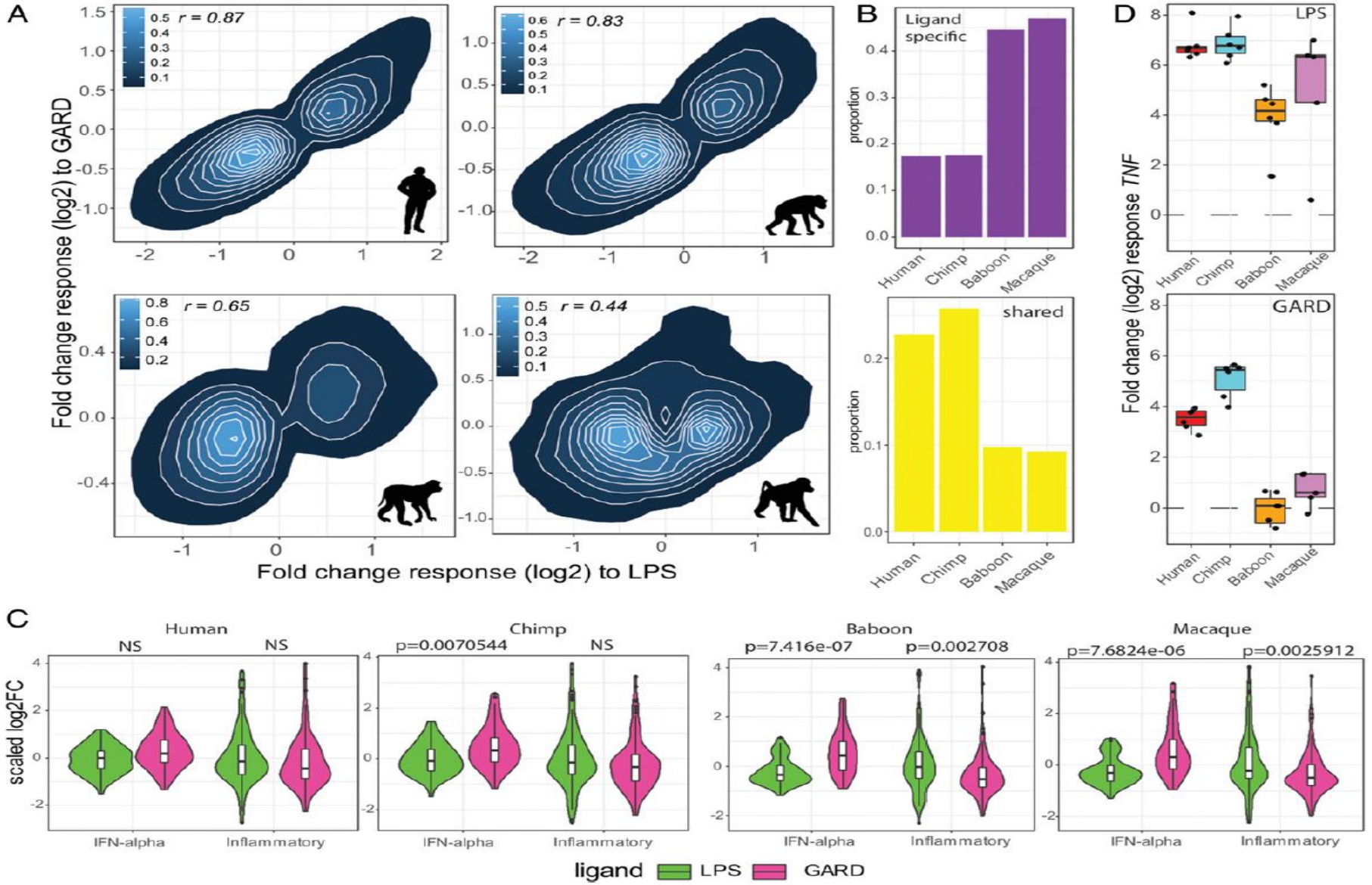
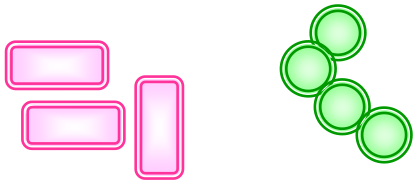


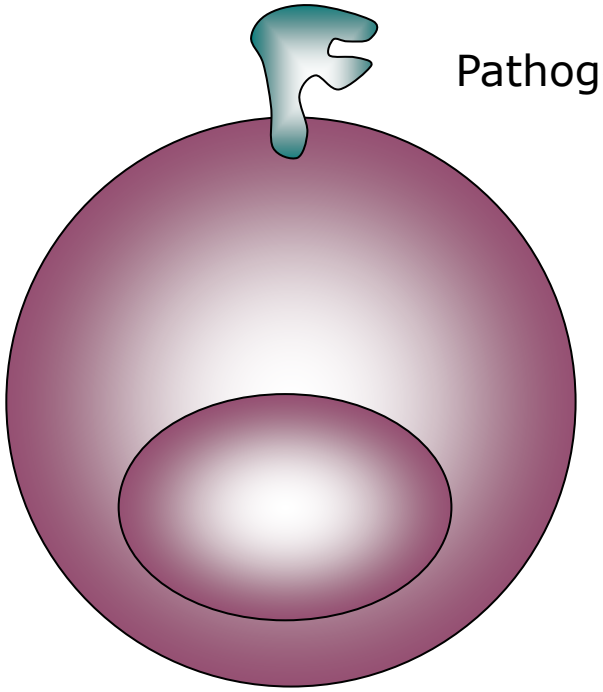
Fig. 5. Apes engage a less-specific innate immune response than AAMs. (*A*) Correlation plots of the magnitude of the fold-change responses between LPS (*x*-axis) and GARD-stimulated cells (*y*-axis). For each of the species, we only include genes that were differentially expressed (FDR < 0.05) in response 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.

Hawash, PNAS 2021

Mécanismes



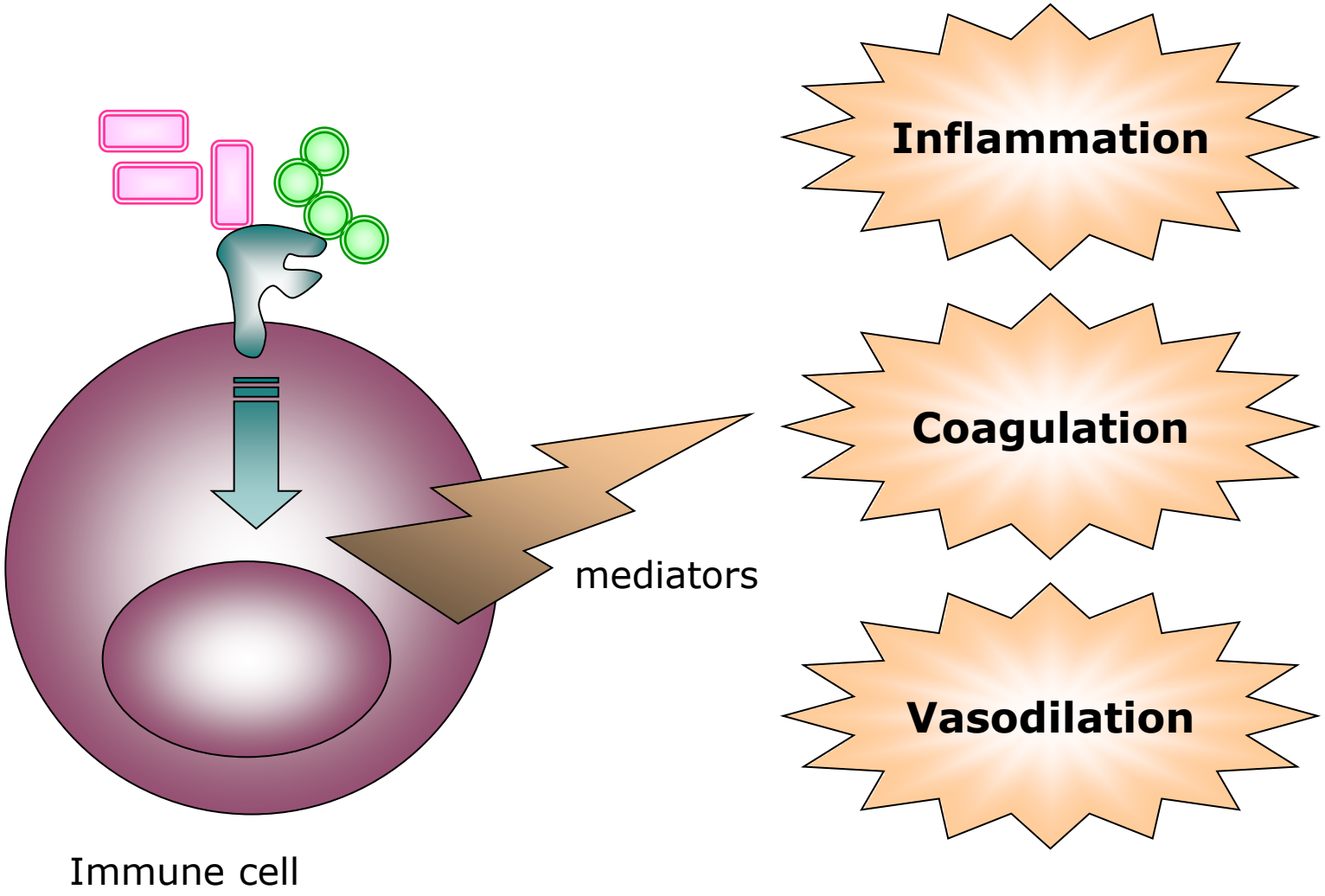
Bacteria



Pathogen Associated Mollecular Pattern

Immune cell

Mécanismes


Inflammation
Coagulation
Vasodilation
mediators
Immune cell

Phase Soluble

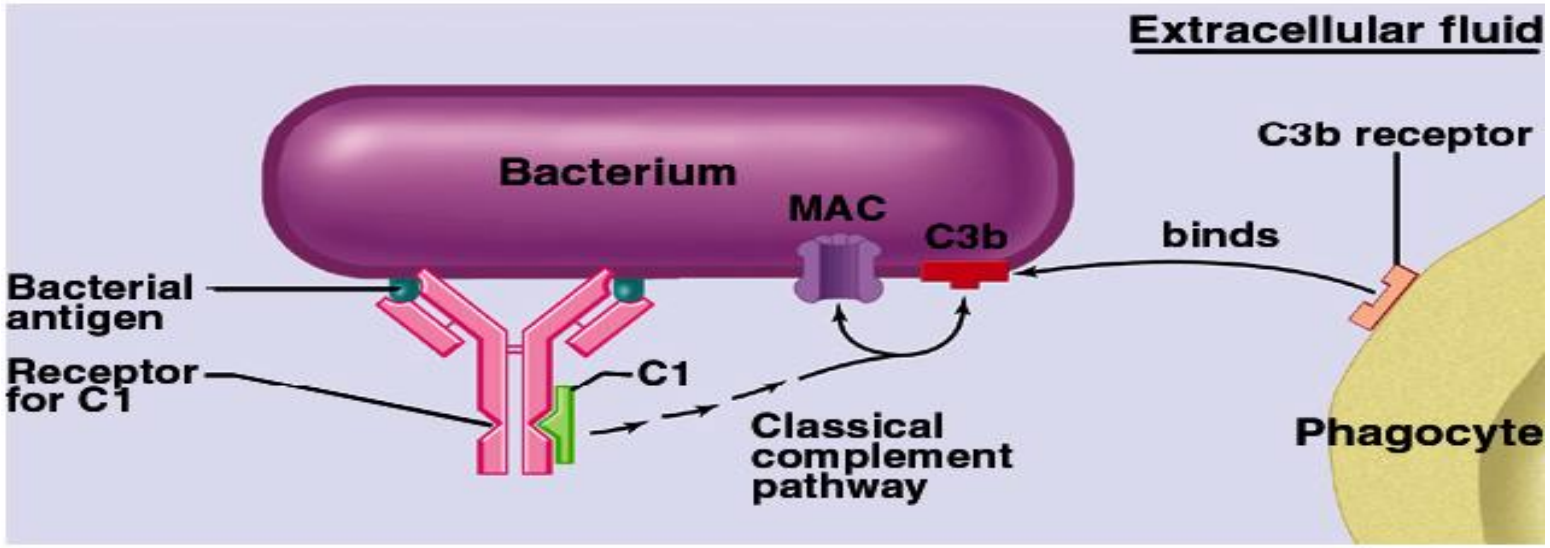
« Soluble » phase of bacteria recognition (sang, autres milieux)

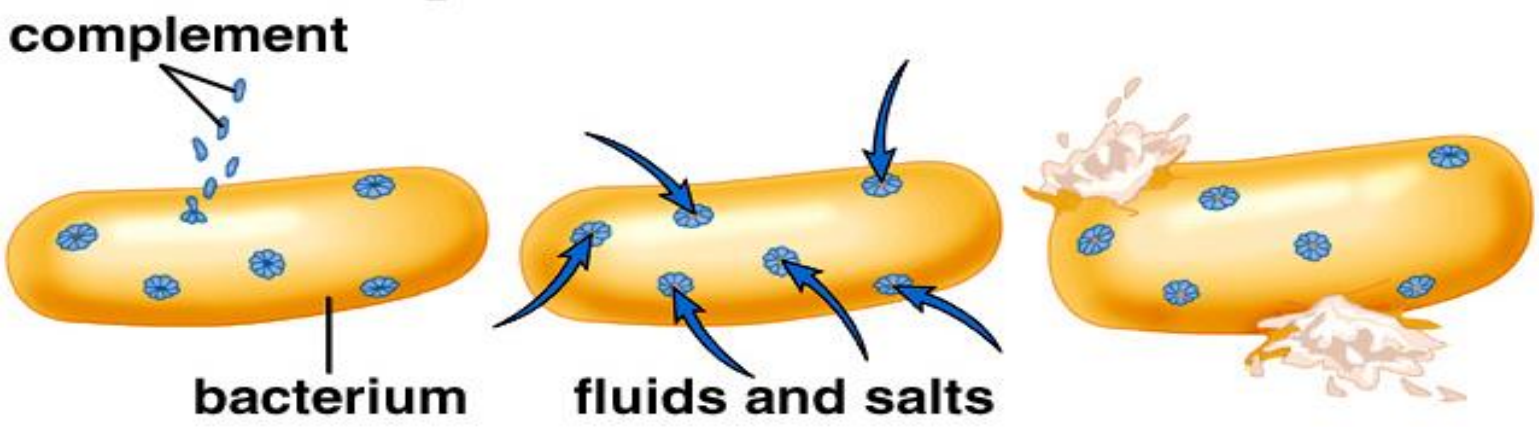
- Molécules qui reconnaissent les bactéries
(LBP, sCD14, sMD-2)

- Molécules opsonisantes
(AC, complément/C3b)

- Molécules avec activité bactéricide
(complément, BPI, lysozyme, …)

Ex.: Système du Complément





Phase Cellulaire

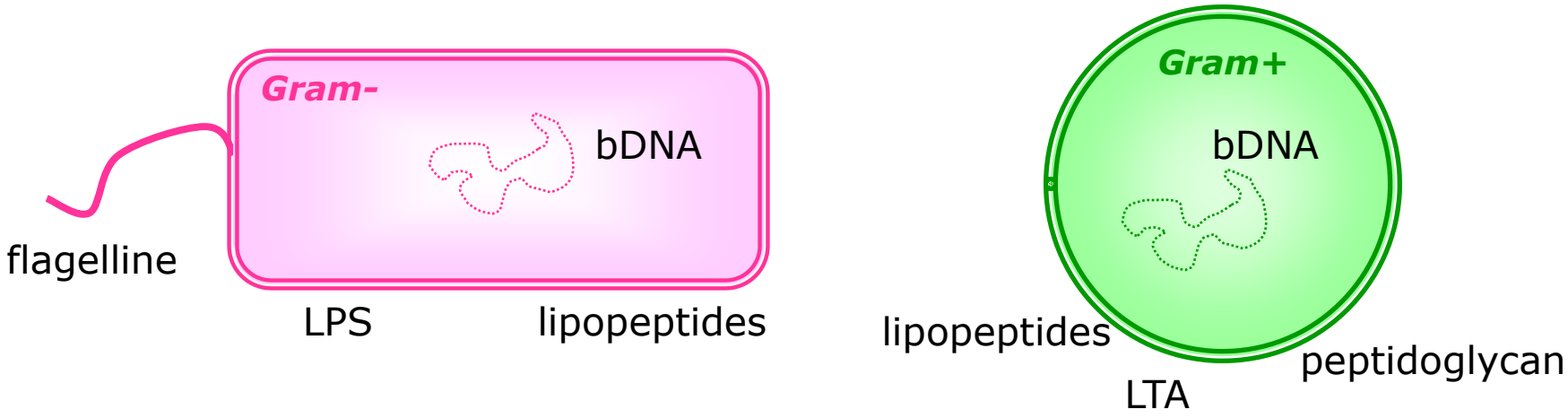
Cellules de immunité innée :

Monocytes/macrophages (bactéries)
Neutrophiles (bactéries, champignons, ...)
Eosinophiles (parasites)
Basophiles/mastocytes (réaction inflammatoire)
NK cellules (virus, cellules tumorales)

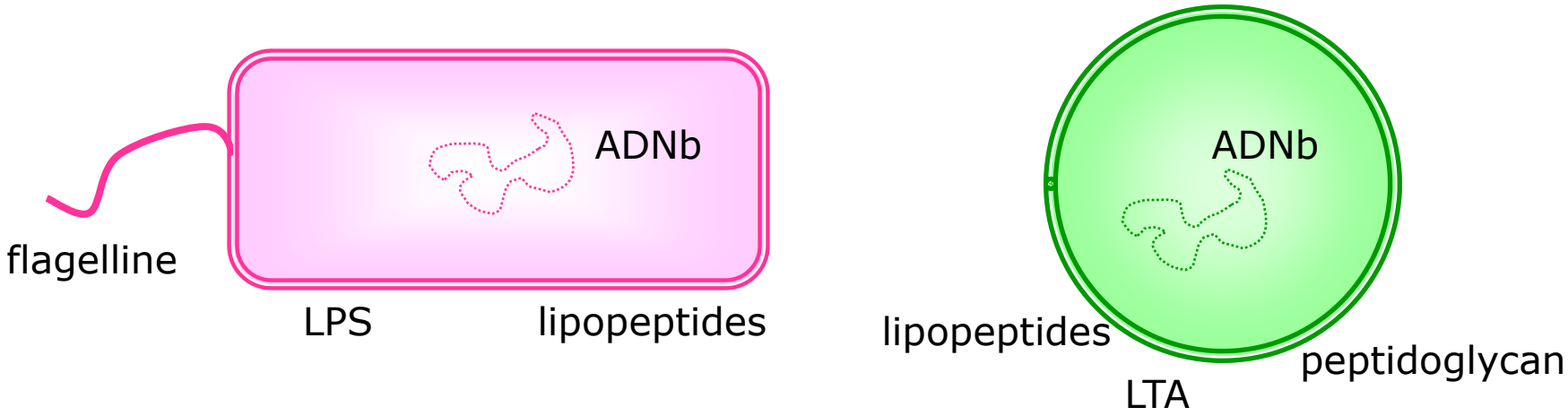
Et aussi: *cellules épithéliales et endothéliales*

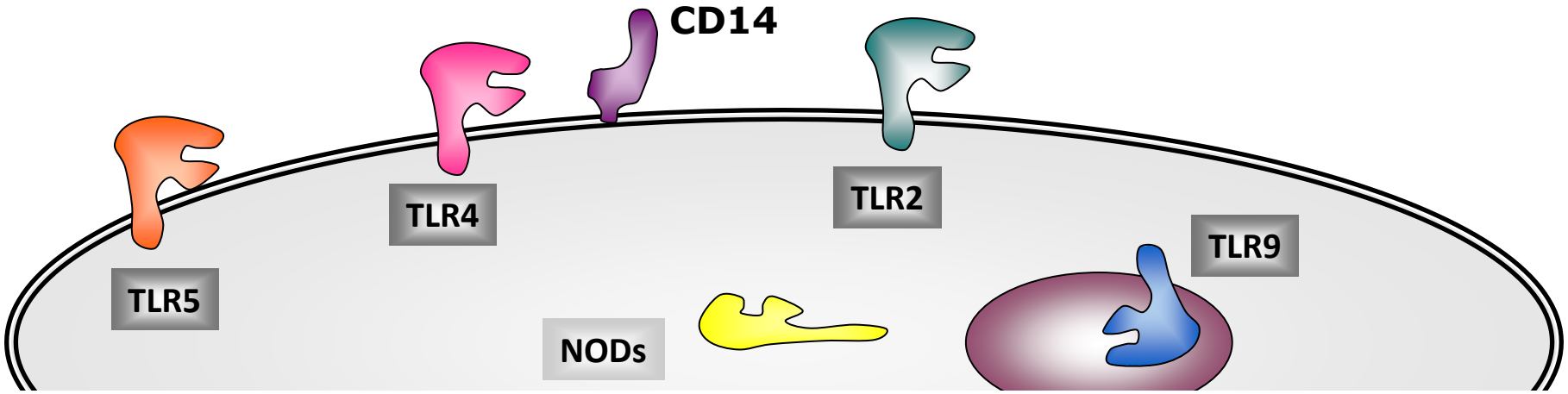
- contribuent à la réponse inflammatoire
- récepteurs aux composants microbiens
- activité phagocytaire
- produisent des molécules anti-microbiennes

Reconnaissance bactérienne

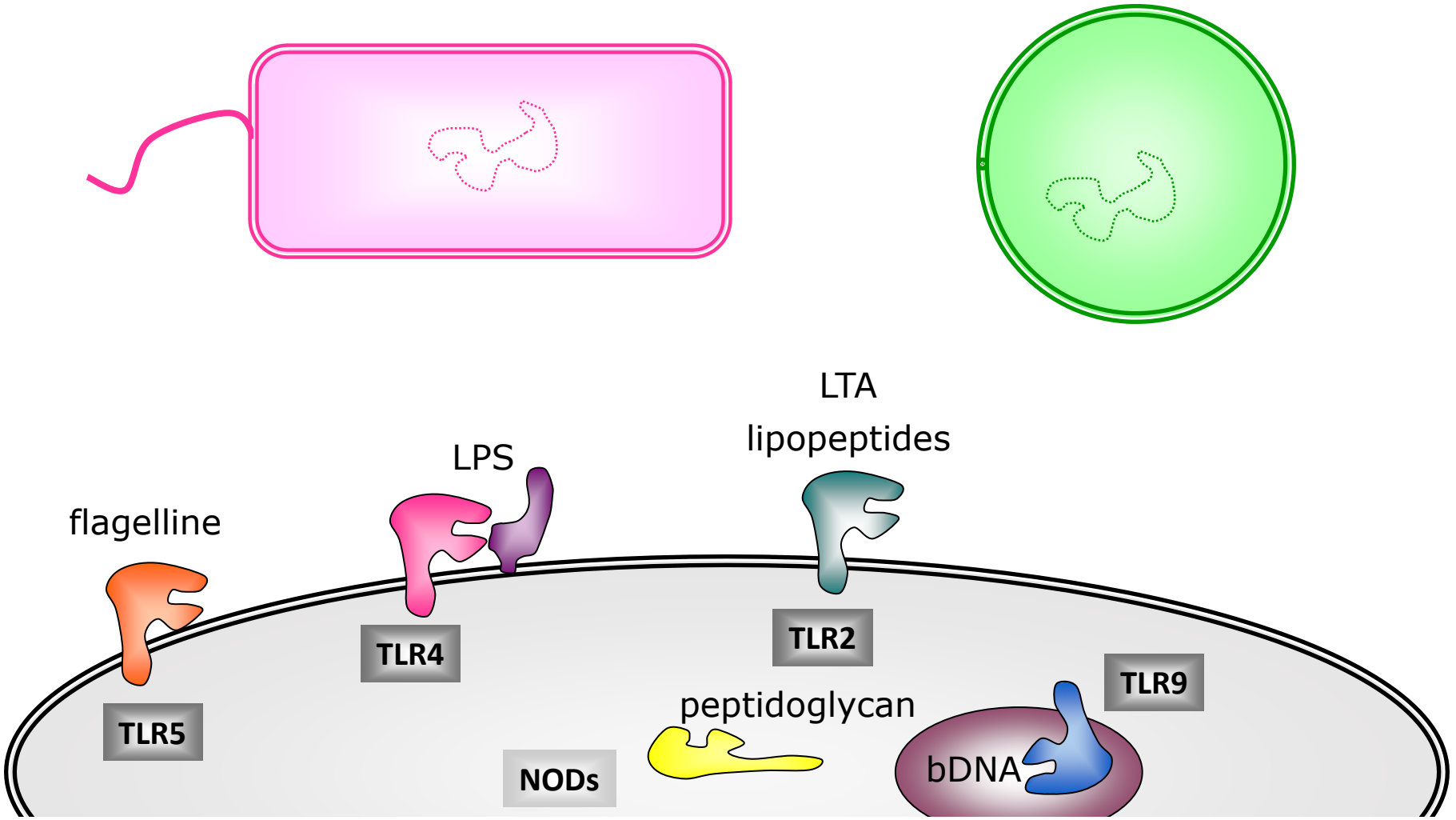


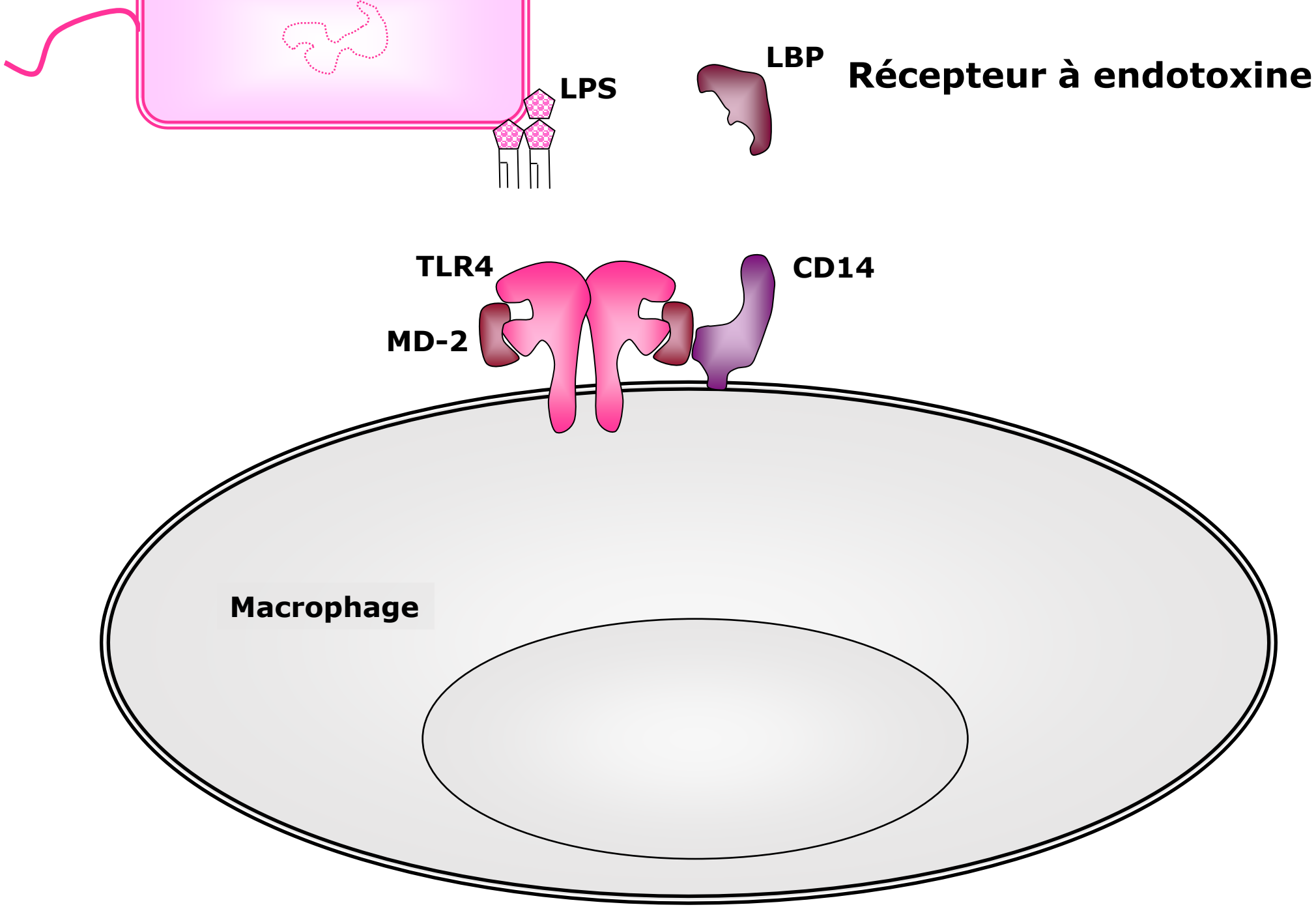
Reconnaissance microbienne : récepteurs Toll



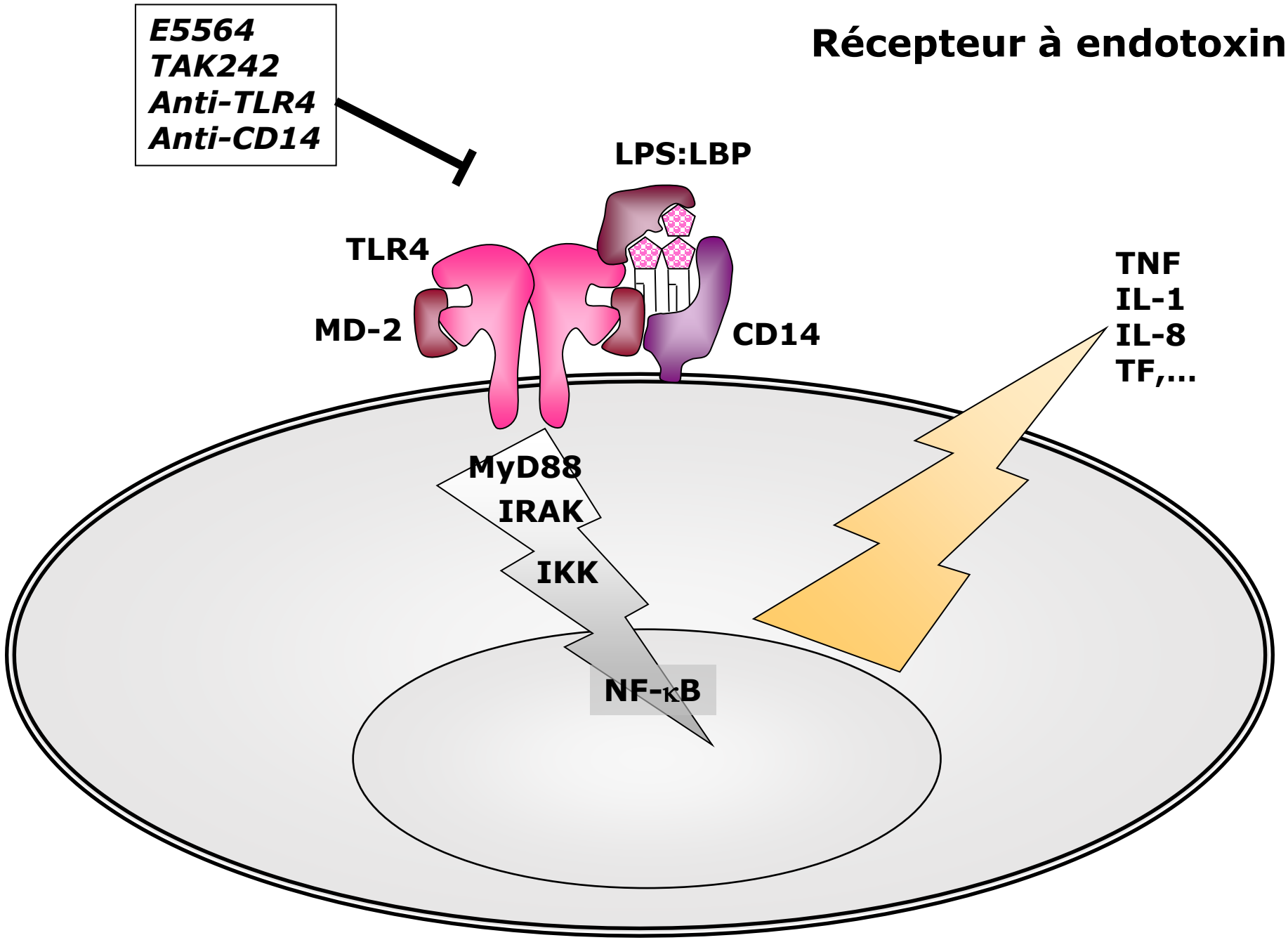


Reconnaissance microbienne : récepteurs Toll




LPS
LBP
Récepteur à endotoxine
TLR4
CD14
MD-2
Macrophage

Récepteur à endotoxine



Tissue damage/necrosis
-
shock/ischemia

DAMPs

Uric acid → **NALP3**

ATP_{ec} → **$P2X_7R$**

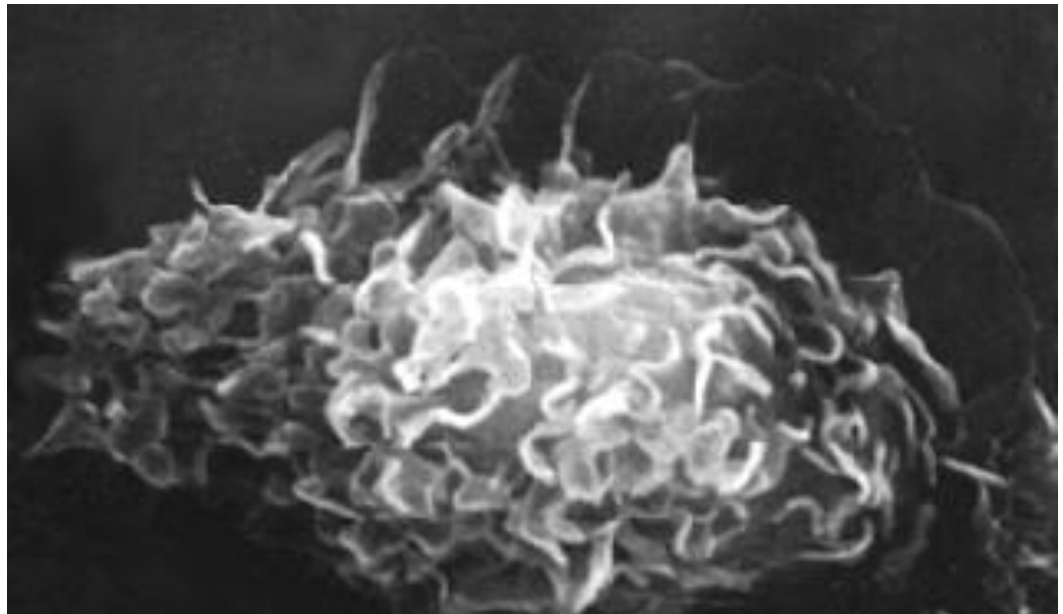
osmolality → **p38**

hypoxia → **ORE**

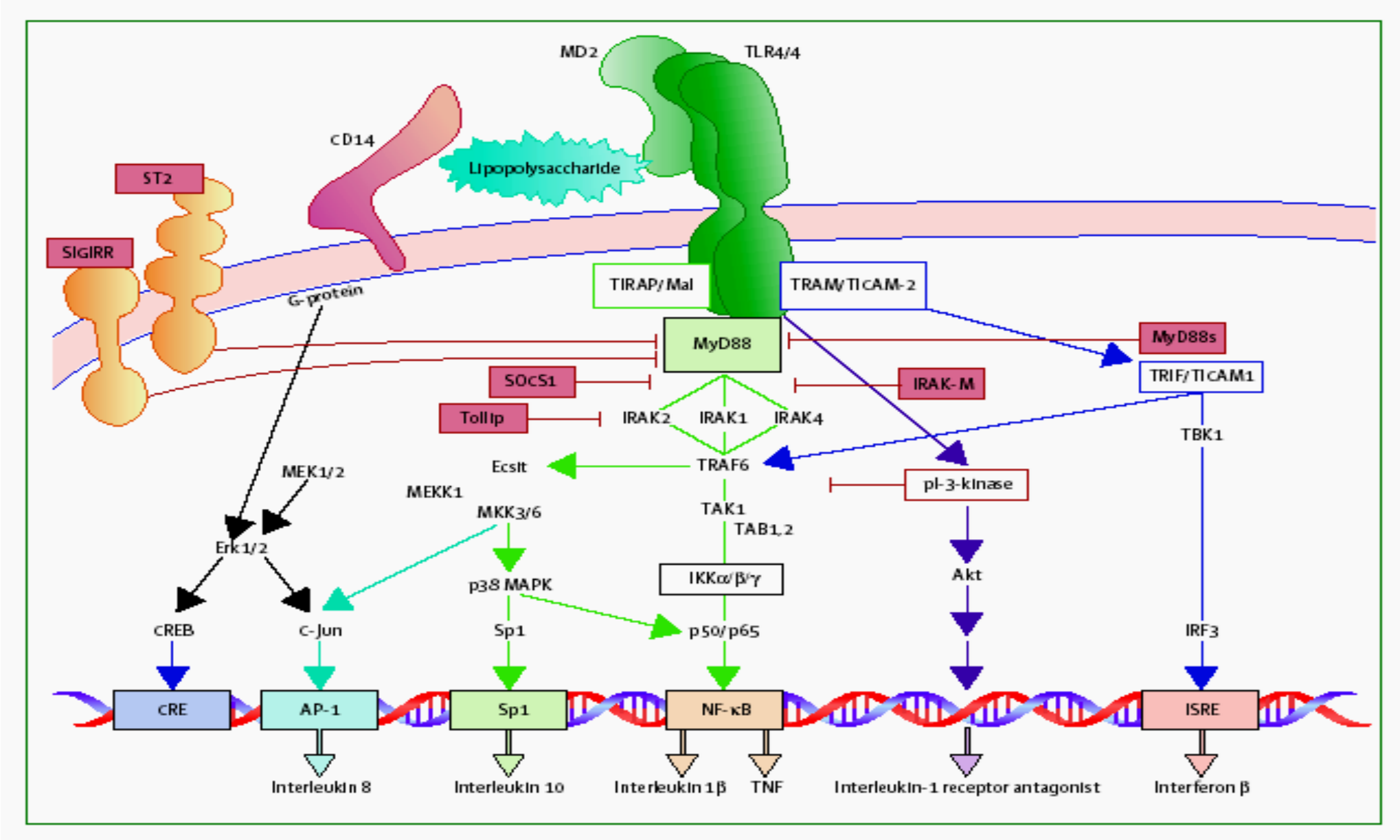
HSPs
HMGB-1 → **TLR2/4**
RAGE

substance P → **Récepteur NK-1**

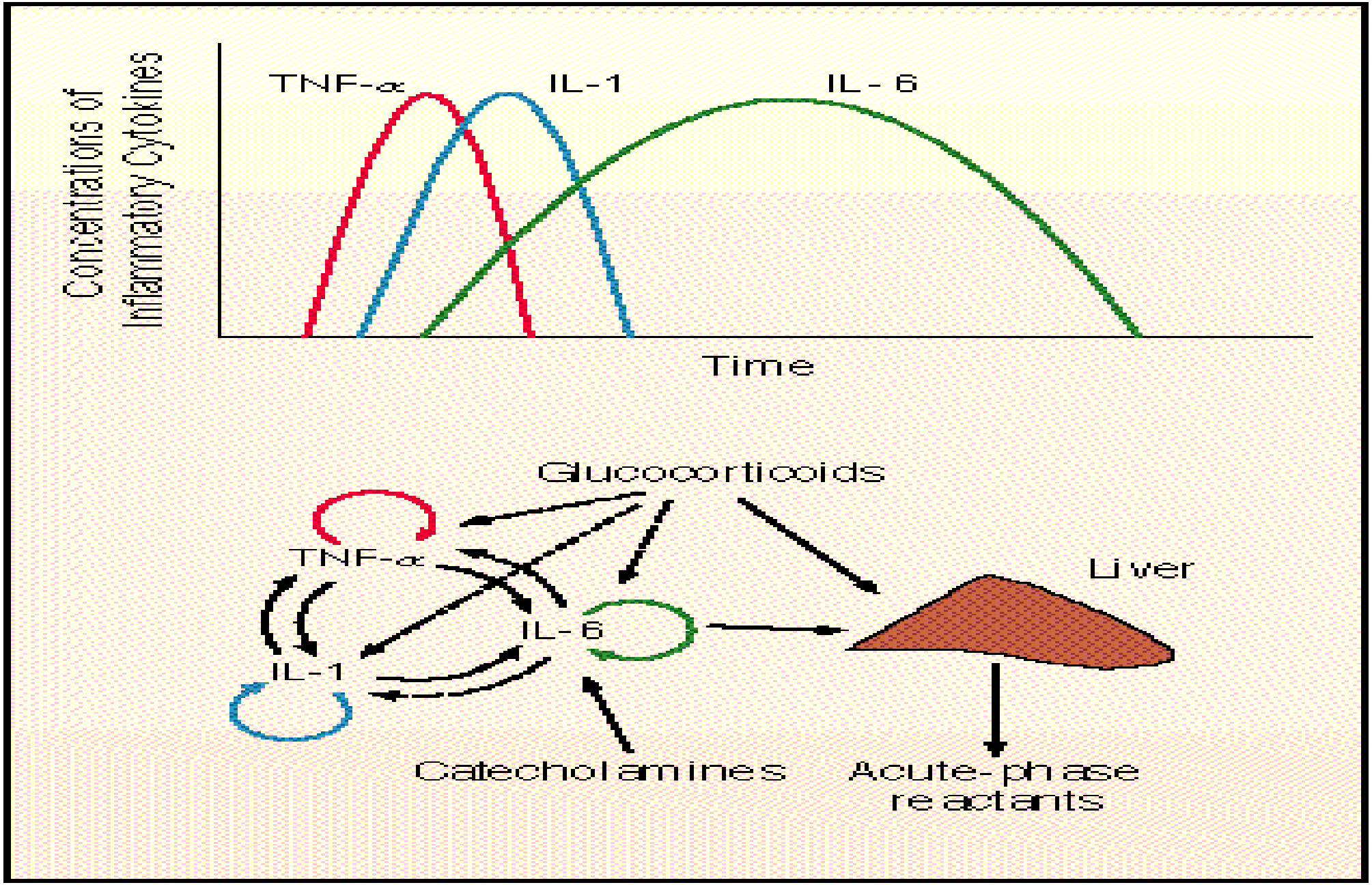
stretch → **Integrins**
FAK, MAPK
NF-κB



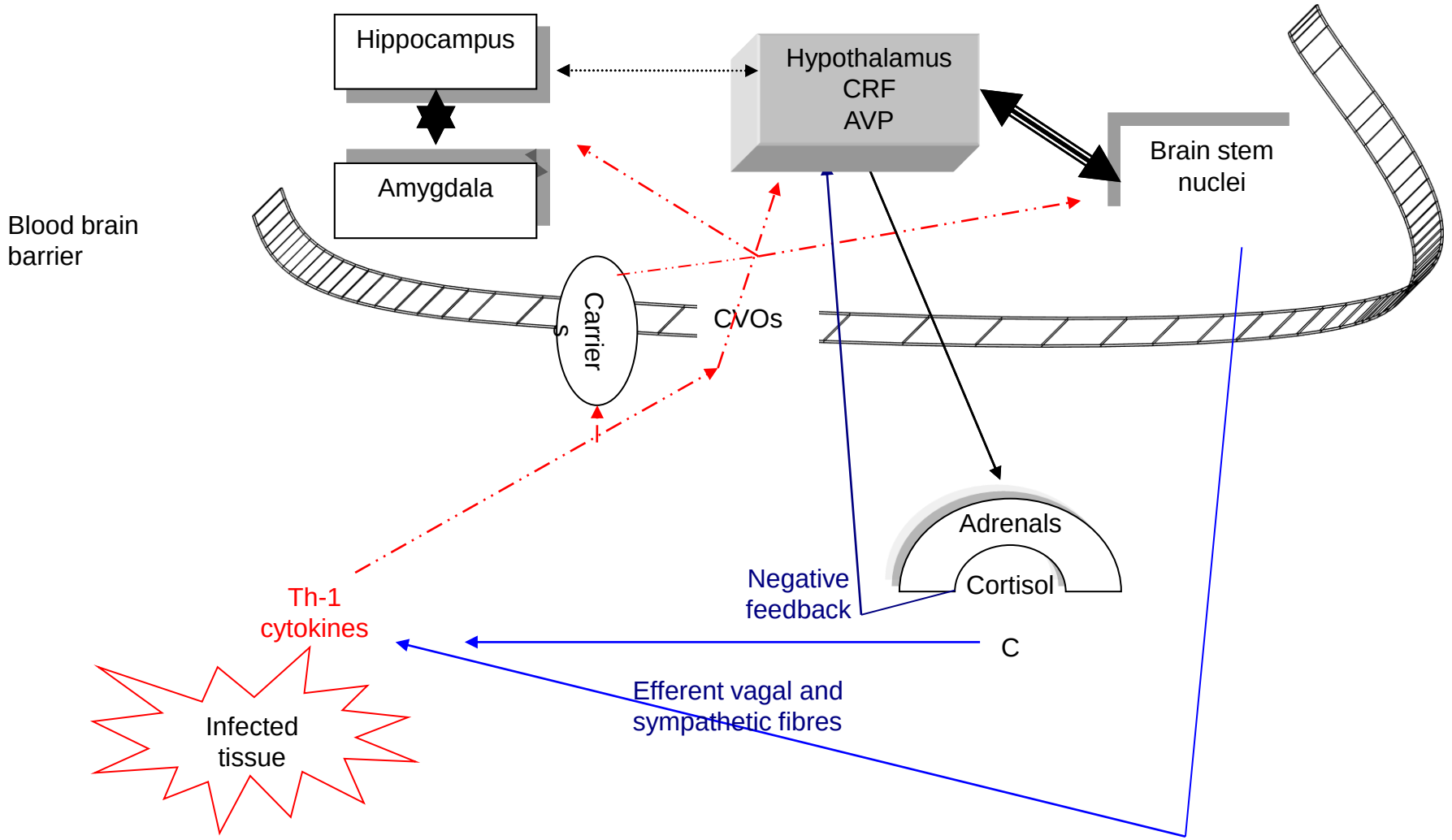
thrombine → **PAR**



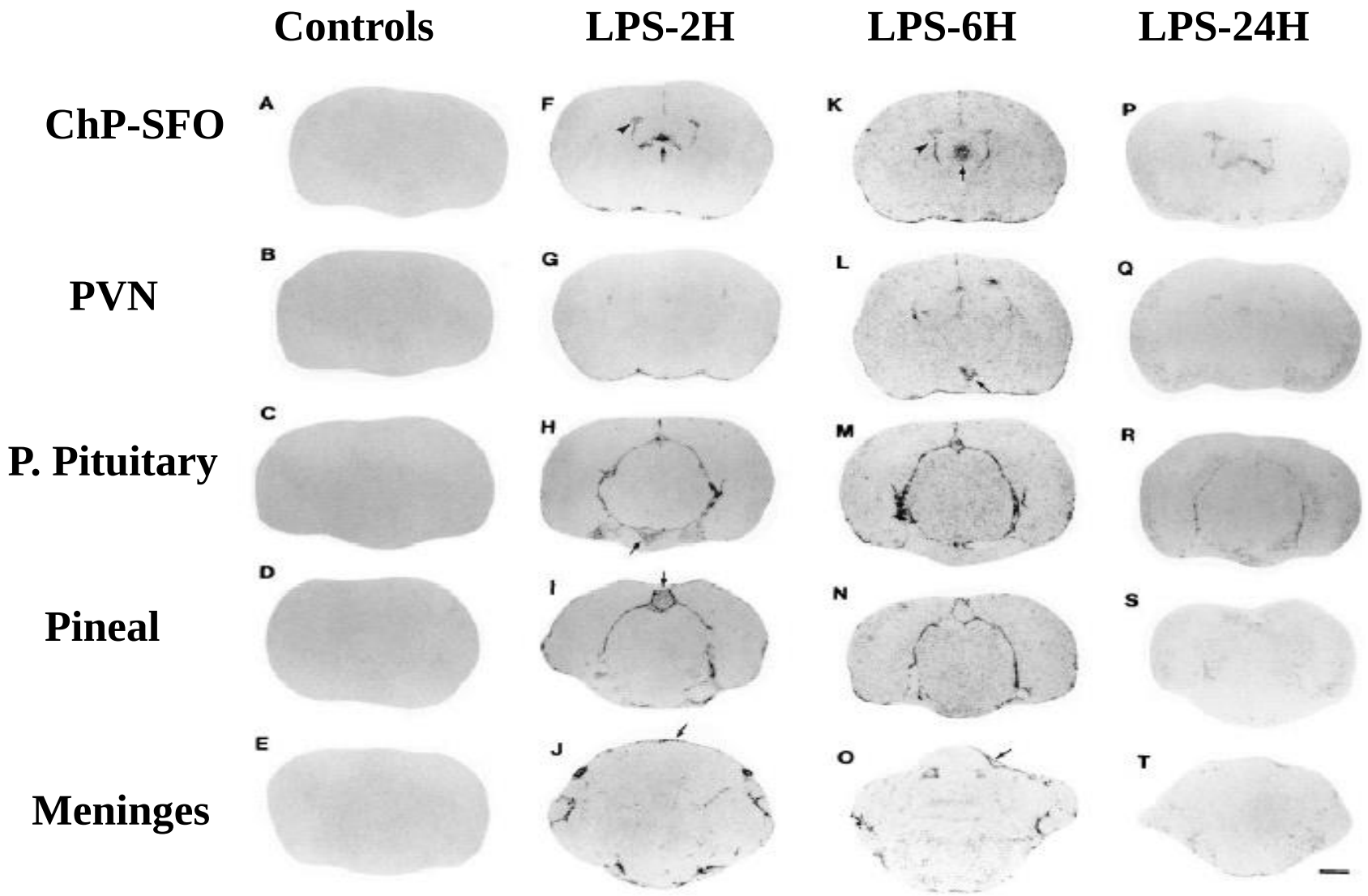
Annane Lancet 2005


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

Cytokines Trafficking to the Brain



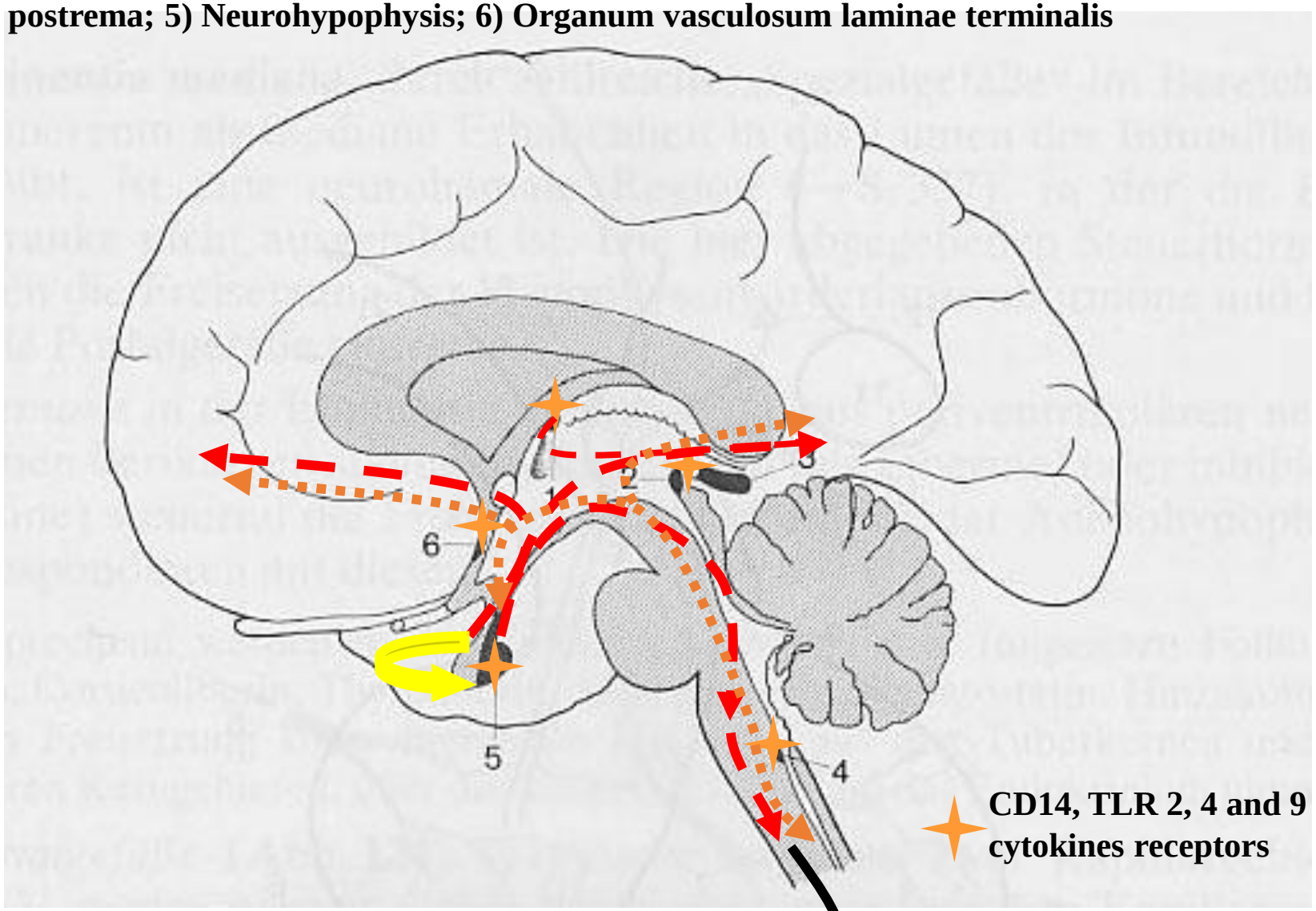
IL-1β mRNA



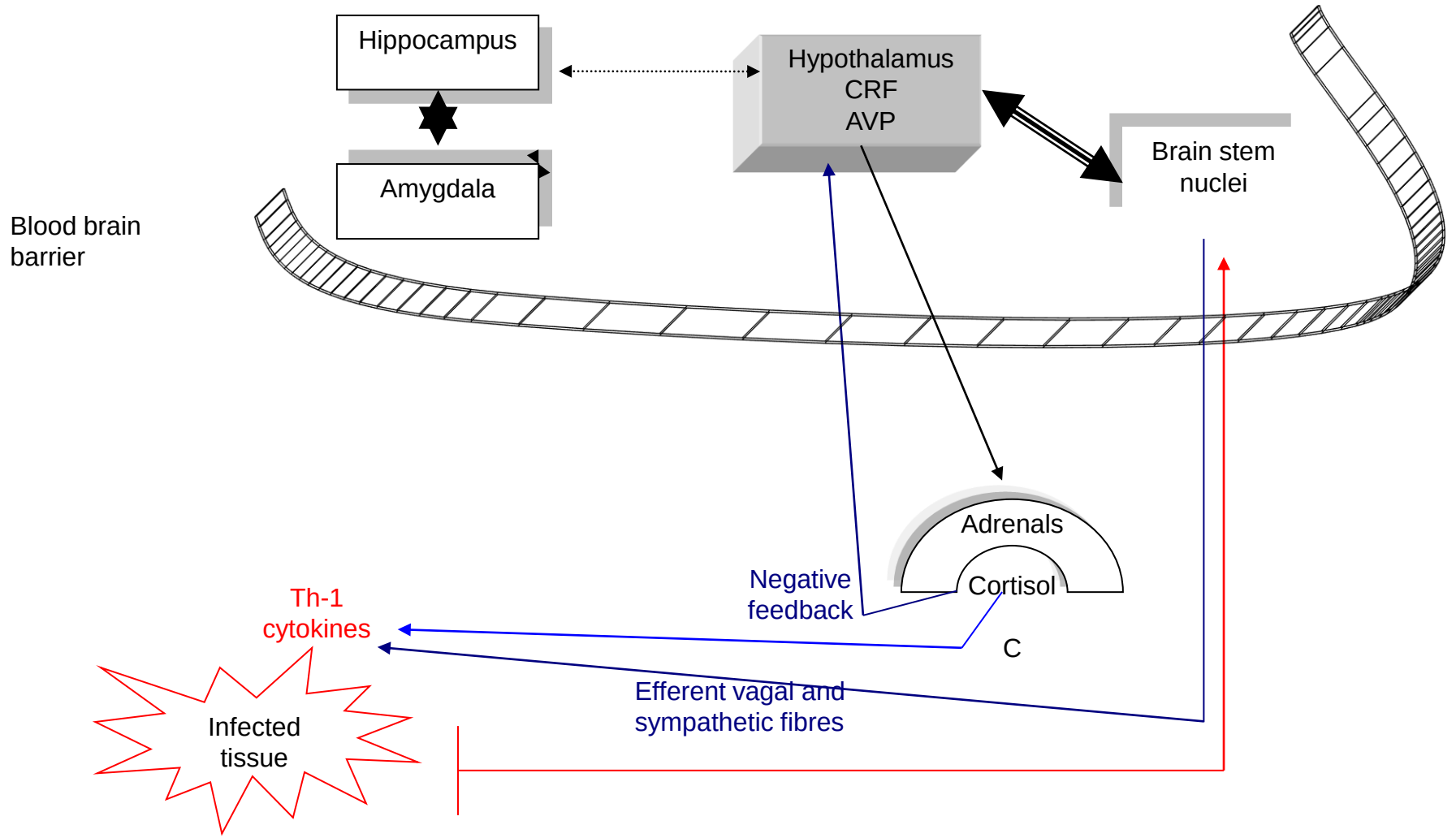
Wong et al PANS 1997

Circumventricular organs:

1) Organum subfornicale; 2) Organum subcomisurale; 3) Corpus pineale 4) Area postrema; 5) Neurohypophysis; 6) Organum vasculosum laminae terminalis

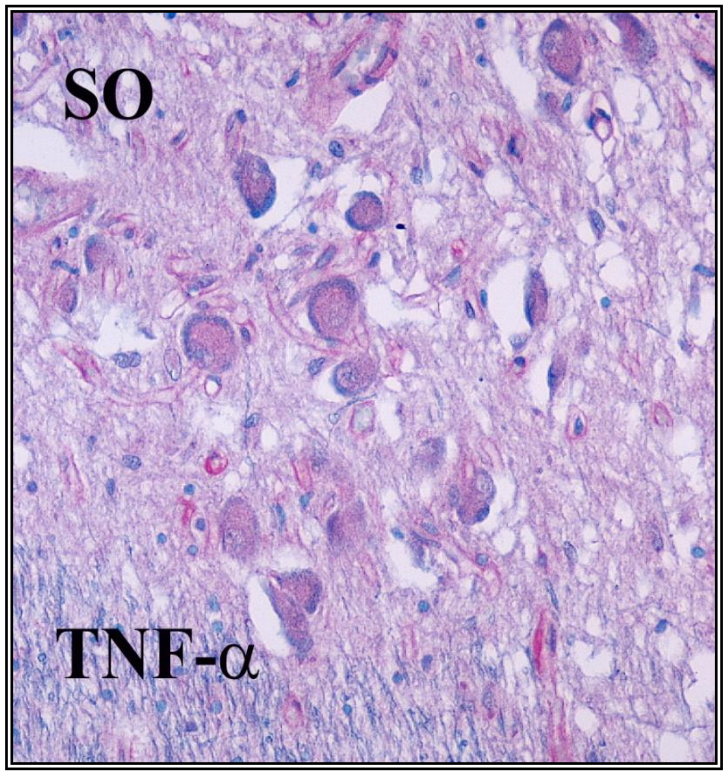


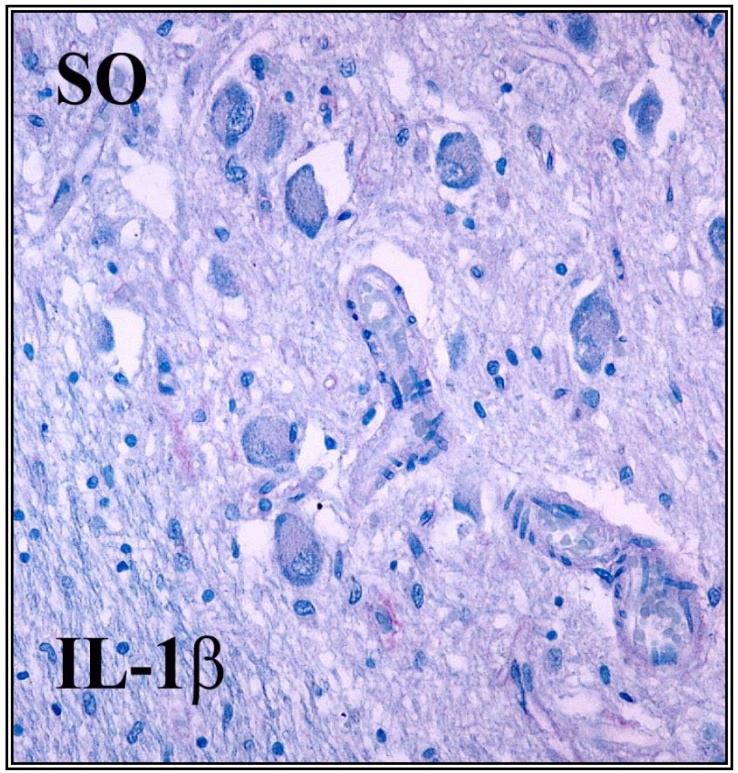
Cytokines Trafficking to the Brain



Brain Expression Cytokines in a Patient with Peritonitis

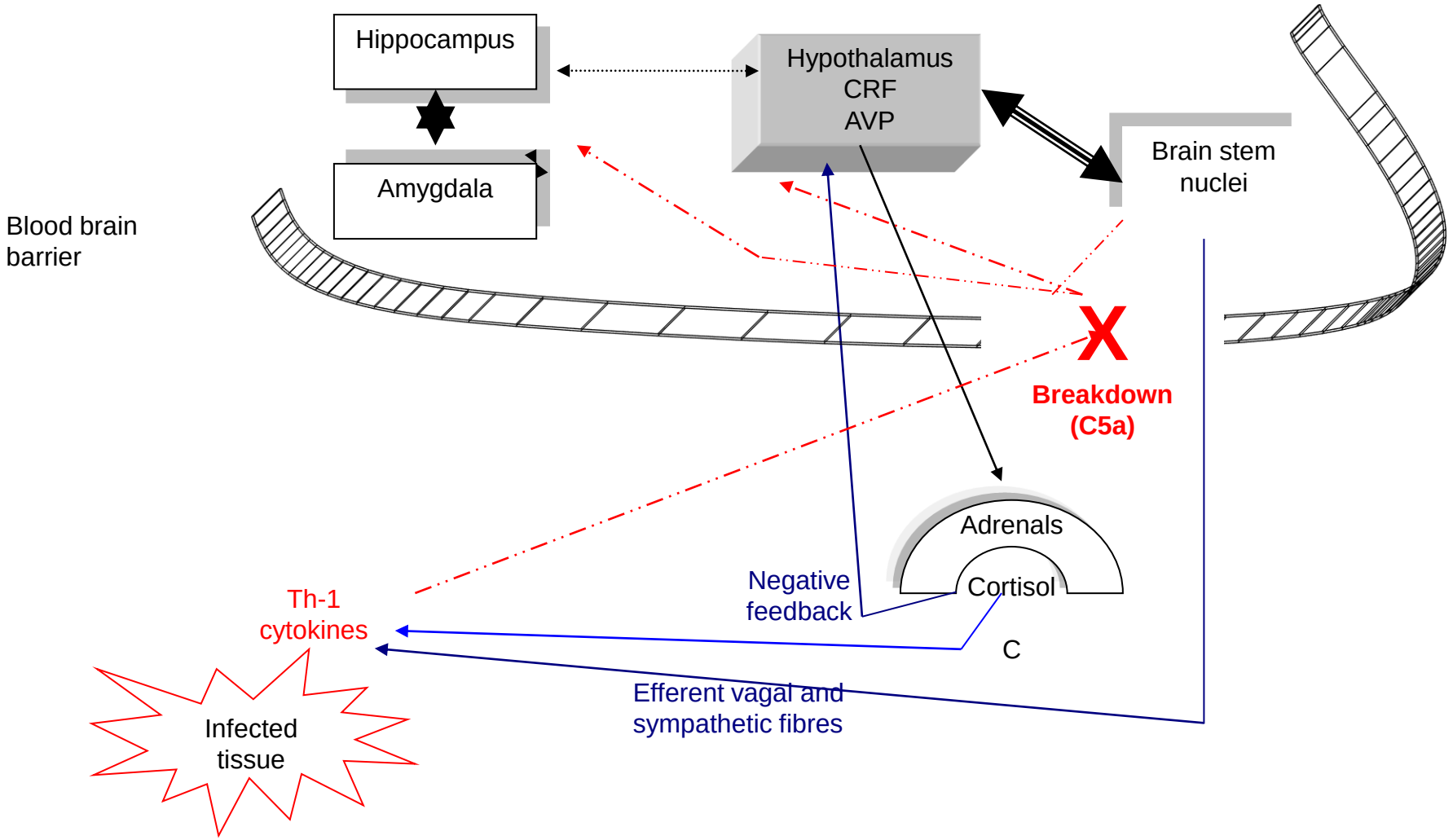
Hypothalamus





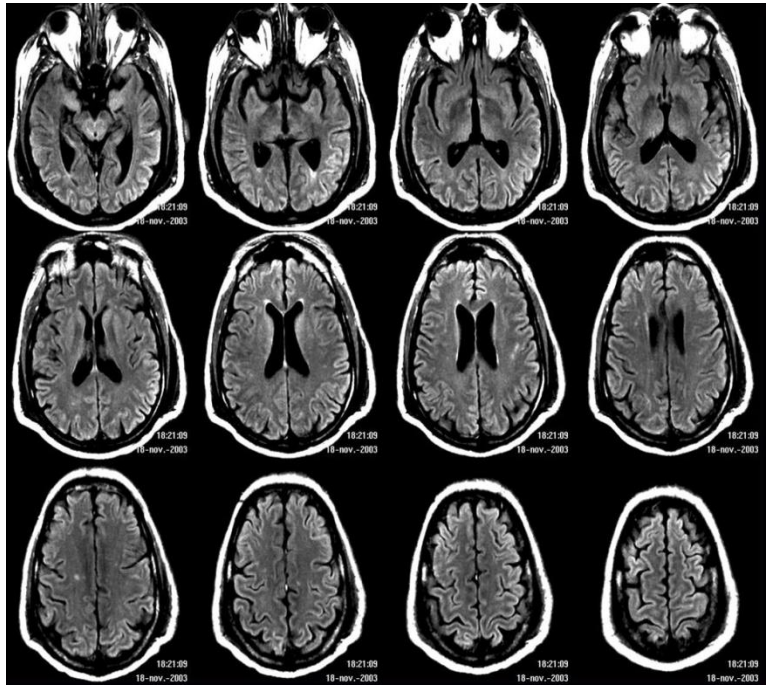
Sharshar, Lancet 2003

Cytokines Trafficking to the Brain

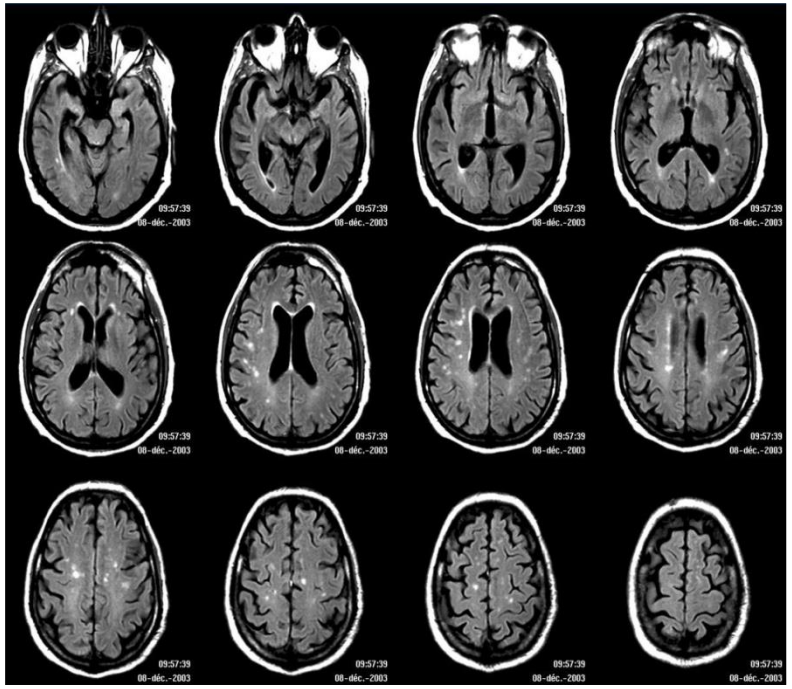


Breakdown of the Blood-Brain-Barrier in a Patient with CAP

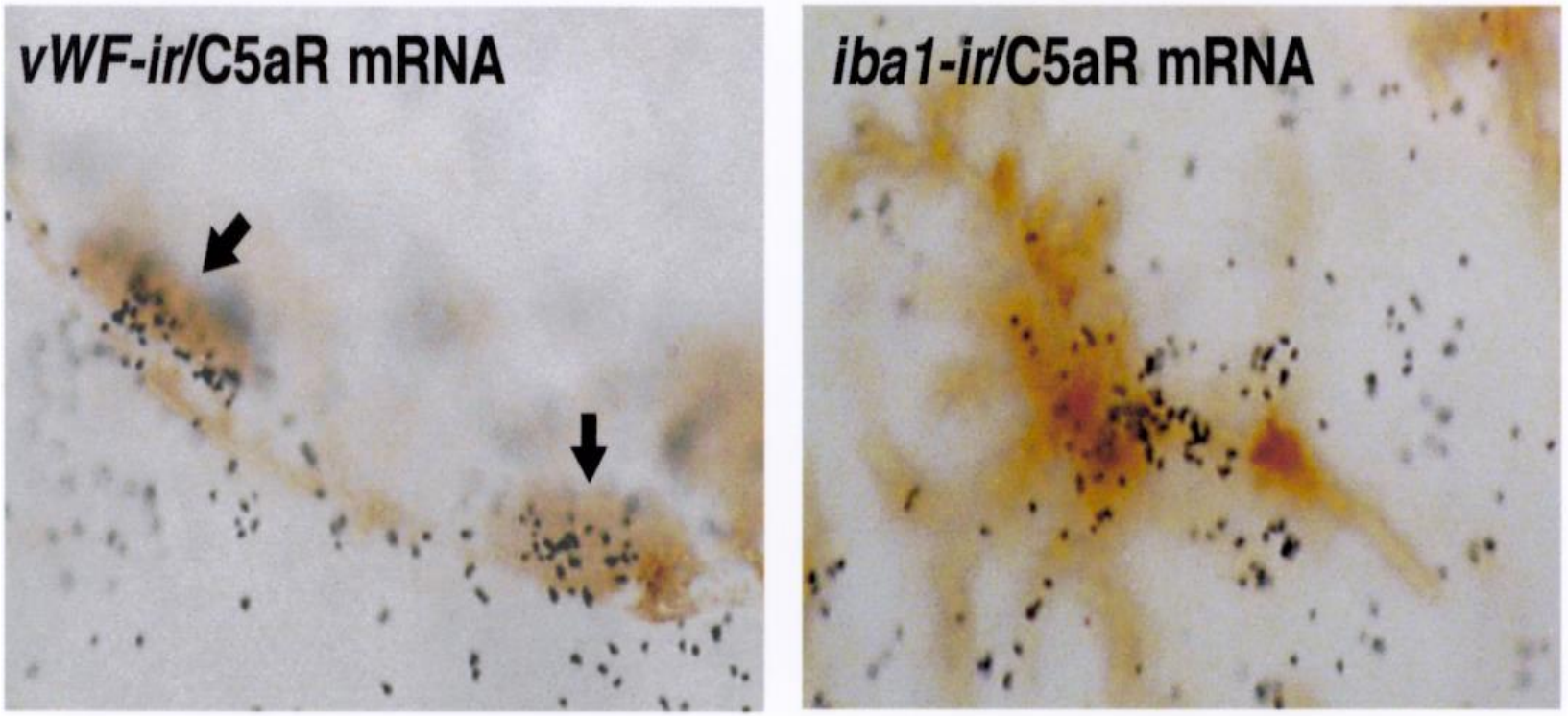
Day 1 of sepsis



Day 3 of sepsis

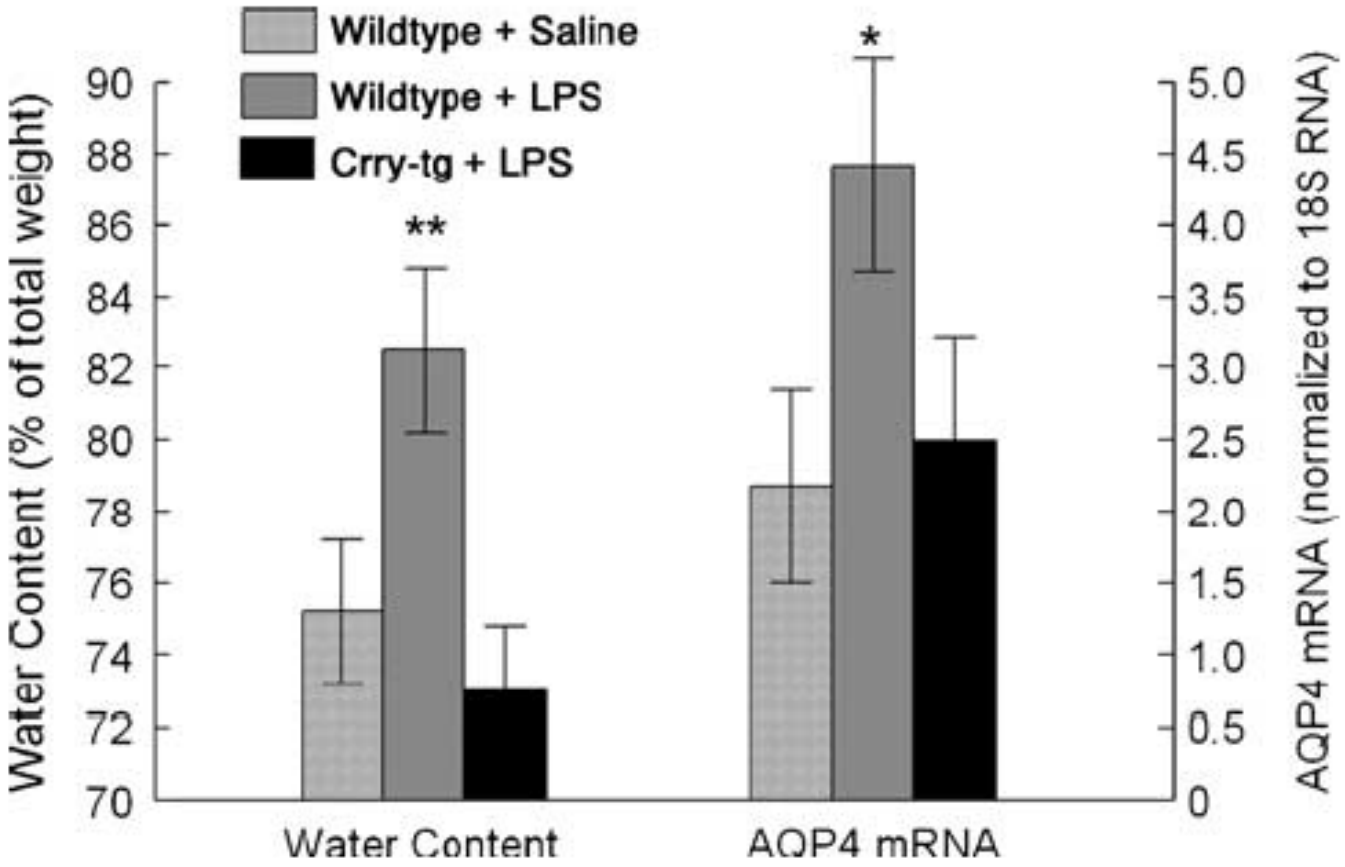


LPS activates Complement Pathway

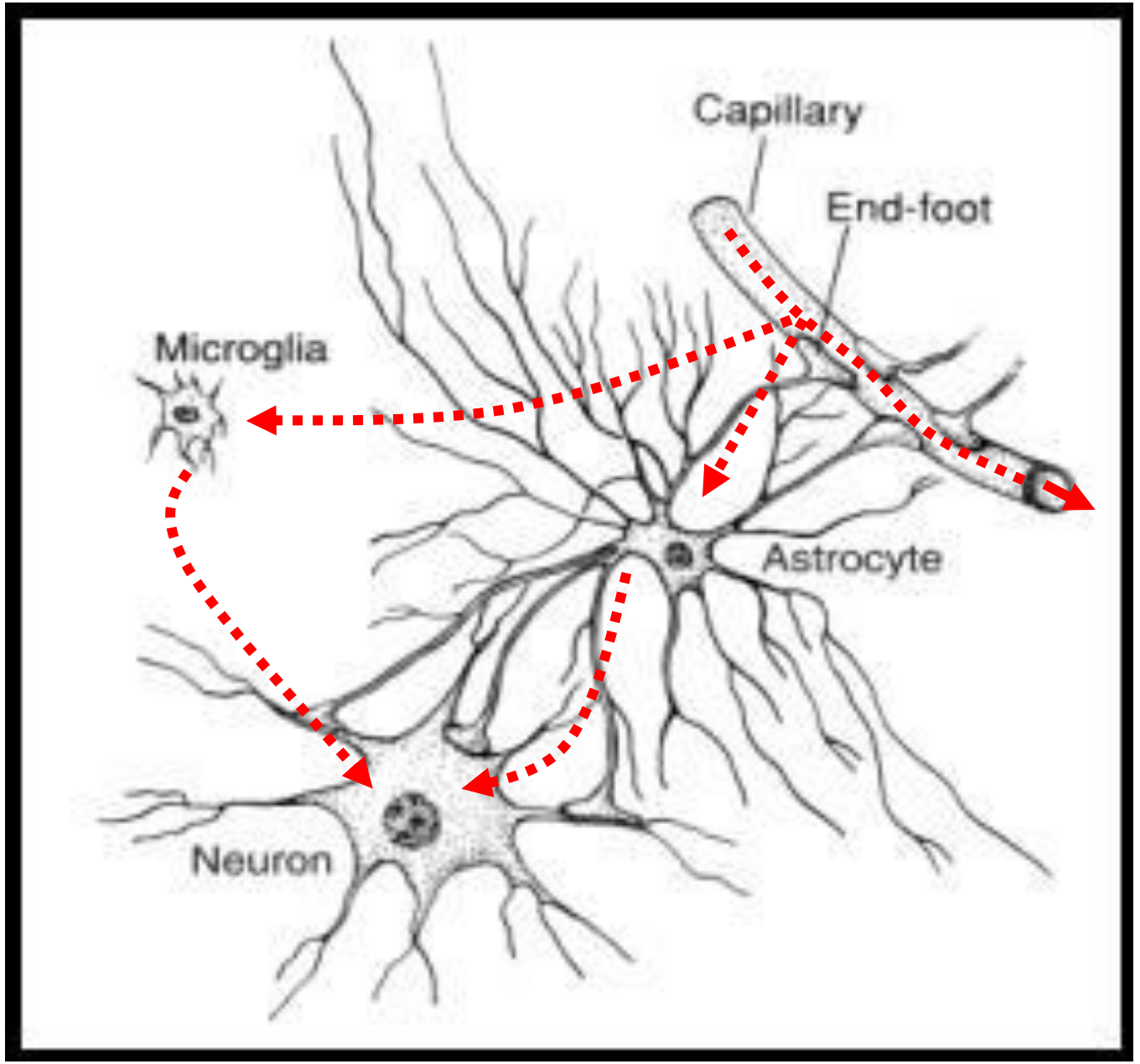


Nadeau, FASEB 2001

Complement activation induces breakdown in the BBB



Jacob, Lab Invest 1997


Capillary
End-foot
Microglia
Astrocyte
Neuron

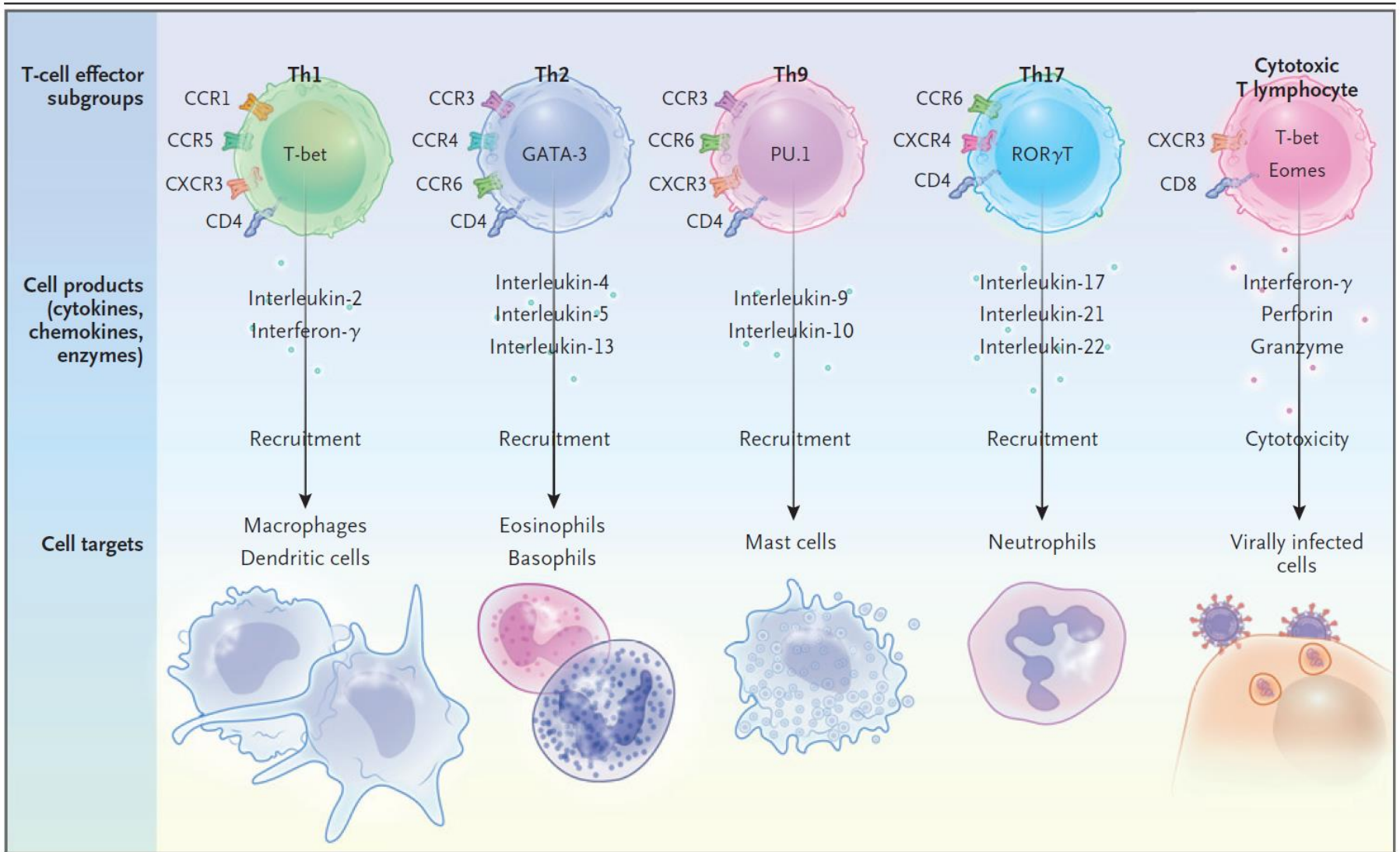
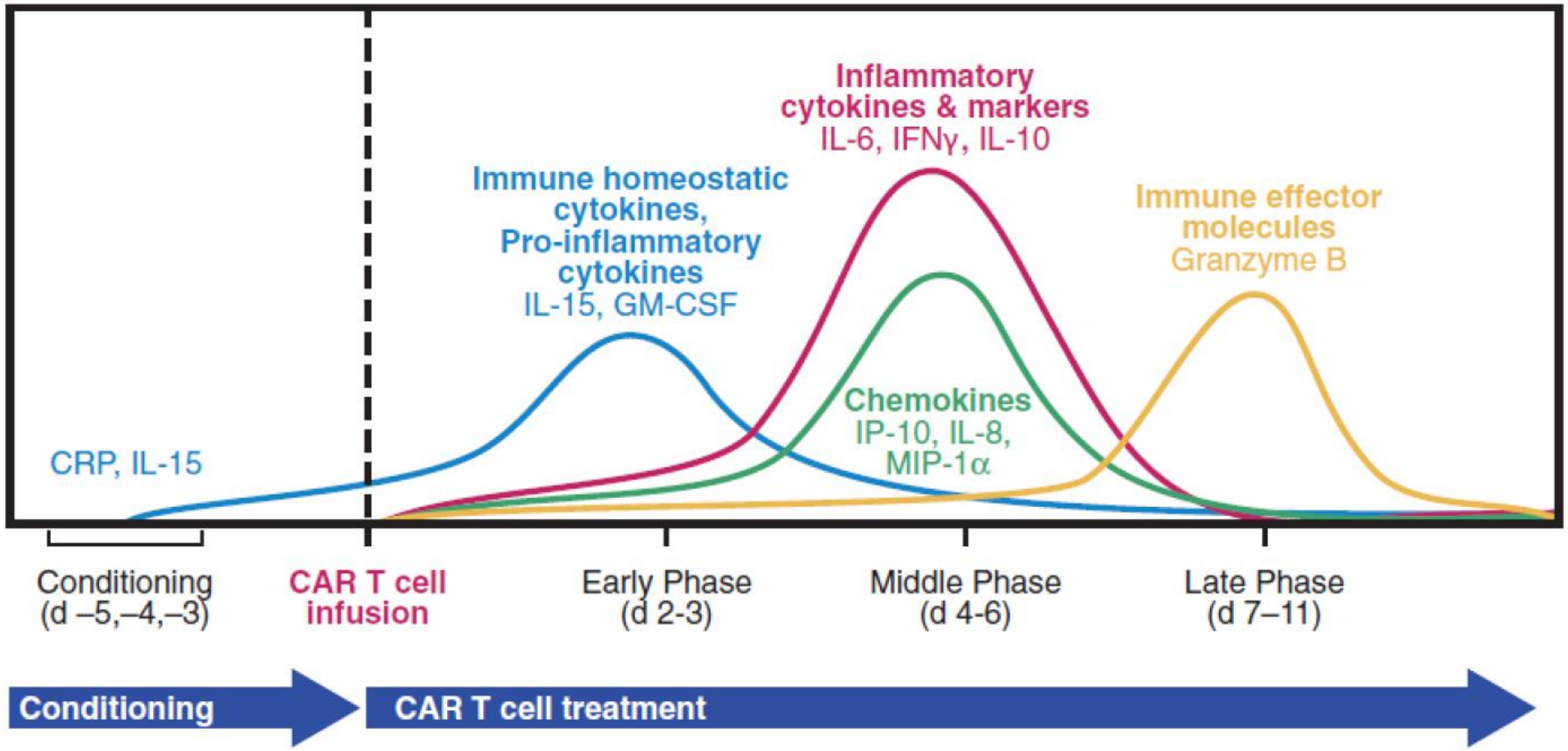


Figure 3. T-Cell Effector Subgroups Involved in Cytokine Storm.

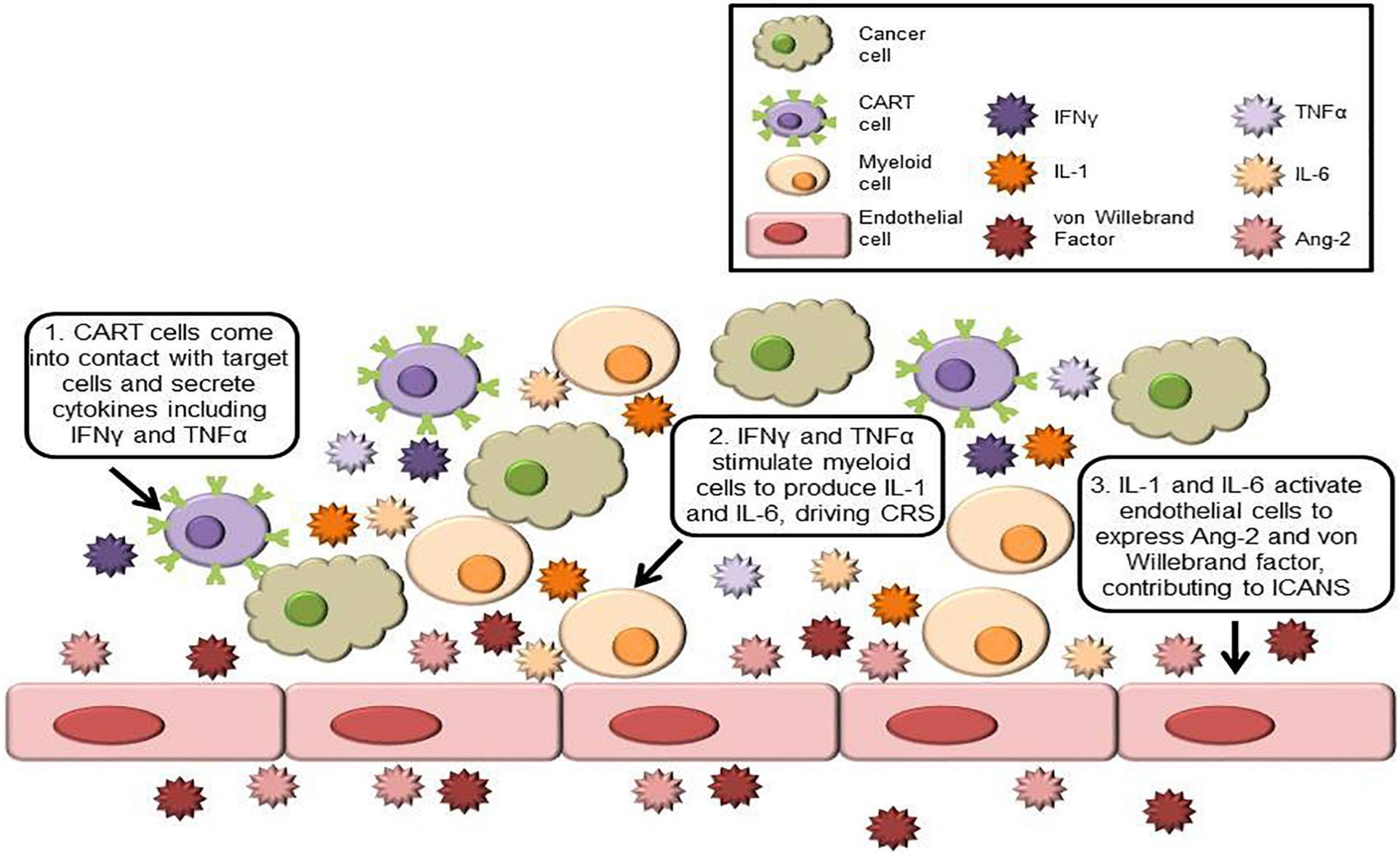
The master transcription factors (T-bet, GATA-3, PU.1, RORγT, and eomesodermin [eomes]), effector molecules, and cell targets are shown for the following T-cell subgroups: types 1, 2, 9, and 17 helper T (Th1, Th2, Th9, and Th17, respectively) cells and cytotoxic T lymphocytes.

Fajgenbaum, NEJM 2021

Mechanisms of CAR-T acute toxicities (CRS & ICANS)

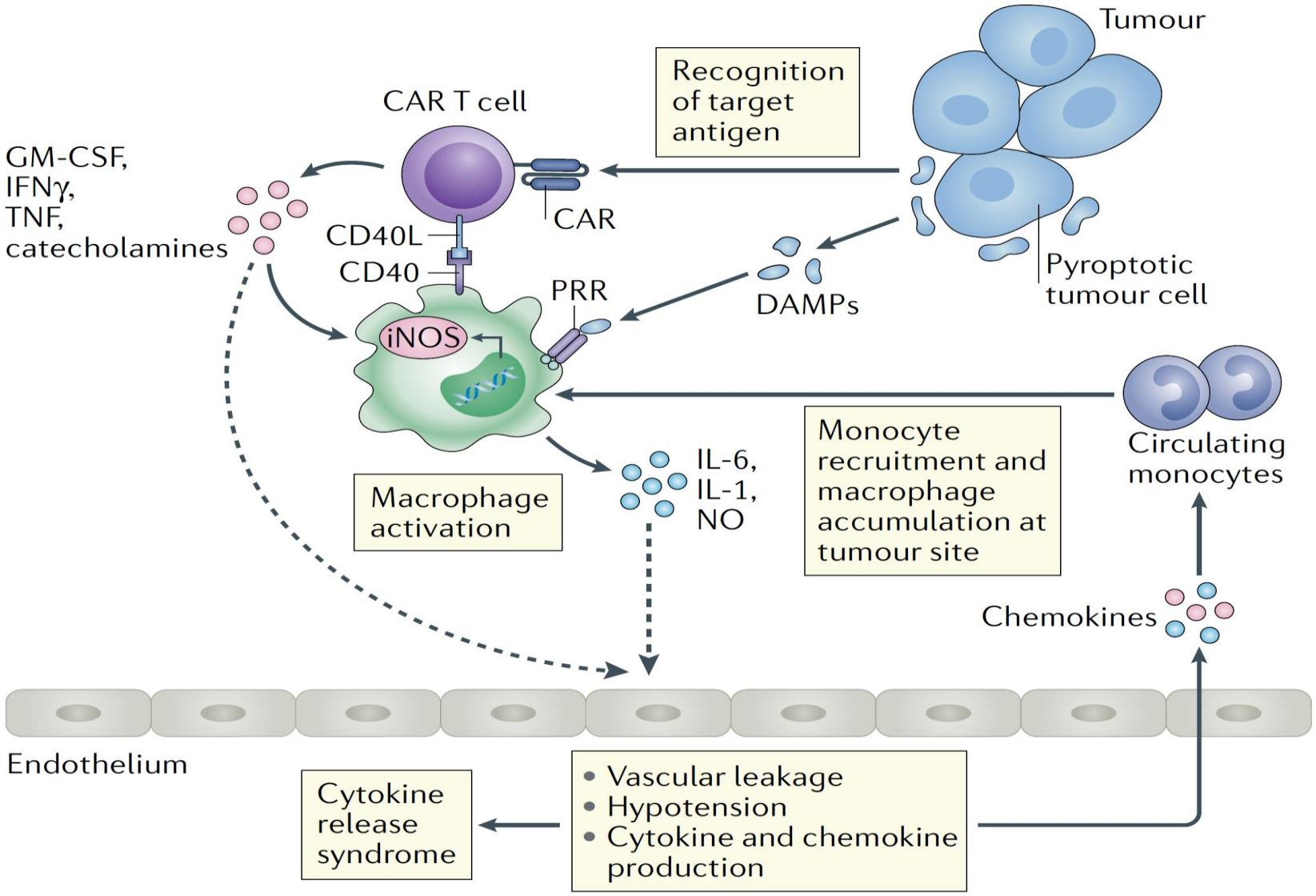


Rooney & Sauer, Nature Med 2018; Norelli et al, Nature Med 2018; Giavridis et al, Nature Med 2018



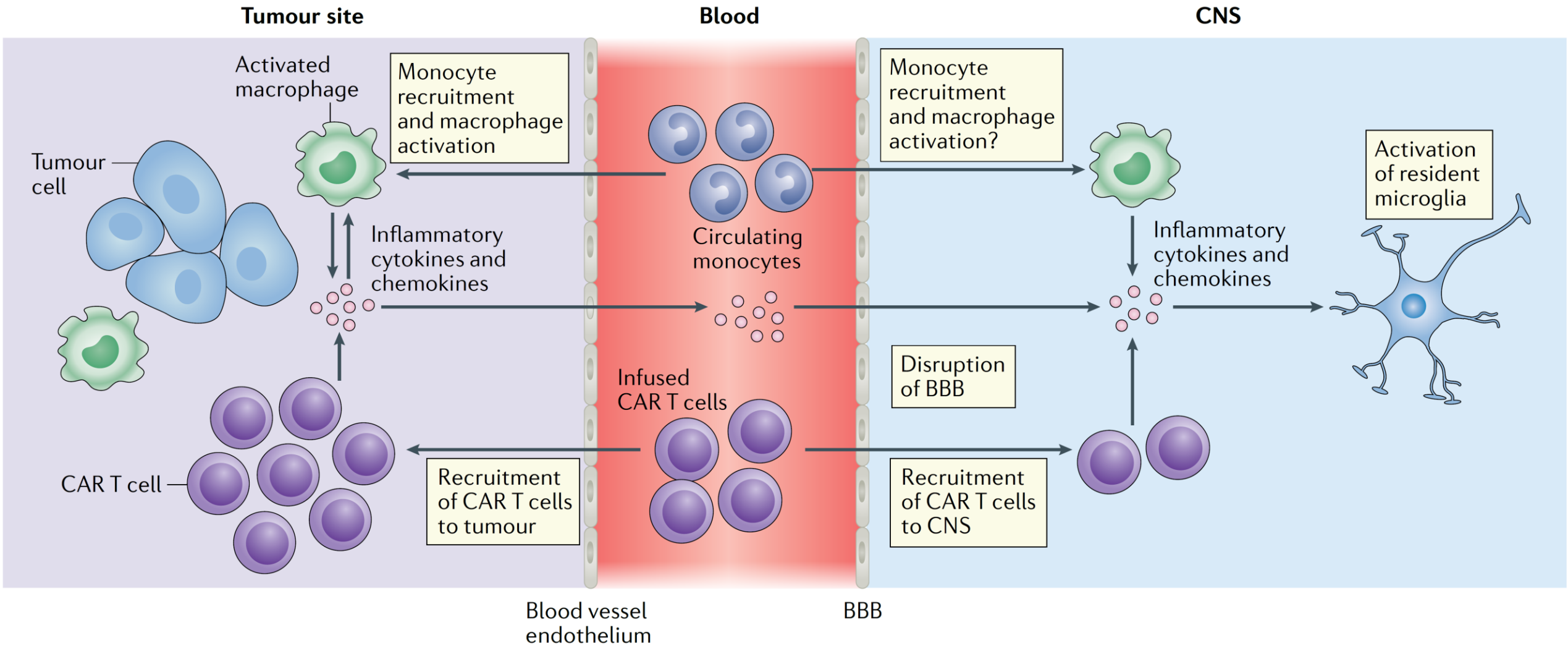
Siegler, Front Immunol 2020

Pathophysiology of CRS

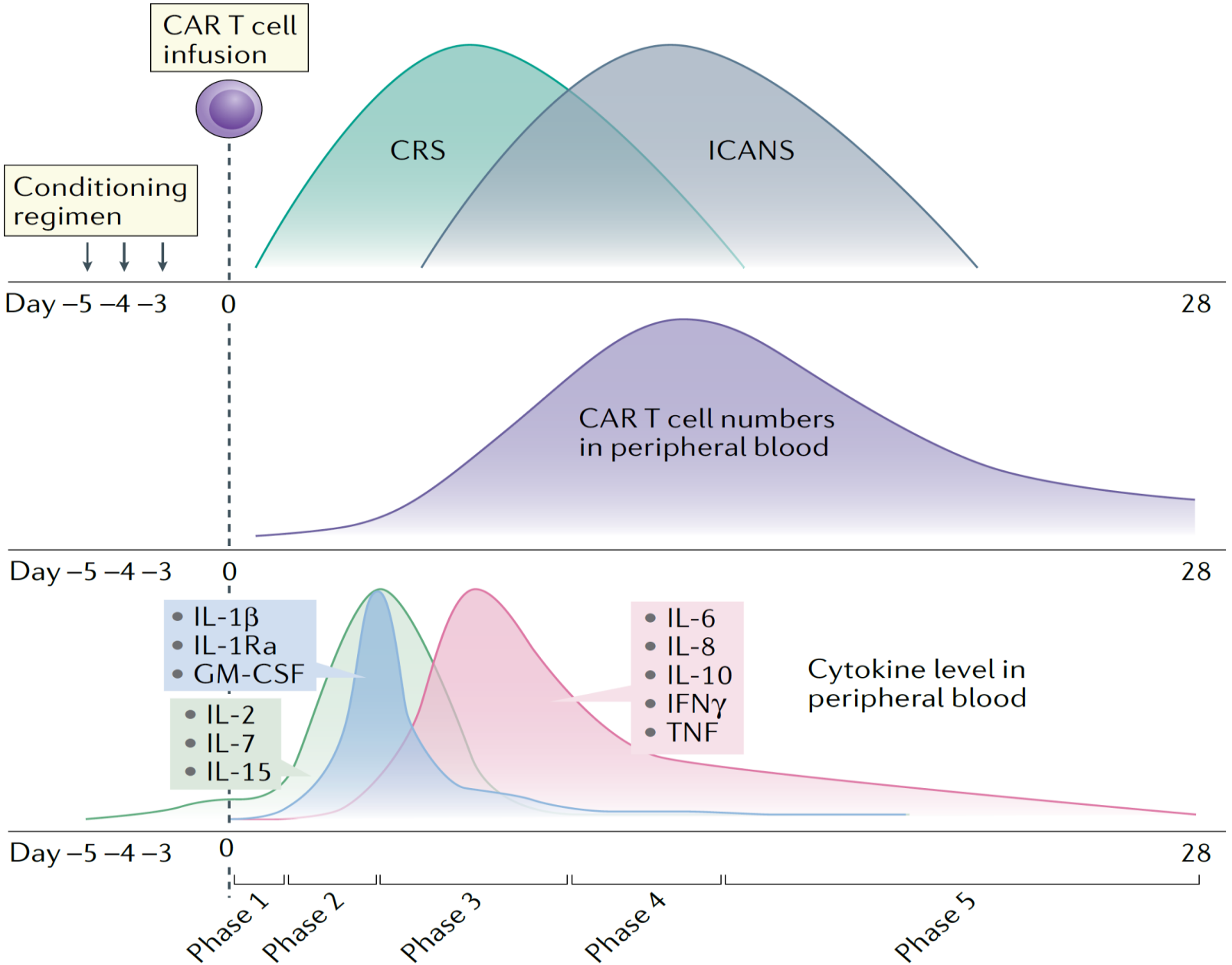


Morris et al, Nat Rev Immunol 2021

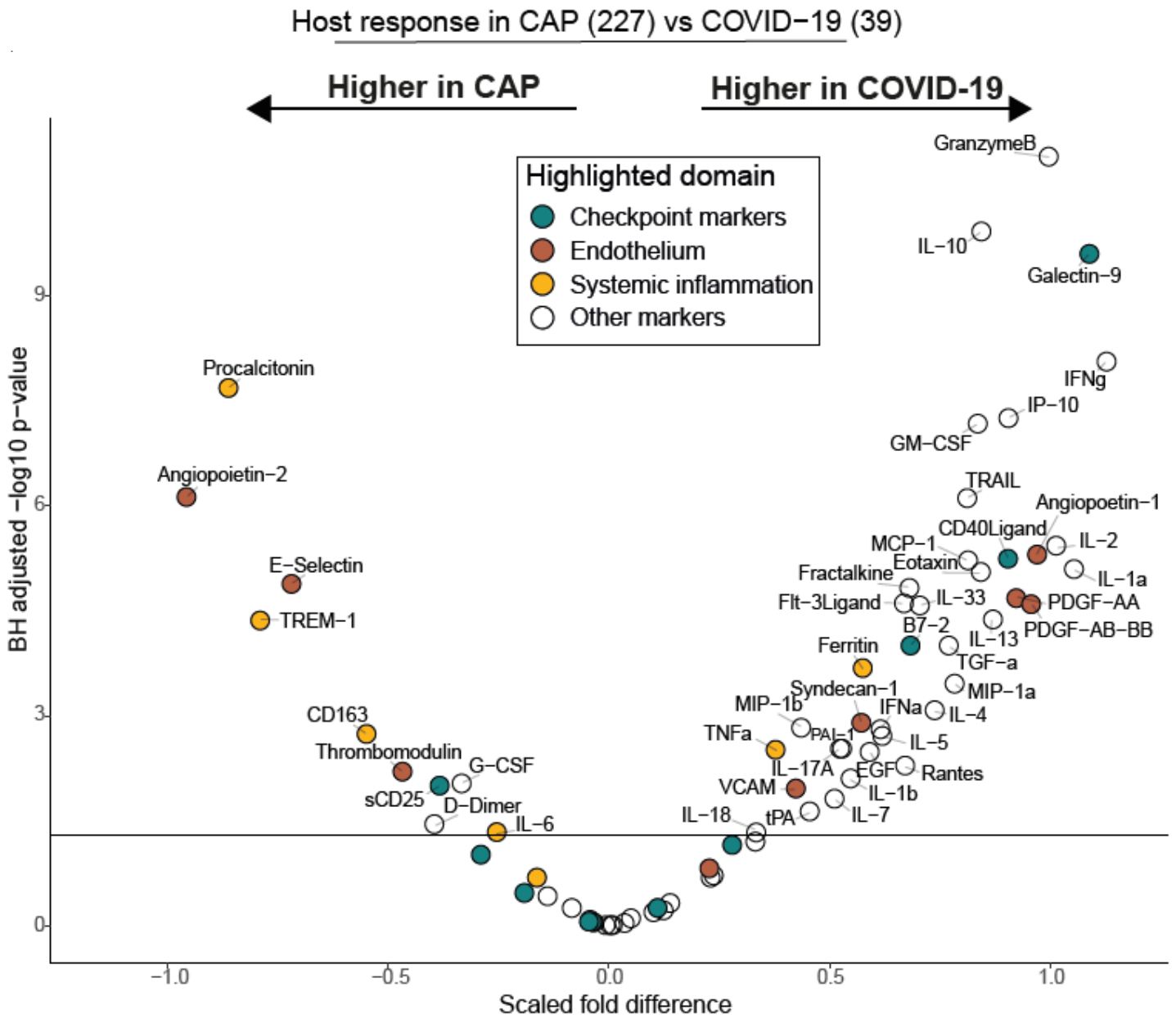
Pathophysiology of ICANS

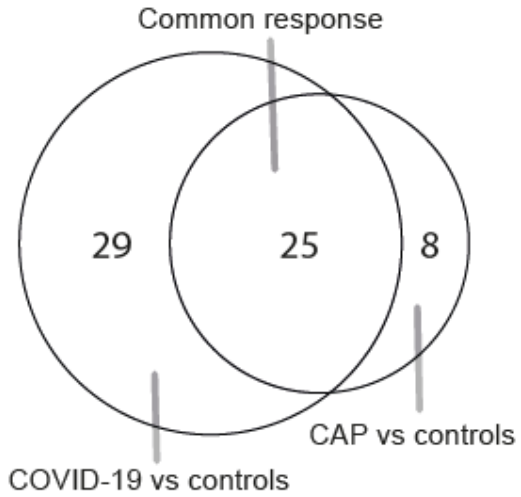


Morris et al, Nat Rev Immunol 2021



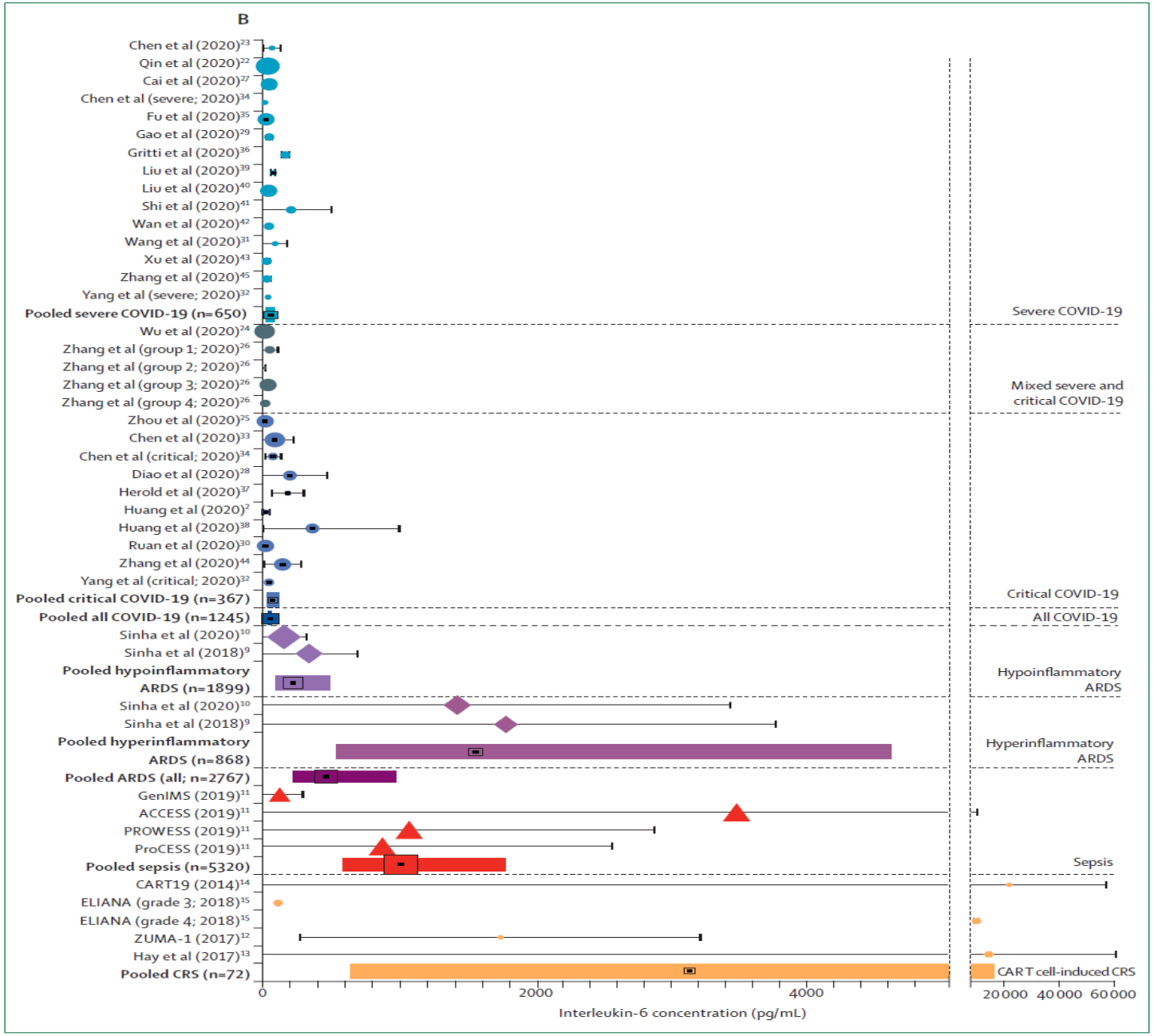
Morris et al, Nat Rev Immunol 2021





Luminex protein panel

Alex Schuurman, eLife, 2021 and data in preparation



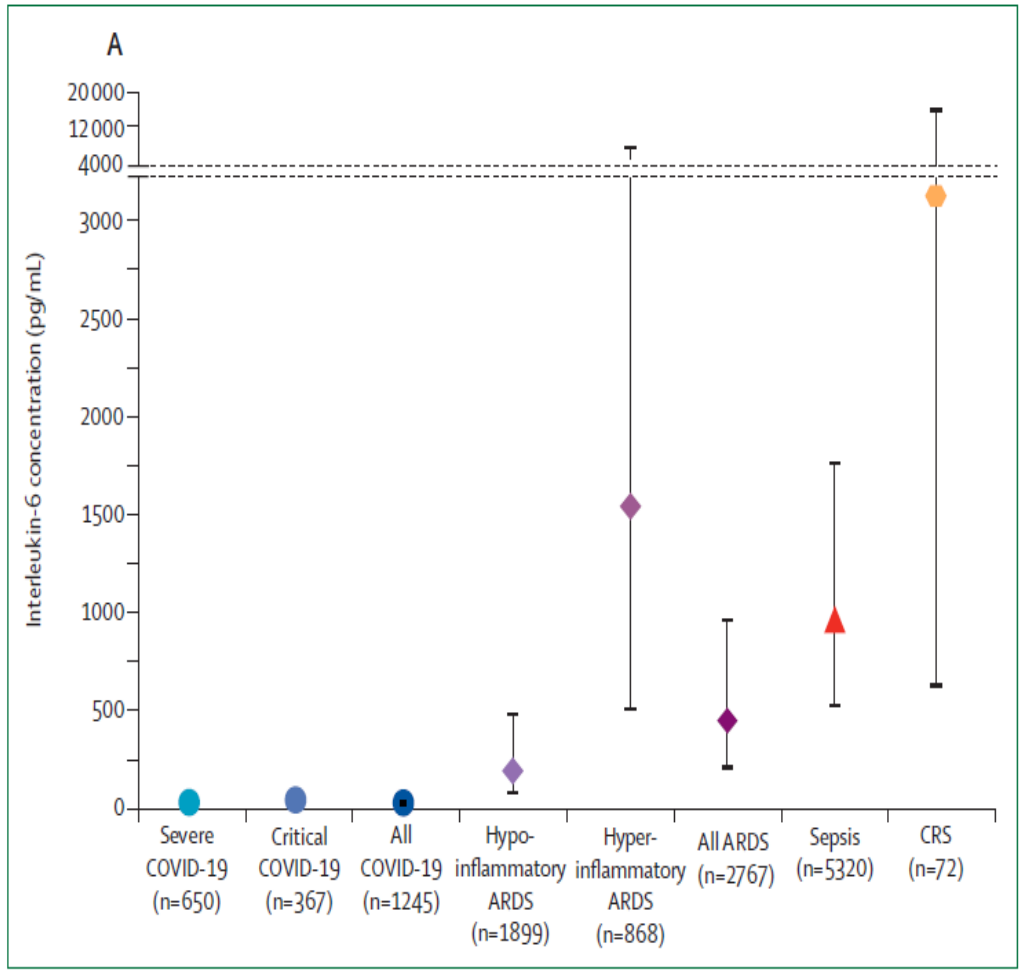


Figure 2: **Interleukin-6 concentrations in patients with COVID-19 versus comparison disorders**
(A) Pooled estimate for each disorder. Markers indicate point estimates and error bars indicate 95% CIs. (B) For individual studies, markers indicate study means and error bars indicate standard deviations. Markers are sized proportionately to the log weight of the study in the analysis. Pooled estimates are represented by the solid bars. The black marking in the centre of the bars indicates the point estimate for the disease. The width of the box is scaled according to the pooled number of participants, whereas the width of the bar indicates the 95% CI. ARDS=acute respiratory distress syndrome. CAR=chimeric antigen receptor. CRS=cytokine release syndrome.

Leisman, LRM 2020

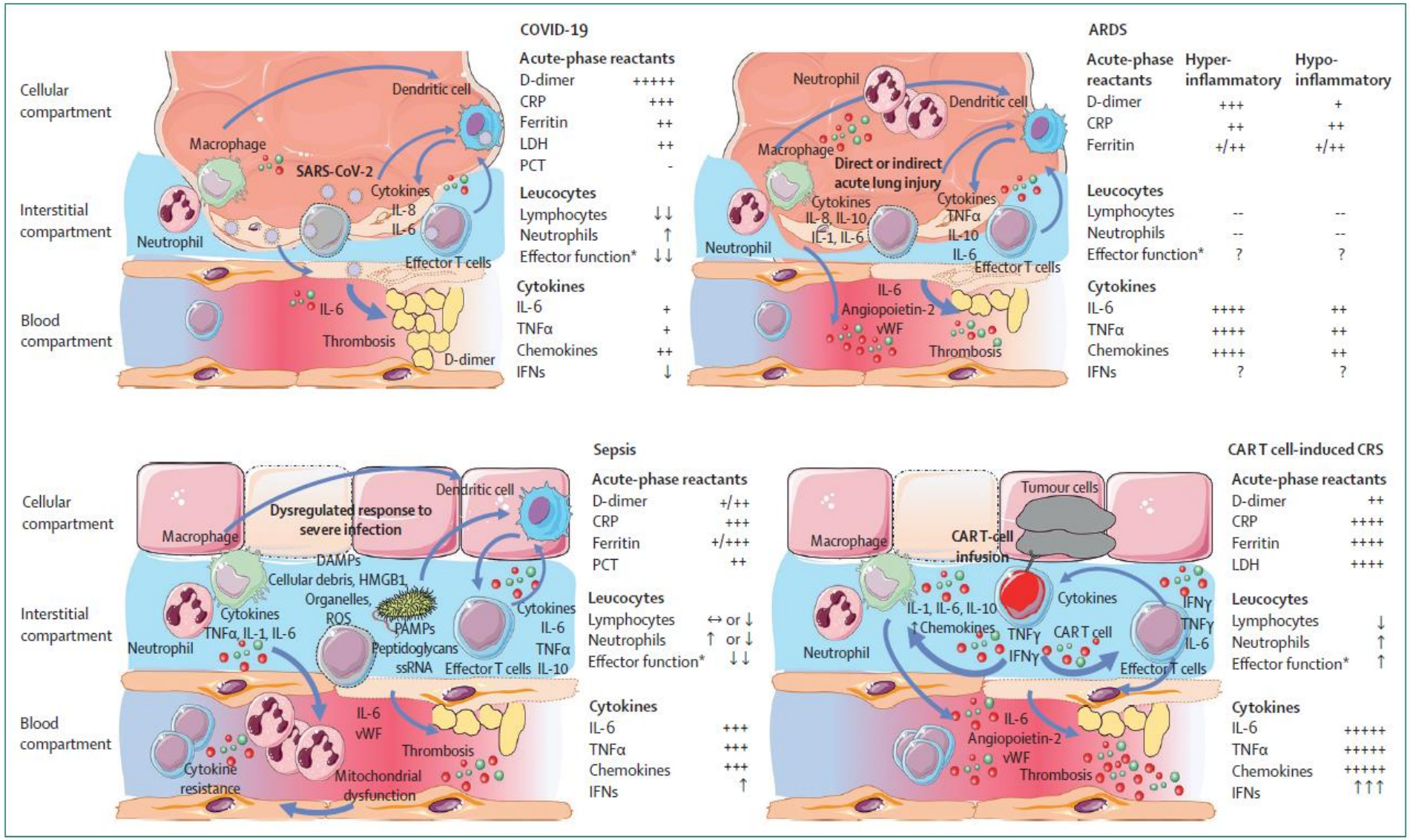
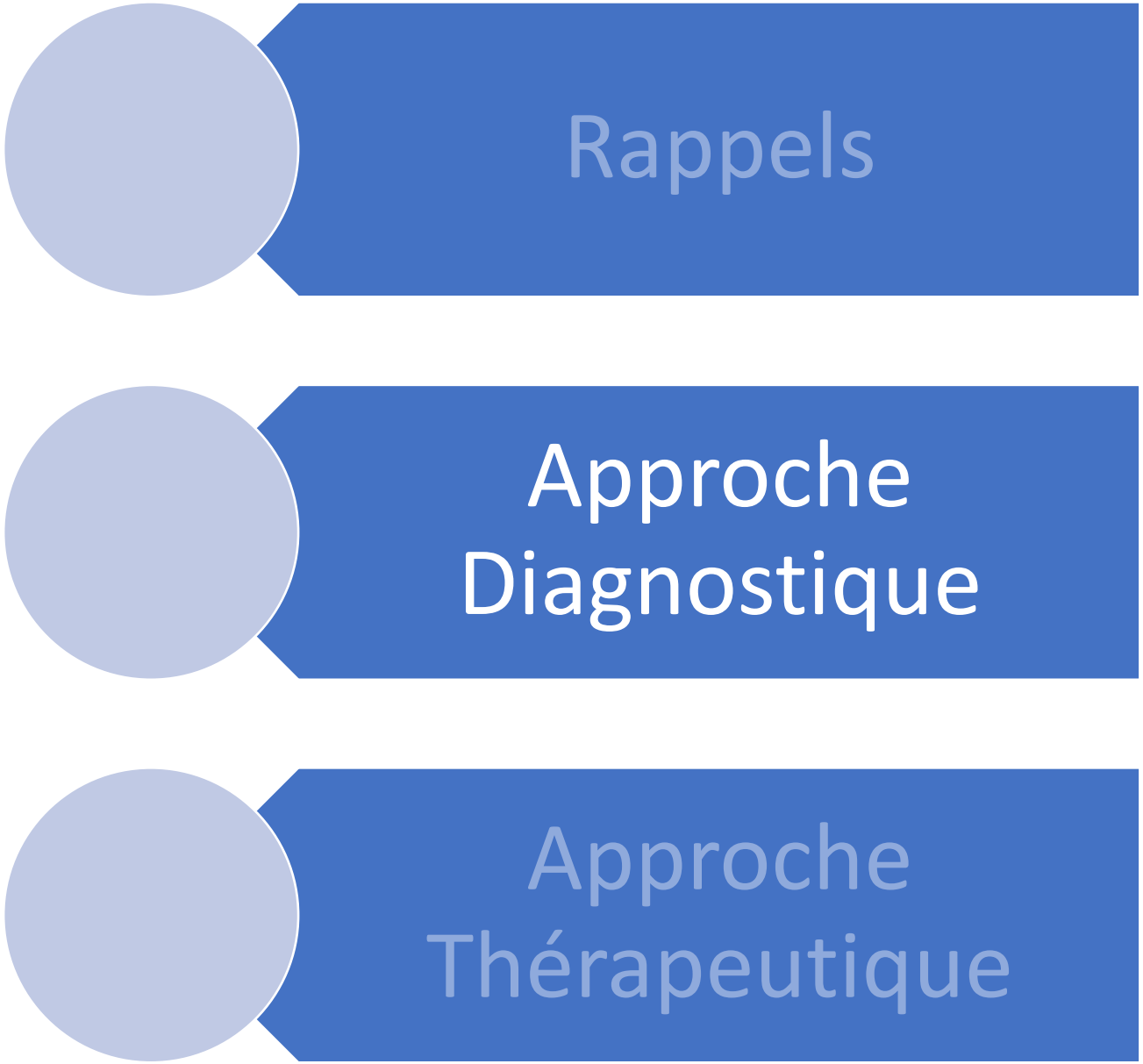


Figure 4: **Mechanistic comparison of inflammatory processes in patients with COVID-19 versus ARDS, sepsis, and CAR T cell-induced CRS**

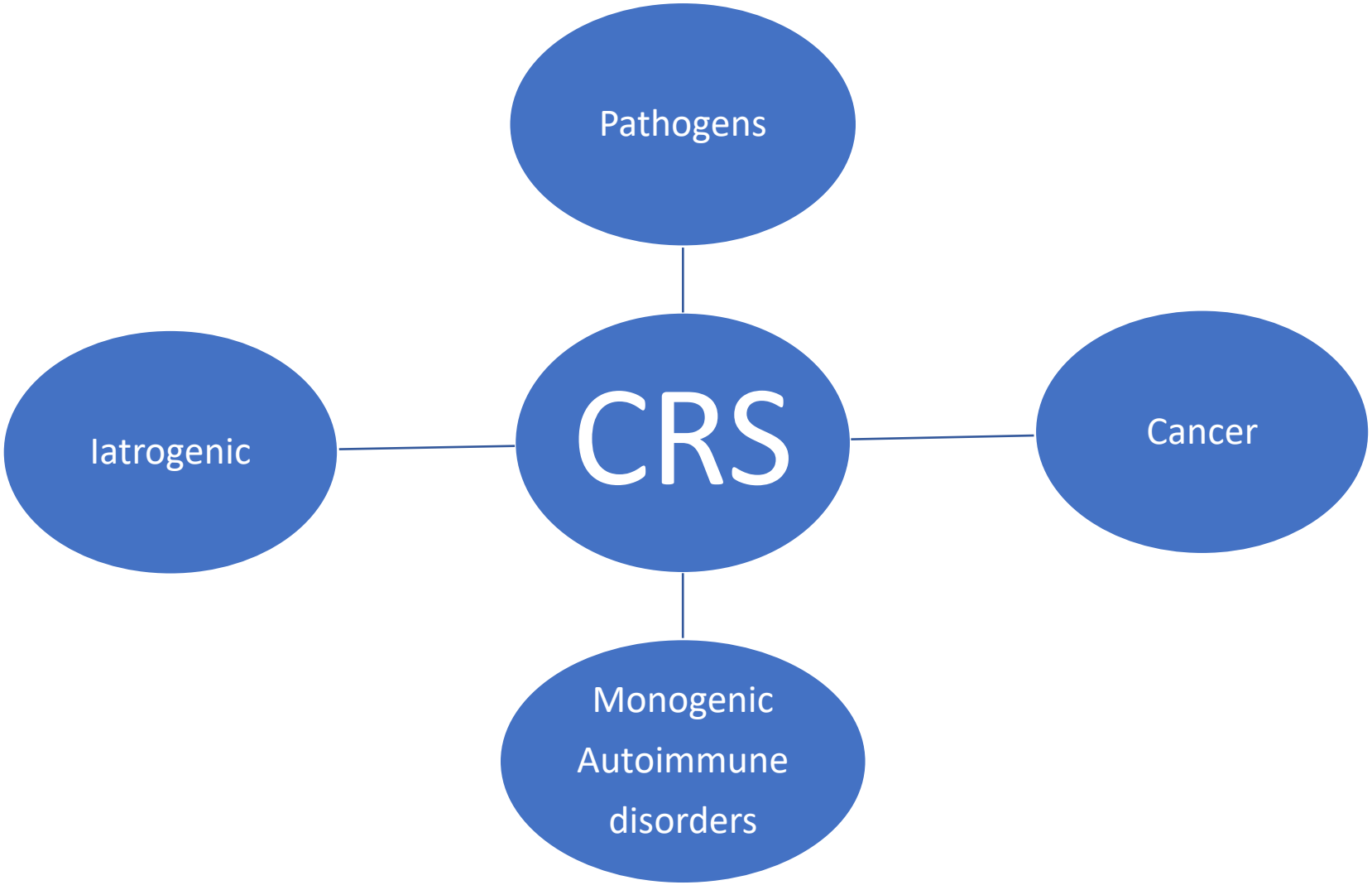
ARDS=acute respiratory distress syndrome. CAR T cell-induced CRS=chimeric antigen receptor T cell-induced cytokine release syndrome. CRP=C-reactive protein. DAMPs=damage-associated molecular patterns. IFN=interferon. IL=interleukin. LDH=lactate dehydrogenase. PAMPs=pathogen-associated molecular patterns. 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

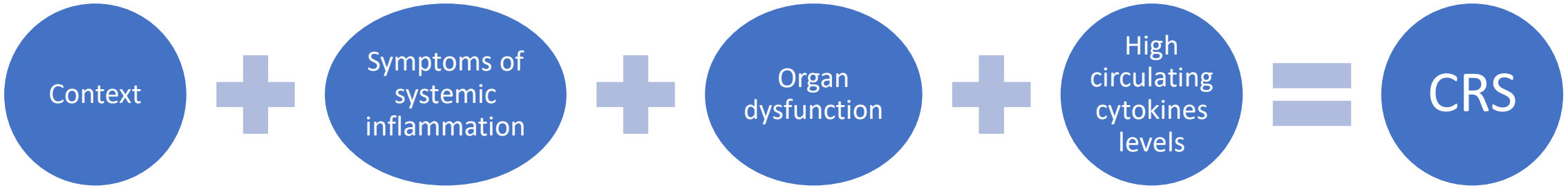
Plan



Clinical Context



Definition


Context
Symptoms of systemic inflammation
Organ dysfunction
High circulating cytokines levels
CRS

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]

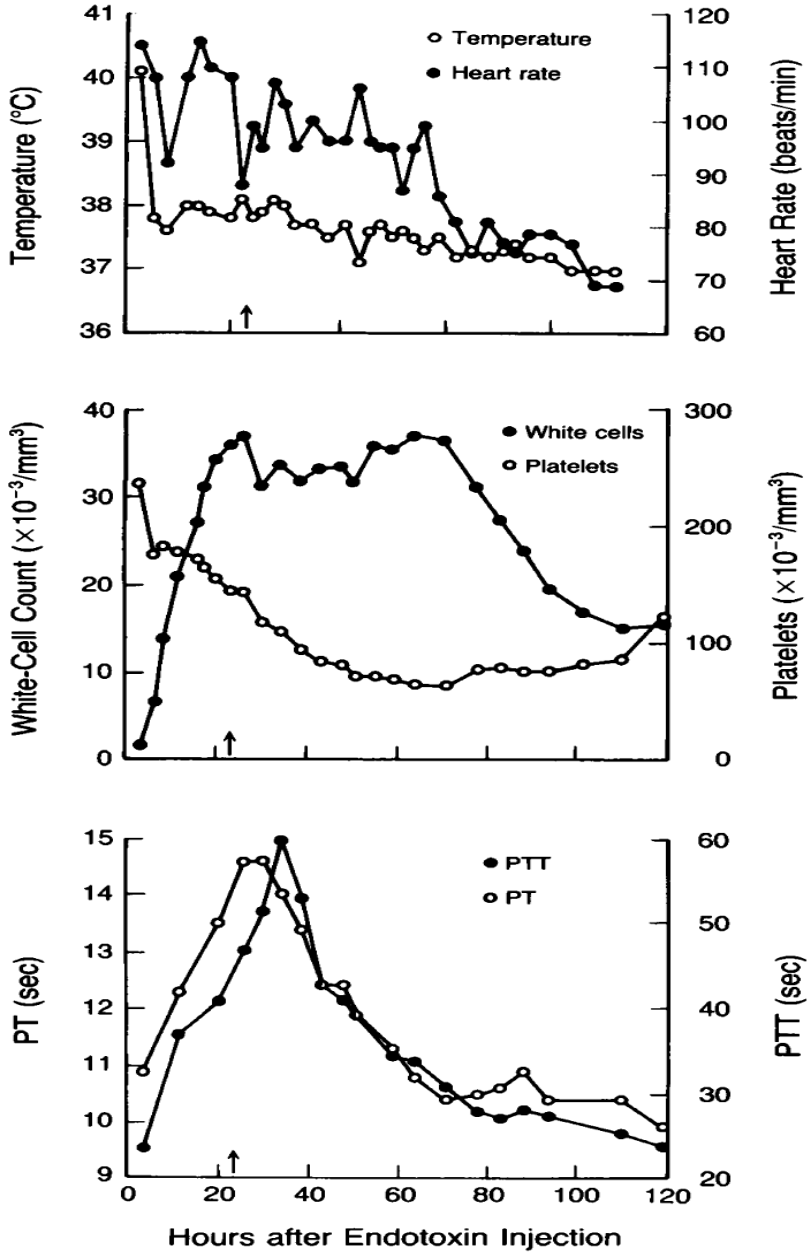


Figure 1. Serial Changes in Body Temperature and Heart Rate, Total White-Cell Count and Platelet Count, and Prothrombin Time (PT) and Partial-Thromboplastin Time (PTT) after the Intravenous Injection of Endotoxin.
The arrows denote the time at which HA-1A antibody was administered.

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.

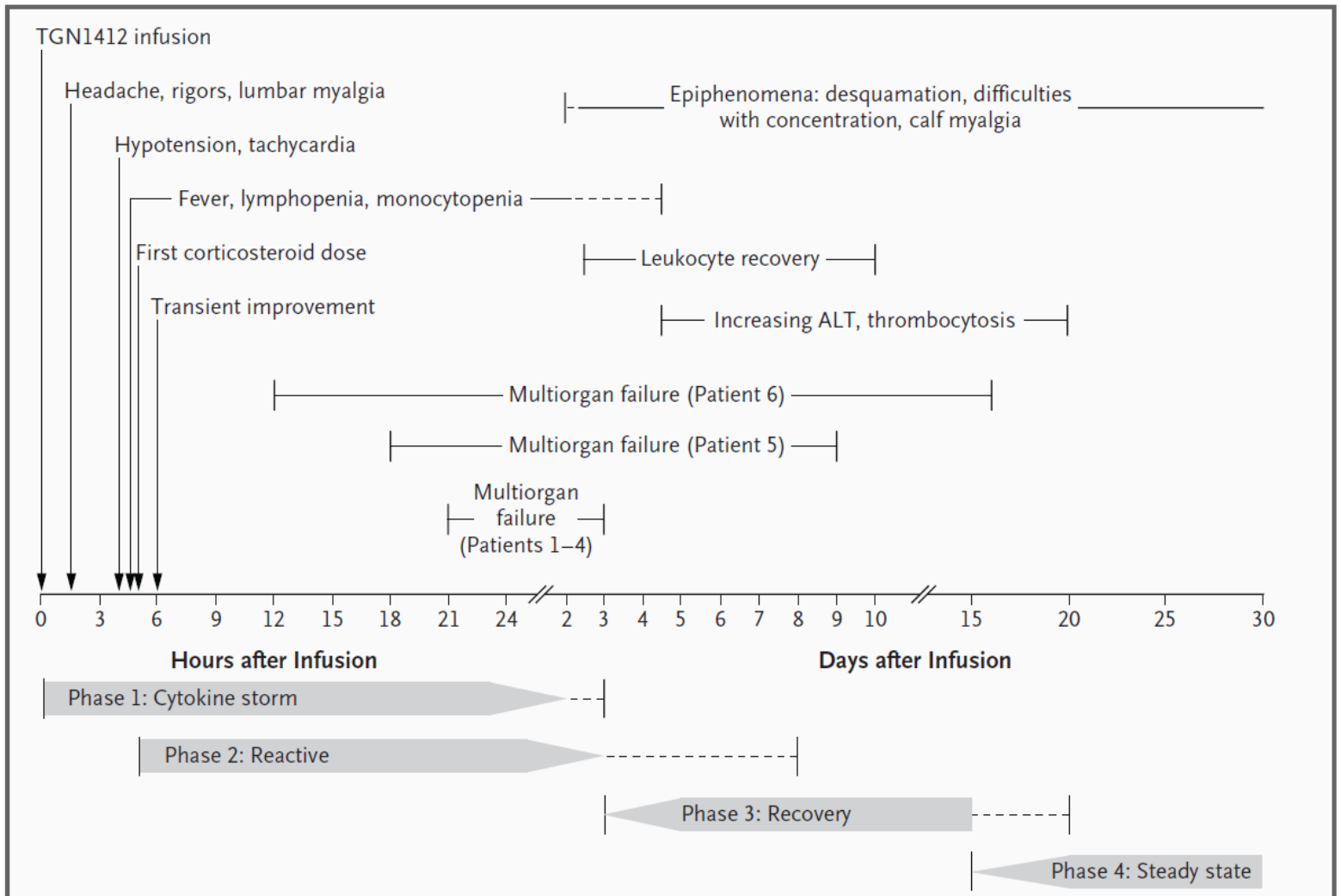
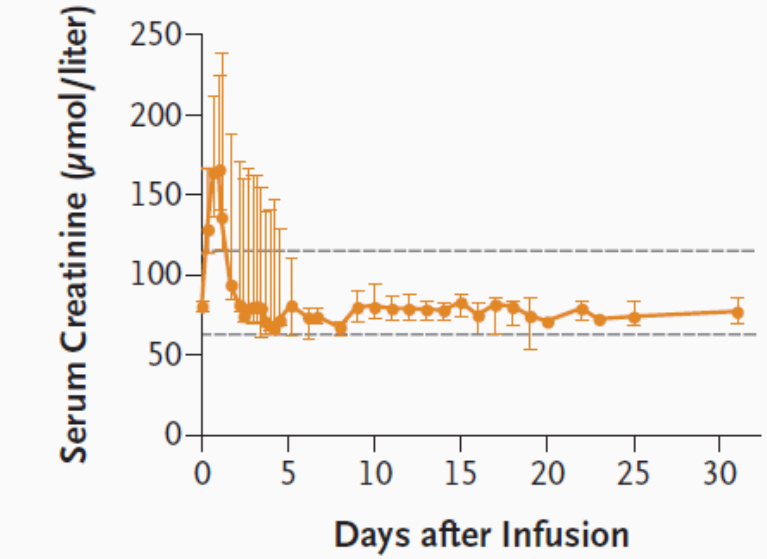
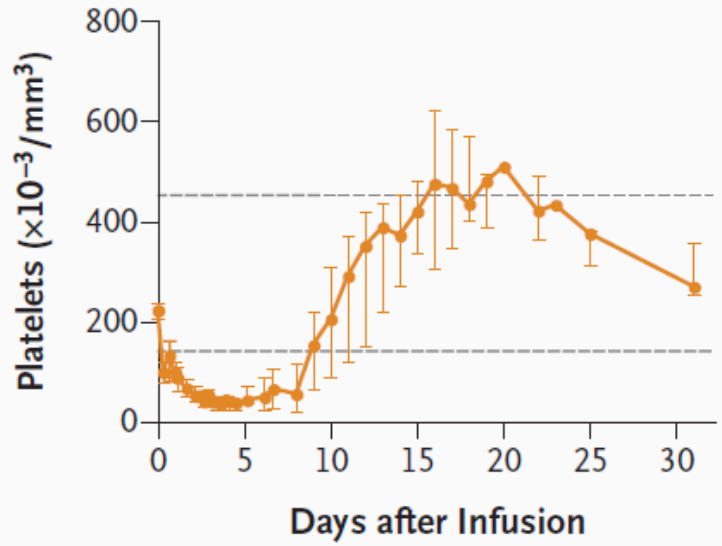
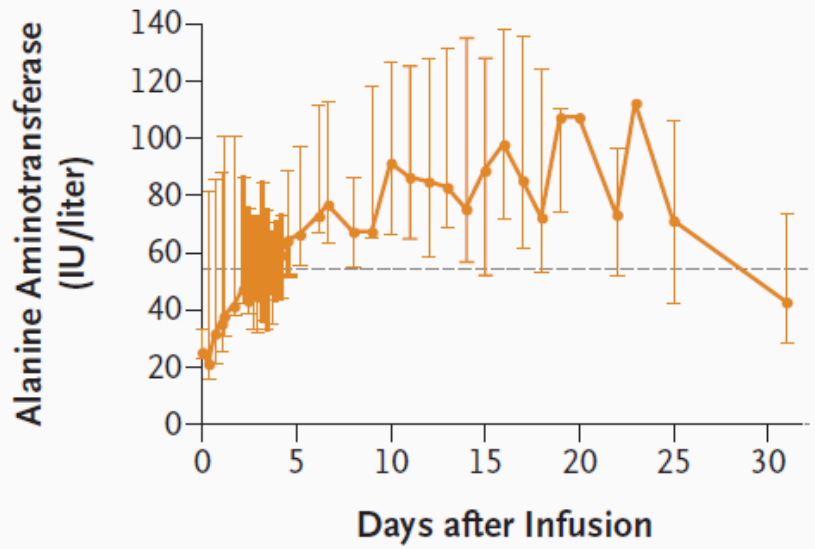


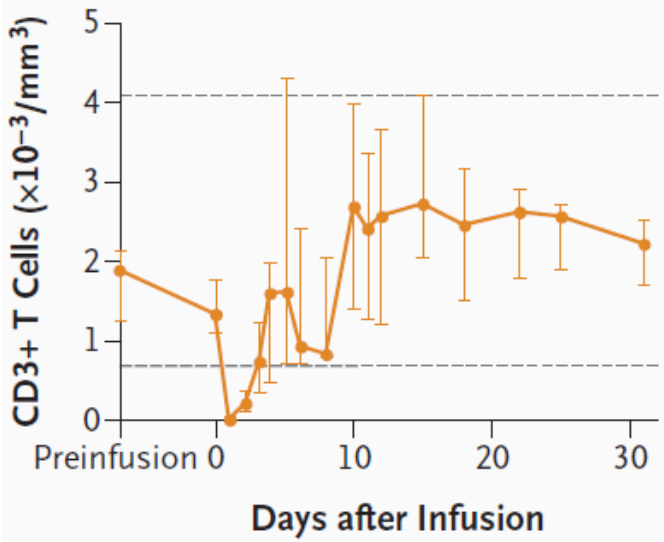
Figure 1. Summary Timeline of the Main Events after Infusion of TGN1412.

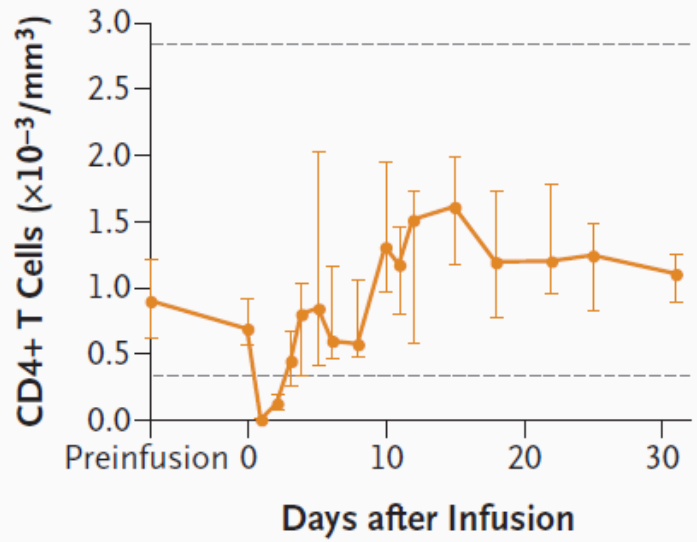
The course is divided into four phases: cytokine storm, reactive, recovery, and steady state. ALT denotes alanine aminotransferase. Dashed lines represent the responses of Patients 5 and 6 (who were the most seriously ill).

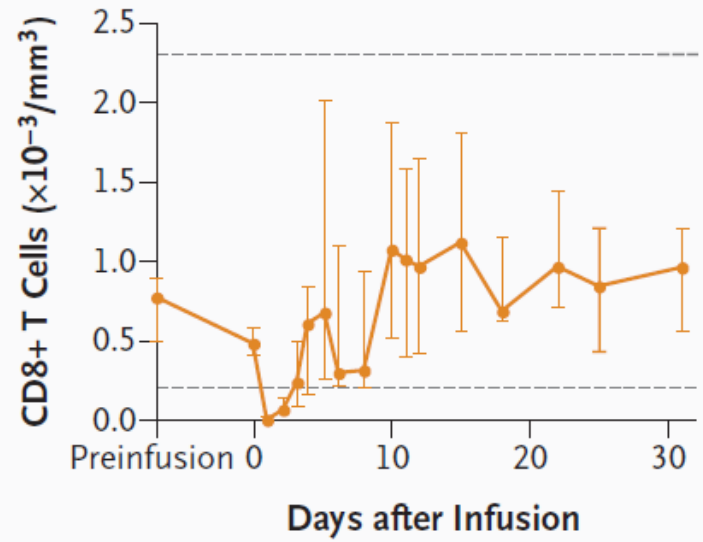

Serum Creatinine (μmol/liter)
250
200
150
100
50
0
0
5
10
15
20
25
30
Days after Infusion

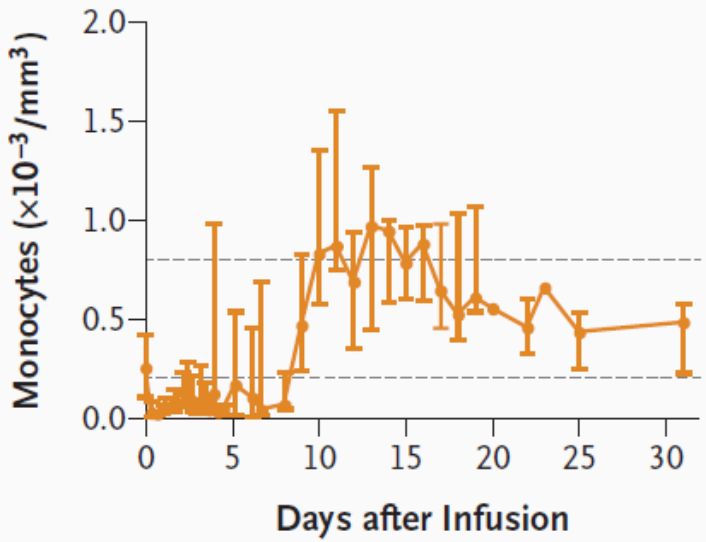

Platelets (×10⁻³/mm³)
800
600
400
200
0
0
5
10
15
20
25
30
Days after Infusion

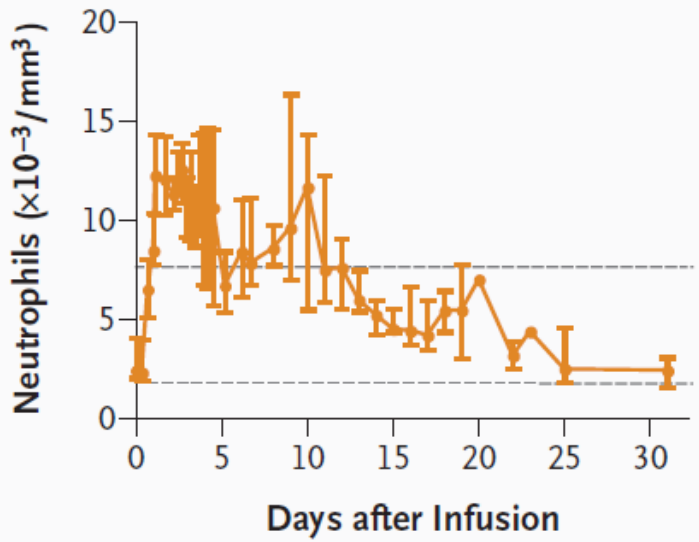

Alanine Aminotransferase (IU/liter)
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
Days after Infusion

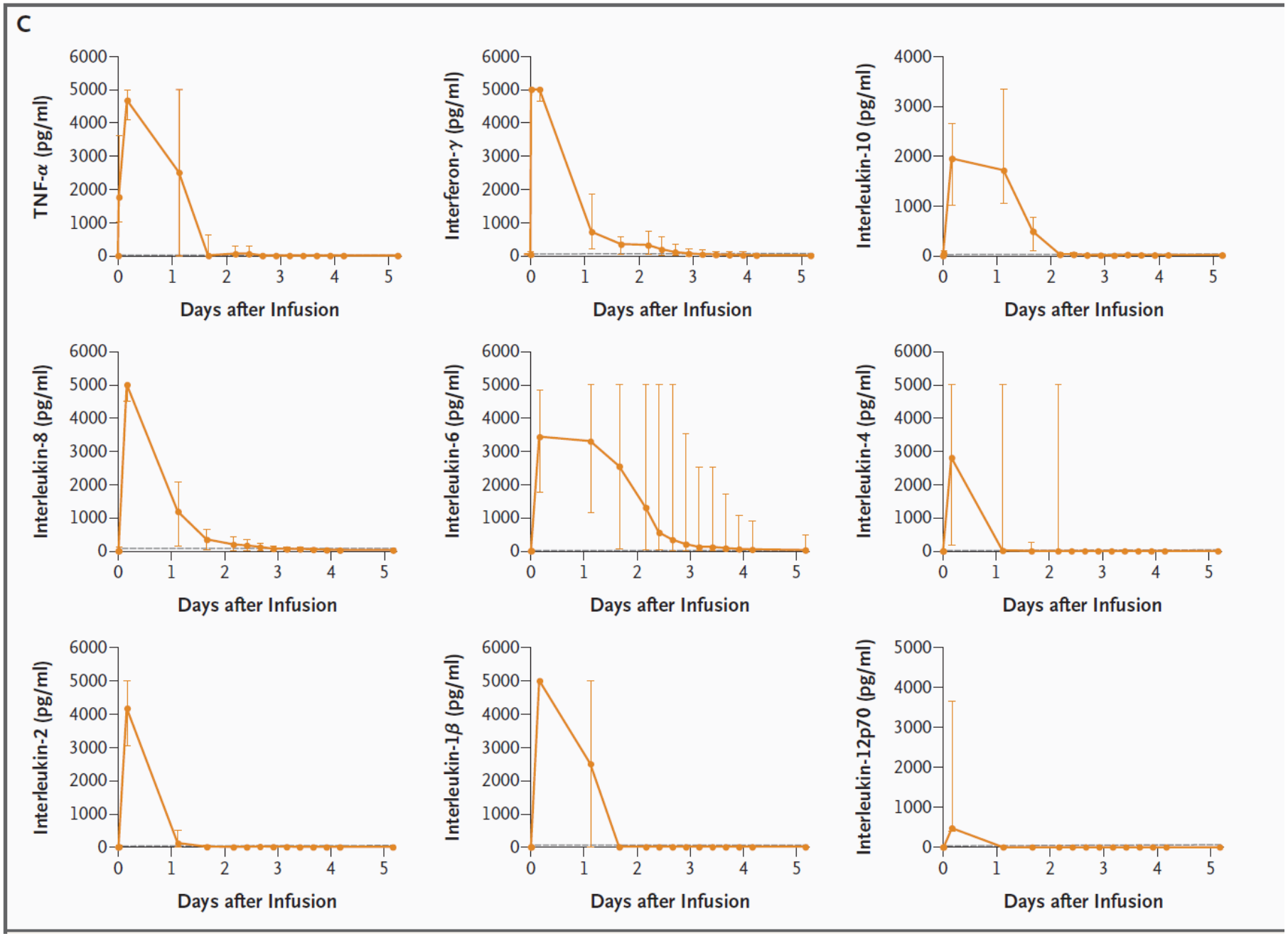

CD3+ T Cells (×10⁻³/mm³)
5
4
3
2
1
0
Preinfusion 0
10
20
30
Days after Infusion

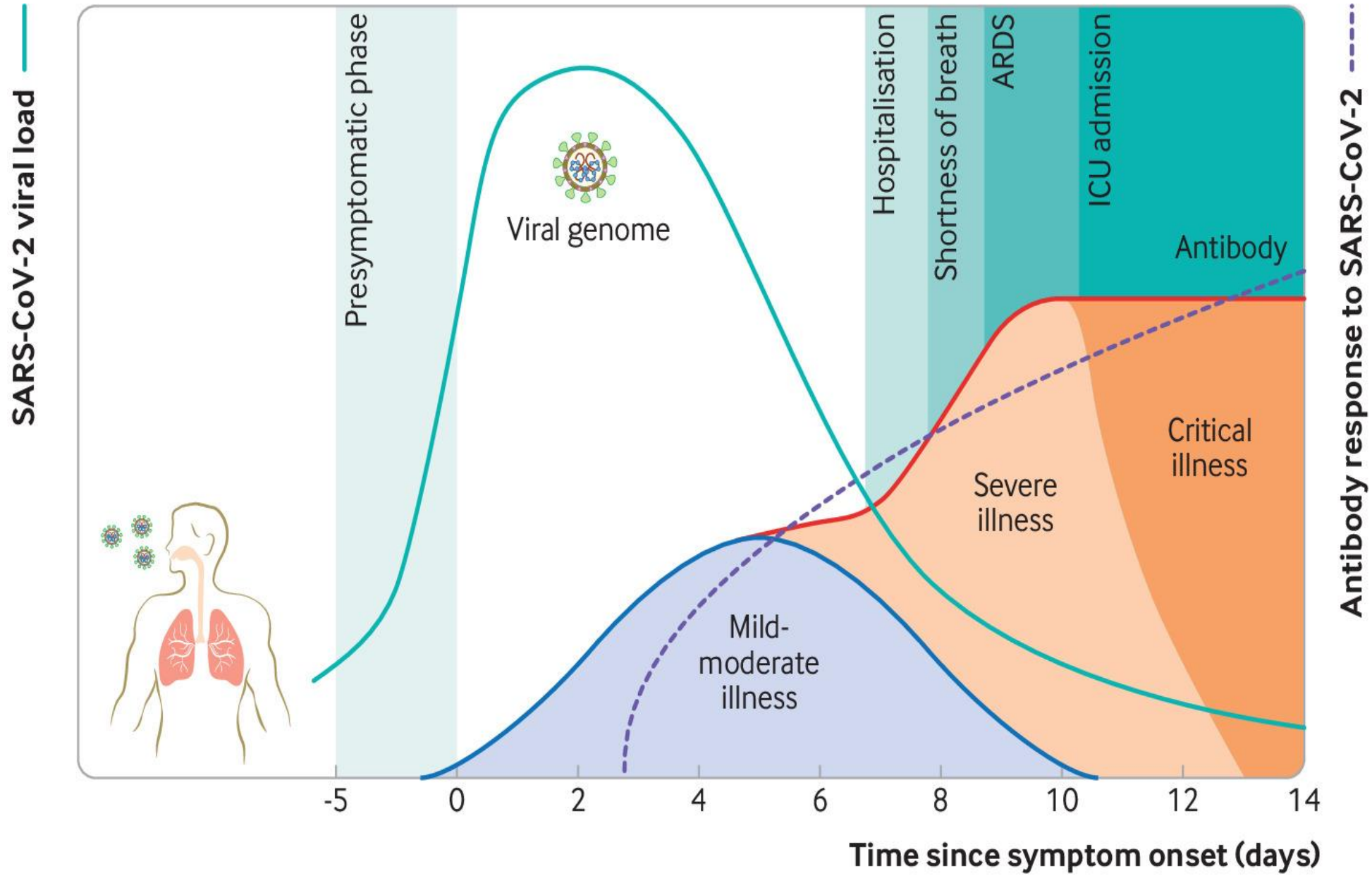

CD4+ T Cells (×10⁻³/mm³)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Preinfusion 0
10
20
30
Days after Infusion


CD8+ T Cells (×10⁻³/mm³)
2.5
2.0
1.5
1.0
0.5
0.0
Preinfusion 0
10
20
30
Days after Infusion

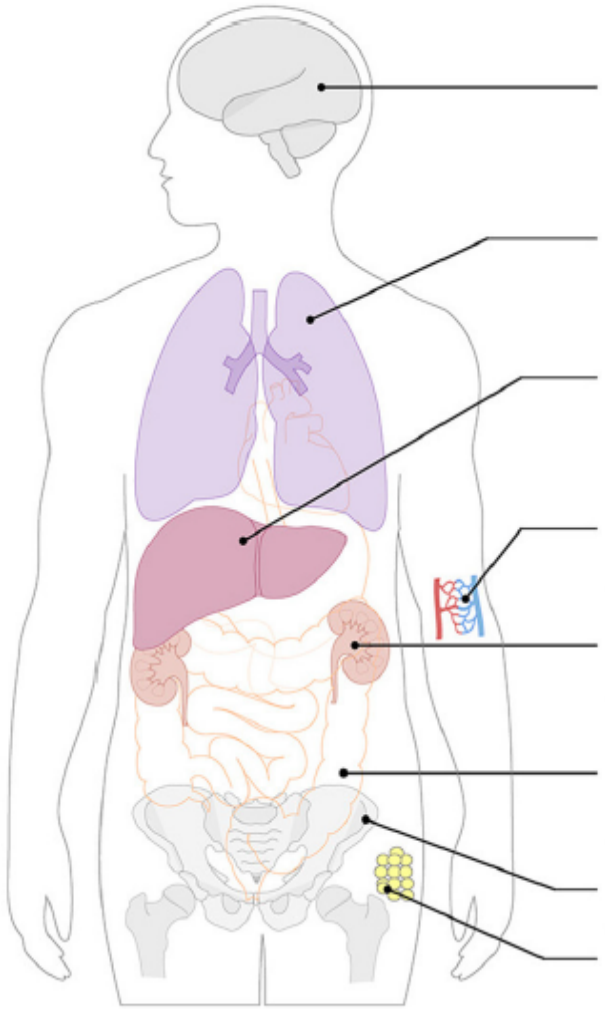

Monocytes (×10⁻³/mm³)
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
25
30
Days after Infusion


Neutrophils (×10⁻³/mm³)
20
15
10
5
0
0
5
10
15
20
25
30
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



Cevik, BMJ 2020



Compartment	Cells of interest	Clinical consequences of	
		Hyperinflammation	Immunoparalysis
Brain	*microglia* *astrocytes* *neurons*	*headache, nausea* *apathy, somnolence* *delirium* *cognitive decline* *behavioural changes*	*unknown, potentially brain-protective*
Lungs	*alveolar macrophages* *epithelial cells, endothelial cells, neutrophils*	*dyspnoea* *lung oedema* *ARDS*	*increased susceptibility to secondary pulmonary infections*
Liver	*Kuppfer cells, LSEGs* *stellate cells, hepatocytes* *MDSC, neutrophils* *lymphocytes, platelets*	*jaundice* *toxin and drug accumulation* *metabolic disturbances* *coagulation disorders*	*unknown*
Blood	*neutrophils, monocytes* *dendritic cells, lymphocytes* *platelets*	*coagulation disorders* *hypotension and oedema* *septic shock*	*increased susceptibility to secondary infections*
Kidney	*renal dendritic cells,* *tissue-resident macrophages,* *lymphocytes, mast cells, RTEC*	*oliguria, anuria* *fluid retention* *toxin and drug accumulation*	*unknown*
Intestines	*epithelial cells, neutrophils,* *intestinal dendritic cells,* *macrophages, M-cells,* *lymphocytes, microbiome*	*ileus* *deteriorating nutrional status* *gut failure (need for TPN)*	*unknown*
Bone marrow	*HSPCs*	*unknown*	*unknown*
Adipose tissue	*adipose tissue macrophages*	*unknown, potentially sustained low-grade inflammation leading to metabolic changes*	*unknown*

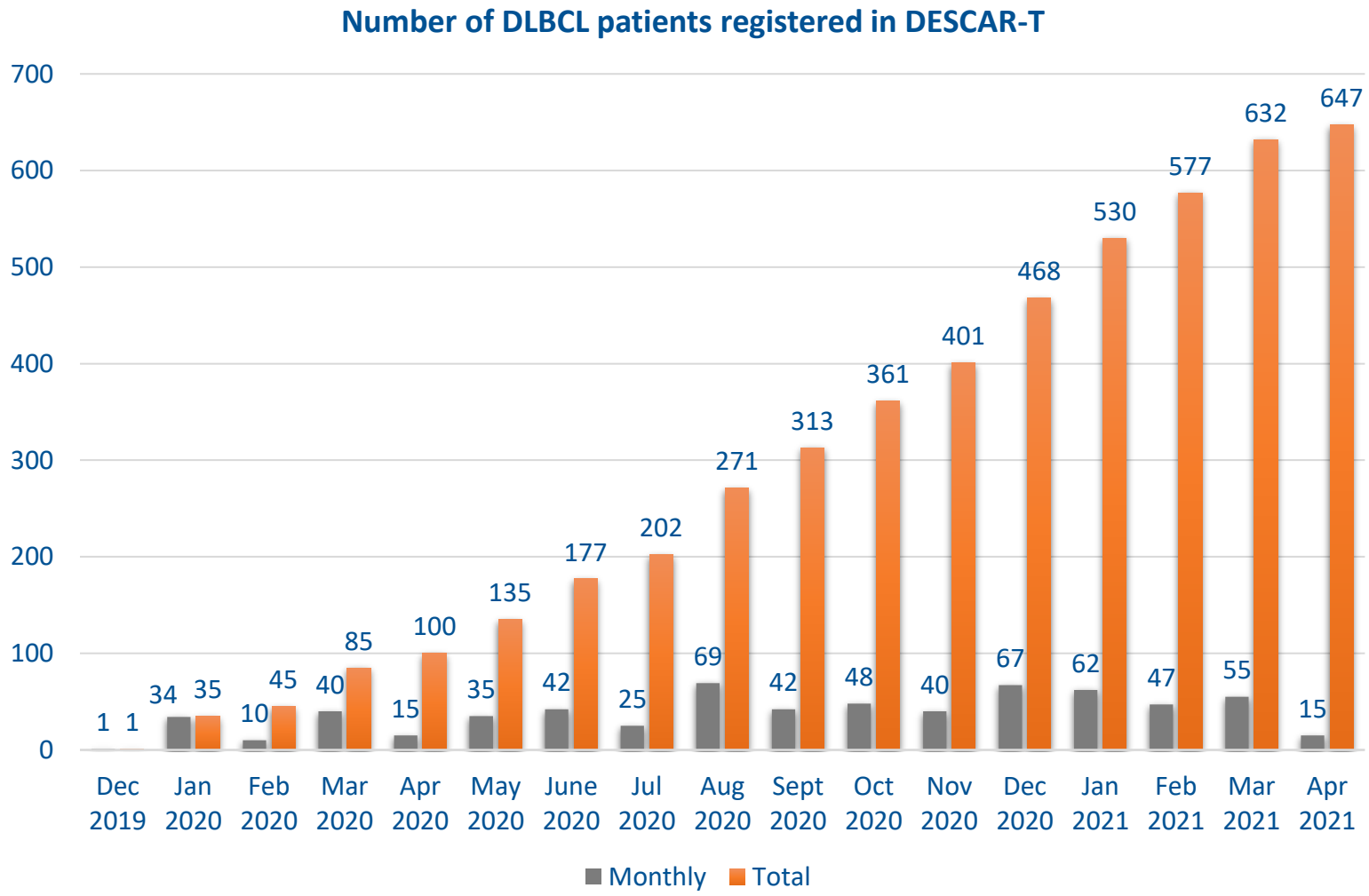
FIGURE 1 | Clinical consequences of hyperinflammation and immunoparalysis to selected tissues. ARDS, acute respiratory distress syndrome; LSEC, liver sinusoidal endothelial cells; MDSC, myeloid-derived suppressor cells; RTEC, renal tubule epithelial cell; M-cell, microfold cell; TPN, total parenteral nutrition; HSPC, hematopoietic stem and progenitor cells.

Van Ton Front Immunol 2018

RESULTS: INCLUSIONS

Le Gouill, Curie

- Date: 12/04/2021
- 23 sites are qualified for CAR-T cells therapy and DESCAR-T
- 19 enrolling sites
- Number of enrolled patients :
  - N = 647 DLBCL



EARLY CRS, NEUROTOXICITY AND INFECTIONS

DESCAR-T

	Toxicities within 10d post CAR-T (data available in 515 pts)
CRS (all grades)	418 (81.2%)
grade 1-2	373
grade ≥ 3	44
missing	1
Neurotoxicity (all grades)	184 (35.7%)
grade 1-2	133
grade ≥ 3	50
missing	1
grade ≥ 3 opportunistic or medically significant infection	163 (31.7%)

NB: DESCAR-T is based on secondary data use and thus expedited reporting of suspected adverse reaction are not mandatory

Axi-cel; Yescarta®

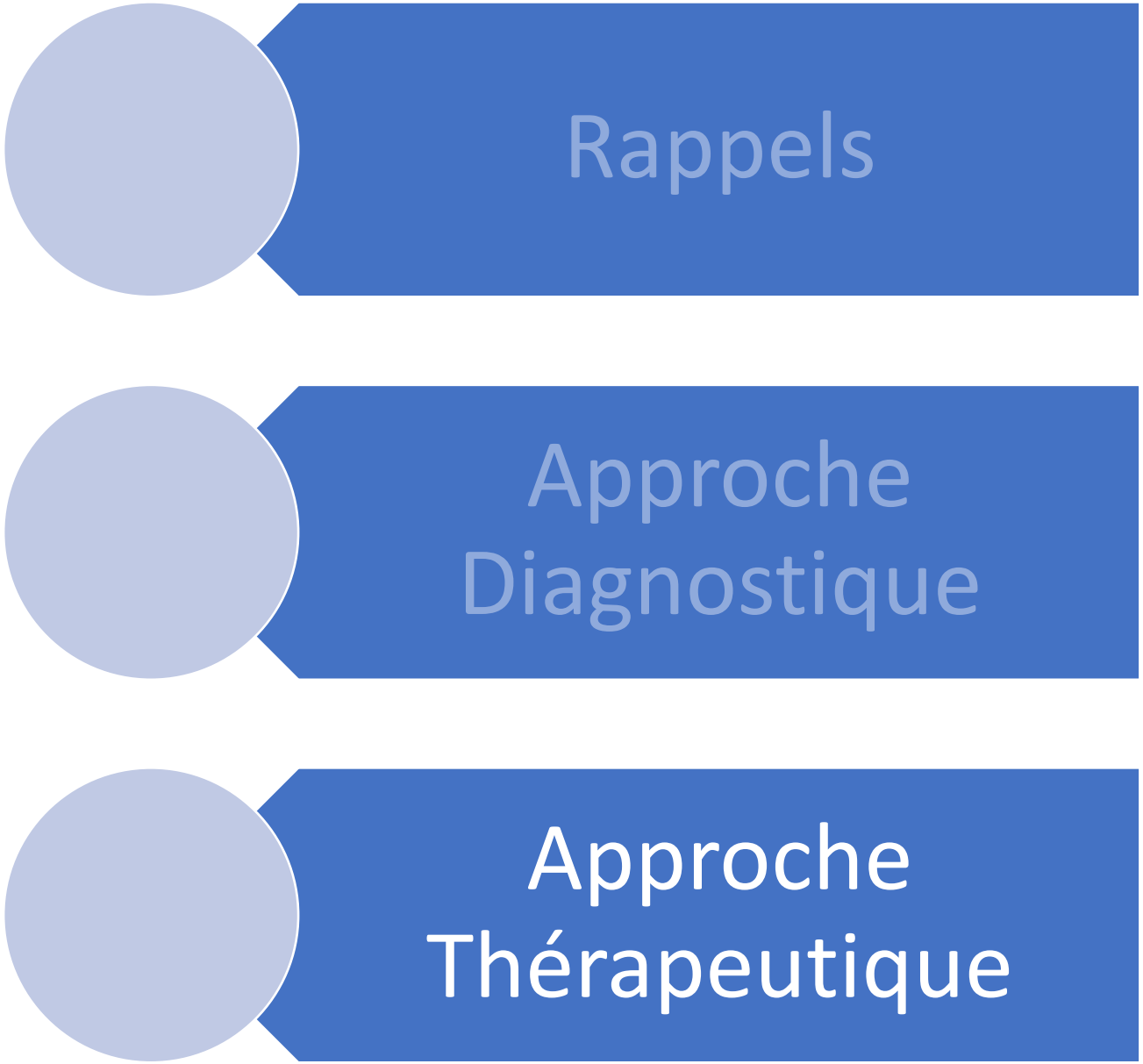
	Toxicities within 10d post CAR-T (data available in 322 pts)
CRS (all grades)	276 (85.7%)
grade 1-2	245
grade ≥ 3	30
missing	1
Neurotoxicity (all grades)	147 (45.7%)
grade 1-2	100
grade ≥ 3	47
missing	/
grade ≥ 3 opportunistic or medically significant infection	100 (31%)

Tisa-cel; Kymriah®

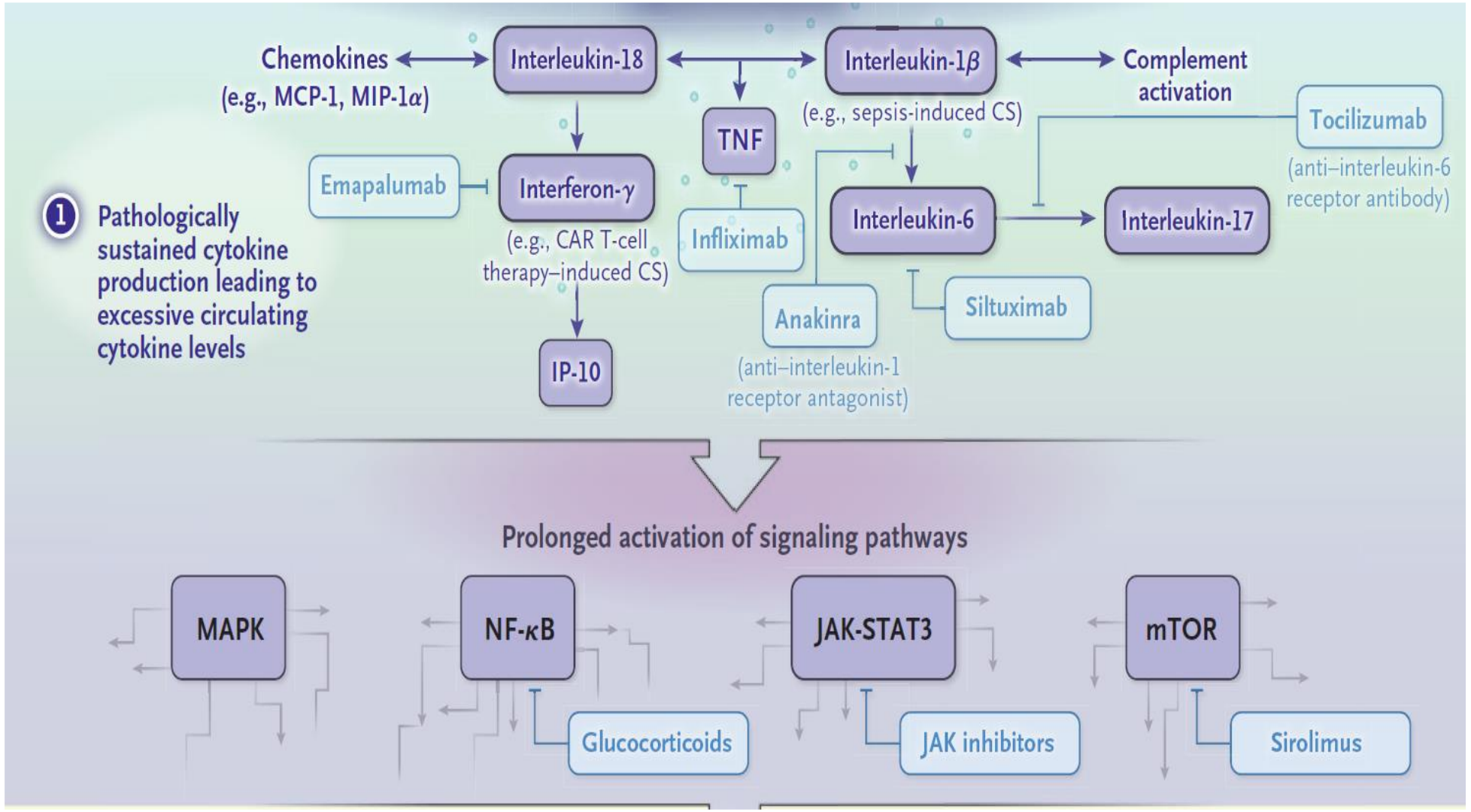
	Toxicities within 10d post CAR-T (data available in 193 pts)
CRS (all grades)	142 (73.6%)
grade 1-2	128
grade ≥ 3	14
missing	/
Neurotoxicity (all grades)	37 (19.2%)
grade 1-2	33
grade ≥ 3	3
missing	1
Grade ≥ 3 opportunistic or medically significant infection	63 (32.6%)

NB: DESCAR-T is based on secondary data use and thus expedited reporting of suspected adverse reaction are not mandatory

Plan

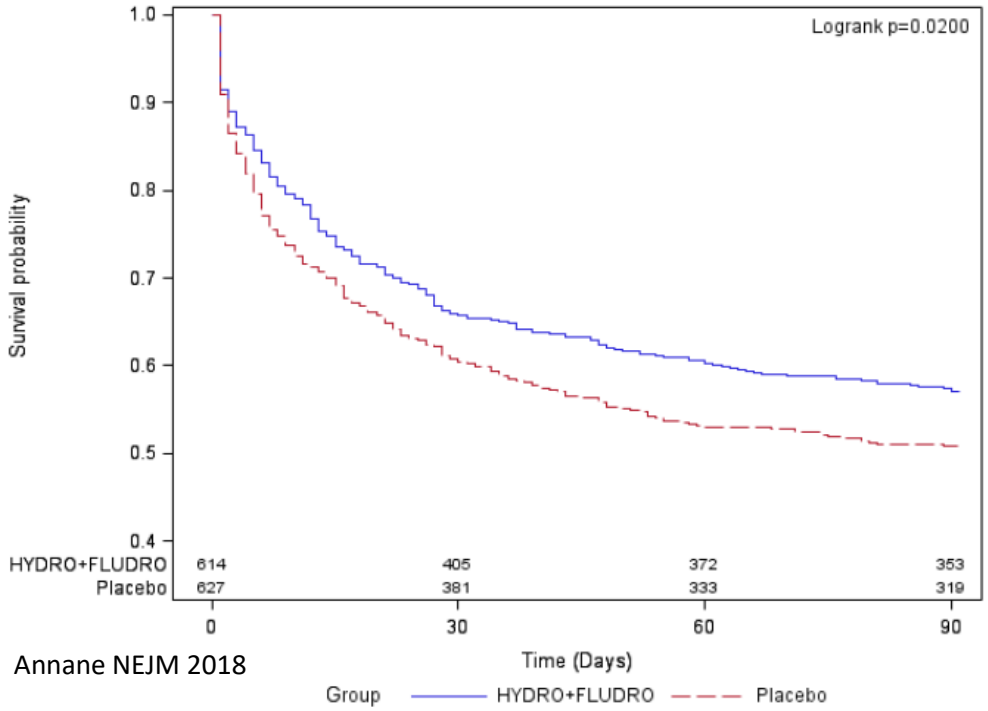


Therapeutic intervention for CRS



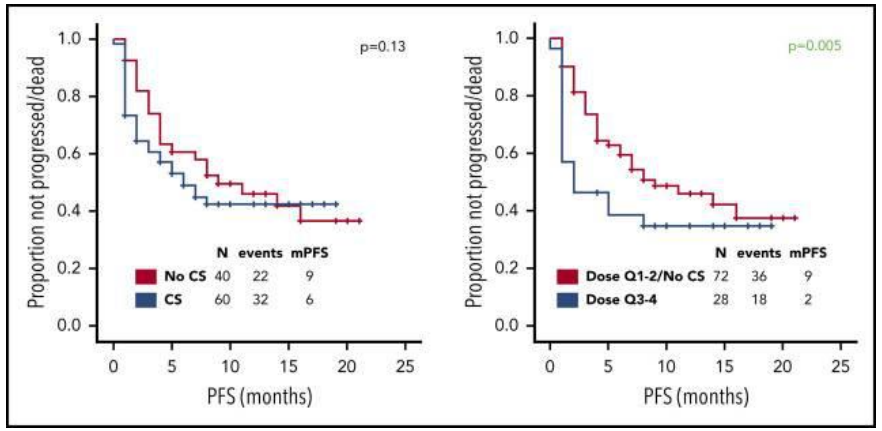
Fajgenbaum, NEJM 2021

Septic Shock



Annane NEJM 2018

CART-T cell B-Lymphoma



Strati Blood 2021

COVID-19

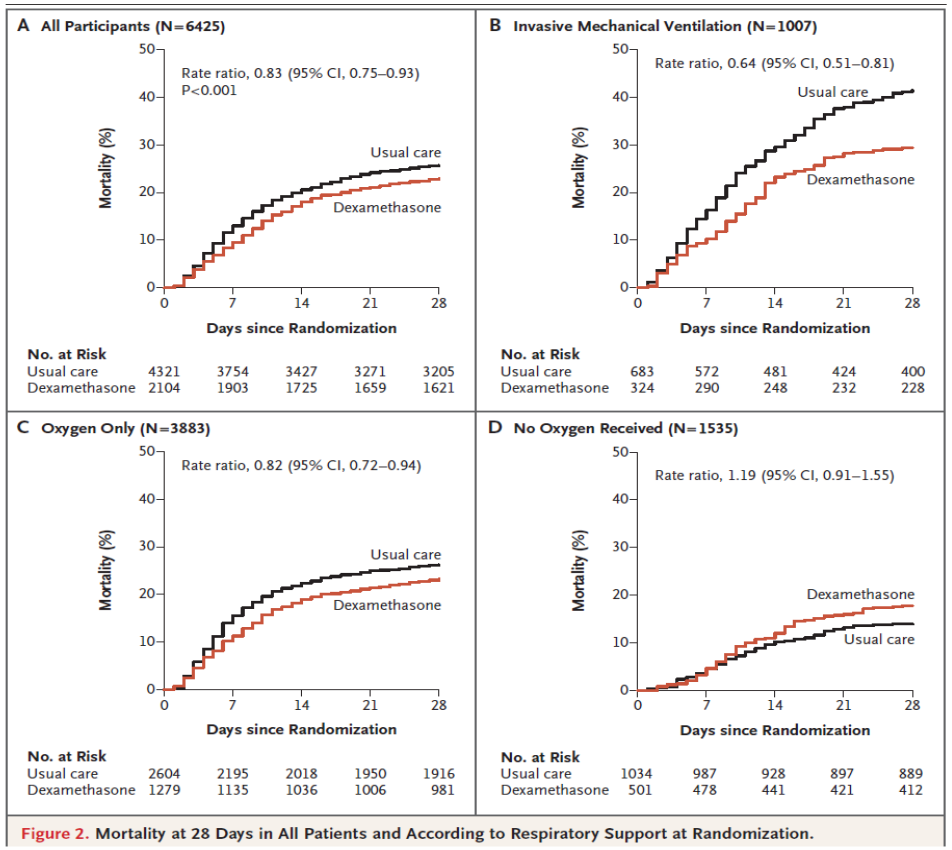


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

RECOVERY NEJM 201

Treatment strategy	Therapeutic agent	Rationale	Stage	Clinical trial identifier	References
IL-6 or IL-6R inhibition	Siltuxumab, tocilizumab	IL-6 highly elevated during CRS, produced by activated myeloid cells, key cytokine in CRS development	Clinical, standard of care (tocilizumab)	–	(9) (10) (58) (19)
Corticosteroids	Dexamethasone, methylprednisolone	Immunosuppression to quiet overactive immune cells	Clinical, standard of care	–	(10) (18, 61) (33) (7)
GM-CSF depletion	Lenzilumab, GM-CSF gene knockout	GM-CSF involved in stimulation of myeloid cells, which are implicated in CRS and ICANS	Preclinical, clinical trial initiated	NCT04314843	(62) (63)
IL-1 inhibition	Anakinra	IL-1 elevated during ICANS, produced by activated myeloid cells, precedes IL-6 secretion	Preclinical, clinical trial initiated	NCT04148430, NCT04150913	(57) (55)
TNFα inhibition	Etanercept	TNFα elevated during CRS, produced by activated CART cells, key cytokine in CRS development	Clinical trials ongoing	NCT03050190	(67) (68) (69) (70)
JAK/STAT inhibition	Ruxolitinib, itacitinib	JAK/STAT pathway utilized by IL-6 and GM-CSF	Preclinical, clinical trial ongiong	NCT04071366	(72) (73) (74)
ITK inhibition	Ibrutinib	Retrospective analysis showed patients previously treated with ibrutinib had improved CART cell therapeutic outcomes, ITK inhibition dampens inflammatory cytokines but enhances Th1 functions	Clinical trials ongoing	NCT02640209, NCT03960840, NCT01865617, NCT04234061, NCT03331198, NCT03310619	(75) (77) (78) (79) (80)
Pharmacological T cell activation switch	Dasatinib	T-cell receptor kinases utilized in CART cell signaling, reversibly inhibited to dampen immune overactivation	Preclinical	–	(98) (99)
Endothelial cell protection	Defibrotide	Endothelial cell activation from systemic inflammation a key driver of ICANS	Clinical trial initiated	NCT03954106	(92)
Suicide genes and selection markers	Inducible caspase 9, truncated EGFR, CD20	CART cells selectively ablated if dangerously overactivated	Clinical trials ongoing	NCT02107963, NCT01822652, NCT03373071, NCT03618381, NCT03084380, NCT02937844, NCT03710421, NCT02159495, NCT02844062	(93, 94, 95, 96, 97)

Siegler, Front Immunol 2020

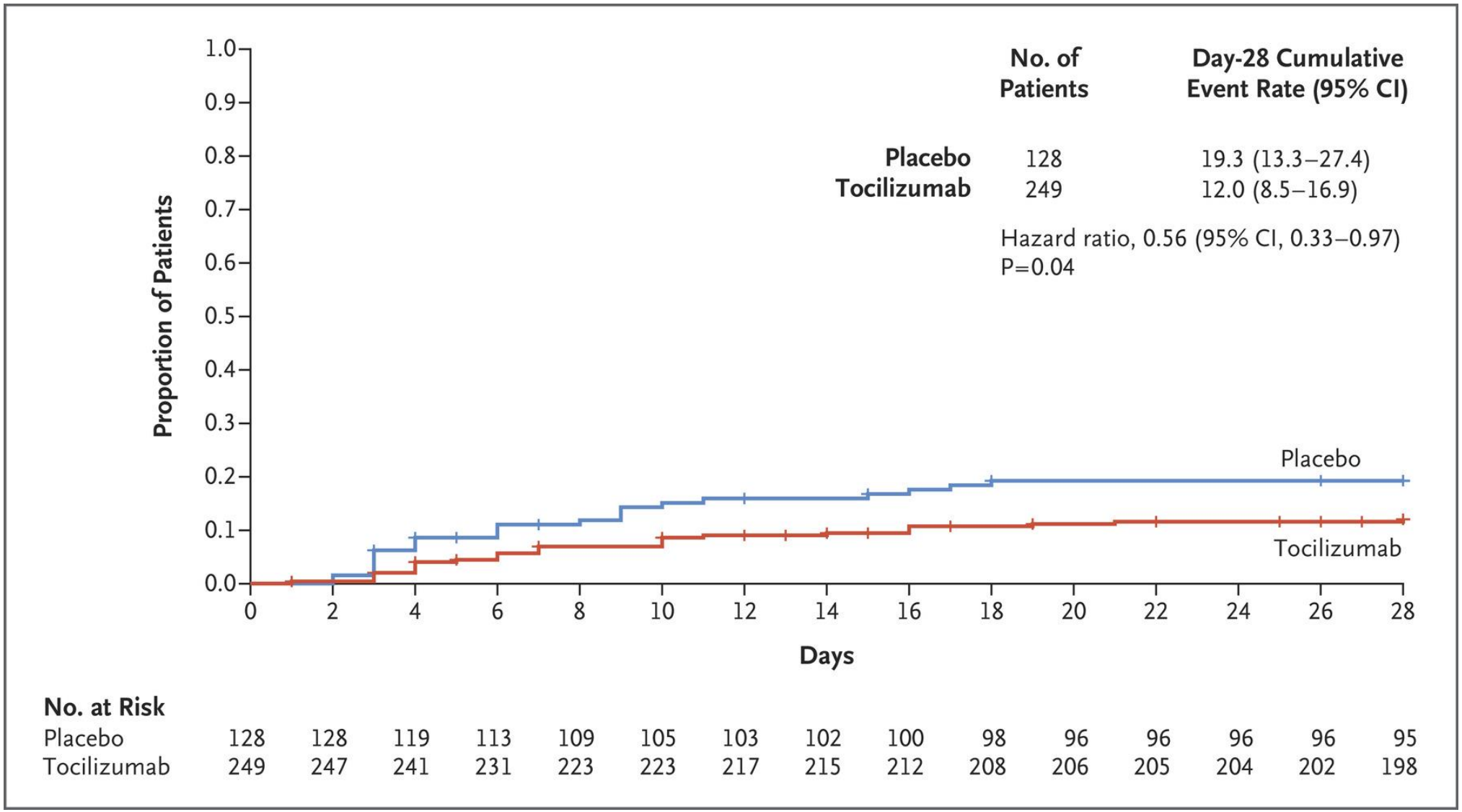
EARLY CRS, NEUROTOXICITY AND INFECTIONS

DESCAR-T

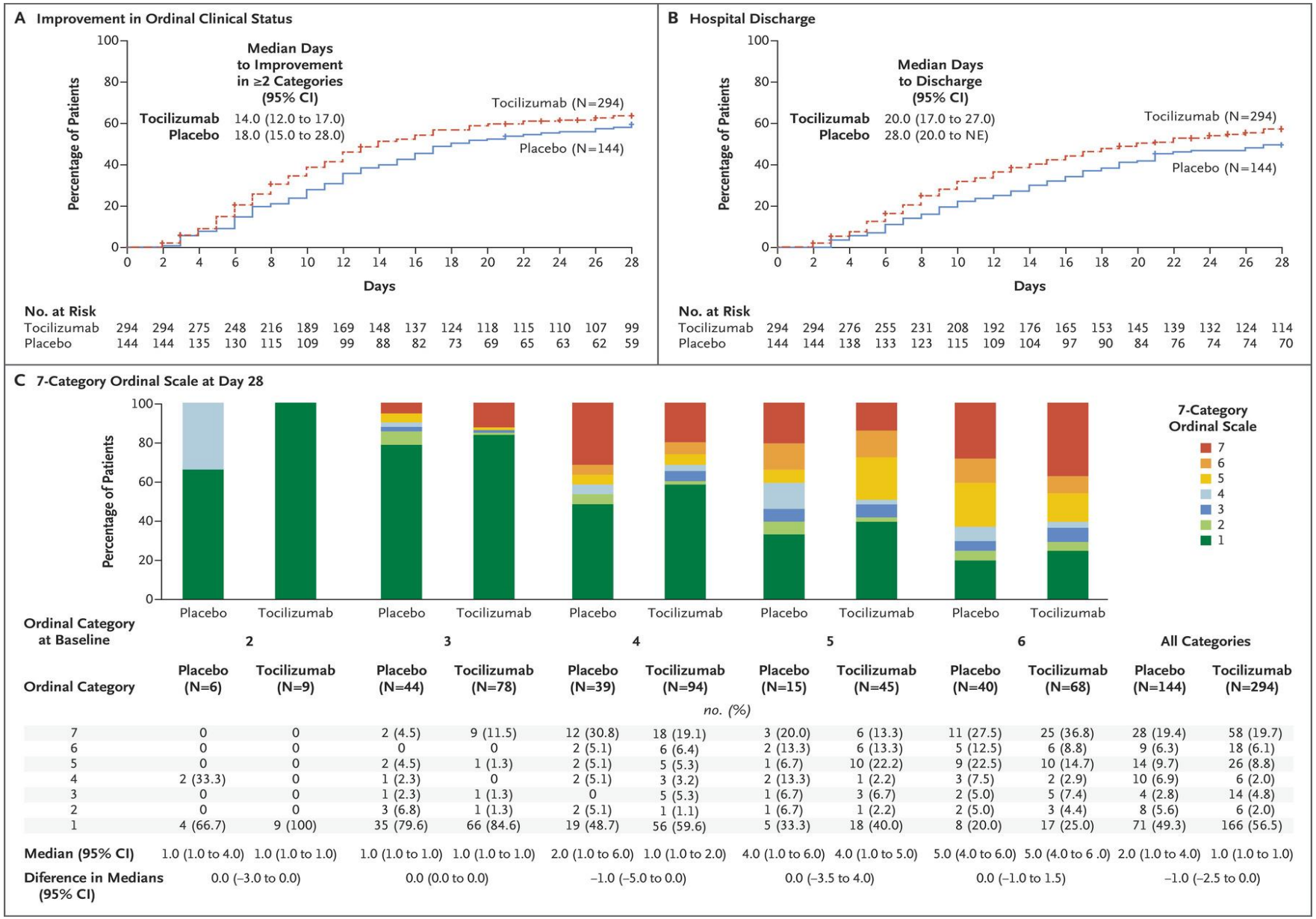
	Toxicities within 10d post CAR-T (data available in 515 pts)
CRS (all grades)	418 (81.2%)
grade 1-2	373
grade ≥ 3	44
missing	1
Neurotoxicity (all grades)	184 (35.7%)
grade 1-2	133
grade ≥ 3	50
missing	1
grade ≥ 3 opportunistic or medically significant infection	163 (31.7%)

	Patients with at least one CAR-T specific toxicity within 10d N=427
ICU hospitalization	139 (32.6%)
Treated for CAR-T specific tox	325 (76.1%)
Tocilizumab	278 (65.1%)
Siltuximab	13 (3%)
Corticosteroïds	176 (41.2%)

NB: DESCAR-T is based on secondary data use and thus expedited reporting of suspected adverse reaction are not mandatory

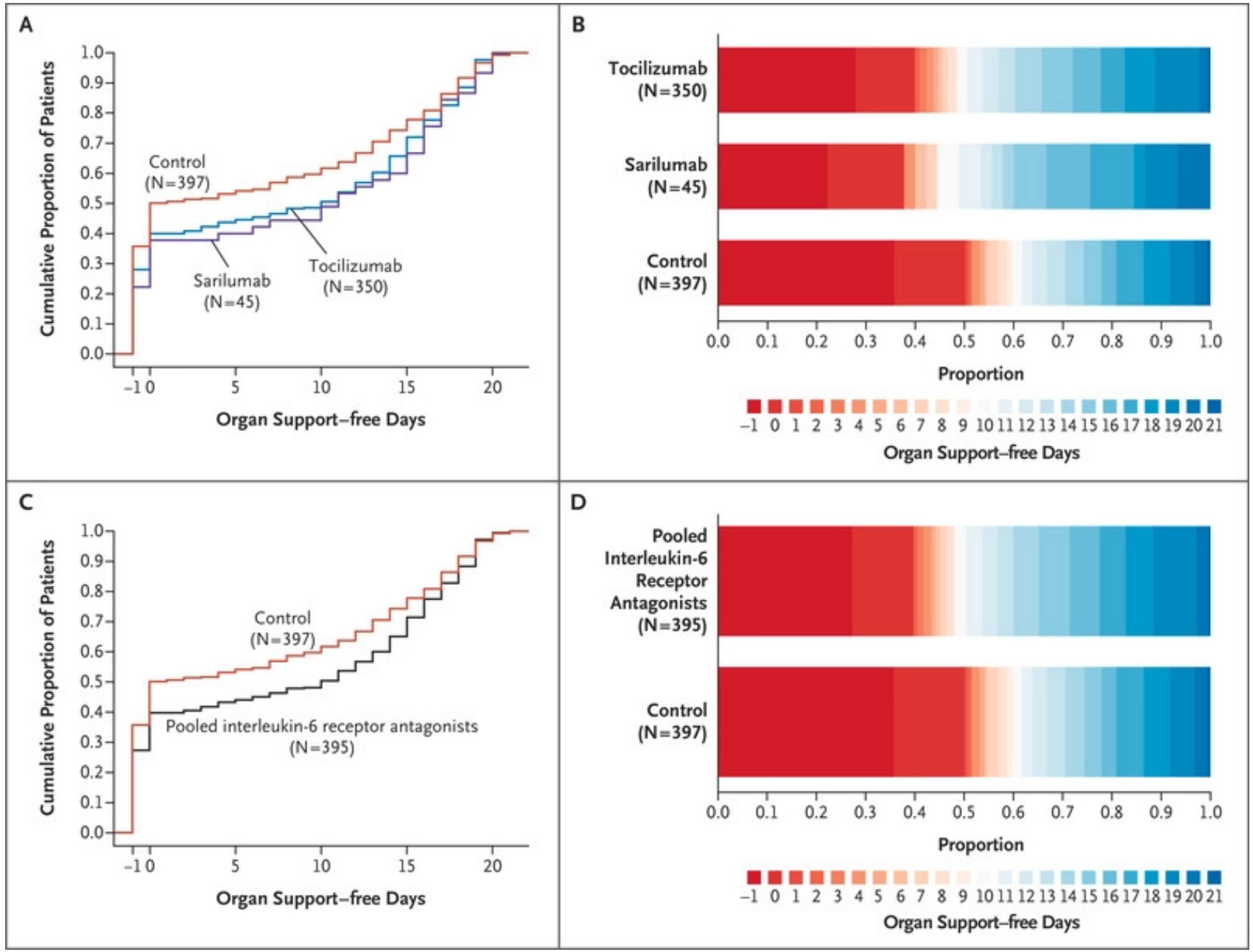


Salama NEJM 2021

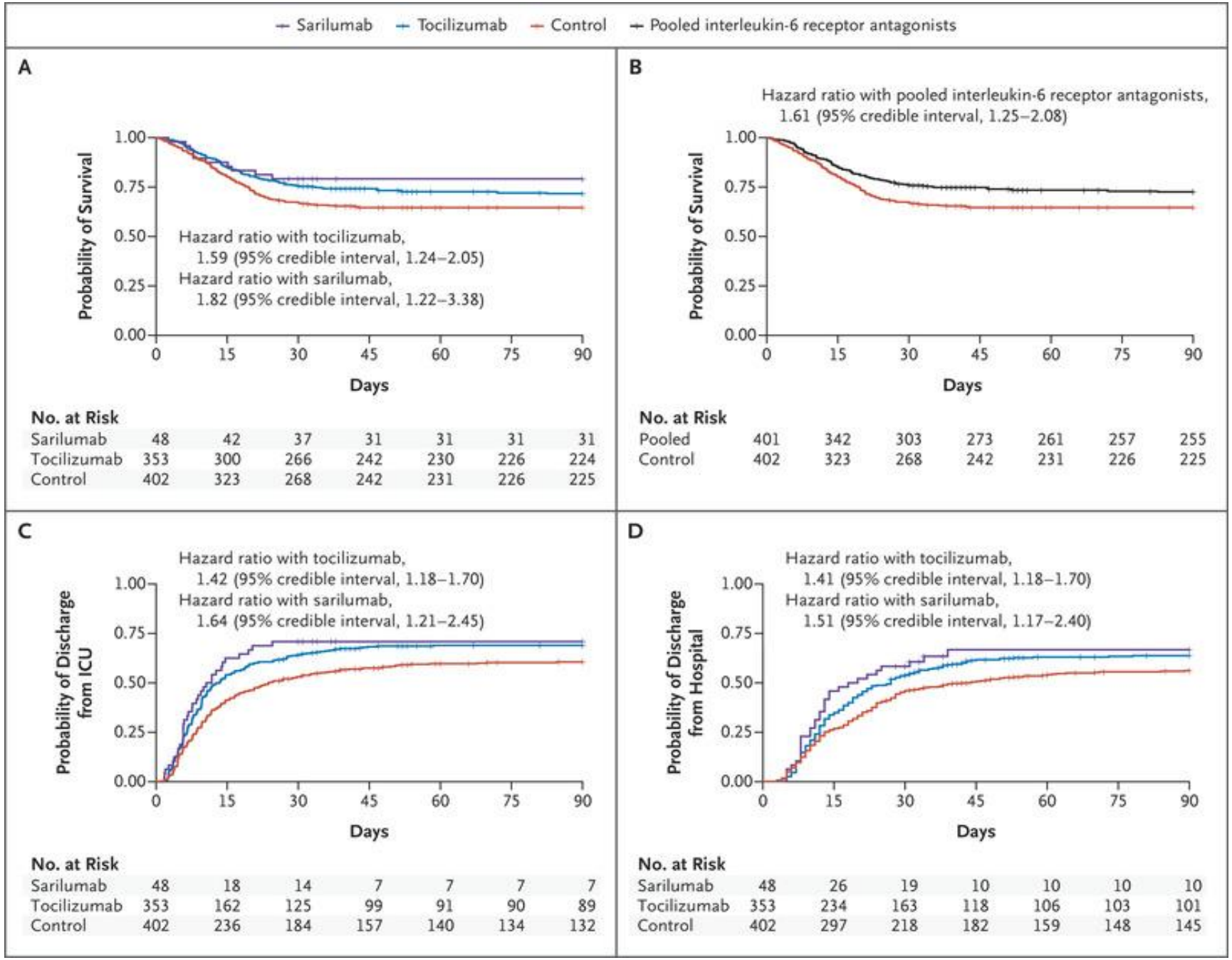


Ordinal Category at Baseline	2		3		4		5		6		All Categories	
Ordinal Category	Placebo (N=6)	Tocilizumab (N=9)	Placebo (N=44)	Tocilizumab (N=78)	Placebo (N=39)	Tocilizumab (N=94)	Placebo (N=15)	Tocilizumab (N=45)	Placebo (N=40)	Tocilizumab (N=68)	Placebo (N=144)	Tocilizumab (N=294)
						no. (%)						
7	0	0	2 (4.5)	9 (11.5)	12 (30.8)	18 (19.1)	3 (20.0)	6 (13.3)	11 (27.5)	25 (36.8)	28 (19.4)	58 (19.7)
6	0	0	0	0	2 (5.1)	6 (6.4)	2 (13.3)	6 (13.3)	5 (12.5)	6 (8.8)	9 (6.3)	18 (6.1)
5	0	0	2 (4.5)	1 (1.3)	2 (5.1)	5 (5.3)	1 (6.7)	10 (22.2)	9 (22.5)	10 (14.7)	14 (9.7)	26 (8.8)
4	2 (33.3)	0	1 (2.3)	0	2 (5.1)	3 (3.2)	2 (13.3)	1 (2.2)	3 (7.5)	2 (2.9)	10 (6.9)	6 (2.0)
3	0	0	1 (2.3)	1 (1.3)	0	5 (5.3)	1 (6.7)	3 (6.7)	2 (5.0)	5 (7.4)	4 (2.8)	14 (4.8)
2	0	0	3 (6.8)	1 (1.3)	2 (5.1)	1 (1.1)	1 (6.7)	1 (2.2)	2 (5.0)	3 (4.4)	8 (5.6)	6 (2.0)
1	4 (66.7)	9 (100)	35 (79.6)	66 (84.6)	19 (48.7)	56 (59.6)	5 (33.3)	18 (40.0)	8 (20.0)	17 (25.0)	71 (49.3)	166 (56.5)
Median (95% CI)	1.0 (1.0 to 4.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	2.0 (1.0 to 6.0)	1.0 (1.0 to 2.0)	4.0 (1.0 to 6.0)	4.0 (1.0 to 5.0)	5.0 (4.0 to 6.0)	5.0 (4.0 to 6 .0)	2.0 (1.0 to 4.0)	1.0 (1.0 to 1.0)
Diference in Medians (95% CI)	0.0 (–3.0 to 0.0)		0.0 (0.0 to 0.0)		–1.0 (–5.0 to 0.0)		0.0 (–3.5 to 4.0)		0.0 (–1.0 to 1.5)		–1.0 (–2.5 to 0.0)	

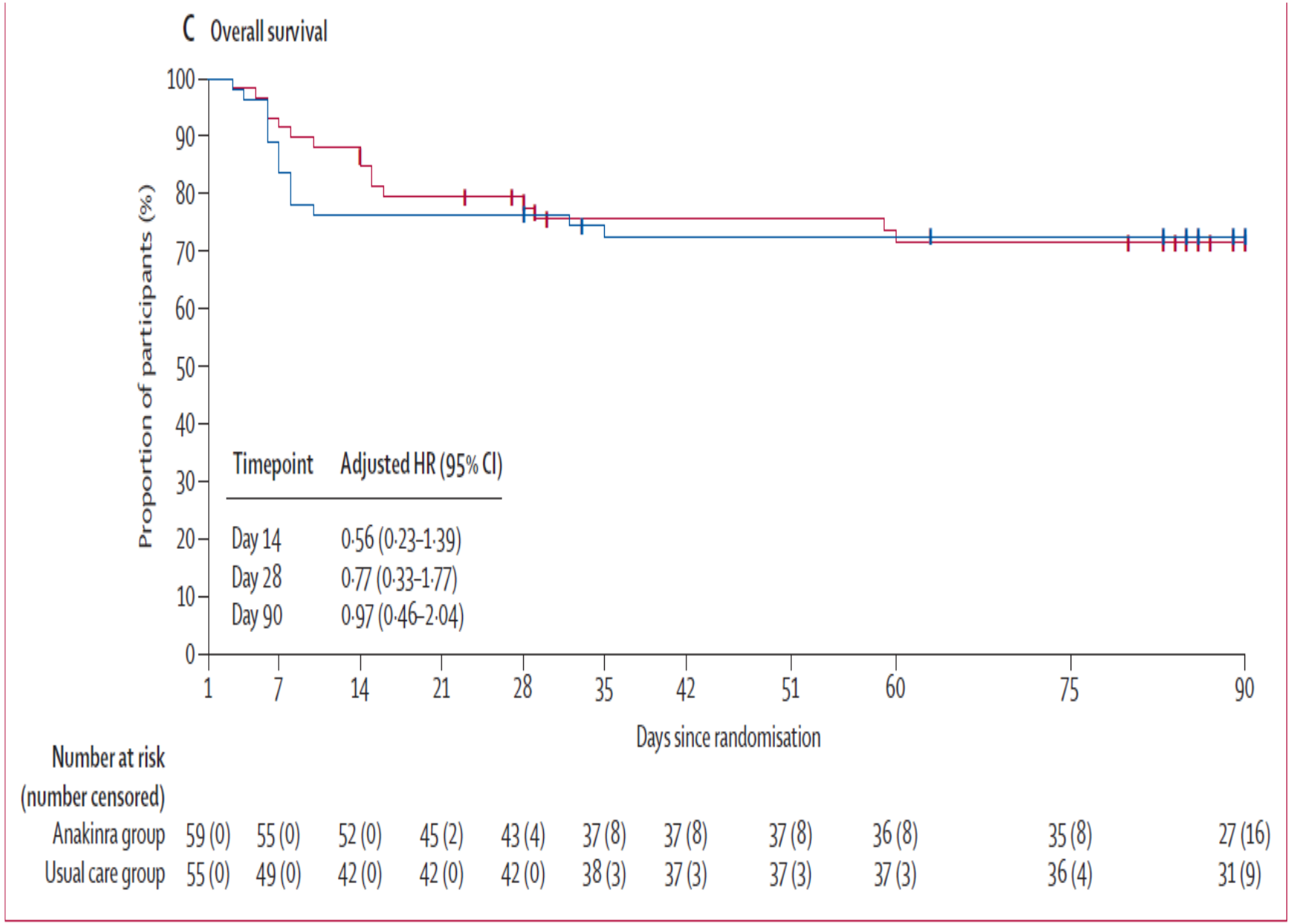
Rosas, NEJM 2021



REMAPCAP NEJM 2021

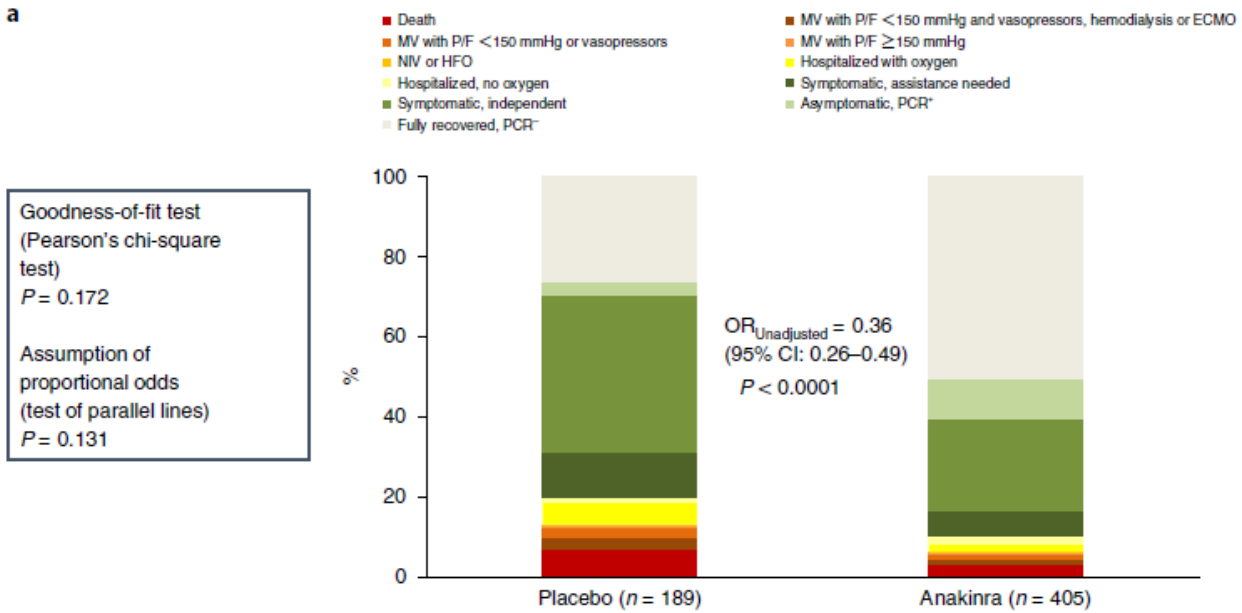


REMAPCAP NEJM 2021



CORIMUNO-ANA-1, LRM 2021

a



b

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Group of treatment (Anakinra vs placebo)	0.36	0.26–0.49	<0.0001	0.36	0.26–0.50	<0.0001
Intake of dexamethasone (Yes/No)	1.90	1.28–2.83	0.002	1.49	0.59–3.80	0.395
Severe COVID-19 by WHO (Yes/No)	1.95	1.31–2.90	0.001	1.29	0.51–3.27	0.582
BMI >30 kg m^{-2} (Yes/No)	1.27	0.87–1.61	0.267	1.10	0.81–1.50	0.530
Country (Italy vs Greece)	1.18	0.74–1.88	0.482	1.25	0.77–2.03	0.350

Fig. 2 | Study primary endpoint. a, Distribution of the WHO-CPS scores at day 28 of patients allocated to treatment with placebo and to treatment with

Kyriazopoulou, 2021

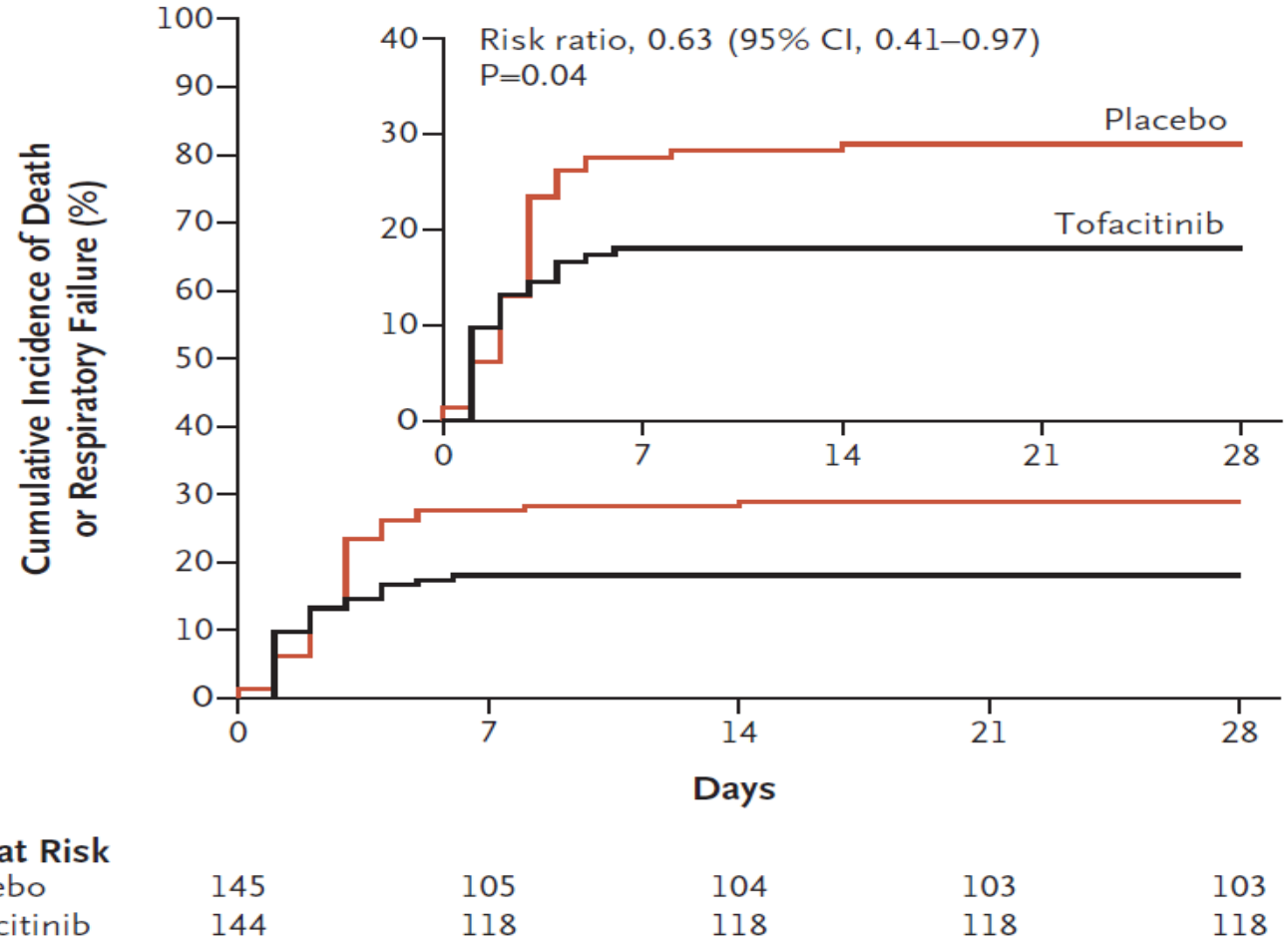


Figure 2. Cumulative Incidence of the Primary Outcome.

The primary outcome was death or respiratory failure through day 28. The risk ratio and P value for the primary outcome were calculated by means of binary regression with Firth correction, with trial group and inclusion of antiviral therapy for Covid-19 as covariates. The inset shows the same data on an expanded y axis.

Guimarães, 2021

The NEW ENGLAND JOURNAL of MEDICINE

Baricitinib + Remdesivir for Hospitalized Adults with Covid-19

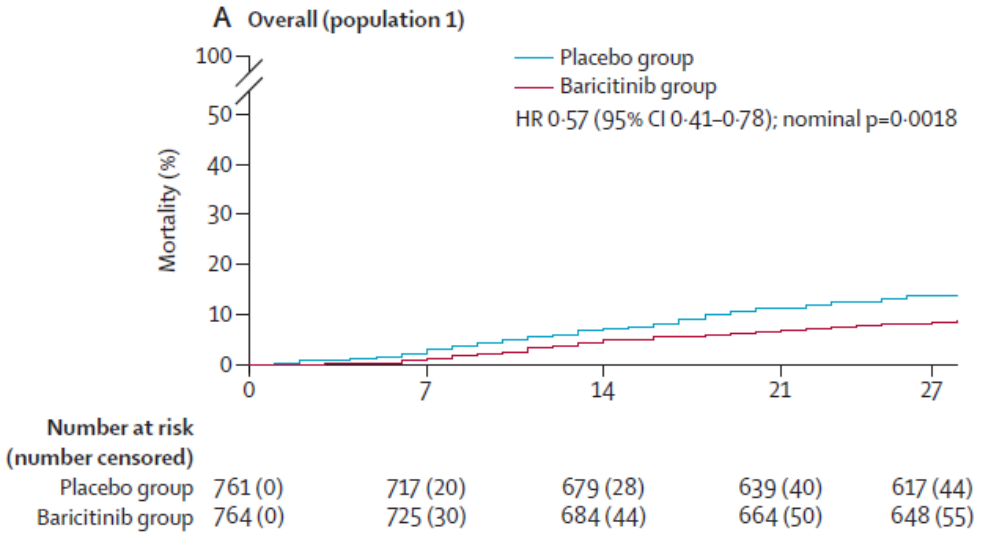
DOUBLE-BLIND, MULTICENTER, RANDOMIZED, CONTROLLED TRIAL

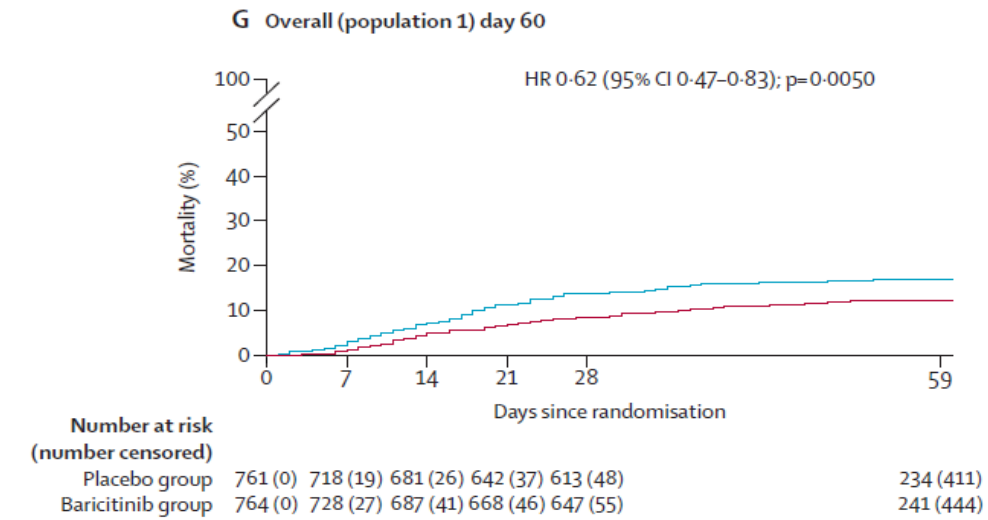
1033 Patients hospitalized with Covid-19

	Baricitinib + Remdesivir (N=515)	Placebo + Remdesivir (N=518)
Median time to recovery	7 Days	8 Days
	Rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03	
Time to recovery among patients receiving high-flow oxygen or noninvasive ventilation	10 Days	18 Days
	Rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08	
Serious adverse events	16%	21%

Baricitinib + remdesivir reduced recovery time and accelerated improvement in clinical status.

A.C. Kalil et al. 10.1056/NEJMoa2031994





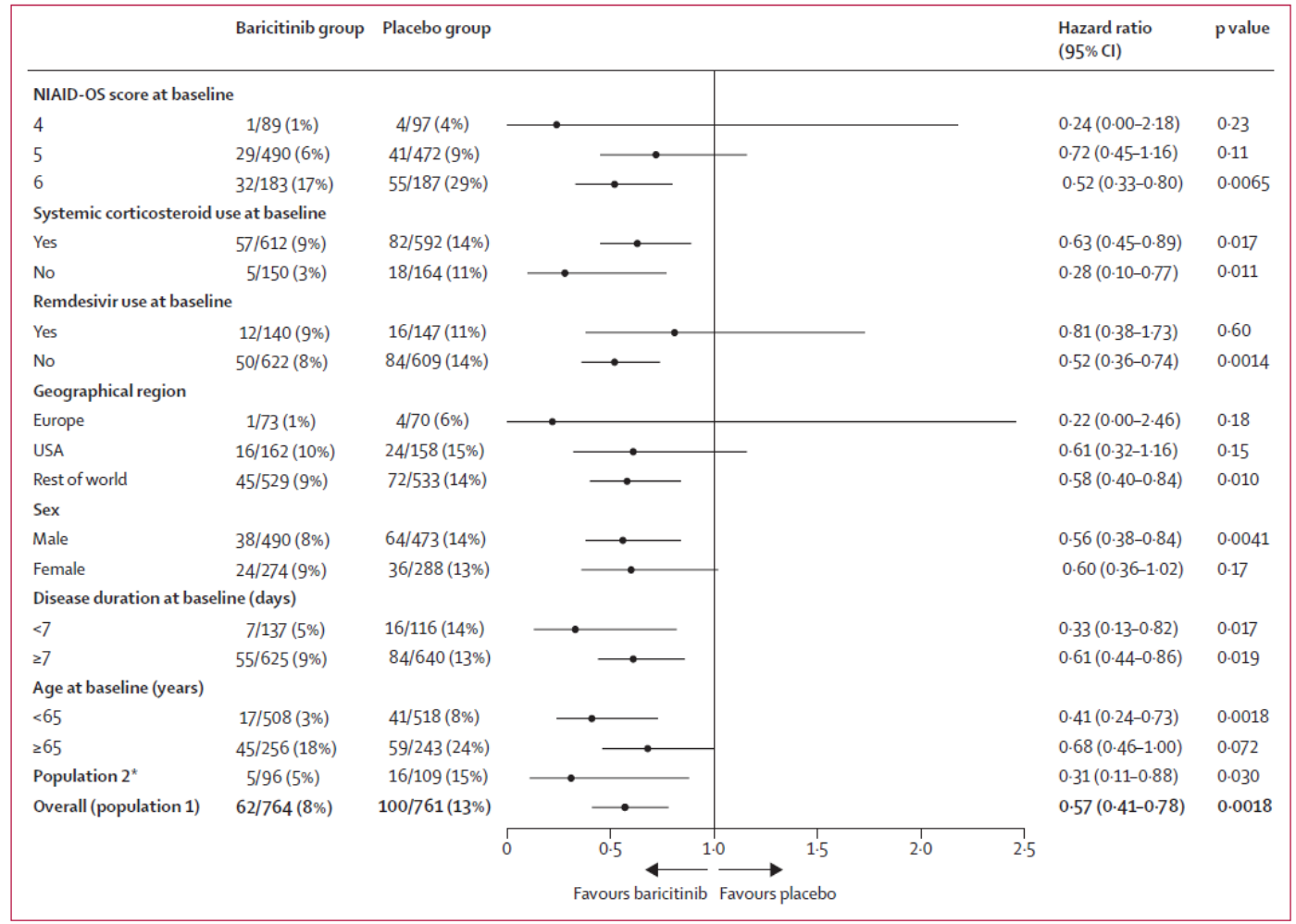


Figure 3: **28-day all-cause mortality by subgroup**
HRs and 95% CIs were calculated with a Cox proportional hazards model. The treatment effect was adjusted by all baseline randomisation factors, except when redundant (eg, for age group [<65 or ≥65 years] in the age subgroup analyses). HR=hazard ratio. NIAID-OS=National Institute of Allergy and Infectious Disease Ordinal Scale. *Participants who, at baseline, required oxygen supplementation and were not receiving dexamethasone or other systemic corticosteroids for the primary study condition.

Marconi, LRM 2021

Conclusion

- Cytokine release syndrome, cytokinic shock, cytokine storm
- Acute complication of infection, cell targeting therapies, autoimmune disorders, cancer
- Can be lethal
- Management includes broadly immune-modulators (corticosteroids, Jak inhibitors), cytokine specific antagonists (IL-6, IL-1…)