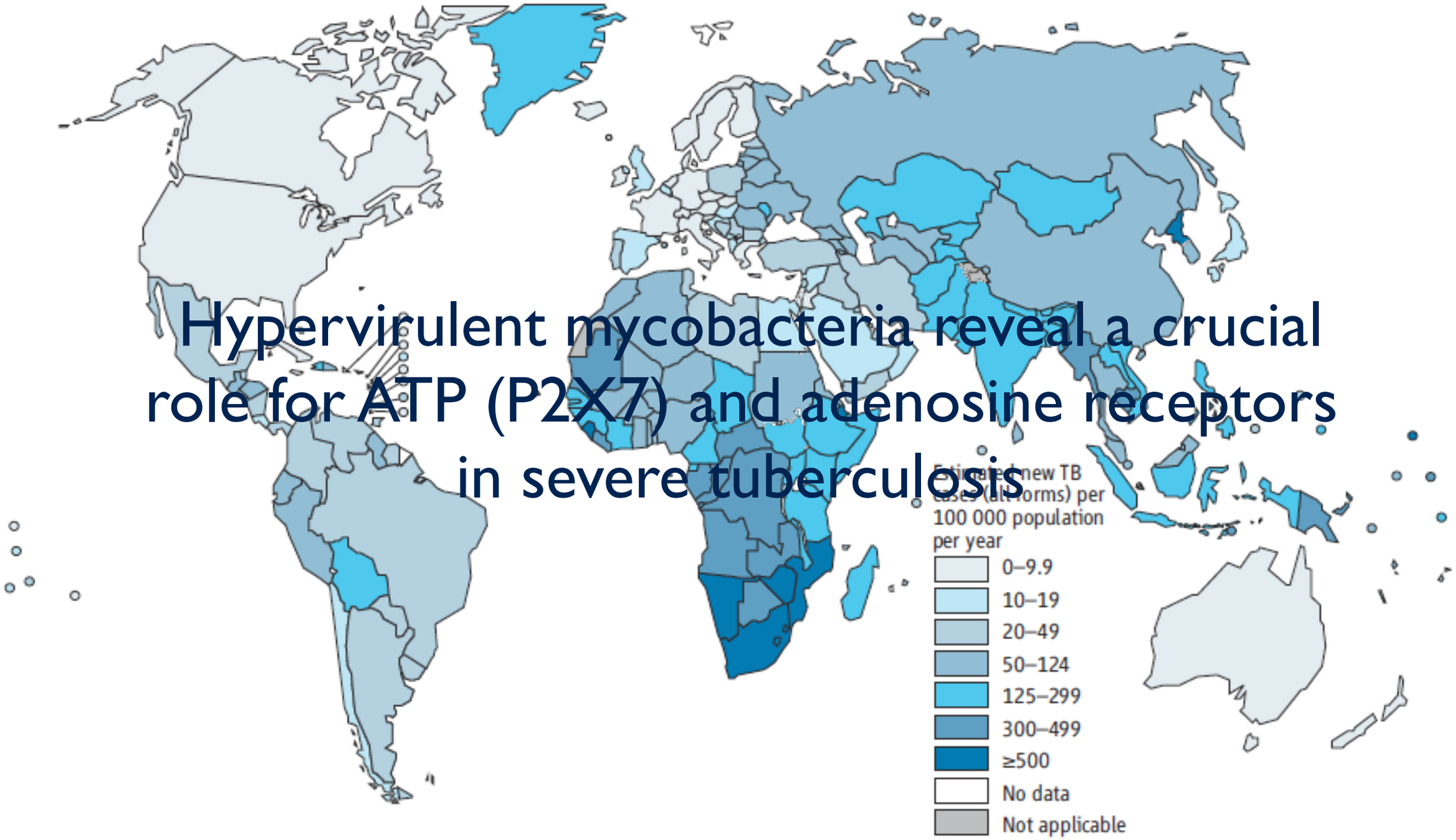
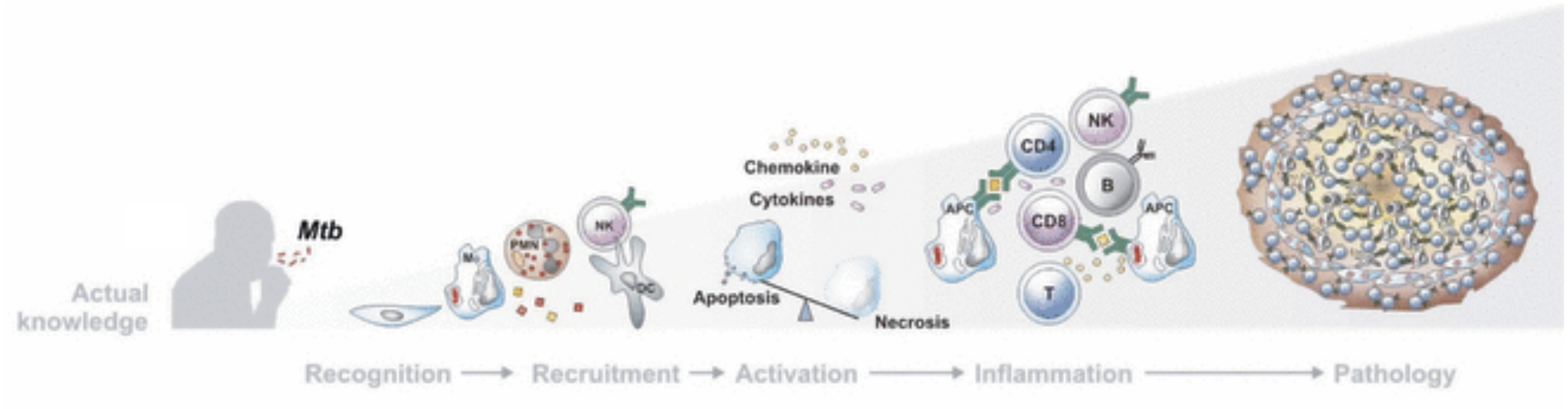


Hypervirulent mycobacteria reveal a crucial role for ATP (P2X7) and adenosine receptors in severe tuberculosis

The immune response against mycobacteria leads to protection and pathology



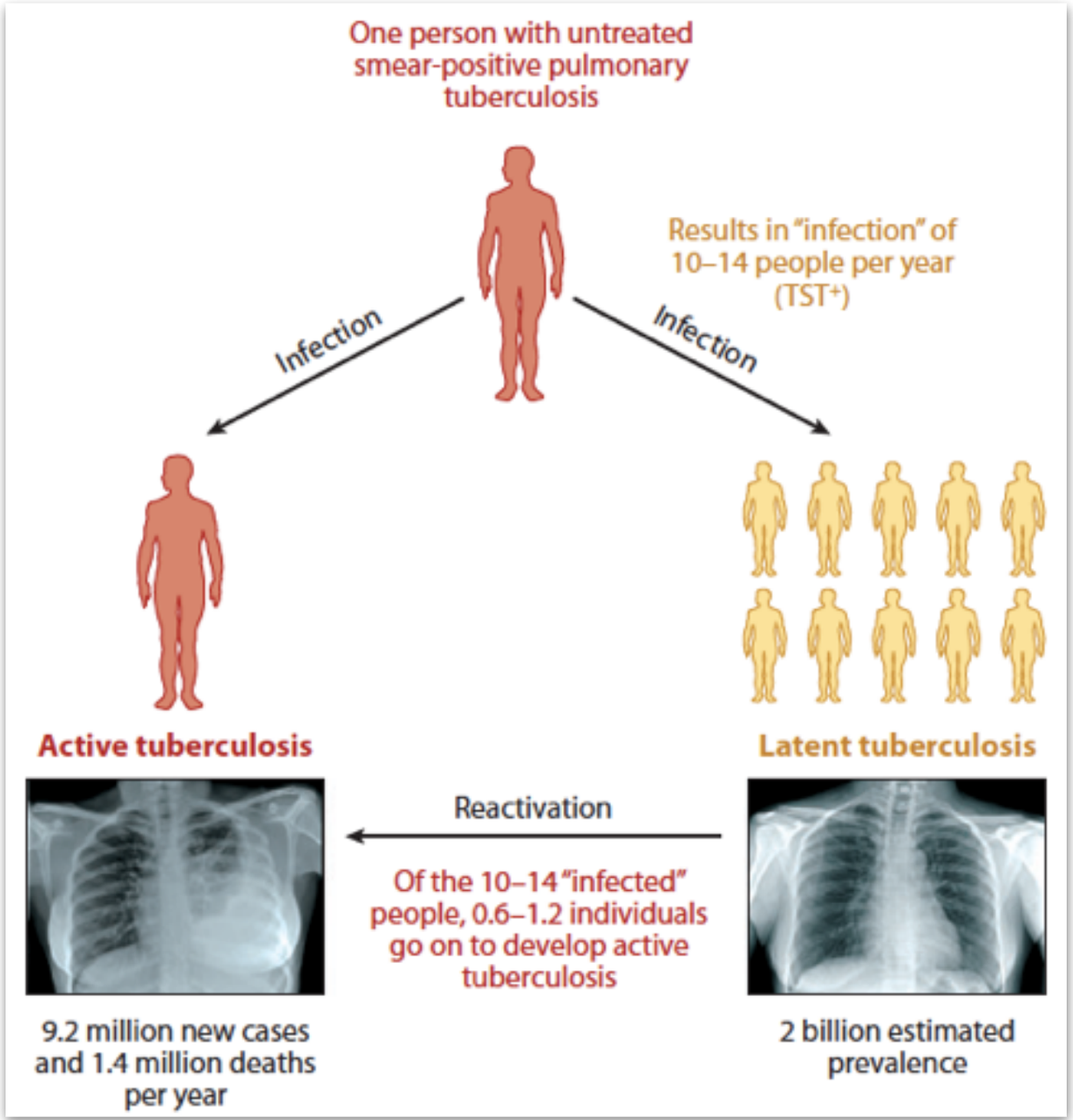
Dorhoi et al. (2011) Immunol. Rev, 240: 235-2511

✓ One third of the world's population is infected with bacteria of the *Mycobacterium tuberculosis* complex (*M. tuberculosis* and *M. bovis*).

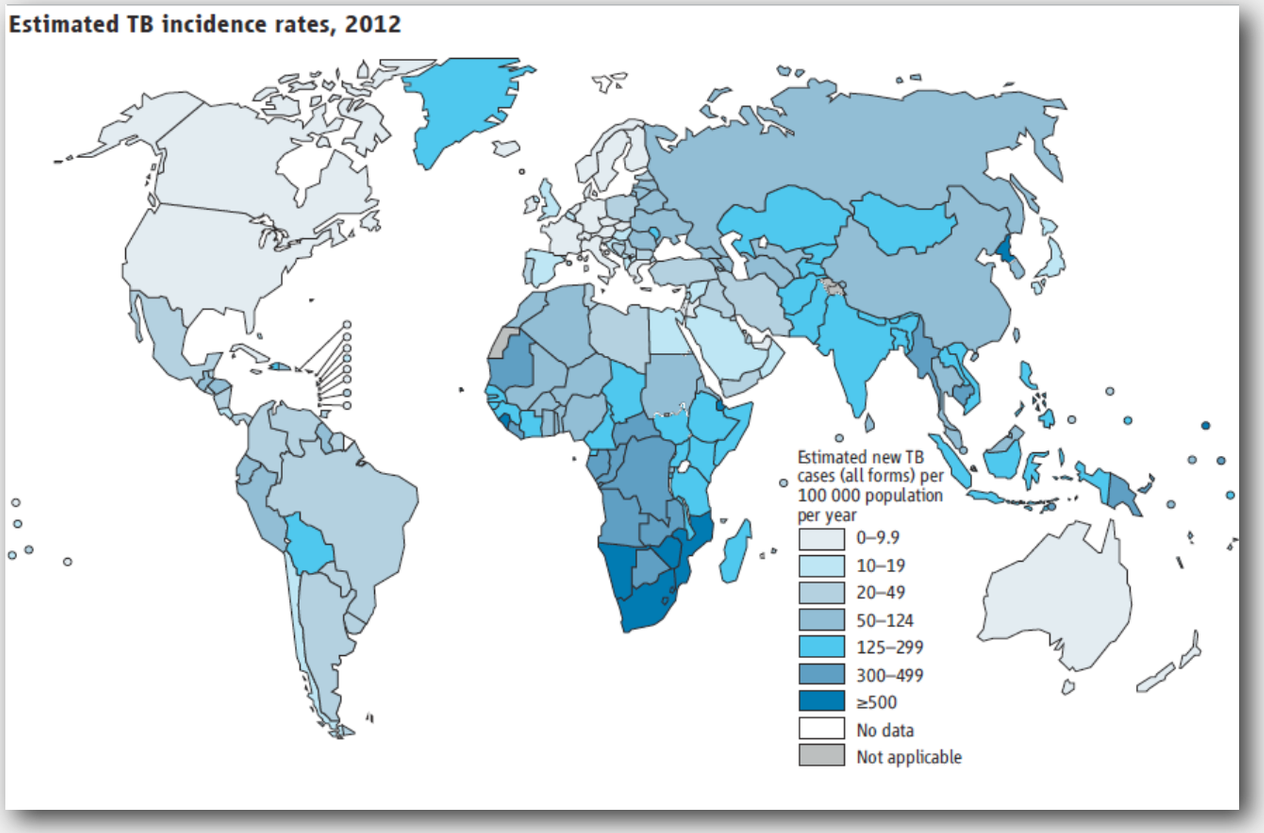
✓ Active TB can develop through progression of recently acquired infection (primary disease) or reactivation of latent infection.

✓ WHO estimated 9.6 million new cases of active tuberculosis (TB) and 1.5 million deaths in 2014.

✓ Progressive primary TB is an aggressive form of the disease that represents about 10% of active TB cases, affecting mostly children under 5 years of age and immunocompromised individuals.

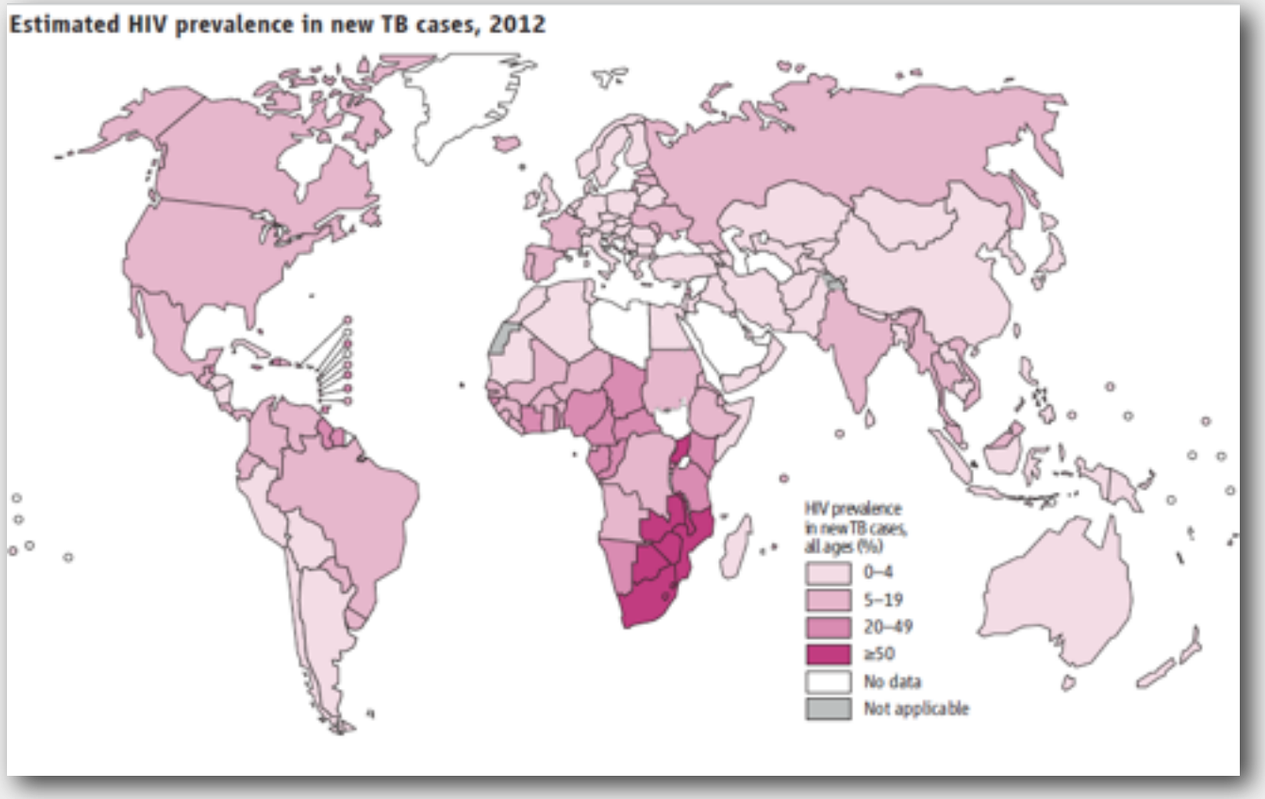


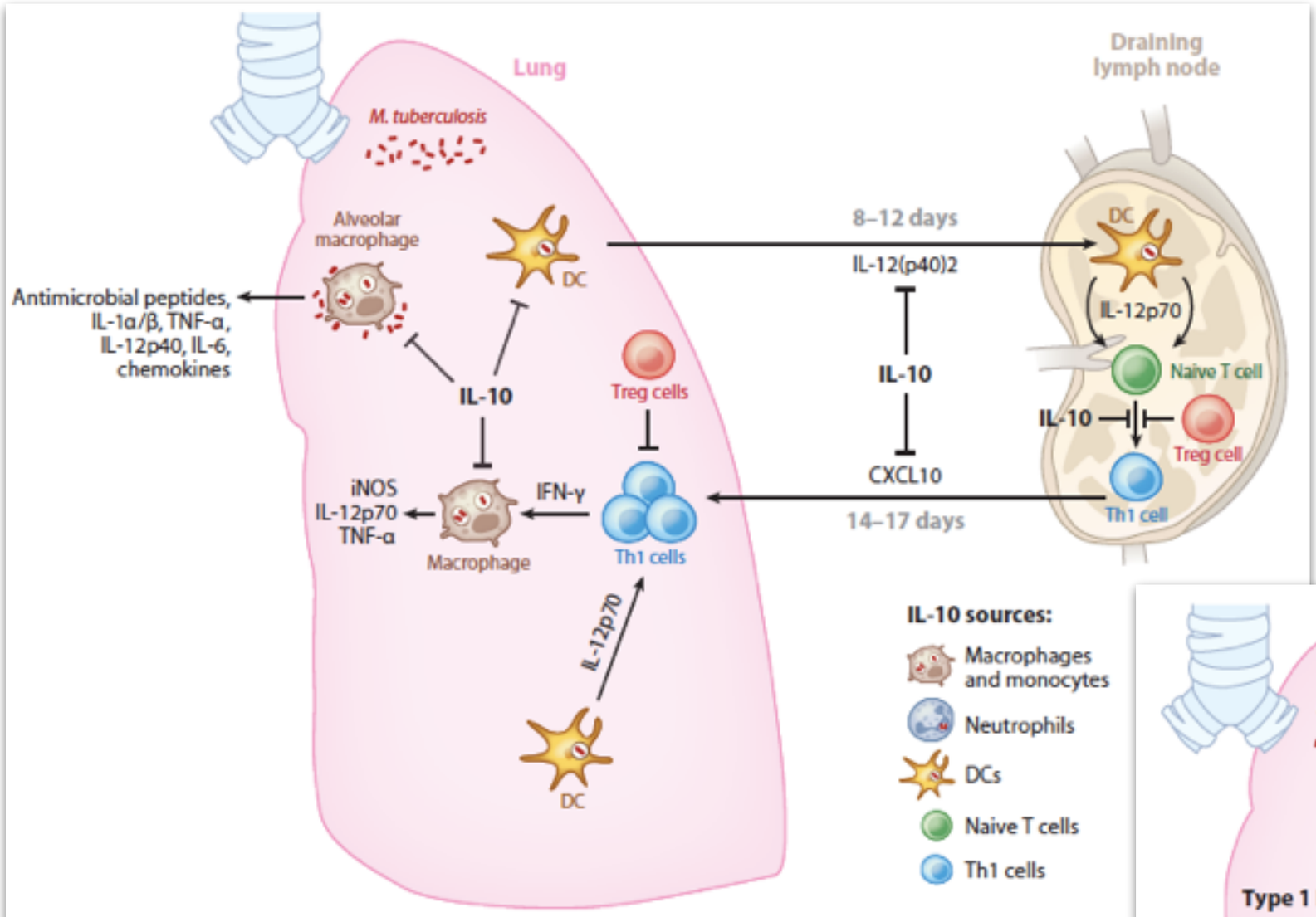
O'Garra t al. (2013) Annu. Rev. Immunol., 31: 475-527



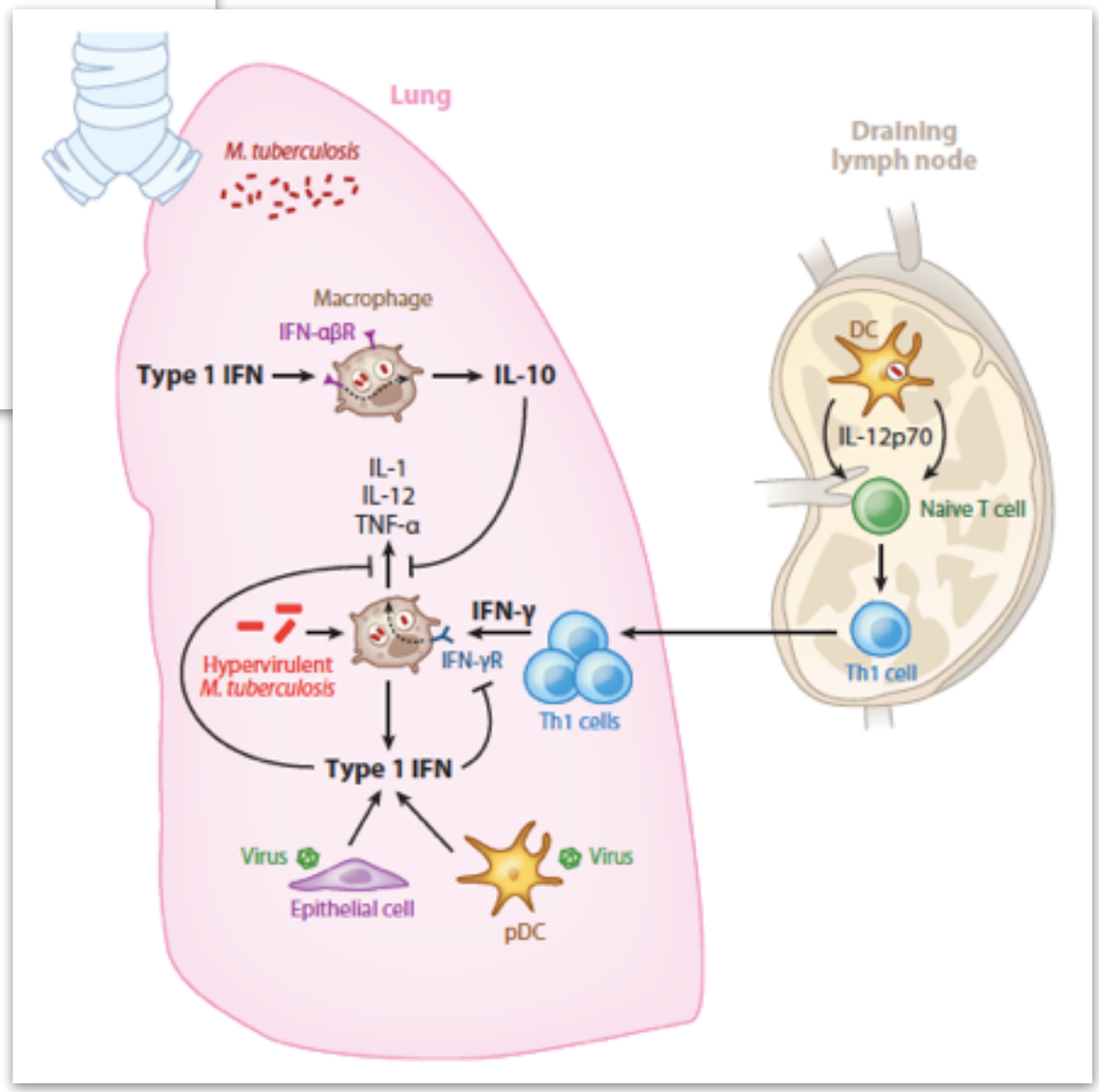
✓ Reactivation of latent infection in immunocompetent individuals occurs in rates ranging from 5-10% per life-time.

✓ Active TB incidence is dramatically increased by HIV co-infection, which was reported in 1.2 million (12%) of the people who developed TB in 2014. Therefore, TB is the most common cause of death among patients with AIDS.



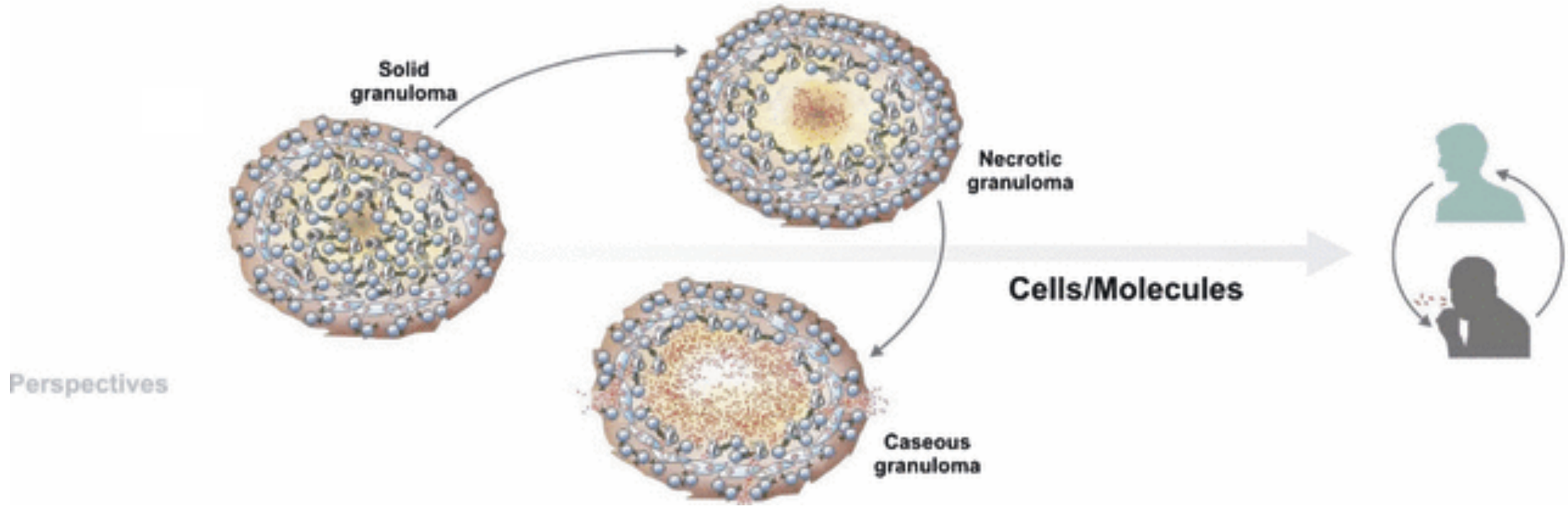


✓ Active TB incidence is also increased after administration of TNF/IL-12/IL-23 blockers.



O'Garra t al. (2013) Annu. Rev. Immunol., 31: 475-527

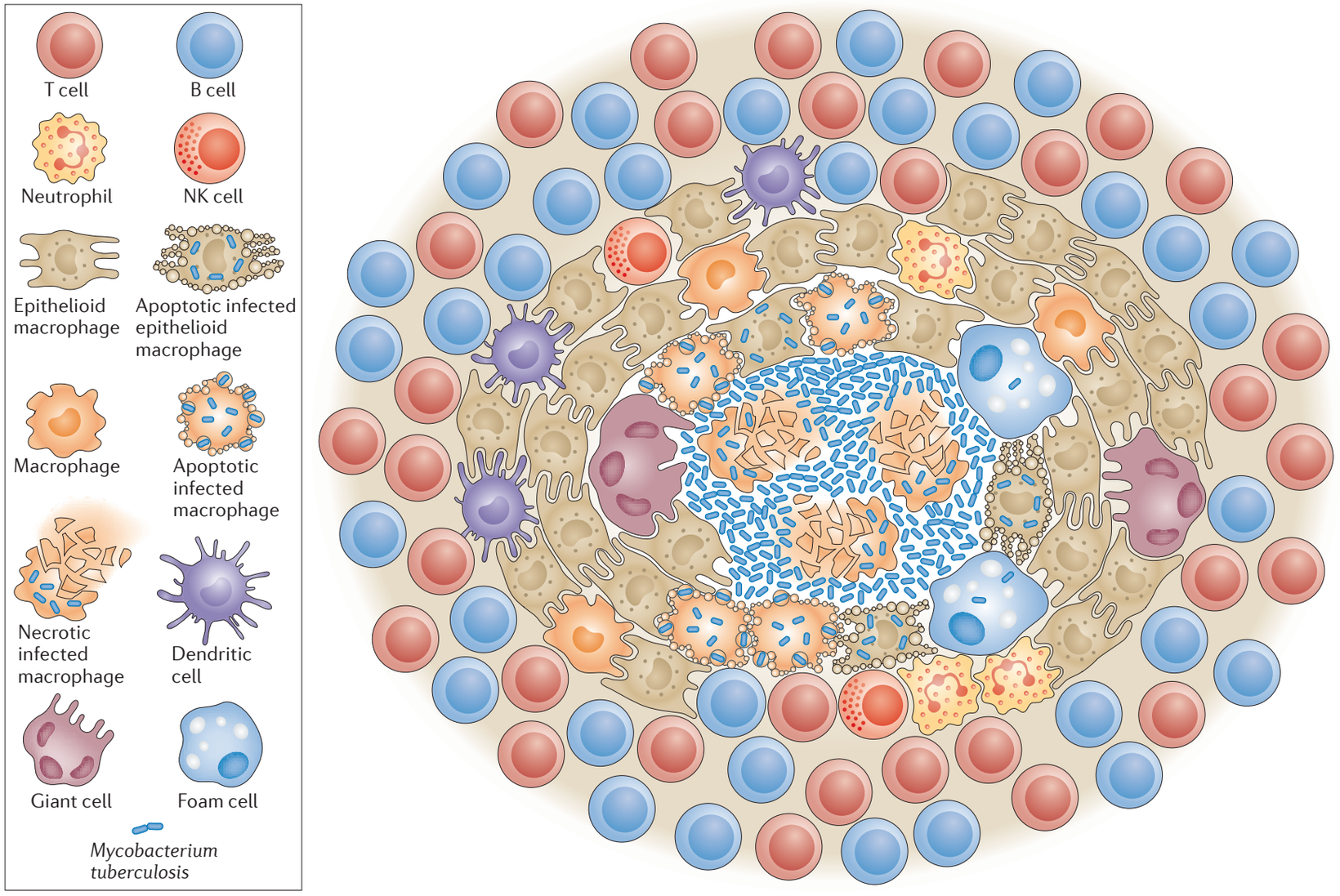
The immune response against mycobacteria leads to protection and pathology



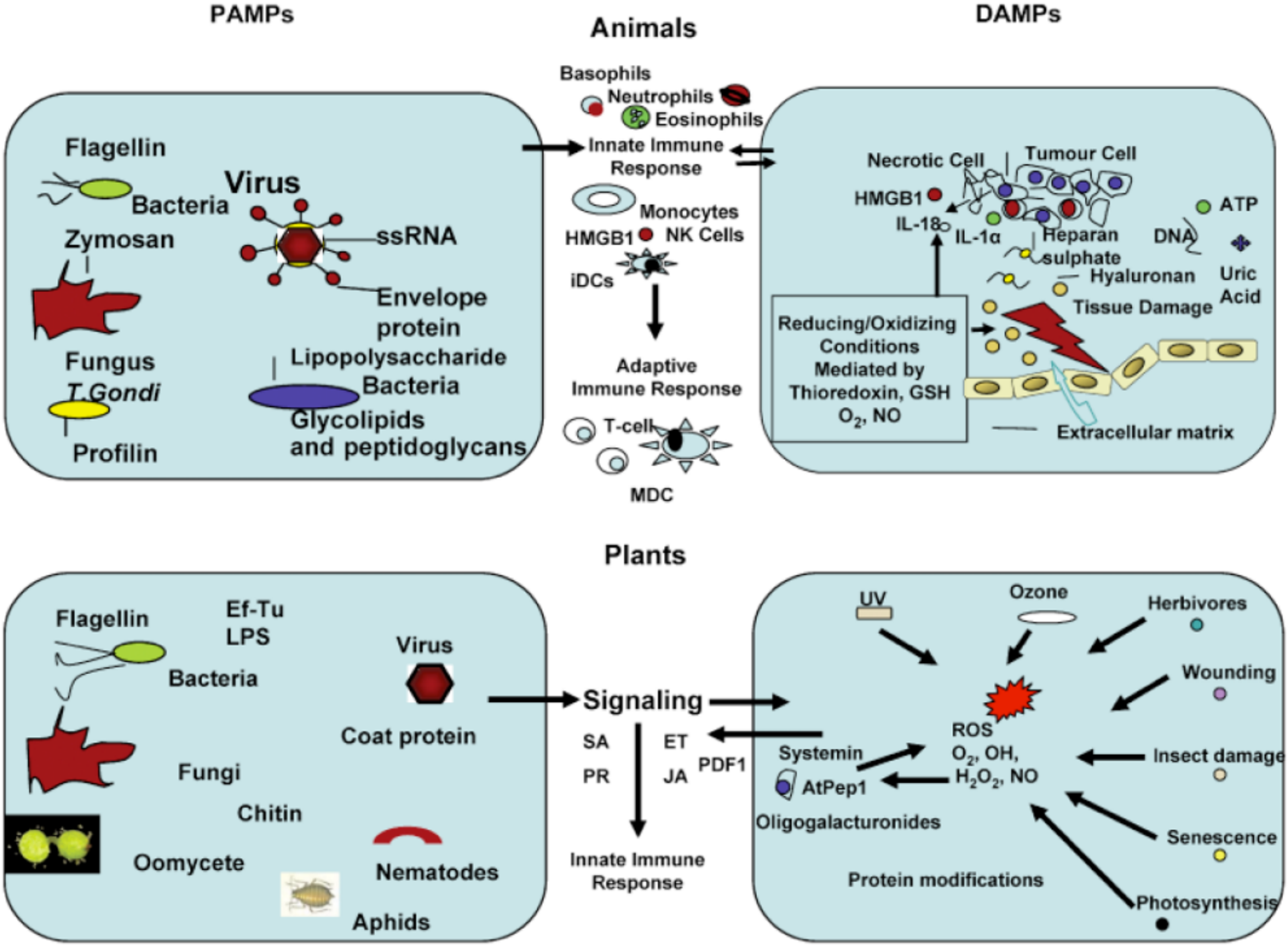
✓ A variety of factors can determine the transition of mycobacterial infection to active TB: genetically determined susceptibility of host organism to the bacilli, environmental factors increasing the host susceptibility and factors associated with bacteria. such as virulence and dose of infection.

✓ Are granulomas purely protective for the host or do they promote infection? Do they contribute to tissue pathology?

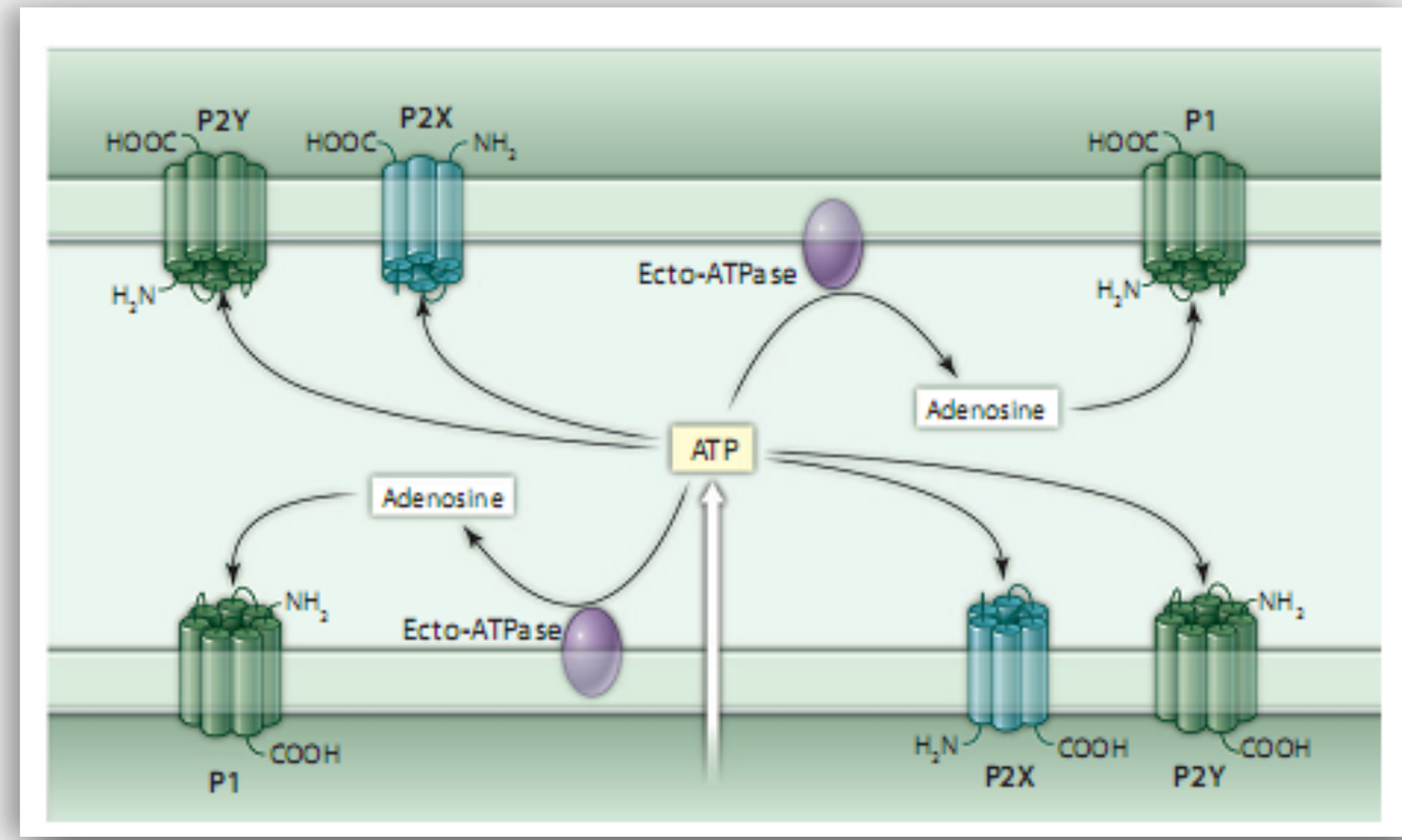
The predominance of apoptotic over necrotic macrophage death ensures the control of mycobacteria



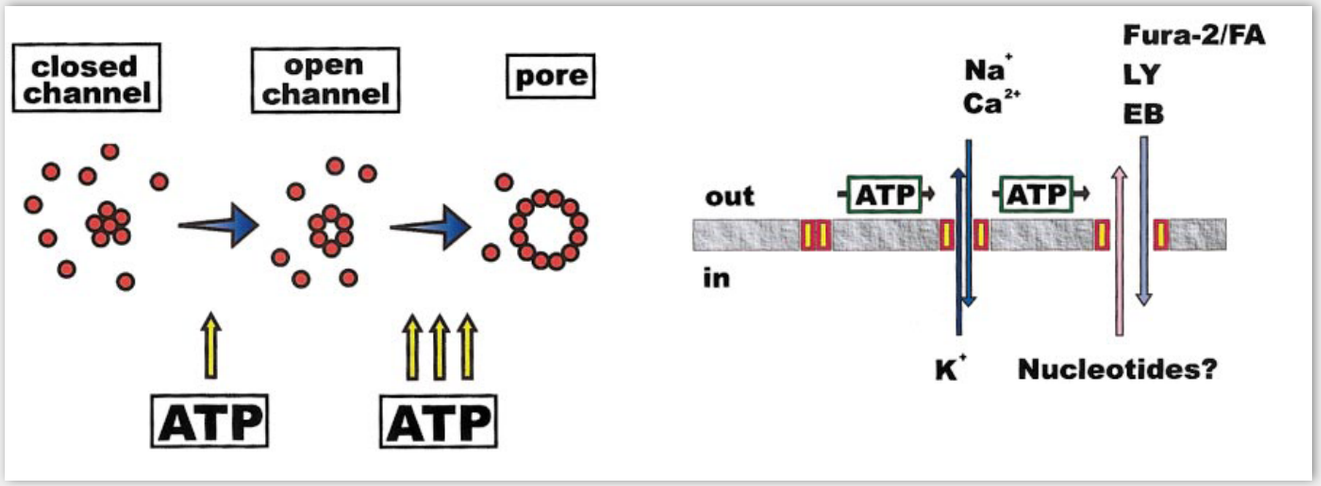
Ramakrishnan (2012) Nat Rev Immunol, 12: 352-366

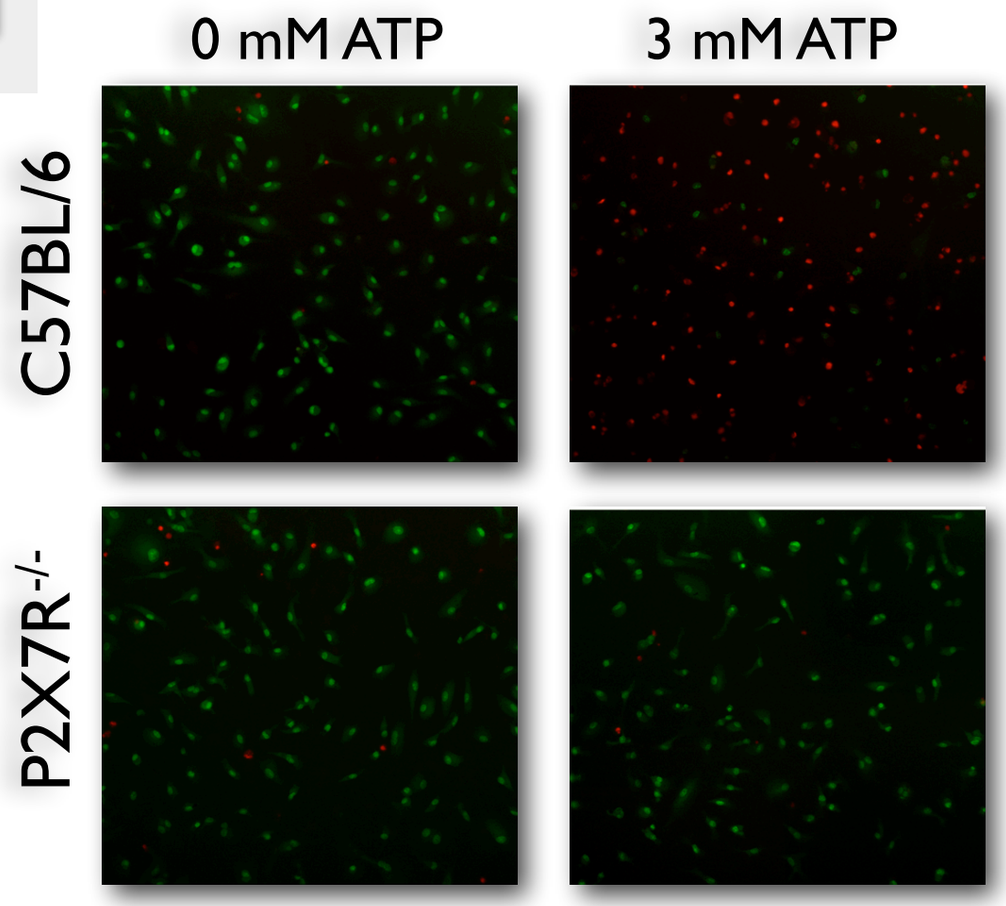

PAMPs
Animals
DAMPs
Flagellin
Bacteria
Virus
Zymosan
ssRNA
Envelope protein
Fungus
T.Gondi
Lipopolysaccharide
Bacteria
Glycolipids and peptidoglycans
Profilin
Basophils
Neutrophils
Eosinophils
Innate Immune Response
Monocytes
HMGB1
NK Cells
iDCs
Adaptive Immune Response
T-cell
MDC
Necrotic Cell
Tumour Cell
HMGB1
IL-18
IL-1α
Heparan sulphate
DNA
ATP
Uric Acid
Hyaluronan
Tissue Damage
Reducing/Oxidizing Conditions Mediated by Thioredoxin, GSH O_2, NO
Extracellular matrix
Plants
Flagellin
Ef-Tu
LPS
Bacteria
Virus
Coat protein
Fungi
Chitin
Oomycete
Nematodes
Aphids
Signaling
SA
ET
PR
JA
PDF1
Innate Immune Response
UV
Ozone
Herbivores
Wounding
ROS
O_2, OH, H_2O_2, NO
Systemin
AtPep1
Oligogalacturonides
Insect damage
Senescence
Protein modifications
Photosynthesis

Extracellular ATP (eATP) is a damage signal



[mM] eATP causes apoptotic or necrotic macrophage death through P2X7R





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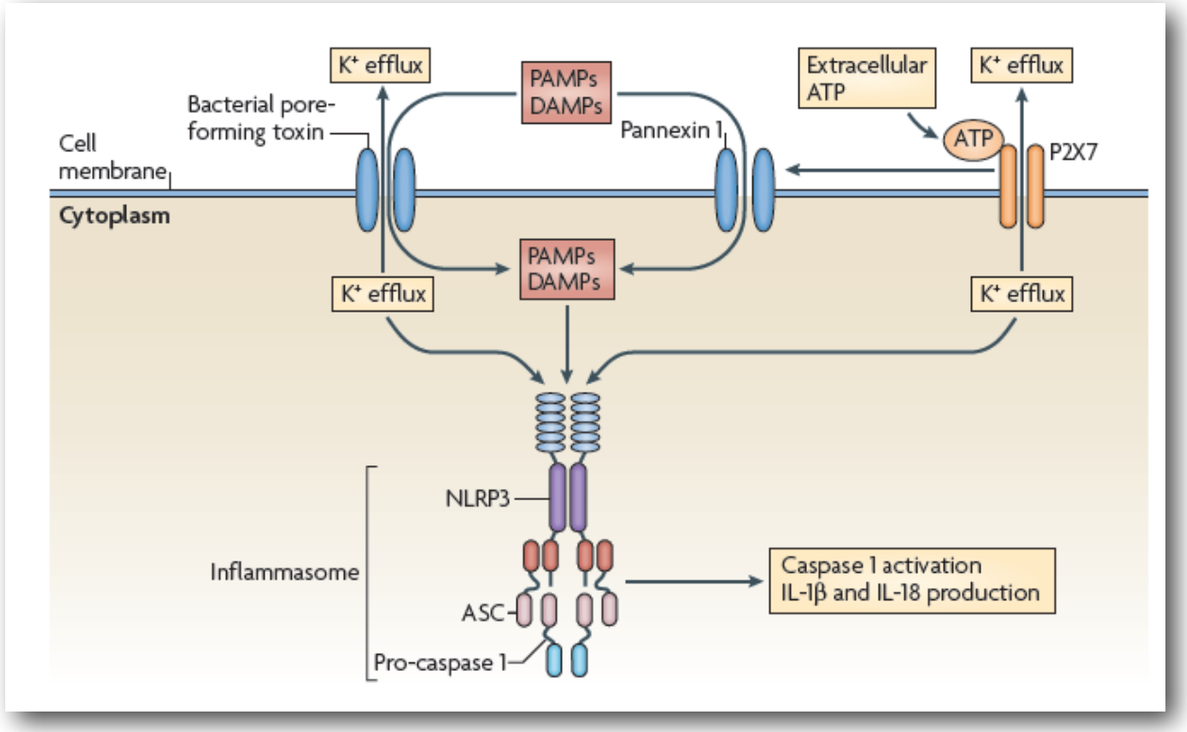
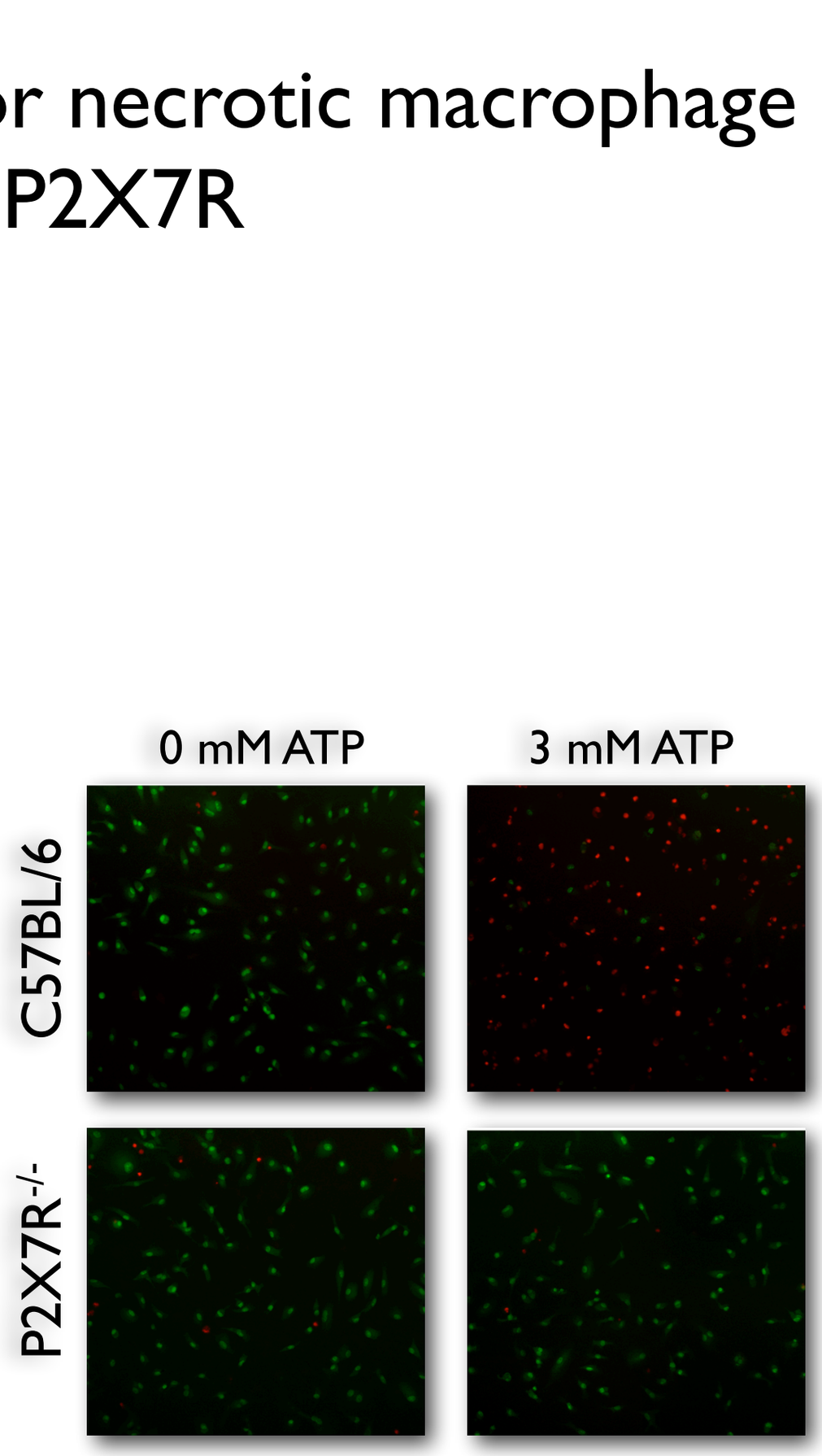
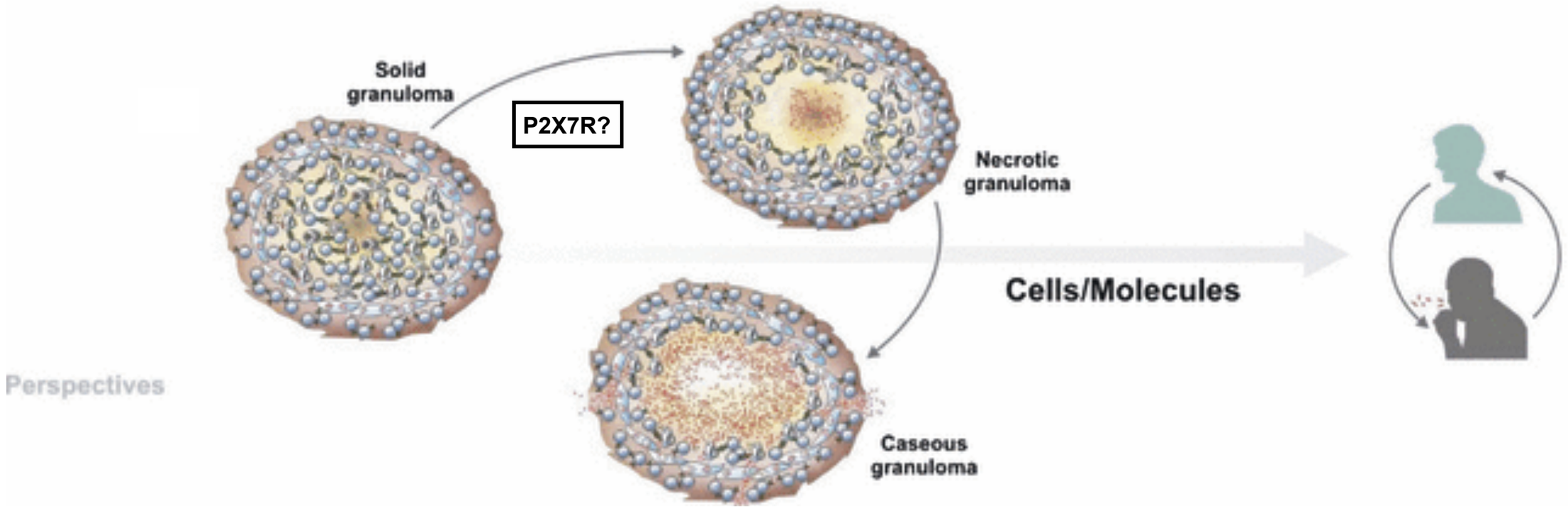


Junger, Nat Rev Immunol, 11: 201-212, 2010

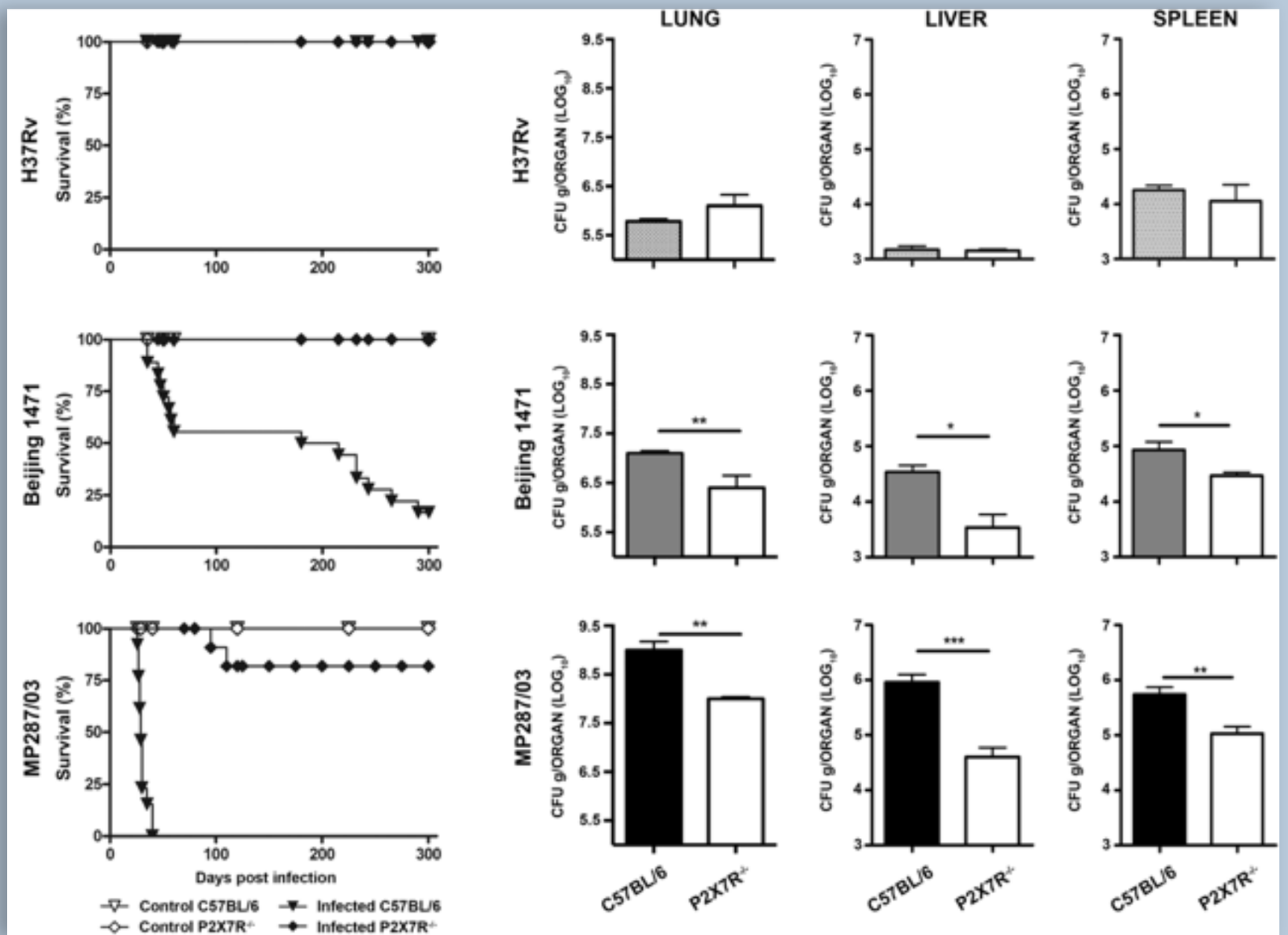


The immune response against mycobacteria leads to protection and pathology

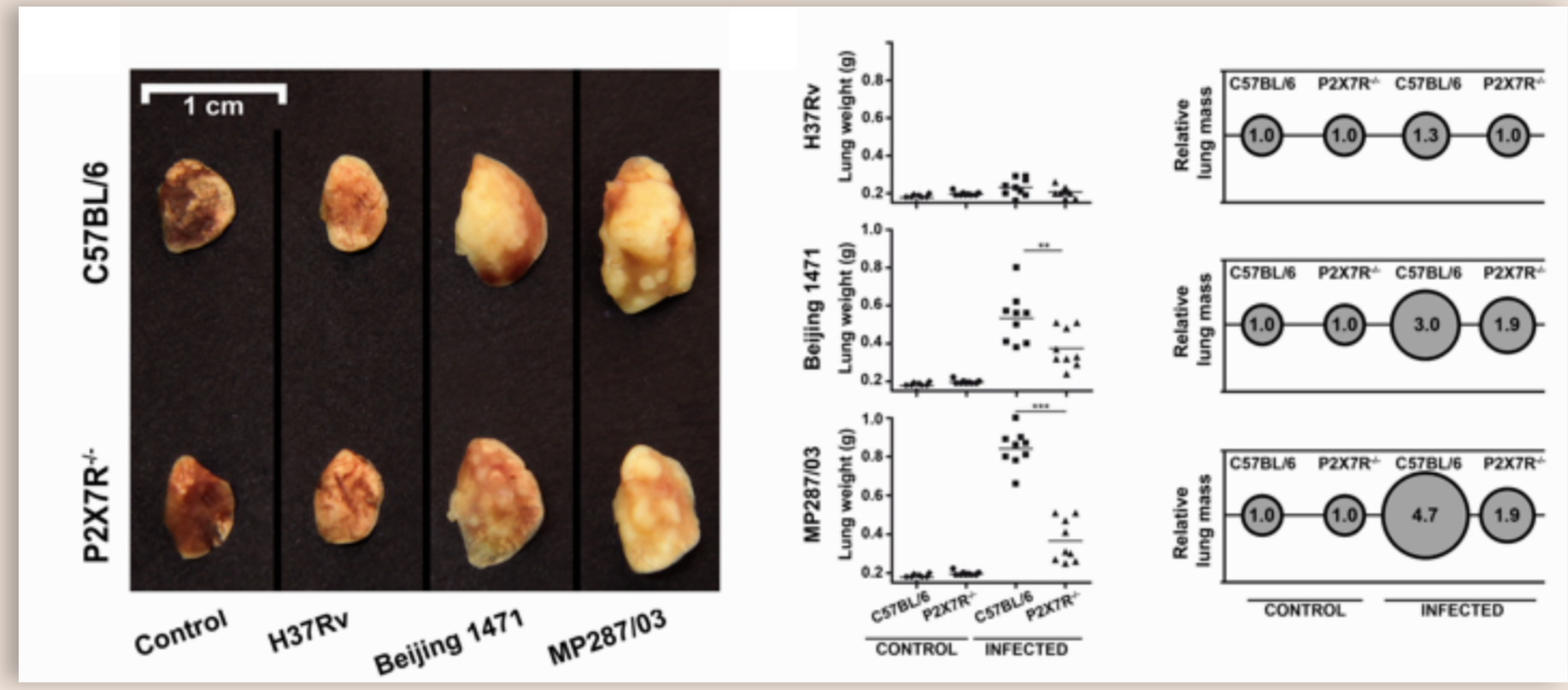


Perspectives

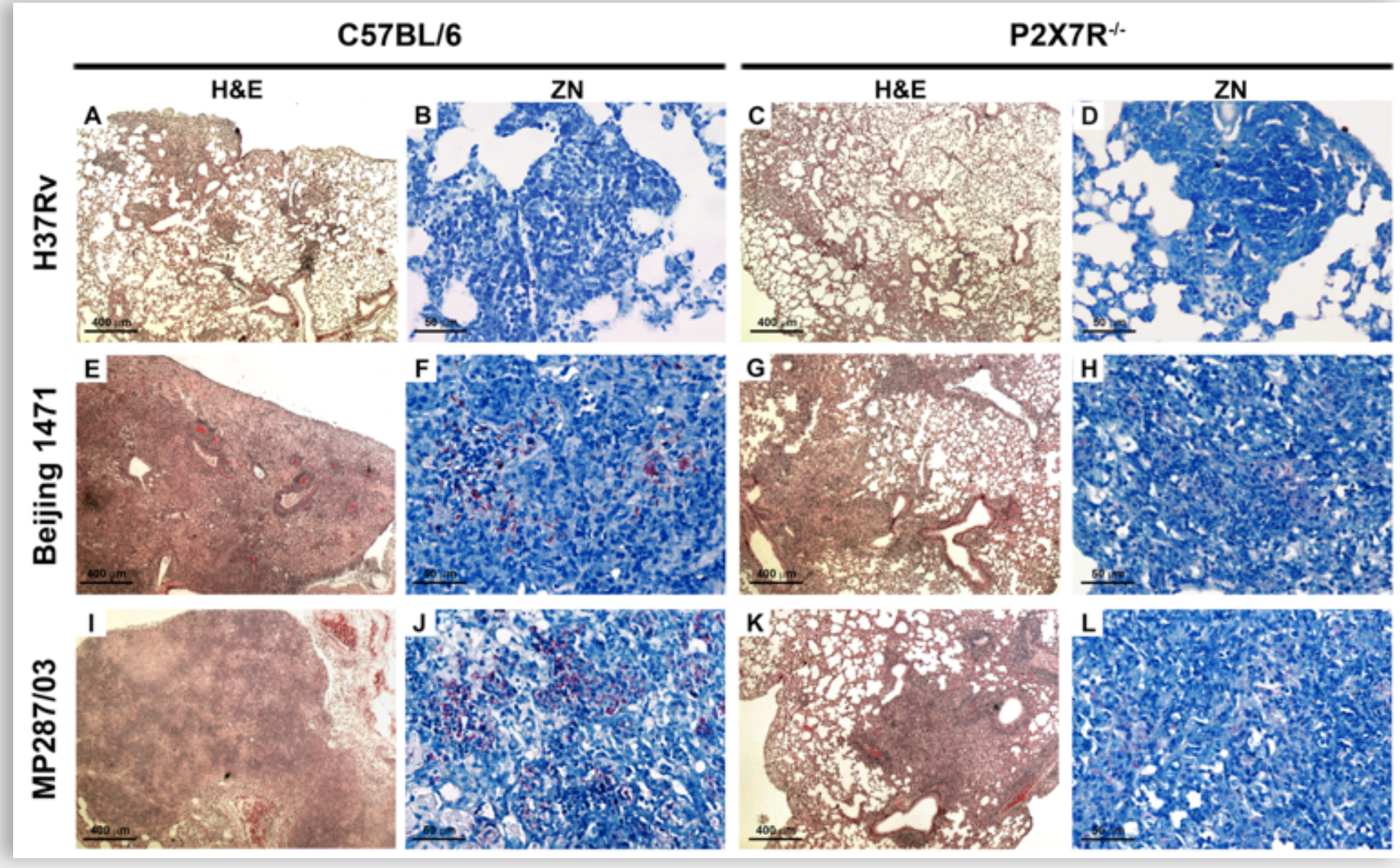
TB induced by hypervirulent mycobacteria is attenuated in mice that lack the P2X7R



TB induced by hypervirulent mycobacteria is attenuated in mice that lack the P2X7R

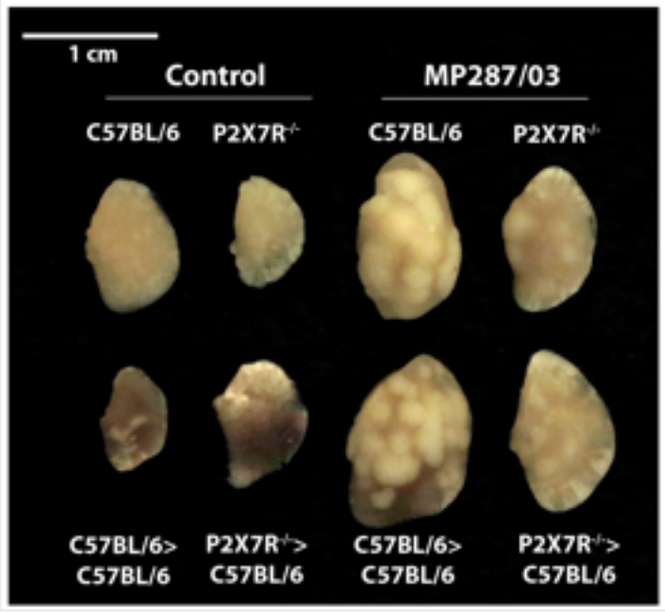


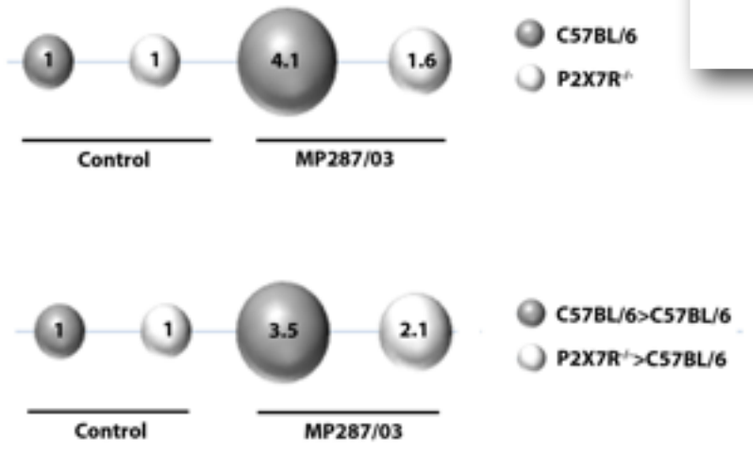
TB induced by hypervirulent mycobacteria is attenuated in mice that lack the P2X7R

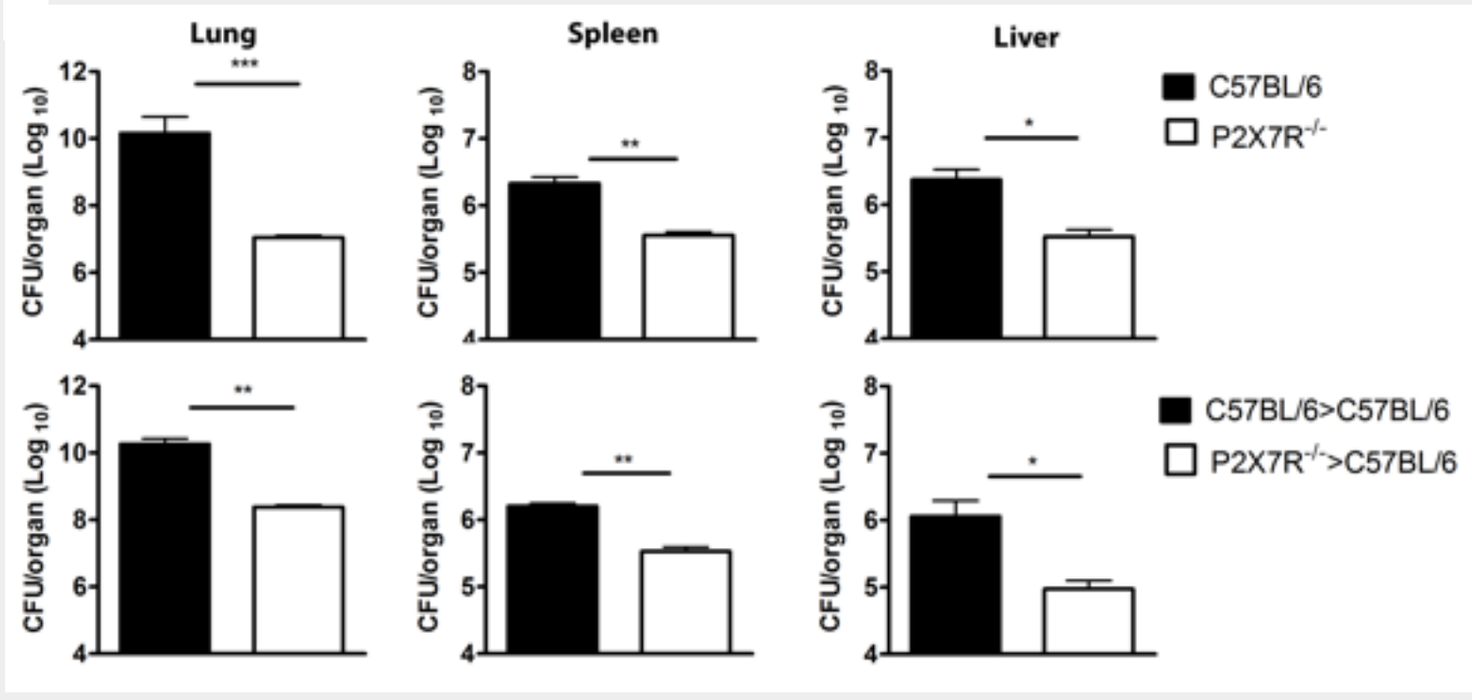


The deleterious role of P2X7R is independent of NLRP3 inflammasome

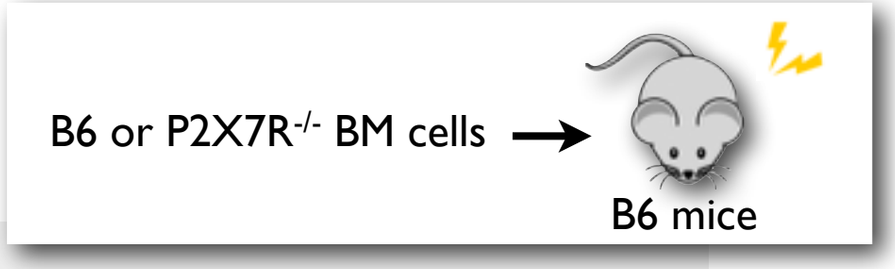
The deleterious effect of P2X7R on severe TB is transferred by bone marrow-derived cells

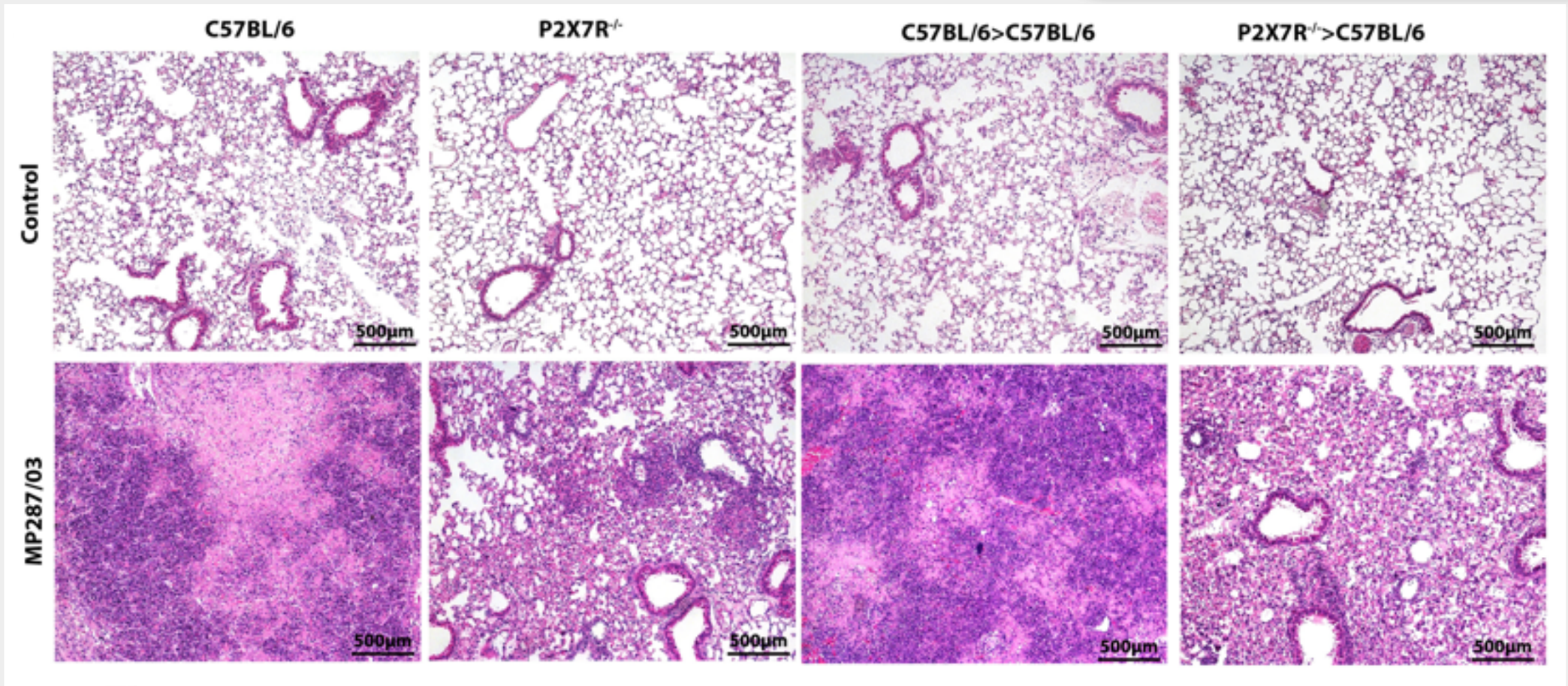






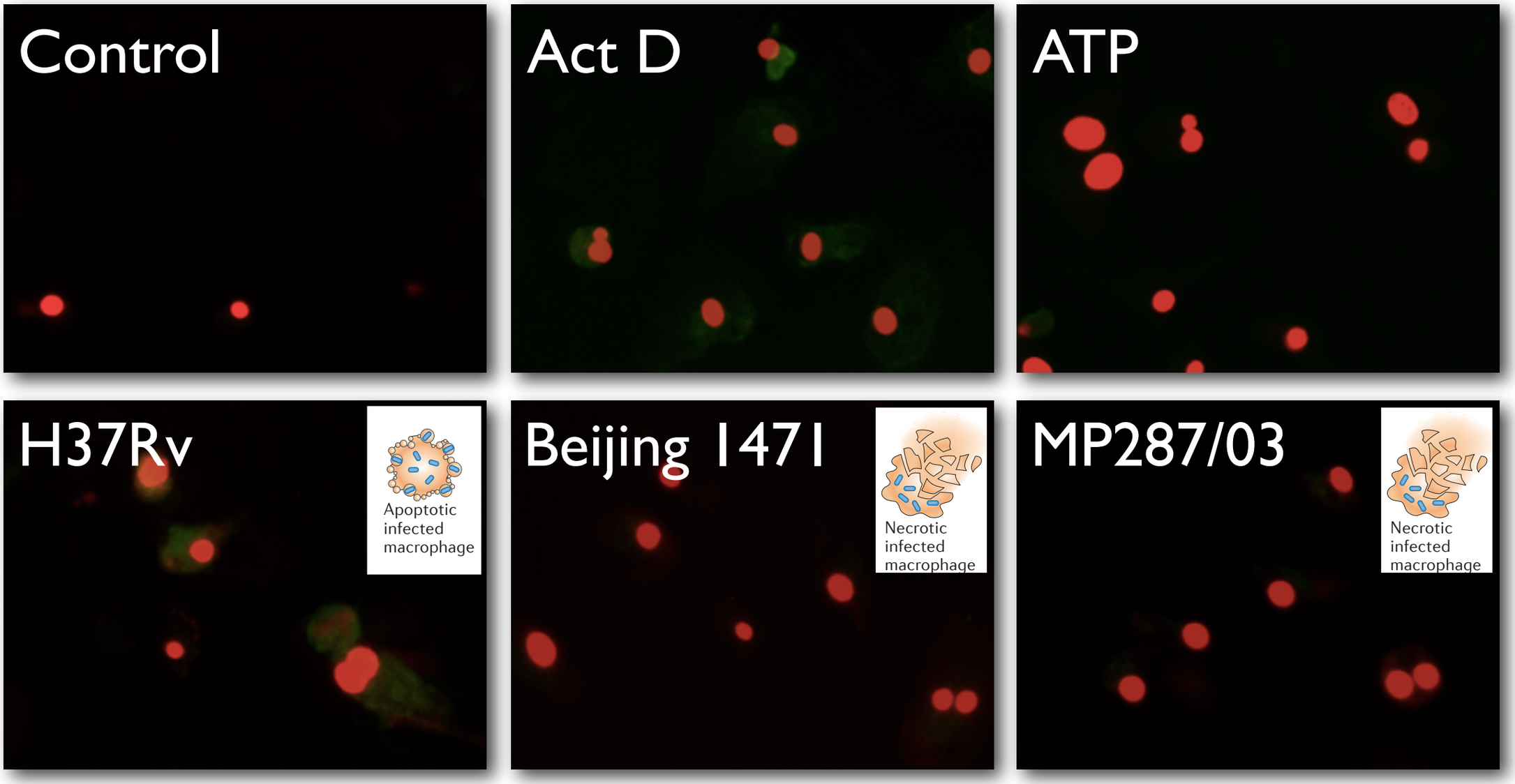
The deleterious effect of the P2X7R on severe TB is transferred by bone marrow-derived cells



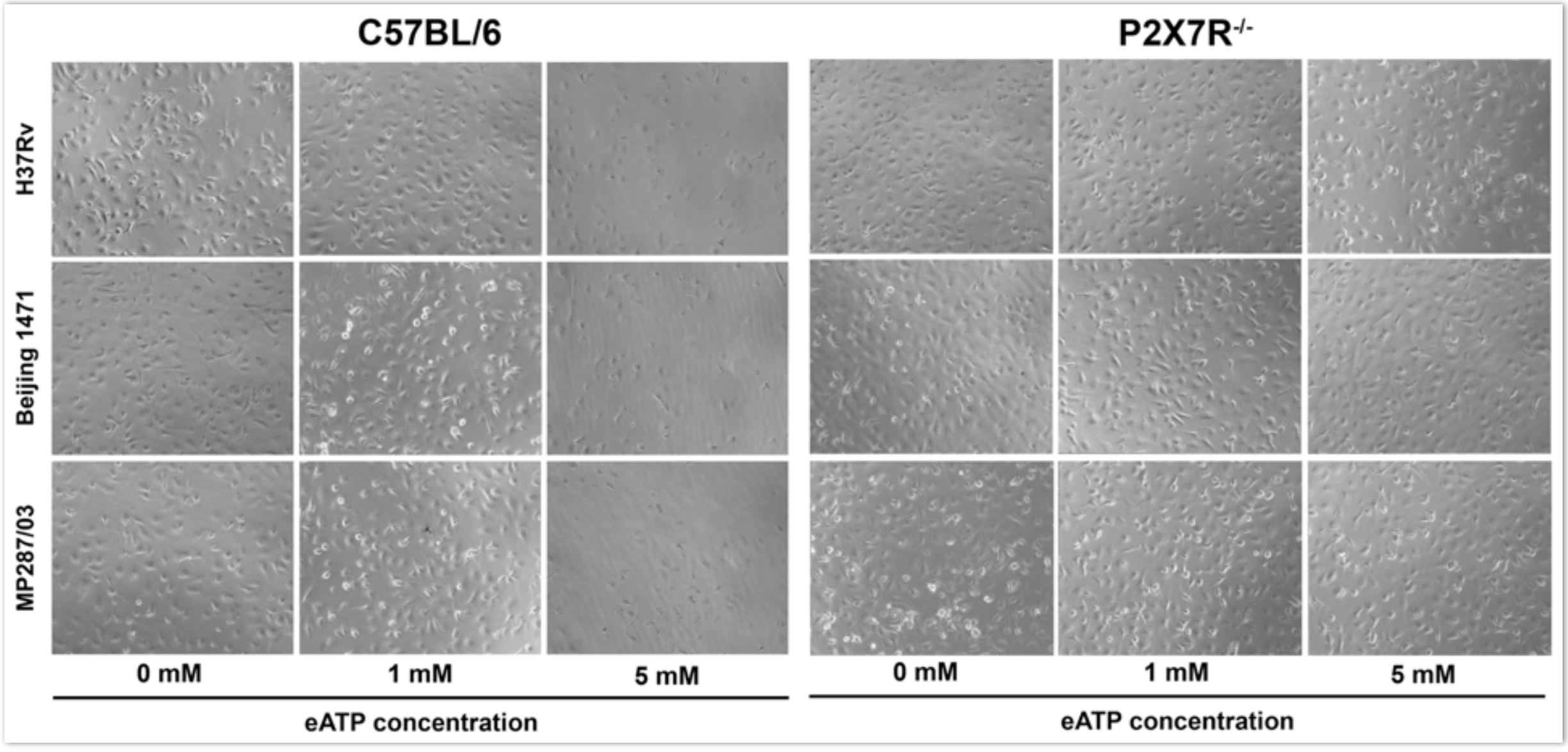


Does P2X7R signaling induce macrophage necrosis and hypervirulent bacillus dissemination?

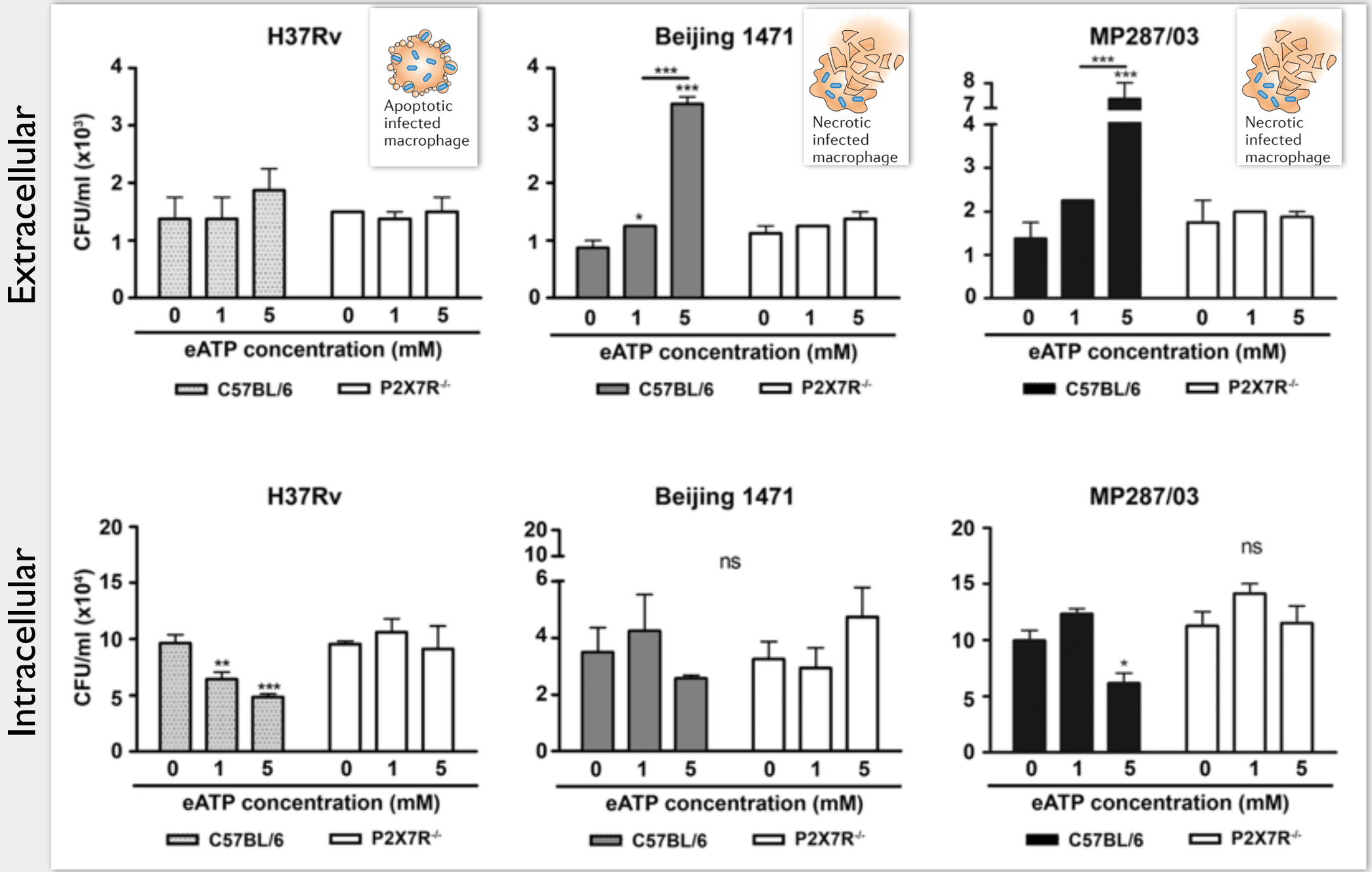
Hypervirulent mycobacteria induce necrotic cell death

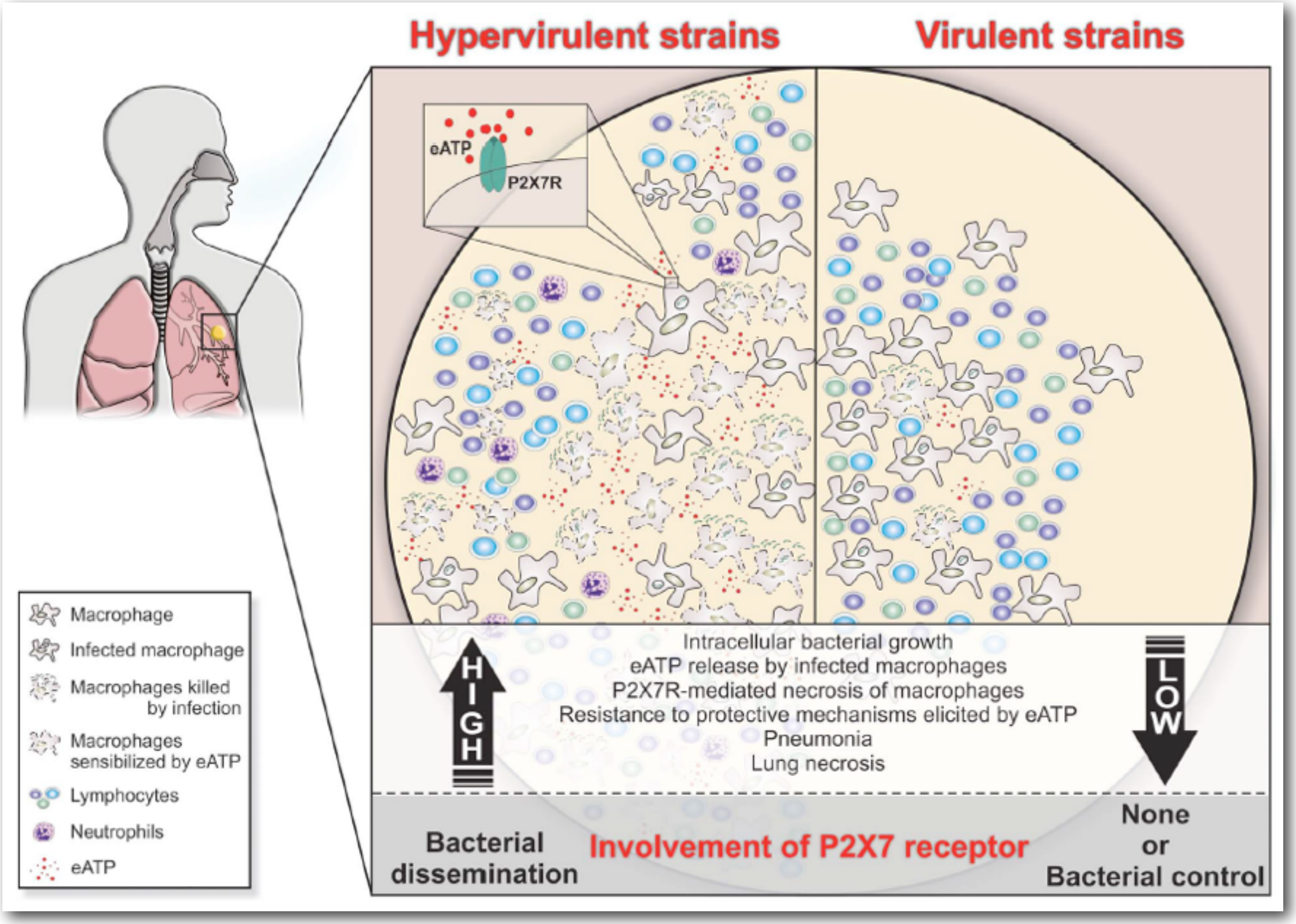


What are the effects of eATP on virulent and hypervirulent intracellular mycobacteria?



Hypervirulent mycobacteria are resistant to eATP-induced effector mechanisms




Hypervirulent strains
Virulent strains
eATP
P2X7R
Macrophage
Infected macrophage
Macrophages killed by infection
Macrophages sensibilized by eATP
Lymphocytes
Neutrophils
eATP
HIGH
Intracellular bacterial growth
eATP release by infected macrophages
P2X7R-mediated necrosis of macrophages
Resistance to protective mechanisms elicited by eATP
Pneumonia
Lung necrosis
LOW
Bacterial dissemination
Involvement of P2X7 receptor
None or Bacterial control

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PLOS | PATHOGENS

Pulmonary Infection with Hypervirulent Mycobacteria Reveals a Crucial Role for the P2X7 Receptor in Aggressive Forms of Tuberculosis

Eduardo P. Amaral[1]*, Simone C. M. Ribeiro[2], Verônica R. Lanes[2], Fabrício M. Almeida[2], Marcelle R. M. de Andrade[2], Caio Cesar Barbosa Bomfim[1], Érika M. Salles[1], Karina R. Bortoluci[3], Robson Coutinho-Silva[4,5], Mario H. Hirata[6], José M. Alvarez[1], Elena B. Lasunskaia[2¶*], Maria Regina D'Império-Lima[1¶*]

1 Departamento de Imunologia, Instituto de Ciências Biomédicas (ICB), Universidade de São Paulo (USP), São Paulo, São Paulo, Brazil, **2** Laboratório de Biologia do Reconhecer, Universidade Estadual do Norte Fluminense (UENF), Campos dos Goytacazes, Rio de Janeiro, Brazil, **3** Centro de Terapia Celular e Molecular, Departamento de Ciências Biológicas, Universidade Federal de São Paulo, São Paulo, São Paulo, Brazil, **4** Programa de Imunobiologia, Instituto de Biofísica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil, **5** Instituto National de Ciência e Tecnologia para Pesquisa Translacional em Saúde e Meio Ambiente da Região Amazônica, Rio de Janeiro, Rio de Janeiro, Brazil, **6** Departamento de Química e Toxicologia Clínica, Faculdade de Ciências Farmacêuticas (FCT), University of São Paulo, São Paulo, São Paulo, Brazil

This study provides a perspective for the development of new therapeutic approaches in which drugs designed to inhibit the P2X7 receptor are used to ameliorate the outcomes of aggressive forms of TB.

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Microbes and Infection 18 (2016) 11–20

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Review

Innate immunity in tuberculosis: how the sensing of mycobacteria and tissue damage modulates macrophage death

Eduardo P. Amaral [a,*], Elena B. Lasunskaia [b], Maria Regina D'Império-Lima [a,*]

[a] Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil
[b] Laboratory of Recognition Biology, Center of Biosciences and Biotechnology, State University of North Fluminense, Campos dos Goytacazes, Rio de Janeiro, Brazil

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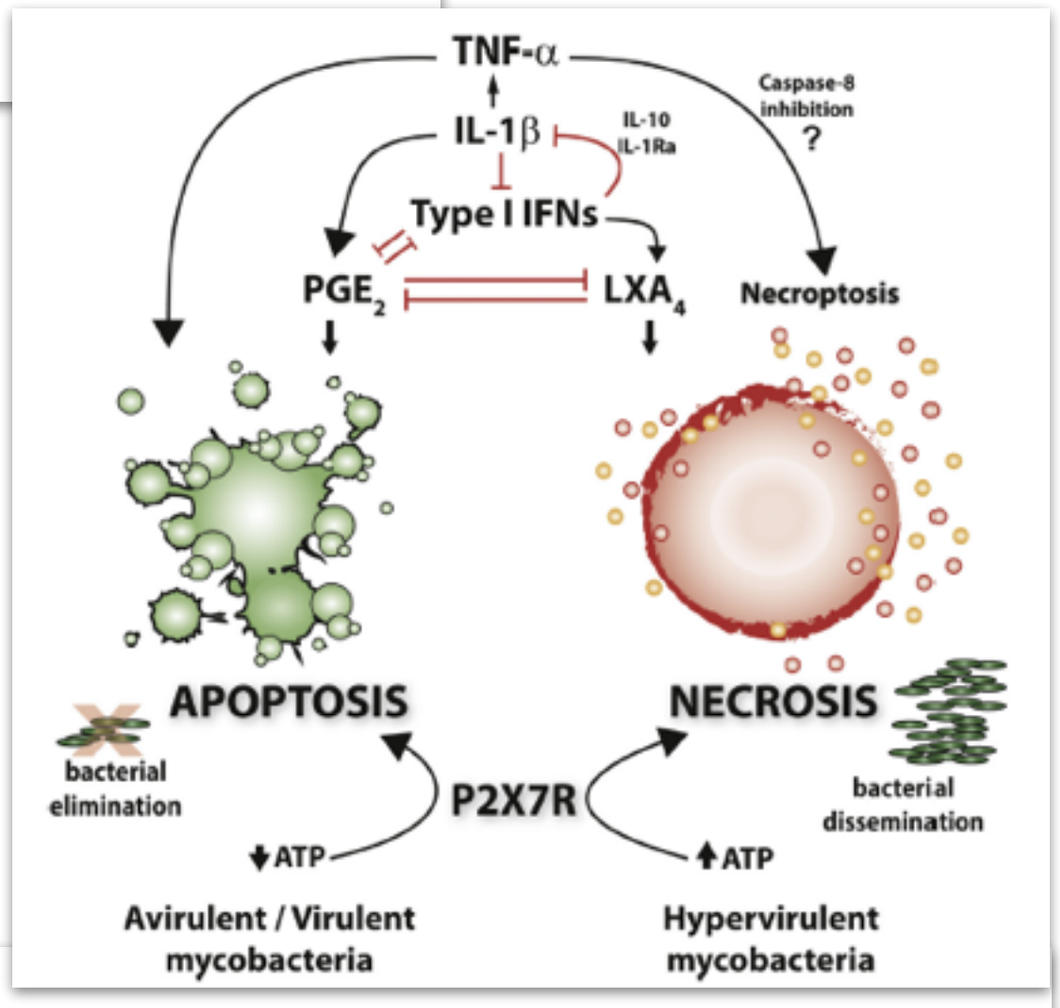
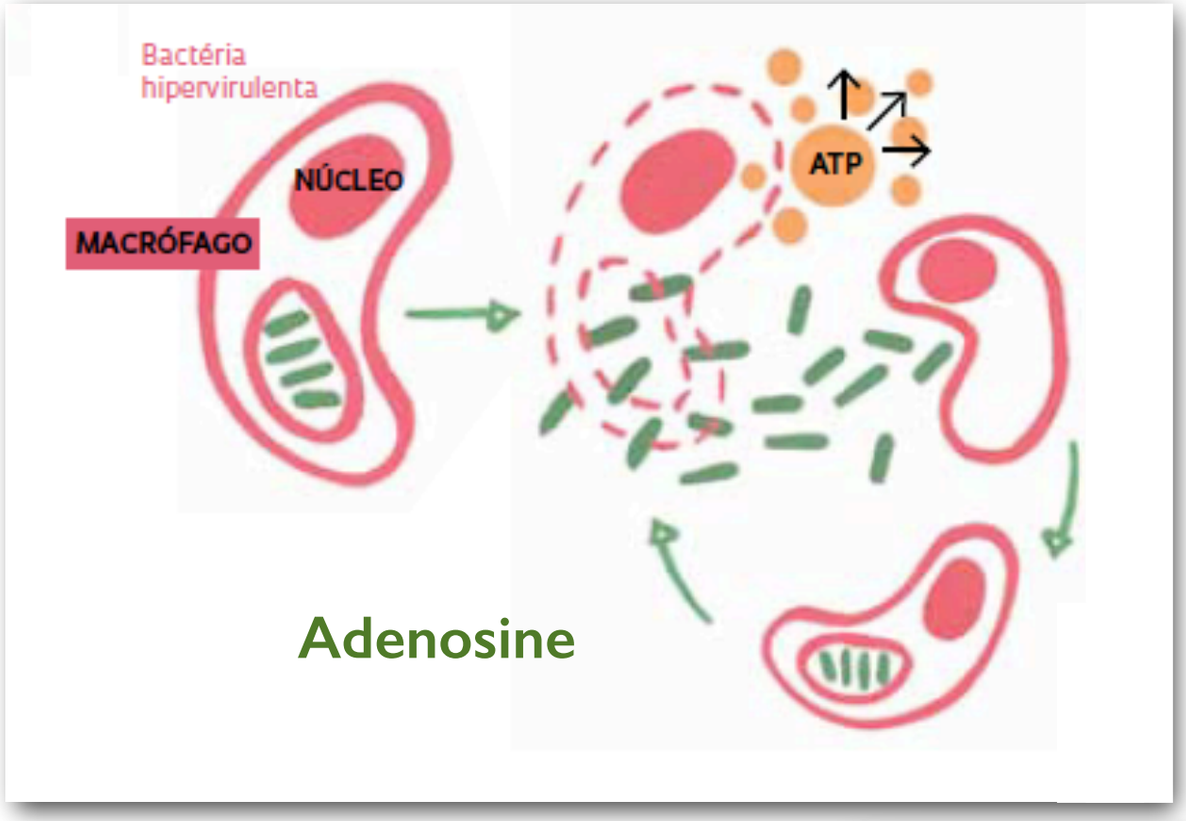


Abstract

The success of *Mycobacterium tuberculosis* as a human pathogen has been attributed to the ability of the bacillus to proliferate inside macrophages and to induce cell death. This review describes how the sensors of the innate immune system modulate the cell death pathways in infected macrophages and, consequently, the pathogenesis of tuberculosis.



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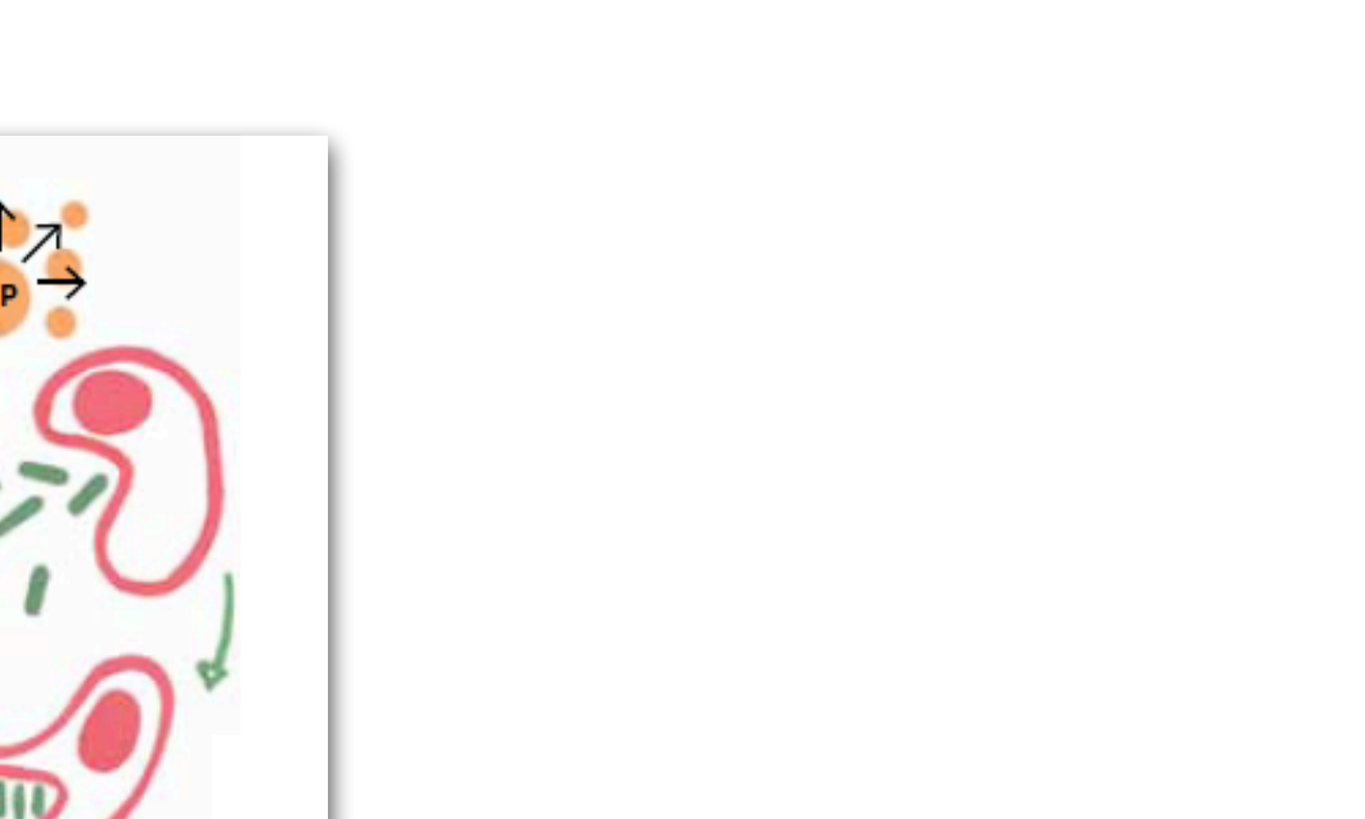
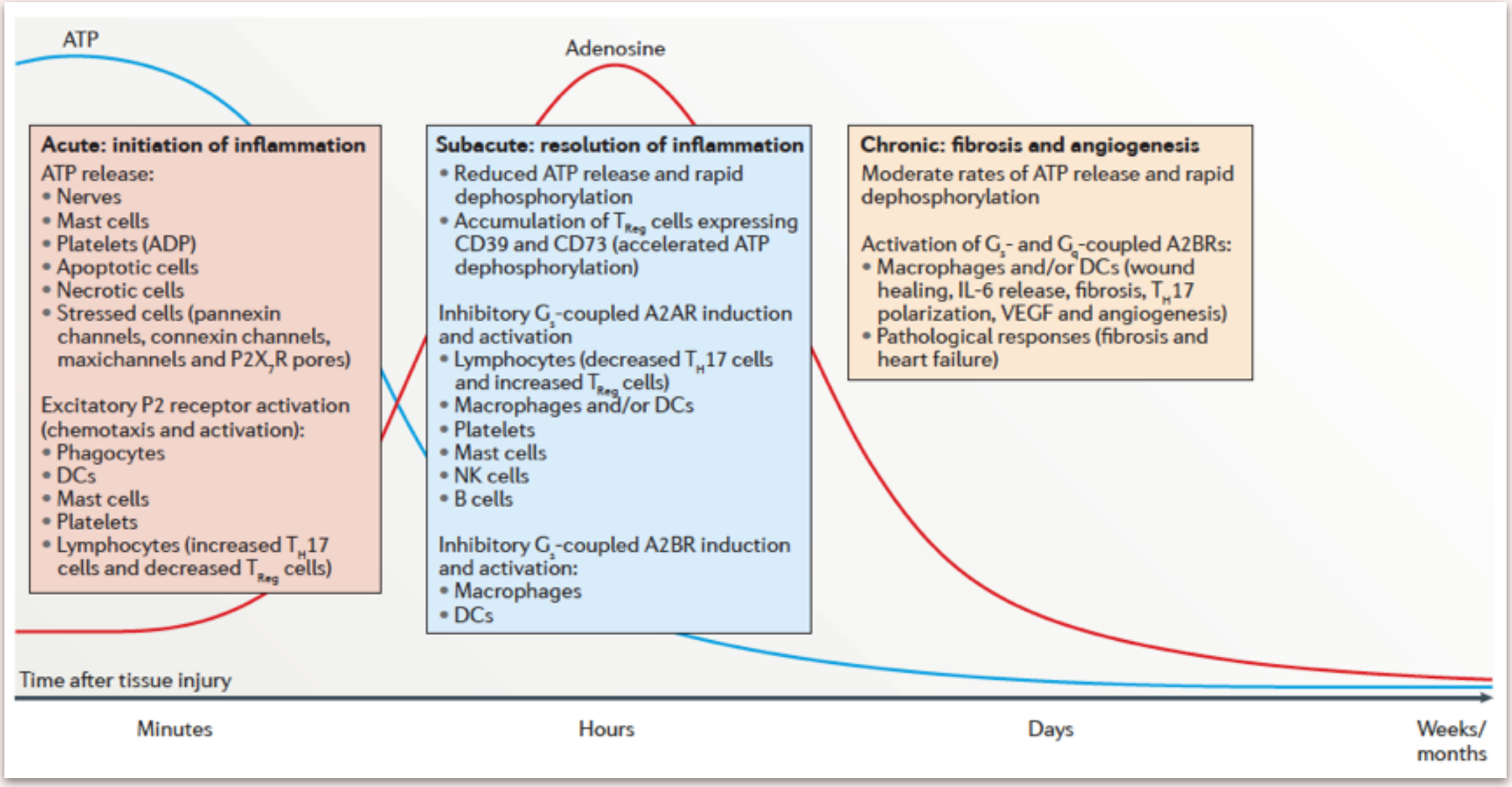
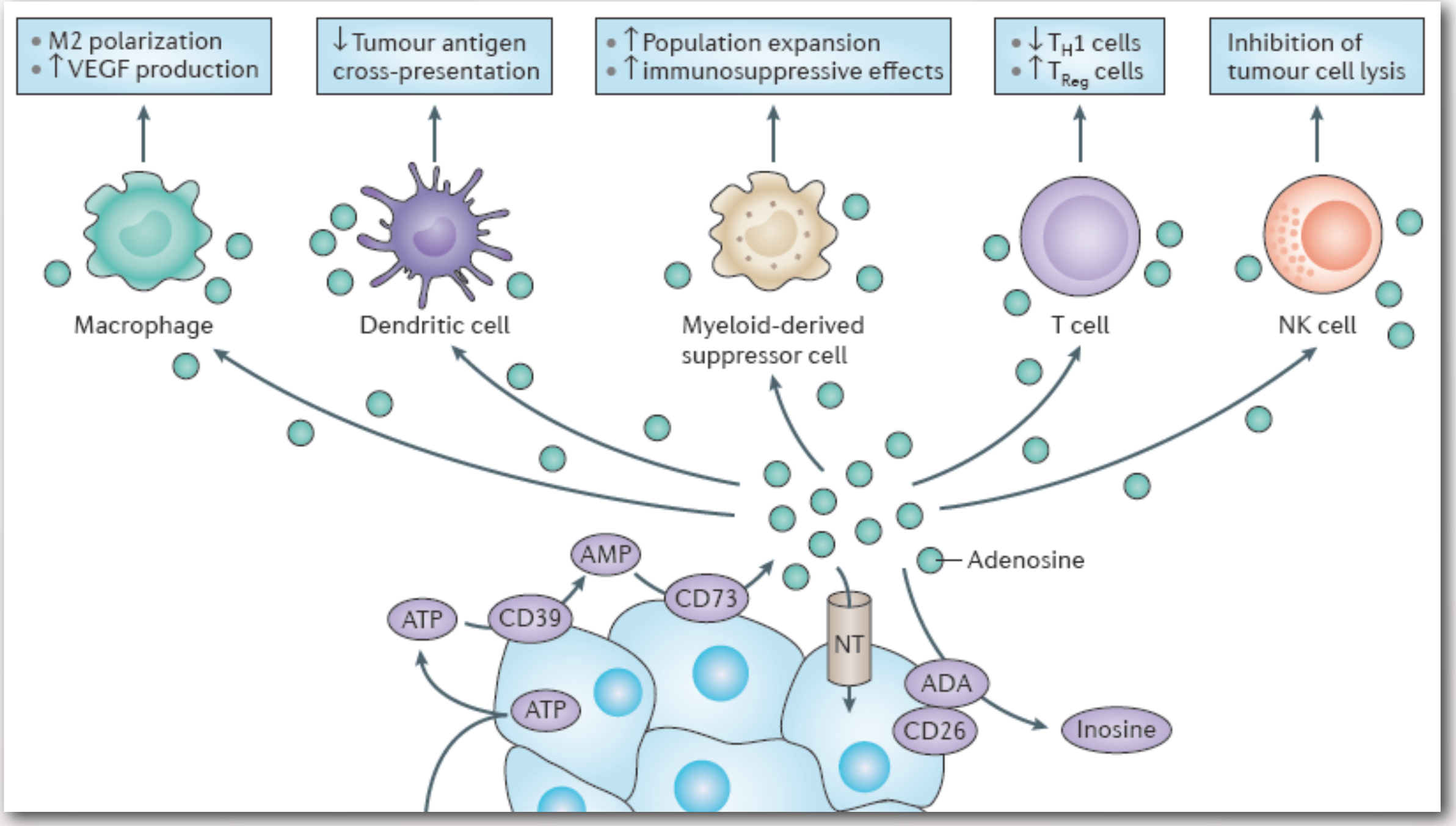


is
cell

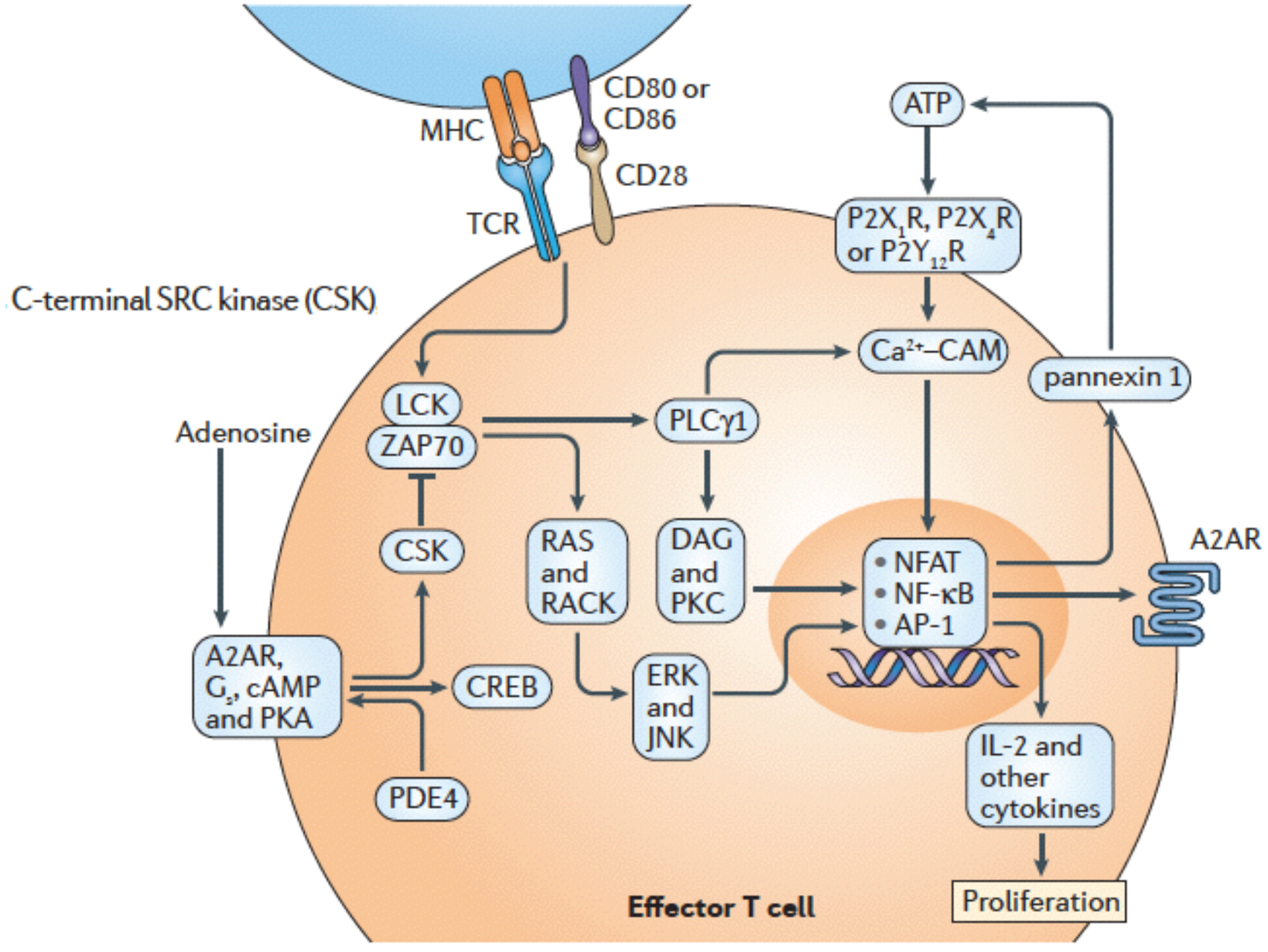
The purinergic signalling following tissue injury has three temporal phases



Cekic and Linden (2015) Nature Rev. Immunol., 16: 177-192.

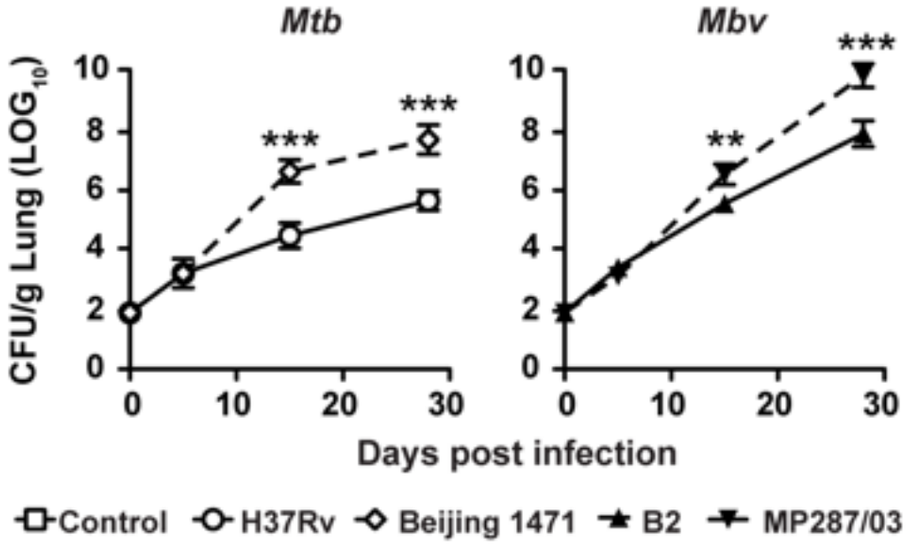

• M2 polarization
• ↑VEGF production
↓Tumour antigen cross-presentation
• ↑Population expansion
• ↑immunosuppressive effects
• ↓T_H1 cells
• ↑T_{Reg} cells
Inhibition of tumour cell lysis
Macrophage
Dendritic cell
Myeloid-derived suppressor cell
T cell
NK cell
Adenosine
AMP
CD73
ATP
CD39
NT
ADA
ATP
CD26
Inosine

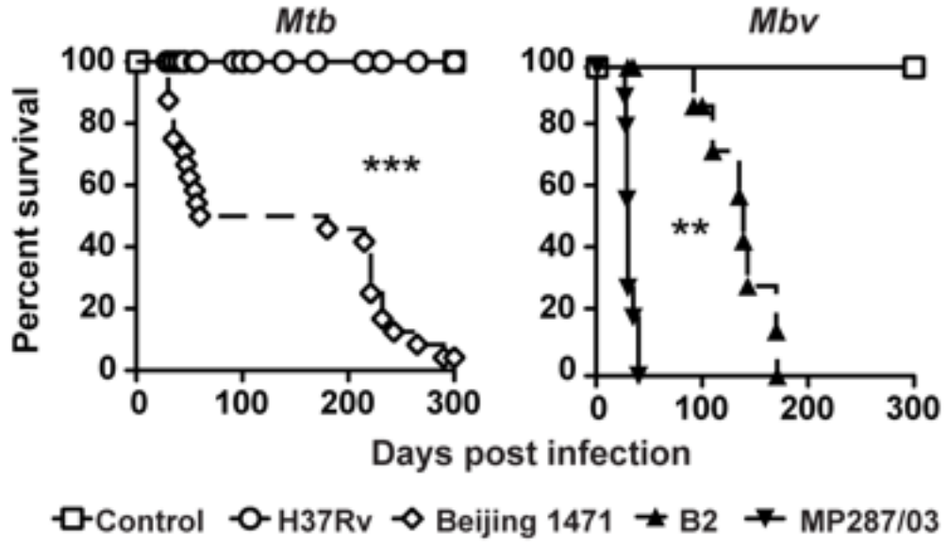
Adenosine inhibits T cell activation

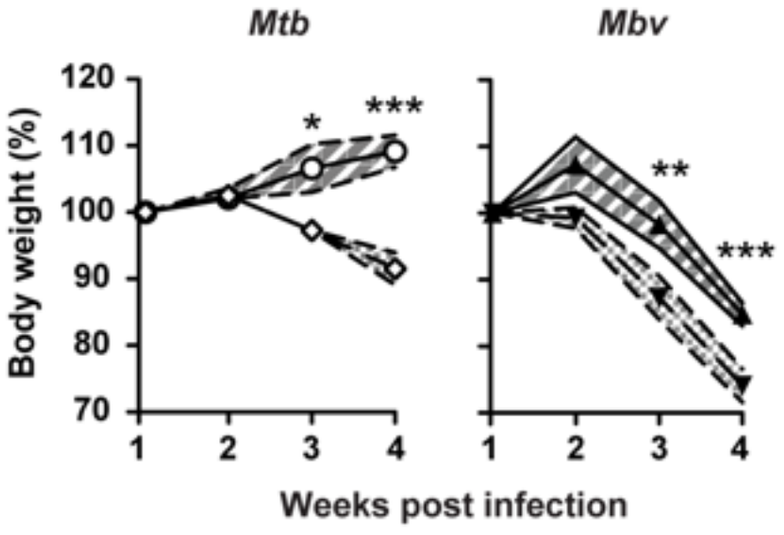


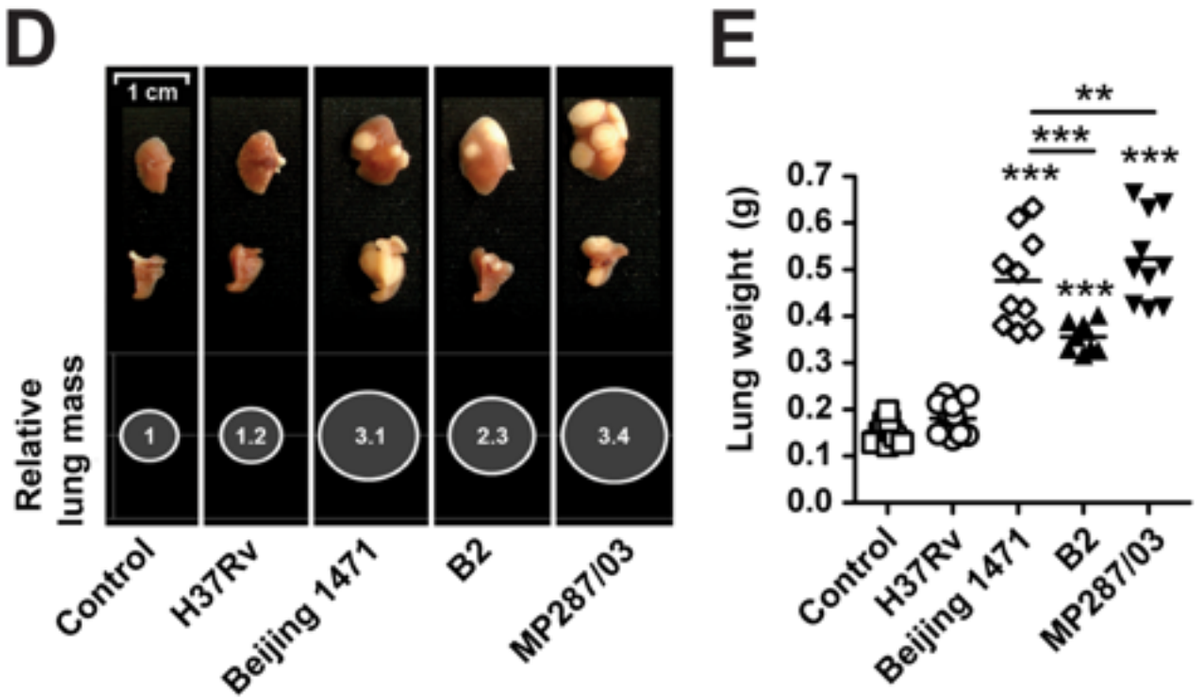
Cekic and Linden (2015) Nature Rev. Immunol., 16: 177-192.

Hypervirulent mycobacterial strains show various degrees of pathogenicity









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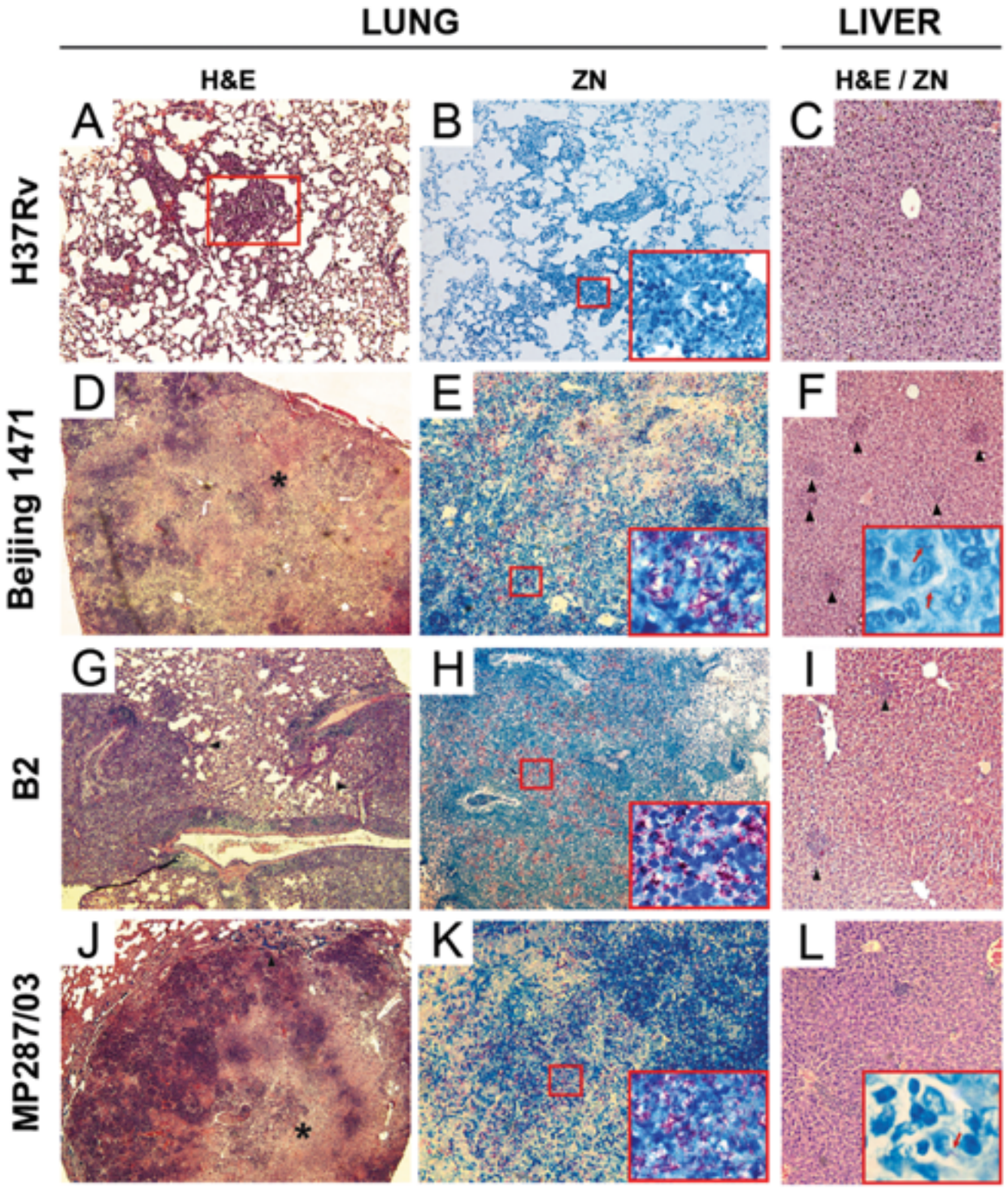
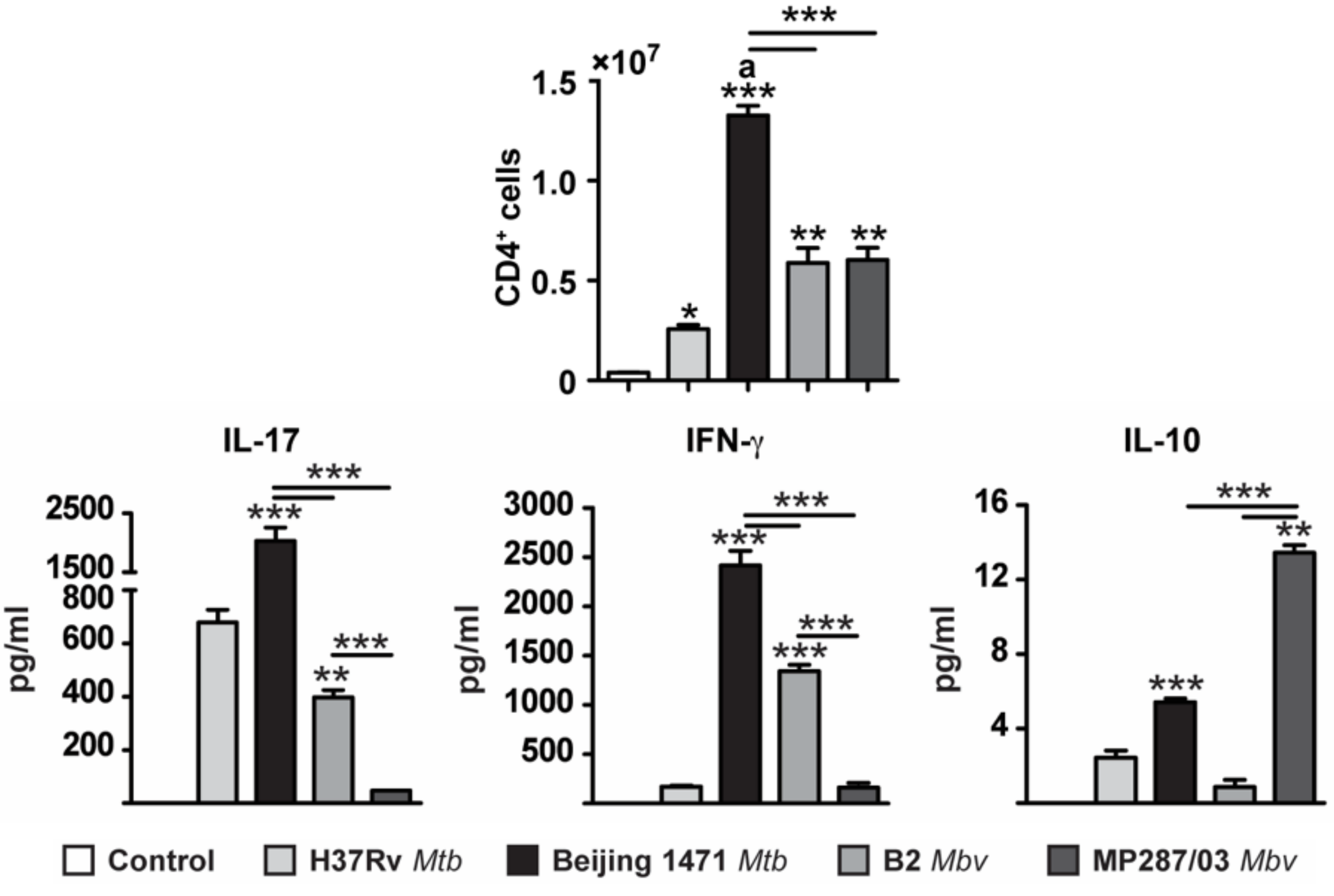


Lung CD4$^+$ T cells from mice infected with most virulent strains are suppressed



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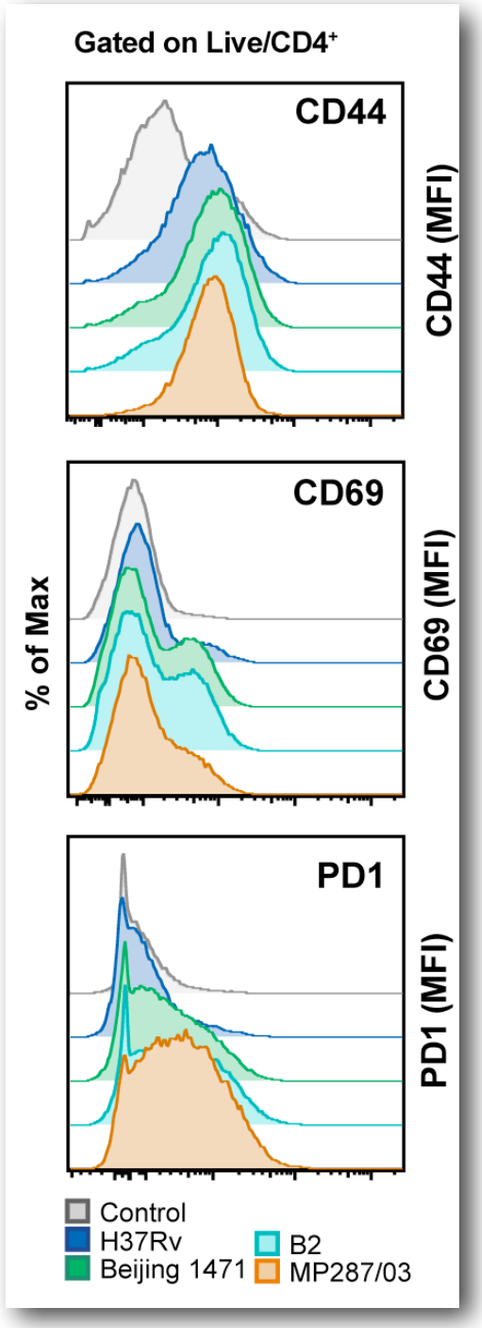
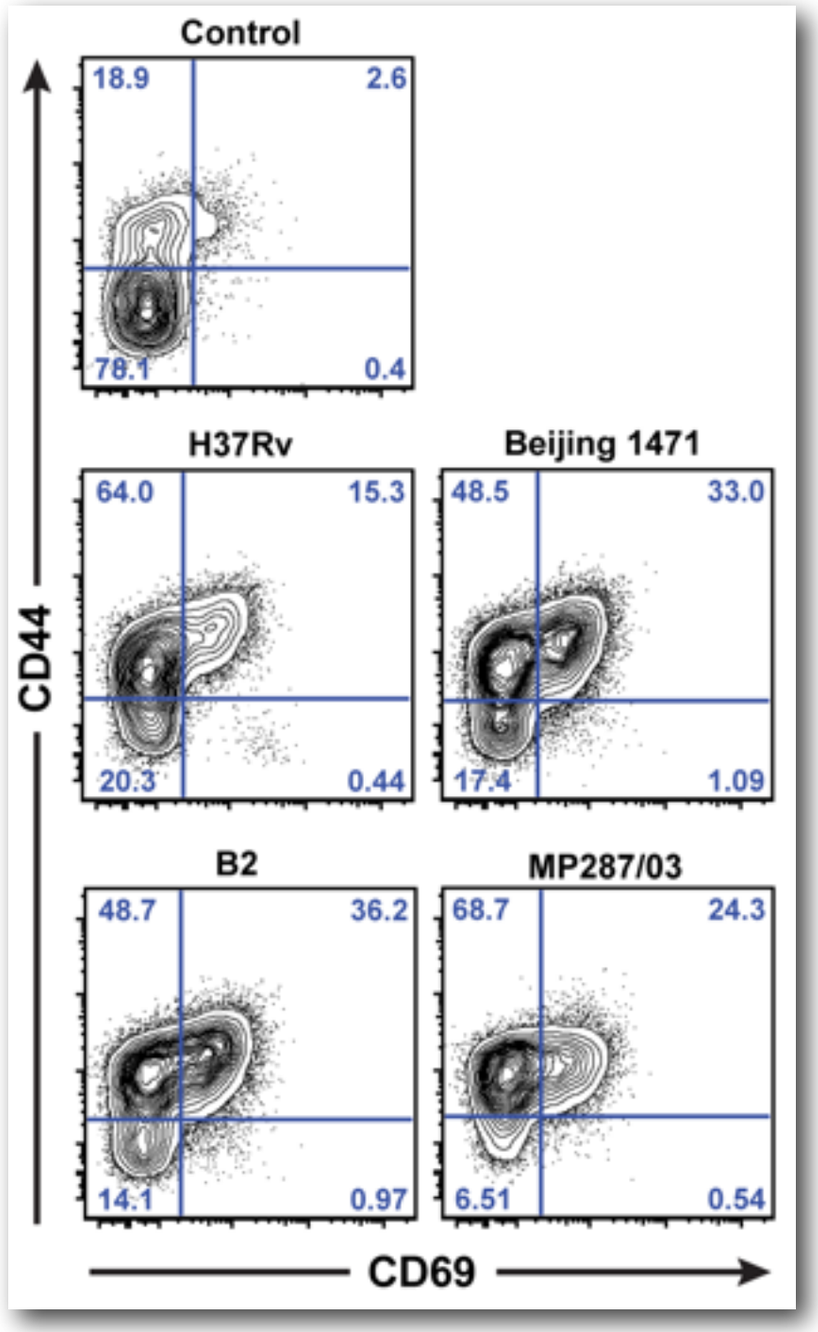
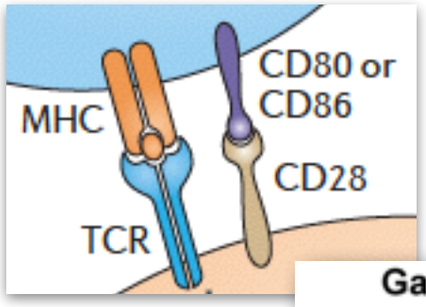
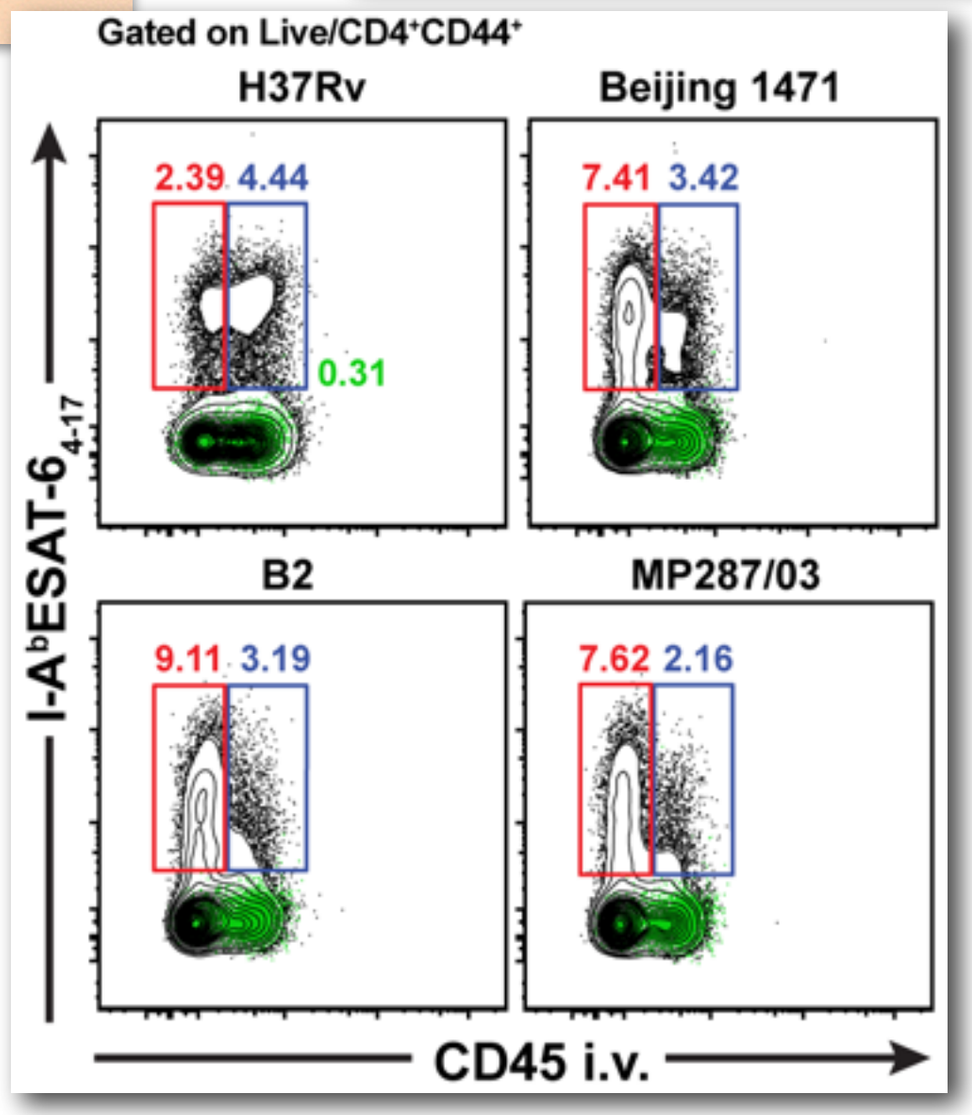


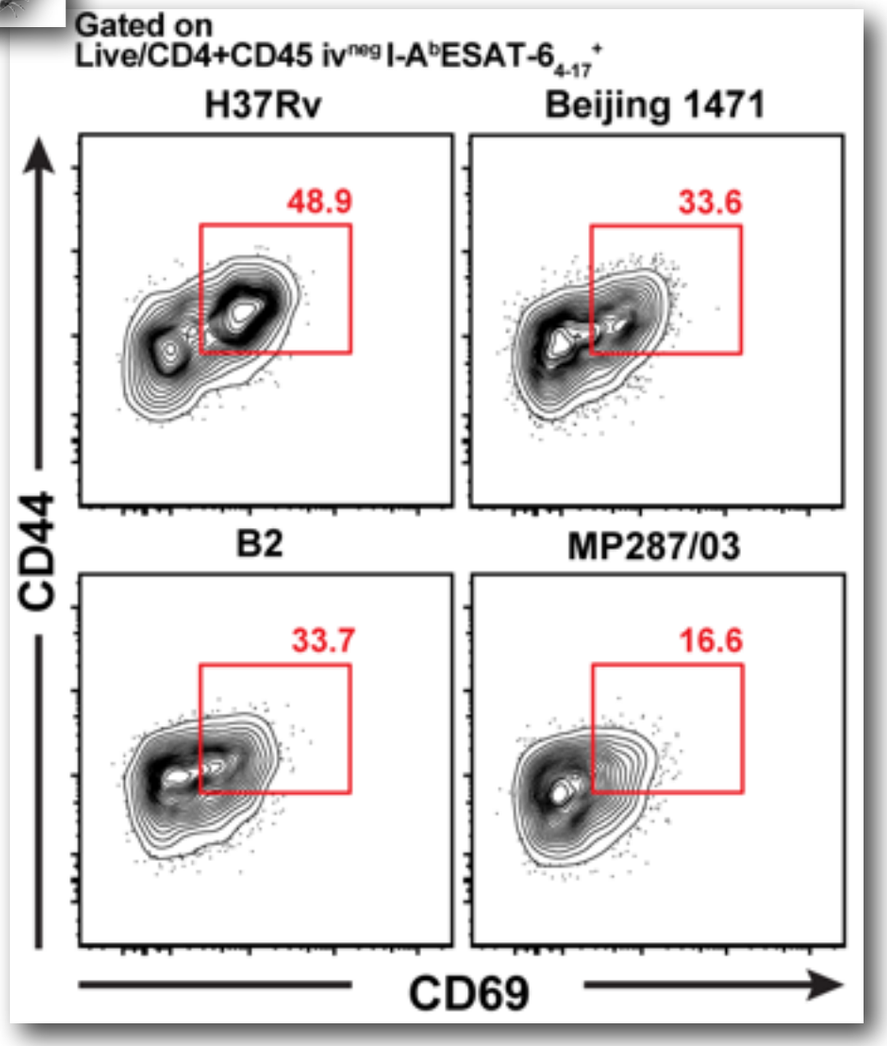


Specific CD4$^+$ T cells in the pulmonary parenchyma of mice infected with most virulent strains are suppressed

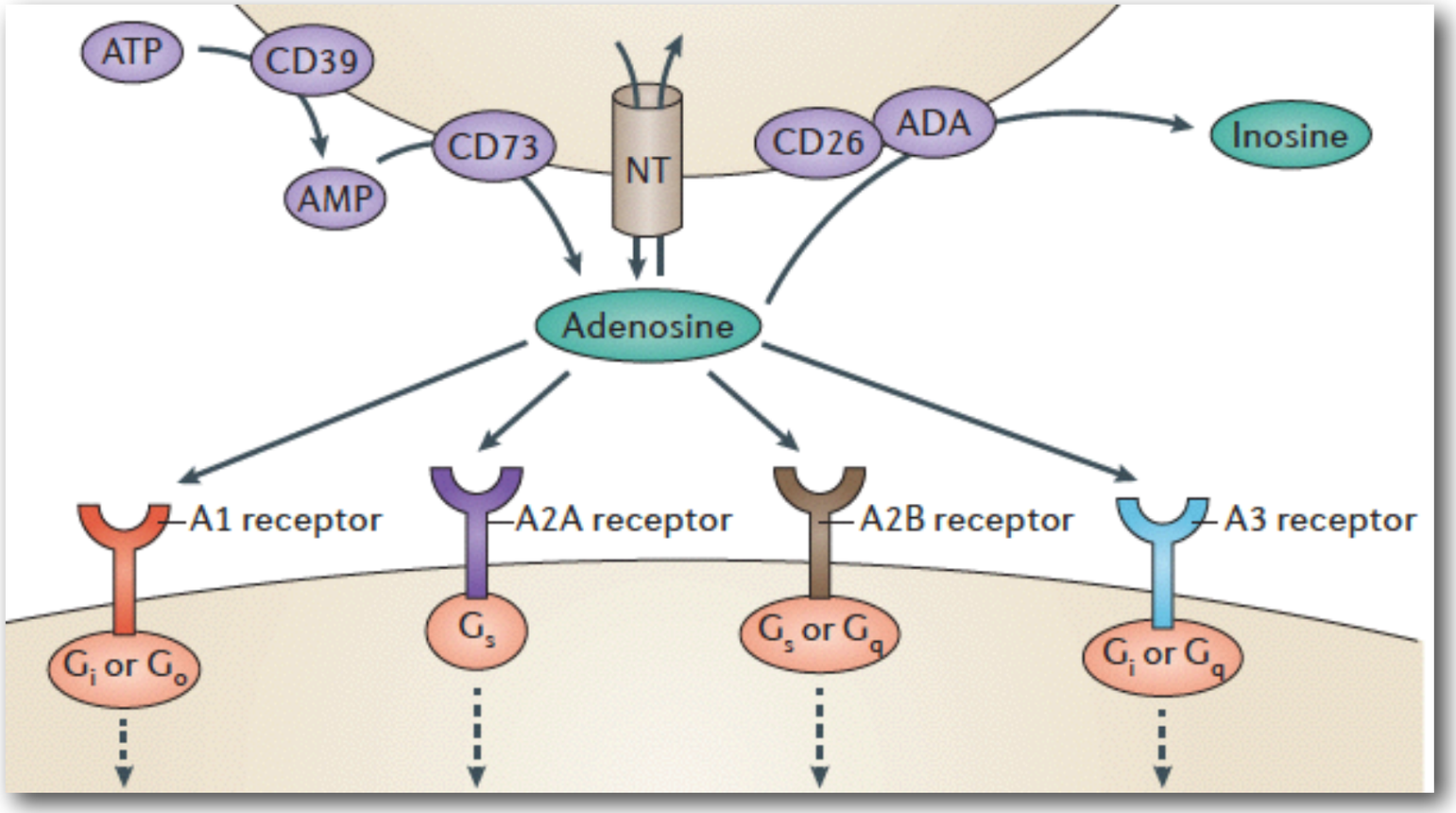


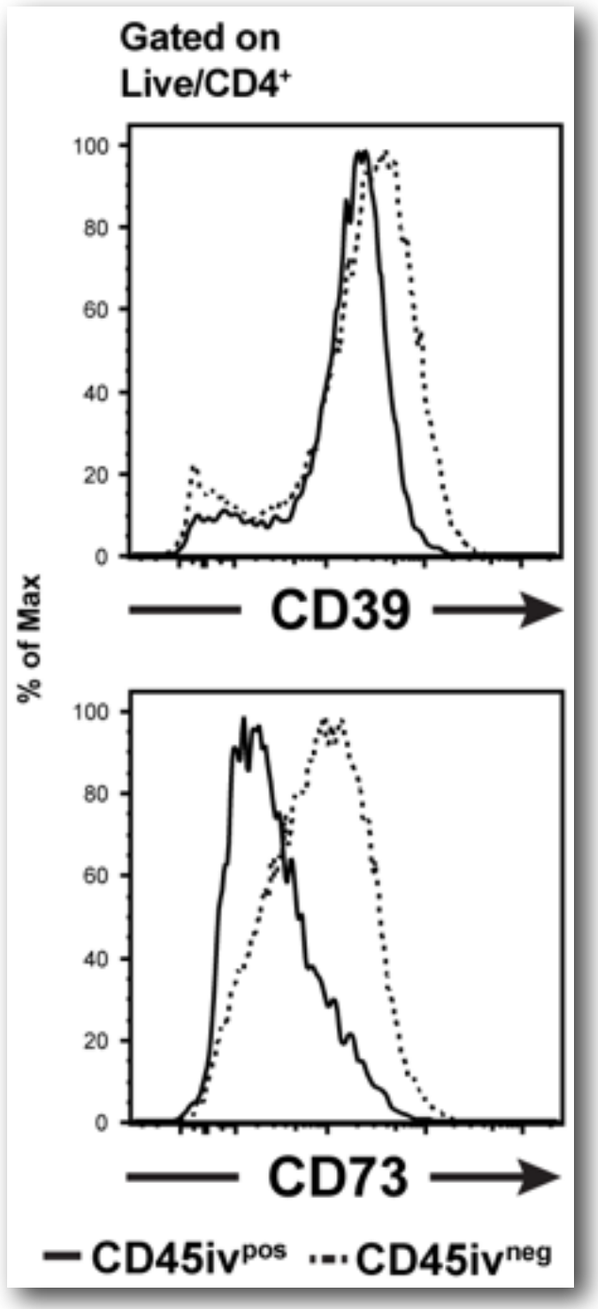
PE-anti-CD45 mAb i.v.
(intravascular cell staining)



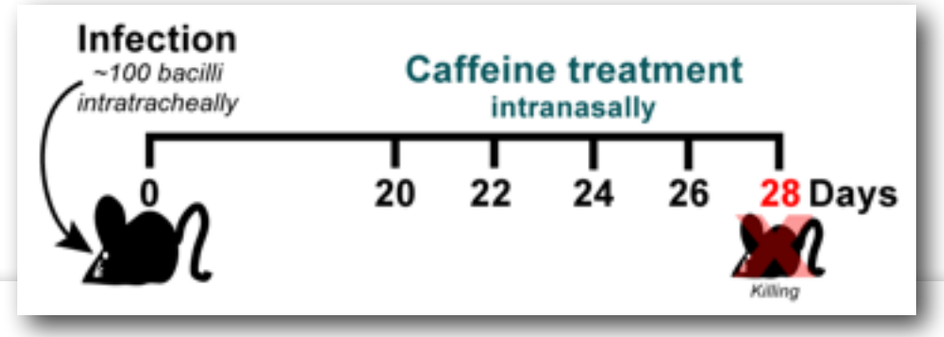


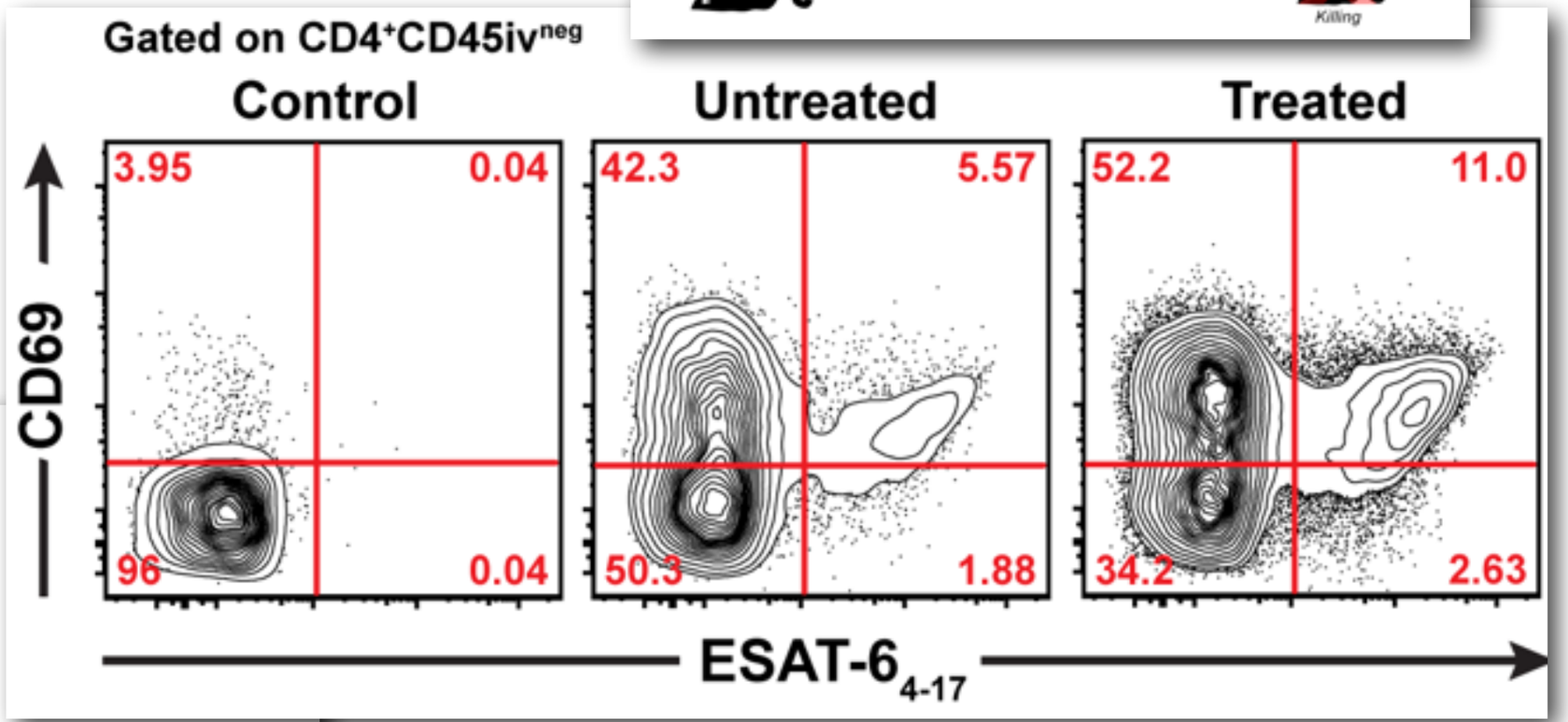
$CD4^+$ T cells in the lung parenchyma of MP287/03 Mbv-infected mice express ecto-ATPases

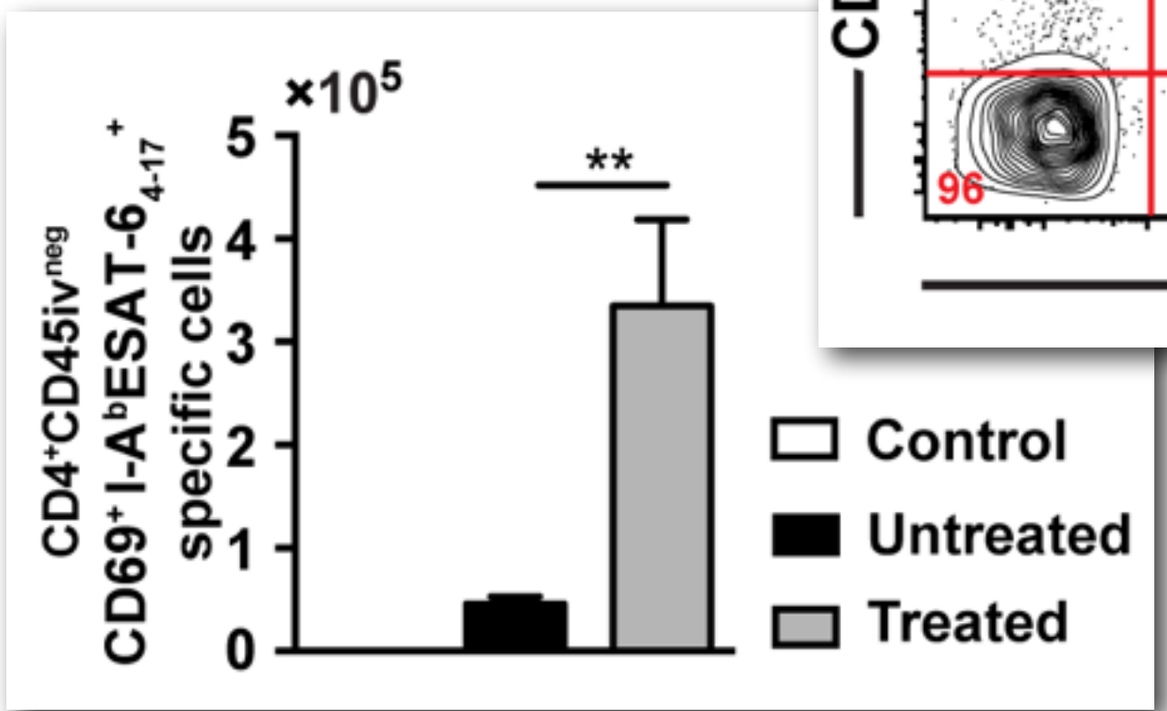




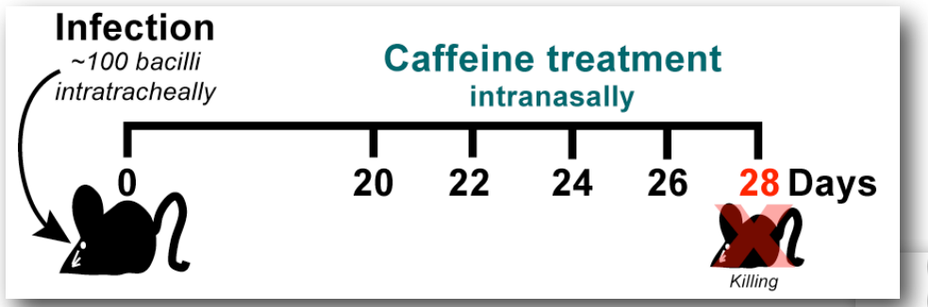
Inhibition of adenosine receptors by caffeine increases $CD4^+$ T cell numbers in the lung parenchyma of MP287/03 Mbv-infected mice

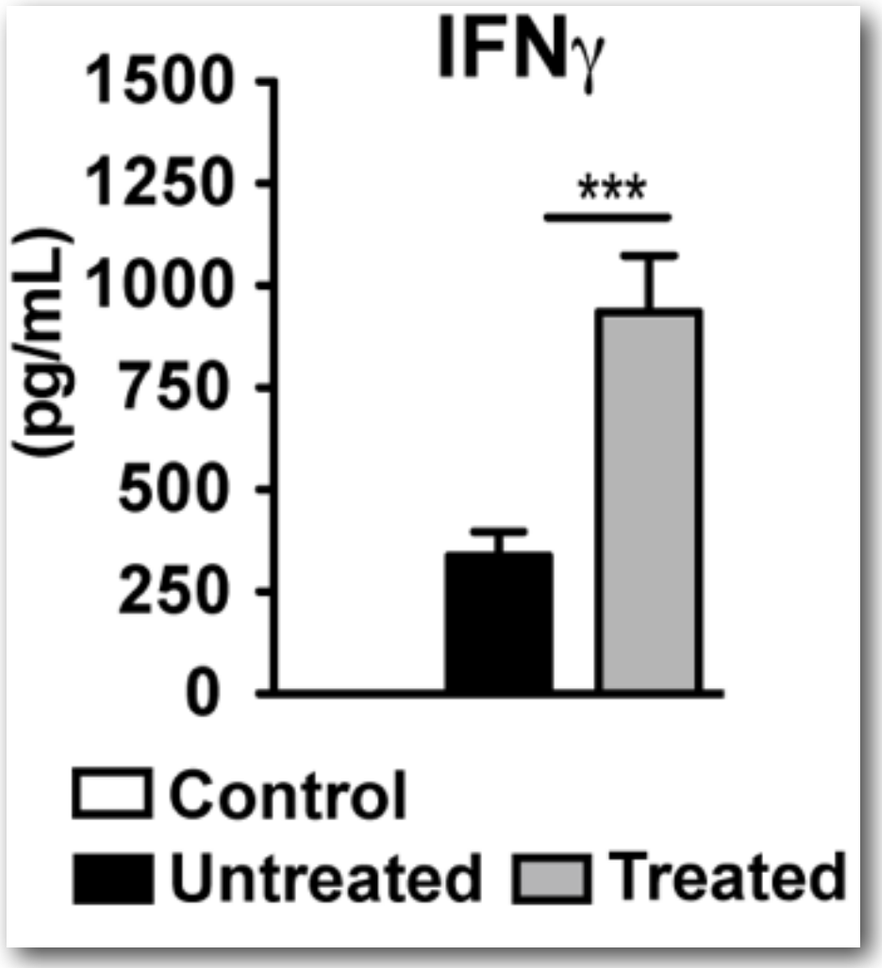


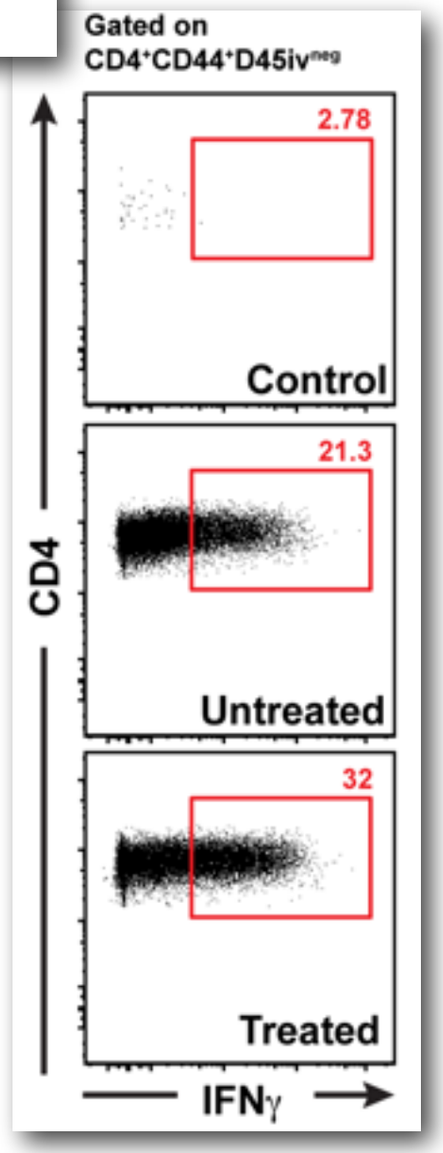


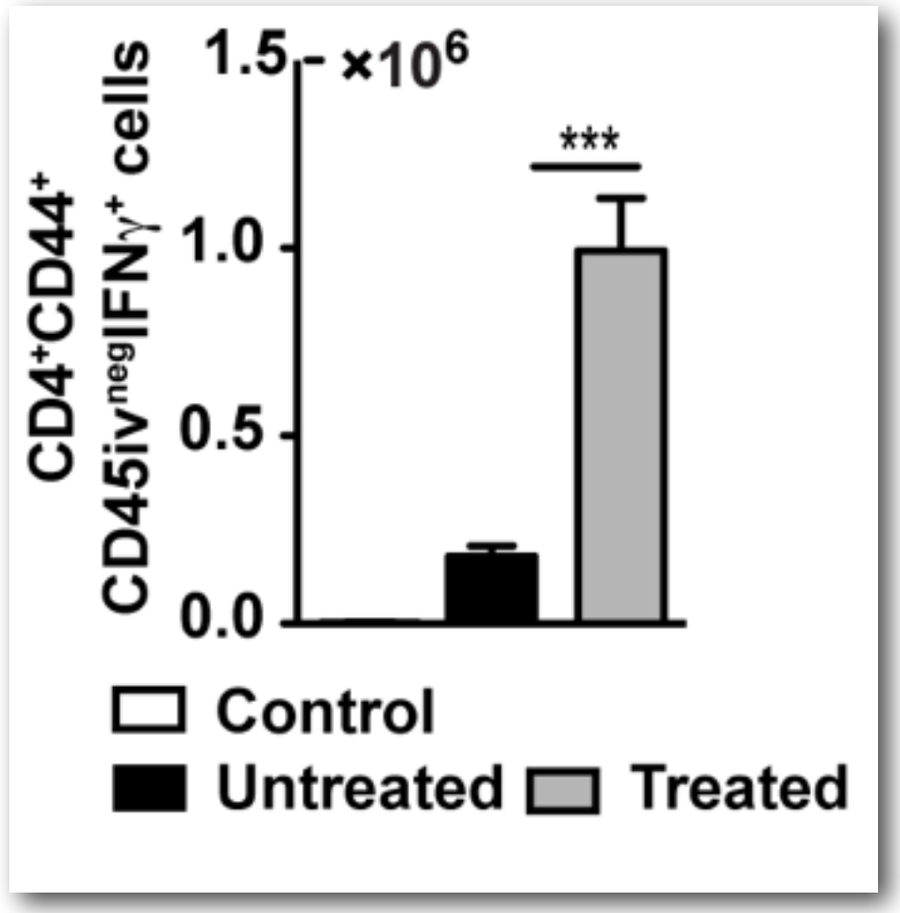


Inhibition of adenosine receptors by caffeine restores IFN-gamma production by specific $CD4^+$ T cells in the lung parenchyma of MP287/03 Mbv-infected mice

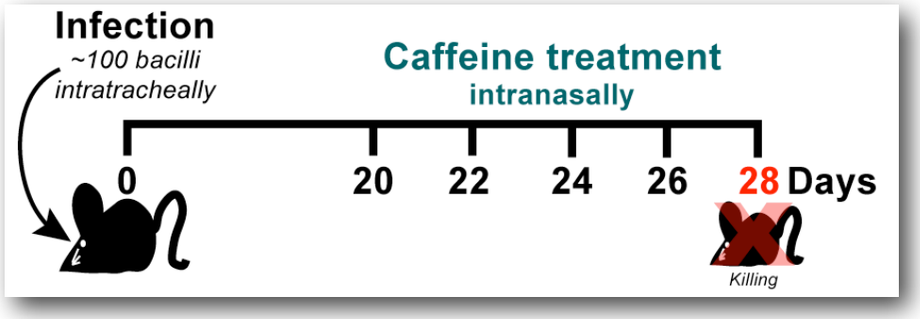


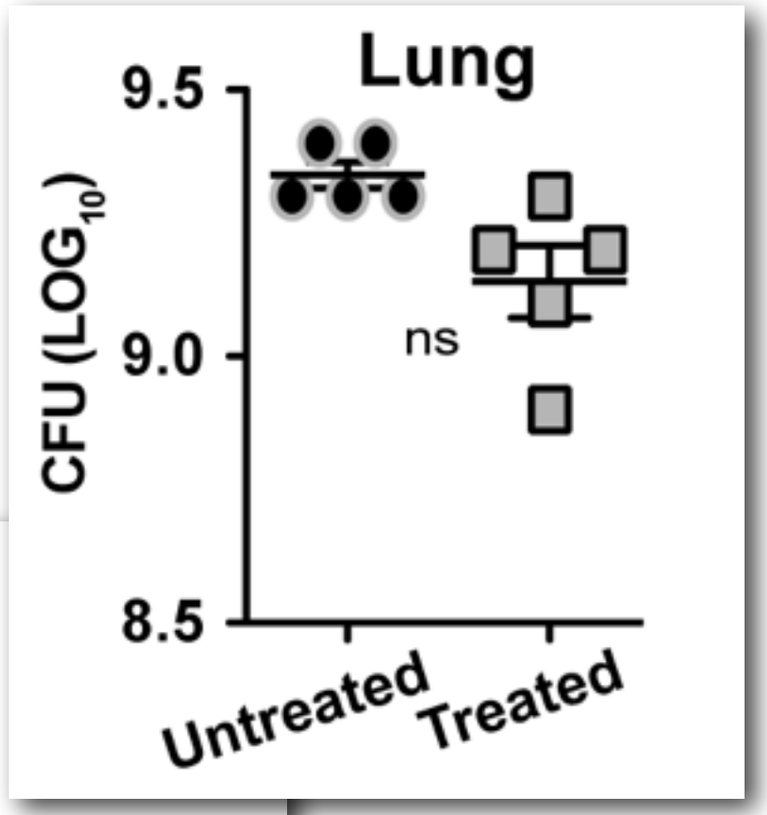


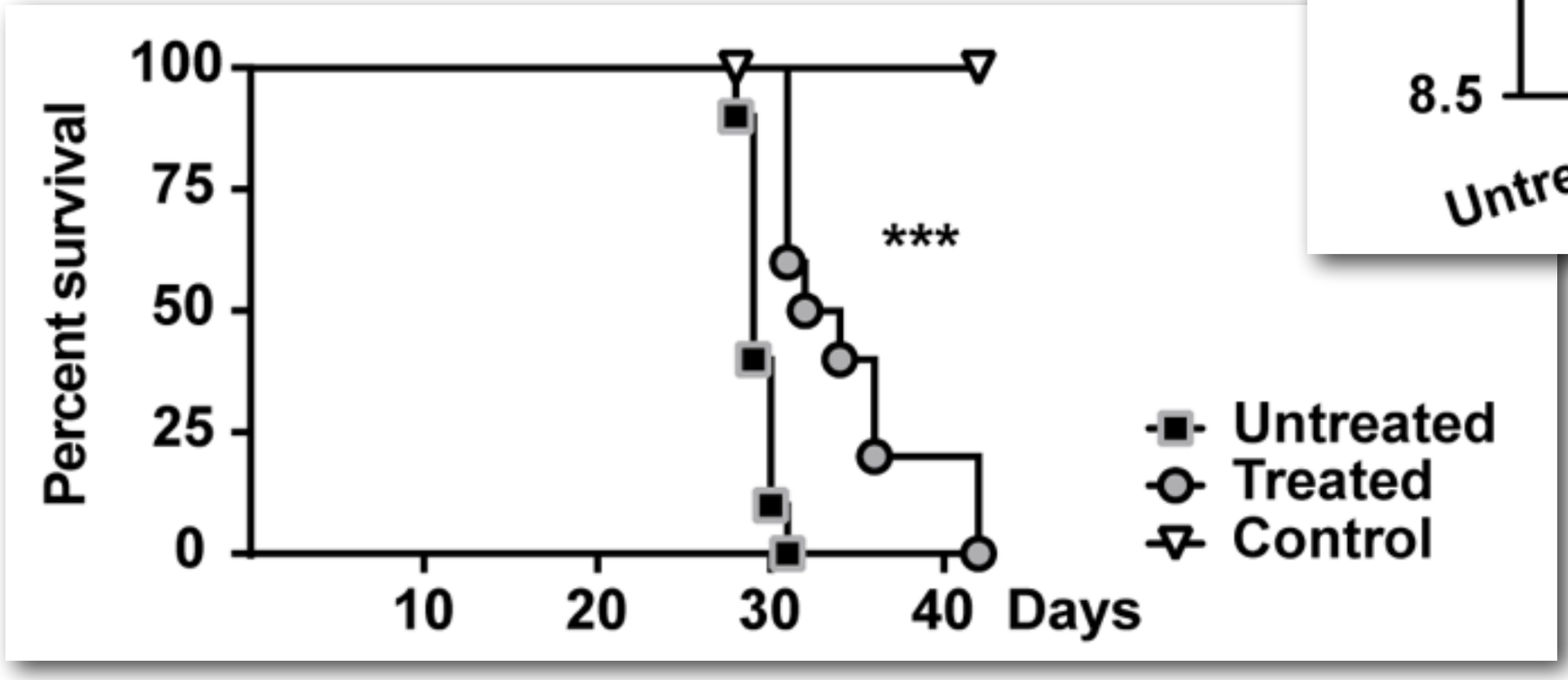


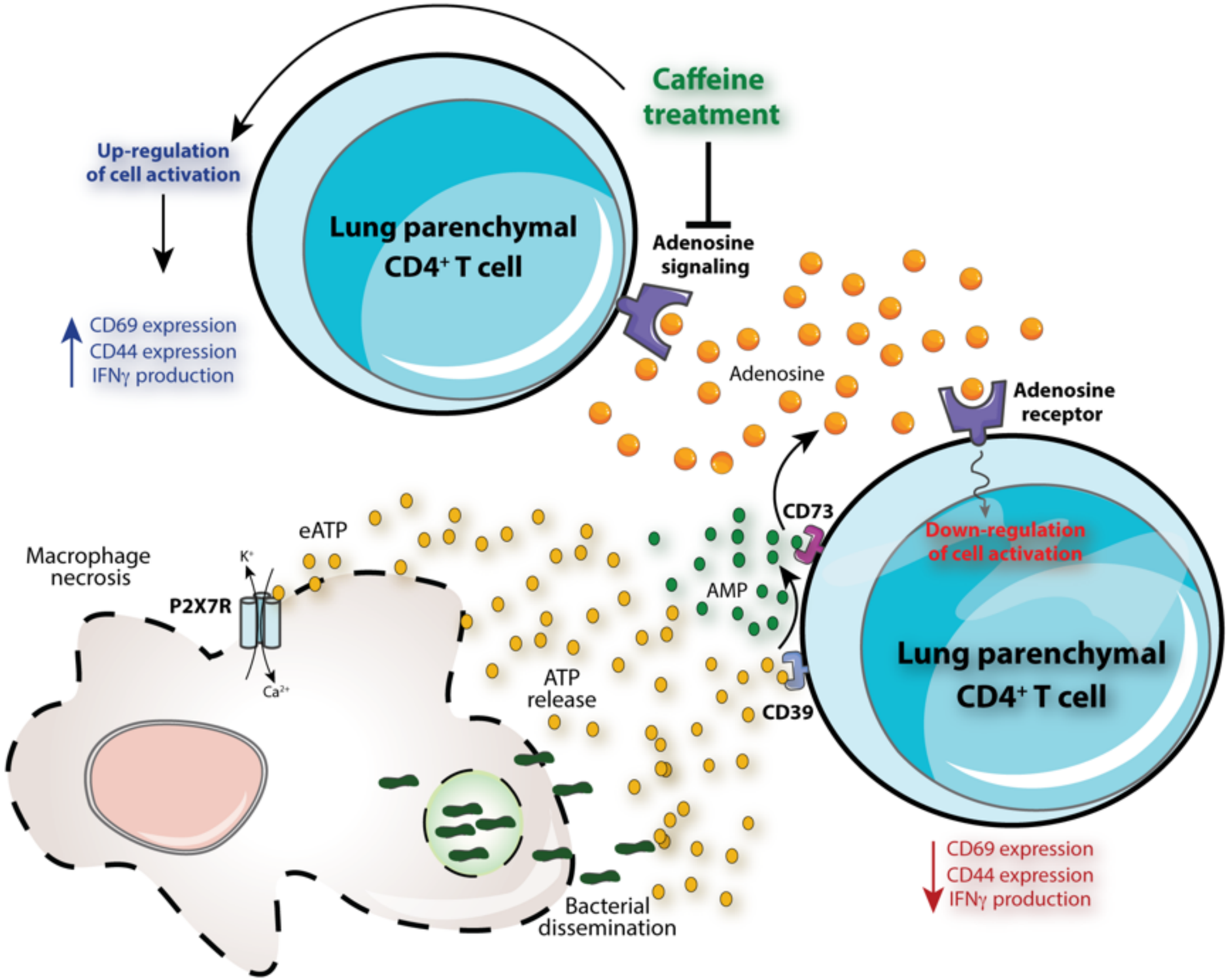


Inhibition of adenosine receptors by caffeine improves protection against MP287/03 Mbv








Caffeine
treatment
Up-regulation
of cell activation
Lung parenchymal
CD4+ T cell
Adenosine
signaling
CD69 expression
CD44 expression
IFNγ production
Adenosine
Adenosine
receptor
CD73
Down-regulation
of cell activation
Macrophage
necrosis
eATP
K+
P2X7R
Ca2+
AMP
ATP
release
CD39
Lung parenchymal
CD4+ T cell
Bacterial
dissemination
CD69 expression
CD44 expression
IFNγ production

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