

# Novel Therapies for Feline Chronic Enteropathy

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Whether it is from internet research, social media, TV advertising, or personal experience, our clients are becoming increasingly aware of therapies beyond those traditionally utilized in our treatment of gastrointestinal disease. Hence, we must make every effort to stay at least one step ahead of our clientele, and take that step using as much evidence-based medicine as possible to support our commentary and our recommendations. This is not an easy task, but it is an important one if we hope to maximize the effectiveness, both therapeutic- and cost-, of our treatment regimens.

## Probiotics

Our knowledge of the GI microbiome is still incomplete. We know there are normal inhabitants, such as Firmicutes, Bacteroidetes, Fusobacteria, etc.; we know there are pathogens including various Clostridium, Campylobacter, Salmonella, and Escherichia spp; and we know that “dysbiosis” is a common finding in dogs with chronic diarrhea as a result of GI disease.

What we know about the use of probiotics in GI disease is even more incomplete. We know that to have any chance of being beneficial, the probiotic supplement must 1) contain a lot of organisms – current human trials are often using orders of magnitude higher doses than those found in veterinary studies; 2) those organisms must be alive; 3) probiotic effects are likely to be rapid onset with minimal staying power once discontinued; 4) probiotics are assumed to work by changing the make-up of the intestinal microbiota, but may in fact exert effects in other ways; 5) fortunately, like cobalamin, probiotics seem to belong on the same “do no harm” poster, with very few and very extra-ordinary exceptions.

Probiotics in the Feline Veterinary Literature			
Citation	Population (n)	Key	Reported Effect
Marshall et al AJVR 2006	Healthy adult cats (12)	2	↑ Lactobacillus, ↓ Clostridium & Enterococcus
Veir et al Vet Ther 2007	Kittens (9)	1	↑ CD4+ cells
Lappin et al JFMS 2009	Chronic FHV-1 cats (12)	1	lessened morbidity
Rishniw et al JFMS 2011	CKD cats (10)	3	Failed to reduce azotemia sprinkled on food
Garcia et al FEMS 2011	Healthy cats & dogs (12/12)	4	↑ abundance of probiotic bacteria in feces
Bybee et al JVIM 2011	Shelter dogs & cats (> 100)	1	Cats sig fewer episodes ≥ 2 days
Hart et al JFMS 2012	Feline chronic diarrhea (53)	4	70% perceived improvement in diarrhea
Lalor & Gunn-Moore ISFM 2012	Trichomonas (Abstract)	1	Concurrent Rx reduces recurrence

1 Enterococcus faecium SF68 (FortiFlora); 2 Lactobacillus acidophilus; 3 Azodyl; 4 Provable-DC (Nutramax)

## Cobalamin

As we race to give the injection of our current “do no harm” poster child, vitamin B12, do not lose sight of the fact that cobalamin levels can be used as a diagnostic tool. Many cats with chronic gastrointestinal signs receive cobalamin supplementation regardless of their endogenous level, and so that level is often left unmeasured. But research suggests that the lowest cobalamin levels are frequently found in cats with GI lymphoma, and gastroenterologist are forever struggling with the important distinction between IBD and GI lymphoma. Of course it is not that easy – cats with IBD can have very low cobalamin levels, and cats with GI lymphoma can have normal cobalamin levels, but we start with a clinical diagnosis and test to support or refute that diagnosis. In that capacity, the initial cobalamin concentration could be an important clue.

It was the Ruaux et al. study of 2005 (JVIM) that alerted the profession to the importance and impact of cobalamin supplementation (250 micrograms SQ once weekly) in cats with GI disease and marked hypocobalaminemia ( $\leq 100$  ng/L). Since that seminal study cobalamin levels are being measured in cats with a wide variety of non-GI diseases and hypocobalaminemia may be a significant contributor to a number of conditions. In 2007 Allenspach et al. (JVIM) identified hypocobalaminemia ( $\leq 200$  ng/L) as a significant risk factor for a negative outcome for dogs with chronic enteropathies, and a cobalamin less than 150 ng/L is suggestive of GI lymphoma in cats.

## Stem cells

The most commonly diagnosed Feline Chronic Enteropathy is inflammatory bowel disease. IBD in cats is not subdivided into ulcerative colitis and Crohn’s disease, as IBD is in human patients. The cytokine profile in cats with IBD compared to cats with non-IBD GI disease shows an increase in both immunomodulatory cytokines IL-10 and TNF- $\beta$  as well as the proinflammatory cytokines IL-6, IL-18, TNF- $\alpha$ , and IL-12p40. In a separate study the proinflammatory cytokines IL-1, IL-8, and IL-12 were increased in cats with IBD. Clearly there is significant immune dysregulation in feline IBD, and although the cytokine profile is complex and incompletely understood, it appears consistent with a Th1 response, as seen in humans with Crohn’s disease. The trophic properties along with the

anti-inflammatory and immunomodulatory effects of MSC administration make it a theoretically beneficial therapeutic modality for the treatment of feline IBD. The early success reported in animal models and clinical trials with human patients suffering from Crohn's disease further suggest that the use of MSC therapy in feline IBD warrants further investigation. Our laboratory has shown that feline adipose-derived MSC (fMSC) can be generated in large quantities to allow for clinical use, and that these fMSC are plastic-adherent, spindle-shaped cells that possess tri-lineage differentiation capabilities and suppress T-cell proliferation in vitro. Allogeneic fMSC have been safely and repeatedly administered to healthy and diseased cats with no notable side effects. We are currently conducting a blinded placebo control study to evaluate the safety, feasibility, and clinical effect of allogeneic fMSC as a treatment for feline IBD.

### **What's all this have to do with my clients and their cats?**

Adipose-derived feline mesenchymal stem cells ARE NOT embryonic stem cells, and so a significant barrier to their use (those based on philosophical, religious, and ethical beliefs) has been removed. Any client with a keyboard can quickly immerse themselves in the internet enthusiasm for the "silver bullet" potential of stem cell therapy – and then they come to see you! As summed up by Dr. Dori Borjesson, (Cyranoski 2013), many veterinarians offer stem cell therapies to satisfy demanding customers, so "Clinicians are sucked into giving treatment" even in the absence of research to support such treatment.

It appears that currently there are 2 veterinary companies vying for your stem cell business; Vet-Stem ([www.vet-stem.com](http://www.vet-stem.com)) which offers Vet-Stem® Regenerative Cell Therapy® and MediVet America, LLC, ([www.medivet-america.com](http://www.medivet-america.com)) which offers an in-house kit. In either case, the majority of these commercial treatments involve patients with orthopedic and musculoskeletal problems: chronic osteoarthritis, soft tissue injuries of the joints, tendons and ligaments, and fractures, although feline gingivitis, kidney disease, IBD, and pulmonary fibrosis are also reported as targets. Neither website provides any references or cites any research on the use of their product in cats with chronic enteropathies, including IBD.

In both cases the process begins with the harvesting of adipose tissue from the patient to be treated (autologous treatment). Vet-Stem has you ship that adipose tissue to their facility for processing, the company returns the injection-ready product (Vet-Stem® Regenerative Cell Therapy®) within 24 hours, at a cost of approximately \$2,000 - \$3,500, and with the requirement that the veterinarian has completed the company's accreditation course. MediVet America provides a kit for the in-house processing of adipose tissue, producing an injection-ready product in approximately 4 hours, at cost of about \$1,800. Both companies claim to have serviced thousands of pets, although neither provides a specific number for the cats that have received treatment.

MediVet America states that "Adult stem cells are highly concentrated in the fat tissue. At this concentration, it is no longer necessary to culture the stem cells to acquire the necessary cell numbers to make a healing impact. The stem cells are contained within a pool of cells in the fat termed the Stromal Vascular Fraction (SVF). The SVF may impart anti-inflammatory effects, add bioactive peptides, and contribute to reformation and architectural organization. These are benefits lost once stem cells are cultured." The company provides a enzyme system to break down the adipose tissue and a filter and antibiotic wash for sterility of the resultant stromal vascular fraction. A key step appears to be the LED light activation of proliferation, differentiation, and induction prior to the reintroduction into the patient. MediVet claims that "we have seen positive clinical improvement in 95% of the arthritic cases performed nationwide."

Vet-Stem processes the adipose tissue within their own facility and returns injection-ready Vet-Stem Regenerative Cells (VSRC™) within 24 hours, "a functionally diverse cell population able to communicate with other cells in their local environment." Bob Harman, Vet-Stem, Inc. CEO is quoted as saying there is "an 80% success rate in improvement of quality of life." (Smith 2013). Again, there are no references or cited research on the use of this therapy in cats with chronic enteropathies, including IBD. The website states that Vet-Stem is currently evaluating the use of stem cells for the treatment of IBD, feline CKD, liver disease, immune-mediated diseases, and heart disease. Their website states that cancer, systemic infection, neurologic disorders (including spinal cord injuries), uncontrolled diabetes mellitus, and any organ disease disqualifies a pet for Vet-Stem therapy.

### **Stem cells - conclusion**

- Stem cell therapy is not currently regulated by the FDA.
- "Stem cell therapy" is actually the injection of a heterogenous population of cells, including mesenchymal stem cells, endothelial progenitor cells, fibroblasts, haematopoietic and immune cells, and others.
- A search of PubMed for studies on MSC therapy in clinical cases of feline diseases produces a single pilot study looking at their use in cats with CKD (Quimby 2011).
- Stem cells have become the latest in a long line of therapies in veterinary medicine where our use is fast and far out-pacing our understanding.
- Proceed with optimism and hope, but significant contemplation and caution.

## Summary

- Dietary intervention may not be the only therapy, but it must be a part of an effective plan
- It takes 3 strikes before a cat is out; even a different version of a diet-type may hit the mark
- 2 weeks, not 12, or “Thank Heaven I’m not a Dermatologist!”, for a GI diet-trial
- Expand the definition of Dietary Intervention beyond Diets

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