

# ImmunoLin<sup>®</sup> for Digestive Health and Immune Support

## FAQ's

ImmunoLin<sup>®</sup> is a protein-based (>90%) dietary supplement containing over 50% (w/w) immunoglobulins that helps support digestive function and a healthy mucosal immune system.

The protein mixture found in ImmunoLin<sup>®</sup> is serum-derived bovine immunoglobulin/protein isolate (SBI) and is manufactured using a tightly-controlled and highly reproducible process at an FDA-inspected facility. Research studies provide evidence that the diversity of immunoglobulins and proteins found in ImmunoLin<sup>®</sup> are safe and help improve digestive health and nutritional status by decreasing immune activation through mechanisms that involve antigen binding and strengthening gut barrier function.



## INTRODUCTION

ImmunoLin® has emerged as a unique alternative to bovine colostrum for the support of healthy digestion and immune function. What follows in this paper is a series of frequently asked questions about ImmunoLin® that dietary supplement manufacturers may find useful.

## HEALTHY DIGESTIVE SYSTEMS, GI DISTRESS AND BUILDING IMMUNITY

A healthy digestive system breaks down foods and liquids into carbohydrates, fats, and proteins so the body can absorb them as nutrients for growth and energy. It also contains much of the body's immune system, protecting against pathogens or other toxic substances consumed in food or water.

As with all complicated systems, the human digestive tract doesn't always run smoothly. Problems caused by genetics, pathogenic microbes, or dysregulation of the immune system may cause gastrointestinal (GI) distress, resulting in symptoms such as bloating, abdominal pain, gas or diarrhea.

A way to support a healthy GI system is to consume active immune factors from another immunologically 'mature' individual, and is best documented through the ingestion of breast milk containing high levels of immunoglobulins by a newborn infant<sup>(1)</sup>.

## FREQUENTLY ASKED QUESTIONS REGARDING IMMUNOLIN®

### Q WHAT IS IMMUNOLIN®?

A ImmunoLin® is the branded ingredient serum-derived bovine immunoglobulin/protein isolate (SBI). SBI is an agglomerated powder purified from edible bovine plasma using a tightly-controlled cGMP manufacturing process at an FDA-inspected facility.

### Q WHAT IS THE COMPOSITION OF SBI?

A SBI is comprised of over 90% protein and consists of more than 50% immunoglobulins, other peptides and growth factors found naturally in milk or colostrum. Proteomics techniques have identified over 180 unique proteins in SBI. A complete product specification sheet for ImmunoLin®/SBI is available upon request.

### Q HOW DOES SBI WORK?

A The mechanism by which immunoglobulins and other bioactive peptides found in SBI help to maintain gut barrier function is believed to involve the direct binding of microbial components found naturally in the digestive tract. In vitro studies have demonstrated that SBI binds to many potentially toxic microbial

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antigens that appear normally in the intestinal tract (see list of microbial components proven to bind to SBI in Table 1).

These microbial antigens (e.g. bacterial endotoxin) are present in the intestinal tract due to the normal breakdown and turnover of resident bacteria and/or result from the consumption of contaminated food or water. These molecules (microbial antigens) have the potential to activate the intestinal immune system if they pass through a damaged intestinal epithelium. By binding to these microbial antigens (Table 1), SBI helps to create a complex so large that it has difficulty penetrating the intestinal epithelium, allowing instead for the antigenic complex to remain in the intestinal lumen and exit the intestinal tract following normal peristalsis.

To demonstrate this action, Detzel, et al.<sup>(2)</sup> conducted a study using an in vitro cell culture model to show that binding of antigens by the immunoglobulins in SBI prevented translocation of the antigens across epithelial cells, which in turn avoided the production of inflammatory cytokines by adjacent immune cells. These results suggest that the binding action of immunoglobulins in SBI helps keep toxic antigens within the lumen of the intestinal tract and avoid their absorption into the blood stream, which may help manage gut permeability and immune activation that occur with exposure to such antigens<sup>(2)</sup>.

**Table 1. ImmunoLin binds a variety of bacterial antigens**

SBI Binding Component	Description	
Bacterial antigen	Lipopolysaccharide (LPS)	Major immune activating cell wall component (lipid & carbohydrate)
	Flagellin	Antigenic proteins that form appendages to provide motility
	Lipoteichoic acid (LTA)	Immunostimulatory cell wall component of Gram(+) bacteria
	PAM3CSK4	Immunostimulatory bacterial lipopeptide (synthetic)
	Poly I:C	Analog of double-stranded RNA; stimulates cytokine production
	Cytosine-p-guanine dinucleotides (CpG)	Bacterial DNA motif
	<i>C. difficile</i> toxins A & B	Virulence factors
Whole Bacteria (lysate)	<i>Helicobacter pylori</i>	Gram-negative bacteria found in the stomach
	<i>Listeria monocytogenes</i>	Gram-positive, anaerobic bacteria
	<i>Mycoplasma spp.</i>	Bacteria lacking cell wall, resistant to most antibiotics



## WHAT ARE THE FUNCTIONAL HEALTH BENEFITS OF SBI?



The following benefits of SBI have been observed in both animal and human studies:

SBI Supports Digestive/Gut Health. Immunoglobulin-containing serum protein preparations (like SBI) have been shown to consistently improve food intake and other nutritional parameters in a variety of animal species<sup>(3)</sup>. Torrallardona<sup>(4)</sup> summarized the results from over 70 animal studies showing that immunoglobulin-containing plasma protein preparations (like SBI) led to improvements in caloric intake and metabolism of nutrients following supplementation in healthy animals. This research has led to the extensive use of plasma protein isolates as an animal feed component since the 1980's to support and maintain health of weanling domesticated animals<sup>(5)</sup>.

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SBI Supports Healthy Gut Barrier Function. Animal models have been utilized to assess the effect of SBI on supporting gut barrier function. In a rodent model of intestinal inflammation SBI supplementation prevented unwanted changes to specific markers of gut barrier function.<sup>(6)</sup> In another study, of intestinal inflammation mice supplemented with SBI maintained colon mucosal height, cecal stromal structure, and colonic glandular tissue, when compared to mice treated similarly but supplemented with a placebo protein<sup>(7)</sup>.

SBI Helps Maintain Intestinal Homeostasis. Intestinal homeostasis refers to the overall “balance” of a functioning, healthy intestinal tract, and is critical for optimal nutrient utilization and immune function. SBI helps maintain intestinal homeostasis by supporting digestive function and maintaining a healthy mucosal immune system through mechanisms that involve antigen binding and strengthening gut barrier function (see previous question, “How does SBI work?” for more information). Human clinical studies have illustrated the nutritive effect of SBI supplementation on intestinal homeostasis<sup>(8,9,10)</sup>.

SBI Maintains Immune Support. Animal models and human studies have evaluated the effect of SBI on intestinal immune function. Perez-Bosque and colleagues studied intestinal inflammation in mice and found SBI supplementation led to significant decreases in the expression of proinflammatory cytokines in gut mucosal tissue, while simultaneously increased levels of certain anti-inflammatory peptides<sup>(11)</sup>. In another study involving mice, SBI resulted in significantly lower concentrations of serum markers for acute gut inflammation and epithelium damage<sup>(7)</sup>. Plasma immunoglobulin concentrates (like SBI) have also been shown to support the health status of pigs that were experimentally infected with enterotoxigenic *Escherichia coli* K88<sup>(12)</sup>.

In an open-label human clinical study, subjects given SBI had increased CD4+ counts in the duodenum<sup>(9)</sup>. In a larger multicenter, placebo-controlled follow-up study<sup>(10)</sup>, SBI led to significant increases in peripheral CD4+ cells, when compared to placebo-controlled subjects. The same study found significant decreases in circulating levels of interleukin-6 (a proinflammatory cytokine) and markers of intestinal barrier damage and enterocyte death in subjects who received SBI.

## **Q** WHAT DATA IS AVAILABLE TO SUPPORT THE SAFETY OF SBI?

**A** Numerous animal and human studies have been conducted to provide evidence of the safety of SBI, including clinical trials involving over 234 subjects and published retrospective chart reviews describing the use of SBI by approximately 298 subjects. In total, over 530 subjects have been exposed to SBI in documented clinical studies for a minimum of 1 day to a maximum of 24 months with doses ranging from 5 g to 20 g per day. There are no known side effects associated with consumption of SBI.

## **Q** WILL SBI NEGATIVELY IMPACT THE EFFICACY OF DAILY PROBIOTICS?

**A** No. While the immunoglobulins in SBI have been shown to bind to a variety of microbial antigens that are associated with immune activation, evidence from preclinical studies have shown the following: 1) SBI does not adversely affect the growth of probiotic or commensal bacteria in vitro and 2) SBI did not change the composition of the intestinal microbiota in an animal model used to evaluate host-microbiota relationships. No significant changes in commensal microflora have been observed following oral administration of SBI in humans, thus making SBI an excellent choice for consumers to use in conjunction with their daily probiotic supplementation.

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## Q HAS SBI RECEIVED A US FOOD AND DRUG ADMINISTRATION'S GRAS DESIGNATION

A Yes. "GRAS" is an acronym for Generally Recognized As Safe. Under sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act (the Act), a substance identified as GRAS is one that is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use<sup>(13)</sup>.

On December 24, 2008, the US FDA issued a letter assigning SBI (identified as "Bovine globulin") GRAS notice No.255. The letter was issued in response to the application for GRAS designation reads, "Based on the information provided by Proliant [a sister company to Entera Health, Inc.], as well as other information available to FDA, the agency has no questions at this time regarding Proliant's conclusion that bovine globulin is GRAS under the intended conditions of use." (see reference<sup>(14)</sup>).

## Q DOES SBI CONTAIN COMMON, ALLERGENIC SUBSTANCES?

A ImmunoLin® contains immunoglobulin protein isolate (SBI) and lecithin and does not contain milk products such as lactose, casein, or whey. SBI is a purified product that is gluten-free, dye-free, and soy-free and manufactured in accordance with current Good Manufacturing Practice (cGMP). However, since SBI is derived from a beef source, individuals who have an allergy to beef should not take this product.

## Q WHAT IS THE RECOMMENDED SERVING SIZE / DOSE OF IMMUNOLIN® (SBI) AS A DIETARY SUPPLEMENT?

A The recommended daily dose of ImmunoLin® is 1000-2000 mg per day. ImmunoLin® doses may be supplemented multiple times daily. This daily dose of ImmunoLin® is intended to supplement the body's normal production of immunoglobulins in the healthy digestive tract, which has been reported to be from 3000 - 5000 mg/day<sup>(15, 16)</sup>.

### KEY POINTS

- ImmunoLin® is the branded ingredient *serum-derived bovine immunoglobulin/protein isolate* (SBI).
- ImmunoLin® aids in the support of healthy gut barrier function and immune balance.
- ImmunoLin® is >90% protein and typically contains ~ 60% immunoglobulins (>50% IgG, ~5% IgM, ~1% IgA).
- ImmunoLin® binds to microbial antigens, including lipopolysaccharides (LPS), which helps to limit antigen absorption.
- There are no known side effects associated with consumption of ImmunoLin®.
- Safety and digestive health benefits of ImmunoLin® are documented in human clinical trials
- Non-allergenic protein sourced from all natural and high-quality materials

## REFERENCES

1. Walker A. Breast milk as the gold standard for protective nutrients. *The Journal of pediatrics*. 2010;156(2 Suppl):S3-7.
2. Detzel CJ, Horgan A, Henderson AL, Petschow BW, Warner CD, Maas KJ, et al. Bovine immunoglobulin/protein isolate binds pro-inflammatory bacterial compounds and prevents immune activation in an intestinal co-culture model. *PloS one*. 2015;10(4):e0120278.
3. Kuchibhatla R, Petschow BW, Odle J, Weaver EM. Nutritional Impact of Dietary Plasma Proteins in Animals Undergoing Experimental Challenge and Implications for Patients with Inflammatory Bowel Disorders: A Meta-analysis. *Adv Nutr*. 2015;6(5):541-51.
4. Torrallardona D. Spray dried animal plasma as an alternative to antibiotics in weanling pigs – A review. *Asian-Australasian J Anim Sci*. 2010;23((1)):131-48.
5. Coffey RD, Cromwell GL. Use of spray-dried animal plasma in diets for weanling pigs. *Pig News and Information*. 2001;22((2)):39N-48N.
6. Perez-Bosque A, Miro L, Maijo M, Polo J, Campbell J, Russell L, et al. Dietary intervention with serum-derived bovine immunoglobulins protects barrier function in a mouse model of colitis. *American journal of physiology Gastrointestinal and liver physiology*. 2015;308(12):G1012-8.
7. Henderson AL, Brand MW, Darling RJ, Maas KJ, Detzel CJ, Hostetter J, et al. Attenuation of Colitis by Serum-Derived Bovine Immunoglobulin/Protein Isolate in a Defined Microbiota Mouse Model. *Digestive diseases and sciences*. 2015;60(11):3293-303.
8. Wilson D, Evans MD, Weaver E, Shaw AL, Klein GL. Evaluation of Serum-Derived Bovine Immunoglobulin Protein Isolate in Subjects with Diarrhea-Predominant Irritable Bowel Syndrome. *Clinical Medicine Insights: Gastroenterology*. 2013;6:49-60.
9. Asmuth DM, Ma ZM, Albanese A, Sandler NG, Devaraj S, Knight TH, et al. Oral Serum-Derived Bovine Immunoglobulin Improves Duodenal Immune Reconstitution and Absorption Function in Patients with HIV Enteropathy. *Aids*. 2013;27:2207-17.
10. Asmuth DM, Somsouk M, Hunt P, Ma ZM, Miller CL, X.D., Hinkle J, et al. Serum-Derived Bovine Immunoglobulin Protein Isolate Increases Peripheral and Mucosal CD4+ T-cell counts in Patients with HIV Enteropathy. 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention (AIDS 2015); MOAA02; Vancouver, Canada 19-22 July; [http://www.ias2015.org/WebContent/File/IAS\\_2015\\_\\_MED2.pdf](http://www.ias2015.org/WebContent/File/IAS_2015__MED2.pdf); 2015.
11. Perez-Bosque A, Miro L, Maijo M, Polo J, Campbell JM, Russell L, et al. Oral Serum-Derived Bovine Immunoglobulin/Protein Isolate Has Immunomodulatory Effects on the Colon of Mice that Spontaneously Develop Colitis. *PloS one*. 2016;11(5):e0154823.
12. Bosi P, Casini L, Finamore A, Cremokolini C, Merialdi G, Trevisi P, et al. Spray-dried plasma improves growth performance and reduces inflammatory status of weaned pigs challenged with enterotoxigenic *Escherichia coli* K88. *Journal of animal science*. 2004;82(6):1764-72.
13. Generally Regarded As Safe (GRAS) [Available from: <https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/default.htm>].
14. Agency response letter to GRAS notification GRN 000255 [Available from: <https://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm154991.htm>].
15. Brandtzaeg P, Pabst R. Let's go mucosal: communication on slippery ground. *Trends in immunology*. 2004;25(11):570-7.
16. Conley ME, Delacroix DL. Intravascular and mucosal immunoglobulin A: two separate but related systems of immune defense? *Annals of internal medicine*. 1987;106(6):892-9.

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