The inflammasomes in recognition and response to intracellular pathogens and evasion mechanisms

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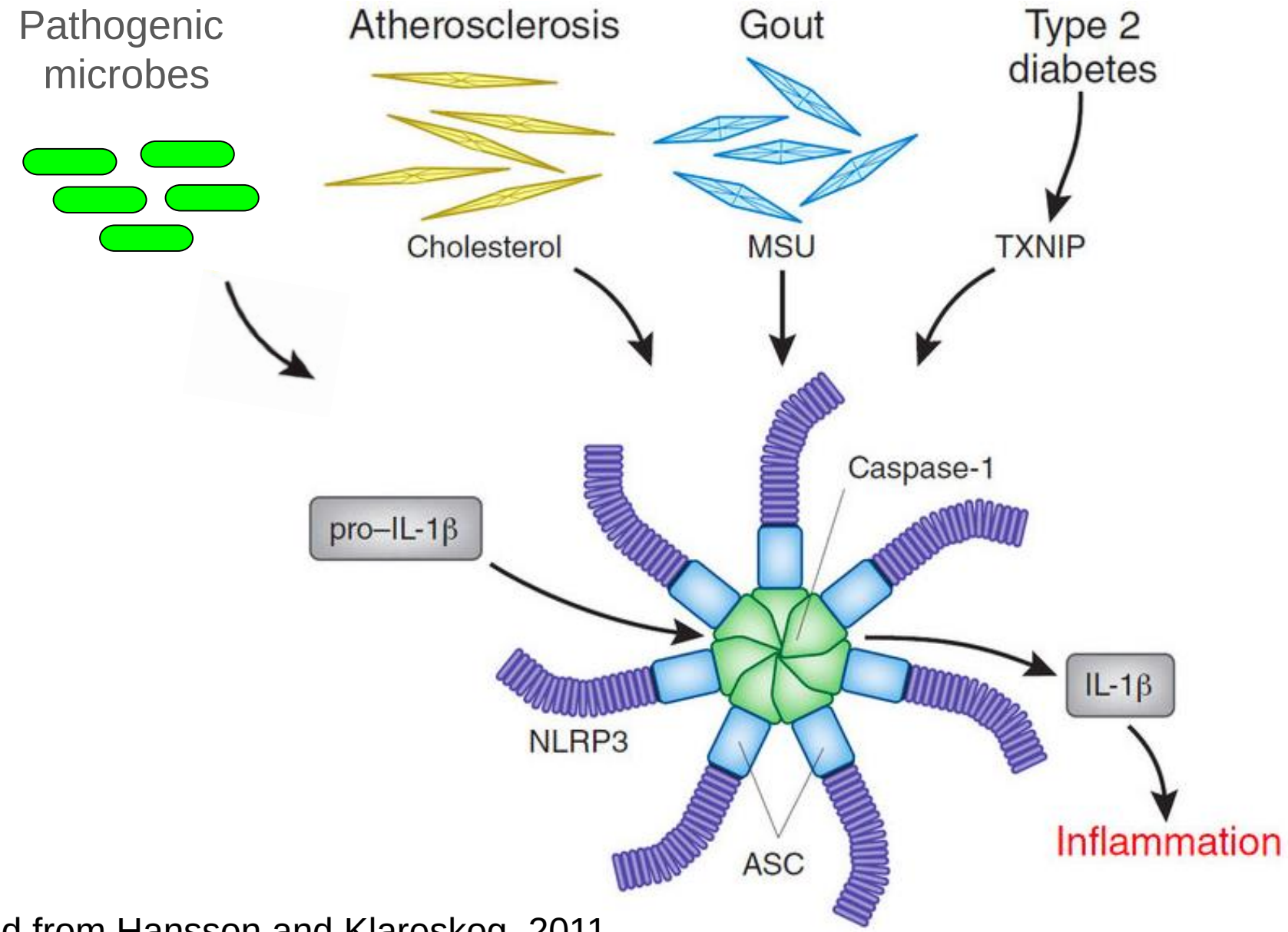
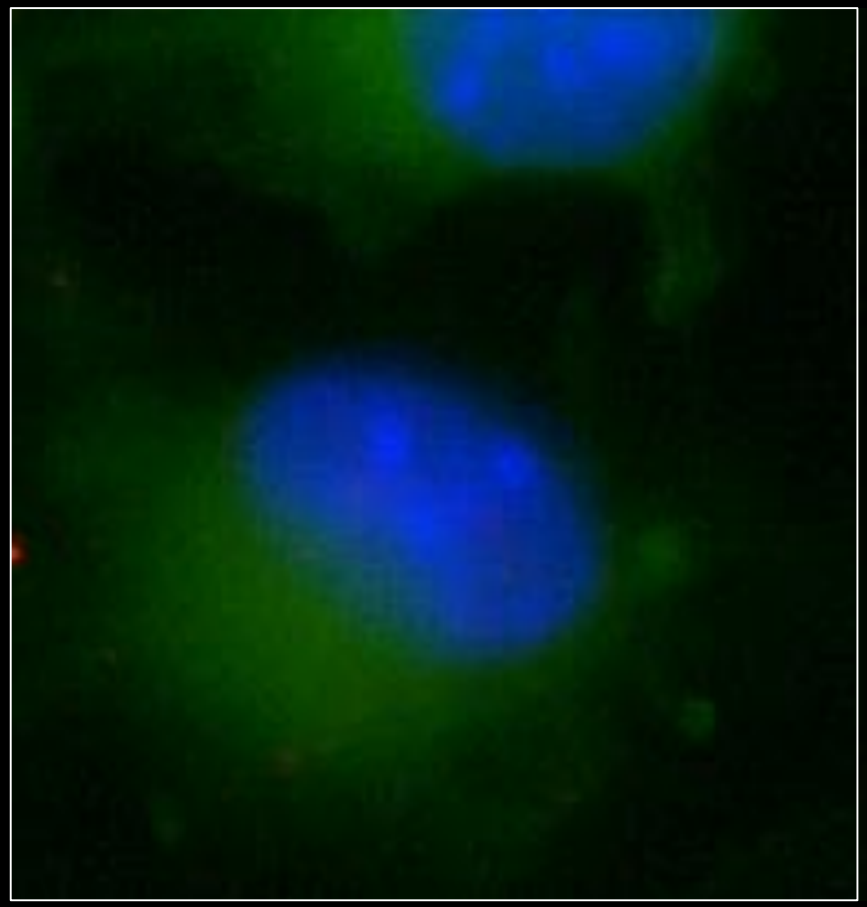
The inflammasomes



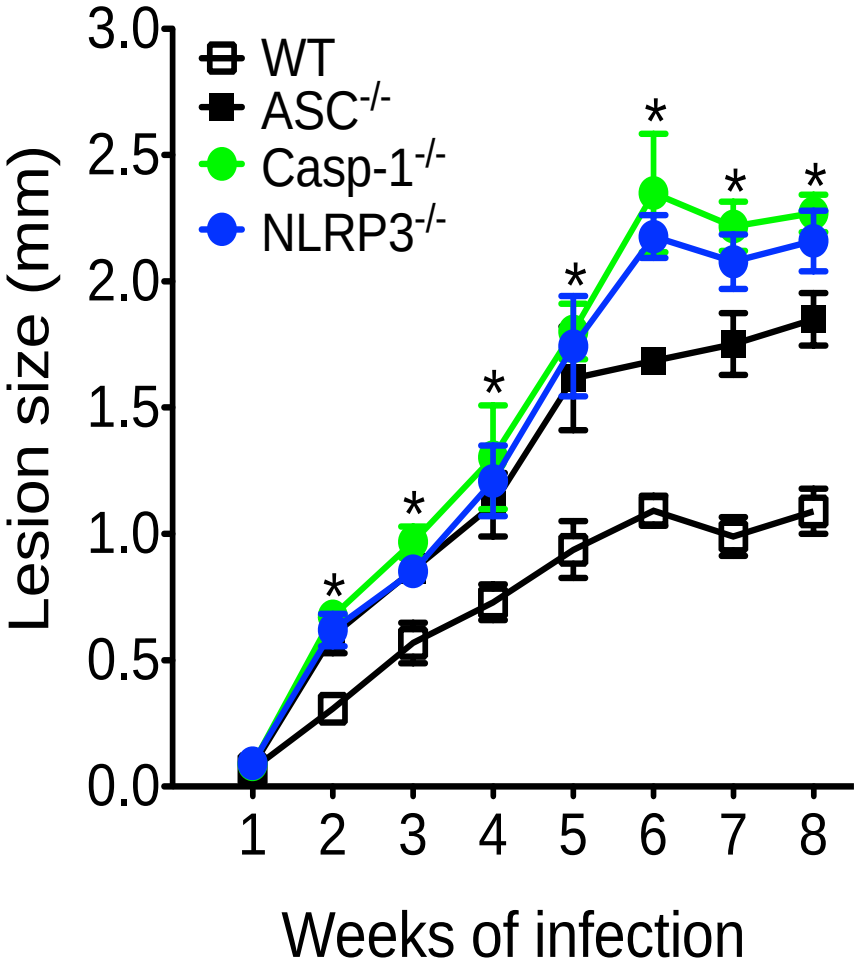
Adapted from Hansson and Klareskog, 2011

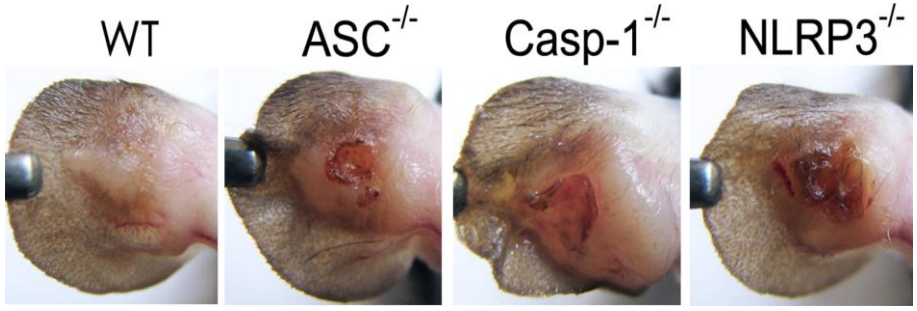
Intracellular pathogens, such as *Leishmania,* trigger activation of NLRP3 inflammasome in macrophages

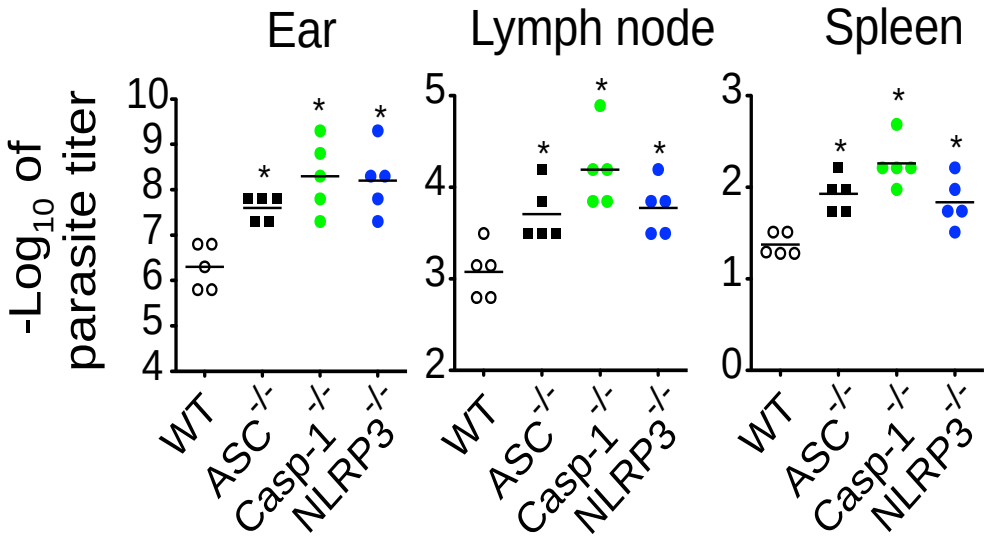


Lima-Junior et al., *Nature Med*. 2013.

The inflammasome is required for restriction of *Leishmania* infection in vivo

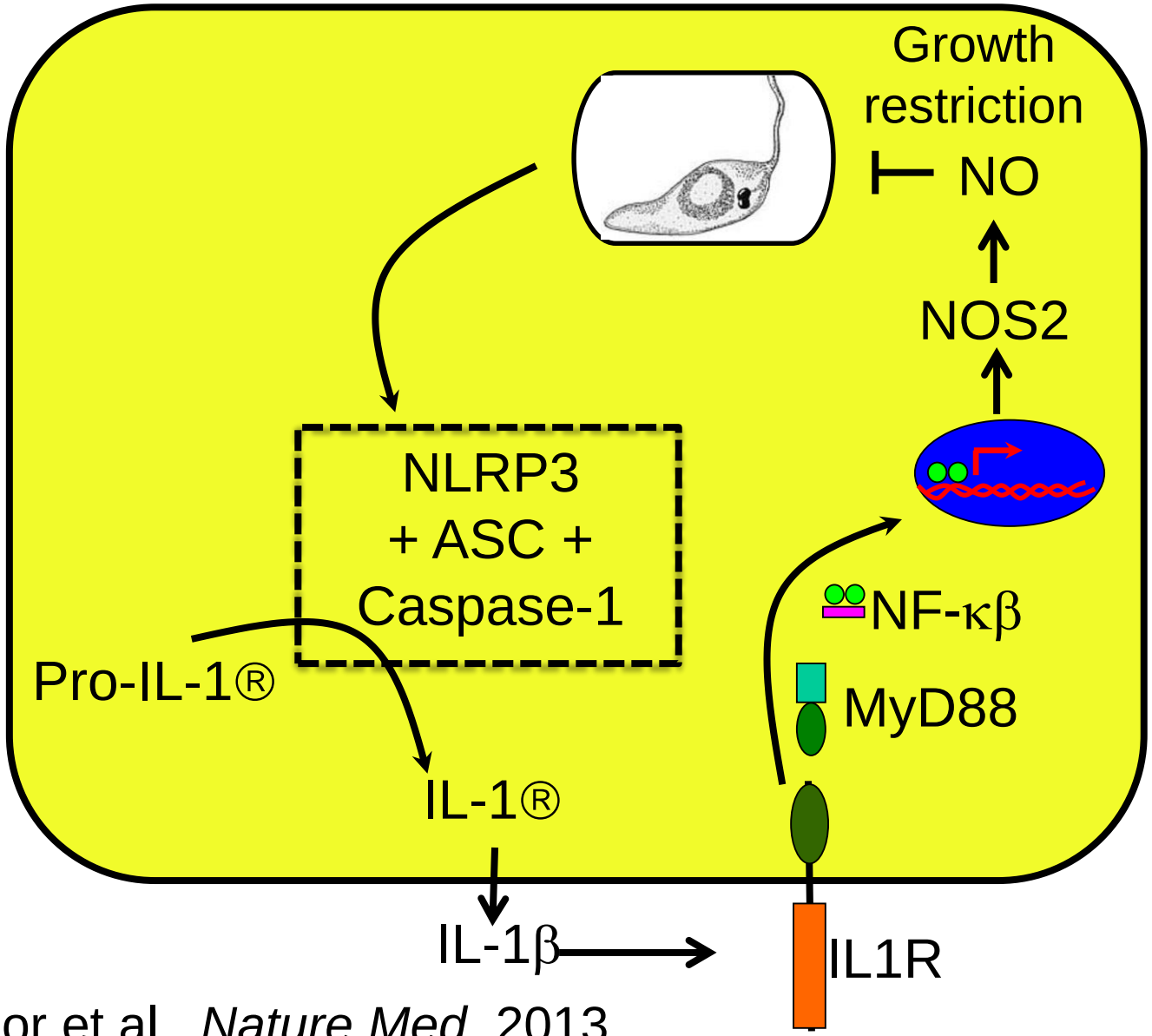






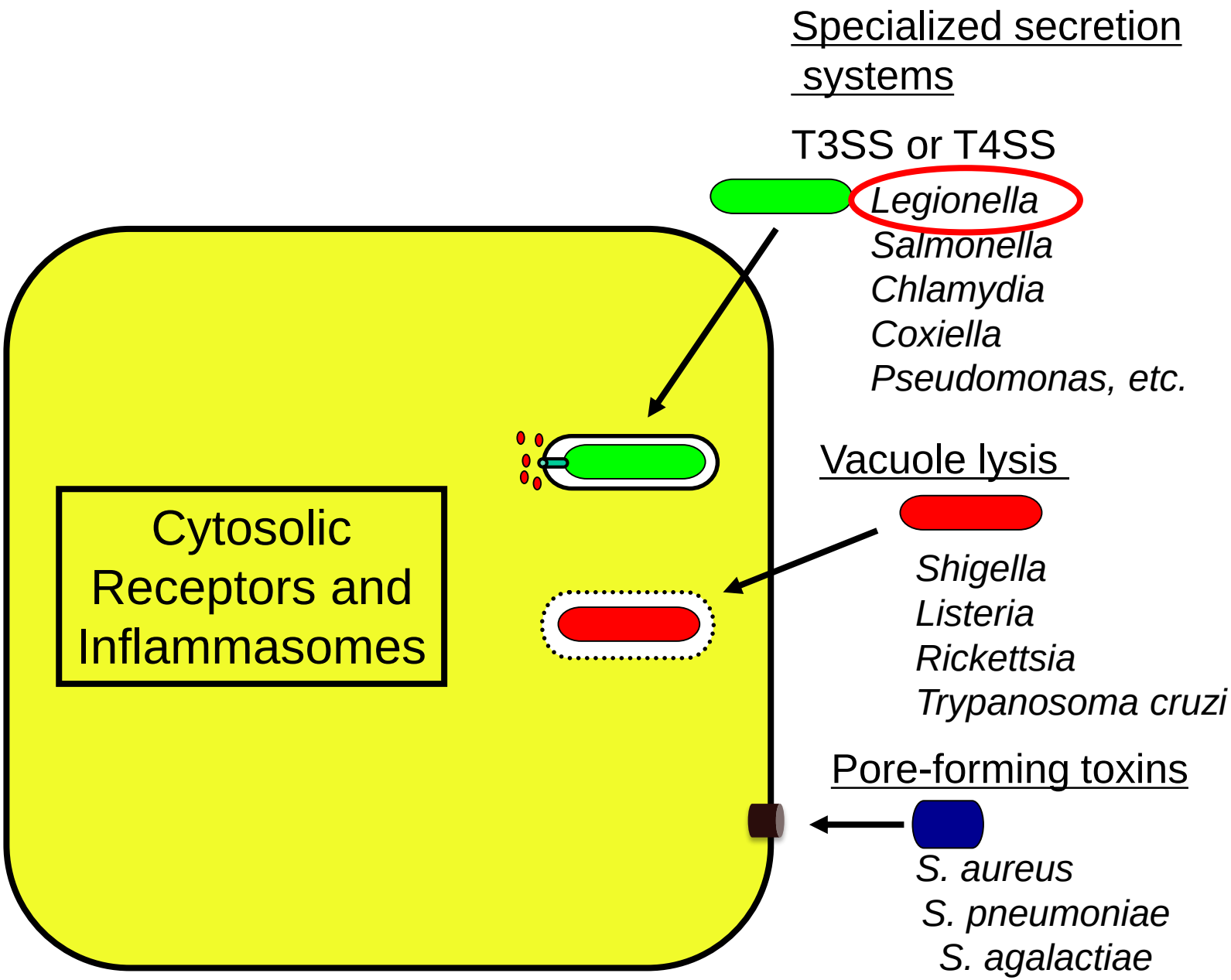
Lima-Junior et al., *Nature Med*. 2013.

Inflammasome-mediated resistance to *Leishmania* infection

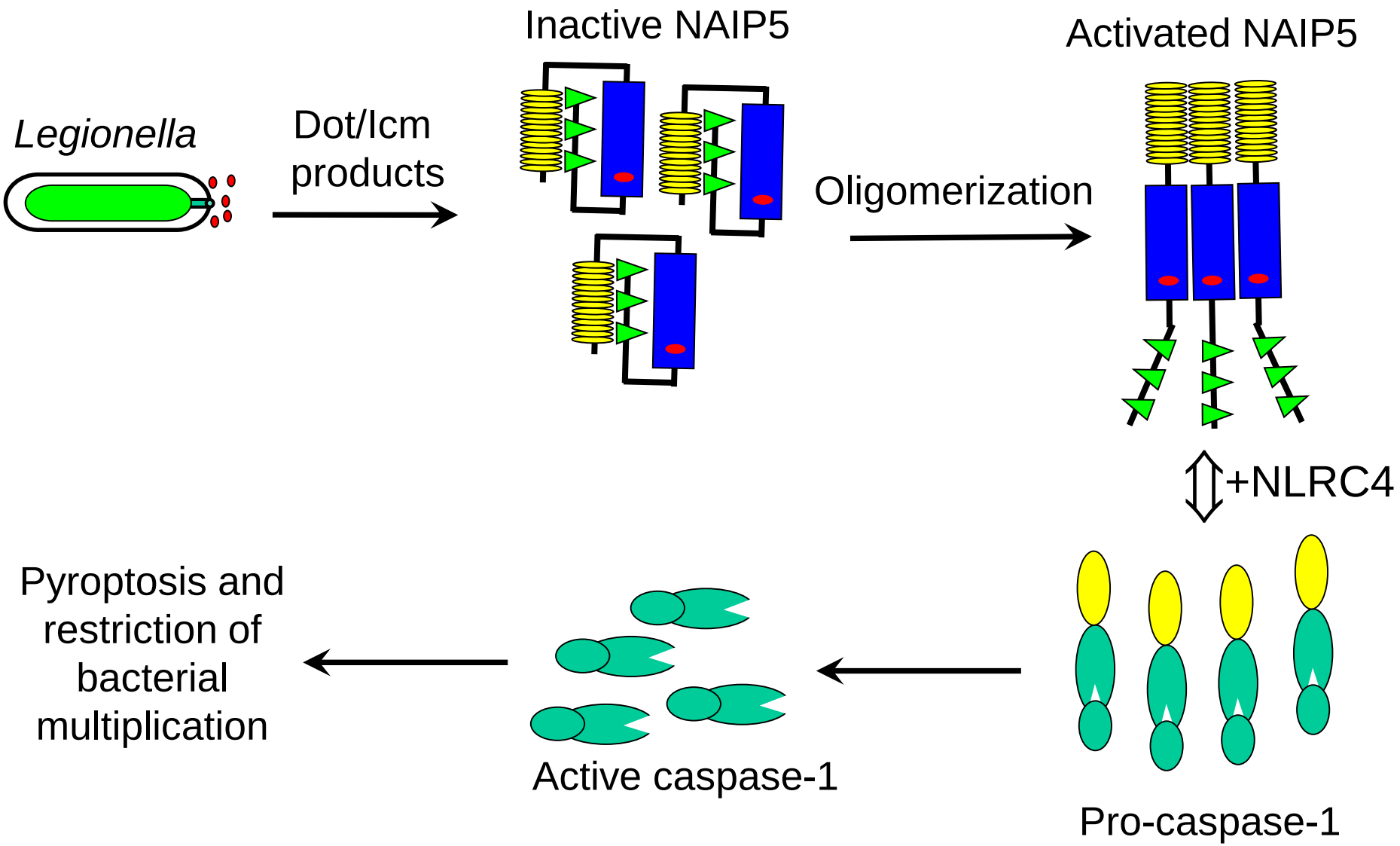


Lima-Junior et al., *Nature Med*. 2013.

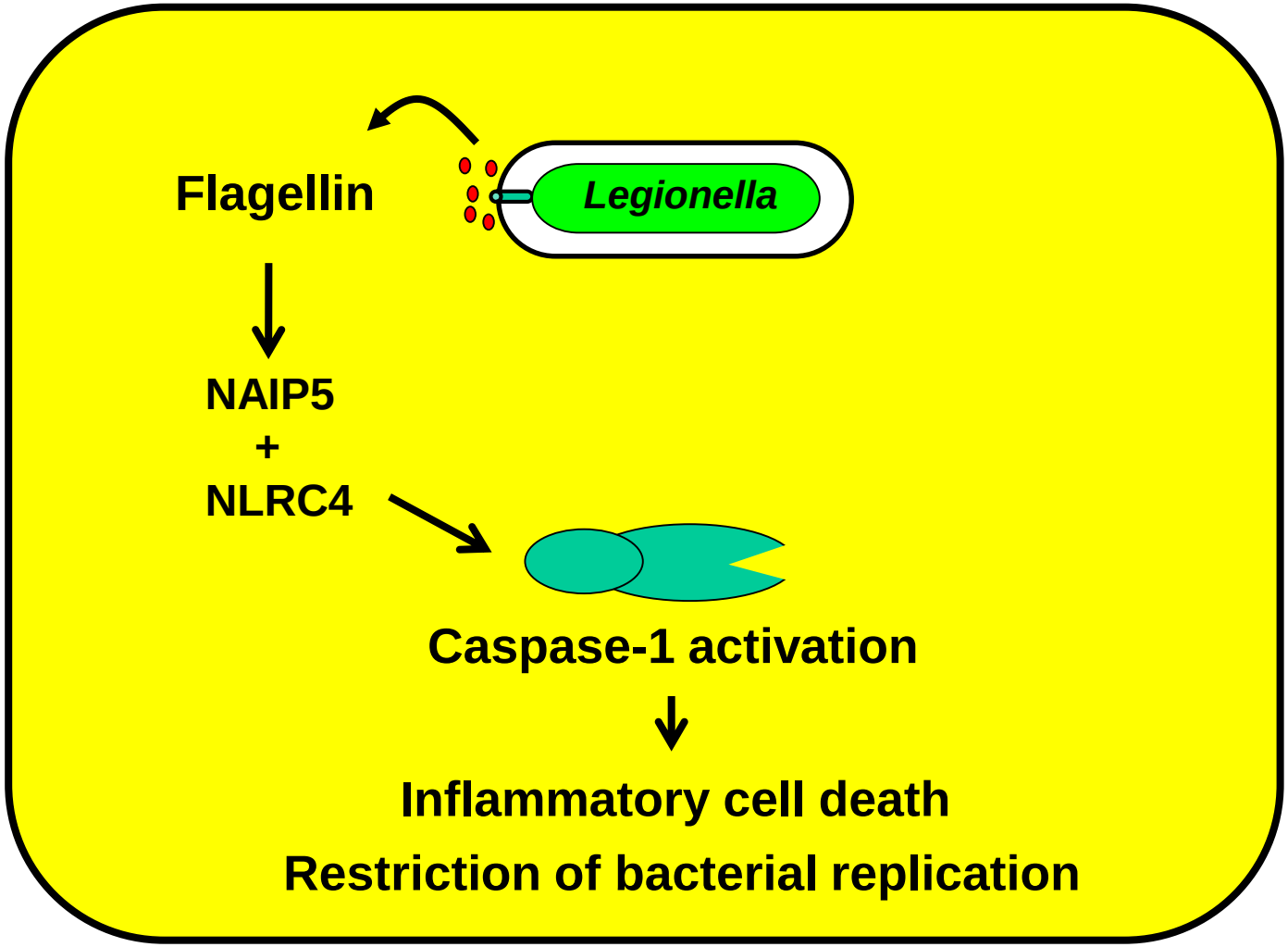
Cysosolic recognition of pathogenic microbes



Activation of the NAIP5/NLRC4 inflammasome in response to *Legionella* infection



Zamboni et al., *Nat. Immunol*. 2006



Ren, Zamboni et al., *Plos Path*. 2006
Molofsky and Swanson, *JEM*. 2006
Amer et al., *JBC*. 2006
Zamboni et al., *Nat. Immunol*. 2006
Miao et al., *Nat Immunol*. 2006
Franchi et al., *Nat. Immunol.* 2006

Pyroptosis: host cell death and inflammation

Tessa Bergsbaken, Susan L. Fink‡ and Brad T. Cookson*§*

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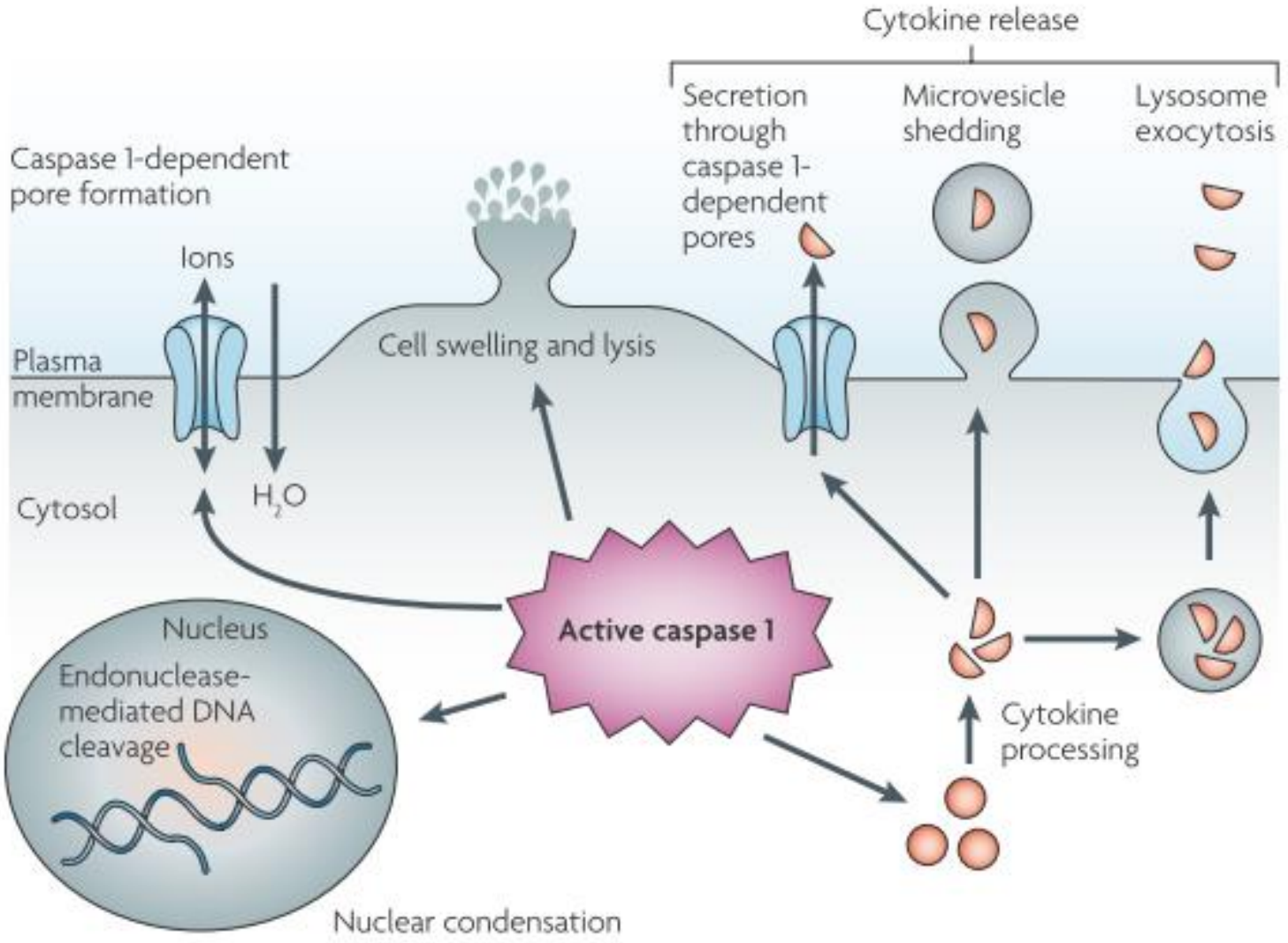
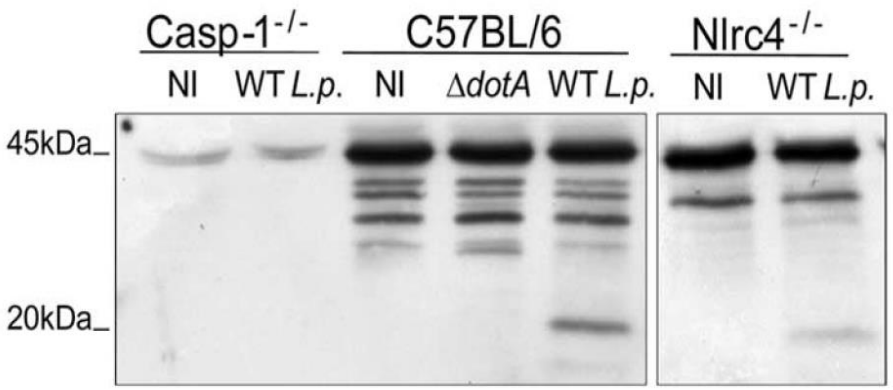
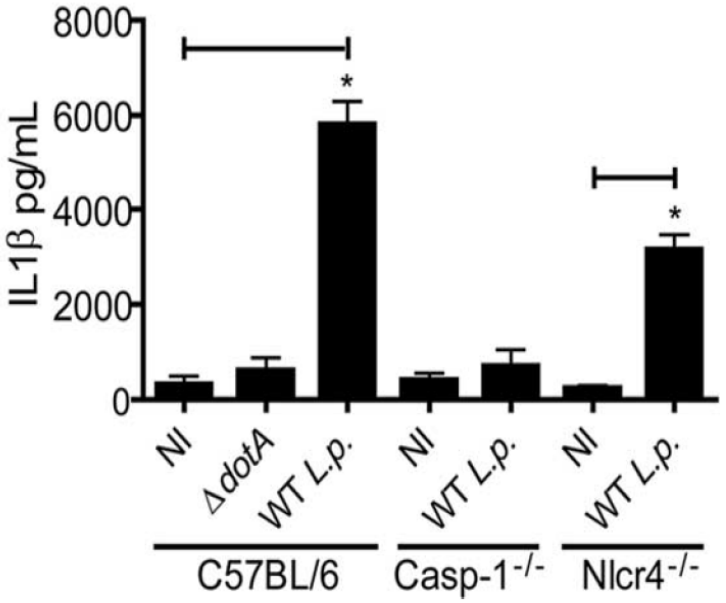
VOLUME 7 | FEBRUARY 2009



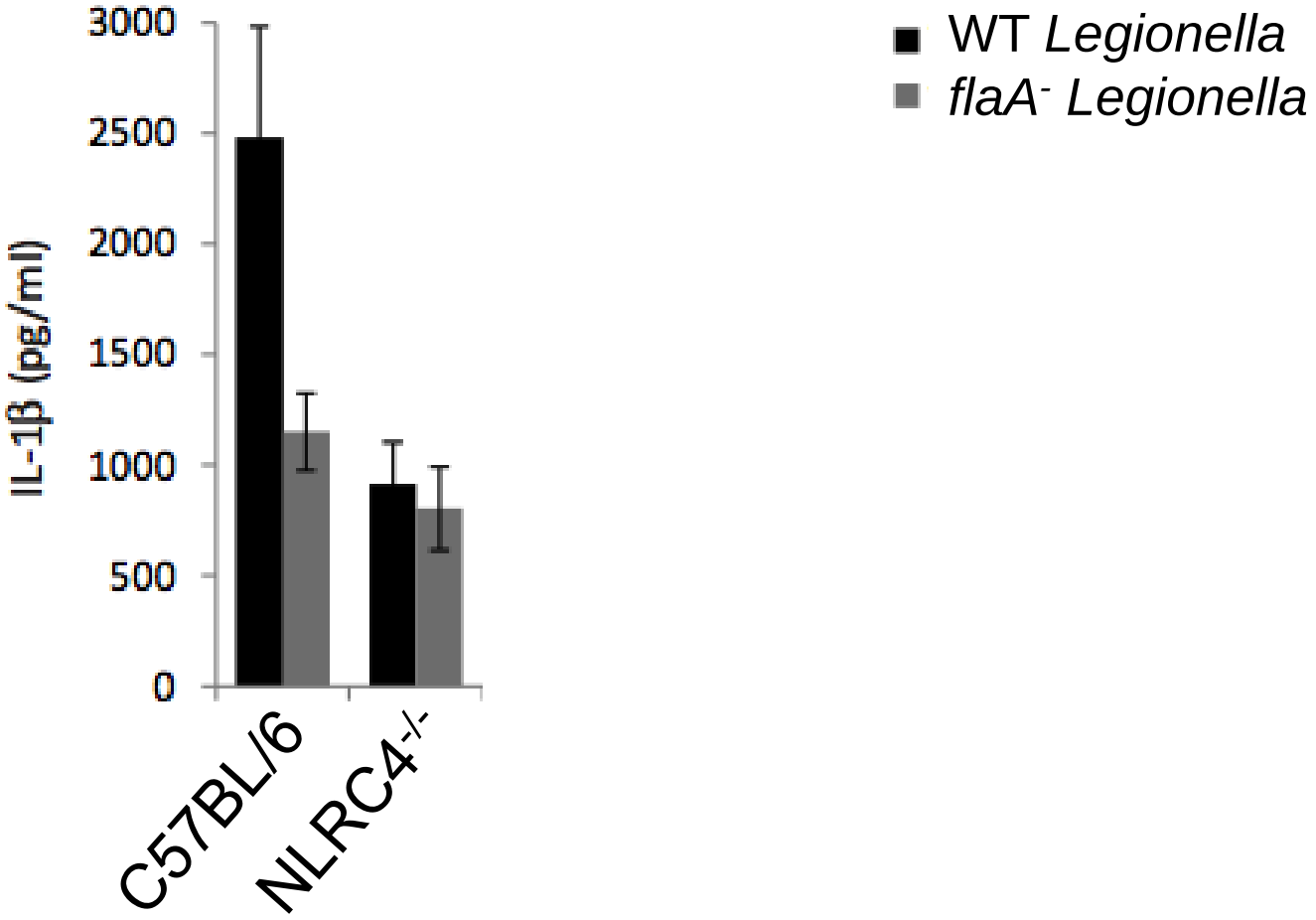
However, caspase-1 is still activated in response to *flaA*$^{-}$ bacteria or in NLRC4$^{-/-}$ cells





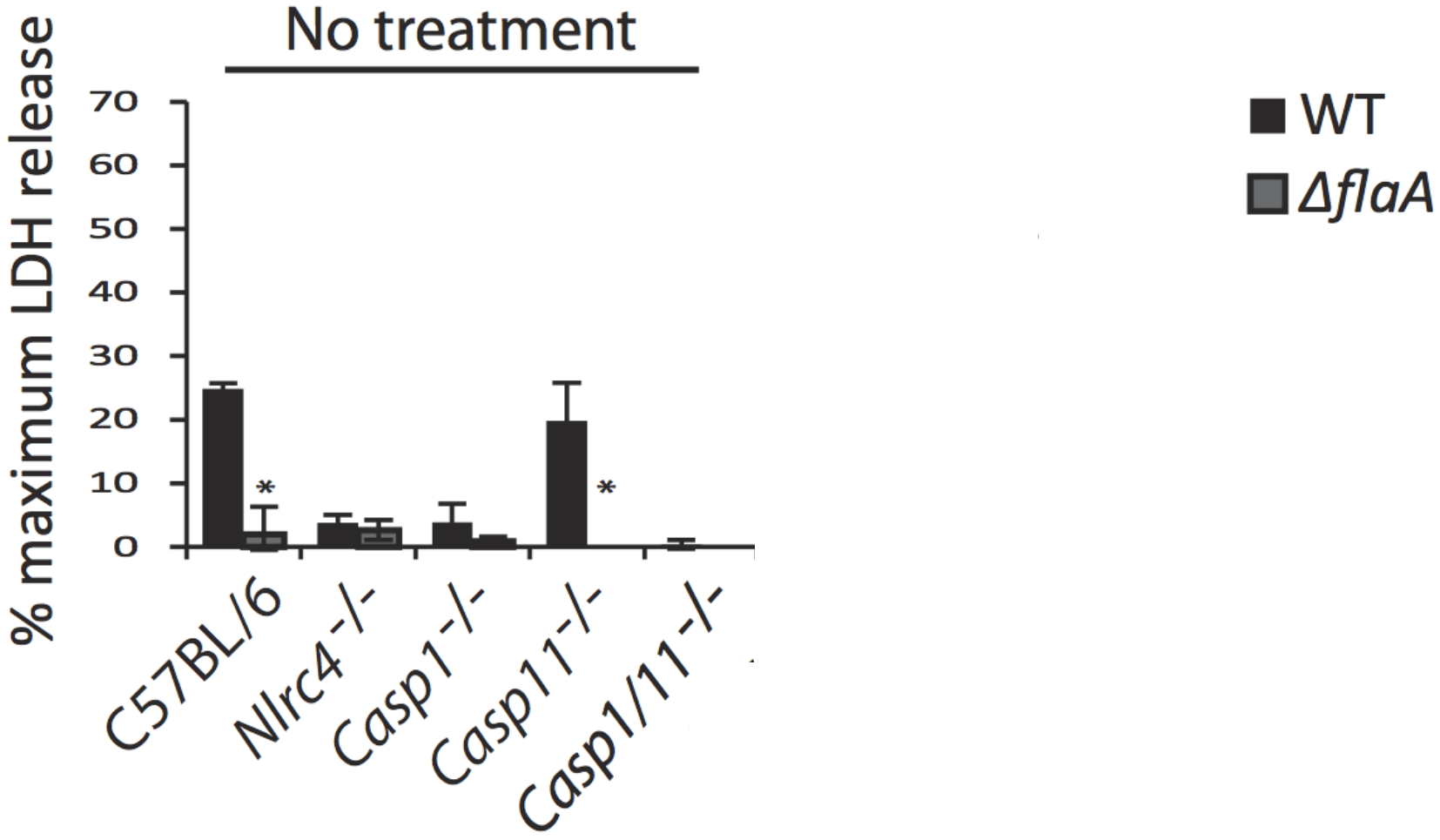
Silveira and Zamboni, *Infect. Immun*. 2010

The flagellin-dependent pathway cooperate with caspase-11 for caspase-1 activation in response to *L. pneumophila*



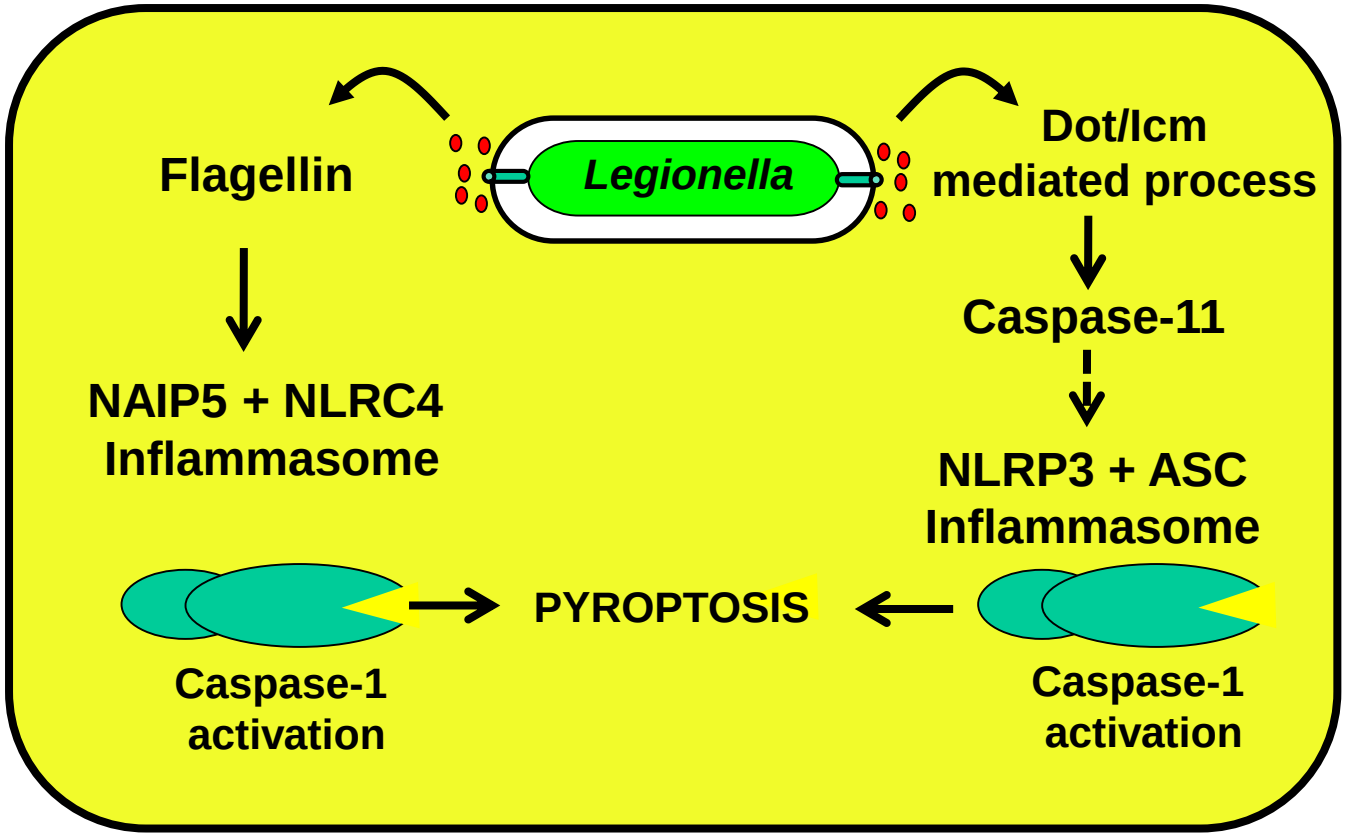
Initial observation: Jonilson B. Lima, 2007

The flagellin-independent pathway for pyroptosis is dependent on caspase-11



Case et al., *PNAS. 2013*

The caspase-11 pathway cooperates with the FlaA/NLRC4 inflammasome for capase-1 activation and pyroptosis in response to *L. pneumophila*



Science AAAS

Noncanonical Inflammasome Activation by Intracellular LPS Independent of TLR4

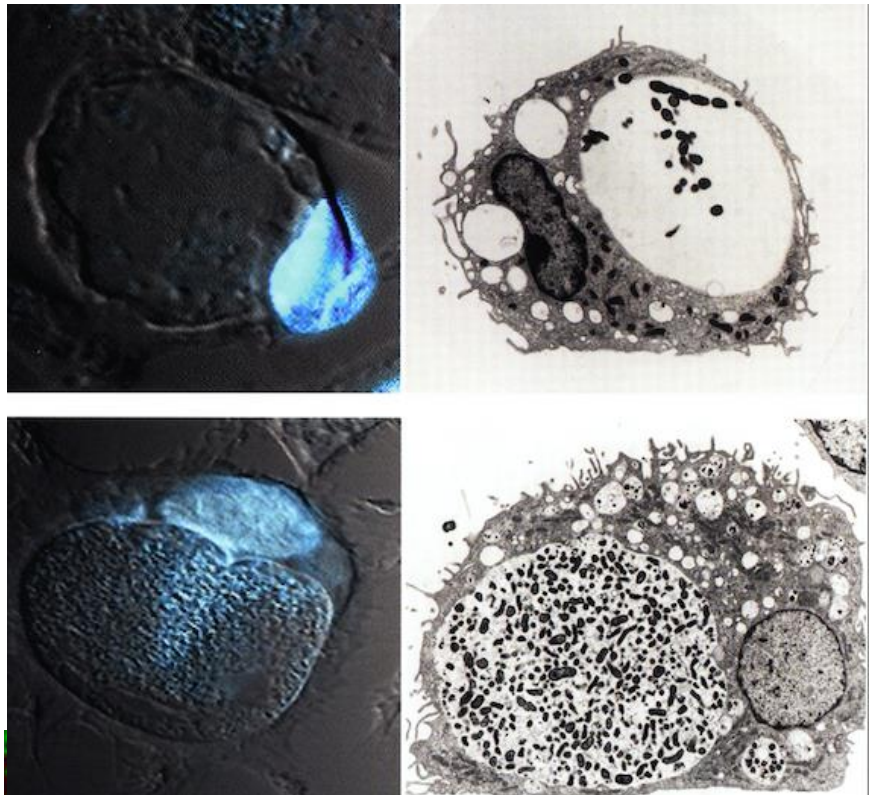
Nobuhiko Kayagaki,[1*] Michael T. Wong,[1] Irma B. Stowe,[1] Sree Ranjani Ramani,[2] Lino C. Gonzalez,[2] Sachiko Akashi-Takamura,[3] Kensuke Miyake,[3] Juan Zhang,[4] Wyne P. Lee,[4] Artur Muszyński,[5] Lennart S. Forsberg,[5] Russell W. Carlson,[5] Vishva M. Dixit[1*]

Cytoplasmic LPS Activates Caspase-11: Implications in TLR4-Independent Endotoxic Shock

Jon A. Hagar,[1] Daniel A. Powell,[2] Youssef Aachoui,[1] Robert K. Ernst,[2] Edward A. Miao[1*]

What about chronic bacterial pathogens that survives longer in macrophages?

Coxiella burnetii

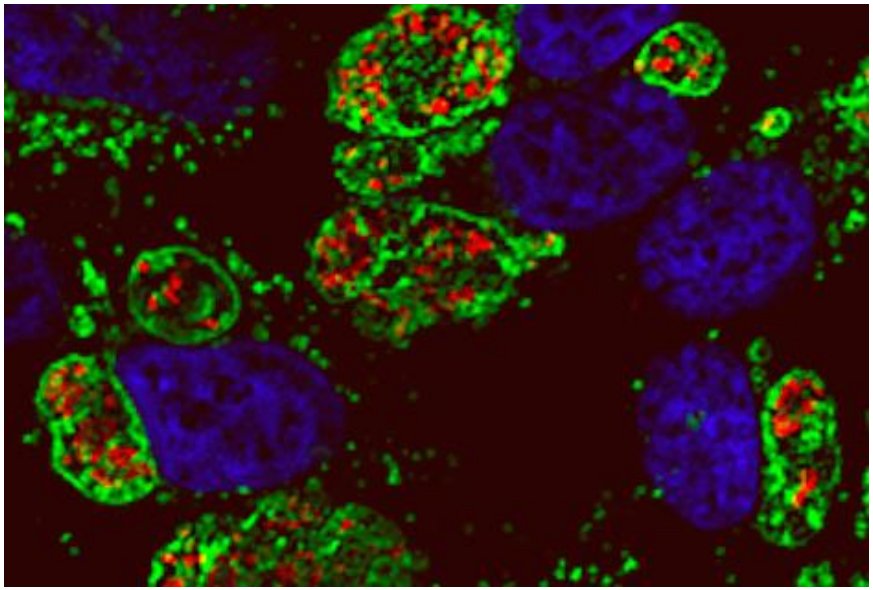


- Gram-negative; obligate intracelular, genetically intractable;

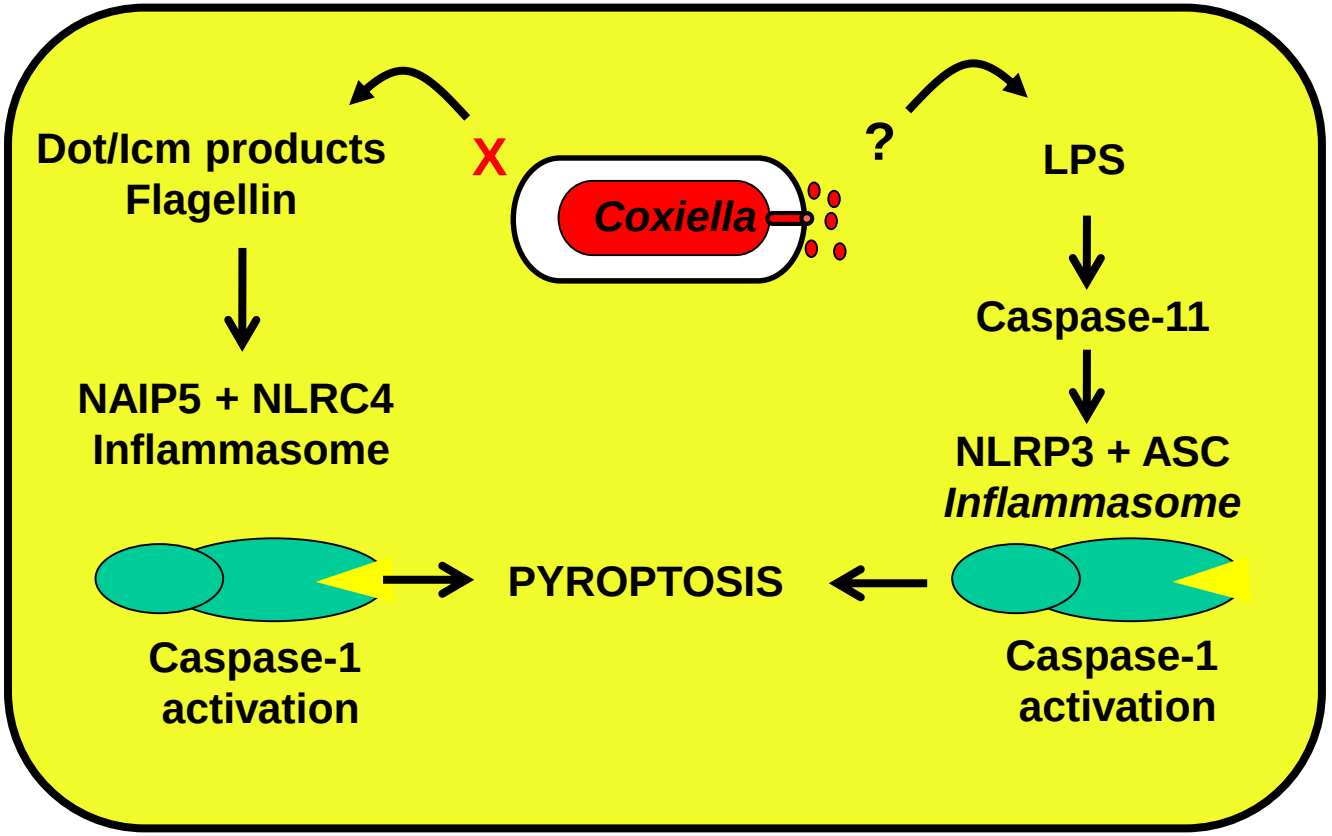
- Expression of Dot/Icm type IV secretion system (very simmilar to *Legionella pneumophila*);

- Evolutionary selected to multiply in mammalian hosts;

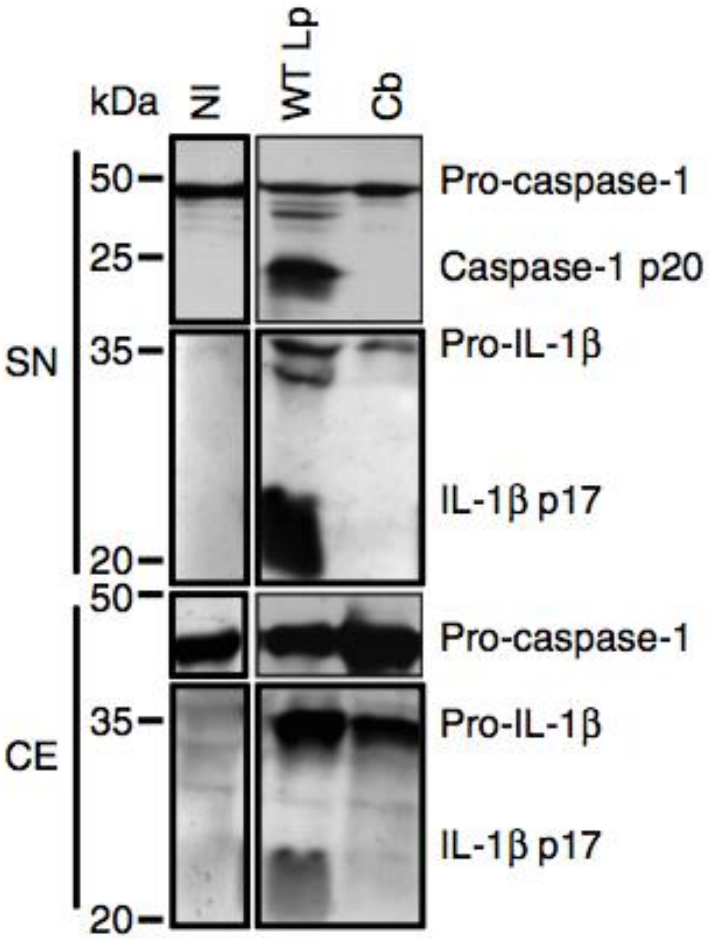
- Higly infective, adapted to subvert mammalian immune system

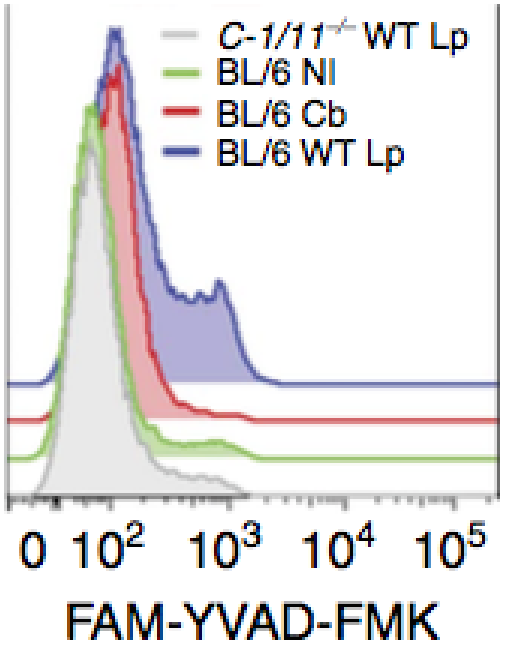


Is the inflammasome activated in response to *Coxiella burnetii* infection?

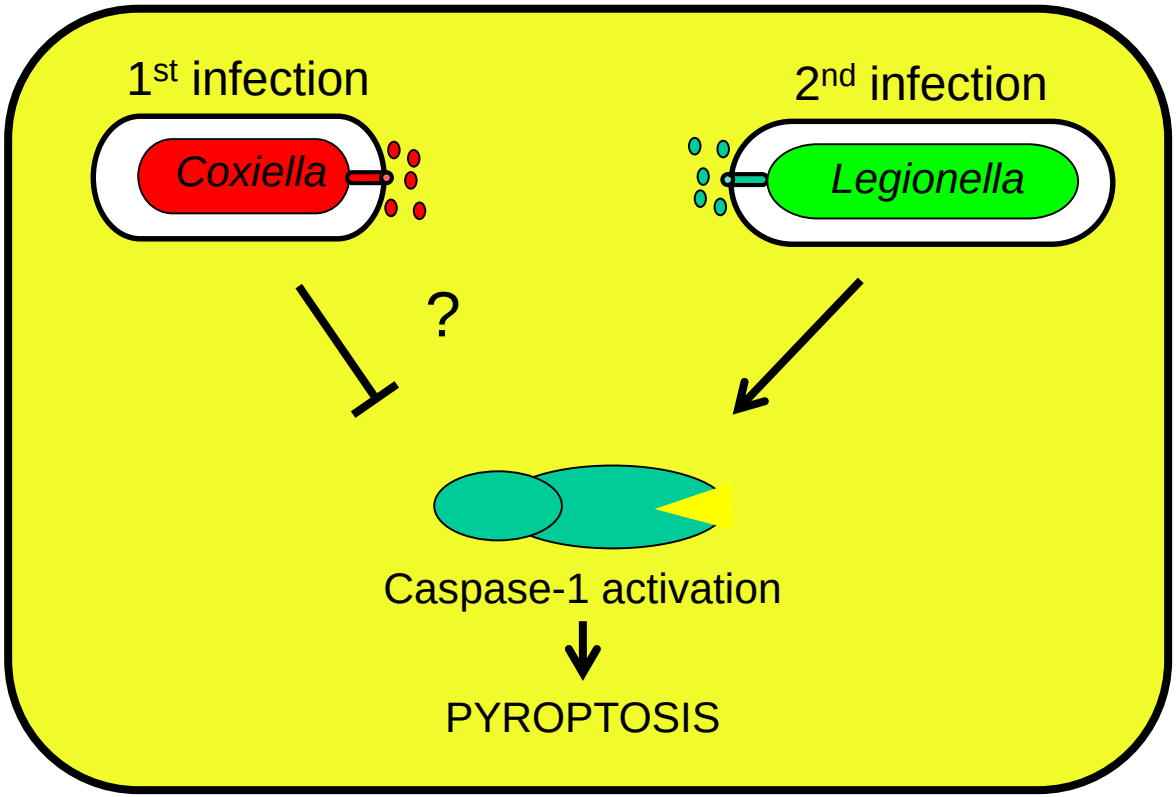


Caspase-1 is not activated in macrophages infected with *Coxiella burnetii*

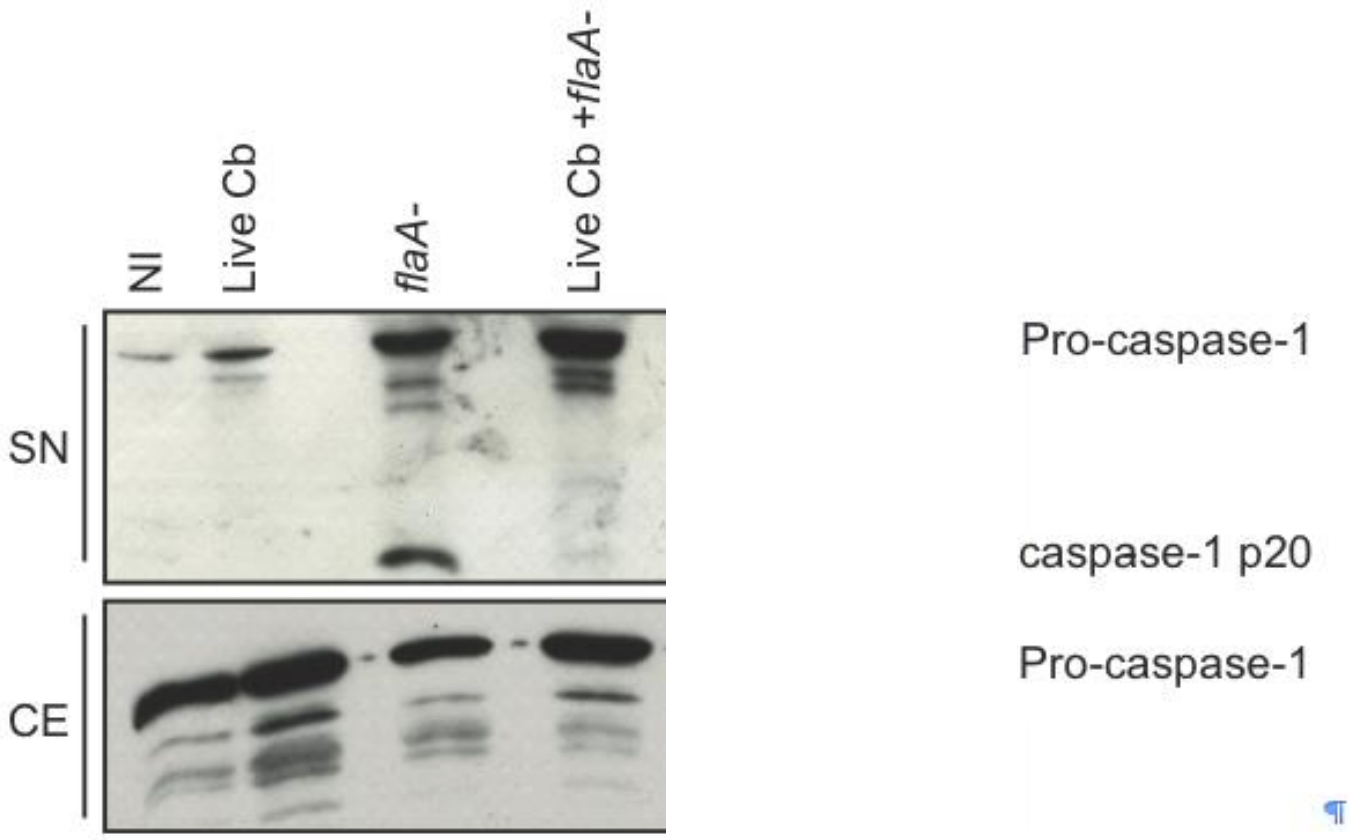




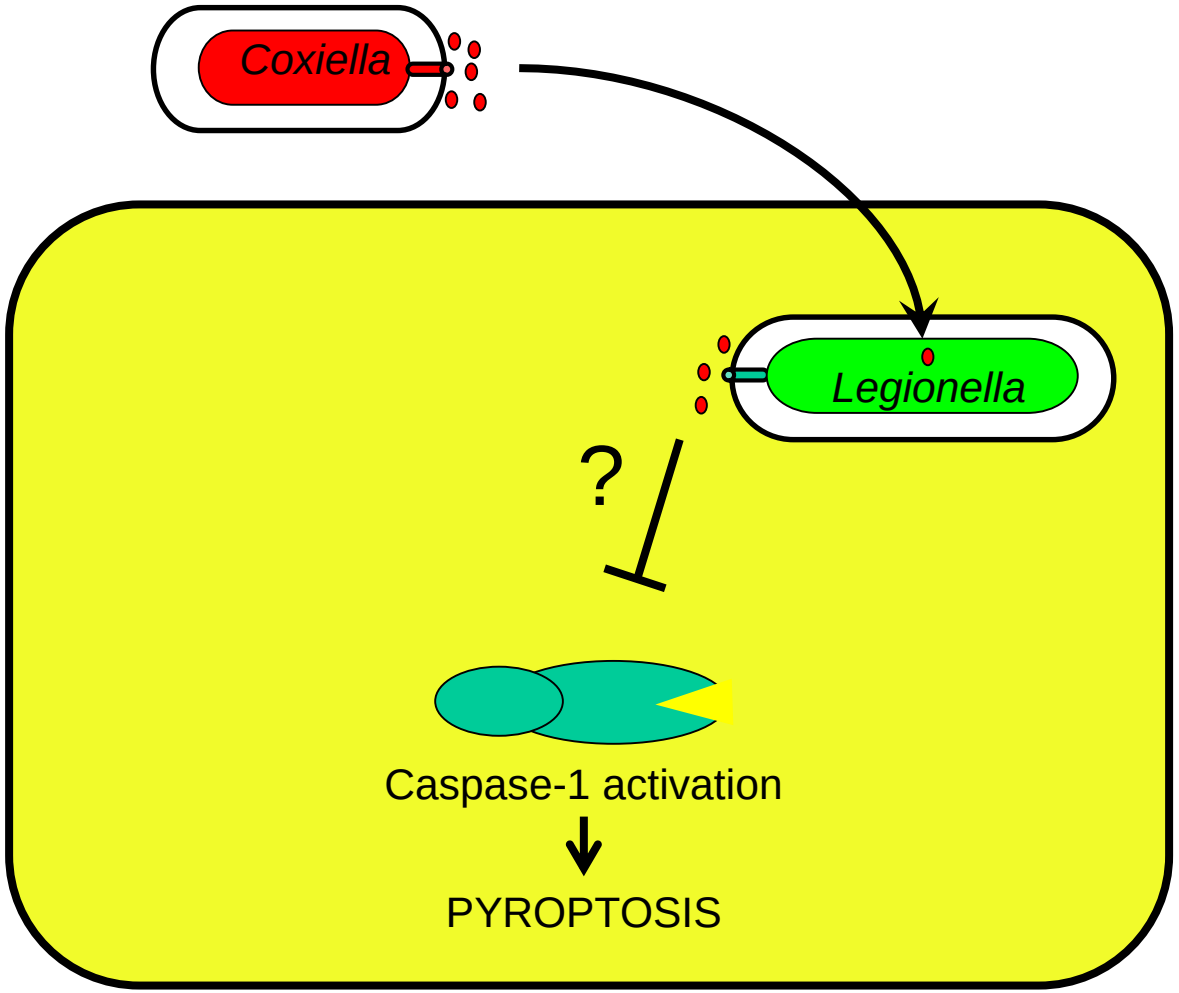
The use of a co-infection strategy to investigate *Coxiella*-mediated inhibition of caspase-1 activation



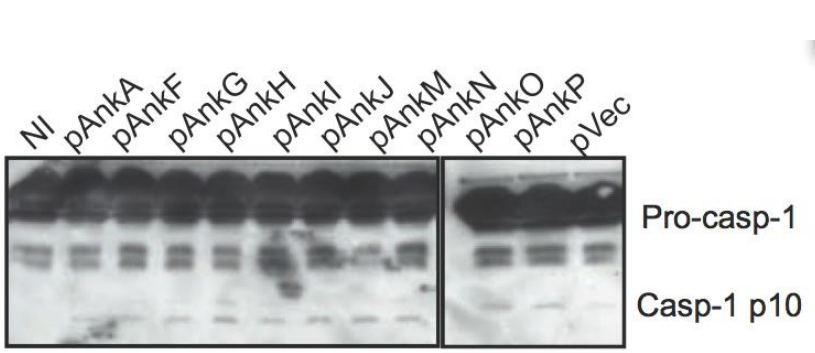
Coxiella actively inhibits the caspase-1 activation induced by *Legionella*

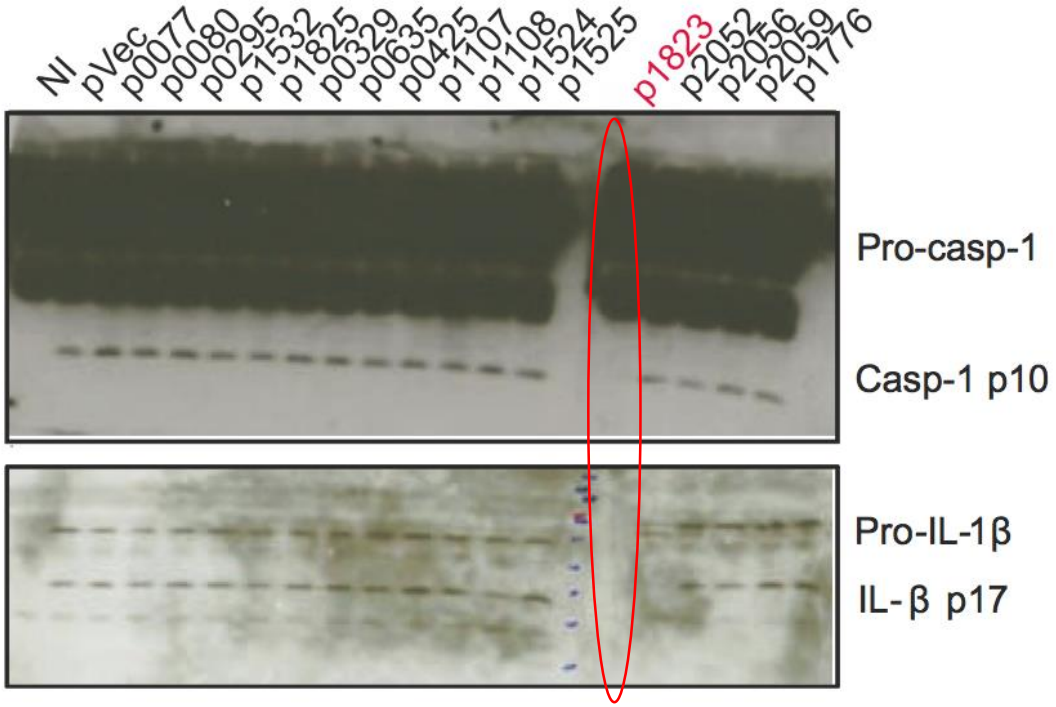


The use of *L. pneumophila* a as a surrogate host to screen for *C. burnetii* effector proteins involved in inhibition of caspase activation



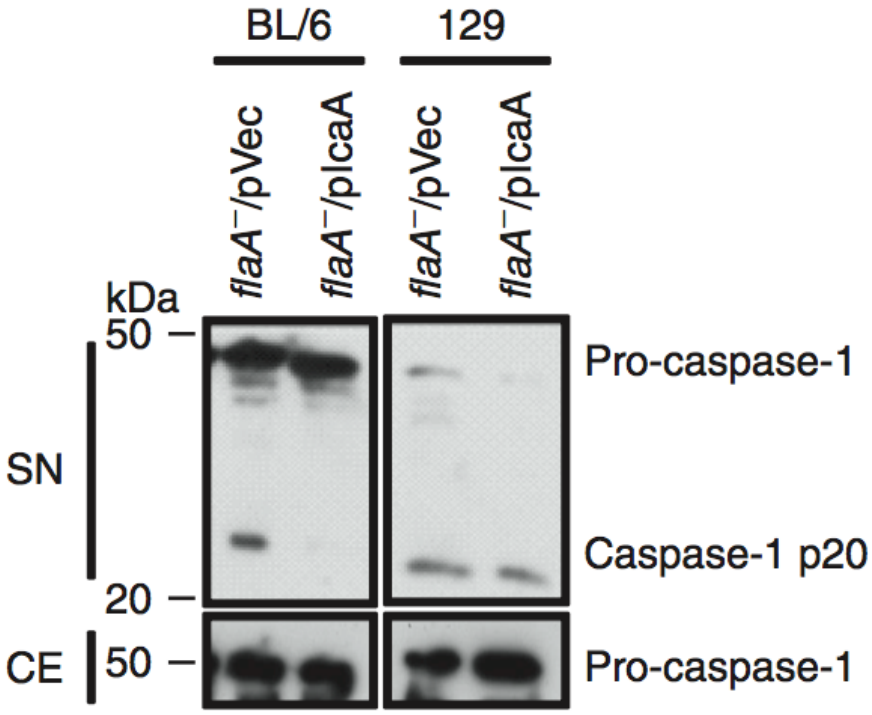
Identification of CBU1823 as a *Coxiella* gene involved in inhibition of caspase-1 activation



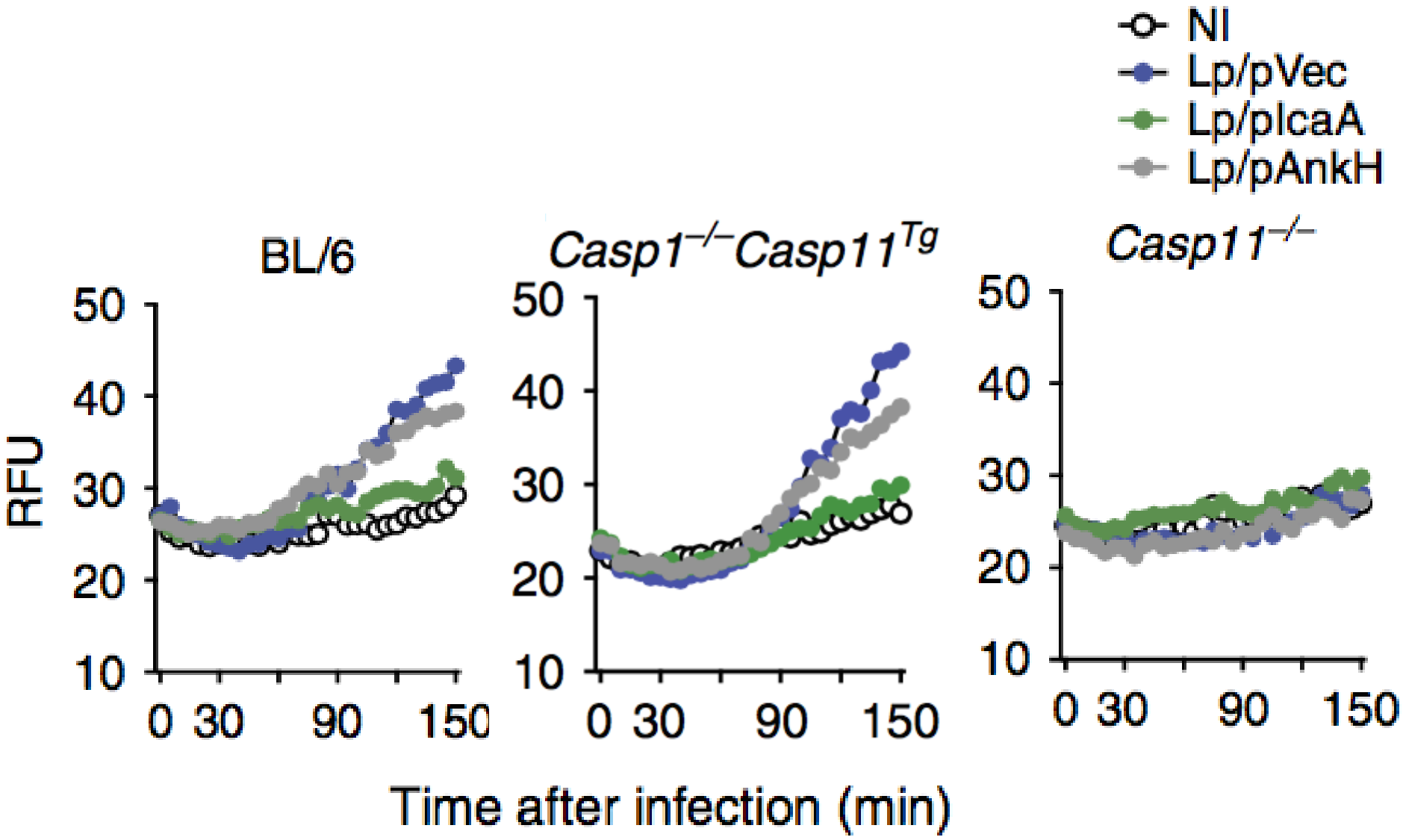


CBU1823 was named IcaA (Inhibition of caspase activation)

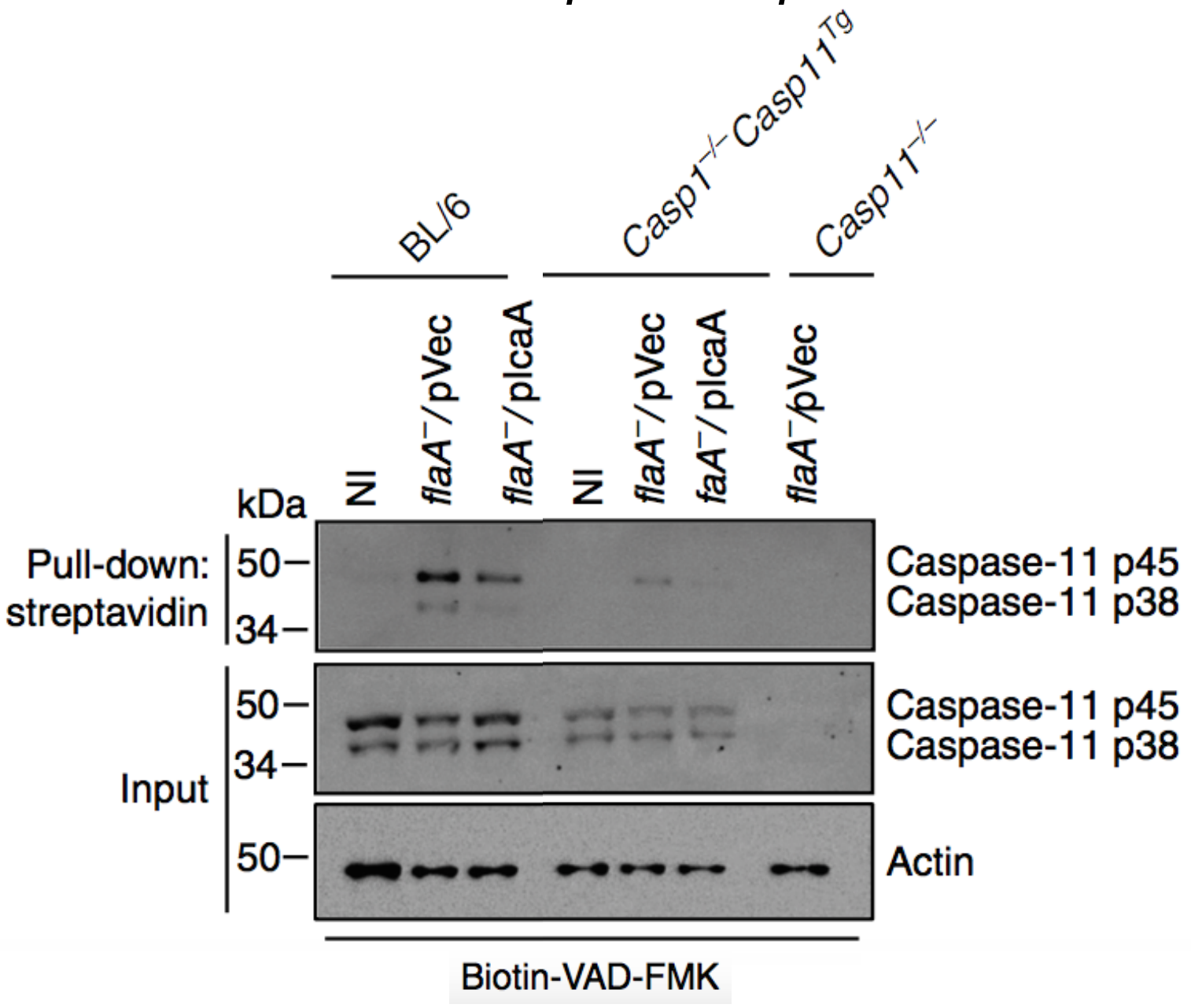
Expression IcaA in *Legionella* inhibits caspase-1 activation (a process that requires caspase-11)

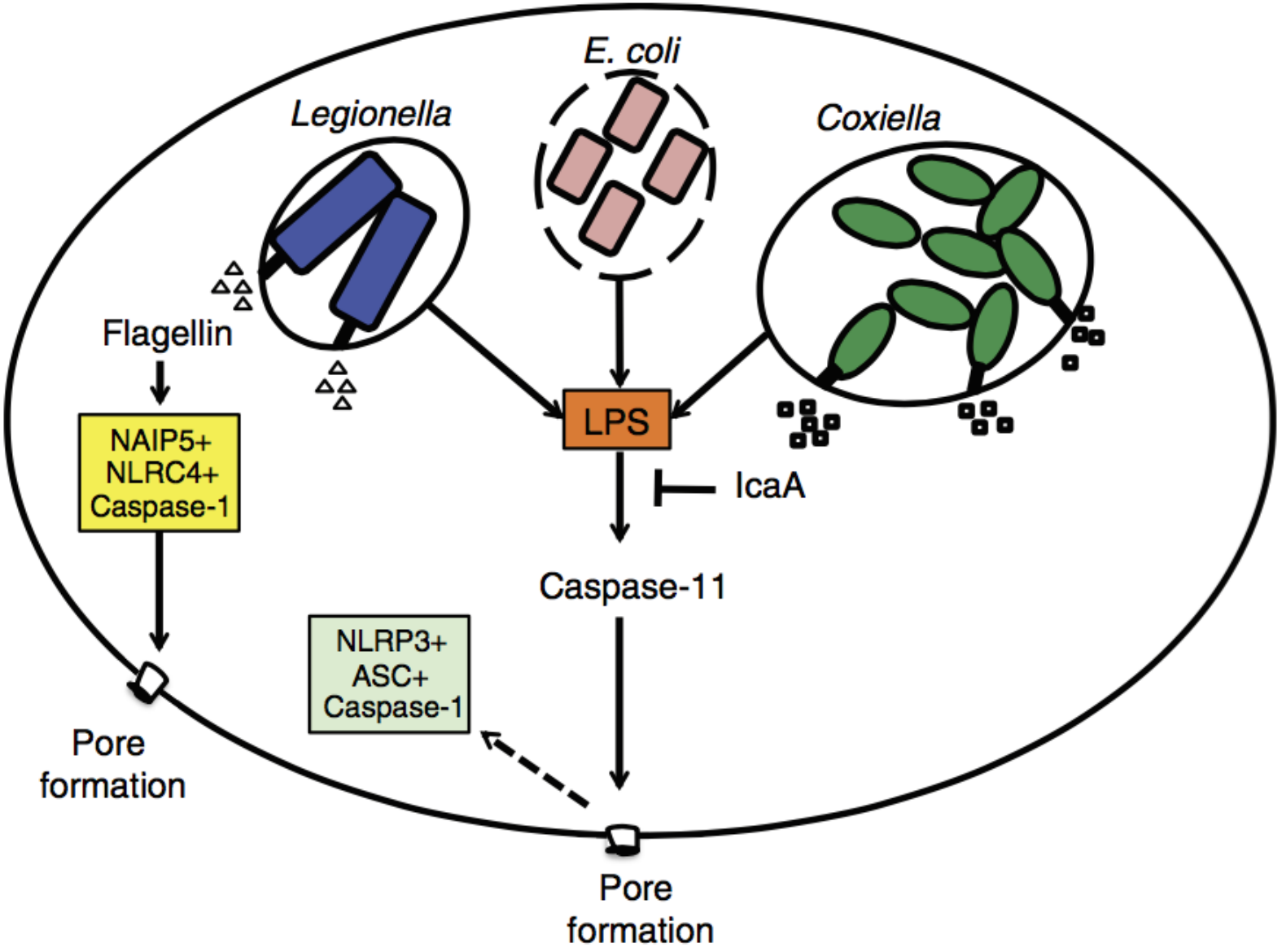


Expression of IcaA in *flaA*$^{-}$ *Legionella* inhibits caspase-11-dependent pore formation



IcaA inhibits caspase-11-activation when expressed in *flaA⁻ L. pneumophila*





Cunha et al, Nat. Commun. 2015

Lab. Patogenicidade Microbiana e Imunidade Inata

(Lab. meeting retreat, dec/2013)

Acknowledgements

Universidade de São Paulo
Faculdade de Medicina de Ribeirão Preto (FMRP/USP)
Departamento de Biologia Celular, Molecular e Bioagentes Patogênicos

Richard Flavell, Yale
Vishva Dixit, Genentech
Junying Yuan, Harvard
João Santana Silva, FMRP/USP
Fernando Cunha, FMRP/USP
Craig R. Roy, Yale
Hayley Newton, U. Melbourne