Transgenesis in tapeworms

At present, there are no reliable methods to make transgenic worms in any free-living or parasitic flatworm. However, tapeworms have many advantages that have represented stumbling blocks in other flatworm systems such as access to a large number of embryos, stereotypical and accessible gonad positions, self-fertilization, and prolific regeneration. Establishing transgenesis using CRISPR/Cas will represent an enormous technological advantage. I propose that one of the reasons transgenesis has been elusive is because of the bias in pursuing generation of indels rather than inserting foreign DNA. Flatworms have lost many players in non-homologous end joining whereas components of homology directed repair (HDR) are still intact. While counterintuitive, HDR-mediated transgenesis may actually be easier to achieve and this is not without precedent in eukaryotic pathogens. An enterprising postdoc with experience in CRISPR/Cas will have the potential to make an important and transformative contribution to the study of tapeworms by pioneering transgenesis. As our findings are likely to translate to other flatworm species, we will also collaborate and share findings with Jim Collins' lab in schistosomes (UTSW) and Phil Newmark's lab in planarians (Morgridge Institute for Research).

Neuronal control of tapeworm regeneration

Tapeworm regeneration is dependent on signals from the head that are necessary to maintain regeneration-competence and that influence stem cell behaviors. Are these head-dependent signals due to signals from the brain? What are the neurotrophic factors that influence stem cell biology and regeneration? Because of the highly polarized organization of the tapeworm body plan, we have the opportunity to transcriptionally profile differential gene expression from the brain vs. the longitudinal nerve cords. This may provide leads for brain-specific factors that can be screened by high throughput in situ hybridization and loss-of-function analyses. To uncover the diversity of neuronal signals, an unbiased approach using single nucleus sequencing can also be used. This research has the potential to open up a large area of research into the regulation of neuronally-derived niche signals during regeneration and for stem cell maintenance and homeostasis.

Quorum sensing among tapeworms and its effect on stem cells

Do tapeworm sense and talk to each other? In the rat intestine, ten tapeworms can grow to over a meter in length and co-exist peacefully. Observations from decades ago suggest that when the number of tapeworms exceeds 20, there is a crowding effect that negatively effects tapeworm growth and the proliferation of stem cells in the regenerative neck. This appears to be more than a competition for resources because of the mass differential in crowded vs sparse conditions and from measurements of carbohydrate utilization. Using fractionation, crowding factors were isolated but these experiments have not been replicated or followed-up on in many years. We have the opportunity to discover if a quorum sensing mechanism exists and how tapeworms might count and signal to each other. Co-culture experiments in combination with heavy isotope labelling and metabolite profiling, as well as RNA sequencing, could reveal the mechanisms underlying these phenomena. Furthermore, we have an opportunity to uncover how external environmental signals may impact stem cell behaviors that are critical for tapeworm growth, regeneration, and reproduction.

Segmentation in tapeworms

Though greater than 95% of the tapeworm's body consists of apparent segments called proglottids, tapeworms are not traditionally classified as segmented animals. This is because of historical definitions and a lack of understanding of how segmentation is regulated. Using a comparative evo-devo approach, we have the opportunity to discover the molecular mechanisms behind segmentation in tapeworms. As each proglottid develops the entire hermaphroditic reproductive repertoire, how segmentation is coupled or uncoupled with germ cell specification and development is also an open question. This project has the potential to make basic biological findings that may contribute to a shift in dogma, as well as to enrich our understanding of a fundamental aspect of parasite reproduction with translational relevance.