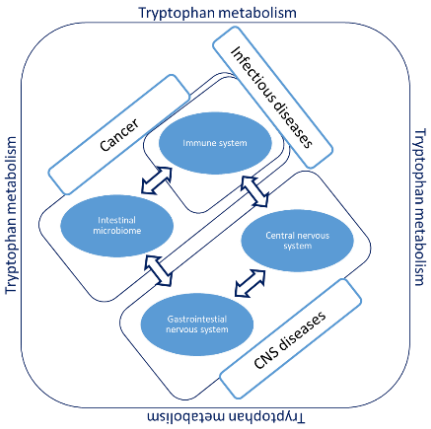
TRYPTOPHAN METABOLITES AND THEIR METAL COMPLEXES AS NEW DRUGS FOR COLORECTAL CANCER TREATMENT AND HUMAN GUT MICROBIOTA REGULATION



Colorectal cancer (CRC) is one of the most malignant cancers, being the second cause of cancer death in Europe (source WHO, regional office for Europe) and the third most common cancer diagnosed in the United States (data from American Cancer Society). Due to its severity, efforts are required for the search for an efficient and targeted strategy for its therapy. **CRC** development, which occurs in the colon or rectum, is highly affected by diverse metabolic abnormalities **CRC** always starts with an inner tumor or tissue in the rectum or colon being the development of the disease highly affected by many metabolic abnormalities. Among them, tryptophan (**Trp**) metabolic disorder is one of the metabolic pathways disfunctions closely associated to **CRC**. **Trp** is an essential amino acid with a large variety of physiological functions, with a fundamental role on the regulation of immune, central nervous and gastrointestinal nervous systems, and with a significative influence on the intestinal microbiota. Due to its physiological relevance, it is not surprising that imbalances in the level of **Trp** and its metabolites (**TrpM**) are associated with a wide range of human pathologies, including depression, schizophrenia, autoimmunity, neurodegeneration, and cancer. **Trp** is metabolized by two different pathways (via kynurenine or serotonin), being the kynurenine metabolic path the main one. It occurs mainly in the small intestine, where **Trp** and **TrpM** have inhibitory effects on inflammatory reactions resulting from intestinal diseases, limiting disease progression and, consequently, playing an active role in human health. Interestingly, the gut microbiota can also regulate the absorption and metabolism of dietary **Trp** contributing to the modulation of intestinal immunity. In summary, **Trp** metabolic disorder can affect the balance of intestinal microbiota leading to inflammation that contributes to the progression of **CRC**, and vice-versa, i.e., **CRC** development results in inflammation that changes the homeostasis of intestinal microbiota affecting **Trp** metabolism. Is also important to highlight the relevance of metal homeostasis on the balance and quality of intestine microbial community, being known that dietary metal ions have the potential to change the distribution and function of the microbiota.

Taking all this information into account, two major questions rise: **"Can TrpM metal complexes tune Trp metabolism? Can they be used as anti-tumoral drugs on colorectal cancer?"** The answer to these questions will be pursued combining the information acquired via dedicated research investigations, namely: i) do **TrpM** metal complexes present antiproliferative and anti-migratory effects on cancer cells? If yes, how is the mechanism that leads to the cell dead? What are the targets? ii) are they cytotoxic (or not) for relevant microbiota bacteria? iii) are they able to tune human microbiota? iv) does their presence affect the usual **Trp** metabolic pathways? And finally, v) can chemical speciation explains their biological activity? Can further biological responses be modeled using thermodynamic data?

All these questions triggered our interest on the systematic study of **TrpM**, seeking for a better understanding on the role of **Trp** and **TrpM** on **CRC,** aiming to ultimately contribute to the development of more effective therapeutic procedures for one of the most malignant cancers.

In this project we will combine diverse techniques and methodologies to detect, understand (and on a later stage predict) the biological action of selected **TrpM.** We envisage to obtain data that will allow us to define in detail the chemical speciation of **TrpM** and their metal complexes in real systems (as growth medium of human cells and bacteria) and we will use it to explain and rationalize the observed biological action. With this strategy, we will combine chemical thermodynamic studies with biological assays in a very innovative and original form. Furthermore, several new metal complexes will be evaluated as anti-cancer and antibacterial agents aiming at its future pharmacological application.