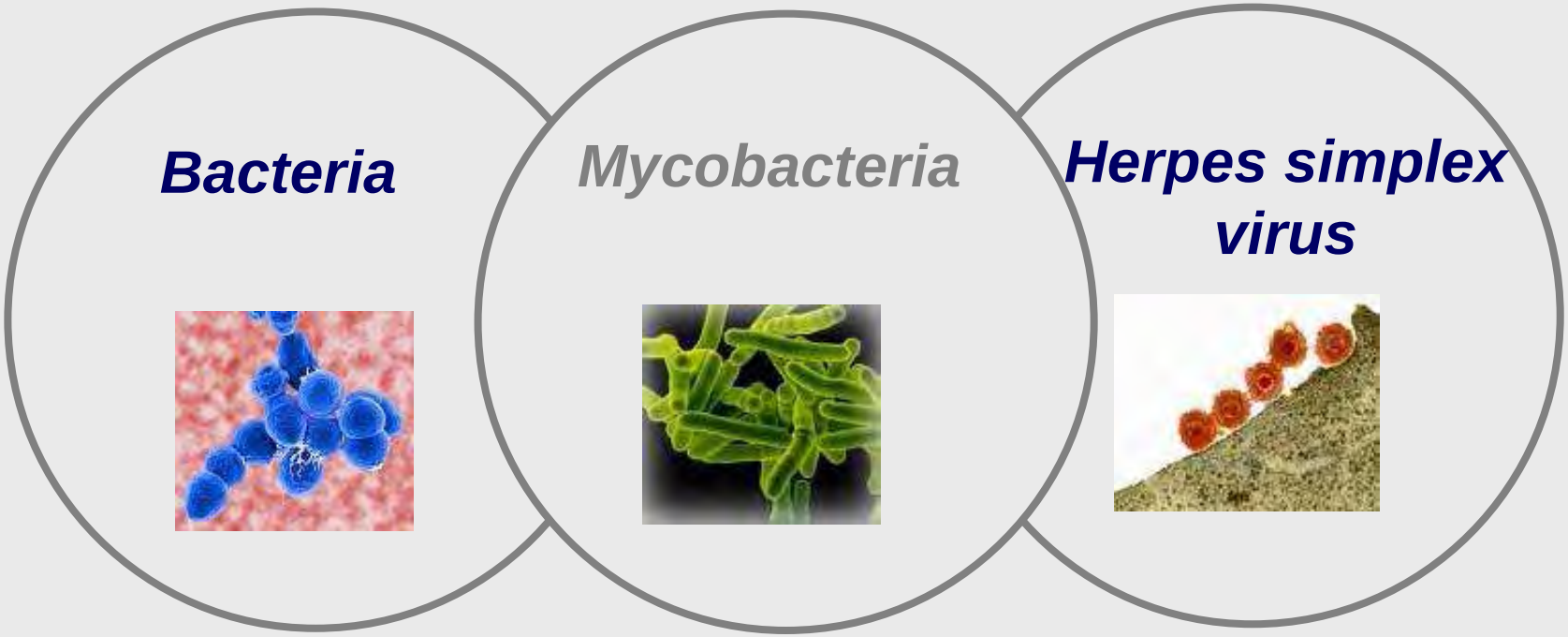
Genetic infectious susceptibility and TLR defects in human



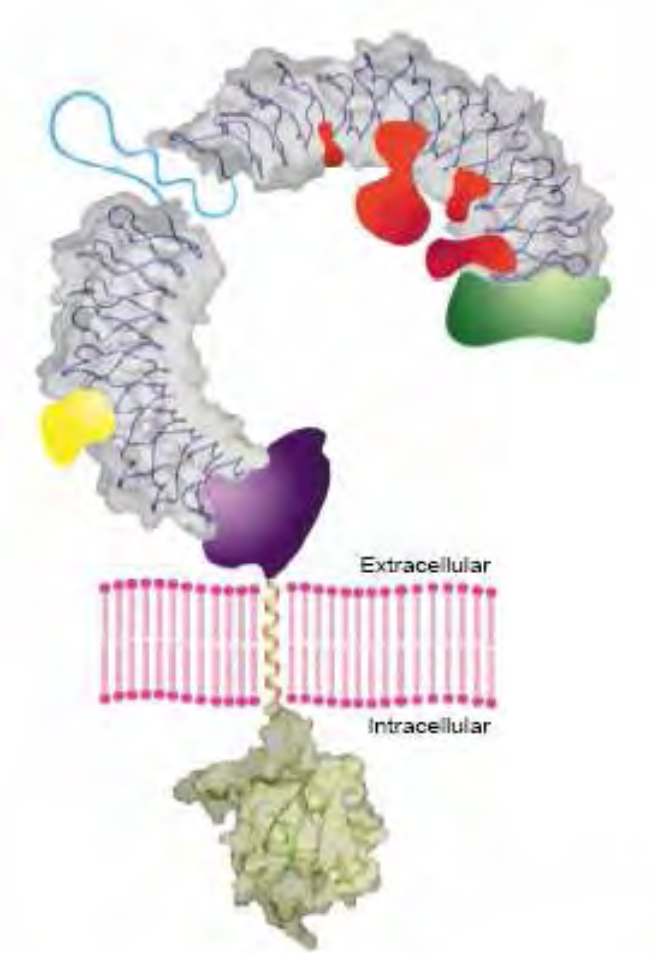
Human Genetics of Infectious Diseases-INSERM U980,

Necker Faculty, Paris Descartes University, Paris, France

capucine.picard@inserm.fr

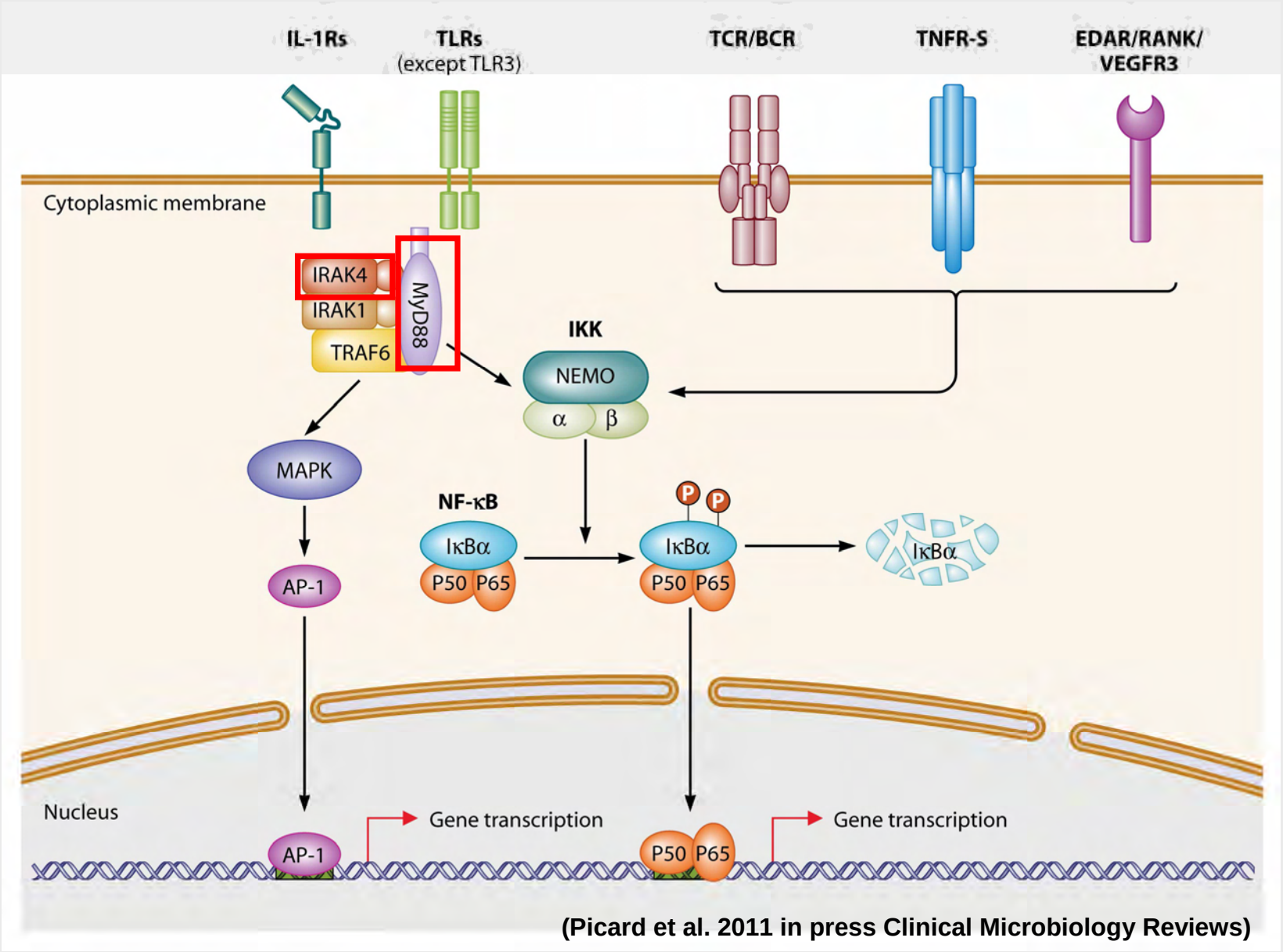
Toll-like receptors (TLR)

- Receptor of innate immunity (11 in human)
- Membrane glycoproteines (90-115 kD)
- Leucin rich repeat (LRR)
- Recognize ligands derived from microorganisms: LPS – TLR4 or dsRNA-TLR3
- Initiation of inflammatory response



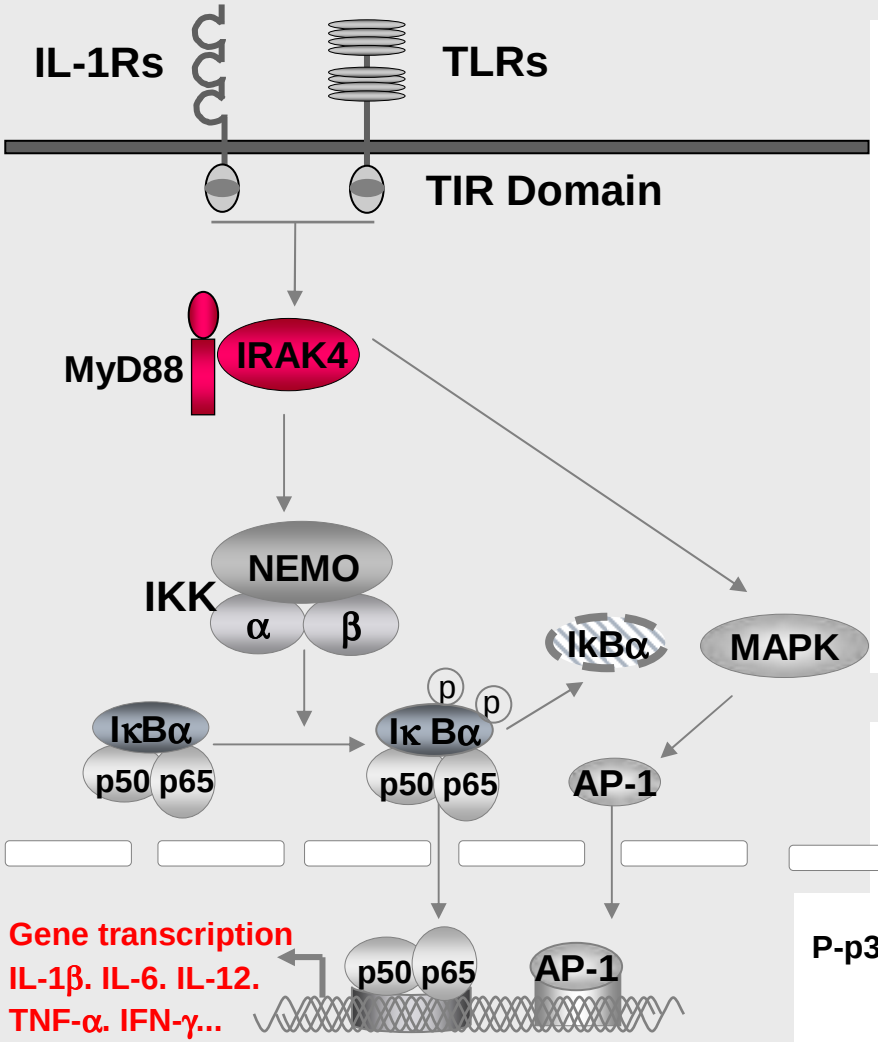
(Bell et al. TRENDS in Immunology 2003)

Toll like receptors and IL-1Rs (TIRs) signalling pathway

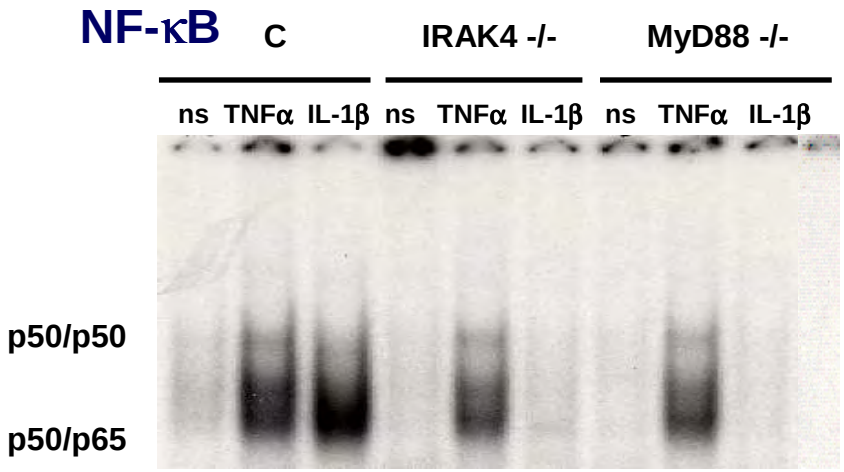


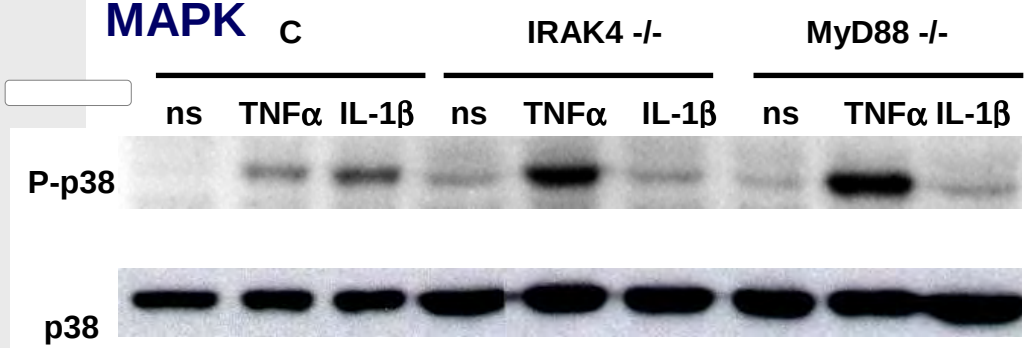
(Picard et al. 2011 in press Clinical Microbiology Reviews)

Inherited human IRAK-4 and MyD88 deficiencies

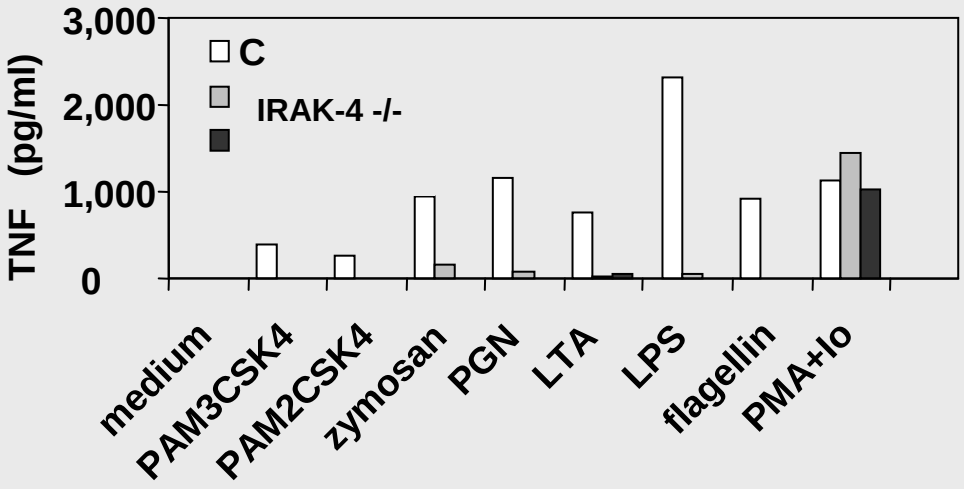


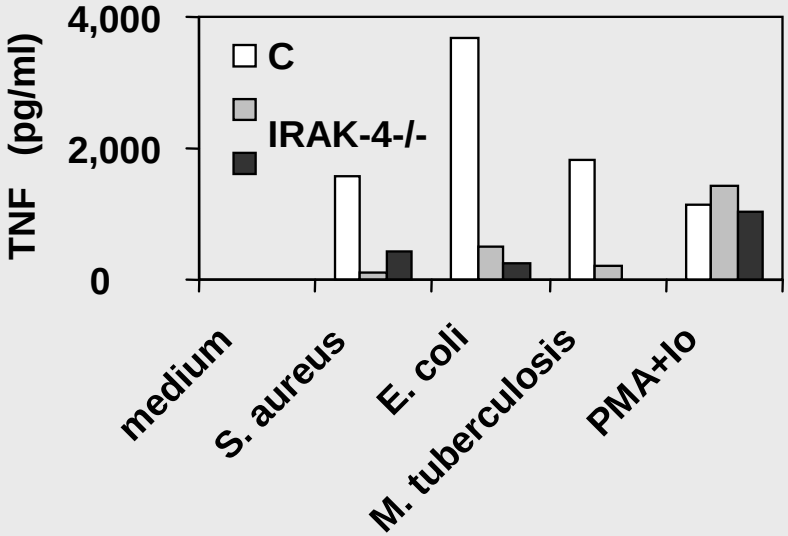
(Picard et al. Science 2003)
(von Bernuth et al. Science 2008)

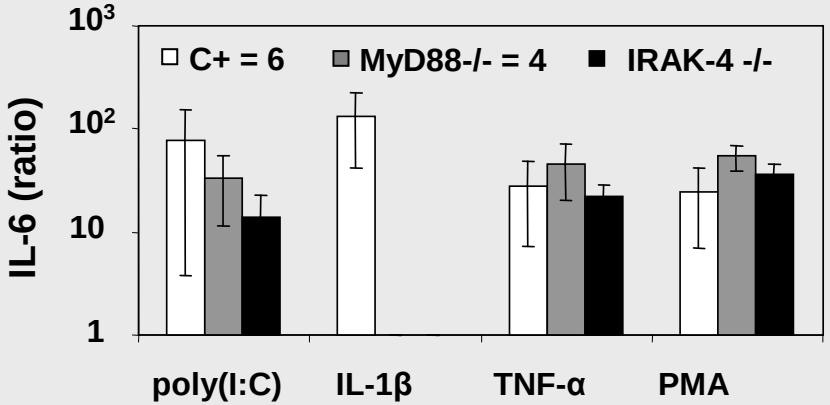


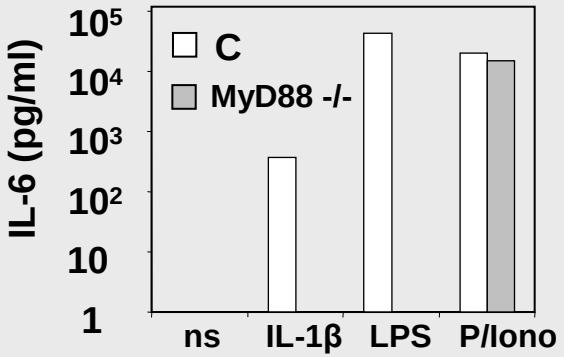


Inherited human IRAK-4 and MyD88 deficiencies





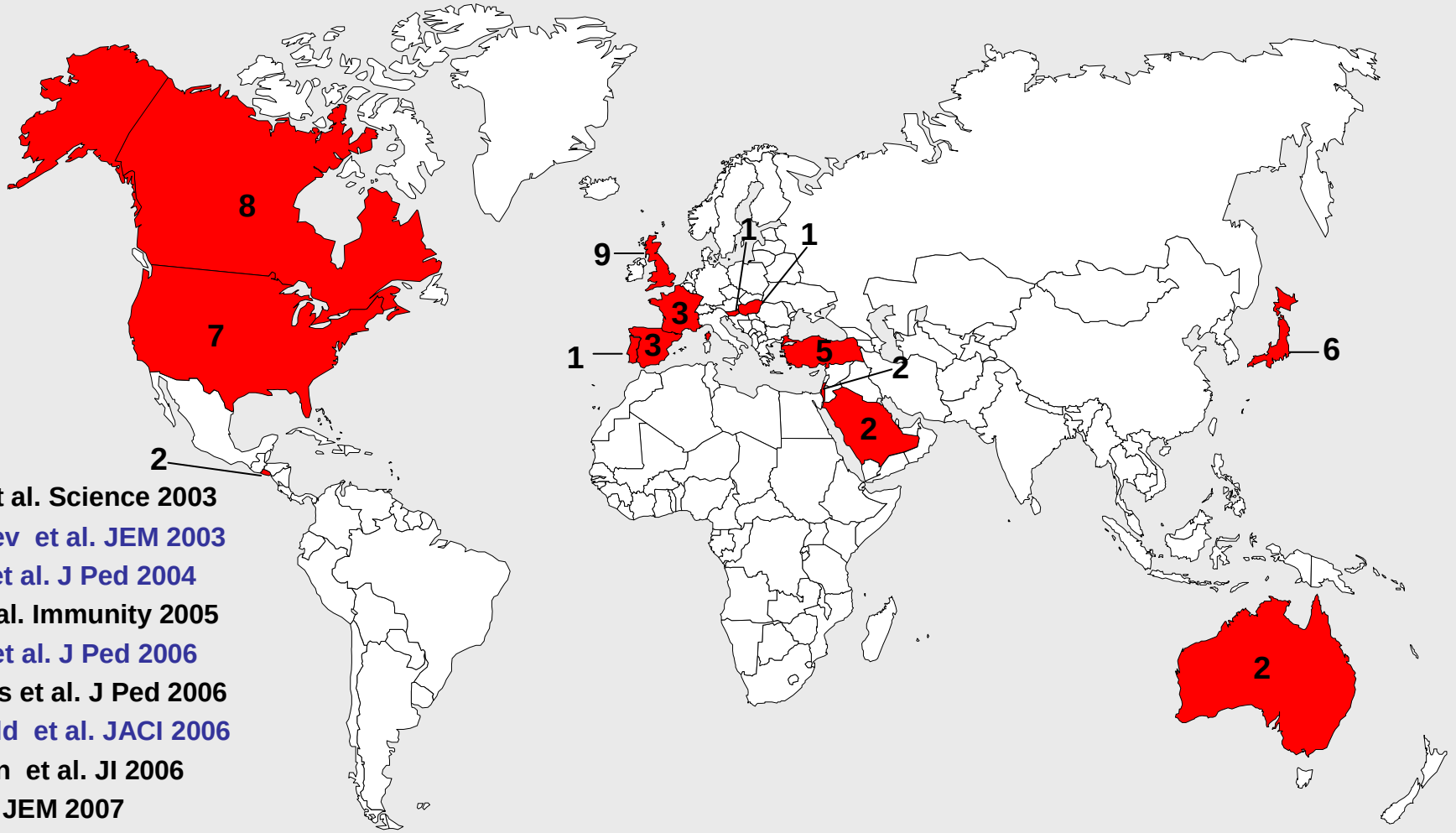




Blood cells of IRAK-4 and MyD88 deficient patients display an impaired responses to TLRs ligands (except TLR3) and IL-1β

(Picard et al. Science 2003. von Bernuth et al. Science 2008)

IRAK-4 deficiency – patients

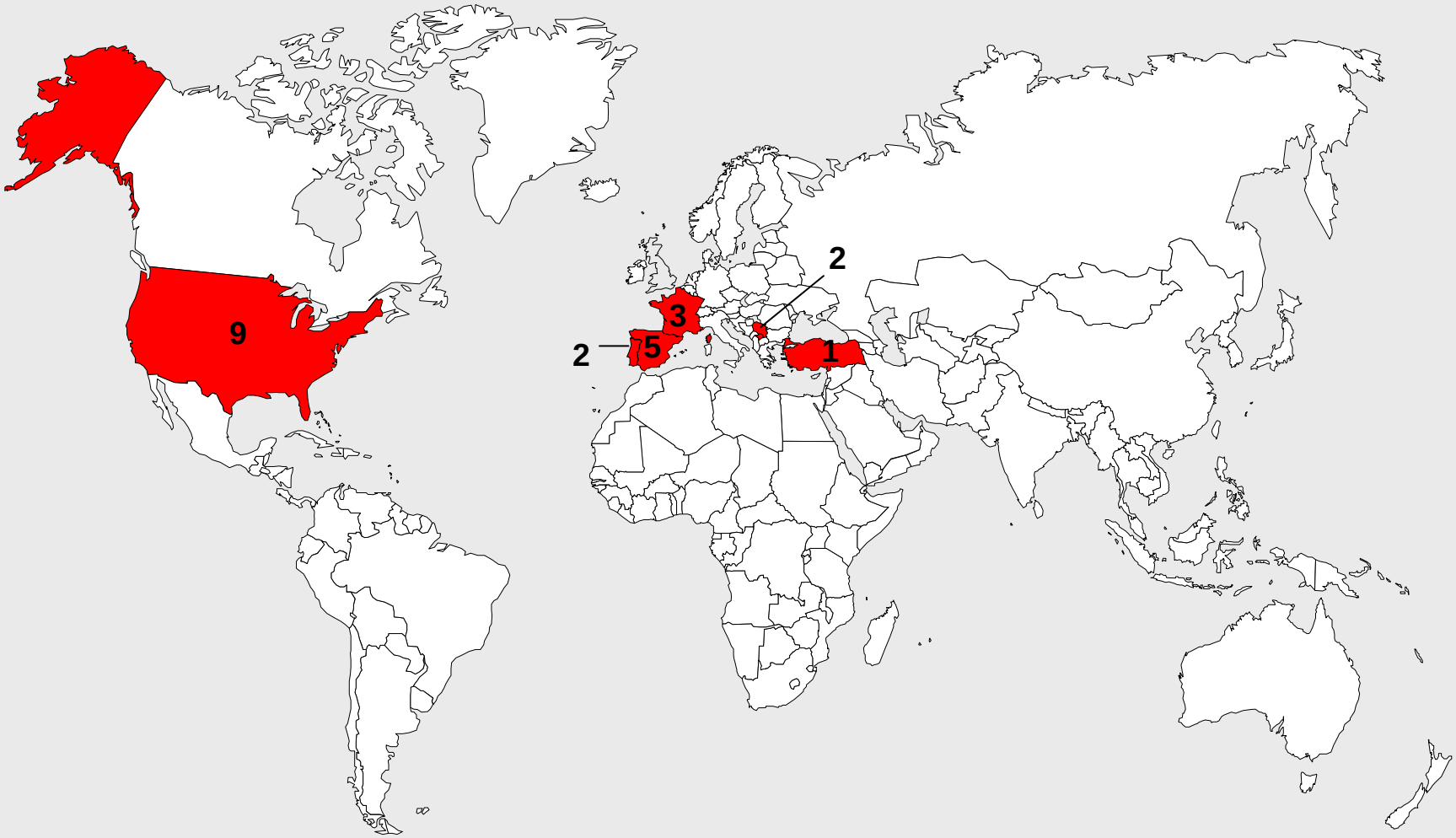


Picard et al. Science 2003
Medvedev et al. JEM 2003
Enders et al. J Ped 2004
Yang et al. Immunity 2005
Takada et al. J Ped 2006
Cardenes et al. J Ped 2006
McDonald et al. JACI 2006
Davidson et al. JI 2006
Ku et al. JEM 2007
Lavine et al. JACI 2007
Krause et al. CID 2009
Bouma et al. BJH 2009
Yoshikawa et al. J Ped 2010
Picard et al. Medicine 2010
Unpublished datas

52 patients from 33 kindreds in 14 countries

(Autosomal recessive disorder)

MyD88 deficiency (AR) – patients



von Bernuth et al. 2008 Science

Conway et al. 2010 JACI

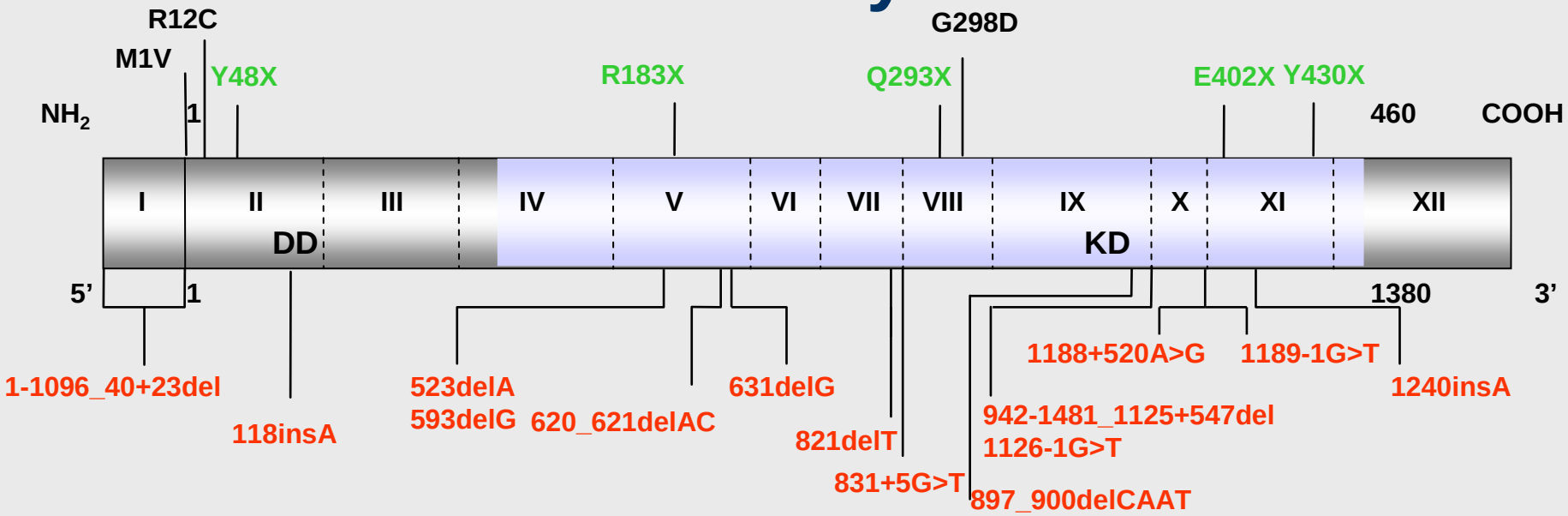
Picard et al. 2010 Medicine

Unpublished datas

22 patients from 7 kindreds

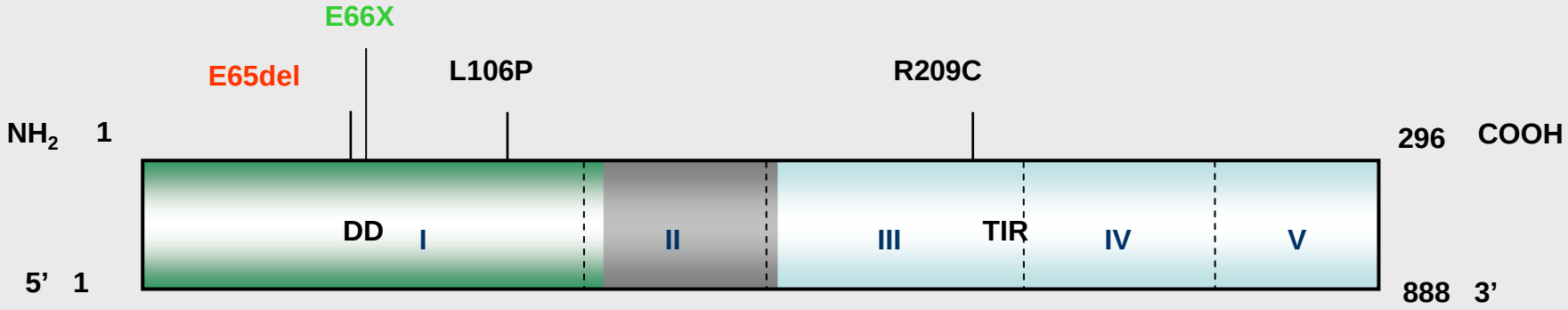
in 6 countries

IRAK-4 deficiency – mutations



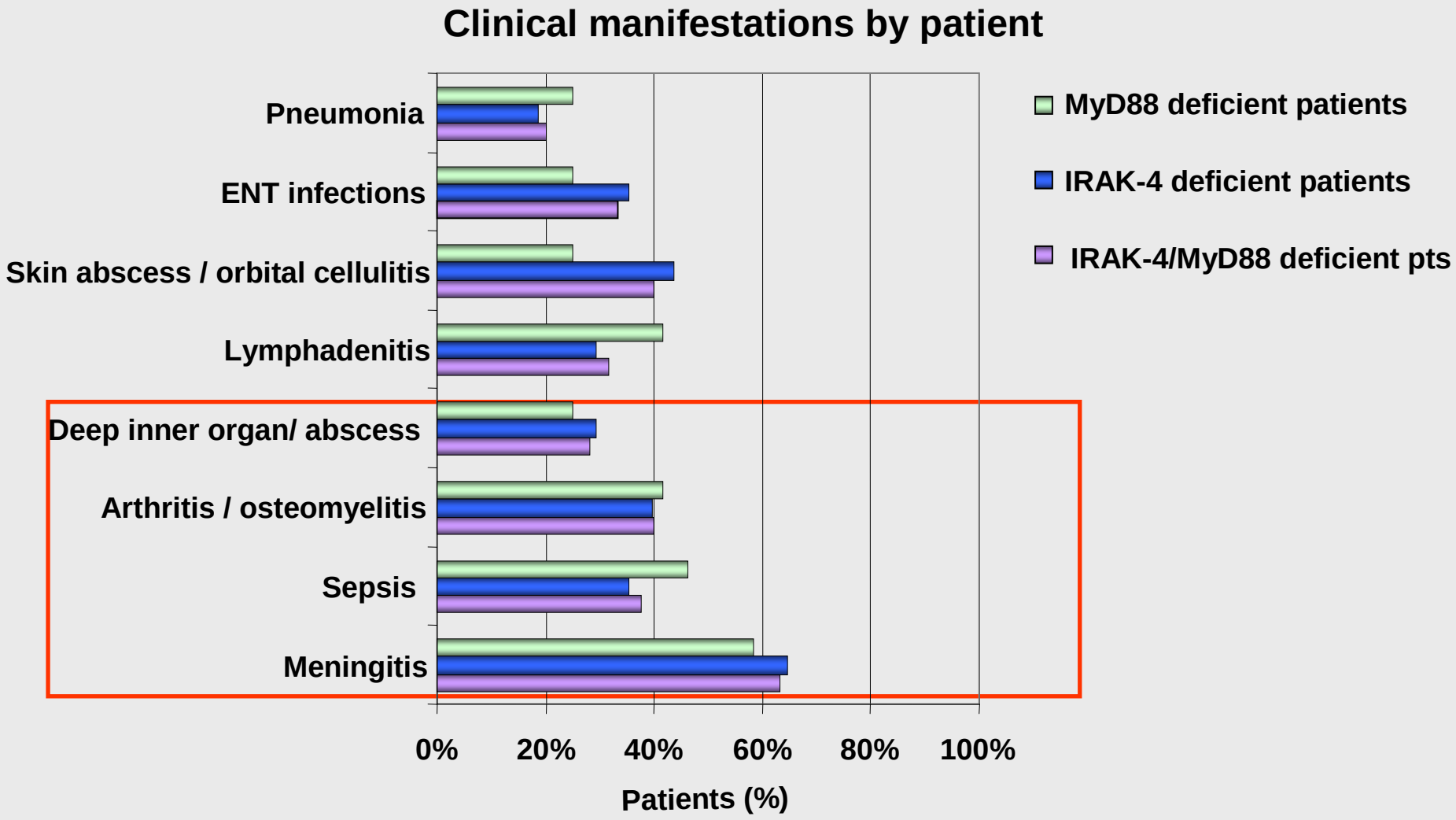
Patients are homozygous or compound heterozygous for mutations in *IRAK4*

MyD88 deficiency – mutations



Patients are homozygous or compound heterozygous for mutations in *MyD88*

IRAK-4/MyD88 deficiencies (n=61)

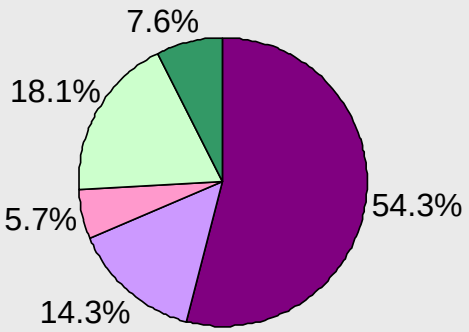


Invasive bacterial infection: 148 reported episodes of InvBD
(n=2.4 episodes/patient. range: 0 to 10)

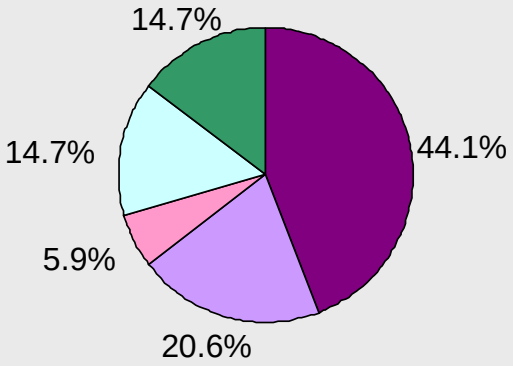
IRAK-4/MyD88 deficiencies: bacterial infections

Invasive infections

IRAK-4 deficient pts

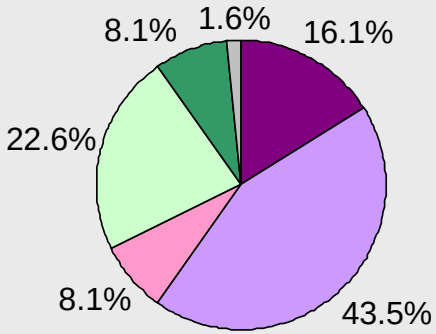


MyD88 deficient pts

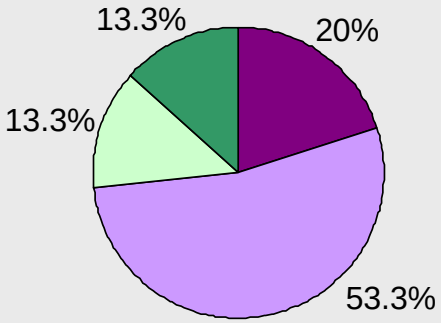


Non invasive infections

IRAK-4 deficient pts



MyD88 deficient pts



S. pneumoniae

S. aureus

Other Gram-pos

P. aeruginosa

Other Gram-neg

S. pneumoniae **= 52% of invasive bacterial infections**

(Meningitis. sepsis. arthritis. osteomyelitis. deep abscess)

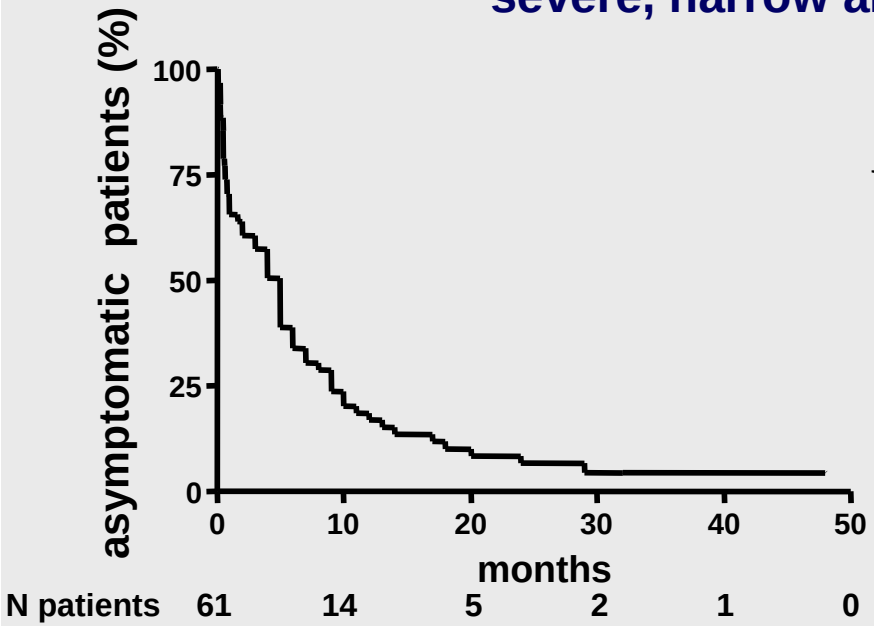
S. aureus **= 45.5% of non invasive bacterial infections**

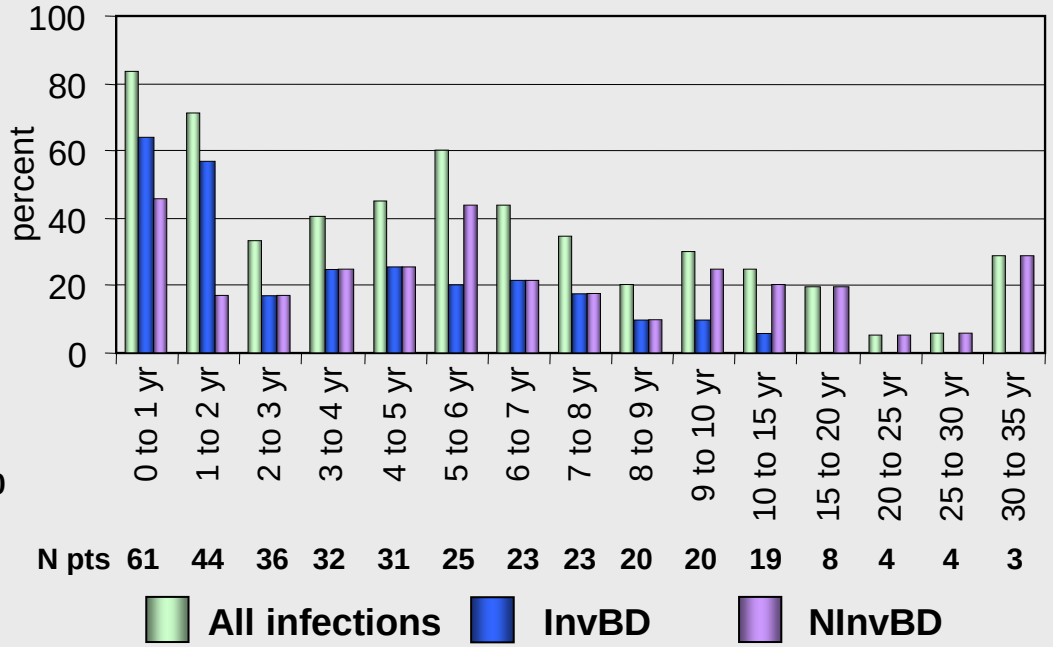
(Cellulitis. omphalitis. sinusitis. ENT infections. pneumonia)

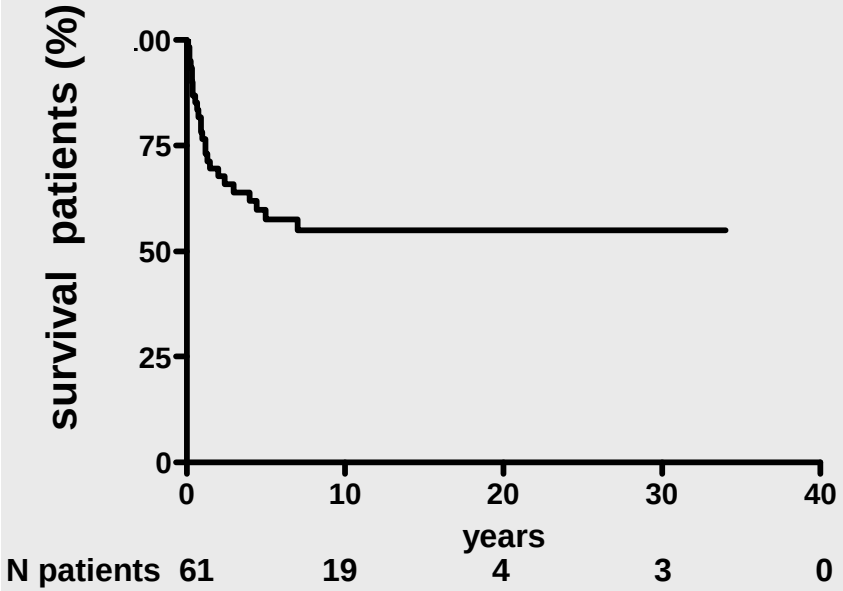
S. pneumoniae isolated in 41 pts / 61 (IPD 67%)

IRAK-4/MyD88 deficiencies:

severe, narrow and transient phenotype







Early clinical phenotype:

1st invasive infection occurred < 2 years

Severe clinical phenotype:

25 patients died of invasive bacterial infections

(16 caused by invasive bacterial *S. pneumoniae* infection)

Transient clinical phenotype:

no severe invasive infections > 14 years

no deaths after the age of 8 years.

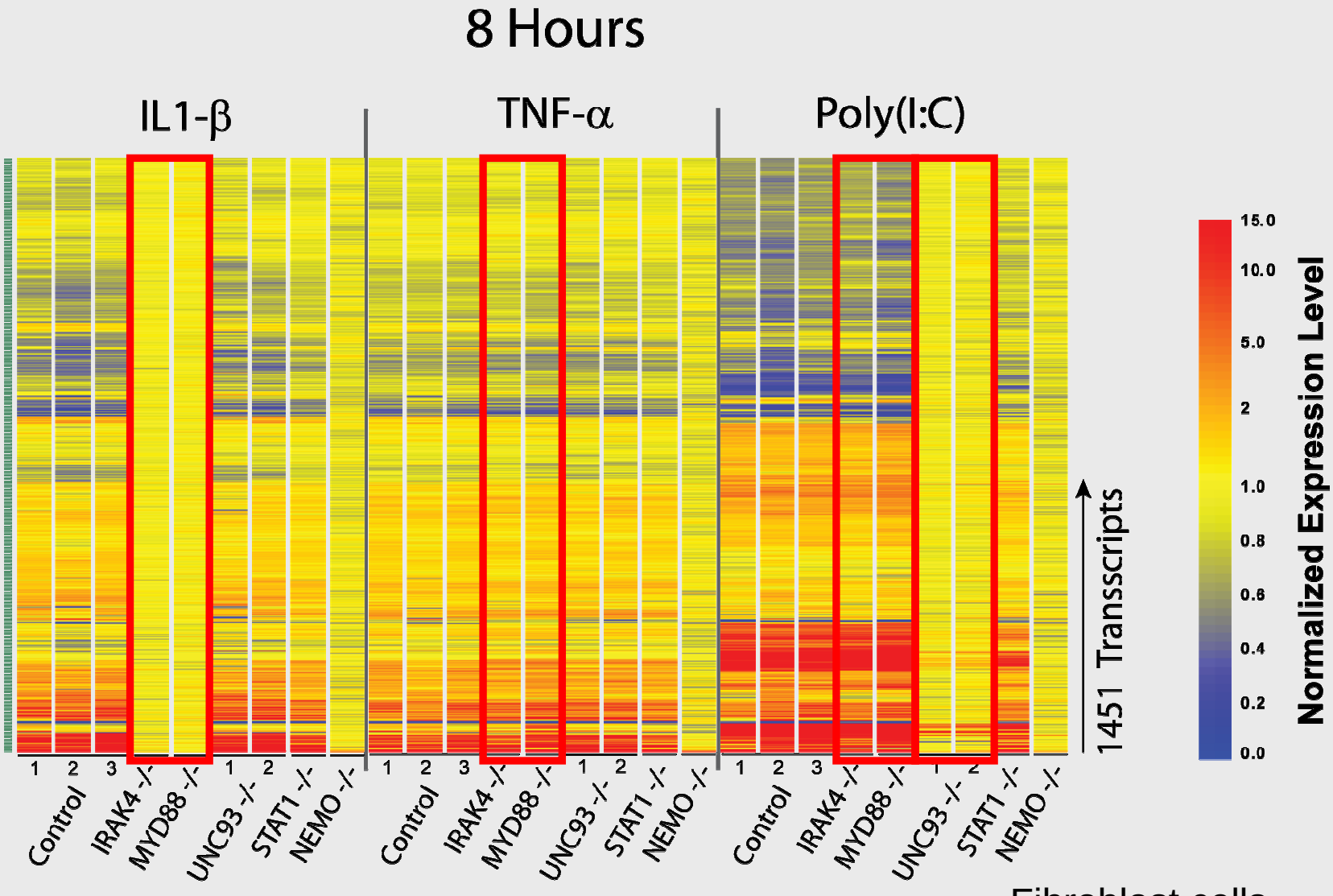
Immunological explorations

- **Blood lymphocyte and monocyte subsets: normal**
- **T cell proliferations (mitogens and antigens): normal**
- **Complement pathways: normal**
- **Ig: normal, except high levels IgG4 (35%) and IgE (65%)**
- **Abs response to proteins: normal**
- **Abs response to polysaccharides: variable**
- **Inflammatory signs (clinical & biological): low**

IRAK-4/MyD88 deficiencies - summary

- **Invasive infections by Gram-positive bacteria, but also Gram-negative (*S. pneumoniae, S. aureus* and *P. aeruginosa)* < 14 years of age**
- **Recurrent episodes of cellulitis (*S. aureus) and* sinusitis persisting**
- **IMMUNODEFICIENCIES THAT IMPROVE WITH AGE**
- **Delayed or low inflammatory signs (fever, PMN, CRP…)**
- **Delayed separation of the umbilical cord (Takada. 2006 J.Ped)**
- **Deficient IL-1β and TLR signalling (except for TLR3)**
- **No other susceptibility to infection, in particular severe viral infection**

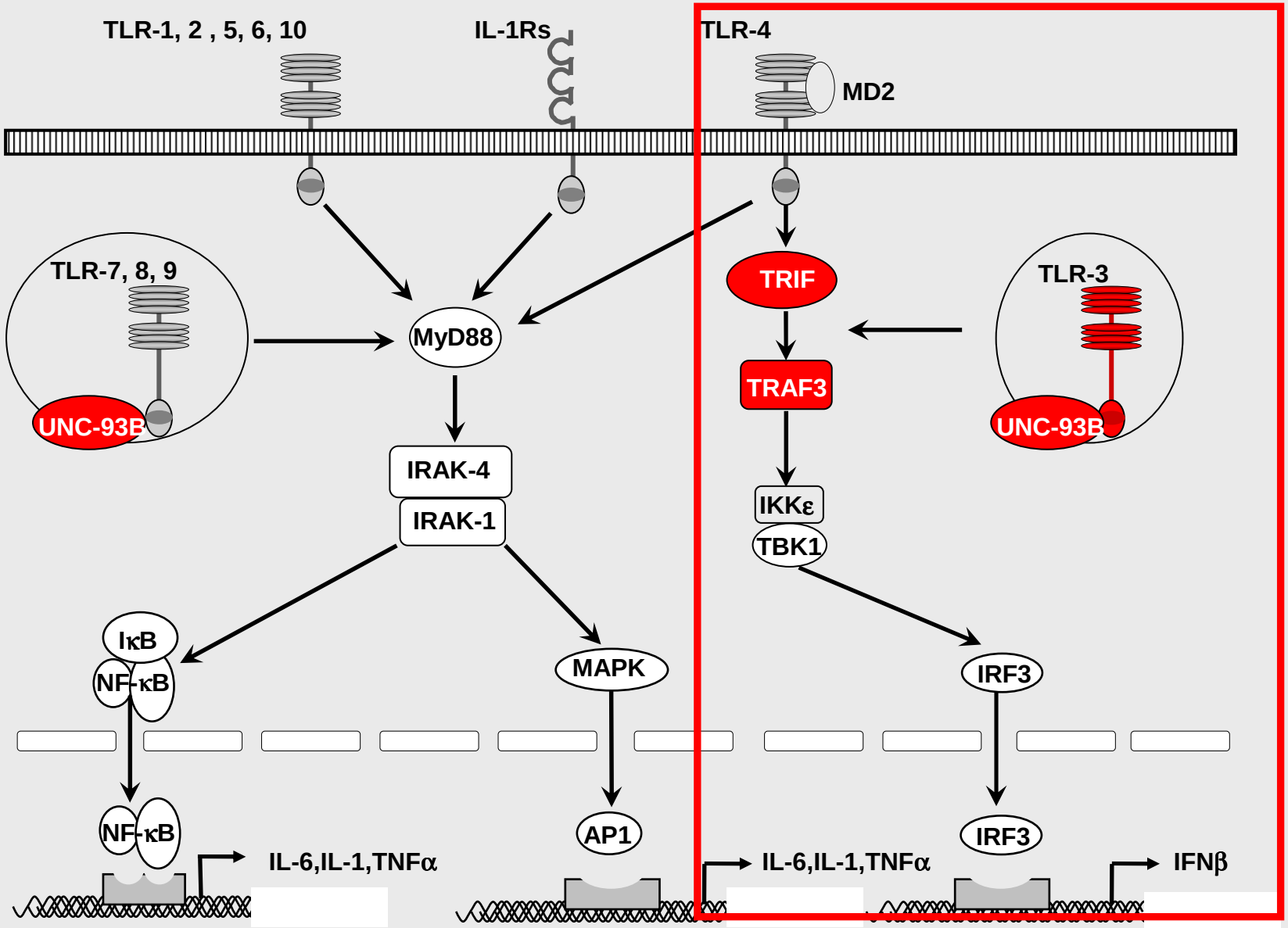
MyD88 and IRAK-4 deficiencies: phenocopies



Fibroblast cells

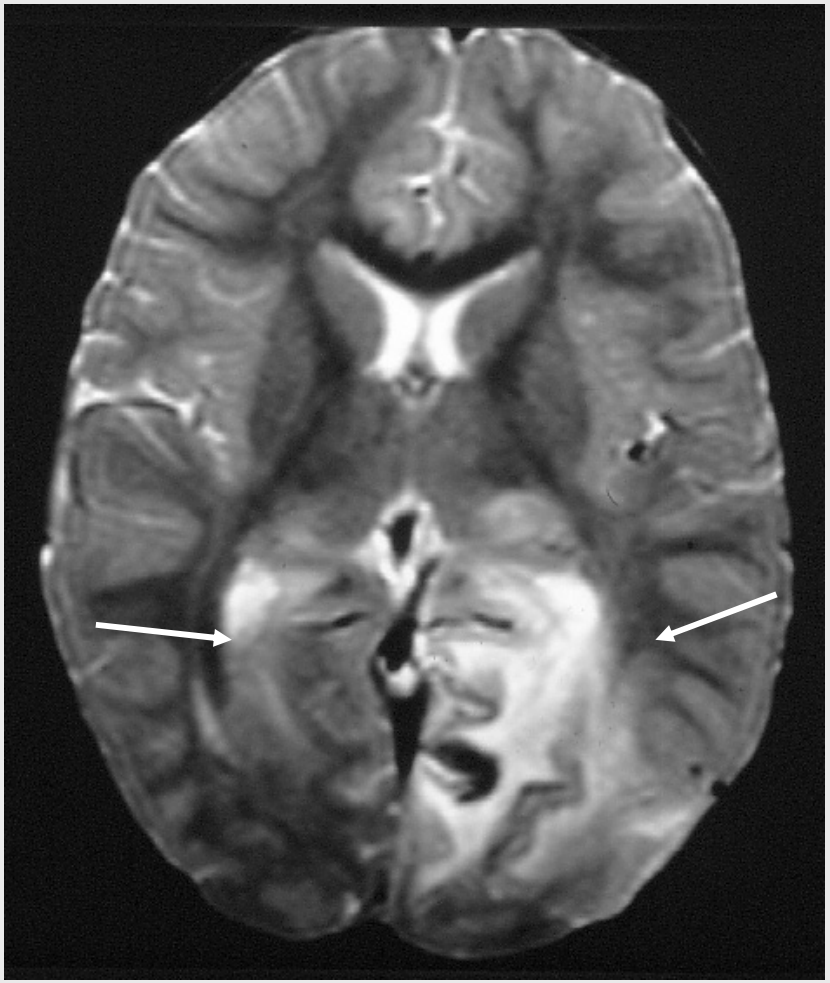
(Damien Chaussabel, Baylor institute, Dallas, USA)

Toll like receptors and IL-1Rs (TIRs) signalling pathway



Herpes Simplex virus Encephalitis (HSE):

a devastating viral disease of unclear pathogenesis



HSV-1 reach the CNS via neurons and do not spread to epithelia and internal organs

Classical Primary Immunodeficiencies, do not usually predispose to HSE

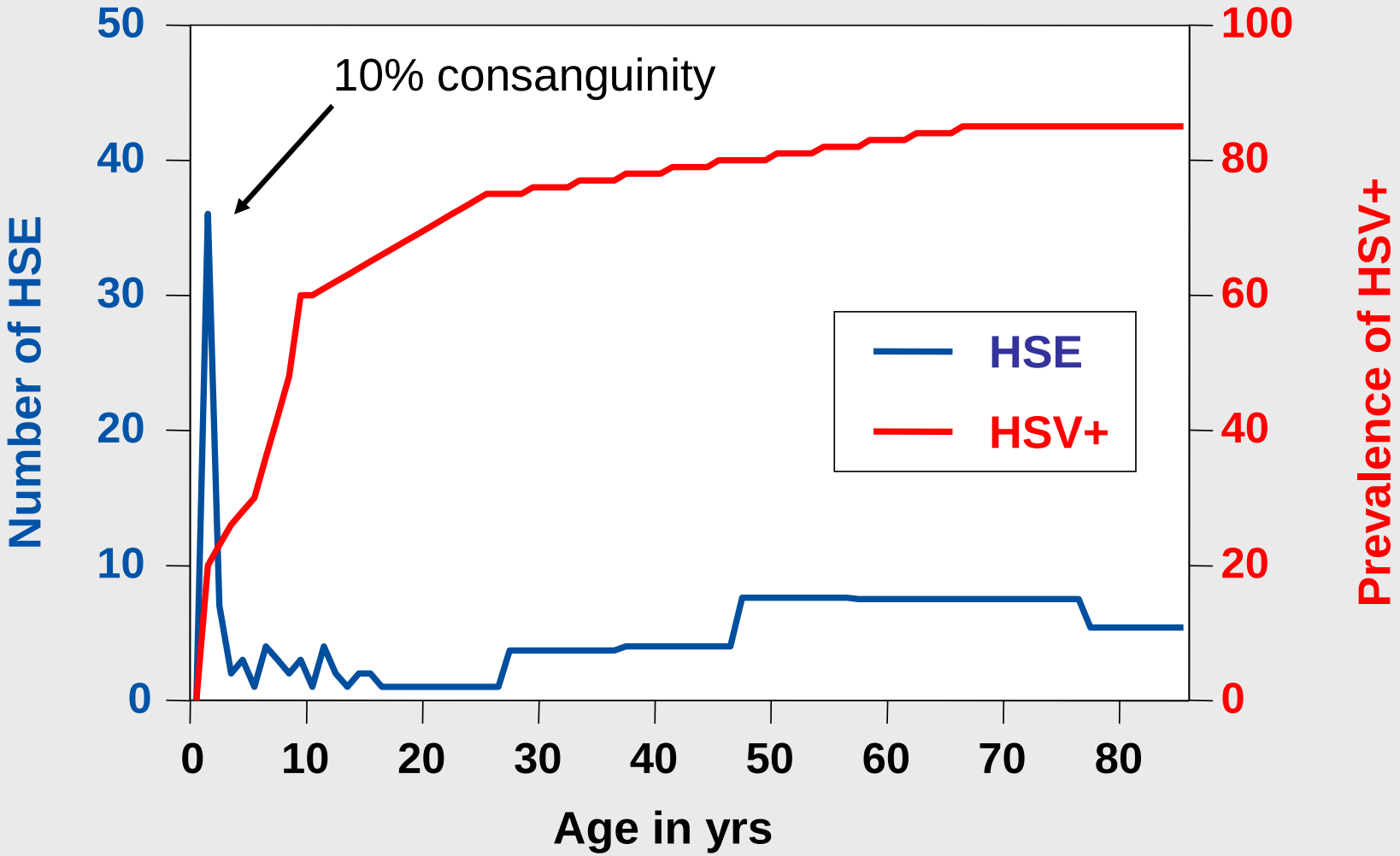
HSE patients are normally resistant to most infectious agents, including neurotropic viruses

2-4 cases/million people/year

Incidence peaks 6 mos-6 yrs during primary infection by HSV-1

Up to 30% mortality in treated individuals

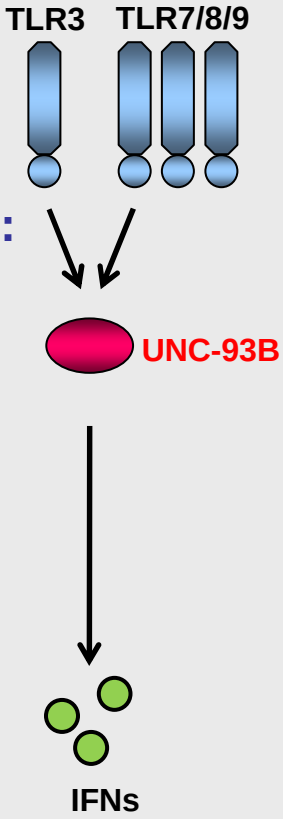
HSE: a genetic epidemiological survey



Autosomal Recessive UNC-93B deficiency: the first genetic etiology of isolated HSE

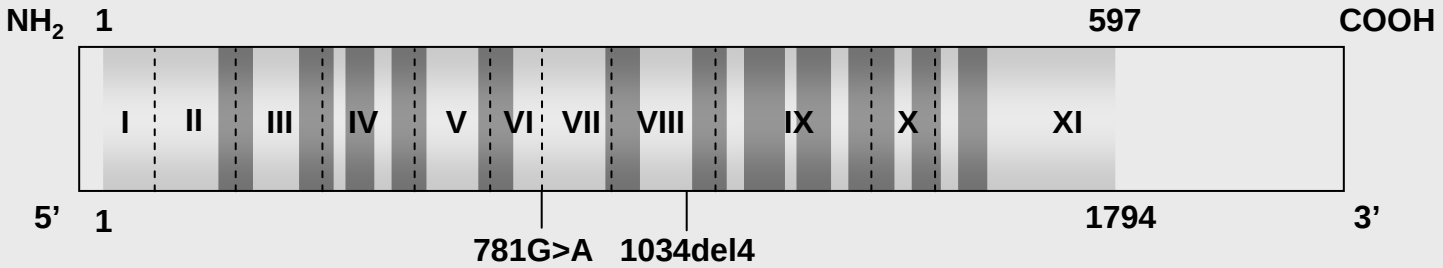
- UNC-93B is a 12-transmembrane domain protein in the ER.

- UNC-93B delivers the nucleotide-sensing receptors TLR3, 7, 8 and 9 from the ER to endolysosomes



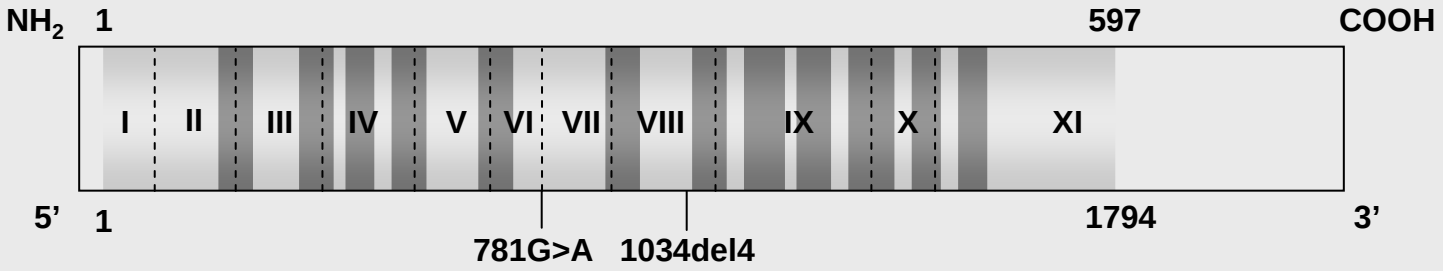
Three individuals, from Portugal and France (2 gypsies)) from 2 consanguineous kindreds with homozygous mutations in *UNC93B1* :

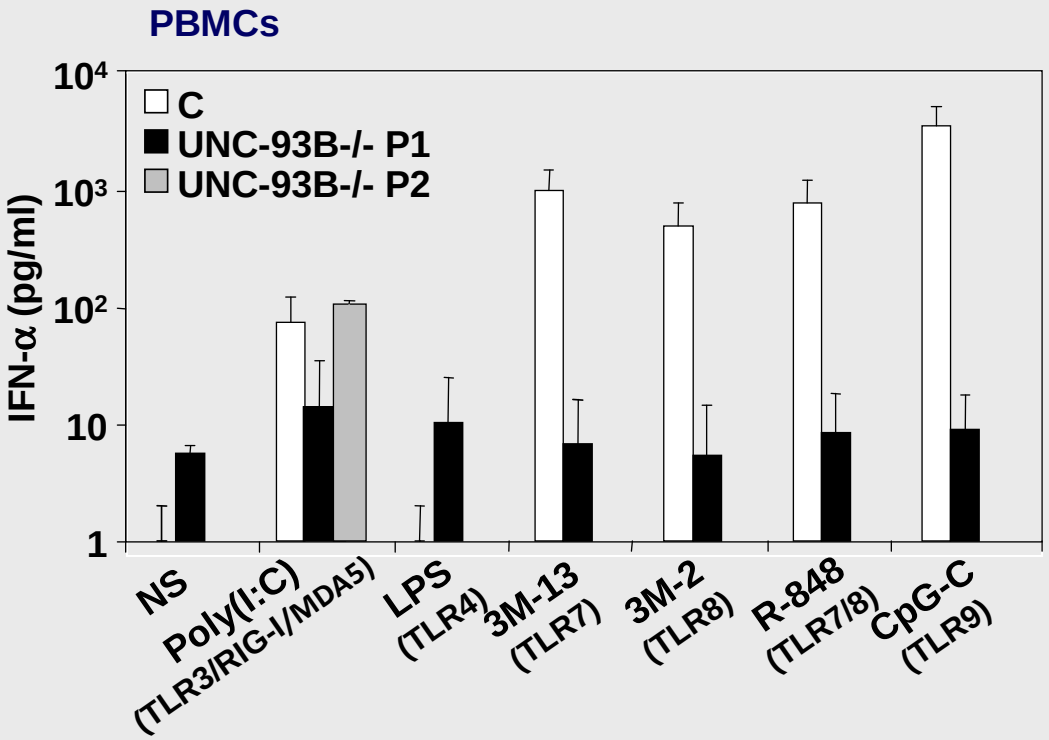
P1 HSE at 11, 14 and 42 months
P2 HSE at 5 and 17 years
P3 asymptomatic at 30 yrs (HSV1) ⇒ incomplete penetrance

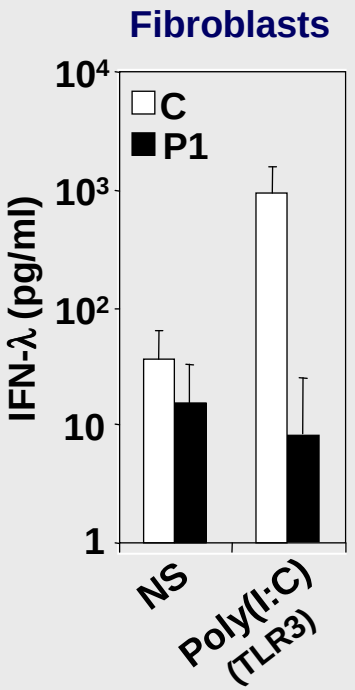


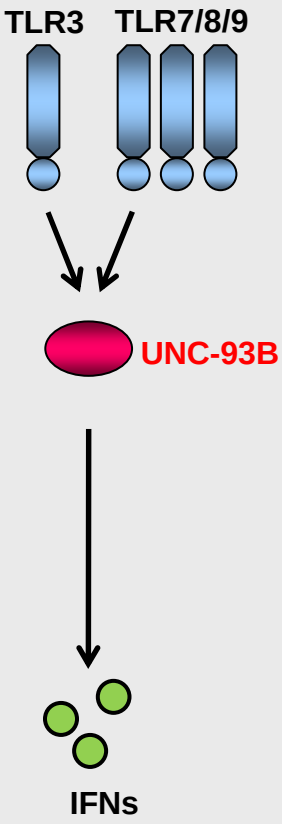
(Casrouge et al. Science 2006)

Autosomal Recessive UNC-93B deficiency: the first genetic etiology of isolated HSE



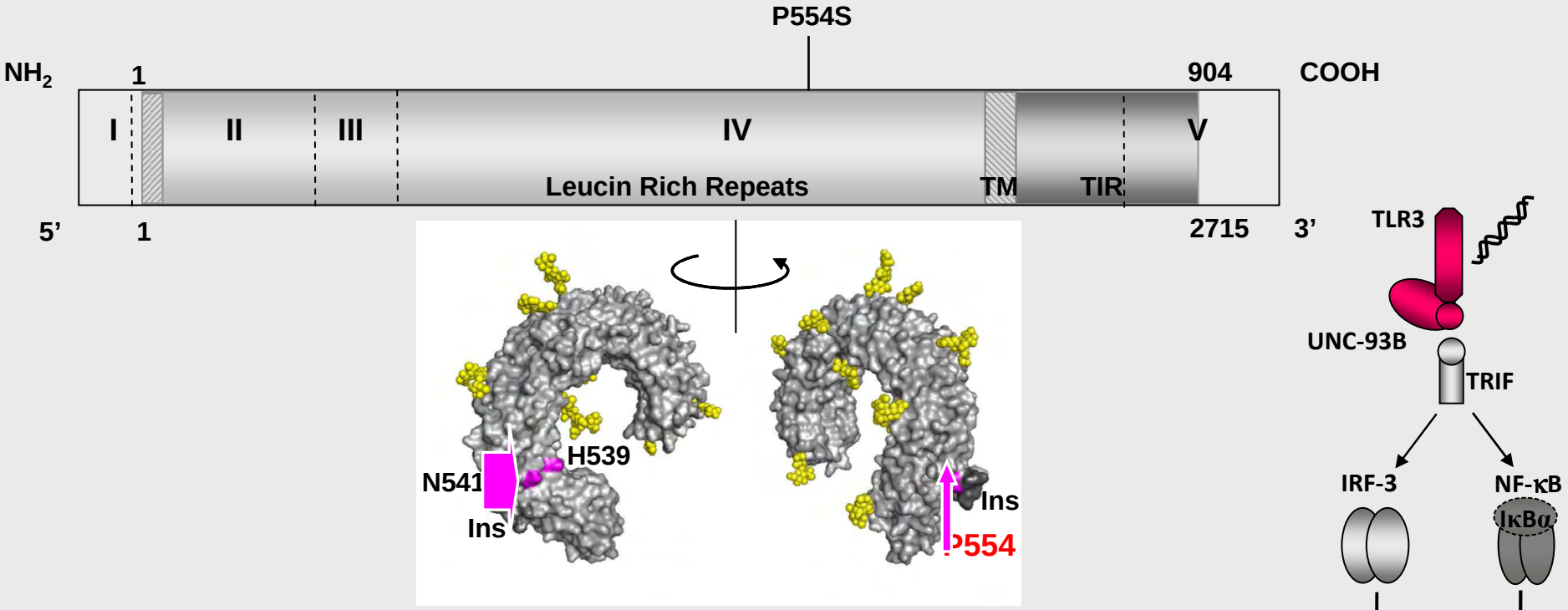






(Casrouge et al. Science 2006)

Autosomal Dominant TLR3 deficiency: The second genetic etiology of HSE



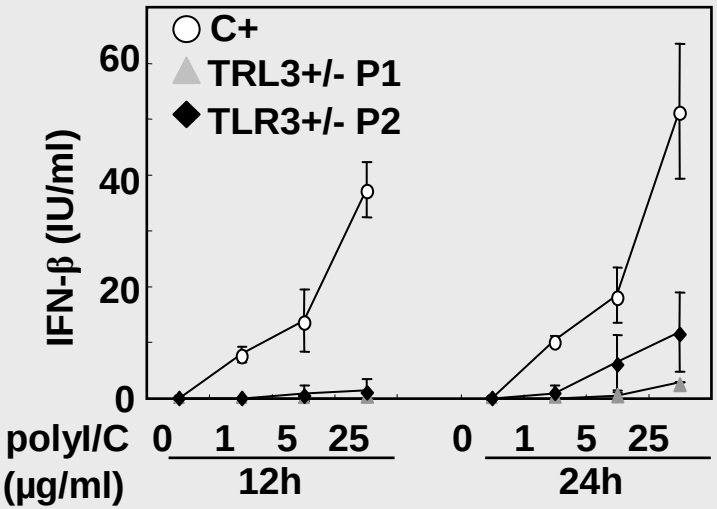
7 individuals bearing *TLR3* AD mutations have been identified from two unrelated kindreds, 2 had HSE (incomplete penetrance)

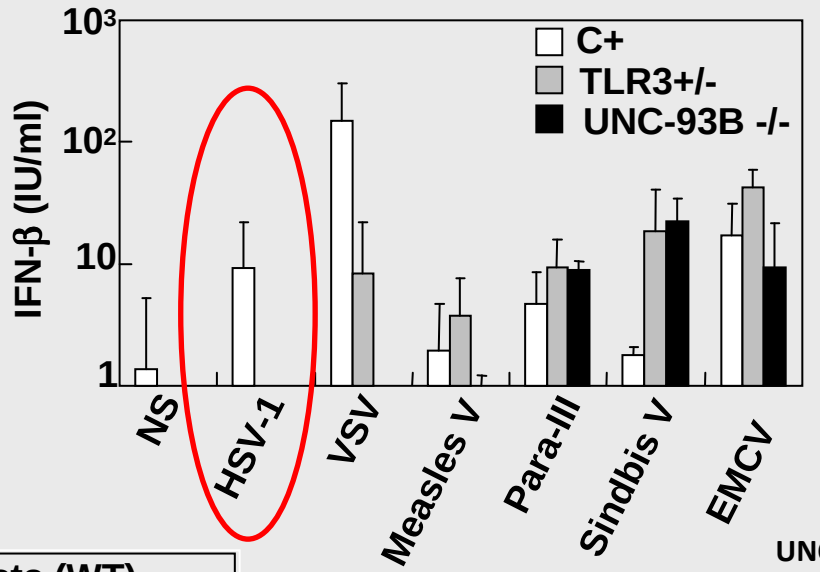
P1 HSE at 5 years

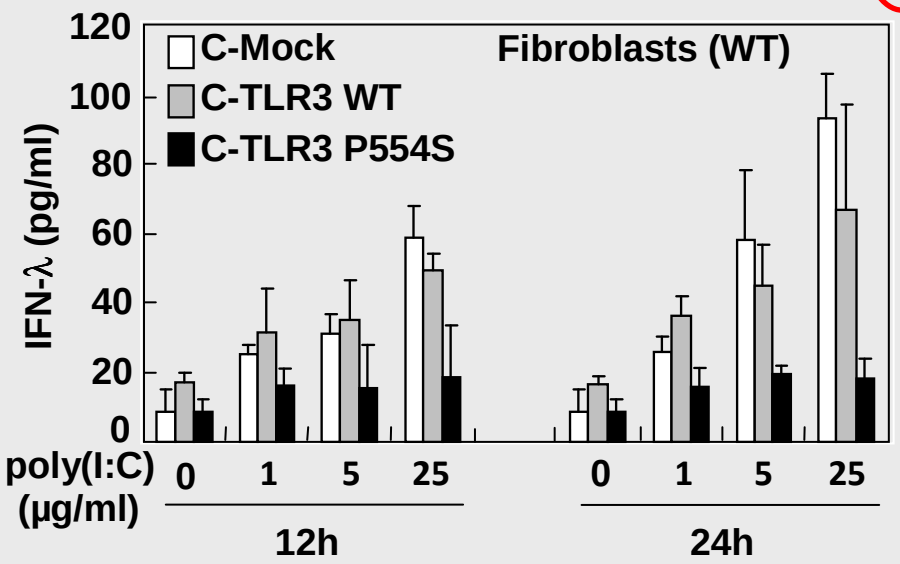
P2 HSE at 5 months

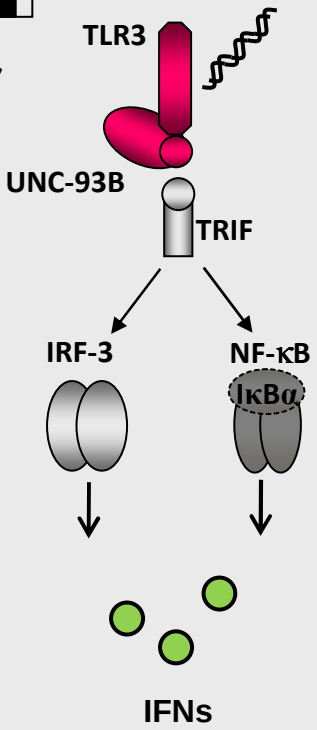
(Zhang Science 2007)

Autosomal Dominant TLR3 deficiency:







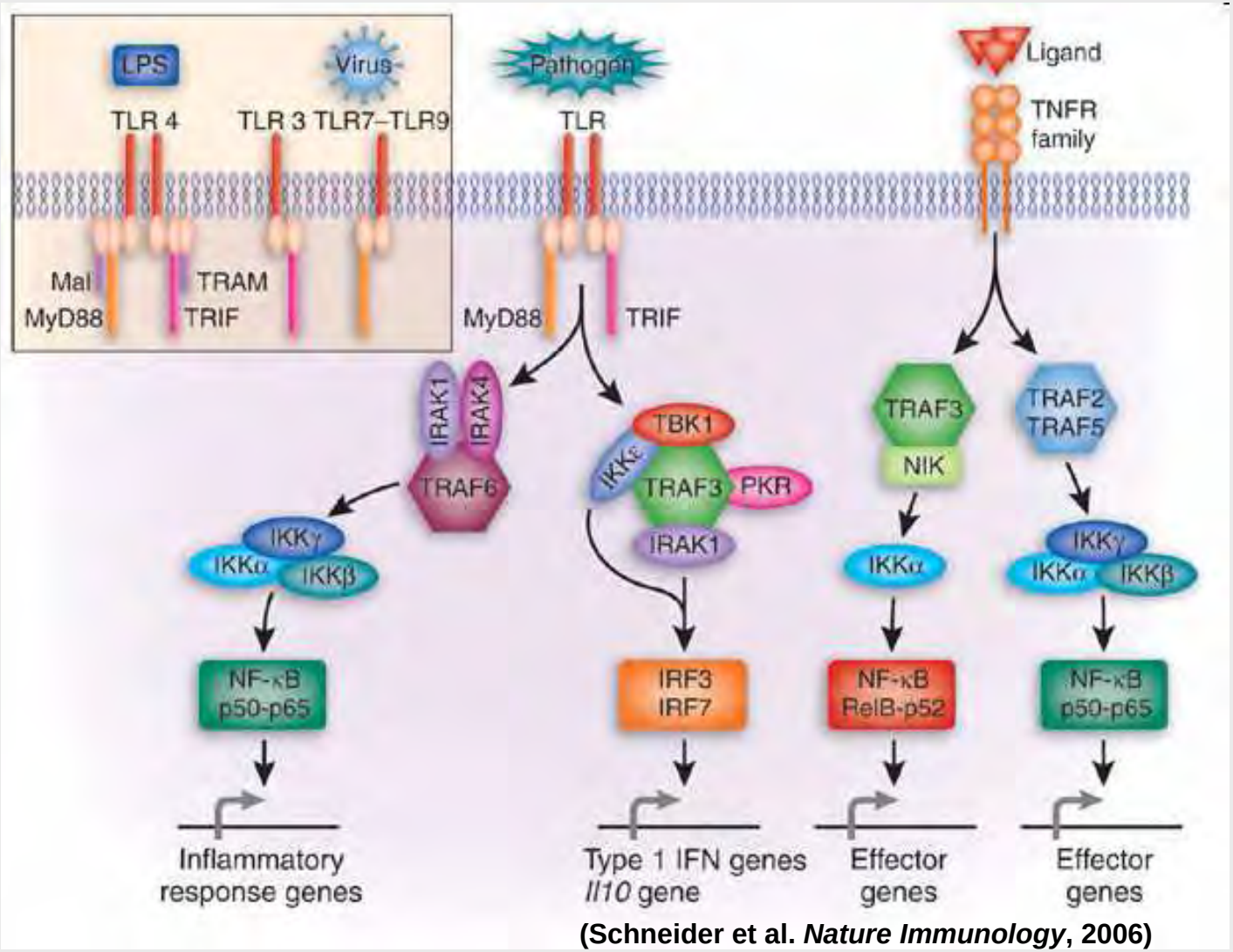


Fibroblast cells from AD TLR3 deficient patients have impaired type 1 and 3 IFN production

(Zhang Science 2007)

Heterozygous TRAF3 mutation in a patient with HSE:

The third genetic etiology of HSE

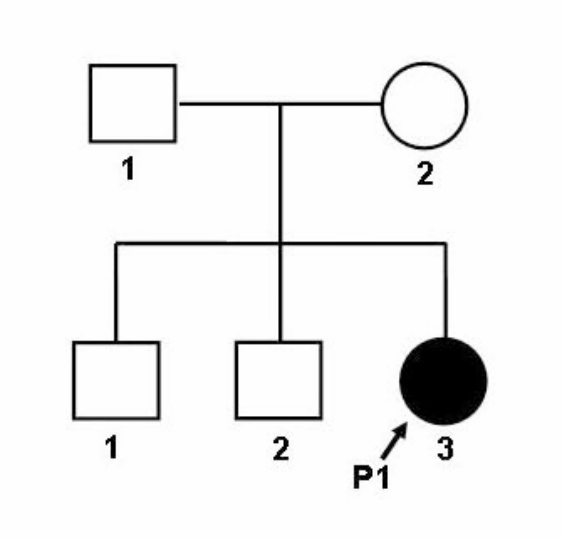


(Schneider et al. *Nature Immunology*, 2006)

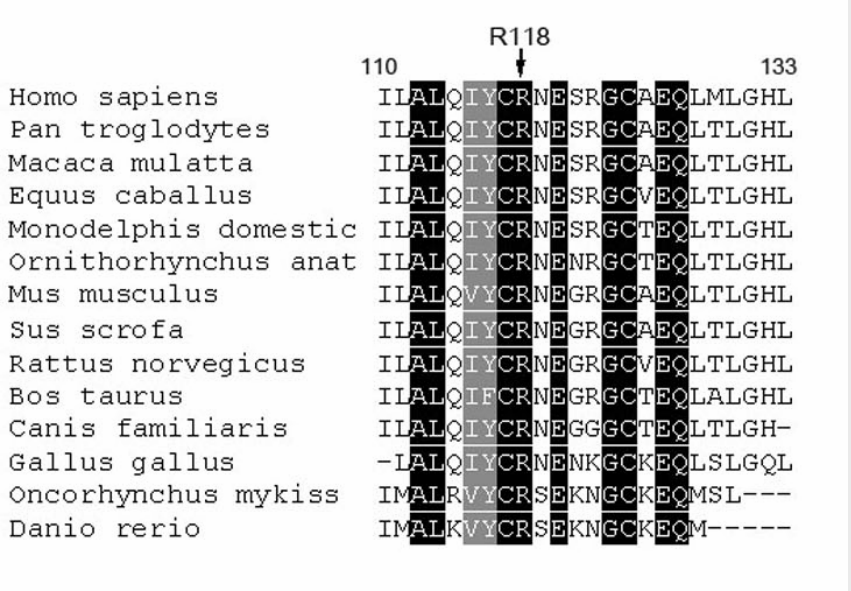
TRAF-3 has functions downstream from multiple TNF receptors and the receptors inducing IFN-α, IFN-β, and IFN-λ production, including TLR3.

Heterozygous TRAF3 mutation in a patient with HSE

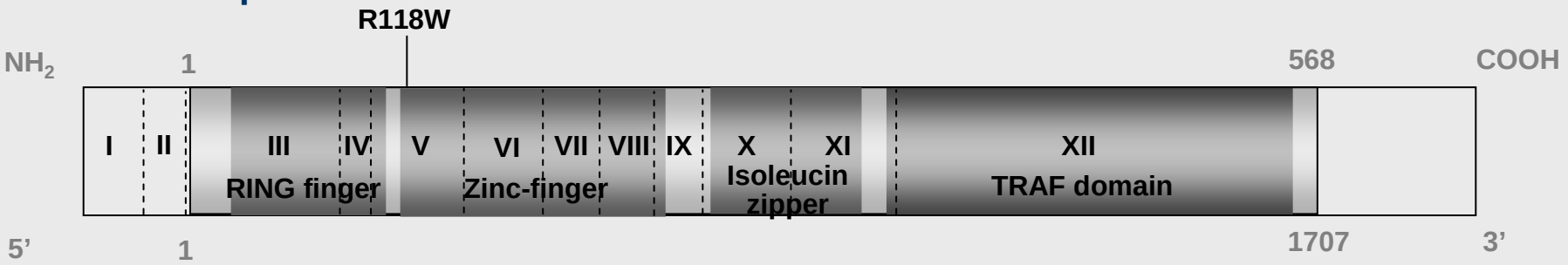
200 patients sequenced



P1 HSE at 4 years

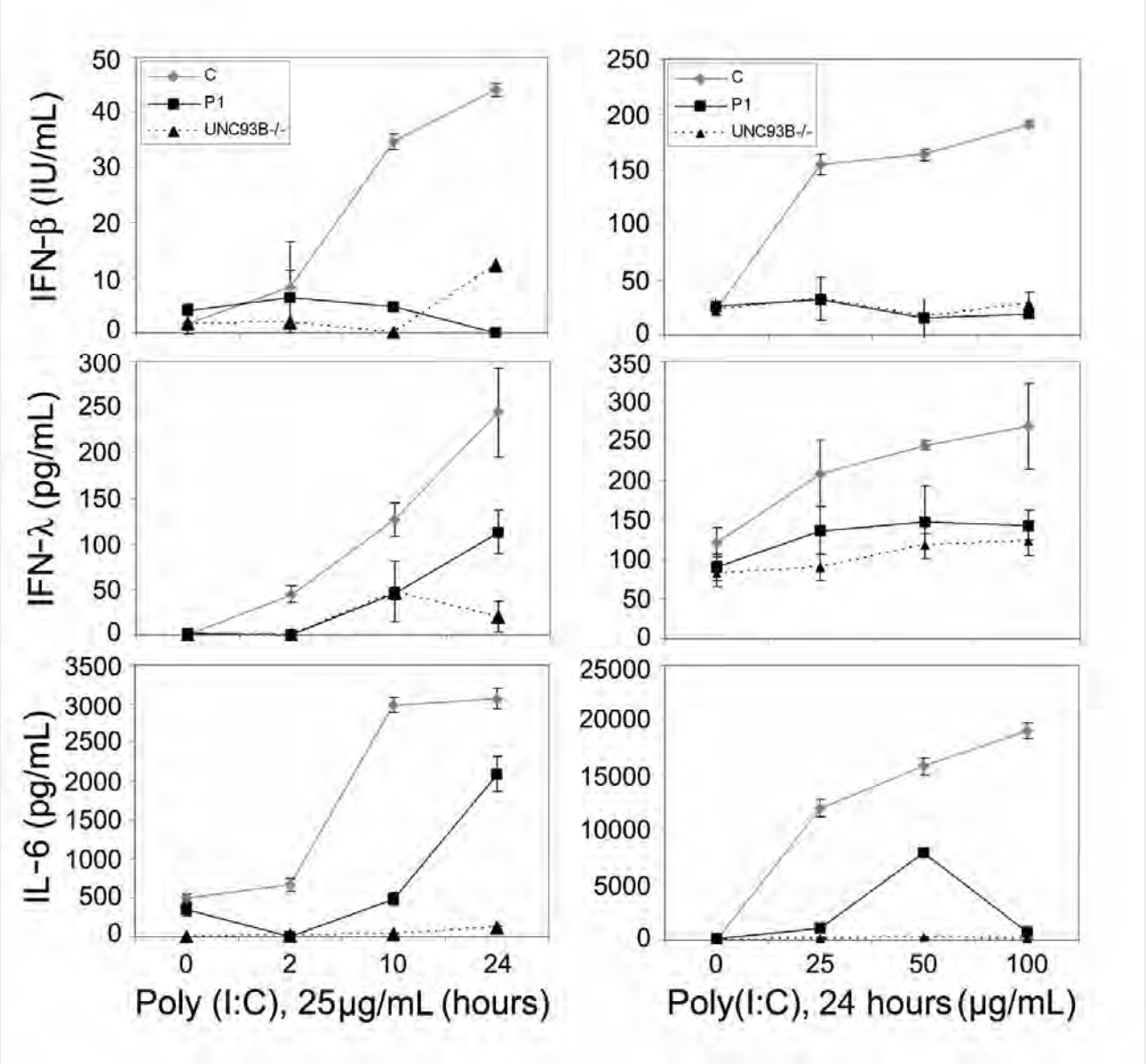


TRAF3 c.705C>T
TRAF3 protein R118W



(Rebeca Pérez de Diego et al. Immunity 2010)

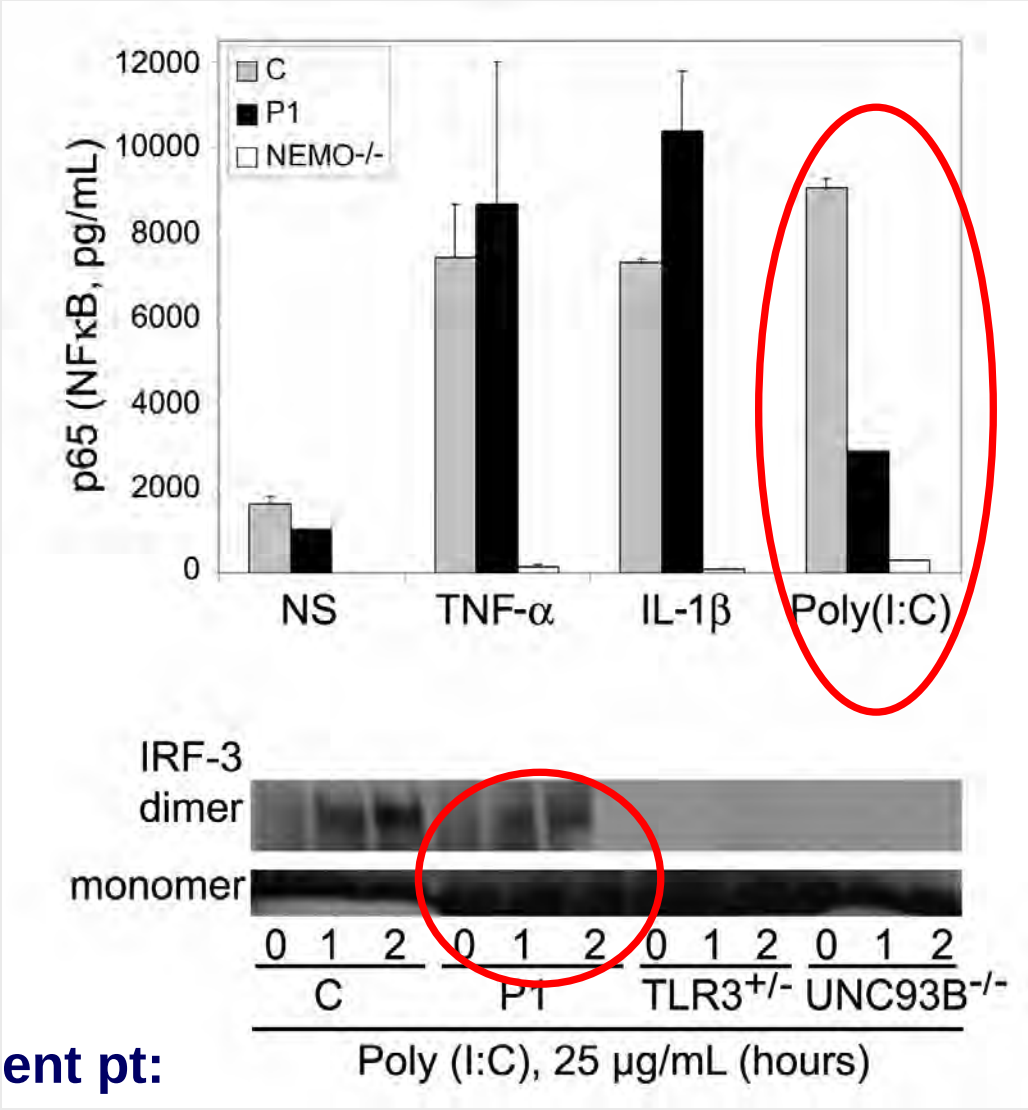
SV40 fibroblast studies: IFN type I and cytokines production



(Rebeca Pérez de Diego et al. Immunity 2010)

SV40 fibroblast studies: Molecular phenotype

NF-κB pathway



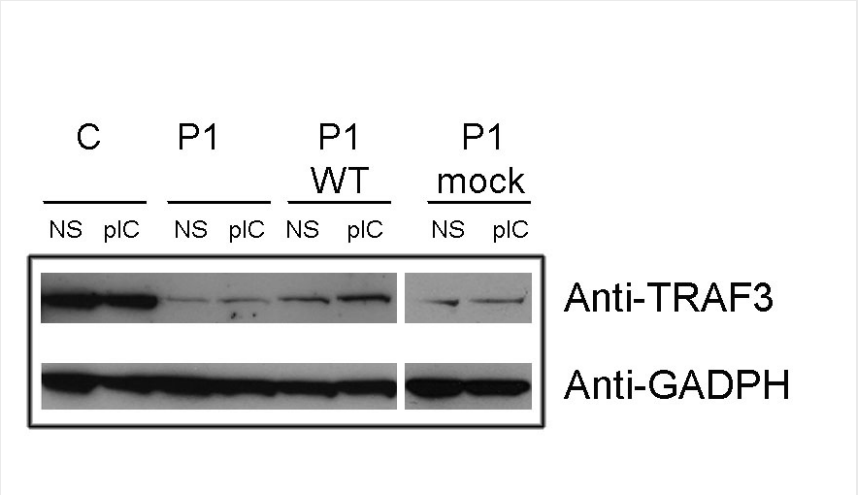
IRF3 dimerization

Fibroblast cells from TRAF3 deficient pt:

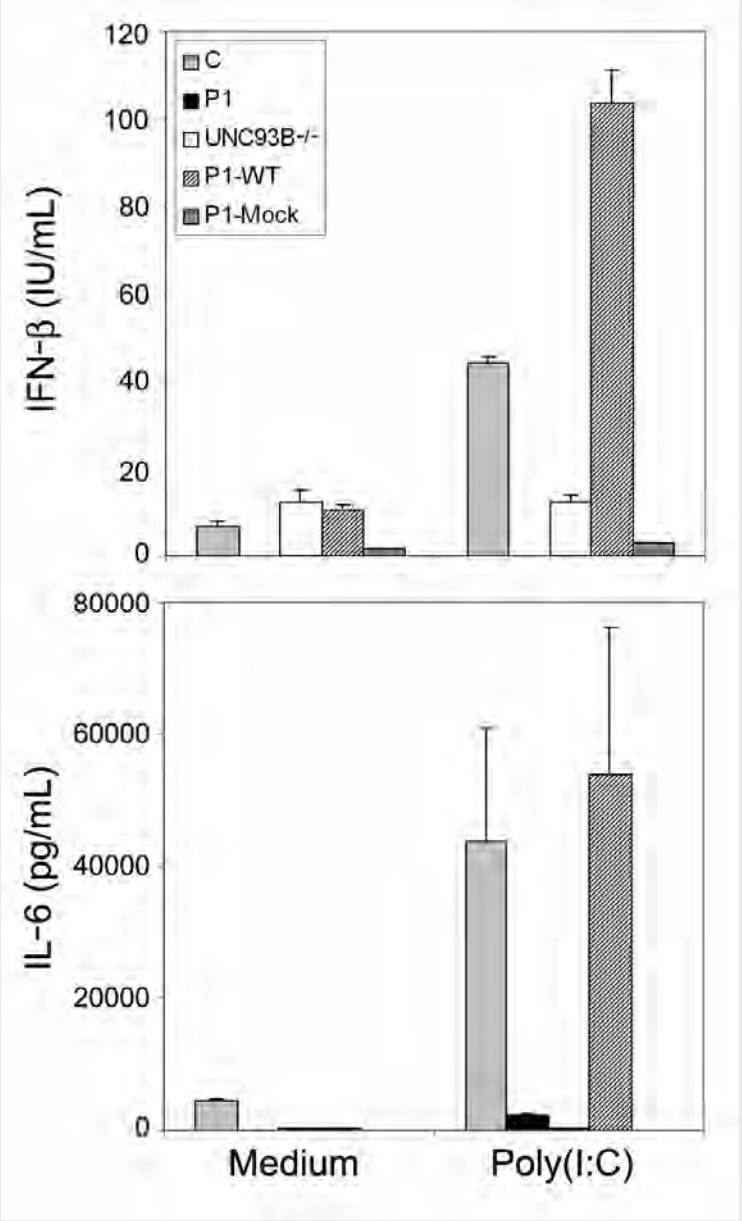
Reduced NF-kB nuclear translocation and IRF3 dimerization in response to TLR3 agonist

(Rebeca Pérez de Diego et al. Immunity 2010)

Complementation studies in SV40 fibroblast of P1



Stable transfectants

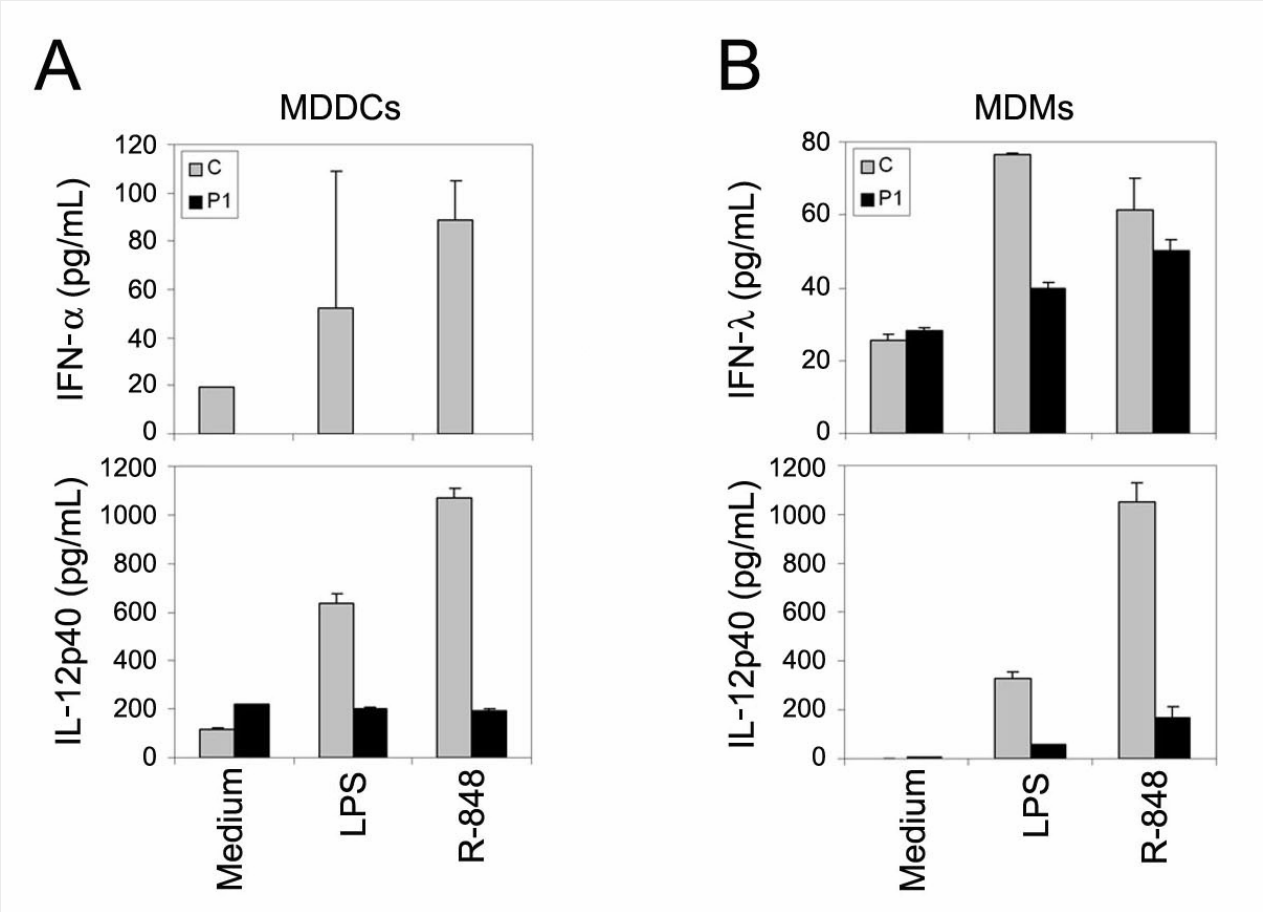


(Rebeca Pérez de Diego et al. Immunity 2010)

TRAF3 in other pathways

TLR4 and TLR7/8

Impaired IFN and cytokines production by MDDC and MDM



Monocyte derived dendritic cells (MDDC)
Monocyte differentiated macrophages (MDM)

(Rebeca Pérez de Diego et al. Immunity 2010)

TRAF3 in other pathways (alternative NF-kB pathway)

CD40

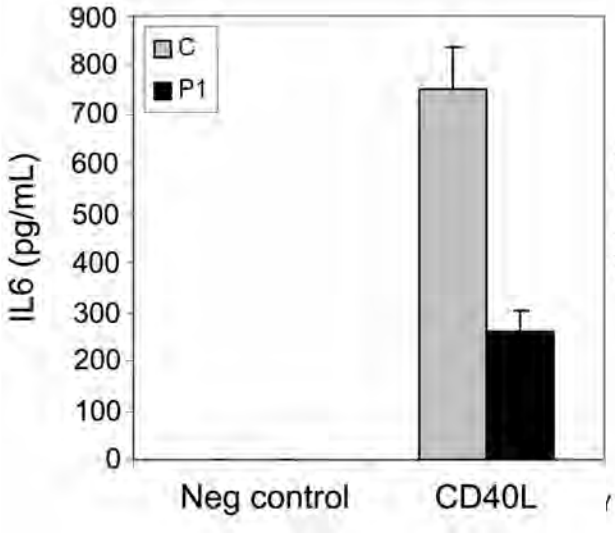
Impaired IL-6 production after CD40L activation by MDDC

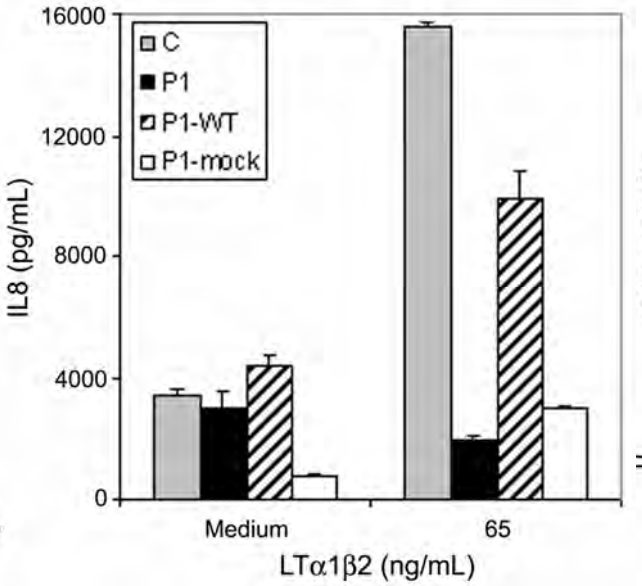
LTβR

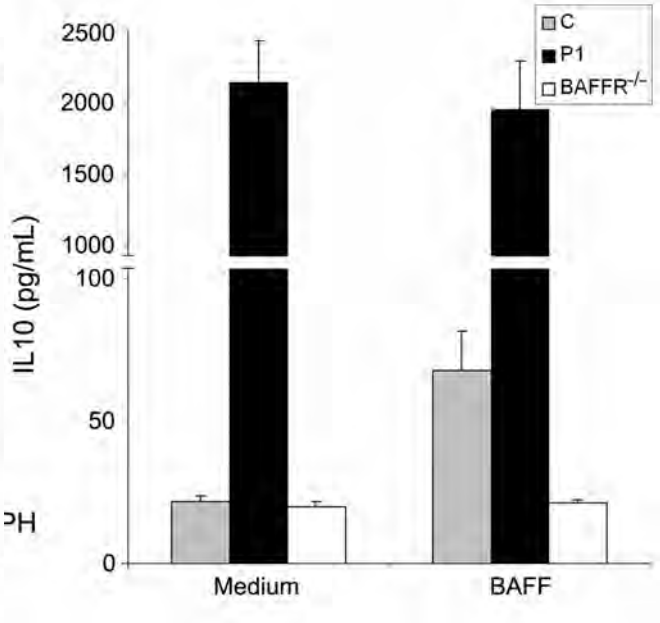
Diminished the production of IL-8 by SV40-fibroblast

BAFFR

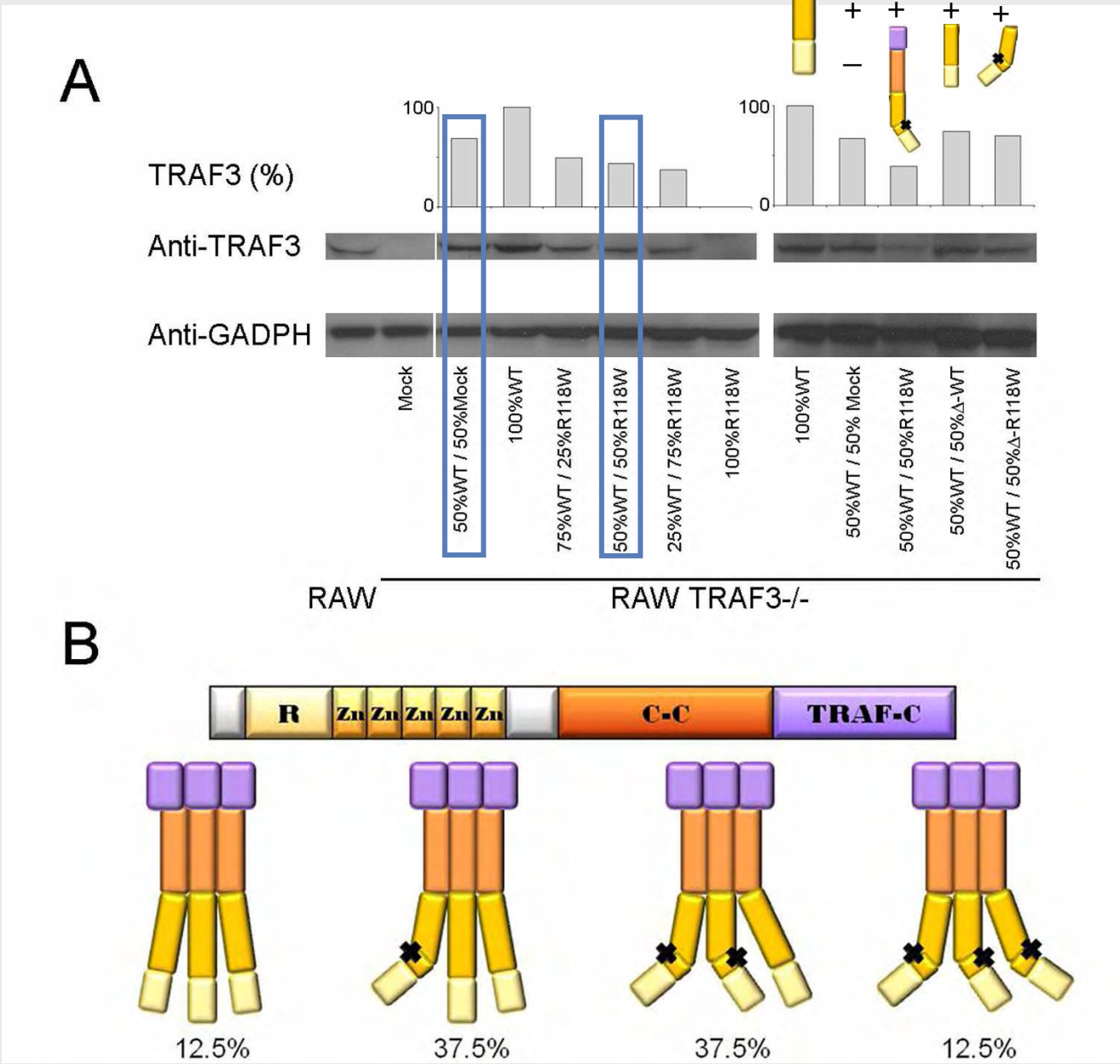
Constitutive activation in B-EBV cells - IL10 production







Negative dominant effect

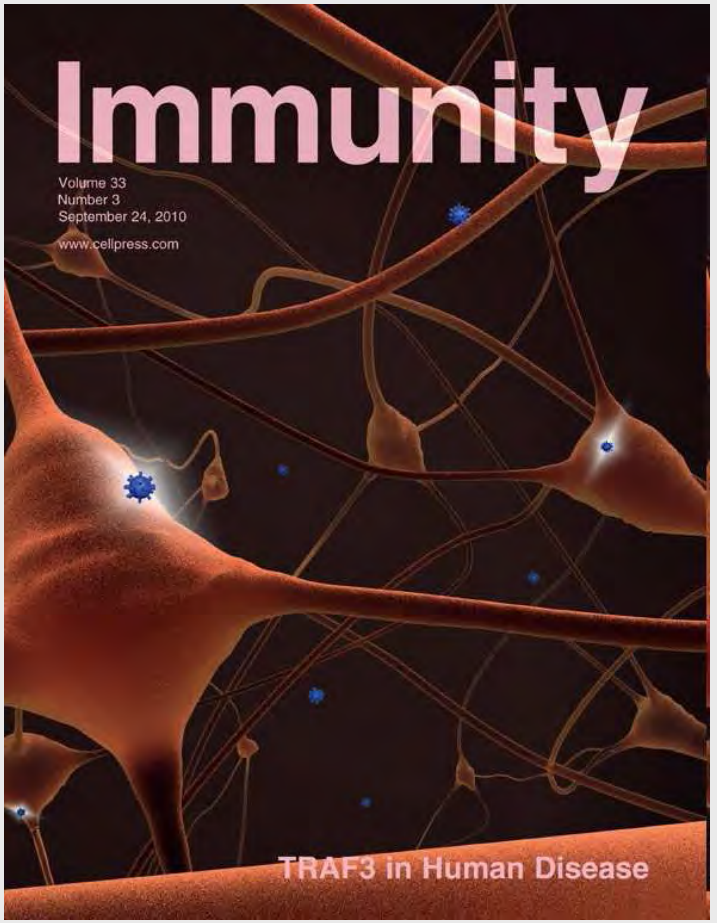


Human AD TRAF3 deficiency

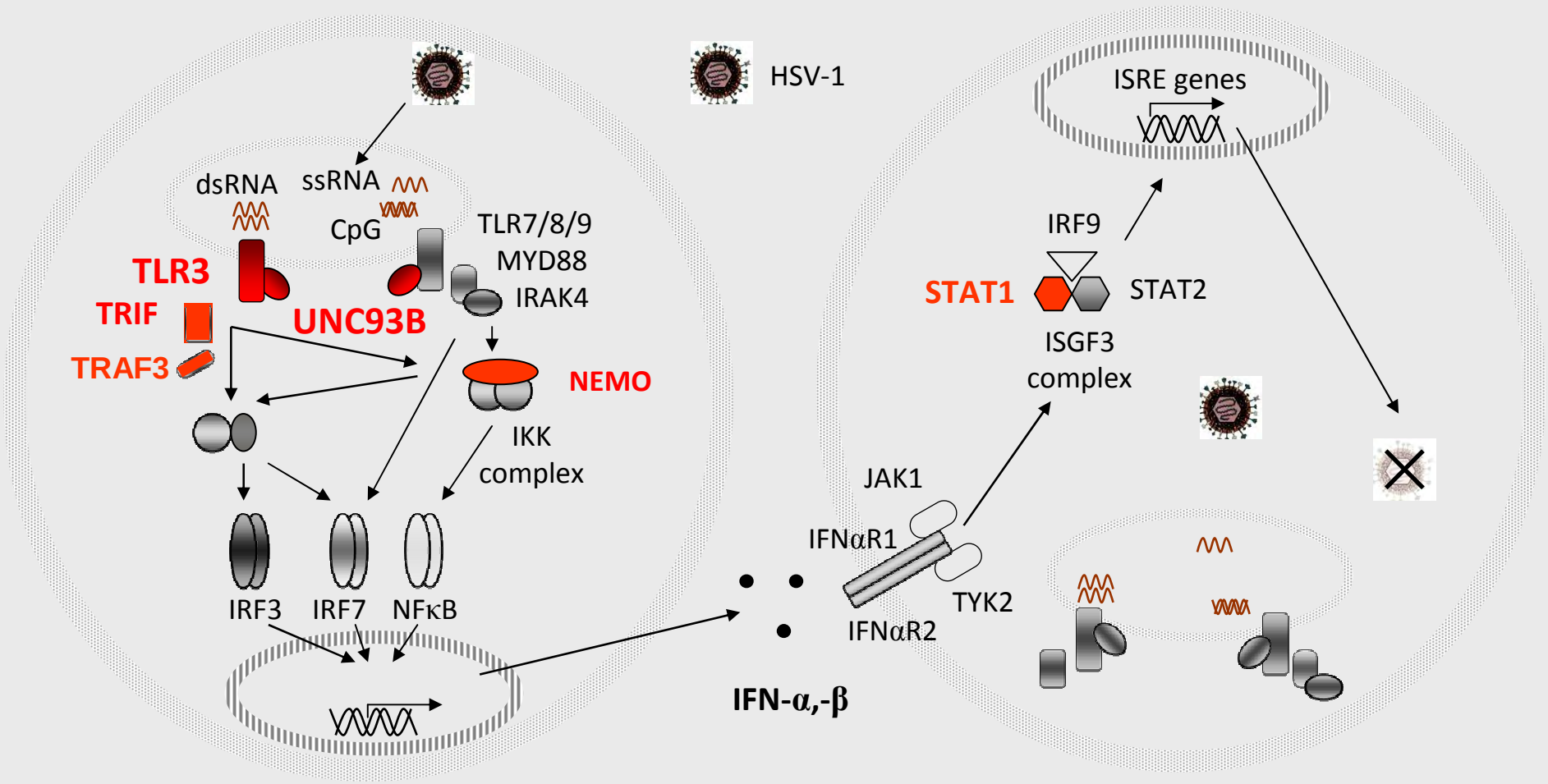
- **Heterozygous R118W mutation in TRAF3**

→ **dominant-negative effect and results in impaired TLR3-dependent induction of IFN and predisposition to HSE**

- **TRAF3 patient displays a broad cellular phenotype:**
  - **with impaired cellular responses to IFN TLR3-independent pathways,**
  - **CD40, LTβR and BAFFR, whose clinical consequences have so far remained silent.**



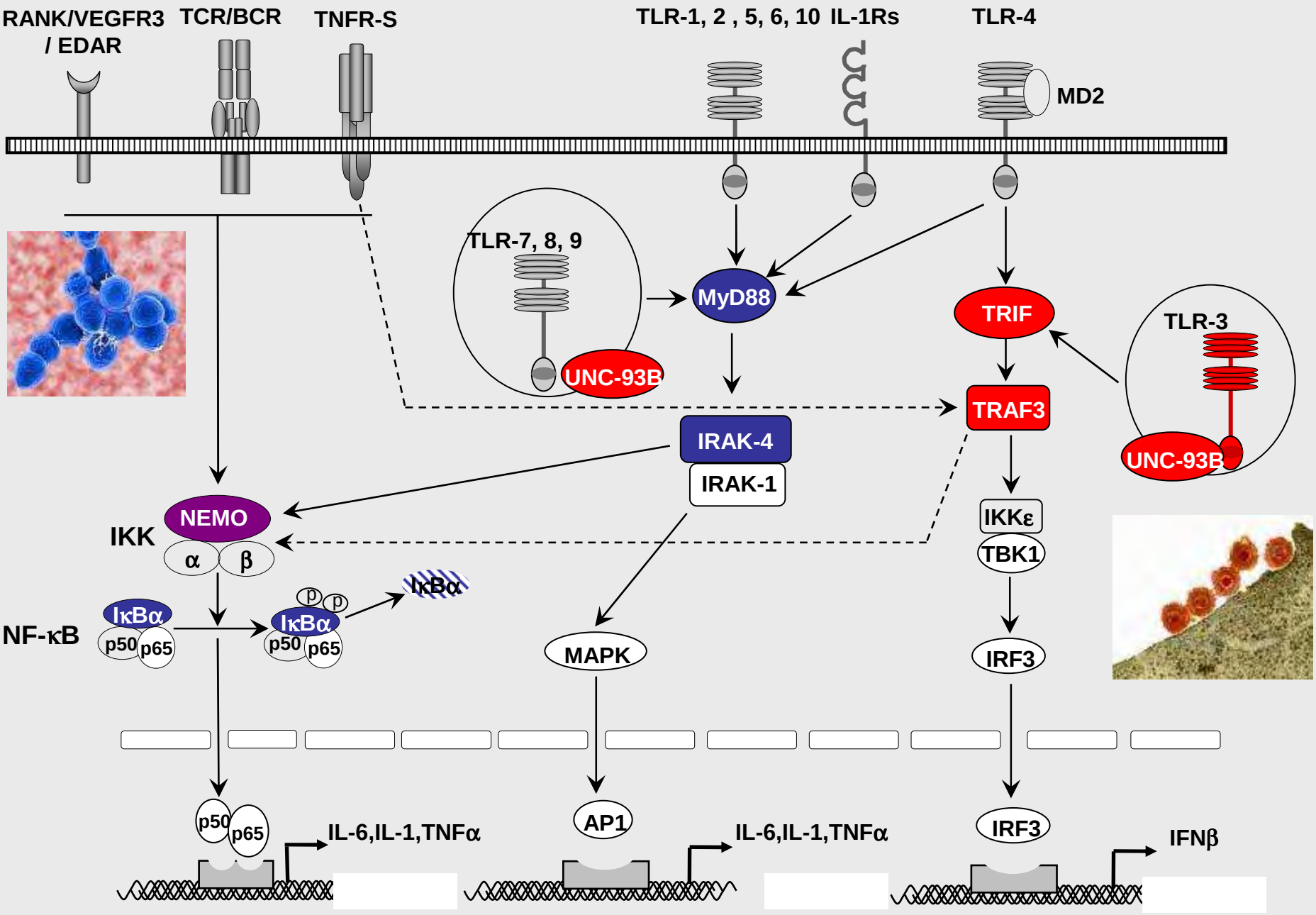
HSE-Specific Immunity



Production of type I IFNs

Response to type I IFNs

Genetic infectious susceptibility and TLR defects in human



Conclusions

- **The TIRs signaling pathway (IRAK-4/MyD88-depend pathway) is crucial to control invasive pyogenic bacterial infection during childhood, by induction and propagation inflammation, and secondary initiation of adaptive immunity.**

- **The integrity of the TLR3-IFN pathway is crucial to control HSV-1 primary infection in the CNS.**

- **The exploration of « idiopathic infections » could contribute to diagnose new primary immunodeficiencies and to a better understanding of immunity against pathogens.**

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HSE

TLR3

TRIF

TRAF3

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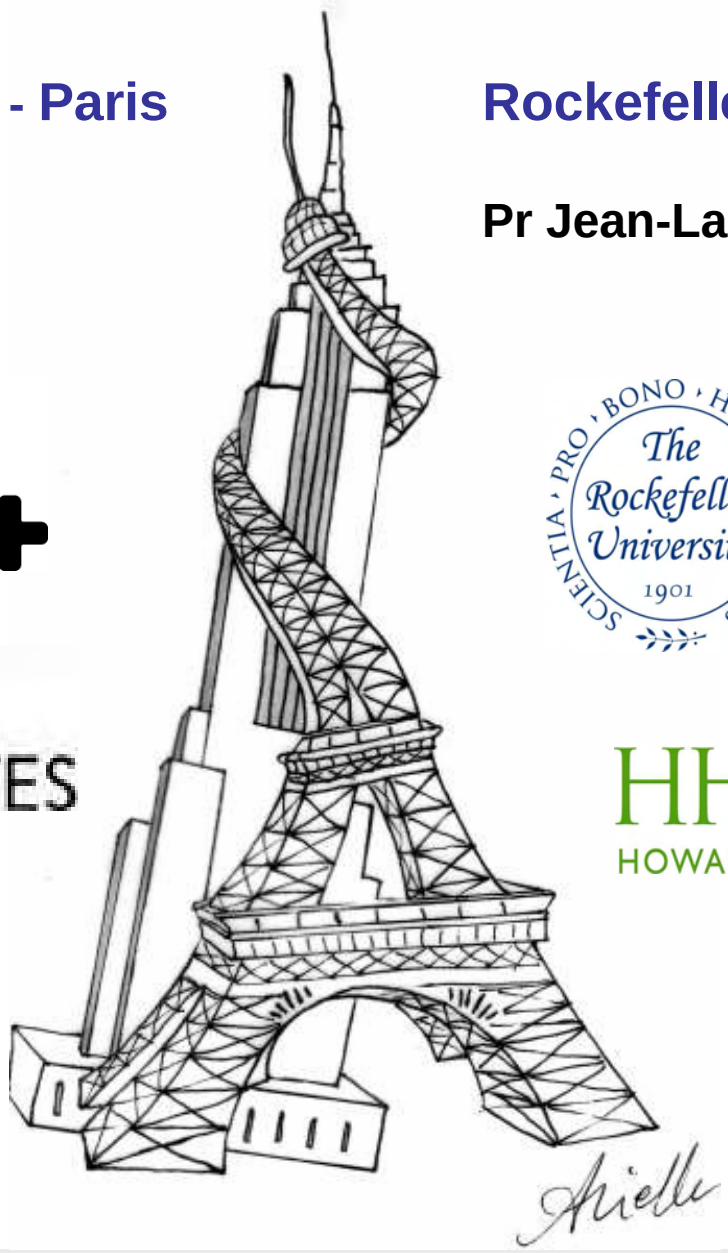

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Children and their families