Helicobacter pylori persistence and immunomodulation

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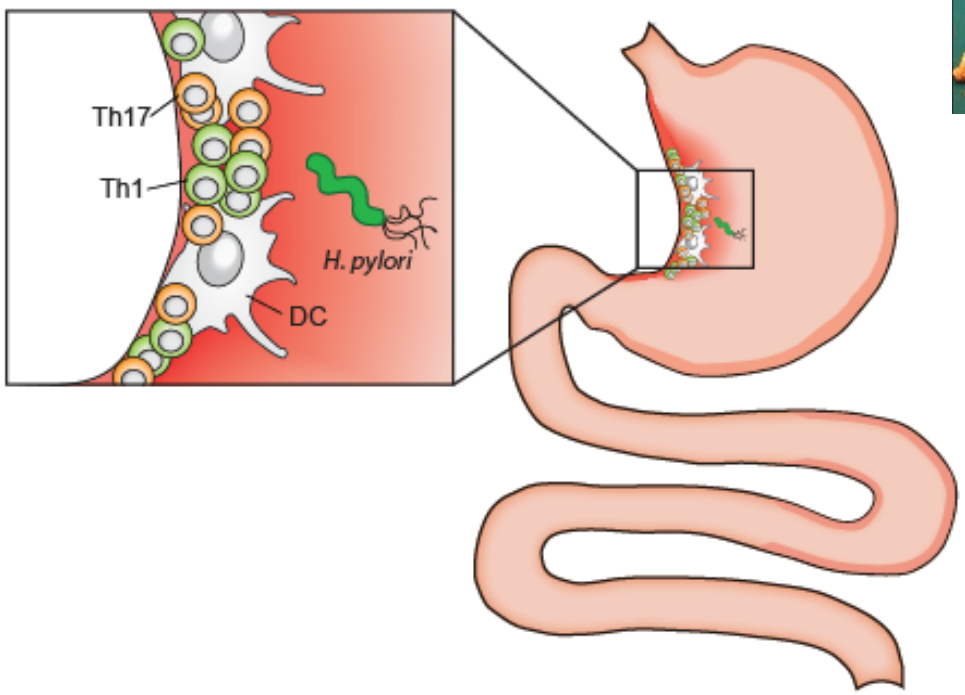
Helicobacter pylori resides in the human stomach, where it can cause gastritis, peptic ulcer disease and gastric cancer

Carriers with clinically overt disease (10-20% of infected population)

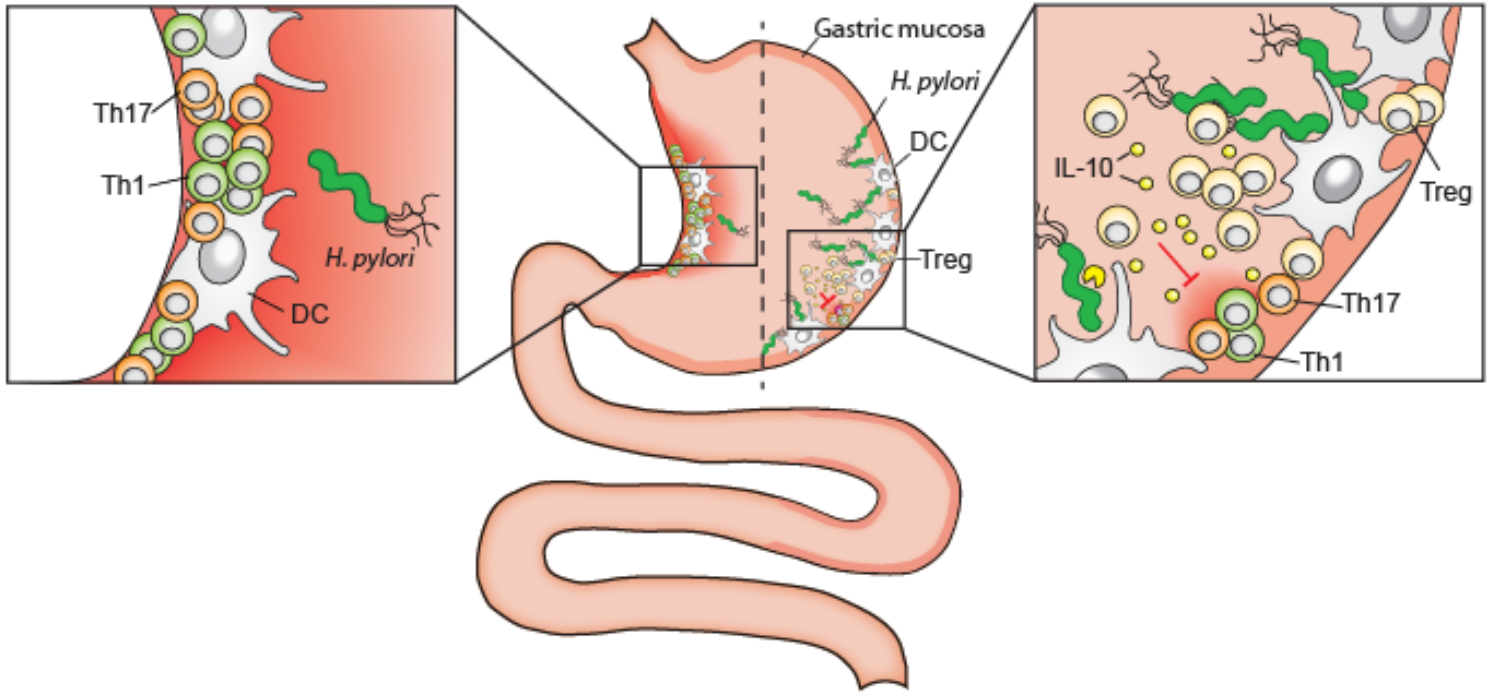


H. pylori **on gastric epithelial cells**

Helicobacter pylori resides in the human stomach, where it can cause gastritis, peptic ulcer disease and gastric cancer… or remain asymptomatic

Carriers with clinically overt disease (10-20% of infected population)

Asymptomatic carriers (>80% of infected population)



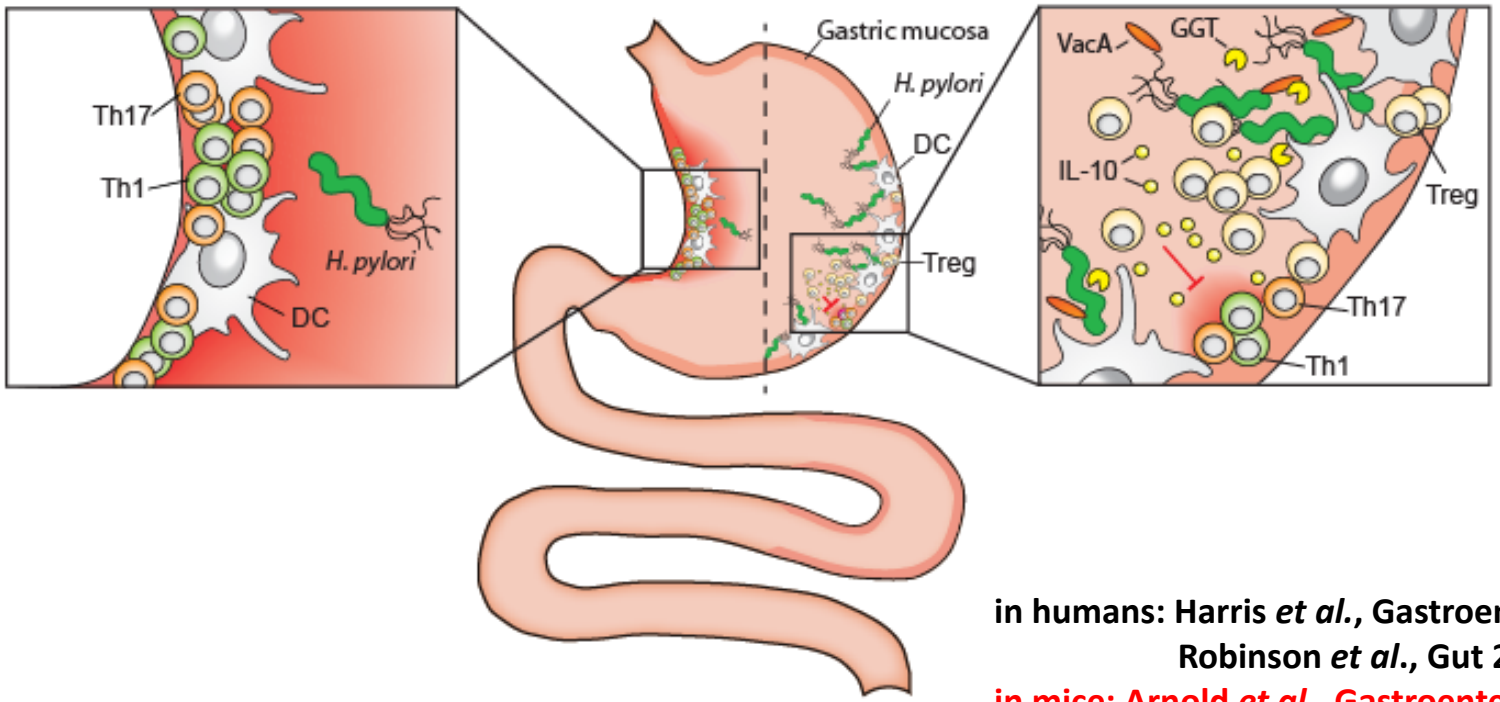
Helicobacter pylori resides in the human stomach, where it can cause gastritis and peptic ulcer disease… or remain asymptomatic

Carriers with clinically overt disease (10-20% of infected population)

modeled by adult infection

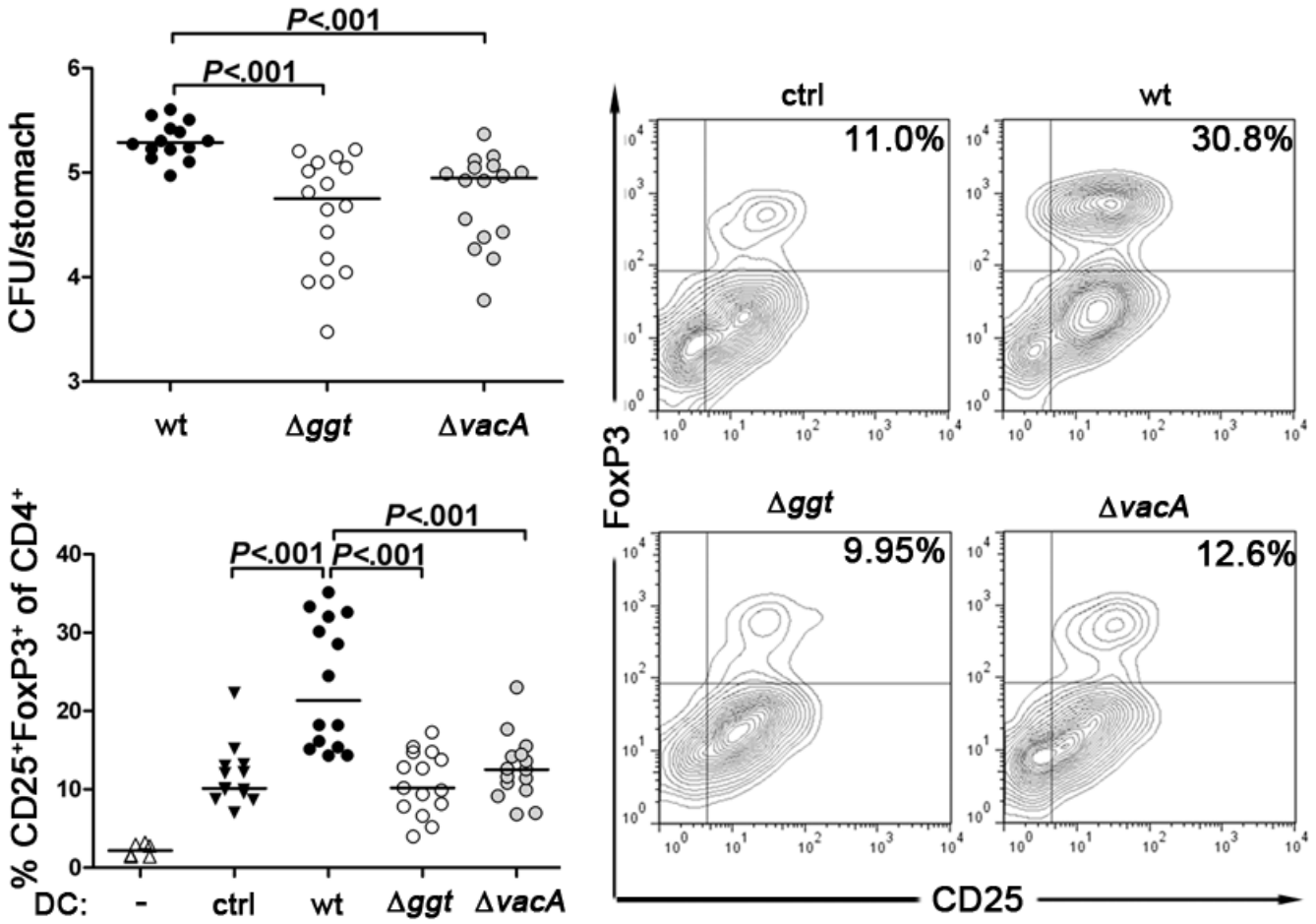
Asymptomatic carriers (>80% of infected population)

modeled by neonatal infection of mice



in humans: Harris *et al.*, Gastroenterology 2008
Robinson *et al.*, Gut 2008
in mice: Arnold *et al.*, Gastroenterology 2011

The *H. pylori* virulence/persistence factors VacA and GGT are required for DC tolerization, regulatory T-cell differentiation and persistence

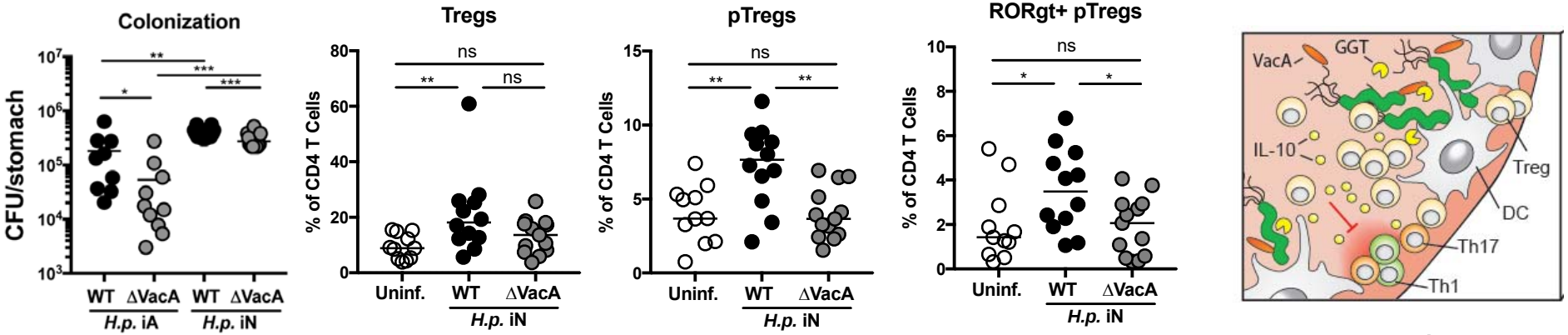


1 month post infection

Oertli *et al.* PNAS 2013

VacA promotes the generation of peripherally induced pTregs in the gastric lamina propria and their enrichment in the lung

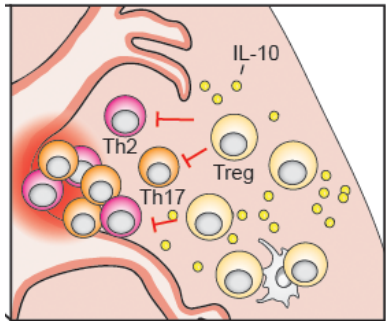
gastric Tregs

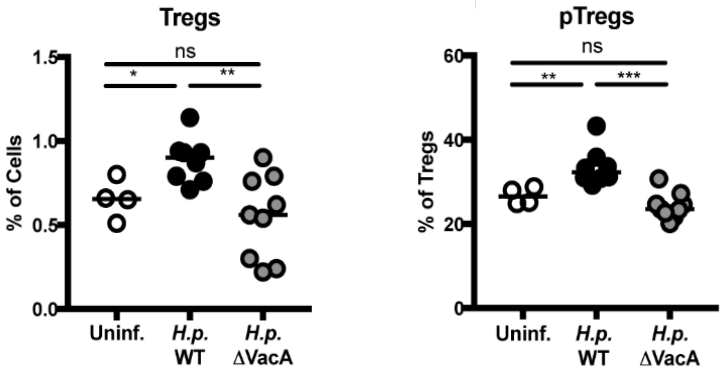


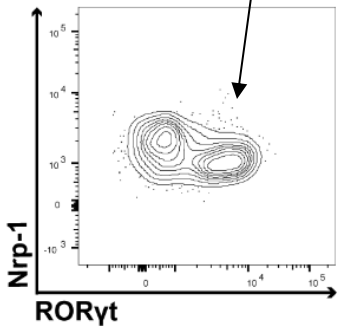
stomach

pTregs: CD4⁺ Foxp3⁺ neuropilin⁻ RORγt⁺ Tbet⁺/⁻
tTregs: CD4⁺ Foxp3⁺ neuropilin⁺

pulmonary Tregs





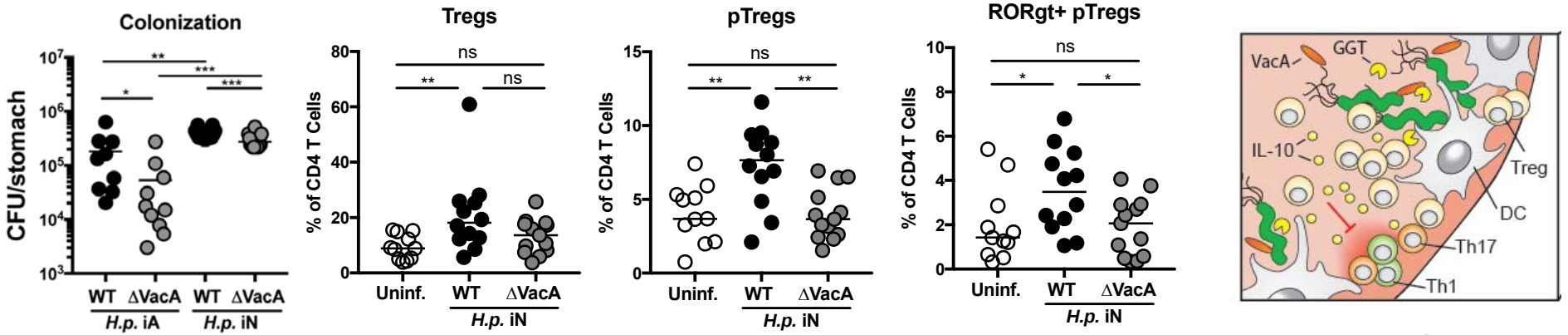


lung

Altobelli *et al.* MBio 2019

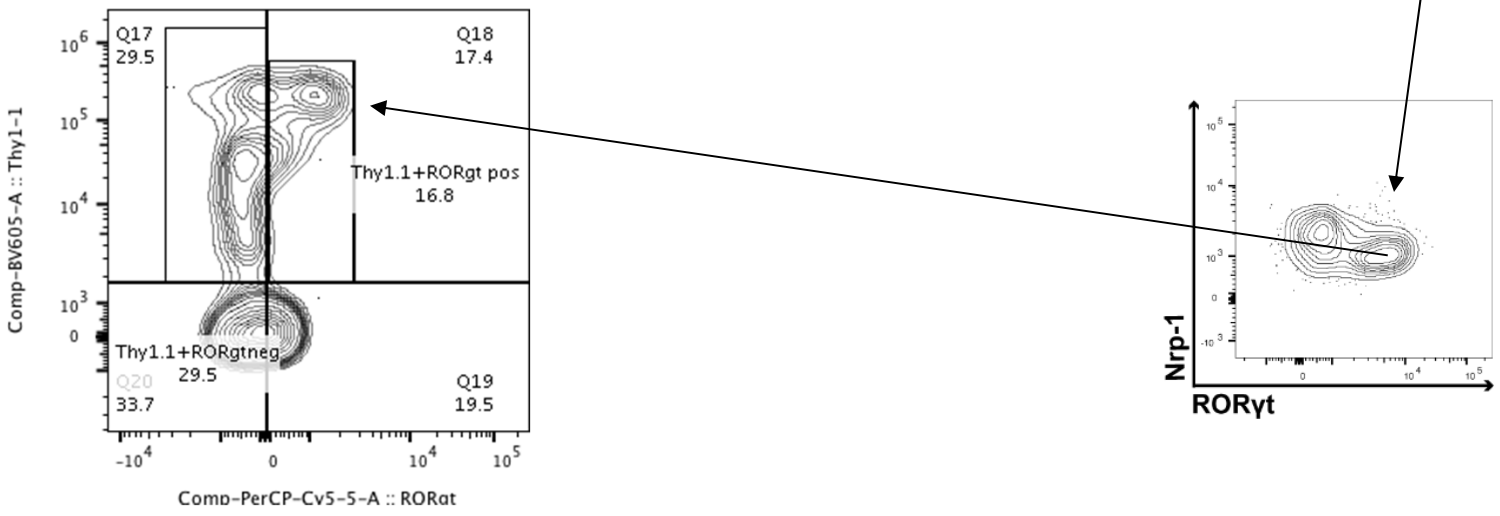
VacA promotes the generation of peripherally induced pTregs in the gastric lamina propria and their enrichment in the lung

gastric Tregs



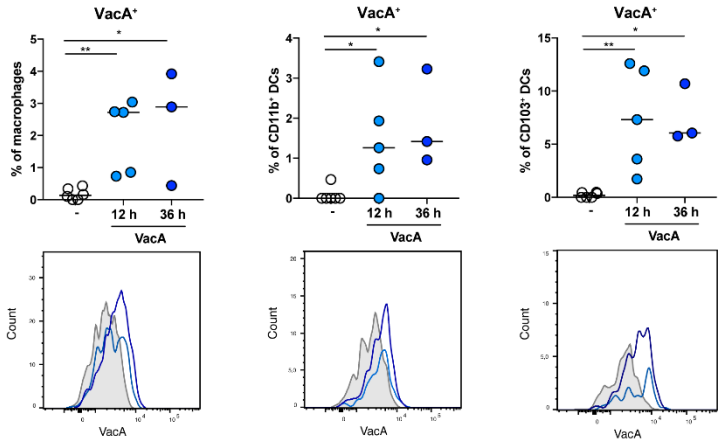
pTregs: CD4$^+$ Foxp3$^+$ neuropilin$^-$ RORγt$^+$ Tbet$^{+/-}$

tTregs: CD4$^+$ Foxp3$^+$ neuropilin$^+$

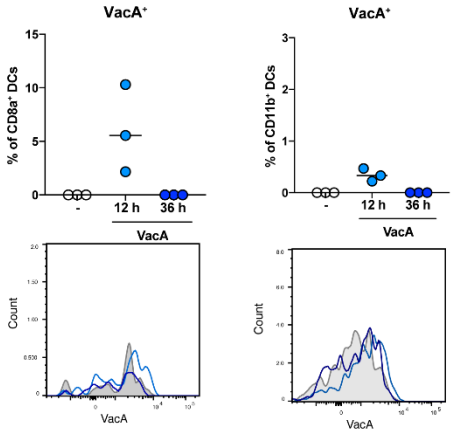


VacA interacts with various myeloid cells in the gastric LP and promotes a tolerogenic transcriptional program

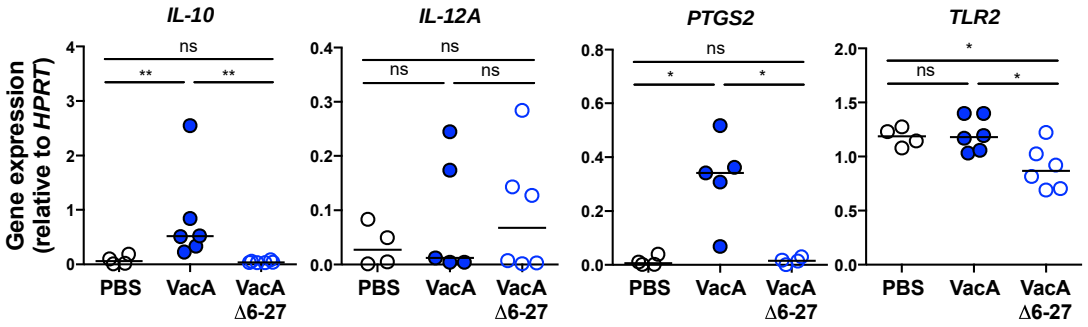
gastric lamina propria

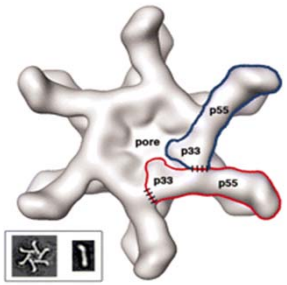


Peyer's patches

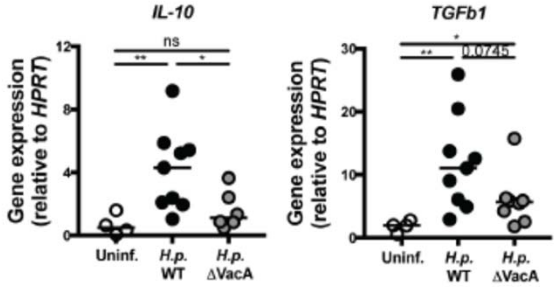


qRT-PCR of CX3CR1+ macrophages after VacA exposure





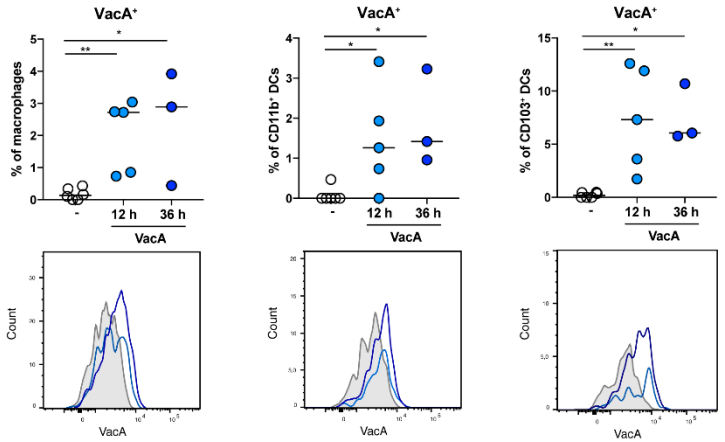
qRT-PCR of CX3CR1+ macrophages after live Hp exposure



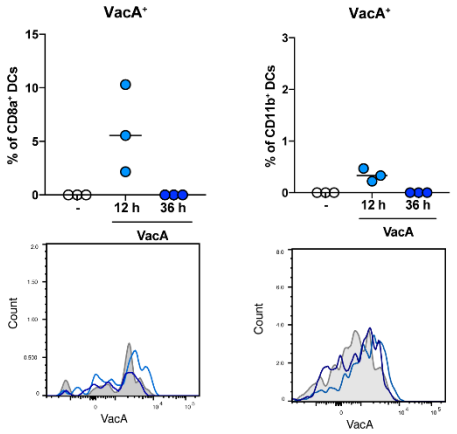
Altobelli *et al.* MBio 2019

VacA interacts with various myeloid cells in the gastric LP and promotes a tolerogenic transcriptional program

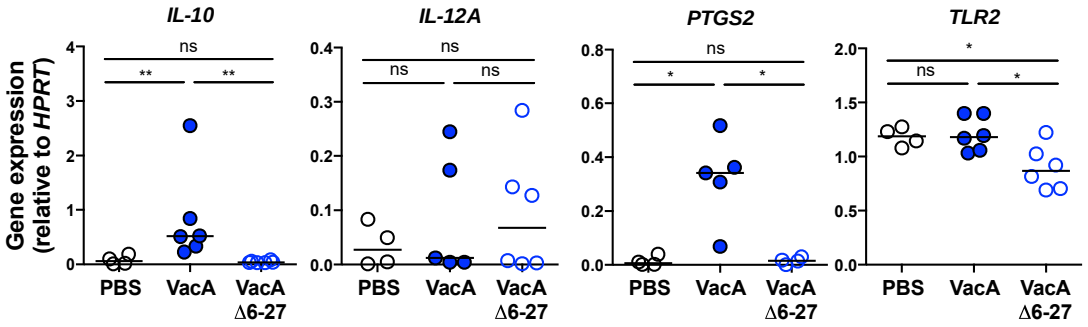
gastric lamina propria

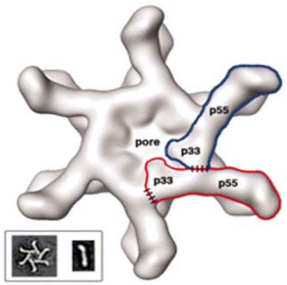


Peyer's patches



qRT-PCR of CX3CR1+ macrophages after VacA exposure





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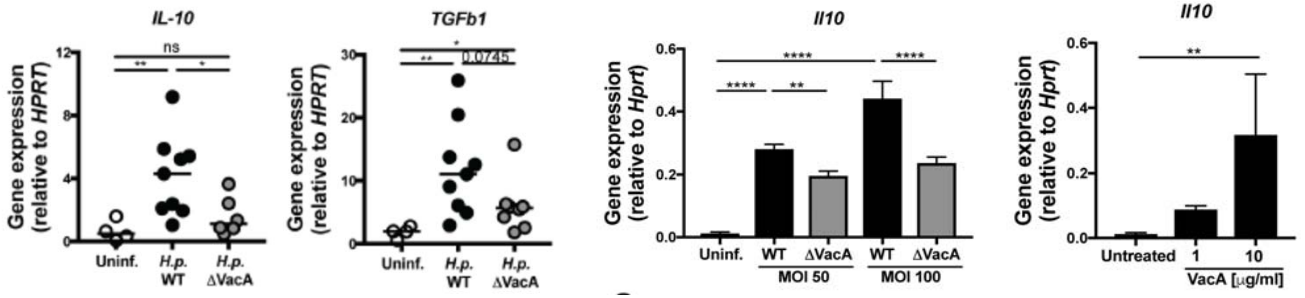
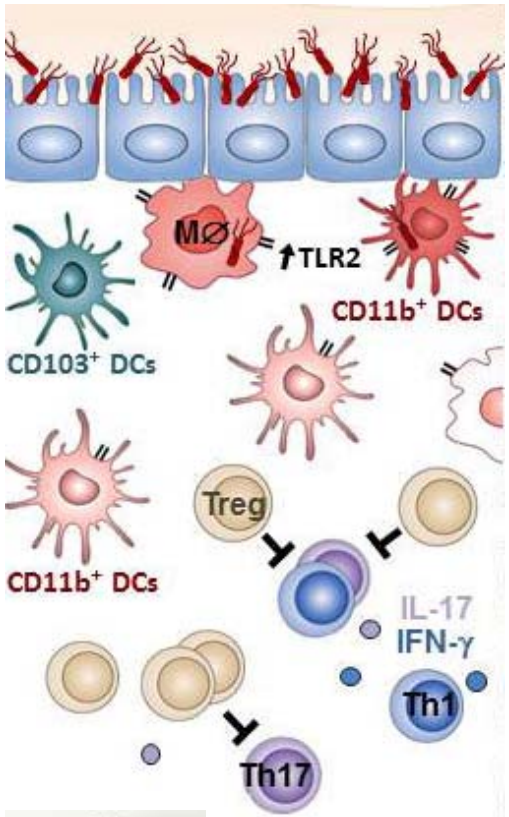
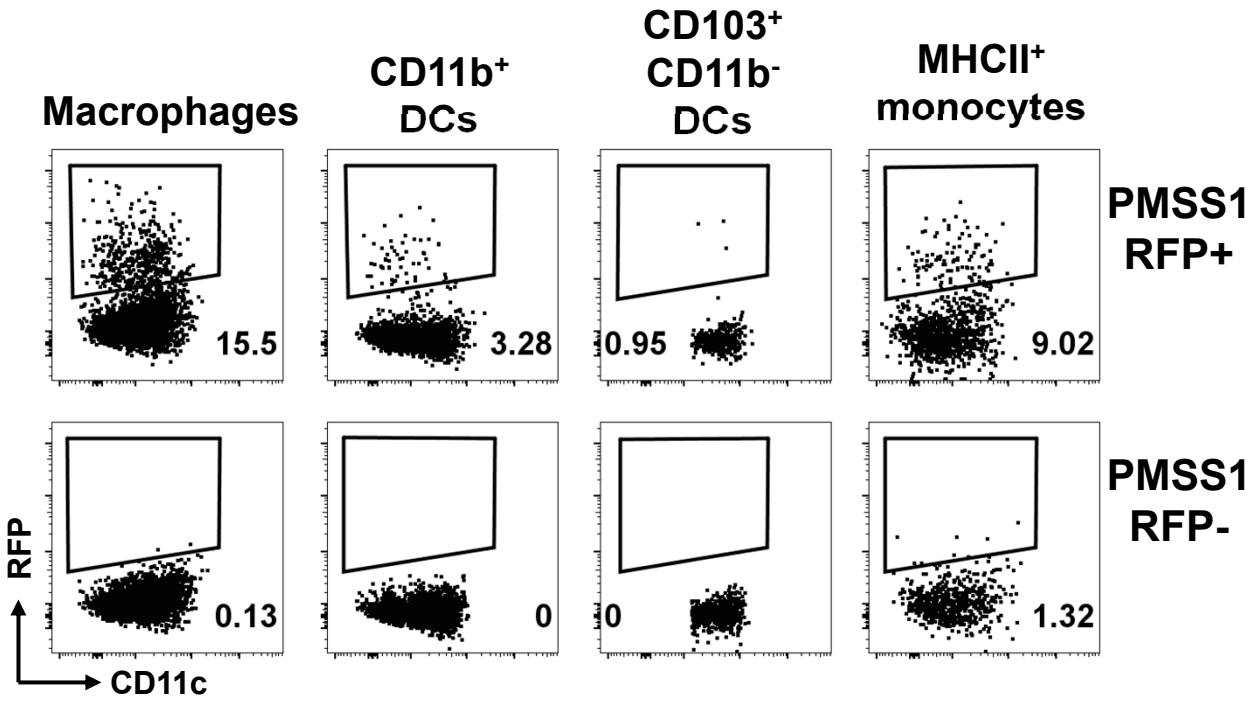
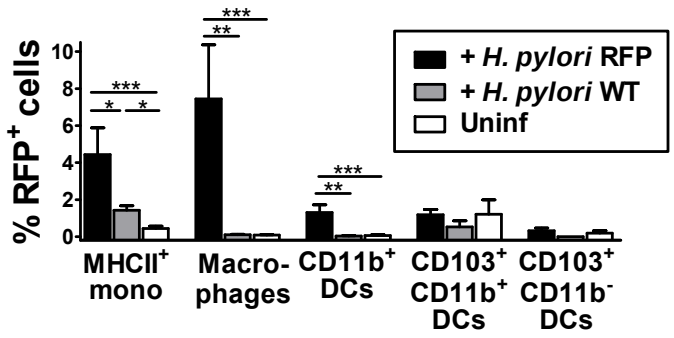
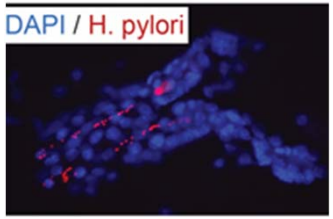


CD11b$^+$ DCs and monocytes and macrophages, but not CD103$^+$ DCs, encounter *H. pylori* in the infected gastric mucosa



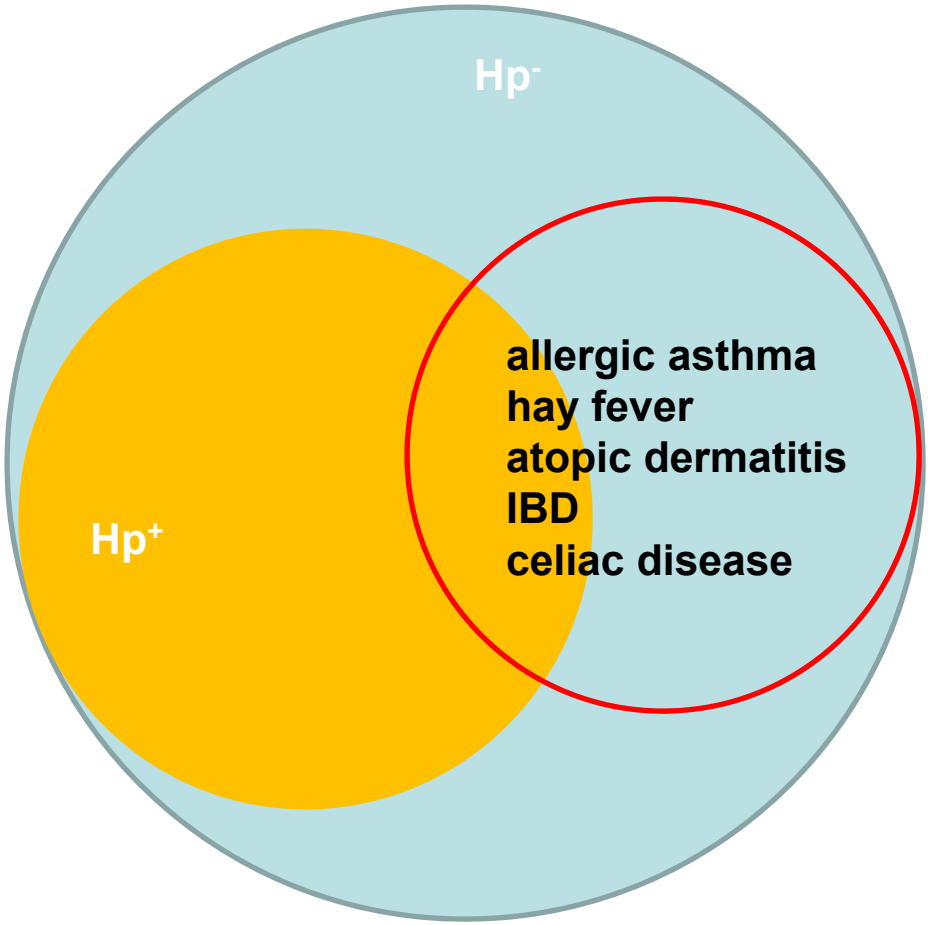






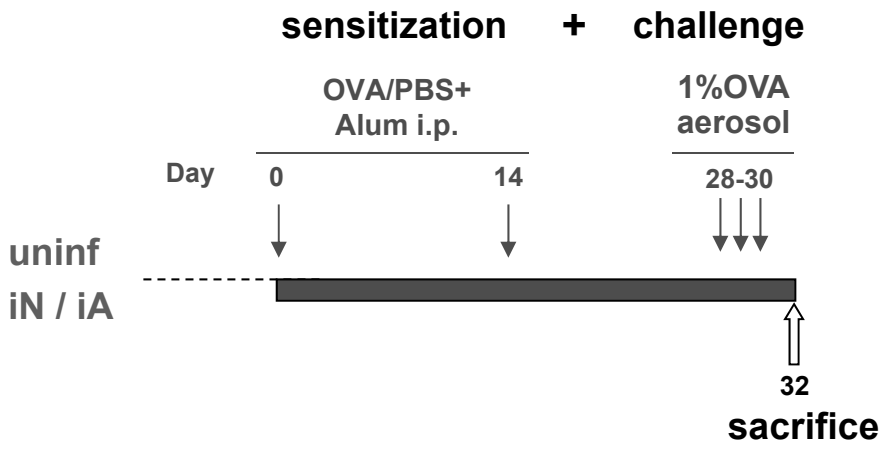
Arnold *et al.* Cell Reports, 2017

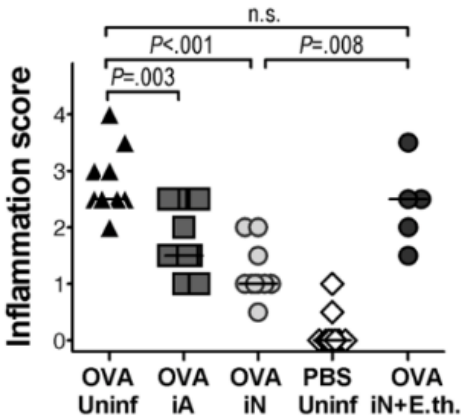
H. pylori is inversely associated with allergies and chronic inflammatory diseases



Chen & Blaser, 2007; Reibman et al., 2008; Chen & Blaser, 2008; Amberbir et al., 2011, 2014, Genta et al, 2015

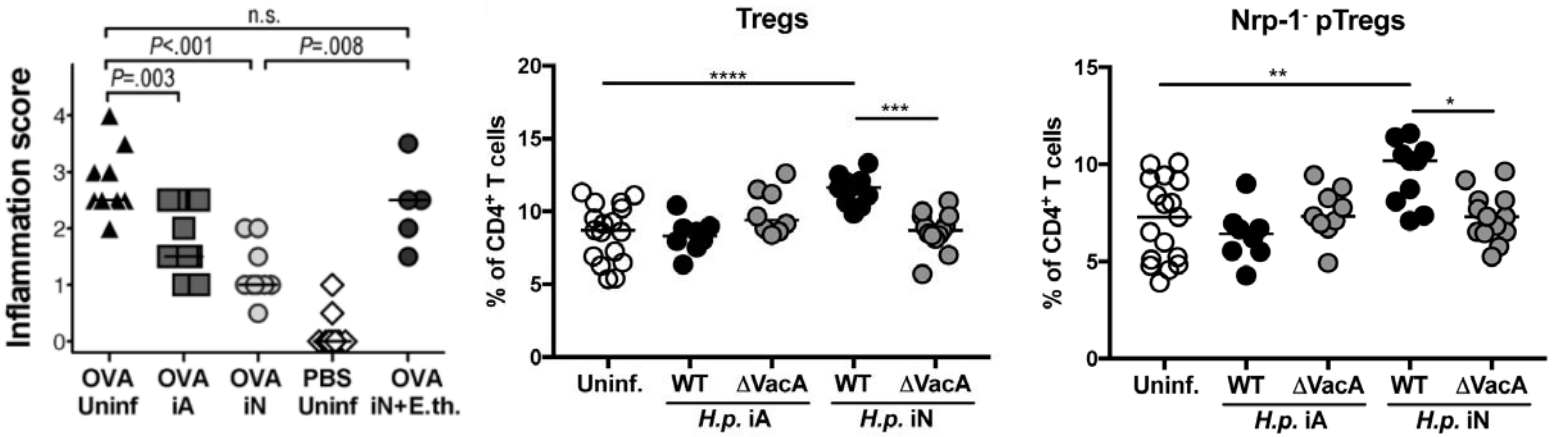
Neonatally infected mice are protected against clinical parameters of ovalbumin-induced asthma/allergic airway disease



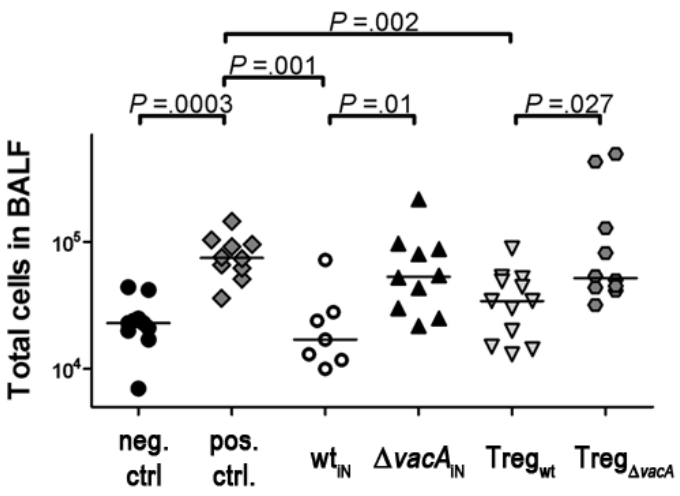


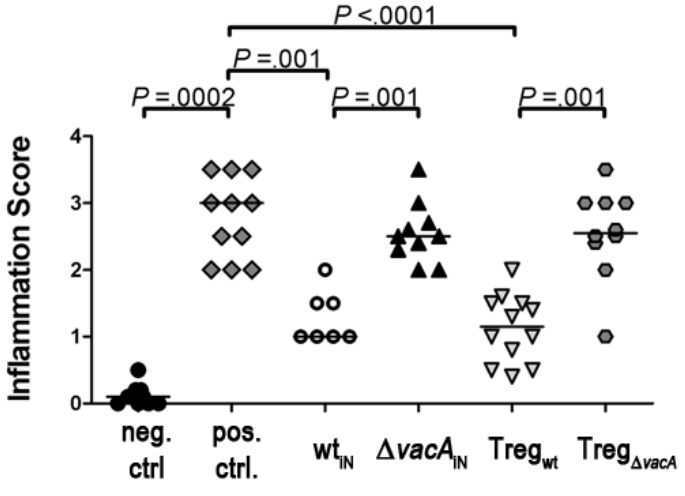
Arnold *et al.* J. Clin. Invest. 2011

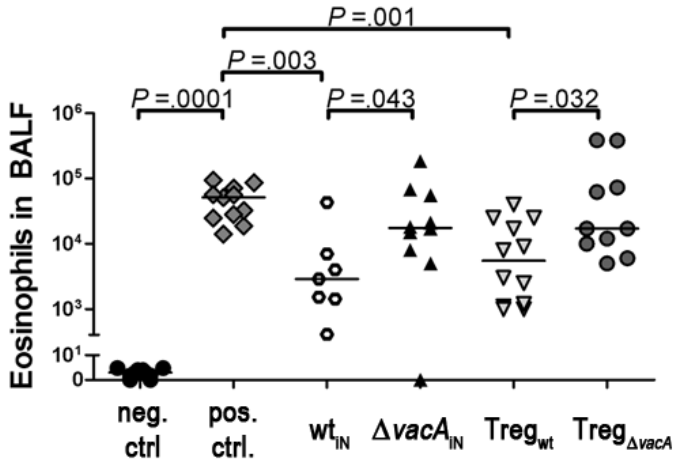
Neonatally infected mice, but not mice infected as adults, have elevated frequencies of pTregs in their lungs

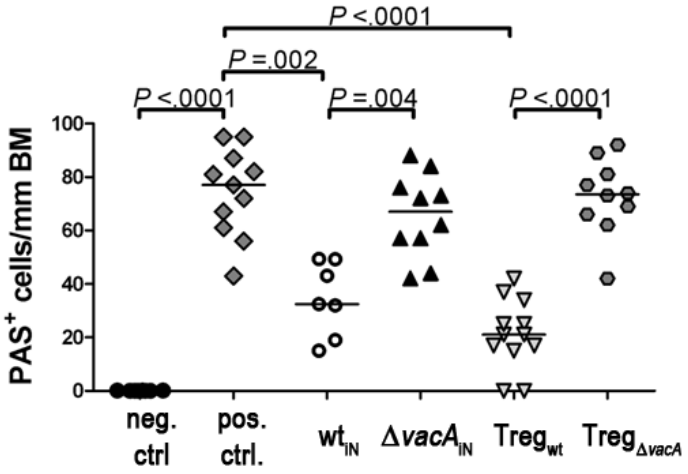


VacA is required for infection-induced asthma protection and induction of allergy-suppressing Tregs

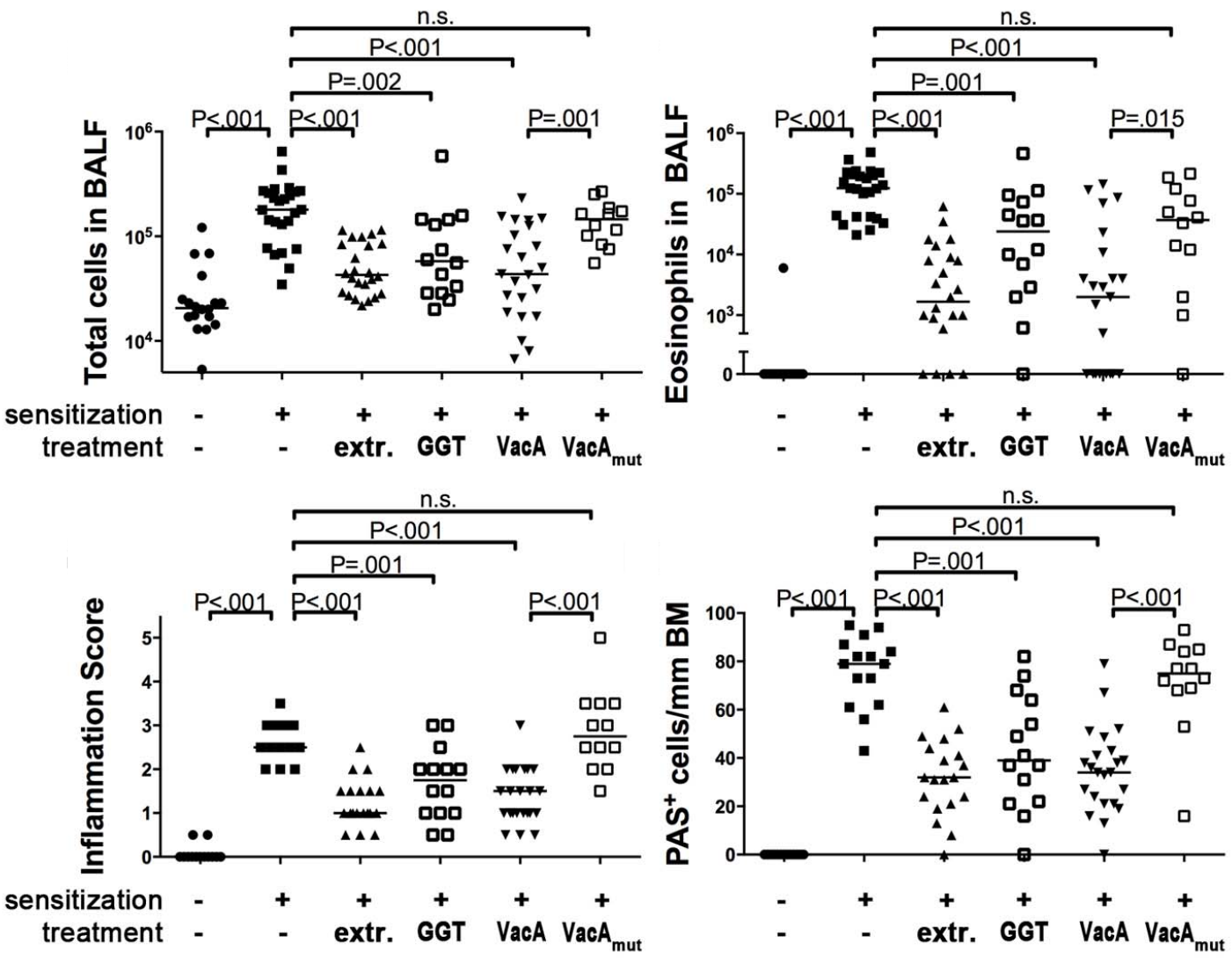




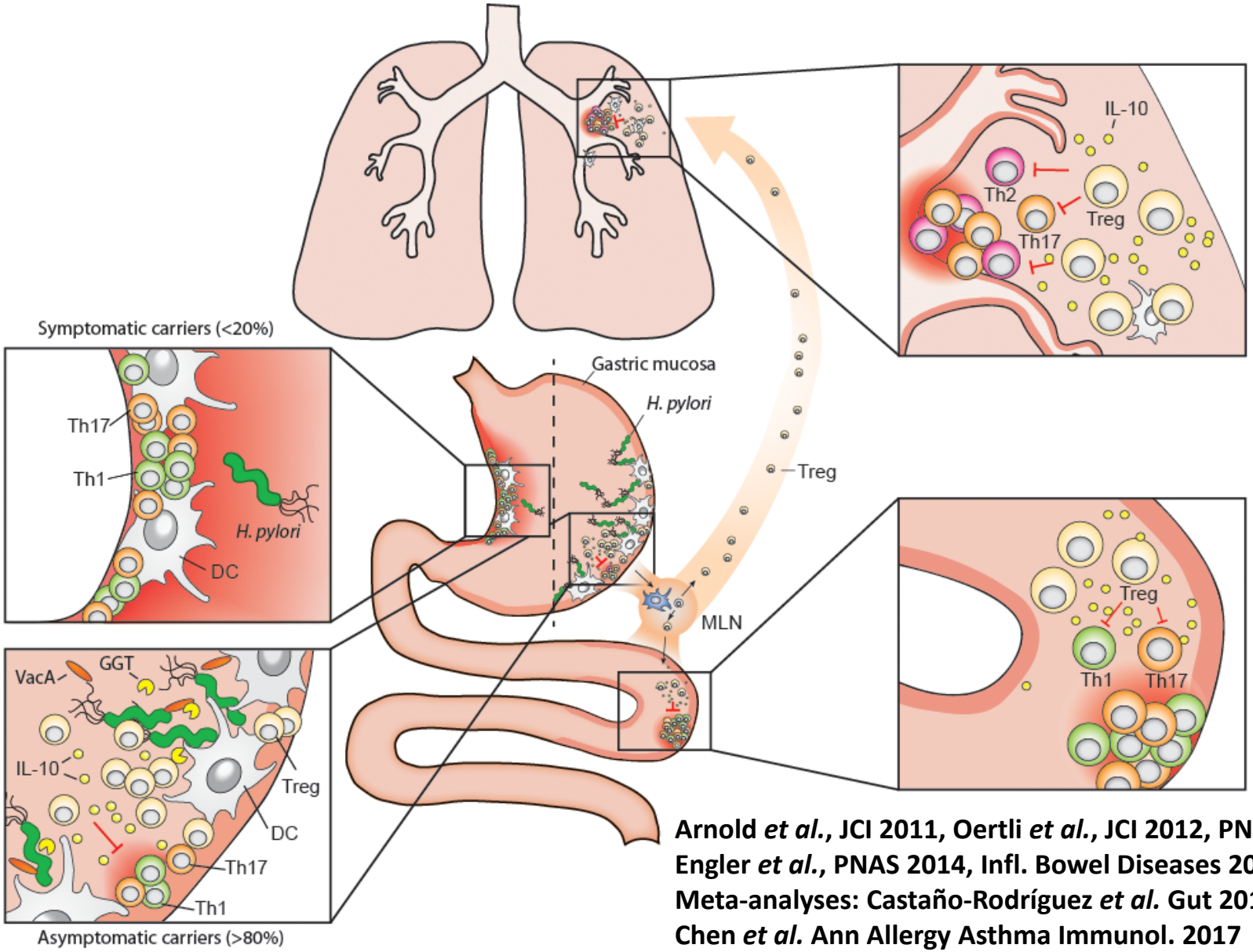




VacA confers asthma protection when administered in purified form, beginning in early life

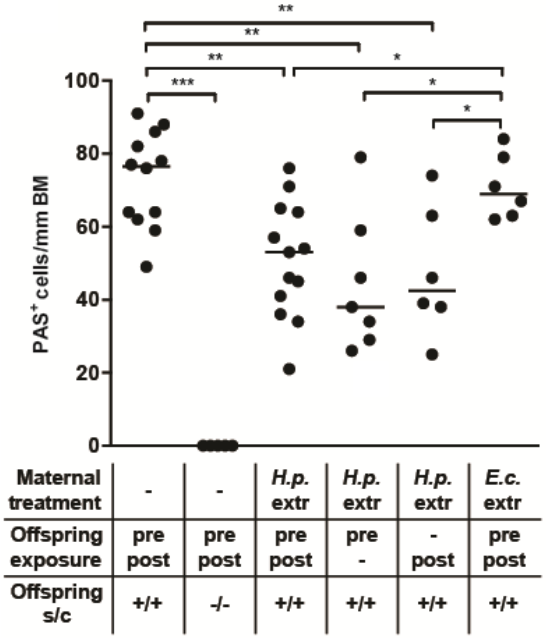


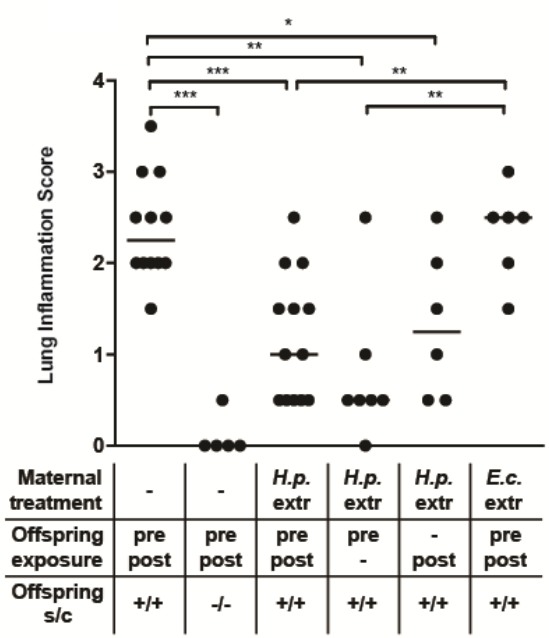
Helicobacter pylori colonization confers protection against allergic asthma (and IBD) through its immunomodulator VacA

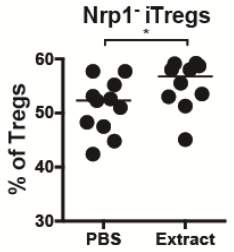


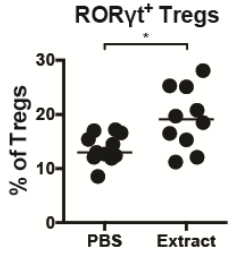
Arnold *et al.*, JCI 2011, Oertli *et al.*, JCI 2012, PNAS 2013
Engler *et al.*, PNAS 2014, Infl. Bowel Diseases 2015
Meta-analyses: Castaño-Rodríguez *et al.* Gut 2017,
Chen *et al.* Ann Allergy Asthma Immunol. 2017

Trans-maternal *Helicobacter pylori* exposure *in utero* and/or during lactation has protective effects on offspring







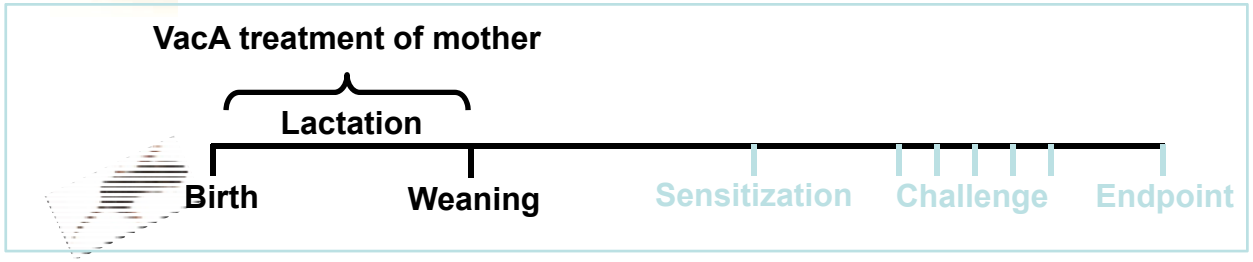


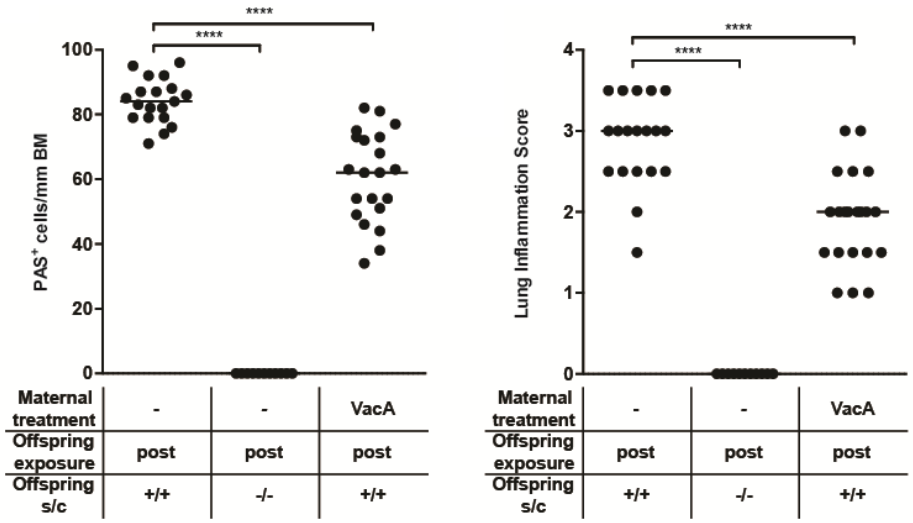
Andreas Kyburz

Kyburz *et al.* JACI 2018

Helicobacter pylori VacA has protective effects on offspring exposed during lactation

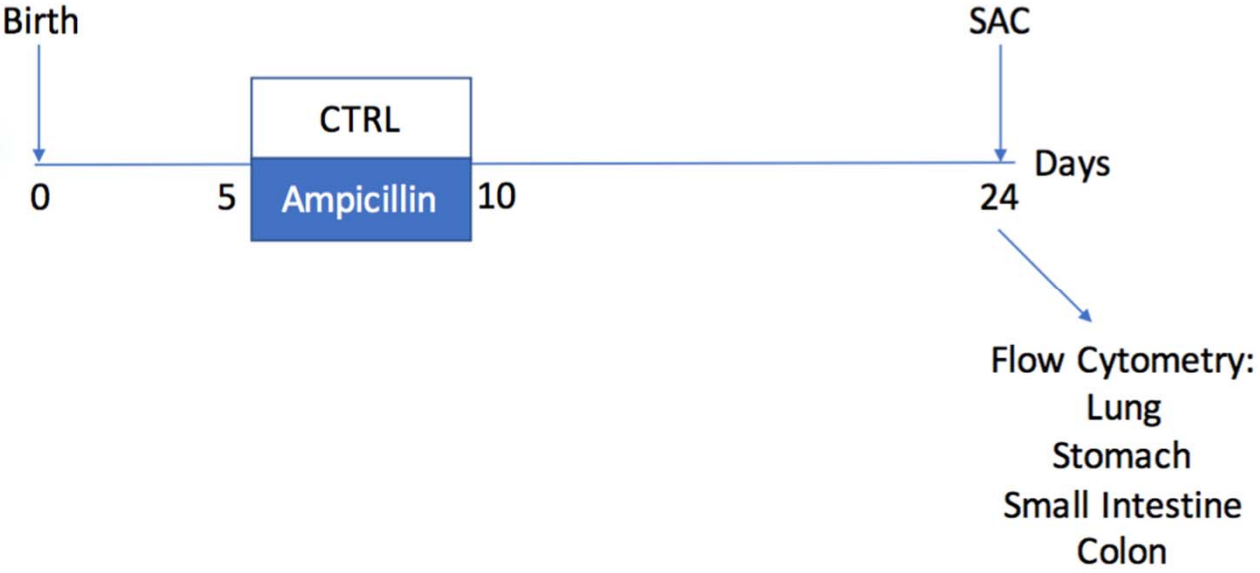
House dust mite (HDM)-induced asthma model



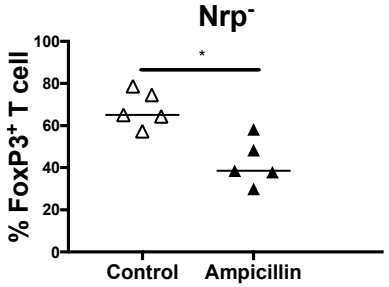


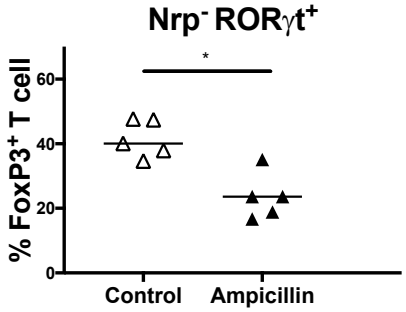
Kyburz *et al.* JACI 2018

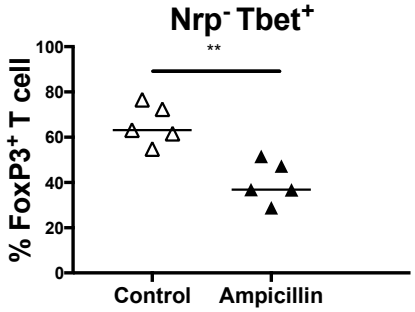
Antibiotic exposure during the second week of life has the opposite effect on pTreg frequencies (and allergic asthma)



Colonic Tregs:

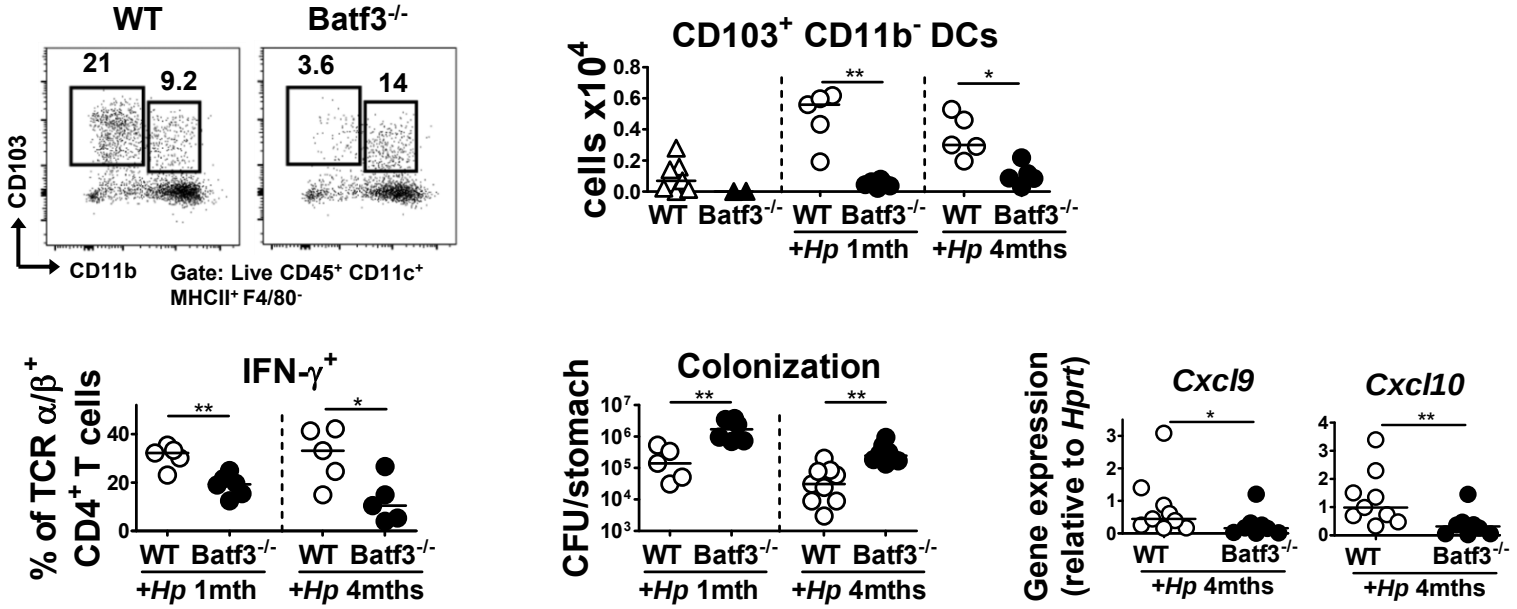






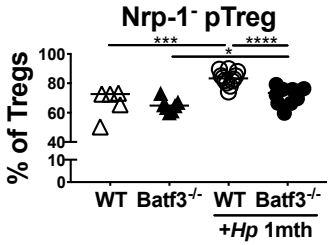
with T. Borbet and M. Blaser

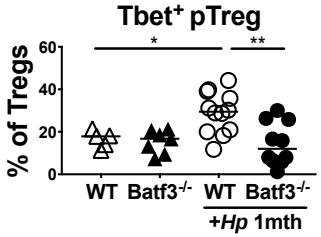
In the absence of BATF3-dependent CD103⁺ DCs, there is less Th1 recruitment to infected tissues => infection control is impaired



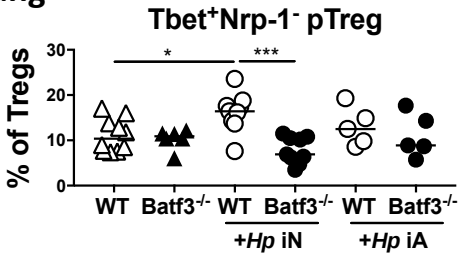
BATF3-dependent DCs are required for pTreg recruitment to the *H. pylori*-infected gastric mucosa

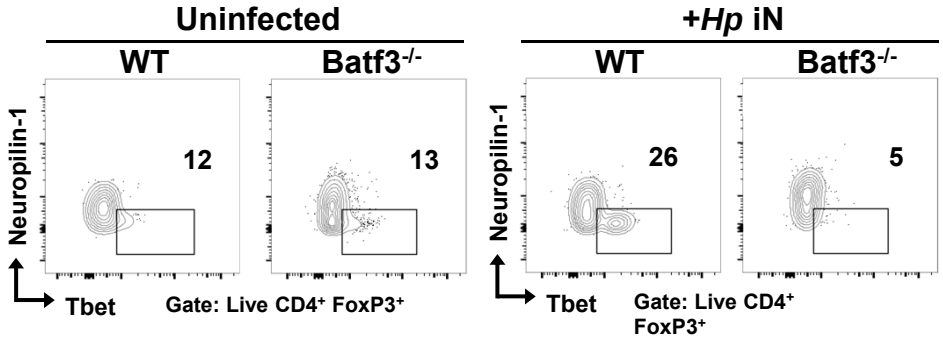
stomach

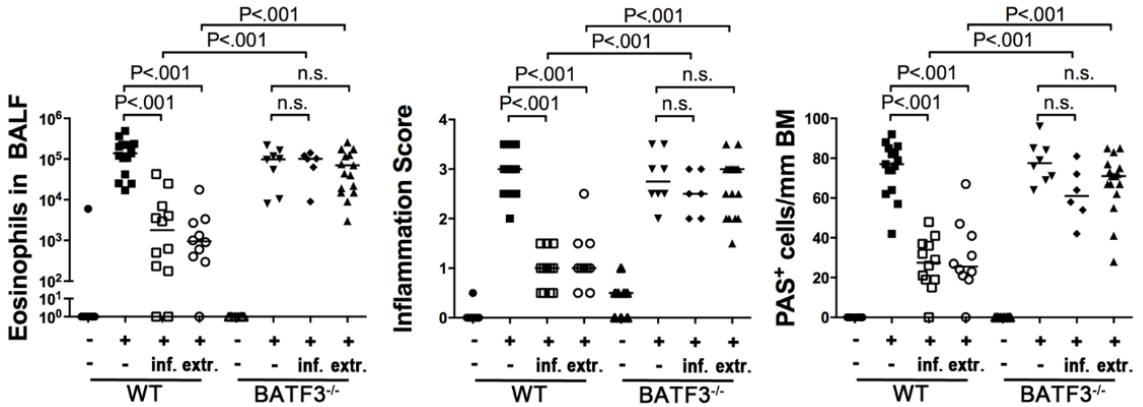




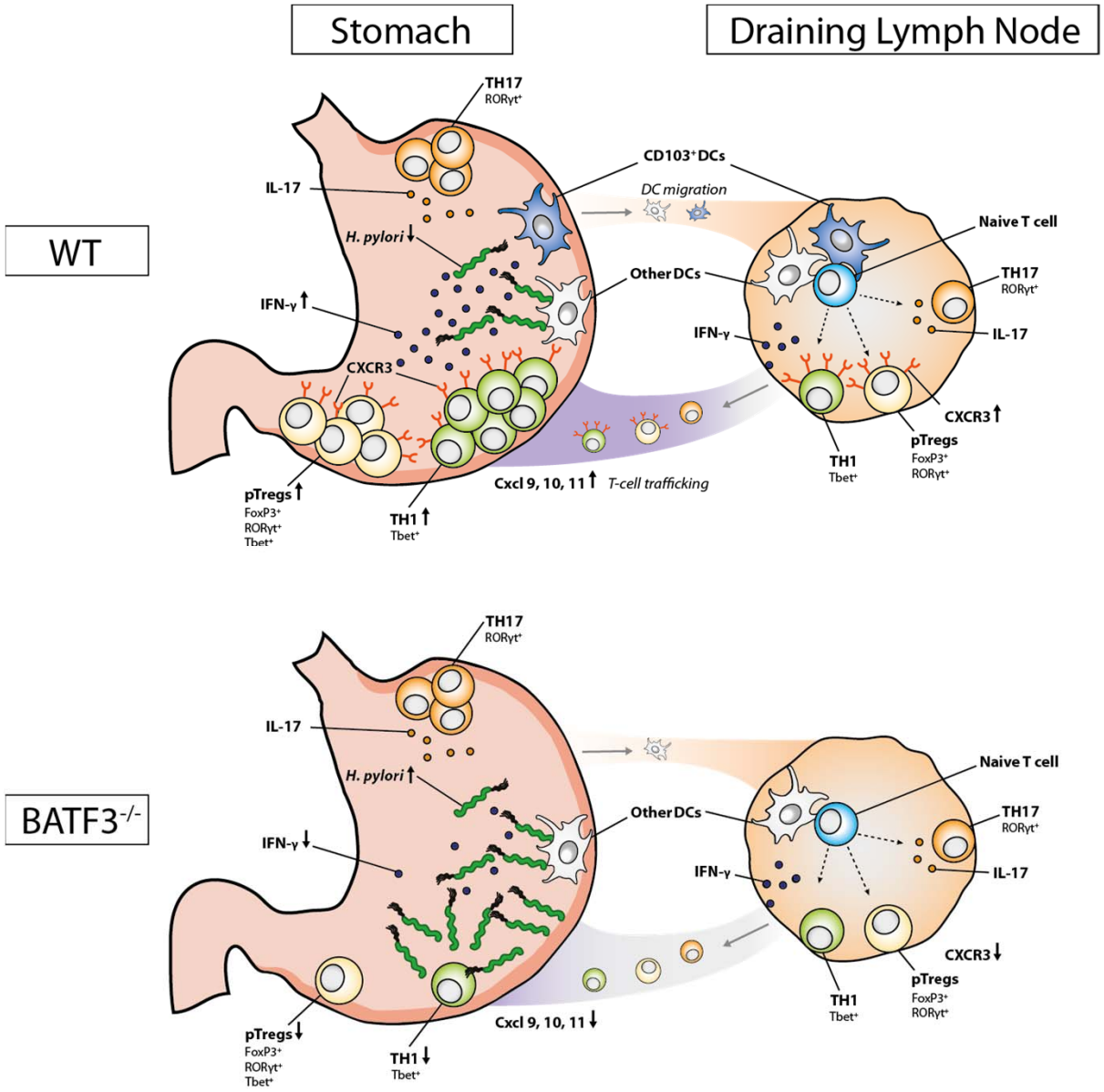
lung







BATF3-dependent DCs promote effector and regulatory T-cell recruitment to infected tissues through two distinct mechanisms



Conclusions

-VacA is a persistence determinant that interacts with myeloid cells in the gastric LP and skews T-cell responses towards Tregs

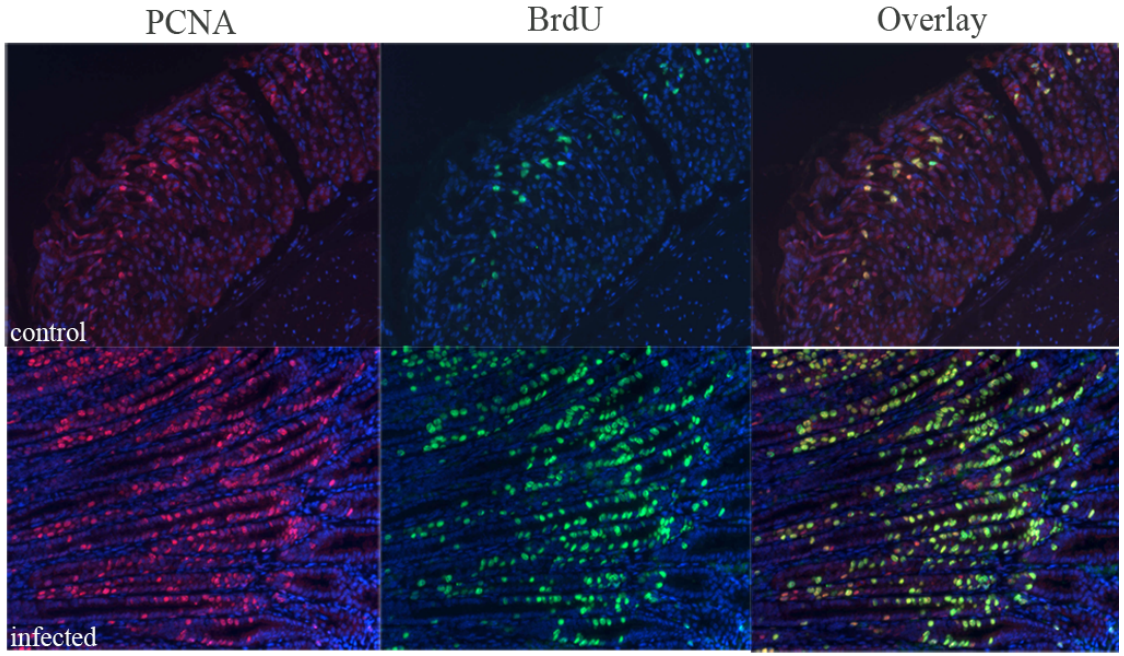
-direct and trans-maternal exposure to *H. pylori* (or VacA) has trans-generational protective effects in models of allergen-induced asthma

-*H. pylori* induces pTregs that express Tbet and RORγt and follow a chemokine gradient to infected tissues

-CD103^{+} DCs have a non-redundant role in T-cell recruitment (effector T-cells and Tregs, to infected and tumor tissues and distant sites)

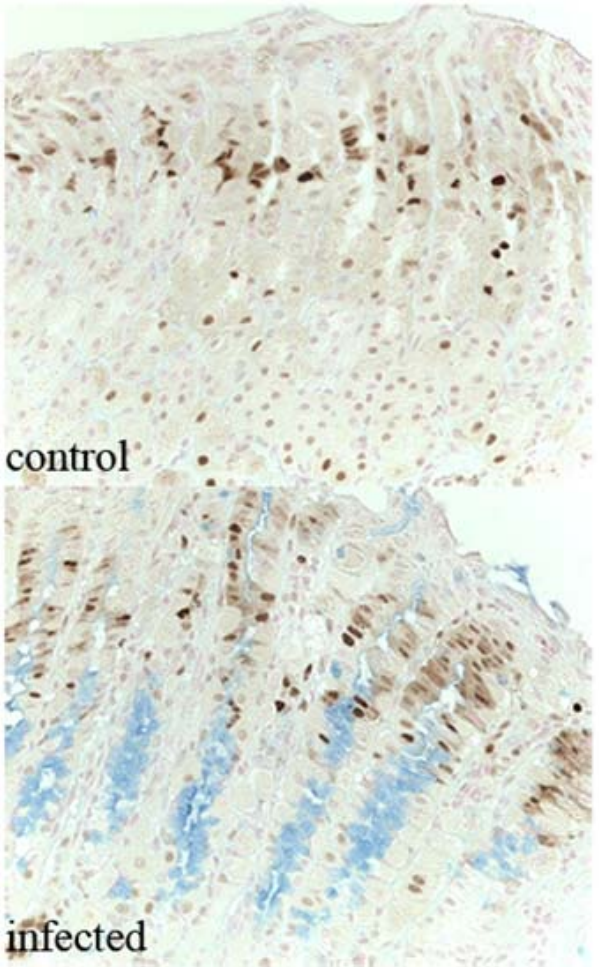
-*H. pylori* interacts with eosinophils in the gastric lamina propria

Chronic *Helicobacter*-induced inflammation results in preneoplastic gastric pathology

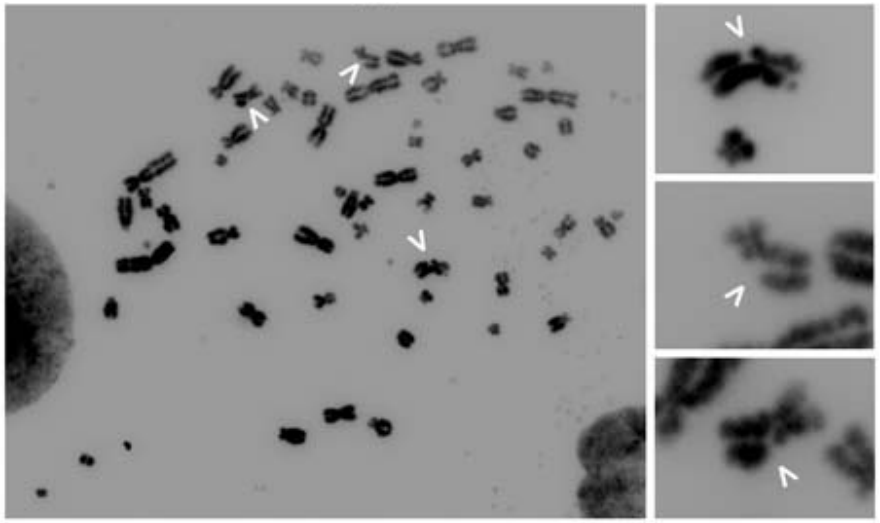


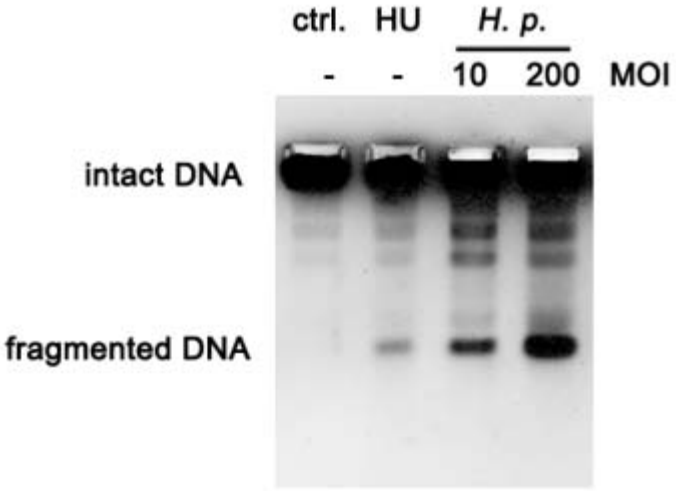
Epithelial hyperplasia

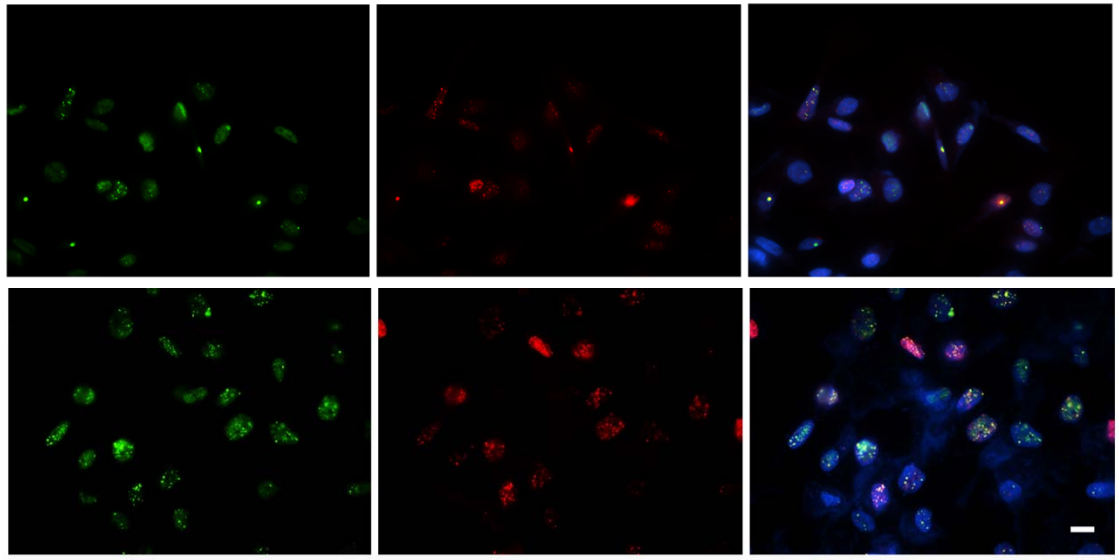
Intestinal metaplasia



H. pylori induces DNA double strand breaks in the nuclear genome of its host cells

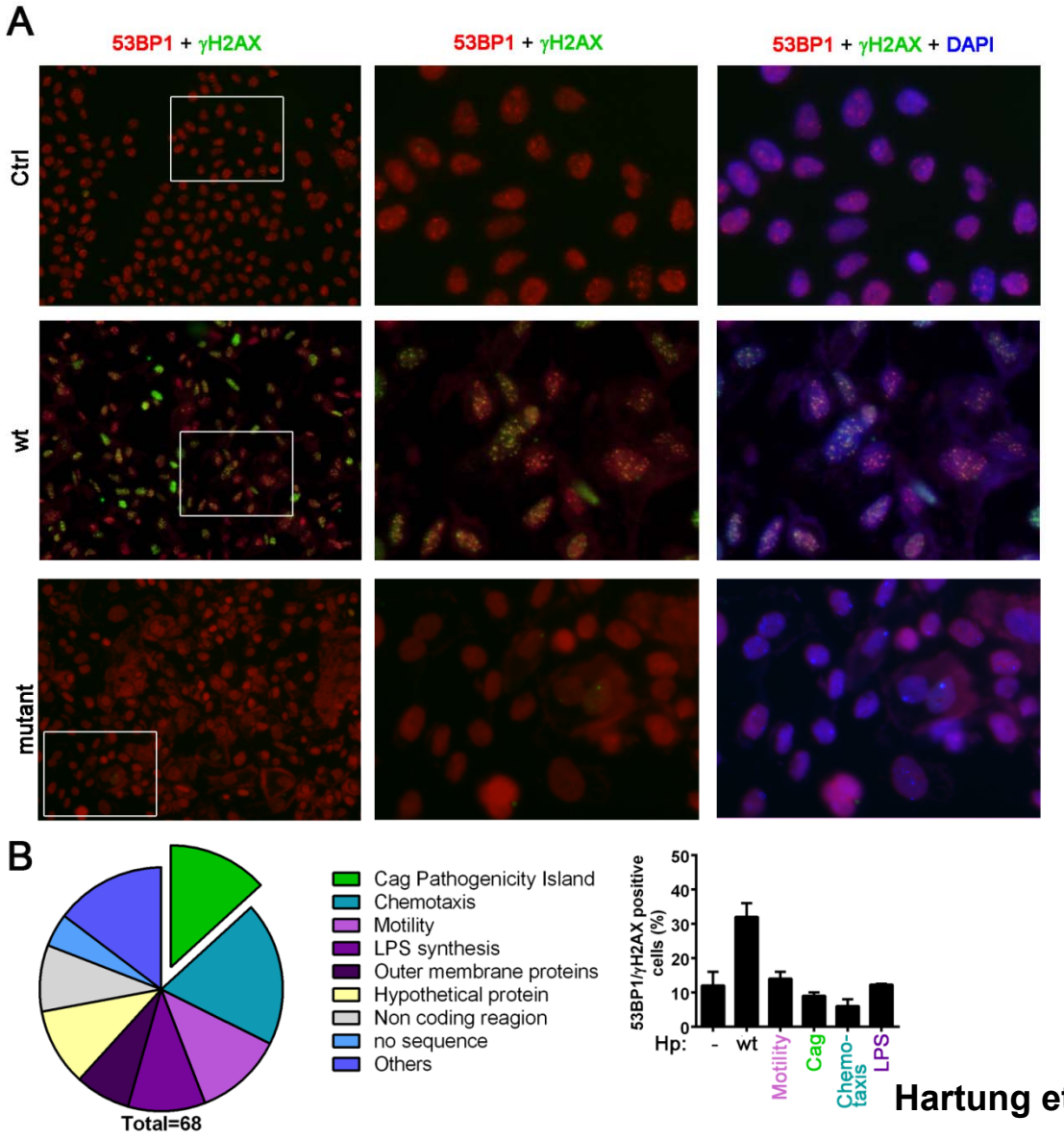






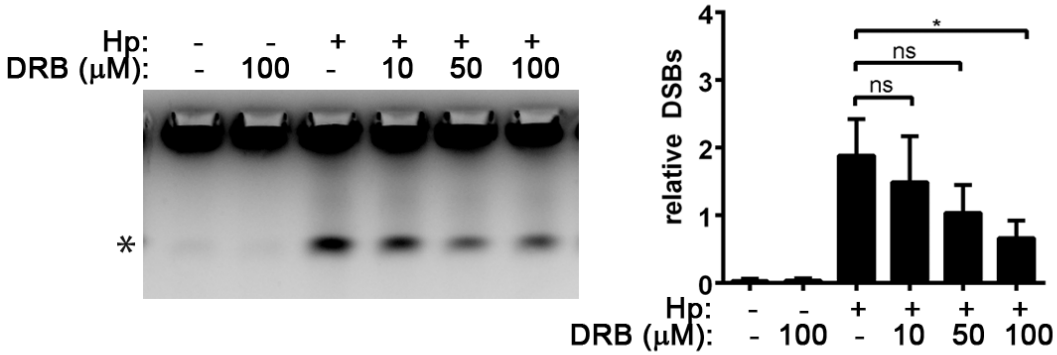
Toller et al., *PNAS* 2011

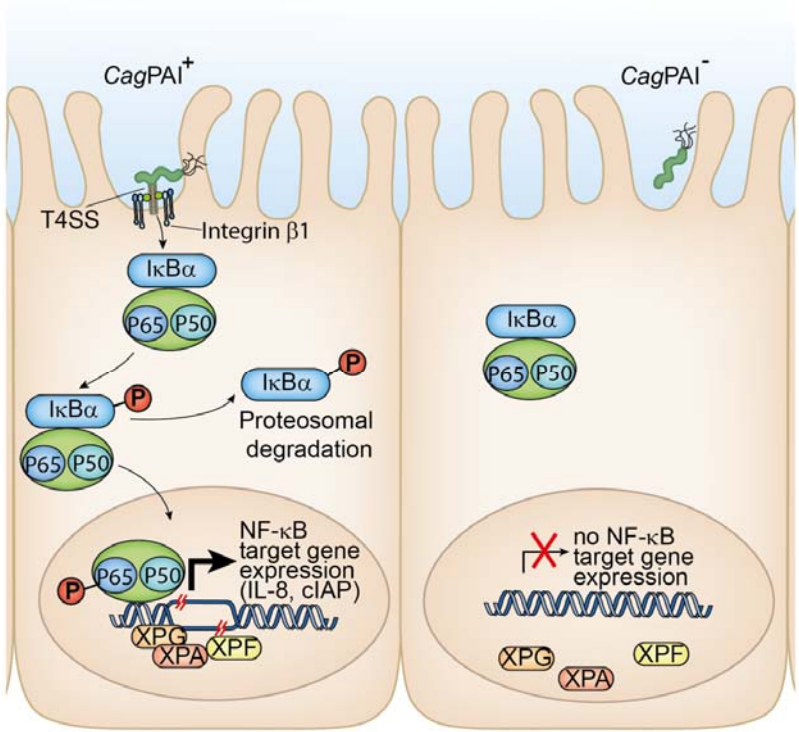
Screening for *H. pylori* factors involved in DNA double strand break induction reveals a role for the type IV secretion system (T4SS)



Hartung et al., *Cell Reports* 2015

H. pylori-induced DNA DSBs require transcription, a functional type IV secretion system and NF-kB signaling





Hartung et al., *Cell Reports* 2015

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krebsliga schweiz
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