### THESIS TOPIC

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**Theoric title:** Multimodal treatment of intestinal carriage of multi-drug resistant bacteria with probiotics, prebiotics and quorum-sensing inhibitors

**3 keywords:** antibacterial agents, resistance, microbiota

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<th>Unit / team:</th>
<th>EE 1701 MiHAR Nantes</th>
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**Supervisor's name:** Michel Dion

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**Socio-economic and scientific context (approximately 10 lines):**

Antimicrobial resistance is one of the biggest public health challenges of our time. Intestinal colonization by a MDRO may evolve from asymptomatic carriage to various infections - mainly urinary, digestive and bloodstream infections. Furthermore, digestive carriage of MDRO can lead to environmental contamination and transmission to healthy or diseased subjects. Hence, decreasing and even deleting the digestive carriage of MDRO is of major importance to limit the world-wide spread of antimicrobial resistance. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Using live bacteria to counter intestinal colonization by MDRO after antimicrobial therapy is becoming increasingly plausible with the improving knowledge of the structure and functions of the intestinal microbiota. Prebiotics are substrates that are selectively utilized by host microorganisms conferring a health benefit. Quorum sensing is a key process for the production of virulence determinants in pathogenic bacteria. *Bacillus*-induced abrogation of *S. aureus* intestinal colonization is mediated by the inhibition of *S. aureus* quorum sensing.

**Working hypothesis and aims (approximately 8 lines):**

The aim of this PhD thesis is to identify multimodal preventive and curative treatments of intestinal carriage of MDROs in a murine experimental model. Multimodal treatments will include non pathogenic bacteria (so-called probiotics), in particular *Bacillus subtilis*, prebiotics and quorum sensing inhibitors. Targeted MDROs are ESBL producing *Escherichia coli* and *Klebsiella pneumoniae*, carbapenemase producing *Klebsiella pneumoniae*, Glycopeptide Resistant *Enterococcus faecium*. 
**Main milestones of the thesis (approximately 12 lines):**

1° *Selection of MDROs and potential treatments of MDRO intestinal carriage*

- **MDROs** that will be used in the intestinal colonization murine model will be selected from clinical isolates that have been studied in the MiHAR Lab.
- **Bacillus spp strains** : *Bacillus spp* strains will be screened from environmental samples or from faeces of mice treated with amoxicillin. They will be selected according to 2 criteria: (i), ability to persist in murine intestinal microbiota; (ii), in vitro activity against targeted MDROs (either growth inhibition or quorum sensing inhibition).
- **Prebiotics** will be selected through a systematic review of the literature, including experimental studies that assessed the efficacy of prebiotics on intestinal colonization and/or infection.

2° *Experimental assessment of the activity of selected treatments on MDRO intestinal carriage*

- **adaptation of the murine model of asymptomatic intestinal colonization by ESBL-producing *E. coli***
  - Intestinal dysbiosis will be induced with amoxicillin according to a murine model currently used in the laboratory. The murine model will be adapted to allow a persistent carriage of *Bacillus spp*. *Bacillus* carriage will be assessed with culture and qPCR.
- **in vivo activity of *Bacillus spp* against intestinal colonization by ESBL-producing *E. coli***
  - The activity of each treatment, alone and in combination, will be assessed on the intestinal and faecal concentrations of cultivable ESBL-producing *E. coli*, by comparison with a control group.

3° *Relationship between microbiome architecture and therapeutic efficacy*

The microbiome structure will be assessed by amplification of the V4 region of bacterial 16S rRNA. Analyses will be conducted to assess whether treatments (*Bacillus spp*, prebiotics, flavonoids) alter the murine intestinal microbiome, and whether treatment efficacy is explained by the alteration of the intestinal microbiotas. Furthermore, if the treatment efficacy shows inter-mouse variability, we will assess whether the individual pre-treatment microbiome predicts treatment's activity.

**Scientific and technical skills required by the candidate (2 lines):**

- Routine methods in bacteriology (including culture, numeration, identification), qPCR
- Murine model

**3 publications from the team related to the topic (last 5 years):**

doi:10.1038/s41598-018-24342-x.


National and international collaborations:

The Knights Lab, University of Minnesota at Minneapolis