Cell death plays an important role in sculpting a developing organism, and in eliminating unwanted and potentially dangerous cells throughout life. Likewise, the degradation of proteins by the ubiquitin-proteasome pathway is required for both protein quality control and the regulation of myriad cellular processes. Steller studies the role of these pathways in normal development and diseases, including age-related neuronal degeneration and cancer.

Central to both development and tissue homeostasis, apoptosis is intimately associated with a variety of human diseases including cancer, autoimmunity, AIDS, neurodegenerative disorders, and liver diseases. This makes cell death proteins promising drug targets. Using both Drosophila melanogaster and mice as model organisms, Steller’s lab investigates the molecular mechanisms that govern the decision between cell death and survival.

Apoptosis has been conserved throughout evolution, from worms to insects to humans. Steller’s team discovered and characterized a family of proteins that act as integrators of many different signaling pathways to ensure that the death program is activated. Reaper, Hid, and Grim activate apoptosis by binding to and inactivating inhibitor of apoptosis (IAP) proteins, which in turn directly inhibit caspases, the key executors of apoptosis. A conserved IAP-binding motif originally discovered in these proteins has provided the basis for a novel class of cancer therapeutics currently in clinical trials.

Many organs and tissues can repair wounds and regenerate cells lost upon injury. Steller discovered that cells undergoing apoptosis in response to stress or injury can stimulate their own replacement by secreting mitogens to induce proliferation of adjacent progenitor cells. These mitogen pathways have been highly conserved throughout evolution, and similar phenomena have been observed in mammals with profound implications for cancer therapy, stem cell biology, and regenerative medicine.

The cell death machinery can also serve nonlethal functions for cellular remodeling in Drosophila and mammals. Steller’s work initially revealed the importance of this process for the generation of mature sperm. Subsequently, similar mechanisms were shown to operate during nervous system development. Steller defined the role of enzymes that control protein degradation by the apoptosis machinery, and his work has revealed that two major proteolytic systems, caspases and proteasomes, are coordinated to achieve “controlled demolition” of unwanted cellular structures. These findings are relevant for human diseases, including cancer.

More recently, work in Steller’s lab has focused on the mechanisms by which cells degrade unwanted or toxic proteins. Many neurodegenerative diseases—including Alzheimer’s, Parkinson’s, Huntington’s, amyotrophic lateral sclerosis (ALS), and retinitis pigmentosa—are defined by the accumulation of abnormal protein aggregates. Steller and his colleagues discovered a potential common root cause for these aggregates. They elucidated the mechanism for fast transport of proteasomes between the neuronal cell body and synapses and found that this process is critical for neuronal function. If proteasome transport is impaired, proteins tagged for degradation at the synapse escape local destruction and form aggregates. This work suggests that stimulating protein transport between the soma and synapses may represent a new treatment strategy for age-related neurodegenerative diseases, and a major new focus in the lab is to develop neuro-protective therapeutics.