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Researcher wins NIH Director's Innovator Award



Dr. Maria Julia Bevilaqua Felipe, associate professor of medicine at the College of Veterinary Medicine, has received the NIH Director's New Innovator Award. The \$1.5 million grant is presented over five years to stimulate highly innovative research and support promising new investigators who are studying biomedical or behavioral research conditions. A diplomate of the American College of Veterinary Internal Medicine, Felipe will use the funds to challenge current thinking on a disease that renders people and horses highly susceptible to recurrent bacterial infections: Common Variable Immunodeficiency (CVID).

CVID is the most frequent clinically relevant primary immunodeficiency in humans and is a mixed group of heterogeneous conditions linked by a lack of ability to produce antibodies that fight pathogens. CVID in human patients has challenged the field of clinical immunology in regards to etiology and, consequently, therapeutic intervention. Although traditional thinking presumes CVID is a genetic disorder, data suggests that only a minor percentage of the affected patients are known to have genetic mutations and the disease manifests later in life, leading Felipe to pursue a different line of thinking.

"We hypothesize that CVID in the horse is an epigenetic disease," Felipe said, explaining that epigenetic conditions alter the activity, or the expression, of genes without changing their structure. "This could explain why the disease does not appear until later in life. It could also account for our inability to link a genetic mutation to the condition in more than 80% of the human patients."

Felipe became interested in the disease as a graduate student in Dr. Douglas Antczak's laboratory in 2001, where she was presented with a 12-year-old horse that contracted recurrent bacterial infections and meningitis. When the referring veterinarian checked the horse's antibodies, none were detected. With Felipe's further investigation of the immune system status, the horse was found to be lacking a class of cells called B cells, which are necessary for antibody production.

"In 2001, this condition had not been characterized in equine," said Felipe. "We reviewed the literature for human diseases and found the link to CVID, a condition that has been studied in people for more than 40 years. The horse is an excellent natural model for the human condition. Our findings will help us improve the diagnosis of the disease and the quality of life for horses and people."

Since 2001, Felipe's research team, including Research Associate Dr. Rebecca Tallmadge Ingram and technician Mary Beth Matychak, has diagnosed 17 cases of equine CVID, testing from samples that have been submitted from equine

referral practices across the country.

“We’ve developed a national network of veterinarians and horse owners who are tremendously supportive and enthusiastic about our work,” said Felipe. “Our access to these samples, our preliminary data, our hypothesis that challenges conventional thinking, and the fact that we have access to resources in Cornell’s Life Sciences Core Laboratories Center that will allow us to do high-throughput screening were all critical to our successful application for the Innovator Award.”

Felipe will use the award to conduct RNA-Seq, quantitative RT-PCR, and DNA methylation analyses.

“These experiments are essential because they will elucidate the status of transcription factors and genes that operate in a complex regulatory network and bind to promoters of several genes involved,” said Felipe, adding that her research team wants to identify areas and groups of genes that are either highly expressed or expressed less than expected in B cell development. “Subsequently, we will study epigenetic mechanisms of silencing of genes relevant to CVID. Although there is accumulating evidence of epigenetic mechanisms involved in many diseases, tradition and well-defined other genetic primary immunodeficiency disorders may have overshadowed this possibility in the study of CVID in human patients to date.”

Felipe expects that the results from the molecular screening will allow the team to reproduce and manipulate the abnormal B cell development in controlled experimental systems, knowledge that will also enable scientists to classify individual cases into categories based on the factors that cause the disease.

“There are only a handful of NIH grants given to study equine conditions,” said Felipe. “I am fortunate to be among the few, and even more fortunate to be surrounded by other NIH grant holders at Cornell who are studying equine conditions that also affect humans.”