

Gut microbiota-dependent modulation of therapeutic response and side effects to irinotecan and new camptothecin analogues

Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018. Irinotecan, an analogue of the plant alkaloid camptothecin, has been used in the treatment of unresectable, metastatic or recurrent cancers of various types for more than a decade. Irinotecan is on the World Health Organization Model List of Essential Medicines, the most important medications needed in a basic health system, however, its clinical use is significantly limited due to severe side-effects. Of different strategies tested that included dose modification, structural modification, pharmacological therapies, probiotics, antibiotics, and other miscellaneous agents, none was obviously effective to prevent unpredictable irinotecan-induced toxicity. We still need, therefore, new strategies to reduce/prevent Irinotecan toxicity and, in a consequence, to improve therapeutic outcome in cancer patients. The intestinal bacteria may change the metabolism of the drug, including Irinotecan, through the generation of its toxic or non-toxic derivatives in the intestines, therefore the composition of intestinal bacteria may determine the success of therapy.

The aim of this project is to link the composition and abundances of bacterial and metabolites in stool samples with the effectiveness of Irinotecan treatment, and the severity of side effects in cancer patients, and in the experimental model of human colorectal cancer, and stool transplantation to immunodeficient mouse. Additionally, in this project we intent to evaluate mechanisms of action and potential clinical application of new camptothecin derivatives with preferable biological properties and increased cytotoxicity towards cancer cells. Our preliminary data indicate antineoplastic effectiveness of these compounds in human cancer xenografts.

We expect that determining the bacteria and metabolites profiles in stool that associate with tolerable and intolerable response to Irinotecan in humans, and in animal models of cancer, will allow defining bacteria or metabolites whose presence could predict the effectiveness of Irinotecan therapy. The results of our studies on new camptothecin derivatives in animal models of cancer will answer how the tumor growth inhibition and side effect compare to Irinotecan what could form the basis for further work on the possibility of these derivatives transition to the clinic.