

# Update

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## Research of Anti-Tumor Drug May Lead to First Feline Cancer Treatment

Cancer, which affects approximately 4 million cats a year, represents 32 percent of disease-related feline deaths. Despite the prevalence of cancer in cats, there are no medications approved by the Food and Drug Administration (FDA) for treating feline cancers. Most cats with cancer are treated using human cancer drugs, which can cause debilitating side effects.

Researchers at the Bauer Research Foundation in Vero Beach, Fla., have designed a vitamin B12-based anti-cancer drug, nitrosylcobalamin (NO-Cbl), and are evaluating whether it can be used to treat a variety of feline and canine tumors. Founded in 2009 by Joseph A. Bauer, Ph.D., the Foundation assists owners whose pets have cancer. Bauer developed the anti-cancer drug in 1997 while he was a graduate student at the University of Akron in Ohio.

Among the difficulties in treating cats with cancer is that cats are good at hiding the signs of disease, says Gerald Post, D.V.M., DACVIM-Oncology, of The Veterinary Cancer Center in Norwalk, Conn. "Cats usually present to veterinarians with a more advanced stage of cancer than dogs or people," he says. "In addition, because their metabolism is quite different from dogs and people, there are fewer clinical trials for cats. The greatest challenge is education —

informing cat owners that cancer is not always a death sentence, that early detection is important, and that cats can handle both chemotherapy and radiation therapy."

Annette M. Sysel, D.V.M., chief veterinary officer and vice president of Bauer, received funding in 2012 from the Winn Feline Foundation and the American Kennel Club (AKC) Canine Health Foundation to determine the susceptibility of feline and canine tumors to NO-Cbl. She is working to move the drug through the FDA approval process to enable the use of NO-Cbl to treat cancer in companion animals.

Sysel was inspired to research cancer in animals after her beloved Siamese cat, "Tiki," died in 2011 following a five-year battle with a rare stomach cancer. "Tiki's valiant fight significantly changed my life," she says. "She went through so much. I am determined to help other people and their cats so they don't go through what she did."

In addition to seeking FDA approval for use of NO-Cbl in cats and dogs, Bauer and Sysel are working to gain its approval for use in humans for the treatment of glioblastoma multiforme, a fatal type of brain cancer. "We are currently conducting the studies necessary to receive investigational

new drug status and hope to begin phase I clinical trials sometime next year," Sysel says.

### A 'Biological Trojan Horse'

When Bauer developed NO-Cbl, a combination of vitamin B12 (cobalamin: Cbl) bound to nitric oxide (NO), he described the compound as having a "biological Trojan horse" effect on cancer cells. Bauer hypothesized that the vitamin B12 component could be used to target NO-Cbl to tumor cells, leaving healthy cells unharmed.

All cells need vitamin B12 for cell replication. Cells lining the blood vessels produce a transport protein called transcobalamin II (TCII) to move vitamin B12 through the bloodstream. TCII also is produced by cancer cells that scavenge the body in search of vitamin B12.

"Vitamin B12 is important in DNA synthesis, as cells cannot divide without it," Sysel explains. "Rapidly growing tumors that are actively dividing have an especially high demand for vitamin B12. Tumor cells produce TCII to obtain all the vitamin B12 they can."

TCII proteins act like "little jeeps shuttling vitamin B12 around and transporting it to cells seeking vitamin B12," she says.

Cells then take up vitamin B12 through a special protein receptor, TCII-R, which must be present on the surface of a cell for vitamin B12 to gain entry into the cell. "A cell must have the right lock, that is TCII-R, for the TCII key, or else vitamin B12 can't get into the cell," says Sysel. "Tumor cells and rapidly dividing normal cells, such as bone marrow, gastrointestinal cells and hair follicles, need a lot of vitamin B12 and likely have more TCII transport proteins and receptors.

"The receptor mechanism is sensitive to changes made to the structure of vitamin B12. The addition of nitric oxide to the vitamin B12 molecule is so subtle that the TCII receptor doesn't recognize NO-Cbl as being different from regular vitamin B12 and thus takes it into the cell in the normal manner."

The nitric oxide component of NO-Cbl is the part of the drug responsible for killing cancer cells. Nitric oxide, which is produced in the body normally as

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### Most Common Feline & Canine Cancers\*

Feline	Canine
Biliary Carcinoma	Transitional Cell Carcinoma of the Bladder
Dermal Carcinoma	Appendicular Osteosarcoma
Vaccine-Associated Fibrosarcoma	Melanoma
Intestinal Adenocarcinoma	Splenic Hemangiosarcoma
Intestinal Lymphoma	Anal Gland Adenocarcinoma
Intestinal Mast Cell Tumor	Lymphoma
Mammary Adenocarcinoma	Prostatic Carcinoma
Nodal Lymphoma	Fibrosarcoma
Oral Squamous Cell Carcinoma	Digital Squamous Cell Carcinoma
Soft Tissue Sarcoma	Thyroid Carcinoma
Splenic Mast Cell Tumor	
Transitional Cell Carcinoma of the Bladder	

Source: Annette M. Sysel, D.V.M., of the Bauer Research Institute, based on a survey of board-certified veterinary oncologists across the country who reported the most common feline and canine tumors they see in their clinics.

\* The cancers are listed in no particular order.

## Anti-Tumor Drug

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part of many metabolic processes, is harmless in the bloodstream when bound to vitamin B12.

"NO-Cbl remains stable in the bloodstream because of the higher pH, or alkaline, environment as compared to the lower pH, or acidic, environment inside cells," Sysel explains. "Once inside a cell, nitric oxide and vitamin B12 separate, and nitric oxide induces cell death. The separation only occurs in the acidic environment inside the cell, not in the bloodstream, where it might otherwise cause devastating side effects."

The Winn Feline Foundation, a nonprofit organization that funds and supports feline health research, awarded Sysel and Bauer a \$17,600 grant to help advance their NO-Cbl research. The funding allowed them to analyze tumor tissue as well as adjacent healthy tissue from a variety of tumors in cats. Their goal was to determine which types of tumors have greater numbers of vitamin B12 transport proteins and receptors and therefore may be more susceptible to the effects of NO-Cbl.

"No one has really quantified how many transport proteins and receptors are expressed by cancer cells compared to normal cells," says Sysel. "Furthermore, we compared different tumor types, such as skin tumors to mammary tumors, to see which ones had a greater number of transport proteins and receptors. We also looked within those tumor types to see if individual tumors varied in their expression."

The Bauer research team studied 12 tumor types from 36 cats, yielding over 140 tissue slides. The slides were stained using antibodies that color the vitamin B12 transport proteins and receptors. More intense staining identified "tissues expressing high numbers of TCII and TCII-R and thus having a great demand for vitamin B12 and the capability to take up more vitamin B12 and subsequently NO-Cbl," Sysel says.

"Every feline tumor sample stained positively for TCII and TCII-R and showed significantly more proteins and receptors than normal tissues," she adds.

A further application of this research is testing the use of vitamin B12 in tumor imaging, a process that could become an important tool in the future. "When radioisotopes are bound to vitamin B12, the compound will be taken up by cancer cells," Sysel says. "Surgeons will be able to see exactly where tumor cells are and verify the complete removal of a tumor as well as to check for the presence of metastatic disease and to monitor tumor response to treatment."

To identify the most common malignant cancers in cats and dogs, Sysel conducted a survey of several board-certified veterinary oncologists across the country. These oncologists reported the most common feline and canine tumors they see in their clinics.

The 12 most common feline tumors identified, in no particular order, included: biliary carcinoma, dermal carcinoma, vaccine-associated fibrosarcoma, intestinal adenocarcinoma, intestinal lymphoma, intestinal mast cell tumor, mammary adenocarcinoma, nodal lymphoma, oral squamous cell carcinoma, soft tissue sarcoma, splenic mast cell tumor, and transitional cell carcinoma of the bladder. The tumor tissues and adjacent normal tissues evaluated were obtained from tumor samples following biopsy or surgical removal.

### NO-Cbl in Canine Cancer

In dogs, cancer is one of the leading causes of death. The National Cancer Institute estimates that a dog is diagnosed with cancer every five seconds in the United States.

The AKC Canine Health Foundation awarded Sysel a \$12,000 grant to study the use of vitamin B12 in tumor imaging

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*GERALD POST, D.V.M., DACVIM-ONCOLOGY, OF THE VETERINARY CANCER CENTER IN NORWALK, CONN.*

and treating cancer. The Canine Health Foundation study, similar to the one conducted in feline tumors, evaluated tumor tissues and adjacent normal tissues from 10 tumor types in 30 dogs.

According to the veterinary oncologist survey that Sysel conducted, the 10 most common tumor types, in no particular order, included: transitional cell carcinoma of the bladder, appendicular osteosarcoma, melanoma, splenic hemangiosarcoma, anal gland adenocarcinoma, lymphoma, prostatic carcinoma, fibrosarcoma, digital squamous cell carcinoma, and thyroid carcinoma.

"Every canine tumor sample stained positively for TCII and TCII-R and showed significantly more proteins and receptors than normal tissues," Sysel says. "Results from this study strongly support the use of vitamin B12-based agents for both the diagnosis and treatment of canine tumors."

Four case studies in dogs showed that NO-Cbl has a significant anti-tumor response against different tumors without systemic or local toxicity. The case studies that tracked the effect of NO-Cbl in dogs were published in the 2010 issue of *Investigational New Drugs*. Daily subcutaneous injections of NO-Cbl performed at home by the owners caused no adverse effects and measurable regression of various types of tumors.

A 10-year-old Bichon Frise named "Oscar" was the first dog to receive NO-Cbl for treatment of anal sac adenocarcinoma and its metastasis to a local lymph node. Oscar received NO-Cbl treatment for over a year without negative side effects.

"When Oscar died naturally at 15 years old, he had not received NO-Cbl therapy for at least two years and there was no evidence of the cancer," Sysel says. "NO-Cbl extended his life span for more than five years, giving him a good quality of life during this time."

The findings from the Winn Feline Foundation and Canine Health Foundation studies will help determine which tumors have the highest demand for vitamin B12. "We'll know what tumor type we want to target in future clinical trials of NO-Cbl in cats and dogs," Sysel says. "I also hope that TCII and TCII-R staining will help veterinarians to diagnose and tailor treatments to individual cancer patients."

"NO-Cbl is a potential game changer in the field of veterinary oncology," Post says. "This therapy would be an entirely new class of compounds that veterinary oncologists could use to help treat many different types of cancers in both cats and dogs. Because of its unique mechanism of action, this therapy may be combined with other types of therapies so that more effective protocols can be developed."

Cats diagnosed with cancer typically are treated with drugs approved for use in humans or dogs. "Veterinarians are forced to extrapolate doses, dosing intervals and treatment schedules that are suitable for cats," Sysel says.

Only two cancer drugs are approved by the FDA for use in animals, and both are labeled exclusively for use in dogs. Side effects that cats may experience from these drugs include nausea, anorexia, vomiting, diarrhea, lethargy, and bone marrow suppression.

"There are a few companies looking to develop veterinary-specific cancer medications, but the numbers are still quite low," Post says. "There is definitely a need for more effective therapies for cats, dogs and even people. By understanding the cancer, the drugs and the mechanisms to mitigate side effects, we are moving in the right direction."

"My research continues Dr. Bauer's original research of NO-Cbl," Sysel says. "I have a heartfelt interest in advancing this anti-cancer treatment for cats since my beloved Tiki died from cancer. There are more cats as pets in this country than any other animal, but the least amount of research money is available to help identify beneficial treatments for them. For me personally, this research is very important." ■

Purina appreciates the support of the Winn Feline Foundation and particularly Vicki L. Thayer, D.V.M., DABVP, president, in helping to identify topics for the *Purina Pro Club Update* newsletter.

## Tips on Getting the Most from Your *Purina Pro Club* Membership

Among the benefits of being a member of *Purina Pro Club* is receiving cat food checks to offset the costs of *Purina* brand cat and kitten foods. Kitten Starter Kits, which members can order to give new owners a head start on a long, happy life with their kittens, and a subscription to the *Purina Pro Club Update* newsletter with the latest information on feline health care and genetic advances are other perks.

Here are tips to help you get the most from your membership.

### Submitting Weight Circles

Weight circles are the colored circles on packages of eligible *Purina* brand cat and kitten foods that allow you to receive cat food checks. When submitting weight circles, keep in mind you should:

- Use a *Pro Club* Cat Weight Circle Submission Form. You can download a form at [https://purinaproclub.com/Content/Download/Cat\\_Weight\\_Circle\\_Form.pdf](https://purinaproclub.com/Content/Download/Cat_Weight_Circle_Form.pdf) or by calling 1-877-PRO-CLUB (1-877-776-2582) between 7 a.m. and 5 p.m. CDT Monday through Friday.
- Fill out the Cat Weight Circle Submission Form completely to expedite the processing.
- Always put your return address on the envelope.
- Submit a minimum of 75 pounds' worth of weight circles in one submission. Submitting smaller amounts is not cost effective for *Pro Club* and increases handling time for all members.
- Submit only weight circles, not UPC codes. Only weight circles are valid for credit to your account. An exception is *Purina Veterinary Diets FortiFlora* brand feline nutritional

supplement, which was added to the *Pro Club* program on Jan. 1, 2013. Until FortiFlora packaging is updated with a weight circle, acceptable proof-of-purchase will be the UPC code from the bottom of the box or the entire box including the UPC code.

- Weight circles and points from redeemed weight circles cannot be purchased or transferred.



- Do not submit torn and worn weight circles or tape multiple weight circles together.
- *Pro Club* recommends that you mail your weight circles by certified first-class mail or other traceable delivery method. This helps to ensure proof of delivery in the event *Pro Club* does not receive your weight circles. *Pro Club* is not responsible for weight circles not in its possession.

### Ordering Kitten Starter Kits

*Pro Club* members may order Kitten Starter Kits that contain important information on caring for new kittens. Space is provided for adding breed information and veterinary records. To order Kitten Starter Kits, you should:

- Order Starter Kits for the kittens you currently have on the ground.

Starter Kit information and coupon expiration dates are continually updated, so make sure you have the most current Starter Kit information and offers available for your new kitten owners.

- Check your Starter Kit shipment upon receipt for materials. Multiple box shipments may have baggies and coupons in only one box.
- Contact *Pro Club* on nondelivery of orders, rather than reordering, so delivery issues can be corrected.

### Redeeming Purina Points

Weight circles turn into Purina Points that can be automatically redeemed for *Purina* cat food checks. When redeeming points, keep in mind:

- Weight circle redemption points are automatically redeemed for \$6 checks good toward the purchase of any 6 pound or larger bag of *Purina* cat or kitten foods; 600 points equal one \$6 check. Points are not "banked" except when totaling less than 600 points. Points totaling less than 600 will remain in the member's account until the next weight circle submission.
- Keep your *Pro Club* account address current. *Pro Club* is not responsible for packages sent to wrong addresses.
- Don't allow your cat food checks to expire. *Purina* cat food checks have a one-year expiration and cannot be reissued if a member allows them to expire.
- As stated on the cat food check, only one \$6 check can be used with the purchase of one bag of a *Purina* product. The terms on the cat food check state "limit one check per bag." ■

## FortiFlora Offers a Nutritional Supplement for the Dietary Management of Cats with Diarrhea

*Purina Veterinary Diets FortiFlora* brand feline nutritional supplement, which is available by prescription only, provides dietary management of cats with diarrhea. The nutritional supplement may be helpful in managing cats experiencing:

- Stressful situations due to travel or change in home environment
- Diet change or consumption of inappropriate foods

- Soft stools in kittens
- Antibiotic therapy

The normal intestinal tract of cats is home to thousands of different types of bacteria, both beneficial and harmful. In the healthy intestine, these bacteria are in balance. In cats with diarrhea, the normal balance of bacteria in the intestine is upset.

Introduced in 2006, FortiFlora with *Enterococcus faecium* SF68, a live beneficial probiotic, or bacteria, offers a way to help re-establish a

normal intestinal balance by increasing the number of beneficial bacteria. FortiFlora also helps support a healthy immune system. ■



### Want to Reach the Editor?

Have comments about *Purina Pro Club Update*? Send them to us at: *Purina Pro Club Update*, c/o Editor, Nestlé Purina PetCare, 2T Checkerboard Square, St. Louis, MO 63164 or via email at [today'sbreeder@purina.com](mailto:today'sbreeder@purina.com).

### Send Us Your Questions

Have questions about your Purina Points or how to redeem weight circles for rewards and rebate checks? Contact *Purina Pro Club* at 877-PRO-CLUB, or 877-776-2582, between 7 a.m. and 5 p.m. CDT Monday through Friday. You also may visit [www.purinaproclub.com](http://www.purinaproclub.com) to review and redeem Purina Points.

## Pro Club Increases the Point Value of Some Cat Foods & Adds FortiFlora

**P**urina Pro Club recently increased the Purina Points members receive when they submit weight circles from *Purina Veterinary Diets* brand therapeutic feline formulas. In addition, *Purina Veterinary Diets* FortiFlora brand feline nutritional supplement has been added to the list of products eligible for Purina Points.

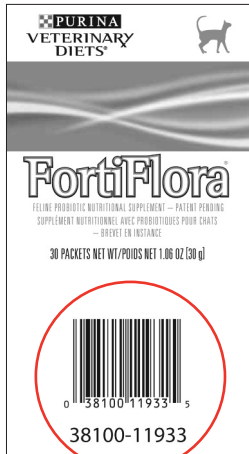
Effective Jan. 1, 2013, submission of weight circles from *Purina Veterinary Diets* feline formulas increased to 16 points per pound. Weight circle submissions from FortiFlora, a nutritional

supplement available by prescription only that provides dietary management of cats with diarrhea, are 390 points per box. Until FortiFlora packaging is updated with a *Pro Club* weight circle, acceptable proof-of-

purchase will be the UPC code from the bottom of the box or the entire box including the UPC code.

"We are excited to add FortiFlora to the *Pro Club* program," says Lisa Walsh, *Purina Pro Club* Communications Manager.

A new *Pro Club* Cat Weight Circle Submission & Reward Order Form that reflects the changes is available online at <https://purinaproclub.com/>



Purina Points Earned for <i>Purina</i> Brand Weight Circles	
Brand	Purina Points
<i>Purina Veterinary Diets</i> FortiFlora brand feline nutritional supplement	390 points per box
<i>Purina Veterinary Diets</i> brand therapeutic feline formulas	16 points per pound
<i>Canyon Creek Ranch</i> brand cat food	16 points per pound
<i>Purina Pro Plan</i> (All Formulas)	16 points per pound
<i>Purina ONE</i> (All Formulas)	16 points per pound
<i>Purina Cat Chow</i> , <i>Purina Kitten Chow</i> , <i>Purina Kit &amp; Kaboodle</i>	8 points per pound

[Content/Download/Cat\\_Weight\\_Circle\\_Form.pdf](#) or by calling 1-877-PRO-CLUB (1-877-776-2582) between 7 a.m. and 5 p.m. CDT Monday through Friday.

Weight circle submissions are processed as Purina Points that can be redeemed for \$6 checks good toward the purchase of any 6 pound or larger bag of *Purina* brand cat or kitten food. Using the Weight Circle Submission & Reward Order Form to submit weight circles is required and also helps speed up the processing of weight circles.

### Reminders from *Pro Club*

*Pro Club* members should be aware of the following:

- *Purina Pro Club* is not a program for institutional organizations, such as rescue groups, humane societies or animal shelters.
- Any retail sale or purchase — including Internet transactions — of *Purina* and *Purina Pro Club* materials is a violation of program terms and

conditions. This includes, but is not limited to, the selling or buying of Kitten Starter Kits and weight circles.

- *Pro Club* is not responsible for fraudulent weight circles. Submitting fraudulent weight circles is a violation of the *Pro Club* program terms and conditions.
- Purina reserves the right to terminate membership or remove or disqualify earnings for any violation of account or program terms ■

### Certify Weight Circles

**P***ro Club* recommends that you mail your weight circles by certified first-class mail or other traceable delivery method. This helps to ensure proof of delivery in the event *Pro Club* does not receive your weight circles. *Pro Club* is not responsible for weight circles not in its possession.

PURINA Pro Club Update

Scan this QR code on your smartphone to visit [www.purinaproclub.com](http://www.purinaproclub.com) for your Purina Points Summary and detailed account activity. You also may call 1-877-PRO-CLUB (1-877-776-2582).



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