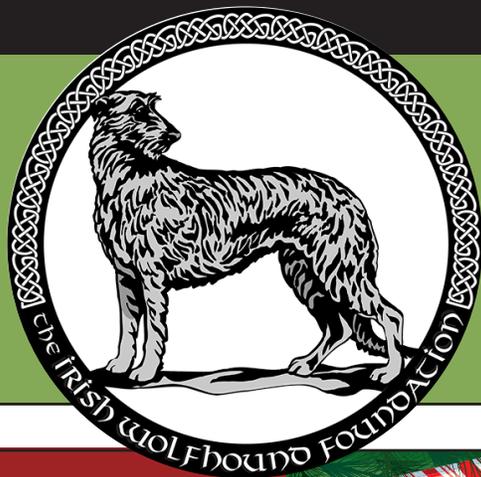


# THE Irish Wolfhound Foundation



# Focus

Winter 2013

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## *Focus*

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Photo by Mary O' Malley

*May Joy and Peace be yours  
throughout the New Year!*

# Update on IWF Heart Studies



**Submitted by Mariellen Dentino MD  
(chairman of the IWF Research Committee)**

Eighty eight hounds participated in heart testing at the recent Delaware Valley regional specialty and at the National. The IWF sponsors these clinics to help individual hounds and also for research.

The incidence of atrial fibrillation which may lead to heart failure is nearly 12% overall in our hounds. Published data by Dr. Neil Harpster showed an incidence of 30% in hounds older than 6. Because the incidence increases with age a normal test at age 3 does not mean the hound will not develop atrial fibrillation. Heart disease IS treatable. Every hound should have annual heart testing.

The present study is evaluating the adequacy of the less expensive EKG (rather than an echocardiogram) as a satisfactory yearly exam for Irish Wolfhounds. 500 individual dogs will be tested to see if a normal EKG is sufficient for yearly screening. At last count 448 individual dogs have been examined with simultaneous EKG/ Echocardiogram.

In the dogs tested at this clinic there was four new cases of atrial fibrillation and no dog with a normal EKG had DCM on echocardiogram. Overall results will be possible when the study reaches 500 individual dogs.

The tallies below of the clinics at the National specialty and Delaware Valley are provided by Dr. Tyrrell. A copy of the echo is provided to the owner of each hound tested and all data is entered into the ongoing study databank. An EKG strip is provided at the owner's request.

The table shows the age and sex of tested hounds. 49 of these 88 hounds tested had no abnormality on their EKG and echocardiogram.

The table lists Equivocal IWH Type DCM. This describes early IW cardiomyopathy which seems to develop in a different pattern than other breeds. Often the first sign is mild enlargement of the atrium or top chamber of the heart. This occurs in hounds with atrial fibrillation although not all hounds with atrial fibrillation have this finding.

IWH Type DCM is a progression of the above with dysfunction of the atria (top part of the heart) and some dysfunction of the ventricle (bottom pumping part of the heart) that is characteristic of IW dilated cardiomyopathy as it progresses.

VPCs are Ventricular Premature Beats. The incidence of these abnormal beats is still not known in IWHs as they occur sporadically and may be missed on screening exams. This is further discussed below.

Pericardial effusion/ aortic tumor means fluid in the sac (pericardium) that surrounds the heart. This may be caused by many things

IWADV Morgantown PA 2013			
Age	Male	Female	
<2	2	1	
2-3 years	4	5	
3-4 years	3	1	
4-5 years	0	2	
5-6 years	2	1	
6-7 years	2	2	
>7 years	7	5	
Totals	20	17	37
Normals	15	14	
Equivocal IWH Type DCM/lone AF	0	0	
IWH Type DCM	3	1	
VCPs	2	2	
Pericardial effusion/aortic tumor	0	0	
Equivocal aortic stenosis	0	0	
True Dilatative type cardiomyopathy	0	0	
	20	17	37
Degenerative valve disease/ incidental findings	7	5	

IWCA National: Asheville NC 2013			
Age	Male	Female	
<2	0	3	
2-3 years	2	5	
3-4 years	7	7	
4-5 years	3	5	
5-6 years	3	4	
6-7 years	1	0	
>7 years	3	8	
Totals	19	32	51
Normals	10	10	
Equivocal IWH Type DCM/lone AF	2	3	
IWH Type DCM	1	2	
VCPs	1	0	
Pericardial effusion/aortic tumor	0	0	
Equivocal aortic stenosis	0	0	
True Dilatative type cardiomyopathy	1	0	
Degenerative valve disease/ incidental findings (normal)	6	15	
	20	31	51
Note: 3 normal dogs did have high normal LVOT flows			

including viral illness, tumors of the heart valves, kidney failure etc. This is very rare in IWs and we have only seen one case in the present study.

Equivocal aortic stenosis describes measurements of the left side heart valve (aortic) that are more narrow than expected. Aortic Stenosis can be significant problem in other breeds and may cause sudden death but true aortic stenosis has not been a problem in IWs.

True dilative type cardiomyopathy has dilated heart chambers with poor function. Atrial fibrillation may not be present and if it occurs late in the course of heart failure. This type of cardiomyopathy is very rare in the Irish Wolfhound.

Degenerative valve disease describes a valve that allows a small leak of blood in the wrong direction. This is an incidental finding and these hearts are considered normal.

## PREMATURE VENTRICULAR BEATS

In Boxers and Dobermans the appearance of a premature ventricular beat on a screening EKG is thought to signal the onset of heart failure. In the Irish Wolfhound these abnormal beats were felt to be negligible and transient. However, because there is sudden death in IWs a study was initiated to evaluate this. On holter monitoring 30% of the dogs had significant and potentially dangerous heart rhythm disturbances. This was not the expected result. The hypothesis was changed. There is a need to determine if PVCs in Irish Wolfhounds with satisfactory holter monitors (i.e. showing only benign premature ventricular beats) are benign and transient. To study this 20 dogs with PVCs on screening EKG need to be monitored with yearly holter and echocardiogram for their lifetime.

This is a very important question. If your young hound has PVCs on his EKG you will really want this information. It is a difficult study with inconvenience for the owner but will be invaluable to future hounds and owners. This study is ongoing and all expenses paid by the IWF. As seen on the above table there was 4 hounds with PVCs in the last clinic.

## GOING FORWARD

There were 12 dogs in this clinic with an incidental finding of mild heart valve dysfunction. These dogs are considered to have normal hearts. There are few cases of clinically significant heart valve disease in Irish Wolfhounds. When the goal of 500 dogs is reached a description of IW heart valves will be available. EKGs have been available at IW events since 1999. It seems by utilizing testing before breeding that the incidence of atrial fibrillation (the most common IW cardiac arrhythmia) has decreased. To examine this EKGs from 2000 to 2007 are being compared to EKGs from 2007 to 2014. EKGs from different age groups must be compared as the incidence of atrial fibrillation increases with age. Many more EKGs are needed.

If you do not wish to get an echo at any event where testing is offered please consider getting an EKG. Every IW needs yearly screening. If this data verifies the decreasing incidence of heart disease in our breed it is a tribute to support from the many dedicated owners and breeders.

The Lifetime Cardiac Study closed in 2010 although data is STILL being collected to close this study. A THANK YOU to all those who participated in this study. Data is being analyzed.

Every hound not followed health wise for their lifetime is a loss to further research especially as DNA is being stored on many of our hounds. A new follow up study sponsored by the IWF will be initiated. This data will be added to the master list of hounds participating in ongoing studies. Each hound will have an identifying number. When researchers need dogs with certain health problems the dog (and his DNA) can be quickly located. This will help focus researchers to consider IWs in future studies. Follow up will be simplified into only one page and can also be returned on line for convenience. Enrollment will be started at the National Specialty this year. Please consider participating.

# IW Foundation Rescue Grant Report:

The Irish Wolfhound Foundation has had 5 Rescue Grant Applications during the period of April 24, 2013 up to August 15, 2013. The total amount requested came to \$1,266.93. Since we are splitting the Rescue Grant amounts with the IWCA Rescue Fund, half of this cost has been reimbursed to the Foundation. Come December, I have one and maybe two more requests scheduled to be processed.

You, our members, make this happen!! So, thank you for your generous support of both organization rescue funds.

Merry Christmas, Jean

Jean A. Minnier  
IWCA & IW Foundation – Rescue Chair  
609-268-9373  
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## IWF Research Committee Members

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Photo by Mary O' Malley

# IWF Sponsored Speaker at IWADV 2013

The IWF sponsored a fascinating lecture by Dr. Nicola Mason BVetMed PhD DACVIM from the University of Pennsylvania on her study entitled "Evaluation of a recombinant bacteria Vaccine to treat bone cancer in dogs."

The following was submitted by Dr Mason.

Nicola Mason B. Vet., (Immunology), DACVIM (Internal Medicine)

Osteosarcoma (OSA) is a highly aggressive and painful bone tumor that affects approximately 10,000 dogs per year in the USA and accounts for approximately 85% of all canine bone tumors. It most frequently affects the long bones of adult large and giant breed dogs including Irish Wolfhounds, Rottweilers, Labradors, Greyhounds, Newfoundlands and Great Danes. Although osteosarcoma initially appears as a local swelling oftentimes at the carpus (wrist), proximal humerus (shoulder) or distal femur/proximal tibia (knee), cancerous cells are thought to spread early in the course of disease from the primary bone tumor to the lungs and other bones. Indeed it is estimated that 90-95% of dogs have microscopic tumor spread (metastasis) at the time of diagnosis. The current standard of care treatment for OSA in dogs consists of limb amputation to remove the painful primary tumor, followed by systemic chemotherapy. Systemic chemotherapy is given after amputation to eliminate any cancer cells that have already spread away from the primary site. Although follow up chemotherapy significantly prolongs survival when compared to amputation alone, approximately 60% of patients still die within one year of diagnosis from tumor spread to the lungs and bone.

In order to improve the survival of dogs with osteosarcoma, we need to be more effective at targeting and killing the tumor cells that remain in the patient's body after amputation and chemotherapy. If these cells can be effectively identified and destroyed then the chances of tumor recurrence and death due to osteosarcoma should be dramatically reduced.

"Cancer immunotherapy" describes the use of the patient's own immune system to specifically target and kill tumor cells. Just as the immune system can specifically target and kill viruses or bacteria, it can also be activated to target and kill cancer cells. Therefore, if the immune system could be taught to recognize cancer cells (by vaccination) then it may be possible for it to destroy tumor cells that remain in the body after amputation and prevent tumor recurrence in dogs with osteosarcoma.

Over 100 years ago, an orthopedic surgeon at Memorial Sloane Kettering, names William Coley, injected a concoction of live bacteria into his human patients with osteosarcoma<sup>1</sup>. He documented some complete remissions in people that were known to have aggressive disease using this early form of "immune therapy." More recently other investigators have used different strategies to activate the immune system in dogs with osteosarcoma to try to achieve the same effect<sup>2-4</sup>. Interestingly in these studies, the use of "immune therapy" prolonged overall survival in a number of dogs with osteosarcoma, after amputation. Finally, it is known that dogs that develop bacterial infections at the surgical site after amputation tend to have longer survival times than dogs that do not develop infections at the surgical site, again suggesting that activation of the immune system (in this case by the natural bacterial infection) may help in preventing the tumor from recurring<sup>5</sup>.

Taken together, these findings suggest that osteosarcoma might be a cancer that is amenable to immune therapy. To enhance the success of immune therapy and to reduce the chance of adverse side effects, it is necessary to identify a particular marker that is uniquely expressed by the cancer cells. The immune system can then be trained to recognize cells that express this marker and then kill them. Osteosarcoma cells express a marker known as Her2/neu (the same marker found in some women with breast cancer)<sup>6-9</sup>. Training the immune system to recognize and kill cells that express Her2/neu represents a promising strategy to treat osteosarcoma in dogs.

## Ongoing phase I clinical trial in dogs with OSA

We are currently performing a phase I clinical trial to evaluate the safety and therapeutic effects of a genetically modified bacterial vaccine known as ADXS31-164 in dogs with naturally occurring OSA. The vaccine, which is supplied by Advaxis Inc. (North Brunswick, NJ) consists of a bacteria known as *Listeria monocytogenes* (*L. monocytogenes*) that has been modified to express Her2/neu. Her2/neu is a growth factor receptor that is expressed to different degrees on cancer cells including canine osteosarcoma cells. The *Listeria* bacteria induces a potent immune response and, as the bacteria also carries the



Photo by Mary O' Malley

## Dr Nicola Mason at IWADV in October

Her2/neu protein, it will stimulate the patient's immune system to recognize and kill target cells that express Her2/neu. Could this vaccine be used safely to stimulate the patient's immune system against osteosarcoma cancer cells that express Her2/neu? Could this result in improved survival times for dogs with osteosarcoma?

Dogs that have been diagnosed with osteosarcoma and that have undergone the standard of care treatment that includes limb amputation and follow up chemotherapy with 4 doses of carboplatin are eligible for enrollment in this ongoing study. Prior to enrollment the dog's bone tumor is evaluated in our laboratory to determine whether the tumor cells express the target protein (Her2/neu). Dogs with Her2/neu positive and Her2/neu negative tumors are both eligible for trial enrollment. Recent data suggests that the tumor cells that are responsible for forming metastatic disease (tumor initiating cells) express Her2/neu regardless of the Her2/neu status of the primary tumor<sup>8</sup>. Therefore dogs with Her2/neu negative primary tumors may also benefit from vaccination.

Three weeks after receiving their last chemotherapy dose, potential trial candidates are evaluated at the University of Pennsylvania's School of Veterinary Medicine. The initial screening of these patients includes full blood work, urine analysis, immune function analysis, chest radiographs and a full cardiac evaluation. Only dogs that are healthy with no other disease processes and no evidence of heart disease are eligible for the study.

All dogs receive the vaccine. There is no placebo control group. The dogs receive one vaccine every 3 weeks for a total of 3 vaccines. The vaccine is given intravenously and the dogs are hospitalized at the University of Pennsylvania's Veterinary School for the day. Following completion of the vaccines, all the dogs are re-examined at UPenn every 2 months. During this time, they have chest radiographs taken, a cardiac evaluation performed and full blood work and urinalysis to make sure they remain systemically healthy.

## Side effects of the vaccine

To date we have vaccinated a total of 12 dogs. Side effects of the vaccine have been minimal and include mild fever several hours after vaccine administration, which resolves spontaneously within a few hours.

## Efficacy of the vaccine

While it is still too early in the course of the study to definitively say whether the vaccine is effective at increasing overall survival in dogs diagnosed with OSA, our preliminary results are very encouraging. Our first vaccinated dog, Sasha was diagnosed over 570 days ago and two more of our dogs vaccinated at the beginning of the study are alive and cancer free over 500 days post diagnosis. Other dogs that were vaccinated more recently are still doing well. We have now started to re-vaccinate long-term survivors on the study. The concept of re-vaccination is to boost the immune system so that it may continue to recognize and kill any cancer cells that may remain or arise again in the body.

## The Broad Collecting Blood at IWANE



Top left: Claire Sharp vet tech at Tufts

Above: Michele Perloski (sample coordinator) with canine friends

Left: Ginger who is a post doc working at the Broad lab with Michele Perloski (sample coordinator).

# Presidents Message

## Winter 2013

Another great year for the Irish Wolfhound Foundation! This organization has really hit its stride in the last few years; I would like to thank the IWF's Board of Directors for helping me realize this accomplishment. I would also like to thank the IWCA for its continued support as well; they and the Irish Wolfhound community at large have rallied around the Foundation in terms of support and fundraising. Our donor renewal rate and the Osteo matching grant donations are just a few examples.

I would like to remind the regional clubs to please contact me if they have funding needs to help support educational opportunities being held in conjunction with club events and specialties. Just recently the IWF had sponsored a lecture on a vaccine to treat bone cancer at the IWADV specialty in October. Since then we have had request for financial support to take this lecture west to other regional clubs. The IWF will consider supporting such events on a case by case basis; don't hesitate to contact us with your ideas.

In closing I would like wish everyone, hounds included a Merry Christmas, Happy Holidays, and a prosperous New Year!

Regards,  
Doug Marx – IWF President

## The Irish Wolfhound Foundation, Inc.

### Treasurer's Report

Balances are as of 10/31/13

**Total Cash Accounts \$239,960.49**

**General Account \$124,106.41**

**General Endowment \$92,401.09**

**Rescue Endowment \$23,452.99**

**2013 Disbursements total \$60,562.42**

**2013 Receipts \$45,122.95**

## The Irish Wolfhound Foundation

The purpose of the Foundation is to promote the appreciation, knowledge, and understanding of Irish Wolfhounds by raising and allocating funds for research, education, and rescue.

# Second Gift to Continue Broad Institute Irish Wolfhound Osteosarcoma Study

Thanks to the generous contributions of owners and friends of the Irish Wolfhound, the Irish Wolfhound Foundation (IWF) is pleased to announce a new gift of \$32,000 to fund the next phase of the search for a genetic basis of osteosarcoma in Irish Wolfhounds. Results of work under the first gift identified several regions that are more frequent in Irish Wolfhounds that have osteosarcoma than in normal dogs. Analysis of the data continues, however, a publication on this work is expected in the near future. The next step is to “zoom in” on these regions looking for the specific gene that results in the changes leading to development of tumors and to elucidate the mechanisms involved.

This step should bring us close to the completion of Phase 3 of a six phase plan to develop risk analysis based on genetic testing and, more importantly, mechanisms that can be used to tailor treatment and development of treatments for osteosarcoma in Irish Wolfhounds. For additional information, visit the IWF website at [IWFfoundation.org](http://IWFfoundation.org).

Those individuals and organizations wishing to contribute to the next stages of this effort will be acknowledged by the IWF. Contributions can

be sent to “Osteosarcoma Fund” c/o David Milne, IWF Treasurer, 150 Creek Rd, Phillipsburg, NJ 08865. The IWF is a 501-3(c) charitable organization. Blood samples and veterinary information on affected dogs are still being sought for this study.

The researcher leading this effort, Prof. Kerstin Lindblad-Toh is a world-renowned researcher in comparative genomics and leads groups in both the United States, where she is Scientific Director of Vertebrate Genome Biology at the Broad Institute and in Sweden where she is a professor at Uppsala University and Co-Director of Science for Life Laboratory.

Prof. Lindblad-Toh leads the dog disease-mapping group at The Broad that has found many disease genes in dogs. Author of over a hundred papers, she is published in a number of journals, including Nature. She was recently elected to the Royal Swedish Academy of Sciences.

For further information on the study and where to send blood samples of affected dogs, contact: Frances Abrams, PhD, Irish Wolfhound Foundation Research Coordinator at [frances.abrams@att.net](mailto:frances.abrams@att.net).

## Speaker (Continued from page 4)

Given that the side effects of the vaccine are mild, the potential benefit of repeat vaccination outweighs the risks.

What is next for immune therapy of canine OSA?

Our initial phase I clinical trial aimed to evaluate the safety of the bone cancer vaccine ADXS31-164 and its ability to prolong overall survival in dogs that have undergone standard of care amputation and chemotherapy. However, some dogs are unable to tolerate limb amputation due to their large size or concurrent orthopedic or neurological problems. Treatment options for these dogs are limited and usually consist of palliative radiation and pain management using drugs such as tramadol and carprofen. Overall survival of dogs that undergo palliative radiation with pain medications is about 4 months. We are now interested in determining whether ADXS31-164 could be effective in dogs that have not undergone limb amputation but have instead received either palliative radiation or stereotactic radiation (CyberKnife). Although immune therapies generally function most effectively when there is a minimal amount of cancer in the body (i.e. after limb amputation when the large primary tumor has been removed), there are indications that radiation therapy and immune therapy function synergistically to increase an anti-tumor immune response. We believe that the effects of the radiation on the primary tumor will reduce the number of viable tumor cells (and reduce associated pain) and promote immune responses against tumor cells. We therefore are now initiating a clinical trial to determine whether palliative radiation followed by vaccination with ADXS31-164 can prolong overall survival in dogs that cannot undergo amputation. We hypothesize that combination radiation and immunotherapy may act together to kill the primary cancer cells and prevent tumor spread from the primary site. In this trial, all patients will receive palliative radiation (2 doses on 2 consecutive days) and then they will be randomized to receive either ADXS31-164 or a placebo. Dogs will receive either the ADXS31-164 vaccine or placebo every three weeks for a total of 8 times. Dogs will be evaluated every three weeks and assessed for lameness and pain, overall well-being and any evidence of tumor spread. This is a unique trial that combines two cancer treatment modalities (radiation and immune therapy) in an attempt to improve the outcome of large and giant breed dogs with osteosarcoma.

In summary, previous work has shown that osteosarcoma may be an “immune responsive” tumor and that the concept of preventing tumor spread using the immune system holds much promise. Furthermore, in light of our early trial results, the vaccine appears to be safe and vaccinated dogs are showing prolonged overall survival when compared to unvaccinated controls. There is still much work to do: Our studies will continue and as more patients are treated, survival trends will become apparent and statistically significance for outcome will be determined. We will also add an additional protocol to our studies to see if the same increases in overall survival would be obtained by vaccinating dogs that do not undergo amputation and receive only palliative radiation. One also wonders whether there would ever be a scenario for prophylactic vaccination – to prevent osteosarcoma in dogs that may be predisposed to this disease. The future for this approach is exciting and it looks set to offer an additional potent weapon in our arsenal against osteosarcoma.

If you have a dog with osteosarcoma and are interested in participating in either of these trials please contact Dr. Nicola Mason at 215 898 3996 or by e-mail at [nmason@vet.upenn.edu](mailto:nmason@vet.upenn.edu)

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### About the Author

Dr. Mason graduated from the Royal Veterinary College, London, performed an internship in small animal internal medicine at the University of Bristol and a small animal internal medicine residency at the University of Pennsylvania. She became board certified in internal medicine in 1995. She completed her PhD in Immunology at the University of Pennsylvania under the guidance of Dr. Christopher Hunter where she investigated the role of NF- $\kappa$ B in regulating immune responses to *Toxoplasma gondii*. She then completed her post-doctoral work in Dr. Carl June's lab at the Abramson Cancer Center, University of Pennsylvania where she developed her interest in cancer immunotherapy. She returned to the University of Pennsylvania's School of Veterinary Medicine as a faculty member with a joint appointment in the Departments of Clinical Studies and Pathobiology. She has built an effective translational program in cancer immunotherapy, where she investigates malignant pathogenesis, identifies potential therapeutic targets and evaluates novel therapies in dogs with spontaneous cancers to inform the development of safer and more efficacious therapies, including vaccines for the treatment of cancer in dogs and in people. She is currently an assistant professor at the School of Veterinary Medicine, UPenn and her lab focuses on developing immune therapies that target malignancies. She is the lead investigator on the current phase I/II clinical trial evaluating a recombinant listeria vaccine to prevent metastatic disease in dogs with osteosarcoma. For this work, she and Dr. Yvonne Paterson, inventor of the listeria technology for cancer vaccines, recently received UPenn's One Health Award, a new award established by the four University of Pennsylvania's health school deans that recognizes exemplary contributions toward expanding interdisciplinary education and improving health care. She is Director of the PennVet Tumor Tissue bank and the Associate Director of the Mari Lowe Comparative Oncology Center.

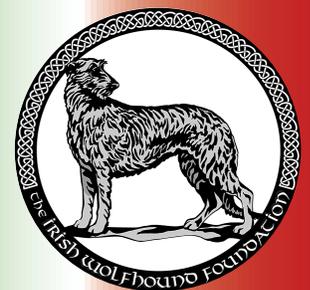
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