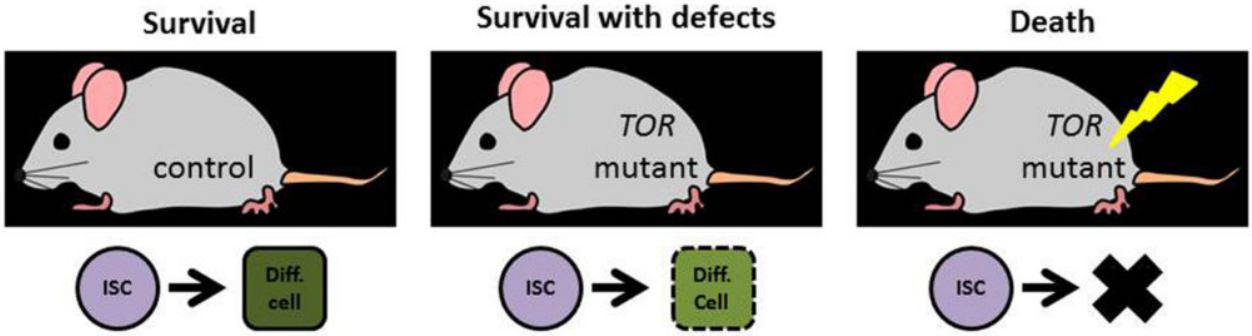
A “TORgeted” way to heal the gut

Our intestine is critical for absorbing the dietary nutrients that we need to survive. It performs this function by producing, from pools of intestinal stem cells (ISCs), a constant stream of new cells (differentiated cells) that have specialized functions to digest and absorb nutrients. All cells, including intestinal stem and differentiated cells, collectively called intestinal epithelial cells, or IECs, communicate through signaling pathways. The Target of Rapamycin (TOR) signaling pathway allows cells to sense their environment and determine if there are enough resources, such as energy, oxygen, and nutrients, to grow and divide to produce more cells. Unfortunately, under some circumstances such as cancer, this pathway can be damaged and stem cells no longer respond properly to signals leading to inappropriate cell division and ultimately tumor formation. As such, there is much interest in targeting this pathway to treat intestinal tumors; however, and rather unfortunately, TOR inhibitor treatments often cause gastrointestinal side effects and the cancer frequently relapses.



TOR signaling loss in mouse intestinal epithelial cells is tolerated with side effects, but additional stress injury causes death of the TOR deficient animals due to intestinal stem cell (ISC) failure. Diff. cell, differentiated cell. Solid line, Diff. cell normal. Dotted line, Diff. cell defective. Yellow bolt, radiation injury.

We generated a mouse model to investigate what happens when we completely remove TOR signaling from IECs. Using this model allows us to gain basic insight into how TOR signaling regulates these cells and to better understand why TOR inhibitor therapies are toxic and largely inefficient against intestinal tumors. To do this, we removed the TOR molecule using genetic tools, thereby completely disrupting the TOR signaling pathway. Surprisingly, we found that IECs without TOR are still produced at similar rates and the mice survive. This result indicates that ISCs do not require *TOR* signaling and may explain why TOR inhibitors are not curing intestinal tumors. While IECs are still produced without TOR, they look different and exhibit functional defects, likely explaining why patients treated with TOR inhibitors can experience diarrhea and ulcers.

In our study we also asked whether the TOR signaling pathway is important for healing the intestine. Throughout our lives we experience many periods of injury and healing, including within our gut. Damage can occur from things such as viral infection, dietary changes, surgery, and radiation. The gut has to be able to repair itself by quickly producing new cells to maintain proper function or death can occur. We exposed normal and *TOR* deficient mice to radiation stress that severely damages the gut and causes a large number of cells to die. After a few days, normal stem cells can start making new differentiated cells to repair the gut. However, we observed that *TOR* mutant stem cells cannot produce a sufficient number of differentiated cells and the mouse dies. Our studies suggest that TOR signaling is required for normal ISC function to regenerate intestinal organ.

***Leesa Sampson**, Ph.D. and **Yi Zheng**, Ph.D.*
Division of Experimental Hematology & Cancer Biology
Cincinnati Children's Hospital Medical Center
Cincinnati, USA

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mTOR disruption causes intestinal epithelial cell defects and intestinal atrophy postinjury in mice.
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