

**An unusual presentation of a
human TLR pathway
deficiency: lessons**

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Prague 2004

Contents

- **Case**
- **Clinical phenotypes**
- **TLRs and signalling pathways**
- **Defects**

Case report - infections

Eldest of 3 siblings - non consanguinous

- **“septic pustules” at birth, IV antibiotics**
- **3 yrs - abscess over scapula**
- **3-6 years - more abscesses over shoulder, hip, knee, cheek**
- **6 yrs - septic arthritis**
- **7 yrs - four more abscesses**
- **10 yrs - Meningitis & septicaemia**

Case: Pathogens

Organisms

- *Pseudomonas aeruginosa*
- *Staph. aureas*
- *Strep. pyogenes*

All from separate sites at separate times

- Septic arthritis - *Strep. Pneumoniae*
- Meningitis/septicaemia - *Shigella sonnei*

Case: *Shigella sonnei* meningitis/septicaemia

- **Outbreak in local water supply**
- **Only individual to be systemically unwell**
- **D & V for 5 days before becoming**
- **Acutely unwell “septic shock”; in ITU**
- ***Shigella sonnei* cultured from stool, CSF, blood**

CH in ITU

CH

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Progress with time

- **1974** **Born**
- **1974 - 84** **11 episodes of serious sepsis**
- **1984** **Meningitis/ septicaemia**
- **1984 - 94** **3 episodes of sepsis: cellulitis, abscess, osteomyelitis**
- **1994 - 00** **2 abscesses, less severe**
- **2000 - 04** **No infections**

Acute phase - poor

- Neonatal abscess - Neutrophils $1.02 \times 10^9/l$
- Septic arthritis - no fever, ESR 7, WBC 7.6
- Abscess -15 mls pus, ESR 5, Neutrophils 3.1
- Meningitis/septicaemia - ESR 10, WBC 7.2
- Osteomyelitis (14yr) - Neutrophils 5.1, ESR 35, CRP 6 mg/l
- Cellulitis knee (16yr) -WBC 5.9, CRP 6, ESR 3

Antibody tests

<i>Serum immunoglobulin concentrations:</i>		
IgG **	16.7	6.0 – 13.0 g/l
IgA	1.1	0.8 – 3.0 g/l
IgM	1.9	0.4 – 2.5 g/l
IgE	400	<125 KU/l
Antibodies to:		
• tetanus,	0.06	>0.01 IU/ml
• diphtheria,	0.18	>0.1 IU/ml
• pneumococcal ags	>100	> 50 U/ml

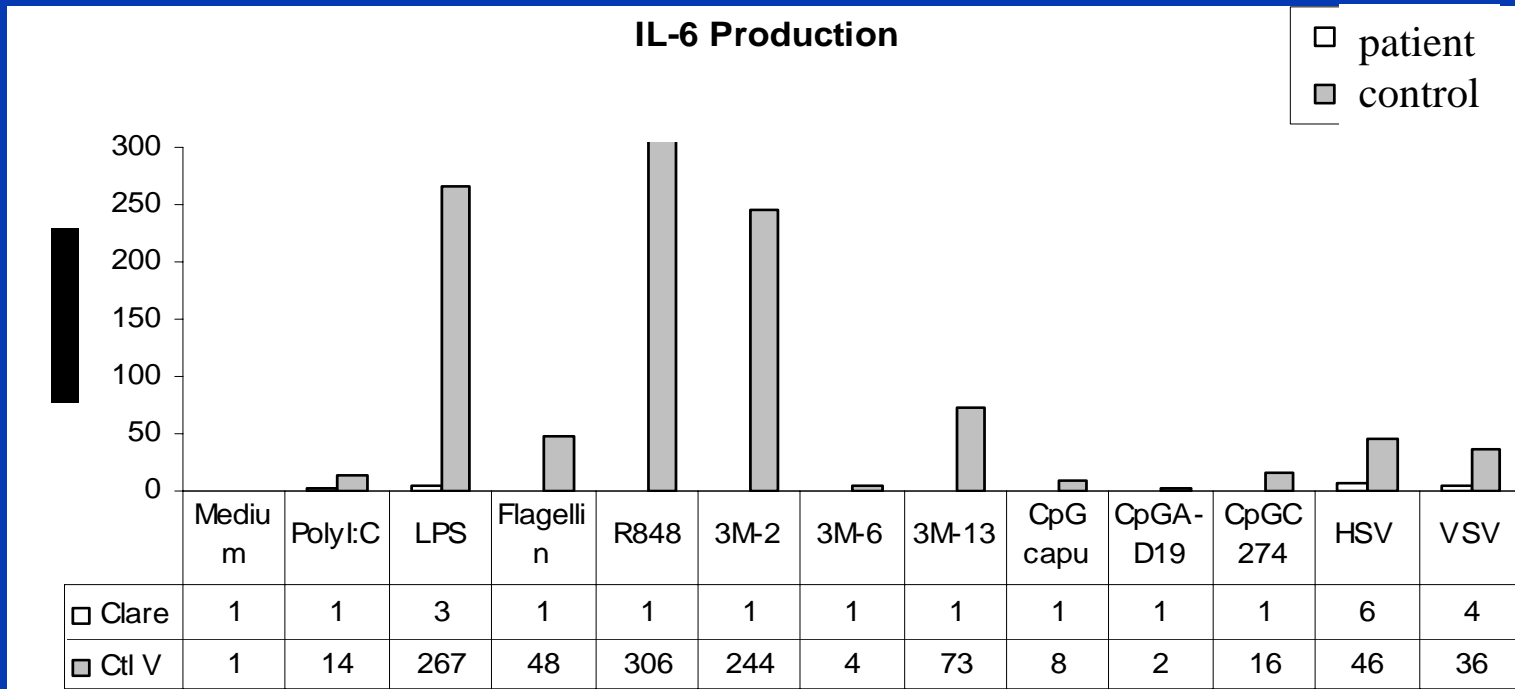
Neutrophil tests

<i>Nitroblue tetrazolium dye test:</i>		
Medium only	2%	8.7 +/- 7.3%
Phorbol myristate acid (PMA)	99%	99.2 +/- 0.9%
Lipopolysaccharide (LPS)	7%	>60%
<i>Chemotaxis to:</i>		
N-formalmethionyl peptides (FMLP)	12%	15.7 – 22.4%
Casein	7.0%	8.4 – 14.4%

Tested for IL-6 production

Casanova's lab - Horst von Bernuth

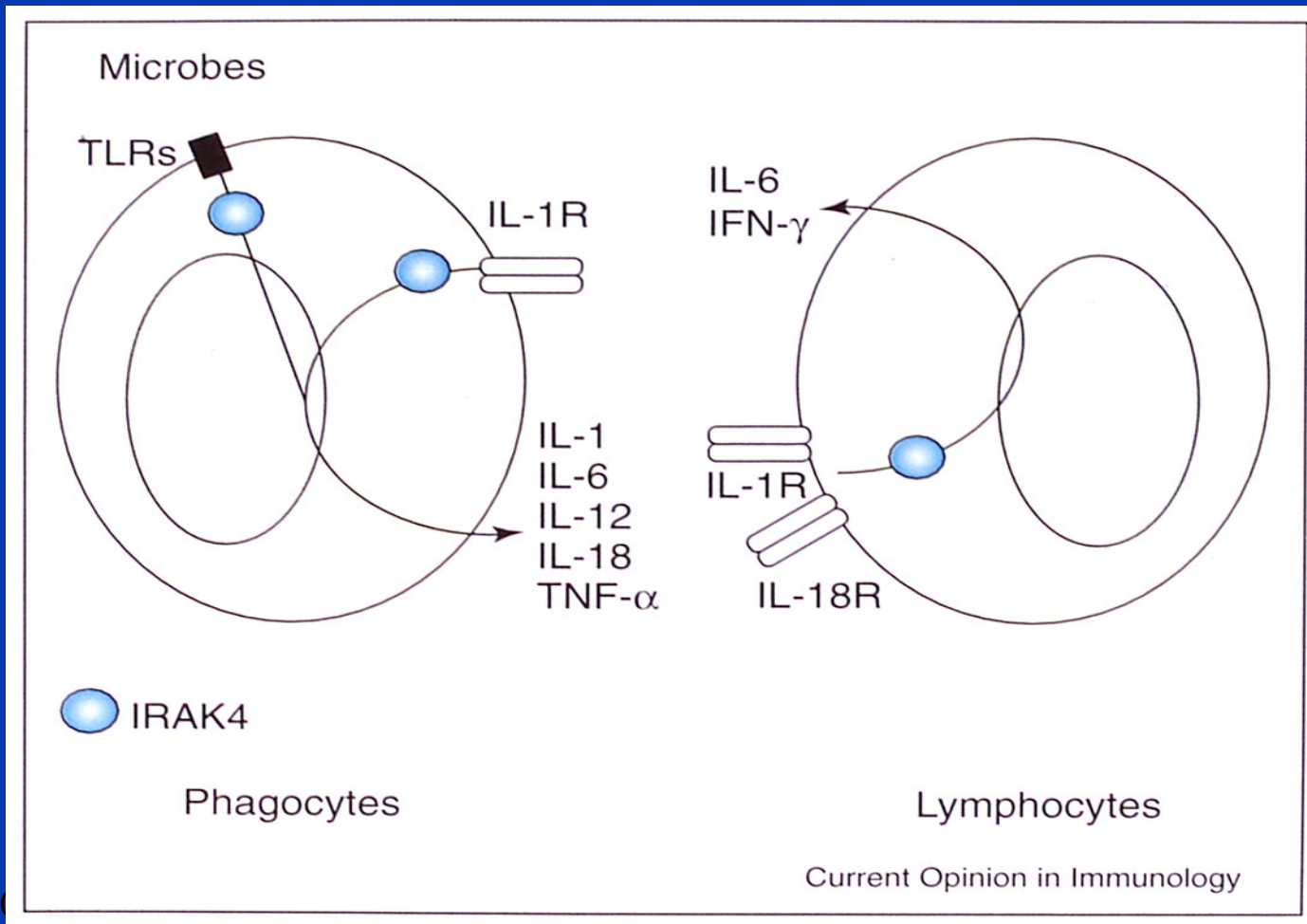
- **Whole blood**
- **Stimulation IL1 / SAC/ LPS / poly I:C stimulation**
- **No pro-inflammatory cytokines [IL-6]**
- **PMA - normal**
- **TNF - normal IL-10 secretion**



Impaired production of IL-6 in response to all the TLRs.

Impact of IRAK-4 deficiency

from Puel et al 2003



IRAK-4 deficiency

- Homozygous *IRAK4* mutation
- Mutation 877 C to T leading to a premature stop Q 293 X in kinase domain
- ? amorphic - *IRAK4* mRNA /protein by Northern and Western blots - *in progress*
- ? recessive, heterozygous members - *being tested*

Thank you

Oxford:

- Patient
- Physicians:
 - Christopher Conlon
 - Martin Moncrieff
 - Siraj Misbah
 - Richard Moxon
 - Simon Kroll
 - David Issacs
- Oxford Immunology Laboratory

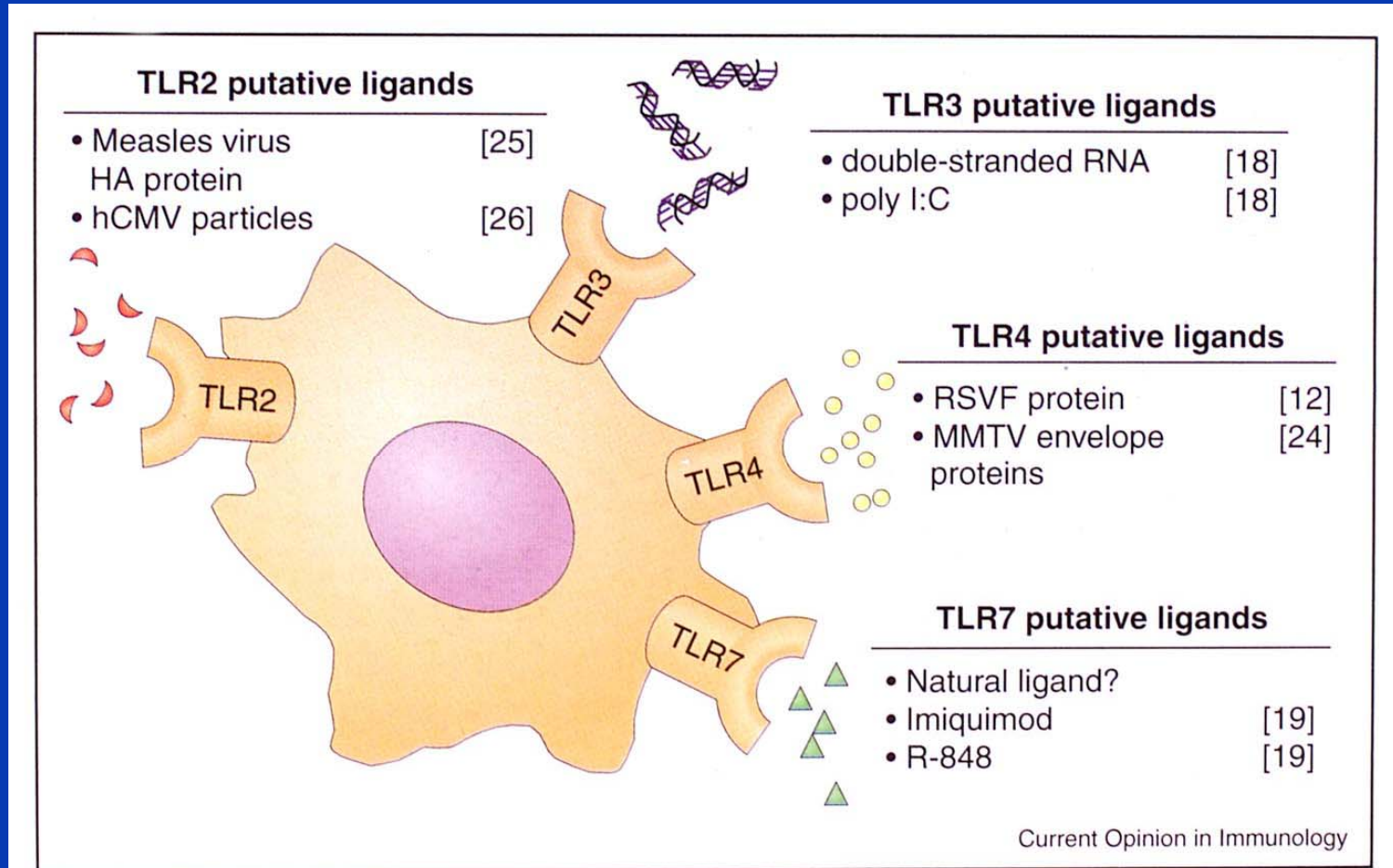
Paris:

- Jean-Laurent Casanova
- Anne Puel
- Horst von Bernuth
 - Tatiana Lawrence
 - Cheng-Lung Ku
 - Estelle Chang

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TLR recognising viral proteins & related molecules



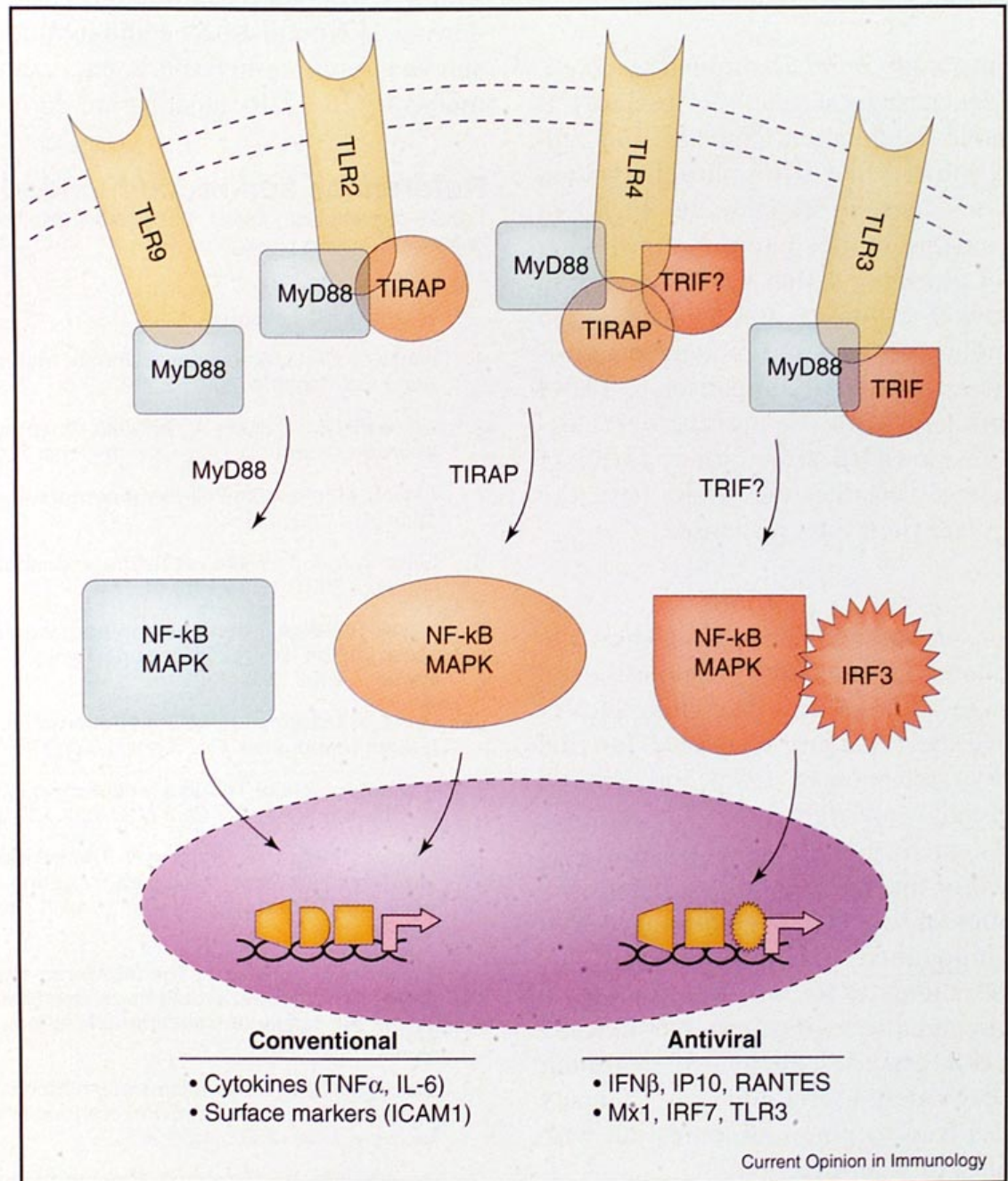
TLR signalling

in macrophages
resulting in

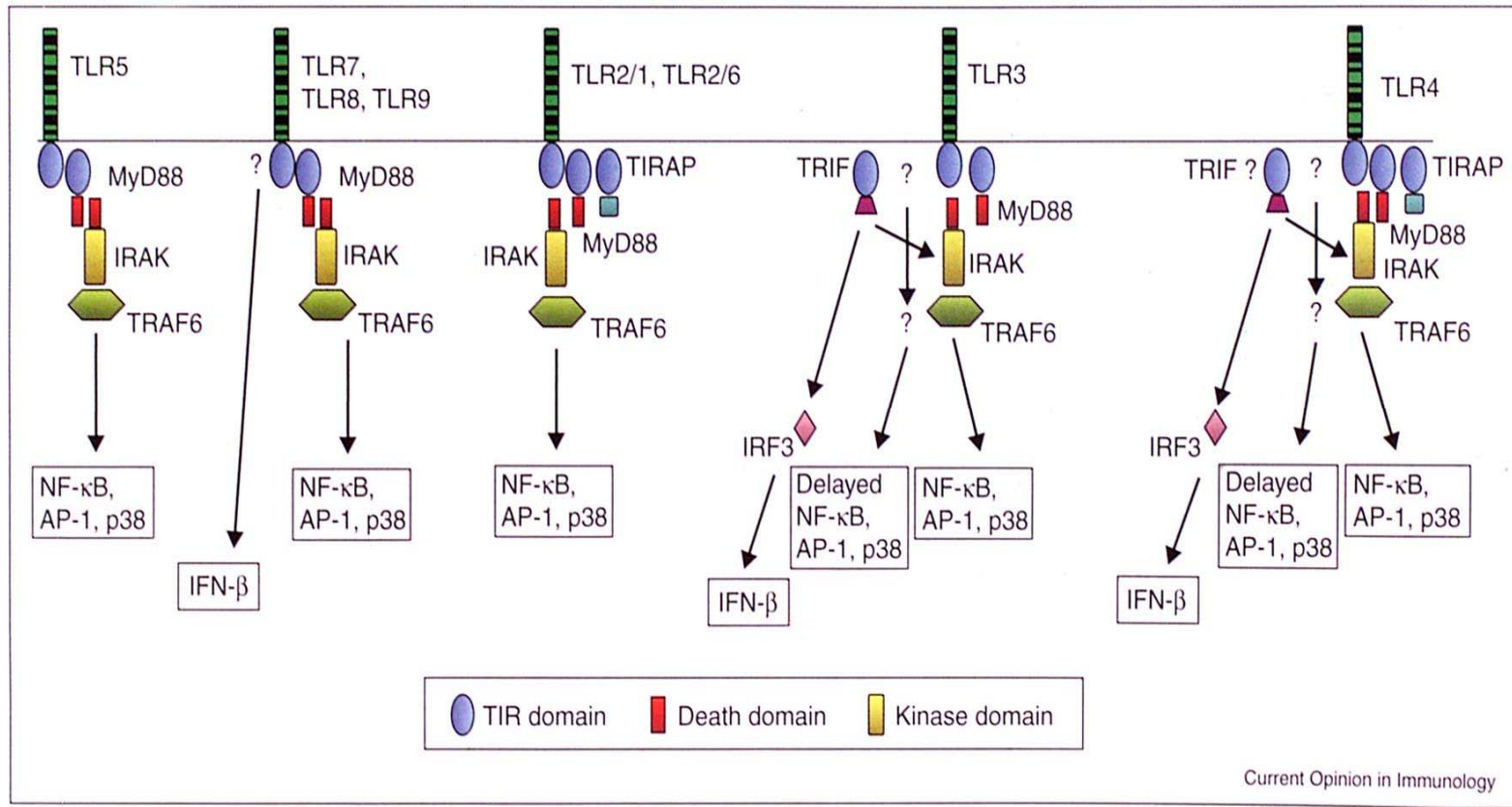
anti viral
gene
expression

from Vaidya & Cheng
2003

12/7/2006



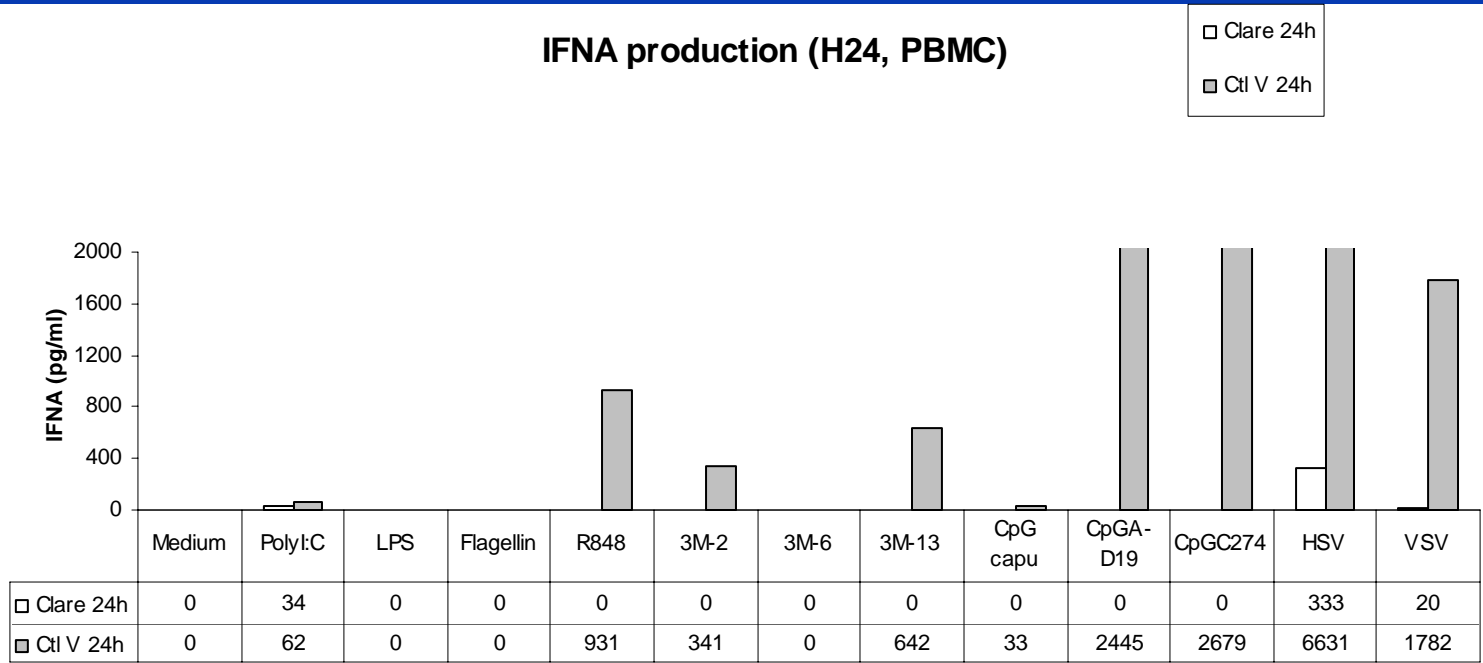
Recognition by mammalian (mice) TLR- pathways



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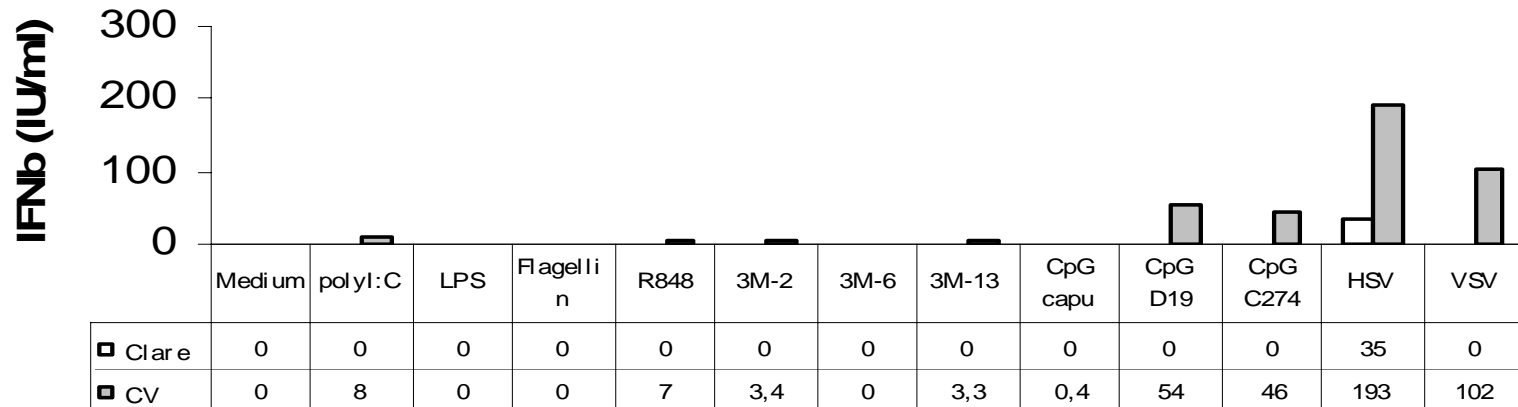
IFNA production (H24, PBMC)



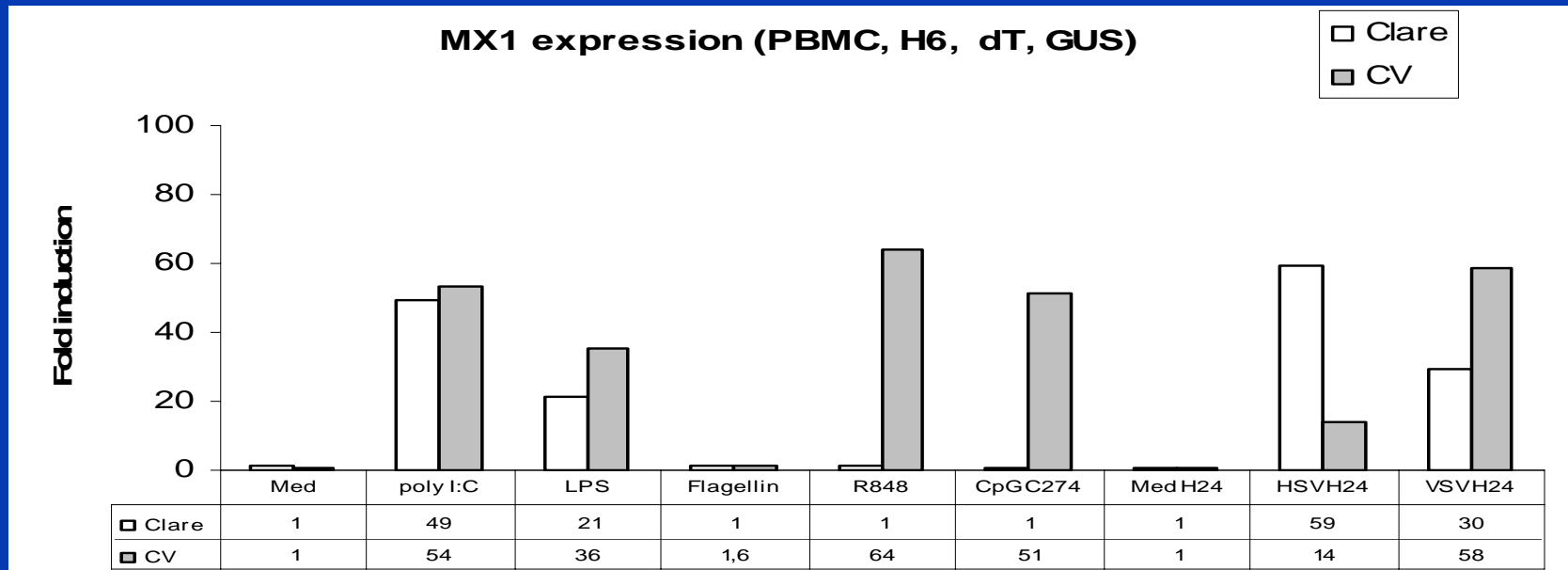
Impaired IFN α production in response to the ligands of **TLR7/8** (R848, 3M), **TLR9** (CpG) and two viruses (HSV, VSV), but a normal response to TLR3 (polyI:C) compared with control.

IFN β production (PBMC, H24)

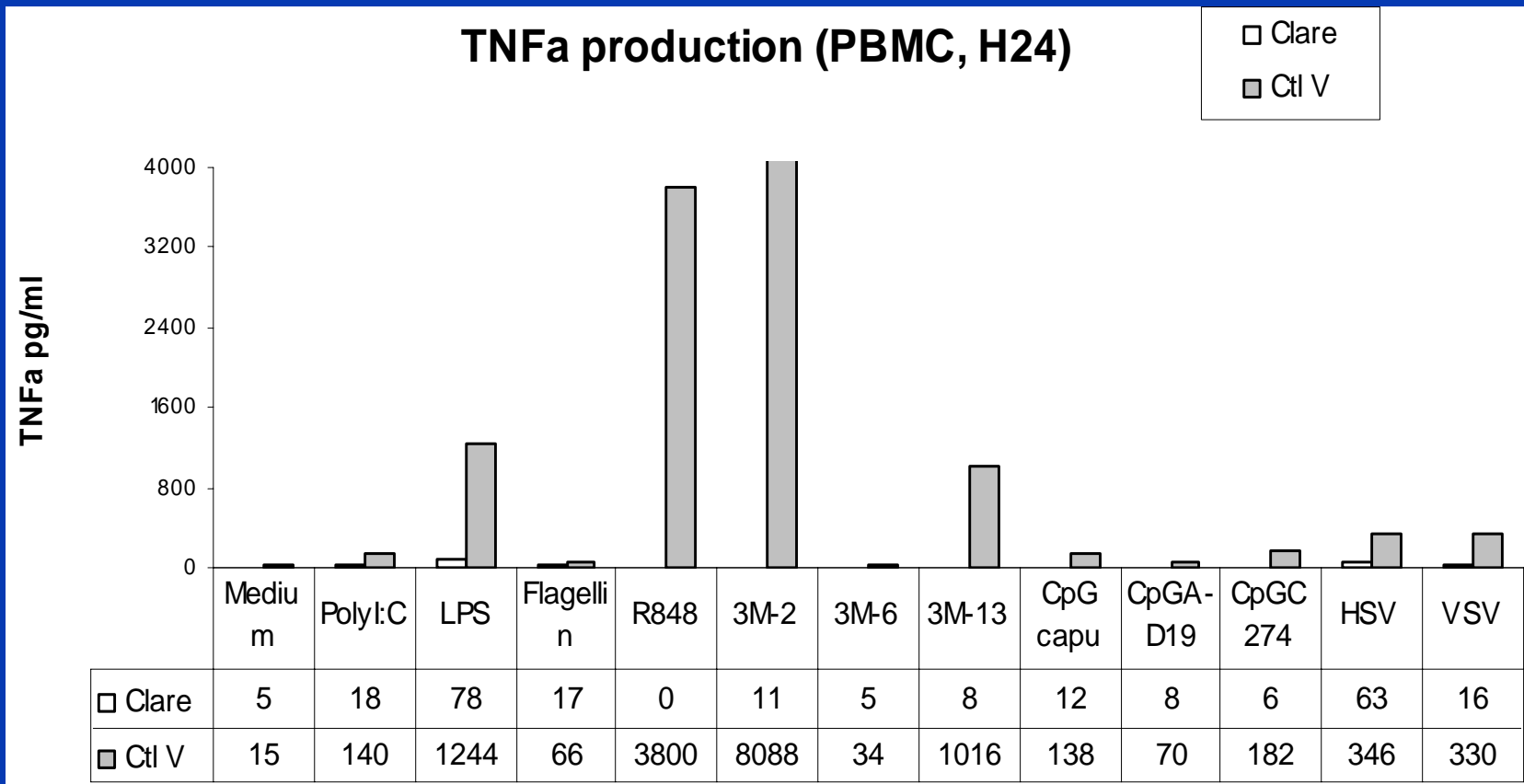
□ Clare
■ CV



Impaired or diminished production of IFN β in response to all the TLRs and tested viruses.



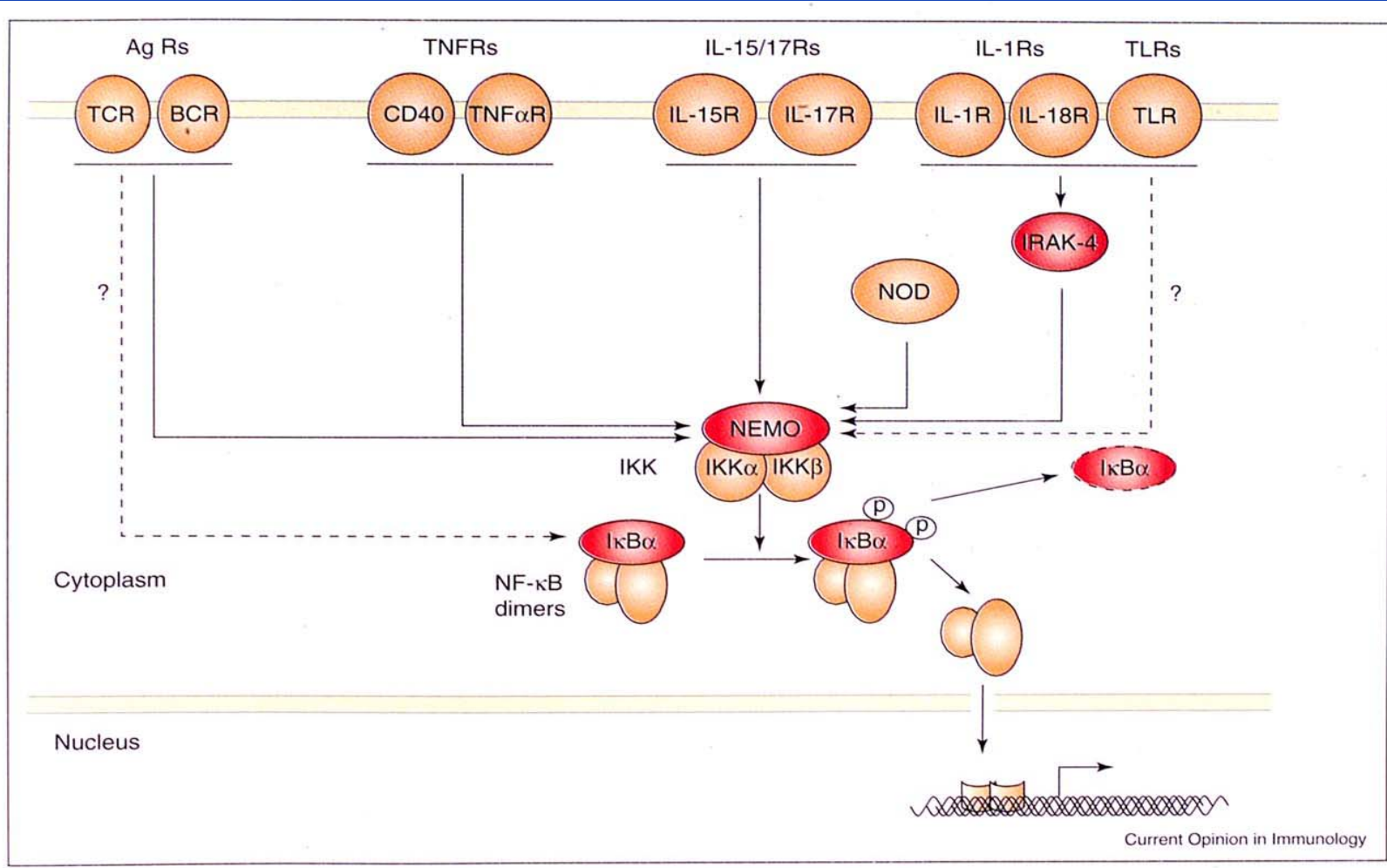
Type I IFN induced MX1 gene expression:
Normal to TLR3(polyI:C), TLR4(LPS) and
HSV, but the response to TLR7/8 & TLR9 is
abolished, the response to VZV is diminished.



Impaired TNFa production in response to all the TLRs tested

Relationship of surface receptors & NF κ B

from Puel et al 2003



From Puel et al 2003

