Pharmacological Testing of Chemotherapy in PDX Models: Impact on Gut Microbiota

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INTRODUCTION

The national project IMODI (Innovative MODels Initiative) including 18 partners, aims to develop new patient-derived tumor graft (PDX) models that will be used for speed up innovative therapeutic approach development. Well characterized PDX models that come from 8 types of human cancer represent a suitable tool for preclinical evaluation of novel therapeutic strategies in cancer.

The microbiota plays a major role in health and disease. In this project, Biofortis Mérieux NutriSciences explores gut microbiota association to cancer. The objective of this study is to identify the impact of pharmacological treatment on microbiota in PDX models, and especially on PDX models of lung cancer.

MICROBIOTA APPROACH

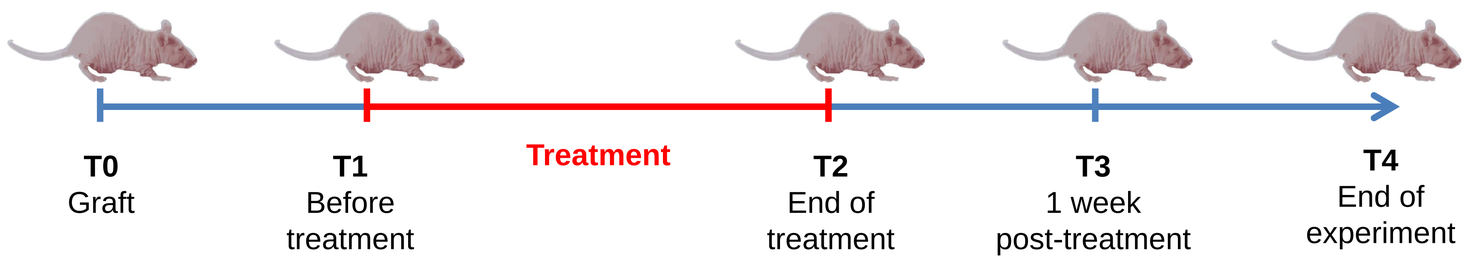
ESTABLISHMENT OF LUNG PDX MODELS → **TREATMENT & STOOL SAMPLE COLLECTION** → **METASEQUENCING** → **ANALYSE OF MICROBIOTA COMPOSITION**

- 5 groups:
  - Vehicule
  - Cisplatin
  - Pemetrexed
  - Gefitinib
  - Docetaxel

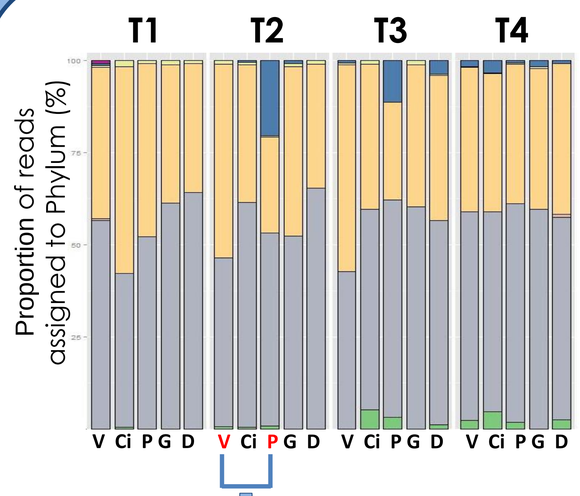
Mesure of Weight & Tumor Volume

- Targeting variable regions of the 16S rRNA gene (V3 & V4 conserved regions)
- Characterization of the microbiota composition and variation during chemotherapy

- Experimental Timeline:



RESULTS



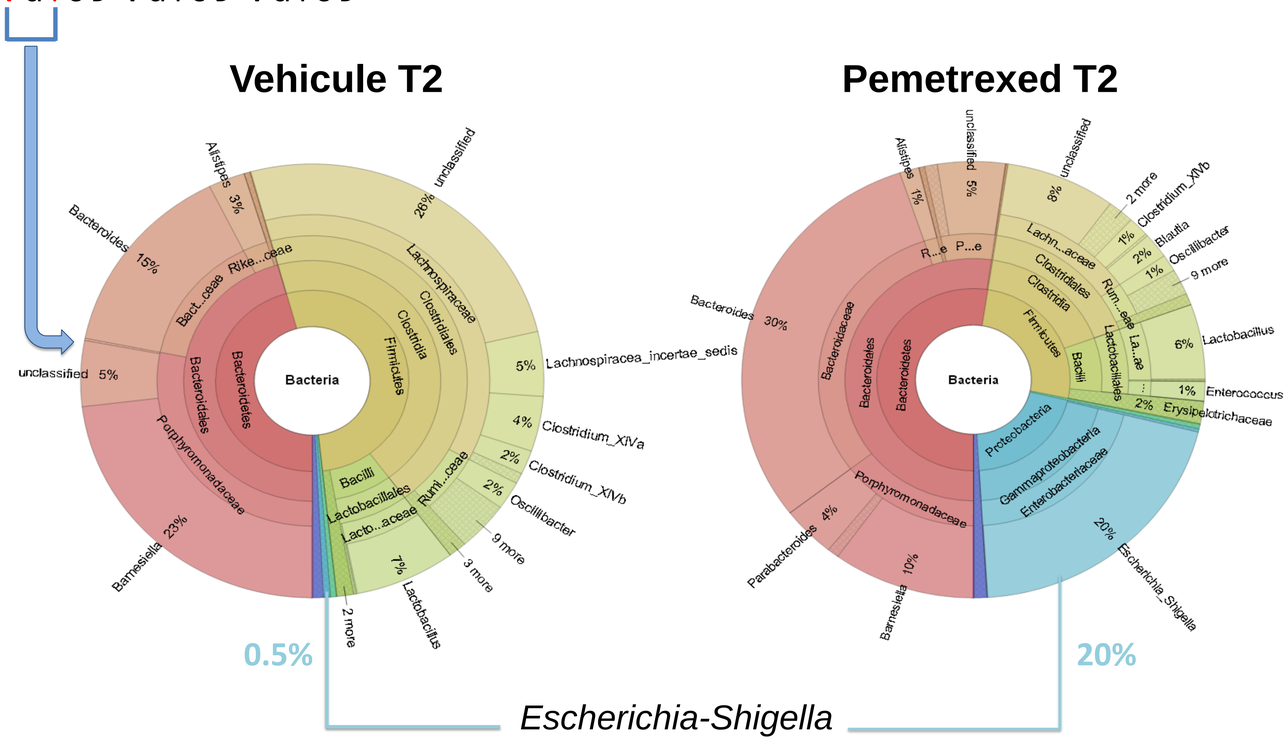
MICROBIOTA COMPOSITION

Phylum: ↗ Proteobacteria

Family: ↗ *Enterobacteriaceae*

Genus: ↗ *Escherichia-Shigella*

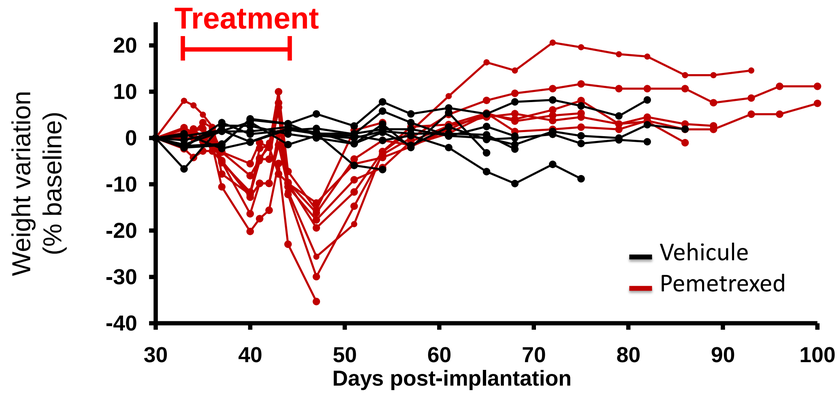
after **Pemetrexed** treatment



Graph based on Krona methodology from Ondov *et al.* BMC Bioinformatics 2011, 12:385

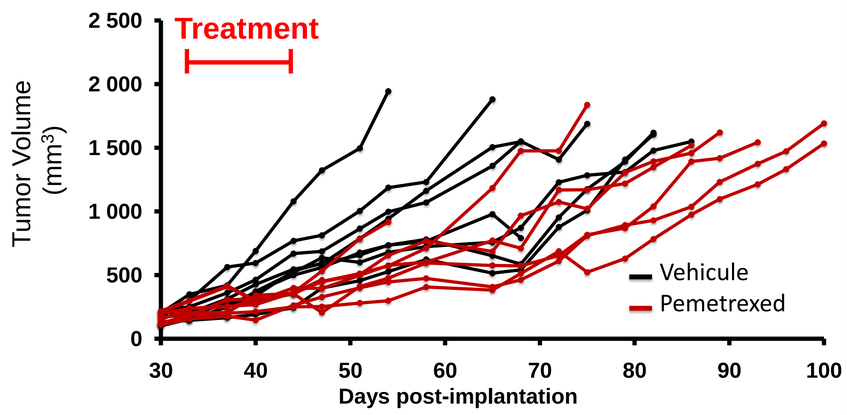
WEIGHT REPORTING

For Pemetrexed per mice



→ Significant weight loss during 4 days following treatment

TUMOR VOLUME



→ No significant decrease of tumor volume

CONCLUSION

Our results support that chemotherapeutic agents would have an effect on the microbiota composition, with a direct or indirect relation between microbiota composition and weight. Following chemotherapy, the proportion of harmful bacteria can raise and consequently increase health disorders.
This study indicates that microbiota represents an important additional “indicator” for evaluating the efficacy of pharmacological treatments and their disturbing effects on microbiota. It would be very interesting to develop therapeutic approach to limit the side effect of chemotherapy and microbiota imbalance.