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# Algal Polysaccharides to improve Gut Health and Immunity in Pets







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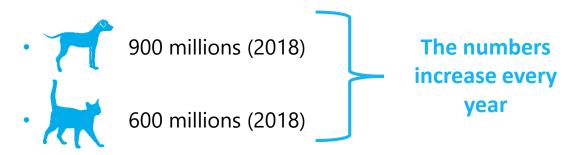




#### CONTEXT Cats and dogs in the world

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• 57% of the world population possess a pet



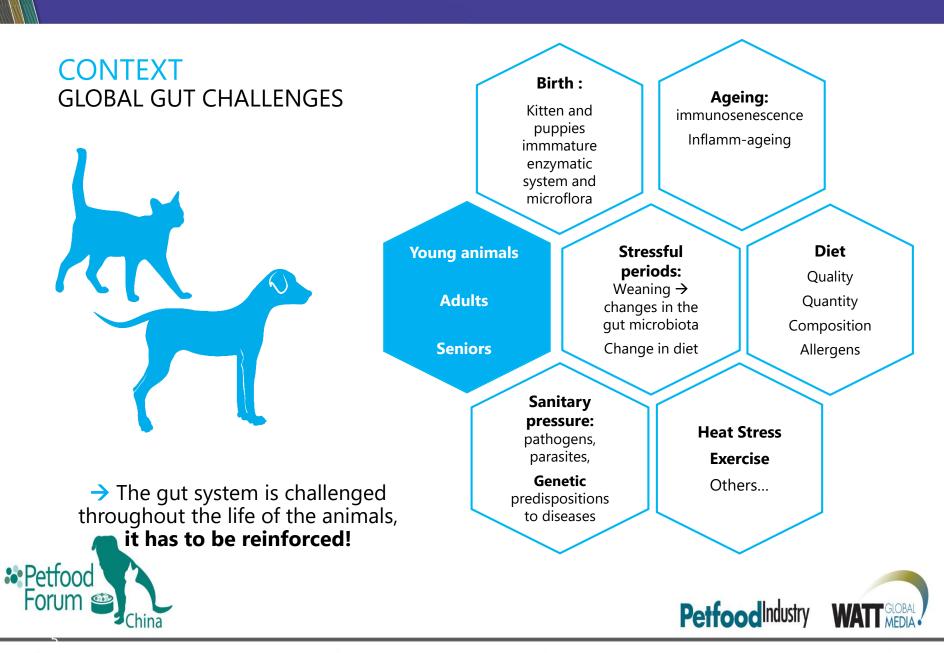
Cats and dogs are considerate as part of the family

- Higher concerns about their health Need to prolong their life expectancy Geriatric
  - 'Exotic' Industrial compound feed

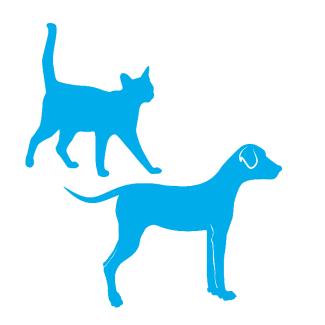








#### CONTEXT GLOBAL GUT CHALLENGES



 The gut system is challenged throughout the life of the animals, it has to be reinforced!

## NUTRITIONAL SOLUTIONS and TOOLS





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#### Hypoallergenic Diets

- The ability to induce an antibody mediated hypersensitivity response appears to be dependent upon the **size and structure of the protein**.
- The allergens in soybean protein, for example, are between 20 and 78 kilodaltons, suggesting that soybean proteins with a molecular weight below this threshold would be less likely to illicit an immune-mediated response.
- Hypoallergenic diets are particularly beneficial as elimination diets for the diagnosis and management of **food hypersensitivity**
- -> when a patient appears to be allergic to multiple allergens,
- -> when a complicated dietary history makes it difficult to identify a "novel" protein,
- -> or when a patient has severe IBD.





#### **Dietary Fiber**

- The **gelling and binding properties of fatty acids** and deconjugated bile acids **in soluble fibers** may be beneficial in certain gastrointestinal diseases. The use of soluble (fermentable) fiber in preference to insoluble (non-fermentable) fiber is generally advocated because most **soluble fibers generate butyrate**, the principle source of energy for the colonocyte, and other short-chain fatty acids.
- Short-chain fatty acids may lower the colonic luminal pH, impeding the growth of pathogens.
- The health benefits derived from dietary supplementation of prebiotics have been documented in humans and feeding **oligofructose** to dogs decreased the concentrations of **fecal ammonia and amines** and increased the numbers of bifidobacteria in dog feces.



Brockett M, Tannock GW. Dietary influence on microbial activities in the cecum of mice. *Can J Microbiol* 1982;28:493-499. Hussein HS, *et al*. Petfood applications of inulin and oligofructose. *J Nutr* 1999;129(7 Suppl):1454S-6S



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### Fat

- Avoiding excessive fat can be instrumental in the management of various gastrointestinal diseases because fat delays gastric emptying in dogs and high-fat foods may contribute to osmotic diarrhea.
- Malabsorbed fatty acids are hydroxylated by intestinal bacteria and stimulate colonic water secretion, exacerbating diarrhea as well as gastrointestinal protein and fluid losses.



Cummings JH, et al. Influence of diets high and low in animal fat on bowel habit, gastrointestinal transit time, fecal microflora, bile acid, and fat excretion. J Clin Invest 1978;61:953-963.



#### PolyUnsaturated Fatty Acids

- Fish oil has been reported to be beneficial in ulcerative colitis and Crohn's disease patients, but the results are controversial.
- Only a <u>few studies</u> found significant decreases in rectal LTB<sub>4</sub> concentrations; the others simply reported clinical improvement.
- There are no published studies in the veterinary literature to date demonstrating the efficacy of n-3 fatty acid supplementation in managing canine or feline patients with IBD.



Seidner DL, *et al*. An oral supplement enriched with fish oil, soluble fiber, and antioxidants for corticosteroid sparing in ulcerative colitis: a randomized, controlled trial. *Clin Gastroenterol Hepatol*. 2005 Apr;3(4):358-69.



#### Probiotics

- Administration of probiotics to dogs and cats with IBD represents a novel alternative therapeutic modality that warrants further investigation.
- It has been demonstrated that colitis in both humans and mice is associated with increased levels of cytokines such as TNF- $\alpha$ , IL-6, IL-12p70 and IL-23. Thus, a proper selection of probiotic strains for the treatment of IBD is crucial and should be based on the **estimation of their capacity to induce anti-inflammatory pattern of cytokines** (IL-10<sup>high</sup>, TGF- $\beta$ <sup>high</sup>, IL-12p70<sup>low</sup>, IL-23<sup>low</sup>, TNF- $\alpha$ <sup>low</sup>).
- Apart from immunomodulatory effects, probiotics have a protective effect on the normal microflora of the human gut by their **competitive antimicrobial activities** directed toward intestinal pathogens.



Becker C., Dornhoff H., Neufert C, *et al*. Cutting edge: IL-23 cross-regulates IL-12 production in T celldependent experimental colitis. *J. Immunol* 2006;177, 2760-2764. Fuss IJ, Becker C, Yang Z, *et al*. Both IL-12p70 and IL-23 are synthesized during active Crohn's disease and are down-regulated by treatment with anti-IL-12 p40 monoclonal antibody. *Inflamm Bowel Dis* 2006;12, 9-



#### Herbs

- Plaintain leaf (*Plantago spp.*) is a ubiquitous weed with dark green, fibrous leaves. It also contains mucilage and tannin constituents, and is rich in antioxidant chlorophyll, fiber, and a very rich assortment of vitamins and minerals, all of which are beneficial in the maintenance of **mucous membranes** and healthy flora.
- Licorice root (*Glycyrhizza glabra*) is well known by herbalists as a powerful antiinflammatory, immune stimulant, vulnerary (speeds wound healing), antimicrobial herbal medicine that is remarkably effective in the digestive tract. It is especially useful for **healing ulceration of the stomach**
- Part of licorice's effect in the gut can be attributed to its glycyrrhizin content. Glycyrrhizin's chemical structure is similar to anti-inflammatory corticoids. The herb contains several other saponin constituents, as well.



Source: Greg Tilford, All You Ever Wanted to Know About Herbs for Pets, (Bowtie, 1999).



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#### Vitamins and Minerals

• Water-soluble vitamins are often depleted by the fluid losses associated with diarrhea and fat-soluble vitamin loss can be significant in animals with steatorrhea. Magnesium deficiency has been well documented in Yorkshire Terriers with severe inflammatory bowel disease and lymphangiectasia. Cats with severe IBD frequently have subnormal serum cobalamin concentrations.

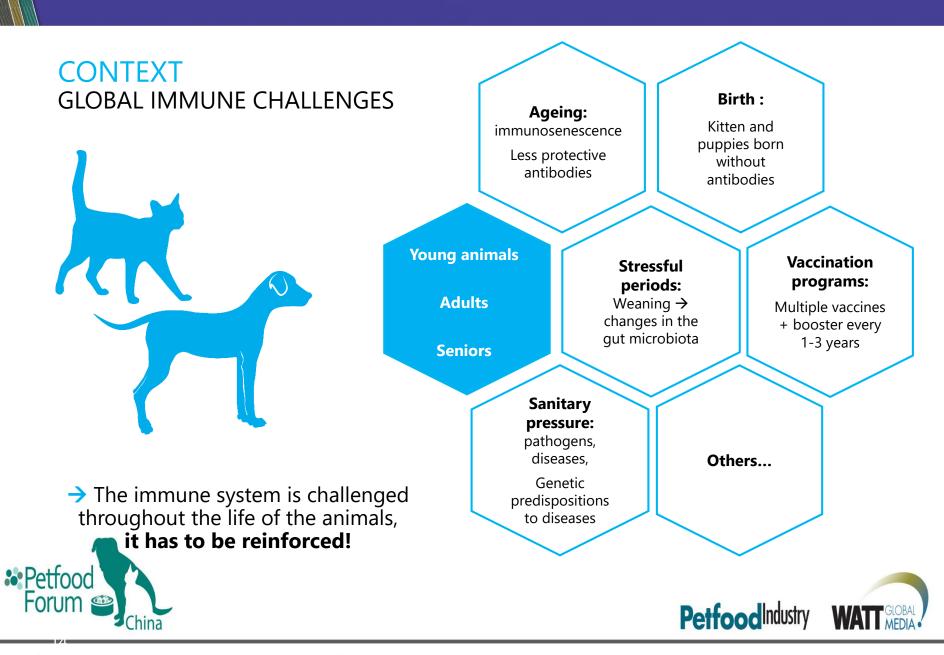
#### Others

- Patients with mild-to-moderate IBD can often be successfully managed with dietary modification and **antimicrobial** (tylosin or metronidazole) administration.
- Dogs and cats with lack of response to more conservative therapy or patients with severe IBD based on activity index scores or histologic findings should be managed with immunomodulatory therapy.



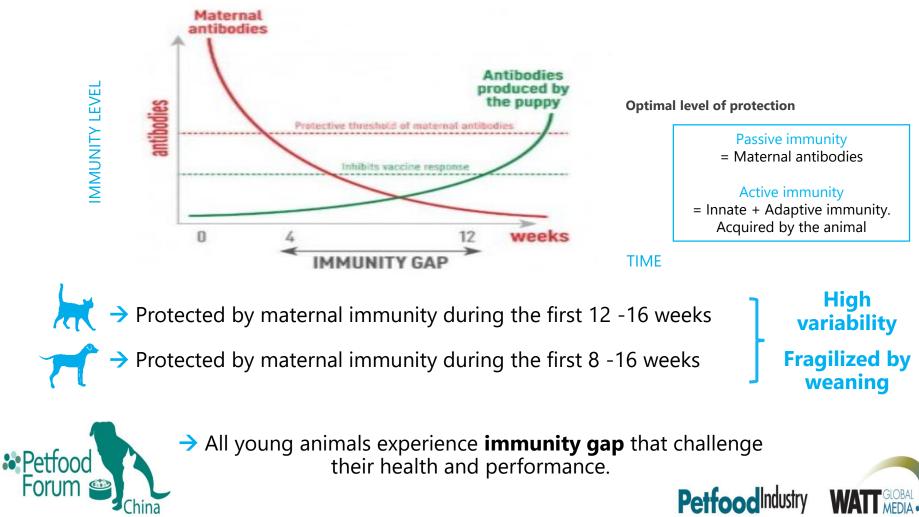
Kimmel SE, *et al*. Hypomagnesemia and hypocalcemia associated with protein-losing enteropathy in Yorkshire terriers: five cases (1992-1998). *J Am Vet Med Assoc* 2000;1;217(5):703-6.



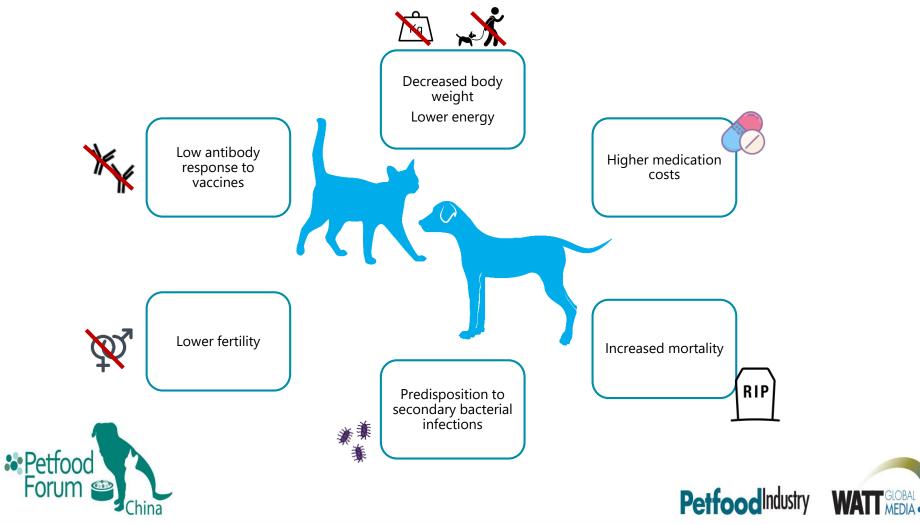


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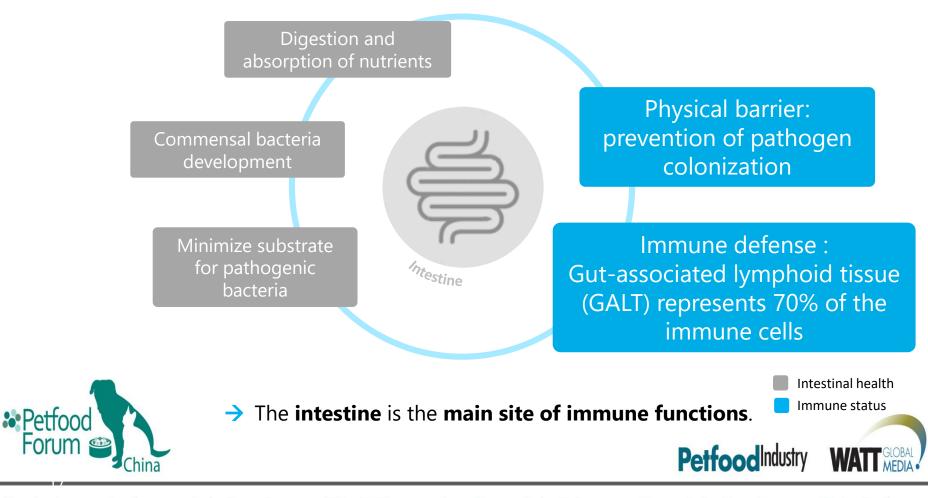
#### CONTEXT IMMUNE PROTECTION VARIES IN THE HOST ANIMAL



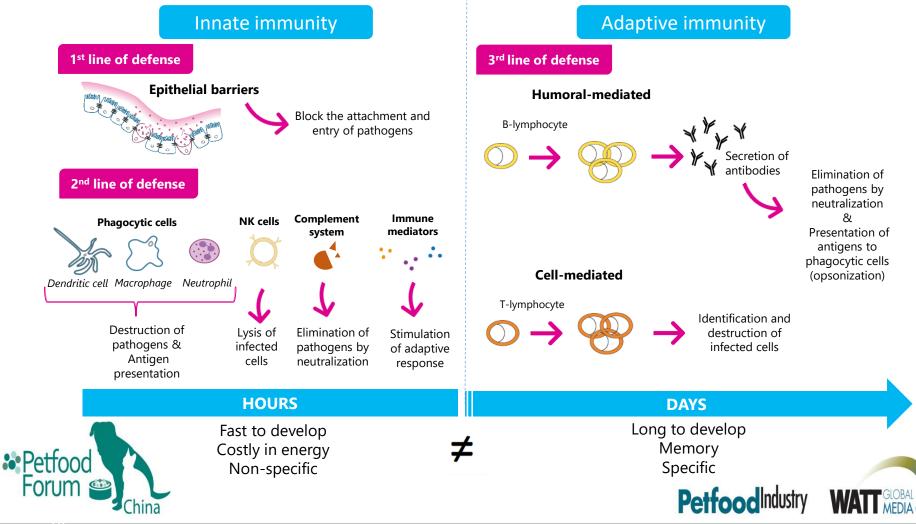
#### CONTEXT NEGATIVE CONSEQUENCES OF IMMUNE CHALLENGE



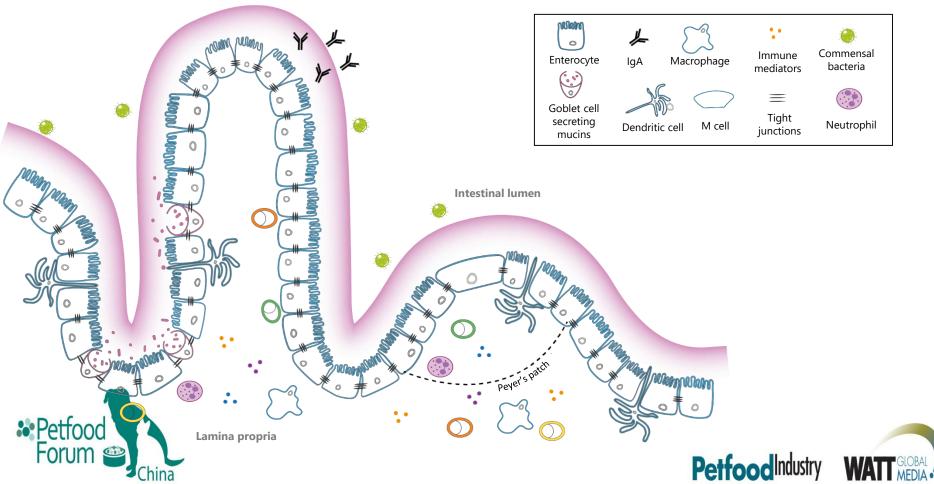
#### CONTEXT INTESTINAL HEALTH AND IMMUNE STATUS



#### CONTEXT IMMUNE SYSTEM



### IMMUNE SYSTEM GLOBAL ORGANIZATION



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#### → A dynamic system to fight microbes

#### CHALLENGE IMPACT ON INTESTINAL HEALTH AND IMMUNE STATUS

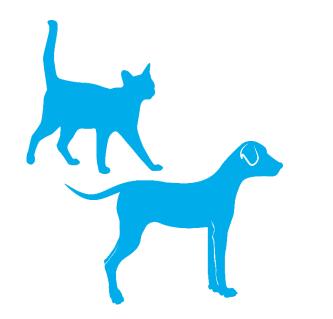
What happens in the gut in case of challenging situation?

- $\rightarrow$  Decrease of the protective mucus layer
- $\rightarrow$  Alteration of tight junctions

As a consequence...

Increase of intestinal permeability
Translocation of pathogens & toxins
Overwhelmed immune system





The immune system is challenged throughout the life of the animals, it has to be reinforced!

## NUTRITIONAL SOLUTIONS and TOOLS





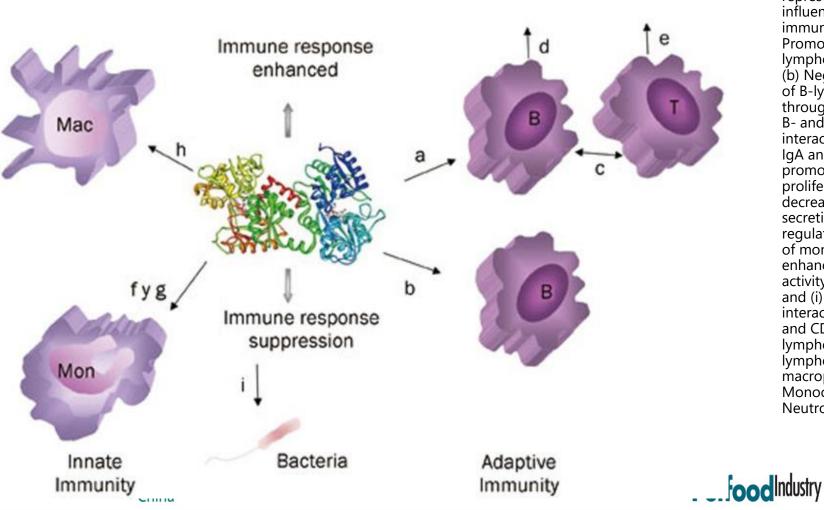
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#### Lactoferrin

- The first occurrence of an infant formula containing Lf was in Japan in 1986, and this product, which was called "BF-L dry milk", was marketed by the Morigana Milk Industry. Currently, Lf can be found in various products, such as yogurt, pet food, cream, and milk and other beverages.
- Lf is the **first line of defense** for any entry point in the body. It is found in small quantities in most body fluids such as saliva, tears, nasal secretions and **intestinal fluids** (*eg*, bile), as well as in **neutrophils** (the secondary granules of white blood cells).
- Lf is synthesized by the mucosal lining (*eg*, in the mouth or intestinal tract) and neutrophils, and it is released in response to inflammatory stimuli. The low physiologic serum levels of Lf increase significantly upon host infection.



#### IMMUNE SYSTEM Lactoferrin



Schematic representation of the influence of host Lf on immune cells. (a) Promotes B- and Tlymphocyte maturation; (b) Negative regulation of B-lymphocytes through LPS binding; (c) B- and T-lymphocyte interaction; (d) induces IgA and IgG secretion; (e) promotes T-lymphocyte proliferation; (f) decreases IL5 and IL10 secretion; (g) down regulates NFκβ activation of monocytes; (h) enhances the phagocytic activity of macrophages; and (i) prevents the interaction between LPS and CD14 as a TLR4. B, B lymphocytes; T, T lymphocytes; Mf, macrophages; Mon, Monocytes; Neu, Neutrophils.

> WATT GLOBAL MEDIA

•

#### IMMUNE SYSTEM Lactoferrin

- Colostrum, the first milk produced by the mammary glands of mammals after giving birth, contains elements with immunomodulatory properties, and these elements have attracted the attention of some pharmaceutical and nutritional industries as a dietary supplement.
- Lf is present in bovine colostrum at a concentration of 500 mg/100 g and is a GRAS (generally recognized as safe) product that is currently used in several countries as a supplement for infants. To date, no adverse effects regarding its use have been documented.
- Lactoferrin did not alter the intestinal morphology and had a minor impact on colonisation with lymphocytes and plasma cells. CD8 lymphocytes were increased in the epithelium of the colon of the lactoferrin groups.



Source : Histological and immunohistochemical evaluation of duodenal and colonic biopsies after oral bovine lactoferrin supplementation in beagle puppies. S. Handl Immunomodulatory effects of lactoferrin, <u>Tania Siqueiros-Cendón</u> et Al. <u>Acta Pharmacol Sin</u> 2014 May; hina 35(5): 557–566.

#### Probiotics

- Probiotics have also been utilized to facilitate eradication of intestinal parasites. A recent study documented the ability of the probiotic organism *Enterococcus faecium* SF68 to antagonize *Giardia intestinalis* infection in mice.
- Oral feeding of *E. faecium* strain SF68 starting 7 d before inoculation with *Giardia* trophozoites significantly increased the production of specific anti-*Giardia* intestinal IgA and blood IgG. This humoral response was mirrored at the cellular level by an increased percentage of CD4(+) T cells in the Peyer's patches and in the spleens of SF68-fed mice.
- The improvement of specific immune responses in probiotic-fed mice was associated with a diminution in the number of active trophozoites in the small intestine as well as decreased shedding of fecal *Giardia* antigens (GSA65 protein).



Benyacoub J, et al. Enterococcus faecium SF68 enhances the immune response to Giardia intestinalis in mice. J Nutr 2005;135(5):1171-6.



#### Prebiotics

- Use of prebiotics in companion animal nutrition is often considered advantageous over probiotics because of the ease of handling, ability to withstand processing and storage etc.
- The results indicated that supplementation of MOS at the rate of 15 g/kg in the diet of dog augmented the cell-mediated immune response and serum lipid profile without any influences on digestibility of nutrients, hindgut fermentation and antioxidants indices.



Effect of dietary mannanoligosaccharide supplementation on nutrient digestibility, hindgut fermentation, immune response and antioxidant indices in dogs. <u>J Anim Sci Technol</u>. 2017; 59: 11.



#### Beta-glucans in dog food

- Beta-glucans are water-soluble plant fibers, comprising chains of up to 2000 glucose units in so-called beta form. Glucose is a simple sugar, existing in solution as mixture of alpha and beta rings. The glucose building blocks of beta-glucans are joined by one of three linkage types. Beta-glucan constructions can differ as to linkage pattern, spatial structure and functionality.
- **Corn, rice, barley, wheat and oat** contain different amounts of similarly linked beta-glucans. Another type of beta-glucans is found in baker's yeast. The five cereal grains and yeast are commonly used as petfood ingredient.
- Dog-food labels rarely highlight the beta-glucans in whole cereals. In contrast, added concentrates of beta-glucans, isolated from the outer layer of baker's yeast, are reputed to strengthen dog's immune system.





#### Beta-glucans in dog food

- Free beta-glucans are **recognized by immune cells in the intestinal wall**. As a result, certain specialized cells may more efficiently capture and disarm harmful bacteria and viruses, while others produce more offensive antibodies.
- Such immunostimulation has been shown in dogs challenged with foreign substances (antigens), while ingesting purified beta-glucans derived from yeast or oyster mushroom. The amount ingested was equivalent to 0.08 % in dry food. Similar diet intervention also relieved symptoms in dogs with inflammation in joints, skin or bowel.
- In dogs, food with added, purified beta-glucans can stimulate the immune response elicited by antigens. The risk, if any, of overstimulation is unknown. There is no evidence that extra intake of beta-glucans, as purified additives, prevents development of diseases in dogs. Nevertheless, beta-glucans did ameliorate inflammatory diseases.





Herbs

- Some herbs demonstrate a direct immune-enhancing activity (Larix, Plantago derivatives...). In most cases this enhancement actually **balances immune function** rather than being purely stimulating.
- Eg. when given as the ground-up parts of the entire (fresh or dried) plant, echinacea has been shown to increase lymphocyte numbers when they are abnormally low, thanks to one of several biochemicals it contains. The same plant contains another biochemical that actually decreases the lymphocytes when their numbers are abnormally high.
- Many herbs, ounce for ounce, have as much or more antioxidant activity than that found in vitamins A, C, and E. Herbs can be given on a daily basis, in the form of a pinch of fresh or dried herb sprinkled over your dog's food or a mild tea made from the herb and poured over his food.





Specific nutrients that are indicated for immune-system health include:

vitamins A (beta-carotene), C, E, and B-6; zinc; selenium; linoleic acid; and lutein.

#### **B-Carotene**

- Dogs (1): Toll-like receptor (TLR) ligands might induce a greater anti-inflammatory gene expression profile in vivo in dogs.
- Cats (1): Domestic cats can readily absorb ß-carotene across the intestinal mucosa. Beta-carotene is also is taken up by peripheral blood leukocytes and is distributed into subcellular organelles, notably the mitochondria. B-carotene may play an important role in maintaining the structural and functional integrity of leukocytes.







## INNOVATIVE SOLUTION from Macro-Algae:





## (Marine Sulfated Polysaccharides)





#### ALGAE TECHNOLOGY INTEGRATED PROCESSING, FROM RESOURCE TO FINAL PRODUCTS

#### **SPECIFIC EXTRACTION of sulfated polysaccharides : MSP®**





COLLECTION

WASHING

PHASE SEPARATION HYDROLYSIS

**EXTRACTION** 



#### **OLMIX ALGAE TECHNOLOGY** SPECIFIC EXTRACTION OF MSP®

#### Algae sulfated polysaccharides (MSP<sup>®</sup>) •

- 3D structure (branching)
- Rare sugars (rhamnose)
- Sulfate content

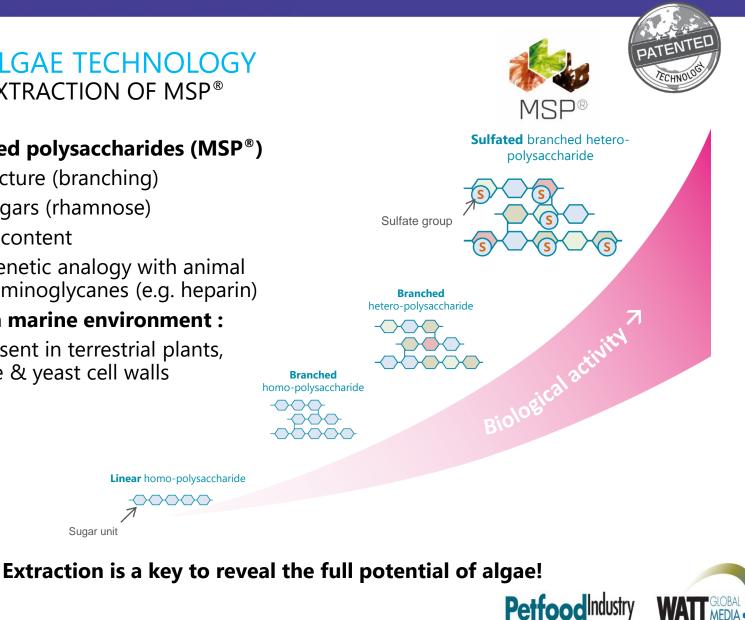
Pettooc

Phylogenetic analogy with animal glycosaminoglycanes (e.g. heparin)

Sugar unit

#### **Only in marine environment :**

 $\rightarrow$  Not present in terrestrial plants, microalgae & yeast cell walls



#### **OLMIX ALGAE TECHNOLOGY** SPECIFIC MSP® USED IN ALGIMUN®

### • GUT HEALTH → MSP<sup>®</sup><sub>BARRIER</sub>

- Extracted from red algae (Solieria chordalis)
- Mode of action:
  - (1) Reinforcement of tight junctions
  - Increase of mucins secretion



- Extracted from green algae (*Ulva sp.*)
- Mode of action:
  - Activation of membrane receptors
  - Stimulation of immune mediators synthesis
- Activation of immune cells





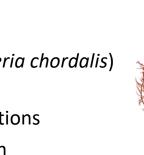




BARRIER



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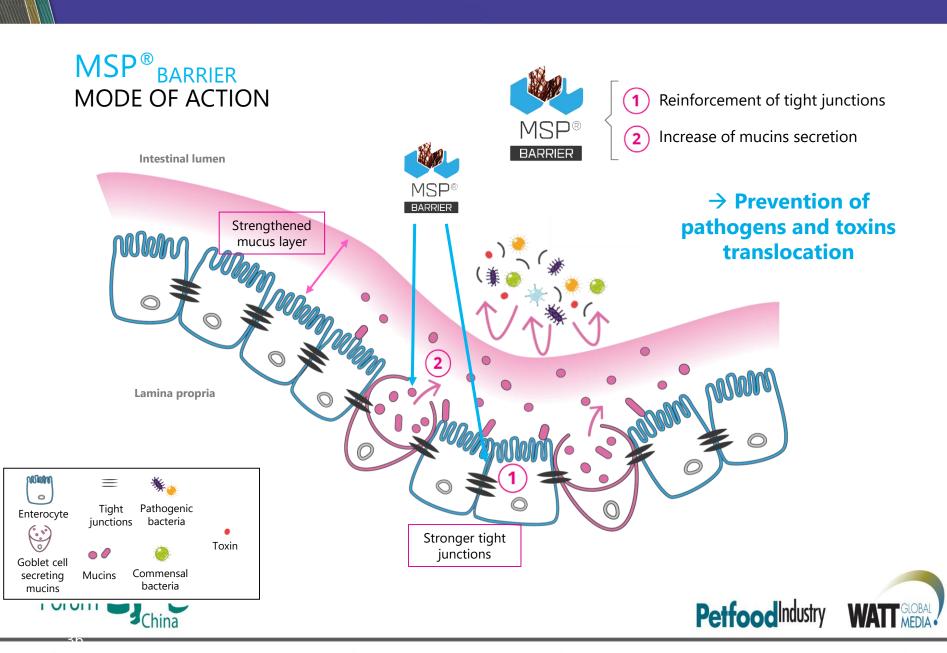












# MSP<sup>®</sup> BARRIER INTESTINAL BARRIER REINFORCEMENT *IN VITRO* (1/2)

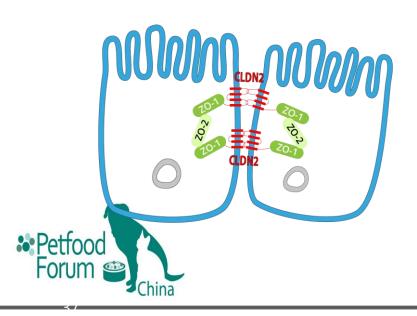




Model: measurement of mRNA expression of two colonic epithelial cell lines.

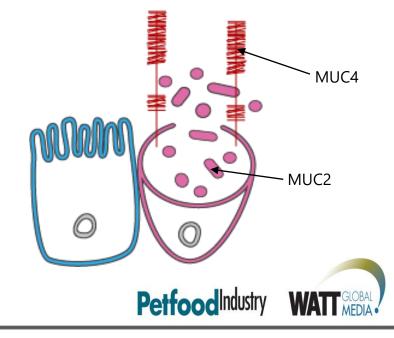
### **1** Reinforcement of tight junctions

Tool: evaluated with Caco2 cells



# **2** Increase of mucins secretion

Tool : evaluated with HT-29 MTX cells

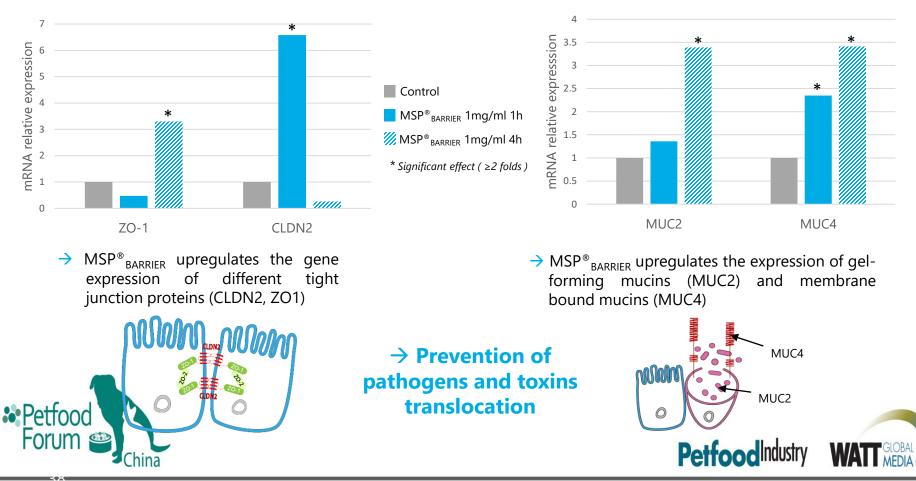


### MSP<sup>®</sup> BARRIER INTESTINAL BARRIER REINFORCEMENT *IN VITRO* (2/2)

Intestinal Biotech Development

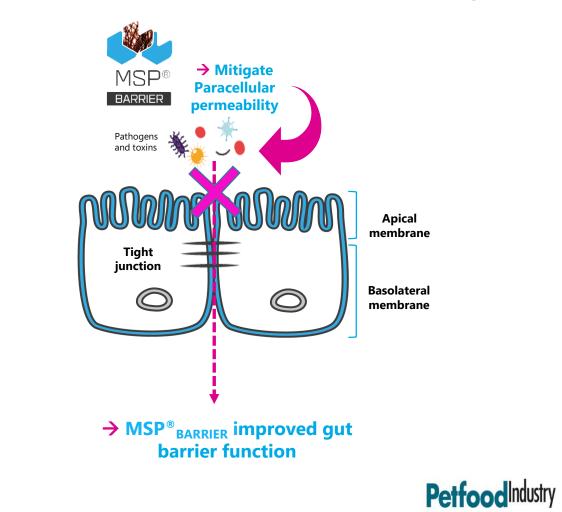
**Increase of mucins secretion** 

# **1** Reinforcement of tight junctions



# MSP<sup>®</sup><sub>BARRIER</sub> REINFORCEMENT OF INTESTINAL BARRIER *IN VIVO* (2/2)

Results



WATI

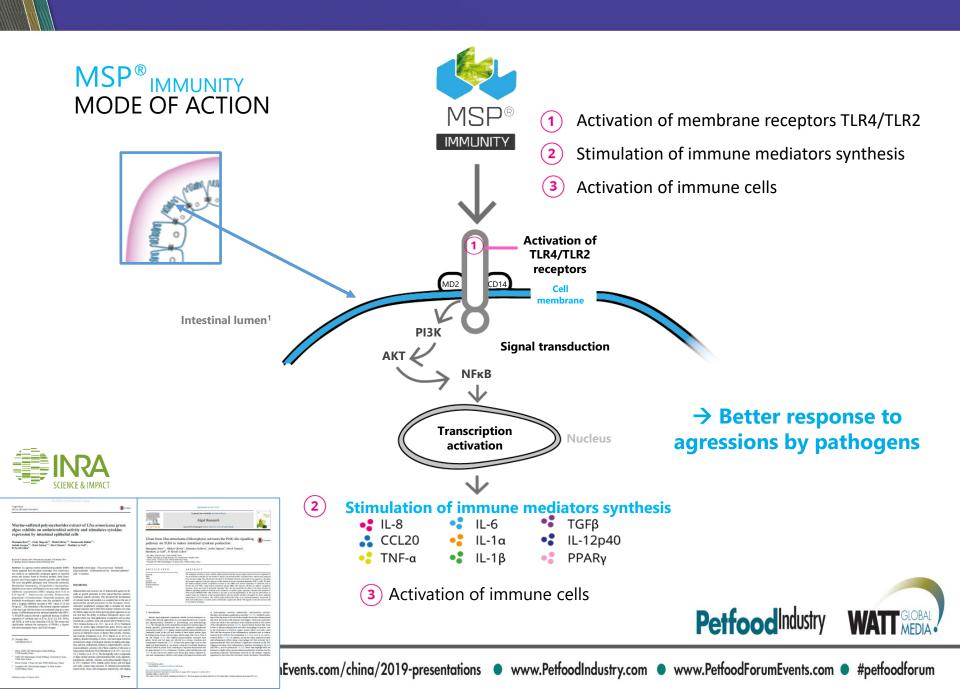




**SCIENCE & IMPAC** 



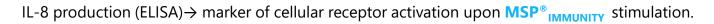


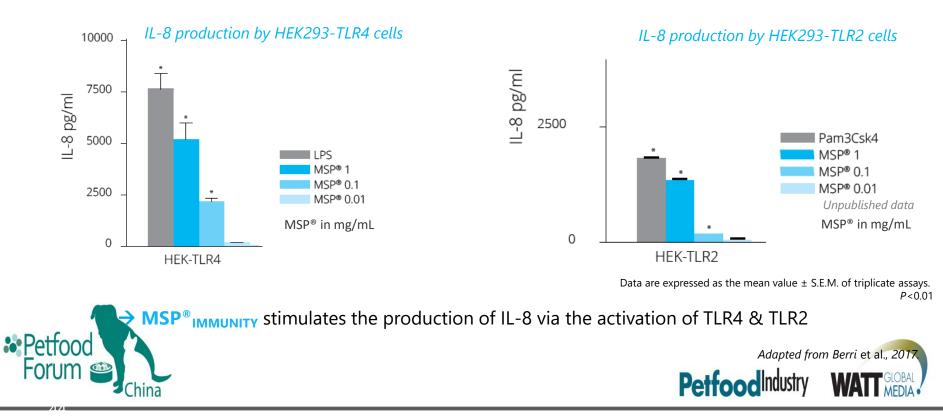


# MSP<sup>®</sup> IMMUNITY IN VITRO IMMUNOMODULATORY EFFECT



#### 1 Activation of membrane receptors TLR4/TLR2



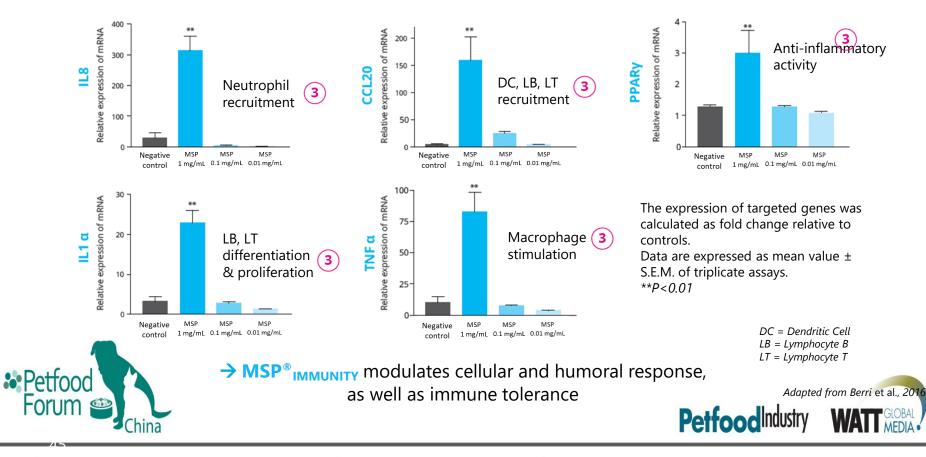


# MSP<sup>®</sup>IMMUNITY IN VITRO IMMUNOMODULATORY EFFECT

#### 2 Stimulation of immune mediators synthesis

IPEC-1 cell line - measure of expression of mediators mRNA
Activation of immune cells





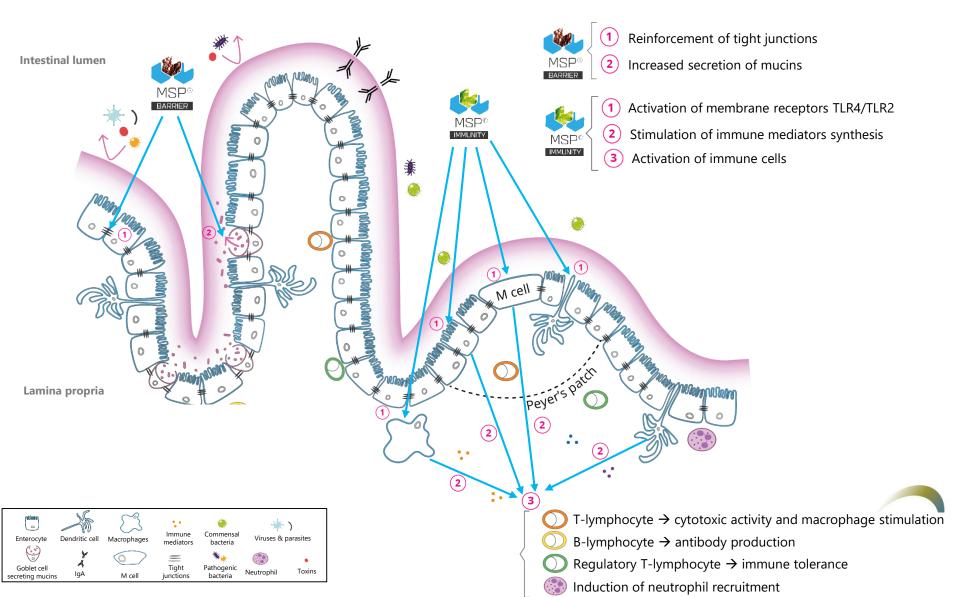


# MODE OF ACTION MSP Barrier + MSP Immunity





# ALGIMUN® MODE OF ACTION



# ALGIMUN<sup>®</sup> MODE OF ACTION SUMMARY: BOOST ANIMALS' NATURAL DEFENSES





- Stronger tight junctions
- Functional mucus layer

Prevention of pathogens and toxins translocation

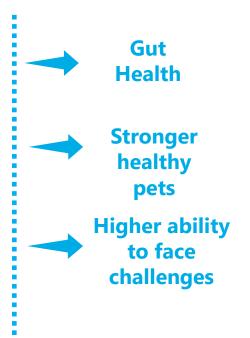


Petfood

### **IMMUNITY** (innate and adaptive)

 Modulation of cell-mediated and humoral immune responses as well as immune tolerance

#### Better response to agressions by pathogens





# ALGIMUN<sup>®</sup> RECOMMENDATIONS AND DOSAGE

- → Recommended for **young animals** (starter and grower phases)
- > Dosage to be adapted according to the specie, stage and sanitary status in the farm

ANIMAL SPECIE	PHYSIOLOGICAL STATE	DOSAGE
PET FOOD		2-3 kg/T





# TAKE HOME MESSAGE

Goal : Boost animal's defenses for optimized and secured performance

How : Association of 2 biologically active macroalgal extracts







When : All cycle but more particularly young/senior/repro

Dosage : 2 to 3 kg/T of feed according to specie and stage

For who: Home-mixers, feed millers, pre-mixers

Strengths :

- 100% natural algae based / Renewable
- Unique technology / Patented
- Stable to heat and EXTRUSION
- Proven mode of action (published)







**Thank you** for your attention!

# vmeallet@olmix.com

