

**Currently, my lab focusses on three interrelated research areas:**

**1. Elucidation of innate immune checkpoints to maintain gut homeostasis**

Immune tolerance to commensal microbiota represents an essential host defence mechanism in order to maintain mucosal hyporesponsiveness in the healthy intestine. In order to avoid overactive and inappropriate immune responses in the intestinal mucosa which may trigger inflammatory disease, TLR (Toll-like receptor) signalling must be tightly controlled. In previous work we have demonstrated that TLR2 exerts important barrier-protective functions in the intestinal epithelium. But emerging evidence suggests that the function of TLR2 is context-dependent and the net result depends on the predominant cell types involved. Intolerance between gut microbiota and mucosal immunity through aberrant TLR2 signalling has recently been implicated in the pathogenesis of inflammatory bowel disease (IBD). My lab explores the signalling mechanisms that prevent TLR2-mediated detrimental and inappropriate inflammatory responses in a cell-specific manner and thus critically assist the innate immune system in preserving mucosal homeostasis in the intestine.

**2. Role and regulation of the intestinal epithelium in health and disease**

The intestinal epithelial cell (IEC) layer serves as an important defensive barrier of the mucosal immune system that forms a bipolar interface between the vast variety of commensals and other antigens of the lumen and subjacent immune cells present in the lamina propria. 3D-cell culture technologies have become available that allow long-term culture of human primary IEC ex-vivo. Our goal is to define the complex mechanistics and functional diversity of IEC innate immunity and determine how this apparatus shapes mucosal homeostasis of the intestine. Using defined standard operating procedures, we have generated human-derived intestinal epithelial organoids from control and patient biopsies (IBD) and surgical specimens (colorectal cancer) and now characterize morphology, proliferation, survival and other cellular functions during long-term growth and cell stimulation experiments. Our aim is to identify novel therapeutic targets for the treatment of major GI disorders that affect the intestinal epithelium. For instance, we have recently shown that adding a TLR2 agonist to 3D-cultures of human colonic biopsies preserves intestinal epithelial tight junctional integrity and polarization ex-vivo.

**3. Regulatory mechanisms of xenobiotic-host metabolism mediated by gut microbiota and their consequences for cancer therapy**

Intestinal mucositis represents a common complication and dose-limiting toxicity of cancer chemotherapy. So far chemotherapy-induced intestinal mucositis remains poorly treatable resulting in significant morbidity and reduced quality of life in cancer patients. We investigate how gut microbiota and innate immunity influence toxic side effects of chemotherapy regimens and modulate anti-cancer treatment responses.

**Our methods:** Besides ex-vivo 3D-organoids, we use murine in-vivo models of acute intestinal injuries, chronic spontaneous colitis and tumorigenesis in combination with genetic and pharmacologic manipulations to test hypotheses about mucosal homeostasis, cell functions, disease progression and systemic consequences.