



THE WINN FELINE FOUNDATION

For the Health and Well-Being of All Cats

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WINN FELINE FOUNDATION ANNOUNCES 2008 GRANT RECIPIENTS

Ten studies funded for a total of \$135,860

The Winn Feline Foundation is pleased to receive proposals from veterinary researchers around the world who are interested in improving feline health. Out of 36 proposals for 2008, our team of outstanding veterinary consultants helped the Foundation select the best studies for funding. We look forward to seeing the results of these studies and being able to share them with the veterinary community as well as cat owners and pedigreed cat breeders.

BREED-FUNDED PROJECTS

#08-015: *Molecular evaluation of the feline myosin binding protein C gene in Siberian cats with familial hypertrophic cardiomyopathy*

Kathryn M. Meurs, DVM, PhD, DACVIM; Washington State University; \$12,988

Feline hypertrophic cardiomyopathy (HCM) is the most common cause of heart disease in the adult cat. Affected cats are at risk of sudden death, breathing difficulties or development of a blood clot. Increasingly, feline HCM is noted to be inherited, with examples reported in the Maine Coon, Ragdoll, British Shorthair, and Siberian cat, among others. Dr. Meurs has previously demonstrated that HCM is associated with a mutation in the myosin binding protein C gene in the Maine Coon and the Ragdoll cat. The Siberian cat also has an inherited form of the disease. Given the importance of the myosin binding protein C gene in both Ragdolls and Maine Coon cats with HCM, it is possible that a mutation in this gene, but perhaps in a different region, is associated with the development of HCM in the Siberian. The objective of this study is to evaluate the DNA of this gene in Siberian cats for a causative mutation.

[This project is approved with funding from the Ricky Fund and pending funding from Siberian cat breeders.]

#08-014: *Molecular evaluation of the feline alpha tropomyosin gene in Norwegian Forest, Sphynx, Siberian, Ragdoll and Maine Coon cats with familial hypertrophic cardiomyopathy*

Kathryn M. Meurs, DVM, PhD, DACVIM; Washington State University; \$14,242

Feline hypertrophic cardiomyopathy (HCM) is the most common cause of heart disease in the adult cat. Dr. Meurs has demonstrated that HCM is associated with a mutation in the myosin binding protein C gene in the Maine Coon and Ragdoll cat. However, in both breeds, a small number of affected cats that develop HCM do not have the known causative mutation for their breed. In human beings, the disease is commonly associated with a mutation in one of several genes that encode for sarcomeric proteins. It is possible that a mutation in the alpha tropomyosin gene is associated with the development of HCM in one or all of these breeds. The objective of this study is to evaluate this gene in both affected and unaffected cats of these breeds for a causative mutation.

[This project is approved pending funding from Norwegian Forest Cat, Sphynx, Siberian, Ragdoll, and Maine Coon breeders. This project is also supported by the Ricky Fund.]

BRIA FUND PROJECTS

#08-004: *Molecular basis of feline coronavirus pathogenesis and development of FIP in cats*

Gary R. Whittaker, PhD; Cornell University; \$15,000

Feline infectious peritonitis (FIP) is a deadly disease of cats, caused by a virus infection. The virus normally resides in the gut of the cat, but can mutate and so infect the immune system of certain cats. Based on an analysis of the genome sequence of different viruses, it is proposed that key changes in the surface protein of the virus make it more efficient at infecting the cells of the immune system. Dr. Whittaker proposes to perform laboratory-based experiments using gut and immune system cells, to define the differences between the different viruses. Our work will characterize the changes that occur in the virus surface protein and will allow a more detailed understanding of the devastating disease of cats known as FIP, for which there remains no effective treatment.

#08-006: *Identification of the cellular receptor for feline coronaviruses*

H.F. Egberink, DVM, PhD and P.J.M. Rottier, PhD; Utrecht University; \$15,000

Feline coronaviruses (FCoVs) are well-known among veterinarians and owners for the devastating and lethal disease they cause: feline infectious peritonitis (FIP). There is presently neither adequate vaccine to prevent nor any therapy to treat this dramatic infection. A tremendous bottleneck that has precluded study of feline coronaviruses has been the lack of a suitable laboratory cell culture system for propagating the viruses and investigating their infection characteristics. Remarkably, all we presently know about FCoV comes from work with some rare hybrid viruses that occasionally arise when feline and canine coronaviruses simultaneously infect a cat or dog. The sole reason for this is that available feline culture cells cannot be infected by the 'real' FCoV, because they do not carry on their surface the molecule ('receptor') that the virus needs for its entry. The investigators aim to develop the necessary susceptible cells. They will artificially synthesize the viral protein that normally binds to the receptor. Using this protein, they will fish the receptor out from a homogenate of natural target cells, i.e. feline intestinal

epithelial cells. The identity of the receptor will then be determined based on its molecular mass properties. This will allow them to obtain the gene encoding the receptor, which they can clone from the target cells. Finally, this gene will be introduced into culture cells in the laboratory, which will thereby become capable of infection by FCoV. This will open the field for studying these viruses.

#08-036: *Blood parameters potentially associated with susceptibility to feline coronavirus in Birman cats*

Saverio Paltrinieri, DVM, PhD, DECVCP; University of Milan; \$14,780

Feline infectious peritonitis (FIP) is caused by the feline coronavirus (FCoV). FCoVs are common in feline populations. Many cats are infected but do not develop FIP. Occasionally, the virus acquires the ability to cause a generalized and lethal infection. The immune system of susceptible cats participates in the development of FIP. By contrast, “resistant” cats (those that are infected without showing clinical signs of the disease) mount a protective immune response. Resistant cats shed large amount of FCoVs in their feces that can re-infect susceptible cats, thus predisposing those cats to FIP. The ability to identify resistant or susceptible cats by blood tests would allow the design of breeding strategies to select resistant cats, or to avoid mixing cats with different susceptibilities to the infection, thus preventing mortality due to FIP. This would be particularly important for Birman cats, one of the breeds in which FIP occurs with a high frequency. Several studies suggested that resistant cats have certain changes in their immune response, such as increased lymphocyte subsets, transient increases of pro-inflammatory molecules (cytokines), or increases of or changes in the inflammatory protein α 1-acid glycoprotein (AGP). The opposite changes are detected in cats with FIP. This study will evaluate these parameters in Birman cats, to assess whether they can be used to explain the susceptibility of this breed and/or to identify families or individuals at high risk to develop FIP.

NEW PROJECTS

#08-020: *Mirtazapine as an Appetite Stimulant and Anti-nausea Therapy for Cats with Chronic Kidney Disease*

Katharine F. Lunn, PhD, MRCVS, DACVIM; Colorado State University; \$14,992

Chronic kidney disease is common in geriatric cats. Clinical signs include increased drinking and urination, decreased appetite, weight loss and vomiting. Decreased appetite can lead to weight loss, muscle weakness, and poor quality of life. Several studies have documented the value of specially formulated diets in the management of kidney disease. Therefore it is important for these patients to maintain their appetite and food intake. Mirtazapine (Remeron®) was introduced to human medicine as an antidepressant; however it has attracted interest in veterinary medicine because of several desirable side-effects, namely its significant anti-nausea, anti-vomiting, and appetite stimulating properties. Mirtazapine doses for cats have been adapted from human medicine; however no studies on how the drug is processed in the body of cats have been performed to verify this information. In order to provide accurate dosing recommendations for best effect and to avoid side-effects, it is necessary to investigate how the drug is processed in cats. The expected outcome of this study will be an understanding of the best dose and frequency of administration of mirtazapine to young and old cats, and cats with kidney disease. The study will also document how well

the drug works as an appetite stimulant and anti-emetic in cats with kidney disease. The results of these studies will allow veterinarians to improve the quality of life of cats with chronic kidney disease.

#08-027: *Feline Squamous Cell Carcinoma: The Effects of 5-Lipoxygenase Inhibition and Prevalence of Upregulation*

Joseph Wakshlag, DVM, PhD; Cornell University; \$14,150

Squamous cell carcinoma is often a terminal cancer in cats, with few successful treatment strategies. Recent evidence in humans suggests that some of the new generation anti-inflammatory drugs have the potential to drastically slow growth of tumors. Preliminary evidence shows that blocking a traditional pathway of inflammation, known as the lipoxygenase (LOX) pathway, can diminish cancer cell growth. Additionally, this class of drugs may help with pain relief in cats with oral tumors. Unfortunately, it is unknown if this enzyme is over-expressed in all feline squamous cell carcinomas. This study is designed to examine the prevalence of LOX in feline squamous cell carcinoma. In addition, cell culture studies will be used to determine how LOX is involved in tumor survival and progression. These molecular based studies will be done using inhibitors of the LOX pathway and genetic “knock-out” techniques in an established feline oral squamous cell carcinoma cell line. Further, studying an archive of feline squamous cell carcinoma tumors with special staining that shows LOX expression will be used to determine the prevalence of over-expression of this enzyme. This will determine how effective treatment with inhibitors of this enzyme might potentially be for feline squamous cell carcinoma. Overall, this study will determine whether inhibition of LOX is a viable option for further clinical examination in cats with squamous cell carcinoma.

#08-028: *Prostaglandin E2 Biosynthesis in Feline Mammary Cancers*

Sakhila K. Banu, MSc, MPhil, PhD; Texas A&M University; \$15,000

In cats, mammary cancer accounts for up to 17% of all non-lymphoid tumors with an average age of occurrence at 10 years. Between 80 and 96% of mammary tumors in cats are malignant, and spread to other tissues. Thus, mammary cancer is a devastating disease in cats. Moreover, treatment strategies are very limited because most of the cancer growth pathways in cats are unknown. Prostaglandin E2 (PGE2), a hormone secreted by cancer tissues promotes tumor cell migration, invasion, spread, and blood vessel growth. PGE2 is synthesized through two major enzymes called COX-2 and PGES-1. An increased level of tumor-derived PGE2 and expression of COX-2 and PGES-1 are hall-marks of mammary cancer. Inhibition of COX-2 by non-steroidal anti-inflammatory drugs decreases the incidence of various cancers. Epidermal growth factor receptor (EGFR)-mediated pathways regulate PGE2 production in metastatic cancers. Therefore, targeting COX-2 and/or PGES-1 to inhibit synthesis of tumor-promoting PGE2 could be a potential target for future cancer therapies. In the present study, specific roles of COX-2/PGES-1 pathways and interactions between EGFR and COX-2/PGES-1 pathways in feline mammary cancers will be determined. This study will determine the role of PGE2 in feline mammary tumors. The critical pathways identified in this research project may lead to new strategies for the treatment and/or prevention of mammary cancers in cats.

#08-030: *The in vitro effects of histone deacetylase inhibitors on feline oral squamous cell carcinoma*

William C. Kisseberth, DVM, PhD; The Ohio State University; \$15,000

Oral squamous cell carcinoma (OSCC) is the third most common tumor in the cat (10% of all tumors) and represents 61% of the tumors in the mouth. Generally, this devastating disease is recognized late in its course and quickly becomes debilitating with survival times of only about 3 months. The location of the tumor combined with the pain it causes prevents the cat from eating, swallowing or grooming. Often feeding tubes are placed and aggressive pain management is required to help maintain basic quality of life and prolong survival. To date, there is no reliable or durable therapy available to treat this disease and, despite efforts, there has been no improvement in quality of life or survival times for these cats. Novel targeted therapies, histone deacetylase (HDAC) inhibitors, have been shown to inhibit growth and kill human OSCC and various canine cancer cells. As a result, the researcher will investigate the response of feline OSCC cell lines to novel targeted therapies in order to determine whether they could be considered for treatment of OSCC in cats to improve survival.

#08-021: *Safety and Bioavailability of Oral L-Arginine Supplementation in Cats with Naturally Occurring Chronic Renal Failure*

Macon Miles, DVM; Animal Emergency Referral Center; Torrance, CA; \$4,708

The amino acid L-arginine is an essential amino acid for cats. It is converted to the amino acid citrulline in the intestines. Citrulline is then re-converted back to L-arginine by the kidneys, the main location of arginine synthesis in cats. L-arginine is a precursor for nitrous oxide (NO) synthesis in the cat kidney. NO is believed to play a crucial role in regulating blood flow through the kidney. Studies have shown that cats with naturally occurring chronic renal failure have decreased levels of L-arginine. It is hypothesized that increasing blood levels of arginine will increase NO production in the kidney and have a beneficial effect on feline kidney disease. No studies have been conducted to determine the safety of oral supplementation of L-arginine in cats with chronic renal failure or if oral supplementation can increase arginine blood levels. In this pilot study, 12 cats with kidney disease will be supplemented orally with either L-arginine or a placebo over a one month period to determine the safety of supplementation and whether increased blood levels of arginine can be achieved. If safe and effective at increasing blood arginine levels, then larger studies would be warranted to determine if survival and quality of life would be improved in cats with chronic renal failure.

[This study has been approved pending further funding. For information on how to donate to this study, please contact us.]

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