

Brain immune interactions after stroke

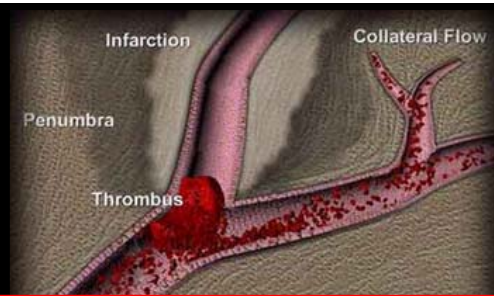
Anna M. Planas

Cerebrovascular Research
IIBB-CSIC, IDIBAPS



ICN 2010
Salzburg, Austria
September 11 – 15, 2010

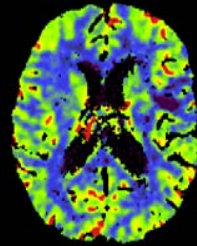
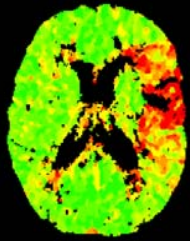




STROKE

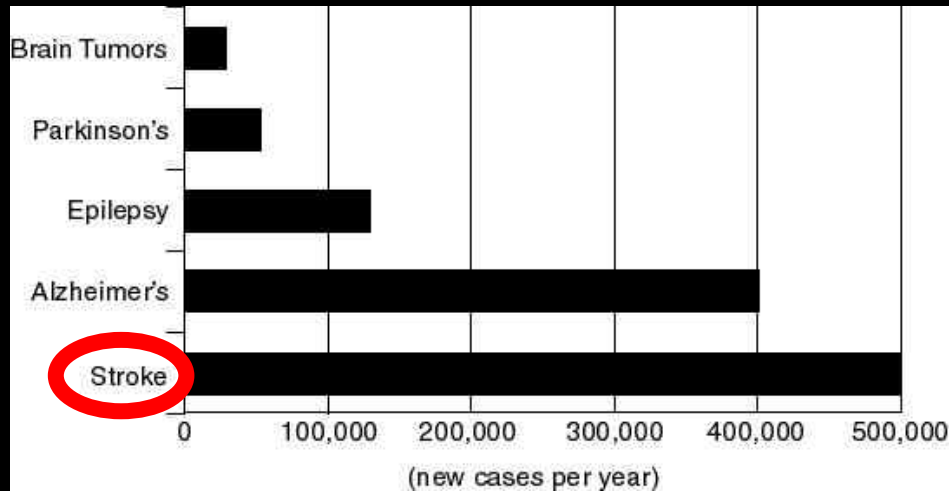
hypoperfusion

infarction

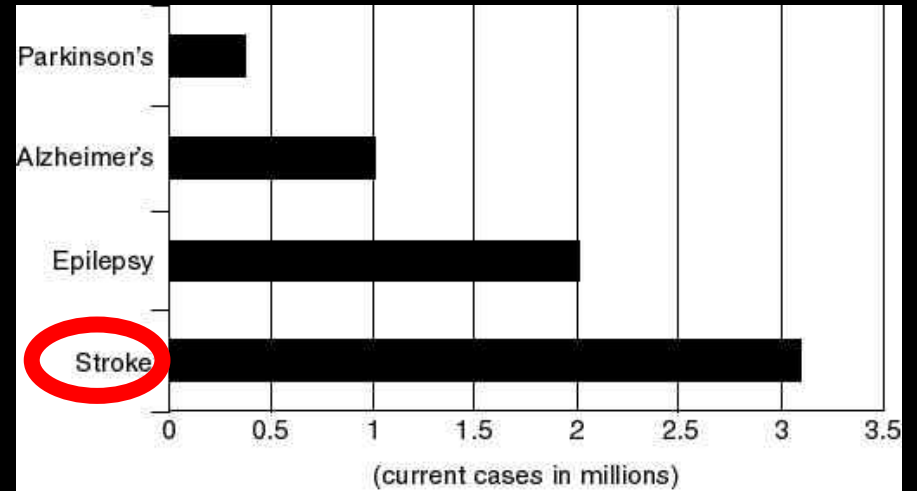


**1st disability
2nd death**

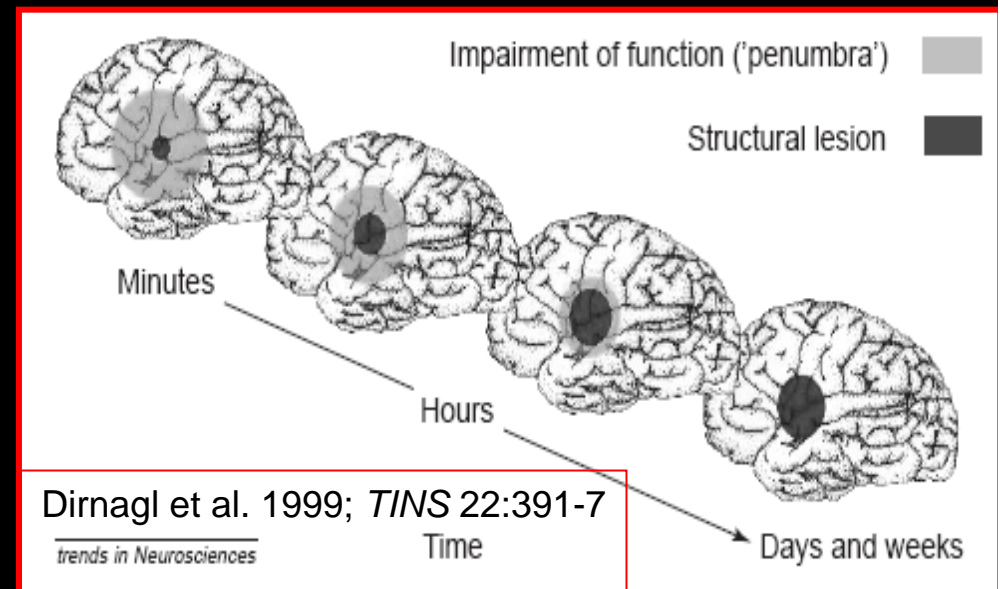
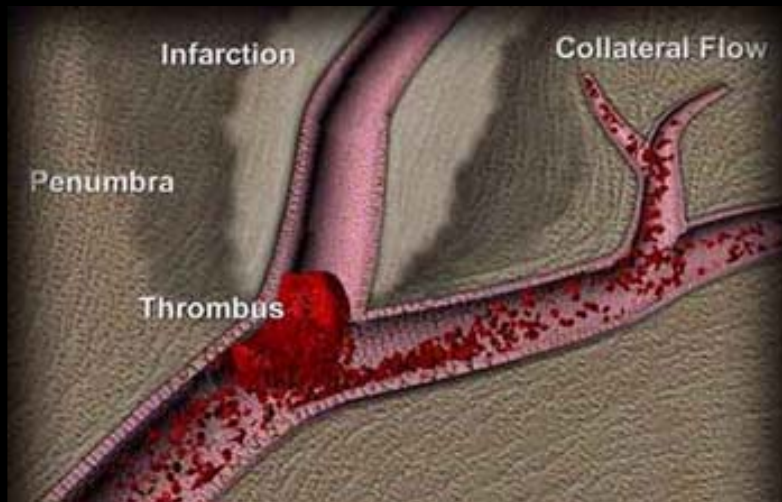
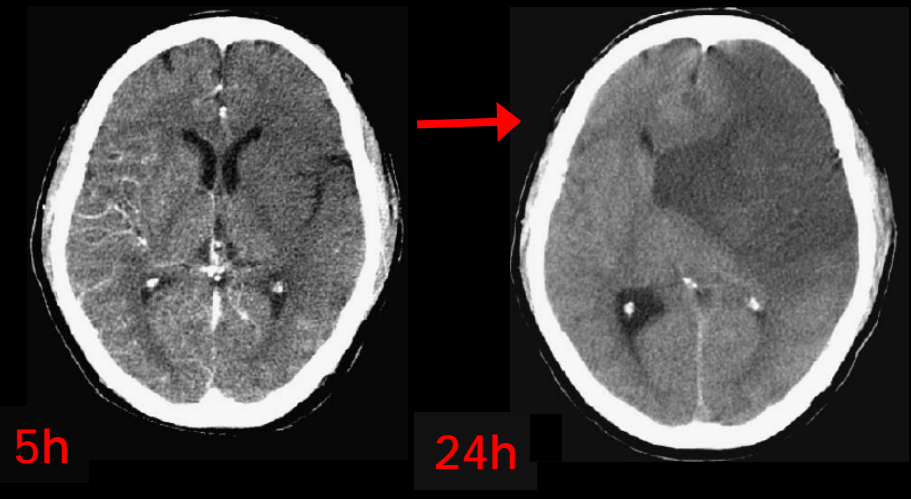
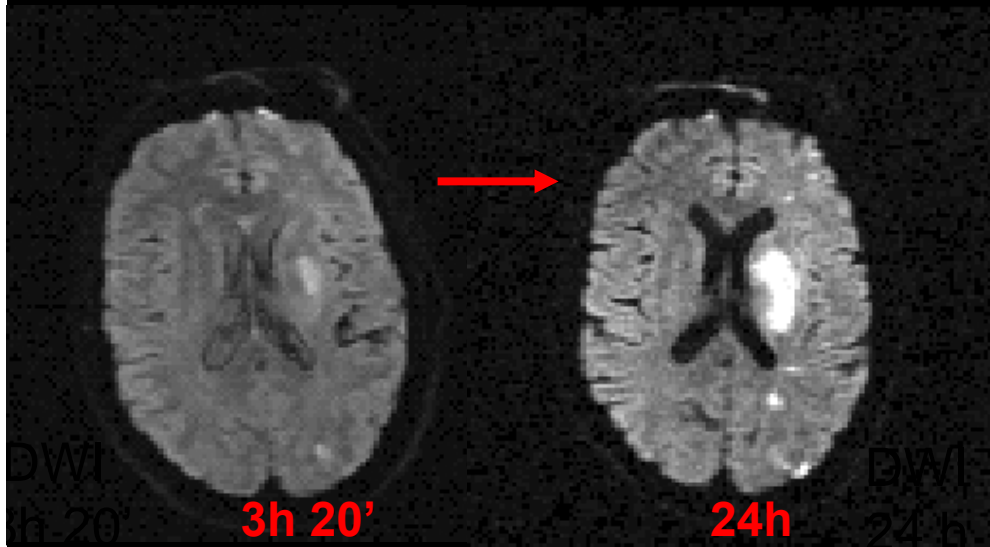
INCIDENCE



PREVALENCE



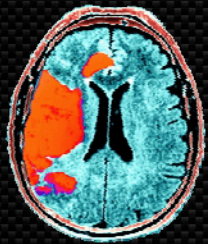
STROKE



Relations between the immune system, inflammation, and stroke



Inflammation as a stroke risk factor



Acute stroke: brain damage and immune responses

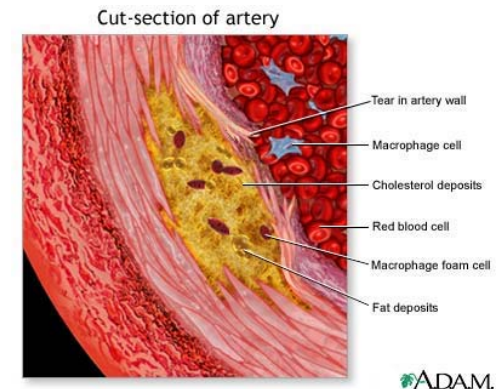
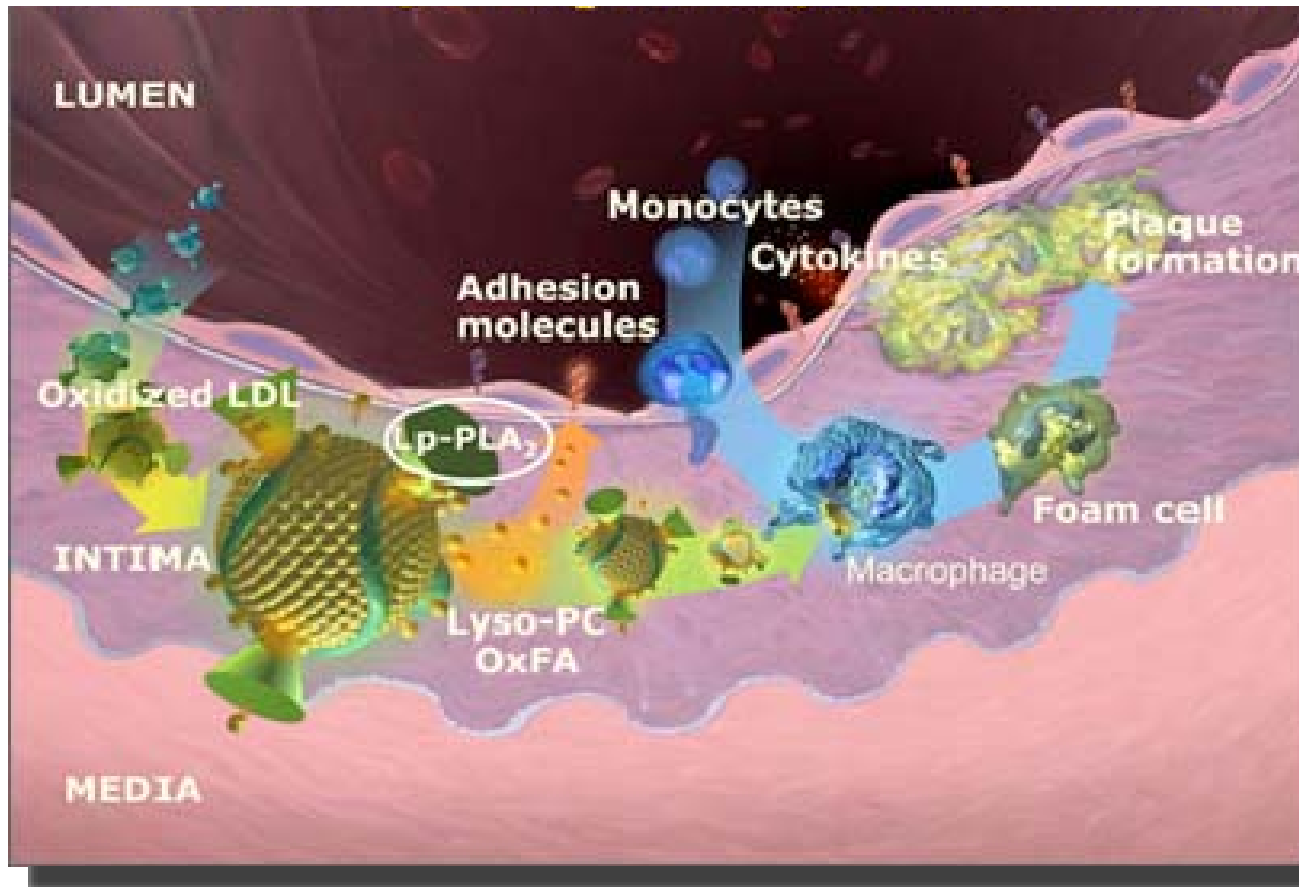


Infection in stroke: immunosuppression vs inflammation



Therapeutic strategies

Inflammation as stroke risk factor: atherosclerosis



Proinflammatory
players

NF-kB

MCSF-1

MCP-1

COX-2

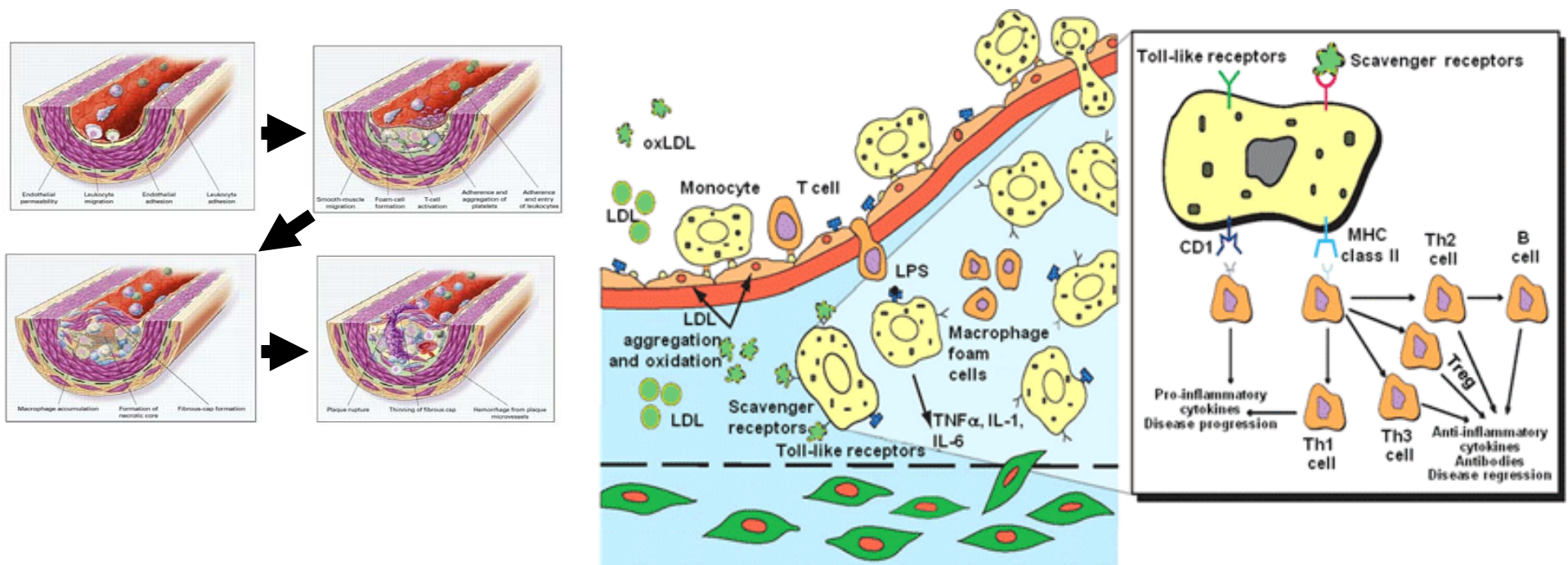
Lp-PLA₂

Interleukins 2, 6, 12

Metalloproteinases 1, 2, 8, 9

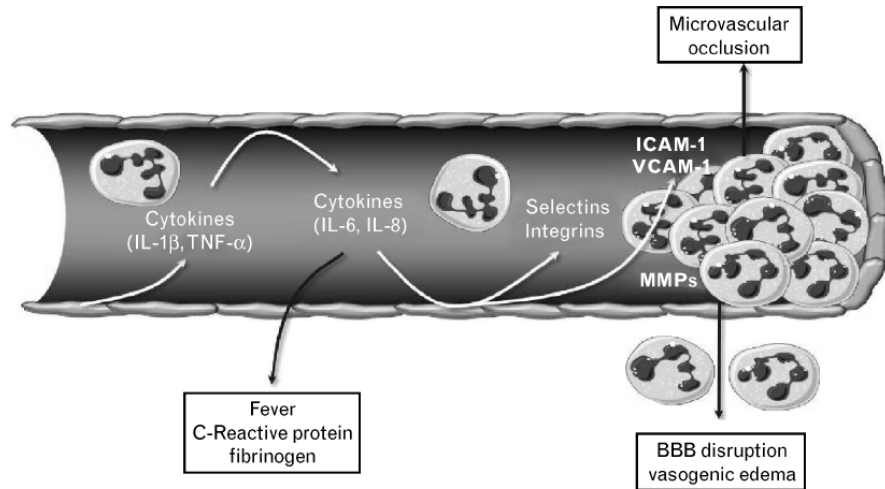
Oxidative products of A lipoprotein

Inflammatory and immune responses in atherosclerosis

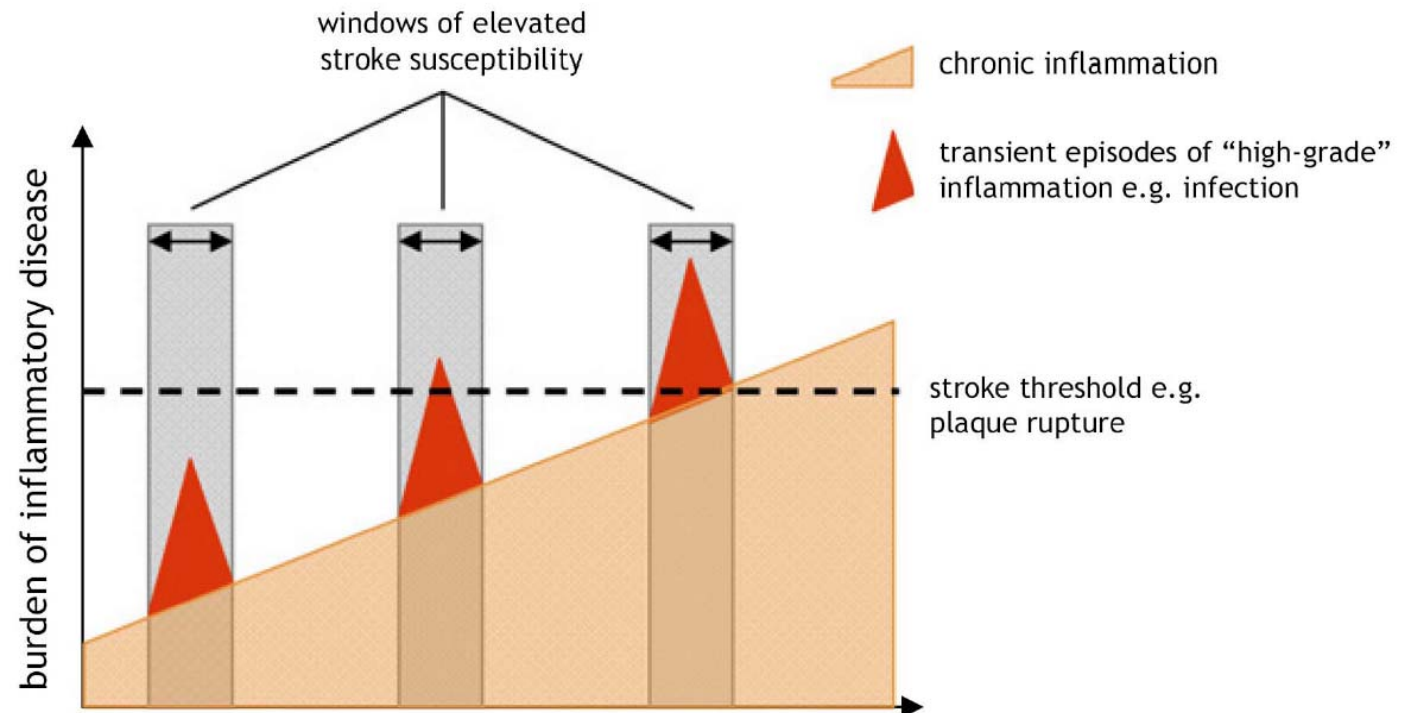


Atherosclerosis is a chronic disease in which inflammatory and immune responses contribute to the initiation, progression, and destabilization of atherosclerotic lesions

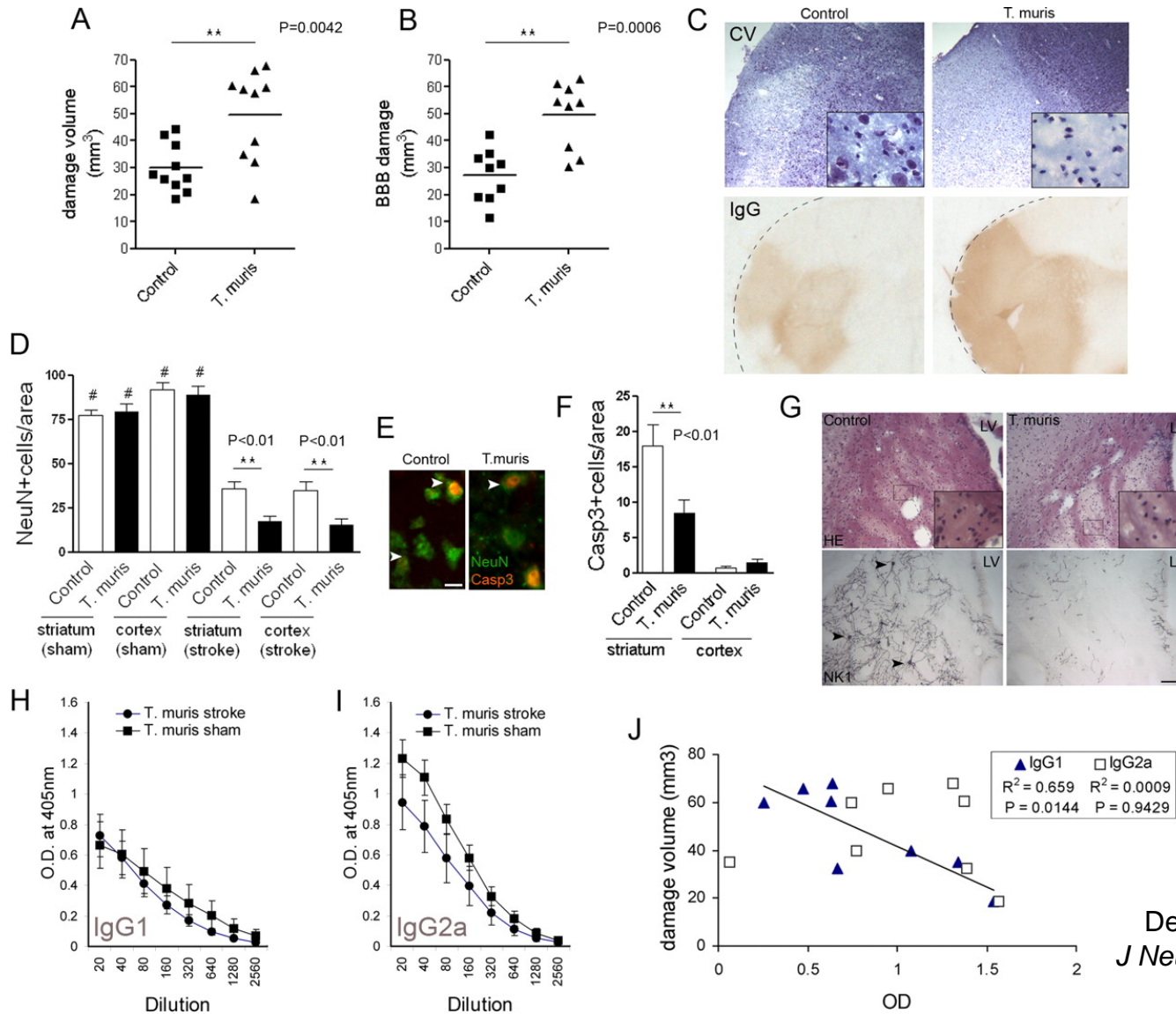
Infection can trigger vascular events and stroke



Infectious Burden and Carotid
Plaque Thickness
The Northern Manhattan Study
Elkind MSV et al. *Stroke*
2010;41:e117-e122



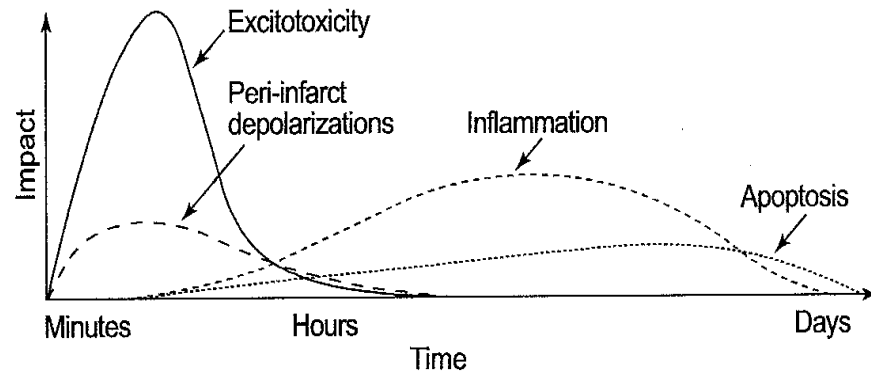
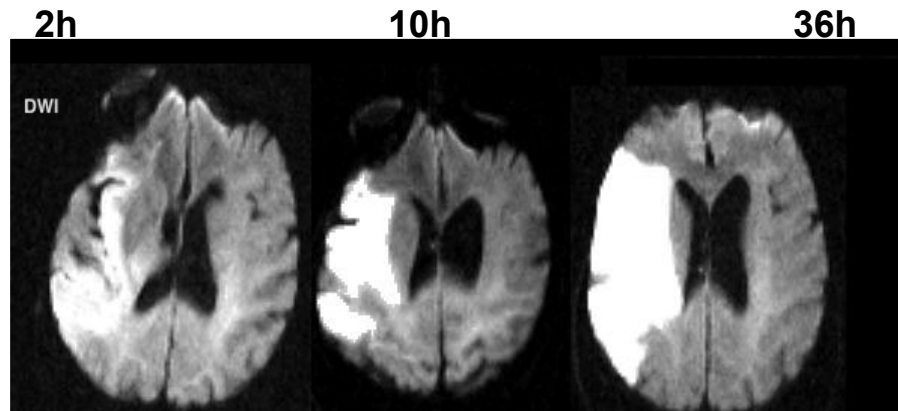
Chronic Th1-type peripheral infection contributes to brain injury after stroke



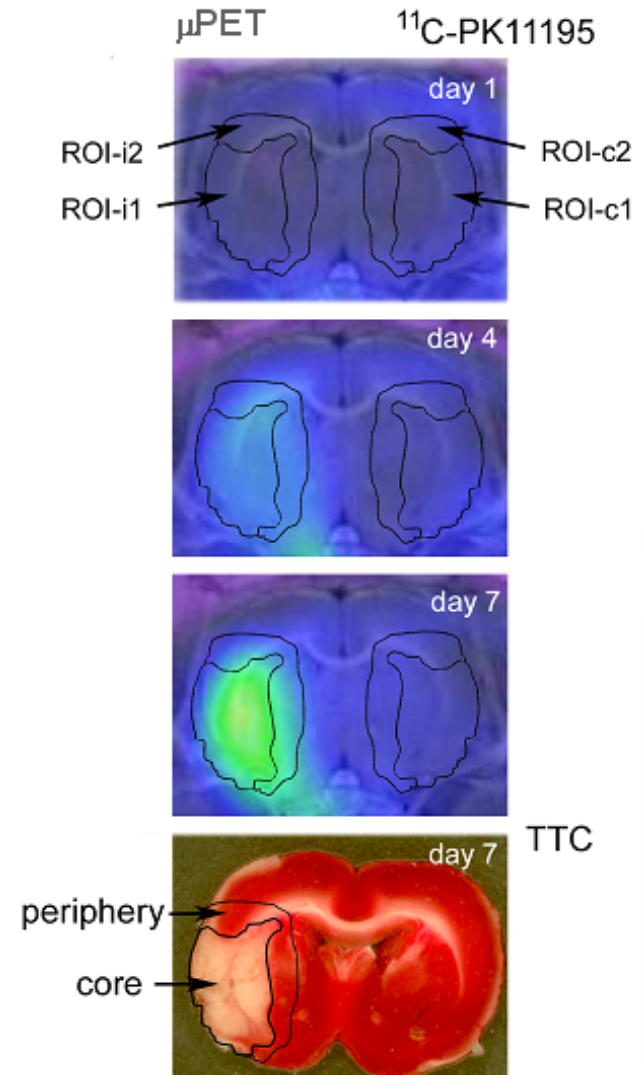
Denés et al., (2010)
J Neurosci. 30:10086-95

Inflammation and innate immunity after brain ischemia

- 1) Reaction of resident cells: glial reaction
- 2) Adhesion and infiltration of leukocytes
- 3) Molecular players: cytokines, chemokines, adhesion molecules, TLR, complement...



Dirnagl et al. 1999; *TINS* 22:391-7



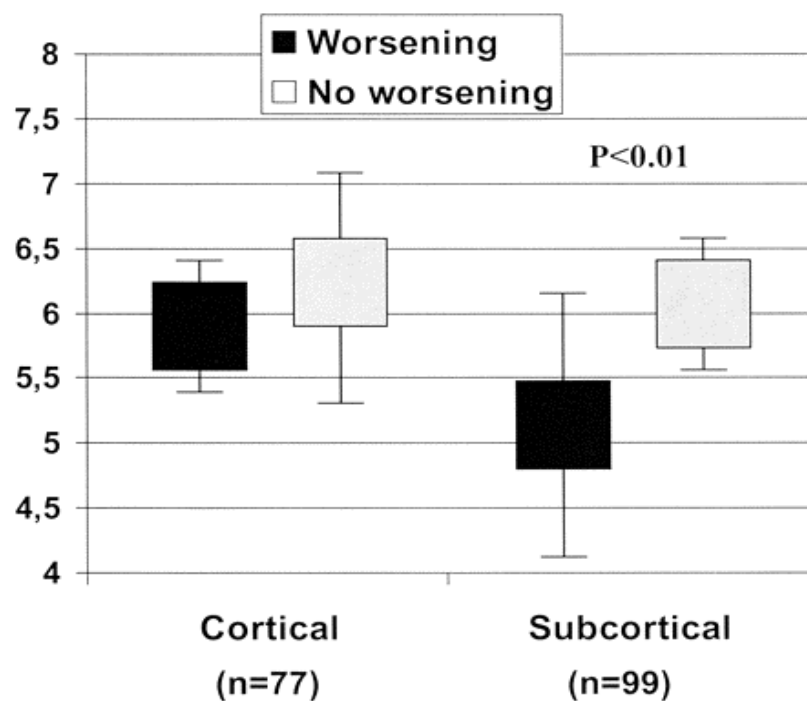
Rojas et al, 07 *JCBF* 27:1975

Cytokines as clinical predictors of outcome in the clinics

- Eritrocyte sedimentation rate
- Reactive C protein (CRP)
- Interleukin-6
- Tumor necrosis fator (TNF)
- Intercellular adhesion molecule (ICAM-1)

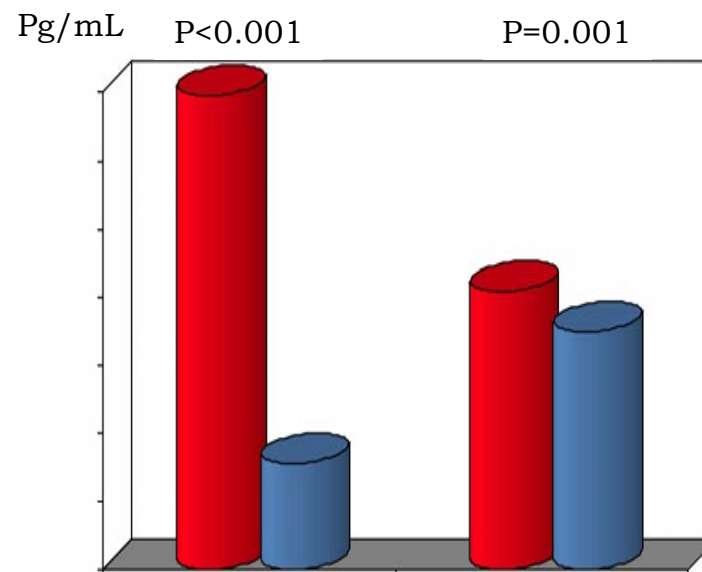
Low plasma levels of IL-10 predict bad outcome and neurological impairment

Vila et al. (2003) *Stroke*



High plasma levels of IL-6 and TNF- α predict bad outcome and neurological impairment

Castellanos et al. (2002) *Stroke*

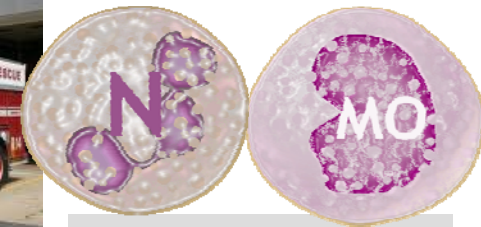


Mean \pm SD delay to sampling 8.2 \pm 5.7 hrs

■ Lacunar stroke (n=113) ■ Controls (n=43)

Stroke activates an innate immune response that contributes to brain injury

Innate Immune System



COMPLEMENT
TOLL-LIKE RECEPTORS

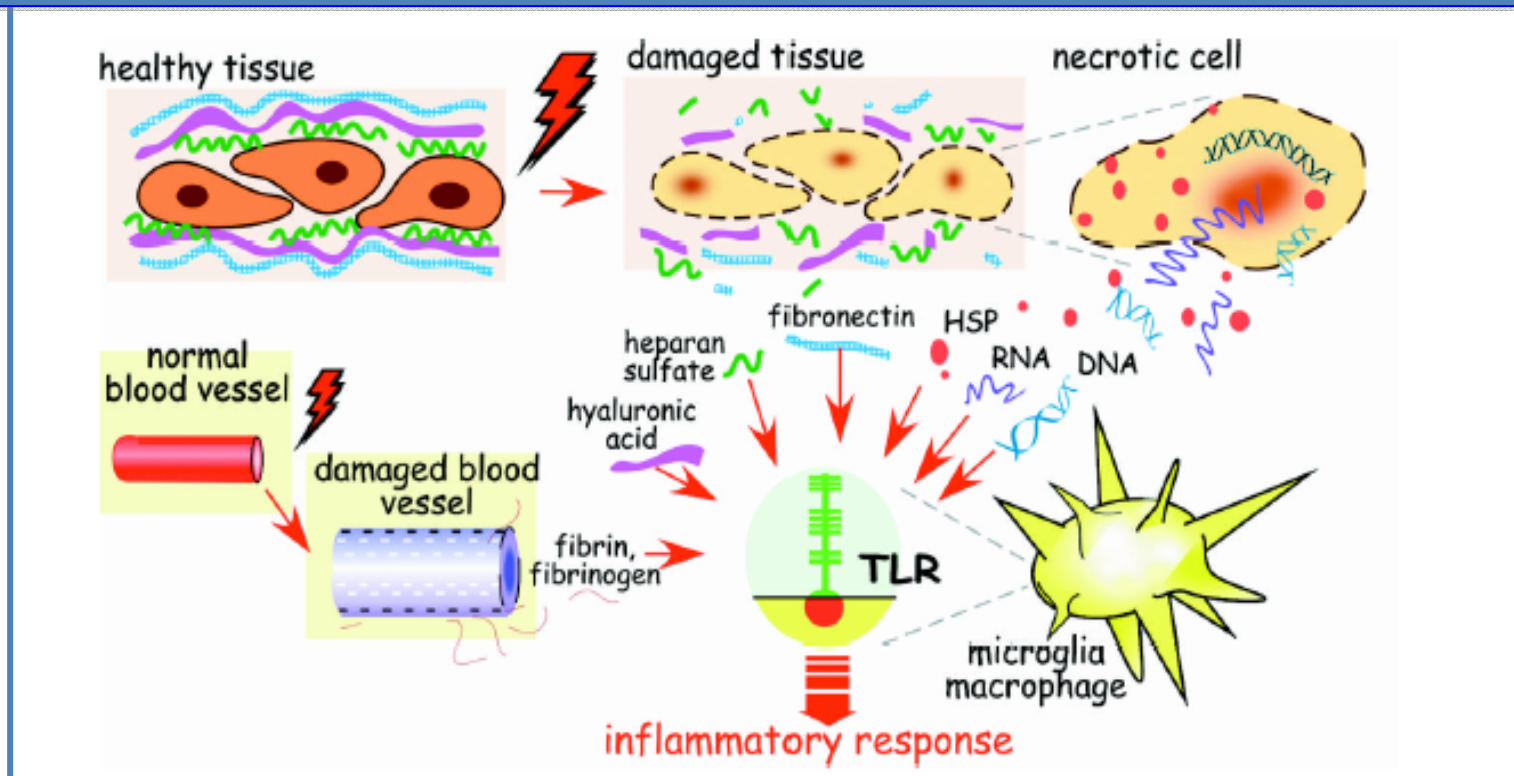
Cytokines
Chemokines
Adhesion molecules

+ IL6 - IL10

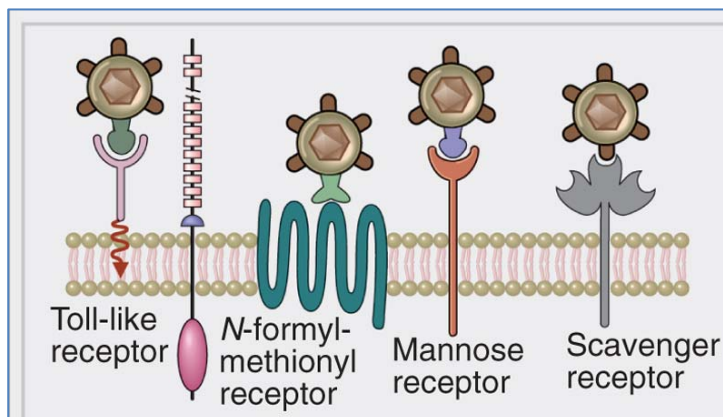
Clinical deterioration



Pattern recognition receptors trigger inflammation

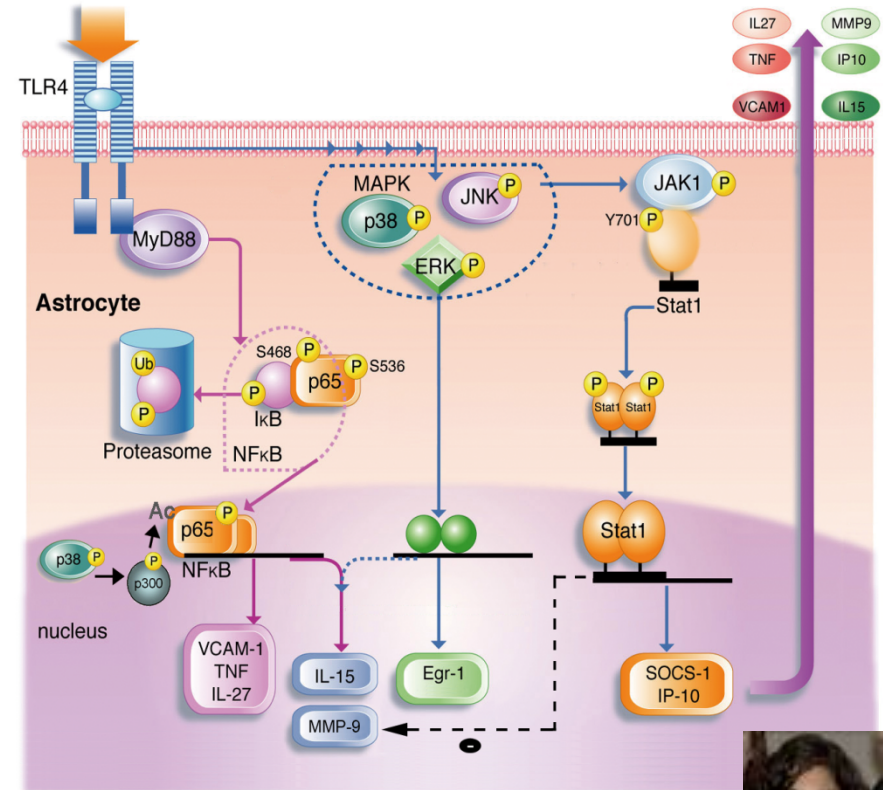
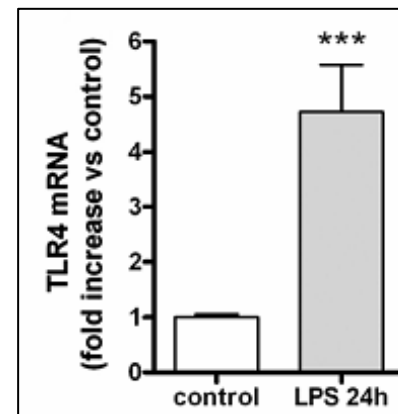
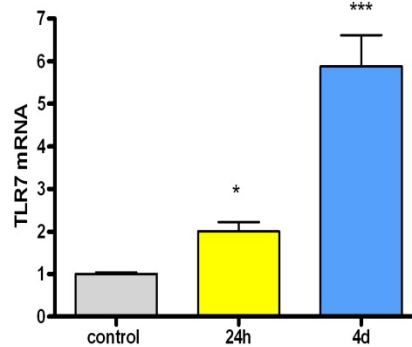
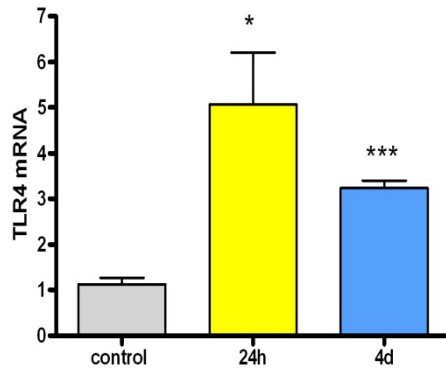
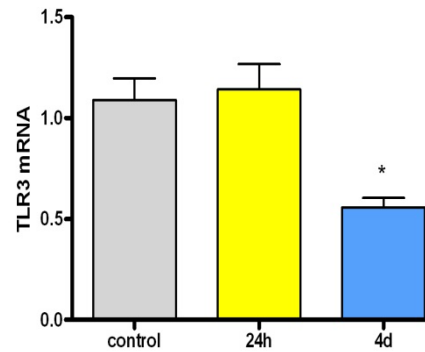
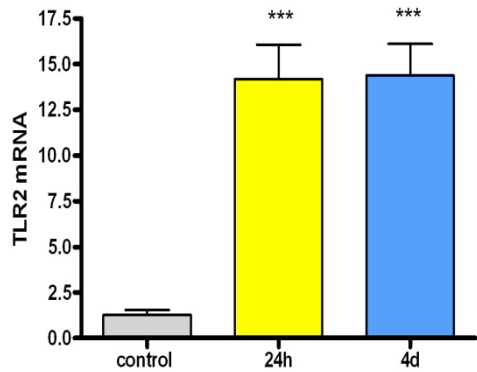


Kariko et al 2004 *JCBF* 24:1288

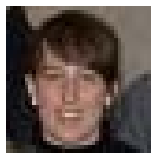


Innate Immunity
Cell Associated Receptors

TLR expression is induced in the brain after ischemia



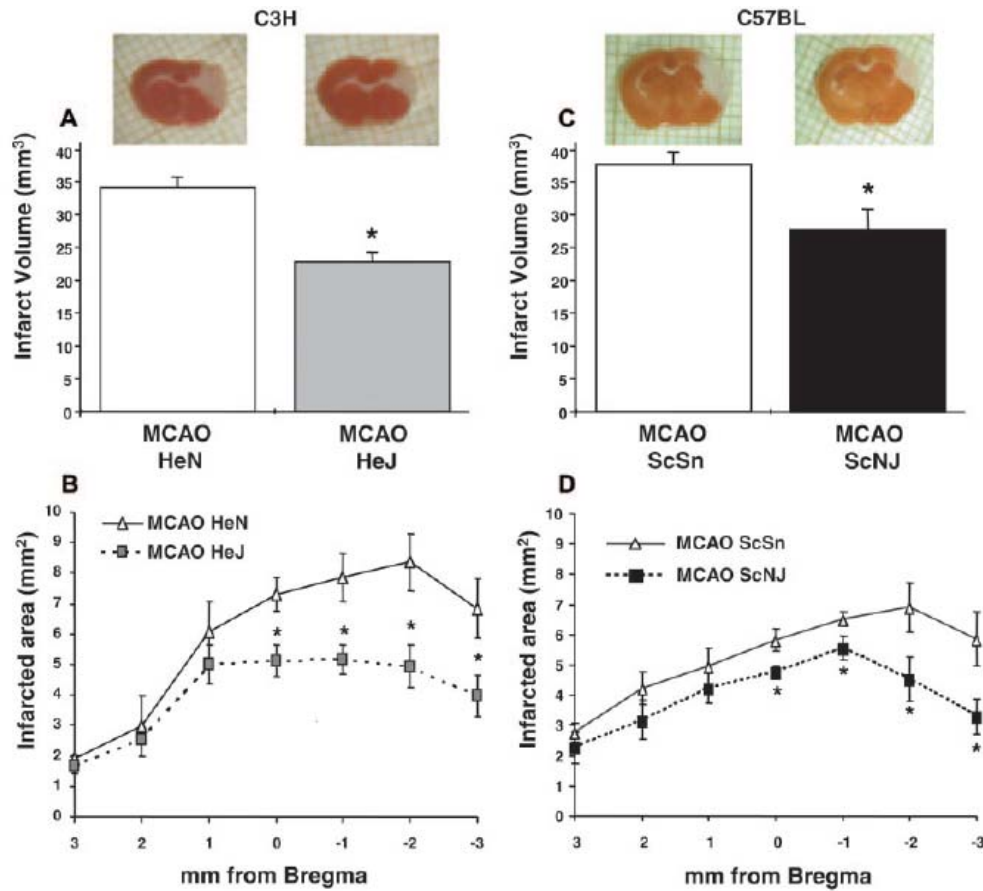
Roser Gorina



Isabel Pérez de Puig

TLR-4 contributes to the brain lesion after ischemia in mice

Caso et al., *Circulation*. 2007

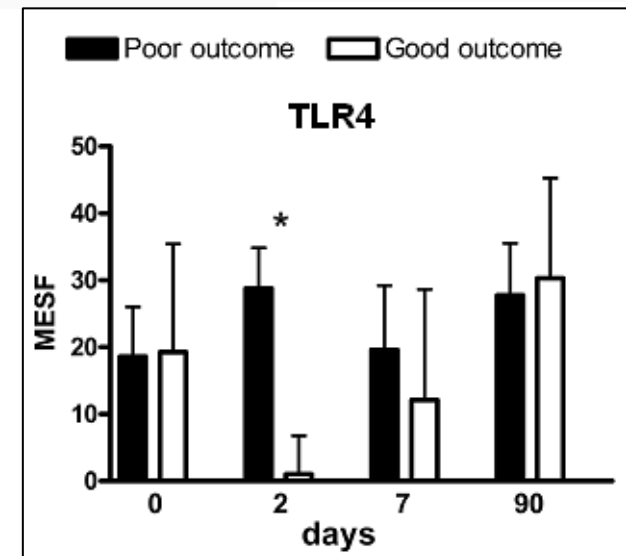
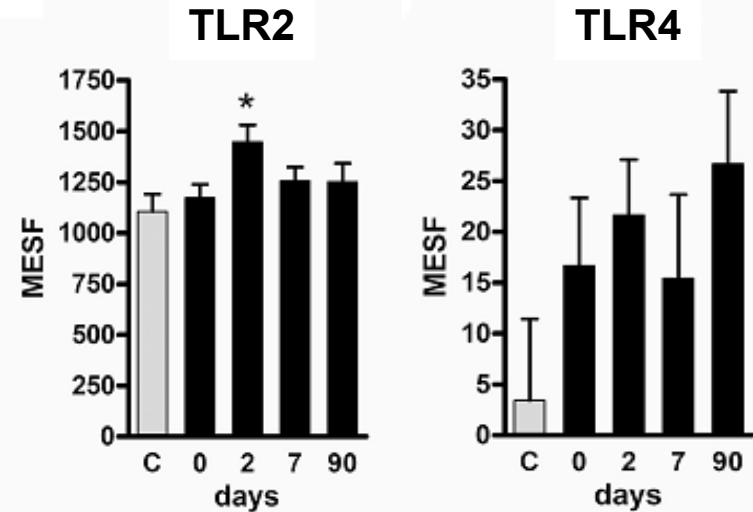


TLRs in monocytes of stroke patients

Urria et al., *Stroke* 2009



Xabier Urria



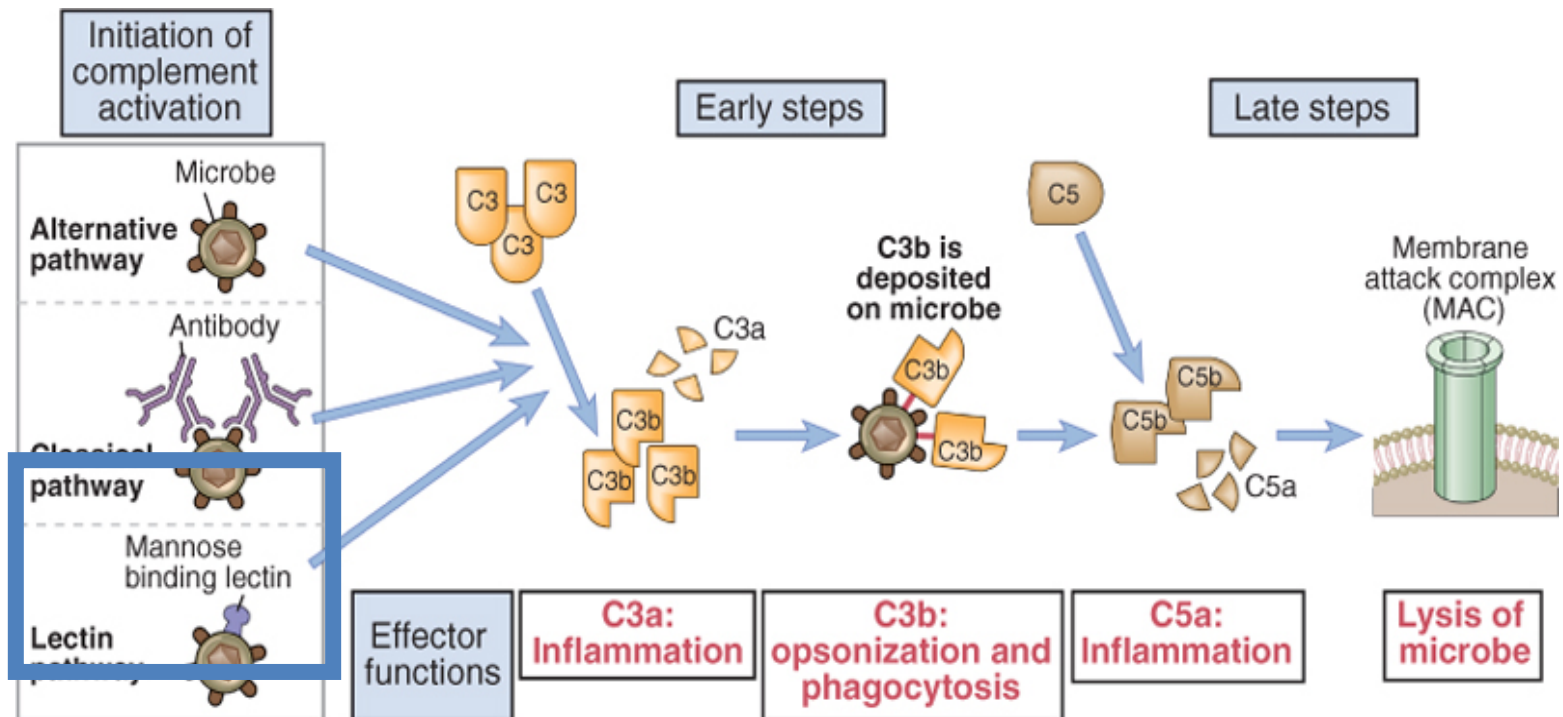
The Complement System

The complement system is activated in rodents after brain ischemia

De Simoni et al., 2004, *Am J Pathol* 164:1857-63

The complement system is activated in patients with acute stroke

Mocco et al., 2006, *Neurosurgery* 59:28-33 and *Circ Res* 99:209-17

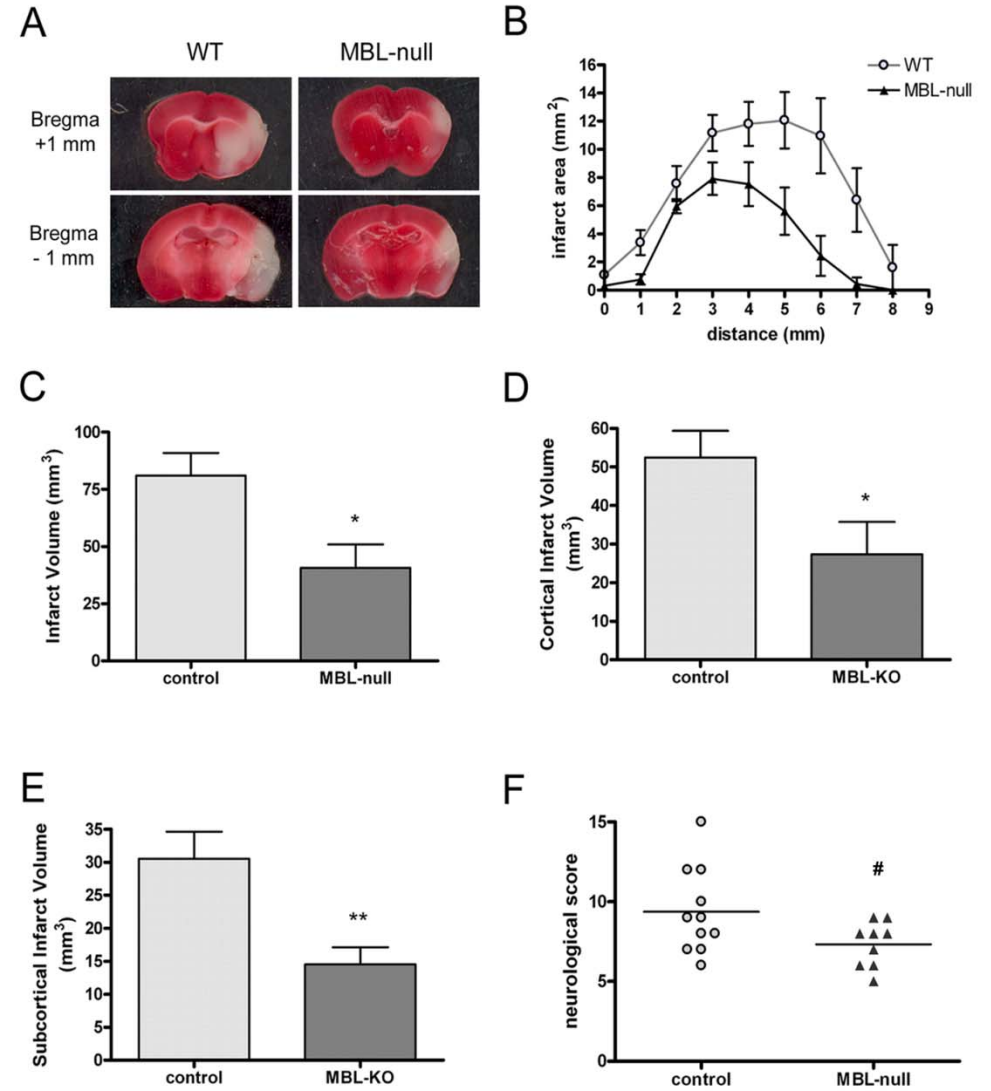
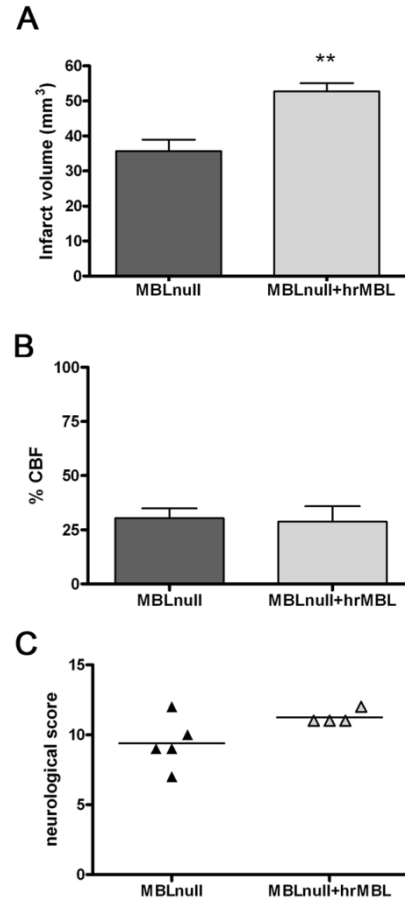
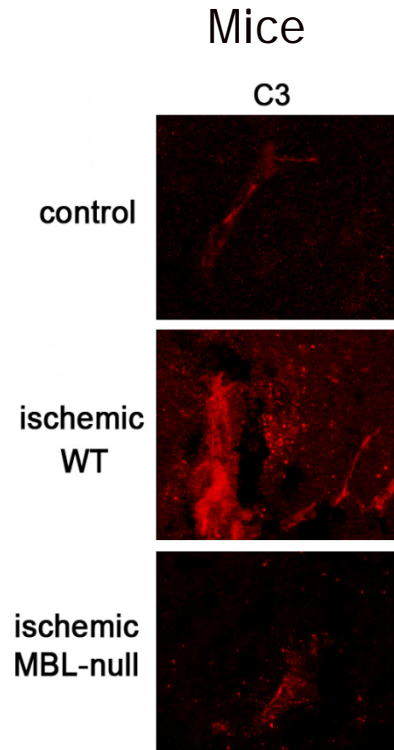




Carles
Justicia

The Lectin Pathway Experimental ischemia/reperfusion in Manose-Binding Lectin (MBL) null and wt mice

2-h MCAO +48h reperfusion in mice WT / MBLnull



The Lectin Pathway



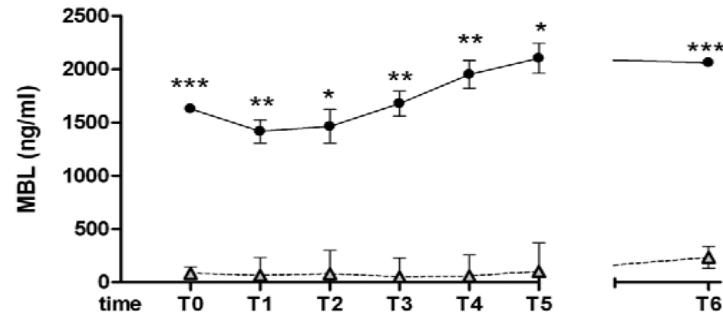
Alvaro
Cervera

Manose-Binding Lectin (MBL) in Stroke patients: MBL-sufficient and MBL-low genotypes

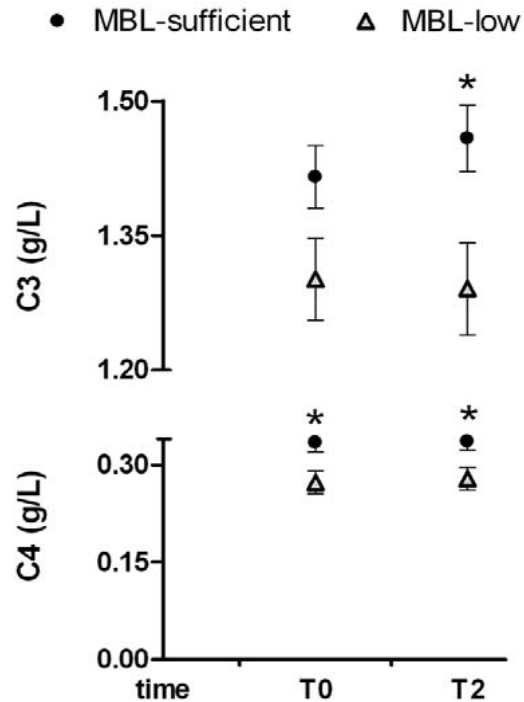
Baseline characteristics in the study population (n=135) according to MBL genotype

	MBL-low N=24 (18%)	MBL-sufficient N=111 (82%)	p value
Age (mean, SD), yrs	73.9 (12.8)	72.9 (11.5)	0.67
Male, no.(%)	9 (37.5)	59 (53.2)	0.16
Active smoking, no. (%)	3 (12.5)	20 (18.0)	0.77
Hypertension, no. (%)	12 (50.0)	73 (65.8)	0.15
Diabetes, no. (%)	6 (25.0)	24 (21.6)	0.72
Coronary heart disease, no. (%)	2 (8.3)	15 (13.5)	0.49
Previous stroke, no. (%)	4 (16.7)	19 (17.1)	1.00
Peripheral artery disease, no. (%)	2 (8.3)	9 (8.1)	1.00
Admission NIHSS score, no. (%)			0.10
	0 to 6	5 (21)	14 (13)
	7 to 17	13 (54)	56 (51)
	>17	6 (25)	41 (37)

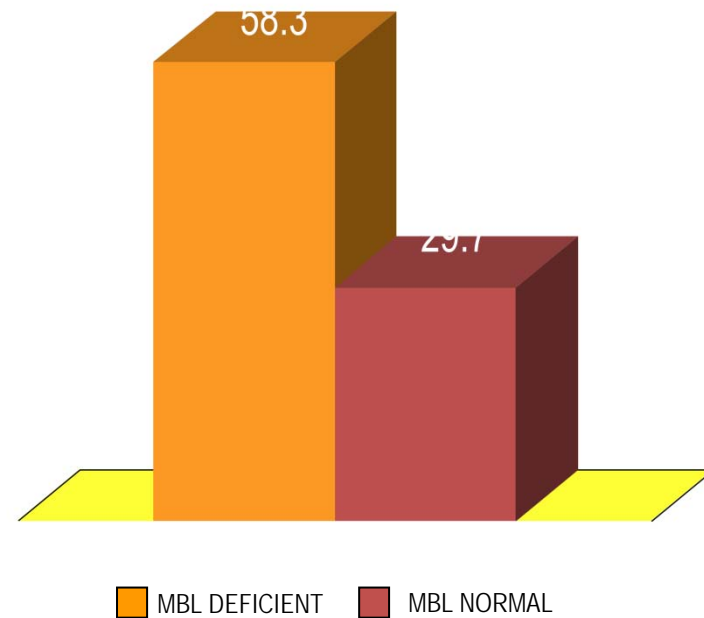
MBL in stroke patients



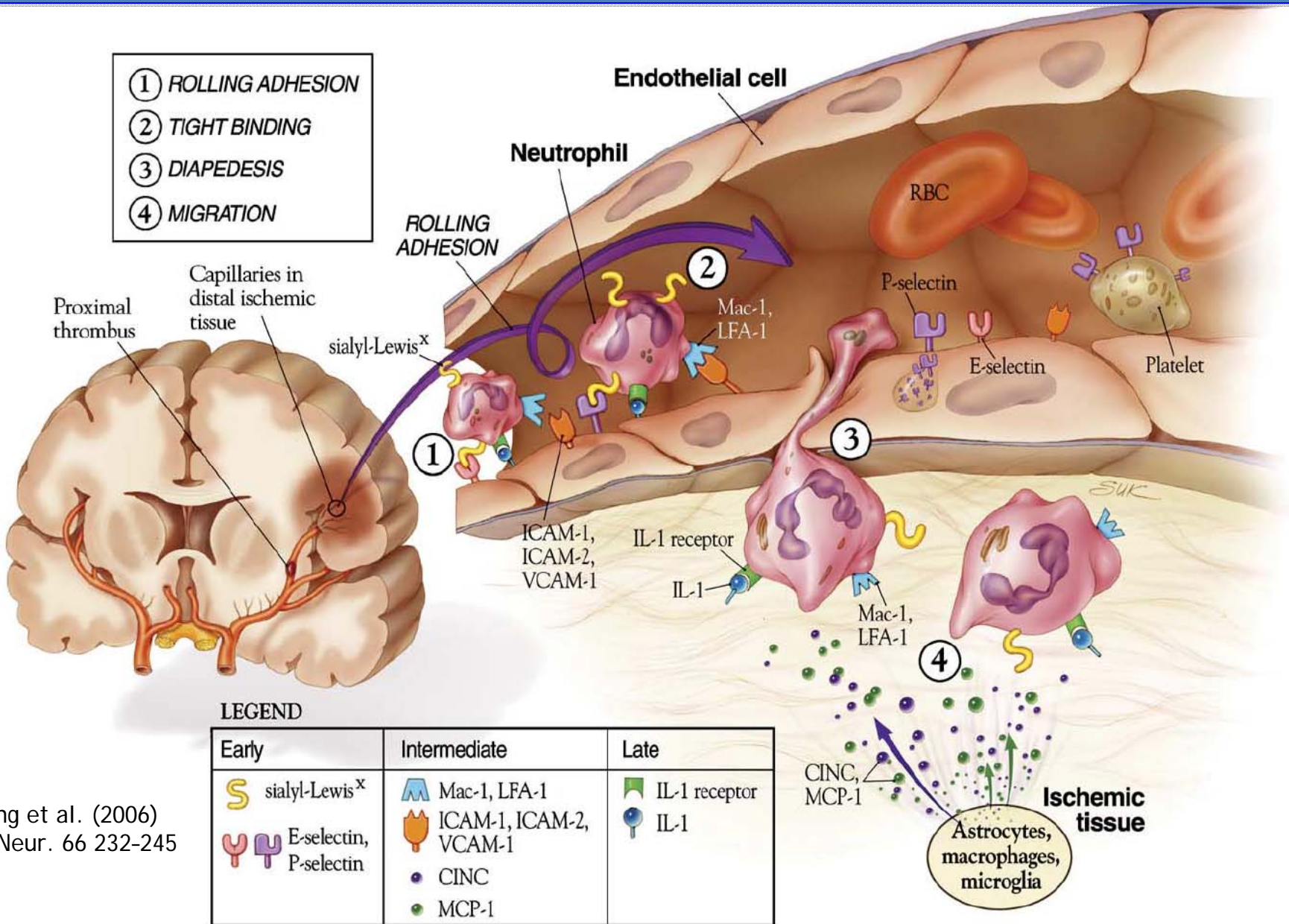
60% MBL-low and 30% MBL-sufficient patients reached functional independence (mRS score 0 to 2) (χ^2 , $p=0.008$)



% GOOD OUTCOME AT 3 MONTHS

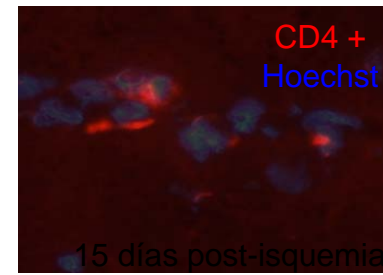
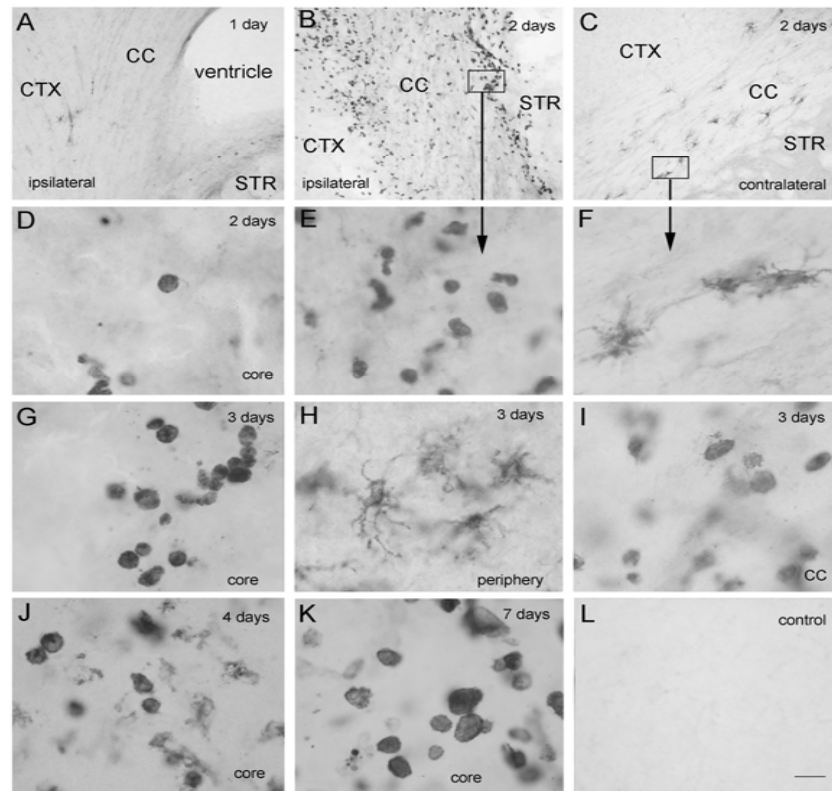


The cellular players

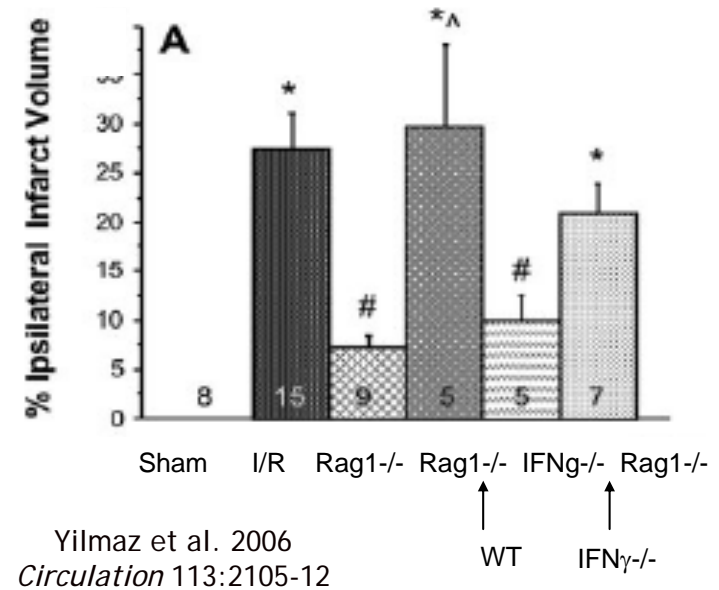


Huang et al. (2006)
 Surg. Neur. 66 232-245

Glial reaction and macrophage infiltration

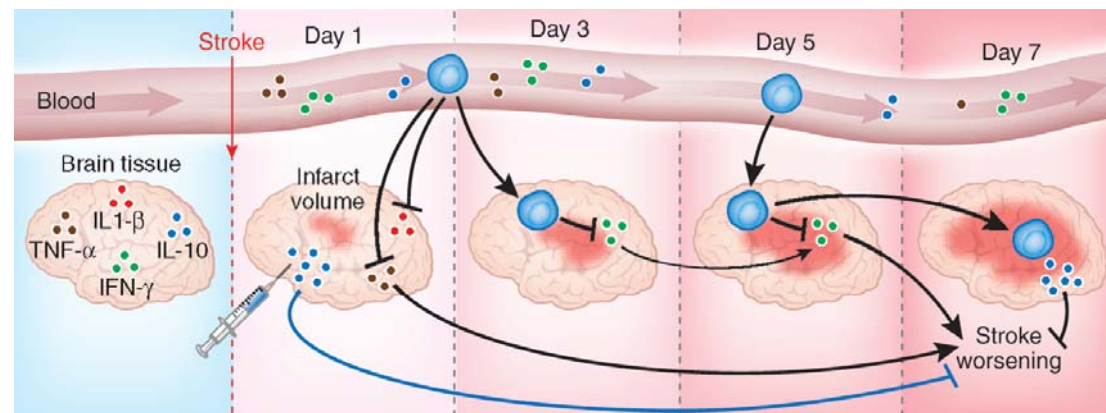


T cell infiltration



Regulatory T cells protect the brain after stroke

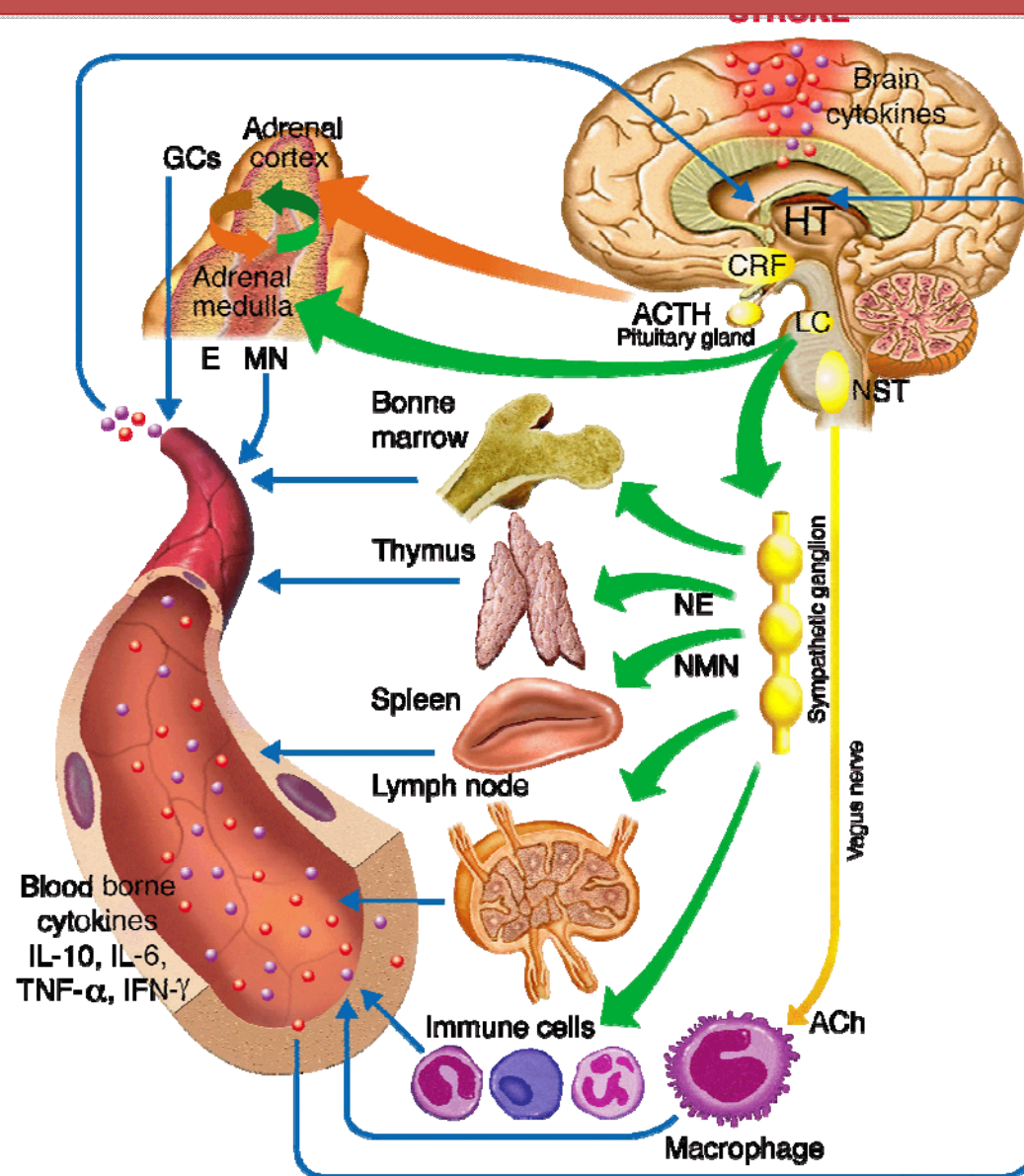
Liesz, et al. *Nat. Med.* (2008)

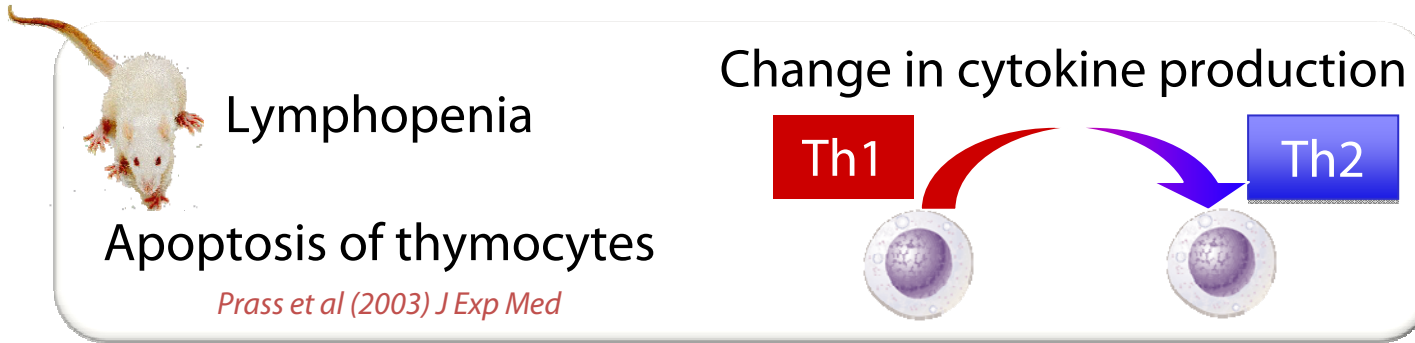


Planas & Chamorro, 2009

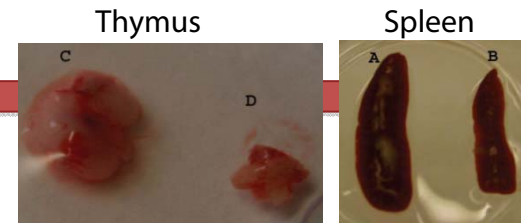
Stroke-associated infection

15-30%

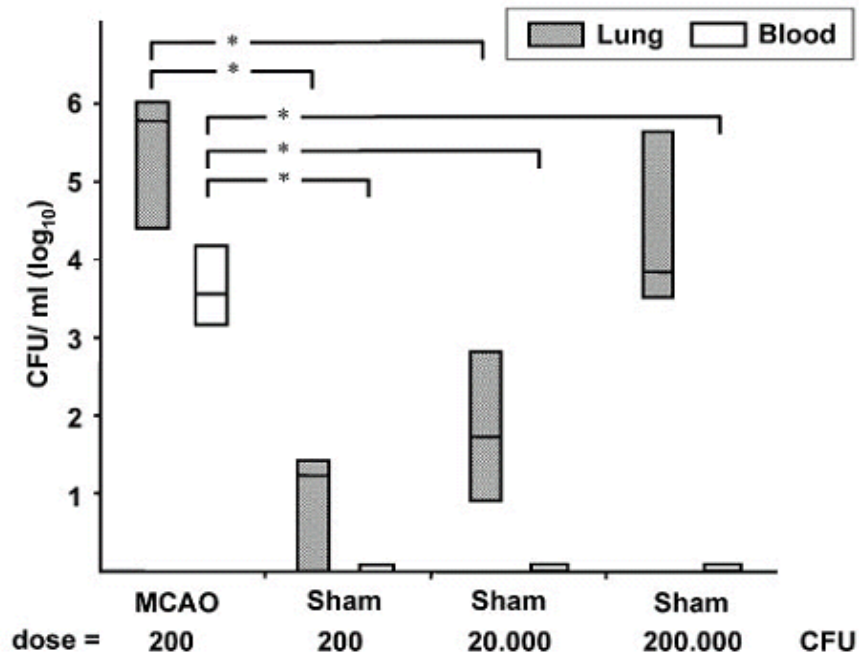




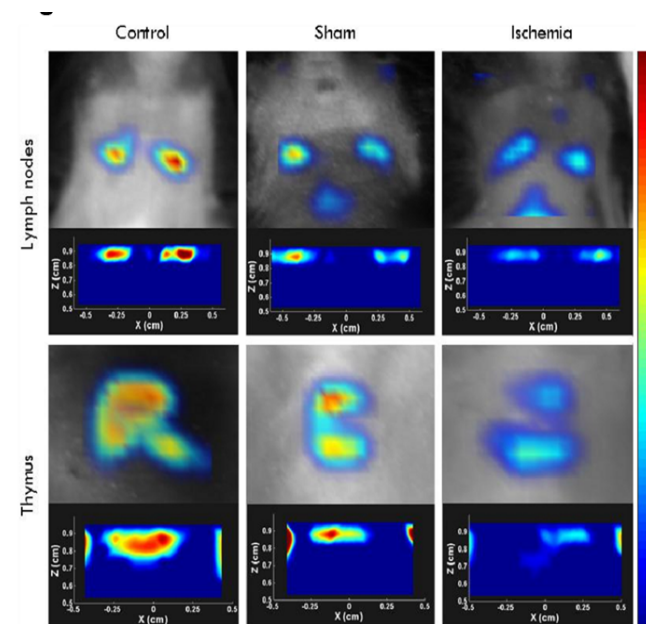
Stroke-induced immunodepression



Offner et al (2006) J Immunol



Prass et al (2006) Stroke

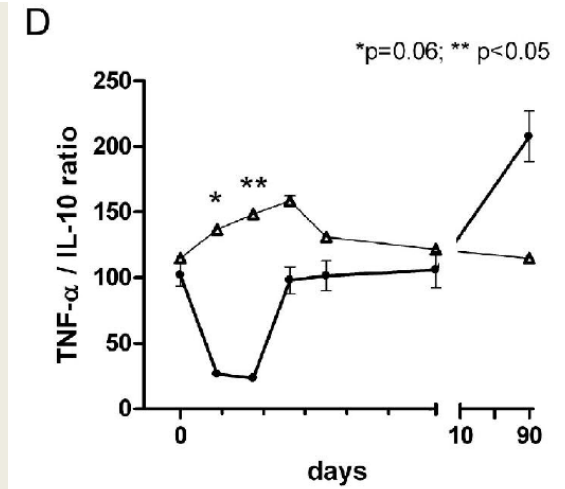
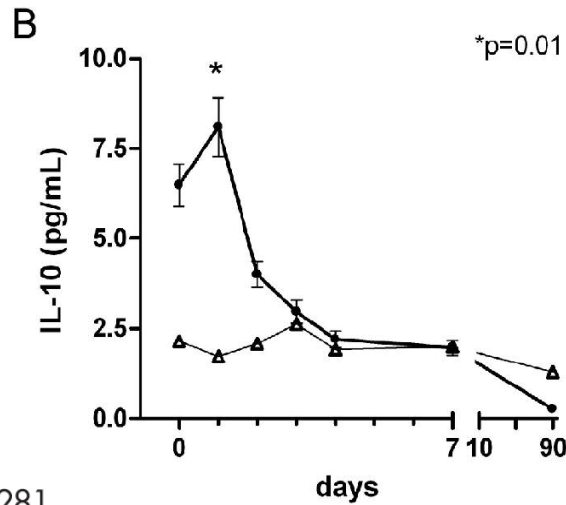


Martin et al (2008) Mol Imaging

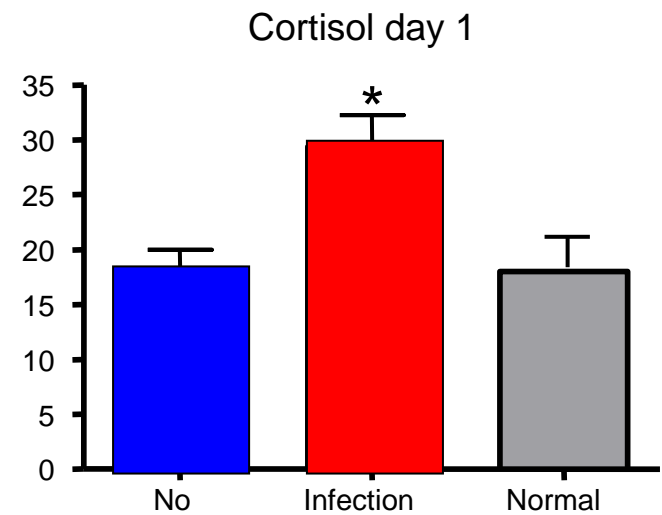
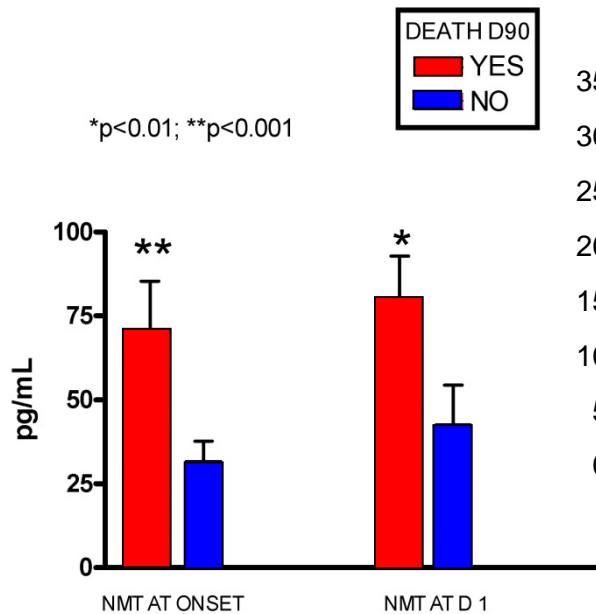
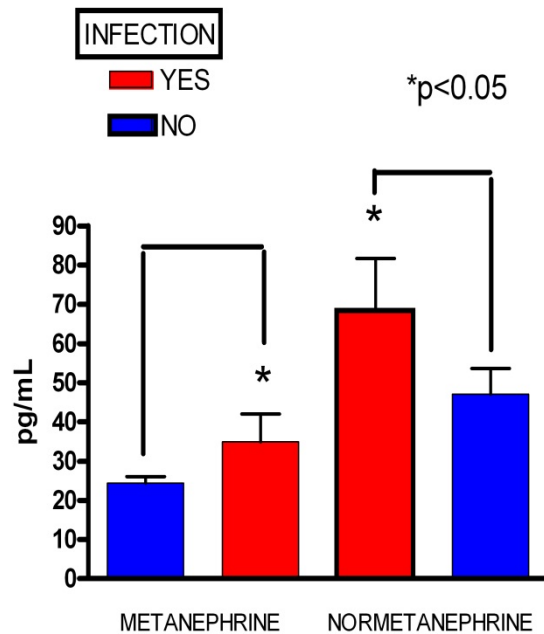
Immunodepression in human stroke?

Changes in cytokines precede stroke-associated infection

● early SAI ▲ NO

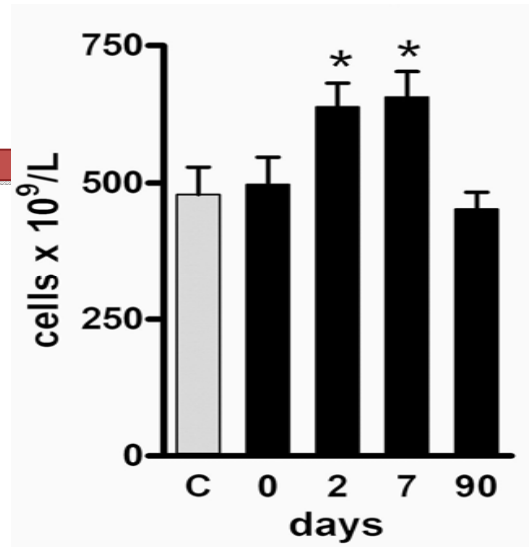


J Neurol Neurosurg Psychiatry 2006;**77**:1279-1281



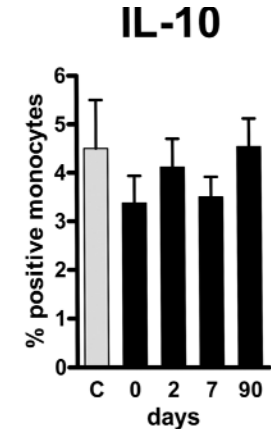
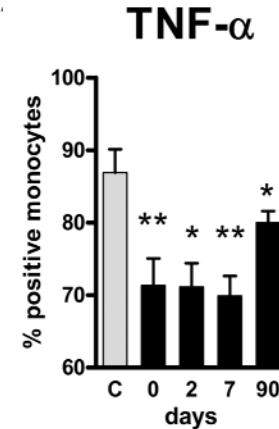
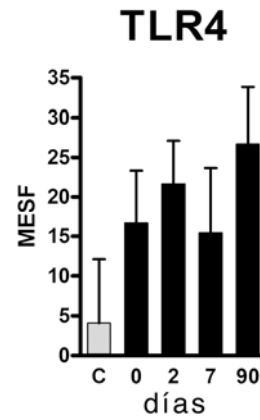
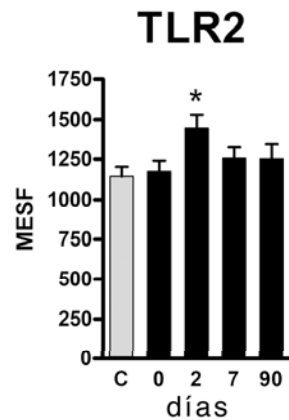
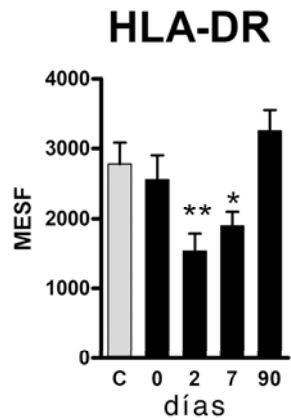
J Neurol Sci. 2007 **15**;252:29-35.

Circulating monocytes



Phenotype

Function



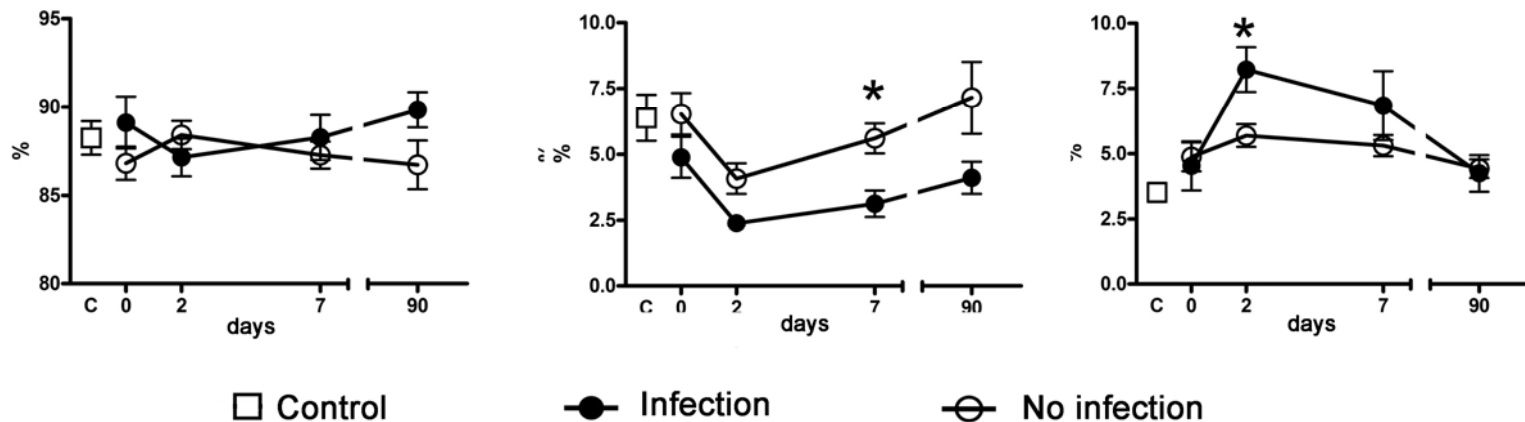
Infection

Prognostics



Monocytes

Phenotype	CD14 ^{high} CD16 ⁻	CD14 ^{dim} CD16 ⁺	CD14 ^{high} CD16 ⁺
Frequency	85%	10%	5%
Function	Inflammation	TNF- α Non-inflammed tissue	IL-10 angiogenesis



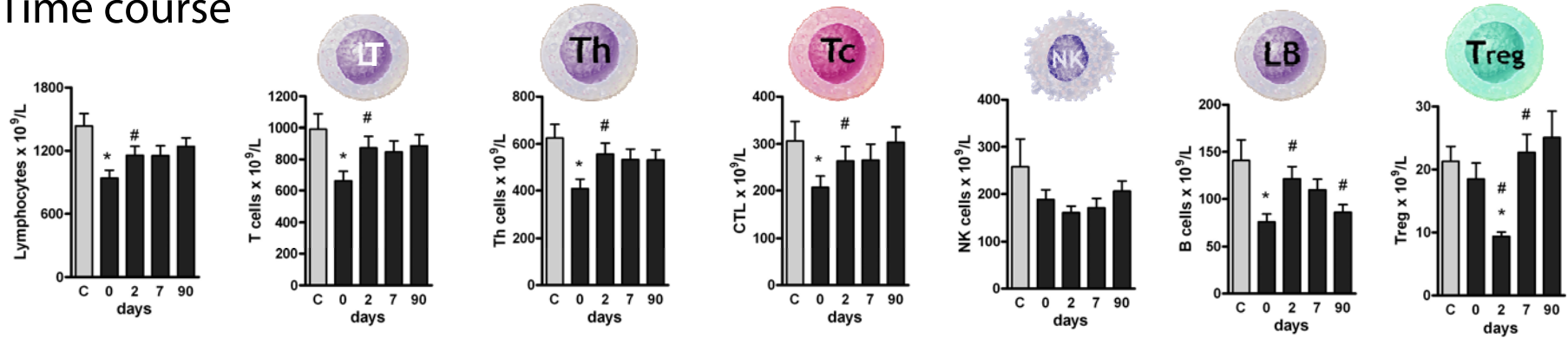
Clinical course

	Early worsening	Bad Outcome	Death
CD14 ^{high} CD16 ⁻ , OR	1,29	1,38	1,40

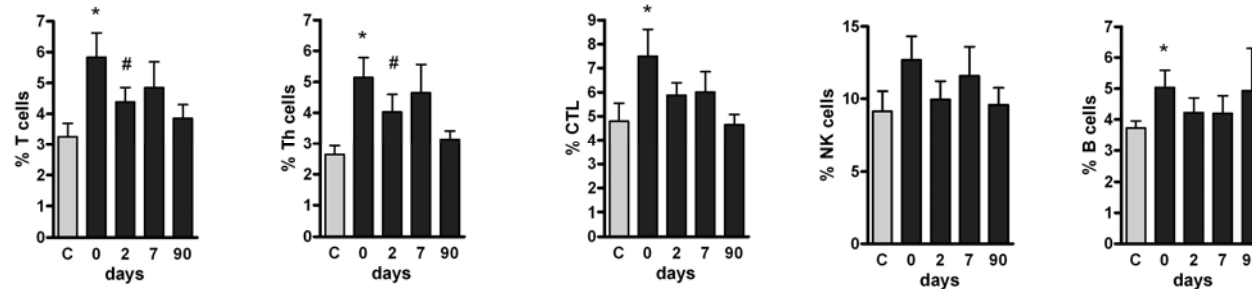
Urra et al (2009) J Cereb Blood Flow Metab; Urra et al (2009) Stroke

Lymphocytes

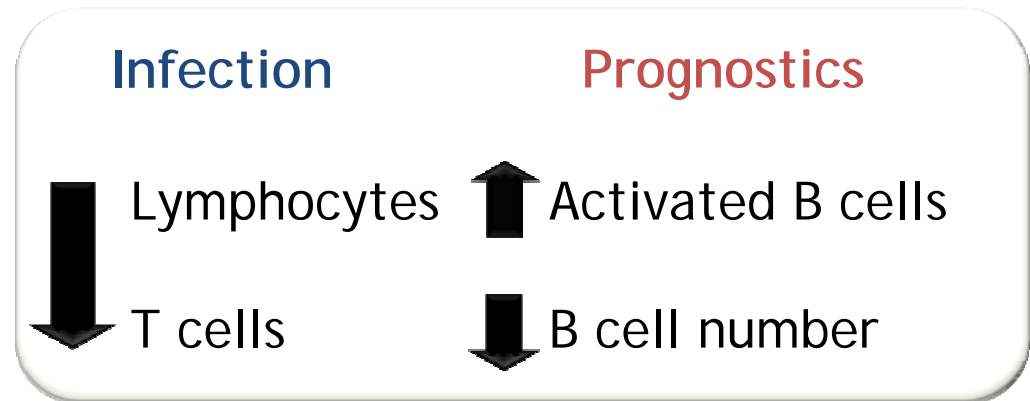
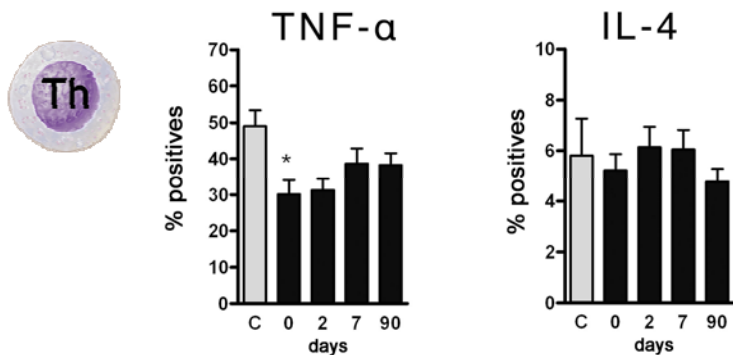
Time course



Apoptosis

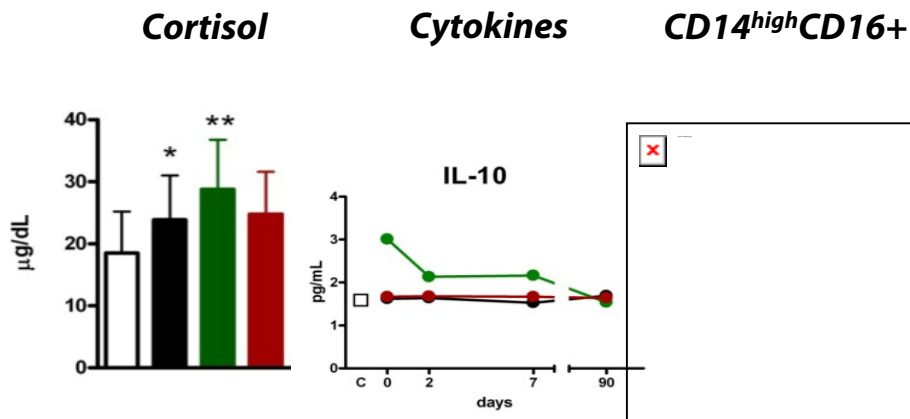
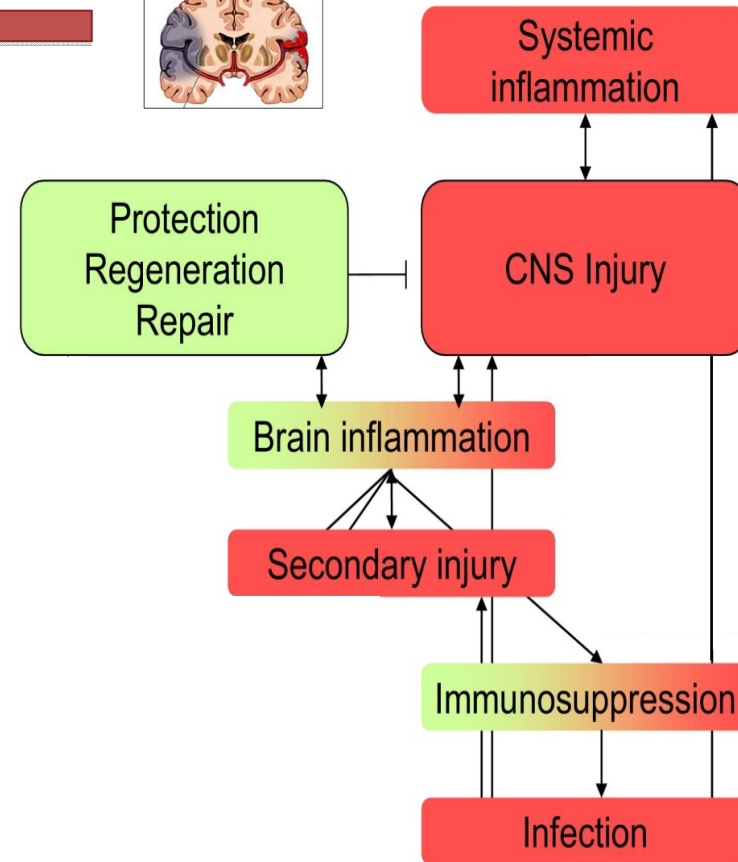
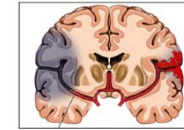


Cytokines



Immunodepression in human stroke

Stress reaction
 Anti-inflammatory cytokines
 Monocyte deactivation
 Lymphopenia



Stroke-Induced Immunodepression Is a Marker of Severe Brain Damage

Xabier Urra and Ángel Chamorro

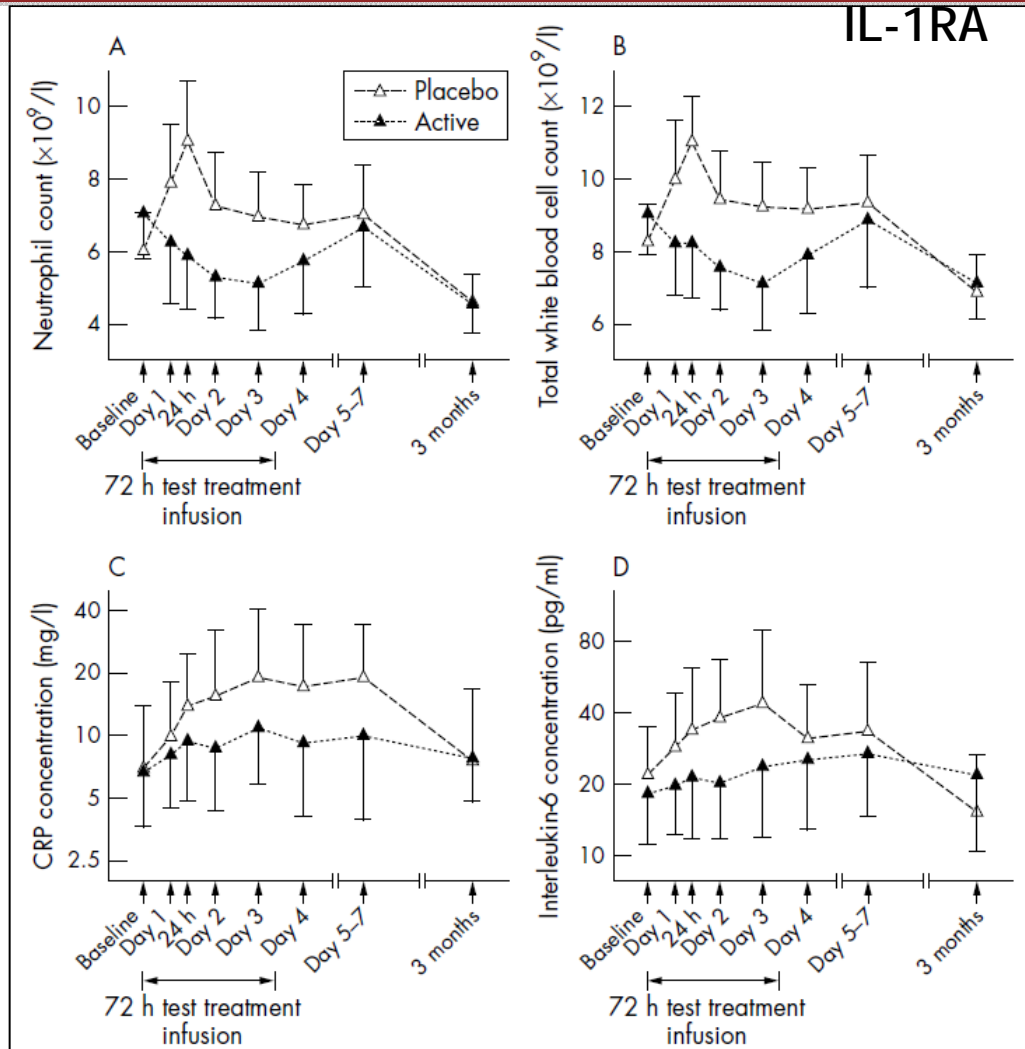
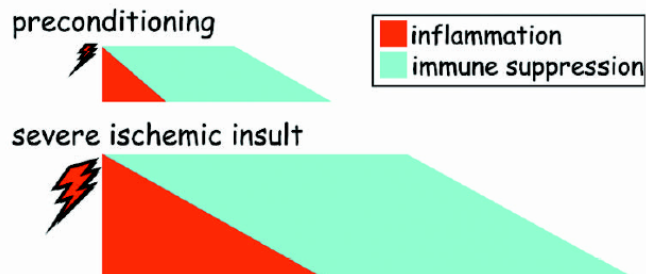
Stroke 2010;41:e110

Immunomodulatory strategies

Antibiotics
Corticosteroids
Heparin
Statins

G-CSF
IL-1RA

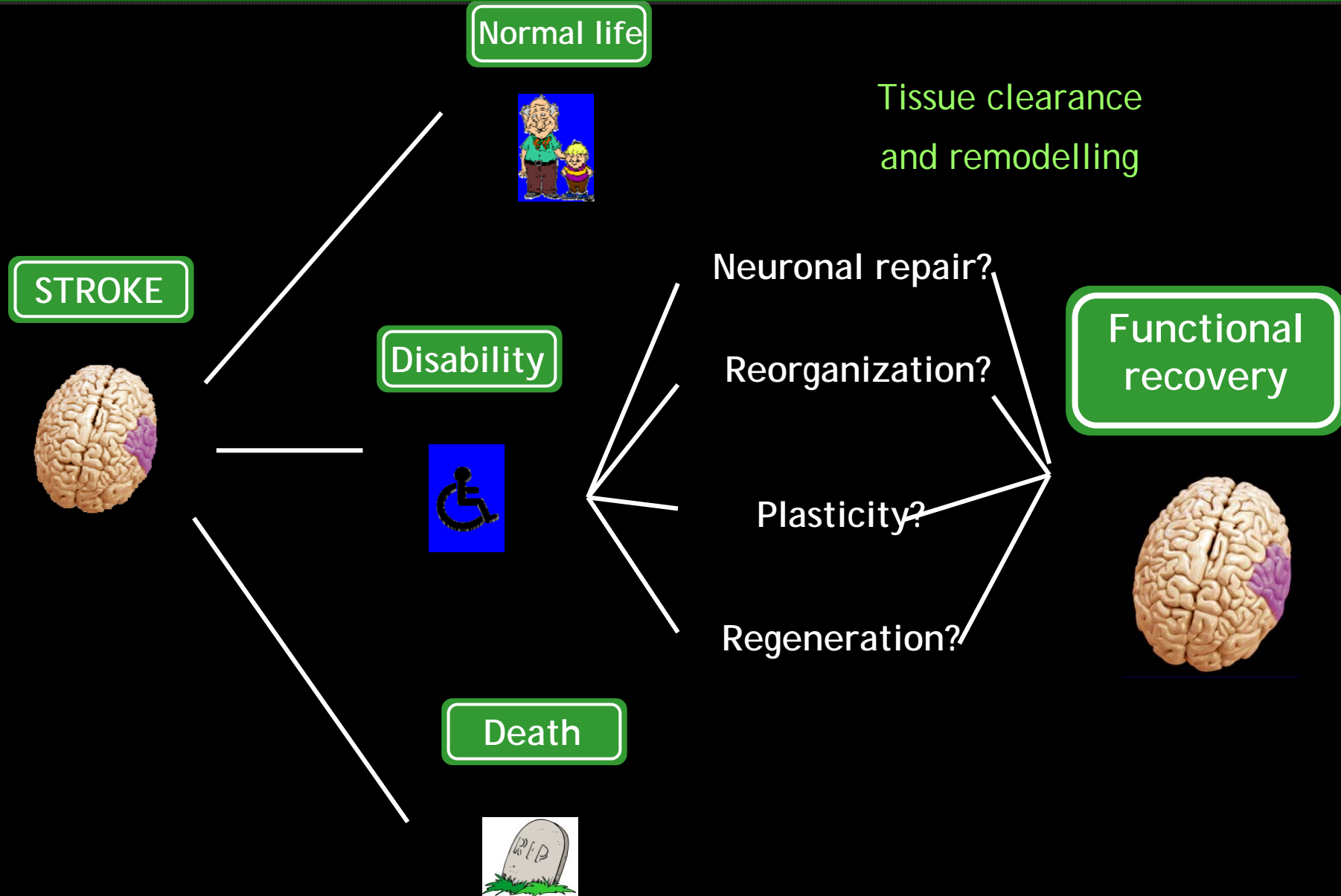
TLR4 antagonists
Treg cells
Monocyte subtypes
Ischemic tolerance



+ 78% infections

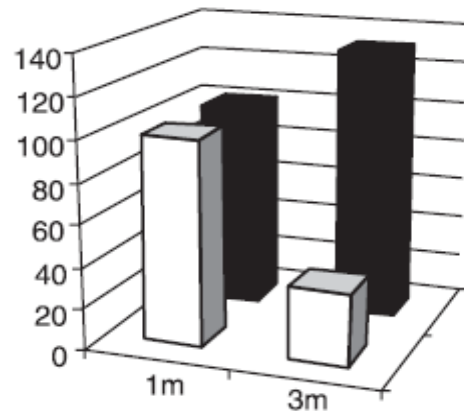
Neurorepair & recovery

Innate immune responses affect neurogenesis and repair

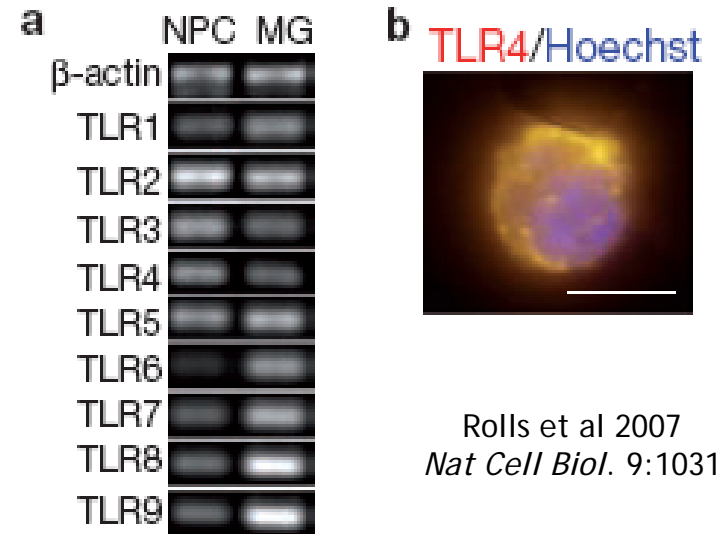


Role of inflammation and innate immunity in neurogenesis

□ Neurogenesis rate (% of 1M, left)
 ■ IFN- γ contribution (% of age matched)



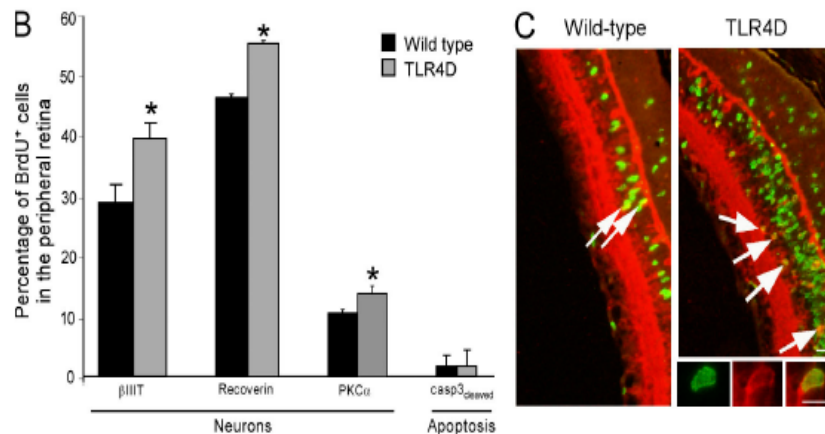
Baron et al. 2008
FASEB J. 22:2843



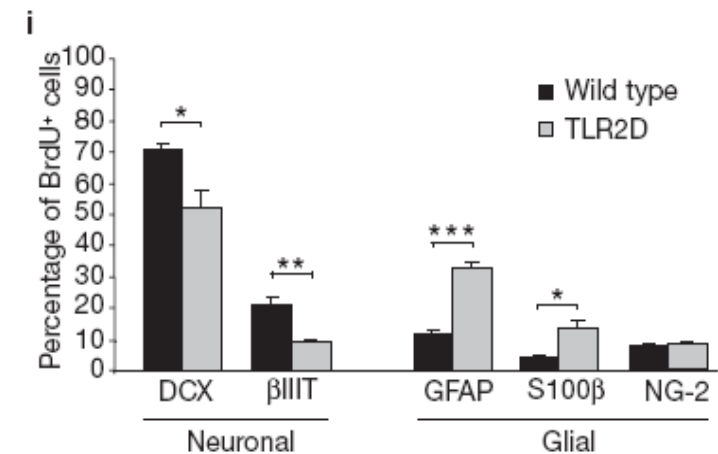
Rolls et al 2007
Nat Cell Biol. 9:1031

Deficiency in TLR4 in the early postnatal retina results in increased neuronal differentiation

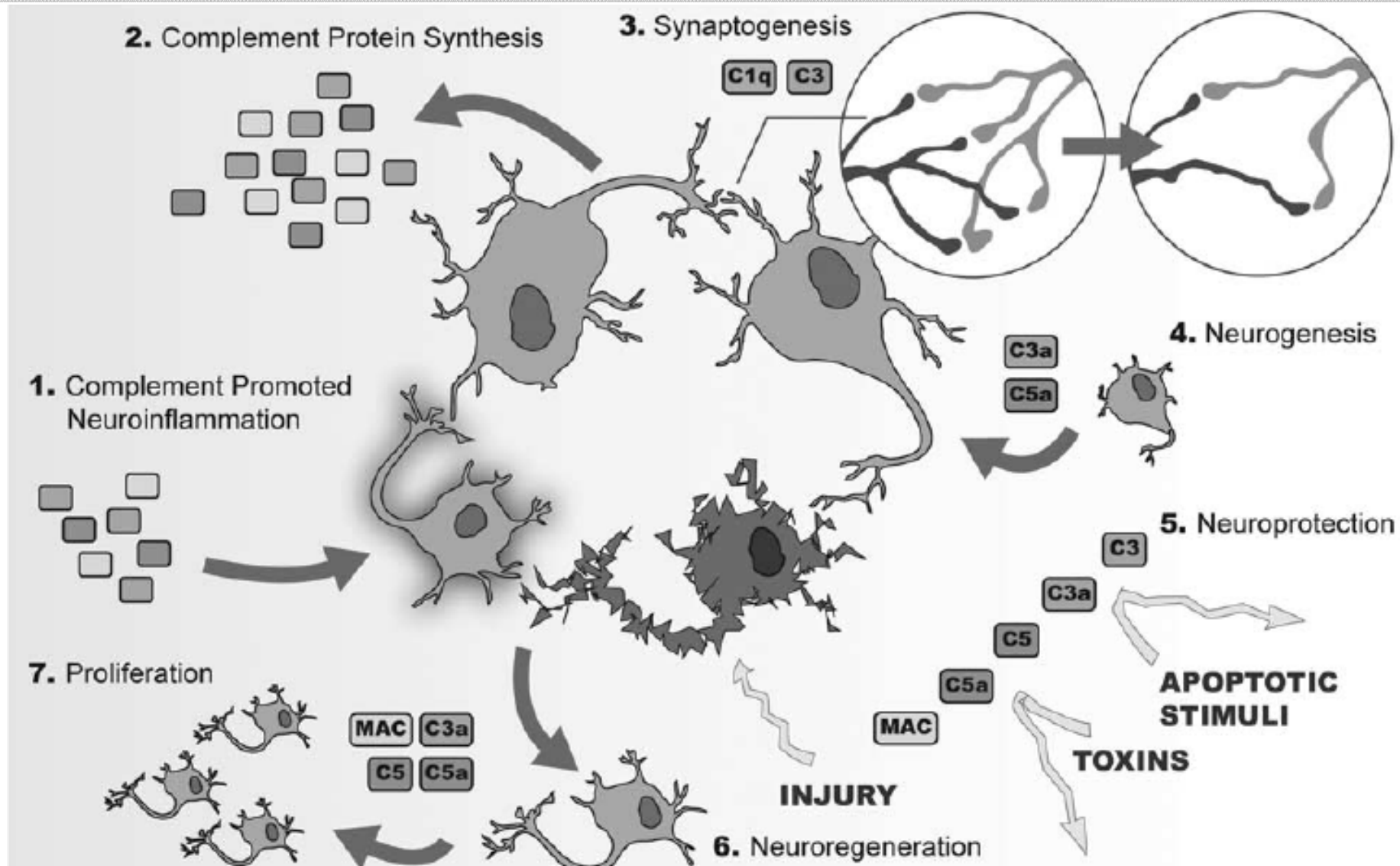
Shechter et al 08 *J Cell Biol* 183:393



Impaired neurogenesis in TLR2-deficient mice



Complement affects neurogenesis and regeneration



Conclusions

- Innate immunity plays an active role in inflammation before and after stroke and influences brain damage .
- Genetics may affect the features and magnitude of inflammatory and/or immune responses: towards a more personalised treatment?
- Stroke is accompanied by immunosuppression favouring infection
- Inflammation and innate immunity affect neurogenesis and repair. Understanding the intensity of the signals and their time course is essential for designing therapeutic strategies

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