Innate Immunity II

Integration

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- Lecture 1
  - Defining Innate Immunity
  - Recognition and effector mechanisms (I)

- Lecture 2
  - Recognition and effector mechanisms (II)
  - Integration of innate and adaptive immune responses

Lethal Toxin

- Dimeric toxin from anthrax delivering a proteolytic subunit to the cytosol
- C57BL/6 macrophages resistant, 129/S1 macrophages sensitive
- Single dominant locus on Ch11
- Currently 5 different alleles in 18 mouse strains (2 resistant; 3 susceptible)
- Protein is Nalp1b
- Caspase 1 deficient cells are protected

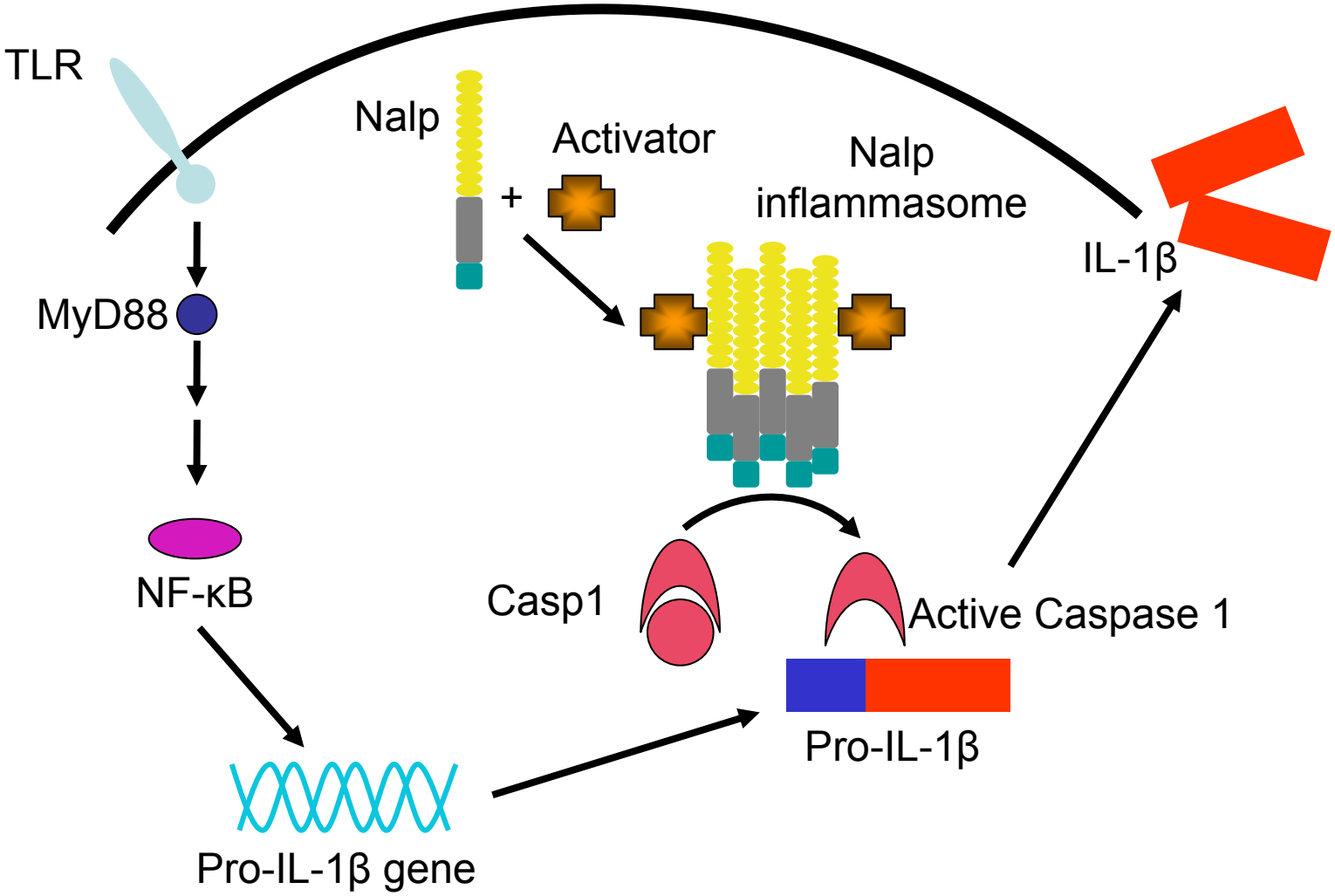
Innate Immunity 2 – Key Concepts

- Extracellular and intracellular sensing
- Pathways to NF-κB and the inflammasome
- Monocyte recruitment
- Macrophage differentiation
- Innate immune activation regulates the progress of an immune response
- Adaptive immune response regulates the nature of the innate immune response

An introduction to the inflammasome

- Inflammation involves the co-ordinated upregulation of a number of genes
- These are co-ordinated by specific transcription factors, particularly NF-κB
- Multiple different ‘danger’ signals are co-ordinated to a common final pathway
- This common final pathway has been called the inflammasome

Activation of the inflammasome



Summary 1

- Multiple activators for the inflammasome through Nalp1 and Nalp3
- Common activation pathway leading to IL-1β secretion
- Genetic defects lead to inherited inflammatory conditions
- Treatment with anti-IL1R is effective

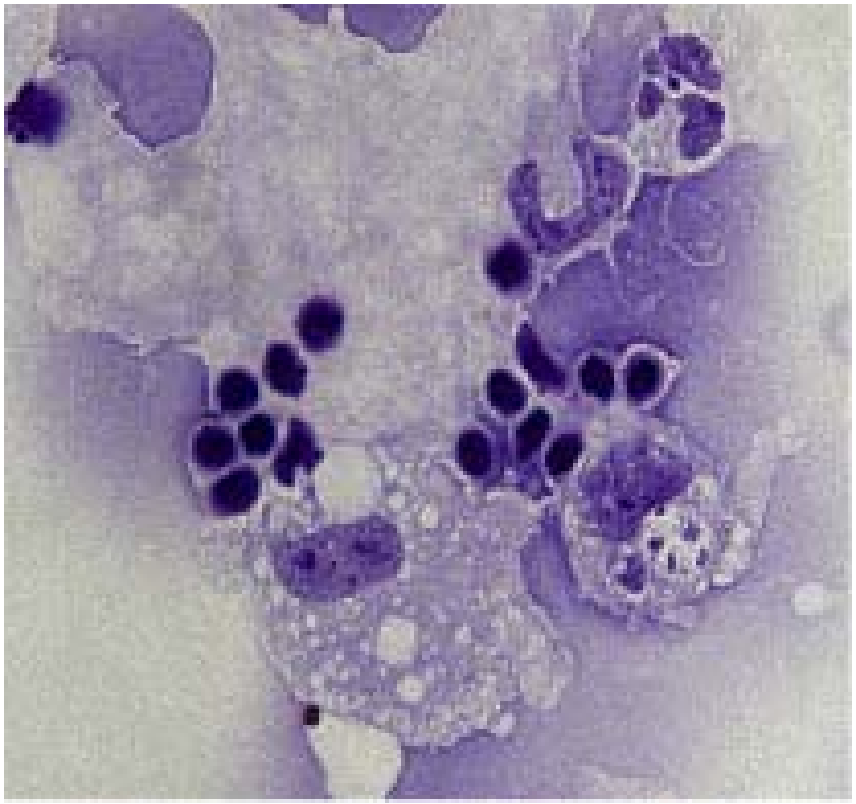
Integration of the Innate Immune Response

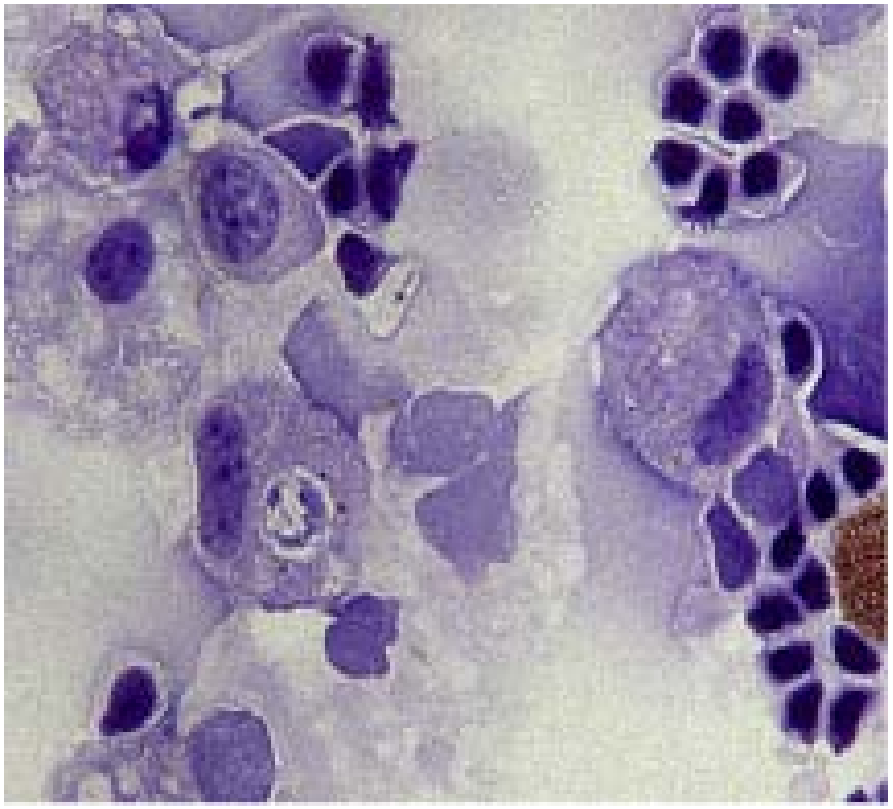
- Extracellular and Cellular Mechanisms

- Extracellular signals
- PAMPs/MAMPs
- Danger
- Complement, proteolysis of extra-cellular matrix, acting as endogenous adjuvants

- Cellular responses
- Receptor dependent recruitment of neutrophils and macrophages in early inflammation
- MyD88 adapter protein key signalling molecule
- Leads to NF-κB driven gene transcription

Inflammation in vivo is a complex environment





Emma Kerr

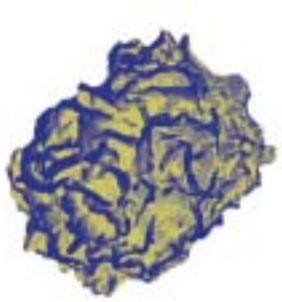
Effector Mechanisms of the Innate Immune Response

Group	**Examples**
Cytokines	IL-1, **IL-6**, TNFα, IL-12, IL-15, IL-18, MIF, IL-10
Chemokines	IL-8, MIP-1a, MIP-1b, MCP-1, 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.

Summary 2

- Innate immune system receptors on leukocytes process information from the environment
- They produce effector molecules that orchestrate the ongoing immune response

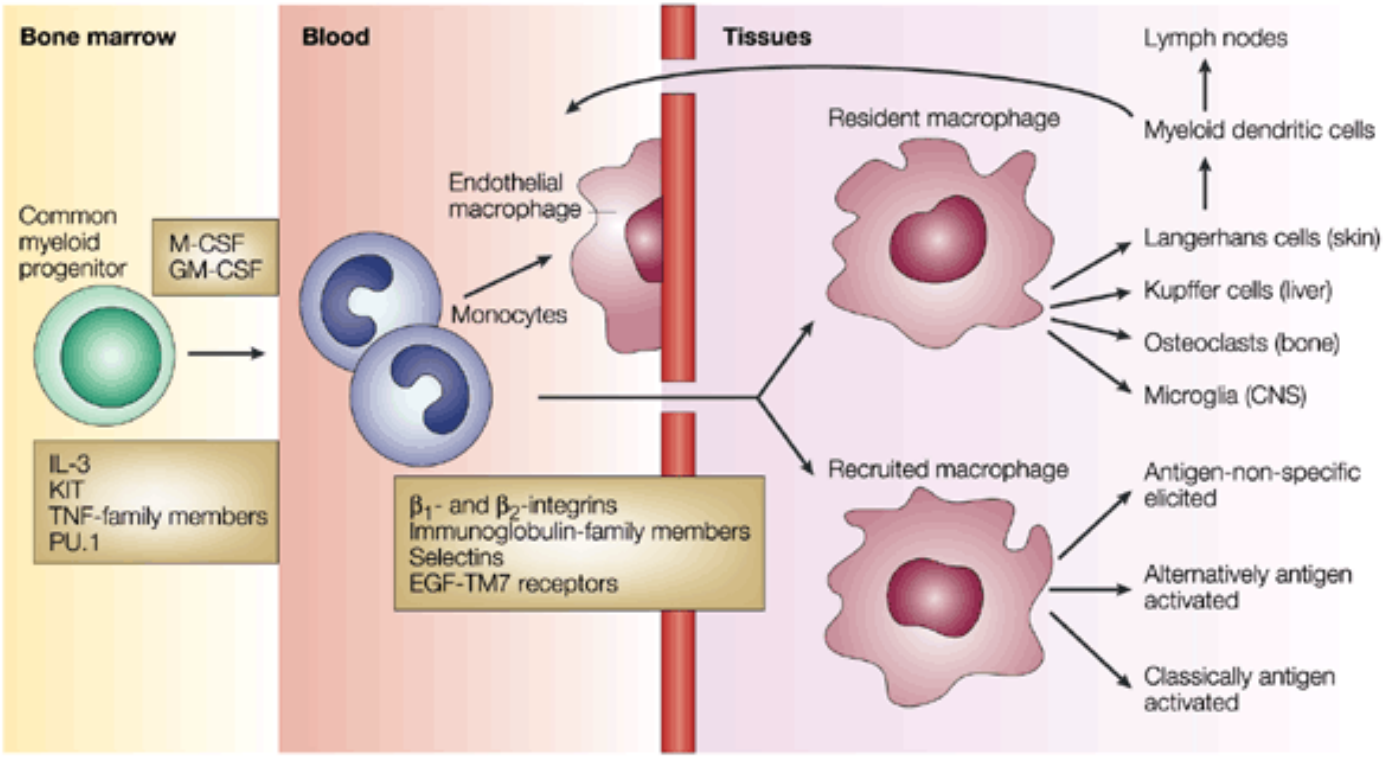
Macrophages



- Large multifuctions mononuclear phagocytic cells.
- Phagocytosis described by Elie Metchnikoff
- His first experiment was to introduce a splinter into a starfish larvae and to observe next morning that it was surrounded by mobile cells.
- In 1891 he proposed that this process was important in human inflammation and immediately came under severe and protracted attack by the humoralists, who believed that immunity depended on soluble factors.

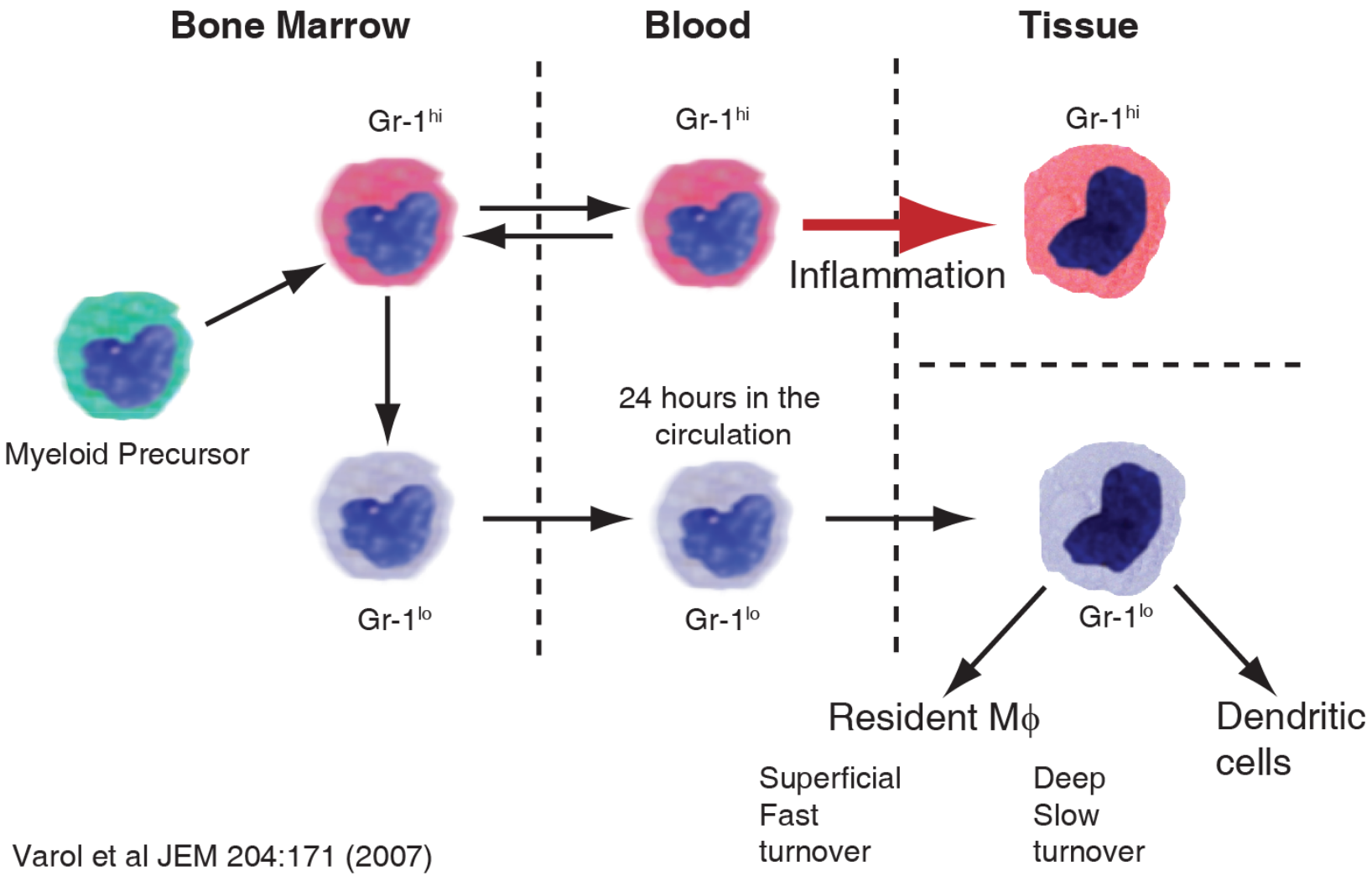
- Express class II MHC and are therefore like DCs, which share overlapping lineage, they are professional APCs.

Macrophage life stories



Nature Reviews Immunology 3, 23 - 35 2003

Macrophage life stories



Varol et al JEM 204:171 (2007)

Macrophage life stories

- Monocytes differentiate into resident and recruited cells. Resident cells (e.g. Langerhans, microglia) may be long lived.
- Recruited macrophages programmed life-span is relatively short *(Ralph Van Furth)*
- Mean turnover time in most tissues <7days.
- Recruited macrophages do not recirculate, so they die either in the tissue or in the lymph node.
- Inflammatory conditions may modulate lifespan

Summary 3

- Macrophages express class II and can function as professional APCs
- Recruited macrophages are dynamic relatively short lived leukocytes

Macrophages and inflammation

- Inflammation e.g. peritonitis
  - Increased promonocyte production
  - Increased in the numbers of leucocytes in the blood
  - Decrease in the mean half-life of the circulating cells

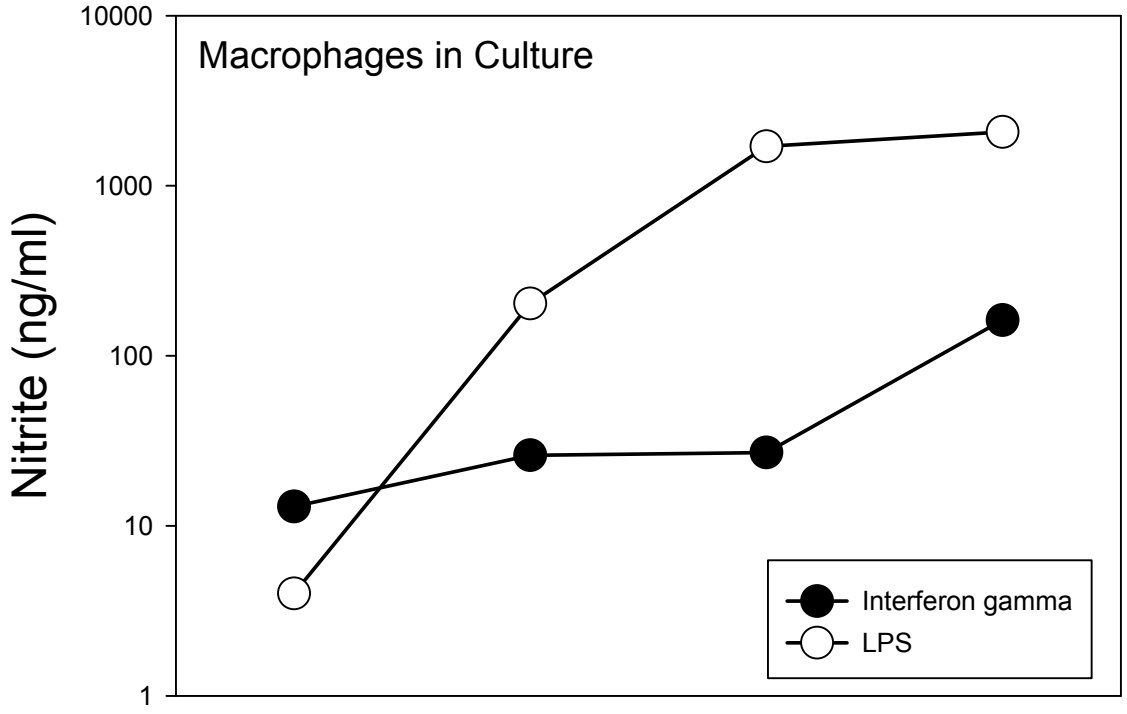
- During acute inflammation most macrophages and neutrophils derive from the bone marrow via the circulation

- Mechanisms
  - Release of soluble activators effecting endothelium e.g. chemokines
  - Upregulation of integrins/addressins on endothelial cells
  - Signals to retain cells in tissues
  - Signals to the bone marrow

Signals integrated at site of inflammation

Signals	Dual receptor	Single receptor	Diffusible
Cognate interactions	+		
Costimulation	+		
ECM interactions	+	+	
Pathogens		+	
PAMPs		+	
Endogenous Innate Immune system ligands		+	
Danger signals		+	
Cytokines		+	
Chemokines		+	
NO; superoxides		+	+

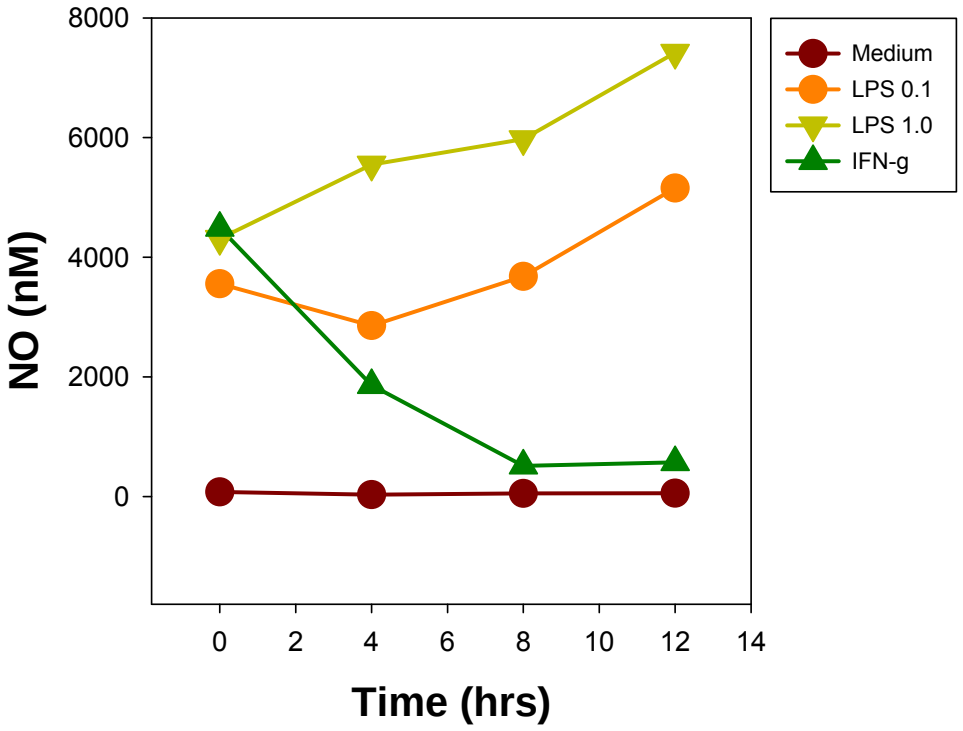
Potent activation by innate stimuli



Sarah Morwood. Unpublished data.

Macrophages and inflammation

- Macrophages are very responsive to the environment

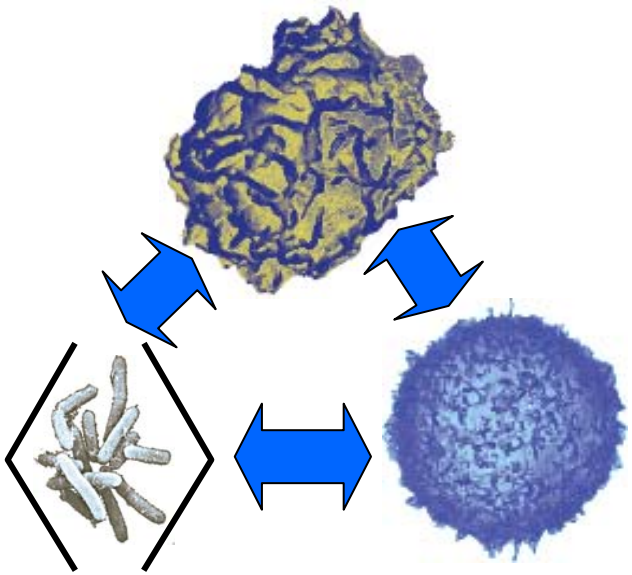


Ben Raveney. Unpublished data.

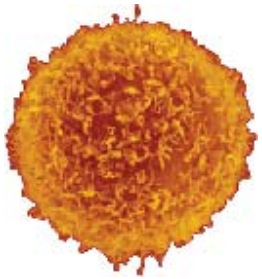
Summary 4

- Macrophages are recruited to sites of inflammation
- Macrophages integrate a large number of different stimuli which determine their response
- Macrophages responses can be modified rapidly by changes in environment

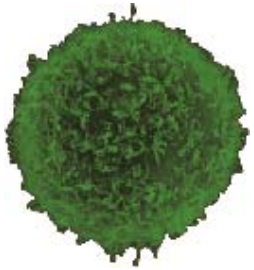
T cells come in different flavours …



Naive T cell

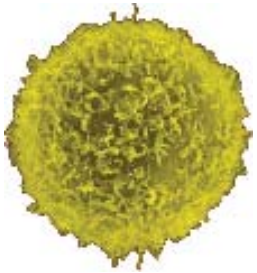


T helper 1
IFN-γ



T helper 2
IL-4

T helper 17
IL-17



T regulatory
TGF-βR

Macrophages and inflammation

- External environment controls the gene programs executed by macrophages
- There are different responses to activation by Th1 or Th2 cytokines

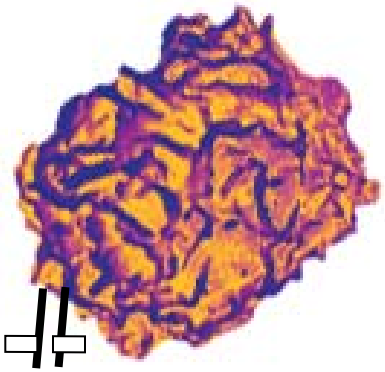
IFNg, IL-12	M1 phenotype; classical activation
IL-4, IL-13	M2 phenotype; alternative activation

But different to T cells

- No clonal burst
- Degree of reversibility is uncertain
- Integrating many other environmental cues, such as stimuli from pattern recognition receptors

Classical and alternative activation

Classical

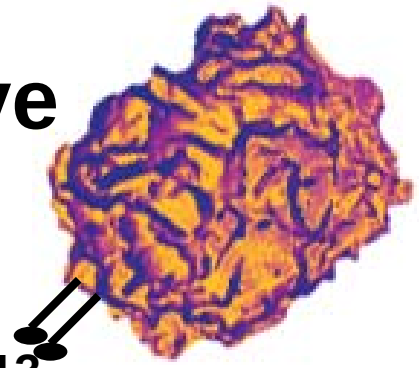


IFN-γ receptor

NO
ROS

Upregulation of
MHC class II
TNF, IL-6, IL-1

Alternative

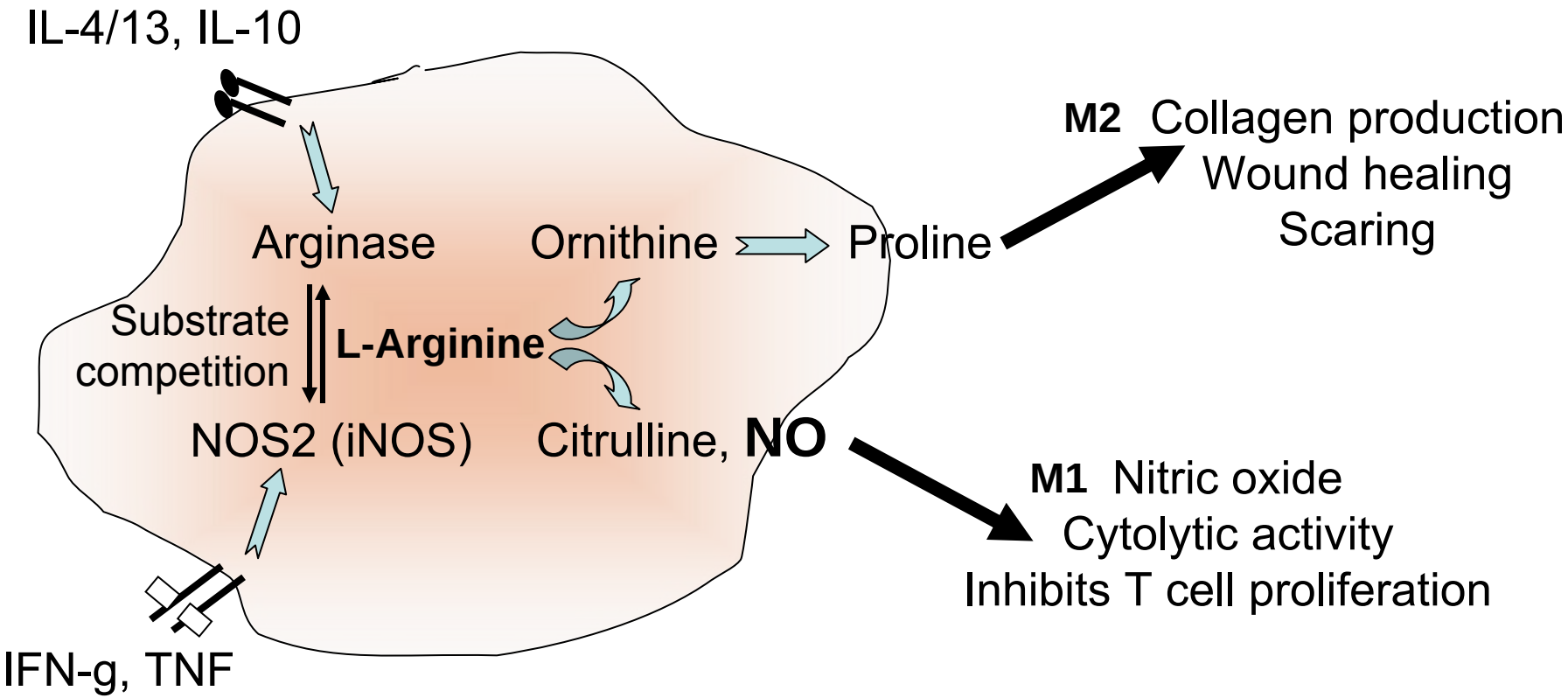


TGF-b/IL-4/IL-13
receptor

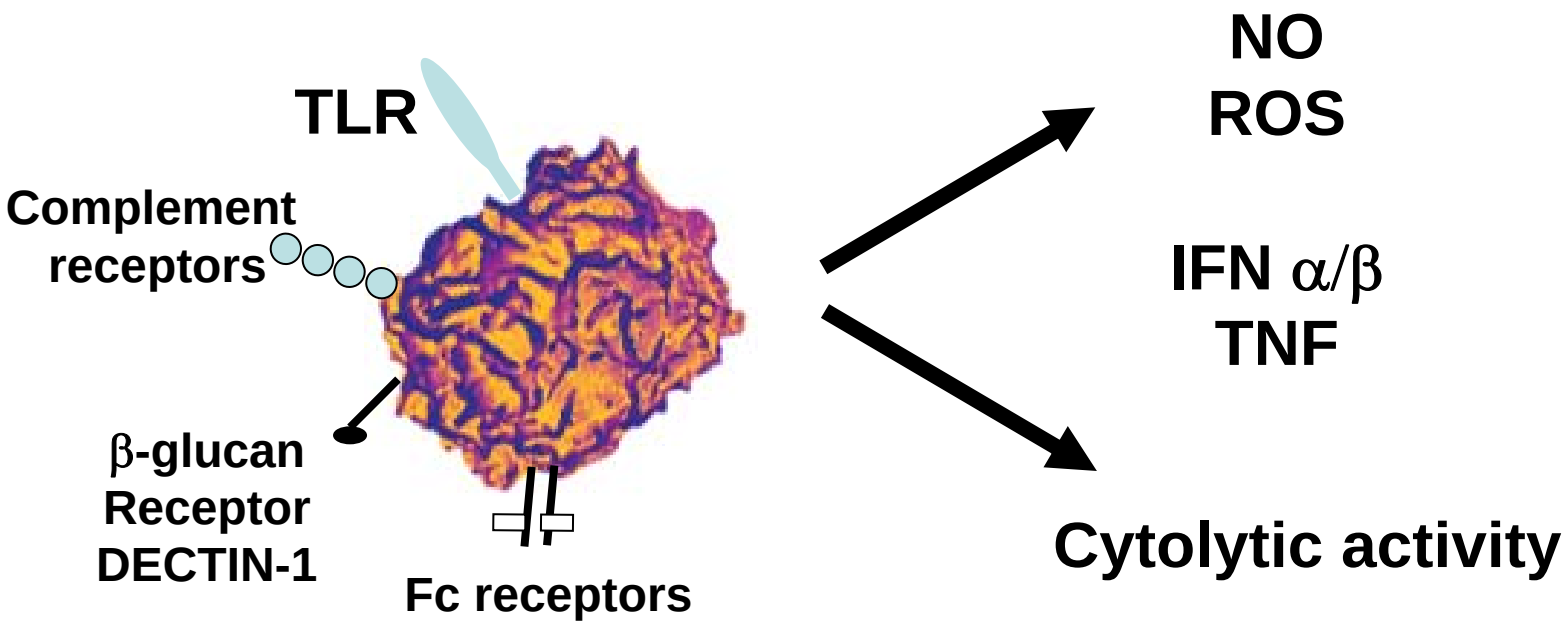
Ag endocytosis
(Mannan-dependent)

MHC class II upregulation

NOS2 expression, nitrite production, and nitrotyrosination are indicators of classical activation



Innate and Humoral activation



Summary 5

- Cytokines are one important variable that can determine macrophage phenotype
- L-arginine is a critical substrate in macrophage function
- Innate immune signals play a large role

Integrated Activation

- Levels of activation within the immune system may vary globally, and in specific microenvironments
- High activation environments convey both potential rewards and potential risks
- Dynamic control of activation is (presumably) an optimal or near optimal strategy

Integrated activation 1: killing mycobacteria

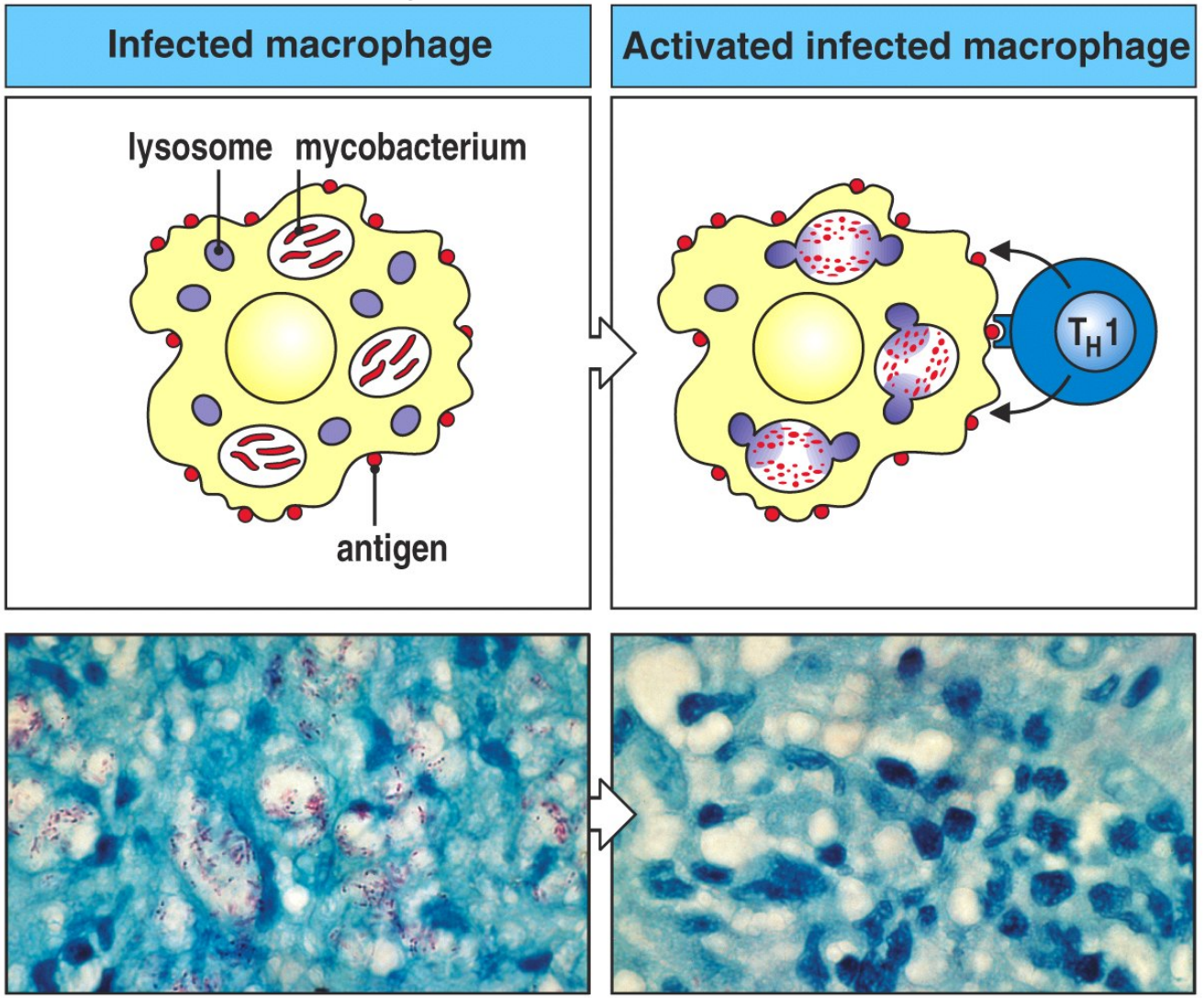
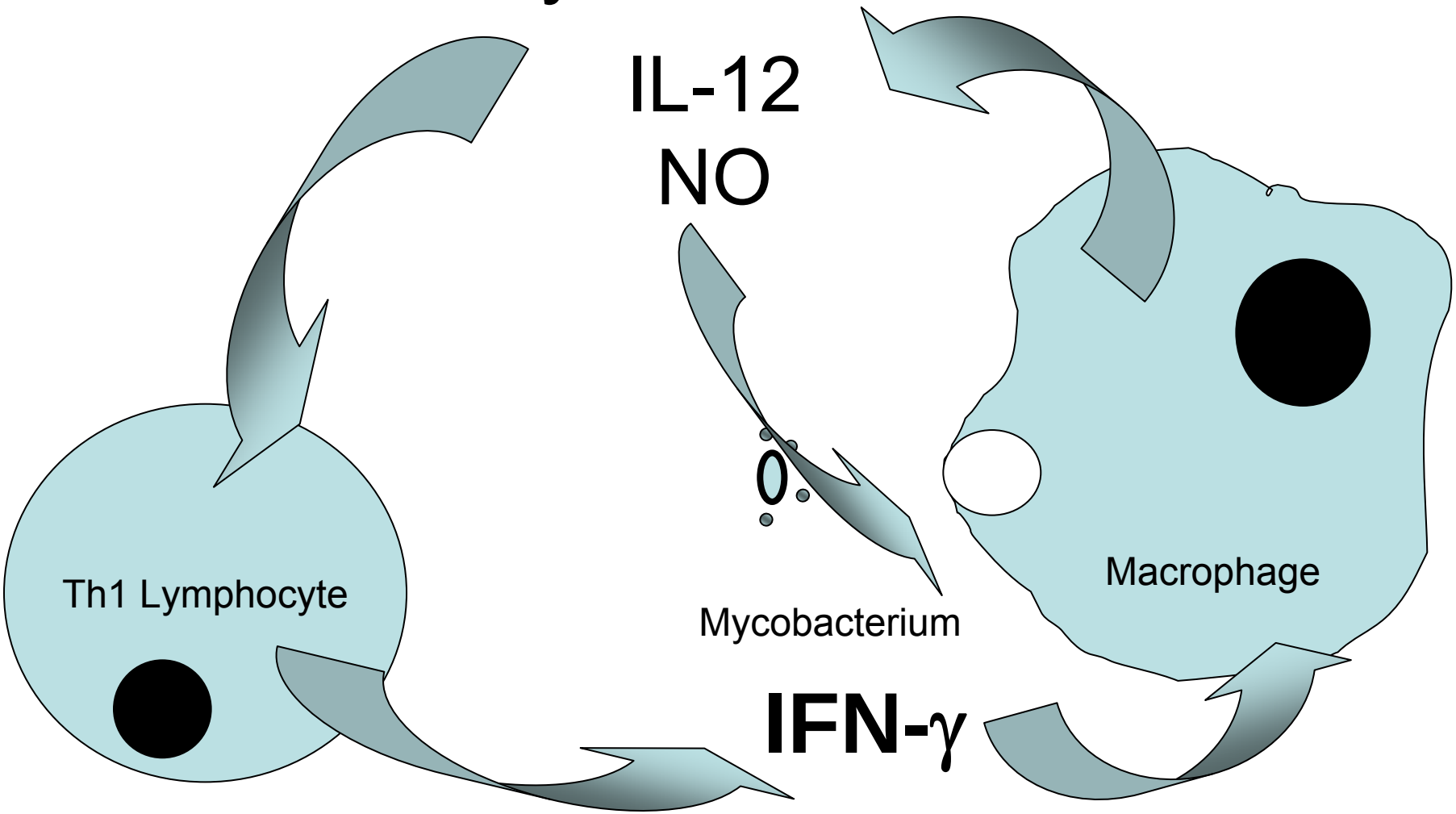


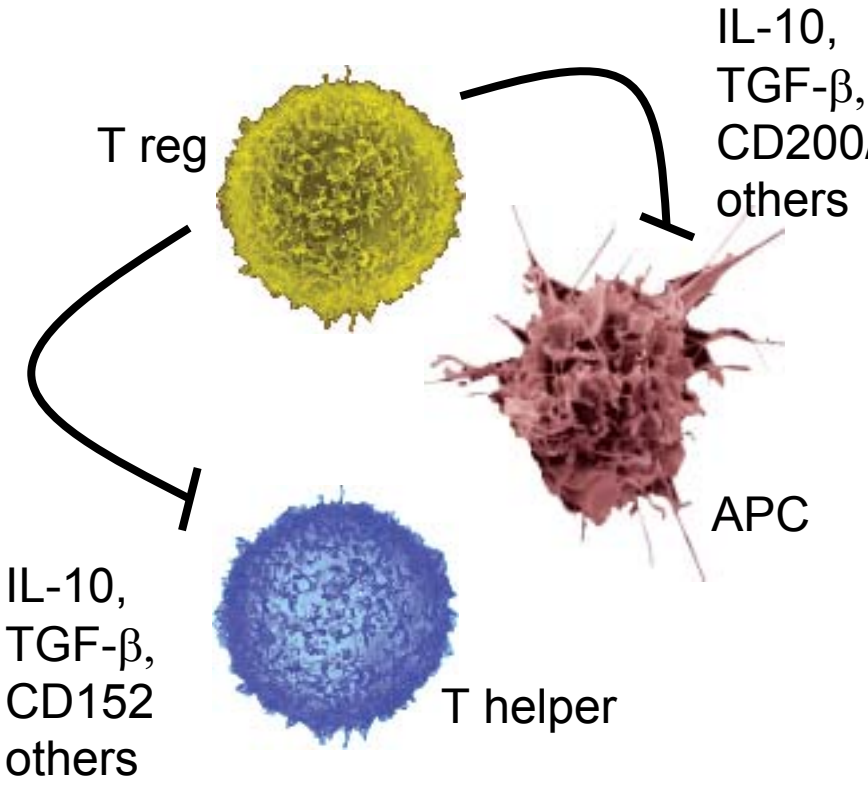
Figure 1-26 Immunobiology, 6/e. (© Garland Science 2005)

Integrated activation 1: killing mycobacteria



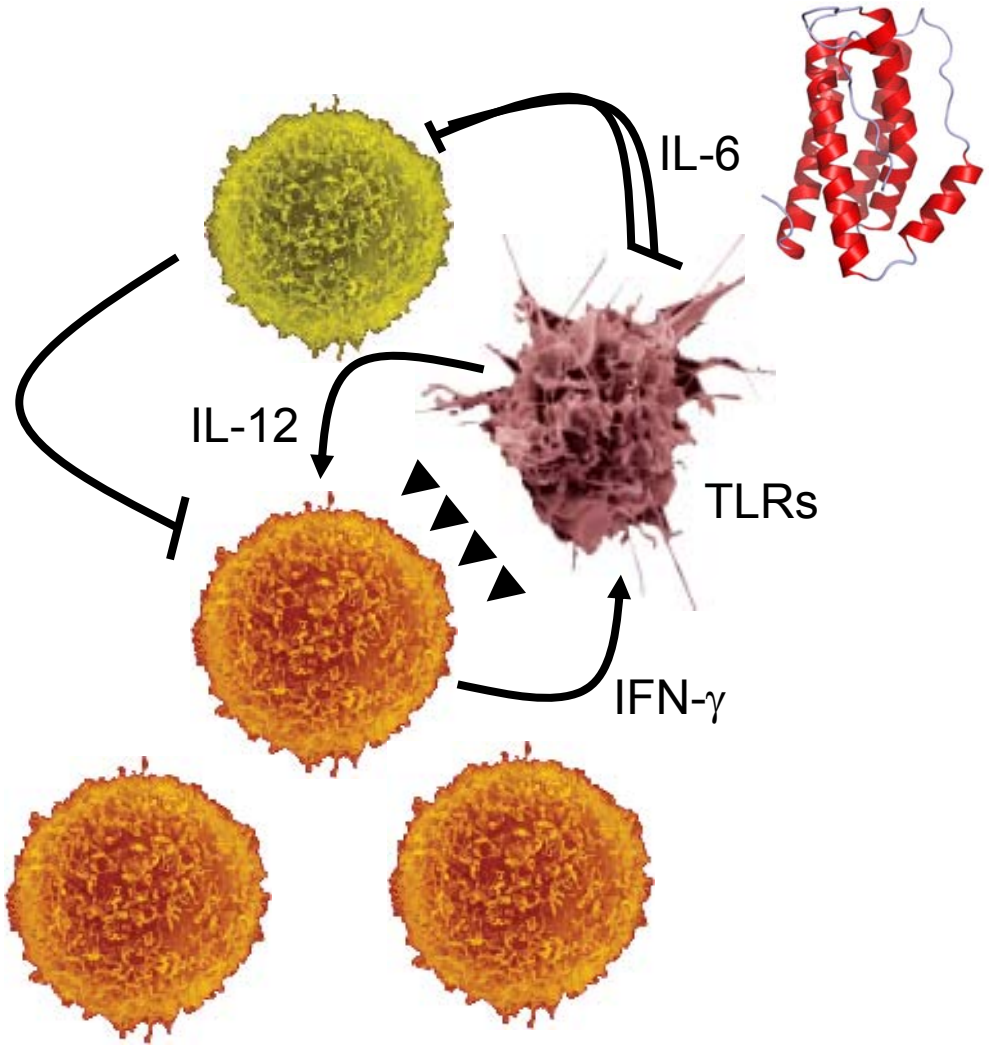
David Wraith

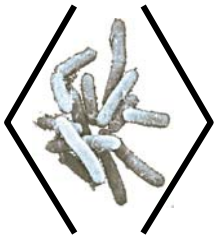
Integrated activation 2: Myd88 dependent ‘deinhibition’



- At ‘rest’ immune activation is checked by regulatory cells
- How is this removed?

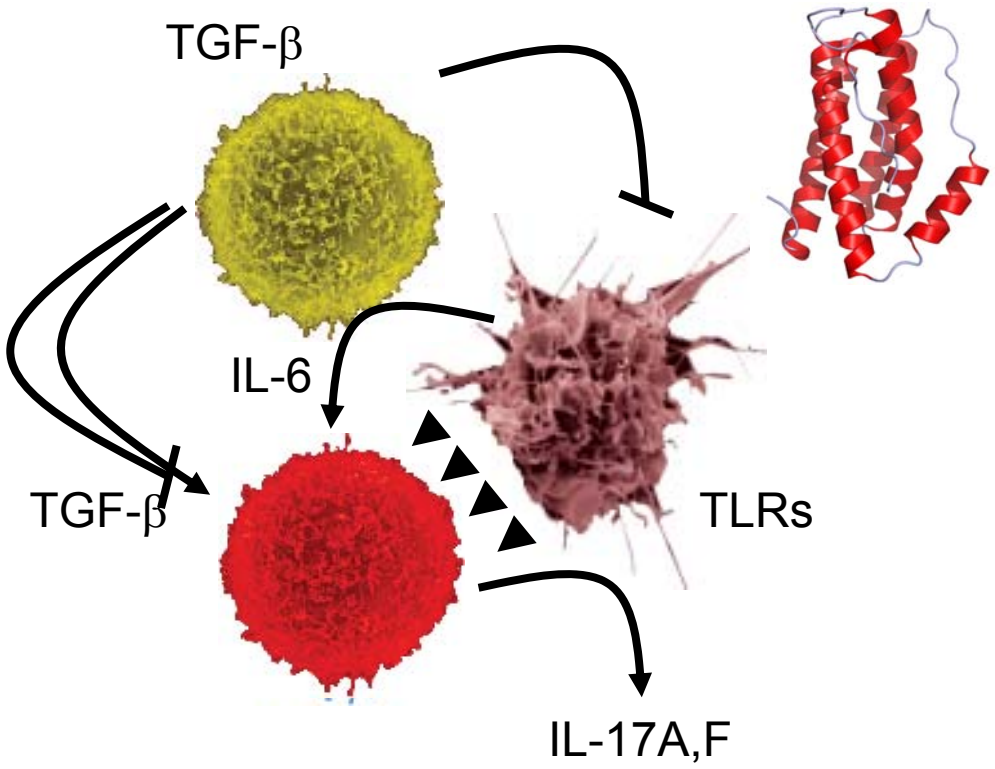
Integrated activation 2: Myd88 dependent ‘deinhibition’

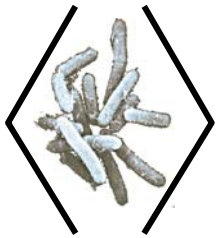




Science. 299:1033-6, 2003

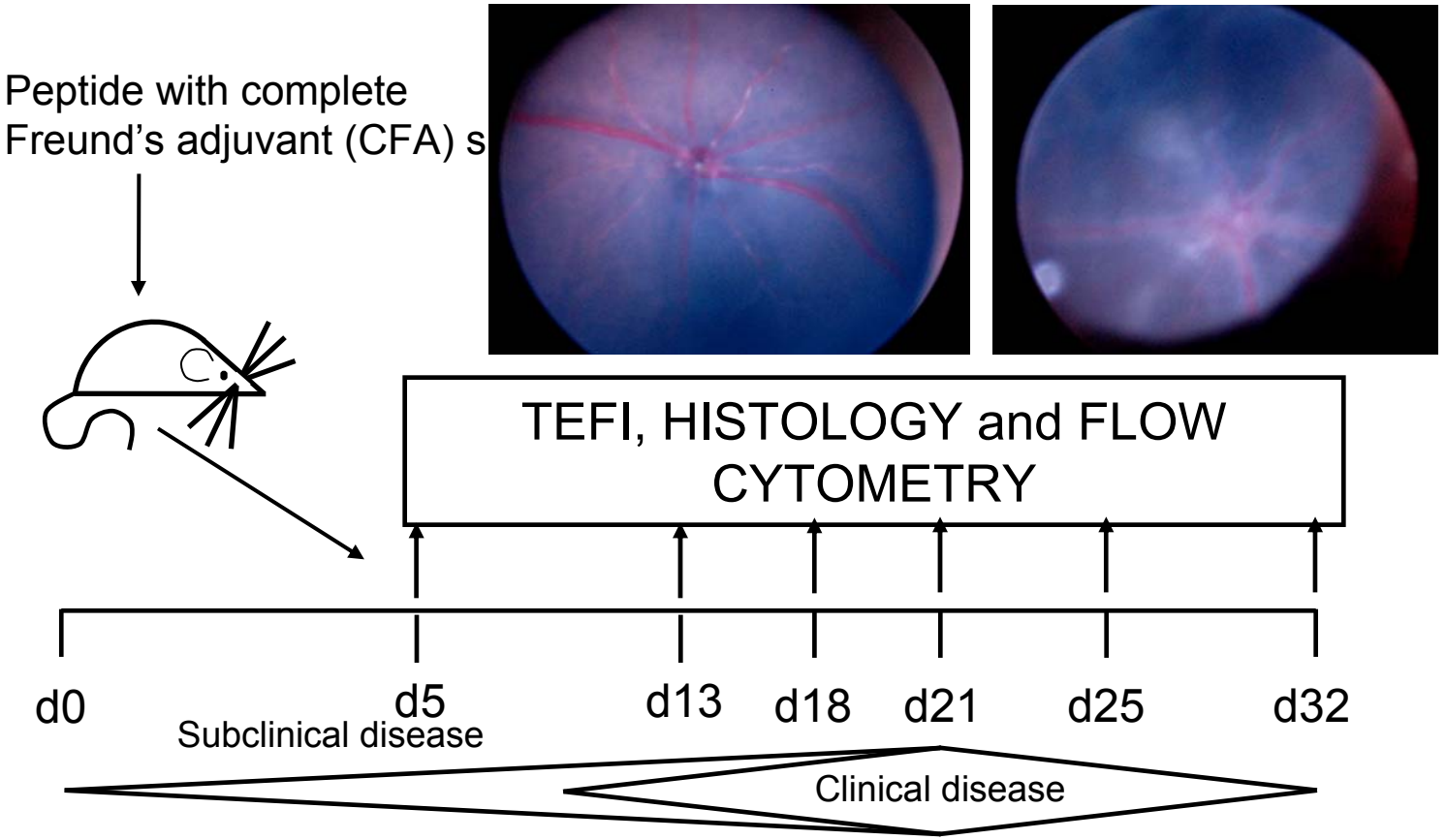
Integrated activation 3: Th17 T cell generation



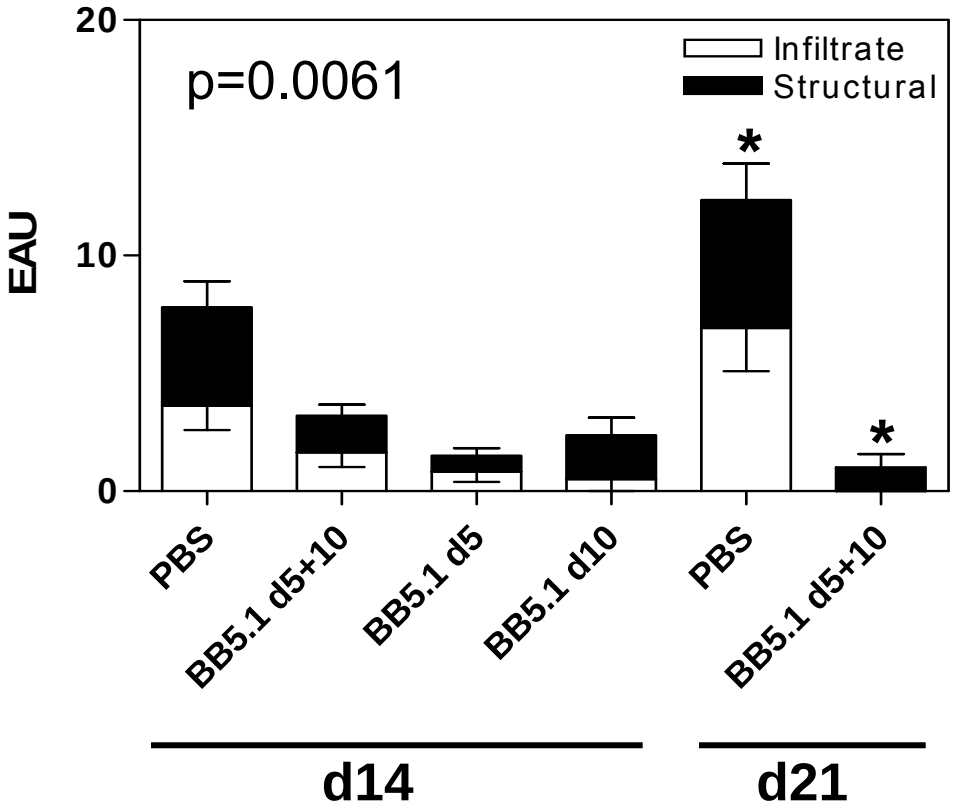


Immunity. 24:179-89, 2006
Nature. 441:231-4, 2006
Nature. 441:235-8, 2006

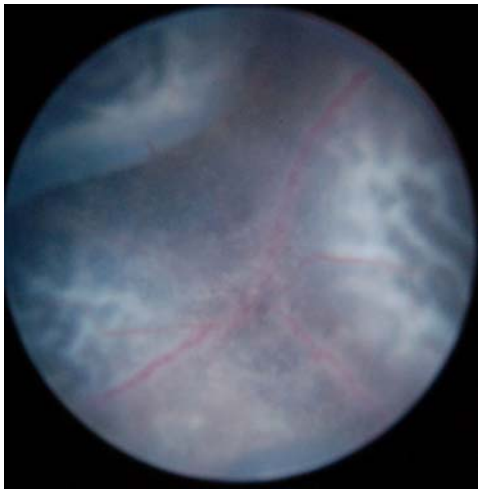
Integrated activation 4: Therapy targeting innate immunity



Treatment targeted at complement C5



PBS



Anti-C5 mAb

Copland et al. unpublished data

Summary 6

- The immune system has different levels of activation; an activated immune system is more effective than a quiescent one
- Innate signals can serve to remove tonic inhibition
- IL-6 is crucial in linking innate and adaptive immune activation
- Therapy that targets the innate immune response can modify adaptive responses

Aberrant Innate Activation?

- In organ specific autoimmunity, T cells target specific proteins
- How do these T cells become activated?
- Is there a role/requirement for innate immune activation?

Innate Immunity 2 – Key Concepts

- Monocyte recruitment
- Macrophage differentiation
- Innate immune activation regulates the progress of an immune response
- Adaptive immune response regulates the nature of the innate immune response