FHU PaCeMM

Fédération Hospitalo-Universitaire
Paris Center for Microbiome Medicine

2ème Séminaire des
Doctorants & Post-doctorants De la FHU

Mardi 16 janvier 2024
09h00 à 13h00
Siège APHP - Hôpital Saint-Antoine, Paris

Titre : *Ruminococcus gnavus* in Spondyloarthritis, story of a commensal killer

Intervenant : Manon Jacoutot

Directeur de thèse : Pr Maxime Breban

Co-directeur de thèse : Pr Dirk Elewaut

Equipe : UMR 1173 INSERM/Université Paris-Saclay

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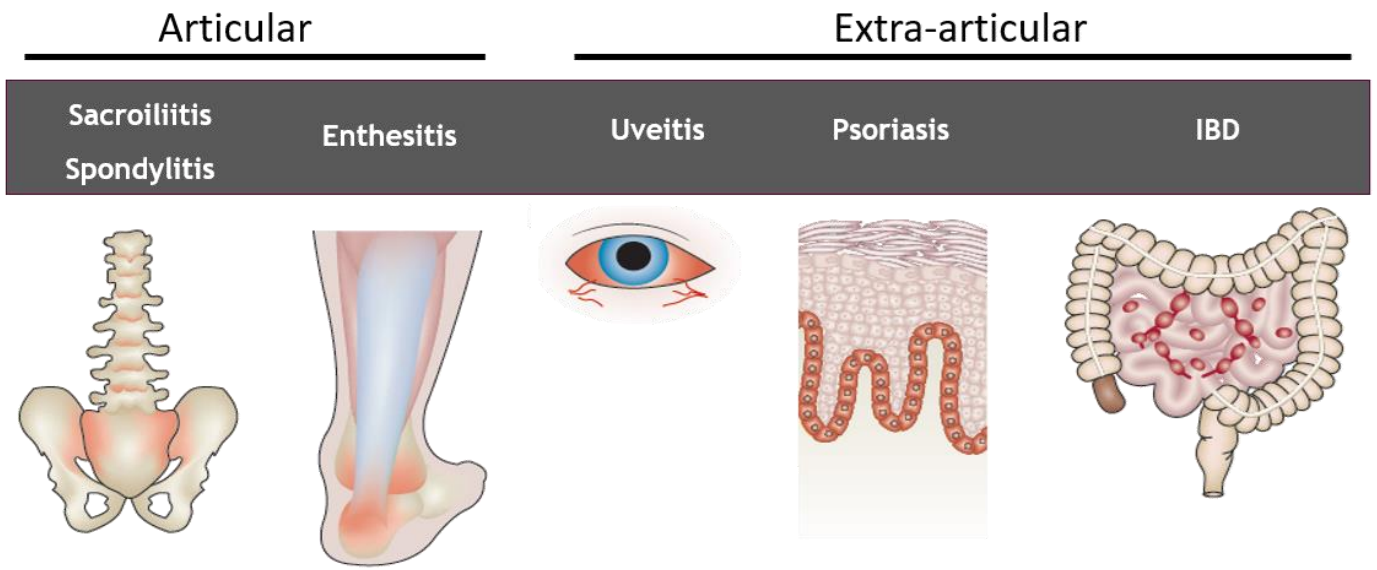
Spondyloarthritis (SpA)

- Chronic inflammatory rheumatism
- Prevalence: 0.43% among french adult population
- Strong association with HLA-B27 (90% of AS patients)



Costantino *et al*, Ann Rheum Dis, 2015

Association between SpA and *R. gnavus*

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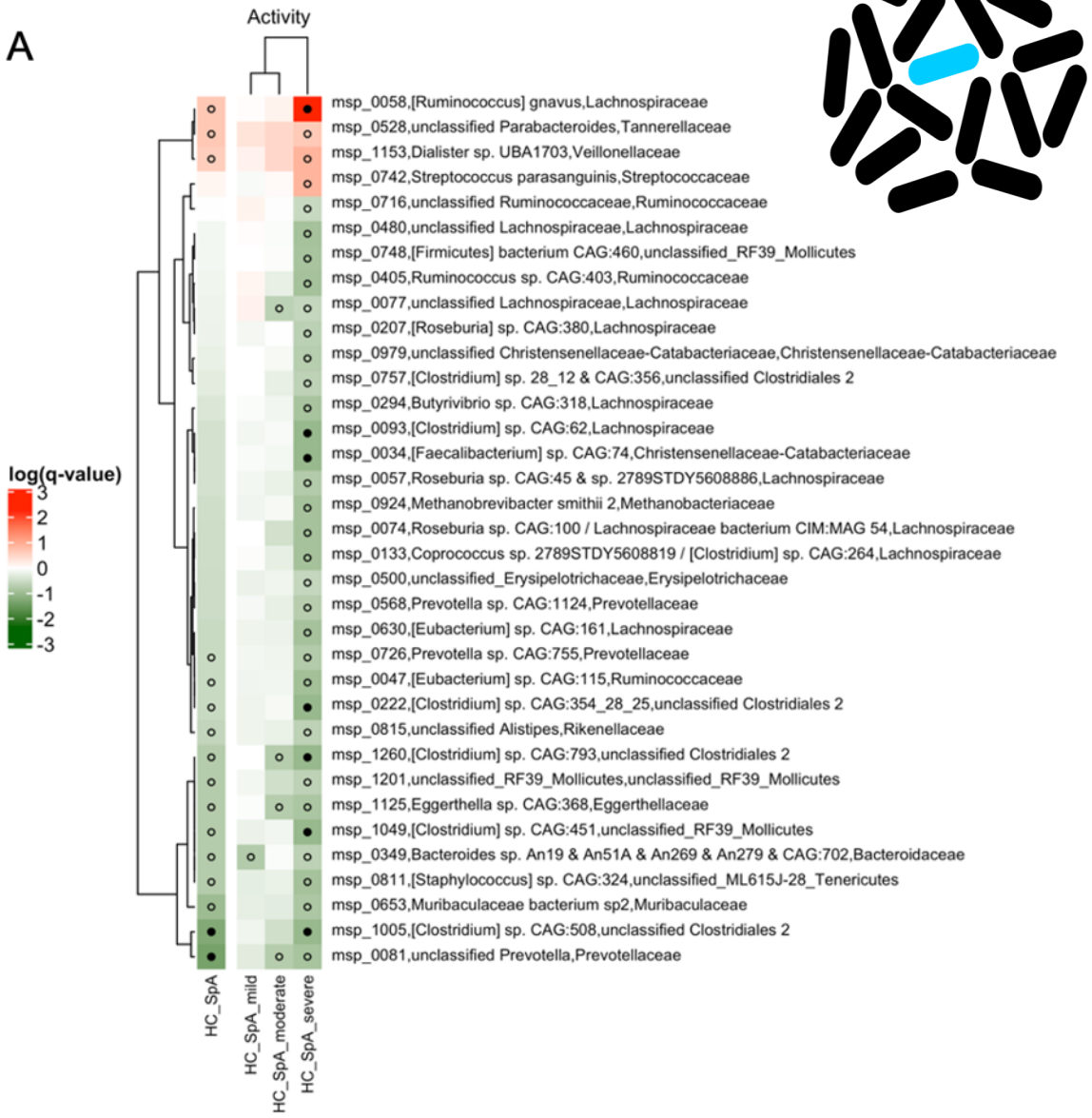
- Specific dysbiosis during SpA different from RA dysbiosis
- Relative abundance of *Ruminococcus gnavus* correlated with SpA activity



Breban *et al.*, Ann Rheum Dis, 2017
Berland *et al.*, Arthrritis Rheumatol, 2022

Ruminococcus gnavus

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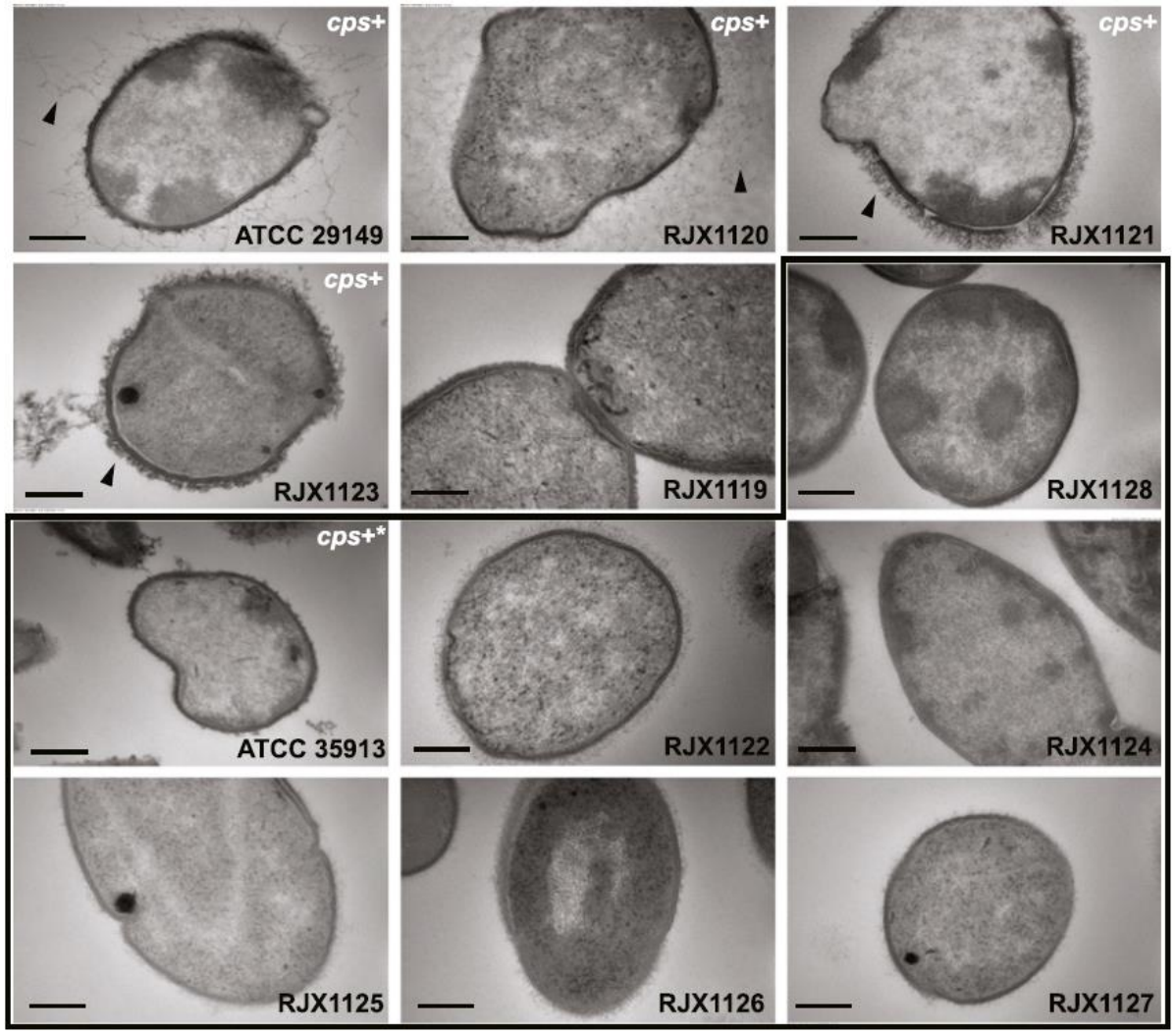

- Anaerobic gram-positive bacterium of the digestive tract, known to be associated with IBD
- Known properties of *R. gnavus* :
  - Mucolytic activity
  - Proinflammatory polysaccharide
  - Aerotolerance
  - Presence of capsule with potential anti-inflammatory features

Moore *et al,* Int. J. Syst. Evol. Microbiol., 1976
Hall *et al. Genome Medicine*, 2017
Henke *et al, PNAS*, 2019
Henke *et al, PNAS*, 2021

Aims of my thesis

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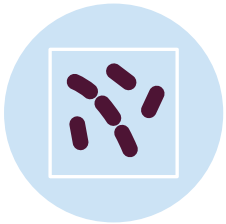
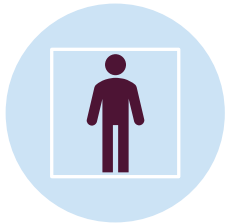
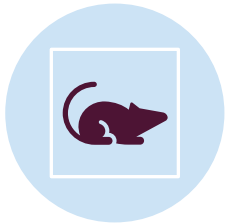


Are *R. gnavus* strains in SpA patients different from those in healthy controls?



Do *R. gnavus* elicit an immune response in SpA and healthy individuals?



Are *R. gnavus* pathogenic in SpA-prone animal models?

R. gnavus isolation protocol

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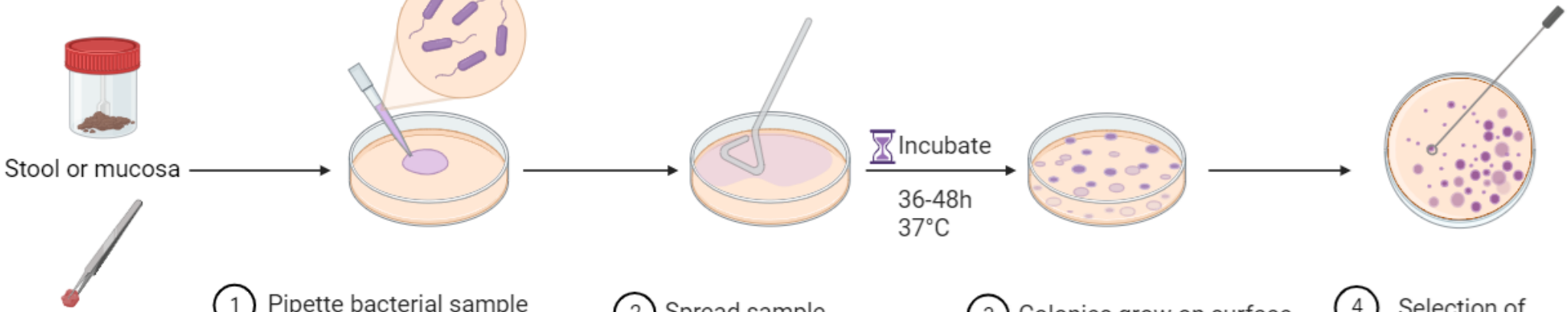
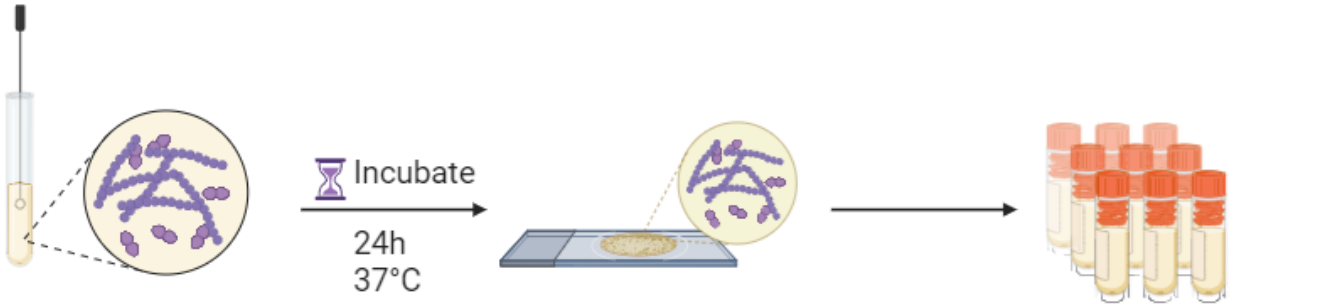
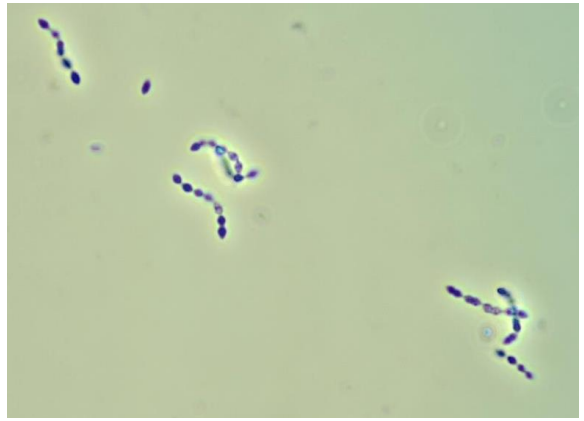
All culture steps are realized in anaerobic conditions



1. Pipette bacterial sample onto surface of rich medium with **colistin**
2. Spread sample evenly over surface
3. Colonies grow on surface
4. Selection of individualized colonies



5. Subculture in liquid rich medium
6. Screening by optic microscopy and specific qPCR
7. Storage at -80°C



R. gnavus biobank establishment

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	SpA patients	Healthy controls (HCs)
Stools	8/21 (38%)	1/11 (9%)
Mucosa	10/11 (91%)	4/11 (36%)
Sequenced strains	22 (from 13 individuals)	6 (from 4 individuals)

SpA patients and HCs are selected for stool sample collection

We generally obtain several colonies per individual. These colonies can be different.

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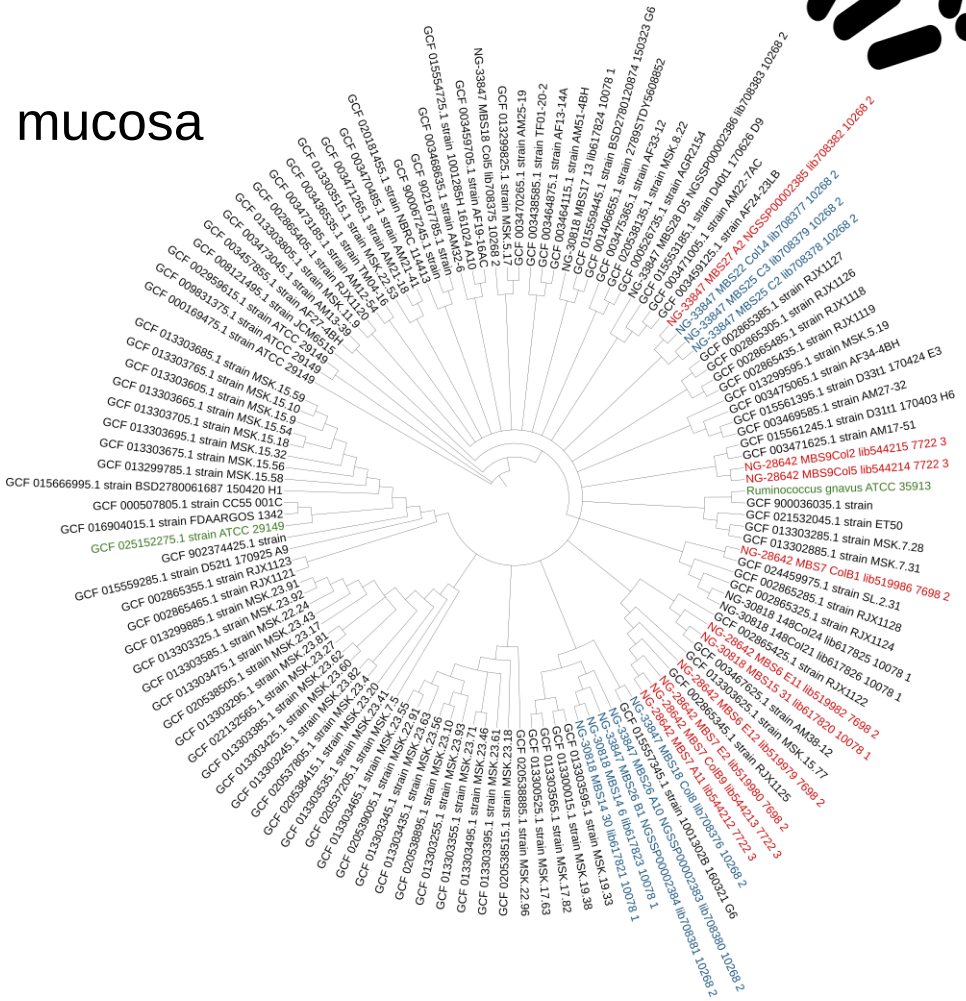
Conclusions 1

- *R. gnavus* isolation is more efficient in SpA patients mucosa
- Sequencing allowed to identify different strains

⇨ Are all *R. gnavus* strains proinflammatory?



Aims of my thesis

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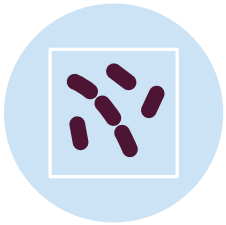

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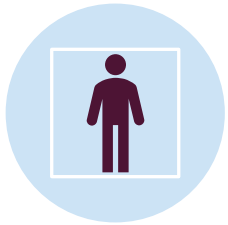

Do *R. gnavus* elicit an immune response in SpA and healthy individuals?

Are *R. gnavus* pathogenic in SpA-prone animal models?

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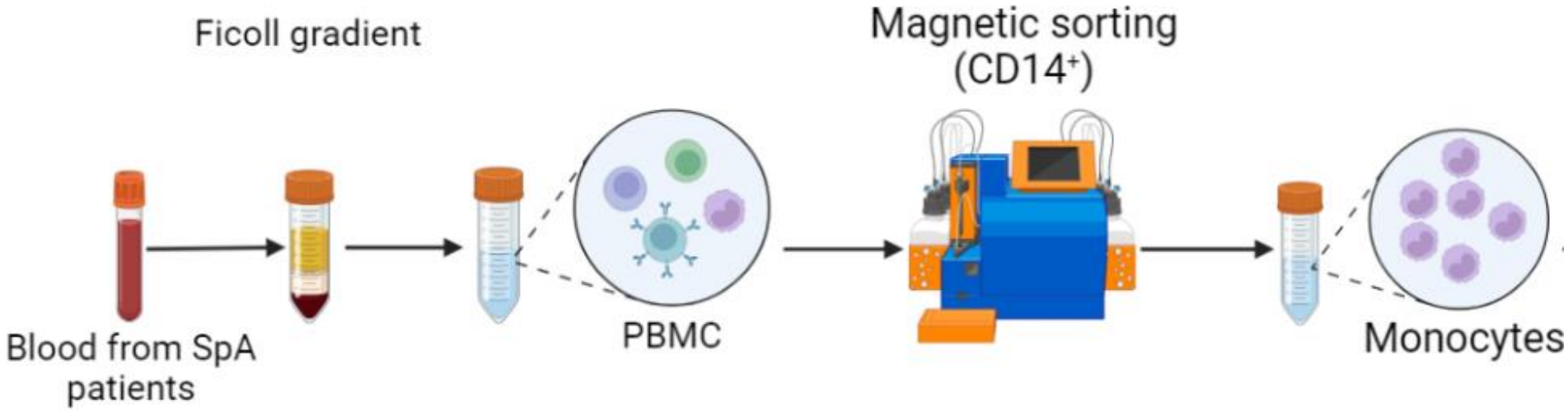
Is *R. gnavus* proinflammatory during SpA?



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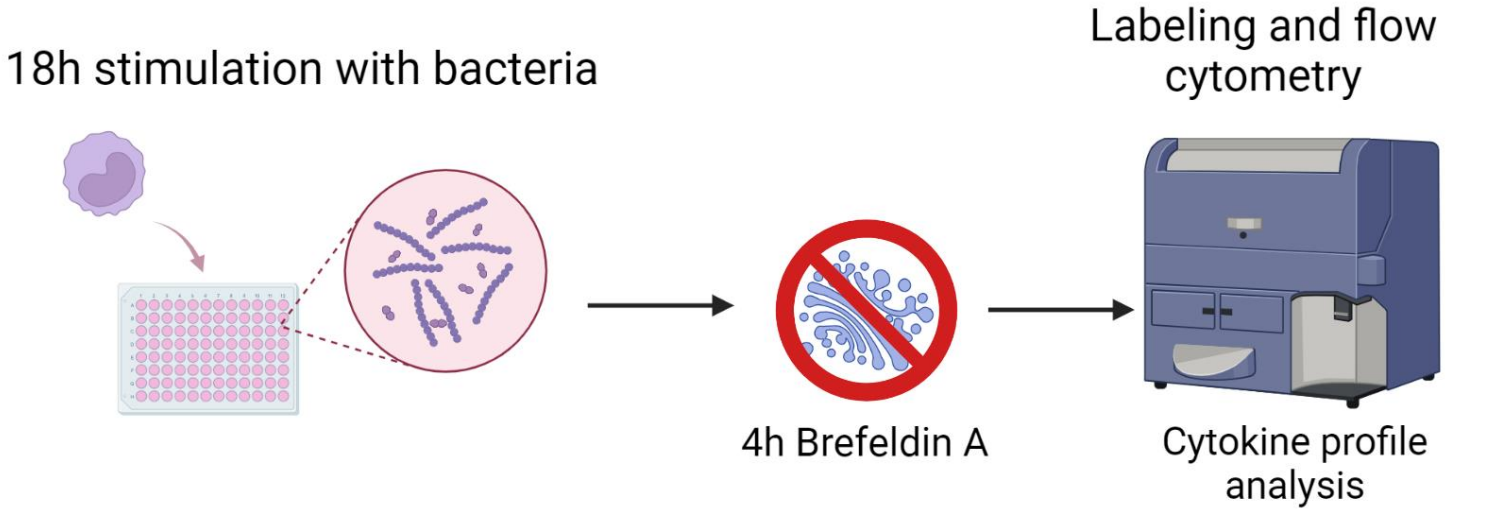

Cytokine analyzed :
TNF

Unstimulated	
SpA1	10 bacteria for 1 cell
SpA2	
SpA3	
SpA4	
HC1	
HC2	
HC3	
HC4	

R. Gnavus strains from SpA3 and HC3 are highly proinflammatory

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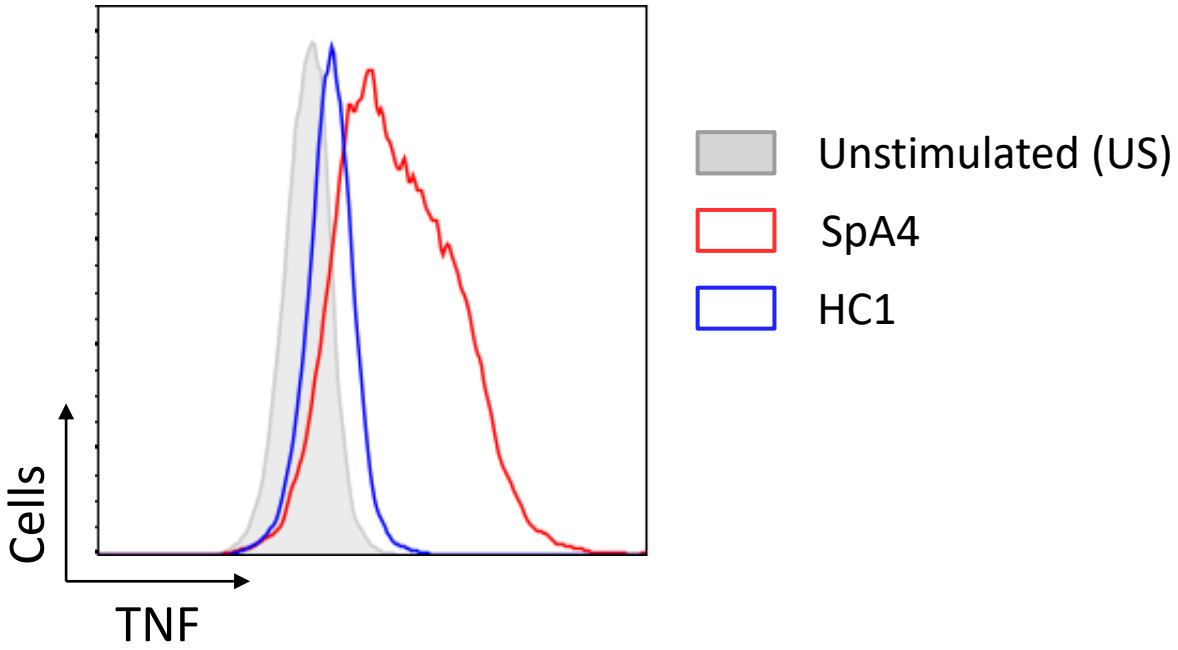

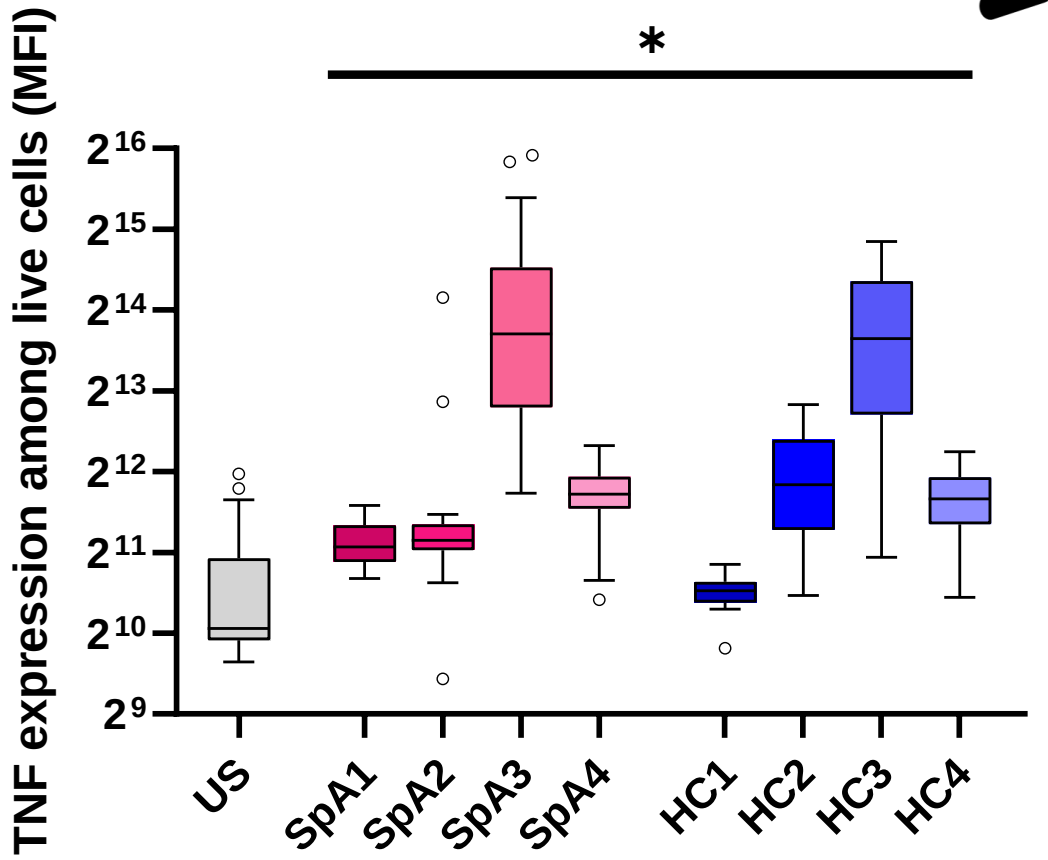

n≥15 SpA patients
Wilcoxon test compared to US, *p<0,05

Identification of different proinflammatory profiles of *R. gnavus* strains

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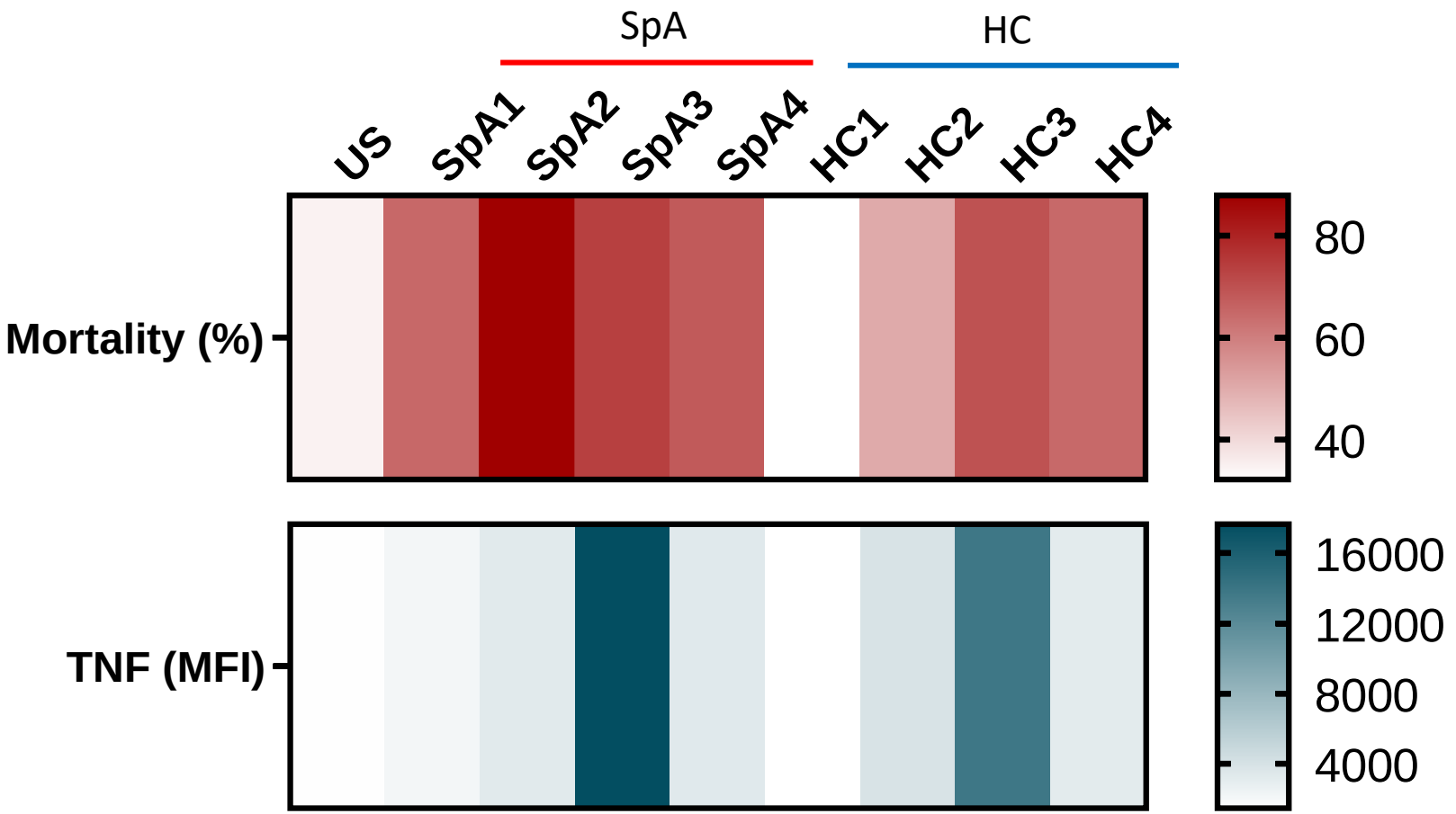

Conclusions

- *R. gnavus* induces TNF production by monocytes

- Different proinflammatory profiles have been identified in a strain-specific manner

Perspectives

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- Growing biobank → 200 sequenced colonies

- Identification of *R. gnavus* recognition pathway:
  - TLR neutralization on monocytes (TLR2, TLR4 and TLR5)
  - Component nature (proteins, DNA, RNA, peptidoglycans)

- *R. gnavus* strains selection during SpA?
  - Growth curves
  - Mucin degradation
  - Aerotolerance

Acknowledgments

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