

# REPORT OF HEALTH AND GENETICS COMMITTEE

## APRIL 2002

The Health and Genetics Committee has been very active since our last reporting in September 2001. To date we have accomplished the following:

**1 - Research Mast Cell Tumor Registry:** This is a program to facilitate sending mast cell tumor samples to Dr. Cheryl London, at the University of California at Davis for research purposes. Small tissue samples are sent via regular mail at the time of surgery. Carlee Davies is the Research Mast Cell Tumor Registry Coordinator and to date has received 13 inquires with approximately 5 samples being submitted. The membership is encouraged to keep this registry in mind if they have a Ridgeback with a suspicious lesion. The logistics need to be in place BEFORE the surgery date.

**2 - Texas A&M hair sample study:** RRCUS received a request for Rhodesian Ridgeback hair samples for a study being conducted at the Texas A&M. The purpose of the study is to determine the feasibility of using hair samples for DNA purposes, as well as for diagnosing skin disorders and studying the difference in the coats of various breeds. This research is funded by the AKC/CHF. I sent a request via RR-members and RR-folk asking for hair samples from Rhodesian Ridgebacks. Within 48 hours I received no less than 2 dozen volunteers. A sincere thank you to all who volunteered and a special thanks to those who were able to send samples.

### 3 - Fund raising:

A. A special thanks to Kathy Thompson who raised \$222.02 at the 2001 National Speciality.

B. The RRDAF mail out for 2001 raised \$3600.27. This is substantially less than the year 2000 but we have to keep in mind that the effects of 9.11.01 impacted all fund-raising efforts throughout the United States that were not directly associated with the events of 9.11.01.

C. The following is the RRDAF balance as of December 2001:

As of January 1, 2001	Balance	\$ 6,038.75
Additions through December 31, 2001		\$27,123.27
Interest Income Allocation for 2001*		<u>\$ 158.98</u>
Total as of December 31, 2001		\$33,321.00

The following deductions were made for Grants:

Grant 2010 <i>"Dissecting the Biology &amp; Genetics of c-Kit Mutations in Canine Mast Cell Tumors"</i>		
Grant 2025 <i>"Growth Signaling Pathways in the Pathogenesis &amp; Treatment of Canine Cancer"</i>	TOTAL	\$
Total as of December 31, 2001		(6,094.00)
		\$27,227.00

\*Interest Income is added to fund at the end of each year.

Obviously our RRDAF has benefitted tremendously from a \$23,523.00 donation from the R.E.D. Estate and we thank Gary Danford, the executor of this estate, for making this donation possible.

D. As of April 2002, RRCUS has joined the Purina Parent Club Partnership Program whereby RRCUS members who are also members of the Purina Pro Club can elect to have 10% of the value of their weight circle points donated to the RRDAF. RRCUS members who are members of the Purina Pro-Club should have received a mailing from Purina asking them to identify their Parent Breed Club. This program will only run to December 2002. More details will be published in the next Ridgeback Newsletter.

#### **4 - Research**

The first 3 research proposals RRCUS funded through either the RRDAF or through general funds are being concluded in the next few months. The principle investigators have been kind enough to send a lay update/conclusion and they are as follows.

#### **AKC/CHF Grant Number 2038 - The Molecular Cytogenetics of Canine Lymphosarcoma: Correlating Chromosomal Changes With Clinical Disease.**

The major objective of this study is to apply molecular cytogenetic technology to the analysis of canine lymphosarcoma and to correlate the findings with clinical presentation. A unique strength in this project is that a team of oncologists and pathologists familiar with the clinical features, cytology, histology and immunohistochemical features of canine lymphosarcoma are examining all cases and a detailed molecular cytogenetic analyses will then be correlated with the clinical phenotype. To date we have established a robust series of molecular cytogenetic methods

that are needed to complete this work. Using these methods, we have started to analyze the chromosomal changes of recruited cases in detail. We have already observed some very interesting findings with some exciting early indications. However, we need to analyze at least 30 cases in detail before we will be able to determine if there are any significant correlations with prognosis. It is anticipated that we will complete the analysis of these case within the coming nine months.

Matthew Breen PhD, C.Biol. M.I.Biol  
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Dept. of Microbiology, Pathology and Parasitology,  
College of Veterinary Medicine  
North Carolina State University

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#### **AKC/CHF Grant # 2025 - Growth Signaling Pathways in the Pathogenesis and Treatment of Canine Cancer**

In part one of our study, we have been investigating a potential genetic derangement in the causation of canine hemangiosarcoma, while in part two, we have started to develop a novel treatment approach for this dreaded cancer. Hemangiosarcoma is a cancer that arises from endothelial cells, the cells that form blood vessels. Most often, the tumor begins in the spleen and substances that stimulate the growth of blood vessels in health may be important in

perpetuating the growth of malignant endothelial cells. The PTEN gene can negatively regulate production of a growth factor called vascular endothelial cell growth factor (VEGF) that stimulates the growth of endothelial cells. If a cell loses its PTEN function, it may not be able to stop VEGF production. We have analyzed the PTEN gene from more than 20 canine hemangiosarcomas obtained from dogs at surgery. In most specimens, despite identifying a variety of mutations in each dog's PTEN gene, it appeared that PTEN function was still preserved, suggesting regulation of VEGF in canine hemangiosarcoma may be more complex than first thought. Additionally, experiments seek to clarify if mutations in other genes can be important in the genesis of canine hemangiosarcoma. As to treatment, we are developing a method to target a protein (cytokine), interleukin -12 (IL-12), directly to dividing endothelial cells. IL-12 can both stimulate cells in the immune system to kill cancer cells and it can also suppress the growth of endothelial cells directly. Thus, its dual actions make it potentially important for the treatment of hemangiosarcoma. At the present time, we have successfully isolated and grown canine hemangiosarcoma cells in the laboratory and have developed a model to test our targeted IL-12 approach. We are excited by these developments but still have a long way to go before this approach can be tried in dogs with hemangiosarcoma.

Principal Investigator: Stuart C. Helfand, D.V.M., Diplomate, ACVIM  
University of Wisconsin-Madison  
Co-Investigator: Jaime F. Modiano, V.M.D., PhD.  
AMC Cancer Research Center

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### **AKC/CHF Grant # 2010 - Dissecting the Biology and Genetics of c-Kit Mutations in Canine Mast Cell Tumors**

The most common malignant tumor in dogs is the mast cell tumor (MCT, a form of skin cancer), occurring with an incidence of close to 20% in the canine population. MCTs range from relatively benign to extremely aggressive, leading to tumor spread and eventual death. Particular breeds of dogs are at risk for development of this tumor, indicating a role for genetic factors. We have previously identified mutations in the gene c-kit in dog MCTs. Kit (encoded by the gene c-kit) plays a critical role in regulating the growth and function of normal mast cells. As the mutations we discovered cause uncontrolled function of Kit (essentially turning the protein on all the time), it is likely they influence MCT development in dogs. A recent retrospective analysis was undertaken to determine the prevalence of c-Kit mutations in dog MCTs. We found that 35% of Grade II and Grade III MCTs possess such mutations, and that those tumors with a mutation were twice as likely to recur or metastasize after surgical excision. Based on the finding that Kit is dysregulated in a substantial portion of mast cell tumors, we have worked with an industry partner (SUGEN/Pharmacia, Inc) to explore the utility of a novel kinase inhibitor in the treatment of dog MCTs. Specifically, this inhibitor works to block Kit function, thereby disrupting the ability of the malignant mast cells to grow. Studies are currently underway to determine the effectiveness of this kinase inhibitor in treating dogs with MCTs. Preliminary results are very encouraging and further clinical trials are planned.

Cheryl London, D.V.M., PhD  
University of California, Davis

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Currently RRCUS is funding the following ongoing research:

- A. AKC/CHF Grant 2254 - Heritable and Sporadic Genetic Lesions in Canine Lymphoma and Osteosarcoma. Principle Investigator: James Modiano, VMD, PhD
- B. AKC/CHF Grant 2209 - Galactokinase 1: A candidate Gene for Juvenile Cataracts in Dogs. Principle Investigator: Kathryn Graves, PhD at the University of Kentucky.
- C. AKC/CHF Grant 2234 - Basophil/Mast Cell Response to Lectins as a Predictor for Risk of Allergic Disease in Genetically Susceptible Dogs. Principle Investigator: Bruce Hammerberg, DVM, PhD at North Carolina State University.

The Health and Genetics Committee is currently in the process of reviewing research proposals for 2002 and we expect our recommendations will go to the Board of Directors in late summer.

#### 5. **Health Survey**

Approximately 134 dogs have been added to our health survey database since the last re-tabulation in 2000 bringing our total to 1870 dogs. Tentatively, another re-tabulation is planned when we have a total of about 2200 dogs. All members are reminded to submit health surveys on all new Ridgebacks and to update existing surveys if the health of a Ridgeback changes.

Breeders are encouraged to incorporate a health monitoring program in their breeding programs by contacting puppy buyers when puppies are 1 year old and have the new owners submit a health survey.

**6. CHIC - Canine Health Information Center:** RCCUS volunteered for the CHIC pilot program in 2000. CHIC has matured to become an exciting program where OFA, AKC, AKC/CHF and GDC have come together for the benefit of purebred dogs and established a novel genetic testing registry. CHIC works with parent breed clubs to maintain a central health information system that will support research in canine disease and provide health information to owners and breeders. Breeders can provide copies of CHIC reports for new puppy owners and other breeders or refer them to the CHIC website for accurate information about the results of their health testing. In addition, the data base will serve as a resource for scientists who need accurate information on multiple generations of dogs.

When a dog meets the testing criteria established by the Parent Breed Club, a CHIC number is assigned. Currently the required testing for Rhodesian Ridgebacks include:

- A. Hips and elbows certifying clear of dysplasia: Accepted from OFA, GDC, Pen Hip, and OVC.
- B. CEFF examinations - annually
- C. Thyroid testing: OFA protocol or certified by a board certified Endocrinologist or Pathologist - annually between 1 - 5 years of age.

Optional but recommended testing includes:

- A. Cardiac testing no earlier than 1 year of age.

B. Baer testing no earlier than 1 year of age.

These testing requirements can be altered to meet our needs at any time and are not rigidly in place. Test results on individual dogs is only made public with the consent of owners. At this time RRCUS strongly urges complete disclosure. Even if the owner does not make complete disclosure of test results a CHIC number is still assigned indicating that the testing has been done. We expect CHIC numbers will be routinely issued in the coming year. Some persons may have already received CHIC numbers from the pilot phase of this project as they were issued based on data already in the OFA data bank.

Jacque Rex is the CHIC coordinator for RRCUS.

7. **Special projects:** Periodically the Canine Health Foundation gets requests for research samples and these requests are forwarded to parent breed clubs. The Research Mast Cell Tumor Registry was such a request. We have also received request for samples or pedigree data on dogs with hemangiosarcoma and epilepsy. These have been published in The Ridgeback Newsletter. RRCUS members are encouraged to submit any and all information at their disposal to assist these investigators in their research endeavors. The hemangiosarcoma study is of particular interest to RRCUS as we have sponsored this research.

7. **AKC/CHF Rhodesian Ridgeback online seminar:** The AKC/Canine Health Foundation is sponsoring an online seminar for the RRCUS membership. We have asked AKC/CHF to center the seminar of dermoid cysts/sinuses and perhaps address the neural tube defect connect. Alternately, we have asked for a seminar on atopic dermatitis. AKC/CHF will advise RRCUS members of the dates of this online seminar.

Respectfully submitted by:

Cynthia Roethel  
Chairman, Health and Genetics Committee/CHF Liaison to RRCUS