“A major goal of my laboratory is to understand the defense strategies that enable a host to survive and even thrive when interacting with microbes. Knowledge of these defense mechanisms should lead to new treatments for infectious and inflammatory disease.”

When faced with a microbial threat, such as infectious bacteria or viruses, hosts can utilize two defense strategies to protect their health: resistance and tolerance. Resistance mechanisms allow the host to directly attack microbes to eliminate the infection. Tolerance mechanisms minimize the harm caused by microbes, for example, by neutralizing toxins generated by the pathogen. Ayres provided some of the first evidence that tolerance is crucial for defense against infections in animals. Using fruit flies infected with lethal bacteria, she identified genes and environmental factors, such as diet, that are important for tolerance and, ultimately, survival of infections. Furthermore, she demonstrated that a single gene could influence both resistance and tolerance so that conditions that enhance tolerance against one type of infection also can influence resistance against a different pathogen.

Recently, to identify mechanisms involved in tolerance of bacteria, Ayres turned to the mammalian intestine. Humans and other mammals tolerate the colonization of trillions of bacteria in their intestines, and these communities perform important functions for host physiologies. Within this microbial community live pathobionts, microbial species that can cause disease when homeostasis is disrupted, such as when antibiotics disrupt this complex community. Pathobionts have been implicated in triggering a number of diseases, including Crohn’s, rheumatoid arthritis and sepsis, an inflammatory response to infection that can lead to shock, organ failure and even death.

In studies in mice, Ayres found that antibiotics caused overgrowth of a multi-antibiotic-resistant E. coli pathobiont in the intestine, which spread to the lung and liver following intestinal injury. This triggered hypothermia and multi-organ damage—hallmarks of sepsis. She discovered that infection with this E. coli pathobiont leads to an overly exuberant inflammatory response and sepsis due to inappropriate stimulation of the inflammasome, a component of the body’s innate immune system. Ayres suggests that the inflammasome may be a useful therapeutic target in patients harboring antibiotic-resistant pathobionts.

In the future, Ayres will expand her studies to determine the mechanisms that facilitate tolerance of pathobiont colonization in the intestine under homeostatic conditions. She will also determine how members of the intestinal microbial community influence tolerance of pathogenic infections. Her work will provide a better understanding of host defense against microbes and suggest new therapeutic approaches for treating infectious and inflammatory diseases.