Title: Coordinated regulation of intestinal homeostasis and injury repair by CCN1-matricellular signaling

Abstract: Successful maintenance of homeostasis in the gut requires diverse cellular processes stemming from a complex, spatiotemporal interaction between various cell types in the epithelium and stroma. Mature intestinal epithelial cells are routinely lost due to exposure to environmental toxins, chemicals, or pathogens in the gastrointestinal system, but these are readily replenished by intestinal stem cells (ISCs) which have the capacity to differentiate into mature epithelial cells and restore homeostatic function. Dysregulation of this regenerative process in the epithelium or the stroma impairs gut homeostasis, resulting in acute epithelial barrier leak as well as severe chronic inflammatory diseases. The matricellular protein CCN1 (CYR61), which promotes wound healing through direct binding to distinct integrin receptors in different cell types is a key mediator of stromal-epithelial interaction required for homeostasis. We focus on the role of CCN1 in epithelial regeneration during routine homeostasis or limited damage, which is accomplished by ISC proliferation and differentiation into mature epithelial cells to replenish damaged epithelium, as well as severe injuries that can directly damage and deplete the regenerative ISC pools. Furthermore, we examine regenerative functions of cellular senescence in the stromal cells during intestinal injury. These studies will provide new insights into how matricellular signaling coordinates intestinal epithelial regeneration and pave the way for novel treatment options in intestinal injury.