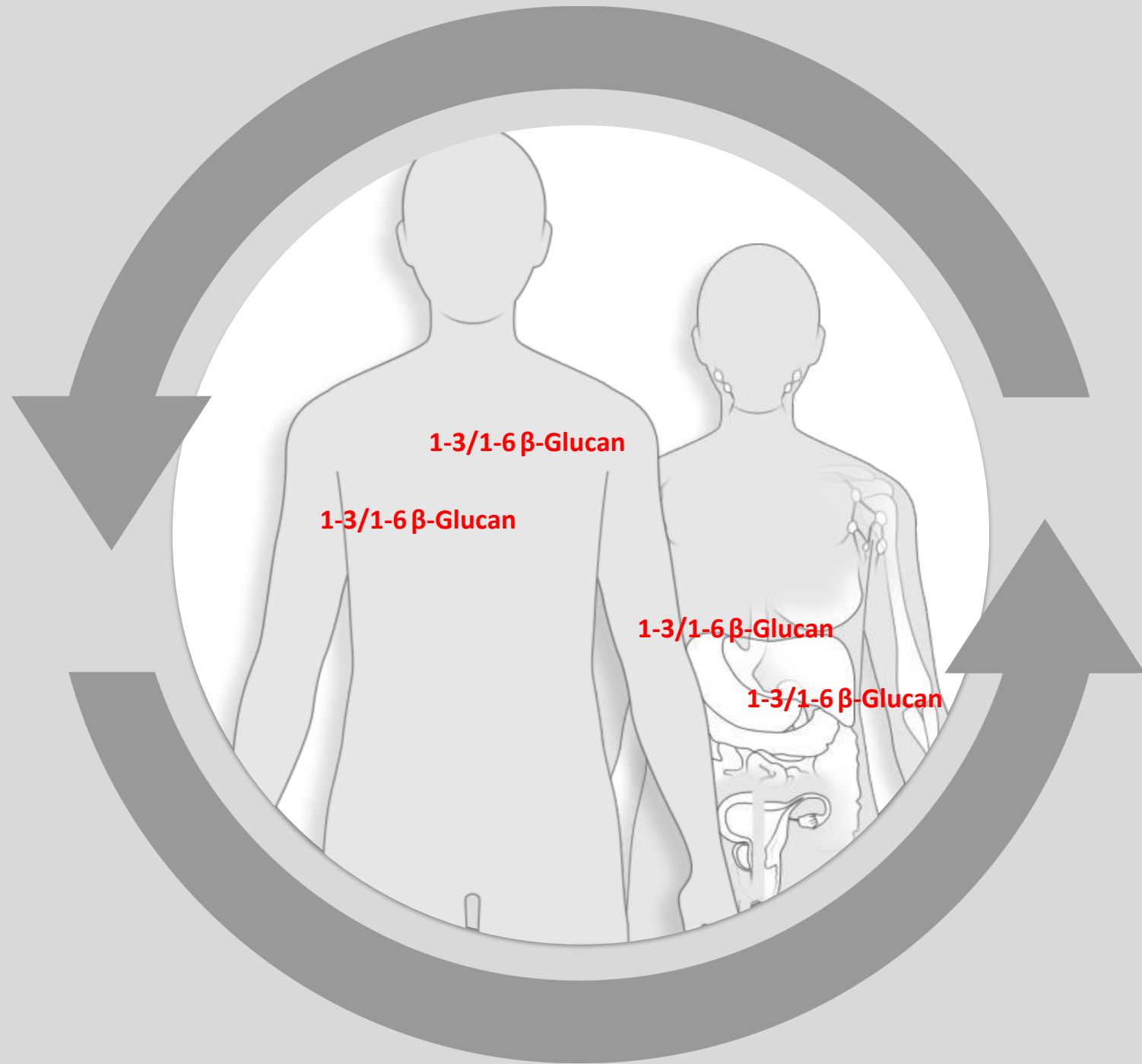


**Micronized beta-
glucan Clinical
Studies
Summary**

**Highly purified Micronized 1-3/1-6 β -
Glucan, is a scientifically proven
biological defense modifier (BDM) from
the cell wall of *Saccharomyces
Cerevisiae* (Baker's yeast)**



β -Glucan at a glance Immune stimulation/Key Specifications

Respiratory tract infections in Children

Recurrent aphthous stomatitis

**Oral mucositis in H&N cancer Adjuvant for
advanced breast cancer**

Allergic rhinitis

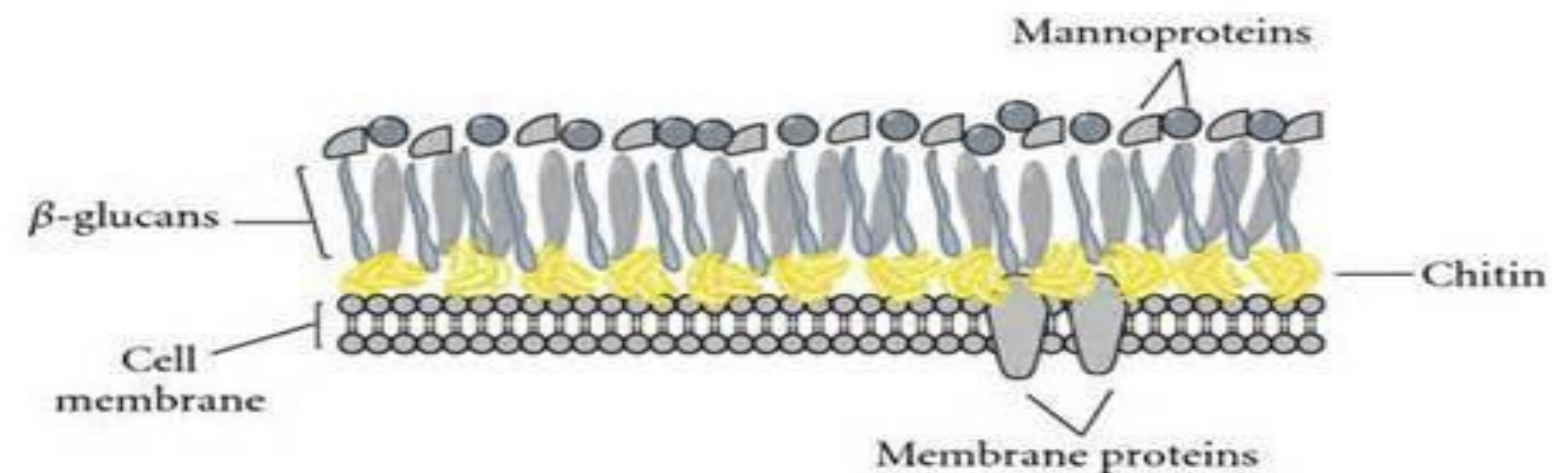
Common cold prophylaxis

Summary[®]

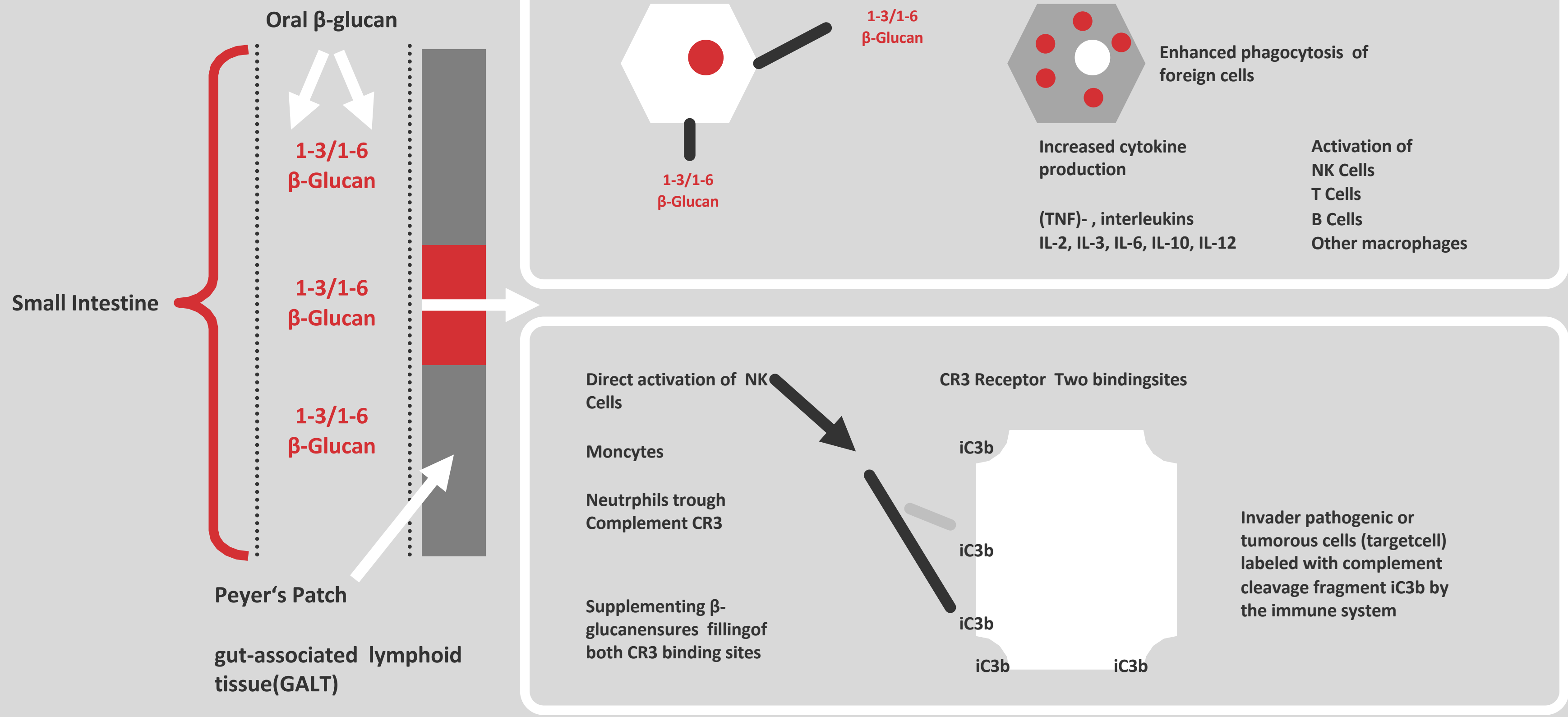
At a glance

- ✓ B-glucans have been found in a variety of microorganisms and plants.
- ✓ The two most consumed sources of β -glucan today are cereal grains and yeast
- ✓ Oats and barley contain chains of linear beta-(1,3;1,4)-D-glucan
 - ✓ helps to reduce cholesterol and is commonly used as a food thickener
 - ✓ **Shows no interaction with the immune system !**
- ✓ Baker's Yeast (*Saccharomyces cerevisiae*) β -glucan contains chains of β -(1,3)- glucan connected by β -(1,6) linkages
 - ✓ **potent non-specific immune-activator!**

- ✓ Structure yeast cell wall



Immunes stimulation



Key Specifications for β -glucan effectiveness

Neither the volume nor weight of β -glucan determines its effectiveness

The key Specification is described as the degree of activation of the immune response by any given glucan

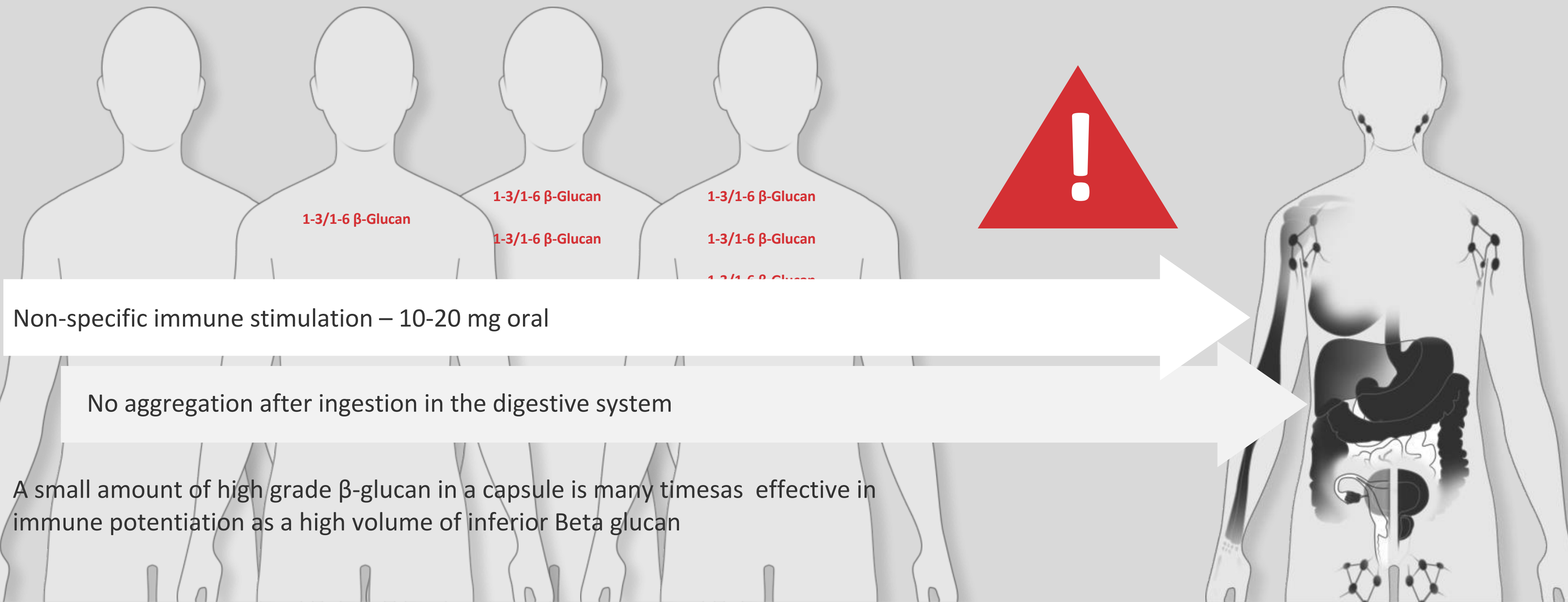
Key Specifications for a potent response

- ✓ β -glucan source – yeast !
- ✓ Processing and Purity – highly purified from cell components, fett etc. (> 80% purity)
- ✓ Uniform microparticulate sizes (at least 80% < 10 micron)

Multiple studies have demonstrated that 10-20 mg of Micronaized high purity -1,3- (D)-glucan with β - 1,6-glucan linkage extracted from yeast cell wall is the proper dosage amount

The Correlation between size of β -glucan and activation of immune system is widely accepted for Many Years

Marketing often hypes high milligram or percentage per capsule content, science measures only immune potentiation by the amount of β -glucan actually contained



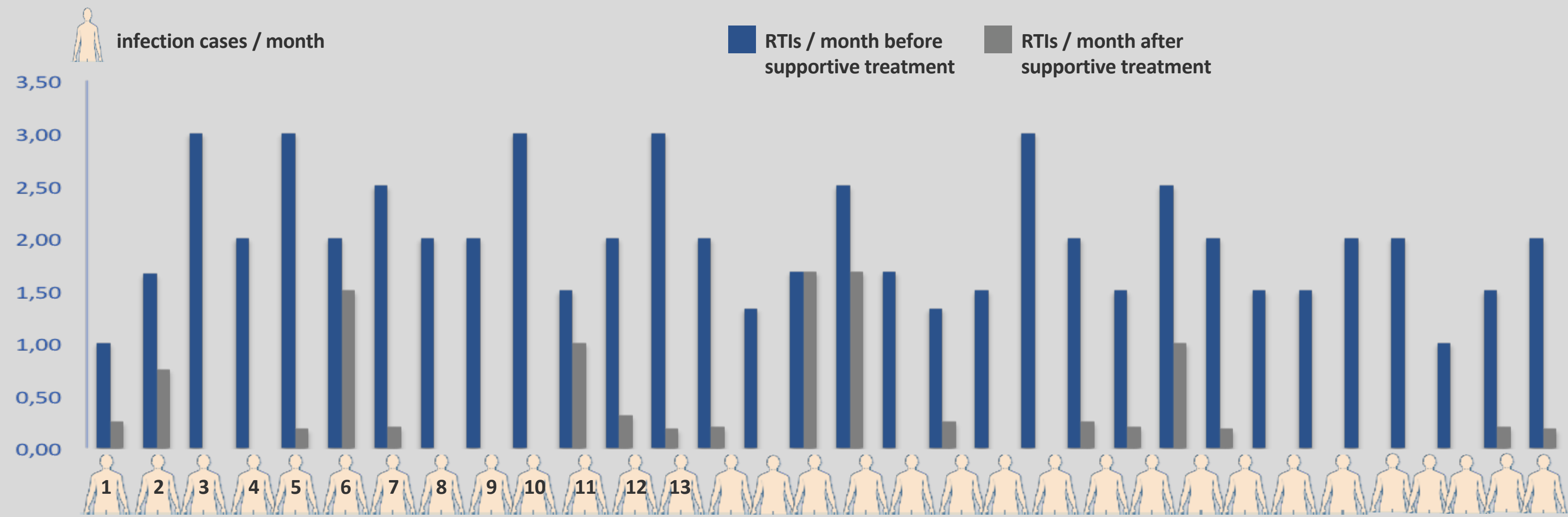
The effect of Micro β -glucan on the frequency of respiratory tract infections in children

The aim of this study was to investigate the effect of micronized β -glucan to the frequency of respiratory tract infections in children.

- ✓ Open label trial (n=32)
- ✓ Daily Dosage of 10mg of **micronized beta glucan**
- ✓ A total of 32 children between 1 and 8 years (mean 3,4 years) with recurrent respiratory tract infections which attempted to hospital between September 2013 and April 2014
- ✓ Infections were not separated into upper and lower RTIs nor the ethological reason for the infection was determined
- ✓ „RTIs before“ and after supplementing with β -glucan „RTIs after“ were compared in the same patient
- ✓ After the beginning of β -glucan therapy (any time after September 2003) the children were followed until the end of April 2004

Individual reduction of RTIs after the supportive treatment with Micronized beta-glucan

- ✓ 14 of 32 patients did not show any RTI after the supplementation with micronized beta glucan- 44%
- ✓ 26 of 32 patients showed at least a reduction of 75% in RTI cases / months
- ✓ Over all 81% reduction in the occurrence of RTIs were shown during the testing period



The effect of 1.3-1.6 β -glucan (Micronized beta-glucan) in vitro proliferation of lymphocytes in treatment of recurrent aphthous stomatitis

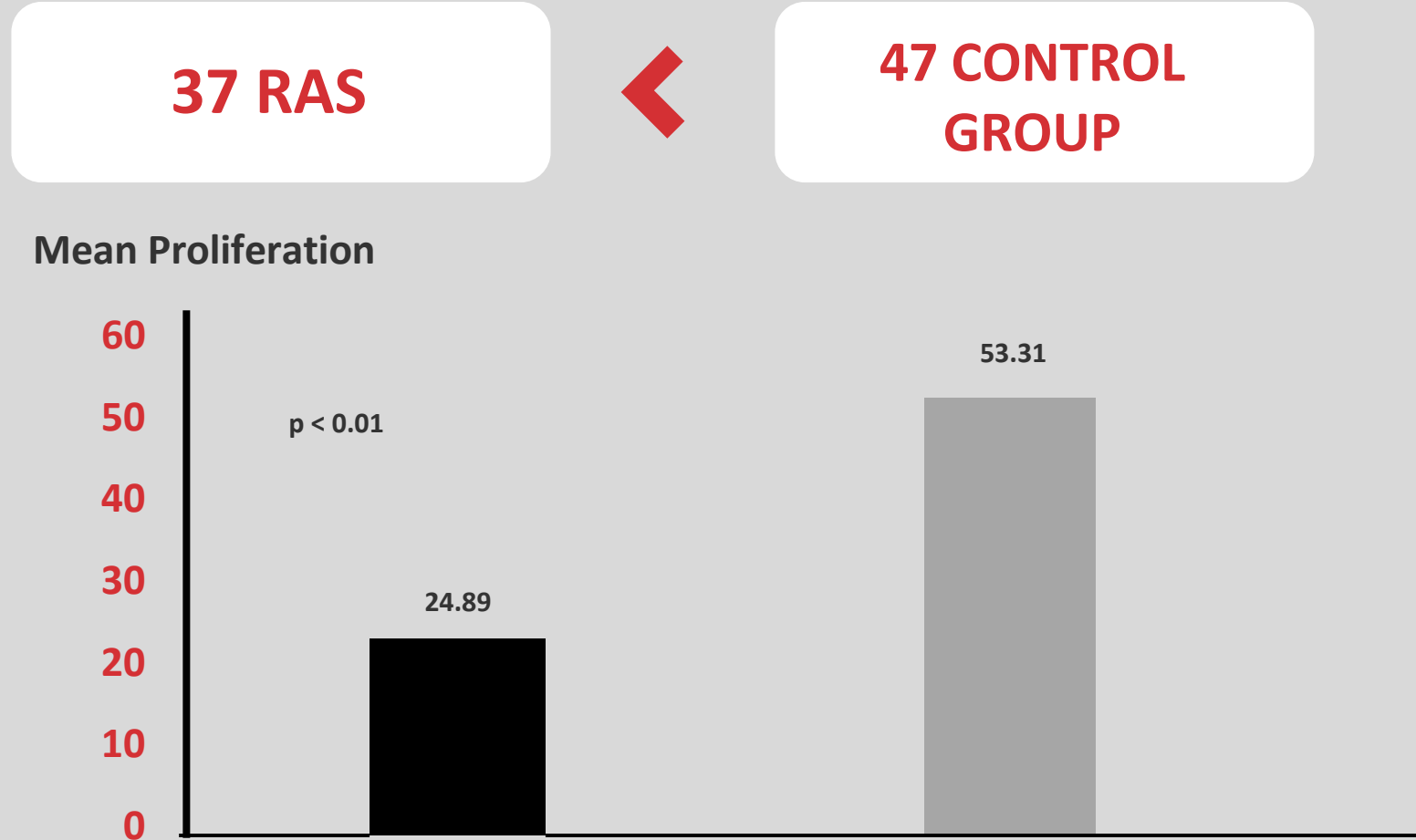
The aim of this study was to investigate the effects of 1.3-1.6 Beta-glucan (Micronized beta-glucan) on the response of lymphocytes with and without phytohemagglutinin A (PHA), a T lymphocyte mitogen in treatment of Recurrent Aphthous Stomatitis (RAS).

- ✓ Open label trial (n=79) in accordance with the ICH guidelines of good clinical practice
- ✓ The study consisted of 37 patients with RAS and 42 healthy control group without RAS
- ✓ Of the 37 patients with RAS, 27 patients were given 10 mg Micronized beta-glucan[®] twice per day and 10 patients given a placebo twice per day.
- ✓ RAS, estimated by the Ulcer Severity Score (USS), shows ulcer characteristics (number, size, duration, ulcer-free period, site and pain).
- ✓ The response of lymphocytes to PHA and USS values were recorded before the treatment, at the end of the treatment and once again 1 month later (treatment free period)

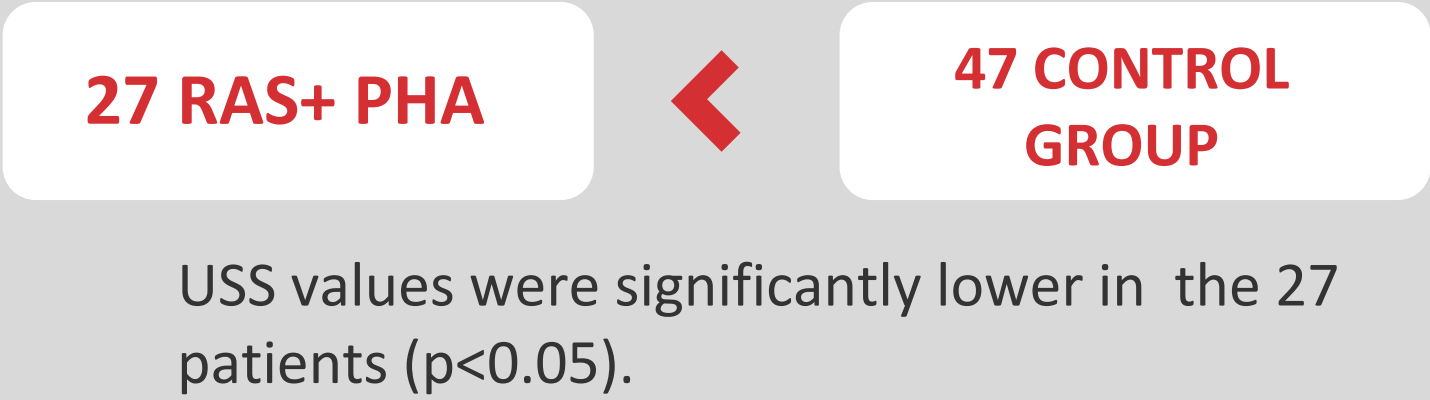
The effect of 1.3-1.6 β-glucan (Micronized beta-glucan) in vitro proliferation of lymphocytes in tretament of recurrent aphthousstomatitis

Outcome & Conclusion

1 Proliferation of lymphocytes without PHA was significantly lower in the 37 patients with RAS when compared to the 42 healthy control group without RAS



2 Response of lymphocytes to PHA was significantly higher in the 27 patient study group when compared to the 10 patients in the placebo group (z=- 1.966, p< 0.05).



Oral mucositis in H&N cancer **Micronized beta-glucan**
addition to systemic chemotherapy on the leukocyte
values

Table 2. Leucocytes values and the degree of mucositis in the patients with head-neck tumors receiving chemotherapy + β -glucan (ImmuneKs)

Patient's No.	Patient's age	Leucocytes values before chemotherapy + β -glucan	Leucocytes values after chemotherapy + β -glucan	Degree of mucositis
1	65	5800	5000	—
2	57	4700	3200	++
3	52	6700	6000	—
4	49	7200	6700	—
5	44	3800	3500	+
6	52	4600	4000	+
7	50	7400	6800	—
8	63	9200	8000	—
9	69	7400	8500	—
10	71	5300	5000	—
11	60	5400	6200	—
12	59	6200	5000	—
13	64	8000	7200	—
14	52	3900	2500	++
15	49	3800	3200	+
16	56	5700	6000	—
17	61	6200	5700	—
18	71	6800	7500	—
19	67	8200	7800	—
20	43	7400	8600	—

Study design

- Three cures of chemotherapy were administered to both of the groups. Second group received oral B-glucan (10 mg/day for the patients weighing up to 60 kg's, 20 mg/day for the patients over60 kg's) in addition to chemotherapy . No side effects was observed in any of the patients during three months.
- Leucocytes count ($2750\pm631,20$) after chemotherapy was significantly($p<0.001$) lower than before chemotherapy, (4305 ± 1139). However, more limited downfall was observed (6185 ± 1549.96 and 5820 ± 1859.99 , significance at the level of $p=0.05$) in the second group following the treatment.
- In addition, oral mucositis secondary to chemotherapy and radiotherapy was seen significantly less in patients who received **Micronized beta-glucan®**

Beta glucan induces proliferation and activation of monocytes in peripheral blood of patients with advanced breast cancer

Table 1
Blood parameters and flow cytometry findings of healthy controls and breast cancer patients

Cell type/marker	Healthy controls	<i>p</i> *	Breast cancer patients		<i>p</i> **
			Initial	15th day	
WBC /mm ³	6130±1356	NS	4777±1920	4947±1701	NS
Lymphocytes/mm ³	1930±573	0.04	1281±306	1173±204	NS
Platelets /mm ³	218.000±55.000	NS	235.190±54.611	223.187±48.512	NS
Hematocrit %	38±3.7	NS	34.5±4.2	35.3±2.7	NS
Monocytes/mm ³	350±158	NS	326±124	496±194	0.015
CD14/CD95 %	13.89±6.36	0.001	48.17±17.83	69.23±24.53	0.002
CD14/CD45RA %	48.2±7.3	NS	49.92±21.78	61.52±15.15	0.001
CD14/CD4 %	21.46±13.56	NS	31,09±22.96	37.17±16.28	NS

*Comparison between healthy controls and initial values of the breast cancer patients.
**Comparison between the initial values and 15th day values of the breast cancer patients.
NS, not significant.

- Two 10-mg capsules of 1–3, 1–6, D-beta glucan derived from *Saccharomyces cerevisiae* (Micronized beta-glucan® 10 mg micro glucan) were given orally in the morning for 15 days
- The mean monocyte count which was 326+124/mm3 at the beginning, was increased to 496+194/mm3 at the 15th day (p=0.015). The percentage of monocytes was also increased from 7.4% to 12% after 14 days of **Micronized beta-glucan** therapy (p=0.003).
- Expression of CD95 (Apo1/Fas) on CD14 positive monocytes which was 48.17% at the beginning, was increased to 69.23 % at the 15th day (p=0.002). Similarly, expression of CD45RA on CD14 positive monocytes which was 49.9% at the beginning, was increased significantly to 61.52% on day 15 (p=0.001).

Effects of Micronized beta-glucan on patients with allergic rhinitis and on Th1/Th2 levels

- ✓ Th1 cytokines (IL-12 ve IFN- γ) are known to play an important role in the immune response induced by Th2. Micronized beta-glucan has been shown to induce an anti-tumor response through an immune response.
- ✓ The objective of the study was to determine the effects of **Micronized beta-glucan** on the immunopathogenic developments in patients with allergic rhinitis.
- ✓ Before and after the administration of **Micronized beta-glucan** nasal provocation test was done with Olea europaea. Subjects that had a reaction were administered a nasal lavage. The levels of IL4, IL 5, IFN γ , IL12 were analysed from the nasal lavage samples that were positive.

Effects of Micronized beta-glucan on patients with allergic rhinitis and on Th1/Th2 levels

RESULTS:

- ✓ The Th2 based IL-4 and IL-5 levels responsible for the allergic reaction in patients with AR decreased with Micronized beta-glucan whilst the Th1 based IL-12 levels have increased.
- ✓ Post treatment levels of IL-4 and IL-5 have decreased significantly ($p = 0.027$, $p = 0.04$ respectively), whilst there was significant increase in IL-12 levels. ($p = 0.008$).
- ✓ IFN- γ levels were not altered in either group, whilst the cytokine levels of the placebo group did not show any significant change.
- ✓ The eosinophil% significantly decreased after treatment with Micronized beta-glucan whereas there was no significant change with the placebo group.

The effects of Imuneks 10mg capsules for the prophylaxis of common cold.

The purpose of the study was to assess the effects of Micronized beta-glucan 10mg capsules on the prophylaxis of common cold and general well being of healthy volunteers

- ✓ Open Label study(n = 70)
- ✓ Daily dose: 2 x 10mg capsules.
- ✓ During the study period of 6 weeks, 70 healthy volunteers, self administered 2 capsules 2 hours after breakfast.
- ✓ Common cold symptoms including; runny nose, coughing, nasal congestion, etc.. Were reported to investigators during the study period of 6 weeks. Due to the fact that the prophylactic effect could not be assessed for the first week, the symptoms during the first week were discarded.(only one such case was reported)
- ✓ Immunologic parameters including effects on lymphocytes, macrophages, monocytes, neutrophils were also recorded before and at the end of the study period.

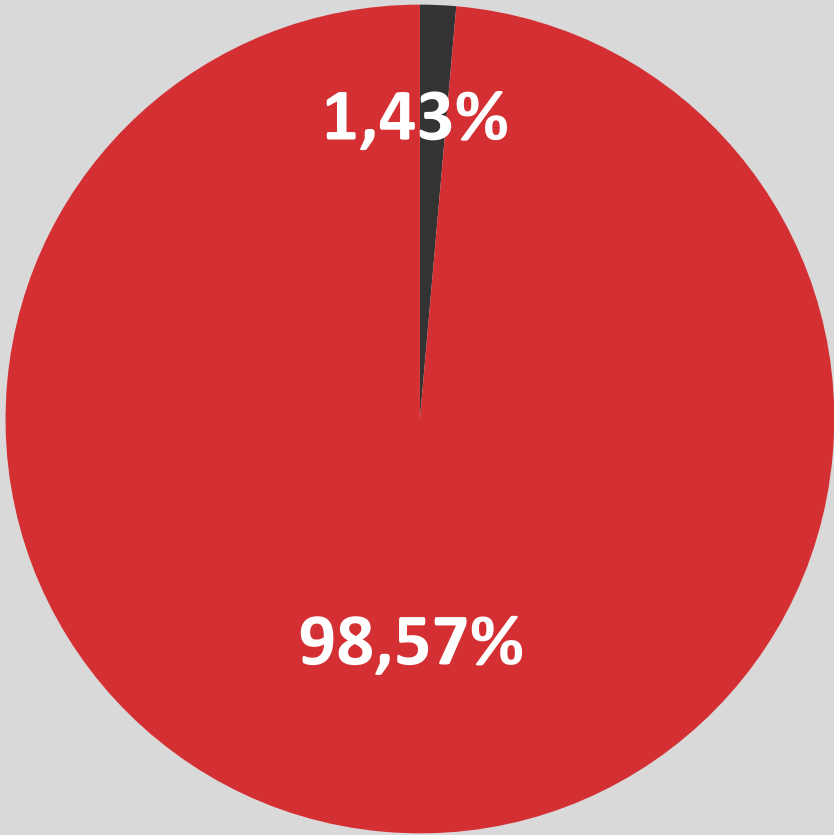
The effects of Imuneks 10mg capsules for the prophylaxis of common cold.

- ✓ There were no adverse events associated with Micronized beta-glucan 10mg administration.
- ✓ During the study period of 6 weeks, there was only a single person with cold symptoms.
- ✓ The percentage of cold symptom free subjects was 98.57 % (69/70)

The effects of Micronized beta-glucan 10mg capsules for the prophylaxis of common cold.

- ✓The study was done during late February to early April, in a period where the incidence of common cold was very high.
- ✓The population of the city where the study was performed was 1.358.980. According to IMS sales data, there was more than 750.000 units of cold preparations sold(excludingantibiotics)

70 SUBJECTS



IMS DATA

	Grand Total
REGIONS	UNITS REPORT
KAYSERİ BUNYAN+TALAS	75.278
KAYSERİ DEVELİ+TOMARZA	56.035
KAYSERİ DOĞU İLÇELER	17.653
KAYSERİ GÜNEY İLÇELER	52.404
KAYSERİ KOCASINAN -1	76.694
KAYSERİ KOCASINAN -2	39.596
KAYSERİ KOCASINAN -3	128.170
KAYSERİ KOCASINAN -4	10.773
KAYSERİ KOCASINAN -5	56.971
KAYSERİ MELİKGAZI -1	14.236
KAYSERİ MELİKGAZI -2	48.580
KAYSERİ MELİKGAZI -3	156.430
KAYSERİ MELİKGAZI -4	35.347
KAYSERİ MELİKGAZI -5	19.735
GRAND TOTAL:	787.902

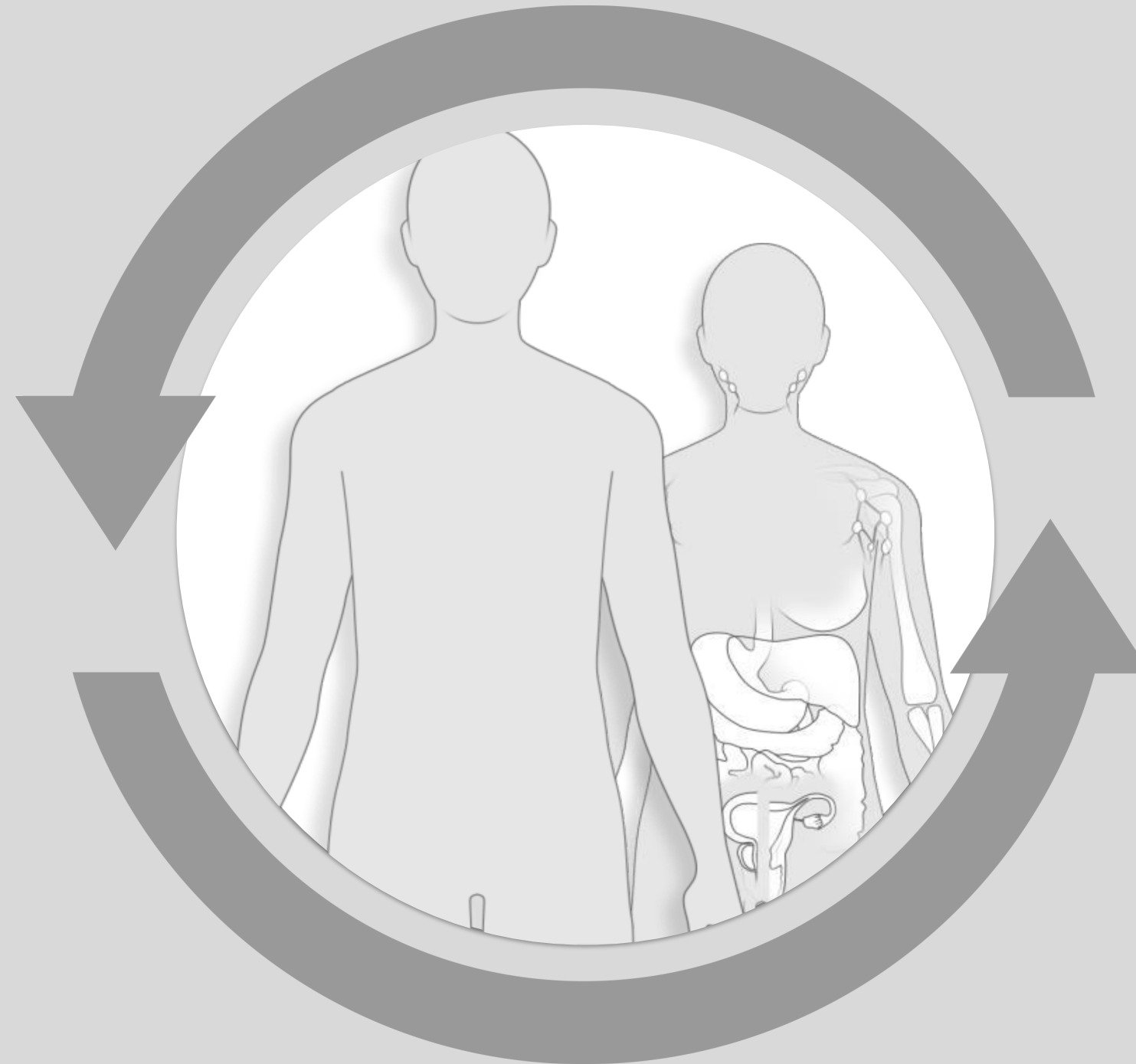
Specifications of the Micronized beta-glucan used in the studies

✓ Beta-glucan assay	min. 80%
✓ Total lipid	less than 1%
✓ Total ash	less than 6%
✓ Total protein	less than 3%
✓ Particle size	min. 80% ≤ 10μ
✓ Total microbiological count	less than 1000 CFU/gr
✓ ColorZ	cream-white powder

**Unique. Proven.
Safe. Proprietary**

WELL KNOWN

- Potent non- specific immune-modulator
- Mechanism of action
- Well established doses and tech file
- Safe for consumption (FDA Gras status) and safe for consumption by EFSA

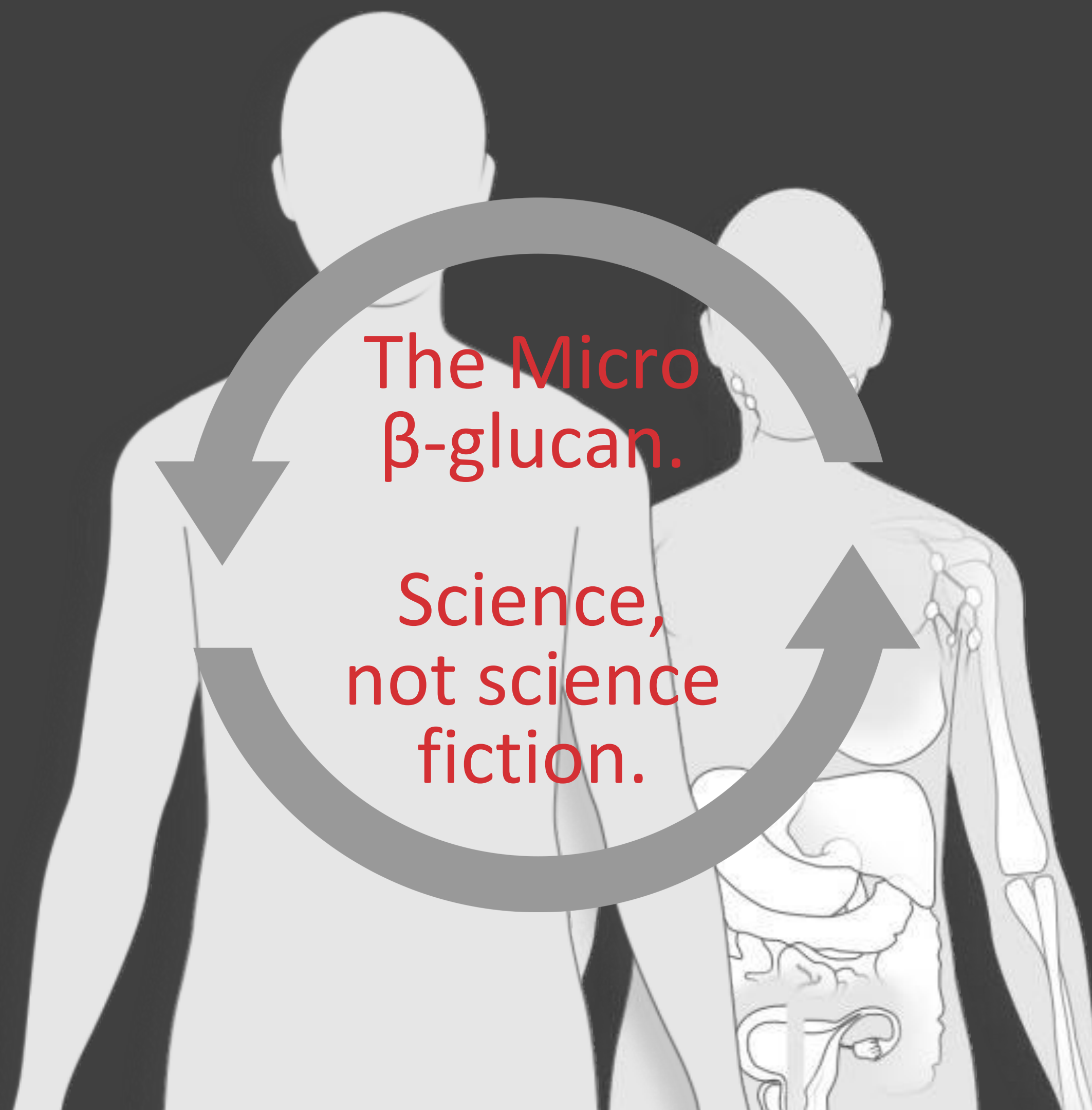


PROVEN EFFICACY

- Multiple clinical trials

FROMULATION

- Long term 3 Yrs + stability data



The Micro
 β -glucan.

Science,
not science
fiction.