



The innate immune system

The innate immune system is a complex network of immune cells (including monocytes/ macrophages, neutrophils and natural killer cells) that circulate throughout the body to identify and destroy foreign pathogens and damaged cells.

It is well documented that cancer rates are higher in those who are on immunosuppressant medication and those with poor innate immune cell function.

Of all the natural compounds known to activate the innate immune system, the best documented and most effective are the 1-3, 1-6 beta glucans, generally derived from baker's yeast. (Kernodle et al '98, Wakshull et al '99, Mansell et al '75, Hahn & Albersheim '78, Robertsen et al '94, Song & Hsieh '94).

1-3, 1-6 Beta Glucans – priming the immune system

There is clear evidence that supplementation with a purified 1-3, 1-6 extract of baker's yeast can enhance the action of innate immune cells to increase resistance to bacterial and viral infection (Seljelid et al '87, Jung et al '04) reduce allergy response and even enhance the tumour-killing effect of cancer immunotherapy approaches. (Salvador et al, Clinical Cancer Research 2008;1239 14(4) February 15, 2008)

As the immune system evolved, it became very adept at killing yeast and other fungal infections by recognizing certain molecules that commonly occur on the cell surface of these challenges. One such recognition molecule is a natural complex carbohydrate or gluco polysaccharride (Beta Glucan). As yeasts are so universal, the innate immune system actually became acclimatised to them, and dependent on them to function at peak effectiveness.

Then very late in the evolutionary day, modern technology effectively sterilised our food chain and much of our environment. Levels of yeast and other fungi in our foods, on our bodies and in our houses dropped away; and left the innate immune system weaker as a consequence.

Adding 1-3, 1-6 beta glucans back into the diet restores the effectiveness of the innate immune system, with considerable health benefits.

Several beta glucan supplements are available derived from a variety of mushroom, algae, oat and yeast extracts. Of these the most potent are 1-3, 1-6 beta glucans generally derived from baker's yeast (*Saccharomyces cerevisiae*). This is due to the molecular structure of the 1-3, 1-6 side chain which provides a perfect "lock and key" fit onto CR3 receptors on the surface of innate immune cells which are essential for innate immune cell function.

Biothera, a leading company in the research of yeast-derived beta glucans, have produced a highly-refined and patented source of 1-3, 1-6 beta glucans (WGP 3-6). WGP 3-6 has been subjected to a significant number of clinical trials and has recently been chosen by the US Government for trials in situations where the public may face radiation hazards, whether accidental or deliberate.

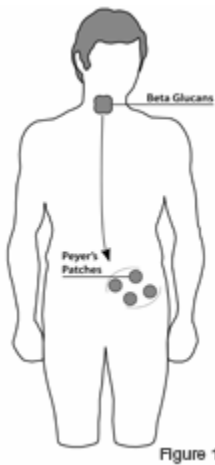
1-3, 1-6 Beta Glucan for Optimal Immune Function

After ingestion, the purified *Saccharomyces* extracts are absorbed in lymphatic tissue called Peyer's Patches in the bowel wall. Immune cells called macrophages digest the 1-3, 1-6 beta glucan extract into smaller fragments and slowly release them around the body over a number of days, where they bind to neutrophils. The specific 1-3, 1-6 side chain pattern on the *Saccharomyces*-derived extract provides the optimal "lock and key" fit with CR3 receptors on the surface of neutrophils.

This primes innate immune cells to:

- respond more rapidly and in greater numbers to the required site (increased chemotaxis)
- increase the phagocytic respiratory burst essential for a successful immune response
- enhance important cytokine messenger release which triggers further immune cell cascades
- reduce allergy response associated with an over-dominant acquired immune system





How does WGP 3-6 work?

1. Once swallowed, whole beta glucans particles pass through the stomach into the small intestine where they are taken up by specialised regions called the Peyer's Patches.

In the Peyer's patches, the beta glucan molecules are encountered by circulating macrophages – immune cells whose function is to engulf and digest foreign invaders - whether bacterial, fungal or viral.

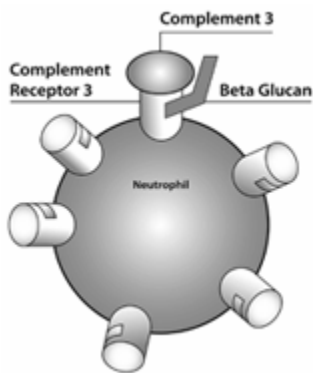
Macrophages have receptors which specifically recognise 1-3, 1-6 beta glucans (Czop & Austen '85), because they occur in the cell walls of many bacteria and fungi. This means that when you ingest beta glucans your innate immune system thinks, not unreasonably, that an enemy has arrived and it rises to the challenge.

This important first line of defence is now fully activated, and several well-conducted research papers have shown that resistance to infection is greatly enhanced (Onderdonk et al '92, Kernodle et al '98, Vetvicka et al '02).

2. Specialised cells called M-Cells transport the whole glucan particles to macrophages and these macrophages, in turn, convey the whole glucan particles to various regions of the immune system – such as lymph nodes, bone marrow and the Thymus. **Figure 2**

3. The macrophages then breakdown the beta glucans 1-3, 1-6 into smaller particles. These active fragments bind or lock onto the surface of neutrophils – which are the most abundant immune cells in the body.

They then lock on to a receptor called CR3 – Complement Receptor 3. **Figure 3**



Stage 10

Figure 3

The neutrophil is now activated or 'primed' and ready to seek out foreign challengers or pathogens.

4. For a neutrophil to kill a foreign challenger – or pathogen – the CR3 receptor (Complement Receptor 3) must be occupied by both complement - a blood protein – and beta glucan.

The CR3 receptor is occupied naturally by moulds and yeasts . But there are other threats, including bacteria, viruses and cancer, where beta glucan is not present.

Thus, by taking beta glucans, the neutrophils are provided with the missing element they need to trigger the neutrophil's natural killing mechanism

5. A fully primed neutrophil now migrates to the site of a pathogen (whether virus, cancer or bacterium) through a process called chemotaxis.

The neutrophil then binds to the surface of this pathogen - and recognises it as 'non-self' ie foreign. It is now able to destroy that pathogen by releasing toxic chemicals **Figure 4**

6. At the same time, other killer cells retain fragments of the pathogens (ie. foreign invaders) that they have destroyed and 'present' them on their surface. These send signals to other members of the immune system family, which become memory cells.

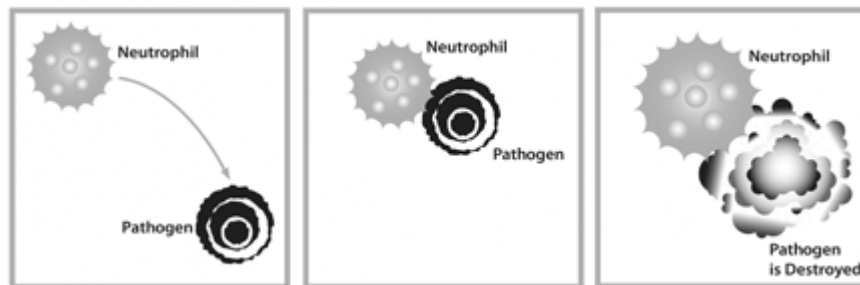


Figure 4

Next time the same virus or pathogen is encountered, these newly programmed memory cells will recognise the virus and produce antibodies. These antibodies stick to the surface of the virus and prevent it from infecting healthy cells.

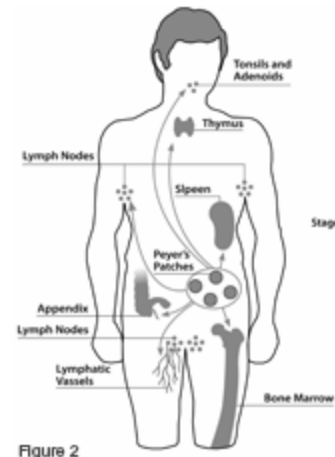


Figure 2



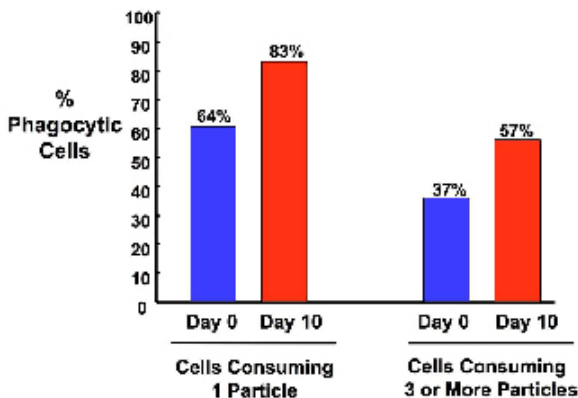
7. The molecular size of the beta glucans also appears to be important. Particles of approximately 2-6 microns in size appear to be most effective.

The Historical Perspective

Dietary levels of beta glucans are significantly less today than in the past, where beta glucans from the traditional fermenting and production process of beer, wine and bread, and environmental mould and yeast contamination provided continued low level beta glucan absorption and innate cell priming. By removing yeasts from our food chain, today's over-sanitised environment has left our innate immune systems weakened and unbalanced.

Consequently we have become more vulnerable to infection and allergy. Supplementing with a product such as Immiflex therefore not only enhances a weakened innate immune system but has been found to reduce the allergy response which has become so prevalent. (Rylander R, Holt PG. 1-3 beta-D-glucan and endotoxin modulate immune response to inhaled allergen. *Mediators Inflamm.* 1998;7(2):105-)

Clinical Studies



Enhanced Phagocytic Activity

An article published in the *Journal of Immunology* demonstrated that the 1-3 1-6 beta glucan found in Immiflex increased phagocytic capacity — the ability of the innate immune cells to ingest and destroy foreign intruders — from 64 per cent to 83 per cent, and increased the number of highly phagocytic cells from 37 per cent to 50 per cent after just 10 days of supplementation. (Ref. Li B, et al. Yeast β -glucan amplifies phagocyte killing of iC3b-opsonized tumor cells via CR3-Syk-PI3-kinase pathway *J Immun* 2006 Aug 1;177(3):1661-9.)

The first human study on this specific glucan's systemic effect was performed in the mid 1980's on advanced HIV infection. Even in these severely immunologically challenged individuals, an increase in serum cytokines IL-1, IL-2 and Interferon was measured¹⁴ Mansell PWA. Employment of soluble glucan in the treatment of patients with Acquired Immunodeficiency Syndrome. M.D Anderson Cancer Center, IND., 1986..)

Post-Operative Recovery

Early Clinical trials also showed significant **decrease in mortality rates** from infectious complications in severe trauma patients¹⁵ Browder W, Williams D, Pretus H, et al. Beneficial Effect of Enhanced Macrophage Function in the Trauma Patients. *Ann. Surg.* 1990;Vol 211:605-613.)

Support for athletes and highly active people

Several recent studies have shown benefit in supplementing highly active people and athletes. A randomized double-blind study presented at the 2008 American College of Sports Medicine annual meeting showed that wildland firefighters who took the yeast derived supplement had **23 per cent fewer upper respiratory tract infections** (URTI's) compared to a placebo group.

A double-blind, placebo-controlled study included 75 **marathon runners** showed significant benefit compared to placebo in patient led outcomes, with reductions in URTI symptoms, tension and fatigue scores, and significantly increased general health scores.

Enhanced Resistance to viral and bacterial infection

Significant improvement in resistance to infection has been demonstrated in several well controlled animal studies. In mice challenged with **Anthrax**, prophylactic oral 1-3, 1-6 beta glucan for one week prior to infection increased survival from 50 to 100%; therapeutic administration for ten days post infection increased survival from 30% up to 90% in treatment groups. (Kournikakis B, Anthrax-Protective Effects of Yeast Beta 1,3 Glucans *MedGenMed.* 2003 March 24. Significantly **increased clearance of the resistant bacteria MRSA** have also been demonstrated in a rat study.



Flu infection - *Saccharomyces cerevisiae* beta-glucan reduced the pulmonary lesion score (pneumonia severity) and viral replication rate in SIV (swine flu virus) infected pigs. Porcine immune models closely relate to those of a human and findings therefore support the potential application of beta-glucan as a prophylactic/treatment agent in influenza virus infection. (J Vet Med B Infect Dis Vet Public Health. 2004 Mar;51(2):72-6.)

Radiation Induced Tissue Damage

In a controlled study done at the US Armed Forces Radiobiology Institute, 70% of rats given a lethal dose of radiation were completely protected from radiation effects when given baker's yeast derived beta glucan by mouth after the radiation exposure. WGP 3-6 has also been shown to enhance the recovery of white blood cells following bone marrow injury from radiation via CR3 positive stem cells (hematopoietic progenitor cells) which move to the site of injury, bind to injured bone marrow stromal cells via iC3b-CR3 axis and mature into new blood cells. (Eagen MN et al, *Blood*. 2005 Sep 22)

Cancer therapy – Enhanced immune tumour response

Several studies have shown significant benefit in combining monoclonal antibodies with 1-3, 1-6 beta glucans in the treatment of metastatic cancer. For effective monoclonal antibody therapy both iC3b complement and CR3 receptors need activation. Combination of monoclonal antibody with yeast-derived beta glucan has been shown to produce significantly greater tumor regression. (Salvador et al, *Clinical Cancer Research* 2008; 1239 14(4) February 15, 2008)

A study published in February 2009 compared the therapeutic efficacy of various beta glucans in combination with monoclonal antibodies in a mouse tumour model. This indicated that yeast derived beta glucans such as those contained in Immiflex, were superior to mushroom extracts in tumor therapy. (*Cancer Biology & Therapy* 8:3, 214-221; 1 February 2009)

Immiflex

Immiflex contains 250mg 1-3, 1-6 (WGP 3-6) beta glucan per capsule

WGP 3-6 benefits from an extensive published evidence base demonstrating the potent immune enhancing qualities of this natural compound. Unlike many barley or mushroom beta glucan supplements which act only as partial activators at CR3 receptor sites, WGP 3-6 has the exact molecular shape for optimum CR3 activation to prime innate immune cells.

Recommended dosage: take one to three capsules daily.

Further supplementation and dosage advice is available from the medical team (www.doveclinic.com)

Safety: The safety of any supplement, or treatment, has to be the first priority. Beta glucans are natural supplements derived from food, and are safe for people of all ages.

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