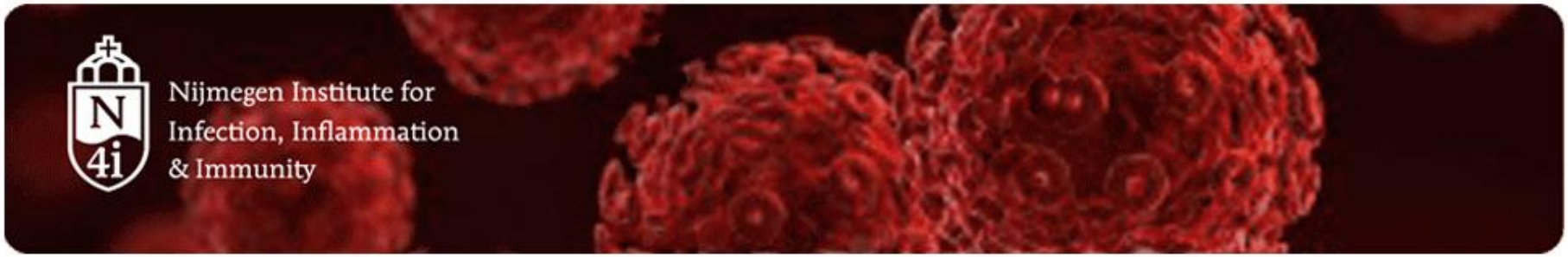

A short history of immunology: from phagocytosis to the human genome

Mihai G. Netea

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The Toll of infectious diseases

MEDIEVAL MAGAZINE

Monday, August 5, 1352

Black Death kills 3000 in one week

This week more than 3,000 people in Britain have died from the Black Death.

This brings the total dying across Europe to 15 million dying from the bubonic plague and 10 million dying from the terrible pneumonic plague. Will this ever stop? Will anyone survive?

Already 17 of our best writers have died and 20 are at home sick.

Whose fault is it? In Strasbourg, it is said that the Jews are to blame, in Italy, God has supposedly brought this upon them. However the real reason is that our roads are simply not clean enough.

The Lord Mayor of London has ordered the streets to be cleaned and others are following this ingenious order.

With doctors still not being able to find a cure we can only hope that this disease simply goes away.

The Black Death is usually associated with Europe but it neither began nor ended then. The earliest records of this pestilence are in China.

In 46 AD an epidemic in Mongolia killed two-thirds of the population.

In 312 northern and central China became a wasteland and in the province of Shensi, only one or two out of 100 taxpayers survived. In 468, 140,000 people died in the Chinese cities of Honan, Hopei, Shantung and others.

Estimated population of Europe from 1000 to 1352.

- 1000 38 million
- 1100 48 million
- 1200 59 million
- 1300 70 million
- 1347 75 million
- 1352 50 million

25 million people died in just under five years between 1347 and 1352.

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Miasmae vs germs

A representation of the cholera epidemic of the 19th century depicts the spread of the disease in the form of poisonous air

-The theory of miasma disease made sense to the English sanitary reformers of the mid-19th century.
- Miasma explained why cholera and other disease were epidemic in places where water was undrained and foul-smelling.
- the theory led to improvements in water drainage and sanitation, which decrease cholera outbreaks, leading increase support for the theory.

- Florence Nightingale was a strong supporter of the theory

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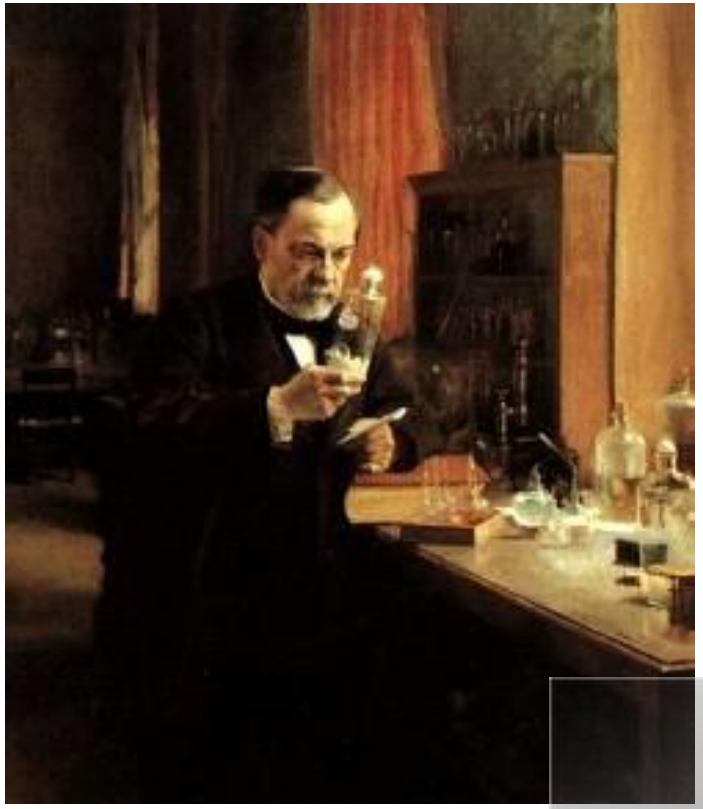
The golden age of microbiology



Louis Pasteur

Robert Koch

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How do we kill microorganisms ?

By eating them:

the phagocytosis

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Ilya Metchnikov

1905 Nobel speech:

“eventually molecules will be identified on the surface of leukocytes which could identify microorganisms”

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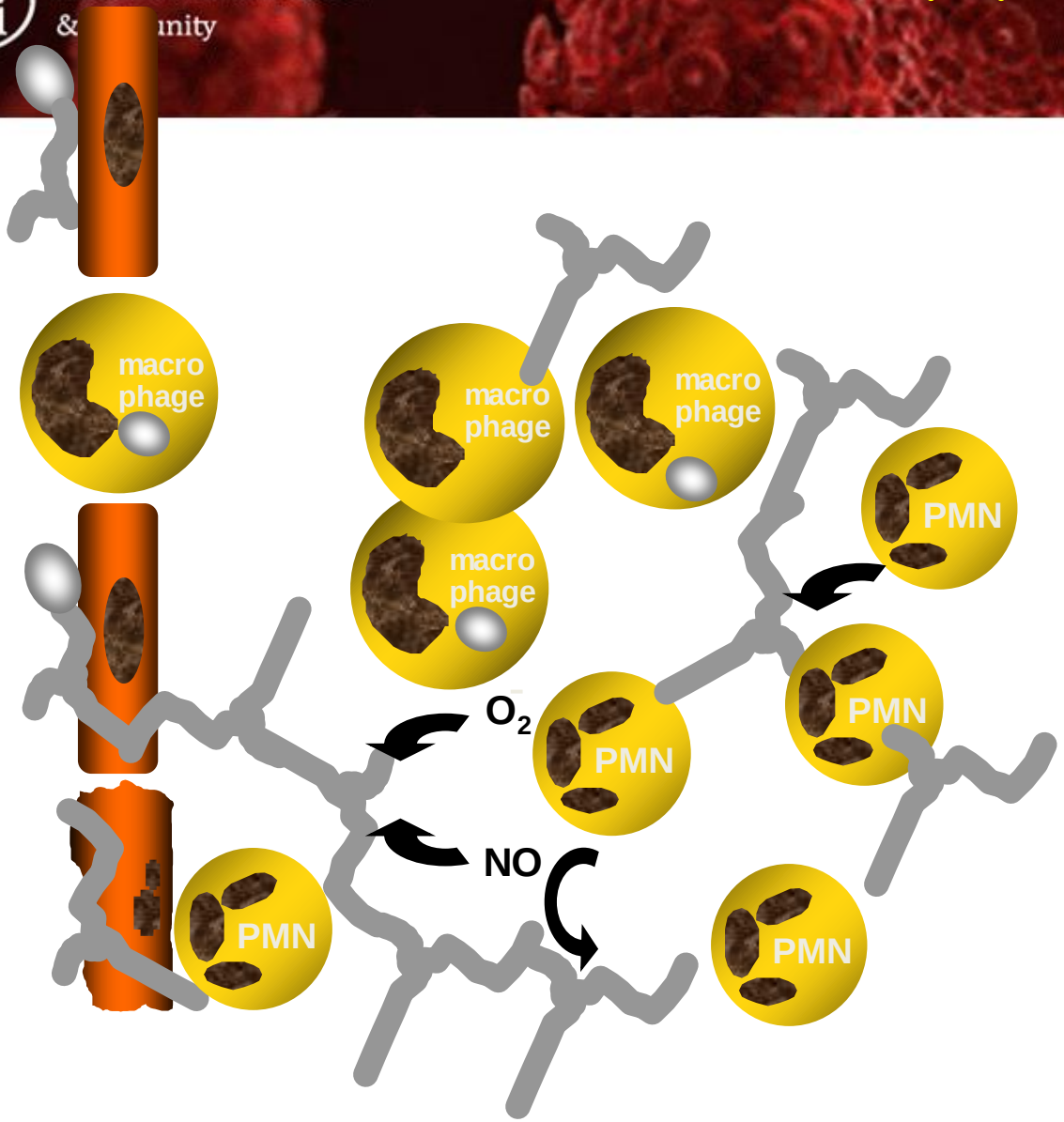
Innate immunity



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Humoral immunity

Emile von Behring

Paul Ehrlich

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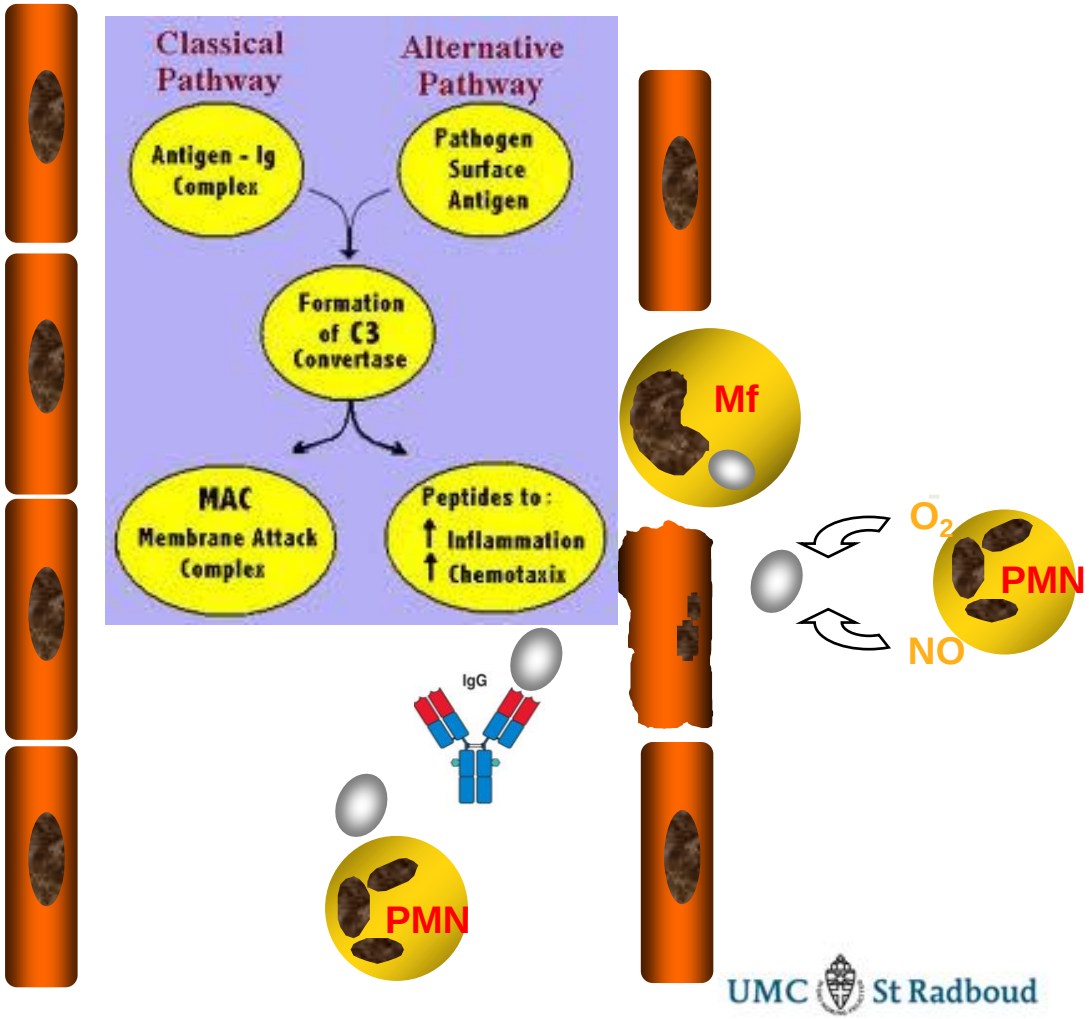
Complement

Jules Bordet



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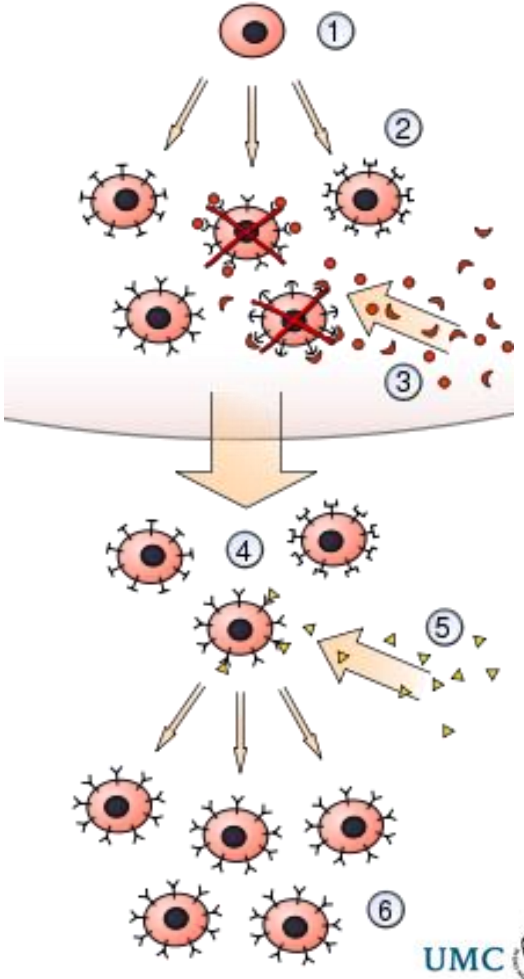
Clonal selection

Frank Macfarlane Burnet



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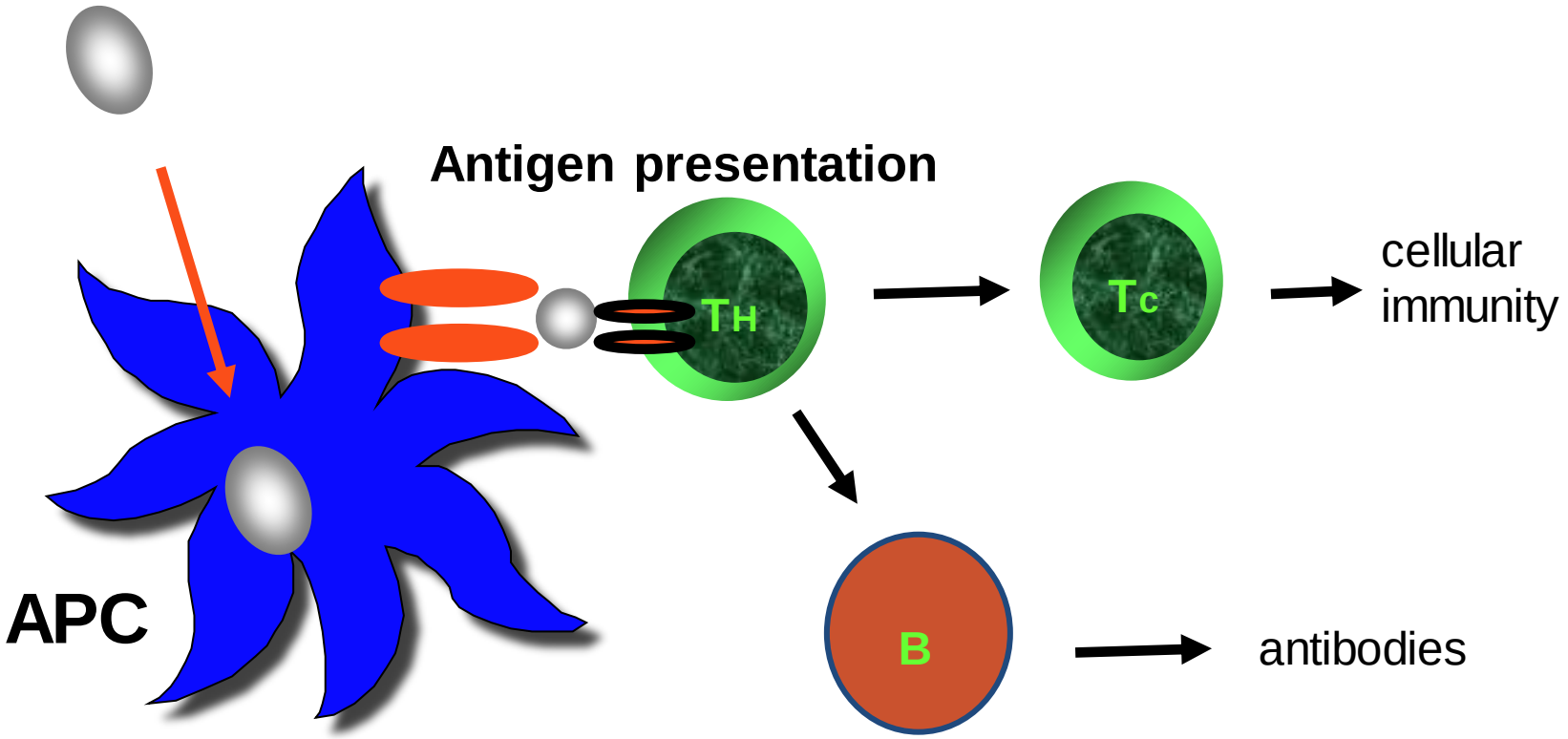
Adaptive immunity



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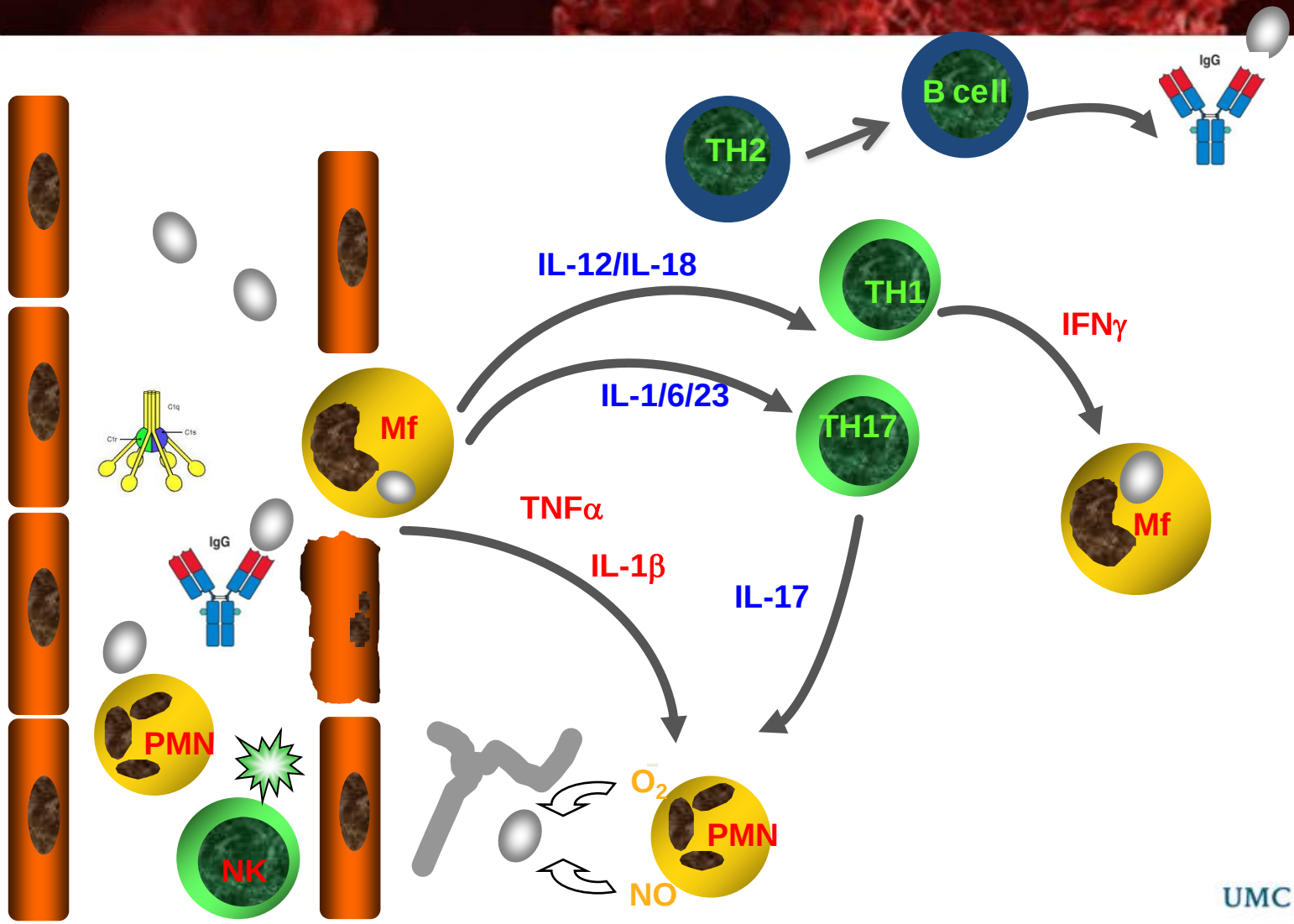
The host defense



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Innate versus adaptive immunity

- **Innate immunity:**
- STRONG but STUPID
- - rapid
- effective
- - not-specific, indiscriminate

- **Specific immunity:**
- LAZY but SMART
- - needs 10-14 days
- - a specific activation against a particular microorganism, enhancing the effectivity of the response

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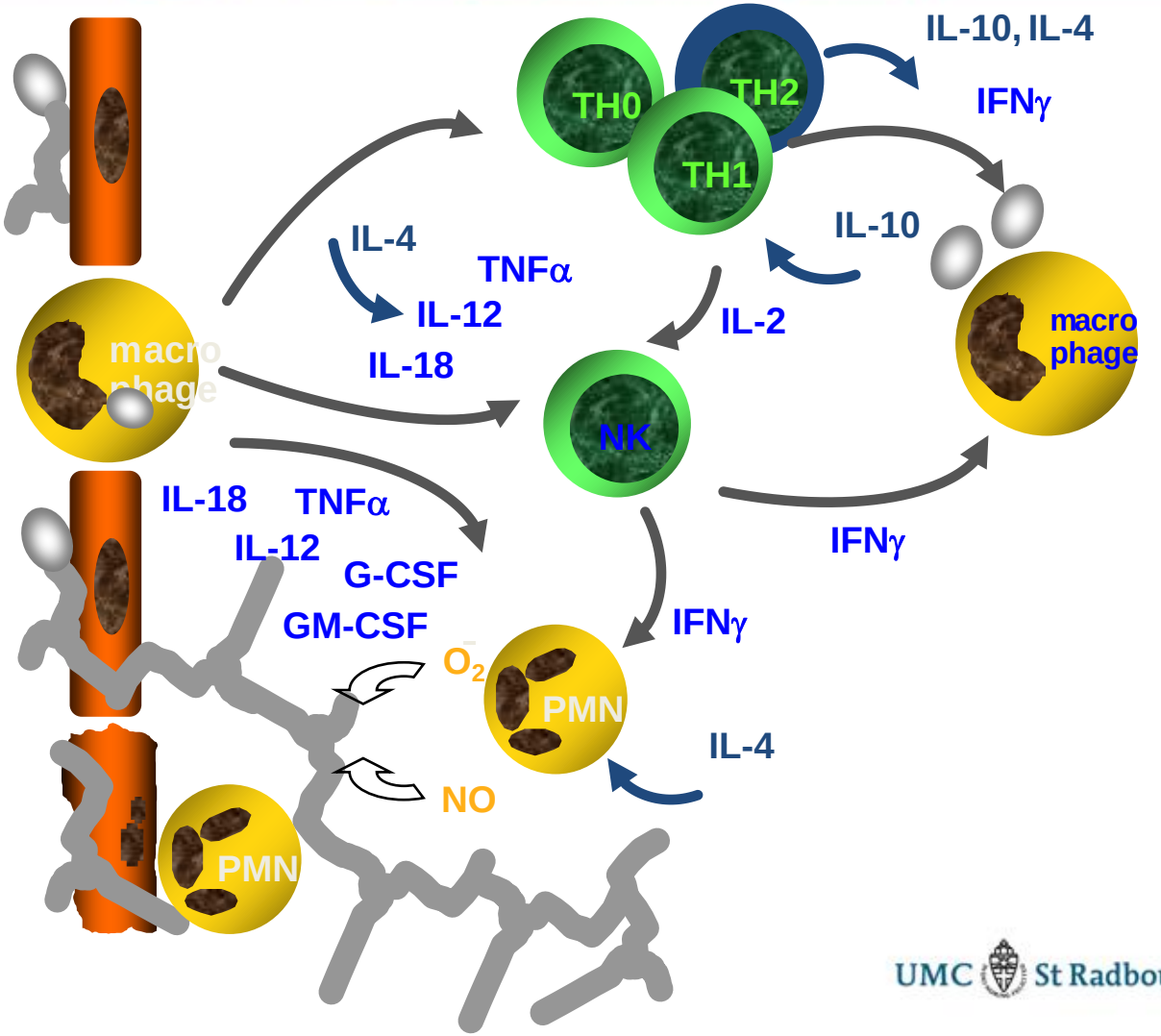
Cytokines: the information network of innate immunity

Charles Dinarello



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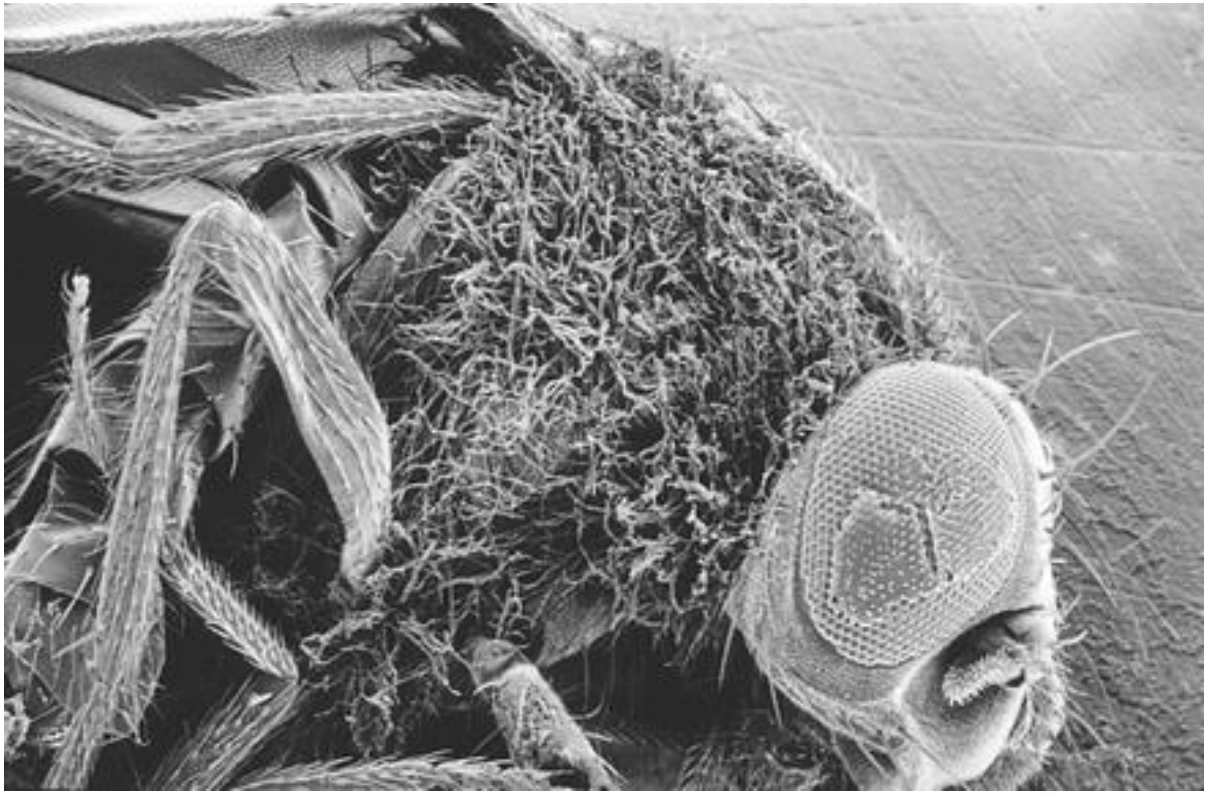
Cell. 1996 Sep 20;86(6):973-83.

The dorsoventral regulatory gene cassette spatzle/Toll/cactus controls the potent antifungal response in Drosophila adults.

Lemaitre B, Nicolas E, Michaut L, Reichhart JM, Hoffmann JA.



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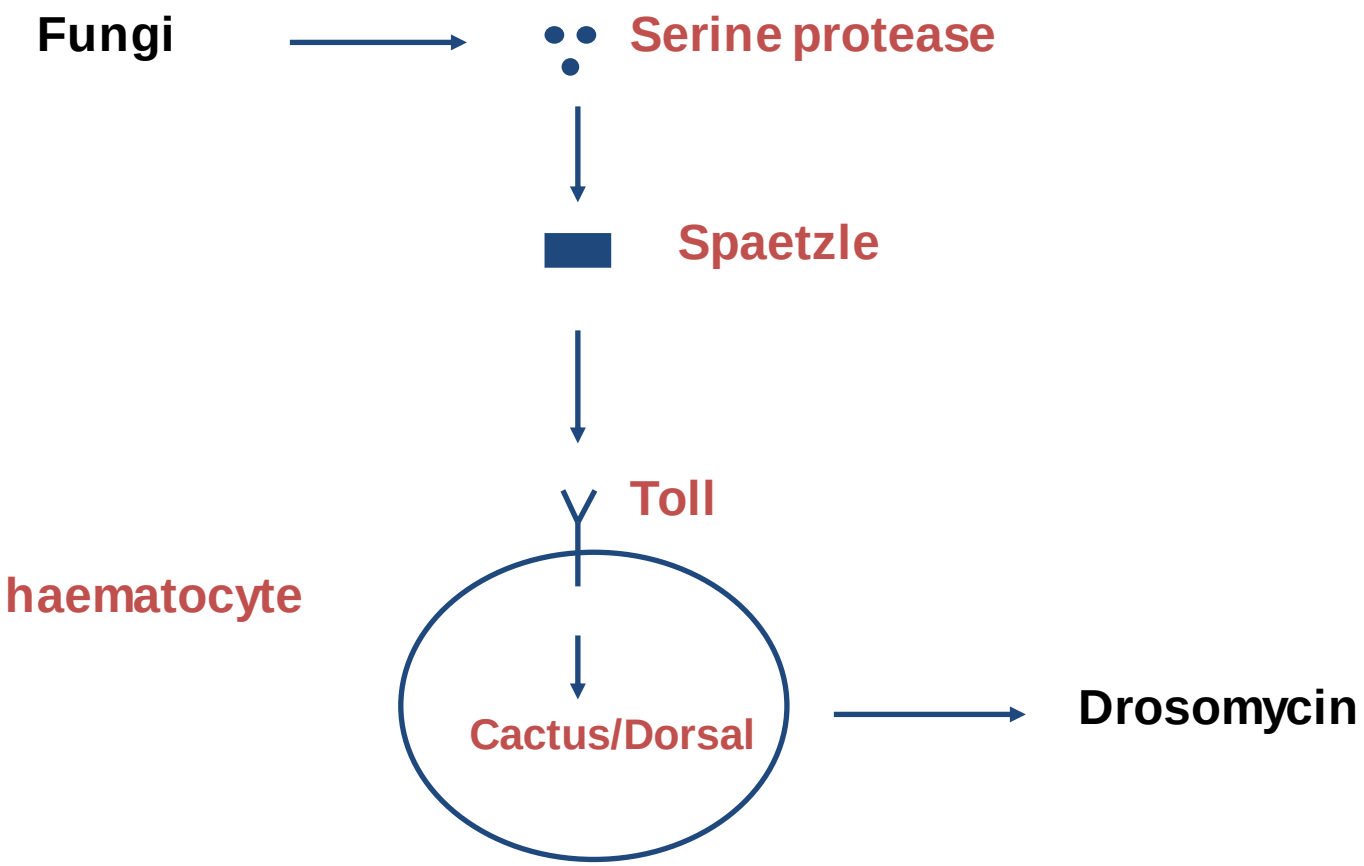
Drosophila Toll receptor



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The Toll-like receptor signal pathway

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	Drosophila	Human
Ligands	Spaetzle	IL-1
	↓	↓
Receptors	Toll	IL-1R
	↓	↓
Signaling proteins	Tube	MyD88
	Pelle	IRAK, Traf6
	↓	↓
	Cactus	ikB
	Dorsal, Dif	NFkB
	↓	↓
Target proteins	Drosomycin	IL-6, TNF

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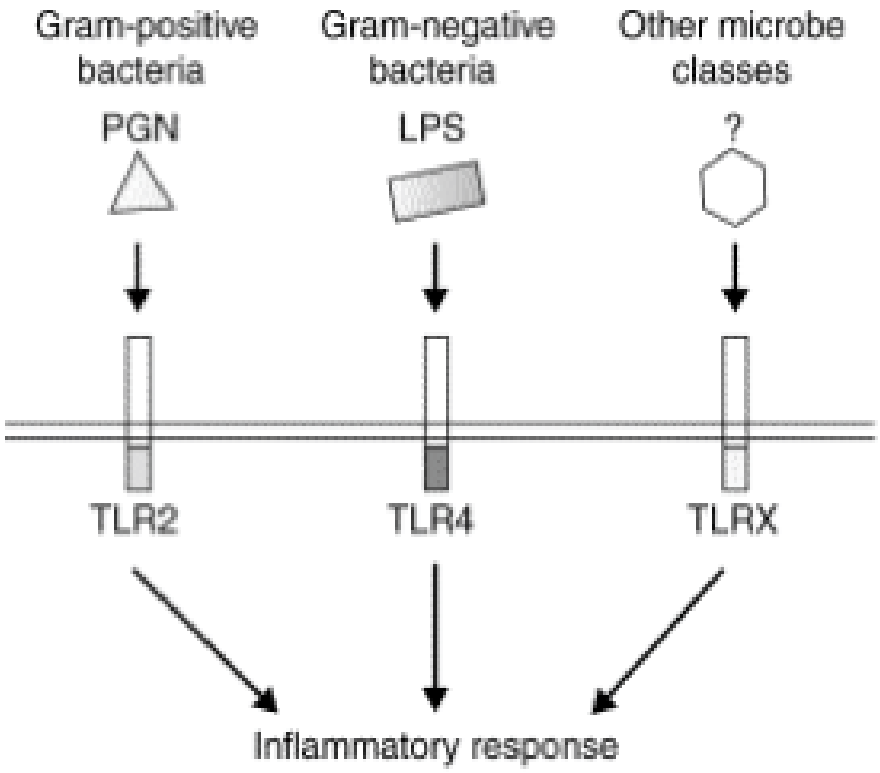
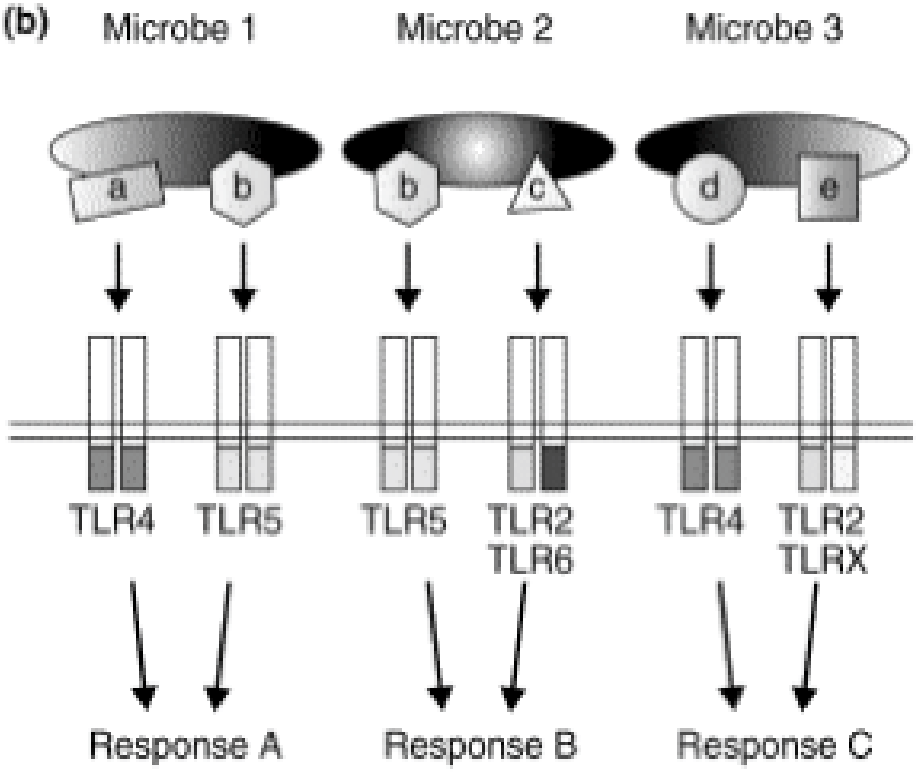
Pattern recognition receptors





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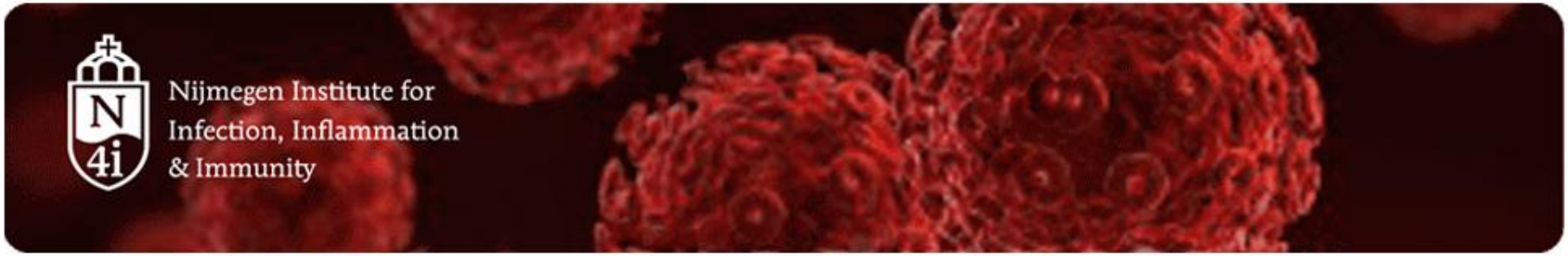

Trained Immunity:
a memory for innate host defense

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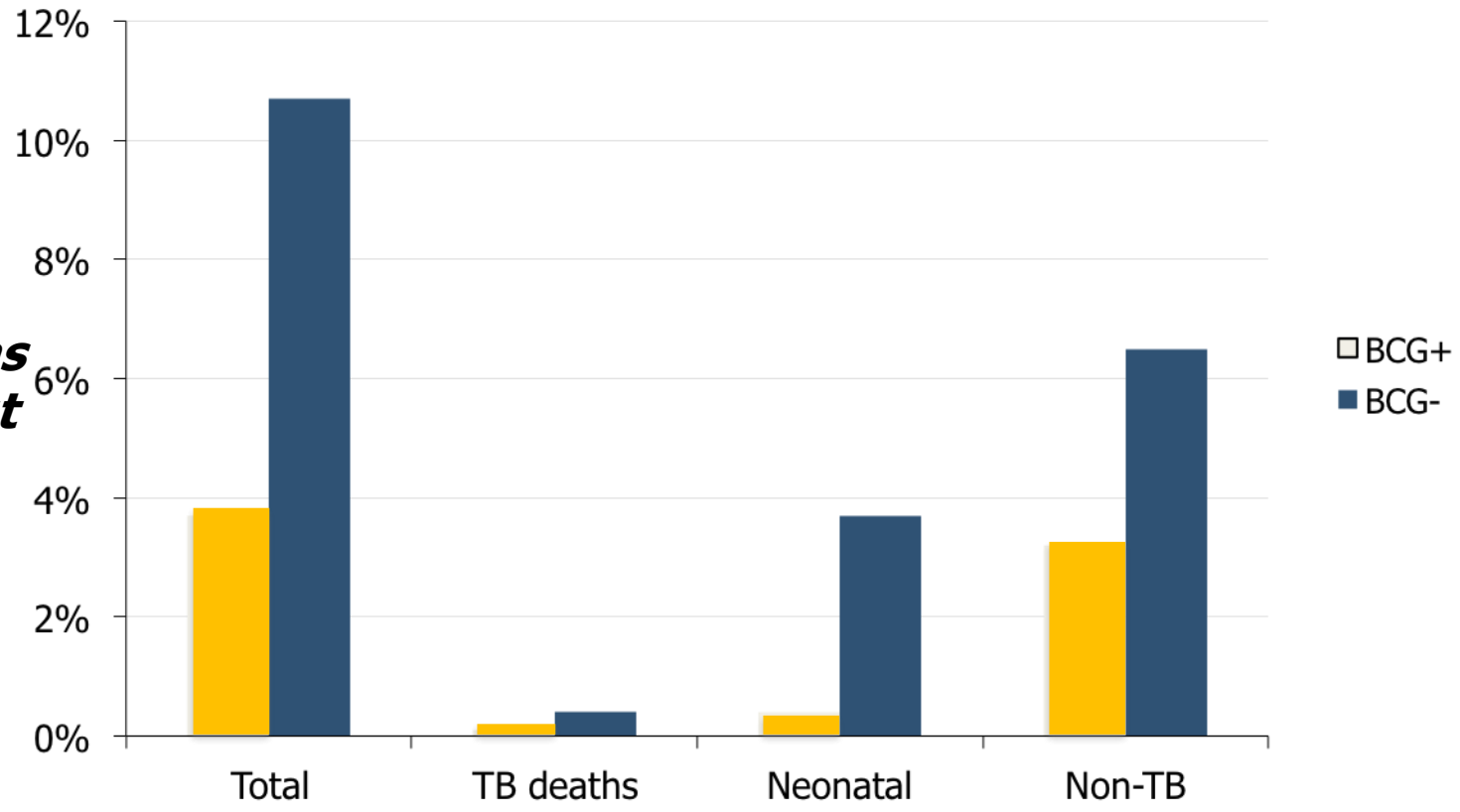
Introducing BCG in Norrbotten, Sweden, 1927-31: Mortality at 0-4 years - 20,000 children

Coverage highest in families with TB

Reduction was in infancy, but TB deaths occur later

This made little sense



"One could evidently be tempted to find an explanation for this much lower mortality among vaccinated children in the idea that BCG provokes *a **non-specific immunity**...*"

Carl Naeslund 1932

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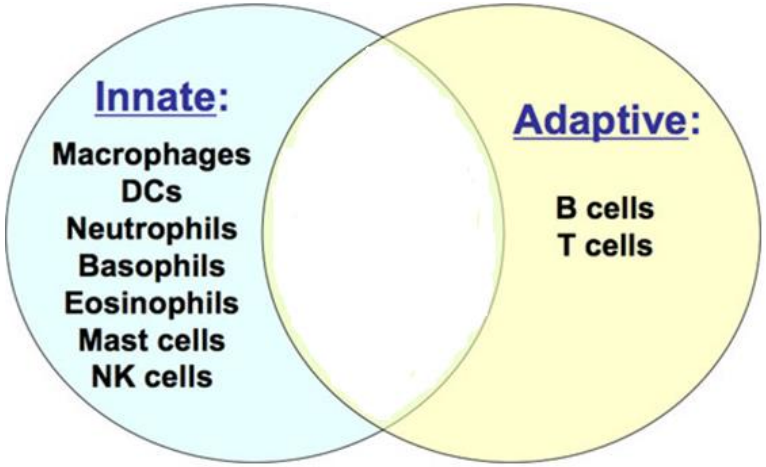
Innate versus specific immunity



Innate immunity:

- rapid
- effective
- not-specific, indiscriminate
- lacks immunological memory

Adaptive immunity:

- needs 10-14 days
- a specific activation against a particular microorganism, enhancing the effectivity of the response
- builds immunological memory

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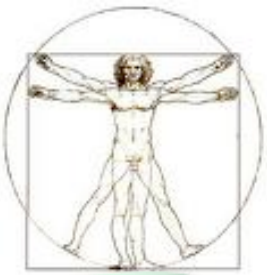
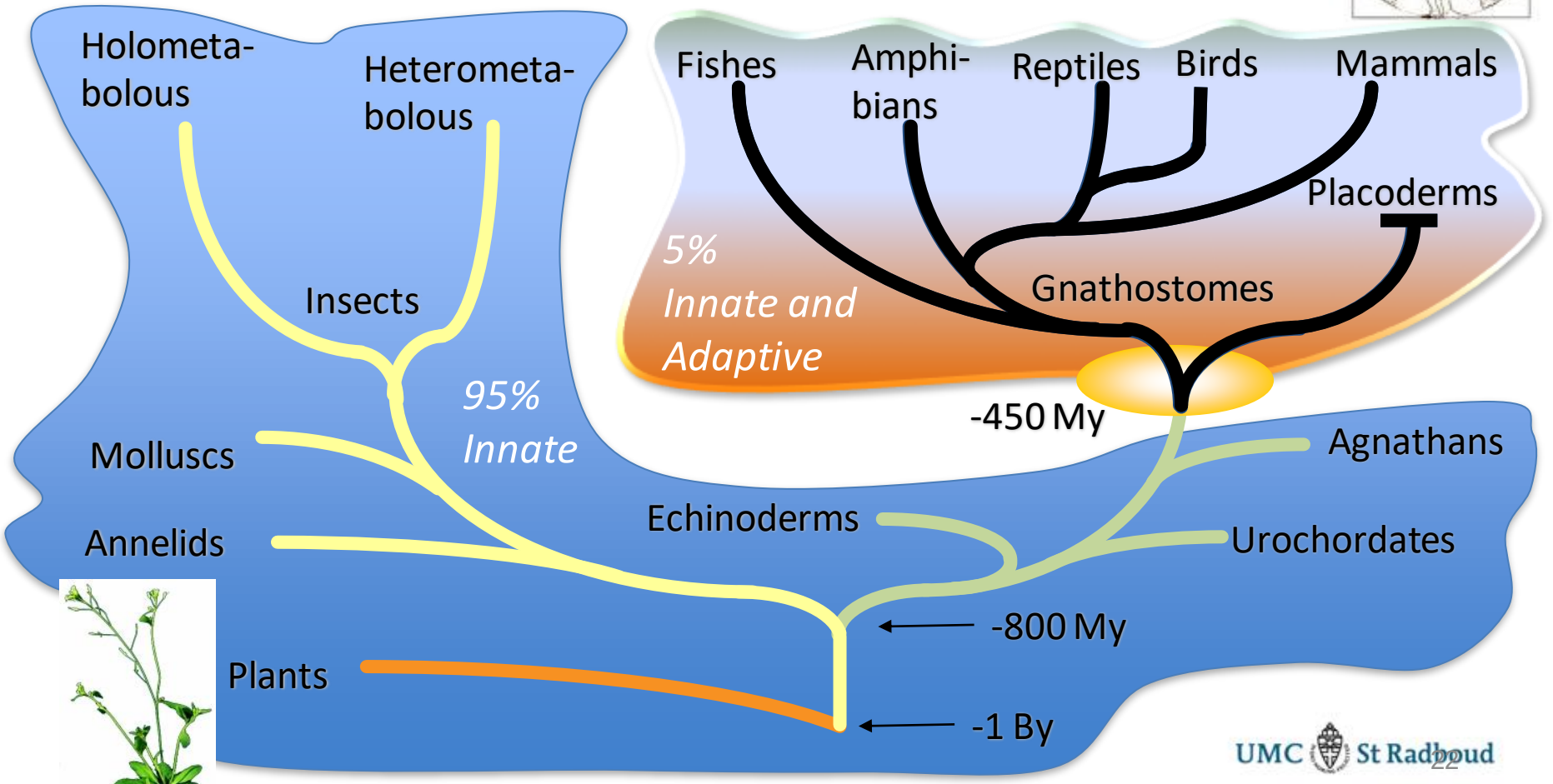
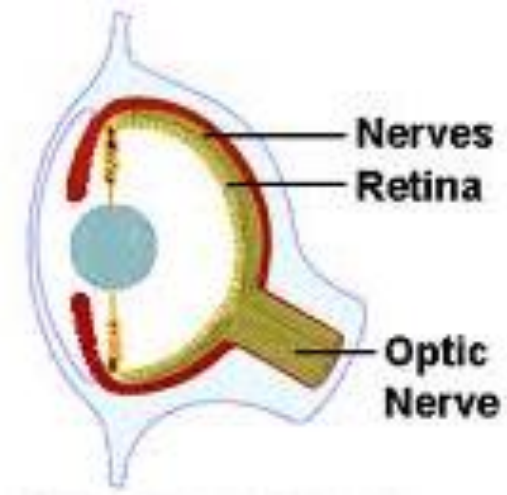
"Memory: the ability of a system to store and recall information on previously encountered characteristics"

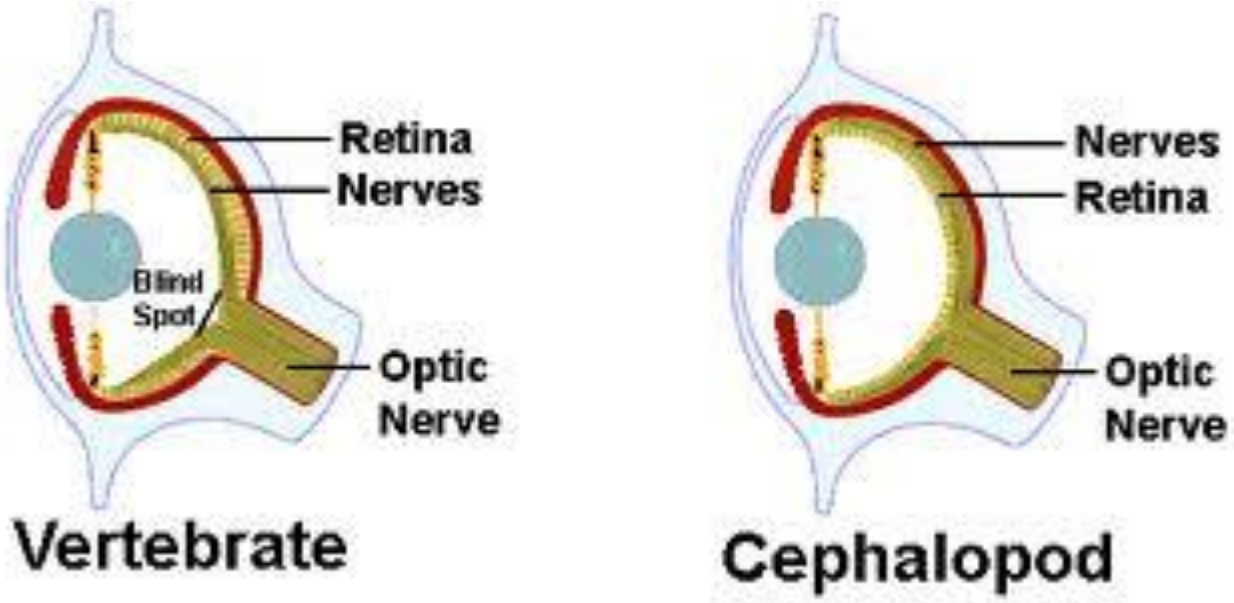


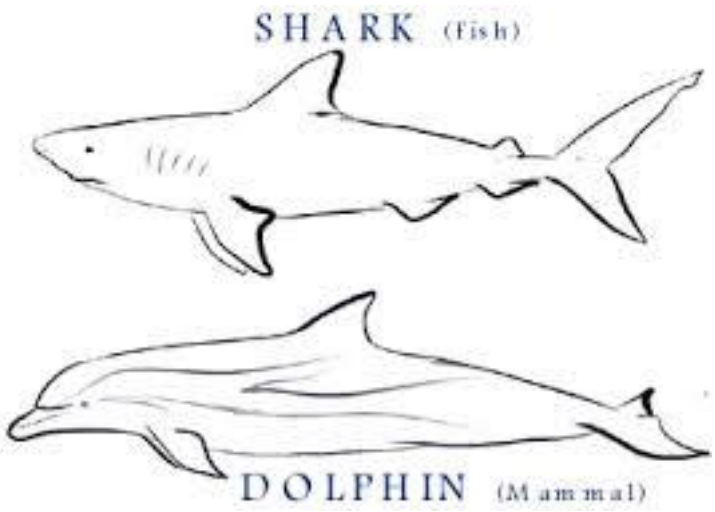


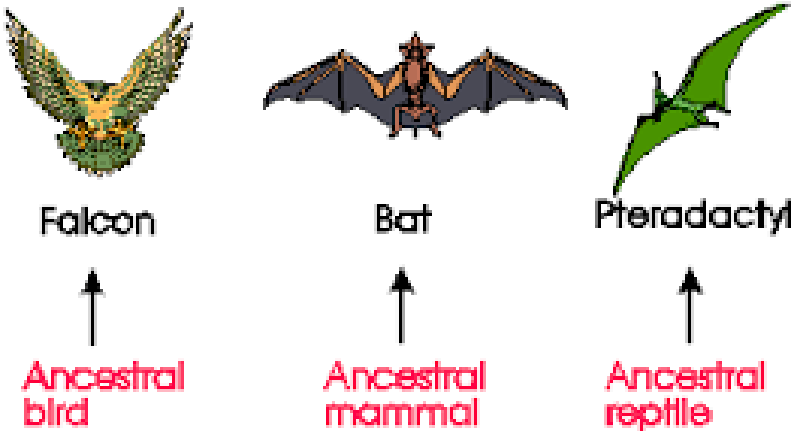
- **Convergent evolution**: development of the same property in independent group of organisms



- **Convergent evolution**: development of the same property in independent group of organisms




SHARK (Fish)
DOLPHIN (Mammal)


Falcon
Bat
Pteradactyl
Ancestral bird
Ancestral mammal
Ancestral reptile


Giant Armadillo
North America
Giant Pangolin
Africa
Giant Anteater
South America
Spiny Anteater
Oceania


OMG we have such similar beaks!!!! Are we related? :o
No...I think it's just because we live in the same area...:D

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Increased response to secondary infection

Table 1. Selected Experimental Models in which Biological Activity Compatible with the Concept of Trained Innate Immunity Has Been Reported

Organism	Experimental Model	Biological Effect	Specificity	References
Plants—Systemic Acquired Resistance				
Large variety of plants	Viruses, bacteria, fungi	Protection against reinfection	Variable	Durrant and Dong, 2004; Sticher et al., 1997
Nonvertebrates				
Mealworm beetle	LPS, or bacterial prechallenge	Protection against secondary infection	No	Moret and Siva-Jothy, 2003
Drosophila	*S. pneumoniae* prechallenge	Protection against *S. pneumoniae*	Uncertain	Pham et al., 2007
Anopheles gambiae	*Plasmodium* prechallenge	Protection against *Plasmodium*	No	Rodrigues et al., 2010
Sponges	Transplantation	Rejection	Yes	Hildemann et al., 1979
Corals	Transplantation	Rejection	Yes	Hildemann et al., 1977
Vertebrates				
Mice	BCG	Protection against candidiasis	No	Van 't Wout et al., 1992
Mice	*Candida* vaccination	T/B cell-independent protection	No	Bistoni et al., 1986, 1988
Mice	Murine CMV infection	NK-dependent protection	No	Sun et al., 2009
Humans	BCG	Nonspecific protection to secondary infections	No	Garly et al., 2003

Netea et al: Cell Host and Microbe 2011

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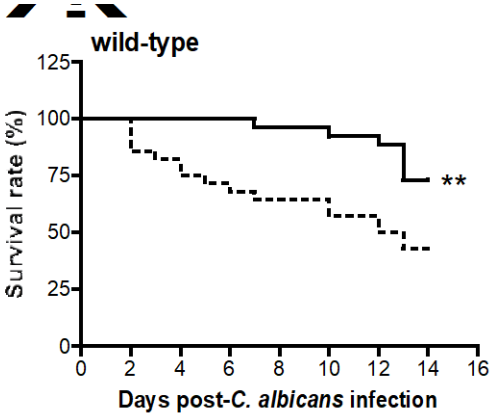
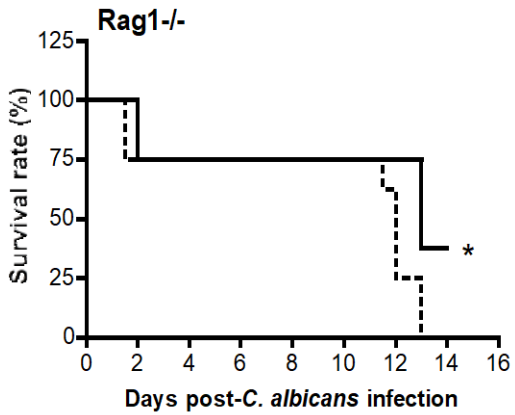
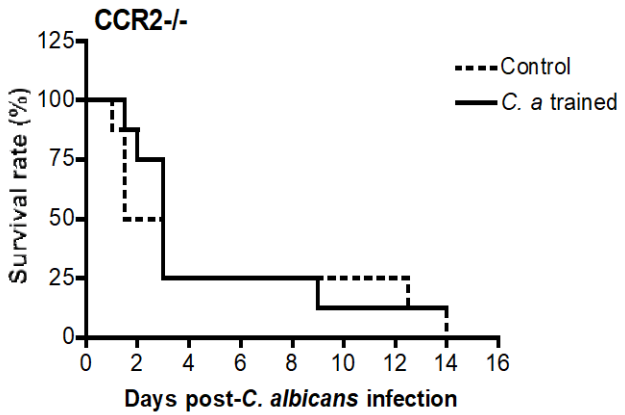
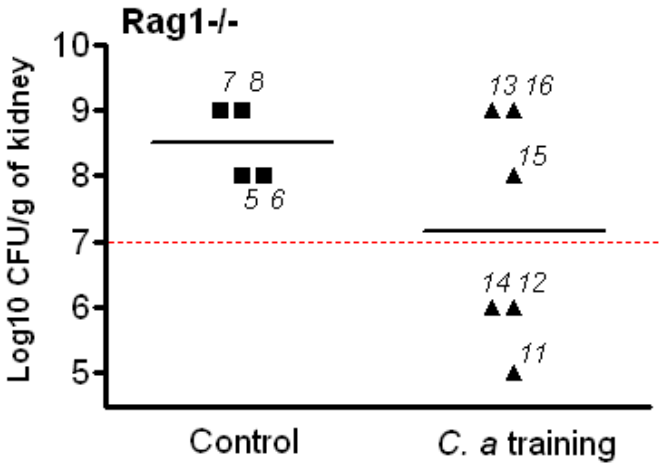
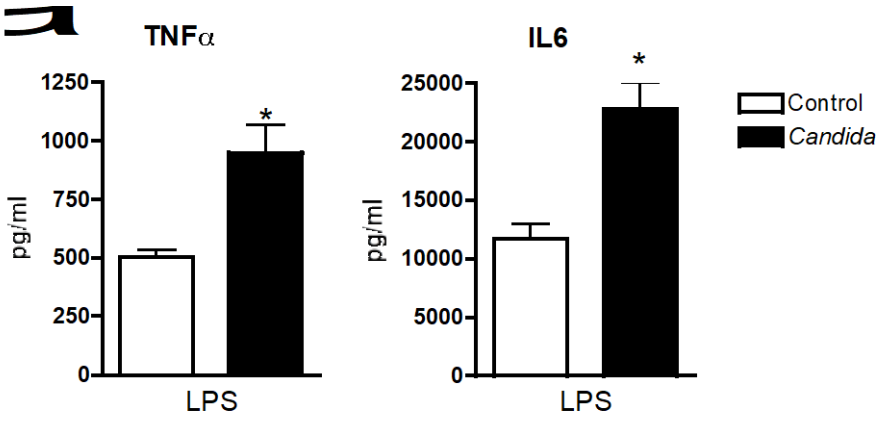
Innate immunity-dependent protection in mice











Quintin et al, Cell H&M, 2012

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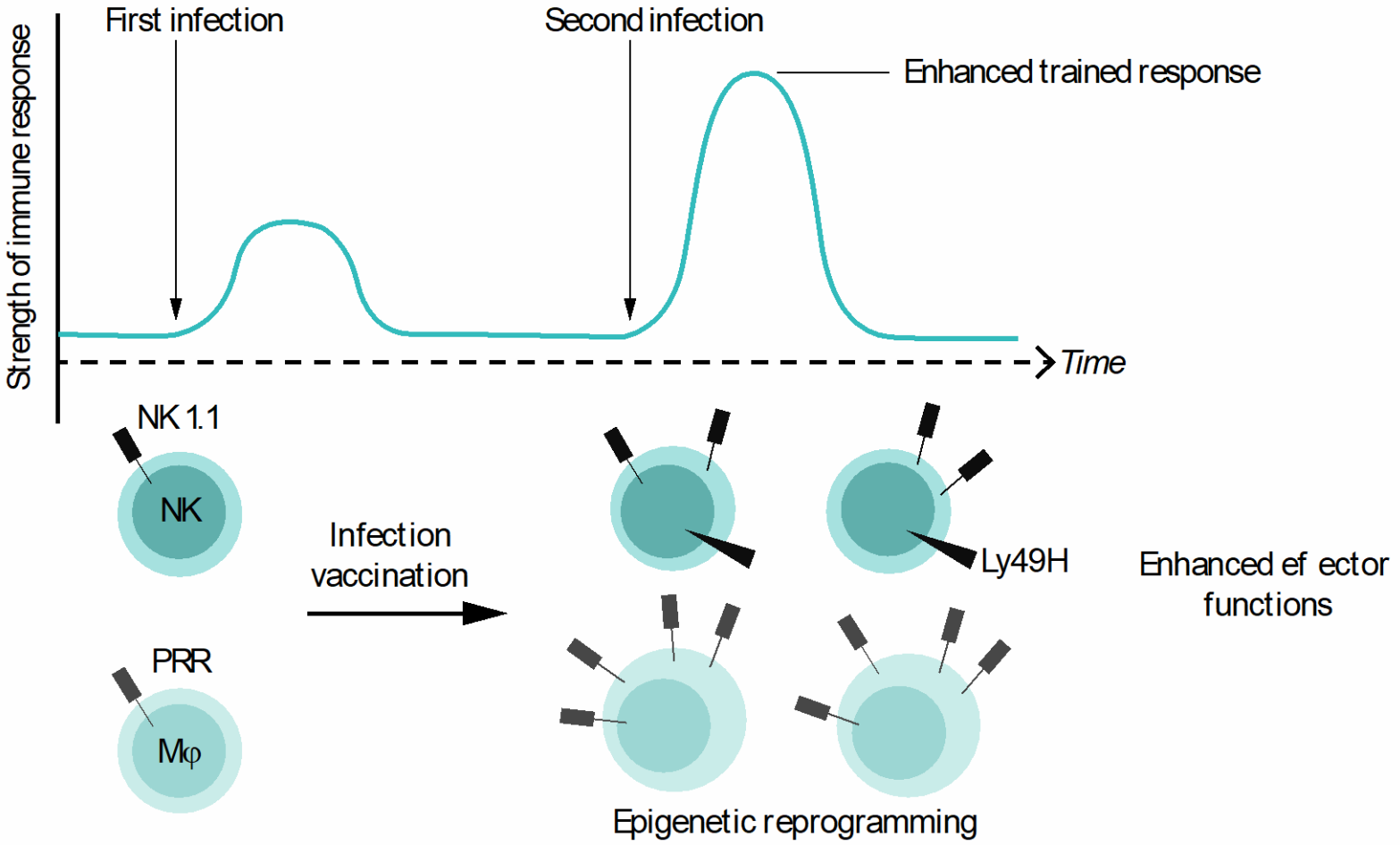
Trained immunity



Netea et al. Science 2016

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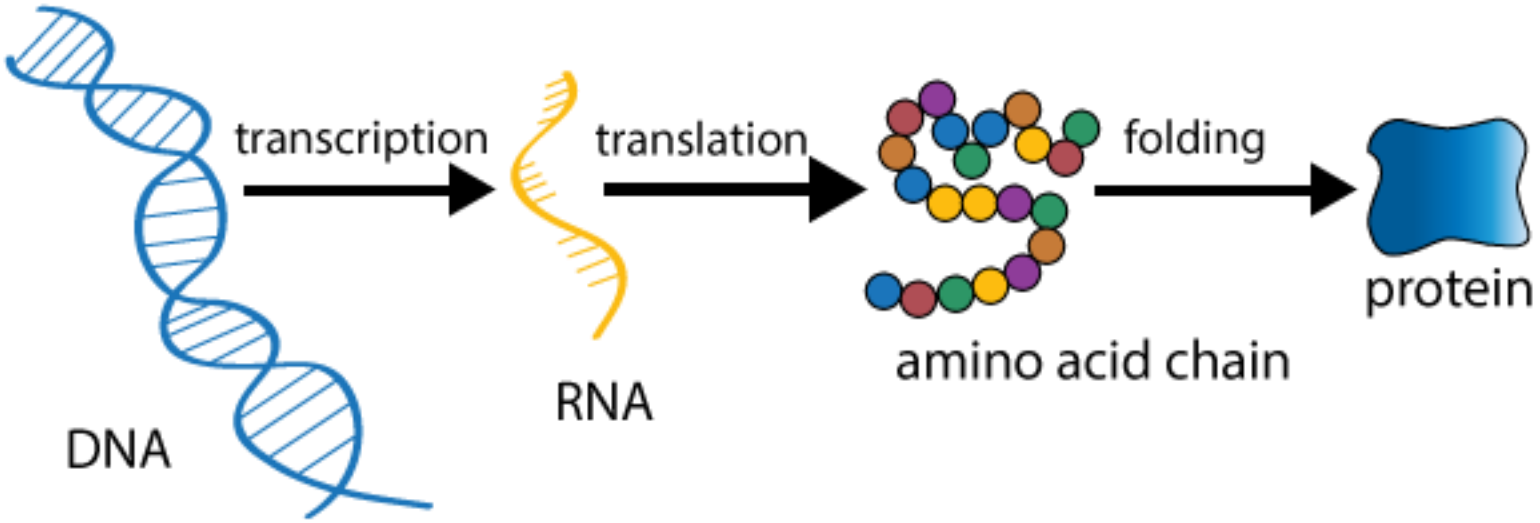
From DNA to protein



Netea et al. Science 2016

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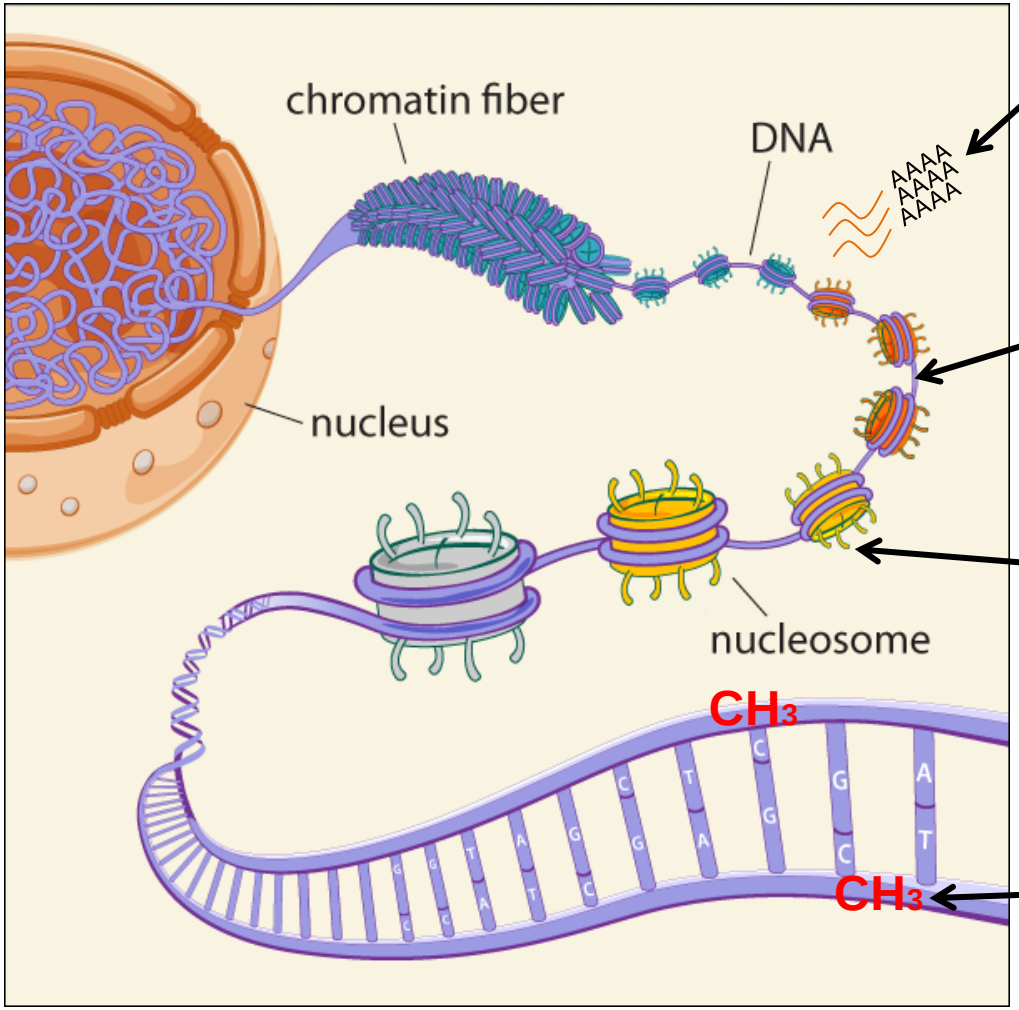
Long-term epigenetic reprogramming in myeloid cells



RNA-seq
Gene expression
Non-coding regulatory RNAs

ATAC-seq
Open chromatin (i.e. nucleosome-free regions) can be bound by TFs, which can be identified by motif sequence

ChIP-seq
Histone tail modifications determine 'activity' by attracting TFs
(we use 5 histone modifications)

WGBS – whole genome bisulfite sequencing
DNA methylation maintains DNA in a closed state

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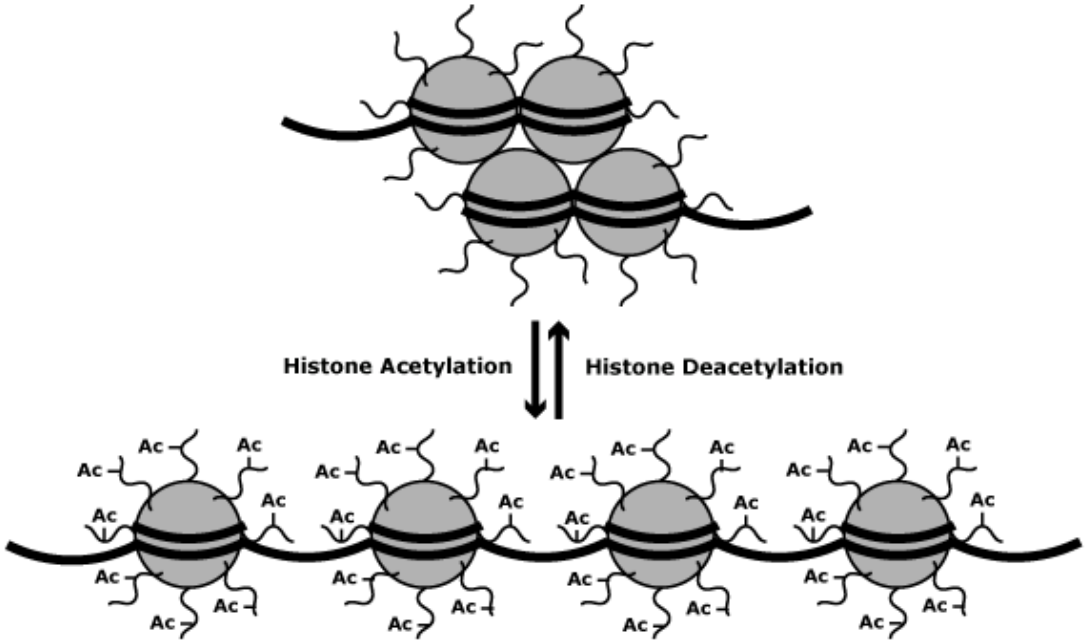
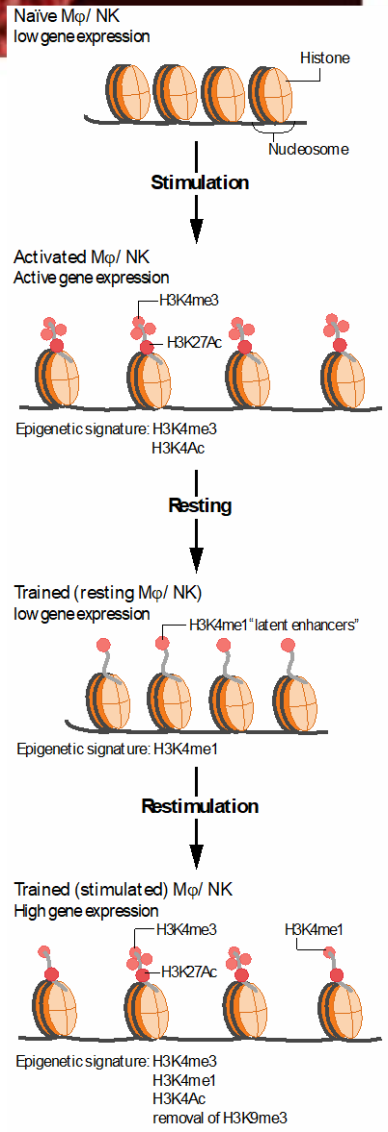
Chromatin architecture



DNA in the nucleus



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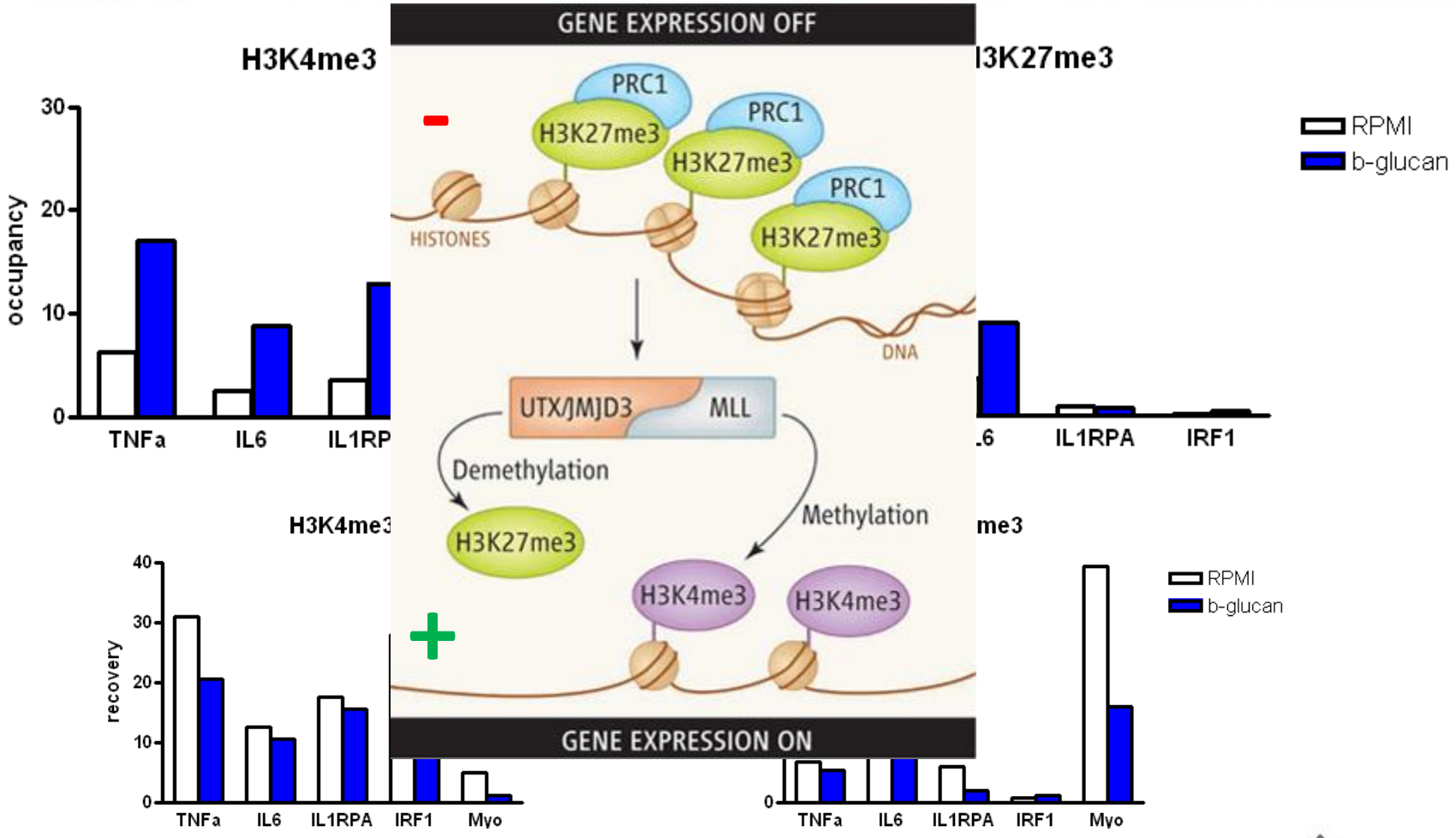
Methylation status of H3



Quintin et al, Cell H&M, 2012

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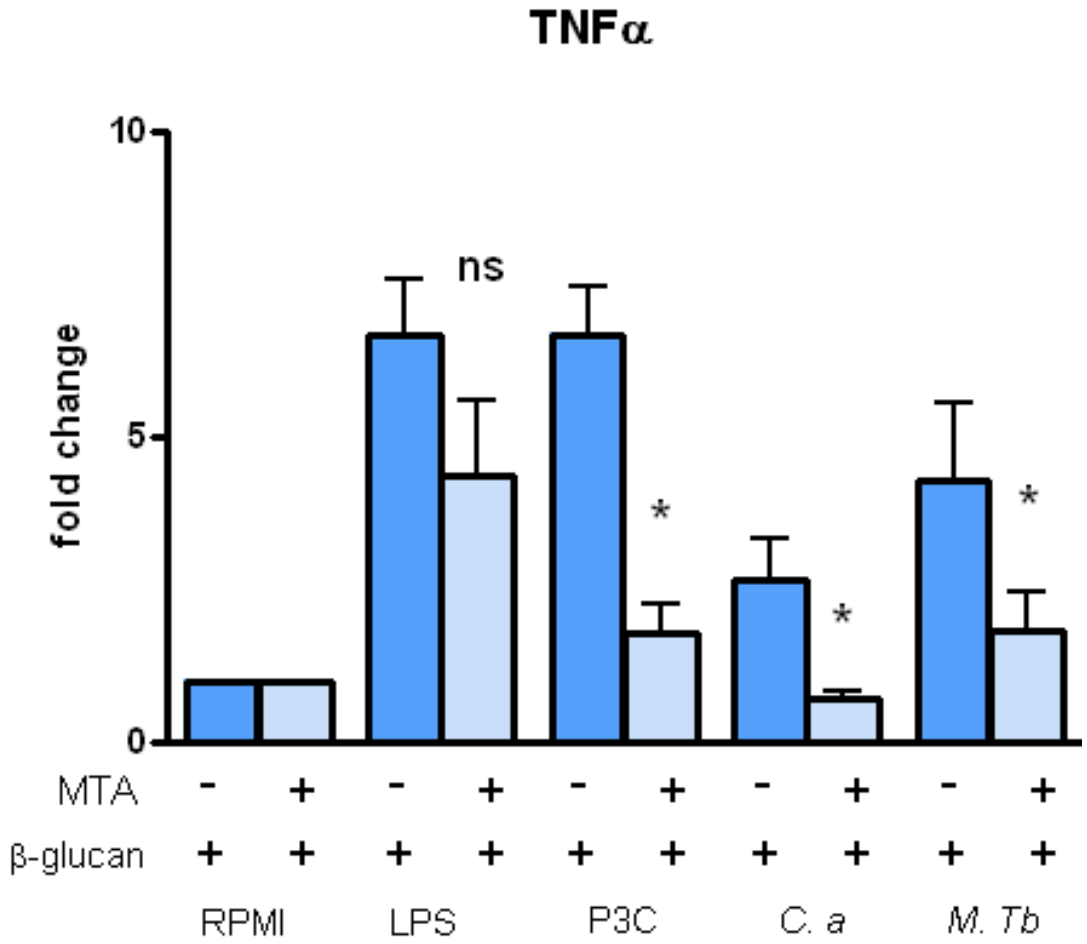
MTA: Histone methyltransferase inhibitor

Less Methylation



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Quintin et al, Cell H&M, 2012

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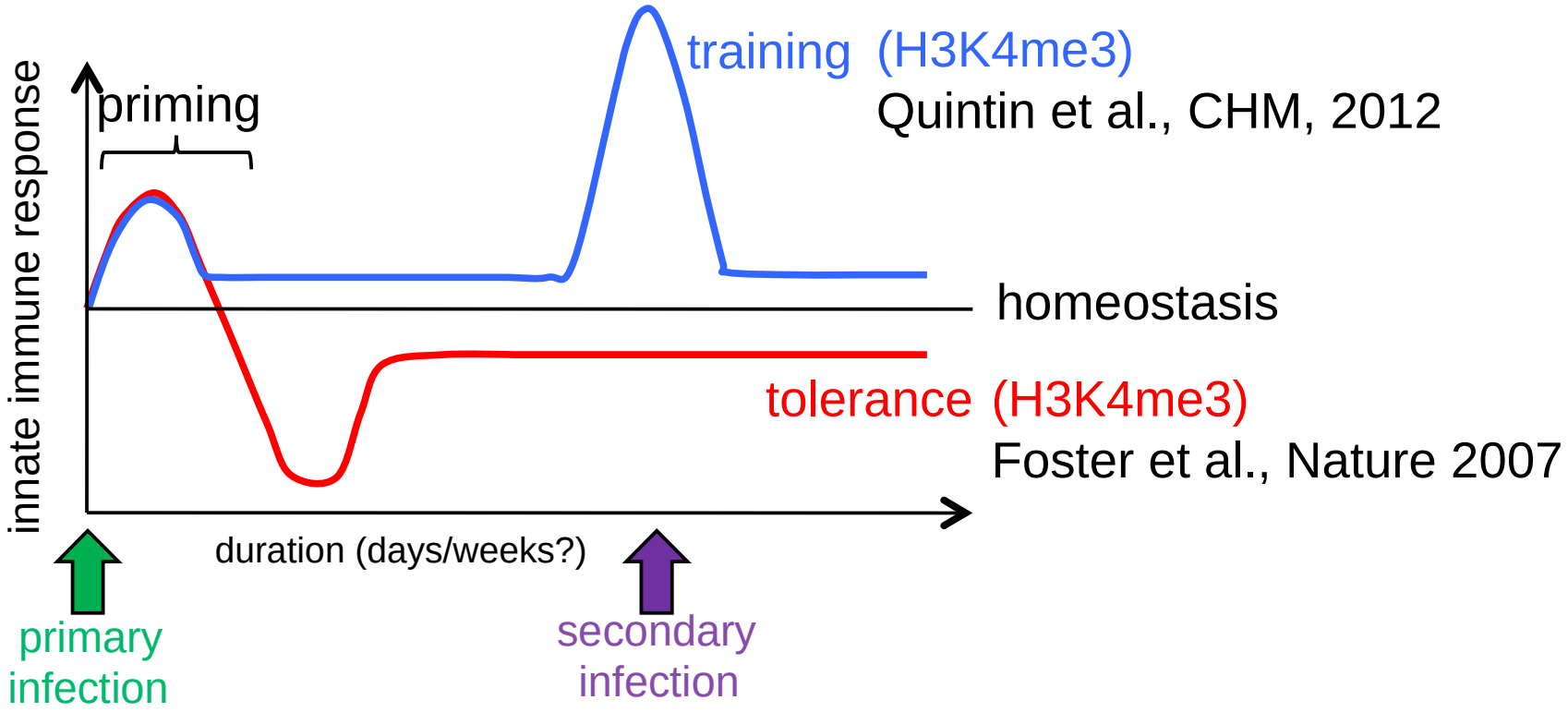
Trained immunity versus tolerance



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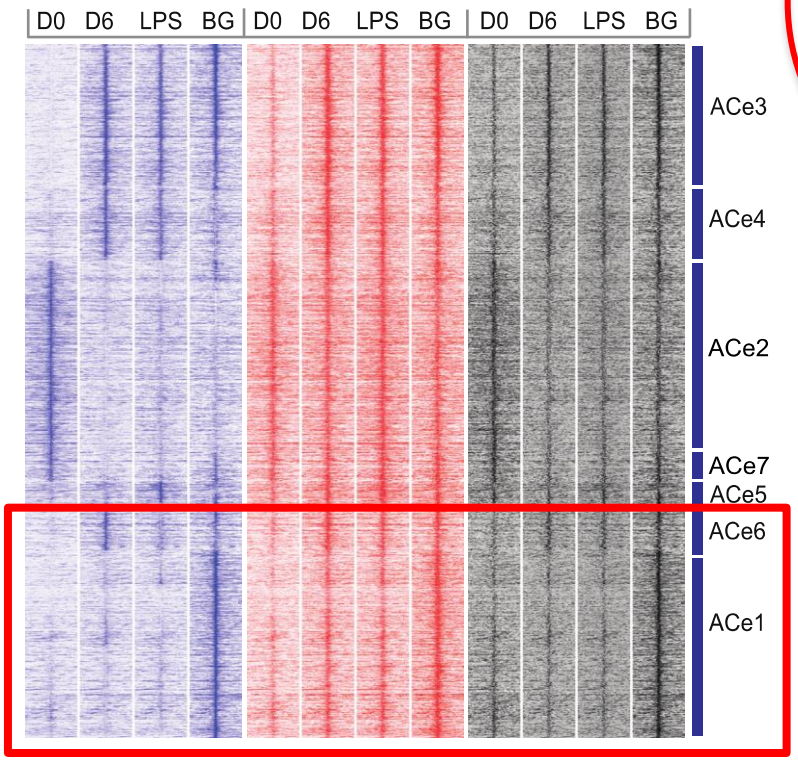
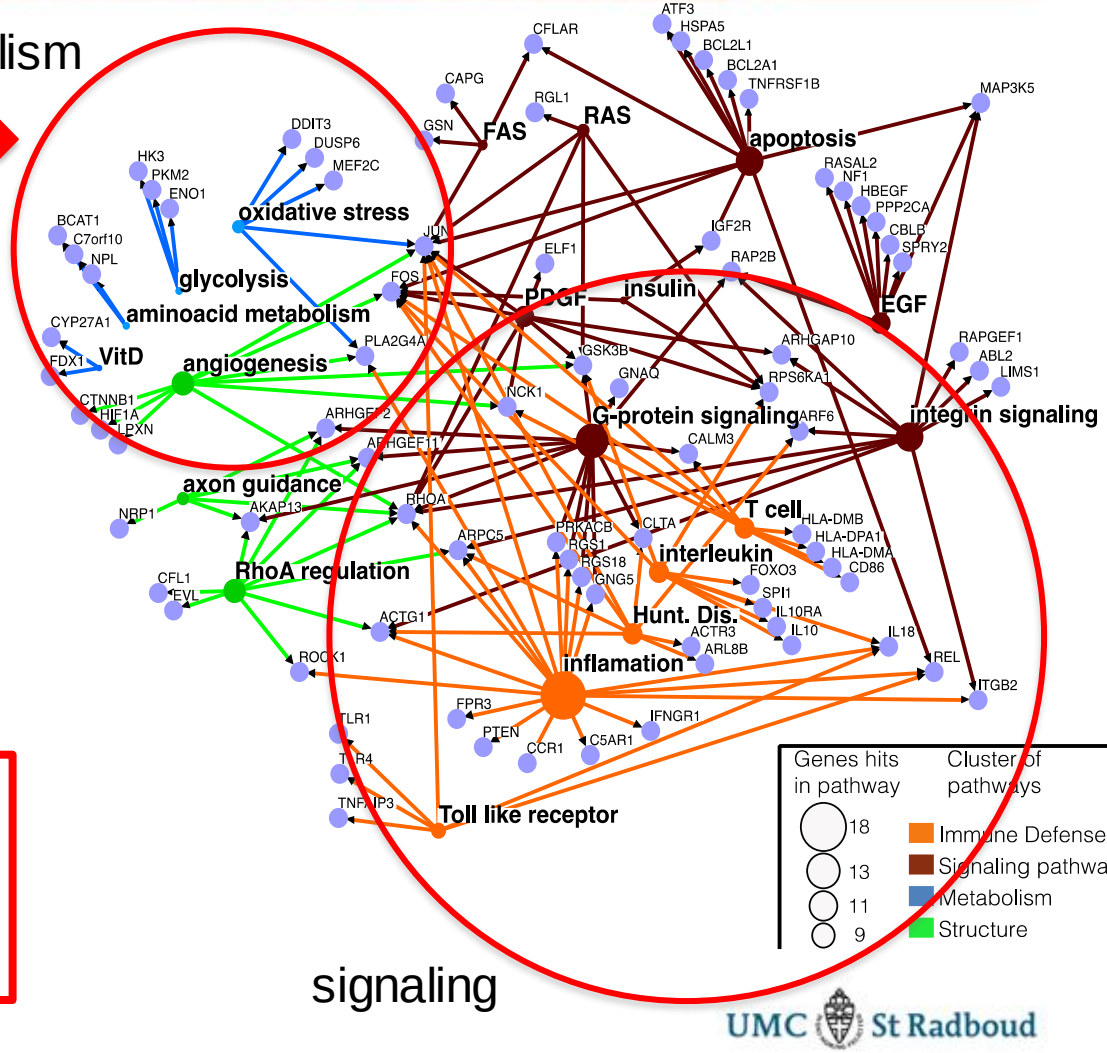
What are the pathways distinguishing Training vs Tolerance ?





Saeed et al, Science, 2014

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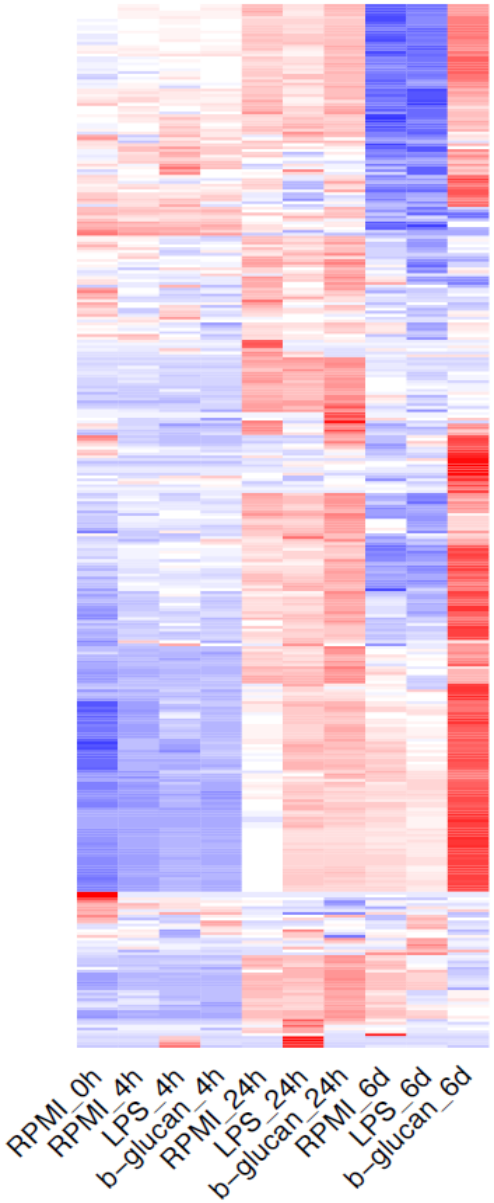
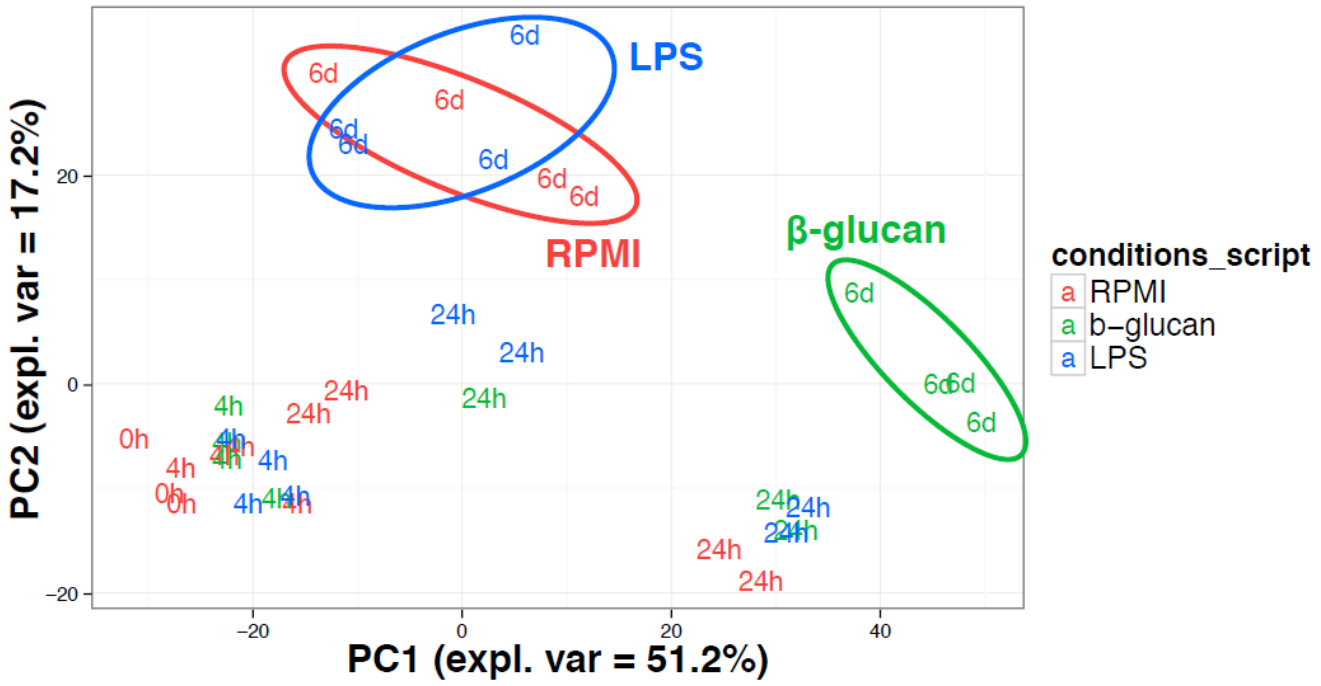
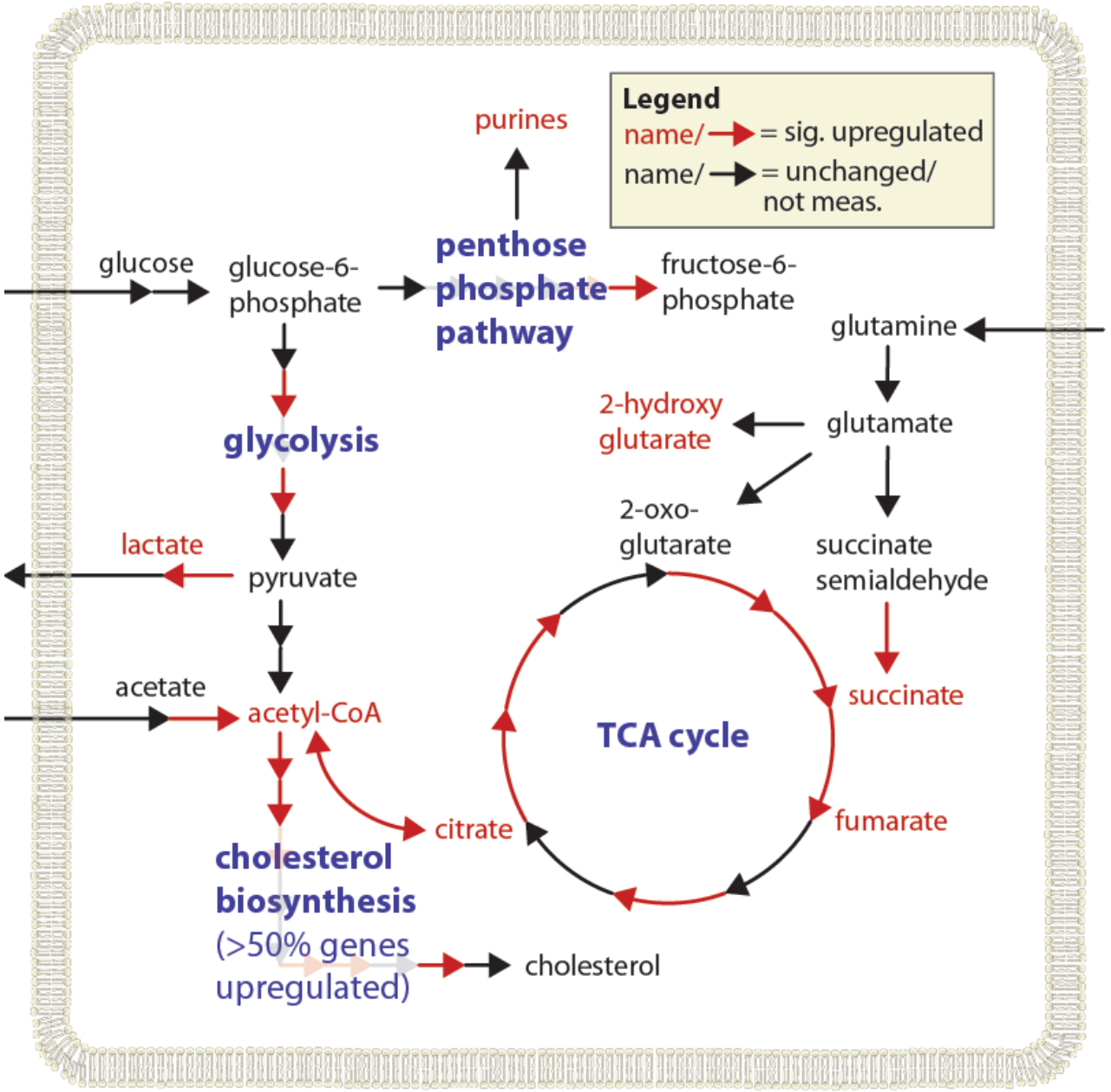
Metabolic status in trained monocytes



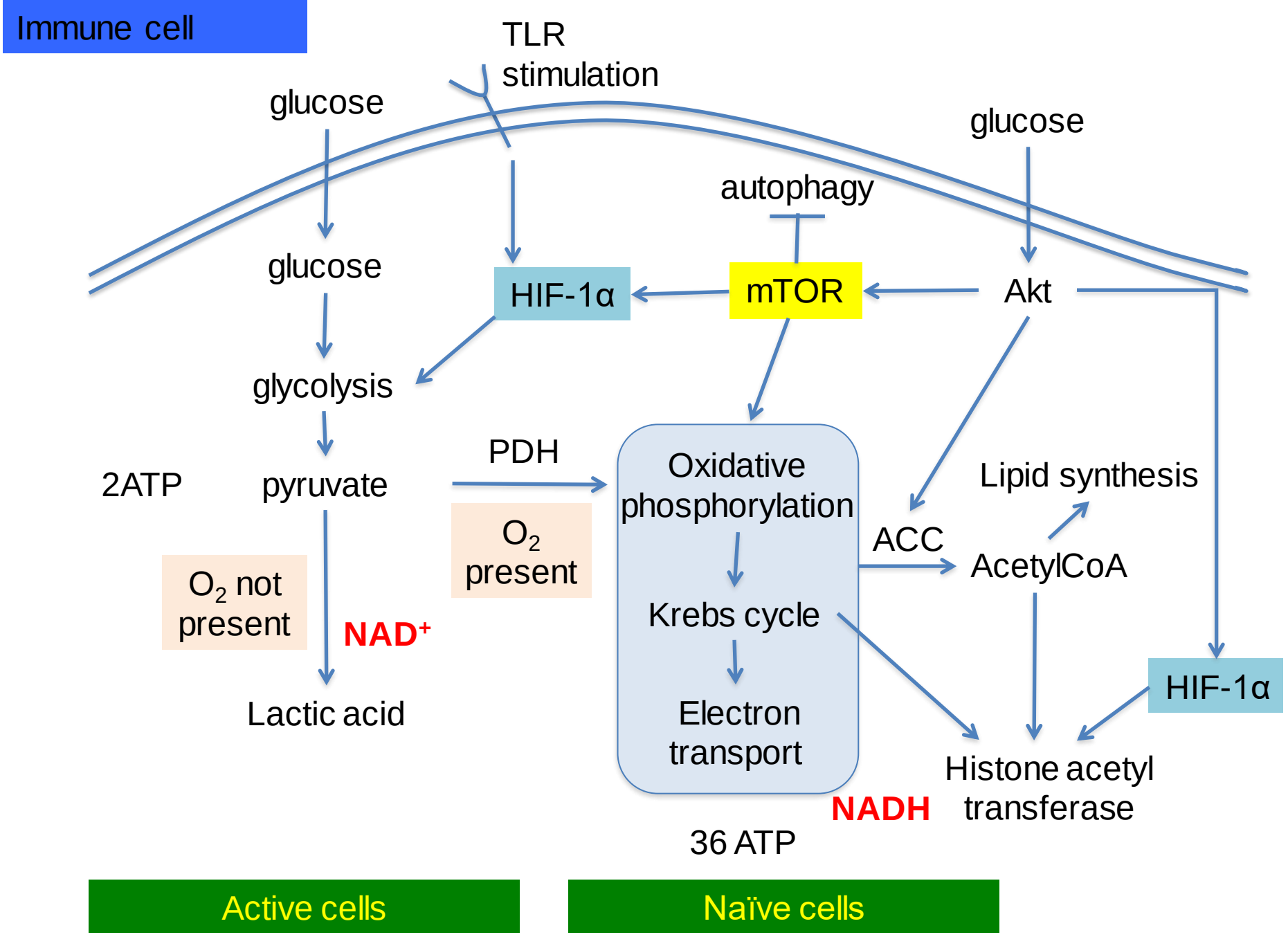


Arts et al, Cell Metabolism 2016

Metabolic status in trained monocytes

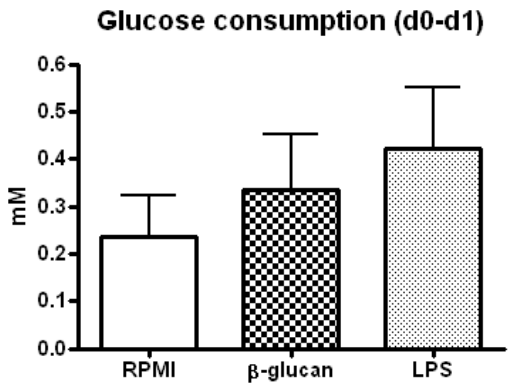


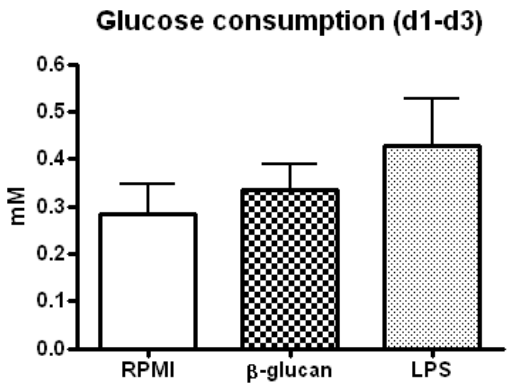
Arts et al, Cell Metabolism 2016

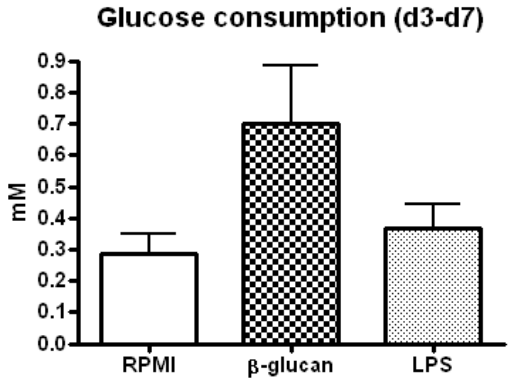

Immune cell
TLR stimulation
glucose
glucose
glucose
autophagy
HIF-1α
mTOR
Akt
glycolysis
2ATP
pyruvate
PDH
Oxidative phosphorylation
Lipid synthesis
ACC
AcetylCoA
O2 not present
O2 present
NAD+
Krebs cycle
HIF-1α
Lactic acid
Electron transport
Histone acetyl transferase
NADH
36 ATP
Active cells
Naïve cells

Glucose consumption & lactate secretion

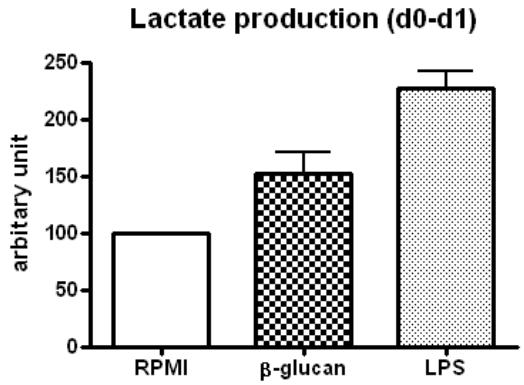
Glucose consumption

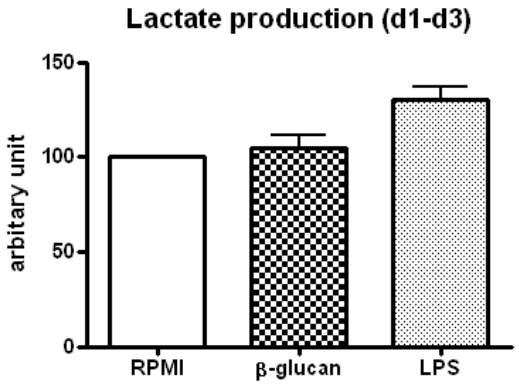


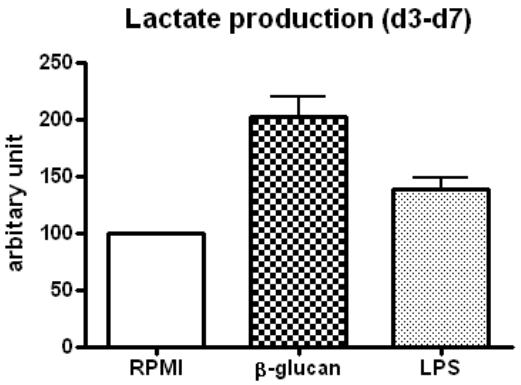




Lactate secretion







Cheng et al, Science, 2014

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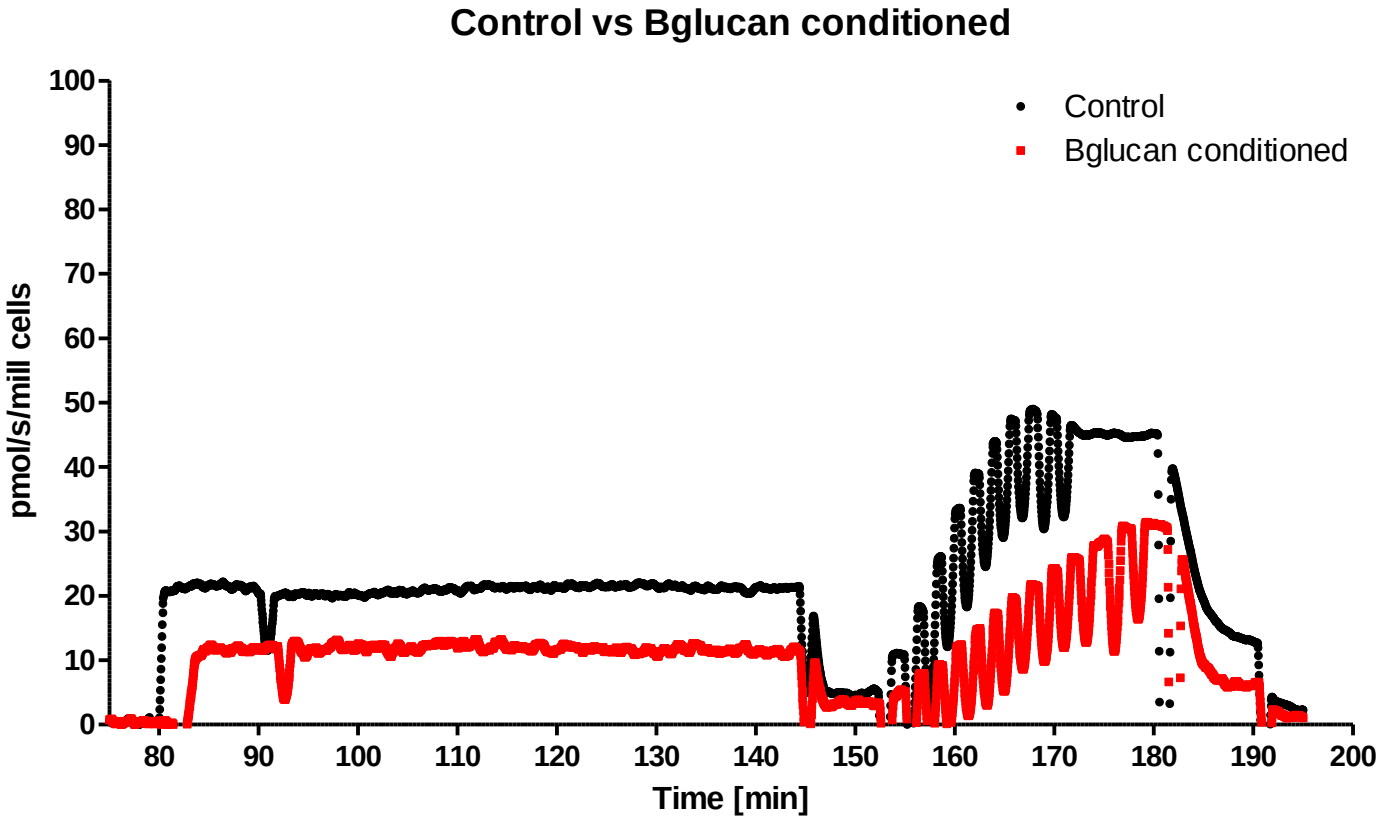
Reduced ATP-induced respiration



Cells	Basal	LPS 50 ng/ml	Oligomycin sensitive	Oli + FCCP	Rot + AA
Control	21.58	21.27	3.7	48.7	2.36
Bglucan conditioned	11.77	11.54	3.7	31.06	2.36

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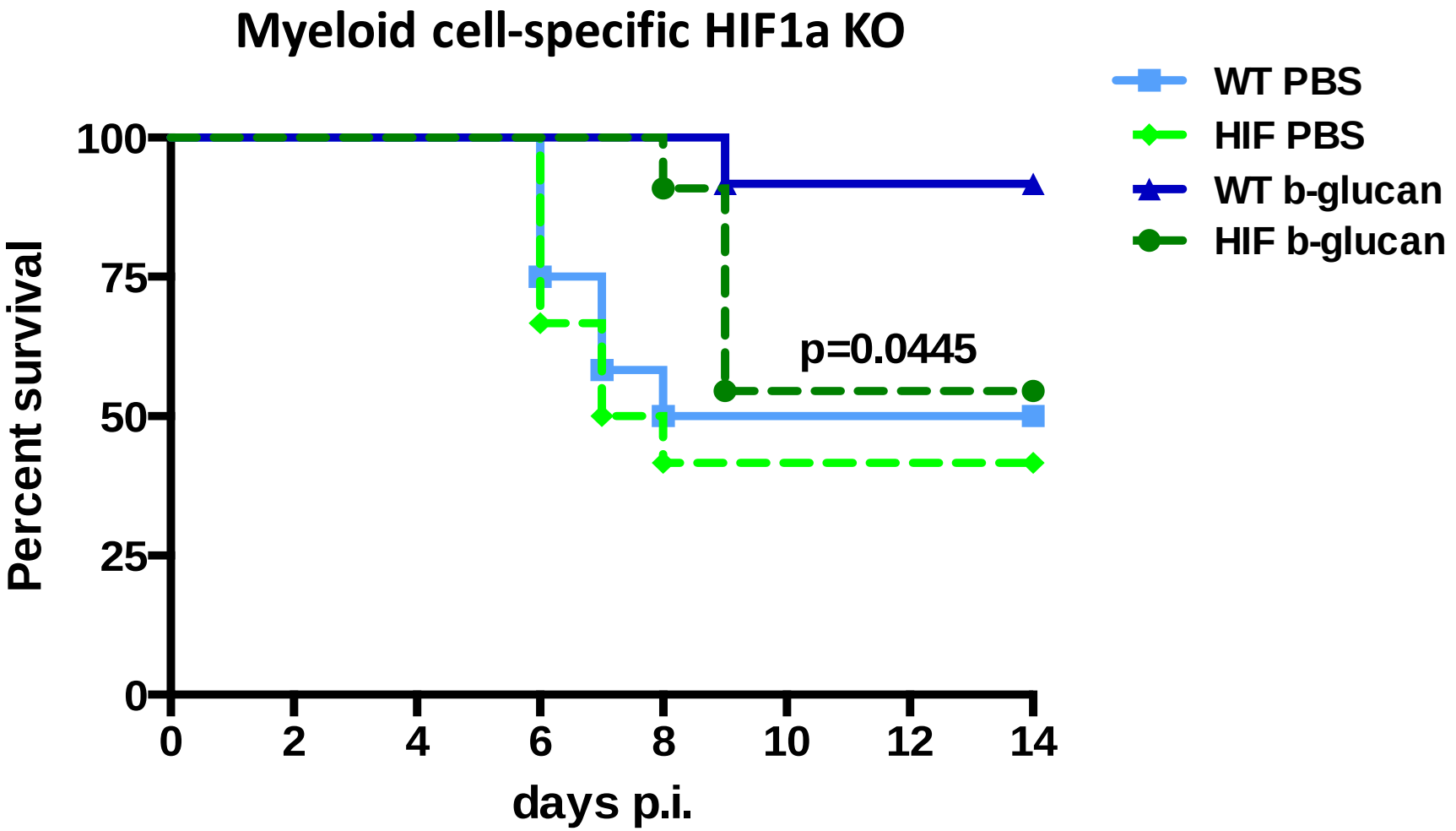
Cheng et al, Science, 2014

Blocking glucose consumption in-vivo inhibits trained immunity



Cheng et al, Science, 2014

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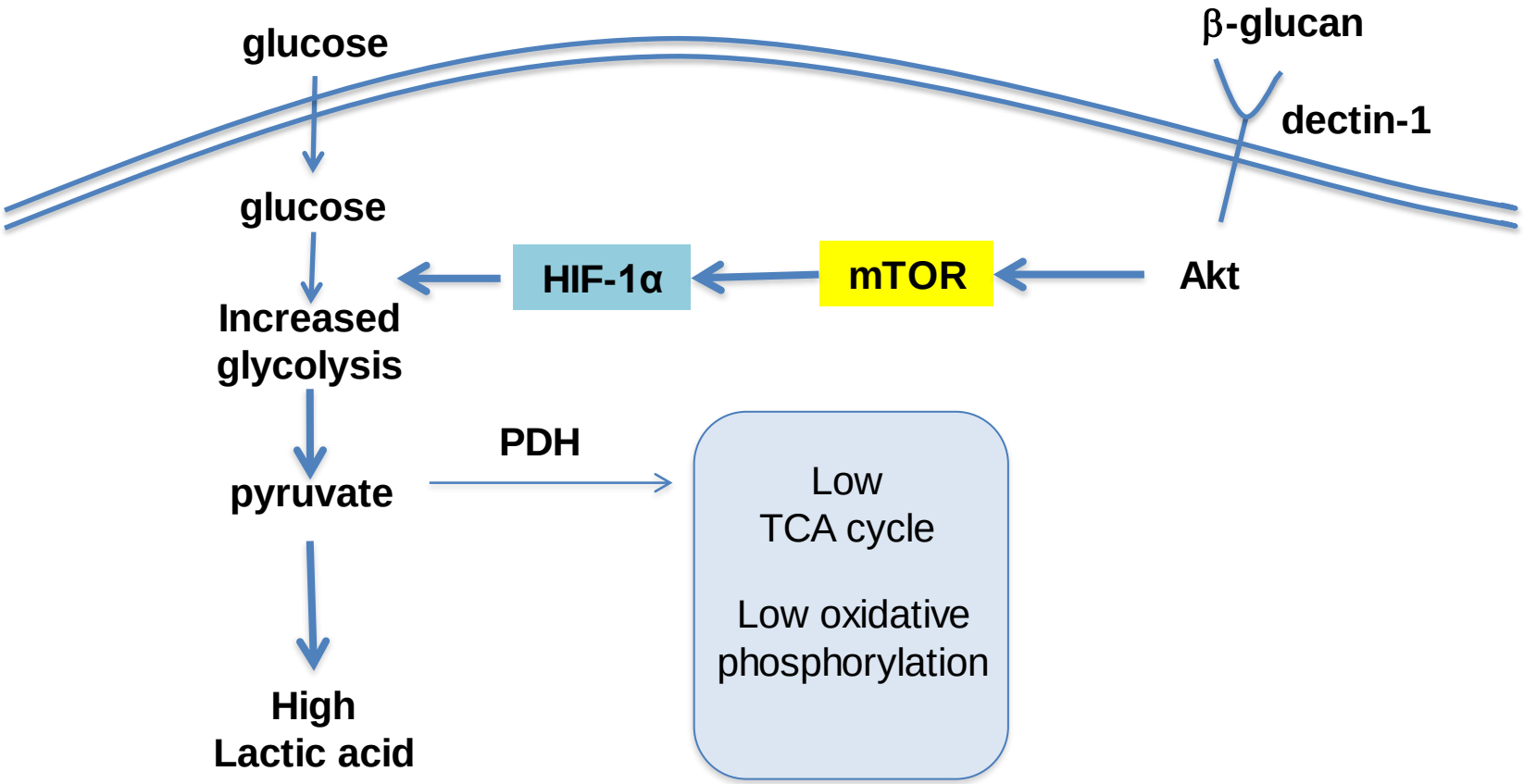
Model of metabolic activation of trained monocytes



Cheng et al, Science, 2014

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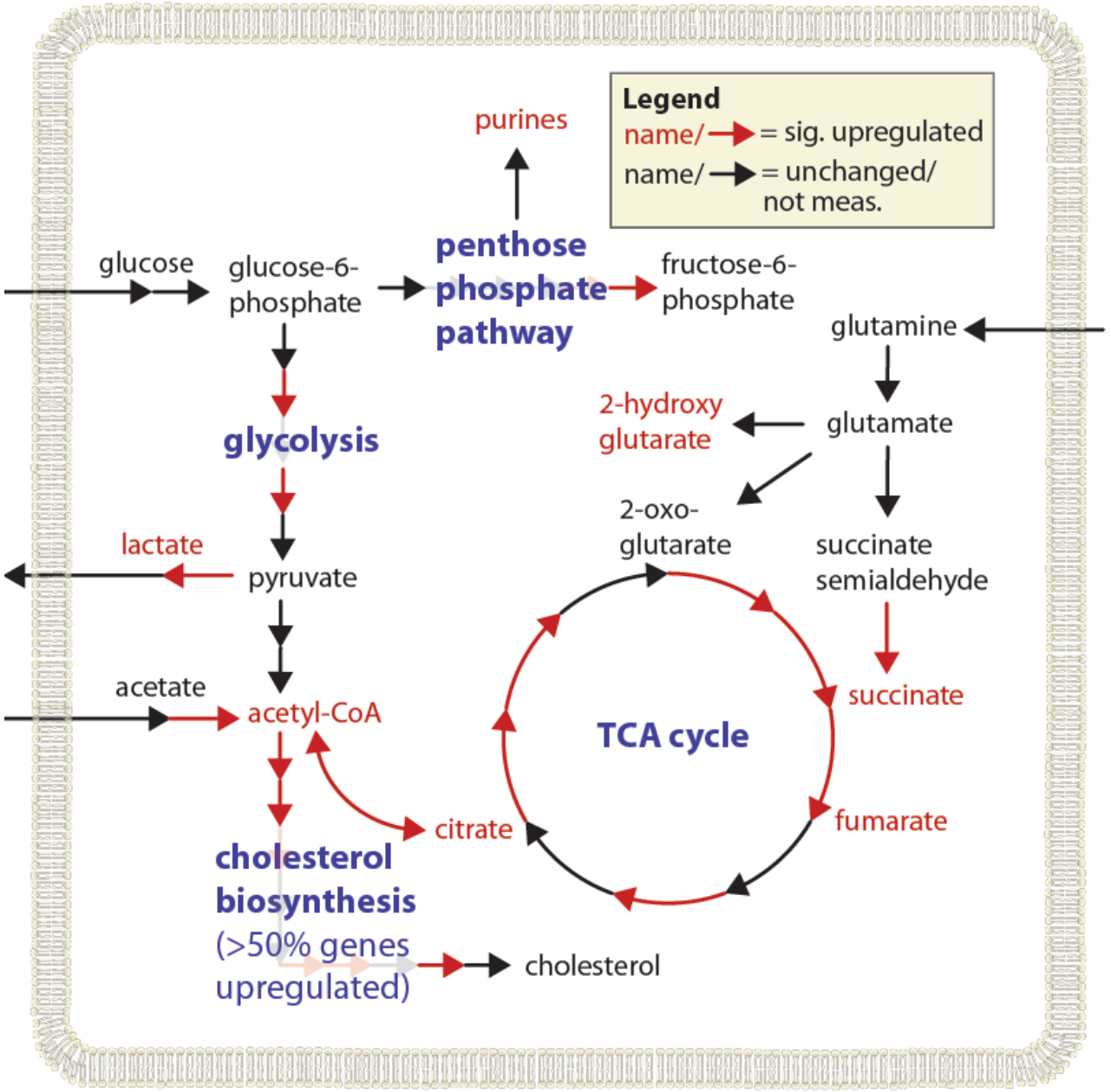
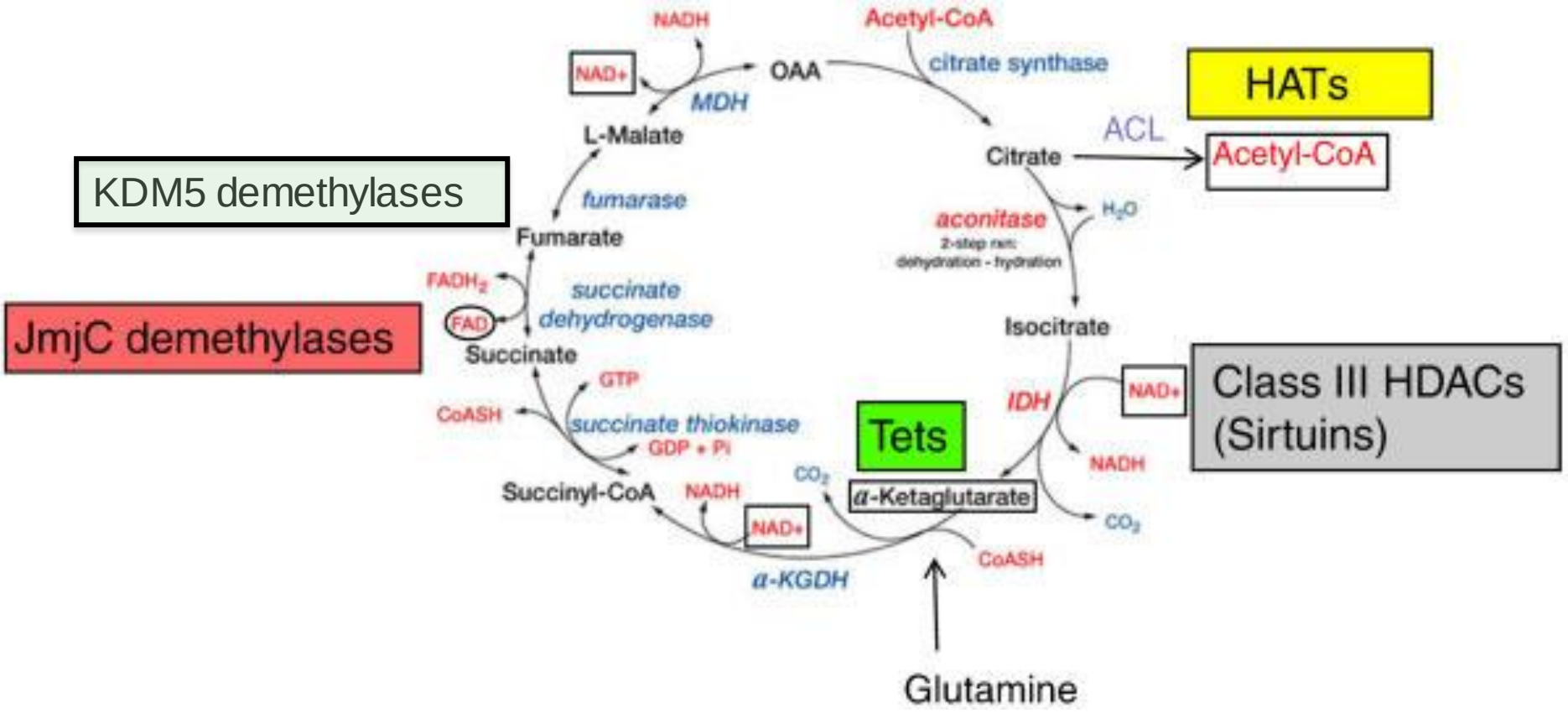
Metabolic status in trained monocytes



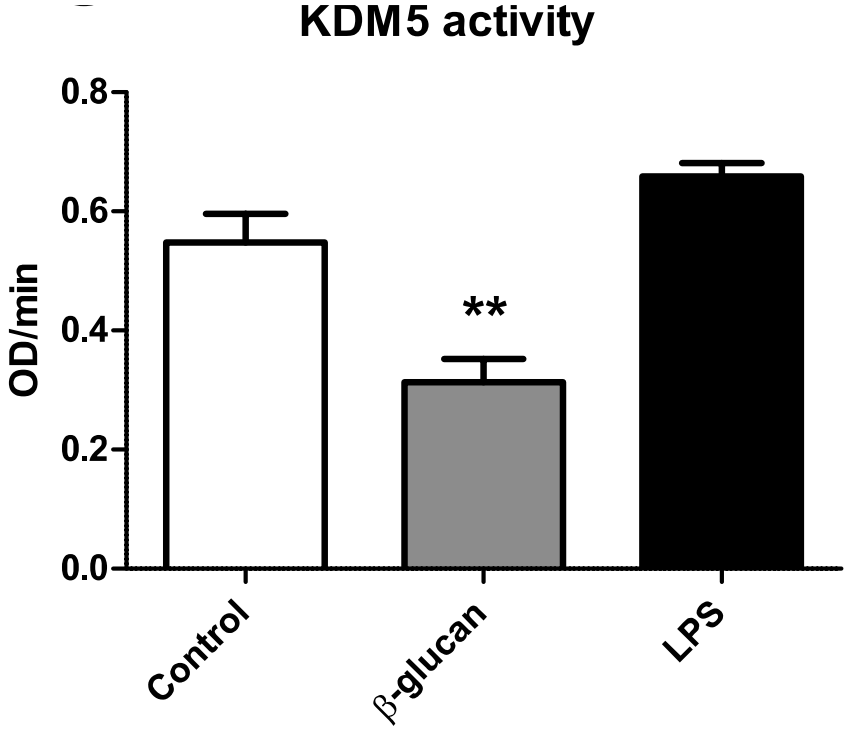
Arts et al, Cell Metabolism 2016

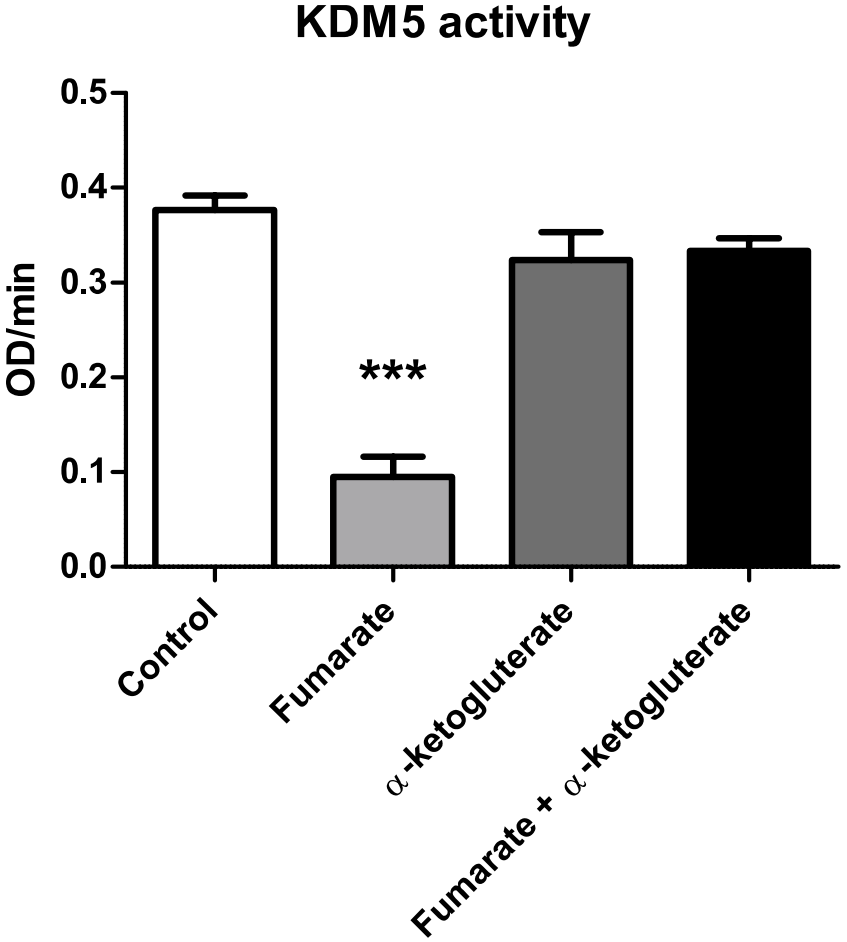
Metabolites are co-factors for epigenetic enzymes



Donohoe & Bultman, J Cell Physiol 2012

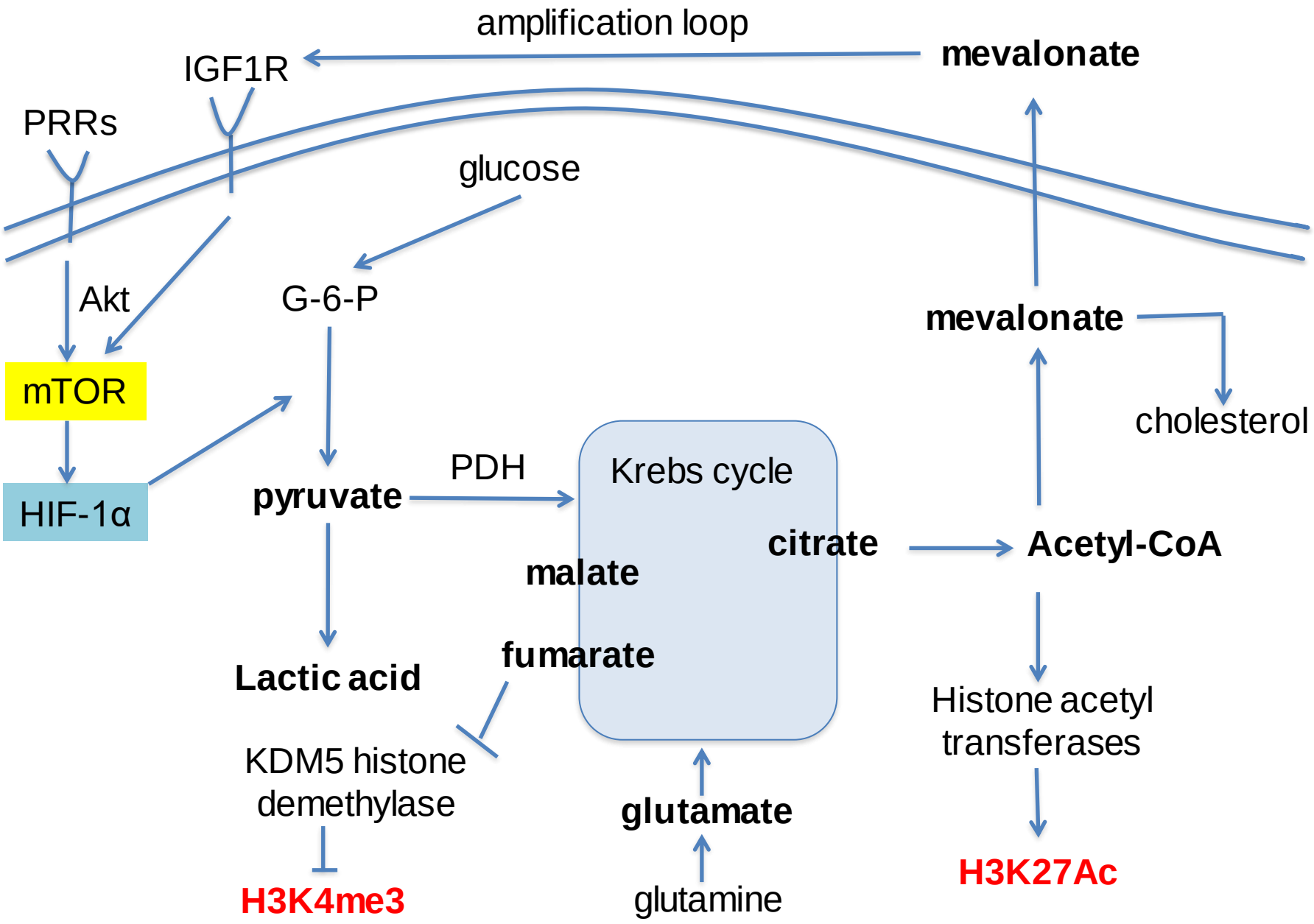
Fumarate induces trained immunity





Arts et al, Cell Metabolism 2016

Metabolic status in trained monocytes



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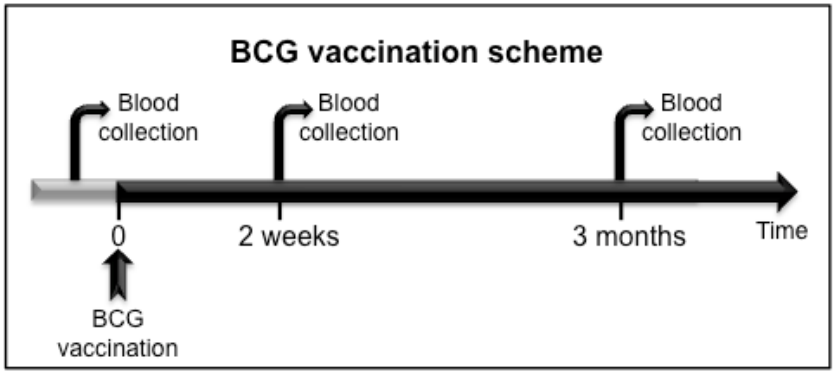
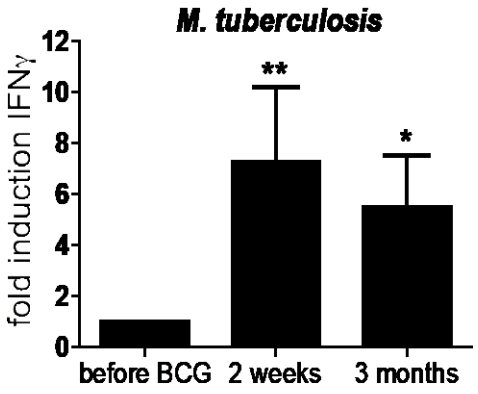
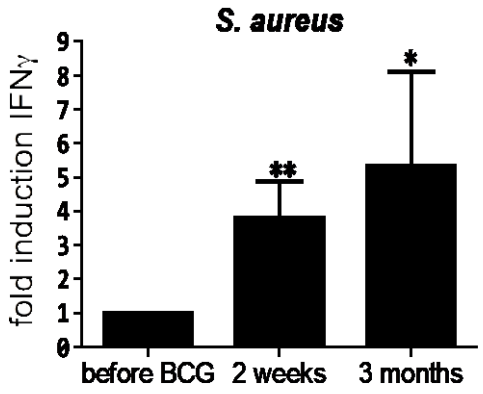
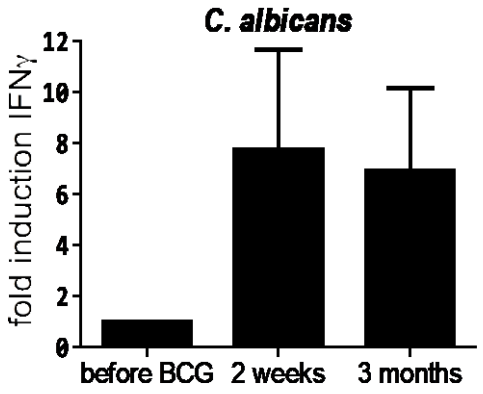
Does this happen in vivo in humans?









Kleinnijenhuis et al, PNAS, 2012

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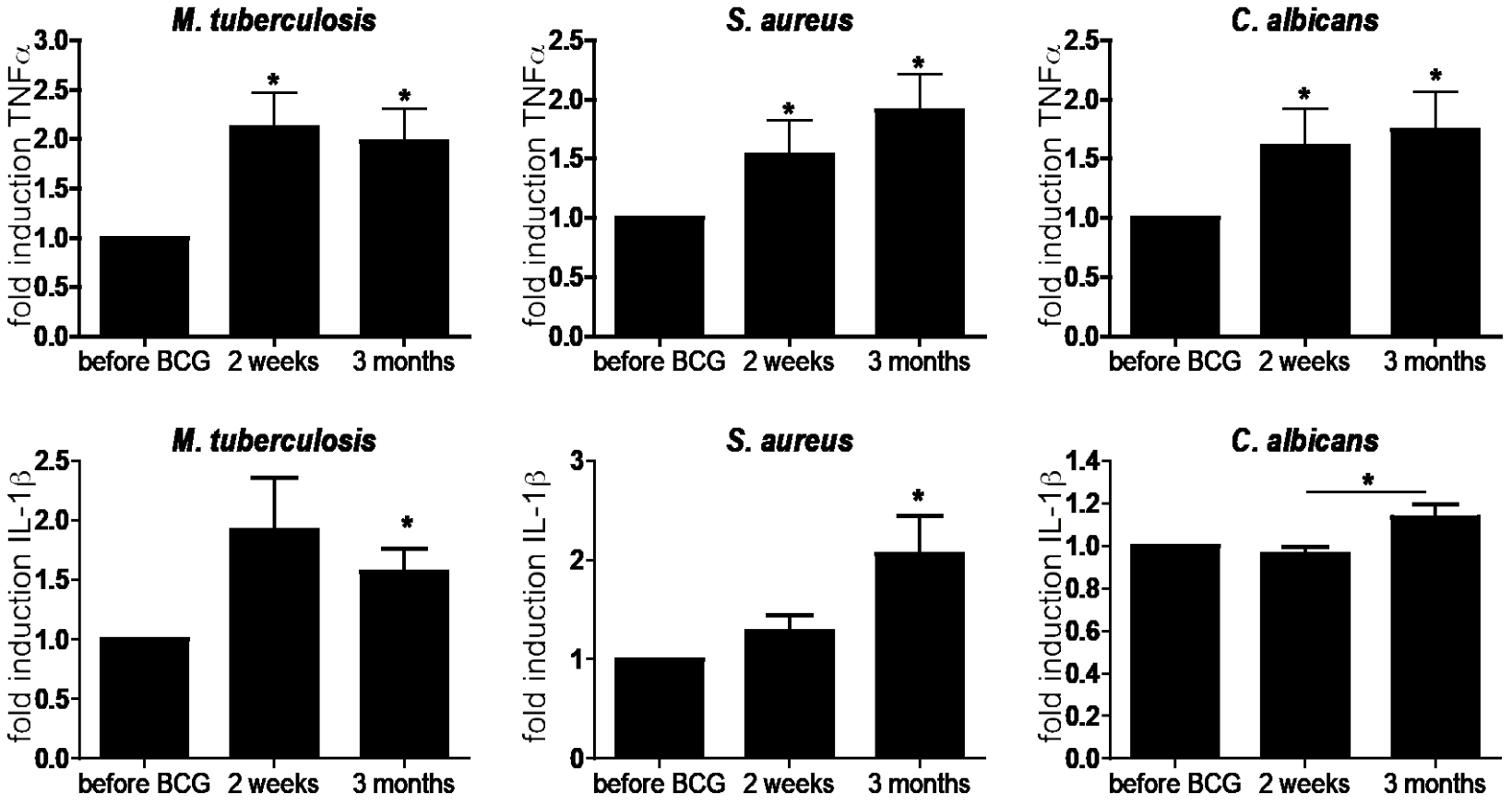
BCG enhances monocyte-derived cytokines



Kleinnijenhuis et al, PNAS, 2012

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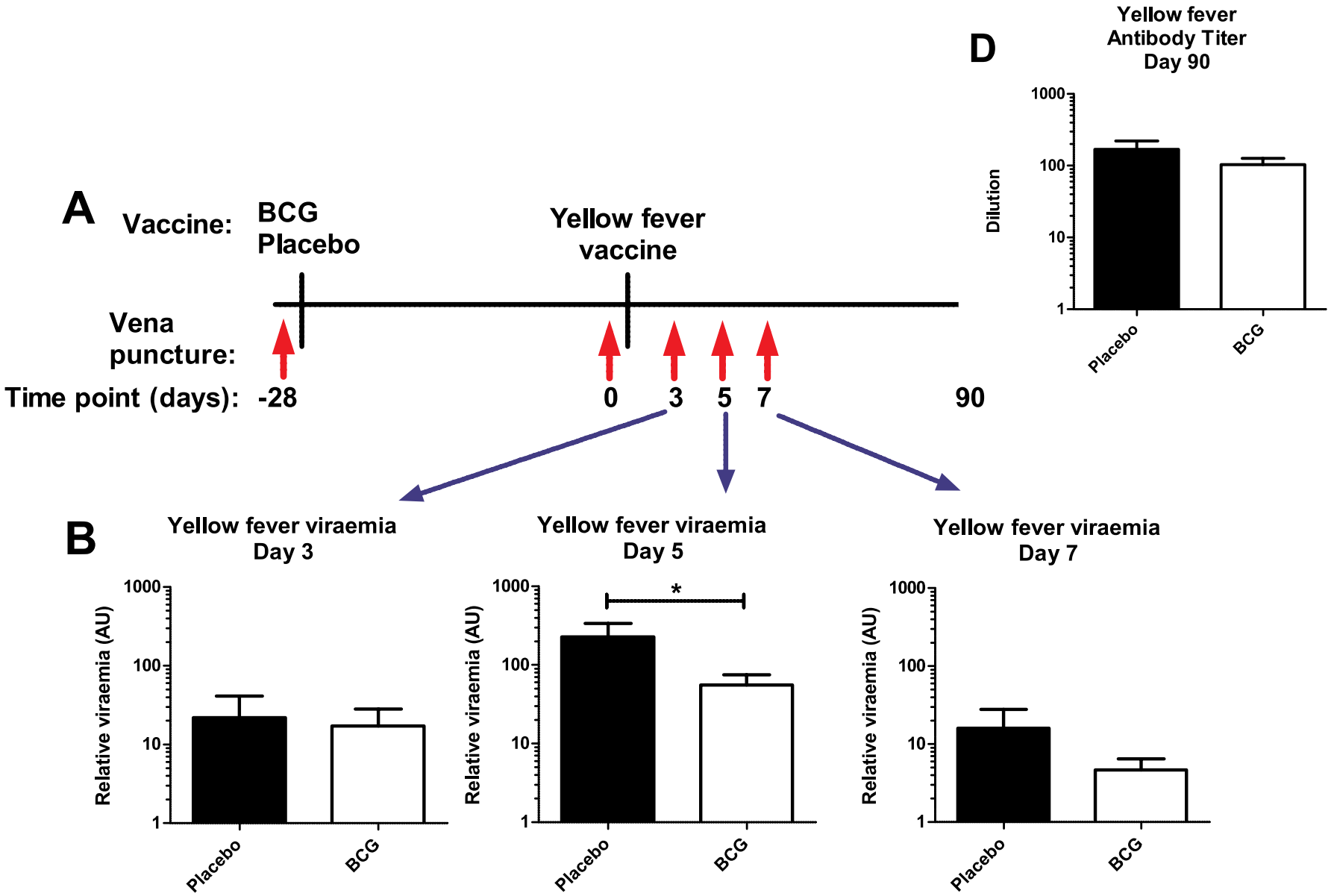
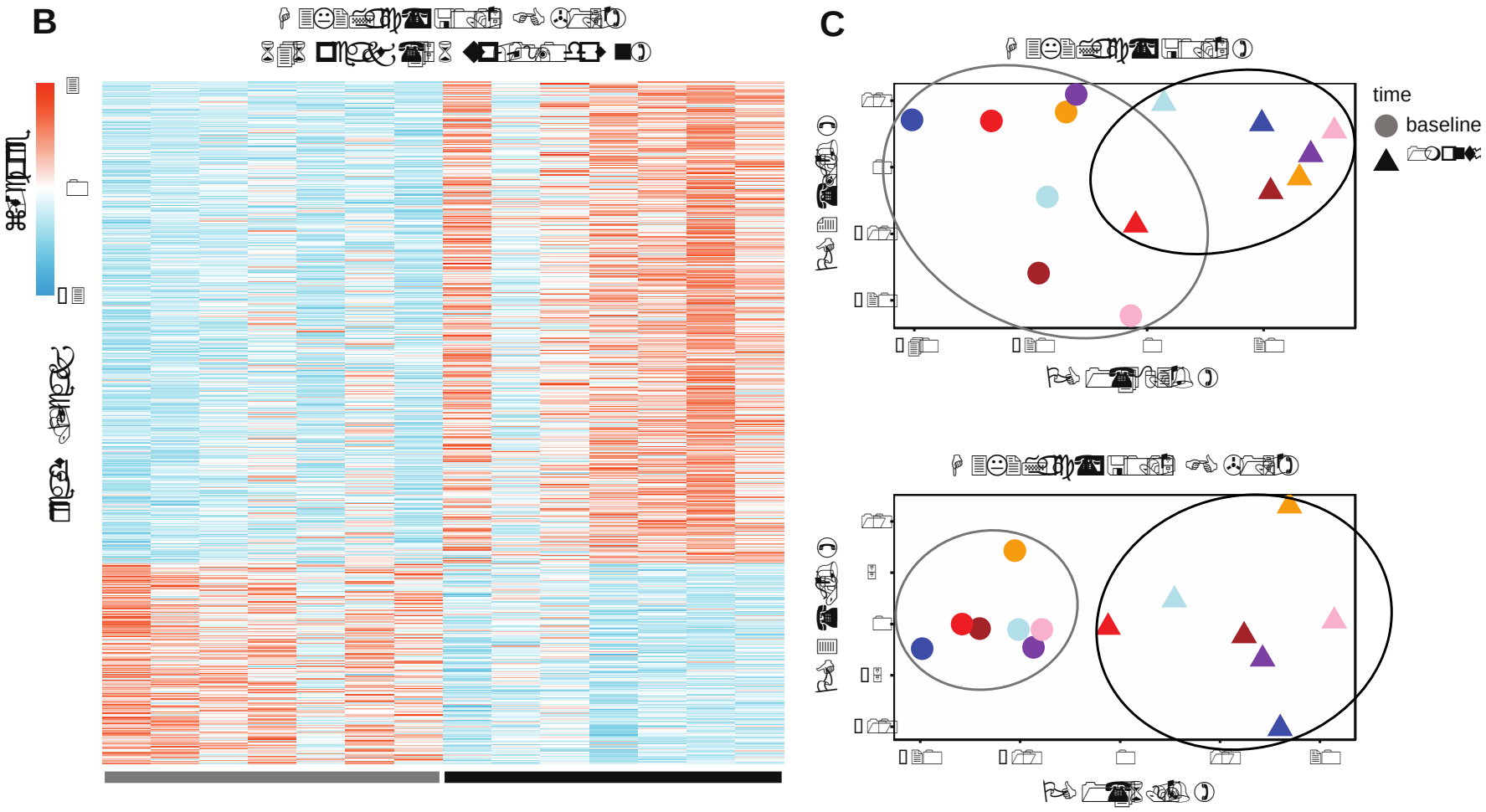
BCG vaccination in vivo yellow fever vaccine



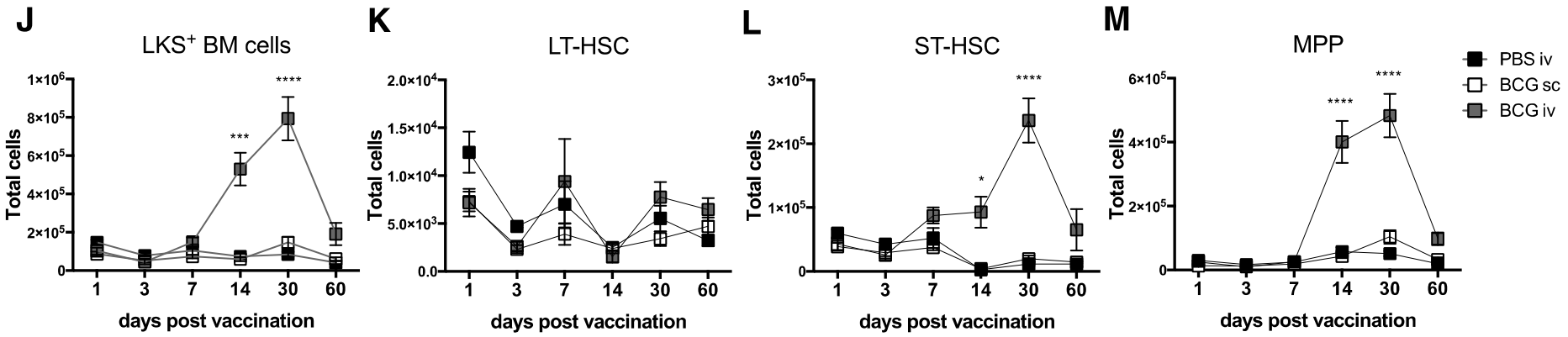
Arts et al, Cell Host Microbe, 2018 in press

BCG vaccination induces epigenetic reprogramming



Arts et al, Cell Host Microbe, 2018

BCG acts on myeloid cell progenitors



Kaufmann et al, Cell 2018

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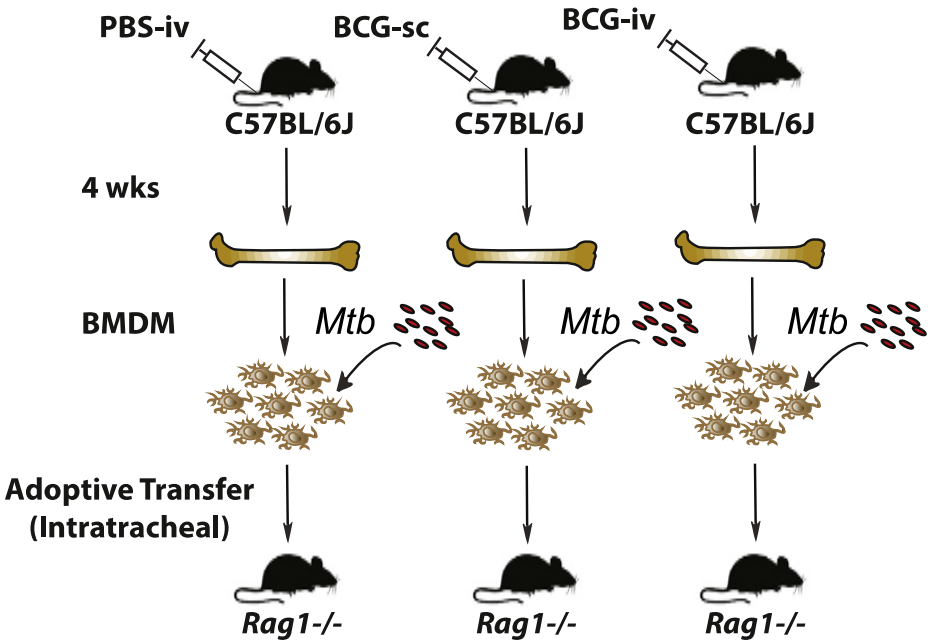
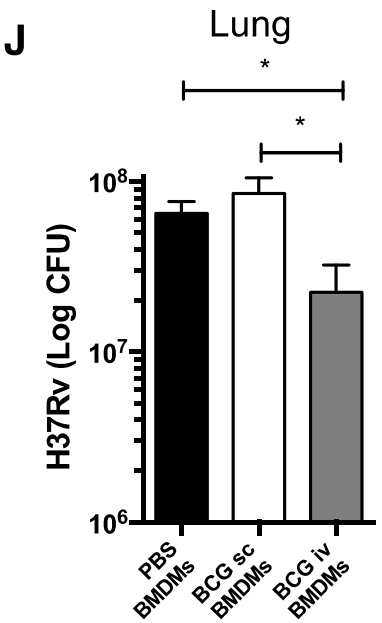
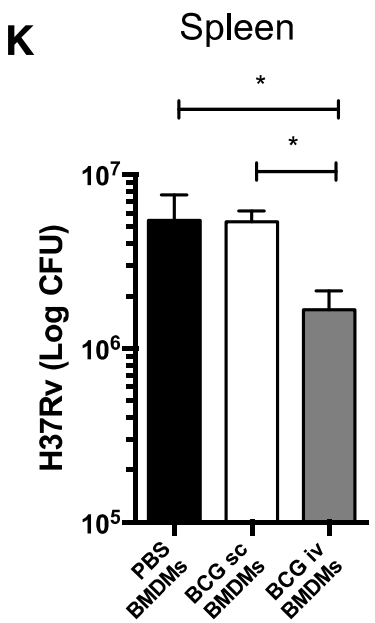
BCG trained effects are sustainable in vivo







Kaufmann et al, Cell 2018

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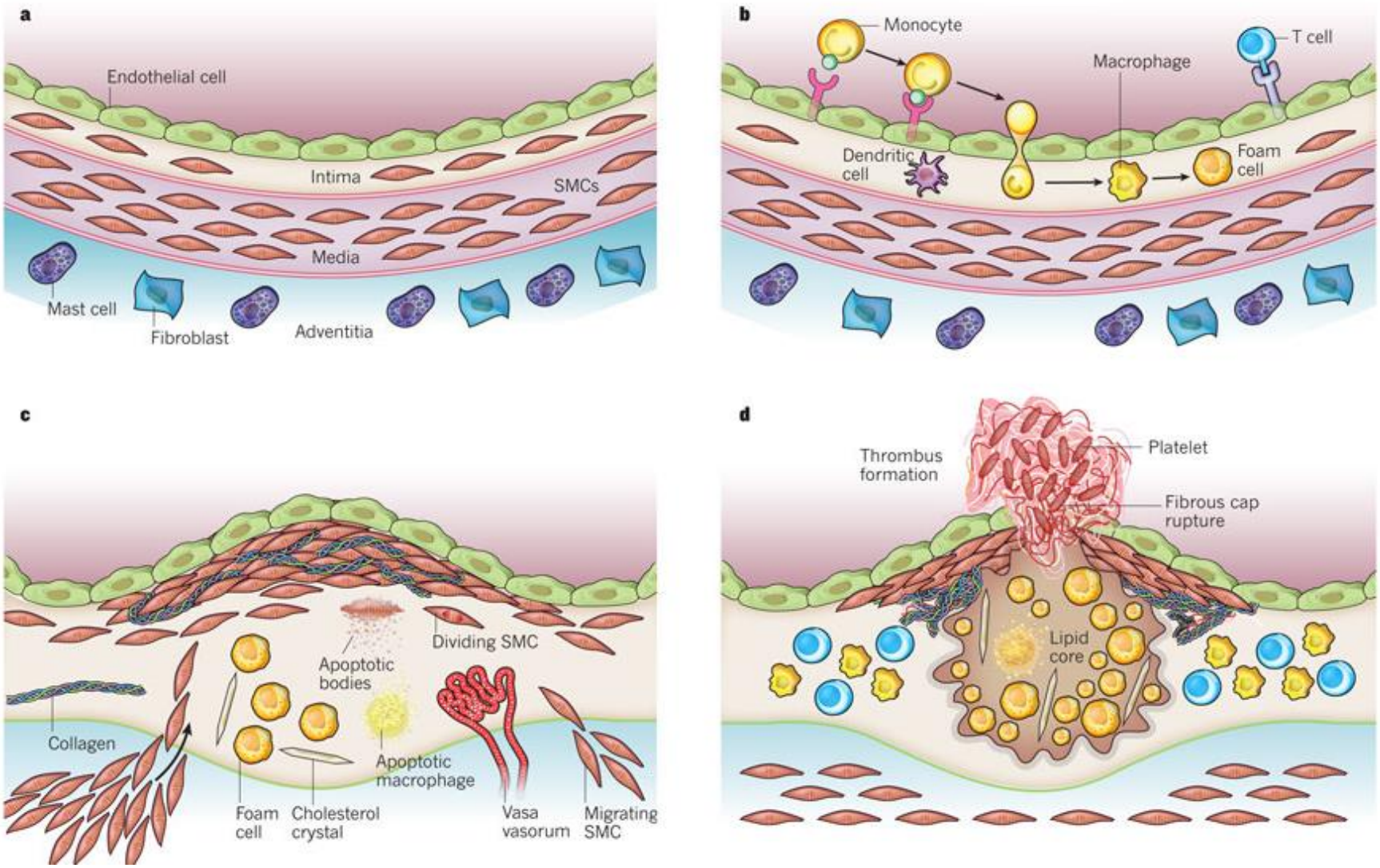
Conclusions BCG vaccination

- BCG vaccination induces trained immunity in circulating monocytes
- BCG induces long-term reprogramming at the level of myeloid cell progenitors in the bone marrow
- BCG vaccination leads to non-specific protection against unrelated infections: e.g. yellow fever vaccine viremia, malaria
- Responses to other vaccines are influenced as well

Atherosclerosis: non-resolving inflammation



Libby et al, Nature 2011

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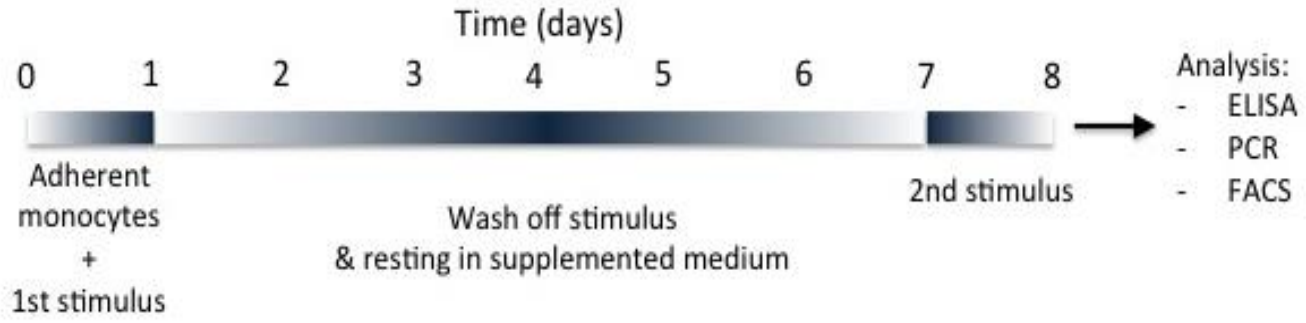
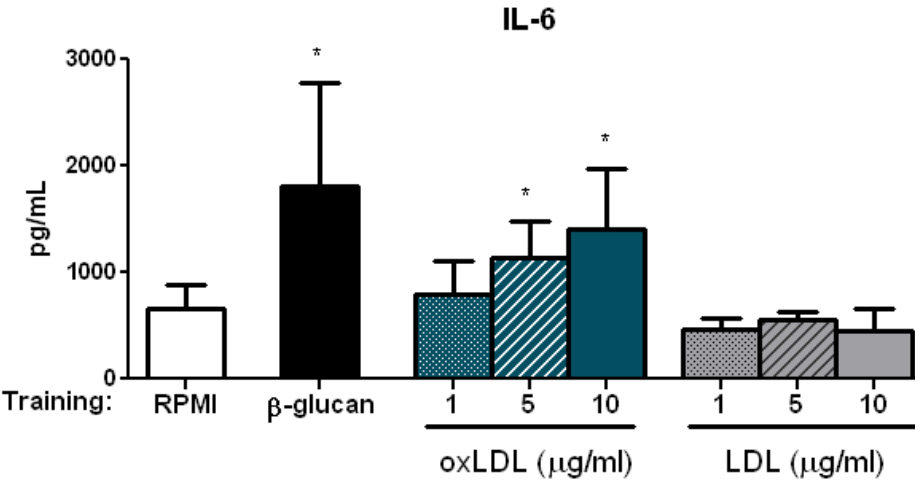
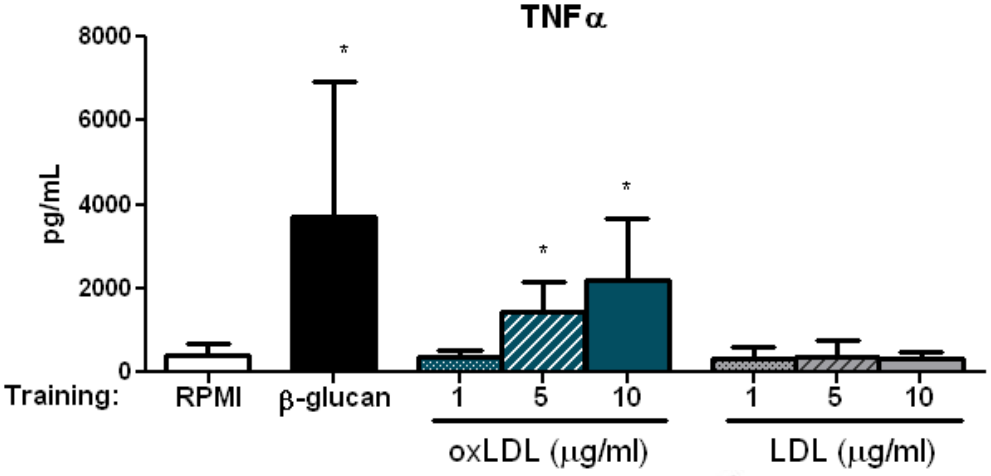
oxLDL but not LDL can train monocytes *in vitro*

Methods:







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Bekkering et al, ATVB 2014

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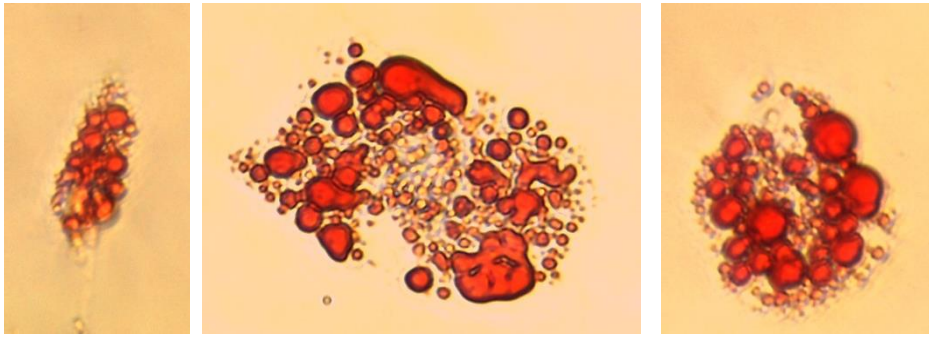
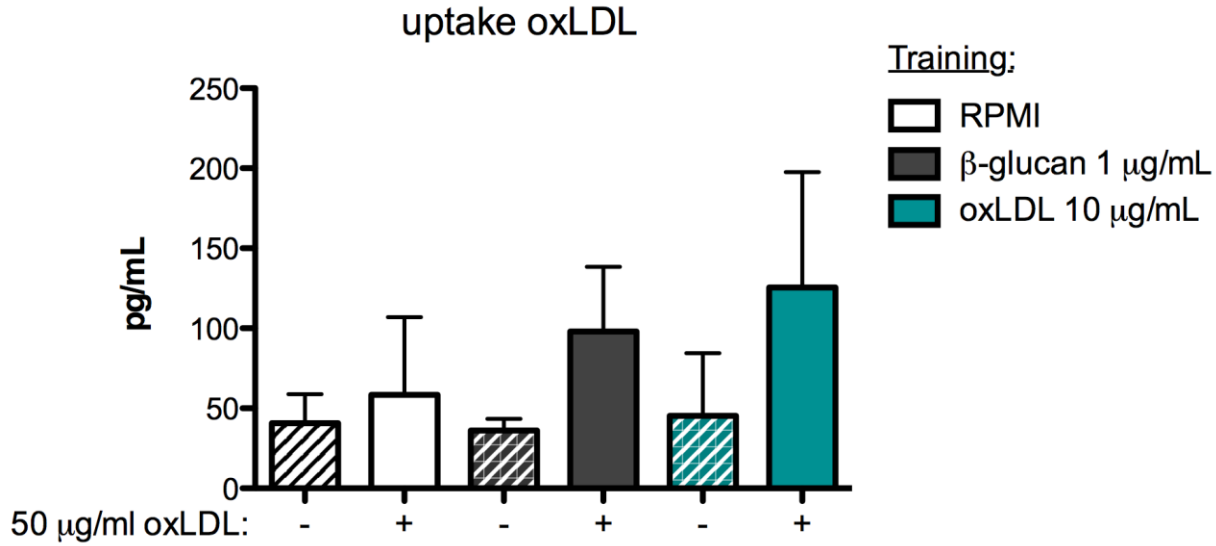
Trained monocytes show increased foam cell formation



RPMI β-glucan oxLDL



Bekkering et al, ATVB 2014

MC St Radboud

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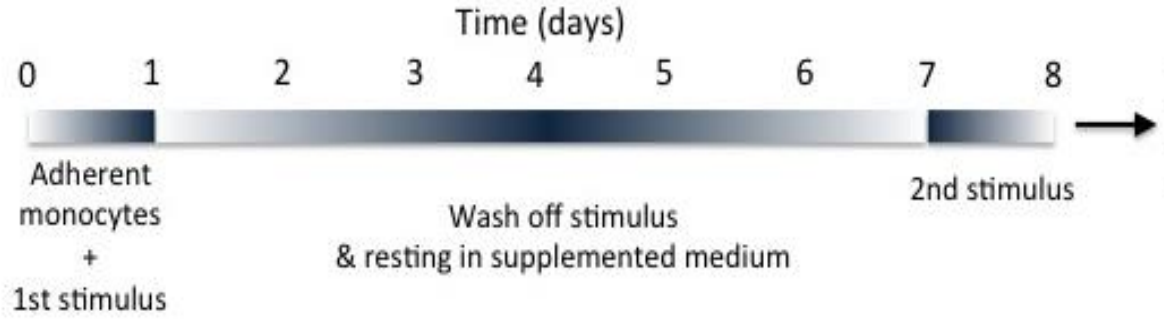
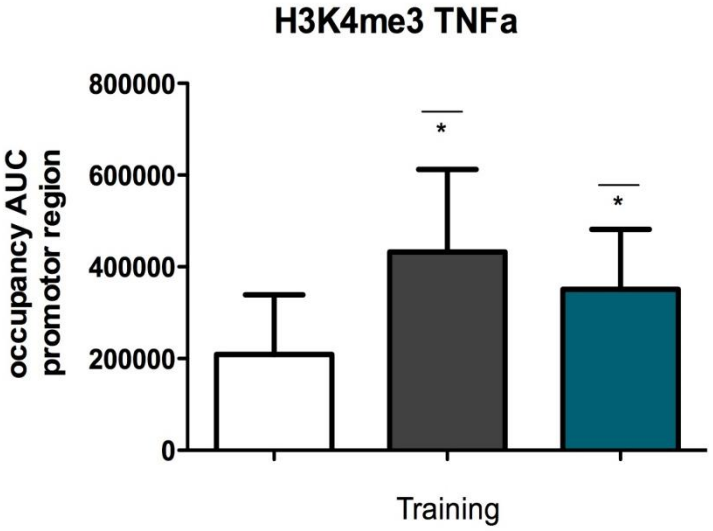
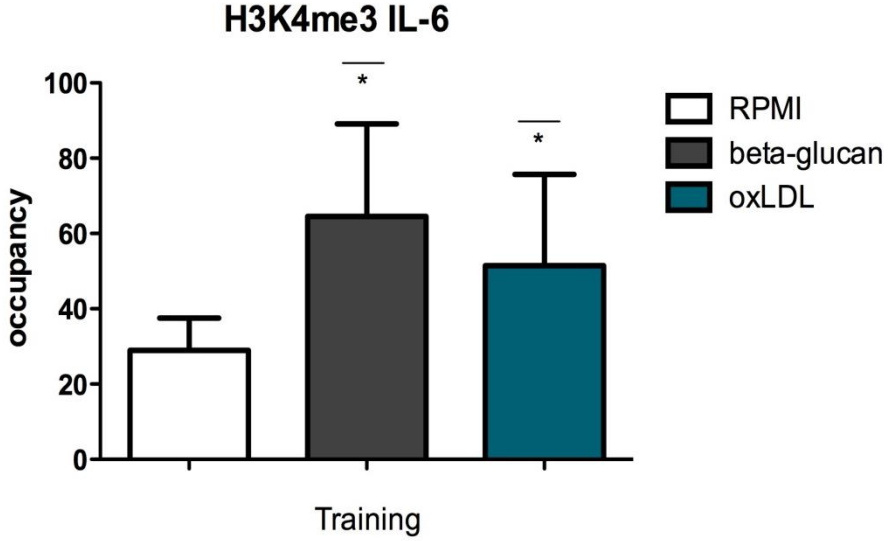
oxLDL training induces upregulated H3K4me3 on the promotor of TNFα



Analysis:
ChIP
H3K4me3





Bekkering et al, ATVB 2014

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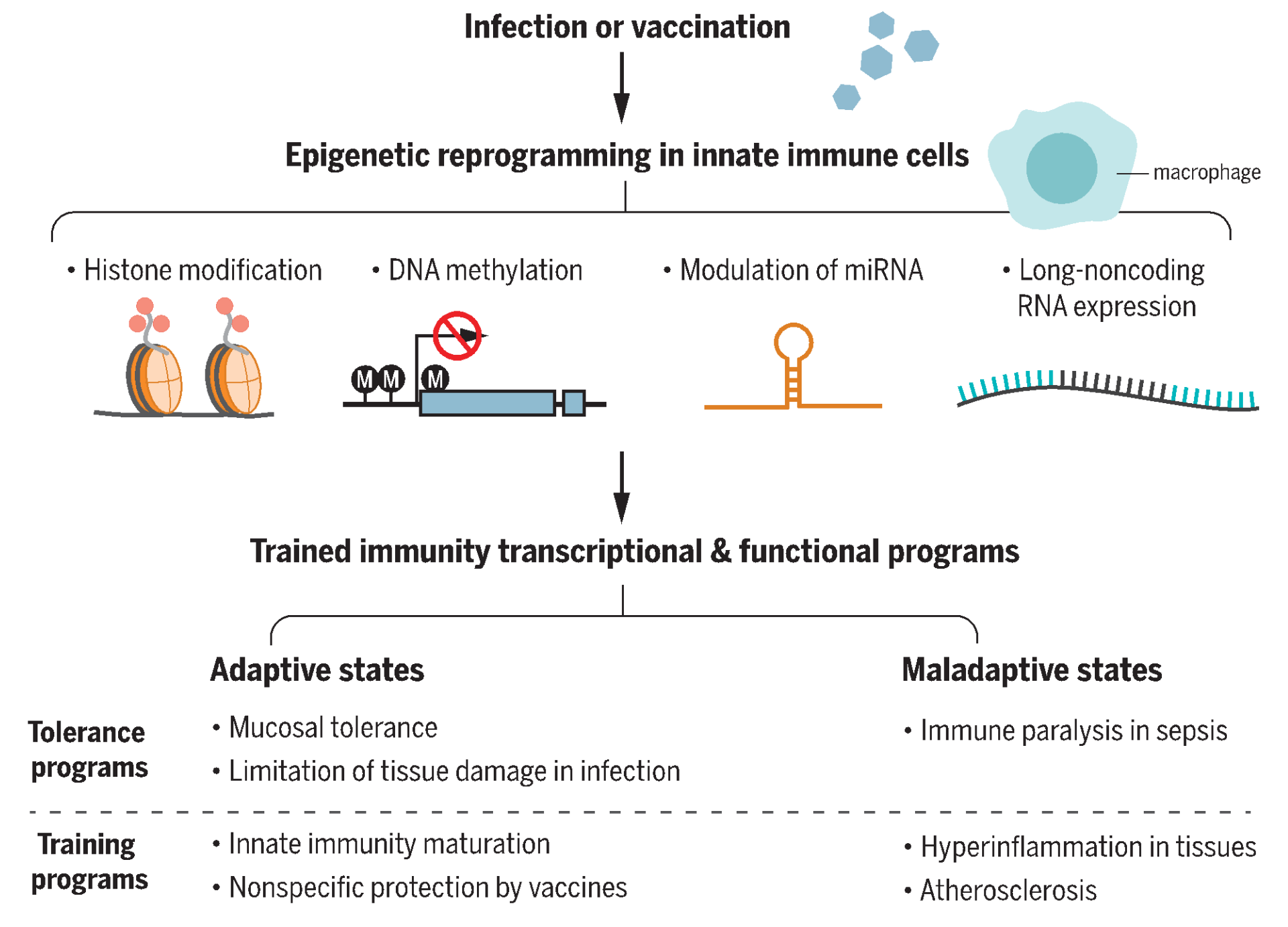

Netea et al, Science 2016