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Article

Bacterial lysate "Lantigen B" induces proliferation of B and NK cells and the release of related cytokines

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Abstract: Background: The present is an exploratory study, to evaluate the immune effect of a bacterial chemical lysate: Lantigen-B (Lan-B). PBMCs were stimulated with the concentration of the drug utilized in the clinical setting to evaluate its effects on lymphocyte subpopulation and cytokine release. **Methods:** PBMCs, from 7 healthy donors, were cultured alone or incubated with Lan-B at 199.45 Antigen Units/mL concentrations. Lymphocyte subpopulations were evaluated by Facs-Scan and cytokines by Cytometer. **Results:** A significant increase of IL-1β, IFN-γ, TNF-α, IL-17, and IL-18 release and of CD19+ and CD16+/56+ cells proportion was found in stimulated compared to unstimulated cultures along with a significant decrease of MCP1 and a trend for an increase of CD8+ cells and IL12-p40. **Conclusions:** The study shows that Lantigen-B drives a Th1-reaction and stimulates the differentiation / activation of B and NK cells. Changes in lymphocyte subpopulations and in cytokines are well correlated. The observed changes can result in a state of "prealert" of the immune system able to successfully fight infections also induced by bacteria and viruses different from those administered, the so-called "Trained Immunity". Finally, the reduction of MCP1, which drives a Th2 reaction, can explain the beneficial effects on allergies observed in some clinical studies.

Keywords: immunostimulants; respiratory tract infections; Th1 immune reaction; cytotoxicity; trained immunity

1. Introduction

Bacterial lysates (BLs) are medicines made from bacterial cells that are broken down and are intended to stimulate the immune system to recognize and fight infections (European Medicines Agency). They are made up of bacterial antigens of the strains most frequently responsible for recurrent respiratory tract infections (RTIs) obtained by chemical (alkaline) or mechanical lysis; heat or detergents have also been used [1]. BLs can be administered via orally, nasally, or sublingually. BLs are prescribed for the prevention of RTIs, and overall, most studies show that the number of RTIs and their severity are reduced in patients pretreated by BLs, with no relevant side effects [2–5].

Lantigen B (Lan-B) is one of the most interesting BLs, being administered sublingually and therefore stimulating directly the immune cells locally to the site of infections. Its effect on salivary IgA which are increased after treatment is particularly

interesting [6]. It is composed of chemical lysate of the most frequently isolated bacteria during RTIs: *Staphylococcus aureus* type 3, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* group A, *Branhamella catarrhalis*, and *Haemophilus influenzae* type b.

Its clinical effectiveness has been evaluated by numerous clinical trials, all showing positive results. A multicenter study involving adults (n. 118) and children (n. 94) reported a relative reduction in RTIs of 30.4% in adults and 35.7% in children [7]. In a study conducted in China [8], children treated with Lan-B experienced a significant decrease in the number of fever days and RTIs compared to the control group ($p < 0.05$). Alongside clinical improvement, a significant increase in both serum and salivary IgA levels was observed after treatment ($p < 0.05$). Recent reviews have confirmed the efficacy of Lan B, analyzing clinical data from 22 randomized controlled trials involving 4571 patients. These reviews showed an overall reduction of 47% in the number of infectious episodes, as well as a decrease in the number of work or school days missed [4,9].

However, the European Medicines Agency recently reviewed the existing literature on the efficacy of BLs and confirmed their use for the prophylaxis of RTIs. At the same time, it recommended conducting new clinical trials using the most up-to-date study designs to definitively establish their efficacy. In line with this recommendation, all interested pharmaceutical companies are currently planning double-blind, placebo-controlled (DBPC) clinical trials for their respective products.

The mechanism of action of BLs lies in their ability to modulate the immune system, targeting both the innate and adaptive branches. Studies have shown that BLs help restore the integrity and immune function of the epithelial barrier and activate type 3 innate lymphoid cells (ILC3) and dendritic cells, promoting an enhanced Th1 response. This, in turn, stimulates B cells to produce serum IgG, as well as serum and salivary IgA specific to the administered bacterial antigens. Mechanistic studies with Lan-B have demonstrated increases in both serum and salivary IgA levels [6,8,10], as well as its ability to modulate the expression of the SARS-CoV-2 cellular receptor ACE2 on oropharyngeal cells [11]. Unlike other BLSs, there are very few studies on the immune effects of Lan-B. Therefore, alongside the planned DBPC clinical trials, a series of in vitro studies are currently underway to investigate the immune mechanisms specific to Lan-B. The present study is an exploratory in vitro investigation aimed at evaluating the ability of Lan-B to influence the proportions of various lymphocyte subpopulations and to modulate the release of selected cytokines that play key roles in immune responses. Positive results from this study would support further experimental research to assess the effects of Lan-B on epithelial cells, dendritic cells, cytotoxic lymphocytes, and the specificity of the immune response. It is noteworthy that nearly all studies on the various BLs have been conducted using antigen concentrations different from those used in clinical practice. The only study to date that employed a BL concentration identical to that used in human treatment was conducted with Lan-B, focusing on its effect on the ACE2 receptor [11]. In the present study as well, the same concentration used in clinical settings was applied in all experimental procedures.

2. Materials and methods

2.1. Bacterial lysate

Lan-B was supplied by Piam-Bruschettini Ltd (Genoa, Italy). It contains both the particulate and soluble fractions obtained through chemical lysis of six microbial species commonly responsible for respiratory tract infections (reported in the introduction). The product was supplied with the following Antigen Unit (AU) concentrations: *S. pneumoniae* KAU 14,788.8; *S. pyogenes*: KAU 29,530.8, *B. catarrhalis* KAU 9336.6, *K. pneumoniae* KAU 9313.2, *S. aureus* KAU 18,626.4, *H. influenzae* KAU 11,746.8. The bacterial suspension was submitted to two homogenization cycles at 630 bar. The bacterial suspension underwent two homogenization cycles at 630 bar. It was then diluted in RPMI 1640 culture medium and sonicated for 5 minutes to reach the antigen concentrations used in the commercial formulation: *Streptococcus pneumoniae* AU 63.2, *Streptococcus pyogenes* AU 126.2, *Branhamella catarrhalis* AU 39.9, *Klebsiella pneumoniae* AU 39.8, *Staphylococcus aureus* AU 79.6, *Haemophilus influenzae* AU 50.2. The diluted preparation was aliquoted and stored at -80°C until use.

2.2. Peripheral blood mononuclear cells and Lan-B stimulation

Peripheral blood mononuclear cells (PBMCs) were isolated from seven healthy human donors using Ficoll-Hypaque gradient centrifugation. Mononuclear cells collected from the interface were harvested, washed, and resuspended at a concentration of 2×10^6 cells/mL in RPMI 1640 culture medium supplemented with 50 U/mL penicillin, 50 µg/mL streptomycin, and 5% heat-inactivated fetal calf serum. PBMCs were cultured either alone (control) or in the presence of Lan-B at a final concentration of 199.45 AU/mL. Cultures were incubated at 37 °C in a humidified atmosphere with 5% CO_2 for 24 hours. After incubation, cells and culture supernatants were collected separately and stored for subsequent analyses.

2.3. Detection of cell surface phenotypes

At the end of the 24-hour incubation with Lan-B, cells were harvested, washed, and resuspended in phosphate-buffered saline (PBS−/−) containing 0.5% bovine serum albumin (BSA) and 0.1% *sodium azide*. Cells were aliquoted at 1×10^6 per sample for staining. To determine cell surface phenotypes, 50 µL of each fluorochrome-conjugated monoclonal antibody (mAb) was used for staining the following markers: CD45, CD4, CD8, CD16/56, and CD19. The antibodies included APC-Cy7-conjugated mouse anti-human CD45 (clone REA747, Miltenyi Biotec), PE-conjugated mouse anti-human CD4 (clone REA623, Miltenyi Biotec), AmCyan-conjugated mouse anti-human CD8 (Miltenyi Biotec), FITC-conjugated mouse anti-human CD19 (clone H1B19, eBioscience™, Thermo Fisher), and PerCP-Vio700-conjugated mouse anti-human CD16/56 (clone REA196, Miltenyi Biotec). Cells were incubated with the antibodies for 15 minutes at room temperature. For negative controls, unstained aliquots of cell suspensions were included. Following incubation, cells were washed twice and resuspended in PBS−/− for flow cytometric analysis. Flow cytometry was performed using a BD FACSCanto™ flow cytometer (Becton

Dickinson, Mountain View, CA, USA), and data were analyzed with BD FACSDiva™ Software (BD Biosciences).

2.4. Cytokine determination

At the end of the incubation period, cell cultures were harvested and centrifuged to collect cell-free supernatants, which were stored at –80°C until analysis. The concentrations of the following cytokines were measured: IL-1β, IFN-α, IFN-γ, TNF-α, IL-6, IL-8, IL-10, IL-17, IL-18, IL-23, IL-33 and IL-12-p40 subunit. Cytokine levels in the culture supernatants were quantified by flow cytometry using commercial reagent kits (LEGENDplex™ Human Inflammation Panel 1, 13-plex) following the manufacturer's instructions. The assay data files (FCS format) were analyzed using BioLegend's LEGENDplex™ data analysis software. Cytokine concentrations were reported in pg/mL.

2.5. Statistical analysis

The values were expressed as mean and standard deviation. Statistical significance of the differences in the proportion of lymphocyte phenotypes and in cytokine release was determined using Mann-Whitney U test. *P* values of < 0.05 were considered statistically significant. The False Discovery Rate (FDR) method was applied to adjust for multiple comparisons.

3. Results

The results of this preliminary study are quite promising, showing a clear modulation in the proportion of certain lymphocyte subpopulations and changes in cytokine release in Lan-B treated cultures, compared to untreated, consistent with the observed lymphocyte changes.

3.1. Effects on the proportion of Lymphocyte subpopulations

Significant changes in the proportions of both CD19+ and CD16+56+ cells were observed in Lan-B stimulated cultures compared to unstimulated ones (**Figure 1**).

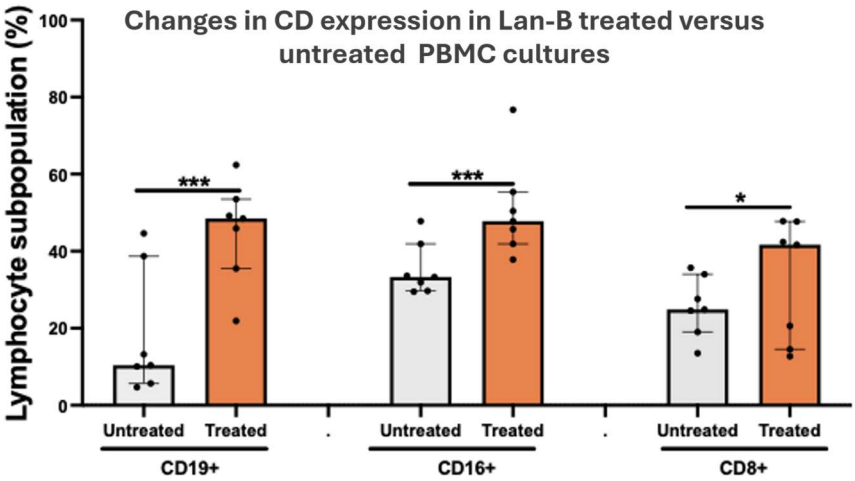

Figure 1. Lymphocyte subpopulation changes in LAN-B treated cultures.
***$p < 0.01$; *$p = 0.055$ (Mann-whitney u test, with false discovery rate)

In particular, the proportions of both B cells ($CD19^+$) and natural killer (NK) cells ($CD16^+$) significantly increased in Lan-B-treated PBMC cultures compared to untreated controls, rising from 18.20% to 45.27% for $CD19^+$ cells and from 32% to 44% for $CD16^+$ cells ($p = 0.01$; MWU test adjusted with False Discovery Rate). **Figure 2** shows a FACS illustrating changes in the proportion of various CD markers in untreated vs Lan-B treated PBMCs, highlighting a significant increase in CD19+ and in CD16+56+ cells. **Figure 3** presents similar FACS plots along with the flow cytometry gating strategy used. Although an increase in $CD8^+$ cells was observed, the high variability among experiments rendered this change statistically non-significant ($p = 0.055$, Mann–Whitney U test adjusted with False Discovery Rate), indicating only a trend toward increase. No significant changes were found in the proportion of $CD4^+$ cells.

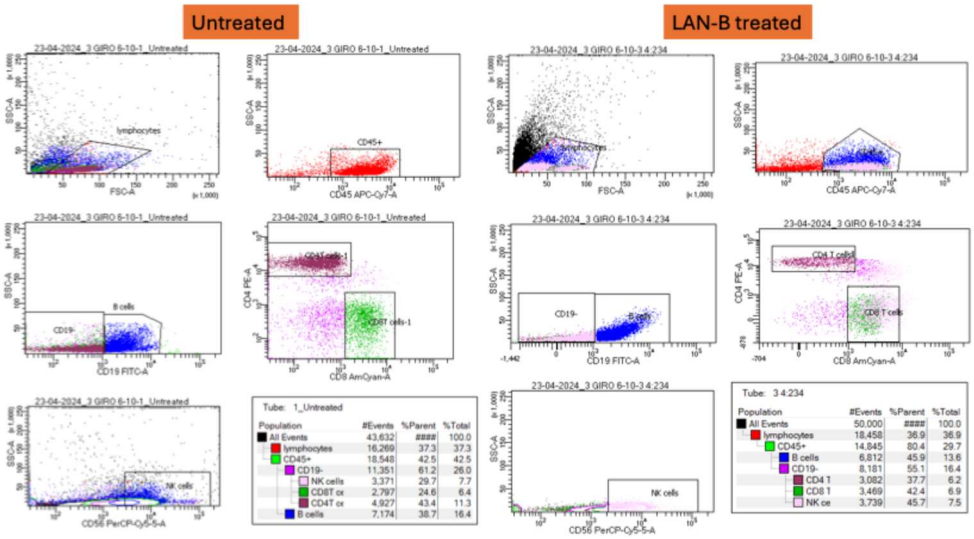

Figure 2. Representative FACS of untreated vs LAN-B treated PBMCs.

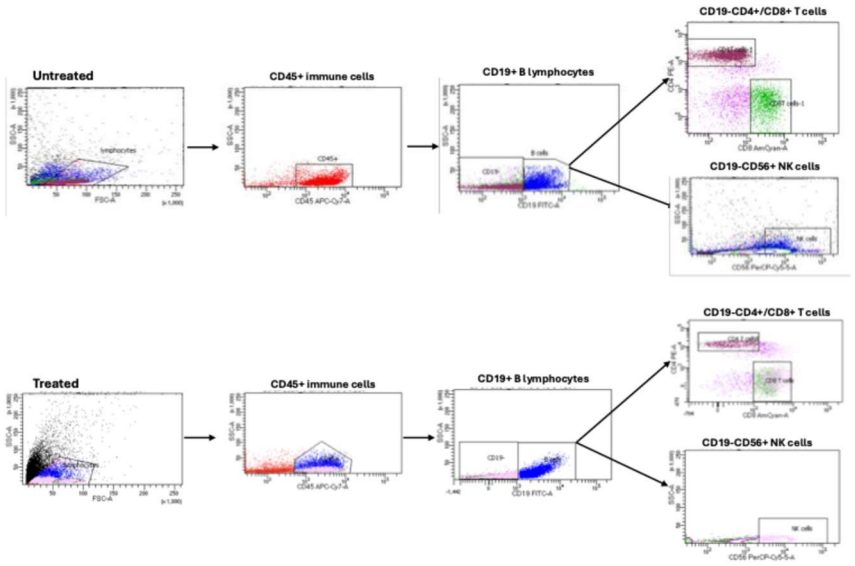

Figure 3. Representative FACS of untreated vs LAN-B treated PBMCs showing flow cytometry gating strategy.

3.2. Effects of Lan-B on the release of cytokines by PBMCs

Table 1 shows mean±SD of each cytokine tested. Variations are also expressed as cytokine fold changes between untreated and Lan-B treated cultures **(Figure 4)**. The logarithm base 2 Fold changes (Log2FC) clearly differentiate cytokines that increased from those that decreased. Statistical significance of the changes evaluated by the Mann-Whitney U test and adjusted applying False Discovery Rate is reported in **Table 1**.

Table 1. Mean (SD) values of evaluated cytokines in untreated and treated PBMC cultures. Variations are expressed as fold changes of treated versus untreated cultures. Significance has been evaluated by the Mann-Whitney U test. Values are picograms/mL.

Disease type	Mean (SD) in untreated samples (values are p/ml)	Mean (SD) in treated samples (values are *p*/ml)	Fold change (treated vs untreated cultures)	log2FC	Mann witney U test; adjusted with false discovery rate
IL1	80.9 (61.2)	7837.11 (2970.3)	157.40	7.30	0.01
IFN	14.55 (21.2)	1913.09 (1828.6)	45.55	5.51	0.05
TNF	205.25 (155.2)	7970.11 (6187.1)	75.40	6.24	0.02
IL6	4026.15 (1898.8)	6883.82 (3301.8)	2.34	1.23	NS
Il12	0.51 (0.88)	4.3 (4.2)	28.67	4.84	0.052
IL17	0.004 (0.006)	7.65 (7.7)	7653.5	12.90	0.01
IL18	4.24 (4.7)	162.85 (107.2)	68.43	6.1	0.01
IL33	0.17 (0.16)	2.38 (2.28)	23.83	4.57	NS
IFN a	0.09 (0.1)	0.28 (0.14)	7.08	2.82	NS
MCP1	7681.72 (0.1)	174.65 (188.1)	0.02	-5.46	0.01
IL6	9692.91 (3700.9)	10,632.6 (2204.1)	1.30	0.38	NS
IL10	74.08 (62.2)	156.27 (155.1)	1.40	0.48	NS
IL23	94.70 (124.4)	250.16 (259.2)	21.66	4.43	NS

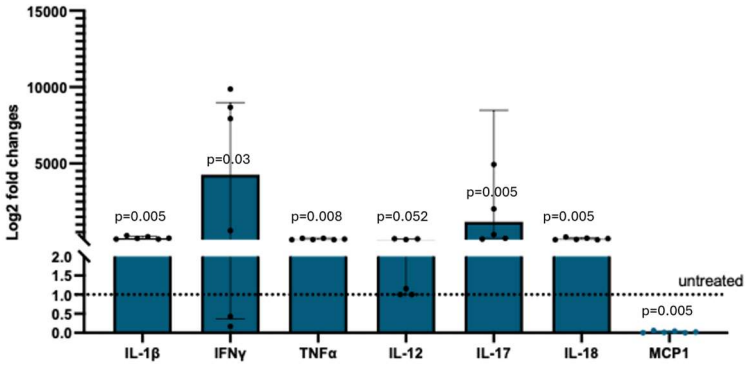

Figure 4. Cytokines with significant changes in Lan-B treated vs untreated cultures. The values are expressed as Logarithm base 2 of fold changes.

In particular, IL-1β, IFN-γ, TNF-α, IL-17, IL-18 significantly increased whereas MCP1 significantly decreased (**Table 1**, **Figure 3**). No significant changes were found for IFN-α, IL-6, IL-17, IL-18, and IL-12-p40. However, a trend for an increase of this last cytokine, even though not significant, has been shown ($p = 0.055$).

3.3. Limitations

The primary limitation of this study is the small sample size. However, as an exploratory investigation, it serves as a foundation for future mechanistic studies exploring the effects of Lan-B on additional cellular components of both innate and adaptive immunity. Moreover, while the in vitro detection of immunomodulatory activity is promising, its clinical relevance will need to be confirmed through in vivo studies, complementing the already established clinical efficacy of the drug.

Another important consideration is donor heterogeneity—the inherent variability among individual donors—which can influence experimental outcomes and complicate the generalization of findings. This variability may contribute to inconsistencies across replicates. To address this, statistical adjustments for multiple comparisons were applied using the False Discovery Rate (FDR), helping to reduce the impact of such variability. Nevertheless, the current findings provide a rationale for future clinical trials aimed at confirming the observed immunomodulatory effects of Lan-B in vivo other that its clinical efficacy.

4. Discussion

While the clinical effectiveness of Lan-B in preventing recurrent respiratory infections is well established in the literature [4,5,8,9], limited laboratory data exist regarding the immune changes induced by the drug. The present study successfully met its endpoints: Lan-B was shown to modulate the proportions of lymphocyte subpopulations and to influence cytokine release at a concentration equivalent to that used in clinical practice.

The findings indicate that Lan-B promotes a Th1-type immune response, stimulates B cell differentiation, and activates NK cells. The cytokines modulated by Lan-B play key roles in host defense mechanisms and resistance to pathogens, supporting the immunomodulatory potential of the drug observed in clinical contexts. It can be hypothesized that NK cells are activated by bacterial antigens through the engagement of activating surface receptors, which trigger intracellular signaling cascades involving protein kinases, phosphatases, and other signaling molecules. These receptors, associated with ITAM-containing adaptors, activate intracellular signaling pathways so promoting NK cell activation. [12,13]. Similarly, antigenic stimulation of B cells activates a complex signaling cascade initiated by the B-cell receptor (BCR). Upon antigen binding, the BCR triggers activation of the tyrosine kinase Syk and downstream effectors such as phospholipase Cγ2 (PLCγ2), leading to calcium mobilization and diacylglycerol (DAG) production. This signaling ultimately drives B-cell activation, differentiation, and antibody production [14].

The observed changes in lymphocyte subpopulations are well correlated with the cytokine profile alterations. Several of the cytokines found to be elevated in this study are known to promote NK cell activation and support the clonal expansion and activation of B lymphocytes, which may explain the increases in serum IgG and both serum and salivary IgA reported in clinical studies [6,8,10]. Conversely, some of these same cytokines are also produced by activated NK and B cells, suggesting a bidirectional interaction that amplifies the immune response.

More specifically, IFN-γ plays a central role in coordinating both innate and adaptive immune responses. During the innate immune phase, it is produced predominantly by NK cells [15]. Its secretion by macrophages and dendritic cells further enhances NK cell cytotoxicity, increasing their tumoricidal activity [16,17]. In the context of adaptive immunity, IFN-γ is produced by Th1 and cytotoxic T lymphocytes [18], where it amplifies antigen presentation by antigen-presenting cells (APCs) to naïve $CD4^+$ T cells, promoting their differentiation into $CD4^+$ Th1 lymphocytes [19]. This Th1 polarization leads to further IFN-γ release, which contributes to the activation of effector cells and the maturation of B cells into plasma cells, driving antibody production against the invading antigen [20]. Therefore, the increased IFN-γ release observed in our cultures may explain the elevated proportion of B lymphocytes. Furthermore, Th1 cells can interact directly with B cells, releasing IL-12, which activates the STAT4 pathway and induces further IFN-γ production by B cells themselves [21,22]. These tightly regulated interactions enhance the antimicrobial effects of IFN-γ, including the upregulation of reactive oxygen species and reactive nitrogen intermediates [23,24], activation of macrophages, induction of autophagy for clearance of intracellular pathogens [25–27], increased phagocytosis, secretion of pro-inflammatory cytokines [21], recruitment of lymphocytes to infection sites [28–30], and support for the survival and function of effector memory T cells [31].

TNF-α is one of the key mediators of the innate immune reaction. It is mainly produced by monocytes/macrophages [32,33] and T cells and to a lesser extent by B cells, dendritic cells, and mast cells [34–36]. Together with IFN-γ, TNF-α contributes to the initiation and amplification of cell-mediated immune responses against pathogens [37]. It is essential for the maturation of macrophages [38,39], promotes the differentiation of monocytes into dendritic cells [40] and is also fundamental for the differentiation and maturation of NK cells [41], and for the migration of inflammatory cytokines to sites of infection [42], with a role in the inhibition of viral replication [43]. TNF-α activates B cells proliferation [44] in infection-related polyclonal B-cell expansion, activating the transcription factor NF-κB of B cells [45] and increasing DNA synthesis and immunoglobulin production [46].

IL-1β, under physiological conditions, is produced primarily by monocytes, but also by activated macrophages, dendritic cells and NK cells [47,48]. It is a key mediator of the inflammatory response [49], exerting a broad range of immunomodulatory functions [50]. Active IL-1β is secreted in response to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) [49], through mechanisms involving calcium influx [51], exosomes containing NLRP3 inflammasome components, pro–IL-1β, caspase-1, and MHC class II molecules [52], or via plasma membrane–derived microvesicles [53]. The active IL-1β favors T-cell–APC interaction promoting the antigen-specific helper T-cell differentiation and function and it also plays a role in T-cell-dependent antibody production [54]. Of note, the direct action of IL-1β on CD4+ and CD8+ T cells that influence T cell differentiation is synergistic with other polarizing cytokines [55].

IL-18 belongs to the IL-1 family and, similarly to IL-1β, has a role in orienting acquired immune response often acting synergistically with IL-1β [56,57]. It is

produced by monocytes, macrophages, and dendritic cells. Together with IL-12, IL-18 stimulates T lymphocytes to produce IFN-γ, thereby promoting a Th1-mediated immune response. The same IFN-γ inducing effect is also observed in macrophages, dendritic cells, B cells, CD8+ cells, ILC1 and NK cells [58–61]. Moreover, IL-18 stimulates NK cells by engaging IL-1R8 receptor that is highly expressed on their surface, promoting their differentiation and activation during infections [62]. The critical role of IL-18 in activating NK cells has been demonstrated in IL-18 deficient mice, which together with an impaired NK cell activity have an increased susceptibility to infections [63].

IL-12p40 is produced by activated macrophages and plays a crucial role in the development of Th1 response. IL-12p40 serves as a key the link between the innate and adaptive immune responses by directing T-cell reactions toward the production of Th1-associated cytokines [64]. Moreover, it has a role in the long-term protection against intracellular pathogens, favoring the differentiation of memory and effector Th1 cells [65]. Furthermore, binding to the IL-12 receptor, IL-12p40 induces the proliferation and activation of NK cells [66,67].

IL-18 and IL-12p40 play pivotal roles in shaping long-term immune memory, particularly in the context of T cell responses and antiviral immunity. Acting synergistically, these cytokines enhance the production of IFN-γ, which is crucial for activating cytotoxic T lymphocytes (CTLs) and establishing durable immune protection [56,68]. IL-12p40, a subunit of IL-12, is known to be a key driver of Th1 immune responses [69]. IL-18, on the other hand, enhances the effects of IL-12 by promoting IFN-γ production from various immune cells, including T cells and natural killer (NK) cells [70]. When administered together, IL-12 and IL-18 significantly enhance both the proliferation and cytotoxic activity of $CD8^+$ T cells, which are essential for the clearance of viral infections and tumor cell elimination [70]. Their combined activity is critical for controlling viral infections [56]. In murine models, the absence of both IL-12p40 and IL-18 leads to increased susceptibility to infection, impaired CD8+ T cell responses, and reduced numbers of virus-specific CD8+ T cells [71]. By amplifying IFN-γ production and facilitating broader cytokine responses, IL-12 and IL-18 promote a more robust and enduring immune reaction, crucial for effective antiviral immunity [72]. While the exact mechanisms by which these cytokines contribute to memory formation are still being investigated, existing evidence strongly supports their role in the activation, expansion, and maintenance of antigen-specific $CD8^+$ T cells. Taken together, these findings highlight IL-18 and IL-12p40 as key immunoregulatory cytokines, with synergistic functions that support both immediate immune defense and long-term immune memory [70,71].

IL-17, in addition to Th17 cells, is produced also by NK cells, and IL-1β-stimulated CD8 and CD4 T. It mediates protective immunity against fungal and bacterial infections [73,74]. Its protective function is mainly due to its ability to recruit neutrophils [75] and NK cells [76] to the site of infection. IL-17 is essential for the protection against extracellular bacterial pathogens; for example, IL-17 signaling-deficient mice exhibit impaired neutrophil recruitment and reduced clearance of Klebsiella pneumoniae in a pneumonia model [77].

Clinical trials have reported that patients treated with bacterial lysates (BLs) exhibit protection not only against the specific bacterial strains contained in the product but also against unrelated bacterial and viral pathogens [78,79]. This broader protective effect may be attributed to the activation of the innate immune system, which subsequently enhances adaptive immune responses against novel pathogens. In our study, the observed increase in the proportion of NK cells—and a trend toward increased $CD8^+$ T cells—along with the associated cytokine profile, can be well framed in this perspective. This broad activation suggests that BLs may induce a "pre-alert" state in the immune system, enhancing its readiness to respond to infections [80]. This phenomenon is consistent with the concept of trained immunity—a functional adaptation of the innate immune system characterized by an enhanced response to secondary infections, even those caused by unrelated pathogens [81]. Trained immunity involves long-term epigenetic and metabolic reprogramming of innate immune cells, particularly monocytes, with IL-1β playing a key role in this process [57,82,83]. Trained immunity is increasingly recognized as a form of innate immunological memory. Both experimental and clinical studies have demonstrated that exposure to exogenous pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPs) can induce this heightened state of readiness. Vaccines, for example, are capable of stimulating trained immunity by activating innate immune cells—especially NK cells and dendritic cells—which then amplify adaptive immune responses to both specific and bystander antigens [84,85].

Finally, our experiments demonstrated that Lan-B induces a decrease in the release of MCP-1. MCP-1 is known to selectively suppresses naïve T cell differentiation into Th1 effector cells by modulating IL-12 releasing ability of dendritic cells [86]. Additionally, it activates the IL-4 promoter, which results in the enhancement of type 2 immune response through IL-4 production by T cells. MCP-1 also promotes chemotaxis and activates basophils [87]. In the context of our findings—where Lan-B was shown to enhance cytokines and immune cell populations associated with Th1 responses—the observed decrease in MCP-1 suggests a potential immunological shift away from Th2 dominance. This implies that Lan-B may help prevent allergic sensitization by promoting a Th1-skewed immune profile. The hypothesis is that BLs act on the immune system mimicking the protective effects of natural exposure to microbe-rich environments for the prevention of allergic disease [88]. It has been also hypothesized that BLs can ameliorate already-developed respiratory allergies while preventing infections that are responsible for the exacerbation of allergic asthma and rhinitis [89]. Notably, a placebo-controlled clinical trial in children with seasonal allergic rhinitis showed a reduction in seasonal symptoms when patients were treated with Lan-B during the pollen season [90].

The Th1 modulation induced by Lan-B may help explain the clinical benefits observed in multiple studies, particularly regarding the prevention of recurrent respiratory bacterial infections. Th1 immune responses, characterized by the production of cytokines such as IFN-γ, are essential for the effective clearance of intracellular pathogens. However, during early childhood, the immune system is still maturing, and Th1 responses are often underdeveloped, contributing to increased susceptibility to infections. Conversely, in the elderly, a natural decline in immune

function, referred to as immunosenescence, leads to diminished Th1 activity and altered cytokine production, similarly increasing the risk of recurrent infections. In both age groups, impaired Th1 responses play a key role in vulnerability to respiratory infections. Therefore, Lan-B, through its capacity to enhance Th1-driven immunity, may be particularly beneficial in preventing such infections in these at-risk populations. Nevertheless, it is important to note that in other conditions of high susceptibility to infections, such as the immunodeficiencies the safety and efficacy of Lan-B have not yet been demonstrated.

5. Conclusions

The aims of the study have been reached: Lan-B was able to modulate the immune system, inducing an activation of the innate immune system, in particular NK cells, and of the adaptive immune system being the significantly modified cytokines typical of a Th1-mediated reaction. Such modification can justify the demonstrated clinical activity of Lan-B. This is a preliminary study that will be followed by the evaluation of the activity of Lan-B on dendritic cell maturation, epithelial cells, cytotoxic lymphocytes and the specificity of the immune response in vitro and the evaluation of the observed immune modulation in clinical trials in vivo.

Author contributions: Conceptualization, MDG, QN and FS; methodology, RL, MA and MT; validation, RL, MA, PDM, and MT; formal analysis, RL, MA and MT; investigation, MDG; resources, FS; data curation, RL; writing—original draft preparation, MDG; writing—review and editing, MDG, FS, and QN; supervision, MDG and FS; project administration, FS; funding acquisition, MDG. All authors have read and agreed to the published version of the manuscript.

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Ethical approval: This study was reviewed and approved by the Institutional Review Board (IRB) of the G. d'Annunzio University (approval number: 1643/25).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Conflict of interest: The authors declare no conflict of interest.

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