Dangerous liaisons between gene and microbiota: the example of Card9 in IBD

Harry SOKOL

UPMC PARIS UNIVERSITAS
Inserm
Institut national de la santé et de la recherche médicale

Equipe AVENIR U1157

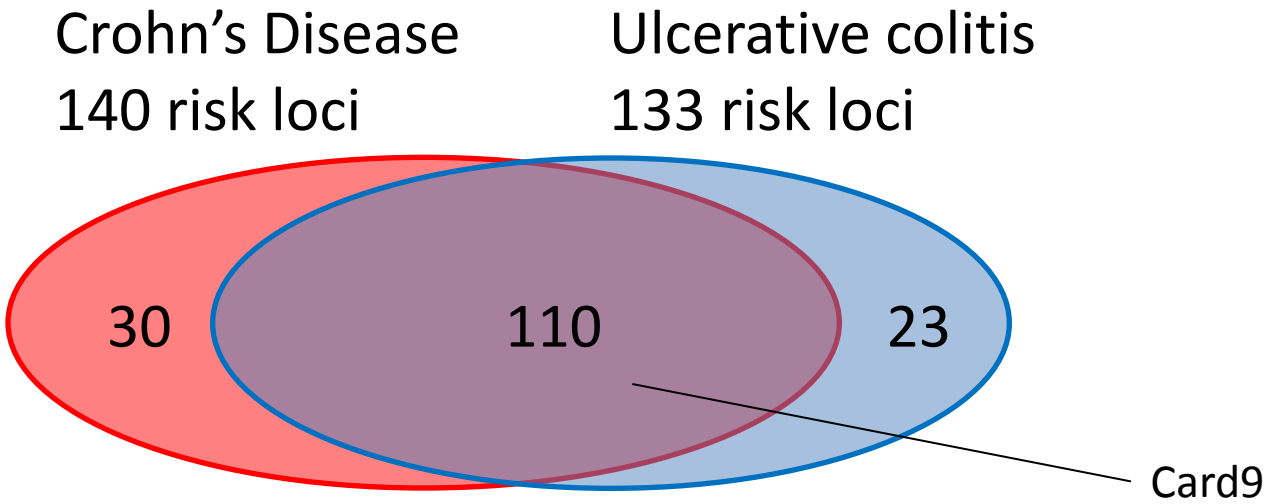
i2B INFLAMMATION IMMUNOPATHOLOGIE BIOTHÉRAPIE
DÉPARTEMENT HOSPITALO-UNIVERSITAIRE - DHU
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Gastroenterology Department
Saint-Antoine Hospital

INRA SCIENCE & IMPACT
Micalis

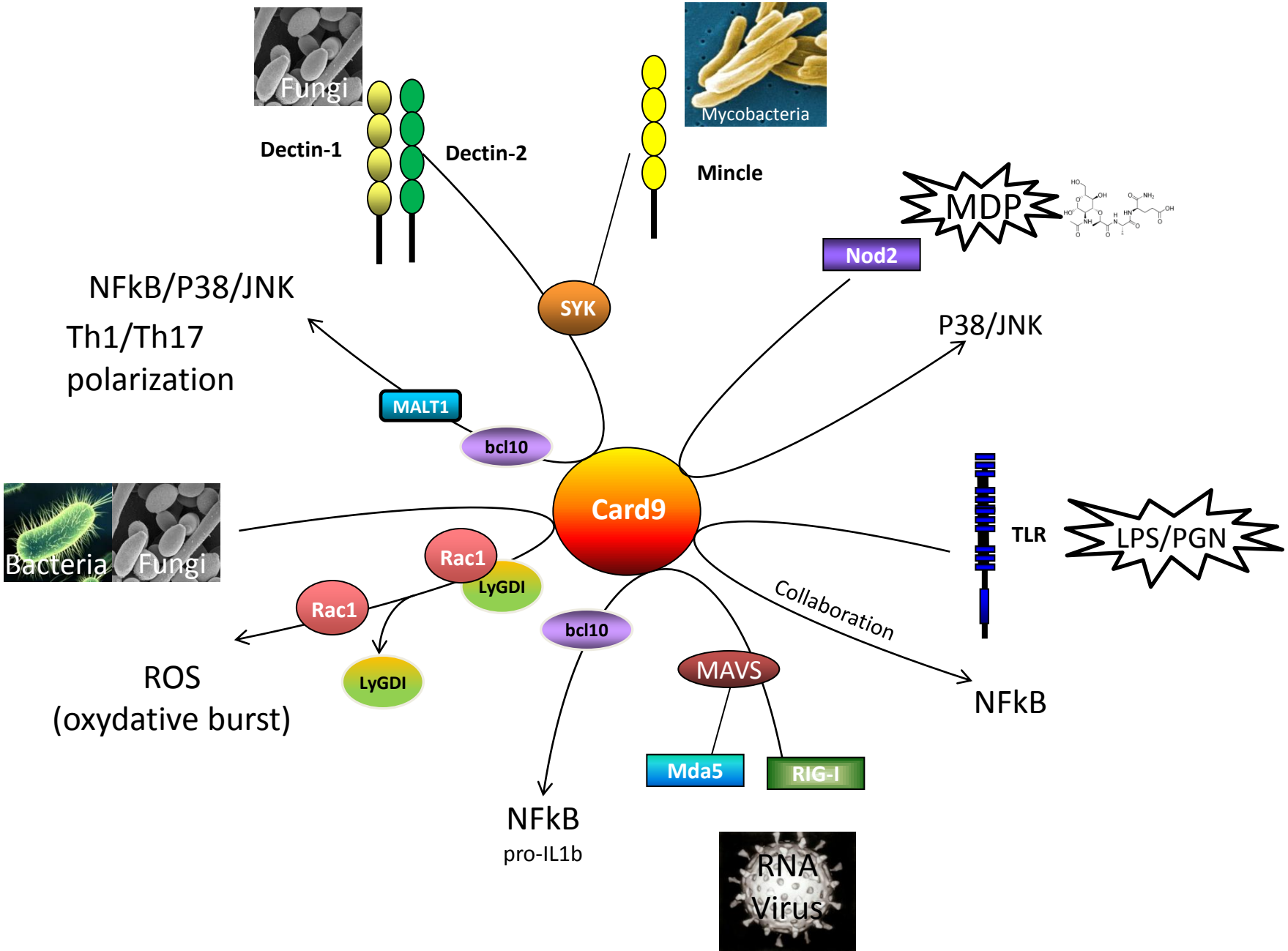
ProbiHote

Genes in IBD

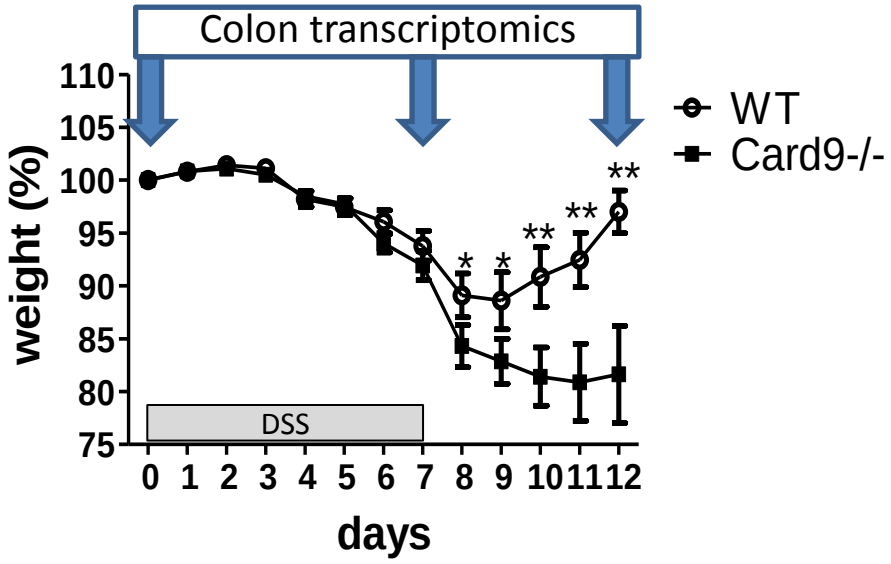


Khor et al. Nature 2011
Jostins et al. Nature 2012

Card9 : a central adaptor molecule in innate immunity



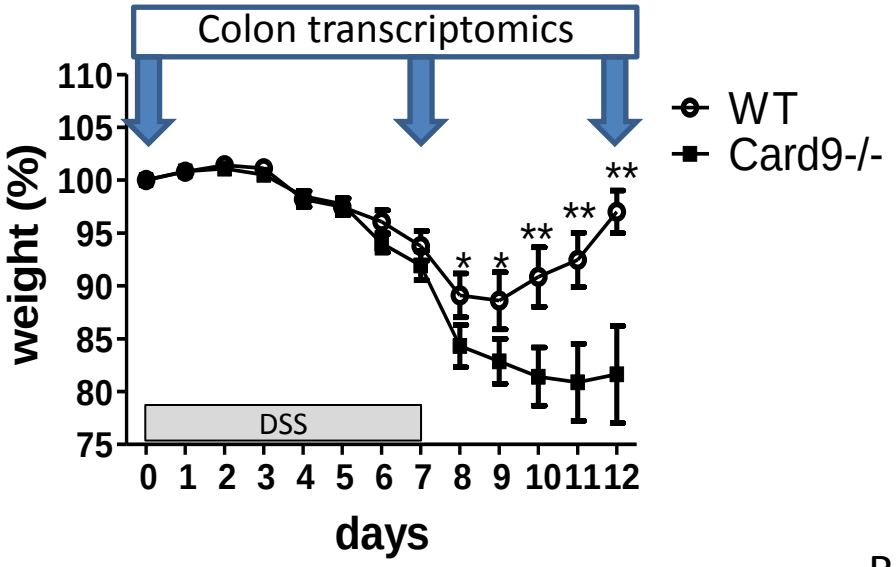
Card9 KO mice are more susceptible to DSS-induced colitis

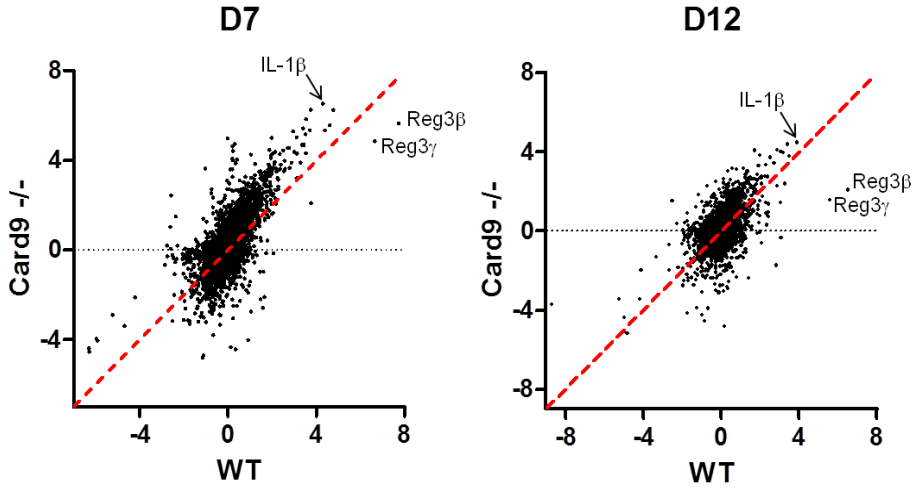


Sokol et al. Gastroenterology 2013

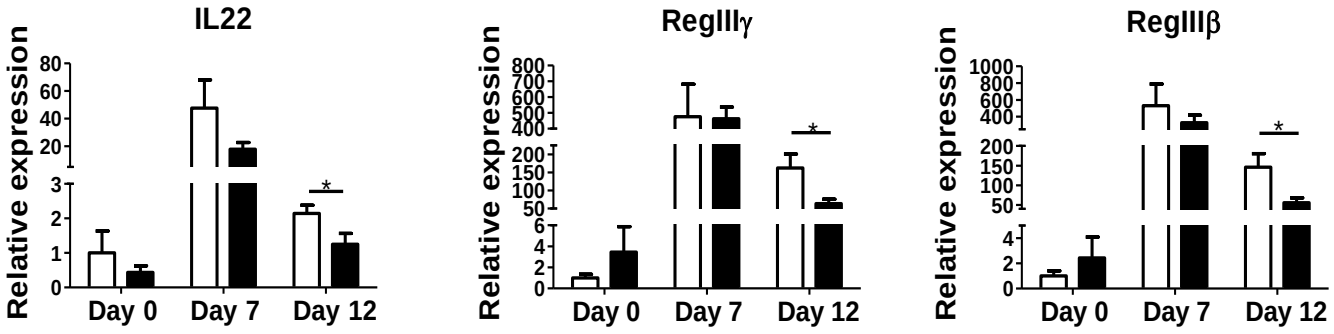
Lamas et al. Nature Medicine 2016

Card9 KO mice are more susceptible to DSS-induced colitis



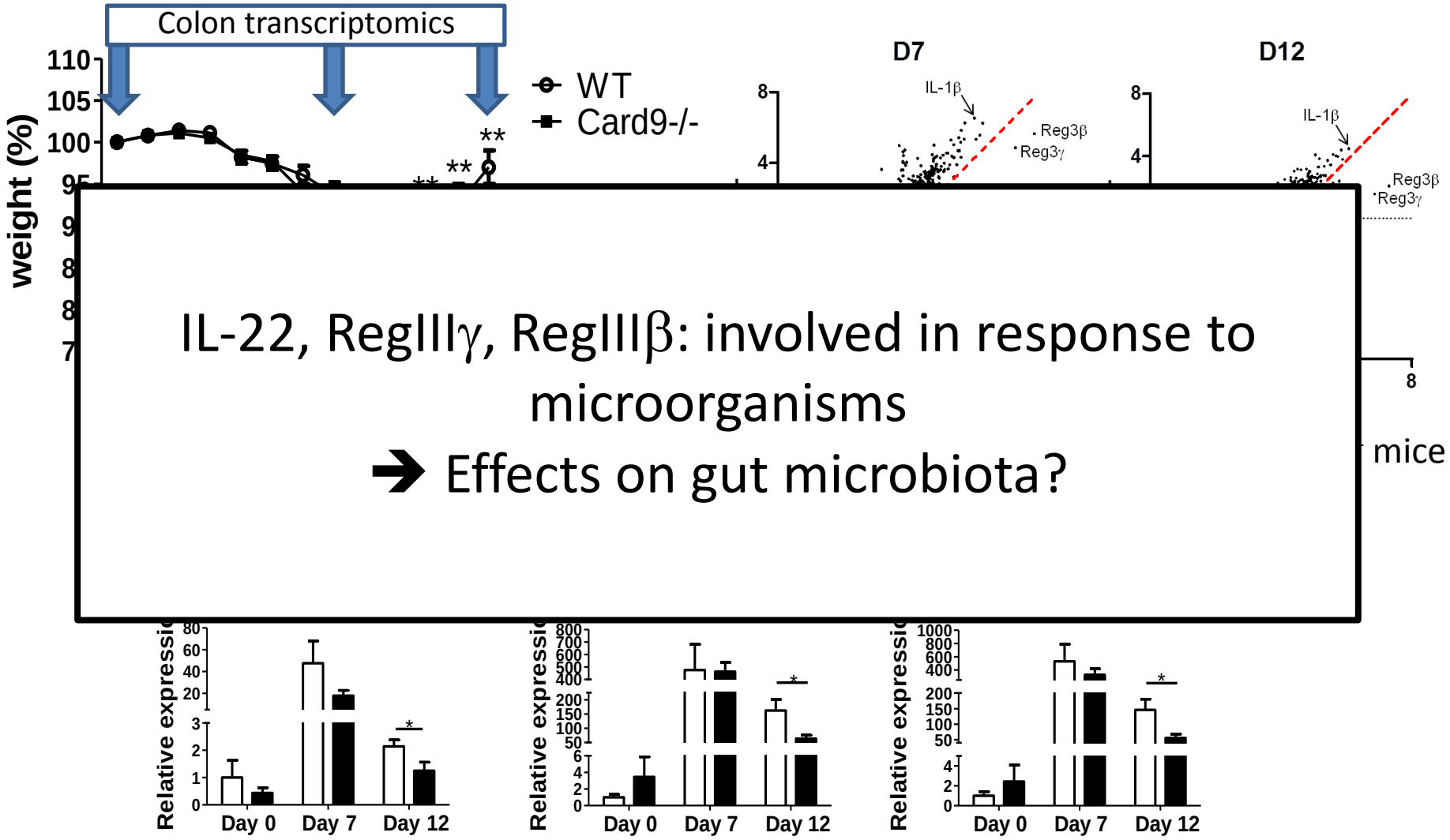


Reg3γ and Reg3β down regulated in Card9$^{-/-}$ mice



Lamas et al. Nature Medicine 2016

Card9 KO mice are more susceptible to DSS-induced colitis

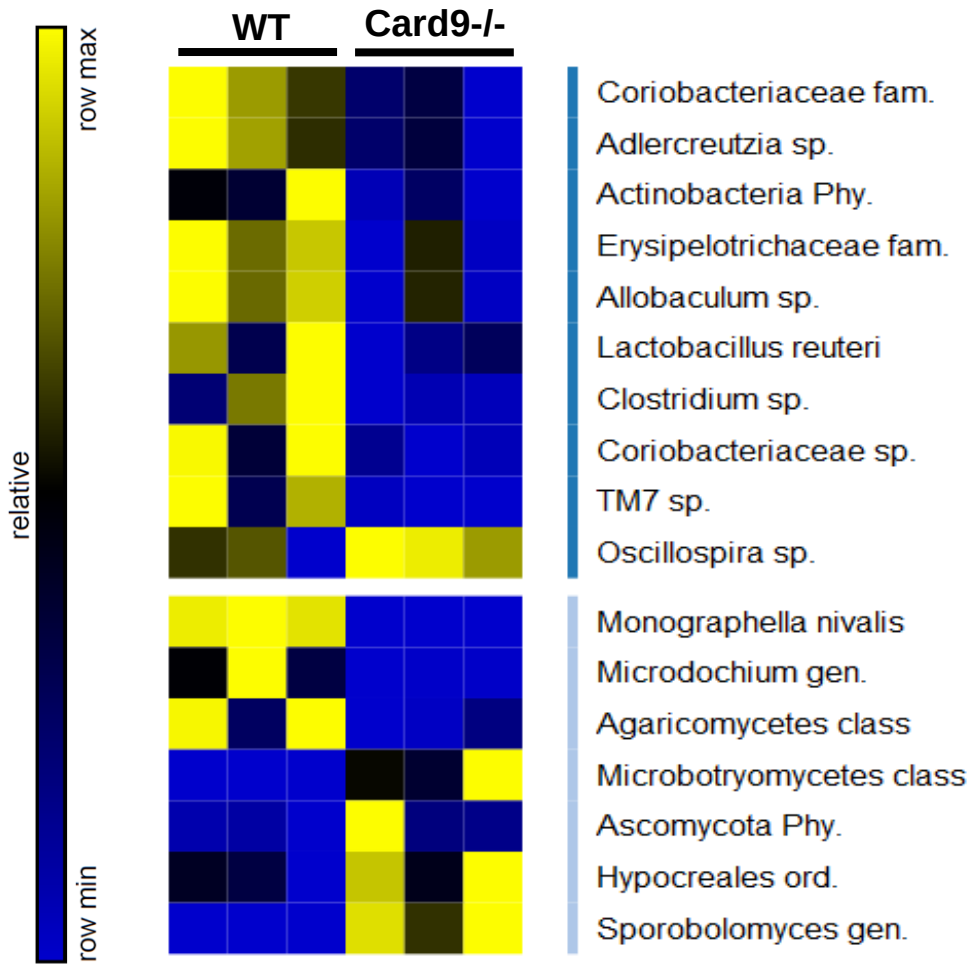


IL-22, RegIIIγ, RegIIIβ: involved in response to microorganisms

➔ Effects on gut microbiota?

Lamas et al. Nature Medicine 2016

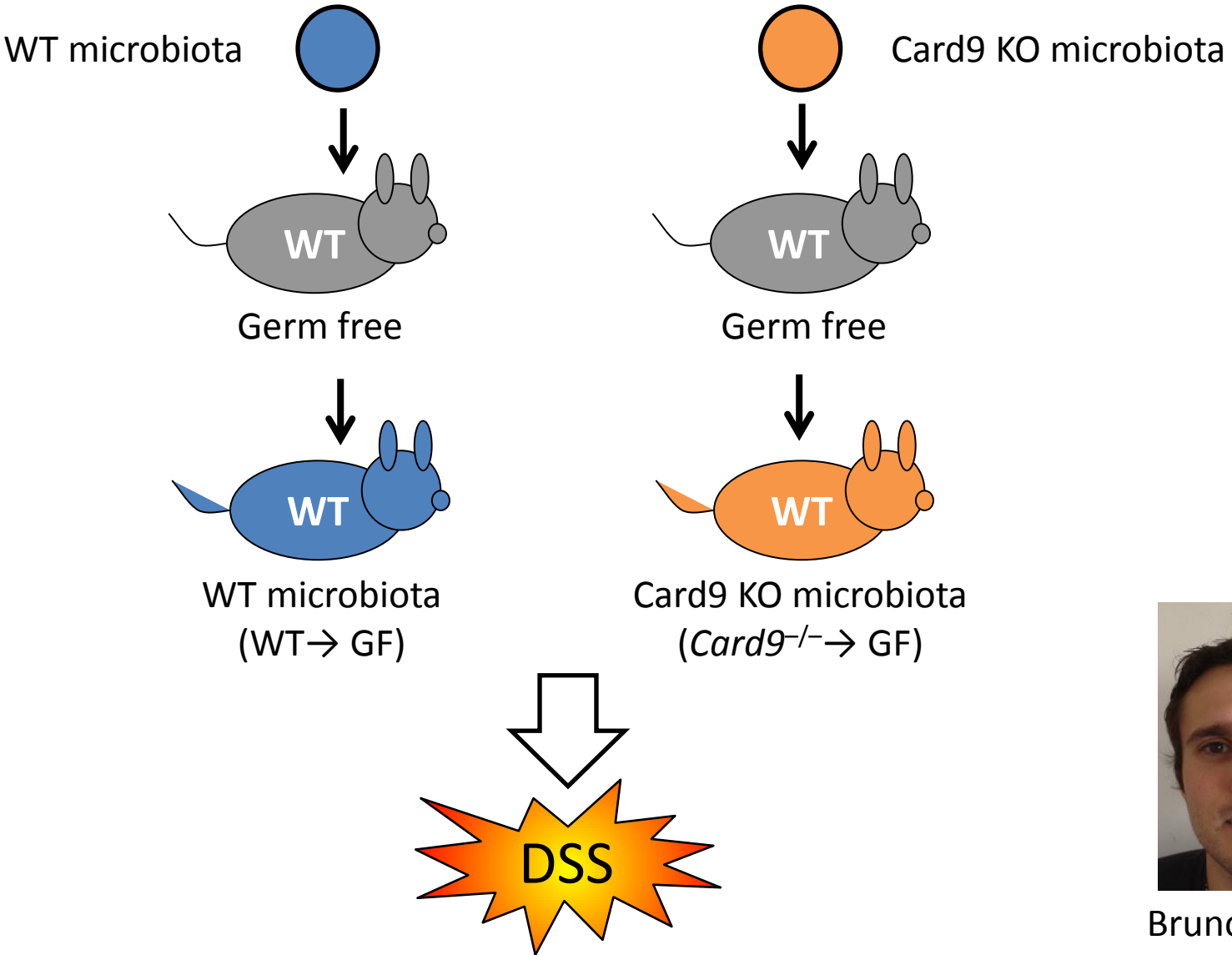
Card9 KO mice have an altered bacterial and fungal microbiota



Does the dysbiotic microbiota play a role in inflammation by itself?

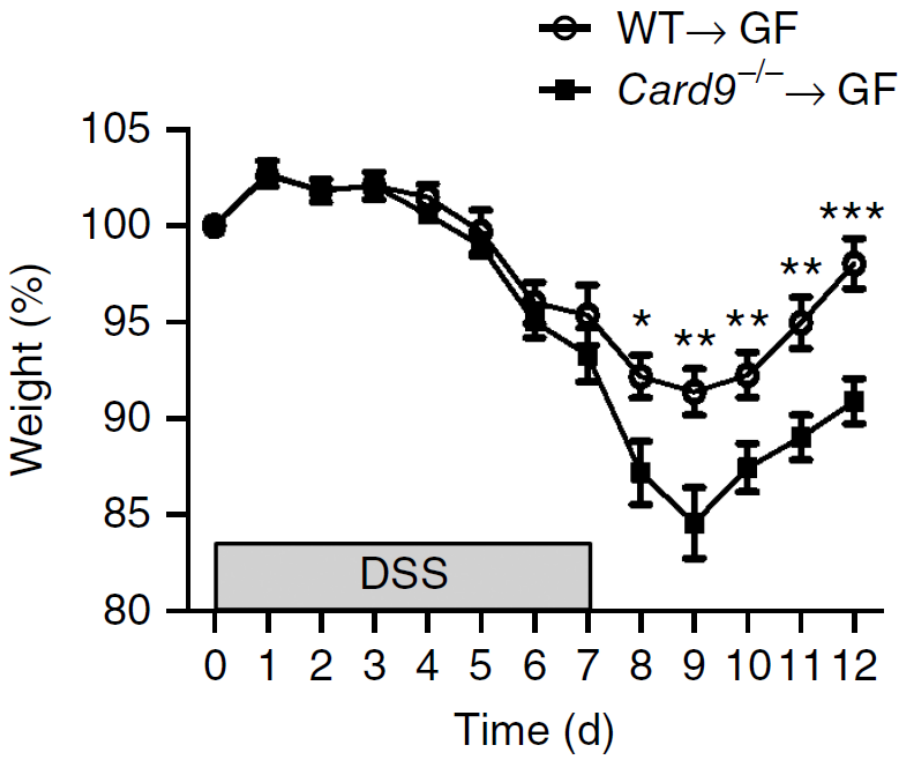
Lamas et al. Nature Medicine 2016

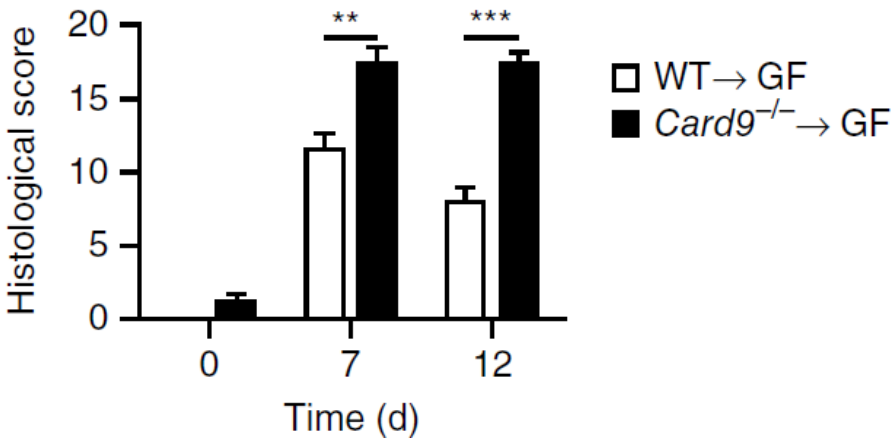
Role of the microbiota in Card9 KO-mice susceptibility to inflammation

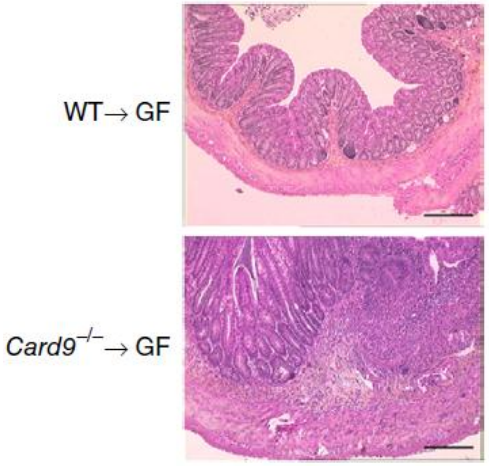


Bruno Lamas

The microbiota from *Card9*$^{-/-}$ mice exerts proinflammatory effects





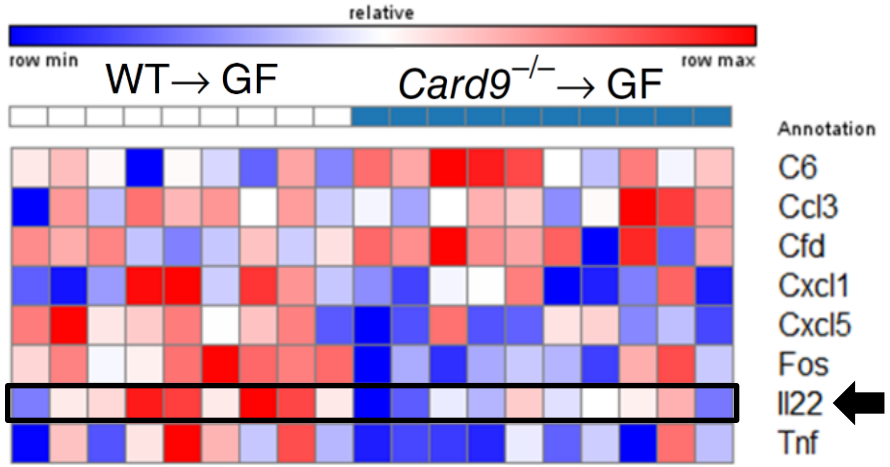


day 12

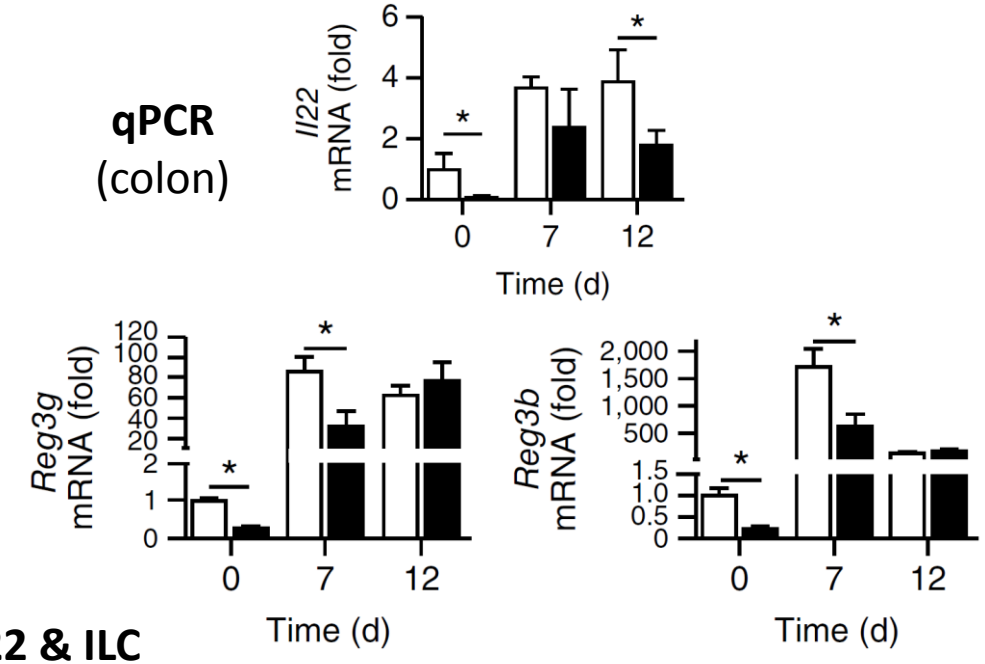
Lamas et al. Nature Medicine 2016

The IL22 pathway is impaired *Card9*$^{-/-}$→ GF mice

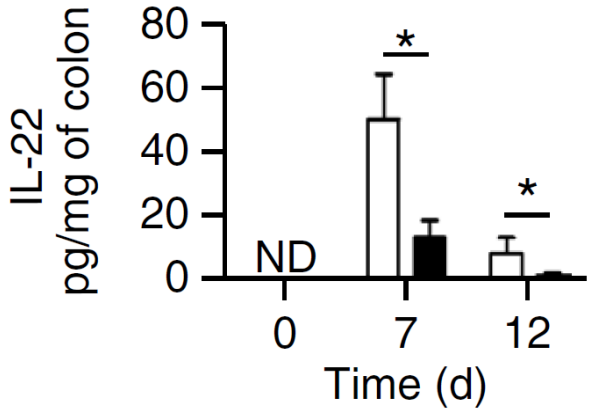
Transcriptomic (Nanostring)



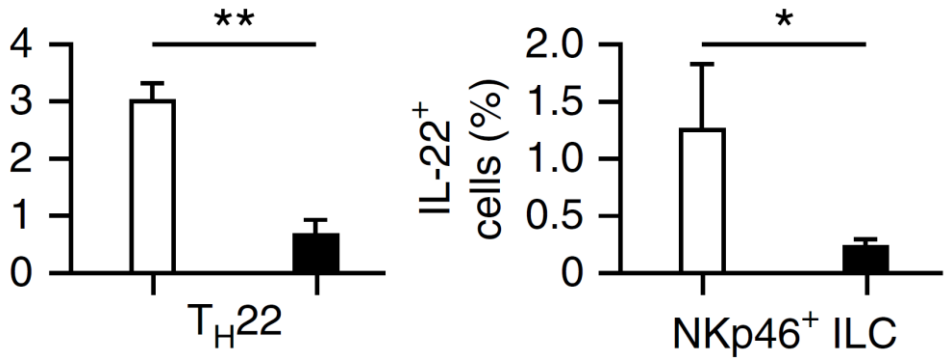
qPCR (colon)



Protein in colon

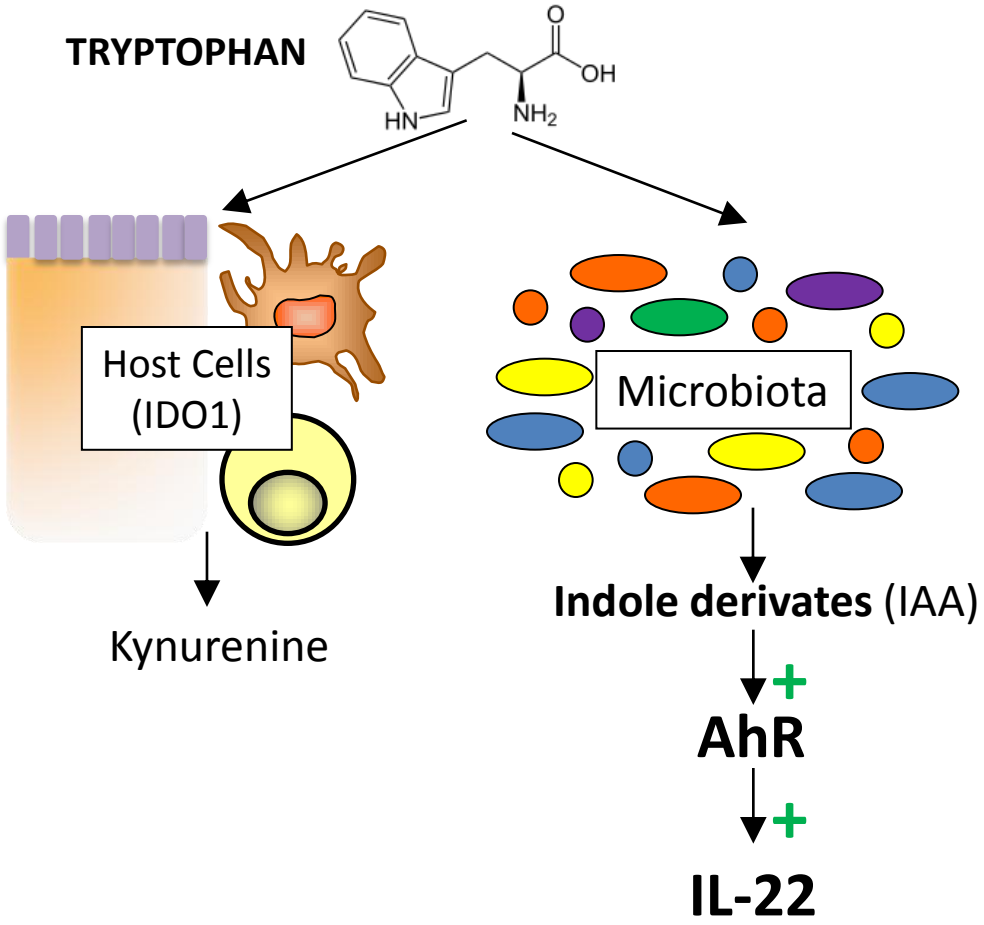


Th22 & ILC

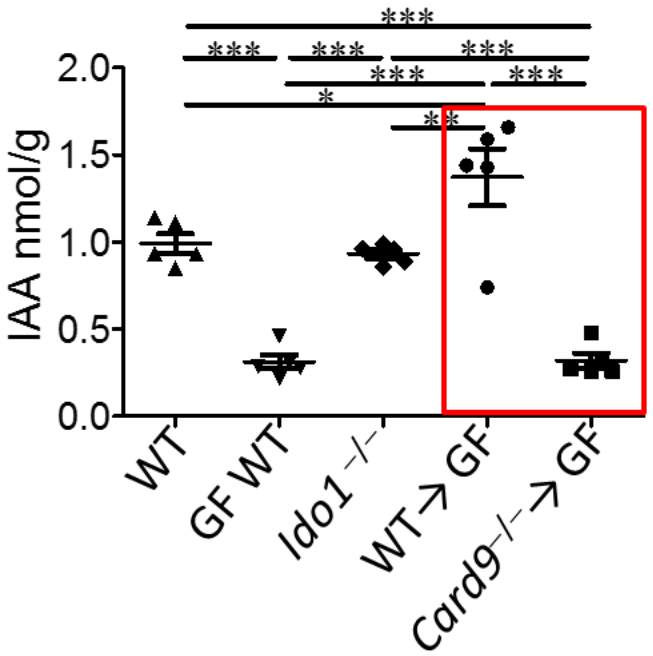


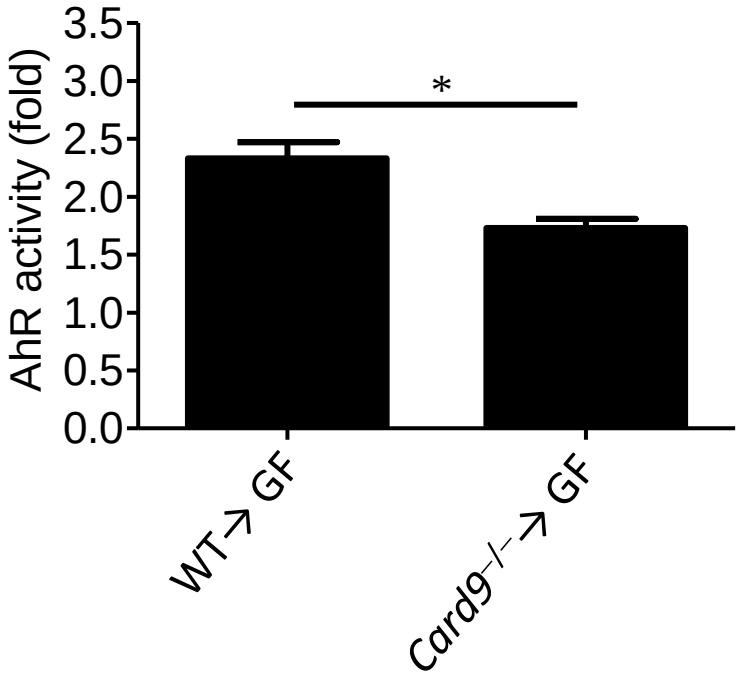
Transfer of the IL22 defect through microbiota

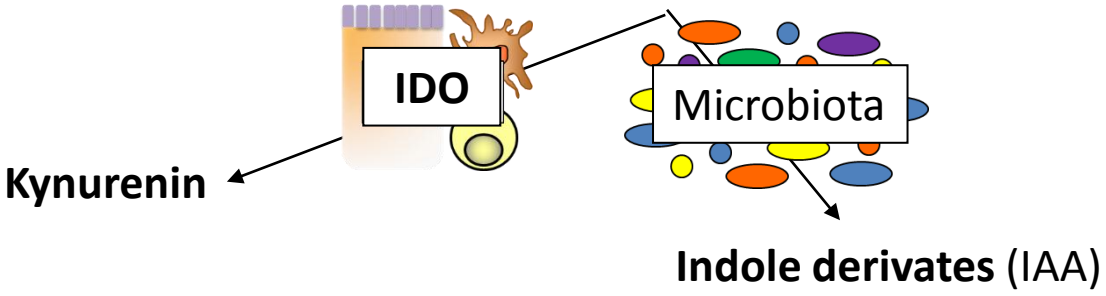
hypothesis = impaired function of the microbiota



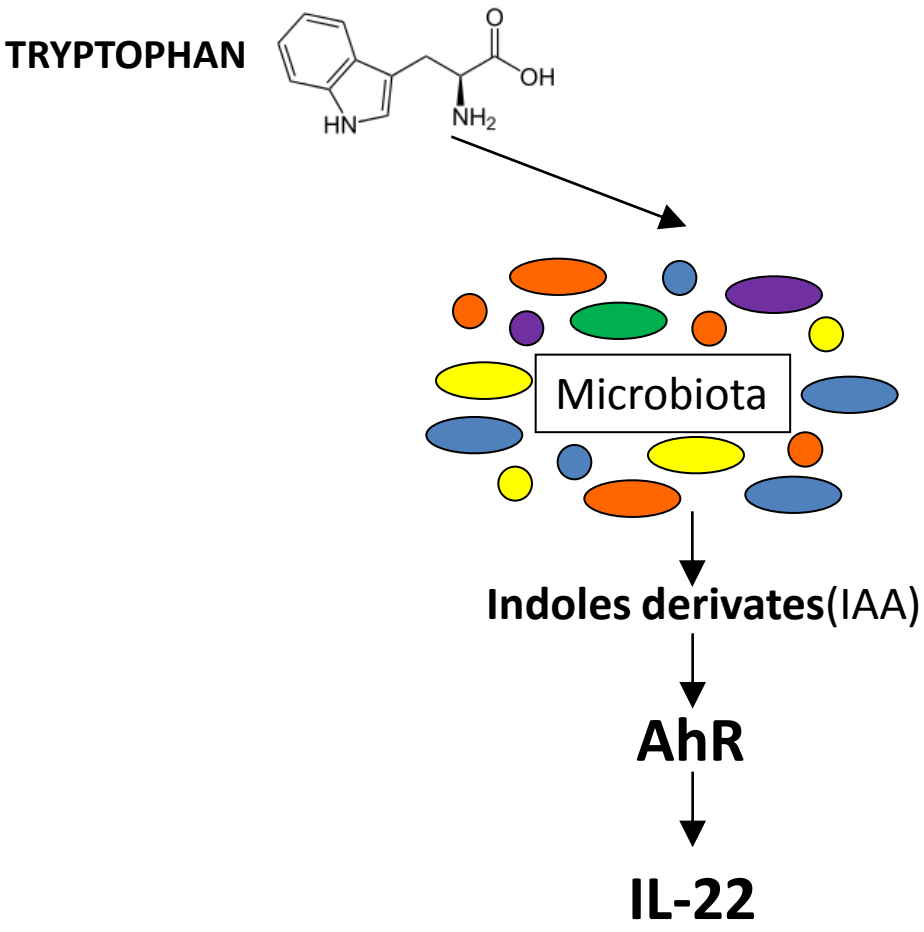
Card9$^{-/-}$→ GF mice exhibits impaired tryptophan metabolism



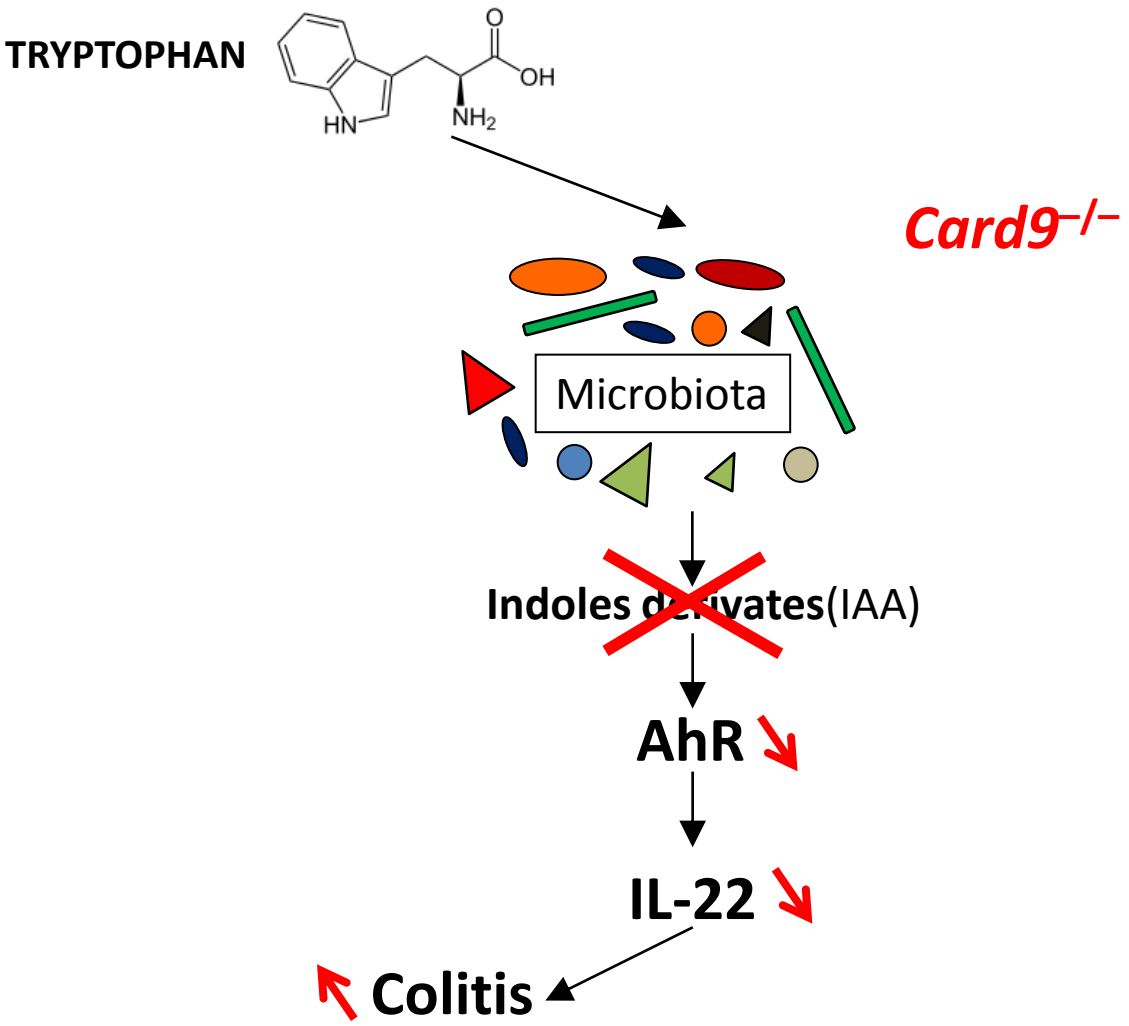




Card9$^{-/-}$ mice exhibits impaired tryptophan metabolism

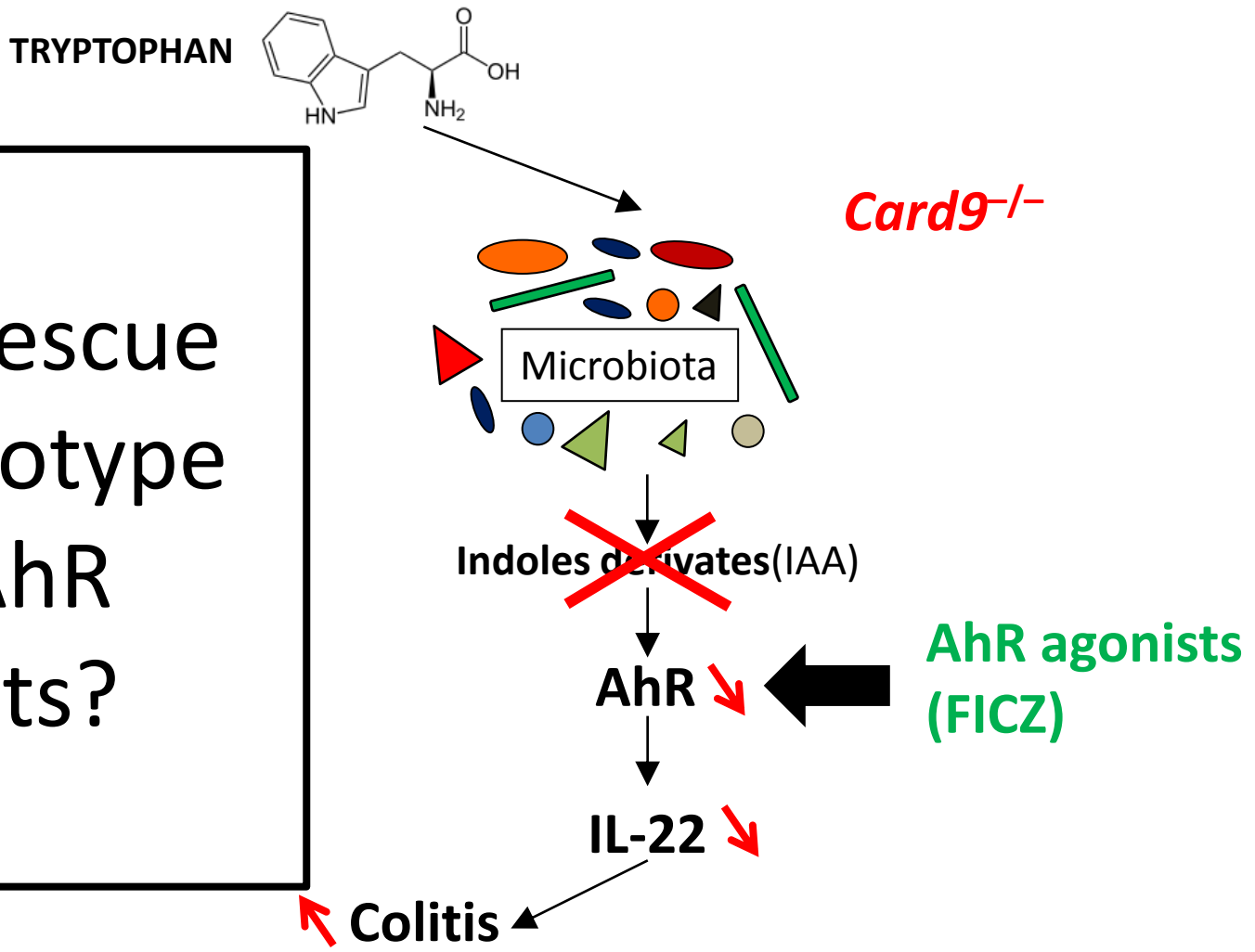


Card9$^{-/-}$ mice exhibits impaired tryptophan metabolism

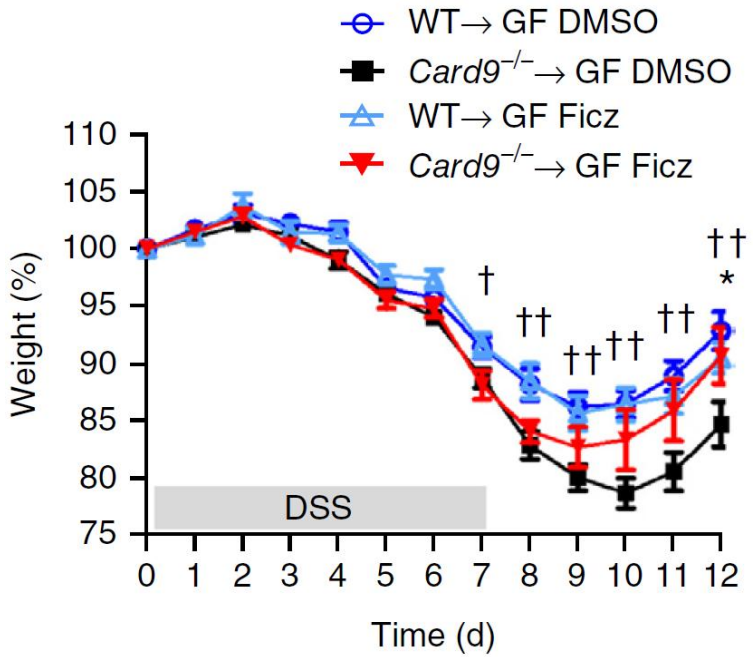


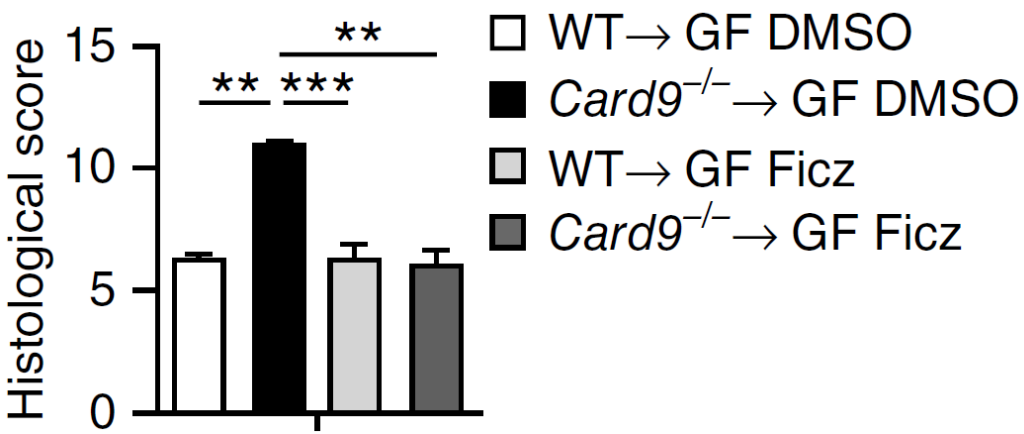
Card9$^{-/-}$ mice exhibits impaired tryptophan metabolism

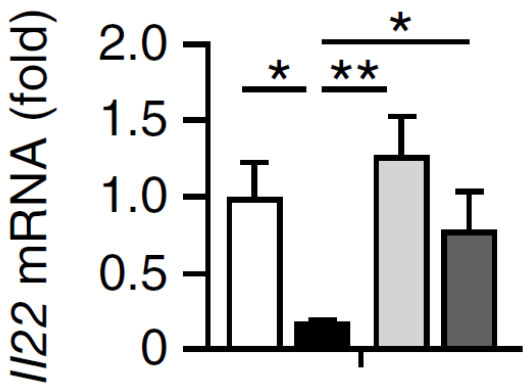
Can we rescue the phenotype with AhR agonists?

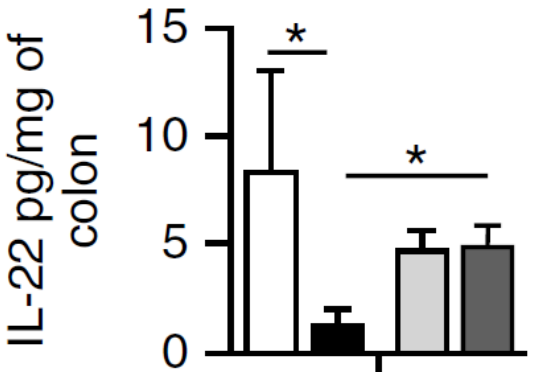


AhR agonist rescue the phenotype in *Card9*$^{-/-}$→ GF mice



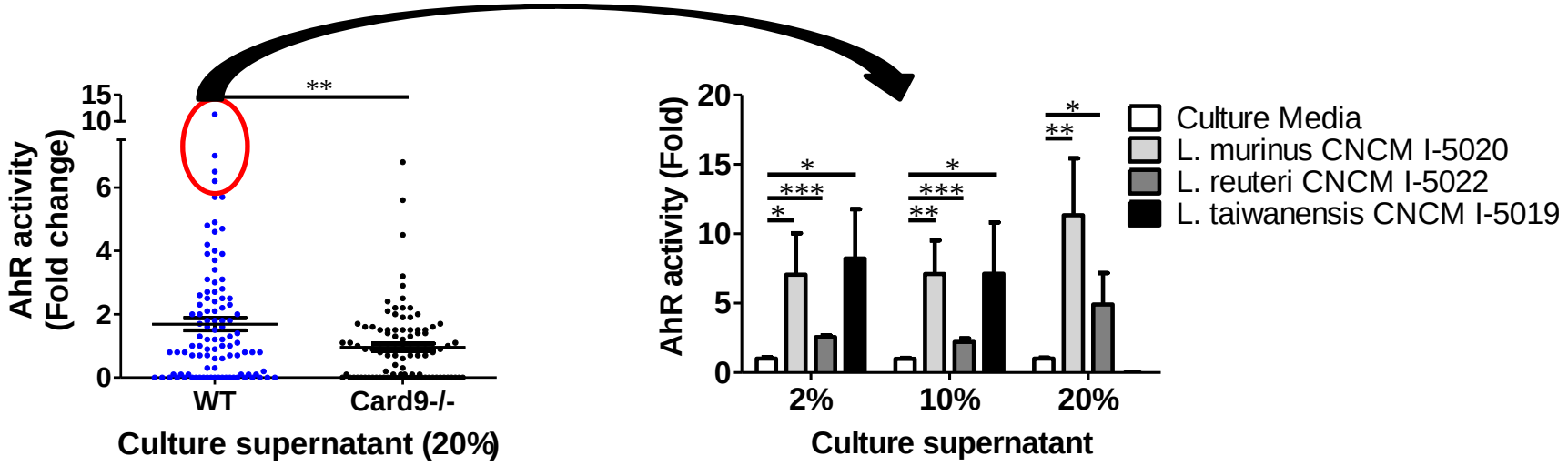


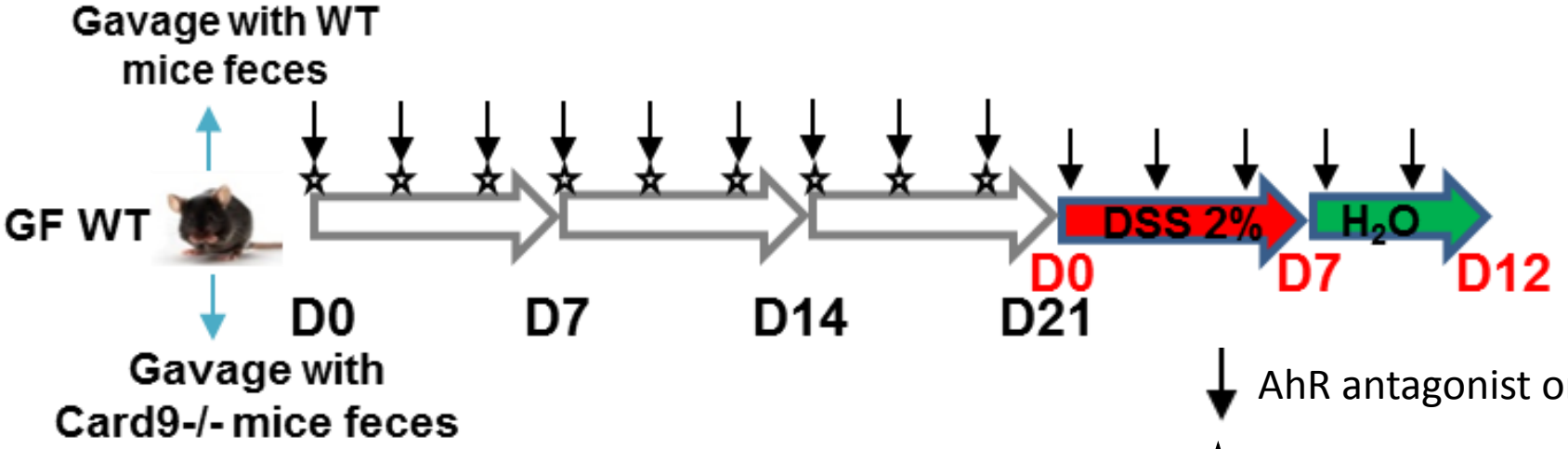




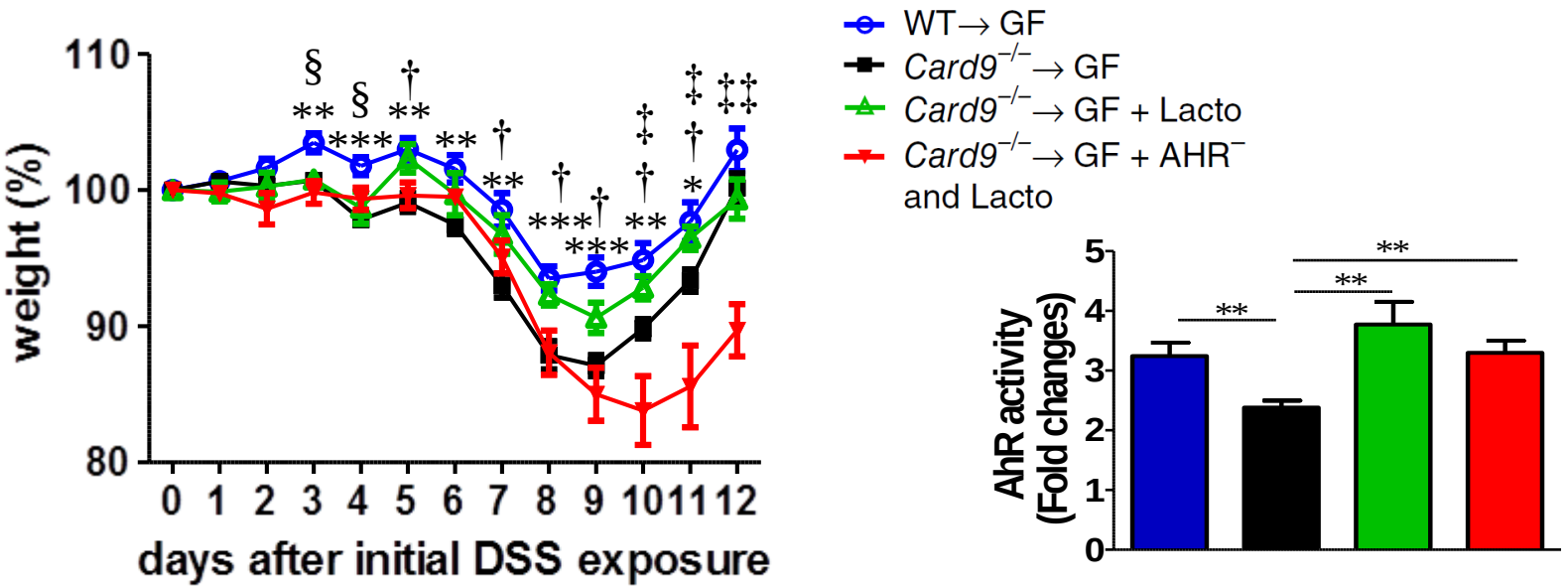
Lamas et al. Nature Medicine 2016

AhR ligand-producing bacteria rescue the phenotype in *Card9*$^{-/-}$→ GF mice



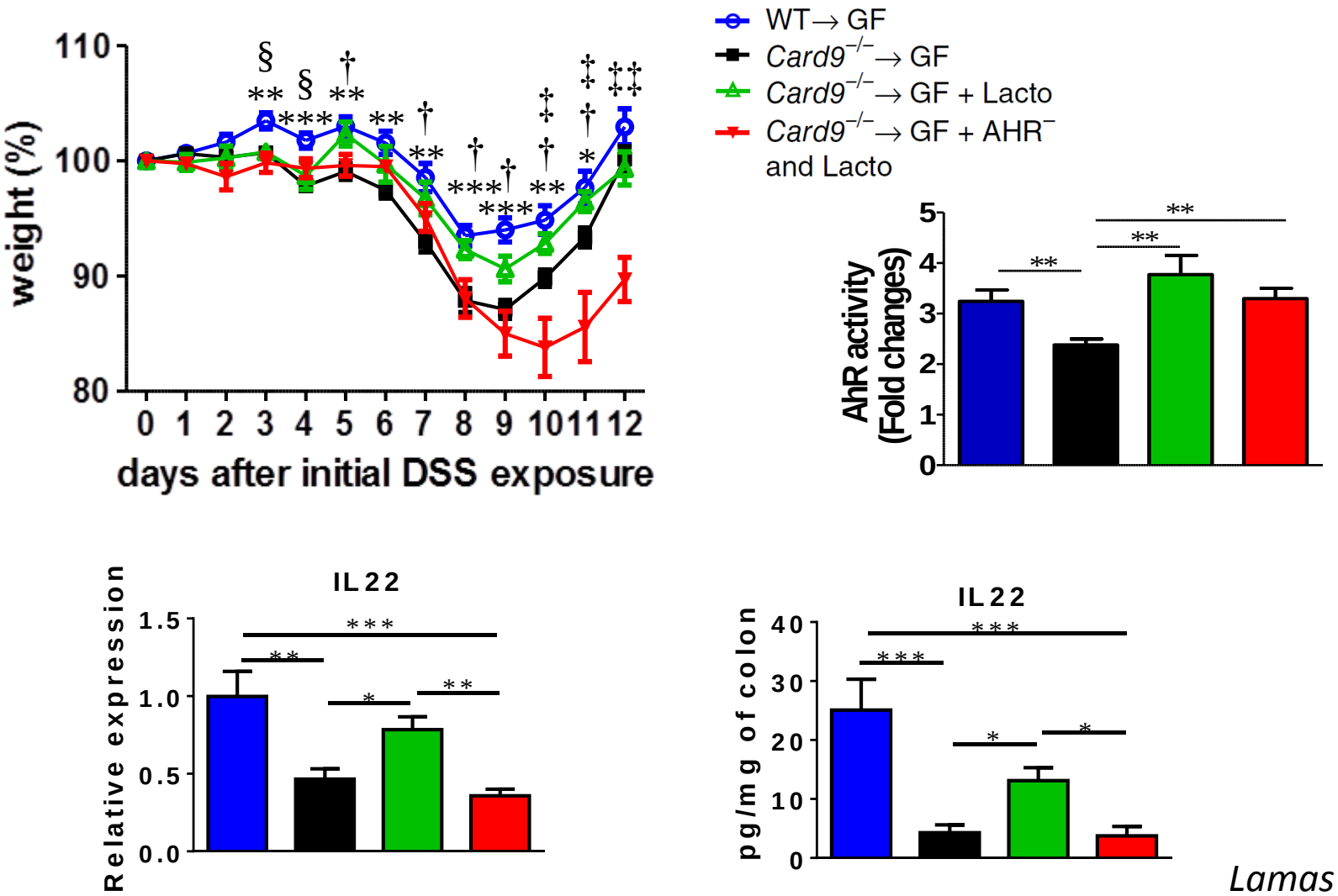


AhR ligand-producing bacteria rescue the phenotype in *Card9*$^{-/-}$→ GF mice



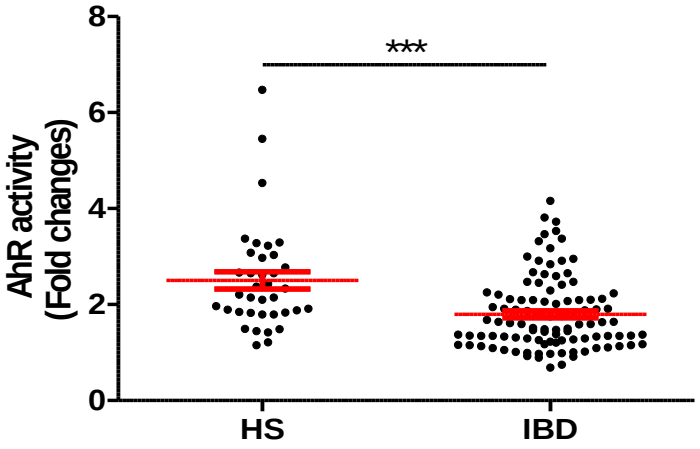
Lamas et al. Nature Medicine 2016

AhR ligand-producing bacteria rescue the phenotype in *Card9*$^{-/-}$→ GF mice

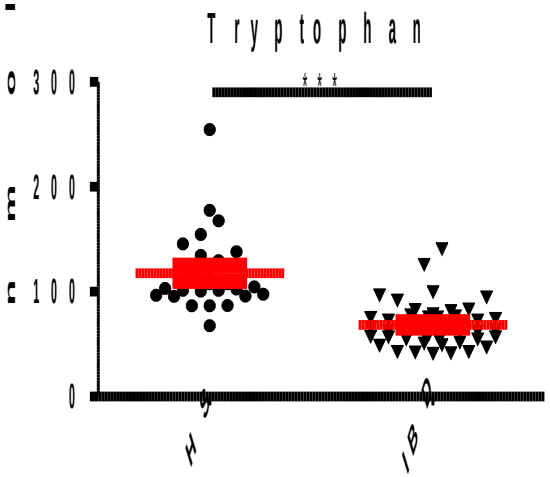


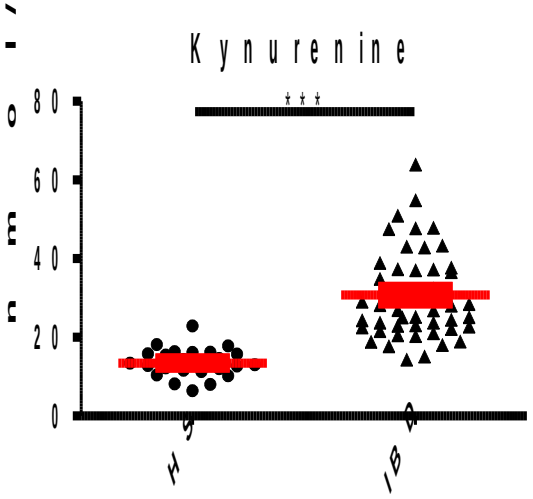
Lamas et al. Nature Medicine 2016

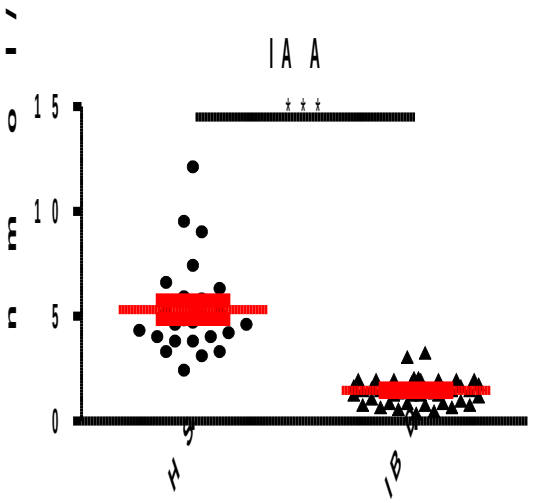
Relevance in Human?



IBD: n = 112
HS : n = 37



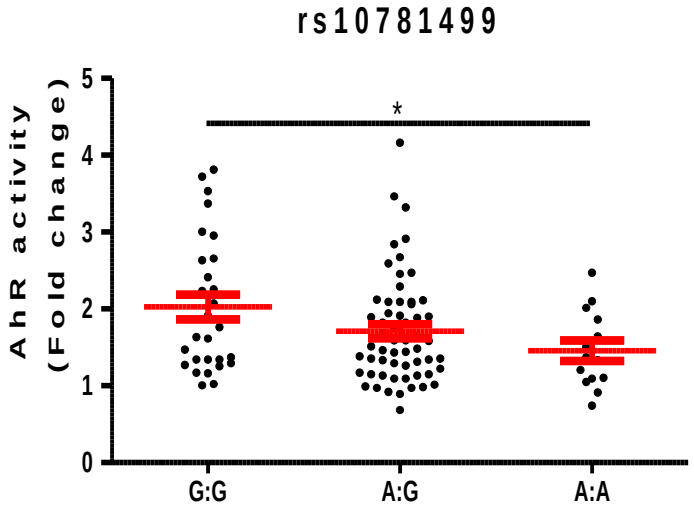


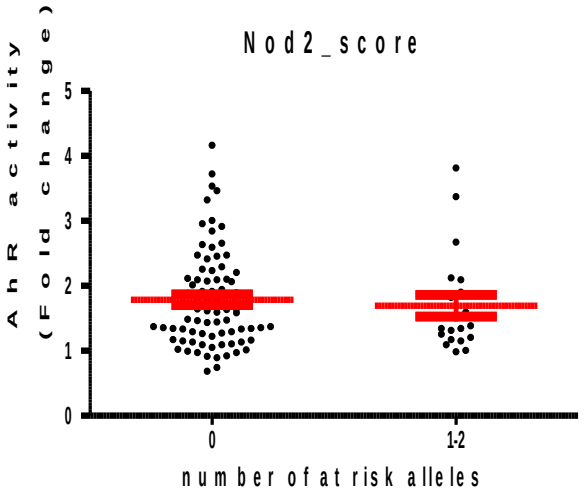


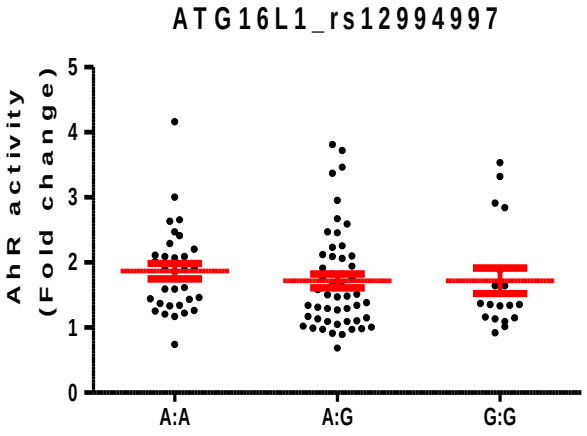
Lamas et al. Nature Medicine 2016

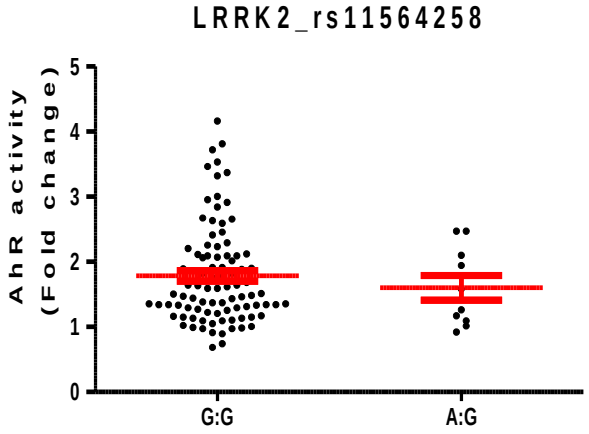
Relevance in Human?

Card9 SNP associated with IBD





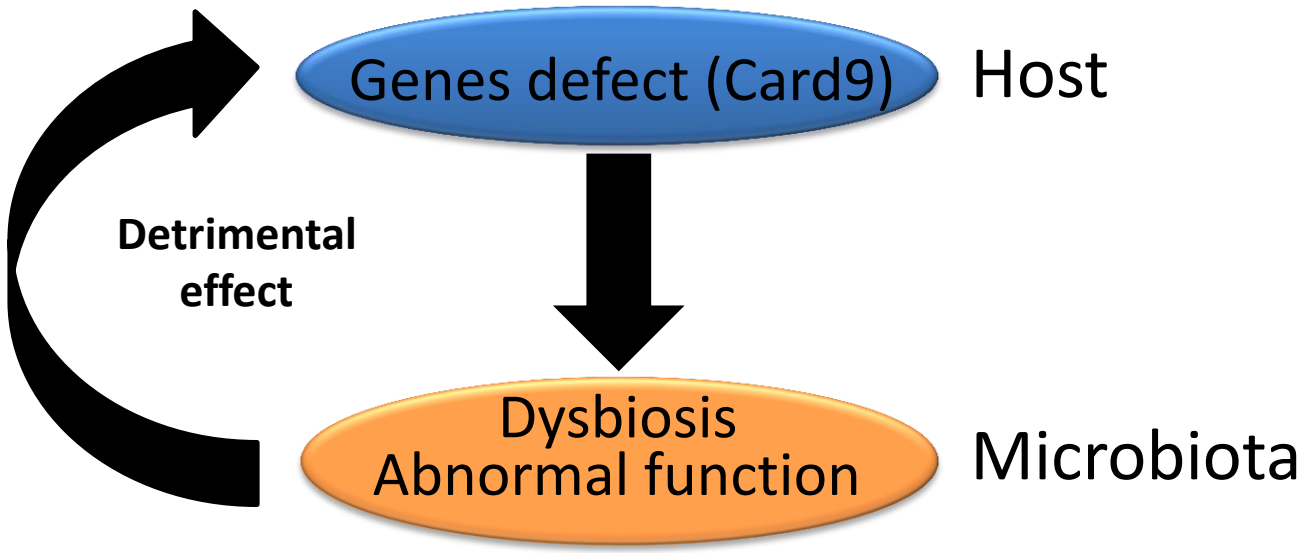




Lamas et al. Nature Medicine 2016

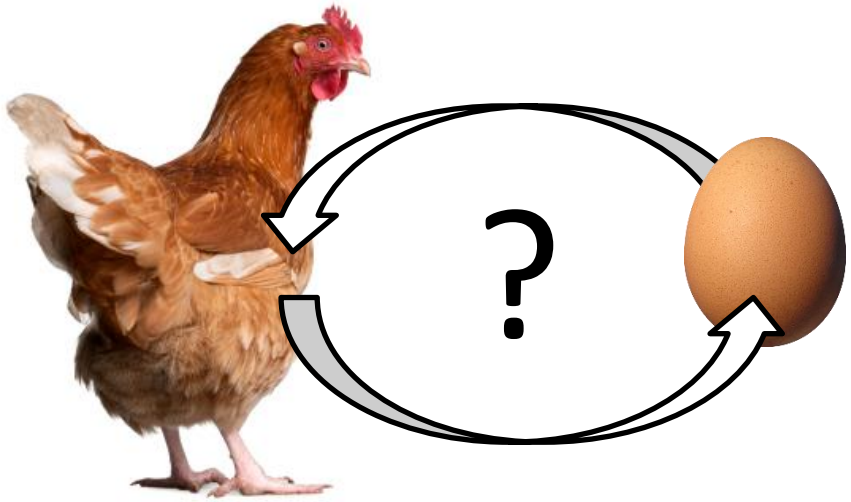
Conclusion

- Gut microbiota has a central role in IBD pathogenesis
- It is under the influence of both environmental and genetic factors



Conclusion

- Gut microbiota in IBD pathogenesis: chicken or egg?



Both!

P Seksik
D Rainteau
JP Grill
L Brot

Inserm U1157

UPMC PARIS UNIVERSITAS

Sokol's lab

INRA SCIENCE & IMPACT

Micalis

P Langella
L Bermudes
JM Chatel
M Thomas
F Chain

B Lamas
V Leducq
S Jegou
C McQuitty

M Lavie-Richard
ML Michel
C Bridonneau
G Da Costa
J Natividad
B Sovran
J Planchais
A Demoget
N Breyner

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Saint Antoine Hospital

L Beaugerie I Nion-Larmurier
J Cosnes A Bourrier
P Seksik C Landman

Collaborators
HP Pham ILTOO Pharma
S Taleb UMRS 942 Inserm
JM Launay Unit 970 Inserm
RJ Xavier Broad /Harvard / MGH

Agence Nationale de la Recherche ANR

erc

JPI HDHL

harry.sokol@aphp.fr