# Innate Immunity I

What is it and what does it do?

Lindsay Nicholson
Advanced Immunology L1
l.nicholson@bristol.ac.uk

- Lecture 1
  - Defining Innate Immunity
  - Recognition and effector mechanisms (I)
- Lecture 2
  - Recognition and effector mechanisms (II)
  - Integration of innate and adaptive immune responses

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Autoimmune Inflammation Research

- Our goals
- Our research
- How we work
- For lab members
- For students
- For fun
- Questions & answers
- Copyright statement

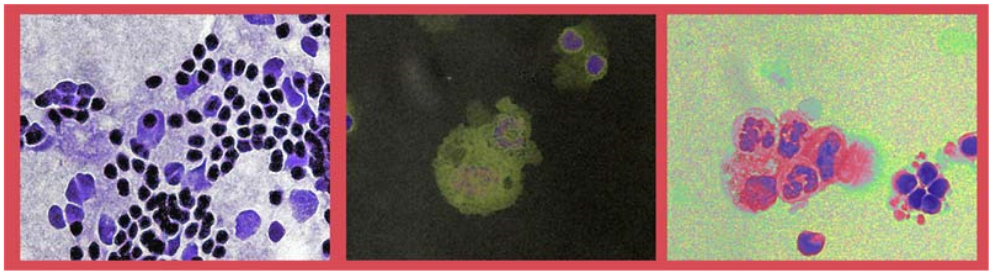
## Welcome to Autoimmune Inflammation Research

This is the home page for the Nicholson Lab

Recent Advances

### Featured this month

How to write a paper
Why do we use experimental models to study human disease?
Immune recognition



http://www.bris.ac.uk/cellmolmed/air

# Innate Immunity 1 – Key Concepts

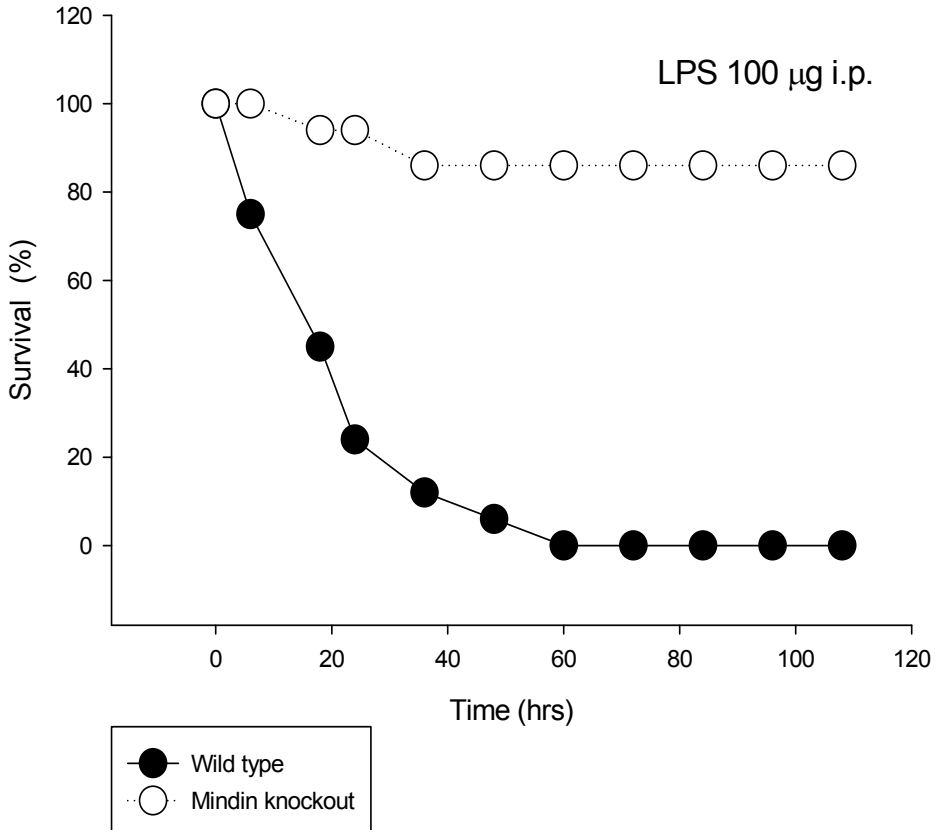
- Hard wired specificity
- Multiple molecular mechanisms; common effector pathways
- Tightly integrated with adaptive immune responses

# Endotoxin

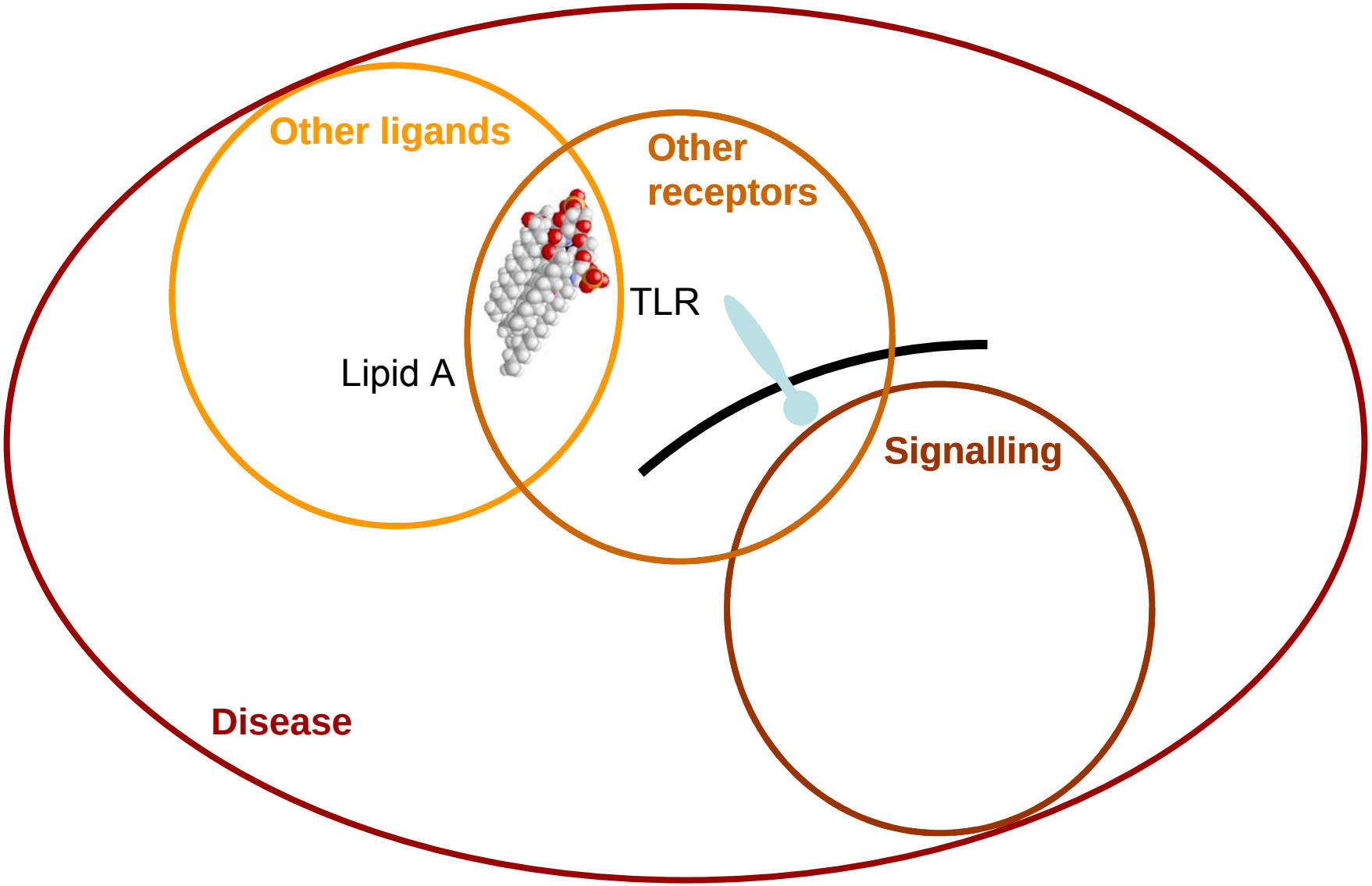
- 1890 **Richard Pfeiffer** described a heat stable intrinsic poison derived from the cholera vibrio later called endotoxin
- Endotoxin is identified as lipopolysaccharide, (and later as lipid A) a component of the gram negative bacterial cell wall
- Administration of small amounts leads to fever, shock and death …
- 1960s …except in C3H/HeJ mice which can be filled up with endotoxin and still remain happy. They are, however, very susceptible to bacterial infection.
- 1997 **Medzhitov and Janeway** identify TLR4 as mediating an activating immune signal
- 1998 **Bruce Beutler** uses a positional cloning strategy to identify the LPS receptor as TLR4

# Endotoxin activates the Innate Immune Response

adapted from Nature Imm. 5: 88-97 (2004)



# A simple paradigm for innate immunity



# How do we define the Innate Immune System

- An ancient set of immune responses, predating bony fish
- Those parts of the immune system that are not adaptive
- A collection of specific cells and effector mechanisms

# Each definition has problems

- The innate immune system continues to co-evolve with the adaptive immune system
- The adaptive and innate immune responses are an integrated whole
- New cells/cytokines are discovered on a regular basis

# Janeway, Travers, Walport and Shlomchik

- “Defense mechanisms that do not require a prolonged period of induction because they do not rely on the clonal expansion of antigen-specific lymphocytes are the mechanisms of innate immunity"

# Summary 1

- The Innate Immune system is an integrated part of the immune response characterised by mechanisms and molecules that respond rapidly to infection and adapt on an evolutionary timescale, rather than over a single lifespan.

# What’s the trigger ?

- Foreign Pattern Recognition
- Danger
- Missing Self

# Foreign Pattern Recognition

- Charlie Janeway 1989 Cold Spring Harb. Symp. Quant. Biol. 54:1-13

  "The immune system has evolved specifically to recognize and respond to infectious microorganisms, and that this involves recognition not only of specific antigenic determinants, but also of certain characteristics or patterns common on infectious agents but absent from the host"
- Called PAMPs (pathogen associated molecular patterns) or MAMPs (microbe associated molecular patterns)
- This implies co-evolution

- Medzhitov, Preston-Hurlburt & Janeway

  Nature 388:394 1997
  TLR-4 signals adaptive immune activation

# Danger

- Polly Matzinger
  Ann. Rev. Immunol. 12:991-1045 1994

  Cells may die in ways that are associated with normal function (apoptosis: good death) or with trauma (necrosis: bad death)

- Shi and Rock
  Nature 425:516 2003
  Identified crystals of uric acid as an endogenous adjuvant released by stressed cells.

- HSPs, fragments of extracellular matrix.
  Beware LPS.

- DAMPs (Danger associated molecular patterns)
  May use common PRR (pattern recognition receptors)
  e.g. TLR-2 (Immunity **27**:321 – 333 2007)

# Extracellular Pattern Recognition

- Toll-like receptors (e.g. TLR2, TLR4 etc)
  - TLR4 works in combination with LPS binding protein, CD14 and MD2 binds the lipid A (endotoxin) component of LPS.
  - TLR9 works through intracellular sensing of unmethylated CpGs in monocytes, dendritic cells and lymphocytes
- Mannan-binding lectin (MBL)
  Binds mannose on pathogen surface and triggers complement
- Dectin-1
  C-type lectin
  Innate immune response to fungal pathogens
- Invariant chain TCRs ($\alpha\beta$ and $\gamma\delta$)
  Found on NKT-cells and use non-classical MHC molecules which, recognise a range of targets including lipid antigens found eg on Salmonella, mycobacteria

# Intracellular Pattern Recognition

- Toll-like receptor 9 (TLR9)
  Intracellular sensing of unmethylated CpGs in monocytes, dendritic cells and lymphocytes

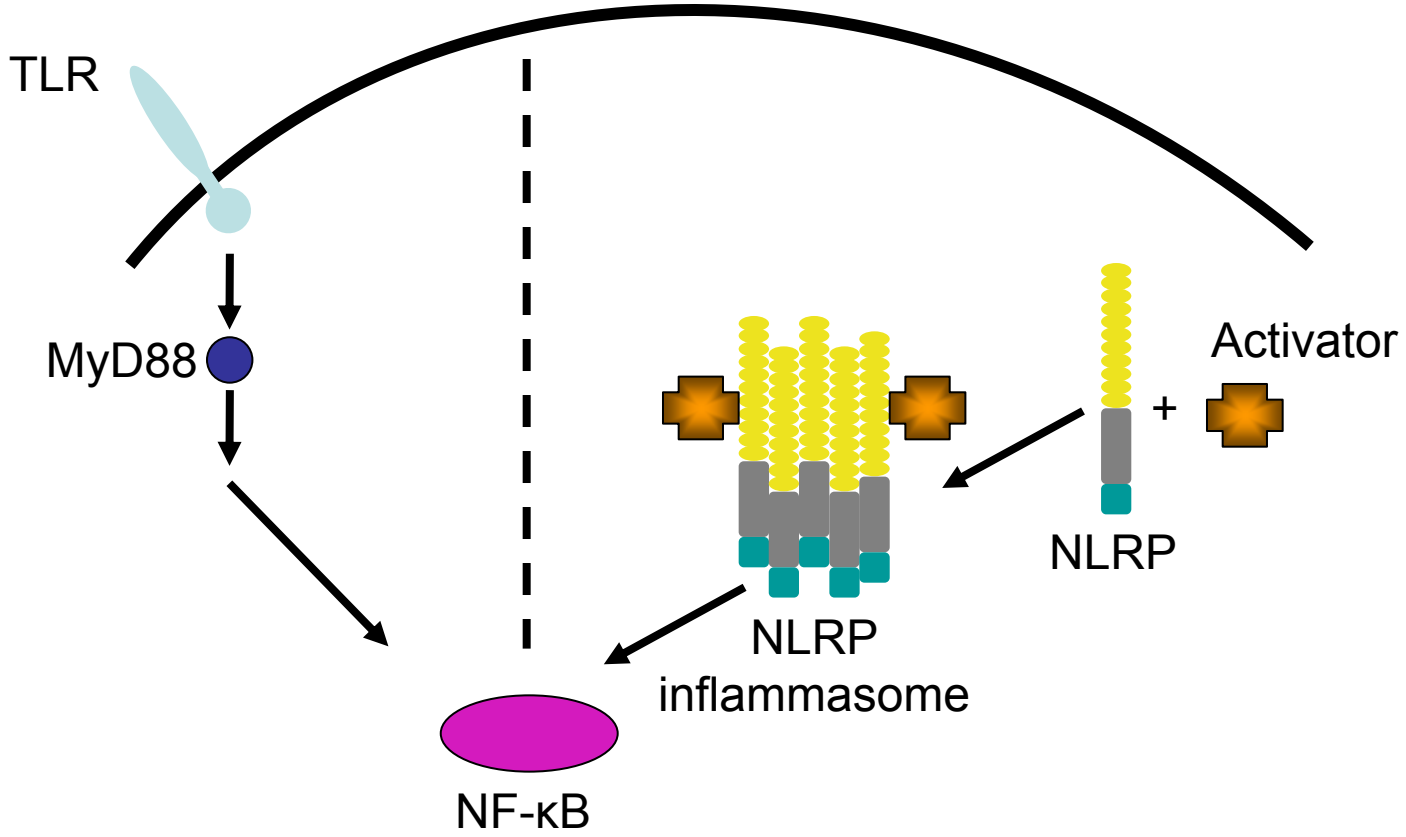
- NOD2 (CARD15)

  Muramyl dipeptide binding intracellular protein, signalling via NF-κb
  Mutations increase the risk of Crohn's disease and other granulomatous conditions

- NLRP1 (Nalp1) NLR family, pyrin domain containing 1
  Intracellular sensing of anthrax lethal toxin (LT); caspase-1 activation of IL-1β etc.

- RIG-I
  Intracellular sensing of RNA viruses e.g. Hepatitis C.
  Induces type I interferons

# Extracellular and intracellular pattern sensing




Extracellular sensing

Intracellular sensing

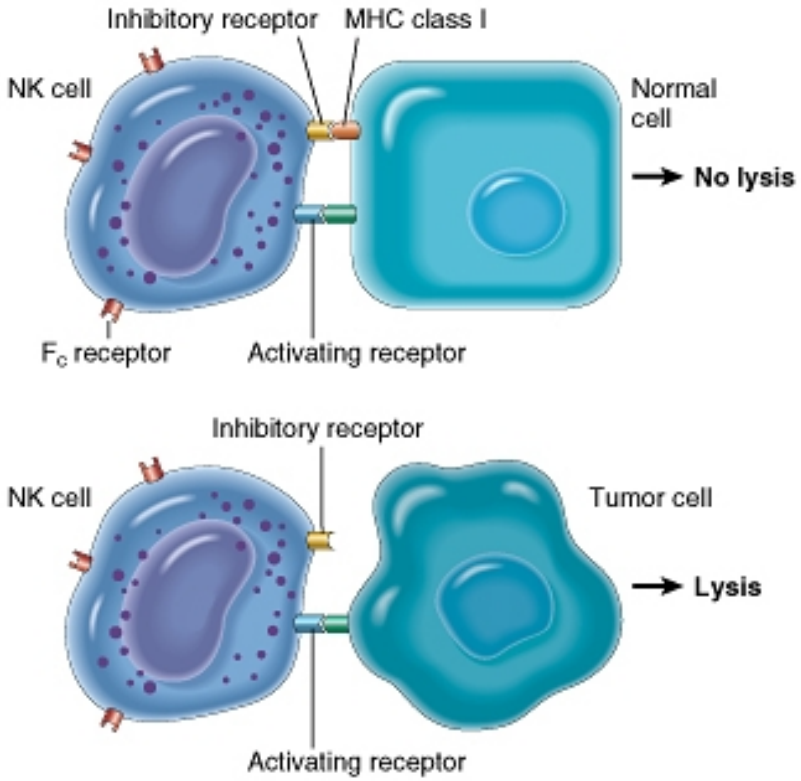
# Missing Self

- Viruses target MHC I molecules
  - Adenovirus
  - Herpes viruses
- Tumours downregulate MHC I molecules
  - Failure of immunosurveillance

# Missing Self

- NK cells
- Large lymphocytes that kill tumours (1973)
- NK cells in mice (1977)
- Require constitutive inhibition (1992)
- Mouse and humans use different families of inhibitory molecules

# Missing Self



# Missing Self

- NK cells
- Inhibited from killing by the presence of MHC molecules interacting with KIRs
- When pathogens or transformation interfere with the expression of MHC, NK cells kill the deficient cell
- They also release cytokines which stimulate other parts of the immune response

# Summary 2: Activating the Innate Immune System

- What does the innate response look for?
  - Danger
  - Foreign patterns
  - Missing self
- The end result is an **adjuvant** effect
- It takes more than just **antigen specificity** to get a productive immune response going

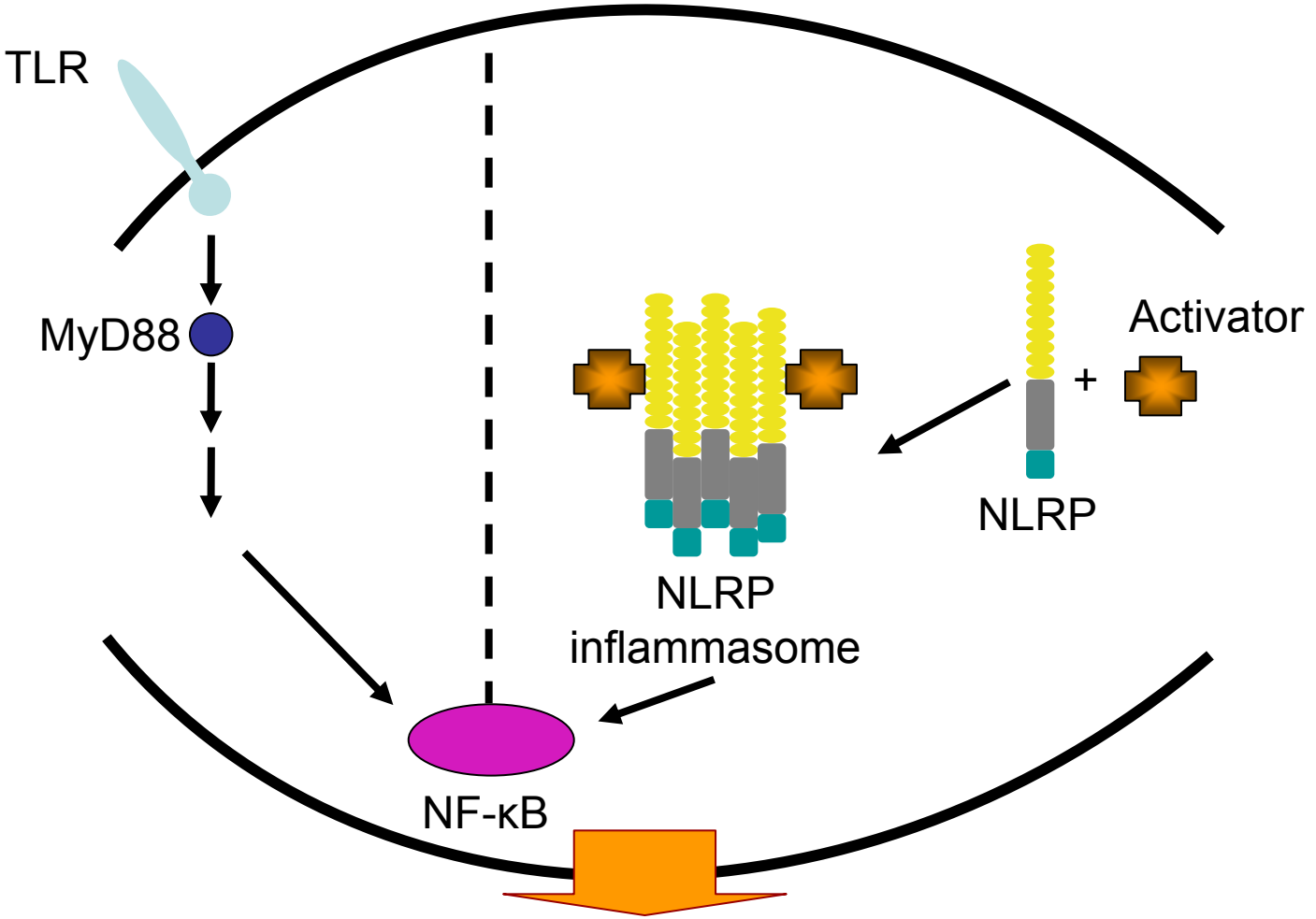
# What is an adjuvant?

**Paul Ehrlich**: A heat labile component of blood that complements the cellular immune response

**Charlie Janeway**:  Freund's adjuvant - The immunologists 'dirty little secret'

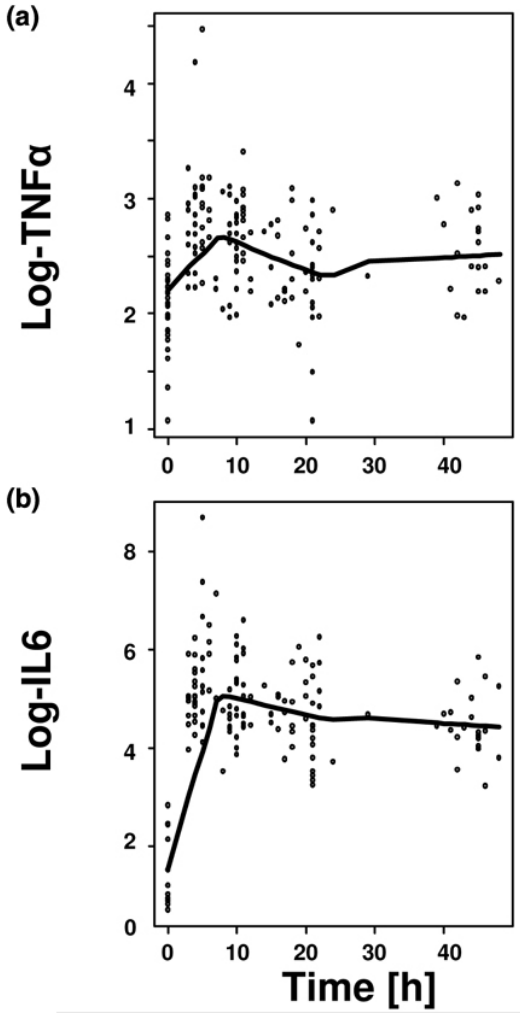
Lowers the threshold for productive immune activation

# Cell autonomous sensing leading to systemic activation




**TNFα IL-6 IL-1β**

# Systemic inflammatory response to stress




37 non-diabetic patients scheduled for cardiac surgery with cardiopulmonary bypass

*Critical Care* 2008, **12:**R157doi:10.1186/cc7152

# Cells associated with the innate immune response

- Macrophages
- Neutrophils
- NK cells
- NKT cells
- Invariant $\alpha\beta$ T cells
- $\gamma\delta$ T cells

# Summary 3

- Innate immune activation uses a number of different strategies:
  Foreign pattern recognition; Recognition of danger; Absent self.
- These processes are mediated by a number of different specific receptor ligand interactions (some known and some as yet unknown)
- They commonly lead to the expression of a large number of proteins induced by the NF-kB transcription factor family
- Many effectors act as adjuvants of the adaptive immune response

# Effector Mechanisms of the Innate Immune Response

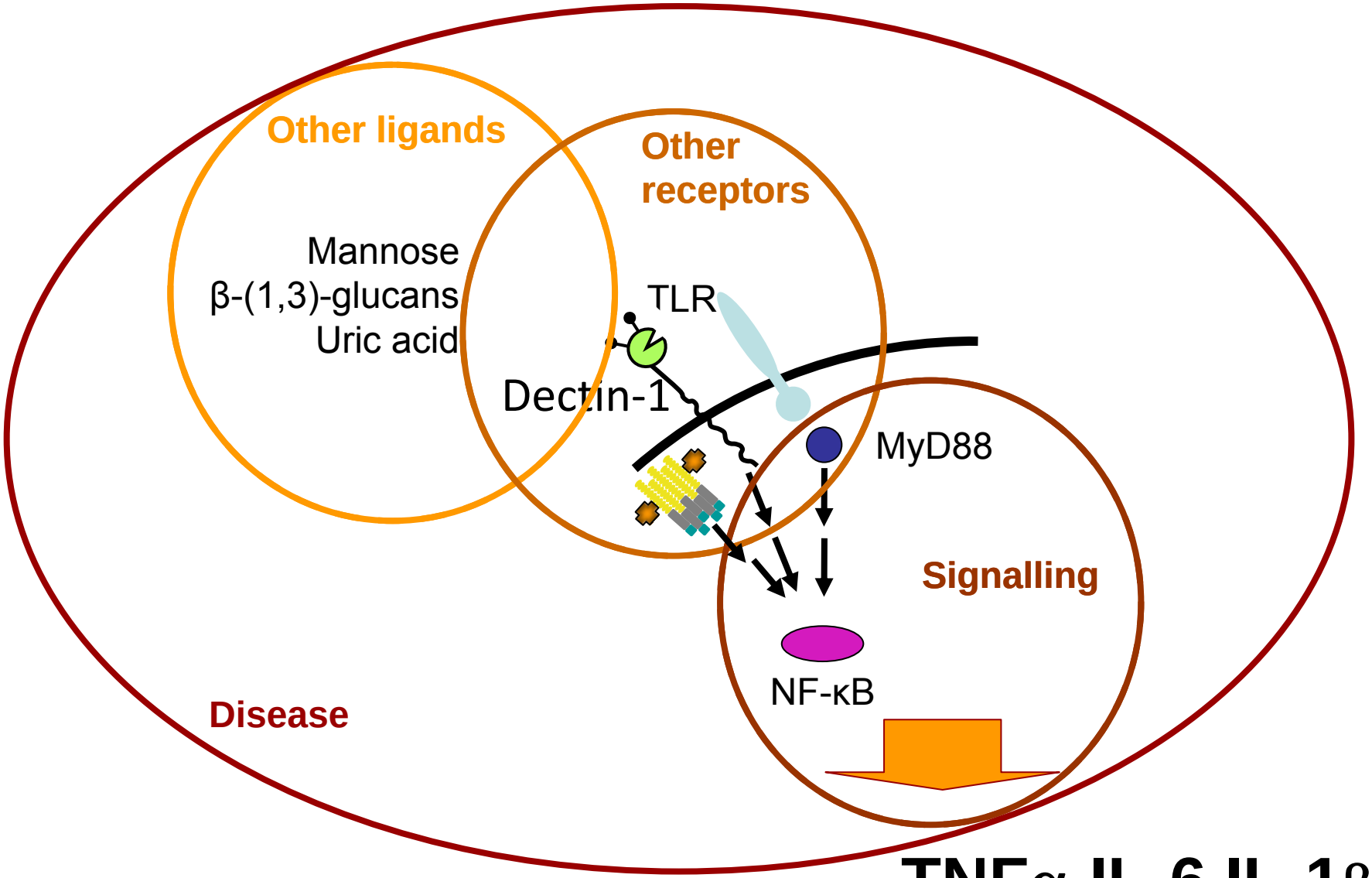
| Group | Examples |
|---|---|
| Cytokines | IL-1, IL-6, TNFα, IL-12, IL-15, IL-18, MIF, IL-10, type I interferons |
| Chemokines | IL-8, CCL2 (MCP-1), CCL3 (MIP-1a), CCL4 (MIP-1b), CCL7 (MCP-3) |
| Lipid mediators | PAF, eicosanoids (prostaglandins, leukotrienes, thromboxane, etc), tissue factor |
| Oxygen radicals | Superoxide and hydroxyl radical, nitric oxide |
| Killer cell products | Perforin, caspase activators, FasL. |

**This is inflammation**

# Are defects in innate immunity important?

| **Deficiency** | **Infection** |
| --- | --- |
| Complement C3 (direct or indirect) | Pyogenic bacteria. H. influenzae and S. pneumoniae |
| Complement C5-C9 | Neisseria species |
| Complement mannan-binding lectin | Pyogenic bacteria in childhood |
| NK cells | Herpes viral infections |
| IRAK-4 (Toll and IL-1 signalling) | Pyogenic bacteria |

# Interfacing with the environment




**TNFα IL-6 IL-1β**

# Summary 4

- Innate immune responses entrain powerful inflammatory processes with the potential to prevent the spread of infection
- The innate immune system is adaptable over evolutionary time scales, though not individual lifetimes.
- Deficiencies relate to specific micro-organisms, emphasising the process of co-evolution
- They integrate adaptive immune responses into the ongoing process by activating professional antigen presenting cells (dendritic cells and macrophages), thus providing an adjuvant effect

# Innate Immunity 1 – Key Concepts

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- Tightly integrated with adaptive immune responses

**Further reading**

Rock, K. L., Hearn, A., Chen, C. J., and Shi, Y.
Natural endogenous adjuvants.
Springer Semin. Immunopathol. 26 (2005) 231-246.