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Collinsella: genomics, physiology and putative biomarker in response to immunotherapy

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State of the Art

1.1 The human gut microbiota

The number of microorganisms present in human body is approximately **10^{13} - 10^{14}** cells, ten times the number of cells in an individual. These microorganisms encode a number of unique genes that is **100 times** higher than our own, constituting **a true second genome**. Most of these microorganisms reside in the gastrointestinal tract in a mutualistic relationship with the host. The host and its symbionts should be studied as a single evolutionary unit, they are a complex organism, a true ecosystem. Disruption of the homeostatic composition of the microbiota, known as "**dysbiosis**", has been associated with numerous diseases, including inflammatory bowel disease (IBD), cancer, autism, and metabolic disorders such as diabetes, cardiovascular diseases, and obesity.
These microorganisms influence metabolic processes and have recently been found to play a **key role** in modulating the immune response.

1.2 Immunotherapy

Immunotherapy with immune checkpoint inhibitors (**ICIs**) has dramatically improved survival in a range of tumours over the past decade. ICIs targeting PD-1 and PD-L1, alone or in combination with CTLA-4, are used as first-line therapy for advanced-stage tumours, including metastatic melanoma (MM), non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The 5-year overall survival rates for patients with MM have increased from 16% to 52% following the introduction of combined anti-CTLA-4 and anti-PD-1 therapy. However, at least half of the **patients do not respond** to the therapy.
Despite the emerging success of immunotherapy, it remains clinically important to identify, in advance, patients who may respond to treatment based on the **composition of the gut microbiota** through metagenomic studies. Numerous studies are enriching the scientific literature, focusing on identifying microbial biomarkers that can characterize responders and non-responders to immunotherapy, with the aim of predicting and enhancing their response to the drug.
Immune checkpoint inhibitor-based therapy does not directly target tumour cells but rather their interaction with the patient's immune cells. Several studies report that the composition of the gut microbiota mediates the complex interaction that determines the immune response. Therefore, a thorough analysis of the gut microbiota could prove crucial for optimizing the efficacy of immunotherapeutic treatments and personalizing cancer care based on the individual characteristics of patients.

Future objectives of the project:

- Expand the metagenome dataset to increase data robustness and representativity.
- Continuing studies on the physiology and comparative genomics of *Collinsella* genus, aiming to better understand its role in the response to immunotherapy and in human gut microbiota.
- Refine, implement and optimize the work pipeline useful to identify microbial biomarkers that predict response to immunotherapy, with the aim of improving the accuracy and efficiency of these therapies by exploiting the microbial populations that colonize the human gut microbiota.

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Gantt diagram for this PhD thesis project		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*
A1)	***Dataset Creation***																								
A2)	***Taxonomic Classification***																								
A3)	***Microbial Composition Analysis***																								
A4)	***Search for Microbial Biomarkers***																								
A5)	***Comparative study***																								
	Physiology																								
	Genomics																								
A6)	***Thesis and Paper preparation***																								

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